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Chiral Amine–Polyoxometalate Hybrids as Recoverable Asymmetric Enamine Catalysts under Neat and Aqueous Conditions

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Solid acid–chiral amine hybrids have been synthesized and explored as recyclable and reusable enamine-type asymmetric catalysts. Simple chiral amine–polyoxometalate (CA–POM) hybrids were identified as the optimal catalysts to promote a range of enamine-based transformations with high activity and excellent stereoselectivity under either neat or aqueous conditions. A catalyst loading as low as 0.33 mol-% (1 mol-% loading of chiral amine) was sufficient to achieve fast reactions and high stereoselectivities. Under both conditions, the CA–POM hybrid catalysts could be easily recycled and reused up to seven times with essentially unchanged stereoselectivity, although diminished activity was observed upon extensive reuse, especially under aqueous conditions.

Introduction

Besides transition-metal catalysts and enzymes, organocatalysts are increasingly recognized as the third most important class of asymmetric catalysts for chiral synthesis.[1] However, organocatalysts are generally of low efficiency as a result of the high catalyst loading and the difficulties in catalyst separation and recycling. Accordingly, immobilization of these small molcular catalysts has attracted extensive research activities in order to address the above challenges ever since the renaissance of organocatalysts.[2] In this regard, various immobilizing strategies, including attaching the catalysts to supports,[3] adsorbing them onto solid surfaces,[4] and the so-called biphasic technology,[5] have been extensively explored. Though good stereoselectivity was achieved in many cases,[2c] a large amount of supported organocatalysts in terms of both weight and molar ration are still required to achieve reasonable yields due to their reduced activity upon immobilization. A new strategy that overcomes the above shortcomings is therefore highly desirable.

Aqueous-phase asymmetric catalysis has attracted intensive research interest due to the favorable features of water as an inexpensive, safe, and environmentally benign medium.[6] In terms of both atomic economy and green synthesis, chiral amine catalysts that work actively in water with low loadings (<5 mol-%) are highly desirable. In spite of the tremendous efforts dedicated to exploring chiral amine catalysis in water, examples of highly active aqueous catalysts, for example, with a loading as low as 1 mol-%, are quite limited.[7] In this context, reusable chiral amine catalysts in water have been much less explored. Several polymer-supported chiral amine catalysts have been reported to work favorably in aqueous conditions,[8] but the immobilized catalysts generally demonstrated inferior activity to their homogeneous counterparts and catalyst loadings in the range of 10–30 mol-% were frequently employed. To the best of our knowledge, a highly active, reusable chiral amine catalyst that can be used with a loading as low as 1 mol-% in water has not been reported.

Acid–base assembly of chiral amines has proved to be one of the most efficient bifunctional enamine catalysts.[9] The acids used in these examples were essential units that dramatically impacted the catalytic activity and stereoselectivity. Taking advantage of the acid–base principle, we developed a noncovalent immobilization strategy for chiral amines by utilizing solid acids.[5q] Inspection of a range of solid acids including some polymeric Brønsted acids revealed that polyoxometalates serve as a promising type of solid acid. As is well known, polyoxometalates (POMs) have been applied as catalysts or catalyst supports due to their intrinsic properties such as high acidity, favorable redox potentials, and large framework.[10] However, asymmetric catalysis utilizing POMs has remained largely unexplored.[11] During our studies, we found that chiral amine–POM hybrids acted as highly efficient and recoverable asymmetric enamine catalysts. Catalyst loadings as low as 1 mol-% were achieved under both neat and aqueous conditions. Herein, we report the full details of these studies.[12]

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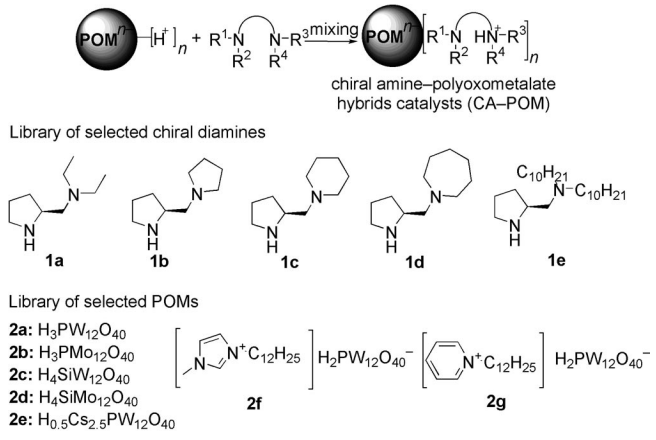
Results and Discussions

Design and Synthesis of CA–POM Hybrid Catalysts

Our design is based on the well-applied "acid–base" strategy in organocatalysis by utilizing the intrinsic high acidity of POMs and the proven catalytic capability of chiral amines (Scheme 1). Because both amines and POMs are readily available, the noncovalent features of the current strategy thus allow for combinatorial screening of the catalysts for the target reaction by simply switching the chiral amine and the POM and their combinations. In addition, organic modifications of POM have been well applied to tune their physical properties and/or structure diversity[13] and POM-type surfactants have been developed by using this approach.[13h] Hydrophobic CA–POM hybrids that work preferentially in aqueous media may therefore be evolved by organic modification of POM with chiral amines.



Scheme 1. Strategy for the construction of CA–POM hybrid catalysts.

The CA–POM hybrids were prepared by slow addition of a POM acid into a solution of the chiral amine in dry THF. After removal of the solvent, the resulting powders were washed with ethyl ether and dried under vacuum. NMR and IR spectroscopic studies and elemental analysis confirmed that the compositions of the hybrid compounds were consistent with the structures shown in Scheme 1. In general, the hybrid solids, for example **1d**–**2a**, have biphasic characteristics and are soluble in polar organic solvents such as acetone, NMP, DMF, and DMSO, but they insoluble in less-polar solvents like hexane, toluene, and ethyl ether. These properties, together with their easy preparations, are sufficient for practical applications in biphasic asymmetric organocatalysis. Interestingly, all the CA–POM hybrids are well dispersed in water as a milk-like solution (Figure 1c), and optical microscopy shows uniform micelle-like aggregates with 0.4 μm mean diameter (Figure 1a). This surfactant-like property would make the CA–POM hybrids potential asymmetric catalysts in water as usually observed with many other surfactant-type catalysts.[14]

Evaluation of CA–POM Hybrid Catalysts

The CA–POM hybrid catalysts were next tested in a typical direct aldol reaction.[15] The screening results of the model reaction between acetone or cyclohexanone and *p*-nitrobenzaldehyde are listed in Table 1. All the CA–POM hybrid catalysts could catalyze the asymmetric reaction smoothly. In general, stronger acids gave better results in terms of both activity and enantioselectivity. Following this trend, $H_3PW_{12}O_{40}$, the most acidic POM, provided the best results. With $H_3PW_{12}O_{40}$ as the selected solid acid, a variety of chiral diamines were then tested, and hybrid **1d**–**2a** was identified as the optimal catalyst for the reaction of acetone (Table 1, entry 10). To our delight, the loading of the catalyst could be reduced to less than 0.33 mol-%, while still maintaining good activity and selectivity (Table 1, entry 11; 24 h, 87% yield, 91%*ee*). In comparison to nonsupported catalyst **1d**–TfOH (Table 1, entry 12), less dehydration product was detected with **1d**–**2a** and the only byproduct was the bis(aldol) adduct in this case. These results highlight the synergistic effect by combining chiral amine and POM.

Encouraged by the results above and bearing in mind the unique surfactant-like features of CA–POM hybrids in water, we next examined the use of CA–POM hybrids as reusable catalysts in water. However, the reaction did not work well with the aldol reaction of acetone (Table 1, entries 6 and 7), and both activity and selectivity were signifi-

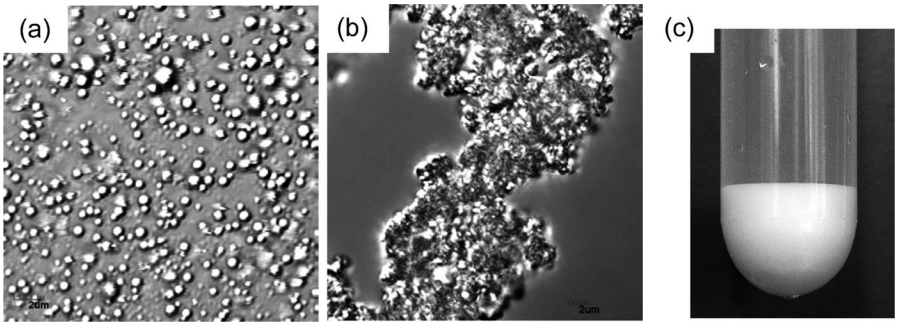
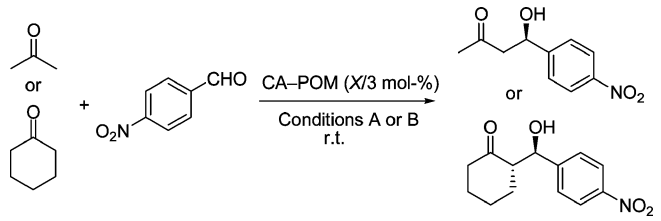


Figure 1. Laser scanning confocal microscopy images of (a) freshly prepared hybrid catalyst **1d**–**2a** in water and (b) catalyst **1d**–**2a** in water after its sixth reuse. Picture (c) refers to fresh **1d**–**2a** in water.

Table 1. Screening of chiral amine hybrid catalysts in a direct aldol reaction.



Entry	Cat. (*X*/3)	Conditions[a]	Time [h]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	**1a**–**2a** (10)	A	10	87	–	90
2	**1a**–**2b** (10)	A	15	78	–	86
3	**1a**–**2c** (10)	A	15	78	–	89
4	**1a**–**2d** (10)	A	15	79	–	84
5	**1a**–**2e** (10)	A	19	84	–	75
6[e]	**1e**–**2a** (10)	A	24	21	–	19
7[e]	**1d**–**2f** (10)	A	24	27	–	32
8	**1b**–**2a** (5)	A	15	87	–	86
9	**1c**–**2a** (5)	A	12	86	–	90
10	**1d**–**2a** (5)	A	7	86	–	92
11	**1d**–**2a** (1)	A	24	87	–	91
12	**1d**–TfOH (1)	A	24	78	–	91
13	**1a**–**2a** (5)	B	12	92	87:13	97
14	**1b**–**2a** (5)	B	12	90	84:16	95
15	**1c**–**2a** (5)	B	10	96	88:12	96
16	**1d**–**2a** (5)	B	4	97	89:11	97
17	**1e**–**2a** (5)	B	10	88	86:14	96
18	**1d**–TfOH (5)	B	16	89	82:18	85
19	**1d**–DBSA (5)	B	7	95	78:22	62
20	**1d**–PTSA (5)	B	16	57	72:28	53
21	**1d**–**2c** (5)	B	4	95	87:13	96
22	**1d**–**2f** (5)	B	5	96	86:14	97
23	**1d**–**2g** (5)	B	5	91	85:15	97
24	**1d**–**2a** (1)	B	12	98	90:10	97
25[f]	**1d**–**2a** (1)	B	24	87	90:10	97

[a] Unless otherwise stated, A: acetone as aldol donor, aldehyde (0.5 mmol) in neat acetone (0.5 mL); B: cyclohexanone as donor, *p*-nitrobenzaldehyde (0.5 mmol) and cyclohexanone (1 mmol) in H_2O (0.5 mL). [b] Isolated yields. [c] Determined by ^1H NMR spectroscopy. [d] Determined by chiral HPLC. [e] Aldehyde (0.5 mmol) with acetone (0.2 mL) in H_2O (0.4 mL). [f] Cyclohexanone (1 equiv.) was used. DBSA: *p*-dodecylbenzenesulfonic acid; PTSA: *p*-toluenesulfonic acid.

cantly reduced under aqueous condition. Subsequent experiments indicated that the reaction of cyclic ketones such as cyclohexanone proceeded very well, a reason partially ascribed to the hydrophobicity of cyclic ketone donors as previously reported.[7p,7s] Cyclohexanone was therefore selected for further screening. An initial test of a typical Brønsted acid, such as TfOH, suggested that acidity would be a key factor influencing the stereoselectivity and that more acidic compounds would lead to better stereoselectivity in water (Table 1, entries 18 and 20). In addition, surfactant Brønsted acids, such as DBSA, gave better results than *p*-toluenesulfonic acid (Table 1, entries 19 and 20). On the basis of these observations, surfactant POMs such as **2f** and **2g** and the nonmodified POMs were then tested in the model reaction in water. Quite interestingly, the reactions with simple CA–POM hybrids such as **1d**–**2a** and **1d**–**2c** gave excellent yields and stereoselectivities (Table 1, entries 16 and 21), whereas surfactant-type POMs **2f** and **2g** did not provide additional benefits for catalysis (Table 1, entries 22 and 23). These results suggest that a simple POM in concert with a chiral amine like **1d** is sufficient to provide the necessary hydrophobic environment for efficient catalysis in water.

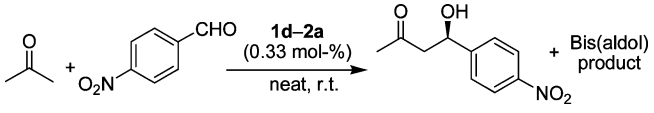
The CA–POM hybrid catalysis in water was further optimized in terms of different chiral amines. Hybrid **1d**–**2a** turned out to be the optimal catalyst (Table 1, entry 16). Both smaller chiral amines such as **1a**, **1b**, and **1c** and a larger surfactant-type chiral amine such as **1e** demonstrated inferior activities (Table 1, entries 13–15 and 17). Remarkably, the loading of catalyst **1d**–**2a** could be reduced to 0.33 mol-% while still maintaining high activity and excellent stereoselectivity (Table 1, entry 24). Under these conditions, the reaction with the use of a stoichiometric amount of cyclohexanone still gave reasonably good results (Table 1, entry 25). In comparison, the same reaction under neat conditions required a large excess of donors. These results also stand in contrast to the same reaction in less-polar organic solvents such as CH_2Cl_2, diethyl ether, THF, and so on, wherein CA–POM catalysts were hardly dissolved and virtually inactive. CA–POM hybrid **1d**–**2a** gave optimal results in the model reactions under both neat and aqueous conditions, which was therefore selected for further studies.

Recycling and Reusing of Catalyst

The recyclability and reusability of the CA–POM hybrid catalysts were next evaluated. Under neat conditions, catalyst **1d**–**2a** could be recovered from the homogeneous reaction system by precipitation with diethyl ether. After removing the residue organic solvent, the recovered catalyst could be reused seven times while maintaining high enantioselectivity, but with a slightly reduced activity (Table 2). However, the formation of a bis(aldol) byproduct increased in the recycling experiments.

Under aqueous conditions, catalyst **1d**–**2a** could also be easily recycled and reused and no problems of emulsion

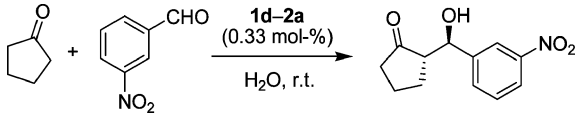
Table 2. Reusability of catalyst **1d**–**2a** under neat conditions.



Run[a]	Time [h]	Aldol product yield[b] [%]	Bis(aldol) product yield[b] [%]	*ee*[c] [%]
1	24	87	7	91
2	24	82	10	92
3	24	78	16	91
4	26	70	16	92
5	30	70	20	91
6	30	67	18	92
7	30	60	17	92

[a] Reaction of aldehyde (0.5 mmol) in neat ketone (0.5 mL). [b] Isolated yield. [c] The *ee* value of aldol product determined by HPLC.

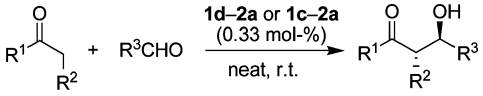
Table 3. Reusability of catalyst **1d**–**2a** under aqueous conditions.



Run[a]	Time [h]	Yield[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]
1	10	88	87:13	98
2	18	85	85:15	97
3	24	80	85:15	95
4	30	79	86:14	92
5	36	71	83:17	94
6	40	66	84:16	93

[a] Reaction of aldehyde (0.5 mmol) with ketone (1 mmol) in water (0.5 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC.

Table 4. POM–CA hybrid catalyst **1d**–**2a** or **1c**–**2a** catalyzed direct aldol reactions under neat condition.



Entry[a]	R^1, R^2	R^3	Time [h]	Yield[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]
1	Me, H	4-$NO_2C_6H_4$	24	87 (78)[e]	–	91 (91)[e]
2	Me, H	3-$NO_2C_6H_4$	24	86 (73)	–	89 (90)
3	Me, H	2-$NO_2C_6H_4$	22	82 (78)	–	91 (86)
4	Me, H	4-CNC_6H_4	48	86 (80)	–	91 (91)
5	Me, H	4-$CF_3C_6H_4$	48	90 (77)	–	90 (90)
6	Me, H	4-ClC_6H_4	96	73 (64)	–	88 (90)
7	Me, H	2-ClC_6H_4	72	91 (84)	–	92 (87)
8	Me, H	3-BrC_6H_4	90	88 (46)	–	90 (90)
9	Me, H	2-BrC_6H_4	72	92 (87)	–	90 (89)
10	Me, H	Ph	144	37 (14)	–	90 (89)
11	Me, H	4-$MeOC_6H_4$	144	11	–	87
12	–$(CH_2)_4$–	4-$NO_2C_6H_4$	16	99 (99)[e]	87:13 (80:20)[e]	99 (97)[e]
13	–$(CH_2)_4$–	3-$NO_2C_6H_4$	19	94	83:17	>99
14	–$(CH_2)_4$–	2-$NO_2C_6H_4$	24	92	87:13	98
15	–$(CH_2)_4$–	4-CNC_6H_4	30	99	86:14	97
16	–$(CH_2)_4$–	4-$CF_3C_6H_4$	30	94	90:10	>99
17	–$(CH_2)_4$–	4-ClC_6H_4	96	95	88:12	98
18	–$(CH_2)_4$–	3-BrC_6H_4	75	64	88:12	98
19	–$(CH_2)_4$–	Ph	96	51	87:13	96
20	–$(CH_2)_3$–	4-$NO_2C_6H_4$	6	86	77:23	95
21	–$(CH_2)_3$–	3-$NO_2C_6H_4$	6	90	71:29	95
22	–$(CH_2)_3$–	2-$NO_2C_6H_4$	8	88	67:33	90
23	–$(CH_2)_3$–	4-CNC_6H_4	19	91	75:25	94
24[f]	Me, Me	4-$NO_2C_6H_4$	19	59[g]	90:10[g]	98[g]
				40[h]	–	94[h]
25[f]	H[i]	4-$NO_2C_6H_4$	72	90	–	98

[a] Reaction of aldehyde (0.5 mmol) in neat ketone (10–20 equiv.), catalyst (0.33 mol-%; equal to 1 mol-% chiral amine); **1d**–**2a** was used for acyclic ketone donors (entries 1–11) and **1c**–**2a** for cyclic ketone donors (entries 2–23). [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC. [e] Data in parentheses refer to that obtained by nonsupported catalyst **1c**–TfOH. [f] Catalyst **1d**–**2a** (1.67 mol-%; equal to 5 mol-% chiral amine) was used. [g] Data for the branched product. [h] Data for the linear product. [i] Isobutyraldehyde was used as the aldol donor.

were encountered in all the cases examined. In practice, catalyst **1d**–**2a** was directly used for next run after simply extracting the product with a minimum amount of diethyl ether. As demonstrated in Table 3, the catalyst could be reused six times with similar stereoselectivity but reduced activity, likely due to the slow aggregations of POM hybrid for extending reuse as shown by microscopy (Figure 1b). Nonetheless, *catalyst **1d**–**2a**, to the best of our knowledge, still represents the first reusable enamine catalyst that works efficiently with 0.33 mol-% loading in water*. A turnover frequency of ca. 25 h^{-1} was achieved in the catalysis of **1d**–**2a** in water.

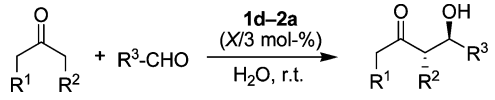
CA–POM-Catalyzed Direct Asymmetric Aldol Reactions under Neat and Aqueous Conditions: Substrate Scope

With optimal catalyst **1d**–**2a**, a series of aldehyde accepters and aldol donors were then examined under neat conditions. In the presence of catalyst **1d**–**2a** (0.33 mol-%), various aromatic aldehydes reacted with acetone to afford the desired product with low-to-high yield and high enantioselectivity. The results obtained from the same reaction with the use of the nonsupported catalyst are listed in Table 4 for comparison. Catalyst **1d**–**2a** performed better in nearly all the cases tested, which proves the synergistic effect of the POM supports. Other aldol donors including cyclic ketones, linear ketones, and aldehydes were also examined with the CA–POM catalyst. Homogeneous or semi-homogeneous solutions were generally observed. In the cases of cyclic ketones, the reaction catalyzed by catalyst **1c**–**2a** gave better results in terms of selectivity despite a lower activity than that with catalyst **1d**–**2a**. All the donors tested worked very well, and the desired products were obtained with excellent yields and enantioselectivities (up to 99% yield and >99%*ee*), which demonstrates the wide scope of the CA–POM catalyst in asymmetric direct aldol reactions.

With identified catalyst **1d**–**2a**, we also examined the scopes of reactions with a variety of aldol donors and acceptors under aqueous conditions. In general, the reactions were carried out with two equivalents of donor in the presence of 0.33 mol-% of hybrid **1d**–**2a**. As shown in Table 5, both cyclopentanone and cyclohexanone work with a range of aromatic aldehydes bearing either electron-donating or electron-withdrawing groups in water. The reactions afforded mainly the *anti* aldol products with high yields and excellent enantioselectivities. For comparison, the same reactions with nonsupported catalyst **1d**–TfOH under neat conditions have also been examined, showing considerably lower activities and stereoselectivities (Table 5, entries 2 and 12). Furthermore, the diastereoselectivity was significantly improved relative to that obtained under neat conditions.

Notably, the reaction of cyclopentanone afforded high *anti* selectivity in all the cases examined, whereas many other secondary amine catalysts just gave low *anti* selectivity or *syn* selectivity.[16] Aliphatic aldehydes such as cyclo-

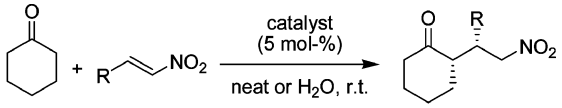
Table 5. CA–POM hybrid **1d**–**2a**-catalyzed direct aldol reaction in water.



Entry[a]	*X*	R^1, R^2	R^3	Time [h]	Yield[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]
1	1	$-(CH_2)_2-$	4-$NO_2C_6H_4$	8	90 (8)[f]	86:14	97
2 [e]	1	$-(CH_2)_2-$	4-$NO_2C_6H_4$	6	79 (17)[f]	82:18	94
3	1	$-(CH_2)_2-$	3-$NO_2C_6H_4$	10	88 (7)[f]	87:13	98
4	1	$-(CH_2)_2-$	2-$NO_2C_6H_4$	8	84 (13)[f]	72:28	97
5	1	$-(CH_2)_2-$	4-CNC_6H_4	14	83 (10)[f]	87:13	96
6	1	$-(CH_2)_2-$	4-$CF_3C_6H_4$	18	73	83:17	97
7	5	$-(CH_2)_2-$	4-ClC_6H_4	36	86	86:14	96
8	5	$-(CH_2)_2-$	1-naph	48	29	49:51	84 (18)
9	5	$-(CH_2)_2-$	cyclohexal	48	45	99:1	95
10	5	$-(CH_2)_2-$	4-$MeOC_6H_4$	48	27	85:15	93
11	5	$-(CH_2)_2-$	3-BrC_6H_4	48	86	79:21	94
12[e]	5	$-(CH_2)_2-$	3-BrC_6H_4	48	89	47:53	85
13	5	$-(CH_2)_2-$	4-MeC_6H_4	48	36	87:13	95
14	1	$-(CH_2)_3-$	4-$NO_2C_6H_4$	12	98	90:10	97
15	1	$-(CH_2)_3-$	3-$NO_2C_6H_4$	12	97	90:10	98
16	1	$-(CH_2)_3-$	2-$NO_2C_6H_4$	12	91	92:8	98
17	1	$-(CH_2)_3-$	4-CNC_6H_4	12	69	91:9	97
18	1	$-(CH_2)_3-$	4-$CF_3C_6H_4$	12	73	89:11	98
19	5	$-(CH_2)_3-$	4-ClC_6H_4	24	77	87:13	98
20	5	$-(CH_2)_3-$	Ph	30	31	88:12	94
21[g]	5	H, H	4-$NO_2C_6H_4$	48	41	–	29
22[g]	5	H, CH_3	4-$NO_2C_6H_4$	48	38[h]	82:18	41[h]
					21[i]	–	23[i]

[a] Unless otherwise stated, reaction of aldehyde (0.5 mmol) with aldol donor (1 mmol) in water (0.5 mL). [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy. [d] Determined by HPLC. [e] The reaction with **1d**–TfOH as the catalyst under neat condition. [f] Bis(aldol) adduct isolated. [g] Aldol donor (4 equiv.) was used. [h] Data for the branch product. [i] Data for the linear product.

Table 6. CA–POM hybrid catalyst **1d**–**2c** catalyzed Michael addition reactions.



Entry	Catalyst	R	Conditions[a]	Time [h]	Yield[b] [%]	*syn*/*anti*[c]	*ee* [%][d]
1	**1c**–**2a**	Ph	A	48	41	92:8	84
2	**1d**–**2a**	Ph	A	48	37	93:7	85
3	**1d**–**2a**	Ph	B	48	47	92:8	83
4	**1d**–**2c**	Ph	A	40	94	94:6	85
5	**1d**–**2c**	Ph	B	48	96	95:5	87
6	**1d**–**2c**	4-MeC_6H_4	A	40	86	93:7	86
7	**1d**–**2c**	4-MeC_6H_4	B	48	99	95:5	88
8	**1d**–**2c**	2-ClC_6H_4	A	40	83	93:7	89
9	**1d**–**2c**	2-ClC_6H_4	B	30	98	94:6	87
10	**1d**–**2c**	4-$MeOC_6H_4$	A	40	97	95:5	86
11	**1d**–**2c**	1-naph	A	40	95	94:6	80
12	**1d**–**2c**	1-naph	B	48	79	93:7	86
13	**1d**–**2c**	4-$NO_2C_6H_4$	A	28	95	92:8	87
14	**1d**–**2c**	4-$NO_2C_6H_4$	B	24	89	96:4	86
15	**1d**–**2c**	3-$NO_2C_6H_4$	A	28	91	94:6	89
16	**1d**–**2c**	2-$NO_2C_6H_4$	A	24	96	95:5	86

[a] Conditions A: Reaction of nitrostyrene (0.5 mmol) in neat cyclohexanone (0.5 mL), catalyst (5 mol-%, based on chiral amine used); Conditions B: Reaction of nitrostyrene (0.5 mmol) with cyclohexanone (4 equiv.) in water (0.5 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC.

hexanecarboxylaldehyde also applied under the present conditions to afford the desired aldol product with excellent *anti* diastereoselectivity and enantioselectivity (Table 5, entry 9; 99:1 *anti*/*syn*, 95%*ee*). Other aldol donors such as acetone and 2-butanone were also examined in the current reactions but with lower yields and enantioselectivities (Table 5, entries 21 and 22), suggesting the hydrophobicity of aldol donors is critical for effective reactions in the present catalytic reaction in water.

Michael Addition Reaction Under Neat and Aqueous Conditions

To further demonstrate the potential of the current immobilization strategy, CA–POM hybrid catalysts were tested in another important C–C bond-formation reaction: the Michael addition reaction.[17] A quick screening indicated that **1d**–**2c** was the optimal catalyst, and the reaction in the presence of 5 mol-% of **1d**–**2c** proceeded smoothly to afford the desired products with high yield and selectivity under both neat and aqueous conditions (Table 6, entries 4 and 5). CA–POM hybrid **1d**–**2c** showed significantly improved activity over the corresponding nonsupported chiral diamine catalyst.[17q] In the presence of 5 mol-% of **1d**–**2c**, the reaction gave equally good activity and selectivity under neat or aqueous conditions. Notably, much less cyclohexanone was used under aqueous conditions, showing the advantage of the aqueous system.

Conclusions

We developed highly efficient and reusable CA–POM hybrid catalysts for aldol reactions under neat and aqueous conditions. Under neat conditions, biphasic catalysis was achieved to afford the desired product in high yield and enantioselectivity with a catalyst loading of 0.33 mol-%. Under aqueous conditions, the same catalyst forms micelle-like aggregates that serve as hydrophobic reaction sites, a unique feature likely to arise from the large framework of the POM anions. Excellent yields and stereoselectivities were again achieved with a catalyst loading as low as 0.33 mol-% in pure water. In addition, the hybrid catalysts could be recycled and directly reused up to seven times with unchanged stereoselectivity but with a slightly lower activity. The hybrid catalysts can also be applied to other enamine-based reactions, for example, the Michael addition to nitrostyrenes, with high activity and stereoselectivity.

Experimental Section

General Method: Commercial reagents were used as received, unless otherwise indicated. ^{1}H NMR and ^{13}C NMR were recorded with a Bruker AMX-300 instrument, as noted, and are internally referenced to residual protic solvent signals. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. Elemental analysis was obtained from ThermoQuest (Flash 1112Ea, ITALY). IR spectra were obtained with a Jasco FT/IR-480 Plus instrument; HPLC analysis was performed by using Chiralcel AD-H, OD-H, AS-H, and OJ-H columns. Absolute configurations were determined by correlation to literature reported results.

Representative Procedure for the Preparation of CA–POM Hybrid 1d–2a: Chiral amine **1d** (910 mg, 5.0 mmol) was dissolved in dry THF (20 mL) in a 50-mL round-bottomed flask under an atmosphere of argon. $H_3PW_{12}O_{40}$ (4.98 g, 1.67 mmol) was then added slowly, and the resulting mixture was stirred for 1 h. The volatiles were then removed under vacuum. The obtained solid was washed

extensively with ether and dried under vacuum at 40 °C to give quantitatively hybrid catalyst (5.89 g) **1d**–**2a** as a pale-yellow powder. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.16–1.28 and 1.70–1.82 [m, 2 H, (R$_2$)N-CH$_2$], 1.50–1.63 [br., 10 H, 4-CH$_2$ and C-(CH$_2$)$_4$-C], 2.31–2.45 (m, 2 H, 3-CH$_2$), 2.56–2.62 (m, 4 H, CH$_2$-*N*-CH$_2$), 2.70–2.74 and 2.80–2.83 (m, 2 H, 5-CH$_2$), 2.98–3.08 (m, 1 H, N-CH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 24.7, 26.6, 28.0, 29.7, 45.61, 55.2, 56.4, 62.9 ppm. ^{31}P NMR (400 MHz, acetone): δ = –14.240 ppm. IR (KBr): $\tilde{\nu}$ = 811, 895, 982, 1621, 1081, 2945, 3445 cm^{-1}. $C_{33}H_{69}N_6O_{40}PW_{12}$ (3426.97): calcd. C 11.55, H 2.01, N 2.45; found C 11.54, H 2.29, N 2.75.

Other hybrid catalysts were prepared by using a similar procedure.

Catalyst 1c–2a: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.42–1.52 (m, 2 H, CH$_2$), 1.55–1.67 [m, 4 H, CH$_2$-C(H$_2$)-CH$_2$], 1.76–1.83 (m, 2 H, 4-CH$_2$), 1.89–2.01 and 2.04–2.18 [m, 2 H, (R$_2$)N-CH$_2$], 2.56–2.78 (br., 4 H, CH$_2$NCH$_2$), 3.14–3.27 (m, 2 H, 3-CH$_2$), 3.60–3.68 (m, 2 H, 5-CH$_2$), 3.72–3.85 (m, 1 H, N-CH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 23.06, 24.88, 25.09, 28.04, 44.90, 53.80, 55.89, 66.98 ppm. ^{31}P NMR (400 MHz, cyclohexanone): δ = –14.770 ppm. IR (KBr): $\tilde{\nu}$ = 810, 892, 978, 1082, 1627, 2934, 3449 cm^{-1}. $C_{30}H_{63}N_6O_{40}PW_{12}$ (3384.54): calcd. C 10.63, H 1.86, N 2.48; found C 9.97, H 2.03, N 2.46.

Catalyst 1d–2c: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.46–1.74 [br., 10 H, 4-CH$_2$ and C-(CH$_2$)$_4$-C], 1.85–2.01 [m, 2 H, (R$_2$)N-CH$_2$], 2.02–2.14 (m, 1 H, NH), 2.60–2.85 (m, 6 H, 4-CH$_2$ and CH$_2$-*N*-CH$_2$), 3.11–3.27 (m, 2 H, 5-CH$_2$), 3.59–3.75 (m, 1 H, N-CH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 23.2, 26.4, 27.1, 27.8, 44.8, 54.7, 57.1, 57.8 ppm. IR (KBr): $\tilde{\nu}$ = 795, 883, 972, 1621, 1014, 2928, 3441 cm^{-1}. $C_{33}H_{70}N_6O_{40}SiW_{12}$ (3424.71): calcd. C 14.6, H 2.55, N 3.10; found C 13.9, H 2.44, N 3.19.

General Procedure for the Aldol Reactions under Neat Conditions: To a given anhydrous ketone (10–20 equiv.) was added the corresponding catalyst (0.00167 mmol). The obtained homogeneous solution was stirred for 10 min and the corresponding aldehyde (0.5 mmol) was then added. The resulting mixture was stirred at room temperature for 16–96 h. Ethyl ether was added to precipitate the catalyst. The product layer was separated, and the catalyst was washed with ether (3×). The combined organic layer was concentrated. The residue was purified by flash chromatography (FC) on silica gel to afford the pure product. The recovered catalyst (>98%) can be directly used after removing the volatile residues under vacuum. All the aldol products are known compounds.[5r,5s,16]

General Procedure for the Aldol Reactions under Aqueous Condition: To a given ketone (2 equiv.) in water (0.5 mL) was added catalyst **1d**–**2a** (0.00167 mmol). The solution was stirred vigorously for 10 min and then the corresponding aldehyde (0.5 mmol) was added. The resulting mixture was stirred at room temperature for 16–48 h. Ethyl ether was added to extract the product. The combined organic layer was concentrated. The residue was purified by FC on silica gel to afford the pure product. The catalyst in water (>98% recovery yield) can be directly used after removing the organic residue by heating to 40 °C. All the aldol products are known compounds.[5q,5r,5s,16]

General Procedure for the Michael Addition Reactions under Neat Conditions: To cyclohexanone (0.4 mL) was added catalyst **1d**–**2c** (0.00625 mmol). The semihomogeneous solution was stirred for 10 min and nitrostyrene (0.5 mmol) was then added. The resulting mixture was stirred at room temperature for 24–48 h. Ethyl ether was then added to precipitate the catalyst. The product layer was separated, and the catalyst was washed with ether (3×). The combined organic layer was concentrated. The residue was purified by FC on silica gel to afford the pure product. The recovered catalyst (>98%) can be directly used after removing the volatiles residue under vacuum. All the Michael addition products are known compounds.[5o,5p,5s]

General Procedure for the Michael Addition Reactions under Aqueous Conditions: To a mixture of cyclohexanone (0.2 mL) in water (0.5 mL) was added catalyst **1d**–**2c** (0.00625 mmol). The solution was vigorously stirred for 10 min and the corresponding nitrostyrene (0.5 mmol) was then added. The resulting mixture was stirred at room temperature for 24–48 h. Ethyl ether was added to extract the product. The product layer was separated, and the catalyst in water was extracted with ether (3×). The combined organic layer was concentrated. The residue was purified by FC on silica gel to afford the pure product. The catalyst (>98% recovery yield) in water can be directly used after removing the organic residue by heating to 40 °C. All the Michael addition products are known compounds.[5o,5p,5s]

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