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# Recyclable chiral diamine-polyoxometalate (POM) acids catalyzed asymmetric direct aldol reaction of aromatic aldehydes with long-chain aliphatic ketones

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### ABSTRACT

In this Letter, we studied the asymmetric direct aldol reaction of long-chain aliphatic ketones with aromatic aldehydes, using chiral diamine–polyoxometalate acid combined organocatalysts. High yields (up to 90%) and enantioselectivities (up to 90% ee) were obtained under solvent-free conditions with the optimized catalyst. Furthermore, such organocatalysts could be easily recycled and reused for four times without significant loss of reactivity and enantioselectivity.

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Aldol reaction is one of the most important carbon–carbon bond-forming reactions in organic chemistry.<sup>1</sup> Since the pioneering works on proline–catalyzed asymmetric direct aldol reactions were reported by List et al.<sup>2</sup>, organocatalysis has been proved to be a powerful tool for aldol reactions and great efforts have been devoted to design varieties of organocatalysts and to extend the substrate scopes.<sup>3</sup> Although significant progresses have been achieved in the organo-catalyzed asymmetric direct aldol reactions, there are still some limitations. For example, all of the aldol reactions needed high catalyst loading, and in most cases, the catalyst loading was up to 20 mol %, which inspired us to discover recyclable organocatalysts for the aldol reaction.

In asymmetric aldol reactions, substrates using simple ketones (such as acetone, cyclohexanone, and cyclopentanone) as donors have been extensively studied, while long-chain aliphatic ketones are less investigated, which can provide a useful chiral synthon for linear  $\beta$ -hydroxy carbonyl or polyoxygenated compounds in organic synthesis.<sup>1a,b,4</sup> Recently, examples of asymmetric aldol reactions using long-chain aliphatic ketones have been reported by Gong and co-workers,<sup>5</sup> in the presence of 20 mol % amino acid derived organocatalysts, affording corresponding products in high yields and enantioselectivities. Other groups used the long-chain aliphatic ketone just as an example in the studies on the substrate scope.<sup>6</sup> Here we report a solvent-free direct aldol reaction of aldehydes with long-chain aliphatic ketones catalyzed by chiral diamine-polyoxometalate (POM) acids combined catalysts. Such catalysts can afford the aldol products with high enantioselectivities (up to 90% ee). Moreover, such chiral diamine-POM combined organocatalysts can be recycled for four times without significant loss of reactivity and enantioselectivity.

Considering the recoverability of the catalyst, the chiral diamine-POM combined catalysts (1-5c; Fig. 1) were selected as the catalysts to investigate the target reaction. Initially, asymmetric direct aldol reaction of 2-octanone ( $\mathbf{6}$ ) with *p*-nitrobenzaldehyde ( $\mathbf{7}$ ) was selected as the model reaction for screening the catalysts and reaction conditions. The results were listed in Table 1. All the catalysts we used are powders and prepared from POM acids and chiral diamines in THF, which were developed by Luo and coworkers.<sup>7</sup> All catalysts gave the product **9** as the only regional isomer in the model reaction. Using H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> as POM acid, the reactions were carried out under solvent-free condition. As the poor solubility of catalysts 1-3 in the 2-octanone, the reactions using catalysts 1-3 were heterogeneous and performed with low yields and enantioselectivities (Table 1, entries 1–3). However, catalyst **4** and **5a** with the longer alkyl chain at the tertiary amine could gradually dissolve during the reaction, and the products with much higher yields and enantioselectivities (entries 4-5 vs entries 1-3) were obtained. The results indicated that the solubility of the catalysts plays an important role in the reaction. Different solvents were also screened for the reaction by utilizing **5a** as the catalyst. The results (entries 6–9) showed that the using of solvents such as



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Figure 1. Chiral diamine-POM combined organocatalysts.

Tab

#### Table 1

Direct ald ol reaction of 2-octanone with  $p\mbox{-nitrobenzaldehyde}$  under different reaction conditions a



Entry	Catalyst	Solvent	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	1	_	10	53
2	2	_	13	54
3	3	_	46	77
4	4	_	74	83
5	5a	_	90	90
6	5a <sup>d</sup>	DMSO	37	45
7	5a <sup>d</sup>	MeOH	40	50
8	5a <sup>d</sup>	$CH_2Cl_2$	42	43
9	5a <sup>e</sup>	H <sub>2</sub> O	85	82
10	5b	_	63	80
11	5c <sup>f</sup>	_	42	80
12	5a <sup>g</sup>	_	<5	_
13	5a <sup>h</sup>	-	96	86

<sup>a</sup> Reactions were performed with neat **6** (0.5 mL), 2.5 mol % catalyst, *p*-nitrobenzaldehyde **7** (0.5 mmol), at room temperature for 48 h, unless otherwise specified.

- <sup>b</sup> Isolated yields based on aldehydes.
- <sup>c</sup> Determined by chiral-phase HPLC.
- <sup>d</sup> Reactions were performed with **6** (0.1 mL), solvents (0.4 mL), 2.5 mol % catalyst **5a**, **7** (0.5 mmol), at rt for 48 h.
- e 0.125 mL H<sub>2</sub>O was added.
- <sup>f</sup> 1.875 mol % catalyst was used.
- <sup>g</sup> The reaction was performed at  $4 \,^{\circ}$ C.
- <sup>h</sup> The reaction was performed at 35 °C.

dimethylsulfoxide, methanol, dichloromethane and water had negative effect in the reaction, giving the product in lower yields and enantioselectivities. The catalysts **5b** and **5c**, using  $H_3PMo_{12}O_{40}$ and  $H_4SiW_{12}O_{40}$  as POM acids, respectively, were also examined in the reaction. Due to the poor solubility of catalysts, they also gave the products with lower yields and enantioselectivities (entries 10 and 11). Different reaction temperatures were then examined. Trace of the product could be detected because of the poor solubility of catalyst under 4 °C (entry 12). Higher yield but lower ee were obtained while the reaction was carried out under 35 °C (entry 13 vs entry 5).

Under the optimized conditions, the substrate scope using the catalyst **5a** was expanded to series of aromatic aldehyde acceptors

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Aldol reactions promoted by catalyst **5a**<sup>a</sup>



Entry	п	R	Product	Time (h)	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	8	2-NO <sub>2</sub> Ph	9a	48	87	89
2	8	3-NO <sub>2</sub> Ph	9b	48	93	82
3	8	3-CNPh	9c	48	81	89
4	8	2-CF₃Ph	9d	48	77	91
5	8	3-CF <sub>3</sub> Ph	9e	48	80	87
6	8	1-Naphtyl	9f	72	60	80
7	8	2-Naphtyl	9g	72	67	84
8	3	4-NO <sub>2</sub> Ph	9h	18	95	90
9 <sup>d</sup>	4	4-NO <sub>2</sub> Ph	9i	36	54	88
10	6	4-NO <sub>2</sub> Ph	9j	48	94	84
11	10	4-NO <sub>2</sub> Ph	9k	48	89	83
12	12	4-NO <sub>2</sub> Ph	91	48	80	84

 $^{\rm a}$  Reactions were performed with neat ketone (0.5 mL), 2.5 mol % catalyst, aromatic aldehyde (0.5 mmol), at room temperature.

<sup>b</sup> Isolated yields based on aldehydes.

<sup>c</sup> Determined by chiral-phase HPLC.

<sup>d</sup> The other isomer was obtained in 40% yield, >20:1 dr and 98% ee.

and ketone donors. In most cases, aldol products in high yields and excellent enantioselectivities were obtained. The nature of substituents on the aromatic aldehydes has great effect on the yield of the product. With the highly electron-withdrawing substituent, no matter at 2- or 3-position of the benzaldehyde, the reactions proceeded smoothly, giving the products in high yields (Table 2, entries 1-5). For the 1-naphthaldehyde and 2-naphthaldehyde, the yields of the products were slightly lower (entries 6 and 7). However, electron-rich aromatic aldehydes such as p-tolualdehyde and o-anisaldehyde failed to provide the desired products. Nevertheless, the products produced from nitrobenzaldehydes could be readily converted to hydroxyl substituted products (electron-rich products).8 The long-chain ketones with different length were next examined in reactions with *p*-nitrobenzaldehyde (entries 8-12). Except for 2-butanone, the reactions with all the other ketones gave single product in high yield and enantioselectivity. For the 2-butanone, two regional isomers were obtained. With the increasing of the chain length of the ketone, the enantioselectivity of the product decreased slightly.

#### Table 3

Investigation on the recyclability of the organocatalyst 5a<sup>a</sup>



Entry	Recycle	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	1st	87	90
2	2nd	85	89
3	3rd	85	88
4	4th	79	89
5	5th	60	85

<sup>a</sup> Reactions were performed with neat 2-octanone (0.5 mL), 2.5 mol % catalyst **5a**, *p*-nitrobenzaldehyde (0.5 mmol), at rt for 48 h.

<sup>b</sup> Isolated yields based on aldehyde.

<sup>c</sup> Determined by chiral-phase HPLC.

After the reaction, catalyst **5a** can be easily separated in the form of precipitation by adding diethyl ether and other low polar solvents. The reusability of the catalyst was evaluated using 2-octanone (**6**) with *p*-nitrobenzaldehyde (**7**). The results showed that the recovered catalyst **5a** could be reused for four times without obvious loss of enantioselectivity and its activity decreased slightly (Table 3, entries 1–5). After the 4th recycle, the activity began to decrease, which could be attributed to the loss of catalyst while recycling.

In summary, we have disclosed a direct asymmetric aldol reaction of long-chain aliphatic ketones with aromatic aldehydes, providing the product in high yields and enantioselectivities. The reactions were carried out under solvent-free conditions and the chiral diamine–polyoxometalate acids combined organocatalysts can be easily recovered and reused for four times with nearly unchanged enantioselectivity and reactivity.

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# Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.053.

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