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Dendritic MonoPhos: synthesis and application in Rh-catalyzed asymmetric hydrogenation

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Dedicated to Professor Jack Halpern on the occasion of his 80th birthday

Abstract—A new class of dendritic monodentate phosphoramidite ligands were synthesized through substitution of the dimethylamino moiety in MonoPhos by the Fréchet-type dendritic wedge and applied in the asymmetric hydrogenation of α-dehydroamino acid esters and dimethyl itaconate. High enantioselectivities (up to 97.9% ee) and catalytic activities (up to 4850 h^{-1} TOF) were achieved, which are better or comparable to those obtained from MonoPhos. The third generation dendrimer catalyst gave the slightly lower catalytic activity relative to the lower generation ones. The steric shielding by the dendrimer could stabilize the rhodium complex against decomposition caused by hydrolysis in a protic solvent. The inactive catalysts (RhL_3 and RhL_4) were activated by addition of a free metal precursor $Rh(COD)_2BF_4$, and showed high enantioselectivities and catalytic activities.

1. Introduction

Dendrimers are highly branched macromolecules, which have precisely defined molecular structures with nanoscale size. Since the pioneering work of van Koten et al. reported in 1994,[1] dendritic catalysts have become a subject of intensive research.[2] Compared to the linear soluble polymeric chiral catalysts, the dendrimer architecture might offer better control of the disposition of the catalytic species than soluble polymer-based catalysts. Thus, it is possible to fine-tune the catalytic properties of the dendritic catalysts through the adjustment of their structure, size, shape, and solubility. Although a number of organometallic dendrimers with catalytic sites at the core or at the periphery, have been reported, only a few dendrimer catalysts have shown different properties from those of small molecule analogues.[3] In the case of the core-functionalized dendrimers, it is expected that the steric shielding or blocking effect of the specific microenvironment created by the dendritic structure could modulate the catalytic behavior of the core.[3e] Recently, we developed two types of chiral dendritic ligands for asymmetric catalysis through the incorporation of BINAP[4] or BINOL[5] into the core of the Fréchet-type dendrimers, respectively. In both cases, it was found that the size of the dendritic wedges influenced the reactivity and/or the enantioselectivity of the dendritic catalysts. As an extension of our research,[3e,4–6] herein we report the synthesis of dendritic chiral monodentate phosphoramide ligands through the attachment of MonoPhos onto the focal point of Fréchet's polyether dendrimers and their applications in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters and dimethyl itaconate.

After being neglected for about 30 years, the monodentate phosphorus ligands[7] are gaining more and more attention. Pioneering studies from the groups of Pringle, Reetz, Feringa, and others[8] have shown that the use of a conformationally rigid symmetric bidentate ligand is not essential to obtain good stereo-discrimination. Chiral monodentate phosphonite, phosphoramidite, or phosphites have proven to be able to induce excellent enantioselectivity in rhodium-catalyzed asymmetric hydrogenation reactions, comparable to or better than those obtained by diphosphine ligands.[8,9] So far, a number of monodentate phosphorus ligands have been designed and reported. Three outstanding examples are listed in Scheme 1. The easy synthesis and modular structure of monodentate phosphoramidites in general

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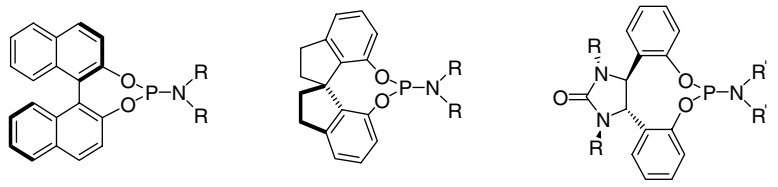


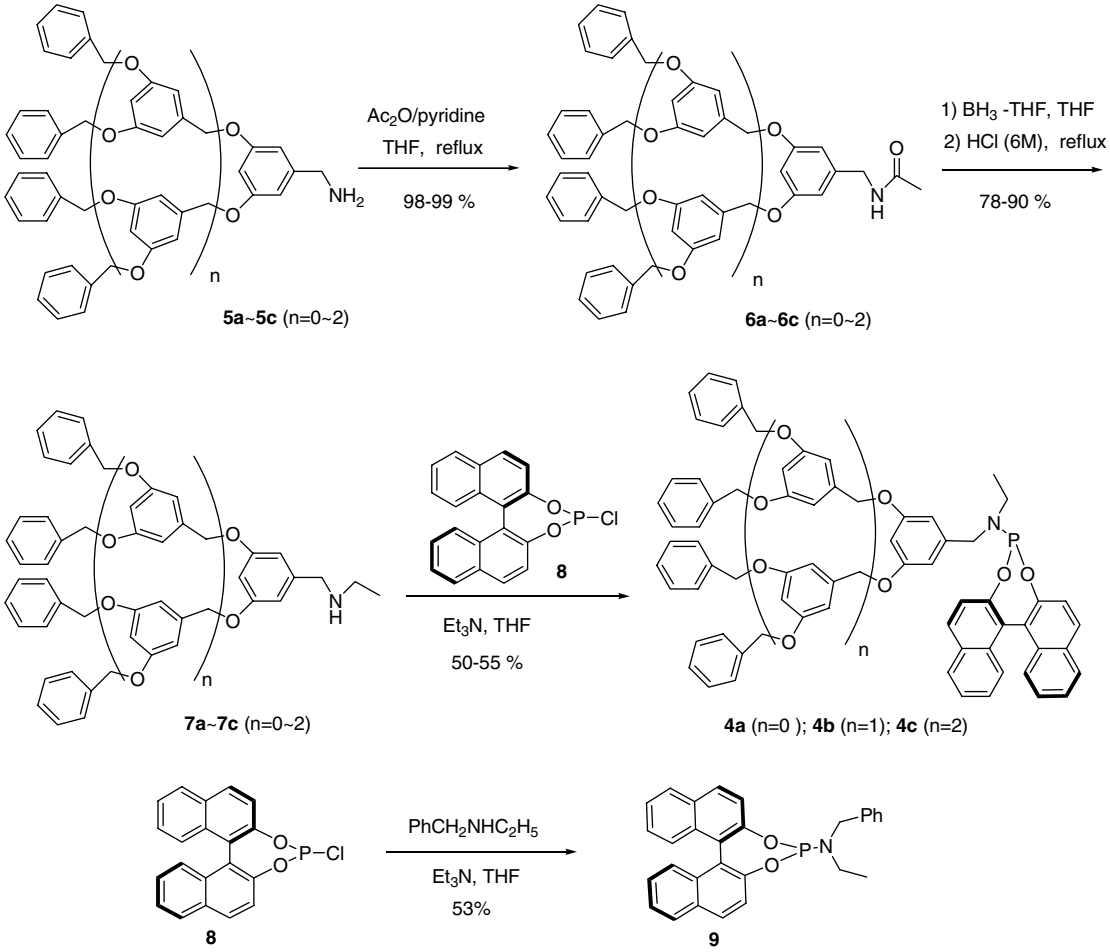
Scheme 1. Examples of phosphoramidite.

allow the tuning of the catalyst to find highly effective ligands. Substitution by the dimethylamino group was most often used to tune the catalytic efficiency. It was found that substituents on the nitrogen atom played an important role on the enantioselectivity of the catalyst.[9e,k] Although different types of substituents have been studied, however, to the best of our knowledge, there have been no reports on the use of dendritic wedge as the substituent. In addition, it has proven that the higher ligated rhodium species such as RhL_3 and RhL_4 are inactive, and the structure of the catalytically active specie is still not very clear.[9b,f,h] In the case of a dendritic ligand, it is possible in principle that the sterically demanding dendritic wedge can suppress the formation of higher ligated rhodium species and consequently influence the catalytic properties. To extend the small substituents to macromolecular ones and study the possible 'dendritic effect', we synthesized a new series of dendritic phosphoramidite by choosing Ferringa's MonoPhos as a model ligand. This study demonstrated that the macromolecular substituent on the nitrogen atom did not lead to any deterioration of the enantioselectivity.

2. Results and discussion

2.1. Synthesis of dendritic MonoPhos ligands

Ferringa's MonoPhos was chosen as the model ligand for our study due to its modular structure and excellent efficiency in the asymmetric hydrogenation of a variety



Scheme 2. Synthesis of dendritic MonoPhos **4a**–**4c** and **9**.

of prochiral olefins.[8c,9b] Recently, immobilization of MonoPhos has been reported by several research groups.[10] Doherty et al. reported the first polymer-supported Rh–MonoPhos for asymmetric hydrogenation of methyl 2-acetamido cinnamate.[10b] The MonoPhos ligand bearing a styrene moiety on the nitrogen atom was attached onto the polymer backbone through radical copolymerization. However, the resulting supported rhodium catalyst gave a much lower enantioselectivity (up to 80% ee) relative to that of MonoPhos (95% ee). This was probably due to the ligand modification and the heterogeneous reaction conditions. In our case, substitution on the dimethylamino moiety in MonoPhos was also used for the attachment of a dendrimer. The synthetic routes for these new dendritic ligands are outlined in Scheme 2.

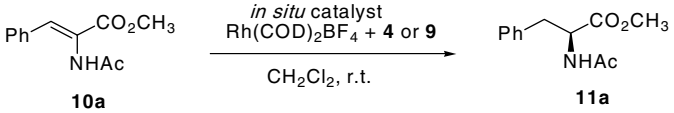
Firstly, a polyether dendrimer was chosen as the support to ensure catalyst stability under the reaction conditions.[11] Dendrons **5a**–**5c** bearing an amino group located at the focal point were synthesized by using the convergent method reported by Fréchet and co-workers.[12] Dendrons **6a**–**6c** were prepared quantitatively by acetylation of **5** with acetic anhydride in the presence of pyridine. Then, **6** was reduced by $NaBH_4/I_2$ or BH_3·THF to give the dendritic secondary amine **7a**–**7c** in high yields, respectively.

Chiral chlorophosphite **8** was prepared by the slow addition of phosphorus trichloride to (*R*)-BINOL and triethylamine in THF. Dropwise addition of the appropriate dendron **7** to an ice-cooled THF solution of the resulting chiral chlorophosphite **8** and a base gave the dendritic chiral ligands **4a**–**4c** in moderate yields, as air-stable white powders after purification by flash column chromatography. For comparison, a model compound of a small molecule **9** was also synthesized using the same method. All these dendritic MonoPhos ligands were well characterized by ^1H, ^{13}C, and ^{31}P NMR spectroscopy, elemental analyses, and/or HRMS and MALDI-TOF mass spectrometry. All results are consistent with the compounds synthesized.

2.2. Homogeneous rhodium-catalyzed hydrogenation of dehydroamino acid esters and dimethyl itaconate

Firstly, the rhodium-catalyzed asymmetric hydrogenation of methyl 2-acetamido cinematic **10a** was used as the model reaction to study the catalytic behavior of the new dendritic ligands **4** and **9**. The rhodium catalysts were prepared in situ by reaction of 2 equiv of the appropriate dendrimer ligands with $[Rh(COD)_2]BF_4$ in dichloromethane at room temperature. Typically, the reactions were carried out at room temperature in dichloromethane as the solvent. The experimental results are listed in Table 1. To our delight, all catalysts gave high enantioselectivities (up to 97.9% ee), which are better than that (95% ee)[9b] obtained from MonoPhos **9** (entries 1–4). These results indicated that the size of the dendritic substituents on the nitrogen atom would not result in any negative effect on the selectivity, which is in contrast to the results obtained with the corresponding small monodentate phosphoramidite ligands bearing different substituents on the nitrogen atom.[9k] Generally, small alkyl groups on the nitrogen atom of MonoPhos ligands are necessary for obtaining high enantioselectivity in the asymmetric hydrogenation of dehydroamino acid derivatives. In addition, complete

Table 1. Asymmetric hydrogenation of methyl 2-acetamido cinnamate **10a** with dendritic Rh–MonoPhos catalysts



10a **11a**

Entry	Ligand	Sub./Cat.	H_2 (atm)	Time[a]	ee (%)[b] (config.)
1	**4a**	100	20	10 h	97.5 (*S*) (95)[c]
2	**4b**	100	20	10 h	97.4 (*S*)
3	**4c**	100	20	10 h	97.9 (*S*)
4	**9**	100	20	10 h	97.6 (*S*)
5	**4b**	100	1	10 h	97.8 (*S*)
6	**4a**	1000	15	1 h	97.7 (*S*)
7	**4c**	1000	15	1 h	97.8 (*S*)
8	**9**	1000	15	1 h	97.6 (*S*)
9	**4a**	1000	10	12 min (95.8%)	97.3 (*S*)
10	**4b**	1000	10	12 min (97.0%)	97.5 (*S*)
11	**4c**	1000	10	12 min (74.0%)	97.3 (*S*)
12	**9**	1000	10	12 min (89.9%)	96.7 (*S*)
13[d]	**4b**	100	20	4 h	97.2 (*S*)
14[e]	**4b**	100	20	4 h	96.1 (*S*)
15[d]	**9**	100	20	4 h	93.6 (*S*)
16[e]	**9**	100	20	4 h	87.5 (*S*)

[a] Conversion is 100% unless noted otherwise.
[b] Determined by chiral GC analysis.
[c] Ee value for Rh–MonoPhos catalyst taken from Ref. 9b.
[d] CH_2Cl_2/MeOH = 2:1 (v/v) as the reaction solvent.
[e] CH_2Cl_2/MeOH = 1:1 (v/v) as the reaction solvent.

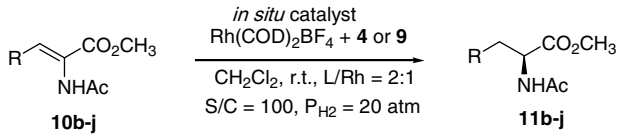
conversion and high enantioselectivities were achieved when the reactions were carried out at either lower H_2 pressure (1 atm) or with low catalyst loading (S/C = 1000) (entries 5–8). In order to study the dendritic effect on the reaction rate, we performed the reactions at a substrate to catalyst ratio of 1000 at 10 atm for 12 min (entries 9–12). It was found that the first and the second generation catalysts showed very similar catalytic activity as compared to the monomer catalyst Rh–**9**, albeit the third one gave slightly lower reaction rate. The second generation catalyst **4b**–Rh gave the highest catalytic activity (up to 4850 h^{-1} TOF). This size effect was probably due to the encapsulation of the catalytically active center by the high generation dendritic wedges.

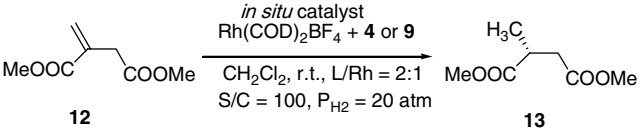
Most importantly, this encapsulation, may stabilize the rhodium complex against decomposition caused by hydrolysis in the protic solvent. Thus, the second generation catalyst gave almost the same enantioselectivity when the reaction was performed in dichloromethane/methanol as the solvent, while the monomer catalyst Rh–**9** gave much lower enantioselectivity in the protic solvent (entries 13–16 vs entries 2 and 4).

We then applied our dendritic catalysts to the hydrogenation of other α-dehydroamino acid ester substrates (Table 2). As shown in Table 2, excellent enantioselectivities were also achieved in all cases, which are better or comparable to those obtained from MonoPhos **9**. Hydrogenation of substrates with electron donating and withdrawing *meta*- (entries 1–3) or *para*-substituents (entries 4–18) on the phenyl group gave slightly higher ee values as compared to the *ortho*-substituted substrates (entries 19–28). It was noted that the dendritic catalysts showed slightly higher enantioselectivities for all *ortho*-substituted substrates than those obtained from the monomer ligand **9** (entries 19–28). Hydrogenation of dimethyl itaconate **12** also gave excellent enantioselectivities, which are better than those of MonoPhos (entries 29–31).[9b]

Feringa[9b] and Zhou[9f] reported that the L/Rh ratio significantly influenced the catalytic activity. For example, when the L/Rh ratio was increased to 3 and 4, catalytic activity ceased. In order to investigate the possible different catalytic performance of the dendritic catalysts, we performed the reactions with L/Rh ratio from 1:2 to 4.2:1 in dichloromethane as the solvent (Table 3). As shown in Table 3, the reactions with 2.1:1 and 1:1 L/Rh ratio gave exactly the same ee values, but the latter showed slightly higher activity (entries 1 and 2). This results are in agreement with those observed by MonoPhos.[9b] Even more interesting was the finding that a similar ee value was also observed when the L/Rh ratio was lowered to 1:2 (entry 3). Due to the strong binding between the ligand and Rh, the reactions with a L/Rh ratio between 3.0:1 and 4.2:1 was much slower even at high H_2 pressure when the low generation dendritic catalysts were used (entries 4–8, 10, and 12). Most interestingly, when the third generation catalyst Rh–**4c** was used with L/Rh of 4.2:1 (entry 9), the catalytic system remained partially active and gave very similar ee values.

Table 2. Asymmetric hydrogenation of α-dehydroamino acid esters **10b–10j** and dimethyl itaconate **12** with dendritic Rh–MonoPhos catalysts[a]





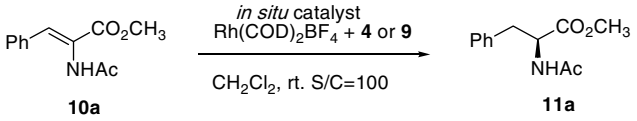
Entry	Ligand	Substrate (R)	ee[b] (%) (config.)
1	**4a** (G_1)	3-ClC_6H_5 (**10b**)	97.8 (*S*)
2	**4b** (G_2)	3-ClC_6H_5 (**10b**)	97.6 (*S*)
3	**9** (G_0)	3-ClC_6H_5 (**10b**)	97.1 (*S*)
4	**4a** (G_1)	4-ClC_6H_5 (**10c**)	96.0 (*S*)
5	**4b** (G_2)	4-ClC_6H_5 (**10c**)	97.3 (*S*)
6	**9** (G_0)	4-ClC_6H_5 (**10c**)	97.6 (*S*)
7	**4a** (G_1)	4-FC_6H_5 (**10d**)	97.4 (*S*)
8	**4b** (G_2)	4-FC_6H_5 (**10d**)	97.1 (*S*)
9	**9** (G_0)	4-FC_6H_5 (**10d**)	97.6 (*S*)
10	**4a** (G_1)	4-BrC_6H_5 (**10e**)	97.5 (*S*)
11	**4b** (G_2)	4-BrC_6H_5 (**10e**)	97.0 (*S*)
12	**9** (G_0)	4-BrC_6H_5 (**10e**)	97.3 (*S*)
13	**4a** (G_1)	4-$CH_3OC_6H_5$ (**10f**)	97.7 (*S*)
14	**4b** (G_2)	4-$CH_3OC_6H_5$ (**10f**)	97.7 (*S*)
15	**9** (G_0)	4-$CH_3OC_6H_5$ (**10f**)	97.9 (*S*)
16	**4a** (G_1)	4-$NO_2C_6H_5$ (**10gj**)	96.2 (*S*)
17	**4b** (G_2)	4-$NO_2C_6H_5$ (**10g**)	97.0 (*S*)
18	**9** (G_0)	4-$NO_2C_6H_5$ (**10g**)	93.9 (*S*)
19	**4a** (G_1)	2-$CH_3C_6H_5$ (**10h**)	96.3 (*S*)
20	**4b** (G_2)	2-$CH_3C_6H_5$ (**10h**)	96.2 (*S*)
21	**4c** (G_3)	2-$CH_3C_6H_5$ (**10h**)	97.3 (*S*)
22	**9** (G_0)	2-$CH_3C_6H_5$ (**10h**)	95.1 (*S*)
23	**4a** (G_1)	2-$CH_3OC_6H_5$ (**10i**)	95.6 (*S*)
24	**4b** (G_2)	2-$CH_3OC_6H_5$ (**10i**)	95.0 (*S*)
25	**9** (G_0)	2-$CH_3OC_6H_5$ (**10i**)	93.8 (*S*)
26	**4a** (G_1)	2-ClC_6H_5 (**10j**)	95.6 (*S*)
27	**4b** (G_2)	2-ClC_6H_5 (**10j**)	94.6 (*S*)
28	**9** (G_0)	2-ClC_6H_5 (**10j**)	94.1 (*S*)
29	**4a** (G_1)	**12**	97.7 (*R*) (94)[c]
30	**4b** (G_2)	**12**	97.0 (*R*)
31	**9** (G_0)	**12**	96.8 (*R*)

[a] Conversion is 100% in all cases.
[b] Determined by chiral GC analysis.
[c] Ee value for Rh–MonoPhos catalyst taken from Ref. 9b.

This result indicated that the catalytically active center could be encapsulated by the dendritic wedges,[3e] which consequently suppressed, to some extent, the formation of unwanted higher ligated rhodium species at higher L/Rh ratio during the hydrogenation.

Feringa[9b] used electrospray mass spectrometry to investigate the rhodium species at 2:1 L/Rh ratio that are present during hydrogenation. Different species including complexes containing 1, 2, or 3 ligands and 1 substrate molecule were observed. Their study showed that some of higher ligated rhodium species were formed during the hydrogenation, which could not be

Table 3. Effect of L/Rh ratio on asymmetric hydrogenation of methyl 2-acetamido cinnamate **10a**



Entry	Ligand (L/Rh)	H_2 (atm)	Time (h)	Conv. (%)[a]	ee (%)[a]
1	**4b** (2.1:1)	1	3	88.0	97.9
2	**4b** (1:1)	1	3	98.7	97.8
3	**4b** (1:2)	1	3	100	94.5
4	**4b** (3.0:1)	1	3	4.4	nd
5	**4b** (4.0:1)	1	3	1.4	nd
6	**4b** (4.2:1)	20	5	5.7	nd
7	**9** (4.2:1)	20	5	3.0	nd
8	**4a** (4.2:1)	20	5	4.0	nd
9	**4c** (4.2:1)	20	5	46.6	97.0
10	**4b** (3.5:1)	1	4	4.0	nd
11	**4b** (3.5:1→2.0:1)[b]	1	4	97.6	97.2
12	**9** (3.5:1)	1	4	3.7	nd
13	**9** (3.5:1→2.0:1)[b]	1	4	92.0	95.6

[a] Determined by chiral GC.
[b] The in situ prepared Rh complexes (**4a**/Rh or **9**/Rh = 3.5:1) was added $Rh(COD)_2BF_4$, giving the catalyst mixtures with L/Rh = 2.0:1.

transferred to the active species again under the reaction conditions. In order to test the possibility of dissociation of these inactive catalysts (RhL_3 and RhL_4) during hydrogenation, we used the mixtures of the preformed inactive complexes with a 3.5:1 L/Rh ratio and metal precursor $Rh(COD)_2BF_4$ as the catalysts (totally L/Rh = 2:1) for hydrogenation of **10a** at 1 atm H_2 pressure for 4 h. Interestingly, a similar enantioselectivity and conversion were achieved as compared to those obtained from the preformed catalyst with a 2:1 L/Rh ratio (entry 10 vs 11 and entry 12 vs 13). In addition, we determined the dependency of conversion versus time to further demonstrate this finding (Fig. 1). Obviously, the catalyst mixtures showed very similar reaction rates to those of the preformed catalyst. This showed that the inactive catalysts could be activated by addition of free metal precursor $Rh(COD)_2BF_4$, and similar active species were probably formed during hydrogenation.

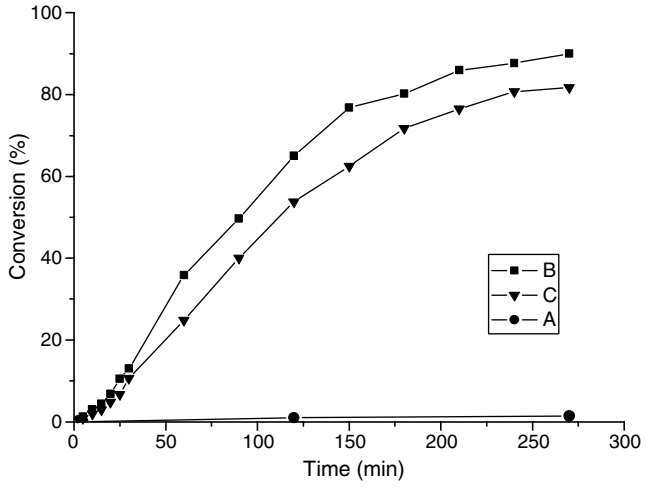


Figure 1. Dependency of conversion versus time ($T = 10$ °C, P_{H_2} = 1 atm, [**9a**] = 0.025 M, [Rh] = 0.25 mM). Curve A: **4a**/Rh = 4:1; Curve B: **4a**/Rh = 1:1; Curve C: catalyst A + 3 equiv $Rh(COD)_2BF_4$ (totally L/Rh = 1:1).

3. Conclusion

We have developed a new class of dendritic monodentate phosphoramidite ligands through substitution of dimethylamino moiety in MonoPhos by the Fréchet-type dendritic wedge. These dendrimer catalysts were successfully applied in the asymmetric hydrogenation of α-dehydroamino acid esters and dimethyl itaconate. Higher or comparable enantioselectivities were achieved as compared to that obtained from MonoPhos. The steric shielding by the dendrimer could stabilize the rhodium complex against decomposition caused by the hydrolysis in protic solvent. The third generation dendrimer catalyst gave slightly lower catalytic activity relative to the lower generation ones due to the encapsulation of the catalytically active center by the dendritic wedge. This encapsulation effect could also suppress, to some extent, the formation of unwanted higher ligated inactive rhodium species at higher L/Rh ratio during the hydrogenation. It was demonstrated that the inactive catalysts (RhL_3 and RhL_4) could be activated by addition of free metal precursor $Rh(COD)_2$-BF_4, and similar active species was probably formed during hydrogenation. We are currently studying the synthesis of more rigid dendritic monodentate phosphorus ligands and their applications in different catalytic asymmetric transformations.

4. Experimental

4.1. Materials and equipment

All solvents were dried using standard, published methods and were distilled under nitrogen atmosphere before

use. Except as specified, commercial reagents were used as received without further purification. Dendrimers **5a**–**5c** were synthesized according to the published method.[12]

NMR spectra were recorded on a BRUKER Model ADVANCE DPX 300 spectrometer (300 MHz ^{1}H and 122 MHz ^{31}P) using tetramethylsilane for ^{1}H as an internal standard, 85% of H_3PO_4 in D_2O for ^{31}P as an external standard. All signals are reported in parts per million unit. MALDI-TOF-MS were recorded on a Bruker Biflex spectrometer with α-cyano-4-hydroxycinnamic acid (CCA) as a matrix. Elemental analysis was performed with a Carlo Erba 1106 Elemental Analyzer. Optical rotations were measured with AA-10R automatic polarimeter. For high-pressure hydrogenation, 50 mL stainless autoclave equipped with a glass liner was used. The ee values were determined by chiral GC with a 25 m × 0.25 mm Chrompack Chirasil-L-Val column.

4.2. General procedure for synthesis of dendritic *N*-ethyl acetyl compounds 6a–6c

A 50 mL round-bottomed flask equipped with a stirrer and a condenser, charged with the dendritic amine **5** (**5a**–**5c**) (15.0 mmol), acetic anhydride (3.0 mL), pyridine (0.2 mL), and THF (30 mL). The reaction mixture was refluxed for 5 h under nitrogen atmosphere. After being cooled to room temperature, THF was evaporated under reduced pressure. Aqueous NaOH solution (2 M, 10 mL) was added, and the mixture was extracted three times with CH_2Cl_2 (100 mL × 3). The organic layer was washed with saturated $NaHCO_3$ solution and brine in turn, dried over anhydrous $MgSO_4$, and evaporated to give a white solid.

4.2.1. The first generation dendritic acetyl amine 6a. Yield 99%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (s, 3H), 4.25 (d, $J = 5.7$ Hz, 2H), 4.91 (s, 4H), 5.77 (br, 1H), 6.43 (3H), 7.21–7.33 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.28, 43.75, 70.10, 100.98, 106.86, 127.58, 128.08, 128.64, 136.74, 140.72, 160.20, 169.94.

4.2.2. The second generation dendritic acetyl amine 6b. Yield 98%: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97 (s, 3H), 4.32 (d, $J = 5.6$ Hz, 2H), 4.93 (s, 4H), 5.01 (s, 8H), 5.74 (br, 1H), 6.48–6.66 (m, 9H), 7.28–7.42 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.26, 43.77, 69.97, 70.14, 101.05, 101.56, 106.39, 106.91, 127.60, 128.05, 128.62, 136.77, 139.22, 140.68, 160.11, 160.20, 169.93.

4.2.3. The third generation dendritic acetyl amine 6c. Yield 98%: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (s, 3H), 4.28 (d, $J = 5.6$ Hz, 2H), 4.89–5.05 (m, 28H), 5.72 (br, 1H), 6.46–6.66 (m, 21H), 7.29–7.40 (m, 40H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.19, 43.66, 69.97, 70.11, 100.96, 101.59, 105.93, 106.40, 106.88, 127.14, 127.55, 127.78, 128.00, 128.17, 128.23, 128.30, 128.37, 128.57, 129.05, 136.37, 136.76, 137.14, 139.23, 140.74, 160.06, 160.16, 169.81.

4.3. General procedure for synthesis of dendritic *N*-ethyl amine compounds 7a and 7b

To a 250 mL three-necked round-bottomed flask equipped with a magnetic stirrer, a dropping funnel and a reflux condenser, compound **6** (**6a** or **6b**) (12 mmol), $NaBH_4$ (36 mmol), and dry THF (80 mL) was added. After a solution of iodine (36 mmol) in 10 mL THF was added dropwise over 30 min at 0 °C, the mixture was heated to reflux for 24 h. When the reaction mixture was cooled to 0 °C and quenched by saturated NH_4Cl solution (10 mL), the pH was adjusted to 12 with 20% aqueous NaOH solution. THF was removed, and the residue was extracted with CH_2Cl_2 (100 mL × 3). The organic layer was washed with brine and evaporated to give an oily product. This oil was added to a 50 mL round-bottomed flask charged with 30 mL THF and 6 M hydrochloric acid (10 mL). After the mixture was stirred at refluxing temperature for 6 h, it was cooled to 0 °C and the pH was adjusted to 12 again followed by evaporation, extraction, and concentration. The crude product was purified by silica gel column chromatography (eluent: dichloromethane/methanol 10:1) to afford a yellow oil.

4.3.1. Compound 7a. Yield 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27–1.32 (m, 3H), 2.74–2.76 (m, 2H), 3.88 (s, 2H), 4.96 (s, 4H), 6.50 (d, $J = 1.8$ Hz, 1H), 6.80 (2H), 7.22–7.32 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.14, 40.80, 50.01, 70.12, 103.00, 108.76, 127.64, 127.93, 128.44, 132.20, 136.38, 160.19; HRMS (ESI) for $C_{23}H_{25}NO_2$ $[M+1]^+$ calcd 348.1964, found 348.1942.

4.3.2. Compound 7b. Yield 78%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33–1.38 (m, 3H), 2.79 (br, 2H), 3.90 (s, 2H), 4.98–5.03 (s, 12H), 6.53–6.84 (m, 9H), 7.27–7.40 (m, 20H), 9.93 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.14, 40.84, 50.02, 70.04, 101.59, 103.30, 106.50, 108.86, 127.57, 127.98, 128.56, 132.05, 136.75, 138.96, 160.08, 160.18; HRMS (ESI) for $C_{51}H_{49}NO_6$ $[M+1]^+$ calcd 772.3638, found 772.3621.

4.3.3. Compound 7c. To a solution of 1.00 M borane in tetrahydrofuran (12 mL) in a 50 mL flask (nitrogen atmosphere) was added **6c** (3 mmol) in 30 mL THF over 30 min. The temperature was maintained at 0 °C during the addition. The colorless solution was then heated at reflux for 24 h. The mixture was cooled to room temperature and 6 M hydrochloric acid (3 mL) was added. After refluxing for further 6 h, the final product was obtained with the same procedure used for compound **7a** (eluent: dichloromethane/methanol 20:1), yield 90%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26–1.32 (m, 3H), 2.77–2.79 (br, 2H), 3.90 (s, 2H), 4.85–4.95 (m, 28H), 6.47–6.79 (m, 21H), 7.25–7.36 (m, 40H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.21, 41.12, 50.22, 69.93, 70.06, 101.61, 103.22, 106.45, 106.61, 108.83, 127.54, 127.78, 127.95, 128.54, 132.27, 136.81, 139.02, 139.27, 160.00, 160.13, 160.25; HRMS (FAB) for $C_{107}H_{97}NO_{14}$ $[M+1]^+$ calcd 1620.6987, found 1620.6993.

4.4. General procedure for synthesis of dendritic phosphoramidite ligands (4a–4c and 9)

To a solution of (*R*)-BINOL (0.5 g, 1.75 mmol) and triethylamine (0.5 mL) in THF (10 mL) was added dropwise 0.2 mL phosphorus chloride at 0 °C under a nitrogen atmosphere. After the mixture was stirred for 6 h, evaporation of excess reagent, and azeotropic distillation of the residue with anhydrous toluene (5 mL) gave the intermediate chlorophosphite in quantitative yield. To this residue was added *N*-ethyl benzylamine (2.0 mmol) and triethylamine (0.5 mL) in THF (10 mL). The mixture was stirred overnight at room temperature. The crude product was purified by column chromatography on silica gel (eluent: dichloromethane/petroleum ether = 1:1, v/v) to afford **9** as a white foam. Yield 55%; mp 82–84 °C; $[\alpha]_D^{16} = +315.2$ (*c* 0.33, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, $J =$ 7.05 Hz, 3H), 2.59–2.66 (m, 1H), 2.97–3.02 (m, 1H), 3.76–3.85 (m, 1H), 4.22–4.30 (m, 1H), 7.25–7.42 (m, 12H), 7.57 (d, $J = 8.8$ Hz, 1H), 7.85–8.00 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.18, 14.21, 38.61, 38.90, 47.61, 47.87, 121.77, 122.17, 122.61, 122.63, 123.99, 124.53, 124.77, 126.04, 126.96, 127.05, 127.15, 128.23, 128.31, 129.97, 130.23, 130.70, 131.41, 132.60, 132.85, 138.34, 138.37, 149.49, 149.84, 149.90 ppm; ^{31}P NMR (122 MHz, $CDCl_3$) δ 147.85; HRMS (FAB) for $C_{29}H_{24}NO_2P$ $[M+1]^+$ calcd 450.1623, found 450.1611.

4.4.1. Compound 4a. The dendritic phosphoramidite ligands were prepared using the same procedures. Yield 53%; mp 81–83 °C; $[\alpha]_D^{16} = +254.5$ (*c* 0.33, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, $J = 7.04$ Hz, 3H), 2.61–2.68 (m, 1H), 2.97–3.02 (m, 1H), 3.66–3.74 (m, 1H), 4.12–4.19 (m, 1H), 5.03 (s, 4H), 6.49–6.51 (m, 1H), 6.57 (s, 2H), 7.25–7.43 (m, 17H), 7.53–7.56 (d, $J = 8.8$ Hz, 1H), 7.85–7.99 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.25, 14.27, 38.84, 39.16, 47.66, 47.90, 70.07, 100.78, 107.40, 121.75, 122.12, 122.58, 123.97, 124.04, 124.56, 124.78, 126.04, 126.97, 127.04, 127.59, 127.98, 128.24, 128.32, 128.58, 130.02, 130.25, 130.69, 131.40, 132.58, 132.84, 136.87, 141.00, 149.42, 149.79, 149.85, 159.95; ^{31}P NMR (122 MHz, $CDCl_3$) δ 147.44; HRMS (FAB) for $C_{43}H_{35}NO_4P$ $[M+1]^+$ calcd 662.2460, found 662.2446.

4.4.2. Compound 4b. Yield 52%; mp 77–79 °C; $[\alpha]_D^{16} = +151.5$ (*c* 0.33, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, $J = 7.04$ Hz, 3H), 2.62–2.67 (m, 1H), 2.95–3.00 (m, 1H), 3.67–3.76 (m, 1H), 4.13–4.21 (m, 1H), 4.97 (s, 4H), 5.00 (s, 8H), 6.48–6.68 (m, 9H), 7.22–7.39 (m, 27H), 7.52–7.55 (d, $J = 8.8$ Hz, 1H), 7.83–7.91 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.23, 14.26, 38.82, 39.12, 47.80, 48.06, 69.99, 70.13, 100.91, 101.64, 106.43, 107.49, 121.74, 122.12, 122.56, 122.59, 123.97, 124.54, 124.76, 126.05, 126.95, 127.02, 127.53, 127.96, 128.26, 128.32, 128.55, 130.02, 130.27, 130.70, 131.41, 132.59, 132.82, 132.83, 136.80, 139.38, 141.02, 141.04, 149.43, 149.82, 149.88, 159.90, 160.21 ppm; ^{31}P NMR (122 MHz, $CDCl_3$) δ 147.77; MALDI-TOF MS for $C_{71}H_{60}NO_8P$ $[M]^+$ calcd 1085.4, found 1085.5; Anal. Calcd for $C_{71}H_{60}NO_8P$: C, 78.51; H, 5.57; N, 1.29. Found C, 78.49; H, 5.47; N, 1.41.

4.4.3. Compound 4c. Yield 50%; mp 69–71 °C; $[\alpha]_D^{16} = +72.7$ (*c* 0.33, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (t, $J = 7.04$ Hz, 3H), 2.59–2.67 (m, 1H), 2.95–3.00 (m, 1H), 3.66–3.75 (m, 1H), 4.12–4.20 (m, 1H), 4.83–5.03 (m, 28H), 6.50–6.57 (m, 9H), 6.64–6.67 (m, 12H), 7.19–7.40 (m, 47H), 7.50–7.53 (d, $J =$ 8.8 Hz, 1H), 7.81–7.91 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.24, 38.82, 39.10, 47.69, 47.91, 69.97, 70.07, 100.73, 101.57, 106.37, 106.45, 107.38, 121.70, 122.09, 122.57, 123.90, 124.54, 124.74, 126.03, 126.91, 126.96, 127.14, 127.56, 127.79, 127.99, 128.25, 128.32, 128.57, 130.04, 130.29, 130.65, 131.34, 132.52, 132.76, 136.74, 139.15, 139.29, 141.01, 149.37, 149.74, 149.81, 159.87, 160.06, 160.13; ^{31}P NMR (122 MHz, $CDCl_3$) δ 147.13; MALDI-TOF MS for $C_{127}H_{108}NO_{16}P$ $[M]^+$ calcd 1933.7, found 1933.6. Anal. Calcd for $C_{127}H_{108}NO_{16}P$: C, 78.82; H, 5.63; N, 0.72. Found C, 78.35; H, 5.50; N, 0.57.

4.5. General procedure for the hydrogenation of methyl 2-acetamido cinnamate

Dendritic MonoPhos ligand (7.85×10^{-3} mmol) and $Rh(COD)_2BF_4$ (3.74×10^{-3} mmol) in CH_2Cl_2 (10 mL) were stirred at room temperature for 10 min under a nitrogen atmosphere. Then, a 50 mL glass-lined stainless steel reactor with a magnetic stirring bar was charged with substrate **10a** (16.4 mg, 0.0748 mmol), the in situ prepared catalyst (2 mL, 7.74×10^{-3} mmol). The autoclave was closed and pressurized with hydrogen to 20 atm. The mixture was stirred at ambient temperature for 20 h. After careful venting of hydrogen, conversion and enantioselectivity of the reduced product was determined by chiral GC with a 25 m Chirasil-L-Val capillary column.

4.6. General procedure for the measurement of conversion time data of 4a–Rh with different L/Rh ratio

To a solution of $Rh(COD)_2BF_4$ (3.74×10^{-3} mmol) in CH_2Cl_2 (7 mL) was added dropwise dendritic ligand **4a** (3.74×10^{-3} mmol) in CH_2Cl_2 (7 mL) in 10 min. The reaction mixture was stirred for a further 10 min at room temperature. Then the substrate **10a** (82 mg, 0.374 mmol) was added. The flask was sealed with a plug and nitrogen was exchanged by hydrogen. The mixture was stirred under H_2 atmosphere (1 atm) at 10 °C. For sample taking, the stirrer was stopped at distinct times, and a small quantity of the reaction mixtures was taken with a dipping tube. The stirrer was then restarted under the same H_2 pressure. The sample was used to determine the ee value and conversion by using ^{1}H NMR and GC. Data of **4a**–Rh with different L/Rh ratio were obtained by the same method.

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References

1. Knapen, J. W. J.; van der Made, A. W.; de Wilde, J. C.; van Leeuwen, P. W. N. M.; Wijkens, P.; Grove, D. M.; van Koten, G. *Nature* **1994**, *372*, 659.
2. (a) Oosterom, G. E.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1828; (b) Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991; (c) van Heerbeek, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Chem. Rev.* **2002**, *102*, 3717; (d) Crooks, R. M.; Zhao, M.; Sun, L.; Chechik, V.; Yueng, L. K. *Acc. Chem. Res.* **2001**, *34*, 181; (e) Kreiter, R.; Kleij, A. W.; Gebbink, R. J. M. K.; van Koten, G. *Top. Curr. Chem.* **2001**, *217*, 163; (f) Twyman, L. J.; King, A. S. H.; Martin, I. K. *Chem. Soc. Rev.* **2002**, *31*, 69; (g) Dahan, A.; Portnoy, M. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 235; (h) Seebach, D.; Rheiner, P. B.; Greiveldinger, G.; Butz, T.; Sellner, H. *Top. Curr. Chem.* **1998**, *197*, 125; (i) Fan, Q. H.; Li, Y. M.; Chan, A. S. C. *Chem. Rev.* **2002**, *102*, 3385.
3. (a) Ooe, M.; Murata, M.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2004**, *126*, 1604; (b) Müller, C.; Ackerman, L. J.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2004**, *126*, 14960; (c) Fujihara, T.; Obora, Y.; Tokunaga, M.; Sato, H.; Tsuji, Y. *Chem. Commun.* **2005**, 4526; (d) Liu, W.; Cui, X.; Cun, L.; Wu, J.; Zhu, J.; Deng, J.; Fan, Q. *Synlett* **2005**, 1591; (e) Yi, B.; Fan, Q. H.; Deng, G. J.; Li, Y. M.; Qiu, L. Q.; Chan, A. S. C. *Org. Lett.* **2004**, *6*, 1361, and references cited therein.
4. Deng, G. J.; Fan, Q. H.; Chen, X. M.; Liu, D. S.; Chan, A. S. C. *Chem. Commun.* **2002**, 1570.
5. (a) Fan, Q. H.; Liu, G. H.; Chen, X. M.; Deng, G. J.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1559; (b) Liu, G. H.; Tang, W. J.; Fan, Q. H. *Tetrahedron* **2003**, *59*, 8603.
6. (a) Deng, G. J.; Fan, Q. H.; Chen, X. M.; Liu, D. S.; Chan, A. S. C. *Chem. Commun.* **2002**, 1570; (b) Deng, G. J.; Fan, Q. H.; Chen, X. M.; Liu, G. H. *J. Mol. Catal. A: Chem.* **2003**, *193*, 21; (c) Yang, B. Y.; Chen, X. M.; Deng, G. J.; Zhang, Y. L.; Fan, Q. H. *Tetrahedron Lett.* **2003**, *44*, 3535; (d) Tang, W. J.; Yang, N. F.; Yi, B.; Deng, G. J.; Huang, Y. Y.; Fan, Q. H. *Chem. Commun.* **2004**, 1378; (e) Deng, G. J.; Yi, B.; Huang, Y. Y.; Tang, W. J.; He, Y. M.; Fan, Q. H. *Adv. Synth. Catal.* **2004**, *346*, 1440–1444; (f) Huang, Y. Y.; Zhang, H. L.; Deng, G. J.; Tang, W. J.; Wang, X. Y.; He, Y. M.; Fan, Q. H. *J. Mol. Catal. A: Chem.* **2005**, *227*, 91; (g) Deng, G. J.; Li, G. R.; Zhu, L. Y.; Zhou, H. F.; He, Y. M.; Fan, Q. H.; Shuai, Z. G. *J. Mol. Catal. A: Chem.* **2005**, *244*, 118.
7. (a) Horner, L.; Siegel, H.; Büthe, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 942; (b) Knowles, W. S.; Sabacky, M. J. *J. Chem. Soc., Chem. Commun.* **1968**, 1445.
8. (a) Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun.* **2000**, 961; (b) Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889; (c) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539; (d) Komarov, I. V.; Börner, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 1197.
9. (a) Peña, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552; (b) van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Henderickx, H. J. W.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 308; (c) Jia, X.; Li, X.; Xu, L.; Shi, Q.; Yao, X.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 4539; (d) Fu, Y.; Xie, J. H.; Hu, A. G.; Zhou, H.; Wang, L. X.; Zhou, Q. L. *Chem. Commun.* **2002**, 480; (e) Hu, A. G.; Fu, Y.; Xie, J. H.; Zhou, H.; Wang, L. X.; Zhou, Q. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2348; (f) Fu, Y.; Guo, X. X.; Zhu, S. F.; Hu, A. G.; Xie, J. H.; Zhou, Q. L. *J. Org. Chem.* **2004**, *69*, 4648; (g) Reetz, M. T.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 790; (h) Reetz, M. T.; Li, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 2959; (i) Reetz, M. T.; Ma, J. A.; Goddard, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 412; (j) Hoen, R.; Boogers, J. A. F.; Bernsmann, H.; Minnaard, A. J.; Meetsma, A.; Tiemersma-Wegman, T. D.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4209; (k) Bernsmann, H.; van den Berg, M.; Hoen, R.; Minnaard, A. J.; Mehler, G.; Reetz, M. T.; de Vries, J. G.; Feringa, B. L. *J. Org. Chem.* **2005**, *70*, 943; (l) Liu, Y.; Ding, K. *J. Am. Chem. Soc.* **2005**, *127*, 10488; (m) Jerphagnon, T.; Renaud, J.-L.; Bruneau, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2101.
10. (a) Huttenloch, O.; Laxman, E.; Waldmann, H. *Chem. Commun.* **2002**, 673; (b) Doherty, S.; Robins, E. G.; Pál, I.; Newman, C. R.; Hardacre, C.; Rooney, D.; Mooney, D. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1517; (c) Simons, C.; Hanefeld, U.; Arends, I. W. C. E.; Minnaard, A. J.; Maschmeyer, T.; Sheldon, R. A. *Chem. Commun.* **2004**, 2830; (d) Botman, P. N. M.; Amore, A.; van Heerbeek, R.; Back, J. W.; Hiemstra, H.; Reek, J. N. H.; van Maarseveen, J. H. *Tetrahedron Lett.* **2004**, *45*, 5999; (e) Wang, X.; Ding, K. *J. Am. Chem. Soc.* **2005**, *126*, 10524.
11. Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.
12. Vogtle, F.; Plevoets, M.; Nachtsheim, G.; Worsdorfer, U. *J. Prakt. Chem.* **1998**, *340*, 112.