Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry 17 (2006) 151–160
Tetrahedron: Asymmetry

Parallel synthesis of modular chiral Schiff base ligands and evaluation in the titatium(IV) catalyzed asymmetric trimethylsilylcyanation of aldehydes

Belén Rodríguez,[a] Mireia Pastó,[a] Ciril Jimeno[b] and Miquel A. Pericàs[a,b,*]

[a]*Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans, 16, E-43007 Tarragona, Spain*
[b]*Parc Científic de Barcelona, Departament de Química Orgànica, Universitat de Barcelona, c/Martí i Franquès, 1-11, E-08028 Barcelona, Spain*

Received 10 November 2005; accepted 21 November 2005
Available online 9 January 2006

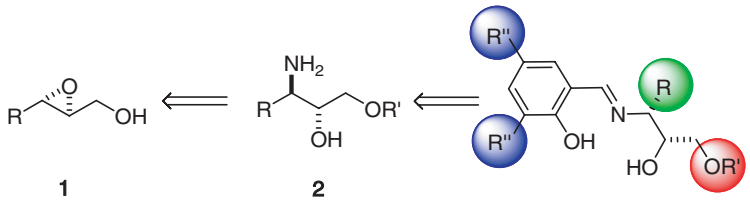
Abstract—Highly modular tridentate Schiff base ligands arising from enantiopure epoxyalcohols have been prepared and evaluated in catalysis using parallel methods. The key structural motifs and experimental parameters have been identified, allowing enantioselectivities of up to 77% ee in the titatium-catalyzed trimethylsilyl cyanide addition to aldehydes.

1. Introduction

Enantiomerically pure cyanohydrins are important intermediates for the preparation of a variety of biologically active compounds, since they can be easily converted into different functional groups.[1] For this reason, their preparation using catalytic asymmetric methods has received great attention and continued interest.[2] In particular, the combination of Schiff base ligands and Ti(IV) Lewis acids has proven to be among the most active and efficient catalytic systems available for the cyanation of aldehydes.[3]

In the context of our research project devoted to the synthesis of modular ligands for asymmetric catalysis from synthetic, yet enantiopure epoxides, and taking into account useful chiral catalysts that have been developed through the analysis of ligand libraries prepared by parallel methods,[4] we turned our attention to the preparation of modular Schiff base tridentate ligands arising from the condensation of salicylaldehydes with enantiopure amino alcohols. The amino alcohols would be prepared by regioselective and stereospecific ring-opening of enantiopure epoxyalcohols **1** with nitrogen nucleophiles (Scheme 1). These epoxyalcohols, in turn, are readily available through the catalytic asymmetric Sharpless epoxidation.[5]

Amino alcohols such as **2** have previously been prepared in our group and used as ligands for the enantioselective reduction of ketones with borane,[6] for the asymmetric Ru catalyzed hydrogen transfer to ketones,[7] and as starting materials for the preparation of C_2-symmetric bis(oxazolines) for asymmetric allylic alkylation.[8] It is



Scheme 1. Modular enantiopure Schiff base ligands from epoxyalcohols. In color, controllable sources of structural diversity.

* Corresponding author. Tel.: +34 977 920 211; fax: +34 977 920 222; e-mail: mapericas@iciq.es

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.11.022

noteworthy that there are three sources of structural diversity present in this type of ligands: (i) the protecting group of the primary alcohol in the starting epoxyalcohol (H, methyl, benzyl, benzhydryl, trityl, or Si^iPr_3), (ii) the substituents on the aromatic ring in the salicylaldehyde moiety (typically H or *tert*-butyl), and (iii) the nature of the substituent (phenyl or *n*-propyl) at C-3 in the epoxyalcohol hydrocarbon chain. The selected motifs cover a great range of steric and electronic characteristics.

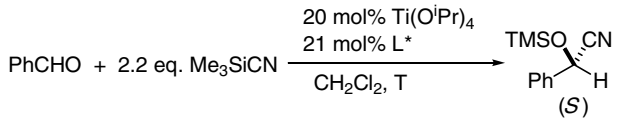
2. Results and discussion

In order to proceed with the synthesis of the target ligands, the initial ring opening of (2*S*,3*S*)-phenylglycidol and its O-protected derivatives[9] was carried out directly with aqueous ammonia in a sealed tube[10] (Scheme 2A). It should be noted, though, that the ring opening of (2*S*,3*S*)-3-(propyloxiran-2-yl)methanol under the aforementioned conditions was not successful: low conversions were recorded and the process was not regioselective. Therefore, the corresponding amino alcohols had to be synthesized using a somewhat lengthy approach through the intermediacy of azido alcohols: $Ti(N_3)_2(O^iPr)_2$ was the reagent of choice for the stereospecific and regioselectively ring opening,[11] and the intermediate azido alcohols were subsequently reduced with $LiAlH_4$ to afford the desired amino alcohols (Scheme 2B).

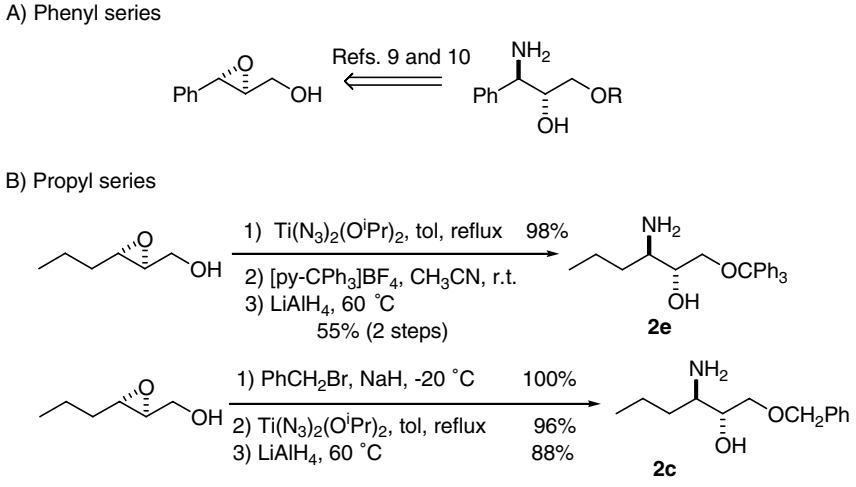
The order of the ring opening and primary alcohol protection steps was adapted so as to avoid interference with the functional groups that are already present in the substrate. Thus, the trityl group (triphenylmethyl) had to be introduced via selective alkylation of the primary alcohol in the corresponding azido diol, since no ring opening took place otherwise. On the other hand, the benzyl group was best introduced on a (2*S*,3*S*)-3-(propyloxiran-2-yl)methanol to ensure site selectivity. The corresponding ether was then submitted to ring opening with $Ti(N_3)_2(O^iPr)_2$. In any case, azide reduction with $LiAlH_4$ was the final step in the sequence, which allowed the isolation of the desired amino alcohols **2** in excellent overall yield.

A family of Schiff base ligands was then constructed by simple condensation reactions using parallel synthesis methods: an excess of aldehyde was used to ensure complete reaction of amino alcohols **2**, while the remaining unreacted aldehyde was scavenged with a polyamine resin HL in 'tea bags', so that not even solid phase extraction was necessary to isolate the ligands from the scavenger polymer. In this way, **3a**–**3f**, **4a**–**4f**, **5c**, **5e**, **6c**, and **6e** were isolated in quantitative yields with no need for any conventional purification step (Scheme 3).

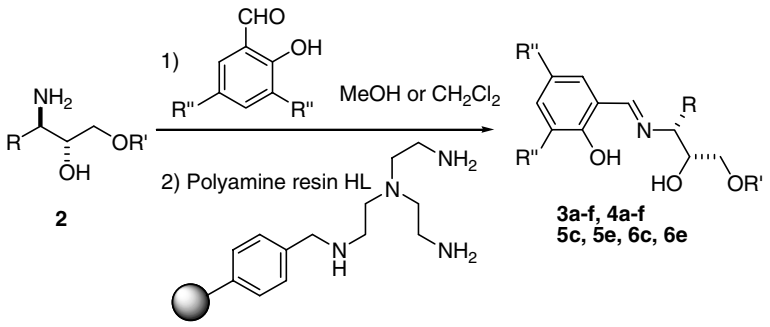
With these ligands in hand, their catalytic activity in the asymmetric cyanide addition to aldehydes was evaluated using parallel techniques in this case also. The experimental conditions originally developed by Oguni et al. were used while optimizing the reaction temperature.[12] Thus, 20 mol % of $Ti(O^iPr)_4$ and ligand were used to form in situ the active catalyst, and an excess (2.2 equiv) of TMSCN was added as a source of cyanide. High throughput sampling of the crude reaction mixtures containing benzaldehyde cyanohydrin (TMS-protected) and subsequent GC analysis with a chiral stationary phase (β-DEX column), allowed conversions and enantioselectivities to be determined simultaneously (Fig. 1). The absolute configuration of the cyanohydrins was determined to be *S* by comparison of the specific rotation using their acetyl derivatives, and comparison with literature data.[12]



As can be readily appreciated, ligands derived from (2*S*,3*S*)-3-(propyloxiran-2-yl)methanols **5**–**6** (R = *n*-propyl) exhibited poor catalytic activity and enantioselectivity. The best example in this series was ligand **5e**, which induced a modest 58% conversion and 64% ee at −80 °C. Ligands derived from (2*S*,3*S*)-phenylglycidol (**3**–**4**) seemed better suited for this particular reaction. Within these series, however, imines bearing an unprotected primary alcohol **3a** and **4a** or a very bulky Si^iPr_3 group **3f** and **4f** were still inefficient.



Scheme 2. Synthesis of the starting amino alcohols.



R=Ph, R''=H	R=Ph, R''=^{t}Bu	R=*n*-Pr
3a R'=H	**4a** R'=H	**5c** R'=CH_2Ph, R''=H
3b R'=Me	**4b** R'=Me	**5e** R'=CPh_3, R''=H
3c R'=CH_2Ph	**4c** R'=CH_2Ph	**6c** R'=CH_2Ph, R''=^{t}Bu
3d R'=$CHPh_2$	**4d** R'=$CHPh_2$	**6e** R'=CPh_3, R''=^{t}Bu
3e R'=CPh_3	**4e** R'=CPh_3	
3f R'=Si^{i}Pr$_3$	**4f** R'=Si^{i}Pr$_3$	

Scheme 3. Synthesis of Schiff base ligands **3a**–**3e**, **4a**–**4e**, **5c**, **5e**, **6c**, and **6e**.

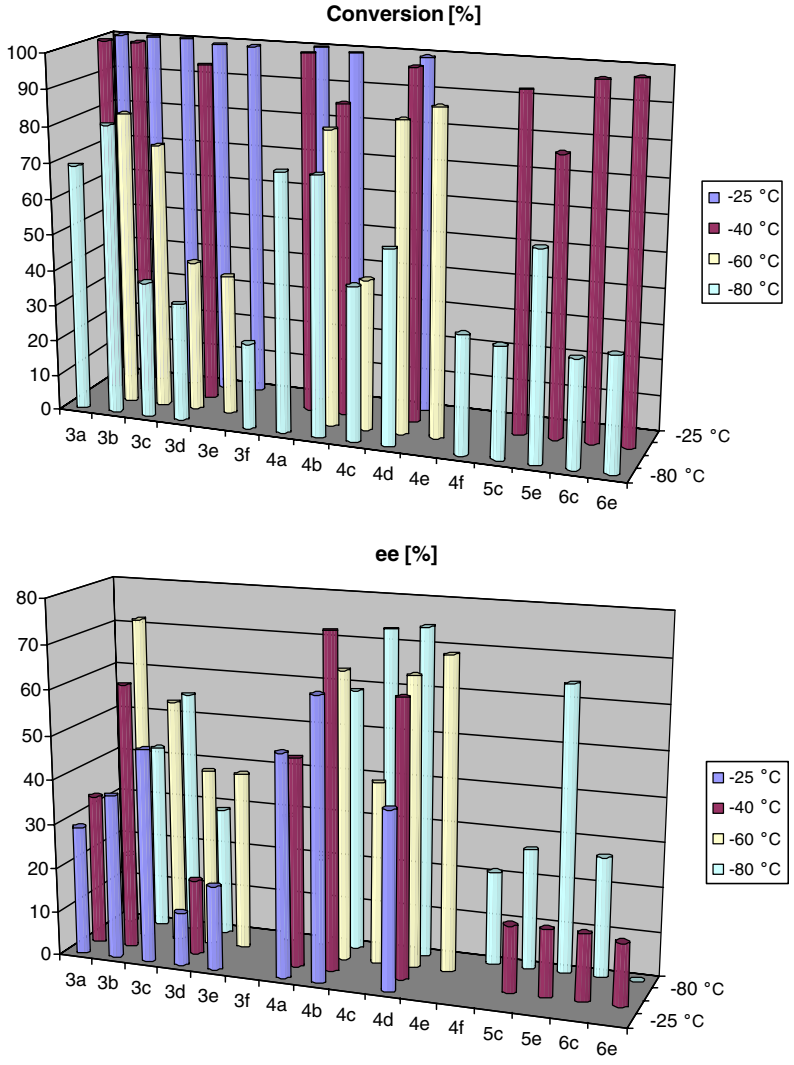


Figure 1. High throughput screening of modular Schiff base ligands at different temperatures in the cyanide addition to benzaldehyde. In all cases, the (*S*)-enantiomer predominates.

The most interesting results were recorded for the O-protected ligands **3b**–**3e** and **4b**–**4e**. Thus, under the optimal reaction temperature, good enantioselectivities, and high conversions were achieved. These results were highly dependent on the steric hindrance of the O-protecting group. In Figure 2, we have graphically represented these data.

It is clear from Figure 2 that, for the **3b**–**3e** series (containing salicylaldehyde as a building block), both the conversion and enantioselectivity decrease as the bulkiness of the O-protecting group increases from methyl to trityl. Thus, **3b** (R′ = Me) is the best catalyst in the series, affording 82% conversion and 73% ee in the asymmetric addition of trimethylsilylcyanide to benzaldehyde under optimal conditions (−60 °C, 3.5 days). In the case of the **4b**–**4e** series (containing the 3,5-di-*tert*-butylsalicylaldehyde moiety), higher conversions were recorded for ligands **4b** and **4e** (87% and 90%, respectively), whereas enantioselectivities in the range of 70–75% ee were observed in all cases. In terms of efficiency, ligand **4b** must be considered as the most suitable for this reaction within this series of ligands (87% conversion, 75% ee) at the optimal reaction temperature (−40 °C).

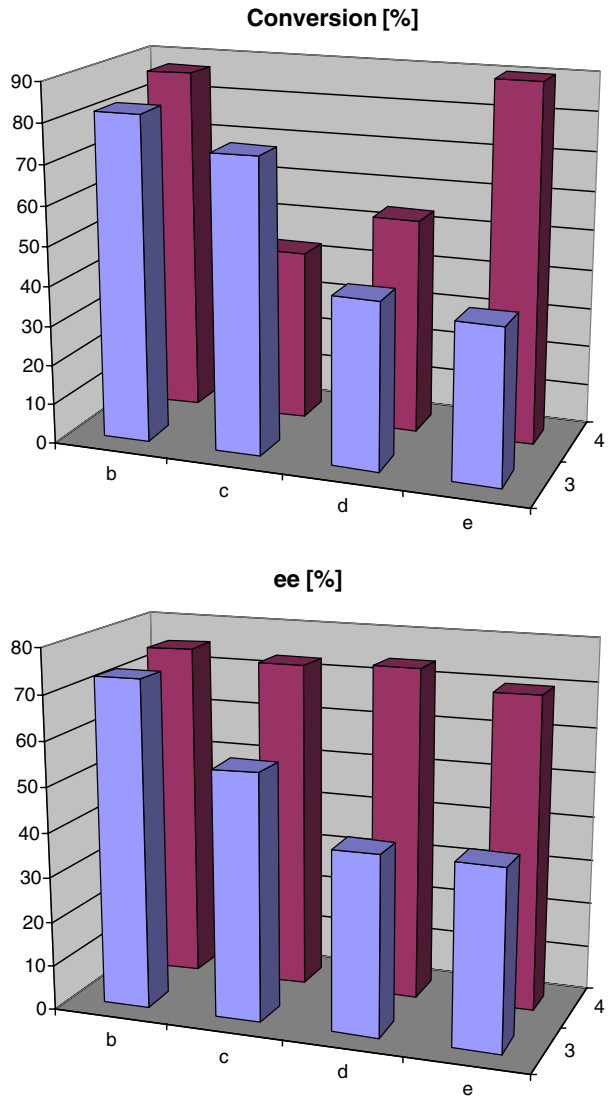


Figure 2. Optimized conversions and ees for ligands **3b**–**3e** and **4b**–**4e**. Ligands **3b**–**3e**: −60 °C, 3.5 days. Ligand **4b**: −40 °C, 4 days. Ligands **4c** and **4d**: −80 °C, 7 days. Ligand **4e**: −60 °C, 3.5 days. In all cases the *S* enantiomer predominates.

It is worth mentioning that both the best matches for the catalytic asymmetric cyanation of benzaldehyde (ligands **3b** and **4b**) present a very similar catalytic behavior regardless of the completely different steric hindrance at the salicylaldehyde moiety. This trend indicates that this part of the ligand does not affect either the catalyst structure or activity,[13] and that the enantioselective step (the cyanide addition) does not take place through the spatial region of the Ti(IV)–Schiff base complex occupied by this moiety. Conversely, it was suggested that the methoxy group in the ligand may play an important role in the activity of the catalyst. According to the model proposed by Oguni[12b] and more recent structural and mechanistic considerations,[14–16] it may be possible that an oxygen-assisted, intramolecular cyanide delivery to the coordinated aldehyde takes place.[16] In that case, the neighboring group participation of the methoxy group would help release the cyanide on the *Si* face of the titanium-coordinated aldehyde through hydrogen-bonding stabilization of the approaching hydrogen cyanide molecule (Fig. 3).

The aldehyde, in turn, would adopt the necessary *anti* coordination mode by steric repulsion minimization with the phenyl group of the amino alcohol. This model also justifies the small effect (if any) on the enantioselectivity of the bulky subtituents at the salicylaldehyde moiety.

To test the scope of its applicability, ligand **4b** was then used in the asymmetric cyanide addition to a representative family of aldehydes. Aromatic aldehydes with diverse substituents placed at different positions at the aromatic ring were tested, as well as some aliphatic aldehydes. Results are summarized in Table 1. Conversions were high in all cases, with the best enantioselectivities being recorded for the *o*-methyl and *o*-chloro derivatives and for benzaldehyde (73–77% ee; entries 1, 2, and 6). Good enantioselectivities (66–68% ee) were also obtained for the fluorine containing benzaldehydes (entries 8–10).

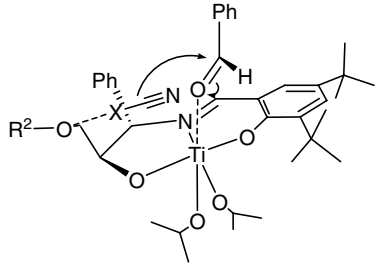
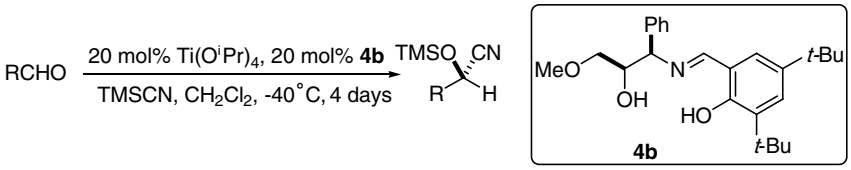
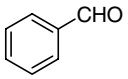
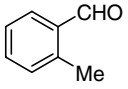
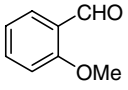
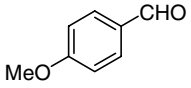
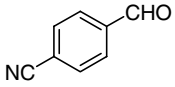
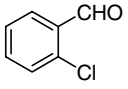
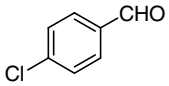
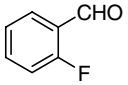
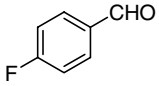
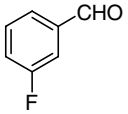
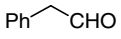
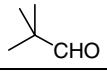


Figure 3. Model for the cyanide addition mediated by neighboring group participation. X = H or Me_3Si.

Table 1. Catalytic asymmetric addition of TMSCN to a family of aldehydes using ligand **4b**



Entry	RCHO	Conv (%)	ee (%)
1		87	75
2		100	73
3		100	52
4		96	48
5		98	40
6		98	77
7		99	53
8		100	68
9		99	66
10		100	68
11		97	67
12		77	28

For the rest of the aromatic aldehydes, enantioselectivities were in the range of 40–52% ee, while for the two aliphatic aldehydes tested, a reasonable 67% ee was recorded in the case of phenylacetaldehyde while only 28% ee was achieved for pivalaldehyde (entries 11 and 12).

3. Conclusion

In conclusion, a new family of modular tridentate chiral Schiff base ligands has been constructed and evaluated using parallel synthesis methods and high throughput screening. Enantioselectivities up to 77% have been achieved in the asymmetric cyanation of aldehydes catalyzed by Ti(O^{i}Pr)$_4$. Analysis of the results obtained with diversely substituted ligands allows the formulation of a working hypothesis on the mechanism of cyanide delivery. Research aimed at the synthesis and evaluation of a second generation of modular imines, characterized by increased basicity at the primary alcohol site and modified steric characteristics of the skeletal C-3 substituent is currently under way in our laboratory and will be reported in due course.

4. Experimental

4.1. General

Optical rotations were measured at 23 °C (concentration in g/100 mL). Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded as film between NaCl plates or by KBr pellet techniques. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution. Carbon multiplicities have been assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Elemental analyses were carried out by the Servei d'Anàlisis Elementals del CSIC de Barcelona. CH_2Cl_2 was distilled from CaH_2 and stored under N_2 prior to use. Toluene was distilled from Na wire and stored under N_2 prior to use. THF was freshly distilled from Na/benzophenone under N_2. All reagents were purchased from Aldrich or Acros, and used without purification unless otherwise stated. Polyamine resin HL was purchased from Novabiochem.

(2*S*,3*S*)-Phenylglycidol and (2*S*,3*S*)-3-(propyloxiran-2-yl)methanol are known compounds and were prepared according to the Sharpless epoxidation procedure.[5] Phenylglycidol ethers have been previously describe.[9] (2*S*,3*S*)-3-(Propyloxiran-2-yl)methanol *O*-benzyl ether was prepared according to the literature methods,[17] as well as (2*R*,3*R*)-3-azido-hexan-1,2-diol[11] and $Ti(N_3)_2(O^iPr)_2$.[18]

4.2. Synthesis of amino alcohol 2e

4.2.1. Attempted synthesis of 2e through a protection plus ring-opening strategy

4.2.1.1. Preparation of (2*S*,3*S*)-2-triphenylmethoxymethyl-3-propyloxirane. (2*S*,3*S*)-3-Propyl-2,3-epoxypropan-1-ol (0.49 g, 4.22 mmol) was dissolved in 8 mL of acetonitrile (HPLC grade) under an N_2 atmosphere. A solution of 2.10 g (5.13 mmol) of triphenylmethylpyridinium tetrafluoroborate in 2 mL of acetonitrile was the added via canula, and the resulting mixture stirred at room temperature for 72 h. Then, the reaction was quenched with 15 mL of diethyl ether and precipitates were removed by vacuum filtration. The crude product obtained after removal of the solvent was purified by flash chromatography on silica gel (2.5% Et_3N by volume) eluting with a mixture of hexane–ethyl acetate 98:2. The product was isolated as a colorless oil (0.71 g, 61% yield). $[\alpha]_D^{23} = -3.8$ (*c* 1.0, $CHCl_3$). IR (film, ν_{max}/cm^{-1}): 3058, 3023, 2959, 2930, 2871, 1491, 1448, 1220, 1074, 1032, 902, 763, 747. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (m, 3H), 1.40–1.58 (m, 4H), 2.80 (m, 1H), 2.92 (m, 1H), 3.14 (dd, $J = 10.6$ Hz, $J' = 5.4$ Hz, 1H), 3.25 (dd, $J = 10.6$ Hz, $J' = 3.4$ Hz, 1H), 7.20–7.32 (m, 9H), 7.44–7.47 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8 (CH_3), 18.9 (CH_2), 33.4 (CH_2), 55.8 (CH), 56.7 (CH), 64.3 (CH_2), 86.3 (C), 126.7 (CH), 127.5 (CH), 128.3 (CH), 143.6 (C) ppm. MS (CI, NH_3) *m*/*z*: 358 (1%, $C_{25}H_{26}O_2^+$), 243 (100%, CPh_3^+). HRMS (CI) calculated for $C_{25}H_{26}O_2$ (M^+): 358.1933. Found: 358.1928.

4.2.1.2. Attempted ring-opening of (2*S*,3*S*)-2-triphenylmethoxymethyl-3-propyloxirane. (2*S*,3*S*)-2-Triphenylmethoxiymethyl-3-propyloxirane (100 mg, 0.279 mmol) in 2 mL of toluene was added via canula to a hot suspension (75 °C) of 83 mg (0.330 mmol) of $Ti(N_3)_2(O^iPr)_2$ in 3 mL of toluene, prepared in a flame-dried flask under nitrogen. After 60 min, the reaction was allowed to cool down to rt, and the solvent removed under vacuum. The resulting mixture was treated with 10 mL of Et_2O and 4 mL of 5% aq H_2SO_4, and stirred until two clear phases separated. The aqueous phase was extracted with 3×10 mL of Et_2O, and the combined organic extracts dried over $MgSO_4$. The starting material was recovered in an almost quantitative yield.

4.2.2. Synthesis of 2e through a ring-opening plus protection strategy

4.2.2.1. Preparation of (2*R*,3*R*)-3-azido-1-triphenylmethoxyhexan-2-ol. (2*R*,3*R*)-3-Azidohexan-1,2-diol (330 mg, 2.09 mmol) was dissolved in 4 mL of acetonitrile (HPLC grade) under a nitrogen atmosphere. A solution of 1.00 g (2.44 mmol) of *N*-triphenylmethylpyridinium tetrafluoroborate in 2 mL of acetonitrile was then added via canula, and the resulting mixture stirred at rt for 4 days. The reaction was quenched with 10 mL of Et_2O and the precipitates removed by filtration. The solvents were then removed in vacuo, and the reaction crude purified by flash chromatography on silica gel (2.5% Et_3N by volume) eluting with mixtures of hexane–ethyl acetate 99:1–93:7. The tritylated azido alcohol was isolated (800 mg) as a colorless oil, and used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.0$ Hz, 3H), 1.22–1.55 (m, 4H), 2.65 (br s, 1H), 3.26–3.33 (m, 2H), 3.39 (m, 1H), 3.66 (m, 1H), 7.17–7.28 (m, 15H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7 (CH_3), 19.3 (CH_2), 31.8 (CH_2), 63.8 (CH), 64.2 (CH_2), 72.6 (CH), 87.0 (C), 127.1 (CH), 127.8 (CH), 128.5 (CH), 143.5 (C) ppm.

4.2.2.2. Preparation of (2*R*,3*R*)-3-amino-1-triphenylmethoxyhexan-2-ol, 2e. $LiAlH_4$ (260 mg, 6.51 mmol) was suspended in 10 mL of anhydrous THF in a flame-dried flask, under a nitrogen atmosphere. A solution of 800 mg (0.50 mmol) of (2*R*,3*R*)-3-azido-1-triphenylmethoxyhexan-2-ol in 10 mL of anhydrous THF was then added via canula, and the mixture heated at 65 °C for 4 h. The reaction was quenched and after applying the same work up and purification than in the previous recipe, 390 mg (55% yield for two steps-tritylation and reduction) of product were isolated as a colorless oil. $[\alpha]_D^{23} = -18.8$ (*c* 5.6, $CHCl_3$). IR (film, ν_{max}/cm^{-1}): 3370, 2958, 2930, 2872, 1491, 1449, 1477, 1033. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, $J = 7.0$ Hz, 3H), 1.05–1.45 (m, 4H), 2.85 (m, 1H), 3.16 (dd, $J = 9.6$ Hz, $J' = 6.0$ Hz, 1H), 3.34 (dd, $J = 9.6$ Hz, $J' = 4.0$ Hz, 1H), 3.59 (m, 1H), 7.47 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (CH_3), 19.4 (CH_2), 35.2 (CH_2), 53.3 (CH), 64.5 (CH_2), 73.1 (CH), 86.7 (C), 126.9 (CH), 127.7 (CH), 128.5 (CH), 143.8 (C) ppm. MS (CI, CH_4) *m*/*z*: 376 (1.3%, $C_{25}H_{29}NO_2{\cdot}H^+$), 243 (100%, CPh_3^+). HRMS (CI) calculated for $C_{25}H_{29}NO_2{\cdot}H^+$ (M^++1): 376.2277. Found: 376.2293.

4.3. Synthesis of amino alcohol 2c using a protection plus ring-opening strategy

4.3.1. Preparation of (2*R*,3*R*)-3-azido-1-benzyloxyhexan-2-ol. (2*S*,3*S*)-2-Benzyloximethyl-3-propyloxirane (220 mg, 1.10 mmol) in 5.5 mL of toluene was added via canula to a hot suspension (75 °C) of 310 mg (1.20 mmol) of $Ti(N_3)_2(O^iPr)_2$ in 10 mL of toluene, prepared in a flame-dried flask under nitrogen. After 60 min, the reaction was allowed to cool down to rt, and the solvent removed under vacuum. The resulting mixture was treated with 20 mL of Et_2O and 8 mL of 5% aq H_2SO_4, and stirred until two clear phases separated. The aqueous phase was extracted with 3×10 mL of Et_2O and the combined organic extracts dried over $MgSO_4$. The product was isolated after removal of the volatiles in 96% yield (260 mg), and used in the next step without further purification. $[\alpha]_D^{23} = +3.2$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, $J = 7.0$ Hz, 3H), 1.67–1.32 (m, 4H), 2.57 (br s, 1H), 3.44 (m, 1H), 3.57 (dd, $J = 9.6$ Hz, $J' = 6.4$ Hz, 1H), 3.61 (dd, $J = 9.6$ Hz, $J' = 3.6$ Hz, 1H), 3.75 (m, 1H), 4.56 (d, $J = 11.8$ Hz, 1H), 4.60 (d, $J = 11.8$ Hz, 1H), 7.30–7.40 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7 (CH_3), 19.4 (CH_2), 32.3 (CH_2), 63.9 (CH), 70.8 (CH_2), 72.4 (CH), 73.1 (CH_2), 127.75 (CH), 127.82 (CH), 128.4 (CH), 137.5 (C) ppm.

4.3.2. Preparation of (2*R*,3*R*)-3-amino-1-benzyloxyhexan-2-ol, 2c. $LiAlH_4$ (33 mg, 0.83 mmol) was suspended in 6 mL of anhydrous THF in a flame-dried flask, under nitrogen atmosphere. A solution of 124 mg (0.50 mmol) of (2*R*,3*R*)-3-azido-1-benzyloxihexan-2-ol in 6 mL of THF was slowly added via canula, and the reaction was heated to 60 °C for 1 h. After cooling to rt, 1.5 mL of methanol and 2 mL of water were successively added dropwise to quench the reaction. After diluting with more water, the mixture was extracted with CH_2Cl_2 (3×10 mL), and the combined organic extracts dried over $MgSO_4$, and the solvents removed in vacuo. The crude was purified by flash chromatography on silica gel (2.5% Et_3N by volume) eluting with mixtures of CH_2Cl_2–MeOH 97:3 to afford 98 mg (88% yield) of the desired product. $[\alpha]_D^{23} = -11.5$ (*c* 4.1, $CHCl_3$). IR (film, ν_{max}/cm^{-1}): 3362, 2957, 2929, 2870, 1587, 1496, 1454, 1364, 1101, 738. ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, $J =$ 6.8 Hz, 3H), 1.20–1.55 (m, 4H), 1.90 (br s, 3H), 2.91 (m, 1H), 3.55–3.65 (m, 2H), 3.68 (m, 1H), 4.55 (s, 2H), 7.29–7.36 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (CH_3), 19.4 (CH_2), 35.0 (CH_2), 53.3 (CH), 71.4 (CH_2), 72.8 (CH), 73.3 (CH_2), 127.6 (CH), 128.3 (CH), 137.9 (C) ppm. MS (CI, CH_4) *m*/*z*: 224 (100%, $C_{13}H_{21}NO_2{\cdot}H^+$). HRMS (CI) calculated for $C_{13}H_{21}NO_2{\cdot}H^+$ (M^++1): 224.1651. Found: 224.1652.

4.4. General method for the preparation of chiral Schiff base ligands

Amino alcohol (1 mmol) and aldehyde (1.1 mmol) were mixed in 5 mL of MeOH with Na_2SO_4 and stirred at reflux for 4–80 h. After cooling to rt, the reaction was filtered through a pack of Celite® and the solvent was removed in vacuo. Excess aldehyde was then removed by redisolving the crude in 5 mL of CH_2Cl_2 and scavenging it with 250 mg of polyamine resin HL (Novabiochem®) in tea bags. Isolated yields were $\geqslant$95% in all cases.

4.4.1. (2*R*,3*R*)-3-(*N*-Salicyliden)-amino-3-phenylpropan-1,2-diol, 3a. $[\alpha]_D^{23} = +111.4$ (*c* 1.0, $CHCl_3$). Mp 88–91 °C. IR (film, ν_{max}/cm^{-1}): 3400, 3058, 3026, 2926, 2877, 1628, 1581, 1494, 1453, 1277, 1051, 757. ^1H NMR (400 MHz, $CDCl_3$): δ 3.50 (dd, $J = 11.3$ Hz, $J' = 6.2$ Hz, 1H), 3.62 (d, $J = 11.1$ Hz, 1H), 4.00 (m, 1H), 4.39 (d, $J = 6.6$ Hz, 1H), 6.82 (dd, $J = 7.4$ Hz, $J' = 7.4$ Hz, 1H), 6.91 (d, $J = 8.3$ Hz, 1H), 7.16 (d, $J = 7.6$ Hz, 1H), 7.32–7.32 (m, 6H), 8.28 (s, 1H), 12.90–13.80 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.6 (CH_2), 75.0 (CH), 75.1 (CH), 117.0 (CH), 118.5 (C), 118.7 (CH), 127.5 (CH), 127.7 (CH), 128.7 (CH), 131.8 (CH), 132.7 (CH), 139.4 (C), 161.2 (C), 166.2 (CH). MS (CI, CH_4) *m*/*z*: 272 (100%, $C_{16}H_{17}NO_3{\cdot}H^+$). HRMS (CI) calculated for $C_{16}H_{17}NO_3{\cdot}H^+$ (M^++1): 272.1287. Found: 272.1292.

4.4.2. (1*R*,2*R*)-1-(*N*-Salicyliden)-amino-1-phenyl-3-methoxypropan-2-ol, 3b. $[\alpha]_D^{23} = +114.9$ (*c* 1.0, $CHCl_3$). Mp 103–107 °C. IR (film, ν_{max}/cm^{-1}): 3450, 3062, 2929, 2829, 2850, 1629, 1578, 1495, 1457, 1277, 1147, 762. ^1H NMR (400 MHz, $CDCl_3$): δ 13.60–12.90 (br s, 1H), 8.43 (s, 1H), 7.43–7.25 (m, 7H), 6.98 (d, $J = 8.4$ Hz, 1H), 6.88 (ddd, $J = 7.5$ Hz, $J' = 7.5$ Hz, $J'' = 0.9$ Hz, 1H), 4.53 (d, $J = 6.4$ Hz, 1H), 4.20 (ddd, $J = 6.4$ Hz, $J' = 6.3$ Hz, $J'' = 3.1$ Hz, 1H), 3.52 (dd, $J = 9.8$ Hz, $J' = 3.1$ Hz, 1H), 3.46 (dd, $J = 9.8$, $J' = 6.3$ Hz, 1H), 3.34 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3 (CH), 161.0 (C), 139.5 (C), 132.7 (CH), 131.7 (CH), 128.8 (CH), 127.8 (CH), 127.5 (CH), 118.8 (C), 116.9 (CH), 75.4 (CH), 73.9 (CH), 72.6 (CH_2), 59.1 (CH_3) ppm. MS (CI, NH_3) *m*/*z*: 286 (100%, $C_{17}H_{19}NO_3{\cdot}H^+$). HRMS (CI) calculated for $C_{17}H_{19}NO_3{\cdot}H^+$ (M^++1): 286.1443. Found: 286.1431.

4.4.3. (1*R*,2*R*)-1-(*N*-Salicyliden)-amino-3-benzyloxy-1-phenylpropan-2-ol, 3c. $[\alpha]_D^{23} = +53.3$ (*c* 0.8, $CHCl_3$). IR (film, ν_{max}/cm^{-1}): 3490, 3062, 3031, 2947, 2865, 1630, 1582, 1495, 1455, 1279, 1117, 756. ^1H NMR (400 MHz, $CDCl_3$): δ 3.58 (dd, $J = 9.8$ Hz, $J' = 5.9$ Hz, 1H), 3.63 (dd, $J = 9.8$, $J'' = 3.2$ Hz, 1H), 4.36 (m, 1H), 4.51 (m, 3H), 6.88 (ddd, $J = 7.5$ Hz, $J' = 7.4$ Hz, $J'' = 1.0$ Hz, 1H), 6.97 (d, $J = 8.2$ Hz, 1H), 7.22–7.42 (m, 12H), 8.39 (s, 1H), 13.25 (br s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 70.4 (CH_2), 73.5 (CH_2), 73.9 (CH), 75.4 (CH), 116.9 (CH), 118.7 (C), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.3 (CH), 128.7 (CH), 131.7 (CH), 132.6 (CH), 137.6 (C), 139.5 (C), 160.9 (C), 166.1 (CH) ppm. MS (CI, NH_3) *m*/*z*: 362 (23%, $C_{23}H_{23}NO_3{\cdot}H^+$), 361 (100%, $C_{23}H_{23}NO_3^+$). HRMS (CI) calculated for $C_{23}H_{23}NO_3{\cdot}H^+$ (M^++1): 362.1756. Found: 362.1751.

4.4.4. (1*R*,2*R*)-1-(*N*-Salicyliden)-amino-1-phenyl-3-diphenylmethoxypropan-2-ol, 3d. $[\alpha]_D^{23} = +29.4$ (*c* 1.0, $CHCl_3$). IR (film, ν_{max}/cm^{-1}): 3568, 3460, 3061, 3028,

2918, 2868, 1629, 1581, 1494, 1453, 1278, 757. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (br s, 1H), 3.57 (dd, $J = 9.9$ Hz, $J' = 5.4$ Hz, 1H), 3.63 (dd, $J = 9.9$ Hz, $J' = 3.3$ Hz, 1H), 4.25 (m, 1H), 4.55 (d, $J = 7.1$ Hz, 1H), 5.33 (s, 1H), 6.87 (ddd, $J = 7.5$ Hz, $J' = 7.4$ Hz, $J'' = 1.0$ Hz, 1H), 6.95 (d, $J = 8.3$ Hz, 1H), 7.17–7.41 (m, 17H), 8.37 (s, 1H), 13.15 (br s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 69.6 (CH_2), 74.2 (CH), 75.6 (CH), 84.4 (CH), 116.9 (CH), 118.7 (C), 118.8 (CH), 126.5 (CH), 126.8 (CH), 127.0 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 127.40 (CH), 128.41 (CH), 128.5 (CH), 128.7 (CH), 131.7 (CH), 132.6 (CH), 139.6 (C), 141.5 (C), 141.7 (C), 160.9 (C), 166.1 (CH) ppm. MS (CI, NH_3) *m/z*: 438 (100%, $C_{29}H_{27}NO_3{\cdot}H^+$). HRMS (CI) calculated for $C_{29}H_{27}NO_3{\cdot}H^+$ (M^++1): 438.2069. Found: 438.2067.

4.4.5. (1*R*,2*R*)-1-(*N*-Salicyliden)-amino-1-phenyl-3-triisopropylsilyloxypropan-2-ol, 3f. $[\alpha]_D^{23} = +51.6$ (*c* 1.2, $CHCl_3$). IR (film, ν_{max}/cm^{-1}): 3500, 2942, 2890, 2866, 1630, 1494, 1462, 1277, 1119, 883, 755. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00–1.10 (m, 21H), 2.66 (br s, 1H), 3.77 (dd, $J = 10.2$ Hz, 6.0 Hz, 1H), 3.83 (dd, $J = 10.2$ Hz, 3.6 Hz, 1H), 4.37 (m, 1H), 4.54 (d, $J = 6.8$ Hz, 1H), 6.87 (ddd, $J = 7.5$ Hz, $J' = 7.5$ Hz, $J'' = 1.0$ Hz, 1H), 6.97 (d, $J = 8.0$ Hz, 1H), 7.22–7.43 (m, 7H), 8.43 (s, 1H), 13.25 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8 (CH), 17.9 (CH_3), 63.6 (CH_2), 75.0 (CH), 75.1 (CH), 116.9 (CH), 118.7 (C), 118.8 (CH), 127.6 (CH), 127.7 (CH), 128.7 (CH), 131.7 (CH), 132.6 (CH), 139.7 (C), 161.0 (C), 166.2 (CH) ppm. MS (CI, CH_4) *m/z*: 428 (47%, $C_{25}H_{37}NO_3Si{\cdot}H^+$), 427 (35%, $C_{25}H_{37}NO_3Si^+$), 384 (37%, $[C_{25}H_{37}NO_3Si–(CH(CH_3)_2)]^+$). HRMS (CI) calculated for $C_{25}H_{37}NO_3Si{\cdot}H^+$ (M^++1): 428.2647. Found: 428.2612.

4.4.6. (1*R*,2*R*)-1-(*N*-Salicyliden)-amino-1-phenyl-3-triphenylmethoxypropan-2-ol, 3e. $[\alpha]_D^{23} = +27.9$ (*c* 1.0, $CHCl_3$). IR (film, ν_{max}/cm^{-1}): 3450, 3059, 3031, 2930, 2876, 1629, 1582, 1492, 1449, 1278, 1064, 757. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 (m, 1H), 3.16 (dd, $J = 10.0$ Hz, $J' = 4.9$ Hz, 1H), 3.40 (dd, $J = 10.0$ Hz, $J' = 3.4$ Hz, 1H), 4.08 (m, 1H), 4.58 (d, $J = 7.3$ Hz, 1H), 6.85 (ddd, $J = 7.5$ Hz, $J' = 7.5$, $J'' = 1.0$ Hz, 1H), 6.91 (d, $J = 8.3$ Hz, 1H), 7.11–7.40 (m, 22H), 8.32 (s, 1H), 12.98 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.7 (CH_2), 74.4 (CH), 75.6 (CH), 86.8 (C), 116.8 (CH), 118.60 (CH), 118.62 (C), 127.0 (CH), 127.47 (CH), 127.71 (CH), 127.74 (CH), 127.8 (CH), 127.9 (CH), 128.54 (CH), 128.6 (CH), 131.7 (CH), 132.5 (CH), 139.6 (C), 143.6 (C), 160.9 (C), 165.9 (CH) ppm. MS (CI, CH_4) *m/z*: 514 (1%, $C_{35}H_{31}NO_3{\cdot}H^+$), 243 (100%, CPh_3^+). HRMS (CI) calculated for $C_{35}H_{31}NO_3{\cdot}H^+$ (M^++1): 514.2382. Found: 514.2387.

4.4.7. (2*R*,3*R*)-3-(*N*-3′,5′-Di-*tert*-butylsalicyliden)-amino-3-phenylpropan-1,2-diol, 4a. $[\alpha]_D^{23} = +81.0$ (*c* 1.0, $CHCl_3$). Mp 75–76 °C. IR (film, ν_{max}/cm^{-1}): 3395, 2959, 2905, 2870, 1627, 1599, 1468, 1441, 1250, 1173, 1053, 759. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 9H), 1.48 (s, 9H), 2.36–2.82 (br s, 2H), 3.65 (dd, $J = 11.4$, $J' = 5.8$ Hz, 1H), 3.78 (dd, $J = 11.4$, $J' = 2.6$ Hz, 1H), 4.12 (m, 1H), 4.46 (d, $J = 7.6$ Hz, 1H), 7.10 (d, $J = 2.4$ Hz, 1H), 7.30 (m, 1H), 7.36–7.44 (m, 5H), 8.44 (s, 1H), 13.50 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.4 (CH_3), 31.4 (CH_3), 34.1 (C), 35.0 (C), 63.0 (CH_2), 75.2 (CH), 75.4 (CH), 117.8 (C), 126.4 (CH), 127.5 (CH), 127.8 (CH), 127.9 (CH), 128.8 (CH), 136.7 (C), 139.7 (C), 140.4 (C), 157.9 (C), 167.6 (CH). MS (CI, CH_4) *m/z*: 384 (100%, $C_{24}H_{33}NO_3{\cdot}H^+$), 383 (32%, $C_{24}H_{33}NO_3^+$). HRMS (CI) calculated for $C_{24}H_{33}NO_3{\cdot}H^+$ (M^++1): 384.2539. Found: 384.2533.

4.4.8. (1*R*,2*R*)-1-(*N*-3′,5′-Di-*tert*-butylsalicyliden)-amino-1-phenyl-3-methoxypropan-2-ol, 4b. $[\alpha]_D^{23} = +90.6$ (*c* 0.7, $CHCl_3$). IR (film, ν_{max}/cm^{-1}): 3450, 2958, 2900, 2867, 1628, 1600, 1443, 1250, 1147, 758. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 9H), 1.46(s, 9H), 3.36 (s, 3H), 3.48 (dd, $J = 9.8$ Hz, $J' = 6.4$ Hz, 1H), 3.54 (dd, $J = 9.8$, $J' = 3.1$ Hz, 1H), 4.23 (ddd, $J = 6.6$ Hz, $J' = 6.5$ Hz, $J'' = 3.1$ Hz, 1H), 4.50 (d, $J = 6.9$ Hz, 1H), 7.09 (d, $J = 2.5$ Hz, 1H), 7.27–7.45 (m, 6H), 8.43 (s, 1H), 13.50 (br s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.4 (CH_3), 31.4 (CH_3), 34.1 (C), 35.0 (C), 59.1 (CH_3), 72.8 (CH_2), 73.9 (CH), 75.6 (CH), 117.9 (C), 126.4 (CH), 127.4 (CH), 127.66 (CH), 127.73 (CH), 128.7 (CH), 136.7 (C), 139.8 (C), 140.3 (C), 158.0 (C), 167.3 (CH) ppm. MS (CI, NH_3) *m/z*: 398 (28%, $C_{25}H_{35}NO_3{\cdot}H^+$), 397 (100%, $C_{25}H_{35}NO_3^+$). HRMS (CI) calculated for $C_{25}H_{35}NO_3{\cdot}H^+$ (M^++1): 398.2695. Found: 398.2702.

4.4.9. (1*R*,2*R*)-1-(*N*-3′,5′-Di-*tert*-butylsalicyliden)-amino-3-benzyloxy-1-phenylpropan-2-ol, 4c. $[\alpha]_D^{23} = +40.6$ (*c* 1.8, $CHCl_3$). IR (film, ν_{max}/cm^{-1}): 3430, 3031, 2958, 2919, 2869, 1629, 1472, 1452, 1250, 1094, 1065, 735. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 9H), 1.46 (s, 9H), 4.26 (m, 1H), 4.47 (d, $J = 11.8$ Hz, 1H), 4.51 (d, $J = 6.9$ Hz, 1H), 4.56 (d, $J = 11.8$ Hz, 1H), 7.06 (d, $J = 2.5$ Hz, 1H), 7.26–7.43 (m, 11H), 8.40 (s, 1H), 13.45 (br s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.4 (CH_3), 31.4 (CH_3), 35.0 (C), 70.5 (CH_2), 73.4 (CH_2), 74.0 (CH), 75.5 (CH), 117.9 (C), 126.3 (CH), 127.3 (CH), 127.68 (CH), 127.74 (CH), 127.8 (CH), 128.4 (CH), 128.7 (CH), 136.6 (C), 137.7 (C), 139.8 (C), 140.2 (C), 157.9 (C), 167.3 (CH) ppm. MS (CI, NH_3) *m/z*: 475 (34%, $C_{31}H_{39}NO_3{\cdot}H^+$), 474 (100%, $C_{31}H_{39}NO_3^+$). HRMS (CI) calculated for $C_{31}H_{39}NO_3{\cdot}H^+$ (M^++1): 474.3008. Found: 474.3017.

4.4.10. (1*R*,2*R*)-1-(*N*-3′,5′-Di-*tert*-butylsalicyliden)-amino-1-phenyl-3-diphenylmethoxypropan-2-ol, 4d. $[\alpha]_D^{23} = +34.2$ (*c* 1.0, $CHCl_3$). Mp 64–66 °C. IR (film, ν_{max}/cm^{-1}): 3437, 3029, 2958, 2907, 2868, 1627, 1468, 1453, 1250, 1089, 1064, 758. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 9H), 1.44 (s, 9H), 2.33 (br s, 1H), 3.60 (dd, $J = 10.0$, $J' = 5.5$ Hz, 1H), 3.66 (dd, $J = 10.0$, $J' = 3.3$ Hz, 1H), 4.28 (m, 1H), 4.52 (d, $J = 7.2$ Hz, 1H), 5.34 (s, 1H), 7.02 (d, $J = 2.0$ Hz, 1H), 7.20–7.40 (m, 16H), 8.37 (s, 1H), 13.40 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.4 (CH_3), 31.5 (CH_3), 34.1 (C), 35.0 (C), 69.7 (CH_2), 74.1 (CH), 75.6 (CH), 84.3 (CH), 117.8 (C), 126.3 (CH), 126.8 (CH), 127.0 (CH), 127.3 (CH), 127.5 (CH), 127.6 (CH), 127.7

(CH), 127.8 (CH), 128.4 (CH), 128.7 (CH), 136.6 (C), 139.9 (C), 140.2 (C), 141.6 (C), 141.8 (C), 157.9 (C), 167.3 (CH) ppm. MS (CI, NH_3) *m/z*: 549 (100%, $C_{37}H_{43}NO_3^+$), 550 (40%, $C_{37}H_{43}NO_3{\cdot}H^+$). HRMS (CI) calculated for $C_{37}H_{43}NO_3{\cdot}H^+$ (M^++1): 550.3347. Found: 550.3333.

4.4.11. (1*R*,2*R*)-1-(*N*-3′,5′-Di-*tert*-butylsalicyliden)-amino-1-phenyl-3-triphenylmethoxypropan-2-ol, 4e. $[\alpha]_D^{23}$ = +19.8 (*c* 1.0, $CHCl_3$). IR (film, ν_{max}/cm^{-1}): 3375, 3060, 3031, 2957, 2870, 1628, 1597, 1468, 1448, 1250, 1064, 760. ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 9H), 1.43 (s, 9H), 2.47 (d, $J = 4.4$ Hz, 1H), 3.16 (dd, $J = 10.0$, $J' = 5.4$ Hz, 1H), 3.41 (dd, $J = 10.0$ Hz, $J' = 3.2$ Hz, 1H), 4.20–4.33 (m, 1H), 4.54 (d, $J = 6.8$ Hz, 1H), 6.93 (d, $J = 2.8$ Hz, 1H), 7.16–7.40 (m, 47H), 8.32 (s, 1H), 13.20 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.4 (CH_3), 31.4 (CH_3), 34.0 (C), 35.0 (C), 64.2 (CH_2), 74.5 (CH), 75.6 (CH), 86.8 (C), 117.8 (C), 126.3 (CH), 127.0 (CH), 127.6 (CH), 127.8 (CH), 127.87 (CH), 127.89 (CH), 128.5 (CH), 128.6 (CH), 136.5 (C), 139.9 (C), 140.1 (C), 143.7 (C), 157.9 (C), 167.2 (CH) ppm. MS (CI, CH_4) *m/z*: 626 (7%, $C_{43}H_{47}NO_3{\cdot}H^+$), 625 (7%, $C_{43}H_{47}NO_3^+$), 243 (100%, CPh_3^+). HRMS (CI) calculated for $C_{43}H_{47}NO_3^+$ (M^+): 625.3556. Found: 625.3563.

4.4.12. (1*R*,2*R*)-1-(*N*-3′,5′-Di-*tert*-butylsalicyliden)-amino-1-phenyl-3-triisopropylsilyloxypropan-2-ol, 4f. $[\alpha]_D^{23}$ = +62.4 (*c* 1.0, $CHCl_3$). IR (film, ν_{max}/cm^{-1}): 3568, 3464, 3063, 3031, 2958, 2867, 1629, 1466, 1442, 1250, 1116, 881. ^1H NMR(400 MHz, $CDCl_3$): δ 1.12 (m, 47H), 1.28 (s, 9H), 1.45 (s, 9H), 2.58 (d, $J = 4.0$ Hz, 1H), 3.78 (dd, $J = 10.1$ Hz, $J' = 6.2$ Hz, 1H), 3.85 (dd, $J = 10.1$ Hz, $J' = 3.5$ Hz, 1H), 4.12 (m, 1H), 4.50 (d, $J = 7.1$ Hz, 1H), 7.06 (d, $J = 2.4$ Hz, 1H), 7.25–7.44 (m, 6H), 8.42 (s, 1H), 13.50 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.9 (CH), 17.9 (CH_3), 29.4 (CH_3), 31.4 (CH_3), 34.1 (C), 35.0 (C), 63.9 (CH_2), 75.06 (CH), 75.11 (CH), 117.9 (C), 126.3 (CH), 127.2 (CH), 127.6 (CH), 127.8 (CH), 128.6 (CH), 136.6 (C), 140.0 (C), 140.2 (C), 158.0 (C), 167.2 (CH) ppm. MS (CI, CH_4) *m/z*: 540 (100%, $C_{33}H_{53}NO_3Si{\cdot}H^+$), 539 (41%, $C_{33}H_{53}NO_3Si^+$), 496 (37%, $[C_{33}H_{53}NO_3Si^{\cdot}–(CH(CH_3)_2)]^+$). HRMS (CI) calculated for $C_{33}H_{53}NO_3Si{\cdot}H^+$ (M^++1): 540.3873. Found: 540.3879.

4.4.13. (2*R*,3*R*)-3-(*N*-Salicyliden)-amino-1-benzyloxyhexan-2-ol, 5c. $[\alpha]_D^{23}$ = −48.5 (*c* 1.0, $CHCl_3$). IR (film, ν_{max}/cm^{-1}): 3456, 2957, 2929, 2870, 1630, 1581, 1497, 1455, 1278, 1091, 756. ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, $J = 7.3$ Hz, 3H), 1.15–1.40 (m, 2H), 1.57–1.85 (m, 2H), 2.55 (br s, 1H), 3.28 (m, 1H), 3.45 (dd, $J = 9.6$, $J' = 6.7$ Hz, 1H), 3.63 (dd, $J = 9.6$, $J' = 2.9$ Hz, 1H), 4.45 (d, $J = 11.7$ Hz, 1H), 3.91 (m, 1H), 4.51 (d, $J = 11.7$ Hz, 1H), 6.88 (ddd, $J = 7.5$ Hz, $J' = 7.4$ Hz, $J'' = 1.0$ Hz, 1H), 6.95 (d, $J = 8.0$ Hz, 1H), 7.23–7.33 (m, 7H), 8.27 (s, 1H), 13.25 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8 (CH_3), 19.3 (CH_2), 34.3 (CH_2), 71.2 (CH_2), 71.9 (CH), 72.7 (CH_2), 73.4 (CH), 116.9 (CH), 118.6 (CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 131.4 (CH), 132.3 (CH), 137.7 (C), 161.1 (C), 165.3 (CH) ppm. MS (CI, CH_4) *m/z*: 328 (7%, $C_{20}H_{25}NO_3{\cdot}H^+$), 327 (8%, $C_{20}H_{25}NO_3$), 177 (31%, $C_{11}H_{14}NO{\cdot}H^+$). HRMS (CI) calculated for $C_{20}H_{25}NO_3{\cdot}H^+$ (M^++1): 328.1913. Found: 328.1914.

4.4.14. (2*R*,3*R*)-3-(*N*-Salicyliden)-amino-1-triphenylmethoxyhexan-2-ol, 5e. $[\alpha]_D^{23}$ = −19.0 (*c* 1.0, $CHCl_3$). IR (film, ν_{max}/cm^{-1}): 3455, 3058, 2957, 2930, 2871, 1630, 1582, 1491, 1448, 1278, 1074, 758. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.4$ Hz, 3H), 1.10–1.34 (m, 2H), 1.54 (m, 1H), 1.78 (m, 1H), 2.35 (br s, 1H), 3.11 (dd, $J =$ 10.0 Hz, $J' = 5.6$ Hz, 1H), 3.32 (m, 1H), 3.37 (dd, $J = 10.0$ Hz, $J' = 3.0$ Hz, 1H), 3.74 (m, 1H), 6.86 (dd, $J = 7.6$ Hz, $J' = 7.6$ Hz, 1H), 6.90 (d, $J = 8.4$ Hz, 1H), 7.14–7.89 (m, 17H), 8.19 (s, 1H), 12.95 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8 (CH_3), 19.2 (CH_2), 34.3 (CH_2), 64.2 (CH_2), 71.8 (CH), 73.3 (CH), 86.8 (C), 116.9 (CH), 118.4 (CH), 118.5 (C), 127.1 (CH), 127.9 (CH), 128.5 (CH), 131.4 (CH), 132.2 (CH), 143.6 (C), 161.1 (C), 165.1 (CH) ppm. MS (CI, CH_4) *m/z*: 480 (6%, $C_{32}H_{33}NO_3{\cdot}H^+$), 243 (100%, CPh_3^+). HRMS (CI) calculated for $C_{32}H_{33}NO_3{\cdot}H^+$ (M^++1): 480.2539. Found: 480.2532.

4.4.15. (2*R*,3*R*)-3-(*N*-3′,5′-Di-*tert*-butylsalicyliden)-amino-1-benzyloxyhexan-2-ol, 6c. $[\alpha]_D^{23}$ = −37.3 (*c* 1.0, $CHCl_3$). IR (film, ν_{max}/cm^{-1}): 3460, 2957, 2910, 2870, 1629, 1596, 1468, 1454, 1441, 1361, 1273, 1250, 733. ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, $J = 7.3$ Hz, 3H), 1.32 (s, 9H), 1.44 (s, 9H), 1.16–1.50 (m, 2H), 1.59–1.86 (m, 2H), 2.44 (d, $J = 4.9$ Hz, 1H), 3.26 (m, 1H), 3.47 (dd, $J = 9.6$ Hz, $J' = 6.8$ Hz, 1H), 3.65 (dd, $J = 9.6$ Hz, $J' = 3.1$ Hz, 1H), 3.92 (m, 1H), 4.47 (d, $J = 11.9$ Hz, 1H), 4.55 (d, $J = 11.7$ Hz, 1H), 7.09 (d, $J = 2.4$ Hz, 1H), 7.26–7.32 (m, 5H), 7.40 (d, $J =$ 2.8 Hz, 1H), 8.28 (s, 1H), 13.50 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8 (CH_3), 19.3 (CH_2), 29.4 (CH_3), 31.5 (CH_3), 34.1 (C), 34.4 (CH_2), 35.0 (C), 71.3 (CH_2), 72.0 (CH), 72.8 (CH), 73.4 (CH_2), 117.7 (C), 126.1 (CH), 127.1 (CH), 127.8 (CH), 128.4 (CH), 136.7 (C), 137.8 (C), 140.1 (C), 158.1 (C), 166.4 (CH) ppm. MS (CI, CH_4) *m/z*: 440 (100%, $C_{20}H_{25}NO_3{\cdot}H^+$), 439 (97%, $C_{20}H_{25}NO_3$). HRMS (CI) calculated for $C_{28}H_{41}NO_3{\cdot}H^+$ (M^++1): 440.3165. Found: 440.3155.

4.4.16. (2*R*,3*R*)-3-(*N*-3′,5′-Di-*tert*-butylsalicyliden)-amino-1-triphenylmethoxyhexan-2-ol, 6e. $[\alpha]_D^{23}$ = −16.3 (*c* 1.0, $CHCl_3$). IR (film, ν_{max}/cm^{-1}): 3450, 3060, 2959, 2871, 1631, 1448, 1391, 1362, 1250, 1076, 762. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.4$ Hz, 3H), 1.30 (s, 9H), 1.14–1.34 (m, 2H), 1.42 (s, 9H), 1.56 (m, 1H), 1.75 (m, 1H), 3.07 (dd, $J = 9.8$ Hz, $J' = 6.0$ Hz, 1H), 3.26 (m, 1H), 3.40 (dd, $J = 9.8$ Hz, $J' = 3.2$ Hz, 1H), 3.83 (m, 1H), 6.98 (d, $J = 2.4$ Hz, 1H), 7.17–7.39 (m, 16H), 8.19 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 19.2 (CH_2), 29.5 (CH_3), 31.5 (CH_3), 34.1 (C), 34.3 (CH_2), 35.0 (C), 64.6 (CH_2), 72.0 (CH), 73.5 (CH), 86.8 (C), 117.6 (C), 126.1 (CH), 126.8 (CH), 127.1 (CH), 127.8 (CH), 128.5 (CH), 136.5 (C), 139.9 (C), 143.7 (C), 158.1 (C), 166.2 (CH) ppm. EM (CI, CH_4) *m/z*: 592 (25%, $C_{40}H_{49}NO_3{\cdot}H^+$), 243 (100%, CPh_3^+). HRMS (CI) calculated for $C_{40}H_{49}NO_3{\cdot}H^+$ (M^++1): 592.3791. Found: 592.3777.

4.4.17. General method for the asymmetric addition of trimethylsilylcyanide to benzaldehyde. In a flame-dried flask, 0.033 mmol of the corresponding Schiff base was weighed, and the system purged with argon. A 0.2 M solution of $Ti(O^iPr)_4$ (150 μL, 0.030 mmol) in CH_2Cl_2 were added via syringe, and the mixture was stirred at rt for 1 h. The mixture was then cooled to −78 °C and 45 μL (0.33 mmol) of TMSCN, and 15 μL of freshly distilled benzaldehyde successively added. The reaction was then kept at the desired temperature and time, and eventually quenched with water and extracted with CH_2Cl_2. The crude product was analyzed by GC: β-DEX chiral column (30 m) [Isocratic 105 °C, $P = 15$ psi]: $t_{PhCHO} =$ 17.0 min, $t_S = 108.5$ min, $t_R = 110.0$ min.

Acknowledgements

We thank DGI-MCYT (Grant No. BQU2002-02459), DURSI (Grant No. 2001SGR50), Fundación Ramón Areces, and ICIQ Foundation for financial support. B.R. thanks MCYT, for a predoctoral fellowship.

References

1. (a) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649–3682; (b) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147–176.
2. For a recent review, see: Brunel, J.-M.; Holmes, I. P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2752–2778.
3. For some recent key references using Ti(IV)–Schiff base ligands complexes for cyanide addition to aldehydes, see: (a) Lundgren, S.; Wingstrand, E.; Penhoat, M.; Moberg, C. *J. Am. Chem. Soc.* **2005**, *127*, 11592–11593; (b) Li, Z.-B.; Rajaram, A. R.; Decharin, N.; Qin, Y.-C.; Pu, L. *Tetrahedron Lett.* **2005**, *46*, 2223–2226; (c) Belokon, Y. N.; Carta, P.; North, M. *Lett. Org. Chem.* **2004**, *1*, 81–83; (d) Belokon, Y. N.; Blacker, A. J.; Clutterbuck, L. A.; North, M. *Org. Lett.* **2003**, *5*, 4505–4507; (e) Belokon, Y. N.; Gutnov, A. V.; Moskalenko, M. A.; Yashkina, L. V.; Lesovoy, D. E.; Ikonnikov, N. S.; Larichev, V. S.; North, M. *Chem. Commun.* **2002**, 244–245; (f) Belokon, Y. N.; Carta, P.; Gutnov, A. V.; Maleev, V.; Moskalenko, M. A.; Yashkina, L. V.; Ikonnikov, N. S.; Voskoboev, N. V.; Khrustalev, V. N.; North, M. *Helv. Chim. Acta* **2002**, *85*, 3301–3311; (g) Noth, M.; Parkins, A. W.; Shariff, A. N. *Tetrahedron Lett.* **2004**, *45*, 7625–7627; (h) Huang, W.; Song, Y.; Bai, C.; Cao, G.; Zheng, Z. *Tetrahedron Lett.* **2004**, *45*, 4763–4767; (i) Huang, W.; Song, Y.; Wang, J.; Cao, G.; Zheng, Z. *Tetrahedron* **2004**, *60*, 10469–10477; (j) Liang, S.; Bu, X. R. *J. Org. Chem.* **2002**, *67*, 2702–2704; (k) Gama, A.; Flores-López, L. Z.; Aguirre, G.; Parra-Hake, M.; Somanathan, R.; Cole, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1167–1174; (l) Gama, A.; Flores-López, L. Z.; Aguirre, G.; Parra-Hake, M.; Somanathan, R.; Walsh, P. J. *Tetrahedron: Asymmetry* **2002**, *13*, 149–154; (m) Li, Y.; He, B.; Qin, B.; Feng, X.; Zhang, G. *J. Org. Chem.* **2004**, *69*, 7910–7913; (n) Jiang, Y.; Gong, L.; Feng, X.; Hu, W.; Pan, W.; Li, Z.; Mi, A. *Tetrahedron* **1997**, *53*, 14327–14338.
4. Gennari, C.; Piarulli, U. *Chem. Rev.* **2003**, *103*, 3071–3100.
5. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
6. Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 7902–7911.
7. (a) Pastó, M.; Riera, A.; Pericàs, M. A. *Eur. J. Org. Chem.* **2002**, 2337–2341; (b) Ferrer, S.; Pastó, M.; Rodríguez, B.; Riera, A.; Pericàs, M. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1747–1752.
8. Pericàs, M. A.; Puigjaner, C.; Riera, A.; Vidal-Ferran, A.; Gómez, M.; Jiménez, F.; Muller, G.; Rocamora, M. *Chem. Eur. J.* **2002**, *8*, 4164–4178.
9. Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970–4982.
10. Pastó, M.; Rodríguez, B.; Riera, A.; Pericàs, M. A. *Tetrahedron Lett.* **2003**, *44*, 8369–8372.
11. Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185.
12. (a) Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1991**, 1752–1753; (b) Hayashi, M.; Inoue, T.; Miyamoto, Y.; Oguni, N. *J. Org. Chem.* **1993**, *58*, 1515–1522; (c) Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *Tetrahedron* **1994**, *50*, 4385–4398.
13. The *tert*-butyl groups on the salicylaldehyde are supposed to prevent the formation of inactive complexes such as $Ti(L^*)_2$. See Refs. 12 and 14.
14. Flores-López, L. Z.; Parra-Hake, M.; Somanathan, R.; Walsh, P. J. *Organometallics* **2000**, *19*, 2153–2160.
15. Belokon, Y. N.; Blacker, A. J.; Carta, P.; Clutterbuck, L. A.; North, M. *Tetrahedron* **2004**, *60*, 10433–10447.
16. Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594–11599.
17. (a) Arbelo, D. O.; Prieto, J. A. *Tetrahedron Lett.* **2002**, *43*, 4111–4114; (b) Thurner, A.; Faigl, F.; Tóke, L.; Mordini, A.; Valacchi, M.; Reginato, G.; Czira, G. *Tetrahedron* **2001**, *57*, 8173–8180; (c) Bonini, C.; Righi, G.; Sotgiu, G. *J. Org. Chem.* **1991**, *56*, 6206.
18. Choukroum, R.; Gervais, D. *J. Chem. Soc., Dalton Trans.* **1980**, 1800.