Assembled Dendritic Titanium Catalysts for Enantioselective Hetero-Diels–Alder Reaction of Aldehydes with Danishefsky's Diene

Baoming Ji,[a, b] Yu Yuan,[a] Kuiling Ding,*[a] and Jiben Meng*[b]

Abstract: A new type of dendritic 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN)-derived Schiff-base ligands have been synthesized and applied to the titanium-catalyzed hetero-Diels–Alder reaction of Danishefsky's diene with aldehydes. These reactions afforded the corresponding 2-substituted 2,3-dihydro-4*H*-pyran-4-ones in quantitative yields and with excellent enantioselectivities (up to 97.2% *ee*). The disposition of the dendritic wedges and the dendron size in the ligands were found to have significant impact on the enantioselectivity of the reaction. The recovered dendritic catalyst could be reused without further addition of the Ti source or a carboxylic acid additive for at least three cycles, retaining similar activity and enantioselectivity. The high stability of this type of assembled dendritic titanium catalyst may be attributed to the stabilization effect of large-sized dendron units in the catalyst molecule. The other important phenomenon observed with this catalyst system is that a higher degree of asymmetric amplification has been achieved by attachment of the dendron unit to the chiral ligand, which represents a new advantage of dendrimer catalysts for asymmetric reactions using chiral ligands of lower optical purity.

Keywords: asymmetric catalysis · dendrimers · hetero-Diels–Alder reactions · nonlinear effect · titanium

Introduction

Dendrimers are highly branched macromolecules that have precisely defined molecular structures of nanoscale dimensions.[1] Since the pioneering work of van Koten,[2] the use of dendrimer-based catalysts, particularly of chiral dendrimer catalysts, has been an interesting topic because these structurally well-defined macromolecules not only serve as a homogeneous catalyst in solution, but are also readily recoverable after the reaction by means of physical methods, such as supra-filtration or solvent precipitation.[3] The other advantage of dendritic catalysts over linear, soluble polymeric catalysts is that the dendrimer architecture offers better control and fine-tuning of the catalyst properties through adjustment of its structure, size, shape, and solubility.[3]

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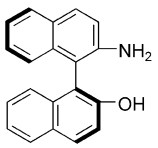
Recently, 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN, **1**), a non-C_2-symmetric chiral scaffold, and its derivatives have been the subject of extensive interest in asymmetric



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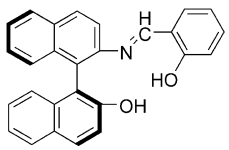

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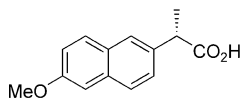

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catalysis.[4] In particular, chiral Ti^{IV} Lewis acids modified by NOBIN-derived tridentate Schiff-base ligand (**2**) and 3,5-di-*tert*-butylsalicylic acid have shown excellent asymmetric induction in Mukaiyama aldol-type reactions.[4a–c] However, a titanium complex of a polymer-supported salicylaldimine ligand showed rather poor reactivity and enantioselectivity (32% conversion and 26% *ee*) for the same reaction.[5] In our recent work, we disclosed that 2:1 (**2**:Ti) titanium complexes of **2** could be dramatically activated by addition of a carboxylic acid (**3**), so as to promote hetero-Diels–Alder (HDA) reaction of Danishefsky's diene with aldehydes with high efficiency and enantioselectivity.[6] We surmised that in the catalytic system two chiral ligands (**2**) and one carboxylate group might be involved in the active species of the tita-

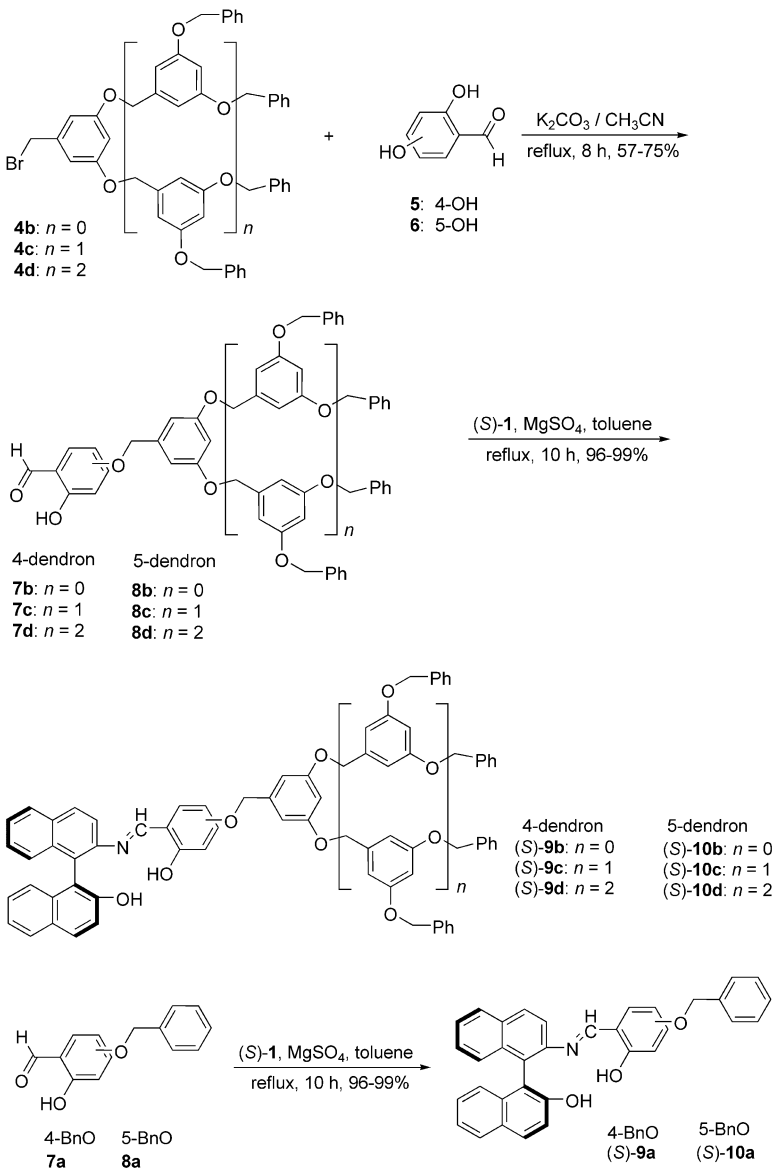
 DOI: 10.1002/chem.200305286

nium complex.[6b] Therefore, it would be hard for a cross-linked polymer ligand to form an active complex of this kind. To overcome this shortcoming of the polymer ligand, herein we report the first synthesis of dendritic tridentate ligands and the molecular assembly of dendritic catalysts through asymmetric activation[7] of tridentate titanium complexes with (*S*)-naproxen (**3**). The catalyst system that we have devised combines the advantages of high enantioselectivity of homogeneous catalysts in HDA reactions[8–10] with the ready recoverability of dendrimer molecules.

Results and Discussion

Synthesis of dendrimer-based NOBIN-derived Schiff-base ligands: The dendrimer-based NOBIN-derived Schiff-base ligands (*S*)-**9b**–(*S*)-**9d** and (*S*)-**10b**–(*S*)-**10d** were synthesized in a straightforward manner by simple condensation of (*S*)-NOBIN ((*S*)-**1**) with the corresponding dendritic salicylaldehydes (**7b–d** and **8b–d**) in 96–99% yields (Scheme 1). The dendritic salicylaldehydes were prepared by coupling of Fréchet-type dendron units (**4b–d**)[3v] with 2,4-dihydroxybenzaldehyde (**5**) and 2,5-dihydroxybenzaldehyde (**6**) under basic conditions in yields of 57–75%. Enantiomerically pure **1** could be easily obtained by optical resolution of racemic **1** through molecular complexation with *N*-benzylcinchonidium chloride following a literature procedure, where racemic **1** was prepared by cross-coupling of 2-naphthol and 2-naphthylamine with $FeCl_3$ in water.[11] The non-dendritic ligands (*S*)-**9a** and (*S*)-**10a** were prepared by condensation of (*S*)-**1** with the corresponding 4- and 5-BnO-substituted salicylaldehydes (**7a** and **8a**), respectively (Scheme 1). All eight dendritic and non-dendritic Schiff-base ligands (*S*)-**9a**–(*S*)-**9d** and (*S*)-**10a**–(*S*)-**10d** shown in Scheme 1 were characterized by ^{1}H NMR, MS, IR, and elemental analysis or HRMS.

Dendrimer effect in enantioselective hetero-Diels–Alder (HDA) reactions of aldehydes with Danishefsky's diene: Enantioselective hetero-Diels–Alder (HDA) reaction of carbonyl compounds with 1,3-dienes constitutes one of the most important asymmetric C–C bond-forming reactions in organic synthesis.[8] The reaction between 1-methoxy-3-(trimethylsilyloxyl)buta-1,3-diene (Danishefsky's diene) **11** and aldehydes **12** provides a powerful access to 2-substituted 2,3-dihydro-4*H*-pyran-4-ones (**13**), a class of heterocycles with extensive synthetic applications in both natural and non-natural products.[9,10] Seebach and co-workers have reported that a cross-linked dendritic salen–Cr^{III} catalyst promotes the HDA reaction of Danishefsky's diene with aldehydes to give the corresponding adducts with less than 80% *ee* and in 82% conversion.[3i] With the aforementioned two series of dendritic ligands (*S*)-**9b**–(*S*)-**9d** and (*S*)-**10b**–(*S*)-**10d** in hand, we investigated their asymmetric induction in the titanium-catalyzed HDA reaction of Danishefsky's diene (**11**) with benzaldehyde (**12a**) [Eq. (1)]. On the basis of our previous discovery of a synergistic effect of an added carboxylic acid on the activity of the catalyst and the enantioselectivity



Scheme 1. Synthesis of non-dendritic (**9a** and **10a**) and dendritic (**9b–d** and **10b–d**) Schiff-base ligands.

of the reaction, (*S*)-naproxen (**3**) was used as an additive to activate the titanium catalysts formed in situ by reaction of (*S*)-**9a**–(*S*)-**9d** (20 mol%) or (*S*)-**10a**–(*S*)-**10d** (20 mol%) with [Ti(O*i*Pr)$_4$] (10 mol%). As expected, the addition of 5 mol% of (*S*)-naproxen significantly enhanced the enantioselectivity of the reaction from 32.6% *ee* (12% yield) and 48.7% *ee* (63% yield) to 93.7% *ee* (99% yield) and 95.1% *ee* (99% yield), respectively, when non-dendritic ligands (*S*)-**9a** and (*S*)-**10a** were used (Figure 1). This observation again demonstrates the importance of the carboxylic acid additive for the activation of the tridentate titanium complex.[6] Accordingly, the evaluation of different generations of dendritic chiral ligands was carried out under standard conditions with a molar ratio of dendritic ligand/[Ti(O*i*Pr)$_4$]/**3**/**11**/**12a** = 0.2:0.1:0.05:1.6:1.

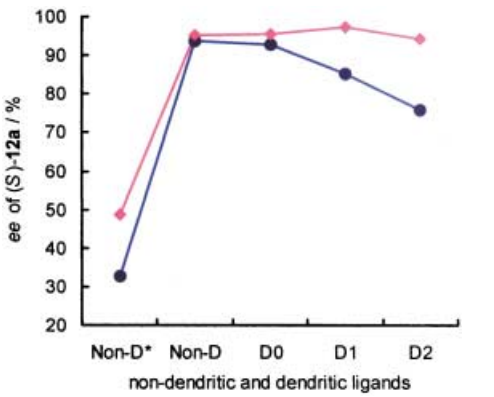
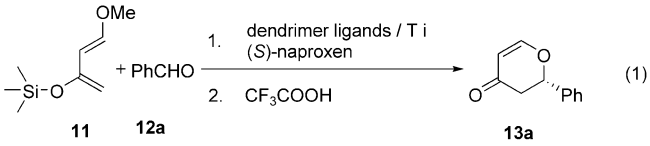


Figure 1. Effect of dendrimer size and disposition of the dendritic wedges on the enantioselectivity of the HDA reactions. Bottom line: 4-substituted ligands ((*S*)-**9a**–(*S*)-**9d**); top line: 5-substituted ligands ((*S*)-**10a**–(*S*)-**10d**). Non-D: non-dendritic ligands (*S*)-**9a** and (*S*)-**10a**; *In the absence of **3**; D0–D2: dendritic ligands (*S*)-**9b**–(*S*)-**9d** and (*S*)-**10b**–(*S*)-**10d** with n = 0–2.

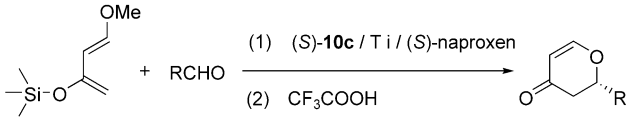


(1)

As shown in Figure 1, catalysts composed of various generations of the dendritic ligands ((*S*)-**9b**–(*S*)-**9d** and (*S*)-**10b**–(*S*)-**10d**) promoted the reaction of **11** with **12a** to give the cycloadduct (*S*)-**13a** with good to excellent enantioselectivities in quantitative yields. A general trend in the asymmetric induction efficiency is that the 5-substituted dendritic ligands ((*S*)-**10b**–(*S*)-**10d**) proved to be superior to the 4-substituted derivatives ((*S*)-**9b**–(*S*)-**9d**). This observation clearly demonstrates the importance of the disposition of the dendritic wedge on the enantioselectivity of the reaction. In the catalysis using 4-substituted dendrimer ligands ((*S*)-**9b**–(*S*)-**9d**), the enantioselectivities of the reaction gradually diminished with increasing size of the dendron attached to the NOBIN-derived salicylaldimine core. Evidently, steric hindrance is disadvantageous with regard to the enantioselectivity of this reaction. Therefore, attachment of the dendron moiety at the 5-position of salicylaldimine was envisaged as a way of obviating this problem. As expected, titanium complexes of 5-substituted dendritic ligands ((*S*)-**10b**–(*S*)-**10d**) in the presence of **3** showed excellent enantioselectivities (94.4–97.2% *ee*) in the HDA reaction of **11** with **12a**. The synergistic effect of the dendrons was also observed with these ligands. With increasing size of the dendron moiety attached to the ligands, the enantioselectivities of the reaction were improved from 95.1% *ee* ((*S*)-**10a**) and 95.4% *ee* ((*S*)-**10b**) to 97.2% *ee* ((*S*)-**10c**). When the dendron size was further increased to n = 2 ((*S*)-**10d**), the enantioselectivity dropped slightly without any loss of catalytic activity. Taken together, the results demonstrate that correct disposition of the dendron wedges at the NOBIN-derived salicylaldimine core and adjustment of dendron size are key points for achieving maximum asymmetric induction in the present catalyst system.

Scope of substrates and reusability of the dendrimer catalyst: On the basis of the results outlined above, we selected dendritic ligand (*S*)-**10c** for further studies extending the scope of the substrates used in the reaction. As shown in Table 1, the catalyst prepared from (*S*)-**10c** and [Ti(O*i*Pr)$_4$] in the presence of **3** was applicable to the promotion of HDA reactions of **11** with a variety of aldehydes **12a–l**, including aromatic, olefinic, and aliphatic derivatives (entries 1–12), to give the corresponding 2-substituted 2,3-dihydro-4*H*-pyran-4-ones **13a–l** in quantitative yields and with excellent enantioselectivities (up to 97.2% *ee*). These results are comparable to, or even better than, those achieved using

Table 1. Dendritic chiral Schiff-base Ti^{IV}-catalyzed asymmetric HDA reactions of Danishefsky's diene **11** with aldehydes **12**.[a]



Entry	R	Yield [%][b]	*ee* [%][c]
1	phenyl (**a**)	99	97.2
2	3-methylphenyl (**b**)	99	96.6
3	4-methylphenyl (**c**)	99	94.0
4	3-methoxyphenyl (**d**)	99	93.3
5	4-methoxyphenyl (**e**)	99	93.2
6	3-chlorophenyl (**f**)	99	94.0
7	4-chlorophenyl (**g**)	99	90.2
8	3-bromophenyl (**h**)	99	95.4
9	4-bromophenyl (**i**)	99	90.2
10	4-nitrophenyl (**j**)	99	90.1
11	*trans*-cinnamyl (**k**)	99	92.0
12	phenylethyl (**l**)	99	63.6
13	phenyl (**a**) (cycle 1)[d]	99	97.0
14	phenyl (**a**) (cycle 2)[d]	95	96.8
15	phenyl (**a**) (cycle 3)[d]	90	95.3

[a] All of the reactions were carried out with (*S*)-**10c**/[Ti(O*i*Pr)$_4$]/additive/substrate = 0.2:0.1:0.05:1 at room temperature in toluene for 48 h. [b] Yields of isolated products for two steps. [c] The enantiomeric excesses were determined by HPLC on a Chiralcel OD column. [d] Recovered catalyst was used.

non-dendritic catalysts.[6a] The advantage of reusability of this type of dendritic catalyst was exemplified in the catalysis of the reaction of **11** with **12a**. Upon completion of the reaction, hexane was added to the reaction mixture, whereupon the catalyst was quantitatively precipitated and could be recovered by filtration. The recovered catalyst could be reused for at least three cycles, retaining its activity and enantioselectivity (Table 1, entries 13–15). The common problems associated with the use of dendritic catalysts in catalyst recycling, such as catalyst decomposition, metal leaching, and catalyst deactivation, were not observed with our catalyst system. In the recycling experiments, further addition of $[Ti(O\mathit{i}Pr)_4]$ and the (*S*)-naproxen additive proved to be unnecessary. This result demonstrates that the active species of the dendritic titanium complex was sufficiently stable to tolerate the recovery process. The high degree of stability of this type of titanium catalyst might be attributed to the presence of the large-sized dendron units in the catalyst molecule, which prevent decomposition of the active site in the catalyst core.

Influence of the dendrimer on the positive nonlinear effect: The influence of the dendrimer on the degree of positive nonlinear effect (NLE)[12] of the present catalytic system was also substantial. As shown in Figure 2, the *S* product could be obtained with 90% *ee* using (*S*)-**10c** of only

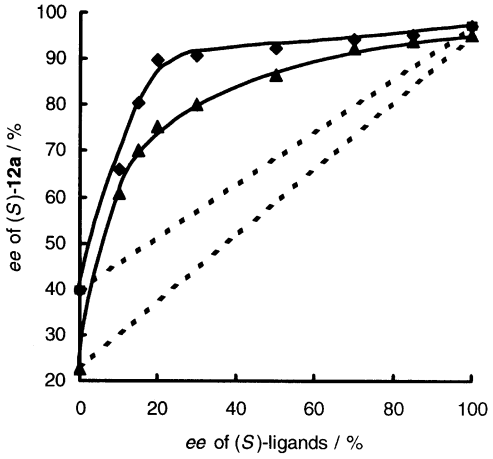
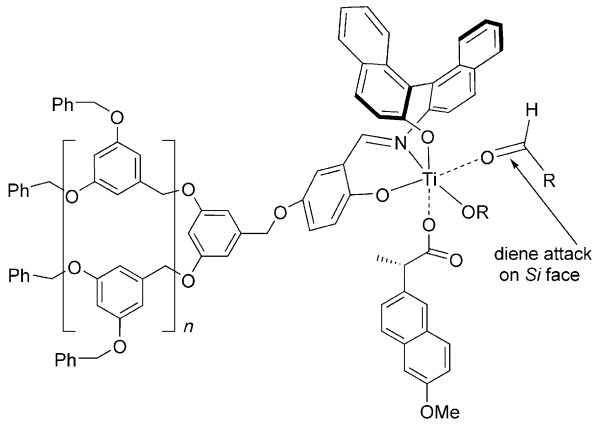


Figure 2. Comparison of nonlinear effects with dendritic ((*S*)-**10c**, top line) and non-dendritic ((*S*)-**10a**, bottom line) catalyst systems in the HDA reaction of **11** with **12a**. The broken line indicates the expected *ee* values without a nonlinear effect.

20% *ee*, which is much higher than that expected (top line). This observation again demonstrates the existence of a positive NLE with the present catalyst system.[6] Moreover, the positive NLE with this dendritic catalyst system is much stronger than that observed for non-dendritic catalyst systems (bottom line), which indicates a higher difference of turnover efficiency between the homochiral pre-catalyst ($[(S)$-**10c**$]_2$Ti) and the heterochiral one ($[(\pm)$-**10c**$]_2$Ti) than that between non-dendritic pre-catalysts ($[(S)$-**10a**$]_2$Ti and $[(\pm)$-**10a**$]_2$Ti). Therefore, a higher degree of asymmetric amplification in the catalysis of the HDA reaction could be achieved by the attachment of the dendron moiety to the chiral ligand, and this represents *a new advantage of dendrimer catalysts in asymmetric reactions in that chiral ligands of lower optical purity can be used*.

Working model proposed to rationalize the asymmetric induction: On the basis of our previous results from mechanistic studies[6] and the present observations of a synergistic effect of the chiral carboxylic acid additive on the enantioselectivity of the dendritic catalyst, as well as a very strong positive NLE in the catalytic system, a working model of the assembled dendritic catalyst in HDA reactions of Danishefsky's diene with aldehydes is outlined in Scheme 2. Here, the active species of the titanium complex is five-coor-



Scheme 2. Working model of the assembled dendritic catalyst in HDA reactions of Danishefsky's diene with aldehydes.

dinate and the aldehyde coordinates to the titanium atom at the remaining coordination site as depicted. Accordingly, the bound aldehyde undergoes attack of the diene from the *Si* face to give the product with *S* configuration, as observed. Clearly, the dendron moiety in the catalyst molecule has no significant direct impact on the active site of the titanium complex, but its large size might influence the stability of the catalyst precursor and the activated species and, as a result, make the catalyst system highly stable, such that it tolerates the recovery process, and impart a much more strongly positive NLE, such that asymmetric catalysis can be carried out using ligands of lower enantiopurity.

Conclusion

In summary, we have devised a new type of dendritic titanium catalysts by molecular assembly of chiral dendritic Schiff-base ligands, titanium(IV) ions, and a chiral activator ((*S*)-naproxen). The present catalytic system represents an excellent dendritic catalyst for asymmetric reactions, on the basis of the following features: i) very high enantioselectivity (up to 97.2% *ee*) and catalytic activity (>99% yields) were achieved with a broad range of substrates, which exceed those obtained with non-dendritic ligands in some cases; ii) enhanced enantioselectivity was observed by optimizing

the disposition and size of the dendron moieties in the ligands; iii) large-sized dendron units in the catalyst molecule would seem to stabilize the active species of the titanium complex, enabling its reuse for at least three cycles while retaining similar activity and enantioselectivity; iv) a higher degree of asymmetric amplification in the catalysis of HDA reactions was observed with the dendritic chiral ligand than with non-dendritic species, which represents a new advantage of dendrimer catalysts for asymmetric reactions in that chiral ligands of lower optical purity can be used.

Experimental Section

General methods: Unless otherwise stated, all reagents were purchased from Aldrich, Acros or TCI and were used without further purification. Powdered 4 Å molecular sieves (>5 micron) were dried in a vacuum oven at 135 °C prior to use. Liquid aldehydes were freshly distilled before use. Solid aldehydes were purified by column chromatography before use. Acetonitrile and dichloromethane were distilled from calcium hydride prior to use. Tetrahydrofuran (THF) and toluene were distilled from sodium/benzophenone prior to use. Acetone was distilled from phosphorus pentoxide. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-300 BB NMR spectrometer (300 MHz) with $CDCl_3$ as solvent and are reported in ppm relative to tetramethylsilane as an internal standard. Coupling constants, *J*, are listed in hertz. IR spectra were recorded on a Bio-Rad FTS-185 spectrometer. EI mass spectra were obtained on a HP 5989 A spectrometer. ESI and MALDI mass spectra were determined on a Bruker APEX III 7.0 TESLA FT-MS. C, H, and N elemental analyses were performed with an elemental Foss-Heraeus VARIO EL apparatus. Optical rotations were measured with a PE-341 automatic polarimeter. Liquid chromatographic analyses were conducted on a JASCO 1580 system. All experiments that were sensitive to moisture or air were carried out under argon atmosphere using standard Schlenk techniques.

General procedure for the synthesis of dendritic salicylaldehyde derivatives: 2-Hydroxy-4-benzyloxy-benzaldehyde (**7a**), 2-hydroxy-5-benzyloxybenzaldehyde (**8a**), and dendritic benzyl bromides (**4b**, **4c**, and **4d**) were prepared according to literature procedures.[13,14] A mixture of dendritic benzyl bromide (1.00 equiv), 2,4-dihydroxybenzaldehyde or 2,5-dihydroxybenzaldehyde (1.2 equiv), dried potassium carbonate (1.5 equiv), and potassium iodide (0.1 equiv) in dry acetonitrile was heated to reflux and stirred vigorously under argon atmosphere for 10 h. The mixture was allowed to cool and then concentrated to dryness under reduced pressure. The residue was partitioned between 1 N aqueous HCl and CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were then washed with saturated aqueous $NaHCO_3$ and with brine, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude product was then purified as outlined in the following paragraphs.

7b: This compound was prepared by the reaction of **4b** with 2,4-dihydroxybenzaldehyde and was purified by flash chromatography on silica gel with CH_2Cl_2/hexane (1:2) as eluent. Yield: 70.5 %. M.p. 95–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 11.47 (s, 1H; OH), 9.72 (s, 1H; CHO), 7.47–7.26 (m, 10H; ArH), 6.64–6.47 (m, 6H; ArH), 5.04 (s, 4H; $PhCH_2O$), 5.03 ppm (s, 2H; $PhCH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.35, 165.63, 164.29, 160.13, 137.97, 136.52, 135.24, 128.53, 127.99, 127.47, 127.27, 115.25, 108.75, 106.22, 101.60, 70.07, 70.02 ppm; IR (KBr): $\tilde{\nu}$ = 3031, 2926, 2833, 1674, 1641, 1597, 1515, 1498, 1454, 1472, 1340, 1289, 1218, 1165, 1049, 1038, 981, 857, 834, 808, 744, 695, 648 cm^{-1}; EI-MS (70 eV): *m*/*z* (%): 440 (5.8) [M^+], 91 (100), 303 (21.7), 65 (9.2), 181 (5.2), 92 (4.5), 211 (4.1), 304 (3.3); elemental analysis calcd (%) for $C_{28}H_{24}O_5$: C 76.36, H 5.45; found: C 76.03, H 5.58.

7c: This compound was prepared by the reaction of **4c** with 2,4-dihydroxybenzaldehyde and was purified by flash chromatography on silica gel with CH_2Cl_2/hexane (1:1) as eluent. Yield: 75.2 %. M.p. 134–136 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 11.48 (s, 1H; OH), 9.70 (s, 1H; CHO), 7.45–7.33 (m, 20H; ArH), 6.69–6.90 (m, 11H; ArH), 6.49 (d, *J* = 1.8 Hz, 1H; ArH), 5.04 (s, 8H; $PhCH_2O$), 4.98 ppm (s, 6H; $PhCH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.39, 165.65, 164.31, 160.10, 160.06, 139.02, 138.02, 136.65, 135.28, 128.54, 127.97, 127.51, 125.32, 115.27, 108.79, 106.27, 101.66, 101.62, 101.46, 70.09, 70.01, 69.92 ppm; IR (KBr): $\tilde{\nu}$ = 3034, 2862, 1648, 1629, 1598, 1507, 1498, 1452, 1376, 1342, 1291, 1222, 1159, 1055, 1032, 980, 863, 822, 806, 734, 695, 678 cm^{-1}; EI-MS (70 eV): *m*/*z* (%): 864 (0.24) [M^+], 91 (100), 303 (17.7), 773 (16.1), 92 (12.5), 211 (9.4), 302 (9.0), 213 (7.8), 181 (6.6); elemental analysis calcd (%) for $C_{56}H_{48}O_9$: C 77.78, H 5.56; found: C 77.33, H 5.96.

7d: This compound was prepared by the reaction of **4d** with 2,4-dihydroxybenzaldehyde and was purified by flash chromatography on silica gel with CH_2Cl_2/hexane (2:1) as eluent. Yield: 57.2 %. M.p. 122–124 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 11.44 (s, 1H; OH), 9.65 (s, 1H; CHO), 7.45–7.25 (m, 40H; ArH), 6.73–6.45 (m, 24H; ArH), 5.01–4.95 (m, 16H; $PhCH_2O$), 4.89 ppm (s, 14H; $PhCH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.35, 165.58, 164.26, 160.04, 159.95, 139.08, 139.06, 139.01, 138.06, 137.84, 136.64, 135.25, 128.72, 128.49, 127.92, 127.78, 127.48, 126.93, 115.22, 108.72, 106.26, 101.56, 101.43, 70.32, 70.13, 69.94, 69.83 ppm; IR (KBr): $\tilde{\nu}$ = 3032, 2927, 2871, 1595, 1498, 1449, 1373, 1295, 1217, 1151, 1049, 830, 736, 696, 680 cm^{-1}; ESI-MS [M+Na$^+$]: 1736.7; elemental analysis calcd (%) for $C_{112}H_{96}O_{17}$: C 78.50, H 5.61; found: C 78.22, H 5.82.

8b: This compound was prepared by the reaction of **4b** with 2,5-dihydroxybenzaldehyde and was purified by flash chromatography on silica gel with EtOAc/hexane (1:5) as eluent. Yield: 74.2 %. M.p. 98–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = (s, 1H; OH), 9.81 (s, 1H; CHO), 7.45–7.34 (m, 10H; ArH), 7.22–7.18 (m, 1H; ArH), 7.02 (d, *J* = 3.0 Hz, 1H; ArH), 6.94 (d, *J* = 9.0 Hz, 1H; ArH), 6.68 (d, *J* = 3.0 Hz, 2H; ArH), 6.60–6.59 (m, 1H; ArH), 5.06 (s, 4H; $PhCH_2O$), 5.01 ppm (s, 2H; $PhCH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.07, 160.11, 156.14, 151.54, 138.92, 136.58, 128.54, 127.98, 127.44, 125.94, 119.95, 118.64, 116.68, 106.13, 101.47, 70.61, 70.00 ppm; IR (KBr): $\tilde{\nu}$ = 3033, 2926, 2832, 1661, 1598, 1486, 1373, 1346, 1296, 1272, 1218, 1166, 1062, 1047, 1019, 959, 862, 830, 814, 742, 693, 675, 632 cm^{-1}; EI-MS (70 eV): *m*/*z* (%): 440 (1.8) [M^+], 91 (100), 303 (32.5), 57 (16.4), 43 (13.5), 69 (10.0), 71 (9.8), 55 (9.6), 41 (9.2); elemental analysis calcd (%) for $C_{28}H_{24}O_5$: C 76.36, H 5.45; found: C 76.16, H 5.66.

8c: This compound was prepared by the reaction of **4c** with 2,5-dihydroxybenzaldehyde and was purified by flash chromatography on silica gel with CH_2Cl_2/hexane (3:1) as eluent. Yield: 76.0 %. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 10.71 (s, 1H; OH), 9.80 (s, 1H; CHO), 7.46–7.35 (m, 20H; ArH), 7.22–7.15 (m, 1H; ArH), 7.08–6.90 (m, 2H; ArH), 6.71–6.59 (m, 9H; ArH), 5.06 (s, 8H; $PhCH_2O$), 5.01 ppm (s, 6H; $PhCH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.08, 160.05, 159.99, 156.11, 151.53, 139.05, 138.94, 136.60, 128.63, 127.96, 127.49, 125.87, 119.95, 118.63, 116.68, 106.25, 106.11, 101.51, 101.35, 70.58, 69.98, 69.85 ppm; IR (KBr): $\tilde{\nu}$ = 3034, 2862, 1648, 1629, 1598, 1507, 1498, 1452, 1376, 1342, 1291, 1222, 1159, 1055, 1032, 980, 863, 822, 806, 734, 695, 678 cm^{-1}; ESI-MS [M+Na$^+$]: 887.3; HR-MS (ESI): calcd for $C_{56}H_{48}O_9Na$ [M+Na$^+$] 887.3190; found: 887.3213.

8d: This compound was prepared by the reaction of **4d** with 2,5-dihydroxybenzaldehyde and was purified by flash chromatography on silica gel with CH_2Cl_2/hexane (10:1) as eluent. Yield 63.2 %. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = (s, 1H; OH), 9.63 (s, 1H; CHO), 7.43–7.31 (m, 40H; ArH), 6.74–6.57 (m, 24H; ArH), 5.02 (s, 16H; $PhCH_2O$), 4.96 ppm (s, 14H; $PhCH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.05, 160.02, 159.97, 159.93, 156.04, 151.46, 139.06, 138.94, 136.63, 128.47, 128.14, 127.89, 127.45, 127.03, 125.77, 119.91, 118.54, 118.49, 116.64, 106.25, 106.13, 101.52, 101.40, 70.47, 70.32, 69.91, 69.80 ppm; IR (KBr): $\tilde{\nu}$ = 3031, 2870, 1656, 1595, 1497, 1450, 1374, 1295, 1270, 1152, 1045, 830, 735, 695 cm^{-1}; ESI-MS [M+Na$^+$]: 1736.7; HRMS (ESI): calcd. for $C_{112}H_{96}O_{17}Na$ [M+Na$^+$] 1735.6540; found: 1735.6546.

General procedure for the preparation of dendritic Schiff-base derivatives: Enantiopure NOBIN was prepared according to the reported procedure.[11] A mixture of the appropriate dendritic salicylaldehyde derivative (1.00 equiv), (*S*)-NOBIN (1.05 equiv), dried magnesium sulfate (10.00 equiv), and *p*-toluenesulfonic acid (0.01 equiv) in dry toluene was refluxed and stirred vigorously under argon atmosphere for 10 h. The mixture was then allowed to cool to ambient temperature and filtered through Celite. The Celite was washed with dichloromethane. The organ-

ic filtrate was then concentrated to dryness under reduced pressure. The crude product was purified as outlined in the following paragraphs.

9a: Reaction of (*S*)-NOBIN with **7a** and purification of the product by recrystallization from CH_2Cl_2/hexane (1:5) gave **9a** as a yellow crystalline solid in 99% yield; m.p. 114–116°C; $[\alpha]_D^{20} = -207.6°$ (c = 0.33, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 12.55 (s, 1H; OH), 8.63 (s, 1H; CH=N), 8.11 (d, J = 8.7 Hz, 1H; ArH), 7.97 (dd, J = 8.1 Hz, J = 6.0 Hz, 2H; ArH), 7.89 (d, J = 7.8 Hz, 1H; ArH), 7.68 (d, J = 8.7 Hz, 1H; ArH), 7.50 (d, J = 4.2 Hz, 1H; ArH), 7.40–7.14 (m, 11H; ArH), 7.02 (d, J = 8.1 Hz, 1H; ArH), 6.45 (dd, J = 2.4 Hz, J = 6.0 Hz, 1H; ArH), 6.33 (d, J = 2.1 Hz, 1H; ArH), 4.98 ppm (s, 2H; $PhCH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.80, 163.54, 161.04, 151.39, 144.61, 136.41, 133.91, 133.84, 133.78, 132.76, 130.87, 130.48, 129.28, 128.82, 128.51, 128.50, 128.33, 127.81, 127.69, 126.85, 126.54, 126.36, 125.28, 124.80, 123.55, 117.92, 117.67, 115.97, 113.38, 108.12, 102.14, 70.16 ppm; IR (KBr): $\tilde{\nu}$ = 3523, 3053, 2928, 2829, 1609, 1589, 1508, 1433, 1346, 1283, 1244, 1218, 1202, 1115, 994, 979, 811, 748, 738, 698 cm^{-1}; EI-MS (70 eV): m/z (%): 495 (88.6) [M^+], 268 (100), 91 (50.8), 496 (49.6), 478 (48.9), 239 (16.2), 269 (13.4), 497 (12.3); HRMS (MALDI): calcd. for $C_{34}H_{26}O_3$ [M+H$^+$] 496.1907; found: 496.1897.

9b: Reaction of (*S*)-NOBIN with **7b** and purification of the product by flash chromatography on silica gel with CH_2Cl_2/hexane/Et_3N (4:6:1) as eluent gave **9b** in 97.7% yield as a yellow glass. $[\alpha]_D^{20} = -137.5°$ (c = 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 12.51 (s, 1H; OH), 8.62 (s, 1H; CH=N), 8.10 (d, J = 9.0 Hz, 1H; ArH), 7.98–7.93 (m, 2H; ArH), 7.87 (d, J = 8.1 Hz, 1H; ArH), 7.67 (d, J = 9.0 Hz, 1H; ArH), 7.51–7.12 (m, 18H; ArH), 7.01 (d, J = 8.4 Hz, 1H; ArH), 6.55–6.54 (m, 2H; ArH), 6.42 (dd, J = 2.4 Hz, J = 9.0 Hz, 1H; ArH), 6.29 (d, J = 2.1 Hz, 1H; ArH), 5.02 (s, 4H; $PhCH_2O$), 4.92 ppm (s, 2H; $PhCH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.16, 163.20, 160.27, 159.99, 151.37, 143.70, 138.54, 136.63, 133.57, 132.37, 130.34, 130.12, 128.89, 128.46, 128.19, 128.14, 127.88, 127.44, 127.26, 126.48, 126.27, 125.94, 125.39, 124.44, 123.15, 118.69, 118.02, 117.84, 117.21, 115.63, 113.02, 107.67, 106.16, 101.91, 101.56, 69.94, 69.58 ppm; IR (KBr): $\tilde{\nu}$ = 3525, 3052, 2927, 2828, 1606, 1561, 1508, 1452, 1376, 1342, 1294, 1245, 1202, 1148, 1116, 1061, 1026, 977, 833, 812, 747, 696 cm^{-1}; ESI-MS [M+H$^+$]: 708.4; HRMS (MALDI): calcd. for $C_{48}H_{38}O_5N$ [M+H$^+$] 708.2744; found: 708.2747.

9c: Reaction of (*S*)-NOBIN with **7c** and purification of the product by flash chromatography on silica gel with CH_2Cl_2/hexane/Et_3N (4:4:1) as eluent gave **9c** in 96.5% yield as a yellow glass. $[\alpha]_D^{20} = -66.1°$ (c = 0.925, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 12.50 (s, 1H; OH), 8.60 (s, 1H; CH=N), 8.10 (d, J = 8.7 Hz, 1H; ArH), 7.85–8.00 (m, 2H; ArH), 7.86 (d, J = 7.8 Hz, 1H; ArH), 7.66 (d, J = 9.1 Hz, 1H; ArH), 7.50–7.02 (m, 30H; ArH), 6.67–6.29 (m, 9H; ArH), 5.03 (s, 8H; $PhCH_2O$), 4.94 (s, 4H; $PhCH_2O$), 4.91 ppm (s, 2H; $PhCH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.88, 139.05, 138.58, 136.65, 135.20, 133.57, 133.44, 132.34, 130.11, 129.95, 129.27, 128.74, 128.45, 128.15, 128.09, 127.86, 127.44, 127.10, 127.02, 126.76, 126.39, 125.84, 124.41, 123.68, 123.41, 123.00, 122.49, 118.09, 117.95, 117.12, 115.91, 113.14, 108.65, 107.52, 106.24, 106.13, 101.81, 101.57, 101.46, 69.91, 69.78, 69.57 ppm; IR (KBr): $\tilde{\nu}$ = 3524, 3052, 2924, 2826, 1595, 1508, 1498, 1452, 1375, 1342, 1295, 1245, 1203, 1154, 1116, 1054, 1028, 978, 832, 813, 736, 696 cm^{-1}; ESI-MS [M+H$^+$]: 1132.4; HRMS (MALDI): calcd for $C_{76}H_{62}O_9N$ [M+H$^+$] 1132.4419; found: 1132.4407.

9d: Reaction of (*S*)-NOBIN with **7d** and purification of the product by flash chromatography on silica gel with CH_2Cl_2/hexane/Et_3N (4:4:1) as eluent gave **9d** in 99.0% yield as a yellow glass. $[\alpha]_D^{20} = -36.6°$ (c = 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 12.49 (s, 1H; OH), 8.54 (s, 1H; CH=N), 8.06–7.81 (m, 4H; ArH), 7.61 (d, J = 9.0 Hz, 1H; ArH), 7.42–7.27 (m, 47H; ArH), 7.09–6.98 (m, 2H; ArH), 6.68–6.52 (m, 20H; ArH), 6.41–6.26 (m, 2H; ArH), 5.01 (s, 16H; $PhCH_2O$), 4.94 (s, 8H; $PhCH_2O$), 4.93 (s, 4H; $PhCH_2O$), 4.88 ppm (s, 2H; $PhCH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.06, 160.04, 159.97, 159.93, 151.02, 144.51, 139.14, 139.10, 138.66, 136.67, 133.59, 133.50, 133.43, 132.43, 130.52, 130.13, 128.93, 128.58, 128.51, 128.45, 128.40, 128.33, 128.24, 128.17, 127.93, 127.85, 127.73, 127.56, 127.50, 127.43, 127.37, 126.52, 126.22, 126.04, 125.10, 124.45, 123.25, 117.57, 117.20, 115.79, 113.18, 106.30, 106.08, 101.48, 69.98, 69.85, 69.59 ppm; IR (KBr): $\tilde{\nu}$ = 3525, 3032, 2924, 2854, 1595, 1508, 1498, 1451, 1375, 1342, 1295, 1203, 1153, 1051, 831, 814, 735, 696, 681 cm^{-1}; ESI-MS [M+H$^+$]: 1981.9; HRMS (MALDI): calcd for $C_{132}H_{110}O_{17}N$ [M+H$^+$] 1980.7768; found: 1980.7735.

10a: Reaction of (*S*)-NOBIN with **8a** and purification of the product by recrystallization from CH_2Cl_2/hexane gave **10a** as a red crystalline solid in 95.5% yield. M.p. 112–114°C; $[\alpha]_D^{20} = -66.0°$ (c = 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 11.57 (s, 1H; OH), 8.64 (s, 1H; CH=N), 8.12 (d, J = 9.0 Hz, 1H; ArH), 7.97 (d, J = 8.4 Hz, 2H; ArH), 7.88 (d, J = 7.8 Hz, 1H; ArH), 7.67 (d, J = 9.0 Hz, 1H; ArH), 7.54–7.49 (m, 1H; ArH), 7.41–7.18 (m, 10H; ArH), 7.01 (d, J = 8.1 Hz, 1H; ArH), 6.99–6.83 (m, 2H; ArH), 6.70 (d, J = 8.7 Hz, 1H; ArH), 4.98 ppm (s, 2H; $PhCH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.26, 155.68, 151.35, 151.17, 145.21, 137.19, 133.86, 133.71, 133.03, 130.97, 130.57, 129.32, 128.83, 128.56, 128.53, 128.23, 127.82, 127.69, 126.95, 126.65, 126.63, 125.83, 124.75, 123.67, 121.82, 118.99, 118.39, 117.80, 117.64, 116.95, 116.04, 71.14 ppm; IR (KBr): $\tilde{\nu}$ = 3328, 3053, 2926, 2830, 1625, 1575, 1516, 1490, 1454, 1436, 1280, 1344, 1274, 1209, 1151, 1042, 1024, 979, 945, 927, 861, 808, 787, 747, 734, 695 cm^{-1}; ESI-MS [M+Na$^+$] 518.3; HRMS (MALDI): calcd for $C_{34}H_{26}O_3$ [M+H$^+$] 496.1907; found: 496.1902.

10b: Reaction of (*S*)-NOBIN with **8b** and purification of the product by flash chromatography on silica gel with CH_2Cl_2/hexane/Et_3N (4:6:1) as eluent gave **10b** in 98.8% yield as a red glass. $[\alpha]_D^{20} = -52.9°$ (c = 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 11.59 (s, 1H; OH), 8.62 (s, 1H; CH=N), 8.12 (d, J = 9.0 Hz, 1H; ArH), 7.97 (t, J = 8.4 Hz, 2H; ArH), 7.87 (d, J = 7.8 Hz, 1H; ArH), 7.67 (d, J = 9.0 Hz, 1H; ArH), 7.55–7.49 (m, 1H; ArH), 7.43–7.27 (m, 14H; ArH), 7.24–7.19 (m, 1H; ArH), 7.01 (d, J = 8.4 Hz, 1H; ArH), 6.88 (dd, J = 3.0 Hz, J = 9.0 Hz, 1H; ArH), 6.78 (d, J = 3.0 Hz, 1H; ArH), 6.79 (d, J = 9.0 Hz, 1H; ArH), 6.63 (d, J = 2.7 Hz, 2H; ArH), 6.57 (t, J = 2.4 Hz, 1H; ArH), 5.01 (d, J = 6.9 Hz, 4H; $PhCH_2O$), 4.92 ppm (s, 2H; $PhCH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.78, 160.06, 155.38, 151.23, 150.86, 144.71, 139.45, 136.66, 133.57, 133.50, 132.68, 130.40, 130.12, 128.88, 128.49, 128.20, 128.16, 127.92, 127.44, 127.34, 126.55, 126.40, 126.21, 124.41, 123.68, 123.21, 121.37, 118.70, 118.01, 117.74, 117.29, 116.51, 115.90, 106.11, 101.45, 70.60, 69.99 ppm; IR (KBr): $\tilde{\nu}$ = 3523, 3054, 2923, 2824, 1595, 1577, 1488, 1452, 1375, 1343, 1273, 1210, 1153, 1027, 980, 929, 811, 747, 696 cm^{-1}; ESI-MS [M+Na$^+$]: 730.4; HRMS (MALDI): calcd for $C_{48}H_{38}O_5N$ [M+H$^+$] 708.2744; found: 708.2737.

10c: Reaction of (*S*)-NOBIN with **8c** and purification of the product by flash chromatography on silica gel with CH_2Cl_2/hexane/Et_3N (4:4:1) as eluent gave **10c** in 96.9% yield as a red glass. $[\alpha]_D^{20} = -35.9°$ (c = 0.935, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 11.59 (s, 1H; OH), 8.60 (s, 1H; CH=N), 8.07 (d, J = 9.0 Hz, 1H; ArH), 7.97–7.90 (m, 2H; ArH), 7.84 (d, J = 7.5 Hz, 1H; ArH), 7.63 (d, J = 9.0 Hz, 1H; ArH), 7.53–7.18 (m, 27H; ArH), 6.98 (d, J = 8.7 Hz, 1H; ArH), 6.86 (dd, J = 3.0 Hz, 9.0 Hz, 1H; ArH), 6.77 (d, J = 2.7 Hz, 1H; ArH), 6.67–6.65 (m, 5H; ArH), 6.59 (d, J = 1.8 Hz, 2H; ArH), 6.53 (t, J = 2.1 Hz, 2H; ArH), 5.00 (s, 8H; $PhCH_2O$), 4.95 (s, 4H; $PhCH_2O$), 4.90 ppm (s, 2H; $PhCH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.06, 155.35, 150.92, 144.73, 139.48, 139.12, 136.66, 133.53, 133.40, 132.69, 130.55, 130.19, 128.93, 128.51, 128.20, 127.93, 127.51, 127.41, 127.19, 126.86, 126.59, 126.32, 126.28, 125.88, 124.42, 123.65, 123.55, 123.29, 121.31, 118.69, 118.00, 117.57, 117.22, 116.72, 116.55, 115.79, 106.26, 106.03, 101.44, 70.56, 69.99, 69.85 ppm; IR (KBr): $\tilde{\nu}$ = 3525, 3051, 2924, 2827, 1595, 1488, 1452, 1375, 1295, 1272, 1210, 1154, 1052, 1028, 929, 812, 736, 696 cm^{-1}; ESI-MS [M+H$^+$]: 1132.4; HRMS (MALDI): calcd for $C_{76}H_{62}O_9N$ [M+H$^+$] 1132.4419; found: 1132.4430.

10d: Reaction of (*S*)-NOBIN with **8d** and purification of the product by flash chromatography on silica gel with CH_2Cl_2/hexane/Et_3N (4:4:1) as eluent gave **10d** in 96.3% yield as a red glass. $[\alpha]_D^{20} = -21.7°$ (c = 1.07, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 11.58 (s, 1H; OH), 8.55 (s, 1H; CH=N), 8.06 (d, J = 9.0 Hz, 1H; ArH), 7.96–7.89 (m, 2H; ArH), 7.85 (d, J = 7.6 Hz, 1H; ArH), 7.62 (d, J = 8.9 Hz, 1H; ArH), 7.41–7.26 (m, 47H; ArH), 7.02 (d, J = 8.8 Hz, 1H; ArH), 6.66–6.54 (m, 23H; ArH), 4.99 (s, 16H; $PhCH_2O$), 4.95 (s, 4H; $PhCH_2O$), 4.94 (s, 8H; $PhCH_2O$), 4.92 ppm (s, 2H; $PhCH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.65, 159.98, 159.88, 157.70, 155.26, 151.00, 150.74, 144.57, 139.48, 139.09, 139.06, 136.97, 136.61, 133.46, 133.36, 132.63, 130.46, 130.14, 128.85, 128.47, 128.33, 128.16, 127.90, 127.70, 127.57, 127.47, 127.34, 127.04, 126.54, 126.29, 126.21, 125.93, 124.38, 123.24, 121.13, 118.65, 117.90, 117.59, 117.07, 116.50, 115.82, 106.26, 105.90, 101.41, 70.37, 69.90, 69.78 ppm; IR (KBr): $\tilde{\nu}$ = 3526, 3032, 2927, 2871, 1595, 1497, 1451, 1374,

1342, 1295, 1273, 1210, 1153, 1051, 1029, 831, 813, 736, 696, 682 cm^{-1}; ESI-MS [M+H^+]: 1981.8; HRMS (MALDI): calcd for $C_{132}H_{110}O_{17}N$ [M+H^+] 1980.7768; found: 1980.7754.

General procedure for catalytic enantioselective hetero-Diels–Alder reactions: A 10 mL Schlenk tube was equipped with a magnetic stirrer bar. The air in the tube was replaced by argon. Activated powdered 4 Å molecular sieves (50 mg), the (*S*)-dendritic Schiff-base ligand (0.05 mmol), and naproxen (0.0125 mmol) were added under argon atmosphere. Dried toluene (1 mL) and [Ti(O*i*Pr)$_4$] in dichloromethane (0.5 M, 50 μL, 0.025 mmol) were introduced by means of microsyringes. The resulting red solution was heated at 50 °C for 2 h and then cooled to room temperature. The aldehyde (25 μL, 0.25 mmol) and Danishefsky's diene (80 μL, 0.4 mmol) were added sequentially. The mixture was stirred at room temperature for 48 h, and then quenched with 10 drops of TFA. After stirring for a further 5 min, the mixture was neutralized with saturated $NaHCO_3$ solution (about 3 mL) and extracted with diethyl ether (3× 6 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by flash chromatography on silica gel to give the cycloadduct.

(*S*)-2-Phenyl-2,3-dihydro-4*H*-pyran-4-one (13a): Yield: >99%; 97.2% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.49 (d, J = 6.0 Hz, 1H), 7.47–7.39 (m, 5H), 5.54 (dd, J = 6.0 Hz, J = 0.98 Hz, 1H), 5.44 (dd, J = 14.2 Hz, J = 3.5 Hz, 1H), 2.97–2.87 (m, 1H), 2.70–2.63 ppm (m, 1H). Enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane:2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, t_{R1} = 13.500 min (*S*), t_{R2} = 16.450 min (*R*).

2-(3-Methylphenyl)-2,3-dihydro-4*H*-pyran-4-one (13b): Yield: >99%; 96.6% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.48 (d, J = 6.0 Hz, 1H), 7.29–7.16 (m, 4H), 5.53 (dd, J = 6.0 Hz, J = 0.9 Hz, 1H), 5.42 (dd, J = 14.4 Hz, J = 3.6 Hz, 1H), 2.97–2.86 (m, 1H), 2.68–2.61 (m, 1H), 2.39 ppm (s, 3H). Enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane:2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, t_{R1} = 10.492 min (major), t_{R2} = 12.683 min (minor).

2-(4-Methylphenyl)-2,3-dihydro-4*H*-pyran-4-one (13c): Yield: >99%; 94.0% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = (dd, J = 6.0 Hz, J = 0.6 Hz, 1H), 7.31–7.22 (m, 4H), 5.52 (dd, J = 5.5 Hz, J = 0.9 Hz, 1H), 5.42 (dd, J = 14.4 Hz, J = 3.6 Hz, 1H), 2.92 (m, 1H), 2.70–2.63 (m, 1H), 2.38 ppm (s, 3H). Enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane:2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, t_{R1} = 10.600 min (major), t_{R2} = 12.150 min (minor).

2-(3-Methoxyphenyl)-2,3-dihydro-4*H*-pyran-4-one (13d): Yield: >99%; 93.3% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.49 (d, J = 6.0 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 6.99–6.90 (m, 3H), 5.54 (dd, J = 6.1 Hz, J = 1.2 Hz, 1H), 5.42 (dd, J = 14.4 Hz, J = 3.5 Hz, 1H), 3.83 (s, 3H), 2.95–2.85 (m, 1H), 2.70–2.62 ppm (m, 1H). Enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane:2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, t_{R1} = 18.633 min (major), t_{R2} = 25.492 min (minor).

2-(4-Methoxyphenyl)-2,3-dihydro-4*H*-pyran-4-one (13e): Yield: >99%; 93.2% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.45 (d, J = 6.0 Hz, 1H), 7.35 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 8.4 Hz, 2H), 5.51 (d, J = 6.0 Hz, 1H), 5.37 (dd, J = 14.4 Hz, J = 3.1 Hz, 1H), 3.83 (s, 3H), 2.98–2.88 (m, 1H), 2.66–2.59 ppm (m, 1H). The enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane:2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, t_{R1} = 16.542 min (major), t_{R2} = 18.683 min (minor).

2-(3-Chlorophenyl)-2,3-dihydro-4*H*-pyran-4-one (13f): Yield: >99%; 94.0% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.49 (d, J = 6.0 Hz, 1H), 7.43 (t, J = 0.6 Hz, 1H), 7.40–7.30 (m, 2H), 7.28–7.26 (m, 2H), 5.54 (dd, J = 6.6 Hz, J = 1.2 Hz, 1H), 5.41 (dd, J = 14.4 Hz, J = 3.6 Hz, 1H), 2.91–2.81 (m, 1H), 2.70–2.63 ppm (m, 1H). The enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane: 2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, t_{R1} = 13.671 min (major), t_{R2} = 17.825 min (minor).

2-(4-Chlorophenyl)-2,3-dihydro-4*H*-pyran-4-one (13g): Yield: >99%; 90.3% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.58 (d, J = 6.0 Hz, 1H), 7.52–7.44 (m, 4H), 5.65 (dd, J = 6.1 Hz, J = 1.0 Hz, 1H), 5.55 (dd, J = 14.2 Hz, J = 3.6 Hz, 1H), 3.02–2.92 (m, 1H), 2.79–2.72 ppm (m, 1H). Enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane:2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, t_{R1} = 15.667 min (major), t_{R2} = 19.575 min (minor).

2-(3-Bromophenyl)-2,3-dihydro-4*H*-pyran-4-one (13h): Yield: >99%; 95.4% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.58 (s, 1H), 7.54–7.47 (m, 2H), 7.33–7.27 (m, 2H), 5.55 (dd, J = 6.0 Hz, J = 1.23 Hz, 1H), 5.42 (dd, J = 14.2 Hz, J = 3.6 Hz, 1H), 2.91–2.80 (m, 1H), 2.69–2.62 ppm (m, 1H). Enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane:2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, t_{R1} = 14.175 min (*S*), t_{R2} = 19.133 min (*R*).

2-(4-Bromophenyl)-2,3-dihydro-4*H*-pyran-4-one (13i): Yield: >99%; 90.2% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.58–7.57 (m, 2H), 7.46 (dd, J = 5.9 Hz, J = 0.5 Hz, 1H), 7.31–7.27 (m, 2H), 5.53 (dd, J = 6.1 Hz, J = 1.2 Hz, 1H), 5.43 (dd, J = 14.2 Hz, J = 3.4 Hz, 1H), 2.91–2.81 (m, 1H), 2.68–2.61 ppm (m, 1H). Enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane:2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, t_{R1} = 14.175 min (major), t_{R2} = 19.133 min (minor).

2-(4-Nitrophenyl)-2,3-dihydro-4*H*-pyran-4-one (13j): Yield: >99%; 90.1% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.31 (d, J = 11.6 Hz, 2H), 7.61 (d, J = 11.0 Hz, 2H), 7.51 (d, J = 6.1 Hz, 1H), 5.59–5.57 (m, 1H), 5.53 (d, J = 4.3 Hz, 1H), 2.89–2.68 ppm (m, 2H). Enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane:2-propanol = 85:15, flow rate = 1.0 mL min^{-1}, t_{R1} = 32.167 min (major), t_{R2} = 46.767 min (minor).

2-((*E*)-Styryl)-2,3-dihydro-4*H*-pyran-4-one (13k): Yield: >99%; 92.0% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.43–7.27 (m, 6H), 6.72 (d, J = 15.9 Hz, 1H), 6.31 (dd, J = 15.9 Hz, J = 6.6 Hz, 1H), 5.49 (d, J = 5.7 Hz, 1H), 5.11–5.04 (m, 1H), 2.79–2.58 ppm (m, 2H). Enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane:2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, t_{R1} = 22.817 min (*S*), t_{R2} = 53.908 min (*R*).

(*S*)-2-Phenylethyl-2,3-dihydro-4*H*-pyran-4-one (13l): Yield: >99%; 63.6% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.39 (d, J = 6.1 Hz, 1H), 7.34–7.19 (m, 5H), 5.42–5.40 (m, 1H), 4.43–4.36 (m, 1H), 2.85–2.75 (m, 2H), 2.61–2.40 (m, 2H), 2.19–2.06 (m, 1H), 2.01–1.88 ppm (m, 1H). Enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane:2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, t_{R1} = 21.008 min (*S*), t_{R2} = 38.558 min (*R*).

Procedure for investigation of the nonlinear effect using (*S*)-10a- and (*S*)-10c-modified catalysts: The degree of nonlinear effect (NLE) was assessed using benzaldehyde (**12a**) as the substrate. The procedure followed was similar to that outlined above, using 10 mol% of catalysts prepared from (*S*)-**10a** and (*S*)-**10c** with different *ee*'s at room temperature. The enantiomeric excesses of the products were determined by using a HPLC analytical system and a Chiralcel OD column: eluent hexane/2-propanol (90:10); flow rate 1.0 mL min^{-1}; UV detection at λ = 254 nm; retention time = 13.5 min (*S* enantiomer), 16.5 min (*R* enantiomer). The results are shown in Figure 2.

Procedure for recovery of the dendrimer catalyst: The second-generation ligand (*S*)-**10c** was used in assessing the recycling potential of the catalyst. Upon completion of the reaction, (*S*)-**10c** titanium catalyst was quantitatively precipitated by the addition of dried hexane. The solvent was withdrawn by means of a syringe under argon atmosphere, and the precipitate was washed with hexane. The combined organic fractions were concentrated to dryness under reduced pressure. The residue was treated with TFA and neutralized with saturated $NaHCO_3$ and then extracted with diethyl ether. The crude product was purified by flash chromatography on silica gel. The precipitate was dried under vacuum, resuspended in toluene, and fresh substrates were added as described above.

Acknowledgement

Financial support from the National Natural Science Foundation of China, the Chinese Academy of Sciences, the Major Basic Research Development Program of China (Grant no. G2000077506), and the Ministry of Science and Technology of Shanghai Municipality is gratefully acknowledged.

[1] For reviews on dendrimers, see: a) G. R. Newkome, C. N. Moorefield, F. Vögtle, *Dendritic Molecules: Concepts, Synthesis and Perspectives*, VCH, Weinheim, Germany, **1996**; b) M. Fisher, F. Vögtle, *Angew. Chem.* **1999**, *111*, 935; *Angew. Chem. Int. Ed.* **1999**, *38*, 884; c) M. A. Hearshaw, J. R. Moss, *Chem. Commun.* **1999**, *1*.d) A. W. Bosman, H. M. Janssen, E. W. Meijer, *Chem. Rev.* **1999**, *99*, 1665.

[2] J. W. J. Knapen, A. W. van der Made, J. C. De Wilde, P. W. N. M. van Leeuwen, P. Wijkens, D. M. Grove, G. van Koten, *Nature* **1994**, *372*, 659.

[3] For comprehensive reviews on dendrimer-based chiral catalysts or ligands, see: a) R. van Heerbeek, P. C. J. Kamer, P. W. N. M. van-Leeuwen, J. N. H. Reek, *Chem. Rev.* **2002**, *102*, 3717; b) Q. H. Fan, Y. M. Li, A. S. C. Chan, *Chem. Rev.* **2002**, *102*, 3385; c) R. Kreiter, A. W. Kleij, R. J. M. K. Gebbink, G. van Koten, *Top. Curr. Chem.* **2001**, *217*, 163; for recent examples of chiral dendritic catalysts or ligands, see: d) D. Seebach, R. E. Martin, T. Hiutermann, *Helv. Chim. Acta* **1996**, *79*, 1710; e) P. B. Rheiner, H. Sellner, D. Seebach, *Helv. Chim. Acta* **1997**, *80*, 2027; f) P. B. Rheiner, D. Seebach, *Chem. Eur. J.* **1999**, *5*, 3221; g) H. Sellner, D. Seebach, *Angew. Chem.* **1999**, *111*, 2039; *Angew. Chem. Int. Ed.* **1999**, *38*, 1918; h) H. Sellner, C. Faber, P. B. Rheiner, D. Seebach, *Chem. Eur. J.* **2000**, *6*, 3692; i) H. Sellner, J. K. Karjalainen, D. Seebach, *Chem. Eur. J.* **2001**, *7*, 2873; j) H. Sellner, P. B. Rheiner, D. Seebach, *Helv. Chim. Acta* **2002**, *85*, 352; k) Q. H. Fan, Y. M. Chen, X. M. Chen, D. Z. Jiang, F. Xi, A. S. C. Chan, *Chem. Commun.* **2000**, 789; l) J. G. Deng, Q. H. Fan, X. M. Chen, D. S. Liu, A. S. C. Chan, *Chem. Commun.* **2002**, 1570; m) Y. C. Chen, T. F. Wu, J. G. Deng, H. Liu, Y. Z. Jiang, M. C. K. Choi, A. S. C. Chan, *Chem. Commun.* **2001**, 1488; n) Y. M. Chung, H. K. Rhee, *Chem. Commun.* **2002**, 238; o) S. Yamago, M. Furukawa, A. Azuma, J. Yoshida, *Tetrahedron Lett.* **1998**, *39*, 3783; p) C. Kollner, B. Pugin, A. Togni, *J. Am. Chem. Soc.* **1998**, *120*, 10274; q) A. R. Schmitzer, S. Franceschi, E. Perez, I. Rico-Lattes, A. Lattes, L. Thion, M. Erard, C. Vidal, *J. Am. Chem. Soc.* **2001**, *123*, 5956; r) Q. S. Hu, V. Pugh, M. Sabat, L. Pu, *J. Org. Chem.* **1999**, *64*, 7528; s) R. Breinbauer, E. N. Jacobsen, *Angew. Chem.* **2000**, *112*, 3750; *Angew. Chem. Int. Ed.* **2000**, *39*, 3604; t) C. Bolm, N. Derrien, A. Seger, *Chem. Commun.* **1999**, 2087; u) C. Bolm, N. Derrien, A. Seger, *Synlett* **1996**, 387; v) K. Matyjaszewski, T. Shigemoto, J. M. J. Fréchet, M. Leduc, *Macromolecules* **1996**, *29*, 4167.

[4] For examples of asymmetric catalysis using NOBIN-derived ligands, see: a) E. M. Carreira, R. A. Singer, L. Wheeseong, *J. Am. Chem. Soc.* **1994**, *116*, 8837; b) E. M. Carreira, L. Wheeseong, R. A. Singer, *J. Am. Chem. Soc.* **1995**, *117*, 3649; c) R. A. Singer, E. M. Carreira, *J. Am. Chem. Soc.* **1995**, *117*, 12360; d) X. Hu, H. Chen, X. Zhang, *Angew. Chem.* **1999**, *111*, 3720; *Angew. Chem. Int. Ed.* **1999**, *38*, 3518; e) S. Vyskocil, S. Jaracz, M. Smrcina, M. Sticha, V. Hanus, M. Polasek, P. Kocovsky, *J. Org. Chem.* **1998**, *63*, 7727; f) S. Vyskocil, M. Smrcina, V. Hanus, M. Polasek, P. Kocovsky, *J. Org. Chem.* **1998**, *63*, 7738; g) P. Kocovsky, S. Vyskocil, I. Cisarova, J. Sejbal, I. Tislerova, M. Smrcina, G. C. Lloyd-Jones, S. C. Stephen, C. P. Butts, M. Murray, V. Langer, *J. Am. Chem. Soc.* **1999**, *121*, 7714; h) Y. Wang, H. Guo, K. Ding, *Tetrahedron: Asymmetry* **2000**, *11*, 4153; i) Y. Wang, X. Li, K. Ding, *Tetrahedron Lett.* **2001**, *42*, 159; j) Y. N. Belokon, K. A. Kochetkov, T. D. Churkina, N. S. Ikonnikov, O. V. Larionov, S. R. Harutyunyan, S. Vyskocil, M. North, H. B. Kagan, *Angew. Chem.* **2001**, *113*, 2002; *Angew. Chem. Int. Ed.* **2001**, *40*, 1948; k) G. C. Lloyd-Jones, S. C. Stephen, M. Murray, C. P. Butts, S. Vyskocil, P. Kocovsky, *Chem. Eur. J.* **2000**, *6*, 4348; l) Y. Wang, X. Li, J. Sun, K. Ding, *Organometallics* **2003**, *22*, 1856; m) Y. Hu, X. Liang, J. Wang, Z. Zheng, X. Hu, *J. Org. Chem.* **2003**, *68*, 4542; n) J. J. Van-Veldhuizen, S. B. Garber, J. S. Kingsbury, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 4954; o) J. Yin, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 12051; for a more recent review, see: p) P. Kocovsky, S. Vyskocil, M. Smrcina, *Chem. Rev.* **2003**, *103*, 3213.

[5] A. Mandoli, D. Pini, S. Orlandi, F. Mazzini, P. Salvadori, *Tetrahedron: Asymmetry* **1998**, *9*, 1479.

[6] a) Y. Yuan, J. Long, J. Sun, K. Ding, *Chem. Eur. J.* **2002**, *8*, 5033; b) Y. Yuan, X. Li, J. Sun, K. Ding, *J. Am. Chem. Soc.* **2002**, *124*, 14866.

[7] For comprehensive reviews on asymmetric activation, see: a) K. Mikami, M. Terada, T. Korenaga, Y. Matsumoto, M. Ueki, R. Angelaud, *Angew. Chem.* **2000**, *112*, 3676; *Angew. Chem. Int. Ed.* **2000**, *39*, 3532; b) K. Mikami, M. Terada, T. Korenaga, Y. Matsumoto, S. Matsukawa, *Acc. Chem. Res.* **2000**, *33*, 391–401; for a more recent review, see**:** c) K. Mikami, M. Yamanaka, *Chem. Rev.* **2003**, *103*, 3369.

[8] a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley-Interscience, New York, **1994**; b) *Catalysis in Asymmetric Synthesis*, (Ed.: I. Ojima), 2nd ed., Wiley-VCH, New York, **2000**; c) H. B. Kagan, *Comprehensive Organic Chemistry*, Pergamon, Oxford, **1992**, *Vol. 8*; d) *Comprehensive Asymmetric Catalysis*, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, Vols. I–III; e) *Lewis Acids in Organic Synthesis* (Ed.: H. Yamamoto), Wiley-VCH, New York, **2001**.

[9] For reviews, see: a) S. J. Danishefsky, M. P. Deninno, *Angew. Chem.* **1987**, *99*, 15; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 15; b) K. A. Jorgensen, *Angew. Chem.* **2000**, *112*, 3702; *Angew. Chem. Int. Ed.* **2000**, *39*, 3558; c) K. Maruoka, in *Catalysis in Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., Wiley-VCH, New York, **2000**, Chapter 8A.

[10] For Ti-catalyzed asymmetric HDA of Danishefsky's diene with aldehydes, see: a) K. Mikami, Y. Motoyama, M. Terada, *J. Am. Chem. Soc.* **1994**, *116*, 2812; b) G. E. Keck, X. Y. Li, D. Krishnamurthy, *J. Org. Chem.* **1995**, *60*, 5998; c) B. Wang, X. Feng, X. Cui, H. Liu, Y. Jiang, *Chem. Commun.* **2000**, 1605; d) J. Long, J. Hu, X. Shen, B. Ji, K. Ding, *J. Am. Chem. Soc.* **2002**, *124*, 10.

[11] a) K. Ding, Y. Wang, H. Yun, J. Liu, Y. Wu, M. Terada, Y. Okubo, K. Mikami, *Chem. Eur. J.* **1999**, *5*, 1734; b) K. Ding, Q. Xu, Y. Wang, J. Liu, Z. Yu, B. Du, Y. Wu, H. Koshima, T. Matsuura, *Chem. Commun.* **1997**, 693.

[12] For comprehensive reviews on NLE in asymmetric catalysis, see: a) C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, *110*, 3088; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922; b) C. Bolm in *Advanced Asymmetric Catalysis* (Ed.: G. R. Stephenson), Chapman & Hall, London, **1996**, pp. 9–26; c) D. Heller, H.-J. Drexler, C. Fischer, H. Buschmann, W. Baumann, B. Heller, *Angew. Chem.* **2000**, *112*, 505; *Angew. Chem. Int. Ed.* **2000**, *39*, 495.

[13] W. L. Mendelson, M. Holmes, J. Dougherty, *Synth. Commun.* **1996**, *26*, 593–601.

[14] C. J. Hawker, J. M. J. Fréchet, *J. Am. Chem. Soc.* **1990**, *112*, 7638–7647.

Received: June 27, 2003 [F5286]