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ARTICLE

Highly Efficient Reduction of Carbonyls, Azides, and Benzyl Halides by NaBH4 in Water Catalyzed by PANF-immobilized Quaternary Ammonium Salts

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A series of polyacrylonitrile fiber-supported quaternary ammonium salts (PANF-QAS) were prepared and applied to the catalytic reduction of aldehydes, ketones, azides, and benzyl halides in water with NaBH4 as reducing reagent in a highly efficient, economic, and environmentally benign way. The structure-activity relationship was investigated which showed that catalysts made up of quaternary ammonium salts with longer alkyl chains, larger cationic radii and better lipophilicity speed up the reduction to afford ecxellent yields. Moreover, the optimized catalyst can be applied to the reduction of 1-naphthaldehyde in continuous flow process with outstanding reactivitiy and recyclability.

Introduction

Recently, more and more synthetic chemists are devoted to the development of environmentally benign alternatives to traditional environmentally-unfriendly processes due to the increasing recognition of the importance of environmental protection. When a synthetic strategy is planned, two factors must be taken into account to make sure it is environmentally friendly and cost-efficient. First, solvents should better be non-toxic and cheap which indicates that water is a good choice where the reaction should be optimized.[1] Second, the key catalysts and additives should be easily recycled and reused.[2] As a result, green chemistry has received much attention with exploration of aqueous phase organic reactions. However, the incompatibility of water as solvent and organic substrates necessitates the use of phase-transfer catalysts (PTCs) due to their ability to facilitate the migration of a reactant from one phase (such as aqueous phase) into another phase (such as organic phase) where reaction occurs to realize a variety of synthetic transformations under milder conditions.[3]

Although phase-transfer catalysts are widely used in organic synthesis, one major shortcoming of PTCs remaining to be conquered is their recovery from reaction media due to their generally high cost. As a result, PTCs have been immobilized onto supports to simplify their recovery by simple filtration

after the organic reaction was completed.[4] This strategy can be further adapted to continuous processes (Flow Chemistry).[5] General supports available for immobilization of PTCs include polymeric matrices such as polystyrene,[6] polyacrylamine,[7] PEG,[8] and inorganic supports such as silica-gel,[9] alumina,[10] and montmorillonite.[11] Nevertheless, polymer-supported PTCs have some drawbacks such as diffusion limitations, high costs, tendency to swell, as well as mechanical and thermal instabilities. Therefore, it is of utmost importance to choose suitable support and anchor groups to take advantage of immobilized catalyst while maintaining the high reactivity of soluble catalysts, which necessitate the development of new support for PTCs.
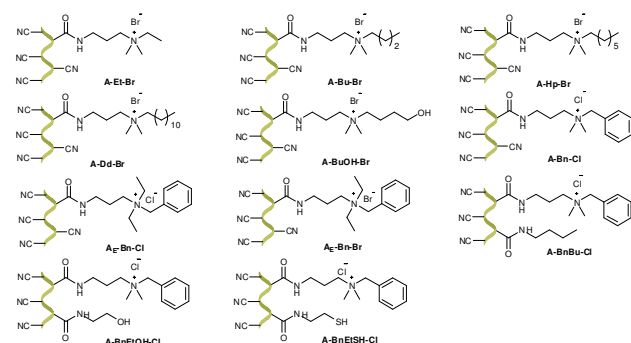
In the recent years, novel insoluble supports, such as fibers[12] and filter papers,[13] have been developed for the immobilization of homogeneous catalyst. Although fibers have drawn the attention of many material chemists and various types of fibers have been developed with novel properties including flame resistance,[14] self-cleaning,[15] thermal regulation,[16] and electrical conduction,[17] they have been seldom applied in the field of organic synthesis until recently. In 2013, List[12] group developed a simple approach to immobilize homogeneous organocatalyst on nylon fiber which presage a brand new area of application for fibers beyond their general application in material science. Furthermore, the good flexibility of fibers makes them labile to be spun into desired shapes, which is an attractive virtue to be applied to the fixed-bed reactors in chemical industry.

Polyacrylonitrile fiber (PANF), which is well known as "artificial wool", has been widely applied to textile industry due to its excellent properties of low cost, simple production technology, softness, light density, high mechanical intensity, as well as corrosion and mildew resistance. Moreover, PANF is abundant with cyano groups which can be easily derived into carboxyl, amide, or other functional groups.[18] These

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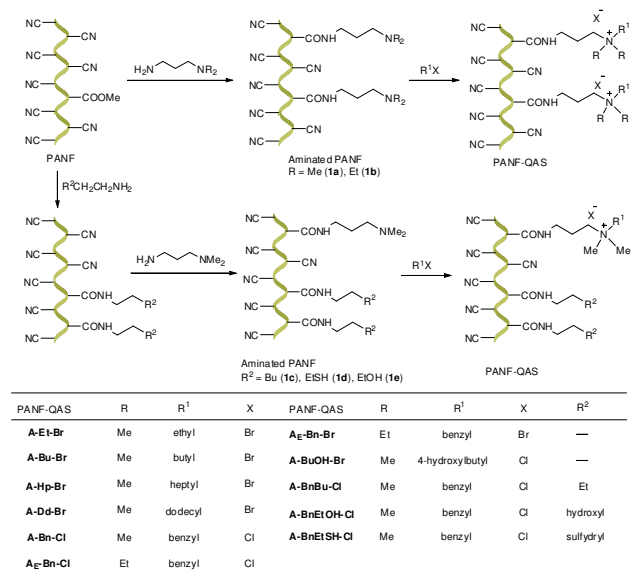[b.] Science and Engineering Department, Dehong Teachers' College, No.14, Xianchi Road Dehong 678400 (P.R.China).

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Scheme 1. PANF supported quaternary ammonium salts.

Table 1. Weight gain and acid exchange capacity of **1a**, **1b**.

Amination PANF	Weight gain (%)[a]	Acid exchange capacity (mmol/g)
1a	24	2.29
1b	17	1.74

[a] Weight gain = $[(W_2 - W_1)/W_1] \times 100\%$, where W_1 and W_2 are the weights of PANF and amination fiber, respectively.

make PANF an appealing novel candidate as support for immobilization of soluble catalysis. In our previous studies, PANF has been proved to be an effective novel support for catalysts varying from Brönsted acid, ionic liquid to organocatalysts and the modified PANFs have been successfully applied in organic synthesis such as Knoevenagel condensation, iminocoumarin synthesis and sulfone synthesis.[19] Here, the immobilization of phase transfer catalyst on PANF fibers and the discussion of relationships between loading amount/structure and catalytic activity will be reported in this paper.

A series of PANF supported quaternary ammonium salts (PANF-QAS, hereafter) (Scheme 1) with different substitution or loading were designed, synthesized, and evaluated in this paper. It is well known that the reduction of aldehyde/ketones to alcohols by $NaBH_4$ is an important and general transformation in organic chemistry.[20] Although aqueous reduction proved to be successful for some water soluble aldehydes, the reduction of hydrophobic aldehyde or ketones in aqueous condition is difficult to realize due to the separation of reducing reagents and substrates in different phase which requires the use of phase-transfer catalyst.

Therefore, the catalytic reduction of hydrophobic 1-naphthaldehyde by $NaBH_4$ in water was chosen as model reaction to elucidate both structure and loading-catalytic activity relationships of PANF-QAS.

Results and discussion

Preparation and characterization of PANF-QAS

Most of the PANF-QAS catalysts were prepared via a simple two-step or three-step procedure as shown in Scheme 2. First, the tertiary amines were introduced successfully through aminolysis of cyano group on the PANF. Then, reaction of aminated PANF with various halides afforded the desired PANF-QAS. Meanwhile, catalysts **A-BnBu-Cl**, **A-BnEtSH-Cl**, and **A-BnEtOH-Cl** were also prepared by modifying **A-Bn-Cl** with *n*-butylamine, cysteamine, and ethanolamine, respectively. All the aminated PANF were characterized by weight gain and acid exchange capacities (Table 1).[21] Quaternization of aminated PANF was also determined by the weight gain. The details for the synthesis and characterization of other PANF-QAS are presented in the supporting information.

The derivatization steps could be semi-qualitatively traced by IR spectrum with the samples being ground into powder in the presence of KBr and compressed under high pressure to give a thin transparent KBr pellet prior to analysis. The IR spectra of PANF, aminated PANF **1a**, catalyst **A-Hp-Br** are shown in Figure 1. In the IR spectrum of PANF (Curve a, Figure 1), the sharp absorption at 2242 cm^{-1} is characteristic of C≡N stretching and the absorption at 1731 cm^{-1} is characteristic to C=O stretching which is due to the methyl acrylate unit in the
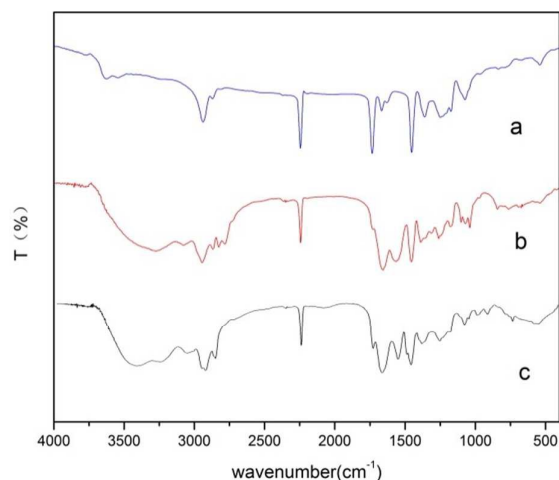

Scheme 2. Preparation of PANF-immobilized quaternary ammonium salts.

PANF-QAS	R	R^1	X	PANF-QAS	R	R^1	X	R^2
A-Et-Br	Me	ethyl	Br	**A$_E$-Bn-Br**	Et	benzyl	Br	—
A-Bu-Br	Me	butyl	Br	**A-BuOH-Br**	Me	4-hydroxylbutyl	Cl	—
A-Hp-Br	Me	heptyl	Br	**A-BnBu-Cl**	Me	benzyl	Cl	Et
A-Dd-Br	Me	dodecyl	Br	**A-BnEtOH-Cl**	Me	benzyl	Cl	hydroxyl
A-Bn-Cl	Me	benzyl	Cl	**A-BnEtSH-Cl**	Me	benzyl	Cl	sulfydryl
A$_E$-Bn-Cl	Et	benzyl	Cl					

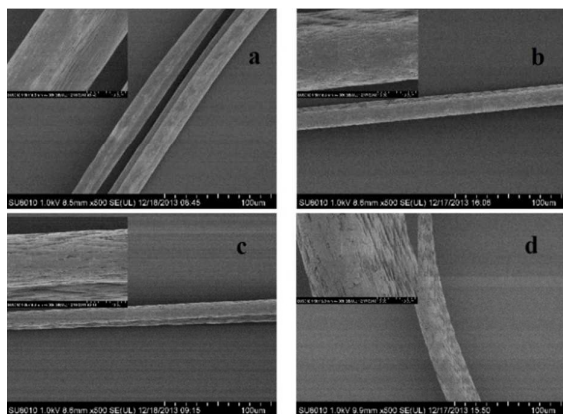**Figure 1.** IR spectra of PANF (a), aminated PANF **1a** (b), PANF-QAS **A-Hp-Br** (c)

Figure 2. SEM of PANF (a), **1a** (b), **A-Hp-Br** (c), and **A-Hp-Br** (15) (d)

copolymer. In the IR spectrum of **1a** (Curve b, Figure 1), the broad absorption from 3700-3100 cm^{-1} appears due to the N-H amide stretching vibrations. The IR spectrum of **A-Hp-Br** (Curve c, Figure 1) is similar to that of **1a** since there is no characteristic IR absorption for the quaternary ammonium groups.

Figure 2 displays the SEM photographs of PANF, **1a**, **A-Hp-Br**, and **A-Hp-Br**(15) (**A-Hp-Br** catalyst recovered after the 15th run of the reaction). After amination, the surface of **1a** is rougher than that of PANF. The surfaces of **A-Hp-Br** and **A-Hp-Br**(15) are almost the same proving that the integrity of the catalyst was maintained after being used for 15 cycles.

The elemental analysis data for PANF, **1a**, **A-Hp-Br**, **A-Hp-Br**(1) (**A-Hp-Br** catalyst recovered after the first run of reaction), and **A-Hp-Br**(15) were shown in Table 2. Compared to the original PANF, the carbon content of **1a** decreased noticeably and the hydrogen content increased as expected since *N*,*N*-dimethyl-1,3-propanediamine has lower carbon content and higher hydrogen content than the original PANF. The decrease in nitrogen content of **1a** can be attributed to its reaction with *N*,*N*-dimethyl-1,3-propanediamine and the partial hydrolysis of the cyano groups which resulted in the formation of amide and the release of ammonia. **A-Hp-Br** has higher hydrogen content and lower carbon content than **1a** due to the addition of 1-bromoheptane.

Table 2. Elemental analysis data of PANF, **1a**, **A-Hp-Br**, **A-Hp-Br**(1),^{a} and **A-Hp-Br**(15).^{b}

Fiber	Elemental analysis data		
	C(%)	H(%)	N(%)
PANF	66.01	6.07	23.78
1a	61.75	7.57	22.11
A-Hp-Br	56.28	7.77	15.54
A-Hp-Br(1)	58.04	8.16	16.11
A-Hp-Br(15)	58.72	7.53	15.08

^{a} Recovered after the first run of the reaction.
^{b} Recovered after the 15th run of the reaction.

The amounts of carbon, hydrogen, and nitrogen in **A-Hp-Br** (1) are slightly higher than those in **A-Hp-Br**. These results may be explained by the fact that BH$_4^-$ can exchange but not completely with Br$^-$ in the catalyst regeneration process. Moreover, the subtle change of the contents of carbon, hydrogen and nitrogen in **A-Hp-Br**(15) compared with those in **A-Hp-Br**(1) demonstrates that the **A-Hp-Br**(15) keeps almost the same component as the original catalyst**.** According to the elemental results and SEM results above, the integrity of the catalyst was supposed to be maintained after being used in 15th reactions.

Structure-activity relationship of the PANF-QAS

Structure-activity relationship of the catalysts was investigated with the reduction of 1-naphthaldehyde by NaBH$_4$ in water as a model reaction. Unlike polystyrene-supported PTC[6] which needs swelling before using, the PANF-QAS could be used directly without preconditioning in water which might be due to the large amount of polar cyano groups on the surface.

First, the dependence of reaction rates on the stirring speed was investigated. The results in Figure 3 showed that reaction rates are almost proportional to stirring speed until the stirring speed up to about 500 rpm, and then remained constant beyond this value. Therefore, all the reactions in this paper were carried out with stirring at 600 rpm.

Then the catalytic activities of various functionalized PANF-QAS were evaluated and the results listed in Table 3 showed that all the catalysts could accelerate the reduction efficiently compared with non-functionalized PANF , amine-functionalized **1a**, and **1b** (entries 12-14, Table 3) and afforded moderate to excellent yields (36-99%). The corresponding catalytic activities varied significantly with different structures. Catalysts **A-Et-Br**, **A-Bu-Br**, **A**-**Hp-Br**, and **A**-**Dd-Br** which have similar structures but with different alkyl chain lengths were designed to investigate the effect of the alkyl chain length on the catalytic activity.
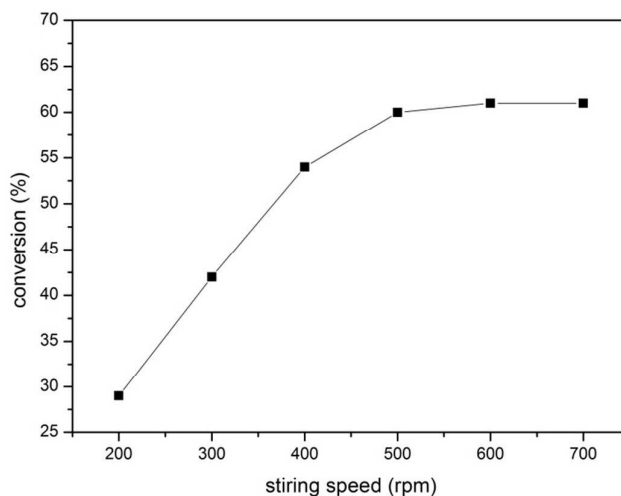

Figure 3. Dependence of the conversion on the stirring speed. Reaction conditions: 4 mmol of 1-naphthaldehyde , 2 mmol of NaBH$_4$, 10 mol % catalyst **A-Hp-Br**, 0.5 h, 25 °C, pH = 12. Yields were calculated from GC results using naphthalene as an internal standard.

Table 3. Reduction of 1-naphthaldehyde with 10 mol % catalyst.[a]

Entry	Catalyst	Yield (%)	Entry	Catalyst	Yield (%)
1	**A-Et-Br**	36	8	**A-BnEtSH-Cl**	97
2	**A-Bu-Br**	86	9	**A-BnEtOH-Cl**	73
3	**A-Hp-Br**	99	10	**A$_E$-Bn-Cl**	90
4	**A-Dd-Br**	98	11	**A$_E$-Bn-Br**	91
5	**A-Bn-Cl**	83	12	PANF	18
6	**A-BuOH-Br**	44	13	**1a**	16
7	**A-BnBu-Cl**	99	14	**1b**	17

[a] Reaction conditions: 4 mmol of 1-naphthaldehyde , 2 mmol of NaBH$_4$, 1 h, 25 °C , pH = 12. Yields were calculated from GC results using naphthalene as an internal standard and all the catalysts have similar catalyst loading of 1.1 mmol/g.

Figure 4. Effect of catalyst loading on the reduction reaction with the **A-Bn-Cl** catalyst. Reaction conditions: 4 mmol of 1-naphthaldehyde , 2 mmol of NaBH$_4$, 10 mol % catalyst **A-Bn-Cl**, 0.5 h, 25 °C, pH = 12. Yields were calculated from GC analysis using naphthalene as an internal standard.

During the given time, the yields with **A**-**Et-Br, A**-**Bu-Br** were 36% and 86%, (entries 1 and 2, Table 3) respectively, whereas that with **A-Hp-Br** was 99% (entry 3, Table 3). So the activity of the fiber catalyst increased when the length of the longest alkyl chain increased from C2 to C7. When the length of longest alkyl chain was further increased from C7 to C12, (*i.e.* **A-Dd-Br**) the conversion remained almost the same (98%, entry 4 in Table 3) since it has already reached the upper limit of the reaction.[22]

Catalyst **A-Bn-Cl** with an aryl tail group showed poorer activity (83% yield, entry 5 in Table 3) than that of **A-Hp-Br** (99% yield, entry 3 in Table 3) under the same conditions. These findings imply that alkyl groups which are more flexible than aryl groups might attract more substrates to the active sites, thus catalysts with alkyl groups are more efficient than those with aryl groups.

Then the effect of the hydrophilicity of the fibers was investigated. Catalyst **A-BuOH-Br** with a hydrophilic OH group exhibited a much lower activity (entry 6, Table 3) than **A-Bu-Br** (entry 2, Table 3). Meanwhile, catalyst **A-BnBu-Cl** and **A-BnEtSH-Cl** with hydrophobic chains exhibited excellent activities with
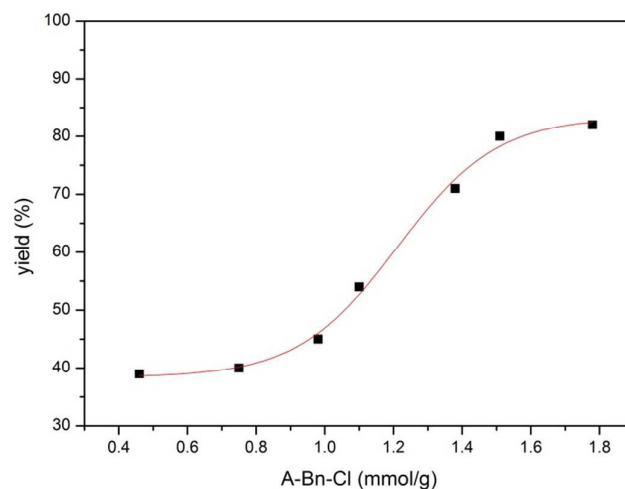
yields of 99% and 97%, respectively (entries 7 and 8 in Table 3), but a rather lower yield of 73% was obtained for **A-BnEtOH-Cl** (entry 9 in Table 3) due to the introduction of the hydrophilic hydroxyl group. All these results indicated that the hydrophobic group played a significant role in increasing the catalytic activity of the PANF supported catalysts while hydrophilic group played an adverse effect. In fact, the aliphatic chain PTC catalyst does not play a direct role in the catalytic mechanism, but rather tune the transportation of the hydrophobic substrates into the surface layer and water away from the surface layer.[23]

Loading-activity relationship of the catalysts

As the **A-Bn-Cl** can obtain the highest catalyst loading (1.74 mmol/g, i.e., 1 g of **A-Bn-Cl** contains 1.74 mmol quaternary ammonium functional group) among these catalysts (see supporting information), the relationship between the catalyst
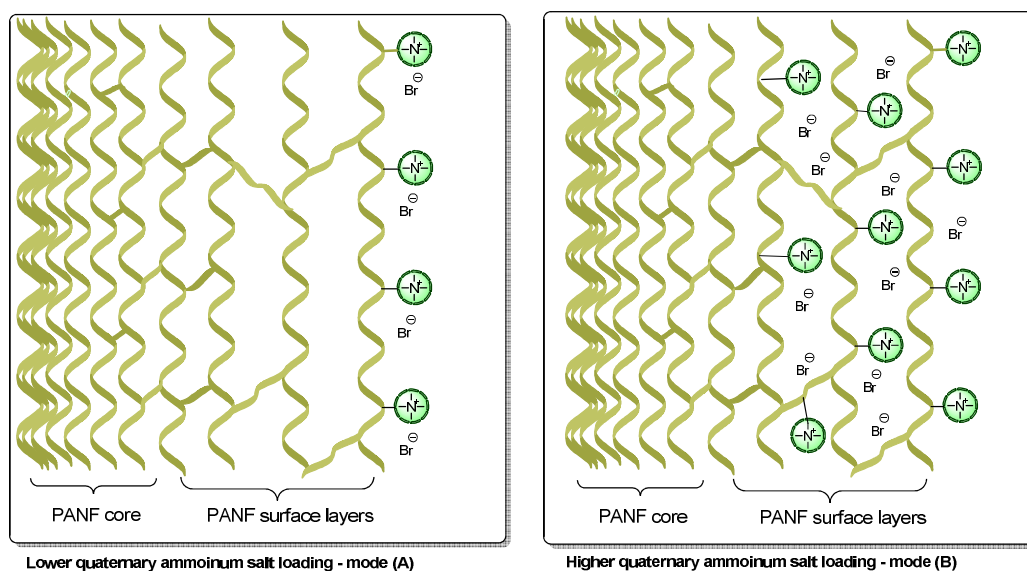

Lower quaternary ammoinum salt loading - mode (A)

Higher quaternary ammoinum salt loading - mode (B)

Figure 5. Two modes of quaternary ammonium salt loading.

loading and the activity was explored by using this catalyst as an example. As shown in Figure 4, the catalytic activity increased with catalyst loading. A yield of 39% was obtained when the catalyst loading was 0.46 mmol/g, whereas a 85% yield was obtained when the catalyst loading was increased to 1.74 mmol/g.

A nonlinear relationship between the yield and loading density was observed, which showed that the reaction rate increased slightly (lower than 1.0 mmol/g) followed by radical increase (in the range of 1.0-1.5 mmol/g) while remained constant beyond 1.5 mmol/g. The mechanism might be different for high loading fibers and low loading fibers for the catalysis of reactions. At lower catalyst loadings (mode A, Figure 5), the quaternary ammonium active sites were only sporadically immobilized on the surface of the insoluble support. In these cases, the ammonium sites are independently and seperately present in the surface of the fiber catalyst, forming independent micro-reactors where the reactions occurred, which is the case for general supported PTCs catalyzed reactions such as PTCs immobilized on silica gel, and polystyrene matrices. However, with the increase of the catalyst loading, the quaternary ammonium salts might root not only on the surface of the fiber but also onto the multilayered polymer chains inside the fiber (mode B, Figure 5). In this case, a microenvironment formed and the anions can move freely in it beneath the surface of the fiber.

The different mechanisms suggested in Figure 5 could also be applied to explain the results in Table 3. For example, when the length of the longest alkyl chain was gradually increased from C2 to C7 (entries 1-3), the reaction yields increased from 36% to 99%. This is because the reactants are much easier to permeate into the surface layers of fiber due to the hydrophobic interaction among long alkyl chains. According to Figure 5, we can deduce that a topological structure which allows sufficient separation between the anions and cationic centers will be prone to enhance the move of the anions in the organic phase more freely.[24] Thus when the two methyl groups in **A-Bn-Cl** were replaced by two ethyl groups to give **A$_E$-Bn-Cl**, the cationic radius was increased and anions were further away from the cationic centers. Consequently, the reaction yields increased from 83% (catalyzed by **A-Bn-Cl,** entry 5) to 90% (catalyzed by **A$_E$-Bn-Cl**, entry 10). Approximately the same yields were produced by **A$_E$-Bn-Cl** (90%, entry 10) and **A$_E$-Bn-Br** (91%, entry 11), indicating that the type of anion has little impact on the catalytic activity. Again this result can be attributed to the fact that the anions (Cl$^-$, Br$^-$) can freely move throughout the surface layers and exchange with BH$_4^-$ ions. These structure-activity results show that the catalytic activity of these catalysts can be effectively tuned by varying the length of the alkyl chain, the cationic radius of the quaternary ammonium cation, or the lipophilicity of the salt.

Effect of reaction conditions on the reduction reaction

Among all the catalysts screened, catalysts **A-Hp-Br** and **A-BnBu-Cl** afforded the highest yields (entries 3 and 7 in Table 3) for the reduction of 1-naphthaldehyde in the given time.
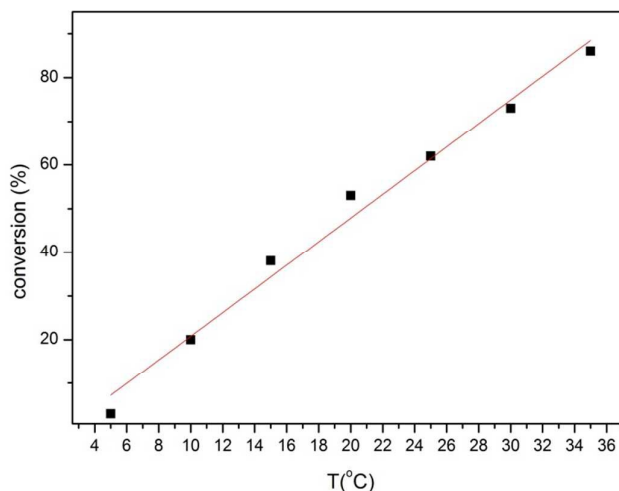

Figure 6. Effect of temperature on the reduction reaction. Reaction conditions: 4 mmol of 1-naphthaldehyde, 2 mmol of NaBH$_4$, 10 mol % of **A-Hp-Br**, 15 mL of pH=12 aqueous solution, 0.5 h. Yields were calculated from GC analysis using naphthalene as an internal standard.

Catalyst **A-Hp-Br** was selected as model catalyst for further optimization because it was easier to prepare.

First, the effect of temperature on the reaction was investigated and the results were shown in Figure 6. The reaction rate of the reduction of 1-naphthaldehyde increased linearly with temperature.

Next, the effect of the amount of catalyst on the reaction was studied and the results were presented in Figure 7. Different from ordinary heterogeneous catalytic reactions which have maximum amount of catalyst, the rate of reduction was found to be linearly dependent on the amount of catalyst. These results are typical for a soluble PTC[22,25] which means that the PANF-immobilized catalyst **A-Hp-Br** maintains the high activity as homogeneous catalyst.
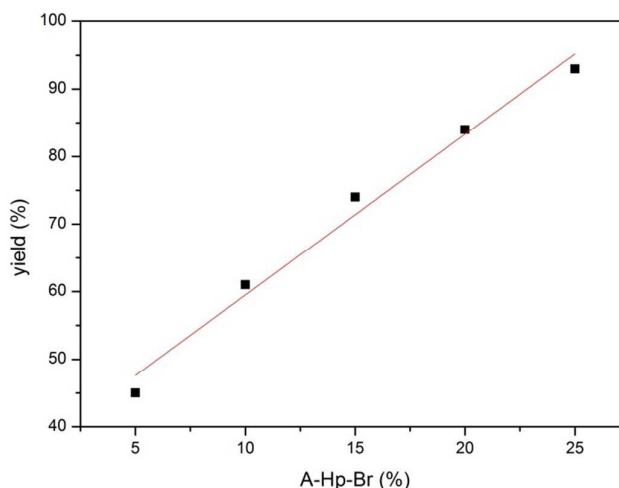

Figure 7. Effect of the catalyst concentration on the reduction reaction. Reaction conditions: 4 mmol of 1-naphthaldehyde, 2 mmol of NaBH$_4$, 15 mL of pH = 12 aqueous solution, 0.5 h, 25 °C. Yields were calculated from GC analysis using naphthalene as an internal standard and the catalyst loading of **A-Hp-Br** was 1.56 mmol/g.

Table 4. Effect of pH on the reduction of 1-naphthaldehyde.

Entry	Original pH[a]	Actual pH[b]	$t_{1/2}$[c]	Yield (%) /0.5 h[d]	Yield (%) /1 h[d]
1	7.0-10.0	9.7	31 min	66	88
2	11.0	9.9	45 min	65	92
3	12.0	11.9	81 h	62	99
4	13.0	12.9	812 h	60	98

[a] The original pH values of NaOH aqueous solution. [b] The pH values of stable solution after addition of NaBH$_4$. [c] The half-life of hydrolysis of NaBH$_4$ calculated by Kreevoy's equation. [d] GC yield using naphthalene as an internal standard

Finally, the effect of pH on the yield was also investigated. According to the Kreevoy's equation,[26] the hydrolysis of NaBH$_4$ in water is closely related to the pH value and temperature. After addition of NaBH$_4$, a buffer solution with pH value of 9.7 was formed. It has great impact on the original NaOH solution with lower pH values from 7 to 11 (entries 1-2, Table 4), however, it has less influence on those NaOH solutions with higher pH values (entries 3 and 4).

When the reactions were performed at 25 ^{o}C for 0.5 h, the reaction was incomplete. The yields decreased from 66% to 60% with the increasing of the actual pH from 9.7 to 12.9. This suggested that the reduction slows down slightly at high pH values and the lower yields may attribute to the interference of hydroxyl ion.

According to the Kreevoy's equation, the $t_{1/2}$ (the half-life) for NaBH$_4$ at 298 K is 31 min when the pH is 9.7 while it prolongates to 81 h when the pH is 11.9. Therefore, NaBH$_4$ consumed in a large amount due to rapid hydrolysis at low pH value of 9.7 within 0.5 h, and only a yield of 88% was obtained even the reaction time was prolonged to 1 h. However, the hydrolysis of NaBH$_4$ was much slower under high pH values and the remained NaBH$_4$ continues to reduce the reactants to afford higher yields (entries 3 and 4).

Besides, the hydrolysis of NaBH$_4$ speeds up with the increasing of temperature and decreasing of pH value according to the Kreevoy's equation. In order to perform the reduction in water, some solid reactants listed in Tables 5-7 must be heated to melt (up to 70 ^{o}C), so that high pH value was required to restrain the hydrolysis of NaBH$_4$. Based on the above discussion, pH of 12 was chosen as the optimal value for standard reduction condition.

Application of the PTC to organic synthesis

Most aldehydes, ketones,[20] and azides[27] can be reduced by NaBH$_4$ in methanol with good yields but the solvent was environmentally unfriendly. Although the reduction of aldehydes, ketones,[28] and azides[29] with PTC can increase the reaction rates in aqueous phase, the catalysts are hard to recover from the reaction mixture. However, the use of the PANF-QAS catalysts can effectively reduce the amount of NaBH$_4$ and shorten the reaction time. After the reaction, the PANF-QAS catalyst can be washed and reused in another cycle without additional treatment.

A series of aldehydes, ketones, azides, and halides were reduced using NaBH$_4$ in the presence of **A-Hp-Br** as catalyst in water and the results were given in Tables 5-7. For solid substrates, the temperature was adjusted according to their

Table 5. Reduction of aldehyde by A-Hp-Br catalyst in water.

Entry	Aldehyde	Product	NaBH$_4$ (eq)	Time (min)	Temp (°C)	Yield (%)	Blank Yield (%)[b]
1	2a	3a	0.5	40	35	97	12
2	2b	3b	0.5	10	35	99	70
3[a]	2c	3c	0.5	40	35	95	15
4	2d	3d	0.5	30	70	99	3
5[a]	2e	3e	0.5	90	55	96	8
6[a]	2f	3f	0.5	60	35	94	7
7[a]	2g	3g	0.5	30	35	93	6
8	2h	3h	0.5	20	35	99	16
9	2i	3i	0.5	15	35	98	46
10	2j	3j	0.5	25	35	99	13
11	2k	3k	0.5	15	35	98	5
12[c]	2l	3l	0.5	10	50	99	8
13[a,c]	2m	3m	1	60	35	95	3
14[c]	2n	3n	1	90	50	94[d]	9

[a] Isolated yield by column chromatograph. [b] Blank yield relates to the reaction with no catalyst. [c] Addition of 3 mL of ethyl acetate to dissolve the reactants. [d] The yield was determined by HPLC using naphthalene as internal standard and 3% of 4-nitrobenzoic acid was observed.

melting point. For the liquid substrates, a reaction temperature of 35 ^{o}C was used. All of the substrates shown in Tables 5 and 6 were efficiently reduced by NaBH$_4$ with yields of 91%-99% in water.

In order to evaluate the effect of **A-Hp-Br** as the catalyst, blank experiments were performed for comparison. Although NaBH$_4$ can reduce water-soluble aldehydes and ketones with moderate yields (**2b**, **2n** and **2o**), excellent yields were obtained when catalyst **A-Hp-Br** was added. For water-insoluble aldehydes and ketones such as 4-benzyloxybenzaldehyde (**2d**) and diphenylmethanone (**2q**) only 3% and 10% yields respectively were afforded with NaBH$_4$ in water. However, upon the addition of **A-Hp-Br**, yields of 99% and 97% were obtained respectively (entry 4, Table 5 and entry 4, Table 6). When an electron-deficient aldehyde (entry 14, Table 5) was used, 4-nitrobenzyl alcohol was obtained in 94% yield by HPLC, and only 3% of 4-nitrobenzoic acid, the product of Cannizzaro reaction, was observed. It's well known that the Cannizzaro reaction was performed under strongly alkaline condition, so the condition of pH value of 12 was too weak to promote this reaction.

| #	Substrate	Product					
1	2o	3o	0.5	1.5	35	99	65
2	2p	3p	0.5	0.7	35	97	52
3[a]	2q	3q	0.5	2.5	35	91	18
4	2r	3r	1.0	4	50	97	10
5[a]	2s	3s	1.0	2	55	91	8
6	2t	3t	1.0	0.5	35	99	30
7[c]	2u	3u	2.0	1.5	50	98	5

[a] Isolated yield by column chromatograph. [b] Blank yield relates to the reaction with no catalyst. [c] Addition of 3 mL of ethyl acetate to dissolve the reactants.

#	Substrate	Product					
1[a]	4a	5a	1.5	5	50	68	15
2	4b	5b	1.0	4	50	98	13
3	4c	5c	1.0	4	50	trace	—
4	4d	5d	0.5	0.3	35	98	4
5[a]	4e	5e	0.5	0.5	50	94	4
6[c]	4f	5f	2.0	1.5	60	99	8
7[a,c]	4g	5g	2.0	2.5	70	95	10

[a] Isolated yield by column chromatograph. [b] Blank yield relates to the reaction with no catalyst. [c] Buffer solution (pH = 12) of Na_2HPO_4/NaH_2PO_4 was used as aqueous solution.

Finally, a steroid of progesterone was also reduced by this system with a yield of 98% (entry 7, Table 6) and the configuration of the product was confirmed by comparing its ^{1}H NMR spectrum (using $CDCl_3$ as solvent) with that in literature.[30] These obvious improvement in activity prove that **A-Hp-Br** is an efficient catalyst to reduce highly lipophilic (water insoluble) aldehydes and ketones in water.

The reduction of azides with **A-Hp-Br** was strongly affected by the substituent. As shown in Table 7, electron withdrawing groups facilitated the reduction, but electron donating groups
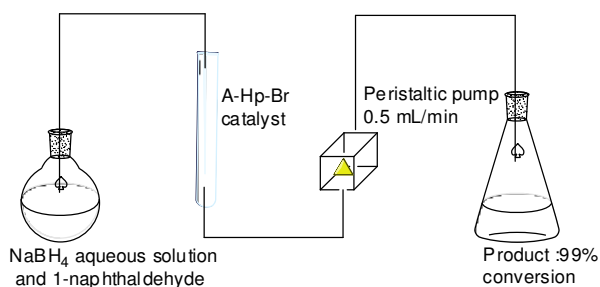
Scheme 3. Diagrammatic sketch of continuous flow process

hindered the reaction. For example, a 94% yield was obtained when 2-azidonitrobenzene (**4e**, entry 5 in Table 7) was reduced by 0.5 equiv of $NaBH_4$ for 0.5 h, but the reduction of azidobenzene (**4b**, entry 2 in Table 7) required as long as 4 h with 1 equiv of $NaBH_4$ to get a similar yield. Furthermore, only a trace amount of product was obtained in the reduction of 4-methoxyphenylazide (**4c**, entry 3 in Table 7) under the same conditions. With the addition of catalyst **A-Hp-Br**, benzyl halides(**4f**, **4g**) were also reduced in water with nearly quantitative yields (entries 6-7, Table 7).

Flow chemistry of the A-Hp-Br catalyst

The high catalytic activity exhibited by **A-Hp-Br** and its robustness make it a suitable candidate for a continuous flow processing. The very simple flow reactor used to test this hypothesis involved 370 mg of catalyst **A-Hp-Br** (c = 1.08 mmol/g) packed into a silicone column between flask and peristaltic pump. The catalytic column was kept 25^oC while a solution of $NaBH_4$ and 1-naphthaldehyde (4 mmol) were pumped into the system at 0.5 mL/min. Finally, the effluent liquid contains 99% conversion of the product and the blank reaction (the catalyst was replaced by PPF) afforded only 10% yield (Scheme 3).
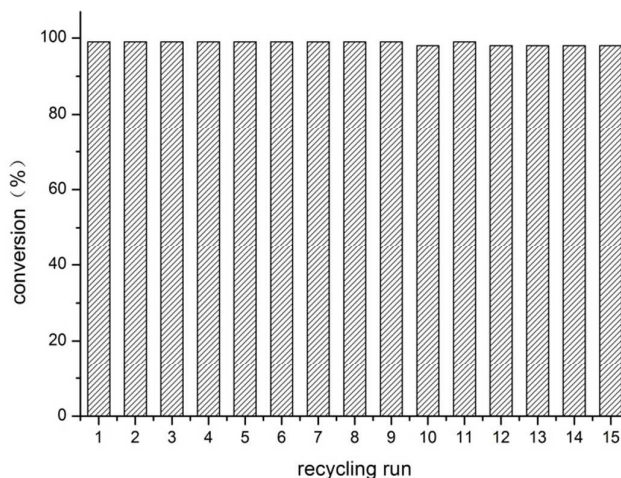

Figure 8. Reusability of the **A-Hp-Br** catalyst in continuous flow process. Reaction conditions: 4 mmol of 1-naphthaldehyde, 2 mmol of $NaBH_4$, 10 mol% of **A-Hp-Br**,. Yields were calculated from GC analysis using naphthalene as an internal standard.

The reusability of **A-Hp-Br** catalyst was also investigated in flow condition and the results are summarized in Figure 8. After each run, 10 mL of ethyl acetate was pumped into the system at 0.1 mL/min to regenerate the fiber catalyst. After fifteen recycles, **A-Hp-Br** catalyst was still as active as the original catalyst (Figure 8). Compared with commonly used PTCs, the PANF-QAS catalyst has advantages of simple work-up procedure for recovery and excellent reusability.

Experimental

Typical procedure for PANF-QAS catalyzed reduction

Corresponding aldehydes, ketones, aryl azides, or benzyl halides (4 mmol), $NaBH_4$ (2 mmol) and **A-Hp-Br** (10 mol%) were added to 15 mL of pH = 12 aqueous solution. The solution was stirred at appropriate temperature and monitored by TLC. After completion, the reaction was quenched by 10% HCl aqueous solution to pH = 7 and filtered to recycle catalyst **A-Hp-Br**, which was washed with ethyl acetate (5 mL×2) and directly used for the next run. The eluted ethyl acetate was used to extract aqueous phase of the reaction mixture and dried over Na_2SO_4. Then the solvent was evaporated (recycled) to give the products (most ones have high purity, a few products with low purities were simply purified through silica gel column).

Typical procedure for continuous flow process

Silicone column was filled with 370 mg of catalyst **A-Hp-Br** (c = 1.08 mmol/g) between flask and peristaltic pump. The catalytic column was kept 25°C while a solution of the $NaBH_4$ (2 mmol) in 20 mL water (pH = 12) and 1-naphthaldehyde (4 mmol) in 1 mL of ethyl acetate were pumped into the system at 0.5 mL/min. Notably, the water and 1-naphthaldehyde were stirred by magnetic stirrer in flask to ensure the mixture is emulsion. After completion, the reaction was pumped into 10 mL of 10% HCl aqueous solution at 0.1 mL/min to quench the reaction, then ethyl acetate (5 mL×2) was pumped in to system at 0.1 mL/min to regenerate the catalyst and directly used for the next run. The eluted ethyl acetate was used to extract aqueous phase of the reaction mixture and dried over Na_2SO_4. Then the solvent was evaporated (recycled) to give the products with high purity without further purification.

Conclusions

A series of quaternary ammonium salts were integrated onto polyacrylonitrile fibers and the structure/loading-activity relationships were investigated which showed that the catalysts containing quaternary ammonium salts with longer alkyl chains, bigger cationic radii, and lipophilic functional groups lead to higher reduction rates. These fiber supported catalysts showed excellent catalytic activities (91%-99%) for a wide scope of substrates including aldehydes, ketones, aryl azides, and benzyl halides. The reduction of 1-naphthaldehyde by the optimized catalyst was performed in continuous flow

processing and the catalyst displays outstanding recyclability and reusability. Further application of PANF-QAS in organic synthesis is on-going in this group.

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