Tetrahedron: *Asymmetry* 25 (2014) 554–562

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Enantioselective cyanosilylation of aldehydes catalyzed by novel camphor derived Schiff bases-titanium(IV) complexes

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ARTICLE INFO

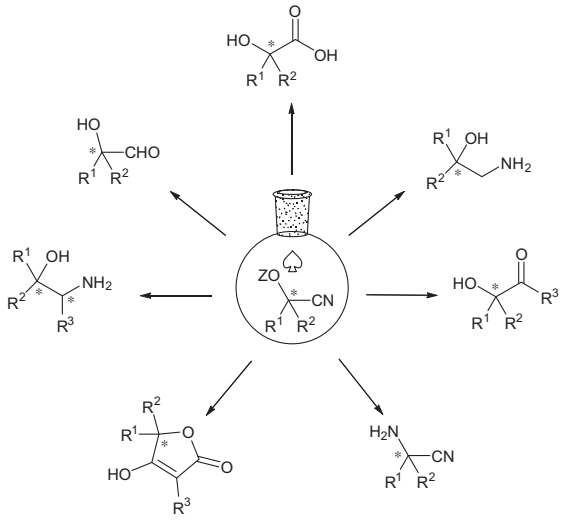
Article history:
Received 4 February 2014
Accepted 4 March 2014

ABSTRACT

Five tridentate Schiff bases have been prepared from (1*R*,2*S*,3*R*,4*S*)-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol and salicylaldehydes. X-ray structure investigation revealed differences in their molecular conformation, and their titanium(IV) complexes have been studied with NMR techniques. Among them the complex with the Schiff base obtained from 2-hydroxy-3-isopropylbenzaldehyde, is the most selective catalyst for the cyanosilylation of aliphatic, alicyclic, aromatic, and heteroaromatic aldehydes. The highest enantioselectivity, >99%, was achieved for the addition of trimethylsilyl cyanide to cinnamaldehyde.

1. Introduction

In recent years, interest in optically active cyanohydrin has increased significantly due to their easy conversion into a number of valuable functional groups (Scheme 1), and their utility in the synthesis of many natural products and biologically active compounds.[1] At present, the asymmetric cyanosilylation of aldehydes, catalyzed by metal complexes with chiral auxiliary ligands, followed by acidic hydrolysis, seems to be the best cyanohydrin synthesis.



Scheme 1. Various transformations of chiral cyanohydrins.

After the pioneering work by Hayashi and Oguni[2] on the catalytic enantioselective cyanosilylation of aldehydes using chiral Schiff base ligands and Ti(O-*i*-Pr)$_4$, various chiral catalytic systems have been developed. However, the enantioselective cyanosilylation of a broad range of substrates, including aliphatic aldehydes and ketones, with low catalyst loadings, under mild reaction conditions, is still a challenge. Extensive studies on these systems, employing a variety of Schiff bases derived from different chiral amino alcohols or diamine compounds, revealed that the enantioselective cyanosilylation of aldehydes is highly dependent on the type of Schiff base.[3]

Camphor derivatives are highly interesting ligands for asymmetric catalysts due to their rigid structure and defined configuration. Hence we decided to investigate camphor derived Schiff bases in the catalytic asymmetric cyanosilylation of aldehydes.[4,5]

2. Results and discussion

Enantiomerically pure amino alcohol (1*R*,2*S*,3*R*,4*S*)-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol **4**, was prepared in five steps, according to the literature.[6] The chiral Schiff bases **6a–e** were prepared from **4** by condensation with an appropriate commercially available aldehyde in toluene or methanol (Scheme 2).

Schiff bases **6a–c** were found to be efficient Ti(IV)—catalyst ligands in the enantioselective cyanosilylation of aldehydes with

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http://dx.doi.org/10.1016/j.tetasy.2014.03.001
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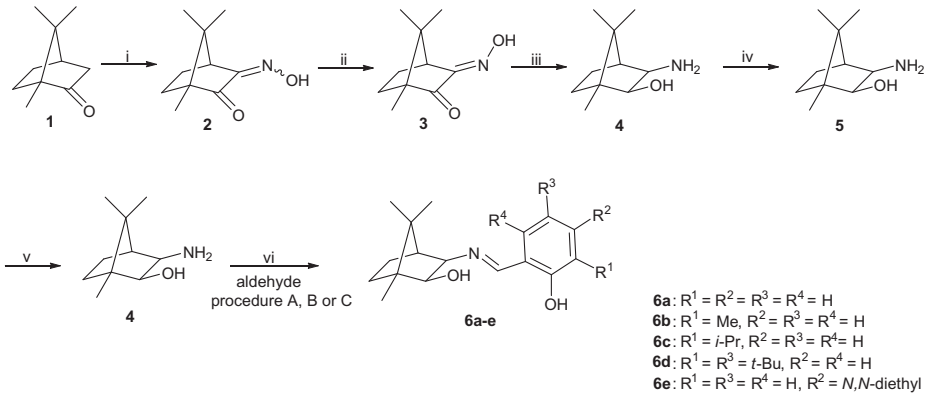

Scheme 2. Synthesis of (1*R*,2*S*,3*R*,4*S*)-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol.[4] Reagents and conditions: (i) (1) *t*-BuOK, 0 °C; (2) *i*-AmylONO, 0 °C, THF, 18 h; (ii) H_2O, reflux, 16 h; (iii) (1) $LiAlH_4$, 0 °C, 50 min, reflux, 24 h; (2) 10% $NaOH_{aq}$, H_2O, rt; (iv) (1) $(Cl_3CO)_2CO$, CH_2Cl_2, −5 °C, 1 h, rt, 2.5 h, (2) crystallization; (v) 3 M NaOH, EtOH/H_2O, reflux, 6 h; (vi) procedure A: *p*-TsOH, anhydrous $MgSO_4$, toluene, reflux, 24 h. Procedure B: Et_3N, anhydrous $MgSO_4$, MeOH, rt, 72 h. Procedure C: Et_3N, anhydrous $MgSO_4$, MeOH, rt, 96 h.

trimethylsilylcyanide (TMSCN). The reaction with benzaldehyde was optimized, by changing solvent, catalyst load, and temperature (Table 1). In all cases Ti(O-*i*-Pr)$_4$, was used as the pre-catalyst and the reaction time was 48 hours. The molar ratio ligand/Ti(O-*i*-Pr)$_4$, was 1:1.

When the reaction was carried out at −20 °C in toluene or THF, the enantiomeric excess was 7% ee and 19% ee, respectively. Using dichloromethane as the solvent, under the same conditions, the enantiomeric excess and yield increased significantly (65% ee, 80%), while at 0 °C the selectivity was lower (55% ee). Next, **6b**–**e** were examined in the enantioselective cyanosilylation of benzaldehydes under the above optimal conditions.

The results presented in Table 2 indicate the significant influence of the Schiff base structure on the reaction enantioselectivity. The presence of substituents R^1, R^2, and R^3, in the aromatic ring leads to increased steric hindrance, thus providing an opportunity to control the asymmetric induction. The relatively small steric hindrance of the methyl group in **6b** results in the same value of ee as for **6a**. Higher enantioselectivity was achieved for the isopropyl group in **6c** at the same position (81% ee), but the two *tert*-butyl groups in **6d** lead to a significant decrease of enantiomeric excess (27% ee). The *N*,*N*-diethyl substituent at the R^2 position gave the product with the lowest ee value.

The Ti(O-*i*-Pr)$_4$/**6c**, 1:1 molar ratio, catalytic system was used for the cyanosilylation of substituted aromatic, aliphatic, cyclic, and α,β-unsaturated aldehydes. The results are shown in Table 3.

Cyclic aliphatic aldehydes gave only slightly lower yields and ee values than the *para*-substituted aromatic aldehydes. High enantioselectivity was also obtained for the reaction with furan-2-carbaldehyde (91% ee).

The best results for the asymmetric cyanosilylation were obtained with cinnamaldehyde (entry 27); this prompted us to examine the effect of the catalyst load on the enantioselectivity. The results are shown in Table 4.

Table 2
The asymmetric addition of TMSCN to benzaldehyde catalyzed by Ti(O-*i*-Pr)$_4$/**6b**–**e** in dichloromethane

Ligand	Catalyst load (mol %)	Time (h)	Temperature (°C)	Yield[a] (%)	Ee[b] (%)/ config.[c]
6b	20	48	−20	80	65 (*S*)
6b	20	48	20	73	69 (*S*)
6c	20	48	−20	**86**	**81 (*S*)**
6c	20	48	20	59	32 (*S*)
6d	20	48	−20	79	27 (*S*)
6d	20	48	20	35	17 (*S*)
6e	20	48	−20	74	8 (*S*)

[a] Isolated by chromatography.
[b] Enantiomeric excesses were determined for acetyl derivatives by HPLC using a chiral OD-H column.
[c] Configurations were established by comparing the signs of the specific rotation with the literature data.[2]

Lowering the Ti(O-*i*-Pr)$_4$/**6c** load to 1 mol % did not affect the enantioselectivity of the reaction and only slightly decreased its yield.

2.1. Titanium(IV)/6c complex structure

Oguni[2] and Flores-Lopez[8] examined the cyanosilylation of aldehydes catalyzed by titanium tetraisopropoxide/chiral Schiff base complexes, in 1:1 and 1:2 molar ratios, and identified the catalytically active complex L*Ti(O-*i*-Pr)$_2$ and the inactive L$_2^*$Ti.

We have studied the reaction of **6c** with Ti(O-*i*-Pr)$_4$, and found a similarity with Flores-Lopez[8] results. Figure 1A shows the ^{13}C NMR spectrum of **6c**, and based on ^{13}C NMR, DEPT90, DEPT135, ^1H–^{13}C HMQC, and HMBC, the following signals were identified: at 167.91 ppm from the imine C–H carbon and at 159.91 ppm from the quaternary carbon atom coupled with the –OH of the aromatic

Table 1
The asymmetric addition of TMSCN to benzaldehyde catalyzed by Ti(O-*i*-Pr)$_4$/**6a**

Ligand	Catalyst load (% mol)	Time (h)	Temperature (°C)	Solvent	Yield[a] (%)	Ee[b] (%)/config.[c]
6a	20	48	−20	Toluene	68	7 (*S*)
6a	20	48	−20	THF	72	19 (*S*)
6a	20	48	−20	CH_2Cl_2	80	65 (*S*)
6a	20	48	0	CH_2Cl_2	83	55 (*S*)

[a] Product isolated by flash chromatography.
[b] Enantiomeric excesses were determined for acetyl derivatives by HPLC using an OD-H or OJ colum.
[c] Configurations were established by comparing the signs of specific rotation with literature data.[2]

Table 3
The asymmetric addition of TMSCN to aldehydes catalyzed by Ti(O-*i*-Pr)$_4$/**6c**

Entry	Aldehyde	Yield[a] (%)	ee[b] (%)	Configuration[c]
1	*o*-Methoxybenzaldehyde	17	13	(*S*)
2	*m*-Methoxybenzaldehyde	5	97	(*S*)
3	*p*-Methoxybenzaldehyde	91	98	(*R*)
4	*o*-Methylbenzaldehyde	2	87	(*S*)
5	*m*-Methylbenzaldehyde	3	49	(*R*)
6	*p*-Methylbenzaldehyde	7	80	(*R*)
7	*o*-Bromobenzaldehyde	48	34	(*S*)
8	*m*-Bromobenzaldehyde	88	*rac*	—
9	*P*-Bromobenzaldehyde	28	2	(*R*)
10	*o*-Chlorobenzaldehyde	72	59	(*S*)
11	*m*-Chlorobenzaldehyde	87	65	(*R*)
12	*p*-Chlorobenzaldehyde	55	62	(*R*)
13	*o*-Nitrobenzaldehyde	—	—	—
14	*m*-Nitrobenzaldehyde	76	61	(*S*)
15	*p*-Nitrobenzaldehyde	—	—	—
16	*o*-Fluorobenzaldehyde	24	15	(*S*)
17	*m*-Fluorobenzaldehyde	42	*rac*	—
18	*p*-Fluorobenzaldehyde	47	74	(*S*)
19	1-Naphthalenoaldehyde	83	83	(*S*)
20	2-Naphthalenoaldehyde	65	35	(*R*)
21	Furan-2-carbaldehyde	50	91	(*S*)
22	Cyclohexanecarbaldehyde	81	88	(*R*)
23	Cyclopentanecarbaldehyde	68	78	(*R*)
24	Butyraldehyde	10	98	(*S*)
25	Hexanal	49	49	(*S*)
26	Decanal	7	45	(*S*)
27	Cinnamaldehyde	93	>99	(*S*)

[b] Enantiomeric excesses were determined for the acetyl derivatives by HPLC using a Chiracel OD-H or OJ column or by GC using a capillary column β-dex (120 or 325).
[c] The absolute configuration was determined by comparing the sign of the specific rotation with literature data.[2,7]
[a] Isolated by flash chromatography.

Table 4
The asymmetric addition of TMSCN to cinnamaldehyde catalyzed by Ti(O-*i*-Pr)$_4$/**6c** after 48 h at −20 °C.

Entry	Catalyst load (mol %)	Yield[a] (%)	ee[b] (%)/config.[c]
1	20	93	>99 (*S*)
2	10	87	>99 (*S*)
3	5	70	>99 (*S*)
4	1	65	>99 (*S*)

[a] Isolated by flash chromatography.
[b] Enantiomeric excesses were determined for the acetyl derivatives by GC using a capillary column β-dex (325).
[c] Configurations were established by comparing the signs of specific rotations with literature data.[2]

ring. When equimolar amounts of titanium tetraisopropoxide and **6c** were combined, two titanium complexes, L*Ti(O-*i*-Pr)$_2$ and L$_2^*$Ti were observed (Fig. 1B). Signals at 165.05 and 162.73 ppm were assigned to the imine carbon atoms and signals at 163.85 and 161.93 ppm to the quaternary carbon atoms coupled with the –OH.

For **6c** and Ti(O-*i*-Pr)$_4$ in a 2:1 molar ratio, the ^{13}C NMR spectrum revealed only signals assigned to L$_2^*$Ti (Fig. 1C). A comparison of the spectra 1B and 1C proved that the in situ generated catalyst for the enantioselective cyanosilylation, prepared from an eqiumolar ratio of **6c** and Ti(O-*i*-Pr)$_4$, consisted of two titanium complexes, of which only one, L*Ti(O-*i*-Pr)$_2$, is catalytically active.

In the ^{1}H NMR spectrum of a 1:1 mixture of **6c** and Ti(O-*i*-Pr)$_4$, three signals appeared, which were assigned to aldimine protons at 8.50, 8.50, and 8.47 ppm in a 1:1:2 ratio. These signals come from the catalytically inactive forms of L$_2^*$Ti and active complex L*Ti(O-*i*-Pr)$_2$. The absence of a signal at 8.41 ppm indicates that all of **6c** has been consumed during the reaction (see Fig. 2).

The results are in agreement with Oguni's[2] results who found that ligands containing small substituents at the 3-position of the salicylaldehyde moiety did not exclusively form L*Ti(O-*i*-Pr)$_2$, but gave a mixture of products.

Formation of a certain amount of L$_2^*$Ti entails the presence of some quantity of unreacted Ti(O-*i*-Pr)$_4$, which is responsible for the formation of the racemic cyanosilylation product.

3. X-ray structures of Schiff bases 6a–c

3.1. Crystal structure of 6c

The configuration of the reported compound was (1*R*,2*S*,3*R*,4*S*) as determined by the Flack method, and corresponds to the (1*R*)-camphor derivative (Fig. 3). The electron density maps have revealed the presence of the H atom to be positioned between O2 and Schiff base N1, with the O2–H1O2 and N1–H1O2 distances of 1.268 and 1.396 Å, respectively. Such a proton shift is frequently observed for other Schiff bases with a hydroxyl group.

The valence geometry of the camphor and phenolic moieties is typical for such ring systems. The C2–O1 distance of 1.424(2) Å is typical. The phenolic C13–O2 distance is 1.343(2) Å. In the Schiff base, the distances between C3–N1 and N1–C11 are 1.461(2) and 1.283(2) Å, respectively, while the C3–N1–C11 angle is 119.83(17) deg. The presence of the intramolecular H-bond N1...O2 affects the position of the Schiff base moiety relative to the camphor ring system, which can be described with the C2–C3–N1–C11 torsion angle being 157.99(18) deg. The imine moiety is planar, with the torsion angle C3–N1–C11–C12 of 179.55(16) deg. The position of the camphor ring system relative to the imine moiety is indicated by the torsion angles N1–C11–C12–C13 and C11–C12–C13–O2 being 5.6(3) and −1.4(3) deg, respectively. The position of the isopropyl substituent is indicated by the torsion angles C13–C14–C18–C19 being −77.8(2) and C13–C14–C18–C20 of 157.49(19) deg. Analysis of the crystal packing revealed the presence of intermolecular interactions C17–H17A...O1[*x*,*y*,1+*z*] with the C...O distance being 3.449(3) Å.

3.2. Crystal structure of 6b

The absolute configuration of **6b** could not be reliably determined by the Flack method, but was assumed to be (1*R*,2*S*,3*R*,4*S*), since this was consistent with the chirality of the substrate (1*R*)-camphor (Fig. 4), and with **6a** and **6c**.

Contrary to the structure of **6c**, the electron density maps revealed that the H atom was localized on the phenolic O2, and no additional peak was positioned near the Schiff base N1. The resulting intramolecular O2...N1 interaction was formed with an O2...N1 distance of 2.5933(19) Å.

The valence geometry of the camphor and phenolic moieties is typical for such systems. The C2–O1 distance of 1.418(2) Å and the phenolic C13–O2 is 1.345(2) Å. In the imine moiety, the C3–N1 and N1–C11 distances are 1.443(2) and 1.268(2) Å, respectively, and are significantly different from those for **6c** mentioned above. These differences seem to reflect the differences in the imine bond order, since it is affected by the different proton location between the reported compounds. The C3–N1–C11 angle of 119.38(16) deg is almost identical to that reported for **6c**.

The O1–H camphor hydroxyl is involved in the intermolecular H-bond with the phenolic O2–H, with the O1...O2[1/2−*y*,1/2+*x*,1/4+*z*] of 3.055(2) Å. As a result, the position of the imine moiety relative to the camphor ring system is different to that of **6c**, with the C2–C3–N1–C11 torsion angle of 121.61(18) deg. The intramolecular distances N1...O1 and N1...O2 are 2.697(2) and 2.5933(19) Å, respectively. The C8 methyl group participates in

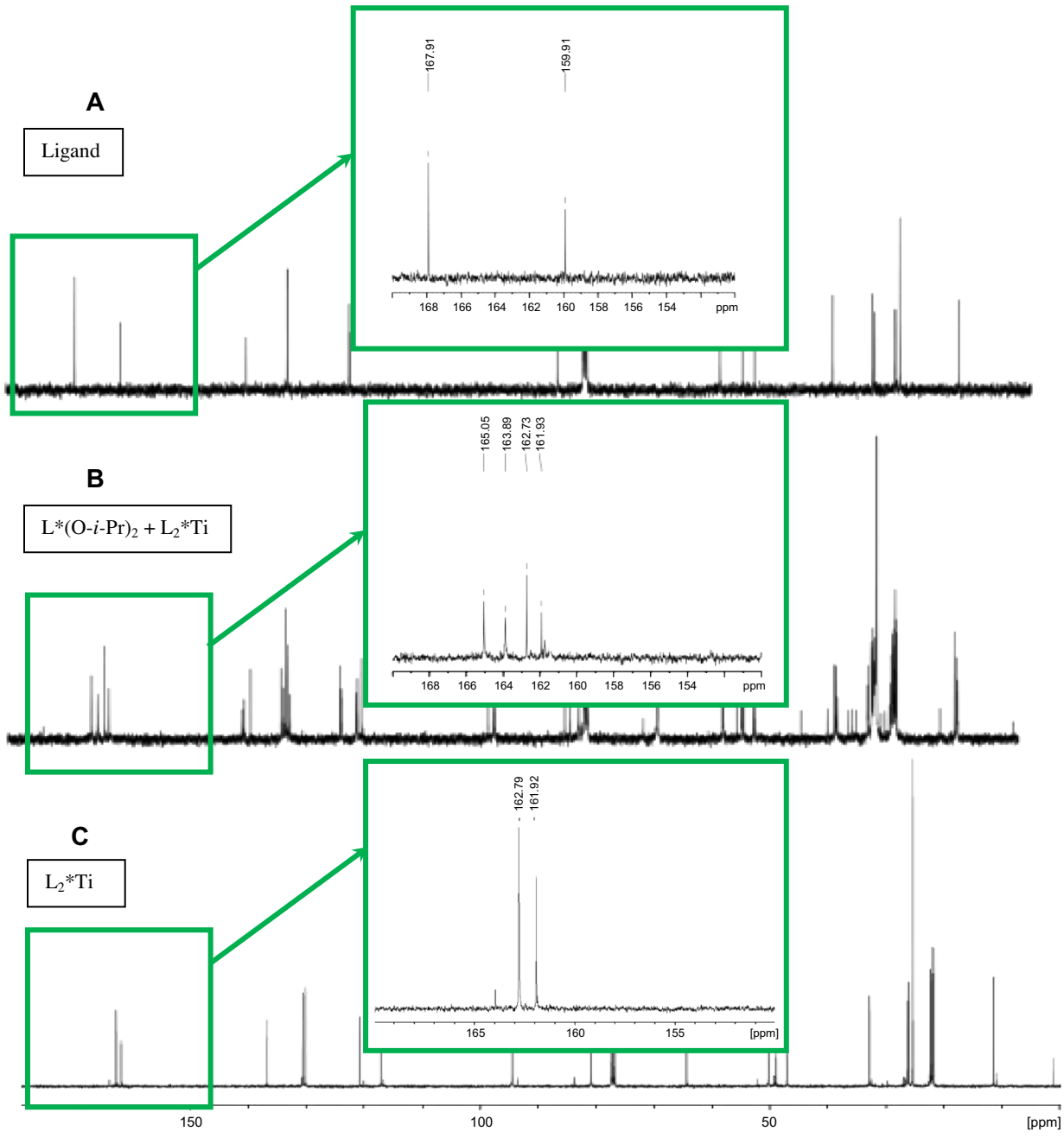

Figure 1. ^{13}C NMR spectra of **6c** and complex Ti(O-*i*-Pr)$_4$/**6c**.

intramolecular interactions with O1 and N1, the C8...O1 and C8...N1 distances of 3.014(3) and 3.080(3) Å, respectively, which are almost identical to those reported for **6c**.

The Schiff base moiety is planar, with the torsion angle C3–N1–C11–C12 of −178.54(17) deg. The intramolecular H-bond, with the O2–H...N1 results in the co-planar arrangement of the Schiff base and phenolic ring, with the torsion angles N1–C11–C12–C13 of 3.7(3) deg and C11–C12–C13–O2 of 1.7(3) deg.

3.3. Crystal structure of 6a

The absolute configuration of **6a** was assigned to be consistent with the substrate used and corresponds to (1*R*,2*S*,3*R*,4*S*).

The electron density maps for **6a** revealed two alternative positions for the H atom bonded to the phenolic O2 and the imine N1 (Fig. 5), with the assumed population 50/50%. The alternative intramolecular H-bonds are formed with the O2...N1 distance of 2.574(2) Å. In the monoclinic polymorph of the reported Schiff base[12] (CCDC-823886), the proton is bonded to the imine nitrogen.

The valence geometry of the camphor and phenolic moieties in the reported structure is typical for such systems. The C2–O1 distance of 1.415(2) Å and the phenolic C13–O2 is 1.344(2) Å. In the imine moiety, the distances of C3–N1 and N1–C11 are 1.453(2) and 1.274(2) Å, respectively. These values are between those found for **6c** with a proton located between O2 and N1, and **6b** where the O2–H hydroxyl is found, clearly indicating the contribution of imine protonation to the imine bond order. The C3–N1–C11 angle of 120.92(16) deg, is similar to the other structures reported herein. However in the monoclinic polymorph,[12] this angle is 123.76(19) deg, and the C17–O2 distance is 1.299(3) Å, which fur-

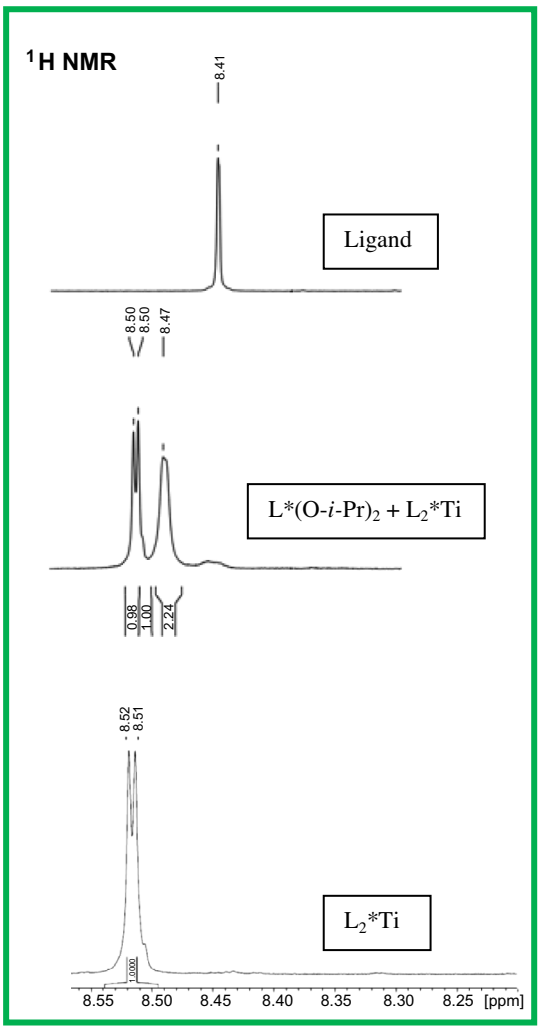

Figure 2. ^{1}H NMR spectra of **6c** and Ti(O-*i*-Pr)$_4$/**6c**.

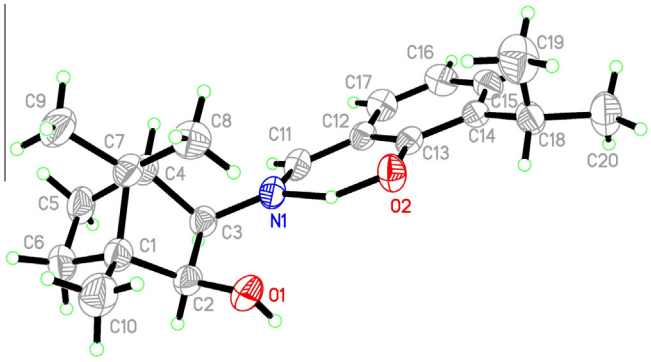

Figure 3. Asymmetric unit of the crystal structure of **6c** with the atom labeling scheme. Atomic ellipsoids are plotted at the 30% probability level (CCDC 987576).

ther emphasizes the differences related to the different protonation scheme.

The O1–H camphor hydroxyl is involved in an intermolecular H-bond O1–H1O1...O2[−*x*,1−*y*,*z*] to the phenolic O2–H group, with the O1...O2 distance being 3.239(2) Å. The position of the imine moiety relative to the camphor ring system is almost identical to that found for **6b** with a C2–C3–N1–C11 torsion angle of 122.97(18) deg, different from that found for **6c** (Fig. 6). The corresponding angle reported for the monoclinic polymorph[12] is

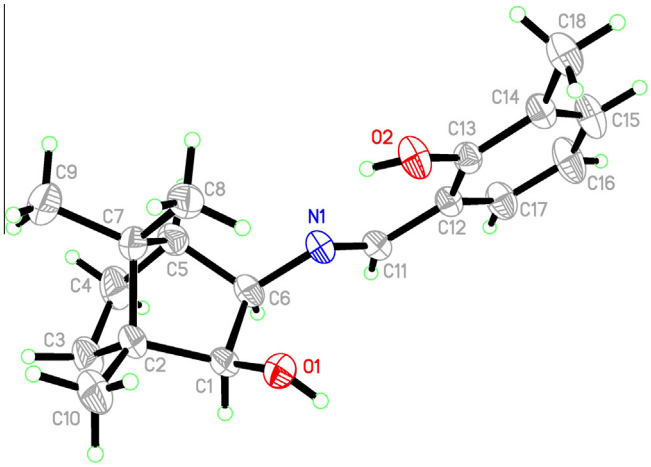

Figure 4. Asymmetric unit of the crystal structure of **6b** with the atom labeling scheme. Atomic ellipsoids are plotted at 30% probability level (CCDC 987577).

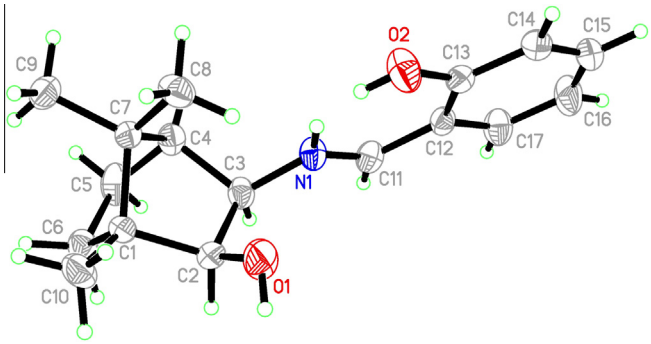

Figure 5. Asymmetric unit of the crystal structure of **6a** with the atom labeling scheme. Atomic ellipsoids are plotted at 30% probability level (CCDC 987578).

112.6(2) deg. The intramolecular distances N1...O1 and N1...O2 are 2.675(2) and 2.574(2) Å, respectively; these values are similar to those found for **6b**. The C8 methyl group participates in intramolecular interactions with O1 and N1, the C8...O1 and C8...N1 distances of 2.985(2) and 3.125(2) Å, respectively, which are almost identical to those found for other compounds reported herein.

The Schiff base moiety of **6a** is planar, with a torsion angle C3–N1–C11–C12 of −178.08(16) deg. As for the other structures reported herein, the co-planar arrangement of the Schiff base and phenolic ring was found, with the torsion angles N1–C11–C12–C13 of 2.2(3) deg and C11–C12–C13–O2 of −1.1(3) deg. The

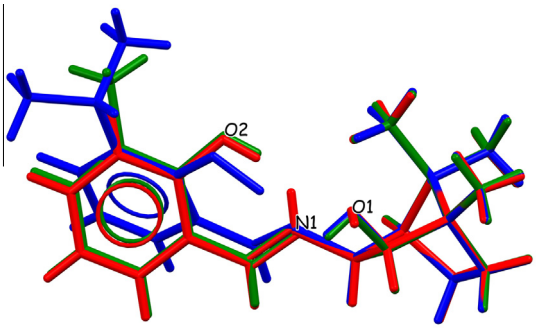

Figure 6. The superposition of **6c** (blue), **6b** (green) and **6a** (red) Schiff bases illustrates the differences in the molecular conformation. The least-squares fit was performed for the camphor ring non-hydrogen atoms.

conformation of the (1*R*)-camphor analogue[12] is similar, with the corresponding torsion angles being −0.8(3); 2.1(3) deg and −0.7(3); 4.9(3) for the molecules in the asymmetric unit.

Analysis of the crystal packing reveals C2–H2A...π[−*x*,1−*y*,*z*] and C5–H5A...π[−1/2−*x*,1/2+*y*,−1−*z*] interactions involving the phenolic C12–C17 ring, with distances between the respective H atom and the ring gravity center being 2.88 and 2.99 Å, and C–H...π angles of 164 and 142 deg.

4. Conclusion

In conclusion, a new class of camphor derived Schiff base ligands **6a–c** has been prepared and used for the titanium(IV) catalyzed asymmetric cyanosilylations of aldehydes. Two types of titanium complexes have been formed from the mixture Ti(O-*i*-Pr)$_4$/**6c**; the catalytically active **6c***Ti(O-*i*-Pr)$_2$ and inactive **6c**$_2^*$Ti, with their ratio depending on the starting mixture.

The best enantioselectivity (>99) was achieved for the addition of trimethylsilylcyanide to cinnamaldehyde catalyzed by **6c***Ti(O-*i*-Pr)$_2$, which was generated from the equimolar mixture Ti(O-*i*-Pr)$_4$/**6c** (1% mol). The selectivity decreased with other molar ratios of the mixture. Consequently, the catalyst activity depends on the ligand structure, the ratio of Ti(O-*i*-Pr)$_4$/ligand, and the reaction conditions.

5. Experimental

5.1. General

Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer and were measured as a HCB mull. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance III 400 MHz or Bruker Advance III 700 MHz instrument at ambient temperature. Chemical shifts in $CDCl_3$ are reported in the scale relative to $CHCl_3$ (7.26 ppm) for ^{1}H NMR and 77.0 ppm for ^{13}C NMR. GC was performed on a Perkin–Elmer AutoSystem XL chromatograph using B-Dex 125 capillary column (30 m, 0.25 mm). The enantiomeric excess was determined by HPLC analysis. HPLC analysis was performed on Shimadzu LC-10AT chromatograph using a Chiralcel OD-H column (250 × 4.6 mm). Optical rotations were measured using a PolAAr 3000 automatic polarimeter in a 10 cm cell at 589 nm. Melting points were determined with a Büchi SMP 32 and Barnstead-Thermolyne Mel-Temp II apparatus in open capillaries and are uncorrected. Elemental analyses were performed with an Elementary Analysensysteme GmbH VarioMACRO CHNanalyzer.

5.2. Materials

Experiments with air and moisture sensitive materials were carried out under a nitrogen atmosphere. Glassware was oven dried for several hours, assembled hot, and cooled in a stream of nitrogen. Silica gel 60, Merck (0.06–0.2 mm) was used for preparative column chromatography. Analytical TLC was performed using Macherey-Nagel Polygram Sil G/UV$_{254}$ 0.2 mm plates. Reagents were commercially available from Sigma–Aldrich and were used without further purification. Solvents were purchased from POCh Gliwice, Poland and Sigma–Aldrich. Toluene and THF were distilled from sodium benzophenone ketyl, dichloromethane was distilled from P_2O_5, diethyl ether was distilled from lithium aluminum hydride prior to use. 2-Hydroxy-3-methylbenzaldehyde, 3,5-di-*tert*-butyl-2-hydroxy benzaldehyde, 2-hydroxy-3-isopropylbenzaldehyde, 4-(diethylamino)-2-hydroxy benzaldehyde, and 2-hydroxy-3-isopropylbenzaldehyde were obtained according to the literature procedures.[9–11]

5.3. General procedure for Schiff base synthesis

5.3.1. Method A

An appropriate aldehyde (1 equiv) was added under a nitrogen atmosphere to a solution of (1*R*,2*S*,3*R*,4*S*)-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (1 equiv) in dry toluene, followed by catalytic amounts of *p*-toluenesulfonic acid and anhydrous magnesium sulfate. The mixture was stirred for 24 h at reflux. After cooling to room temperature, the mixture was filtered onto a celite pad of 1 cm thickness in a fritted glass funnel. The solvent was removed on a rotary evaporator. The crude product was purified by crystallization.

5.3.2. Method B

An appropriate aldehyde (1 equiv) was added under a nitrogen atmosphere to a solution of (1*R*,2*S*,3*R*,4*S*)-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (1 equiv) in methanol, followed by catalytic amounts of triethylamine and anhydrous magnesium sulfate. The mixture was stirred at room temperature for 72 h. The mixture was filtered onto a Celite pad of 1 cm thickness in a fritted glass funnel. The solvent was removed on a rotary evaporator. The crude product was purified by crystallization.

5.3.3. Method C

An appropriate aldehyde (1 equiv) was added under a nitrogen atmosphere to a solution of (1*R*,2*S*,3*R*,4*S*)-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (1 equiv) in methanol, followed by catalytic amounts of triethylamine and anhydrous magnesium sulfate. The mixture was stirred at room temperature for 96 h. The mixture was filtered onto a Celite pad of 1 cm thickness in a fritted glass funnel. The solvent was removed on a rotary evaporator. The crude product was purified by crystallization.

5.3.4. (1*R*,2*S*,3*R*,4*S*)-3-((*E*)-(2-Hydroxybenzylidene)amino)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol 6a[12]

Schiff base **6a** was prepared from 2-hydroxybenzaldehyde (0.5 g; 2.95 mmol) according to method A. The crude product was purified by crystallization from toluene, 0.65 g; 80%. Mp. 134–137 °C, $[\alpha]_D^{20} = +104.6$ (*c* 0.182, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.10–1.18 (m, 2H, CH_2), 1.29 (s, 3H, CH_3), 1.57–1.63 (m, 1H, CH), 1.81–1.85 (m, 2H, CH_2), 2.05 (br s, 1H, OH), 3.59 (d, *J* = 7.6 Hz, 1H, CH), 3.85 (d, *J* = 7.2 Hz, 1H, CH), 6.86–6.98 (m, 2H, 2× CH_{Ar}), 7.26–7.35 (m, 2H, 2× CH_{Ar}), 8.37 (s, 1H, (N)CH), 13.30 (br s, 1H, OH). ^{13}C NMR (700 MHz, $CDCl_3$): δ = 12.33 (CH_3), 22.53 (CH_3), 22.64 (CH_3), 27.48 (CH_2), 34.56 (CH_2), 48.24 (C), 50.30 (C), 54.28 (CH), 77.61 (CH), 82.78 (CH), 118.25 (CH), 119.52 (CH), 119.80 (C), 132.60 (CH), 133.67 (CH), 162.55 (C), 166.90 (CH). IR (HCB film) 3591.03, 2954.56, 2873.94, 1687.09, 1636.12, 1611.01, 1563.28, 1384.61 1170.06, 981.94, 941.76, 852.72, 824.35, 791.84, 655.75, 536.89 cm^{-1}, Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.77; H, 8.46; N: 5.14.

5.3.5. (1*R*,2*S*,3*R*,4*S*)-3-((*E*)-(2-Hydroxy-3-methylbenzylidene)amino)-1,7,7-trimethylbicyclo [2.2.1]heptan-2-ol 6b[12]

Compound **6b** was prepared from 2-hydroxy-3-methylbenzaldehyde (0.40 g; 2.95 mmol) according to method B. The crude product was purified by crystallization from methanol, 0.72 g; 86%. Mp. 138–141 °C, $[\alpha]_D^{20} = +95.4$ (*c* 0.268, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.10–1.22 (m, 2H, CH_2), 1.32 (s, 3H, CH_3), 1.57–1.65 (m, 1H, CH), 1.80–1.90 (m, 3H, CH_2, OH), 2.30 (s, 3H, CH_3), 3.60 (d, *J* = 7.6 Hz, 1H, CH), 3.84 (dd, *J* = 7.6 Hz, *J* = 2.4 Hz, 1H, CH), 6.81 (t, *J* = 7.6 Hz, 1H, CH_{Ar}), 7.13 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H, CH_{Ar}), 7.21 (dd, *J* = 7.6 Hz, *J* = 0.8 Hz, 1H, CH_{Ar}), 8.38 (s, 1H, (N)CH), 13.33 (br s, 1H, OH). ^{13}C NMR (700 MHz, $CDCl_3$): δ = 12.35 (CH_3), 16.56 (CH_3),

22.67 (2× CH_3), 27.52 (CH_2), 34.56 (CH_2), 48.22 (C), 50.30 (C), 54.30 (CH), 77.77 (CH), 82.80 (CH), 119.09 (C), 119.12 (CH), 127.15 (C), 130.29 (CH), 134.55 (CH), 160.64 (C), 167.21 (CH). IR (HCB film) 3518.20, 3187.67 2950.47, 2879.55, 2520.16, 1604.16, 1611.20, 1564.94, 1457.34, 1170.09, 1051.74, 955.73, 941.92, 853.43, 790.41, 746.85, 656.33, 525.99 cm^{-1}, Anal. Calcd. for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.31; H, 8.80; N: 4.88.

5.3.6. (1*R*,2*S*,3*R*,4*S*)-3-((*E*)-(2-Hydroxy-3-isopropylbenzylidene) amino)-1,7,7-trimethylbicyclo [2.2.1]heptan-2-ol 6c

Compound **6c** was prepared from 2-hydroxy-3-isopropylbenzaldehyde (0.48 g; 2.95 mmol) according to method B. The crude product was purified by crystallization from methanol, 0.83 g; 90%. Mp. 100–103 °C, $[\alpha]_D^{20} = +87.4$ (*c* 0.270, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.11–1.22 (m, 2H, CH_2), 1.26 (dd, *J* = 7.0 Hz, *J* = 2.8 Hz, 2H, CH_2), 1.31 (s, 6H, 2× CH_3), 1.37 (S, 3H, CH_3), 1.56–1.86 (m, 5H, 2× CH_2, OH), 3.43 (sep, *J* = 14.0 Hz, 1H, CH), 3.61 (d, *J* = 7.2 Hz, 1H, CH), 3.84 (d, *J* = 4.0 Hz, 1H, CH), 6.88 (t, *J* = 7.6 Hz, 1H, CH_{Ar}), 7.13 (dd, *J* = 7.6 Hz, *J* = 1.4 Hz, 1H, CH_{Ar}), 7.29 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H, CH_{Ar}), 8.41 (s, 1H, (N)CH), 13.29 (br s, 1H, OH). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 11.34 (CH_3), 21.68 (2× CH_3), 22.50 (CH_3), 22.56 (CH_3), 26.17 (CH), 26.54 (CH_2), 33.57 (CH_2), 47.22 (C), 49.31 (C), 53.31 (CH), 76.88 (CH), 81.80 (CH), 118.29 (C), 118.37 (CH), 129.17 (CH), 129.21 (CH), 136.50 (C), 158.57 (C), 166.52 (CH). IR (HCB film) 3378.15, 2956.27, 2879.55, 1686.90, 1628.93, 1610.96, 1560.19, 1439.36, 1384.61, 1403.62, 1261.53, 1170.27, 1095.91, 1046.15, 980.76, 941.63, 853.02, 824.35, 793.01, 749.65, 655.37, 495.10 cm^{-1}, Anal. Calcd. for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.34; H, 9.26; N: 4.34.

5.3.7. (1*R*,2*S*,3*R*,4*S*)-3-((*E*)-(3,5-Di-*tert*-butyl-2-hydroxybenzylidene) amino)-1,7,7-trimethylbicyc-lo[2.2.1]heptan-2-ol 6d[12]

Compound **6d** was prepared from 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (0.69 g; 2.95 mmol) according to method B. The crude product was purified by crystallization from methanol, 1.04 g; 95%. Mp. 82–85 °C, $[\alpha]_D^{20} = +68/2$ (*c* 0.290, MeOH). ^{1}H NMR (700 MHz, $CDCl_3$): δ = 0.91 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.13–1.21 (m, 2H, CH_2), 1.31 (s, 3H, CH_3), 1.34 (s, 9H, 3× CH_3), 1.47 (s, 9H, 3× CH_3), 1.59–1.63 (m, 1H, CH), 1.81–1.87 (m, 2H, CH_2), 1.96 (d, *J* = 5.6 Hz, 1H, OH), 3.62 (d, *J* = 7.7 Hz, 1H, CH), 3.84 (dd, *J* = 7.7 Hz, *J* = 4.9 Hz, 1H, CH), 7.14 (d, *J* = 2.8 Hz, 1H, CH_{Ar}), 7.43 (d, *J* = 2.8 Hz, 1H, CH_{Ar}), 8.45 (s, 1H, (N)CH), 13.18 (br s, 1H, OH). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 11.36 (CH_3), 21.66 (CH_3), 21.71 (CH_3), 26.57 (CH_2), 29.41 (3× CH_3), 31.49 (3× CH_3), 33.58 (CH_2), 34.14 (C), 35.08 (C), 47.18 (C), 49.31 (C), 53.35 (CH), 77.05 (CH), 81.71 (CH), 118.05 (C), 126.23 (CH), 127.27 (CH), 136.79 (C), 140.21 (C), 157.90 (C), 167.44 (CH), IR (HCB film) 3398.70, 2954.63, 2860.61, 1678.48, 1640.55, 1608.39, 1559.29, 1450.63, 1439.99, 1389.16, 1272.72, 1252.02, 1171.61, 1092.92, 1057.34, 976.50, 941.27, 854.75, 792.18, 656.65, 520.37 cm^{-1}, Anal. Calcd. for $C_{25}H_{39}NO_2$: C, 77.87; H, 10.19; N, 3.63. Found: C, 77.84; H, 10.16; N: 3.69.

5.3.8. (1*R*,2*S*,3*R*,4*S*)-3-((*E*)-(3-Diethylamino-2-hydroxybenzylidene)amino)-1,7,7-trimethylbicyclo [2.2.1]heptan-2-ol 6e

Compound **6e** was prepared from 2-hydroxy-3-*N*,*N*-diisopropylbenzaldehyde (0.57 g; 2.95 mmol) according to method B. The crude product was purified by crystallization from methanol, 0.60 g; 57%. Mp. 204–207 °C, $[\alpha]_D^{20} = +57.4$ (*c* 0.270, MeOH). ^{1}H NMR (700 MHz, $CDCl_3$): δ = 0.80 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.07–1.12 (m, 2H, CH_2), 1.21 (t, *J* = 7.0 Hz, 6H, 2× CH_3), 1.53–1.57 (m, 1H, CH), 1.76–1.79 (m, 2H, CH_2), 2.15 (br s, 1H, OH), 3.36–3.44 (m, 5H, CH, 2× CH_2), 3.88 (d, *J* = 7.0 Hz, 1H, CH), 6.03 (d, *J* = 2.1 Hz, 1H, CH_{Ar}), 6.12 (dd, *J* = 9.1 Hz, *J* = 2.8 Hz, 1H, CH_{Ar}), 6.90 (d, *J* = 2.1 Hz, 1H, CH_{Ar}), 7.66 (s, 1H, (N)CH), 13.40 (br s, 1H, OH). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 11.41 (CH_3), 12.79 (2× CH_3), 21.39 (CH_3), 21.67 (CH_3), 26.52 (CH_2), 33.54 (CH), 44.55 (2× CH_2), 47.14 (C), 59.14 (C), 53.10 (CH), 73.54 (CH), 80.83 (CH), 98.84 (CH), 103.44 (CH), 108.44 (C), 133.63 (CH), 152.43 (C), 162.95 (CH), 168.84 (C), IR (HCB film) 3294.11, 2924.36, 2857.14, 2717.08, 2358.54, 2252.10, 1686.71, 1608.39, 1559.59, 1496.50, 1345.45, 1166.43, 1132.86, 980.34, 937.06, 851.96, 792.47, 654.51, 542.65 cm^{-1}, Anal. Calcd. for $C_{21}H_{32}N_2O_2$: C, 73.22; H, 9.36; N, 8.13. Found: C, 73.18; H, 9.35; N: 8.14.

5.4. Typical procedure for the asymmetric trimethylsilylcyanation of aldehydes

At first, Ti(O-*i*-Pr)$_4$ (0.05 m; 0.18 mmol) was added to a solution of Schiff base (0.20 mmol) in dry dichloromethane (2.5 ml) and stirred at room temperature for 1 h under a nitrogen atmosphere. The mixture was then cooled to an adequate temperature and TMSCN (0.29 ml; 2.3 mmol) was added followed by the aldehyde (1.0 mmol). The mixture was stirred at the same temperature for 48 h and poured into a mixture of 1 M HCl (30 ml) and ethyl acetate (150 ml) and stirred vigorously for 12 h at rt. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 ml). The combined extracts were washed with saturated $NaHCO_3$ (4 × 50 ml) and brine (2 × 50 ml), dried over anhydrous sodium sulfate, and then evaporated. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 5:1 (v/v)). The pure cyanohydrin (1 equiv) was then converted directly into the corresponding acetate by reaction with acetyl chloride (0.09 ml), and pyridine (0.004 ml) in dry CH_2Cl_2 (4 ml) at room temperature under a nitrogen atmosphere for 1 hour. The reaction was quenched by water (5 ml) and extracted with CH_2Cl_2 (3 × 10 ml). The organic extracts were washed with brine (10 ml) and dried over anhydrous sodium sulfate. Evaporation of the solvents gave the corresponding acetate. The enantiomeric excess of the cyanohydrin acetate was determined by an HPLC or GC method.

5.5. Retention times for the cyanohydrins

5.5.1. 2-Hydroxy-2-phenylacetonitrile

HPLC conditions: Chiralcel OD-H (250 × 4.6 mm, 5 μm), *T* = 25 °C, eluent: hexane/*i*-PrOH (99:1), flow rate: 0.7 ml/min, detection: UV–vis, λ = 254 nm, t_R = 27.6 min (*R*), t_R = 35.8 min (*S*). $[\alpha]_D^{20} = -8.6$ (*c* 0.500, $CHCl_3$) for the (*S*)-enantiomer in 81% ee, {lit.[13] $[\alpha]_D^{24} = +36.8$ (*c* 2.0, $CHCl_3$) for the (*R*)-enantiomer in 85% ee}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.31 (br s, 1H, OH), 5.53 (s, 1H, CH(CN)), 7.31–7.43 (m, 5H, 5× CH_{Ar}).

5.5.2. 2-Hydroxy-2-(2-methoxyphenyl)acetonitrile

HPLC conditions: Chiralcel OD-H (250 × 4.6 mm, 5 μm), *T* = 25 °C, eluent: hexane/*i*-PrOH (99:1), flow rate: 0.7 ml/min, detection: UV–vis, λ = 220 nm, t_R = 19.3 min (*R*), t_R = 21.3 min (*S*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.68 (br s, 1H, OH), 3.86 (s, 3H, CH_3), 5.51 (s, 1H, CH(CN)), 6.90–7.23 (m, 4H, 4× CH_{Ar}).

5.5.3. 2-Hydroxy-2-(3-methoxyphenyl)acetonitrile

HPLC conditions: Chiralcel OD-J (250 × 4.6 mm, 5 μm), eluent: hexane/*i*-PrOH (90:10), flow rate: 1 ml/min, detection: UV–vis, λ = 220 nm, t_R = 24.5 min (*R*), t_R = 25.8 min (*S*), $[\alpha]_D^{20} = -10.2$ (*c* 0.69, $CHCl_3$) for the (*S*)-enantiomer in 97% ee, {lit.[13] $[\alpha]_D^{25} = -37.2$ (*c* 2.36, $CHCl_3$) for the (*S*)-enantiomer in 90% ee}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.68 (br s, 1H, OH), 3.83 (s, 3H, CH_3), 5.52 (s, 1H, CH(CN)), 6.90–7.30 (m, 4H, 4× CH_{Ar}).

5.5.4. 2-Hydroxy-2-(4-methoxyphenyl)acetonitrile

HPLC conditions: Chiralcel OD-J (250 × 4.6 mm, 5 μm), eluent: hexane/*i*-PrOH (90:10), flow rate: 1 ml/min, detection: UV–vis,

λ = 220 nm, t_R = 31.34 min (*R*), t_R = 37.11 min (*S*), $[\alpha]_D^{20} = +23.9$ (*c* 0.54, $CHCl_3$) for the (*R*)-enantiomer in 98% ee, {lit.[13] $[\alpha]_D^{25} = -44.8$ (*c* 1.30, $CHCl_3$) for the (*S*)-enantiomer in 93% ee}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.69 (br s, 1H, OH), 3.82 (s, 3H, CH_3), 5.51 (s, 1H, CH(CN)), 6.91 (d, *J* = 7.6 Hz, 2H, 2× CH_{Ar}), 7.26 (d, *J* = 7.6 Hz, 2H, 2× CH_{Ar}).

5.5.5. 2-Hydroxy-2-(2-methylphenyl)acetonitrile

HPLC conditions: Chiralcel OD-J (250 × 4.6 mm, 5 μm), eluent: hexane/*i*-PrOH (90:10), flow rate: 1 ml/min, detection: UV–vis, λ = 254 nm, t_R = 9.8 min (*R*), t_R = 11.4 min (*S*), $[\alpha]_D^{20} = -28.9$ (*c* 0.46, $CHCl_3$) for the (*S*)-enantiomer in 87% ee {lit.[14] $[\alpha]_D^{25} = -33.1$ (*c* 1.10, $CHCl_3$) for the (*S*)-enantiomer in 80% ee}. ^{1}H NMR (700 MHz, $CDCl_3$): δ = 2.50 (s, 3H, CH_3), 3.68 (br s, 1H, OH), 5.52 (s, 1H, CH(CN)), 7.22–7.41 (m, 4H, 4× CH_{Ar}).

5.5.6. 2-Hydroxy-2-(3-methylphenyl)acetonitrile

HPLC conditions: Chiralcel OD-J (250 × 4.6 mm, 5 μm), eluent: hexane/*i*-PrOH (95:5), flow rate: 1 ml/min, detection: UV–vis, λ = 220 nm, t_R = 33.7 min (*S*), t_R = 37.8 min (*R*), $[\alpha]_D^{20} = +8.9$ (*c* 0.54, $CHCl_3$) for the (*R*)-enantiomer in 49% ee, {lit.[13] $[\alpha]_D^{25} = -36.1$ (*c* 2.00, $CHCl_3$) for the (*S*)-enantiomer in 88% ee}. ^{1}H NMR (700 MHz, $CDCl_3$): δ = 2.46 (s, 3H, CH_3), 5.51 (s, 1H, CH(CN)), 7.17–7.52 (m, 4H, 4× CH_{Ar}), 7.61 (br s, 1H, OH).

5.5.7. 2-Hydroxy-2-(4-methylphenyl)acetonitrile

HPLC conditions: Chiralcel OD-J (250 × 4.6 mm, 5 μm), *T* = 25 °C, eluent: hexane/*i*-PrOH (90:10), flow rate: 1 ml/min, detection: UV–vis, λ = 254 nm, t_R = 15.0 min (*R*), t_R = 18.1 min (*S*), $[\alpha]_D^{20} = +11.5$ (*c* 0.60, $CHCl_3$) for the (*R*)-enantiomer in 80% ee, {lit.[13] $[\alpha]_D^{25} = -42.1$ (*c* 2.04, $CHCl_3$) for the (*S*)-enantiomer in 93% ee}. ^{1}H NMR (700 MHz, $CDCl_3$): δ = 2.49 (s, 3H, CH_3), 5.56 (s, 1H, CH(CN)), 7.18–7.29 (m, 4H, 4× CH_{Ar}), 11.87 (br s, 1H, OH).

5.5.8. 2-(2-Bromophenyl)-2-hydroxyacetonitrile

HPLC conditions: Chiralcel OD-H (250 × 4.6 mm, 5 μm), *T* = 25 °C, eluent: hexane/*i*-PrOH (90:10), flow rate: 0.7 ml/min, detection: UV–vis, λ = 215 nm, t_R = 9.9 min (*S*), t_R = 11.8 min (*R*), $[\alpha]_D^{20} = -1.2$ (*c* 0.98, $CHCl_3$) for the (*S*)-enantiomer in 34% ee. ^{1}H NMR (700 MHz, $CDCl_3$): δ = 5.56 (s, 1H, CH(CN)), 6.96 (br s, 1H, OH), 7.21–7.59 (m, 4H, 4× CH_{Ar}).

5.5.9. 2-(3-Bromophenyl)-2-hydroxyacetonitrile

HPLC conditions: Chiralcel OD-H (250 × 4.6 mm, 5 μm), *T* = 25 °C, eluent: hexane/*i*-PrOH (97:3), flow rate: 0.7 ml/min, detection: UV–vis, λ = 220 nm, t_R = 18.2 min (*S*), t_R = 20.9 min (*R*). ^{1}H NMR (700 MHz, $CDCl_3$): δ = 5.54 (s, 1H, CH(CN)), 7.31–7.56 (m, 4H, 4× CH_{Ar}), 7.81 (br s, 1H, OH).

5.5.10. 2-(4-Bromophenyl)-2-hydroxyacetonitrile

HPLC conditions: Chiralcel OD-H (250 × 4.6 mm, 5 μm), *T* = 25 °C, eluent: hexane/*i*-PrOH (90:10), flow rate: 0.7 ml/min, detection: UV–vis, λ = 220 nm, t_R = 13.3 min (*S*), t_R = 15.7 min (*R*), $[\alpha]_D^{20} = +1.7$ (*c* 0.92, $CHCl_3$) for the (*R*)-enantiomer in 28% ee. ^{1}H NMR (700 MHz, $CDCl_3$): δ = 3.69 (br s, 1H, OH), 5.56 (s, 1H, CH(CN)), 7.26–7.59 (m, 4H, 4× CH_{Ar}).

5.5.11. 2-(2-Chlorophenyl)-2-hydroxyacetonitrile

HPLC conditions: Chiralcel OD-J (250 × 4.6 mm, 5 μm), *T* = 25 °C, eluent: hexane/*i*-PrOH (95:5), flow rate: 1 ml/min, detection: UV–vis, λ = 254 nm, t_R = 22.4 min (*R*), t_R = 24.0 min (*S*), $[\alpha]_D^{20} = -1.0$ (*c* 0.98, $CHCl_3$) for the (*S*)-enantiomer in 59% ee, {lit.[13] $[\alpha]_D^{25} = -2.2$ (*c* 2.72, $CHCl_3$) for the (*S*)-enantiomer in 76% ee}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.70 (br s, 1H, OH), 5.59 (s, 1H, CH(CN)), 7.22–7.31 (m, 3H, 3× CH_{Ar}), 7.76 (d, *J* = 7.6 Hz, 1H, CH_{Ar}).

5.5.12. 2-(3-Chlorophenyl)-2-hydroxyacetonitrile

HPLC conditions: Chiralcel OD-H (250 × 4.6 mm, 5 μm), *T* = 25 °C, eluent: hexane/*i*-PrOH (95:5), flow rate: 1 ml/min, detection: UV–vis, λ = 254 nm, t_R = 34.9 min (*R*), t_R = 38.6 min (*S*), $[\alpha]_D^{20} = +15.5$ (*c* 0.51, $CHCl_3$) for the (*R*)-enantiomer in 65% ee, {lit.[13] $[\alpha]_D^{25} = -41.3$ (*c* 1.90, $CHCl_3$) for the (*S*)-enantiomer in 90% ee}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.68 (br s, 1H, OH), 5.56 (s, 1H, CH(CN)), 7.21–7.50 (m, 4H, 4× CH_{Ar}).

5.5.13. 2-(4-Chlorophenyl)-2-hydroxyacetonitrile

HPLC conditions: Chiralcel OD-J (250 × 4.6 mm, 5 μm), *T* = 25 °C, eluent: hexane/*i*-PrOH (95:5), flow rate: 1 ml/min, detection: UV–vis, λ = 254 nm, t_R = 24.3 min (*R*), t_R = 31.4 min (*S*), $[\alpha]_D^{20} = +14.8$ (*c* 0.79, $CHCl_3$) for the (*R*)-enantiomer in 62% ee, {lit.[13] $[\alpha]_D^{25} = -34.5$ (*c* 1.70, $CHCl_3$) for the (*S*)-enantiomer in 87% ee}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (br s, 1H, OH), 5.58 (s, 1H, CH(CN)), 7.28–7.40 (m, 4H, 4× CH_{Ar}).

5.5.14. 2-Hydroxy-2-(3-nitrophenyl)acetonitrile

HPLC conditions: Chiralcel OD-J (250 × 4.6 mm, 5 μm), *T* = 25 °C, eluent: hexane/*i*-PrOH (70:30), flow rate: 1 ml/min, detection: UV–vis, λ = 254 nm, t_R = 35.1 min (*S*), t_R = 43.7 min (*R*), $[\alpha]_D^{20} = -15.2$ (*c* 0.95, $CHCl_3$), the (*S*)-enantiomer in 61% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (br s, 1H, OH), 5.75 (s, 1H, CH(CN)), 7.80–8.70 (m, 4H, 4× CH_{Ar}).

5.5.15. 2-(2-Fluorophenyl)-2-hydroxyacetonitrile

HPLC conditions: Chiralcel OD-J (250 × 4.6 mm, 5 μm), *T* = 25 °C, eluent: hexane/*i*-PrOH (98:2), flow rate: 1 ml/min, detection: UV–vis, λ = 254 nm, t_R = 20.7 min (*R*), t_R = 22.5 min (*S*). ^{1}H NMR (700 MHz, $CDCl_3$): δ = 3.80 (br s, 1H, OH), 5.82 (s, 1H, CH(CN)), 7.15–7.67 (m, 4H, 4× CH_{Ar}).

5.5.16. 2-(3-Fluorophenyl)-2-hydroxyacetonitrile

HPLC conditions: Chiralcel OD-J (250 × 4.6 mm, 5 μm), *T* = 25 °C, eluent: hexane/*i*-PrOH (95:5), flow rate: 1 ml/min, detection: UV–vis, λ = 220 nm, t_R = 28.2 min (*R*), t_R = 31.0 min (*S*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (br s, 1H, OH), 5.56 (s, 1H, CH(CN)), 7.11–7.46 (m, 4H, 4× CH_{Ar}).

5.5.17. 2-(4-Fluorophenyl)-2-hydroxyacetonitrile

HPLC conditions: Chiralcel OD-H, eluent: hexane/*i*-PrOH (99:1), flow rate: 0.4 ml/min, detection: UV–vis, λ = 220 nm, t_R = 41.3 min (*R*), t_R = 43.4 min (*S*), $[\alpha]_D^{20} = -16.2$ (*c* 0.79, $CHCl_3$) for the (*S*)-enantiomer in 74% ee, {lit.[13] $[\alpha]_D^{25} = -33.6$ (*c* 1.62, $CHCl_3$) for the (*S*)-enantiomer in 92% ee}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.00 (br s, 1H, OH), 5.53 (s, 1H, CH(CN)), 7.10–7.15 (m, 2H, 2× CH_{Ar}), 7.48–7.52 (m, 2H, 2× CH_{Ar}).

5.5.18. 2-Hydroxy-2-(naphthalene-1-yl)acetonitrile

HPLC conditions: Chiralcel OD-J (250 × 4.6 mm, 5 μm), *T* = 25 °C, eluent: hexane/*i*-PrOH (95:5), flow rate: 0.4 ml/min, detection: UV–vis, λ = 220 nm t_R = 70.6 min (*S*), t_R = 77.6 min (*R*), $[\alpha]_D^{20} = -60.1$ (*c* 0.89, $CHCl_3$) for the (*S*)-enantiomer in 83% ee, {lit.[13] $[\alpha]_D^{25} = -67.4$ (*c* 1.00, $CHCl_3$) for the (*S*)-enantiomer in 82% ee}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.31 (br s, 1H, OH), 6.20 (s, 1H, CH(CN)), 7.51–7.61 (m, 3H, 3× CH_{Ar}), 7.85 (d, *J* = 7.2 Hz, 1H, CH_{Ar}), 7.93–7.97 (m, 2H, CH_{Ar}), 8.17 (d, *J* = 8.8 Hz, 1H, CH_{Ar}).

5.5.19. 2-Hydroxy-2-(naphthalene-2-yl)acetonitrile

HPLC conditions: Chiralcel OD-J (250 × 4.6 mm, 5 μm), *T* = 25 °C, eluent: hexane/*i*-PrOH (99:1), flow rate: 1 ml/min, detection: UV–vis, λ = 220 nm, t_R = 74.5 min (*S*), t_R = 81.1 min (*R*), $[\alpha]_D^{20} = +18.1$ (*c* 0.67, $CHCl_3$) for the (*R*)-enantiomer in 35% ee, {lit.[13] $[\alpha]_D^{25} = -29.1$ (*c* 1.00, $CHCl_3$) for the (*S*)-enantiomer in 75%

ee}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.86 (br s, 1H, OH), 5.56 (s, 1H, CH(CN)), 7.02–7.57 (m, 7H, 7× CH_{Ar}).

5.5.20. 2-(Furan-2-yl)-2-hydroxyacetonitrile

GC conditions: capillary column Supelco B-Dex 325 (30 m, 0.25 mm), isotherm T = 140 °C, gas flow: 35 cm/s, t_R = 5.35 min (*R*), t_R = 5.78 min (*S*), $[\alpha]_D^{20} = -14.7$ (*c* 0.35, $CHCl_3$) for the (*S*)-enantiomer in 91% ee, {lit.[13] $[\alpha]_D^{25} = -18.7$ (*c* 0.52, $CHCl_3$) for the (*S*)-enantiomer in 89% ee}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.60 (br s, 1H, OH), 5.79 (s, 1H, CH(CN)), 6.38–6.50 (m, 2H, 2× CH_{Ar}), 7.66 (d, J = 7.6 Hz, 1H, CH_{Ar}).

5.5.21. (*E*)-2-Hydroxy-4-phenylbut-3-enenitrile

GC conditions: capillary column Supelco B-Dex 325 (30 m, 0.25 mm), isotherm T = 130 °C, gas flow: 35 cm/s, t_R = 14.38 min (*R*), t_R = 17.97 min (*S*), $[\alpha]_D^{20} = -21.8$ (*c* 0.97, $CHCl_3$) for the (*S*)-enantiomer in 99% ee, {lit.[13] $[\alpha]_D^{25} = -27.3$ (*c* 2.68, $CHCl_3$) for the (*S*)-enantiomer in 82% ee}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (br s, 1H, OH), 4.92 (d, J = 7.6 Hz, 1H, CH(CN)), 6.25–6.31 (m, 1H, CH), 6.65 (d, J = 7.2 Hz, 1H, CH), 7.20–7.41 (m 5H, 5× CH_{Ar}).

5.5.22. 2-Cyclopentyl-2-hydroxyacetonitrile

GC conditions: capillary column Supelco B-Dex 325 (30 m, 0.25 mm), isotherm T = 130 °C gas flow: 35 cm/s, t_R = 32.1 min (*S*), t_R = 32.3 min (*R*), $[\alpha]_D^{20} = +3.1$ (*c* 0.470, $CHCl_3$), for the (*R*)-enantiomer in 78% ee, {lit.[15] $[\alpha]_D^{23} = -10.4$ (*c* 1.15, $CHCl_3$) for the (*S*)-enantiomer in 92% ee}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27–1.63 (m, 5H, 4× CH_2, CH), 3.81 (br s, 1H, OH), 4.21 (d, J = 7.6 Hz, 1H, CH(CN).

5.5.23. 2-Cyclohexyl-2-hydroxyacetonitiyle

GC conditions: capillary column Supelco B-Dex 325 (30 m, 0.25 mm), isotherm T = 150 °C, gas flow: 35 cm/s, t_R = 22.3 min (*S*), t_R = 22.8 min (*R*). $[\alpha]_D^{20} = +2.3$ (*c* 0.56, $CHCl_3$) for the (*R*)-enantiomer in 88% ee, {lit.[15] $[\alpha]_D^{25} = +8.2$ (*c* 2.00, $CHCl_3$) for the (*R*)-enantiomer in 90% ee}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27–1.59 (m, 6H, 5× CH_2, CH), 3.90 (br s, 1H, OH), 4.28 (d, J = 7.6 Hz, 1H, CH(CN)).

5.5.24. 2-Hydroxypentanonitrile

HPLC conditions: Chiralcel OD-J (250 × 4.6 mm, 5 μm), T = 25 °C, eluent: hexane/*i*-PrOH (95:5), flow rate: 1 ml/min, detection: UV–vis, λ = 220 nm, t_R = 23.1 min (*R*), t_R = 26.9 min (*S*), $[\alpha]_D^{20} = -21.8$ (*c* 0.970, $CHCl_3$) for the (*S*)-enantiomer in 98% ee, {lit.[13] $[\alpha]_D^{25} = +5.5$ (*c* 3.40, $CHCl_3$) for the (*R*)-enantiomer in 26% ee}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.6 Hz, 3H, CH_3), 1.30 (qw, J = 7.8 Hz, J = 4.6 Hz, J = 2.2 Hz, 2H, CH_2), 1.89 (q, J = 7.6 Hz, 2H, CH_2) 3.86 (br s, 1H, OH), 4.31 (t, J = 7.6 Hz, 1H, CH(CN)).

5.5.25. 2-Hydroxyheptanonitrile

GC conditions: capillary column Supelco β-Dex 120 (30 m, 0.25 mm), isotherm T = 90 °C, gas flow: 35 cm/s, t_R = 39.8 min (*R*), t_R = 40.3 min (*S*), $[\alpha]_D^{20} = -17.8$ ($CHCl_3$, *c* 0.77) for the (*S*)-enantiomer in 49% ee, {lit.[14] $[\alpha]_D^{25} = -13.2$ (*c* 0.40, $CHCl_3$) for the (*S*)-enantiomer in 57% ee}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, J = 7.6 Hz, 3H, CH_3), 1.22–1.36 (m, 6H, 3× CH_2), 1.82 (q, J = 7.7 Hz, 2H, CH_2), 3.88 (br s, 1H, OH), 4.29 (t, J = 7.6 Hz, 1H, CH(CN)).

5.5.26. 2-Hydroxyundecannitrile

HPLC conditions: Chiralcel OD-J (250 × 4.6 mm, 5 μm), T = 25 °C, eluent: hexane/*i*-PrOH (90:10), flow rate: 0.5 ml/min, detection: UV–vis, λ = 220 nm, t_R = 30.1 min (*R*), t_R = 34.1 min (*S*). $[\alpha]_D^{20} = -3.4$ (*c* 0.61, $CHCl_3$) for the (*S*)-enantiomer in 45% ee {lit.[13] $[\alpha]_D^{25} = +7.9$ (*c* 4.03, $CHCl_3$) for the (*R*)-enantiomer in 85% ee}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.8 Hz, 3H, CH_3), 1.22–1.33 (m, 14H, 7× CH_2), 1.86 (q, J = 7.6 Hz, 2H, CH_2), 3.61 (br s, 1H, OH), 4.26 (t, J = 7.6 Hz, 1H, CH(CN)).

5.6. Reaction of titanium(IV) isopropoxide with 1 or 2 equiv of ligand 6c (for NMR measurements)

5.6.1. Procedure for the titanium complex of a Schiff base in a 1:1 molar ratio

To the solution of orange ligand **4c** (0.0715 g, 0.2 mmol) in $CDCl_3$ (3.5 ml) at 20 °C, 1 equiv of Ti(O-*i*-Pr)$_4$ (0.0568 g, 0.06 ml, 0.2 mmol) was added. After stirring for 1 h the dark red solution was transferred into 5 mm NMR tube and the NMR spectrum was recorded on a 700 MHz Bruker Avance III spectrometer.

5.6.2. Procedure for the titanium complex of a Schiff base in a 1:2 molar ratio

To the solution of orange ligand **4c** (0.1430 g, 0.4 mmol) in $CDCl_3$ (3.5 ml) at 20 °C, 2 equiv of Ti(O-*i*-Pr)$_4$ (0.0568 g, 0.06 ml, 0.2 mmol) was added. After stirring for 1 h the dark red solution was transferred into 5 mm NMR tube and the NMR spectrum was recorded on a 700 MHz Bruker Avance III spectrometer.

5.6.3. Spectroscopic parameters

^{1}H NMR: spectrometer Bruker Avance III 400 MHz, f = 400 MHz, solvent: $CDCl_3$, programpulse: zg30, ns = 16, acquisition time: 3.99 s. ^{13}C NMR spectrometer Bruker Avance III 400 MHz, f_1 = 100 MHz (13C), f_2 = 400 MHz (^{1}H), solvent: $CDCl_3$, the program pulse: zgpg30, ns = 64, acquisition time: 1.30 s.

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