Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 3705–3712

TETRAHEDRON: *ASYMMETRY*

Chiroptical properties and applications in PTC of new dendritic cinchonidine-derived ammonium salts

Gabriela Guillena,[a] Robert Kreiter,[a] Rob van de Coevering,[a] Robertus J. M. Klein Gebbink,[a] Gerard van Koten,[a,*] Patricia Mazón,[b] Rafael Chinchilla[b] and Carmen Nájera[b,*]

[a]*Debye Institute, Department of Metal-Mediated Synthesis, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands*
[b]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo 99, E-03080 Alicante, Spain*

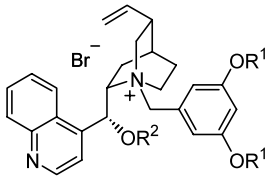
Received 25 July 2003; accepted 27 August 2003

Abstract—Chiral nanosize molecules, derived from cinchonidine and Fréchet dendritic wedges up to generation three, have been synthesized. The chiroptical properties, optical rotation and circular dichroism of these systems have been studied. These chiral dendritic molecules have been used as phase transfer catalysts in the alkylation of a glycine imine ester, showing a promising level of asymmetric induction.

1. Introduction

Dendrimers are three-dimensional macromolecules characterized by a well-defined structure of nanoscopic dimensions and ideally with a globular shape.[1] The potential application of these macromolecules, which resemble in size biomolecules such as proteins or enzymes, in (bio)chemical and material science have been envisaged.[2] A promising development has been the use of (metallo)dendrimers as homogeneous catalysts, providing systems large enough to be recovered by means of ultra- or nano-filtration or size exclusion techniques.[3] In this research field, the use of chiral dendrimers for asymmetric catalytic transformations has already been reported.[4] However, only in a few examples has a high level of chiral induction been achieved.[5] In most cases, the chiral dendritic species were part of the ligands of catalytically active metal complexes. So far, metal-free, chiral dendrimers have rarely been used in asymmetric catalysis.[6] There are various possibilities of rendering a dendritic species chiral; (i) by introducing chiral peripheral units; (ii) by employing chiral building blocks or (iii) by using a chiral core. Following the last strategy, the chiral information of the core might even be enhanced by the steric congestion created by using higher generations of the dendritic wedges, while the catalysts become recoverable by means of (nano)filtration or dialysis techniques. Phase transfer catalysis (PTC) processes offer another possibility for continuous separation of catalytic dendrimers from product streams.

In PTC processes, impressive improvements in the level of asymmetric induction have been achieved by using *Cinchona* derived ammonium salts.[7] For instance, *N*-aryl methyl substituted *Cinchona* alkaloids have shown to be highly efficient for the practical asymmetric synthesis of α-amino acids.[8] Several attempts to recover and re-use these chiral alkaloid-derived ammonium salts by anchoring them to a solid support have been also described.[9]



1a; R^1 = Bn, R^2 = H
1b; R^1 = Bn, R^2 = Allyl
1c; R^1 = Bn, R^2 = Bn
1d; R^1 = Me, R^2 = H

Recently, we have reported the synthesis and use as catalysts of new cinchonidinium salts bearing 3,5-

* Corresponding authors. Tel.: +31-30-2533120; fax: +31-30-2523615 (G.v.K.); tel.: +34-96-5903728; fax: +34-96-5903549 (C.N.); e-mail: g.vankoten@chem.uu.nl; cnajera@ua.es

0957-4166/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2003.08.030

dialkoxybenzyl groups **1**.[10] Unexpectedly, these catalysts have shown a metal base-dependent inversion in the enantioselectivity in the asymmetric synthesis of α-amino acids. These unexpected results prompted us to investigate the synthesis, as well as the study of the chiroptical properties, of phase transfer catalysts derived from cinchonidine as a chiral core and having *N*-bound Fréchet dendritic wedges of higher generations.

2. Results and discussion

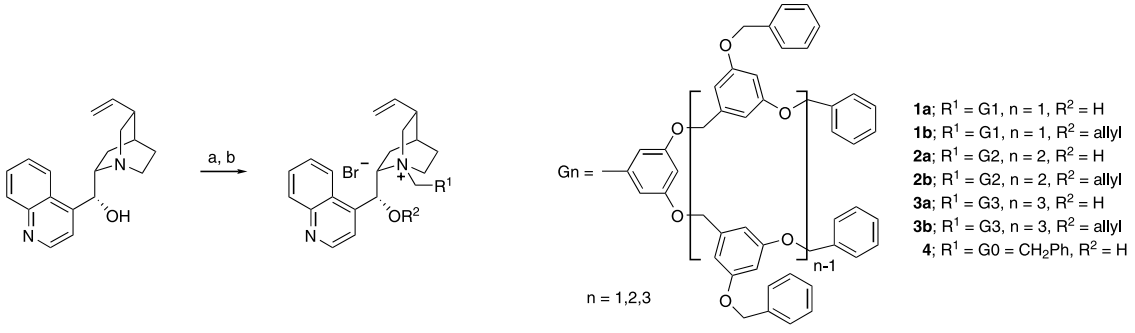
(−)-Cinchonidine was derivatized with Fréchet dendritic wedges up to generation three. These wedges were prepared using a convergent approach, involving standard K_2CO_3/18-crown-6 mediated ether formation steps and alcohol to bromide conversions using PBr_3.[11] In addition, *N*-benzylcinchonidinium bromide **4** (G0-cinchonidine) was prepared according to the literature.[12] The quaternization of the nitrogen of the quinuclidine moiety was performed by refluxing the corresponding dendritic wedges (as the bromide), with cinchonidine in acetone (Scheme 1).[13] The resulting salts were purified by precipitation (CH_2Cl_2/Et_2O) and centrifugation, rendering derivatives **1a** and **2a** in about 65% yield. This purification method was not suitable for G3-cinchonidine salt **3a** due to the high solubility of this compound in common solvents. However, in this case, due to the high molecular weight of the salt, dialysis techniques can be used as a convenient and efficient purification method. Thus, **3a** was dissolved in a minimum quantity of acetone and submitted to dialysis for 48 h,[14] giving pure **3a** in 84% yield.

As under the reaction conditions employed in PTC processes, the hydroxyl group of the ammonium salts can be converted to the corresponding ethers, species **1a**–**3a** were transformed into the corresponding allyl ethers by reaction with allyl bromide in a biphasic mixture of CH_2Cl_2/KOH (50%), to give compounds **1b**–**3b** in about 70% yield. All compounds were characterized and identified by ^1H, and ^{13}C NMR, MALDI-TOF or ESI mass spectrometry as well as elemental analysis, the results being in full agreement with the proposed structures (Scheme 1).

2.1. Chiroptical properties

Measurements of the optical activity of **1a**–**3a** and **1b**–**3b** showed that the $[\alpha]_D$ value decreases with increasing generation number. This is in concert with earlier findings[5e] showing that attachment of achiral branches to a chiral core leads to a kind of dilution effect of the optical activity. The molar rotation ($[\Phi]_D$) values were similar for G1- and G2-cinchonidine compounds **1a** and **2a**, respectively. However, a lower value, was observed for **3a**. For the allylic ethers **1b** and **3b**, an different behavior was observed as they show a similar $[\Phi]_D$ value, whereas the G2-cinchonidine allyl ether salt **2b** has a higher value for both $[\alpha]_D$ and $[\Phi]_D$ rotation (Fig. 1).

CD spectra of 10^{-5} M solutions of **1**–**4** in CH_2Cl_2 were recorded in order to study the influence of dendritic wedges on the spectroscopic properties. To avoid distortion of the dichroic absorption caused by the presence of an increasing number of benzene chromophores



Scheme 1. *Reagents and conditions:* (a) GnBr, acetone, Δ; (b) allyl bromide, KOH (50%), CH_2Cl_2, rt.

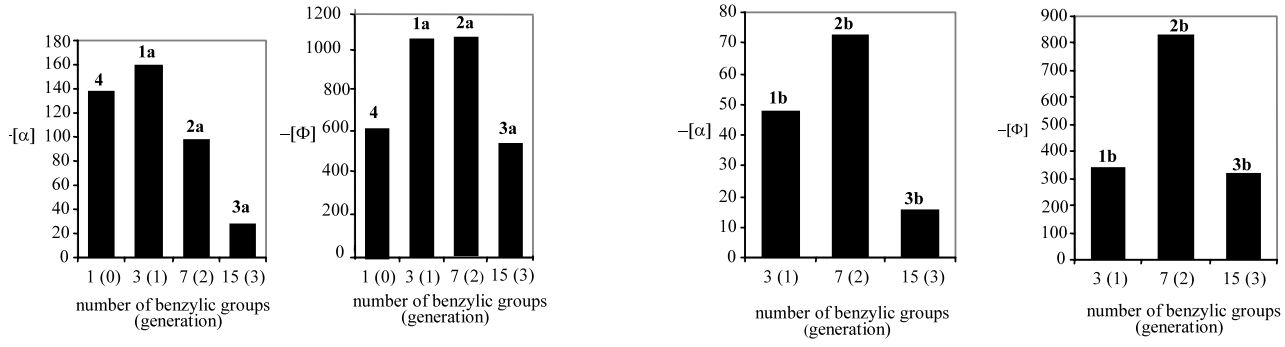


Figure 1. Comparison between the specific and molar rotation for dendrimers **1a**–**4** and **1b**–**3b**.

in the dendrimer, the obtained $\Delta\varepsilon$ values were divided by the number of benzylic rings present in each dendrimer, i.e. one for **4**, three for **1a**, etc. All compounds show a negative Cotton effect in the region of 315 and 305 nm which corresponds to adsorption of the chiral cinchonidine moiety, i.e. these absorptions decrease as the generation increases. A positive Cotton effect was observed when the benzylic moiety was introduced in the molecule. Thus, for the G0-cinchonidine **4** a maximum at ca. 275 nm was observed, while this effect decreases with the increasing generation number as expected. The same trend was observed for the CD spectra of the allyl ether derivatives **1b**–**3b** (Fig. 2).

2.2. Use as catalysts

In order to check if these chiroptical properties would correlate with the enantioselectivities when the chiral dendritic compounds would be applied in catalysis, compounds **1**–**3** were tested in the biphasic alkylation reaction of *N*-(diphenylmethylene)glycine isopropyl ester **5** with benzyl bromide under different reaction conditions (Table 1). The ee's were determined by chiral GLC analysis[15] of the corresponding *N*-trifluoroacetamide amido esters.[16]

A study of the influence of base, temperature and solvent on the catalytic reaction was performed using

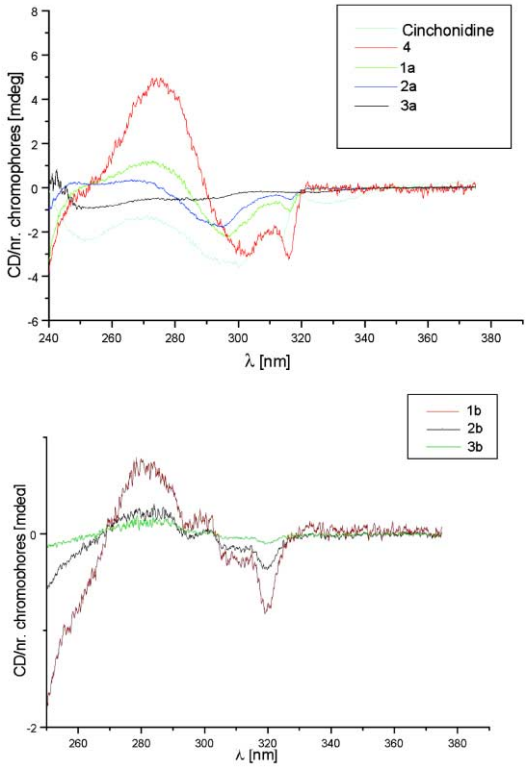
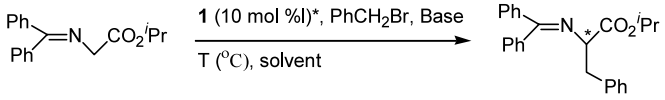


Figure 2. CD spectra of compounds **1**–**4**.

Table 1. Optimization of conditions on the alkylation of *N*(diphenyliminemethylene)glycine **5** with catalyst **1**



5 **6a**

Entry	Cat.	Solvent	Base	T (°C)	t_R (h)[a]	Yield (%)[b]	Ee (%)[c]	Abs. conf.[c]
1	**1a**	CH_2Cl_2	$CsOH{\cdot}H_2O$	(−78)–(−50)	1	85	26	(*S*)
2	**1a**	CH_2Cl_2	50% KOH	0	2	96	34	(*S*)
3	**1a**	CH_2Cl_2	50% NaOH	0	2.5	98	36	(*S*)
4	**1a**	PhMe	50% KOH	0	0.75	96	44	(*S*)
5	**1a**	PhMe	50% NaOH	0	3	93	8	(*S*)
6	**1a**	PhMe	25% NaOH	0	7	76	46	(*S*)
7	**1a**	PhMe	25% KOH	0	2	88	40	(*S*)
8	**1a**	PhMe	50% KOH	rt	1	88	35	(*S*)
9	**1a**	PhMe	25% NaOH	rt	2	84	38	(*S*)
10	**1a**	PhMe/$CHCl_3$	50% KOH	−20	3	80	58	(*S*)
11	**1a**	PhMe/$CHCl_3$	50% KOH	−40	7	91	66	(*S*)
12	**1a**	PhMe/$CHCl_3$	50% NaOH	−20	7	96	40	(*R*)
13	**1a**	PhMe/$CHCl_3$	50% NaOH	−40	15	93	40	(*R*)
14	**1a**	PhMe/$CHCl_3$	50% NaOH	0	2.5	94	26	(*R*)
15	**1a**	PhMe/$CHCl_3$	50% NaOH	rt	1	83	43	(*S*)
16	**1b**	PhMe/$CHCl_3$	50% KOH	−20	1	84	76	(*S*)
17	**1b**	PhMe/$CHCl_3$	50% NaOH	−20	6	85	30	(*S*)
18	**1b**	PhMe/$CHCl_3$	50% CsOH	−20	5.5	76	76	(*S*)

[a] The reaction was monitored by GLC and quenched when the conversion was more than 90%.
[b] Isolated crude yield determined by ^{1}H NMR (300 MHz).
[c] Determined by chiral GLC[15] of the corresponding *N*-trifluoroacetamide amido esters.[16]

Table 2. Influence of the generation of the catalysts in the alkylation process of **5** with benzyl bromide

Entry	Cat.	Solvent	Base	T (°C)	t_R (h)[a]	Yield (%)[b]	Ee (%)[c]	Abs. conf.[c]
1	**1a**	PhMe	25% NaOH	0	7	76	46	(*S*)
2	**1b**	PhMe	25% NaOH	0	4	80	58	(*S*)
3	**2a**	PhMe	25% NaOH	0	4	88	76	(*S*)
4	**2b**	PhMe	25% NaOH	0	4	80	54	(*S*)
5	**3a**	PhMe	25% NaOH	0	5	85	40	(*S*)
6	**3b**	PhMe	25% NaOH	0	8.5	80	44	(*S*)
7	**2a**	PhMe/$CHCl_3$	50% KOH	–20	3.5	94	72	(*S*)
8	**2b**	PhMe/$CHCl_3$	50% KOH	–20	3	89	76	(*S*)
9	**2a**	PhMe/$CHCl_3$	50% NaOH	–20	7	88	24	(*S*)
10	**2b**	PhMe/$CHCl_3$	50% NaOH	–20	15	78	54	(*S*)

[a] The reaction was monitored by GLC and quenched when the conversion was more than 90%.
[b] Isolated crude yield determined by ^1H NMR (300 MHz).
[c] Determined by chiral GLC[15] of the corresponding *N*-trifluoroacetamide amido esters.[16]

derivative **1a** as catalyst, the results being summarised in Table 1. When CH_2Cl_2 was used as solvent, the best results were achieved using aq. KOH or NaOH as base at 0°C (Table 1, entries 1–3). Changing the solvent to toluene, a dramatic effect on the enantioselectivity of the reaction was observed, especially when aq. NaOH was used as base. In this case (Table 1, entry 5) a poor 8% ee was obtained for **6a**, the enantioselection being recovered when aq. 25% NaOH at 0°C was used (Table 1, entry 6). However, the same increase of the enantioselection was not observed when aq. 25% KOH was used as base (Table 1, entry 7). Next, using aq. 25% NaOH or 50% KOH as base for the alkylation process, the temperature was raised to rt, leading to a decrease on the enantioselection (Table 1 compare entries 4 and 6 with 8 and 9). The use of a mixture of toluene/$CHCl_3$ (7/3 v/v) as solvent for the alkylation reaction would allow to decrease the temperature below 0°C. Therefore, the reaction was carried out using aq. 50% KOH as base at –20 and –40°C. As expected the best enantioselection for the alkylated product was obtained at the lower temperature (Table 1, entries 10 and 11). Surprisingly, when the base was changed to aq. 50% NaOH the opposite (*R*)-enantiomer was obtained at –40, –20 and 0°C, with higher enantioselection as the temperature decreases. This effect of reversal of the enantioselectivity was not observed at rt (Table 1, entries 12–16). To the best of our knowledge this base-dependent stereoselectivity was not shown before at PTC reactions using ammonium salts as catalyst. The inversion of enantioselectivity was also not observed for the related allylated catalysts. Thus, **1b** gave the best results when aq. 50% KOH or 50% CsOH was used as base in toluene/$CHCl_3$ achieving 76% ee of **6a**, the enantioselectivity was only 30% for the (*S*)-enantiomer with aq. 50% NaOH (Table 1, entries 16–18).

Then, the influence of the catalysts generation on the enantioselection of the reaction was considered. For this process, benzyl bromide was chosen as standard electrophile and the reaction was performed using aq. 25% NaOH in toluene as solvent or aq. 50% KOH in a mixture of toluene/$CHCl_3$ (7/3 v/v). Finally, the inversion of enantioselectivity using aq. 50% NaOH was studied, being all results collected in Table 2.

Comparing the results obtained with the three different generation catalysts, best enantioselections (76% ee) were achieved using second generation catalysts **2a** or **2b** and aq. 25% NaOH or aq. 50% KOH, respectively (Table 2, entries 3 and 8), the enantioselectivity achieved with third generation catalysts **3a** being similar to that obtained with first generation salt **1a** (Table 2, compare entries 1 and 5). Therefore, the increment of the sterical hindrance due to the bulkiness of the dendrimer seems to have little effect in the enantioselection, being the results of the catalytic experiments not easily correlated with the optical activities and CD values of the dendritic salts **1**–**3**. When aq. 50% NaOH and catalysts **2a** was used as a base for the alkylation process a reversal on the enantioselection was not observed. However, the use of this conditions led to low enantioselectivities of the (*S*)-isomer (Table 2, entries 7 and 9).

Finally, other alkyl halides were used as electrophiles for the alkylation process catalyzed by **1a** or **2a**. In all cases the enantioselectivity achieved with aq. 50% KOH was much higher than the obtained with aq. 50% NaOH, being in both cases the (*S*)-stereoisomer preferentially formed (Table 3).The high molecular weight of the catalysts of higher generations would allow their retention by dialysis membranes commonly used to purify proteins.[17] With this idea in mind, the dendritic catalysts could be dissolved and placed into a dialysis membrane tube, which then can be submerged as a 'tea bag'[18] in the reaction media. Reactants would flow through the membrane pores and the catalyst contained in the membrane could be recovered and reused in a next catalytic run. Therefore, we tried this concept using catalysts **2a** and **3a** contained in a dialysis membrane to perform the alkylation reaction of **5** with aq. 25% NaOH as a base.

Similar results were obtained at the first and second run for both catalytic salts **2** and **3** (Table 4, entries 1–2 and 4–5) although for catalysts **2** a dramatic increase of the reaction time was need to complete the reaction. This

Table 3. Alkylation of (diphenyliminemethylene)glycine **5** with different electrophiles. Preparation of compounds **6**

Entry	Cat.	RX	Base	t_R (h)[a]	Yield (%)[b]	Ee (%)[c]
1	**1a**	4-$CNC_6H_4CH_2Br$	KOH	3	90	62 (*S*)
2	**1a**	2-$NaphCH_2Br$	KOH	4	95	60 (*S*)
3	**1a**	2-$NaphCH_2Br$	NaOH	30	95	28 (*S*)
4	**1a**	$CH_3CH_2CH_2CH_2I$	KOH	18	65	44 (*S*)
5	**1a**	$CH_3CH_2CH_2CH_2I$	NaOH	20	78	32 (*S*)
6	**1a**	3,5-$(CH_3O)_2C_6H_3CH_2Br$	KOH	3	85	72 (*S*)
7	**1a**	3,5-$(CH_3O)_2C_6H_3CH_2Br$	NaOH	24	83	18 (*S*)
8	**2a**	4-$CNC_6H_4CH_2Br$	KOH	4	87	70 (*S*)
9	**2a**	3,5-$(CH_3O)_2C_6H_3CH_2Br$	KOH	6.5	91	68 (*S*)
10	**2a**	3,5-$(CH_3O)_2C_6H_3CH_2Br$	NaOH	2.5	86	18 (*S*)

[a] The reaction was monitored by GLC and quenched when the conversion was more than 90%.
[b] Isolated crude yield determined by ^1H NMR (300 MHz).
[c] Determined by chiral GLC[15] of the corresponding *N*-trifluoroacetamide amido esters.[16] In parenthesis, absolute configuration of the major enantiomer.

Table 4. Alkylation of *N*(diphenyliminemethylene)glycine **5** using catalyst-dialysis membrane process[a]

Entry	Catalysts	Run	t_R (h)	Yield (%)	Ee (%)
1	**2a**	1	72	45	64
2	**2a**	2	96	90	60
3	**2a**	3	120	78	40
4	**3a**[b]	1	24	65	40
5	**3a**[b]	2	25	65	39

[a] The reaction was conducted using benzyl bromide as electrophile, aq. 25% NaOH as base in toluene at 0°C.
[b] The reaction was carried out at rt.

behaviour could be attributed to leaching of the catalyst out of the dialysis tube or decomposition of the membrane under the reaction conditions. However, for catalyst **3**, the yields, ee and reaction times were the same for both catalytic runs. Probably the higher molecular weight of these catalysts prevent leaching of the salt out of the membrane allowing the use of this type of catalysts in a membrane reactor.

3. Conclusions

We have demonstrated that dendritic cinchonidine ammonium salts can be applied as phase transfer catalysts. These systems show to be good PTC catalysts reaching a moderate level of asymmetric induction, while the chiroptical properties are independent of the enantioselection achieved. Furthermore, for first generation catalysts a reversal on the stereoselectivity can be achieved changing the nature of the inorganic base from KOH to NaOH. Promising results have been obtained in the recovery and reuse of higher generation salts by dialysis membranes. Current research aims at in the variation of the molecular structure to improve enantioselectivity in this and other organic transformation.

4. Experimental

4.1. General

All reagents were obtained commercially and used without further purification. Benzoylated dialysis tubing (Sigma D-7884, cut-off mass = 1500 $gmol^{-1}$) was stored in methanol or acetone prior to use. The ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 300 at 300 and 75 MHz, respectively, at 25°C and were referenced to external $SiMe_4$ ($\delta = 0.00$, J in Hz). Elemental analyses were performed by Kolbe, Mikroanalytisches Laboratorium (Mülheim, Germany). ESI-MS were obtained from the Biomolecular Mass Spectrometry Department of the Utrecht University. MALDI-TOF-MS spectra were acquired using a Voyager-DE BioSpectrometry Workstation (PerSeptive Biosystems Inc., Framingham, MA) mass spectrometer equipped with a nitrogen laser emitting at 337 nm. The instrument was operated in the linear mode at an accelerating voltage in the range 22000 V. External calibration was performed using C_{60}/C_{70}, and detection was performed by means of a linear detector and digitizing oscilloscope operating at 500 MHz. Sample solutions of $\sim$10 mg/mL in THF were used, and the matrix was 3,5-dihydroxybenzoic acid in THF (10 mg/mL). A solution of silver(I) trifluoroacetate in THF was added to the sample in order to improve the peak resolution. The sample solution (0.2 μL) and the matrix solution (0.2 μL) were combined and placed on a gold MALDI target and analyzed after evaporation of the solvents. CD spectra were recorded on a Jasco J-810 spectropolarimeter. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. HRMS spectra were measured on a Finnigan MAT 95S spectrometer at the Research Technical Services in the University of Alicante.

4.2. Synthesis of dendritic ammonium salts 1–3a

To a solution of cinchonidine (2.94 g, 10 mmol) in acetone (40 mL) was added the corresponding Frechet's bromide (10 mmol). The mixture was

refluxed for 3 h. After this time the solvent was removed and the residue was dissolved in CH_2Cl_2 and Et_2O was slowly added until the solution appeared to be cloudy. Then, the flask was kept at −20°C until the crystallization was completed. The purification of **3a** was achieved by dialyzing the salt in a membrane tubing for 24 h in acetone.

4.2.1. *N*-3,5-Di(benzyloxy)benzylcinchonidinium bromide 1a. Mp 215°C. IR (KBr) ν 3187, 2939, 2878, 1602, 1454, 1381, 1320, 1152, 1058, 858, 754, 696 cm^{-1}. ^1H NMR δ 8.78 (d, $J=4.6$, 1H), 8.15 (m, 1H), 7.83 (d, $J=4.6$, 1H), 7.61 (m, 1H), 7.49 (d, $J=7.3$, 4H), 7.28 (m, 6H), 7.05 (m, 2H), 6.88 (s, 2H), 6.68 (d, $J=5.5$, 1H), 6.49 (s, 1H), 6.42 (br.s 1H), 5.89 (d, $J=11.6$, 1H), 5.37 (d, $J=11.6$, 1H), 5.31 (d, $J=4.3$, 2H), 5.08 (dd, $J=12.2$, 17.7, 4H), 4.89 (app.t, 1H), 4.38 (m, 1H), 4.08 (m, 1H), 3.78 (bd, $J=12.8$, 1H), 2.94 (bt, $J=10.5$, 1H), 2.56 (app.t, $J=11.5$, 1H), 2.23 (m, 1H), 1.80 (m, 1H), 1.41 (m, 1H), 0.90 (m, 1H). ^{13}C NMR δ 159.3, 149.0, 137.0, 136.2, 129.1, 128.9, 128.7, 128.0, 127.95, 127.7, 123.7, 123.2, 119.9, 118.0, 112.9, 104.7, 70.0, 66.7, 65.5, 62.2, 60.0, 50.2, 37.9, 26.4, 25.3, 22.7. MS MALDITOF $[M^+-Br]$ 598.8. Anal. calcd for $C_{40}H_{41}BrN_2O_3$: C, 70.89; H, 6.10; Br, 11.79; N, 4.13; found C, 70.74; H, 5.98; Br, 11.63; N, 4.08. $[\alpha]_D^{25}=-160$ (c 1, $CHCl_3$).

4.2.2. *N*-Bis-3,5-[(3′,5′-di(benzyloxy)phenylmethoxy]-benzylcinchonidinium bromide 2a. Mp 164°C. IR (KBr) ν 3409, 3040, 2939, 2878, 1596, 1454, 1381, 1347, 1300, 1159, 1072, 937, 857, 743, 696 cm^{-1}. ^1H NMR δ 8.76 (d, $J=3.1$, 1H), 8.17 (m, 1H), 7.78 (m, 1H), 7.67 (m, 1H), 7.32 (m, 20H), 7.13 (m, 1H), 6.88 (m, 1H), 6.79 (s, 6H), 6.47 (s, 3H), 6.42 (br.s, 1H), 5.84 (d, $J=11.0$, 1H), 5.38 (d, $J=11.6$, 2H), 5.03 (s, 14H), 4.89 (app.dd, 1H), 4.33 (m, 1H), 4.00 (m, 1H), 3.55 (m, 1H), 2.70 (m, 2H), 2.19 (m, 1H), 1.86 (m, 2H), 1.42 (m, 1H), 1.23 (m, 1H), 0.89 (m, 1H). ^{13}C NMR δ 159.6, 158.6, 148.9, 146.5, 144.1, 140.0, 136.4, 135.5, 128.9, 128.1, 127.5, 127.4, 127.2, 122.9, 122.5, 119.3, 117.0, 112.3, 105.9, 104.0, 101.3, 69.5, 69.4, 66.1, 61.4, 59.4, 49.6, 37.0, 29.2, 25.6, 24.5, 22.0. MS ES $[M^+-Br]$ 1022.8. Anal. calcd for $C_{68}H_{65}BrN_2O_7$: C, 74.10; H, 5.94; Br, 7.25; N, 2.54; found: C, 74.25; H, 5.90; N, 2.03. $[\alpha]_D^{25}=-98$ (c 1, $CHCl_3$).

4.2.3. *N*-Tris-{3,5-[bis-3′,5′-(3″,5″-di(benzyloxy)-phenylmethoxy]}benzylcinchonidinium bromide 3a. IR (KBr) 3409, 3040, 2939, 2878, 1596, 1454, 1381, 1347, 1300, 1159, 1072, 937, 857, 743, 696 cm^{-1}. ^1H NMR δ 8.66 (d, $J=3.5$, 1H), 8.09 (m, 1H), 7.73 (m, 1H), 7.55 (m, 1H), 7.32 (m, 41H), 7.13 (m, 2H), 7.06 (m, 2H), 6.97 (m, 4H), 6.68 (s, 9H), 6.54 (m, 8H), 5.84 (d, $J=10.2$, 1H), 5.42–4.79 (m, 32H), 4.31 (m, 1H), 4.00 (m, 1H), 3.50 (m, 1H), 2.78 (m, 2H), 2.19 (m, 1H), 1.86 (m, 2H), 1.42 (m, 1H), 1.23 (m, 4H), 0.89 (m, 1H). ^{13}C NMR δ 160.4, 160.35, 159.4, 158.6, 149.6, 147.2, 144.8, 149.7, 137.1, 136.2, 129.6, 128.8, 128.3, 127.8, 123.6, 123.1, 120.0, 117.9, 113.1, 106.7, 104.7, 102.6, 101.8, 100.2, 70.3, 66.9, 65.5, 60.2, 50.5, 37.8, 32.5, 30.0, 26.4, 25.3, 22.7. MS ES $[M^+-Br]$ 1871.4. Anal. calcd for $C_{124}H_{113}BrN_2O_{15}$: C, 76.33; H, 5.84; N, 1.44; found: C, 76.26; H, 5.95; N, 1.44. $[\alpha]_D=-29$ (c 1, $CHCl_3$).

4.3. Synthesis of dendritic ammonium salts 1–3b

To a solution of the corresponding ammonium salt (1 mmol) in CH_2Cl_2 (40 mL) was added allyl bromide (3 mmol) and 0.6 mL of a 50% soln. of KOH. The mixture was stirred for 4 h. Then, the organic layer was washed with water and brine, dried, filtered and solvents removed. The resulting orange solid was recrystallized from CH_2Cl_2 and Et_2O. The purification of **3b** was achieved by dialysing the salt in a membrane tubing for 24 h in acetone.

4.3.1. *O*-Allyl *N*-3,5-di(benzyloxy)benzylcinchonidinium bromide 1b. Mp 164°C. IR (KBr) ν 3409, 3040, 2939, 2878, 1596, 1454, 1381, 1347, 1300, 1158, 1072, 937, 857, 743, 696 cm^{-1}. ^1H NMR δ 8.95 (d, $J=4.4$, 1H), 8.81 (d, $J=8.4$, 1H), 8.13 (d, $J=8.4$, 1H), 7.94 (m, 1H), 7.78 (t, $J=7.6$, 1H), 7.49 (m, 4H), 7.25–7.36 (m, 6H), 7.15 (m, 2H), 6.75 (s, 1H), 6.39 (d, $J=11.6$, 1H), 6.15 (s, 1H), 6.05 (m, 1H), 5.66 (m, 1H), 5.38 (m, *3*H), 5.20 (d, $J=11.9$, 1H), 5.14 (d, $J=11.8$, 1H), 5.02 (d, $J=10.4$, 1H), 4.77 (m, 1H), 4.58 (m, 1H), 4.43 (d, $J=11.7$, 1H), 4.22 (dd, $J=12.5$, 5.1, 1H), 4.15 (m, 2H), 3.98 (dd, $J=12.5$, 6.7, 1H), 3.25 (m, 1H), 2.94 (t, $J=11.7$, 1H), 2.41 (m, 1H), 2.00–2.23 (m, 5H), 1.65 (m, 1H), 1.36 (m, 1H). ^{13}C NMR δ 159.7, 149.3, 148.4, 139.8, 136.4, 136.1, 132.4, 130.2, 129.8, 129.1, 128.4, 127.9, 127.8, 125.1, 124.5, 119.8, 118.3, 113.0, 104.2, 70.2, 66.1, 62.1, 59.6, 51.21, 37.7, 26.7, 25.1, 22.6. MS MALDITOF $[M^+-Br]$ 638.5. Anal. calcd for $C_{43}H_{45}BrN_2O_3$: C, 71.96; H, 6.32; N, 3.90; found: C, 71.85; H, 6.27; N, 3.81. $[\alpha]_D^{25}=-48$ (c 1, $CHCl_3$).

4.3.2. *O*-Allyl-*N*-bis-3,5-[(3′,5′di(benzyloxy)phenylmethoxy]benzylcinchonidinium bromide 2b. Mp 91°C. IR (KBr) ν 3409, 3066, 3033, 2932, 2878, 1596, 1454, 1381, 1300, 1159, 1051, 843, 743, 696 cm^{-1}. ^1H NMR δ 8.95 (d, $J=4.4$, 1H), 8.78 (app t, $J=9.5$, 1H), 8.14 (d, $J=8.4$, 1H), 1H), 7.93 (m, 1H), 7.79 (m, 1H), 7.12–7.51 (m, 21H), 6.73 (m, 5H), 6.54 (s, 2H), 6.36 (app t, $J=13.0$, 1H), 6.15 (s, 1H), 6.03 (m, 1H), 5.64 (m, 1H), 5.26–5.42 (m, 4H), 4.92–5.22 (m, 12H), 4.58 (m, 1H), 4.43 (app. t, $J=12.8$, 1H), 4.08–4.23 (m, 2H), 3.95 (m, 1H), 3.30 (m, 1H), 2.84–3.03 (m, 1H), 2.43 (m, 1H), 2.02 (m, 6H), 1.67 (m, 1H), 1.38 (m, 1H). ^{13}C NMR δ 160.1, 159.8, 149.4, 148.5, 139.9, 139.0, 136.7, 136.5, 136.2, 136.0, 132.4, 130.4, 129.9, 128.9, 128.5, 128.4, 128.3, 128.0, 127.6, 127.1, 124.5, 120.0, 119.8, 118.4, 113.0, 112.9, 106.5, 104.3, 101.6, 72.3, 72.2, 70.1, 62.4, 59.8, 59.7, 51.2, 51.1, 37.8, 37.7, 26.8, 26.7, 25.2, 22.7. MS ES $[M^+-Br]$ 1061.7. Anal. calcd for $C_{71}H_{69}BrN_2O_7$: C, 74.66; H, 6.09; N, 2.45; found: C, 74.57; H, 6.16; N, 2.53. $[\alpha]_D=-73$ (c 1, $CHCl_3$).

4.3.3. *O*-Allyl-*N*-tris-3,5-[bis-3′,5′-(3″,5″-di(benzyloxy)phenylmethoxy]benzylcinchonidinium bromide 3b. IR (KBr) ν 3409, 3040, 2939, 2878, 1596, 1454, 1381, 1347, 1300, 1159, 1072, 937, 857, 743, 696 cm^{-1}. ^1H NMR δ 8.95 (d, $J=3.6$, 1H), 8.88 (m, 1H), 8.27 (m, 1H), 8.14 (d, $J=7.6$, 1H), 8.05 (m, 1H), 7.88–7.21 (m, 40H), 6.79 (m, 4H), 6.71 (s, 15H), 6.59 (m, 10H), 6.03 (m, 2H), 5.37–4.88 (m, 35H), 4.62 (m, 1H), 4.40 (m, 1H), 4.17 (m, 1H), 3.93 (m, 2H), 3.42 (m, 2H), 2.98 (m, 2H), 2.43

(m, 2H), 1.95 (m, 2H), 1.30 (m, 2H), 0.96 (m, 1H). ^{13}C NMR δ 160.0, 159.8, 159.6, 150.0, 149.3, 148.4, 139.7, 139.3, 139.2, 139.1, 138.9, 135.9, 133.7, 132.3, 130.3, 129.8, 129.3, 129.1, 128.8, 128.4, 128.1, 127.8, 127.4, 126.8, 125.5, 124.6, 121.1, 119.9, 112.9, 106.3, 105.6, 104.0, 101.4, 100.5, 70.1, 66.9, 65.9, 62.2, 51.2, 37.6, 29.6, 26.6, 25.2, 22.7. MS ES [M$^+$–Br] 1911.2. Anal. calcd for $C_{127}H_{117}BrN_2O_{15}$: C, 76.61; H, 5.92; N, 1.41; found: C, 76.69; H, 5.87; N, 1.43. $[\alpha]_D = -16$ (*c* 1, $CHCl_3$).

4.4. Alkylation general procedure. Synthesis of 6

A mixture of **5** (0.5 mmol, 140 mg), benzyl bromide (2.5 mmol, 425 μL) and the catalyst (0.05 mmol) in toluene/$CHCl_3$ (7/3 v/v, 2.5 mL) was cooled and an aq. 50% solution of KOH (0.75 mL) or NaOH (0.55 mL) was added. The mixture was vigorously stirred and monitored by GLC. When the reaction was finished, water (15 mL) was added and the mixture was extracted with AcOEt (3×15 mL). The organics extracts were combined and dried (Na_2SO_4) then evaporated to dryness in vacuo.

4.4.1. Isopropyl 2-diphenylmethyleneamino-3-phenyl-propionate 6a. IR (film) *v* 3063, 3032, 2976, 2935, 1742, 1629 cm^{-1}. ^{1}H NMR δ 7.79 (d, $J=7.9$, 1H), 7.03–7.60 (m, 13H), 6.62 (m, 1H), 5.04 (hept, $J=6.1$, 1H), 4.19 (dd, $J=9.2$, 4.3, 1H), 3.17, 3.27 (2dd, $J=13.1$, 9.2, 4.3, 2H), 1.21 (2d, $J=6.5$, 6H). ^{13}C NMR δ 171.1, 170.5, 139.4, 138.0, 136.1, 132.3, 130.1, 130.0, 129.7, 128.6, 128.1, 128.0, 127.8, 127.5, 126.1, 68.2, 67.3, 39.5, 21.7. MS *m*/*z* [M$^+$], 371. HRMS calcd for $C_{22}H_{25}NO_2$: 371.1885. Found 371.1847.

4.4.2. Isopropyl 3-(4-cyanophenyl)-2-diphenylmethyleneaminopropanoate 6b. Mp 145°C. IR (KBr) *v* 3066, 2979, 2932, 2905, 2227, 1737, 1622 cm^{-1}. ^{1}H NMR δ 7.80 (d, $J=8.4$, 1H), 7.66 (d, $J=6.7$, 1H), 7.26–7.62 (m, 10H), 7.18 (d, $J=8.3$, 2H), 6.70 (m, 1H), 5.04 (hept, $J=6.3$, 1H), 4.20 (dd, $J=8.6$, 4.8, 1H), 3.24, 3.31 (2dd, $J=13.3$, 8.6, 4.8, 2H), 1.22 (2d, $J=6.3$, 6H). ^{13}C NMR δ 171.1, 170.5, 144.0, 139.0, 135.9, 132.6, 132.3, 131.8, 130.5, 130.0, 128.7, 128.6, 128.3, 128.2, 128.0, 127.7, 127.5, 127.0, 119.0, 110.1, 68.8, 64.6, 39.6, 21.7. MS *m*/*z* [M$^+$], 396 HRMS calcd for $C_{22}H_{17}N_2$: 309.1384. Found 309,1392.

4.4.3. Isopropyl 3-(2-naphthyl)-2-diphenylmethyleneaminopropanoate 6c. IR (film) 3023, 3057, 2979, 2931, 2868, 1732, 1664 cm^{-1}. ^{1}H NMR δ 7.81–7.14 (m, 15H), 6.54 (d, $J=7.0$, 2H), 5.04 (hept, $J=6.3$, 1H), 4.31 (dd, $J=9.2$, 4.4, 1H), 3.33, 3.47 (2dd, $J=13.3$, 9.2, 4.4, 2H), 1.22 (2d, $J=6.3$, 6H). ^{13}C NMR δ 171.2, 170.7, 139.4, 137.5, 136.1, 135.6, 133.4, 132.3, 132.1, 130.1, 129.0, 128.7, 128.3, 128.2, 128.0, 127.6, 127.5, 127.4, 125.7, 125.2, 68.4, 67.3, 39.7, 21.7. MS *m*/*z* [M$^+$], 421 HRMS calcd for $C_{29}H_{27}NO_2$: 421.2042. Found 421.2065.

4.4.4. Isopropyl 2-diphenylmethyleneaminohexanoate 6d. IR (film) *v* 3063, 2965, 2924, 2848, 1742, 1655 cm^{-1}3023, 3057, 2979, 2931, 2868, 1732, 1664 cm^{-1}. ^{1}H NMR δ 7.66–7.51 (m, 3H), 7.81 (m, 1H), 7.48–7.29 (m, 5H), 7.17 (m, 1H), 5.06 (m, 1H), 3.98 (m, 1H), 1.89 (m, 2H), 1.34 (m, 2H), 1.25 (m, 8H), 0.8 (t, $J=7.2$, 3H). ^{13}C NMR δ 171.2, 171.6, 137.7, 132.4, 130.1, 128.3, 69.8, 60.4, 29.7, 22.2, 21.7, 13.6. MS *m*/*z* [M$^+$], 337. HRMS calcd for $C_{22}H_{27}NO_2$: 337.2042. Found 337.2077.

4.4.5. Isopropyl 3-(3,5-dimethoxyphenyl)-2-diphenylmethyleneaminopropanoate 6e. IR (film) *v* 3062, 2979, 2941, 2839, 1741, 1606, 1209, 1156 cm^{-1}. ^{1}H NMR δ 7.80 (d, $J=7.0$, 1H), 7.58 (m, 2H), 7.48 (t, $J=7.3$, 1H), 7.39–7.23 (m, 4H), 7.17 (d, $J=7.4$, 1H), 6.66 (d, $J=7.4$, 1H), 6.28 (t, $J=2.3$, 1H), 6.20 (d, $J=2.3$, 2H), 5.05 (hept, $J=6.2$, 1H), 4.19 (dd, $J=9.3$, 4.3, 1H), 3.63 (s, 6H), 3.11, 3.20 (2dd, $J=13.2$, 9.3, 4.3, 2H), 1.24 (2d, $J=6.2$, 6H). ^{13}C NMR δ 171.2, 170.6, 160.4, 140.3, 139.4, 136.1, 132.4, 130.2, 130.1, 129.0, 128.7, 128.25, 128.2, 128.15, 128.0, 127.9, 125.7, 125.3, 107.4, 99.1, 68.4, 67.2, 55.1, 39.9, 21.8. MS *m*/*z* [M$^+$], 431. HRMS calcd for $C_{27}H_{29}NO_4$: 431.2097. Found 431.2057.

Acknowledgements

This work was supported by the Council for Chemical Sciences from the Dutch Organisation for Scientific Research (CW-NOW), the Netherlands Research School Combination Catalysis (NRSC-C), University of Utrecht, the Ministerio de Ciencia y Tecnología (MCyT) of Spain (DG, research project BQU2001-0724-C02-01), Generalitat Valenciana (CTIOIB/2002/320) and the University of Alicante. G.G. thanks the European Commission for a Marie Curie fellowship (Contract No. HPMF-CT-2000-00472).

References

1. (a) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A., III *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138–157; (b) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Molecules*: *Concepts*, *Syntheses*, *Perspectives*; VCH: Weinheim, 1996.
2. (a) Ardoin, N.; Astruc, D. *Bull. Soc. Chim. Fr.* **1995**, *132*, 875–909; (b) Bosman, A. W.; Jansen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665–1688.
3. (a) Kreiter, R.; Kleij, A. W.; Klein Gebbink, R. J. M.; van Koten, G. *Top. Curr. Chem.* **2001**, *217*, 163–199; (b) Oosterom, G. E.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1828–1849; (c) Kleij, A. W.; Ford, A.; Jastrzebski, J. T. B. H.; van Koten, G. *Dendrimers and other Dendritic Polymers*; John Wiley & Sons: Sussex, 2001; pp. 485–514; (d) Dijkstra, H. P.; Van Klink, G. P. M.; Van Koten, G. *Acc. Chem. Res.* **2002**, 798–810; (e) Romagnoli, B.; Hayes, W. *J. Mater. Chem.* **2002**, *12*, 767–799.
4. (a) Peerlings, H. W. I.; Meijer, E. W. *Chem. Eur. J.* **1997**, *3*, 1563–1570; (b) Seebach, D.; Rheiner, P. B.; Greiveldinger, G.; Butz, T.; Sellner, H. *Top. Curr. Chem.* **1998**, *197*, 125–164; (c) Thomas, C. W.; Tor, Y. *Chirality* **1998**, *10*, 53–59.

5. (a) Sanders-Hovens, M. S. T. H.; Jansen, J. F. G. A.; Vekemans, J. A. J. M.; Meijer, E. W. *Polym. Mater. Sci. Eng*. **1995**, *73*, 338–339; (b) Bolm, C.; Derrien, N.; Seger, A. *Synlett* **1996**, 387–388; (c) Yamago, S.; Furukawa, M.; Azuma, A.; Yoshida, J.-L. *Tetrahedron Lett*. **1998**, *39*, 3783–3786; (d) Hovestad, N. J.; Jastrzebski, J. T. B. H.; van Koten, G. *Polym. Mater. Sci. Eng*. **1999**, *80*, 53–54; (e) Rheiner, P. B.; Seebach, D. *Chem. Eur. J*. **1999**, *5*, 3221–3236; (f) Hu, Q.-S.; Pugh, V.; Sabat, M.; Pu, L. *J. Org. Chem*. **1999**, *64*, 7528–7536; (g) Sato, I.; Shibata, T.; Ohtabe, K.; Kodaka, R.; Hirokawa, Y.; Shirai, N.; Soai, K. *Tetrahedron Lett*. **2000**, *41*, 3123–3126; (h) Fan, Q.-H.; Chen, Y.-M.; Chen, X.-M.; Jiang, D.-Z.; Xi, F.; Chan, A. S. C. *Chem. Commun*. **2000**, 789–790; (i) Breinbauer, R.; Jacobsen, E. N. M. *Angew. Chem., Int. Ed*. **2000**, *39*, 3604–3607; (j) Engel, G. D.; Gade, L. H. *Chem. Eur. J*. **2002**, *8*, 4319–4329; (k) Sato, I.; Kodaka, R.; Hosoi, K.; Soia, K. *Tetrahedron: Asymmetry* **2002**, *13*, 805–808; (l) Malkoch, M.; Hallman, K.; Lutsenko, S.; Hult, A.; Malmström, E.; Moberg, C. *J. Org. Chem*. **2002**, *67*, 8197–8202; (m) Arai, T.; Sekiguti, T.; Iizuka, Y.; Takizawa, S.; Sakamoto, S.; Yamaguchi, K.; Sasai, H. *Tetrahedron: Asymmetry* **2002**, *13*, 2083–2087; (n) Yang, B.-Y.; Chen, X.-M.; Deng, G.-J.; Zhang, Y.-L.; Fan, Q.-H. *Tetrahedron Lett*. **2003**, *44*, 3535–3538.
6. (a) Shmitzer, A.; Pérez, E.; Ricco-Lattes, I.; Lattes, A. *Tetrahedron Lett*. **1999**, *40*, 2947–2950; (b) Habicher, T.; Diedrich, F.; Gramlich, V. *Helv. Chim. Acta* **1999**, *82*, 1066–1095.
7. For reviews, see: (a) Martyres, D. *Synlett* **1999**, 1508–1508; (b) Nelson, A. *Angew. Chem., Int. Ed*. **1999**, *38*, 1583–1585; (c) Abellán, T.; Chinchilla, R.; Galindo, N.; Guillena, G.; Nájera, C.; Sansano, J. M. *Eur. J. Org. Chem*. **2000**, 2689–2697; (d) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*; Ojima, I.; Ed.; VCH: New York, 2000; pp. 389–411; (e) O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3–13; (f) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961–998; (g) Nájera, C. *Synlett* **2002**, 1388–1403.
8. (a) O'Donnel, M. J.; Delgado, F.; Pottorf, R. *Tetrahedron* **1999**, *55*, 6347–6362; (b) Corey, E. J.; Bo, Y.; Busch-Peterson, J. *J. Am. Chem. Soc*. **1998**, *20*, 13000–13001; (c) Lygo, B.; Crosby, J.; Lowdon, T. R.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2391–2402; (d) Jew, S.; Jeong, B.; Yoo, M.; Huh, H.; Park, K. *Chem. Commun*. **2001**, 1244–1245; (e) Chinchilla, R.; Mazón, P.; Nájera, C. *Tetrahedron: Asymmetry* **2002**, *13*, 927–931; (f) Park, K.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.; Lee, Y.-J.; Kim, M.-J.; Jew, S. *Angew. Chem., Int. Ed*. **2002**, *41*, 3036–3038.
9. (a) Zuang, Z.; Wang, Y.; Zhen, W.; Hodge, P. *React. Funct. Polym*. **1999**, *41*, 37–43; (b) Chinchilla, R.; Mazón, P.; Nájera, C. *Tetrahedron: Asymmetry* **2000**, *11*, 3277–3281; (c) Thierry, B.; Plaquevent, J.-C.; Cahard, D. *Tetrahedron: Asymmetry* **2001**, *12*, 983–986.
10. Mazón, P.; Chinchilla, R.; Nájera, C.; Guillena, G.; Kreiter, K.; Klein Gebbink, R. J. M.; van Koten, G. *Tetrahedron: Asymmetry* **2002**, *13*, 2181–2185.
11. Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc*. **1990**, *112*, 7638–7647.
12. O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507–4518.
13. The use of toluene as a solvent for this reaction led to the partial decomposition of the dendritic wedges, affording the desired product in low yields.
14. Most of the G3-cinchonidine salt **3a** was retained inside the dialysis tube, detecting in the outside layer only the excess of dendron. This experiment was repeated using dichloromethane as solvent affording similar results.
15. Chirasil-L-Val (Chrompack), 1 min 85°C, 2°C/min to 180°C. Reference racemic mixtures were prepared using tetrabutylammonium bromide as phase-transfer catalyst.
16. Obtained after HCl_g/Et_2O hydrolysis of the imine function and further reaction with trifluoroacetic anhydride. See: Oppolzer, W.; Moretti, R.; Zhou, C. *Helv. Chim. Acta* **1994**, *77*, 2363–2380.
17. De Smet, K.; Pleyser, A.; Vankelecom, I. V. J.; Jacobs, P. A. *Chem. Eur. J*. **2003**, *9*, 334–338.
18. Comina, P. J.; Beck, A. K.; Seebach, D. *Org. Process Res. Dev*. **1998**, *2*, 18–26.