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Pyrrolidine Modified PANF Catalyst for Asymmetric Michael Addition of Ketones to Nitrostyrenes in Aqueous Phase

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Three chiral pyrrolidine functionalized polyacrylonitrile fiber catalysts have been designed, prepared, and evaluated for their catalytic performance in asymmetric Michael addition of ketones to nitrostyrenes in water. With the optimized catalyst and condition in hand, the reaction scope has been explored with respect of nitrostyrenes. Then the fiber catalyst was further applied to packed-bed reactor for continuous-flow Michael addition. Based on the fact that organic solvent can inhibit the catalytic activity, novel microenvironment catalytic mechanism is proposed.

Introduction

Organocatalysis of asymmetric Michael addition of ketones to nitrostyrenes[1-5] provides an expedient method for the synthesis of nitroalkanes which are versatile synthetic intermediates in organic chemistry.[6] Many recyclable chiral organocatalysts have been developed for this reaction, such as fluoropyrrolidine sulfonamide,[7] ionic liquid-supported pyrrolidine-based catalyst,[8-12] Diarylprolinolsilyl ether salts.[1] Besides, many heterogeneous catalysts were also developed, such as polymer-supported pyrrolidine,[13-16] functionalized periodic mesoporous organosilica,[17] and silica gel supported pyrrolidine moieties.[18, 19] Considering green chemistry, many works of asymmetric Michael addition were performed in water.[1,6,10,20-22] Therefore, heterogeneous catalysis of asymmetric Michael addition in water is of vital importance for the green chemistry.

In the recent years, application of fiber materials as supporters for immobilization of homogeneous catalyst has become an area of interest in the design and synthesis of immobilized catalysts.[23-27] Polyacrylonitrile fiber (PANF), which is well known as "artificial wool" as a synthetic fiber material, offers an ideal starting material for preparing various functionalized catalysts since it contains abundant modifiable cyano groups.[28, 29] Considering its excellent properties of low cost, simple production technology, softness, light density, high mechanical intensity, and easy derivatization,[30-32] PANF has been the focus of our interest as immobilized supporter for various types of catalysts. Based on this, PANF can be further adapted to continuous processes (Flow Chemistry).[33-35] During last few years, a bunch of PANF immobilized catalysts (such as Brönsted acid catalyst, ionic liquid catalyst, and organocatalyst) have been designed, synthesized, and successfully applied in organic synthesis such as Knoevenagel condensation, iminocoumarin synthesis and sulfone synthesis in our group.[26, 36-41] All these results presage a brand new area of application for fibers beyond their general application in material science. Especially, in 2013, List group[42] developed a simple approach to immobilize homogeneous chiral organo-catalyst on nylon fiber, which was the first example of asymmetric reactions catalyzed by fiber-supported organo-catalysts.

Different from the nylon supported catalyst which was modified by photochemical immobilization with catalyst loading of 0.014-0.025 mmol/g, PANF can be modified by chemical immobilization with various functional groups with high catalyst loading in green solvents.[6] Consequently, we wonder that if the chiral organo-catalyst could be introduced on the PANF surface, the modified catalyst could provide a recoverable chiral organo-catalyst with higher catalyst loading in green solvent and obtain higher activity by tailoring the structure of catalysts. In order to validate this thought, three types of chiral pyrrolidine modified polyacrylonitrile fiber with different linkers (**3**, **6**, and **7** in Scheme 1) were designed, prepared and evaluated for their catalytic performance in the asymmetric Michael addition of cyclohexanone to β-nitrostyrene. Then the supported organocatalyst was applied to flow reactor technology which represents an improvement in terms of reliability, safety, and costs over traditional batch reaction condition.

Results and discussion

Synthesis of catalyst

Considering its dual role as linker and key structural element complementary to pyrrolidine in the asymmetric Michael

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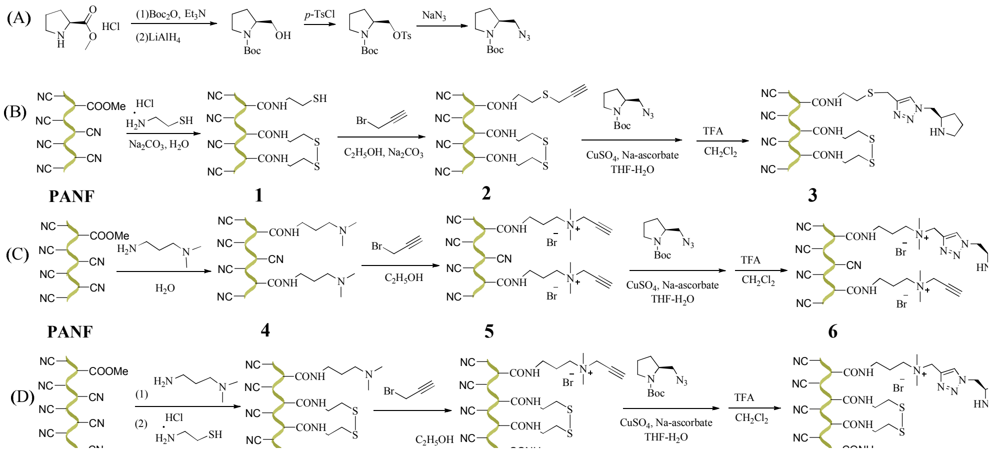


Scheme 1. Preparation of polyacrylonitrile fiber supported catalyst **3**, **6**, and **7**.

reactions,[43-45] 1,2,3-triazole moiety was chosen as the linker between PANF and pyrrolidine. First, the catalyst precursor was synthesized according to the steps in (A) of Scheme 1. Protection of *L*-proline methyl ester with di-*tert*-butyldicarbonate followed by subsequent reduction with $LiAlH_4$ afforded alcohol *N*-Boc-(*L*)-prolinol. Then the alcohol was subsequently activated by tosyl chloride to afford O-tosyl-*N*-Boc-prolinol, which underwent S_N2 substitution by sodium azide to afford *N*-boc-2-azidomethylpyrrolidine.[15, 46] On the other hand, PANF was successively treated with cysteamine hydrochloride and 3-bromopropyne to provide the alkyne modified fiber **2**. Finally, *N*-boc-2-azidomethylpyrrolidine was grafted onto fiber **2** through copper-catalyzed Huisgen cycloaddition[47-49] to afford, upon deprotection by trifluoroacetic acid (TFA), the supported catalyst **3**. For fiber **1**, free thiols are not stable and part of them can be readily oxidized in the air to form the hydrophobic disulfide bond. In order to validate this assumption, the amount of free thiol group and disulfide of fibers **1**, **3**, and **7** were measured by Ellman's reagent (see SI). The loadings of disulfide bond, alkynyl, and chiral pyrrolidinyl group of catalyst **3** are 0.66 mmol/g, 0.42 mmol/g, and 0.46 mmol/g, respectively, which implied the active sites are surrounded by the chemical microenvironment of hydrophobic disulfide and alkynyl moieties. By the similar synthetic method, the catalyst **6** and **7** with chemical microenvironment of hydrophilic quaternary ammonium moiety were synthesized.

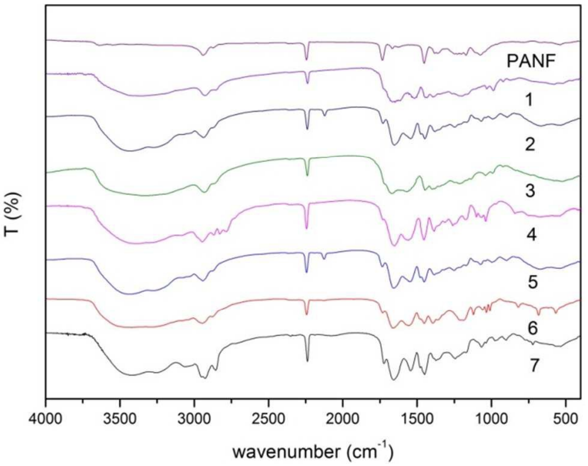


Figure 1. FTIR spectra of PANF and fiber **1**-**7**.

Characterization of catalyst 3, 6, and 7

Prior to analysis, PANF and its derivative fibers **1-7** were ground into powders and prepared as KBr pellets. The obtained FTIR spectra are showed in Figure 1. For the FTIR spectrum of starting **PANF** in Figure 1, the absorption band at 2242 cm^{-1} corresponds to the C≡N stretching vibration and the absorption band at 1731 cm^{-1} corresponds to the C=O vibration indicating the existence of methyl acrylate units in the copolymer. The broad absorption bands at 3700-3100 cm^{-1} in the FTIR spectra of **1** and **4** are attributed to the stretching vibrations of the N-H of amide, representing the successful amidation of PANF to afford fibers **1** and **4**. Obviously, the 2126 cm^{-1} peaks in spectra of **2** and **5** are characteristic to C≡C vibration which provides an evidence for the introduction of C≡C group in these fibers. No characteristic absorption band could be identified in FTIR spectra of catalysts **3**, **6** and **7** compared to their precursor fibers, which are attributed to the absence of obvious characteristic absorption band for 1,2,3-triazoles substituent.

Figure 2 displays the SEM photographs of **PANF** and fibers **1**, **3**, **4**, **6**, and **7**. The SEM photos show that these fibers are fibrous materials which have diameters around 20-30 μm. Compared with the original PANF, the surface of amidated fibers **1** and **4** are much rougher. It might be attributed to the high degree of modification of PANF with 2.43 mmol/g thiol moiety for fiber **1** and 2.29 mmol/g tertiary amine for fiber **4**. Apparently, the photographs of final fibers catalysts **3**, **6**, and **7** become increasingly coarser as compared with their parent fibers, which are due to that further modification lead to the damage of fiber surface.

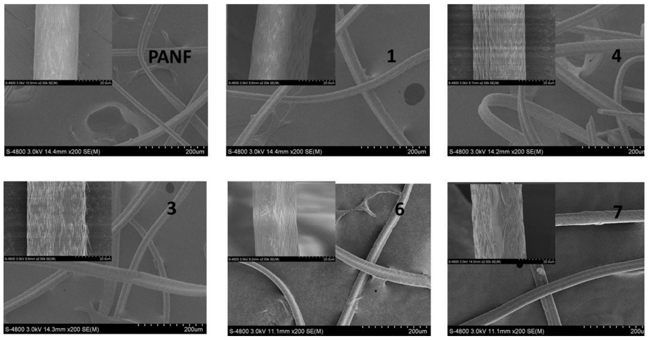


Figure 2. SEM of PANF and fibers **1**, **3**, **4**, **6,** and **7.**

The EA data for PANF and fibers **1**-**7** were shown in Table 1. Compared with the original PANF, the sulfur content in fiber **1** increased evidently due to the introduction of cysteamine which contains high sulfur content. This can also explain the decrease of carbon, hydrogen, nitrogen contents in fiber **1**. Fiber **1** was subsequently modified by propargyl group with higher carbon and hydrogen contents resulting in the increase of carbon and hydrogen contents in fiber **2** and the decrease of nitrogen and sulfur contents. Obviously, the observation of the much higher nitrogen content in catalyst **3** compared to its parent fiber **2** representing the successful synthesis of fiber **3** with chiral pyrrolidine ligated by 1,2,3-triazoles moiety which is rich of nitrogen.

Because of the modification by *N*,*N*-dimethyl-1,3-propanediamine, the fiber **4** has a lower carbon content and higher hydrogen content compared to the original PANF. The decrease in nitrogen content of **4** can be attributed to the partial hydrolysis of the C≡N groups and to its reaction with *N*,*N*-dimethyl-1,3-propanediamine which results in the release of ammonia and the formation of amide. As the bromide acts as the counter anion of quaternized fiber **5**, the carbon, hydrogen, nitrogen contents of **5** is lower than the aminated fiber **4**. In addition, the higher nitrogen content of catalyst **6** relative to **5** also suggests that the highly nitrogen-rich 1,2,3-triazole moiety has been successfully formed in fiber catalyst **6**. Noting that the only difference between catalyst **6** and **7** is the hydrophobic thiol group and alkyl sulfide, it is reasonable to observe the higher sulfur content and lower carbon, hydrogen, nitrogen contents in catalyst **7** compared to **6**.

Table 1. Elemental analysis data of PANF and fibers 1 - 7.

Sample	C (%)	H (%)	N (%)	S (%)
PANF	70.75	5.94	26.11	0.10
1	53.26	5.42	15.86	14.95
2	54.89	5.96	11.96	10.11
3	55.40	5.79	13.62	9.36
4	61.28	7.06	21.07	0.22
5	58.63	6.91	17.77	0.23
6	68.93	7.25	20.51	0.16
7	61.25	7.17	14.62	4.79

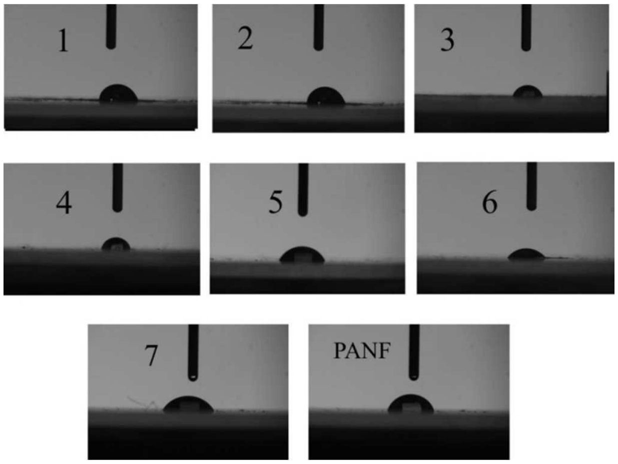


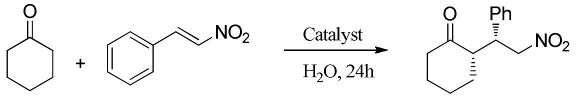
Figure 3. WCA photographs of fibers **1** - **7**.

The measurement of water contact angle (WCA) is a common macroscopic method for the detection of the surface hydrophilicity of solid materials. Therefore, the WCAs of the modified fibers **1**-**7** were measured and displayed in Figure **3**. Before the measurement, the samples were prepared by dissolving the fibers in DMSO and subsequently evaporating the solvent on a glass slide to form the corresponding thin films. The WCA value of **PANF** is observed to be 84 °, which means that the PANF is a weak hydrophilic material. After the amination of PANF, the WCA values of its derivatives of fiber **1** and **4** are slightly decreased to 81° and 76°, respectively, which implies that the tertiary amine modified fiber **4** is more hydrophilic than the thiol modified fiber **1**. Furthermore, the WCA of fibers **2** with a value of 79° is similar to its parent fiber **1** whereas the value of fiber **5** is observed decreased to 57°. This result clearly shows that the quaternary ammonium moiety functions as spacer group between the active and fiber backbone strongly enhanced the hydrophilicity of the modified fiber **5**. The providing WCA values of 78° and 56° for catalysts **3** and **6**, respectively, which are quite similar to that of fiber **2** and **5**, demonstrating the little effect on the hydrophilicity of fibers by introducing of 1,2,3-triazole moiety. Because of the quaternary ammonium moiety in catalyst **6** was replaced by a more hydrophobic disulfide group, the resulting catalyst **7** obtains moderate WCA value of 63°. These results strongly confirm that it is feasible to control the hydrophilicity of the fiber catalysts by changing the modifying groups.

Optimization of the reaction conditions

All the three catalysts were tested for the Michael addition of cyclohexanone to *β*-nitrostyrene under a variety of conditions as results shown in Table 2.

Table 2. Optimization of the reaction conditions.[a,b]



Entry	Cat	Solvent	Additive	Yield/ %	syn/ anti	ee /%
1	3	CH_3COOEt	-	trace	-	-
2	3	C_2H_5OH	-	trace	-	-
3	3	H_2O	-	32	95:5	69
4	6	CH_3COOEt	-	trace	-	-
5	6	C_2H_5OH	-	trace	-	-
6	6	$CH_3COOEt:H_2O=1:1$	-	trace	-	-
7	6	$CH_3COOEt:H_2O=1:10$	-	48	94:6	78
8	6	$C_2H_5OH:H_2O=1:1$	-	52	95:5	78
9	6	H_2O	-	58	94:6	78
10	6	H_2O	C_6H_5COOH (pKa = 4.2)	56	96:4	82
11	6	H_2O	*p*-$O_2NC_6H_4COOH$ (pKa = 3.44)	60	96:4	83
12	6	H_2O	CF_3COOH (pKa = 0.23)	63	96:4	83
13	6	H_2O	TsOH (pKa = -2.8)	86	97:3	83
14	6	H_2O	HBr (pKa = -9.0)	65	96:4	45
15	6	H_2O	$HClO_4$ (pKa = -10.0)	58	97:3	66
16[c]	3	H_2O	TsOH	39	95:5	89
17[c]	7	H_2O	TsOH	56	96:4	99
18[c]	6	H_2O	TsOH	83	97:3	99
19[c]	6	$C_2H_5OH:H_2O=1:1$	TsOH	72	96:4	99
20[d]	6	H_2O	TsOH	58	97:3	99

[a] All reactions were performed with 0.8 mmol of nitrostyrene, 20 equiv of cyclohexanone (16 mmol) and 10 mol % of catalyst in 20 mL of water at 35 °C for 24 h, the additive amount is 9 mol % based on the amount of nitrostyrene. [b] The yield were calculated by column chromatography, the diasteromeric ratio (syn/anti) were determined by ^1H NMR of the products and enantiomeric excess (ee) were determined by HPLC. [c] The reaction was performed at 20 °C for 36 h. [d] The reaction was performed at 20 °C for 36 h with 5 mol % catalyst.

Table 2 showed that both catalyst **3** and its relative hydrophilic analogue catalyst **6** failed to catalyze the Michael addition in organic solvents (entries 1, 2, 4, and 5), even in mixed solvent (H_2O:EtOAc = 1:1) (entry 6). However, increasing the ratio of water to ten times of EtOAc led to a yield of 48% and an enantioselectivity of 78% ee with catalyst **6** as catalyst (entry 7). A yield of 52% and an enantioselectivity of 78% ee were afforded with catalyst **6** in the mixed solvent (H_2O:EtOH = 1:1) (entry 8). This result implied the important role of protic solvent in this reaction. To our delighted, in pure water, a slightly higher yield of 58% (entry 9) for catalyst **6** was obtained, suggesting that water was good solvent for this reaction. For the relative hydrophobic analogue catalyst **3**, the activity was much lower with a yield of 32% and an enantioselectivity of 69% ee (entry 3). The higher activity of catalyst **6** compared to catalyst **3** and **7** may be attributed to the good compatibility between the hydrophilic fiber **6** and water.

The effect of various acids as co-catalysts on catalytic activity and enantioselectivity was also investigated (entries 10-15). Adding 9 mol% of benzoic acid to the aqueous reaction with catalyst **6,** a 56% yield and 82% ee (entry 10) were obtained. *p*-Nitrobenzoic acid and trifluoroacetic acid were also tested as co-catalysts (entries 11 and 12), we are glad to see that both of the reaction activity and enantioselectivity are slightly increased further. Significantly, a yield of 86% with enantioselectivity of 83% ee was obtained by using *p*-toluenesulfonic acid (TsOH) as co-catalyst (entry 13). These results that organic acids accelerate the activity and increase the enantioselectivity implied the involving of acids in the formation and hydrolysis of the enamine intermediate.[9] However, addition of inorganic acids, such as HBr (entry 14) and $HClO_4$ (entry 15), obviously decrease the enantioselectivities of this reaction.

When the temperature decreases from 35 °C to 20 °C, the ee increases from 83% to 99% (entry 18) and a yield of 83% was obtained by prolonging the time to 36 h by catalyst **6**. It's clear that decrease the temperature of this reaction can enhance the enantioselectivity efficiently but inhibit the reaction activity. Besides, when the amount of catalyst was decreased to 5 mol %, the reaction activity obviously declined with a yield of 58% (entry 20).

Under the same temperature of 20 °C, the activity and enantioselectivity of catalysts **3**, **6**, and **7** were investigated in this aqueous Michael addition. Catalyst **3** provided a yield of 39% and 89% ee (entry 16), whereas a yield of 83% and 99% ee were obtained by catalyst **6** (entry 18). For the moderate hydrophilic catalyst **7**, a medium yield of 56% with high enantioselectivity of 99% ee was afforded (entry 17). The only difference in catalyst **6** as opposed to **7** was the presence of thiol (0.44 mmol/g) and disulfide group (0.36 mmol/g) in catalyst **7**, while the other groups, such as tertiary amine, quaternary ammonium moiety, and active species, were identical for them. Therefore, the increase in yield for catalyst **6** over **7** was attributed to the presence of hydrophobic disulfide bond that strongly decreased the hydrophililicity of catalyst **7**, which influenced the swelling effect in water. Based on this, the hydrophilic effect can also be applied to explain the higher yield for catalyst **7** relative to catalyst **3**. Besides the enhanced activity of catalyst **7**, the enantioselectivity was also increased obviously from 89% ee by catalyst **3** to 99% ee. For catalyst **7**, the amount of thiol, disulfide, tertiary amine, alkynyl, and chiral site are 0.44 mmol/g, 0.36 mmol/g, 0.30 mmol/g, 0.89 mmol/g and 0.54 mmol/g (see SI), respectively. In other words, the active sites locate in a complex chemical microenvironment constituted by a variety of functional groups. Compared with catalyst **3**, this enhancement in enantioselectivity of catalyst **6** or **7** might be the result of the ionic microenvironment formed by quaternary ammonium moiety which intervene the formation of intermediate.

Table 3. The optimization of amount of cyclohexanone in Michael reaction.

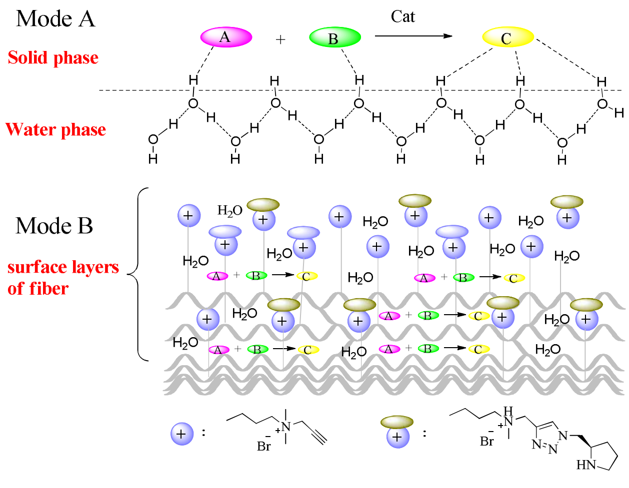
Entry	Cyclohexanone/mmol	Yield/%	syn/anti	ee/%
1	5	46	95:5	99
2	10	63	96:4	99
3	20	65	96:4	99

[a] All reactions were performed with 0.8 mmol of nitrostyrene, 10 mol % of catalyst in 10 mL of water and 10 mL of ethanol at 20 °C for 24 h, the additive amount is 9 mol % based on the amount of nitrostyrene. [b] Its ^1H NMR spectrum was integrated to calculate the diasteromeric ratio and the product was purified by flash chromatography on silica gel (EtOAc/Hexane) to afford the syn Michael adduct as a white solid. [c] The enantiomeric excess was determined by HPLC on a chiral phase chiralpak AD-H column.

Considering the miscibility of solid *trans-β*-nitrostyrene in the reaction mixture, the amount of cyclohexanone was optimized under the mixed solvent of water and ethanol. As shown in Table 3, yield increased with the amount of cyclohexanone. However, since only slight increase of yield (from 63% to 65%) was observed with the amount of cyclohexanone increasing from 10 equivalent to 20 equivalent, 10 equivalent of cyclohexanone was chosen as the optimized amount for the continuous-flow system.

Proposed catalytic mechanisms for PANF based pyrrolidine catalysts

The catalytic mechanism for polyacrylonitrile fiber supported organocatalyst is different from that of the traditional polymer-supported organo-catalysts for the Michael addition reaction in water. Although the catalytic mechanism of polymer-supported organo-catalysts[15, 16] for heterogeneous Michael addition in water is still not clear right now, it is supposed to occur on the oil-water surface where both the hydrogen-bonding activation and hydrophobic effect work together to achieve the accelerating effect(model A, Scheme 2). Generally, the introduction of hydrophobic aliphatic chains is necessary. However, according to our results, the optimized catalyst **6** is much more hydrophilic, which indicate that this reaction occurs in bulk water instead on the oil-water interface**.** Furthermore, **PANF** is a unique material that its polymer chains can be modified in depth to construct a three dimensional environment (model **B**, Scheme **2**). Therefore, an ionic microenvironment that can be tailored by second group, such as thiol, tertiary amine, and quaternary ammonium moieties, is formed on the surface layers of fiber. The organic substrates can penetrate, accumulate, and then interact with the active sites inside the microenvironment to afford the product with high enantioselectivity. Thus, this new "in bulk water" mechanism based on the ionic microenvironment effect and hydrophilicity effect of fiber catalysts could well explain the enhanced yields and enantioselectivities in this Michael reaction.

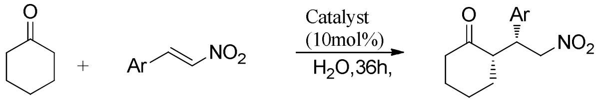


Scheme 2. The catalytic mechanisms of polymers (model A) and fibers supported catalysts in water (model B).

Michael addition of cyclohexanone to nitrostyrenes

To further investigate the scope of the reaction, a series of nitroolefins were tested under the optimized conditions catalyzed by **6** and the results are summarized in Table 4. Both electron-rich and electron-deficient *β*-nitrostyrenes were tested as the Michael acceptors, however, the yields, diastereo- and enantioselectivities were independent on the electronic or steric properties of the substrates (entries 1-8). All the reactions proceeded smoothly to generate the Michael adducts in excellent yields (83-96%), high diastereoselectivities (d.r.>92:8) and excellent enantioselectivities (83–99% ee). For example, the electron-rich *β*-nitrostyrene (entry **9**) afforded

Table 4. Michael addition of ketones to nitrostyrenes.[a,b]



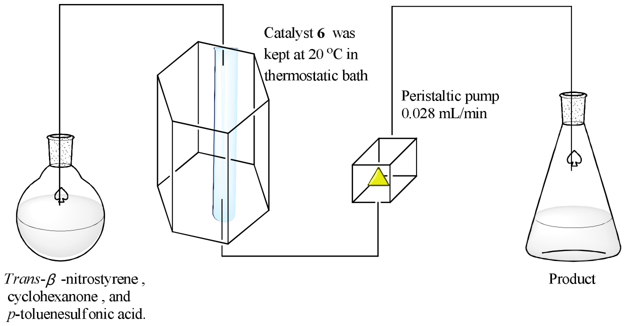
Entry	Ar	Yield/%	syn/ anti	ee/%
1	C_6H_5	83	94:6	99
2	4-$NO_2C_6H_5$	85	94:6	91
3	4-FC_6H_5	87	94:6	91
4	4-ClC_6H_5	96	96:4	94
5	4-BrC_6H_5	83	94:6	91
6	3-$C_6H_5OC_6H_5$	93	93:7	85
7	3-$CH_3OC_6H_5$	89	98:2	87
8	2-ClC_6H_5	95	92:8	90
9	4-$CH_3OC_6H_5$	94	95:5	93
10	2-furanyl	90	96:4	83
11	1-naphthyl	92	94:6	84

[a] All reactions were performed with 0.8 mmol of the nitroolefin, 20 equiv of the ketone, 10 mol % of catalyst 6 and 9 mol% of TsOH in 20 mL of water at 20 °C for 36 h.[b] The yield were calculated by column chromatography, the diasteromeric ratio (syn/anti) were determined by ^1H NMR of the products and enantiomeric excess (ee) were determined by HPLC.

the product with 84% yield and 93% ee, while the electron-deficient *β*-nitrostyrene (entry 2) afforded 85% yield and 91% ee. Besides, the heterocyclic *β*-nitroethenylfuran (entry 10) also performed well with high yield (90% yield), excellent diastereo- (d.r. = 96:4) and enantioselectivities (83% ee). These results unequivocally suggest the importance of adaptability of substrate to the microenvironment in this aqueous reaction, which shields the influence of electronic effect and steric effect of substrates. Such phenomenon is consistent with our previously proposed reaction mechanism.

Application into continuous-flow reaction.

With the above promising results in hand, the high catalytic activity exhibited by catalyst **6** and its robustness indicate its potential as a suitable candidate for a continuous flow processing. The very simple flow reactor used to test this hypothesis involved a silicone column between flask and peristaltic pump. The catalytic column packed with 208 mg of catalyst **6** (0.48 mmol/g) was kept at 20 °C in thermostatic bath. A solution of *trans-β*-nitrostyrene (149 mg, 1 mmol), cyclohexanone (1 mL, 10 mmol), and 9 mol% *p*-toluenesulfonic acid in 10 mL of ethanol and 10 mL of water was pumped into the system at 0.028 mL/min. Considering the better solubility of organic substrates and product in ethanol, a solvent mixture was used instead of pure water for better results. Finally, the effluent liquid contains 68% yield of the product with syn/anti = 97:3 and ee = 99%. This result showed that flow reaction can positively compete with the batch one (68% in 12 hours vs 63% in 24 hours), which might be due to higher concentration of fiber catalyst. However, decreasing the flow rate has little influence on the reactivity and stereoselectivity. The yields and ee values were also determined in a time-on-stream format and the results were listed in Table 4 in the SI. Further optimization in flow reactor is still ongoing in this group.



Scheme 3. Diagrammatic sketch of flow chemistry for catalyst **6**.

Table 5. Reuse of catalyst **6** in the Michael addition of cyclohexanone to trans-β-nitrostyrene.[a,b]

Cycle	Yield/%	syn/ anti	ee/%
1	68	97:3	99
2	68	96:4	99
3	66	97:3	99
4	63	95:5	99

[a] The solution was performed with 0.8 mmol of nitrostyrene, 10 equiv of cyclohexanone and 10 mol % of catalyst and 9 mol% of TsOH in 10 mL of water and 10 mL of ethanol at 20 °C at 0.028 mL/min . [b] The yield were calculated by column chromatography, the diasteromeric ratio (syn/anti) were determined by ^{1}H NMR of the products and enantiomeric excess (ee) were determined by HPLC.

The reusability of catalyst 6 in packed-bed flow reactor

In order to further demonstrate the practicability of our packed-bed flow reactor, the reusability of catalyst **6** was investigated by catalyzing the Micheal addition of cyclohexanone to *trans-β*-nitrostyrene (Table 5). After the reaction, the catalyst was washed with ethanol. Then it was directly reused for the next iteration. The results show that the recovered catalyst retains its high activity (63-68% yields) and high levels of enantioselectivity (99% ee) and diastereoselectivity (syn:anti > 95:5) even after four cycles (Table 4), which demonstrates the high reusability of this catalyst.

Conclusion

Here we report the preparation of three types of pyrrolidine modified polyacrylonitrile fiber (**3**, **6**, and **7**) and their application as catalyst in Michael addition of cyclohexanone to nitrostyrenes in water. The catalyst **6**, with ionic microenvironment constructed by quaternary ammonium moiety, was chosen as optimized catalyst since it is capable of achieving the highest enantioselectivity (99% ee). Such an obvious enhancement in enantioselectivity might be attributed to the ion effect surrounding the active sites. The activity of this aqueous reaction could be effectively improved by increasing the hydrophilicity of microenvironment. Based on this, a new catalytic "in bulk water" mechanism was proposed which is different from the on-water mechanism of supported polymers. The investigation of substrates scope of nitroolefins shows high activity (83-96% yields) and enantioselectivity (83-99% ee) for this aqueous reaction. The flow reaction was also tested and shown to positively compete with the batch ones, due to faster reaction and simpler separation procedures. In the future, the flow system will be further tested by sequentially converting different substrates to Michael addition products with the same column.

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