DOI: 10.1002/ejoc.200900594

Chiral Primary Amine–Polyoxometalate Acid Hybrids as Asymmetric Recoverable Iminium-Based Catalysts

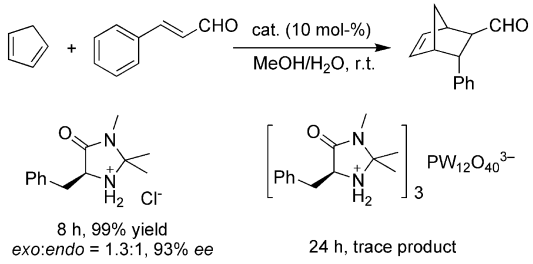
Jiuyuan Li,[a] Xin Li,[a] Pengxin Zhou,[b] Long Zhang,[b] Sanzhong Luo,*[a] and Jin-Pei Cheng*[b]

Keywords: Polyoxometalates / Amines / Asymmetric catalysis / Supported catalysts / Diels–Alder reactions

A new strategy for the immobilization of iminium organocatalysts through the acid–base assembly of multidentate chiral primary amines and solid polyacids is presented. A suitable structurally distinctive C_2-symmetric chiral primary amine (CPA) was identified in this study and the optimal CPA–POM hybrid obtained catalyzed the Diels–Alder cycloaddition of α-substituted acroleins in high yields and fair-to-high selectivity under aqueous conditions. The primary amine in the metal–organic-framework (MOF)-like catalyst acted as the catalytic center as well as multidentate basic centers, whereas phosphotungstic acid played dual roles as both catalyst anchors and modulators of the activity and stereoselectivity. Furthermore, the MOF-like catalyst showed both high reactivity and physical stability and thus could be recycled and reused six times with only a small loss of activity and selectivity.

Introduction

As one of the oldest methods of amino catalysis, iminium catalysis has been used in organic synthesis for more than 100 years and can be traced back to the well-known Knoevenagel condensation reactions.[1] The most recent breakthrough in this field was the identification of chiral amines as asymmetric LUMO-lowering iminium catalysts for a range of chiral transformations.[2] The chiral amines, exemplified by MacMillan catalysts[3] (Scheme 1), are an important class of asymmetric organocatalysts in the burgeoning field of organocatalysis. Parallel to the efforts to develop new iminium catalysts, the immobilization of chiral amine catalysts has also been widely explored to solve some of the problems limiting the use of iminium-based catalysts, such as low efficacy, high catalyst loading, and problems relating to catalyst recovery and recycling.[4] Although the facile recovery of iminium catalysts has been achieved in a number of examples,[5] most of these catalysts demonstrate limited reusability and inferior efficiency and stereoselectivity in comparison with their nonsupported counterparts. Consequently, high loading (both wt.-% and mol-%) of catalysts is still required to achieve reasonable yields. In addition, the construction of these supported catalysts relies heavily on covalent modifications to the small chiral skeletons that involve tedious synthetic manipulations and, as a result, fine-tuning of the catalysts as well as combinatorial screening are generally not feasible in these examples. A new strategy to address the above drawbacks is therefore highly desirable.



Scheme 1. Noncovalent immobilization of a MacMillan catalyst.

Chiral amine–Brønsted acid conjugates are common types of bifunctional organocatalysts in both enamine and iminium catalysis. Taking advantage of the "acid–base" strategy,[6] we have developed a noncovalent strategy for the immobilization of chiral amines by utilizing solid acids such as polystyrene sulfonic acids and hetero-polyacids.[7] The noncovalent nature of the procedure avoids tedious modifications to the parent chiral amines and allows fine-tuning and combinatorial screening of highly efficient, recoverable aminocatalysts, leading to reusable chiral enamine catalysts with a loading as low as 1 mol-%. Considering the well-recognized success of chiral amine–Brønsted acid conjugates in asymmetric imminium catalysis, noncovalent immobilization of iminium catalysts using solid acids is very conceivable. However, our initial attempts with a MacMil-

[a] Beijing National Laboratory for Molecular Sciences (BNLMS), CAS Key Laboratory of Molecular recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, P. R. China
Fax: +86-10-62554449
E-mail: luosz@iccas.ac.cn
[b] Department of Chemistry and State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071, P. R. China
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900594.

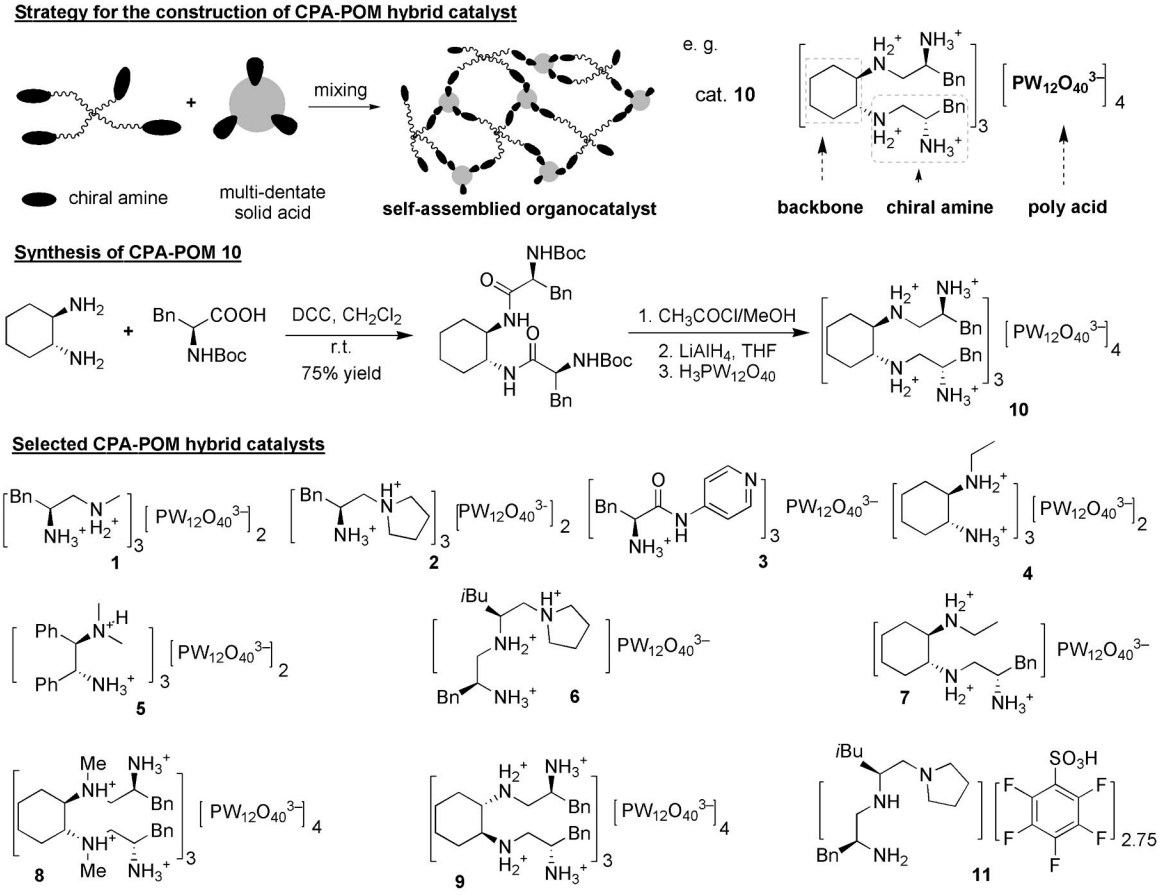
lan catalyst gave an unexpectedly inert catalyst (Scheme 1), a result at least partially ascribed to the strong acidity and bulkiness of the polyoxometalate (POM) that leads to deactivated and insoluble amine hybrids.[3,8]

Inspired by the success of the metal–organic framework (MOF) in asymmetric catalysis,[9] we proposed a new strategy to address the problems of immobilizing iminium catalysts in which multidentate chiral amines are employed instead of monodentate chiral amines such as imidazolines. In this strategy, the acid–base assembly of multidentate chiral amines and solid polyacids may lead to a MOF topology that is easily accessible for iminium activation and meanwhile enable facile recovery and reuse of the resulting hybrid catalysts. As a continuation of our study of polyoxometalates in asymmetric catalysis,[7a,7c,7d] polyoxometalate acids were selected as the polyacids due to their well-defined framework and polyacidic sites.[10] In this way, a C_2-symmetric tetramine with a *trans*-1,2-diaminocyclohexane skeleton and the $H_3PW_{12}O_{40}$ conjugate **10** was identified as the optimal catalyst for the Diels–Alder cycloaddition reactions of α-substituted acroleins, with up to 96% yields, *exo*/*endo* ratios of 95:5, and 83% *ee* under aqueous conditions, and the catalyst could be recycled and reused six times with little loss of activity and selectivity. Herein, we report the full details of these studies.

Results and Discussions

Design and Synthesis of CA–POM Hybrid Catalysts

Our design was based on the "acid–base" strategy often used in organocatalysis. Primary amines were selected as the desired multidentate amines due to their increasingly recognized catalytic capability in iminium-based transformations[11] as well as their readily accessible structural diversity, particularly the multidentate structures.[12] A series of primary amines bearing different skeletons were readily prepared. The chiral primary amine–polyoxometalate (CPA–POM) hybrids were easily synthesized according to a previously published procedure[7a] (Scheme 2) and characterized by IR, SEM, and elemental analysis. The hybrid catalysts were insoluble in protic solvents such as H_2O and MeOH and in less polar solvents such as *n*-hexane, toluene and THF, but soluble in highly polar aprotic solvents such as NMP and DMF. Interestingly, the catalysts were highly soluble in the mixed solvent THF/H_2O (1:1, v/v), which was later proved to be the optimal solvent system for iminium catalysis that enables biphasic catalysis. The SEM images show that the hybrid catalysts are composed of micrometer particles in the solid state (Figure 1, A, 1–2 μm particle and pore size) that form uniform globules under wet conditions (Figure 1, B, 1–2 μm diameter).



Scheme 2. Construction of CPA–POM hybrid catalysts.

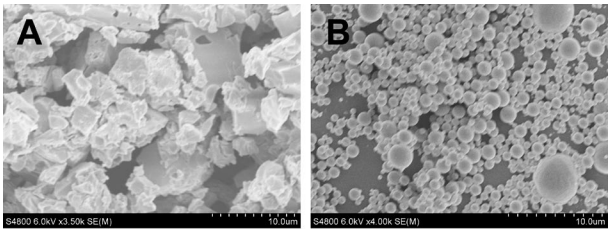


Figure 1. SEM images of catalyst **10** in the solid state (A) and under wet conditions (B).

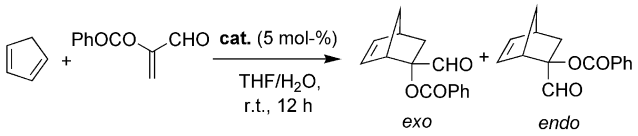
Evaluation of CA–POM Hybrid Catalysts

The asymmetric Diels–Alder reaction of α-substituted acroleins was selected as the model reaction because of its versatile utility in the total synthesis of natural products.[13,14] Recently, Ishihara and Maruoka and their co-workers[15] independently showed that chiral primary amines were viable catalysts for this type of reaction. Although good selectivities were achieved in several cases, most of these catalysts showed only moderate activities especially at the optimal low temperatures. Furthermore, none of these catalysts could be recovered and reused.

To develop a CPA–POM hybrid catalyst for the targeted reaction, we started with the chiral primary amine catalyst of Ishihara and co-workers. However, the stereoselectivity obtained with the hybrid catalyst **6** was low and reduced enantioselectivity was observed compared with the unsupported monochiral primary amine catalyst **11** (67 vs. 80% *ee*, Table 1, entry 6 vs. entry 11). Various synthetic primary amines with different skeletons, including primary–secondary diamines such as **1** and **4**, primary–tertiary diamines such as **2** and **5**, and primary-amine–pyridine–amide **3**, were also examined. The CPA–POMs **1–5** obtained generally exhibited high catalytic activity but only low-to-moderate selectivity in the model Diels–Alder reaction under optimized conditions (5 mol-% loading of amine, THF/H_2O, room temp.). By using the strategy presented in Scheme 2 we found that bidentate CPA–POM hybrids provided significantly improved enantioselectivity and the best result was achieved with the C_2-symmetric CPA–POM hybrid **10**; in the presence of 1.67 mol-% of **10** (equivalent to 5 mol-% amine), the reaction gave 92% yield, an *exo*/*endo* ratio of 79:21, and 79% *ee*, a result comparable with the unsupported catalyst **11**. Interestingly, a match–mismatch effect was observed between the chiral primary amine and the chiral C_2 skeleton. Despite a similar structure and catalytic activity, CPA–POM **9** gave much lower enantioselectivity than CPA–POM **10** (66 vs. 79% *ee*), which indicates a chirality mismatch in CPA–POM **9**. In addition, the lower enantioselectivity obtained with CPA–POM **8**, a methylated derivative of CPA–POM **10**, suggests that a primary–secondary diamine moiety is critical for stereocontrol (Table 1, entry 8 vs. entry 10).

The use of other solvents in the model reaction with the hybrid catalyst **10** was examined. As shown in Table 2, the reactions proceeded smoothly in less polar solvents such as *n*-hexane, toluene, CH_2Cl_2, and THF but with low enantioselectivity. The selectivity was improved in protic solvents such as EtOH and MeOH (Table 2, entries 5 and 6) and in polar solvents such as DMF and NMP (Table 2, entries 8 and 9). Discernable improvements in the activity and stereoselectivity were observed in aqueous media (Table 2, entries 7 and 10–13) and the reaction in THF/H_2O (1:1, v/v) gave the optimal results (Table 2, entry 14). In this case, the

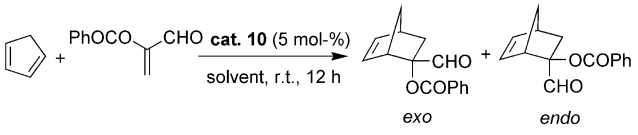
Table 1. Examination of various conjugate catalysts in the model Diels–Alder reaction.[a]



Entry	Catalyst	Yield [%][b]	*exo*/*endo*[c]	*ee* [%][d]
1	**1**	88	77:23	52
2	**2**	72	74:26	49
3	**3**	67	74:26	37
4	**4**	90	71:29	43
5	**5**	92	78:22	31
6	**6**	82	79:21	67
7	**7**	93	75:25	64
8	**8**	88	76:24	50
9	**9**	92	81:19	66
10	**10**	92	79:21	79
11[e]	**11**	97	86:14	80

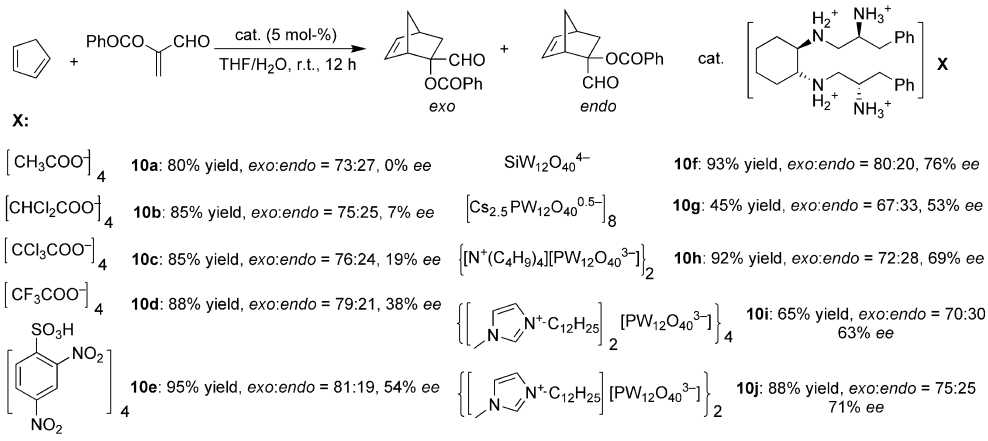
[a] Reaction conditions: 0.25 mmol of α-acyloxyacrolein and 0.75 mmol of cyclopentadiene in 0.2 mL of THF/H_2O (1:1, v/v), 5 mol-% catalyst (equiv. to amine). [b] Isolated yield of a mixture of the *exo* and *endo* products. [c] Determined by ^{1}H NMR spectroscopy. [d] *ee* of the *exo* product, as determined by HPLC. [e] Reaction was performed at 4 °C with 10 mol-% catalyst.

Table 2. Solvent effect on the model Diels–Alder reaction performed with the CPA–POM hybrid catalyst.[a]



Entry	Solvent	Yield [%][b]	*exo*/*endo*[c]	*ee* [%][d]
1	*n*-hexane	62	64:36	0
2	toluene	77	71:29	0
3	CH_2Cl_2	68	63:37	4
4	THF	55	75:25	14
5	EtOH	87	85:15	50
6	MeOH	85	84:16	57
7	H_2O	90	78:22	56
8	DMF	72	85:15	60
9	NMP	68	85:15	52
10	MeOH/H_2O	95	80:20	62
11	EtOH/H_2O	93	82:18	54
12	DMF/H_2O	93	81:19	59
13	dioxane/H_2O	90	82:18	59
14	THF/H_2O	92	79:21	79

[a] Reaction conditions: 0.25 mmol of α-acyloxyacrolein and 0.75 mmol of cyclopentadiene in 0.2 mL of solvent and 5 mol-% catalyst (equiv. to amine). [b] Isolated yield of a mixture of the *exo* and *endo* products. [c] Determined by ^{1}H NMR spectroscopy. [d] *ee* of the *exo* product, as determined by HPLC.



Scheme 3. Evaluation of the performance of other acids in the model Diels–Alder reaction.

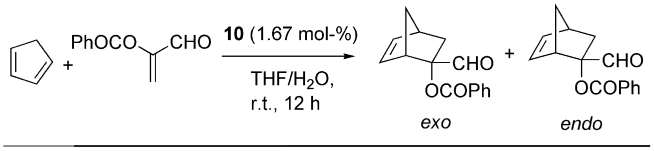
reaction produced the desired product in 92% yield with 79:21 *dr* and 79% *ee*. The beneficial effect of water on this reaction is consistent with previous observations in iminium catalysis.[16]

The effect of the acidity of the acid component on the model reaction was briefly examined with the "privileged" C_2-symmetric diamine.[17] As shown in Scheme 3, the use of a stronger acid in general led to higher activity and selectivity.[18] Following this trend, the best result was achieved with the POM acid with the strongest acidity, phosphotungstic acid. Phosphotungstic acids modified with organic cations were also examined in the hope of further enhancing the stereoselectivity of the reaction. However, none of these hybrid catalysts gave a better catalytic performance than the simple CPA–$H_3PW_{12}O_{40}$ hybrid **10** (Scheme 3).

Recycling and Reuse of Catalyst

With the optimal catalyst CPA–POM **10** (Table 3), we next examined its recyclability and reusability. After the reaction, the catalyst was easily precipitated with a minimal amount of diethyl ether and the organic layer containing the products was separated. The filtered catalyst could be used directly in the next run after removing residual diethyl ether under vacuum. The catalyst could be reused six times with only a small reduction in the reactivity and selectivity. To the best of our knowledge, this represents the first example of an effective recoverable asymmetric primary amine as an iminium catalyst and also one of the best recoverable asymmetric iminium catalysts.

Table 3. Recyclability and reusability of the catalyst **10**.[a]



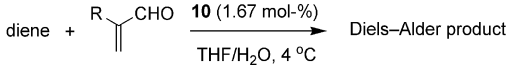
Run	Yield [%][b]	*exo*/*endo*[c]	*ee* [%][d]
1	92	79:21	79
2	90	78:22	79
3	87	78:22	78
4	88	79:21	76
5	85	76:24	79
6	77	77:23	76

[a] Reaction conditions: 0.25 mmol of α-acyloxyacrolein and 0.75 mmol of cyclopentadiene in 0.2 mL of THF/H_2O (1:1, v/v) and 5 mol-% catalyst (equiv. to amine). [b] Isolated yield of a mixture of the *exo* and *endo* products. [c] Determined by ^{1}H NMR spectroscopy. [d] *ee* of the *exo* product, as determined by HPLC.

Substrate Scope of CA–POM Hybrid Catalyst 10 in Diels–Alder Reactions Under Aqueous Conditions

The application of CPA–POM **10** in Diels–Alder reactions with different α-substituted acroleins and dienes was briefly examined (Table 4). The reactions of α-acyloxyacro-

Table 4. Substrate scope for the Diels–Alder reaction catalyzed by **10**.[a]

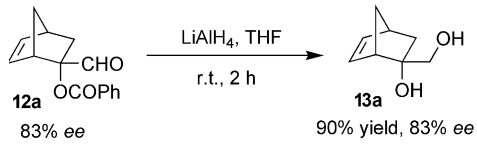


Entry	Diene[b]	R	Product/ Yield [%][c]	*exo*/*endo*[d]	*ee* [%][e]
1	CP	$PhCO_2$	**12b**/88	85:15	83
2	CP	4-MeOPhCO_2	**12b**/93	82:18	82
3[f]	CP	4-MeOPhCO_2	**12b**/97	86:14	80
4	CP	Bn	**12c**/96	88:12	42
5[g]	CP	Bn	**12c**/94	91:9	24
6	CP	4-MeBn	**12d**/92	90:10	42
7[g]	CP	4-MeBn	**12d**/90	90:10	25
8	CP	Me	**12e**/80	89:11	64
9	CH	$PhCO_2$	**12f**/84	6:94	82
10	CH	4-MeOPhCO_2	**12g**/93	5:95	78
11	HD	4-MeOPhCO_2	**12h**/26	80:20	58

[a] Reaction conditions: 0.25 mmol of acrolein with 0.75 mmol of diene in 0.2 mL of solvent and 5 mol-% catalyst (equiv. to amine). The reaction times were 6–96 h. [b] CP: 1,3-cyclopentadiene; CH: 1,3-cyclohexadiene; HD: 2,4-hexadiene. [c] Isolated yield of a mixture of the *exo* and *endo* products. [d] Determined by ^{1}H NMR spectroscopy. [e] *ee* of the *exo* product, as determined by HPLC. [f] Results reported by Ishihara and co-workers using 10 mol-% of catalyst **11** (see ref.[15b]). [g] With **10e** as catalyst.

leins consistently gave high yields and good stereoselectivity in the presence of 5 mol-% of CPA–POM **10** (Table 4, entries 1, 2, and 10). With α-alkyl-substituted acroleins, the reactions also proceeded very smoothly to give the desired Diels–Alder products in high yields and good diastereoselectivity (Table 4, entries 4, 6, and 8). Although only moderate enantioselectivities were obtained in these cases, they were significantly better than the enantioselectivities obtained with the unsupported catalyst (catalyst **10e**; Table 4, entry 4 vs. entry 5 and entry 6 vs. entry 7), thus highlighting the advantage of our CPA–POM hybrid catalysts.

The Diels–Alder product **12a** could be transformed into the 1,2-diol **13a** containing a chiral quaternary alcohol, an important building block in many natural products and bioactive synthetic molecules, by reduction with $LiAlH_4$ (Scheme 4).[19] By comparison of the optical rotation with the known compound, the absolute configuration was determined to be (–)-(1*S*,2*S*,4*S*).[15b]



Scheme 4. Transformation of the Diels–Alder products to 1,2-diols.

Conclusions

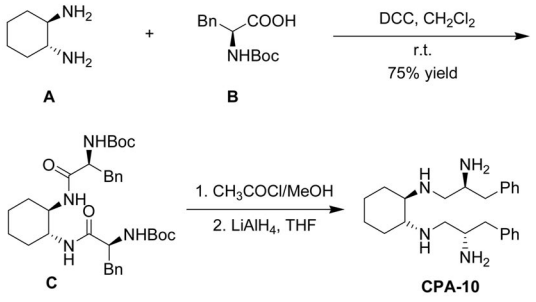
We have developed a new noncovalent strategy for the immobilization of iminium catalysts by utilizing multidentate chiral amines and polyoxometalates. Accordingly, a suitable structurally distinctive C_2-symmetric chiral primary amine was identified and the chiral primary amine–POM hybrid **10** obtained was found to effectively catalyze the Diels–Alder reactions of α-substituted acroleins under aqueous conditions to afford up to 96% yields, 95:5 *exo*/*endo* ratios, and 83% *ee*. In addition, the catalyst could be recycled and reused six times with only slightly reduced activity and selectivity.

Experimental Section

General: Commercial reagents were used as received unless otherwise indicated. ^1H and ^{13}C NMR were recorded with a Bruker AMX-300 instrument; chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The elemental analysis was obtained with a ThermoQuest apparatus (Flash 1112Ea, Italy). The IR spectrum was recorded with a Jasco FT/IR-480 Plus instrument. HPLC and GC analyses were performed by using Chiralcel columns. The SEM images were obtained with an S-4800 instrument. Absolute configurations were determined by correlation to known compounds.

Representative Procedure for the Synthesis of Primary Amine 10: The intermediate compound **C** was synthesized according to the literature[20] in 75% yield. CH_3COCl (5 mL) was slowly added to **C** (4.56 g) in anhydrous MeOH (40 mL). The reaction mixture was then heated at reflux for 1 h. After removal of the solvent by standard methods, the reaction mixture was diluted with CH_2Cl_2 (80 mL) and H_2O (60 mL). The solution was adjusted to pH = 11 by the addition of solid K_2CO_3. The organics were separated and dried with anhydrous Na_2SO_4. After removing the solvent, the residue was purified by flash chromatography to afford the desired intermediate as a white solid (2.90 g, 95%). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.20–1.36 (m, 8 H, 4 CH_2), 1.75 (d, J = 8.3 Hz, 2 H, NH_2), 2.00 (d, J = 12 Hz, 2 H, NH_2), 2.52 (dd, J = 13.5, 3.6 Hz, 2 H, $ArCH_2$), 3.30 (dd, J = 13.5, 3.6 Hz, 2 H, $ArCH_2$), 3.52 (dd, J = 9.9, 2.8 Hz, 2 H, CH), 3.67 (m, 2 H, NCH), 7.17–7.35 (m, 12 H, 10 CH_{Ar} and 2 CONH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.7, 32.3, 41.7, 53.1, 56.9, 126.8, 128.7, 129.2, 138.1, 174.6 ppm.

The above product was dissolved in anhydrous THF (20 mL) and this solution was then slowly added to a suspension of $LiAlH_4$ (1.14 g, 30 mmol) in dry THF (40 mL). The mixture was then heated at reflux for 6 h. After cooling to room temperature, a sat. Na_2SO_4 solution (4 mL) was added. The solid formed was filtered and washed with THF several times. The combined organics were dried with anhydrous Na_2SO_4. After removing the solvent, the residues were purified by FC with ethyl acetate/MeOH (5:1, v/v) as eluent to afford a wax-like solid **CPA-10** (2.30 g, 85% yield). $[a]_D^{20}$ = –36.9 (c = 1.0, MeOH). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.99 (m, 2 H), 1.22 (m, 3 H), 1.43 (m, 4 H), 1.70 (m, 3 H), 2.08 (m, 4 H), 2.30 (m, 4 H), 2.82 (m, 4 H, NCH_2), 3.04 (m, 2 H, NCH), 7.17–7.30 (m, 10 H, 10 CH_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.1, 32.1, 42.8, 53.4, 53.5, 62.4, 126.2, 128.4, 129.3, 139.4 ppm. HRMS: calcd. for $C_{24}H_{36}N_4$ $[M]^+$ 380.2940; found 380.2939.



Other chiral primary amines, such as **CPA-1**, **CPA-2**, **CPA-4**, **CPA-5**, and **CPA-6** are known compounds[7d,15b] and chiral primary amines **CPA-3**, **CPA-7**, **CPA-8**, and **CPA-9** were synthesized according to the above procedure.

(*S*)-2-Amino-3-phenyl-*N*-(pyridin-4-yl)propanamide (CPA-3): $[a]_D^{20}$ = +7.1 (c = 1.0, MeOH). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.62 (br., 2 H, NH_2), 2.77–2.84 (dd, J = 13.8, 4.1 Hz, 1 H, $PhCH_2$), 3.31–3.37 (dd, J = 13.8, 4.0 Hz, 1 H, $PhCH_2$), 3.71–3.75 (m, 1 H, CH), 7.21–7.35 (m, 5 H, 5 CH, Ph), 7.51–7.53 (dd, J = 4.8, 2.3 Hz, 2 H, 2 CH_{Ar}), 8.47–8.49 (dd, J = 4.8, 2.3 Hz, 2 H, 2 CH_{Ar}), 9.72 (br., 1 H, CONH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 40.5, 56.8, 113.4, 127.1, 128.9, 129.2, 137.2, 144.5, 150.7, 173.4 ppm. HRMS: calcd. for $C_{14}H_{15}N_3O$ $[M]^+$ 242.1215; found 242.1216.

(2*S*)-*N*^{1}-[(*S*)-4-Methyl-1-(pyrrolidin-1-yl)pentan-2-yl]-3-phenylpropane-1,2-diamine (CPA-6): $[a]_D^{20}$ = +56.3 (c = 1.0, MeOH). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.83–0.93 (m, 6 H, CH_3), 1.10–1.28 (m, 2 H), 1.64 (m, 4 H), 1.74 (br., 4 H), 2.12 (m, 1 H), 2.37 (m, 2 H), 2.44 (m, 6 H), 2.75 (m, 2 H), 3.09 (m, 1 H, CH), 7.21–7.30 (m, 5 H, 5 CH_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 12.5, 13.5, 23.6, 26.5, 35.6, 42.4, 52.8, 54.4, 54.5, 56.1,

59.5, 126.1, 128.4, 129.3, 139.6 ppm. HRMS: calcd. for $C_{19}H_{33}N_3$ $[M]^+$ 303.2674; found 303.2672.

(1*R*,2*R*)-*N*^{1}-[(*S*)-2-Amino-3-phenylpropyl]-*N*^{2}-ethylcyclohexane-1,2-diamine (CPA-7): $[\alpha]_D^{20}$ = –69.1 (*c* = 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.09 (m, 2 H, CH_2), 1.18 (t, *J* = 5.6 Hz, 3 H, CH_3), 1.25 (m, 5 H), 1.70 (m, 4 H), 2.11 (m, 4 H), 2.48 (m, 1 H), 2.56 (m, 2 H), 2.84 (m, 3 H), 3.04 (m, 1 H), 7.18–7.32 (m, 5 H, 5 CH_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.8, 25.0, 25.2, 31.7, 32.1, 41.3, 42.5, 53.3, 53.4, 61.9, 62.0, 126.1, 128.4, 129.1, 139.4 ppm. HRMS: calcd. for $C_{17}H_{29}N_3$ $[M]^+$ 275.2361; found 275.2362.

(1*R*,2*R*)-*N*^{1},*N*^{2}-Bis[(*S*)-2-amino-3-phenylpropyl]-*N*^{1},*N*^{2}-dimethylcyclohexane-1,2-diamine (CPA-8): $[\alpha]_D^{20}$ = +22.5 (*c* = 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.10–1.26 (m, 6 H, CH_2), 1.71–1.75 (m, 8 H, CH_2), 2.16 (s, 6 H, CH_3), 2.29 (m, 3 H), 2.42 (m, 5 H), 2.64 (m, 4 H), 3.11 (m, 2 H, CH), 7.17–7.30 (m, 10 H, 10 CH_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.6, 25.7, 34.9, 42.3, 50.1, 50.4, 62.8, 65.5, 126.1, 128.4, 129.2, 139.8 ppm. HRMS: calcd. for $C_{16}H_{20}N_2$ $[M]^+$ 408.3253; found 408.3254.

(1*S*,2*S*)-*N*^{1},*N*^{2}-Bis[(*S*)-2-amino-3-phenylpropyl]cyclohexane-1,2-diamine (CPA-9): $[\alpha]_D^{20}$ = +20.7 (*c* = 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.00 (m, 2 H), 1.22 (m, 8 H, CH_2), 1.68 (m, 2 H), 2.26 (m, 4 H, NH_2), 2.32 (m, 2 H), 2.52 (m, 2 H), 2.82 (m, 4 H), 3.06 (m, 2 H, CH), 7.17–7.30 (m, 10 H, 10 CH_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.1, 32.1, 42.8, 53.4, 53.5, 62.4, 126.2, 128.4, 129.3, 139.4 ppm. HRMS: calcd. for $C_{24}H_{36}N_4$ $[M]^+$ 380.2940; found 380.2941.

Representative Procedure for the Synthesis of CPA–POM Hybrid Catalyst 10: $H_3PW_{12}O_{40}$ (7.68 g, 2.67 mmol) was slowly added to a solution of **CPA-10** (760 mg, 2 mmol) in THF (60 mL) and the resulting mixture was stirred for another 1 h. After removing the solvent under vacuum, the solid obtained was dried under vacuum at 50 °C overnight to give catalyst **10** (8.4 g, yield >99%) as a pale-yellow powder. IR (KBr): $\tilde{\nu}$ = 3469, 3138, 2559, 2872, 1616, 1495, 1454, 1261, 1078, 980, 956, 809, 702, 518 cm^{-1}. $C_{72}H_{120}O_{160}N_{12}P_4W_{48}$ (12665.7): calcd. C 6.83, H 0.96, N 1.33; found C 6.90, H 0.93, N 1.24.

General Procedure for the Diels–Alder Reaction: CPA–POM hybrid catalyst **10** (53 mg, 0.0125 mmol amine) was added to THF/H_2O (0.2 mL, 1:1, v/v). After stirring for 10 min, 1-formylvinyl benzoate (44 mg, 0.25 mmol) and 1,3-cyclopentadiene (0.06 mL, 0.75 mmol) were added. The mixture was stirred for 12 h at 4 °C. Diethyl ether (4 mL) was then added to precipitate the catalyst. The catalyst was washed three times with diethyl ether (4 mL) and used directly in next run after removing the residual solvent under vacuum at 50 °C. The combined organics were concentrated and purified by flash chromatography to afford **12a** as a colorless oil (56 mg, 92% yield). The *exo*/*endo* ratio was determined by ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.74 (*exo*), 9.53 (*endo*) ppm. For the *exo* product: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.34 (dd, *J* = 13, 3.8 Hz, 1 H, CH_2), 1.47 (dd, *J* = 9, 2.9 Hz, 1 H, CH_2), 1.74 (d, *J* = 9.2 Hz, 1 H, CH_2), 2.62 (dd, *J* = 13, 3.6 Hz, 1 H, CH), 3.00 (s, 1 H, CH_2), 3.28 (d, *J* = 1 Hz, 1 H, CH), 6.23 (dd, *J* = 5.5, 1.4 Hz, 1 H, CH), 6.47 (dd, *J* = 5.5, 1.4 Hz, 1 H, CH), 7.43 (m, 2 H, 2 CH_{Ar}), 7.57 (m, 1 H, 1 CH_{Ar}), 7.97 (m, 2 H, 2 CH_{Ar}), 9.74 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 38.1, 42.3, 45.7, 48.7, 92.0, 128.5, 129.3, 129.8, 132.4, 133.5, 140.9, 166.9, 198.5 ppm. HRMS: calcd. for $C_{15}H_{14}O_3$ $[M]^+$ 242.0943; found 242.0941. For the *endo* product: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.74 (m, 1 H, CH_2), 1.94 (m, 2 H, CH_2), 2.23 (dd, *J* = 13.4, 3.2 Hz, 1 H, CH), 3.05 (s, 1 H, CH_2), 3.31 (d, *J* = 1.1 Hz, 1 H, CH), 5.95 (dd, *J* = 5.6, 3.0 Hz 1 H, CH), 6.46 (dd, *J* = 5.6, 3.0 Hz, 1 H, CH), 7.46 (m, 2 H, 2 CH_{Ar}), 7.60 (m, 1 H, 1 CH_{Ar}), 8.08 (m, 2 H, 2 CH_{Ar}), 9.53 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 36.9, 40.9, 47.7, 49.1, 89.9, 127.2, 128.2, 128.5, 129.0, 132.2, 140.6, 165.0, 196.8 ppm. The enantiomeric excess was determined by HPLC (OD-H column, 254 nm, 2-propanol/*n*-hexane = 1:99 as eluent, 0.5 mL/min): t_R = 17.07 (major *exo* product), t_R = 19.43 (minor *exo* product), 23.01 (major *endo* product), 25.62 (major *endo* product); 83% *ee* for the *exo* isomer. The absolute configuration was (–)-(1*S*,2*S*,4*S*) determined by comparison of the HPLC chromatogram with the results obtained with Ishihara's catalyst. All the Diels–Alder adducts are known compounds.[14d,14e,15]

2-Formylbicyclo[2.2.1]hept-5-en-2-yl 4-Methoxybenzoate (12b): Yield 63 mg, 93%; colorless oil. *exo*: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.24 (dd, *J* = 13, 3.7 Hz, 1 H, CH_2), 1.42 (m, 1 H, CH_2), 1.68 (dd, *J* = 9.2, 3.2 Hz, 1 H, CH_2), 2.52 (dd, *J* = 13, 3.7 Hz, 1 H, CH_2), 3.18 (d, *J* = 1.2 Hz, 1 H, CH), 3.40 (s, 1 H, CH), 3.78 (s, 3 H, OCH_3), 6.14 (dd, *J* = 5.5, 3.0 Hz, 1 H, CH), 6.39 (dd, *J* = 5.5, 3.0 Hz, 1 H, CH), 6.84 (m, 2 H, 2 CH_{Ar}), 7.84 (d, *J* = 6.9 Hz, 2 H, 2 CH_{Ar}), 9.66 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 38.0, 42.3, 45.7, 48.7, 55.5, 91.6, 113.8, 121.5, 131.9, 132.4, 140.9, 163.9, 166.3, 198.8 ppm. HRMS: calcd. for $C_{15}H_{14}O_3$ $[M]^+$ 272.1049; found 272.1048. *endo*: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.76 (m, 1 H, CH_2), 1.96 (m, 2 H, CH_2), 2.23 (dd, *J* = 13.3, 3.8 Hz, 1 H, CH_2), 3.03 (s, 1 H, CH), 3.28 (d, *J* = 1.3 Hz, 1 H, CH), 3.87 (s, 3 H, OCH_3), 5.95 (dd, *J* = 5.6, 3.0 Hz, 1 H, CH), 6.45 (dd, *J* = 5.6, 3.0 Hz, 1 H, CH), 6.94 (d, *J* = 5.3 Hz, 2 H, 2 CH_{Ar}), 8.03 (d, *J* = 6.9 Hz, 2 H, 2 CH_{Ar}), 9.53 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 38.3, 42.2, 49.1, 50.3, 55.5, 90.8, 113.8, 121.8, 130.3, 131.9, 141.9, 163.8, 166.1, 198.4 ppm. HRMS: calcd. for $C_{15}H_{14}O_3$ $[M]^+$ 272.1049; found 272.1047.

2-Benzylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (12c): Yield 51 mg, 96%; colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.99 (dd, *J* = 12.1, 2.7 Hz, 1 H, CH_2), 1.27 (d, *J* = 8.8 Hz, 1 H, CH_2), 1.39 (dd, *J* = 6.1, 2.8 Hz, 1 H, CH_2), 2.20 (dd, *J* = 12.1, 2.7 Hz, 1 H, CH_2), 2.70 (m, 1 H, CH), 2.95 (m, 3 H, CH and $PhCH_2$), 6.25 (m, 1 H, CH), 6.39 (m, 1 H, CH), 7.06 (m, 2 H, 2 CH_{Ar}), 7.24 (m, 3 H, 3 CH_{Ar}), 9.75 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.0, 33.1, 41.6, 42.6, 47.3, 47.5, 59.9, 126.4, 128.4, 129.4, 133.3, 137.9, 140.1, 206.1 ppm. HRMS: calcd. for $C_{15}H_{16}O$ $[M]^+$ 212.1201; found 212.1202.

[2-(4-Methylbenzyl)bicyclo[2.2.1]hept-5-en-2-yl]methanol: The product was obtained as a white solid by reduction of **12d** with $NaBH_4$. Yield 52 mg, 92%. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.00 (dd, *J* = 12, 2.5 Hz, 1 H, CH_2), 1.41 (m, 2 H, CH_2), 1.57 (m, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.56–2.67 (m, 3 H, CH and $ArCH_2$), 2.82 (br., 1 H, OH), 3.52 (m, 2 H, CH_2), 6.30 (m, 2 H, CH), 7.07–7.24 (m, 4 H, 4 CH_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.0, 35.4, 40.9, 42.6, 47.0, 47.2, 68.0, 129.0, 129.8, 135.7, 137.5 ppm. HRMS: calcd. for $C_{16}H_{20}O$ $[M]^+$ 228.1514; found 228.1516.

(2-Methylbicyclo[2.2.1]hept-5-en-2-yl)methanol: The product was obtained as a white solid by reduction of **12e** with $NaBH_4$. Yield 28 mg, 80%. ^{1}H NMR (300 MHz, $CDCl_3$, 26 °C): δ = 0.78 (dd, *J* = 11.7, 2.7 Hz, 1 H, CH_2), 0.94 (s, 3 H, CH_3), 1.36 (dd, *J* = 7.2, 2.4 Hz, 1 H, CH_2), 1.44 (dd, *J* = 5.8, 2.7 Hz, 1 H, CH), 1.56 (m, 2 H, CH_2), 2.57 (br., 1 H, OH), 2.79 (s, 1 H, CH), 3.59 (m, 2 H, CH_2), 6.12 (m, 2 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 22.8, 37.3, 43.1, 47.6, 47.8, 72.3, 135.4, 136.8 ppm. HRMS: calcd. for $C_9H_{14}O$ $[M]^+$ 138.1045; found 138.1044.

2-Formylbicyclo[2.2.2]oct-5-en-2-yl Benzoate (12f): Yield 54 mg, 84%; colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.29–1.39 (m, 2 H, CH_2), 1.60–1.67 (m, 2 H, CH_2), 2.26 (m, 1 H, CH_2), 2.43 (m, 1 H, CH_2), 2.79 (t, J = 5.4 Hz, 1 H, CH), 3.02 (t, J = 5.4 Hz, 1 H, CH), 6.08 (m, 1 H, CH), 6.46 (m, 1 H, CH), 7.47 (m, 2 H, 2 CH_{Ar}), 7.62 (m, 1 H, 1 CH_{Ar}), 8.06 (m, 2 H, 2 CH_{Ar}), 9.44 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.8, 23.9, 30.0, 35.2, 35.4, 86.1, 128.5, 128.8, 129.5, 129.9, 133.5, 137.3, 166.1, 197.7 ppm. HRMS: calcd. for $C_{16}H_{16}O_3$ $[M]^+$ 256.1099; found 256.1101.

2-Formylbicyclo[2.2.2]oct-5-en-2-yl 4-Methoxybenzoate (12g): Yield 67 mg, 93%; colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.29–1.38 (m, 2 H, CH_2), 1.57–1.66 (m, 2 H, CH_2), 2.25–2.44 (m, 2 H, CH_2), 2.78 (t, J = 5.4 Hz, 1 H, CH), 3.00 (t, J = 5.4 Hz, 1 H, CH), 3.87 (s, 3 H, OCH_3), 6.04 (dd, J = 14.2, 5.1 Hz, 1 H, CH), 6.44 (dd, J = 14.5, 5.1 Hz, 1 H, CH), 6.95 (d, J = 4.6 Hz, 2 H, 2 CH_{Ar}), 8.02 (d, J = 4.7 Hz, 2 H, 2 CH_{Ar}), 9.43 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.8, 23.9, 30.0, 35.1, 35.4, 55.5, 85.7, 113.8, 121.8, 128.9, 132.0, 137.2, 163.9, 165.9, 197.8 ppm. HRMS: calcd. for $C_{17}H_{18}O_4$ $[M]^+$ 286.1205; found 286.1206.

1-Formyl-2,5-dimethylcyclohex-3-enyl 4-Methoxybenzoate (12h): Yield 19 mg, 26%; colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.85–1.06 (m, 6 H, CH_3), 1.66 (m, 1 H, CH_2), 2.19 (m, 1 H, CH_2), 2.42 (m, 1 H, CH), 2.61 (m, 1 H, CH), 3.86 (s, 3 H, OCH_3), 5.56–5.68 (m, 2 H, CH), 6.90 (m, 2 H, 2 CH_{Ar}), 7.96 (m, 2 H, 2 CH_{Ar}), 9.72 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 17.3, 20.8, 27.4, 28.9, 34.6, 55.5, 86.2, 113.8, 121.5, 128.0, 131.8, 132.0, 163.9, 165.7, 198.9 ppm. HRMS: calcd. for $C_{17}H_{20}O_4$ $[M]^+$ 288.1362; found 288.1362.

2-(Hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol (13a): The product was obtained by reduction of **12a** with 2 equiv. of $LiAlH_4$ in THF in 90% yield. $[\alpha]_D^{20}$ = +89.8 (c = 0.5, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.08 (dd, J = 12.7, 2.5 Hz, 1 H, CH_2), 1.46 (m, 1 H, CH_2), 1.55 (m, 1 H, CH_2), 1.77 (dd, J = 12.7, 2.5 Hz, 1 H, CH_2), 1.96 (br., 1 H, OH), 2.48 (br., 1 H, OH), 2.87 (m, 1 H, CH), 2.93 (s, 1 H, CH), 3.74 (m, 2 H, OCH_2), 6.18 (m, 1 H, CH), 6.49 (m, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 40.7, 42.4, 48.6, 49.0, 69.2, 81.8, 133.0, 140.6 ppm. HRMS: calcd. for $C_8H_{12}O_2$ $[M]^+$ 140.0837; found 140.0836.

Supporting Information (see also the footnote on the first page of this article): IR spectrum of CPA–POM hybrid catalyst **10**, SEM images of **10**-catalyzed Diels–Alder reactions, NMR spectra of the chiral primary amines and Diels–Alder products, and HPLC traces of the Diels–Alder reactions.

Acknowledgments

This work was supported by the Natural Science Foundation of China (NSFC 20421202, 20632060, and 20702052), the Ministry of Science and Technology of China (2008CB617501, 2009ZX09501-018), and the Chinese Academy of Sciences.

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Received: May 30, 2009
Published Online: July 30, 2009

