Chiral Amine–Polyoxometalate Hybrids as Highly Efficient and Recoverable Asymmetric Enamine Catalysts

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ABSTRACT
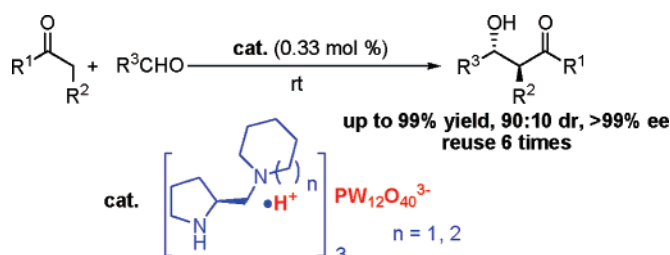
Chiral amine and polyoxometalate (POM) acids were combined to give highly efficient, stereoselective, and recoverable enamine-based catalysts. Less than 1 mol % of chiral amine loading was sufficient for good catalytic activity, and the catalyst could be recovered and reused 6 times with unchanged enantioselectivity and slightly decreased activity.

Ever since the debut of asymmetric organocatalysts,[1] immobilization of these small molecular catalysts has attracted extensive research activities in regard to solve some bottle-neck problems such as low efficacy, high catalyst loading, and problems related to catalyst recovery and recycling.[2] Various immobilizing strategies, including attaching the catalysts to supports,[3] adsorbing them onto solid surfaces,[4] and biphasic catalysis using ionic liquids and fluorous tags,[5] have been explored for this end. Although good stereoselectivity has been achieved in several cases,[2c,6] most of the immobilized organocatalysts often show reduced activity and enantioselectivity and limited reusability and are also less

effective than their nonimmobilized small-molecular counterparts. As a result, large amounts of supported organo-

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catalysts in terms of both weight and molar ratio are normally required to achieve reasonable yields. A new immobilization strategy that overcomes the above shortcomings is therefore highly desirable.

Polyoxometalates (POMs) belong to a large family of metal−oxide clusters that have diverse catalytic applications due to their intrinsic properties such as high acidity and favorable redox potentials.[7] Besides serving as catalysts, POMs can also act as supports for catalysts via ion-pair interaction or by covalent immobilization. Such constructed POM hybrids combine these two types of catalytically active species in one and, also, can be recycled and reused many times by taking advantage of the large framework of POMs. For example, transition metal−POM hybrids have been used as effective and recoverable catalysts in hydrogenation reactions and aerobic oxidations.[8] Lanthanide−POM hybrids were recently reported as reusable Lewis acid catalysts.[9]

However, to the best of our knowledge, there are only a few reports on asymmetric catalysis involving POMs despite the numerous catalytic applications of POMs and their hybrid compounds.[10] In addition, though organic modifications of POMs are well applied to tune their physical properties and/or structural diversity to improve the performance and reusability of the catalysts,[11] the catalytic potentials of organic groups in organic−POM hybrids remain unexplored. Thus, we envisaged that if POMs were combined with functionalized chiral organocatalysts the assemblies may be able to act as recoverable asymmetric organocatalysts. This 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 diamines (Scheme 1).[12] The chiral diamine moieties would also
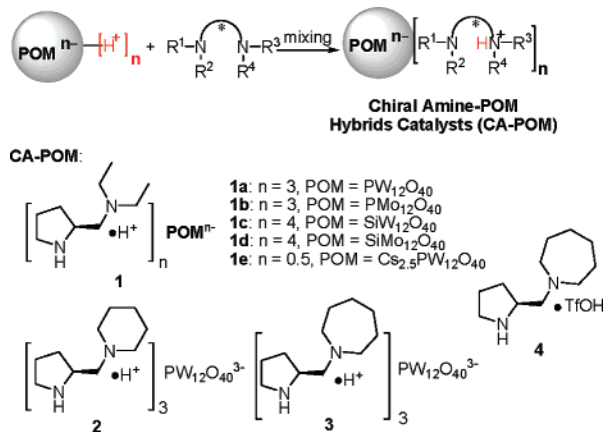
function as solubility modulators for the resulting hybrids to render biphasic organocatalysis, so that the chiral amine−POM (CA−POM) hybrids can be separated by precipitation with ether or by nanofiltration.[13] Indeed, we found that CA−POM hybrid catalysts such as **2** and **3** were highly efficient and reusable asymmetric enamine-based catalysts with only 1 mol % of loading (loading amount based on chiral amines).

The CA−POM hybrids were obtained by slow addition of a POM acid into a solution of chiral amine in THF. After removal of the solvent, the resulting powders were washed with ethyl ether and dried under a vacuum. NMR 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, **2** and **3**, have biphasic characteristics and are soluble in polar organic solvents such as acetone, DMF, and DMSO but insoluble in less polar solvents like hexane, toluene, and ethyl ether. These properties, together with their easy preparations, suffice for practical applications in biphasic asymmetric organocatalysis.

The hybrid catalysts were then examined for the direct aldol reaction of acetone and *p*-nitrobenzaldehyde. Some screening results are listed in Table 1. To our delight, the

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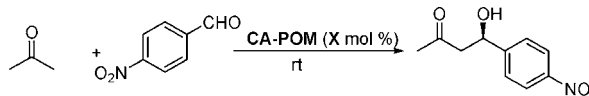
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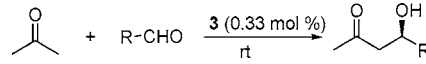
Table 1. Selected Screening Results[a]

entry	catalyst	X (mol %)[b]	time (h)	yield (%)[c]	ee (%)[d]
1	**1a**	10	10	87	90
2	**1b**	10	15	78	86
3	**1c**	10	15	78	89
4	**1d**	10	15	79	84
5	**1e**	10	19	84	75
6	**2**	5	12	86	90
7	**3**	5	7	86	92
8	**3**	1	24	87	91
9	**4**	1	24	78	91
10[e]	**3**	1	24	82	92
11[e]	**3**	1	24	78	91
12[e]	**3**	1	26	70	92
13[e]	**3**	1	30	70	91
14[e]	**3**	1	30	67	92

[a] Reaction in neat acetone (0.5 M). [b] Refers to the loading of chiral amine. [c] Isolated yields. [d] Determined by chiral HPLC. [e] Second−sixth reuse of the catalyst **3** in entry 8.

CA−POM hybrids do effectively catalyze the asymmetric reactions. Among a series of commercially available POMs, the hybrid catalyst with $H_3PW_{12}O_{40}$ gave the best results (Table 1, entry 5). Subsequent screening of a range of chiral amines led to an optimal hybrid catalyst **3** for the model reaction (Table 1, entry 7; for details see Supporting Information). Significantly, the loading of chiral amine (of catalyst **3**) could be reduced to as low as 1 mol % while still maintaining very good activity (24 h, 87%, 91% ee; Table 1, entry 8). In comparison, the nonsupported catalyst **4** gave 78% yield under identical conditions (Table 1, entry 9). The dehydration bypathway normally observed in the catalysis of **4** was considerably diminished in the reactions catalyzed by **3**, and the only detected byproduct is a bisaldol adduct (see Supporting Information). These results highlight the synergistic effect by combining chiral amine and POMs together. More importantly, the CA−POM hybrid catalysts could be easily recycled from the homogeneous reaction by precipitation with diethyl ether. The enantioselectivity obtained using the recovered catalyst **3** maintained the same enantioselectivity after six runs with slightly reduced activity (Table 1, entries 10−14). [14] *To our knowledge, this represents the first example of a highly efficient and reusable asymmetric organocatalyst with a chiral amine loading as low as 1 mol %.*
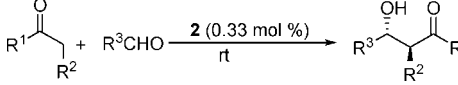
The scope of the hybrid catalyst was then examined with a series of aldehyde acceptors (Table 2) and aldol donors (Table 3). In the presence of 0.33 mol % of **3**, acetone reacted with various aromatic aldehydes to afford the desired products with high yields and enantioselectivity (Table 2). For comparison, the results obtained from the same reactions

(14) The formation of the bisaldol byproduct was increased. 1st run, 7%; 2nd run, 10%; 3rd run, 16%; 4th run, 16%; 5th run, 20%; 6th run, 18%.

Table 2. CA−POM Hybrid **3** Catalyzed Aldol Reactions of Acetone[a]

entry	R	time (h)	yield (%)[b]	ee (%)[c]
1	2-NO_2Ph	22	82 (78)	91 (86)
2	3-NO_2Ph	24	86 (73)	89 (90)
3	4-CF_3Ph	48	90 (77)	90 (90)
4	4-CNPh	48	86 (80)	91 (91)
5	4-ClPh	96	73 (64)	88 (90)
6	2-ClPh	72	91 (84)	92 (87)
7	3-BrPh	90	88 (46)	90 (90)
8	2-BrPh	72	92 (87)	90 (89)
9	Ph	6d	37 (14)	90 (89)
10	4-MeOPh	6d	11	87

[a] Reaction in neat acetone (0.5 M) with 0.33 mol % of **3** (equal to 1 mol % of chiral amine). Data in the parentheses refer to that obtained with catalyst **4** under identical conditions. [b] Isolated yields. [c] Determined by chiral HPLC.

using the nonsupported catalyst **4** were also listed in Table 2 (see also Table 3, entry 1). Obviously, catalyst **3** performed better in all the cases examined, again highlighting a synergistic effect of the POM supports. Other aldol donors including cyclic ketones, linear ketones, and aldehydes also worked very well in the catalysis of CA−POM, and the desired products were obtained with excellent yields and enantioselectivity (51−99% yield, 95 to >99% ee, Table 3). In the cases of cyclic ketones, catalyst **2** gave the best results in terms of both reactivity and stereoselectivity (for screening details, see Supporting Information).

Table 3. CA−POM Hybrid **2** or **3** Catalyzed Aldol Reactions of Various Aldol Donors[a]

entry	R^1, R^2	R^3	time (h)	yield (%)[b]	dr[c] anti/syn	ee (%)[d]
1	−(CH$_2$)$_4$−	4-NO_2Ph	16	99 (99)[e]	87:13 (80:20)[e]	99 (97)[e]
2	−(CH$_2$)$_4$−	3-NO_2Ph	19	94	83:17	>99
3	−(CH$_2$)$_4$−	2- NO_2Ph	24	92	87:13	98
4	−(CH$_2$)$_4$−	4-CF_3Ph	30	94	90:10	>99
5	−(CH$_2$)$_4$−	4-ClPh	96	95	88:12	98
6	−(CH$_2$)$_4$−	Ph	96	51	87:13	96
7	−(CH$_2$)$_3$−	4-NO_2Ph	6	86	77:23	95
8	−(CH$_2$)$_3$−	4-CNPh	19	91	75:25	94
9	Me, Me	4-NO_2Ph	19	59 (40)[f]	90:10	98 (94)[f]
10	H[g]	4-NO_2Ph	72	90	−	98

[a] Reaction with 10−20 equiv of ketones under neat conditions with 0.33 mol % of **2** (equal to 1 mol % of chiral amine). [b] Isolated yields. [c] Determined by ^{1}H NMR. [d] Determined by HPLC. [e] Reaction with catalyst **4** under identical conditions. [f] Data for the linear product in the presence of 1.67 mol % of **3** (equal to 5 mol % of chiral amine). [g] Isobutyraldehyde was used as a donor in the presence of 1.67 mol % of **3** (equal to 5 mol % of chiral amine).

Homogeneous or semihomogeneous solutions were generally observed in all the cases examined under neat conditions, proving the biphasic characteristics of the CA−POM hybrid catalysis.[15] The absolute configurations of the aldol products were determined to be the same as those obtained from the catalysis of **4** by comparison of their HPLC spectra; therefore, the reaction mode of the present catalysis should be consistent with that in previous publications.[1,12]

28 h, 91% yield, syn:anti = 94:6, 89% ee
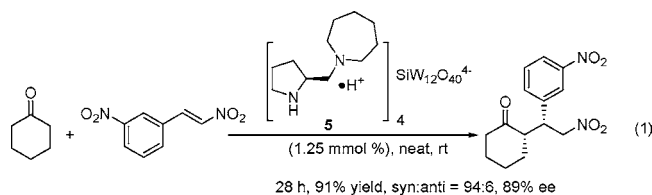
To further demonstrate the potentials of our strategy, CA−POM hybrids were tested in asymmetric Michael addition (eq 1). An initial quick screening identified our first hit, hybrid catalyst **5**, that catalyzed the reaction with as little as 5 mol % of chiral amine loading, affording the desired products with comparable yield (91%) and stereoselectivity (syn/anti, 94:6, 89% ee) but significantly improved activity over the corresponding nonsupported chiral−diamine analogue catalysts.[16] The catalyst can also be readily recycled by precipitation with ether and reused.

In conclusion, we have developed a new and very facile approach for deriving efficient and recoverable asymmetric enamine-based catalysts by combining chiral amines and the POM acids. The CA−POM hybrid catalysts demonstrated high activity, excellent stereoselectivity, and good reusability in asymmetric direct aldol reactions for a broad range of substrates. As low as 1 mol % of chiral amine loading was sufficient for effective catalysis. This study provided a new strategy to the development of practical asymmetric organocatalytic synthesis. Further applications of this strategy in other organocatalytic systems and the development of heterogeneous CA−POM catalysts[17] will be reported shortly.

Note Added after ASAP Publication. There were spelling errors in author names in refs 3h, 9, 11e, and 11g in the version published ASAP August 7, 2007; the revised version was published ASAP August 14, 2007.

Supporting Information Available: Experimental details and characterization of catalysts. This material is available free of charge via the Internet at http://pubs.acs.org.

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