# Synthesis of Novel Dendritic 2,2′-Bipyridine Ligands and Their Application to Lewis Acid-Catalyzed Diels−Alder and Three-Component Condensation Reactions

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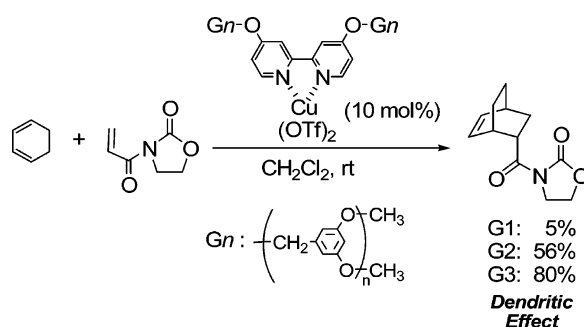
A series of dendritic ligands with a 2,2′-bipyridine core was synthesized through the coupling of 4,4′-dihydroxy-2,2′-bipyridine with poly(aryl ether) dendrons. The corresponding dendritic $Cu(OTf)_2$ catalysts were used for Diels−Alder and three-component condensation reactions. The dendritic $Cu(OTf)_2$-catalyzed Diels−Alder reaction proceeded smoothly, and these dendritic catalysts could be recycled without deactivation by reprecipitation. Three-component condensation reactions such as Mannich-type reactions also proceeded not only in dichloromethane but also in water. Furthermore, a positive dendritic effect on chemical yields was observed in both Diels−Alder reactions and aqueous-media three-component condensation reactions.

Introduction

In contemporary organic synthesis, Lewis acid-catalyzed carbon−carbon bond formation reactions are among the most important; therefore, more powerful and versatile Lewis acid catalysts have been required.[1] During the past two decades, metal trifluoromethanesulfonates (triflates) such as $Sc(OTf)_3$,[2] $Yb(OTf)_3$,[3] and $Cu(OTf)_2$,[4] have been developed, because they have excellent Lewis acidity. Furthermore, they also work well even in aqueous media.[5] From the perspectives of green chemistry, these water-compatible Lewis acid catalysts are very

powerful tools for synthetic organic chemistry. Furthermore, the development of a recyclable catalyst has also been required. One of the most certain methods of recycling a catalytic metal is its immobilization on a macromolecular ligand.[6] Polystyrene beads containing Lewis acids are one of the better known modalities for recyclable Lewis acid catalysts.[7] However, they are heterogeneous catalysts, and their reactivity is relatively low. Therefore, novel synthetic macromolecular ligands, which have good solubility for various solvents as well as recyclability, are required.

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Dendrimers are fascinating macromolecules due to their unique physical and chemical properties, which are caused by their well-defined hyperbranched framework.[8] Metallodendrimers, with catalytic sites immobilized within the dendrimer, are particularly useful as synthetic catalysts not only because of their unique reactivity and fair solubility but also because of their recyclability by reprecipitation or by nanofiltration based on their nano-order size.[9] Presently, metallodendrimers with a catalytic site at the core have received considerable attention because of their unique selectivity and reactivity caused by specific reaction fields constructed by the dendron.[10] Some of them show a positive dendritic effect on regio- or stereoselectivity, meaning that their selectivity is enhanced by an increase in the generation number of the dendrimer.[11,12] However, examples of a positive dendritic effect on reactivity are at present limited.[13,14]

We report herein the simple synthesis of novel dendritic 2,2′-bipyridine core ligands, the preparation of the corresponding dendritic copper(II) triflate (Cu(OTf)$_2$) and their application to the Diels−Alder reaction and three-component condensation reactions such as the Mannich-type reaction, and the positive dendritic effect on chemical yields. A dendritic effect was observed in aqueous-media reactions, especially in the case of three-component condensation reactions. We found that in both reactions these dendritic Cu(OTf)$_2$ catalysts were recyclable by reprecipitation.

Results and Discussion

Preparation of Dendritic Ligands Having Bipyridine Core 3(G*n*[R]). In the chemistry of dendritic catalysts, one of the most attractive goals is the construction of a specific reaction field for organic synthesis. To construct it effectively, G*n*[R] having a poly(aryl ether) skeleton and one of a variety of
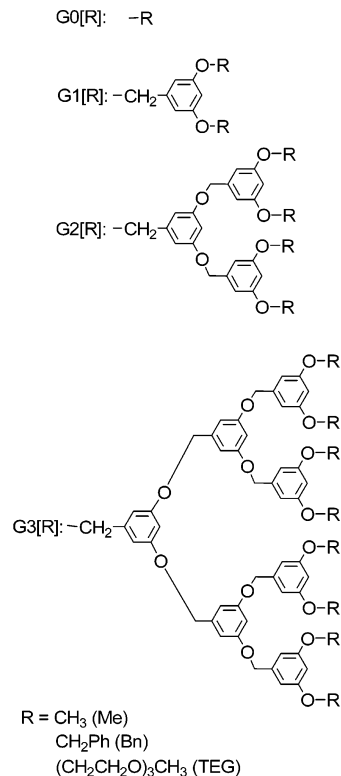

FIGURE 1. Structual formulas of G*n*[R].

periphery groups R was used as a dendron (Figure 1).[15] This is because G*n*[R] has a perfect, defect-free dendritic structure. We noticed that bidentate ligands, which coordinate with nitrogen, are the core units of the dendritic ligand. This is because they can coordinate the various transition metals and ligate them more strongly than monodentate ligands. We chose 4,4′-dihydroxy-2,2′-bipyridine as the core unit of the dendritic ligands.[16] The 2,2′-bipyridine unit has fair coordination ability in relation to various transition metals, and the introduction of dendrons to the 2,2′-bipyridine unit is easy because it has a phenolic hydroxyl group. We expected that defect-free rigid dendrons and strong bidentate coordination would enable us to effectively construct the desired reaction field around the catalytic metal.

Dendritic 2,2′-bipyridine ligands 3(G*n*[R]) were prepared from 4,4′-dihydroxy-2,2′-bipyridine 1 and the corresponding poly(aryl ether) dendritic benzyl bromide 2(G*n*[R]) in the presence of potassium carbonate and a catalytic amount of 18-crown-6 in tetrahydrofuran. Chemical yields of 3(G*n*[R]) are shown in Table 1.[14a]

All of the dendritic ligands 3(G*n*[R]), except for 3(G1[Me]) (Table 1, entry 1), were obtained in fair yields. The reason for the poor yield of entry 1 was probably due to the nucleophilic attack of the nitrogen of bipyridine on 1, owing to the small size of the G1[Me] dendron.

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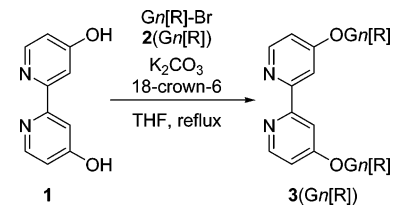
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TABLE 1. Preparation of 3(G*n*[R])

entry	R	G*n*	yield (%)
1	Me	G1	8
2	Me	G2	86
3	Me	G3	86
4	Bn	G1	83
5	Bn	G2	80
6	Bn	G3	85
7	TEG	G1	91

In the case of the preparation of **3**(G1[Me]), it was found that **1** was coupled with 3,5-dimethoxybenzyl alcohol (G1[Me]-OH) **4** under Mitsunobu conditions[17] to provide **3**(G1[Me]) in a 50% yield (Scheme 1).

SCHEME 1. Preparation of 3(G1[Me])
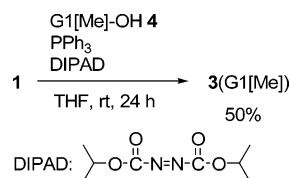
Diels−Alder Reaction with Dendritic Cu(OTf)₂ Catalyst. In this study, Cu(OTf)₂ was selected as the Lewis acid catalyst, because this compound has a fair Lewis acidity not only in organic solvents but also in aqueous media,[4b] and furthermore, Cu(OTf)₂ has better azaphilicity[18] than other Lewis acids such as aluminum chloride and scandium triflate. We examined the utility of the dendritic 2,2′-bipyridine-Cu(OTf)₂ core catalyst by performing Lewis acid-catalyzed Diels−Alder reactions (Table 2).[19]
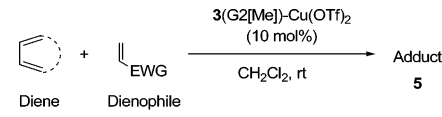
First, by employing 10 mol % of the **3**(G2[Me])-Cu(OTf)₂ catalyst, which was prepared in situ in dichloromethane, Diels−Alder reactions of cyclopentadiene with various dienophiles proceeded at room temperature to afford the corresponding adducts **5** in excellent yields (Table 2, entries 1−3). In these reactions, the *endo/exo* ratios were almost similar to those previously reported.[2,20]

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TABLE 2. Diels−Alder Reaction with 3(G2[Me])-Cu(OTf)₂ as the Catalyst

| entry	Diene	Dienophile	Adduct		Yield (%)	*endo:exo*[a]
1				**5a**	95	81:19
2				**5b**	88	93:7
3				**5c**	95	91:9
4				**5d**	56	*endo* only
5				**5e**	91	*endo* only
6				**5f**	86	–
7				**5g**	76	–

[a] Determined by ¹H NMR spectra.

On the other hand, when a dichloromethane solution of cyclopentadiene and various dienophiles at room temperature was stirred in the presence of 10 mol % Cu(OTf)₂, which was not immobilized on the dendritic ligand, the corresponding Diels−Alder adduct was not obtained. Cu(OTf)₂ promoted the cationic polymerization of cyclopentadiene. Furthermore, even by employing the modified Cu(OTf)₂ catalyst, which was coordinated by nondendritic 4,4′-dimethoxy-2,2′-bipyridine (= **3**(G0[Me])), the corresponding Diels−Alder adduct was obtained in only a 1% yield. Thus, the immobilization of Cu(OTf)₂ on the dendrimer is effective for the modulation of its Lewis acidity.

Encouraged by these results, we applied the dendritic **3**(G2[Me])-Cu(OTf)₂ catalyst to other dienes such as cyclohexadiene and 2,3-dimethyl-1,3-butadiene; in these cases, only the corresponding Diels−Alder reaction proceeded smoothly (Table 2 entries 4−7).

Recently, it has been discovered that the reactivities of dendritic catalysts depend on the generation number of the dendrimers; this unique phenomenon has been called a "dendritic effect".[11] First, we performed a Diels−Alder reaction of cyclopentadiene and 3-crotonyl-2-oxazolidinone, which had the same substrates as entry 1 in Table 2, with 10 mol % of various-generation dendritic catalysts **3**(G*n*[R])-Cu(OTf)₂ to confirm the dendritic effect on chemical yields (Table 3).

The second generation **3**(G2[Me])-Cu(OTf)₂ afforded a better yield of the Diels−Alder adduct **5a** than the first generation **3**(G1[Me])-Cu(OTf)₂ (Table 3, entries 1 and 2); however, the yield of **5a** in the case of **3**(G3[Me])-Cu(OTf)₂ was lower than

TABLE 3. Diels−Alder Reaction of Cyclopentadiene with 3(Gn[R])-Cu(OTf)$_2$ as the Catalyst

5a

endo:exo
(8:2)
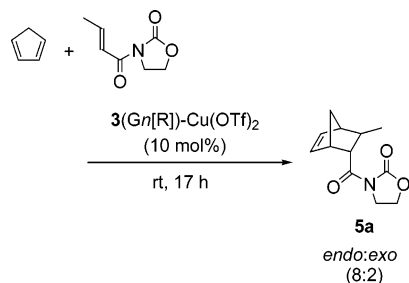
entry	R	Gn	solvent	yield (%)
1	Me	G1	CH$_2$Cl$_2$	20
2	Me	G2	CH$_2$Cl$_2$	96
3	Me	G3	CH$_2$Cl$_2$	58
4	Me	G3	PhCH$_3$	85
5	Bn	G1	CH$_2$Cl$_2$	45
6	Bn	G2	CH$_2$Cl$_2$	57
7	Bn	G2	PhCH$_3$	93

that in the case of **3(G2[Me])-Cu(OTf)$_2$** (Table 3, entries 2 and 3). In entry 3, the polymerization product of cyclopentadiene was also obtained. The reason for the low yield in entry 3 was probably that **3(G3[Me])-Cu(OTf)$_2$** catalyzed not only the Diels−Alder reaction but also the cationic polymerization of cyclopentadiene. To retard the cationic polymerization of cyclopentadiene, the solvent was changed from dichloromethane to toluene. As a result, the Diels−Alder adduct **5a** was obtained in an 85% yield without the polymerization of cyclopentadiene (Table 3, entry 4). In the case of having a peripheral benzyl substituent, the first generation **3(G1[Bn])-Cu(OTf)$_2$** gave **5a** in a 45% yield exclusively, without the polymerization of cyclopentadiene. On the other hand, the second generation **3(G2[Bn])-Cu(OTf)$_2$** catalyzed not only the Diels−Alder reaction but also the cationic polymerization of cyclopentadiene. Then, by changing the solvent from dichloromethane to toluene, again using **3(G2[Bn])-Cu(OTf)$_2$**, the chemical yield of **5a** was significantly enhanced, in a way similar to **3(G3[Me])-Cu(OTf)$_2$** (Table 3, entries 6 and 7). These results show that a reactive diene such as cyclopentadiene is easily polymerized by a higher generation **3(Gn[R])-Cu(OTf)$_2$** catalyst. Therefore, in Table 3, we could not confirm the dendritic effect on the chemical yields of the Diels−Alder adduct **5a**.

Generally, cyclohexadiene is less reactive than cyclopentadiene for cationic polymerization. By employing cyclohexadiene and 3-crotonyl-2-oxazolidinone with **3(G2[Me])-Cu(OTf)$_2$** as a catalyst, even the corresponding Diels−Alder reaction did not proceed. We next performed the Diels−Alder reaction of cyclohexadiene and 3-acryloyl-2-oxazolidinone, which was more reactive than crotonyl derivatives, with 10 mol % of the various-generation dendritic catalysts **3(Gn[R])-Cu(OTf)$_2$**. All reactions were carried out in dichloromethane for 17 h at room temperature (Table 4).

As a result, only the corresponding Diels−Alder reaction proceeded, and the cationic polymerization did not proceed. Furthermore, the chemical yield of the Diels−Alder adduct **5d** was enhanced by increasing the generation number of the dendritic catalysts **3(Gn[R])-Cu(OTf)$_2$** in the case of both **3(Gn[Me])** and **3(Gn[Bn])**.[14a] This relationship between the generation number of the dendritic catalyst and the chemical yield is one of the positive dendritic effects.[11,13]

TABLE 4. Diels−Alder Reaction of Cyclohexadiene with 3(Gn[R])-Cu(OTf)$_2$ as the Catalyst

5d

endo only
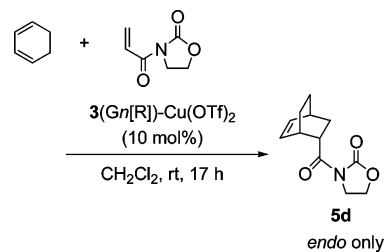
entry	R	Gn	yield (%)
1	Me	G1	5
2	Me	G2	56
3	Me	G3	80
4	Bn	G1	77
5	Bn	G2	87
6	Bn	G3	94

On the other hand, the negative dendritic effect on reaction rate in the Diels−Alder reaction caused by employing the dendritic bis(oxazoline)-Cu(OTf)$_2$ catalyst has been reported by Chow's group.[21] They reported that the reason of their negative dendritic effect was due to the steric hindrance of its bulky dendritic skeleton. We assume that our profound dendritic effect is probably derived from the increase of the Lewis acidity due to the distorted bipyridine skeleton of the **3(Gn[R])-Cu(OTf)$_2$** complex by the steric repulsion of the dendritic wedge,[22] thus affording better chemical yield while increasing the generation number of the dendrimer. Exactly, by a comparison of the chemical yields in the same generation, **3(Gn[Bn])**, which possesses bulkier groups at its periphery, affords better chemical yields than **3(Gn[Me])** in all generations.

Since dendrimers have a polymer-like character, the reprecipitation of dendrimers is often used to recover them.[23] In other groups' reports, several dendritic catalysts were recovered by reprecipitation and subsequently reused.[13c,24] In this study, we examined the recycling of the dendritic catalyst in Diels−Alder

TABLE 5. Catalyst Recycling in Diels−Alder Reactions

5c

endo:exo
(9:1)
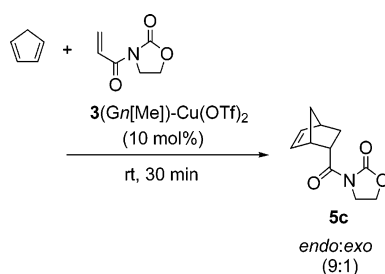
Gn	yield (%)				
	-	first[a]	second	third	fourth
G2[b]	88	98	99	95	88
G3[c]	94	94	99	99	99

[a] Number of recycle. [b] Carried out in CH$_2$Cl$_2$. [c] Carried out in toluene.

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TABLE 6. Three-Component Condensation Reaction in CH₂Cl₂

$$R^1CHO + \underset{NH_2}{\overset{OMe}{\bigodot}} + \text{Nucleophile} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{ rt, 2 h}]{\substack{3(Gn[Me])\text{-Cu(OTf)}_2 \\ (10 \text{ mol\%})}} \underset{R^1 \quad X}{\overset{OMe}{\bigodot}} NH$$

entry	Gn	R^1	nucleophile	X	product	yield (%)
1	G1	Ph	CH₂=C(OTMS)Ph **6**	CH₂COPh	**9a**	31
2	G2	Ph	**6**	CH₂COPh	**9a**	47
3	G3	Ph	**6**	CH₂COPh	**9a**	49
4	G2	PhCH₂CH₂	**6**	CH₂COPh	**9b**	38
5	G2	Ph	CMe₂=C(OTMS)OMe **7**	CMe₂CO₂Me	**10a**	34
6	G2	PhCH₂CH₂	**7**	CMe₂CO₂Me	**10b**	36
7	G2	Ph	P(OEt)₃ **8**	PO(OEt)₂	**11a**	63
8	G2	PhCH₂	**8**	PO(OEt)₂	**11b**	53
9	G2	PhCH₂CH₂	**8**	PO(OEt)₂	**11c**	72
10	G3	PhCH₂CH₂	**8**	PO(OEt)₂	**11c**	73

reactions of cyclopentadiene and acryloyl derivatives with 10 mol % of the **3**(Gn[Me])-Cu(OTf)₂ catalyst. After the reaction had proceeded for 30 min, the reaction mixture was poured into hexane and was stirred to precipitate the dendritic catalyst **3**(Gn[Me])-Cu(OTf)₂, which was collected by filtration and was subsequently reused. Both the second- and the third-generation dendritic Cu(OTf)₂ catalysts could be used five times without deactivation (Table 5). However the precipitated dendritic catalyst included a small amount of the Diels−Alder adduct **5c**, and yields were slightly lower when virgin catalysts, which had not been recycled, were used (G2: 88%, G3: 94%).

Three-Component Condensation Reaction with Dendritic Cu(OTf)₂ Catalyst. Lewis acid-catalyzed condensation reactions, such as aldol and Mannich-type reactions, have been very important transformations for organic synthesis. Today, aqueous-media condensation reactions have attracted a great deal of attention not only because water is an ideal solvent from the perspective of safety, but also because unique reactivities are often observed in aqueous media.[25]

In the various Lewis acid-catalyzed condensation reactions, three-component condensation reactions such as Mannich-type reactions are basic and useful transformations for the synthesis of β-carbonyl amines and α-aminophosphonates, which are important synthetic intermediates for various pharmaceuticals and natural products.[26] Thus, we employed dendritic Cu(OTf)₂ catalysts to perform these three-component condensation reactions not only in dichloromethane but also in water.

According to Table 6, three-component condensation reactions in dichloromethane were carried out for 2 h by use of aldehyde, *o*-anisidine, and nucleophiles **6**−**8**, with 10 mol % of various generations of the dendritic catalyst **3**(Gn[Me])-Cu(OTf)₂.

First, by employing silyl enolates **6** and **7** as nucleophiles, the corresponding Mannich-type products were obtained in rather low yields (Table 6, entries 1−6). In entries 1−6, the corresponding aldol product was not obtained. The low yields of **9** and **10** were due to the decomposition of silyl enolates **6** and **7** to afford the corresponding carbonyl compounds catalyzed by **3**(Gn[Me])-Cu(OTf)₂. Contrary to our expectations, no remarkable dendritic effect on chemical yields was observed (Table 6, entries 1−3).

Next, by employing triethyl phosphite **8** as a nucleophile, the corresponding α-aminophosphonate **11** was obtained in fair yields (Table 6, entries 7−10).[27] Also in the case of **8**, no dendritic effect on chemical yields was observed (Table 6 entries 9 and 10).

In this transformation, we tried the catalyst recycling experiment. 3-Phenylpropanal, *o*-anisidine, and triethyl phosphite, which were the same substrates as entries 9 and 10 in Table 6, were stirred for 2 h in the presence of **3**(G2[Me])-Cu(OTf)₂ or **3**(G3[Me])-Cu(OTf)₂ as a catalyst in dichloromethane (Table 7). After the reaction was completed, the reaction mixture was poured into hexane. The dendritic Cu(OTf)₂ catalyst was recovered as a tar-like oil, and subsequently reused. Both the second- and third-generation dendritic catalysts were used five times without deactivation.

TABLE 7. Catalyst Recycling in Three-Component Condensation Reactions

$$PhCH_2CH_2CHO + \underset{NH_2}{\overset{OMe}{\bigodot}} + \underset{\mathbf{8}}{P(OEt)_3}$$

$$\xrightarrow[\text{CH}_2\text{Cl}_2, \text{ rt, 2 h}]{\substack{3(Gn[Me])\text{-Cu(OTf)}_2 \\ (10 \text{ mol\%})}} \underset{PhCH_2CH_2 \quad PO(OEt)_2}{\overset{OMe}{\bigodot}} NH$$

11c

			yield (%)		
Gn	-	first^a	second	third	fourth
G2	0	63	68	66	68
G3	63	71	66	70	67

^{a} Number of recycle.

Recently, novel Lewis acid catalysts such as surfactant-supported scandium triflate and polymer-micelle incarcerated

(23) (a) Yamazaki, N.; Washio, I.; Shibasaki, Y.; Ueda, M. *Org. Lett.* **2006**, *8*, 2321−2324. (b) Catalano, V. J.; Parodi, N. *Inorg. Chem.* **1997**, *36*, 537−541.

(24) (a) Ji, B.; Yuan, Y.; Ding, K.; Meng, J. *Chem. Eur. J.* **2003**, *9*, 5989−5996. (b) Yang, B.-Y.; Chen, X.-M.; Deng, G.-J.; Zhang, Y.-L.; Fan, Q.-H. *Tetrahedron Lett.* **2003**, *44*, 3535−3538.

(25) (a) Azizi, N.; Torkiyan, L.; Saidi, M. R. *Org. Lett.* **2006**, *8*, 2079−2082. (b) Loncaric, C.; Manabe, K.; Kobayashi, S. *Adv. Synth. Catal.* **2003**, *345*, 1187−1189. (c) Iimura, S.; Nobutou, D.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 1644−1645.

(26) (a) Ollevier, T.; Nadeau, E. *Synlett* **2006**, 219−222. (b) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102−112. (c) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044−1070.

(27) (a) Lee, S.-g.; Park, J. H.; Kang, J. Lee, J. K. *Chem. Commun.* **2001**, 1698−1699. (b) Manabe, K.; Kobayashi, S. *Chem. Commun.* **2000**, 669−670. (c) Ranu, B. C.; Hajra, A.; Jana, U. *Org. Lett.* **1999**, *1*, 1141−1143. (d) Qian, C.; Huang, T. *J. Org. Chem.* **1998**, *63*, 4125−4128. (e) Kukhar, V. P.; Solodenko, V. A. *Russ. Chem. Rev.* **1987**, *56*, 859−874.

scandium triflate, which promoted aqueous-phase three-component condensation reactions such as a Mannich-type reaction were reported.[28] Then, we applied the dendritic catalysts **3**(G*n*[R])-Cu(OTf)$_2$ to an aqueous-media Mannich-type reaction.

First, in order to examine the catalytic activity in water and the solubility of the dendritic Cu(OTf)$_2$ catalysts, we employed various peripheral group-containing dendritic catalysts **3**(G*n*[R])-Cu(OTf)$_2$ (R = Me, Bn, TEG) in aqueous-media Mannich-type reactions (Table 8).

TABLE 8. Reactivity of Various Cu(OTf)$_2$ Catalysts in Water
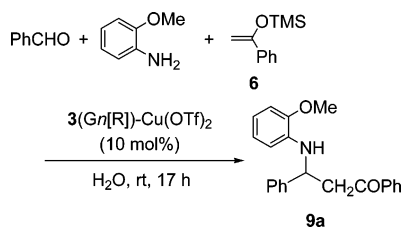
entry	**3**(G*n*[R])	yield (%)
1	none[a]	23
2	G0[Me]	18
3	G1[Me]	47
4	G1[Bn]	48
5	G1[TEG]	32

[a] Only Cu(OTf)$_2$ was used.

Benzaldehyde, *o*-anisidine, and silyl enolate **6** were treated with 10 mol % of **3**(G1[R])-Cu(OTf)$_2$ catalysts in water, and the reaction mixture was stirred at room temperature for 17 h. **3**(G1[Me])-Cu(OTf)$_2$ and **3**(G1[Bn])-Cu(OTf)$_2$, which were hardly dissolved in water to afford a dispersion mixture, gave better chemical yields of **9a** than Cu(OTf)$_2$ alone, which was easily soluble in water (Table 8, entries 1, 3, and 4). In contrast, the nondendritic catalyst **3**(G0[Me])-Cu(OTf)$_2$ was not effective for this Mannich-type reaction in water (Table 8, entry 2). Meanwhile, although **3**(G1[TEG])-Cu(OTf)$_2$ showed good solubility in water, the yield was rather low, contrary to our expectations (Table 8, entry 5). This low yield may be caused by reduction in the Lewis acidity due to coordination of the ethylene glycol unit to a copper atom. The results in Table 8 suggest that dendritic Cu(OTf)$_2$ catalysts containing hydrophobic dendrons with peripheral alkyl groups are effective for carrying out Mannich-type reactions in water.[29]

Then, the second-generation dendritic catalyst **3**(G2[Me])-Cu(OTf)$_2$, which had peripheral methyl substituents, was used in various aqueous-media three-component condensation reactions with several aldehydes and nucleophiles **6**–**8** (Table 9).

Interestingly, compared with the chemical yields in Table 6, which were carried out in dichloromethane, almost all substrates in Table 9 gave better yields. When using ketene silyl acetal **7** or triethyl phosphite **8** as the nucleophile, the corresponding three-component condensation reaction proceeded smoothly in water in fair yields (Table 9, entries 3−7). In particular, 3-phenylpropanal gave the corresponding products **10b**, **11c** in 97% and 99% yields, respectively (Table 9, entries 4 and 7).

(28) (a) Manabe, K.; Mori, Y.; Wakabayashi, T.; Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 7202−7207. (b) Takeuchi, M.; Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2005**, *127*, 13096−13097.

(29) The dendritic ligand **3**G1[Bn] did not catalyze an aqueous-media Mannich-type reaction.

TABLE 9. Three-Component Condensation Reactions in Water

entry	R^1	nucleophile	X	product	yield (%)
1	Ph	CH$_2$=C(OTMS)Ph **6**	CH$_2$COPh	**9a**	53
2	PhCH$_2$CH$_2$	**6**	CH$_2$COPh	**9b**	51
3	Ph	CMe$_2$=C(OTMS)OMe **7**	CMe$_2$CO$_2$Me	**10a**	78
4	PhCH$_2$CH$_2$	**7**	CMe$_2$CO$_2$Me	**10b**	97
5	Ph	P(OEt)$_3$ **8**	PO(OEt)$_2$	**11a**	61
6	PhCH$_2$	**8**	PO(OEt)$_2$	**11b**	83
7	PhCH$_2$CH$_2$	**8**	PO(OEt)$_2$	**11c**	99

The high yields obtained in water are probably due to the hydrophobic effect owing to the cohesion of organic substrates in water.[30] However, the yields of β-amino ketones **9** from silyl enolate **6** were not so high (Table 9, 53% for entry 1 and 51% for entry 2).

We subsequently performed these Mannich-type reactions with a silyl enolate **6** using 10 mol % of various generations of the dendritic catalyst **3**(G*n*[Me])-Cu(OTf)$_2$; these reactions were carried out in water for 17 h (Table 10). For both benzaldehyde and 3-phenylpropanal, the chemical yields of the Mannich products **9** were enhanced by increasing the generation numbers of the dendritic Cu(OTf)$_2$ catalysts. This relationship between the generation number of the dendritic catalyst and the chemical yield shows a positive dendritic effect.[14b]

TABLE 10. Dendritic Effect on Chemical Yields of 9
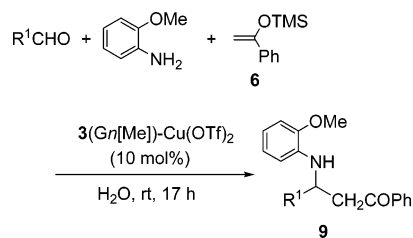
entry	R^1	G*n*	**9**	yield (%)
1	Ph	G0	**9a**	18
2	Ph	G1	**9a**	47
3	Ph	G2	**9a**	53
4	Ph	G3	**9a**	61
5	PhCH$_2$CH$_2$	G0	**9b**	37
6	PhCH$_2$CH$_2$	G1	**9b**	47
7	PhCH$_2$CH$_2$	G2	**9b**	51
8	PhCH$_2$CH$_2$	G3	**9b**	61

On the basis of these results, we have hypothesized that the hydrophobic reaction field constructed by the dendritic Cu(OTf)$_2$ catalyst is essential to increasing the chemical yield of organic synthesis in water.

We finally confirmed the effects of the hydrophobic dendron in the dendritic Cu(OTf)$_2$ catalysts. According to Scheme 2, a Mannich-type reaction was carried out in water by employing 10 mol % of the nondendritic catalyst **3**(G0[Me])-Cu(OTf)$_2$ in the presence of 20 mol % G2[Me]-OPh **12**, which possessed a hydrophobic dendritic group. The yield of the Mannich product **9a** was only 16%;[31] thus, the addition of **12** was not effective in increasing the chemical yield of **9a**. It can be concluded that

(30) (a) Blokzijl, W.; Engberts, J. B. F. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1545−1579. (b) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 164−170.

SCHEME 2. Mannich-Type Reaction in Water by Employing Nondendritic Cu(OTf)₂ Catalyst in the Presence of 12
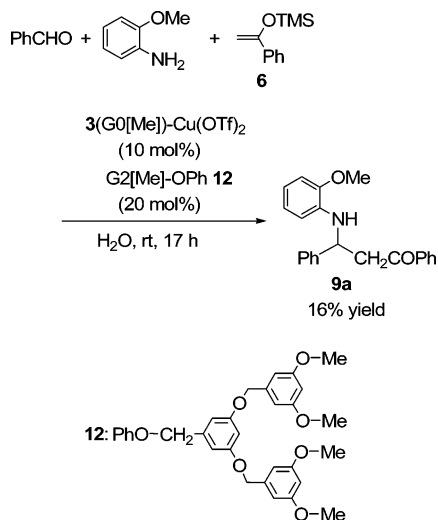
the hydrophobic dendron surrounding Cu(OTf)₂ is essential to organic syntheses in water as the hydrophobic reaction fields.

Conclusion

We synthesized novel bipyridine-core dendritic ligands for the preparation of dendritic Cu(OTf)₂ complexes to be used as Lewis acid catalysts. In Diels–Alder reactions, they showed a positive dendritic effect on the chemical yields of adducts. Furthermore, these dendritic Cu(OTf)₂ catalysts were easily recovered by reprecipitation and could be reused without deactivation. By immobilization of Lewis acids on dendrimers at the core position, unique reactivities such as the positive dendritic effect caused by dendritic reaction fields can be expected.

Furthermore, in Mannich-type reactions, a positive dendritic effect on chemical yields was observed in water, because the dendron of the dendritic Cu(OTf)₂ catalyst acted as an effective hydrophobic reaction field in water. It was found that the immobilization of Lewis acids on dendrimers at the core position is suitable for the design of water-compatible Lewis acid catalysts.

Experimental Section

Preparation of Dendritic Ligands 3(G*n***[R]) from 1 and 2(G***n***[R]): Typical Procedure.** A dry THF solution (15 mL) of 4,4′-dihydroxy-2,2′-bipyridine **1** (0.189 g, 1.00 mmol), 3,5-bis(3,5-dimethoxybenzyloxy)benzyl bromide **2(G2[Me])** (1.057 g, 2.10 mmol), anhydrous potassium carbonate (0.375 g, 2.71 mmol), and 18-crown-6 (75.1 mg, 0.284 mmol) was refluxed for 7 h under an argon atmosphere. The reaction mixture was filtered with Celite to remove inorganic salts, and the filtrate was evaporated to dryness. The residue was purified with silica gel column chromatography (chloroform/methanol/triethylamine = 95/4/1 as eluent) to obtain **3(G2[Me])** (0.890 g, 0.861 mmol) in an 86% yield.

4,4′-Bis[3,5-bis(3,5-dimethoxybenzyloxy)benzyloxy]-2,2′-bipyridine (3(G2[Me])): white powder; mp 151.5–152.5 °C; IR (CH₂-

Cl₂) 3001, 2937, 2838, 1597, 1458, 1374, 1296, 1230, 1204, 1155, 1055, 833 cm⁻¹; ¹H NMR (CDCl₃) δ (ppm) 8.47 (d, *J* = 5.6 Hz, 2H), 8.06 (d, *J* = 2.7 Hz, 2H), 6.88 (dd, *J* = 5.6, 2.7 Hz, 2H), 6.69 (d, *J* = 2.2 Hz, 4H), 6.59–6.57 (m, 10H), 6.41 (t, *J* = 2.2 Hz, 4H), 5.15 (s, 4H), 4.99 (s, 8H), 3.79 (s, 24H); ¹³C NMR (CDCl₃) δ (ppm) 165.7, 161.0, 160.1, 157.8, 150.2, 139.0, 138.2, 111.4, 107.1, 106.4, 105.2, 101.9, 100.0, 70.1, 69.7, 55.3; FAB MS for C₆₀H₆₁N₂O₁₄ *m/z*: Calcd: 1033.4 [(M + H)⁺]; Found: 1033.5; Anal. Calcd for C₆₀H₆₀N₂O₁₄: C, 69.75; H, 5.85; N, 2.71%. Found: C, 69.74; H, 6.03; N, 2.60%.

4,4′-Bis[3,5-bis[3,5-bis(3,5-dimethoxybenzyloxy)benzyloxy]-benzyloxy]-2,2′-bipyridine (3(G3[Me])): white powder; mp 149.7–150.7 °C; IR (KBr) 3001, 2937, 1595, 1459, 1374, 1246, 830 cm⁻¹; ¹H NMR (CDCl₃) δ (ppm) 8.45 (d, *J* = 5.8 Hz, 2H), 8.07 (d, *J* = 2.4 Hz, 2H), 6.87 (dd, *J* = 5.8, 2.4 Hz, 2H), 6.68–6.67 (m, 12H), 6.57–6.55 (m, 22H), 6.40 (t, *J* = 2.4 Hz, 4H), 5.13 (s, 4H), 4.97 (s, 8H), 4.96 (s, 16H), 3.77 (s, 48H); ¹³C NMR (CDCl₃) δ (ppm) 165.7, 161.0, 160.1, 157.8, 150.3, 139.1, 138.2, 111.5, 107.1, 106.44, 106.38, 105.2, 101.9, 101.6, 100.0, 70.1, 70.0, 69.7, 55.3; Anal. Calcd for C₁₂₄H₁₂₄N₂O₃₀: C, 70.17; H, 5.89; N, 1.32%. Found: C, 70.07; H, 5.80; N, 1.30%.

4,4′-Bis(3,5-dibenzyloxybenzyloxy)-2,2′-bipyridine (3(G1[Bn])): white powder; mp 166.5–167.5 °C; IR (CH₂Cl₂) 3000, 1585, 1451, 1376, 1295, 1159, 1027 cm⁻¹; ¹H NMR (CDCl₃) δ (ppm) 8.47 (d, *J* = 5.8 Hz, 2H), 8.06 (d, *J* = 2.5 Hz, 2H), 7.56–7.30 (m, 20H), 6.88 (dd, *J* = 5.8, 2.5 Hz, 2H), 6.70 (d, *J* = 2.4 Hz, 4H), 6.59 (t, *J* = 2.2 Hz, 2H), 5.15 (s, 4H), 5.04 (s, 8H); ¹³C NMR (CDCl₃) δ (ppm) 165.7, 160.2, 157.9, 150.3, 138.2, 136.7, 128.6, 128.0, 127.5, 111.5, 107.1, 106.4, 101.9, 70.2, 69.7; FAB MS for C₅₂H₄₄N₂O₆ *m/z*: Calcd: 792.9 M⁺; Found: 793; Anal. Calcd for C₅₂H₄₄N₂O₆: C, 78.77; H, 5.59; N, 3.53%. Found: C, 78.75; H, 5.53; N, 3.44%.

4,4′-Bis[3,5-bis(3,5-dibenzyloxybenzyloxy)benzyloxy]-2,2′-bipyridine (3(G2[Bn])): white powder; mp 149.0–150.0 °C; IR (KBr) 3031, 2867, 1595, 1448, 1375, 1297, 1158, 827 cm⁻¹; ¹H NMR (CDCl₃) δ (ppm) 8.45 (d, *J* = 5.6 Hz, 2H), 8.07 (d, *J* = 2.7 Hz, 2H), 7.41–7.27 (m, 40H), 6.87 (dd, *J* = 5.6, 2.5 Hz, 2H), 6.68 (bs, 12H), 6.57–6.55 (m, 6H), 5.13 (s, 4H), 5.02 (s, 16H), 4.98 (s, 8H); ¹³C NMR (CDCl₃) δ (ppm) 165.7, 160.2, 160.1, 157.8, 150.3, 139.1, 138.2, 136.8, 129.0, 128.6, 128.0, 127.6, 111.5, 107.1, 106.5, 106.4, 101.9, 101.6, 70.1, 70.0, 69.7; FAB MS for C₁₀₈H₉₂N₂O₁₄ *m/z*: Calcd: 1640.7 M⁺; Found: 1641; Anal. Calcd for C₁₀₈H₉₂N₂O₁₄: C, 79.00; H, 5.65; N, 1.71%. Found: C, 78.96; H, 5.49; N, 1.61%.

4,4′-Bis[3,5-bis[3,5-bis(3,5-dibenzyloxybenzyloxy)benzyloxy]-benzyloxy]-2,2′-bipyridine (3(G3[Bn])): colorless glass; IR (KBr) 3031, 2870, 1595, 1448, 1375, 1295, 1160, 1051, 829 cm⁻¹; ¹H NMR (CDCl₃) δ (ppm) 8.42 (d, *J* = 5.7 Hz, 2H), 8.05 (d, *J* = 2.5 Hz, 2H), 7.39–7.26 (m, 80H), 6.82 (dd, *J* = 5.7, 2.5 Hz, 2H), 6.67–6.65 (m, 28H), 6.57 (t, *J* = 2.1 Hz, 2H) 6.54 (t, *J* = 2.1 Hz, 8H), 6.53 (t, *J* = 2.1 Hz, 4H), 5.07 (s, 4H), 4.98 (s, 32H), 4.95 (s, 8H), 4.93 (s, 16H); ¹³C NMR (CDCl₃) δ (ppm) 165.7, 160.15, 160.07, 157.8, 150.3, 139.2, 139.1, 138.3, 136.8, 128.6, 128.0, 127.5, 111.5, 107.1, 106.4, 101.6, 70.1, 70.0, 69.7; MALDI-TOF MS for C₂₂₀H₁₈₉N₂O₃₀ *m/z*: Calcd: 3338.3 (M + H)⁺; Found: 3338.4; Anal. Calcd for C₂₂₀H₁₈₈N₂O₃₀: C, 79.12; H, 5.67; N, 0.84%. Found: C, 79.13; H, 5.48; N, 0.78%.

4,4′-Bis[3,5-bis[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ben-zyloxy]-2,2′-bipyridine (3(G1[TEG])): white powder; mp 44.0–44.5 °C; IR (neat) 2876, 1585, 1458, 1295, 1109, 848 cm⁻¹; ¹H NMR (CDCl₃) δ (ppm) 8.48 (d, *J* = 5.6 Hz, 2H), 8.06 (d, *J* = 2.5 Hz, 2H), 6.89 (dd, *J* = 5.6, 2.5 Hz, 2H), 6.61 (d, *J* = 2.3 Hz, 4H), 6.47 (t, *J* = 2.3 Hz, 4H), 5.14 (s, 4H), 4.12 (t, *J* = 4.8 Hz, 8H), 3.85 (t, *J* = 4.9 Hz, 8H), 3.75–3.73 (m, 8H), 3.70–3.65 (m, 16 H), 3.55 (dd, *J* = 5.8, 3.7 Hz, 8H), 3.38 (s, 12H); ¹³C NMR (CDCl₃) δ (ppm) 165.7, 160.2, 150.2, 138.1, 111.5, 107.1, 106.1, 101.4, 72.0, 70.8, 70.7, 70.6, 69.8, 69.7, 67.6, 59.0; FAB MS for C₅₂H₇₆N₂O₁₈ *m/z*: Calcd: 1016.5 M⁺; Found: 1017; Anal. Calcd

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(31) Scheme 2 was carried out by use of 1.5 equiv of silyl enolate **6** as compared with benzaldehyde according to the procedure, which was shown in the Supporting Information. **6** was recovered in 59%, and acetophenone was also obtained in 15%. These ratios are based on the amount of used silyl enolate **6**.

for $C_{52}H_{76}N_2O_{18}$: C, 61.40; H, 7.53; N, 2.75%. Found: C, 61.10; H, 7.57; N, 2.63%.

Preparation of Dendritic Ligand 3(G1[Me]) from 1 and 4. The dry THF solution (3 mL) of diisopropyl azodicarboxylate (0.765 g, 3.78 mmol) was added to the THF solution (7 mL) of 4,4′-dihydroxy-2,2′-bipyridine **1** (0.283 g, 1.50 mmol), 3,5-dimethoxybenzyl alcohol **4** (0.600 g, 3.57 mmol), and triphenylphosphine (1.01 g, 3.85 mmol) at 0 °C under an argon atmosphere. The resulting mixture was stirred for 24 h at room temperature, and 5 mL of dichloromethane was added to dissolve the newly formed triphenylphosphine oxide. After filtration of the reaction mixture, the white powder that was collected was poured into 100 mL of chloroform and was stirred for 6 h to dissolve **3**(G1[Me]) completely. The mixture solution was filtered to remove unreacted **1**, and the filtrate was concentrated to obtain **3**(G1[Me]) (0.369 g, 0.755 mmol) in a 50% yield.

4,4′-Bis(3,5-dimethoxybenzyloxy)-2,2′-bipyridine (3(G1[Me])): white powder; mp 197.0−198.0 °C; IR (KBr) 3016, 2942, 1586, 1455, 1374, 1292, 1235, 1209, 890, 872 cm⁻¹; ¹H NMR (CDCl₃) δ (ppm) 8.49 (d, J = 5.8 Hz, 2H), 8.08 (d, J = 2.5 Hz, 2H), 6.91 (dd, J = 5.8, 2.5 Hz, 2H), 6.61 (d, J = 2.2 Hz, 4H), 6.44 (t, J = 2.2 Hz, 2H), 5.17 (s, 4H), 3.81 (s, 12H); ¹³C NMR (CDCl₃) δ (ppm) 165.8, 161.1, 157.7, 150.2, 111.5, 107.2, 105.3, 69.8, 55.4; EI MS for $C_{28}H_{28}N_2O_6$ *m/z*: Calcd: 488.1947 M⁺; Found: 488.1939; Anal. Calcd for $C_{28}H_{28}N_2O_6 \cdot 0.5H_2O$: C, 67.59; H, 5.87; N, 5.63%. Found: C, 67.61; H, 5.63; N, 5.56%.

Supporting Information Available: Procedures for Lewis acid-catalyzed reactions and the preparation of **12**, characterization data for new compounds **5e**, **5g**, **9b**, **10b**, **11a**, **11b**, **11c**, and **12**, and copies of ¹H NMR and ¹³C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070767A