Applied Catalysis A: General 389 (2010) 19–26

Contents lists available at ScienceDirect

Applied Catalysis A: General

journal homepage: www.elsevier.com/locate/apcata

Continuous Henry reaction to a specific product over nanoporous silica-supported amine catalysts on fixed bed reactor

Ankush V. Biradar[a,b], Krishna K. Sharma[c], Tewodros Asefa[a,b,*]

[a] Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, 610 Taylor Road, Piscataway, NJ 08854, USA
[b] Department of Chemical and Biochemical Engineering, Rutgers, The State University of New Jersey, 98 Brett Road, Piscataway, NJ 08854, USA
[c] Department of Chemistry, Syracuse University, 111 College Place, Syracuse, NY 13244, USA

ARTICLE INFO

Article history:
Received 4 May 2010
Received in revised form 25 August 2010
Accepted 29 August 2010
Available online 6 September 2010

Keywords:
Continuous reaction
Henry reaction
Nitroaldol condensation
Solid-base nanocatalyst
Heterogeneous catalyst

ABSTRACT

We report a method for continuously producing the nitroaldol, the nitrostyrene, or the Michael product by performing the Henry reaction over a fixed bed reactor that is packed with primary or secondary amine-functionalized nanoporous materials. The % conversion of the reactants as well as the % selectivity to the particular product were found to be strongly dependent on the residence time of the reactants in the reactor (weight hourly spatial velocity or WHSV) as well as the type of reactant, catalyst and reaction temperature used. When a 0.08 M p-hydroxybenzaldehyde solution in nitromethane was passed over the fixed bed reactor containing primary amine-functionalized mesoporous silica catalyst by postgrafting in toluene (AP-T) at 90 °C with WHSV of 0.20, the reactor continuously and selectively generated for hours the p-hydroxy-β-nitrostyrene product with 100% selectivity at 31% reactant conversion (or with 90% selectivity at 88% reactant conversion for WHSV of 0.10). The remaining 12% product in the latter case was the Michael product. The corresponding primary amine-functionalized sample prepared by postgrafting of 3-aminopropyltrimethoxysilane (APTS) in isopropanol (AP-I) also gave similar results with slightly higher efficiency and selectivity to p-hydroxy-β-nitrostyrene. When the same reactant solution was passed over the bed-reactor packed with secondary amine grafted mesoporous silica catalyst by postgrafting in toluene (MAP-T) with WHSV of 0.25 at 90 °C, the reactor also continuously produced selectively the p-hydroxy-β-nitrostyrene product but less efficiently; i.e. with 91% selectivity at 21 reactant conversion for WHSV of 0.20 (or with 85% selectivity at 34% reactant conversion for WHSV of 0.10). Here also, the remaining product was the Michael addition product. Increasing the reaction temperature of the reactor containing the primary amine catalyst to 150 °C at WHSV of 0.10 for p-hydroxybenzaldehyde reactant led to the reversal of the product type from being 90% p-hydroxy-β-nitrostyrene to >85% Michael product with ~100% reactant conversion. Raising the reaction temperature of the reactor containing a secondary amine catalyst for p-hydroxybenzaldehyde reactant also increasingly favored the formation of the Michael product. When changing the reactant to 0.08 M p-nitrobenzaldehyde, the reactor packed with secondary amine catalyst resulted in the nitroalcohol product with 90% selectivity at 40% reactant conversion for WHSV of 0.15. These results indicate that higher WHSV lead to greater selectivity to a particular product; however, lower WHSV and higher temperatures favor greater reactant conversion reaching as high as ~100% in all the cases although they can be accompanied by less % selectivity. By simply adjusting the WSHV's or the temperatures to optimum values, one of the products can be exclusively generated in a continuous manner. The continuous reactor and the catalysts were proven to catalyze the reactions and give the respective product(s) continuously for several days. This method can be used as a route for the mass production of industrially and pharmaceutically important p-substituted nitroalcohol, nitrostyrene, or Michael addition product with high selectivity, by simply packing mesoporous catalysts within a fixed bed reactor.

1. Introduction

Base-catalyzed reactions have gained growing attention for homogeneous and heterogeneous catalytic transformation of a number of chemical compounds. In this context, supported amine catalysts have been demonstrated to have great utility in hetero-

* Corresponding author at: Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, 610 Taylor Road, Piscataway, NJ 08854, USA. Tel.: +1 732 445 2970; fax: +1 732 445 5312.
E-mail address: tasefa@rci.rutgers.edu (T. Asefa).

0926-860X/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.apcata.2010.08.056

geneous base catalysis, especially for the production of organic compounds with new carbon–carbon bonds. Notable examples include the aldol [1], Knoevenagel [2], the Michael [3] and the Henry reactions [4]. The Henry reaction, also called the nitroaldol condensation, is one of the most important C–C bond formation reactions [5] that allows the synthesis of a plethora of key molecular frameworks such as β-hydroxynitroalkanes, 1,2-aminoalcohols and α-hydroxy carboxylic acids in a simple and convenient manner [6]. These compounds are widely used as intermediates for making various types of pharmaceutical products, insecticides, fungicides, bactericides, rodent-repellant, and antitumor agents [7–9]. The Henry reaction can also be used in the preparation of prostaglandins, pyrroles, and porphyrins [10,11]. Because of its importance, many homogeneous and heterogeneous catalysts have been developed for the Henry reaction. These include alkali metal hydroxides, carbonates, bicarbonates, and alkoxides, barium and calcium hydroxides, magnesium and aluminum ethoxides, organometallic complexes, rhodium complexes, potassium exchanged zirconium phosphate [5,6] and organic bases, either in homogeneous form or tethered onto solid support materials [12].

Recent literature reveals that new synthetic strategies to develop efficient solid-base heterogeneous catalysts for the Henry reaction have still been in progress. Among these, methods for the synthesis of heterogeneous base catalysts by immobilizing organoamine groups including primary, secondary or tertiary amines, either individually or together, on silica based materials such as mesoporous silica (MCM-41) [12–16], silica gel [17], and silica–alumina surfaces [18] have been reported. Many of these solid-base catalysts predominantly produce the dehydrated, nitrostyrene product from the Henry reaction between substituted benzaldehydes and nitroalkanes. In some cases, the Michael addition and polymeric products were also reported to form. In a few cases, base-catalyzed nitroaldol condensation reactions over catalysts such as hydrotalcite and other systems were reported to exclusively produce the nitroalcohol product in yields often exceeding 80% [19,20]. The formation of a mixture of the two or more of these Henry reaction products is also quite common in the Henry reaction depending on the catalyst [21]. Furthermore, many of these base-catalyzed Henry reactions require a relatively large amount of catalyst with respect to the reactants, while producing limited or milligram quantities of the dehydrated, and in some cases, the mixture of the dehydrated, aldol or the Michael addition products. Consequently, it is very difficult to produce the Henry reaction products in large quantities and with less byproducts, with batch reactions and using many of the aforementioned catalysts.

Continuous flow catalytic processes are important in modern synthetic chemistry as they are efficient in converting reactants and forming products continuously and in large quantities [22–25]. Furthermore, they enable simpler catalytic processes and result in reusable catalysts with longer life-times. Another significant advantage of a continuous flow catalytic system includes its ability to prevent significant leaching of the active catalyst in it, as the catalytic sites are covalently attached to a solid support, which in turn is packed within a bed reactor. Continuous flow methods also make catalytic operations simpler due to the ease of catalyst preparation, continuous product formation, and fewer work-up procedures that they involve. Using continuous flow techniques, the synthesis of various organic compounds have already been successfully demonstrated [26–35]. This includes base-catalyzed reactions capable of producing α-ketoesters or other products in a continuous flow [26]. Very recently, successful continuous tandem reaction catalyzed in a one column-reactor packed with propylamine (KG-60-NH_2)- and guanidine TBD (KG-60-TBD-$SiMe_3$)-functionalized amorphous silica (KG-60) was reported [36]. In this reactor, the aromatic aldehyde substrate reacted with nitroalkane via nitroaldol condensation over the propylamine (KG-60-NH_2) catalyst to form nitrostyrene product, which subsequently underwent the Michael addition with β-dicarbonyl over the second catalyst (KG-60-TBD$SiMe_3$).

We have recently reported the synthesis of efficient heterogeneous multifunctional catalysts for various base-catalyzed batch reactions including the Henry and aldol condensation reactions [37–40]. These catalysts were synthesized by a simple grafting or functionalization of the surface of mesoporous silica with organoamines. In these previous works, we have also demonstrated that using polar-protic solvents in the grafting step improved the materials' catalytic performance in base-catalyzed reactions [37,38]. Here we report that these efficient catalysts can also be used in industrial type continuous reactions for the production of large quantities of one of the Henry reaction products, without producing much byproducts. This is very useful especially considering the fact that there is a high demand industrially for the Henry reaction products in pure form and in large quantity for making a variety of compounds [6–8].

2. Experimental

2.1. Materials and reagents

Cetyltrimethylammonium bromide (CTAB), tetraethylorthosilicate (TEOS), 3-aminopropyltrimethoxysilane (APTS), sodium hydroxide, anhydrous toluene, anhydrous ethanol, p-hydroxybenzaldehyde, p-nitrobenzaldehyde, nitromethane and anhydrous ethanol were obtained from Sigma–Aldrich. 3-(N-methylaminopropyl)trimethoxysilane (MAPTS) was obtained from Gelest, Inc. All reagents were used as received without any further purification.

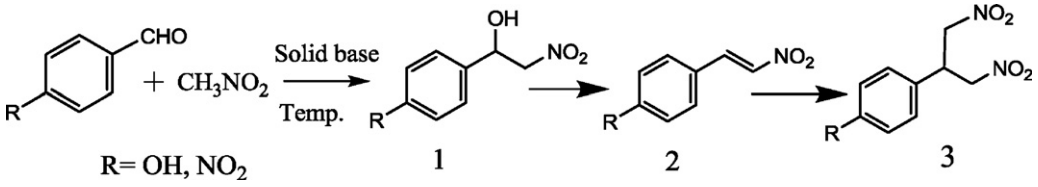
2.2. Preparation of catalysts

Mesoporous silica (MCM-41) was prepared as reported previously [39–41]. Typically, 11 mmol CTAB was dissolved in 960 mL of Millipore water and 14 mL of 2.0 M NaOH solution. After moderately stirring the solution at 80 °C for 30 min, 22.6 mL (101.2 mmol) of TEOS was added into it. The resulting solution was stirred for another 2 h at 80 °C. The hot solution was then filtered and the solid product was washed with Millipore water (4× 80 mL), followed by ethanol (4× 80 mL), and then dried in oven at 80 °C. This resulted in as-synthesized mesostructured MCM-41. To remove the surfactant template, 6 g of the as synthesized MCM-41 was suspended in a mixture of 3 mL (12.1 N) hydrochloric acid and 600 mL anhydrous ethanol and stirred at 50 °C for 5 h. The resulting solution was filtered and the solid sample was washed with copious amount of Millipore water and ethanol (3× 80 mL in each case). The extracted mesoporous silica (MCM-41) was dried in oven at 80 °C overnight before being functionalized with the aminoorganosilanes.

The organoamine functionalized mesoporous samples were prepared by grafting APTS (or MAPTS) onto MCM-41 in toluene (or isopropanol). Typically, 2.5 g of the MCM-41 was stirred with 9.2 mmol of 3-aminopropyltrimethoxysilane (APTS) or 3-(N-methylaminopropyl)trimethoxysilane (MAPS) in 750 mL of anhydrous toluene (or isopropanol) at 80 °C for 5 h. The resulting solution was filtered while it was still hot. The solid sample on the filter paper was washed with ethanol, followed by dichloromethane and finally ethanol, and let to dry at ambient conditions in air. The solid samples obtained from APTS and MAPTS in toluene were labelled as AP-T and MAP-T, respectively. Similarly, the APTS grafted sample in isopropanol was labelled as AP-I.

2.3. Catalysis

The continuous catalytic nitroaldol (Henry) reaction to produce one or a mixture of the three possible C–C coupled products shown



Scheme 1. Amine-functionalized mesoporous catalyst packed fixed bed reactor catalyzed continuous Henry reaction and its possible reaction products.

in Scheme 1 was carried out using a down-flow fixed bed glass reactor (Fig. 1) at atmospheric pressure. To prepare the reactor, 2 g of the amine grafted mesoporous particles (catalyst) was first pressed into small pellets of ~2 mm in diameter and ~1–2 mm thick. These pellets were then loaded in a tubular glass reactor of 15 mm in diameter and 25 cm in length, that was already partially filled with some inert glass beads underneath. After packing the catalyst into the reactor, the upper part of the reactor was further packed with an additional inert glass beads to serve as a preheating zone for the reactants to make them reach to the required reaction temperatures before they contact the catalyst. The glass reactor was wrapped with a heating tape and equipped with a thermocouple to monitor its temperature. Then, 0.08 M solution of p-substituted aromatic aldehyde in nitromethane was injected with different flow rates into the flow reactor using syringe pumps. The reaction mixture was condensed at 10 °C with a condenser, that was placed under the reactor, and collected. The samples were periodically collected and analyzed by gas chromatography (GC), gas chromatography–mass spectrometry (GC–MS) and ^{1}H NMR spectroscopy. The latter was measured in deutrated acetone. Resonances in acetone d_6 ppm: (1) 4-(1-hydroxy-2-nitroethyl)phenol: 7.29 (2H, d), 6.78 (2H, d), 4.91 (2H, s), and 2.8 (1H, s); (2) 4-(2-nitrovinyl)phenol: 7.62 (2H, d), 6.70 (2H, d), 8.25 (1H, d), and 7.87 (1H, d); (3) 4-(1,3-dinitropropan-2-yl)phenol: 7.19 (2H, d), 6.78 (2H, d), 4.64 (2H, s), and 4.48 (1H, m); (4) 1-nitro-4(2-nitrovinyl)-benzene: 8.19 (2H, d), 8.108 (1H, d), 8.38 (2H, d), and 7.87 (1H, d); (5) 1-(4-nitrophenyl)-2-nitroethanol: 8.19 (2H, d), 7.72 (2H, d), 5.53 (1H, m), and 4.61 (2H, m); (6) 1-(1,3-dinitro propanyl)-4-nitro benzene: 8.20 (2H, m), 7.56 (2H, d), 4.85 (2H, m), 4.75 (2H, m), and d 4.36 (1H, m).

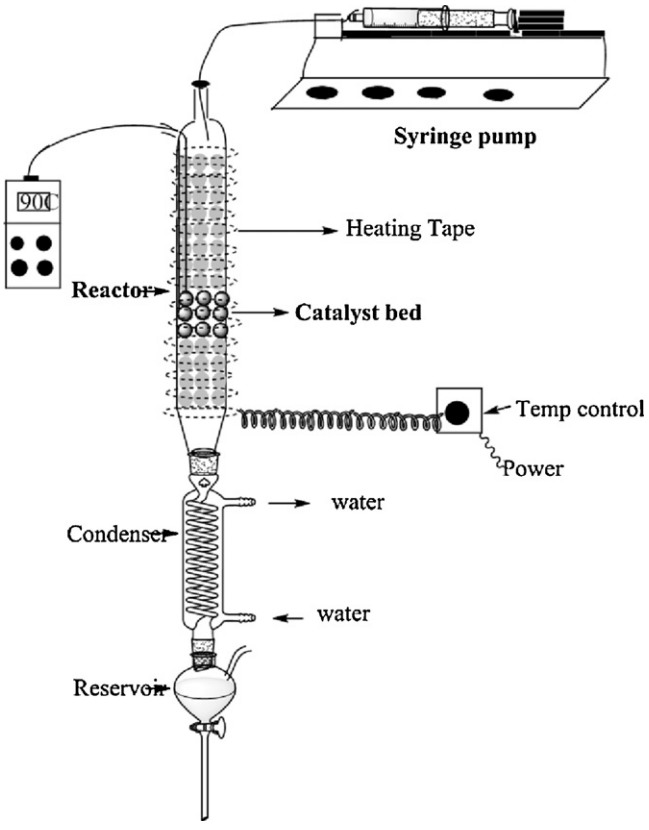


Fig. 1. Schematic diagram of amine-functionalized mesoporous silica catalyst packed fixed bed reactor for the continuous Henry reaction.

2.4. Characterization

The nitrogen gas adsorption–desorption measurements were carried out on Micromeritics Tristar 3000 volumetric adsorption analyzer after degassing the samples at 160 °C for 12 h. The TEM images were acquired by using a FEI Tecnai T-12 S/TEM transmission electron microscope that was working at 120 keV. The samples for TEM analysis were prepared by sonicating the mesoporous catalysts in ethanol for 3 min, casting a few drop of the solutions on a formvar-carbon coated copper grid and letting them to dry under ambient conditions. The GC was performed on Agilent HP 6850 containing a flame ionization detector and HP-1, MS 30 m × 0.200 mm × 0.25 μm capillary column. The GC–MS experiment was conducted with HP-5890 equipped with 5972 MSD and HP-5 MS 50 m × 0.200 mm × 0.33 μm capillary column. The ^{1}H NMR spectra of the reaction mixture was run with a Brüker DPX-300 NMR spectrometer.

3. Results and discussion

The Henry reaction products (nitrostyrene, nitroaldol, or the Michael product) (Scheme 1) were produced in a continuous flow by using continuous flow fixed bed reactors (Fig. 1) that are packed with different solid-base, selective mesoporous silica catalysts. The catalysts included primary and secondary amine-functionalized mesoporous materials, which were prepared as reported previously [37]. Briefly, a solution of 3-aminopropyltrimethoxysilane (APTS) or 3-(N-methylaminopropyl)trimethoxysilane (MAPS) in toluene (or isopropanol) was stirred with mesoporous silica (MCM-41) at 80 °C. This resulted in highly ordered primary amine and secondary amine-functionalized mesoporous silica microparticles, respectively, with average BJH pore diameter of 2.7 nm, as measured by nitrogen gas adsorption (Fig. 2). The microparticles have sizes ranging between 400 and 900 nm (Fig. 3). These microparticles were pressed into small pellets and packed into a glass capillary microreactor. Before packing them into the fixed bed reactor, one-third of the glass reactor was filled with inert glass beads in order to create a uniform heating zone for the catalyst in the reactor. After packing the pellets on top of the beads in the reactor, additional inert glass beads were added into the remaining one-third of the reactor, above the top layer of the catalyst. The latter glass beads enabled us to pre-heat the reactants to a particular reaction temperature before the reactants reached the catalyst, that was sandwiched between the two layers of the glass beads. The temperature of the reactor was controlled by a heating tape with a very high precision digital temperature regulator. The reactants were then continuously run through the fixed bed reactor at different WHSV's. To start the reaction, 0.08 M solution of the p-substituted

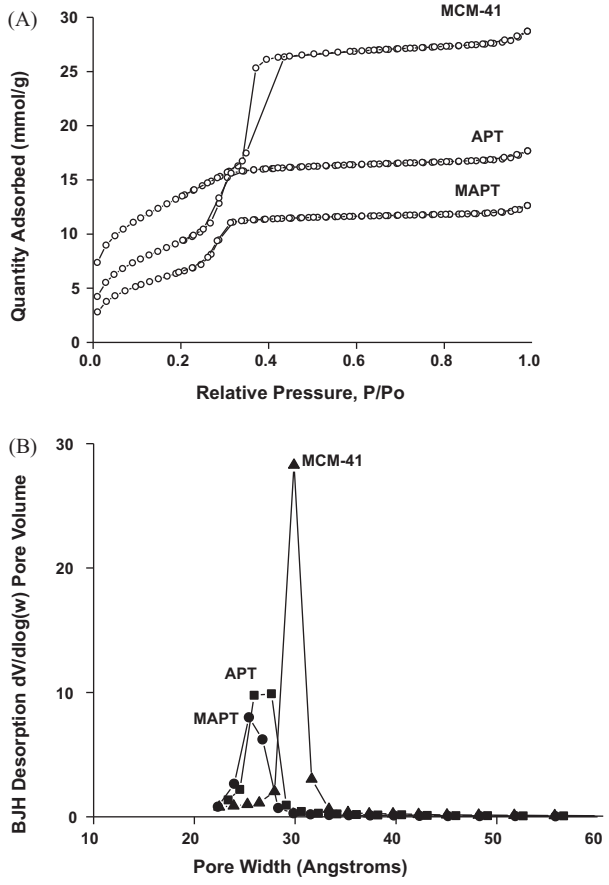


Fig. 2. N_2 gas adsorption isotherms (A) and pore size distributions (B) of the parent mesoporous silica (MCM-41) and primary and secondary amine-functionalized mesoporous silica catalysts (AP-T and MAP-T, respectively) used in the fixed bed reactor for the continuous Henry reaction.

benzaldehyde in nitromethane was injected at different WHSV's from the top of the reactor using a syringe pump with controlled flow rate. The product was cooled and collected in a reservoir at the bottom of the reactor. Depending on the catalyst, the reaction temperature, the reactant type, and the flow rates, the reactor gave the p-substituted nitroaldol (1), nitrostyrene (2), the corresponding Michael addition product (3), or even a mixture of the two or three products in different ratios (see below) in a continuous flow.

First, 0.08 M solution of p-hydroxybenzaldehyde in nitromethane was poured at different weight hourly spatial velocities (WHSV's) into the top of the reactor packed with primary amine-functionalized mesoporous catalyst at 90 °C. This gave the p-hydroxy-β-nitrostyrene or a mixture of p-hydroxy-β-nitrostyerene and its corresponding Michael product with different % reactant conversions, depending on the WHSV's used (Table 1 and Fig. 4). For instance, at lower WHSV of 0.05, ~100% conversion of p-hydroxybenzaldehyde occurred; however, it was accompanied by lower selectivity to either product, giving a 57%:43% ratio of p-hydroxy-β-nitrostyrene: Michael. Upon increasing the flow rate of the reactants (or decreasing the WHSV), the reaction produced significantly more proportion of p-hydroxy-β-nitrostyerene, although the % reactant conversion became lower. When the WHSV was increased to 0.10, 88% conversion of p-hydroxybenzaldehyde with 90% p-hydroxy-β-nitrostyrene product was obtained. While further increase in WHSV led to lower % conversion, it gave exclusively (~100%) p-hydroxy-β-nitrostyrene product (Table 1, entries 3–5). These results indicated that the reactor with primary amine catalyst favored the formation of nitroalcohol in the initial period of the reaction and its selectivity

Table 1
Effect of reactant flow rate (WHSV) on the Henry reaction in AP-T reactor for p-hydroxybenzaldehyde reactant[a].

Entry	Catalyst	WHSV	% Conversion	% Selectivity	
				2	3
1	AP-T	0.05	100	57	43
2	AP-T	0.10	88	90	10
3	AP-I	0.10	96	94	6
4	AP-T	0.15	64	96	4
5	AP-T	0.20	31	100	0
6	AP-T	0.25	10	100	0

[a] Reaction conditions: reactants: 0.08 M p-hydroxybenzaldehyde in nitromethane; temperature: 90 °C; and catalyst: AP-T (or AP-I), 2 g in pellet form.

to the Michael product with respect to the nitrostyrene product was affected mainly by the value of WHSV. As the residence time increased (or WHSV is lowered), the p-hydroxy-β-nitrostyrene product in the reaction bed increasingly underwent the Michael addition reaction with the excess nitromethane, resulting in the corresponding Michael product. This clearly suggests that the reaction gives first the p-hydroxy-β-nitrostyrene product, which is subsequently converted into the corresponding Michael addition product if the reaction mixture stays in the reactor for longer enough times. Such conversion of p-substituted β-nitrostyrenes into their corresponding Michael products is very common for the Henry reaction when catalyzed with similar or related catalysts [12–18,22].

Similarly, sample (AP-I) gave similar results as sample AP-T. It in fact, exhibited higher catalytic efficiency with 96% conversion of p-hydroxybenzaldehyde at WHSV of 0.10 and a slightly better selectivity of 94% to product 2 (p-hydroxy-β-nitrostyrene) compared to AP-T. The remaining 6% product was product 3 (the Michael product) (Table 1, Entry 3). For comparison, AP-T gave 88% conversion of p-hydroxybenzaldehyde at WHSV of 0.10 with selectivity of 90% to product 2 under the same conditions. This result is not surprising in light of our previous reports on amine-functionalized mesoporous catalysts prepared by grafting 3-aminopropyltrimethoxysilane in isopropanol versus in toluene [37,38], except that the differences here are relatively less dramatic.

Next, the effect of the reaction temperature on the Henry reaction between p-hydroxybenzaldehyde and nitromethane over the primary amine catalyst bed-reactor was studied in the range of 70–150 °C at a constant WHSV of 0.1 (Table 2). At 70 °C, the % conversion of p-hydroxybenzaldehyde was very low (5%) for WHSV of 0.1; however, it was accompanied by 100% p-hydroxy-β-nitrostyrene product. At 90 °C for the same WHSV of 0.10, the % conversion increased drastically, giving 88% reactant conversion and 90% p-hydroxy-β-nitrostyrene product. The remaining 10% of the product in this case was the Michael product. Further increase in temperature resulted in a higher % conversion of the p-hydroxybenzaldehyde reactant, reaching ~100%, while at the same time, favoring the conversion of p-hydroxy-β-nitrostyrene

Table 2
Effect of temperature on the Henry reaction in AP-T reactor for p-hydroxybenzaldehyde reactant[a].

Entry	Temperature (°C)	% Conversion	% Selectivity	
			2	3
1	70	5	100	0
2	90	88	90	10
3	110	100	68	32
4	130	100	41	59
5	150	100	15	85

[a] Reaction conditions: reactants: 0.08 M p-hydroxybenzaldehyde in nitromethane; WHSV: 0.10; and catalyst: AP-T, 2 g in pellet form.

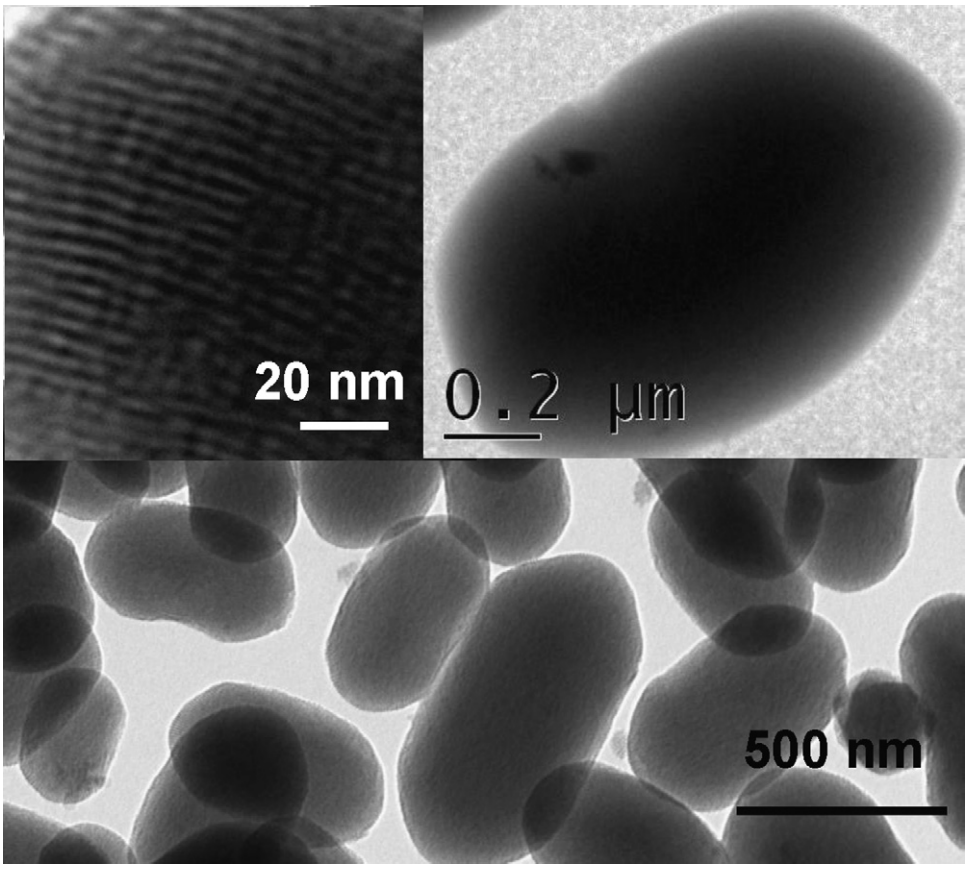


Fig. 3. TEM images showing the microparticles of the amino-functionalized mesoporous catalysts used in the fixed bed reactor.

into the corresponding Michael product (Table 2, entries 3–5). For instance, at 150 °C, a 100% reactant conversion with 85% Michael product and only 15% p-hydroxy-β-nitrostyrene was obtained. Consequently, raising the temperature helped the reactor generate the Michael product in a continuous manner rather than p-hydroxy-β-nitrostyrene, while at the same time, increased the reaction's rate and % reactant conversion. In other words, increasing the reaction's temperature could reverse the % selectivity or the type of reaction product that the primary amine reactor forms from being p-hydroxy-β-nitrostyrene to the Michael product. The type of reaction product that the reactor generated was also qualitatively confirmed from the different color observed for the reaction mixtures at different temperatures as seen in Fig. 5.

To further compare the effect of the type of amine groups of the catalyst on the reactor's catalytic activity and property, we used a bed reactor that was packed with secondary amine

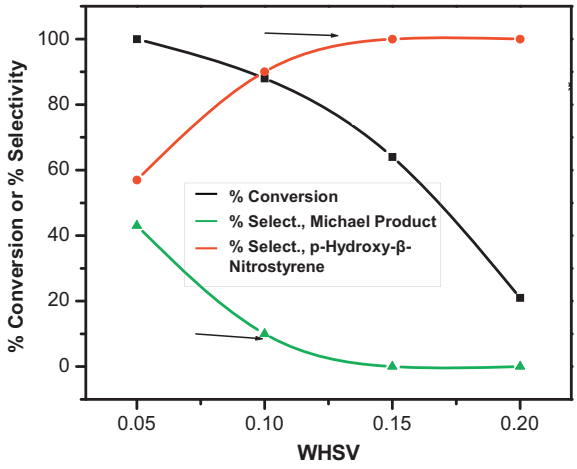


Fig. 4. Plot of % conversion or selectivity versus weight hourly specific velocity (WHSV) (or mass flow/mass of catalyst) for AP-T catalyst with p-hydroxybenzaldehyde reactant. The black curve shows the % conversion with respect to WHSV. The red curve shows the % selectivity to nitrostyrene product with respect to WHSV. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

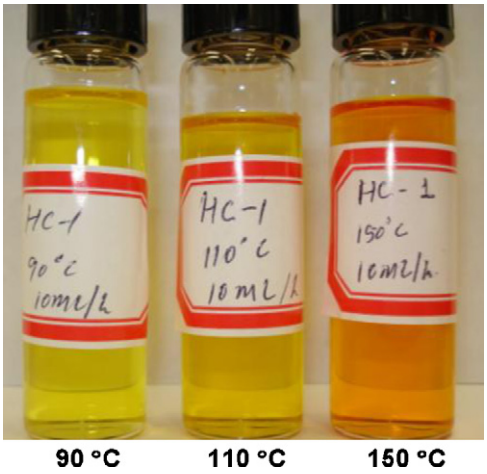


Fig. 5. Digital images of the reaction mixture of p-hydroxybenzaldehyde and nitromethane with AP-T catalyst in fixed bed reactor at different temperatures. While the yellow color is indicative of the formation of p-hydroxy-β-nitrostyrene, the orange color suggests the presence of a significant amount of the Michael product. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

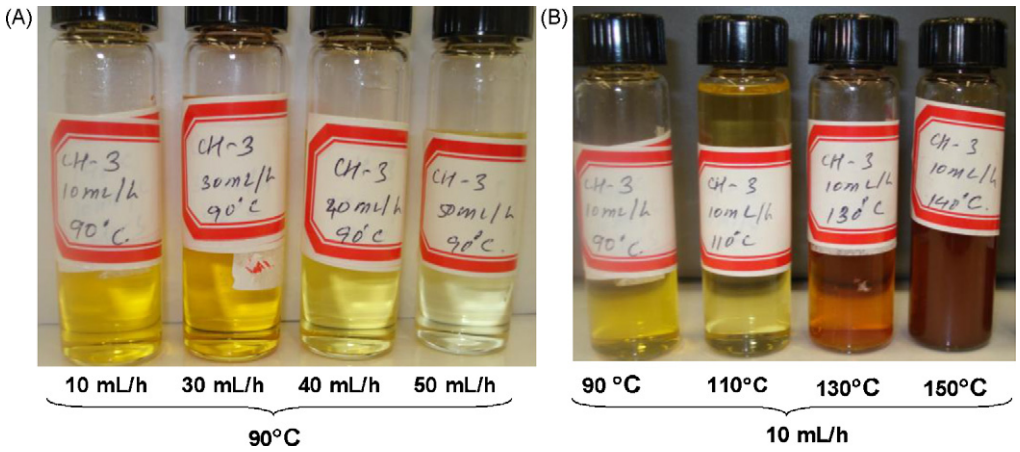


Fig. 6. Digital images of the reaction mixture of p-hydroxybenzaldehyde and nitromethane after reaction with MAP-T catalyst at different (A) WHSV at 90 °C and (B) temperatures. The burgundy color for the reaction mixture at 150 °C was indicative of the formation a significant amount of the Michael product. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 3
Effect of reactant flow rate on the Henry reaction MAP-T reactor for p-hydroxybenzaldehyde reactant[a].

Entry	WHSV	% Conversion	% Selectivity	
			2	3
1	0.05	48	67	33
2	0.10	34	85	15
3	0.15	30	90	10
4	0.20	21	91	9
5	0.25	13	100	0

[a] Reaction conditions: reactants: 0.08 M p-hydroxybenzaldehyde in nitromethane; WHSV = 0.10; and catalyst: MAP-T, 2 g in pellet form.

grafted mesoporous catalyst (MAP-T) and performed the Henry reactions of p-hydroxybenzaldehyde and p-nitrobenzaldehyde in it. As shown in Fig. 6, the color of the reaction mixture again varied for different WHSV's and reaction temperatures. This clearly suggests that for the same reactant composition, the % conversion and/or the product distribution may depend on the value of WHSV as well as the reaction temperature. When WHSV was increased in the MAP-T reactor, the % conversion of the p-hydroxybenzaldehyde decreased drastically as shown in Table 3. The MAP-T reactor with p-hydroxybenzaldehyde reactant also produced p-hydroxy-β-nitrostyrene (and Michael addition product at greater residence time or lower WHSV). Furthermore, the MAP-T reactor also afforded higher % reactant conversion at lower WHSV in much the same way as in the AP-T bed reactor did. For instance, at WHSV of 0.05, the MAP-T reactor gave a higher % p-hydroxybenzaldehyde conversion of 48% (although it was accompanied by less % selectivity to either one of the two products, producing 67% nitrostyrene and 33% Michael product). Raising the WHSV led to less % reactant conversion but produced higher % of nitrostyrene product, reaching as high as ~100% (Table 3). For instance, for WHSV of 0.25, 0.20, and 0.15, the % reactant conversions were 13, 21, and 30%, respectively, while the corresponding % selectivities toward the nitrostyrene product were 100, 91, and 90%, respectively.

Upon raising the reaction's temperature, the % reactant conversion as well as the % Michael addition product were found to increase for p-hydroxybenzaldehyde reactant in MAP-T reactor as well (Table 4). For instance, at 70 °C and WHSV of 0.1, the reaction gave only 5% reactant conversion but exclusively (~100%) nitrostyrene product, with no Michael addition product. However, increasing the temperature to 150 °C for the same WHSV of 0.1 led to significantly higher (50%) reactant conversion with 55% Michael addition and 45% nitrostyrene products. These clearly revealed that the % conversion of p-hydroxybenzaldehyde as well as the % Michael addition product in the MAP-T reactor could be increased by using greater residence time for the reactant in the reactor or a higher reactor temperature.

The catalytic activity of MAPT reactor on a different reactant, p-nitrobenzaldehyde, which contains electron withdrawing substituent was also investigated (Table 5). We found that the rate of reactant conversion in the reactor was faster for p-nitrobenzaldehyde compared to that of p-hydroxybenzaldehyde (compare Tables 3 and 5). For instance, for the same WHSV of 0.05 and 0.1, the % conversion of p-hydroxybenzaldehyde in MAPT reactor were 48 and 34%, respectively. However, the corresponding % conversion for p-nitrobenzaldehyde were 62 and 52%, respectively. The change from hydroxyl (electron donating) to nitro (electron withdrawing) group on the p-substituted benzaldehyde reactant clearly increased the rate of reaction. Similar trends were also reported for batch reactions [42]. It is also worth noting that the change from hydroxyl to nitro group significantly

Table 4
Effect of temperature on the Henry reaction in MAP-T reactor for p-hydroxybenzaldehyde reactant[a].

Entry	Temperature (°C)	% Conversion	% Selectivity	
			2	3
1	70	5	100	0
2	90	34	85	15
3	110	39	70	30
4	130	45	56	44
5	150	50	45	55

[a] Reaction conditions: reactants: 0.08 M p-hydroxybenzaldehyde in nitromethane; WHSV = 0.1; and catalyst: MAP-T, 2 g in pellet form.

Table 5
Effect of reactant flow rate on Henry reaction in MAP-T reactor for p-nitrobenzaldehyde reactant[a].

Entry	WHSV	% Conversion	% Selectivity		
			1	2	3
1	0.05	62	70	26	4
2	0.10	52	84	15	1
3	0.15	40	90	9	1
4	0.20	21	91	9	0
5	0.25	10	92	8	0

[a] Reaction conditions: reactants: 0.08 M p-nitrobenzaldehyde in nitromethane; temperature: 90 °C; catalyst: MAP-T, 2 g in pellet form.

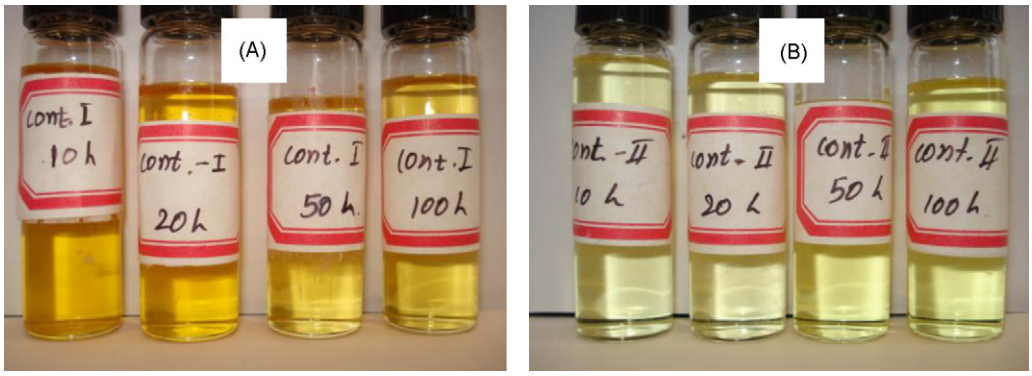


Fig. 7. Digital images of the reaction mixture of p-hydroxybenzaldehyde and nitromethane after reaction with (A) AP-T catalyst and (B) AP-I catalyst for several days (or 100 h). The results show that the catalysts give the required products for a long time and have long shelf-lives.

Table 6
Shelf-life of the catalyst in action in the continuous Henry reaction in AP-T fixed bed reactor[a].

Entry	Time (h)[b]	% Conversion	% Selectivity	
			2	3
1	1	75	97	3
2	3	75	97	3
3	5	73	98	2
4	7	75	98	2
5	10	75	96	4
6[c]	100	85[c]	90	10

[a] Reaction conditions: reactants: 0.08 M p-hydroxybenzaldehyde in nitromethane; WHSV: 0.13; and catalyst: AP-T, 2 g in pellet form.
[b] The time that the reaction was run continuously before collecting the product for analysis.
[c] WHSV: 0.10 for this run (for others, it was 0.13).

lowers the rate of the reaction. Although a similar trend of a complete reversal of the reaction product for batch reaction case upon changing the substituent of the p-substituted benzaldehyde from hydroxyl to nitro group was reported [42], the results from the reaction in the continuous reactor was still different from the ones in the batch reactions, as the types of products to form in the former are also strongly dependent on WHSV. The reaction of p-hydroxybenzaldehyde in the MAP-T reactor favored the formation of p-hydroxy-β-nitrostyrene product, along with its subsequent Michael addition product and no residual nitroalcohol. However, the reaction of p-nitrobenzaldehyde formed nitroalcohol in significant amount with only very little nitrostyrene and Michael products under the same conditions. The p-nitrobenzaldehyde preferentially forms the aldol product over secondary amine mesoporous catalyst due to its favorable ion-pair intermediate that it goes through during the Henry reaction [17,43]. The greater selectivity to nitroalcohol product for p-nitrobenzaldehyde reactant (Table 5) compared to p-hydroxybenzaldehyde (Table 3) in the MAP-T reactor occurs despite the relatively faster reactivity of the former than the latter. In other words, although the former required shorter residence time to give about the same % reactant conversion as the latter, most of the resulting nitroalcohol product from it remains in the solution without undergoing further dehydration. Although p-nitrobenzaldehyde and p-hydroxybenzaldehyde gave different results, the trends in lower % reactant conversion at higher residence time as well as the higher selectivity to a single specific product at lower WHSV remained the same for both reactants (compare Table 3 and Table 5).

The shelf-life of the reactor's catalytic activity in continuously generating one or any of the products was tested by passing the reactants in the reactor for hours and by collecting and analyzing the reaction products at intervals of time. We observed that the catalyst continued to give almost the same % conversion and selectivity for several days while maintaining its catalytic efficiency and product selectivity (Table 6 and Fig. 7). This indicated that catalyst can be used for continuous reactions for many hours without losing its catalytic activity and property as long as the WSHV and temperature in the reactor were maintained.

4. Conclusions

In conclusion, we have demonstrated a simple and industrially viable continuous Henry reaction using a fixed bed glass reactor that was packed with efficient, amine-functionalized mesoporous silica catalysts containing primary or secondary amine catalytic groups. The type of catalyst used in the reactor, the flow rates of reactants in the reactor, their residence times in the reactor (weight hourly spatial velocity or WHSV) and the reaction temperatures were found to affect the % reactant conversion and the type of reaction product the reactor produced continuously. When p-hydroxybenzaldehyde was passed through the reactor packed with the primary amine catalyst, it generated higher % p-hydroxy-β-nitrostyrene or the Michael product at moderate to good % reactant conversion, depending on the value of WHSV and reaction temperatures used. Typical value for % conversion of p-hydroxybenzaldehyde in the reactor packed with primary amine catalyst at 90 °C was 31% with ~100% selectivity to p-hydroxy-β-nitrostyrene product at WHSV of 0.2 (or 64% reactant conversion with 96% selectivity to p-hydroxy-β-nitrostyrene product at WHSV of 0.15). When using the reactor with a secondary amine catalyst, instead of nitroalcohol, a significant amount of nitrostyrene with some Michael addition product was obtained for the same reactant. The relative proportions of the products were again dependent on the value of WHSV and reaction temperatures. Typically, the reactor gave a 100% nitrostyrene product with 13% reactant conversion at WHSV of 0.25 (or 90% selectivity to nitrostyrene product at 30% reactant conversion at WHSV of 0.15) for the same reactant solution 90 °C. On the other hand, when p-nitrobenzaldehyde with the same secondary amine packed reactor was used, 90% selectivity to nitroalcohol product at 40% reactant conversion for WHSV of 0.15 in a continuous flow was obtained. Upon increasing the residence time significantly for the latter, the amount of nitrostyrene and Michael product increased at the expense of nitroalcohol. These results clearly indicate that these catalytic systems can allow the continuous production of large quantity of the Henry reaction's products with moderate to good % reactant conversion and moderate to good selectivity to the particular product, by simply using optimized reaction conditions. The bed reactor was proved to be highly stable and work continuously for many days while maintaining its catalytic efficiency and product selec-

tivity. These catalytic systems may provide "greener" routes to a large scale production of industrially and pharmaceutically important products with less byproduct in the chemical industry of the next millennium. We believe that with minor additional reactor engineering involving scale ups, these catalytic bed reactors may become industrially viable substitutes to the current state-of-the-art commercial catalysts for the Henry and related reactions involving soluble bases such as KOH, NaOH, KH_2PO_4, Na_2CO_3, and NEt_3 [44]. The latter are in homogenous phase and are, therefore, difficult to separate from the final products compared to a simple filtration necessary to do so for typical heterogeneous catalysts, as the ones reported here. Furthermore, the homogenous catalysts are known to result in a mixture of nitroalcohol and nitrostyrene products with lower selectivities. With our experimental demonstration of continuous catalytic transformations of the Henry reaction with unaltered catalytic efficiency for over 100 h, we feel that the transformation of these inexpensive catalysts into technologically and commercially viable process could be feasible.

Acknowledgments

We gratefully acknowledge the financial assistance by the US National Science Foundation (NSF), CAREER Grant No. CHE-0645348 and NSF DMR-0804846. TA thanks NSF for nominating him as one of the 10 NSF American Competitiveness and Innovation (NSF-ACI) Fellows for 2010 and an accompanying grant supporting his group's nanocatalysis work.

References

[1] P.I. Dalko, L. Moisan, Angew. Chem. Int. Ed. 43 (2004) 5138–5175.
[2] J.S. Yadav, B.V.S. Reddy, A.K. Basak, B. Visali, A.V. Narsaiah, K. Nagaiah, Eur. J. Org. Chem. 3 (2004) 546–551.
[3] T. Hara, S. Kanai, K. Mori, T. Mizugaki, K. Ebitani, K. Jitsukawa, K. Kaneda, J. Org. Chem. 71 (2006) 7455–7462.
[4] F.A. Luzzio, Tetrahedron 57 (2001) 915–945.
[5] L. Henry, C.R. Hebd, Seances Acad. Sci. 120 (1895) 1265–1270.
[6] For recent reviews on nitroaldol reaction see:
(a) G. Rosini, in: B.R. Trost (Ed.), Comprehensive Organic Synthesis, Pergamon, Oxford, 1996;
(b) N. Ono, H. Izumi, The Nitro Group in Organic Synthesis, Wiley-VCH, New York, 2001.
[7] P.W.J.F. Grove, J.C. Mcgowan, Ann. Appl. Biol. 35 (1948) 25–36.
[8] P.W. Brian, J.F. Grove, J.C. McGowan, Nature 158 (1946) 876–1876.
[9] G. Rosini, in: C.H. Heathcock, B.M. Trost, I. Fleming (Eds.), Comprehensive Organic Synthesis, vol. 2, Pergamon Press, Oxford, 1991, p. 321 (ch. 1.10).
[10] A.G. Barrett, G. Grabowski, Chem. Rev. 86 (1986) 751–762.
[11] R.S. Varma, R. Dahiya, S. Kumar, Tetrahedron Lett. 38 (1997) 5131–5134.
[12] S. Huh, H.-T. Chen, J.W. Wiench, M. Pruski, V.S.-Y. Lin, J. Am. Chem. Soc. 126 (2004) 1010–1011.
[13] H. Seong, H.-T. Chen, J.W. Wiench, M. Pruski, V.S.-Y. Lin, Angew. Chem. Int. Ed. 44 (2005) 1826–1830.
[14] B.M. Choudary, M.L. Kantam, P. Sreekanth, T. Bandopadhyay, F. Figueras, A. Tuel, J. Mol. Catal. A: Chem. 142 (1999) 361–365.
[15] G. Demicheli, R. Maggi, A. Mazzacani, P. Righi, G. Sartori, F. Bigi, Tetrahedron Lett. 42 (2001) 2401–2404.
[16] D. Brunel, A.C. Blanc, A. Galarneau, F. Fajula, Catal. Today 73 (2002) 139–152.
[17] J.D. Bass, A. Solovyov, A.J. Pascall, A. Katz, J. Am. Chem. Soc. 128 (2006) 3737–3747.
[18] K. Motokura, M. Tada, Y. Iwasawa, J. Am. Chem. Soc. 129 (2007) 9540–9541.
[19] V.J. Bulbule, V.H. Deshpande, S. Velu, A. Sudalai, S. Sivasankar, V.T. Sathe, Tetrahedron 55 (1999) 9325–9332.
[20] B. Qin, X. Xiao, X. Liu, J. Huang, Y. Wen, X. Feng, J. Org. Chem. 72 (2007) 9323–9328.
[21] R. Ballini, A. Palmieri, Curr. Org. Chem. 10 (2006) 2145–2169.
[22] A. Kirschning, H. Monenschein, R. Wittenberg, Angew. Chem. Int. Ed. 40 (2001) 650–679.
[23] D.H. Drewry, D.M. Coe, S. Poon, Med. Res. Rev. 19 (1999) 97–148.
[24] S.V. Ley, I.R. Baxendale, Nat. Rev. Drug Discov. 1 (2002) 573–586.
[25] S.B. Umbarkar, A.V. Biradar, S.M. Mathew, S.B. Shelke, K.M. Malshe, P.T. Patil, S.P. Dagde, S.P. Niphadkar, M.K. Dongare, Green Chem. 8 (2006) 488–493.
[26] G. Jas, A. Kirschning, Chem. Eur. J. 9 (2003) 5708–5723.
[27] F. Mutulis, M. Tysk, I. Mutule, J.E.S. Wikberg, J. Comb, Chemistry 5 (2003) 1–7.
[28] Z. Liu, J. Zhang, C. Chen, P.G. Wang, Chem. BioChem. 3 (2002) 348–355.
[29] J. Nahalka, Z. Liu, X. Chen, P.G. Wang, Chem. Eur. J. 9 (2003) 372–377.
[30] E. Angelletti, C. Canepa, G. Martinetti, P. Venturello, J. Chem. Soc., Perkin Trans. 1 (1989) 105–1105.
[31] P. Nahass, H.K. Bowen, Mater. Sci. Eng. 100 (1988) 235–240.
[32] W. Ehrfeld (Ed.), Microreaction Technology, Springer, Berlin, 1998.
[33] W. Ehrfeld, V. Hessel, H. Löwe, Microreactors, Wiley-VCH, Weinheim, 2000.
[34] A. Manz, H. Becker (Eds.), Microsystem Technology in Chemistry and Life Sciences, Springer, Berlin, 1999.
[35] S.A. Khan, K.F. Jensen, Adv. Mater. 19 (2007) 2556–2560.
[36] L. Soldi, W. Ferstl, S. Loebbeckeb, R. Maggi, C. Malmassari, G. Sartori, S. Yada, J. Catal. 258 (2008) 289–295.
[37] K.K. Sharma, T. Asefa, Angew. Chem. Int. Ed. 46 (2007) 2879–2882.
[38] K.K. Sharma, A. Anan, R.P. Buckley, W. Ouellette, T. Asefa, J. Am. Chem. Soc. 130 (2008) 218–288.
[39] K.K. Sharma, R.P. Buckley, T. Asefa, Langmuir 24 (2008) 14306–14320.
[40] Y. Xie, K.K. Sharma, A. Anan, G. Wang, A.V. Biradar, T. Asefa, J. Catal. 265 (2009) 131–140.
[41] C.T. Kresge, M.E. Leonowicz, W.J. Roth, J.C. Vartuli, J.S. Beck, Nature 359 (1992) 710–728.
[42] K.K. Sharma, A.V. Biradar, T. Asefa, ChemCatChem 2 (2010) 61–66.
[43] A. Anan, R. Vathyam, T. Asefa, Catal. Lett. 126 (2008) 142–148.
[44] B.M. Choudary, M.L. Kantam, C.V. Reddy, K.K. Rao, F. Figueras, Green Chem. 1 (1999) 187–189.