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Structural Effects on the Catalytic, Emulsifying, and Recycling Properties of Chiral Amphiphilic Dendritic Organocatalysts

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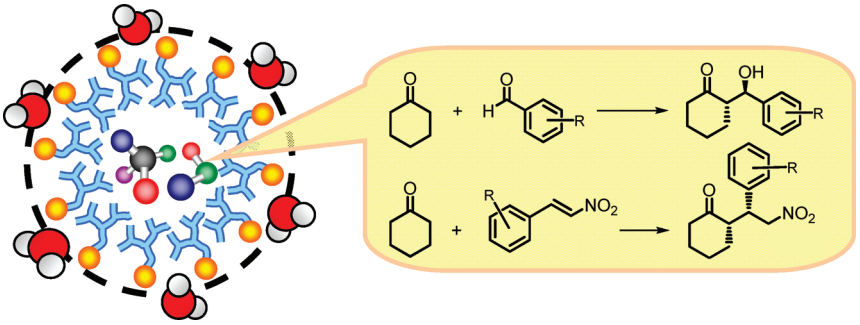

Three series of chiral amphiphilic G1−G3 dendritic organocatalysts containing an optically active polar proline-derived core and one or two nonpolar hydrocarbon dendrons were prepared. These dendritic organocatalysts were employed in the asymmetric aldol and nitro-Michael additions in oil-in-water emulsions to reveal the effects of dendron size and branching on the catalytic properties. The incorporation of larger hydrophobic dendrons has the advantages of promoting emulsion formation in water, improving the reaction enantioselectivity, decreasing catalyst loading (to 1 mol %), and facilitating catalyst recovery after the reactions. In general, the larger dendrons tended to lower catalyst reactivity due to their increasing steric blocking effect. However, some astonishing observations were found in some of the G1 and G2 dendritic organocatalysts, wherein an increase in the steric bulkiness and branching of the dendron resulted in better catalyst reactivity. It was also found that higher product yields and enantioselectivities were obtained in the aldol reactions when the aromatic aldehyde contains an electron-withdrawing substituent. The catalysts could be recycled and reused five times without significant drop in product yields and enantioselectivities. In addition, cross product contamination was not found when the recovered G3 catalyst was subsequently used in another reaction involving different substrates.

Introduction

Proline and its derivatives are most commonly employed as catalysts in the asymmetric aldol[1] and Michael reactions.[2] These reactions involve the formation of an enamine between the secondary amino group in proline with the ketone substrate and protonation of the aldehyde/imine reaction partner via the carboxylic acid group of the proline moiety. The stereochemical outcome of the reaction can be rationalized by the Zimmerman−Traxler transition state model.[3]

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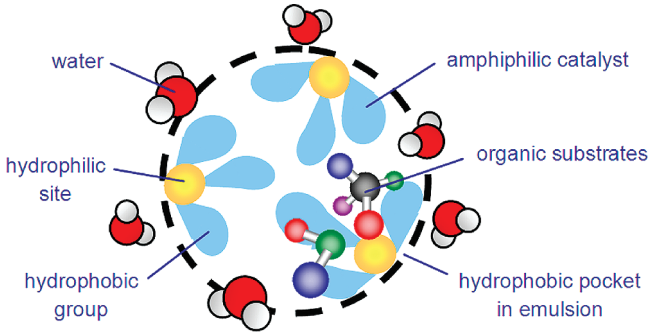
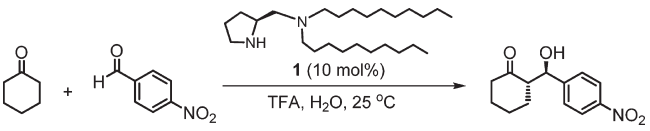


FIGURE 1. Organic transformation inside an emulsion system.

In general, good to excellent product enantioselectivities (ee = 60−96%) could be achieved with electronically suitably substituted substrates. However, two major drawbacks of the reactions are the requirements of high catalyst loading (>20 mol %) and excess amount of ketone donor to compete against the undesirable decarboxylative side reaction of proline.[4] In view of these shortcomings, proline derivatives with an alternative type of proton donor group, such as the conjugated acid of a tertiary amine, were designed.[5] Such modified proline catalysts generally possess better solubility in organic solvents and, hence, a lower catalyst loading can be employed.

To further improve product yields and enantioselectivities of the reactions, several research groups began to utilize the hydrophobic effect of the catalyst system in water or in an emulsion system.[6] In the presence of water, the amphiphilic organocatalyst will form a micelle structure, exposing the hydrophilic sites to water, while the hydrophobic parts will pack together to form a nonpolar pocket (Figure 1). Once the organic reactants are added, they tend to penetrate into the hydrophobic pocket. As a result, the reaction proceeds in a concentrated organic phase generated by the organic substrates and the organocatalyst inside the emulsion droplets. Barbas reported the first use of (*S*)-proline in the presence of sodium dodecyl sulfate as a surfactant to catalyze the aldol reaction in aqueous phosphate buffer (pH = 7.4) to give aldol products in moderate to high reaction yields (50−99%).[7] However, the ee values were poor, as only racemates were obtained. Developments in this field progressed rapidly afterward and there were significant breakthroughs in asymmetric organocatalysis in water due to major contributions by Hayashi,[8] Barbas,[9] and Córdova.[10] One of the promising results reported by Barbas involved the use of surfactant-type amphiphilic organocatalysts (e.g., **1**) to give high product yields and good ee values (87−99%) in the asymmetric aldol reactions between ketones and aldehydes in water (Scheme 1).[11] As a result of incorporating the surfactant appendage into the catalyst, such amphiphilic diamino organocatalysts obviated the necessity of adding an external surfactant into the reaction medium. Because the organocatalysts do not contain acidic functionalities, trifluoroacetic acid (TFA, 1 equiv) was added as the proton source to enhance the electrophilicity of the aldehyde substrate. The two long alkyl chains in the catalyst then acted as the surfactant parts to promote the formation of emulsion in water and to enhance the reactivity and selectivity of the asymmetric aldol reactions. In addition, the emulsion system could also overcome mixing problems due to incompatible solubility properties between the reactants.[12] Hence, formation of a steady emulsion is of ultimate importance to ensure high product yields and good product enantioselectivities. Despite these promising findings, there are little studies on the effect of the size and shape of the surfactant appendages on the micelle formation efficiency and the catalyst properties.

SCHEME 1. Aldol Reaction Promoted by Amphiphilic Organocatalysts 1



In this paper, we report (a) the synthesis of several series of G1-G3 chiral amphiphilic dendritic organocatalysts **Di-L-Gn** (doubly dendronized, longer spacer), **Mono-L-Gn** (singly dendronized, longer spacer), and **Mono-S-Gn** (singly dendronized, shorter spacer) that contain a proline catalytic core with one or two nonpolar hydrocarbon (HC) dendron(s) on the dendrimer surface, (b) their applications in asymmetric aldol reactions and nitro-Michael additions, (c) the effect of dendron size (i.e., G1 vs G2 vs G3), degree of branching (i.e., Di vs Mono), and spacer chain length (i.e., L vs S) between the proline catalytic core and the dendron on the reaction reactivity and enantioselectivity, and (d) their catalyst recovery property and reusability in different aldol reactions without product cross contaminations. Our studies reveal a positive branching effect of the nonpolar HC dendrons on emulsion formation and catalyst reactivity, and provide the first assessment of the size and geometry of the dendritic appendages on the efficiency of emulsion formation. By incorporating the catalytic center inside a dendritic skeleton, recovery and recycling of the dendritic organocatalysts become feasible. Furthermore, the branching nature of the dendrons can promote better stereodifferentiation to give higher product enantioselectivity. Although applications of dendritic catalysts are well documented in the literature,

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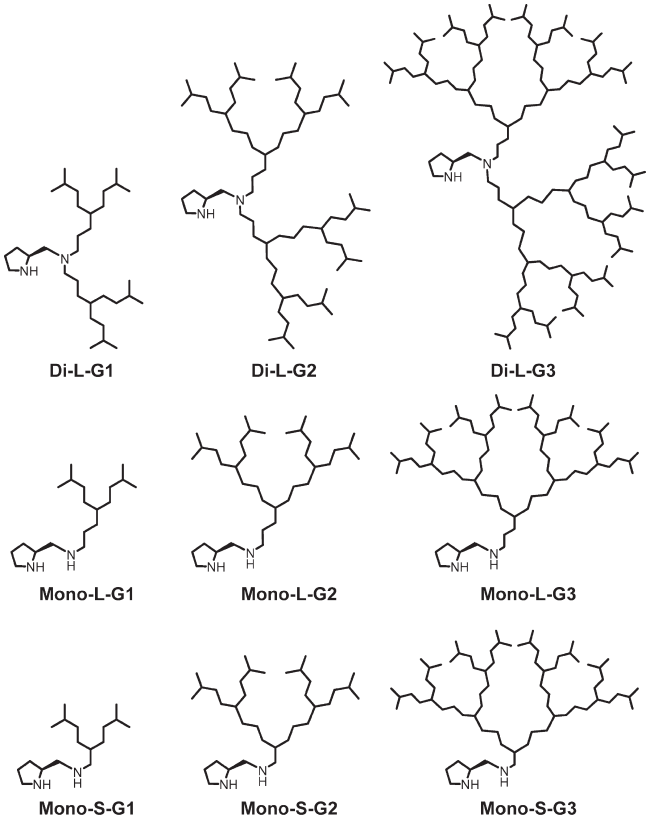
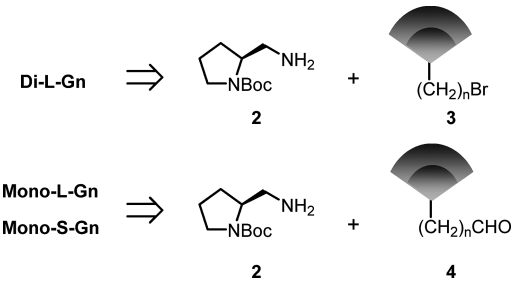
however, amphiphilic dendritic organocatalysts worked on an emulsion system have not been disclosed before.



Results and Discussion

Catalyst Design. Due to the amphiphilic nature of the catalyst, the dendrons used in the design must be highly hydrophobic in nature. Previous reports showed that even oligoether dendrons were highly polar,[13] hence, only HC dendrons were suitable candidates. Due to the high crystallinity of oligo(phenylene),[14] oligo(phenylenevinylene),[15] and oligo(phenyleneethynylene) dendrons,[16] they are less desirable than aliphatic HC dendrons[17] to be used in this study. To explore the structural effects on the reactivity, enantioselectivity, emulsion formation and recovery properties of the catalysts, three classes of amphiphilic dendritic HC organocatalysts were designed. The **Di-L-Gn** series are compounds bearing two (Di) dendronized HC sectors with a relatively longer three-carbon spacer (L) connecting the proline and two HC dendrons. The **Mono-L-Gn** series feature the attachment of one single (Mono) dendronized HC sector via the same three-carbon spacer unit (L) to the proline core. Finally, the **Mono-S-Gn** series denote compounds that employ a relatively short one carbon spacer (S) linking one single dendronized HC sector and the proline core. The differences in the number of dendron(s) and the spatial distance between dendron(s) and catalytic core should allow one to compare the effect of steric shielding on the reactivity, enantioselectivity, and other properties of the catalyzed reactions.

SCHEME 2. Retrosynthetic Analysis of Amphiphilic Dendritic Organocatalysts



Synthesis. The preparation of doubly dendronized **Di-L-Gn** catalysts is best achieved via a di-*N*-alkylation of a proline-derived amine **2**[18] to a HC dendron **3** bearing a good leaving group (Scheme 2). The singly dendronized catalysts, **Mono-L-Gn** and **Mono-S-Gn**, could be prepared by a reductive amination starting from the same amine **2** to a HC dendron **4** bearing an aldehyde focal point functionality.

The elongated G1−G3 HC dendritic bromides **5**−**7** were prepared from the known α,β-unsaturated esters **8**−**10** (Scheme 3).[17] Hydrogenation of compounds **8**−**10** gave the corresponding saturated esters **11**−**13** in 94−99% yield. Subsequent reduction with $LiAlH_4$ in THF at 0 °C gave the corresponding alcohols **14**−**16** in 90−99% yield. The target bromides **5**−**7** could be obtained from bromination of **14**−**16**, respectively, with NBS and PPh_3 in CH_2Cl_2 in 92−97% yield (details of the synthesis of all intermediates can be found in Supporting Information).

For the preparation of **Di-L-G1** and **Di-L-G2** catalysts, di-*N*-alkylation of the proline-derived compound **2** with the elongated G1 **5** and G2 dendritic bromide **6** in the presence of K_2CO_3, KI, 18-crown-6, and *i*-Pr_2NEt in DMF at 60 °C afforded the Boc-protected dialkylation product **Boc-Di-L-G1** and **Boc-Di-L-G2** in 74 and 77% yields, respectively. After removal of Boc group by TFA, the target dendritic catalysts, **Di-L-G1** and **Di-L-G2**, were obtained in 99% in both cases. However, for the synthesis of **Di-L-G3** dendritic catalyst, the di-*N*-alkylation reaction was very sluggish, possibly due to the highly sterically hindered environment caused by the larger dendrons. The resulting di-*N*-alkylation product **Boc-Di-L-G3** was obtained only in 37% yield. At a higher reaction temperature (100 °C), competing hydrolysis of the G3 bromide **7** back to the corresponding alcohol **16** became a prominent side reaction. The corresponding G3 iodide was then used as a substitute for the G3 bromide, but no improvement in reaction yield was realized. Fortunately, addition of toluene to the reaction medium gave the di-*N*-alkylation product **Boc-Di-L-G3**

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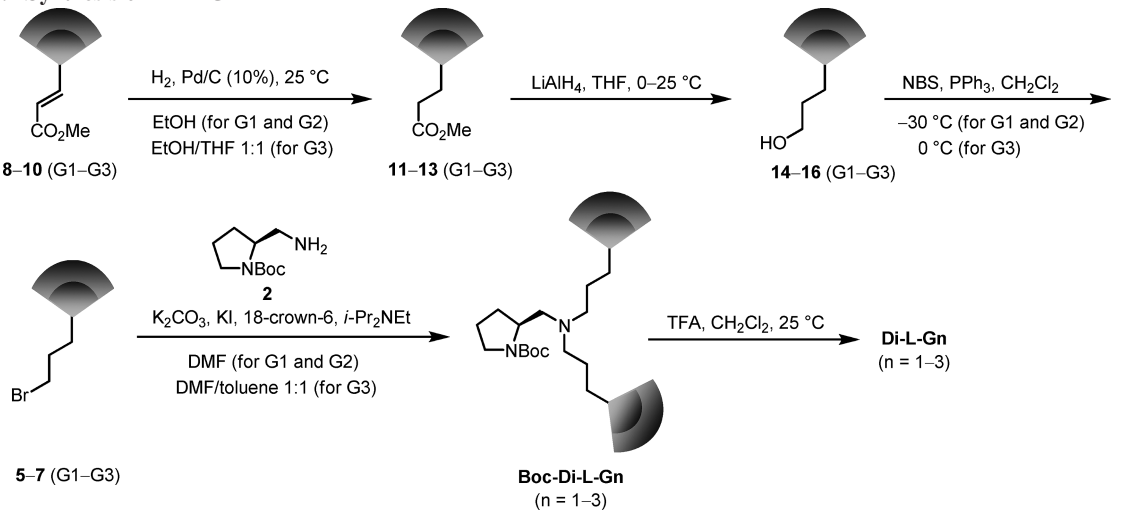
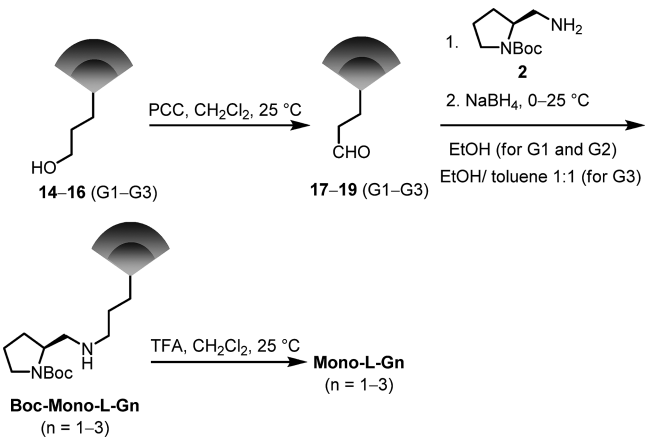
SCHEME 3. Synthesis of Di-L-Gn



SCHEME 4. Synthesis of Mono-L-Gn



in 56% yield. Subsequent removal of the Boc group by TFA afforded the desired catalyst **Di-L-G3** in 97% yield.

The reductive amination method was used to prepare the singly dendronized **Mono-L-Gn** and **Mono-S-Gn** catalysts (Schemes 4 and 5). Oxidation of the alcohols **14**−**16** with PCC afforded the corresponding aldehydes **17**−**19** in 98−99% yield, respectively. Treatment of a mixture of the amine **2** and the aldehydes **17**−**19** in ethanol with $NaBH_4$ gave the monoalkylated products **Boc-Mono-L-Gn** in 65−85% yield, respectively. Subsequent removal of Boc group afforded the target **Mono-L-Gn** in 95−97% yield.

The **Mono-S-Gn** catalysts were also prepared from the reductive amination of the known shorter chain aldehydes **20**−**22**[17] and the amine core **2** to give the Boc-protected monoalkylated products **Boc-Mono-S-Gn**. Removal of the Boc protective group by TFA then produced the target **Mono-S-Gn**. The overall yields of **Mono-S-G1**, **Mono-S-G2**, and **Mono-S-G3** were 67, 61, and 59%, respectively, from the aldehydes **20**−**22**.

Catalytic Properties. The catalytic properties of the amphiphilic dendritic organocatalysts were then examined. It was found that, to form a stable emulsion, the catalyst and TFA had to be mixed and sonicated before adding the substrates. Otherwise, an emulsion might not be formed and the reaction proceeded extremely slowly, resulting in a very low product conversion and hence poor product ield. If a creamy oil-in-water (O/W) emulsion was formed (Figure 2a), the reaction usually proceeded to give products in excellent reaction yield. Good results could also be obtained even though some oil droplets (Figure 2b) or thin layers of oil (Figure 2c) coexisted with the turbid emulsion. However, if the reaction mixture became macroscopically separated phases (Figure 2d,e), the reaction generally failed to proceed.

Asymmetric Aldol Reactions. The catalytic properties of the dendritic organocatalysts were examined by conducting the asymmetric aldol reactions using cyclopentanone **23** and 3-nitro-benzaldehyde **24** in an emulsion. The preliminary results of the different dendritic organocatalysts were summarized in Table 1. The amphiphilic catalyst **1**[11] reported by Barbas was also used as a standard for comparison.

It was found that the various dendritic organocatalysts were very effective in the aldol reaction. The aldol adduct **25** was formed in 64−93% yields (entries 2−9) that were comparable to that from using the nondendritic organocatalyst **1**. Among the three series of compounds, the **Di-L-Gn** series (entries 2−4) gave the best product ee values and those (70−86%) obtained from **Di-L-G1** and **Di-L-G2** were even better than that of the organocatalyst **1** (65%). On the other hand, the **Mono-S-Gn** series (entries 8−10) gave moderate to high ee values (52−68%), while the **Mono-L-Gn** series (entries 5−7) were the least enantioselective catalysts (7−59%). The results could be rationalized by the higher steric hindrance of the **Di-L-Gn** series, in which there are two bulky dendron groups to provide the steric shielding. The extremely low ee value (7%) in the case of **Mono-L-G1** may be due to the poor stereodifferentiating effect of the smallest G1 dendron, which is located quite far away from the pyrrolidine ring by the longer three-carbon linker. However, as the generation increases, the size of the dendron becomes larger, which enables better shielding of the reaction site, and hence, higher ee values were observed with the **Mono-L-G2** and **Mono-L-G3** dendritic catalysts. The **Mono-S-Gn** series also offered higher steric hindrance than the **Mono-L-Gn** series due to the closer proximity of the dendron to the catalytic

proline core. However, addition of an extra G1 dendron to **Mono-S-G1** (i.e., **Di-S-G1**) resulted in a drastic reduction of product yield (20%), although a relatively good product ee value (67%) could still be obtained (see Supporting Information for details). Hence, increasing steric hindrance although provided better enantioselectivities, it also retarded the reaction rate and decreased product yields.

Among these dendritic catalysts, the **Di-L-Gn** series were found to form very stable emulsions. Their O/W emulsions remained stable within 1 h even without stirring, while those of the **Mono-L-Gn** separated into two phases in minutes once stirring was stopped. The **Di-L-Gn** catalysts also promoted better product yields and good enantioselectivities. Hence, we decided to focus our investigations mainly on this series of compounds (Table 2). Different aromatic aldehydes **26** were chosen and reacted with cyclohexanone **27** in creamy O/W emulsion. In all cases, the *anti*-aldol **28** was obtained as the major product. For the cases of electron deficient nitro-substituted benzaldehydes (entries 1−8), the reaction proceeded smoothly to give aldol products in high reaction yields (58−86%). This was expected as the electron withdrawing nitro group increased the electrophilicity of the aldehyde. The yield gradually decreased from the slightly electron deficient 4-bromobenzaldehye (entries 9−12) to benzaldehyde (entries 13−16), and became extremely poor (5−10%) for the electron-rich 4-methoxybenzaldehyde (entries 17−20). It was noted that the reaction yields were comparable and, in some cases (entries 2, 3, 10, 15, and 18), even better than those of the nondendritic catalyst **1**.

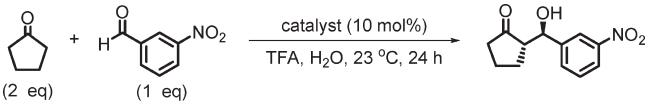
With regard to product ee values, the various dendritic catalysts behaved differently with different substrates. In some situations, higher ee values could be achieved (entries 6, 7, 11, and 18−20) as compared to that of the nondendritic catalyst **1**, while slight inferior ee values were also observed (entries 4, 8, 10, 12, 15, and 16). Some anomalies in the relationship between steric shielding and product ee values were also observed. For examples, **Di-L-G1** was better than **Di-L-G2** for the aldol reaction for 4-methoxybenzaldehyde (entry 18 vs 19), while **Di-L-G2** was better than **Di-L-G1** involving 4-bromobenzaldehyde (entry 10 vs 11).

FIGURE 2. (a) Creamy O/W emulsion; (b) O/W emulsion with a little amount of oil droplets; (c) O/W emulsion with thin layers of oil; (d) turbid solution that separates into immiscible layers when the stirring is stopped; (e) insoluble reactants in the reaction mixture.

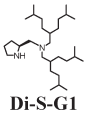
We also found out that the aldol reaction could still proceed with a catalytic loading of 1% with no obvious drop of product yield and ee value (see Supporting Information for details). Creamy O/W emulsions could still be maintained even though the amount of catalyst present was less.

Relative Catalytic Reactivity. The relative reactivities of the different generation of dendritic catalysts were determined to examine the effect of branching on the catalyst reactivity. The percentage conversions against time were obtained from ^{1}H NMR measurements. The parameter that could be extracted from such experiments was the ratio of aldol product to the remaining aldehyde. The percentage conversion was calculated by assuming all the aldehyde was converted to the desired aldol without producing other side products. However, as the reactions were carried out in an

TABLE 1. Aldol Reactions between Cyclopentanone 23 and 3-Nitrobenzaldehyde 24 Catalyzed by Various Catalysts[a]



23 **24** **25**

Entry	Catalyst	Yield (%)[b]	*anti* : *syn*[c]	ee (%)[d]
1	**1**	79	67 : 33	65
2	**Di-L-G1**	80	69 : 31	70
3	**Di-L-G2**	78	59 : 41	86
4	**Di-L-G3**	88	47 : 53	60
5	**Mono-L-G1**	69	36 : 64	7
6	**Mono-L-G2**	78	54 : 46	59
7	**Mono-L-G3**	93	52 : 48	53
8	**Mono-S-G1**	64	60 : 40	61
9	**Mono-S-G2**	81	53 : 47	68
10	**Mono-S-G3**	71	58 : 42	52
11	 **Di-S-G1**	20	44 : 56	67

[a]Conditions: cyclopentanone **23** (375 μmol), 3-nitrobenzaldehyde **24** (187 μmol), catalyst (18.7 μmol), and TFA (18.7 μmol) in water (0.5 mL) at 23 °C for 24 h. [b]Isolated yield after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude product. [d]Determined by chiral-phase HPLC (Chiralcel OD-H) analysis on the major *anti*-product.

SCHEME 5. Synthesis of Mono-S-Gn

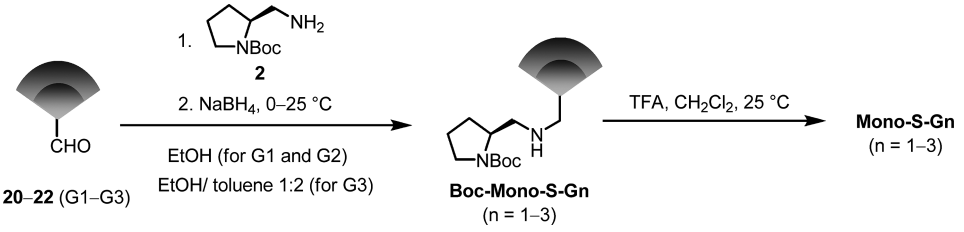
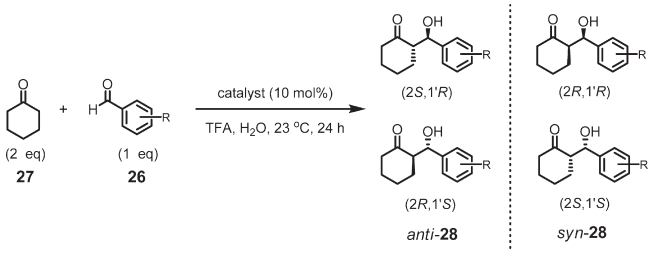


TABLE 2. Aldol Reactions between Cyclohexanone 27 and Substituted Benzaldehydes 26 Catalyzed by Di-L-Gn[a]



entry	catalyst	R	yield (%)[b]	*anti*/*syn*[c]	ee (%)[d]
1	**1**	4-NO_2	75	83:17	95
2	**Di-L-G1**	4-NO_2	85	87:13	93
3	**Di-L-G2**	4-NO_2	80	87:13	93
4	**Di-L-G3**	4-NO_2	61	74:26	85
5	**1**	3-NO_2	86	78:22	76
6	**Di-L-G1**	3-NO_2	85	81:19	91
7	**Di-L-G2**	3-NO_2	71	88:12	91
8[e]	**Di-L-G3**	3-NO_2	58	67:33	41
9	**1**	4-Br	50	81:19	66
10	**Di-L-G1**	4-Br	95	70:30	35
11	**Di-L-G2**	4-Br	45	80:20	79
12	**Di-L-G3**	4-Br	38	79:21	13
13	**1**	H	34	78:22	91
14	**Di-L-G1**	H	35	79:21	88
15	**Di-L-G2**	H	45	59:41	60
16[e]	**Di-L-G3**	H	28	61:39	20
17	**1**	4-OMe	6	73:27	44
18	**Di-L-G1**	4-OMe	10	66:34	80
19	**Di-L-G2**	4-OMe	5	64:36	49
20	**Di-L-G3**	4-OMe	6	63:37	57

[a]Conditions: cyclohexanone **27** (375 μmol), aldehyde (187 μmol), catalyst (18.7 μmol), and TFA (18.7 μmol) in water (0.5 mL) at 23 °C for 24 h. [b]Isolated yield after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude product. [d]Determined by chiral-phase HPLC (Chiralcel OD-H) analysis on the major *anti*-product. [e]Reaction time = 72 h.

emulsion system, the aliquot taken out from the reaction mixture at each time interval was actually a heterogeneous mixture containing both organic and aqueous phases. Hence, there was an uncertainty during samplings, as the relative volume of aqueous to organic phases could not be standardized. However, as the aldehyde and the aldol adduct were present mainly in the organic layer, the variation of the organic/aqueous volume ratio should not lead to a huge deviation from the true figures. Hence, the measured relative reactivity could still provide a semiquantitative picture of the catalyst efficiency.

The catalytic efficiencies of the different types of G1 and G2 dendritic catalysts were measured (Figure 3). The nondendritic catalyst **1** was the most effective one as the reaction was completed within 2 h. In comparison, the shorter chain catalysts **Mono-S-G1** and **Di-S-G1** were clearly inferior as compared to the others. This must be attributed to a higher steric hindrance of the S series. For the L series, the order of reactivity exhibited a very interesting trend. It was found that the doubly dendronized catalysts (L) showed better reactivity than the singly dendronized catalysts (S) of the same generation (i.e., **Di-L-G1** > **Mono-L-G1** and **Di-L-G2** > **Mono-L-G2**). This trend was in contradiction to the presumed higher steric effect of the doubly dendronized series but could be explained by their much better emulsion formation capability described earlier. Hence, the larger hydrophobic HC dendron on one hand retarded the reaction due to larger steric effect, but on the other hand promoted the formation of a more stable emulsion and hence an increase of the reaction rate. The latter effect is similar to a positive dendritic catalytic effect, that is, increasing dendrimer generation leads to higher catalyst reactivity.[19] Strictly speaking, dendritic catalytic effect should be ascribed to the reactivity pattern of different generations of the same type of compounds, while in our case we are comparing the same generation of compounds belonging to two different dendrimer series (i.e., **Di-L-Gn** vs **Mono-L-Gn**). However, if one realizes that the **Di-L-Gn** series of compounds actually contain an extra degree of branching at the nitrogen center, then **Di-L-Gn** sterically can be considered to be equivalent to **Mono-L-G(n+1)**. Hence, in our case we actually observed reactivity enhancement due to increasing bulkiness of the HC dendron. The larger HC dendron could in turn stabilize the resulting emulsion, which was known to be critical in ensuring good product yields and enantioselectivities. When one examined the reactivity of the three generations of doubly dendronized catalysts of the same series, it was shown that the reactivity trend was **Di-L-G1** > **Di-L-G2** > **Di-L-G3** (Figure 4). Hence, one could conclude that steric inhibition was still the dominating factor in determining the rate of the reaction, while the emulsion stabilization effect was of second importance. Nonetheless, the product yields were all >95% for all three generations of catalyst when the reaction was allowed to extend to 24 h. Hence, the increasing steric effect just slowed down the reaction rate, but did not lower the product yield.

Solvent Effects. We also examined the solvent effects on the aldol reactions between cyclopentanone **23** and 3-nitrobenzaldehyde **24** using **Di-L-G1** (Table 3). A range of solvents, from nonpolar solvent such as hexane to polar ones such as water were tested. All reactions proceeded to give high reaction yields (75−80%) with moderate diastereoselectivities (*anti*/*syn* from 2:3 to 2:1). In nonpolar solvents such as hexane (entry 1), where both the ketone and aldehyde substrates were poorly soluble, low ee (16%) was observed. For polar nonaqueous solvents such as ethanol (entry 2) and methanol (entry 3), in which the reaction was homogeneous, moderate ee values (48%) were observed. In water (0.5 mL) as an O/W emulsion (entry 4), a higher ee value (70%) was obtained. Interestingly, decreasing the amount of water to 0.1 mL resulted in the formation of a water-in-oil (W/O) emulsion (entry 5), which separated into two layers when stirring was interrupted. In this case, the product ee value was only 52%. In the absence of solvent (entry 6), the reaction still proceeded despite of the high viscosity. However, the product ee value further dropped to 41%. Hence, a stable O/W emulsion was necessary to produce good product ee values.

Asymmetric Nitro-Michael Additions. We next examined the effectiveness of our dendritic organocatalysts in

(19) (a) Lee, J.-J.; Ford, W. T.; Moore, J. A.; Li, Y. *Macromolecules* **1994**, *27*, 4632–4634. (b) Francavilla, C.; Bright, F. V.; Detty, M. R. *Org. Lett.* **1999**, *1*, 1043–1046. (c) Drake, M. D.; Bright, F. V.; Detty, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 12558–12566. (d) Chow, H.-F.; Leung, C.-F.; Wang, G.-X.; Yang, Y.-Y. C. R. *Chimie* **2003**, *6*, 735–745.

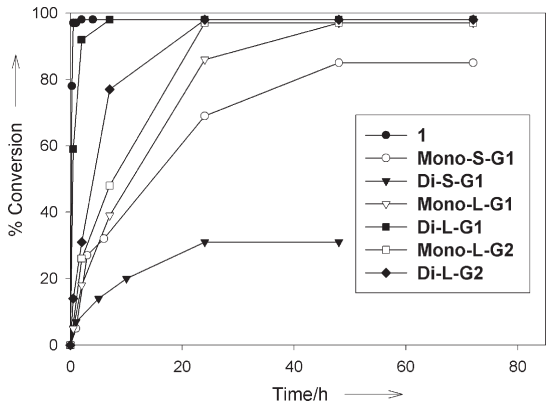


FIGURE 3. Plot of conversion against time for aldol reactions between cyclopentanone **23** and 3-nitrobenzaldehyde **24** employing different dendritic organocatalysts.

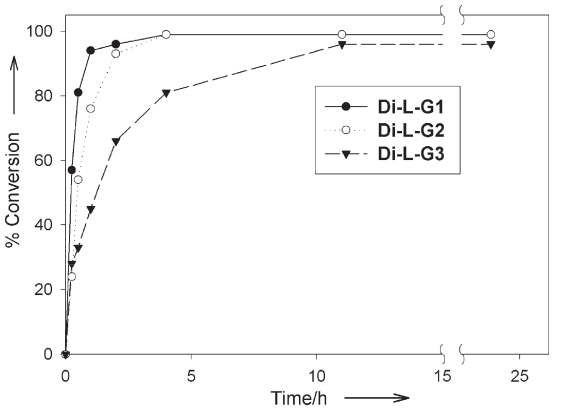


FIGURE 4. Plot of conversion against time for aldol reactions between cyclopentanone **23** and 3-nitrobenzaldehyde **24** employing different **Di-L-Gn** dendritic organocatalysts.

asymmetric nitro-Michael reactions (Table 4). All reactions proceeded in creamy O/W emulsions and showed good diastereoselectivities (*syn*/*anti* > 82:18). Except **Mono-L-G1** and **Mono-S-G1** (entries 5, 8, 15, and 18), all other catalysts gave high reaction yields (61−88%) and good ee values (70−90%), and the results were comparable to those using the nondendritic catalyst **1**. Similar to aldol reactions, catalysts **Mono-L-G1** and **Mono-S-G1** with only one G1 dendron produced products with lower ee values (31−67%), while **Di-L-G1** gave good results (70−89%). Hence, the extra G1 dendron in **Di-L-G1** produced a better stereodifferentiating and emulsifying effect. It was also found that the electronic properties of the substituents on the nitrostyrene substrates did not have any significant effect on the reaction yields. Hence, both electron donating OMe functionality and withdrawing NO_2 and Br groups underwent nitro-Michael addition smoothly to afford good product yields (51−88%).

Catalyst Recovery. Because the catalysts were synthesized in multiple steps, the recovery of the catalysts and reusability in another reaction without cross contamination are very important. Normally, soluble polymer- or dendrimer-supported catalysts can be recovered by precipitation in a different solvent system[20] or by membrane dialysis if they have a relatively high molecular weight.[21] In the case of our HC organodendritic catalysts, such methods are not useful as they are oily liquids with a relatively low molecular weight. Hence, a special recovery method was used in this study. As the HC dendrons are highly nonpolar, they are highly soluble in nonpolar HC solvents such as hexane or heptane. Incidentally, the aldol products are more polar and more soluble in methanol. Making use of the immiscibility between nonpolar HC solvent and MeOH, catalyst recovery was possible by partitioning the reaction mixture between the two solvent systems.

The relative amount of our dendritic catalysts in the HC solvent and MeOH layers after partition (*v*/*v* 1:1) could be determined quantitatively by ^{1}H NMR spectroscopy using standard addition method (Table 5). As expected, the largest HC organocatalyst **Di-L-G3** possessed the highest partition ratio in hexane, heptane and octane. On the other hand, the smallest **Di-L-G1** behaved similarly to the nondendritic catalyst **1**, and partitioned mainly in the MeOH layer and hence could not be extracted and recovered by these nonpolar HC solvents.

For the three nonpolar extraction solvents, heptane showed better recovery than hexane for **Di-L-G2** and **Di-L-G3** due to its higher nonpolar character. Although octane was expected to give a better recovery due to its even greater nonpolar character, the recovery was worse than using hexane. One reason was due to the similar density between octane and MeOH, which produced problems in the separation of the two phases. In the cases of hexane and heptane, they have a relatively larger density difference as compared to MeOH (ρ_{hexane} = 0.659, $\rho_{heptane}$ = 0.684, ρ_{octane} = 0.708, ρ_{MeOH} = 0.791) and the layers were easily separable. Hence, heptane was chosen as the solvent to recover the **Di-L-G2** and **Di-L-G3** catalysts after the reactions.

Catalyst recycling by heptane/MeOH partition after nitro-Michael reaction between cyclohexanone **27** and *trans*-β-nitrostyrene **29** (R = H) was then performed. The catalyst (**Di-L-G2** or **Di-L-G3**) was recovered by extraction with heptane/MeOH (*v*/*v* 3:1). The heptane layer was then back-washed with MeOH (*v*/*v* 1:1), NaOH (1 M) and saturated NaCl solutions successively and concentrated in vacuo to obtain the recovered catalyst. It was then reused in the same nitro-Michael addition (Table 6). To our delight, the reaction yields (78−87%), product diastereoselectivities (*syn*/*anti* > 90:10), and enantioselectivities (80−84%) could be retained even after five successive runs. Hence, heptane was found to be a good nonpolar solvent for extracting the catalysts by partitioning with MeOH. On the other hand, the nondendritic organocatalyst **1** could not be recycled by heptane extraction as it partitioned in both HC solvent and MeOH layers, the majority of which was present in the MeOH layer together with the nitro-Michael adducts. Similarly, catalyst recycling was also highly efficient for the aldol reactions (see Supporting Information for details).

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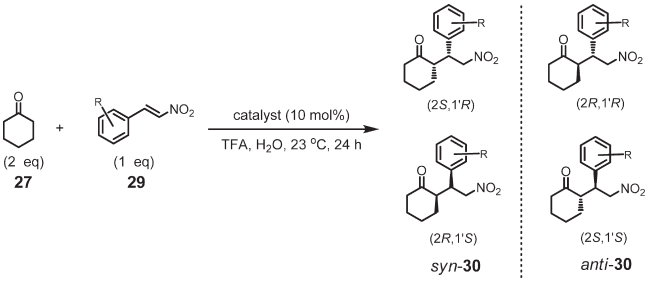
(21) Dijkstra, H. P.; van Klink, G. P. M.; van Koten, G. *Acc. Chem. Res.* **2002**, *35*, 798–810.

TABLE 3. Aldol Reaction between Cyclopentanone 23 and 3-Nitrobenzaldehyde 24 Catalyzed by Di-L-G1 in Different Solvent Systems[a]

entry	solvents	yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	hexane	79	40:60	16
2	ethanol	77	55:45	48
3[e]	methanol	79	63:37	48
4	water	80	69:31	70
5	water[f]	80	63:37	52
6	[g]	75	60:40	41

[a]Conditions: cyclopentanone **23** (375 μmol), 3-nitrobenzaldehyde **24** (187 μmol), **Di-L-G1** (18.7 μmol), and TFA (18.7 μmol) in different solvent (0.5 mL) at 23 °C for 24 h. [b]Isolated yield after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude product. [d]Determined by chiral-phase HPLC (Chiralcel OD-H) analysis on the *anti*-product. [e]Reaction time was 72 h. [f]0.1 mL of water used. [g]Neat without water.

TABLE 4. Nitro-Michael Reactions between Cyclohexanone 27 and Substituted β-Nitrostyrenes 29 Catalyzed by Various Catalysts[a]



entry	catalyst	R	yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	**1**	H	87	11:89	82
2	**Di-L-G1**	H	84	10:90	72
3	**Di-L-G2**	H	80	7:93	83
4	**Di-L-G3**	H	78	5:95	76
5	**Mono-L-G1**	H	79	7:93	59
6	**Mono-L-G2**	H	88	6:94	83
7	**Mono-L-G3**	H	81	6:94	80
8	**Mono-S-G1**	H	77	14:86	67
9	**Mono-S-G2**	H	83	6:94	86
10	**Mono-S-G3**	H	87	5:95	86
11	**1**	4-OMe	84	5:95	86
12	**Di-L-G1**	4-OMe	61	5:95	71
13	**Di-L-G2**	4-OMe	68	4:96	87
14	**Di-L-G3**	4-OMe	75	4:96	90
15	**Mono-L-G1**	4-OMe	59	5:95	31
16	**Mono-L-G2**	4-OMe	88	5:95	78
17	**Mono-L-G3**	4-OMe	82	5:95	80
18	**Mono-S-G1**	4-OMe	51	6:94	41
19	**Mono-S-G2**	4-OMe	71	4:96	88
20	**Mono-S-G3**	4-OMe	76	5:95	89
21	**1**	4-Br	82	5:95	73
22	**Di-L-G1**	4-Br	79	3:97	70
23	**1**	2-NO_2	76	18:82	86
24	**Di-L-G1**	2-NO_2	66	8:92	89

[a]Conditions: cyclohexanone **27** (375 μmol), nitrostyrene **29** (187 μmol), catalyst (18.7 μmol), and TFA (18.7 μmol) in water (0.5 mL) at 23 °C for 24 h. [b]Isolated yield after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude product. [d]Determined by chiral-phase HPLC (Chiralcel OD-H) analysis on the *syn*-product.

It is desirable that the recovered catalysts could also be used in different reactions without cross-contamination. It is important that the recovered catalyst from the heptane layer does not contain any starting materials or reaction products carried down from the previous experiment. Interestingly,

TABLE 5. Partition Ratios ($[Catalyst]_{HC\ solvent}/[Catalyst]_{MeOH}$) of Different Organocatalysts in a Mixture of Nonpolar HC Solvent and MeOH (*v*/*v* 1:1)[a]

solvent	**1**	**Di-L-G1**	**Di-L-G2**	**Di-L-G3**
hexane	0.1	1.2	2.1	15.7
heptane	0.2	0.1	3.3	50.5
octane	0.2	0.4	1.8	6.1

[a]See Supporting Information for details.

TABLE 6. Asymmetric Nitro-Michael Addition[a] **between Cyclohexanone 27 and *trans*-β-Nitrostyrene 29 (R = H) in Water Using Recovered Organodendritic Catalysts from Heptane/MeOH Partition**

catalyst	run	yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
Di-L-G2	1	85	6:94	81
Di-L-G2	2	84	6:94	80
Di-L-G2	3	87	6:94	84
Di-L-G2	4	81	8:92	84
Di-L-G2	5	83	9:91	82
Di-L-G3	1	78	6:94	84
Di-L-G3	2	79	6:94	81
Di-L-G3	3	79	6:94	83
Di-L-G3	4	80	9:91	83
Di-L-G3	5	81	8:92	81

[a]Conditions of nitro-Michael addition: cyclohexanone **27** (375 μmol), *trans*-β-nitrostyrene **29** (187 μmol), recovered catalyst, and TFA (1 equiv to the catalyst) in water (0.5 mL) at 23 °C for 24 h. [b]Isolated yield after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude product. [d]Determined by chiral-phase HPLC (Chiralcel OD-H) analysis on the *syn*-product.

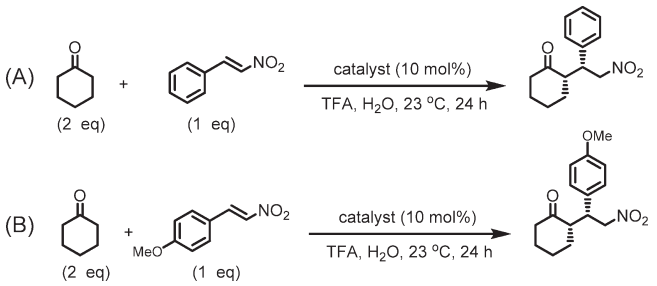
examination of the composition of the heptane layer after the first nitro-Michael addition by ^{1}H NMR spectroscopy revealed one clear difference between the purity of the recovered **Di-L-G2** and **Di-L-G3**. While the recovered heptane layer from the **Di-L-G3** catalyzed reaction contained only pure **Di-L-G3**, the heptane layer from the **Di-L-G2** catalyzed reaction was contaminated with 5 mol % of the nitro-Michael adduct **30** (R = H) and 1 mol % of *trans*-β-nitrostyrene. In principle, the partition coefficients of the nitro-Michael adduct and *trans*-β-nitrostyrene should be independent of the catalyst used. However, due to the much higher lipophilicity of **Di-L-G3** than **Di-L-G2**, the former catalyst "saturated" the heptane layer and produced an extrusion effect that prevented the dissolution of other chemical species in the same solvent during the extraction process.

Di-L-G3 was then reused in alternative nitro-Michael additions with different substrates to see whether any cross contamination occurred after the recycling process (Table 7). In the first, third, and fifth runs, nitro-Michael addition (reaction A) between cyclohexanone **27** and *trans*-β-nitrostyrene was performed, and the substrates were changed to cyclohexanone **27** and *trans*-4-methoxy-β-nitrostyrene **29** (R = 4-OMe) in the second, fourth, and sixth runs (reaction B). After repeating different nitro-Michael addition several times, the recovered **Di-Li-G3** was still capable of producing high reaction yields, good product diastereoselectivities, and enantioselectivities. Most notably, cross contamination of products from previous runs was not observed as revealed by ^{1}H NMR analysis of the crude product mixture.

Conclusion

Three series of G1-G3 amphiphilic dendritic organocatalysts were synthesized and characterized. The structural

TABLE 7. Di-L-G3/TFA-Catalyzed Asymmetric Nitro-Michael Additions[a] with Different Substrates in Water Using Recovered Catalysts Obtained from Heptane/MeOH Partition



run	reaction	yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	A	81	17:83	88
2	B	78	6:94	78
3	A	71	17:83	85
4	B	82	7:93	81
5	A	78	16:84	83
6	B	76	5:95	82

[a]Conditions of nitro-Michael additions: cyclohexanone **27** (375 μmol), nitrostyrene **29** (187 μmol), recovered catalyst, and TFA (1 equiv to the catalyst) in water (0.5 mL) for 24 h. [b]Isolated yield after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude product. [d]Determined by chiral-phase HPLC (Chiralcel OD-H) analysis on the *syn*-product.

effects of the dendron on the emulsion forming abilities, catalytic efficiencies, product enantioselectivities, and product yields were investigated. It was found that increasing the size and number of dendrons led to higher product enantioselectivity due to their better steric stereodifferentiation property. The larger hydrophobic HC dendrons have self-counteracting roles on the catalyst reactivity. They first retard the reaction due to steric inhibition but promote the formation of a more stable emulsion and, hence, result in rate acceleration. Hence, we observed the unusual catalytic reactivity profile of **Di-L-G2** > **Mono-L-G2** and **Di-L-G1** > **Mono-L-G1**, that is, increasing branching leads to higher reactivity. On the other hand, the catalytic reactivity decreases with increasing generation within the same series of dendrons, that is, **Di-L-G1** > **Di-L-G2** > **Di-L-G3**. The optimal catalysts are the G2 dendritic catalysts; most of them exhibited good reactivities and enantioselectivities toward asymmetric aldol and nitro-Michael additions in emulsion systems. In addition, the highest generation G3 dendritic organocatalysts could be recovered by partition between MeOH and heptane and reused in the same or different reactions with little loss of reactivity and stereoselectivity. Most importantly, no cross contamination was found when the recovered catalysts were used in different reactions. Hence, the incorporation of hyperbranched hydrophobic dendrons in dendritic organocatalysts was found to have the advantages of promoting emulsion formation in water, enhancing the selectivity of the asymmetric reactions, and facilitating catalyst recovery after the reactions.

Experimental Section

General Procedure for the Synthesis of Boc-Di-L-Gn. A mixture of *N*-Boc-(*S*)-2-aminomethylpyrrolidine **2** (1.0 equiv), the bromide (2.1 equiv), K_2CO_3 (10 equiv), KI (2.2 equiv), and 18-crown-6 and *i*-Pr_2NEt (10 equiv) in dry DMF (or DMF/toluene 1:1) was heated at 60 °C for 24−120 h. The mixture was cooled to 25 °C, diluted with H_2O and extracted with EtOAc. The combined extracts were washed with H_2O, saturated NaCl solution, dried ($MgSO_4$), and filtered. After evaporation of solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel to afford the target compound.

Boc-Di-L-G1. Starting from *N*-Boc-(*S*)-2-aminomethylpyrrolidine **2** (0.16 g, 0.80 mmol), **5** (0.48 g, 1.73 mmol), K_2CO_3 (1.09 g, 7.89 mmol), KI (0.29 g, 1.75 mmol), 18-crown-6 (10 mg), and *i*-Pr_2NEt (1.38 mL, 7.92 mmol) in dry DMF (5 mL). Upon heating for 24 h, the product (0.35 g, 74%) was obtained as a colorless oil after flash column chromatography (eluent: hexane/EtOAc/Et_3N 88:11:1). R_f = 0.23 (hexane/EtOAc 5:1). $[\alpha]_D$ −61.4 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$; rotameric mixture): δ 0.85 (24 H, d, J = 6.9 Hz), 1.00−1.57 (30 H, m), 1.45 (9 H, s), 1.68−2.08 (4 H, m), 2.08−2.62 (6 H, m), 3.15−3.42 (2 H, m), 3.64−3.95 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$; rotameric mixture): δ 22.6, 22.8, 23.5, 24.7, 28.5, 28.7, 29.3, 31.3, 31.4, 31.5, 36.0, 37.9, 46.3 + 46.7, 55.6, 56.1, 56.6 + 57.5, 78.8 + 79.1, 154.6. MS (ESI) m/z (%): 594 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{38}H_{77}N_2O_2^+$, 593.5980; found, 593.5986. Elem anal. Calcd (%) for $C_{38}H_{76}N_2O_2$: C, 76.96; H, 12.92; N, 4.72. Found: C, 76.83; H, 12.95; N, 4.39.

Boc-Di-L-G2. Starting from *N*-Boc-(*S*)-2-aminomethylpyrrolidine **2** (0.32 g, 1.60 mmol), **6** (1.76 g, 3.32 mmol), K_2CO_3 (2.19 g, 15.8 mmol), KI (0.58 g, 3.49 mmol), 18-crown-6 (20 mg), and *i*-Pr_2NEt (2.76 mL, 15.8 mmol) in dry DMF (20 mL). Upon heating for 48 h, the product (1.34 g, 77%) was obtained as a pale yellow oil after flash column chromatography (eluent: hexane/EtOAc/Et_3N 100:5:1). R_f = 0.61 (hexane/EtOAc 5:1). $[\alpha]_D$ −22.9 (c = 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$; rotameric mixture): δ 0.87 (48 H, d, J = 6.6 Hz), 1.00−1.58 (78 H, m), 1.47 (9 H, s), 1.68−2.08 (4 H, m), 2.08−2.63 (6 H, m), 3.18−3.43 (2 H, m), 3.63−3.98 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$; rotameric mixture): δ 22.6, 22.9, 23.8, 24.8, 28.3, 28.5, 28.7, 29.4, 31.4, 31.6, 34.2, 36.0, 37.4, 37.9, 46.3 + 46.7, 55.7, 56.2, 56.6 + 57.4, 78.7 + 78.9, 154.5. MS (ESI) m/z (%): 1098 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{74}H_{149}N_2O_2^+$, 1098.1614; found, 1098.1624. Elem anal. Calcd (%) for $C_{74}H_{148}N_2O_2$: C, 80.95; H, 13.59; N, 2.55. Found: C, 80.69; H, 13.68; N, 2.25.

Boc-Di-L-G3. Starting from *N*-Boc-(*S*)-2-aminomethylpyrrolidine **2** (104 mg, 0.52 mmol), **7** (1.08 g, 1.04 mmol), K_2CO_3 (0.72 g, 5.21 mmol), KI (0.19 g, 1.14 mmol), 18-crown-6 (7 mg), and *i*-Pr_2NEt (1.0 mL, 5.74 mmol) in dry DMF/toluene (v/v 1:1, 10 mL). Upon heating for 120 h, the product (0.62 g, 56%) was obtained as a pale yellow oil after flash column chromatography (eluent: CH_2Cl_2 gradient to CH_2Cl_2/EtOAc/Et_3N 88:11:1). R_f = 0.54 (hexane/EtOAc 10:1). $[\alpha]_D$ −14.8 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$; rotameric mixture): δ 0.88 (96 H, d, J = 6.9 Hz), 1.01−1.62 (174 H, m), 1.47 (9 H, s), 1.70−2.10 (4 H, m), 2.10−2.70 (6 H, m), 3.14−3.48 (2 H, m), 3.64−3.97 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$; rotameric mixture): δ 23.0, 23.8, 24.1, 24.8, 28.4, 28.6, 28.8, 29.5, 31.5, 31.8, 34.3, 34.5, 34.6, 36.1, 37.5, 37.8, 38.0, 46.4 + 46.9, 55.9, 56.3, 56.7 + 57.4, 78.8 + 79.1, 154.6. MS (ESI) m/z (%): 2108 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{146}H_{293}N_2O_2^+$, 2107.2882; found, 2107.2864. Elem anal. Calcd (%) for $C_{146}H_{292}N_2O_2$: C, 83.19; H, 13.96; N, 1.33. Found: C, 82.99; H, 14.25; N, 1.17.

General Procedure for the Synthesis of Boc-Mono-L/S-Gn. A mixture of *N*-Boc-(*S*)-2-aminomethylpyrrolidine **2** (1.0 equiv) and the aldehyde (1.0 equiv) in EtOH was stirred at 25 °C for 12 h. $NaBH_4$ (10 equiv) was then added at 0 °C. The mixture was allowed to warm to 25 °C and stirred for 6−24 h. It was acidified to pH = 5 with HCl solution (1 M) and stirred for 15 min. The pH of the solution was adjusted to 10 by the addition of saturated KOH solution (2.5 M) at 0 °C. The mixture was then

extracted with EtOAc, and the combined extracts were washed with saturated NaCl solution, dried ($MgSO_4$), and filtered. After evaporation of solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel to afford the target product.

Boc-Mono-L-G1. *N*-Boc-(*S*)-2-aminomethylpyrrolidine **2** (0.14 g, 0.69 mmol), **17** (0.15 g, 0.69 mmol), and $NaBH_4$ (0.26 g, 6.90 mmol) in EtOH (10 mL) were combined. Upon heating for 6 h, the product (0.20 g, 73%) was obtained as a pale yellow oil after flash column chromatography (eluent: EtOAc/Et_3N 100:1). R_f = 0.24 (EtOH). $[\alpha]_D$ −27.0 (c = 0.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$; rotameric mixture): δ 0.79 (12 H, d, J = 6.6 Hz), 0.92−1.56 (16 H, m), 1.39 (9 H, s), 1.62−2.02 (4 H, m), 2.34−2.88 (4 H, m, 3.10−3.50 (2 H, m), 3.65−3.94 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$; rotameric mixture): δ 22.7, 23.1, 23.8, 27.4, 28.4, 28.6, 29.3, 29.7, 31.2, 35.9, 37.8, 46.4 + 46.8, 50.7, 53.3, 57.2, 79.1, 154.89 + 154.91. MS (ESI) m/z (%): 397 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{24}H_{49}N_2O_2^+$, 397.3789; found, 397.3795.

Boc-Mono-L-G2. *N*-Boc-(*S*)-2-aminomethylpyrrolidine **2** (0.14 g, 0.71 mmol), **18** (0.33 g, 0.71 mmol), and $NaBH_4$ (0.27 g, 7.10 mmol) in EtOH (10 mL) were combined. Upon heating for 24 h, the product (0.30 g, 65%) was obtained as a pale yellow oil after flash column chromatography (eluent: hexane/EtOAc 10:1 gradient to EtOAc/Et_3N 100:1). R_f = 0.07 (hexane/EtOAc 1:1). $[\alpha]_D$ −20.3 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$; rotameric mixture): δ 0.86 (24 H, d, J = 6.6 Hz), 0.98−1.70 (39 H, m), 1.45 (9 H, s), 1.70−2.06 (5 H, m), 2.40−2.92 (4 H, m), 3.18−3.50 (2 H, m), 3.70−3.98 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$; rotameric mixture): δ 22.8, 23.2, 23.8, 24.0, 27.5, 28.5, 28.7, 29.5, 29.6, 29.9, 31.4, 34.1, 34.2, 36.0, 37.4, 37.9, 46.5 + 46.9, 50.7, 53.4, 57.3, 79.3, 154.9 + 155.0. MS (ESI) m/z (%): 650 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{42}H_{85}N_2O_2^+$, 649.6606; found, 649.6611. Elem anal. Calcd (%) for $C_{42}H_{84}N_2O_2$: C, 77.71; H, 13.04; N, 4.32. Found: C, 77.71; H, 13.34; N, 4.24.

Boc-Mono-L-G3. *N*-Boc-(*S*)-2-aminomethylpyrrolidine **2** (32 mg, 0.16 mmol), **19** (0.16 g, 0.16 mmol), and $NaBH_4$ (61 mg, 1.61 mmol) in EtOH/toluene (v/v 1:1, 10 mL) were combined. Upon heating for 24 h, the product (0.15 g, 85%) was obtained as a pale yellow oil after flash column chromatography (eluent: hexane/EtOAc 3:1 gradient to hexane/EtOAc/Et_3N 50:50:1). R_f = 0.16 (hexane/EtOAc 1:1). $[\alpha]_D$ −10.7 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$; rotameric mixture): δ 0.86 (48 H, d, J = 6.6 Hz), 0.98−1.70 (87 H, m), 1.46 (9 H, s), 1.72−2.08 (5 H, m), 2.43−2.92 (4 H, m), 3.20−3.53 (2 H, m), 3.64−4.00 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$; rotameric mixture): δ 22.9, 23.8, 24.0, 27.5, 28.6, 28.7, 29.5, 29.8, 31.4, 34.2, 34.3, 34.5, 36.1, 37.5, 37.7, 37.9, 46.6 + 46.9, 50.8, 53.4, 57.3, 79.3, 154.9. MS (ESI) m/z (%): 1154 (100) [$(M + H)^+$]. HRMS (ESI) Calcd for $C_{78}H_{157}N_2O_2^+$, 1154.2240; found, 1154.2244. Elem anal. Calcd (%) for $C_{78}H_{156}N_2O_2$: C, 81.18; H, 13.62; N, 2.43. Found: C, 80.72; H, 13.73; N, 1.96.

Boc-Mono-S-G1. *N*-Boc-(*S*)-2-aminomethylpyrrolidine **2** (0.16 g, 0.78 mmol), **20** (0.14 g, 0.78 mmol), and $NaBH_4$ (0.29 g, 7.78 mmol) in EtOH/toluene (v/v 1:1, 10 mL) were combined. Upon heating for 6 h, the product (0.20 g, 71%) was obtained as a pale yellow oil after flash column chromatography (eluent: EtOAc/Et_3N 100:1). R_f = 0.13 (EtOAc). $[\alpha]_D$ −38.3 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$; rotameric mixture): δ 0.79 (12 H, d, J = 6.6 Hz), 0.96−1.52 (11 H, m), 1.38 (9 H, s), 1.52−2.02 (4 H, m), 2.18−2.74 (5 H, m), 3.08−3.42 (2 H, m), 3.60−3.98 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$; rotameric mixture): δ 22.7, 23.0, 23.8, 28.4, 28.5, 29.6, 35.8, 35.9, 38.1, 38.4, 46.4 + 47.0, 53.4, 53.6, 57.0, 79.2, 154.7 + 155.3. MS (ESI) m/z (%): 369 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{22}H_{45}N_2O_2^+$, 369.3476; found, 369.3488. Elem anal. Calcd (%) for $C_{22}H_{44}N_2O_2$: C, 71.69; H, 12.03; N, 7.60. Found: C, 71.28; H, 12.39; N, 7.56.

Boc-Mono-S-G2. *N*-Boc-(*S*)-2-aminomethylpyrrolidine **2** (0.25 g, 1.25 mmol), **21** (0.54 g, 1.25 mmol), and $NaBH_4$ (0.47 g, 12.5 mmol) in EtOH/toluene (v/v 1:1, 10 mL) were combined. Upon heating for 24 h, the product (0.47 g, 62%) was obtained as a pale yellow oil after flash column chromatography (eluent: hexane/EtOAc 4:1 gradient to EtOAc/Et_3N 100:1). R_f = 0.29 (hexane/EtOAc 1:1). $[\alpha]_D$ −19.6 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$; rotameric mixture): δ 0.84 (24 H, d, J = 6.6 Hz), 0.96−1.58 (35 H, m), 1.44 (9 H, s), 1.58−2.07 (5 H, m), 2.37−2.90 (4 H, m), 3.08−3.58 (2 H, m), 3.61−4.08 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$; rotameric mixture): δ 22.8, 23.8, 23.9, 28.5, 28.6, 29.4, 29.8, 31.3, 31.4, 32.6, 34.2, 36.00, 36.04, 37.9, 38.1, 46.5 + 46.9, 53.5, 53.9, 57.2, 79.2, 154.8. MS (ESI) m/z (%): 622 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{40}H_{81}N_2O_2^+$, 621.6293; found, 621.6301. Elem anal. Calcd (%) for $C_{40}H_{80}N_2O_2$: C, 77.35; H, 12.98; N, 4.51. Found: C, 77.18; H, 13.41; N, 4.21.

Boc-Mono-S-G3. *N*-Boc-(*S*)-2-aminomethylpyrrolidine **2** (94 mg, 0.47 mmol), **22** (0.44 g, 0.47 mmol), and $NaBH_4$ (0.18 g, 4.76 mmol) in EtOH/toluene (1/2, 30 mL) were combined. Upon heating for 24 h, the product (0.34 g, 64%) was obtained as a pale yellow oil after flash column chromatography (eluent: hexane/EtOAc 10:1 gradient to hexane/EtOAc/Et_3N 50:50:1). R_f = 0.20 (hexane/EtOAc 3:1). $[\alpha]_D$ −11.9 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$; rotameric mixture): δ 0.83 (48 H, d, J = 6.6 Hz), 0.96−1.57 (83 H, m), 1.42 (9 H, s), 1.61−2.00 (5 H, m), 2.29−2.96 (4 H, m), 3.08−3.48 (2 H, m), 3.59−4.00 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$; rotameric mixture): δ 22.9, 23.7, 24.0, 28.5, 28.6, 29.3, 29.8, 31.3, 32.8, 34.2, 34.4, 36.0, 37.4, 37.8, 38.4, 46.5 + 46.9, 53.5, 53.9, 57.3, 79.0, 154.7 + 154.9. MS (ESI) m/z (%): 1126 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{76}H_{153}N_2O_2^+$, 1126.1927; found, 1126.1932. Elem anal. Calcd (%) for $C_{76}H_{152}N_2O_2$: C, 81.06; H, 13.61; N, 2.49. Found: C, 81.14; H, 14.00; N, 2.05.

General Procedure for the Synthesis of Di-L-Gn. A mixture of TFA (20 equiv) and the Boc-protected amine (1.0 equiv) in CH_2Cl_2 was stirred at 25 °C for 12−24 h. The pH of the solution was adjusted to 10 by the addition of saturated Na_2CO_3 solution at 0 °C. The mixture was then extracted with CH_2Cl_2 and the combined extracts were washed with saturated NaCl solution, dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure to afford the target product.

Di-L-G1. Starting from TFA (2.02 mL, 26.2 mmol) and **Boc-Di-L-G1** (0.78 g, 1.32 mmol) in CH_2Cl_2 (10 mL), the product (0.64 g, 99%) was obtained as a yellow oil after stirring for 12 h. R_f = 0.10 (EtOH). $[\alpha]_D$ +12.8 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (24 H, d, J = 6.6 Hz), 1.00−1.28 (22 H, m), 1.28−1.57 (9 H, m), 1.64−1.79 (2 H, m), 1.79−1.94 (1 H, m), 2.03 (1 H, br s), 2.23−2.50 (6 H, m), 2.76−3.02 (2 H, m), 3.20 (1 H, quintet, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.8, 24.3, 24.9, 28.5, 29.6, 31.3, 31.5, 36.0, 37.9, 45.7, 55.2, 56.4, 59.9. MS (ESI) m/z (%): 493 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{33}H_{69}N_2^+$, 493.5455; found, 493.5457. Elem anal. Calcd (%) for $C_{33}H_{68}N_2$: C, 80.41; H, 13.91; N, 5.68. Found: C, 80.21; H, 14.09; N, 5.70.

Di-L-G2. Starting from TFA (0.76 mL, 9.86 mmol) and **Boc-Di-L-G2** (1.08 g, 0.98 mmol) in CH_2Cl_2 (5 mL), the product (0.97 g, 99%) was obtained as a yellow oil after stirring for 12 h. R_f = 0.10 (EtOH). R_f = 0.12 (EtOH). $[\alpha]_D$ +2.62 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (48 H, d, J = 6.6 Hz), 1.00−1.31 (66 H, m), 1.31−1.57 (13 H, m), 1.64−1.81 (2 H, m), 1.81−1.96 (1 H, m), 2.21−2.50 (6 H, m), 2.50−2.70 (1 H, m), 2.80−3.02 (2 H, m), 3.21 (1 H, quintet, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$; with overlapping of C signals): δ 22.9, 23.8, 24.3, 24.9, 28.6, 29.7, 31.4, 31.7, 34.3, 36.1, 37.5, 37.9, 45.8, 55.3, 56.5, 59.7. MS (ESI) m/z (%): 998 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{69}H_{141}N_2^+$, 998.1089; found, 998.1091.

Di-L-G3. Starting from TFA (0.33 mL, 4.28 mmol) and **Boc-Di-L-G3** (0.90 g, 0.43 mmol) in CH_2Cl_2 (5 mL), the product (0.84 g, 97%) was obtained as a yellow oil after stirring for 24 h. R_f = 0.12 (hexane/EtOAc 6:1). $[\alpha]_D$ +2.3 (c = 0.5, $CHCl_3$). ^{1}H NMR

(300 MHz, $CDCl_3$): δ 0.88 (96 H, d, J = 6.6 Hz), 1.00−1.35 (154 H, m), 1.35−1.61 (21 H, m), 1.64−1.80 (2 H, m), 1.80−1.99 (1 H, m), 2.16−2.56 (6 H, m), 2.57−2.77 (1 H, br s), 2.80−3.06 (2 H, m), 3.23 (1 H, quintet, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$; with overlapping of C signals): δ 22.9, 23.8, 24.0, 24.3, 24.9, 28.6, 29.7, 31.4, 31.8, 34.3, 34.4, 34.5, 36.1, 37.5, 37.7, 37.9, 45.8, 55.4, 56.6, 59.6. MS (ESI) m/z (%): 2008 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{141}H_{285}N_2^+$, 2007.2357; found, 2007.2366. Elem anal. Calcd (%) for $C_{141}H_{284}N_2$: C, 84.35; H, 14.26; N, 1.40. Found: C, 83.86; H, 14.40; N, 1.25.

Mono-L-G1. Starting from TFA (0.62 mL, 8.07 mmol) and **Boc-Mono-L-G1** (0.32 g, 0.81 mmol) in CH_2Cl_2 (2 mL), the product (0.22 g, 95%) was obtained as a yellow oil after stirring for 12 h. R_f = 0.31 (EtOH/Et_3N 100:1). $[\alpha]_D$ +9.2 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77 (12 H, d, J = 6.6 Hz), 0.94−1.48 (16 H, m), 1.48−1.72 (2 H, m), 1.72−1.90 (1 H, m), 1.86 (2 H, br s), 2.34−2.58 (4 H, m), 2.72−2.92 (2 H, m), 3.06−3.24 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$; with overlapping of C signals): δ 22.85, 22.87, 25.8, 27.4, 28.6, 29.9, 31.4, 36.1, 38.0, 46.6, 50.9, 55.1, 58.4. MS (ESI) m/z (%): 297 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{19}H_{41}N_2^+$, 297.3264; found, 297.3270.

Mono-L-G2. Starting from TFA (0.35 mL, 4.58 mmol) and **Boc-Mono-L-G2** (0.30 g, 0.46 mmol) in CH_2Cl_2 (2 mL), the product (0.24 g, 95%) was obtained as a yellow oil after stirring for 12 h. R_f = 0.31 (EtOH/Et_3N 100:1). $[\alpha]_D$ +5.7 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (24 H, d, J = 6.6 Hz), 0.96−1.57 (40 H, m), 1.57−1.79 (2 H, m), 1.79−1.86 (1 H, m), 2.42−2.70 (4 H, m), 2.80−2.96 (2 H, m), 3.01 (2 H, br s), 3.18−3.36 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.8, 23.7, 25.6, 27.2, 28.5, 29.7, 31.3, 31.4, 34.06, 34.14, 36.0, 37.4, 37.8, 46.3, 50.8, 54.6, 58.4. MS (ESI) m/z (%): 549 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{37}H_{77}N_2^+$, 549.6081; found, 549.6080.

Mono-L-G3. Starting from TFA (30 μL, 0.38 mmol) and **Boc-Mono-L-G3** (44 mg, 38 μmol) in CH_2Cl_2 (2 mL), the product (39 mg, 97%) was obtained as a yellow oil after stirring for 12 h. R_f = 0.12 (EtOH/Et_3N 100:1). $[\alpha]_D$ +2.6 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (48 H, d, J = 6.6 Hz), 0.97−1.60 (88 H, m), 1.60−1.81 (2 H, m), 1.81−1.88 (1 H, m), 2.48 (2 H, br s), 2.50−2.70 (4 H, m), 2.84−2.98 (2 H, m), 3.18−3.34 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$; with overlapping of C signals): δ 22.9, 23.8, 23.9, 25.8, 27.3, 28.5, 29.8, 31.4, 34.2, 34.3, 34.4, 36.0, 37.5, 37.6, 37.9, 46.5, 50.9, 55.0, 58.4. MS (ESI) m/z (%): 1054 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{73}H_{149}N_2^+$, 1054.1715; found, 1054.1723.

Mono-S-G1. Starting from TFA (0.19 mL, 2.50 mmol) and **Boc-Mono-S-G1** (92 mg, 0.25 mmol) in CH_2Cl_2 (2 mL), the product (63 mg, 94%) was obtained as a yellow oil after stirring for 12 h. R_f = 0.37 (EtOH/Et_3N 100:1). $[\alpha]_D$ +8.8 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.71 (12 H, d, J = 6.9 Hz), 0.86−1.42 (12 H, m), 1.50−1.71 (2 H, m), 1.71−1.87 (1 H, m), 2.24−2.40 (2 H, m), 2.44 (1 H, dd, J = 12.0 and 4.8 Hz), 2.54 (1 H, dd, J = 12.0 and 4.8 Hz), 2.75−2.95 (2 H, m), 3.10−3.28 (1 H, m), 3.45 (2 H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.5, 25.1, 28.2, 29.2, 29.5, 35.70, 35.74, 38.2, 45.9, 53.7, 53.9, 58.3. MS (ESI) m/z (%): 269 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{17}H_{37}N_2^+$, 269.2951; found, 269.2960.

Mono-S-G2. Starting from TFA (0.24 mL, 3.06 mmol) and **Boc-Mono-S-G2** (0.19 g, 0.31 mmol) in CH_2Cl_2 (2 mL), the product (0.15 g, 98%) was obtained as a yellow oil after stirring for 12 h. R_f = 0.40 (EtOH/Et_3N 100:1). $[\alpha]_D$ +2.0 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80 (24 H, d, J = 6.6 Hz), 0.96−1.54 (36 H, m), 1.61−1.81 (2 H, m), 1.81−1.98 (1 H, m), 2.34−2.52 (2 H, m), 2.54 (1 H, dd, J = 11.7 and 8.1 Hz), 2.64 (1 H, dd, J = 11.7 and 4.5 Hz), 2.84−3.06 (2 H, m), 3.20−3.43 (1 H, m), 3.82 (2 H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.8, 23.7, 23.8, 25.2, 28.4, 29.4, 31.2, 31.3, 32.5, 34.1, 35.9, 36.0, 37.8, 37.9, 46.0, 53.9, 54.0, 58.5. MS (ESI) m/z (%): 521 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{35}H_{73}N_2^+$, 521.5768; found, 521.5763.

Mono-S-G3. Starting from TFA (0.15 mL, 1.95 mmol) and **Boc-Mono-S-G3** (0.23 g, 0.20 mmol) in CH_2Cl_2 (2 mL), the product (0.19 g, 92%) was obtained as a yellow oil after stirring for 12 h. R_f = 0.46 (EtOH/Et_3N 100:1). $[\alpha]_D$ +1.1 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (48 H, d, J = 6.6 Hz), 0.98−1.58 (84 H, m), 1.62−1.80 (2 H, m), 1.80−1.96 (1 H, m), 2.38−2.77 (6 H, m), 2.84−3.02 (2 H, m), 3.18−3.36 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$; with overlapping of C signals): δ 22.9, 23.8, 24.0, 25.6, 28.5, 29.7, 31.4, 32.9, 34.2, 34.4, 36.0, 37.5, 37.9, 38.3, 46.4, 54.1, 55.0, 58.5. MS (ESI) m/z (%): 1026 (100) [$(M + H)^+$]. HRMS (ESI) calcd for $C_{71}H_{145}N_2^+$, 1026.1402; found, 1026.1395.

General Procedures of Asymmetric Aldol Reactions. All aldol reactions were carried out under air in a closed system. TFA (1.4 μL, 18.7 μmol) was added to a mixture of the catalyst (18.7 μmol) in H_2O (0.5 mL) at 23 °C with sonication for 15 min. Ketone (375 μmol) and aldehyde (187 μmol) were then sequentially added. The mixture was sonicated and then stirred vigorously in a closed vial for 24 h to maintain an emulsion. The reaction was quenched by adding EtOAc/saturated NaCl solution (v/v 1:1, 4 mL) to allow for phase separation. The organic layer was collected and the aqueous layer was extracted with EtOAc (2 × 1 mL). The combined organic extracts were washed with saturated NaCl solution, dried ($MgSO_4$), and filtered. After evaporation of solvent under reduced pressure, the diastereoselectivity (*anti*/*syn*) of the crude product was determined by ^{1}H NMR analysis. The sample was purified by passing through a short column of silica gel to remove the faster running and baseline materials to obtain the product yield. The ee value of the *anti*-adduct was determined by chiral HPLC (Chiralcel OD-H) analysis.

General Procedures of Asymmetric Nitro-Michael Additions. All nitro-Michael additions were carried out under air in a closed system. TFA (1.4 μL, 18.7 μmol) was added to a mixture of catalyst (18.7 μmol) in H_2O (0.5 mL) at 23 °C with sonication for 15 min. Ketone (375 μmol) and nitrostyrene (187 μmol) were then sequentially added. The mixture was sonicated and then stirred vigorously in a closed vial for 24 h to maintain an emulsion. The reaction was quenched by adding EtOAc/saturated NaCl solution (v/v 1:1, 4 mL) to allow for phase separation. The organic layer was collected and the aqueous layer was extracted with EtOAc (2 × 1 mL). The combined organic extracts were washed with saturated NaCl solution, dried ($MgSO_4$), and filtered. After evaporation of solvent under reduced pressure, the diastereoselectivity (*syn*/*anti*) of the crude product was determined by ^{1}H NMR analysis. The sample was purified by passing through a short column of silica gel to remove the faster running and baseline materials to obtain the product yield. The ee value of the *syn*-product was determined by chiral HPLC (Chiralcel OD-H) analysis.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra and SEC chromatograms of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.