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Synthesis and applications of non-racemic cyanohydrins and α-amino nitriles

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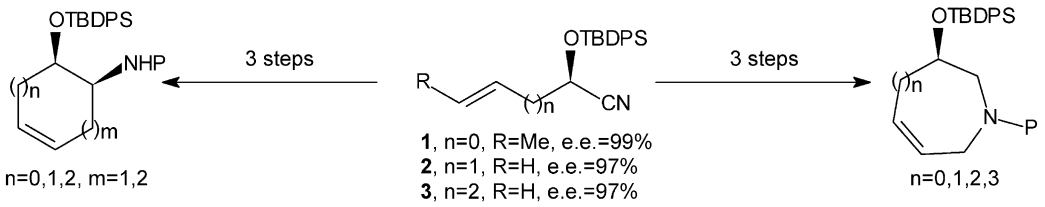
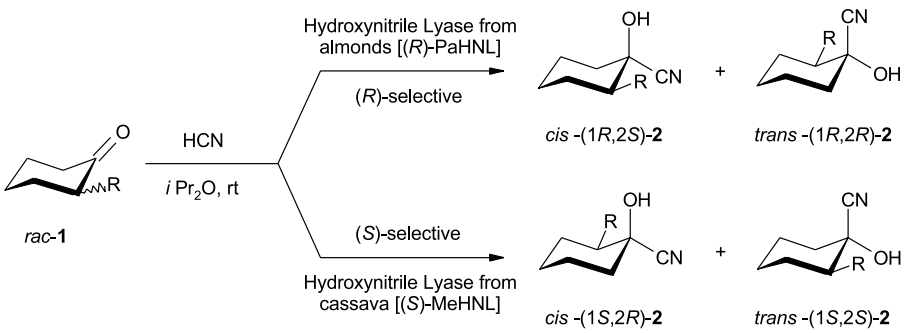
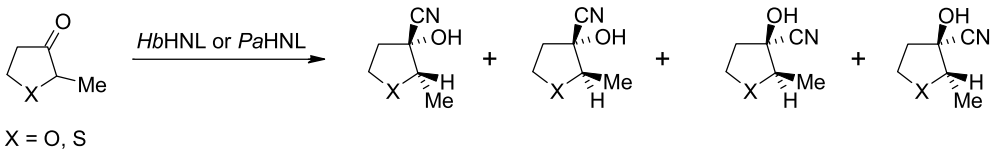
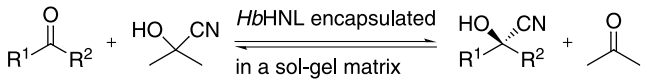
Contents

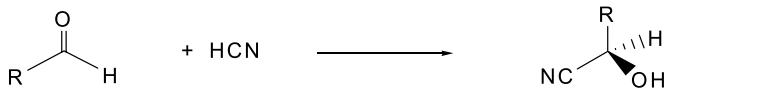




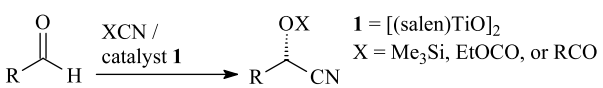


The resulting cyanohydrins were stereochemically characterised and the mechanistic course of the transformations interpreted by molecular modelling.

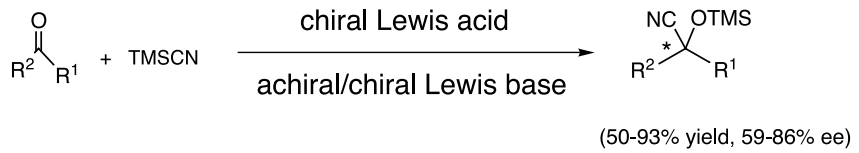


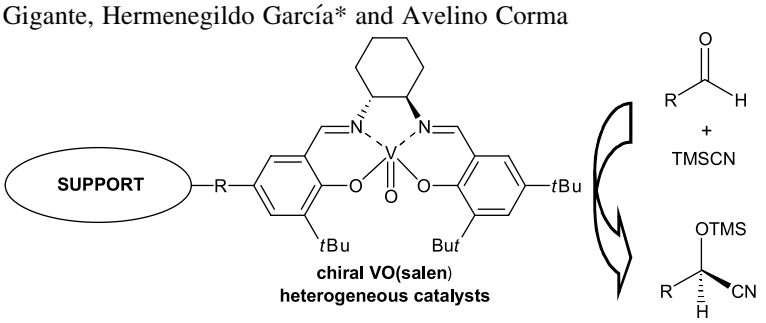


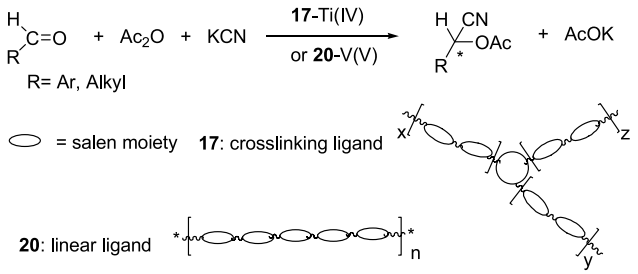
R = phenyl, cinnamyl, 2-methyl-2-butenyl, 2-pentenyl, 2,4-pentadienyl

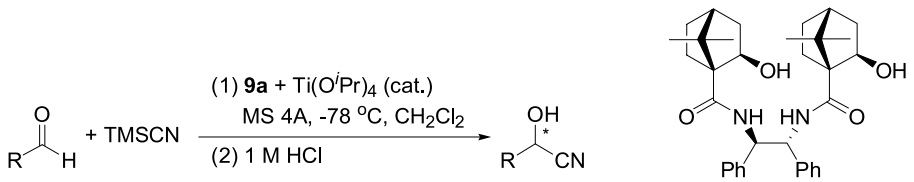


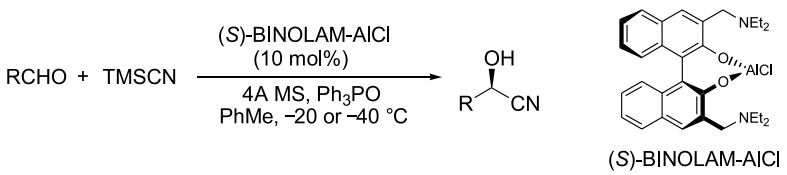
Synthetic and mechanistic studies on the use of titanium(IV) complexes for asymmetric cyanohydrin synthesis are reported. In addition to synthetic studies on the synthesis of both cyanohydrin esters and cyanohydrin carbonates, mechanistic studies concerning the structure of the catalyst in solution are also described.

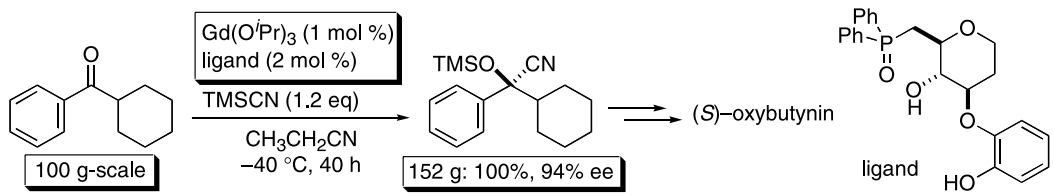


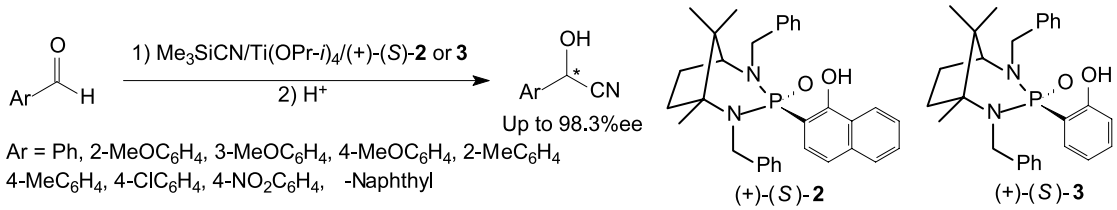


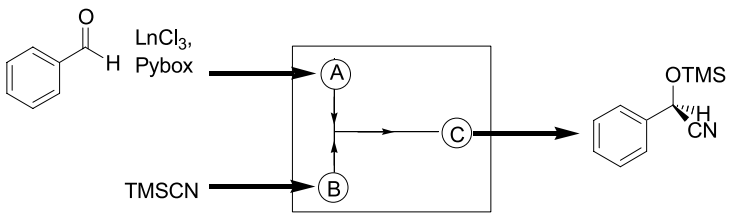


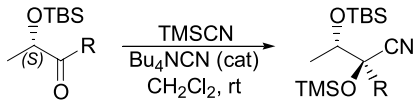




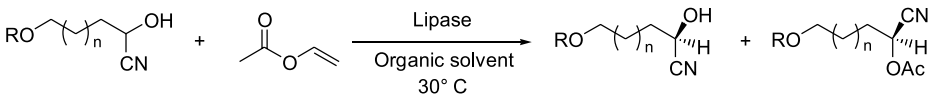




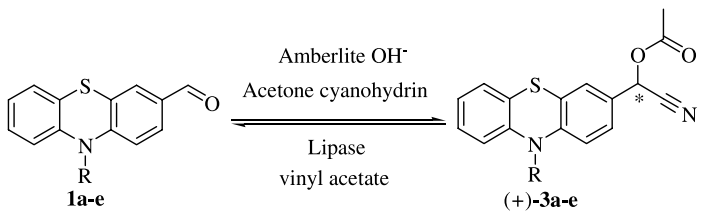




R = CH_3, *de* = 50%; R = Ar, *de* > 80%

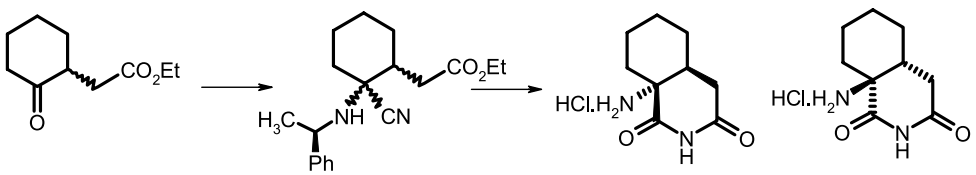


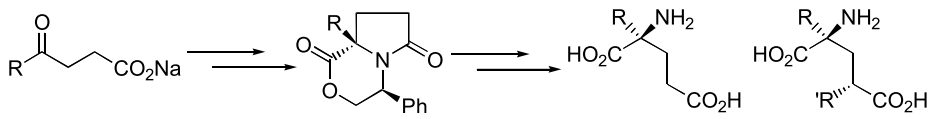
R: Ac; Bz; MOM; CPh_3.
n: 1; 2; 3.

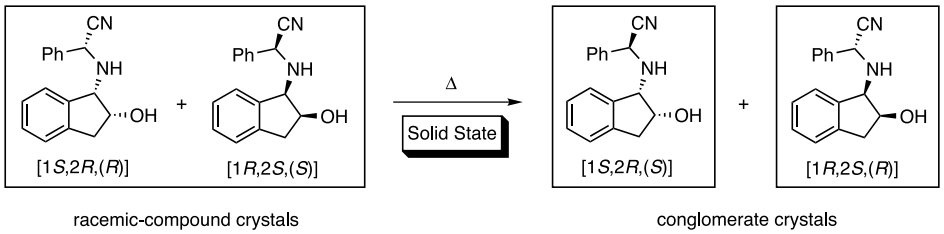


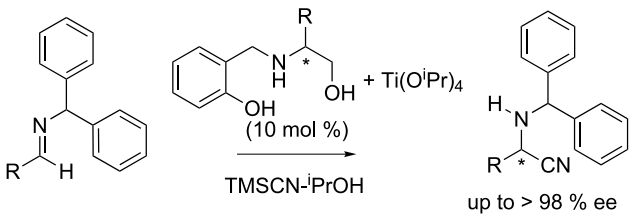
1a-e (+)-**3a-e**

1-3	R
a	CH_3
b	C_2H_5
c	C_3H_7
d	*iso*-C_5H_{11}
e	C_7H_{15}









An enantioselective Strecker synthesis employing novel chiral titanium complex catalysts derived from chiral *N*-salicyl-β-amino alcohols is described. *N*-Benzhydrylimines derived from aromatic and aliphatic aldehydes gave Strecker products in excellent yields and in up to >98% ee.

OTHER CONTENTS

*Corresponding author

COVER

The cover graphic illustrates the chemistry and stereochemistry of the transformation of carbonyl compounds into both cyanohydrins and α-amino nitriles. It highlights the various methods which can be used to achieve these transformations. *Tetrahedron* **2004**, *60*, 10371–10568.

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Preface

Synthesis and applications of non-racemic cyanohydrins and α-amino nitriles

The addition of cyanide to carbonyl compounds and imines has a long history. The first synthesis of a cyanohydrin (mandelonitrile) was reported in 1832 by Winkler. Eighteen years later, Strecker first reported the synthesis of amino nitriles by the three-component condensation reaction of a carbonyl compound, amine and cyanide, which bears his name. In the subsequent 170 years, both cyanohydrins and amino nitriles established themselves as key intermediates in organic synthesis, largely due to the wide variety of 1,2-bifunctional compounds into which they could readily be transformed. The mechanism of cyanohydrin synthesis under standard basic aqueous conditions was determined by Lapworth in 1903, making this one of the first chemical reactions to be fully understood.

The first catalytic asymmetric cyanohydrin synthesis was reported just five years later in 1908 by Rosenthaler. Thus it was found that an extract of almonds would catalyse the asymmetric addition of hydrogen cyanide to aldehydes, giving (*R*)-cyanohydrins. The oxynitrilase enzyme isolated from almonds remains the most studied enzyme for asymmetric cyanohydrin synthesis. Over the last almost 100 years, methods for the isolation and utilisation of this enzyme (which constitutes 0.4% of the weight of almonds) have been optimised and the substrate tolerance has been thoroughly investigated. The application of this enzyme to asymmetric synthesis is the topic of papers within this symposium by Brussee, Effenberger and Griengl. Whilst the almond enzyme remains the most conveniently isolated oxynitrilase enzyme, oxynitrilases are widespread in the plant kingdom and have also been isolated from many other sources. The oxynitrilase enzymes obtained from *Sorgham bicolour* and the rubber tree are particularly notable as they catalyse the synthesis of (*S*)-cyanohydrins and so are complementary to the almond oxynitrilase. The application of the *S. bicolour* enzyme is illustrated in the paper by Effenberger, whilst the use of the rubber tree oxynitrilase is the topic of papers by Griengl and Hanefeld. The use of a new (*R*)-selective oxynitrilase isolated from *Pouteria sapota* (Mamey) is discussed in the paper of Solis.

The first synthetic catalysts for the asymmetric addition of cyanide to aldehydes were purely organic catalysts such as synthetic polymers, cyclic dipeptides, alkaloids, β-cyclodextrins, imidazolidinediones and ε-caprolactams. These compounds have in common that they are all basic organic compounds, and in the 1980's and 1990's, the cyclic peptide derived catalysts attracted considerable synthetic and mechanistic interest as exceptionally high levels of asymmetric induction could be obtained, especially with aromatic aldehydes as substrates. However, these systems were found to be difficult to study and optimise and required the use of hydrogen cyanide, which restricted their academic utility. There appears to be no ongoing work in this area.

The main current alternative to the use of enzymes as catalysts for the asymmetric addition of hydrogen cyanide to carbonyl compounds is the use of chiral transition metal complexes to catalyse the addition of a cyanide species to aldehydes or ketones. The first report in this area appeared in 1986, but it is only in the last decade that truly effective catalysts have been developed. The early systems suffered from the need for very low reaction temperatures, long reaction times, high catalyst to substrate ratios and limited substrate tolerance. All of these problems have been overcome during the development of the latest catalysts and this work is described in a series of papers within this symposium. The two most developed systems are those based on salen ligands, and those which use binol complexes. The paper by North details the latest developments in the use of titanium(salen) complexes as catalysts for the asymmetric addition of various cyanide sources to aldehydes, whilst the paper by Feng illustrates the use of titanium(salen) complexes to catalyse the asymmetric addition of trimethylsilyl cyanide to ketones, accelerated by Lewis bases as a cocatalyst. Corma and García describe the anchoring of the corresponding vanadium(salen) complex to insoluble supports and their use as a catalyst for the asymmetric addition of trimethylsilyl cyanide to aldehydes under heterogeneous conditions. Zheng describes the synthesis of polymeric versions of both titanium and vanadium salen complexes and their application to the asymmetric synthesis of cyanohydrin acetates. A C_2-symmetric 1,2-diamine also forms the basis of the β-hydroxyamide ligands developed by Uang. Full details of the applications of the titanium complexes of these ligands to asymmetric cyanohydrin synthesis are reported in the paper from this group.

The development of functionalised binol complexes of aluminium as catalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes is discussed in the paper by Najera. Shibasaki carried out much of the key work on the use of binol complexes in asymmetric cyanohydrin synthesis, and in recent years he has developed a new

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system based around the gadolinium complex of a chiral ligand bearing phenolic and phosphine oxide substituents. The paper by Shibasaki in this symposium illustrates the use of this catalyst in the asymmetric addition of trimethylsilyl cyanide to ketones and the use of the resulting cyanohydrins in the synthesis of pharmaceuticals. The use of chiral ligands based on phosphine oxides is also discussed in the paper by Zhou and Tang. In this case, the titanium complex of the ligand is used to catalyse the asymmetric addition of trimethylsilyl cyanide to aldehydes with high enantioselectivity. Another common catalyst system for asymmetric cyanohydrin synthesis is the pybox complex of a lanthanide. The use of this catalyst system in a micro reactor is discussed in the paper by Moberg.

Not all methods for the synthesis of non-racemic cyanohydrins rely upon the enantioselective addition of cyanide to an aldehyde or ketone. The diastereoselective addition of cyanide to chiral α-hydroxy-ketones is discussed in the paper of Plumet. Lipase enzymes can be used to resolve racemic cyanohydrins as illustrated in a paper by Goter, providing an alternative approach to non-racemic cyanohydrins and their esters. An extension of this process combines a reversible racemic cyanohydrin synthesis with a lipase catalysed enantioselective esterification, to provide a dynamic kinetic resolution approach to cyanohydrin acetates. This is detailed in the paper by Kanerva.

In contrast to the well established asymmetric addition of cyanide to aldehydes, the corresponding addition to imines is considerably less developed. This is despite the fact that asymmetric α-amino nitrile synthesis can be achieved using internal stereocontrol through a chiral auxiliary attached to the nitrogen atom, whereas for asymmetric cyanohydrin synthesis, only external stereocontrol is available.

The first diastereoselective addition of cyanide to an imine bearing a chiral auxiliary (1-phenylethyl) on the nitrogen atom was reported in 1970. In the subsequent 30 years, a wide range of chiral auxiliaries have been investigated for this reaction, but the two most commonly used chiral amines remain 1-phenylethylamine and phenylglycinol. In this symposium, the use of both of these auxiliaries in the asymmetric synthesis of glutamic acid derivatives is described. The paper by Frahm illustrates the use of 1-phenylethylamine, whilst that of Ma discusses the application of phenylglycinol. Hattori et al. demonstrate in their paper that a diastereomeric mixture of amino nitriles bearing a 1-aminoindan-2-ol chiral auxiliary can undergo thermal epimerisation in the solid state leading to stereochemically pure products.

The first report of a catalytic, asymmetric synthesis of α-amino nitriles did not appear until 1996, and interestingly, as for cyanohydrin synthesis, this was a purely organic catalyst based on a cyclic dipeptide. A number of other purely organic catalysts for the asymmetric addition of hydrogen cyanide or trimethylsilyl cyanide to imines have subsequently been reported. Two years later, the first transition metal complex (an aluminium(salen) derivative) capable of catalysing the asymmetric addition of hydrogen cyanide to imines was described. This sparked a number of subsequent reports of the use of various chiral ligands and metals as catalysts for asymmetric Strecker reactions. In this symposium, the paper by Vilaivan describes the synthesis of α-amino nitriles with up to $>98\%$ enantiomeric excess by use of a titanium-*N*-salicyl-β-aminoalcohol complex as the catalyst.

The papers in this symposium which come from some of the leading groups in the field should illustrate to the reader the state of the art in what can currently be achieved in the synthesis of non-racemic cyanohydrins and α-aminonitriles. However, they also show the utility of these compounds in asymmetric synthesis, and perhaps show where there are still limitations to current methodology which could be solved by future developments.

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Conversion of chiral unsaturated cyanohydrins into chiral carba- and heterocycles via ring-closing metathesis

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Abstract—Aliphatic unsaturated cyanohydrins **1–3** served as starting materials in the synthesis of a set of new chiral unsaturated cyclic 1,2-ethanolamines. Combining a Grignard addition–$NaBH_4$ reduction sequence with a ring-closing metathesis afforded unsaturated cyclic 1,2-ethanolamines **7–11** and **22–25** in good yields and high ee (96–99%). The conversion of cyanohydrins **1–3** via a DIBAL reduction–transimination–$NaBH_4$ reduction sequence, using allylamine, followed by ring-closing metathesis yielded tetrahydropyridines **28**, tetrahydroazepinols **33** and tetrahydroazocinols **34** in high yields and excellent ee (97–99%).

1. Introduction

Chiral non-racemic cyanohydrins have proven to be expedient starting materials for the synthesis of several classes of compounds.[1–6] Over the past twenty years our research has focussed on the synthesis and application of chiral cyanohydrins with high enantiomeric purity, employing the enzyme hydroxynitrile lyase (*Pa*HNL, E.C. 4.1.2.10) from almonds. In previous communications we reported on the synthesis of several aliphatic unsaturated cyanohydrins.[7–9] Three particular examples are depicted in Figure 1.

It was envisioned that cyanohydrins **1–3**, after conversion to bis-olefinic compounds, would be excellent starting materials for the ring-closing metathesis (RCM) mediated synthesis of a unique set of chiral unsaturated carba- and heterocyclic compounds.[10] Conversion of cyanohydrin **1** via a one-pot Grignard addition–$NaBH_4$ reduction[11] sequence, using an olefinic Grignard reagent, followed by subsequent *N*-protection and RCM, would provide an efficient methodology for the synthesis of chiral unsaturated cyclic 1,2-ethanolamines (Scheme 1, path a).

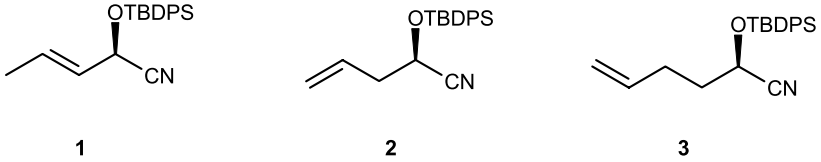
In a similar fashion, a DIBAL reduction–transimination–$NaBH_4$ reduction[12] sequence, using allylamine, would lead to a bis-olefinic secondary amine after *N*-protection, an obvious precursor for a RCM using the now readily available Grubbs' catalyst.[13,14] In this way, 3-hydroxy-tetrahydropyridines could be obtained (Scheme 1, path b).

Applying the same chemistry to cyanohydrins **2** and **3** should lead to a set of compounds depicted in Figure 2. This report presents our results in the exploration of these routes.

2. Results and discussion

2.1. Cyclic unsaturated 1,2-ethanolamines

Our attention was first focussed on the conversion of



1 2 3

Figure 1. Unsaturated *O*-protected cyanohydrins **1–3**: starting materials for the synthesis of chiral carba- and heterocyclic compounds.

Keywords: Cyanohydrins; Ring-closing metathesis; Cyclic ethanolamines; Heterocycles.
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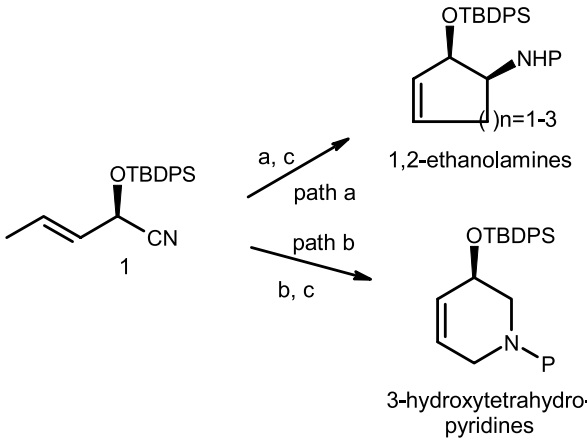


Scheme 1. General pathways for the conversion of cyanohydrin **1** into cyclic derivatives. (a) Grignard addition–$NaBH_4$ reduction. (b) DIBAL reduction–transimination–$NaBH_4$ reduction; (c) Grubbs catalyst.

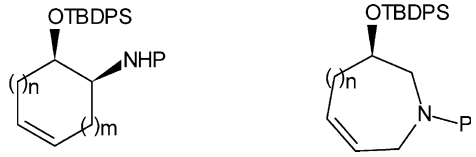
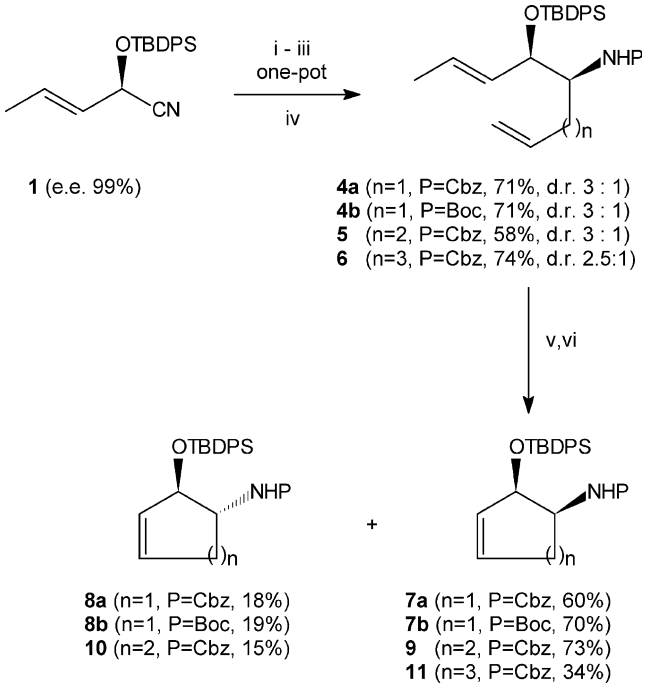
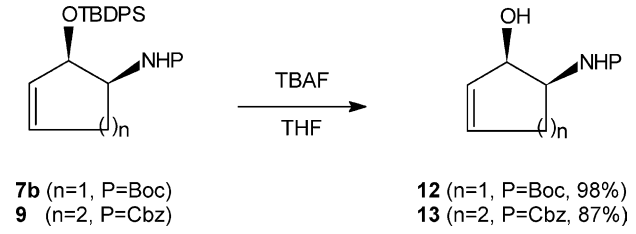


Figure 2. Set of compounds (n, $m=1$, 2) obtainable from *O*-protected cyanohydrins **2** and **3**.

protected cyanohydrin **1** into cyclic 1,2-ethanolamines. Starting from cyanohydrin **1**, addition of 1.5 equiv of the appropriate Grignard reagent led, after quenching with methanol, to the formation of a primary imine. Subsequent in situ $NaBH_4$ reduction, followed by *N*-protection, afforded



Scheme 2. Conversion of cyanohydrin **1** into *O*,*N*-protected unsaturated cyclic 1,2-ethanolamines. For compounds **4**–**6** the major diastereoisomer is depicted. Reagents: (i) $H_2C{=}CH(CH_2)_mMgBr$; (ii) MeOH; (iii) $NaBH_4$; (iv) Cbz-Cl or Boc_2O; (v) Grubbs catalyst; (vi) silicagel column separation.

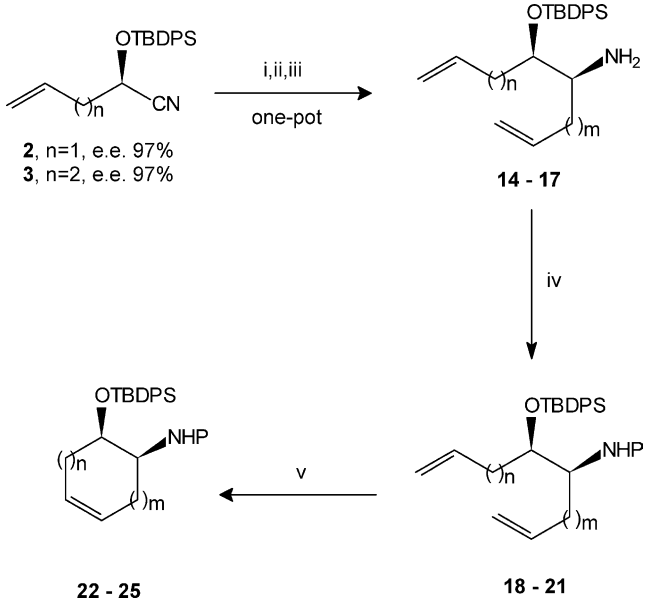


Scheme 3. *O*-deprotection of compounds **7b** and **9** to obtain the previously described compounds **12** and **13**.

bis-olefinic compounds **4**–**6** in yields of 72–85%. During the reduction a mixture of two diastereoisomers was formed with the depicted erythro isomers **4**–**6** as the predominant products (Scheme 2). It was not possible to separate the diastereoisomers at this stage.

RCM reactions were performed in refluxing dichloromethane using 4 mol% of Grubbs catalyst.[14] For the 5- and 6-membered rings the RCM proceeded with good yields (78–89%). The diastereoisomers were readily separated by silicagel column chromatography, affording pure ethanolamines **7**–**10**. In the case of the 7-membered ring **11**, dimerization at the terminal double bond was the prominent reaction. Ethanolamine **11** was obtained in 34% yield as a mixture of two unseparable diastereoisomers. To be able to determine the enantiomeric excess (ee) of these compounds, the racemic forms were also synthesized. Chiral HPLC of compounds **7**–**10** showed that all these cyclic ethanolamines were obtained with excellent enantiomeric purity (ee 96–98%).

Additional proof of the stereochemistry of these ethanolamines was obtained by *O*-deprotection of compounds **7b** and **9** resulting in the formation of the known compounds **12**[15] and **13**[16] (Scheme 3). For both compounds spectral and physical data were in agreement with the literature.



Scheme 4. Conversion of cyanohydrins **2** and **3** into *O*,*N*-protected cyclic 1,2-ethanolamines. For compounds **14**–**25** the major diastereoisomer is depicted. Reagents: (i) $H_2C{=}CH(CH_2)_mMgBr$; (ii) MeOH; (iii) $NaBH_4$; (iv) Cbz-Cl or Boc_2O; (v) Grubbs catalyst (4 mol%).

Extension of our strategy to cyanohydrins **2** and **3** afforded *O*,*N*-protected ethanolamines **14**–**17** (Scheme 4). The Grignard addition–$NaBH_4$ reduction sequence generally afforded diastereomeric mixtures (dr $\pm$2.5:1), with the depicted compounds as the major diastereoisomers. Subsequent *N*-protection of the crude amines **14**–**17**, followed by RCM afforded new cyclic 1,2-ethanolamines **22**–**25** in good overall yields (Table 1). Attempts to separate the obtained diastereomeric mixtures remained without success.

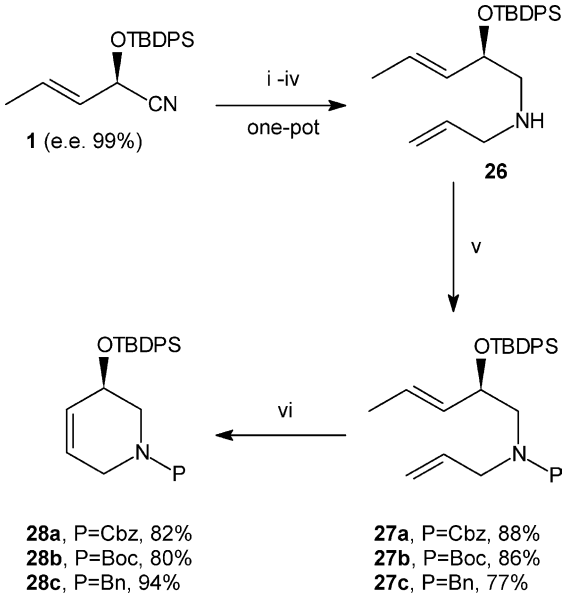
Table 1. Results for the conversion of cyanohydrins **2** and **3** into *O*,*N*-protected cyclic 1,2-ethanolamines **22**–**25**

Comp.	*n*	*m*	P	Yield (%)
18a	1	1	Cbz	69
18b	1	1	Boc	89
19a	1	2	Cbz	79
19b	1	2	Boc	81
20a	2	1	Cbz	68
20b	2	1	Boc	56
21	2	2	Cbz	68
22a	1	1	Cbz	87
22b	1	1	Boc	77
23a	1	2	Cbz	96
23b	1	2	Boc	66
24a	2	1	Cbz	94
24b	2	1	Boc	86
25	2	2	Cbz	66[a]

[a] Yield based on 55% converted starting material.

2.2. Unsaturated *N*-heterocycles

Next, our efforts were directed towards the synthesis of *O*,*N*-protected (*R*)-3-hydroxy-2*H*−1,2,3,6-tetrahydro-pyridines **28a**–**c** (Scheme 5).

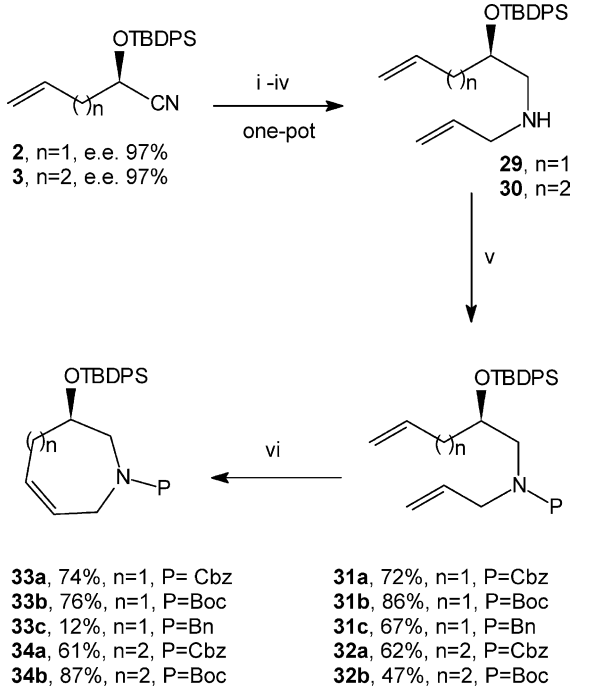


Scheme 5. Synthesis of (*R*)-*N*-protected 3-[(*t*-butyldiphen-ylsilyl)oxy]-2*H*-1,2,3,6-tetrahydropyridines. Reagents: (i) DIBAL; (ii) MeOH; (iii) Allylamine; (iv) $NaBH_4$; (v) Cbz-Cl or Boc_2O or BnBr; (vi) Grubbs catalyst (4 mol%).

Employing the previously described[12] DIBAL reduction–transimination–$NaBH_4$ reduction sequence to cyanohydrin **1**, using allylamine in the transimination step, afforded the secondary amine **26** in quantitative yield. Crude **26** was protected with a Cbz-, Boc- or Bn-group to give *N*-protected dienes **27a**–**c** in good yields (77–88%). Tetrahydropyridines **28a**–**c** were obtained in 80–94% (69–72% overall based on 1) yields via a ring- closing metathesis reaction with Grubbs' catalyst in refluxing dichloromethane.[13,14]

The smooth transformation of **27c** into **28c** is remarkable, as the Grubbs catalyst is generally ineffective for the conversion of tertiary amines.[13] The ee of **28c** was determined by chiral HPLC and found to be 99%. *O*-TBDPS-protected tetrahydropyridine **28a** was deprotected to afford benzyl (*R*)-3-hydroxy-3,6-dihydropyridine-1(2*H*)-carboxylate, an earlier described compound.[17] The spectroscopic and physical data were in complete agreement. It should be noted that the authors assigned the configuration of this compound incorrectly as *S*.[17] The ee (98%) was determined by chiral HPLC. Recently the *O*-MOM-protected analog of **28b** served as the starting compound in a synthesis of 5-des-(hydroxymethyl)-1-deoxynojir-mycin, reportedly a potent glycosidase inhibitor.[18]

Application of the same chemistry to cyanohydrins **2** and **3** led to the synthesis of the new *O*,*N*-protected tetrahydro-azepinols **33a**–**c** and azocinols **34a**,**b** (Scheme 6). In general, the yields were slightly lower than in the synthesis of the tetrahydropyridines. Carbamate protected 7- and 8-membered heterocycles **33a**,**b** and **34a**,**b** were obtained in 53–65% and 38–41% overall yields respectively. RCM with the tertiary amine **31c** failed completely. Using the HCl salt of **31c** in a RCM afforded azepinol **33c** in 12% yield.



Scheme 6. Transformation of cyanohydrins **2** and **3** into *O*,*N*-protected tetrahydroazepinols (**33a**–**c**) and tetrahydro-azocinols (**34a**,**b**). Reagents: (i) DIBAL; (ii) MeOH; (iii) allylamine; (iv) $NaBH_4$; (v) Cbz-Cl or Boc_2O or BnBr; (vi) Grubbs catalyst (4 mol%).

3. Conclusion

Cyanohydrins **1**–**3** were found to be excellent starting materials for the enantioselective synthesis of a number of new chiral *N*-heterocycles and cyclic 1,2-ethanolamines. The combination of either a DIBAL reduction–transimination–$NaBH_4$ reduction or a Grignard addition–$NaBH_4$ reduction sequence with ring-closing metathesis employing the Grubbs' catalyst, proved to be a powerful methodology for the preparation of these compounds in only three steps and high yields.

4. Experimental

4.1. General procedures and remarks

Reactions were carried out in an inert nitrogen or argon atmosphere. For reactions involving DIBAL or Grignard reagents flame dried equipment was used. All compounds were synthesized in both racemic and non-racemic form. ees were determined by comparing racemic with non-racemic compounds on chiral HPLC employing a Daicel CHIRALCEL OD or ODH column, using hexane (HEX) 2-propanol (IPA) mixtures as the eluent, and UV detection at 254 nm. Eluents are specified in each case. TLC-analyses were performed on Merck plastic silica gel 60 F_{254} plates. Detection by UV (254 nm); ammonium molybdate (50 g L^{-1}) and cerium(IV) sulfate (1 g L^{-1}) in aqueous 10% H_2SO_4, followed by heating to 150 °C; or 5% (w/v) aqueous $KMnO_4$. Column chromatography was performed on Fluka silica gel (0.063–0.200 mm). Solvents for chromatography were distilled before use (PE = petroleum ether 40–60; DEE = diethyl ether; EtOAc = ethyl acetate). Other solvents were of p.a. quality and stored over molecular sieves (3 Å). Commercial chemicals were used as received. ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Bruker AC-200 instrument. Samples were measured in $CDCl_3$, using TMS as an internal standard for ^1H NMR, and $CDCl_3$ as internal standard for ^{13}C NMR. Optical rotations were measured on a Propol automatic polarimeter (Sodium D line, $\lambda = 589$ nm). ESI-MS was performed on a Perkin Elmer SCIEX API 165 instrument. ESI-HRMS was performed on a Finnigan LTQ FTMS instrument.

General procedure for the one-pot Grignard addition–$NaBH_4$ reduction reactions. Under an argon atmosphere the appropriate *O*-TBDPS-protected cyanohydrin (3.0 mmol) was dissolved in dry DEE (30 mL). At room temperature a solution of Grignard reagent (4.5 mmol) was added dropwise. The reaction was stirred at room temperature for 1 h, cooled to −20 °C and quenched with dry MeOH (5.0 mL). After a few minutes the mixture was cooled to −80 °C and $NaBH_4$ (0.29 g, 7.5 mmol) added. The mixture was slowly warmed to room temperature at which it was stirred for 2 h. Then the reaction was poured into water (50 mL) and extracted with DEE (3×30 mL). The combined DEE layers were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo to afford the crude amines as colorless oils in quantitative yield.

General procedure for the one-pot DIBAL reduction–transimination–$NaBH_4$ reductions. Under an argon atmosphere the appropriate *O*-TBDPS-protected cyanohydrin (3.0 mmol) was dissolved in dry DEE (30 mL). At −78 °C DIBAL (4.5 mL, 4.5 mmol, 1.0 M in hexanes) was added. The reaction was allowed to warm up slowly to 0 °C. After recooling to −90 °C anhydrous methanol (5.0 mL) was added at once followed after 5 min, by allyl amine (1.20 mL, 16 mmol). The cooling bath was removed and the reaction was stirred for 2 h at room temperature. The resulting suspension was cooled to −20 °C and $NaBH_4$ (0.28 g, 7.4 mmol) was added in three portions. After stirring for 2 h at room temperature the suspension was poured into an aqueous 0.4 M NaOH (40 mL) solution. The layers were separated and the water layer was extracted with DEE (2×20 mL). After washing the combined organic layers with brine (20 mL), drying ($MgSO_4$), filtration and evaporation of the solvent in vacuo the crude amines were obtained as colorless oils in quantitative yield.

General procedure for carbobenzyloxy (Cbz) protections. The crude amine (1.0 mmol) was dissolved in an ice cold mixture of CH_2Cl_2 (5.0 mL) and saturated aqueous $NaHCO_3$ solution (10 mL). Benzyl chloroformate (0.30 mL, 2.0 mmol) was added dropwise and the reaction stirred vigorously overnight while warming to room temperature. The layers were separated and the water layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo to afford the crude *N*-Cbz-protected product.

General procedure for butyloxycarbonyl (Boc) protections. The crude amine (1.0 mmol) was dissolved in CH_2Cl_2 (5.0 mL). Triethylamine (TEA, 0.16 mL, 1.1 mmol) and di-*t*-butyl dicarbonate (654 mg, 3.0 mmol) were added. After stirring overnight at room temperature the solvent was evaporated at reduced pressure to obtain the crude *N*-Boc-protected product.

General procedure for benzyl (Bn) protections. The amine (1.0 mmol) was dissolved in CH_2Cl_2 (4.0 mL) and $Na_2CO_3 \cdot 10H_2O$ (0.60 g, 2.1 mmol), water (2.0 mL) and benzyl bromide (0.16 mL, 1.3 mmol) were added. The reaction was stirred vigorously overnight. After separation of the layers the water layer was extracted with CH_2Cl_2 (2×2 mL). All organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to afford the crude benzylated product.

General procedure for ring closing metathesis reactions. The appropriate diene was dissolved in CH_2Cl_2 (1 mmol/10 mL) and argon was bubbled through the solution for 3 min. Grubbs' catalyst (4 mol%) was added and the mixture refluxed (maximum 24 h). Progress of reaction was monitored by TLC with the new cyclic products running slightly lower. Upon completion, the solvent was evaporated to obtain the crude product.

For 8-membered rings the RCM reactions were performed at 0.005 M concentration of diene in toluene at 60 °C.

4.1.1. (2*R*,3*E*)-2-[(*t*-Butyldiphenylsilyl)oxy]pent-3-ene nitrile (1). Prepared as described earlier,[7] $[\alpha]_D^{20} = -4.2$ ($c = 1$, $CHCl_3$). ee 99%, Chiralcel OD, HEX/IPA = 99.75:0.25, 1.0 mL/min, RT 7.3 min (*R*-enantiomer), RT

11.0 min (*S*-enantiomer). ^{1}H NMR ($CDCl_3$): δ 1.09 (s, 9H, *t*-Bu); 1.68 (d, 3H, J=5.9 Hz, CH_3); 4.75 (d, 1H, J=5.8 Hz, CHO); 5.50 (m, 1H, =CH); 5.72 (m, 1H, =CH); 7.35 (m, 6H, SiPh); 7.66 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 17.3, 19.1, 26.5, 63.3, 118.4, 125.8, 127.7, 127.8, 130.1, 130.2, 131.3, 131.5, 131.9, 135.6.

4.1.2. (2*R*)-2-[(*t*-Butyldiphenylsilyl)oxy]pent-4-ene nitrile (2). Prepared as described earlier,[8] $[\alpha]_D^{25}=+30.3$ (c=1.2, CH_2Cl_2). ee 97%, Chiralcel ODH, HEX/IPA=99.75:0.25, 1.0 mL/min, RT 5.9 min (*R*-enantiomer), RT 8.6 min (*S*-enantiomer). ^{1}H NMR ($CDCl_3$): δ 1.10 (s, 9H, *t*-Bu); 2.35–2.61 (m, 2H, CH_2); 4.35 (dd, 1H, J=5.5, 7.0 Hz, CHO); 5.16 (m, 2H, =CH_2); 5.77 (m, 1H, =CH); 7.42 (m, 6H, SiPh); 7.64 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 18.6, 26.4, 40.1, 62.4, 118.6, 119.9, 127.7, 130.1, 130.3, 131.2, 131.6, 135.4, 135.5.

4.1.3. (2*R*)-2-[(*t*-Butyldiphenylsilyl)oxy]hex-5-ene nitrile (3). Prepared as described earlier,[9] $[\alpha]_D^{20}=+29.0$ (c=1, $CHCl_3$). ee 97%, Chiralcel ODH, HEX/IPA=99.75:0.25, 1.0 mL/min, RT 5.4 min (*R*-enantiomer), RT 7.3 min (*S*-enantiomer). ^{1}H NMR ($CDCl_3$): δ 1.10 (s, 9H, *t*-Bu); 1.84 (m, 2H, CH_2); 2.21 (m, 2H, CH_2); 4.35 (t, 1H, J=6.2 Hz, CHO); 4.97 (m, 2H, =CH_2); 5.63 (m, 1H, =CH); 7.42 (m, 6H, Ph); 7.68 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$): δ 19.1, 26.5, 28.2, 35.0, 62.2, 115.9, 119.7, 127.5, 127.8, 129.3, 129.9, 130.2, 131.6, 134.7, 135.1, 135.5.

4.2. Preparation of cyclic unsaturated 1,2-ethanolamines

4.2.1. (5*R*,6*E*)-5-(*t*-Butyldiphenylsilyl)oxyocta-1,6-diene-4-amine. Prepared from cyanohydrin **1** and allylmagnesium bromide as a mixture of two diastereoisomers in a 3:1=(4*S*,5*R*)–(4*R*,5*R*) ratio as determined by ^{1}H NMR. ESI-MS m/z 380.0 $[M+H]^+$. ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 1.44 (d, 3H, J=6.2 Hz, CH_3, minor isomer); 1.52 (d, 3H, J=5.2 Hz, CH_3 major isomer); 1.93–2.17 (m, 2H, CH_2); 2.73–2.84 (m, 1H, CHN); 3.54–3.68 (m, 2H, NH_2); 3.96 (m, 1H, CHO); 4.94–5.74 (m, 5H, CH=CH+CH=CH_2); 7.37 (m, 6H, Ph); 7.67 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$): δ 17.4, 19.0, 26.8, 37.1, 55.3, 77.3, 116.7, 127.0, 127.2, 127.4, 128.7, 128.9, 129.2, 129.3, 129.8, 130.3, 133.7, 133.9, 134.7, 135.2, 135.5, 135.7, 136.2. Observed for minor isomer: 18.7, 26.5, 55.7, 78.4, 117.8.

4.2.2. (6*R*,7*E*)-6-(*t*-Butyldiphenylsilyl)oxynona-1,7-diene-5-amine. Prepared from cyanohydrin **1** and but-3-en-1-ylmagnesium bromide as a mixture of two diastereoisomers in a 3:1=(5*S*,6*R*)–(5*R*,6*R*) ratio as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 1.19–1.69 (m, 5H, CH_3 and CH_2); 1.87–2.21 (m, 2H, CH_2); 2.66–2.75 (m, 1H, CHN); 3.97 (dd, 1H, J=4.4, 7.3 Hz CHO); 4.86–5.10 (m, 3H, CH=CH_2); 5.36 (m, 1H, =CH); 5.62–5.83 (m, 1H, =CH); 7.38 (m, 6H, Ph); 7.66 (m, 4H, Ph). Observed for minor isomer: 3.86 (dd, 1H, J=5.2, 7.3 Hz, CHO). ^{13}C NMR ($CDCl_3$): δ 17.6, 19.3, 27.1, 30.3, 32.1, 55.6, 77.7, 114.4, 127.3, 127.5, 127.6, 128.8, 129.4, 129.5, 129.6, 134.0, 135.4, 135.7, 135.9, 138.2. Observed for minor isomer: 26.7, 30.0, 55.9, 79.1, 115.5.

4.2.3. (7*R*,8*E*)-7-(*t*-Butyldiphenylsilyl)oxydeca-1,8-diene-6-amine. Prepared from cyanohydrin **1** and pent-4-en-1-ylmagnesium bromide as a mixture of two diastereoisomers in a 3:1=(6*S*,7*R*)–(6*R*,7*R*) ratio as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 1.16–1.66 (m, 7H, CH_3 and CH_2); 1.80–2.05 (m, 2H, CH_2); 2.54–2.72 (m, 1H, CHN); 3.96 (dd, 1H, J=5.1, 10.2 Hz, CHO); 4.92 (m, 2H, =CH_2); 5.15–5.41 (m, 2H, CH=CH); 5.62–5.79 (m, 1H, =CH); 7.39 (m, 6H, Ph); 7.66 (m, 4H, Ph). Observed for minor isomer: 3.86 (dd, 1H, J=5.1, 8.0 Hz). ^{13}C NMR ($CDCl_3$): δ 17.6, 19.2, 25.3, 27.0, 32.3, 33.6, 55.9, 77.7, 114.4, 127.3, 127.5, 127.8, 128.5, 128.7, 128.8, 129.4, 129.6, 131.0, 134.0, 134.9, 135.1, 135.7, 135.9, 138.4, 138.5. Observed for minor isomer: 17.4, 25.7, 32.4, 33.8, 56.4, 79.2.

4.2.4. Benzyl [(2*R*,3*E*)-1-allyl-2-(*t*-butyldiphenylsilyl)-oxy-pent-3-en-1-yl]carbamate (4a). Obtained as a mixture of two diastereoisomers in a 3:1=(1*S*,2*R*)–(1*R*,2*R*) ratio as determined by ^{1}H NMR. Yield 71% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). ESI-MS m/z 514.3 $[M+H]^+$; 536.2 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ 1.05 (s, 9H, *t*-Bu); 1.42 (d, 3H, J=7.7 Hz, CH_3, minor isomer); 1.48 (d, 3H, J=4.6 Hz, CH_3 major isomer); 2.02–2.44 (m, 2H, CH_2); 2.64 (m, 1H, CHN); 4.18 (m, 1H, CHO); 4.63 (m, 1H, NH); 4.90–5.08 (m, 5H, CH=CH_2, CH_2Ph); 5.35 (m, 1H, =CH); 5.61 (m, 1H, =CH); 7.30 (m, 11H, SiPh, Ph); 7.62 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 17.5, 19.3, 27.0, 34.4, 55.6, 66.3, 76.4, 117.2, 127.4, 127.5, 127.8, 128.3, 128.8, 129.0, 129.3, 129.4, 129.6, 133.6, 134.7, 135.5, 135.8, 135.9, 136.6, 155.9. Observed for minor isomer: 18.9, 26.5, 36.2, 66.5, 76.1, 118.5, 156.1.

4.2.5. *t*-Butyl [(2*R*,3*E*)-1-allyl-2-(*t*-butyldiphenylsilyl)-oxypent-3-en-1-yl]carbamate (4b). Obtained as a mixture of two diastereoisomers in a 3:1=(1*S*,2*R*)–(1*R*,2*R*) ratio as determined by ^{1}H NMR. Yield 71% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=97:3). ESI-MS m/z 480.1 $[M+H]^+$; 502.4 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 1.40 (s, 9H, *t*-Bu); 1.48 (d, 3H, J=4.4 Hz, CH_3); 2.24 (m, 2H, CH_2); 3.63 (m, 1H, CHN); 4.12 (m, 1H, CHO); 4.51 (m, 1H, NH); 5.00 (m, 2H, =CH_2); 5.32 (m, 2H, =CH); 5.59–5.76 (m, 1H, =CH); 7.40 (m, 6H, SiPh); 7.65 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 17.4, 19.2, 26.9, 28.2, 34.5, 54.9, 76.0, 78.5, 116.8, 127.2, 127.4, 128.4, 128.6, 129.3, 129.5, 129.7, 130.1, 133.5, 133.6, 133.8, 134.9, 135.7, 155.3. Observed for minor isomer: 36.2, 75.5, 155.4.

4.2.6. Benzyl [(2*R*,3*E*)-1-(but-3-enyl)-2-(*t*-butyl-diphenylsilyl)oxypent-3-en-1-yl]carbamate (5). Obtained as a mixture of two diastereoisomers in a 3:1=(1*S*,2*R*)–(1*R*,2*R*) ratio as determined by ^{1}H NMR. Yield 58% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). ^{1}H NMR ($CDCl_3$): δ 1.04 (s, 9H, *t*-Bu); 1.41–1.61 (m, 5H, CH_3 and CH_2); 1.81–2.25 (m, 2H, CH_2); 3.65 (m, 1H, CHN); 4.12 (m, 1H, CHO); 4.66 (d, 1H, J=9.5 Hz, NH); 4.90–5.10 (m, 5H, $PhCH_2$, CH=CH_2); 5.34 (m, 1H, =CH); 5.75–5.92 (m, 1H, =CH); 7.34 (m, 11H, Ph); 7.63 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$): δ 17.7, 19.4, 27.1, 29.5, 30.3, 56.0, 66.4, 76.6, 114.7, 127.4, 127.6, 127.9, 128.3, 128.4, 128.7, 129.6, 129.8, 133.9, 134.9, 135.9, 136.0, 138.0, 156.2.

4.2.7. Benzyl [(2*R*,3*E*)-1-(pent-4-enyl)-2-(*t*-butyl-diphenylsilyl)oxypent-3-en-1-yl]carbamate (6). Obtained as a mixture of two diastereoisomers in a 2.5:1=(1*S*,2*R*)–(1*R*,2*R*) ratio as determined by ^{1}H NMR. Yield 74% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). ^{1}H NMR ($CDCl_3$): δ 1.04 (s, 9H, *t*-Bu); 1.26–1.56 (m, 7H, CH_3 and CH_2); 1.96 (m, 2H, CH_2); 3.60 (m, 1H, CHN); 4.07–4.16 (m, 1H, CHO); 4.63 (d, 1H, J=9.5 Hz, NH); 4.79–5.18 (m, 4H, $PhCH_2$, =CH_2); 5.34 (m, 2H, CH=CH); 5.72 (m, 1H, =CH); 7.36 (m, 11H, Ph); 7.62 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$): δ 17.6, 19.4, 25.2, 27.1, 29.6, 33.5, 56.2, 66.3, 76.5, 114.7, 126.6, 127.4, 127.6, 127.9, 128.4, 128.6, 128.8, 129.3, 129.7, 130.4, 133.7, 133.9, 134.9, 135.9, 136.0, 136.9, 138.5, 156.3. Observed for minor isomer: 25.4, 26.7, 31.2, 66.5, 76.1.

4.2.8. Benzyl (1*S*,2*R*)-(2-[*t*-butyldiphenylsilyl]oxycyclopent-3-en-1-yl)carbamate (7a). Major isomer, obtained from diastereomeric mixture **4a**. Yield 60% (colorless oil, purified by silicagel column chromatography, first fraction, eluent PE/EtOAc=96:4). $[\alpha]_D^{25}=-19.6$ (c=0.53, CH_2Cl_2). ESI-MS m/z 472.2 $[M+H]^+$; 494.2 $[M+Na]^+$; 965.3 $[M_2+Na]^+$; 1437.0 $[M_3+Na]^+$; ee 96%, Chiralcel OD, HEX/IPA=99:1, 1.0 mL/min, RT 9.4 min (1*S*,2*R*-enantiomer), RT 10.4 min (1*R*,2*S*-enantiomer). ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 2.33 (m, 1H, CH_2); 2.62 (m, 1H, CH_2); 4.17 (m, 1H, CHN); 4.66 (m, 1H, CHO); 5.12 (s, 2H, CH_2Ph); 5.46 (m, 1H, =CH); 5.64 (d, 1H, J=10.1 Hz, NH); 5.82 (m, 1H, =CH); 7.39 (m, 11H, Ph, SiPh); 7.66 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.0, 26.8, 37.8, 52.4, 66.1, 75.7, 127.4, 127.5, 127.6, 128.2, 129.6, 131.7, 132.9, 133.0, 133.5, 135.4, 135.5, 136.6, 155.8. HRMS calculated for $[M+H]^+$ 472.23025, found: 472.23090.

4.2.9. *t*-Butyl (1*S*,2*R*)-(2-[*t*-butyldiphenylsilyl]oxycyclopent-3-en-1-yl)carbamate (7b). Major isomer, obtained from diastereomeric mixture **4b**. Yield 70% (colorless oil, purified by silicagel column chromatography, first fraction, eluent PE/EtOAc=95:5). $[\alpha]_D^{20}=-27.0$ (c=1.0, CH_2Cl_2). ESI-MS m/z 438.1 $[M+H]^+$; 460.0 $[M+Na]^+$; 875.5 $[M_2+H]^+$; 897.6 $[M_2+Na]^+$; ee 98%, Chiralcel ODH, HEX/IPA=99.75:0.25, 1.0 mL/min, RT 7.0 min (1*S*,2*R*-enantiomer), RT 8.8 min (1*R*,2*S*-enantiomer). ^{1}H NMR ($CDCl_3$): δ 1.08 (s, 9H, *t*-Bu); 1.46 (s, 9H, *t*-Bu); 2.30 (m, 1H, CH_2); 2.60 (dd, 1H, J=7.3, 16.8 Hz, CH_2); 4.11 (m, 1H, CHN); 4.65 (d, 1H, J=6.6 Hz, CHO); 5.40 (m, 2H, =CH, NH); 5.82 (m, 1H, =CH); 7.41 (m, 6H, SiPh); 7.67 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.2, 26.9, 28.3, 38.1, 51.9, 75.8, 78.8, 127.5, 127.7, 129.7, 131.6, 131.9, 132.5, 133.1, 133.4, 133.9, 135.7, 155.6. HRMS calculated for $[M+H]^+$ 438.24590, found: 438.24622.

4.2.10. Benzyl (1*R*,2*R*)-(2-[*t*-butyldiphenylsilyl]-oxycyclo-pent-3-en-1-yl)carbamate (8a). Minor isomer, obtained from diastereomeric mixture **4a**. Yield 18% (colorless solid, purified by silicagel column chromatography, second fraction, eluent PE/EtOAc=96:4). $[\alpha]_D^{25}=-16.5$ (c=0.51, CH_2Cl_2). ESI-MS m/z 494.2 $[M+Na]^+$; 965.2 $[M_2+Na]^+$; 1436.5 $[M_3+Na]^+$; ee 98%, Chiralcel OD, HEX/IPA=97:3, 1.0 mL/min, RT 8.0 min (1*R*,2*R*-enantiomer), RT 17.6 min (1*S*,2*S*-enantiomer). ^{1}H NMR ($CDCl_3$): δ 1.05 (s, 9H, *t*-Bu); 2.04 (m, 1H, CH_2); 2.88 (m, 1H, CH_2); 4.17 (m, 1H, CHN); 4.52 (m, 1H, NH); 4.61 (m, 1H, CHO); 5.02 (d, 1H, J=12.5 Hz, CH_2Ph); 5.08 (d, 1H, J=12.5 Hz, CH_2Ph); 5.54 (m, 1H, =CH); 5.78 (m, 1H, =CH); 7.38 (m, 11H, Ph, SiPh); 7.64 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.0, 26.8, 37.9, 60.1, 66.4, 83.2, 127.5, 127.9, 128.3, 129.6, 131.5, 132.5, 133.5, 133.9, 135.7, 136.5, 155.7. HRMS calculated for $[M+H]^+$ 472.23025, found: 472.23062.

4.2.11. *t*-Butyl (1*R*,2*R*)-(2-[*t*-butyldiphenylsilyl]-oxycyclo-pent-3-en-1-yl)carbamate (8b). Minor isomer, obtained from diastereomeric mixture **4b**. Yield 19% (colorless oil, purified by silicagel column chromatography, second fraction, eluent PE/EtOAc=95:5). $[\alpha]_D^{20}=-17.4$ (c=0.94, CH_2Cl_2). ESI-MS m/z 460.1 $[M+Na]^+$; HPLC Chiralcel ODH, HEX/IPA=99.75:0.25, 1.0 mL/min, RT 8.7 min (1*S*,2*S*-enantiomer), RT 9.3 min (1*R*,2*R*-enantiomer), no base line separation. ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 1.42 (s, 9H, *t*-Bu); 2.03 (m, 1H, CH_2); 2.84 (dd, 1H, J=6.6, 16.8 Hz, CH_2); 4.11 (m, 1H, CHN); 4.28 (m, 1H, NH); 4.59 (m, 1H, CHO); 5.50 (m, 1H, =CH); 5.75 (m, 1H, =CH); 7.41 (m, 6H, SiPh); 7.68 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.0, 26.9, 28.4, 38.3, 59.8, 79.0, 83.4, 127.6, 129.6, 131.7, 131.9, 132.5, 133.4, 133.6, 134.1, 135.7, 135.9, 155.3. HRMS calculated for $[M+H]^+$ 438.24590, found: 438.24640.

4.2.12. Benzyl (1*S*,2*R*)-(2-[-*t*-butyldiphenylsilyl]-oxycyclo-hex-3-en-1-yl)carbamate (9). Major isomer, obtained from diastereomeric mixture **5**. Yield 73% (colorless oil, purified by silicagel column chromatography, first fraction, eluent PE/EtOAc=95:5). $[\alpha]_D^{25}=-71.4$ (c=1.0, CH_2Cl_2). ee 97%, Chiralcel OD, HEX/IPA=99:1, 1.0 mL/min, RT 7.7 min (1*R*,2*S*-enantiomer), RT 10.3 min (1*S*,2*R*-enantiomer). ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 1.85–2.35 (m, 4H, CH_2); 3.73 (m, 1H, CHN); 4.21 (m, 1H, CHO); 5.06 (d, 1H, J=12.4 Hz, CH_2Ph); 5.13 (d, 1H, J=12.4 Hz, CH_2Ph); 5.32 (m, 2H, =CH and NH); 5.66 (m, 1H, =CH); 7.15–7.45 (m, 11H, Ph, SiPh); 7.69 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.4, 24.1 (C5 and C6), 27.1, 50.8, 66.4, 67.1, 127.6, 127.8, 127.9, 128.5, 129.3, 129.8, 129.9, 130.3, 133.4, 133.9, 134.9, 135.8, 135.9, 136.9, 155.9. HRMS calculated for $[M+H]^+$ 486.24590, found: 486.24658.

4.2.13. Benzyl (1*R*,2*R*)-(2-[-*t*-butyldiphenylsilyl]-oxycyclo-hex-3-en-1-yl)carbamate (10). Minor isomer, obtained from diastereomeric mixture **5**. Yield 15% (colorless solid, purified by silicagel column chromatography, first fraction, eluent PE/EtOAc=95:5). $[\alpha]_D^{20}=-23.0$ (c=1.0, CH_2Cl_2). ee 97%, Chiralcel OD, HEX/IPA=99:1, 1.0 mL/min, RT 9.8 min (1*R*,2*R*-enantiomer), RT 14.8 min (1*S*,2*S*-enantiomer). ^{1}H NMR ($CDCl_3$): δ 1.04 (s, 9H, *t*-Bu); 2.10 (m, 4H, CH_2); 3.85 (m, 1H, CHN); 3.95 (broad s, 1H, NH); 4.39 (d, 1H, J=8.0 Hz, CHO); 4.96 (d, 1H, J=11.7 Hz, CH_2Ph); 5.07 (d, 1H, J=11.7 Hz, CH_2Ph); 5.47 (d, 1H, J=10.2 Hz, =CH); 5.68 (d, 1H, J=9.5 Hz, =CH); 7.31–7.45 (m, 11H, Ph, SiPh); 7.66 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.2, 23.1, 25.5, 26.8, 52.9, 66.4, 70.4, 126.6 127.5, 127.6, 127.9, 128.4, 129.2, 129.6, 133.4, 135.8, 135.9, 136.5, 155.6. HRMS calculated for $[M+H]^+$ 486.24590, found: 486.24649.

4.2.14. Benzyl (2*R*)-(2-[-*t*-butyldiphenylsilyl]-oxycyclo-hept-3-en-1-yl)carbamate (11). Obtained as a

diastereomeric mixture, (1*S*,2*R*)–(1*R*,2*R*)=2.5:1, from diastereomeric mixture **6** in 34% yield as a colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5. ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 1.25–1.62 (m, 2H, CH_2); 1.78–2.42 (m, 4H, CH_2); 3.60–3.95 (m, 1H, CHN); 4.44 (m, 1H, CHO); 4.84–5.11 (m, 2H, CH_2Ph); 5.38 (m, 1H, NH); 5.56 (m, 1H, =CH); 5.83 (m, 1H, =CH); 7.15–7.45 (m, 11H, Ph, SiPh); 7.69 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.2, 21.7, 26.9, 28.1, 32.3, 53.9, 66.4, 73.7, 125.9, 127.5, 127.6, 127.9, 128.4, 129.6, 129.7, 129.9, 133.4, 135.8, 136.0, 156.0. Observed for minor isomer: 27.0, 28.0, 52.8.

4.2.15. *t*-Butyl (1*S*,2*R*)-(2-hydroxycyclopent-3-en-1-yl)-carbamate (12). Compound **7b** (172 mg, 0.394 mmol) was dissolved in THF (6 mL) and excess TBAF (3 equiv) was added. After 2 h the reaction was completed as monitored by TLC. The solvent was evaporated and the residue purified by column chromatography. Yield 77 mg (98%). (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5→1:1). $[\alpha]_D^{20}=-41.4$ ($c=1.0$, CH_2Cl_2). Enantiomers could not be separated by chiral HPLC on Daicel Chiralcel ODH, OJ and Chiralpak AD columns. ^{1}H NMR ($CDCl_3$) lit[15b]: δ 1.46 (s, 9H, *t*-Bu); 2.01 (broad s, 1H, OH); 2.23 (m, 1H, CH_2); 2.70 (m, 1H, CH_2); 4.12 (m, 1H, CHN); 4.58 (broad d, 1H, CHO); 5.17 (broad s, 1H, NH); 5.88 (m, 1H, CH=CH); 6.00 (m, 1H, CH=CH). ^{13}C NMR ($CDCl_3$) lit[15b]: δ 28.3, 37.4, 52.2, 74.2, 79.3, 131.7, 134.5, 156.1.

4.2.16. Benzyl (1*S*,2*R*)-(2-hydroxycyclohex-3-en-1-yl)-carbamate (13). Silyl ether **9** (422 mg, 0.866 mmol) was dissolved in THF (8 mL) and excess TBAF (3 equiv) was added. TLC showed complete conversion after 1 h. The solvent was evaporated and the residue purified by silicagel column chromatography, eluent PE/EtOAc=95:5→3:1→2:3 to afford the title compound (188 mg, 87%) as a colorless oil. $[\alpha]_D^{20}=-100.6$ ($c=1.0$, CH_2Cl_2, [lit.[16], $[\alpha]_D^{20}=-55.6$ ($c=1.0$, CH_2Cl_2 for ee=58%]). ee 98%, Chiralcel ODH, HEX/IPA=90:10, 1.0 mL/min, RT 10.9 min (1*S*,2*R*-enantiomer), RT 19.0 min (1*R*,2*S*-enantiomer). ^{1}H NMR ($CDCl_3$) lit[16]: δ 1.62 (d, 1H, $J=5.1$ Hz, OH); 1.57–1.69 (m, 1H, CH_2); 1.73–1.84 (m, 1H, CH_2); 2.15 (m, 2H, CH_2); 3.79 (m, 1H, CHN); 4.14 (m, 1H, CHO); 5.11 (s, 2H, CH_2Ph); 5.31 (m, 1H, NH); 5.77–5.95 (m, 2H, CH=CH); 7.35 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) lit[16]: δ 23.1, 24.4, 50.4, 64.5, 66.4, 127.0, 127.8, 128.2, 129.1, 131.0, 136.2, 155.9.

4.2.17. (5*R*)-5-(*t*-Butyldiphenylsilyl)oxyocta-1,7-diene-4-amine (14). Obtained as a mixture of two diastereoisomers in a (4*S*,5*R*)–(4*S*,5*R*)=2.5:1 ratio as determined by ^{1}H NMR. ESI-MS *m*/*z* 380.0 $[M+H]^+$. ^{1}H NMR ($CDCl_3$): δ 1.07 (s, 9H, *t*-Bu); 1.91–2.41 (m, 4H, CH_2); 2.79 (m, 1H, CHN); 3.73 (m, 1H, CHO); 4.77–5.09 (m, 4H, =CH_2); 5.49–5.72 (m, 2H, =CH); 7.39 (m, 6H, SiPh); 7.70 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.0, 26.8, 36.6, 36.8, 54.0, 76.0, 116.4, 116.8, 127.1, 127.2, 127.6, 128.7, 129.0, 129.2, 129.3, 133.3, 133.5, 134.1, 134.6, 135.5. Observed for minor isomer: 18.6, 26.4, 37.2, 37.8, 52.8, 75.4, 115.7, 117.7.

4.2.18. (4*R*)-4-(*t*-Butyldiphenylsilyl)oxynona-1,8-diene-5-amine (15). Obtained as a mixture of two diastereoisomers in a (4*R*,5*S*)–(4*R*,5*R*)=2:1 ratio as determined by ^{1}H NMR. ESI-MS *m*/*z* 394.2 $[M+H]^+$, 787.6 $[M_2+H]^+$. ^{1}H NMR ($CDCl_3$): δ 1.07 (s, 9H, *t*-Bu); 1.16–1.61 (m, 2H, CH_2); 1.86–2.51 (m, 4H, CH_2); 2.60–2.76 (m, 1H, CHN); 3.61–3.74 (m, 1H, CHO); 4.82–4.99 (m, 4H, =CH_2); 5.44–5.82 (m, 2H, =CH); 7.40 (m, 6H, SiPh); 7.66 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 18.9, 26.7, 31.3, 33.3, 36.1, 54.2, 76.5, 114.1, 116.2, 127.0, 127.1, 129.1, 129.3, 129.9, 130.9, 132.8, 133.2, 133.6, 134.7, 134.9, 135.4. Observed for minor isomer: 18.6, 26.1, 35.1, 37.7, 52.6, 75.7, 113.9, 116.5.

4.2.19. (5*R*)-5-(*t*-Butyldiphenylsilyl)oxynona-1,8-diene-4-amine (16). Obtained as a mixture of two diastereoisomers in a (4*S*,5*R*)–(4*R*,5*R*)=2.4:1 ratio as determined by ^{1}H NMR. ESI-MS *m*/*z* 394.3 $[M+H]^+$. ^{1}H NMR ($CDCl_3$): δ 1.07 (s, 9H, *t*-Bu); 1.26–2.27 (m, 6H, CH_2); 2.79 (m, 1H, CHN); 3.66 (m, 1H, CHO); 4.77–4.96 (m, 2H, =CH_2); 5.02–5.18 (m, 2H, =CH_2); 5.47–5.70 (m, 2H, =CH); 7.41 (m, 6H, SiPh); 7.67 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.1, 26.8, 29.5, 30.6, 37.1, 54.3, 76.2, 114.1, 116.6, 127.2, 127.3, 128.8, 129.3, 129.4, 133.5, 133.8, 134.6, 135.6 135.8, 137.6, 137.9. Observed for minor isomer: 26.4, 29.4, 31.3, 38.7, 53.1, 75.6, 117.9.

4.2.20. (6*R*)-6-(*t*-Butyldiphenylsilyl)oxydeca-1,9-diene-5-amine (17). Obtained as a mixture of two diastereoisomers in a (5*S*,6*R*)–(5*R*,6*R*)=2:1 ratio as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$): δ 1.07 (s, 9H, *t*-Bu); 1.10–2.27 (m, 8H, CH_2); 2.61–2.79 (m, 1H, CHN); 3.42–3.66 (m, 1H, CHO); 4.77–4.99 (m, 4H, =CH_2); 5.42–5.83 (m, 2H, =CH); 7.40 (m, 6H, SiPh); 7.67 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 18.9, 26.6, 29.1, 30.1, 31.4, 33.0, 54.2, 76.4, 113.8, 114.1, 126.9, 127.0, 129.1, 133.1, 133.5, 133.8, 134.4, 135.3 137.3, 137.7, 137.9. Observed for minor isomer: 29.5, 30.4, 31.7, 52.6, 75.6, 113.5.

4.2.21. Benzyl [(2*R*)-1-allyl-2-(*t*-butyldiphenylsilyl)oxy-pent-4-en-1-yl]carbamate (18a). Obtained as a mixture of two diastereoisomers in a (1*S*,2*R*)–(1*R*,2*R*)=2.5:1 ratio as determined by ^{1}H NMR. Yield 69% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). ESI-MS *m*/*z* 514.3 $[M+H]^+$. ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 2.04–2.35 (m, 4H, CH_2); 3.70 (m, 1H, CHN); 3.90 (m, 1H, CHO); 4.71–5.09 (m, 6H, =CH_2, $PhCH_2$); 5.49–5.78 (m, 2H, =CH); 7.38 (m, 11H, SiPh, $PhCH_2$); 7.63 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.3, 27.0, 32.8, 38.8, 53.5, 66.2, 75.0, 117.1, 117.5. 127.5, 127.9, 128.3, 129.6, 129.7, 133.5, 134.6, 135.0, 135.8, 155.6. Observed for minor isomer: 37.5, 52.4, 66.5, 74.1, 118.1, 156.0.

4.2.22. *t*-Butyl [(2*R*)-(1-allyl-*t*-butyldiphenylsilyl)-oxy-pent-4-en-1-yl]carbamate (18b). Obtained as a mixture of two diastereoisomers in a (1*S*,2*R*)–(1*R*,2*R*)=2.5:1 ratio as determined by ^{1}H NMR. Yield 89% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). ESI-MS *m*/*z* 480.2 $[M+H]^+$. ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 1.37 (s, 9H, *t*-Bu); 1.95–2.45 (m, 4H, CH_2); 3.64 (m, 1H, CHN); 3.91 (m, 1H, CHO); 4.59 (br d, 1H, NH); 4.83–5.09 (m, 4H, =CH_2); 5.43–5.61 (m, 1H, =CH); 5.67–5.79 (m, 1H, =CH); 7.40 (m, 6H, SiPh);

7.65 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 18.5, 26.4, 26.9, 32.1, 38.1, 52.0, 74.3, 77.9, 115.7, 116.0. 126.7, 126.8, 128.9, 129.0, 131.5, 131.8, 132.6, 132.9, 134.0, 134.4, 135.0, 135.2, 154.3. Observed for minor isomer: 36.8, 51.0, 73.6, 115.4, 116.5, 154.8.

4.2.23. Benzyl [(2*R*)-(1-but-3-en-1-yl)-2-(*t*-butyl-diphenylsilyl)oxypent-4-en-1-yl]carbamate (19a). Obtained as a mixture of two diastereoisomers in a (1*S*,2*R*)–(1*R*,2*R*)=2:1 ratio as determined by ^{1}H NMR. Yield 79% (colorless oil, purified by silicagel column chromatography, eluent PE/DEE=95:5). ESI-MS *m*/*z* 528.3 $[M+H]^+$; 550.4 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 1.43–1.68 (m, 2H, CH_2); 1.92–2.22 (m, 4H, CH_2); 3.65 (m, 1H, CHN); 3.86 (m, 1H, CHO); 4.71–5.13 (m, 6H, $=CH_2$, CH_2Ph); 5.28–5.83 (m, 2H, =CH); 7.37 (m, 11H, SiPh, $PhCH_2$); 7.65 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.3, 26.9, 27.5, 30.0, 38.7, 53.6, 66.1, 75.4, 114.6, 117.4. 127.4, 127.6, 127.9, 128.2, 129.6, 129.7, 129.8, 133.5, 135.7, 136.6, 137.7, 137.9, 155.7. Observed for minor isomer: 32.4, 52.4, 66.4, 74.7, 114.4, 118.0, 156.1.

4.2.24. *t*-Butyl [(2*R*)-(1-but-3-en-1-yl)-2-(*t*-butyl-diphenyl-silyl)oxypent-4-en-1-yl]carbamate (19b). Obtained as a mixture of two diastereoisomers in a (1*S*,2*R*)–(1*R*,2*R*)=2:1 ratio as determined by ^{1}H NMR. Yield 81% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). ESI-MS *m*/*z* 494.3 $[M+H]^+$; 516.2 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ 1.07 (s, 9H, *t*-Bu); 1.39 (s, 9H, *t*-Bu); 1.30–1.60 (m, 2H, CH_2); 1.84–2.19 (m, 4H, CH_2); 3.45–3.65 (m, 1H, CHN); 3.86 (m, 1H, CHO); 4.57 (d, 1H, J=10.2 Hz, NH); 4.66–5.07 (m, 4H, $=CH_2$); 5.39–5.60 (m, 1H, =CH); 5.64–5.92 (m, 1H, =CH); 7.41 (m, 6H, SiPh); 7.65 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.3, 26.9, 28.2, 30.1, 32.5, 38.8, 52.8, 76.4, 78.4, 114.7, 117.2, 127.4, 127.5, 129.5, 129.8, 132.7, 133.3, 133.5, 133.7, 134.0, 135.6, 137.8, 138.0, 155.1. Observed for minor isomer: 27.1, 52.5, 75.5, 78.6, 114.5, 117.8, 155.5.

4.2.25. Benzyl [(2*R*)-(1-allyl-*t*-butyldiphenylsilyl)-oxyhex-5-en-1-yl]carbamate (20a). Obtained as a mixture of two diastereoisomers in a (1*S*,2*R*)–(1*R*,2*R*)=2.5:1 ratio as determined by ^{1}H NMR. Yield 68% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). ESI-MS *m*/*z* 528.3 $[M+H]^+$; 550.3 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 1.37–2.04 (m, 4H, CH_2); 2.18–2.45 (m, 2H, CH_2); 3.69–3.85 (m, 2H, CHN, CHO); 4.70–5.17 (m, 6H, $=CH_2$, CH_2Ph); 5.31–5.84 (m, 2H, =CH); 7.37 (m,11H, SiPh, CH_2Ph); 7.64 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.2, 26.8, 29.3, 32.9, 37.1, 53.6, 66.0, 75.1, 114.5, 117.0, 127.3, 127.5, 127.7, 128.0, 128.1, 128.9, 129.4, 129.5, 133.2, 133.4, 134.4, 134.6, 134.8, 135.6, 137.1, 137.2, 155.4. Observed for minor isomer: 18.8, 26.4, 33.1, 52.5, 66.3, 73.5, 118.0, 156.0.

4.2.26. *t*-Butyl [(2*R*)-(1-allyl-*t*-butyldiphenylsilyl)-oxyhex-5-en-1-yl]carbamate (20b). Obtained as a mixture of two diastereoisomers in a (1*S*,2*R*)–(1*R*,2*R*)=2.5:1 ratio as determined by ^{1}H NMR. Yield 56% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). ESI-MS *m*/*z* 494.4 $[M+H]^+$; 516.4 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ 1.10 (s, 9H, *t*-Bu); 1.41 (s, 9H, *t*-Bu); 1.30–1.59 (m, 2H, CH_2); 1.77–1.92 (m, 2H, CH_2); 2.33 (m, 2H, CH_2); 3.69 (m, 1H, CHN); 3.86 (m, 1H, CHO); 4.61–5.12 (m, 4H, $=CH_2$); 5.46–5.82 (m, 2H, =CH); 7.42 (m, 6H, SiPh); 7.68 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.4, 27.1, 28.3, 29.5, 33.1, 37.6, 53.2, 75.5, 78.6, 114.5, 116.8, 127.5, 127.6, 129.6, 129.7, 133.5, 133.9, 135.0, 135.3, 135.8, 137.7, 155.2. Observed for minor isomer: 27.3, 33.4, 52.0, 73.8, 78.8.

4.2.27. Benzyl [1-but-3-enyl-(2*R*)-(*t*-butyldiphenylsilyl)-oxyhex-5-en-1-yl]carbamate (21). Obtained as a mixture of two diastereoisomers in a (1*S*,2*R*)–(1*R*,2*R*)=2.5:1 ratio as determined by ^{1}H NMR. Yield 68% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). ESI-MS *m*/*z* 564.3 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ 1.05 (s, 9H, *t*-Bu); 1.25–2.05 (m, 5H, CH_2); 2.31 (m, 1H, CH_2); 3.76 (m, 1H, CHN); 3.90 (m, 1H, CHO); 4.70 (m, 2H, $=CH_2$); 4.83–5.18 (m, 4H, $=CH_2$, $PhCH_2$); 5.45–5.82 (m, 2H, =CH); 7.37 (m, 11H, SiPh, $PhCH_2$); 7.66 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.5, 27.1, 29.6, 30.2, 33.1, 33.4, 53.9, 66.3, 75.9, 114.6, 115.1, 127.5, 127.7, 127.9, 128.0, 128.4, 129.7, 129.8, 129.9, 133.5, 133.8, 135.9, 137.5, 138.0, 155.8. Observed for minor isomer: 18.8, 26.4, 32.4, 52.5, 66.6, 74.1, 156.3.

4.2.28. Benzyl (6*R*)-6-[(*t*-butyldiphenylsilyl)-oxycyclohex-3-en-1-yl]carbamate (22a). Obtained as a mixture of two diastereoisomers in a (1*S*,6*R*)–(1*R*,6*R*)=2.5:1 ratio as determined by HPLC. Yield 87% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). ESI-MS *m*/*z* 486.7 $[M+H]^+$. ee 96%, Chiralcel OD, HEX/IPA=99.5:0.5, 1.0 mL/min, major diastereoisomer RT 16.4 min (1*S*,6*R*-enantiomer), RT 25.6 min (1*R*,6*S*-enantiomer). Minor diastereoisomer RT 33.5 min (1*S*,6*S*-enantiomer), RT 35.3 min (1*S*,6*S*-enantiomer) no baseline separation. ^{1}H NMR ($CDCl_3$): δ 1.04 (s, 9H, *t*-Bu); 2.04–2.24 (m, 4H, CH_2); 3.84 (m, 1H, CHN); 4.08 (m, 1H, CHO); 4.79–5.02 (m, 2H, $PhCH_2$); 5.48 (m, 1H, =CH); 5.61 (m, 1H, =CH); 7.35 (m, 11H, SiPh, $PhCH_2$); 7.66 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.2, 26.8, 28.3, 32.3, 50.3, 66.2, 69.0, 123.4, 124.5, 127.4, 127.6, 127.8, 128.2, 129.1, 129.5, 129.6, 133.3, 134.0, 134.6, 135.6, 136.5, 155.7. Observed for minor isomer: 19.0, 26.4, 30.1, 51.2, 69.5, 124.2. HRMS calculated for $[M+H]^+$ 486.24649, found: 486.24590.

4.2.29. *t*-Butyl (6*R*)-6-[(*t*-butyldiphenylsilyl)-oxycyclohex-3-en-1-yl]carbamate (22b). Obtained as a mixture of two diastereoisomers in a (1*S*,6*R*)–(1*R*,6*R*)=2.5:1 ratio as determined by HPLC. Yield 77% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). ESI-MS *m*/*z* 474.4 $[M+H]^+$. ee 98%, Chiralcel OD, HEX/IPA=99.75:0.25, 1.0 mL/min, major diastereoisomer RT 10.4 min (1*S*,6*R*-enantiomer), RT 12.3 min (1*R*,6*S*-enantiomer). Minor diastereoisomer RT 8.3 min (1*S*,6*S*-enantiomer), RT 13.9 min (1*R*,6*R*-enantiomer). ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 1.43 (s, 9H, *t*-Bu); 1.94–2.24 (m, 4H, CH_2); 3.76 (m, 1H, CHN); 4.10 (m, 1H, CHO); 4.77 (br s, 1H, NH); 5.46 (m, 1H, =CH); 5.63 (m, 1H, =CH); 7.39 (m, 6H, SiPh); 7.67 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.4, 26.9, 28.3, 32.5 (C2 and C5), 49.7, 69.2, 78.9, 123.4, 124.8, 127.4, 127.6, 129.6, 129.7, 133.5, 133.6, 134.3, 135.6, 155.3. Observed for minor isomer:

27.3, 50.8, 69.5, 124.2. HRMS calculated for $[M+H]^+$ 452.26155, found: 452.26230.

4.2.30. Benzyl (2*R*)-[(*t*-butyldiphenylsilyl)oxycyclohept-4-en-1-yl]carbamate (23a). Obtained as a mixture of two diastereoisomers in a (1*S*,2*R*)–(1*R*,2*R*)=2.8:1 ratio as determined by HPLC. Yield 96% (colorless oil, purified by silicagel column chromatography, eluent PE/DEE=92:8). ESI-MS *m/z* 500.3 $[M+H]^+$; 522.6 $[M+Na]^+$. Chiral HPLC, ee 98%, Chiralcel OD, HEX/IPA=99.5:0.5, 1.0 mL/min, major diastereoisomer RT 16.8 min (1*R*,2*S*-enantiomer); RT 26.1 min (1*S*,2*R*-enantiomer). Minor diastereoisomer RT 15.4 min (1*R*,2*R*-enantiomer), RT 27.4 min (1*S*,2*S*-enantiomer). ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 1.51–1.88 (m, 2H, CH_2); 1.95–2.38 (m, 4H, CH_2); 3.71 (m, 1H, CHN); 4.02 (m, 1H, CHO); 4.52 (d, 1H, J=8.0 Hz, NH); 5.02 (s, 2H, $PhCH_2$); 5.39 (m, 1H, =CH); 5.68–5.91 (m, 1H, =CH); 7.36 (m, 11H, SiPh, $PhCH_2$); 7.66 (m, 4H, SiPh). Observed for minor isomer: 3.52 (m, CHN); 3.89 (m, CHO). ^{13}C NMR ($CDCl_3$): δ 19.1, 24.5, 26.9, 27.7, 31.9, 58.0, 66.2, 71.1, 126.0, 127.4, 127.6, 127.7, 128.0, 128.3, 129.6, 132.3, 133.1, 133.5, 133.6, 134.1, 135.6, 135.8, 136.6, 155.3. Observed for minor isomer: 23.5, 30.2, 59.0, 66.4, 73.7, 155.5. HRMS calculated for $[M+H]^+$ 500.26155, found: 500.26172.

4.2.31. *t*-Butyl (2*R*)-2-[(*t*-butyldiphenylsilyl)-oxycyclohept-4-en-1-yl]carbamate (23b). Obtained as a mixture of two diastereoisomers in a (1*S*,2*R*)–(1*R*,2*R*)=2.5:1 ratio as determined by HPLC. Yield 66% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). ESI-MS *m/z* 466.2 $[M+H]^+$; 488.2 $[M+Na]^+$. Chiral HPLC, Chiralcel OD, HEX/IPA=99.75:0.25, 1.0 mL/min, major diastereoisomer, RT 7.9 min (1*S*,2*R*- and 1*R*,2*S*-enantiomers), minor diastereoisomer RT 9.3 min (1*S*,2*S*- and 1*R*,2*R*-enantiomers). ^{1}H NMR ($CDCl_3$): δ 1.08 (s, 9H, *t*-Bu); 1.40 (s, 9H, *t*-Bu); 1.72–2.27 (m, 6H, CH_2); 3.45–3.76 (m, 1H, CHN); 3.83–4.05 (m, 1H, CHO); 4.84 (br s, 1H, NH); 5.36 (m, 1H, =CH); 5.71–90 (m, 1H, =CH); 7.40 (m, 6H, SiPh); 7.68 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.4, 26.9, 27.0, 27.8, 28.3, 32.0, 58.9, 71.5, 78.7, 125.9, 126.2, 127.5, 127.6, 129.6, 132.4, 133.3, 133.7, 133.9, 134.3, 135.7, 135.9, 154.9. Observed for minor isomer: 19.2, 30.5, 34.0, 57.6, 73.8, HRMS calculated for $[M+H]^+$ 466.27720, found: 466.27753.

4.2.32. Benzyl (7*R*)-[(*t*-butyldiphenylsilyl)oxycyclohept-3-en-1-yl]carbamate (24a). Obtained as a mixture of two diastereoisomers in a (1*S*,7*R*)–(1*R*,7*R*)=2.8:1 ratio as determined by HPLC. Yield 94% (colorless oil, purified by silicagel column chromatography, eluent PE/DEE=95:5). ESI-MS *m/z* 500.2 $[M+H]^+$; 522.4 $[M+Na]^+$. ee 98%, Chiralcel OD, HEX/IPA=99.5:0.5, 1.0 mL/min, RT 10.3 min (1*R*,7*R*-enantiomer), RT 11.4 min (1*R*,7*S*-enantiomer), RT 16.1 (1*S*,7*R*- and 1*S*,7*S*-enantiomers). ^{1}H NMR ($CDCl_3$): δ 1.10 (s, 9H, *t*-Bu); 1.38–1.58 (m, 2H, CH_2); 1.65–2.17 (m, 2H, CH_2); 2.26–2.45 (m, 1H, CH_2); 2.50–2.88 (m, 1H, CH_2); 3.77 (m, 1H, CHN); 4.01 (m, 1H, CHO); 4.79 (d, 1H, J=8.8 Hz, NH); 5.00 (s, 2H, $PhCH_2$); 5.68 (m, 1H, =CH); 5.81 (m, 1H, =CH); 7.35 (m, 11H, SiPh, $PhCH_2$); 7.69 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.3, 21.8, 27.0, 28.8, 32.3, 53.1, 66.1, 75.3, 127.5, 127.7, 128.3, 129.3, 129.7, 133.3, 133.6, 133.7, 134.7, 135.7, 135.8, 136.6, 155.3. Observed for minor isomer: 19.0, 21.6, 26.5, 29.6, 32.1, 52.5, 66.4 HRMS calculated for $[M+H]^+$ 500.26155, found: 500.26215.

4.2.33. *t*-Butyl (7*R*)-[(*t*-butyldiphenylsilyl)oxycyclohept-3-en-1-yl]carbamate (24b). Obtained as a mixture of two diastereoisomers in a (1*S*,7*R*)–(1*R*,7*R*)=2.5:1 ratio as determined by ^{1}H NMR. Yield 86% (colorless oil, purified by silicagel column chromatography, eluent PE/DEE=95:5). ESI-MS *m/z* 466.2 $[M+H]^+$; 488.2 $[M+Na]^+$. Chiral HPLC, ee 98%, Chiralcel OD, HEX/IPA=99.75:0.25, 0.6 mL/min, Major diastereoisomer RT 10.8 min (1*S*,7*R*-enantiomer); RT 14.4 min (1*R*,7*S*-enantiomer). Minor diastereoisomer RT 8.1 min (1*S*,7*S*-enantiomer), RT 8.6 min (1*R*,7*R*-enantiomer). ^{1}H NMR ($CDCl_3$): δ 1.09 (s, 9H, *t*-Bu); 1.39 (s, 9H, *t*-Bu); 1.46–1.65 (m, 2H, CH_2); 1.70–2.17 (m, 2H, CH_2); 2.22–2.40 (m, 1H, CH_2); 2.65–2.84 (m, 1H, CH_2); 3.66–3.85 (m, 1H, CHN); 3.93–4.08 (m, 1H, CHO); 4.85 (d, 1H, J=9.5 Hz, NH); 5.60–5.95 (m, 2H, =CH); 7.41 (m, 6H, SiPh); 7.69 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.4, 21.7, 27.1, 28.3, 29.0, 32.3, 52.6, 75.5, 78.6, 127.5, 127.7, 128.0, 129.7, 130.6, 130.7, 133.1, 133.7, 135.8, 154.9. HRMS calculated for $[M+H]^+$ 466.27720, found: 466.27728.

4.2.34. Benzyl (8*R*)-[(*t*-butyldiphenylsilyl)oxycycloocta-4-en-1-yl]carbamate (25). Obtained as a mixture of two diastereoisomers in a (1*S*,8*R*)–(1*R*,8*R*)=2.2:1 ratio as determined by HPLC. Yield 66% at 55% conversion. (Colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). ESI-MS *m/z* 514.2 $[M+H]^+$; 536.6 $[M+Na]^+$. Chiral HPLC, Chiralcel OD, HEX/IPA=99.5:0.5, 1.0 mL/min, major diastereoisomer RT 24.2 min (1*S*,8*R*-enantiomer and 1*R*,8*S*-enantiomer). Minor diastereoisomer RT 10.6 min (1*S*,8*S*-enantiomer and 1*R*,8*R*-enantiomer). ^{1}H NMR ($CDCl_3$): δ 1.10 (s, 9H, *t*-Bu); 1.41–1.63 (m, 2H, CH_2); 1.77–2.04 (m, 4H, CH_2); 2.28–2.65 (m, 1H, CH_2); 2.75–2.86 (m, 1H, CH_2); 3.77–3.89 (m, 1H, CHN); 4.06 (m, 1H, CHO); 4.32 (d, 1H, J=8.8 Hz, NH); 4.93 (s, 2H, $PhCH_2$); 5.51–5.78 (m, 2H, =CH); 7.33 (m, 11H, SiPh, $PhCH_2$); 7.67 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.4, 21.8, 22.8, 27.1, 31.0, 34.3, 53.4, 66.1, 77.5, 127.5, 127.7, 127.8, 128.3, 128.5, 129.7, 129.9, 131.2, 134.0, 134.7, 135.8, 135.9, 136.7, 155.2. HRMS calculated for $[M+H]^+$ 514.27720, found: 514.27783.

4.3. Preparation of *N*-heterocycles

4.3.1. (2*R*,3*E*)-1-Allylamino-2-[(*t*-butyldiphenylsilyl)-oxy]-pent-3-ene-2-ol (26). $[\alpha]_D^{20}=-14.2$ (c=1.0, CH_2Cl_2). ESI-MS *m/z*=380.2 $[M+H]^+$. ^{1}H NMR ($CDCl_3$): δ 1.05 (s, 9H, *t*-Bu); 1.50 (d, 3H, J=5.9 Hz, CH_3); 2.51–2.73 (m, 2H, CH_2); 3.12 (d, 2H, J=5.8 Hz, CH_2); 4.23 (m, 1H, CHO); 5.07 (m, 2H, $=CH_2$); 5.19–5.45 (m, 2H, =CH); 5.72–5.91 (m, 1H, =CH); 7.35 (m, 6H, SiPh); 7.66 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$); δ 17.3, 19.1, 26.9, 51.8, 55.3, 73.7, 115.6, 127.1, 127.3, 127.5, 129.3, 129.4, 132.0, 134.0, 135.6, 135.8, 136.5.

4.3.2. Benzyl 1-allyl[(2*R*,3*E*)-2-(*t*-butyldiphenylsilyl)-oxy-pent-3-en-1-yl]carbamate (27a). Yield 88% (colorless oil, purified by silicagel column chromatography, eluent PE/DEE=95:5). $[\alpha]_D^{25}=-14.8$ (c=1.0, CH_2Cl_2). ESI-MS

m/z=414.3 $[M+H]^+$. ^1H NMR ($CDCl_3$): δ 1.03 (s, 9H, *t*-Bu); 1.43 (d, 3H, J=5.9 Hz, CH_3); 3.14–3.40 (m, 2H, CH_2); 3.78 (m, 2H, CH_2); 4.19–4.39 (m, 1H, CHO); 4.91–5.13 (m, 5H, $PhCH_2$, $CH{=}CH_2$); 5.26 (m, 1H, =CH); 5.59–5.76 (m, 1H, =CH); 7.28 (m, 11H, SiPh, $PhCH_2$); 7.60 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 17.4, 19.1, 26.9, 50.7, 52.6, 66.9, 73.0, 116.3, 127.2, 127.4, 127.7, 128.0, 128.3, 129.4, 131.3, 133.4, 133.6, 133.9, 135.8, 136.0, 156.0.

4.3.3. *t*-Butyl 1-allyl[(2*R*,3*E*)-2-(*t*-butyldiphenylsilyl)-oxy-pent-3-en-1-yl]carbamate (27b). Yield 86% (colorless oil, purified by silicagel column chromatography, eluent PE/DEE=95:5). $[\alpha]_D^{25}=-17.0$ (c=1.0, CH_2Cl_2). ESI-MS m/z=480.2 $[M+H]^+$. ^1H NMR ($CDCl_3$): δ 1.05 (s, 9H, *t*-Bu); 1.38 (d, 3H, J=5.9 Hz, CH_3); 1.41 (s, 9H, *t*-Bu); 3.07–3.40 (m, 2H, CH_2); 3.63–3.84 (m, 2H, CH_2); 4.25 (m, 1H, CHO); 5.00 (m, 2H, $=CH_2$); 5.12–5.37 (m, 2H, =CH); 5.58–5.75 (m, 1H, =CH); 7.35 (m, 6H, SiPh); 7.64 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 17.4, 19.0, 26.9, 28.1, 50.4, 52.4, 73.3, 79.1, 115.6, 127.1, 127.3, 129.3, 131.6, 133.8, 135.6, 135.8, 155.0.

4.3.4. (2*R*,3*E*)-1-[Allyl(benzyl)amino-2-(*t*-butyl-diphenylsilyl)oxypent-3-en-2-ol (27c). Yield 77% (colorless oil, purified by silicagel column chromatography, eluent PE/DEE=100:0→90:10). $[\alpha]_D^{25}=+15.2$ (c=1.0, CH_2Cl_2). ESI-MS m/z=470.2 $[M+H]^+$. ^1H NMR ($CDCl_3$): δ 1.03 (s, 9H, *t*-Bu); 1.52 (d, 3H, J=6.6 Hz, CH_3); 2.50 (m, 2H, CH_2); 2.92 (d, 2H, J=6.6 Hz, $C{=}CCH_2$); 3.43 (s, 2H, $PhCH_2$); 4.14 (m, 1H, CHO); 5.04 (m, 2H, $=CH_2$); 5.20–5.47 (m, 2H, $=CH_2$); 5.62–5.79 (m, 1H, =CH); 7.21 (s, 5H, $PhCH_2$); 7.37 (m, 6H, SiPh); 7.66 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 17.6, 19.2, 27.1, 57.3, 58.8, 60.4, 73.1, 116.9, 126.2, 126.6, 127.2, 127.4, 127.9, 128.1, 128.3, 128.7, 128.9, 129.3, 129.4, 133.3, 134.3, 134.4, 135.9, 136.0, 139.7.

4.3.5. Benzyl (3*R*)-3-[(*t*-butyldiphenylsilyl)oxy]-3,6-dihydropyridine-1(2*H*)-carboxylate (28a). Yield 82% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). $[\alpha]_D^{25}=-18.8$ (c=1.0, CH_2Cl_2). ESI-MS m/z=472.5 $[M+H]^+$, 943.5 $[M_2+H]^+$. Chiralcel OD, HEX/IPA=99.8:0.2, 1.0 mL/min, RT 16.7 min (*R*-enantiomer) and 18.3 min (*S*-enantiomer) no baseline separation. ^1H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 3.29 (m, 1H, CH_2); 3.67 (m, 1H, CH_2); 3.96 (m, 2H, CH_2); 4.23 (m, 1H. CHO); 5.06 (m, 2H, $PhCH_2$); 5.71 (m, 2H, CH=CH); 7.32 (m, 11H, Ph, SiPh); 7.64 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.1, 26.9, 43.2, 47.4, 64.9, 67.0, 124.9, 125.9, 127.6, 127.9, 128.4, 129.2, 129.8, 132.3, 133.7, 135.7, 136.6, 155.1. HRMS calculated for $[M+Na]^+$ 494.21219, found: 494.21271.

4.3.6. *t*-Butyl (3*R*)-3-[(*t*-butyldiphenylsilyl)oxy]-3,6-dihydropyridine-1(2*H*)-carboxylate (28b). Yield 80% (colorless oil, purified by silicagel column chromatography, eluent PE/DEE=95:5). $[\alpha]_D^{25}=-25.4$ (c=1.0, CH_2Cl_2). ESI-MS m/z=438.0 $[M+H]^+$. Chiralcel OD, HEX/IPA=99.8:0.2, 1.0 mL/min, RT 10.0 min (*R*-enantiomer) and 10.6 min (*S*-enantiomer) no baseline separation. ^1H NMR ($CDCl_3$): δ 1.07 (s, 9H, *t*-Bu); 1.41 (s, 9H, *t*-Bu); 3.21 (dd, 1H, J=7.2, 12.9 Hz, CH_2); 3.68–3.93 (m, 3H, CH_2); 4.27 (m, 1H, CHO); 5.65 (m, 2H, CH=CH); 7.38 (m, 6H, SiPh); 7.65 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.1, 26.9, 28.3, 42.9, 48.7, 65.2, 79.3, 125.8, 127.4, 127.5, 127.7, 129.4, 129.5, 129.6, 133.9, 134.1, 135.6, 154.4. HRMS calculated for $[M+Na]^+$ 460.22812, found: 460.22784.

4.3.7. (3*R*)-1-Benzyl-3-[(*t*-butyldiphenylsilyl)oxy]-1,2,3,6-tetrahydropyridin-3-ol (28c). Yield 94% (colorless oil, purified by silicagel column chromatography, eluent PE/DEE=95:5). $[\alpha]_D^{25}=-18.2$ (c=1.0, CH_2Cl_2). ESI-MS m/z=428.0 $[M+H]^+$. ee >99%, Chiralcel OD, HEX/IPA=99.75:0.25, 1.0 mL/min, RT 9.8 min (*R*-enantiomer), RT 12.2 min (*S*-enantiomer). ^1H NMR ($CDCl_3$): δ 1.05 (s, 9H, *t*-Bu); 2.36 (dd, 1H, J=6.6, 11.0 Hz, CH_2); 2.68 (dd, 1H, J=5.1, 11.0 Hz, CH_2); 2.90 (m, 2H, CH_2); 3.53 (m, 2H, CH_2); 4.36 (m, 1H, CHO); 5.69 (m, 2H, CH=CH); 7.23–7.41 (m, 11H, Ph, SiPh); 7.64 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.1, 26.9, 52.4, 57.2, 62.1, 66.9, 127.0, 127.5, 128.2, 128.9, 129.3, 129.6, 134.1, 135.7, 135.8, 138.0. HRMS calculated for $[M+H]^+$ 428.24042, found: 428.24097.

4.3.8. Benzyl (3*R*)-3-hydroxy-3,6-dihydropyridine-1(2*H*)-carboxylate. Compound **28a** (132 mg, 0.280 mmol) was dissolved in THF (5.0 mL) and an excess of tetrabutylammonium fluoride (3 equiv) was added. After 2 h TLC showed complete conversion of **28a**. The solvent was evaporated in vacuo and the residue purified by silicagel column chromatography, eluent PE/EtOAc=3:1→1:3, to give the title compound (56 mg) in 99% yield as a colorless oil. $[\alpha]_D^{21}=-65.4$ (c=1.0, $CHCl_3$, lit.[17], $[\alpha]_D^{30}=-67.0$ (c=0.96, $CHCl_3$)). ee 98%, Chiralcel ODH, HEX/IPA=85:15, 1.0 mL/min, RT 8.3 min (*R*-enantiomer), 10.5 min (*S*-enantiomer). ^1H NMR ($CDCl_3$): δ 2.19 (broad s, 1H, OH); 3.63 (m, 2H, CH_2); 3.92 (m, 2H, CH_2); 4,21 (m, 1H, CHO); 5.15 (s, 2H, $PhCH_2$); 5.90 (m, 2H, CH=CH); 7.35 (s, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 43.1, 47.4, 63.1, 67.2, 125.9, 126.8, 127.8, 127.9, 128.4, 136.3, 155.6.

4.3.9. (2*R*)-1-Allylamino-2-[(*t*-butyldiphenylsilyl)-oxy]-pent-4-en-2-ol (29). $[\alpha]_D^{20}=-9.4$ (c=1.0, CH_2Cl_2). ESI-MS m/z=380.1 $[M+H]^+$. ^1H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 2.26 (m, 2H, CH_2); 2.61 (d, 2H, J=5.1 Hz, CH_2); 3.08 (d, 2H, J=5.8 Hz, CH_2); 3.89 (m, 1H, CHO); 4.96 (m, 4H, $=CH_2$); 5.57–5.85 (m, 2H, =CH); 7.40 (m, 6H, SiPh); 7.66 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.2, 26.9, 39.9, 52.1, 53.9, 72.4, 115.3, 117.0, 125.2, 127.5, 128.1, 128.9, 129.6, 134.0, 134.4, 135.8, 136.8.

4.3.10. (2*R*)-1-Allylamino-2-[(*t*-butyldiphenylsilyl)-oxy]-hex-5-en-2-ol (30). $[\alpha]_D^{20}=-3.0$ (c=1.0, CH_2Cl_2). ESI-MS m/z=394.0 $[M+H]^+$. ^1H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 1.43–1.64 (m, 2H, CH_2); 1.77–2.03 (m, 2H, CH_2); 2.60 (d, 2H, J=5.1 Hz, CH_2); 3.07 (d, 2H, J=5.8 Hz, CH_2); 3.84–3.93 (m, 1H, CHO); 4.80–4.91 (m, 2H, $=CH_2$); 4.99–5.11 (m, 2H, $=CH_2$); 5.50–5.88 (m, 2H, 2×=CH); 7.38 (m, 6H, SiPh); 7.69 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.3, 27.0, 29.4, 34.4, 52.2, 54.2, 72.4, 114.3, 115.4, 127.5, 129.5, 129.6, 134.1, 135.7, 135.8, 136.8, 138.2.

4.3.11. Benzyl 1-allyl[(2*R*)-2-(*t*-butyldiphenylsilyl)-oxy-pent-4-en-1-yl]carbamate (31a). Yield 72% (colorless oil,

purified by silicagel column chromatography, eluent PE/EtOAc=97:3→95:5). $[\alpha]_D^{20}=-20.2$ ($c=1.0$, CH_2Cl_2). ESI-MS $m/z=514.4$ $[M+H]^+$. ^1H NMR ($CDCl_3$): δ 1.04 (s, 9H, *t*-Bu); 2.10 (m, 2H, CH_2); 3.16 (m, 1H, CH_2); 3.29–3.61 (m, 1H, CH_2); 3.75 (m, 2H, CH_2); 4.02 (m, 1H, CHO); 4.77–5.07 (m, 6H, $=CH_2$, $PhCH_2$); 5.67 (m, 2H, 2×=CH); 7.35 (m, 11H, SiPh, $PhCH_2$); 7.63 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.1, 26.9, 39.2, 50.6, 51.5, 66.9, 71.1, 116.3, 117.2, 127.5, 127.7, 127.9, 128.2, 129.6, 130.0, 130.3, 133.3, 133.4, 133.7, 135.7, 135.8, 136.5, 155.9.

4.3.12. *t*-Butyl 1-allyl[(2*R*)-2-(*t*-butyldiphenylsilyl)-oxy-pent-4-en-1-yl]carbamate (31b). Yield 86% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). $[\alpha]_D^{20}=-19.6$ ($c=1.0$, CH_2Cl_2). ESI-MS $m/z=480.3$ $[M+H]^+$. ^1H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 1.40 (s, 9H, *t*-Bu); 2.06 (dd, 2H, $J=6.6$, 13.9 Hz, CH_2); 3.00–3.88 (m, 4H, 2×CH_2); 4.00 (m, 1H, CHO); 4.83–5.05 (m, 4H, $=CH_2$); 5.65 (m, 2H, =CH); 7.40 (m, 6H, SiPh); 7.67 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.0, 26.8, 28.1, 39.3, 50.6, 51.3, 71.4, 79.0, 115.6, 117.0, 127.4, 129.5, 133.7, 133.9, 135.1, 135.6, 155.1.

4.3.13. (2*R*)-1-Allyl-1-benzyl-2-[(*t*-butyldiphenylsilyl)-oxy]-1-aminopent-4-ene-2-ol (31c). Yield 67% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=100:0→90:10). $[\alpha]_D^{20}=+30.8$ ($c=1.0$, CH_2Cl_2). ESI-MS $m/z=470.3$ $[M+H]^+$. ^1H NMR ($CDCl_3$): δ 1.04 (s, 9H, *t*-Bu); 2.18 (m, 1H, CH_2); 2.35 (m, 2H, CH_2); 2.54 (m, 1H, CH_2); 2.83 (m, 2H, CH_2); 3.33 (dd, 2H, $J=2.2$, 13.9 Hz, $PhCH_2$); 3.85 (m, 1H, CHO); 4.80–5.05 (m, 4H, $=CH_2$); 5.61–5.85 (m, 2H, =CH); 7.20–7.43 (m, 11H, $PhCH_2$, SiPh); 7.67 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.3, 27.1, 33.2, 39.4, 57.4, 58.9, 71.5, 116.9, 117.2, 126.7, 127.5, 128.0, 128.3, 128.7, 128.9, 129.6, 134.2, 134.4, 135.1, 135.7, 136.0, 136.5, 139.6.

4.3.14. Benzyl 1-allyl[(2*R*)-2-(*t*-butyldiphenylsilyl)-oxy-hex-5-en-1-yl]carbamate (32a). Yield 62% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). $[\alpha]_D^{20}=-12.2$ ($c=1.0$, CH_2Cl_2). ESI-MS $m/z=528.2$ $[M+H]^+$. ^1H NMR ($CDCl_3$): δ 1.04 (s, 9H, *t*-Bu); 1.25–1.56 (m, 2H, CH_2); 1.84–2.05 (m, 2H, CH_2); 3.13 (m, 1H, CH_2); 3.31–3.83 (m, 3H, CH_2); 3.94 (m, 1H, CHO); 4.71–5.18 (m, 6H, $=CH_2$, $PhCH_2$); 5.40–5.71 (m, 2H, =CH); 7.36 (m, 11H, SiPh, $PhCH_2$); 7.64 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.0, 26.8, 28.6, 33.6, 50.3, 51.3, 66.8, 70.8, 114.2, 116.1, 127.3, 127.6, 128.1, 129.4, 133.1, 133.7, 135.6, 136.3, 137.8, 155.8.

4.3.15. *t*-Butyl 1-allyl[(2*R*)-2-(*t*-butyldiphenylsilyl)-oxy-hex-5-en-1-yl]carbamate (32b). Yield 47% (colorless oil, purified by silicagel column chromatography, eluent PE/DEE=98:2→95:5). $[\alpha]_D^{20}=-18.6$ ($c=1.0$, CH_2Cl_2). ESI-MS $m/z=494.6$ $[M+H]^+$, 516.3 $[M+Na]^+$. ^1H NMR ($CDCl_3$): δ 1.05 (s, 9H, *t*-Bu); 1.40 (s, 9H, *t*-Bu); 1.25–1.53 (m, 2H, CH_2); 2.00 (m, 2H, CH_2); 3.02 (m, 1H, CH_2); 3.55 (m, 2H, CH_2); 3.77 (m, 1H, CH_2); 3.92 (m, 1H, CHO); 4.80–5.03 (m, 4H, 2×$=CH_2$); 5.47–5.68 (m, 2H, 2×=CH); 7.40 (m, 6H, SiPh); 7.67 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.1, 26.9, 28.2, 28.7, 33.7, 50.2, 51.2, 71.2, 79.3, 114.1, 115.6, 127.5, 127.8, 129.5, 133.8, 134.0, 135.7, 136.7, 138.1, 138.3, 155.2.

4.3.16. Benzyl (3*R*)-3-[(*t*-butyldiphenylsilyl)oxy]-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate (33a). Yield 74% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). $[\alpha]_D^{20}=-12.6$ ($c=1.0$, CH_2Cl_2). ESI-MS $m/z=486.3$ $[M+H]^+$, 508.3 $[M+Na]^+$. ee 98%, Chiralcel OD, HEX/IPA=99.75:0.25, 1.2 mL/min, RT 24.1 min (*S*-enantiomer); RT 25.8 min (*R*-enantiomer). ^1H NMR ($CDCl_3$): δ 1.05 (s, 9H, *t*-Bu); 2.25 (dd, 2H, $J=5.1$, 5.9 Hz, CH_2); 3.32 (m, 1H, CH_2); 3.68–4.24 (m, 4H, CH_2, CHO); 5.06 (m, 2H, $PhCH_2$); 5.55 (m, 1H, =CH); 5.74 (m, 1H, =CH); 7.32 (m, 11H, SiPh, $PhCH_2$); 7.64 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.0, 26.8, 34.8, 46.6, 54.5, 66.7, 69.8, 126.7, 127.2, 127.5, 127.7, 128.2, 129.2, 129.3, 129.6, 133.7, 135.6, 155.5. HRMS calculated for $[M+H]^+$ 486.24590, found: 486.24637.

4.3.17. *t*-Butyl (3*R*)-3-[(*t*-butyldiphenylsilyl)oxy]-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate (33b). Yield 76% (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). $[\alpha]_D^{20}=-23.4$ ($c=1.0$, CH_2Cl_2). ESI-MS $m/z=452.2$ $[M+H]^+$, 474.3 $[M+Na]^+$. ee 97%, Chiralcel OD, HEX/IPA=99.8:0.2, 1.0 mL/min, RT 9.3 min (*R*-enantiomer), 10.9 min (*S*-enantiomer). ^1H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu); 1.37 (s, 9H, *t*-Bu); 2.25 (m, 2H, CH_2); 3.19 (dd, 1H, $J=8.0$, 13.9 Hz, CH_2); 3.45–4.09 (m, 3H, CH_2); 4.24 (m, 1H, CHO); 5.53 (m, 1H, =CH); 5.68 (m, 1H, =CH); 7.39 (m, 6H, SiPh), 7.65 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.2, 27.2, 28.3, 34.5, 46.8, 54.3, 70.4, 79.5, 126.2, 126.9, 127.6, 129.6, 129.7, 133.8, 135.7, 154.8. HRMS calculated for $[M+H]^+$ 452.26155, found: 452.26239.

4.3.18. (3*R*)-1-Benzyl-3-[(*t*-butyldiphenylsilyl)oxy]-2,3,4,7-tetrahydroazepine (33c). For this reaction diene **31c** (184 mg, 0.392 mmol) was dissolved in CH_2Cl_2 (40 mL) and HCl (4 M in dioxane, 0.11 mL, 0.440 mmol) was added. Argon was bubbled through the solution for 5 min and the Grubbs catalyst (13 mg, 4 mol%) was added. The reaction was refluxed for 24 h, cooled, washed with an aqueous saturated $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated to afford the crude product. Purification gave the title compound (20 mg) in 12% yield. (colorless oil, purified by silicagel column chromatography, eluent PE/EtOAc=95:5). $[\alpha]_D^{20}=+161$ ($c=0.4$, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 1.02 (s, 9H, *t*-Bu); 2.42 (m, 2H, CH_2); 2.84 (dd, 1H, $J=8.0$, 13.2 Hz, CH_2); 3.14 (m, 3H, CH_2); 3.54 (d, 1H, $J=13.2$ Hz, CH_2Ph); 3.62 (d, 1H, $J=13.2$ Hz, CH_2Ph); 3.94 (m, 1H, CHO); 5.61 (m, 2H, CH=CH); 7.25 (s, 5H, Ph); 7.39 (m, 6H, SiPh); 7.61 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): 19.2, 26.9, 36.5, 52.4, 56.6, 59.9, 68.2, 127.4, 127.6, 128.3, 128.7, 129.3, 129.7, 135.7, 137.2.

4.3.19. Benzyl (3*R*)-3-[(*t*-butyldiphenylsilyl)oxy]-3,4,5,8-tetrahydroazocine-1(2*H*)-carboxylate (34a). Yield 61%, based on converted starting material, conversion 50% after 24 h. (colorless oil, purified by silicagel column chromatography, eluent PE/DEE=9:1). $[\alpha]_D^{21}=+20.4$ ($c=1$, CH_2Cl_2). ESI-MS $m/z=500.2$ $[M+H]^+$, 522.4 $[M+Na]^+$. ee 97%, Chiralcel OD, HEX/IPA=99.75:0.25, 1.0 mL/min, RT 22.6 min (*S*-enantiomer), 25.1 min (*R*-enantiomer). ^1H NMR ($CDCl_3$): δ 1.04 (s, 9H, *t*-Bu); 1.55–2.27 (m, 4H, CH_2); 3.30–4.13 (m, 5H, CH_2, CHO); 5.01 (s, 2H, $PhCH_2$); 5.11 (s, 2H, $PhCH_2$); 5.30 (m, 1H, =CH); 5.63

(m, 1H, =CH); 7.15–7.41 (m, 11H, SiPh, $PhCH_2$); 7.64 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.1, 21.5, 26.9, 34.9, 47.4, 52.9, 67.0, 69.7, 125.0, 126.3, 127.5, 127.8, 128.0, 128.3, 129.6, 130.9, 133.9, 134.3, 134.9, 135.7, 136.8, 155.8. HRMS calculated for $[M+H]^+$ 500.26155, found: 500.26251.

4.3.20. *t*-Butyl (3*R*)-3-[(*t*-butyldiphenylsilyl)oxy]-3,4,5,8-tetrahydroazocine-1(2*H*)-carboxylate (34b). Yield 87%, based on converted starting material, conversion 52% after 24 h. (colorless oil, purified by silicagel column chromatography, eluent PE/DEE=95:5). $[\alpha]_D^{21}=+23.4$ ($c=1$, CH_2Cl_2). ESI-MS m/z=466.2 $[M+H]^+$, 488.2 $[M+Na]^+$, 954.0 $[M_2+Na]^+$. Chiral HPLC, Chiralcel OD, no separation. ^1H NMR ($CDCl_3$): δ 1.05 (s, 9H, *t*-Bu); 1.38 (s, 9H, *t*-Bu); 1.66–1.94 (m, 3H, CH_2); 2.21 (m, 1H, CH_2); 3.12–3.54 (m, 2H, CH_2); 3.70–3.92 (m, 2H, CH_2); 4.01–4.13 (m, 1H, CHO); 5.27 (m, 1H, =CH); 5.60 (m, 1H, =CH); 7.40 (m, 6H, SiPh,); 7.67 (m, 4H, SiPh). ^{13}C NMR ($CDCl_3$): δ 19.1, 21.3, 26.9, 28.9, 35.1, 47.5, 53.0, 69.7, 79.4, 125.9, 127.5, 128.4, 129.6, 129.9, 133.9, 134.2, 134.3, 135.7, 155.1. HRMS calculated for $[M+H]^+$ 466.27720, found: 466.27924.

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Hydroxynitrile lyase-catalyzed addition of HCN to 2- and 3-substituted cyclohexanones☆

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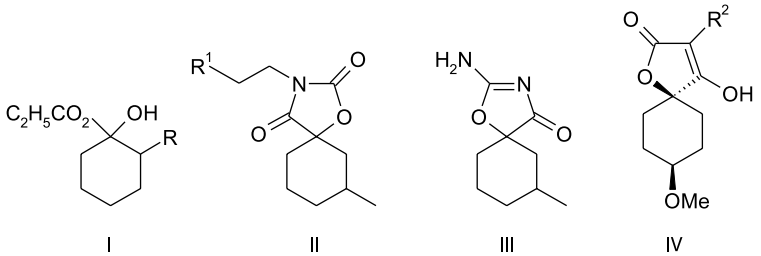
Abstract—The addition of HCN to monosubstituted cyclohexanones yielding cyanohydrins is strongly catalyzed by hydroxynitrile lyases (HNLs). With PaHNL from bitter almonds, the addition to 2-alkyl cyclohexanones **1b–g** is highly (*R*)-selective, whereas the methyl compound **1a** reacts (*S*)-selectively. With MeHNL from cassava, all 2-alkyl derivatives **1** react (*S*)-selectively. The catalytic activity of both PaHNL and MeHNL decreases with increasing size of the substituent in substrates **1**. The diastereoselectivity of HCN additions to 2-alkoxy cyclohexanones **4** and 3-substituted cyclohexanones **6**, however, is only moderate. The absolute configuration of the synthesized cyanohydrins was determined by X-ray crystallography of *O*-*p*-bromobenzoyl derivatives.

1. Introduction

Monosubstituted cyclohexanone cyanohydrins, which can be hydrolyzed easily to the corresponding α-hydroxy-carboxylic acids, are important starting materials for the synthesis of pharmaceuticals and plant protective agents. 2-Alkyl-1-hydroxy-1-carbalkoxy-cyclohexanes **I**, for example, are repellents against mosquitos.[3] The spirocyclic cyclohexanone derivatives **II** and **III** are applied as pharmaceuticals in central nervous system diseases,[4] while 4-substituted-1,1-tetronic acid cyclo-hexanes **IV** are interesting herbicides (Scheme 1).[5]

Since the different stereoisomers of one compound often reveal very distinct biological activities, the stereoselective preparation of exclusively one isomer is an important target. Although each of the compounds **I**, **II** and **III** has two stereogenic centres, until now not a single stereo-selective chemical synthesis for these interesting products is described in the literature. The hydroxynitrile lyase (HNL) catalyzed addition of HCN to 3-methyl cyclohexanone **5a** has been performed, but the stereochemistry of the corresponding cyanohydrin obtained could not be determined.[6]

In a recent publication we have described the hydroxynitrile lyase-catalyzed addition of HCN to 4-substituted cyclo-hexanones, which unexpectedly results in a high



I II III IV

Scheme 1.

☆ Enzyme-catalyzed reactions, part 49; for part 48 see ref. 1.

Keywords: Enzyme; Hydroxynitrile lyase; Cyclohexanones; Cyanohydrins; Stereochemistry.
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cis/*trans*-selectivity.[7] In the present paper we report on our systematic investigations of HNL-catalyzed HCN additions to 2- as well as to 3-substituted cyclohexanones.

2. Results and discussion

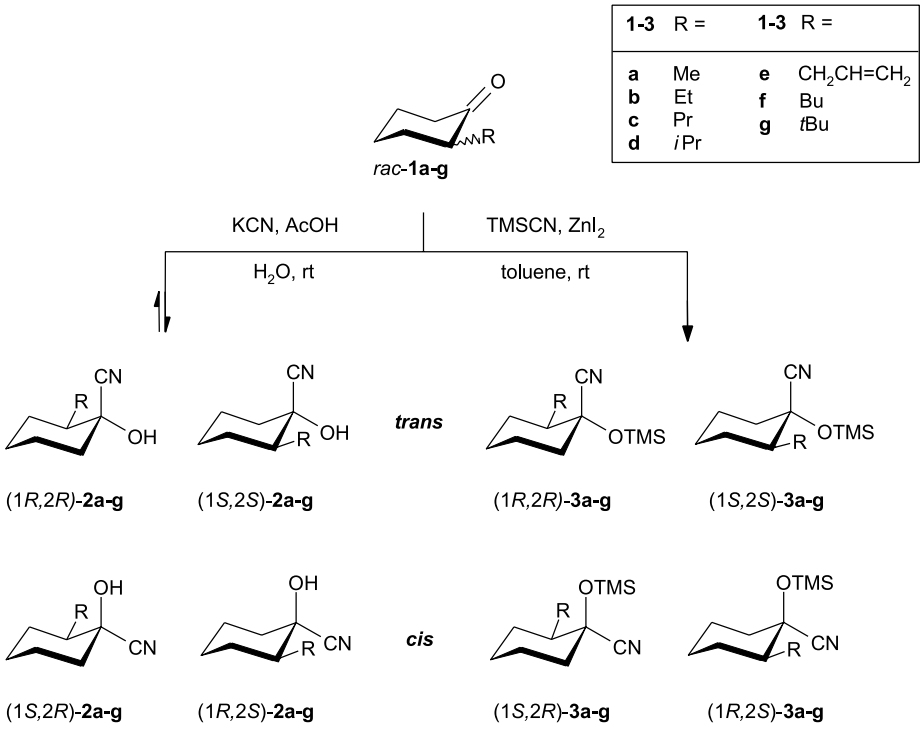
2.1. Chemical addition of HCN to 2- and 3-substituted cyclohexanones 1, 4 and 6

Prior to starting enzyme-catalyzed reactions we have investigated the chemical addition of HCN, prepared in situ in aqueous solution from KCN with acetic acid,[8] to racemic 2-alkyl cyclohexanones *rac*-**1a–g** (Scheme 2, Table 1).

Table 1 reveals *trans*-selectivity of the HCN addition to racemic 2-alkyl cyclohexanones *rac*-**1a–f** to give the corresponding cyclohexanone cyanohydrins **2a–f**. The 2-*tert*-butyl cyclohexa-none **1g**, however, could not be converted. An alternative chemical method is the addition of trimethylsilyl cyanide (TMSCN) to 2-alkyl cyclohexanones **1a–g** using ZnI_2 as a catalyst.[9] Analogously to the HCN addition, the reaction with TMSCN yielded the *trans* isomers of the *O*-trimethylsilyl cyanohydrins **3a–f** as major products (Table 1). The reaction of the *tert*-butyl compound turns out to be unselective, giving the *cis* and *trans* isomers of **3g** in almost equal amounts.

In contrast to 2-alkyl cyclohexanones, the reaction of 2-alkoxy cyclohexanones **4a–e** with KCN and acetic acid shows, with the exception of **4a**, a slight preference for *cis*-products (Scheme 3, Table 2).

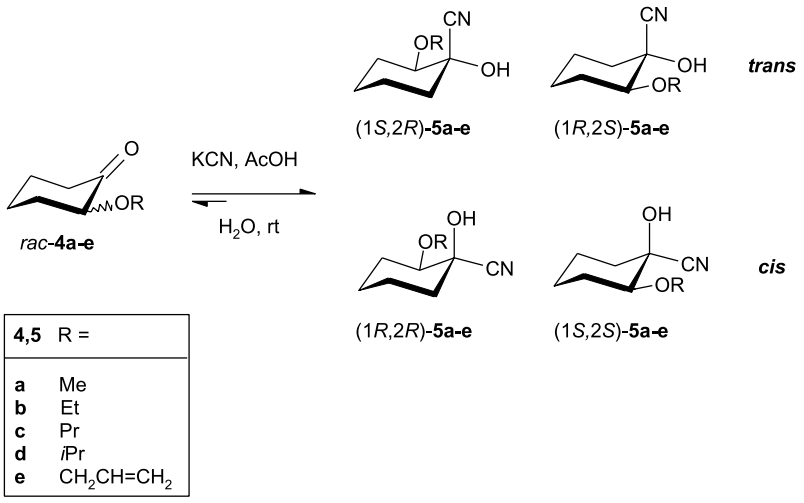
In the chemical HCN addition to 3-substituted cyclohexanones **6a–c** (Scheme 4) the formation of *cis*-products dominates (Table 2). This result may be explained by an



Scheme 2.

Table 1. *cis*/*trans*-Selectivities and yields of the HCN and TMSCN addition to racemic 2-alkyl cyclohexanones *rac*-**1a–g**

Ketones *rac*-**1**		Cyanohydrins **2**			*O*-Silylated cyanohydrins **3**		
	R=		Yield	*rac-cis*:*rac-trans*		Yield	*rac-cis*:*rac-trans*
1a	Methyl-	**2a**	90	22:78	**3a**	65	25:75
1b	Ethyl-	**2b**	70	24:76	**3b**	73	22:78
1c	*n*-Propyl-	**2c**	83	25:75	**3c**	53	23:77
1d	*iso*-Propyl-	**2d**	64	28:72	**3d**	37	36:64
1e	Allyl-	**2e**	61	14:86	**3e**	53	25:75
1f	*n*-Butyl-	**2f**	84	35:65	**3f**	83	26:74
1g	*tert*-Butyl	**2g**	—	—	**3g**	27	51:49



Scheme 3.

Table 2. *cis*/*trans*-Selectivities and yields of the HCN addition to racemic 2-alkoxy cyclohexanones *rac*-**4** and racemic 3-substituted cyclohexanones *rac*-**6**

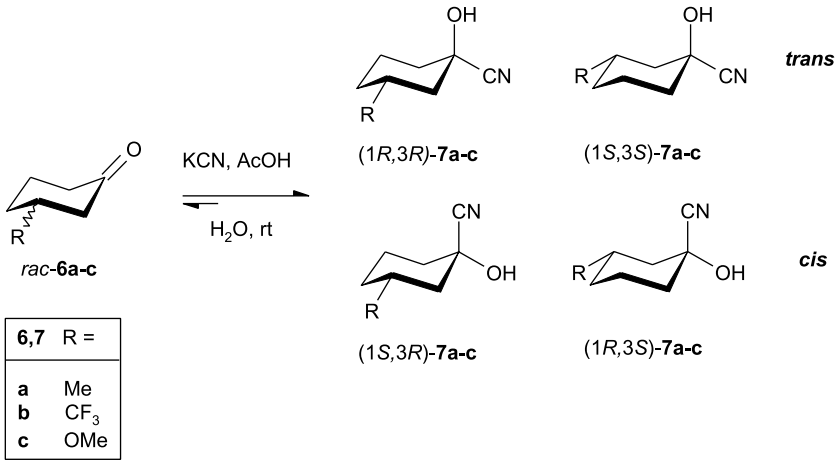
rac-**4**	Cyanohydrins **5**			*rac*-**6**	Cyanohydrins **7**		
		Yield	*rac-cis*:*rac-trans*			Yield	*rac-cis*:*rac-trans*
4a	**5a**	84	39:61	**6a**	**7a**	95	86:14
4b	**5b**	82	54:46	**6b**	**7b**	92	59:41
4c	**5c**	96	58:42	**6c**	**7c**	87	92:8
4d	**5d**	91	59:41				
4e	**5e**	86	54:46				

electronically favored axial attack of the carbonyl group by the cyanide nucleophile.[10]

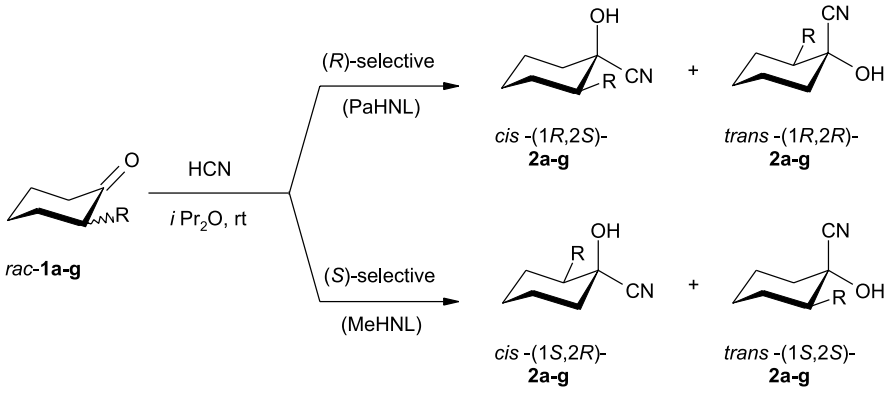
2.2. (*R*)-PaHNL- and (*S*)-MeHNL-catalyzed addition of HCN to racemic 2-alkyl cyclohexanones, *rac*-1

Both the hydroxynitrile lyases (*R*)-PaHNL from bitter almond and (*S*)-MeHNL from cassava were used for the HCN addition to cyclohexanones **1**. In contrast to the chemical reactions described above, where *cis*/*trans*-selectivity is observed, the enzyme-catalyzed additions reveal *R*/*S*-selectivity concerning the new stereogenic center formed in the 1-position. One should expect (*R*)-selectivity by using (*R*)-PaHNL[11a] yielding the *cis*-(1*R*,2*S*)- and *trans*-(1*R*,2*R*)-diastereomers and (*S*)-selectivity by applying (*S*)-MeHNL[11b] to give the *cis*-(1*S*,2*R*)- and *trans*-(1*S*,2*S*)-diastereomers **2** as shown in Scheme 5.

All HNL-catalyzed cyanohydrin formations have been performed under optimized standard conditions.[12] In order to estimate the contribution of chemical addition, for each substrate the reaction was also performed under the same conditions without enzyme (Section 4.4). Table 3 summarizes the results of (*R*)-PaHNL-catalyzed addition of HCN to racemic 2-alkyl cyclohexanones *rac*-**1a**–**g**.



Scheme 4.



Scheme 5.

Table 3. (*R*)-PaHNL catalyzed addition of HCN to *rac*-2-alkyl cyclohexanones **1a–g**

rac-**1**	*t* [h]	Cyanohydrins **2**					Blank exp.	
			Conv. [%]	*cis*:*trans*	*cis*-(1*R*,2*S*) de [%]	*trans*-(1*R*,2*R*) de [%]	Conv. [%]	*cis*:*trans*
1a	18	**2a**	98	51:49	98[a]	93[b]	3	36:64
1b	216	**2b**	95	52:48	93	79	4	35:65
1c	336	**2c**	50	48:52	67	79	5	39:61
1d	336	**2d**	< 2	22:78	—	—	< 2	29:71
1e	96	**2e**	92	42:58	93	91	4	30:70
1f	192	**2f**	2	45:55	—	—	< 2	44:56
1g	336	**2g**	< 1	n.d.	—	—	< 1	n.d.

[a] de (*cis*-(1*S*,2*R*)).
[b] de (*trans*-(1*S*,2*S*)).

The cyclohexanones **1b**, **1c** and **1e** react as expected with high (*R*)-selectivity to give the *cis*-(1*R*,2*S*) and *trans*-(1*R*,2*R*)-diastereomers of **2b**, **2c** and **2e**, respectively (Table 3). Since there is no *cis*/*trans*-selectivity observed, both (1*R*)-diastereomers are obtained in almost equal amounts. The reaction behavior of the methyl derivative **1a**, however, is absolutely unexpected. The (*R*)-PaHNL-* catalyzed reaction turns out to be completely (*S*)-selective, affording the *cis*-(1*S*,2*R*)- and *trans*-(1*S*,2*S*)-**2a** diastereomers in a 1:1 ratio (Table 3). Because the precise structure of the active site of (*R*)-PaHNL is not yet known,[13] a convincing explanation for the inversion of stereoselectivity in the case of the methyl compound **1a** is not currently possible.

From Table 3 it is also apparent that the catalytic activity of the enzyme is reduced with increasing size of the alkyl substituent R. Even after a reaction time of 336 h, the conversion of the *n*-propyl derivative **1c** is only 50% and the corresponding cyanohydrin of the isopropyl compound **1d** could not be detected at all under these conditions. Similar results are found for the butyl derivatives **1f** and **1g**, respectively, whereas the allyl compound **1e** turned out to be a good substrate for (*R*)-PaHNL giving high conversions in shorter reaction times. It must be noted that under the standard conditions the chemical addition of HCN to ketones **1** can be suppressed almost completely, even at long reaction times (Table 3).

In Table 4, the results of the (*S*)-MeHNL-catalyzed addition of HCN to the racemic 2-alkyl cyclohexanones **1a–g** (Scheme 5) are listed. The (*S*)-MeHNL-catalyzed conversion of cyclohexanone derivatives **1a–c**,**e**,**f** afforded selectively the corresponding (1*S*)-cyanohydrins, including the methyl derivative **1a**, to give *cis*-(1*S*,2*R*)- and *trans*-(1*S*,2*S*)-**2a–c**, **2e**, **f** (Table 4). Obviously 2-alkyl cyclo-hexanones **1** with the exception of **1d** and **1g** are better substrates for (*S*)-MeHNL than for (*R*)-PaHNL. The reaction times, for example, are considerably shorter and the dependence on bulky substituents is lower as can be demonstrated by

Table 4. (*S*)-MeHNL catalyzed addition of HCN to *rac*-2-alkyl cyclohexanones **1a–g**

rac-**1**	*t* [h]	Cyanohydrins **2**					Blank exp.	
			Conv. [%]	*cis*:*trans*	*cis*-(1*S*,2*R*) de [%]	*trans*-(1*S*,2*S*) de [%]	Conv. [%]	*cis*:*trans*
1a	3	**2a**	96	60:40	74	33	<1	34:66
1b	24	**2b**	98	38:62	94	88	1	32:68
1c	24	**2c**	97	55:45	99	74	1	n.d.
1d	48	**2d**	<1	n.d.	—	—	<1	n.d.
1e	24	**2e**	90	43:57	97	87	1	24:76
1f	48	**2f**	15	76:24	94	76	≪1	38:62
1g	48	**2g**	≪1	n.d.	—	—	≪1	n.d.

comparing the reactions of the *n*-propyl derivative **1c**. Only 50% of **1c** was converted after 336 h reaction time applying PaHNL, whereas the corresponding cyanohydrin **2c** is obtained in 97% yield after 24 h using MeHNL (Table 4).

The exclusive (*S*)-selectivity of MeHNL-catalyzed additions of HCN to 2-alkyl cyclohexanones **1** can be rationalized by the mechanism of cyanogenesis.[14] From the X-ray crystal structure of (*S*)-MeHNL it is known that the active site is accessible via a narrow channel and consists of a small (S1) and a larger (S2) binding pocket. In the active site the carbonyl group of the incoming substrate is fixed by two hydrogen bonds from Thr11 and from Ser80.[14] Cyclohexanones are assumed to bind to the active site of the enzyme in the channel either in an upright or in a flat mode.[7a] In both cases, the cyanide ion attacks the substrate from below, where His236 is located as a base.[14] From Figure 1 it is apparent that for steric reasons fixation of substrates with equatorial alkyl substituentes[15] in the larger pocket, S2, is strongly favored, thus leading to the *cis*-(1*S*,2*R*) configuration with the cyclohexanone ring in an upright position (Fig. 1a), whereas the *trans*-(1*S*,2*S*)-configuration results from the flat position (Fig. 1b).

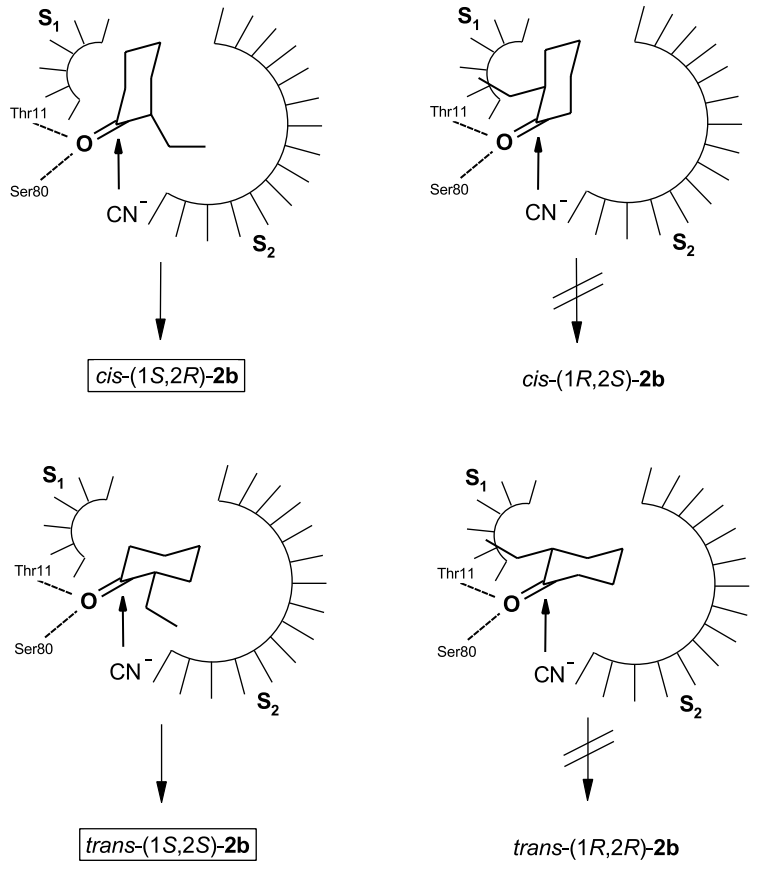
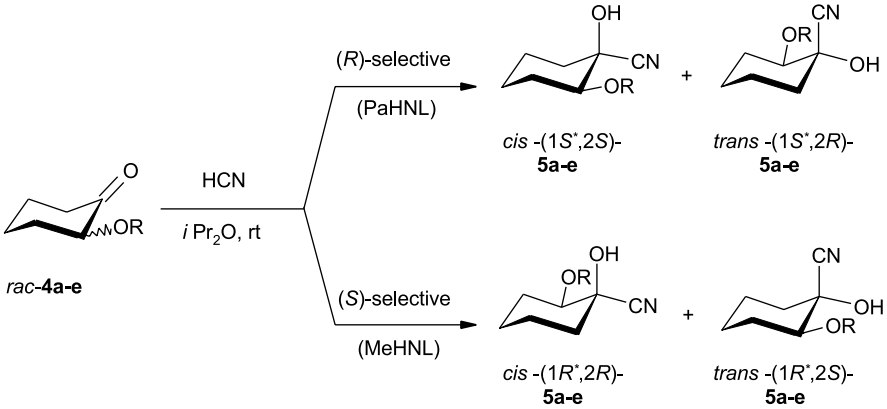


Figure 1. Schematic illustration of HCN addition to 2-ethyl cyclohexanone **1b** in the active site of (*S*)-MeHNL. Configurations of 2-ethyl cyclohexanone cyanohydrin **2b** obtained in upright position (a) and in flat position (b).



*The apparent inversion of configuration at C1 is an artefact of the CIP-priority rules.

Scheme 6.

Table 5. (*R*)-PaHNL catalyzed addition of HCN to *rac*-2-alkoxy cyclohexanones **4a–e** to form the corresponding cyanohydrins **5a–e**

rac-**4**	*t* [h]	Cyanohydrins **5**					Blank exp.	
			Conv. [%]	*cis*:*trans*	*cis*-(1S[a],2*S*) *de*[%]	*trans*-(1S[a],2*R*) de [%]	Conv. [%]	*cis*:*trans*
4a	5	**5a**	19	64:36	48	8	7	58:42
4b	48	**5b**	34	48:52	8	16	8	60:40
4c	48	**5c**	3	45:55	—	—	1	65:35
4d	48	**5d**	10	62:38	—	—	2	61:39
4e	48	**5e**	19	50:50	14	18	5	58:42

[a] The apparent inversion of configuration at C_1 is an artefact of the CIP-priority rules.

Table 6. (*S*)-MeHNL catalyzed addition of HCN to *rac*-2-alkoxy cyclohexanones **4a–e** to form the cyanohydrins **5a–e**

rac-**4**	*t* [h]	Cyanohydrins **5**					Blank exp.	
			Conv. [%]	*cis*:*trans*	*cis*-(1R[a],2*R*) de [%]	*trans*-(1R[a],2*S*) de [%]	Conv. [%]	*cis*:*trans*
4a	5	**5a**	84	59:41	98	83	7	58:42
4b	48	**5b**	23	62:38	37	5[b]	8	60:40
4c	24	**5c**	1	58:42	—	—	< 1	65:35
4d	48	**5d**	5	63:37	—	—	2	61:39
4e	48	**5e**	27	61:39	50	13	5	58:42

[a] The apparent inversion of configuration at C_1 is an artefact of the CIP-priority rules.
[b] de (*cis*-(1*S*,2*S*)).

Owing to the reduced steric demand of the methyl group in **1a**, a fixation of the substrate with the methyl group in the small pocket S1 is also possible, resulting in a diminished stereo-selectivity of the HCN addition (Table 4).

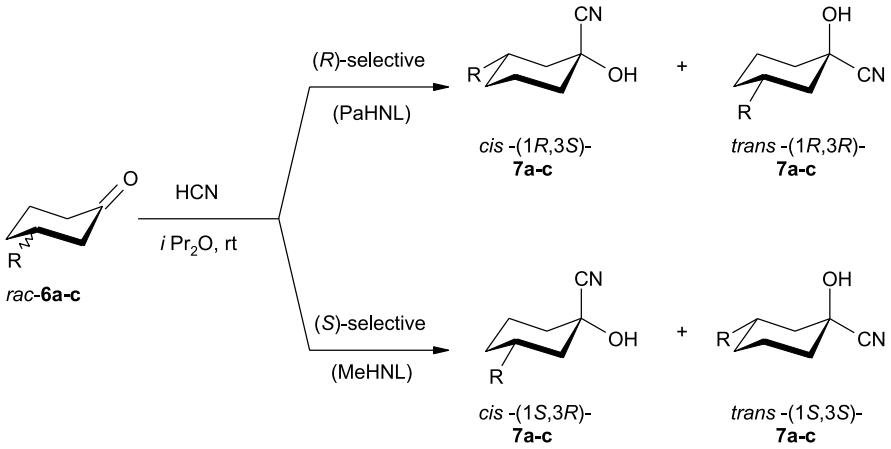
2.3. (*R*)-PaHNL- and (*S*)-MeHNL-catalyzed addition of HCN to racemic 2-alkoxy cyclohexanones, *rac*-4

HNL-catalyzed additions of HCN to racemic 2-alkoxy cyclohexanones *rac*-**4** are depicted in Scheme 6. In contrast to the 2-alkyl cyclohexanones **1**, the comparable 2-alkoxy compounds **4** are poorer substrates for both PaHNL and MeHNL. Due to the fast chemical addition of HCN to the alkoxy derivatives **4** not only the yields, but also the stereoselectivities of HNL-catalyzed cya-nohydrin formations of 2-alkoxy cyclohexanones are unsatisfactory (Tables 5 and 6).

The only exception is the MeHNL-catalyzed addition of HCN to 2-methoxy cyclohexanone (**5a**) which occurs relatively quickly with high diastereoselectivity (Table 6). A comparison of these investigations with additions of HCN to α- and β-substituted aldehydes catalyzed by the hydroxynitrile lyase from *Hevea brasiliensis* (HbHNL)[16] gave similar results. Whereas alkyl substituted aldehydes reacted highly diastereoselectively, the corresponding O-analogues gave only low de values.[16]

2.4. (*R*)-PaHNL- and (*S*)-MeHNL-catalyzed addition of HCN to racemic 3-substituted cyclohexanones *rac*-6

The 3-substituted cyclohexanones **6a–c** were reacted with HCN in the presence of both (*R*)-PaHNL and (*S*)-MeHNL as biocatalyst (Scheme 7, Tables 7 and 8). As can be seen from Table 7, the PaHNL-catalyzed additions are highly (*R*)-selective for the (3*S*)-enantiomers of *rac*-**6a–c** leading to the *cis*-(1*R*,3*S*) diastereomers of **7a–c** (Table 7). The (*R*)-selectivity, however, is only moderate for the



Scheme 7.

Table 7. (*R*)-PaHNL catalyzed addition of HCN to racemic 3-substituted cyclohexanones **6a–c** to form cyanohydrins **7a–c**

rac-**4**	*t* [h]	Cyanohydrins **5**					Blank exp.	
			Conv. [%]	*cis*:*trans*	*cis*-(1*R*,3*S*) de [%]	*trans*-(1*R*,3*R*) de [%]	Conv. [%]	*cis*:*trans*
6a	5	**7a**	99	61:39	87	49	2	78:22
6b	6	**7b**	88	64:36	99	73	4	88:12
6c	3	**7c**	99	92:8	95	69[a]	15	88:12

[a] de (*cis*-(1*S*,3*R*)).

Table 8. (*S*)-MeHNL catalyzed addition of HCN to racemic 3-substituted cyclohexanones **6a–c** to form the corresponding cyanohydrins **7a–c**

rac-**4**	*t* [h]	Cyanohydrins **5**					Blank exp.	
			Conv. [%]	*cis*:*trans*	*cis*-(1*S*,3*R*) de [%]	*trans*-(1*S*,3*S*) de [%]	Conv. [%]	*cis*:*trans*
6a	5	**7a**	99	42:58	61	94	2	78:22
6b	6	**7b**	99	46:54	77	88	4	88:12
6c	1	**7c**	98	55:45	90	76	14	88:12

(3*R*)-enantiomers of *rac*-**6a**,**b** and even inverted for *rac*-**6c**, which reacts preferentially to give the *cis*-(1*S*,3*R*) diastereomer (Table 7). In Table 8, the results of (*S*)-MeHNL-catalyzed additions of HCN to racemic 3-substituted cyclohexanones **6a–c** are summarized.

For all substrates **6a–c** the reaction is (*S*)-selective as expected, yielding the *cis*-(1*S*,3*R*)- and the *trans*-(1*S*,3*S*)-diastereomers as major products (Table 8).

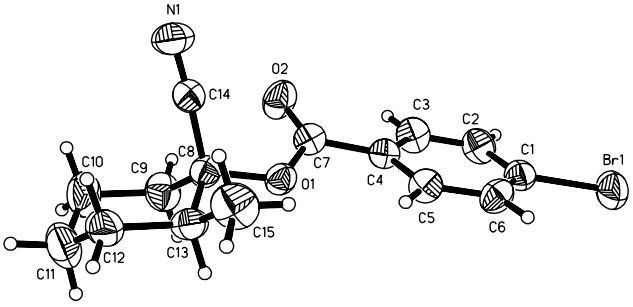


Figure 3. ORTEP view of *trans*-(1*S*,2*S*)-1-(4-bromobenzoyloxy)-2-methylcyclohexanecarbonitrile (*trans*-(1*S*,2*S*)-**2a**′).

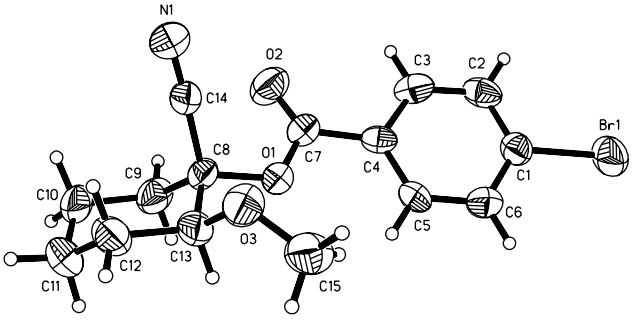


Figure 4. ORTEP view of *trans*-(1*R*,2*S*)-1-(4-bromobenzoyloxy)-2-methoxycyclohexanecarbonitrile (*trans*-(1*R*,2*S*)-**5a**′).

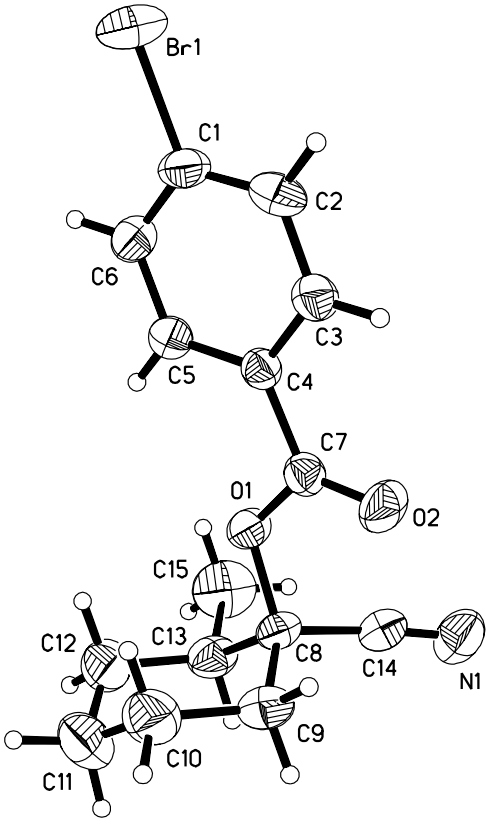


Figure 2. ORTEP view of *cis*-(1*S*,2*R*)-1-(4-bromobenzoyloxy)-2-methylcyclohexanecarbonitrile (*cis*-(1*S*,2*R*)-**2a**′).

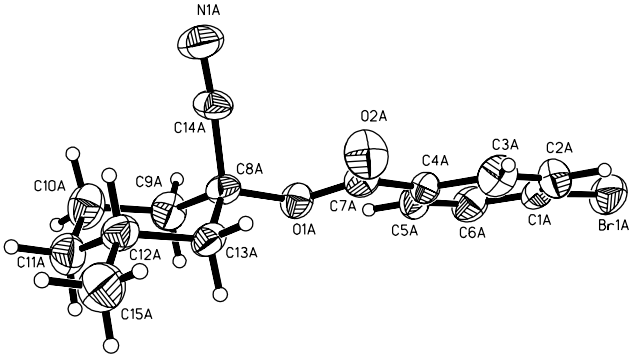


Figure 5. ORTEP view of *cis*-(1*S*,3*R*)-1-(4-bromobenzoyloxy)-3-methylcyclohexanecarbonitrile (*cis*-(1*S*,3*R*)-**7a**′).

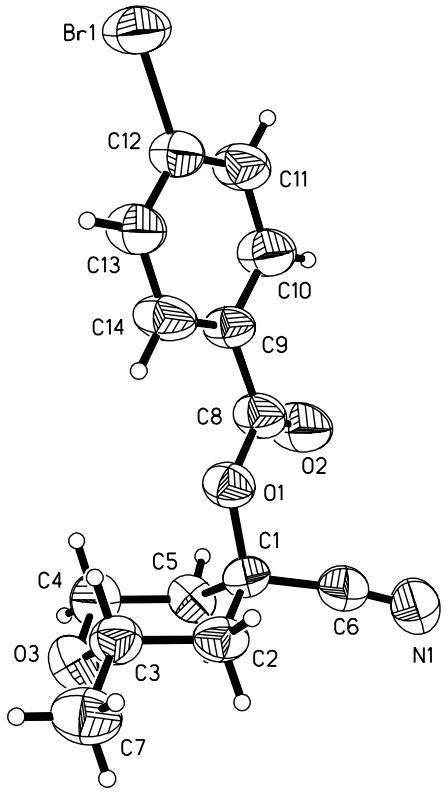


Figure 6. ORTEP view of *trans*-(1*S*,3*S*)-1-(4-bromobenzoyloxy)-3-methylcyclohexanecarbonitrile (*trans*-(1*S*,3*S*)-**7a**′).

2.5. Structural assignment of 2- and 3-substituted cyanohydrins 2, 5 and 7, respectively

Structure determinations were performed on the 2-methyl, the 2-methoxy and the 3-methyl compounds **2a**, **5a** and **7a**, respectively. The *cis*/*trans*-mixtures obtained in the HNL-catalyzed reactions were reacted with *p*-bromobenzoyl chloride to give the corresponding *O*-benzoyl derivatives, which could be separated by column chromatography. After recrystallization, the pure enantiomers *cis*-(1*S*,2*R*)-**2a**′, *trans*-(1*S*,2*S*)-**2a**′, *trans*-(1*R*,2*S*)-**5a**′, *cis*-(1*S*,3*R*)-**7a**′, and *trans*-(1*S*,3*S*)-**7a**′ were obtained as single crystals suitable for X-ray structure determination (Figs. 2–6, Table 9).[17] The absolute configurations were elucidated from diffraction data using anomalous dispersion.

By correlation of GC-data on achiral and chiral phases and analyses of NMR-data, an unambiguous assignment of structures for all the prepared cyanohydrins **2**, **5** and **7** was possible (Section 4). X-ray structure determinations were also performed on the *O*-benzoyl derivatives of the MeHNL-catalyzed reaction products of **7b** and **7c**, respectively.[17]

3. Conclusions

Cyanohydrins of 2- and 3-monosubstituted cyclohexanones contain two stereogenic centers with the implication of four possible stereoisomers. Although derivatives of the corresponding carboxylic acids are applied as pharmaceuticals, stereoselective syntheses of these interesting compounds are not described in the literature. For the enantioselective

Table 9. X-Ray crystal data collection and refinement for *cis*-(1*S*,2*R*)-**2a**′, *trans*-(1*S*,2*S*)-**2a**′, *trans*-(1*R*,2*S*)-**5a**′, *cis*-(1*S*,3*R*)-**7a**′ *trans*-(1*S*,3*S*)-**7a**′

	cis-(1*S*,2*R*)-**2a**′	*trans*-(1*S*,2*S*)-**2a**′	*trans*-(1*R*,2*S*)-**5a**′	*cis*-(1*S*,3*R*)-**7a**′	*trans*-(1*S*,3*S*)-**7a**′
Formula	$C_{15}H_{16}NO_2Br$	$C_{15}H_{16}NO_2Br$	$C_{15}H_{16}NO_3Br$	$C_{15}H_{16}NO_2Br$	$C_{15}H_{16}NO_2Br$
FW	322.18	322.18	338.21	322.18	322.18
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Monoclinic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$
a (Å)	9.764(2)	7.1676(9)	7.303(2)	7.5856(13)	7.115(3)
b (Å)	11.889(3)	7.6999(12)	11.350(3)	7.2175(12)	12.274(5)
c (Å)	12.922(2)	27.057(4)	18.455(4)	27.630(4)	17.334(6)
α (°)	90	90	90	90	90
β (°)	90	90	90	90.809(12)	90
γ (°)	90	90	90	90	90
V (Å^3)	1500.1(5)	1493.3(4)	1529.8(6)	1512.5(4)	1513.7(10)
Z	4	4	4	4	4
ρ_{calc} (mg m^{-3})	1.427	1.433	1.468	1.415	1.414
F(000)	656	656	688	656	656
μ (mm^{-1})	2.738	2.750	2.693	2.715	2.713
θ range (°)	2.33–27.50	1.51–25.99	2.11–26.00	1.47–26.00	2.03–27.49
Data collection[a]					
Reflections collected/unique	13726/3442	6316/2932	1736/1736	3469/3220	2004/2004
Data/restraints/parameters	3238/0/173	2835/0/173	1590/0/182	2928/1/344	1809/0/173
Goodness-of-fit on F^2	1.052	1.039	1.111	1.094	1.100
Final *R* indices					
[$I>2\sigma(I)$]	$R1=0.0433$	$R1=0.0452$	$R1=0.0538$	$R1=0.0549$	$R1=0.0608$
	$wR2=0.0813$	$wR2=0.1031$	$wR2=0.1003$	$wR2=0.0880$	$wR2=0.1060$
R indices (all data)	$R1=0.0749$	$R1=0.0615$	$R1=0.0898$	$R1=0.1018$	$R1=0.1121$
	$wR2=0.0930$	$wR2=0.1149$	$wR2=0.1288$	$wR2=0.1151$	$wR2=0.1294$
Absolute structure parameter	0.006(11)	−0.01(2)	0.02(2)	0.01(2)	0.01(3)
Largest diff.	0.297	0.539	0.360	0.306	0.389
Peak and hole (e Å^{-3})	−0.373	−0.354	−0.285	−0.359	−0.362

[a] $T=293$ K, Nicolet P3 diffractometer, Mo Kα ($l=0.71073$) or Siemens P4 diffractometer, Cu Kα ($l=1.54178$) radiation.

Table 10. Spectroscopic data of the 2- and 3-substituted cyclohexanone cyanohydrins **2**, **5**, and **7**

Compound	^{1}H NMR (250 MHz) (J in Hz) δ	^{13}C NMR (125.8 MHz) δ
rac-**2a**	1.12 (d, ^3J=6.8, 0.7H, *cis*-CH_3), 1.15 (d, ^3J=6.6, 2.3H, *trans*-CH_3), 1.22–1.45 (m, 2H, 2CH), 1.52–1.91 (m, 6H, 6CH), 2.09–2.25 (m, 1H, C^6H_{eq}), 2.55, 2.93 (br s, 1H, OH)	16.01 (*cis*-CH_3), 16.10 (*trans*-CH_3), 19.97 (*cis*-C^5H_2), 23.62 (*trans*-C^5H_2), 24.28 (*cis*-C^4H_2), 24.80 (*trans*-C^4H_2), 28.21 (*cis*-C^3H_2), 31.68 (*trans*-C^3H_2), 37.05 (*cis*-C^6H_2), 38.62 (*trans*-C^6H_2), 39.19 (*cis*-C^2H), 41.65 (*trans*-C^2H), 70.77 (*cis*-C^1), 74.84 (*trans*-C^1), 120.21 (*trans*-CN), 122.51 (*cis*-CN)
rac-**2b**	0.97 (t, ^3J=7.4, 2.3H, *trans*-CH_2CH_3), 0.98 (t, ^3J=7.3, 0.7H, *cis*-CH_2CH_3), 1.11–1.44 (m, 4H, 4CH), 1.53–2.02 (m, 6H, 6CH), 2.08–2.24 (m, 1H, C^6H_{eq}), 2.62 and 3.03 (br s, 1H, OH)	11.59 (*trans*-CH_2CH_3), 11.86 (*cis*-CH_2CH_3), 20.24 (*cis*-C^5H_2), 22.85 (*trans*-C^5H_2), 23.29 (*cis*-CH_2CH_3), 23.44 (*trans*-CH_2CH_3), 24.18, 24.66, 24.71, 27.81 (C^4H_2), (C^3H_2), 37.49 (*cis*-C^6H_2), 39.08 (*trans*-C^6H_2), 45.99 (*cis*-C^2H), 48.33 (*trans*-C^2H), 71.40 (*cis*-C^1), 74.20 (*trans*-C^1), 120.50 (*trans*-CN), 122.66 (*cis*-CN)
rac-**2c**	0.94 (t, ^3J=7.1, 2.3H, *trans*-CH_2CH_3), 0.95 (t, ^3J=7.0, 0.7H, *cis*-$CH_2CH_2CH_3$), 1.12–1.36 (m, 4H, 1CH, $CH_2CH_2CH_3$, $CH_AHCH_2CH_3$), 1.41–1.98 (m, 8H, 7CH, $CH_BCH_2CH_3$), 2.09–2.27 (m, 1H, $1C^6H_{eq}$), 2.55 and 2.95 (br s, 1H, OH)	14.12 (*cis*-$CH_2CH_2CH_3$), 14.20 (*trans*-$CH_2CH_2CH_3$), 20.19 ($CH_2CH_2CH_3$), 20.35 (*cis*-C^5H_2), 23.41 (*trans*-C^5H_2), 24.22 (*cis*-C^4H_2), 24.73 (*trans*-C^4H_2), 25.29 (*cis*-C^3H_2), 28.42 (*trans*-C^3H_2), 32.24 (*trans*-$CH_2CH_2CH_3$), 32.59 (*cis*-$CH_2CH_2CH_3$), 37.49 (*cis*-C^6H_2), 39.04 (*trans*-C^6H_2), 43.97 (*cis*-C^2H), 46.41 (*trans*-C^2H), 71.44 (*cis*-C^1), 74.20 (*trans*-C^1), 120.52 (*trans*-CN), 122.64 (*cis*-CN)
rac-**2d**	0.97–1.04 (m, 6H, $CH(CH_3)_2$), 1.18–1.90 (m, 8H, 8CH), 2.02 (br s, 0.3H, OH), 2.09–2.26 (m, 2H, C^6H_{eq}, 1CH), 2.47 (br s, 0.7H, OH)	17.45, 18.67, 23.23, 23.32 ($CH(CH_3)_2$)*), 20.13, 20.26, 23.65, 23.90, 25.28, 25.33 (C^5H_2), (C^4H_2), (C^3H_2), 26.29, 29.71 ($CH(CH_3)_2$), 39.71 (*cis*-C^6H_2), 41.07 (*trans*-C^6H_2), 49.42 (*cis*-C^2H), 52.36 (*trans*-C^2H), 71.20 (*cis*-C^1), 72.53 (*trans*-C^1), 121.23 (*trans*-CN), 121.69 (*cis*-CN)*) rotamers
rac-**2e**	1.11–1.40 (m, 2H, 2CH), 1.53–1.92 (m, 6H, 6CH), 2.03–2.36 (m, 2H, 2CH), 2.47–2.73 (m, 1H, 1CH), 3.19 (br s, 1H, OH), 5.06–5.28 (m, 2H, $CH_2CH{=}CH_2$), 5.74–5.97 (m, 1H, $CH_2CH{=}CH_2$)	20.15 (*cis*-C^5H_2), 23.29 (*trans*-C^5H_2), 24.23 (*cis*-C^4H_2), 24.75 (*trans*-C^4H_2), 25.03 (*cis*-C^3H_2), 29.20 (*trans*-C^3H_2), 35.36 (*cis*-$CH_2CH{=}CH_2$), 36.19 (*trans*-$CH_2CH{=}CH_2$), 37.59 (*cis*-C^6H_2), 38.80 (*trans*-C^6H_2), 43.97 (*cis*-C^2H), 46.38 (*trans*-C^2H), 71.17 (*cis*-C^1), 74.68 (*trans*-C^1), 117.62 (*cis*-$CH_2CH{=}CH_2$), 117.79 (*trans*-$CH_2CH{=}CH_2$), 120.21 (*trans*-CN), 122.35 (*cis*-CN), 136.00 (*cis*-$CH_2CH{=}CH_2$), 136.86 (*trans*-$CH_2CH{=}CH_2$)
rac-**2f**	0.91 (t, ^3J=7.1, 2H, *trans*-$CH_2CH_2CH_2CH_3$), 0.92 (t, ^3J=7.0, 1H, *cis*-$CH_2CH_2CH_2CH_3$), 1.11–1.47 (m, 7H, 3CH, $CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$), 1.52–1.95 (m, 7H, 7CH), 2.09–2.23 (m, 1H, C^6H_{eq}), 2.45 and 2.90 (br s, 1H, OH)	14.00 (*cis*-$CH_2CH_2CH_2CH_3$), 14.03 (*trans*-$CH_2CH_2CH_2CH_3$), 20.21 (*cis*-C^5H_2), 22.74 (*trans*-C^5H_2), 22.83, 23.42 ($CH_2CH_2CH_2CH_3$), 24.24 (*cis*-C^4H_2), 24.74 (*trans*-C^4H_2), 25.31 (*cis*-C^3H_2), 28.45 (*trans*-C^3H_2), 29.23, 29.40, 29.73, 30.12 ($CH_2CH_2CH_2CH_3$), ($CH_2CH_2CH_2CH_3$), 37.50 (*cis*-C^6H_2), 39.05 (*trans*-C^6H_2), 44.19 (*cis*-C^2H), 46.66 (*trans*-C^2H), 71.47 (*cis*-C^1), 74.23 (*trans*-C^1), 120.50 (*trans*-CN), 122.61 (*cis*-CN)
rac-**5a**	1.19–1.97 (m, 6H, 6CH), 2.14–2.26 (m, 2H, C^6H_{ax}, C^6H_{eq}), 3.13 (dd, ^3J (C^2H_{ax}, C^3H_{eq})=4.1 Hz, ^3J (C^2H_{ax}, C^3H_{ax})=11.0, 0.6H, *trans*-C^2H_{ax}), 3.39 (dd, ^3J (C^2H_{ax}, C^3H_{eq})=4.4, ^3J (C^2H_{ax}, C^3H_{ax})=10.1, 0.4H, *cis*-C^2H_{ax}), 3.46 and 3.52 (s, 3H, OCH_3), 3.70 (br s, 1H, OH)	19.59 (*cis*-C^5H_2), 22.38 (C^4H_2), 23.24 (*trans*-C^5H_2), 25.19 (*cis*-C^3H_2), 26.85 (*trans*-C^3H_2), 35.01 (*cis*-C^6H_2), 35.40 (*trans*-C^6H_2), 56.88 (*trans*-OCH_3), 57.60 (*cis*-OCH_3), 69.94 (*cis*-C^1), 73.92 (*trans*-C^1), 81.18 (*cis*-C^2H), 84.24 (*trans*-C^2H), 119.75 (*trans*-CN), 121.79 (*cis*-CN)
rac-**5b**	1.22–1.96 (m, 6H, 6CH), 1.25 (t, ^3J=7.0, 3H, OCH_2CH_3), 2.10–2.25 (m, 2H, C^6H_{ax}, C^6H_{eq}), 3.21 (dd, ^3J (C^2H_{ax}, C^3H_{eq})=4.2, ^3J (C^2H_{ax}, C^3H_{ax})=11.1, 0.5H, C^2H_{ax}), 3.40–3.52 (m, 0.5H, C^2H_{ax}), 3.62–3.83 (m, 3H, OCH_2CH_3, OH)	15.38 (OCH_2CH_3), 15.47 (OCH_2CH_3), 19.54 (C^5H_2), 22.39 (C^4H_2), 22.58 (C^4H_2), 23.37 (C^5H_2), 26.12 (C^3H_2), 27.68 (C^3H_2), 35.02 (C^6H_2), 35.34 (C^6H_2), 64.62 (OCH_2CH_3), 65.64 (OCH_2CH_3), 70.10 (C^1), 73.91 (C^1), 79.38 (C^2H), 82.61 (C^2H), 119.87 (CN), 121.91 (CN)
rac-**5c**	0.95 (t, ^3J=7.4, 1.5H, $OCH_2CH_2CH_3$), 0.96 (t, ^3J=7.4, 1.5H, $OCH_2CH_2CH_3$), 1.21–1.31 (m, 1H, $OCH_2CH_2CH_3$), 1.42–1.90(m, 7H, 6CH, $OCH_2CH_2CH_3$), 2.09–2.24 (m, 2H, C^6H_{ax}, C^6H_{eq}), 3.19 (dd, ^3J (C^2H_{ax}, C^3H_{eq})=4.2, ^3J (C^2H_{ax}, C^3H_{ax})=11.3, 0.5H, C^2H_{ax}), 3.23 (bs, 0.5H, OH), 3.33–3.38 (m, 0.5H, $OCH_AHCH_2CH_3$), 3.46 (dd, ^3J (C^2H_{ax}, C^3H_{eq})=4.5, ^3J (C^2H_{ax}, C^3H_{ax})=10.2, 0.5H, C^2H_{ax}), 3.55–3.66 (m, 2H, $OCH_AHCH_2CH_3$, OH, $OCH_BCH_2CH_3$)	10.53 ($OCH_2CH_2CH_3$), 19.60, 22.39, 22.51, 23.08, 23.17, 23.34 (C^5H_2), (C^4H_2), ($OCH_2CH_2CH_3$), 26.02 (*cis*-C^3H_2), 27.58 (*trans*-C^3H_2), 35.01 (*cis*-C^6H_2), 35.31 (*trans*-C^6H_2), 70.12 (*trans*-$OCH_2CH_2CH_3$), 70.82 (*cis*-$OCH_2CH_2CH_3$), 71.83 (*cis*-C^1), 74.03 (*trans*-C^1), 79.54 (*cis*-C^2H), 82.73 (*trans*-C^2H), 119.85 (*trans*-CN), 121.88 (*cis*-CN)
rac-**5d**	1.17–1.24 (m, 6H, $OCH(CH_3)_2$), 1.42–1.83 (m, 6H, 6CH), 2.02–2.09 (m, 1H, C^6H_{ax}, C^6H_{eq}), 2.25–2.35 (m, 1H, C^6H_{ax}, C^6H_{eq}), 3.22–3.28 (br s, 0.5H, OH), 3.24 (dd, ^3J (C^2H_{ax}, C^3H_{eq})=4.1 Hz, ^3J (C^2H_{ax}, C^3H_{ax})=10.8, 0.5H, C^2H_{ax}), 3.51 (dd, ^3J (C^2H_{ax}, C^3H_{eq})=4.2 Hz, ^3J (C^2H_{ax}, C^3H_{ax})=10.2, 0.5H, C^2H_{ax}), 3.60 (br s, 0.5H, OH), 3.78 (sept, ^3J=6.1, 0.4H, *trans*-$OCH(CH_3)_2$), 3.91 (sept, ^3J=5.9, 0.6H, *cis*-$OCH(CH_3)_2$)	19.42, 21.87, 22.31, 22.38, 22.82, 23.09, 23.41, 23.54 (C^5H_2), (C^4H_2), ($OCH(CH_3)_2$)*), 27.19 (*cis*-C^3H_2), 28.54 (*trans*-C^3H_2), 35.01 (*cis*-C^6H_2), 35.28 (*trans*-C^6H_2), 70.08 (*trans*-$OCH(CH_3)_2$), 70.35 (*cis*-$OCH(CH_3)_2$), 71.66 (*cis*-C^1), 73.94 (*trans*-C^1), 77.26 (*cis*-C^2H), 80.33 (*trans*-C^2H), 119.95 (*trans*-CN), 122.01 (*cis*-CN)*) rotamers
rac-**5e**	1.43–1.88 (m, 6H, 6CH), 2.09–2.14 (m, 1H, CH), 2.21–2.27 (m, 1H, CH), 3.21 (br s, 0.5H, OH), 3.25–3.29 (m, 0.5H, C^2H_{ax}), 3.52–3.55 (m, 0.5H, C^2H_{ax}), 3.63 (br s, 0.5H, OH), 3.99–4.03 (m, 0.5H, $OCH_AHCH{=}CH_2$), 4.15–4.25 (m, 1.5H, $OCH_AHCH{=}CH_2$, $OCH_BCH{=}CH_2$), 5.22-5.24 (m, 1H, $OCH_2CH{=}CH_AH$), 5.30–5.34 (m, 1H, $OCH_2CH{=}CH_BH$), 5.88–5.98 (m, 1H, $OCH_2CH{=}CH_2$)	19.53, 22.37, 22.55, 23.33 (C^5H_2), (C^4H_2), 26.09 (*cis*-C^3H_2), 27.70 (*trans*-C^3H_2), 35.08 (*cis*-C^6H_2), 35.44 (*trans*-C^6H_2), 70.05, 70.87 ($OCH_2CH{=}CH_2$), 70.13 (*cis*-C^1), 73.95 (*trans*-C^1), 78.75 (*cis*-C^2H), 82.11 (*trans*-C^2H), 117.88, 118.02 ($OCH_2CH{=}CH_2$), 119.76 (*trans*-CN), 121.81 (*cis*-CN), 134.14, 134.21 ($OCH_2CH{=}CH_2$)
rac-**7a**	0.82–1.04 (m, 1H, CH), 0.92 (d, ^3J=6.4 Hz, 0.5H, *trans*-CH_3), 0.98 (d, ^3J=6.3 Hz, 2.5H, *cis*-CH_3), 1.16–1.26 (m, 1H, CH), 1.38–1.90 (m, 5H, 5CH), 2.06–2.21 (m, 2H, C^2H_{eq}, C^6H_{eq}), 3.14 (br s, 1H, OH)	19.89 (*trans*-C^5H_2), 21.64 (*cis*-C^5H_2), 21.80 (*trans*-CH_3), 22.91 (*cis*-CH_3), 26.25 (*trans*-C^3H), 30.14 (*cis*-C^3H), 33.19 (*trans*-C^4H_2), 33.39 (*cis*-C^4H_2), 36.21 (*trans*-C^6H_2), 37.78 (*cis*-C^6H_2), 44.48 (*trans*-C^2H_2), 46.15 (*cis*-C^2H_2), 67.25 (*trans*-C^1), 70.54 (*cis*-C^1), 121.89 (*cis*-CN), 122.95 (*trans*-CN)

Table 10 (*continued*)

Compound	^{1}H NMR (250 MHz) (J in Hz) δ	^{13}C NMR (125.8 MHz) δ
rac-**7b**	1.22–1.38 (m, 1H, CH), 1.45–1.81 (m, 3H, 3CH), 1.95–2.03 (m, 2H, 2CH), 2.13–2.16 (m, 0.4H, *trans*-CH), 2.23–2.27 (m, 0.6H, *cis*-CH), 2.32–2.56 (m, 2H, CH, C^3H_{ax}), 3.09 (br s, 1H, *trans*-OH), 3.40 (br s, 1H, *cis*-OH)	18.45 (s, *trans*-CH_2), 21.51 (s, *cis*-CH_2), 23.38 (q, ^3J(C,F)=2.0 Hz, *cis*-C^4H_2), 23.46 (q, ^3J(C,F)=2.1 Hz, *trans*-C^4H_2), 34.93 (q, ^3J(C,F)=2.2 Hz, *trans*-C^2H_2), 35.80 (s, *cis*-C^2H_2), 36.30 (q, ^2J(C,F)=27.7 Hz, *trans*-C^3H), 36.62 (q, ^3J(C,F)=2.5 Hz, *trans*-CH_2), 37.39 (s, *cis*-CH_2), 39.87 (q, ^2J(C,F)=27.9 Hz, *cis*-C^3H), 65.98 (*trans*-C^1), 69.47 (*cis*-C^1), 120.61 (*cis*-CN), 121.78 (*trans*-CN), 126.55 (q, ^1J(C,F)=278.4 Hz, *cis*-CF_3), 127.11 (q, ^1J(C,F)=278.3 Hz, *trans*-CF_3)
rac-**7c**	1.52–1.70 (m, 3H, 3CH), 1.85–2.08 (m, 4H, 4CH), 2.17–2.20 (m, 1H, *cis*-CH), 3.37 (s, 3H, *cis*-OCH_3), 3.58–3.63 (m, 1H, *cis*-C^3H_{ax}), 4.35 (br s, 1H, OH)	16.69 (*cis*-C^5H_2), 28.22 (*cis*-C^4H_2), 37.21 (*cis*-C^2H_2), 40.61 (*cis*-C^6H_2), 56.46 (*cis*-OCH_3), 68.50 (*cis*-C^1), 75.86 (*cis*-C^3H), 121.84 (*cis*-CN)

Table 11. Spectroscopic data of the racemic silylated 2-substituted cyclohexanone cyanohydrins **3**

Compound	^{1}H NMR (500 MHz) (J in Hz) δ	^{13}C NMR (125.8 MHz) δ
rac-**3a**	0.24 (s, 6.8H, *trans*-$Si(CH_3)_3$), 0.25 (s, 2.2H, *cis*-$Si(CH_3)_3$), 1.03 (d, ^3J=6.7, 0.8H, *cis*-CH_3), 1.08 (d, ^3J=6.5, 2.2H, *trans*-CH_3), 1.18–1.42 (m, 2H, 2CH); 1.50–1.85 (m, 6H, 6CH); 2.06–2.22 (m, 1H, C^6H_{eq})	1.08 (*cis*-$Si(CH_3)_3$), 1.42 (*trans*-$Si(CH_3)_3$), 16.40 (CH_3), 20.15 (*cis*-C^5H_2), 23.72 (*trans*-C^5H_2), 24.45 (*cis*-C^4H_2), 24.87 (*trans*-C^4H_2), 28.26 (*cis*-C^3H_2), 31.50 (*trans*-C^3H_2), 38.14 (*cis*-C^6H_2), 39.70 (*trans*-C^6H_2), 40.81 (*cis*-C^2H), 43.13 (*trans*-C^2H), 71.60 (*cis*-C^1), 75.98 (*trans*-C^1), 120.17 (*trans*-CN), 122.45 (*cis*-CN)
rac-**3b**	0.24 (s, 9H, $Si(CH_3)_3$), 0.93 (t, ^3J=7.3, 3H, CH_2CH_3), 1.03–1.36 (m, 4H, 4CH), 1.48–1.83 (m, 4H, 4CH), 1.85–2.03 (m, 2H, 2CH), 2.06–2.12 (m, 0.25H, *cis*-C^6H_{eq}), 2.15–2.20 (m, 0.75H, *trans*-C^6H_{eq})	1.12 (*cis*-$Si(CH_3)_3$), 1.46 (*trans*-$Si(CH_3)_3$), 11.71 (CH_2CH_3), 20.47 (*cis*-C^5H_2), 22.92, 23.47, 23.56 ((*trans*-C^5H_2), (CH_2CH_3)), 24.26 (*cis*-C^4H_2), 24.63 (*cis*-C^4H_2), 24.79 (*trans*-C^5H_2), 27.70 (*trans*-C^3H_2), 38.46 (*cis*-C^6H_2), 39.99 (*trans*-C^6H_2), 47.57 (*cis*-C^2H), 49.81 (*trans*-C^2H), 72.25 (*cis*-C^1), 75.50 (*trans*-C^1), 120.49 (*trans*-CN), 122.71 (*cis*-CN)
rac-**3c**	0.24 (s, 9H, $Si(CH_3)_3$), 0.91 (t, ^3J=7.0, 3H, $CH_2CH_2CH_3$), 1.10–1.31 (m, 4H, $CH_2CH_2CH_3$, 2CH), 1.36–1.92 (m, 8H, $CH_2CH_2CH_3$, 6CH), 2.03–2.12 (m, 0.25H, *cis*-C^6H_{eq}), 2.15–2.20 (m, 0.75H, *trans*-C^6H_{eq})	1.18 (*cis*-$Si(CH_3)_3$), 1.51 (*trans*-$Si(CH_3)_3$), 14.24 (*cis*-($CH_2CH_2CH_3$)), 14.31 (*trans*-($CH_2CH_2CH_3$)), 20.24 (*cis*-($CH_2CH_2CH_3$)), 20.32 (*trans*-($CH_2CH_2CH_3$)), 20.50 (*cis*-C^5H_2), 23.58 (*trans*-C^5H_2), 24.34 (*cis*-C^4H_2), 24.85 (*trans*-C^4H_2), 25.32 (*cis*-C^3H_2), 28.45 (*trans*-C^3H_2), 32.48 (*trans*-($CH_2CH_2CH_3$)), 32.86 (*cis*-($CH_2CH_2CH_3$)), 38.52 (*cis*-C^6H_2), 40.01 (*trans*-C^6H_2), 45.56 (*cis*-C^2H), 47.84 (*trans*-C^2H), 72.35 (*cis*-C^1), 75.55 (*trans*-C^1), 120.59 (*trans*-CN), 122.76 (*cis*-CN)
rac-**3d**	0.24 (s, 5.8H, *trans*-$Si(CH_3)_3$), 0.25 (s, 3.2H, *cis*-$Si(CH_3)_3$), 0.90–0.99 (m, 6H, $CH(CH_3)_2$)), 1.13–1.61 (m, 6H, 6CH), 1.69–1.83 (m, 2H, 2CH), 2.05–2.34 (m, 2H, C^6H_{eq}, $CH(CH_3)_2$)	1.16 (*cis*-$Si(CH_3)_3$), 1.52 (*trans*-$Si(CH_3)_3$), 17.11, 18.20, 23.40, 23.51 ($CH(CH_3)_2^*$)), 20.22, 20.35, 23.55, 23.77, 25.38, 25.46, (C^5H_2, C^4H_2, C^3H_2), 25.83, 29.85 ($CH(CH_3)_2$), 39.77 (*cis*-C^6H_2), 41.08 (*trans*-C^6H_2), 51.01 (*cis*-C^2H), 53.71 (*trans*-C^2H), 73.52 (*cis*-C^1), 73.80 (*trans*-C^1), 121.38 (*trans*-CN), 122.86 (*cis*-CN)*) rotamers
rac-**3e**	0.24 (s, 6.8H, *trans*-$Si(CH_3)_3$), 0.25 (s, 2.2H, *cis*-$Si(CH_3)_3$), 1.11–1.36 (m, 2H, 2CH), 1.43–2.22 (m, 8H, 6CH, $CH_2CH{=}CH_2$), 2.43–2.51 (m, 0.25H, *cis*-C^6H_{eq}), 2.65–2.76 (m, 0.75H, *trans*-C^6H_{eq}), 5.01–5.10 (m, 2H, $CH_2CH{=}CH_2$), 5.65–5.85 (m, 1H, $CH_2CH{=}CH_2$)	1.13 (*cis*-$Si(CH_3)_3$), 1.45 (*trans*-$Si(CH_3)_3$), 20.42 (*cis*-C^5H_2), 23.63 (*trans*-C^5H_2), 24.13 (*cis*-C^4H_2), 24.74 (*trans*-C^4H_2), 25.04 (*cis*-C^3H_2), 28.46 (*trans*-C^3H_2), 34.89 (*trans*-$CH_2CH{=}CH_2$), 35.35 (*cis*-$CH_2CH{=}CH_2$), 38.35 (*cis*-C^6H_2), 39.97 (*trans*-C^6H_2), 45.63 (*cis*-C^2H), 47.90 (*trans*-C^2H), 71.87 (*cis*-C^1), 75.14 (*trans*-C^1), 116.64 ($CH_2CH{=}CH_2$), 120.21 (*trans*-CN), 122.42 (*cis*-CN), 136.42 (*cis*-$CH_2CH{=}CH_2$), 136.48 (*trans*-$CH_2CH{=}CH_2$)
rac-**3f**	0.23 (s, 6.7H, *trans*-$Si(CH_3)_3$), 0.24 (s, 2.3H, *cis*-$Si(CH_3)_3$), 0.90 (t, ^3J=7.0, 3H, $CH_2CH_2CH_2CH_3$), 1.06–1.44 (m, 8H, $CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, 4CH), 1.48–1.94 (m, 6H, $CH_2CH_2CH_2CH_3$, 4CH), 2.01–2.12 (m, 0.25H, *cis*-C^6H_{eq}), 2.15-2.20 (m, 0.75H, *trans*-C^6H_{eq})	1.18 (*cis*-$Si(CH_3)_3$), 1.51 (*trans*-$Si(CH_3)_3$), 13.99 (*trans*-$CH_2CH_2CH_2CH_3$), 14.05 (*cis*-$CH_2CH_2CH_2CH_3$), 20.47 (*cis*-C^5H_2), 22.79 ($CH_2CH_2CH_2CH_3$), 23.55 (*trans*-C^5H_2), 24.27 (*cis*-C^4H_2), 24.82 (*trans*-C^4H_2), 25.30 (*cis*-C^3H_2), 28.43 (*trans*-C^3H_2), 29.31, 29.79 ($CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$), 38.45 (*cis*-C^6H_2), 39.98 (*trans*-C^6H_2), 45.71 (*cis*-C^2H), 48.00 (*trans*-C^2H), 72.32 (*cis*-C^1), 75.51 (*trans*-C^1), 120.55 (*trans*-CN), 122.72 (*cis*-CN)
rac-**3g**	0.25 (s, 4.5H, $Si(CH_3)_3$), 0.27 (s, 4.5H, $Si(CH_3)_3$), 1.06 (s, 4.5H, $C(CH_3)_3$), 1.07 (s, 4.5H, $C(CH_3)_3$), 1.14–1.94 (m, 8H, 8CH), 2.13–2.25 (m, 1H, 1CH)	1.48, 1.87 ($Si(CH_3)_3$), 20.71, 23.08 (C^5H_2), 24.08, 25.92, 26.00, 26.06 (C^4H_2, C^3H_2), 29.56, 30.08 ($C(CH_3)_3$), 34.15, 34.52 ($C(CH_3)_3$), 42.71, 43.40 (C^6H_2), 53.56, 56.63 (C^2H), 71.24, 75.75 (C^1), 121.64, 124.65 (CN)

preparation of optically active cyanohydrins, hydroxynitrile lyases (HNLs) are excellent biocatalysts. With (*R*)-PaHNL from bitter almonds, (*R*)-selective addition of HCN to 2- as well as 3-substituted cyclohexanones is possible, enabling specifically the preparation of two diastereomers which can be separated by column chromatography after *O*-acylation. With the enzyme (*S*)-MeHNL from cassava, the complementary two diastereomers can be synthesized and separated analogously. Increasing bulkiness of the substituents in the 2- as well as in the 3-position diminishes the catalytic activity of both enzymes.

4. Experimental

4.1. Materials and methods

Melting points were determined on a Büchi SMP-20 and are

Table 12. Spectroscopic data of the acetylated 2- and 3-substituted cyclohexanone cyanohydrins **5″**, and **7″**

Compound	^{1}H NMR (250 Hz) (J in Hz) δ	^{13}C NMR (62.9 MHz) δ
rac-**5a″**	1.29–1.37 (m, 0.5H, CH), 1.39–1.45 (m, 0.5H, CH), 1.53–1.96 (m, 6H, 6CH), 2.13, 2.15 (s, 3H, OCOCH_3), 2.36–2.40 (m, 0.5H, C^{6}H$_{eq}$), 2.54–2.59 (m, 0.5H, C^{6}H$_{eq}$), 3.45, 3.51 (s, 3H, OCH_3), 3.52–3.55 (m, 0.5H, C^{2}H$_{ax}$), 3.59–3.81 (m, 0.5H, C^{2}H$_{ax}$)	20.24, 21.12, 21.26, 21.35 (C^{5}H$_2$), (C^{4}H$_2$), (OCOCH$_3$), 26.09 (*cis*-C^{3}H$_2$), 26.75 (*trans*-C^{3}H$_2$), 31.01 (*cis*-C^{6}H$_2$), 32.02 (*trans*-C^{6}H$_2$), 56.26 (*cis*-OCH$_3$), 58.58 (*trans*-OCH$_3$), 74.30 (*cis*-C^1), 76.34 (*trans*-C^1), 78.93 (*cis*-C^{2}H), 79.90 (*trans*-C^{2}H), 116.85 (*trans*-CN), 117.89 (*cis*-CN), 168.62 (*trans*-OCOCH$_3$), 168.95 (*cis*-OCOCH$_3$)
rac-**5b″**	1.21 (t, ^3J=7.0 Hz, 1.5H, *cis*-OCH$_2$CH$_3$), 1.23 (t, ^3J=7.0 Hz, 1.5H, *trans*-OCH$_2$CH$_3$), 1.26–1.97 (m, 7H, 7CH), 2.13 (s, 1.5H, *cis*-OCOCH_3), 2.15 (s, 1.5H, *trans*-OCOCH_3), 2.35–2.49 (m, 0.5H, C^{6}H$_{eq}$), 2.51–2.60 (m, 0.5H, C^{6}H$_{eq}$), 3.52–3.73 (m, 2.5H, OCH_2CH$_3$, C^{2}H), 3.87–3.91 (m, 0.5H, C^{2}H)	15.51, 15.53 (OCH$_2$CH$_3$), 20.39, 21.11, 21.22 (C^{5}H$_2$), (C^{4}H$_2$), 21.14, 21.24 (OCOCH$_3$), 27.06 (*cis*-C^{3}H$_2$), 27.48 (*trans*-C^{3}H$_2$), 31.05 (*cis*-C^{6}H$_2$), 31.85 (*trans*-C^{6}H$_2$), 66.24 (*cis*-OCH$_2$CH$_3$), 66.58 (*trans*-OCH$_2$CH$_3$), 74.37 (*cis*-C^1), 76.18 (*trans*-C^1), 77.08 (*cis*-C^{2}H), 77.75 (*trans*-C^{2}H), 117.09 (*trans*-CN), 118.04 (*cis*-CN), 168.63 (*trans*-OCOCH$_3$), 169.01 (*cis*-OCOCH$_3$)
rac-**5c″**	0.93 (t, ^3J=7.4 Hz, 1.8H, *cis*-OCH$_2$CH$_2$CH$_3$), 0.95 (t, ^3J=7.4 Hz, 1.2H, *trans*-OCH$_2$CH$_2$CH$_3$), 1.25–1.99 (m, 9H, 7CH, OCH$_2$CH$_2$CH$_3$), 2.13 (s, 1.8H, *cis*-OCOCH_3), 2.14 (s, 1.2H, *trans*-OCOCH_3), 2.30–2.41 (m, 0.6H, *cis*-C^{6}H$_{eq}$), 2.48–2.58 (m, 0.4H, *trans*-C^{6}H$_{eq}$), 3.40–3.66 (m, 2.5H, OCH_2CH$_2$CH$_3$, C^{2}H), 3.90–4.00 (m, 0.5H, C^{2}H)	10.59 (OCH$_2$CH$_2$CH$_3$), 20.11, 21.08, 21.26, 23.20 (C^{5}H$_2$), (C^{4}H$_2$), (OCH$_2$CH$_2$CH$_3$), 21.14, 21.23 (OCOCH$_3$), 26.90 (*cis*-C^{3}H$_2$), 27.18 (*trans*-C^{3}H$_2$), 30.93 (*cis*-C^{6}H$_2$), 31.79 (*trans*-C^{6}H$_2$), 72.42 (*cis*-OCH$_2$CH$_2$CH$_3$), 72.77 (*trans*-OCH$_2$CH$_2$CH$_3$), 74.47 (C^1), 76.94 (*cis*-C^{2}H), 77.83 (*trans*-C^{2}H), 117.14 (*trans*-CN), 118.01 (*cis*-CN), 168.62 (*trans*-OCOCH$_3$), 169.02 (*cis*-OCOCH$_3$)
rac-**5d″**	1.16, 1.17, 1.22 (d*), $^3J_{d1}$=$^3J_{d2}$=$^3J_{d3}$= 6.1 Hz, 3H, OCH(CH_3)$_2$), 1.24–1.97 (m, 7H, 7CH), 2.12 (s, 1.5H, OCOCH_3), 2.14 (s, 1.5H, OCOCH_3), 2.32–2.43 (m, 0.6H, *cis*-C^{6}H$_{eq}$), 2.46–2.56 (m, 0.4H, *trans*-C^{6}H$_{eq}$), 3.69–3.88 (m, 1.5H, OCH(CH$_3$)$_2$, C^{2}H), 3.90–3.98 (m, 0.5H, C^{2}H)*) rotamers	20.31, 20.98, 21.08, 21.16, 22.35, 22.43, 22.86, 22.95 (C^{5}H$_2$), (C^{4}H$_2$), (OCOCH$_3$), (OCH(CH_3)$_2$)*), 28.16 (*cis*-C^{3}H$_2$), 28.36 (*trans*-C^{3}H$_2$), 30.87 (*cis*-C^{6}H$_2$), 31.72 (*trans*-C^{6}H$_2$), 72.32 (*cis*-OCH(CH$_3$)$_2$), 72.68 (*trans*-OCH(CH$_3$)$_2$), 74.52, 75.08, 75.52, 76.08 (C^1), (C^{2}H), 117.28 (*trans*-CN), 118.11 (*cis*-CN), 168.63 (*trans*-OCOCH$_3$), 169.05 (*cis*-OCOCH$_3$)*) rotamers
rac-**5e″**	1.29–2.00 (m, 7H, 7CH), 2.13 (s, 1.8H, *cis*-OCOCH_3), 2.14 (s, 1.2H, *trans*-OCOCH_3), 2.36–2.45 (m, 0.6H, *cis*-C^{6}H$_{eq}$), 2.53–2.63 (m, 0.4H, *trans*-C^{6}H$_{eq}$), 3.66–3.71 (m, 0.5H, C^{2}H), 3.94–4.21 (m, 2.5H, C^{2}H, OCH_2CH=CH$_2$), 5.17–5.37 (m, 2H, OCH$_2$CH=CH_2), 5.83–6.00 (m, 1H, OCH$_2$CH=CH$_2$)	20.27, 21.10, 21.15, 21.24, 21.34 (C^{5}H$_2$), (C^{4}H$_2$), (OCOCH$_3$), 27.00 (*cis*-C^{3}H$_2$), 27.51 (*trans*-C^{3}H$_2$), 30.99 (*cis*-C^{6}H$_2$), 31.99 (*trans*-C^{6}H$_2$), 71.57, 71.85 (OCH$_2$CH=CH$_2$), 74.36 (*cis*-C^1), 76.27 (*trans*-C^1), 77.31 (C^{2}H), 116.92 (*trans*-CN), 117.28 (*cis*-OCH$_2$CH=CH$_2$), 117.52 (*trans*-OCH$_2$CH=CH$_2$), 117.91 (*cis*-CN), 134.38 (*trans*-OCH$_2$CH=CH$_2$), 134.57 (*cis*-OCH$_2$CH=CH$_2$), 168.59 (*trans*-OCOCH$_3$), 168.96 (*cis*-OCOCH$_3$)
rac-**7c″**	1.13–1.30 (m, 1H, 1CH), 1.52–2.02 (m, 4H, 4CH), 2.06–2.13 (m, 1H, 1CH), 2.11 (s, 3H, *cis*-OCOCH$_3$), 2.41–2.48 (m, 1H, *cis*-CH), 2.74–2.82 (m, 1H, *cis*-C^{2}H$_{eq}$), 3.33–3.51 (m, 1H, *cis*-C^{3}H$_{ax}$), 3.37 (s, 3H, OCH$_3$)	19.07 (*cis*-C^{5}H$_2$), 21.12 (OCOCH$_3$), 30.45 (*cis*-C^{4}H$_2$), 34.88 (*cis*-C^{2}H$_2$), 39.76 (*cis*-C^{6}H$_2$), 56.38 (*cis*-OCH$_3$), 72.12 (*cis*-C^1), 75.39 (*cis*-C^{3}H), 118.06 (*cis*-CN), 168.75 (OCOCH$_3$)

Table 13. Elemental analysis of racemic silylated cyanohydrins **3** and racemic acetylated cyanohydrins **5″** and **7″**

Compound	Mol. formula (Mol. weight)	Calcd/found			
		C	H	N	O
rac-**3a**	$C_{11}H_{21}NOSi$ (211.38)	62.50	10.01	6.63	7.57
		62.49	10.06	6.57	
rac-**3b**	$C_{12}H_{23}NOSi$ (225.41)	63.94	10.28	6.21	7.10
		63.85	10.16	6.31	
rac-**3c**	$C_{13}H_{25}NOSi$ (239.43)	65.21	10.52	5.85	6.68
		65.24	10.60	5.79	
rac-**3d**	$C_{13}H_{25}NOSi$ (239.43)	65.21	10.52	5.85	6.68
		65.14	10.44	5.81	
rac-**3e**	$C_{13}H_{23}NOSi$ (237.42)	65.77	9.76	5.90	6.74
		66.03	9.69	5.85	
rac-**3f**	$C_{14}H_{27}NOSi$ (253.46)	66.34	10.74	5.53	6.31
		66.46	10.78	5.41	
rac-**3g**	$C_{14}H_{27}NOSi$ (197.23)	66.34	10.74	5.53	6.31
		66.35	10.72	5.31	
rac-**5a″**	$C_{10}H_{15}NO_3$ (197.23)	60.90	7.67	7.10	24.34
		60.81	7.69	7.00	
rac-**5b″**	$C_{11}H_{17}NO_3$ (211.26)	62.54	8.11	6.63	22.72
		62.24	7.91	6.29	
rac-**5c″**	$C_{12}H_{19}NO_3$ (225.29)	63.98	8.50	6.22	21.31
		64.05	8.51	6.04	
rac-**5d″**	$C_{12}H_{19}NO_3$ (225.29)	63.98	8.50	6.22	21.31
		63.88	8.43	6.16	
rac-**5e″**	$C_{12}H_{17}NO_3$ (223.27)	64.55	7.67	6.27	21.50
		64.40	7.76	6.16	
rac-**7c″**	$C_{10}H_{15}NO_3$ (197.23)	60.90	7.66	7.10	24.34
		61.00	7.71	6.82	

uncorrected. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 F (250 MHz) or ARX 500 (500 MHz) spectrometer in $CDCl_3$ with TMS as internal standard. ^{13}C NMR multiplicities were determined with DEPT experiments. Optical rotations were measured with a Perkin–Elmer polarimeter 241 LC in a thermostated glass cuvette $l=10$ cm). Chromatography was performed using silica gel, grain size 0.040–0.063 mm (Fluka). Diastereomeric excess:GC separations were conducted using (a) capillary glass columns (20 m) with OV 1701, carrier gas 0.4–0.6 bar hydrogen; (b) a Chiraldex B-PM (permethylated) column (30 m×0.32 mm), carrier gas 0.6–1.0 bar hydrogen; (c) a Chiraldex B-TA and G-TA column (30 m×0.32 mm), carrier gas hydrogen.

Cyclohexanones **1b–f**,[18] **1g**,[19] **4a–e**,[20] and **6c**[21] were prepared according to literature procedures. Ketones **1a** and **6a** are commercially available, **6b** was donated by Bayer A. G. Racemic cyanohydrins were prepared according to a procedure developed by van der Gen et al.,[8] but reaction time was always 48 h. ^{1}H and ^{13}C NMR data of the racemic cyanohydrins are reported in Tables 10–12.

To obtain elemental analyses of the cyanohydrins (Table 13), either the *O*-silylated derivatives (**3a–g**) or the *O*-acetylated cyanohydrins (**5a″–e″**, **7c″**) were used. Cyanosilylation[9] was performed according to known literature procedures but purification was accomplished either by chromatography on silica gel with CH_2Cl_2 or distillation. The *O*-acetylated derivatives were prepared using acetic anhydride and dimethylaminopyridine (for conditions see determination of conversion rates and isomeric ratio). All yields are not optimized.

4.2. General procedure for the (*R*)-PaHNL-catalyzed preparation of cyclohexanone cyanohydrins 2, 5 and 7

A solution of (*R*)-PaHNL (100 U per 100 mg support, total 200 U, 78 μL) was added to cellulose [Elcema-Cellulose P100PSC (Degussa): 1 g soaked in 10 mL of 0.02 M sodium citrate buffer, pH 3.3, for 2 h, and filtered off], followed by addition of diisopropyl ether (5 mL), substrate **1**, **4** or **6** (1 mmol), and anhydrous HCN[22] (150 μL, 3.9 mmol). After stirring at room temperature for the times given in Tables 3, 5 and 8, the support was removed by filtration, washed twice with diethyl ether, and the combined filtrates were concentrated under vacuum.

4.3. General procedure for the (*S*)-MeHNL-catalyzed preparation of cyclohexanone cyanohydrins 2, 5 and 7

A solution of (*S*)-MeHNL (100 U per 100 mg support, total 200 U, 93 μL) was added to nitrocellulose [Pro-Celloidin (Fluka): 1 g (dry), soaked in 50 μL of 0.02 M sodium citrate buffer, pH 3.3, for 0.5 h; the buffer was decanted and nitrocellulose centrifuged (5700×*g* for 30 min) and dried under high vacuum for 5 h], followed after 15 min by addition of diisopropyl ether (5 μL), substrate **1**, **4** or **6** (1 mmol), and anhydrous HCN[22] (150 μL, 3.9 mmol). The reaction was then performed as described above.

4.4. Blank experiment

The chemical HCN addition was performed analogously to the enzymatic reaction, however, the enzyme solution was replaced by the same volume of 0.02 M sodium acetate buffer, pH 5.4. The reaction times correspond with those of the (*R*)-PaHNL- and (*S*)-MeHNL-catalyzed reaction. ^{1}H and ^{13}C NMR data of the enzyme-catalyzed and the chemically prepared cyanohydrins are identical.

4.5. Determination of conversion rates and isomeric ratio (acetylation)

To a solution of the crude cyclohexanone cyanohydrins **2**, **5**, or **7** (10 μL) in CH_2Cl_2 (500 μL) was added acetic anhydride (50 μL) and dimethylaminopyridine (15 mg). The reaction mixture was allowed to stand at room temperature for 30 min. The mixture was then filtered through a silica gel column (3×0.5 cm) with CH_2Cl_2 (4 mL). Conversion and isomeric ratio were directly determined from the filtrate by gas chromatography.

4.6. General procedure for the preparation of the *p*-bromobenzoylated derivatives 2a′, 5a′, and 7a′–c′

To a solution of **2a**, **5a** or **7a–c** (9.56, 7.47 or 3.35–8.12 mmol), diastereomeric ratio given in Tables 2, 5, and 7 in pyridine (25–70 mL) or in 1:1 pyridine/CH_2Cl_2 (25–70 mL) was added dimethylaminopyridine (ca. 0.2 equiv) and *p*-bromobenzoyl chloride (2.0 equiv), and the reaction mixture was stirred for the time specified. Then water (20–50 mL) was added, the layers were separated, and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined extracts were washed with diluted HCl until neutral, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel with petroleum ether–ethyl acetate (15:1 for **7b**, 50:1 for others) and recrystallized.

4.6.1. *cis*-(1*S*,2*R*)-1-(4-Bromobenzoyloxy)-2-methylcyclohexanecarbonitrile (*cis*-(1*S*,2*R*)-2a′). Reaction time: 14 d at room temperature, $R_f=0.08$, yield: 22% (*cis*-**2a′**, colorless solid), mp 97 °C (diisopropyl ether), $[\alpha]_D^{20}=+3.7$ (*c* 1.0, $CHCl_3$), ^{1}H NMR (500 MHz): δ 1.24 (d, $^{3}J=6.8$ Hz, 3H, CH_3), 1.36–1.47 (m, 2H, C^4H_{ax}, C^5H_{ax}), 1.54–1.66 (m, 2H, CH, C^3H_{ax}), 1.72–1.89 (m, 3H, CH, C^3H_{eq}, C^6H_{ax}), 2.11–2.18 (m, 1H, C^2H_{ax}), 2.85–2.88 (m, 1H, C^6H_{eq}), 7.61–7.90 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 16.33 (CH_3), 20.26 (C^5H), 23.87 (C^4H_2), 29.08 (C^3H_2), 32.78 (C^6H_2), 39.82 (C^2H), 74.88 (C^1), 118.73 (CN), 128.24, 128.95, 131.13, 132.04 (C_{Ph}), 163.56 (OCO). Anal. Calcd for $C_{15}H_{16}NO_2Br$ (322.18):C, 55.92; H, 5.00; N, 4.35; Br, 24.80; O, 9.93. Found: C, 55.96; H, 5.02; N 4.38; Br, 25.01.

4.6.2. *trans*-(1*S*,2*S*)-1-(4-Bromobenzoyloxy)-2-methylcyclohexanecarbonitrile (*trans*-(1*S*,2*S*)-2a′). Reaction conditions see *cis*-(1*S*,2*R*)-**2a′**, $R_f=0.11$, yield: 17% (*trans*-**2a′**, colorless solid), mp 103 °C (diisopropyl ether), $[\alpha]_D^{20}=+44.7$ (*c* 1.0, $CHCl_3$), ^{1}H NMR (500 MHz): δ 1.23 (d, $^{3}J=6.6$ Hz, 3H, CH_3), 1.26–1.39 (m, 1H, C^4H_{ax}), 1.43–1.64 (m, 2H, C^3H_{ax}, C^6H_{ax}), 1.67–1.90 (m, 4H, C^5H_{ax}, C^4H_{eq}, C^3H_{eq}, C^5H_{eq}), 2.08–2.15 (m, 1H, C^2H_{ax}), 2.91–2.94 (m, 1H, C^6H_{eq}), 7.59–7.88 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 16.42 (CH_3), 23.05 (C^5H), 24.45 (C^4H_2),

31.12 (C^3H_2), 34.35 (C^6H_2), 40.26 (C^2H), 78.97 (C^1), 116.37 (CN), 128.30, 128.83, 131.18, 131.92 (C_{Ph}), 163.64 (OCO). Anal. Calcd for $C_{15}H_{16}NO_2Br$ (322.18):C, 55.92; H, 5.00; N, 4.35; Br, 24.80; O, 9.93. Found: C, 56.16; H, 5.02; N 4.31; Br, 24.63.

4.6.3. *cis*-1-(4-Brombenzoyloxy)-2-methoxycyclohexanecarbonitrile (*cis*-5a′). Reaction time: 10 d at room temperature, R_f=0.05, yield: 22% (light yellow oil), ^1H NMR (500 MHz): δ 1.35–1.43 (m, 1H, C^4H_{ax}), 1.64–1.84 (m, 4H, 2CH, C^5H_{ax}, C^6H_{ax}), 1.93–1.98 (m, 2H, 2CH), 2.64–2.69 (m, 1H, C^6H_{eq}), 3.57 (s, 3H, OCH_3), 3.71–3.75 (m, 1H, C^2H_{ax}), 7.61–7.88 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 20.36, 21.06 (C^5H_2, C^4H_2), 26.31 (C^6H_2), 31.93 (C^3H_2), 58.36 (CH_3), 74.83 (C^1), 79.15 (C^2H), 117.78 (CN), 128.07, 128.98, 131.36, 131.96 (C_{Ph}), 163.81 (OCO). Anal. Calcd for $C_{15}H_{16}NO_3Br$ (338.21):C, 53.27; H, 4.77; N, 4.14; Br, 23.63; O, 14.19. Found: C, 53.09; H, 4.73; N 4.08; Br, 23.83.

4.6.4. *trans*-(1*R*,2*S*)-1-(4-Bromobenzoyloxy)-2-methoxycyclohexanecarbonitrile (*trans*-(1*R*,2*S*)-5a′). Reaction conditions see *cis*-5a′, R_f=0.02, yield: 12% (*trans*-5a′, colorless solid), mp 112 °C (ethanol), $[\alpha]_D^{20}=+31.4$ (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz): δ 1.35–1.43 (m, 1H, C^4H_{ax}), 1.64–1.84 (m, 4H, C^5H_{ax}, C^6H_{ax}, 2CH), 1.93–1.98 (m, 2H, 2CH), 2.64–2.69 (m, 1H, C^6H_{eq}), 3.57 (s, 3H, OCH_3), 3.71–3.75 (m, 1H, C^2H_{ax}), 7.61–7.88 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 21.10, 21.27 (C^5H_2, C^4H_2), 26.70 (C^6H_2), 32.03 (C^3H_2), 58.68 (CH_3), 77.15 (C^1), 79.71 (C^2H), 116.83 (CN), 128.09, 129.04, 131.25, 132.00 (C_{Ph}), 163.51 (OCO). Anal. Calcd for $C_{15}H_{16}NO_3Br$ (338.21):C, 53.27; H, 4.77; N, 4.14; Br, 23.63; O, 14.19. Found: C, 53.25; H, 4.88; N, 3.88; Br, 23.48.

4.6.5. *cis*-(1*S*,3*R*)-1-(4-Bromobenzoyloxy)-3-methylcyclohexanecarbonitrile (*cis*-(1*S*,3*R*)-7a′). Reaction time: 14 d at room temperature, R_f=0.15, yield: 34% (*cis*-7a′, colorless solid), mp 86 °C (petroleum ether), $[\alpha]_D^{20}=+1.6$ (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz): δ 0.95 (m, 1H, C^4H_{ax}), 1.02 (d, ^3J=6.5 Hz, 3H, CH_3), 1.39 (dd, $^2J(C^2H_{ax}, C^2H_{eq})$-$\approx{}^3J(C^2H_{ax}, C^3H_{ax})$=12.6 Hz, 1H, C^2H_{ax}), 1.60–1.67 (m, 1H, C^6H_{ax}), 1.72–1.82 (m, 2H, C^4H_{eq}, C^5H_{ax}), 1.88–1.96 (m, 2H, C^3H_{ax}, C^5H_{eq}), 2.63–2.66 (m, 2H, C^2H_{eq}, C^6H_{eq}), 7.59–7.88 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 21.62 (CH_3), 22.41 (C^5H_2), 29.69 (C^3H), 33.33 (C^4H_2), 35.09 (C^6H_2), 43.13 (C^2H_2), 74.48 (C^1), 118.17 (CN), 128.13, 128.89, 131.26, 131.89 (C_{Ph}), 163.59 (OCO). Anal. Calcd for $C_{15}H_{16}NO_2Br$ (322.18):C, 55.92; H, 5.00; N, 4.35; Br, 24.80; O, 9.93. Found: C, 55.98; H, 5.00; N, 4.33; Br, 24.57.

4.6.6. *trans*-(1*S*,3*S*)-1-(4-Bromobenzoyloxy)-3-methylcyclohexanecarbonitrile (*trans*-(1*S*,3*S*)-7a′). Reaction conditions see *cis*-(1*S*,3*R*)-7a′, R_f=0.09, yield: 37% (*trans*-7a′, colorless solid), mp 102 °C (diisopropyl ether), $[\alpha]_D^{20}=+19.3$ (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz): δ= 0.96 (d, ^3J=6.5 Hz, 3H, CH_3), 1.02 (m, 1H, C^4H_{ax}), 1.52–1.65 (m, 2H, C^2H_{ax}, C^5H_{ax}), 1.70–1.85 (m, 4H, C^5H_{eq}, C^3H_{ax}, C^4H_{eq}, C^6H_{ax}), 2.63–2.68 (m, 2H, C^2H_{eq}, C^6H_{eq}), 7.61–7.90 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 20.47 (C^5H), 21.77 (CH_3), 26.99 (C^3H), 33.12 (C^4H_2), 34.08 (C^6H_2), 42.12 (C^2H_2), 71.37 (C^1), 119.26 (CN), 128.10, 128.98, 131.22, 132.00 (C_{Ph}), 163.51 (OCO). Anal. Calcd for $C_{15}H_{16}NO_2Br$ (322.18):C, 55.92; H, 5.00; N, 4.35; Br, 24.80; O, 9.93. Found: C, 55.84; H, 4.99; N, 4.34; Br, 24.47.

4.6.7. *cis*-(1*S*,3*R*)-1-(4-Bromobenzoyloxy)-3-trifluoromethylcyclohexanecarbonitrile (*cis*-(1*S*,3*R*)-7b′). Reaction time: 24 h at 50 °C, R_f=0.23, yield: 25% (*cis*-7b′, colorless solid), mp 106 °C (diisopropyl ether), $[\alpha]_D^{20}=+5.4$ (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz): δ 1.37 (m, 1H, C^4H_{ax}), 1.58–1.87 (m, 3H, C^5H_{ax}, C^6H_{ax}, C^2H_{ax}), 2.06–2.09 (m, 2H, C^4H_{eq}, C^5H_{eq}), 2.54–2.64 (m, 1H, C^3H_{ax}), 2.72–2.75 (m, 1H, C^6H_{eq}), 2.89–2.92 (m, 1H, C^2H_{eq}), 7.60–7.88 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 21.11 (s, C^5H_2), 23.69 (s, C^4H_2), 34.24 (s, C^2H_2), 34.83 (s, C^6H_2), 39.53 (q, ^2J(C,F)=28.1 Hz, C^3H), 73.03 (C^1), 117.15 (CN), 126.56 (q, ^1J(C,F)=278.5 Hz, CF_3), 127.63, 129.46, 131.44, 132.16 (C_{Ph}), 163.56 (OCO). Anal. Calcd for $C_{15}H_{13}NO_2BrF_3$ (376.17):C, 47.89; H, 3.48; N, 3.72; Br, 21.24; O, 8.51; F, 15.15. Found: C, 47.84; H, 3.56; N, 3.69; Br, 21.11.

4.6.8. *trans*-(1*S*,3*S*)-1-(4-Bromobenzoyloxy)-3-trifluoromethylcyclohexanecarbonitrile (*trans*-(1*S*,3*S*)-7b′). Reaction conditions see *cis*-(1*S*,3*R*)-7b′, R_f=0.17, yield: 13% (*trans*-7b′, colorless solid), mp 153 °C (diisopropyl ether), $[\alpha]_D^{20}=+5.7$ (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz): δ 1.43 (m, 1H, C^4H_{ax}), 1.62 (m, 1H, C^5H_{ax}), 1.85–1.97 (m, 3H, C^5H_{eq}, C^2H_{ax}, C^6H_{ax}), 2.02–2.05 (m, 1H, C^4H_{eq}), 2.35–2.45 (m, 1H, C^3H_{ax}), 2.76–2.79 (m, 1H, C^6H_{eq}), 2.89–2.92 (m, 1H, C^2H_{eq}), 7.61–7.89 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 19.04 (s, C^5H_2), 23.27 (q, ^3J(C,F)= 2.6 Hz, C^4H_2), 33.23 (q, ^3J(C,F)=2.8 Hz, C^2H_2), 33.53 (s, C^6H_2), 37.10 (q, ^2J(C,F)=27.9 Hz, C^3H), 69.96 (C^1), 118.12 (CN), 126.69 (q, ^1J(C,F)=278.6 Hz, CF_3), 127.41, 129.51, 131.25, 132.21 (C_{Ph}), 163.22 (OCO). Anal. Calcd for $C_{15}H_{13}NO_2BrF_3$ (376.17):C, 47.89; H, 3.48; N, 3.72; Br, 21.24; O, 8.51; F, 15.15. Found: C, 48.18; H, 3.56; N, 3.74; Br, 21.22.

4.6.9. *cis*-(1*S*,3*R*)-1-(4-Bromobenzoyloxy)-3-methoxycyclohexanecarbonitrile (*cis*-(1*S*,3*R*)-7c′). Reaction time: 10 d at room temperature, R_f=0.02, yield: 16% (*cis*-7c′, colorless solid), mp 105 °C (ethanol), $[\alpha]_D^{20}=+24.6$ (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz): δ 1.30–1.37 (m, 1H, C^4H_{ax}), 1.66–1.74 (m 1H, C^5H_{ax}), 1.79–1.90 (m, 2H, C^6H_{ax}, C^2H_{ax}), 1.96–2.02 (m, 1H, C^5H_{eq}), 2.08–2.12 (m, 1H, C^4H_{eq}), 2.54–2.56 (m, 1H, C^6H_{eq}), 2.84–2.87 (m, 1H, C^2H_{eq}), 3.37 (s, 3H, OCH_3), 3.51–3.57 (m, 1H, C^3H_{ax}), 7.60–7.88 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 18.90 (C^5H_2), 30.37 (C^4H_2), 34.95 (C^6H_2), 39.55 (C^2H_2), 56.43 (CH_3), 72.71 (C^1), 75.28 (C^3H), 117.99 (CN), 127.95, 129.03, 131.31, 131.95 (C_{Ph}), 163.63 (OCO). Anal. Calcd for $C_{15}H_{16}NO_3Br$ (338.21):C, 53.27; H, 4.77; N, 4.14; Br, 23.63; O, 14.19. Found: C, 53.24; H, 4.80; N, 4.12; Br, 23.34.

4.6.10. *trans*-1-(4-Bromobenzoyloxy)-3-methoxycyclohexanecarbonitrile (*trans*-7c′). Reaction conditions see *cis*-(1*S*,3*R*)-7c′, R_f=0.04, yield: 26% (*trans*-7c′, colorless solid), mp 76 °C (ethanol), ^1H NMR (250 MHz): δ 1.39–1.72 (m, 2H, C^4H_{ax}, C^5H_{ax}), 1.85–2.15 (m, 4H, C^6H_{ax}, C^2H_{ax}, C^5H_{eq}, C^4H_{eq}), 2.43–2.49 (m, 1H, C^6H_{eq}), 2.68–2.75 (m, 1H, C^2H_{eq}), 3.38 (s, 3H, OCH_3), 3.41–3.51 (m, 1H, C^3H_{ax}), 7.60–7.89 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 18.65 (C^5H_2), 30.22 (C^4H_2), 34.41 (C^6H_2), 38.77 (C^2H_2), 56.12 (CH_3), 71.91 (C^1), 74.03 (C^3H),118.40 (CN), 127.88,

129.17, 131.23, 132.07 (C_{Ph}), 163.39 (OCO). HRMS (EI, 70 eV): Mol. mass Calcd 337.0314 (for $C_{15}H_{16}NO_3Br$), found 337.0313 (M^+).

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Hydroxynitrile lyase catalysed synthesis of heterocyclic (*R*)- and (*S*)-cyanohydrins

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Abstract—Heterocyclic saturated five- and six-membered ring ketones sometimes bearing a methyl substituent were reacted with HCN under enzyme catalysis using recombinant hydroxynitrile lyase from *Hevea brasiliensis*, as a rule (*S*)-selective, and *Prunus amygdalus*, (*R*)-selective. The resulting cyanohydrins were stereochemically characterised. The steric outcome of these transformations was interpreted by molecular modelling.

1. Introduction

Cyanohydrins are versatile building blocks in organic synthesis. They are easily available by HCN addition to aldehydes or ketones[1–3] and several biocatalytic approaches to this class of compounds have already been described and reviewed.[4–6] The substrate acceptance of hydroxynitrile lyases (HNLs) has been investigated since the early sixties of the last century.[7] Especially the (*R*)-selective HNL of *Prunus amygdalus* (*Pa*HNL, E.C. 4.1.2.10) has been used over a long period as defatted almond meal[8] or purified enzyme preparations adsorbed on various carriers.[9] This *Pa*HNL accepts aliphatic, aromatic or heteroaromatic aldehydes and methyl ketones and has recently been successfully overexpressed in *Pichia pastoris*.[10] The (*S*)-selective enzyme isolated from *Hevea brasiliensis* (*Hb*HNL, E.C. 4.1.2.39) and also overexpressed in Graz[11,12] shows a similar broad substrate range. For example, this enzyme also catalyses the (*S*)-selective HCN-addition to unusual substrates such as formylferrocene and 1,1′-diformylferrocene.[13] The substrate performance of *Pa*HNL has recently been tested on 4-substituted cyclohexanones[14,15] and on bicyclic ketones.[16] Inspired by these results, reports on Acalyphin, a heterocyclic cyanogenic glucoside[17] and our own findings on tetrahydrothiophen-3-one[18] we started monitoring the stereopreferences of HNL-catalysed cyanide addition to saturated heterocyclic ketones with sulfur or oxygen in the ring.

Our first investigation dealt with five- and six-membered cyclic ketones, namely tetrahydrofuran-3-one (**1a**) and tetrahydro-2*H*-3-pyranone (**2**). As will be shown below, both substrates were accepted by the HNLs employed and gave the corresponding cyanohydrins with moderate ees up to 81%. The racemic mixtures of methyl substituted tetrahydrofuran-3-one (**1b**) and tetrahydrothiophen-3-ones (**1c** and **1d**) were also accepted as substrates by both HNLs. The diastereomeric distributions of the corresponding cyanohydrins which depend on different reaction conditions such as pH, reaction time, and solvent properties are accurately analysed below.

2. Results and discussion

The starting materials **1** and **2** used for this investigation are shown in Figure 1. **1b** and **1c** are commercially available as racemates, ketones **1a** and **2** were synthesised according to literature procedures by PCC-oxidation of the corresponding alcohols.[19] The racemic ketone **1d** was obtained by the sequence shown in Scheme 1.

As reported earlier,[13] the enzyme catalysed cyanohydrin forming reactions were performed in a two phase system of aqueous buffer/*tert*-butyl methyl ether at room temperature.

Keywords: Hydroxynitrile lyase; Cyanohydrins; Heterocyclic ketones; Enzyme-catalysed.
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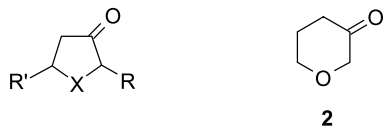
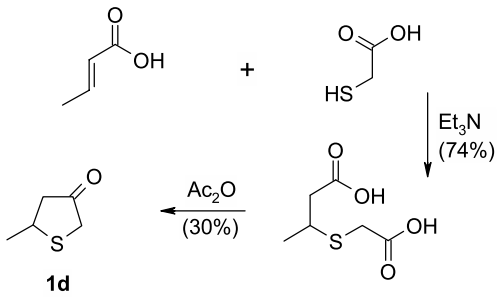


1	X	R	R'
a	O	H	H
b	O	CH_3	H
c	S	CH_3	H
d	S	H	CH_3

Figure 1. Starting materials.



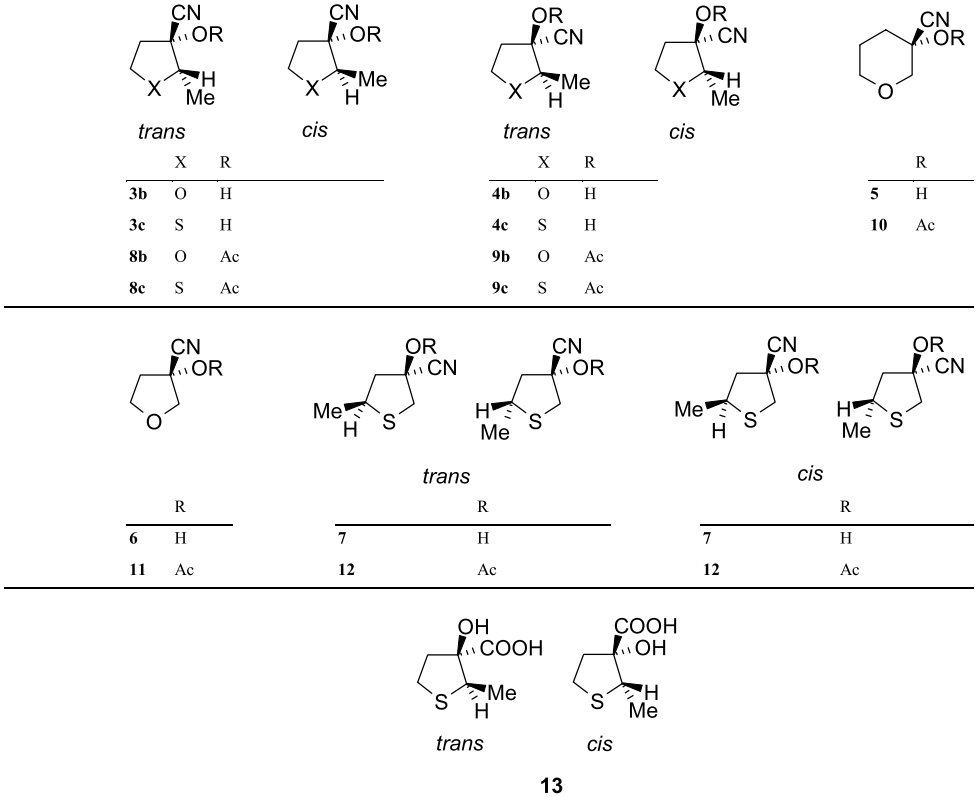
Scheme 1. Synthesis of ketone **1d**.

After 1–5 h the cyanohydrins **3**, **4** and **5** were obtained by reactions catalysed with *Hb*HNL in 90–98% yield. Less enzyme per mmol substrate was used for the transformation with *Pa*HNL which resulted in longer reaction times (up to 1 day) to give **3**, **4** and **6** (76–95% yield), see Figure 2.

The detailed results are shown in Table 1. For comparison as a blank, a non-enzymatic reaction was run catalysed by the weakly basic anion exchange resin Amberlyst A-21. Ketones **1b** and **1c**, having a centre of chirality at C-2, were used as starting materials as a racemate. The *cis*-diastereomer is favoured for the formation of tetrahydrofuran derivatives **3b**, **4b** and tetrahydrothiophene compounds **3c**, **4c** by the non-enzymatic reaction. This result cannot be explained with the bulkiness of the substituents on C-2 and C-3 or by kinetic control. It can be assumed that in this case the transformation is controlled thermodynamically.

This steric outcome is changed by enzyme-catalysis using *Hb*HNL. Contrary to the blank without enzyme, now the formation of the *trans*-diastereomer is favoured. To interpret this result, the mechanism of the *Hb*HNL catalysed cyanohydrin reaction[20] has to be taken into consideration. First the substrate is fixed within the active site of the enzyme by hydrogen bonding. Next, HCN adds after having been deprotonated by a suitably located histidine (H235).

For the interpretation of the steric course of the reaction, all four stereoisomers of the cyanohydrins formed by reaction of 2-methyltetrahydrothiophen-3-one (**1c**) with HCN were modelled (Fig. 3). After docking and restrained energy minimization, the structures with lowest energy of all complexes were in line with the binding mode of cyanohydrins to *Hb*HNL as known from modelling[21] and experimental data.[22,23] At least qualitatively consistent with the experimental results, energy values obtained with



	X	R
3b	O	H
3c	S	H
8b	O	Ac
8c	S	Ac

	X	R
4b	O	H
4c	S	H
9b	O	Ac
9c	S	Ac

	R
5	H
10	Ac

	R
6	H
11	Ac

	R
7	H
12	Ac

	R
7	H
12	Ac

13

Figure 2. Cyanohydrins and derivatives synthesised. For carboxylic acid **13** only one enantiomer is drawn.

Table 1. Table1 Conversion of **1b** and **1c**

Enzyme	pH	Formation of **3b** and **4b**						Formation of **3c** and **4c**					
		Yield (%)	*cis*/*trans*	de *cis* (%)	de *trans* (%)	ee *cis* (%)	ee *trans* (%)	Yield (%)	*cis*/*trans*	de *cis* (%)	de *trans* (%)	ee *cis* (%)	ee *trans* (%)
Blank	—	60	2.3/1	39.1	—	—	—	97	1.8/1	29.2	—	—	—
*Hb*HNL	5.00	90	1/3.3	—	53.5	16.7	1.3	98	1.2/1	8.9	—	6.1	7.4
	4.75	89	1/3.3	—	53.5	24.0	0.0	98	1.1/1	3.3	—	6.8	7.5
	4.50	89	1/3.5	—	55.5	12.1	3.6	90	1/2.5	—	43.7	4.4	0.3
	4.25	87	1/2.6	—	44.6	6.9	5.8	93	1/2.6	—	44.9	3.6	1.3
	4.00	90	1/2.4	—	40.9	14.1	2.9	97	1/4.3	—	62.0	23.6	6.2
*Pa*HNL	4.50	84	2.2/1	39.0	—	7.3	1.6	89	1.9/1	31.8	—	1.4	0.0
	4.25	99	2.3/1	39.9	—	6.8	4.9	92	1.9/1	31.4	—	1.5	0.6
	4.00	74	2.3/1	39.2	—	6.5	5.3	94	1.9/1	31.4	—	0.1	1.0
	3.75	83	2.1/1	35.3	—	8.6	8.9	95	1.8/1	29.7	—	1.7	1.4
	3.55	98	1.9/1	31.3	—	12.1	10.1	96	1.7/1	26.7	—	0.0	5.4

AutoDock and AMBER indicate that the *trans*-diastereomers of both cyanohydrin species bind better to the enzyme. No significant difference was found between the respective enantiomers, which is also in line with the experiment.

A possible explanation for the favoured formation of the *trans*-diastereomers in the enzymatic reaction is the position of the methyl group of the substrate. In the case of the *trans*-cyanohydrins (pictures C and D), the methyl group points towards the more spacious tunnel leading from the outside into the active site of the enzyme (shown on the left side of the drawing: tryptophan W128 is part of the amino acids surrounding this tunnel). For the formation of the *cis*-diastereomers A and B the methyl group has to be accommodated in a sterically rather crowded region within the active site.

When *Pa*HNL is used as catalyst, the steric outcome of the reaction is similar to the blank except for a very small enantiopreference. The *cis*-diastereomer is formed in excess. On the basis of the experimental data it has to be concluded that the non-enzymatic reaction contributes to the results to a large extent.

For the unequivocal assignment of the stereochemistry, enantio-enriched cyanohydrin **4c** (*trans*-diastereomer) was hydrolysed to acid **13**. Subsequently, after recrystallisation its structure was determined by X-ray crystallography. As can be seen in the ORTEP[24] plot (Fig. 4) the product proved to be racemic *trans*-3-hydroxy-2-methyltetrahydrothiophene carboxylic acid (**13**). On this basis **4c** was taken as reference for the steric correlation of the other compounds by NMR.

For comparison purposes also other heterocyclic ketones were investigated. With *Hb*HNL catalysis tetrahydro-2*H*-3-pyranone **2** gave cyanohydrin **5** with low ee (Table 2). This is in accordance with earlier work on substrates bearing an oxygen atom in the neighbourhood of the carbonyl group.[25] In the case of *Pa*HNL only racemic product was obtained. Probably the non-enzymatic reaction took place nearly exclusively under the conditions used. When we applied a larger amount of enzyme per mmol of substrate, the use of *Pa*HNL also led to some enantioselection, although low, as shown by the transformation of tetrahydro-3-furanone (**1a**) to give cyanohydrin (*S*)-**6** (24% ee). *Hb*HNL shows moderate enhancement of the stereoselectivity to give 81% ee for the enantiomer (*R*)-**6** (Table 3). As another example of a heterocycle bearing a methyl group, the reaction of racemic 5-methyltetrahydrothiophene-3-one (**1d**) was investigated using both *Hb*HNL and *Pa*HNL. Within this compound, the distance between the methyl and carbonyl group is larger. Employing the *Pa*HNL, the normal reaction course took place and a diastereomeric product mixture **7** was obtained (86% de).[26] Independent from the stereocentre on C-5, the application of *Hb*HNL showed moderate enantioselectivity with 77 and 66% ee for the *cis*- and *trans*-isomers, respectively.

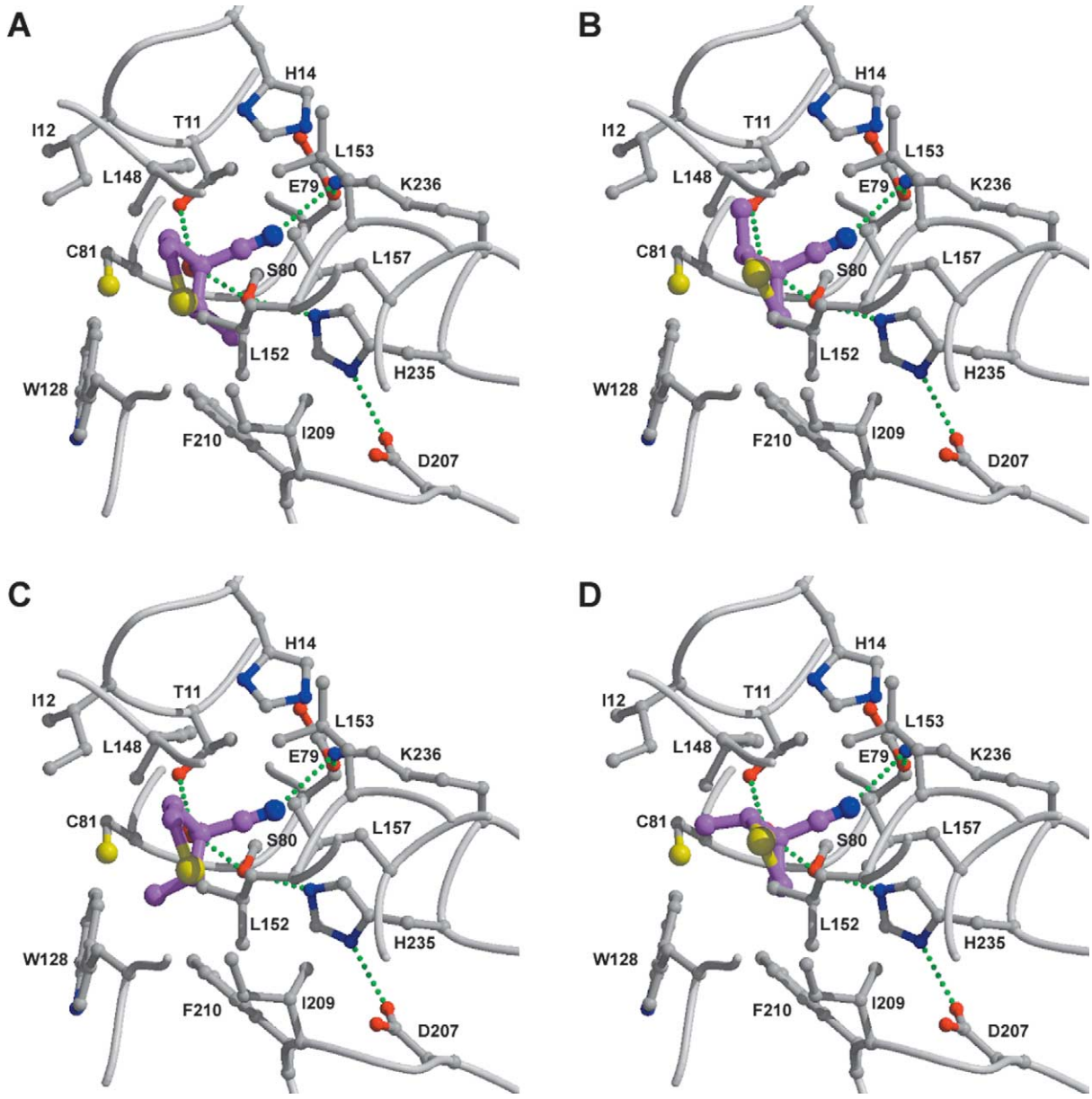


Figure 3. Ball and stick representation of modelled structures of *Hb*HNL complexes with the enantiomers *cis*-**3c** (A) and *cis*-**4b** (B) as compared to the corresponding diastereomers, the enantiomers *trans*-**3c** (C) and *trans*-**4c** (D). Nitrogen, oxygen and sulfur atoms are depicted in blue, red and yellow.

3. Conclusions

Up to now, not very much has been known about the steric course of enzyme catalysed cyanohydrin reactions of heterocyclic ketones. Therefore, several tetrahydrofuranones and thiophenones, some of them bearing a methyl group, and tetrahydro-2*H*-3-pyranone were investigated using both *Pa*HNL and *Hb*HNL. In both areas a nearly racemic mixture of the corresponding *cis*- and *trans*-cyanohydrins was obtained for the methyl bearing substrates. Since the steric course could be interpreted by molecular modelling, this investigation is a tool to deepen the understanding of structural factors contributing to the course of cyanohydrin reactions catalysed by hydroxynitrile lyases. However, although it proved to be possible to chromatographically separate the diastereomers obtained, the preparative value of this reaction applied to the ketones investigated is limited.

4. Experimental

4.1. General

The ketones used were commercially available (**1b**–**1c**) or prepared from commercially available compounds. The hydroxynitrile lyases were kindly provided by DSM Fine Chemicals Austria. Reactions were monitored by TLC (Merck silica gel 60 F_{254}), compounds were visualized by spraying with Mo-reagent (10% H_2SO_4, 10% $(NH_4)Mo_7O_{24}\cdot 4H_2O$) and vanillin-reagent (1 g vanillin in 100 ml of concd H_2SO_4). Flash chromatography was performed on Silica gel 60 (Merck, 70–230 mesh) using mixtures of ethyl acetate and cyclohexane. ^1H and ^{13}C NMR spectra were recorded on VARIAN GEMINI 200 MHz and VARIAN INOVA 500 MHz spectrometers with TMS as an internal reference.

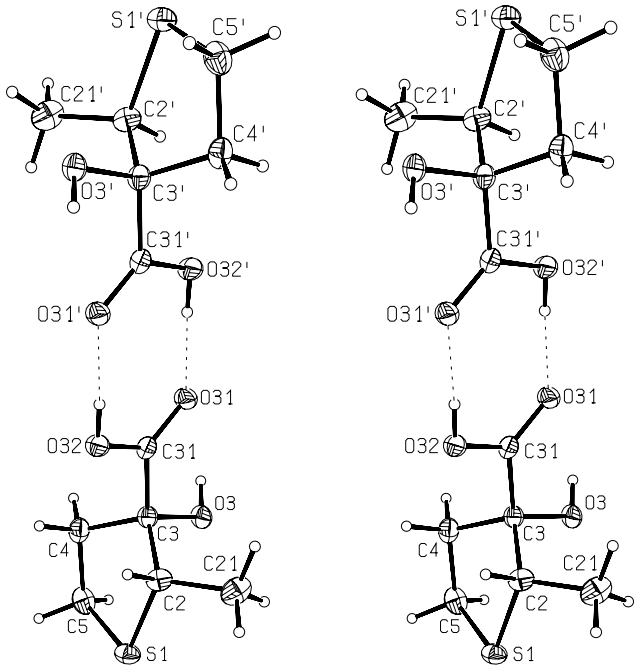


Figure 4. Stereoscopic ORTEP plot of **13** showing the atomic numbering scheme. The probability ellipsoids are drawn at the 50% probability level.

Table 2. Conversion of ketone **2** into cyanohydrin **5**

Enzyme	pH	Yield (%)	ee (%)
Blank	—	99	—
*Hb*HNL	5.00	99	1.8
	4.75	96	48.3
	4.50	99	47.6
	4.25	95	40.8
	4.00	89	12.5
*Pa*HNL	4.50	95	0.1
	4.25	99	0.1
	4.00	80	0.3
	3.75	78	0.4
	3.55	99	0.2

4.2. Synthetic methods

4.2.1. Synthesis of tetrahydro-2*H*-pyran-3-ol. To a suspension of $NaBH_4$ (0.6 equiv) in THF, 3,4-dihydro-2*H*-pyran was added. After dropwise addition of dimethyl sulfate (0.6 equiv) the mixture was cooled to 5 °C. Then water (1/1 v/v educt/water), 3 M NaOH (1/2 v/v educt/NaOH) and 30% H_2O_2 (1/2 v/v educt/H_2O_2) were added slowly. The product was extracted for 27 h with ether and the organic phase dried and evaporated under reduced pressure. Distillation (bp (20 mbar) 60 °C) yielded the pure alcohol. The structure was confirmed by NMR analysis. The spectroscopic data were identical with those previously reported.[19]

4.2.2. Synthesis of tetrahydro-2*H*-3-pyranone (2). To a suspension of pyridinium chlorochromate (PCC, 1.5 equiv) and molecular sieves 3 Å in CH_2Cl_2, a solution of tetrahydro-2*H*-pyran-3-ol in CH_2Cl_2 was added. The mixture was heated to reflux until quantitative conversion, filtered over a bed of Celite 545 and poured into ether (1/10 v/v CH_2Cl_2/ether). The solution was filtered over Celite 545 and extracted with 2 M HCl and water. The aqueous phase was reextracted for 24 h with ether. The organic phase was dried and evaporated under reduced pressure (810 mbar). Distillation (bp (120 mbar) 92–96 °C) yielded the pure ketone **2**. The spectroscopic data were identical with those previously reported.[27]

4.2.3. Synthesis of tetrahydrofuran-3-one (1a). To a suspension of PCC (1.7 equiv) and molecular sieves 3 Å in CH_2Cl_2, a solution of tetrahydrofuran-3-ol in CH_2Cl_2 was added. The mixture was heated to reflux until quantitative conversion, filtered over a bed of Celite 545 and poured into ether (1/5 v/v CH_2Cl_2/ether). The solution was filtered over Celite 545 and extracted with 2 M HCl and water. The aqueous phase was reextracted 24 h with ether. The organic phase was dried and evaporated under reduced pressure (800 mbar). Distillation (bp (81 mbar) 66–68 °C) yielded the pure ketone **1a**. The spectroscopic data were slightly different to the literature.[28] ^{1}H NMR (500 MHz, $CDCl_3$): δ: 4.24 (t, 2H, H5, H5′, J=7.33 Hz); 3.86 (s, 2H, H2, H2′); 2.49 (t, 2H, H4, H4′, J=7.32 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 215.28 (CO); 70.83 (C5); 67.07 (C2); 37.29 (C3).

4.2.4. Synthesis of 3-carboxymethylsulfanyl butyric acid. To a solution of crotonic acid and mercapto acetic acid (1/1) in dioxane, triethylamine (1.3 equiv) was added dropwise. The mixture was stirred at reflux temperature. After completion, the solution was poured onto ice and the pH was adjusted with concd HCl to pH 1. The product was extracted with ether. The organic phase was dried and evaporation of the solvent yielded crude diacid. ^{1}H NMR (200 MHz, $CDCl_3$): δ: 9.90 (broad s, 2H, COOH); 3.42–3.26 (m, 1H, H3, J=7.03 Hz); 3.33 (s, 2H, H2, H2′); 2.80–2.48 (m, 2H, H5, H5′, J=18.9, 7.04 Hz); 1.47 (d, 3H, CH_3, J=7.03 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 176.81 (C1); 175.82 (C6); 41.97 (C5); 37.13 (C2); 33.09 (C3); 21.37 (CH_3).

4.2.5. Synthesis of 5-methyltetrahydrothiophen-3-one (1d). To a solution of 3-carboxymethylsulfanyl butyric acid in acetic anhydride, NaOAc (0.05 equiv) was added and the mixture stirred at 120 °C. After quantitative conversion, ice and concd H_2SO_4 were added and the solution stirred below 25 °C. The product was extracted with ether. The organic phase was neutralised with a saturated $NaHCO_3$ solution, dried and evaporated under reduced pressure. Flash chromatography yielded the pure ketone **1d**. The ^{1}H NMR data were similar to the literature.[29] ^{13}C NMR data: ^{13}C NMR (50 MHz, $CDCl_3$)

Table 3. Conversion of ketone **1a** into cyanohydrin **6**

Enzyme	U/mmol	pH	Yield (%)	ee (%)
*Hb*HNL	900	4.5	63	81.2
*Pa*HNL	250	3.5	72	3.7
	1080	4.0	92	24.0

δ: 212.90 (CO); 48.33 (C4); 39.17 (C5); 37.28 (C2); 21.81 (CH_3).

4.2.6. General procedure for the synthesis of racemic cyanohydrins. To a solution of ketone in TBME (*tert*-butyl methyl ether), weakly basic ion-exchange resin (Amberlyst A-21) and freshly generated HCN (2 equiv)[13] were added. The mixture was stirred at room temperature, and after quantitative conversion (5–24 h), the mixture was filtered over a bed of Na_2SO_4. Evaporation of the solvent yielded the crude cyanohydrins. Structures were confirmed by NMR analysis. NMR data of compounds **3**, **4** and **6** are given below (compounds **5** and **7** are unstable).

4.2.6.1. 3-Hydroxy-2-methyltetrahydrofuran-3-carbonitrile (3b, 4b). ^{1}H NMR (200 MHz, $CDCl_3$): δ: 4.2–3.8 (m, 3H, H2, H5, H5′); 3.8–3.2 (broad s, 1H, OH); 2.7–2.2 (m, 2H, H4, H4′); 1.4 (d, 3H, CH_3 *cis*, J=6.2 Hz); 1.35 (d, 3H, CH_3 *trans*, J=6.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: *cis*-**3b**, -**4b**: 119.89 (CN); 83.25 (C3); 74.23 (C2); 65.99 (C5) 40.41 (C4); 17.36 (CH_3); *trans*-**3b**, -**4b**: 119.89 (CN); 82.24 (C3); 72.63 (C2); 65.99 (C5); 40.86 (C4); 12.96 (CH_3).

4.2.6.2. 3-Hydroxy-2-methyltetrahydrothiophen-3-carbonitrile (3c, 4c). ^{1}H NMR (200 MHz, $CDCl_3$): δ: *cis*-**3c**, -**4c**: 3.4 (q, 1H, H2, J=6.83 Hz); 3.1–2.9 (m, 2H, H5, H5′); 2.5–2.4 (m, 2H, H4, H4′); 1.5 (d, 3H, CH_3, J=6.83 Hz); *trans*-**3c**, -**4c**: 3.7 (q, 1H, H2, J=6.83 Hz); 3.1–2.9 (m, 2H, H5, H5′); 2.60–2.55 (m, 1H, H4); 2.4–2.3 (m, 1H, H4′); 1.4 (d, 3H, CH_3, J=6.83 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: *cis*-**3c**, -**4c**: 118.99 (CN); 79.68 (C3); 50.70 (C2); 40.88 (C4); 27.21 (C5); 13.84 (CH_3); *trans*-**3c**, -**4c**: 119.43 (CN); 75.91 (C3); 51.09 (C2); 42.47 (C4); 27.90 (C5); 19.77 (CH_3).

4.2.6.3. 3-Hydroxytetrahydrofuran-3-carbonitrile (6). ^{1}H NMR (500 MHz, $CDCl_3$): δ: 4.09–4.01 (m, 3H, H5, H5′, H2, J=6.83, 1.46 Hz); 3.99–3.96 (d, 1H, H2′, J=9.76 Hz); 2.52–2.45 (m, 1H, H4, J=8.30, 5.37 Hz); 2.36–2.31 (m, 1H, H4′, J=4.39 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 120.09 (CN); 78.6 (C2); 71.95 (C3); 67.71 (C5); 41.10 (C4).

4.2.7. General procedure for the synthesis of the cyanohydrins with *Hb*HNL. To a solution of ketone in TBME, an aqueous solution of *Hb*HNL (700–1500 IU per mmol ketone) was added and the resulting mixture was stirred until an emulsion was formed. The enzyme was previously diluted with distilled water (1/2 v/v) and the pH was adjusted with 10% citric acid. After addition of freshly generated HCN (2 equiv),[13] the mixture was stirred at room temperature until quantitative conversion. The emulsion was broken with Celite 545, filtered and dried over Na_2SO_4. Evaporation of the solvent yielded the crude cyanohydrins. NMR data of compounds **3**, **4** and **6** are given above (compounds **5** and **7** are unstable).

4.2.8. General procedure for the synthesis of the cyanohydrins with *Pa*HNL. To a solution of ketone in TBME, a solution of *Pa*HNL (200–450 IU per mmol ketone, TBME/enzyme 5/7 v/v) was added and the resulting mixture was stirred until an emulsion was formed. The pH of the enzyme solution was previously adjusted with 10% citric acid. After addition of freshly generated HCN (2 equiv),[13] the mixture was stirred at room temperature until quantitative conversion. The emulsion was broken with Celite 545, filtered and dried over Na_2SO_4. Evaporation of the solvent yielded the crude cyanohydrins. NMR data of compounds **3**, **4** and **6** are given above (compounds **5** and **7** are unstable).

4.2.9. Synthesis of acetoxycarbonitriles. According to standard procedures, the cyanohydrins were acetylated with 1.5 equiv acetic anhydride and 1.1 equiv pyridine in CH_2Cl_2. NMR and MS data of compounds **8b–12** are given below.

4.2.9.1. 3-Acetoxy-2-methyltetrahydrofuran-3-carbonitrile (8b, 9b). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.2–3.8 (m, 3H, H2, H5, H5′); 2.80–2.40 (m, 2H, H4, H4′); 2.26 (s, 3H, Ac–CH_3 *trans*); 2.16 (s, 3H, Ac–CH_3 *cis*); 1.53 (d, 3H, CH_3 *cis*, J=6.2 Hz); 1.4 (d, 3H, CH_3 *trans*, J=6.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: *cis*-**8b**, -**9b**: 169.34 (Ac–CO); 117.18 (CN); 82.28 (C3); 78.98 (C2); 65.99 (C5); 39.06 (C4); 20.95 (Ac–CH_3); 17.50 (CH_3); *trans*-**8b**, -**9b**: 169.24 (Ac–CO); 117.18 (CN); 82.19 (C3); 75.37 (C2); 66.04 (C5); 39.06 (C4); 21.01 (Ac–CH_3); 13.48 (CH_3). MS: 170 (M^+); 153 (M−CH_3); 143 (M−CN); 128 (M−(CN+CH_3)); 110 (M−OAc); 101 (M−(CN+Ac).

4.2.9.2. 3-Acetoxy-2-methyltetrahydrothiophen-3-carbonitrile. ^{1}H NMR (500 MHz, $CDCl_3$) δ: *cis*-**8c**, -**9c**: 3.69 (q, 1H, H2, J=6.84 Hz); 3.01–2.88 (m, 2H, H5,H5′); 2.9–2.8 (m, 1H, H4); 2.57–2.47 (m, 1H, H4′); 2.14 (s, 3H, Ac–CH_3); 1.53 (d, 3H, CH_3, J=6.84 Hz); *trans*-**8c**, -**9c**: 3.88 (q, 1H, H2, J=6.83 Hz); 3.01–2.88 (m, 2H, H5,H5′); 2.9–2.8 (m, 1H, H4); 2.57–2.47 (m, 1H, H4′); 2.18 (s, 3H, Ac–CH_3); 1.38 (d, 3H, CH_3, J=6.84 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: *cis*-**8c**, -**9c**: 169.13 (Ac–CO); 115.69 (CN); 81.59 (C3); 48.26 (C2); 38.91 (C4); 27.15 (C5); 21.03 (Ac–CH_3); 19.72 (CH_3); *trans*-**8c**, -**9c**: 166.63 (Ac–CO); 117.15 (CN); 78.66 (C3); 48.97 (C2); 38.91 (C4); 26.54 (C5); 21.14 (Ac–CH_3); 15.75 (CH_3). MS: 186 (M^+); 159 (M−CN); 144 (M−(CN+CH_3)); 126 (M−OAc).

4.2.9.3. 3-Acetoxytetrahydro-2*H*-pyran-3-carbonitrile (10). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.06 (d, 1H, H2, J=12.2 Hz); 3.82–3.75 (m, 2H, H2′, H6); 3.66–3.60 (m, 1H, H6′, J=5.8 Hz); 2.43–2.37 (m, 1H, H4); 2.15–2.09 (m, 1H, H4′); 2.14 (s, 3H, Ac–CH_3); 1.84 (m, 2H, H5, H5′, J=5.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.91 (Ac–CO); 117.41 (CN); 71.20 (C3); 68.94 (C2); 68.10 (C6); 32.86 (C4); 22.05 (Ac–CH_3); 21.16 (C5). MS: 170 (M^+); 143 (M−CN); 128 (M−Ac); 110 (M−OAc); 101 (M−(CN+Ac).

4.2.9.4. 3-Acetoxytetrahydrofuran-3-carbonitrile (11). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.25 (d, 1H, H2, J=10.7 Hz); 4.07 (d, 1H, H2′, J=10.7 Hz); 4.02–3.94 (m, 2H, H5, H5′, J=5.37 Hz); 2.68–2.62 (m, 1H, H4, J=6.35 Hz); 2.53–2.46 (m, 1H, H4′, J=6.35 Hz); 2.14 (s, 3H, Ac–CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.50 (Ac–CO); 117.52 (CN); 77.06 (C3); 74.76 (C2); 67.40 (C5); 39.38 (C4); 20.92 (Ac–CH_3). MS: 156 (M^+); 129 (M−CN); 96 (M−OAc); 87 (M−(CN+Ac).

4.2.9.5. 3-Acetoxy-5-methyltetrahydrothiophen-3-carbonitrile (12). ^{1}H NMR (200 MHz, $CDCl_3$) δ: *cis*:[26] 3.70 (m, 1H, H5); 3.62 (d, 1H, H2, $J=11.9$ Hz); 3.28 (d, 1H, H2′, $J=11.9$ Hz); 2.88 (dd, 1H, H4, $J=13.2$, 6.6 Hz); 2.13 (s, 3H, $AcCH_3$); 2.12 (dd, 1H, H4′, $J=13.2$, 2.0 Hz); 1.40 (d, 3H, CH_3, $J=6.8$ Hz); *trans*:[26] 3.77–3.36 (m, 3H, H5, H2, H2′); 2.81 (dd, 1H, H4, $J=13.2$, 6.6 Hz); 2.13 (s, 3H, $AcCH_3$); 2.11 (m, 1H, H4′); 1.41 (d, 3H, CH_3, $J=6.8$ Hz);. ^{13}C NMR (50 MHz, $CDCl_3$) δ: *cis*:[26] 168.99 (Ac–CO); 117.47 (CN); 77.41 (C3); 48.47 (C2); 40.54 (C4); 38.51 (C5); 21.99 (Ac–CH_3); 20.89 (CH_3); *trans*:[26] 168.97 (Ac–CO); 117.02 (CN); 76.67 (C3); 49.35 (C2); 41.24 (C4); 38.51 (C5); 22.00 (Ac–CH_3); 20.63 (CH_3).

4.2.10. Synthesis of *trans*-3-hydroxy-2-methyltetrahydrothiophene-3-carboxylic acid (13). A solution of the respective cyanohydrin in 27% HCl was stirred at 80 °C. After quantitative conversion, the mixture was extracted with toluene to remove apolar impurities. HCl was removed under reduced pressure and the residue dissolved in CH_2Cl_2. Filtration, removal of the solvent, flash chromatography and recrystallisation from toluene/CH_2Cl_2 yielded the desired α-hydroxy acid **13**. Mp 89–92 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.87 (q, 1H, H2, $J=6.83$ Hz); 3.12 (m, 1H, H5, $J=10.7$, 6.83 Hz); 3.04 (m, 1H, H4, $J=10.7$, 1.47 Hz); 2.51 (m, 1H, H5′, $J=13.2$, 10.7 Hz); 2.33 (m, 1H, H4′, $J=13.2$, 6.84, 1.47 Hz); 1.27 (d, 3H, CH_3, $J=6.84$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.58 (COOH); 83.74 (C3); 50.56 (C2); 41.70 (C4); 29.29 (C5); 13.52 (CH_3).

4.2.11. X-ray diffraction data of 13. All the measurements were performed using graphite-monochromatized Mo K_α radiation at 100 K: $C_6H_{10}O_3S$, M_r 162.20, monoclinic, space group $P2_1/n$, $a=6.634(2)$ Å, $b=7.007(2)$ Å, $c=15.925(3)$ Å, $\beta=90.87(2)°$, $V=740.2(3)$ Å^3, $Z=4$, $d_{calc}=1.456$ g cm^{-3}, $\mu=0.381$ mm^{-1}. A total of 1863 reflections were collected ($\Theta_{max}=26.0°$), from which 1451 were unique ($R_{int}=0.0203$), with 1332 having $I>2\sigma(I)$. The structure was solved by direct methods (SHELXS-97)[30] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97).[31] The non-hydrogen atoms were refined with anisotropic displacement parameters without any constraints. The H atoms of the OH groups were refined with tetrahedral C–O–H angles, enabling rotation around the C–O bond, O–H distances of 0.84 Å, and with individual isotropic displacement parameters. The H atom of the tertiary C–H group was refined with all X–C–H angles equal at a C–H distance of 1.00 Å. The H atoms of the CH_2 groups were refined with common isotropic displacement parameters for the H atoms of the same group and idealized geometry with approximately tetrahedral angles and C–H distances of 0.99 Å. The H atoms of the methyl group were refined with common isotropic displacement parameters and idealized geometry with tetrahedral angles, enabling rotation around the X–C bond, and C–H distances of 0.98 Å. For 100 parameters final R indices of $R=0.0338$ and w$R^2=0.0827$ (GOF=1.083) were obtained. The largest peak in a difference Fourier map was 0.430 e Å^{-3}.

4.3. Analytical methods

Cyanohydrins were examined after acetylation (Section 4.2.9) by GC (Agilent 6890) using a HP-5MS column (30 m×250 μm, 0.25 μm) with a MS 5973 (EM Voltage 1100).

Enantiomeric purities were analysed on a Chrompack Chirasil-Dex CB (25 m×0.32 mm, 0.25 μm film) (**10**–**12**) or Lipodex-E (**8**–**9**) column (25 m×0.25 mm, 25 μm film) using a HP 6890 gas chromatograph equipped with a FID. 3-Acetoxy-2-methyltetrahydrofuran-3-carbonitrile (**8b**, **9b**): 1 ml/min H_2; 60 °C, 0 min, 5 °C/min, 160 °C, 10 min; 17.8 min, 18.9 min (*cis*), 18.4 min, 18.7 min (*trans*); 3-acetoxy-2-methyltetrahydrothiophen-3-carbonitrile (**8c**, **9c**): 1 ml/min H_2; 110 °C, 0 min, 3 °C/min, 170 °C, 10 min; 12.9 min, 13.5 min (*cis*), 14.5 min, 15.5 min (*trans*). 3-Acetoxytetrahydro-2*H*-pyran-3-carbonitrile (**10**): 1 ml/min H_2; 100 °C, 0 min, 1 °C/min, 140 °C, 10 min; 30.9 min, 32.6 min; 3-acetoxytetrahydrofuran-3-carbonitrile (**11**): 2 ml/min H_2; 100 °C, 0 min, 1 °C/min, 130 °C, 10 min; 12.0 min, 13.5 min; 3-acetoxy-5-methyltetrahydrothiophen-3-carbonitrile (**12**): 1 ml/min H_2; 80 °C, 0 min, 1 °C/min, 105 °C, 0 min, cool 10 min, 80 °C, 0 min, 1 °C/min, 120 °C, 10 min; 32.8 min, 33.39 min (*cis*), 34.88 min, 35.43 min (*trans*).

4.4. Computational methods

All *cis*- and *trans*-isomers of **3b**, **3c**, **4b** and **4c** (Fig. 3, Table 1) were docked into the active site of the hydroxynitrile lyase from *H. brasiliensis* (*Hb*HNL) using a Monte-Carlo-simulated-annealing approach as implemented in the program AutoDock v3.0.[32] The structure of the protein[20] was kept rigid, whereas translational, rotational and three torsional degrees of freedom were varied in the case of the ligand. In order to probe the conformational space of the five-membered rings, a linear structure was created by breaking the bond between C4 and C5. During the simulations, a constraint was applied, keeping the respective distance between 1.4 and 1.7 Å. For each ligand, 100 randomly chosen initial structures were subjected to 150 Monte Carlo steps starting at an *RT*-value of 1000 and using a cooling factor of 0.95 per cycle. In each cycle, a maximum of 10,000 accepted or rejected moves were allowed. The resulting structures were clustered with a root-mean-square tolerance of 1.5 Å. The structure of the lowest-energy representative of each cluster was further optimized using programs from the AMBER v6.0 package.[33]

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The first encapsulation of hydroxynitrile lyase from *Hevea brasiliensis* in a sol–gel matrix

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Abstract—A straightforward process for the encapsulation of *Hb*HNL under low methanol conditions has been developed. By adding a sol, prepared by hydrolysis of TMOS/MTMS at pH 2.8 with continuous removal of methanol, to a stirred solution of the enzyme in a buffer at pH 6.5, at least 65% of the activity of the free enzyme could be recovered after the encapsulation. The aquagels were successfully used in the synthesis of (*S*)-cyanohydrins.

1. Introduction

Hydroxynitrile lyases (HNL's) are a class of enzymes that can be found in a wide range of plants, such as millet and the apple, almond, rubber and plum trees.[1] When the plant material is damaged, for instance by a herbivore, HNL catalyses the breakdown of a cyanohydrin into an aldehyde/ketone and toxic HCN. More interestingly, the enzyme may also catalyse the reverse reaction, enabling the synthesis of enantiopure cyanohydrins from aldehydes/ketones and HCN with excellent yields and enantioselectivities.[2–8] These enantiopure cyanohydrins can in turn readily be converted into a wide range of compounds that are versatile building blocks for the synthesis of fine chemicals, pharmaceuticals and agrochemicals.[2,9,10]

Recently, the immobilisation of enzymes has attracted much attention, increased stability and recyclability being the main research objectives. Cross-linked crystals of HNL's and HNL's adsorbed on solid supports or encapsulated in sol–gels and PVA-gels have been used as catalysts in the synthesis of optically active cyanohydrins.[11–15] However, only the PVA-entrapped HNL from *Prunus amygdalus* and the crosslinked enzyme crystals from *Manihot Esculenta* proved to be stable upon recycling. In this context it is important to notice, that HNL's only have in common that they all catalyse the cyanogenesis. Structurally they can belong to different classes of enzymes and are therefore not always comparable. For example, HNL from *Hevea brasiliensis* is closely related to the α/β hydrolases, which also include lipases, while *Prunus amygdalus* is closely related to FAD dependant oxidoreductases.[16,17]

The (*S*)-hydroxynitrile lyase from *Hevea brasiliensis* (*Hb*HNL) has been used for the addition of HCN to a wide range of aldehydes and ketones.[18–23] In spite of its versatility, the only immobilisation reported is the adsorption of *Hb*HNL onto celite.[11] Here it was found that the maximum activity of the enzyme was only obtained when there was a discrete water layer surrounding the enzyme. This indicates that the enzyme is only active in an aqueous environment. To assure this whilst avoiding a separate aqueous phase in the reaction, the *Hb*HNL can be encapsulated in a sol–gel matrix. The pores of such a matrix can be filled with the aqueous buffer of choice or any organic phase. In this manner, the versatile *Hb*HNL will become available for an even wider range of reaction conditions.

The sol–gel technique allows the synthesis of chemically inert glasses, which can be formed into any desired shape. They have high porosity (up to 98% pore volume) and high mechanical and thermal resistance. In addition they can be produced under conditions that are relatively benign to enzymes. This technique has successfully been applied for the encapsulation of lipases into various sol–gel materials,[24–28] and as the *Hb*HNL is structurally related to lipases, we assumed that the encapsulation of *Hb*HNL should proceed in a similar manner.

Keywords: Asymmetric catalysis; Hydroxynitrile lyase; Oxynitrilase; Sol–gel process; Immobilisation; Cyanohydrins.
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As sol–gel encapsulated CAL-B (33 kDa) which belongs to the α/β hydrolase family just like the *Hb*HNL, has been recycled up to eight times without any loss of activity,[24] it is reasonable to assume that the dimer of *Hb*HNL (58.4 kDa) is equally well encapsulated in a sol–gel matrix (*Hb*HNL is a dimer in aqueous solutions[29]). In spite of this structural similarity, the *Hb*HNL is much more susceptible towards deviations from its optimum conditions.[30–34] Due to this, newly developed methodology rather than the standard immobilisation procedures, is applied.

Here we present the first successful encapsulation of the (*S*)-selective hydroxynitrile lyase from *Hevea brasiliensis* in a sol–gel matrix.

2. Results and discussion

In preliminary experiments, we encapsulated the *Hb*HNL into a sol–gel matrix following standard procedures.[24,26] In these procedures, the methanol released during the formation of the sol was not eliminated, which caused a complete deactivation of the *Hb*HNL during the gelation process. This is in line with the previously described methanol sensitivity of *Hb*HNL.[35] In another procedure, the alkoxy silanes are partially hydrolysed and then transesterified with glycerol. The methanol is removed from the sol, and then the sol is mixed with water containing the biomolecules.[14] This method is so far the best method reported for the encapsulation of methanol sensitive enzymes, however, applied to *Hb*HNL it gave unsatisfactory results.

Therefore, a new procedure was developed, were the alkoxy silanes were almost 100% hydrolysed by acid mediated hydrolysis, and the released methanol was removed by evaporation. The enzyme, dissolved in a buffer with pH 6.5, was then added to this precursor sol. At this pH, the gelation was catalysed and at the same time the enzyme was stabilized.[34,36] As soon as the gel was formed, it was submerged in the same buffer, pH 6.5, to remove any remaining methanol, possibly formed from hydrolysis of residual methoxy groups, by dialysis.

With this procedure, the aquagels[37] showed an activity of at least 65% relative to the free enzyme in the standard aqueous activity test. The apparent decrease of activity is probably due to deactivation by residual methanol and diffusion limitations. Initial rate studies showed that the system is indeed limited by diffusion,[38] which indicates that the actual loss of activity during the encapsulation procedure is lower than 35%. Due to changes of the specific particle size of the ground aquagels under the reaction conditions, quantification of the diffusion limitations was not pursued.

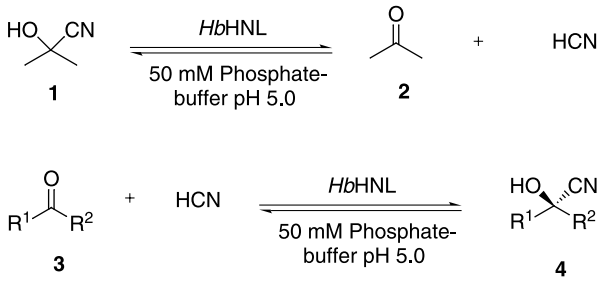
The use of poly vinyl alcohol (PVA) as an additive in the sol–gels is known to increase the activity of lipases in hydrophobic sol–gel materials.[25] Since the structure of *Hb*HNL is comparable with that of lipases, this possibility was also investigated, but, no effect of the PVA on the enzyme activity could be observed.[39] This indicates that the presence of PVA might only have an effect on the lipase activity after or during the drying of the gel.

Varying the MTMS (methyltrimethoxysilane)/TMOS (tetramethoxysilane) ratio is also known to change the activity of the sol–gel entrapped lipases.[40] Aquagels with a concentration of MTMS in TMOS varying from 0 to 50 vol% were prepared[41] and used in the addition of HCN to benzaldehyde, but, no difference in activity could be detected. No higher MTMS concentrations were examined since the gelation process then took several hours and the gels had a paste like aspect. A mixture of 20 vol% MTMS in TMOS was chosen for further studies since this mixture gave the most convenient gelation time.

Attempts to dry the aquagels as aerogels and xerogels resulted in a total loss of activity. In the case of the xerogel there are two possible reasons for deactivation. When the gel is dried by evaporation of the water phase in open air (xerogels), capillary stress will cause partial collapse of the gel structure as the liquid–gas interface moves in through the gel. As the gel shrinks, some of the enzymes will also be crushed. Secondly, it has been suggested that the exposure of *Hb*HNL to a gas–liquid interface drastically reduces the half-life of the enzyme.[34] In the preparation of the aerogels, the water in the aquagel is replaced with acetone, which again is replaced with CO_2 in an autoclave. When the supercritical conditions for CO_2 are reached, by increasing the temperature of the autoclave, the autoclave is slowly evacuated. The acetone is most likely causing the deactivation in this drying procedure. To verify whether this was the case, the buffer filling the pores of the aquagel was exchanged with acetone and then back to the buffer by dialysis. The resulting gel showed no activity, indicating that indeed acetone or the acetone water mixture did deactivate the *Hb*HNL. It has been shown that stirring *Hb*HNL in acetone containing 0.25% water over 15 h at room temperature gives only 15% loss of activity.[35] From this it can be concluded that it is the acetone–water mixture, rather than the acetone itself, that deactivates the enzyme. However, as it is known that *Hb*HNL is inactive at low water concentrations, it is not desirable to dry the gels, but rather to use them directly as aquagels. In this manner the enzyme will be completely hydrated with the buffer of choice. The buffer remains inside the pores of the aquagel and no separate macroscopic water phase is formed in the reaction mixture.

The encapsulated *Hb*HNL was applied in the enantioselective addition of HCN to benzaldehyde **3a**, furaldehyde **3b**, hexanal **3c**, *m*-phenoxybenzaldehyde **3d** and methyl isopropyl ketone **3e** to give their (*S*)-cyanohydrins **4a–e**. For safety reasons acetone cyanohydrin was used as the cyanide source, even though the liberated acetone has a negative effect on the enzyme (Scheme 1).

As both, the generation of HCN and the addition of the HCN to the carbonyl group, are reversible reactions, the maximum conversion will be determined by the equilibrium constants of the two reactions, and, can therefore not be compared to the isolated yields (typically 95–99%) that are obtained in the standard method where a five fold excess of free HCN is used.[21] When the amount of enzyme used in the literature procedure (2.5 times more) is taken into account, the reaction time that we observe, approximately 40–50 min (Fig. 1), is comparable with that found in the literature



	R^1	R^2
a	Phenyl	H
b	2-Furyl	H
c	Hexyl	H
d	*m*-Phenoxy-phenyl	H
e	Isopropyl	Me

Scheme 1. The synthesis of optically active cyanohydrins.

(15 min).[21] The overall equilibrium in Scheme 1 was established rapidly in all cases except for **3d**, a substrate known to be "difficult" for HNL's.[3] A satisfactory result for this substrate has only been described in a highly enzyme loaded emulsion, using free HCN.[21]

The enantiomeric excess of the products is in line with those reported in the literature (>98% for **4a–d**, and 75% for **4e**)[21] for the same reactions. Small differences are due to the chemical background reactions (which form the racemic cyanohydrin) under the specific reaction conditions. To establish the stability of the sol–gel encapsulated *Hb*HNL, it was recycled 3 times in the reaction of HCN with benzaldehyde, using acetone cyanohydrin as the cyanide source. When the gels were washed with diisopropyl ether between each cycle, there was a rapid loss of activity and the gels were completely deactivated after the second recycle (Fig. 2A). This result was improved when the gels were washed with a 50 mM phosphate buffer of pH 5.0 between each cycle. Then, the initial rate only dropped by around 50% for each cycle. In all cases the enantiomeric excess of the product was higher than 98% (Fig. 2B).

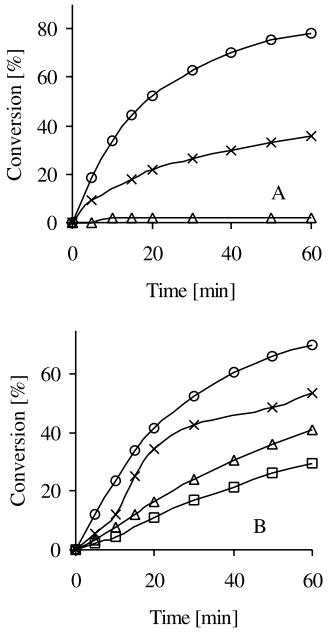


Figure 2. Recycling of the sol–gel encapsulated *Hb*HNL using benzaldehyde as the substrate. In (A) the gel was washed with diisopropyl ether between each cycle and in (B) the gel was washed with a 50 mM phosphate buffer pH 5.0. Cycle 1 (○), cycle 2 (×), cycle 3 (△) and cycle 4 (□).

A gel identical to the one used in the experiment described in Figure 2B was stirred with diisopropyl ether for four hours (which is the same time as it took to perform the first three cycles of the experiment described in Fig. 2B) before benzaldehyde and acetone cyanohydrin were added. The conversion observed for this gel was comparable with the conversion in cycle one of Figure 2B, indicating that there is no deactivation due to the buffer inside the gel or the solvent. Instead, the loss of activity must be caused by HCN,

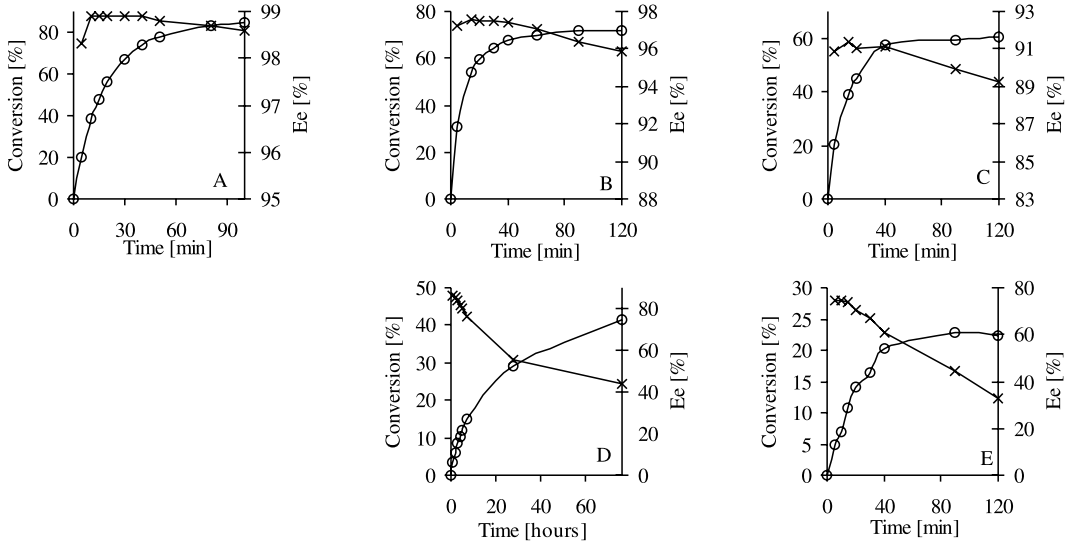


Figure 1. The conversion (○) of **3a** (A), **3b** (B), **3c** (C), **3d** (D) **3e** (E) into their respective (*S*)-cyanohydrins **4a–e**. 0.98 mM **3a–e**, diisopropyl ether, 50 mM phosphate buffer pH 5.0, 3 equiv acetone cyanohydrin and 1.8 KU *Hb*HNL. The enantiomeric excess (×) was determined by chiral GC (see materials and methods).

acetone, acetone cyanohydrin, the substrate, the product or leakage of the enzyme.

In the case of washing with diisopropyl ether, the deactivation is probably due to the acetone, which is formed during the reaction. Firstly, acetone is harmful for the enzyme, secondly, it changes the solubility of the solvent in the aqueous phase and vice versa. When the solvent is used for washing some of the water will be washed away from the gel, lowering the enzyme activity.

When the gels are washed with the buffer, the initial conditions for the enzyme are re-established and the activity is relatively higher than when washing with a solvent. The loss of activity will in this case, too, be due to the acetone formed, but also due to leakage of enzyme during the washing procedure.

In order to rule out any possible leakage of activity into the organic phase, the suspension of one reaction was filtered (taking care that no HCN could escape during the filtration) and the filtrate was monitored for activity. As expected the filtrate showed no activity (Fig. 3). However, when the reaction was performed in water, it was found that up to 17% of the observed activity derives from *Hb*HNL that has leached into the aqueous phase.[42]

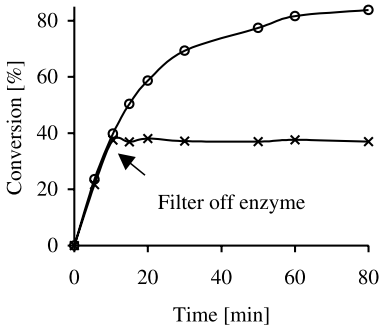


Figure 3. Test for leakage of activity from the gel into the organic phase. Unfiltered reaction (○) and filtered reaction (×).

Encapsulated enzymes are in principle not bound to the sol gel surface. This means that if the gel breaks and the 'capsule' around an enzyme opens, the enzyme will be washed away. Indeed, when the activity of an aquagel, which had been crushed into a fine powder was compared to an aquagel that had been crushed into a fine powder and then washed, a significant difference was found (Fig. 4). The

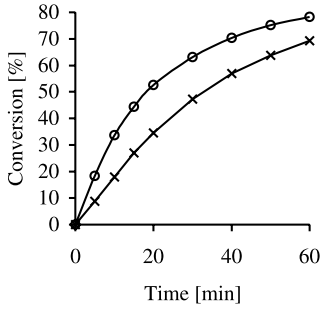


Figure 4. Test for leakage of activity during the washing procedure. Ground gel (○) and ground and washed gel (×).

washed powder showed a decrease of the initial reaction rate by 48% compared to the unwashed sol–gel powder. Even though the gels were shaken and not magnetically stirred in the recycling experiment, it is probable that some of the gels got further crushed leading to loss of activity in the subsequent washing.

In order to characterise the gels, they were dried under supercritical conditions with CO_2 to give aerogels. BET-analysis gave a surface area of 1000 m^2/g and a pore volume of 1.74 cm^3/g. The pore size distribution (Fig. 5) is relatively wide, where the maximum pore radius is 5 nm. In comparison the dimensions of the *Hb*HNL monomer is approximately $3.0\times3.8\times4.8$ nm.[43] After the formation of the gel, the aquagel is usually aged for 12–72 h in order to complete the hydrolysis and condensation. To investigate if there is an optimal ageing time for the *Hb*HNL, we tested the activity of gels aged up to 16 days. The result (Fig. 6) shows that there is a significant drop in activity during the first four to five days; then the activity stabilizes. The initial drop of activity is probably due to the formation of methanol during the beginning of the aging process and structural changes within the gel. The structural changes during the first days then level off.

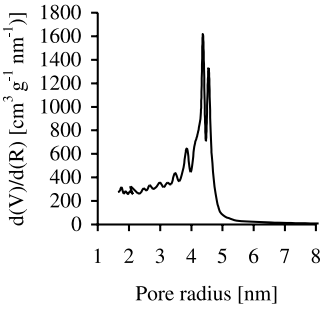


Figure 5. Pore size distribution of the sol–gel; the vertical axis is the differential d*V*/d*R*, where *V* is the adsorbed nitrogen gas volume, at standard conditions, per gram of gel (cm^3/g) and *R* is the pore radius (nm).

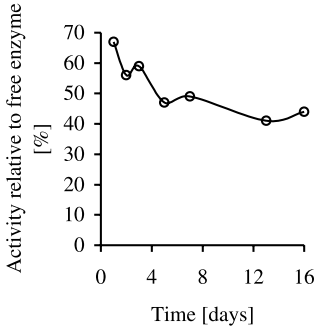


Figure 6. Aging of the gels.

3. Conclusion

*Hb*HNL, an enzyme very sensitive to organic solvents and requiring a near neutral pH, was successfully immobilized in a sol–gel. This low methanol immobilisation and first application of an aquagel holds great potential for the sol–gel encapsulation of many sensitive enzymes.

4. Experimental

4.1. General

*Hb*HNL was made available in a 25 mM potassium phosphate buffer pH 6.5 with 0.09% sodium azide (3600 IU/ml) by Roche Diagnostics (Penzberg, Germany). The activity of the homogenous enzyme was determined as described in the literature.[30] The reactants used in this study were poly vinyl alcohol with an average molar mass of $M=$ 15,000 (Fluka), methyltrimethoxysilane (MTMS, 98%, Aldrich) and tetramethoxysilane (TMOS, 98%, Aldrich). Benzaldehyde, *m*-phenoxybenzaldehyde, furaldehyde, hexanal and methyl isopropyl ketone were all of analytical grade and distilled under a nitrogen atmosphere less than two hours before use. Mandelonitrile was purified by column chromatography at most 24 h prior to use and stored under nitrogen at −4 °C. Acetone cyanohydrin was distilled and stored under nitrogen at 4 °C. Diisopropyl ether was of analytical grade and used without further purification. The derivatised samples were analysed on a β-cyclodextrin column (CP-Chirasil-Dex CB 25 m× 0.25 mm) using a Shimadzu Gas Chromatograph GC-14B equipped with a FID detector and a Shimadzu Auto-injector AOC-20i, using N_2 as the carrier gas. The conversion and the enantiomeric excess were calculated from the peak areas. The temperature programs and retention times are given in Table 1. UV measurements were performed on a UNICAM UV/Vis spectrometer. A Brunauer, Emmett and Teller (BET) analysis of a gel dried as an aerogel, desorbed at 200 °C, gave the specific surface area and the pore size distribution. Buffer A is a 25 mM potassium phosphate buffer pH 6.5 with 0.09% sodium azide, buffer B is a 50 mM citrate/potassium phosphate buffer pH 5.0. Racemic reference compounds were prepared according to standard procedures[44] and their NMR-spectra were in accordance with literature.[44–47]

4.2. General procedure A. Preparation of the sol–gel precursor

Acidic water (1.38 ml, pH adjusted to 2.85 by addition of HCl) was added to a mixture of MTMS (2.10 g, 15.4 mmol), TMOS (9.08 g, 58.5 mmol) and distilled water (10.4 ml) and stirred in a 100 ml round bottom flask until a homogenous mixture was obtained. The formed methanol was continuously removed on a rotary evaporator until the characteristic odours of MTMS, TMOS and MeOH were not detectable any more. The mixture was then cooled to 0 °C and water was added until the total volume corresponded to the initial MTMS/TMOS—volume. The precursor (sol) was used immediately for the encapsulation of *Hb*HNLGeneral procedure B. Encapsulation of *Hb*HNL in a sol–gel matrix for standard activity test.

4.3. General procedure B. Encapsulation of *Hb*HNL in a sol–gel matrix for standard activity test

The stock solution of *Hb*HNL (100 mg, 3.6 KU/ml) was diluted to 6.0 g with buffer A. This solution (40 µl) was added to a mixture of the precursor (500 µl; prepared as described in general procedure A), and buffer A (460 µl) and stirred magnetically for 20 s. The stirring bar was removed and when the mixture gelled (4–5 min), the gel was submerged in buffer A and aged at 4 °C for 24 h. Buffer A was then replaced with distilled water and the gels were aged for further 20 h at 4 °C. The aquagel was ground into a fine powder and tested for catalytic activity.

4.4. General procedure C. Encapsulation of *Hb*HNL in a sol–gel matrix for synthetic reaction

A mixture of the stock solution of *Hb*HNL (0.5 ml, 3.6 KU/ml) and the precursor mixture (500 µl; prepared according to standard procedure A) was stirred magnetically for 20 s. The stirring bar was removed and when the mixture gelled (4–5 min), the gel was submerged in buffer A and aged at 4 °C for 24 h. Then the buffer in the pores was exchanged against buffer B by dialysis over 1 h. The aquagel was ground into a fine powder and used for the synthesis of enantiopure cyanohydrins.

4.5. General procedure D. Standard aqueous activity test for the encapsulated enzyme in aqueous media

Mandelonitrile (80 µl) was dissolved in 10 ml of a citric acid/potassium phosphate buffer (3 mM, pH 3.5). This solution (1.4 ml), and all of the sol–gel encapsulated *Hb*HNL, prepared as described in general procedure B, were added to buffer B (4.9 ml) at 25 °C. The mixture was stirred magnetically for another 6 min, before the reaction was stopped by addition of concentrated HCl (2 drops). A sample was filtered through cotton and the UV-absorption of the supernatant was measured at 280 nm against a blank reaction. The activity was calculated according to the equation below.

$$\text{Activity} = \frac{V}{\varepsilon_{280} l S T} \Delta Abs/\text{min}$$

Activity. The activity of the sample (U/ml); V: total reaction volume (ml); ε_{280}: 1.376 ($\text{l}\times\text{mmol}^{-1}\times\text{cm}^{-1}$); l: path length in the UV-cell (cm); S: volume of enzyme solution added in the preparation of the gel (ml); T: reaction time (min).

Table 1. Temperature programs and retention times for **3a–e**, (*R*)-**4a–e** and (*S*)-**4a–e**

Substrate	Temperature program[a]	R_t (min) **3**	R_t (min) (*R*)-**4**	R_t (min) (*S*)-**4**
a	125 °C (3 min)–20 °C/min–200 °C (0 min)	3.11	6.35	6.64
b	100 °C (3 min)–20 °C/min–200 °C (0 min)	3.17	6.50	6.80
c	75 °C (5 min)–30 °C/min–200 °C (1 min)	5.49	9.03	9.27
d	125 °C (3 min)–20 °C/min–200 °C (13 min)	10.16	19.19	19.58
e	60 °C (5 min)–2 °C/min–98 °C (0 min)	2.80	22.85	23.07

[a] Initial temperature (holding time)–temperature gradient–final temperature (holding time).

4.6. General procedure E. Synthesis of optically active cyanohydrins

At 25 °C, all of the sol–gel encapsulated *Hb*HNL, prepared according to general procedure C (1.8 kU *Hb*HNL), was added to a magnetically stirred solution of the freshly distilled aldehyde/ketone (4.92 mmol) in diisopropyl ether (5 ml) which was saturated with buffer B. The reaction was started by the addition of acetone cyanohydrin (1.35 ml, 14.76 mmol). Samples of 10 µl were taken through the septum at different stages of conversion. The samples were added to a mixture of dichloromethane (0.5 ml), acetic anhydride (40 µl) and pyridine (40 µl). After at least 12 h at room temperature the samples were analysed by chiral GC. The conversion and the enantiomeric excess were calculated from the relative peak areas of the aldehyde and the cyanohydrin derivative. The results are given in Figure 1.

4.7. Recycling, washing with diisopropyl ether saturated with a 50 mM citrate/phosphate buffer pH 5.0

The gels were prepared according to general procedure C and used in the addition of HCN to benzaldehyde according to general procedure E. The synthetic reaction was stopped after 1h and the gel was washed with diisopropyl ether saturated with buffer B before it was reused in a new cycle. The results of three cycles are given in Figure 2A.

4.8. Recycling, washing with a 50 mM citrate/phosphate buffer pH 5.0

The gels were prepared according to general procedure C and used in the addition of HCN to benzaldehyde according to general procedure E, with the following exception: The synthetic reaction was shaken orbitally and after one hour the gel was washed on a filter with a 50 mM phosphate buffer pH 5.0 (40 ml) and then reused in a new cycle. The results of four cycles are given in Figure 2B.

4.9. Test for leakage of activity to the organic solvent

Two gels were prepared according to general procedure C and used in the addition of HCN to benzaldehyde according to general procedure E, in two separate reactions A and B. After 10 min reaction B was filtered in a closed system to avoid any leakage of HCN. No more conversion could be detected in the supernatant. The conversion curves of the two reactions are given in Figure 3.

4.10. Test for leakage of activity by washing

Two gels were prepared according to general procedure C and used in the addition of HCN to benzaldehyde according to general procedure E, in two separate reactions A and B. The crushed gel used in reaction B was washed with buffer B prior to its use in the synthetic reaction. The conversion curves for the two reactions are given in Figure 4.

4.11. The effect of ageing on the gels

Seven gels were prepared according to general procedure B and stored for 1, 2, 3, 5, 7, 13 and 16 days respectively. The activity relative to the free enzyme was then measured according to general procedure D. The results are given in Figure 6.

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37. In an aquagel, the pores of the gel are filled with water.
38. Gels prepared according to standard procedure C were cut or ground into a particle size of 3–5 mm, 1–2 mm and <0.1 and used in the addition of HCN to benzaldehyde according to standard procedure E. The gels showed relative initial rates of 0.2, 0.3 and 1, respectively.
39. Three gels were prepared according to procedure B where the 25 mM phosphate buffer pH 6.5 contained 0.0, 1.0 and 2.0% PVA respectively. The gels were tested for activity according to procedure D.
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41. The gels were prepared according to standard procedure C with different MTMS/TMOS ratios and used in the addition of HCN to benzaldehyde according to standard procedure E.
42. Gels prepared according to standard procedure B and tested for activity according to standard procedure D. After 10 min the reaction mixtures were filtered and the activity of the filtrates were monitored.
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Study on the (*R*)-oxynitrilase activity of *Pouteria sapota*

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Abstract—Mamey (*Pouteria sapota*) defatted meal was used to catalyze the enantioselective addition of HCN to α,β-unsaturated aldehydes. Using a biphasic system of diisopropyl ether and citrate buffer (0.1 M, pH 5.0, 10% v/v), the (*R*)-cyanohydrins obtained showed good conversion (from 54 to 98%) and enantiomeric excess (from 74 to 99%).

1. Introduction

Research on enzymatic processes to prepare optically active compounds has been growing constantly in recent years, due to the advantages enzymes have over metallic chiral catalysts, mainly in the preparation of biologically active compounds. Oxynitrilases or hydroxynitrile lyases are enzymes that biocatalyze the enantioselective addition of HCN to aldehydes or ketones to yield cyanohydrins. These compounds are versatile building blocks that have been used in the preparation of pharmaceuticals and agrochemicals. Oxynitrilases have attracted the attention of many researchers, in such way that actually there are very interesting findings in this field.[1–6]

Hydroxynitrile lyases have been found in a wide variety of plant sources, but the selectivity towards the biocatalyzed addition of HCN to carbonyl compounds is not the same, some accept better aromatic rather than aliphatic aldehydes, some biocatalyze the addition of HCN to aldehydes and ketones, others only to aldehydes. Due to this, it can be said that the different sources of oxynitrilases are complementary.[1–5,7,8] So, the study of alternative sources of oxynitrilases becomes important.

In previous work we found that seeds of *Pouteria sapota* (mamey) are a source of (*R*)-oxynitrilase.[7] We found that in aqueous medium the defatted meal of mamey biocatalizes the addition of HCN to aromatic aldehydes with conversions from 24 to 73% and enantiomeric excesses from 34 to 77%. We extended the study to determine the selectivity towards different aldehydes in organic medium. We tested aromatic, heteroaromatic, cinnamaldehyde and aliphatic aldehydes, and except with cinnamaldehyde, the enantiomeric excesses were good (77–98%) (Fig. 1).

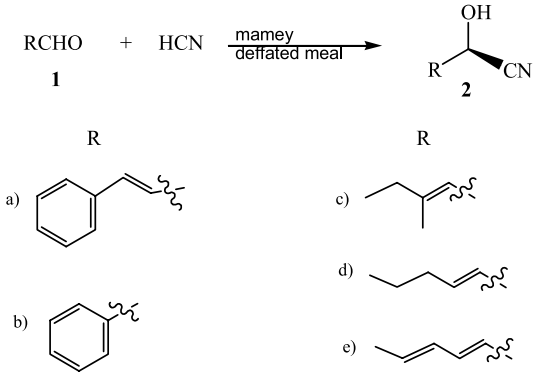

Figure 1.

Due to the promising results with mamey, we extended our study to find the reaction conditions to get the best biocatalytic activity of the defatted meal of mamey seeds, for the addition of HCN to α,β-unsaturated aldehydes. We chose those aldehydes to prepare cyanohydrins which can be used in the preparation of several interesting compounds[9] such as insecticides.[10]

2. Results and discussion

It is well known that oxynitrilases need some water to biocatalyze addition of HCN to aldehydes, but the enantioselectivity of the reaction can be decreased by the chemical reaction that is favored by the aqueous medium. This last reaction can be diminished by lowering the pH and

Keywords: Oxynitrilases; Cyanohydrins; Mamey.
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temperature of the reaction medium or using proper organic solvents. The aim of this work is to improve the addition of HCN to aldehydes biocatalyzed by mamey meal, the study is divided into several parts to determine the solvent, the acid used in the preparation of the HCN source, concentration of buffer solution for the biphasic system, and the water content of the biphasic system. The reactions for this study were carried out with benzaldehyde and cinnamaldehyde, after analysis of the results the best reaction conditions were applied to other α,β-unsaturated aldehydes.

2.1. Effect of solvent

It is reported that the biocatalytic activity of oxynitrilases is better in biphasic systems, and that organic solvent has an important effect on the yield and enantioselectivity.[2,11,12] To determine the most convenient solvent for the reaction of addition of HCN to cinnamaldehyde (**1a**) to get the corresponding cyanohydrin (**2a**) catalyzed by mamey meal, different solvents were tested to extract the HCN from a buffer solution (KCN/citric acid, pH 5.0, 1 M) and use it as reaction solvent, then the reaction was carried out at 4 °C for 24 h, the results are in Figure 2.

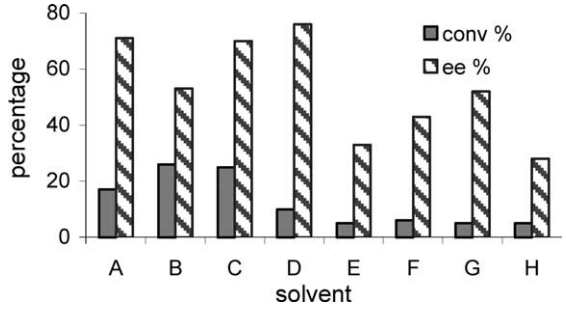

Figure 2. Conversion (determined by ^{1}H NMR) and enantiomeric excess (determined by HPLC using an OD Chiracel column) of cyanohydrin **2a**, in different solvents. A: diethyether, B: diisopropyl ether, C: methyl *tert*-butyl ether (MTBE), D: ethyl acetate, E: hexanes, F: heptane, G: octane, H: toluene.

From the results in Figure 2, it can be observed that the addition of HCN to cinnamaldehyde catalyzed by mamey defatted meal is not favorable in hydrocarbons such as hexanes (E), heptane (F), octane (G) and toluene (H), since the conversion was less than 10%, and the enantiopurity was also low. When ethyl acetate was used in this reaction the enantioselectivity was the highest (72%), but as with hydrocarbon solvents the conversion was also very low (10%).

By using diethyl ether (A) as solvent, the enantiomeric excess was also high (70%) and the conversion was a little higher (17%) than with the previously mentioned solvents. The best reactivities were obtained with diisopropyl ether (B) and MTBE (C), the conversions were 26 and 25% respectively, but with MTBE the enantiomeric excess was superior (70%).

A decrease in enantiomeric excess can be due to the formation of the racemic cyanohydrin because of the non-biocatalized addition of HCN to the aldehyde. To determine the effect of this unwanted addition, a reaction under the same conditions but without the meal was carried out, and after 24 h no cyanohydrin was detected. We can conclude that the enantiomeric excess of cyanohydrin **2a** is not so high because mamey meal is not very selective towards aldehyde **1a**, under the conditions of reaction tested.

2.2. Effect of the acid used to prepare the KCN/acid buffer

Another important condition in the addition of HCN to aldehydes is the acid used in the preparation of the buffer solution of KCN/acid (pH 5.0, 1 M), which is the source of HCN.[13] Acetic, citric, phosphoric, lactic and tartaric acids were chosen to prepare KCN/acid buffer, the reaction of addition of HCN was performed with benzaldehyde (**1b**) using diisopropyl ether as solvent in microaqueous medium[12,14] and after 24 h of reaction at 4 °C the reaction was analyzed. Although the enantiomeric excess of the obtained mandelonitrile (**2b**) was >99%, with all the acids, the conversion was not the same. From the results in Figure 3 it can be stated that conversion was the highest for citric and phosphoric (93%), than with the other acids. One disadvantage for the use of phosphoric acid is that the product becomes dark and it is difficult to purify.

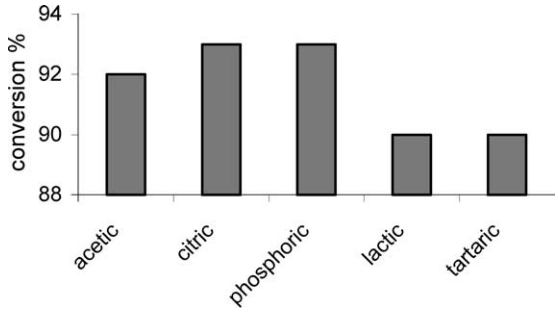

Figure 3. Effect of the acid used to prepare KCN/acid, in the conversion (determined by ^{1}H NMR) of benzaldehyde (**1b**) to mandelonitrile (**2b**).

Since cinnamaldehyde seems to be the less accepted substrate for mamey oxynitrilase, we decided to do an experiment similar to the one described above, to determine the effect of the acid on the reactivity and enantioselectivity with this aldehyde. Acetic, citric, ascorbic and lactic acids were selected, the mixture was analyzed after 24 h of reaction at 4 °C and the results are shown in Figure 3. The enantiomeric excesses are similar in all the cases (approximately 50%), but the conversion is very low with acetic acid (8%) and practically the same with citric, ascorbic and lactic acids (approximately 25%). Due to the results obtained, we decided to continue our studies with mamey meal using diisopropyl ether and MTBE as solvents, and citric acid for the KCN/acid buffer solution.

2.3. Effect of the concentration of the citrates buffer solution

We evaluated the effect of the concentration of the citrate buffer solution,[13] on the preparation of cyanohydrin **2a** catalyzed by the defatted meal of mamey. The citrate buffer

solution in concentrations of 0.02, 0.05, 0.1, 0.15 and 0.5 M (pH 5.0) was added in a ratio of 1% (v/v) to the solution of diisopropyl ether and HCN, then the meal and the aldehyde **1a** were added, after 6 and 12 h at 4 °C the reaction mixture was analyzed.

The enantiomeric excess of the product obtained in all the cases was very high (99%), so the enantioselectivity of the reaction was not affected by the concentration of the buffer solution, but the degree of conversion showed a dependence of the concentration. From Figure 4 it is clear that there is an increase in the conversion as the solution becomes more concentrated until a maximum of activity of the mamey meal is reached, at a concentration of 0.1 M of the buffer solution, then the reactivity is decreased with more concentrated solutions (Fig. 5).

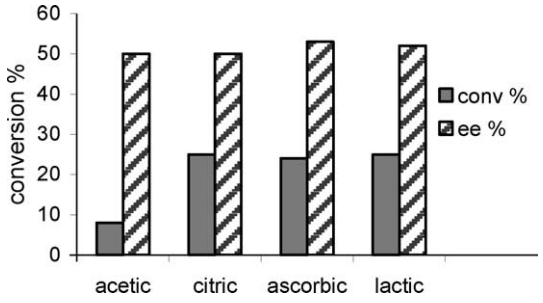

Figure 4. Effect of the acid used to prepare KCN/acid, in the conversion (determined by ^{1}H NMR) and enantiomeric excess (determined by HPLC using an OD Chiracel column) of aldehyde (**1a**) to cyanohydrin (**2a**).

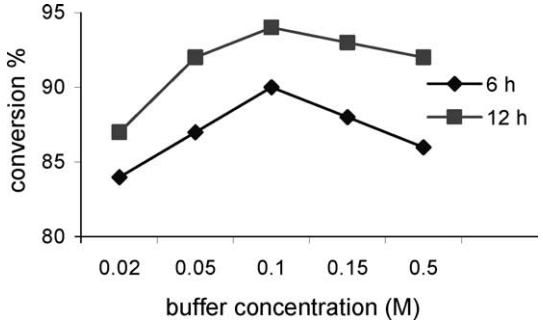

Figure 5. Effect of buffer concentration (M) on the conversion (determined by ^{1}H NMR) of benzaldehyde (**1b**) to mandelonitrile (**2b**), biocatalyzed by mamey meal.

2.4. Effect of the water content of the biphasic system

It is well known that some quantity of water is necessary for the optimum activity of oxynitrilases, but there is not an agreement on the minimum and maximum water content needed for these enzymes to work. It is also known that at high water content the undesirable chemical addition of HCN to aldehydes is a favored reaction, resulting in a lower enantiomeric excess. Some examples are the following: Straathof[15] found that a 50% aqueous phase is the optimum for (*R*)-mandelonitrile production; the same author determined that a 15% aqueous phase is the optimum for (*R*)-4-hydroxymandelonitrile production,[16] Kanerva determined 13.5% as optimum for the resolution of 2-hydroxy-2-phenylpropanenitrile,[17] and Lin reported that higher yields and enantioselectivity in the preparation of several cyanohydrins are obtained in microaqueous medium (0.32%, v/v of water content).[12,14] All these studies were done using almond meal.

Since there are no data about the effect of water content on the oxynitrilase activity of mamey meal, we carried out the following experiment. To a solution of HCN in diisopropyl ether or MTBE were added different quantities of citrate buffer solution, then the mamey meal, followed by cinnamaldehyde (**1a**), the reaction was monitored at 24, 48, 72, and 96 h, at 4 °C.

From the results in Figure 6 it can be stated that the conversion is higher when the reaction is carried out in diisopropyl ether than in MTBE. It is also observed that the conversion increases proportionally with the increase in water content, in such way that after 48 h the maximum conversion (54%) is obtained with 90% of aqueous phase in diisopropyl ether (f), but it is noticeable that after that time the cyanohydrin began to transform into the aldehyde. Waiting longer than 48 h for a higher conversion degree will decrease cyanohydrin concentration, due to the reversibility of the reaction.

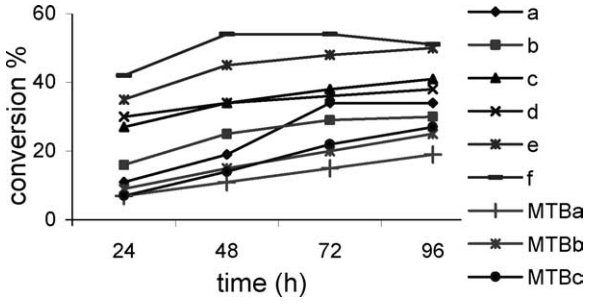

Figure 6. Effect of water content on conversion (determined by ^{1} H NMR) % of aldehyde (**1a**) to cyanohydrin (**2a**) catalyzed by mamey meal. Water content in diisopropyl ether, a: microaqueous medium, b: 1%, c: 5%, d: 10%, e: 50%, f: 90%. Water content in methyl *tert*-butyl ether, MTBa: microaqueous medium, MTBb: 1%, MTBc: 5%.

In the rest of the reactions, an important increase in conversion from the beginning of the reaction until approximately 48 h is observed, but from 72 to 96 h the change in the degree of conversion is minimal, and in some cases there is no change at all (a and b). It is possible that around this time the biocatalyzed reaction has reached an equilibrium. From Figure 7 some interesting facts can be observed: with the highest water content (f, 90% of water in diisopropyl ether) and the lowest (a, microaqueous medium in diisopropyl ether and MTBa, microaqueous medium in methyl *tert*-butyl ether), the enantiomeric excess have the lowest values. In Figure 7 it is noticeable that in almost all the cases the enantiomeric excess reaches a maximum at 48 h and after that time the enantiomeric excess begins to decrease. This can be explained by an important competition between the biocatalyzed and chemical addition of HCN to the aldehyde. In addition, the cyanohydrin began to decompose and racemize, this behavior is similar to that observed for conversion (Fig. 6).

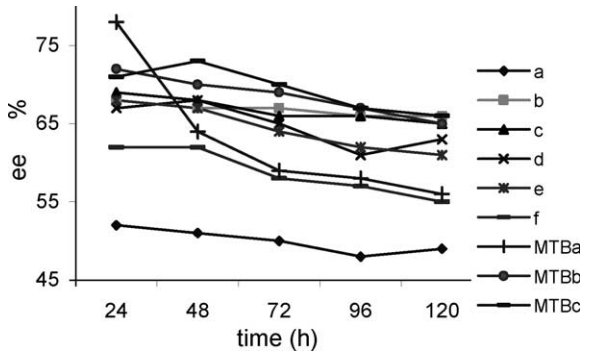

Figure 7. Effect of water content on enantiomeric excess % (determined by HPLC using an OD Chiracel column) of cyanohydrin (**2a**) catalyzed by mamey meal. Water content in diisopropyl ether, a: microaqueous medium, b: 1%, c: 5%, d: 10%, e: 50%, f: 90%. Water content in methyl *tert*-butyl ether, MTBa: microaqueous medium, MTBb: 1%, MTBc: 5%.

The highest enantiopurity is reached after 48 h with MTBE (water content of 5 and 10%, v/v) and diisopropyl ether at water content of 5 and 10%. In the case of diisopropyl ether it is very interesting that with 1, 5, 10 and 50% of water content, enantiomeric excess are very similar at 48 h, but after that time the decrease is much more significant with 10 and 50% of water. This could be because of the competition between biocatalyzed and chemical reaction, which results in racemization of the reaction.

From these results the best conditions for the addition of HCN to cinnamaldehyde biocatalyzed by mamey meal were: the use of diisopropyl ether in a biphasic system, with a water content of 5%, with reaction times not longer than 48 h, at 4 °C.

2.5. Preparation of cyanohydrins from α,β-unsaturated aldehydes

Due to their synthetic utility and because they are precursors of insecticides, we explored the effect of water content on the addition of HCN to α,β-unsaturated aldehydes (**1c**, **1d**, **1e**), catalyzed by mamey meal. According to results from previous experiments, the solvent selected was diisopropyl ether, KCN/citric acid buffer (pH 5.0, 1 N) as HCN source, for the aqueous phase citrate buffer (pH 5.0, 0.1 M), the amounts of the last one were: microaqueous medium (approximately 0.32%), 1, 5, 10 and 50%, v/v. After 48 h at 4 °C the reaction mixture was analyzed, the results are shown in Table 1.

From the results in Table 1, it can be observed that the reactivity and enantioselectivity of the addition of HCN to aldehydes **1c**, **1d**, **1e** catalyzed by mamey meal, increases constantly with the increase in water content in the reaction medium. These facts are in agreement with that shown in Figures 6 and 7. The best results were obtained with 50% water content in the reaction, however, the disadvantage of employing 50% of water is that the recovery of the product becomes difficult, so it is better to use 10% of water since the results obtained were similar to those with 50%.

Although all the aldehydes investigated were α,β-unsaturated (**1a**, **1c**, **1d**, **1e**), except for benzaldehyde (**1b**), the reactivity towards addition of HCN catalyzed by mamey was very different. With cinnamaldehyde (**1a**), the maximum conversion and enantioselectivity were not so high, 54 and 75%, respectively (Figs. 6 and 7). Something similar was observed with 1,4-hexadienal (**1e**), the highest conversion was 69% (Table 1) and enantioselectivity 79% (Table 1).

2-Methyl-2-pentenal (**1c**) and *trans*-2-hexenal (**1d**) were found to be more reactive under the reaction conditions tested and had better enantiopurities, for **2c** 84 and 90%, respectively (Table 1), for **2d** 88 and 98%, respectively (Table 1). For some reason it seems that substrates having more extended conjugated systems become less reactive to the addition of HCN catalyzed by mamey meal, this can explain the less favorable results with substrates **1a** and **1e**. It is worth mentioning that 1,4-addition was not observed in these experiments.

3. Conclusions

From the results obtained we determined that mamey meal is an (*R*)-oxynitrilase source which displays its best biocatalytic activity in the addition of HCN to aldehydes in the following reaction conditions, diisopropyl ether as the solvent, citric acid for the preparation of KCN/acid buffer as HCN source, and a water content of 10% in a biphasic system. Benzaldehyde (**1b**), 2-methyl-2-pentenal (**1c**) and *trans*-2-hexenal (**1d**) proved to be more reactive under the mentioned reaction conditions, whereas cinnamaldehyde (**1a**) and 1,4-hexadienal (**1e**) showed less reactivity.

Table 1. Effect of water content on conversion and enantiomeric excess of cyanohydrins **2c**, **2d** and **2e** of the reaction catalyzed by mamey meal

% of water content (v/v)	Cyanohydrin **2c**		Cyanohydrin **2d**		Cyanohydrin **2e**	
	Conv. %[a]	ee %[b]	Conv. %[a]	ee %[b]	Conv. %[a]	ee %[b]
Microaqueous medium	68	70	37	87	27	52
1	74	77	56	94	51	79
5	77	88	67	98	50	72
10	84	89	62	92	63	70
50	83	90	88	95	69	75

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC using an OD Chiracel column.

4. Experimental

4.1. Chemicals and sources of enzymes

Ripe mamey (*Pouteria sapota*) seeds were obtained from a fresh fruit purchased in a local grocery store. The mamey seeds were ground and washed three times with acetone and once with diisopropyl ether, after filtration by suction the powder was air dried and stored at 4 °C. Commercial aldehydes were purchased from Aldrich.

Optical rotations were measured in a Perkin–Elmer polarimeter model 341. Enantiomeric excesses were determined by HPLC analyses, using a Chiracel OD column using hexanes–isopropanol as eluent in a Hewlett–Packard 1050 series, equipped with a diode array detector. Conversion percentages were determined by NMR. ^{1}H NMR spectra were recorded on a Varian at 400 MHz using $CDCl_3$ as a solvent and TMS as internal reference.

4.2. General procedure for enzymatic reactions

HCN (1.5 equiv) was extracted from a buffer solution (KCN/citric acid, 1 M, pH 5.0) with the proper solvent (2× 2.5 mL). To this solution was added the citrate buffer solution (0.1 M, pH 5.0); the quantity added to the reaction medium depended on the experiment, then 200 mg of mamey defatted meal were added and stirred for 10 min at room temperature, after this 1 mmol of the aldehyde was added. The reaction mixture was stirred for the necessary time at 4 °C, filtered, dried over sodium sulfate and the solvent was evaporated to dryness. Enantiomeric excess was determined by HPLC using a Chiracel OD column with hexanes–isopropyl alcohol as eluent and conversion percentage was determined by ^{1}H NMR, of the crude product.

4.2.1. (*R*)-(+)-2-Hydroxy-4-phenyl-3*E*-butenenitrile (2a). Conversion 54%, $[\alpha]_D^{22}=+17$ (*c* 1, CH_2Cl_2), ee 72%; lit.:[12] $[\alpha]_D^{13}=+26.1$ (*c* 0.78, $CHCl_3$), ee 69.3%. ^{1}H NMR ($CDCl_3$): $\delta=5.18$ (d, $J=6.0$ Hz, 1H), 6.26 (dd, $J=16.0$, 6.0 Hz, 1H), 6.9 (d, $J=6.0$ Hz, 1H), 7.35 (m, 5H).

4.2.2. (*R*)-(+)-2-Hydroxybenzeneacetonitrile (2b). Conversion 95%, $[\alpha]_D^{22}=+46$ (*c* 1.9, CH_2Cl_2); lit.:[12] $[\alpha]_D^{20}=+47.5$ (*c* 1.89, $CHCl_3$), ee >99%. ^{1}H NMR ($CDCl_3$): $\delta=5.52$ (s, 1H), 7.49 (m, 5H).

4.2.3. (*R*)-(−)-2-Hydroxy-3-methyl-3*E*-hexanenitrile (2c). Conversion 84%, $[\alpha]_D^{22}=-72$ (*c* 3.9, CH_2Cl_2), ee 89%. ^{1}H NMR ($CDCl_3$): $\delta=1.0$ (t, $J=7.6$ Hz, 3H), 1.78 (s, 3H), 2.09 (m, 2H), 3.42 (br, 1H), 4.83 (s, 1H), 5.72 (t, $J=7.6$ Hz, 1H). Configuration was assigned on the basis of mamey meal selectivity, and of elution order of the enantiomers on chiracel OD column using hexanes–ispropanol (95:5) as eluent, (*R*)-enantiomer $t_r=11.37$ min, (*S*)-enantiomer $t_r=11.036$ min.

4.2.4. (*R*)-(−)-2-Hydroxy-3*E*-heptanenitrile (2d). Conversion 88%, $[\alpha]_D^{22}=-60$ (*c* 3.16, CH_2Cl_2), ee 95%; lit.:[9] $[\alpha]_D^{20}=+20.3$ (*c* 0.3, $CHCl_3$), (*S*)-enantiomer, ee 95%. ^{1}H NMR ($CDCl_3$): $\delta=0.92$ (t, $J=7.6$ Hz, 3H), 1.43 (m, 2H), 2.08 (m, 2H), 3.72 (br, 1H), 4.94 (d, $J=6.4$ Hz, 1H), 5.59 (dd, $J=15.5$, 6.4 Hz, 1H), 6.03 (m, 1H).

4.2.5. (*R*)-(−)-2-Hydroxy-3*E*,5*E*-heptadienenitrile (2e). Conversion 79%, $[\alpha]_D^{22}=-52$ (*c* 3.85, CH_2Cl_2) ee 69%; lit.:[18] $[\alpha]_D^{23}=-24.9$ (*c* 1, $CHCl_3$), ee 96%. ^{1}H NMR ($CDCl_3$): $\delta=1.8$ (d, $J=6.45$ Hz, 3H), 3.87 (br, 1H), 4.99 (d, $J=6.0$ Hz, 1H), 5.62 (dd, $J=15.2$, 6.0 Hz, 1H), 5.91 (m, 1H), 6.06 (dd, $J=15.0$, 10.4 Hz, 1H), 6.46 (dd, $J=15.0$, 10.4 Hz, 1H).

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Synthetic and mechanistic studies on asymmetric cyanohydrin synthesis using a titanium(salen) bimetallic catalyst

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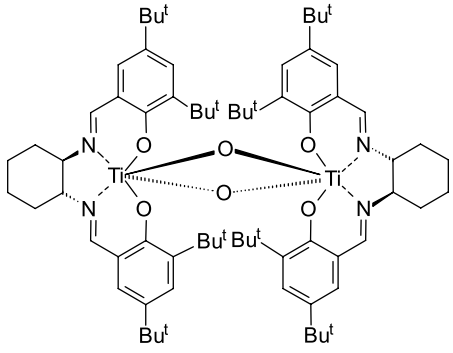
Abstract—A bimetallic titanium(salen) complex **1** was found to catalyse the asymmetric addition of ethyl cyanoformate to aldehydes. Best results were obtained using 5 mol% of the catalyst at −40 °C and under these conditions, both aromatic and aliphatic aldehydes were converted into cyanohydrin carbonates with up to 99% enantiomeric excess. The same catalyst could also be used to catalyse the asymmetric addition of potassium cyanide to aldehydes in the presence of propionic anhydride, leading to cyanohydrin esters. Mechanistic studies showed that the enantiomeric excess of the product increased during the early stages of this reaction. However, by adding a 'sacrificial aldehyde' this effect could be eliminated. The structure of the catalyst in solution was investigated using variable concentration, variable temperature and variable solvent NMR studies. These experiments showed that the catalyst exists as a mixture of monometallic **4** and bimetallic **1** species, a result which is consistent with previous mechanistic studies on the asymmetric addition of trimethylsilyl cyanide to aldehydes and ketones catalysed by the same catalyst. A mechanistic rationale for all of these observations is reported.

1. Introduction

Interest in asymmetric cyanohydrin synthesis has increased significantly in recent years due to the synthetic versatility of chiral cyanohydrins and their utility as chiral starting materials for natural product synthesis. Various types of catalyst are available for this reaction including oxynitrilase enzymes, cyclic-dipeptides, chiral Lewis-bases and chiral transition metal complexes.[1] However, most of these methods require the use of either hydrogen cyanide or trimethylsilyl cyanide as the cyanide source. Both of these reagents are volatile and hence hazardous, and trimethylsilyl cyanide is also expensive, especially for large scale use. Over the last eight years, we have developed titanium complex **1** as a highly active catalyst for the addition of trimethylsilyl cyanide to both aldehydes[2–4] and ketones.[5] This methodology has been applied to the asymmetric synthesis of fluorinated norepinephrines and fluorinated epinephrines.[6] A closely related vanadium(salen) complex was also found to catalyse the asymmetric addition of trimethylsilyl cyanide to aldehydes.[7] We have shown that complex **1** (and the related vanadium(salen) complex) will catalyse the asymmetric addition of potassium cyanide to an aldehyde in the presence of an anhydride, thus providing an asymmetric synthesis of cyanohydrin esters (Scheme 1).[8–11] This reaction has the advantage of avoiding the use of volatile cyanide reagents. In this manuscript, we give full details of our results using different anhydrides and report the results of mechanistic studies on this reaction.



Scheme 1.

Keywords: Titanium; Salen; Cyanohydrin; Ethyl cyanoformate; Ester.
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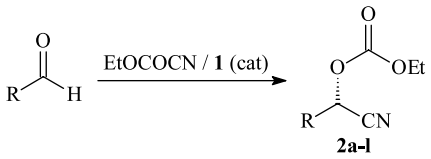
Cyanoformate esters (ROCOCN) are known to react with aldehydes and ketones, to form cyanohydrin carbonates.[12] Only recently, however, have asymmetric catalysts for this reaction been reported. In 2001, Tian and Deng showed that dimeric cinchona alkaloid derivatives would catalyse the asymmetric addition of ethyl cyanoformate to ketones, giving cyanohydrin ethyl carbonates with 59–97% enantiomeric excess.[13] It is notable that this first report involved the use of ketones rather than aldehydes as substrates. This reaction does however, require 10–30 mol% of the catalyst and reactions take up to 7 days. Subsequently, a heterobimetallic complex derived from three binol units, three lithium ions and a yttrium ion was shown by Shibasaki to catalyse the asymmetric addition of ethyl cyanoformate to aldehydes, producing non-racemic cyanohydrin carbonates.[14] Best results were obtained at −78 °C using 10 mol% of the catalyst and three additives: water (30 mol%); butyl-lithium (10 mol%) and tri(2,6-dimethoxyphenyl)phosphine oxide (10 mol%). Under these conditions, products with 87–98% enantiomeric excess could be obtained. A third catalytic system was developed by Nájera et al. Thus, an aluminium binol complex was found to catalyse the asymmetric addition of methyl cyanoformate to aldehydes at room temperature.[15] Cyanohydrin carbonates with up to 80% enantiomeric excess were obtained from reactions employing 10 mol% of the catalyst along with 4 Å molecular sieves. The Nájera catalyst has also recently been reported to be compatible with the use of diethyl cyanophosphonate as the cyanide source.[16] Most recently, an oxynitrilase enzyme has been used to catalyse the asymmetric addition of ethyl cyanoformate to benzaldehyde, producing mandelonitrile ethyl carbonate with excellent (95–>99%) enantiomeric excess, but only moderate (maximum of 66%) chemical yield.[17]

In view of the above precedents, and the fact that cyanohydrin carbonates are configurationally stable and significantly less prone to hydrolysis than cyanohydrin trimethethylsilyl ethers, it was attractive to investigate the use of catalyst **1** in the asymmetric addition of ethyl cyanoformate to aldehydes (Scheme 2) and ketones. Ethyl cyanoformate is also less expensive than trimethylsilyl cyanide, and this, combined with the homogeneous nature of the reactions was expected have significant advantages for large scale preparations. It is also notable that the reaction shown in Scheme 2 is 100% atom-economical. In this manuscript we give full details of this work.[18]



2a-l

2a: R = Ph; **2b:** R = 4-$MeOC_6H_4$
2c: R = 3-$MeOC_6H_4$; **2d:** R = 2-$MeOC_6H_4$
2e: R = 4-MeC_6H_4; **2f:** R = 4-$F_3CC_6H_4$
2g: R = 4-ClC_6H_4; **2h:** R = PhCH=CH
2i: R = C_8H_{17}; **2j:** R = Me_2CH
2k: R = Cy; **2l:** R = Me_3C

Scheme 2.

We have previously reported the results of extensive studies to investigate the mechanism by which complex **1** catalyses the asymmetric addition of trimethylsilyl cyanide to aldehydes.[4] In this manuscript, we present additional evidence on the structure of complex **1** in solution which supports this mechanism and we show how the mechanism can be extended to reactions involving potassium cyanide or ethyl cyanoformate.

2. Results and discussion

2.1. Asymmetric synthesis of cyanohydrin ethyl carbonates

Initial studies were carried out using benzaldehyde as the substrate. The addition of ethyl cyanoformate (2 equiv) catalysed by complex **1** was studied under various conditions as shown in Table 1. First reactions were carried out in dichloromethane at a low temperature to enhance any enantioselectivity and with 1 mol% of the catalyst as this amount had previously been found to be optimal for reactions involving potassium cyanide.[8] When the reaction was carried out at −85 °C, no product was detected (Table 1: entry 1). Raising the reaction temperature to −73 °C did give (*S*)-mandelonitrile ethyl carbonate **2a** with a highly encouraging 94% enantiomeric excess though the reaction required 48 h to go to completion (Table 1: entry 2). The absolute configuration of product **2a** was determined by comparison of its specific rotation with literature data.[14a] At temperatures above −73 °C, the reaction rate increased, but at the expense of a reduction in the enantiomeric excess of the product. Thus, at −40 °C (Table 1: entry 3) the reaction was complete in 19 h, but the product was obtained with only 83% enantiomeric excess. Attempts to reduce the amount of catalyst to 0.1 mol% (the optimal amount for the addition of trimethylsilyl cyanide to aldehydes[2]) gave unsatisfactory results even at room temperature (Table 1: entries 4 and 5).

Whilst the result at −73 °C (Table 1: entry 2) was encouraging, the long reaction time was felt to be impractical. Therefore, the effect of increasing the amount of catalyst was investigated to see if similar enantiomeric excess could be obtained at a temperature where the rate of reaction was faster. Gratifyingly, the use of 5 mol% of catalyst **1** at −40 °C resulted in the complete formation of (*S*)-**2a** with 95% enantiomeric excess after a reaction time of 18 h (Table 1: entry 6). This combination of catalyst mol%, reaction temperature, and product enantiomeric excess is a significant improvement on any of the previously known catalysts[13–15] and was taken to be the optimal conditions for the use of complex **1** since a further increase in the amount of catalyst used (Table 1: entry 7) was not beneficial.

The effect of the reaction solvent was investigated using 5 mol% of catalyst **1**, a reaction temperature of −40 °C, and 1.2 equiv of ethyl cyanoformate. The results are shown in Table 2. These reactions were significantly slower than the optimised conditions, an effect which is mainly due to the reduced concentration of ethyl cyanoformate used (compare Table 1: entry 6 with Table 2: entry 7). An aromatic solvent gave product **2a** with a very low enantiomeric excess (Table

Table 1. The asymmetric addition of ethyl cyanoformate to benzaldehyde catalysed by complex **1**[a]

Entry	Temperature (°C)	**1** (mol%)	Time (h)	Completion (%)	ee[b] (%)
1	−85	1	19	<3	
2	−73	1	48	100	94 (*S*)
3	−40	1	19	100	83 (*S*)
4	−40	0.1	72	<3	
5	25	0.1	148	<3	
6	−40	5	18	100	95 (*S*)
7	−40	10	51	100	93 (*S*)

[a] All reactions were carried out using 2 equiv of ethyl cyanoformate in dichloromethane.
[b] Enantiomeric excesses were determined by chiral GC and are accurate to +/−3%.

2: entry 1). Oxygenated solvents gave a greater degree of asymmetric induction, though the reactions failed to go to completion after 2 days and ethyl acetate gave a particularly slow reaction (Table 2: entries 2–4). Only chloroform gave a high conversion to product with a high enantiomeric excess (Table 2: entry 5), though even in this case the enantiomeric excess of product **2a** was 7% lower than that obtained when dichloromethane was used as the solvent (Table 2: entry 7). Use of the non-polar chlorinated solvent, tetrachloromethane, resulted in a very slow reaction even though the reaction was carried out at −20 °C. Insufficient product was formed after 4 days to allow the enantiomeric excess to be determined (Table 2: entry 6). On the basis of these results, it was apparent that dichloromethane was both the most effective and the most convenient solvent for these reactions.

The addition of ethyl cyanoformate to other aldehydes was then investigated under the optimized conditions (Table 1: entry 6). The results are shown in Table 3. Electron rich aromatic aldehydes (all three isomers of methoxybenzaldehyde and 4-methylbenzaldehyde) were found to be excellent substrates for this reaction, giving cyanohydrin carbonates **2b–e** in high chemical yield and with excellent enantiomeric excesses (94–99%) (Table 3: entries 2–5). Cinnamaldehyde was also found to be an excellent substrate giving cyanohydrin carbonate **2h** with 94% enantiomeric excess (Table 3: entry 8). The electron deficient aromatic aldehyde 4-trifluoromethylbenzaldehyde was a very fast reacting substrate (Table 3: entry 6), though it gave product **2f** with a relatively low enantiomeric excess (76%). This may be due to a competing uncatalysed addition of ethyl cyanoformate to this particularly reactive aldehyde. 4-Chlorobenzaldehyde was however an excellent substrate, giving cyanohydrin ethyl carbonate **2g** in high yield and with 94% enantiomeric excess (Table 3: entry 7). For all of these reactions, the use of 2 equiv of ethyl cyanoformate was necessary for the reactions to be complete in less than 20 h. The quantity of ethyl cyanoformate used could however be reduced to just 1.2 equiv, at the expense of extended reaction times of 45–68 h.

A series of aliphatic aldehydes was also studied as substrates for this reaction (Table 3: entries 9–12) and all gave products (**2i–l**) with similar enantiomeric excesses (76–84%). The primary aldehyde nonanal gave the product with the highest enantiomeric excess (Table 3: entry 9), but there was no significant difference between the enantioselectivity observed with the secondary and tertiary aldehydes (Table 3: entries 10–12). For aliphatic aldehydes, the amount of ethyl cyanoformate used could be reduced to 1.2 equiv without the reaction time being extended beyond 20 h. The only exception to this was pivaldehyde which is a slow reacting substrate, presumably for steric reasons (Table 3: entry 12).

Two ketones, acetophenone and 2-butanone, were also investigated as substrates. Catalyst **1** is known to catalyse the asymmetric addition of trimethylsilyl cyanide to ketones,[5] but no conditions were found under which it would catalyse the addition of ethyl cyanoformate to either of these ketones. Even at room temperature and with prolonged reaction times, only unreacted starting materials were observed.

2.2. Asymmetric synthesis of cyanohydrin esters

The reaction shown in Scheme 1 provides a very convenient, one-pot synthesis of configurationally stable cyanohydrin esters. This reaction was developed using

Table 2. The influence of the solvent on the asymmetric addition of ethyl cyanoformate to benzaldehyde catalysed by complex **1**[a]

Entry	Solvent	Time (h)	Conversion (%)	ee[b] (%)
1	Toluene	45	100	30
2	EtOAc	90	23	42
3	Ether	47	73	51
4	Thf	73	49	52
5	Chloroform	53	96	84
6	Tetrachloromethane[c]	96	<5	
7	Dichloromethane	42	98	91

[a] All reactions were carried out using 1.2 equiv of ethyl cyanoformate.
[b] Enantiomeric excesses were determined by chiral GC and are accurate to +/−3%.
[c] Reaction carried out at −20 °C.

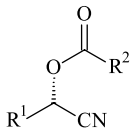
Table 3. The asymmetric addition of ethyl cyanoformate to aldehydes catalysed by complex **1** in dichloromethane

Entry	Aldehyde (product)	Time (h)	EtOCOCN (equiv)	Yield (%)[a]	ee[b] (%)
1	PhCHO (**2a**)	18	2	90	95
2	4-$MeOC_6H_4CHO$ (**2b**)	18	2	92	95
3	3-$MeOC_6H_4CHO$ (**2c**)	17	2	94	99
4	2-$MeOC_6H_4CHO$ (**2d**)	48	1.2	95	98
5	4-MeC_6H_4CHO (**2e**)	48	1.2	67 (95)	94
6	4-$(F_3C)C_6H_4CHO$ (**2f**)	6	2	84	76
7	4-ClC_6H_4CHO (**2g**)	68	1.2	96	94
8	PhCH=CHCHO (**2h**)	45	1.2	47 (99)	94
9	$C_8H_{17}CHO$ (**2i**)	22	2	54	88
10	Me_2CHCHO (**2j**)	20	1.2	23 (88)	79
11	CyCHO (**2k**)	18	1.2	82	79
12	Me_3CCHO (**2l**)	48	1.2	69	73

[a] After purification by distillation. Number in brackets is the yield before distillation.
[b] Enantiomeric excesses were determined by chiral GC and are accurate to +/−3%.

acetic anhydride, and was found to give good to excellent enantioselectivities with a range of aromatic and aliphatic aldehydes.[8,9,11] Whilst acetic anhydride is the experimentally most convenient anhydride for synthetic work, we decided to see if the structure of the anhydride had any influence on the enantioselectivity, rate, or yield of the reaction.[10] Three anhydrides were chosen for an initial study, propionic anhydride, pivalic anhydride and benzoic anhydride. Propionic anhydride is only slightly larger than acetic anhydride, whilst pivalic anhydride is significantly sterically hindered. Thus, comparison of these two anhydrides with acetic anhydride would allow the influence of steric effects to be investigated. In contrast, benzoic anhydride was included as it has very different electronic properties to the three aliphatic anhydrides.[19] Both racemic[20–22] and non-racemic[23–25] cyanohydrin esters derived from all three of these anhydrides have previously been reported.

An initial study was carried out under the reaction conditions shown in Scheme 1, using benzaldehyde as the substrate and the three different anhydrides. The reactions were monitored by GC and the enantiomeric excess of the product **3b–d** was determined by chiral GC. The results of this study are shown in Table 4. Compared to previous work with acetic anhydride (Table 4: entry 1), the use of propionic anhydride (Table 4: entry 2) or pivalic anhydride (Table 4: entry 3) was found to have little effect on the enantioselectivity of the reaction. However, benzoic anhydride gave a product **3d** with significantly lower enantiomeric excess (Table 4: entry 4). Reactions involving propionic, pivalic or benzoic anhydride were much slower than reactions using acetic anhydride, requiring at least 48 h to go to completion. The use of benzoic anhydride resulted in a particularly slow reaction.



3a: R^1 = Ph; R^2 = Me
3b: R^1 = Ph; R^2 = Et
3c: R^1 = Ph; R^2 = CMe_3
3d: R^1 = Ph; R^2 = Ph
3e: R^1 = PhCH=CH; R^2 = Et
3f: R^1 = PhCH=CH; R^2 = CMe_3
3g: R^1 = 4-$(F_3C)C_6H_4$; R^2 = Et
3h: R^1 = 4-$(F_3C)C_6H_4$; R^2 = CMe_3
3i: R^1 = 3-$MeOC_6H_4$; R^2 = Me
3j: R^1 = 3-$MeOC_6H_4$; R^2 = Et
3k: R^1 = 4-$MeOC_6H_4$; R^2 = Me
3l: R^1 = 4-$MeOC_6H_4$; R^2 = Et
3m: R^1 = Me_2CH; R^2 = Me
3n: R^1 = Me_2CH; R^2 = Et
3o: R^1 = Me_3C; R^2 = Me
3p: R^1 = Me_3C; R^2 = Et
3q: R^1 = 2-MeC_6H_4; R^2 = Et
3r: R^1 = 3-MeC_6H_4; R^2 = Et
3s: R^1 = 4-MeC_6H_4; R^2 = Et
3t: R^1 = 4-ClC_6H_4; R^2 = Et
3u: R^1 = C_8H_{19}; R^2 = Et
3v: R^1 = Cy; R^2 = Et

Based on the above results, the use of benzoic anhydride was discontinued. However, both propionic and pivalic anhydride were felt to be worthy of further investigation since although they offered no improvement in enantioselectivity in the case of benzaldehyde, this would not necessarily be the case for other aldehydes. Therefore, a range of aromatic, aliphatic, and α,β-unsaturated aldehydes were studied with these two anhydrides, and the results are shown in Table 5. Two additional aldehydes

Table 4. The asymmetric addition of potassium cyanide to benzaldehyde catalysed by complex **1** in the presence of different anhydrides

Entry	Anhydride	Time (h)	Product	Conversion (%)	ee[a] (%)
1	Acetic	10	**3a**	93	90[8]
2	Propionic	48	**3b**	100	92
3	Pivalic	48	**3c**	85	88
4	Benzoic	72	**3d**	95	56

[a] Enantiomeric excesses were determined by chiral GC and are accurate to +/−3%.

Table 5. The asymmetric addition of potassium cyanide to aldehydes catalysed by complex **1** in the presence of different anhydrides[a]

Entry	Aldehyde	Anhydride	Product	Time (h)	Conversion (%)	ee[b] (%)
1	PhCH=CHCHO	Propionic	**3e**	48	73 (62% isolated yield)	95
2	PhCH=CHCHO	Pivalic	**3f**	72	50	75
3	4-$(CF_3)C_6H_4CHO$	Propionic	**3g**	50	100	94
4	4-$(CF_3)C_6H_4CHO$	Pivalic	**3h**	50	100	62
5	3-$MeOC_6H_4CHO$	Acetic	**3i**	10	99	93[8]
6	3-$MeOC_6H_4CHO$	Propionic	**3j**	48	100	90
7	4-$MeOC_6H_4CHO$	Acetic	**3k**	10	74	93[8]
8	4-$MeOC_6H_4CHO$	Propionic	**3l**	48	100 (71% isolated yield)	91
9	Me_2CHCHO	Acetic	**3m**	10	62	72[8]
10	Me_2CHCHO	Propionic	**3n**	62	100	17
11	Me_3CCHO	Acetic	**3o**	10	40	62[8]
12	Me_3CCHO	Propionic	**3p**	48	100	78
13	2-MeC_6H_4CHO	Propionic	**3q**	28	100	81
14	3-MeC_6H_4CHO	Propionic	**3r**	36	98	95
15	4-MeC_6H_4CHO	Propionic	**3s**	36	98	89
16	4-ClC_6H_4CHO	Propionic	**3t**	16	100	90
17	$C_8H_{17}CHO$	Propionic	**3u**	50	74	82
18	CyCHO	Propionic	**3v**	72	95	41

[a] All reactions were carried out at −40 °C in dichloromethane in the presence of water (0.5 equiv) and *tert*-butanol (1.0 equiv).
[b] Enantiomeric excesses were determined by chiral GC and are accurate to +/−3%.

(cinnamaldehyde and *para*-trifluoromethylbenzaldehyde) were investigated with both propionic and pivalic anhydrides (Table 5: entries 1–4). However, the products obtained using pivaldehyde (**3f** and **3h**) had enantiomeric excesses at least 20% lower than those obtained using propionic anhydride (**3e** and **3g**), so the use of pivalic anhydride was not pursued further. Whilst most of the cyanohydrin esters were found to be chemically and configurationally stable, the products obtained from *para*-trifluoromethylbenzaldehyde (**3g** and **3h**) were both found to racemize on standing at room temperature. Thus, over a period of 3 days, the enantiomeric excess of compound **3g** decreased from 94 to 78% and that of **3h** decreased from 62 to 48%.

To allow a further direct comparison between the use of acetic and propionic anhydrides, four aldehydes previously used as substrates with acetic anhydride were investigated using propionic anhydride as well. The first two aldehydes chosen were the electron rich aromatic aldehydes 3- and 4-methoxybenzaldehyde. For both of these substrates, the products derived from acetic (**3i** and **3k**) and propionic (**3j** and **3l**) anhydrides were obtained with essentially identical enantiomeric excesses (Table 5: entries 5–8). The other two aldehydes used in this study were aliphatic, and in this case a significant difference between the two anhydrides was observed. In the case of 2-methyl-propanal, product **3m** obtained using acetic anhydride was found to have a much higher enantiomeric excess (72%) than product **3n** (17%) derived from propionic anhydride (Table 5: entries 9 and 10). By contrast, for cyanohydrin esters **3o** and **3p** derived from pivaldehyde, product **3p** obtained from propionic anhydride had a higher enantiomeric excess (78%) than product **3o** (62%) derived from acetic anhydride (Table 5: entries 11 and 12). Thus, whilst for aromatic aldehydes there is little or no difference in the enantioselectivity observed with acetic and propionic anhydrides, for aliphatic aldehydes the structure of the anhydride does appear to play a major role in determining the enantioselectivity of the process. Finally, four aromatic and two aliphatic aldehydes not previously used as substrates with acetic anhydride were investigated as substrates with propionic anhydride (Table 5: entries 13–18). Of the aromatic substrates, only the *ortho*-substituted aldehyde gave a product **3q** with an enantiomeric excess significantly below 90% (Table 5: entry 13). For *meta*- and *para*-substitued benzaldehydes, products with enantiomeric excesses >89% were consistently obtained irrespective of the electronic nature of the substituent (Table 5: entries 3, 6, 8, 14–16). The primary aldehyde nonal (Table 5: entry 17) gave product **3u** with a higher enantiomeric excess than that observed for secondary or tertiary aliphatic aldehydes (compare entry 17 with entries 10, 12, and 18). Cyclohexane carboxaldehyde gave product **3v** with a rather low enantiomeric excess (Table 5: entry 18), though not as low as that observed for product **3n** derived from 2-methyl propanal.

2.3. Variation of enantiomeric excess with time

Reactions carried out at −40 °C using propionic anhydride were sufficiently slow that they could be easily monitored by chiral GC. This revealed that the enantiomeric excess of the product (mandelonitrile propionate **3b**) increased significantly during the course of the reaction as shown in Figure 1. Thus, after 1 h of reaction, the enantiomeric excess

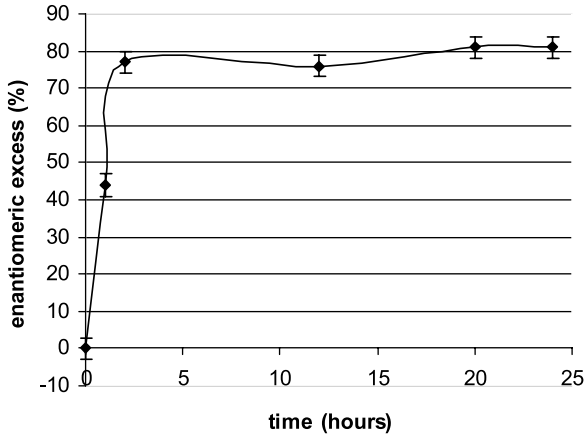


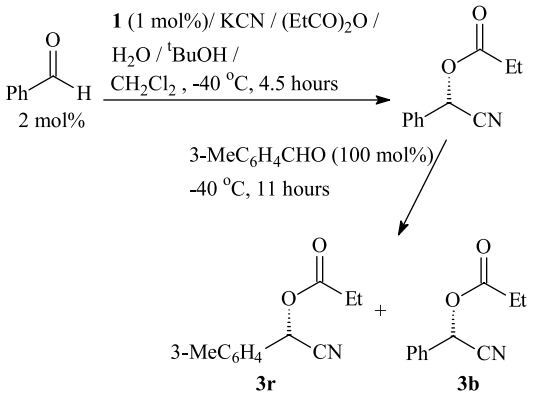
Figure 1. The variation of the enantiomeric excess of product **3b** with time. Error bars correspond to +/−3%, which is the approximate error in the enantiomeric excess determined by chiral GC.

of the product was just 44%. After 24 h however, the enantiomeric excess of compound **3b** had increased to 81%.

The most likely explanation for this effect is that complex **1** is only slowly converted into species on the catalytic cycle, and during the early stages of the reaction, less enantioselective catalysis occurs due to other species. Details of the mechanisms of these reactions will be discussed in Section 2.5. However, this suggested a way of potentially increasing the enantiomeric excess of products **3**. Addition of a small amount of one aldehyde (a 'sacrificial aldehyde') should convert complex **1** into a species on the catalytic cycle. A few hours later, the real aldehyde could be added. In this way, the enantiomeric excess of the second aldehyde should not be reduced by competing processes with low or no enantioselectivity in the early stages of the reaction.

To test this hypothesis, a reaction was carried out as shown in Scheme 3. In this reaction, benzaldehyde functions as the 'sacrificial aldehyde' and 3-methylbenzaldehyde as the real substrate. Initially, catalyst **1** (1 mol% relative to the amount of 3-methylbenzaldehyde to be added later) and benzaldehyde (2 mol%) were added under standard conditions and allowed to react for 4.5 h. At this stage, 3-methylbenzaldehyde (100 mol%) was added and the reaction allowed to continue. The enantiomeric excess of both products (**3b** and **3r**) was simultaneously monitored by chiral GC, and the results are shown in Figure 2.

The experiment was at least partially successful, since it is quite clear that the enantiomeric excess of product **3r** remains constant at 90% throughout the reaction. At the end of the reaction, both aldehydes had undergone greater than 90% conversion to cyanohydrin propionates. However, the enantiomeric excess of product **3r** obtained in this way was actually slightly lower than the 95% obtained using only 3-methylbenzaldehyde as substrate (Table 5: entry 14). One explanation for this is that the catalytically active species formed in the reaction depend on the aldehyde from which they are formed. For example, a molecule of cyanohydrin could be bound to a titanium ion during the catalytic cycle. The catalyst obtained in this sacrificial experiment would then be different to that obtained in a normal reaction and so could exhibit different enantioselectivity. To further investigate this effect, the experiment was reversed: 3-methylbenzaldehyde (2 mol%) was used as the sacrificial aldehyde and benzaldehyde as the actual substrate. As Figure 3



Scheme 3.

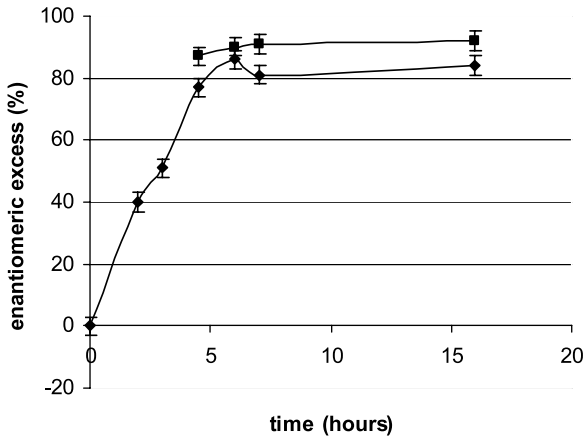


Figure 2. The variation of the enantiomeric excess of products **3b** and **3r** with time when benzaldehyde is used as a 'sacrificial' aldehyde. Error bars correspond to +/−3%, which is the approximate error in the enantiomeric excess determined by chiral GC. Diamonds refer to product **3b**, and squares to product **3r**.

shows, exactly the same effects were observed: the enantiomeric excess of the sacrificial aldehyde increased during the reaction, but that of the real substrate stayed constant. However, the enantiomeric excess of product **3b** obtained in this way (80%) was again lower than that obtained using benzaldehyde as the only substrate (92%, Table 4: entry 2).

To try to find a sacrificial aldehyde system which did give enhanced enantioselectivities, four different sacrificial aldehydes with differing electronic properties were studied. In each case, benzaldehyde (90 mol%) was used as the real substrate and 10 mol% of the sacrificial aldehyde was used. The reactions were not followed by chiral GC, but Table 6 records the enantiomeric excess of product **3b** isolated in each case. The results of this series of experiments (Table 6: entries 1–4) were remarkably consistent; product **3b** was obtained with 78–80% enantiomeric excess whatever the nature of the sacrificial aldehyde. Finally, we carried out an experiment in which benzaldehyde was used as both the sacrifical aldehyde (10 mol%) and the real substrate

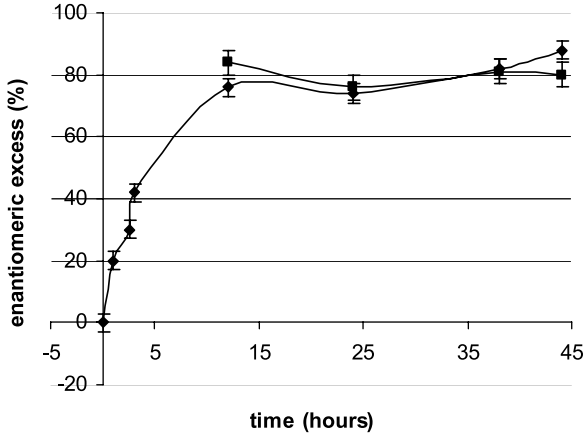


Figure 3. The variation of the enantiomeric excess of products **3b** and **3r** with time when 3-methylbenzaldehyde is used as a 'sacrificial' aldehyde. Error bars correspond to +/−3%, which is the approximate error in the enantiomeric excess determined by chiral GC. Diamonds refer to product **3r**, and squares to product **3b**.

Table 6. The use of different sacrificial aldehydes for the asymmetric synthesis of product **3b**

Entry	Sacrificial aldehyde	ee[a] of **3b** (%)
1a	Nonal	80
2	Cinnamaldehyde	80
3	4-Methoxybenzaldehyde	80
4	4-Trifluoromethylbenzaldehyde	78
5	Benzaldehyde	80

[a] Enantiomeric excesses were determined by chiral GC and are accurate to +/−3%.

(90 mol%). This was expected to give product **3b** with 92% enantiomeric excess (cf. Table 4: entry 2), but actually again gave product **3b** with just 80% enantiomeric excess (Table 6: entry 5).

To explain these results, we propose that the sacrificial aldehyde does achieve its role of converting precatalyst **1** into species which lie on the catalytic cycle, but that these species are unstable in the absence of a high concentration of aldehyde. Thus, by the time that the real substrate is added (typically 4–5 h), some of the catalyst has decomposed, resulting in a reduced mol% of the catalyst being available to carry out the catalysis, and hence a lower enantiomeric excess of the final product.

2.4. Structure of the catalyst and its significance

During the course of this work, we studied the nature of catalyst **1** in solution. It has previously been determined by X-ray crystallography that the catalyst exists as a bimetallic complex in the solid state.[3] Kinetic studies on the asymmetric addition of trimethylsilyl cyanide to aldehydes and ketones catalysed by complex **1** however, indicated that the catalyst dissociated in solution to form both monometallic and bimetallic species.[4]

Routine ^{1}H NMR spectra (recorded in $CDCl_3$) obtained during the preparation of batches of catalyst **1** exhibited significant variability which initially led to concerns about the purity of the catalyst and its true structure. However, a variable concentration NMR study showed that the ^{1}H NMR spectrum of the catalyst was highly concentration dependent, with the changes in the aromatic and imine hydrogen region (6–9 ppm) being particularly pronounced. A representative set of spectra recorded in deuterated chloroform are shown in Figure 4.

At the highest concentration studied (0.0822 M), four aromatic peaks and two imine signals are observed as expected for bimetallic structure **1**. Only very small peaks corresponding to any other species are visible in the spectrum (Fig. 4a). However, as the concentration of the NMR solution is decreased, the intensity of the minor peaks increases (Fig. 4b and c), until at a concentration of 5×10^{-4} M, all the signals are of comparable intensity (Fig. 4d). At still lower concentrations, the signals corresponding to the originally minor species become dominant (Fig. 4e), until at the lowest concentration we could acquire a spectrum (8.3×10^{-6} M), the original signals virtually disappear from the spectrum (Fig. 4f).

Both species present in the spectra shown in Figure 4 give rise to two imine signals and four aromatic signals. Thus, in both cases the salen ligand lacks C_2 symmetry. These results indicate that catalyst **1** exists in chloroform solution as an equilibrium mixture of dimeric **1** and monomeric **4** species as shown in Scheme 4. At high concentrations, formation of the dimeric species is favoured, whilst at lower concentrations, formation of the monomeric species becomes more favourable. Dimeric species **1** has overall C_2 symmetry, but within each salen ligand the two aromatic rings are diastereotopic due to the *cis*-β conformation forced upon the ligand by the two bridging oxygens.[3] The monomeric complex **4** is square pyramidal and so again lacks C_2-symmetry. Asymmetric cyanation reactions carried out using catalyst **1** are typically carried out at a catalyst concentration between 8×10^{-4} and 1×10^{-2} M depending on the cyanide source. (With trimethylsilyl cyanide only 0.1 mol% of catalyst is needed;[3] the potassium cyanide/acetic anhydride system requires 1 mol% catalyst;[8] and for use of ethyl cyanoformate as the cyanide source, 5 mol% of catalyst is necessary[18]). These concentrations are all covered by the spectra shown in Figure 4a–d in which a significant amount of both monomeric and dimeric species are present. The equilibrium constant between the dimeric **1** and monomeric **4** species (calculated using data from the spectrum obtained at 0.02 M) was determined to be 3×10^{-3} M.

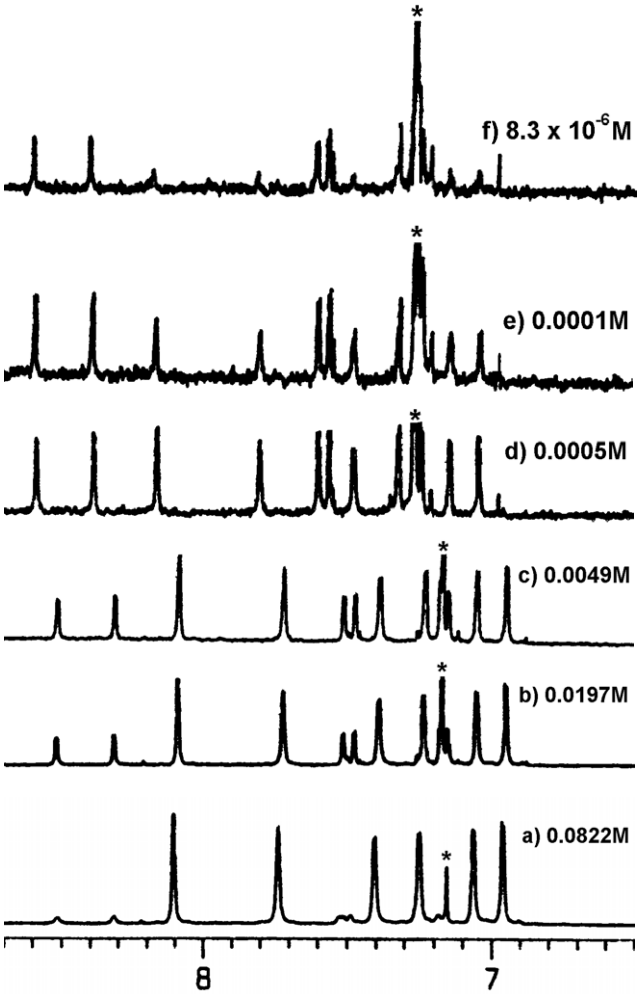
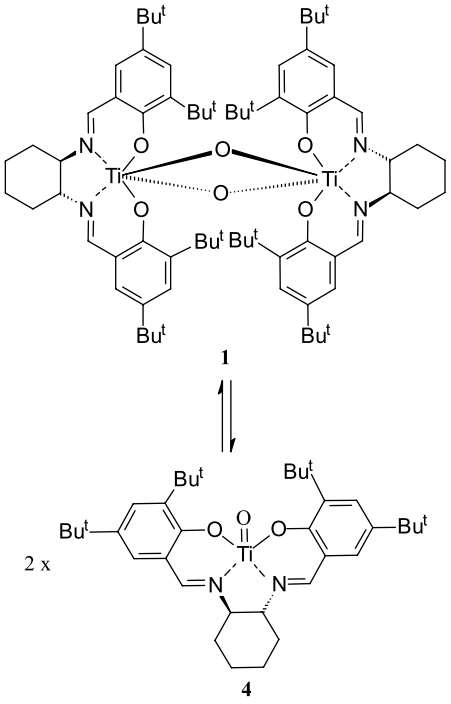


Figure 4. ^{1}H NMR spectra of compound **1** in $CDCl_3$ at different concentrations. *Signal due to $CHCl_3$.

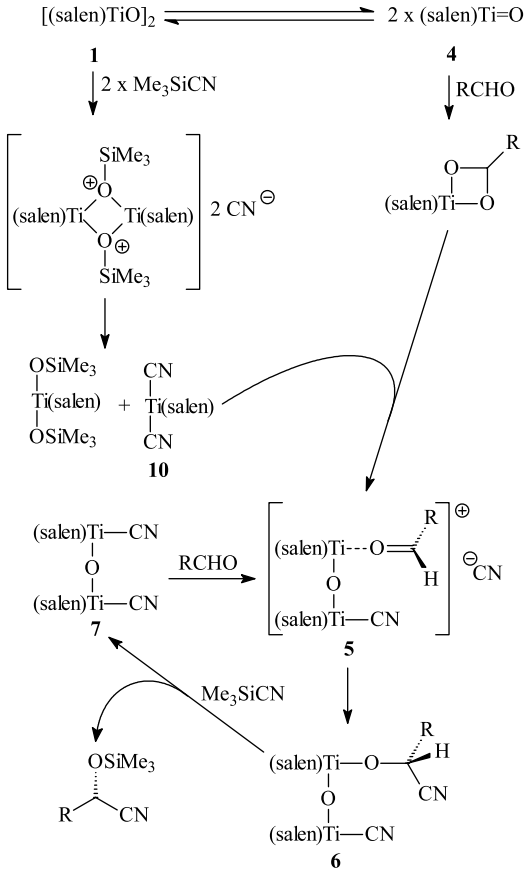


Scheme 4.

A variable temperature study of catalyst **1** in $CDCl_3$ at 0.01 M concentration was also undertaken. Between 213 and 333 K, no significant changes in chemical shift were observed. However, as the temperature was lowered, the signals for the minor species **4** became significantly sharper and decreased in intensity. Thus, at 333 K the ratio of the minor to major signals is 0.25:1 and this decreases to 0.1:1 at 213 K. This is consistent with the equilibrium shown in Scheme 4, since at higher temperatures, more energy is available to break the relatively weak Ti–O bonds, and hence the amount of monomeric species **4** present will increase. The X-ray structure of compound **1** shows that the central Ti_2O_2 unit is rectangular, with two normal Ti–O bonds and two longer bonds.[3] Cleavage of the latter is all that would be required for formation of the monomeric species.

This result may also be relevant to the amount of catalyst needed for the various asymmetric cyanation reactions. Thus, reactions using trimethylsilyl cyanide are sufficiently enantioselective that they can be carried out at 20 °C.[3] Only 0.1 mol% of the catalyst is needed in these reactions, and at this 'high' temperature this will give rise to a relatively high concentration of monometallic complex **4**. Formation of the monometallic complex is essential to allow it to react with the aldehyde and start the catalytic cycle[4] as shown in Scheme 5. In contrast, reactions using potassium cyanide[8] or ethyl cyanoformate[18] exhibit optimal enantioselectivity at −40 °C. These reactions also require much more catalyst 1–5 mol% and it may be that the reason for this is to maintain the required concentration of monometallic species at the lower temperature.

The dissociation of complex **1** is solvent dependent as in d_6-benzene, a 0.02 M solution of complex **1** exhibited a very



Scheme 5.

simple spectrum consisting of just two imine signals and four aromatic signals as shown in Figure 5. This concentration corresponds to that used for Figure 4b where the signals for the monomeric species were clearly visible. To prove that the species present in d_6-benzene was bimetallic species **1** rather than the monomeric species **4**, a solvent titration was carried out at constant concentration. As the %chloroform in the solvent decreased, the intensity of the minor signals also decreased and they became undetectable when the %chloroform was less than 20%.

Reactions involving catalyst **1** are usually carried out in dichloromethane rather than chloroform or benzene. Therefore, NMR spectra of catalyst **1** were recorded at various concentrations in CD_2Cl_2. The results were very similar to the spectra obtained in $CDCl_3$, with peaks corresponding to monomeric species **4** increasing in intensity as the concentration was reduced. The equilibrium constant in dichloromethane was calculated as 8×10^{-4} M which is a factor of four lower than that observed in chloroform.

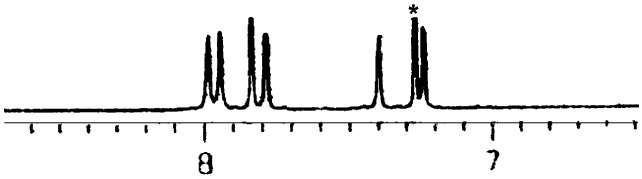


Figure 5. ^{1}H NMR spectrum of compound **1** in C_6D_6 at a concentration of 0.02 M. *Signal due to benzene.

To further prove that the species observed by NMR in $CDCl_3$ were catalytically relevant, the asymmetric addition of potassium cyanide and acetic anhydride to benzaldehyde was carried out under the conditions of Scheme 1 (R^1=Ph, R^2=Me) except that the solvent was changed to chloroform. Under these conditions, an 85% conversion of benzaldehyde into *O*-acetyl (*S*)-mandelonitrile **3a** with 72% enantiomeric excess was observed after a reaction time of 4 days. This reaction is slower and less enantioselective than that carried out under the optimized conditions[8] (93% yield with 90% enantiomeric excess in 10 h), but does prove that the species detected in chloroform are catalytically relevant. The asymmetric addition of ethyl cyanoformate to benzaldehyde catalysed by complex **1** could also be carried out in chloroform (Table 2: entry 4).

2.5. Mechanistic analysis

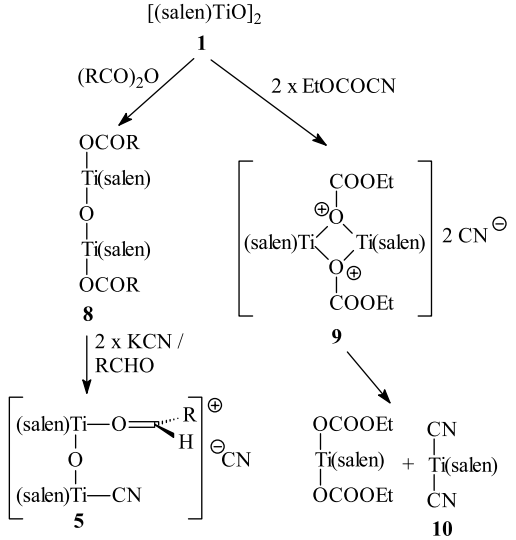
The mechanism shown in Scheme 5 for the addition of trimethylsilyl cyanide to aldehydes catalysed by complex **1** can reasonably be assumed to form the basis of reactions involving ethyl cyanoformate and potassium cyanide/an anhydride as well. There are however, two areas where the mechanism must be modified:

1. How is catalyst **1** converted into one of complexes **5**–**7** present in the catalytic cycle in the absence of trimethylsilyl cyanide?
2. How is the cyanohydrin derivative removed from complex **6**?

We have previously shown[9] that reaction of catalyst **1** with acetic anhydride generates bimetallic *bis*-acetate **8**. Reaction of compound **8** with potassium cyanide and an aldehyde would lead to species **5** as shown in Scheme 6. To start the catalytic cycle when ethyl cyanoformate is used as the cyanide source, it is possible that a complex such as **9** is formed and collapses to titanium *bis*-cyanide complex **10**. This could then enter the catalytic cycle as shown in Scheme 5.

Conversion of complex **6** into *bis*-cyanide **7** in the presence of ethyl cyanoformate presents no difficulty as the ethyl cyanoformate can react with the titanium bound cyanohydrin to give products **2** and complex **7**. In the potassium cyanide/anhydride system however, this step cannot be quite so straightforward. Acylation of the titanium bound cyanohydrin **6** would give products **3** and titanium complex **11** (Scheme 7). Complex **11** could either react with potassium cyanide to give *bis*-cyanide **7**, or directly react with another molecule of aldehyde to reform complex **5**. There is however a further possibility. Since the potassium cyanide chemistry is carried out in the presence of water and *tert*-butanol, complex **6** could be protonated to form a free cyanohydrin and complex **11**. The free cyanohydrin would then be acylated in a non-catalytic step to give the observed product. One consequence of this mechanism is that the enantiomeric excess of product **3** would directly depend on the rate at which the free cyanohydrin was protected by reaction with the anhydride. This fits the observed results since the most reactive anhydrides gave the products with highest enantiomeric excess (acetic anhydride ≥ propionic anhydride > pivalic anhydride > benzoic anhydride). It is also possible that more than one of these routes operate simultaneously, or that the exact process by which the cyanohydrin ester is formed differs from substrate to substrate.

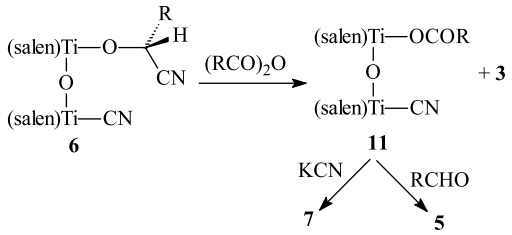
The results of experiments using a sacrificial aldehyde in the potassium cyanide system can be explained as follows. The role of the sacrificial aldehyde is to allow the formation of complex **5** by the route shown in Scheme 6. Complex **5** is one of the three key bimetallic complexes on the catalytic cycle, and its formation appears to take about 4–5 h at −40 °C (based on Fig. 1). During this time, other titanium containing species (e.g., **1**, **4**, **8**) are present in the reaction mixture and could give rise to less enantioselective catalysts resulting in the enantiomeric excess of the product derived from the sacrificial aldehyde being observed to increase with time. Assuming that at least one of complexes **5**–**7** is unstable in the absence of excess aldehyde and therefore causes the partial decomposition of the catalyst prior to the addition of the real substrate, the observed enantiomeric excess of the product derived from the real substrate would be expected to be constant throughout the reaction, but lower than that observed if only one aldehyde was used.



Scheme 6.

3. Conclusions

Catalyst **1** has been shown to catalyse the asymmetric addition of ethyl cyanoformate to a range of aliphatic and aromatic aldehydes. Optimal results were obtained using 5 mol% of catalyst **1** in dichloromethane at −40 °C and under these conditions, twelve aldehydes were converted



Scheme 7.

into (*S*)-cyanohydrin ethyl carbonates with 75–99% enantiomeric excess.

The same catalyst was shown to catalyse the asymmetric addition of potassium cyanide to aldehydes in the presence of an anhydride, leading to cyanohydrin esters. For this process, only 1 mol% of the catalyst was required and best results were again obtained at −40 °C. Of the anhydrides studied, acetic anhydride generally gave the fastest reaction rates and highest enantioselectivities. Propionic anhydride gave much slower reaction rates, but for aromatic aldehydes gave products with comparable enantiomeric excesses (81–95%) to those obtained using acetic anhydride. When aliphatic aldehydes were used as substrates, the results were more variable and there was no obvious correlation between anhydride structure and enantioselectivity. The other anhydrides studied gave products with significantly lower enantiomeric excesses.

The structure of catalyst **1** was investigated in various solvents to complement a previous X-ray study and to provide mechanistic information. In chloroform, a concentration dependent equilibrium between the dimeric **1** and monometallic **4** forms of the catalyst was detected. In dichloromethane, the equilibrium is shifted in favour of the undissociated form **1**, and in benzene only the undissociated complex is detected. The equilibrium is also temperature dependent, with the monometallic form of the catalyst **4** being less favoured at lower temperatures. These results provide an explanation for the observation that whilst the asymmetric addition of trimethylsilyl cyanide to aldehydes (at room temperature) is catalysed by just 0.1 mol% of catalyst **1**, the corresponding additions of potassium cyanide and ethyl cyanoformate (both of which have to be carried out at −30 to −40 °C to obtain good asymmetric induction) require much larger amounts of catalyst **1**.

For the potassium cyanide system, it was found that the enantiomeric excess of the product increased during the course of the reaction. Experiments in which two different aldehydes were used suggest that this is due to the slow conversion of precatalyst **1** into catalytically active species under the reaction conditions. A complete mechanistic rationale for asymmetric cyanohydrin synthesis (using three different cyanide sources) induced by precatalyst **1** which explains all of the observed effects has been presented.

4. Experimental

4.1. General methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 360 Spectrometer, (^{1}H 360 MHz, ^{13}C 90 MHz). Variable temperature experiments were carried out on a Bruker Avance 400 Spectrometer, (^{1}H 400 MHz). The solvent for a particular spectrum is given in parentheses. Spectra were referenced to TMS and chemical-shift (δ) values, expressed in parts per million (ppm), are reported downfield of TMS. The multiplicity of signals is reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or a combination of any of these. For ^{13}C NMR spectra, the peak assignments were made with the assistance of DEPT experiments.

Infrared spectra were recorded on a Perkin–Elmer FT-IR Paragon 1000 spectrometer, as a thin film between NaCl plates in the reported solvent, or as KBr disks. The characteristic absorption is reported as broad (br), strong (s), medium (m) or weak (w). Low and high resolution mass spectra were recorded at the EPSRC national service at the University of Wales, Swansea, or on a Bruker Apex III FTMS or Jeol AX505W spectrometer within the chemistry department at King's College. The sample was ionized by electron ionization (EI), chemical ionization (CI) fast atom bombardment (FAB) or electrospray ionization (ES). The major fragment ions are reported and only the molecular ions are assigned.

Optical rotations were recorded on a Perkin–Elmer 343 polarimeter in a thermostated cell of length 1 dm at 20 °C using the sodium D-line, and a suitable solvent that is reported along with the concentration (in g/100 mL).

Chromatographic separations were performed with silica gel 60 (230–400 mesh) and thin-layer chromatography was performed on polyester backed sheets coated with silica gel 60 F254, both supplied by Merck. Chiral GC was carried out on a Hewlett Packard 5890 gas chromatograph fitted with a thermal conductivity detector, using a γ-CD butyryl, fused silica capillary column (30 m×0.25 mm) and hydrogen as the carrier gas (flow rate 2.3 mL/min).

4.2. General procedure for the asymmetric addition of ethyl cyanoformate to aldehydes

A stirred solution of aldehyde (4.7 mmol) in dichloromethane (20 mL) and (*R*,*R*)-**1** (0.264 g, 0.22 mmol, 5 mol%) was cooled to −84 °C and EtOCOCN (0.93 mL, 9.42 mmol) was added in one portion. The yellow solution was then allowed to warm to −40 °C and was stirred vigorously for 19 h. The reaction mixture was then passed through a pad of silica eluting with dichloromethane. The eluent was concentrated in vacuo and the resulting orange–brown liquid was micro-distilled to give the cyanohydrin ethyl carbonate as a clear liquid.

4.2.1. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-phenyl-acetonitrile 2a. Yield 0.87 g, 90%; $[\alpha]_D^{20}=-20.1$ (*c* 1.8, $CHCl_3$) [lit.[14a] $[\alpha]_D^{20}=+16.2$ (*c* 2.8, $CHCl_3$) for (*R*)-enantiomer with 94% ee]; δ_H 1.26 (3H, t $J=7.1$ Hz, CH_3), 4.2–4.3 (2H, m, OCH_2), 6.19 (1H, s, OCHCN), 7.2–7.5 (5H, m, ArH); δ_C 153.82 (CO_3), 131.64 (ArC), 131.04 (ArCH), 129.68 (ArCH), 128.29 (ArCH), 116.19 (CN), 66.76 (OCH), 66.03 (OCH_2), 14.51 (CH_3); *m*/*z* (EI) 205 (M^+, 35), 116 (78), 133 (55), 105 (100). Found (ES) 206.0829, $C_{11}H_{12}NO_3$ (MH^+) requires 206.0817. GC conditions: initial temperature 100 °C, ramp rate 0.2 °C/min. T_R 121.8 (minor isomer) and 124.2 (major isomer) min.

4.2.2. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-methoxyphenyl)acetonitrile 2b. Yield 1.02 g, 92%; $[\alpha]_D^{20}=+1.8$ (*c* 1.8, $CHCl_3$); ν_{max} ($CHCl_3$) 2981 s, 2845 m, 2250 w, 1753 s, 1611 s, 1580 m, and 1512 cm^{-1} s; δ_H 1.15 (3H, t $J=$ 7.2 Hz, CH_3), 3.76 (3H, s, OCH_3), 4.3–4.4 (2H, m, OCH_2),

6.13 (1H, s, OCHCN), 6.88 (2H, d $J=8.8$ Hz, ArH), 7.41 (2H, d $J=8.8$ Hz, ArH); δ_C 161.73 (CO_3), 153.86 (ArC), 130.11 (ArCH), 123.73 (ArC), 116.34 (CN), 114.97 (ArCH), 66.53 (OCH), 65.86 (OCH_2), 55.82 (OCH_3), 14.50 (CH_3); *m/z* (ES) 253 ($M+NH_4^+$, 15), 146 (100). Found (ES) 253.1186, $C_{12}H_{17}N_2O_4$ ($M+NH_4^+$) requires 253.1183. GC conditions: initial temperature 100 °C, ramp rate 0.4 °C/min. T_R 46.3 (major isomer) and 47.3 (minor isomer) min.

4.2.3. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(3-methoxyphenyl)acetonitrile 2c. Yield 1.04 g, 94%; $[\alpha]_D^{20}=-11.3$ (*c* 1.2, $CHCl_3$); ν_{max} ($CHCl_3$) 3095 s, 2975 s, 2835 s, 2342 w, and 1755 cm^{-1} s; δ_H 1.38 (3H, t $J=7.1$ Hz, CH_3), 3.86 (3H, s, OCH_3), 4.2–4.3 (2H, m, OCH_2), 6.25 (1H, s, OCHCN), 7.0–7.4 (4H, m, ArH); δ_C 160.53 (CO_3), 153.80 (ArC), 132.92 (ArC), 130.79 (ArCH), 120.36 (ArCH), 116.79 (ArCH), 116.13 (CN), 113.48 (ArCH), 66.64 (OCH), 66.05 (OCH_2), 55.84 (OCH_3), 14.52 (CH_3); *m/z* (EI) 235 (M^+, 30), 146 (100), 134 (93). Found (ES) 236.00902, $C_{12}H_{14}NO_4$ (MH^+) requires 236.0923. GC conditions: initial temperature 100 °C, ramp rate 0.3 °C/min. T_R 174.3 (minor isomer) and 178.6 (major isomer) min.

4.2.4. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(2-methoxyphenyl)acetonitrile 2d. Yield 1.05 g, 95%; $[\alpha]_D^{20}=+57.0$ (*c* 1.4, $CHCl_3$); ν_{max} ($CHCl_3$) 2976 s, 2839 s, 2508 w, 2248 w, 1760 s, and 1598 cm^{-1} s; δ_H 1.26 (3H, t $J=7.1$ Hz, CH_3), 3.81 (3H, s, OCH_3), 4.2–4.3 (2H, m, OCH_2), 6.51 (1H, s, OCHCN), 6.85 (1H, dd $J=8.3$, 1.6 Hz, ArH), 6.96 (1H, dt $J=8.2$, 1.6 Hz, ArH), 7.38 (1H, dt $J=8.2$, 1.6, Hz, ArH), 7.51 (1H, dd $J=8.2$, 1.6 Hz, ArH); δ_C 157.41 (CO_3), 154.17 (ArC), 132.69 (ArCH), 129.53 (ArCH), 121.63 (ArCH), 120.17 (ArC), 116.58 (CN), 111.75 (ArCH), 66.06 (OCH_2), 62.35 (OCH), 56.04 (OCH_3), 14.79 (CH_3); *m/z* (EI) 235 (M^+, 10), 145 (73), 135 (100), 116 (26), 91 (28). Found (CI) 253.1188, $C_{12}H_{17}N_2O_4$ ($M+NH_4^+$) requires 253.1183. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 0.2 °C/min. T_R 163.5 (minor isomer) and 167.6 (major isomer) min.

4.2.5. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-methylphenyl)acetonitrile 2e. Yield 0.69 g, 67%; $[\alpha]_D^{20}=-5.1$ (*c* 2.0, $CHCl_3$); ν_{max} ($CHCl_3$) 2986 s, 2874 m, 2247 w, 1756 s, 1616 s, 1576 w, and 1516 cm^{-1} s; δ_H 1.33 (3H, t $J=7.1$ Hz, CH_3), 2.41 (3H, s, CH_3Ar), 4.3–4.4 (2H, m, OCH_2), 6.25 (1H, s, OCHCN), 7.18 (2H, d $J=7.9$ Hz, ArH), 7.45 (2H, d $J=8.2$ Hz, ArH); δ_C 153.86 (CO_3), 141.33 (ArC), 130.30 (ArCH), 128.76 (ArC), 128.31 (ArCH), 116.28 (CN), 66.69 (OCH), 65.91 (OCH_2), 21.70 (CH_3Ar), 14.50 (CH_3CH_2); *m/z* (EI) 219 (M^+, 50), 146 (40), 130 (100), 119 (90), 103 (38), 77 (23). Found (CI) 237.1232, $C_{12}H_{17}N_2O_3$ ($M+NH_4^+$) requires 237.1234. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 0.2 °C/min. T_R 109.5 (minor isomer) and 111.1 (major isomer) min.

4.2.6. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-trifluoromethylphenyl)acetonitrile 2f. Yield 1.08 g, 84%; ν_{max} ($CHCl_3$) 2982 m, 2939 m, 2356 w, 1760 s, and 1621 cm^{-1} m; δ_H 1.37 (3H, t $J=7.1$ Hz, CH_3), 4.3–4.4 (2H, m, OCH_2), 6.35 (1H, s, OCHCN), 7.69–7.77 (4H, m, ArH) δ_C 153.61 (CO_3), 135.38 (ArC), 133.05 (q $J=8$ Hz, Ar*C*CF_3), 128.55 (ArCH), 125.39 (q $J=68$ Hz, CF_3), 126.72 (ArCH), 115.51 (CN), 66.71 (OCH_2), 65.86 (OCH), 14.46 (CH_3); *m/z* (EI) 273 (M^+, 18), 201 (100), 173 (99), 134 (35). Found (ES) 274.0674, $C_{12}H_{11}NO_3F_3$ (MH^+) requires 274.0691. GC conditions: initial temperature 100 °C, ramp rate 0.4 °C/min. T_R 80.2 (minor isomer) and 83.5 (major isomer) min.

4.2.7. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-chlorophenyl)acetonitrile 2g. Yield 1.08 g, 96%; $[\alpha]_D^{20}=-2.9$ (*c* 1.3, $CHCl_3$); ν_{max} ($CHCl_3$) 3096 m, 3071 m, 2986 s, 2875 m, 2249 w, 1758 s, 1599 s, and 1582 cm^{-1} m; δ_H 1.29 (3H, t $J=7.2$ Hz, CH_3), 4.2–4.3 (2H, m, OCH_2), 6.17 (1H, s, OCHCN), 7.2–7.5 (4H, m, ArH); δ_C 153.68 (CO_3), 137.31 (ArC), 130.17 (ArC), 129.96 (ArCH), 129.65 (ArCH), 115.78 (CN), 66.17 (OCH_2), 66.01 (OCH), 14.49 (CH_3); *m/z* (EI) 241 ((^{37}Cl)M^+, 15), 239 ((^{35}Cl)M^+, 50), 211 (17), 167 (70), 150 (97), 139 (100), 114 (38). Found (ES) 257.0685, $C_{11}H_{14}N_2O_3{}^{35}Cl$ ($M+NH_4^+$) requires 257.0687. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 0.2 °C/min. T_R 129.1 (minor isomer) and 131.5 (major isomer) min.

4.2.8. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-4-phenyl-but-3-enonitrile 2h. Yield 0.51 g, 47%; $[\alpha]_D^{20}=-23.4$ (*c* 1.9, $CHCl_3$); ν_{max} ($CHCl_3$) 3060 m, 2987 s, 2862 m, 2341 w, 2206 w, 1957 w, 1754 s, 1655 m, 1619 m, 1577 m, 1556 m, and 1541 cm^{-1} m; δ_H 1.29 (3H, t $J=7.1$ Hz, CH_3), 4.1–4.2 (2H, m, OCH_2), 5.81 (1H, d $J=6.8$ Hz, OCHCN), 6.14 (1H, dd $J=15.8$, 6.8 Hz, PhCH=C*H*), 6.92 (1H, d $J=15.9$ Hz, PhCH=), 7.2–7.4 (5H, m, ArH); δ_C 153.50 (CO_3), 138.80 (ArCH), 134.67 (ArC), 129.94 (=CH), 129.36 (ArCH), 127.67 (ArCH), 118.25 (=CH), 115.51 (CN), 65.96 (OCH_2), 65.36 (OCH), 14.53 (CH_3); *m/z* (EI) 231 (M^+, 3), 158 (64), 142 (100), 131 (70), 115 (90). Found (ES) 249.1235, $C_{13}H_{17}N_2O_3$ ($M+NH_4^+$) requires 249.1234. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 0.2 °C/min. T_R 212.8 (minor isomer) and 220.0 (major isomer) min.

4.2.9. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-decanonitrile 2i. Yield 0.61 g, 54%; $[\alpha]_D^{20}=-66.0$ (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 2925 s, 2861 s, 2351 w, and 1756 cm^{-1} s; δ_H 0.90 (3H, t $J=6.8$ Hz, CH_3), 1.36 (3H, t $J=7.2$ Hz, CH_3), 1.3–1.6 (12H, m, $(CH_2)_6$), 1.9–2.0 (2H, m, CH_2), 4.2–4.4 (2H, m, OCH_2), 5.20 (1H, t $J=6.7$ Hz, OCHCN); δ_C 154.01 (CO_3), 116.96 (CN), 65.74 (OCH_2), 65.10 (OCH), 32.75 (CH_2), 32.12 (CH_2), 29.56 (CH_2), 29.43 (CH_2), 29.16 (CH_2), 24.78 (CH_2), 24.98 (CH_2), 14.50 (CH_3), 14.47 (CH_3); *m/z* (CI) 242 (MH^+, 20), 168 (20), 122 (58), 98 (90), 81 (100). Found (ES) 259.2013, $C_{13}H_{27}N_2O_3$ ($M+NH_4^+$) requires 259.2016. GC conditions: initial temperature 100 °C, ramp rate 0.4 °C/min. T_R 101.3 (minor isomer) and 103.1 (major isomer) min.

4.2.10. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-3-methyl-butanonitrile 2j. Yield 0.18 g, 23%; $[\alpha]_D^{20}=-59.8$ (*c* 1.2, $CHCl_3$); ν_{max} ($CHCl_3$) 2976 m, 2881 m, 2236 w, and 1758 cm^{-1} s; δ_H 1.1–1.2 (6H, m, $(CH_3)_2$), 1.34 (3H, t $J=7.2$ Hz, CH_3CH$_2$), 2.1–2.2 (1H, m, $CHMe_2$), 4.3–4.4 (2H, m, OCH_2), 5.05 (1H, d $J=5.8$ Hz, OCHCN); δ_C 154.12 (CO_3), 116.05 (CN), 70.36 (OCH), 65.75 (OCH_2), 31.61 (Me_2CH), 18.04 (CH_3CH), 17.65 (CH_3CH), 14.50 (CH_3CH$_2$); *m/z* (ES) 172 (MH^+, 100), 145 (7), 128 (6),

82 (13), 57 (33). Found (CI) 189.1229, $C_8H_{17}N_2O_3$ ($M+NH_4^+$) requires 189.1234. GC conditions: initial temperature 60 °C, ramp rate 5.0 °C/min. T_R 16.1 (minor isomer) and 16.2 (major isomer) min.

4.2.11. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-cyclohexyl-ethanonitrile 2k. Yield 0.81 g, 82%; $[\alpha]_D^{20}=-32.2$ (*c* 1.3, $CHCl_3$); ν_{max} ($CHCl_3$) 2934 s, 2857 s, 2245 m, and 1756 cm^{-1} s; δ_H 1.2–1.3 (6H, m, $(CH_2)_3$), 1.33 (3H, t $J=7.2$ Hz, CH_3), 1.7–2.0 (5H, m, CH_2CHCH_2), 4.2–4.3 (2H, m, OCH_2), 5.04 (1H, d $J=5.8$ Hz, OCHCN); δ_C 154.16 (CO_3), 116.21 (CN), 69.63 (OCH), 65.71 (OCH_2), 40.52 (CH), 28.34 (CH_2), 28.16 (CH_2), 26.06 (CH_2), 25.68 (CH_2), 25.60 (CH_2), 14.49 (CH_3); *m/z* (CI) 212 (MH^+, 100), 129 (46), 95 (33), 83 (79), 55 (90). Found (CI) 229.1548, $C_{11}H_{21}N_2O_3$ ($M+NH_4^+$) requires 229.1547. GC conditions: initial temperature 60 °C, hold at initial temperature for 2 min then ramp rate 0.2 °C/min. T_R 274.0 (minor isomer) and 276.4 (major isomer) min.

4.2.12. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-3,3-dimethyl-butanonitrile 2l. Yield 0.60 g, 69%; $[\alpha]_D^{20}=-48.5$ (*c* 2.0, $CHCl_3$); ν_{max} ($CHCl_3$) 2976 s, 2237 w, and 1754 cm^{-1} s; δ_H 1.05 (9H, s, $C(CH_3)_3$), 1.26 (3H, t $J=7.1$ Hz, CH_3CH_2), 4.2–4.3 (2H, m, OCH_2), 4.85 (1H, s, OCHCN); δ_C 151.32 (CO_3), 116.14 (CN), 73.57 (OCH), 65.65 (OCH_2), 35.27 (CMe_3), 25.48 (CH_3CH_2), 14.51 ($C(CH_3)_3$); *m/z* (CI) 186 (MH^+, 88), 96 (43), 57 (100), 41 (49). Found (CI) 203.1396, $C_9H_{19}N_2O_3$ ($M+NH_4^+$) requires 203.1390. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 0.2 °C/min. T_R 13.9 (minor isomer) and 14.2 (major isomer) min.

4.3. General procedure for the asymmetric addition of potassium cyanide and an anhydride to aldehydes

To a stirred mixture, cooled at −90 °C, of KCN (2.54 g, 39.2 mmol) and catalyst **1** (118 mg, 0.098 mmol) in dry dichloromethane (20 mL), *t*-BuOH (0.98 mL, 10.3 mmol), water (0.1 mL, 4.4 mmol), aldehyde (9.8 mmol) and anhydride (39.2 mmol) were added. The reaction was warmed to −40 °C, monitored by chiral GC at suitable intervals and allowed to stir until the reaction was >90% complete. Solid salts were filtered and washed thoroughly with dichloromethane. The filtrate was passed through a pad of silica (10 mm×50 mm) eluting with dichloromethane to remove catalyst **1**. The solvent was evaporated in vacuo, and the residue purified by distillation or flash chromatography (ethyl acetate/hexane 1/5) to give the (*S*)-cyanohydrin ester.

4.3.1. *O*-Propanoyl (*S*)-2-hydroxy-2-phenyl-acetonitrile 3b.[23a] Yield 99%; $[\alpha]_D^{25}-5.09$ (*c* 1.1, $CHCl_3$); ν_{max} (neat) 2987 m, and 1756 cm^{-1} s; δ_H 1.20 (3H, t $J=7.5$ Hz, CH_2CH_3), 2.4–2.5 (2H, m, CH_2CH_3), 6.62 (1H, s, CH), 7.4–7.6 (5H, m, ArH); δ_C 170.67 (CO_2), 131.29 (ArC), 129.69 (ArCH), 128.59 (ArCH), 127.16 (ArCH), 115.65 (CN), 62.13 (OCH), 26.70 (CH_2), 7.70 (CH_3); *m/z* (EI) 189 (M^+, 15), 133 (30), 116 (34), 57 (100)). Found (ES) 212.0685, $C_{11}H_{11}NO_2Na$ ($M+Na^+$) requires 212.0685. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 14.5 (minor isomer) and 14.9 (major isomer) min.

4.3.2. *O*-Pivaloyl (*S*)-2-hydroxy-2-phenyl-acetonitrile 3c.[24a] Yield 85%; $[\alpha]_D^{25}-1.1$ (*c* 3.0, $CHCl_3$); ν_{max} (neat) 2978 s, 1809 m, and 1742 cm^{-1} s; δ_H 1.26 (9H, s, $(CH_3)_3$), 6.40 (1H, s, CH), 7.4–7.6 (5H, m ArCH); δ_C 174.25 (CO_2), 132.43 (ArC), 130.54 (ArCH), 129.55 (ArCH), 127.80 (ArCH), 116.61 (CN), 63.14 (OCH), 40.49 (C), 26.94 (CH_3); *m/z* (EI) 217 (M^+, 75), 116 (68), 57 (100). Found (ES) 240.0996, $C_{13}H_{15}NO_2Na$ ($M+Na^+$) requires 240.1000. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 0.4 °C/min. T_R 18.6 (minor isomer) and 18.8 (major isomer) min.

4.3.3. *O*-Benzoyl (*S*)-2-hydroxy-2-phenyl-acetonitrile 3d.[25a] Yield 98%; $[\alpha]_D^{25}-9.3$ (*c* 2.0, $CHCl_3$); ν_{max} (neat) 3065 m, 1785 s, and 1598 cm^{-1} s; δ_H 6.61 (1H, s, CH), 7.3–7.4 (6H, m, ArH), 7.5–7.6 (2H, m, ArH), 8.0–8.0 (2H, m, ArH); δ_C 162.78 (CO_2), 135.30 (ArC), 134.99 (ArC), 131.32 (ArCH), 130.68 (ArCH), 129.32 (ArCH), 128.98 (ArCH), 128.27 (ArCH), 116.68 (CN), 63.80 (OCH), *m/z* (ES) 475 ($2M+H^+$, 55), 411 (15), 260 ($M+Na^+$, 40), 249 (100). Found (ES) 238.0873, $C_{15}H_{12}NO_2$ (MH^+) requires 238.0868. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 17.3 (minor isomer) and 18.0 (major isomer) min.

4.3.4. *O*-Propanoyl (*S*)-2-hydroxy-4-phenyl-but-3-enonitrile 3e. Yield 62%; $[\alpha]_D^{25}-2.0$ (*c* 1.0, $CHCl_3$); ν_{max} (neat) 2989 m, and 1760 cm^{-1} s; δ_H 1.11 (3H, t $J=7.3$ Hz, CH_2CH_3), 2.4–2.5 (2H, m, CH_2CH_3), 6.06 (1H, d $J=7.5$ Hz, CHCN), 6.17 (1H, dd $J=15.8$, 6.7 Hz, PhCH=CH), 6.96 (1H, d $J=15.8$ Hz, PhCH=), 7.2–7.5 (5H, m, ArH); δ_C 172.84 (CO_2), 138.15 (ArC), 134.83 (=CH), 129.78 (ArCH), 129.24 (ArCH), 127.57 (ArCH), 118.87 (=CH), 116.00 (CN), 61.81 (OCH), 27.54 (CH_2), 9.15 (CH_3); *m/z* (EI) 215 (M^+, 14), 159 (51), 141 (93), 115 (100), 57 (74). Found (ES) 238.0911, $C_{13}H_{13}NO_2Na$ ($M+Na^+$) requires 238.0838. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 2.0 °C/min. T_R 43.0 (minor isomer) and 44.9 (major isomer) min.

4.3.5. *O*-Pivaloyl (*S*)-2-hydroxy-4-phenyl-but-3-enonitrile 3f. Yield 50%; $[\alpha]_D^{25}+10.1$ (*c* 4.0, $CHCl_3$), ν_{max} (neat) 2976 s, 1744 s, and 1480 cm^{-1} s; δ_H 1.19 (9H, s, $(CH_3)_3$), 5.94 (1H, d *?*=6.7 Hz, CHCN), 6.12 (1H, dd $J=15.8$, 6.7 Hz, PhCH=CH), 6.89 (1H, d $J=15.8$ Hz, PhCH=), 7.2–7.4 (5H, m, ArH); δ_C 176.89 (CO_2), 138.03 (=CH), 134.87 (ArC), 129.77 (ArCH), 129.24 (ArCH), 127.58 (ArCH), 118.90 (=CH), 116.05 (CN), 61.92 (OCH), 39.30 (CMe_3), 27.30 (CH_3); *m/z* (ES) 509 ($2M+Na^+$, 12), 488 (31), 467 (36), 266 ($M+Na^+$, 85), 245 (100), 223 (67), 209 (45), 142 (85). Found (ES) 509.2430 and 266.1148, $C_{30}H_{34}N_2O_4Na$ ($2M+Na^+$) requires 509.2416, $C_{15}H_{17}NO_2Na$ ($M+Na^+$) requires 266.1157. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 25.5 (minor isomer) and 25.7 (major isomer) min.

4.3.6. *O*-Propanoyl (*S*)-2-hydroxy-2-(4-trifluoromethyl-phenyl)-acetonitrile 3g. Yield 99%; $[\alpha]_D^{25}-1.1$ (*c* 12.0, $CHCl_3$); ν_{max} (neat) 2989 m, and 1760 cm^{-1} s; δ_H 1.16 (3H, t $J=7.5$ Hz, CH_2CH_3), 2.4–2.5 (2H, m, CH_2CH_3), 6.45 (1H, s, CH), 6.6–7.7 (4H, m, ArH); δ_C 172.64 (CO_2), 135.99

(ArC), 132.70 (q $J=33$ Hz, CF_3), 126.69 (ArCH), 125.41 (ArCH), 116.00 (CN), 62.39 (OCH), 27.47 (CH_2), 9.08 (CH_3); *m/z* (EI) 257 (M^+, 25), 238 (30), 201 (75), 184 (80), 57 (100). Found (ES) 280.0555, $C_{12}H_{10}NO_2F_3Na$ ($M+Na^+$) requires 280.0551. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 3.0 °C/min. T_R 21.2 (minor isomer) and 22.0 (major isomer) min.

4.3.7. *O*-Pivaloyl (*S*)-2-hydroxy-2-(4-trifluoromethylphenyl)-acetonitrile 3h. Yield 99%; $[\alpha]_D^{25}-5.4$ (*c* 2.0, $CHCl_3$); ν_{max} (neat) 2979 s, 1808 m, and 1749 cm^{-1} s; δ_H 1.29 (9H, s, $(CH_3)_3$), 6.48 (1H, s, CH), 7.66 (2H, d $J=8.3$ Hz, ArCH), 7.74 (2H, d $J=8.3$ Hz ArCH); δ_C 175.31 (CO_2), 136.19 (ArC), 132.99 (q $J=33$ Hz, CF_3), 128.25 (ArC), 126.72 (ArCH), 122.41 (ArCH), 116.02 (CN), 62.46 (OCH), 39.29 (C), 27.18 (CH_3); *m/z* (ES) 308 ($M+Na^+$, 100), 184 (40). Found (ES) 308.0867, $C_{14}H_{14}NO_2F_3Na$ ($M+Na^+$) requires 308.0869. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 0.4 °C/min. T_R 21.3 (minor isomer) and 21.6 (major isomer) min.

4.3.8. *O*-Propanoyl (*S*)-2-hydroxy-2-(3-methoxyphenyl)-acetonitrile 3j. Yield 87%; $[\alpha]_D^{25}-2.1$ (*c* 3.0, $CHCl_3$); ν_{max} (neat) 2984 m, 2945 m, and 1754 cm^{-1} s; δ_H 1.19 (3H, t $J=7.6$ Hz, CH_2CH_3), 2.4–2.5 (2H, m, CH_2CH_3), 3.84 (s, 3H, OCH_3), 6.40 (1H, s, CH), 7.0–7.4 (4H, m, ArH); δ_C 172.80 (CO_2), 160.49 (ArC), 133.58 (ArC), 130.74 (ArCH), 120.58 (ArCH), 116.60 (ArCH), 116.31 (CN), 113.61 (ArCH), 62.99 (OCH), 55.81 (OCH_3), 27.51 (CH_2), 9.14 (CH_3); *m/z* (EI): 219 (M^+, 42), 163 (100), 146 (39), 57 (34). Found (ES) 242.0787, $C_{12}H_{13}NO_3Na$ ($M+Na^+$) requires 242.0782. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 15.1 (minor isomer) and 15.3 (major isomer) min.

4.3.9. *O*-Propanoyl (*S*)-2-hydroxy-2-(4-methoxyphenyl)-acetonitrile 3l. Yield 71%; $[\alpha]_D^{25}+12.7$ (*c* 11.4, $CHCl_3$); ν_{max} (neat) 3022 w, 2944 m, and 1752 cm^{-1} s; δ_H 1.23 (3H, t $J=7.5$ Hz, CH_2CH_3), 2.4–2.5 (2H, m, CH_2CH_3), 3.89 (3H, s, OCH_3), 6.43 (1H, s, CH), 6.9–7.0 (2H, m, ArH), 7.4–7.5 (2H, m, ArH); δ_C 172.82 (CO_2), 160.48 (ArC), 133.57 (ArC), 130.75 (ArCH), 120.28 (ArCH), 116.62 (CN), 63.01 (OCH), 55.82 (OCH_3), 27.52 (CH_2), 9.14 (CH_3); *m/z* (EI) 219 (M^+, 32), 163 (35), 146 (100). Found (ES) 242.0783, $C_{12}H_{13}NO_3Na$ ($M+Na^+$) requires 242.0782. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 16.9 (minor isomer) and 17.3 (major isomer) min.

4.3.10. *O*-Propanoyl (*S*)-2-hydroxy-3-methyl-butanonitrile 3n.[23a] Yield 99%; $[\alpha]_D^{25}+3.0$ (*c* 5.0, $CHCl_3$); ν_{max} (neat) 2970 s, 2879 s, and 1754 cm^{-1} s; δ_H 1.07 (6H, d $J=6.8$ Hz, $(CH_3)_2CH$), 1.17 (3H, t $J=7.6$ Hz, CH_3CH_2), 2.1–2.2 (1H, m, $CHMe_2$), 2.3–2.5 (2H, m, CH_2CH_3), 5.17 (1H, d $J=5.8$ Hz, OCH); δ_C 173.03 (CO_2), 116.48 (CN), 66.55 (OCH), 31.44 (CH), 27.43 (CH_2), 18.12 (CH_3), 17.73 (CH_3), 9.17 (CH_3); *m/z* (CI) 156 (MH^+, 26), 57 (100). GC conditions: initial temperature 60 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 14.1 (minor isomer) and 14.5 (major isomer) min.

4.3.11. *O*-Propanoyl (*S*)-2-hydroxy-3,3-dimethyl-butanonitrile 3p. Yield 99%; $[\alpha]_D^{25}-3.8$ (*c* 2.0, $CHCl_3$); ν_{max} (neat) 2971 s, 2878 s, and 1754 cm^{-1} s; δ_H 1.09 (9H, s, $(CH_3)_3$), 1.18 (3H, t $J=7.5$ Hz, CH_2CH_3), 2.38 (2H, q $J=7.6$ Hz, CH_3CH_2), 5.07 (1H, s, OCH); δ_C 171.59 (CO_2), 116.56 (CN), 69.59 (OCH), 35.08 (CMe_3), 32.84 (CH_2), 25.60 (CH_3), 8.42 (CH_3); *m/z* (CI) 170 (MH^+, 42), 113 (15), 57 (100). GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 20.7 (minor isomer) and 21.2 (major isomer) min.

4.3.12. *O*-Propanoyl (*S*)-2-hydroxy-2-(2-methylphenyl)-acetonitrile 3q. Yield 99%; $[\alpha]_D^{25}-13.0$ (*c* 6.0, $CHCl_3$); ν_{max} (neat) 2984 m, and 1753 cm^{-1} s; δ_H 1.23 (3H, t $J=7.4$ Hz, CH_2CH_3), 2.4–2.5 (2H, m, CH_2CH_3), 2.45 (3H, s, CH_3Ar), 6.55 (1H, s, OCH), 7.2–7.4 (3H, m, ArH), 7.5–7.6 (1H, m, ArH); δ_C 172.78 (CO_2), 137.05 (ArC), 131.70 (ArC), 130.83 (ArCH), 130.36 (ArCH), 128.89 (ArCH), 127.18 (ArCH), 116.49 (CN), 61.34 (OCH), 27.40 (CH_2), 19.29 ($ArCH_3$), 9.16 (CH_3); *m/z* (EI) 203 (M^+, 10), 129 (100), 103 (48). Found (ES) 226.0837, $C_{12}H_{13}NO_2Na$ ($M+Na^+$) requires 226.0838. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 19.4 (minor isomer) and 19.9 (major isomer) min.

4.3.13. *O*-Propanoyl (*S*)-2-hydroxy-2-(3-methylphenyl)-acetonitrile 3r. Yield 98%; $[\alpha]_D^{25}-2.0$ (*c* 1.0, $CHCl_3$); ν_{max} (neat) 2985 m, 2945 m, and 1753 cm^{-1} s; δ_H 1.26 (3H, t $J=5.9$ Hz, CH_2CH_3), 2.32 (3H, s, CH_3Ar), 2.4–2.5 (2H, m, CH_2CH_3), 6.32 (1H, s, OCH), 7.2–7.3 (4H, m, ArH); δ_C 172.84 (CO_2), 139.60 (ArC), 132.21 (ArC), 131.49 (ArCH), 129.51 (ArCH), 128.81 (ArCH), 122.30 (ArCH), 116.49 (CN), 61.18 (OCH), 27.53 (CH_2), 21.72 ($ArCH_3$), 9.14 (CH_3); *m/z* (ES) 226 ($M+Na^+$, 100). Found (ES) 226.0837, $C_{12}H_{13}NO_2Na$ ($M+Na^+$) requires 226.0838. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 16.3 (minor isomer) and 16.5 (major isomer) min.

4.3.14. *O*-Propanoyl (*S*)-2-hydroxy-2-(4-methylphenyl)-acetonitrile 3s. Yield 98%; $[\alpha]_D^{25}+3.5$ (*c* 6.0, $CHCl_3$); ν_{max} (neat) 2985 m, 2845 m, and 1755 cm^{-1} s; δ_H 1.18 (3H, t $J=7.5$ Hz, CH_2CH_3), 2.15 (3H, s, CH_3Ar), 2.3–2.5 (2H, m, CH_2), 6.40 (1H, s, CHO), 7.26 (2H, d $J=8.0$ Hz, ArCH), 7.46 (2H, d $J=8.1$ Hz, ArCH); δ_C 172.87 (CO_2), 140.99 (ArC), 130.26 (ArC), 129.39 (ArCH), 128.20 (ArCH), 116.79 (CN), 63.05 (OCH), 27.51 (CH_2), 21.65 ($ArCH_3$), 9.10 (CH_3); *m/z* (ES) 226 ($M+Na^+$, 100), 130 (22). Found (ES) 226.0790, $C_{12}H_{13}NO_2Na$ ($M+Na^+$) requires 226.0838. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 16.4 (minor isomer) and 16.6 (major isomer) min.

4.3.15. *O*-Propanoyl (*S*)-2-hydroxy-2-(4-chlorophenyl)-acetonitrile 3t. Yield 99%; $[\alpha]_D^{25}+13.3$ (*c* 3.0, $CHCl_3$); ν_{max} (neat) 2986 s, 2945 s, and 1754 cm^{-1} s; δ_H 1.15 (3H, t $J=7.4$ Hz, CH_2CH_3), 2.4–2.5 (2H, m, CH_2CH_3), 6.37 (1H, s, OCH), 7.4–7.5 (4H, m, ArH); δ_C 172.72 (CO_2), 136.99 (ArC), 130.79 (ArC), 129.91 (ArCH), 129.61 (ArCH), 116.24 (CN), 62.43 (OCH), 27.49 (CH_2), 9.22 (CH_3); *m/z* (EI) 225 (($^{37}Cl)M^+$, 18), 223 (($^{35}Cl)M^+$, 51), 150 (100), 57 (90). Found (ES) 246.0293, $C_{11}H_{10}NO_2^{35}ClNa$ (($^{35}Cl)M+$

Na^+) requires 246.0230. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 21.9 (minor isomer) and 23.0 (major isomer) min.

4.3.16. *O*-Propanoyl (*S*)-2-hydroxy-decanonitrile 3u. Yield 74%; $[\alpha]_D^{25}$ −3.7 (*c* 10.6, $CHCl_3$); ν_{max} (neat) 2928 s, 2850 m, and 1752 cm^{-1} s; δ_H 0.88 (3H, t J=7.1 Hz, $CH_3(CH_2)_7$), 1.19 (3H, t J=7.5 Hz, CH_2CH_3), 1.30–1.32 (12H, m, $(CH_2)_6$), 1.9–2.0 (2H, m, CH_2CH), 2.4–2.5 (2H, m, CH_2CO), 5.34 (1H, t J=6.8 Hz, OCH); δ_C 173.06 (CO_2), 117.44 (CN), 61.37 (OCH), 32.71 (CH_2), 32.15 (CH_2), 29.47 (CH_2), 29.19 (CH_2), 27.48 (CH_2), 24.92 (CH_2), 23.01 (CH_2), 17.73 (CH_2), 14.45 (CH_3), 9.16 (CH_3); *m/z* (CI) 226 (MH^+, 24), 81 (51), 57 (100). Found (ES) 248.1617, $C_{13}H_{23}NO_2Na$ ($M+Na^+$) requires 248.1628. GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 16.6 (minor isomer) and 17.2 (major isomer) min.

4.3.17. *O*-Propanoyl (*S*)-2-hydroxy-2-cyclohexyl-acetonitrile 3v.[23a] Yield 95%; $[\alpha]_D^{25}$ −7.5 (*c* 13.6, $CHCl_3$); ν_{max} (neat) 3025 w, 2931 m, 1813 m, and 1752 cm^{-1} s; δ_H 1.19 (3H, t J=7.4 Hz, CH_3), 1.1–1.4 (6H, m, $(CH_2)_3$), 1.7–2.0 (4H, m, (CH_2CHCH_2), 2.4–2.5 (3H, m, $CH(CH_2)_2+CH_3CH_2$), 5.20 (1H, d J=6.0 Hz, OC*H*); δ_C 170.84 (CO_2), 116.61 (CN), 65.73 (OCH), 40.30 (CH), 29.06 (CH_2), 28.69 (CH_2), 28.40 (CH_2), 27.01 (CH_2), 26.35 (CH_2), 25.61 (CH_2), 9.09 (CH_3); *m/z* (CI) 196 (MH^+, 80), 113 (45), 57 (100). GC conditions: initial temperature 100 °C, hold at initial temperature for 2 min then ramp rate 5.0 °C/min. T_R 16.7 (minor isomer) and 16.9 (major isomer) min.

4.4. General procedure for the use of a sacrificial aldehyde

To a stirred mixture, cooled to −40 °C, of KCN (2.54 g, 39.21 mmol), complex **1** (9 mg, 0.098 mmol), *t*-BuOH (0.098 mL, 10.3 mmol) and water (0.1 mL, 4.4 mmol), in dry dichloromethane (20 mL), the sacrificial aldehyde (2 or 10 mol%, 0.16 mmol or 0.83 mmol) and propionic anhydride (5.03 mL, 39.3 mmol) were added. The reaction was left for 3–5 h at −40 °C and monitored by GC chiral analysis. The real aldehyde (90 or 98 mol%, 8.5 or 9.25 mmol) was then added and the reaction was monitored by TLC (ethyl acetate/hexane) and chiral GC (for both aldehydes) until the reaction was complete (ca 48 h). The reaction was warmed to room temperature; solids were removed by filtration and washed thoroughly with dichloromethane. To remove the catalyst, the filtrate was passed through a pad of silica (10 mm×50 mm) eluting with dichloromethane. The solvent was evaporated in vacuo, and the resulting yellowish residue purified by flash chromatography (ethyl acetate/hexane) or distillation.

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Enantioselective cyanosilylation of ketones catalyzed by double-activation catalysts with *N*-oxides

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Abstract—Enantioselective addition of trimethylsilyl cyanide to ketones by a catalytic double-activation method is described. By combinatorially using 2.0 mol% of a chiral salen-titanium complex and 1.0 mol% of an achiral tertiary amine *N*-oxide, aromatic, aliphatic and α,β-unsaturated ketones are converted into corresponding cyanohydrin trimethylsilyl ethers with 50–93% yield and 59–86% ee. The effects of ligand structure, catalyst loading and substrate concentration, solvents, the nature of Lewis base, counter ion and other additives, temperature, and substrate structure on the enantioselectivity are discussed. Three possible paths to achieve the asymmetric version of double-activation catalysis and two independent examples of it are proposed.

1. Introduction

Cyanohydrins are versatile intermediates in organic synthesis.[1] They can be easily converted into a large range of organic compounds such as α-hydroxy carbonyl compounds and α-amino alcohols. Due to the increasing demand for chiral drugs, agrochemicals and other non-racemic compounds, the asymmetric synthesis of optically active cyanohydrins has received great attention in recent decades.[2] Much progress has been made in the asymmetric hydrocyanation of aldehydes.[1,3]

Compared to aldehydes, the low reactivity and greater steric hindrance of ketones have delayed the asymmetric synthesis of tertiary cyanohydrins.[4] However, encouraging progress has been achieved in the last ten years. Besides (*R*/*S*)-oxynitrilase catalyzed hydrocyanation of ketones[3a–c] and diastereoselective substitution of chiral cyanophosphoramidates,[5] tertiary cyanohydrins were synthesized from ketones with Lewis acid and Lewis base catalysts. Choi reported the chiral triol titanium complex-catalyzed asymmetric addition of TMSCN (trimethylsilyl cyanide) to ketones at high pressure.[6] Belokon and North have reported the enantioselective cyanosilylation of aromatic ketones using a C_2-symmetric dinuclear titanium complex as the catalyst.[7] Shibasaki developed a bifunctional catalyst containing phosphoryl moieties to promote the asymmetric cyanosilylation of aromatic and aliphatic ketones.[8] Deng has outlined a method for cyanide addition to ketones by employing cinchona derivatives as the catalysts.[9] Snapper disclosed an enantioselective addition of TMSCN to aromatic and aliphatic ketones with a recyclable peptide aluminum complex.[10] Feng reported bifunctional *N*-oxide titanium-catalyzed enantioselective cyanosilylation of ketones.[11] Our group also employed chiral *N*-oxides to promote the asymmetric Strecker reaction between TMSCN and aldimines.[12] Subsequently, we developed double-activation catalysts with achiral *N*-oxides for the syntheses of racemic and non-racemic cyanohydrins.[13] This paper describes studies of the relationship between the catalyst efficiency and ligand structure, substrate generality and mechanism studies.

2. Results and discussion

Building on the understanding of the chiral inductive capabilities of salen-Ti(IV) complexes in the asymmetric hydrocyanation of aldehydes,[14] and of the coordination between the N–O dipolar group and the silicon atom of TMSCN,[11,12] a double-activation catalyst system composed of titanium complexes of ligands **1a**-**m** and **2a**-**g** as the Lewis acids, and achiral tertiary amine *N*-oxides **3a**-**f** as the

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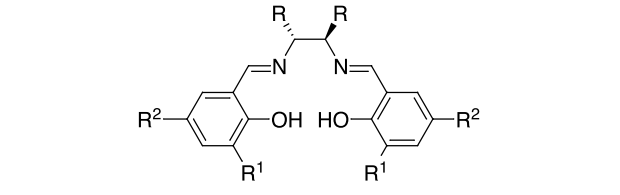
Lewis bases (Fig. 1) has been developed to activate both reaction components simultaneously. In this way, enhanced catalytic reactivity and chiral inductivity were accomplished in the enantioselective addition of TMSCN to ketones.

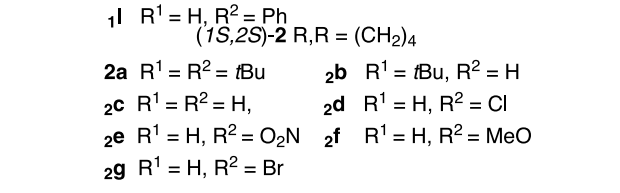
2.1. Optimization of the catalysts

To assess the catalytic reactivity of ligands **1a**-**m** and **2a**-**g**, their complexes with Ti(O*i*Pr)$_4$ were used to catalyze the enantioselective addition of TMSCN to acetophenone (**4a**) giving cyanohydrin trimethylsilyl ether (**5a**) as the model reaction. The results are summarized in Table 1. The substituents on the salicylidene phenolic rings of the ligands played an important role on the enantioselectivity. While bromine substituent gave a passable ee value, chlorine atom(s) at the 3′/5′-position(s) led to the disappearance of the catalytic reactivity (Table 1, entries 2–4). Catalysts derived from ligands with electron-withdrawing or electron-donating substituents showed considerable decrease in enantioselectivity (Table 1, entries 5, 6). On the other hand, alkyl substituted catalysts exhibited a promising increase of the ee values (Table 1, entries 7–10). However, the most hindered alkyl group, adamantly, nullified the benefit of alkyl substituents (Table 1, entry11). This is in contrast to other reactions.[15a,b] Attempts to introduce other symmetry or interaction with phenyl rings into the catalyst turned out to be ineffective (Table 1, entries 12, 13).[15c] Additionally, the structurally similar Jacobsen's ligands **2a**-**g** gave comparable or lower enantioselectivities with the same substituent effect as compared to **1a**-**m** (Table 1, entries 14–20). Thus, the 3′,5′-di-*tert*-butyl substituted ligand **1j** gave the highest enantioselectivity.



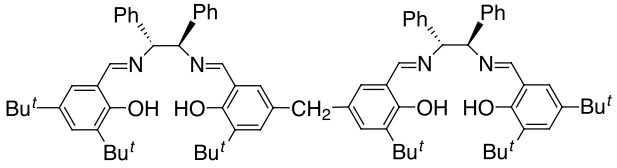
(*1R,2R*)-**1** R,R = Ph

1a $R^1 = R^2 = H$ **1b** $R^1 = R^2 = Cl$
1c $R^1 = H$, $R^2 = Cl$ **1d** $R^1 = H$, $R^2 = Br$
1e $R^1 = H$, $R^2 = O_2N$ **1f** $R^1 = H$, $R^2 = MeO$
1g $R^1 = H$, $R^2 = Me$ **1h** $R^1 = H$, $R^2 = tBu$
1i $R^1 = tBu$, $R^2 = Me$ **1j** $R^1 = R^2 = tBu$
1k R^1 = adamantanyl, $R^2 = tBu$
1l $R^1 = H$, $R^2 = Ph$

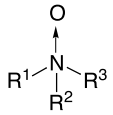


(*1S,2S*)-**2** R,R = $(CH_2)_4$

2a $R^1 = R^2 = tBu$ **2b** $R^1 = tBu$, $R^2 = H$
2c $R^1 = R^2 = H$, **2d** $R^1 = H$, $R^2 = Cl$
2e $R^1 = H$, $R^2 = O_2N$ **2f** $R^1 = H$, $R^2 = MeO$
2g $R^1 = H$, $R^2 = Br$

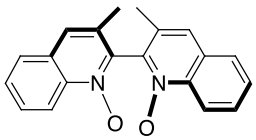


(*1R,1′R,2R,2′R*)-**1m**



3

3a $R^1 = R^2 = R^3 = Me$
3b $R^1 = R^2 = R^3 = Et$
3c $R^1 = R^2 = Me$, R^3 = cyclohexyl
3d $R^1 = R^2 = Me$, $R^3 = Ph$
3e $R^1 = R^2 = Me$, $R^3 = o\text{-}MeC_6H_4$
3f $R^1 = R^2 = Me$, $R^3 = p\text{-}MeC_6H_4$



(*R*)-**3g**

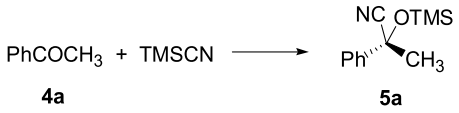
Figure 1. Ligands evaluated in this study.

Various Lewis bases were next evaluated with the results listed in Table 2. In terms of chemical yield, *N*-oxides derived from tertiary amines with stronger basicity were preferable to those derived from less basic amines (Table 2, entries 1–3). However, aromatic amine *N*-oxides exhibited higher asymmetric induction than those derived from aliphatic amines (Table 2, entry 5 vs. entries 3 and 4). *Ortho*- (**3e**) or *para*-methyl (**3f**) substituted anilines showed no higher asymmetric induction than **3d**.[15d] Pyridine *N*-oxide (PyNO) might strongly coordinate to titanium leading to the disappearance of the catalytic activity and no reaction occurred, whilst hexamethylphosphoramide (HMPA) showed moderate reactivity and enantioselectivity (Table 2, entries 6 and 7). These phenomena are consistent with Shibasaki's bifunctional phosphine oxides[8] and Denmark's phophoramides.[16] *N*,*N*-dimethylaniline *N*-oxide **3d** is the most appropriate catalyst component for **1j**-Ti(O*i*Pr)$_4$ complex.

The influence of the reaction solvent was then investigated with results listed in Table 3. Solvents have more effect on chemical yield than on enantioselectivity. Aromatic solvents and diethyl ether decreased the enantioselectivity slightly to a similar extent (Table 3, entries 1–3). However, the ee value was remarkablely reduced to 23% ee with only traces of product formed in the polar solvent CH_3CN, and no reaction occurred in THF (Table 3, entries 4 and 5). Halogenated alkanes were appropriate solvents, and the optimal choice was CH_2Cl_2 (Table 3, entries 6, 7). If the catalyst was prepared without removing the generated *i*PrOH, the chemical yield suffered a considerable decrease from 95% down to 20% with only a small change in enantioselectivity (Table 3, entry 7 vs. 8). When the reaction was carried out in the presence of the generated *i*PrOH and additional 4 Å MS, no product could be detected in the reaction mixture (Table 3, entry 9).

The effects of catalyst loading and substrate concentration on the enantioselectivity were systematically studied, with results summarized in Table 4. Interestingly, these two factors enhanced enantioselectivity and chemical yield cooperatively. On reducing the catalyst loading from 20 to 2.5 mol%, the enantioselectivity increased slightly from 67 to 74% ee, while the chemical yield decreased stepwise from 94 down to 11% (Table 4, entries 1–5). But further lowering the amount of the catalysts led to a reduction in the enantioselectivity by 6% ee (Table 4, entry 6). Fortunately, the low chemical yield caused by lowering the amount of the catalysts was recovered by increasing the concentration

Table 1. Structural effect of the ligands **1a**-**m** and **2a**-**g** on the enantioselective cyanosilylation of acetophenone[a]



Entry	Ligand	Yield (%)[b]	ee (%)[c]	Entry	Ligand	Yield (%)[b]	ee (%)[c]
1	**1a**	13	46	11[d]	**1k**	9	11
2	**1b**	NR	—	12[d]	**1l**	25	51
3	**1c**	NR	—	13[e]	**1m**	21	63
4	**1d**	61	39	14	**2a**	77	64
5	**1e**	16	20	15	**2b**	41	47
6	**1f**	32	33	16	**2c**	65	25
7	**1g**	51	45	17	**2d**	Trace	30
8	**1h**	49	57	18	**2e**	Trace	11
9	**1i**	47	60	19	**2f**	NR	—
10	**1j**	95	67	20	**2g**	NR	—

[a] Conditions: 20 mol% of **1/2**–Ti(O*i*Pr)$_4$ complex (1:1), 20 mol% of **3d**, concentration of acetophenone = 0.12 M in CH_2Cl_2, 0 °C, 84 h.
[b] Isolated yield. NR = no reaction
[c] Determined by GC on Chirasil DEX CB.
[d] Under the optimized conditions: 2 mol% of **1**–Ti(O*i*Pr)$_4$ complex (1:1), 1 mol% of **3d**, concentration of acetophenone = 1.1 M in CH_2Cl_2, −20 °C, 120 h.
[e] Under the optimized conditions: 1 mol% of **1m**–Ti(O*i*Pr)$_4$ complex (1:2), 1 mol% of **3d**, concentration of acetophenone = 1.1 M in CH_2Cl_2, −20 °C, 120 h.

Table 2. Enantioselective cyanosilylation of acetophenone catalyzed by **1j**–Ti(O*i*Pr)$_4$ complex and Lewis bases[a]

Entry	Lewis base	Yield (%)[b]	ee (%)[c]
1	**3a**	5	44
2	**3b**	53	66
3	**3c**	63	51
4	NMNO	32	60
5	**3d**	95	67
6	PyNO	NR	—
7	HMPA	30	34

[a] Conditions: 20 mol% of **1j**–Ti(O*i*Pr)$_4$ complex (1:1), 20 mol% of Lewis base, 0 °C, 84 h, concentration of acetophenone = 0.12 M.
[b] Isolated yield.
[c] Determined by GC analysis on Chirasil DEX CB. NMNO = *N*-methylmorpholine *N*-oxide.

Table 3. Solvent effects on the enantioselectivity of the asymmetric addition of TMSCN to acetophenone[a]

Entry	Solvent	Yield (%)[b]	ee (%)[c]
1	Benzene	34	53
2	Toluene	9	50
3	Et_2O	18	52
4	CH_3CN	Trace	23
5	THF	NR	—
6	$CHCl_3$	87	58
7	CH_2Cl_2	95	67
8[d]	CH_2Cl_2	20	65
9[e]	CH_2Cl_2	NR	—

[a] All reactions were carried out at 0 °C for 84 h with 20 mol% of **3d** and 20 mol% of **1j**–Ti(O*i*Pr)$_4$ complex (1:1) as the catalysts. The concentration of acetophenone was 0.12 M.
[b] Isolated yield. NR = no reaction.
[c] Determined by GC on Chirasil DEX CB.
[d] This reaction was carried out in the presence of the *i*PrOH generated during the preparation of the catalyst.
[e] This reaction was performed in the presence of additional 4 Å MS and the *i*PrOH generated during the preparation of the catalyst.

of the reaction components without any loss of enantioselectivities (Table 4, entries 6–9). The reaction did not proceed smoothly without solvent at 0 °C (Table 4, entry 10).

Low temperature had a positive effect on the enantioselectivity to some extent as shown in Table 5. As the reaction temperature was reduced from 0 to −20 °C, the enantioselectivity increased a little from 67 to 81% ee but with a reduced reaction rate (Table 5, entries 1–3). However, further lowering of the temperature resulted in remarkable decreases of both reaction rate and enantioselectivity (Table 5, entry 4). At −78 °C the above positive temperature effect was nullified, and only traces of product with poor enantioselectivity was obtained (Table 5, entry 5).

In view of the coordinative property of the titanium atom of the catalyst, a diverse range of counter ions were investigated in the model reaction, with results listed in Table 6. *n*-Butoxide and ethoxide titanium complexes gave less asymmetric induction than the isopropoxide one (Table 6, entries 2 and 3 vs. entry 1). *para*-Nitrophenolate and cyanide did enhance the Lewis acidities of the catalysts, but poor catalyst efficiency was observed with low chemical yields (Table 6, entries 4, 5). Sterically hindered phenolic derivatives exhibited comparable enantioselec-tivities (Table 6, entries 6, 7).

The molar ratio between ligand **1j**, Ti(O*i*Pr)$_4$ and *N*-oxide **3d** was finely tuned to obtain the optimum enantioselectivity, with results listed in Table 7. More than 1 equiv. of Lewis base with respect to the titanium complex led to a sharp decrease of the enantioselectivity from 82% down to 46% ee (Table 7, entry 2 vs. 1). By contrast, a less than equivalent amount of **3d** benefited the enantioselectivity (Table 7, entries 3–5). The optimum molar ratio of Lewis

Table 4. Effects of catalyst loading and substrate concentration on the enantioselectivity and chemical yield[a]

Entry	Cat. Loading (mol%)	Concentration of **4a** (M)	Yield (%)[b]	ee (%)[c]
1	50	0.12	NR	—
2	20	0.12	95	67
3	10	0.12	41	71
4	5	0.12	22	75
5	2.5	0.12	11	74
6	1	0.12	9	68
7	1	0.23	30	75
8	1	0.52	39	76
9	1	1.1	98	75
10	0.1	No solvent	Trace	36

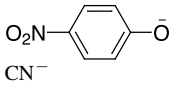
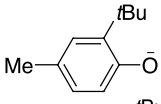
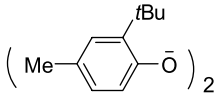
[a] All reactions were carried out at 0 °C for 84 h with the indicated amount of **3d** and **1j**–Ti(O*i*Pr)$_4$ complex (1:1), and indicated concentration of acetophenone in CH_2Cl_2.
[b] Isolated yield. NR = no reaction.
[c] Determined by GC analysis on Chirasil DEX CB.

Table 5. Temperature effect on the enantioselectivity of the asymmetric cyanosilylation of acetophenone[a]

Entry	*T* (°C)	Yield (%)[b]	ee (%)[c]
1	0	95	67
2	−10	61	80
3	−20	62	81
4[d]	−40	30	76
5[d]	−78	Trace	59

[a] Conditions: 20 mol% of **1j**–Ti(O*i*Pr)$_4$ complex (1:1), 20 mol% of **3d**, concentration of acetophenone = 0.12 M in CH_2Cl_2, 84 h.
[b] Isolated yield.
[c] Determined by GC analysis on Chirasil DEX CB.
[d] 120 h.

Table 6. Counter ion effects on the enantioselectivity[a]

Entry	Counter ion	Yield (%)[b]	ee (%)[c]
1	$(OiPr)_2$	61	82
2	$(OnBu)_2$	11	66
3	$(OEt)_2$	43	59
4		19	53
5	CN^-	26	69
6		15	81
7		15	72

[a] Conditions: 2 mol% of **1j**–Ti(O*i*Pr)$_4$ complex (1:1), 1 mol% of **3d**, concentration of acetophenone = 1.1 M in CH_2Cl_2, −20 °C, 120 h.
[b] Isolated yield.
[c] Determined by GC analysis on Chirasil DEX CB.

acid **1j**-Ti(O*i*Pr)$_4$ complex to **3d** was 2:1. The best result (75% yield, 85% ee) was obtained using 2 mol% of **1j**-Ti(O*i*Pr)$_4$ complex and 1 mol% of **3d** at −20 °C in CH_2Cl_2 (Table 7, entry 6). Deviation of the molar ratio of ligand **1j** and Ti(O*i*Pr)$_4$ from 1:1 decreased the enantioselectivity (Table 7, entry 6 vs. entries 7–10). These phenomena could be explained by control experiments on the mechanism of the reaction (vide infra).

Subsequent investigations revealed that, titanium was the most appropriate central metal atom and 2 equiv. of TMSCN with respect to the ketone were needed to obtain

Table 7. Effects of molar ratio between ligand, Ti(O*i*Pr)$_4$ and *N*-oxide on the enantioselectivity[a]

Entry	**1j**:Ti(O*i*Pr)$_4$:**3d** (mol%)	Yield (%)[b]	ee (%)[c]
1	1:1:1	61	82
2	1:1:2	ND	46
3	1:1:0.85	27	75
4	1:1:0.5	21	84
5	1:1:0.25	ND	76
6	2:2:1	75	85
7	2:1:1	56	84
8	2:2.2:1	73	82
9	2.4:2:1	69	84
10	2:2.2:1	81	83

[a] All reactions were performed at −20 °C for 120 h with indicated amount of catalysts, and the concentration of acetophenone was 1.1 M.
[b] Isolated yield. ND = Not determined.
[c] Determined by GC analysis on Chirasil DEX CB.

the optimum enantioselectivity. Complexes of Zr(O*i*Pr)$_4$, Ni(acac)$_2$ and Cu(OTf)$_2$ gave racemic products, whilst aluminum isopropoxide exhibited an enantioselectivity of 14% ee.

Under the optimized conditions, a range of aromatic, aliphatic and α,β-unsaturated ketones **4a**-**m** was converted into their corresponding cyanohydrin trimethylsilyl ethers **5a**-**m**, with results listed in Table 8. While *para*-methyl and *ortho*-fluoro acetophenone gave lower enantioselectivities (Table 8, entries 1–3), *para*-fluoro- and chloroacetophenones gave similar enantioselectivities to acetophenone (Table 8, entries 4–6). In terms of chemical yield, *para*-substituted aromatic ketones were inferior to *meta*- or *ortho*-substituted ones. Curiously, the electron-deficient 4-nitroacetophenone was converted with higher chemical yield and enantioselectivity in the absence of **3d** than in the presence of it (Table 8, entry 7). β-Acetonaphthone afforded similar enantioselectivity to acetophenone (Table 8, entry 8 vs. 1). The cyclic ketones: α-tetralone and α-indanone were converted into products with comparable ee values (Table 8, entries 9, 10). In contrast to Snapper's report,[10a] an α,β-unsaturated ketone demonstrated lower enantioselectivity than the corresponding α,β-saturated one (Table 8, entry 11 vs. 12), which was consistent with Shibasaki's result.[8a] A simple aliphatic ketone was converted into product with high chemical yield and moderate enantioselectivity (Table 8, entry 13).

Table 8. Enantioselective cyanosilylation of ketones catalyzed by **1j**–Ti(O*i*Pr)$_4$ complex and *N*-oxide **3d**[a]

Entry	Ketone **4**	**5**	Yield (%)[b]	ee (%)[c]
1	**4a** $C_6H_5COCH_3$	**5a**	75	85[d]
2	**4b** 4-$MeC_6H_4COCH_3$	**5b**	57	73
3	**4c** 2-$FC_6H_4COCH_3$	**5c**	80	76
4	**4d** 4-$FC_6H_4COCH_3$	**5d**	71	83
5	**4e** 4-$ClC_6H_4COCH_3$	**5e**	58	84
6	**4f** 3-$ClC_6H_4COCH_3$	**5f**	93	80
7[e]	**4g** 4-$O_2NC_6H_4COCH_3$	**5g**	14(93)[f]	11(65)[f]
8	**4h** β-Acetophenone	**5h**	50	84[g]
9[h]	**4i** α-Tetralone	**5i**	67	86
10	**4j** α-Indanone	**5j**	91	70
11	**4k** (*E*)-$C_6H_5CH{=}CHCOCH_3$	**5k**	79	64[i]
12	**4l** Benzylacetone	**5l**	85	84[i]
13	**4m** 2-Heptanone	**5m**	90	59

[a] Conditions: 2 mol% of **1j**–Ti(O*i*Pr)$_4$ complex (1:1), 1 mol% of **3d**, concentration of ketones = 1.1 M, −20 °C, 120 h, unless otherwise indicated.
[b] Isolated yield.
[c] Determined by GC analysis on Chirasil DEX CB (unless otherwise indicated).
[d] The absolute configuration was established to be *S* by comparison the sign of optical rotation value with that of literature.[8a]
[e] The yield and ee value in the parentheses were obtained when the reaction was conducted in the absence of **3d**.
[f] Determined by HPLC on Chiralcel AD-H.
[g] Determined by HPLC on Chiralcel OJ.
[h] Ligand **2a** was used instead of **1j**.
[i] Determined by HPLC on Chiralcel OD.

2.2. Preliminary mechanistic studies

To identify the double-activation catalysis, results of control experiments and spectroscopic data were collected. As shown in Table 9, neither Ti(O*i*Pr)$_4$ nor *N*-oxide **3d** was effective enough to promote the addition of TMSCN to acetophenone (Table 9, entries 1, 2). Entry 3 in Table 9 suggested that a background reaction occurred in the presence of the non-coordinated Ti(O*i*Pr)$_4$ and *N*-oxide, which was in line with the results in Table 7. While 2 mol% of **1j**-Ti(O*i*Pr)$_4$ complex catalyzed this reaction with 3% yield and 66% ee, additional activation of TMSCN with 1 mol% of **3d** led to a sharp increase in both chemical yield and enantioselectivity up to 75% yield and 85% ee (Table 9, entries 4, 5), respectively. However, when the catalyst was generated in situ by mixing the ligand **1j**, Ti(O*i*Pr)$_4$ and **3d** all together at the start of the reaction, not following the typical procedure (refer to the experimental section), the product **5a** was obtained in much lower yield (31%) and enantioselectivity (75% ee, Table 9, entry 6).

Direct evidence of the coordination between *N*-oxide and TMSCN was obtained from ^{1}H NMR (400 MHz, $CDCl_3$) studies. The chemical shift of free TMSCN is located at $\delta =$ 0.35 ppm. However, in the presence of *N*-oxide a new signal appeared at $\delta = 0.17$ ppm as a result of condensed electron density around the silicon atom caused by the coordination of TMSCN to *N*-oxide.[17] This coordination was also supported by reactions using (*R*)-BINOL titanium complex and (*R*)-*N*,*N*′-dioxide **3g**, which suggested that TMSCN coordinates to the N–O dipolar group and thus partially controls the enantioselectivity (Table 9, entry 7 vs. 8). In turn, these observations support the hypothesis that *N*-oxide was not acting as an additive in the double-activation method.[18]

The non-linear effect of this reaction was investigated. As shown in Figure 2, the ee values between ligand **1j** and **5a** were highly linearly correlated. This suggested that there might be one molecule of salen ligand in the transition state.[19]

The above results proved the hypothesis that the enantioselective cyanosilylation of ketones could be accomplished under double-activation catalysis. In this case, the chiral titanium complex played the role of a Lewis acid to activate the ketone substrate (intermediate **A**, Fig. 3), and the achiral *N*-oxide as a Lewis base to simultaneously activate TMSCN

Table 9. Control experiments for identification of the double-activation catalysis[a]

Entry	Lewis acid	Lewis base	Yield (%)[b]	ee (%)[c]
1	Ti(O*i*Pr)$_4$	None	0	—
2	None	**3d**	0	—
3	Ti(O*i*Pr)$_4$	3d	13	0
4	**1j**–Ti(O*i*Pr)$_4$	None	3	66
5	**1j**–Ti(O*i*Pr)$_4$	**3d**	75	85
6[d]	**1j**–Ti(O*i*Pr)$_4$	**3d**	31	75
7[e]	(*R*)-BINOL-Ti(O*i*Pr)$_4$	(±)-**3g**	11	43
8[e]	(*R*)-BINOL-Ti(O*i*Pr)$_4$	(*R*)-**3g**	21	51

[a] Conditions: 2 mol% of Lewis acid, and/or 1 mol% of **3d**, concentration of acetophenone = 1.1 M in CH_2Cl_2, −20 °C, 120 h.
[b] Isolated yield.
[c] Determined by GC analysis on Chirasil DEX CB.
[d] The ligand **1j**, **3d** and Ti(O*i*Pr)$_4$ were mixed all together in one tube to generate the catalyst, not following the typical procedure.
[e] Conditions: 20 mol% of (*R*)-BINOL-Ti(O*i*Pr)$_4$ complex, 20 mol% of **3g**, 0 °C, 84 h, concentration of acetophenone = 0.12 M in CH_2Cl_2.

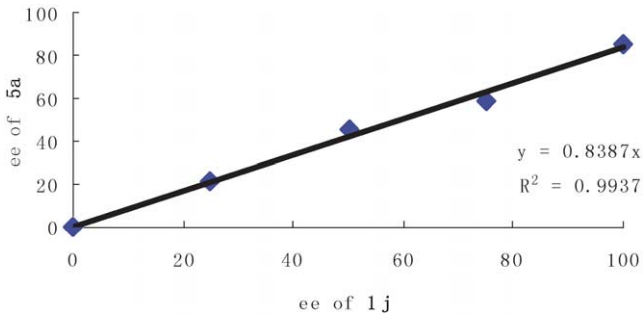


Figure 2. Non-linear effect studies.

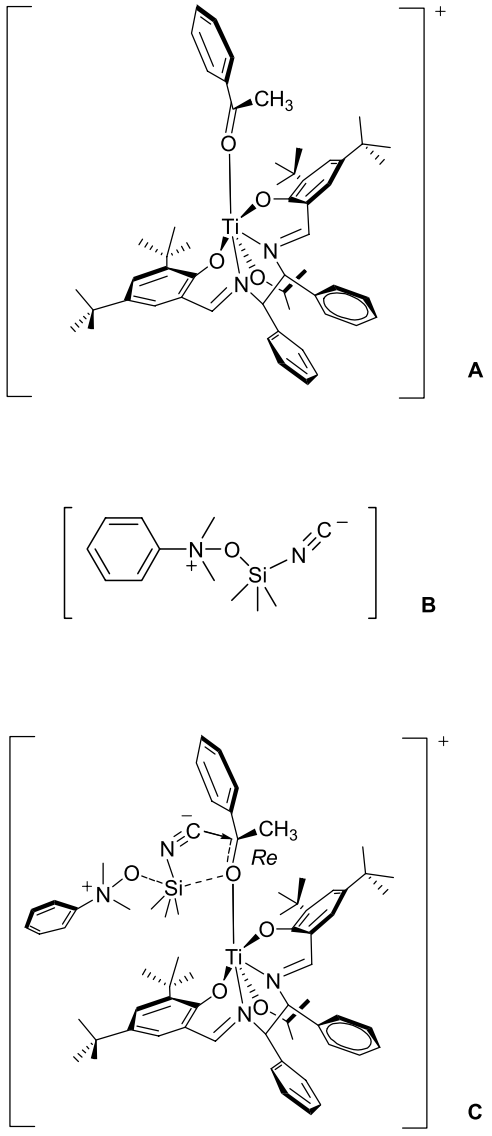


Figure 3. The proposed three transition states.

(intermediate **B**, Fig. 3), respectively. As these two intermediates attract and draw close to each other, the transition state **C** is arranged for the formation of the product with *S*-configuration from attack on the *Re*-face, and the release of the catalysts as shown in Figure 3.

Therefore, a double-activation mechanism with two

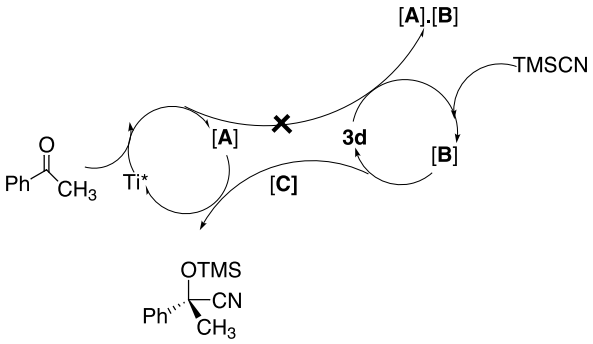


Figure 4. The proposed two independent catalytic cycles

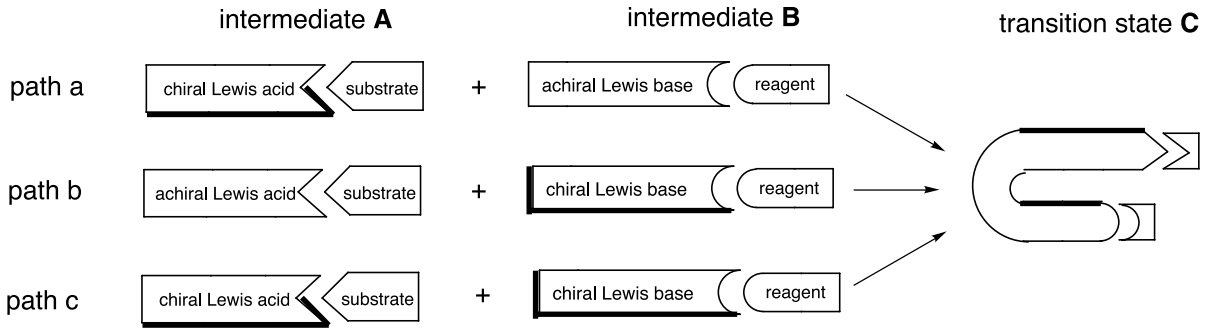
independent cycles is proposed as shown in Figure 4. In this mechanism, substrate ketone and nucleophile TMSCN are coordinated simultaneously and separately, and the transition state **C** subsequently arranged in its optimum chiral environment. Titanium complex and *N*-oxide are recycled via transition state **C** with release of the product. As they coordinate to each of the two reaction components, these two catalytic cycles proceed cooperatively for about 50 times in this system. However, in the case of PyNO (Table 2, entry 8), this recycling was blocked by the binding between titanium complex and PyNO in the formation of the inactive [Ti*]·[PyNO] or [**A**]·[**B**] complex.

Although *N*-oxides are known to coordinate to diverse metals yielding stable complexes,[20] the above observations not only demonstrated the feasibility of double-activation catalysis in the enantioselective silylcyanation of ketones, but also removed the general concern that Lewis acid and Lewis base might strongly bind to each other leading to the disappearance of the catalytic capabilities.[21] Moreover, the independent catalyst screening, which distinguished double-activation catalysis from Shibasaki's bifunctional and other bimetallic catalysts,[22] has greatly enlarged the ligand candidates. Therefore, double-activation catalysis may provide a promising alternative in the context of organic synthesis.[23]

In general, there are three logical paths to achieve asymmetric double-activation catalysis as illustrated in Scheme 1. Path a employs a chiral Lewis acid and achiral Lewis base as exemplified in this paper. Path b is speculated to use achiral Lewis acid and chiral Lewis base. This has not yet been accomplished. Path c involves combined use of both optically active Lewis acid and Lewis base (Table 9, entry 8). Corey has reported a dual activation example in the asymmetric hydrocyanation of aldehydes by using a chiral bisoxazoline-magnesium complex as the Lewis acid and non-coordinated bisoxazoline as the Brönsted base.[24]

3. Conclusion

An effective double-activation catalyst system has been developed for the enantioselective cyanosilylation of ketones by using chiral titanium complexes and achiral or chiral *N*-oxides. The best results were obtained employing 2 mol% of **1j**-Ti(O*i*Pr)$_4$ complex and 1 mol% of *N*-oxide **3d** at −20 °C in CH_2Cl_2. Under the optimized conditions, a range of aromatic, aliphatic and α,β-unsaturated ketones



Scheme 1. General concept of double-activation catalysis and three possible paths in asymmetric synthesis.

were converted into corresponding cyanohydrin trimethylsilyl ethers with 50–93% yield and 59–86% ee. The mechanism of the double-activation catalysis was investigated, and two independent catalytic cycles were proposed to account for all aspects of this transformation. Three possible paths for asymmetric double-activation catalysis were proposed. However, further efforts should be directed to improve the enantioselectivities of cyanosilylation of ketones and to determine the mechanism of chirality transfer during double-activation catalysis.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on INOVA 400 (400 MHz) or on Bruker (600, 300 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ_H 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, m=multiplet), coupling constants (*J*, Hz), integration, and assignment. ^{13}C NMR data were collected on INOVA 400 (100 MHz) or Bruker (125, 75 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ_C 77.0). Elemental analyses were performed on a Carlo-1160. Enantiomer ratios were determined by chiral GC analysis on Chirasil DEX CB or by chiral HPLC analysis on Chiralcel OD/OJ in comparison with the authentic racemates. Optical rotation data were recorded on a Polarimeter-341. All ketones, TMSCN and substituted salicylaldehydes were purchased from Acros, Aldrich or Fluka, and used directly without further purification. CH_2Cl_2 was distilled over CaH_2 prior to use. Other solvents were purified by the usual methods.

4.2. Preparation of salen ligands

Salen ligands **1a**-**m** were prepared according to the literature.[14a]

4.2.1. (1*R*,2*R*)-*N*,*N*′-Bis(salicylidene)-1,2-diphenylethylene-diimine (1a). Mp 155–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 4.73 (s, 2H, CH–CH), 6.81 (td, J=8.4 Hz, 2.0 Hz, 2H, aromatic H), 6.95 (d, J=8.4 Hz, 2H, aromatic H), 7.11–7.28 (m, 14H, aromatic H), 8.29 (s, 2H, 2CH=N), 13.32 (s, 2H; 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 80.2, 116.9, 118.5, 118.7, 127.6, 127.8, 128.3, 131.7, 132.5, 139.3, 160.9, 166.1; $[\alpha]_D^{22}=+12.4$ (c=1.37, CH_2Cl_2), {lit. $[\alpha]_D^{20}=-11.9$ (c=1.0, $CHCl_3$ for (1*S*,2*S*)-enantiomer)}.[14]

4.2.2. (1*R*,2*R*)-*N*,*N*′-Bis(3′,5′-dichloro-salicylidene)-1,2-diphenylethylenediimine (1b). Mp 109–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 4.76 (s, 2H, CH–CH), 7.09 (d, J=2.4 Hz, 2H, aromatic H), 7.12–7.15 (m, 4H, aromatic H), 7.20–7.23 (m, 6H, aromatic H), 7.38 (d, J=2.8 Hz, 2H, aromatic H), 8.27 (s, 2H, 2CH=N), 14.07 (s, 2H, 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 80.0, 119.4, 122.5, 123.4, 127.7, 128.1, 128.7, 129.5, 132.6, 138.0, 155.6, 164.6; HRMS (ESI): Calcd for $C_{28}H_{20}Cl_4N_2O_2$ 557.0352, found 557.0356 (M+H).

4.2.3. (1*R*,2*R*)-*N*,*N*′-Bis(5′-chloro-salicylidene)-1,2-diphenyl-ethylenediimine (1c). Mp 101–104 °C, [lit. 86–88 °C for (1*S*,2*S*)-**1c**].[14] ^{1}H NMR (400 MHz, $CDCl_3$): 4.75 (s, 2H, 2CH–CH), 6.92 (d, J=8.8 Hz, 2H, aromatic H), 7.10 (d, J=2.8 Hz, 2H, aromatic H), 7.16–7.25 (m, 12H, aromatic H), 8.18 (s, 2H, 2CH=N), 13.26 (s, 2H, 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 80.0, 118.6, 119.2, 123.4, 127.7, 127.9, 128.6, 130.7, 132.6, 138.8, 159.5, 165.1; $[\alpha]_D^{22}=+12.7$ (c=1.12, CH_2Cl_2), {lit. $[\alpha]_D^{20}=-12.2$ (c=1.0, CH_2Cl_2 for (1*S*,2*S*)-enantiomer)}.[14]

4.2.4. (1*R*,2*R*)-*N*,*N*′-Bis(5′-bromo-salicylidene)-1,2-diphenyl-ethylenediimine (1d). Mp 125–127 °C, [lit. 156–158 °C for (1*S*,2*S*)-**1d**].[14] ^{1}H NMR (400 MHz, $CDCl_3$): 4.75 (s, 2H, CH–CH), 6.87 (d, J=8.8 Hz, 2H, aromatic H), 7.16–7.26 (m, 12H, aromatic H), 7.34–7.37 (m, 2H, aromatic H), 8.18 (s, 2H, 2CH=N), 13.29 (s, 2H, 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 80.0, 110.3, 119.0, 119.8, 127.7, 127.9, 128.6, 133.7, 135.4, 138.8, 160.0, 165.0; $[\alpha]_D^{22}=-22.9$ (c=1.54, CH_2Cl_2), {lit. $[\alpha]_D^{20}=-2.2$ (c=1.0, CH_2Cl_2 for (1*S*,2*S*)-enantiomer)}.[14]

4.2.5. (1*R*,2*R*)-*N*,*N*′-Bis(5′-nitro-salicylidene)-1,2-diphenyl-ethylenediimine (1e). Mp 148–150 °C, (lit. 150–152 °C for (1*S*,2*S*)-**1e**).[14] ^{1}H NMR (400 MHz, $CDCl_3$): 4.89 (s, 2H, CH–CH), 7.07 (m, 2H, aromatic H), 7.20–7.30 (m, 12H, aromatic H), 8.13–8.21 (m, 2H, aromatic H), 8.31 (s, 2H, 2CH=N), 14.39 (s, 2H, ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 79.3, 117.3, 118.3, 127.6, 128.0, 128.3, 128.4, 128.9, 137.9, 138.0, 165.1, 166.8; $[\alpha]_D^{22}=+31.2$ (c=1.06, DMF), {lit. $[\alpha]_D^{20}=-32.1$ (c=1.0, DMF, for (1*S*,2*S*)-**1e**)}.[14]

4.2.6. (1*R*,2*R*)-*N*,*N*′-Bis(5′-methoxy-salicylidene)-1,2-diphenyl-ethylenediimine (1f). Mp 91–93 °C, [lit. 89–91 °C for (1*S*,2*S*)-**1f**].[14] ^{1}H NMR (400 MHz, $CDCl_3$): 3.70 (s, 6H, $2CH_3O$), 4.71 (s, 2H, CH–CH), 6.64 (s, 2H, aromatic H), 6.89 (m, 4H, aromatic H), 7.16–7.21 (m, 10H, aromatic H), 8.26 (s, 2H, 2CH=N), 12.82 (s, 2H, 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 55.8, 80.3, 114.9, 117.6, 118.1, 119.8, 127.6, 127.8, 128.4, 139.3, 152.0, 155.1, 165.9; $[\alpha]_D^{22}=-12.0$ ($c=3.58$, CH_2Cl_2), {lit. $[\alpha]_D^{20}=+4.9$ ($c=4.0$, CH_2Cl_2, for (1*S*,2*S*)-enantiomer)}.[14]

4.2.7. (1*R*,2*R*)-*N*,*N*′-Bis(5′-methylsalicylidene)-1,2-diphenyl-ethylenediimine (1g). Mp 55–56 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.21 (s, 6H, 2Me), 4.69 (s, 2H, CH–CH), 6.86 (m, 2H, aromatic H), 6.92 (m, 2H, aromatic H), 7.06–7.09 (m, 2H, aromatic H), 7.16–7.21 (m, 10H, aromatic H), 8.26 (s, 2H, 2CH=N), 13.07 (s, 2H, 2ArOH); $[\alpha]_D^{22}=-13.0$ ($c=1.61$, CH_2Cl_2); HRMS (ESI): Calcd for $C_{30}H_{28}N_2O_2$ 449.2224, found 449.2222 (M+H).

4.2.8. (1*R*,2*R*)-*N*,*N*′-Bis(5′-*tert*-butylsalicylidene)-1,2-diphenyl-ethylenediimine (1h). Mp 188–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.23 (s, 18H, 2*t*Bu), 4.72 (s, 2H, CH–CH), 6.89 (d, $J=8.8$ Hz, 2H, aromatic H), 7.12 (d, $J=0.8$ Hz, 2H, aromatic H), 7.15–7.19 (m, 10H, aromatic H), 7.31 (dd, $J=8.8$ Hz, 1.2 Hz, 2H, aromatic H), 8.34 (s, 2H, 2CH=N), 13.12 (s, 2H, 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 31.3, 33.9, 80.2, 116.3, 117.9, 127.5, 127.9, 128.2, 128.3, 129.9, 139.6, 141.4, 158.6, 166.6; $[\alpha]_D^{22}=+8.3$ ($c=1.32$, CH_2Cl_2); HRMS (ESI): Calcd for $C_{36}H_{40}N_2O_2$ 533.3163, found 533.3173 (M+H).

4.2.9. (1*R*,2*R*)-*N*,*N*′-Bis(3′-*tert*-butyl-5′-methylsalicylidene)-1,2-diphenylethylenediimine (1i). Mp 69–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.41 (s, 18H, 2*t*Bu), 2.18 (s, 6H, 2Me), 4.68 (s, 2H, CH–CH), 6.77 (d, $J=1.6$ Hz, 2H, aromatic H), 7.05 (d, $J=1.6$ Hz, 2H, aromatic H), 7.17–7.21 (m, 10H, aromatic H), 8.30 (s, 2H, 2CH=N), 13.50 (s, 2H, 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 20.6, 29.3, 34.7, 80.2, 118.2, 126.5, 127.4, 128.0, 128.3, 130.0, 130.6, 136.7, 140.0, 157.9, 166.9; $[\alpha]_D^{22}=+140.4$ ($c=0.99$, CH_2Cl_2).

4.2.10. (1*R*,2*R*)-*N*,*N*′-Bis(3′,5′-di-*tert*-butylsalicylidene)-1,2-diphenylethylenediimine (1j). Mp 195–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.22 (d, $J=1.6$ Hz, 18H, $2C(CH_3)_3$), 1.42 (d, $J=2.0$ Hz, 18H, $2C(CH_3)_3$), 4.73 (d, $J=1.6$ Hz, 2H, CH–CH), 6.98 (m, 2H, aromatic H), 7.16–7.20 (m, 10H, aromatic H), 7.31 (d, $J=2.4$ Hz, 2H, aromatic H), 8.40 (d, $J=1.2$ Hz, 2H, 2CH=N), 13.60 (d, $J=2.0$ Hz, 2H, exchangeable with D_2O); ^{13}C NMR (100 MHz, $CDCl_3$): 29.4, 31.4, 34.0, 35.0, 80.1, 117.8, 126.3, 127.1, 127.4, 128.0, 128.2, 136.3, 139.8, 140.0, 157.9, 167.2; $[\alpha]_D^{22}=-33.3$ ($c=0.6$, $CHCl_3$) [lit. $[\alpha]_D^{20}=+32.4$ ($c=0.25$, $CHCl_3$ for (1*S*,2*S*)-**1j**)].[14a]

4.2.11. (1*R*,2*R*)-*N*,*N*′-Bis(3′-adamantyl-5′-*tert*-butylsalicylidene)-1,2-diphenylethylenediimine (1k). The precursor 3-adamantyl-5-*tert*-butylsalicylaldehyde was synthesized similarly to the literature procedure.[15a] Mp 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.33 (s, 9H, *t*Bu), 1.79 (s, 6H, adamantanyl H), 2.09–2.14 (m, 9H, adamantanyl H), 7.33 (d, $J=1.6$ Hz, 1H, aromatic H), 7.53 (s, 1H, aromatic H), 9.86 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): 28.9, 31.3, 34.3, 37.0, 37.2, 40.2, 119.9, 127.7, 132.0, 137.8, 141.7, 159.3, 197.5; ν_{max} (KBr): 2954, 1649, 1618, 1459 cm^{-1}. (**1k**) Mp 190–192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.22 (s, 18H, 2*t*Bu), 1.57 (s, 4H, adamantanyl H), 1.84 (m, 10H, adamantanyl H), 2.08–2.16 (m, 16H, adamantanyl H), 4.72 (s, 2H, CH–CH), 6.97 (s, 2H, aromatic H), 7.18 (m, 10H, aromatic H), 7.26 (d, 1.2 Hz, 2H, aromatic H), 8.40 (s, 2H, 2CH=N), 13.52 (s, 2H, 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 29.1, 31.4, 34.1, 37.2, 40.2, 80.1, 117.9, 126.3, 127.1, 127.3, 128.0, 128.2, 136.6, 139.8, 140.0, 158.2, 167.4; ν_{max} (KBr): 1626 cm^{-1} (CH=N); $[\alpha]_D^{22}=+75.0$ ($c=1.2$, CH_2Cl_2); HRMS (ESI): Calcd for $C_{56}H_{68}N_2O_2$ 801.5354 (M+H), found 801.5374 (M+H).

4.2.12. (1*R*,2*R*)-*N*,*N*′-Bis(5′-phenylsalicylidene)-1,2-diphenyl-ethylenediimine (1l). Mp 188–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 4.79 (s, 2H, CH–CH), 7.04 (d, $J=8.8$ Hz, 2H, aromatic H), 7.20–7.24 (m, 10H, aromatic H), 7.29 (d, $J=7.6$ Hz, 2H, aromatic H), 7.38 (t, $J=7.6$ Hz, 6H, aromatic H), 7.45 (d, $J=7.6$ Hz, 4H, aromatic H), 7.51 (dd, $J=8.8$ Hz, 0.8 Hz, 2H, aromatic H), 8.38 (s, 2H, 2CH=N), 13.38 (s, 2H, 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 80.2, 117.4, 118.6, 126.5, 126.8, 127.7, 127.8, 128.4, 128.8, 130.1, 131.4, 132.0, 139.3, 140.1, 160.4, 166.3; $[\alpha]_D^{22}=+64.8$ ($c=1.1$, CH_2Cl_2); HRMS (ESI): Calcd for $C_{40}H_{32}N_2O_2$ 573.2537, found 573.2544 (M+H).

4.2.13. 5,5-Methylene-di[(1*R*,2*R*)-*N*-(3′-*tert*-butylsalicylidene)-*N*′-(3′,5′-di-*tert*-butylsalicylidene)-1,2-diphenyl-ethylene-diimine] (1m). The precursor 5,5-methylene-bis(3-*tert*-butylsacylaldehyde) was prepared according to the literature procedure.[25] Mp 98–100 °C, (lit. mp 99–100 °C).[25] ^{1}H NMR (400 MHz, $CDCl_3$): 1.41 (d, $J=2.0$ Hz, 18H, 2*t*Bu), 3.94 (s, 2H, CH_2), 7.15 (d, $J=2.4$ Hz, 2H, aromatic H), 7.37 (d, $J=2.0$ Hz, 2H, aromatic H), 9.81(d, $J=3.6$ Hz, 2H, 2CHO), 11.71 (d, $J=2.4$ Hz, 2H, 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 29.1, 34.8, 40.0, 120.4, 131.1, 131.2, 134.9, 138.5, 159.8, 197.0. (**1m**) Mp 72–74 °C. ^{1}H NMR (600 MHz, $CDCl_3$): 1.34 (s, 36H, 4*t*Bu), 1.48 (s, 18H, 2*t*Bu), 2.10 (s, 2H, CH_2), 4.86 (s, 4H, 2CH–CH), 7.07 (s, 4H, aromatic H), 7.14–7.20 (m, 20H, aromatic H), 7.29 (s, 4H, aromatic H), 9.76 (s, 4H, 4CH=N), 11.63 (s, 4H, 4ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 29.2, 29.3, 29.4, 31.4, 34.8, 34.9, 35.0, 40.0, 40.1, 80.0, 80.1, 117.8, 120.5, 126.3, 128.0, 128.27, 128.31, 129.8, 130.3, 131.1, 131.2, 134.9, 135.0, 138.6, 139.7, 157.9, 159.8, 166.7, 167.2, 197.0, 197.2; ν_{max} (KBr): 3450, 1650 (m, CH=N) cm^{-1}; $[\alpha]_D^{22}=-24.6$ ($c=1.26$, CH_2Cl_2); HRMS (ESI): Calcd for $C_{81}H_{96}N_4O_4$ 1189.7504, found 1189.7503 (M+H).

Jacobsen's ligands (1*S*,2*S*)-**2a**-**g** were synthesized according to the literature procedure.[26]

4.2.14. (1*S*,2*S*)-*N*,*N*′-Bis(3′,5′-di-*tert*-butylsalicylidene)-cyclohexane-1,2-diimine (2a). Mp 206–207 °C, (lit. 200–203 °C).[26] ^{1}H NMR (400 MHz, $CDCl_3$): 1.23 (s, 18H, 2*t*Bu), 1.41 (s, 18H, 2*t*Bu), 1.48 (m, 2H, cyclic H), 1.72–1.96 (m, 6H, cyclic H), 3.30–3.33 (m, 2H, CH–CH), 6.98 (d, $J=2.4$ Hz, 2H, aromatic H), 7.30 (d, $J=2.0$ Hz, 2H, aromatic H), 8.30 (s, 2H, 2CH=N), 13.72 (s, 2H, 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 24.3, 29.4, 31.4,

33.3, 34.0, 34.9, 72.4, 117.8, 126.0, 126.7, 136.3, 139.8, 158.0, 165.8; $[\alpha]_D^{22}=+323.8$ ($c=1.3$, CH_2Cl_2), {lit. $[\alpha]_D^{20}=-315$ ($c=4.0$, CH_2Cl_2 for (1*R*,2*R*)-enantiomer)}.[26]

4.2.15. (1*S*,2*S*)-*N*,*N*′-Bis(3′-*tert*-butylsalicylidene)-cylcohexane-1,2-diimine (2b). Mp 72–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.40–1.48 (m, 20H, 2*t*Bu and cyclic H), 1.72–1.98 (m, 6H, cyclic H), 3.33 (m, 2H, CH–CH), 6.69–6.73 (m, 2H, aromatic H), 6.99 (d, $J=3.2$ Hz, 2H, aromatic H), 7.24 (d, $J=7.6$ Hz, 2H, aromatic H), 8.28 (s, 2H, 2CH=N), 13.90 (s, 2H, 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 24.3, 29.3, 33.1, 34.7, 72.3, 117.7, 118.5, 129.2, 129.8, 137.0, 160.3, 165.4; $[\alpha]_D^{22}=+510.7$ ($c=1.5$, CH_2Cl_2).

4.2.16. (1*S*,2*S*)-*N*,*N*′-Bis(salicylidene)-cylcohexane-1,2-diimine (2c). ^{1}H NMR (400 MHz, $CDCl_3$): 1.45–1.50 (m, 2H, cyclic H), 1.74 (m, 2H, cyclic H), 1.87–1.96 (m, 4H, cyclic H), 3.30–3.35 (m, 2H, CH–CH), 6.79 (t, $J=7.6$ Hz, 2H, aromatic H), 6.89 (d, $J=8.4$ Hz, 2H, aromatic H), 7.15 (dd, $J=7.6$ Hz, 1.2 Hz, 2H, aromatic H), 7.22–7.26 (m, 2H, aromatic H), 8.26 (s, 2H, 2CH=N), 13.33 (s, 2H, 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 24.1, 33.1, 72.6, 116.7, 118.56, 118.60, 131.4, 132.1, 160.9, 164.7; $[\alpha]_D^{22}=+418.3$ ($c=1.69$, CH_2Cl_2).

4.2.17. (1*S*,2*S*)-*N*,*N*′-Bis(5′-chloro-salicylidene)-cylcohexane-1,2-diimine (2d). Mp 187–189 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.47 (m, 2H, cyclic H), 1.72 (m, 2H, cyclic H), 1.90 (m, 4H, cyclic H), 3.31–3.33 (m, 2H, CH–CH), 6.84 (d, $J=8.8$ Hz, 2H, aromatic H), 7.12 (d, $J=2.4$ Hz, 2H, aromatic H), 7.20 (dd, 6.0 Hz, $J=2.6$ Hz, 2H, aromatic H), 8.18 (s, 2H, 2CH=N), 13.21 (s, 2H, 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 24.0, 32.9, 72.6, 118.4, 119.2, 123.2, 130.6, 132.1, 159.5, 163.6; $[\alpha]_D^{22}=+199.2$ ($c=1.21$, CH_2Cl_2).

4.2.18. (1*S*,2*S*)-*N*,*N*′-Bis(5′-nitro-salicylidene)-cylcohexane-1,2-diimine (2e). Mp 109–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.55 (m, 2H, cyclic H), 1.78 (m, 2H, cyclic H), 1.94–2.04 (m, 4H, cyclic H), 3.46–3.48 (m, 2H, CH–CH), 6.96 (m, 2H, aromatic H), 8.13–8.16 (m, 4H, aromatic H), 8.36 (s, 2H, 2CH=N), 14.31 (s, 2H, 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 23.9, 32.7, 71.9, 117.2, 118.3, 127.9, 128.1, 139.8, 163.7, 167.4; $[\alpha]_D^{22}=+24.1$ ($c=1.16$, CH_2Cl_2).

4.2.19. (1*S*,2*S*)-*N*,*N*′-Bis(5′-methyoxy-salicylidene)-cylcohexane-1,2-diimine (2f). Mp 117–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.46 (m, 2H, cyclic H), 1.86–1.95 (m, 6H, cyclic H), 3.29 (m, 2H, CH–CH), 3.70 (s, 6H, $2CH_3O$), 6.40 (d, $J=2.4$ Hz, 2H, aromatic H), 6.81–6.87 (m, 4H, aromatic H), 8.19 (s, 2H, 2CH=N), 12.82 (s, 2H, 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 24.1, 33.0, 55.8, 72.7, 114.7, 118.2, 119.3, 151.9, 155.0, 164.4; $[\alpha]_D^{22}=+304.7$ ($c=2.77$, CH_2Cl_2).

4.2.20. (1*S*,2*S*)-*N*,*N*′-Bis(5′-bromo-salicylidene)-cylcohexane-1,2-diimine (2g). Mp 183–185 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.49 (m, 2H, cyclic H), 1.69–1.72 (m, 2H, cyclic H), 1.90 (m, 4H, cyclic H), 3.32 (d, $J=9.6$ Hz, 2H, CH–CH), 6.78 (d, $J=8.8$ Hz, 2H, aromatic H), 7.255 (d, $J=2.0$ Hz, 2H, aromatic H), 7.31–7.34 (m, 2H, aromatic H), 8.17 (s, 2H, 2CH=N), 13.20 (s, 2H, 2ArOH); ^{13}C NMR (100 MHz, $CDCl_3$): 24.0, 32.9, 72.6, 110.1, 118.9, 119.9, 133.5, 134.9, 159.9, 163.4; $[\alpha]_D^{22}=+108.5$ ($c=1.17$, CH_2Cl_2).

4.3. Preparation of *N*-oxides

N-Oxides were prepared by direct oxidation of the corresponding tertiary amines.[27] They were mostly recrystallized from MeOH and Et_2O.

4.3.1. Trimethylamine *N*-oxide (3a). ^{1}H NMR (400 MHz, d_6-DMSO): 3.31 (s, 9H, $3CH_3$); ^{13}C NMR (100 MHz, d_6-DMSO): 61.2.

4.3.2. Triethylamine *N*-oxide (3b). ^{1}H NMR (400 MHz, d_6-DMSO): 1.10 (t, $J=3.2$ Hz, 6H, 2Me), 3.01 (q, $J=7.2$ Hz, 4H, $2CH_2$); ^{13}C NMR (100 MHz, d_6-DMSO): 8.1, 58.5.

4.3.3. *N*,*N*-Dimethyl-cyclohexylamine *N*-oxide (3c). ^{1}H NMR (400 MHz, d_6-DMSO): 2.03–2.09 (m, 1H, cyclic H), 2.16–2.35 (m, 4H, cyclic H), 2.55–2.58 (m, 1H, cyclic H), 2.77–2.81 (m, 2H, cyclic H), 3.20–3.23 (m, 2H, cyclic H), 3.49 (s, 1H, cyclic H), 3.93 (s, 6H, $(CH_3)_2N$)); ^{13}C NMR (100 MHz, d_6-DMSO): 24.99, 25.03, 26.5, 55.1, 76.6.

4.3.4. *N*,*N*-Dimethylaniline *N*-oxide (3d). ^{1}H NMR (400 MHz, $CDCl_3$): 3.66 (s, 6H, CH_3), 7.39–7.50 (m, 3H, aromatic H), 7.93 (d, $J=8.0$ Hz, 2H, aromatic H); ^{13}C NMR (100 MHz, $CDCl_3$): 62.7, 119.7, 129.1, 129.3, 153.6.

4.3.5. *N*,*N*-Dimethyl *o*-methylaniline *N*-oxide (3e). ^{1}H NMR (400 MHz, d_6-DMSO): 2.73 (s, 3H, CH_3), 3.46 (s, 6H, $(CH_3)_2N$)), 7.22–7.27 (m, 3H, aromatic H), 8.10 (d, $J=7.6$ Hz, 2H, aromatic H); ^{13}C NMR (100 MHz, d_6-DMSO): 21.7, 61.6, 120.6, 126.4, 128.5, 130.8, 133.7.

4.3.6. *N*,*N*-Dimethyl *p*-methylaniline *N*-oxide (3f). ^{1}H NMR (600 MHz, d_6-DMSO): 2.08 (s, 3H, CH_3), 2.32 (s, 6H, $(CH_3)_2N$), 7.25 (d, $J=8.4$ Hz, 2H, aromatic H), 7.93 (d, $J=8.4$ Hz, 2H, aromatic H); ^{13}C NMR (100 MHz, d_6-DMSO): 20.4, 62.7, 120.2, 129.1, 138.1, 152.4.

4.3.7. (*R*)-3,3′-Dimethyl-2,2′-bisquinolin-*N*,*N*′-dioxide (3g). It was prepared by the literature procedure.[12] Mp 223–225 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.27 (s, 6H; $2CH_3$), 7.73–7.64 (m, 6H; aromatic H), 7.86 (d, $J=7.6$ Hz, 2H; H_5 and $H_{5'}$), 8.72 (d, $J=9.2$ Hz, 2H; H_8 and $H_{8'}$); ^{13}C NMR (100 MHz, $CDCl_3$): 17.7, 119.8, 125.1, 127.3, 128.9, 129.1, 130.0, 131.6, 140.1; $[\alpha]_D^{20}=-88.6$ ($c=0.64$, $CHCl_3$).

4.4. Preparation of optically active cyanohydrin trimethylsilyl ethers 5

Typical procedure. $Ti(OiPr)_4$ (32 μL, 1 M in toluene, 0.032 mmol) was stirred with **1j** (20.8 mg, 0.032 mmol) in dry CH_2Cl_2 (1 mL) at 35 °C for 1 h under a N_2 atmosphere. After the solvents were removed in vacuo, the resulting yellow powder was redissolved in CH_2Cl_2 (0.5 mL), cooled to −20 °C, and acetophenone (1.6 mmol) was added. Finally, to the reaction mixture, was added a solution of

3d (2.1 mg, 0.016 mmol) that had been separately treated with TMSCN (3.2 mmol, 2 equiv.) in CH_2Cl_2 (1.0 mL) at 35 °C for 1 h. The reaction was performed at −20 °C. On completion, the reaction mixture was concentrated and added to a silica gel column to give the pure product with ethyl ether/petroleum ether (1/200, *V/V*) as the eluent. The desired product was obtained as colorless oil (280 mg, 75%). The ee was determined by chiral GC analysis on Chirasil DEX CB to be 85% ee. The absolute configuration was established as *S* by comparing the sign of the optical rotation value with that in literature.

4.4.1. 2-Trimethylsilyloxy-2-phenylpropanenitrile (5a). Colorless oil, 75% yield, 85% ee. ^{1}H NMR (300 MHz, $CDCl_3$): 0.19 (s, 9H, $(CH_3)_3Si$), 1.87 (s, 3H, CH_3), 7.38–7.58 (m, 5H, aromatic H); $[\alpha]_D^{22}=-22.1$ ($c=1.04$, $CHCl_3$, 85% ee) [lit. $[\alpha]_D^{20}=+21.9$ ($c=1.18$, $CHCl_3$, for *R* enantiomer with 93% ee)];[8c] GC (CP-Chirasil DEX CB, column temperature = 100 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r(major) = 24.5 min, t_r(minor) = 5.4 min.

4.4.2. 2-Trimethylsilyloxy-2-(4′-methylphenyl)propanenitrile (5b). Colorless oil, 57% yield, 73% ee. (Found: C, 66.78; H, 8.03; N, 6.39. $C_{13}H_{19}NOSi$ requires: C, 66.90; H, 8.21; N, 6.00); ^{1}H NMR (400 MHz, $CDCl_3$): 0.16 (s, 9H, $(CH_3)_3Si$), 1.84 (s, 3H, CH_3), 2.36 (s, 3H, ArCH_3), 7.21 (m, 2H, aromatic H), 7.43 (m, 2H, aromatic H); $[\alpha]_D^{22}=-19.3$ ($c=0.57$, $CHCl_3$, 73% ee) [lit. $[\alpha]_D^{20}=+21.3$ ($c=1.28$, $CHCl_3$, 90% ee)];[8c] GC (CP-Chirasil DEX CB, column temperature = 105 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r(major) = 34.9 min, t_r(minor) = 36.0 min.

4.4.3. 2-Trimethylsilyloxy-2-(2′-fluorophenyl)propanenitrile (5c). Colorless oil, 80% yield, 76% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 0.26 (s, 9H, $(CH_3)_3Si$), 1.94 (s, 3H, CH_3), 7.07–7.12 (m, 1H, aromatic H), 7.16–7.20 (m, 1H, aromatic H), 7.33–7.38 (m, 1H, aromatic H), 7.56–7.60 (m, 1H, aromatic H); ^{13}C NMR (100 MHz, $CDCl_3$): 1.0, 30.8 (d, $J=3.0$ Hz), 68.4, 116.5 (d, $^2J_{CCF}=21.9$ Hz), 120.6, 124.2 (d, $^4J_{CCCCF}=3.6$ Hz), 126.7 (d, $J=3.0$ Hz), 130.6 (d, $^3J_{CCCF}=8.5$ Hz), 159.4 (d, $^1J_{CF}=248.2$ Hz); $[\alpha]_D^{22}=-12.7$ ($c=1.18$, $CHCl_3$, 76% ee); GC (CP-Chirasil DEX CB, column temperature = 105 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r(major) = 20.8 min, t_r(minor) = 21.7 min.

4.4.4. 2-Trimethylsilyloxy-2-(4′-fluorophenyl)propanenitrile (5d). Colorless oil, 71% yield, 83% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 0.18 (s, 9H, $(CH_3)_3Si$), 1.84 (s, 3H, CH_3), 7.08 (m, 2H, aromatic H), 7.52 (m, 2H, aromatic H); ^{13}C NMR (100 MHz, $CDCl_3$): 1.0, 33.5, 71.0, 115.6 (d, $^2J_{CCF}=21.9$ Hz), 121.4, 126.5 (d, $^3J_{CCCF}=8.5$ Hz), 138.0, 162.2 (d, $^1J_{CF}=246.4$ Hz); $[\alpha]_D^{22}=-18.6$ ($c=1.4$, $CHCl_3$, 83% ee); GC (CP-Chirasil DEX CB, column temperature = 115 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r(major) = 13.1 min, t_r(minor) = 13.9 min.

4.4.5. 2-Trimethylsilyloxy-2-(4′-chlorophenyl)propanenitrile (5e). Colorless oil, 58% yield, 84% ee. ^{1}H NMR (400 MHz, $CDCl_3$): 0.19 (s, 9H, $(CH_3)_3Si$), 1.83 (s, 3H, CH_3), 7.38 (m, 2H, aromatic H), 7.48 (m, 2H, aromatic H); ^{13}C NMR (100 MHz, $CDCl_3$): 1.0, 33.5, 71.0, 121.2, 126.1, 128.8, 134.6, 140.7; (Found: C, 56.82; H, 6.41; N, 5.93. $C_{12}H_{16}NOSiCl$ requires: C, 56.79; H, 6.35; N, 5.52); $[\alpha]_D^{22}=-19.5°$ ($c=0.89$, $CHCl_3$, 84% ee) [lit. $[\alpha]_D^{20}=+29.5$ ($c=1.04$, $CHCl_3$, 92% ee)];[8c] GC (CP-Chirasil DEX CB, column temperature = 125 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r (major) = 21.5 min, t_r(minor) = 22.7 min.

4.4.6. 2-Trimethylsilyloxy-2-(3′-chlorophenyl)propanenitrile (5f). Colorless oil, 93% yield, 80% ee. ^{1}H NMR (300 MHz, $CDCl_3$): 0.22 (s, 9H, $(CH_3)_3Si$), 1.86 (s, 3H, CH3), 7.34–7.55 (m, 4H, aromatic H); ^{13}C NMR (75 MHz, $CDCl_3$): 1.0, 33.4, 70.9, 121.0, 122.7, 124.8, 128.8, 129.9, 134.6, 144.0; (Found: C, 56.61; H, 6.39; N, 5.90. $C_{12}H_{16}NOSiCl$ requires: C, 56.79; H, 6.35; N, 5.52); $[\alpha]_D^{22}=-19.7$ ($c=0.76$, $CHCl_3$, 80% ee); GC (CP-Chirasil DEX CB, column temperature = 120 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r(major) = 16.7 min, t_r(minor) = 17.0 min.

4.4.7. 2-Trimethylsilyloxy-2-(4′-nitrophenyl)propanenitrile (5g). 93% Yield, 65% ee. ^{1}H NMR (300 MHz, $CDCl_3$): 0.26 (s, 9H, $(CH_3)_3Si$), 1.89 (s, 3H, CH_3), 7.75 (d, 9.0 Hz, 2H, aromatic H), 8.30 (d, 9.0 Hz, 2H, aromatic H); $[\alpha]_D^{22}=+13°$ ($c=1.65$, CH_2Cl_2, 65% ee) [lit. $[\alpha]_D^{20}=+16.2$ ($c=1.67$, $CHCl_3$, 88% ee)];[10a] HPLC (Chiralcel AD-H, *i*PrOH/*n*-hexane, 1/99 *V/V*, 1.0 mL/min, 23 °C, 254 nm): t_r(major) = 5.68 min, t_r(minor) = 6.78 min.

4.4.8. 2-Trimethylsilyloxy-2-(2′-naphthyl)propanenitrile (5h). 50% Yield, 84% ee. ^{1}H NMR (300 MHz, $CDCl_3$): 0.22 (s, 9H, $(CH_3)_3Si$), 1.97 (s, 3H, CH_3), 7.54–7.66 (m, 3H, aromatic H), 7.90–7.93 (m, 3H, aromatic H), 8.07 (d, $J=1.8$ Hz, 1H, aromatic H); $[\alpha]_D^{22}=-10.6$ ($c=0.85$, $CHCl_3$, 84% ee) [lit. $[\alpha]_D^{20}=+12.6$ ($c=1.99$, $CHCl_3$, 94% ee)];[10a] HPLC (Chiralcel OJ, *i*PrOH/*n*-hexane, 1/99 *V/V*, 1.0 mL/min, 23 °C, UV 254 nm): t_r(minor) = 5.9 min, t_r(major) = 7.0 min.

4.4.9. 1-Trimethylsilyloxy-1,2,3,4-tetrahydronaphthane-1-carbonitrile (5i). Colorless oil, 67% yield, 86% ee. ^{1}H NMR (300 MHz, $CDCl_3$): 0.24 (s, 9H, $(CH_3)_3Si$), 2.06 (m, 2H, CH_2), 2.23 (m, 1H, CH_2), 2.35 (m, 1H, CH_2), 2.85 (m, 2H, CH_2), 7.13 (m, 1H, aromatic H), 7.29 (m, 2H, aromatic H), 7.67 (m, 1H, aromatic H); ^{13}C NMR (75 MHz, $CDCl_3$): 1.3, 18.6, 28.2, 37.6, 69.8, 122.0, 126.6, 127.9, 129.0, 129.2, 135.6, 136.0; (Found: C, 68.30; H, 7.70; N, 6.11. $C_{14}H_{19}NOSi$ requires: C, 68.52; H, 7.80; N, 5.71); $[\alpha]_D^{22}=-12.9$ ($c=0.66$, $CHCl_3$, 86% ee); GC (CP-Chirasil DEX CB, column temperature = 125 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r(minor) = 45.7 min, t_r(major) = 46.9 min.

4.4.10. 1-Trimethylsilyloxy-indane-1-carbonitrile (5j). Colorless oil, 91% yield, 70% ee. ^{1}H NMR (600 MHz, $CDCl_3$): 0.20 (s, 9H, $(CH_3)_3Si$), 2.43–2.47 (m, 1H, cyclic H), 2.70–2.74 (m, 1H, cyclic H), 2.97–3.02 (m, 1H, cyclic H), 3.10–3.15 (m, 1H, cyclic H), 7.28 (d, $J=7.2$ Hz, 1H, aromatic H), 7.31 (t, $J=14.4$ Hz, 1H, aromatic H), 7.36 (td, $J=1.2$ Hz, $J=14.4$ Hz, 1H, aromatic H), 7.55 (d, $J=7.2$ Hz, 1H, aromatic H); $[\alpha]_D^{22}=-24.7$ ($c=1.1$, CH_2Cl_2,

70% ee) [lit. $[\alpha]_D^{20}=+31.6$ ($c=1.52$, $CHCl_3$, 88% ee)];[10a] GC (CP-Chirasil DEX CB, column temperature = 120 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r(minor) = 30.6 min, t_r(major) = 31.2 min.

4.4.11. 2-Trimethylsilyloxy-2-methyl-4-phenyl-3-butenenitrile (5k). Colorless oil, 79% yield, 64% ee. ^{1}H NMR (300 MHz, $CDCl_3$): 0.27 (s, 9H, $(CH_3)_3Si$), 1.77 (s, 3H, CH_3), 6.15 (d, $J=15.9$ Hz, 1H, CH=), 6.91 (d, $J=15.9$ Hz, 1H, CH=), 7.33–7.45 (m, 5H, aromatic H); ^{13}C NMR (75 MHz, $CDCl_3$): 1.3, 30.8, 69.9, 120.6, 126.8, 128.5, 128.7, 129.5, 130.9, 135.1; $[\alpha]_D^{22}=-48.0$ ($c=0.5$, $CHCl_3$, 64% ee) [lit. $[\alpha]_D^{20}=+62.3$ ($c=1.76$, $CHCl_3$, 95% ee)];[10a] HPLC (Chiralcel OD, *i*PrOH/*n*-hexane, 1/99 *V*/*V*, 1.0 mL/min, 23 °C, 254 nm): t_r(major) = 5.0 min, t_r(minor) = 5.8 min.

4.4.12. 2-Trimethylsilyloxy-2-methyl-4-phenylbutanenitrile (5l). Colorless oil, 85% yield, 84% ee. ^{1}H NMR (300 MHz, $CDCl_3$): 0.29 (s, 9H, $(CH_3)_3Si$), 1.65 (s, 3H, CH_3), 2.02–2.08 (m, 2H, CH_2), 2.80–2.91 (m, 2H, CH_2), 7.22–7.33 (m, 5H, aromatic H); $[\alpha]_D^{22}=-10.6$ ($c=1.08$, $CHCl_3$, 84% ee) [lit. $[\alpha]_D^{20}=+9.7$ ($c=1.78$, $CHCl_3$, 80% ee)];[10a] HPLC (Chiralcel OD, *i*PrOH/*n*-hexane, 1/99 *V*/*V*, 1.0 mL/min, 23 °C, 254 nm): t_r(major) = 5.2 min, t_r(minor) = 5.9 min.

4.4.13. 2-Trimethylsilyloxy-2-methyl-heptanenitrile (5m). Colorless oil, 90%, 59% ee. ^{1}H NMR (300 MHz, $CDCl_3$): 0.25 (s, 9H, $(CH_3)_3Si$), 0.92 (t, $J=6.9$ Hz, 3H, CH_3), 1.34 (m, 4H, CH_2), 1.42 (m, 1H, CH_2), 1.50 (m, 2H, CH_2), 1.58 (s, 3H, CH_3), 1.70 (m, 2H, CH_2); $[\alpha]_D^{22}=-6.6$ ($c=1.36$, CH_2Cl_2, 59% ee) [lit. $[\alpha]_D^{20}=+10.6$ ($c=2$, $CHCl_3$, 76% ee)];[8c] GC (CP-Chirasil DEX CB, column temperature = 80 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r(minor) = 30.4 min, t_r(major) = 31.7 min.

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Chiral vanadyl salen complex anchored on supports as recoverable catalysts for the enantioselective cyanosilylation of aldehydes. Comparison among silica, single wall carbon nanotube, activated carbon and imidazolium ion as support

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Abstract—The activity and enantiomeric excess (ee) (in some cases >85%) obtained for the asymmetric addition of trimethylsilyl cyanide to aldehydes using different heterogeneous chiral catalysts are compared. A library of recoverable catalysts was developed by immobilization of a chiral vanadyl salen complex having a terminal carbon–carbon double bond onto a series of scaffolds including silica, single-wall carbon nanotubes, activated carbon and room-temperature ionic liquids. The covalent linkage has been achieved by radical initiated addition of mercapto groups to C=C. The highest enantiomeric excesses, similar to those obtained in the homogeneous phase, were achieved using silica as support or with the homogeneous tetra-*tert*-butyl salen catalyst dissolved in an imidazolium ionic liquid. The use of silica as support permits an easier separation and reuse of the catalyst from the reaction media.

1. Introduction

Among the chiral synthetic intermediates produced on an industrial scale, cyanohydrins play an important role, since these molecules can be used as precursor in the preparation of a wide range of pharmaceuticals, agrochemicals and insecticides. For example, enantiomerically pure mandelonitrile is currently produced in multi-hundred ton scale, and so represents one of the compounds that is produced with high ee in large quantities.[1,2]

Chiral vanadyl salen complexes are among the most active and selective catalysts for the asymmetric cyanosilylation of aromatic and aliphatic aldehydes.[3,4] A general strategy to convert a successful homogeneous catalyst into a heterogeneous system consists of the covalent anchoring of the catalytically active site onto an insoluble support.[5–7] Heterogeneous catalysts are easily separated from the reaction mixture and can be recovered and reused provided that they do not become deactivated during recycling. Also if deactivation occurs, a suitable re-activation protocol can be devised. Heterogeneous catalysts permit continuous flow operations simplifying the process for large-scale operation.[8]

Our groups have been involved in a project aimed at developing suitable solid catalysts containing immobilized chiral metal salen complexes. In addition to polymer supported complexes, amorphous and structured inorganic oxides have also been used.[9] More recently, we have been interested in the use of covalently functionalised single wall carbon nanotubes (SWNT), particularly in comparison to activated carbon (AC).[10] A parallel strategy that we have also developed based on the concept of 'ionophilicity', is to append an imidazolium moiety to the complex to make the catalyst resemble room-temperature ionic liquids and unrecoverable from them by extraction with conventional organic solvents.[11,12]

In the present work, we provide a comparison of the asymmetric induction ability of a library of solid catalysts in which a chiral vanadyl salen complex derived from cyclohexanediamine has been covalently anchored either onto a solid support such as silica or carbon or functionalised by appending an imidazolium unit to make the system 'ionophilic' to be used in room temperature ionic liquids.

Keywords: Cyanohydrins; Heterogeneous asymmetric catalysis; Chiral vanadyl salen complex; Silica as support; Single-wall carbon nanotubes; Activated carbon; Ionic liquids.
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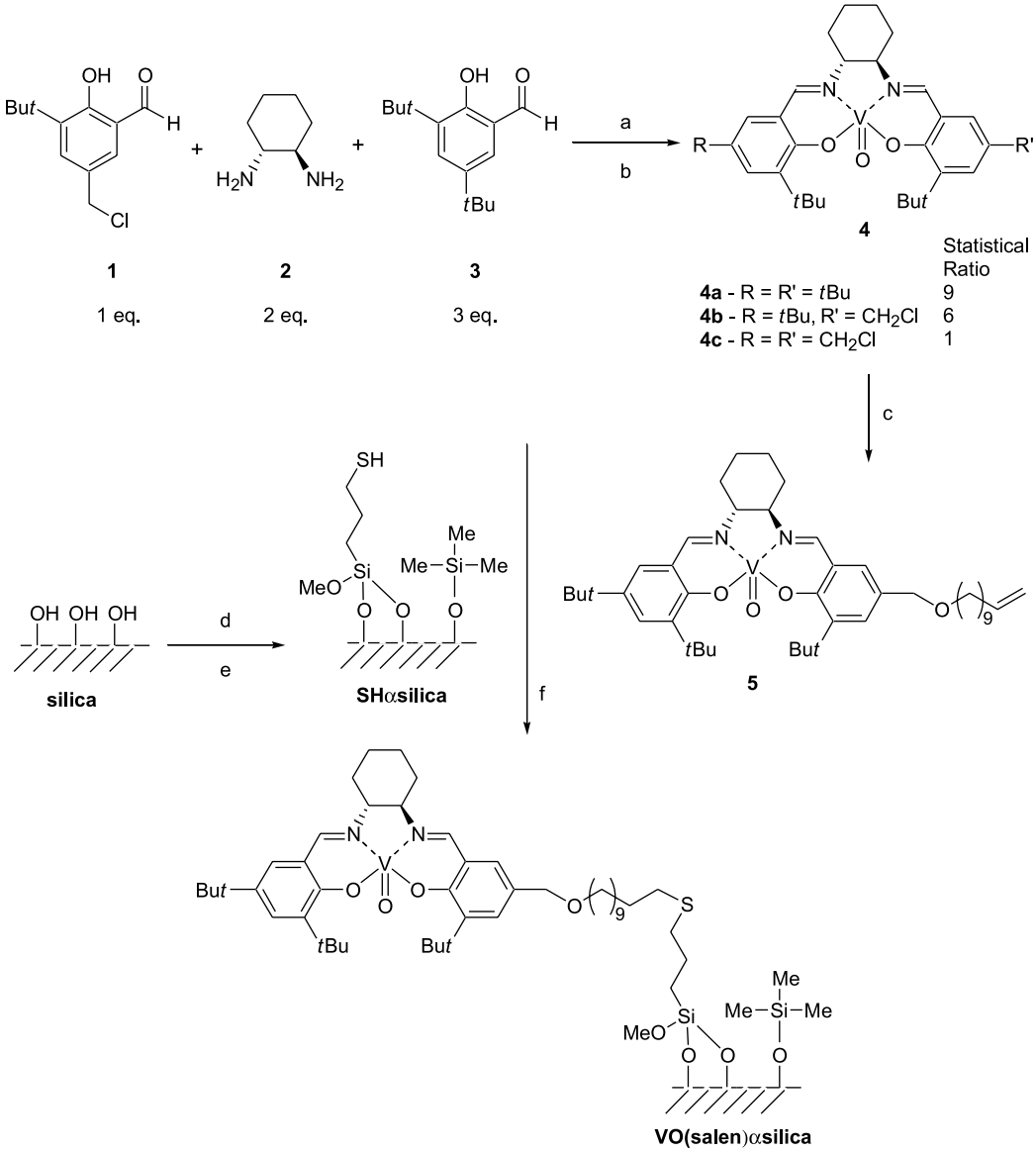
2. Results and discussion

2.1. Preparation of the library of recoverable vanadyl salen catalysts

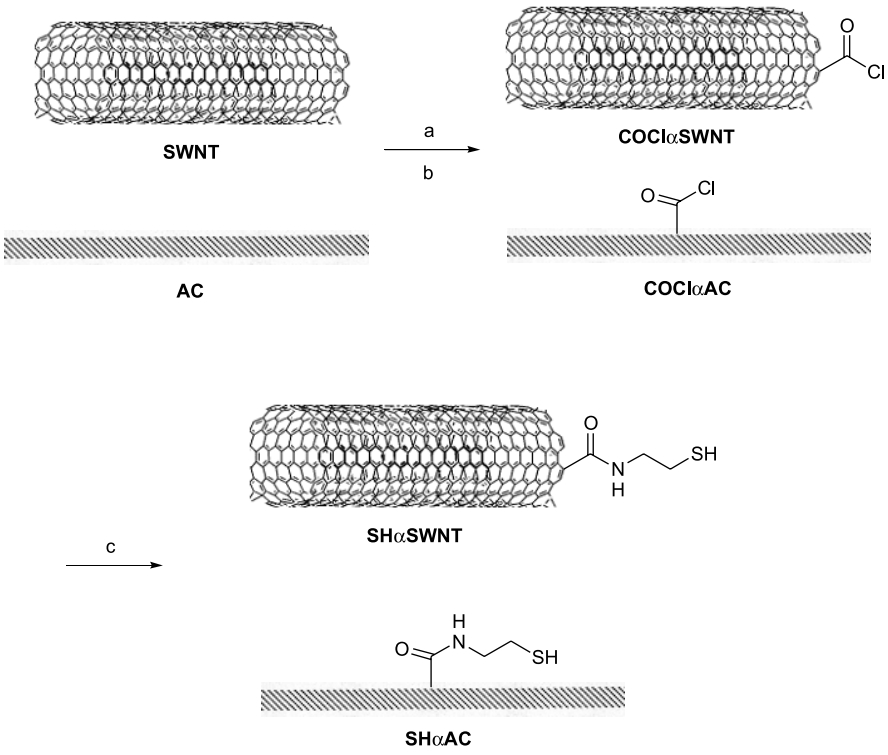
The series of catalysts used in the present study encompasses three different types of recoverable and reusable catalysts depending on the support to which the complex has been anchored or on the presence of an imidazolium unit.

In the first catalyst, we covalently anchored an asymmetric vanadyl salen precursor having in the *para*-position of one of the two phenolic moieties a ω-alkenyloxy chain to the surface of silica particles that have been previously functionalised with 3-mercaptopropyltrimethoxysilane. In particular, we used a ω-undecenyl chain because earlier studies from us have shown that a long alkene chain linking the chiral vanadyl complex to the silica surface has a positive effect on the ee of the resulting cyanohydrin.[9] A long alkyl chain permits a larger distance between the solid surface and the vanadyl complex that eventually can interact with the solvent and reagents similarly to homogeneous catalysis. The synthetic route followed for the preparation of this solid catalyst (**VOsalen∝silica**) is shown in Scheme 1.

The key point in the preparation of the precursor is the synthesis of a statistical mixture of an asymmetrically substituted chiral salen ligand **4b** in which the predominant component **4a** cannot anchor to the solid and the desired target ligand **4b** is formed predominantly in a ratio 6:1 with respect to the symmetrical ligand **4c**. Ligand **4c** is doubly functionalised and, therefore, will also be firmly anchored to the support. Although the complex derived from **4c** will also be catalytically active, its asymmetric induction ability is believed to be lower than the complex derived from **4b** due to the lower steric encumbrance around the active vanadyl center. This statistical mixture **4a**, **4b** and **4c** was used without purification in the following steps. The actual stoichiometry of the starting material and the resulting mixture of salen ligands are also indicated in the Scheme 1.



Scheme 1. Reactions and conditions: (a) molecular sieves 3 Å, CH_2Cl_2, rt, 24 h; (b) $VOSO_4 \cdot 3H_2O$, EtOH, reflux, 1 h; (c) $HO(CH_2)_9CH{=}CH_2$, xylene, reflux, 24 h; (d) $HS(CH_2)_3Si(OMe)_3$, toluene, reflux, N_2, 48 h; (e) $EtOSi(CH_3)_3$, toluene, reflux, N_2, 24 h; (f) AIBN, $CHCl_3$, N_2, 80 °C, 24 h.



Scheme 2. Reactions and conditions: (a) HNO_3 (3 M), reflux, 24 h; (b) $SOCl_2$, DMF, N_2, 65 °C, 24 h; (c) $H_2NCH_2CH_2SH{\cdot}HCl$, Et_3N, N_2, CH_2Cl_2, 48 h.

This strategy to obtain the target complex **5** in a single step (although not pure) overcomes other alternative time-consuming, multistep synthesis.

It has to be noted that although complexes **4** and **5** were prepared under inert atmosphere and are drawn as V(IV) complexes, it is very likely that they undergo an spontaneous oxidation either during manipulation or during the catalytic reactions to V(V) as it has been previously reported.[13]

Concerning the modification of the silica support, we first introduced a given amount of 3-mercaptopropyl groups and the large proportion of the silanol groups remaining on the silica surface were subsequently masked by reacting them with an excess of ethoxytrimethylsilane. In previous work it has been demonstrated that the presence of free silanol groups plays a negative role in the catalysis by decreasing the ee.[9]

The propose of this work is to compare the catalytic activity and the asymmetric induction ability of recoverable vanadyl salen complexes linked to different supports. Thus the performance of **VOsalen∝silica** will be compared with other type of catalysts. The second catalyst type contains the vanadyl salen complex covalently anchored on carbonaceous supports. In particular, we used as supports a conventional activated carbon (AC) with a very large specific surface area and the recently discovered single wall carbon nanotubes (SWNT). It is known that during the purification of SWNT to remove catalyst particles with hot concentrated nitric acid, SWNT becomes partly oxidized; the average length of SWNT is shortened and carboxylic acid groups are created at the tips of the tubes. We have taken advantage of the appearance of carboxylic acid groups and after formation of the corresponding acyl chloride, reacted them with 2-mercaptoethylamine (Scheme 2). Activated carbon also undergoes a partial oxidation upon treatment with hot concentrated nitric acid. In this case, the reaction is more complex and other groups such as quinones or sulphonic acids are also known to be formed during the treatment in addition to the carboxylic groups. These carboxylic groups were subsequently modified by transformation into acyl chlorides and reaction with 2-mercaptoethylamine to form the corresponding 2-mercaptoethylamide (Scheme 2).

At this point, it is interesting to remark on the large differences in terms of structure and composition between SWNT and activated carbons. Thus, while SWNT have a regular geometry formed by bundles of long (<100 nm) flexible narrow (1–3 nm) cylinders made of a single wall of graphite sp^2 carbons with a large periodicity of the local structure around the sites, the situation in activated carbons is completely different. In the later case, significant amounts of heteroatoms, particularly oxygen, nitrogen and sulphur, are also present and the structure is undefined consisting of a wide distribution of graphitic platelets of various sizes interconnected by different types of bridges. Also the specific surface area of SWNT is considerably smaller than that of activated carbons (see Table 1).

Mercapto functionalised SWNT (**SH∝SWNT**) and activated carbons (**SH∝AC**) were finally connected to the chiral vanadyl salen complex using a statistical mixture containing the unsymmetrical complex **9b** substituted with a *p*-styryl group in one of the phenolic rings. Preparation of this precursor was accomplished following a synthetic route

Table 1. Structural, textural and analytical data for the library of recoverable catalysts

Catalyst	Main feature	Surface area ($m^2\ g^{-1}$)	*V* content (mmol g^{-1})
VOsalen∝silica	Amorphous particles (1 μm diameter)	350	0.04
VOsalen∝SWNT	Long tubes >100 nm of 1.3 nm diameter made of a single graphite wall	300	0.082
VOsalen∝AC	Carbon platelets	1100	0.06
VOsalen∝IL	Positively charged imidazolium unit	—[a]	0.039
^{t}BuVOsalen	Unsupported complex with ^{t}Bu substituents in *o*- and *p*- positions of the phenolic rings	—[a]	8.34

[a] Soluble in ionic liquids.

analogous to that used in the case of **VOsalen∝silica**. Scheme 3 outlines the synthesis of precursor **9b** in which the key step is the preparation of 3-*tert*-butyl-2-hydroxy-5-(4-vinylphenyl)benzaldehyde (**8**), obtained by Suzuki cross-coupling between 5-bromo-3-*tert*-butylsalicylaldehyde and 4-vinylphenyl boronic acid catalysed by palladium tetrakis(triphenylphosphine).[15]

The linkage between SWNT or AC and the catalytically active chiral vanadyl salen complex (**9b**) was accomplished through a radical chain addition of the mercapto group to the terminal C═C initiated by AIBN (Scheme 4).

The last type of recoverable chiral vanadyl salen catalyst prepared was **VOsalen∝IL** in which precursor **9b** was attached through the AIBN initiated radical chain reaction to *N*-(3-mercaptopropyl)-*N′*-methyl imidazolium (**SH∝IL**). The actual synthetic route is indicated in Scheme 4.

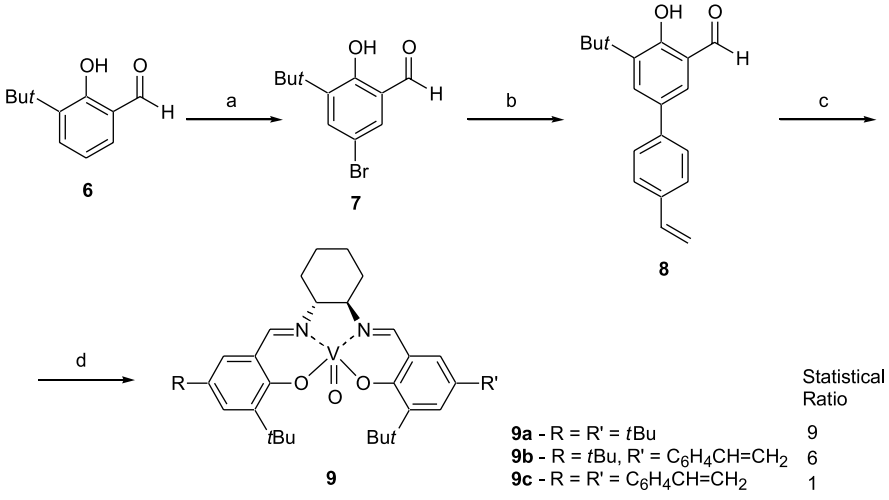
The above sequences exemplify how from a common precursor having a terminal C═C double bond, a library of vanadyl salen catalyst can be easily obtained provided that the scaffolds are suitably functionalised with a mercapto group. The list of vanadyl salen catalysts that have been prepared and their main analytical and physicochemical parameters are included in Table 1.

All the catalysts prepared exhibit in UV visible spectroscopy an absorption at about 380 nm corresponding to the ligand-to-metal charge transfer band characteristic of the vanadyl salen complexes. Also in IR spectroscopy the expected peak for the vanadyl salen complexes at 1540 cm^{-1} was recorded. The vanadium content was determined by quantitative absorption spectroscopy from an aqueous solution of the catalyst (in the case of **VOsalen∝IL**) or in the resulting liquor after dissolving the solid with concentrated hydrofluoric acid (in the case of **VOsalen∝silica**). In the case of **VOsalen∝SWNT** and **VOsalen∝AC** catalysts, the vanadium content was estimated indirectly by combustion chemical analyses from the differences in the percentage of nitrogen in the support before and after anchoring the complex. The vanadium content data is also indicated in Table 1. For the sake of comparison, we have also included in our study as reference catalyst the chiral vanadyl tetra *tert*-butyl salen complex that was the catalyst initially reported by North and co-workers to give high ee in dichloromethane.[3]

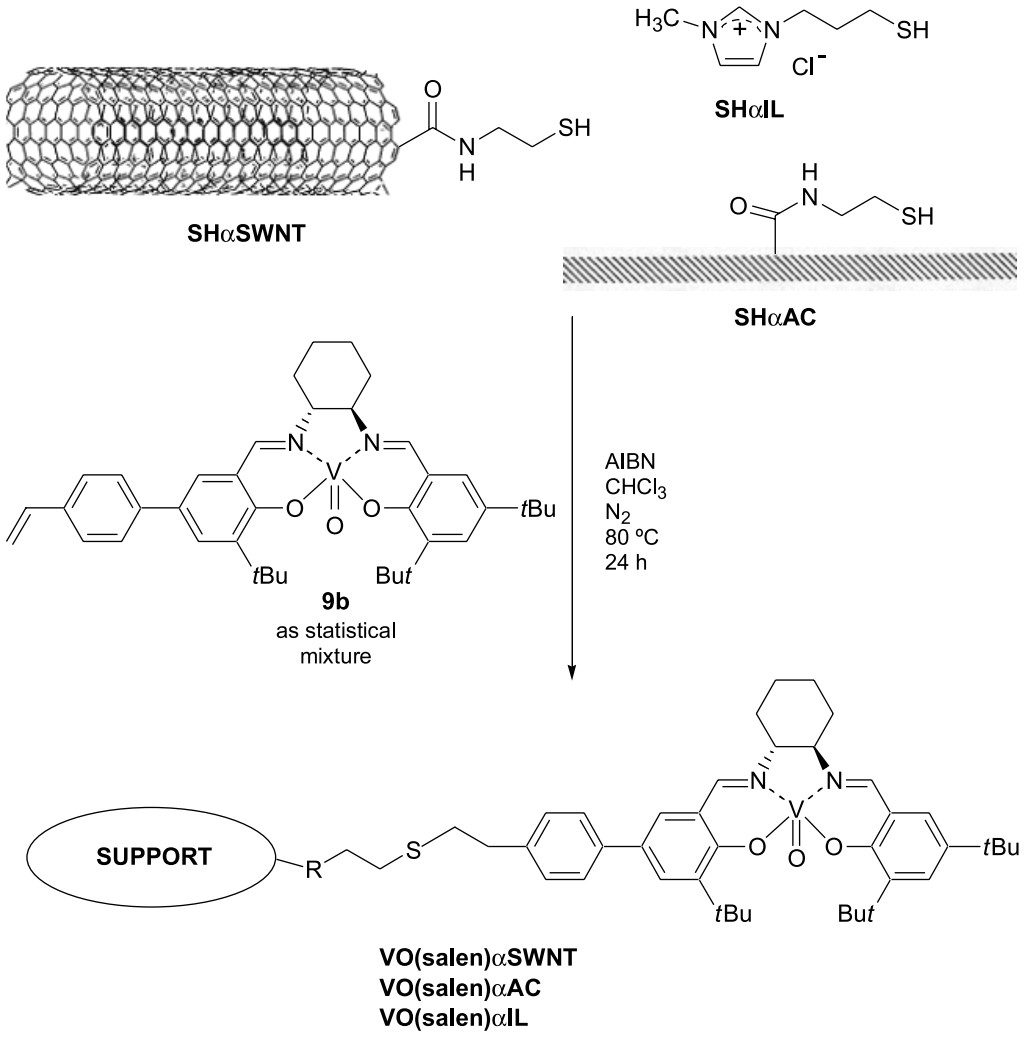
2.2. Catalytic tests

The four recoverable catalysts and the standard chiral vanadyl tetra *tert*-butyl salen complex were initially tested for enantioselective cyanosilylation of benzaldehyde using trimethylsilyl cyanide (TMSCN) (Scheme 5). The experiments were carried out at 0 °C, except for the reactions in ionic liquids which were conducted at room temperature. All catalysts exhibited moderate to high conversions, with the corresponding silylated cyanohydrins being the only detectable product. The results of the catalytic activity obtained for benzaldehyde are indicated in Table 2.

Concerning the ee, the best catalyst of the library was the tetra ^{t}BuVOsalen complex dissolved in 1-butyl-3-ethylimidazolium hexafluorphosphate (beim PF_6) ionic liquid, but it

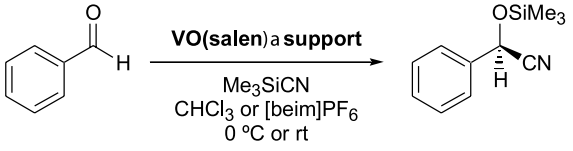


Scheme 3. Reactions and conditions: (a) Br_2, CH_2Cl_2, 0 °C, 30 min; (b) *para*-$(CH_2{=}CH)C_6H_4B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, THF, reflux, 6 h; (c) **2**, **3**, molecular sieves 3 Å, CH_2Cl_2, rt, 24 h; (d) VOacac, MeOH, rt, 16 h.



Scheme 4. Pictorial representation of the covalent anchoring of chiral vanadyl salen complex on three different scaffolds.

is noteworthy that the **VOsalen∝silica** exhibits a very similar ee in spite of being a solid catalyst. The activity of **VOsalen∝IL** was high but the ee is considerably reduced compared to the soluble ^{t}BuVOsalen complex. One possible explanation for this reduced asymmetric induction ability of **VOsalen∝IL** is the interaction of the vanadyl group of the complex with the associated chloride anion present in **SH∝IL**. In this regard we performed an alternative experiment in which the amount of chloride was increased, whereby a diminution of the ee was observed. The catalytic activity of the **VOsalen∝IL** is, however, very high giving the highest turnover frequency values (TOF) for the library of vanadyl salen catalysts.



Scheme 5. Catalytic cyanosilylation of benzaldehyde.

In the case of activated carbon, the ill-defined structure of the support, together with the possible presence of

Table 2. Results of the enantioselective catalytic addition of TMSCN to benzaldehyde in the presence of different chiral vanadyl salen systems in homogeneous and heterogeneous phases

Catalyst	Conditions	Conversion (%)[a]	TOF (h^{-1})	ee (%)[b]
VOsalen∝silica	$CHCl_3$, 0.24 mol%, 0 °C	78	2.7	85
VOsalen∝silica	3rd use	75	2.6	85
Tetra $^{t\mathrm{Bu}}$**VOsalen**	[beim]PF_6, 1 mol%, rt	85[b]	3.5	89
Tetra $^{t\mathrm{Bu}}$**VOsalen**	5th use	83[b]	3.5	89
VOsalen∝SWNT	$CHCl_3$, 0.3 mol%, 0 °C	67	3.1	66
VOsalen∝AC	$CHCl_3$, 0.3 mol%, 0 °C	81	3.75	48
VOsalen∝IL	[bmim]PF_6, 0.2 mol%, rt	88[b]	18.3	57

[a] Determined using a GC column (TRB5, 30 m, 0.25 mm), using nitrobenzene as internal standard.
[b] Determined using a chiral GC column (Chiraldex γ-TA, 30 m, 0.25 mm).

functional groups derived from the sulphur and oxygen groups could be responsible for the low ee. Also in the case of SWNT, the presence of a residual population of free carboxylic groups is the most likely factor responsible for the moderate ee value. Some additional treatments to the SWNT or activated carbons to decrease the population of sites playing a negative role would be necessary to test this hypothesis. It is interesting to note that the TOF for the reaction of benzaldehyde in the presence of both **VOsalen∝SWNT** and **VOsalen∝AC** is also high with comparable values to those observed for the tetra ^{t}BuVOsalen complex in homogeneous phase and higher than observed for catalyst anchored to silica and, therefore, it may be worth while to try to optimise the asymmetric induction of these two catalysts.

One of the most important issues when studying a heterogeneous catalyst is its performance upon reuse. In the case of homogeneous phase tetra ^{t}BuVOsalen complex in [beim]PF_6 ionic liquid, upon extraction of the product with hexane, the extracted solution becomes green indicating that some fraction of the vanadyl catalyst present in the ionic liquid was also extracted together with the reaction products. Although, a second use of the ionic liquid containing chiral tetra ^{t}BuVOsalen complex gave essentially the same conversion and ee values as in the first use, it is clear that over the long term a depletion of the vanadyl salen chiral complex would eventually lead to a reduction of this activity. Also, separation of the vanadium traces from the reaction mixture would be problematic. In the case of the **VOsalen∝silica** as catalyst, reuse of the solid after one run was simply achieved by filtration of the solid and subsequent washings with fresh aliquots of chloroform. Upon removal of the solid catalyst **VOsalen∝silica**, the reaction mixture was surveyed for the presence of catalytic active species. In no case was it observed that the reaction progresses in a solution that has been reacted up to 40% conversion in the presence of **VOsalen∝silica** when the solid has subsequently been removed and the supernatant allowed to react further under normal conditions.

Based on the results achieved with benzaldehyde, we selected two systems, namely chiral tetra ^{t}BuVOsalen complex in [beim]PF_6 and **VOsalen∝silica** in $CHCl_3$ as the systems with the highest asymmetric induction ability and studied the transformation of two more aldehydes into the corresponding chiral silylated cyanohydrins in order to expand the scope of the heterogeneous catalysts and to show the generality of our system. The results achieved are listed in Table 3.

As can be seen in Table 3, although as in the case of benzaldehyde the activity and TOF for the cyanosilylation of a substituted benzaldehyde (4-methoxybenzaldehyde) and an aliphatic aldehyde (hexanal) using **VOsalen∝silica** as solid catalyst is somewhat lower than that of the chiral tetra ^{t}BuVOsalen complex in [beim]PF_6, the ee values of both catalytic systems were very similar with the additional advantage that the solid catalyst can be easily separated and reused.

3. Conclusions

In the present work, we have developed a library of chiral vanadyl salen complexes that are covalently attached to solid supports or with a high ionophilicity that makes the catalyst soluble in ionic liquids and not extractable by conventional organic solvents. The preparation of this library illustrates a simple methodology to obtain heterogeneous catalysts based on the addition of mercapto groups to terminal C=C double bonds. From this series, we have prepared a chiral vanadyl salen complex anchored to silica (**VOsalen∝silica**) through a 14 membered chain whose activity and asymmetric induction ability is very similar to that of chiral tetra ^{t}BuVOsalen complex in ionic liquid. The activity of the latter complex in solution can be considered as the maximum intrinsic activity achievable for the vanadyl salen complexes and, therefore, **VOsalen∝silica** is considered as an optimum recoverable catalyst since it exhibits the activity of the homogeneous complex plus the advantages of heterogeneous catalysts in terms of recovery and reusability. No vanadium leaching has been observed for this system.

4. Experimental

Silica (Aldrich), SWNT (Carbolex, HiPCO, >80% purity), activated carbon (Norit), and [bmim]PF_6 (Aldrich) were commercial samples.

Chiral tetra ^{t}BuVOsalen complex was prepared by dissolving in methanol tetra *tert*-butyl ligand **4** (R=R′=^{t}Bu) (1 mmol) and VOacac (1.1 mmol) and stirring the solution overnight at room temperature. The complex was purified by a short chromatographic column using silica as stationary phase and eluting initially with hexane to remove the ligand followed by diethyl ether. Tetra *tert*-butyl salen ligand (**4**, R=R′=^{t}Bu) was prepared by condensation at room temperature of 2 equiv of 3,5-di-*tert*-butylsalicylaldehyde and 1 equiv of (+)-*R*,*R*′-1,2-cyclohexanediamine in ethanol and following the reported procedure.[16]

Precursor **5** was obtained as a mixture starting from 3-*tert*-butyl-5-chloromethylsalicylaldehyde, 3,5-di-*tert*-butylsalicylaldehyde and (+)-*R*,*R*′-1,2-cyclohexanediamine in ethanol in the proportions indicated in Scheme 1, and adding vanadyl sulphate before reacting the complex with undecen-1-ol in xylene at reflux temperature, following the detailed experimental procedure previously reported by us.[9]

Functionalised silica containing 3-mercaptopropylsilyl groups was obtained by reacting silica (ALDRICH) with 3-mercaptopropyl trimethoxysilane in toluene at reflux temperature under an inert atmosphere, and subsequently submitting the resulting solid to exhaustive silylation using excess of ethoxytrimethylsilane under the same conditions as for 3-mercaptopropylsilylation. The anchoring of precursor **5** to the functionalised silica was accomplished using AIBN as radical initiator in the absence of oxygen following a procedure described elsewhere.[9]

Precursor **8** was synthesized starting from 5-bromo-3-methylsalicylaldehyde that was submitted to Suzuki

Table 3. Results of the cyanosilylation of several aldehydes with TMSCN using as catalysts either chiral tetra ^{t}BuVOsalen complex or **VOsalen∝silica**

Catalyst	Data	4-OMe benzaldehyde	Hexanal
VOsalen∝silica[a]	Conversion (%)	70[b]	85[b]
	TOF (h^{-1})	2.4	2.9
	ee (%)[c]	78	82
Tetra $^{t\text{Bu}}$**VOsalen**[d]	Conversion (%)	88[b]	97[b]
	TOF (h^{-1})	3.7	4.1
	ee (%)[c]	81	83

[a] $CHCl_3$, 0.24 mol%, 0 °C.
[b] Determined using a GC column (TRB5, 30 m, 0.25 mm), using nitrobenzene as internal standard.
[c] Determined using a chiral GC column (Chiraldex γ-TA, 30 m, 0.25 mm).
[d] [beim]PF_6, 1 mol%, rt.

cross-coupling with 4-vinylphenylboronic acid and in the presence of Pd[$(PPh_3)_4$] followed by condensation with 3,5-di-*tert*-butylsalicylaldehyde and (+)-*R*,*R*′-1,2-cyclohexanediamine and VOacac. The experimental procedure has been reported in detail in a previous work.[14]

Activated carbon and commercial HiPCO SWNT were treated at reflux temperature with a 3 M aqueous solution of HNO_3 for 24 h. After this treatment the carbonaceous materials were filtered, washed with distilled water and THF and dried under vacuum. The resulting black solids once dried, were suspended in a solution of $SOCl_2$ in DMF and stirred at 65 °C for 24 h. Then, the solids were recovered by filtration, washed with anhydrous THF and treated with a solution of 2-mercaptoethylamine hydrochloride and triethylamine in dry dichloromethane. The suspension was allowed to react under nitrogen at 40 °C for 48 h.

N-Methyl-*N*′-(3-mercaptopropyl)-imidazolium chloride (SH∝IL) was obtained by reaction between 3-chloropropanethiol and *N*-methyl-imidazolium at 80 °C for 96 h, following the detailed experimental procedure previously reported by us.[12]

Immobilization of precursor **9** on the modified supports (SH∝SWNT, SH∝AC and SH∝IL) was accomplished using AIBN at 80 °C for 20 h in degassed chloroform under an inert atmosphere, and submitting the resulting solids to exhaustive solid–liquid extraction with dichloromethane.[10,12]

4.1. General procedure for the asymmetric addition of trimethylsilyl cyanide to aldehydes catalysed by heterogeneous catalysts

The heterogeneous catalyst was suspended in dry chloroform (1.9 ml) followed by the addition of the aldehyde (1.64 mmol) and nitrobenzene as internal standard (1.64 mmol). The suspension was stirred for 5 min and then TMSCN (4.92 mmol) was added. The reaction mixture was stirred at 0 °C and the course of the reaction followed by analysing the organic phase by GC (TRB5, 30 m, 0.25 mm). The physical and analytical data of the trimethylsilyl ethers of corresponding cyanohydrins were in agreement with those reported in the literature.[16,17] In all cases, the (*R*,*R*)-isomer of the catalyst gave an excess of the (*S*)-enantiomer of the cyanohydrin derivative, whose configuration was determined by comparison with the existing literature reports.[3,4]

4.2. General procedure for the asymmetric addition of trimethylsilyl cyanide to aldehydes catalysed by VOsalen in ionic liquids

The ionic liquid (1 ml) was dried by heating at 50 °C under reduced pressure for 12 h (0.1 Torr). The vanadyl salen complex either ^{t}BuVOsalen or VOsalen∝IL was added and the liquid stirred at room temperature for 15 min. Aldehyde (1.64 mmol) and TMSCN (1.1 equiv) were added to the ionic liquid containing the previously dissolved catalyst and the mixture stirred at room temperature under N_2. The course of the reaction was followed by removal of a given amount of ionic liquid, which was weighed and dissolved in dichloromethane. To this solution, nitrobenzene (5 μl) was added as external standard and the solution injected into GC (TRB5, capillary column). At the end of the reaction, the ionic melt was exhaustively extracted with hexane (2× 10 ml). The ee was determined in a chiral GC column (Chiraldex γ-TA, 30 m, 0.25 mm).

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Polymeric salen-Ti(IV) or V(V) complex catalyzed asymmetric synthesis of *O*-acetylcyanohydrins from KCN, Ac_2O and aldehydes

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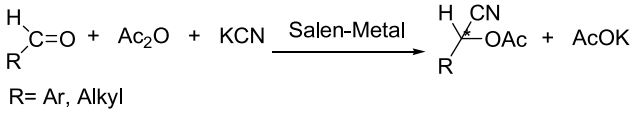
Abstract—Polymeric salen-Ti(IV) and V(V) complexes were employed in the enantioselective *O*-acetyl cyanation of aldehydes with potassium cyanide and acetic anhydride. The crosslinked polymeric salen-Ti(IV) catalyst exhibited good activities and enantioselectivities, up to 91% ee with 99% conversion was obtained at −20 °C with 1 mol% of catalyst (based on bimetallic catalytic unit). Moreover, six consecutive recyclings with the easily recovered crosslinked polymeric catalyst showed no obvious decrease in either activity or enantioselectivity. Linear polymeric salen-V(V) catalyst showed good catalytic efficiency too, up to 94% ee with 99% conversion was obtained at −42 °C with 5 mol% of catalyst.

1. Introduction

As chiral cyanohydrins have potential applications in pharmaceuticals, agrochemicals and other fields, many efficient and successful synthetic methods for their preparation have been developed. The catalytic process with metal complexes is one of the most attractive methods in which great progress has been made over the past decade.[1–3] Among the metal-complex catalysts, chiral salen-Ti(IV) and salen-V(IV) complexes have shown excellent catalytic efficiency in the asymmetric trimethylsilylcyanation of aldehydes or ketones.[4–8] Recently, many efforts have been devoted to recyclable metal catalysts, such as, organic or inorganic supported catalysts,[9–13] and improving the catalytic efficiency, for example, using an ionic liquid as the reaction media.[14,15] However, these processes always use volatile and expensive trimethylsilyl cyanide as the cyanide source. Although some less expensive cyanide sources, such as ethyl cyanoformate and benzoyl cyanide, have been employed in synthesis of *O*-protected cyanohydrins,[16–22] exploring a non-volatile and less expensive cyanide source is still interesting. Recently, Belokon and North et al. developed an attractive method to synthesize chiral *O*-acetyl cyanohydrins (Scheme 1), which were obtained from potassium cyanide, acetic anhydride and aldehydes catalyzed by bimetallic salen Ti–(μ-O)$_2$-Ti complex **1** (Fig. 1) and monometallic salen-V(V) complex **2** (Fig. 2),[23,24] and this is the first report of the asymmetric synthesis of cyanohydrin derivatives using a cyanide source which is non-volatile and inexpensive.



Scheme 1. Synthesis of chiral *O*-acetyl cyanohydrins promoted by chiral salen-metal complexes.

Over the past few years, we have developed some chiral polymeric salen catalysts, which were successfully employed in the enantioselective epoxidation and hydrolytic kinetic resolution (HKR) of terminal epoxides and could be easily recovered and reused.[25–27] Our former research indicated that linear polymeric salen-Ti(IV) showed good activity, but much lower enantioselectivity compared to complex **1** in the trimethylsilylcyanation of aldehydes, and we ascribed this result to the spatial block of polymeric ligand.[28] In subsequent work on the HKR of terminal epoxides, which was based on a known bimetallic cooperation mechanism, we found that flexible crosslinked polymeric catalysts showed excellent enantioselectivity and

Keywords: *O*-Acetyl cyanohydrins; Recyclable polymeric salen-Ti(IV) complexes; Polymeric salen-V(V) complexes; Potassium cyanide; Aldehyde; Asymmetric cyanation.
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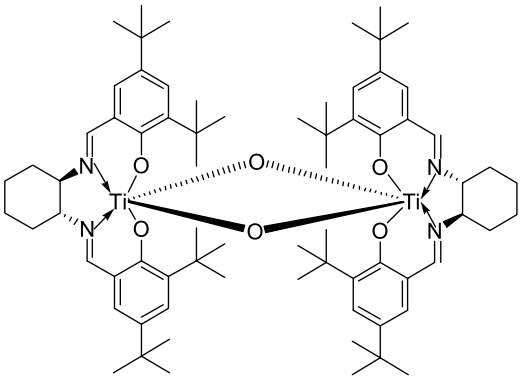
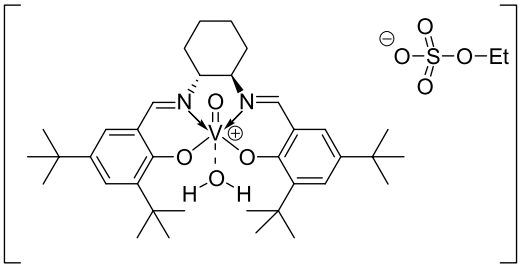


(*R*)-**1**

Figure 1. The bimetallic salen-Ti(IV) complex.



(*R*)-**2**

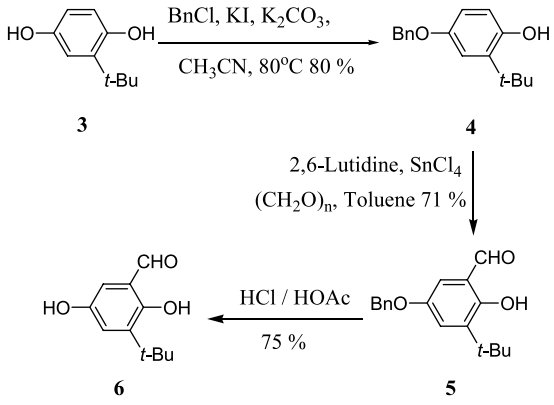
Figure 2. The salen-V(V) complex.

activity, but the crosslinked polymeric catalysts were somewhat degraded in the reaction system.[29] In this paper, to extend the application of polymeric salen metal complexes in other asymmetric catalytic reactions, the crosslinked polymeric salen-Ti(IV) and linear polymeric salen-V(V) complexes were applied to the *O*-acetyl cyanation of aldehydes with potassium cyanide as cyanide source. Our preliminary results showed that the polymeric ligands of Ti(IV) complexes needed a more flexible structure to form the active Ti–(μ-O)$_2$-Ti complex and induce high catalytic efficiency.[30] The current research on the V(V) complex showed that the linear polymeric salen ligand with a rigid structure provided the same efficiency as the monomeric complex **2**.

2. Results and discussion

2.1. Synthesis of polymeric salen ligands

The syntheses of crosslinked polymeric ligands and their analogues were achieved as described in Schemes 2–4. 3-*tert*-Butyl-2,5-dihydroxy benzaldehyde **6** was prepared according to the literature procedure[31] with some modifications. The benzyl protecting group of **5** could be conveniently removed in a HCl/HOAc system (Scheme 2). The condensation of **6** with the corresponding acids **10**, **11** and **12** produced the key intermediate aldehydes **13**, **14** and **15**, respectively, (Scheme 3). The reaction of aldehydes (**13** and/or **14**) with chiral 1,2-diaminocyclohexane stoichiometrically afforded the corresponding chiral polymeric ligands (Scheme 4). When only dialdehyde **14** was



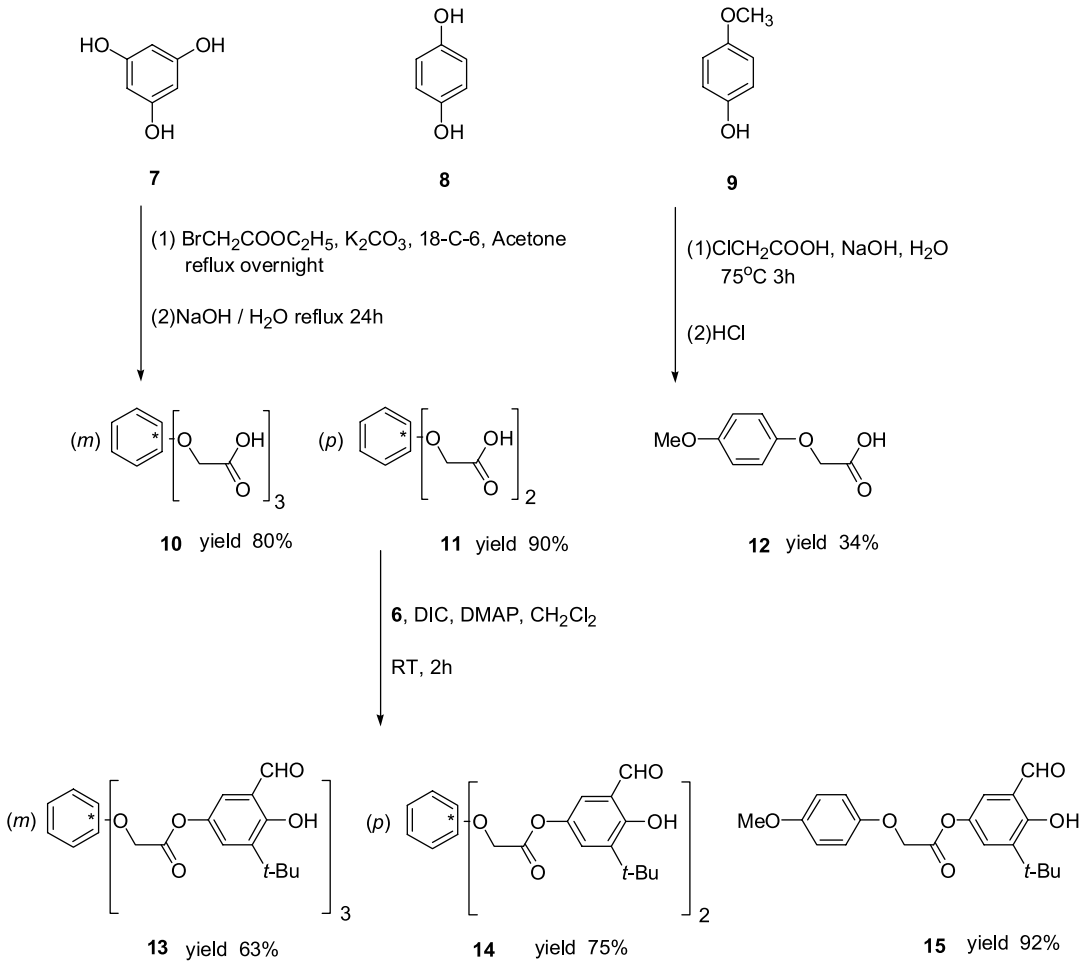
3 **4** **5** **6**

Scheme 2. Synthesis of 3-*tert*-butyl-2,5-dihydroxybenzaldehyde.

employed, an oligomeric ligand **16** was formed. The crosslinked polymeric ligands **17** could be obtained by reaction of different proportions of trialdehyde **13** (the crosslinking agent) and dialdehyde **14**. The degree of crosslinking of the polymeric ligand, which was closely related with the Ti–(μ-O)$_2$-Ti species formation, could be finely tuned by changing the ratio of **13** to **14**. The average molecular weights of the polymeric ligands were between 4000 and 10,000, as determined by GPC. The completely crosslinked polymeric ligand **18** derived from **13** and (*R*,*R*)-1,2-diaminocyclohexane was a gel, which was partially soluble in THF. The analogous monomeric salen **19** (Fig. 3) was synthesized by a similar process to that used for **16**, **17** and **18**. The synthesis of linear polymeric salen ligand **20** (Fig. 4) was described in our previous report.[26]

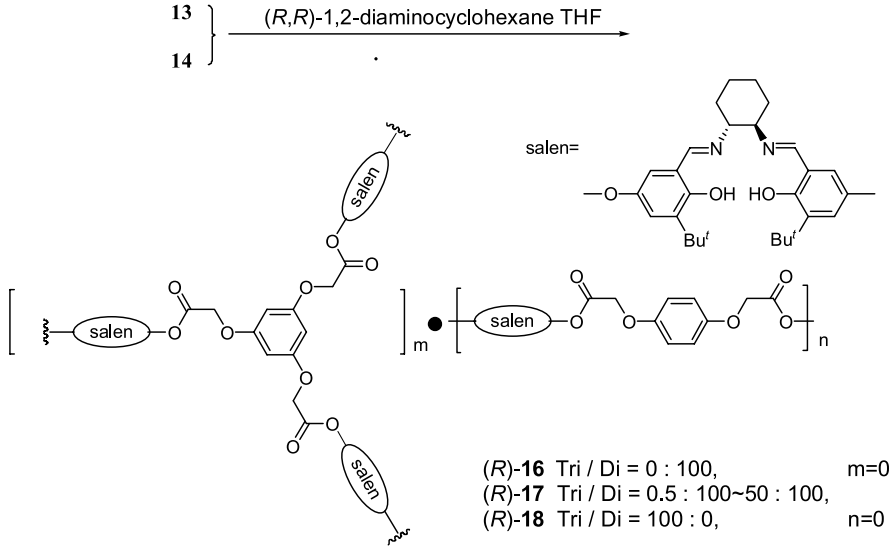
2.2. Ti(IV)-catalyzed asymmetric *O*-acetyl cyanation of aldehydes

Synthesis of polymeric salen-Ti(IV) complexes and their applications in the *O*-acetyl cyanation of aldehydes were carried out by literature procedures.[5,23,24] Benzaldehyde was used as the substrate for screening the catalytic efficiencies in the *O*-acetyl cyanation with polymeric salen-Ti(IV) complexes at 20 and −20 °C and the results are summarized in Table 1. As a comparison, the result obtained using salen-Ti(IV) bimetallic complex **1** is also listed in Table 1 (entry 1).[24] The results indicated that ligands **17** with appropriate degrees of crosslinking, whose ratios of **13** to **14** were between 0.5:100 and 2:100, exhibited good results in the asymmetric *O*-acetyl cyanation of benzaldehyde (Table 1, entries 2–4). These results were comparable with those obtained from complex **1**. However, the enantioselectivities decreased gradually with the increase of the ratio of **13** to **14** (Table 1, entries 5–9). When the completely crosslinked ligand **18** was used, both the reactivity and enantioselectivity of the catalyst were dramatically reduced (Table 1, entry 10). The same trend could be observed at both 20 and −20 °C, and better results were obtained at −20 °C. These results meant that the ratio of **13** to **14** played an important role in forming the bimetallic Ti–(μ-O)$_2$-Ti species. When the proportions of **13** and **14** were between 0.5:100 and 2:100, the bimetallic species could be formed more easily, thus a comparable ee to that shown by complex **1** could be obtained. The polymeric ligand with an excess of **13**, which had a more



Scheme 3. Synthesis of the key aldehydes.

rigid structure, had difficulty forming the key species and exhibited an inferior catalytic capability. To further clarify the importance of the degree of crosslinking, we used oligomeric ligand **16** without the crosslinking agent **13** to perform the asymmetric cyanation under identical conditions. The results showed that ligand **16** had the same enantioselective induction as that of the ligand **17** (0.5:100), but a lower conversion was observed even when the reaction time was prolonged (Table 1, entry 11). The poor results obtained by linear polymeric salen ligand **20** could further confirm that a rigid ligand within the Ti(IV) complex was unfavorable for obtaining the best results (Table 1, entry



Scheme 4. Synthesis of the crosslinked salen ligands.

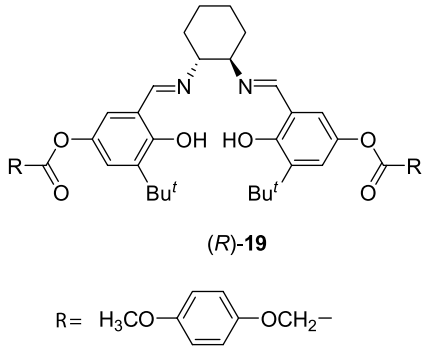


Figure 3. The monomeric analogue of the salen ligand.

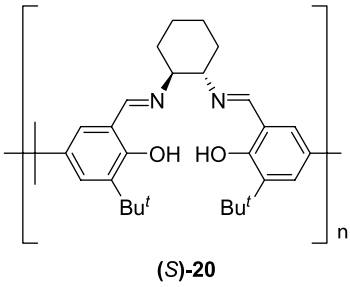


Figure 4. The linear polymeric salen ligand.

12). Finally, monomeric salen analogue **19** (Fig. 3) was also screened, and similar enantioselectivity and activity as for complex **1** were obtained (Table 1, entry 13), which indicated that the phenolic ester group in the ligand had little influence in the asymmetric *O*-acetyl cyanation of benzaldehyde.

Next, we used the Ti(IV) complex of **17** (**13/14**=0.5:100) as a catalyst to examine the influence of the other reaction conditions in the *O*-acetyl cyanation of benzaldehyde, and the results are listed in Table 2. Lowering temperature to −30 or −42 °C just gave the equivalent ee to that obtained at −20 °C (Table 2, entries 1 and 2). When the ratio of potassium cyanide to substrate was reduced, a slightly lower conversion and the same enantioselectivity were observed (Table 2, entry 3). Attempts to reduce the catalyst loading and changing the solvent were unsuccessful (Table 2, entries 4–10).

Under the optimal conditions, a variety of substituted benzaldehydes, several aliphatic aldehydes and heteroaromatic aldehydes were used as substrates for this *O*-acetyl cyanation catalysed by Ti(IV)-(*R*)-**17** complex (**13/14**=0.5:100). The results are listed in Table 3. As a comparison, the results obtained using the Ti(IV) complex of linear polymeric salen (*S*)-**20** are listed too. The substituent of the benzaldehyde derivative had a great influence on the reactivity and enantioselectivity. When 4-fluorobenzaldehyde was used as substrate, the best result of 91% ee with 99% conversion was obtained (Table 3, entry 5). As for the aliphatic aldehydes, the chiral products were obtained in 81–86% ee with moderate to excellent conversion (Table 3, entries 11–13), while only 67% ee was obtained when isobutyraldehyde was used as substrate (Table 3, entry 14). These results were comparable to those observed with catalyst **1** at a lower reaction temperature (−42 °C).[23,24] The *O*-acetyl cyanation of heteroaromatic aldehydes could also proceed smoothly. By using 2-furaldehyde and 2-thiophenecarboxaldehyde as substrates, good enantioselectivities could be obtained (Table 3, entries 15 and 16). However, only 6.4% ee was obtained using 2-pyridinecarboxaldehyde as substrate (Table 3, entry 17). The results of linear ligand **20** were obviously inferior to those of **17** (Table 3, entries 1, 5, 10–12, 15), which could confirm our presumption that the linear polymeric salen ligand would have great difficulty to form the Ti–(μ-O)$_2$-Ti species completely for spatial reasons.

Table 1. Enantioselective synthesis of the *O*-acetyl cyanohydrin from benzaldehyde, potassium cyanide and acetic anhydride catalyzed by different salen-Ti(IV) complexes[a]

Entry	Ligand (**13/14**)[b]	20 °C		−20 °C		Conf.[c]
		Conv.[d]	Ee[e]	Conv.[d]	Ee[e]	
1	(*R*)-**1**[f]	>90	74		88	*S*
2	(*R*)-**17** (0.5:100)	83	78	91	89	*S*
3	(R)-**17** (1:100)	88	78	89	88	*S*
4	(*R*)-**17** (2:100)	92	78	85 (99)[g]	87 (87)[g]	*S*
5	(*R*)-**17** (6:100)	95	75	84	85	*S*
6	(*R*)-**17** (14:100)	86	63	79	81	*S*
7	(*R*)-**17** (18:100)	87	59	60	77	*S*
8	(*R*)-**17** (25:100)	92	56	60 (99)[g]	79 (79)[g]	*S*
9	(*R*)-**17** (50:100)	ND[h]	ND[h]	39	70	*S*
10	(*R*)-**18** (100:0)	35	44	13	55	*S*
11	(*R*)-**16** (0:100)	72	62	58 (83)[g]	89 (89)[g]	*S*
12	(*R*)-**20**	77	47	52	68	*S*
13	(*R*)-**19**	ND[h]	ND[h]	68 (96)[g]	86 (83)[g]	*S*

[a] Reaction conditions: benzaldehyde (1 mmol), potassium cyanide, acetic anhydride (ratio=1:4:4) in 5 mL solvent mixture (CH_2Cl_2 5 mL, ^{t}BuOH 90 μL and H_2O 1.8 μL) in presence of catalyst prepared from 2 mol% (*R*)-ligand and 2 mol% Ti(*i*-OPr)$_4$, stirred for 4 h.
[b] The proportion of trisalicylaldehyde **13** and disalicylaldehyde **14** calculated as a weight ratio.
[c] Absolute configurations were assigned by comparison with literature data in Ref. 24.
[d] Based on GC integral area.
[e] Determined by GC analysis using a chiral capillary column (cyclodex-β, 2,3,6-methylated, 30 m×0.25 mm (i.d.)).
[f] Results obtained by catalyst **1** in Ref. 24.
[g] The results in parentheses were obtained after a reaction time of 16 h.
[h] ND, not determined.

Table 2. Enantioselective synthesis of the *O*-acetyl cyanohydrin from benzaldehyde, potassium cyanide and acetic anhydride catalyzed by the Ti(IV) complex of (*R*)-**17** (**13/14**=0.5:100)[a]

Entry	Cat. (mol%)	KCN/benzaldehyde	Solvent	Temp. (°C)	Time (h)	Conv. (%)	Ee (%)
1	1	4	CH_2Cl_2	−30	16	99	89
2	1	4	CH_2Cl_2	−42	16	99	89
3	1	1.5	CH_2Cl_2	−20	20	96	89
4	0.5	4	CH_2Cl_2	−20	16	84	47
5	0.25	4	CH_2Cl_2	−20	16	74	35
6	0.1	4	CH_2Cl_2	−20	16	17	12
7	1	4	Toluene	−20	27	14	61
8	1	4	Ether	−20	4	8	43
9	1	4	THF	−20	4	31	18
10	1	4	Hexane	−20	4	16	39

[a] The reaction conditions were the same as in Table 1, except for the indicated conditions.

Table 3. Enantioselective synthesis of *O*-acetyl cyanohydrins from aldehydes, potassium cyanide and acetic anhydride catalyzed by polymeric catalysts[a]

Entry	Substrate	Time (h)	Ti(IV)-(*R*)-**17** 1 mol% (**13/14**=0.5:100)			Ti(IV)-(*S*)-**20** 1 mol%		
			Conv. (%)	Ee (%)	Conf.	Conv. (%)	Ee (%)	Conf.
1	PhCHO	16	100	89	*S*	79	64	*R*
2	2-$CH_3C_6H_4CHO$	16	99	88	*S*			
3	3-$CH_3C_6H_4CHO$	16	98	86	*S*			
4	4-$CH_3C_6H_4CHO$	16	95	89	*S*			
5	4-FC_6H_4CHO	16	99	91	*S*	89	63	*R*
6	4-ClC_6H_4CHO	16	99	85	*S*			
7	4-BrC_6H_4CHO	16	99	81	*S*			
8	4-$CF_3C_6H_4CHO$	4	99	70	*S*			
9	4-$MeOC_6H_4CHO$	40	57	87	*S*			
10	3-$PhOC_6H_4CHO$	16	98	84	*S*	80	48	*R*
11	$PhCH_2CH_2CHO$	16	99	83	*S*	90	41	*R*
12	Cyclohexanecarboxaldehyde	16	97	81	*S*	87	41	*R*
13	Me_2CHCH_2CHO	20	62[b]	86	*S*			
14	Me_2CHCHO	20	61[b]	67	*S*			
15	2-Furaldehyde	16	99	66	ND	81	27	ND
16	2-Thiophenecarboxaldehyde	16	62	78	ND			
17	2-Pyridinecarboxaldehyde	16	100	6.4	ND			

[a] The reaction conditions are the same as in Table 1, and stirred at −20 °C.
[b] Isolated yield based on the aldehydes, after flash chromatography (silica gel).

Recycling the catalysts derived from these crosslinked polymeric ligands was investigated in the *O*-acetyl cyanation of benzaldehyde. Initially, the optimized ligand **17** (**13/14**=0.5:100) was applied in the recycling experiment, however, the result was discouraging in that the recovered catalyst showed extremely low activity and enantioselectivity, which was probably due to the instability of the slightly crosslinked ligand. Therefore, we used ligand **17** with a higher degree of crosslinking (**13/14**=25:100) to examine the recycling ability of the catalysts, and the results are listed in Table 4. As expected, the catalyst derived from the more highly crosslinked polymeric salen ligand showed excellent reusability in the *O*-acetyl cyanation of benzaldehyde, up to 74% ee and 95% conversion were obtained even after seven consecutive runs.

Table 4. The recycling of crosslinked polymeric salen-Ti(IV) catalyst in the enantioselective synthesis of the *O*-acetyl cyanohydrin from benzaldehyde, potassium cyanide and acetic anhydride[a]

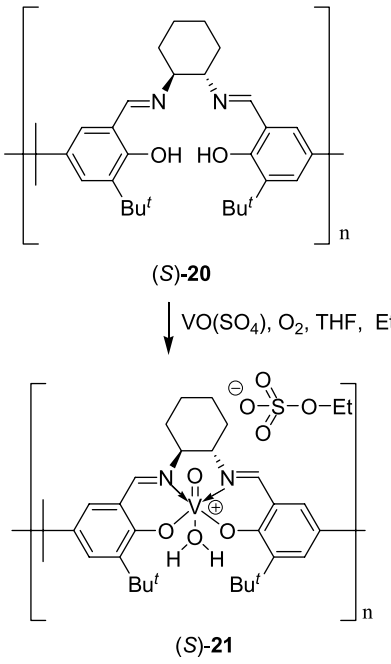
Cycle	Time (h)	Conv. (%)	Ee (%)
Fresh	9	99	80
1	16	99	78
2	16	98	78
3	16	99	78
4	16	99	80
5	20	99	80
6	20	95	74

[a] The reaction conditions are the same as in Table 3, but 4 mol% of the ligand **17** (**13/14**=25:100) and 4 mol% of Ti(*i*-OPr)$_4$ were used.

2.3. V(V)-catalyzed asymmetric *O*-acetyl cyanation of aldehydes

Salen-V(V) had been applied in the *O*-acetyl cyanation of aldehydes.[24] To further explore the relationship between the structure of polymeric salen ligand and the variety of the central metal, the linear polymeric salen complex of V(V) was applied to the *O*-acetyl cyanation of aldehydes with potassium cyanide as the cyanide source.

The V(V) complex **21** of the linear salen ligand **20** was synthesized according to the literature procedure[24] with a slight modification (Scheme 5), and the subsequent *O*-acetyl cyanation of aldehydes was carried out under similar conditions to those employed for the Ti(IV) complexes.



Scheme 5. Synthesis of chiral linear polymeric salen–V(V) complexes.

Benzaldehyde was chosen as the substrate to optimize catalyst loading and the reaction temperature for the *O*-acetyl cyanation (Table 5). As shown in Table 5, both catalyst loading and the reaction temperature have a great affect on the enantioselectivity of the reaction. Up to 99% conversion and 94% ee were obtained at −42 °C with 5 mol% of the complex **21** (Table 5, entry 1), which is comparable with the result obtained using catalyst **2** except for the relatively high catalyst loading. The reactivity and enantioselectivity decreased as the amount of catalyst was reduced (Table 5, entries 1–5). When 0.1 mol% of complex **21** was used, only 20% conversion with 82% ee was obtained (Table 5, entry 5). If the reaction temperature was increased, much lower ee values were obtained (Table 5, entries 6–9). It is notable that when the reaction was carried out at 0 °C or higher, both the activity and the enantioselectivity were dramatically decreased. At these higher temperatures, the color of the catalyst became light-green (similar to the color of salen-V(IV)) from initially dark-green (the color of V(V) complex) in 10 min, which showed that the valence of the central metal had been changed to some degree.

Reactions with different substrates were carried out at −20 °C using 2 mol% catalyst (Table 6). The substituent of the benzaldehyde derivative had a great influence on the activity and enantioselectivity. Substituted benzaldehydes with electron-donating groups showed poor reactivity and lower enantioselectivity than benzaldehyde (Table 6, entry 9). By the use of 2-furaldehyde as substrate, a moderate ee could be obtained (Table 6, entry 11). As for the aliphatic aldehydes, the chiral products were obtained in 72–83% ee with moderate to excellent conversion (Table 6, entries

Table 5. Enantioselective synthesis of the *O*-acetyl cyanohydrin from benzaldehyde, potassium cyanide and acetic anhydride catalyzed by (*S*)-**21** under different reaction conditions[a]

Entry	**21** (mol%)	Temp. (°C)	Time (h)	Conv. (%)	Ee (%)
1	5.0	−42	4 (16)	88 (99)[b]	94 (94)[b]
2	2.0	−42	4 (16)	62 (85)[b]	94 (90)[b]
3	1.0	−42	4	47	90
4	0.5	−42	4	37	83
5	0.1	−42	4	20	82
6	2.0	−30	4 (16)	88 (97)[b]	91 (90)[b]
7	2.0	−20	4	90	90
8	2.0	0	4	85	64
9	2.0	10	4	69	28

[a] Reaction conditions: aldehyde (1 mmol), potassium cyanide, acetic anhydride (ratio = 1:4:4) in 5 mL solvent mixture (CH_2Cl_2 5 mL, ^tBuOH 90 μL and H_2O 1.8 μL) in the presence of (*S*)-**21**, stirred at the indicated temperature.
[b] The results in parentheses were obtained after a reaction time of 16 h.

Table 6. Enantioselective synthesis of *O*-acetyl cyanohydrins from aldehydes, potassium cyanide and acetic anhydride catalyzed by (*S*)-**21**[a]

Entry	Substrate	Time (h)	Conv. (%)	Ee (%)	Conf.
1	PhCHO		99	89	*R*
2	2-$CH_3C_6H_4CHO$	16	99	88	*R*
3	3-$CH_3C_6H_4CHO$	16	94	89	*R*
4	4-$CH_3C_6H_4CHO$	16	93	90	*R*
5	4-FC_6H_4CHO	16	99	90	*R*
6	4-ClC_6H_4CHO	16	99	84	*R*
7	4-BrC_6H_4CHO	16	99	82	*R*
8	4-$CF_3C_6H_4CHO$	16	99	68	*R*
9	4-$MeOC_6H_4CHO$	16	49	79	*R*
10	3-$PhOC_6H_4CHO$	16	97	80	*R*
11	2-Furaldehyde	16	95	55	ND
12	$PhCH_2CH_2CHO$	16	99	80	*R*
13	Cyclohexanecarboxal-dehyde	16	85	83	*R*
14	Me_2CHCH_2CHO	20	71	83	*R*
15	Me_2CHCHO	20	ND	72	*R*

[a] The reaction conditions are the same as in Table 5, but in the presence of 2 mol% (*S*)-**21**, stirred at −20 °C.

12–15). All results catalyzed by linear polymeric salen V(V) complexes were superior to those obtained with linear salen-Ti(IV) catalysts (Table 3). We speculated that the coordination environment of the active species of salen-V(V) was more tolerant than the active species of salen-Ti(IV) in the *O*-acetyl cyanation of aldehydes, so the drawback of the spatial block of the linear polymeric ligand is partly overcome in the V(V) complex.

A recycling experiment using (*S*)-**21** was also performed. Unfortunately, using the recovered catalyst for next run was not successful. Probably, the valence of the central metal had changed during the reaction process.

3. Conclusion

In conclusion, crosslinked polymeric salen-Ti(IV) and linear polymeric salen-V(V) were successfully employed as asymmetric catalysts in the asymmetric addition of potassium cyanide and acetic anhydride to aldehydes. Moreover, salen-Ti(IV) catalysts with a higher degree of crosslinking exhibited excellent recyclability. These results were superior to those of linear polymeric salen-Ti(IV), which clarified that the polymeric ligand structure must be compatible with the catalytic mechanism to enhance the catalytic efficiency and this is meaningful for the design of efficient polymeric catalysts.

4. Experimental

4.1. General

Melting points were measured on a Yazawa micro melting point apparatus (uncorrected). The molecular weights of polymers were measured on a PL-GPC210 instrument. Optical rotations were measured on a JASCO P-1020 polarimeter. The ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX 400 system with TMS as an internal standard. The conversion and ee values were determined by GC (HP4890) with a chiral capillary column (cyclodex-β, 2,3,6-methylated, 30 m×0.25 mm (i.d.)). The absolute configuration was assigned by comparison with literature data.[24] High resolution mass spectra (HRMS) were recorded on ABMS 5303 (APCI). All solvents were dried using standard procedures and freshly distilled before use. All experiments were carried out under an argon atmosphere except where specified. All liquid aldehydes were freshly distilled before use. Potassium cyanide was recrystallized according to the literature.[32] Other reagents were commercially available and used directly without purification. The catalytic unit weight of a polymeric catalyst was calculated based on a single salen-metal unit. The catalyst loading of Ti(IV) complexes was calculated based on a bimetallic catalytic unit to be consistent with the literature.[23,24]

4.2. Synthesis of polymeric salen ligands

4.2.1. Synthesis of aldehydes.

4.2.1.1. 3-*tert*-Butyl-2,5-dihydroxy benzaldehyde 6. A mixture of **5**[31] (28.6 g, 0.1 mmol), acetic acid (225 mL) and 36% HCl (35 mL) was heated to 65–70 °C overnight. After the reaction was complete (detected by TLC), the solvent was removed under reduced pressure. The residue was mixed with CH_2Cl_2 (100 mL), stirred for 30 min, and filtered. The filtration residue was washed with CH_2Cl_2 (20 mL×5), water (20 mL×5) and dried to afford of 3-*tert*-butyl-2,5-dihydroxy benzaldehyde **6** (15.1 g, 75% yield), which could be used in next reaction without further purification, as a grass green solid: mp 140–142 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (s, 9H), 6.92 (d, J=2.8 Hz, 1H), 7.02 (d, J=2.8 Hz, 1H), 9.28 (s, 1H), 9.85 (s, 1H), 11.20 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.02, 34.42, 115.33, 120.70, 122.85, 138.43, 149.61, 153.08, 198.24.

4.2.1.2. 1,3,5-Phenylenetrioxytri-acetic acid tri-(3-*tert*-butyl-5-formyl-4-hydroxy-phenyl)ester 13 (trialdehyde). 1,3,5-Trihydroxybenzene dihydrate **7** (3.24 g, 20.0 mmol) was dissolved in acetone (30 mL), dried over 3A molecular sieves for 24 h, and then filtered into a mixture of anhydrous K_2CO_3 (10.37 g, 75 mmol) and 18-crown-6 (15 mg, 0.06 mmol). The mixture was stirred at room temperature for 10 min. Ethyl bromoacetate (11.02 g, 66.0 mmol) was added and then the reaction was heated to reflux for 24 h. After the reaction was complete (detected by TLC; if the reaction was not complete, additional ethyl bromoacetate was added), the reaction solution was cooled to room temperature and filtered. The filtration residue was washed with ether (20 mL×5), and the combined filtrates were evaporated. The residue was dissolved in CH_2Cl_2, washed with 1 N HCl (50 mL×2), saturated NaCl (20 mL×3), and then dried over anhydrous Na_2SO_4. The solution was filtered, evaporated and recrystallized from anhydrous ethanol to afford ethyl 1,3,5-tris(carboxymethoxy)benzene (6.15 g, 80% yield) as white needles. The crystals were boiled with 10% NaOH (50 mL) overnight and the reaction system became homogeneous. The reaction was cooled to room temperature, 36% HCl was added slowly until pH<1 and a white solid was deposited, which was filtered and dried to afford 1,3,5-tris(carboxymethoxy)benzene **10** (4.78 g, >99%). A mixture of **10** (1.46 g, 4.9 mmol), **6** (2.80 g, 15 mmol), 4-(dimethylamino)pyridine (DMAP) (0.17 g, 1.4 mmol), DMF (1 mL) and CH_2Cl_2 (20 mL, freshly distilled from CaH_2) was cooled to 0 °C, and diisopropylcyanamide (DIC) (2.5 mL, 16.6 mmol) was added and stirred for 5 min. The reaction was allowed to warm to room temperature and stirred for 2 h, then diluted with CH_2Cl_2 (100 mL), washed with 1 N HCl (50 mL×2), saturated NaCl (20 mL×3). The organic layer was separated, and dried over anhydrous Na_2SO_4. The solution was filtered, evaporated and purified by flash chromatography on a silica column (eluted with petroleum ether/ethyl acetate=10:1) to give **13** (2.55 g, 63% yield) as a white solid; mp 84–86 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 27H), 4.87 (s, 6H), 6.32 (s, 3H), 7.20–7.23 (m, 6H), 9.72 (s, 3H), 11.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 28.86, 34.99, 65.21, 95.48, 119.89, 122.93, 127.41, 140.37, 141.57, 159.15, 167.38, 171.17, 196.24.

4.2.1.3. *p*-Phenylenedioxydiacetic acid di-(3-*tert*-butyl-5-formyl-4-hydroxy-phenyl)ester 14 (dialdehyde). Following the same method for the synthesis of **13**, dialdehyde **14** (3.12 g, 75% yield) was prepared from *p*-phenylenedioxydiacetic acid **11** (1.61 g, 7 mmol) and **6** (2.80 g, 15 mmol) as a white solid: mp 144–146 °C; ^{1}H

NMR ($CDCl_3$) δ 1.40 (s, 18H), 4.85 (s, 4H), 6.98–7.23 (m, 8H), 9.81 (s, 2H), 11.74 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 28.92, 35.04, 66.15, 116.14, 119.92, 122.84, 127.52, 140.40, 141.84, 152.84, 159.17, 167.82, 196.25.

4.2.1.4. (4-Methoxy-phenoxy)-acetic acid 3-*tert*-butyl-5-formyl-4-hydroxy-phenyl ester 15. A mixture of *p*-methoxyphenol **9** (6.20 g, 50 mmol) and chloroacetic acid (5.00 g, 53 mmol) was stirred at room temperature, and then 25% NaOH (17.0 g, 106 mmol) was added dropwise. The mixture was heated to 75 °C for 3 h, and then cooled to room temperature, acidified to pH 6 with 36% HCl and extracted with 4-methyl-2-pentanone (50 mL×2). The aqueous phase was acidified to pH=1 and filtered to obtain 5.81 g of a white solid which was recrystallized from distilled water (100 mL) to afford (4-methoxy-phenoxy)-acetic acid **12** (3.10 g, 34% yield) as white needles. Following the same method for the synthesis of **13**, monoaldehyde **15** (1.64 g, 92% yield) was prepared from **12** (0.91 g, 5 mmol) as a white solid: mp 89–91 °C; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 3.78 (s, 3H), 4.83 (s, 2H), 6.86–7.26 (m, 6H), 9.81 (s, 1H), 11.74 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.62, 35.74, 56.34, 67.06, 115.44, 116.77, 120.62, 123.61, 128.30, 141.05, 142.48, 152.49, 155.49, 159.86, 168.75, 196.98; HRMS (*m/z*): (M^--1) Calcd for $C_{20}H_{22}O_6$-H 357.1344, found 357.1351.

4.2.2. Synthesis of ligands. The ligands **16**, **17**, **18** and **19** were synthesized by the same method.

4.2.2.1. Typical procedure for the synthesis of (*R*,*R*)-crosslinked polymeric salen ligand 17. A mixture of **13** (1.5 mg, 0.0018 mmol) and **14** (300 mg, 0.52 mmol) in THF (10 mL) was added dropwise to a solution of (*R*,*R*)-1,2-diaminocyclohexane (59.4 mg, 0.52 mmol) in THF (10 mL) at reflux and maintained at reflux temperature for 2 h. After the reaction was complete (detected by TLC), the reaction solution was evaporated in vacuo. The residue was washed with hexane (40 mL×2), filtered, and dried to obtain the crosslinked polymeric salen ligand **17** (**13/14**=0.5:100) as a yellow solid in quantitative yield. GPC: M_p=38,518, M_w=39,575, M_n=8240, M_z=84,860, M_w/M_n=4.803.

4.2.2.2. Synthesis of the monomeric salen ligand 19. A solution of **15** (32.1 mg, 0.09 mmol) in THF (5 mL) was added dropwise to a solution of (*R*,*R*)-1,2-diaminocyclohexane (5.0 mg, 0.04 mmol) in THF (2 mL) at reflux for 2 h. After the reaction was complete (detected by TLC), the reaction solution was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (40 mL), and washed with saturated NaCl (20 mL×3). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and evaporated to obtain **19** as a yellow solid in quantitative yield: mp 70–72 °C; $[\alpha]_D^{25}=-191$ (*c* 0.1, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.37 (s, 18H); 1.40–1.94 (m, 8H); 3.33 (s, 2H); 3.78 (s, 6H); 4.77 (s, 4H); 6.80–7.22 (m, 12H); 8.23 (s, 2H); 13.81 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 24.83, 29.75, 33.67, 35.59, 56.34, 67.11, 72.89, 115.39, 116.78, 118.74, 121.74, 123.26, 139.50, 141.67, 152.61, 155.37, 159.01, 165.29, 168.82.

4.3. Asymmetric synthesis of *O*-acetylcyanohydrins from potassium cyanide, acetic anhydride and aldehydes catalyzed by polymeric salen-metal complexes

4.3.1. The typical procedure catalyzed by salen-Ti(IV). The synthesis of salen-Ti(IV) catalyst was carried out according to the reported procedure.[5] A solution of ligand (*R*)-**17** (**13/14**=0.5:100) (13.0 mg, 0.020 mmol) and titanium tetraisopropoxide (6.0 μL, 0.020 mmol) in dry CH_2Cl_2 (2 mL) was stirred at room temperature under argon for 2 h. H_2O (0.36 μL, 0.020 mmol) was added and the reaction mixture was stirred at room temperature for 3 h. The resulting yellow solution was concentrated in vacuo to leave complex as a yellow solid. The residue was dissolved in CH_2Cl_2 (2 mL) and benzaldehyde (100 μL, 0.98 mmol), H_2O (1.8 μL, 0.10 mmol), and ^{t}BuOH (90 μL, 0.94 mmol) added. The mixture was cooled to the indicated temperature and Ac_2O (360 μL, 3.81 mmol), KCN (0.24 g, 3.7 mmol) and CH_2Cl_2 (3 mL) added. After the reaction was completed (detected by TLC) or at the indicated time, the catalyst and solid residue were filtered through a plug of silica (hexane/ether=5:1). The conversion and enantiomeric excess were determined by GC analysis.

4.3.2. The typical procedure catalyzed by salen-V(V). The synthesis of (*S*)-**21** was carried out according to the reported procedure with slight modification.[24] The solution of linear polymeric salen ligand (*S*)-**20** (0.50 g, 1.05 mmol) in THF (20 mL) was added to vanadyl sulfate hydrate (0.50 g, 2.0 mmol) in hot EtOH (32 mL) under reflux in an argon atmosphere for 3 h and then stirred under an air atmosphere overnight. The solvent was evaporated and the residue stirred in water (100 mL) for 0.5 h, and filtered. The filtration residue was washed with water (50 mL×2), hexane (50 mL×2), and then dried to give the dark-green solid (*S*)-**21** (0.53 g, 73% yield). The molecular weight was calculated according to the literature,[24] which is the summation of a single salen unit, V=O, H_2O and ethylsulfonate anion. A mixture of the salen-V(V) (13.6 mg, 0.02 mmol), benzaldehyde (100 μL, 0.98 mmol), H_2O (1.8 μL, 0.10 mmol), and ^{t}BuOH (90 μL, 0.94 mmol) in CH_2Cl_2 (2 mL) was cooled to the indicated temperature and Ac_2O (360 μL, 3.81 mmol), KCN (0.24 g, 3.7 mmol) and CH_2Cl_2 (3 mL) added. After the reaction was complete (detected by TLC) or at the indicated time, the catalyst and solid residue were filtered through a plug of silica (hexane/ether=5:1). The conversion and enantiomeric excess was determined by GC analysis.

4.3.3. Recycling of the catalyst. The polymeric salen-metal complexes, which were partly soluble in the reaction system, could be precipitated from the reaction mixture by the addition of hexane. When the reaction was complete (detected by TLC), hexane (10 mL) was poured into the reaction solution, stirred for 10 min and then filtered. The filtrate was analyzed by GC and the catalyst precipitate was washed with H_2O thoroughly, and then washed with hexane (20 mL), dried in vacuo at 50 °C for 45 min and used in the next run.

Acknowledgements

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Development of β-hydroxyamide/titanium complexes for catalytic enantioselective silylcyanation of aldehydes

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Abstract—A highly enantioselective addition of trimethylsilylcyanide to aldehydes catalyzed by chiral titanium complexes is described. The chiral titanium complexes were prepared in situ from $Ti(O^iPr)_4$ and β-hydroxyamide ligands, that could easily be synthesized from ketopinic acid and C_2 symmetrical chiral diamines in a small number of steps.

1. Introduction

Enantiomerically pure cyanohydrins are versatile intermediates,[1,2] useful in the synthesis of a variety of natural and unnatural biologically active molecules owing to their potential for selective transformations given by the presence of a single asymmetric center bearing two reactive functionalities. The cyanohydrin functionality is also a component of commercially important compounds such as the pyrethroid insecticides cypermethrin and fluvalinate.[3,4] Due to their synthetic versatility for the production of pharmaceuticals and agrochemicals, there is currently significant interest in the asymmetric synthesis of cyanohydrins, especially by methods that utilize a chiral catalyst.

A wide range of catalysts are available for this reaction,[5–7] including enzymes, synthetic peptides, chiral Lewis bases, and chiral transition metal complexes. The structural modification of enzymes and peptides to improve their substrate compatibility is a long and difficult undertaking. In contrast, the modification of the structures of chiral transition metal complexes is a straightforward undertaking, thus offering the potential for this class of asymmetric catalysts to generate a desired cyanohydrin with high enantiomeric excess. Of the chiral metal complexes reported so far, titanium-based Lewis acids have attracted the most interest. The chiral ligand for titanium-based catalysts include TADDOLs,[8–10] BINOLs,[11–16] tartrate esters,[17,18] sulfoximines,[19,20] peptides,[21] Schiff bases[22–29] and others.[30–34] In each case, complexation of the ligand to a suitable titanium salt generated a chiral complex that induced the asymmetric addition of hydrogen and/or trimethylsilyl cyanide to aldehydes. Herein we describe an enantioselective silylcyanation of aldehydes catalyzed by $Ti(O^iPr)_4$ and a series of C_2 symmetrical chiral hydroxyamide ligands.

2. Results and discussion

At the outset, we synthesized the dihydroxyamide ligand **4a** and its diastereoisomer **4b** from ketopinic acid chloride **1**[35] and diamine **2** (Scheme 1). On treatment with optically pure (+)- or (−)-*trans*-1,2-diaminocyclohexane in dichloromethane in the presence of triethylamine, ketopinic acid chloride was converted to the *trans*-diketoamide **3a** or **3b**, respectively. Diketoamides **3a** and **3b** could also be obtained in pure form by reacting ketopinic acid chloride with *rac-trans*-1,2-diaminocyclohexane in the same fashion as above followed by separation of the resulting diastereomeric mixture by column chromatography on silica gel. Subsequent reduction of **3a** and **3b** using L-selectride® in tetrahydrofuran at −78 °C for 1 h and then at room temperature for 2 h gave **4a** and **4b** respectively, with the hydroxy group at the *exo*-position.[36] The absolute stereochemistry of ligand **4a** was further confirmed by X-ray crystallographic analysis.[34]

Ligand **4a** was found to be a useful chiral ligand for asymmetric induction. In conjunction with titanium tetraisopropoxide, ligand **4a** was shown to effect the

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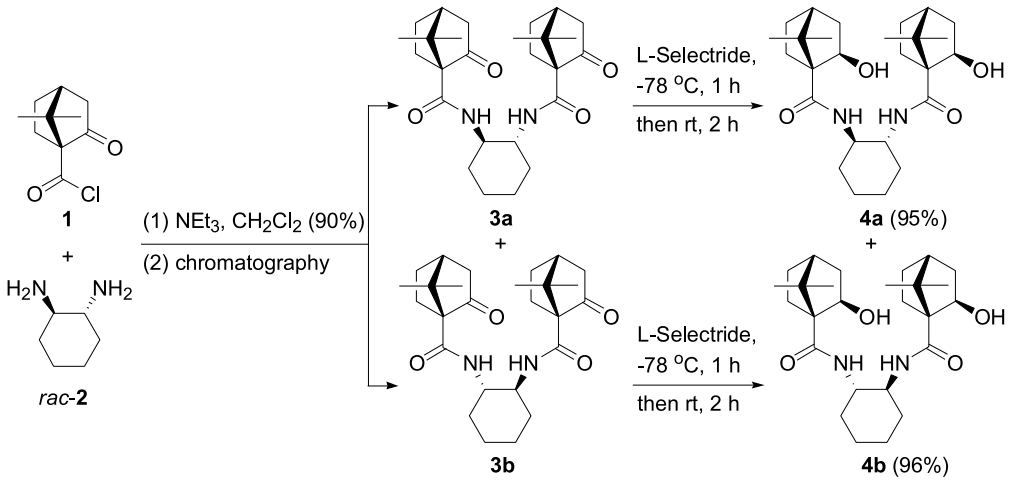


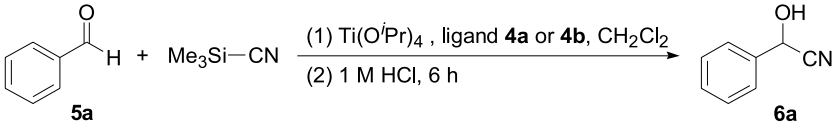
Scheme 1. Synthesis of ligand **4a** and **4b**.

enantioselective addition of trimethylsilyl cyanide to benzaldehyde **5a** (Table 1). Optimum results were obtained when the reaction was carried out at −78 °C in dichloromethane using the complex prepared from 16.5 mol% of ligand **4a** and 15 mol% of titanium tetraisopropoxide in the presence of 4 Å molecular sieves (entry 6). Under these conditions, the desired cyanohydrin was isolated in 79% yield and 94% ee after hydrolysis of the initial addition product with 1 M HCl at room temperature. At the same time, chiral ligand **4a** was recovered in 92% yield. Interestingly, in the absence of molecular sieves, the reaction was extremely slow and no sign of reaction was observed after 24 h at −30 °C (entry 2). This observation is in agreement with those reported previously by Narasaka.[9] It is also noteworthy that the degree of enantioselectivity appears to be proportional to the amount of the complex employed. Thus, when the amount of the catalyst was reduced by half, the enantioselectivity of the reaction was found to depreciate considerably (entries 4 and 5). The selectivity was also found to be temperature dependent as expected; when the reaction was carried out at −30 °C, mandelonitrile was obtained in 71% ee after hydrolysis (entry 5). This level of enantioselectivity was considerably inferior to that observed for the addition reaction carried out at −78 °C. Not surprisingly, however, the improved selectivity at −78 °C was at the expense of the reaction rate. Ligand **4b** was not a useful ligand when applied under the same reaction conditions; only 4% ee was observed in this case (entry 7).

To examine the efficacy of this catalytic process with regards to substrate structure, a variety of aromatic and aliphatic aldehydes were subjected to the conditions optimized in the case of benzaldehyde, employing **4a** with titanium tetraisopropoxide as the catalyst, and the results are summarized in Table 2. The asymmetric induction achieved with both aromatic (>94% ee) and aliphatic aldehydes (>87% ee) is quite high.

It was envisaged that replacement of the cyclohexane ring with two vicinal phenyl groups in the chiral diamide moiety of **4a** would result in a better catalyst which could provide greater facial selectivity in the silylcyanation of the aldehydes. A relatively bulky phenyl group would increase the energy difference between the two diastereomeric transition structure orientations, thereby enhancing the enantioselectivity. Chiral compound **9a** with the desired structural and stereochemical features was prepared starting

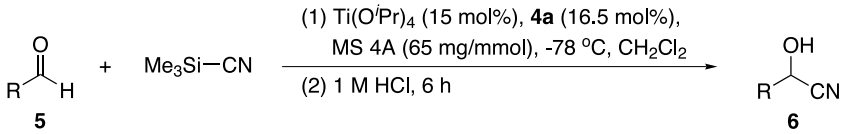
Table 1. Enantioselective addition of TMSCN to benzaldehyde catalyzed by ligand **4** and $Ti(O^iPr)_4$



Entry	Ligand (mol%)	$Ti(O^iPr)_4$ (mol%)	4 Å MS[a] (mg/mmol)	Temperature (°C)	Time (h)	Yield[b] (%)	ee[c] (%)	Configuration[d]
1	**4a** (22)	20	—	0	10	78	20	*S*
2	**4a** (22)	20	—	−30	24	0	—	—
3	**4a** (11)	10	65	30	6	78	48	*S*
4	**4a** (11)	10	65	−30	24	74	55	*S*
5	**4a** (22)	20	65	−30	18	75	71	*S*
6	**4a** (16.5)	15	65	−78	48	79	94	*S*
7	**4b** (16.5)	15	65	−78	48	77	4	*R*

[a] Powder, dried at 300 °C/0.1 mmHg for 24 h before use.
[b] Isolated yield.
[c] Determined by HPLC after being protected as a TBDMS ether.
[d] Absolute configurations were determined by comparison of optical rotations with literature values.

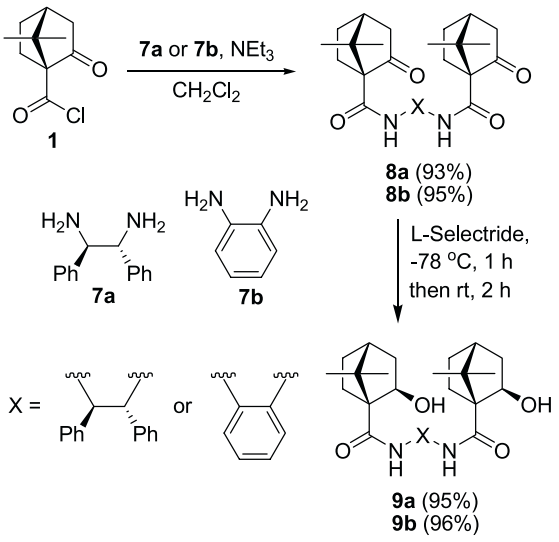
Table 2. Enantioselective addition of TMSCN to aldehydes catalyzed by **4a**/Ti(O^{i}Pr)$_4$ at −78 °C



5 **6**

Entry	Aldehyde	Time (h)	Yield[a] (%)	ee[b] (%)	Configuration[c]
1	Benzaldehyde (**5a**)	48	79	94	*S*
2	3-Phenoxybenzaldehyde (**5b**)	120	57 (76)	97	*S*
3	4-Methoxybenzaldehyde (**5c**)	120	53 (75)	97	*S*
4	2-Naphthaldehyde (**5d**)	120	76 (85)	96	*S*
5	(*E*)-Cinnamaldehyde (**5e**)	120	51 (80)	95	*S*
6	3-Phenylpropionaldehyde (**5f**)	120	62 (78)	98	*S*
7	2-Methylbenzaldehyde (**5g**)	120	68 (85)	97	*S*
8	Cyclohexanecarboxaldehyde (**5h**)	60	94	87	*S*
9	Valeraldehyde (**5i**)	30	96	89	*S*

[a] Numbers in parentheses are percent conversions.
[b] Determined by HPLC after being protected as a TBDMS ether (entry 1) or acetate (entries 2–9).
[c] Absolute configurations were determined by comparison of optical rotations with literature values.



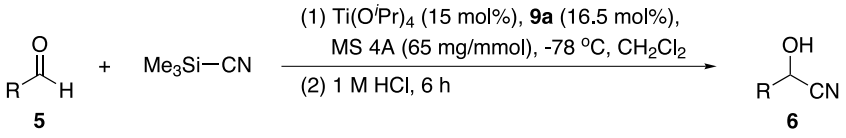
Scheme 2. Synthesis of ligands **9a** and **9b**.

from (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine **7a** in the same manner as described above for ligand **4a** (Scheme 2).

Excellent results were again obtained when the reaction was carried out under the optimum conditions (Table 3). The desired cyanohydrin was isolated with high enantioselectivity using both aromatic (>93% ee) and aliphatic aldehydes (>97% ee) as substrates. Compared to our former ligand **4a**, there is a pronounced enhancement of enantioselectivity in the reaction of aliphatic aldehydes (entries 8 and 9). At the same time, the chiral ligand **9a** was also recovered in high yield.

To ascertain the effect of the chirality of the diamide moiety of **9a** on the extent of enantioselectivity, compound **9b** lacking chirality in the diamide functionality was prepared from 1,2-phenylenediamine **7b** following the same procedure used for **9a**. Ligand **9b** was then employed as a constituent of a catalyst for the silylcyanation of benzaldehyde (Table 4). As expected, the enantioselectivity was significantly lower with a maximum of 61% ee under optimum reaction condition (entry 4). Apparently, chirality in the diamide moiety facilitates the higher

Table 3. Enantioselective addition of TMSCN to aldehydes catalyzed by **9a**/Ti(O^{i}Pr)$_4$ at −78 °C

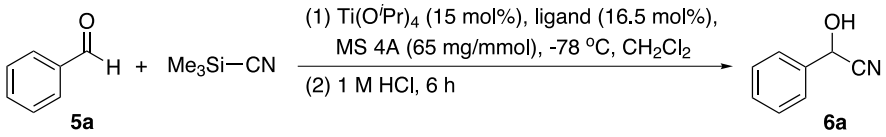


5 **6**

Entry	Aldehyde	Time (h)	Yield[a] (%)	ee[b] (%)	Configuration[c]
1	Benzaldehyde (**5a**)	48	87	93	*S*
2	3-Phenoxybenzaldehyde (**5b**)	120	54 (78)	95	*S*
3	4-Methoxybenzaldehyde (**5c**)	120	47 (72)	99	*S*
4	2-Naphthaldehyde (**5d**)	120	67 (78)	99	*S*
5	(*E*)-Cinnamaldehyde (**5e**)	120	49 (74)	97	*S*
6	3-Phenylpropionaldehyde (**5f**)	120	61 (73)	97	*S*
7	2-Methylbenzaldehyde (**5g**)	120	56 (80)	94	*S*
8	Cyclohexanecarboxaldehyde (**5h**)	48	90	>99	*S*
9	Valeraldehyde (**5i**)	36	92	97	*S*

[a] Numbers in parentheses are percent conversions.
[b] Determined by HPLC after being protected as a TBDMS ether (entry 1) or acetate (entries 2–9).
[c] Absolute configurations were determined by comparison of optical rotations with literature values.

Table 4. Effect of the chirality of ligands on the extent of enantioselectivity



Entry	Ligand	Time (h)	Yield[a] (%)	ee[b] (%)	Configuration[c]
1	**4a**	48	79	94	*S*
2	**4b**	48	77	4	*R*
3	**9a**	48	87	93	*S*
4	**9b**	60	89	61	*S*
5[d]	**3a**	36	73	0	—
6[d,e]	**10**	36	70	0	—
7[d,e]	**11**	36	61	0	—
8[d,e]	**12**	36	72	0	—
9[d]	**13**	24	76	13	*S*
10[d]	**14**	24	73	4	*S*

[a] Isolated yield.
[b] Determined by HPLC after being protected as a TBDMS ether.
[c] Absolute configurations were determined by comparison of optical rotations with literature values.
[d] Reactions were performed at −30 °C.
[e] 33 mol% of ligand was used.

enantioselectivity. Compound **3a** which bears two ketone functionalities instead of the two hydroxy groups of **4a** was also tested as a ligand for the silylcyanation of benzaldehyde. To our surprise, no enantioselectivity was found when ketoamide **3a** was used as the chiral ligand in this reaction (entry 5). We then studied cyclohexanediamides **10**,[37] **11**[38] and **12**[39] as chiral ligands in the same reaction (Fig. 1), but again there was no enantioselectivity under these conditions (entries 6–8). Such results suggested that the hydroxy groups of the chiral ligands play an important role in the construction of the chiral catalysts. A diamide moiety alone might not be efficient enough to coordinate to the titanium(IV) ion, thus no efficient chiral catalyst was generated and the silylcyanation reaction proceeded via a non-stereoselective route.

To further study the influence of ligand structure on the enantioselectivity of the silylcyanation of aldehydes, α-hydroxyamides **13** and **14** were prepared from (1*R*,2*R*)-1,2-diaminocyclohexane and (*R*)- or (*S*)-mandelic acid, respectively according to the literature procedure.[40] Enhancement of reactivity was observed when the titanium complex of either α-hydroxyamide **13** or **14** was used as catalyst for the reaction (entries 9–10). However, low enantioselectivities were obtained in both cases. The low enantioselectivity might result from the sterically less hindered phenyl group when compared to the bornane skeleton of ligands **4a** and **9a** and from the nature of the α- or β-hydroxyamides. More efforts will be needed to understand the nature of the catalysts.

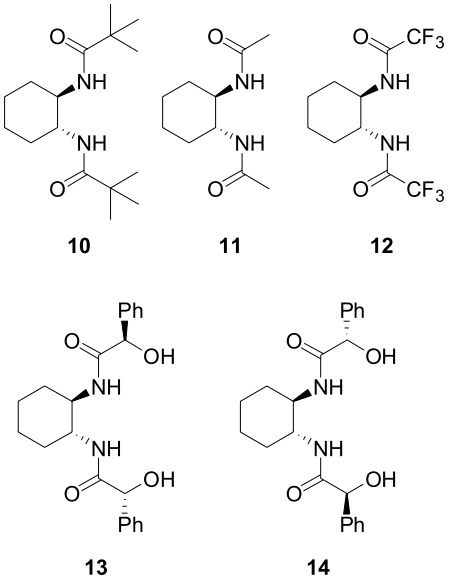


Figure 1.

3. Conclusions

In conclusion, an efficient catalyst for the asymmetric silylcyanation of both aromatic and aliphatic aldehydes with excellent enantioselectivity has been developed. The high degree of enantioselectivity coupled with the high stability and recoverability of chiral component **9a** of the catalyst constitutes a major improvement on existing methods.

4. Experimental

4.1. General

All melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were measured on Varian GEMINI-300, Varian UNITY-400 and Bruker AC-300 MHz NMR spectrometers. HPLC analyses were performed on a HITACHI L-6200 chromatograph fitted with a L-4200 UV detector and a Waters 410 RI detector. Chiracel OD column was purchased from Daicel Chemical Industries, Ltd. Optical rotations were measured with a DIP-1000 polarimeter.

4.2. Materials

CH_2Cl_2 was distilled from CaH_2. THF was distilled from

potassium. $Ti(O^iPr)_4$ and TMSCN were purchased from Aldrich.

4.3. Procedure for the synthesis of 3a and 3b

Ketopinic acid chloride (**1**) (20.1 g, 100 mmol) in CH_2Cl_2 (50 mL) was added to a stirred solution of triethylamine (7.2 g, 100 mmol) and racemic *trans*-1,2-diamino-cyclohexane (**2**) (5.7 g, 50 mmol) in CH_2Cl_2 (50 mL) at 0 °C over a 1 h period. The reaction was then allowed to come to room temperature and then stirred for an additional 1 h period. The reaction was then quenched by pouring into water (200 mL) and extracted with CH_2Cl_2. The organic phase was washed with brine, dried with Na_2SO_4, followed by evaporation and chromatographic separation (EtOAc/hexane=1/2) to give **3a** (9.9 g) and **3b** (9.8 g) (90%).

4.3.1. (1*R*,2*R*)-1,2-*N*,*N*′-Bis[(1*S*,4*R*)-7,7,-dimethyl-2-oxo-bicyclo[2.2.1]heptylcarboxyl]cyclohexyldiamine (3a). Mp 153.5–154.3 °C; $[\alpha]_D^{26}=+51.5$ (*c* 1.25, $CHCl_3$); IR (KBr) 3324, 1733, 1659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 6H), 1.18 (s, 6H), 1.20–1.39 (m, 4H), 1.47–1.54 (m, 2H), 1.65–1.70 (brs, 4H), 1.90 (d, $J=20$ Hz, 2H), 2.01–2.10 (m, 6H), 2.40–2.49 (m, 4H), 3.76–3.81 (m, 2H), 7.43 (d, $J=8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.9 (C), 169.0 (C), 64.7 (C), 52.3 (CH), 49.7 (C), 43.6 (CH_2), 43.2 (CH), 32.6 (CH_2), 27.9 (CH_2), 27.4 (CH_2), 24.5 (CH_2), 20.7 (CH_3), 20.4 (CH_3); HRMS (M^+) calcd for $C_{26}H_{38}O_4N_2$ 442.2832, found 442.2846.

4.3.2. (1*S*,2*S*)-1,2-*N*,*N*′-Bis[(1*S*,4*R*)-7,7,-dimethyl-2-oxo-bicyclo[2.2.1]heptylcarboxyl]cyclohexyldiamine (3b). Mp 117.3–117.9 °C; $[\alpha]_D^{26}=+55.5$ (*c* 1.5, $CHCl_3$); IR (KBr) 3406, 3343, 3309, 1750, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 6H), 1.18 (s, 6H), 1.20–1.41 (m, 4H), 1.53–1.69 (m, 6H), 1.89 (d, $J=20$ Hz, 2H), 2.01 (t, $J=4$ Hz, 2H), 2.02–2.15 (m, 4H), 2.38–2.46 (m, 4H), 3.75 (brs, 2H), 7.63 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.0 (C), 169.4 (C), 64.7 (C), 52.3 (CH), 49.9 (C), 43.7 (CH_2), 43.2 (CH), 32.1 (CH_2), 28.3 (CH_2), 27.5 (CH_2), 24.3 (CH_2), 20.7 (CH_3), 20.5 (CH_3); HRMS (M^+) calcd for $C_{26}H_{38}O_4N_2$ 442.2832, found 442.2817.

4.4. Procedure for the synthesis of 4a and 4b

To a solution of **3a** or **3b** (4 mmol) in THF (5 mL) at −78 °C was added 1 M L-selectride® in THF (18.0 mL) dropwise. The reaction mixture was stirred at −78 °C for 1 h followed by 2 h at room temperature, then cooled to 0 °C and quenched by the successive addition of H_2O (4.0 mL), EtOH (12 mL), 3 M aq. NaOH (16 mL), followed by the dropwise addition of 30% aq. H_2O_2 (12 mL) over a 30 min period. The aqueous phase was saturated with K_2CO_3 and extracted with CH_2Cl_2. The organic phase was dried with Na_2SO_4, and filtered. Evaporation of solvent followed by crystallization (EtOAc/hexane=1/5) from the organic phase gave **4a** (95%) or **4b** (96%).

4.4.1. (1*R*,2*R*)-1,2-*N*,*N*′-Bis[(1*S*,2*R*,4*R*)-7,7,-dimethyl-2-hydroxy-bicyclo[2.2.1]heptylcarboxyl]cyclohexyl-diamine (4a). Mp 208.2–208.3 °C; $[\alpha]_D^{26}=-55.3$ (*c* 1.0, $CHCl_3$); IR (KBr) 3328, 1629 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.85 (s, 6H), 0.90–1.02 (m, 4H), 1.14 (s, 6H), 1.16–1.40 (m, 4H), 1.67–1.95 (m, 12H), 2.30–2.38 (m, 2H), 3.70–3.76 (m, 4H), 5.20 (d, $J=6$ Hz, 2H), 6.89 (d, $J=9$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7 (C), 77.4 (CH), 58.4 (C), 53.4 (CH), 49.5 (CH), 45.5 (CH), 41.0 (CH_2), 32.4 (CH_2), 29.0 (CH_2), 26.3 (CH_2), 24.9 (CH_2), 21.0 (CH_3), 20.9 (CH_3); HRMS (M^+) calcd for $C_{26}H_{42}O_4N_2$ 446.3145, found 446.3136.

4.4.2. (1*S*,2*S*)-1,2-*N*,*N*′-Bis[(1*S*,2*R*,4*R*)-7,7,-dimethyl-2-hydroxy-bicyclo[2.2.1]heptylcarboxyl]cyclohexyl-diamine (4b). Mp 224.8–225.4 °C; $[\alpha]_D^{26}=-17.8$ (*c* 1.0, $CHCl_3$); IR (KBr) 3367, 3319, 1626 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (s, 6H), 1.21 (s, 6H), 1.09–1.40 (m, 6H), 1.60–1.93 (m, 14H), 2.04 (d, $J=12$ Hz, 2H), 3.72 (brs, 2H), 3.96 (dt, $J=3$, 3 Hz, 2H), 5.14 (d, $J=1.5$ Hz, 2H), 6.71 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8 (C), 78.0 (C), 56.7 (C), 53.3 (CH), 49.8 (CH), 45.6 (CH), 40.8 (CH_2), 32.5 (CH_2), 30.2 (CH_2), 27.4 (CH_2), 24.6 (CH_2), 21.8 (CH_3), 20.8 (CH_3); HRMS (M^+) calcd for $C_{26}H_{42}O_4N_2$ 446.3145, found 446.3115.

4.5. Procedure for the synthesis of 8a and 8b

Ketopinic acid chloride (**1**) (20.1 g, 100 mmol) in CH_2Cl_2 (200 mL) was added to a stirred solution of triethylamine (7.2 g, 100 mmol) and the appropriate diamine (**7a** or **7b**) (50 mmol) in CH_2Cl_2 (50 mL) at 0 °C over a 1 h period. The reaction was then allowed to warm to room temperature and then stirred for an additional 1 h period. The reaction was then quenched by pouring into water (100 mL) and extracted with dichloromethane (2×200 mL). The organic phase was washed with brine (2×200 mL), dried (Na_2SO_4) and concentrated. The residue was purified by passing through a silica column eluting with EtOAc/hexane (1/3 for **8a** and 1/2 for **8b**) to provide **8a** (93%) or **8b** (95%) as a white solid.

4.5.1. (1*R*,2*R*)-1,2-*N*,*N*′-Bis[(1*S*,4*R*)-7,7,-dimethyl-2-oxo-bicyclo[2.2.1]heptylcarboxyl]diphenylethylenediamine (8a). Mp 243.5–244.3 °C; $[\alpha]_D^{24}=+39.9$ (*c* 1.46, $CHCl_3$); IR (KBr) 3346, 1740, 1664, 1649 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.83 (s, 6H), 1.11 (s, 6H), 1.34–1.35 (m, 2H), 1.48–1.55 (m, 2H), 1.92–2.08 (m, 6H), 2.36–2.51 (m, 4H), 5.41 (dd, $J=2.0$, 6.0 Hz, 2H), 7.05–7.08 (m, 4H), 7.12–7.19 (m, 6H), 8.41 (d, $J=6.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.9 (C), 168.8 (C), 138.8 (C), 127.9 (2CH), 127.1 (3CH), 64.3 (C), 57.2 (CH), 49.9 (C), 43.5 (CH_2), 43.1 (CH), 28.3 (CH_2), 27.5 (CH_2), 20.6 (CH_3), 20.1 (CH_3); HRMS (M^+) calcd for $C_{34}H_{41}O_4N_2$: 541.2988($M+1$), found 541.3066.

4.5.2. 1,2-*N*,*N*′-Bis[(1*S*,4*R*)-7,7,-dimethyl-2-oxo-bicyclo[2.2.1]heptylcarboxyl]phenyldiamine (8b). Mp 136.3–136.8 °C; $[\alpha]_D^{26}=+29.0$ (*c* 1.0, $CHCl_3$); IR (KBr) 3282, 2968, 1730, 1683, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (s, 6H), 1.28 (s, 6H), 1.40–1.49 (m, 2H), 1.74–1.83 (m, 2H), 1.96 (s, 1H), 2.02 (s, 1H), 2.07–2.18 (m, 4H), 2.50–2.65 (m, 4H), 7.12–7.15 (m, 2H), 7.69–7.72 (m, 2H), 9.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.0 (C), 168.2 (C), 129.9 (C), 125.6 (CH), 124.8 (CH), 65.2 (C), 50.4 (C), 43.7 (CH_2), 43.4 (CH), 28.8 (CH_2), 27.7 (CH_2), 20.9 (CH_3), 20.5 (CH_3); HRMS (M^+) calcd for $C_{26}H_{32}N_2O_4$: 436.2362, found 436.2358.

4.6. Procedure for the synthesis of 9a and 9b

To a solution of **8a** or **8b** (4 mmol) in THF (5 mL) at −78 °C was added 1 M L-selectride® in THF (18.0 mL) dropwise. The reaction mixture was stirred at −78 °C for 1 h, followed by 2 h at room temperature, then cooled to 0 °C and quenched by the successive addition of H_2O (4.0 mL), EtOH (12 mL), 3 M aq. NaOH (16 mL), followed by the dropwise addition of 30% aq. H_2O_2 (12 mL) over a 30 min period. The aqueous phase was saturated with K_2CO_3 and extracted with CH_2Cl_2. The organic phase was dried with Na_2SO_4, and filtered. Evaporation of solvent followed by crystallization (EtOAc/hexane = 1/5) from the organic phase gave **9a** (95%) or **9b** (96%).

4.6.1. (1*R*,2*R*)-1,2-*N*,*N*′-Bis[(1*S*,2*R*,4*R*)-7,7,-dimethyl-2-hydroxy-bicyclo[2.2.1]heptylcarboxyl]diphenylethylenediamine (9a). Mp 259.7–260.5 °C; $[\alpha]_D^{24} = -222.8$ (*c* 1.00, $CHCl_3$); IR (KBr) 3366, 2936, 1642, 1545, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.78 (s, 6H), 0.94 (s, 6H), 1.02–1.10 (m, 4H), 1.68–1.75 (m, 4H), 1.84–1.97 (m, 4H), 2.38–2.49 (m, 2H), 3.86–3.89 (m, 2H), 5.27 (dd, J = 7.2, 2.6 Hz, 2H), 5.38–5.40 (m, 2H), 7.00–7.03 (m, 4H), 7.12–7.17 (m, 6H), 7.86 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5 (C), 137.9 (C), 128.4 (2CH), 127.5 (CH), 126.9 (2CH), 77.2 (CH), 59.2 (CH), 58.3 (C), 49.9 (C), 45.2 (CH), 40.9 (CH_2), 28.8 (CH_2), 26.3 (CH_2), 20.6 (CH_3), 20.5 (CH_3); HRMS calcd for $C_{34}H_{44}O_4N_2$: 544.3301, found 544.3301.

4.6.2. 1,2-*N*,*N*′-Bis[(1*S*,2*R*,4*R*)-7,7,-dimethyl-2-hydroxy-bicyclo[2.2.1]heptylcarboxyl]phenyldiamine (9b). Mp 121.1–121.3 °C; $[\alpha]_D^{26} = +4.68$ (*c* 0.52, $CHCl_3$); IR (KBr) 3422, 2940, 1659, 1596 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (s, 6H), 1.08–1.14 (m, 2H), 1.22–1.26 (m, 2H), 1.28 (s, 6H), 1.80–2.03 (m, 8H), 2.28–2.35 (m, 2H), 4.06–4.08 (m, 2H), 4.49 (br, 2H), 7.19–7.21 (m, 2H), 7.42–7.45 (m, 2H), 9.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5 (C), 130.5 (C), 126.0 (CH), 125.6 (CH), 77.3 (CH), 58.0 (C), 50.5 (C), 45.6 (CH), 41.7 (CH_2), 30.0 (CH_2), 27.2 (CH_2), 21.5 (CH_3), 20.7 (CH_3); HRMS calcd for $C_{26}H_{36}N_2O_4$: 440.2675, found 440.2666.

4.7. General procedure for enantioselective trimethylsilylcyanation of aldehydes

To a stirred solution of compound **9a** (0.180 g, 0.33 mmol) and 4 Å molecular sieves (powder, 130 mg) in dichloromethane (5 mL) was added titanium tetraisopropoxide (0.09 mL, 0.3 mmol) under Ar at room temperature and the mixture was stirred for 1 h. Trimethylsilyl cyanide (0.45 mL, 3.5 mmol) was added to the reaction mixture and stirred for an additional 0.5 h. Then, the reaction mixture was cooled to −78 °C and aldehyde **5** (2 mmol) was added to the reaction mixture. The disappearance of the aldehyde was monitored by thin layer chromatography (EtOAc/hexane = 1/5). The reaction mixture was quenched with 1 M HCl (20 mL) and stirred vigorously at room temperature for 6 h. After being filtered, the mixture was extracted with dichloromethane (5×5 mL). The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$, then concentrated in vacuo. The residue was distilled under reduced pressure (100 °C/0.3 mmHg) or purified by column chromatography to afford the corresponding (*S*)-cyanohydrin **6**. Compound **9a** was recovered in 80–92% yield through column chromatography purification of the remaining residue.

4.8. Determination of enantiomeric excess (ee) of the cyanohydrin

Method A (*for 2-hydroxy-2-phenylacetonitrile*, **6a**). The ee of the cyanohydrin was determined by HPLC analysis of the corresponding TBDMS ether (detected by UV detector at 254 nm). The required TBDMS ether was prepared by the following procedure:[27] To a CH_2Cl_2 (2 mL) solution of cyanohydrin (10 mg) was added TBDMSOTf (30 μL) and 2,6-lutidine (30 μL) at 0 °C. The mixture was stirred at room temperature for 1 h, poured into water (5 mL) and extracted with CH_2Cl_2 (2×5 mL). The combined extracts were washed with brine (2×5 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatographic separation on a silica gel column (EtOAc/hexane = 1/30) to afford the corresponding TBDMS ether.

Method B (*for other cyanohydrins*, **6b–i**). The ee for the other cyanohydrins was determined by HPLC analysis of the corresponding cyanohydrin acetate (detected by UV detector at 254 nm for **6b–g** and RI detector for **6h–i**) prepared by the following procedure:[41] To a $CHCl_3$ (2 mL) solution of cyanohydrin (10 mg) was added acetyl chloride (0.5 mL) and pyridine (0.1 mL) at 23 °C. The mixture was stirred at 23 °C for 1 h after which it was poured into water (5 mL) and extracted with chloroform (2×5 mL). The combined extracts were washed with brine (2×10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/30) to afford the corresponding cyanohydrin acetate.

4.8.1. 2-Hydroxy-2-phenylacetonitrile (6a). Crude product was purified by bulb-to-bulb distillation (100 °C/0.3 mmHg) to give *S*-enriched product (87%); IR (neat) 3430, 2260, 1700, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.90 (brs, 1H), 5.55 (s, 1H), 7.4–7.6 (m, 5H). The product was determined as 93% ee by HPLC analysis of its *tert*-butyl dimethylsilylether. The t_R of the *R*-isomer is 6.12 min and that of the *S* isomer is 8.02 min [hexane/isopropanol (100/0.25), 1.0 mL/min].

4.8.2. 2-Hydroxy-2-(3-phenoxyphenyl)acetonitrile (6b). Crude product was purified by column chromatography (EtOAc/acetonitrile/hexane = 2/1/6) to give *S*-enriched product [54% (78% conversion)]; IR (neat) 3430, 3070, 2250, 1690, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.6 (brs, 1H), 5.47 (s, 1H), 7.0–7.4 (m, 9H). The product was determined as 95% ee by HPLC analysis of its acetate. The t_R of the *S*-isomer is 18.26 min and that of the *R*-isomer is 26.12 min [hexane/isopropanol (97.5/2.5), 1.0 mL/min].

4.8.3. 2-Hydroxy-2-(4-methoxyphenyl)acetonitrile (6c). Crude product was purified by column chromatography (EtOAc/acetonitrile/hexane = 2/1/6) to give *S*-enriched product [47% (72% conversion)]; IR (neat) 3430, 3010, 2250, 1710, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.7 (brs, 1H), 3.84 (s, 3H), 5.49 (s, 1H), 6.96 (d, J = 8.5 Hz, 2H), 7.46

(d, J=8.5 Hz, 2H). The product was determined as 99% ee by HPLC analysis of its acetate. The t_R of the *S*-isomer is 12.12 min and that of the *R*-isomer is 10.66 min [hexane/isopropanol (95/5), 1.0 mL/min].

4.8.4. 2-Hydroxy-2-naphthylacetonitrile (6d). Crude product was purified by column chromatography (EtOAc/acetonitrile/hexane=2/1/6) to give *S*-enriched product [67% (78% conversion)]; IR (neat) 3480, 3060, 2250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.01 (brs, 1H), 5.70 (s, 1H), 7.50–7.60 (m, 3H), 7.80–8.00 (m, 3H), 8.05 (s, 1H). The product was determined as 99% ee by HPLC analysis of its acetate. The t_R of the *S*-isomer is 12.32 min and that of the *R*-isomer is 14.62 min [hexane/isopropanol/acetonitrile (40/1/1), 1.0 mL/min].

4.8.5. (*E*)-2-Hydroxy-4-phenyl-3-butenenitrile (6e). Crude product was purified by column chromatography (EtOAc/acetonitrile/hexane=2/1/6) to give *S*-enriched product [49% (74% conversion)]; IR (neat) 3370, 3030, 2250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.7 (brs, 1H), 5.16 (dd, J=5.7, 1.1 Hz, 1H), 6.25 (dd, J=15.8, 5.7 Hz, 1H), 6.93 (dd, J=15.8, 1.1 Hz, 1H), 7.3–7.5 (m, 5H). The product was determined as 97% ee by HPLC analysis of its acetate. The t_R of the *S*-isomer is 14.56 min and that of the *R*-isomer is 18.79 min [hexane/isopropanol/acetonitrile (40/1/1), 1.0 mL/min].

4.8.6. 2-Hydroxy-4-phenylbutanenitrile (6f). Crude product was purified by column chromatography (EtOAc/acetonitrile/hexane=2/1/6) to give *S*-enriched product [61% (73% conversion)]; IR (neat) 3430, 3050, 2250, 1720, 1610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.0–2.20 (m, 2H), 2.80–2.90 (m, 2H), 4.10 (brs, 1H), 4.43 (t, J= 6.7 Hz, 1H), 7.20–7.40 (m, 5H). The product was determined as 97% ee by HPLC analysis of its acetate. The t_R of the *S*-isomer is 13.18 min and that of the *R*-isomer is 17.36 min [hexane/isopropanol/acetonitrile (40/1/1), 1.0 mL/min].

4.8.7. 2-Hydroxy-2-(2-methylphenyl)acetonitrile (6g). Crude product was purified by column chromatography (EtOAc/acetonitrile/hexane=2/1/6) to give *S*-enriched product [56% (80% conversion)]; IR (neat) 3400, 3070, 2250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 2.80 (brs, 1H), 5.65 (s, 1H), 7.21–7.32 (m, 3H), 7.59 (d, J= 6 Hz, 1H). The product was determined as 94% ee by HPLC analysis of its acetate. The t_R of the *S*-isomer is 19.14 min and that of the *R*-isomer is 21.64 min [hexane/EtOAc (60/1), 1.0 mL/min].

4.8.8. 2-Cyclohexyl-2-hydroxyacetonitrile (6h). Crude product was purified by bulb-to-bulb distillation (120 °C/0.6 mmHg) to give *S*-enriched product (90%); IR (neat) 3450, 2250, 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.0–1.40 (m, 5H), 1.60–2.0 (m, 6H), 2.80 (brs, 1H), 4.27 (d, J=6.1 Hz, 1H). The product was determined as >99% ee by HPLC analysis of its acetate. The t_R of the *S*-isomer is 7.32 min and that of the *R*-isomer is 6.62 min [hexane/isopropanol (60/1), 1.0 mL/min].

4.8.9. 2-Hydroxyhexanenitrile (6i). Crude product was purified by bulb-to-bulb distillation (80 °C/0.6 mmHg) to give *S*-enriched product (92%); IR 3430, 2250, 1630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, J=6.0 Hz, 3H), 1.32–1.51 (m, 4H), 1.78–1.86 (m, 2H), 2.92 (brs, 1H), 4.45 (t, J=6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.2 (C), 61.0 (CH), 34.6 (CH_2), 26.5 (CH_2), 21.9 (CH_2), 13.6 (CH_3); HRMS (M^+) calcd for $C_6H_{11}NO$: 113.0841, found 113.0837. The product was determined as 97% ee by HPLC analysis of its acetate. The t_R of the *S*-isomer is 7.09 min and that of the *R*-isomer is 6.45 min [hexane/isopropanol (60/1), 1.0 mL/min].

Acknowledgements

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Enantioselective addition of trimethylsilyl cyanide to aldehydes catalysed by bifunctional BINOLAM-AlCl versus monofunctional BINOL-AlCl complexes

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Abstract—A highly enantioselective cyanation of aldehydes takes place by using a bifunctional catalyst derived from 3,3′-bis(diethylaminomethyl) substituted binaphthol (BINOLAM) and dimethylaluminium chloride. The addition is of wide scope and runs best in toluene at temperatures ranging from −20 to −40 °C, in the presence of 4 Å MS and triphenylphosphine oxide as additives. The (*R*)- or (*S*)-cyanohydrins result when using (*S*)- or (*R*)-BINOLAM-AlCl complexes, respectively. The valuable ligand can be recovered by simple extractive work-up and recycled without loss of efficiency (both in terms of chemical and stereochemical yields). This methodology is applied to the Shibasaki synthesis of epothilone A. All the evidence available for the BINOLAM-AlCl enantioselective addition of TMSCN to aldehydes call for the intervention of a hydrocyanation reaction, addition of a catalytic amount of hydrogen cyanide, generated in situ, to an aldehyde, followed by *O*-silylation. In order to determine the role of the basic amino groups of BINOLAM, comparative studies are carried out with the monofunctional 1,1′-binaphthol-derived complex BINOL-AlCl.

1. Introduction

The preparation of non-racemic cyanohydrins is an important goal for current asymmetric organic synthesis.[1] The reason for this is clear-cut: enantiomerically pure cyanohydrins are important building blocks for the synthesis of several 1,2-bifunctional products such as α-hydroxycarbonyl compounds, β-amino alcohols, α-amino acids and new materials.[1,2] Ten years ago, cyclic peptides and enzymes were overwhelmingly used in the synthesis of non-racemic cyanohydrins rather than chiral metal complexes,[2d] but this order has nowadays been completely reversed.[2a] Many metal complexes have been successfully employed as Lewis acids for the addition of HCN or TMSCN to aldehydes and ketones,[2] as for example, magnesium, zirconium, titanium, aluminium, yttrium, lanthanum, samarium, vanadium and gadolinium complexes containing mono- or polydentate ligands.[2] Nakai et al.[3] were the first to employ monofunctional BINOL-metal complexes (titanium in particular) for the enantioselective cyanosilylation of aldehydes, but only observed modest enantioselectivity for aliphatic aldehydes. Fortunately though, a new generation of bifunctional BINOL-derived complexes[2a,4] emerged as valuable synthetic tools. These catalysts possess functional groupings to simultaneously bind a basic substrate and an acidic reactant in a proper manner so that rate, among other factors, is favourably affected.[2a,4] In particular, Shibasaki et al. reported a series of bifunctional Lewis Acid-Lewis Base catalysts (LALB) **1** (Fig. 1) derived from BINOL as the chiral scaffold where an aluminium atom of a bisaryloxyaluminium chloride moiety functions as the Lewis acid centre (LA) and a suitable functionality at the 3,3′ positions works as the Lewis base centre (LB).[5] Specifically, the phosphine oxide-derived catalysts **1** (R=H, X=$POAr_2$) were found to be very efficient for the asymmetric cyanosilylation of aldehydes,[6] imines[7] (Strecker synthesis) and isoquinolines[8] (Reissert-type reaction). As an added-value goal, a polymer-supported catalyst **1** [R=linker-(polymer, X=$P(O)Ph_2$] was eventually developed in order to recover and recycle the chiral ligand, however with some loss of enantioselectivity.[7]

Recently, we have developed a bifunctional Lewis Acid-Brönsted Base (LABB) aluminium complex, namely (*S*)- or (*R*)-BINOLAM-AlCl **3**, which retains the C_2-symmetric BINOL scaffold but possesses two diethylaminomethyl arms, instead of the phosphine oxide ones, presumably working as Brönsted bases.[9–11] BINOLAM-AlCl complexes

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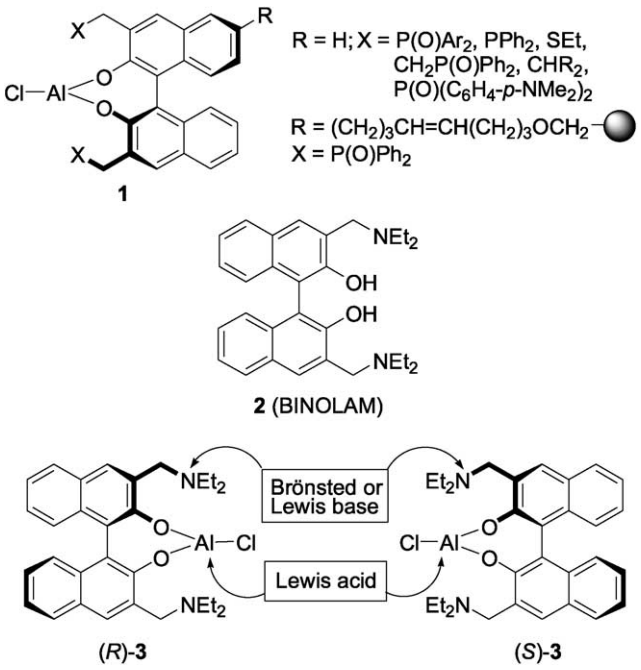
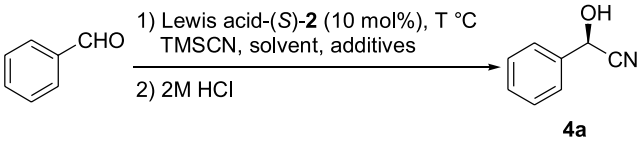


Figure 1.

have been proved to be versatile bifunctional catalysts in the asymmetric synthesis of cyanohydrins,[9] *O*-methoxycarbonyl cyanohydrins[10] and *O*-phosphorylated cyanohydrins[11] from aldehydes, in excellent chemical yields and very high enantiomeric ratios using TMSCN, $CNCO_2Me$ and $CNPO(OEt)_2$ as cyanation agents, respectively. In continuing with our studies on the synthetic applications of chiral (*S*)- and (*R*)-BINOLAM-AlCl complexes, we describe in this article a comprehensive study of these catalysts for the enantioselective synthesis of cyanohydrins upon reaction of aldehydes with TMSCN.[9] Also, as a reference point, this analysis includes the study of the enantioselective catalysis promoted by the analogous monofunctional BINOL-AlCl catalyst.

2. Results and discussion

The optimisation of the variables of the reaction between benzaldehyde and commercial TMSCN was started by examining a number of selected Lewis acids and additives (Scheme 1 and Table 1). For this purpose, all catalysts were generated in situ by mixing a weighed amount of the ligand **2**[12] (BINOLAM, 10 mol%, relative to aldehyde) with the appropriate Lewis acid (10 mol%), at room temperature for 1 h, in the selected solvent. This operation was then followed by the addition of benzaldehyde and commercial TMSCN (300 mol%) in one portion, at 0 °C, in the presence of 4 Å molecular sieves (MS) (200 mg/mmol of aldehyde). The reaction was monitored by ^{1}HNMR spectroscopy and, at the end, after acidic extractive workup with 2 M hydrochloric acid (more advantageous than neutral workup which led to mixtures of partially silylated cyanohydrins), we isolated the pure cyanohydrin **4a**. Its enantiomeric purity, and those of other cyanohydrins **4** was checked by HPLC (Chiracel OD-H, Chiralpack AD and AS) on appropriate derivatives (see Section 3 for details). The acidic aqueous phase was treated with a buffered solution of 1 M ammonia/1 M ammonium chloride until the pH turned basic. Upon extraction with ethyl acetate we recovered ligand **2** (BINOLAM) in almost quantitative yield (>95%) and purity (>98% according to its optical rotation).



Scheme 1.

Initial experiments with titanium(IV) complexes, generated with $TiCl_2(OPr^i)_2$ or $Ti(OPr^i)_2$, gave satisfactory enantiomeric ratios (er) when working in toluene in the presence of 4 Å molecular sieves, even slightly better than the aluminium(III) complex obtained from dimethylaluminium chloride (Table 1, entries 1–4). However, unlike the

Table 1. Cyanation of benzaldehyde catalysed by preformed Lewis acid (*S*)-**2** complexes

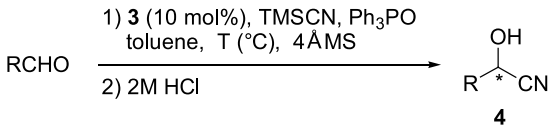
Run	Lewis acid	Solvent	Additives	*T* (°C)	*T* (h)	**4a** (%)[a]	er[b]
1	$TiCl_2(OPr^i)_2$	CH_2Cl_2	4 Å MS	0	24	65	55/45
2	$TiCl_2(OPr^i)_2$	$PhCH_3$	4 Å MS	0	24	83	88/12
3	$Ti(Opr^i)_4$	$PhCH_3$	4 Å MS	0	1	99	78/22
4	$AlClMe_2$	$PhCH_3$	4 Å MS	0	26	87	67/33
5	$AlClMe_2$	$PhCH_3$	4 Å MS/Ph_3PO	0	3	99	88/12
6	$AlClEt_2$	$PhCH_3$	4 Å MS/Ph_3PO	0	8	99	90/10
7	$AlClMe_2$	CH_2Cl_2	4 Å MS/Ph_3PO	0	14	99	77/23
8	$AlClMe_2$	$PhCH_3$	Ph_3PO	0	20	99	75/25
9	$AlClMe_2$	$PhCH_3$	4 Å MS/Ph_3PO	−20	6	99	>99/1
10	$AlClMe_2$[c]	$PhCH_3$	4 Å MS/Ph_3PO	−20	6	99	>1/99
11	$AlClMe_2$	$PhCH_3$	3 Å MS/Ph_3PO	−20	16	83	94/6
12	$AlClMe_2$	$PhCH_3$	5 Å MS/Ph_3PO	−20	9	99	91/9
13	$AlClMe_2$[d]	$PhCH_3$	4 Å MS/Ph_3PO	−20	12	89	96/4
14	$AlMe_3$	$PhCH_3$	4 Å MS/Ph_3PO	−20	4	99	50/50
15	$AlCNEt_2$	$PhCH_3$	4 Å MS/Ph_3PO	−20	3	99	55/45

[a] The isolated yields given refer to the cyanohydrins obtained after acidic hydrolysis.
[b] Enantiomeric ratios were determined by chiral HPLC analysis (Chiralcel OD-H).
[c] Reaction performed with (*R*)-BINOLAM.
[d] A 5 mol% charge of (*S*)-**3** was used as catalyst.

titanium complexes, the activity of the aluminium complex could be further modulated by manipulation of additives and temperature. For this reason, we then focussed our study on the enantioselective addition of TMSCN to aldehydes catalysed by aluminium(III) complexes. A crucial discovery to the optimisation process was the favourable effect observed on addition of triphenylphosphine oxide (40 mol%)[6] to the aluminium complexes,[13] which led to an increase of both reaction rate and er (Table 1, entries 4 and 5). In the course of these optimisations we also recognized the importance of a second additive, namely 4 Å MS.[14] Mediocre results (both in terms of rate and er) were obtained in its absence (Table 1, entry 8), whereas in the presence of 4 Å MS, dried at 120 °C for 4 h, excellent results were obtained (Table 1, entry 5). Thermogravimetric analysis of this partially dried 4 Å MS revealed the presence of 7.5% of water content. On the other hand, the use of ultradried 4 Å MS (200 °C, 6 h, under high vacuum) led to an extremely slow reaction. So, a small amount of water seemed to be required for activity.[15] However, water itself can not be used, as suggested by the fact that operating without 4 Å MS, but in the presence (added at the start in one portion) of an equivalent amount of water leads to cyanohydrin **4a** in very low yield and enantiomeric ratio, possibly because water destroys the catalyst. Accordingly we realised at this point that 4 Å MS were possibly acting as an excellent carrier of a limited amount of water, as recently demonstrated for a similar reaction.[16] So, what is the role of water? Since water could induce a limited hydrolysis of TMSCN to HCN, we examined and proved by NMR (^{1}H and ^{13}C) that adding either water or 4 Å MS to an NMR tube containing TMSCN produced HCN. It appeared then that, under these reaction conditions, the enantioselective addition of trimethylsilyl cyanide to the aldehyde was actually a hydrocyanation reaction followed by *O*-silylation. The use of 3 or 5 Å MS also led to excellent er, at −20 °C, but nevertheless inferior to those obtained with 4 Å MS (Table 1, entries 9, 11 and 12). In further optimising work we also learned that the highest er was reached by operating at −20 °C in the presence of triphenylphosphine oxide (40 mol%) and 4 Å MS in toluene as solvent (the mixture was somewhat heterogeneous in this solvent). Other suitable solvents such as dichloromethane (Table 1, entries 5 and 7), THF, chloroform and diethyl ether (not included in Table 1) led to poorer results. As precursory aluminium species we found dimethylaluminium chloride to be preferred over diethylaluminium chloride because the former induced a faster reaction (Table 1, entries 5 and 6). On the other hand, trimethylaluminium or, more interestingly, diethylaluminium cyanide led to no asymmetric induction (Table 1, entries 14 and 15), thereby proving that aluminium cyanide species were not the key derivatives involved in the enantioselective cyanation observed. The best catalyst charge was established as 10% molar (relative to aldehyde), after realising that a substantial reduction in rate occurred using a 5% molar charge (Table 1, entry 13).

Concerning the stereochemical issues, we noticed the following systematic trends: the (*S*)-BINOLAM-AlCl complex leads to the enantiomerically enriched (*R*)-configured cyanohydrins **4**, and the opposite was also true: (*R*)-BINOLAM-AlCl complex leads to (*S*)-configured cyanohydrins **4** (Table 1, entries 2, 6, 10). The only exception to this rule, namely that of furfural, is simply due to a change in the CIP priority of the substituents. Absolute configurations were assigned on the basis of literature data (see Section 3 for individual details). The enantiomeric ratios reported here were determined by chiral HPLC (Chiralcel OD-H and Chiralpack AD and AS) analyses of the corresponding *O*-acetyl, *O*-benzoyl, *O*-TMS, or *O*-TBDMS cyanohydrins (see Section 3 for individual details). Prior control tests demonstrated that no racemisation occurred during these derivatisations. So, it can be taken for granted that the enantiomeric ratios given actually represent the enantiomeric ratios of cyanohydrins themselves.

As shown below, the cyanation reactions appear to be of general applicability (Scheme 2 and Table 2). Thus, aromatic aldehydes led to the corresponding cyanohydrins with excellent er's and chemical yield by working at −20 °C (Table 2, entries 1–11). Somewhat lower er's were obtained for the case of *m*-phenoxybenzaldehyde, possibly because of the steric demand of the phenoxy group, as illustrated in Table 2 (entries 8 and 9). The behaviour of heteroaromatic aldehydes also provided indirect evidence in favour of the hydrocyanation mechanism. Thus, whilst furfural gave good results when lowering the temperature down to −40 °C (96/4 er), nicotinaldehyde behaved as a special case as it required a large excess of TMSCN for the reaction to give 99% yield (Table 2, entries 12–14), the enantioselectivity being always a mediocre 75/25 er. In this case, the heterocyclic nitrogen atom of the pyridine ring works as a basic site (Brönsted base, BB) to capture the HCN involved in the hydrocyanation reaction, thereby slowing down the reaction rate and facilitating the competition of non-asymmetric routes. Conjugated aldehydes were also suitable substrates for this cyanation reaction, the best er's being obtained when operating at −20 and −40 °C, depending on the structure of the aldehyde (Table 2, entries 15–17). Aliphatic aldehydes, on the other hand, gave cyanohydrins **4** in very good yields and er's when operating at −40 °C in short reaction times (Table 2, entries 18–22). For the particular case of heptanal, we checked the influence of (a) using an alkylphosphine oxide such as tri-*n*-butylphosphine oxide (40 mol%) instead of triphenylphosphine oxide, and (b) lowering the temperature to −60 °C, but no improvement was detected (Table 2, entries 20 and 21, respectively). The ketones did not react under these conditions, similarly as reported for the Shibasaki's conditions employing complexes **1**.[6]



Scheme 2.

Several operational advantages of our methodology with the BINOLAM-AlCl catalyst need to be mentioned: (a) the procedure is operationally simple as all reagents are added at once (no slow pump addition was needed as required by Shibasaki's method)[8] and takes place in short reaction times and easy-to-reach operating temperatures; (b) the chiral ligand employed is stable and it can be recovered almost

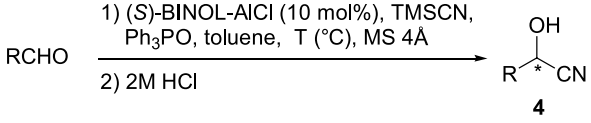
Table 2. Synthesis of enantiomerically enriched **4** catalysed by either (*R*)- or (*S*)-**3** complexes

Run	R	**3**	*T* (°C)	Time (h)	**4**	Yield (%)[a]	Conf.[b]	er[c]
1	Ph	(*S*)	−20	6	**4a**	99	(*R*)	>99/1
2	Ph	(*R*)	−20	6	**4a**	99	(*S*)	>99/1
3	Ph	(*S*)[d]	−20	6	**4a**	99	(*R*)	>99/1
4	4-(MeO)C_6H_4	(*S*)	−20	20	**4b**	99	(*R*)	>99/1
5	4-(Me_2N)C_6H_4	(*S*)	−20	22	**4c**	>95	(*R*)	99/1[e]
6	2-ClC_6H_4	(*R*)	−20	8	**4d**	99	(*S*)	98/2
7	4-ClC_6H_4	(*S*)	−20	21	**4e**	99	(*R*)	>99/1
8	3-(PhO)C_6H_4	(*S*)	−20	48	**4f**	70	(*R*)	85/15
9	3-(PhO)C_6H_4	(*S*)	−40	48	**4f**	45	(*R*)	89/11
10	3,4-(OCH_2O)C_6H_3	(*R*)	−20	24	**4g**	55	(*S*)	97/3
11	6-(MeO)-2-naphthyl	(*S*)[f]	−20	39	**4h**	90	(*R*)	95/5
12	3-Pyridyl	(*R*)	−20	8	**4i**	99	(*S*)	75/25[e]
13	2-Furyl	(*S*)	−20	5	**4j**	99	(*S*)	88/12
14	2-Furyl	(*S*)	−40	12	**4j**	99	(*S*)	96/4
15	(*E*)-C_5H_{11}CH=CH	(*S*)	−20	21	**4k**[g]	59	(*R*)	98/2
16	(*E*)-PhCH=CH	(*S*)	−20	6	**4l**	99	(*R*)	91/9
17	(*E*)-PhCH=CH	(*R*)	−40	12	**4l**	99	(*S*)	>99/1
18	$PhCH_2CH_2$	(*R*)	−40	4.5	**4m**	99	(*S*)	94/6[h]
19	$CH_3(CH_2)_5$	(*R*)	−40	3.5	**4n**	99	(*S*)	83/17[i]
20	$CH_3(CH_2)_5$[j]	(*R*)	−40	3.5	**4n**	99	(*S*)	65/35[i]
21	$CH_3(CH_2)_5$	(*R*)	−60	10	**4n**	87	(*S*)	65/35[i]
22	*c*-(C_6H_{11})	(*R*)	−40	12	**4o**	99	(*S*)	60/40[k]

[a] Isolated yields of the cyanohydrins **4** after acidic hydrolysis with 2 M hydrochloric acid, except for **4i**, which was obtained after quenching with water.
[b] Assigned by comparison to literature data.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H, Chiralpak AD and AS) on the corresponding *O*-acetyl derivatives.
[d] Reaction performed with recovered ligand obtained by extractive work-up and recrystallisation.
[e] Six equivalents of TMSCN were required.
[f] Determined by chiral HPLC analysis (Chiralcel OD-H) of the corresponding *O*-TMS derivative.
[g] This compound was characterised as its methoxycarbonyl derivative.
[h] Determined by chiral HPLC analysis (Chiralcel OD-H) on the corresponding *O*-TBDMS derivative.
[i] Determined by chiral HPLC analysis (Chiralcel OD-H) on the corresponding *O*-benzoyl derivative.
[j] Tri-*n*-butylphosphine oxide (40 mol%) was added instead of triphenylphosphine oxide.
[k] Determined by chiral GC analysis (γ-cyclodextrin) of the corresponding *O*-methoxycarbonyl derivative.

quantitatively and reused without loss in efficiency (Table 2, entry 3); (c) the process can be scaled-up to 2.5 mmol, at least, thereby affording compound **4a** after 12 h in >95% yield and 98.5/1.5 er.

We have made efforts to clarify the non-trivial classification of the BINOLAM-AlCl catalyst as being bifunctional or monofunctional. For that purpose, we focussed our attention on monofunctional complexes (*R*)- or (*S*)-BINOL-AlCl **5**, which lack the amino arms at C3 and C3′ characteristic of BINOLAM-AlCl, and comparatively studied their efficiency in the enantioselective addition of TMSCN to aldehydes. We prepared complex (*S*)-BINOL-AlCl **5** as described before for BINOLAM-AlCl, and then we optimised the conditions for the addition of TMSCN to benzaldehyde. Once again, we found that both triphenylphosphine oxide and 4 Å MS (7.5% water content) accelerated the reaction and pushed the enantioselectivity of the process towards excellence. Best results were actually obtained using (*S*)-BINOL-AlCl together with 4 Å MS (200 mg/mmol relative to aldehyde) and triphenylphosphine oxide (40 mol%), in toluene, at −20 °C. In this manner, after acidic workup (2 M HCl), cyanohydrin **4a** was isolated in high yield and er (Scheme 3, Table 3, entry 1). The total or partial absence of 4 Å MS and triphenylphosphine oxide did not benefit either the chemical or optical yields (Table 3, entries 1–3). As shown above for the catalysis by BINOLAM-AlCl, the key operation behind the overall addition of TMSCN to aldehydes catalysed by BINOL-AlCl **5**, under the above reaction conditions, should also be considered a hydrocyanation reaction.



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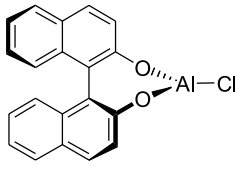
Scheme 3.



5

The absence of a clear-cut basic site in BINOL-AlCl **5** (as compared to BINOLAM-AlCl **3**) suggested that addition of an external base might erode or even annihilate the enantioselectivity of the reaction by opening-up competing non-asymmetric processes. This reasoning was actually supported by experiment as the addition of a substoichiometric amount of triethylamine (20 mol%) to the otherwise standard reaction conditions led to almost racemic (er 60/40) product (Table 3, entry 6). This result also suggested that other basic centres in the substrates or otherwise, capable of capturing HCN might affect the chemical yield and/or result in lower enantioselectivities. The results actually found for a variety of aldehydes can be defined as capricious. Thus, arylaldehydes and heteroarylaldehydes and α,β-unsaturated aldehydes either did not react or afforded almost racemic cyanohydrins (Table 3,

Table 3. Synthesis of enantiomerically enriched **4** catalysed by the (*S*)-BINOL-AlCl complex

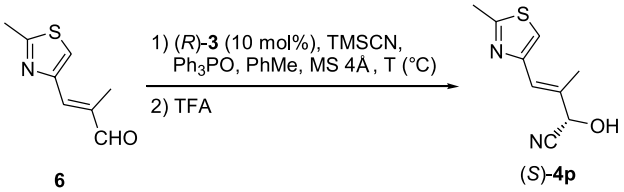
Run	R	*T* (°C)	Time (h)	**4**	Yield (%)[a]	Conf.[b]	er[c]
1	Ph[d]	−20	24	**4a**	9	(*R*)	—
2	Ph[e]	−20	24	**4a**	10	(*R*)	90/10
3	Ph[f]	−20	24	**4a**	11	(*R*)	92/8
4	Ph	−20	4	**4a**	99	(*R*)	96/4
5	Ph[g]	−20	3	**4a**	99	(*R*)	95/5
6	Ph[h]	−20	9	**4a**	99	(*R*)	60/40
7	4-(MeO)C_6H_4	−20	48	**4b**	24	—	50/50
8	4-ClC_6H_4	−20	24	**4e**	—	—	—
9	6-(MeO)-2-Naphthyl	−20	48	**4h**	40	(*R*)	56/44
10	3-Pyridyl[i]	−20	40	**4i**	99	(*R*)	97/3[j]
11	2-Furyl	−20	24	**4j**	—	—	—
12	(*E*)-C_5H_{11}CH=CH	−20	24	**4k**	—	—	—
13	(*E*)-PhCH=CH	−20	24	**4l**	—	—	—
14	$PhCH_2CH_2$	−20	12	**4m**	>95	(*R*)	90/10[k]
15	$PhCH_2CH_2$	−40	18	**4m**	>95	(*R*)	94/6[k]
16	$CH_3(CH_2)_5$	−20	14	**4n**	>95	(*R*)	54/46[l]

[a] Isolated yields of the cyanohydrins **4** after acidic hydrolysis using 3 equiv. of TMSCN.
[b] By comparison to known optical rotations.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H, Chiralpak AD and AS) of the corresponding *O*-acetyl derivatives.
[d] In the absence of both additives.
[e] In the absence of 4 Å MS.
[f] In the absence of triphenylphosphine oxide.
[g] The aluminium source was Et_2AlCN.
[h] 20 mol% of dry triethylamine was added.
[i] The reaction was quenched with water.
[j] Determined by chiral HPLC analysis (Chiralcel OD-H) of the corresponding *O*-TMS derivative.
[k] Determined by chiral HPLC analysis (Chiralcel OD-H) of the corresponding *O*-TBDMS derivative.
[l] Determined by chiral HPLC analysis (Chiralcel OD-H) of the corresponding *O*-benzoyl derivative.

entries 7–9 and 11–13). The case of nicotinaldehyde, however, came as a surprise as the cyanohydrin was obtained in high yield and er (Table 3, entry 10). This result is now understood as a consequence of the intermediate formation of the pyridinium salt, likely the actual species undergoing reaction. Aliphatic aldehydes, on the other hand, gave different results according to their structures (Table 3, entries 14–16), that suggest the likely influential role of CH-π interactions. Thus, whereas strictly aliphatic aldehydes yielded almost racemic mixtures (Table 3, entry 16), those having a β-phenyl substituent yielded the corresponding cyanohydrin in good chemical yield and er (Table 3, entries 14–15). As for the processes catalysed by (*S*)-BINOLAM-AlCl **3**, those catalysed by the (*S*)-BINOL-AlCl **5** complex gave (*R*)-configured cyanohydrins.

Some of the examples depicted in Tables 2 and 3 are interesting molecules, for example, **4a** is a part of new cyanogenic glycosides isolated from the leaves and roots of *Phyllagatis rotundifolia*,[17] **4b** is used in the synthesis of the naturally occurring (−)-tembamide and (−)-aegeline,[3,18] cyanohydrin **4f**[19,20] is an intermediate in the industrial production of pyrethroid insecticides,[21] compound **4d** is an intermediate in the synthesis of the anti-thrombotic agent clopidogrel,[22] cyanohydrins **4g** and **4i** are direct precursors of biogenic amines and chiral 2-amino-1-(3-pyridinyl)ethanol,[23] respectively, and product **4k** is employed in the preparation of sphingosines[24] and coriolic acid.[25] In addition, a direct application of this methodology was the elaboration of the key intermediate (*S*)-**4p**, used in the synthesis of epothilone A,[26] involving the cyanation of the aldehyde **6** containing a thiazole moiety (Scheme 4). Previously, compound (*S*)-**4p** was prepared at −40 °C in 48 h by adding 1.5 equiv. of TMSCN very slowly (syringe pump).[6b,27] In our case, slow addition of 2 equiv. of TMSCN was not productive (Table 4, entry 3) because a large amount of unreacted aldehyde **6** was observed in the crude reaction product. Fortunately, when the reaction was carried out at −20 °C using an excess of TMSCN (9 equiv.), added in one portion, the reaction was completed in 36 h in excellent chemical yield and very good enantiomeric ratio (Table 4, entry 4). Lowering the operating temperature to −40 °C did not produce a substantial improvement in the enantiomeric ratio of compound **4p** (Table 4, entry 5). It is worth noting that the thiazole ring (pK_a=2.4), is less basic than the pyridine ring (pK_a=5.2), and so is not able to induce by itself a racemic side-process. (*S*)-BINOL-AlCl **5** was also tested as a catalyst in this transformation but the yield was quite low and the cyanohydrin **4p** was finally isolated as a racemic mixture. In all of the examples the reaction was quenched by the addition of trifluoroacetic acid at −20 or −40 °C (see Table 4), the enantiomeric ratios were determined by chiral HPLC analyses (Daicel Chiralpak AD) of its *O*-TBDMS derivative and the absolute configuration was determined by comparing the optical rotation with that obtained from a pure sample.[6b]

The proposed mechanism for this reaction significantly departs from that reported by Shibasaki et al. in a number of



6 (*S*)-**4p**

Scheme 4.

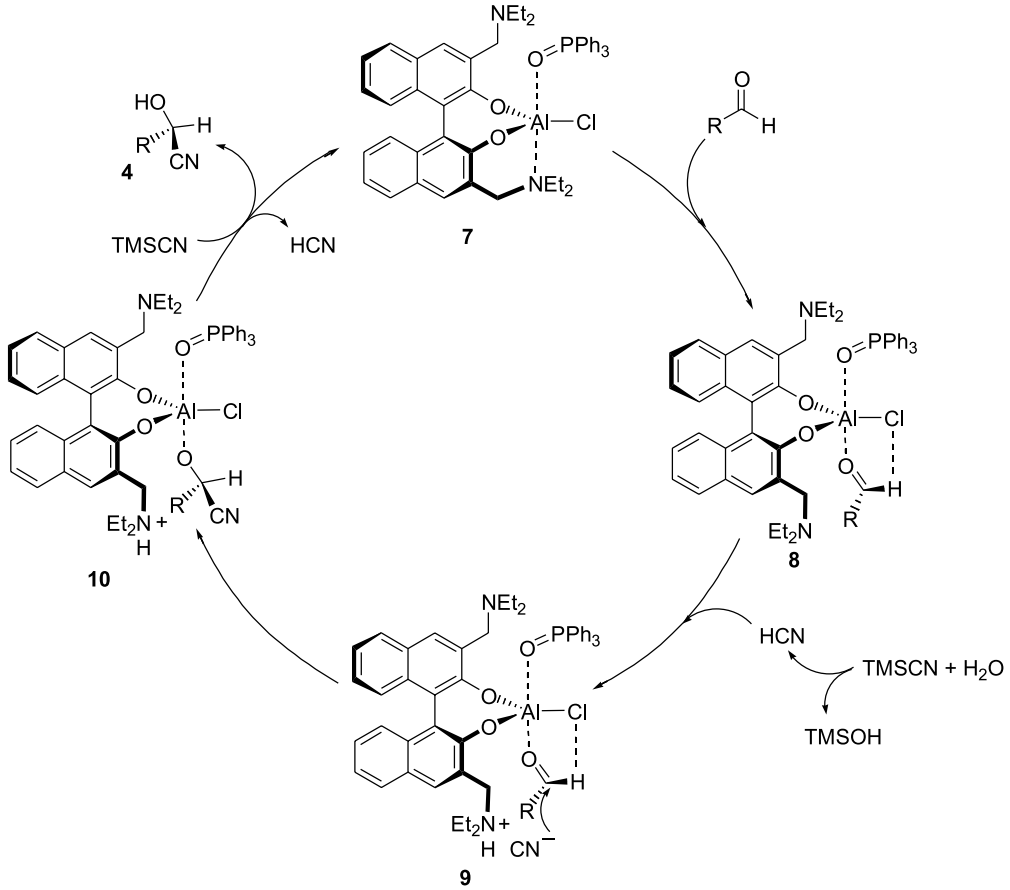
Table 4. Enantioselective synthesis of compound **4p**

Run	TMSCN (equiv)	*T* (°C)	T (h)	**4p** (%)[a]	er[b]
1	3	−20	22	33	96/4
2	1.5+1.5[c]	−20	48	52	88/12
3	2[d]	−20	24	0	—
4	9	−20	36	>98	96/4
5	9	−40	48	>98	96/4
6[e]	6	−20	24	54	50/50

[a] Isolated yields given refer to the cyanohydrin obtained after quenching the reaction with trifluoroacetic acid.
[b] Enantiomeric ratios were determined by chiral HPLC analysis (Chiralpak AD) of the *O*-TBDMS derivative.
[c] The second 1.5 equiv. of TMSCN was added after 1 d.
[d] Slow syringe pump addition over 24 h.
[e] Performed with (*R*)-BINOL-AlCl **5** complex.

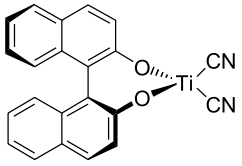
relevant issues. According to kinetic studies they showed that the two existing phosphine oxide units should play two different roles: the phosphine oxide located in the integrated arm of the ligand activated the trimethylsilyl cyanide while the added phosphine oxide was required to generate a pentavalent aluminium complex and prevent oligomerisation.[6,13] The study of the ^{31}P NMR spectra of an equivalent amount of BINOLAM-AlCl complex and triphenylphosphine oxide showed only one signal at 29.5 ppm (free triphenylphosphine oxide 30.1 ppm) supporting the existence of catalytic species **7** (Scheme 5). This reaction also presented linear effects when the enantiomeric excess of cyanohydrin **4a** was plotted versus the corresponding enantiomeric excess of the catalytic complex; unlike other reactions catalysed by chiral BINOLAM-AlCl **3** complexes, such as the asymmetric synthesis of *O*-methoxycarbonyl[10] and *O*-phosphorylated[11] cyanohydrins, which, in absence of triphenylphosphine oxide, exhibited moderate and strong positive non-linear effects (NLE),[28] respectively. The pentacoordinated, highly stable,[29] intermediate species **8** (Scheme 5) was proposed from the very broad band observed at 47 ppm in the ^{27}Al NMR experiment.[30]

The contribution of the chlorine to the catalytic cycle of BINOLAM-AlCl **3** complex was important; when it was not present the reaction was not so enantioselective as deduced from entries 14 and 15 of Table 1. A weak interaction of the aldehydic proton and the chlorine atom,[31] together with a stronger interaction between the carbonyl oxygen atom and the aluminium centre, presumably fixed the aldehyde to the chiral catalytic domain.

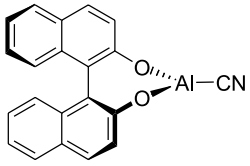


Scheme 5.

The ^{13}C and ^{1}H NMR spectra of equimolar mixtures of TMSCN/water of 4 Å MS, TMSCN/Ph_3PO and TMSCN/Et_3N revealed that water contained in 4 ÅMS interacted instantaneously to form hydrogen cyanide and trimethylsilanol and no noticeable chemical shifts, apart from the pure compound signals, were observed for the other two mixtures, thus indicating that triphenylphosphine and triethylamine are not so good activating agents of TMSCN. So, the small amount of HCN, generated by the water content of molecular sieves would react with a diethylamino group of the ligand in **9** (Scheme 5). As described above, if we add an exact amount of water (equivalent to the amount contained by the MS) the reaction failed and the er of **4a** was also very low working with extremely anhydrous molecular sieves (high vacuum, 200 °C, 6 h) or with molecular sieves saturated in water (overnight, air, rt). The diethylaminomethyl group would act as a Brönsted base capturing the HCN and, consequently, activating the nucleophile, which is supported by the fact that the addition of a competing base such as triethylamine (20 mol%), at −20 °C, lowered the er down to 60:40 and also by the basic nitrogen of 3-pyridinecarboxaldehyde also favouring a racemic pathway in the reaction with (*S*)-BINOLAM-AlCl **3** (Table 2, entry 12). A further indirect proof for the intervention of pentacoordinated aluminum species in the above reactions resulted from examination of the (*S*)-BINOL-AlX catalysed cyanation of benzaldehyde. In a previous work published by Nakai et al. the in situ formed dicyanotitanium(IV) complex **11** was predicted as the catalytically active species.[3] By analogy, since both (*S*)-BINOL-AlCN **12** and (*S*)-BINOL-AlCl **5** lack the Brönsted base arm present in the BINOLAM ligand we assumed that catalysis, if occurring, would take place through the standard tetracoordinated species. In agreement with this reasoning we found that, in both cases, benzaldehyde cyanohydrin was obtained in quantitative yield and high enantioselection as revealed by a 95/5 or 96/4 er, respectively. Therefore we tentatively conclude that pentacoordinated aluminum catalysts (LABB catalysts) are more efficient hydrocyanation catalysts than tetracoordinated ones (LA catalysts) alone.



11



12

The absence of a NLE in the reaction catalysed by complexes **5** and **12** also suggest that monomeric species control the process. Thus, the BINOL-AlCN complex **12** would participate as a monofunctional catalytic species in the catalytic cycle through a direct cyanide ion transfer from the aluminium centre in the tetracoordinated complex obtained from compound **12** and the ligated aldehyde, regenerating the active complex after a silylation reaction of the aluminium alcoholate with TMSCN. In order to experimentally justify this hypothesis, ^{27}Al NMR (CD_2Cl_2, 500 MHz) experiments were recorded. The ^{27}Al NMR experiments of BINOL-AlCl **5** and BINOL-AlCN **12** alone and with additives afforded very confusing results, but never with a typical band of pentacoordinated aluminium species at 47 ppm being observed. The ^{31}P NMR spectra of an equivalent amount of BINOL-AlCl complex and triphenylphosphine oxide revealed six different signals at 41.2, 41.5, 42.1, 43.6, 45.3 and 46.3 ppm (free triphenylphosphine oxide 30.1 ppm) corresponding to, at least, six different coordination sites.

In summary, we have shown that the BINOLAM-AlCl catalytic complex is more efficient than the otherwise simpler LA catalyst BINOL-AlCl in the hydrocyanation of aldehydes. The catalyst works as a bifunctional LABB by ligating the carbonyl group to the chiral aluminium, thereby becoming a pentacoordinated chloro-aluminium species. This LABB catalyst has similar efficiency to Shibasaki's LALB phosphine oxide catalyst while allowing reactions to be carried out at higher temperatures and with easier set up. In addition, we have demonstrated that the chiral ligand (*S*)-BINOLAM **3** can be easily and quantitatively recovered at the end of the reaction and recycled, thus suggesting the possible application of this methodology in large-scale processes.

3. Experimental

3.1. General

All reactions were carried out under argon, including the transfer of the solid reagents to the reaction vessel. Anhydrous solvents were freshly distilled under an argon atmosphere and aldehydes were also distilled prior to use. Molecular sieves were treated at 120 °C for 4 h. (*S*)- and (*R*)-BINOLAM were prepared according to the literature protocol.[9–12] Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. IR spectra were recorded on a Nicolet 510 P-FT and only the structurally most important peaks are listed. NMR spectra were obtained on a Bruker AC-300 using $CDCl_3$ as solvent and TMS as internal standard unless otherwise stated. Optical rotations were measured on a Perkin Elmer 341 polarimeter. HPLC analyses were performed on a Shimadzu LC-10AD equipped with the corresponding chiral column (Chiralcel OD-H and Chiralpack AD and AS) described for each compound, using mixtures of n-hexane/isopropyl alcohol as mobile phase. Chiral GC analysis was performed on a HP-5890 using a WCOT γ-cyclodextrin column. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV on a Shimadzu QP-5000 and high resolution mass spectra were obtained on a Finnigan VG Platform. HRMS (EI) were recorded on a Finnigan MAT 95S. Microanalyses were performed on a Perkin–Elmer 2400 and a Carlo Erba EA1108. Analytical TLC was performed on Schleicher and Schuell F1400/LS silica gel plates and the spots were visualized with UV light at 254 nm. Flash chromatography employed Merck silica gel 60 (0.040–0.063 mm).

3.2. General procedure for the enantioselective synthesis of cyanohydrins 4 mediated by (*S*)- or (*R*)-BINOLAM-AlCl or by (*S*)-BINOL-AlCl

To a suspension of enantiopure (*S*)- or (*R*)-BINOLAM **2**[12]

or (*S*)- or (*R*)-BINOL (0.025 mmol), triphenylphosphine oxide (0.1 mmol, 28 mg) and 4 Å molecular sieves (previously dried at 120 °C for 4 h) in dry toluene (1 mL), under an inert atmosphere (argon), was added dimethylaluminium chloride (1 M solution in hexanes, 0.025 mmol, 25 μL). The resulting suspension was then stirred at room temperature for 1 h. This mixture was cooled at −20 or −40 °C (see Table 2) and then freshly distilled aldehyde (0.25 mmol) and TMSCN (0.75 mmol, 100 μL) were added in one portion. The reaction was monitored by ^{1}H NMR spectroscopy and when it was judged complete a 2 M aqueous solution of hydrochloric acid (2 mL) and ethyl acetate (2 mL) were added, stirring vigorously the resulting mixture for 1 h. The emulsion was filtered trough a celite pad and the organic layer was separated, dried ($MgSO_4$) and evaporated, affording a residue which was purified by flash chromatography obtaining pure cyanohydrins **4**. These compounds were derivatised for chiral HPLC analysis by treatment with 3 equiv. of the base in dry dichloromethane and 1.2 equiv. of the corresponding chloride (AcCl/pyridine, TBDMSCl/imidazole/DMAP(cat), BzCl/triethylamine or MeOCOCl/triethylamine) overnight at room temperature. Yields, enantiomeric ratios and other conditions are given in Tables 1–4. The retention time of the major enantiomer is given in bold. The physical and spectroscopic data for compounds **4** follow:

3.2.1. (*R*)-Mandelonitrile (4a).[32] Colorless oil; $[\alpha]_D^{25}=+42.2$ (*c* 1, $CHCl_3$, 99% ee from HPLC) [lit.[3] $[\alpha]_D^{25}=+36.8$ (*c* 2, $CHCl_3$, 85% ee)]; IR (film) ν_{max}: 3222 and 2249 cm^{-1}; ^{1}H NMR δ_H: 3.18 (br. s, 1H), 5.53 (s, 1H), 7.42–7.45 (m, 3H), 7.50–7.53 (m, 2H); ^{13}C NMR δ_C: 63.6, 118.7, 126.6, 129.2, 129.8, 135.0; MS (EI) *m/z*: 107 (M^+-26, 8%), 106 (78), 105 (88), 77 (100), 51 (74); HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=$ **11.0** and 14.0 min for the *O*-acetylcyanohydrin.

3.2.2. (*R*)-2-Hydroxy-2-(4-methoxyphenyl)acetonitrile (4b).[34] Colorless oil; $[\alpha]_D^{25}=+40.7$ (*c* 1, $CHCl_3$, 99% ee from HPLC) [lit.[34] $[\alpha]_D^{25}=+36.3$ (*c* 0.97, $CHCl_3$, 83% ee)]; IR (film) ν_{max}: 3420 and 2249 cm^{-1}; ^{1}H NMR δ_H: 3.65 (br. s, 1H), 3.81 (s, 3H), 5.46 (s, 1H), 6.93 (d, $J=8.7$ Hz, 2H), 7.42 (d, $J=8.7$ Hz, 2H); ^{13}C NMR δ_C: 55.3, 63.1, 114.4, 119.0, 127.6, 128.2, 160.4; MS (EI) *m/z*: 161 (M^+-2, 1%), 145 (3), 135 (100), 107 (13), 92 (15), 77 (40); HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=$ **11.2** and 12.6 min for the *O*-acetylcyanohydrin.

3.2.3. (*R*)-2-Hydroxy-2-[4-(*N*,*N*-dimethylamino)phenyl]-acetonitrile (4c). Pale yellow prisms, mp 105–106 °C (from *n*-hexane/ethyl acetate); $[\alpha]_D^{25}=+83.3$ *c* 0.6, $CHCl_3$, 98% ee from HPLC) [lit.[34] $[\alpha]_D^{25}=+45.1$, $CHCl_3$, 53% ee)]. IR (film) ν_{max}: 3432 and 2244 cm^{-1}; ^{1}H NMR δ_H: 2.56 (br. s, 1H), 2.99 (s, 6H), 5.43 (s, 1H), 6.75 (d, $J=8.8$ Hz, 2H), 7.39 (d, $J=8.8$ Hz, 2H); ^{13}C NMR δ_C: 40.36, 63.31, 112.45, 119.31, 123.05, 127.97, 151.16; MS (EI) *m/z*: 14 (M^+-27, 84%), 148 (100), 132 (14), 77 (22), 51 (13); HRMS calcd. for $C_{10}H_{12}N_2O$: 176.2194, found: 176.2198. HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=6.7$ and **7.2** min for the *O*-TMS-cyanohydrin.

3.2.4. (*S*)-2-(2-Chlorophenyl)-2-hydroxyacetonitrile (4d). Colorless oil; $[\alpha]_D^{25}=-7.0$ (*c* 0.77, $CHCl_3$, 96% ee from HPLC) [lit.[34] $[\alpha]_D^{25}=-2.5$, for the (*R*) enantiomer (*c* 2.9, $CHCl_3$, 67% ee)]; IR (film) ν_{max}: 3409 and 2253 cm^{-1}; ^{1}H NMR δ_H: 3.82 (br. s, 1H), 5.86 (s, 1H), 7.36–7.44 (m, 3H), 7.69–7.73 (m, 1H); ^{13}C NMR δ_C: 60.8, 117.9, 127.6, 128.3, 130.0, 131.0, 132.6, 132.8; MS (EI) *m/z*: 143 (M^+-14, 2%), 139 (100), 111 (41), 75 (26), 51 (18); HRMS calcd. for C_8H_6NOCl: 167.5961, found: 167.5959. HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=7.9$ and **9.2** min for the *O*-acetylcyanohydrin.

3.2.5. (*R*)-2-(4-Chlorophenyl)-2-hydroxyacetonitrile (4e).[32] Colorless oil; $[\alpha]_D^{25}=+31.2$ (*c* 0.8, $CHCl_3$, 98% ee from HPLC) [lit.[32,33] $[\alpha]_D^{25}=+27.2$ (*c* 1.48, $CHCl_3$, 66% ee)]; IR (film) ν_{max}: 3411 and 2252 cm^{-1}; ^{1}H NMR δ_H: 3.89 (br. s, 1H), 5.54 (s, 1H), 7.41–7.50 (m, 4H); ^{13}C NMR δ_C: 62.8, 118.4, 127.9, 129.3, 133.6, 135.9; MS (EI) *m/z*: 163 (M^+, 4%), 139 (75), 111 (37), 75 (25), 49 (13); HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=$ **12.8** and 14.5 min for the *O*-acetylcyanohydrin.

3.2.6. (*R*)-2-Hydroxy-2-(3-phenoxyphenyl)acetonitrile (4f).[35] Colorless oil; $[\alpha]_D^{25}=+12.9$ (*c* 1, $CHCl_3$, 78% ee from HPLC); [lit.[33] $[\alpha]_D^{25}=+14.0$ (*c* 0.83, $CHCl_3$, 79% ee)]; IR (film) ν_{max}: 3414 and 2251 cm^{-1}; ^{1}H NMR δ_H: 2.78 (br. s, 1H), 5.51 (s, 1H), 7.02–7.42 (m, 9H); ^{13}C NMR δ_C: 63.2, 116.6, 118.5, 119.3, 119.6, 120.9, 123.9, 129.9, 130.6, 137.0, 156.3, 158.1; MS (EI) *m/z*: 199 (M^+-26, 13%), 198 (100), 169 (55), 141 (49), 115 (29), 77 (52); HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 90/10, 1.0 mL/min, $t_r=14.0$ and **20.4** min for the *O*-acetylcyanohydrin.

3.2.7. (*S*)-2-Hydroxy-2-(3,4-methylenedioxyphenyl)-acetonitrile (4g).[36] Colorless oil; $[\alpha]_D^{25}=-41.7$ (*c* 1, $CHCl_3$, 94% ee from HPLC) [lit.[34] $[\alpha]_D^{25}=+40.8$, (*R*) enantiomer (*c* 1.1; $CHCl_3$, 73% ee)]; IR (film) ν_{max}: 3454 and 2239 cm^{-1}; ^{1}H NMR δ_H: 3.07 (br. s, 1H), 5.43 (s, 1H), 6.00 (s, 2H), 6.81–6.84 (m, 1H), 7.01–7.12 (m, 2H); ^{13}C NMR δ_C: 63.4, 101.6, 107.2, 108.6, 118.7, 120.7, 128.8, 143.3, 143.8; MS (EI) *m/z*: 151 (M^+-26, 8%), 150 (84), 149 (100), 121 (31), 91 (10), 63 (26); HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=16.1$ and **18.2** min for the *O*-acetylcyanohydrin.

3.2.8. (*R*)-2-Hydroxy-2-(6-methoxynaphthalen-2-yl)-acetonitrile (4h).[36] Pale yellow needles, mp 113–114 °C (from *n*-hexane/ethyl acetate); $[\alpha]_D^{25}=+24.0$ (*c* 0.9, $CHCl_3$) (90% ee from HPLC); IR (KBr) ν_{max}: 3439 and 2240 cm^{-1}; ^{1}H NMR δ_H: 3.91 (s, 3H), 4.81 (br. s, 1H), 5.89 (s, 1H), 7.19 (dd, $J=2.4$, 8.9 Hz, 1H), 7.32 (d, $J=2.3$ Hz, 1H), 7.61 (m, 1H), 7.87 (m, 2H), 7.98 (s, 1H); ^{13}C NMR (d_6-DMSO) δ_C: 55.6, 63.5, 106.6, 120.2, 120.7, 125.4, 126.3, 128.4, 129.3, 130.4, 133.1, 135.8, 159.3; MS (EI) *m/z*: 186 (M^+-27, 100%), 157 (38), 115 (41); HRMS calcd. for $C_{13}H_{11}NO_2$: 187.0759, found: 187.0739; Microanalyses required for $C_{13}H_{11}NO_2$: C, 72.0%; H, 5.1%; N, 6.3%; found: C, 73.2%; H, 5.2%; N, 6.5%; HPLC: Daicel Chiralcel OD-H,

$\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=$ **22.3** and 26.4 min for the *O*-acetylcyanohydrin.

3.2.9. (*S*)-2-Hydroxy-2-(3-pyridinyl)acetonitrile (4i).[37] Pale yellow oil; $[\alpha]_D^{25}=-22.1$ (*c* 1$CHCl_3$) (50% ee from HPLC) [lit.[37] $[\alpha]_D^{25}=+21.4$, (*R*) enantiomer (*c* 0.95, $CHCl_3$) 50% ee)]; IR (film) ν_{max}: 3429 and 2239 cm^{-1}; ^1H NMR δ_H: 5.53 (br. s, 1H), 5.65 (s, 1H), 7.34 (dd, $J=4.8$, 7.9 Hz, 1H), 7.82 (d, $J=7.9$ Hz, 1H), 8.61 (d, $J=4.8$ Hz, 1H), 8.66 (s, 1H); ^{13}C NMR δ_C: 61.5, 118.9, 123.7, 132.2, 134.1, 147.6, 150.4; MS (EI) *m/z*: 108 (M^+-26, 4%), 84 (100); HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=12.1$ and **15.3** min. for the *O*-trimethylsilyl cyanohydrin.

3.2.10. (*S*)-2-(2-Furyl)-2-hydroxyacetonitrile (4j).[38] Colorless oil; $[\alpha]_D^{25}=+45.6$ (*c* 0.8, $CHCl_3$, 92% ee from HPLC) [lit[38] $[\alpha]_D^{25}=+50.3$ (*c* 1.6, $CHCl_3$, 99% ee)]; IR (film) ν_{max}: 3270 and 2258 cm^{-1}; ^1H NMR δ_H: 2.98 (br. s, 1H), 5.54 (s, 1H), 6.43 (dd, $J=3.0$, 1.9 Hz, 1H), 6.60 (d, $J=$ 3.0 Hz, 1H), 7.49 (d, $J=1.9$ Hz, 1H); ^{13}C NMR δ_C: 60.7, 109.9, 110.8, 117.0, 144.2, 148.5; MS (EI) *m/z*: 106 (M^+- 17, 1%), 96 (100); HPLC: Daicel Chiralpak AS, $\lambda=254$ nm, *n*-hexane/2-propanol 95/5, 1.0 mL/min, $t_r=21.0$ and **28.9** min for the *O*-acetylcyanohydrin.

3.2.11. (2*R*,3*E*)-2-(Methoxycarbonyloxy)-3-nonenenitrile (*O*-methoxycarbonyl-4k). Colorless oil; $[\alpha]_D^{25}=-14.4$ (*c* 2.0, $CHCl_3$, 96% ee from HPLC); IR (film) ν_{max}: 2249 and 1763 cm^{-1}; ^1H NMR δ_H: 0.89 (t, $J=6.7$ Hz, 3H), 1.25–1.30 (m, 4H), 1.40–1.45 (m, 2H), 2.13 (m, 2H), 3.86 (s, 3H), 5.54–5.61 (m, 1H), 5.66–5.68 (m, 1H), 6.19 (dt, $J=14.6$, 7.2 Hz, 1H); ^{13}C NMR δ_C: 13.8, 22.3, 27.8, 31.1, 31.9, 55.6, 65.1, 115.2, 119.4, 141.5, 154.0; 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; HPLC: Daicel Chiralcel OD-H, $\lambda=$ 210 nm, *n*-hexane/2-propanol 95/5, 0.5 mL/min, $t_r=$**9.6** and 10.8 min.

3.2.12. (2*S*,3*E*)-2-Hydroxy-4-phenyl-3-butenenitrile (4l).[39] Colorless oil; $[\alpha]_D^{25}=-22.7$ (*c* 1, $CHCl_3$, 99% ee from HPLC) [lit.[33] $[\alpha]_D^{25}=+19.2$, (*R*) enantiomer (*c* 1.9, $CHCl_3$, 72% ee)]; IR (film) ν_{max}: 3413 and 2249 cm^{-1}; ^1H NMR δ_H: 3.65 (br. s, 1H), 5.14 (d, $J=5.9$ Hz, 1H), 6.25 (dd, $J=15.8$, 5.9 Hz, 1H), 6.91 (d, $J=15.8$ Hz, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR δ_C: 61.8, 118.1, 122.3, 127.0, 128.8, 129.0, 134.7, 135.2; MS (EI) *m/z*: 142 (M^+-17, 1%), 131 (100), 103 (53), 77 (39); HPLC: Daicel Chiralpak AS, $\lambda=$ 254 nm, *n*-hexane/2-propanol 99.3/0.7, 1.0 mL/min, $t_r=$ 16.5 and **18.8** min for the *O*-acetylcyanohydrin.

3.2.13. (*S*)-2-Hydroxy-4-phenylbutanenitrile (4m).[6b] Colorless oil; $[\alpha]_D^{25}=+11.3$ (*c* 0.9; $CHCl_3$, 88% ee from HPLC) [lit.[6b] $[\alpha]_D^{25}=+6.6$ (*c* 0.68, $CHCl_3$, 97% *ee*)]; IR (film) ν_{max}: 3433 and 2248 cm^{-1}; ^1H NMR δ_H: 2.11–2.19 (m, 2H), 2.83 (t, $J=7.1$ Hz, 2H), 3.55 (br. s, 1H), 4.40 (t, $J=6.7$ Hz, 1H), 7.18–7.33 (m, 5H); ^{13}C NMR δ_C: 30.6, 36.5, 60.3, 119.8, 126.5, 128.4, 128.6, 139.5; MS (EI) *m/z*: 135 (M^+-26, 6%), 134 (63), 105 (33), 91 (100), 78 (45), 65 (17), 51 (22); HPLC: Daicel Chiralcel OD-H, $\lambda=$ 254 nm, *n*-hexane/2-propanol 99/1, 1.0 mL/min, $t_r=8.9$ and **12.2** min for the *O*-TBDMS-cyanohydrin.

3.2.14. (*S*)-2-Hydroxy-*n*-octanenitrile (4n).[6b] Colorless oil; $[\alpha]_D^{25}=-8.0$ (*c* 1.3, $CHCl_3$, 66% ee from HPLC) [lit.[6b] $[\alpha]_D^{25}=-13.3$ (*c* 1, $CHCl_3$, 98% *ee*)]; IR (film) ν_{max}: 3327 and 2247 cm^{-1}; ^1H NMR δ_H: 0.9 (t, $J=7.0$ Hz, 3H), 1.22–1.38 (m, 6H), 1.42–1.54 (m, 2H), 1.82–1.88 (m, 2H), 2.19 (br. s, 1H), 4.47 (t, $J=6.7$ Hz, 1H); ^{13}C NMR δ_C: 13.9, 22.4, 24.4, 28.5, 31.5, 36.2, 61.4, 120.0; MS (EI) *m/z*: 141 (M^+, 6%), 129 (11), 114 (19), 101 (28), 75 (40), 55 (100); HPLC: Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 99.6/0.4, 0.5 mL/min, $t_r=$**31.8** and 35.6 min for the *O*-benzoylcyanohydrin.

3.2.15. (*S*)-2-Cyclohexyl-2-hydroxyacetonitrile (4o).[39] Pale yellow oil; $[\alpha]_D^{25}=-2.3$ (*c* 2.0, $CHCl_3$, 20% ee from GC) [lit.[39] $[\alpha]_D^{25}=+8.2$, (*R*) enantiomer (*c* 0.77, $CHCl_3$, 79% ee)]; IR (film) ν_{max}: 3441 and 2249 cm^{-1}; ^1H NMR δ_H: 1.07–1.35 (m, 6H), 1.68–1.88 (m, 5H), 3.47 (br. s, 1H), 4.26 (d, $J=6.6$ Hz, 1H); ^{13}C NMR δ_C: 25.8, 27.7, 28.1, 45.7, 66.1, 119.4; MS (EI) *m/z*: 112 (M^+-27, 6%), 94 (18), 83 (46), 68 (27), 55 (100); GC: WCOT γ-CD column (0.25 nm diameter, stationary phase FS-Lipodex-E with a film thick of 0.25 μm), $T_{injector}=250$ °C, $T_{detector}=260$ °C, $T_{column}=$ 90 °C (3 min) and 180 °C (10 °C/min), $P=120$ kPa, $t_r=$ 21.2 and **21.5** min for the *O*-methoxycarbonylcyanohydrin.

3.2.16. Synthesis of (*S*)-2-hydroxy-3-methyl-4-(2-methyl-4-thiazolyl)-3-butenenitrile (4p).[6b] The reaction was performed as described before starting from the aldehyde **6**[6b] adding 9 equiv. of trimethylsilylcyanide in one portion, keeping the reaction at −20 °C for 38 h. The work up and purification methods were done according to the literature[6b] obtaining pure compound **4p** as colorless oil; $[\alpha]_D^{25}=-14.8$ (*c* 0.7, $CHCl_3$, 92% ee from HPLC) [lit.[6b] $[\alpha]_D^{25}=-16.5$, (*c* 0.7, $CHCl_3$, 99% ee)]; IR (film) ν_{max}: 3354 and 2346 cm^{-1}; ^1H NMR δ_H: 2.19 (s, 3H), 2.73 (s, 3H), 4.92 (s, 1H), 6.66 (s, 1H), 7.05 (s, 1H); ^{13}C NMR δ_C: 14.3, 19.2, 67.7, 117.7, 118.5, 121.6, 133.9, 151.6, 165.2; *m/z*: 193 (M^+, 1%), 177 (49), 150 (46), 136 (41), 75 (49); HPLC: Daicel Chiralpak AD, $\lambda=254$ nm, *n*-hexane/2-propanol 99/1, 0.5 mL/min, $t_r=11.2$ and **12.3** min, for the *O*-TBDMS-cyanohydrin.

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Catalytic asymmetric synthesis of (*S*)-oxybutynin and a versatile intermediate for antimuscarinic agents

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Abstract—A practical synthesis of (*S*)-oxybutynin, a muscarinic receptor antagonist, using catalytic enantioselective cyanosilylation of cyclohexyl phenyl ketone (**9a**) as a key step is described. The key reaction proceeded with 94% ee using 1 mol% of Gd-**1** catalyst, and was performed on a 100 g-scale. In addition, a short catalytic enantioselective synthesis of the versatile intermediate for Scios Nova analogues of antimuscarinic agents (**7**) is described. Application of the catalytic enantioselective cyanosilylation to ketones containing two sterically similar substituents on the carbonyl group is also discussed.

1. Introduction

In 2000, we developed a general catalytic enantioselective cyanosilylation of ketones using a catalyst derived from ligand **1** and $Ti(O^iPr)_4$ in a 1:1 ratio (Scheme 1).[1,2] (*R*)-Ketone cyanohydrins are obtained with high enantioselectivity through a presumed dual activation[3] transition state depicted as **3**, which was suggested based on kinetic studies and results using a control catalyst lacking the Lewis base moiety. The efficiency (enantioselectivity and catalyst turnover number) of the Ti-catalyzed reaction was further improved by developing a tuned ligand **2** containing an electron-withdrawing benzoyl group at the catechol moiety.[4] For the synthesis of (*S*)-ketone cyanohydrins, we developed a catalyst prepared from **1** and $Gd(O^iPr)_3$ in a 1:2 ratio.[5] This (*S*)-selective Gd-catalyst is more reactive than the (*R*)-selective Ti-catalyst. Mechanistic studies suggested that the active catalyst is a 2:3 complex of gadolinium cyanide and **1**, and the reaction proceeds through an intramolecular cyanide transfer from the nucleophilic gadolinium cyanide activated by the phosphine oxide, to the ketone activated by the Lewis acidic gadolinium cyanide (**4**). These reactions are practical and of broad substrate scope, and the catalytic enantioselective syntheses of fostriecin[6] (a natural anticancer compound) and camptothecin[5] (an important anticancer drug) were achieved using these reactions as key steps.

Oxybutynin (Ditropan: **5**) is a widely utilized muscarinic receptor antagonist for the treatment of urinary urgency, frequency, and incontinence.[7] A number of derivatives have been synthesized mainly by modifying the ester (or the amide) and the cycloalkyl parts (for examples, see Fig. 1).[8] Some of these analogues have improved M_3-receptor subtype selectivity and thus the side effects caused by antagonizing other subtypes, such as M_1- and M_2-receptors, are minimized. A structurally common feature of oxybutynin and related compounds is the chiral tertiary α-hydroxy carbonyl moiety. Although oxybutynin is currently prescribed in racemic form, the (*S*)-enantiomer is proposed to have an improved therapeutic profile. Therefore, there is a high demand for the development of an efficient enantioselective synthetic route. Previously reported methods utilized diastereoselective reactions that require a stoichiometric amount of chiral auxiliary or a chiral starting material to construct the chiral stereocenter of **5**.[9] We reported the first practical catalytic enantioselective synthesis of the key synthetic intermediate **11**, utilizing catalytic cyanosilylation of the ketone as a key step.[10] Our synthesis produced high enantioselectivity (up to 94% ee) from cyclohexyl phenyl ketone (**9a**). Based on the high enantioselectivity obtained from a ketone containing two sterically similar substituents (phenyl and cyclohexyl), we investigated the applicability of the Gd-catalyst to other related ketones. Among the substrates studied, excellent enantioselectivity (97% ee) was obtained from cyclobutyl phenyl ketone (**9f**). This finding led us to apply the catalytic

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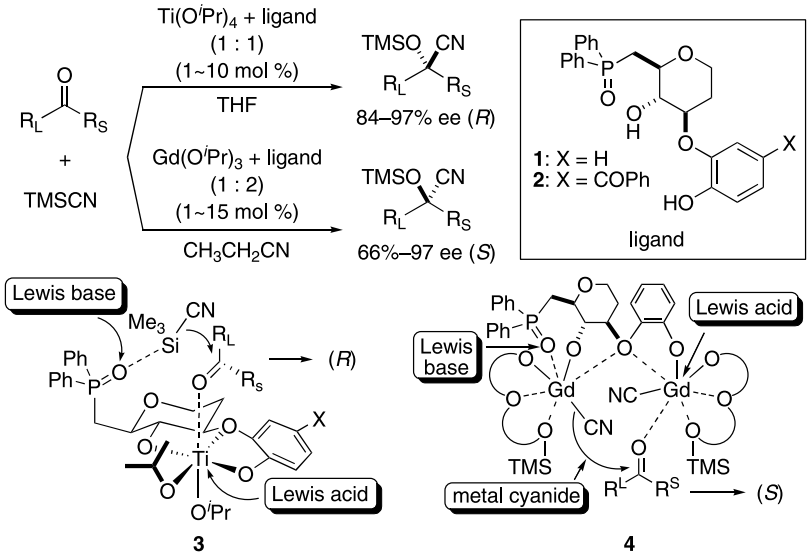


Scheme 1. Catalytic enantioselective cyanosilylation of ketones.

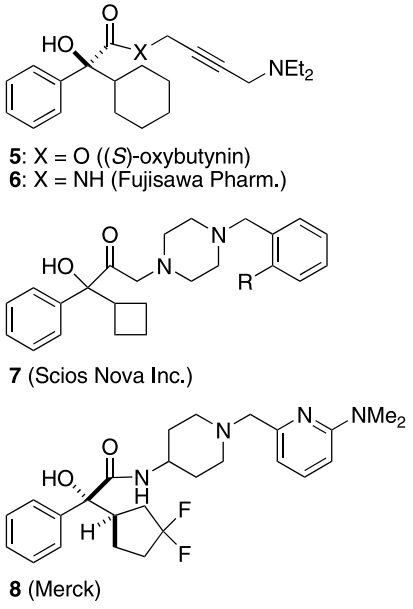


Figure 1.

enantioselective cyanosilylation to a short synthesis of the versatile synthetic intermediate for Scios Nova analogues (for example, see **7**)[8b] of subtype-selective antimuscarinic agents. This paper describes the details of these syntheses.

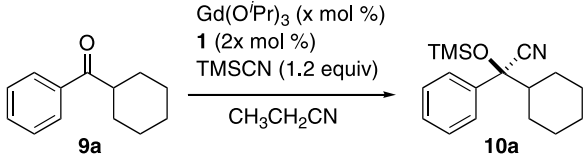
2. Results and discussion

2.1. Catalytic enantioselective synthesis of (*S*)-oxybutynin

Substrate **9a** for the oxybutynin synthesis is an extremely challenging ketone with respect to the induction of enantioselectivity. In general, to achieve high enantioselectivity of a nucleophilic addition to carbonyl compounds, the chiral catalyst needs to differentiate two lone pairs of the carbonyl oxygen atom for the coordination to the Lewis acid metal of the chiral catalyst. In the case of ketone **9a**, however, the difference in the steric demand of these lone pairs is not sufficient because these lone pairs are *cis* to sterically similar phenyl or cyclohexyl groups.[11]

Despite the expected difficulties, the catalytic enantioselective cyanosilylation of ketone **9a** proceeded at −60 °C

Table 1. Catalytic enantioselective cyanosilylation of ketone **9a**



Entry	Cat. (×mol%)	Temperature (°C)	Time (h)	Yield (%)[a]	ee (%)[b]
1	5	−60	21	96	95
2	5	−40	1.5	99	91
3	1	−40	50	99	85
4[c]	1	−40	40	100	94

[a] Isolated yield.
[b] Determined by chiral HPLC analysis.
[c] The ketone was added prior to TMSCN (see Section 4 for details). In other entries, ketones were added at the last stage.

for 21 h in the presence of 5 mol % of Gd-catalyst, affording the desired (*S*)-**10a** in 96% yield with 95% ee (Table 1, entry 1, catalyst concentration = 0.075 M, ketone concentration = 1.5 M). The absolute configuration of **10a** was determined after conversion to carboxylic acid **11**, and by comparing the optical rotation with the reported value.[9a] This is the same enantioselectivity as obtained with other previously studied simple ketones such as acetophenone,[5] suggesting that the catalyst recognizes the cyclohexyl group as being smaller than the phenyl group. For comparison of the reactivity, we investigated the reaction using the (*R*)-selective Ti-catalyst; however the Ti-complex did not promote the reaction of **9a** at low temperature. The reaction proceeded at room temperature with the Ti-catalyst, and (*R*)-**10a** was obtained in 96% yield with only 7% ee (36 h).

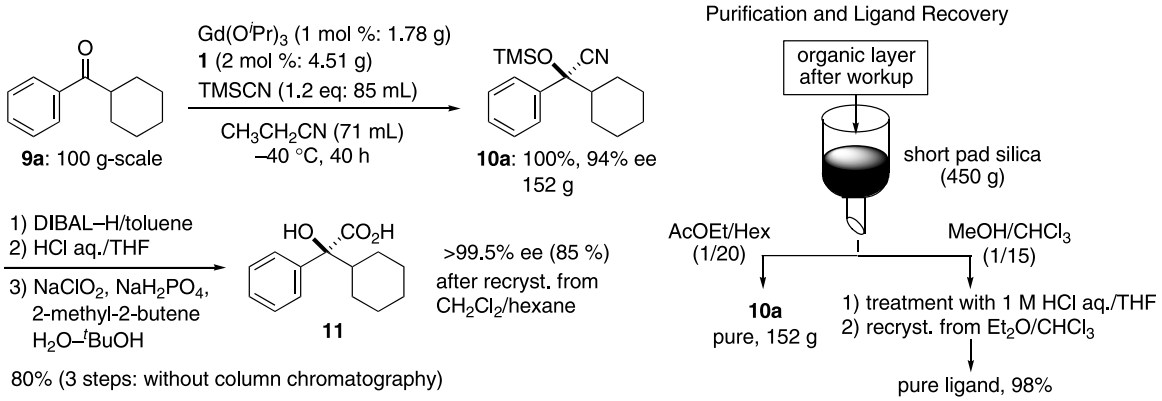
To improve the practicality of the Gd-catalyzed ketone cyanosilylation for (*S*)-oxybutynin synthesis, we decreased the catalyst loading. Using 1 mol% Gd-catalyst, however, resulted in a sluggish reaction at −60 °C, giving the product in 39% yield with 64% ee (9 days, catalyst concentration = 0.015 M, ketone concentration = 1.5 M). Increasing the reaction temperature to −40 °C and using a higher concentration, the reaction proceeded to completion to give the product in 99% yield with 85% ee (entry 3, catalyst concentration = 0.075 M, ketone concentration = 7.5 M). We hypothesized that the decrease in enantioselectivity with the lower amount of catalyst was due in part to the initial heat generation when a large amount of substrate ketone was added in one portion to a mixture of the catalyst and TMSCN, following the previous general procedure. Therefore, we first added the substrate ketone to the catalyst, then cooled the reaction temperature to −40 °C, added the solvent, and slowly added the TMSCN (over 15 min). This procedure improved the results and the product was obtained with 94% ee (entry 4). The reaction and purification procedures are practical and we performed the reaction on a 100 g-scale. After the usual aqueous workup, the crude oil was purified through short-pad silica gel column chromatography (Scheme 2). Pure **10a** was obtained with EtOAc/hexane (1:20) elution, followed by MeOH/$CHCl_3$ (1:15) elution to obtain the ligand-containing fraction (a mixture of ligand **1** and the silylated ligand). The pure ligand **1** was recovered in 98% yield after acidic desilylation (1 M HCl aq in THF) and recrystallization. The recovered ligand can be reused many times without any loss of efficiency.

Having established a practical method for the catalytic enantioselective cyanosilylation of the ketone, the next task was to convert the cyanide to the carboxylic acid. The conversion was initially problematic, however, probably due to steric hindrance. Acidic hydrolysis or alcoholysis gave predominantly ketone **9a** through the elimination of HCN. Basic hydrolysis after conversion to the THP-protected cyanohydrin resulted in no reaction. Therefore, we investigated the reduction–oxidation procedure (Scheme 2). Careful reduction of **10a** with DIBAL-H in toluene, desilylation with 4 M HCl aq in THF, followed by oxidation with $NaClO_2$ gave the known α-hydroxy carboxylic acid **11** in 80% overall yield (3 steps). Chemically pure **11** was obtained through a base/acid aqueous workup without silica gel column chromatography. Recrystallization from CH_2Cl_2/hexane gave an enantiomerically pure intermediate for oxybutynin synthesis.[12]

2.2. Catalytic enantioselective cyanosilylation of ketones containing two sterically similar substituents on the carbonyl carbon

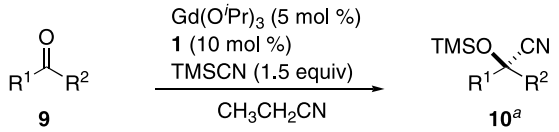
The unusually high enantio-differentiation ability of the catalyst on the apparently difficult substrate **9a** led us to study the applicability of the Gd-catalyzed enantioselective cyanosilylation to other ketones containing two sterically similar substituents on the carbonyl carbon. High to excellent enantioselectivity was obtained except in the cases of cyclopentyl phenyl ketone (**9e–H**: entry 4) and isopropyl phenyl ketone (**9l–H**: entry 14: Table 2). Even simple linear ketone **9n** gave the product with 85% ee (entry 17). Therefore, differentiation of the two carbonyl oxygen lone pair by the Gd-**1** catalyst might be due mainly to the electronic characteristics of the two substituents on the carbonyl group.[11] Some of the products obtained with high enantioselectivity should be very useful for synthesizing new chiral oxybutynin analogues (for example, see Section 4).

The sharp contrast in the enantiomeric excess of **10e–H** and **10l–H**, and products from other ketones is intriguing from a mechanistic point of view. The results cannot be explained from the ground state structure difference, based on the

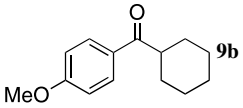
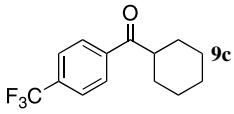
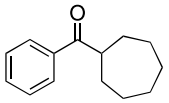
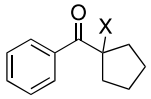
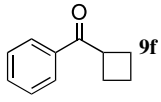
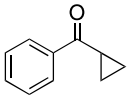
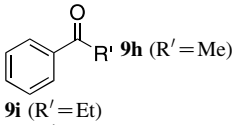
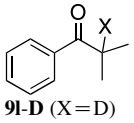
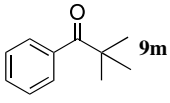
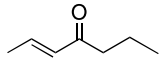


Scheme 2. Practical catalytic enantioselective synthesis of (*S*)-oxybutynin key intermediate.

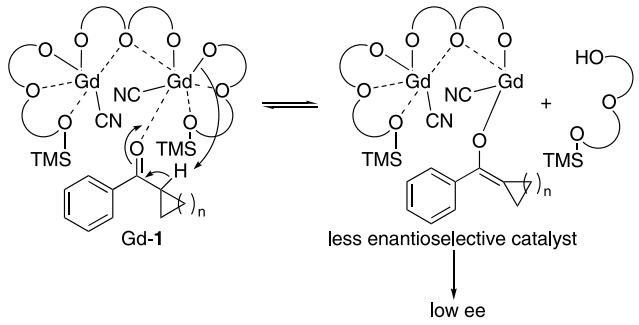
Table 2. Catalytic enantioselective cyanosilylation of ketones containing sterically similar substituents



9 **10**[a]

Entry	Ketone	Temperature (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	 **9b**	−40	22	99	94
2	 **9c**	−40	1	96	83
3	 **9d**	−40	5	99	94
4	 **9e-H** (X=H)	−40	64	87	22
5[d]	**9e-D**	−40	1	99	95
6[e]	**9e-D**	−40	1	99	95
7[f]	**9e-D** (X=D)	−40	18	99	78
8	 **9f**	−40	2	99	97
9	 **9g**	−40	48	97	82
10	 **9h** (R′=Me)	−40	1	89	95
11	**9i** (R′=Et)	−60	14	93	97
12	**9j** (R′-Pr)	−60	2.5	94	97
13	**9k** (R′=Bu)	−60	14	91	87
14	 **9l-H** (X=H)	−40	20	99	38
15[g]	**9l-D** (X=D)	−40	1	81	96
16	 **9m**	−60	2.5	90	80
17	 **9n**	−40	1	87	85

[a] The absolute configuration of the product was temporarily assigned based on the analogy to **10a**.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] 85%-D.
[e] 65%-D.
[f] 21%-D.
[g] 80%-D.



Scheme 3.

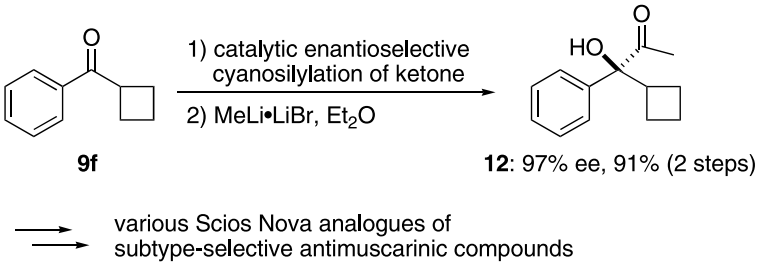
comparison of the most stable conformation of these substrates; molecular modeling studies indicated that **9e–H** and **9l–H** contain similar conformation and electronic characteristics to other ketones. The reactivity-enantioselectivity relation indicated a general trend in that high enantioselectivity was obtained when the reactions proceeded smoothly (Table 2). To explain this trend, we hypothesized that the asymmetric catalyst might act as a Brönsted base to deprotonate the starting ketones. Based on the analogy from the fact that the equilibrium acidity of nitrocyclopentane is significantly higher (pK_a units of ca. 2) than nitrocyclobutane or nitrocyclohexane due to the difference in the released strain energy in the nitronate formation,[13] it might be reasonable to assume that the α-proton of **9e–H** is more acidic than that of **9a** or **9f**. Thus, **9e–H** (and maybe **9l–H**) might be more prone to deprotonation. This competitive deprotonation pathway might cause a ligand exchange to produce a less enantioselective catalyst (Scheme 3). Based on this hypothesis, we planned to utilize a deuterium kinetic isotope effect to prevent the undesired deprotonation.[14] As we expected, the reactions using **9e–D** and **9l–D** proceeded rapidly and the products were obtained with up to 95 and 96% ee, respectively (Table 2, entry 5 vs entry 4 and entry 15 vs entry 14). Even using the starting ketone with 21% deuterium incorporation at the α-position, the enantioselectivity was significantly higher than the non-deuterated one (entry 7 vs entry 4). Thus, the enantioselectivity of the product should be determined by the population ratio of the highly enantioselective Gd-**1** and ligand-exchanged catalyt(s) with reduced enantioselectivity (see Scheme 3), as well as the reaction kinetics promoted by these complexes. To our knowledge, this is the first example of a dramatic advantage using an isotope effect in catalytic enantioselective reactions. The results provide very important insight for a new use of the Gd-catalyst as a Brönsted base.

2.3. Short-step synthesis of a versatile intermediate for subtype-selective muscarinic receptor antagonists

The research group of Scios Nova Inc., reported a series of compounds with M_3-subtype-selective antimuscarinic activity.[8b] These compounds contain a tertiary alcohol with phenyl and cyclobutyl groups as substituents on the tetrasubstituted carbon (for example, see **7**) as the common structure. These compounds were readily synthesized using the methyl ketone **12** as a versatile synthetic intermediate; α-bromination followed by the substitution with amines. Although the Scios Nova group reported promising biological activities using racemic compounds, it is highly probable that the (*S*)-enantiomer possesses higher potency than the (*R*)-enantiomer, based on the analogy to oxybutynin. Thus, we developed a short synthetic route to (*S*)-**12**, using the catalytic enantioselective cyanosilylation of ketone **9f**. As described in the above section, the corresponding precursor cyanohydrin **10f** was obtained with excellent enantioselectivity (97% ee: Table 2, entry 6). The addition of MeLi to **10f**[15] followed by hydrolysis with silica gel gave the methyl ketone **12** with no decrease in enantioselectivity (91% yield over 2 steps). Thus, a two-step catalytic enantioselective synthesis of the versatile intermediate for subtype-selective antimuscarinic lead compounds from commercially available ketone **9f** was achieved (Scheme 4).

3. Conclusions

We developed a practical synthetic route for an important pharmaceutical, (*S*)-oxybutynin. The chiral center of the core tertiary α-hydroxy carboxylic acid was constructed by the catalytic enantioselective cyanosilylation of ketones using 1 mol% of Gd-**1** complex. These procedures are suitable for large-scale synthesis with minimal silica gel column chromatography purification. In addition, a two-step catalytic enantioselective synthesis of the versatile intermediate for subtype-selective antimuscarinic compounds (Scios Nova analogues) was developed. Furthermore, the excellent enantioselectivity obtained in the reaction of ketones containing two sterically similar substituents indicated that the Gd-**1** catalyst differentiates the electronic characteristics of the substituents. There was a dramatic deuterium isotope effect on the reaction kinetics and enantioselectivity in the case of ketones **9e** and **9l**, which suggested that ketone deprotonation might be a possible competitive pathway for some ketones. Based on these new findings, studies to develop a new chiral Brönsted base catalyst are currently ongoing.



Scheme 4. Short-step synthesis of versatile intermediate for subtype-selective antimuscarinic compounds.

4. Experimental

4.1. 100 g-Scale cyanosilylation of 9a

$Gd(O^iPr)_3$ (5.31 mmol, 0.2 M stock solution in THF, purchased from Kojundo Chemical Laboratory Co., Ltd. Fax: +81-492-84-1351) in THF (26.6 ml) was added to a suspension of chiral ligand **1** (4.51 g, 10.6 mmol) in THF (106 ml) in an ice bath and the mixture was stirred for 30 min at 45 °C. After cooling to room temperature, THF was evaporated and the residue was dried for 6 h under vacuum (5 mmHg). To this catalyst powder, ketone **9a** (100 g, 0.531 mol) was added. Propionitrile (71 ml) and TMSCN (85 ml, 0.637 mol) were successively added at −40 °C, and the mixture was stirred for 40 h at −40 °C. H_2O was added to quench the reaction (caution: HCN is generated), and the product and the ligand were extracted with EtOAc. The combined organic layers was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a crude oil, which was purified through short pad SiO_2 column chromatography (450 g; EtOAc/hexane=1:20) to give pure **10a** as a colorless oil (152 g, 100% yield). The ligand and the silylated ligand were eluted from the column with $CHCl_3$/MeOH=15:1, treated with HCl aq in THF, extracted, and purified by recrystallization to recover pure ligand **1** in 98% yield.

4.2. General procedure for the conversion to benzoyl amide for ee determination

To a solution of **10a** (16.7 mg, 0.0581 mmol) in THF (0.2 ml) was added $LiAlH_4$ (6.3 mg, 0.166 mmol) at room temperature, and the resulting mixture was stirred at 40 °C for 1 h H_2O (1 drop), 15% NaOH (1 drop) and H_2O (3 drops) were successively added to the reaction mixture in an ice bath and ether (2 ml) was added to the resulting mixture. After stirring at room temperature for 30 min, Et_3N (2 drops) and benzoyl chloride (14 μl, 0.121 mmol) were added to the reaction mixture in an ice bath. After stirring for 20 min, water was added and the mixture was extracted with EtOAc. The organic layer was washed with satd $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to give a crude product, which was purified by preparative TLC (EtOAc/hexane, 1:3) to give the corresponding benzoyl amide.

4.2.1. Cyclohexyl(phenyl)[(trimethylsilyl)oxy]acetonitrile (10a). Colorless oil; ^1H NMR ($CDCl_3$) δ 7.47–7.45 (m, 2H), 7.39–7.32 (m, 3H), 2.03–1.99 (m, 1H), 1.82–1.79 (m, 1H), 1.75–1.68 (m, 2H), 1.65–1.62 (m, 1H), 1.39–1.35 (m, 1H), 1.21–1.02 (m, 5H), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 140.33, 128.60, 128.35, 125.96, 120.35, 79.71, 50.84, 27.49, 27.40, 26.13, 26.09, 26.07, 0.97; EI-MS *m/z* 287 (M^+); EI-HRMS calcd for $C_{17}H_{25}NOSi$ (M^+): 287.1705, Found: 287.1705; $[\alpha]_D^{27}=-19.4$ ($c=1.41$, $CHCl_3$) (94% ee). HPLC (the corresponding benzoyl amide; DAICEL CHIRALPAK AD-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 18.9 min (major), 20.8 min (minor).

4.2.2. (2*S*)-Cyclohexyl(hydroxy)phenylacetic acid (11). DIBAL-H (1.0 M in toluene, 34.8 ml, 34.8 mmol) was added dropwise to a solution of cyanohydrin **10a** (5.00 g, 17.4 mmol) in toluene (50 ml) at −78 °C for 75 min. Then, the bath temperature was increased to −40 °C and the solution was stirred for 11 h. After the reaction was completed, satd NH_4Cl aq was added, followed by the addition of 1 M HCl. After stirring for 30 min, the product was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was dissolved in THF (30 ml) and 4 M HCl aq (30 ml) was added at room temperature for desilylation (2 h). Extraction with EtOAc, successive wash with satd $NaHCO_3$ aq and brine, and evaporation of the organic solvent gave the corresponding hydroxy aldehyde, which was subjected to the following oxidation. $NaClO_2$ (79%, 2.99 g, 26.1 mmol) was added portionwise to a solution of the residue, 2-methyl-2-butene (8.1 ml), and NaH_2PO_4 (2.09 g, 17.4 mmol) in ^{t}BuOH (50 ml) and H_2O (12.5 ml) for 15 min in an ice bath, and the mixture was stirred for 1 h at room temperature. After cooling in an ice bath, 2 M NaOH aq was added until pH was greater than 10, and the solution was slowly added to Na_2SO_3 (4.84 g, 38.4 mmol) in H_2O (80 ml). ^{t}BuOH was evaporated under reduced pressure and the water layer (pH >10) was washed with Et_2O (×3). The water layer was acidified with conc. HCl to pH=1 and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Filtration and evaporation of the solvent gave a white powder of **11** (3.28 g, 80%). The enantiomeric excess of **11** was determined by chiral HPLC [DAICEL CHIRALPAK AS, hexane/2-propanol/TFA=95:5:0.1, 1.0 ml/min, t_R 7.3 (minor) and 10.6 min (major)]. Enantiomerically pure (>99% ee) **11** was obtained by recrystallization from CH_2Cl_2/hexane (1:30) in 85% yield. ^1H NMR ($CDCl_3$) δ 7.64 (d, 2H, $J=7.6$ Hz), 7.36–7.33 (m, 2H), 7.29–7.26 (m, 1H), 2.29–2.23 (m, 1H), 1.83–1.81 (m, 1H), 1.67–1.61 (m, 3H), 1.49–1.41 (m, 1H), 1.38–1.29 (m, 1H), 1.21–1.02 (m, 4H); ^{13}C NMR (C_6D_6) δ 180.71, 140.04, 128.36, 127.88, 126.09, 81.21, 45.88, 27.55, 26.43 (overlap), 26.29, 25.60; mp 142–143 °C; EI-MS *m/z* 234 (M^+); EI-HRMS calcd for $C_{14}H_{18}O_3$ (M^+): 234.1256, Found: 234.1257; $[\alpha]_D^{27}=+21.8$ ($c=1.00$, EtOH) (>99% ee) (lit.[9c] $[\alpha]^{22}{}_D=+22.6$ (EtOH)).

4.3. General procedure for the catalytic asymmetric cyanosilylation of ketones

$Gd(O^iPr)_3$ (0.015 mmol, 0.2 M stock solution in THF) in THF (75 μl) was added to a suspension of chiral ligand **1** (12.7 mg, 0.030 mmol) in THF (0.3 ml) in an ice bath and the mixture was stirred for 30 min at 45 °C. After cooling to room temperature, THF was evaporated and the residue was dried for 1 h under vacuum (5 mmHg). Propionitrile (0.2 ml) was added to this catalyst powder, and TMSCN (60 μl, 0.45 mmol) and a ketone (0.300 mmol) were added at −40 or −60 °C, and the mixture was stirred at the temperature shown in Table 2 until the starting ketone disappeared on TLC. Workup and purification procedures are the same as for the large-scale reaction (vide supra). ee was determined after conversion to the corresponding benzoyl amide (1. LAH, THF, 2. benzoyl chloride, Et_3N).

4.3.1. Cyclohexyl(4-methoxyphenyl)[(trimethylsilyl)oxy]acetonitrile (10b). Colorless oil; ^1H NMR ($CDCl_3$) δ 7.39–7.36 (m, 2H), 6.90–6.87 (m, 2H), 3.82 (s, 3H), 2.04–2.01 (m, 1H), 1.82–1.80 (m, 1H), 1.73–1.68 (m, 2H), 1.65–1.63

(m, 1H), 1.38–1.35 (m, 1H), 1.22–1.00 (m, 5H), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 159.79, 132.40, 127.24, 120.50, 113.67, 79.43, 55.41, 50.90, 27.52 (overlap), 26.17, 26.12, 26.10, 1.02; EI-MS *m/z* 317 (M^+); EI-HRMS calcd for $C_{18}H_{27}NO_2Si$ (M^+): 317.1811, found: 317.1807; $[\alpha]_D^{27} = -20.8$ ($c=1.16$, $CHCl_3$) (94% ee). HPLC (the corresponding benzoyl amide; DAICEL CHIRALCEL OD-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 13.2 min (minor), 17.4 min (major).

4.3.2. Cyclohexyl[4-(trifluoromethyl)phenyl] [(trimethylsilyl)oxy]acetonitrile (10c). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.65 (d, 2H, $J=8.4$ Hz), 7.60 (d, 2H, $J=8.4$ Hz), 1.97–1.95 (m, 1H), 1.83–1.80 (m, 1H), 1.72 (m, 2H), 1.66–1.64 (m, 1H), 1.40–1.38 (m, 1H), 1.22–1.05 (m, 5H), 0.13 (s, 9H); EI-MS *m/z* 355 (M^+); EI-HRMS calcd for $C_{18}H_{24}F_3NOSi$ (M^+): 355.1579, Found: 355.1577; $[\alpha]_D^{26} = -14.2$ ($c=1.98$, $CHCl_3$) (83% ee). HPLC (the corresponding benzoyl amide; DAICEL CHIRALPAK AD-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 14.4 min (major), 22.6 min (minor).

4.3.3. Cycloheptyl(phenyl)[(trimethylsilyl)oxy] acetonitrile (10d). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.50–7.48 (m, 2H), 7.39–7.32 (m, 3H), 2.08–2.04 (m, 1H), 1.97–1.92 (m, 1H), 1.82–1.75 (m, 1H), 1.65–1.40 (m, 8H), 1.33–1.22 (m, 2H), 0.07 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 140.64, 128.64, 128.42, 126.15, 120.65, 80.02, 52.34, 29.34, 28.75, 28.28, 27.92, 26.69, 26.68, 1.02; EI-MS *m/z* 301 (M^+); EI-HRMS calcd for $C_{18}H_{27}NOSi$ (M^+): 301.1862, found: 301.1862; $[\alpha]_D^{26} = -27.9$ ($c=0.31$, $CHCl_3$) (94% ee). HPLC (the corresponding benzoyl amide; DAICEL CHIRALPAK AD-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 18.1 min (major), 23.3 min (minor).

4.3.4. Cyclopentyl(phenyl)[(trimethylsilyl)oxy] acetonitrile (10e). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.52–7.49 (m, 2H), 7.39–7.31 (m, 3H), 2.43–2.36 (m, 1H), 1.77–1.62 (m, 4H), 1.58–1.46 (m, 2H), 1.44–1.39 (m, 2H), 0.10 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 141.28, 128.60, 128.49, 125.55, 120.72, 79.10, 53.72, 28.28 (overlap), 25.68, 25.62, 1.04; EI-MS *m/z* 273 (M^+); EI-HRMS calcd for $C_{16}H_{23}NOSi$ (M^+): 273.1549, found: 273.1553; $[\alpha]_D^{26} = -5.8$ ($c=0.48$, $CHCl_3$) (22% ee). HPLC (the corresponding benzoyl amide; DAICEL CHIRALPAK AD-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 15.9 min (major), 18.1 min (minor).

4.3.5. Cyclobutyl(phenyl)[(trimethylsilyl)oxy]acetonitrile (10f). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.46 (m, 2H), 7.37–7.3 (m, 3H), 2.71 (m, 1H), 2.18 (m, 1H), 2.03 (m, 1H), 1.87–1.73 (m, 4H), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 140.04, 128.63, 128.54, 125.18, 120.34, 77.76, 47.79, 23.32, 23.13, 16.51, 1.06; EI-MS *m/z* 259 (M^+); EI-HRMS calcd for $C_{15}H_{21}NOSi$ (M^+): 259.1392, found: 259.1401; $[\alpha]_D^{25} = -7.0$ ($c=0.60$, $CHCl_3$) (97% ee). HPLC (the corresponding benzoyl amide; DAICEL CHIRALCEL OJ-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 8.5 min (major), 10.3 min (minor).

4.3.6. Cyclopropyl(phenyl)[(trimethylsilyl)oxy] acetonitrile (10g). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.57–7.55 (m, 2H), 7.41–7.34 (m, 3H), 1.41–1.35 (m, 1H), 0.86–0.81 (m, 1H), 0.70–0.57 (m, 3H), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 141.53, 128.83, 128.64, 125.41, 120.35, 75.64, 24.17, 3.02, 2.74, 1.14; EI-MS *m/z* 245 (M^+); EI-HRMS calcd for $C_{14}H_{19}NOSi$ (M^+): 245.1236, found: 245.1233; $[\alpha]_D^{24} = -12.2$ ($c=1.23$, $CHCl_3$) (82% ee). HPLC (the corresponding benzoyl amide; DAICEL CHIRALPAK AD-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 16.3 min (minor), 37.1 min (major).

4.3.7. Phenyl-2-[(trimethylsilyl)oxy]pentanenitrile (10i).[16] HPLC (the corresponding benzoyl amide; DAICEL CHIRALPAK AS, hexane/2-propanol=9:1, 1.5 ml/min) t_R 15.3 min (major), 21.0 min (minor).

4.3.8. Phenyl-2-[(trimethylsilyl)oxy]hexanenitrile (10k). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.52–7.50 (m, 2H), 7.40–7.33 (m, 3H), 2.04–1.99 (m, 1H), 1.93–1.87 (m, 1H), 1.52–1.43 (m, 1H), 1.35–1.24 (m, 3H), 0.87 (t, 3H, $J=7.2$ Hz), 0.13 (s, 9H); HPLC (the corresponding benzoyl amide; DAICEL CHIRALPAK AS-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 22.9 min (major), 27.5 min (minor).

4.3.9. 3-Methyl-2-phenyl-2-[(trimethylsilyl)oxy] butanenitrile (10l).[17] GC (Varian Chirasil DEX CB (0.25 mm×25 m), column temperature=100 °C (isothermal), injector temperature=250 °C, detector temperature=280 °C, inlet pressure=1.3 kg/cm^2): t_R 25.9 min (major), 27.7 min (minor).

4.3.10. 3,3-Dimethyl-2-phenyl-2-[(trimethylsilyl)oxy] butanenitrile (10m).[18] GC (Varian Chirasil DEX CB (0.25 mm×25 m), column temperature=100 °C (isothermal), injector temperature=250 °C, detector temperature=280 °C, inlet pressure=1.3 kg/cm^2): t_R 31.7 min (major), 33.5 min (minor).

4.3.11. 2-Propyl-2-[(trimethylsilyl)oxy]-3-pentenenitrile (10n). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 6.05–5.98 (m, 1H), 5.39 (dq, $J=1.7$, 15.5 Hz, 1H), 1.81–1.75 (m, 4H), 1.69–1.61 (m, 1H), 1.56–1.47 (m, 1H), 1.46–1.36 (m, 1H), 0.94 (t, $J=7.5$ Hz, 3H), 0.18 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 131.27, 128.25, 120.33, 73.65, 45.23, 17.29, 13.70, 1.31; IR (neat, cm^{-1}) 2963; ESI-MS *m/z* 234 ($M+Na^+$); EI-HRMS calcd for $C_{11}H_{21}NOSi$ (M^+): 211.1392, Found: 211.1396; $[\alpha]_D^{22} = +3.6$ ($c=2.87$, $CHCl_3$) (80% ee). HPLC (DAICEL CHIRALPAK AS-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 14.4 min (minor), 16.8 min (major).

4.4. General procedure for preparation of α-D ketones (9e-D and 9l-D)

To a solution of KHMDS (0.5 M solution in toluene, 1.2 ml, 0.60 mmol), a ketone (0.50 mmol) was added at room temperature, and the mixture was stirred for 3.5 h in the case of **9e** and 10 h in the case of **9l**. After cooling in an ice bath, CD_3OD (0.2 ml, 5.0 mmol) was added, and the mixture was stirred for 10 min. Satd NH_4Cl was added, and the product was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. Filtration, evaporation of the solvent, and purification through silica gel column chromatography (EtOAc/hexane=1:19) gave the deuterated ketone. The D-incorporation ratio was determined to be 87% for **9e-D** and 80% for **9l-D**, respectively, based on ^{1}H NMR analysis.

4.4.1. Synthesis of methyl ketone 12. To a solution of the cyanohydrin **10f** (100 mg, 0.386 mmol) in ether (0.5 ml), MeLi·LiBr (1.5 M in ether, 0.39 ml, 0.578 mmol) was added in an ice bath. The reaction temperature was allowed to increase to room temperature for 3 h, and the reaction was continued at room temperature for 1 h. Silica gel was added, and the resulting suspension was stirred for 15 min. Filtration, evaporation, and purification through silica gel column chromatography gave the product methyl ketone in 91% yield as a colorless oil.

4.4.2. 1-Cyclobutyl-1-hydroxy-1-phenyl-propan-2-one (12). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.39–7.41 (m, 2H), 7.34 (m, 2H), 7.28 (m, 1H), 4.70 (s, 1H), 3.47 (quintet, J=8.3 Hz, 1H), 2.16 (m, 1H), 2.04 (m, 1H), 2.03 (s, 3H), 1.94 (m, 2H), 1.75–1.83 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 208.67, 139.85, 128.59, 127.78, 126.59, 83.09, 38.75, 23.50, 22.59, 20.56, 17.64; IR (neat, cm^{-1}) 3460, 1705; EI-MS *m/z* 204 (M^+), 186 (M+1-OH), 161 (M−$COCH_3$); EI-HRMS calcd for $C_{11}H_{13}O$ (M−$COCH_3$): 161.0961, found: 161.0322; $[\alpha]^{22}_D$=+149.0 (c=1.76, $CHCl_3$) (97% ee). HPLC (DAICEL CHIRALPAK AS-H, hexane/2-propanol=99:1, 1.0 ml/min) t_R 6.9 min (minor), 7.4 min (major).

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Synthesis of some new chiral bifunctional *o*-hydroxyarylphosphonodiamides and their application as ligands in Ti(IV) complex catalyzed asymmetric silylcyanation of aromatic aldehydes

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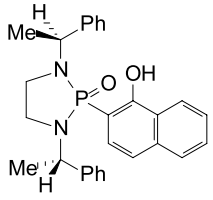
Abstract—Some new chiral bifunctional *o*-hydroxyarylphosphonodiamides were synthesized starting from (+)-*cis*-1,2,2-trimethylcyclopentane-1,3-diamine and the absolute configuration of the phosphorus atom was determined by X-ray diffraction analysis. Excellent enantioselectivity (up to 98% ee) was achieved in asymmetric silylcyanation of aromatic aldehydes using a chiral titanium complex formed in situ from $Ti(O^iPr)_4$ and *o*-hydroxyarylphosphonodiamide as the catalyst.

1. Introduction

Optically active cyanohydrins are important intermediates in organic synthesis for the synthesis of a variety of valuable classes of chiral compounds, such as α-amino acids, α-hydroxy carboxylic acids, β-amino alcohols, vicinal diols, α-hydroxyketones, etc. Many efficient approaches have been reported for obtaining them by biochemical and chemical methods.[1] In the latter, the most important one is the asymmetric silylcyanation of aldehydes with trimethylsilylcyanide catalyzed by a Lewis acid, such as $Ti(O^iPr)_4$, $TiCl_4$, $AlCl_3$, $SmCl_3$ etc. in the presence of a chiral ligand. In this reaction, a wide range of chiral ligands have been elaborated, such as bis-Schiff bases (salen),[2] Schiff bases,[3] dihydroxy compounds,[4] phosphorus compounds,[5] bis-oxazolines,[6] diamides,[7] ferrocenes,[8] sulfur[9] and boron compounds,[10] etc. As shown in the literature, most of the effective chiral ligands have a free hydroxyl group or an amino group bearing at least a N–H bond which is favorable to coordinate conveniently with the metal atom in the Lewis acid. Thus the moiety of the coordinated metal atom should work as a Lewis acid center (LA) which will activate the substrate aldehyde. Moreover, if a phosphoryl group (P═O) exists at an appropriate position in the ligand molecule, the unshared electron pair on the oxygen atom should act as a Lewis base (LB) which will activate the nucleophile trimethylsilyl cyanide. If the catalyst, contains both a Lewis acid center and a Lewis base center, namely, LALB catalyst, it is a new type of chiral bifunctional catalyst.[4a,b,5e,11] Based on these findings, recently, a new chiral bifunctional cyclic *o*-hydroxynaphthylphosphonodiamide **1** was synthesized starting from (−)-α-phenylethylamine and employed in the asymmetric silylcyanation of aromatic aldehydes in the presence of $Ti(O^iPr)_4$ by our research group. The corresponding cyanohydrins were obtained in high chemical yields with good to excellent enantiomeric excesses up to 90%.[5a] In order to further improve the enantioselectivity of this type of bifunctional cyclophosphonodiamde, in this paper, we will report the synthesis of two new cyclic *o*-hydroxyarylphosphonodiamides **2** and **3** containing a phosphorus stereocenter starting from (+)-*cis*-1,2,2-trimethylcyclopentane-1,3-diamine **4** and their application in asymmetric silylcyanation of aromatic aldehydes.



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Keywords: Chiral cyclophosphonodiamide; Asymmetric silylcyanation; Catalysis; Enantioselectivity; Aromatic aldehyde.
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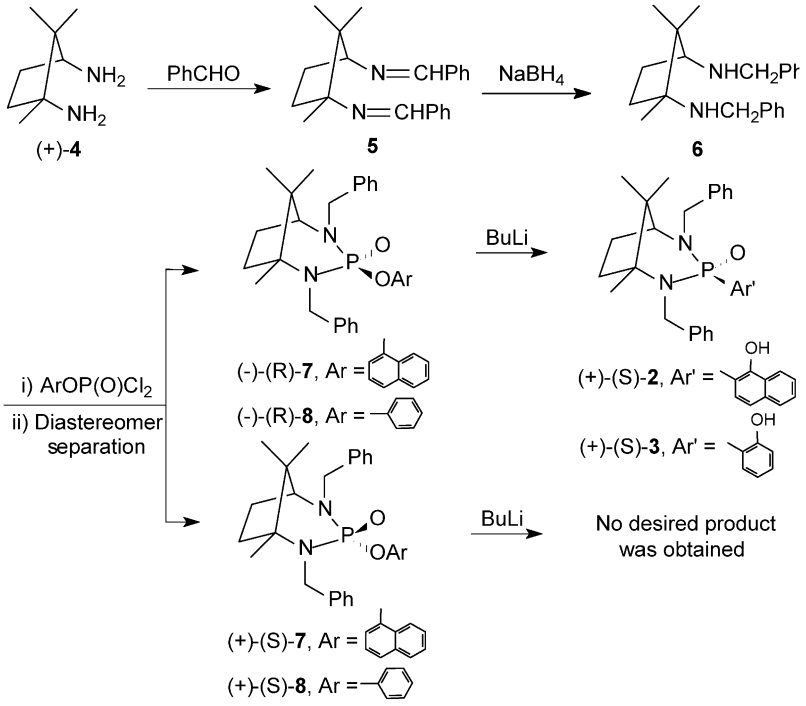


Scheme 1.

2. Results and discussion

2.1. Synthesis of ligands (+)-2, (+)-3 and determination of their stereochemistry

Condensation of 2 equiv of benzaldehyde with (+)-*cis*-trimethylcyclopentane-1,3-diamine **4**[12,13] derived from D-camphor led to *N*,*N*′-dibenzylidene-1,2,2-trimethylcyclopentane-1,3-diamine **5**. The reduction of the latter with sodium borohydride gave *N*,*N*′-dibenzyl-1,2,2-trimethylcyclopentane-1,3-diamine **6**. Then cyclization of compound **6** with *O*-aryl phosphorodichloridate afforded cyclic phosphorodiamidate **7** (Ar=1-naphthyl) or **8** (Ar=phenyl). A pair of diastereomers of **7** and **8** was obtained and separated via column chromatography. A subsequent P–O to P–C rearrangement upon treatment of (−)-**7** and (−)-**8** with *n*-BuLi resulted in the formation of (+)-cyclophosphonodiamides **2** and **3**. The rearrangement of (+)-**7** and (+)-**8** was carried out under the same condition, unfortunately, a complicated mixture rather than the desired corresponding rearrangement product was obtained (Scheme 1).

The absolute configuration of the phosphorus atom in (+)-**7** was determined as *S* via X-ray diffraction analysis (shown in Fig. 1).[14] Thus the absolute configuration of the phosphorus atom in (−)-**7** should be *R*. At the same time, a crystallographic study showed that the absolute configuration of the phosphorus atom in (+)-**2** was *S* (shown in Fig. 2).[15] Therefore, the rearrangement from (−)-(*R*)-**7** to (+)-(*S*)-**2** proceeded with retention of configuration at the phosphorus atom.

The trigonal bipyrimidal (TBP) concept and Berry's pseudorotation theory[16] could be used to explain the mechanism of this type of rearrangement. Firstly, the nucleophilic attack of carbanion formed at the α-position of the naphthalene ring in (−)-(*R*)-**7** occurs at the phosphorus opposite the N′ atom in the 1,3-diazaphosphorine, which results in the formation of the TBP-1 intermediate in which the β-carbon of naphthalene and the N′ atom are both placed at apical positions. The P–O–C in the oxaphosphetane has better apicophilicity than the N′ atom, and at the same time it is also a good leaving group. Therefore, ligand reorganization through Berry pseudorotation (BPR) of the initially formed TBP-1 to form the TBP-2 intermediate is possible.[17] Then the leaving group, naphthoxy, departs from

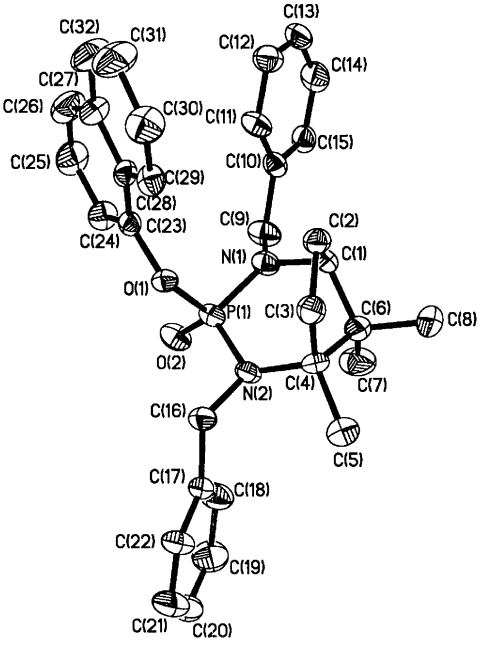


Figure 1. Molecular structure of (+)-(*S*)-**7**.

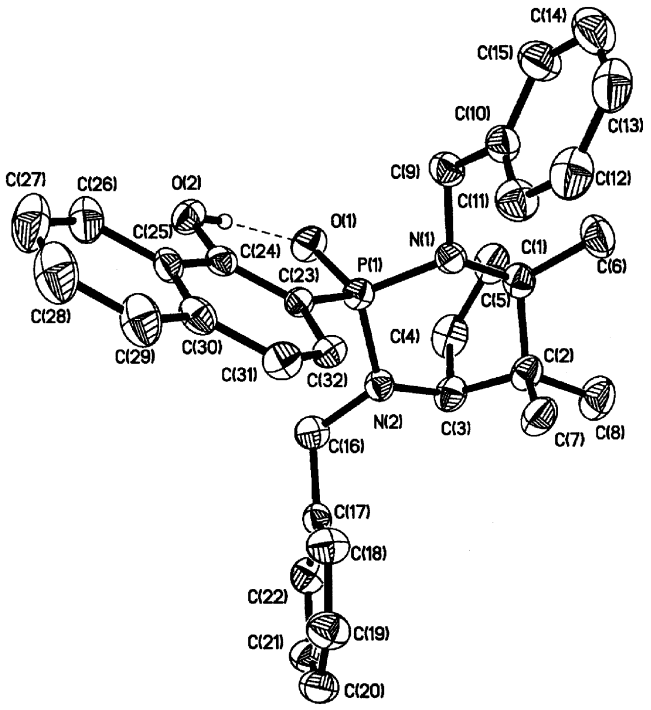


Figure 2. Molecular structure of (+)-(*S*)-**2**.

the apical position and the rearranged product with retention of configuration is obtained (Scheme 2).

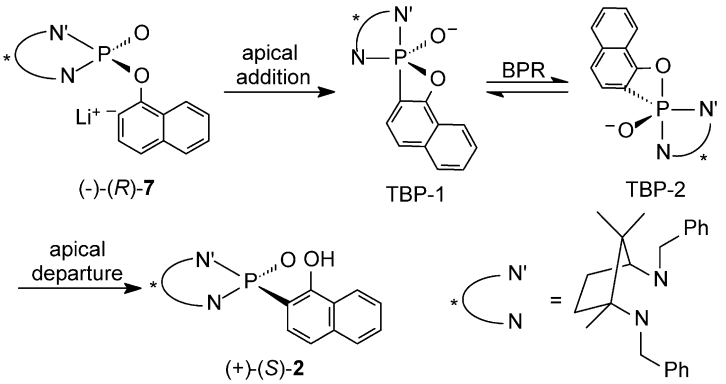
2.2. (+)-(*S*)-2/Ti(O^{i}Pr)$_4$ catalyzed asymmetric silylcyanation of aldehydes

The catalytic effect of the titanium complex formed in situ from (+)-(*S*)-**2** and Ti(O^{i}Pr)$_4$ in the asymmetric silylcyanation of aromatic aldehydes was investigated. The experimental results are listed in Table 1.

Usually, the silylcyanation reaction was best conducted in methylene chloride. We first examined the influence of the amount of ligand used on the enantioselectivity of the reaction. It was found that a decrease in yield and enantiomeric excesses value was observed, depending on the substrate employed, with a reduction of the amount of (+)-(*S*)-**2** from 40 to 20 mol%. As to the substrate, *o*-methoxybenzaldehyde the ee value for which was 98 and 97%, respectively, only a very slight change in yield and enantioselectivity was observed (entries 6 and 7). In contrast, for some other substrates, such as *p*-methoxybenzaldehyde, *m*-methoxybenzaldehyde and α-naphthyl aldehyde, this change led to an obvious decrease in enantioselectivity (entries 12 and 13, 14 and 15, 18 and 19). Further reducing the amount of (+)-(*S*)-**2** to 10 mol% resulted in a remarkable decrease both in yield and enantioselectivity (entry 8). These results showed that the change from the ligand **1** to (+)-(*S*)-**2** led to a significant improvement in the enantioselectivity. Under the same conditions, the use of 40 mol% of ligand **1** led to only 90% ee for the substrate *o*-methoxybenzaldehyde.[5a] Although a slightly high ligand loading (20–40 mol%) was required for the silylcyanation, it is gratifying that ligand (+)-(*S*)-**2** was very stable and could be readily recovered and reused without loss of its catalytic activity and asymmetric induction ability. It was found that a 4:1 molar ratio of ligand to Ti(O^{i}Pr)$_4$ resulted in better enantioselectivity, whereas the use of 1 equiv of ligand (+)-(*S*)-**2** per Ti(O^{i}Pr)$_4$ led to higher chemical yield (entries 1 and 5 and 6 and 9). Buono reported that the introduction of *i*-PrOH as an additive has a dramatic influence on the enantioselectivity in asymmetric silylcyanation.[5f] However, only a small increase in selectivity was observed in our research (entries 1 and 4 and 6 and 11). The reaction temperature was also found to be an essential factor to the reaction. The reaction at 20 °C generally led to better results than that carried out at 0 °C. An increase in reaction temperature resulted in a detrimental effect to the reaction due to the instability of the adduct silyl ether. The nature of the substrate aromatic aldehyde has a dramatic influence on the catalytic effect. Generally, the enantioselectivity of aldehydes substituted with electron donating groups (methyl and methoxy) on the benzene ring was better than that of electron withdrawing group (chloro and nitro) substituted ones. Moreover, the enantioselectivity was also affected by the position of the substituent on the benzene ring. When methoxy substituted benaldehyde was employed as the substrate, it was found that the enantioselectivity falls in the order: $o > m > p$ (entries 6, 14 and 12). This finding indicates that not only the electronic effect but also the position of the subtituent (or steric effect) had a decisive role on the enantioselectivity of the reaction.

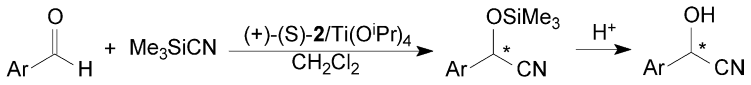
2.3. (+)-(*S*)-3/Ti(O^{i}Pr)$_4$ catalyzed asymmetric silylcyanation of aldehydes

The catalytic effect of the titanium complex formed in situ



Scheme 2.

Table 1. Asymmetric silylcyanation of aromatic aldehydes catalyzed by (+)-(*S*)-**2**/Ti(O^{i}Pr)$_4$



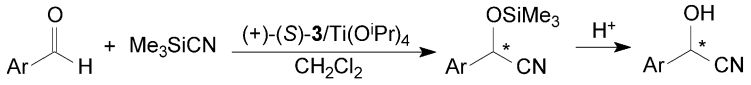
Entry	Ar	(+)-(*S*)-**2** (mol%)	Ti(O^{i}Pr)$_4$ (mol%)	*i*-PrOH (mol%)	React. temperature (°C)	Yield[a] (%)	$[\alpha]_D$ (*c* 1, $CHCl_3$)	ee[b] (%)
1	Ph	40	10	20	20	84	+23.8	53 (54.2)[c]
2	Ph	20	5	10	20	74	+19.6	44
3	Ph	40	10	20	0	90	+15.1	34
4	Ph	40	10	/	20	90	+12.5	28
5	Ph	40	40	20	20	96	+22.2	47
6	2-MeOC$_6$H$_4$	40	10	20	20	87	+26.8	98 (98.3)[c]
7	2-MeOC$_6$H$_4$	20	5	10	20	78	+26.4	97
8	2-MeOC$_6$H$_4$	10	2.5	5	20	69	+14.4	53
9	2-MeOC$_6$H$_4$	40	40	20	20	91	+24.5	90
10	2-MeOC$_6$H$_4$	40	10	20	0	78	+25.0	92
11	2-MeOC$_6$H$_4$	40	10	/	20	86	+24.8	91
12	4-MeOC$_6$H$_4$	40	10	20	20	64	+25.5	54
13	4-MeOC$_6$H$_4$	20	5	10	20	50	+15.4	32
14	3-MeOC$_6$H$_4$	40	10	20	20	78	+34.6	84
15	3-MeOC$_6$H$_4$	20	5	10	20	73	+10.6	26
16	2-MeC$_6$H$_4$	40	10	20	20	75	+32.5	78
17	2-MeC$_6$H$_4$	20	5	10	20	74	+30.5	72 (70.0)[c]
18	α-Naphthyl	40	10	20	20	66	+55.0	84
19	α-Naphthyl	20	5	10	20	55	+37.3	57
20	4-MeC$_6$H$_4$	40	10	20	20	81	+40.0	78
21	4-ClC$_6$H$_4$	40	10	20	20	71	+22.5	55
22	4-NO$_2$C$_6$H$_4$	40	10	20	20	73	+5.5	35

[a] Isolated yield.
[b] Determined by comparison of specific rotation values: Ar=Ph, $[\alpha]_D^{20}=+45$ (*c* 1, $CHCl_3$) in Ref. 1c; Ar=2-MeOC$_6$H$_4$, $[\alpha]_D^{20}=-21.0$ (*c* 1.25, $CHCl_3$) with 77% ee in Ref. 1c; Ar=4-MeOC$_6$H$_4$, $[\alpha]_D^{20}=+45.5$ (*c* 1, $CHCl_3$) with 95% ee in Ref. 1c; Ar=3-MeOC$_6$H$_4$, $[\alpha]_D^{20}=-40.8$ (*c* 1.25, $CHCl_3$) with 99% ee in Ref. 1c; Ar=2-MeC$_6$H$_4$, $[\alpha]_D^{20}=+21.3$ (*c* 1.03, $CHCl_3$) with 99% ee in Ref. 18; Ar=α-Naphthyl, $[\alpha]_D^{20}=+48.0$ (*c* 1.325, $CHCl_3$) with 73% ee in Ref. 18; Ar=4-MeC$_6$H$_4$, $[\alpha]_D^{20}=+47.4$ (*c* 1.822, $CHCl_3$) with 92% ee in Ref. 18; Ar=4-ClC$_6$H$_4$, $[\alpha]_D^{20}=+27.2$ (*c* 1.487, $CHCl_3$) with 66% ee in Ref. 18; Ar=4-NO$_2$C$_6$H$_4$, $[\alpha]_D^{20}=+4.6$ (*c* 1.417, $CHCl_3$) with 29% ee in Ref. 18.
[c] Determined by HPLC analysis of the silyl ether on a chiralcel OD column.

from (+)-(*S*)-**3** and Ti(O^{i}Pr)$_4$ in the asymmetric silylcyanation of aromatic aldehydes was also examined. The experimental results are listed in Table 2.

As shown in Table 2, the observed enantioselectivity of (+)-(*S*)-**3**/Ti(O^{i}Pr)$_4$ catalyzed asymmetric silylcyanation of aromatic aldehydes was obviously lower than that of the (+)-(*S*)-**2**/Ti(O^{i}Pr)$_4$ catalyzed process. For example, when *o*-methoxybenzaldehyde was employed as substrate, the enantioselectivity of (+)-(*S*)-**3** and (+)-(*S*)-**2** at 0 °C was 73% (Table 2, entry 8) and 92% (Table 1, entry 10), respectively. This difference was more obvious when the reaction was run at 20 °C, 57% ee (Table 2, entry 6) and 98% ee (Table 1, entry 6), respectively, was obtained. These findings show that the nature of the ligand has a dramatic influence on the enantioselectivity of the reaction. The introduction of a bulky naphthyl group into the ligand molecule has a great advantage over a phenyl group, which reveals that the steric effect of the naphthyl group plays a decisive role on the enantioselectivity of the reaction.

Table 2. Asymmetric silylcyanation of aromatic aldehydes catalyzed by (+)-(*S*)-**3**/Ti(O^{i}Pr)$_4$



Entry	Ar	(+)-(*S*)-**3** (mol%)	Ti(O^{i}Pr)$_4$ (mol%)	*i*-PrOH (mol%)	React. temperature (°C)	Yield[a] (%)	$[\alpha]_D$ (*c* 1, $CHCl_3$)	ee[b] (%)
1	Ph	40	10	20	20	84	+19.6	44
2	Ph	40	1	/	20	90	+5.5	12
3	Ph	40	10	20	0	84	+15.1	34
4	Ph	20	10	20	20	73	+23.8	53
5	Ph	40	40	20	20	96	+21.2	47
6	2-MeOC$_6$H$_4$	40	10	20	20	64	+15.5	57
7	2-MeOC$_6$H$_4$	40	10	/	20	82	+11.2	41
8	2-MeOC$_6$H$_4$	40	10	20	0	73	+19.8	73 (70.0)[c]

[a] Isolated yield.
[b] Determined by comparison of specific rotation values: Ar=Ph, $[\alpha]_D^{20}=+45$ (*c* 1, $CHCl_3$) in Ref. 1c; Ar=2-MeOC$_6$H$_4$, $[\alpha]_D^{20}=-21.0$ (*c* 1.25, $CHCl_3$) with 77% ee in Ref. 18.
[c] Determined by HPLC analysis of the silyl ether on a chiralcel OD column.

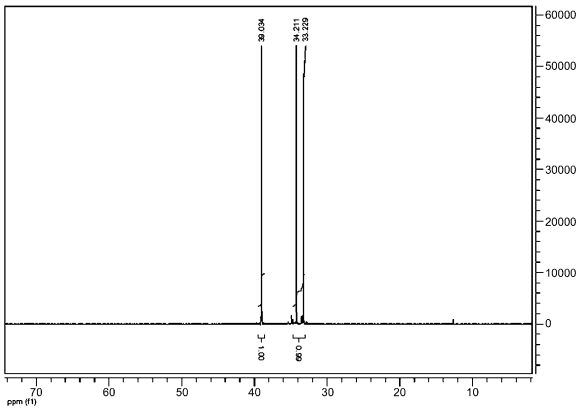


Figure 3. ^{31}P NMR spectrum of a 4:1 mixture of (+)-(*S*)-**3** and Ti(O^{i}Pr)$_4$.

2.4. Mechanism of the silylcyanation

A 4:1 and 2:1 (molar ratio) mixture of (+)-(*S*)-**3** and Ti(O^{i}Pr)$_4$ was stirred at room temperature for 1 h and analyzed by ^{31}P nucleus magnetic resonance spectroscopy, respectively (Figs. 3 and 4). As shown in Figure 3, a new doublet peak (δ 34.21 and 33.23 ppm, respectively) corresponding to the chemical shift of the Ti(IV) complex formed in situ from (+)-(*S*)-**3** and Ti(O^{i}Pr)$_4$ appeared at higher field than the single signal (δ 39.03 ppm) of (+)-(*S*)-**3**. The integral value of the signal of (+)-(*S*)-**3** and that of the Ti(IV) complex had a ratio of 1:1. Moreover, in Figure 4, the integral value of the signal of (+)-(*S*)-**3** and that of the Ti(IV) complex had a ratio of 1:10.4, which indicated that almost all of (+)-(*S*)-**3** had coordinated with the titanium atom to form the Ti(IV) complex. These results showed that it was favored to form a Ti(IV) complex with a molar ratio of 2:1 when mixing (+)-(*S*)-**3** and Ti(O^{i}Pr)$_4$ together. Based on this finding and the LALB concept a possible mechanism for this type of asymmetric silylcyanation is shown in Scheme 3.

First, intermediate complex **A** is formed from a 2:1 molar ratio of (+)-(*S*)-**3** and Ti(O^{i}Pr)$_4$. With the addition of aryl aldehyde the central titanium metal acts as a Lewis acid to activate and control the orientation of the substrate aldehyde through the formation of a new complex **B** in which the oxygen of the carbonyl group is coordinated to the central titanium atom. The introduction of trimethylsilyl cyanide results in the formation of intermediate complex **C** via the interaction between the electropositive silicon and the oxygen of phosphoryl group, which leads to the activation and control of the orientation of nucleophile trimethylsilyl cyanide by the Lewis base phosphoryl group. Then the cyanide anion attacks the carbonyl of the aldehyde from its *si*-face to afford the adduct mandelonitrile silyl ether. Finally, the oxygen of the phosphoryl group is again coordinated to the central titanium atom to release the product cyanohydrin silyl ether and regenerate the intermediate complex **A**.

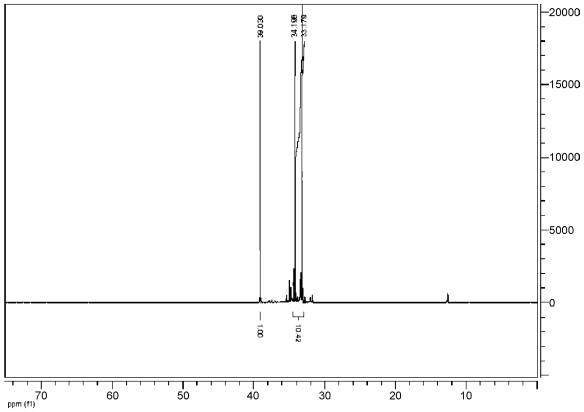


Figure 4. ^{31}P NMR spectrum of a 2:1 mixture of (+)-(*S*)-**3** and Ti(O^{i}Pr)$_4$.

3. Conclusions

In conclusion, a new type of chiral bifunctional cyclic *o*-hydroxyarylphosphonodiamide was synthesized and the absolute configuration of the phosphorus atom was determined by X-ray diffraction analysis. Excellent results (up to 98% ee) were achieved in the asymmetric silylcyanation of aromatic aldehydes using these bifunctional phosphorus reagents as the catalyst ligand in the presence of Ti(O^{i}Pr)$_4$. Investigations on further extending the range of substrates and application of this kind of bifunctional LALB catalyst for other asymmetric reaction are continuing in our laboratory.

4. Experimental

4.1. General methods

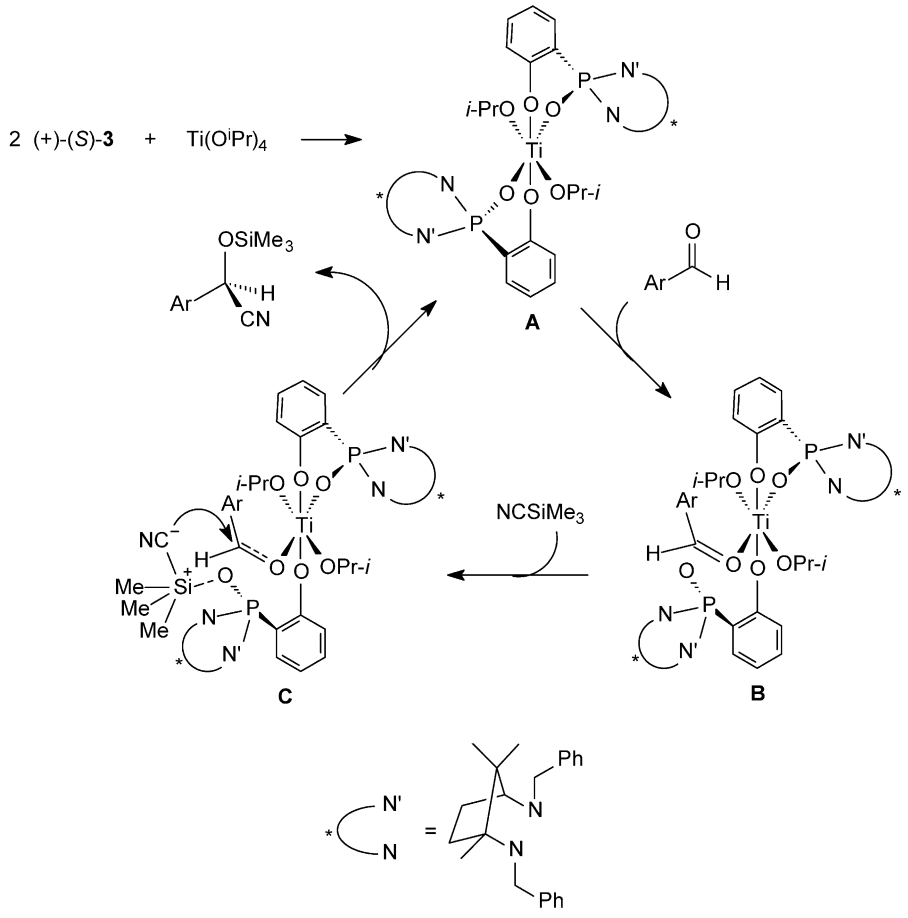
^{1}H and ^{31}P NMR spectra were recorded in $CDCl_3$ on a Bruker AC-P300 instrument using TMS as an internal standard for ^{1}H NMR and 85% H_3PO_4 as an external standard for ^{31}P NMR. Specific rotations were measured on a Perkin–Elmer 341MC polarimeter. Elemental analyses were conducted on a Yanaco CHN Corder MT-3 automatic analyzer. Melting points were determined on a T-3 melting point apparatus. All temperatures and pressures were uncorrected. All solvents were dried and used after fresh distillation. Ti(O^{i}Pr)$_4$ was purchased from Fluka.

4.1.1. Trimethylsilyl cyanide.[19] Trimethylsilyl cyanide was prepared through the reaction of silver cyanide and trimethylsilyl chloride in a 68% yield, bp 116–118 °C, n_D^{20} 1.3911 (literature:[19] bp 114–117 °C).

4.1.2. *O*-Phenyl phosphorodichloridate.[20] Reaction of phenol and phosphorus trichloride in the presence of sodium chloride afforded *O*-phenyl phosphorodichloridate in 80% yield, bp 138–140 °C/2.80 kPa, n_D^{20} 1.5264 (literature:[20a] bp 106–107.5 °C/0.92 kPa).

4.1.3. *O*-Naphthyl phosphorodichloridate.[20] The reaction between 1-naphthol and phosphorus trichloride in the presence of sodium chloride resulted in the formation of *O*-1-naphthyl phosphorodichloridate in 78% yield, bp 224–226 °C/2.80 kPa, n_D^{20} 1.6012 (literature:[20b] bp 199–201 °C/2.67 kPa, n_D^{22} 1.5960).

4.1.4. (+)-*cis*-1,2,2-Trimethylcyclopentane-1,3-diamine 4. Diamine **4** was prepared from the reaction of (1*R*,3*S*)-(+)-camphoric acid with sodium azide in the presence of



Scheme 3. Proposed mechanism for silylcyanation of aromatic aldehydes.

concentrated sulfuric acid in 91% yield and used directly without further purification.

4.1.5. (+)-*cis*-*N*,*N*′-Dibenzylidene-1,2,2-trimethylcyclopentane-1,3-diamine 5. To a stirring mixture of (+)-**4** (7.11 g, 0.05 mol), *p*-toluenesulfonic acid (0.5 g) and toluene (100 mL) was added dropwise a solution of benzaldehyde (10.6 g, 0.1 mol) in toluene (40 mL) at room temperature. The resulting mixture was stirred at 80 °C for 8 h. After removal of solvent **5** (14.2 g) was obtained as a pale yellow solid. Yield: 89%; mp 77–78 °C; ^{1}H NMR (δ, $CDCl_3$): 0.91 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.66–2.40 (m, 4H, $2CH_2$), 3.57 (t, 1H, J= 8.3 Hz, CH), 7.38–7.76 (m, 10Harom), 8.26 (s, 2H, 2CH).

4.1.6. (+)-*cis*-*N*,*N*′-Dibenzyl-1,2,2-trimethylcyclopentane-1,3-diamine 6. To a solution of **5** (3.18 g, 0.01 mol) in chloroform (40 mL) was added sodium borohydride (1.14 g, 0.03 mol) at intervals at room temperature. After stirring for an additional 10 min, the reaction mixture was warmed to reflux (60–65 °C) for 10 h. The resulting mixture was cooled to room temperature and adjusted to pH 1–2 with 2 M hydrochloric acid. The organic layer was separated and washed with distilled water, the combined water phase was adjusted to pH >12 with 10% aqueous sodium hydroxide solution and extracted with chloroform. After drying over anhydrous magnesium sulfate and removal of solvent, the crude product was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to afford **6** (2.20 g) as a pale yellow oil. Yield: 68%; ^{1}H NMR (δ, $CDCl_3$): 1.00 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.39–2.18 (m, 6H, $2CH_2$ and 2NH), 2.88 (t, 1H, J= 7.1 Hz), 3.66–3.92 (m, 4H, $2CH_2$), 7.28–7.36 (m, 10Harom).

4.1.7. *O*-1-Naphthyl cyclophosphorodiamidate 7. To a stirring mixture of **6** (3.22 g, 0.01 mmol), triethylamine (2.40 g, 0.024 mol) and methylene chloride (40 mL) was added dropwise *O*-1-naphthyl phosphorodichloridate (3.13 g, 0.012 mol) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 24 h, then washed successively with distilled water and brine. The organic layer was separated and dried over anhydrous magnesium sulfate. After removal of solvent the residue was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to afford a pair of diastereomers of **7**.

Compound (+)-(*S*)-**7**. White solid, 1.25 g. Yield: 25%; mp 140–142 °C, $[\alpha]_{578}^{20}$ = +39.9 (c=1, $CHCl_3$); ^{1}H NMR (δ, $CDCl_3$): 0.78 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.87–2.76 (m, 4H, CH_2CH_2), 2.94 (dd, 1H, $^3J_{P-H}$= 34.0 Hz, J_{H-H}=8.0 Hz, CH), 4.15–4.69 (m, 4H, $2CH_2Ph$), 7.14–8.24 (m, 17Harom); ^{31}P NMR (δ, $CDCl_3$): 12.17.

Anal. Calcd for $C_{32}H_{35}N_2O_2P$: C, 75.29; H, 6.86; N, 5.49. Found: C, 75.23; H, 6.85; N, 5.59.

Compound (−)-(*R*)-**7**. Pale yellow viscous liquid, 3.14 g. Yield: 62%; $[\alpha]_{578}^{20}=-21.5$ ($c=1$, $CHCl_3$); ^1H NMR (δ, $CDCl_3$): 0.84 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.70–2.43 (m, 4H, CH_2CH_2), 2.98 (dd, 1H, $^3J_{P-H}=27.6$ Hz, $J_{H-H}=5.2$ Hz, CH), 3.98–4.92 (m, 4H, $2CH_2Ph$), 7.11–8.30 (m, 17Harom); ^{31}P NMR (δ, $CDCl_3$): 12.21. Anal. Calcd for $C_{32}H_{35}N_2O_2P$: C, 75.29; H, 6.86; N, 5.49. Found: C, 75.26; H, 6.70; N, 5.70.

4.1.8. *O*-1-Phenyl cyclophosphorodiamidate 8. A pair of diastereomers of **8** was obtained from **6** (3.22 g, 0.01 mol), triethylamine (2.40 g, 0024 mol) and *O*-phenyl phosphorodichloridate (2.53 g, 0.012 mol) following the same procedure for the preparation of **7** (Section 4.1.7).

Compound (+)-(*S*)-**8**. White solid, 1.16 g. Yield: 25%; mp 125–126 °C, $[\alpha]_{578}^{20}=+53.3$ ($c=1$, $CHCl_3$); ^1H NMR (δ, $CDCl_3$): 0.74 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.76–2.75 (m, 4H, CH_2CH_2), 2.88 (dd, 1H, $^3J_{P-H}=26.0$ Hz, $J_{H-H}=6.0$ Hz, CH), 4.07–4.70 (m, 4H, $2CH_2Ph$), 7.19–7.37 (m, 15Harom); ^{31}P NMR (δ, $CDCl_3$): 12.17. Anal. Calcd for $C_{28}H_{33}N_2O_2P$: C, 73.06; H, 7.17; N, 6.08. Found: C, 72.70; H, 7.23; N, 6.24.

Compound (−)-(*R*)-**8**. Pale yellow viscous liquid, 2.53 g. Yield: 55%; $[\alpha]_{578}^{20}=-3.2$ ($c=1.5$, $CHCl_3$); ^1H NMR (δ, $CDCl_3$): 0.78 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.70–2.45 (m, 4H, CH_2CH_2), 2.88 (dd, 1H, $^3J_{P-H}=27.2$ Hz, $J_{H-H}=5.3$ Hz, CH), 3.90–4.89 (m, 4H, $2CH_2Ph$), 7.06–7.49 (m, 15Harom); ^{31}P NMR (δ, $CDCl_3$): 14.77. Anal. Calcd for $C_{32}H_{35}N_2O_2P$: C, 73.06; H, 7.17; N, 6.08. Found: C, 72.93; H, 7.25; N, 5.90.

4.1.9. (+)-(*S*)-1-Hydroxy-2-naphthyl cyclophosphonodiamidate 2. To a stirring solution of (−)-**7** (4.74 g, 8.1 mmol) in dry THF (30 mL) was added dropwise a solution of *n*-BuLi (12.7 mL, 1.8 M in *n*-hexane) at −78 °C under a nitrogen atmosphere. After 15 min the cold bath was removed and the reaction mixture was poured into saturated aqueous NH_4Cl (50 mL). The resulting mixture was extracted with ethyl acetate (3×30 mL). The combined organic layer was dried over anhydrous magnesium sulfate. After removal of solvent the crude product was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to recover (−)-**7** (3.20 g, conversion: 23%) and give compound (+)-**2** (0.51 g) as a white solid. Yield: 54%; mp 206–207 °C, $[\alpha]_{578}^{20}=+7.2$ ($c=1$, $CHCl_3$); ^1H NMR (δ, $CDCl_3$): 0.80 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.82–2.75 (m, 4H, CH_2CH_2), 2.99 (dd, 1H, $^3J_{P-H}=25.5$ Hz, $J_{H-H}=5.0$ Hz, CH), 3.84–4.52 (m, 4H, $2CH_2Ph$), 7.04–8.32 (m, 16Harom), 12.00 (s, 1H, OH); ^{31}P NMR (δ, $CDCl_3$): 40.59. Anal. Calcd for $C_{32}H_{35}N_2O_2P$: C, 75.29; H, 6.86; N, 5.49. Found: C, 75.29; H, 6.77; N, 5.54.

4.1.10. (+)-(*S*)-1-Hydroxyphenyl cyclophosphonodiamidate 3. In the same manner described in Section 4.1.10, (+)-**3** (0.69 g) was obtained as a white solid through the rearrangement of (−)-**8** (3.60 g, 7.8 mmol) upon treatment with *n*-BuLi. Conversion: 31% (2.50 g of (−)-**8** was recovered). Yield: 63%; mp 174–175 °C, $[\alpha]_{578}^{20}=+5.2$ ($c=1$, $CHCl_3$); ^1H NMR (δ, $CDCl_3$): 0.79 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.79–2.75 (m, 4H, CH_2CH_2), 2.99 (dd, 1H, $^3J_{P-H}=25.2$ Hz, $J_{H-H}=5.4$ Hz, CH), 3.84–4.49 (m, 4H, $2CH_2Ph$), 6.80–8.00 (m, 14Harom), 11.96 (s, 1H, OH); ^{31}P NMR (δ, $CDCl_3$): 39.06. Anal. Calcd for $C_{28}H_{33}N_2O_2P$: C, 73.06; H, 7.17; N, 6.08. Found: C, 72.94; H, 7.19; N, 6.05.

4.2. (+)-2 or (+)-3/Ti(O^{i}Pr)$_4$ Catalyzed silylcyanation of aromatic aldehyde (general preceedure)

To a solution of ligand (+)-(*S*)-**2** (or (+)-(*S*)-**3**) (0.54 mmol) in methylene chloride (5 mL) was added $Ti(O^iPr)_4$ (37.2 μL, 0.13 mmol) under a nitrogen atmosphere at room temperature and the resulting mixture was stirred for 1 h. Then *iso*-propanol (15.6 μL, 0.26 mmol), methylene chloride (2 mL), aldehyde (1.34 mmol) and trimethylsilyl cyanide (200 μL, 1.6 mmol) were added and the reaction stirred for 24 h at the same temperature. Different work-up was carried out according to the methods used for determination of the enantiomeric excess.

(1) After removal of solvent, the residue was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to afford the silyl ether of the corresponding cyanohydrin which was used for determination of the ee by chiral HPLC analysis.
(2) The reaction mixture was poured into a mixture of 1 M hydrochloric acid (30 mL) and ethyl acetate (40 mL) and stirred vigorously for 6 h at room temperature. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×20 mL). The combined organic phase was washed with brine and dried over anhydrous magnesium sulfate. After removal of solvent the residue was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to give the corresponding cyanohydrin. The ee value was determined by comparison of specific rotation values of the cyanohydrin or by chiral HPLC analysis of the corresponding acetated cyanohydrin.

Recovery of ligand (+)-**2**. (+)-**2** was recovered in 86% yield as pale yellow solid during the process of purification of the cyanohydrin by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate). Mp 205–207 °C, $[\alpha]_{578}^{20}=+7.1$ ($c=1$, $CHCl_3$).

4.2.1. (±)-*o*-Methoxymandelonitrile silyl ether.[1c] To a stirring solution of $Ti(O^iPr)_4$ (37.2 μL, 0.13 mmol) and *iso*-propanol (15.6 μL, 0.26 mmol) in methylene chloride (5 mL) was added successively *o*-methoxybenzaldehyde (0.183 g, 1.34 mmol) and trimethylsilyl cyanide (200 μL, 1.6 mmol) at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 24 h. After removal of solvent the crude product was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to yield racemic *o*-methoxymandelonitrile silyl ether for comparison in chiral HPLC analysis.

4.2.2. *o*-Methoxymandelonitrile acetate. To a stirring mixture of *o*-methoxymandelonitrile (164 mg, 1 mmol), acetic anhydride (204 mg, 2 mmol) and methylene chloride (5 mL) was added pyridine (80 mg) at room temperature, and the reaction was stirred at the same temperature for 12 h. The mixture was washed sequentially with 5% H_2SO_4, distilled water and saturated aqueous $NaHCO_3$, and dried over anhydrous magnesium sulfate. After removal of solvent the crude product was purified by column chromatography on silica gel (200–300 mesh, 5:1 petroleum ether/ethyl acetate as eluent) to give the acetylated cyanohydrin which was analyzed by HPLC with a chiral column to determine the ee.

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Asymmetric catalysis in a micro reactor—Ce, Yb and Lu catalysed enantioselective addition of trimethylsilyl cyanide to benzaldehyde

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Abstract—A T-shaped micro reactor was used for the optimisation of reaction conditions for the enantioselective silylcyanation of benzaldehyde catalysed by lanthanide–pybox complexes. Compared to a conventional batch procedure, higher conversion was observed within shorter reaction time. The micro reactor process involving Lu(III) afforded essentially the same enantioselectivity as the batch process (73 vs 76% ee), whereas the enantioselectivity was lower in the micro reactor for catalysts containing Yb(III) (53 compared to 72%). Ce(III) provided very low selectivity in both types of processes (1 and 11% ee, respectively). A study of the effect of additives showed that the enantioselectivity in the Yb catalysed reaction performed in the micro reactor could be increased to 66%, whereas only a minor improvement, to 78% ee, was observed in the reaction with Lu.

1. Introduction

Asymmetric metal catalysis constitutes a powerful method for the preparation of chiral compounds in enantiomerically pure form.[1] Although highly selective catalysts have been found for a large number of catalytic processes, the structure of the catalyst and the reaction conditions usually need to be optimised for each particular reaction and for each particular substrate. To achieve this in an efficient manner, procedures based on combinatorial chemistry and parallel synthesis techniques involving high throughput screening are frequently used today.[2] As screening of large numbers of reaction parameters and reaction conditions often requires large quantities of reagents and consumables, downsizing of reactions,[3] enabling fast screening with minimal consumption of reagents, is desirable. For this reason, various types of micro reactors have been constructed.[4]

A micro reactor can consist of sensors, pumps, valves and mixers, integrating chemistry with mechanics, electronics, optics and analysis. The mobilisation of the reagents/solvents within the device is usually achieved by external pumps (syringe pumps or microfabricated pumps) or by electroosmosis.[5] The use of an electroosmotic flow (EOF) is well-explored[6] and some of the most recent applications within the field of organic synthesis using EOF are multi-step syntheses of peptides,[7] Wittig reactions[8] and aldol condensations,[9] as well as metal catalysed reactions such as Suzuki couplings.[10]

Whilst both homogeneous[11] and heterogeneous[8,12] catalysis have been performed using micro reactor technology, asymmetric catalysis has not yet been explored. In this communication we describe lanthanide catalysed silyl-cyanations of benzaldehyde performed in a micro reactor under electroosmotic control. Cyanohydrins are important building blocks in synthetic organic chemistry as they can both be incorporated into complex molecules and easily be transformed into other types of compounds.[13] We selected a relatively robust cyanohydrin synthesis, a process catalysed by lanthanide(III) complexes of 2,6-bis(oxazolin-2-yl)-pyridine (pybox)[14] derivatives.[15] In a micro reactor, where the mobilisation of the reagents was achieved by EOF, reaction parameters such as applied voltage, reagent concentrations, reaction time and catalyst loading were optimised. The effect of additives on the conversion and the enantioselectivity was also studied. The results obtained using the micro reactors were compared to those obtained using the conventional batch technique.

Keywords: Asymmetric metal catalysis; Lanthanide; Pybox; Silylcyanations; Micro reactor.
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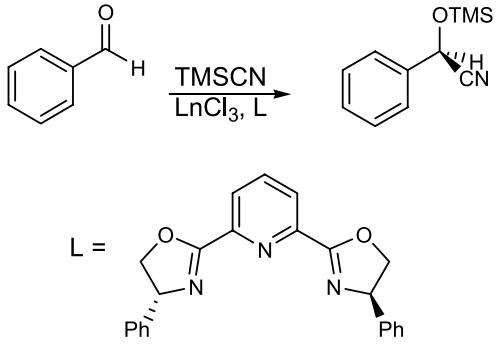
2. Results and discussion

The enantioselective addition of trimethylsilyl cyanide to benzaldehyde in the presence of 2–8 mol% of 2,6-bis(4-(*R*)-phenyloxazolin-2-yl)pyridine and $LnCl_3$ to yield a scalemic mixture of a chiral silylated cyanohydrin, with the (*R*)-enantiomer as the major product (Scheme 1), was carried out in a micro reactor.



Scheme 1. Enantioselective addition of trimethylsilyl cyanide to benzaldehyde.

A T-shaped borosilicate micro reactor, operating in a continuous mode using electroosmotic flow, with two inlets (A and B, Fig. 1) and one outlet (C), was employed for the catalytic reactions. Voltages were applied between A (+ve) and C (−ve), and B (+ve) and C (−ve). The reaction volumes used were 100 μL.

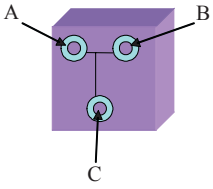


Figure 1. A schematic of the micro reactor consisting of two inlets (A and B) and one outlet (C).

The enantioselectivity of the catalytic reaction studied varied with the reaction conditions. The value reported in the literature for reactions employing $YbCl_3$, 89% ee,[15] could not be repeated by us; in our hands merely 84% ee was observed.[16] To facilitate analysis of the product and to avoid clogging, non-optimal reaction conditions were used for initial reactions in the micro reactor. Suitable conditions were found with more concentrated solutions and a lower amount of the catalyst (1.84 mmol of benzaldehyde per mL acetonitrile compared to 0.2 mmol/mL and 1–8 mol% catalyst instead of 10 mol%). Under these conditions 52–53% ee was achieved (Table 1). The results obtained were compared to those of the analogous reactions run under conventional batch conditions using the same concentration of reagents. Reactions performed in the micro reactor resulted in ee values about 10–20% lower than those achieved in batch reactions, whereas the reactivity was similar or even higher in the micro reactor process. The results of the catalytic reaction were rather insensitive to the amount of catalyst loading, permitting a decrease of the amount of catalyst down to 2 mol% without any significant decrease in reactivity (Table 1).

To explore the usefulness of the micro reactor for optimising the reaction conditions, the effect of additives on the selectivity and reactivity of the catalytic reaction was studied. It was found that each additive (Yb:additive molar ratio 1:1) influenced reactions run in the micro reactor and under conventional conditions in a similar manner, although lower selectivity was always found for the micro reactor reactions. Of the additives employed, only tritylamine had a positive effect on the enantioselectivity affording the product with 66 and 81% ee in micro reactor and batch processes, respectively, compared to 53 and 72% ee for reactions without any additive (Chart 1).

The silylcyanation is known to be catalysed by pybox complexes with other lanthanides as well, although amongst the elements investigated, Yb was found to result in highest enantioselectivity.[15] A correlation between the ionic radius of the lanthanide ion and the enantioselectivity has been observed in a related catalytic procedure.[17] We therefore decided to study reactions with Ce(III), with larger ionic radius than Yb(III), and also Lu(III), having a smaller ionic radius. These ions were not previously tested in this catalytic reaction. $CeCl_3$ was found to result in only low enantioselectivity, 11% in a batch process and only 1% ee in the micro reactor. In contrast, we were pleased to find that a catalyst prepared from $LuCl_3$ afforded the product with 76% ee in the batch reaction and with only slightly lower enantioselectivity in the micro reactor process (73% ee). The conversions in the Ce and Lu catalysed reactions in the micro reactor were lower (82 and 89%, respectively) than that in the Yb catalysed process.

In order to study whether higher conversion in the Lu catalysed reaction could be achieved, the reaction

Table 1. Results collected during optimisation of experimental conditions of the Yb catalysed reaction within the micro reactor

Catalyst loading	Concentration of reagent	Collection after 30 min; Voltage: A, B	Conversion. I for batch; II for micro reactor	Ee; I for batch; II for micro reactor
2 mol%	1.84 mmol per mL solvent	12 μL A: 240 V B: 440 V	I: 99% II: 95%	I: 70% II: 52%
4 mol%	1.84 mmol per mL solvent	13 μL A: 280 V B: 390 V	I: 92% II: 98%	I: 72% II: 53%
8 mol%	1.84 mmol per mL solvent	12 μL A: 270 V B: 400 V	I: 100% II: 99%	I: 72% II: 52%

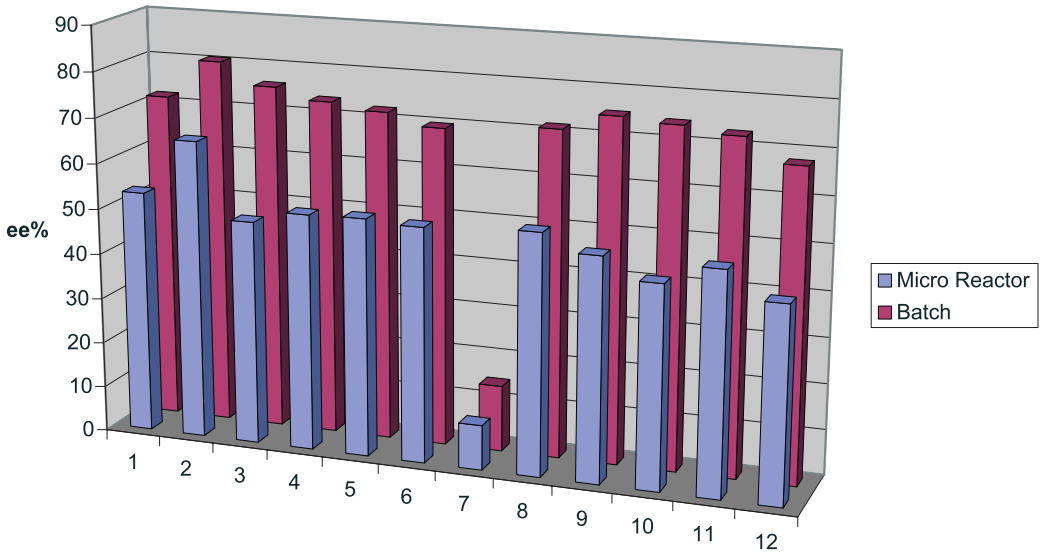


Chart 1. The influence of additives on the enantioselectivity of the $YbCl_3$ catalysed reaction. All reactions were carried out in acetonitrile at room temperature using 1.2 equiv TMSCN, 8 mol% pybox ligand, 4 mol% $YbCl_3$ and 4 mol% of the additive. 1: No additive; 2: Tritylamine; 3: Neomenthol; 4: L-Menthol; 5: *R*-(−)-2-Butanol; 6: Diethyl ether; 7: Sparteine; 8: *R*-1-Ethylphenylamine; 9: Methanol; 10: Ethanol; 11: Water; 12: *tert*-Butanol. The ee was determined by GC analysis using a chiral column (Chiraldex, G-TA).

conditions were optimised by varying the voltages. Each reaction was run for 30 min. The highest conversion was achieved when the applied voltages were 140 V on inlet A and 220 V on inlet B (97%) (Chart 2). Higher voltages resulted in lower conversion. The conversion achieved in batch reaction using the same stock solutions was 87% after 30 min.

In order to achieve further optimisation, the effect of additives was studied for the Lu catalysed reaction (Chart 3). In contrast to the situation with Yb(III), the enantioselectivity in the Lu(III) catalysed reaction was not improved by the addition of tritylamine or additives such as *N*-oxides and phosphine oxides, which are known to enhance the selectivity for related reactions.[18] Addition of D-menthol resulted in a slight improvement of the enantioselectivity (to 78% ee).

In order to verify that the catalytic reaction really occurred in the channel of the micro reactor and not in the outlet reservoir, some further experiments were performed. In the first experiment, the results from a batch reaction performed under conditions mimicking those in the outlet reservoir were compared to the results obtained using the micro reactor system. The standard solutions (4 mol%) used in the batch reaction were diluted three times since, when the reaction mixture in the micro reactor reaches the outlet reservoir, it is mixed with an additional 20 μL of acetonitrile

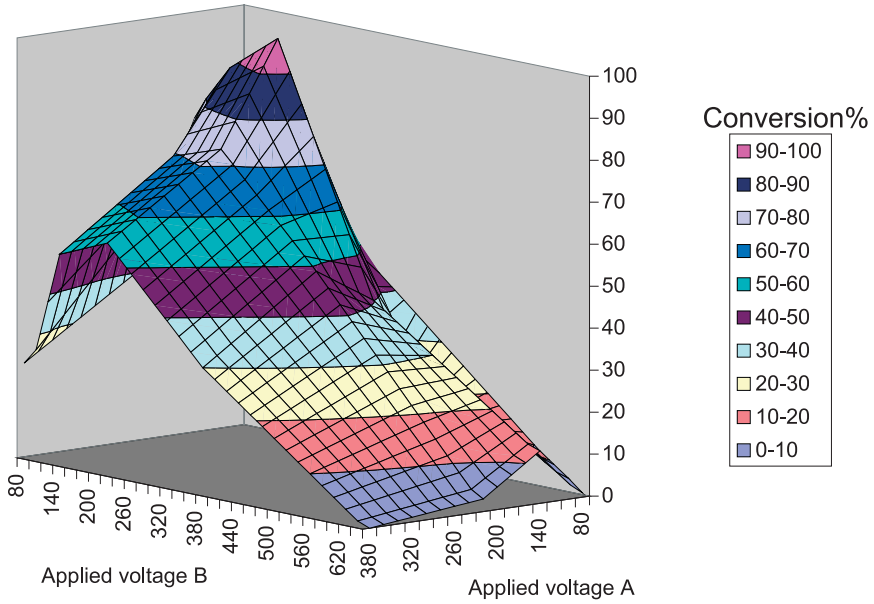


Chart 2. Results collected during optimisation of experimental conditions of the Lu catalysed reaction within the micro reactor. All reactions were carried out in acetonitrile at room temperature using 1.2 equiv TMSCN, 8 mol% pybox ligand and 4 mol% $LuCl_3$.

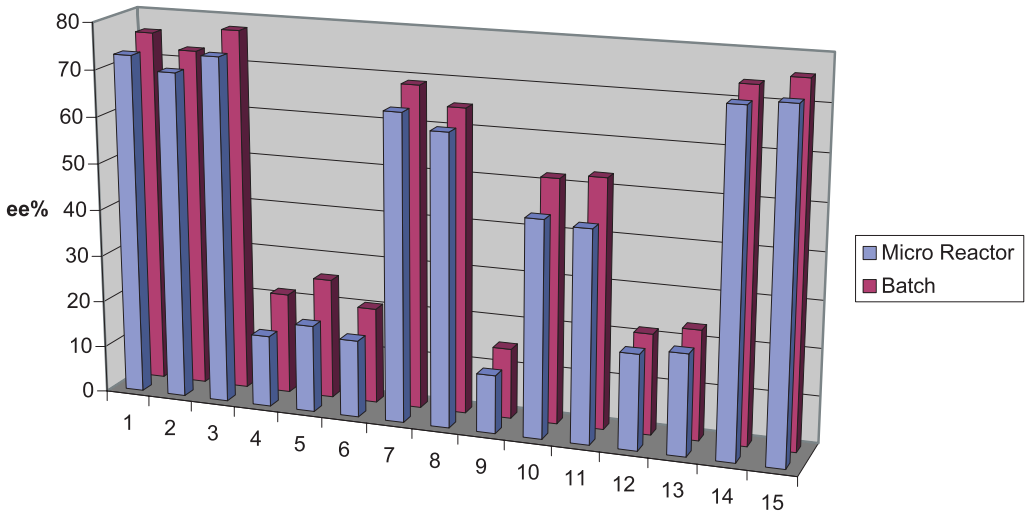


Chart 3. The influence of additives on the enantioselectivity of the $LuCl_3$ catalysed reaction. All reactions were carried out in acetonitrile at room temperature using 1.2 equiv TMSCN, 8 mol% pybox ligand, 4 mol% $LuCl_3$ and 4 mol% of the additive. 1: No additive; 2: L-Menthol; 3: D-Menthol; 4: *N*,*N*-Dimethylaniline *N*-oxide; 5: Pyridine *N*-oxide; 6: Tritylamine; 7: Neomenthol; 8: *R*-(−)-2-Butanol; 9: (−)-Sparteine; 10: *R*-(+)-1-Ethylphenylamine; 11: *S*-(−)-1-Ethylphenylamine; 12: Triphenylphosphine oxide; 13: Dimethylphenylphosphine oxide; 14: THF; 15: Diethyl ether. The ee was determined by GC analysis using a chiral column (Chiraldex, G-TA).

and the collection in that reservoir is between 8 and 15 μL (i.e. a total volume of 28–35 μL). In batch, this resulted in a conversion of 37% after 30 min, as compared to conversions around 98% within the same period of time in the micro reactor, indicating that the catalytic reaction indeed occurs in the channels of the micro reactor.

In the second experiment the reaction time in the outlet reservoir of the micro reactor was increased. The reaction mixture was run through the micro reactor channels for a period of 10 min, after which the flow was halted and the reaction mixture was allowed to stand for an additional 20 min in the outlet reservoir. GC analyses directly after halting the flow and 20 min later showed the conversions to be around 91 and 93%, respectively. Running the batch reaction for 10 min resulted in 45% conversion. These results provide further indication that the reaction indeed takes place in the channel network. In addition, if the reaction had occurred in the outlet reservoir, the reaction outcome would not have been influenced by the applied voltages.

The fact that the selectivity was lower for the Yb catalysed reaction performed in the micro reactor than for batch reactions run under the same conditions, may be due to several reasons. Slow diffusion of the lanthanide complex or decomposition of the chiral ligand may be reasons for the low enantioselectivity observed, although this should have influenced the Lu catalysed reaction in a similar manner. Another reason could be that Yb, which is known to be quite oxophilic,[19] binds to oxygen in the silicon oxide surface of the channels, thereby forming achiral ytterbium complexes which may catalyse a non-enantioselective reaction to give racemic product. This assumption is in agreement with recent investigations showing lutetium to be less oxophilic than ytterbium,[20] explaining why the selectivity for the Lu catalysed reaction was less affected by the conditions in the micro reactor.

3. Conclusions

In this study we have shown that it is possible to use a flow-through micro reactor for asymmetric catalysis employing a homogenous chiral metal complex and that EOF can be used to pump relatively large metal complexes within a micro reactor device. It was demonstrated that the catalytic reaction indeed takes place in the channels of the micro reactor and not in the collection reservoir. The reactivity achieved using optimal micro reactor operating conditions was higher than that observed in analogous batch reactions. Lower enantioselectivity was observed for the Yb catalysed reaction in the micro reactor than for that of a similar batch reaction. Finally, it was demonstrated that a flow-through micro reactor could be used for screening of additives, making this type of micro reactor a promising tool for optimisation studies.

4. Experimental

4.1. General

The micro reactor used in this study was fabricated in borosilicate glass following a standard procedure developed at Hull University.[10,21] A T-shaped micro reactor design with three reservoirs, two inlets (A and B) and one outlet (C, Fig. 1), with approximate channel dimensions of 100×50 μm and outer dimensions of 20×20×25 mm was used. The chemicals used were purchased from Aldrich or Strem, or prepared according to literature procedures. In order to trap the metal complexes, all reaction mixtures were passed through a plug of silica, using dry acetonitrile as eluent, prior to analysis. Conversions were determined by GC/MS and the enantiomeric excesses by GC (Chiraldex, G-TA (gamma cyclodextrin trifluoroacetyl), 30 m×0.25 m).[22]

4.1.1. Synthesis of 2,6-bis(4-(*R*)-phenyloxazolin-2-yl)pyridine. (*R*)-Phenylglycinol (4.85 g, 35.4 mmol) and

dimethyl 2,6-pyridine dicarboxylate (3.45 g, 17.7 mmol) were heated at 120 °C for 16 h. Tosyl chloride (6.8 g, 34.8 mmol), Et_3N (10 mL), and CH_2Cl_2 (20 mL) were added. The reaction mixture was refluxed for 20 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with water, dried ($MgSO_4$), and the solvent was evaporated. The product was purified by recrystallisation from ethanol. Yield: 92%. Spectral data were in accordance with those previously published.[23]

4.2. General procedure for preparation of standards solutions

In order to allow simultaneous addition of reagents into the separate inlets, two standard solutions, S1 and S2, were prepared: S1: Phenyl-pybox (25 mg, 0.068 mmol, 4 mol%) was added to anhydrous $LnCl_3$ (0.034 mmol) in dry acetonitrile (0.22 mL) and the mixture was stirred for 1 h at rt. Benzaldehyde (86.25 μL, 0.85 mmol) was then added and the solution was finally cooled to 0 °C. S2: TMSCN (136.3 μL, 1.02 mmol) was dissolved in dry acetonitrile (0.22 mL) and the solution was cooled to 0 °C. The standard solutions could be used for 2–3 days without any loss of activity of the catalytic complex, in agreement with the previous observations.[12] For the additive study, 4% of the selected compound was added to S1 1 h before use.

4.3. General procedure for batch reaction

Equal amounts of standard solutions S1 and S2 were added to a dry round-bottomed flask. The reaction mixture was allowed to warm to rt while stirring under air for 10–30 min before analysis.

4.4. General procedure for micro reactor based reaction

The channels of the micro reactor were primed with dry acetonitrile prior to the addition of standard solutions S1 and S2, (50 μL of each) to reservoirs A and B, and the addition of dry acetonitrile (20 μL) to the collection reservoir, C. EOF was generated by applying appropriate voltages to platinum electrodes (A and B ranging from 150 to 750 V, C set to ground) placed in each reservoir using a power supply supplied by Kingfield electronics, Sheffield. Reactions were performed over a 10–30 min period in order to ensure that a sufficient volume of the reaction product was present in reservoir C for analysis. The micro reactor was primed with dry acetonitrile prior to each experiment in order to remove any residue from the system.

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Tetrabutylammonium cyanide catalyzed diasteroselective cyanosilylation of chiral α-hydroxyketones

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Dedicated to Dr. Juan Carlos del Amo. In Memoriam

Abstract—Tetrabutylammonium cyanide has been used as non-metallic catalyst for the diastereoselective cyanosilylation of α-hydroxyketones derived from the chiral pool. This affords α-substituted-α,β-dihydroxynitriles with high levels of asymmetric induction.

1. Introduction

The addition of cyanide to carbonyl compounds to afford cyanohydrins is a useful procedure for the synthesis of a variety of compounds, including α-hydroxyacids, β-amino-alcohols and derivatives thereof, all of them important starting materials for the preparation of biologically active compounds.[1] Various cyanide sources have been reported for this purpose. In particular, the use of TMSCN in organic synthesis has proven valuable from safety standpoints.[2] However, this compound is only effective in the transfer of the CN group to the carbonyl compound of aldehydes or ketones under the action of activators.[3]

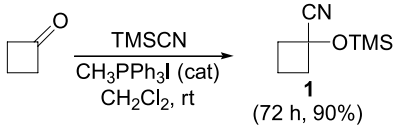
Despite the ubiquitous use of the cyanosilylation reaction for the functionalization of aldehydes, few methods have still been reported for the case of ketones and the use of non-metallic catalysts in this area is scarce.[4] In particular, the cyanation of α-hydroxyketones derived from the chiral pool is especially attractive, as this would render optically pure densely functionalized α,β-dihydroxinitriles, provided good levels of asymmetric induction could be attained. We describe herein our results on the use of ammonium salt catalysis for the diastereoselective cyanosilylation of optically pure α-hydroxyketones derived from lactic acid.

2. Results and discussion

Among others, in the search for new efficient non-metallic catalysts for cyanosilylation reactions with TMSCN, the use of phosphonium salts has been reported as a convenient catalytic method for the cyanosilylation of aldehydes.[5] Therefore, the utility of methyltriphenylphosphonium iodide as a catalyst for the cyanosilylation of ketones was tested first, using a variety of cyclic, acyclic and aromatic ketones under the reaction conditions previously reported for aldehydes (1 equiv TMSCN, 0.1 equiv CH_3PPh_3I, CH_2Cl_2, rt). However, only the higly reactive cyclobutanone was converted to the corresponding OTMS-cyanohydrin **1** (90% yield) after prolonged reaction time (Scheme 1).

Next, we turned our attention towards the closely related ammonium salts.[6] Treatment of acetophenone (Scheme 2), which was taken as model compound, with TMSCN (1 equiv) in the presence of Bu_4NCN (0.1 equiv) as catalyst readily afforded the corresponding OTMS-cyanohydrin **2** (95% yield, CH_2Cl_2, rt, 1 h).

In light of this result, a set of TBS-protected α-hydroxy-ketones **3** was tested in the cyanosilylation reaction with TMSCN catalyzed by Bu_4NCN (Scheme 3). The starting materials **3** were readily prepared from (*S*)-lactic acid and



Scheme 1.

Keywords: Tetrabutylammonium cyanide; α-Hydroxyketones; α,β-Dihydroxynitriles.
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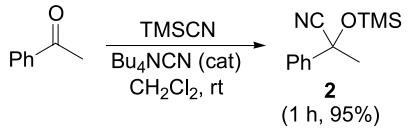
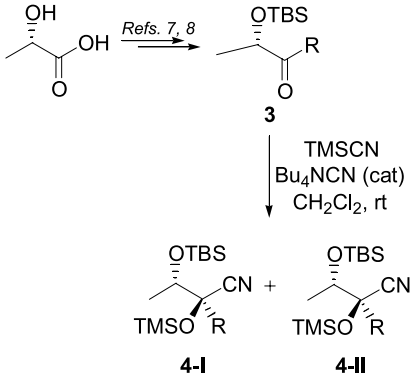


Scheme 2.



Scheme 3.

aryllithiums or Grignard reagents following literature procedures.[7,8]

Treatment of compounds **3** with TMSCN (1.0 equiv, CH_2Cl_2, rt, 1 h) in the presence of Bu_4NCN (0.1 equiv) afforded the corresponding α-substituted-α,β-dihydroxynitriles **4** in high yields in favor of diastereomers **4-I**. The results are gathered in Table 1.

Inspection of these data revealed that, although the cyanosilylation reaction of aliphatic ketones took place with low diastereoselectivity (entry 1), reactions with aromatic ketones (entries 2 and 3) and heteroaromatic ketones (entries 4 and 5) gave rise to compounds **4-I** with high yields and diastereoselective excesses superior to 80% in all cases. These results contrast with those previously reported using metal catalysts for the addition of TMSCN to α-hydroxyketones, where low levels of diastereoselectivity have been found.[4d]

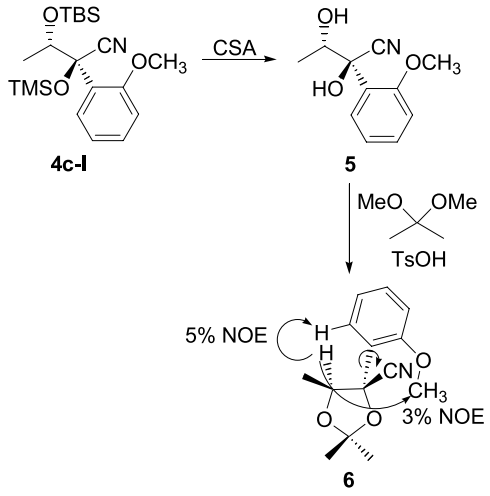
The stereochemical assignment of compounds **4** was carried out by using compound **4c-I** as model (Scheme 4). Deprotection of both silyl groups (CSA, MeOH, rt, 24 h) afforded diol **5**, which was cyclized to diolane **6** (2,2-dimethoxypropane, TsOH, toluene, rt, 16 h).

NOE measurements were carried out on the ^1H NMR

Table 1. Cyanosilylation of α-hydroxyketones **3**[a]

Entry	R	**3** (%[b])	**4** (%[b], **4-I**: **4-II**[c])
1	CH_3	**3a** (92)	**4a** (95, 75: 25)
2	Ph	**3b** (90)	**4b** (90, 90: 10)
3	*o*-CH_3O-Ph	**3c** (80)	**4c** (90, 100: 0)
4	2-Furyl	**3d** (75)	**4d** (90, 90: 10)
5	2-Thiazolyl	**3e** (90)	**4e** (95, 95: 05)

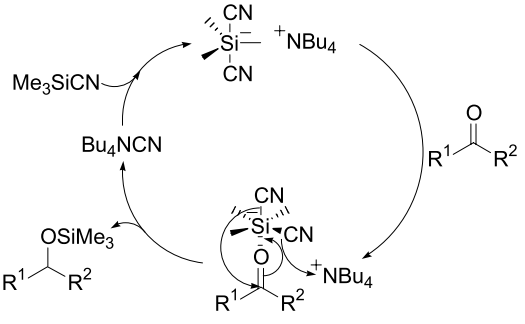
[a] Reactions carried out in CH_2Cl_2 at rt for 1 h, using 1 equiv of TMSCN and 0.1 equiv of Bu_4NCN.
[b] Pure, isolated yields.
[c] Determined by integration of the signals of the ^1H NMR spectra ($CDCl_3$, 250 MHz) of the crude reaction products.



Scheme 4.

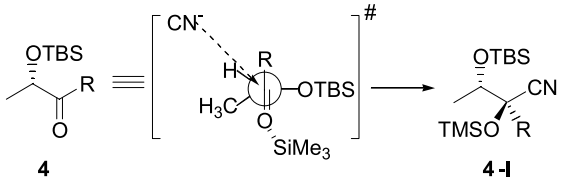
($CDCl_3$, 300 MHz) spectrum of compound **6**. Thus, saturation of the β-H signal (1H, $\delta=4.16$ ppm, q, $^3J=6.2$ Hz) gave rise to a 3% enhancement of the aryl-OCH_3 signal (3H, $\delta=3.92$ ppm, s) and a 5% enhancement of the *ortho*-H signal (1H, $\delta=7.63$ ppm, dd, $^3J=8.1$ Hz, $^4J=1.6$ Hz). This allowed a 1,2-*cis* relative configuration of the α-H and the aryl moiety in compound **6** to be established, and hence compound **4c-I** was assigned as (2*R*,3*S*)-3-(*t*butyldimethyl-silyloxy)-2-(2-methoxyphenyl)-2-trimethylsilyloxybutyro-nitrile.

The activation of TMSCN by Bu_4NCN can be interpreted (Scheme 5) by asumming the formation of a hypervalent silicon species by the interaction between both reagents, which can further coordinate the carbonyl group of the ketone and transfer one CN group, with regeneration of the catalyst at the same time.[9]



Scheme 5.

The stereochemical outcome of the cyanosilylation reaction (Scheme 6) can be understood under non-chelating conditions,[10] assuming therefore the reactive conformation



Scheme 6.

predicted by the Felkin–Ahn model. Thus, the attack of the CN group should take place *anti* to the oxygen substituent and from the diastereotopic face of the carbonyl group flanked by the smallest H group, following the Bürgi–Dunitz trajectory, to afford compounds **4** with a *syn* relative stereochemistry for both hydroxyl functionalities as major diastereomers.

3. Conclusion

In conclusion, the use of Bu_4NCN as a catalytic reagent for the diastereoselective cyanosilylation of α-hydroxyketones derived from the chiral pool with TMSCN has been reported in this paper. The method is simple, and reactions take place with high yields and diastereoselectivities in short reaction times, avoiding the use of metal catalysts.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere. Column chromatography was performed on silica gel Merck 230–400 mesh. Optical rotations were determined using a Perkin–Elmer Instruments 241 polarimeter, concentrations are given in g/100 mL. NMR spectra were recorded on Bruker 200-AM (200 MHz) and on Bruker AM300 (300 MHz) instruments, using $CDCl_3$ as solvent. Compounds **3a**, **3b**, **3c**, and **3d** were synthesized using the method described by B. Stammen et al.[7] Compound **3e** was prepared using the method described by A. Dondoni et al.[8] Other chemicals were obtained from commercial sources and were used without further purification. Solvents were distilled and dried over molecular sieves.

4.2. Typical procedure for the cyanosilylation of α-(*tert*-butylsilyloxy)ketones 3

To a solution of the carbonyl compound (0.10 mmol) in dry CH_2Cl_2 (0.5 mL) was added, under argon and at room temperature, TMSCN (0.024 mL, 0.20 mmol) followed by a solution of Bu_4NCN (2.7 mg, 0.01 mmol) in dry CH_2Cl_2 (0.5 mL). The mixture was stirred at room temperature for 90 min. The solvent was eliminated by distillation under vacuum. The crude was diluted with Et_2O (10 mL) and washed with H_2O (2×10 mL). Drying of the organic phase with $MgSO_4$ was followed by evaporation of the solvent under vacuum. The products were purified by chromatography on silica gel (ethyl acetate/hexane).

4.2.1. 3-(*tert*-Butyldimethylsilyloxy)-2-methyl-2-trimethylsilyloxybutyronitrile, 4a. $[\alpha]_D^{20}=-4.6$ ($c=0.3$, $CHCl_3$) (diastereomeric mixture **4a-I**:**4a-II**=75:25). Data for **4a-I**, ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 0.08 (s, 3H, CH_3–Si, TBS), 0.10 (s, 3H, CH_3–Si, TBS), 0.25 (s, 9H, 3×CH_3–Si, TMS), 0.91 (s, 9H, ^{t}Bu, TBS), 1.15 (d, 3H, $^3J=6.3$ Hz, CH_3–CH), 1.48 (s, 3H, CH_3–C–CN), 3.87 (q, 1H, $^3J=6.3$ Hz, CH–O) ppm; ^{13}C NMR: ($CDCl_3$, 50 MHz) δ −4.83 (CH_3–Si, TBS), −4.38 (CH_3–Si, TBS), 1.30 (3×CH_3–Si, TMS), 16.92 (*C*H_3–CH), 17.90 (Si–*C*–$(CH_3)_3$), 22.03 (*C*H_3–C–CN), 25.69 (3×CH_3, ^{t}Bu, TBS), 72.92 (CH–O), 74.21 (O–*C*–CN), 122.19 (CN) ppm. Data for **4a-II**: ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 0.15 (s, 6H, 2×CH_3–Si, TBS), 0.25 (s, 9H, 3×CH_3–Si, TMS), 0.90 (s, 9H, ^{t}Bu, TBS), 1.30 (d, 3H, $^3J=6.1$ Hz, CH_3–CH), 1.57 (s, 3H, CH_3–C–CN), 3.64 (q, 1H, $^3J=6.1$ Hz, CH–O) ppm. Anal. calcd for $C_{14}H_{31}NO_2Si_2$: C, 55.76; H, 10.36; N, 4.64. Found: C, 55.89; H, 10.32; N, 4.58.

4.2.2. 3-(*tert*-Butyldimethylsilyloxy)-2-phenyl-2-trimethylsilyloxybutyronitrile, 4b. Data for **4b-I**, ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 0.09 (s, 3H, CH_3–Si, TBS), 0.14 (s, 9H, 3×CH_3–Si, TMS), 0.16 (s, 3H, CH_3–Si, TBS), 0.93 (d, 3H, $^3J=6.2$ Hz, CH_3–CH), 0.94 (s, 9H, ^{t}Bu, TBS), 4.00 (q, 1H, $^3J=6.2$ Hz, CH–O), 7.00–7.80 (m, 5H, Ph) ppm; ^{13}C NMR: ($CDCl_3$, 50 MHz) δ −4.69 (CH_3–Si, TBS), −4.64 (CH_3–Si, TBS), 0.94 (3×CH_3–Si, TMS), 18.04 (Si–*C*–$(CH_3)_3$), 18.23 (*C*H_3–CH), 25.77 (3×CH_3, ^{t}Bu, TBS), 75.38 (CH–O), 80.05 (O–*C*–CN), 119.90 (CN), 126.50 (2×CH, Ph), 127.16 (CH, Ph), 128.09 (2×CH, Ph), 137.91 (C, Ph) ppm. Data for **4b-II**: ^{1}H NMR: ($CDCl_3$, 300 MHz) δ −0.48 (s, 3H, CH_3–Si, TBS), −0.09 (s, 3H, CH_3–Si, TBS), 0.12 (s, 9H, 3×CH_3–Si, TMS), 0.76 (s, 9H, ^{t}Bu, TBS), 1.39 (d, 3H, $^3J=6.0$ Hz, CH_3–CH), 3.85 (q, 1H, $^3J=6.0$ Hz, CH–O), 7.00–7.80 (m, 5H, Ph) ppm. Anal. calcd for $C_{19}H_{33}NO_2Si_2$: C, 62.75; H, 9.15; N, 3.85. Found: C, 62.83; H, 9.18; N, 3.64.

4.2.3. (2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-(2-methoxyphenyl)-2-trimethylsilyloxy-butyronitrile, 4c. $[\alpha]_D^{20}=+22.0$ ($c=0.7$, $CHCl_3$), ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 0.10 (s, 9H, 3×CH_3–Si, TMS), 0.13 (s, 6H, 2×CH_3–Si, TBS), 0.85 (s, 9H, ^{t}Bu, TBS), 1.16 (d, 3H, $^3J=6.2$ Hz, CH_3–CH), 3.89 (s, 3H, OCH_3), 4.52 (q, 1H, $^3J=6.2$ Hz, CH–O), 6.89 (d, 1H, $^3J=7.9$ Hz, CH_{Ar}–C–OCH_3), 6.97 (t, 1H, $^3J=7.5$ Hz, CH_{Ar}), 7.33 (td, 1H, $^3J=7.5$ Hz, $^4J=1.5$ Hz, CH_{Ar}), 7.54 (dd, 1H, $^3J=7.7$ Hz, $^4J=1.5$ Hz, CH_{Ar}) ppm; ^{13}C NMR: ($CDCl_3$, 50 MHz) δ −5.09 (CH_3–Si, TBS), −4.92 (CH_3–Si, TBS), 1.00 (3×CH_3–Si, TMS), 17.98 (Si–*C*–$(CH_3)_3$), 19.08 (*C*H_3–CH), 25.71 (3×CH_3, ^{t}Bu, TBS), 55.35 (OCH_3), 72.13 (CH–O), 78.96 (O–*C*–CN), 111.65 (*C*H_{Ar}–C–OCH_3), 119.55 (CN), 120.42 (CH_{Ar}), 126.57 (C_{Ar}), 129.06 (CH_{Ar}), 130.05 (CH_{Ar}), 156.30 (C_{Ar}–OCH_3) ppm. Anal. calcd for $C_{20}H_{35}NO_3Si_2$: C, 61.02; H, 8.96; N, 3.56. Found: C, 60.90; H, 8.74; N, 3.64.

4.2.4. 3-(*tert*-Butyldimethylsilyloxy)-2-(furan-2-yl)-2-trimethylsilyloxy-butyronitrile, 4d. $[\alpha]_D^{20}=+6.0$ ($c=0.4$, $CHCl_3$) (diastereomeric mixture **4d-I**:**4d-II**=90:10). Data for **4d-I**, ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.05 (s, 6H, 2×CH_3–Si, TBS), 0.07 (s, 9H, 3×CH_3–Si, TMS), 0.91 (s, 9H, ^{t}Bu, TBS), 1.00 (d, 3H, $^3J=6.3$ Hz, CH_3–CH), 4.20 (q, 1H, $^3J=6.3$ Hz, CH–O), 6.38 (dd, 1H, $^3J=3.4$, 1.7 Hz, CH, Furyl), 6.58 (dd, 1H, $^3J=3.4$ Hz, $^4J=0.7$ Hz, CH, Furyl), 7.41 (dd, 1H, $^3J=1.7$ Hz, $^4J=0.7$ Hz, CH–O, Furyl) ppm; ^{13}C NMR: ($CDCl_3$, 50 MHz) δ −4.78 (CH_3–Si, TBS), −4.61 (CH_3–Si, TBS), 0.34 (3×CH_3–Si, TMS), 18.04 (Si–*C*–$(CH_3)_3$), 18.83 (*C*H_3–CH), 25.71 (3×CH_3, ^{t}Bu, TBS), 73.79 (CH–O), 77.18 (O–*C*–CN), 110.28 (CH, Furyl), 110.66 (CH, Furyl), 118.19 (CN), 142.53 (CH–O, Furyl), 149.85 (C–O, Furyl) ppm. Data for **4b-II**: ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.04 (s, 6H, 2×CH_3–Si, TBS), 0.09 (s, 9H, 3×CH_3–Si, TMS), 0.90 (s, 9H, ^{t}Bu, TBS), 1.41 (d, 3H, $^3J=6.0$ Hz, CH_3–CH), 4.21 (q, 1H, $^3J=6.0$ Hz, CH–

O), 6.38 (dd, 1H, ^3J=3.4, 1.7 Hz, CH, Furyl), 6.62 (dd, 1H, ^3J=3.4 Hz, ^4J=0.7 Hz, CH, Furyl), 7.40 (dd, 1H, ^3J=1.7 Hz, ^4J=0.7 Hz, CH–O, Furyl) ppm. Anal. calcd for $C_{17}H_{31}NO_3Si_2$: C, 57.74; H, 8.84; N, 3.96. Found: C, 57.73; H, 8.79; N, 3.89.

4.2.5. 3-(*tert*-Butyldimethylsilyloxy)-2-(thiazol-2-yl)-2-trimethylsilyloxybutyronitrile, 4e. $[\alpha]_D^{20}=+33.6$ (c=1.2, $CHCl_3$) (diastereomeric mixture **4e-I**:**4e-II**=95:5).Data for **4e-I**, ^{1}H NMR: ($CDCl_3$, 300 MHz) δ −0.01 (s, 3H, CH_3–Si, TBS), 0.05 (s, 3H, CH_3–Si, TBS), 0.18 (s, 9H, 3×CH_3–Si, TMS), 0.88 (s, 9H, ^{t}Bu, TBS), 1.16 (d, 3H, ^3J=6.1 Hz, CH_3–CH), 4.17 (q, 1H, ^3J=6.1 Hz, CH–O), 7.39 (d, 1H, ^3J=3.2 Hz, CH–S, Thiazolyl), 7.82 (d, 1H, ^3J=3.2 Hz, CH–N, Thiazolyl) ppm; ^{13}C NMR: ($CDCl_3$, 75 MHz) δ −4.38 (2×CH_3–Si, TBS), 1.19 (3×CH_3–Si, TMS), 18.36 (Si–*C*–$(CH_3)_3$), 18.94 (*C*H_3–CH), 26.05 (3×CH_3, ^{t}Bu, TBS), 68.78 (CH–O), 77.85 (O–*C*–CN), 118.19 (CN), 121.04 (CH–S, Thiazolyl), 143.32 (CH–N, Thiazolyl), 168.91 (C, Thiazolyl) ppm. Data for **4e-II**: ^{1}H NMR: ($CDCl_3$, 300 MHz) δ −0.08 (s, 3H, CH_3–Si, TBS), 0.08 (s, 3H, CH_3–Si, TBS), 0.18 (s, 9H, 3×CH_3–Si, TMS), 0.83 (s, 9H, ^{t}Bu, TBS), 1.25 (d, 3H, ^3J=6.1 Hz, CH_3–CH), 4.32 (q, 1H, ^3J=6.1 Hz, CH–O), 7.39 (d, 1H, ^3J=3.2 Hz, CH–S, Thiazolyl), 7.82 (d, 1H, ^3J=3.2 Hz, CH–N, Thiazolyl) ppm. Anal. calcd for $C_{16}H_{30}N_2O_2SSi_2$: C, 51.85; H, 8.16; N, 7.56. Found: C, 51.59; H, 8.16; N, 7.58.

4.2.6. (2*R*,3*S*)-2,3-Dihydroxy-2-(2-methoxyphenyl)butyro-nitrile, 5. $[\alpha]_D^{20}=-5.3$ (c=2.3, $CHCl_3$), ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 1.28 (d, 3H, ^3J=6.6 Hz, CH_3–CH), 2.72 (d, 1H, ^3J=4.4 Hz, *H*O–CH), 3.95 (s, 3H, OCH_3), 4.30 (m, 1H, CH–O), 4.63 (s, 1H, *H*O–C–CN), 7.00 (d, 1H, ^3J=8.3 Hz, CH_{Ar}–C–OCH_3), 7.08 (t, 1H, ^3J=7.9 Hz, CH_{Ar}), 7.39 (td, 1H, ^3J=7.9 Hz, ^4J=1.7 Hz, CH_{Ar}), 7.60 (dd, 1H, ^3J=7.7 Hz, ^4J=1.7 Hz, CH_{Ar}) ppm; ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 18.11 (*C*H_3–CH), 56.28 (OCH_3), 71.80 (CH–O), 79.91 (O–*C*–CN), 112.35 (*C*H_{Ar}–C–OCH_3), 118.94 (CN), 121.90 (CH_{Ar}), 124.29 (C_{Ar}), 128.79 (CH_{Ar}), 131.28 (CH_{Ar}), 156.74 (C_{Ar}–OCH_3) ppm. Anal. calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.98; H, 6.39; N, 6.81.

4.2.7. (4*R*,5*S*)-4-Cyano-4-(2-methoxyphenyl)-2,2,5-trimethyl-1,3-dioxolane, 6. $[\alpha]_D^{20}=-2.1$ (c=1.4, $CHCl_3$), ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 1.52 (s, 3H, CH_3, *C*−2), 1.66 (d, 3H, ^3J=6.2 Hz, CH_3–CH), 1.72 (s, 3H, CH_3, *C*-2), 3.92 (s, 3H, OCH_3), 4.16 (q, 1H, ^3J=6.2 Hz, CH–O), 6.98 (d, 1H, ^3J=8.2 Hz, CH_{Ar}–C–OCH_3), 7.15 (t, 1H, ^3J=7.8 Hz, CH_{Ar}), 7.38 (td, 1H, ^3J=7.8 Hz, ^4J=1.6 Hz, CH_{Ar}), 7.63 (dd, 1H, ^3J=8.1 Hz, ^4J=1.6 Hz, CH_{Ar}) ppm; ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 16.81 (*C*H_3–CH), 26.53 (CH_3, *C*−2), 27.78 (CH_3, *C*-2), 55.87 (OCH_3), 80.73 (O–*C*–CN), 81.17 (CH–O), 111.18 (O–C–O), 112.24 (*C*H_{Ar}–C–OCH_3), 118.36 (CN), 121.44 (CH_{Ar}), 123.80 (C_{Ar}), 126.96 (CH_{Ar}), 131.09 (CH_{Ar}), 156.87 (C_{Ar}–OCH_3) ppm. Anal. calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.84; H, 6.90; N, 5.68.

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Enzymatic acylation reactions on ω-hydroxycyanohydrins

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Abstract—The enzymatic acylation of certain ω-hydroxycyanohydrins protected at the primary alcohol has been studied. The best enantioselectivities are obtained with *Pseudomonas cepacia* lipase (PSL-C) and *Candida antarctica* lipase A (CAL-A), for the ω-*O*-tritylated cyanohydrins. The effect of the protecting group in the enzymatic reactions has been studied using molecular modeling.

1. Introduction

Cyanohydrins have a great synthetic potential in organic synthesis. As α-substituted carboxylic acid derivatives, cyanohydrins may serve as stereochemically pure starting materials for the preparation of important classes of compounds.[1] Our interest in the preparation of optically active ω-functionalized cyanohydrins and their application to the synthesis of nitrogen heterocycles,[2] led us to study the (*R*)-oxynitrilase catalyzed addition of acetone cyanohydrin to 4-hydroxybutanal and 5-hydroxypentanal.[3] These aldehydes can be considered difficult substrates for (*R*)-oxynitrilase because of their relatively high water solubility.[4] The main problem of these processes was the competition with the non-enzymatic hydrocyanation. Even though by varying the reaction parameters we could reduce the extent of the undesirable competing reaction and optimize the optical purity of the obtained cyanohydrins, the highest enantiomeric excess obtained was only 62%. On the other hand, the preparation of the corresponding (*S*)-cyanohydrins using (*S*)-oxynitrilases as catalysts, is more difficult because of the low availability of these enzymes and their more restrictive substrate specificity. In recent years, several reviews on the use of these biocatalysts for the synthesis of chiral cyanohydrins have been reported.[5]

The lipase catalyzed resolution of racemic cyanohydrins is an alternative catalytic method which has been exploited for the preparation of certain optically active cyanohydrins.[6] The main disadvantage of these kinetic resolutions is that the maximum obtainable yield of each enantiomer cannot exceed the 50%. However, several strategies, like a coupled racemization[7] or in situ Mitsunobu esterification,[8] have been developed in order to increase the theoretical yield.

Molecular modeling has been used as a potent tool for the explanation of many results in biotransformations.[9] Thus, as a qualitative tool, these methods are greatly useful. They can predict, for example, how to increase the selectivity by site-directed mutagenesis.[10] However, for quantitative predictions, such as the degree of enantioselectivity, they are still not reliable.[11] Modeling is limited by the availability of three-dimensional structures of the enzymes. The force field (FF) methods and molecular mechanics are empirically based. The FF relates the geometry and the potential energy of a molecule using an analytical function. Among them, AMBER is one of the most appropriate for the study of proteins and other natural products.[12]

Here we studied the lipase-catalyzed resolution of ω-hydroxycyanohydrins. The enantioselectivity of the process strongly depends on the protecting group at the primary hydroxyl group, and some of these enzymatic reactions have been examined using molecular modeling, explaining the important effect of the protecting group on the ω-hydroxyl.

2. Results and discussion

In order to prevent the possible competition of the non-enzymatic acylation on the primary alcohol, we used as substrates the *O*-protected derivatives (±)-**3a–f**. Four protecting groups were selected, presenting different sizes and electronic properties, so we could compare the effect of these parameters on the reaction rate and the enantioselectivity of the resolutions. Cyanohydrins (±)-**3a–e** were prepared from the corresponding aldehydes,[3] and subsequent protection of the free hydroxycyanohydrins (±)-**1a–b**. For the synthesis of (±)-**3f**, the less stable 6-hydroxyhexanal was

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prepared by reduction of ε-caprolactone under mild conditions. The free hydroxyaldehyde was protected in situ by treatment with trityl chloride and pyridine to obtain 7-trityloxyheptanal **2**, and then converted into the racemic *O*-protected hydroxycyanohydrin (Scheme 1).

Our initial experiments were designed to find the most suitable lipase for catalyzing the acylation of 5-acetoxy-2-hydroxypentanenitrile (±)-**3a** with 5 equiv of vinyl acetate (Table 1). A first set of experiments were carried out at 30 °C in toluene, using vinyl acetate as acylating agent. In all the resolutions, the (*S*)-enantiomer is preferentially acylated by the lipases, while the remaining substrate possesses (*R*)-configuration. Three of the tested enzymes catalyzed the reaction in toluene: Lipases A and B from *Candida antarctica* (CAL-A and CAL-B) and the immobilized form of the *Pseudomonas cepacia* lipase, PSL-C. In all the cases, the enantioselectivities were low. CAL-B showed the highest enantiomeric ratio ($E=9.4$, entry 1),[13] but the reaction was very slow. When CAL-A or PSL-C were used (entries 2 and 3), the reaction rates were increased, with similar enantiomeric ratios.

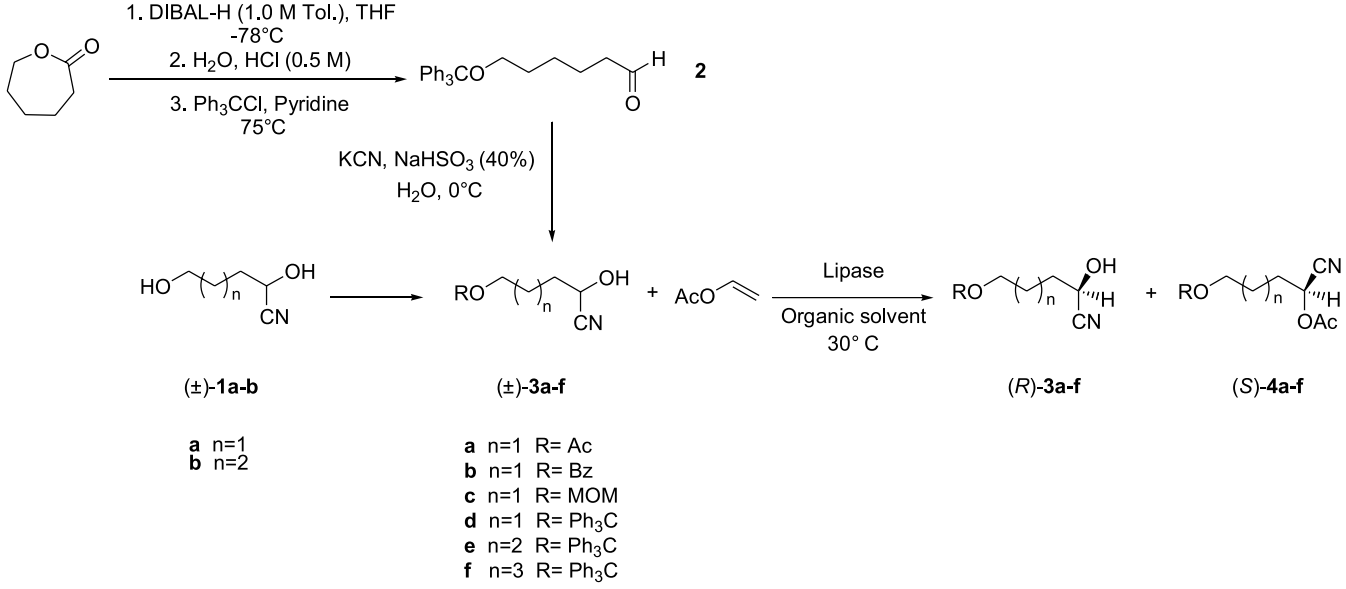
In order to improve the rate and enantioselectivity of these processes, we examined the influence of the organic solvent in the resolution of substrate (±)-**3a** carried with the PSL-C. The reaction in *t*-BuOMe was faster than in toluene but when 1,4-dioxane was used, the reaction rate decreased significantly. In both cases, there was no improvement in the enantioselectivity (entries 4 and 5).

Then, we studied the influence of the protecting group in the processes catalyzed by CAL-A and PSL-C. For 5-benzoyloxy-2-hydroxypentanenitrile, (±)-**3b** reaction rates were faster than for the acetylated cyanohydrin (±)-**3a**, but the enantioselectivities were not significantly modified (entries 6 and 7). Better results were observed when methoxymethyl was used as protecting group. For substrate (±)-**3c**, moderate enantioselectivities can be obtained using CAL-A ($E=16$, entry 8) and PSL-C ($E=19$, entry 9) with only a small decrease of the reaction rate.

The best results in the lipase catalyzed acetylation of these 2,5-dihydroxypentanenitriles were obtained using trityl as the protecting group (Scheme 1, Table 2). For substrate (±)-**3d**, the resolution catalyzed by PSL-C in toluene showed a very high enantioselectivity ($E=125$, entry 2), with a good reaction rate (after only 4 h, 46% conversion was achieved). The use of CAL-A as catalyst in the same solvent (entry 1), resulted in a lower reaction rate and enantioselectivity compared to PSL-C, nevertheless the *E* value obtained was also high ($E=72$). In view of these excellent results, we also tested CAL-B as catalyst for this substrate (entry 3), but the reaction was slower and less enantioselective.

Finally, once trityl was found to be the best protecting group for the resolution of these hydroxycyanohydrins, we studied the enzymatic acetylation in toluene of two longer chain ω-hydroxycyanohydrins, (±)-**3e** (entries 4 and 5) and (±)-**3f** (entries 6 and 7). CAL-A and PSL-C showed less enantioselectivity towards the cyanohydrins (±)-**3e** and **3f** than towards the shorter chain cyanohydrin (±)-**3d**. In both cases, the reaction rates were much higher when the processes were catalyzed by CAL-A, although PSL-C showed the higher enantioselectivities, $E=51$ for substrate (±)-**3e** and $E=62$ for substrate (±)-**3f**.

To rationalize these experimental facts, we used computer modeling. First, we chose a X-ray crystal structure of the *Pseudomonas cepacia* lipase[14] from the Brookhaven Protein Data Bank.[15] Then, we built the phosphonates shown in Figure 1 into the active site of PSL. These intermediates mimic the acetylation of the substrates (±)-**3a**–**d**.[16] We had to use a chloride instead of cyanide because of the impossibility of the FF for applying a potential to the second group. We thought the first one was the best choice to mimic the real intermediate due to the bond linearity and the similar electronic properties.



Scheme 1. Synthesis and lipase catalyzed resolution of ω-*O*-protected hydroxycyanohydrins using vinyl acetate as acylating agent.

Table 1. Lipase catalyzed acylations of substrates (±)-**3a–c** using vinyl acetate[a] at 30 °C in organic solvents

Entry	R	Lipase	Solvent	t (h)	c (%)[b]	ee (%)[c] (*R*)-**3a–c**	ee (%)[c] (*S*)-**4a–c**	E[d]
1	Ac	CAL-B	Toluene	20	29	30	75	9.4
2	Ac	CAL-A	Toluene	1	26	31	63	5.9
3	Ac	PSL-C	Toluene	2	38	38	62	6.1
4	Ac	PSL-C	^{t}BuOMe	2	52	57	53	3.5
5	Ac	PSL-C	1,4-Dioxane	72	12	10	71	6.5
6	Bz	CAL-A	Toluene	1	52	66	59	7.5
7	Bz	PSL-C	Toluene	2	49	43	44	3.8
8	MOM	CAL-A	Toluene	4	45	63	78	16
9	MOM	PSL-C	Toluene	2	42	60	82	19

[a] Reactions were carried using 5 equiv of vinyl acetate.
[b] Conversion, $c = ee_S/(ee_S + ee_P)$.
[c] Determined by HPLC or GC.
[d] Enantiomeric ratio, $E = \ln[(1-c)(1+ee_p)]/\ln[(1-c)(1-ee_p)]$.

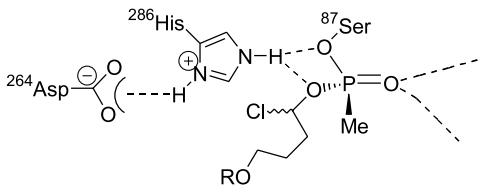


Figure 1. Phosphonate analogue for the PSL-C-catalyzed acetylation of ω-*O*-protected hydroxycyanohydrins.

We studied the extreme cases, with the smallest protecting group (R = Ac), and the biggest one (R = Ph_3C). Thus, for the cyanohydrin **3a**, which had been found to be a bad substrate for lipase-resolution, the structures obtained for both enantiomers are detailed in Figure 2. As we expected, one stable conformation could be found for both cases. The structure of (*S*)-**3a** (Fig. 2a), fits well into the medium alcohol-binding site and is pointing to the large acyl pocket. For the enantiomer (*R*)-**3a** (Fig. 2b), we observed another disposition of the aliphatic chain. It fits in the alternate hydrophobic pocket perfectly because of the small size of the acetyl protecting group. This site was discovered by Kazlauskas' group and it has been used for the explanation of the surprising reactivity from this lipase.[17]

Next, we studied the acylation of substrate **3d**, which had shown a great preference for the reaction with its *S*-enantiomer. Thus, for (*S*)-**3d** (Fig. 3a), we obtained a stable-minimized structure, which is relatively rigid, where the chain fits well into the medium pocket, and the trityl protecting group places, one part into the alternate hydrophobic pocket, and the rest is pointing to the organic solvent. In this case, due to the great size of the trityl, we obtained a similar intermediate for (*R*)-**3d** (Fig. 3b), but as can be noted, the C-α to the hydroxyl is placed very close to the histidine residue of the catalytic triad, which makes this amino acid moves away from the nucleophile, disrupting the necessary interaction between them.

The absolute configuration of the products and the remaining substrates was established as follows. The specific rotation sign of the cyanohydrin ester (*S*)-**3a** was opposite to that reported for the (*R*)-configuration, $[\alpha]_D^{18} = +2.8$ (*c* 1.14, $CHCl_3$).[3] The deprotection of the ω-*O*-protected cyanohydrins (*R*)-**2b–e** afforded the free hydroxycyanohydrins (*R*)-**1a–b**, whose specific rotation signs were in agreement with the values obtained for (*R*)-**1a**, $[\alpha]_D^{18} = +2.7$ (*c* 1.00, acetone) and for (*R*)-**1b**, $[\alpha]_D^{18} = +3.2$ (*c* 1.00, acetone).[3] In the case of substrate **2f**, its specific rotation was compared with the value obtain for (*R*)-**2f** in an enzymatic transcyanation using the (*R*)-oxynitrilase of *Prunus amygdalus*, $[\alpha]_D^{18} = +4.6$ (*c* 1.38, MeOH; ee 51%). This *O*-tritylated cyanohydrin possesses (*R*)-configuration.

3. Conclusions

This paper describes the resolution of different size chain ω-hydroxycyanohydrins via lipase-catalyzed acylation. High enantioselectivities can be achieved by an appropriate selection of the protecting group at the primary alcohol and the reaction parameters. The best results were obtained using the trityl protecting group in the acylation catalyzed by PSL-C. The process was carried out in toluene using vinyl acetate as acyl donor. The influence of the protecting group has been studied using molecular modeling. When

Table 2. Lipase catalyzed acylations of the *O*-tritylated hydroxycyanohydrins (±)-**3d–f** using vinyl acetate[a] at 30 °C in toluene

Entry	n	Lipase	t (h)	c (%)[b]	ee (%)[c] (*R*)-**3d–f**	ee (%)[c] (*S*)-**4d–f**	E[d]
1	1	CAL-A	6	25	32	96	72
2	1	PSL-C	4	46	82	96	125
3	1	CAL-B	22	22	21	75	8.6
4	2	CAL-A	4	53	91	80	28
5	2	PSL-C	4	27	35	95	51
6	3	CAL-A	4	55	87	71	16
7	3	PSL-C	4	32	44	95	62

[a] Reactions were carried using 5 equiv of vinyl acetate.
[b] Conversion, $c = ee_S/(ee_S + ee_P)$.
[c] Determined by HPLC.
[d] Enantiomeric ratio, $E = \ln[(1-c)(1+ee_p)]/\ln[(1-c)(1-ee_p)]$.

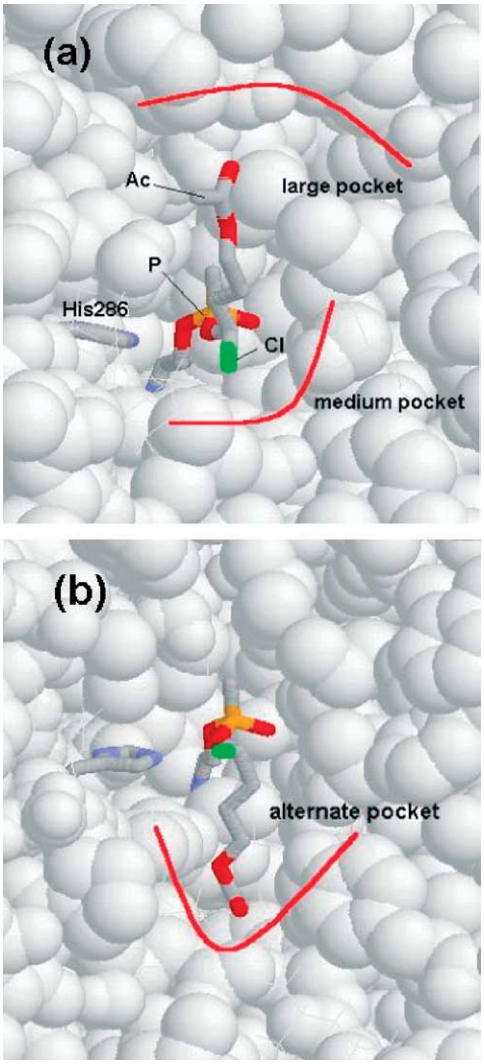


Figure 2. Molecular modeling of the intermediates in the enzymatic acetylation of the cyanohydrins: (a) (*S*)-**3a**. (b) (*R*)-**3a**. In these intermediates, red represents oxygen atoms, blue represents nitrogen atoms, yellow represents the phosphorus atom, and green represents the chlorine atom.

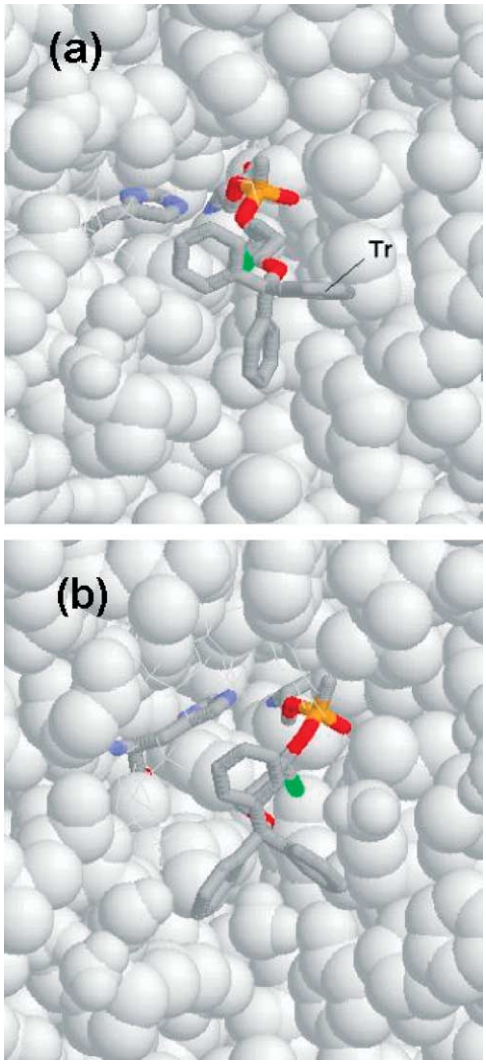


Figure 3. Molecular modeling of the intermediates in the enzymatic acetylation of the cyanohydrins: (a) (*S*)-**3d**. (b) (*R*)-**3d**.

this group is small, as in the case of the acetyl, due to the flexibility of these compounds, they can adopt different conformations in the active site, allowing the reaction for both enantiomers. However, when the protecting group is much bigger, as in the case of trityl, the substrate is more fixed into the lipase, and then the *S*-enantiomer fits better than the *R* one in it.

4. Experimental[18]

4.1. General methods

Candida antarctica lipase B (CAL-B, Novozym 435, 7300 PLU/g) was a gift from Novo Nordisk Co. Lipase A from *Candida antarctica* (CAL-A, CHIRAZYME L-5, 1 kU/g) was purchased from Roche Molecular Biochemicals. *Pseudomonas cepacia* lipase immobilized (PSL-C, 1019 units/g) was a product of Amano Co. All these commercial lipases were carrier-fixed products. Other chemicals or solvents were of the highest quality grade available.

Optical rotations were measured using a Perkin–Elmer 241 polarimeter and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Melting points were taken using a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1720-X FT Infrared spectrophotometer. ^{1}H and ^{13}C NMR were obtained with TMS (tetramethylsilane) as internal standard, using Bruker AC-200 (^{1}H, 200.13 MHz and ^{13}C, 50.3 MHz), AC-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) or DPX-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) spectrometers. Mass spectra were recorded on a Hewlett–Packard 1100 Series spectrometer. Microanalyses were performed on a Perkin–Elmer 240B elemental analyzer. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). The ee's were determined by chiral HPLC on a Shimazdu LC liquid chromatograph or by GC analysis on a Hewlett–Packard 6890 Series II chromatograph. Two well resolved peaks were obtained for all the racemic compounds.

Molecular modeling was performed using Discover, version

2.9.7 (Biosym/MSI, San Diego, CA), with the AMBER force field.[12] We used a distance dependent dielectric constant of 4 and scaled the 1–4 van der Waals interactions by 50%. Results were displayed using Insight II, version 2000.1 (Biosym/MSI). The structure of PSL (3LIP),[19] was obtained from the PDB.[15] Using the Biopolymer module of Insight II, hydrogen atoms were added. The catalytic histidine (His286) was protonated. The corresponding phosphonates were built and covalently linked to Ser87. Energy minimization proceeded in six stages. First, iterations of steepest descent algorithm, with all protein atoms constrained with a force constant of 10 kcal mol^{-1} $Å^{-2}$; second, iterations of conjugate gradients algorithm with the same constraints; third, iterations of steepest descent algorithm with only the backbone of the protein constrained by a 10 kcal mol^{-1} $Å^{-2}$; fourth, iterations of conjugate gradients algorithm with the same constraints; for the fifth stage, minimization was continued using iterations of steepest descent algorithm without any constraints. In all these cases, we used iterations until the rms deviation value reached less than 0.03 Å mol^{-1}. Finally, in the sixth stage, we used iterations of conjugate gradients algorithm without any constraints until the rms deviation reached less than 0.005 Å mol^{-1}. Water molecules and the substrate were not constrained through any of the minimization cycles. Protein structures in Figures 2 and 3 were created using RasMac v2.6.

4.2. Synthesis of (±)-5-acetoxy-2-hydroxypentanenitrile, (±)-3a

Vinyl acetate (1.96 mL, 21.5 mmol) was added to a solution of 2,5-dihydroxypentanenitrile (±)-**1a** (0.5 g, 4.3 mmol) and molecular sieves (4 Å, 800 mg) in ^{t}BuOMe (40 mL). The reaction was stirred at 40 °C and 250 rpm in a rotatory shaker. After 5 days, the mixture was filtered over Celite, washed with ^{t}BuOMe, and the solvent evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel using hexane/EtOAc (1:1) to afford compound (±)-**3a** as a colourless oil (0.49 g, 73%).

4.3. Synthesis of (±)-5-benzoyloxy-2-hydroxypentanenitrile, (±)-3b

Benzoyl chloride (0.60 mL, 5.2 mmol) was added dropwise to a solution of (±)-**1a** (500 mg, 4.3 mmol) in CH_2Cl_2 (20 mL) and pyridine (0.42 mL, 5.2 mmol), and stirred at room temperature for 12 h. The resulting mixture was washed with 2 N HCl. The organic fraction was dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel, using Et_2O/CH_2Cl_2 (8:2) to afford compound (±)-**3b** as a colourless oil (0.60 g, 64%).

4.4. Preparation of (±)-2-hydroxy-5-(methoxy)-methoxypentanenitrile, (±)-3c

Methoxymethyl chloride (0.39 mL, 5.2 mmol) was added dropwise to a 0 °C solution of (±)-**1a** (0.5 g, 4.3 mmol) and diisopropylethylamine (1.84 mL, 10.7 mmol) in dry CH_2Cl_2 (15 mL). The mixture was refluxed for 8 h. After this time, the reaction was washed with 3 N HCl until pH 1–2, and extracted with CH_2Cl_2. The organic fraction was dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The crude residue was purified by flash chromatography using Et_2O/CH_2Cl_2 (5:95) to afford compound (±)-**3c** as a colourless oil (0.40 g, 59%).

4.5. General procedure for the synthesis of the ω-*O*-trityloxyhydroxycyanohydrins (±)-3d–e

To a solution of the hydroxycyanohydrins (±)-**1a–b** (0.5 g, 1 equiv) in dry pyridine (30 mL), trityl chloride (1.2 equiv) was added, and the reaction was stirred at 75 °C for 14 h. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude residue was purified by flash chromatography with hexane/EtOAc (8:2) to give the corresponding products (±)-**3d** (1.00 g, 67%), and (±)-**3e** (0.89 g, 62%) as white solids.

4.6. Synthesis of 7-trityloxyheptanal, 2

A solution of DIBAL-H 1 M in toluene (52 mL) was added dropwise to a solution of ε-caprolactone (5.0 g, 43.8 mmol) in THF (40 mL). The mixture was stirred at −70 °C for 8 h and then quenched by slow addition of H_2O. The reaction was warmed up to room temperature and stirred for 15 min. Then, HCl 0.5 N was added and the reaction was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. To a solution of the crude residue (2.15 g, 18.5 mmol) in pyridine (40 mL), trityl chloride (6.1 g, 22.2 mmol) was added, and the reaction was stirred at 75 °C for 10 h. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The aldehyde was purified by flash chromatography using hexane/EtOAc (8:2) to afford **2** as a white solid (5.92 g, 35%).

4.7. Preparation of 2-hydroxy-7-trityloxyheptanenitrile, (±)-3f

To a solution of **2** (1.0 g, 2.79 mmol) in water (1 mL) containing KCN (0.25 g, 3.89 mmol), an aqueous solution of $NaHSO_3$ 40% (1.5 mL) were added dropwise at 0 °C. The reaction was stirred for 20 h. Then, the mixture was extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated. The crude residue was purified by flash chromatography using hexane/EtOAc (8:2) to give (±)-**3f** (0.61 g, 57%).

4.8. Typical procedure for the enzymatic acetylation of the racemic ω-*O*-protected hydroxycyanohydrins, (±)-3a–f

The lipase (60 mg) and vinyl acetate (1.5 mmol) were added to a solution of the hydroxycyanohydrins (±)-**3a–f** (0.3 mmol) in the corresponding solvent (12 mL). The mixture was stirred at 30 °C and 250 rpm in a rotatory shaker. Once the reaction was finished, the enzyme was removed by filtration, washed with EtOAc and the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel to afford the hydroxycyanohydrin acetates (*S*)-**4a–f** and the corresponding hydroxycyanohydrins (*R*)-**3a–f**.

4.9. Cleavage of the benzoyl group

To a solution of **3b** (0.20 g, 0.91 mmol) in methanol (4 mL), NaOH 1.0% (2 mL) was added. The reaction was stirred at room temperature and monitored by TLC. After this, HCl 2 N was added until acidic pH. Then, the mixture was extracted with CH_2Cl_2. The organic phase was dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography using Et_2O/CH_2Cl_2 (8:2) to obtain **1a** (17 mg, 16%).

4.10. Cleavage of the methoxymethyl group

HCl 6 N (0.25 mL) was added to a solution of **3c** (100 mg, 0.62 mmol) in isopropanol (5 mL). The mixture was stirred at 50 °C for 10 h. Then, the reaction was extracted with CH_2Cl_2. The organic phase was dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography using Et_2O/CH_2Cl_2 (5:95) to obtain **1a** (29 mg, 41%).

4.11. General procedure for the cleavage of the trityl group

The trityloxycyanohydrins **3d-e** (200 mg) were dissolved in CH_2Cl_2 (1.0 mL) and HCl 2 N (1.5 mL). The reaction was stirred for 20 h at room temperature. After this, the mixture was extracted with CH_2Cl_2. The organic phase was dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography using hexane/EtOAc (8:2) to afford **1a** (21 mg, 66%) or **1b** (17 mg, 54%).

4.11.1. 6-Trityloxyhexanal, 2. White solid; mp (°C): 75.5–76.9; IR (KBr): ν 3019, 2936, 1724, 1596, 1490 and 1215 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.42–1.55 (m, 2H), 1.61–1.74 (m, 4H), 2.42 (t, 2H, $^3J_{HH}=6.2$ Hz), 3.08 (t, 2H, $^3J_{HH}=6.3$ Hz), 7.24–7.33 (m, 9H), 7.44–7.51 (m, 6H) and 9.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 22.1 (CH_2), 26.1 (CH_2), 29.9 (CH_2), 44.0 (CH_2), 63.4 (CH_2), 86.5 (C), 127.1 (CH), 127.9 (CH), 128.9 (CH), 144.1 (C) and 203.0 (C=O); MS (ESI^+, *m/z*): 381 [$(M+Na)^+$, 100] and 359 [$(M+H)^+$, 23]. Anal. Calcd (%) for $C_{25}H_{26}O_2$: C, 83.76; H, 7.31. Found: C, 83.9; H, 7.2.

4.11.2. (*R*)-5-Acetoxy-2-hydroxypentanenitrile, 3a. Colourless oil; $[\alpha]_D^{18}=+7.5$ (*c* 1.36, EtOH; ee 57%); IR (KBr): ν 3417, 2963, 2244, 1730, 1442 and 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.99–2.07 (m, 4H), 2.26 (s, 3H), 2.81 (br s, 1H), 4.33 (t, 2H, $^3J_{HH}=6.1$ Hz) and 5.31 (t, 1H, $^3J_{HH}=6.2$ Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 21.3 (CH_3), 25.7 (CH_2), 33.6 (CH_2), 61.7 (CH), 65.3 (CH_2), 122.1 (C≡N) and 173.3 (C=O); MS (ESI^+, *m/z*): 180 [$(M+Na)^+$, 100] and 158 [$(M+H)^+$, 2]. Anal. Calcd (%) for $C_7H_{11}NO_3$: C, 57.49; H, 7.05; N, 8.91. Found: C, 57.3; H, 7.2; N, 9.1; GC conditions for the analysis after acetylation: column Rt-βDEXse, 1 mL min^{-1} N_2, 100 °C, 5 min; 5 °C min^{-1} until 200 °C, t_R (min): 22.17.

4.11.3. (*R*)-5-Benzoyloxy-2-hydroxypentanenitrile, 3b. Colourless oil; $[\alpha]_D^{18}=+3.8$ (*c* 1.44, EtOH; ee 66%); IR (KBr): ν 3421, 3073, 2942, 2246, 1717, 1601, 1434, and 1268 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.03–2.12 (m, 4H), 3.41 (br s, 1H), 4.41 (t, 2H, $^3J_{HH}=5.8$ Hz), 4.60 (t, 1H, $^3J_{HH}=6.1$ Hz), 7.46 (t, 2H, $^3J_{HH}=7.6$ Hz), 7.57 (t, 1H, $^3J_{HH}=7.6$ Hz) and 8.04 (dd, 2H, $^3J_{HH}=7.6$ Hz, $^4J_{HH}=1.4$ Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 23.9 (CH_2), 31.7 (CH_2), 60.6 (CH), 63.8 (CH_2), 119.5 (C≡N), 128.3 (CH), 129,4 (CH), 129.6 (C), 1331. (CH) and 166.7 (C=O); MS (ESI^+, *m/z*): 258 [$(M+K)^+$, 53], 242 [$(M+Na)^+$, 100] and 220 [$(M+H)^+$, 20]. Anal. Calcd (%) for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.9; H, 5.8; N, 6.6; HPLC conditions after acetylation: column Chiralcel OD, eluent hexane/*i*-propanol (90:10), 0.8 mL min^{-1}, 35 °C; t_R (min): 28.78.

4.11.4. (*R*)-2-Hydroxy-5-(methoxy)methoxypentanenitrile, 3c. Colourless oil; $[\alpha]_D^{18}=+9.2$ (*c* 1.02, EtOH; ee 63%); IR (KBr): ν 3390, 2951, 2247, 1445 and 1215 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.86–2.09 (m, 4H), 3.39 (s, 3H), 3.58–3.69 (m, 2H), 4.18 (br s, 1H), 4.54–4.60 (m, 1H) and 4.67 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 24.9 (CH_2), 32.7 (CH_2), 55.3 (CH_3), 60.8 (CH), 66.7 (CH_2), 96.2 (CH_2) and 119.5 (C≡N); MS (ESI^+, *m/z*): 198 [$(M+K)^+$, 12], 182 [$(M+Na)^+$, 100] and 160 [$(M+H)^+$, 2]. Anal. Calcd (%) for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 53.0; H, 8.1; N, 8.7; GC conditions after acetylation: column Rt-βDEXse, 1 mL min^{-1} N_2, 100 °C, 5 min; 5 °C min^{-1} until 200 °C, t_R (min): 20.81.

4.11.5. (*R*)-2-Hydroxy-5-trityloxypentanenitrile, 3d. White solid; mp (°C): 84.2–86.0; $[\alpha]_D^{18}=+7.0$ (*c* 0.98, EtOH; ee 91%); IR (KBr): ν 3430, 3019, 2928, 2239, 1596, 1448 and 1217 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.80–2.04 (m, 4H), 3.03–3.14 (m, 1H), 3.28–3.35 (m, 1H), 3.92 (d, 1H, $^3J_{HH}=10.2$ Hz), 4.53 (t, 1H, $^3J_{HH}=6.4$ Hz), 7.26–7.38 (m, 9H) and 7.42–7.50 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 25.2 (CH_2), 33.2 (CH_2), 61.1 (CH), 63.2 (CH_2), 87.6 (C), 119.7 (C≡N), 127.1 (CH), 127,9 (CH), 128.4 (CH) and 143.4 (C); MS (ESI^+, *m/z*): 396 [$(M+K)^+$, 19], 380 [$(M+Na)^+$, 100] and 358 [$(M+H)^+$, 2]. Anal. Calcd (%) for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.5; H, 6.6; N, 4.0. HPLC conditions after acetylation: column Chirobiotic T, eluent hexane/*i*-propanol (95:5), 0.3 mL min^{-1}, 20 °C; t_R (min): 26.51.

4.11.6. (*R*)-2-Hydroxy-6-trityloxyhexanenitrile, 3e. White solid; mp (°C): 87.4–88.8; $[\alpha]_D^{18}=+5.0$ (*c* 1.15, EtOH; ee 82%); IR (KBr): ν 3437, 3058, 2979, 2248, 1596, 1490 and 1218 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.60–1.72 (m, 4H), 1.77–1.87 (m, 2H), 2.42 (d, 1H, $^3J_{HH}=11.8$ Hz), 3.11 (t, 2H, $^3J_{HH}=5.9$ Hz), 4.44 (dd, 1H, $^3J_{HH}=6.6$, $^3J_{HH}=11.8$ Hz), 7.24–7.39 (m, 9H) and 7.43–7.51 (m, 6H); ^{13}C NMR ($CDCl_3$, 50.4 MHz): δ 21.3 (CH_2), 29.1 (CH_2), 34.8 (CH_2), 61.2 (CH), 62.8 (CH_2), 86.4 (C), 119.7 (C≡N), 126.9 (CH), 127.7 (CH), 128.5 (CH) and 144.1 (C); MS (ESI^+, *m/z*): 394 [$(M+Na)^+$, 100] and 372 [$(M+H)^+$, 5]. Anal. Calcd (%) for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 81.0; H, 7.0; N, 3.7; HPLC conditions after acetylation: column Chiralcel OD, eluent hexane/*i*-propanol (98:2), 0.3 mL min^{-1}, 20 °C; t_R (min): 56.93.

4.11.7. (*R*)-2-Hydroxy-7-trityloxyheptanenitrile, 3f. White solid; mp (°C): 90.4–91.7; $[\alpha]_D^{18}=+7.6$ (*c* 0.75, EtOH; ee 87%); IR (KBr): ν 3434, 3021, 2936, 2250, 1596,

1448 and 1218 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.45–1.56 (m, 4H), 1.64–1.72 (m, 2H), 1.79–1.90 (m, 2H), 2.70 (d, 1H, $^3J_{HH}=9.8$ Hz), 3.10 (t, 2H, $^3J_{HH}=6.3$ Hz), 4.43 (t, 1H, $^3J_{HH}=6.6$ Hz), 7.22–7.37 (m, 9H) and 7.45–7.53 (m, 6H); ^{13}C NMR ($CDCl_3$, 50.4 MHz): δ 24.4 (CH_2), 25.7 (CH_2), 29.8 (CH_2), 35.2 (CH_2), 61.3 (CH), 63.2 (CH_2), 86.4 (C), 119.9 (C≡N), 126.9 (CH), 127.8 (CH), 128.7 (CH) and 144.4 (C); MS (ESI^+, *m/z*): 408 [$(M+Na)^+$, 100] and 386 [$(M+H)^+$, 3]. Anal. Calcd (%) for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 81.2; H, 7.0; N, 3.5; HPLC conditions after acetylation: column Chirobiotic T, eluent hexane/*i*-propanol (97:3), 0.3 mL min^{-1}, 20 °C; t_R (min): 24.68.

4.11.8. (*S*)-2,5-Diacetoxypentanenitrile, 4a. Colourless oil; $[\alpha]_D^{18}=-30.9$ (*c* 0.90, MeOH; ee 75%); GC conditions: column Rt-βDEXse, 1 mL min^{-1} N_2, 100 °C, 5 min; 5 °C min^{-1} until 200 °C, t_R (min): 22.83.

4.11.9. (*S*)-2-Acetoxy-5-benzoyloxypentanenitrile, 4b. Colourless oil; $[\alpha]_D^{18}=-9.0$ (*c* 0.83, MeOH; ee 59%); IR (KBr): ν 3020, 2942, 2246, 1753, 1714, 1622, 1454, and 1215 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.93–2.05 (m, 2H), 2.07–2.16 (m, 2H), 2.19 (s, 3H), 4.41 (t, 2H, $^3J_{HH}=6.0$ Hz), 5.43 (t, 1H, $^3J_{HH}=6.2$ Hz), 7.48 (t, 2H, $^3J_{HH}=7.4$ Hz), 7.60 (t, 1H, $^3J_{HH}=7.4$ Hz) and 8.06 (dd, 2H, $^3J_{HH}=7.4$ Hz, $^4J_{HH}=1.4$ Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 20.2 (CH_3), 24.0 (CH_2), 29.2 (CH_2), 60.6 (CH), 63.4 (CH_2), 116.4 (C≡N), 128.3 (CH), 129.7 (CH), 129.8 (C), 130.1 (CH), 166.3 (C=O) and 169.0 (C=O); MS (ESI^+, *m/z*): 300 [$(M+K)^+$, 21], 284 [$(M+Na)^+$, 100] and 262 [$(M+H)^+$, 5]. Anal. Calcd (%) for $C_{14}H_{15}NO_3$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.5; H, 5.6; N, 5.4; HPLC conditions: column Chiralcel OD, eluent hexane/*i*-propanol (90:10), 0.8 mL min^{-1}, 35 °C; t_R (min): 16.98.

4.11.10. (*S*)-2-Acetoxy-5-(methoxy)methoxypentanenitrile, 4c. Colourless oil; $[\alpha]_D^{18}=-29.0$ (*c* 0.94, MeOH; ee 78%); IR (KBr): ν 2947, 2251, 1752, 1436 and 1215 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.75–1.88 (m, 2H), 2.00–2.11 (m, 2H), 2.16 (s, 3H), 3.37 (s, 3H), 3.59 (t, 2H, $^3J_{HH}=5.9$ Hz), 4.62 (s, 2H) and 5.41 (t, 1H, $^3J_{HH}=6.7$ Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 19.9 (CH_3), 24.3 (CH_2), 29.1 (CH_2), 54.8 (CH_3), 60.4 (CH), 65.8 (CH_2), 95.9 (CH_2), 116.3 (C≡N) and 168.7 (C=O); MS (ESI^+, *m/z*): 224 [$(M+Na)^+$, 100] and 202 [$(M+H)^+$, 15]. Anal. Calcd (%) for $C_9H_{15}NO_3$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.7; H, 7.4; N, 7.0; GC conditions: column Rt-βDEXse, 1 mL min^{-1} N_2, 100 °C, 5 min; 5 °C min^{-1} until 200 °C, t_R (min): 21.52.

4.11.11. (*S*)-2-Acetoxy-5-trityloxypentanenitrile, 4d. Hygroscopic solid; $[\alpha]_D^{18}=-22.4$ (*c* 1.28, MeOH; ee 96%); IR (KBr): ν 3022, 2934, 2240, 1596, 1448 and 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.78–1.84 (m, 2H), 1.97–2.07 (m, 2H), 2.14 (s, 3H), 3.17 (t, 2H, $^3J_{HH}=6.0$ Hz), 5.33 (t, 1H, $^3J_{HH}=6.4$ Hz), 7.26–7.37 (m, 9H) and 7.42–7.47 (m, 6H); ^{13}C NMR ($CDCl_3$, 50.4 MHz): δ 20.8 (CH_3), 25.1 (CH_2), 29.5 (CH_2), 60.9 (CH), 62.1 (CH_2), 86.6 (C), 116.7 (C≡N), 127.1 (CH), 127,8 (CH), 128.5 (CH), 143.9 (C) and 169.0 (C=O); MS (ESI^+, *m/z*): 438 [$(M+K)^+$, 60], 422 [$(M+Na)^+$, 100] and 400 [$(M+H)^+$, 2]. Anal. Calcd (%) for $C_{26}H_{25}NO_2$: C, 78.17; H, 6.31; N, 3.51. Found: C, 78.0; H, 6.6; N, 3.4; HPLC conditions: column Chirobiotic T, eluent hexane/*i*-propanol (95:5), 0.3 mL min^{-1}, 20 °C; t_R (min): 29.40.

4.11.12. (*S*)-2-Acetoxy-6-trityloxyhexanenitrile, 4e. Hygroscopic solid; $[\alpha]_D^{18}=-20.8$ (*c* 0.95, MeOH; ee 95%); IR (KBr): ν 3058, 2933, 2241, 1753, 1596, 1490 and 1219 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.58–1.72 (m, 4H), 1.83–1.90 (m, 2H), 2.14 (s, 3H), 3.11 (t, 2H, $^3J_{HH}=5.9$ Hz), 5.31 (t, 1H, $^3J_{HH}=6.7$ Hz), 7.24–7.37 (m, 9H) and 7.41–7.52 (m, 6H); ^{13}C NMR ($CDCl_3$, 50.4 MHz): δ 20.5 (CH_3), 21.5 (CH_2), 29.1 (CH_2), 32.1 (CH_2), 61.0 (CH), 62.7 (CH_2), 85.5 (C), 116.9 (C≡N), 127.0 (CH), 127.8 (CH), 128.7 (CH), 144.2 (C) and 169.2 (C=O); MS (ESI^+, *m/z*): 452 [$(M+K)^+$, 12] and 436 [$(M+Na)^+$, 100]. Anal. Calcd (%) for $C_{27}H_{27}NO_2$: C, 78.42; H, 6.58; N, 3.39. Found: C, 78.2; H, 6.7; N, 3.3; HPLC conditions: column Chiralcel OD, eluent hexane/*i*-propanol (98:2), 0.3 mL min^{-1}, 20 °C; t_R (min): 50.31.

4.11.13. (*S*)-2-Acetoxy-7-trityloxyheptanenitrile, 4f. Hygroscopic solid; $[\alpha]_D^{18}=-21.2$ (*c* 1.35, MeOH; ee 95%); IR (KBr): ν 3022, 2938, 2240, 1752, 1597, 1448 and 1217 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.46–1.52 (m, 4H), 1.62–1.70 (m, 2H), 1.85–1.92 (m, 2H), 2.11 (s, 3H), 3.09 (t, 2H, $^3J_{HH}=6.2$ Hz), 5.30 (t, 1H, $^3J_{HH}=6.7$ Hz), 7.21–7.36 (m, 9H) and 7.43–7.50 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 20.3 (CH_3), 24.3 (CH_2), 25.5 (CH_2), 29.6 (CH_2), 32.1 (CH_2), 60.9 (CH), 63.0 (CH_2), 86.2 (C), 116.8 (C≡N), 126.9 (CH), 127.6 (CH), 128.6 (CH), 144.4 (C) and 169.1 (C=O); MS (ESI^+, *m/z*): 450 [$(M+Na)^+$, 100] and 438 [$(M+H)^+$, 2]. Anal. Calcd (%) for $C_{28}H_{29}NO_2$: C, 81.72; H, 7.10; N, 3.40. Found: C, 81.5; H, 7.2; N, 3.6; HPLC conditions: column Chirobiotic T, eluent hexane/*i*-propanol (97:3), 0.3 mL min^{-1}, 20 °C; t_R (min): 28.40.

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Biocatalytic enantioselective preparation of phenothiazine-based cyanohydrin acetates: kinetic and dynamic kinetic resolution

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Abstract—Dynamic kinetic resolution is used for the preparation of a series of novel (+)-10-alkyl-phenothiazin-3-ylcyanomethyl acetates. The method exploits a basic resin both for the racemization and formation of phenothiazine-based cyanohydrins and for the decomposition of acetone cyanohydrin in one pot together with *Candida antarctica* lipase A-catalyzed enantioselective acylation with vinyl acetate in acetonitrile. The *Candida antarctica* lipase A-catalyzed methanolysis of racemic 10-alkyl-phenothiazin-3-ylcyanomethyl acetates in acetonitrile with $E \gg 100$ leads to the corresponding (−)-acetates.

1. Introduction

The serendipitous discovery of the antipsychotic activity of phenothiazines in the early 1950s led to a revolution in the treatment of mental diseases.[1] As a consequence, a wide range of 2- and 10-substituted phenothiazine-based drugs are available today. Later the antimicrobial activity of phenothiazines was recognized and recently they were considered to have potential for the management of Creutzfeldt–Jakob disease.[2]

Our interest in the present work has been in the preparation of novel optically active 10-alkylphenothiazin-3-ylhydroxyacetonitriles as stable and highly enantiopure cyanohydrin esters **3a–e** (Scheme 1). Optically active cyanohydrins are important and versatile intermediates for further synthetic development since they can be easily transformed into other optically active compounds such as α-amino and α-hydroxy carboxylic acids and amino alcohols. The most recent reviews describe two common biocatalytic methods: the oxynitrilase-catalyzed enantiofacial addition of hydrogen cyanide to an aldehyde or ketone, and the kinetic resolution of a racemic mixture, for the preparation of highly enantiopure cyanohydrin products.[3,4] Because free cyanohydrins are relatively labile in aqueous solutions, the tendency has been to perform these biotransformations in organic solvents. From the biocatalytic methods, kinetic resolution has been a natural choice in the present work because our model aldehyde **1c** was not a substrate for (*R*)-oxynitrilase in almond meal. This is in accordance with the more general proposal that oxynitrilases dislike polycyclic aldehydes.[5]

The enantioselective acylation of racemic cyanohydrins[5–10] and the enantioselective alcoholysis of racemic cyanohydrin esters[6,7,9,11–14] in organic solvents have been widely used in the presence of a suitable lipase. The main disadvantages of the traditional resolution method are, however, the maximum 50% theoretical yield of one enantiomer and the dependence of enantiomeric excess (ee) on the conversion of a reaction. These disadvantages are overcome in enzymatic dynamic kinetic resolution, where a racemic mixture is transformed into the more reactive enantiomer in a process where the enzyme stays active and the less reactive enantiomer is rapidly racemized in situ in the course of the process. Under such conditions, the maximal enantiopurity (controlled by the value of the enantiomeric ratio *E* for the corresponding kinetic resolution) for the product enantiomer is reached at the theoretical zero conversion throughout the reaction. For the dynamic kinetic resolution of cyanohydrin substrates, the stability of a cyanohydrin ester and the lability of the corresponding free cyanohydrin in the presence of a base can be exploited. As an elegant application of dynamic kinetic resolution, the one-pot synthesis of cyanohydrin esters from the corresponding aldehyde, acetone cyanohydrin (source of HCN) and isopropenyl acetate in the presence of an

Keywords: Dynamic kinetic resolution; Phenothiazine-based cyanohydrin; *Candida antarctica* lipase A; Biocatalysis.
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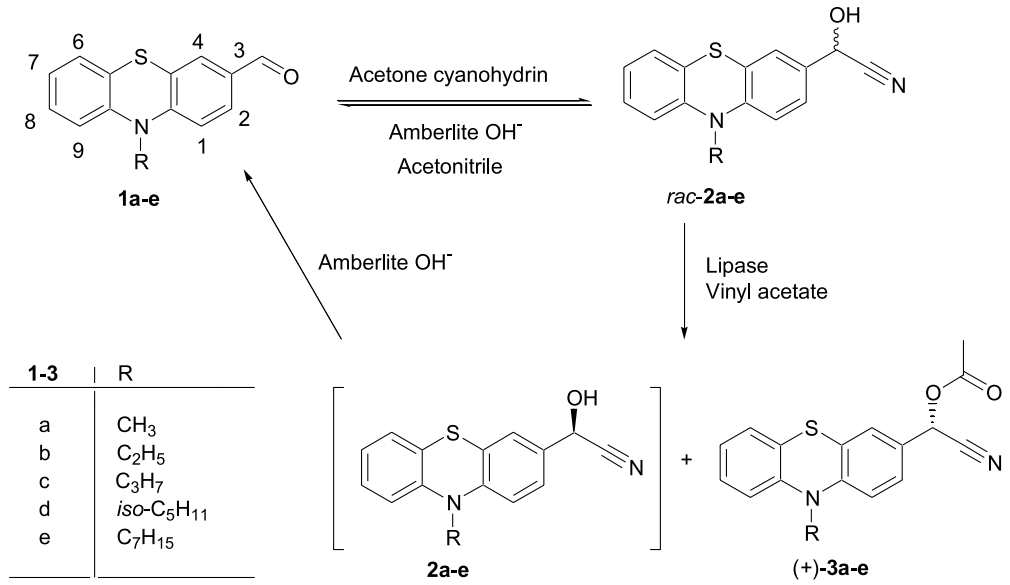


Scheme 1. One pot synthesis of (+)-**3a–e** by dynamic resolution.

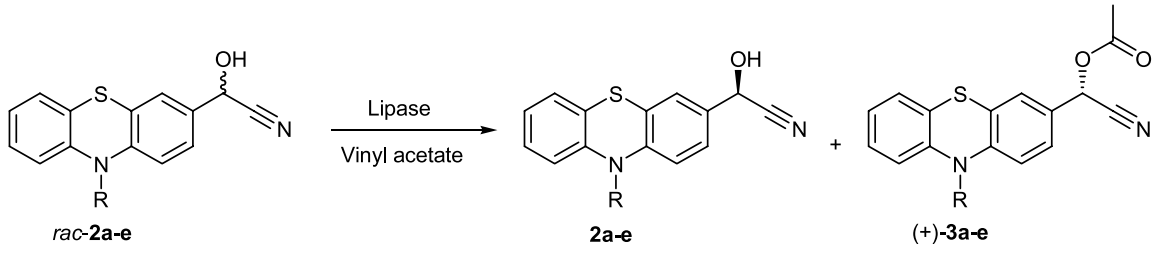
Amberlite IRA-904 basic resin and lipase PS was described over 10 years ago.[15] Slightly modified lipase-catalyzed methods were previously optimized for the preparation of a number of (*S*)-phenyl-, (*R*)-furylbenzotiazol- and (*R*)-phenylfuran-based cyanohydrin esters.[7–9]

The potential of lipases[7,15] as simple and economical dynamic kinetic resolution catalysts have been almost forgotten in the flush of the glorious development of oxynitrilase enzymes for the production of cyanohydrin enantiomers.[3,4] We now intend to describe the work where (+)-10-alkylphenothiazin-3-ylhydroxyacetonitrile acetates **3a–e** have been prepared through the lipase-catalyzed one-pot procedure from the corresponding aldehyde (Scheme 1). In the present work, reaction conditions were first optimized (**2c** as a model substrate) for the lipase-catalyzed acylation of novel cyanohydrins *rac*-**2a–e** with vinyl acetate (Scheme 2). Vinyl acetate was used because the resulting acetates **3a–e** were easily analyzed by the chiral high performance liquid chromatography (HPLC) method. In order to supply the need for (−)-cyanohydrin esters, the lipase-mediated alcoholysis of racemic acetates **3a–e** was investigated (Scheme 3). We propose (although were not able to show) that the *S*-enantiomer of the present substrates reacts faster and draw the Schemes accordingly. The proposal is based on the previously found selectivity of CAL-A and lipase PS for the acylation of structurally different phenyl- and furan-based cyanohydrins.[7–9,15]

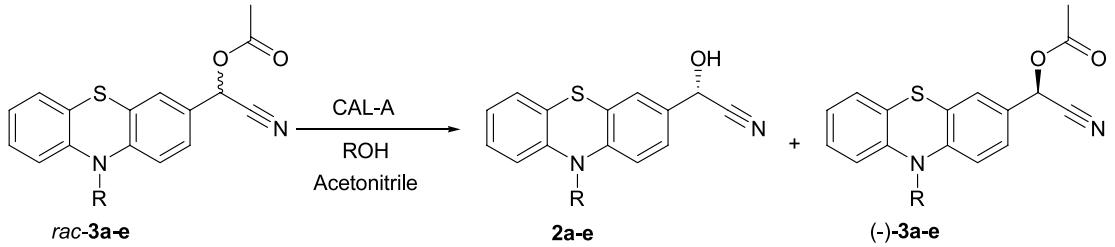
2. Results and discussion

2.1. Kinetic resolution by acylation

A large number of commercially available lipases exhibit a high degree of substrate tolerance, leading to products in



Scheme 2. Kinetic resolution of racemic cyanohydrins **2a–e**.



Scheme 3. Kinetic resolution of racemic cyanohydrin esters **3a–e**.

various degrees of enantioselectivity. Acylation of *rac*-**2c** with vinyl acetate was used as a model reaction for lipase screening in diisopropyl ether (Scheme 2). All lipases showed same enantioprefence in their acylations although the behaviour of lipases greatly differed. Lipases AK and F were catalytically inactive, lipase PS ($E=8\pm0.6$) and CAL-B ($E=13\pm1$) gave moderate selectivity and reactivity whereas CAL-A showed acceptable properties ($E=48\pm2$). Accordingly, CAL-A was used for further studies. It is worth emphasizing that for good catalytic activity and enantioselectivity of CAL-A, it is essential to use the enzyme adsorbed on Celite in the presence of sucrose(enzyme preparation).[16] We suppose that sucrose helps in binding the essential water to the enzyme under otherwise dry conditions. Thus, slow reaction (initial rate $v_o=0.2$ μmol mg^{-1} h^{-1}) and low selectivity ($E=6\pm1$) between **2c** and vinyl acetate was observed in the presence of the native enzyme in acetonitrile whereas $v_o=1.1$ μmol mg^{-1} h^{-1} was observed when the enzyme preparation was used.

In order to enhance enantioselectivity (E values), the CAL-A-catalyzed acylation of *rac*-**2c** with vinyl acetate was carried out in different solvents (Table 1). Acetonitrile proved to be the most appropriate solvent for the present acylation (entry 1). Racemic cyanohydrins **2a–e** were next subjected to CAL-A-catalyzed acylation with vinyl acetate in acetonitrile (Table 2). The degree of enantioselectivity strongly depends on the size of the 10-alkyl moiety, long alkyl chains being clearly favoured. The E value <40 in the case of 10-methyl- (**2a**) and 10-ethyl- (**2b**) substituted substrates (entries 1 and 2) means that the theoretical ee of **3a** and **3b** at zero conversion stays lower than 95%, the value usually demanded for enantiopurity (entries 1 and 2; Table 3).

2.2. Dynamic kinetic resolution

General demands for dynamic kinetic resolution were introduced above. More specific consideration is necessary in the case of cyanohydrin substrates. In the presence of CAL-A, a basic resin and water, both vinyl acetate and the produced cyanohydrin ester (one of **3a–e**) as activated esters can be enzymatically and/or chemically hydrolyzed with the formation of acetic acid. First, it is clear that product hydrolysis proceeds at the expense of product yield. Second, acetic acid (together with hydrogen cyanide if present in the reaction mixture) can neutralize the basic resin as was previously shown.[10] Hydrolysis consumes water from the reaction mixture where the water originates mainly from the organic solvent and from the seemingly dry enzyme preparation. On the other hand, the formation of an acyl enzyme intermediate in the reaction of acetic acid with the serine hydroxyl of the lipase liberates new water into the system. This was previously shown to be possible in the case of butanoic acid for the lipase-catalyzed transeterification of β-lactam derivatives with vinyl butanoate.[17] As a conclusion, as dry conditions as possible are needed in order to minimize acid formation.

Table 1. Solvent effects on the acylation of *rac*-**2** (0.05 M) with vinyl acetate (0.15 M) by CAL-A preparation (10 mg mL^{-1})

Entry	Solvent	E	Time (h)	Conv. (%)
1	Acetonitrile	94 ± 4	16	46
2	Dichloromethane	7 ± 0.5	48	14
3	Diisopropyl ether	48 ± 2	24	47
4	*tert*-Butyl alcohol	10 ± 1	48	32
5	Tetrahydrofuran	16 ± 2	48	29
6	*tert*-Butyl methyl ether	9 ± 0.2	24	35
7	Toluene	69 ± 4	24	46
8	Vinyl acetate	54 ± 3	8	47

Table 2. Acylation of cyanohydrins **2a–e** (0.05 M) with vinyl acetate (0.15 M) in acetonitrile by CAL-A preparation (10 mg mL^{-1})

Entry	Resolution products	E	Time (h)	Conv. (%)
1	**2a** and (+)-**3a**	23 ± 1	8	44
2	**2b** and (+)-**3b**	35 ± 2	12	48
3	**2c** and (+)-**3c**	94 ± 4	16	46
4	**2d** and (+)-**3d**	$\gg100$	24	50
5	**2e** and (+)-**3e**	$\gg100$	24	50

Table 3. Gram-scale preparation of cyanohydrin acetates **3** in acetonitrile through dynamic kinetic resolution starting from an aldehyde and acetone cyanohydrin in the presence of CAL-A preparation and an Amberlite IRA 904 basic resin

Entry	Product	Conv. (%)	Time (h)	Yield (%)	ee (%)	Theoretical ee (%)	$[\alpha]_D^{25a}$
1	(+)-**3a**	>99	24	94	91	92	+14.3
2	(+)-**3b**	>99	24	92	93	93	+15.8
3	(+)-**3c**	>99	48	93	97	97	+17.3
4	(+)-**3d**	>99	48	94	>99	>99	+18.9
5	(+)-**3e**	>99	48	93	>99	>99	+18.6

[a] ($c=1.0$, $CHCl_3$).

For the production of (+)-cyanohydrin acetates **3a–e** (Scheme 1), a fast equilibrium between a cyanohydrin and the corresponding aldehyde (and acetone) and hydrogen cyanide in the presence of a base is essential. In order to show that cyanohydrins are smoothly produced in sufficiently large amounts, a mixture of **1c** (0.15 mmol) and acetone cyanohydrin (0.32 mmol) was studied in acetonitrile at room temperature in the presence of the Amberlite IRA-904 basic resin (5 mg mL^{-1}; 0.65 mmol mL^{-1}). The equilibrium value [**2c**]/[**1c**]=9 was reached in less than 2 h, clearly fulfilling the demand. In order to verify the enantiomeric stability of the products, the effect of the basic resin (5 mg mL^{-1}; 0.65 mmol mL^{-1}) was investigated on the product mixture [(−)-**2a–e** and (+)-**3a–e**] of the above-described kinetic resolutions (Scheme 2). Free cyanohydrins **2a–e** were totally racemic within less than 2 h while the enantiopurity of the corresponding esters **3a–e** was still unchanged after 7 days.

The amount of the basic resin is critical for the dynamic kinetic resolution as was previously pointed out in the case of mandelonitrile as a substrate.[10] That the basic resin was still active at the end of the dynamic kinetic resolution of **2c** was shown by adding a new proportion of acetone cyanohydrin at the end of the reaction. A dark brown colour appeared immediately, indicating that the base-catalyzed decomposition of acetone cyanohydrin was able to produce hydrogen cyanide followed by its base-catalyzed polymerization.[18] A dark brown colour was also introduced when 10 mg mL^{-1} (1.3 mmol mL^{-1}) of the resin was used instead of the normally used 5 mg mL^{-1}. The high base content also prevented enzymatic acylation.

In the present one pot synthesis of (+)-cyanohydrin acetates **3a–e** by CAL-A (Table 3), the observed ee values are in accordance with the theoretical values which can be calculated using the *E* values in Table 2 by extrapolating ee to zero conversion. This result further indicates the existence of the dynamic kinetic resolution conditions. Gram-scale reactions were stopped at high conversions (>99%), indicating that the aldehydes can be almost totally converted to the corresponding (+)-cyanohydrin acetates. The products were also isolated at high chemical yields as is shown in the Section 4.

2.3. Kinetic enzymatic resolution by alcoholysis

For the preparation of cyanohydrin enantiomers by kinetic resolution, it is advantageous to select a reaction which gives the desired enantiomer as a less reactive acylated counterpart because the separation of the resolution products (one enantiomer as a free cyanohydrin and the other as an acylated counterpart) often leads to considerable decomposition and racemization of the free cyanohydrin counterpart. Accordingly, cyanohydrin esters *rac*-**3a–e** were subjected to the CAL-A-catalyzed alcoholysis with methanol and propanol in acetonitrile (Scheme 3). The results in Table 4 show that the alcoholyses all proceed with high enantioselectivity compared to the acylation of the corresponding cyanohydrins (Table 2). Methanol rather than propanol is a more appropriate alcohol and the alcohol concentration of 0.8 M is preferred over the concentration of 0.4 M (entries 3 and 4 vs 5 and 6). Highly enantioselective reactions with methanol tend to stop at 50% conversion, affording the two enantiomers (one as a free cyanohydrin and the other as its ester) simultaneously in the resolution mixture.

3. Conclusion

The present work describes the usability of dynamic kinetic resolution for the preparation of novel cyanohydrin acetates (+)-**3a–e** with a lipase enzyme (Table 3). The method combines the base-catalyzed in situ formation of racemic cyanohydrins **2a–e** from the corresponding aldehydes **1a–e** and hydrogen cyanide with the in situ lipase-catalyzed kinetic resolution and with the base-catalysed in situ racemization of the less reactive **2a–e** enantiomer (Scheme 1). In all cases, more than 99% of an aldehyde was easily transformed into the corresponding (+)-**3**. As an advantage of the present method, the separate preparation and purification of relatively labile cyanohydrins is not necessary. As another benefit, the handling of hydrogen cyanide is avoided by making use of the base-lability of acetone cyanohydrin.

The CAL-A-catalyzed alcoholysis of racemic **3a–e** with methanol in acetonitrile proved to be a convenient method for the preparation of (−)-cyanohydrin acetates **3a–e** through traditional kinetic resolution proceeding with high enantioselectivity ($E \gg 100$).

4. Experimental

4.1. Materials and methods

Phenothiazine, alkyliodides, vinyl acetate, trimethylsilyl cyanide, $POCl_3$ and ZnI_2 were products of Aldrich or Fluka. The synthesis of aldehydes **1a–e** was previously described.[19] All solvents were purified and dried by

Table 4. Alcoholysis of racemic cyanohydrin esters **3a–e** (0.05 M) with ROH in acetonitrile by CAL-A preparation (10 mg mL^{-1})

Entry	Substrate	ROH	Time (h)	Conv. (%)	$ee^{(R)\text{-}3}$ (%)	$ee^{(S)\text{-}2}$ (%)	*E*
1	*rac*-**3a**	Methanol (0.8 M)	12	50	>99	>99	≫100[a]
2	*rac*-**3b**	Methanol (0.8 M)	12	50	>99	>99	≫100[a]
3	*rac*-**3c**	Methanol (0.8 M)	12	50	>99	>99	≫100[a]
4	*rac*-**3c**	Methanol (0.4 M)	12	49	98	98	440±23
5	*rac*-**3c**	Propanol (0.8 M)	24	49	93	81	82±4
6	*rac*-**3c**	Propanol (0.4 M)	24	48	91	84	56±3
7	*rac*-**3d**	Methanol (0.8 M)	24	50	>99	>99	≫100[a]
8	*rac*-**3e**	Methanol (0.8 M)	24	50	>99	>99	≫100[a]

[a] Only one enantiomer was detected by HPLC.

standard methods as required.[20] Amberlite IRA 904 was purchased from Acros and was conditioned as previously described.[15] Dowex 50WX8 ion exchange resin was from Fluka. Lipases from *Pseudomonas fluorescence* (lipase AK), *Pseudomonas cepacia* (currently from *Burkholderia cepacia*; lipase PS) and *Rhizopus oryzae* (lipase F) were from Amano Europe, England. Lipase A (CAL-A) and lipase B (CAL-B, Chirazyme L2) from *Candida antarctica* were purchased from Boehringer-Mannheim. Before use CAL-A and lipases AK and PS were adsorbed on Celite (4.0 g) by dissolving the enzyme and sucrose (0.24 g) in Tris–HCl buffer (pH 7.9) and thereafter left to dry at room temperature. The final lipase content in the enzyme preparation was 20% (w/w).

The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Jeol Alpha 500 spectrometer operating at 500.16 MHz and 125.78 MHz, respectively. All spectra were recorded at 25 °C in $CDCl_3$. ^{1}H spectra were referenced internally to the solvent signal ($CHCl_3$, 7.26 ppm) and ^{13}C spectra to the solvent signal ($CDCl_3$, 77.00 ppm). The correct assignment of the chemical shifts was confirmed by application of two-dimensional correlation measurements, including homonuclear field gradient enhanced double quantum filtered $^{1}H,^{1}H$-correlation spectroscopy measurements (FG DQF COSY), heteronuclear one-bond correlation measurements acquired either using carbon detected CH-shift correlation experiment (CHSHF, f1-decoupled) or proton detected field gradient enhanced multiple quantum coherence experiment (FG HMQC, both optimized for 145 Hz $^{1}J_{CH}$ coupling), and heteronuclear multiple-bond correlation measurements acquired either using carbon detected correlation via long-range coupling spectroscopy experiment (COLOC) or field gradient enhanced multiple-bond correlation experiment (FG HMBC, both optimized to $^{n}J_{CH}$ couplings of 4 and 8 Hz).

HPLC analyses were conducted with a HP 1090 instrument using a CHIRACEL OD column (0.46×25 cm) and a mixture of hexane and isopropyl alcohol (9:1) as eluent. For good baseline separation, the unreacted cyanohydrin in the sample was derivatized with chloroacetyl chloride in the presence of pyridine containing 1% 4-*N*,*N*-dimethylaminopyridine (DMAP) before injections. Baseline enantiomeric separation of all chiral substances **2a**–**e** and **3a**–**e** was achieved. The retention times are given in Table 5. In the case of dynamic kinetic resolution, conversion was determined using the ^{1}H NMR spectra of the reaction mixture by integrating characteristic proton signals for all the chemical species involved (aldehydic proton for **1a**–**e**, proton from the cyanohydrin C*H* group for **2a**–**e** and proton from the acetate CH for the esters **3a**–**e**). Thin layer chromatography (TLC) was carried out using Merck Kieselgel $60F_{254}$ sheets. Spots were visualized by treatment with 5% ethanolic phosphomolybdic acid solution and heating. Preparative chromatographic separations were performed using column chromatography on Merck Kieselgel 60 (0.063–0.200 μm). Melting points were determined by hot plate method and are uncorrected. Optical rotations were determined on a Jasco DIP-360 polarimeter, $[\alpha]_D$ values being in units of 10^{-1} deg cm^2 g^{-1}.

Table 5. Retention times for the enantiomers of acetate (+/−)-**3** and chloroacetates (**/*)-**3′**

	Rf			
	(−)-**3**	(+)-**3′**	(*)-**3′**[a]	(**)-**3′**[a]
a	26.7	28.2	34.2	35.9
b	29.1	32.4	38.7	40.5
c	35.6	37.8	45.6	48.1
d	46.8	49.7	55.7	57.9
e	48.2	50.3	58.5	59.1

[a] In case of the kinetic resolution of the racemic cyanohydrins (*)-**3′** corresponds to the less reactive and (**)-**3′** to the more reactive enantiomer as chloroacetates in the chromatograms; optical rotations were not measured.

Determination of E was based on the equation $E=\ln[(1-c)(1-ee_S)]/\ln[(1-c)(1+ee_S)]$.[21] Using linear regression E is achieved as the slope of a line. All enzymatic reactions were performed at room temperature (23–24 °C).

4.2. Synthesis of racemic cyanohydrins 2a–e

The preparation of racemic cyanohydrins **2a**–**e** followed the procedure previously described.[8,9,22]

To a stirred solution of one of the aldehydes (**1a**–**e**, 1 mmol) in dry dichloromethane (10 mL) a catalytic amount of ZnI_2 (3.2 mg, 10 μmol) and trimethylsilyl cyanide (119 mg, 150 μL, 1.2 mmol) were added. The resulting mixture was stirred at room temperature until all of the aldehyde was transformed. The crude product was purified on silica gel using *vacuum* chromatography. The solvent was evaporated and the crude product was redissolved in acetonitrile (10 mL). The formed trimethylsilyl cyanohydrin decomposed when Dowex 50WX8 strongly acidic ion exchange resin (5 mg) and water (10 μL) were added. The resin was filtered off and the solvent was evaporated. The crude reaction mixture was extracted with water (3 mL) and dichloromethane (6 mL). After separation the aqueous layer was extracted with dichloromethane (6 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed.

4.2.1. 10-Methylphenothiazin-3-ylhydroxyacetonitrile (*rac*-2a). Yield: 90%. Semisolid; HRMS M^+ found (M^+ calcd for $C_{15}H_{12}N_2OS$): 269.0742 (269.0749); MS: *m*/*z* (relative intensity)=269 (0.2) [M^+], 252 (0.2), 243 (18), 242 (100), 241 (3), 215 (7), 214 (30), 213 (78), 212 (17), 201 (4), 200 (15), 199 (67), 198 (12); ^{1}H NMR: $\delta=2.87$ (broad s, 1H, O*H*), 3.37 (s, 3H, N-CH_3), 5.41 (s, 1H, C*H*(OH)CN), 6.80 (d, $J=8.3$ Hz, 1H, C(1)*H*), 6.82 (dd, $J=0.7$, 8.5 Hz, 1H, C(9)*H*), 6.96 (ddd, $J=7.5$, 7.4, 0.7 Hz, 1H, C(7)*H*), 7.13 (dd, $J=7.5$, 1.5 Hz, 1H, C(6)*H*), 7.18 (ddd, $J=1.5$, 7.4, 8.5 Hz, 1H, C(8)*H*), 7.26 (d, $J=2.2$ Hz, 1H, C(4)*H*), 7.29 (dd, $J=8.3$, 2.2 Hz, 1H, C(2)*H*); ^{13}C NMR: 35.41 (*C*H_3-N), 62.99 (*C*H(OH)CN), 114.19 (*C*(1)), 114.33 (*C*(9)), 118.59 (CH(OH)*C*N), 122.53 (*C*(6a)), 122.97 (*C*(7)), 124.61 (*C*(4a)), 125.41 (*C*(4)), 126.04 (*C*(2)), 127.20 (*C*(6)), 127.71 (*C*(8)), 129.28 (*C*(3)), 145.00 (*C*(9a)), 147.17 (*C*(1a)).

4.2.2. 10-Ethylphenothiazin-3-ylhydroxyacetonitrile (*rac*-2b). Yield: 92%. Semisolid; HRMS M^+ found (M^+ calcd for $C_{16}H_{14}N_2OS$): 283.0911 (283.0905); MS: *m*/*z*

(relative intensity)=283 (0.3) [M^+], 266 (0.2), 257 (23), 256 (100), 255 (4), 229 (10), 228 (45), 227 (90), 226 (10), 200 (8), 199 (27), 198 (20), 181 (3), 180 (22); ^{1}H NMR: δ= 1.40 (q, J=7 Hz, 2H, CH_3–CH_2–N), 2.00 (broad s, 1H, O*H*), 3.90 (t, J=7 Hz, 3H, CH_3–CH_2–N), 5.34 (s, 1H, C*H*(OH)CN), 6.83 (d, J=8.4 Hz, 1H, C(1)*H*), 6.86 (dd, J= 1.1, 8.3 Hz, 1H, C(9)*H*), 6.92 (ddd, J=7.6, 7.4, 1.1 Hz, 1H, C(7)*H*), 7.10 (dd, J=7.6, 1.4 Hz, 1H, C(6)*H*), 7.15 (ddd, J=1.4, 7.4, 8.3 Hz, 1H, C(8)*H*), 7.20 (d, J=2.2 Hz, 1H, C(4)*H*), 7.24 (dd, J=8.4, 2.2 Hz, 1H, C(2)*H*); ^{13}C NMR: 12.82 (CH_3–CH_2–N), 41.89 (CH_3–CH_2–N), 62.77 (*C*H(OH)CN), 115.08 (*C*(1)), 115.23 (*C*(9)), 118.74 (CH(OH)*C*N), 122.78 (*C*(7)), 123.49 (*C*(6a)), 125.32 (*C*(4a)), 125.57 (*C*(4)), 125.81 (*C*(2)), 127.36 (*C*(6)), 127.48 (*C*(8)), 129.24 (*C*(3)), 144.18 (*C*(9a)), 146.17 (*C*(1a)).

4.2.3. 10-Propylphenothiazin-3-ylhydroxyacetonitrile (*rac*-2c). Yield: 94%. Semisolid; HRMS M^+ found (M^+ calcd for $C_{17}H_{16}N_2OS$): 297.1054 (297.1062); MS: *m*/*z* (relative intensity)=297 (0.3) [M^+], 280 (0.3), 271 (19), 270 (100), 269 (30), 243 (4), 241 (22), 240 (48), 229 (3), 228 (10), 227 (28), 226 (26), 212 (8), 208 (7), 200 (18), 199 (13), 198 (7); ^{1}H NMR: δ=0.99 (t, J=7.5 Hz, 3H, CH_3–CH_2–CH_2), 1.80 (m, J=7.2, 7.5 Hz, 2H, CH_3–CH_2–CH_2), 3.28 (broad s, 1H, O*H*), 3.79 (t, J=7.2 Hz, 2H, CH_3–CH_2–CH_2), 5.37 (s, 1H, C*H*(OH)CN), 6.82 (d, J=8.4 Hz, 1H, C(1)*H*), 6.85 (dd, J=1.0, 8.2 Hz, 1H, C(9)*H*), 6.93 (ddd, J=7.7, 7.5, 1.0 Hz, 1H, C(7)*H*), 7.11 (dd, J=7.7, 1.5 Hz, 1H, C(6)*H*), 7.15 (ddd, J=1.5, 7.5, 8.2 Hz, 1H, C(8)*H*), 7.22 (d, J= 2.2 Hz, 1H, C(4)*H*), 7.24 (dd, J=8.4, 2.2 Hz 1H, C(2)*H*); ^{13}C NMR: 11.21 (CH_3–CH_2–CH_2–N), 19.93 (CH_3–CH_2–CH_2–N), 49.18 (CH_3–CH_2–CH_2–N), 62.82 (*C*H(OH)CN), 115.47 (*C*(1)), 115.59 (*C*(9)), 118.71 (CH(OH)*C*N), 122.80 (*C*(7)), 123.95 (*C*(6a)), 125.64 (*C*(4)), 125.80 (*C*(4a)), 125.80 (*C*(2)), 127.41 (*C*(6)), 127.42 (*C*(8)), 129.07 (*C*(3)), 144.46 (*C*(9a)), 146.56 (*C*(1a)).

4.2.4. 10-(3-Methylbutyl)phenothiazin-3-ylhydroxyacetonitrile (*rac*-2d). Yield: 91%. Semisolid; HRMS M^+ found (M^+ calcd for $C_{19}H_{20}N_2OS$): 325.1369 (325.1375); MS: *m*/*z* (relative intensity)=325 (0.2) [M^+], 308 (0.3), 299 (26), 298 (100), 297 (42), 271 (6), 270 (10), 269 (21), 241 (8), 240 (47), 229 (21), 228 (14), 227 (21), 226 (30), 212 (12), 200 (14), 199 (8); ^{1}H NMR: δ=0.94 (d, J=6.6 Hz, 6H, (CH_3)$_2$CH–CH_2–CH_2), 1.67 (dd, J=7.3, 6.7 Hz, 2H, (CH_3)$_2$CH–CH_2–CH_2), 1.75 (dd, J=6.7, 6.6 Hz, 1H, (CH_3)$_2$C*H*–CH_2–CH_2), 3.50 (broad s, 1H, O*H*), 3.85 (t, J=7.3 Hz, 2H, (CH_3)$_2$CH–CH_2–CH_2), 5.34 (s, 1H, C*H*(OH)CN), 6.84 (d, J=8.4 Hz, 1H, C(1)*H*), 6.86 (dd, J=1.1, 8.1 Hz, 1H, C(9)*H*), 6.93 (ddd, J=7.6, 7.4, 1.1 Hz, 1H, C(7)*H*), 7.11 (dd, J=7.6, 1.5 Hz, 1H, C(6)*H*), 7.16 (ddd, J=1.5, 7.4, 1.1 Hz, 1H, C(8)*H*), 7.21 (d, J=2.2 Hz, 1H, C(4)*H*), 7.24 (dd, J=8.4, 2.2 Hz, 1H, C(2)*H*); ^{13}C NMR: 22.48 ((CH_3)$_2$CH–CH_2–CH_2), 26.18 ((CH_3)$_2$*C*H–CH_2–CH_2), 35.45 ((CH_3)$_2$CH–CH_2–CH_2), 45.74 ((CH_3)$_2$CH–CH_2–CH_2), 62.74 (*C*H(OH)CN), 115.38 (*C*(1)), 115.50 (*C*(9)), 118.51 (CH(OH)*C*N), 122.77 (*C*(7)), 123.96 (*C*(6a)), 125.65 (*C*(4)), 125.75 (*C*(4a)), 125.80 (*C*(2)), 127.43 (*C*(6)), 127.43 (*C*(8)), 129.13 (*C*(3)), 144.51 (*C*(9a)), 146.52 (*C*(1a)).

4.2.5. 10-*n*-Heptylphenothiazin-3-ylhydroxyacetonitrile (*rac*-2e). Yield: 92%. Semisolid; HRMS M^+ found (M^+ calcd for $C_{21}H_{24}N_2OS$): 353.1684 (353.1688); MS: *m*/*z* (relative intensity)=353 (0.2) [M^+], 336 (0.2), 327 (24), 326 (100), 325 (79), 298 (10), 297 (15), 241 (9), 240 (51), 227 (14), 226 (20), 212 (11), 200 (6), 198 (3); ^{1}H NMR: δ= 0.86 (t, J=7.6 Hz, 3H, CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 1.27 (m, 4H, CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 1.32 (m, J=7.6 Hz, 2H, CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 1.42 (m, J=7.6, 7.6 Hz, 2H, CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 1.79 (m, J=7.2, 7.6 Hz, 2H, CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 2.57 (broad s, 1H, O*H*), 3.84 (t, J=7.2 Hz, 2H, CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 5.42 (s, 1H, C*H*(OH)CN), 6.86 (d, J=8.3 Hz, 1H, C(1)*H*), 6.86 (dd, J=1.2, 8.3 Hz, 1H, C(9)*H*), 6.93 (ddd, J=7.7, 7.5, 1.2 Hz, 1H, C(7)*H*), 7.11 (dd, J=7.7, 1.5 Hz, 1H, C(6)*H*), 7.16 (ddd, J=1.5, 7.5, 8.3 Hz, 1H, C(8)*H*), 7.26 (d, J= 2.2 Hz, 1H, C(4)*H*), 7.29 (dd, J=8.3, 2.2 Hz, 1H, C(2)*H*); ^{13}C NMR: 14.03 (CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 22.52 (CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 26.76 (CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 26.84 (CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 28.88 (CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 31.72 (CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 47.57 (CH_3CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 63.11 (*C*H(OH)CN), 115.48 (*C*(1)), 115.60 (*C*(9)), 118.51 (CH(OH)*C*N), 122.89 (*C*(7)), 124.02 (*C*(6a)), 125.74 (*C*(4)), 125.83 (*C*(2)), 126.10 (*C*(4a)), 127.47 (*C*(6)), 127.49 (*C*(8)), 129.13 (*C*(3)), 144.53 (*C*(9a)), 146.81 (*C*(1a)).

4.3. Preparation of racemic cyanohydrin esters

To a solution of one of the racemic cyanohydrins (*rac*-**2a**–**e**, 0.5 mmol) in dichloromethane (5 mL) acetic anhydride (51 mg, 48 μL, 0.50 mmol), a catalytic amount of DMAP in pyridine (5 μL; 1% solution) and triethylamine (51 mg, 69 μL, 0.50 mmol) were added. After stirring for 15 min at room temperature the solvent was evaporated in vacuo and the crude product was purified by column chromatography using dichloromethane as eluent.

4.3.1. 10-Methylphenothiazin-3-ylcyanomethyl acetate (*rac*-3a). Yield: 73%. Semisolid; HRMS M^+ found (M^+ calcd for $C_{17}H_{14}N_2O_2S$): 311.0858 (311.0854); MS: *m*/*z* (relative intensity)=311 (1), 310 (5) [M^+], 269 (0.1), 252 (0.2), 243 (20), 242 (100), 241 (4), 215 (8), 214 (34), 213 (79), 212 (17), 201 (2), 200 (15), 199 (67), 198 (14); ^{1}H NMR: δ=2.14 (s, 3H, CH(CN)–O–CO–CH_3), 3.38 (s, 3H, N-CH_3), 6.30 (s, 1H, C*H*(CN)–O–CO–CH_3), 6.81 (d, J= 8.4 Hz, 1H, C(1)*H*), 6.82 (dd, J=1.1, 8.2 Hz, 1H, C(9)*H*), 6.96 (ddd, J=7.5, 7.4, 1.1 Hz, 1H, C(7)*H*), 7.13 (dd, J=7.5, 1.5 Hz, 1H, C(6)*H*), 7.19 (ddd, J=1.5, 7.4, 8.2 Hz, 1H, C(8)*H*), 7.26 (d, J=2.2 Hz, 1H, C(4)*H*), 7.28 (dd, J=8.4, 2.2 Hz, 1H, C(2)*H*); ^{13}C NMR: 20.47 (CH(CN)–O–CO–*C*H_3), 35.43 (*C*H_3-N), 62.23 (*C*H(CN)–O–CO–CH_3), 114.08 (*C*(1)), 114.38 (*C*(9)), 116.05 (CH(*C*N)–O–CO–CH_3), 122.46 (*C*(6a)), 123.08 (*C*(7)), 124.70 (*C*(4a)), 125.61 (*C*(3)), 126.57 (*C*(4)), 127.21 (*C*(2)), 127.45 (*C*(6)), 127.73 (*C*(8)), 144.86 (*C*(9a)), 147.67 (*C*(1a)), 168.90 (CH(CN)–O–*C*O–CH_3).

4.3.2. 10-Ethylphenothiazin-3-ylcyanomethyl acetate (*rac*-3b). Yield: 90%. Semisolid; HRMS M^+ found (M^+ calcd for $C_{18}H_{16}N_2O_2S$): 325.1008 (325.1011); MS: *m*/*z* (relative intensity)=325 (1), 324 (5) [M^+], 283 (0.3), 266

(0.2), 257 (21), 256 (100), 255 (4), 229 (13), 228 (42), 227 (94), 226 (10), 200 (9), 199 (31), 198 (25), 181 (3), 180 (27); ^{1}H NMR: δ=1.41 (q, J=7.1 Hz, 2H, CH_3–CH_2–N), 2.14 (s, 3H, CH(CN)–O–CO–CH_3), 3.92 (s, J=7.1 Hz, 3H, CH_3–CH_2–N), 6.29 (s, 1H, CH(CN)–O–CO–CH_3), 6.86 (d, J=8.5 Hz, 1H, C(1)H), 6.87 (dd, J=1.1, 8.3 Hz, 1H, C(9)H), 6.93 (ddd, J=7.7, 7.4, 1.1 Hz, 1H, C(7)H), 7.11 (dd, J=7.7, 1.6 Hz, 1H, C(6)H), 7.16 (ddd, J=1.6, 7.4, 8.3 Hz, 1H, C(8)H), 7.24 (d, J=2.2 Hz, 1H, C(4)H), 7.28 (dd, J=8.5, 2.2 Hz, 1H, C(2)H); ^{13}C NMR: 12.78 (CH_3–CH_2–N), 20.45 (CH(CN)–O–CO–CH_3), 41.91 (CH_3–CH_2N), 62.18 (CH(CN)–O–CO–CH_3), 114.96 (C(1)), 115.28 (C(9)), 116.04 (CH(CN)–O–CO–CH_3), 122.93 (C(7)), 123.34 (C(5a)), 125.37 (C(4a)), 125.48 (C(3)), 126.75 (C(4)), 127.21 (C(2)), 127.37 (C(6)), 127.51 (C(8)), 143.96 (C(9a)), 146.81 (C(1a)), 168.88 (CH(CN)–O–CO–CH_3).

4.3.3. 10-Propylphenothiazin-3-ylcyanomethyl acetate (*rac*-3c). Yield: 81%. Semisolid; HRMS M^+ found (M^+ calcd for $C_{19}H_{18}N_2O_2S$): 339.1169 (339.1167); MS: *m*/*z* (relative intensity)=339 (1), 338 (5) [M^+], 297 (0.3), 280 (0.3), 271 (20), 270 (100), 269 (33), 243 (5), 241 (22), 240 (49), 229 (7), 228 (14), 227 (44), 226 (26), 212 (9), 208 (7), 200 (18), 199 (13), 198 (7); ^{1}H NMR: δ=1.01 (t, J=7.4 Hz, 3H, CH_3–CH_2–CH_2), 1.82 (m, J=7.1, 7.4 Hz, 2H, CH_3–CH_2–CH_2), 2.14 (s, 3H, CH(CN)–O–CO–CH_3), 3.82 (t, J=7.1 Hz, 2H, CH_3–CH_2–CH_2), 6.30 (s, 1H, CH(CN)–O–CO–CH_3), 6.85 (d, J=8.3 Hz, 1H, C(1)H), 6.86 (dd, J=1.1, 8.2 Hz, 1H, C(9)H), 6.94 (ddd, J=7.6, 7.3, 1.1 Hz, 1H, C(7)H), 7.12 (dd, J=7.6, 1.4 Hz, 1H, C(6)H), 7.16 (ddd, J=1.4, 7.3, 8.2 Hz, 1H, C(8)H), 7.25 (d, J=2.2 Hz, 1H, C(4)H), 7.28 (dd, J=8.3, 2.2 Hz, 1H, C(2)H); ^{13}C NMR: 11.21 (CH_3–CH_2–CH_2–N), 19.95 (CH_3–CH_2–CH_2–N), 20.45 (CH(CN)–O–CO–CH_3), 49.21 (CH_3–CH_2–CH_2–N), 62.20 (CH(CN)–O–CO–CH_3), 115.35 (C(1)), 115.66 (C(9)), 116.05 (CH(CN)–O–CO–CH_3), 122.97 (C(7)), 123.92 (C(6a)), 125.40 (C(4a)), 126.02 (C(3)), 126.86 (C(4)), 127.18 (C(2)), 127.46 (C(6)), 127.46 (C(8)), 144.31 (C(9a)), 147.21 (C(1a)), 168.89 (CH(CN)–O–CO–CH_3).

4.3.4. 10-(3-Methylbutyl)phenothiazin-3-ylcyano-methyl acetate (*rac*-3d). Yield: 74%. Semisolid; HRMS M^+ found (M^+ calcd for $C_{21}H_{22}N_2O_2S$): 367.1477 (367.1480); MS: *m*/*z* (relative intensity)=367 (0.5), 366 (4) [M^+], 325 (0.2), 308 (0.3), 299 (21), 298 (100), 297 (44), 271 (6), 270 (13), 269 (22), 241 (4), 240 (49), 229 (23), 228 (14), 227 (21), 226 (30), 212 (13), 200 (17), 199 (8); ^{1}H NMR: δ=0.96 (d, J=6.3 Hz, 6H, (CH_3)$_2$CH–CH_2–CH_2), 1.69 (m, J=7.3, 6.6 Hz, 2H, (CH_3)$_2$CH–CH_2–CH_2), 1.76 (m, J=6.6, 6.3 Hz, 1H, (CH_3)$_2$CH–CH_2–CH_2), 2.14 (s, 3H, CH(CN)–O–CO–CH_3), 3.87 (t, J=7.3 Hz, 2H, (CH_3)$_2$CH–CH_2–CH_2), 6.30 (s, 1H, CH(CN)–O–CO–CH_3), 6.87 (d, J=8.4 Hz, 1H, C(1)H), 6.88 (dd, J=1.1, 8.2 Hz, 1H, C(9)H), 6.94 (ddd, J=7.5, 7.3 1.1 Hz, 1H, C(7)H), 7.12 (dd, J=7.5, 1.5 Hz, 1H, C(6)H), 7.17 (ddd, J=1.5, 7.3, 8.2 Hz, 1H, C(8)H), 7.25 (d, J=2.2 Hz, 1H, C(4)H), 7.29 (dd, J=8.4, 2.2 Hz, 1H, C(2)H); ^{13}C NMR: 20.43 (CH(CN)–O–CO–CH_3), 22.45 ((CH_3)$_2$CH–CH_2–CH_2), 26.17 ((CH_3)$_2$CH–CH_2–CH_2), 35.44 ((CH_3)$_2$CH–CH_2–CH_2), 45.76 ((CH_3)$_2$CH–CH_2–CH_2), 62.18 (CH(CN)–O–CO–CH_3), 115.26 (C(1)), 115.57 (C(9)), 116.04 (CH(CN)–O–CO–CH_3), 122.93 (C(7)), 123.87 (C(6a)), 125.36 (C(4a)), 125.95 (C(3)), 126.83 (C(4)), 127.17 (C(2)), 127.45 (C(6)), 127.46 (C(8)), 144.31 (C(9a)), 147.18 (C(1a)), 168.86 (CH(CN)–O–CO–CH_3).

4.3.5. 10-*n*-Heptylphenothiazin-3-ylcyanomethyl acetate (*rac*-3e). Yield: 79%. Semisolid; HRMS M^+ found (M^+ calcd for $C_{23}H_{26}N_2O_2S$): 395.1791 (395.1793); MS: *m*/*z* (relative intensity)=395 (0.3), 394 (4) [M^+], 353 (0.2), 336 (0.2), 327 (24), 326 (100), 325 (81), 298 (13), 297 (16), 241 (11), 240 (53), 227 (14), 226 (20), 212 (11), 200 (7), 198 (9); ^{1}H NMR: δ=0.86 (t, J=6.8 Hz, 3H, CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 1.27 (m, 4H, CH_3–CH_2–CH_2–CH_2–CH_2–CH_2), 1.31 (m, J=6.3 Hz, 2H, CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 1.42 (m, J=7.6, 7.8 Hz, 2H, CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 1.79 (m, J=7.1, 7.6, 2H, CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 2.14 (s, 3H, CH(CN)–O–CO–CH_3), 3.84 (t, J=7.1 Hz, 2H, CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 6.30 (s, 1H, CH(CN)–O–CO–CH_3), 6.85 (d, J=8.3 Hz, 1H, C(1)H), 6.86 (dd, J=1.1, 8.1 Hz, 1H, C(9)H), 6.94 (ddd, J=7.6, 7.4, J=1.1, 1H, C(7)H), 7.12 (dd, J=7.6, 1.5 Hz, 1H, C(6)H), 7.16 (ddd, J=1.5 7.4 Hz, J=8.1 Hz, 1H, C(8)H), 7.25 (d, J=2.1 Hz, 1H, C(4)H), 7.28 (dd, J=8.3, 2.1 Hz, 1H, C(2)H); ^{13}C NMR: 14.03 (CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 20.51 (CH(CN)–O–CO–CH_3), 22.52 (CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 26.74 (CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 26.85 (CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 28.87 (CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 31.71 (CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 47.59 (CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2), 62.25 (CH(CN)–O–CO–CH_3), 115.34 (C(1)), 115.65 (C(9)), 116.08 (CH(CN)–O–CO–CH_3), 123.00 (C(7)), 123.94 (C(6a)), 125.43 (C(4a)), 126.05 (C(3)), 126.92 (C(4)), 127.23 (C(2)), 127.50 (C(6)), 127.52 (C(8)), 144.37 (C(9a)), 147.28 (C(1a)), 168.94 (CH(CN)–O–CO–CH_3).

4.4. Kinetic resolution of racemic cyanohydrins *rac*-(2a–e)

In a typical small scale experiment, one of the cyanohydrins **2a**–**e** (0.05 mmol) and vinyl acetate (11 mg, 11.5 μL, 0.13 mmol) or one of the corresponding esters **3a**–**e** (0.05 mmol) and methanol (13 mg, 16.4 μL, 0.41 mmol) were dissolved in a dry organic solvent (1 mL). CAL-A preparation (10 mg, corresponding to 2 mg of the enzyme) was added. Samples (5 μL) were taken after 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 h, diluted with hexane/isopropyl alcohol (9:1, 80 μL) and analyzed by the HPLC method.

4.5. One-pot synthesis of cyanohydrin esters (+)-(3a–e)

One of the aldehydes **1a**–**e** (0.15 mmol), acetone cyanohydrin (28 mg, 30 μL, 0.32 mmol) and vinyl acetate (39 mg, 42 μL, 0.45 mmol) were added to dry acetonitrile (3 mL). To this solution Amberlite IRA 904 ($^-$OH form, 5 mg/0.008 equiv) and CAL-A preparation (10 mg mL^{-1}) were added. The reaction mixture was stirred at room temperature for the times indicated in Table 3. The enzyme and the resin were filtered off and washed with acetonitrile (2×0.5 mL). Solvents were distilled off from the filtrate and the residue was purified by column chromatography on silica gel with dichloromethane yielding (+)-**3a**–**e** (Table 3).

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Stereoselective synthesis of (1*R*,2*S*)- and (1*S*,2*R*)-1-amino-*cis*-3-azabicyclo[4.4.0]decan-2,4-dione hydrochlorides: bicyclic glutamic acid derivatives

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Abstract—Asymmetric synthesis of (1*R*,2*S*)- and (1*S*,2*R*)-1-amino-*cis*-3-azabicyclo[4.4.0]decan-2,4-diones has been achieved. The underlying second generation asymmetric synthesis proceeds via a Strecker reaction with commercially available (*R*)-1-phenylethylamine (1-PEA) as chiral auxiliary, TMSCN as cyanide source and racemic ethyl 2-(2-oxocyclohex-1-yl)ethanoate. A ring closure addition–elimination reaction between an amide nitrogen and the ester functionality leads to the 1-amino-3-azabicyclo[4.4.0]decan-2,4-diones. The absolute configurations of the title compounds have been assigned based on detailed NMR-spectroscopic analysis and X-ray data.

1. Introduction

As early as 1850, the German chemist Adolf Strecker described the one-pot synthesis of the amino acid alanine by means of heating a mixture of acetaldehyde, ammonia and hydrogen cyanide in the presence of hydrochloric acid.[1,2a–k] This procedure, named after its originator and extended to a variety of carbonyl substrates, is still the most common method of preparing large amounts of α-amino acids. Nevertheless and in contrast to his assumption, Strecker did not prepare one single compound but a racemic mixture of the enantiomeric D- and L-alanines. Since nowadays enantiomeric purity is one of the major issues in α-amino acid synthesis, tremendous efforts have been put into the development of asymmetric versions of Strecker's protocol. In 1963, a 'Nature' paper of Harada et al.[3] describes a modified three-step asymmetric synthesis of L-alanine with an enantiomeric excess (ee) of 90% and an overall chemical yield of 17%. Starting from acetaldehyde, (*S*)-(−)-phenylethylamine ((*S*)-1-PEA) and hydrogen cyanide, the authors obtained the corresponding secondary α-aminonitriles, which were subsequently hydrolysed and hydrogenolysed to L-alanine. Nevertheless, later investigations showed that the enantiomeric excess was essentially due to fractional crystallisation of the intermediate secondary α-amino acid hydrochlorides. The actual diastereoselectivity of the stereodetermining step of this sequence, namely the cyanide addition, was shown to yield enantiomeric excesses of around 30%.[4]

As medicinal chemists we were particularly interested in stereomerically pure and conformationally restricted analogues of naturally occuring α-amino acids. In order to get access to compounds bearing such structural features we have developed and extensively studied the asymmetric Strecker procedure starting from racemic 2-substituted cycloaliphatic ketones. Depending on the reaction conditions (temperature and nature of the solvent), the established reaction sequence has proven to be a powerful tool for the diastereoselective synthesis of all four feasible stereomers of a series of carbocyclic α-amino acids with vicinal stereocentres.[5,6a–c]

Carbocyclic α-amino acids as representatives of the α,α-disubstituted α-amino acid family are widely used in the isosteric replacement of proteinogenic amino acids resulting in specific backbone conformations and increased stability towards chemical and enzymatic degradations.[7a–c] Moreover, conformationally restricted analogues of glutamic acid such as 1-aminoindanedicarboxylic acid (AIDA) or 1-aminocyclopentane-1,3-dicarboxylic acids (ACPD) have been described as agonists and/or antagonists at both the ionotropic (iGluRs) and the metabotropic glutamate receptors (mGluRs). Recently, they have been used in the characterisation and the subtype classification of mGluRs.[8a,b]

Keywords: Asymmetric Strecker synthesis; 3-Azabicyclo[4.4.0]decan-2,4-dione; Diastereoselectivity; X-ray analysis; Glutamic acid derivatives.
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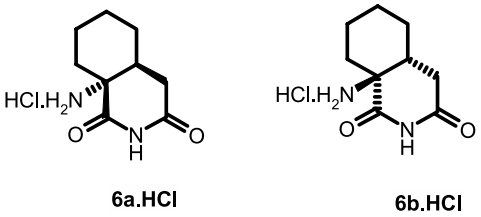


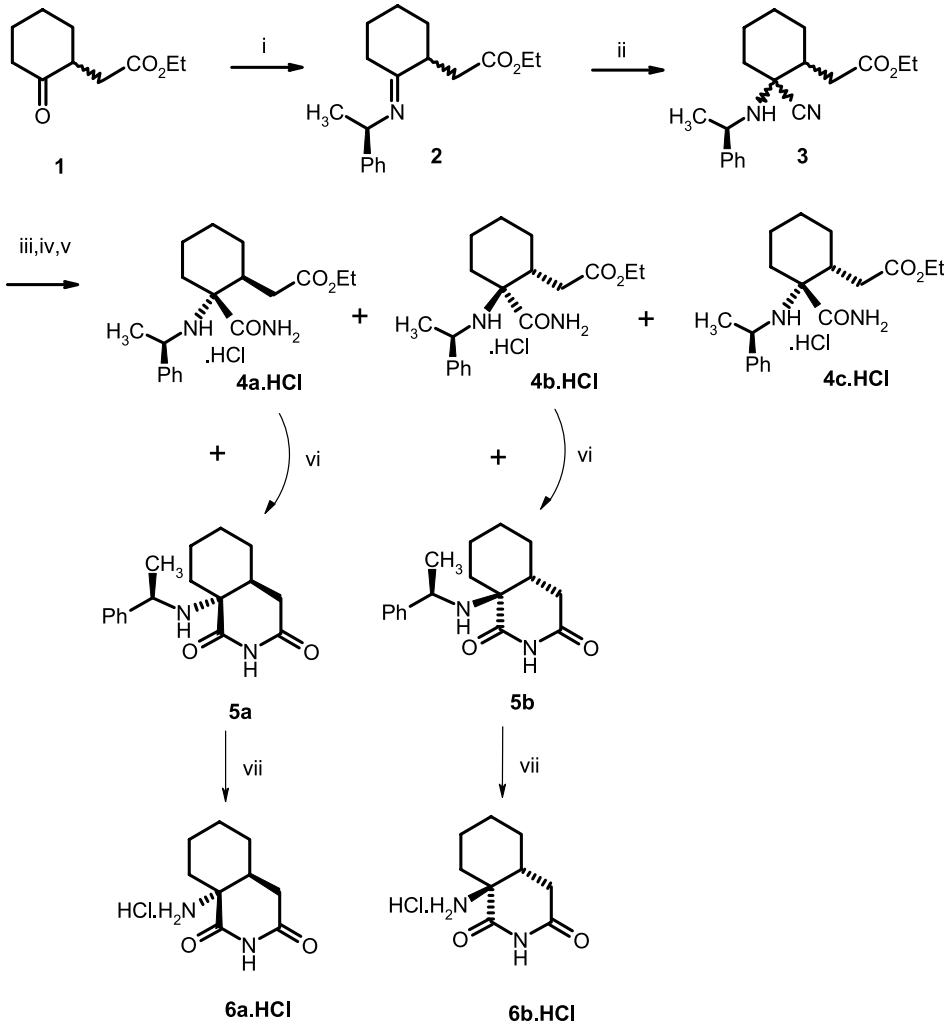
Figure 1. 1-Amino-*cis*-3-azabicyclo[4.4.0]decan-2,4-diones.

Herein, we wish to report on the synthesis of the bicyclic imides **6a**,**b** (Fig. 1) as conformationally restricted templates, which mimic folded conformations of glutamic acid, with a focus on the elucidation of the relative and the absolute stereochemistry of the intermediate α-aminonitriles.

2. Results and discussion

The synthetic route is exemplified using (*R*)-1-phenylethylamine as the chiral auxiliary. Racemic ethyl 2-(2-oxocyclohex-1-yl)ethanoate (**1**), prepared according to the standard Stork-enamine procedure from cyclohexanone, was reacted with enantiomerically pure (*R*)-1-phenylethylamine under acidic catalysis and azeotropic removal of water in benzene to yield a diastereomeric mixture of only the two (*E*)-imines **2**. It is noticable that, if the imine condensation is run in higher boiling solvents, some aminolysis of the ester could be observed.

The imine mixture was subsequently subjected to a Lewis acid ($ZnCl_2$) catalysed cyanide addition using trimethysilylcyanide (TMSCN) affording the four feasible diastereomeric α-aminonitriles **3**. Indeed, since the cyanide addition to the prochiral imine carbon atom provides a new stereocentre, the α-aminonitriles exhibit two adjacent asymmetrically substituted carbon atoms. The stereochemical outcome of this stereodetermining step depends upon the reaction conditions, that is, the nature of the solvent and the reaction temperature which allows the reaction to be carried out either under kinetic (aprotic solvents and low temperatures) or under thermodynamic (protic solvents and higher temperatures) conditions.[5,6a,b] For the purposes of developing a straight-forward synthesis of the bicyclic amino imides **6a**,**b** presented here, the



Scheme 1. Reagents and conditions: (i) (*R*)-1-PEA, *p*-TsOH, benzene, reflux, 16 h; (ii) TMSCN, $ZnCl_{2\ anhyd}$, MeOH, 0 °C to rt, overnight; (iii) $H_2SO_{4\ concd}$, CH_2Cl_2, −20 °C, 3 days; (iv) CC on SiO_2, cyclohexane/EtOAc 3:2; (v) for **4a**–**c**, ether–HCl; (vi) extraction of the base with EtOAc, then stirring with SiO_2, cyclohexane/EtOAc 3:2, rt, 5 days; (vii) $NH_4^+HCO_2^-$, Pd/C (10%), EtOH, reflux, 2 h.

cyanide addition was carried out under thermodynamic control leading preferentially to the required *trans* amino nitriles. Thus, at room temperature in methanol the four feasible α-aminonitriles were obtained in a 44:30:18:8 ratio as determined by ^{13}C NMR-analysis of selected significant carbon atoms.[5]

The subsequent hydrolysis of the nitriles to the corresponding stable secondary α-amino amidoesters **4** proved troublesome. Indeed, the hydrolysis of the sterically hindered cyano group of the α,α-disubstituted aminonitriles needs drastic reaction conditions and the aminonitriles are prone to undergo a 'retro-Strecker-reaction' even in acidic milieu under such conditions. Finally, the hydrolysis was achieved in 73% yield with concd H_2SO_4 at −20 °C over a period of 3 days avoiding any cleavage of the chiral auxiliary. It could be shown by means of ^{13}C NMR spectroscopy that the stereochemical distribution of the four stereoisomers was not altered during this specific type of mild hydrolysis. Thus, we reasoned that the assignment of the configuration of the different stereoisomeric secondary aminonitriles **3** should be deducible from the corresponding derived secondary amino amides **4**. For this purpose, the amino amidoesters **4** were separated by means of column chromatography (CC) on silica gel eluted with cyclohexane/ethyl acetate 3:2. Surprisingly, the CC did not lead to the expected four compounds but to five different structures. Three of the structures could be identified as the amino amidoesters **4a–c**, and two of them, which lack the ethyl ester moiety, as the amino imides **5a**,**b** by means of 1D- and 2D NMR techniques. We reasoned that the imides are the desired follow-up products of the *trans*-amino amidoesters and arise from a ring closure addition–elimination reaction between the amide nitrogen and the ester functionality. In this case, the low nucleophilicity of the amide nitrogen is compensated by the geometric proximity of the electrophilic reaction partner and finally by the extreme thermodynamic stability of the bicyclic imides. We could show that ester **4a**, by far the major compound, is converted to **5a** if stirred with silica gel under exactly the conditions of the CC. The same occurs with **4b**, the second major ester, which is converted to **5b**. The third ester **4c**, with *cis* configuration, did not yield a bicyclic analogue under those reaction conditions. Indeed, neither a bicyclic imide nor the theoretically feasible bicyclic lactam rising from a nucleophilic displacement of the ethyl ester moiety by the secondary amine nitrogen were observed. Note, that neither the fourth diastereomeric ester nor any of the possible follow-up compounds could be traced after column chromatography (Scheme 1).

The relative stereochemistry of **5a** was deduced from a positive NOE effect between H_α and H_2 indicating a *cis*-fusion of the rings (Fig. 2a).

The absolute configuration of **5a** was finally derived from a single crystal X-ray structure analysis and established as α*R*,1*R*,2*S* (Fig. 2b). Thus, the absolute configuration of the parent **4a** could be deduced as *trans*-α*R*,1*R*,2*S*. Subsequent hydrogenolysis of **5a** under transfer catalysis conditions with ammonium formate and Pd on charcoal affords the primary amino imide **6a** with 1*R*,2*S* configuration, whereas hydrogenolysis of **5b** yields the corresponding primary amino imide **6b** with the opposite optical rotation as

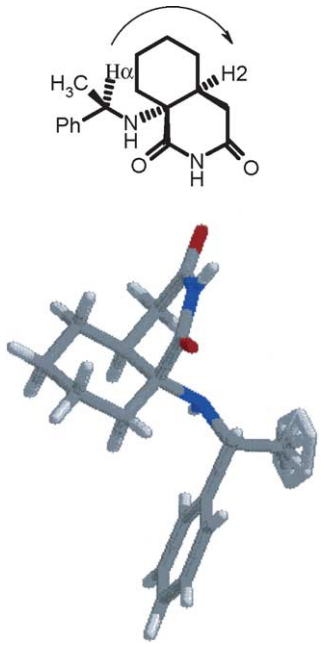


Figure 2. (a) (top) NOE-effect between H-α and H-2 in compound **5a** and (b) (bottom) X-ray structure of **5a**.

compared to **6a**. Thus, the enantiomeric 1*S*,2*R* configuration could be assigned to the parent compounds **4b** and **5b**. Since **4a** and **4b** represent the two feasible *trans* configured esters, the third ester **4c** has to exhibit a *cis* configuration. In this case, the relative stereochemistry cannot be unambiguously confirmed by a NMR analysis since earlier investigations from our group have shown that the exclusively accessible ^3J C–H coupling constants are not a reliable parameter in assessing the relative stereochemistry of 1,1-disubstituted-2-substituted cyclohexane derivatives.[9]

Interestingly, the major ester **4a** features 1*R*-configuration which is the configuration of the chiral auxiliary. This means that the diastereoselective cyanide addition occurs with like-induction at C1 which is in accordance with all our previous observations.[4,5a–c] The two feasible *cis*-aminonitriles represent 18 and 8% of the crude aminonitrile mixture, repectively. Since the amino amidoester **4c** is isolated in more than 8%, it has to arise from the major *cis* aminonitrile formed during the cyanide addition and as we observe like-induction at C1, **4c** must be 1*R*,2*R* configured. The enantiomeric *cis* amino amidoester with 1*S*,2*S* configuration would be accessible by the same pathway, using (*S*)-1-phenylethylamine as chiral auxiliary. The final bicyclic imides **6a** and **6b** are obtained in an approximate ratio of 3:1 from a reaction sequence carried out with the chiral auxiliary (*R*)-1-PEA. The same sequence run with the enantiomeric auxiliary would lead to the same final products with the opposite ratio.

3. Conclusions

The application of the asymmetric Strecker protocol followed by a ring closure reaction led to the synthesis of the previously unknown 1*R*,2*S*- and 1*S*,2*R*-1-amino-*cis*-3-azabicyclo[4.4.0]decan-2,4-dione hydrochlorides.

4. Experimental

4.1. General methods

Melting points were determined with a Mel-Temp II apparatus (Devices Laboratory USA) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.4 MHz, respectively, on a Varian Unity 300 spectrometer with chloroform-*d* and methanol-d_4, respectively, as internal standards. The chemical shifts are reported as δ values using the solvent peaks as reference. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Column chromatography was carried out with Merck silica gel Si60 (0.2–0.063 mm). TLC was performed on Si60 F_{254} TLC plates from Merck. Drying of organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4 with subsequent filtration. Evaporation of the solvents was accomplished under reduced pressure with a rotatory evaporator. HRMS (EI, 70 eV) was performed on a Finnigan MAT 8200 spectrometer at the Department of Biochemistry and Organic Chemistry, University of Freiburg.

4.1.1. (*RS*)-Ethyl 2-(2-oxocyclohex-1-yl)ethanoate (1). Prepared from cyclohexanone by classical 'Stork-enamine' synthesis in a 0.1 M batch (30% yield). For NMR data see Ref. 10.

4.1.2. *E*-Ethyl-2-[(2-(1(*R*)-phenylethyl)imino)cyclohex-1(*RS*)-yl]ethanoate (2). A solution of **1** (5.5 g, 30 mmol), *p*-toluenesulfonic acid (15 mg) and (*R*)-1-phenylethylamine (4.5 g, 37 mmol) in dry benzene was refluxed using a Dean–Stark apparatus for 16 h. The solvent was removed under reduced pressure and the residue was dried under high vacuum to yield the crude ketimine mixture which was used without further purification in the cyanide addition step. ^{13}C NMR ($CDCl_3$) δ 14.0/14.1, 25.4/25.5, 25.5/25.7, 26.9/27.6, 28.7/28.9, 33.9/34.1, 36.6/36.8, 43.8/44.0, 57.4/57.5, 59.6/59.7, 125.9/126.0, 126.3/126.3, 127.8/128.0, 146.5/147.0, 169.2/169.9, 173.2/173.4.

4.1.3. Ethyl-2-[2(*RS*)-cyano-(2(*RS*)-(1(*R*)-phenylethyl)-amino)cyclohex-1(*RS*)-yl]ethanoate (3). To a solution of the ketimine mixture **2** (8.5 g, 29.6 mmol) and anhydrous $ZnCl_2$ (200 mg) in MeOH (100 mL), TMSCN (4.4 mL, 35 mmol) was added at 0 °C over a period of 30 min. The reaction mixture was allowed to warm up to room temperature and stirred over night. The solids were filtered off, the solvent was evaporated and the residue was dried to yield a mixture of the α-amino nitrile mixture **3** (8.9 g, 96%) which was further reacted without purification.

4.2. Hydrolysis of the nitrile mixture 3

A solution of the nitrile mixture **3** (5 g, 16 mmol) in CH_2Cl_2 (3 mL) was added dropwise to concd H_2SO_4 (50 mL) at −20 °C. Stirring was maintained for a period of 3 days. The reaction mixture was poured onto ice (600 mL) and the solids filtered off. The filtrate was adjusted to pH 8 with concd ammonia and extracted with EtOAc (3×150 mL). The combined organic extracts were washed with water, brine, dried with $MgSO_4$, filtered, concentrated and finally dried in high vacuum to yield 4.77 g (89%) of an oily residue. 3 g of the above residue were separated by means of silica gel column chromatography eluting with cyclohexane/EtOAc 3:2 yielding four fractions **A**, **B**, **C**, and **D**. Fraction **D** consisted of pure **4a** (1.04 g, 31%). Fraction **A** consisted of pure **5a** (292 mg, 10%). Fraction **B** was rechromatographed on silica gel eluting with cyclohexane/EtOAc 2:1 yielding **5b** (170 mg, 6%) and **4c** (328 mg, 10%). Fraction **C** was rechromatographed on silica gel eluting with cyclohexane/EtOAc 2:1 yielding **4b** (295 mg, 9%).

The amine bases **4a**–**c** were each taken up in ether and treated with ether–HCl to yield the corresponding hydrochlorides in quantitative yields (**4a·HCl** can be precipitated directly from the crude oily residue upon treatment with acetone and ether–HCl).

4.2.1. *trans*-Ethyl-2-[2(*S*)-carbamoyl-(2(*S*)-(1(*R*)-phenylethyl)amino)cyclohex-1(*R*)-yl]ethanoate hydrochloride (4a·HCl). White solid, mp 200 °C; $[\alpha]_D^{25}=+1.85$ (EtOH, *c* 1.03); ^{1}H NMR (CD_3OD) δ 1.22 (t, $J=7.0$ Hz, 3H), 1.1–1.3 (m, 3H), 1.3–1.6 (m, 3H), 1.74 (d, $J=6.7$ Hz, 3H), 1.7–1.8 (m, 1H), 1.9–2.1 (m, 1H), 2.4–2.6 (m, 2H), 2.7–2.80 (m, 1H), 4.13 (q, $J=7.0$ Hz, 2H), 4.51 (q, $J=6.7$ Hz, 1H), 7.4–7.5 (m, 3H), 7.6–7.7 (m, 2H); ^{13}C NMR (CD_3OD) δ 14.5, 20.8, 21.5, 22.4, 25.8, 26.0, 35.7, 38.9, 60.1, 62.1, 71.7, 129.0, 130.4, 130.9, 138.8, 172.4, 173.4; MS (CI, NH_3, 45 eV): *m/z* (%) 333 (100) $[M+H^+]$; HRMS (EI, 70 eV) calcd for $C_{18}H_{26}NO_2$ $[M-CONH_2]$ 288.1963. Found 288.1968.

4.2.2. *trans*-Ethyl-2-[2(*R*)-carbamoyl-(2(*R*)-(1(*R*)-phenylethyl)amino)cyclohex-1(*S*)-yl] ethanoate hydrochloride (4b·HCl). White solid, mp 195 °C; $[\alpha]_D^{25}=-22.04$ (EtOH, *c* 1.00); ^{1}H NMR (CD_3OD) δ 1.1 (t, $J=7.1$ Hz, 3H), 1.4–1.6 (m, 3H), 1.6–1.8 (m, 2H), 1.78 (d, $J=6.8$ Hz, 3H), 1.9–2.2 (m, 2H), 2.2–2.4 (m, 1H), 2.45 (dd, $J=16.9$, 10.7 Hz, 1H), 2.5–2.7 (m, 2H), 4.12 (q, $J=7.1$ Hz, 2H), 4.50 (q, $J=6.8$ Hz, 1H), 7.3–7.4 (m, 3H), 7.4–7.6 (m, 2H); ^{13}C NMR (CD_3OD) δ 14.5, 22.0, 22.5, 22.6, 27.3, 27.5, 36.1, 39.4, 58.8, 62.0, 70.7, 129.6, 129.9, 130.5, 138.2, 171.6, 173.7; MS (CI, NH_3, 45 eV): *m/z* (%) 333 (100) $[M+H^+]$; HRMS (EI, 70 eV) calcd for $C_{18}H_{26}NO_2$ $[M-CONH_2]$ 288.1963. Found 288.1972.

4.2.3. *cis*-Ethyl-2-[2(*R*)-carbamoyl-(2(*R*)-(1(*R*)-phenylethyl)amino)cyclohex-1(*R*)-yl]ethanoate hydrochloride (4c·HCl). White solid, mp 210 °C; $[\alpha]_D^{25}=+10.8$ (EtOH, *c* 1.12); ^{1}H NMR (CD_3OD) δ 1.12 (t, $J=7.0$ Hz, 3H), 1.4–1.9 (m, 11H with 1.77 (d, $J=6.7$ Hz, 3H)), 2.2–2.4 (m, 3H), 4.12 (q, $J=7.0$ Hz, 2H), 4.47 (q, $J=6.7$ Hz, 1H), 7.3–7.4 (m, 3H), 7.5–7.6 (m, 2H); ^{13}C NMR (CD_3OD) δ 13.3, 20.8, 21.4, 23.0, 26.2, 28.4, 34.3, 39.0, 58.6, 61.0, 70.9, 128.1, 128.8, 129.2, 138.4, 171.0, 172.6; MS (CI, NH_3, 45 eV): *m/z* (%) 333 (100) $[M+H^+]$; HRMS (EI, 70 eV) calcd for $C_{18}H_{26}NO_2$ $[M-CONH_2]$ 288.1963. Found 288.1967.

4.2.4. (1*R*,2*S*)-1-((1(*R*)-Phenylethyl)amino)-*cis*-3-azabicyclo[4.4.0]decan-2,4-dione (5a). White solid, mp 170 °C; $[\alpha]_D^{25}=+12.5$ (EtOH, *c* 1.00); ^{1}H NMR ($CDCl_3$) δ 1.0–1.4 (m, 7H with 1.28 (d, $J=6.7$ Hz, 3H)), 1.4–1.5 (m, 1H), 1.6–1.8 (m, 2H), 1.8–2.0 (m, 1H), 2.18 (dd, $J=18.0$, 2.8 Hz, 1H), 2.3–2.4 (m, 1H), 2.97 (dd, $J=17.9$, 5.5 Hz, 1H), 4.0 (q, $J=6.7$ Hz, 2H) 7.2–7.4 (m, 5H), 7.6 (s br, 1H); ^{13}C NMR (CD_3OD) δ 23.0, 24.5, 26.6, 30.0, 32.1, 35.2,

37.7, 51.9, 61.1, 126.3, 126.83, 128.48, 147.52, 171.90, 173.65; MS (CI, NH_3, 45 eV): *m/z* (%) 287 (100) [M+H$^+$]; HRMS (EI, 70 eV) calcd for $C_{17}H_{22}N_2O_2$ 286.1681. Found 286.1674.

4.2.5. (1*S*,2*R*)-1-((1(*R*)-Phenylethyl)amino)-*cis*-3-azabicyclo[4.4.0]decan-2,4-dione (5b). White solid, mp 156 °C; $[\alpha]_D^{25} = -8.5$ (EtOH, *c* 1.00); ^{1}H NMR ($CDCl_3$) δ 0.9–1.1 (m, 1H), 1.1–1.5 (m, 6H, with 1.32 (d, $J=6.72$ Hz, 3H)), 1.5–1.8 (m, 3H), 1.8–1.9 (m, 1H), 1.9–2.0 (m, 1H), 2.2–2.4 (m, 1H), 2.49 (dd, $J=17.7$, 7.0 Hz, 1H), 2.9–3.0 (m, 1H), 3.82 (q, $J=6.6$ Hz, 1H), 7.1–7.4 (m, 5H), 8.1 (s br, 1H); ^{13}C NMR ($CDCl_3$) δ 21.8, 22.4, 27.1, 27.3, 32.5, 34.8, 35.6, 53.15, 61.19, 126.3, 126.6, 128.1, 146.9, 172.3, 175.4; MS (CI, NH_3, 45 eV): *m/z* (%) 287 (100) [M+H$^+$]; HRMS (EI, 70 eV) calcd for $C_{17}H_{21}NO_2$ 286.1681. Found 286.1688.

4.3. Hydrogenolytic cleavage of the chiral auxiliary

Ammonium formate (150 mg) was added to a solution of **5a** and **5b**, respectively, (100 mg, 0.35 mmol) and Pd/C (10%) (80 mg) in ethanol (10 mL). The reaction mixture was refluxed for 2 h, cooled, filtered through a pad of celite, washed with methanol, concentrated and dried in high vacuum yielding **6a** (49 mg, 76%) and **6b** (52 mg, 81%), respectively. Each of the residues were treated with ether–HCl to yield **6a·HCl** and **6b·HCl**, respectively, in quantitative yields.

4.3.1. (1*R*,2*S*)-1-Amino-*cis*-3-azabicyclo[4.4.0]decan-2,4-dione hydrochloride (6a·HCl). White solid, mp >250 °C (dec); $[\alpha]_D^{25} = +13.1$ (EtOH, *c* 1.00); ^{1}H NMR (CD_3OD) δ 1.5–2.0 (m, 7H), 2.1–2.4 (m, 1H), 2.4–2.6 (m, 1H), 2.70 (dd, $J=18.0$, 5.3 Hz, 1H), 3.00 (dd, $J=18.2$, 10.8 Hz, 1H); ^{13}C NMR (CD_3OD) δ 20.29, 21.01, 25.90, 29.32, 33.98, 34.38, 59.65, 172.67, 172.99; MS (CI, NH_3, 45 eV): *m/z* (%) 183 (100) [M+H$^+$]; HRMS (EI, 70 eV) calcd for $C_9H_{14}N_2O_2$ 182.1055. Found 182.1051.

4.3.2. (1*S*,2*R*)-1-Amino-*cis*-3-azabicyclo[4.4.0]decan-2,4-dione hydrochloride (6b·HCl). White solid, mp >250 °C (dec); $[\alpha]_D^{25} = -14.1$ (EtOH, *c* 0.9); ^{1}H NMR (CD_3OD) δ 1.5–2.0 (m, 7H), 2.1–2.4 (m, 1H), 2.4–2.6 (m, 1H), 2.70 (dd, $J=18.0$, 5.3 Hz, 1H), 3.00 (dd, $J=18.2$, 10.8 Hz, 1H); ^{13}C NMR (CD_3OD) δ 20.29, 21.01, 25.90, 29.32, 33.98, 34.38, 59.65, 172.67, 172.99; MS (CI, NH_3, 45 eV): *m/z* (%) 183 (100) [M+H$^+$]; HRMS (EI, 70 eV) calcd for $C_9H_{14}N_2O_2$ 182.1055. Found 182.1053.

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Asymmetric Strecker reaction of γ-keto acids. Facile entry to α-substituted and α,γ-disubstituted glutamic acids

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Abstract—The Strecker reaction of γ-keto acid derived sodium salts with (*S*)-phenylglycinol followed by treatment of the resultant α-amino nitriles with methanolic HCl and heating at 200 °C give bicyclic lactones **11** and **12**. Hydrolysis and subsequent debenzylation of **11** and their alkylation products **17** furnish α-substituted and α,γ-disubstituted glutamic acids.

1. Introduction

L-Glutamate is an endogenous ligand for more than 40 glutamate receptors, which are subdivided into ionotropic (*i*GluRs) and metabotropic glutamate receptors (*m*GluRs). The ionotropic glutamate receptors mediate fast synaptic transmission through ligand-gated ion channels and have been further subdivided into three groups based on their different response to the ligands NMDA (*N*-methyl-D-asparate), KA (kainite) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate), from which they take their names.[1] The metabotropic glutamate receptors are coupled to G-proteins that mediate a variety of transduction mechanisms.[1] Since individual glutamate receptors show different distributions within the central nervous system, subtype-selective ligands of these receptors hold promise for treatment of some neurological diseases caused by abnormal activities of glutamate receptors. This potential has prompted intensive SAR studies based on the skeleton of L-glutamic acid.[1] To date thousands of L-glutamic acid analogues have been synthesized and some of them displayed great subtype-selectivity. The commonly used concept for designing these molecules is to make conformationally constrained analogues of L-glutamic acid. For example, several α-substituted and γ-substituted glutamic acids such as (*S*)-2-ethyl glutamic acid (EGLU),[2] (*S*)-2-hydroxymethyl glutamic acid **1**[3] and (2*S*,4*S*)-4-(2,2-diphenylethyl)glutamic acid **2**[4] showed selectivity to different *m*GluRs, while γ-substituted glutamic acids with different configuration like LY339180 and LY339434 were found to be selective agonists for kinate receptors.[5] As an extension of our program on the synthesis and biological evaluation of *m*GluR ligands,[6] we have developed a facile method to prepare α-substituted and α,γ-disubstituted glutamic acids based on the asymmetric Strecker reaction of γ-keto acids in order to test their activity to *m*GluRs.[7] Herein we wish to detail these results (Fig. 1).

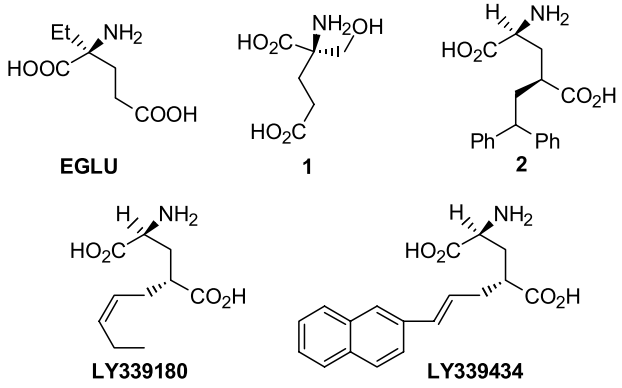

Figure 1. Structures of some selective ligands for glutamate receptors.

The Strecker reaction of γ-keto acids was reported independently by two groups several decades ago,[8] and represents a simple and efficient method for preparation of racemic α-substituted glutamic acids. Based on our studies on the asymmetric synthesis of amino acids using enantiopure phenylglycinol as a chiral auxiliary,[6h] we hoped to develop an asymmetric version of this Strecker reaction. As depicted in Scheme 1, it was expected that condensation of γ-keto acids **3** (X=H) with enantiopure

Keywords: Glutamate receptors; Strecker reaction; γ-Keto acids; Condensation; Alkylation; Deprotection.
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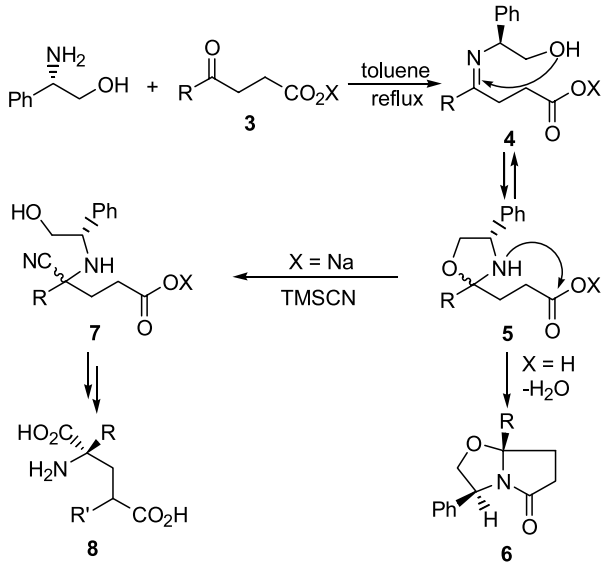


Scheme 1.

phenylglycinol would occur in refluxing toluene to afford exchangeable Schiff's bases **4** and 1,3-oxazolidines **5**, which would be attacked by cyanide anion to form α-amino nitriles **7**, thereby giving either α-substituted or α,γ-disubstituted glutamic acids after further transformations. However, this reaction sequence might not work because it is known that in refluxing toluene, γ-keto acid derived intermediates **5** (X=H) would undergo an intramolecular condensation to produce very stable bicyclic compounds **6**, which have been used by Meyer and others for synthesizing various carbocyclic and heterocyclic products.[9] After careful analysis, we realized that if γ-keto acid sodium salts were employed as the substrates, the resultant 1,3-oxazolidines **5** (X=Na) would not so easily form the bicyclic products **6** because of poorer reactivity of the carboxylate salts towards nucleophilic attack. In this case we would have chance to run asymmetric Strecker reaction.

2. Results and discussion

With this idea in mind, a reaction of levulinic acid sodium salt with (*S*)-phenylglycinol was conducted in refluxing toluene. After the solvent was removed in vacuo the residue was treated with TMSCN in absolute methanol. To our delight, this reaction provided the desired Strecker reaction products, which were exposed to freshly prepared methanolic HCl to afford amino esters **9a** and **10a**. Since they all contained two inseparable isomers, we decided to subject them to cyclization by heating in xylene, which delivered two separable isomers **11a** and **12a**. Their stereochemistry was established by NOESY studies and further confirmed by X-ray analysis of **11a**. The overall yield from **3a** was 73% for **11a** and 10% for **12a** (entry 1, Table 1), which indicated that the diastereoselectivity for the Strecker reaction step was about 7.3/1.

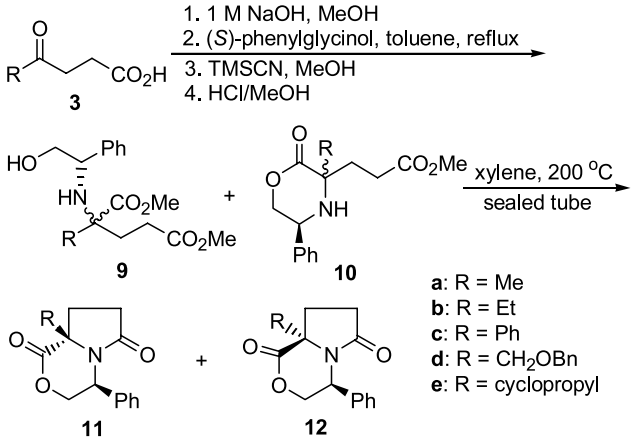
In view of the above encouraging result, other γ-keto acids bearing ethyl, phenyl, benzyloxymethyl and cyclopropyl groups were tested for this process. As indicated in Table 1, they all gave the desired Strecker reaction products isolated

Table 1. Conversion of γ-keto acids **3** to bicyclic compounds **11** and **12**

Entry	γ-Keto acid	Yield (%)[a]	
		11	**12**
1	**3a**	73	10
2	**3b**	58	20
3	**3c**	21	32
4	**3d**	25	16
5	**3e**	40	—[b]

[a] Isolated yield.
[b] An unidentified mixture was determined.

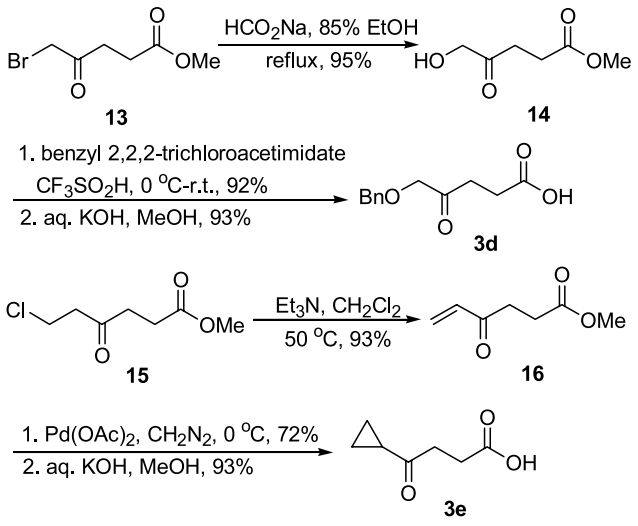
as **11** and **12**. However, poorer diastereoselectivity was observed in these cases (entries 2–5), which implied that bigger R groups decreased the diastereoselectivity. The configuration of each bicyclic product was assigned by NOESY experiments. Noteworthy is that either γ-keto acid **3d** or **3e** was prepared by a new reaction sequence as depicted in Scheme 3. Reaction of methyl 5-bromolevulinate **13** with a slight excess of sodium formate in 85% alcohol afforded 5-hydroxy-4-oxo-pentanoic acid methyl ester **14** in 95% yield, which is superior to the procedure reported by Neier and his co-workers.[10] After introducing the benzyl protecting group under acidic conditions, hydrolysis was carried out to provide **3d**. In a parallel procedure, 6-chloro-4-oxo-hexanoic acid methyl ester **15** was treated with triethylamine gave the elimination product **16**, which was subjected to a $Pd(OAc)_2$-catalyzed cyclopropanation reaction with diazomethane followed by hydrolysis to afford **3e**. This process is more practical for laboratory preparation that is previously reported (Schemes 2 and 3).[11]



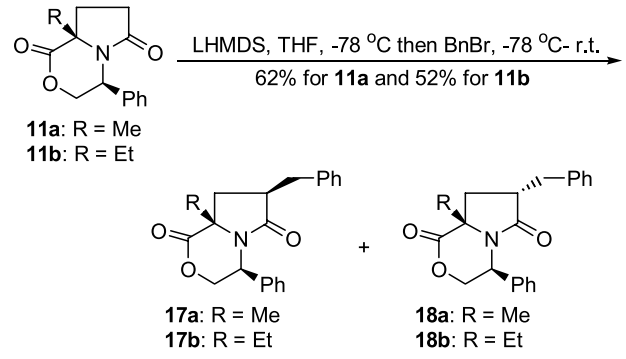
Scheme 2.

Further functionalization of the bicyclic products **11** was exemplified by alkylation. Accordingly, treatment of **11a** with LiHMDS followed by trapping the anion with benzyl bromide produced a separable mixture of **17a** and **18a** in a ratio of 3.3/1 (Scheme 4). In a similar manner, **17b** and **18b** were obtained in a ratio of 1.6/1.

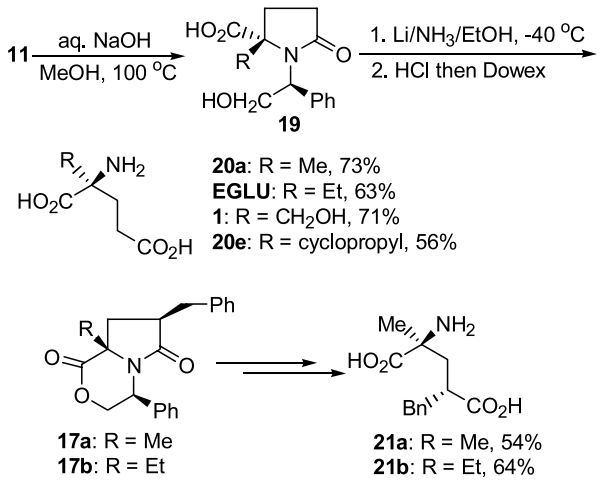
With these bicyclic products in hand, we next attempted to transform them to the corresponding α-substituted glutamic acids and α,γ-disubstituted glutamic acids. After some experiment, we found that the following reaction sequence was suitable for this conversion (Scheme 5): (1) treatment of



Scheme 3.



Scheme 4.



Scheme 5.

11 with NaOH to open the lactone ring; (2) reductive cleavage of the *N*-benzylic bond with lithium/liquid ammonia;[12] (3) hydrolysis with 6 M HCl followed by purification with Dowex eluting with 1% aqueous ammonia. It was notable that attempts to cleave the *N*-benzylic bond by Pd/C or $Pd(OH)_2$/C-catalyzed hydrogenolysis under various conditions failed, probably due to steric hindrance. Using this method the desired α-substituted glutamic acids including (*S*)-α-methyl glutamic acid **20a**, EGLU, (*S*)-α-hydroxymethyl glutamic acid **1**, as well as (*S*)-α-cyclopropyl glutamic acid **20e** were obtained in 56–73% overall yields. Similarly, starting from **17a** and **17b**, α,γ-disubstituted glutamic acids **21a** and **21b** were produced respectively.

3. Conclusions

In conclusion, based on the asymmetric Strecker reaction of γ-keto acids induced by (*S*)-phenylglycinol, we have developed a practical method for the synthesis of α-substituted and α,γ-disubstituted glutamic acids. This method has excellent functional group tolerance, diversified groups could be introduced at both α and γ positions. The preliminary biological evaluation of these glutamic acid analogues indicated that amino acid **20e**, a cyclopropane mimic of EGLU, showed no activity to *m*GluRs, which indicated again that subtle changes to glutamic acid would alter the activity to glutamate receptors. More detailed biological studies are underway and will be reported elsewhere.

4. Experimental

4.1. General procedure for preparation of 11 and 12 from 3

A mixture of anhydrous sodium salt of γ-keto acid (40 mmol) and (*S*)-phenylglycinol (44 mmol) in anhydrous toluene (50 mL) was stirred at room temperature for 1 h before brought to reflux. Water was removed by a Dean–Stark separator. After the distillate became clear, the rest of the toluene was removed by a rotavapor. To the residue was added anhydrous methanol (30 mL). At −25 °C trimethylsilyl cyanide (8.0 mL, 60 mmol) was added dropwise to this solution, and then it was allowed to warm to 0 °C, and stirred for 6 h at this temperature. After freshly prepared methanolic HCl (50 mL) was added at 0 °C, the resultant mixture was stirred overnight at room temperature. The solution was concentrated and then diluted with water and neutralized by the careful addition of saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organic phase was washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed to give crude amino esters.

The above esters were dissolved in anhydrous xylene (50 mL); a catalytic amount of TsOH was added to facilitate the reaction in case of necessity. The solution was transferred to a thick-walled glass reaction tube equipped with a threaded sealing valve and a side-arm. The tube was evacuated and purged with argon several times to remove air through the side-arm. The tube was evacuated again to partial vacuum before being sealed off. The tube was immersed into a silica oil bath, which was gradually brought to 200–210 °C. The xylene solution was stirred at this temperature for 1–2 days. After the reaction was complete,

xylene was rotary evaporated in vacuum. Flash chromatography of the residue afforded cyclization products.

4.1.1. (4*S*,8a*R*)-8a-Methyl-4-phenyltetrahydro-pyrrolo[2,1-*c*][1,4]oxazine-1,6-dione 11a. $[\alpha]_D^{20}=+11.7$ (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.29 (m, 3H), 7.10–7.07 (m, 2H), 5.04 (d, $J=3.9$ Hz, 1H), 4.91 (dd, $J=12.2$, 4.0 Hz, 1H), 4.40 (d, $J=12.2$ Hz, 1H), 2.68–2.55 (m, 2H), 2.47–2.37 (m, 1H), 2.33–2.28 (m, 1H), 1.67 (s, 3H); EI-MS *m/z* 245 (M^+), 230, 201, 187, 174, 159, 131, 104, 77, 51. HRMS Calcd for $C_{14}H_{15}NO_3$ (M^+) 245.1052, found 245.1030; FT-IR (KBr) 1759, 1697 cm^{-1}.

4.1.2. (4*S*,8a*S*)-8a-Methyl-4-phenyltetrahydro-pyrrolo[2,1-*c*][1,4]oxazine-1,6-dione 12a. $[\alpha]_D^{20}=+104.3$ (*c* 6.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.31 (m, 5H), 5.19 (dd, $J=10.2$, 6.5 Hz, 1H), 4.63 (dd, $J=12.4$, 6.4 Hz, 1H), 4.49 (dd, $J=12.4$, 10.2 Hz, 1H), 2.76–2.58 (m, 2H), 2.46–2.34 (m, 1H), 2.26–2.17 (m, 1H), 1.64 (s, 3H); EI-MS *m/z* 246 $(M+H)^+$, 232, 218, 201, 187, 158, 130, 104, 98, 43. HRMS Calcd for $C_{14}H_{15}NO_3$ (M^+) 245.1052, found 245.1023; FT-IR (KBr) 1745, 1698 cm^{-1}.

4.1.3. (4*S*,8a*S*)-8a-Ethyl-4-phenyltetrahydropyrrolo[2,1-*c*][1,4]oxazine-1,6-dione 11b. $[\alpha]_D^{20}=+22.7$ (*c* 19.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.31 (m, 5H), 5.17 (dd, $J=10.8$, 6.6 Hz, 1H), 4.62 (dd, $J=12.5$, 6.7 Hz, 1H), 4.50 (dd, $J=12.4$, 11.0 Hz, 1H), 2.71–2.52 (m, 2H), 2.44–2.26 (m, 2H), 2.05 (m, $J=7.1$ Hz, 1H), 1.94 (m, $J=7.1$ Hz, 1H), 1.05 (t, $J=7.4$ Hz, 3H); EI-MS *m/z* 259 (M^+), 229, 215, 201, 174, 158, 145. HRMS Calcd for $C_{15}H_{17}NO_3$ (M^+) 259.1209, found 259.1204; FT-IR (KBr) 1741, 1705, 1454 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_3$ C, 69.48, H, 6.61, N, 5.40; found C, 69.39, H, 6.63, N, 5.26.

4.1.4. (4*S*,8a*R*)-8a-Ethyl-4-phenyltetrahydropyrrolo[2,1-*c*][1,4]oxazine-1,6-dione 12b. $[\alpha]_D^{20}=+103.0$ (*c* 4.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.21 (m, 3H), 7.02–7.00 (m, 2H), 4.97 (d, $J=4.0$ Hz, 1H), 4.87 (dd, $J=12.1$, 4.0 Hz, 1H), 4.30 (d, $J=12.1$ Hz, 1H), 2.55–2.43 (m, 2H), 2.35 (m, 2H), 1.91 (m, 2H), 1.01 (t, $J=7.6$ Hz, 3H); EI-MS *m/z* 259 (M^+), 229, 215, 104, 42. HRMS Calcd for $C_{15}H_{17}NO_3$ (M^+) 259.1208, found 259.1232; FT-IR (KBr) 1755, 1695, 1452 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_3$ C, 69.48, H, 6.61, N, 5.40; found C, 69.38, H, 6.65, N, 5.40.

4.1.5. (4*S*,8a*R*)-8a-Phenyl-4-phenyltetrahydro-pyrrolo[2,1-*c*][1,4]oxazine-1,6-dione 11c. $[\alpha]_D^{20}=-5.5$ (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.15 (m, 10H), 5.10 (d, $J=3.7$ Hz, 1H), 4.32 (dd, $J=12.0$, 3.9 Hz, 1H), 4.10 (d, $J=12.0$ Hz, 1H), 2.95 (m, 1H), 2.51–2.36 (m, 3H); EI-MS *m/z* 308 $(M+H)^+$, 263, 221, 193, 104. HRMS Calcd for $C_{19}H_{17}NO_3$ (M^+) 307.1208, found 307.1220; FT-IR (KBr) 3062, 1758, 1708 cm^{-1}.

4.1.6. (4*S*,8a*S*)-8a-Phenyl-4-phenyltetrahydro-pyrrolo[2,1-*c*][1,4]oxazine-1,6-dione 12c. $[\alpha]_D^{20}=-25.6$ (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.20 (m, 10H), 5.25 (dd, $J=12.5$, 6.0 Hz, 1H), 4.35 (dd, $J=12.1$, 6.0 Hz, 1H), 4.25 (d, $J=12.4$ Hz, 1H), 3.25 (m, 1H), 2.60 (m, 1H), 2.45–2.20 (m, 2H); EI-MS *m/z* 307 (M^+), 263, 249, 221, 193, 104. HRMS Calcd for $C_{19}H_{17}NO_3$ (M^+) 307.1208, found 307.1201; FT-IR (KBr) 3031, 1745, 1707 cm^{-1}.

4.1.7. (4*S*,8a*R*)-8a-Benzyloxymethyl-4-phenyl-tetrahydropyrrolo[2,1-*c*][1,4]oxazine-1,6-dione 11d. $[\alpha]_D^{20}=+70.9$ (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.28 (m, 8H), 7.25–7.20 (m, 2H), 5.13 (dd, $J=10.4$, 6.6 Hz, 1H), 4.72 (dd, $J=11.9$, 10.4 Hz, 1H), 4.51 (dd, $J=12.0$, 6.6 Hz, 1H), 4.52 and 4.46 (AB q, $J=11.7$ Hz, 2H), 3.75 and 3.68 (AB q, $J=9.6$ Hz, 2H), 2.70–2.45 (m, 2H), 2.39–2.27 (m, 2H); EI-MS *m/z* 352 $(M+H)^+$, 230, 91, 77 55; FT-IR (KBr) 3064, 1755, 1705 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO_4$ C, 71.78, H, 6.02, N, 3.99; found C, 71.84, H, 6.04, N, 4.06.

4.1.8. (4*S*,8a*S*)-8a-Benzyloxymethyl-4-phenyl-tetrahydropyrrolo[2,1-*c*][1,4]oxazine-1,6-dione 12d. $[\alpha]_D^{20}=+116.0$ (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.23 (m, 8H), 7.07–7.04 (m, 2H), 5.09 (dd, $J=11.7$, 4.2 Hz, 1H), 4.94 (d, $J=4.1$ Hz, 1H), 4.56 (s, 2H), 4.21 (d, $J=11.6$ Hz, 1H), 3.76 and 3.72 (AB q, $J=9.7$ Hz, 2H), 2.61–2.28 (m, 4H); EI-MS *m/z* 352 $(M+H)^+$, 260, 230, 184, 82, 55; FT-IR (KBr) 3032, 1759, 1706 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO_4$ C, 71.78, H, 6.02, N, 3.99; found C, 71.41, H, 5.86, N, 3.89.

4.1.9. (4*S*,8a*S*)-8a-Cyclopropyl-4-phenyl-tetrahydropyrrolo[2,1-*c*][1,4]oxazine-1,6-dione 11e. $[\alpha]_D^{20}=-8.1$ (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.35 (m, 3H), 7.34–7.31 (m, 2H), 5.10 (dd, $J=11.7$, 7.0 Hz, 1H), 4.76 (t, $J=12.0$ Hz, 1H), 4.56 (dd, $J=12.2$, 6.9 Hz, 1H), 2.69–2.59 (m, 2H), 2.36–2.30 (m, 2H), 1.44 (dt, $J=8.4$, 2.8 Hz, 1H), 0.81 (m, 2H), 0.67 (t, $J=5.0$ Hz, 1H), 0.50 (t, $J=5.0$ Hz, 1H); EI-MS *m/z* 272 $(M+H)^+$, 227, 213, 156, 104, 91, 77. HRMS Calcd for $C_{16}H_{17}NO$ (M^+-CO_2) 227.13101, found 227.13101.

4.1.10. 5-Hydroxy-4-oxopentanoic acid methyl ester 14. To a stirred solution of methyl 5-bromo-4-oxo-pentanate **13** (1.99 g, 11.4 mmol) in 85% ethanol (20 mL) was added sodium formate dihydrate (1.25 g, 12.0 mmol). The resulting mixture was refluxed overnight, and then concentrated in vacuum and diluted with water. To this solution was added 0.1 M HCl to adjust the pH to 6. EtOAc-extractive work-up followed by chromatography eluting with *n*-hexane/EtOAc (3:2) gave 1.59 g (95%) of **25** as colorless liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 4.29 (d, $J=4.5$ Hz, 2H), 3.65 (s, 3H), 3.05 (t, $J=4.5$ Hz, 1H, OH), 2.67 (s, 4H); EI-MS *m/z* 147 $(M+H)^+$, 129, 115, 59, 55; IR (neat) 3448, 1728, 1440 cm^{-1}. Anal. Calcd for $C_6H_{10}O_4$ C, 49.31, H, 6.90; found C, 48.98, H, 6.90.

4.1.11. 5-Benzyloxy-4-oxo-pentanoic 3d. To a solution of *O*-benzyl 2,2,2-trichloroacetimidate (3.79 g, 15.0 mmol) and **14** (1.46 g, 10.0 mmol) in cyclohexane/dichloromethane (2:1) (60 mL) was added CF_3SO_2H (50 μL) at 0 °C. The resulting mixture was stirred overnight at room temperature before saturated $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. Flash chromatography eluting with 10:1 *n*-hexane/EtOAc afforded 2.17 g (92%) of benzyl ether as a colorless liquid.

A solution of the above compound (6.1 g, 25.8 mmol) and KOH (1.94 g, 28.4 mmol) in MeOH/H_2O (4:1) (25 mL) was stirred at room temperature until the starting material disappeared as monitored by TLC. After the solution was acidified with HCl, EtOAc-extractive work-up followed by flash chromatography eluting with 1:1 hexane/EtOAc gave 5.34 g (93%) of **3d** as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 4.60 (s, 2H), 4.11 (s, 2H), 2.80 (t, J=6.6 Hz, 2H), 2.67 (t, J=6.6 Hz, 2H); EI-MS m/z 223 $(M+H)^+$, 116, 101, 91, 65, 55, 45; IR (neat) 3500–3000 (br), 1725, 1449 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_4$ C, 64.85, H, 6.35; found C, 64.58, H, 6.28.

4.1.12. 4-Oxohex-5-enoic acid methyl ester 16. To a solution of **15** (5.6 g, 31.3 mmol) in $CHCl_3$ (50 mL) was added NEt_3 (4.7 g, 44.2 mmol). The mixture was heated at 50 °C for 6 h. The precipitate was removed by filtration; the filtrate was washed with dilute HCl and brine, dried and concentrated. Flash chromatography eluting with 5:1 *n*-hexane/EtOAc gave 4.14 g (93%) of **16** as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (AB q, dd, J=16.4, 10.2 Hz, 1H), 6.27 (AB q, dd, J=16.4, 1.4 Hz, 1H), 5.87 (dd, J=10.2, 1.4 Hz, 1H), 3.67 (s, 3H), 2.93 (t, J=6.6 Hz, 2H), 2.64 (t, J=6.6 Hz, 2H); EI-MS m/z 143 $(M+H)^+$, 115, 111, 101, 87, 83, 55, 45; IR (neat) 1740, 1703, 1685 cm^{-1}.

4.1.13. 4-Cyclopropyl-4-oxobutyric acid 3e. Excess CH_2N_2/Et_2O was introduced into a stirring solution containing **16** (2.5 g, 17.6 mmol in 20 mL of ether) and $Pd(OAc)_2$ (20 mg) at 0 °C. After 30 min at this temperature, AcOH was added dropwise to decompose the excess diazomethane. The mixture was passed through a short silica gel column and rinsed with ether. The organic phase was dried and concentrated. The residue was hydrolyzed with aqueous KOH (1.33 g, 33.3 mmol in 20 mL of MeOH/H_2O) at room temperature for 3 h. The solution was neutralized with aqueous KH_2PO_4 and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was chromatographed eluting with 3:2 *n*-hexane/EtOAc to afford 1.65 g (66%) of **3e** as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (t, J=6.6 Hz, 2H), 2.64 (t, J=6.6 Hz, 2H), 1.96 (m, 1H), 1.04 (m, 2H), 0.90 (m, 2H); EI-MS m/z 142 (M^+), 125, 97, 69, 45. HRMS Calcd for $C_7H_{10}O_3$ (M^+) 142.0630, found 142.0645; IR (neat) 3500–3000 (br), 1740, 1693 cm^{-1}.

4.2. General procedure for alkylation of 11

To a solution of **11** (1.96 mmol) in anhydrous HMPA (5 mL) and THF (20 mL) was added lithium bis(trimethylsilyl)amide (1.54 mL, 2.16 mmol, 1.4 M in THF) at −78 °C. After 30 min at this temperature, benzyl bromide (0.28 mL, 2.35 mmol) was added and then the solution was stirred at −78 °C for 3 h. The reaction was quenched by adding saturated NH_4Cl and the resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography of the residue afforded the alkylation products.

4.2.1. (4*S*,7*R*,8a*S*)-7-Benzyl-8a-methyl-4-phenyl-tetrahydropyrrolo[2,1-*c*][1,4]oxazine-1,6-dione 17a. $[\alpha]_D^{20}$=+112.5 (c 0.82, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.28 (m, 6H), 7.22–7.11 (m, 4H), 5.03 (dd, J=10.6, 6.8 Hz, 1H), 4.67 (dd, J=12.7, 10.6 Hz, 1H), 4.48 (dd, J=12.6, 6.9 Hz, 1H), 3.21 (dd, J=14.2, 3.8 Hz, 1H), 2.96 (m, 1H), 2.52 (dd, J=14.1, 10.1 Hz, 1H), 2.37 (dd, J=13.7, 9.8 Hz, 1H), 2.13 (dd, J=13.6, 4.5 Hz, 1H), 1.58 (s, 3H); EI-MS m/z 336 $(M+H)^+$, 335 (M^+), 244, 171, 104, 91; FT-IR (KBr) 3317, 1723, 1457 cm^{-1}.

4.2.2. (4*S*,7*S*,8a*S*)-7-Benzyl-8a-methyl-4-phenyl-tetrahydropyrrolo[2,1-*c*][1,4]oxazine-1,6-dione 18a. $[\alpha]_D^{20}$=+210.5 (c 0.46, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.30 (m, 5H), 7.25–7.20 (m, 3H), 7.09–7.07 (m, 2H), 5.03 (d, J=3.9 Hz, 1H), 4.93 (dd, J=12.1, 4.1 Hz, 1H), 4.42 (d, J=12.2 Hz, 1H), 3.18 (d, J=9.4 Hz, 1H), 2.88–2.81 (m, 3H), 2.06 (d, J=12.0 Hz, 1H), 1.51 (s, 3H); EI-MS m/z 335 (M^+), 216, 171, 104, 91, 42. HRMS Calcd for $C_{21}H_{21}NO_3$ (M^+) 335.1521, found 335.1546; FT-IR (KBr) 1755, 1697 cm^{-1}.

4.2.3. (4*S*,7*R*,8a*S*)-7-Benzyl-8a-ethyl-4-phenyl-tetrahydropyrrolo[2,1-*c*][1,4]oxazine-1,6-dione 17b. $[\alpha]_D^{20}$=−25.8 (c 5.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38–7.32 (m, 7H), 7.29–7.18 (m, 3H), 5.26 (dd, J=11.4, 7.8 Hz, 1H), 4.70 (dd, J=12.0, 7.8 Hz, 1H), 4.43 (t, J=12.0 Hz, 1H), 3.08 (dd, J=13.8, 4.2 Hz, 1H), 3.00 (dd, J=13.2, 7.8 Hz, 1H), 2.98 (dd, J=14.4, 11.4 Hz, 1H), 2.87 (m, 1H), 1.90 (dq, J=14.4, 7.2 Hz, 1H), 1.83 (dd, J=13.5, 7.5 Hz, 1H), 1.31 (dq, J=14.4, 7.2 Hz, 1H), 0.83 (t, J=7.2 Hz, 3H); EI-MS m/z 349 (M^+), 305, 291, 214, 104, 91, 78. HRMS Calcd for $C_{22}H_{23}NO_3$ (M^+) 349.1678, found 349.1703; FT-IR (KBr) 1749, 1702 cm^{-1}.

4.2.4. (4*S*,7*S*,8a*S*)-7-Benzyl-8a-ethyl-4-phenyl-tetrahydropyrrolo[2,1-*c*][1,4]oxazine-1,6-dione 18b. $[\alpha]_D^{20}$=+57.4 (c 8.8, $CHCl_3$); ^{1}H NMR (600MHz, $CDCl_3$) δ 7.42–7.31 (m, 7H), 7.27–7.19 (m, 3H), 5.13 (dd, J=10.8, 6.6 Hz, 1H), 4.55 and 4.47 (AB, J=12.4 Hz, the former d with J=6.6 Hz, the later d with J=10.8 Hz, 2H), 3.28 (dd, J=13.8, 3.9 Hz, 1H), 2.91 (dq, J=10.1, 3.9 Hz, 1H), 2.52 (dd, J=13.8, 10.1 Hz, 1H), 2.37 and 2.29 (AB, J=13.6 Hz, the former d with J=8.6 Hz, the later d with J=11.0 Hz, 2H), 2.02 (dq, J=14.4, 7.2 Hz, 1H), 1.91 (dq, J=14.4, 7.2 Hz, 1H), 1.01 (t, J=7.2 Hz, 3H); EI-MS m/z 349 (M^+), 320, 305, 201, 172, 117, 104, 91, 47. HRMS Calcd for $C_{22}H_{23}NO_3$ (M^+) 349.1678, found 349.1698; FT-IR (KBr) 1756, 1705, 1455 cm^{-1}.

4.3. General procedure for transformation of bicyclic compounds into amino acids

To a solution of **11** (5.0 mmol) in methanol (20 mL) was added 1 M KOH (2 mL). The resulting solution was brought to reflux for 2 h. After concentration, the residue was dissolved in water (20 mL), and 6 M HCl (4 mL) was added to acidify the solution. The mixture was extracted with EtOAc, dried with Na_2SO_4 and concentrated. The residue was used directly for next step.

A solution of the above acid (0.21 mmol) in anhydrous THF (5 mL) and absolute ethanol (0.5 mL) was added to an oven dried three-neck round bottom flask charged with argon. The flask was cooled to −40 °C by an CH_3CN/dry ice bath,

liquid NH_3 (approximately 40 mL) was collected into the flask with dry ice cold trap. Fresh polished lithium flakes were added into the reactants at −40 °C until the deep blue color was kept for 5 min. The reaction was quenched by the addition of NH_4Cl powder (1 g), and the reaction was left in the hood until almost all the NH_3 evaporated. The reaction was worked-up with EtOAc and distilled water, the aqueous phase was washed with EtOAc, and partially concentrated under reduced pressure. After 6 M HCl (5 mL) was added, the solution was refluxed overnight and concentrated. Purification of the residue by a Dowex-50WX8 resin column eluting with water to remove the salts and then with a gradient of 0.5%, 1.0% NH_4OH afforded the amino acid as an ammonium salt.

4.3.1. (*S*)-2-Methylglutamic acid 20a. $[\alpha]_D^{20}=+11.7$ (*c* 0.43, MeOH) (lit. $[\alpha]^{21}{}_D=+12.1$ (*c* 4, 6 M HCl)); ^1H NMR (300 MHz, D_2O) δ 2.37 (m, 2H), 2.10 (m, 2H), 1.52 (s, 3H).

4.3.2. (*S*)-2-Ethylglutamic acid (EGLU). $[\alpha]_D^{20}=+47.3$ (*c* 6.9, H_2O); ^1H NMR (300 MHz, D_2O) δ 2.35 (m, 2H), 2.09 (t, $J=7.6$ Hz, 2H), 1.96 and 1.88 (AB, m, 2H), 0.98 (t, $J=7.5$ Hz, 3H); ESI-MS *m*/*z* 259 $(M+2Na)^+$.

4.3.3. (*S*)-2-Hydroxymethylglutamic acid 1. $[\alpha]_D^{20}=+18.5$ (*c* 1.88, MeOH); ^1H NMR (300 MHz, D_2O) δ 3.89 and 3.67 (AB, $J=12.0$ Hz, 2H), 2.36–2.18 (m, 2H), 1.95 (t, $J=7.9$ Hz, 2H); ESI-MS *m*/*z* 200.2 $(M+Na)^+$.

4.3.4. (*S*)-2-Cyclopropylglutamic acid 20e. $[\alpha]_D^{20}=+25.1$ (*c* 8.9, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 2.26 (m, 2H), 2.05 and 1.95 (AB, m, 2H), 1.17 (m, 1H), 0.88 (t, $J=7.4$ Hz, 1H), 0.59 (m, 2H), 0.43 (m, 1H); ESI-MS *m*/*z* 232.2 $(M+2Na-H)^+$.

4.3.5. (2*S*,4*R*)-2-Methyl-4-benzylglutamic acid 21a. $[\alpha]_D^{20}=-113.3$ (*c* 1.1, MeOH); ^1H NMR (300 MHz, D_2O) δ 7.33–7.25 (m, 2H), 7.23–7.20 (m, 3H), 2.84–2.67 (m, 2H), 2.53 (m, 1H), 1.96 (dd, $J=14.8$, 9.1 Hz, 1H), 1.84 (dd, $J=14.9$, 3.2 Hz, 1H), 1.31 (s, 3H); ESI-MS *m*/*z* 292 $(M+Na)^+$.

4.3.6. (2*S*,4*R*)-2-Ethyl-4-benzylglutamic acid 21b. $[\alpha]_D^{20}=-92.3$ (*c* 6.2, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.47–7.15 (m, 5H), 3.04 (dd, $J=14.6$, 7.3 Hz, 1H), 2.85 (m, 1H), 2.72 (m, 1H), 2.21–1.94 (m, 2H), 1.73–1.55 (m, 2H), 0.77 (t, $J=6.9$ Hz, 3H).

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Racemic [1*SR*,2*RS*,(*RS*)]-*N*-cyano(phenyl)methyl-1-aminoindan-2-ol: crystal structure and reactivity towards thermal epimerization in the solid state

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Abstract—A diastereomeric mixture of racemic α-amino nitriles [1*SR*,2*RS*,(*SR*)]- (**1**) and [1*SR*,2*RS*,(*RS*)]-*N*-cyano(phenyl)methyl-1-aminoindan-2-ol (**2**) was thermally epimerized in the solid state to give diastereopure [1*SR*,2*RS*,(*SR*)]-**1**. The reaction was about 26 times slower than the same reaction of a mixture of their enantiopure counterparts, showing that different mechanisms operated between the two transformations. X-ray crystallographic analysis revealed that in the former transformation, racemic-compound crystals of **2** were converted into conglomerate crystals of **1**, while in the latter, enantiomeric crystals of **2** were converted into enantiomeric crystals of **1**. The difference in the reactivity toward the epimerization between the racemic and the enantiopure mixture could be rationalized by the difference in the stability of compound **2** in the two crystal forms.

1. Introduction

In organic crystals, molecules are arranged with good order with defined conformation(s). This steric environment has attracted much interest in asymmetric reactions in crystals. Studies on the asymmetric induction in inclusion crystals by using chiral hosts,[1] as well as the absolute asymmetric synthesis in crystals of achiral molecules which adopt a chiral conformation or arrangement,[2] have developed rapidly and made remarkable achievements. In most of these reactions, chirality of conformation or arrangement of achiral substrates is converted into centrochirality of products. Another type of reaction, which should be feasible in a crystal lattice but has had only limited success to date, is enantiomeric or diastereomeric enrichment, that is, deracemization or epimerization to a single stereoisomer. Wilson and Pincock reported that metastable racemic-compound crystals of 1,1′-binaphthalene were transformed into a nonracemic mixture of stable enantiomeric crystals (conglomerates) in an appropriate temperature range.[3] Solid-state epimerization of atropodiastereomeric teraryls has also been reported.[4] A single crystal of a racemic or diastereomeric (1-cyanoethyl)cobaloxime complex, where a racemic or diastereomeric pair of complexes were in a unit cell but occupied crystallographically distinct positions from each other, was reported to show enantiomeric or diastereomeric enrichment on exposure to X-rays or UV light.[5] Recently, we have reported that a diastereomeric mixture of α-amino nitriles [1*S*,2*R*,(*S*)]-**1** and [1*S*,2*R*,(*R*)]-**2**, which had been prepared by the Strecker reaction of benzaldehyde, (1*S*,2*R*)-1-aminoindan-2-ol[6,7] and cyanotrimethylsilane (TMSCN), thermally epimerized to give the single diastereomer **1** in the solid state.[8] X-ray crystallographic analyses revealed that the two diastereomers crystallized out separately from a solution of the mixture and that the stabilities of the two kinds of crystals were significantly different from each other due to the difference in the hydrogen bonding, leading to the enrichment of more stable one. We have encountered, however, a phenomenon difficult to explain in terms of the

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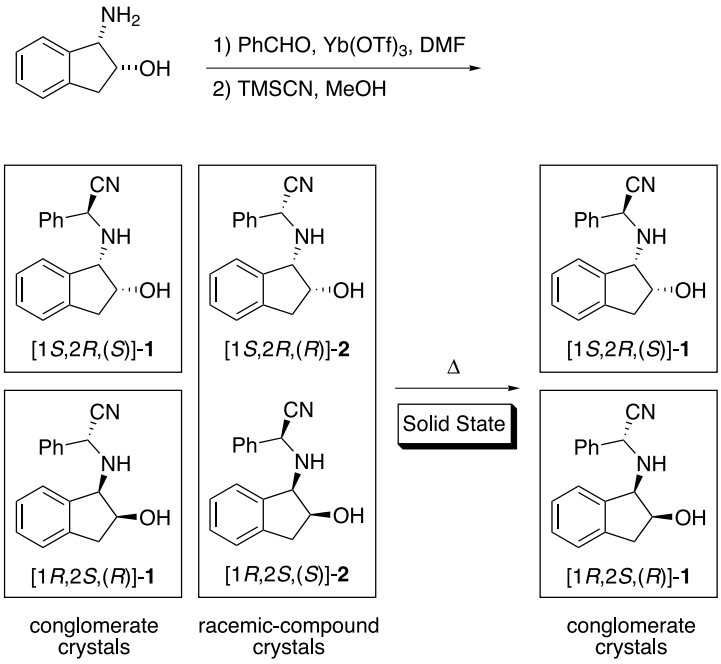

Scheme 1.

relative stability between the two crystals. Thus, a mixture of racemic [1*SR*,2*RS*,(*SR*)]-**1** and [1*SR*,2*RS*,(*RS*)]-**2** epimerized substantially slower than a mixture of the enantiopure [1*S*,2*R*,(*S*)]-**1** and [1*S*,2*R*,(*R*)]-**2**. Herein, we report the whole picture of this phenomenon and discuss the difference in the reactivity.

2. Results and discussion

2.1. Synthesis of a diastereomeric mixture of racemic α-amino nitriles [1*SR*,2*RS*,(*SR*)]-1 and [1*SR*,2*RS*,(*RS*)]-2 and its thermal epimerization in the solid state

The diastereoselective Strecker reaction was performed by treatment of benzaldehyde with an excess of racemic *cis*-1-aminoindan-2-ol in DMF at room temperature in the presence of $Yb(OTf)_3$,[9] followed by cyanation of the resulting imine with TMSCN with induction of desilylation of the *O*-silylated intermediate by simultaneous addition of methanol (Scheme 1). The reaction gave a mixture of racemic [1*SR*,2*RS*,(*SR*)]-**1** and [1*SR*,2*RS*,(*RS*)]-**2** in quantitative yield with a diastereomeric ratio (dr) of 68.5:31.5 (37% de) after chromatographic purification. The dr dropped to 61.5:38.5 (23% de) in a repeated experiment, the reason for which was suspected to be incidental epimerization.

In the previous paper,[8] we reported that a crystalline mixture of enantiopure [1*S*,2*R*,(*S*)]-**1** and [1*S*,2*R*,(*R*)]-**2** with a dr of 83:17 (66% de) completely epimerized to [1*S*,2*R*,(*S*)]-**1** at 65 °C within 24 h. The reaction followed first-order kinetics and the apparent rate constant k_{epi} under the conditions was estimated to be $9.77\times10^{-5}\ s^{-1}$. By comparison, epimerization of a mixture of racemic **1** and **2** has been found to be sluggish under the same conditions ($k_{epi}=3.69\times10^{-6}\ s^{-1}$) and require a higher temperature (85 °C) to achieve a comparable k_{epi} ($1.01\times10^{-4}\ s^{-1}$) to that of the enantiopure mixture obtained at 65 °C (Fig. 1).

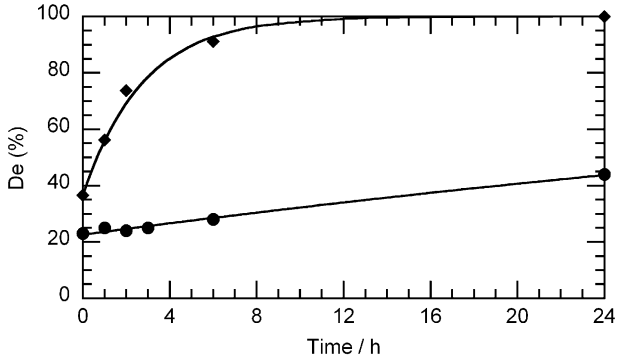

Figure 1. De % change of a crystalline mixture of racemic compounds **1** and **2** at 65 °C (●) and 85 °C (◆).

2.2. X-ray crystallographic analysis of racemic α-amino nitrile [1*SR*,2*RS*,(*RS*)]-2 and consideration of the reactivity towards thermal epimerization

In order to clarify the origin of the difference in the reactivity towards epimerization between the racemic and the enantiopure mixture, X-ray crystallographic analysis was carried out. A mixture of racemic **1** and **2** was dissolved in acetone and kept at −20 °C to give a crystalline mixture, in which a racemic-compound crystal consisting of [1*S*,2*R*,(*R*)]- and [1*R*,2*S*,(*S*)]-**2** could be found by X-ray analysis (Fig. 2). The experimental X-ray powder diffraction pattern of the crystalline mixture of racemic **1** and **2** [Fig. 3(a)] was nicely simulated from the calculated diffraction pattern of this crystal (b), combined with that of an enantiomeric crystal of [1*S*,2*R*,(*S*)]-**1** (c),[8] indicating that the crystalline mixture consisted of three kinds of crystals, that is, enantiomeric crystals of [1*S*,2*R*,(*S*)]- and [1*R*,2*S*,(*R*)]-**1**, which should show the same diffraction

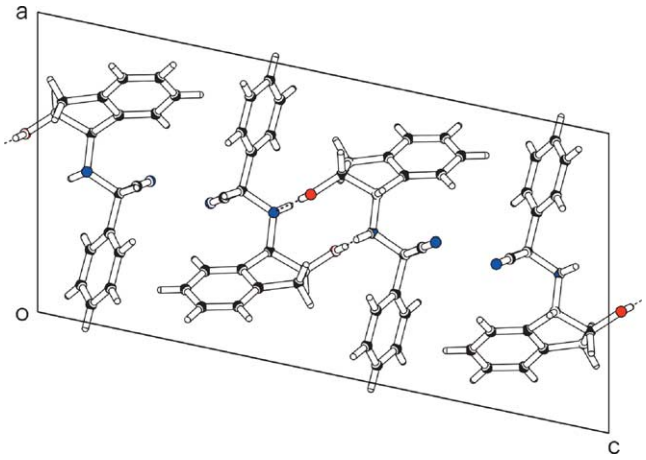

Figure 2. Crystal structure of the racemic-compound crystal of **2**. Dotted lines indicates hydrogen bonds.

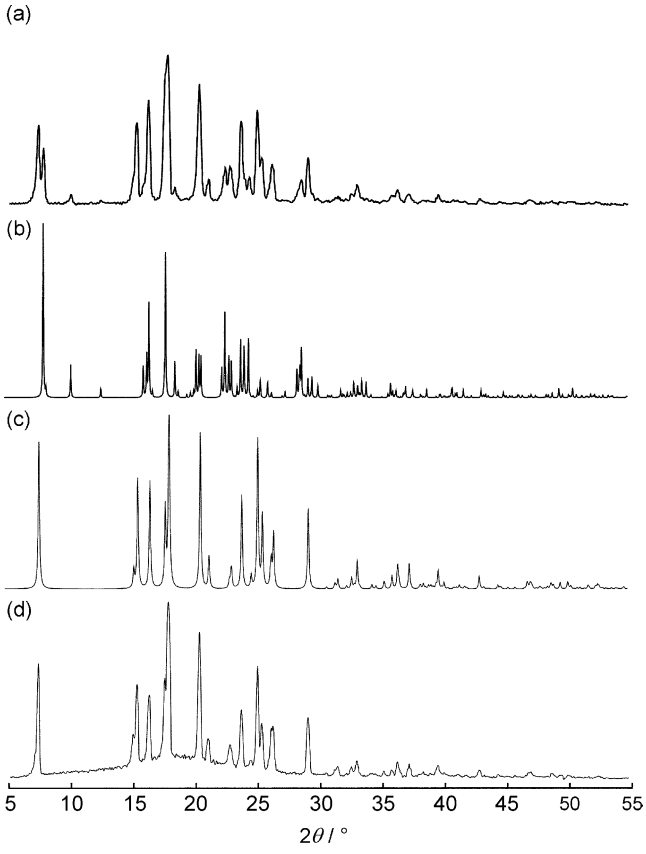

Figure 3. Experimental X-ray powder diffraction pattern of a crystalline mixture of racemic compounds **1** and **2** (a) and that of the same sample measured after heating (d). X-ray powder diffraction patterns of the racemic-compound crystal of **2** (b) and the enantiomeric crystal of [1*S*,2*R*,(*S*)]-**1**[8] (c) simulated from each single-crystal X-ray data by using PLATON.[13]

pattern (c), and the racemic-compound crystal of **2** (Scheme 1); if the mixture included any other kinds of crystals, the corresponding signals should appear on the spectrum. The crystalline mixture, after heating, showed practically the same diffraction pattern (d) as that of the enantiomeric crystal of **1** (c). These observations unambiguously indicate that thermally stable [1*S*,2*R*,(*S*)]- and [1*R*,2*S*,(*R*)]-**1**, during the crystallization, underwent spontaneous resolution to give conglomerate crystals, whereas thermally unstable [1*S*,2*R*,(*R*)]- and [1*R*,2*S*,(*S*)]-**2** formed racemic-compound crystals, and that the racemic-compound crystals of **2** were converted into the conglomerate crystals of **1** by heating. On the other hand, as reported previously,[8] the enantiopure mixture of compounds **1** and **2** consists of enantiomeric crystals of [1*S*,2*R*,(*S*)]-**1** and [1*S*,2*R*,(*R*)]-**2** and the latter crystals are thermally converted into the former. Therefore, it is concluded that the difference in the tendency towards epimerization between the racemic and the enantiopure mixture originated from the nature of racemate **2** to prefer to form racemic-compound crystals rather than conglomerates.

Before discussing the reactivity of the racemic-compound crystal of **2**, we would like to describe briefly our previous consideration of the epimerization mechanism of the enantiopure compound **2** to **1**:[8] The reaction could be rationalized by the relative stability between the two compounds in the corresponding crystals, which originated from the difference in the form of hydrogen bonding. Thus, the enantiomeric crystal of compound **1** had an intramolecular O–H···N bond [Fig. 4(a)], whereas an N–H···O bond existed in the enantiomeric crystal of compound **2** (b). In addition, a 2_1 helical structure was created along the

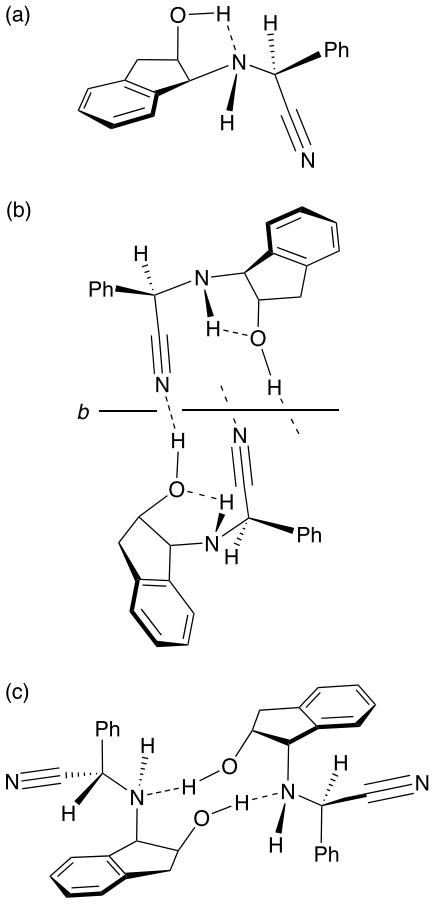

Figure 4. Schematic views of compounds [1*S*,2*R*,(*S*)]-**1** (a) and [1*S*,2*R*,(*R*)]-**2** (b) in each enantiomeric crystal and compound [1*SR*,2*RS*,(*RS*)]-**2** in the racemic compound crystal (c).

b-axis by intermolecular CN···HO bonds in the crystal of **2** (b), while no intermolecular hydrogen bond could be found in the crystal of **1**. It is conceivable that the reaction proceeds by repeated dissociation and recombination of the cyanide anion or hydrogen cyanide from the amino nitrile.[10] The intramolecular hydrogen bond in the crystal of **2** increases the electron density on the amino nitrogen, which mediates dissociation of the cyanide anion with the assistance of the intermolecular hydrogen bond, while the intramolecular hydrogen bond in the crystal of **1** forms an ammonium salt, the positive charge of which retards the dissociation of the cyanide anion. Consequently, compound **2** will selectively epimerize to compound **1** via an iminium or imine intermediate.

In the racemic-compound crystal of **2** [Fig. 4(c)], a pair of the enantiomers are related to each other by an inversion center and bonded together with two intermolecular O–H···N bonds (2.176 Å), which inhibit the dissociation of the cyanide anion. No intramolecular hydrogen bond could be found in the crystal. Therefore, it is concluded that compound **2** is more stable in the racemic-compound crystal (c) than the enantiomeric crystal (b), lowering the reactivity toward the epimerization. The stability of compound **2** in the racemic-compound crystal (c) is expected to be close to that of compound **1** in the enantiomeric crystal (a), considering the fact that both have only the intermolecular or intramolecular O–H···N bond, although the intermolecular hydrogen bond will be somewhat more labile. It is noteworthy that the difference in the stability between the two diastereomers in the corresponding crystals is nevertheless sufficient to complete the epimerization. This showed a sharp contrast to the previous observation that diastereopure compound **2** epimerized in DMSO at room temperature to give a 1:1 mixture of the two diastereomers.[8]

3. Conclusion

We have shown here that racemic α-amino nitrile **2** epimerizes more slowly than the enantiopure counterpart, the origin of which was ascribed to the difference in the stability of compound **2** in the racemic-compound and the enantiomeric crystal. Studies on the precise reaction mechanisms, as well as the scope and limitation of the reaction, are in progress.

4. Experimental

4.1. General

Melting points were taken using a Yanaco MP apparatus. Microanalysis was carried out in the Microanalytical Laboratory of the Institute of Multidisciplinary Research for Advanced Materials, Tohoku University. IR spectra were recorded on a JASCO IR-700 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECP 400 spectrometer using tetramethylsilane (^{1}H NMR) or chloroform (^{13}C NMR) as an internal standard and $CDCl_3$ as a solvent. DSC was carried out using a Seiko DSC-6100 calorimeter. Powder diffraction data were measured on a Rigaku RADIIC using graphite-monochromated Cu Kα radiation ($\lambda=1.5418$ Å, 40 kV, 20 mA) at room temperature (Scan speed: 5.0° min^{-1}; Sampling width: 0.020°). Silica gel columns were prepared by use of Fuji Silysia PSQ 60B (>30 μm).

4.2. Preparation of a mixture of [1*SR*,2*RS*,(*SR*)]- (1) and [1*SR*,2*RS*,(*RS*)]-*N*-cyano(phenyl)methyl-1-aminoindan-2-ol (2)

To a solution of racemic *cis*-1-aminoindan-2-ol (298 mg, 2.00 mmol) in dry DMF (2.0 mL) were added benzaldehyde (106 mg, 1.00 mmol) and $Yb(OTf)_3$ (124 mg, 200 μmol) and the mixture was stirred at room temperature for 2 h. To the mixture were added TMSCN (208 mg, 2.10 mmol) and absolute methanol (481 mg, 15.0 mmol) and the resulting mixture was stirred for 3 h. The mixture was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$ and then evaporated. The residue was chromatographed on silica gel with benzene–acetone (99:1 to 9:1) as the eluent to give a mixture of **1** and **2** (263 mg, 100%) as a crystalline solid; IR (KBr) 2232, 3314, 3444 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25, 2.43 (1H: br, major diastereomer; br, minor diastereomer), 2.64, 3.00 (1H: d, $J=4.4$ Hz, minor diastereomer; d, $J=5.2$ Hz, major diastereomer), 2.95–3.04 (1H, m), 3.05, 3.13 (1H: dd, $J=16.4$, 5.2 Hz, minor diastereomer; dd, $J=16.4$, 5.2 Hz, major diastereomer), 4.31, 4.46 (1H: t, $J=5.2$ Hz, minor diastereomer; t, $J=5.2$ Hz, major diastereomer), 4.40–4.44, 4.64 (1H: m, minor diastereomer; qd, $J=5.2$, 2.4 Hz, major diastereomer), 5.00, 5.04 (1H: d, $J=9.2$ Hz, major diastereomer; d, $J=7.6$ Hz, minor diastereomer), 7.24–7.31 (3H, m), 7.33–7.37 (1H, m), 7.41–7.48 (3H, m), 7.59–7.63 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.3, 39.9, 53.2, 53.4, 63.8, 63.9, 71.3, 72.2, 119.5, 119.8, 124.2, 124.5, 125.5, 125.5, 126.9, 127.0, 127.4, 127.4, 128.4, 128.5, 129.1, 129.2, 129.3, 129.3, 134.3, 134.7, 140.4, 140.4, 140.9, 141.3. The ^{1}H NMR analysis of the sample differentiated well the C_2–H signal of the major diastereomer [1*SR*,2*RS*,(*SR*)]-**1** (4.64 ppm) and the C_1–H signal of the minor diastereomer [1*SR*,2*RS*,(*RS*)]-**2** (4.31 ppm), which determined the diastereomeric ratio to be 68.5:31.5 (37% de).

4.3. Typical procedure for the epimerization of a mixture of racemic α-amino nitriles [1*SR*,2*RS*,(*SR*)]-1 and [1*SR*,2*RS*,(*RS*)]-2 in the solid state

A 68.5: 31.5 mixture of racemic **1** and **2** (100 mg, 378 μmol) was placed in a capped vial and heated at 85 °C in an oil bath for 24 h to give diastereomerically pure **1** (100 mg, 100%) as crystals. The product was spectrometrically pure enough without purification, mp 114.5–116.0 °C; IR (KBr) 2350, 3310, 3440 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (1H, dd, $J=9.2$, 5.2 Hz), 2.97 (1H, d, $J=5.2$ Hz), 3.00 (1H, dd, $J=16.4$, 2.4 Hz), 3.13 (1H, dd, $J=16.4$, 5.2 Hz), 4.46 (1H, t, $J=5.2$ Hz), 4.65 (1H, qd, $J=5.2$, 2.4 Hz), 5.00 (1H, d, $J=9.2$ Hz), 7.24–7.28 (3H, m), 7.34–7.36 (1H, m), 7.41–7.47 (3H, m), 7.60–7.62 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.0, 53.5, 63.9, 71.4, 119.5, 124.3, 125.5, 127.1, 127.4, 128.5, 129.2, 129.3, 134.5, 140.5, 141.0. Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.21; H, 6.27; N, 10.55.

4.4. Single-crystal X-ray structural analysis of a racemic-compound crystal of [1*SR*,2*RS*,(*RS*)]-2

A crystal of compound **2** suitable for a single-crystal X-ray diffraction experiment was obtained from an acetone solution at −20 °C in order to minimize thermal epimerization. X-ray diffraction data for the crystal were collected on a Rigaku AFC-6*R* four-circle diffractometer using graphite-monochromated Cu Kα radiation ($\lambda=1.5418$ Å, 50 kV, 80 mA) at room temperature. The structure was solved by the direct method SIR92[11] and refined by least-square calculations using SHELXL97.[12] Selected crystal structure data are as follows: monoclinic, space group $P2_1/c$, $Z=4$, $a=11.261(2)$ Å, $b=5.595(3)$ Å, $c=21.903(2)$ Å, $\beta=102.034(11)^\circ$, 189 variables for 1619 [$I>2\sigma(I)$] reflections, final $R=0.0519$. The details of the crystal data have been deposited with Cambridge Crystallographic Data Center as supplementary publication no. CCDC 246507.

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A highly enantioselective Strecker reaction catalyzed by titanium-*N*-salicyl-β-aminoalcohol complexes

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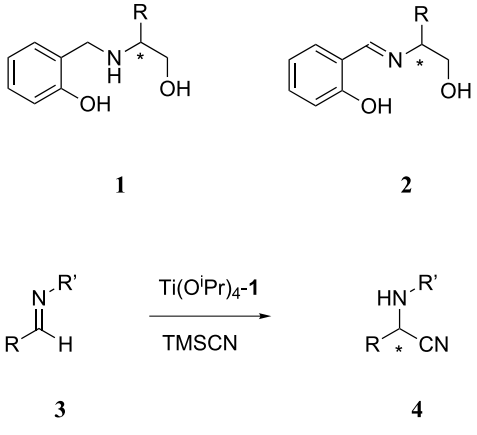
Abstract—*N*-salicyl-β-amino alcohols **1** were synthesized and evaluated as ligands for catalytic asymmetric Strecker reactions. *N*-Benzhydrylaldimines derived from aromatic and aliphatic aldehydes reacted with TMSCN in the presence of 10 mol% of Ti-**1** complex to give the Strecker products in excellent yields and in up to >98% ee. The presence of a protic additive is essential to ensure good conversion and reaction rate. The reaction conditions are simple and the stereochemical outcome is predictable from the configuration of the ligands, both enantiomers of which are readily synthesized.

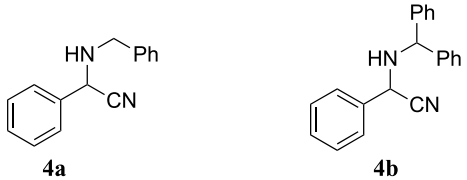
1. Introduction

The Strecker synthesis is one of the most atom-economical methods for the synthesis of α-amino acids. The classical Strecker reaction has been known since 1850, but it was not until 1963 that the first asymmetric Strecker synthesis was reported.[1] The majority of asymmetric Strecker syntheses developed since then involve the use of chiral auxiliaries, generally attached to the imine moiety.[2] Catalytic versions of asymmetric Strecker reactions have a relatively recent history.[3] In 1996, Lipton reported the first enantioselective Strecker reaction catalyzed by a cyclic dipeptide bearing a guanidine side-chain.[4] In less than 10 years, a number of highly effective catalysts have subsequently emerged. These catalysts can be entirely organic molecules such as Corey's cyclic guanidine[5] and Jacobsen's urea-Schiff base.[6] More recently, a number of promising chiral Lewis acid catalysts based on metal complexes of ligands such as BINOL[7] Schiff base,[8] bisoxazoline[9] and a carbohydrate derivative[10] have been developed.

Although many of these catalysts provide excellent enantioselectivities for a wide range of substrates, the most efficient ones are still fairly large and complex molecules with multiple stereogenic centers. From a practical point of view, it would be highly desirable to develop a small molecule catalyst possessing as few stereogenic centers as possible, provided that good reactivity and enantioselectivity can still be retained.



Scheme 1.



The tridentate *N*-salicyl-β-aminoalcohol **1** and its parent Schiff base **2** should form chelating complexes with metals such as titanium or aluminium. These complexes should

Keywords: Asymmetric; Catalyst; Imine; Hydrocyanation.
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behave as Lewis acids whilst providing a rigid asymmetric environment and, therefore, be potentially useful for catalyzing various types of asymmetric reactions. For instance, a heterobimetallic Li–Al complex of **1** was reported to catalyze the Michael addition of dialkyl malonates to cyclic enones.[11] Titanium complexes of **2** are highly efficient catalysts for enantioselective synthesis of cyanohydrins.[12] In view of the mechanistic similarity between hydrocyanation of aldehydes and imines, we envisaged that such catalysts would also perform well in the enantioselective Strecker reaction. The results of our preliminary investigation indicated that chiral *N*-salicyl-β-aminoalcohols **1** in combination with $Ti(O^iPr)_4$ were effective catalysts for asymmetric Strecker reactions of *N*-benzyl substituted imines **3** with TMSCN (Scheme 1).[13,14] The reported enantioselectivities were, however, rather moderate (maximum 86% ee). We have now discovered that the *N*-substituent of the imine substrate exerts a very significant effect on the degree of enantioselective induction. In this paper we disclose the results of our investigation on enantioselective Strecker reactions employing this versatile class of ligands in detail.

2. Results and discussion

2.1. Development of an NMR method for determination of enantiomeric purity

Although analysis of the enantiomeric purity of Strecker adducts is usually performed by chiral HPLC, this method was not available to us at the time of this investigation. We considered ^{1}H NMR spectroscopy as a potential alternative technique since it should require only a short analysis time, consume less solvent, require no expensive accessories such as chiral columns, and most importantly, the sample can be analyzed without any pre-treatment apart from removal of the reaction solvents. The only remaining problem was to find a suitable chiral media to distinguish the signals of each enantiomer. After trying several different chiral shift or chiral solvating agents, optically active camphorsulfonic acids (CSAs) previously used by Hassan et al. proved to be most effective in resolving the signals of the racemic *N*-benzyl α-aminonitrile (**4a**).[15] The splitting of the $C_\alpha H$ signal by up to 0.14 ppm was observed on a 200 MHz NMR spectrometer upon addition of 1–2 equiv of (*S*)-CSA to a 0.1 M solution of **4a** in $CDCl_3$. The $C_\alpha H$ and Ph_2CH peaks of *N*-benzhydryl substituted α-aminonitrile (**4b**) also split in the presence of CSA although the resolution was to a lesser magnitude than that of the *N*-benzyl analogues (up to 0.03 ppm for $C_\alpha H$ signal and 0.05 ppm for Ph_2CH signal). Nonetheless, a baseline resolution was obtained on a 400 MHz NMR spectrometer. Only a single $C_\alpha H$ peak was detected when enantiomerically pure (*S*)-**4b** was treated with CSA. The 'satellite' peaks can be easily detected in enantiomerically enriched samples containing as little as 1% of the other enantiomer (98% ee) prepared by addition of racemic **4b** to enantiomerically pure **4b** (Fig. 1). No racemization was observed after the CSA-treated sample was left at room temperature for several days. As expected, the position of the enantiomeric $C_\alpha H$ peaks reversed if the

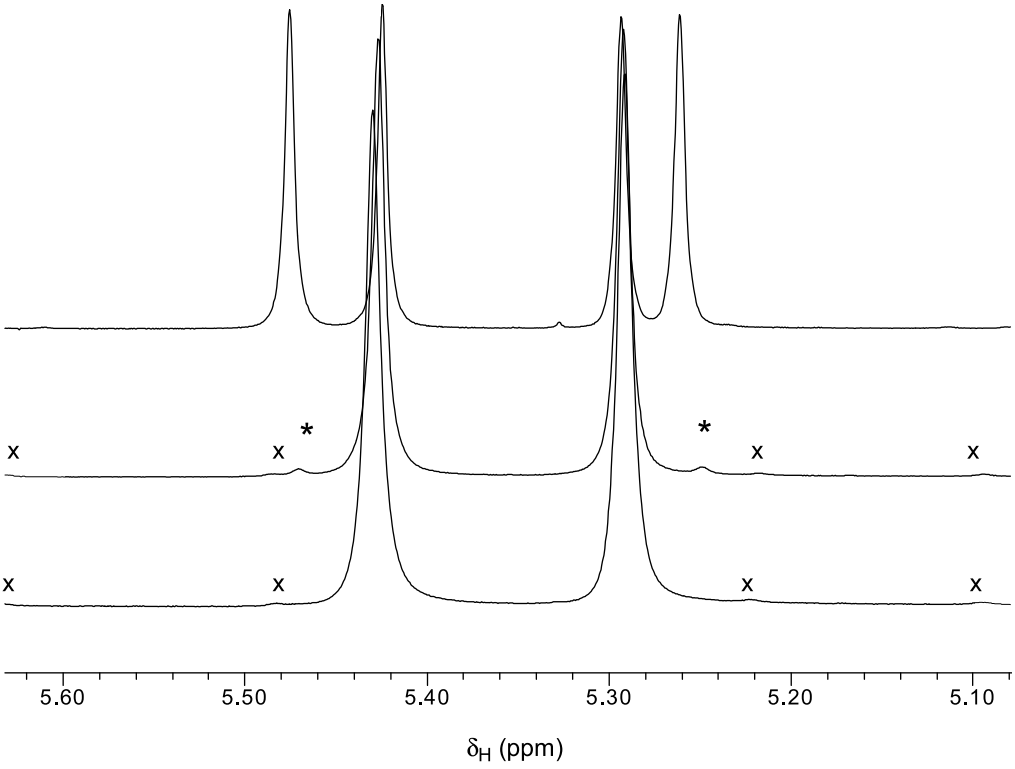
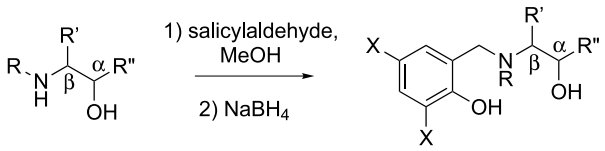


Figure 1. Partial ^{1}H NMR spectra of aminonitrile **4b** (400 MHz, $CDCl_3$) in the presence of (*S*)-CSA showing the Ph_2CH (δ_R: 5.48; δ_S: 5.42 ppm) and $C_\alpha H$ signals (δ_R: 5.26; δ_S: 5.29 ppm): racemic (top); 98% ee (middle); and enantiomerically pure (*S*)-**4b** (bottom). The humps marked by 'x' denote satellites due to ^{1}H–^{13}C couplings ($^1J_{1H-13C} \sim 140$ Hz).

Table 1. Structure and yield of the ligands[a] **1a–1k**



Entry	Ligand	Amino alcohols	R (N)	R′ (β)	R″ (α)	Yield (%)
1	(*S*)-**1a**	(*S*)-phenylalaninol	H	$PhCH_2$	H	74
2	(*R*)-**1a**	(*R*)-phenylalaninol	H	$PhCH_2$	H	72
3	(*S*)-**1b**	(*S*)-alaninol	H	Me	H	51
4	(*S*)-**1c**	(*S*)-valinol	H	^{i}Pr	H	75
5	(*S*)-**1d**	(*S*)-*tert*-leucinol	H	^{t}Bu	H	74
6	(*S*)-**1e**	(*S*)-phenylglycinol	H	Ph	H	73
7	(*S*)-**1f**	(*S*)-leucinol	H	^{i}Bu	H	50
8	(*S*)-**1g**	(*S*)-cyclohexyl-alaninol	H	$^{c}HexCH_2$	H	71
9	(*S*)-**1h**	(*S*,*S*)-isoleucinol	H	^{sec}Bu	H	74
10	(*R*)-**1i**	(*R*)-1-aminopropan-2-ol	H	H	CH_3	49
11	(*S*)-**1j**	(*S*)-prolinol		$-(CH_2)_3-$	H	50
12	(*S*)-**1k**	(*S*)-phenylalaninol	H	$PhCH_2$	H	59

[a] X=H for **1a–1j** (starting from salicylaldehyde); X=^{t}Bu for **1k** (starting from 3,5-di-^{tert}butylsalicylaldehyde).

opposite enantiomer of CSA was added. Importantly, CSA is very general in inducing a chiral environment for many other racemic *N*-benzyl and *N*-benzhydryl substituted α-aminonitriles (**4**) carrying different aromatic and aliphatic α-substituents. Therefore, we conclude that ^{1}H NMR is indeed a very reliable method for the determination of enantiomeric purity of a variety of Strecker adducts.

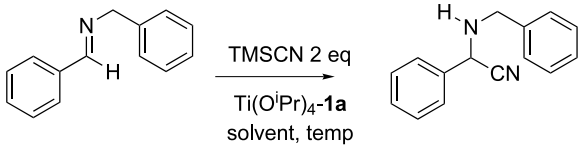
2.2. Synthesis of the ligands

The *N*-salicyl β-aminoalcohol ligand of type **1** is known in the literature. It has been synthesized by several methods including reduction of the salicylimines derived from the corresponding α-amino esters[16] or aminoalcohols.[17] Since a number of chiral β-aminoalcohols are readily available, we chose to synthesize **1** from the corresponding Schiff bases. Ligand (*S*)-**1a** was synthesized in 74% yield from commercially available (*S*)-phenylalaninol and salicylaldehyde via the Schiff base (*S*)-**2a** by $NaBH_4$ reduction. The ligand was obtained as a stable white crystalline solid after routine work-up and column chromatography. It can be kept for years at room temperature without detectable degradation. Many other related ligands can be similarly prepared from the corresponding β-aminoalcohols in 50–75% yield (Table 1).

2.3. Evaluation of the ligands for catalytic asymmetric Strecker reaction and optimization of the reaction conditions

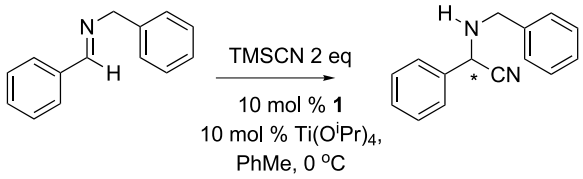
Several 1:1 metal complexes of (*S*)-**1a** and its parent Schiff base (*S*)-**2a** were prepared in situ and tested as catalysts for enantioselective Strecker reactions. The reaction between *N*-benzylidenebenzylamine (**3**: R=Ph; R′=$PhCH_2$) and TMSCN was used as a model. The reaction was performed in toluene at 0 °C in the presence of 10 mol% of the catalyst. Excess TMSCN (2 equiv) was essential to assure a complete reaction. While many complexes of both ligands provided

Table 2. Effect of solvent and temperature



Entry	Solvent	Catalyst (mol %)	*t* (°C)	Time (h)	Conversion (%)	ee (%)
1	Hexanes+PhMe (1:1)	10	0	6	97	72
2	Et_2O	10	0	6	98	52
3	THF	10	0	6	90	48
4	CH_2Cl_2	10	0	6	98	72
5	MeOH	10	0	6	96	0
6	PhMe	10	0	6	98	79
7	PhMe	10	−20	12	36	8
8	PhMe	10	25	6	97	62
9	PhMe	1	0	8	77	24
10	PhMe	5	0	8	96	46
11	PhMe	15	0	8	>99	74
12	PhMe	20	0	8	>99	75

Table 3. Effect of ligand structure



Entry	Ligand	R ligand (position)	Time (h)	Conversion (%)	ee (%)
1	(*S*)-**1a**	$PhCH_2$ (β)	6	98	79 (*S*)
2	(*S*)-**1b**	Me (β)	6	97	20 (*S*)
3	(*S*)-**1c**	^{i}Pr (β)	6	99	82 (*S*)
4	(*S*)-**1d**	^{t}Bu (β)	6	98	86 (*S*)
5	(*S*)-**1e**	Ph (β)	6	98	66 (*S*)
6	(*S*)-**1f**	^{i}Bu (β)	6	97	48 (*S*)
7	(*S*)-**1g**	$^{c}HexCH_2$ (β)	6	98	77 (*S*)
8	(*S*)-**1h**	^{sec}Bu (β)	6	98	87 (*S*)
9	(*R*)-**1i**	Me (α)	8	81	6 (*R*)
10	(*S*)-**1j**	$(CH_2)_3$ (N, β)	8	77	8 (*R*)
11	(*S*)-**1k**	$PhCH_2$ (β)	8	84	16 (*S*)

the desired Strecker product (**4a**) in good to excellent yields, only the titanium complex of the reduced Schiff base (*S*)-**1a** gave a satisfactory outcome in terms of both conversion and enantioselectivity. Interestingly, the presence of TMS groups was not observed in the Strecker adduct, presumably due to the cleavage of the rather labile N–Si bond by trace of moisture during work-up. The reaction parameters including solvent, temperature and catalyst loading were next optimized using this screening system (Table 2). It was evident that toluene is the best solvent for the reaction. Polar solvents resulted in lower degrees of enantioselectivity. The effect of temperature is also quite interesting, the best ee was obtained when the reactions were carried out at 0 °C. Not unexpectedly, higher temperatures resulted in poorer selectivity. At temperatures below 0 °C, the reaction was very slow, and interestingly the enantioselectivity dropped substantially. Decreasing the catalyst loading resulted in lower enantioselectivity while the conversion was not much affected. On the other hand, no improvement in selectivity was found at >10% catalyst loading, therefore, the optimal catalyst loading was 10%.

2.4. Effects of ligand structure

In order to investigate the effect of the ligand structure on the enantioselectivities, the reactions of imine **3** (R=Ph; R′=$PhCH_2$) with TMSCN in the presence of other catalysts were repeated under the best condition obtained for ligand (*S*)-**1a**. A good correlation, at least in a qualitative sense, between the size of the alkyl side-chain and the degree of enantioselectivity was observed. Therefore, only ligands bearing a relatively sterically hindered substituent at the β-position such as **1a** (R=$PhCH_2$), **1c** (R=^{i}Pr), **1d** (R=^{t}Bu), and **1h** (R=^{sec}Bu) provided synthetically useful selectivities (Table 3: entries 1, 3, 4 and 8). Addition of a bulky *tert*-butyl substituent on the salicyl moiety resulted in

Table 4. Enantioselective Strecker reactions of aromatic benzyl and benzhydrylimines (**3**) catalyzed by $Ti(O^{i}Pr)_4$-(*S*)-**1a** complexes[a,b]

Entry	R (substrate)	R′	Conversion (%)	ee (%)
1	Ph	$PhCH_2$	98	79
2	4-ClC_6H_4	$PhCH_2$	96	72
3	4-MeC_6H_4	$PhCH_2$	97	67
4	4-$MeOC_6H_4$	$PhCH_2$	93	45
5	3-$NO_2C_6H_4$	$PhCH_2$	>99	64
6	2-$MeOC_6H_4$	$PhCH_2$	>99	51
7	Ph	Ph_2CH	>99	98
8	4-ClC_6H_4	Ph_2CH	>99	95
9	4-MeC_6H_4	Ph_2CH	>99	96
10	4-$MeOC_6H_4$	Ph_2CH	>99	91
11	3-$MeOC_6H_4$	Ph_2CH	>99	94
12	3-$NO_2C_6H_4$	Ph_2CH	>99	98
13	2-MeC_6H_4	Ph_2CH	>99	97
14	2-ClC_6H_4	Ph_2CH	>99	97[c]
15	2-BrC_6H_4	Ph_2CH	>99	>98[c]
16	2-$MeOC_6H_4$	Ph_2CH	>99	90
17	1-Naphthyl	Ph_2CH	98	98
18	2-Naphthyl	Ph_2CH	97	96
19	2-Furyl	Ph_2CH	>99	98
20	2-Thienyl	Ph_2CH	>99	98

[a] Reaction time: entries 1–6=9 h; entries 7–20=48 h.
[b] For reaction conditions see Table 3.
[c] Baseline separation of the enantiomeric $C_{\alpha}H$ and Ph_2CH signals was not achieved. The reported ee values were estimated by comparison of the optical rotation with known reference compounds (Ref. 8b).

Table 5. Enantioselective Strecker reactions of aliphatic benzhydrylimines catalyzed by Ti(O^iPr)$_4$-**1** complexes[a,b]

Entry	R (substrate)	Ligand	conversion (%)	ee (%)
1	^{t}Bu	(*S*)-**1a**	>99	23
2	^{t}Bu	(*S*)-**1d**	>99	47
3	^{t}Bu	(*S*)-**1h**	>99	51
4	PhCH=CH	(*S*)-**1a**	>99	61
5	PhCH=CH	(*S*)-**1d**	>99	88
6	PhCH=CH	(*S*)-**1h**	>99	91

[a] Reaction time: 24 h.
[b] For reaction conditions see Table 3.

a substantially decreased enantioselectivity (entry 11). In all aforementioned cases, the absolute configuration of the Strecker product **4a** was determined to be *S* based on the chemical shift of the $C_\alpha H$ signal in the presence of (*S*)-CSA and by comparison of the optical rotation with a known standard.[15] Moving the substituent to the α-position also resulted in a poor enantioselectivity (compare entries 2 and 9). Ligand (*S*)-**1j** bearing an *N*-alkyl substituent which is part of a pyrrolidine ring gave, apart from a very low selectivity, the product of opposite absolute configuration (entry 10).

2.5. Effects of substrate structure

The substrate generality of enantioselective Strecker reactions employing this class of ligand was investigated. Various substituted aldimines were subjected to cyanide addition under the best conditions obtained thus far using the Ti complex of (*S*)-**1a**. It was found that optically active α-aminonitriles **4** were obtained in excellent yields and with enantioselectivity ranging from poor to fairly good (45–79% ee) for *N*-benzyl substituted aldimine substrates (**3**: R=Ph; R′=$PhCH_2$) (Table 4, entries 1–6). However, a dramatic breakthrough was achieved when *N*-benzhydryl substituted aldimines (**3**: R′=Ph_2CH) were used as substrates. The Strecker reaction of *N*-benzhydrylimine (**3**: R=Ph; R′=Ph_2CH) in the presence of Ti(O^iPr)$_4$-(*S*)-**1a** required somewhat longer reaction time to reach >99% conversion, but provided the corresponding optically active α-aminonitrile in 98% ee under otherwise identical conditions (Table 4, entry 7). The bulkier ligands **1c**, **1d** and **1h** also gave the same conversion (>99%) and ee range for this substrate (**1c**: 94%; **1d** and **1h**: 97%). Ee values of >90% were routinely observed for various imine substrates derived from aromatic aldehydes and benzhydrylamine (Table 4, entries 8–20). Substituents with various steric and electronic natures appeared to be well-tolerated for virtually all imines derived from substituted benzaldehyde studied. Equally good results were obtained for non-benzaldehyde derived aromatic imines including 1-naphthyl, 2-naphthyl and heteroaromatic substrates. Aliphatic substrates such as those derived from pivalaldehyde and cinnamaldehyde gave much poorer ee's at similar conversion. Nevertheless, the use of ligands bearing bulkier substituents such as **1d** and **1h** gave significantly improved results (Table 5). The *S*-configuration of the Strecker products was assumed in all cases (except for entries 19–20 in Table 4, vide infra) by analogy to **4a** and **4b**.

2.6. The role of protic additives

Upon scaling up the reaction from 0.1 mmol to 0.5 or 1 mmol, the rate of the reaction was found to be significantly slower. In many cases the reaction did not proceed to completion at all although the ee values were practically the same. Previous works in this area have demonstrated the importance of proton sources in similar reactions.[7a,8b] The proton source can generate HCN from TMSCN, which is believed to be the actual cyanating species.[8b] Furthermore, since the catalyst contains free hydroxylic functions which should be susceptible to silylation by TMSCN under the reaction conditions, a proton source should increase the catalyst turnover by preventing silylation of, or by regenerating, the hydroxylic function of the catalyst.[18] We were delighted to find that addition of a proton source such as water or 2-propanol

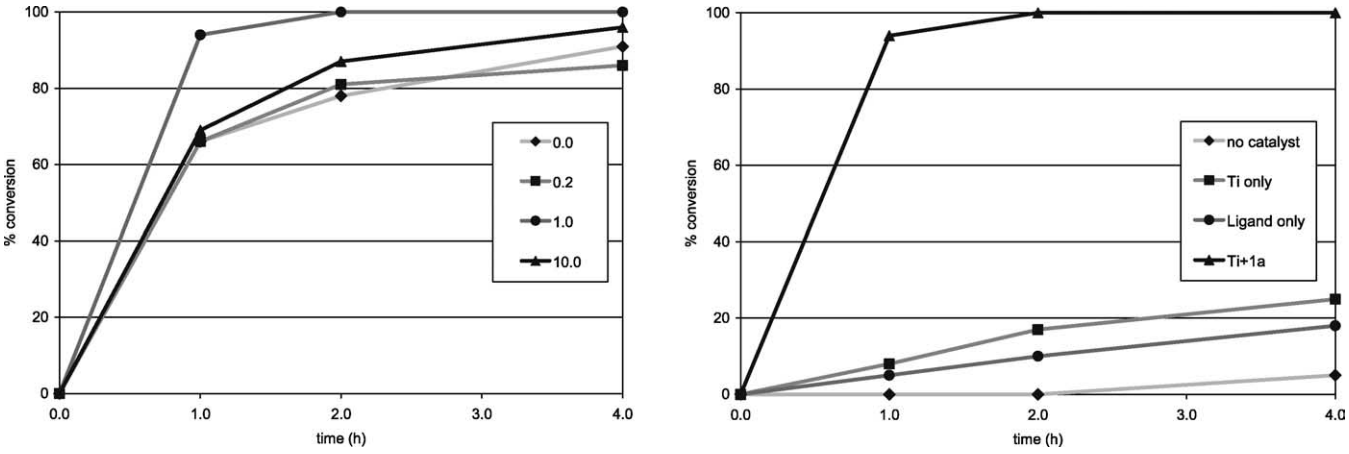
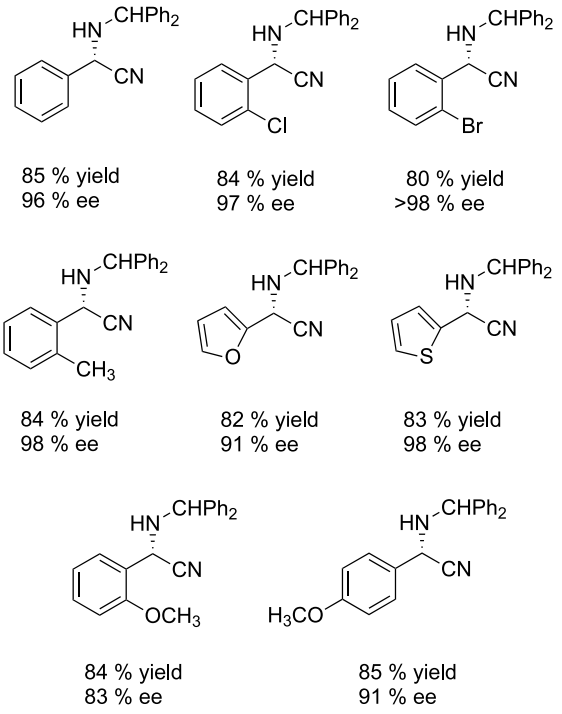


Figure 2. The rate of cyanation of imine **3** (R=Ph; R′=Ph_2CH) at 0 °C the presence of 10 mol% Ti(O^iPr)4-(*S*)-**1a** complex and 0, 0.2, 1.0 and 10 equiv of 2-propanol (left) and in the presence of 10 equiv 2-propanol and with or without Ti(O^iPr)$_4$ and/or (*S*)-**1a** (10 mol%) (right).

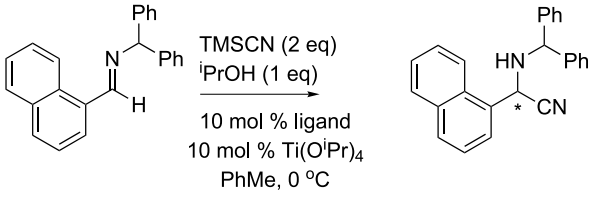
completely restored the catalytic activity. Kinetic analysis by ^{1}H NMR spectroscopy of the Ti-(*S*)-**1a** catalyzed cyanation of imine **3** (R=Ph; R′=Ph_2CH) conducted in the presence of different amounts of 2-propanol additive suggested that the reaction rate was significantly enhanced compared to a reaction without the additive (Fig. 2, left). Most interestingly, the reaction rate reaches a maximum when an equivalent amount of the additive is used and under these conditions. The reaction went to completion within 2 h at 0 °C. A large excess of 2-propanol (10 equiv) resulted not only in a significantly slower reaction rate, but also provided almost racemic product. The reactions in the presence of 1.0 equiv ^{i}PrOH but without the Ti-(*S*)-**1a** catalyst or either of its components were very slow (Fig. 2, right). In all cases the conversion was <20% after 2 h at 0 °C. This suggested that the background hydrocyanation is almost insignificant under the experimental conditions, at least for this particular substrate. Consequently, the slow addition of ^{i}PrOH or performing the reaction at very low temperatures may not be essential to ensure good enantioselectivities. This would greatly simplify the synthetic procedure. Indeed, we have found that the additive can be added at the beginning of the reaction without any adverse effects on the yield and enantioselectivity.[19] The role of the protic additive is probably less important for small scale reactions where the total exclusion of all adventitious moisture was difficult which explains why the reaction proceeded to completion without the need for the protic additive.

To ascertain that the protic additive is generally beneficial for large scale reactions with other substrates, a few more representative reactions were attempted at 1 mmol scale with 1.0 equiv of 2-propanol added at the beginning and 10 mol% catalyst prepared from ligand (*S*)-**1a** (25 mg of the ligand/mmol of substrate). ^{1}H NMR analysis of the crude reaction mixture revealed that all reactions were completed within 4 h at 0 °C, and that the enantioselectivities were comparable to the small scale reactions. Interestingly, after attempted purification by passing through silica gel or an alumina column, significant racemization was observed for products **4** bearing electron donating substituents (e.g., 2-furyl, 2-thienyl, 2-and 4-methoxyphenyls) so that the final products of only 50–75% ee were obtained. We have confirmed that the racemization was catalyzed by weak acids including silica gel and neutral alumina. Fortunately, addition of a small amount of triethylamine to the eluting solvent largely suppressed the racemization. In all cases, the isolated yield of the crystalline products were >80% and the enantioselectivities were good to excellent (Scheme 2). The absolute configuration of all products derived from the ligand (*S*)-**1a** was confirmed to be *S* by comparison of the optical rotations with literature values.[8b] It should be noted that, for R=2-thienyl and 2-furyl, although the sense of asymmetric induction is the same, the absolute configuration must be designated as *R* according to Cahn–Ingold–Prelog sequence rules. The stereoselectivity of the enantioselective Strecker reaction induced by the Ti-**1** catalyst is, therefore, fully controlled by the absolute configuration of the ligand **1** (Scheme 3).

It is obvious that aminonitriles with opposite configuration should be obtained in a highly predictable manner simply by switching to the enantiomeric ligand. The presence of only



Scheme 2.



ligand	yield (%)	% ee (config.)	$[\alpha]_D^{23}$
(*S*)-**1a**	91	> 98 (*S*)	-186 °
(*R*)-**1a**	87	> 98 (*R*)	+185 °

Scheme 3.

one stereogenic center in the ligand moiety means that the other enantiomer is much more easily obtained than those with multiple stereogenic centers. To further demonstrate the application of this novel catalyst system, the two enantiomers of the optically active α-aminonitrile precursor of 1-naphthylglycine were prepared. The reaction of the imine **3** (R=1-naphthyl; R′=Ph_2CH) with TMSCN and 1.0 equiv ^{i}PrOH in the presence of 10 mol% Ti(O^iPr)$_4$-(*S*)-**1a** on a 1 mmol scale afforded the corresponding (*S*)-α-aminonitrile in 91% yield and >98% ee. The opposite enantiomer was similarly obtained in 87% yield and >98% ee by employing (*R*)-**1a** derived from commercially available (*R*)-phenylalaninol as the ligand.

3. Conclusions

In summary, this work has demonstrated that Ti complexes of *N*-salicyl-β-aminoalcohols **1** are highly effective catalysts

for enantioselective Strecker reactions of aldimines. It has been clearly shown that the configuration as well as the bulkiness of the β-substituent exerts a direct influence on both the absolute stereochemical outcome and enantioselectivity of the Strecker product. Furthermore, we have illustrated that excellent yields accompanied by extremely high degrees of enantioselectivity can be obtained when a substrate with a more sterically demanding *N*-substituent was employed. The superiority of this class of optically active ligands can be emphasized due to their low molecular weights and the fact that they possess only one stereogenic center, the starting precursor of which is readily available with any desirable absolute stereochemistry. In addition, it has been shown that the reaction conditions are extremely simple. It is expected that these catalyst systems will offer a very practical access to optically active α-aminonitriles and α-amino acids. Further understanding of the mechanistic details of the catalysis and efforts to improve the catalysts to accommodate aliphatic substrates are currently in progress.

4. Experimental

4.1. General procedure for the preparation of ligands 1

A mixture of ethanol (2 mL), an appropriate amino alcohol (1 mmol), and aldehyde (1 mmol) was stirred at room temperature until the starting materials were totally consumed (monitored by TLC). To the yellow mixture was added $NaBH_4$ (37.8 mg, 1 mmol) with stirring to give a colorless solution. The reaction was then quenched with dil. HCl. After neutralization (sat. $NaHCO_3$), the reaction mixture was concentrated under reduced pressure and the residue was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and the solvent removed. The products were purified by flash column chromatography (hexanes/ethyl acetate).

4.1.1. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol [(*S*)-1a]. White crystalline solid (0.190 g, 74%). Mp 133–134 °C; $[\alpha]_D^{23}=-23.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.89 (1H, A*B*X, $J_{AB}=13.6$ Hz, $J_{BX}=7.6$ Hz, C$H_a$$H_b$Ph), 2.91 (*A*BX, $J_{AB}=13.6$ Hz, $J_{AX}=6.4$ Hz, CH$_a$$H_b$Ph), 3.02 (1H, m, C*H*NH), 3.58 (1H, A*B*X, $J_{AB}=11.0$ Hz, $J_{BX}=5.0$ Hz, CH$_a$$H_b$OH), 3.78 (1H, *A*BX, $J_{AB}=11.0$ Hz, $J_{AX}=3.8$ Hz, CH_aH$_b$OH), 4.05 (2H, s, CH_2NH), 6.82 (1H, apparent t, $J=7.2$ Hz, Ar), 6.87 (1H, d, $J=8.0$ Hz, Ar), 7.01 (1H, d, $J=7.2$ Hz, Ar), 7.19–7.38 (6H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.3, 50.3, 59.7, 62.6, 116.6, 119.2, 122.7, 126.7, 128.3, 128.7, 128.9, 129.2, 138.0, 158.0; Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.66; H, 7.41; N, 5.43%.

4.1.2. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-propanol [(*S*)-1b]. Viscous yellowish oil (0.092 g, 51%). $[\alpha]_D^{25}=+66.0$ (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 1.17 (3H, d, $J=6.4$ Hz, CH_3), 2.92 (1H, m, C*H*CH$_3$), 3.54 (1H, A*B*X, $J_{AB}=10.9$ Hz, $J_{BX}=6.6$ Hz, CH$_a$$H_b$OH), 3.75 (1H, *A*BX, $J_{AB}=10.9$ Hz, $J_{AX}=3.6$ Hz, CH_aH$_b$OH), 4.00 and 4.10 (2H, AB, $J=13.8$ Hz, CH_2NH), 4.20 (br s, N*H* and O*H*) 6.81 (1H, apparent t, $J=7.4$ Hz, Ar), 6.86 (1H, d, $J=8.0$ Hz, Ar), 7.03 (1H, d, $J=7.2$ Hz, Ar), 7.19 (1H, apparent t, $J=7.6$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 16.1, 49.8, 53.9, 65.6, 116.5, 119.1, 121.7, 128.4, 128.9, 158.0; Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.11; H, 8.50; N, 7.75%.

4.1.3. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol [(*S*)-1c]. White crystalline solid (0.157 g, 75%). Mp 52–54 °C; $[\alpha]^{26}{}_D=+15.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 and 1.04 (6H, 2×d, $J=6.8$ Hz, 2×CH_3), 1.99 (1H, m, C*H*(CH$_3$)$_2$), 2.54 (1H, m, C*H*NH), 3.69 (1H, A*B*X, $J_{AB}=11.1$ Hz, $J_{BX}=6.0$ Hz, CH$_a$$H_b$OH), 3.87 (1H, *A*BX, $J_{AB}=11.1$ Hz, $J_{AX}=3.8$ Hz, CH_aH$_b$OH), 4.05 (2H, s, CH_2NH), 6.82 (1H, apparent t, $J=7.4$ Hz, Ar), 6.88 (1H, d, $J=8.0$ Hz, Ar), 7.03 (1H, d, $J=7.6$ Hz, Ar), 7.21 (1H, apparent t, $J=7.7$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3, 19.2, 28.7, 51.0, 61.2, 64.0, 116.5, 119.1, 123.1, 128.2, 128.8, 158.1; Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69; Found: C, 68.65; H, 9.39; N, 6.73%.

4.1.4. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol [(*S*)-1d]. White crystalline solid (0.165 g, 74%). Mp 58−60 °C; $[\alpha]_D^{25}=+5.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (9H, s, 3×CH_3), 2.41 (1H, AB*X*, $J_{AX}=3.6$ Hz, $J_{BX}=5.8$ Hz, C*H*C(CH$_3$)$_3$), 3.74 (1H, A*B*X, $J_{AB}=10.9$ Hz, $J_{BX}=5.8$ Hz, CH$_a$$H_b$OH), 4.00 (1H, *A*BX, $J_{AB}=10.9$ Hz, $J_{AX}=3.6$, CH_aH$_b$OH), 4.02 and 4.10 (2H, AB, $J=13.3$ Hz, CH_2NH), 6.82 (1H, apparent t, $J=7.4$ Hz, Ar), 6.89 (1H, d, $J=8.0$ Hz, Ar), 7.04 (1H, d, $J=7.2$ Hz, Ar), 7.21 (1H, apparent t, $J=7.8$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.5, 34.2, 53.1, 61.2, 67.8, 116.4, 119.3, 123.7, 128.5, 128.8, 157.9; Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27; Found: C, 69.95; H, 9.52; N, 6.27%.

4.1.5. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-2-phenyl-ethanol [(*S*)-1e]. White crystalline solid (0.201 g, 73%). Mp 119–121 °C; $[\alpha]_D^{20}=+64.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.74 (1H, A*B*, $J=13.6$ Hz, CH$_a$$H_b$NH, 3.76–3.87 (3H, m, C$H_2$OH and C*H*NH), 3.97 (1H, *A*B, $J=13.6$ Hz, CH_aH$_b$NH), 5.05 (br s, N*H* and O*H*), 6.79 (1H, apparent t, $J=7.2$ Hz, Ar), 6.87 (1H, d, $J=8.0$ Hz, Ar), 6.92 (1H, d, $J=6.4$ Hz, Ar), 7.19 (1H, apparent t, $J=8.0$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.1, 63.9, 66.5, 116.4, 119.4, 122.8, 127.5, 128.2, 128.6, 128.9, 129.0, 138.7, 157.8; Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.07; H, 7.03; N, 5.79%.

4.1.6. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-4-methyl-pentanol [(*S*)-1f]. Light yellow crystalline solid (0.114 g, 50%). Mp 87–88 °C; $[\alpha]_D^{22}=+15.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (6H, t, $J=6.2$ Hz, 2×CH_3), 1.36 and 1.44 (2H, 2×m, CH_2-CH(CH$_3$)$_2$), 1.74 (1H, m, C*H*(CH$_3$)$_2$), 2.81 (1H, m, C*H*NH), 3.56 (1H, A*B*X, $J_{AB}=11.1$ Hz, $J_{BX}=5.6$ Hz, CH$_a$$H_b$OH), 3.84 (1H, *A*BX, $J_{AB}=11.1$ Hz, $J_{AX}=3.4$ Hz, CH_aH$_b$OH), 4.04 (2H, s, CH_2NH), 4.90 (br s, N*H* and O*H*), 6.79 (1H, apparent t, $J=6.4$ Hz, Ar); 6.87 (1H, d, $J=8.0$ Hz, Ar) 7.02 (1H, d, $J=6.8$ Hz, Ar), 7.19 (1H, apparent t, $J=7.8$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.7, 22.8, 25.0, 40.2, 49.8, 56.2, 63.2, 116.5, 119.1, 122.8, 128.3, 128.7, 158.1; Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.74; H, 9.55; N, 6.04%

4.1.7. N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-cyclohexyl-propanol [(*S*)-1g]. Light yellow crystalline solid (0.200 g, 71%). Mp 82–84 °C; $[\alpha]_D^{25}=+12.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 0.85–1.78 (13H, m, ^{c}Hex ring protons and ^{c}HexCH_2), 2.83 (1H, m, C*H*NH), 3.55 (1H, A*B*X, $J_{AB}=11.1$ Hz, $J_{BX}=5.2$ Hz, CCH_aH_bOH), 3.82 (1H, *A*BX, $J_{AB}=11.1$ Hz, $J_{AX}=3.4$ Hz, CH_aH_bOH), 4.03 (2H, s, CH_2NH), 5.02 (br s, N*H* and O*H*), 6.81 (1H, apparent t, $J=7.2$ Hz, Ar), 6.87 (1H, d, $J=8.0$ Hz, Ar), 7.02 (1H, d, $J=7.2$ Hz, Ar), 7.19 (1H, apprent t, $J=7.8$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.2, 26.5, 33.6, 34.5, 38.6, 49.7, 55.5, 63.2, 116.5, 119.1, 122.8, 128.4, 128.9, 158.1; Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 73.16; H, 9.49; N, 5.46%.

4.1.8. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-(*S*)-3-methyl-pentanol [(*S*)-1h]. Yellowish oil (0.166 g, 74%). $[\alpha]_D^{22}=+54.0$ (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 0.95 (6H, m, CH_3CH_2 and CH_3CH), 1.22 and 1.50 (2H, 2×m, CH_3CH_2), 1.75 (1H, m, CH_3CH), 2.66 (1H, m, C*H*NH), 3.63 (1H, A*B*X, $J_{AB}=11.2$ Hz, $J_{BX}=6.8$ Hz, CH_aH_bOH), 3.83 (1H, *A*BX, $J_{AB}=11.2$ Hz, $J_{AX}=3.6$ Hz, CH_aH_bOH), 3.98–4.09 (2H, AB, $J=13.6$ Hz, CH_2NH), 4.85 (br s, N*H* and O*H*), 6.81 (1H, apparent t, $J=7.4$ Hz, Ar), 6.87 (1H, d, $J=8.0$ Hz, Ar), 7.03 (1H, d, $J=7.2$ Hz, Ar), 7.20 (1H, apparent t, $J=7.8$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.9, 14.8, 26.2, 35.2, 50.7, 61.0, 62.7, 116.5, 119.2, 123.0, 128.4, 128.9, 158.0; Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.85; H, 9.42; N, 6.20%.

4.1.9. *N*-(2′-Hydroxyphenyl)methyl-(*R*)-1-amino-propanol [(*R*)-1i]. Light yellow crystalline solid (0.089 g, 49%). Mp 87–88 °C; $[\alpha]_D^{25.9}=-24.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 1.13 (3H, d, $J=6.4$ Hz, CH_3CH), 2.50 (1H, A*B*X, $J_{AB}=12.0$ Hz, $J_{BX}=8.4$ Hz, CH_aH_bCH), 2.62 (1H, *A*BX, $J_{AB}=12.0$ Hz, $J_{AX}=3.2$ Hz, CH_aH_bCH), 3.91 (1H, m, C*H*OH), 3.90 and 3.99 (2H, AB, $J=14.0$ Hz, CH_2NH), 5.03 (br s, N*H* and O*H*), 6.71 (1H, apparent t, $J=7.4$ Hz, Ar), 6.75 (1H, d, $J=8.2$ Hz, Ar), 6.91 (1H, d, $J=7.2$ Hz, Ar), 7.09 (1H, apparent t, $J=7.6$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 52.5, 55.6, 66.5, 116.4, 119.1, 122.4, 128.5, 128.8, 158.1; Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.14; H, 8.30; N, 7.67%.

4.1.10. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-hydroxymethyl-pyrrolidine [(*S*)-1j]. Viscous yellowish oil (0.103 g, 50%). $[\alpha]_D^{24}=-75.0$ (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 1.76–2.08 (4H, m, pyrrolidine $(CH_2)_2$), 2.37 (1H, m, pyrrolidine N–CH_aH_b), 2.79 (1H, m, pyrrolidine N–CH_aH_b), 3.10 (1H, m, N–C*H*CH_2OH), 3.57 (1H, AB, $J=14.0$ Hz, $ArCH_aH_bN$), 3.69 (1H, A*B*X, $J_{AB}=11.2$ Hz, $J_{BX}=4.8$ Hz, CH_aH_bOH), 3.75 (1H, *A*BX, $J_{AB}=11.2$ Hz, $J_{AX}=3.8$ Hz, CH_aH_bOH), 4.33 (1H, AB, $J=14.0$ Hz, $ArCH_aH_bN$), 6.18 (br s, O*H*), 6.80 (1H, apparent t, $J=7.2$ Hz, Ar), 6.84 (1H, d, $J=8.0$ Hz, Ar), 7.00 (1H, d, $J=7.6$ Hz, Ar), 7.18 (1H, apparent t, $J=7.6$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.2, 27.5, 54.5, 58.3, 64.0, 65.5, 116.0, 119.1, 122.9, 128.1, 128.6, 157.6; Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.14; H, 8.29; N, 6.71%.

4.1.11. *N*-(3′,5′-Di-*tert*-butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol [(*S*)-1k]. Viscous yellowish oil (0.219 g, 59%). $[\alpha]_D^{22}=-33.0$ (*c* 2.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 1.32 and 1.45 (2×9H, 2×s, $C(CH_3)_3$)), 2.86 (1H, A*B*X, $J_{AB}=13.6$ Hz, $J_{BX}=7.6$ Hz, CH_aH_bPh), 2.97 (1H, *A*BX, $J_{AB}=13.4$ Hz, $J_{AX}=6.4$ Hz, CH_aH_bPh), 3.03 (1H, m, C*H*NH), 3.58 (1H, A*B*X, $J_{AB}=11.2$, $J_{BX}=4.8$ Hz, CH_aH_bOH), 3.76 (1H, *A*BX, $J_{AB}=11.2$, $J_{AX}=3.6$ Hz, CH_aH_bOH), 3.99–4.08 (2H, AB, $J=13.6$ Hz, CH_2NH), 6.90 (1H, s, Ar), 7.22–7.37 (6H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.8, 31.8, 34.3, 35.0, 37.4, 51.1, 59.9, 62.7, 122.3, 123.2, 123.3, 126.7, 128.8, 129.4, 136.3, 138.2, 140.9, 154.4; Anal. Calcd for $C_{24}H_{35}NO_2$: C, 78.00; H, 9.55; N, 3.79. Found: C, 78.16; H, 9.71; N, 3.61%.

4.1.12. *N*-(2′-Hydroxyphenyl)methyl-(*R*)-2-amino-3-phenyl-propanol [(*R*)-1a]. White crystalline solid (0.185 g, 72%). Mp 133–134 °C; $[\alpha]_D^{22}=+24.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.85 (1H, A*B*X, $J_{AB}=13.6$ Hz, $J_{BX}=7.6$ Hz, CH_aH_bPh), 2.94 (1H, *A*BX, $J_{AB}=13.6$ Hz, $J_{AX}=6.4$ Hz, CH_aH_bPh), 3.03 (1H, br, C*H*NH), 3.57 (1H, A*B*X, $J_{AB}=11.2$ Hz, $J_{BX}=4.8$ Hz, CH_aH_bOH), 3.76 (1H, *A*BX, $J_{AB}=11.2$ Hz, $J_{AX}=3.2$ Hz, CH_aH_bOH), 4.04 (2H, s, CH_2NH), 6.80 (1H, apparent t, $J=7.2$ Hz, Ar), 6.85 (1H, d, $J=8.0$ Hz, Ar), 7.00 (1H, d, $J=7.2$ Hz, Ar), 7.19–7.38 (6H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.1, 50.1, 59.7, 62.5, 116.6, 119.3, 122.6, 126.7, 128.4, 128.8, 129.0, 129.2, 137.9, 157.9; Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.43; H, 7.29; N, 5.41%.

4.2. General procedure for Ti-catalyzed addition of TMSCN to imines (small scale)

Ligand **1** (0.02 mmol) was dissolved in anhydrous toluene (0.3 mL). $Ti(O^iPr)_4$ (6.0 μL, 0.02 mmol) was added to the reaction and stirred for 10 min at ambient temperature to give a clear yellow solution. The selected imine (0.2 mmol) was added and then cooled to 0 °C (ice–salt bath) for 15 min. TMSCN (50 μL, 0.4 mmol) was then added using syringe. The progress of the reaction and enantioselectivity was monitored by ^{1}H NMR analysis.

4.3. General procedure for Ti-catalyzed addition of TMSCN to imines (large scale)

Ligand (**1a**) (25 mg, 0.1 mmol) placed in a screw-cap vial was dissolved in anhydrous toluene (1.5 mL). $Ti(O^iPr)_4$ (29.8 μL, 0.1 mmol) was added to the reaction and stirred for 10 min at ambient temperature to give a clear yellow solution. 2-Propanol (76.5 μL, 1.0 mmol) was added and left for another 10 min. The selected imine (1.0 mmol) was then added and the reaction cooled to 0 °C. Finally, TMSCN (250 μL, 2.0 mmol) was quickly added in one portion. After 8 h, the crude product was purified by passing through a plug of neutral alumina eluting with ethyl acetate–hexanes plus 0.1% Et_3N to yield the corresponding α-aminonitriles.

4.3.1. (*S*)-Diphenylmethylamino-phenylacetonitrile. White solid (0.253 g, 85%), 96% ee: $[\alpha]_D^{22}=-63.0$ (*c* 1.0, $CHCl_3$) {lit.[8b] $[\alpha]_D^{24}$ (97% ee, *c* 5.0, $CHCl_3$)$=-64.2$}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.18 (1H, d, $J=12.0$ Hz, N*H*CH), 4.63 (1H, d, $J=12.0$ Hz, C*H*CN), 5.28 (1H, s, $CHPh_2$), 7.23–7.55 (11H, m, Ar), 7.60 (4H, m, Ar); ^{13}C

NMR ($CDCl_3$, 100 MHz) δ 52.4, 65.6, 118.8, 127.2, 127.3, 127.5, 127.8, 128.0, 128.8, 129.0, 129.1, 129.2, 135.0, 141.2, 142.8.

4.3.2. (*S*)-Diphenylmethylamino-2-bromophenylacetonitrile. White solid (0.280 g, 80%), >98% ee: $[\alpha]_D^{22} = -121.0$ (*c*1.0, $CHCl_3$) {lit.[8b] $[\alpha]_D^{24}$ (>99% ee, *c* 5.0, $CHCl_3$) = −122}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.92 (1H, s, C*H*CN), 5.24 (1H, s, C*H*Ph_2), 7.22–7.45 (8H, m, Ar), 7.50 (2H, d, *J*=7.2 Hz, Ar), 7.58–7.68 (4H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.6, 65.7, 118.3, 123.4, 127.2, 127.8, 127.9, 128.0, 128.3, 128.8, 128.9, 129.4, 130.8, 133.8, 134.5, 140.7, 142.6.

4.3.3. (*S*)-Diphenylmethylamino-2-chlorophenylacetonitrile. White solid (0.256 g, 84%), 97% ee: $[\alpha]_D^{22} = -118.0$ (*c*1.0, $CHCl_3$) {lit.[8b] $[\alpha]_D^{24}$ (>99% ee, *c* 3.5, $CHCl_3$) = −122} ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.93 (1H, s, C*H*CN), 5.26 (1H, s, C*H*Ph_2), 7.22–7.42 (8H, m, Ar), 7.28 (2H, d, *J*=7.2 Hz, Ar), 7.60 (4H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.3, 65.8, 118.2, 127.2, 127.6, 127.7, 127.8, 128.0, 128.8, 128.9, 129.3, 130.4, 130.6, 132.8, 133.5, 140.7, 142.6.

4.3.4. (*S*)-Diphenylmethylamino-2-methylphenylacetonitrile. White solid (0.245 g, 84%), 98% ee: $[\alpha]_D^{24} = -161.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03 (1H, br, N*H*CH), 2.33 (3H, s, CH_3), 4.62 (1H, s, C*H*CN), 5.32 (1H, s, C*H*Ph_2), 7.22–7.36 (7H, m, Ar), 7.40 (2H, m, Ar), 7.48 (2H, d, *J*=7.2 Hz, Ar), 7.60 (3H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0, 50.4, 65.9, 118.9, 126.8, 127.1, 127.6, 127.7, 128.0, 128.2, 128.9, 129.0, 129.3, 131.2, 133.3, 136.6, 141.1, 142.9.

4.3.5. (*S*)-Diphenylmethylamino-2-methoxyphenylacetonitrile. White solid (0.253 g, 84%), 83% ee: $[\alpha]_D^{24} = -57.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.92 (3H, s, OCH_3), 4.71 (1H, s, C*H*CN), 5.23 (1H, s, C*H*Ph_2), 7.03 (2H, m, Ar), 7.28–7.43 (8H, m, Ar), 7.48 (2H, d, *J*=7.6 Hz, Ar), 7.56 (2H, d, *J*=7.6 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.6, 55.7, 65.4, 111.5, 119.2, 121.1, 123.5, 127.4, 127.6, 127.7, 127.8, 128.8, 128.9, 129.0, 130.7, 141.6, 143.0, 157.1.

4.3.6. (*S*)-Diphenylmethylamino-4-methoxyphenylacetonitrile. White solid (0.256 g, 85%), 91% ee; $[\alpha]_D^{24} = -38.0$ (*c* 1.0, $CHCl_3$) {lit.[8b] $[\alpha]_D^{22}$ (94% ee, *c* 0.54, $CHCl_3$) = −27.7}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.94 (1H, d, *J*=12.0 Hz, N*H*CH), 3.66 (3H, s, OCH_3), 4.39 (1H, d, *J*=12.0 Hz, C*H*CN), 5.06 (1H, s, C*H*Ph_2), 6.78 (2H, d, *J*=8.8 Hz, Ar) 7.02–7.22 (6H, m, Ar), 7.29 (4H, m, Ar), 7.40 (2H, d, *J*=7.6 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.9, 55.4, 65.6, 114.4, 119.1, 127.1, 127.2, 127.5, 127.7, 128.0, 128.6, 128.8, 129.1, 141.3, 142.9, 160.1.

4.3.7. (*R*)-Diphenylmethylamino-furan-2-ylacetonitrile. White solid (0.214 g, 82%), 91% ee: $[\alpha]_D^{21} = -25.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (1H, br, N*H*CH), 4.65 (1H, s, C*H*CN), 5.20 (1H, s, C*H*Ph_2), 6.42 (1H, dd, *J*=3.2, 2.0 Hz, C*H*-furan), 6.49 (1H, d, *J*=3.2 Hz, C*H*-furan), 7.24–7.42 (6H, m, Ar), 7.48 (3H, d, *J*=7.6 Hz, C*H*-furan and Ar), 7.55 (2H, d, *J*=7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.2, 65.2, 109.0, 110.7, 117.1, 127.3, 127.4, 127.9, 128.0, 128.9, 129.1, 140.9, 142.4. 143.7, 147.3.

4.3.8. (*R*)-Diphenylmethylamino-thiophen-2-ylacetonitrile. White solid (0.239 g, 83%), 98% ee: $[\alpha]_D^{24} = -76.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.22 (1H, d, *J*=12.0 Hz, N*H*CH), 4.62 (1H, d, *J*=12.0 Hz, C*H*CN), 5.08 (1H, s, C*H*Ph_2), 6.84 (1H, dd, *J*=5.2, 3.6 Hz, C*H*-thiophene), 7.05–7.28 (8H, m, C*H*-thiophene and Ar), 7.30 (2H, d, *J*=7.2 Hz, Ar), 7.40 (2H, d, *J*=7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.3, 65.5, 118.2, 126.2, 126.8, 127.0, 127.2, 127.4, 127.9, 128.2, 128.9, 129.2, 138.4, 140.9, 142.6.

4.3.9. (*S*)-Diphenylmethylamino-1-naphthylacetonitrile. White solid (0.316 g, 91%), >98% ee: $[\alpha]_D^{23} = -186.0$ (*c*1.0, $CHCl_3$) {lit.[8b] $[\alpha]_D^{22}$ (>99% ee, *c* 2.0, $CHCl_3$) = −182.2}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (1H, br, N*H*CH), 5.20 (1H, s, C*H*CN), 5.41 (1H, s, C*H*Ph_2), 7.21–7.60 (11H, m, Ar), 7.66 (2H, d, *J*=7.2 Hz, Ar), 7.82–7.91 (2H, m, Ar), 7.95 (2H, d, *J*=7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.5, 66.1, 118.9, 123.1, 125.3, 125.9, 126.3, 126.9, 127.0, 127.7, 128.1, 128.3, 128.7, 128.9, 129.0, 130.2, 130.4, 130.6, 134.0, 141.1, 142.6.

4.3.10. (*R*)-Diphenylmethylamino-1-naphthylacetonitrile [from (*R*)-1a ligand]. White solid (0.303 g, 87%), >98% ee: $[\alpha]_D^{23} = +185.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.20 (1H, br, N*H*CH), 5.20 (1H, s, C*H*CN), 5.40 (1H, s, C*H*Ph_2), 7.20–7.60 (11H, m, Ar), 7.64 (2H, d, *J*=7.2 Hz, Ar), 7.82–7.90 (2H, m, Ar), 7.95 (2H, d, *J*=7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.5, 66.1, 118.9, 123.2, 125.3, 125.9, 126.3, 126.9, 127.0, 127.7, 128.1, 128.3, 128.8, 128.9, 129.0, 130.2, 130.4, 130.7, 134.0, 141.1, 142.7.

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