

Synthesis of PVC-TEPA-Supported Proline Derivative and Its Catalytic Behavior in the Direct Asymmetric Aldol Reaction

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Received 5 March 2008; accepted 8 December 2008

DOI 10.1002/app.29892

Published online 28 May 2010 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: PVC-TEPA-supported L-proline catalyst has been synthesized and characterized by IR. It is developed as an efficient catalyst for the direct asymmetric aldol reaction of unmodified ketones with various aldehydes in the presence of water at 0°C. The corresponding aldol products were obtained with high yields (up to 94%) and good enantioselectivities (up to 97% ee) on optimized condi-

tions. Recycling investigations have shown that this material can be reused without loss of catalytic activity and stereoselectivity for at least 15 cycles. © 2010 Wiley Periodicals, Inc. *J Appl Polym Sci* 118: 1020–1026, 2010

Key words: organocatalysis; polymer-supported catalyst; asymmetric aldol reaction; PVC-TEPA; proline

INTRODUCTION

The asymmetric aldol reaction is one of the most powerful tools for the synthesis of complex chiral polyhydroxy compounds.¹ Biocatalysts² and transition metal complexes^{3–5} were first used as catalyst for asymmetric aldol reaction. These traditional catalysts showed high activities and excellent selectivities.^{6,7} However, biocatalyst and transition metal complexes are expensive and could cause environment pollution. Recent research by Barbas and List et al. proved L-proline to be a powerful catalyst in the asymmetric intermolecular direct aldol reaction and developed the concept of small organic molecules as catalysts. Then, proline and its derivatives were used in the asymmetric reactions such as Aldol, Mannich,^{8,9} α -Amination,¹⁰ Aza-Diels-Alder¹¹ reaction, etc.

With the development of green chemistry, one powerful way of promoting organic reaction is the use of highly active, reusable polymer-supported catalyst in water. Polymer-supported catalysts having high activity and selectivity are currently attracting great interests because they can be easily recycled. Initially, Benaglia et al.¹² studied asymmetric aldol reaction by using PEG-supported proline derivative as catalyst, a yield of 81% with ee value

of 98% of the corresponding product was obtained and the catalyst were reused for three times. Subsequently, more and more polymers were used as catalyst support and the heterogenous catalysts including PEG-PS-supported peptide,¹³ polystyrene-supported proline,¹⁴ dendritic catalysts¹⁵ were obtained. All these catalysts showed good catalytic activities for asymmetric aldol reactions, but the preparations of them involved many steps and these polymers were expensive.

In this article, we focus on the studies of the asymmetric aldol reaction catalyzed by simple polymer-supported organocatalyst in water. We have previously synthesized polyvinyl chloride (PVC)–polyethylene–polyamine-supported palladium complex, which could efficiently catalyze in the Heck reaction, and the catalyst was recovered for 12 times without loss of catalytic activities.¹⁶ Herein, PVC–polyethylene polyamine resin-supported proline was proposed to be an efficient catalyst for asymmetric aldol reaction.

EXPERIMENTAL

Materials and equipment

Cyclohexanone was redistilled before use. The common solvents were used directly without further purification. All other reagents were obtained from commercial sources and were used as received.

IR spectra were performed on an Avatar360 Fourier transform infrared (FTIR) spectrometer

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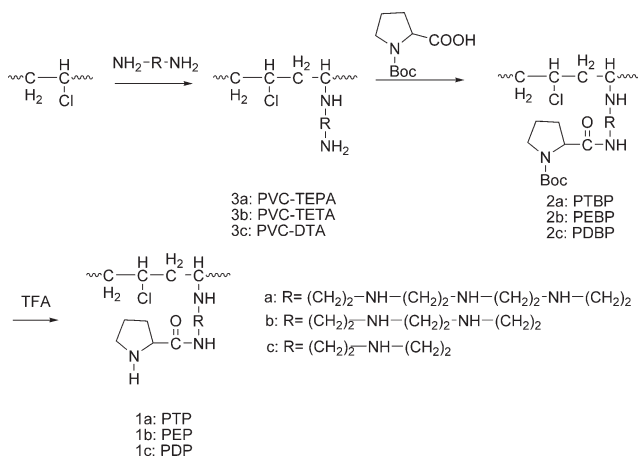
Contract grant sponsor: Henan University.

(Nicolet Company, USA). Thin-layer chromatography was performed on silica gel 60 F₂₅₄ glass backed plates. Melting points were measured on an X₄-type micromelting point apparatus and were uncorrected. ¹H-NMR spectra were recorded on a Varian Mercury-300 spectrometer in necessary D-reagents with tetramethylsilane as an internal standard. The maximum wavelength values were recorded with a TU-1901-type UV-spectrophotometer. Enantiomeric excess values of aldol products were determined by analytical HPLC using Daicel Chiralpak AD or AS analytical columns with 2-propanol in hexanes as the eluent.

Preparation of catalyst

It was presumed that polymer-supported L-prolinamide by amidation of L-proline and PVC-polyethylene polyamine may efficiently catalyze the asymmetric aldol reaction. Polymer-supported proline derivative was prepared from the commercially available Boc-L-Pro-OH and PVC according to the synthetic route shown in Scheme 1.

PVC (2.0 g) was added into tetraethylenepentamine (triethylenetetramine, diethylenetriamine) (20 mL) in a round-bottomed flask, and then the mixture was stirred at 80°C in the air for 2 h. After being cooled to room temperature, the reaction mixture was filtered and washed with plenty of H₂O and dried at 80°C in the air for 12 h to give brown polyvinyl chloride-tetraethylenepentamine (abbreviated as PVC-TEPA) or polyvinyl chloride-triethylenetetramine (abbreviated as PVC-TETA) or polyvinyl chloride-diethylenetriamine (abbreviated as PVC-DTA). Polyvinyl chloride-polyethylene polyamine (2 g), Boc-Pro-OH (2 g), and 2 mL of *N,N'*-diisopropylcarbodiimide (DIC) were added in a three-mouth flask, and then 10 mL of DMF was added and stirred at room temperature for 3 days. The



Scheme 1 Synthesis of polymer-supported L-proline.

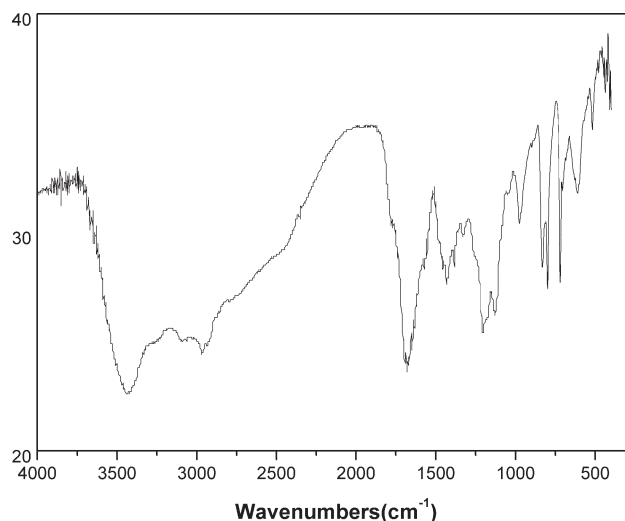


Figure 1 FTIR spectroscopy of PTP.

mixture was filtered and washed with plenty of H₂O and then dried at 30°C in vacuum for 24 h to give pure PVC-TEPA (PVC-TETA, PVC-DTA)-supported Boc-proline (PTBP, PEBP, PDBP). 2 g PTBP (PEBP, PDBP) and 2 mL TFA were added to 10 mL of CH₂Cl₂ in a three-mouth flask and stirred at room temperature for 3 h. The mixture was filtered and washed with plenty of H₂O and then dried at 30°C in vacuum for 24 h. The three corresponding pure catalysts (PTP, PEP, PDP) were obtained.

Characterization of catalyst

As shown in Figure 1, IR spectra of PTP shows a peak at 1685 cm⁻¹, which is assigned to stretch vibration absorption of C=O. This indicated that proline had been supported on the PVC-TEPA. The loaded content (LC) and a grafting rate were obtained by eqs. (1) and (2), respectively.

$$LC = \frac{(W_{PTP} - W_{PVC-TEPA}) / (M_{Pro} - 18)}{W_{PTP}} \quad (1)$$

where $W_{PVC-TEPA}$ is the mass of PVC-TEPA; M_{Pro} is the molecular weight of proline; W_{PTP} is the mass of PTP.

$$GR = \frac{LC_{\text{practical value}}}{LC_{\text{theoretical value}}} \times 100\% \quad (2)$$

$LC_{\text{practical value}}$ is the value of eq. (1) and $LC_{\text{theoretical value}}$ is the mole number of proline in PTP (1 g).

General procedure for aldol reactions

To a solution of aldehyde acceptor (0.5 mmol) and ketone donor (3 mmol) in 2 mL water, catalyst (10

TABLE I
Crosslinking Degree of PVC-TEPA^a

Entry	Time (h)	Mass of PVC before reaction (g)	Mass of PVC after reaction (g)	Weight gain (g)	Gain ratio ^b (%)
1	1	1.0021	1.0910	0.0889	8.87
2	2	1.0017	1.1242	0.1225	12.22
3	3	1.0009	1.1059	0.1047	10.46
4	4	1.0006	1.0921	0.0915	9.14
5	5	1.0043	1.0577	0.0534	5.32
6	6	1.0021	1.0482	0.0463	4.62
7	7	1.0022	1.0260	0.0238	2.37
8	8	1.0010	0.9989	-0.0021	-0.21
9	9	1.0013	0.9911	-0.0102	-1.02

^a The reaction was performed with PVC and 20 mL tetraethylenepentamine at 80°C.

^b Gain ratio = weight gain/the mass of PVC before reaction.

mol %) and base (0.5 mmol) were added and stirred at 0°C for required time. The mixture was extracted with ethyl acetate (10 mL ×3). The combined organic layers were washed with saturated brine, dried over Na₂SO₄, and concentrated. The residue was subjected directly to flash silica gel chromatographic column using petroleum-ethyl acetate as the eluent to afford the corresponding pure aldol adducts.

Reuse of catalyst PTP

p-Nitrobenzaldehyde (0.5 mmol), 3 mmol cyclohexanone with catalyst PTP (10 mol %), 0.5 mmol of Et₃N, 2 mL of water were added in a round-bottomed flask and stirred at 0°C. After the reaction was completed, the mixture was extracted with ethyl acetate (10 mL ×3). The combined organic layer was washed with saturated brine, dried over Na₂SO₄, and concentrated. The residue was subjected directly to flash silica gel chromatographic column using petroleum-ethyl acetate as the eluent to afford the aldol adducts. *p*-Nitrobenzaldehyde (0.5 mmol), 3 mmol cyclohexanone, and 0.5 mmol of Et₃N were added to the water phase. Then, the catalyst was reused for the first time. The others followed as earlier.

RESULTS AND DISCUSSION

Crosslinking degree of PVC-TEPA

In the synthesis of PVC-TEPA, the matrix may be crosslinking. Crosslinking degree of PVC-TEPA was investigated by the change of polymer mass. When a repeating unit of PVC reacts with TEPA, matrix is noncrosslinked. The mass of polymer increases after reaction. When matrix starts to crosslink, weight gain increases, but gain ratio decreases after reaction. Crosslinking degree of PVC-TEPA was investigated in this way. The results are listed in Table I. The gain ratio increased in 2 h, and the matrix was

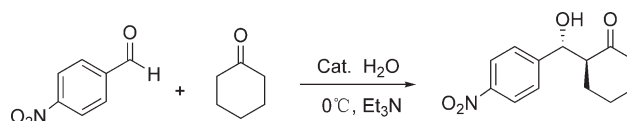
noncrosslinked. After 2 h, the matrix starts to crosslink. Therefore, the matrix in 2 h was used.

Screening of catalysts

The catalytic efficiency of polymer-supported L-proline derivatives was examined by the direct asymmetric aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde in the presence of 50 mol % catalyst at 0°C (Scheme 2), and the results are listed in Table II. The polymer-supported L-proline derivatives provided good enantioselectivities in the aldol reaction in the presence of water. Size of the side chains in polymer significantly influenced the catalytic efficiency. For example, the catalyst 1a containing the largest side chain gave the best result with 86% ee (Entry 1). L-proline and 4-hydroxyproline cannot catalyze asymmetric aldol reaction in water, whereas the heterogeneous catalysts (1a, 1b, 1c) showed good performance in terms of yield and enantioselectivity.

Optimization of catalyst

PTP had been optimized by changing the amount of DIC and reaction time. It can be seen from Table III that the highest LC (2.46 mmol/g) appeared when the amount of DIC was 2 mL and reaction time was 3 days.



Scheme 2 The aldol reaction of *p*-nitrobenzaldehyde with cyclohexanone.

TABLE II
Screening of Catalysts in the Direct Asymmetric Aldol Reaction of Cyclohexanone (4a) with *p*-Nitrobenzaldehyde (5b) in the Presence of Water^a

Entry	Cat.	Time (h)	Yield ^b (%)	TOF (h ⁻¹) ^c	dr ^d anti : syn	ee ^d anti (%)
1	1a	44	91	0.2	84 : 16	86%
2	1b	40	62	0.15	86 : 14	74%
3	1c	40	57	0.14	92 : 8	70%
4	L-Proline	48	nd ^e	–	–	–
5	4-Hydroxyproline	48	nd ^e	–	–	–

^a The reaction was performed at 0.5 mmol scale of aldehyde and 0.5 mmol Et₃N in water (2 mL) in the presence of 50 mol % catalyst.

^b Isolated yield of the corresponding product.

^c TOF = moles of corresponding product/moles of catalyst per hour.

^d Determined by chiral-phase HPLC.

^e nd = not detected.

Optimization of reaction conditions

The catalytic activity of polymer-supported L-proline was tested in the model reaction of *p*-nitrobenzaldehyde with cyclohexanone in the presence of 10 mol % catalyst at 0°C in the presence of water (Scheme 2). It was found that the reaction could be catalyzed and a yield of 54% with an ee value of 91% was gained; however, a long time of 240 h was needed (Entry 1, Table VI). Base can accelerate asymmetric aldol reaction, and thus triethylamine (Et₃N) was used as an additive to accelerate the reaction.¹⁷ The influence of the quantity of catalyst was investigated in the presence of Et₃N at 0°C (Table IV).

From Table IV it can be seen that the catalyst gave good enantioselectivities (>84%), whereas the yields varied (range from 68 to 91%). The highest yield (91%) was gained when catalyst with an amount of 50 mol % was used; however, the enantiomeric excess was 86% (Entry 1, Table I). When the amount of catalyst decreased to 10 mol %, the highest enantioselectivity (92%) appeared (Entry 5, Table I). To our surprise, when the amount of catalyst was decreased to 2.5 mol %, the yield of 68%, ee value of 87%, and the dr value (9 : 91) was obtained in 72 h. The TOF increased with decreasing amount of PTP. It may be attributed to the decrease of the molar ratio of base and catalyst. Considering both catalytic activity and selectivity, the catalyst amount of 10 mol % was chosen for the further research.

Another possibility to enhance the conversion is variation of the amount of ketone. In the presence of 10 mol % catalyst, the direct asymmetric aldol reaction of 4-nitrobenzaldehyde with different amounts of cyclohexanone was carried out. As shown in Table V, the best result (yield of 79%, anti : syn ratio of 91 : 9, ee value of 94%) was gained, when the amount of cyclohexanone was 3 mmol. Therefore, the best molar ratio of aldehyde to ketone was 1 : 6 (the amount of cyclohexanone was 3 mmol).

The critical roles and effects of base in the asymmetric aldol reaction were also investigated; 4-nitrobenzaldehyde as aldol acceptor and cyclohexanone as aldol donor of model reaction were used. As shown in Table VI, a yield of 54% was obtained after 240 h in the absence of base (Entry 1). Compared with Entry 1, the TOF obviously increased with the introduction of the base (Entry 2). Similar to adding Et₃N and catalyst (Entry 2), the TOF was 0.12, ee was 0% without catalyst only base (Entry 3), and base can accelerate the reaction. Therefore, some bases were tested. From Table VI, bases did not increase selectivity but enhance the reaction rate (Entries 4–7). Et₃N was the best amine promoter; the reason could be that it had more strong basic property and less steric hindrance.

The performance of the catalyst in the direct aldol reaction was dramatically influenced by the media.^{18,19} Some common organic solvents and organic–water mixed solvents were therefore examined for the aldol reaction of 4-nitrobenzaldehyde with cyclohexanone. The related results are presented in Table IV. Surprisingly, the

TABLE III
Optimization of Catalyst by Changing the Amount of DIC and Reaction Time^a

Entry	The amount of DIC (mL)	Time (d)	LC (mmol/g)
1	1	3	2.12
2	2	3	2.46
3	3	3	2.43
4	2	1	1.29
5	2	2	2.07
6	2	4	2.44

^a Reaction was performed at 2 g PVC-TEPA and 10 equiv of ketone with catalyst and base (0.5 mmol) in 2 mL water.

TABLE IV
Effect of Catalyst Loading on the Aldol Reaction of *p*-Nitrobenzaldehyde with Cyclohexanone^a

Entry	Amount of PTP (mol %)	Time (h)	Yield (%) ^b	TOF (h ⁻¹) ^c	dr ^d anti : syn	ee ^d anti (%)
1	50	44	91	0.04	84 : 16	86
2	40	45	86	0.05	84 : 16	90
3	30	46	73	0.05	86 : 14	88
4	20	52	54	0.05	87 : 13	89
5	10	48	82	0.17	87 : 13	92
6	5	72	71	0.2	89 : 11	84
7	2.5	72	68	0.38	91 : 9	87

^a Reaction was performed at 0.5 mmol scale of aldehyde and 10 equiv of ketone with catalyst and base (0.5 mmol) in 2 mL water.

^b Isolated yield of the corresponding product.

^c TOF = moles of corresponding product/moles of catalyst per hour.

^d Determined by chiral-phase HPLC.

TABLE V
Effects of the Amount of Cyclohexanone on the Aldol Reaction of *p*-Nitrobenzaldehyde with Cyclohexanone^a

Entry	The amount of cyclohexanone (mmol)	Time (h)	Yield (%) ^b	TOF (h ⁻¹) ^c	dr ^d anti : syn	ee ^d anti (%)
1	0.5	72	38	0.05	78 : 22	68
2	1	72	41	0.06	90 : 10	67
3	2	72	53	0.07	90 : 10	86
4	3	72	79	0.11	91 : 9	94
5	4	72	80	0.11	95 : 5	91

^a The reaction was performed at 0.5 mmol scale of aldehyde and 0.5 mmol Et₃N in water (2 mL) in the presence of 10 mol % PTP.

^b Isolated yield of the corresponding product.

^c TOF = moles of corresponding product/moles of catalyst per hour.

^d Determined by chiral-phase HPLC.

TABLE VI
Effects of Different Bases on the Aldol Reaction of *p*-Nitrobenzaldehyde with Cyclohexanone^a

Entry ^a	Cat.	Base ^b	Time (h)	Yield (%) ^c	TOF (h ⁻¹) ^d	dr ^e anti : syn	ee ^e anti (%)
1	1a	–	240	54	0.02	5 : 1 ^f	91
2	1a	Et ₃ N	72	79	0.11	91 : 9	94
3	–	Et ₃ N	56	68	0.12	1 : 1	0
4	1a	NMM	28	89	0.32	83 : 17	88
5	1a	DABCO	46	78	0.17	67 : 33	74
6	1a	HMTA	46	79	0.17	80 : 20	89
7	1a	1-Methyl-pyrrolidine	46	62	0.13	92 : 8	70

^a Reaction was performed at 0.5 mmol scale of the aldehyde, 6 equiv of ketone with catalyst (10 mol %), and base (0.5 mmol) in 2 mL water.

^b NMM: *N*-methylmorpholine; DABCO: 1,4-diazabicyclo[2,2,2]octane; and HMTA: hexamethylenetetramine.

^c Isolated yield of the corresponding product.

^d TOF = moles of corresponding product/moles of catalyst per hour.

^e Determined by chiral-phase HPLC.

^f Determined by ¹H-NMR of the crude product.

TABLE VII
Solvent Effect on the Aldol Reaction of *p*-Nitrobenzaldehyde with Cyclohexanone^a

Entry	Solvent	Time (h)	Yield (%) ^b	TOF (h ⁻¹) ^c	dr ^d anti : syn	ee ^d anti (%)
1	DMSO	16	28	0.17	74 : 26	55
2	DMF	12	41	0.34	63 : 37	25
3	THF	18	30	0.16	84 : 16	65
4	Ethanol	18	45	0.25	74 : 26	44
5	<i>n</i> -Hexane	18	34	0.19	64 : 36	65
6	H ₂ O + DMSO (v/v = 1 : 1)	14	62	0.44	67 : 33	87
7	H ₂ O + DMF (v/v = 1 : 1)	16	50	0.31	81 : 19	97

^a Reaction was performed at 0.5 mmol scale of the aldehyde, 6 equiv of ketone with catalyst (10 mol %), and base (0.5 mmol Et₃N) in 2 mL solvent.

^b Isolated yield of the corresponding product.

^c TOF = moles of corresponding product/moles of catalyst per hour.

^d Determined by chiral-phase HPLC.

enantioselectivity was excellent (97% of ee, Entry 7 Table VII) using DMF–water mixed solvent. It can be found that better results in terms of both yields and enantioselectivities were obtained in organic–water mixed solvents than in organic solvents. The reaction rate was higher in organic solvents and mixed solvents than in water. It may be due to the fact that organic solvents and mixed solvents have better solubility. The catalyst in water could form a hydrophobic pocket on the inner surface of the resin, and the hydrophilic proline lie at the interface.^{20,21} Such a microenvironment promotes the aldol reaction with high enantioselectivity.²² In Table VII, H₂O + DMF showed better activity, the reason could be coeffect of better solubility of DMF and the three-dimensional hydrogen-bonded network system of bulk water. The mechanism is under research. As shown in Table VII, catalyst PTP displayed better catalytic activity in the presence of water.

Substrate generality

Under the optimized reaction conditions, the application of polymer-supported L-proline in direct asymmetric intermolecular aldol reaction between different acceptors and donors was further explored. A series of aromatic aldehyde acceptors and some ketone donors were examined (Scheme 3). Water as reaction solvent offers a series of advantages over organic solvents, such as safety, convenience, economy, and environmental benign, and was selected as reaction solvent in following experiments. The data were summarized in Table VIII.

As shown in Table VIII, most of the studied aldol reactions catalyzed by catalyst PTP in the presence of water afforded high yields and good selectivities. Three different aldol donors were used (cyclohexanone, cyclopentanone, and acetone), and the best result (94% ee) appeared when cyclohexanone was

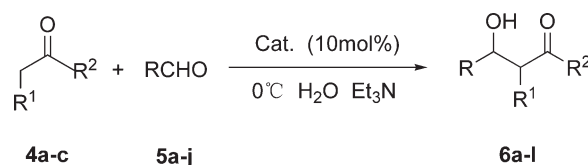
used as donor and 4-nitrobenzaldehyde was used as acceptor. Especially, when cyclohexanone was the donor, the reactions with a series of aldehydes, including aromatic, heteroaromatic, and unsaturated aldehydes performed well (Entries 1–11). It can be concluded from the results that the aromatic aldehydes with 2-position substituted generally gave excellent diastereoselectivities (Entries 4, 6, and 8). We can also summarize that the aromatic aldehydes with electron-withdrawing groups usually afforded higher enantioselectivities.

Recycling of catalyst

An important virtue of polymer-supported catalyst is that the catalyst can be reused. In this way, the amount of catalyst can be effectively decreased. Therefore, we carried out recycling studies. Water, an environmental-friendly solvent, was selected as reaction media. The catalyst PTP was reused for 15 times by extraction without loss of the catalytic activity (Scheme 3, Table IX).

CONCLUSION

In conclusion, some novel polymer-supported L-proline catalysts have been easily synthesized by using inexpensive support and were applied for the asymmetric aldol reaction. The PTP displayed high catalytic



Scheme 3 The aldol reaction of aliphatic and cyclic ketones with various aldehydes.

TABLE VIII
Reaction of Aliphatic and Cyclic Ketones (4a–c) with Various Aldehydes (5a–k)
Catalyzed by Catalyst (PTP) in the Presence of Water^a

Entry	R ¹ , R ²	R	Product	Time (h)	Yield ^b (%)	TOF (h ⁻¹) ^c	dr ^d anti : syn	ee ^d anti (%)
1	–(CH ₂) ₄ – (4a)	Pyridin-4-yl (5a)	6a	20	89	0.44	76 : 24	52
2	–(CH ₂) ₄ – (4a)	4-Nitrophenyl (5b)	6b	72	69	0.09	91 : 9	94
3	–(CH ₂) ₄ – (4a)	3-Nitrophenyl (5c)	6c	24	52	0.22	83 : 17	72
4	–(CH ₂) ₄ – (4a)	2-Nitrophenyl (5d)	6d	24	60	0.25	>99 : 1	86
5	–(CH ₂) ₄ – (4a)	4-Cyanophenyl (5e)	6e	192	64	0.03	75 : 25	68
6	–(CH ₂) ₄ – (4a)	4-Methoxyphenyl (5f)	6f	192	28	0.02	92 : 8	68
7	–(CH ₂) ₄ – (4a)	2-Chlorophenyl (5g)	6g	190	39	0.02	99 : 1	79
8	–(CH ₂) ₄ – (4a)	5-Nitrofuran (5h)	6h	20	93	0.47	76 : 24	71
9	–(CH ₂) ₄ – (4a)	Styryl (5i)	6i	190	44	0.23	95 : 5	77
10	–(CH ₂) ₄ – (4a)	2,4-dinitrophenyl (5j)	6j	72	66	0.92	92 : 8	84
11	H, CH ₃ (4b)	4-Nitrophenyl (5b)	6k	24	72	0.3	–	16
12	–(CH ₂) ₃ – (4c)	4-Nitrophenyl (5b)	6l	40	56	0.14	39 : 61	32

^a Reaction was performed at 0.5 mmol scale of the aldehyde, 6 equiv of ketone with catalyst PTP (10 mol % Et₃N), and base (0.5 mmol) in 2 mL solvent.

^b Isolated yield of the corresponding product.

^c TOF = moles of corresponding product/moles of catalyst per hour.

^d Determined by chiral-phase HPLC.

activity and selectivity in water. The corresponding products were gained with good yields (up to 94%), excellent diastereoselectivities (up to 99 : 1), and enantioselectivities (up to 97%). The polymer-supported catalyst PTP can be reused by extraction more than 15 times without loss of reactivity.

TABLE IX
Recovery of Catalyst 1a to the Aldol Reaction in the Presence of Water^a

Entry	Repeat number	Time (h)	Yield ^b (%)	TOF (h ⁻¹) ^c	dr ^d anti : syn	ee ^d anti (%)
1	0	72	69	0.09	91 : 9	94
2	1	24	57	0.24	87 : 13	91
3	2	24	55	0.23	89 : 11	87
4	3	24	63	0.26	76 : 24	87
5	4	24	69	0.29	89 : 11	90
6	5	24	72	0.3	85 : 15	91
7	6	24	68	0.28	90 : 10	92
8	7	24	55	0.23	87 : 13	91
9	8	24	60	0.25	87 : 13	90
10	9	24	68	0.28	84 : 16	87
11	10	24	75	0.31	90 : 10	87
12	11	24	69	0.29	90 : 10	87
13	12	24	63	0.26	92 : 8	87
14	13	24	71	0.29	93 : 7	87
15	14	24	70	0.29	89 : 11	87
16	15	24	47	0.19	83 : 17	83

^a Reaction was performed at 0.5 mmol scale of the aldehyde, 6 equiv of ketone with catalyst 1 (10 mol %), and base (0.5 mmol Et₃N) in 2 mL solvent.

^b Isolated yield of the corresponding product.

^c TOF = moles of corresponding product/moles of catalyst per hour.

^d Determined by chiral-phase HPLC.

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