# Highly active asymmetric Diels–Alder reactions catalyzed by $C_2$-symmetric bipyrrolidines: catalyst recycling in water medium and insight into the catalytic mode

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## ABSTRACT

A new class of $C_2$-symmetric 3,3′-dialkoxy-2,2′-bipyrrolidines have been designed and synthesized for asymmetric organocatalytic Diels–Alder reactions of α,β-unsaturated aldehydes. The remarkable rate-accelerating effect for the cycloaddition reaction has been observed in aqueous medium. The catalyst **1c**·2HClO$_4$ can be recovered and reused several times by simple extraction without significant loss of catalytic activity and stereoselectivity. The catalytic mode has been demonstrated by DFT calculation, NMR, and X-ray crystallographic studies for diiminium intermediate.

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## 1. Introduction

During the past decade, organocatalysis has witnessed an explosive growth in the field of asymmetric synthesis since it employs small organic molecules that are relatively non-toxic, inexpensive and stable to both air and moisture.[1] Organocatalysis has become the third main branch in catalytic asymmetric synthesis together with enzymatic and organometallic catalysis and great numbers of new asymmetric transformations have been developed by small organic molecules as catalysts. The enantioselective Diels–Alder reaction is one of the most powerful synthetic methods for construction of cyclohexane frameworks, and is a versatile tool for the synthesis of many important chiral building blocks for the total synthesis of bioactive natural products.[2] Since MacMillan and co-workers reported the first metal-free organocatalytic asymmetric Diels–Alder reaction,[3] several efforts have been devoted to the development of organocatalytic systems including active iminium ion intermediates for this important transformation.[4,5] However, in order to achieve reasonable reaction rates with these organocatalysts, high catalyst loading is generally required. This will raise a cost concern when a large amount of chiral catalysts, which are usually prepared in multi-step, are used for a large scale of synthesis in industrial applications. Therefore, the development of highly active organocatalysts aiming to lower catalyst loading is a significant challenging task.
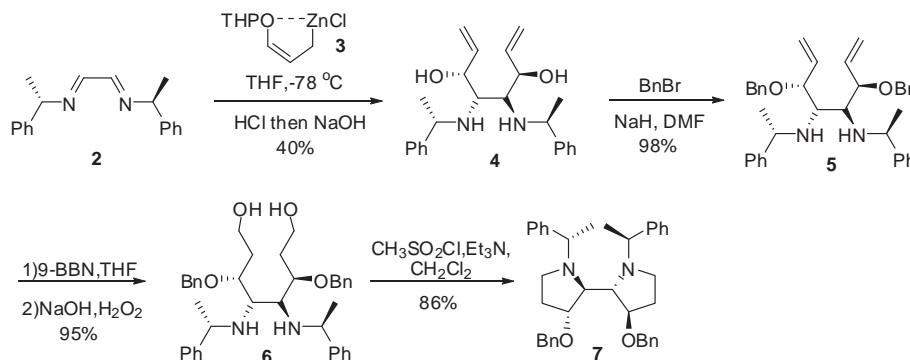
An alternative promising strategy is the development of immobilized and recyclable organocatalytic system.[6] However, although facile recovery of iminium catalysts has been achieved, catalyst modifications are generally required by connection of catalysts to various supporting materials, and inferior efficiency and stereoselectivity were observed in comparison with their nonsupported counterparts. Most recently, some efforts have also been devoted to asymmetric organocatalytic reactions performed using water as reaction medium.[7] The high polarity of water has a possibility to stabilize an ionic intermediate.[8] In addition, the hydrophobicity of organic compounds may give rise to cohesion of substrates, which often enhances reaction kinetics.[9] For Diels–Alder reaction, Breslow demonstrated that the reaction is accelerated in the presence of water.[10] In fact, most of chiral amine-Brønsted acid catalyzed Diels–Alder reactions were performed in wet-solvent system. It was demonstrated that water played a significant role in the acceleration of reaction rates. However, there are only few reports on asymmetric organocatalysis in water for catalyst recycling,[11] despite water is an ideal solvent because it is nontoxic, cheap, hazardless in handling, and environmentally benign.

Quite recently, we designed $C_2$-symmetric bipyrrolidine organocatalysts **1**,[12] which can potentially accelerate the reaction rate of iminium-catalyzed Diels–Alder reaction by providing two identical reaction sites. In this article, we wish to present synthesis of $C_2$-symmetric bipyrrolidine organocatalysts **1**, highly active organocatalytic Diels–Alder reactions using bipyrrolidine organcatalysts **1** in water, and convenient catalyst recycling without further modification of the catalyst structure. Furthermore, we will show that catalytic mode is demonstrated by DFT calculation, NMR, and X-ray crystallographic studies for diiminium intermediate.
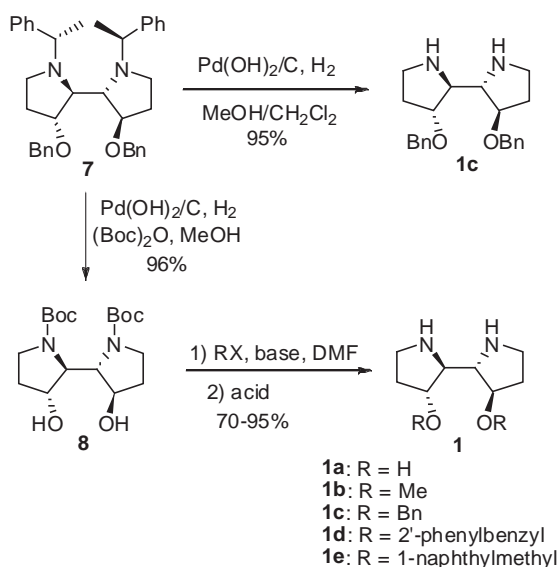
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## 2. Results and discussions

A series of 3,3′-dialkoxy-2,2′-bipyrrolidines **1** have been readily synthesized from chiral diimine **2** as illustrated in Scheme 1 and Scheme 2. Diastereoselective addition of propenylzinc reagent **3** to diimine **2** led to optically pure diamino diol compound **4** after recrystallization in 40% yield.[13] Protection of diol **4** with benzyl bromide in the presence of NaH in DMF gave compound **5** in 98% yield. Hydroboration of terminal alkenes with 9-BBN afforded diol **6** in 95% yield. Mesilation of terminal diol **6** in the presence of excess triethylamine gave key intermediate bipyrrolidine **7** in 86% yield (Scheme 1). Interestingly, hydrogenolysis of **7** with Pd(OH)$_2$/C under 20 bar hydrogen pressure only afforded N-debenzylated product **1c** in quantitative yield. However, under the hydrogenolysis reaction conditions, addition of Boc anhydride furnished O-debenzylated, N-Boc protected product **8** in 96% yield. Direct deprotection of compound **8** gave (3R,2S,2′S,3′R)-3,3′-dihydroxy-2,2′-bipyrrolidine (**1a**) in 95% yield. To test our hypothesis in catalyst design, a number of substituents on oxygen were introduced. O-alkylation of compound **8** with NaH and alkyl halide in DMF followed by deprotection afforded bipyrrolidine catalysts **1b**, **1d**, and **1e** in 70–86% yields (Scheme 2).

performed in organic solvents, lower chemical yields and enantioselectivities were observed (entries 2–7). Surprisingly, when we used water as solvent, the reaction rate was remarkably accelerated (entry 8). The reaction completed only within 2 h and afforded the Diels–Alder adduct in 95% yield with good enantioselectivity and moderate exo-selectivity (exo, 89% ee; endo, 83% ee). The Brønsted acid cocatalyst had large effects on the reaction (entries 9–12). While HCl was used as a cocatalyst, only trace amounts of product was observed (entry 10). The results demonstrated that HClO$_4$ was a best Brønsted acid cocatalyst for the reaction in water. Notably, the reaction with **1c** and HClO$_4$ run in water was much faster (2 h) than the reaction run in MeOH (20 h) and in aqueous MeOH (12 h). When further reducing catalyst loading to 5 and 1 mol %, the reactions still proceeded well without loss of stereoseletivities (entries 13 and 14). The effect of the O-substituent of the bipyrrolidine catalyst on the reaction was also investigated. While 3,3′-dihydroxybipyrrolidine **1a** was used in the combination with HClO$_4$, the reaction did almost not proceed (entry 15). When using other catalysts **1b**, **1d**, and **1e**, it has not significant effect on enantioselectivity and diastereoselectivity even though there is some influence on reactivity (entries 16–18).

Scheme 1.

Scheme 2.

**Table 1**
Asymmetric Diels–Alder reaction between cinnamaldehyde and cyclopentadiene catalyzed by bipyrrolidine **1**[a]
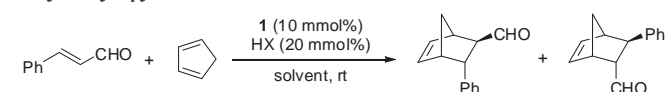
| Entry | 1 | Acid | Solvent | Time (h) | Yield[b] (%) | exo:endo[c] | ee (%)[c] exo, endo |
|---|---|---|---|---|---|---|---|
| 1 | 1c | HClO$_4$ | MeOH/H$_2$O | 12 | 93 | 2.5:1 | 91, 83 |
| 2 | 1c | HClO$_4$ | MeOH | 20 | 91 | 2.5:1 | 83, 69 |
| 3 | 1c | HClO$_4$ | Toluene | 20 | 50 | 0.9:1 | 48, 6 |
| 4 | 1c | HClO$_4$ | Acetonitrile | 20 | 42 | 1.8:1 | 59, 26 |
| 5 | 1c | HClO$_4$ | Dioxane | 20 | 47 | 2.2:1 | 59, 35 |
| 6 | 1c | HClO$_4$ | THF | 20 | 78 | 2.7:1 | 61, 28 |
| 7 | 1c | HClO$_4$ | CH$_2$Cl$_2$ | 20 | 17 | 0.3:1 | 31, 0 |
| 8 | 1c | HClO$_4$ | H$_2$O | 2 | 95 | 2.7:1 | 89, 83 |
| 9 | 1c | TfOH | H$_2$O | 3 | 81 | 3.0:1 | 84, 74 |
| 10 | 1c | HCl | H$_2$O | 3 | Trace | nd | nd |
| 11 | 1c | TsOH | H$_2$O | 3 | 62 | 3.1:1 | 82, 67 |
| 12 | 1c | TFA | H$_2$O | 3 | 27 | 2.7:1 | 81, 71 |
| 13[d] | 1c | HClO$_4$ | H$_2$O | 8 | 91 | 2.8:1 | 87, 79 |
| 14[e] | 1c | HClO$_4$ | H$_2$O | 72 | 97 | 2.4:1 | 87, 82 |
| 15 | 1a | HClO$_4$ | H$_2$O | 3 | Trace | nd | nd |
| 16 | 1b | HClO$_4$ | H$_2$O | 3 | 63 | 2.2:1 | 87, 82 |
| 17 | 1d | HClO$_4$ | H$_2$O | 3 | 84 | 3.1:1 | 88, 82 |
| 18 | 1e | HClO$_4$ | H$_2$O | 3 | 86 | 2.2:1 | 88, 82 |

[a] All the reactions were carried out with 0.25 mmol of (E)-cinnamaldehyde, 0.75 mmol of cyclopentadiene, 0.025 mmol of **1**, and 0.05 mmol of acid in 1 mL of the proper solvent at room temperature.
[b] Isolated yield of a mixture of exo and endo isomers.
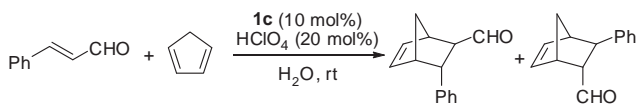[c] exo/endo ratios and ee values were determined by HPLC analysis.
[d] Using 5 mol % catalyst loading.
[e] Using 1 mol % catalyst loading.

Initially, we chose the model reaction between (E)-cinnamaldehyde and cyclopentadiene, which we have found to be promoted by combination of bipyrrolidine **1c** and HClO$_4$ as a cocatalyst in aqueous MeOH (MeOH/H$_2$O=19:1) at room temperature for 12 h (Table 1, entry 1). As shown in Table 1, when the reactions were

With the optimized catalyst **1c**·2HClO$_4$, we next examined its recyclability for the standard reaction in water. As shown in Table 2, after the catalyst was employed to promote the Diels–Alder reaction, we found that the catalyst was effectively immobilized in aqueous medium by simple diethyl ether extraction. The catalyst could be used directly in the next run after removing residual diethyl ether under the vacuum at low temperature. Until fourth cycle, the recovered catalyst retained its high activity, high levels of enantioselectivity, and good diastereoselectivity, even though it was observed that the catalytic activity reduced in fifth cycle. To the best of our knowledge, this is the first example of an effective recyclable asymmetric iminium-catalyzed Diels–Alder reaction in water without further catalyst modification.[14]

**Table 2**
Recycling of bipyrrolidine **1c**·2HClO$_4$ catalyst for asymmetric Diels–Alder reaction between cinnamaldehyde and cyclopentadiene[a]



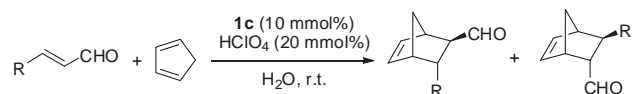| Run | Time (h) | Yield[b] (%) | exo:endo[c] | ee (%)[c] exo, endo |
|---|---|---|---|---|
| 1 | 4 | 95 | 2.7:1 | 89, 83 |
| 2 | 4 | 94 | 2.7:1 | 87, 80 |
| 3 | 4 | 94 | 2.7:1 | 88, 82 |
| 4 | 12 | 88 | 2.5:1 | 86, 80 |
| 5 | 24 | 50 | 2.5:1 | 89, 83 |

[a] The reactions were carried out with 0.25 mmol of (E)-cinnamaldehyde, 0.75 mmol of cyclopentadiene, 0.025 mmol of **1c**, and 0.050 mmol of HClO$_4$ at room temperature in water (1 mL).
[b] Isolated yield of a mixture of exo and endo isomers.
[c] exo/endo ratios and ee values were determined by HPLC analysis.

Having established the recoverable and reusable capacity of bipyrrolidine **1c**·2HClO$_4$ as the catalyst, we next probed the generality of its use as a promoter for Diels–Alder reactions. As revealed in Table 3, substituted cinnamaldehyde dienophiles (entries 1–6) and alkyl-substituted acrolein (entry 7) were subjected to the cycloaddtion reaction with cyclopentadiene in water. All of the reactions afforded Diels–Alder adducts in excellent yields within 2–3.5 h. However, the enantioselectivities decreased comparing with corresponding reactions in aqueous MeOH solution.[12]

**Table 3**
Bipyrrolidine **1c**·2HClO$_4$ catalyzed asymmetric Diels–Alder reaction between various dienophiles and cyclopentadiene in water[a]



| Entry | R | T (h) | Yield[b] (%) | exo:endo[c] | ee (%)[d] exo, endo |
|---|---|---|---|---|---|
| 1e | Ph | 3 | 95 | 2.7:1 | 89, 83 |
| 2 | 2-NO$_2$–Ph | 3.5 | 62 | 0.8:1 | 87, 85 |
| 3 | 4-NO$_2$–Ph | 3.5 | 94 | 1.4:1 | 65, 67 |
| 4 | 4-OMe–Ph | 3.5 | 82 | 2.2:1 | 76, 67 |
| 5 | 4-Cl–Ph | 3.5 | 95 | 1.8:1 | 76, 69 |
| 6 | 4-Br–Ph | 3.5 | 98 | 1.6:1 | 70, 59 |
| 7e | n-Pr | 2 | 94 | 1.3:1 | 76, 79 |

[a] All the reactions were carried out with 0.25 mmol of dienophile, 1.5 mmol of diene, 0.025 mmol of catalyst **1c**, and 0.05 mmol of HClO$_4$ at room temperature in water (1 mL).
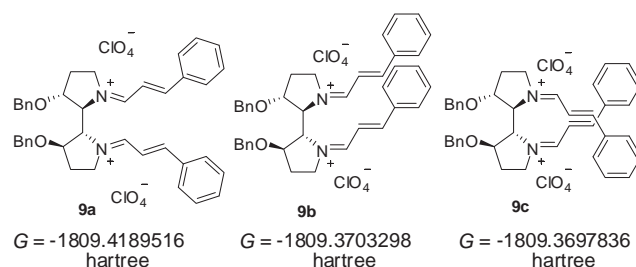[b] Isolated yield of a mixture of exo and endo isomers.
[c] Determined by $^1$H NMR.
[d] The ee was determined by chiral HPLC analysis.
[e] 0.75 mmol of diene was used.

We propose that the mechanism of bipyrrolidine-catalyzed Diels–Alder reaction involves the formation of the diiminium intermediate **9**. Three possible diiminium intermediate are illustrated in Figure 1. For each diiminiium ion, two conjugated iminiums faced each other and the cyclization can occur from above or below. (E,E)-Diiminium intermediate **9a** give two identical Re faces for cycloaddition. (Z,Z)-Diiminium intermediate **9c** afford two identical Si faces for cycloaddition giving opposite absolute configuration in the products. However, for (E,Z)-diiminium intermediate **9b**, two different stereofaces are exposed for cycloaddition, which will kill enantioselection in the Diels–Alder reaction. In order to elucidate the origin of stereoselectivity in the bipyrrolidine-catalyzed Diels–Alder reaction, the energy of three possible diiminium intermediates have been calculated by Density Field Theory. As shown in Figure 1, (E,E)-diiminium intermediate **9a** was calculated to have lowest energy. Intermediate **9a** is 30 kcal mol$^{-1}$ lower in energy compared to **9b** and **9c**. This energy difference predicts the formation of the experimentally formed enantiomer.



| 9a | 9b | 9c |
|---|---|---|
| G = -1809.4189516 hartree | G = -1809.3703298 hartree | G = -1809.3697836 hartree |

**Figure 1.** DFT calculation of possible diiminium intermediates **9**.

With these calculated results in hand, we tried to make iminium intermediate **9** by mixing catalyst **2c** with 2 equiv HClO$_4$ and 2 equiv cinnamaldehyde in MeOH. After stirring for 10 min, we observed that a substantial amount of cinnamaldehyde was consumed and diiminium intermediate **9** was formed on the basis of $^1$H NMR spectroscopic studies. The results demonstrated that diiminium intermediate rapidly formed in the reaction system. In order to gain further evidence for the catalytic mode of the Diels–Alder
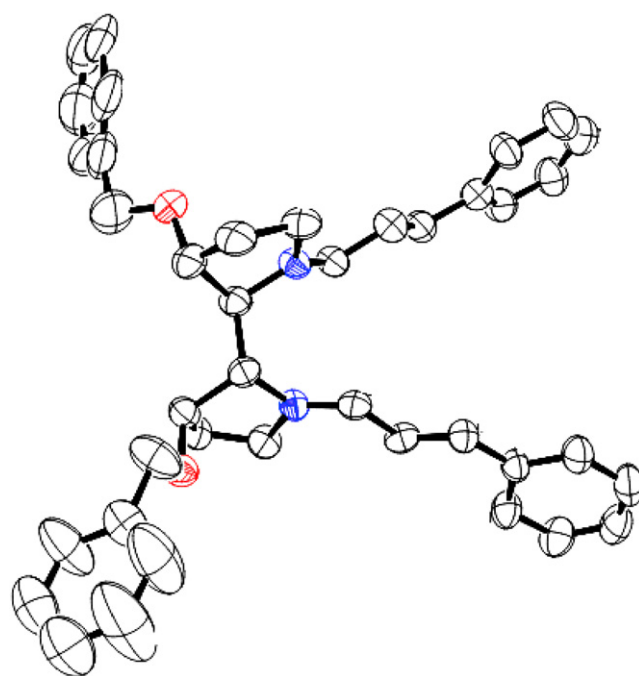


**Figure 2.** X-ray structure of diiminium intermediate **9**.

reaction, a single crystal of diiminium intermediate **9** was grown from methanol and ethyl acetate (20:1, v/v) and submitted for X-ray analysis. As we proposed, two conjugated iminiums faced each other in nearly a parallel fashion, and two *Si* faces of the diiminium are facing each other giving each other the same enantiofacial discriminations (Fig. 2).

## 3. Conclusion

In summary, we have designed and synthesized a new class of $C_2$-symmetric 3,3′-dialkoxy-2,2′-bipyrrolidine catalysts for asymmetric organocatalytic Diels–Alder reactions of $\alpha,\beta$-unsaturated aldehydes. The remarkable rate-accelerating effect for the cycloaddition reaction has been observed in aqueous medium. The catalyst **1c**·2HClO₄ was readily recovered and reused several times without significant loss of catalytic activity and stereoselectivity. The catalytic mode has been demonstrated by DFT calculation, NMR, and X-ray crystallographic studies for diiminium intermediate **9**. Further studies on modification of catalyst structure based on the crystal structure of diiminium intermediate **9** and other asymmetric transformations using $C_2$-symmetric bipyrrolidine catalysts will be described shortly.

## 4. Experimental

### 4.1. General

^{1}H NMR spectra were measured on a MERCURY plus 400 (400 MHz) spectrometer. Chemical shifts were reported in parts per million from tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on a MERCURY plus 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in parts per million from the residual solvent as an internal standard. Optical rotations were taken on a SGW®-1 automatic polarimeter. High performance liquid chromatography (HPLC) was performed on Class-Vp6x using Daicel Chiralcel OJ-H as a column. Mass spectra were recorded by ESI, and HRMS were measured on a HP-5989 instrument. For thin layer chromatography (TLC) analysis throughout this work, TLC plates were used. TLC spots were visualized under ultraviolet light or developed by heating after treatment with potassium permanganate. The products were purified by flash column chromatography on silica gel (100–200 mesh). In experiments requiring dry solvents, tetrahydrofuran (THF), dichloromethane ($CH_2Cl_2$), 1,4-dioxane, acetonitrile, toluene, and *N,N*-dimethylformamide (DMF) were purified according to the standard method. (*E*)-Cinnamaldehyde and cyclopentadiene were distilled and stored under argon atmosphere at −20 °C.

### 4.1.1. Synthesis of (3R,4S,5S,6R)-3,6-bis(benzyloxy)-N⁴,N⁵-bis((S)-1-phenylethyl)octa-1,7-diene-4,5-diamine (5).

To a suspension of NaH (1.8 g, 60%, 44 mmol) in anhydrous DMF (8.0 mL) was added a solution of compound **4** (5.6 g, 14.7 mmol) in anhydrous DMF (15 mL) at 0 °C under a nitrogen atmosphere and stirred at the same temperature for 0.5 h. And then, benzyl bromide (4.8 mL, 44 mmol) was added dropwise, the resulting solution was stirred at room temperature overnight. Water (50 mL) was added at 0 °C and extracted by $Et_2O$ (50 mL×3). The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate=8:1) to afford (3R,4S,5S,6R)-3,6-bis(benzyloxy)-N⁴,N⁵-bis((S)-1-phenylethyl)octa-1,7-diene -4,5-diamine (**5**) (8.1 g, 98% yield): $[\alpha]_D^{25}$ −55.1 (*c* 2.16, EtOH); ^{1}H NMR (CDCl₃) δ 7.08–7.25 (m, 20H), 5.59–5.68 (m, 2H), 5.17 (s, 2H), 5.14 (m, 2H), 4.29 (d, *J*=12 Hz, 2H), 3.66–3.79 (m, 6H), 2.66 (d, *J*=5.6 Hz, 2H), 1.90 (br, 2H), 1.20 (d, *J*=6.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl₃),

δ 146.57, 139.11, 137.85, 128.31, 128.30, 127.77, 127.37, 126.91, 117.60, 82.85, 70.43, 58.60, 56.15, 24.64. HRMS (ESI-TOF) calcd for $C_{38}H_{45}N_2O_2$ ([M+H]⁺): 561.3481, found: 561.3483.

### 4.1.2. Synthesis of (3R,4S,5S,6R)-4,5-bis((S)-1-phenyl ethylamino)-3,6-bis(benzyloxy)octane-1,8-diol (6).

Under a nitrogen atmosphere, to a solution of compound **5** (4.0 g, 7.1 mmol) in anhydrous THF (20 mL), 9-BBN (0.5 M in THF, 49 mL, 25 mmol) was added at 0 °C. The resulting solution was stirred at room temperature overnight, and then cooled to 0 °C. Aqueous NaOH (3 M, 37 mL) was added, followed by $H_2O_2$ (30% in water, 25 mL). The mixture was stirred at room temperature for 8 h, diluted with water, and extracted with $Et_2O$ (60 mL×3). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. The residue was recrystallized from ethyl acetate to afford (3R,4S,5S,6R)-4,5-bis((S)-1-phenylethyl amino)-3,6-bis(benzyloxy)octane-1,8-diol (**6**) (4.0 g, 95% yield): $[\alpha]_D^{21}$ −45.0 (*c* 1.00, CHCl₃); ^{1}H NMR (CDCl₃) δ 7.15–7.31 (m, 20H), 4.36 (d, *J*=11.6 Hz, 2H), 4.04 (d, *J*=11.6 Hz, 2H), 3.72 (m, 2H), 3.62 (m, 2H), 3.51 (m, 2H), 3.33 (m, 2H), 2.57 (d, *J*=7.6 Hz, 2H), 1.94 (m, 2H), 1.76 (m, 2H), 1.17 (d, *J*=6 Hz, H); ^{13}C NMR (100 MHz, CDCl₃), δ 145.09, 137.52, 128.82, 128.74, 128.55, 128.12, 127.45, 127.07, 81.24, 70.74, 60.29, 56.75, 36.60, 23.16. HRMS (ESI-TOF) calcd for $C_{38}H_{49}N_2O_4$ ([M+H]⁺): 597.3692, found: 597.3683.

### 4.1.3. Synthesis of (2S,2′S,3R,3′R)-3,3′-bis(benzyloxy)-1,1′-bis((S)-1-phenylethyl)-2,2′-bipyrrolidine (7).

Et₃N (5.6 mL, 40 mmol) was added to a stirred solution of compound **6** (4.0 g, 6.7 mmol) in anhydrous CH₂Cl₂ (50 mL) under nitrogen at 0 °C, and then methanesulfonyl chloride (1.6 mL, 20 mmol) was added dropwise. The mixture was stirred for 10 min, and quenched by addition of water, extracted with CH₂Cl₂ (50 mL×3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate=10:1) to afford (2S,2′S,3R,3′R)-3,3′-bis(benzyloxy)-1,1′-bis((S)-1-phenylethyl)-2,2′-bipyrrolidine (**7**) (3.2 g, 86% yield): $[\alpha]_D^{20}$ +22.7 (*c* 0.42, CHCl₃); ^{1}H NMR (CDCl₃) δ 7.22–7.44 (m, 20H), 4.61 (d, *J*=12.4 Hz, 2H), 4.56 (d, *J*=12.4 Hz, 2H), 3.82 (d, *J*=5.2 Hz, 2H), 3.67 (q, *J*=6.4 Hz, 2H), 2.76–2.86 (m, 6H), 1.89 (d, *J*=5.2 Hz, 1H), 1.86 (d, *J*=5.2 Hz, 1H), 1.48–1.58 (m, 2H), 1.22 (d, *J*=6.4 Hz, 6H); ^{13}C NMR (100 MHz, CDCl₃), δ 145.22, 139.44, 128.44, 128.31, 128.25, 127.65, 127.39, 126.95, 80.63, 70.40, 69.92, 60.63, 47.31, 32.04, 16.33. HRMS (ESI-TOF) calcd for $C_{38}H_{45}N_2O_2$ ([M+H]⁺): 561.3481, found: 561.3471.

### 4.1.4. Synthesis of (2S,2′S,3R,3′R)-1,1′-bis-tert-butoxy carbonyl-3,3′-dihydroxy-2,2′-bipyrrolidine (8).

A suspension of compound **7** (2.7 g, 4.9 mmol), Pd(OH)₂/C (1.5 g, 20%) and (Boc)₂O (4.3 g, 20 mmol) in MeOH (15 mL) was stirred under 20 atm of H₂ atmosphere for 24 h. After filtration over a Celite pad, which was washed with MeOH, the solvent was concentrated, The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate=2:1) to afford (2S,2′S, 3R,3′R) -1,1′-bis-tert-butoxy-carbonyl-3,3′-dihydroxy-2,2′-bipyrrolidine (**8**) (1.7 g, 96% yield): $[\alpha]_D^{20}$ +67.0 (*c* 1.0, EtOH); ^{1}H NMR (400 MHz, CDCl₃) δ 4.19 (br, 2H), 3.42 (br, 6H), 2.30 (br, 2H), 2.18 (br, 2H), 1.87 (br, 2H), 1.42 (s, 18H); ^{13}C NMR (100 MHz, CDCl₃) δ 155.87, 79.94, 79.79, 79.57, 74.85, 74.39, 73.85, 67.39, 66.95, 60.64, 50.57, 45.30, 45.12, 31.89, 31.64, 31.19, 28.68, 28.59. HRMS (ESI-TOF) calcd for $C_{18}H_{33}N_2O_6$ ([M+H]⁺): 373.2338, found: 373.2339.

### 4.1.5. Synthesis of (2S,2′S,3R,3′R)-2,2′-bipyrrolidine-3,3′-diol dichlorate (1a·2HClO₄).

To a solution of compound **8** (51.2 mg, 0.14 mmol) in CH₂Cl₂ and MeOH (2 mL/1 mL) was added HClO₄ (100 μL, 1.40 mmol). The resulting solution was stirred at room temperature. Upon consumption of the starting material, the solvent was removed via vacuum and the residue was recrystallized

from ethyl acetate to afford (2S,2′S,3R,3′R)-2,2′-bipyrrolidine-3,3′-diol dichlorate (**1a·2HClO₄**) (49.6 mg, 95%): [α]$_D^{19}$ +54.9 (*c* 0.23, EtOH); ¹H NMR (400 MHz, D₂O) δ 4.47 (m, 2H), 3.5 (m, 2H), 3.29–3.42 (m, 4H), 2.13–2.22 (m, 2H), 1.85–1.93 (m, 2H); ¹³C NMR (100 MHz, D₂O) δ 71.4, 64.00, 44.39, 31.65. HRMS (ESI-TOF) calcd for C₈H₁₈Cl₂N₂O₁₀ ([M+H−2HClO₄]⁺): 173.1290, found: 173.1289.

*4.1.6. Synthesis of (2S,2′S,3R,3′R)-3,3′-dimethoxy-2,2′-bipyrrolidine* **1b**. Under a nitrogen atmosphere, to a suspension of NaH (32 mg, 60%, 0.81 mmol) in anhydrous DMF (3.0 mL) was added a solution of compound **8** (0.10 g, 0.27 mmol) in anhydrous DMF (1.0 mL) at 0 °C and stirred for 0.5 h at the same temperature. And then iodomethane (50 μL, 0.81 mmol) was added dropwise and stirred at room temperature. Upon consumption of the starting material, water (10 mL) was added at 0 °C and then extracted by Et₂O (15 mL×3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate=4:1) to afford (2S,2′S,3R,3′R)-1,1′-bis-*tert*-butoxycarbonyl-3,3′-dimethoxy-2,2′-bipyrrolidine (93.2 mg, 86% yield): [α]$_D^{21}$ +60.3 (*c* 0.93, EtOH); ¹H NMR (400 MHz, CDCl₃) δ 3.46–3.65 (m, 4H), 3.27–3.42 (m, 4H), 3.23–3.24 (m, 6H), 1.84–2.31 (m, 4H), 1.35–1.40 (m, 18H). To the solution of this compound (93.2 mg, 0.23 mmol) in MeOH (2 mL) was added acetyl chloride (0.15 mL) at 0 °C and the mixture was stirred at room temperature overnight. The solvent was removed via vacuum and the crude product was dissolved in water, then aqueous solution of sodium hydroxide (3 M) was added till pH=8, the solution was extracted with CH₂Cl₂ (10 mL×3). The combined organic layers were dried over Na₂SO₄ and concentrated to afford (2S,2′S,3R,3′R)-3,3′-dimethoxy-2,2′- bipyrrolidine (**1b**) (46 mg, 100% yield). [α]$_D^{19}$ +11.9 (*c* 0.54, EtOH); ¹H NMR (400 MHz, CDCl₃) δ 3.65 (m, 2H), 3.27 (s, 6H), 2.90–2.96 (m, 6H), 2.27 (br, 2H), 1.73–1.88 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 84.59, 66.84, 56.97, 45.13, 32.00. Compound **2b** and 2 mol equiv HClO₄ was mixed to afford **1b·2HClO₄**; ¹H NMR (400 MHz, CDCl₃) δ 4.21 (m, 2H), 3.76 (m, 6H), 3.53–3.59 (m, 6H), 2.33–2.39 (m, 2H), 2.14–2.17 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 80.27, 62.53, 56.42, 44.81, 28.44. HRMS (ESI-TOF) calcd for C₁₀H₂₂Cl₂N₂O₁₀ ([M+H−2HClO₄]⁺): 201.1603, found: 201.1606.

*4.1.7. Synthesis of (2S,2′S,3R,3′R)-3,3′-bis(benzyloxy)-2,2′-bipyrrolidine (**1c**).* The suspension of compound **7** (4.5 g, 8.1 mmol) and Pd(OH)₂/C (1.5 g, 20%) in MeOH and CH₂Cl₂ (30:15, v/v, 45 mL) was stirred under 20 atm of H₂ atmosphere at room temperature for 24 h. The solution was filtrated and the filtrate was concentrated, the residue was dissolved in water, and an aqueous solution of sodium hydroxide (3 M) was added till pH=8, and extracted with CH₂Cl₂ (100 mL×3). The combined organic layers were dried over K₂CO₃ and concentrated to afford (2S,2′S,3R,3′R)-3,3′-bis(benzyloxy)-2,2′-bipyrrolidine (**1c**) (2.8 g, 95%). [α]$_D^{19}$ +96.1 (*c* 1.10, EtOH); ¹H NMR (400 MHz, CDCl₃) δ 7.24–7.37 (m, 10H), 4.47 (d, *J*=11.6 Hz, 2H), 4.35 (d, *J*=11.6 Hz, 2H), 3.86 (s, 2H), 2.94–3.07 (m, 6H), 2.29 (br, 2H), 1.86–1.91 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 138.56, 128.62, 127.93, 127.84, 82.43, 71.38, 66.69, 45.16, 32.38. HRMS (ESI-TOF) calcd for C₂₂H₂₉N₂O₂ ([M+H]⁺): 353.2229, found: 353.2222.

*4.1.8. Synthesis of (2S,2′S,3R,3′R)-3,3′-bis(biphenyl-2-ylmethoxy)-2,2′-bipyrrolidine (**1d**).* Compound **1d** was prepared in a similar manner as described above (preparation of **1b**) using biphenyl-2-ylmethyl methanesulfonate (85% yield). [α]$_D^{19}$ −72.9 (*c* 0.41, EtOH); ¹H NMR (400 MHz, CDCl₃) δ 7.46–7.48 (m, 2H), 7.31–7.39 (m, 14H), 7.25–7.27 (m, 2H), 4.34 (d, *J*=10.8 Hz, 2H), 4.24 (d, *J*=10.8 Hz, 2H), 3.69 (m, 2H), 2.87–2.99 (m, 6H), 1.93 (br, 2H), 1.69–1.74 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 142.08, 141.06, 135.66, 130.19, 129.65, 129.39, 128.24, 127.92, 127.72, 127.35, 82.92, 69.34, 66.60,

45.29, 32.30. HRMS (ESI-TOF) calcd for C₃₄H₃₇N₂O₂ ([M+H]⁺): 505.2855, found: 505.2852.

*4.1.9. Synthesis of (2S,2′S,3R,3′R)-3,3′-bis(naphthalen-1-ylmethoxy)-2,2′-bipyrrolidine dichlorate (**1e·2HClO₄**).* Under a nitrogen atmosphere, to a suspension of NaH (32 mg, 60%, 0.81 mmol) in anhydrous DMF (3.0 mL) was added the solution of compound **8** (0.10 g, 0.27 mmol) in anhydrous DMF (1.0 mL) at 0 °C and stirred for 0.5 h at the same temperature. And then the solution of 1-(chloromethyl)naphthalene (0.14 g, 0.81 mmol) in dry DMF (0.50 mL) was added dropwise and stirred at room temperature. Upon consumption of the starting material, water (10 mL) was added at 0 °C and then extracted by Et₂O (15 mL×3). The combined organic layers were washed with brine, dried over K₂CO₃, and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate=4:1) to afford (2S,2′S, 3R,3′R)- 1,1′-bis-*tert*-butoxycarbonyl-3,3′-bis(naphthalen-1-ylmethoxy)-2,2′-bipyrrolidine (144 mg, 82% yield), which was dissolved in MeOH (2 mL), and 72% HClO₄ (0.15 mL, 1.8 mmol) was added at 0 °C, stirred at rt overnight. The solvent was removed via vacuum and the residue was purified by flash column chromatography on silica gel (CH₂Cl₂/MeOH=10:1) to afford (2S,2′S,3R,3′R)-3,3′- bis(naphthalen-1-ylmethoxy)-2,2′-bipyrrolidine dichlorate (**1e·2HClO₄**) (0.14 g, 99%). [α]$_D^{19}$ +52.6 (*c* 0.06, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.81 (m, 2H), 7.73 (m, 2H), 7.66 (m, 2H), 7.43–7.50 (m, 4H), 7.22–7.31 (m, 4H), 5.73 (br, 2H), 4.59 (d, *J*=12 Hz, 2H), 4.41 (d, *J*=12 Hz, 2H), 3.86 (s, 2H), 3.67 (s, 2H), 3.44 (m, 4H), 2.00 (m, 2H), 1.86 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 133.80, 132.25, 131.57, 129.27, 128.82, 127.17, 126.76, 126.25, 125.51, 124.03, 78.87, 69.62, 64.06, 45.64, 32.16. HRMS (ESI-TOF) calcd for C₃₀H₃₄Cl₂N₂O₁₀ ([M+H−2HClO₄]⁺): 453.2542, found: 453.2541.

*4.1.10. (2S,2′S,3R,3′R)-3,3′-Bis(benzyloxy)-1,1′-bis((E)-3-phenyl-allylidene)-2,2′-bipyrrolidine-1,1′-diium dichlorate **9a**.* A solution of bipyrrolidine **1c** (0.05 mmol), HClO₄ (0.10 mmol), and (E)-cinnamaldehyde (13 μL, 0.10 mmol) in MeOH was stirred at rt for 10 min. The solvent was removed giving white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.74 (d, *J*=10 Hz, 2H), 8.08 (d, *J*=14.8 Hz, 2H), 7.11–7.59 (m, 20H), 4.96 (t, *J*=12 Hz, 2H), 4.46 (s, 4H), 4.24 (s, 2H), 4.05 (m, 2H), 3.84 (s, 2H), 3.47 (s, 2H), 2.50 (m, 2H), 2.35 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 170.75, 167.56, 136.08, 135.38, 133.31, 131.77, 129.70, 129.22, 128.98, 128.62, 117.26, 78.39, 72.23, 71.84, 51.07, 29.49.

## 4.2. General procedure for bipyrrolidine catalyzed asymmetric Diels–Alder reaction

To a solution of bipyrrolidine (0.025 mmol) in 1 mL of a proper solvent was added the corresponding acid (0.05 mmol). To this solution, freshly distilled (E)-cinnamaldehyde (32 μL, 0.25 mmol) was added at 0 °C and the mixture was stirred at the same temperature for 2 min. And then, freshly distilled cyclopentadiene (62 μL, 0.75 mmol) was added dropwise. The resulting mixture was stirred at room temperature. Upon consumption of (E)-cinnamaldehyde, the reaction mixture was diluted with Et₂O and washed with H₂O and brine. The organic layer was dried over Na₂SO₄, filtrated, and concentrated. When the solvent is moist MeOH or MeOH, hydrolysis of formed dimethyl acetal was performed by stirring the crude product mixture in TFA/H₂O/CHCl₃ (1:1:2) for 2 h at room temperature, followed by neutralization with saturated aqueous NaHCO₃ and extracted with Et₂O. Purification of the Diels–Alder adduct was accomplished by silica gel chromatography. The enantiomeric excess was determined by reduction of the formyl group to the corresponding alcohol with NaBH₄ and HPLC analysis. Enantiomers were separated by HPLC using a Daicel Chiralcel OJ-H column (80/20 hexane/i-PrOH, flow rate 1.0 mL/min, λ=210 nm) *endo* isomer

($T_{R1}$=13.7 min (major), $T_{R}2$=32.9 min (minor)). *exo* Isomer ($T_{R}1$=45.9 min (major), $T_{R}2$=63.2 min (minor)). $^1$H NMR, $^{13}$C NMR data are in agreement with the published data.[4,5]

### 4.3. Recycling procedure of asymmetric Diels–Alder reaction catalyzed by bipyrolidine 1c in combination with HClO$_4$ in water

To an emulsion of bipyrrodine **1c** (8.8 mg, 0.025 mmol), HClO$_4$ (4.2 µL, 0.050 mmol, 72% aqueous solution), and (*E*)-cinnamaldehyde (32 µL, 0.25 mmol) in water (1 mL), freshly distilled cyclopentadiene (62 µL, 0.75 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 4 h. Diethyl ether (2.0 mL) was added and stirred for a few minutes, and then keep the mixture stand for minutes to separate into two layers, and the organic layer was removed via syringe. Repeat this operation for another two times. Combined the organic layers and dried with anhydrous Na$_2$SO$_4$, filtrated, concentrated. The residue was purified by silica gel chromatography. Keeping the aqueous layer above at −78 °C, the residual diethyl ether was removed via vacuum. The dienophile and diene were added, respectively at 0 °C, and the reaction mixture was stirred at room temperature to run next cycle.

### Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.03.042.

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