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Recyclable enamine catalysts for asymmetric direct cross-aldol reaction of aldehydes in emulsion media†

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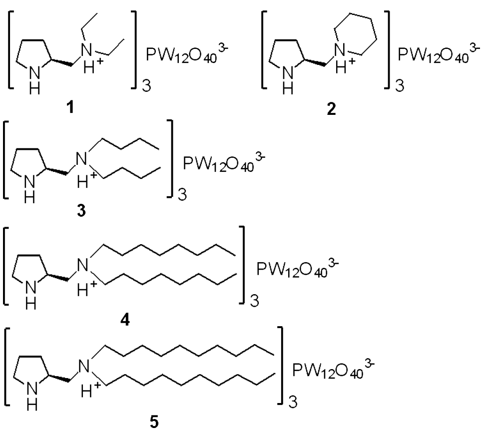
Highly diastereo- and enantioselective cross-aldol reactions of aldehydes (>20 : 1 dr, 99% ee), catalyzed by chiral diamine-polyoxometalate acid combined enamine catalysts in emulsion media, are reported. This type of catalysts can be recycled several times without significant deterioration of activity and selectivity.

Over the past few decades, asymmetric catalysis has been developed into a powerful methodology to obtain chiral compounds with a broad scope of catalytic reactions, high enantioselectivity and activity.[1] Despite this remarkable success, only a few examples of asymmetric catalytic processes have been developed in industry, which is partly due to the high cost of chiral catalysts. Therefore, the development of heterogeneous catalytic systems to achieve the separation and the efficient recycling of expensive chiral catalysts is highly desirable.[2] Recently, catalysis in emulsion systems has attracted much attention as a promising strategy to improve the mass-diffusion limitation in liquid multiphase systems.[3] Various catalytic systems were designed to promote the formation of an emulsion system for the organocatalytic asymmetric direct aldol reactions in water.[4] The previous work in this group reported surfactant-type catalysts, based on quaternary ammonium polyoxometalates (POMs), which can be assembled in emulsion droplets, and showed remarkably high selectivity and activity in the oxidation of organic molecules.[5] The POM anion acting as a novel chiral catalyst support was reported by Luo and coworkers,[4k,6] and the biphasic catalysts afforded the desired products with high yields and enantioselectivities in the aldol reaction of simple ketones with aromatic aldehydes and the Michael addition of cyclohexanone to nitroalkene.

Asymmetric cross-aldol reactions of aldehydes provide an attractive strategy for the construction of α-substituted β-hydroxy aldehydes, which are important synthons in the synthesis of polypropionate and polyacetate products. Despite all that, few examples of highly diastereo- and enantio-selective cross-aldol reactions of aliphatic aldehydes with aromatic aldehydes were reported.[4d,7] The original version of this reaction carried out in organic solvent was reported by MacMillan.[7c] After that, the Hayashi group reported the same reaction catalyzed by 4-substituted proline in the presence of water.[4d] And then, a diastereoselectivity reversed type of cross-aldol reaction was achieved by the Marouka group[7l,7m] and Luo group separately.[7n] However, there were very few recyclable heterogeneous catalytic systems to achieve the highly diastereo- and enantioselective cross-aldol reaction of aliphatic aldehydes with aromatic aldehydes.[7e,7j] So it is highly desired to explore readily available and recyclable catalysts to achieve efficient asymmetric cross-aldol reaction in emulsion media.

In this paper, we report highly diastereo- and enantioselective asymmetric cross-aldol reactions of aldehydes in the presence of water, using recyclable chiral diamine-POM combined enamine catalysts. Our study indicates that a metastable emulsion formed in the organic-aqueous biphasic systems is mainly responsible for the high reactivity and enantioselectivity.

Several enamine catalysts composed of the POM acid ($H_3PW_{12}O_{40}$) and chiral diamines with different lengths of alkyl chain (Scheme 1) were prepared. The quaternary ammonium group with different alkyl chains in these amphiphilic catalysts have different hydrophilic-lipophilic balance values and could



Scheme 1 Chiral diamine-POM combined enamine catalysts with different length of alkyl chain.

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perform as surfactants in the formation of an emulsion. So, whether an emulsion formed or not in the real reaction conditions was then investigated. The mixtures with catalysts **1** and **2** carrying short alkyl chains cannot form the emulsion, even after stirring overnight. However, when catalyst **3** was added, the mixture can form an unstable emulsion (Fig. S2, see ESI†). The mixture using catalyst **4** or **5** with a longer alkyl chain formed much more stable emulsions, which was confirmed by the light microscopic image. The emulsion droplets were observed to be spherical particles with an average size below 50 μm (Fig. 1).

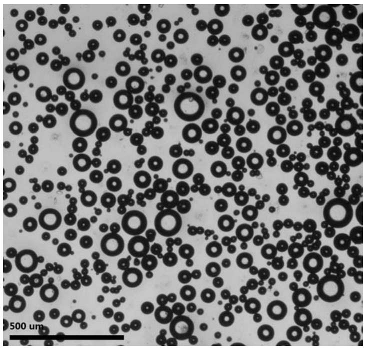
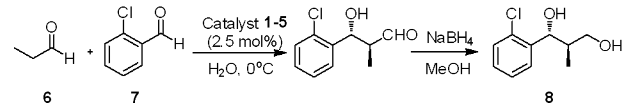


Fig. 1 Light microscopic image was taken after the mixture of 360 μL propionaldehyde, 112 μL 2-chlorobenzaldehyde (1.0 mmol), 2.5 mol% catalyst **5** and 162 μL water (9 mmol) was stirred for 1 h.

Catalysts **1–5** were then tested for the cross-aldol reaction of aldehydes in the aqueous phase. The propionaldehyde (**6**) and 2-chlorobenzaldehyde (**7**) were selected as the model substrates, and the reactions were carried out under 0 °C with a 2.5 mol% catalyst loading. The results were shown in Table 1. All the catalysts could catalyze the reaction and achieve excellent enantioselectivities. However, the reactivities for the cross-aldol reaction of aldehydes were dramatically enhanced from 36% to 98% with the different lengths of alkyl chain from the shortest (**1**) to the longest (**5**) (Table 1, entries 1–5). The results clearly indicate that the emulsion state is critically important for achieving high reactivity in the cross-aldol reaction of aldehydes, and a metastable emulsion can efficiently mix the organic phase and aqueous phase.[8] The amounts of water were also optimized using catalyst **5** (entries 6–8). If the reaction was performed under neat conditions, the cross-aldol product with 73% yield and slightly decreased diastereo- and enantioselectivities was obtained (entry 8). When 4.5 equivalents of water were added, the activity of the cross-aldol reaction was enhanced (entry 7 *vs.* entry 8). The adding of more water decreased the activity and selectivity of the reaction (entry 6). When 9 equivalents of water were added to the reaction mixture, the reaction could afford the corresponding anti-product **8** in 97% ee and nearly quantitative yield.

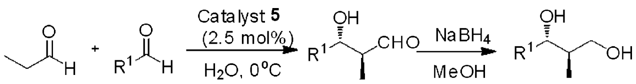
Table 1 Screening the catalysts and amount of water for the cross-aldol reaction of propionaldehyde **6** and 2-chlorobenzaldehyde **7**[a]



Entry	Catalyst	Yield[b] (%)	*Anti*/*Syn*[c]	ee (%)[d]
1	**1**	36	9 : 1	97
2	**2**	40	>20 : 1	99
3	**3**	48	11 : 1	98
4	**4**	78	16 : 1	98
5	**5**	98	>20 : 1	97
6[e]	**5**	57	15 : 1	90
7[f]	**5**	90	19 : 1	94
8[g]	**5**	73	20 : 1	96

[a] Reaction conditions: 360 μL propionaldehyde (5.0 mmol), 1.0 mmol 2-chlorobenzaldehyde, 2.5 mol% catalyst, 162 μL water (9 eq.), 0 °C, 72 h. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy of crude products. [d] Determined by chiral HPLC after conversion into the monobenzoyl ester (see ESI†). [e] 18 eq. of water was added. [f] 4.5 eq. of water was added. [g] No water was added.

Table 2 Direct cross-aldol reaction in the emulsion media promoted by catalyst **5**[a]



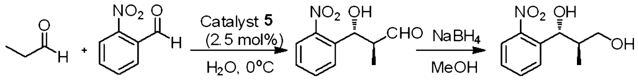
Entry	R^1	Time (h)	Yield[b] (%)	*Anti*/*Syn*[c]	ee[d] (%)
1	4-Nitrophenyl	24	92	>20 : 1	99
2	3-Nitrophenyl	24	83	>20 : 1	98
3	2-Nitrophenyl	24	94	>20 : 1	98
4	2-Methoxyphenyl	80	73	14 : 1	95
5	Phenyl	80	80	>20 : 1	99
6	1-Naphtyl	80	43	>20 : 1	99
7	4-Tolyl	80	70	16 : 1	98
8	4-Fluorophenyl	120	61	>20 : 1	99
9	4-Chlorophenyl	120	79	>20 : 1	96

[a] Reaction conditions: 360 μL propionaldehyde, 1.0 mmol aromatic aldehyde, 2.5 mol% catalyst **5**, 162 μL water, 0 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy of crude products. [d] Determined by chiral HPLC after conversion into the corresponding benzoyl ester (see ESI†).

The scope of cross-aldol reactions of aldehydes using the catalyst **5** was expanded to a series of aromatic aldehyde acceptors. In all the cases, cross-aldol products with excellent diastereo- and enantioselectivities were attained. The substituent of the aromatic aldehyde has great effect on the yield of the products. With the nitro group substituent, no matter at which (2-, 3- or 4-) position of the benzaldehyde, the reaction proceeded smoothly, giving the product in high yield (Table 2, entries 1–3). For the 1-naphthaldehyde, the cross-aldol product with only moderate yield was obtained, even prolonging the reaction time to 80 h (entry 6). When the other aromatic aldehydes carrying either an electron-withdrawing group or electron-donating group were selected as acceptors, the reactions could afford the corresponding products with moderate reactivities and excellent enantioselectivities by prolonging the reaction time (entries 4, 5, 7–9).

Recycling of the present catalyst **5** was also investigated (Table 3). Using 2-nitrobenzaldehyde and propionaldehyde as substrates, catalyst **5** can be easily precipitated and recycled by adding methanol, and we did not observe significant deterioration of activity and selectivity in the recovered catalyst after three times of use (entries 1–3). From the 4th recycle, reactivity and enantioselectivity of the reaction began to drop slowly, this may be attributed to the loss of catalyst while recycling (entries 4–6). Though the catalyst **5** was carefully recycled, the catalyst could not be recycled completely because of its solubility in methanol and its loss while recycling.

Table 3 The recyclability of the catalyst **5**[a]



Entry	Recycle	Yield[b] (%)	*Anti*/*Syn*	ee (%)[c]
1	1st	93	>20 : 1	97
2	2nd	90	>20 : 1	97
3	3rd	92	>20 : 1	98
4	4th	87	>20 : 1	93
5	5th	73	>20 : 1	91
6	6th	61	>20 : 1	90

[a] Reaction conditions: 360 μL propionaldehyde, 1.0 mmol 2-nitrobenzaldehyde, 2.5 mol% catalyst **5**, 162 μL water, 0 °C, 24 h. [b] Isolated yield. [c] Determined by chiral HPLC.

In conclusion, we realized the highly diastereo- and enantioselective cross-aldol reaction of aldehydes in the presence of water (>20 : 1 dr, 99% ee), using recyclable chiral diamine-POM combined enamine catalysts. Organic co-solvents were not neceassary in the reaction. The emulsion formed in the reactions is proposed to be critical for the enhanced reactivity, diastereo- and enantioselectivity. Our findings may provide a general and efficient approach for asymmetric synthesis using emulsion as reaction media.

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