Piperazine-Containing Polymer Brush Layer as Supported Base Catalyst in a Glass Microreactor

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Received: 22 May 2014; accepted: 11 June 2014

The covalent attachment of piperazine onto the inner walls of a microreactor using glycidyl methacrylate polymer brushes has been demonstrated. The piperazine-containing polymer brushes were first grown on a flat silicon oxide surface and were characterized by contact angle, Fourier transform infrared (FT-IR), ellipsometry, and X-ray photoelectron spectroscopy (XPS). The applicability of the catalytic polymer brushes in a microreactor was demonstrated for the Knoevenagel and nitroaldol condensation reactions, and the synthesis of coumarin derivatives. The catalytic activity of the microreactor was still intact even after 2 months.

Keywords: Knoevenagel condensation, nitroaldol condensation, piperazine catalysis, microreactor, coumarin synthesis, polymer brushes

1. Introduction

Supported catalysis is an area of considerable interest in both academia and industry [1]. In recent years, continuous-flow microreactor technology is considered as an enabling technology in organic chemistry, as it exhibits several advantages over classical setups [2–5]. Specific features such as the huge surface area-to-volume ratio and better heat and mass transfer properties are very useful to carry out heterogeneous catalysis [6, 7]. The symbiotic relationship between supported catalysis and microreactors unveils a seamless strategy, which facilitates a cleaner flow methodology to carry out various organic reactions.

Heterogenization of base catalysts has attracted a great deal of attention in continuous-flow organic chemistry [8, 9]. Basic organocatalysts such as 1,5,7-triazabicyclo[4.4.0]undec-3-ene (TBD) [10], 4-dimethylaminopyridine (DMAP) [10], and piperazine [11] have been tethered to a solid support and implemented in microfluidic devices through the packed-bed approach. Although this approach has advantages such as high catalyst loading, a wide range of catalytic supports, and easy fabrication of the catalytic device by filling the channels with functional catalytic particles, however, uncontrolled fluid dynamics, heat transfer limitations, and pressure drop developing along the microchannel are serious limitations. Another approach to carry out heterogeneous catalysis in microreactors is by tethering the catalyst to the inner walls of a microreactor [12], where some of the limitations of the packed-bed approach are circumvented.

Polymer brushes represent a robust platform that offers a myriad of possibilities to perform supported catalysis [13, 14]. Using polymer brushes as a supporting material, we have reported the successful immobilization of catalysts, namely, a basic organocatalyst [15], metallic nanoparticles [16], enzymatic catalysts [17], and a Lewis acid [18], to the interior of the microchannel walls of a glass microreactor.

The catalytic activity of supported-piperazine, as a simple base catalyst, has been reported for a range of reactions under lab-scale conditions [19, 24] and in a microreactor under packed-bed conditions [11]. Herein, we report the anchoring and evaluation of piperazine, by making use of polyglycidyl methacrylate (PGMA) polymer brushes. The catalytic activity of the piperazine-functionalized microreactor was studied for the Knoevenagel and nitroaldol condensation reactions, and the synthesis of coumarins.

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2. Results and Discussion

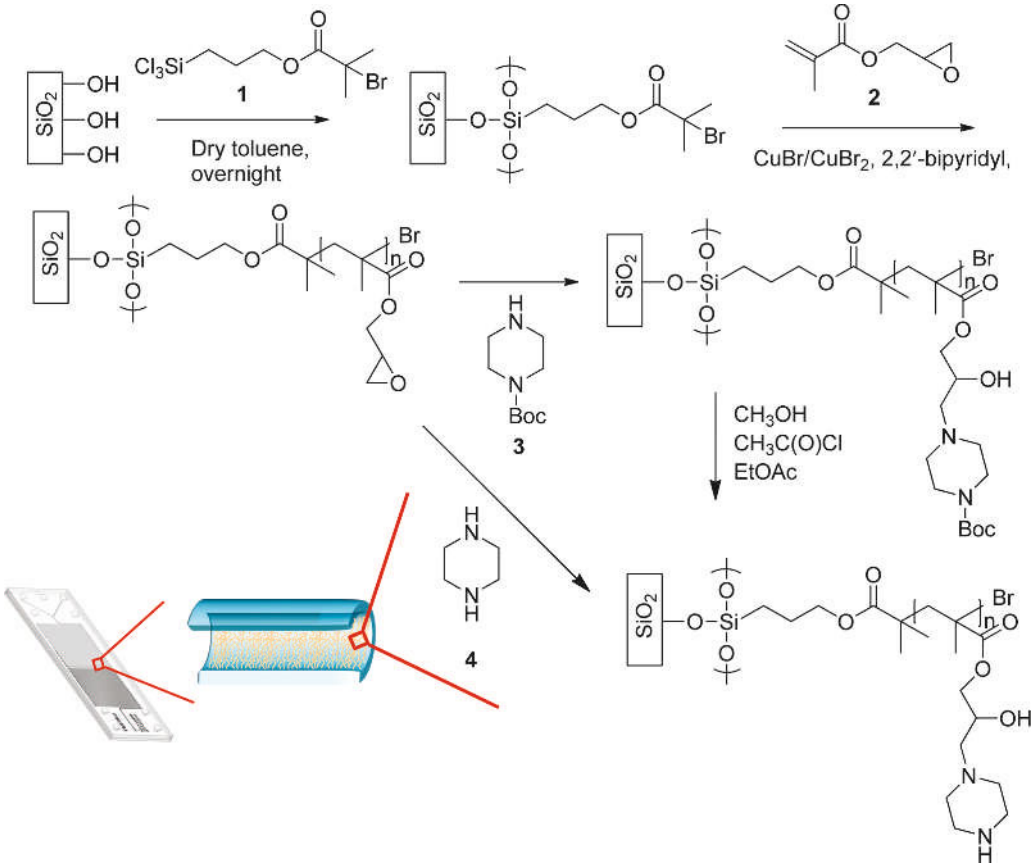
The piperazine-containing catalytic polymer brush layer was first developed on a flat silicon oxide surface. To this end, a monolayer of atom transfer radical polymerization (ATRP) initiator (**1**) was covalently anchored on silicon oxide substrates [25]. Polyglycidyl methacrylate (PGMA) polymer brushes were synthesized using the ATRP polymerization technique with a polymerization time of 1 h by following a literature procedure [15] as summarized in Scheme 1. Subsequently, ring opening of the epoxides was performed with a 100-mM solution of 1-boc-piperazine (**3**) in dimethylformamide (DMF) at 65 °C for 18 h to afford the boc-piperazine-containing polymer brushes, whereupon the boc group was removed by incubating with a mixture of methanol and acetyl chloride in ethyl acetate to get a catalytically active piperazine-containing polymer brush [26].

After ring opening of the epoxide groups in the polymer brushes with 1-boc-piperazine (**3**), the contact angle increased from 69° [27] to a value of 79°. Upon removal of the boc group, the contact angle decreased to a value of 48° indicating the hydrophilic nature of the piperazine-supported polymer brushes. Surface analysis measurements carried out using transmission Fourier transform infrared (FT-IR) spectroscopy showed the disappearance of the epoxide peak at 907/cm, indicating that all the oxirane units were reacted [28]. In addition, a well-defined ester stretching peak appeared at 1695/cm corresponding to the boc group, which disappeared upon removal of the boc group. Additional proof for the functionalization with 1-boc-piperazine (**3**) was obtained by X-ray photoelectron spectroscopy (XPS). The atomic composition of the polymer brushes upon treatment with 1-boc-piperazine (**3**) was found to be C–N–O=11.0:1.4:3.4, which is in decent agreement with the theoretical ratio of C–N–O= 11.0:2.0:3.0.

In another approach, instead of 1-boc-piperazine (**3**), ring opening of the epoxides was performed with a 250-mM solution of piperazine (**4**) in DMF at 65 °C and it took only 6 h to afford the piperazine-containing polymer brushes. As the piperazine molecule contains two nucleophilic centers, it can probably open two neighboring epoxide rings of the PGMA polymer brushes. In that case, the atomic composition of the polymer brushes upon treatment with piperazine (**4**) should theoretically be C–N–O=11.0:1.0:3.0 as against 11.0:2.0:3.0. However, from the XPS measurements, the atomic composition was found to be C–N–O=11.0:1.4:3.2. Since 1-boc-piperazine (**3**) and

DOI: 10.1556/JFC-D-14-00020

Scheme 1. General scheme for anchoring of the initiator, ATRP of glycidyl methacrylate, and ring opening of epoxide with (1-boc-)piperazine (**3**)



piperazine (**4**) both yielded an identical atomic composition, it was concluded that the unprotected piperazine did not open two neighboring epoxide rings. Using ellipsometry, the thickness of the polymer brushes on the flat surfaces was determined to be 208 nm for a polymerization time of 1 h. Using the same polymerization time in flow, the film thicknesses in the microreactors were assumed to have the same value as demonstrated in a previous study [15].

The same protocol described above was followed to immobilize piperazine (**4**) onto the interior of a glass microreactor with channel dimensions of 150 μm in width and depth, and having an internal volume of 13 μL, to give a catalytically active microfluidic reactor. The number of catalytic sites in the piperazine-functionalized microreactor was estimated using Gisin's acid–base titration procedure [29]. The amount of catalyst was calculated to be 4 μg (47 nmol) of piperazine for the catalytic device with a polymerization time of 1 h, considering two molecules of picric acid bind to one molecule of piperazine upon the titration. This corresponds to a loading of about 15%, considering an internal surface available for functionalization of 3.47×10^{14} nm^2 and a polymer thickness of 208 nm and assuming a brush density close to that of the bulk material (1 g/mL). In the case of the TBD-functionalized brushes, there was a loading of 13% [15].

The Knoevenagel condensation reaction between benzaldehyde (**5**) (50 μM) and malononitrile (**6**) (60 mM) in acetonitrile to give 2-benzylidene malononitrile (**7**) was used as a model reaction to study the catalytic activity of the piperazine-functionalized microreactor (Scheme 2). Acetonitrile was chosen as a solvent in this study because, in a previous study, it was proven that TBD-supported PGMA polymer brushes were fully swollen in this solvent [15]. The formation of the product **7** was monitored real-time by in-line ultraviolet-visible (UV-vis) detection. It was obtained in 96% yield with a residence time

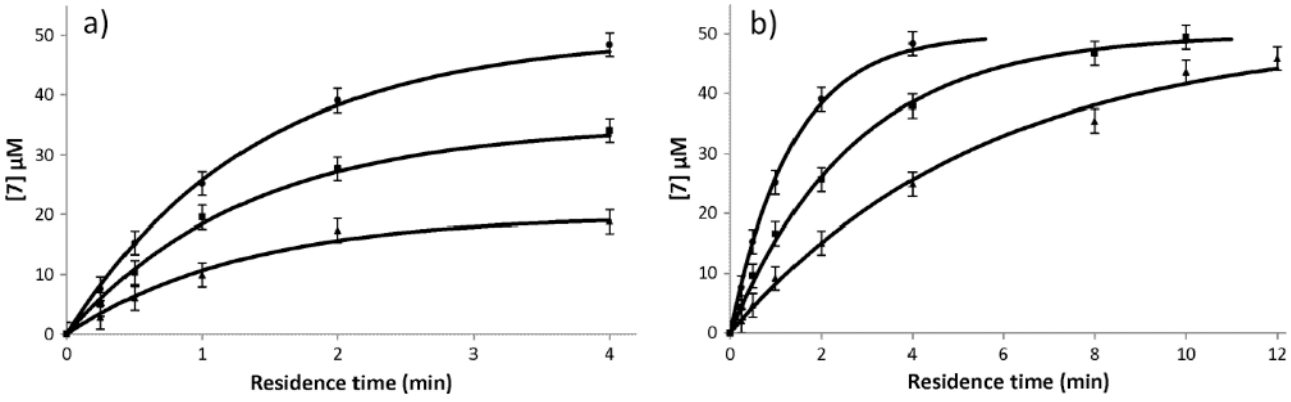
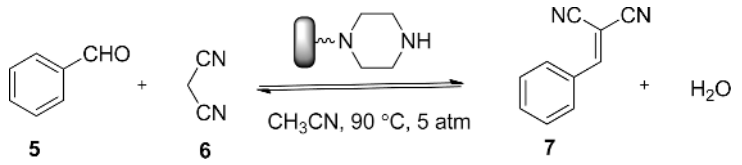


Figure 1. a) Formation of **7** catalyzed by piperazine-containing polymer brushes in the microreactor at different concentrations of **5** ([**6**] = 60 mM, at 90 °C and 5 atm pressure). [**5**] = 50 μM (•), 35 μM (▪), 20 μM (▲). b) Formation of **7** catalyzed by a piperazine-functionalized microreactor at different malononitrile (**6**) concentrations ([**5**] = 50 μM, 90 °C, 5 atm). [**6**] = 60 mM (•), $k_{obs} = 1.21 \times 10^{-2}$/s; 30 mM (▪), $k_{obs} = 6.22 \times 10^{-3}$/s; 15 mM (▲), $k_{obs} = 2.99 \times 10^{-3}$/s

Scheme 2. Knoevenagel condensation reaction between benzaldehyde (**5**) and malononitrile (**6**)



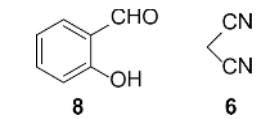
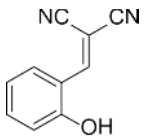
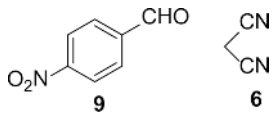
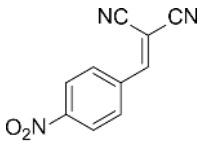
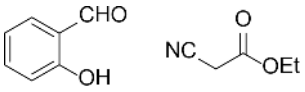
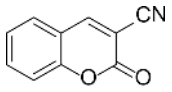
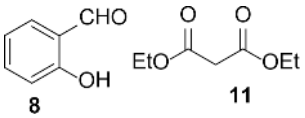
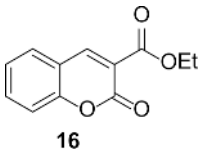
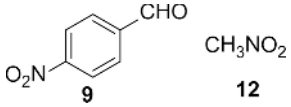
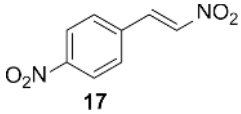
of 4 min at 90 °C and 5 atm pressure, generated using a back pressure regulator in continuous flow. The reaction times were varied by changing the flow rates between 3.25 and 26 μL/min. Under similar reaction conditions, a microreactor containing PGMA polymer brushes in the absence of piperazine showed no detectable conversion, proving that piperazine is the catalytically active species. To study the possible influence of the OH groups in the piperazine-containing polymer brushes on the catalytic activity of the system, they were protected as tetrahydropyranyl (THP) ethers [30]. The choice of THP as the protecting group is because of its remarkable stability under (strongly) basic conditions [31]. The OH-protected piperazine-containing microreactor showed a similar catalytic activity for the model reaction as that containing the bare OH groups under the conditions mentioned above, proving that the OH groups do not play any active role in the catalytic process.

A kinetic study was performed by carrying out the reaction at different concentrations of benzaldehyde (**5**) (20–50 μM, Figure 1a), keeping the concentration of malononitrile (**6**, 60 mM) constant to ensure pseudo-first-order conditions. The experimental data were fitted to a first-order rate equation, giving an observed pseudo-first-order rate constant, k_{obs}, of $1.2\pm0.1\times10^{-2}$/s. The values of the rate constants at different benzaldehyde (**5**) concentrations were the same, within experimental error. The turnover frequency (TOF) values calculated for 20, 35, and 50 μM benzaldehyde (**5**) were calculated to be 7.04×10^{-5}, 1.21×10^{-4}, and 1.67×10^{-4}/s. From the increase in the TOF values upon increasing substrate concentration, it is concluded that the amount of catalyst is not rate-limiting, but the benzaldehyde (**5**) concentration.

Next, the malononitrile (**6**) concentration was varied in the range of 15–60 mM (Figure 1b). The observed rate constants were found to be proportional to the concentration of **6** by plotting the k_{obs} against the concentration of **6** (Figure 2). A second-order rate constant of 0.20±0.01/(s M) was calculated. TBD (pK_a in acetonitrile=26.03) [32] is a stronger basic organocatalyst than piperazine (pK_a in acetonitrile=18.69) [33]. Consequently, when the same reaction was carried out at 65 °C and under ambient pressure conditions as reported for the TBD wall-coated glass microreactor [15], the reaction proceeded about ten times slower with a second-order rate constant of $1.18\pm0.01\times10^{-2}$/(s M) against 0.10±0.01/(s M), reported in the literature for the TBD-catalyzed reaction [15].

The substrate scope of the Knoevenagel condensation reaction was studied by reacting salicylaldehyde (**8**) and 4-nitrobenzaldehyde (**9**) with malononitrile (**6**) using the same reaction conditions as above (Table 1). The presence of either an electron-donating or an electron-withdrawing substituent does not influence the reaction, since the

Table 1. Results of different types of reactions carried out in the piperazine-functionalized catalytic microreactor[a]

Entry	Reactants	Product	Residence time (min)	Conversion (%)[b]
1 [38]	 8 6	 13	4	89
2 [38]	 9 6	 14	4	92
3 [36]	 8 10	 15	52	94
4 [36]	 8 11	 16	52	30
5 [39]	 9 12	 17	52	82

[a] All reactions were performed in acetonitrile at 90 °C, 5 atm pressure, using a back pressure regulator.
[b] Conversions represent the formation of the products which were determined using online UV-vis spectroscopy by following the increase in the extinction coefficient of the product.

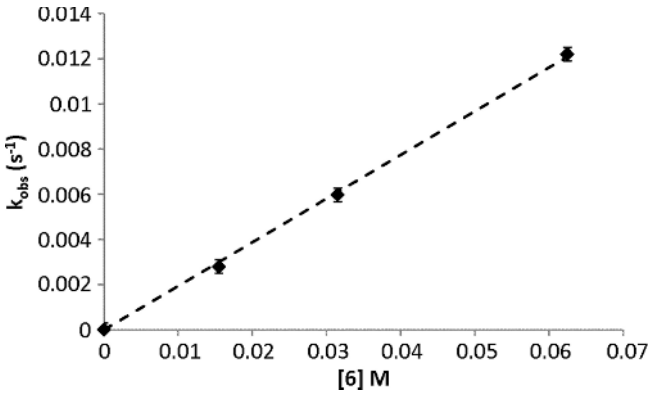


Figure 2. Pseudo-first-order rate constants for the formation of **7** vs. the concentration of malononitrile (**6**)

adducts (2-hydroxybenzylidene) malononitrile (**13**) and 2-(4-nitrobenzylidene) malononitrile (**14**) were formed in 89% and 92% yields, respectively (Table 1, entries 1 and 2).

As a logical extension, α-hydroxybenzaldehyde derivatives were reacted with active methylene compounds that contain at least one ester moiety, after the condensation step, a subsequent cyclization (between the ester moiety and the α-hydroxy substituent of the condensation product) affording coumarin derivatives. This class of compounds has a wide range of pharmaceutical and industrial applications [34, 35]. Using our catalytic device, 3-cyanocoumarin (**15**) and 3-(ethoxycarbonyl)coumarin (**16**) were obtained in 94% and 30% yields, respectively (Table 1, entries 3 and 4). The moderate conversion for the synthesis of **16**, when compared to **15**, is ascribed to the lower reactivity of diethyl malonate (**11**) in comparison to ethyl cyanoacetate (**10**) [36].

Furthermore, the nitroaldol condensation reaction between 4-nitrobenzaldehyde (**9**) and nitromethane (**12**) was performed to give *trans*-4-nitro-β-nitrostyrene (**17**) in 82% yield (Table 1, entry 5). However, using benzaldehyde (**5**), no trace of product could be detected, as it requires relatively harsh conditions when compared to **9** [37].

After each experiment, the catalytic microreactor was treated with a 5% solution of triethylamine in acetonitrile and washed with acetonitrile in order to avoid diminished catalytic activity due to possible protonation [10]. The catalytic activity of the piperazine-containing catalytic microreactor remained intact even after 2 months, when stored in a nitrogen box.

3. Conclusion

A piperazine-functionalized PGMA polymer brush glass microreactor showed a good catalytic activity for several examples of the Knoevenagel and nitroaldol condensation reactions, and the synthesis of coumarin derivatives. The microreactor maintained the catalytic activity even for a period of 2 months, which makes it an interesting vehicle to study different types of reactions.

4. Experimental

4.1. Materials. All chemicals and solvents were purchased from Sigma-Aldrich unless otherwise mentioned and were used without purification unless specified. Silicon wafers with (100) orientation and single side polished were purchased from OKMETIC. The ATRP initiator 3-(5′-trichlorosilylpentyl) 2-bromo-2-methylpropionate (**1**) was synthesized following a literature procedure [25]. CuBr, purified by first washing with glacial acetic acid and later filtered by rinsing with ethanol and acetone, was stored in a vacuum desiccator. Methanol (VWR, analytical reagent grade) was used without further purification, and water was purified with the Milli-Q pulse (MILLIPORE, R=18.2 MΩ cm) ultra-pure water system, dry toluene, and acetonitrile from the encapsulated solvent purification system (MB-SPS-800).

4.2. Methods. Contact angles were measured on a Krüss G10 contact angle measuring instrument, equipped with a CCD camera. Transmission FT-IR spectra were recorded using a Nicolet 6700 FT-IR spectrometer. Ellipsometry measurements to determine the thickness of the polymer brushes were performed with a Spectroscopic Ellipsometer M-2000X (J.A. Woolam Co., Inc.) with light reflected at 70° and a spot size of 2 mm diameter. Over a wavelength range of 340–1000 nm, with spectral resolution of about 2 nm, both Psi and Delta were recorded as well as the intensity and amount of depolarization of the reflected light. The Complete EASE v.4.64 software package (J.A. Woolam Co., Inc.) was used to control the instrument as well as for data analysis and modeling. X-ray photoelectron spectroscopy (XPS) on the piperazine-functionalized silicon oxide wafers was performed on a Quantera Scanning X-ray Multiprobe instrument, equipped with a monochromatic Al-K_α X-ray source producing approximately 25 W of X-ray power. XPS data were collected from a surface area of 1000×300 μm with a pass energy of 224 eV and a step energy of 0.8 eV for survey scans and 0.4 for high resolution scans. For quantitative analysis, high resolution scans were used. In all reactions carried out using a piperazine-containing catalytic microreactor, the formation of the products was followed using online UV–vis spectroscopy as described in ref. 16, and no side products could be detected.

4.3. Setup of the Flow Microreactor. All experiments were performed in a microreactor setup as described in ref. 16. Glass microreactors with dimensions of 150 μm depth and 150 μm width and a residual volume of 13 μL were purchased from Micronit Microfluidics (Enschede, The Netherlands).

4.4. Preparation of the Catalytic Polymer Coating. Covalent immobilization of the trichlorosilane initiator **1** on the silicon oxide surface and the microchannels was performed as described before [15]. PGMA polymer brushes synthesis with a polymerization time of 1 h was carried out using the same procedure, but with a slight modification in the concentration of the polymerization solution (glycidyl methacrylate [5 mL, 37.6 mmol], 2,2′-bipyridyl [320 mg, 2 mmol], $CuBr_2$ [8 mg, 35.8 μmol], CuBr [74 mg, 0.5 mmol], and a 4:1 mixture of methanol and water [10 mL] were used). The silicon wafers functionalized with PGMA polymer brushes were incubated in a 100-mM solution of 1-boc-piperazine (**3**) in DMF at 65 °C for 18 h. Subsequently, the wafers were incubated in 1.5 mL of a stock solution, prepared from methanol (1.15 mL, 3 mmol) and acetyl chloride (2.25 mL, 3 mmol) in ethyl acetate (5 mL), for 6 h to afford piperazine-functionalized polymer brushes.

In the direct approach, the silicon wafers, functionalized with PGMA polymer brushes, were incubated in a 250-mM solution of piperazine (**4**) in DMF at 65 °C. The same solution was flowed with a flow rate of 0.1 μL/min through the microreactor functionalized with PGMA polymer brushes whose temperature was maintained at 65 °C. After 6 h, both the silicon wafers and the microreactor were rinsed with DMF and acetonitrile, and subsequently dried with a stream of nitrogen.

The piperazine-functionalized polymer brushes on silicon wafers were treated with a mixture of solutions of 250 mM 3,4-dihydropyran and 100 mM *para*-toluenesulfonic acid in acetonitrile for 18 h. Subsequently, the wafers were incubated in a 250-mM solution of triethylamine in acetonitrile for 30 min followed by rinsing with acetonitrile. The successful protection of the OH groups was concluded by the increase in the intensity of the $-CH_2$ stretching frequency of the THP ether at 2945/cm in the IR spectrum. The THP ether protected piperazine-functionalized catalytic microreactor was prepared in a similar way using a flow rate of 0.1 μL/min for the first step.

4.5. Kinetic Study. The Knoevenagel condensation between benzaldehyde (**5**) and malononitrile (**6**) (20–50 μM) was carried out in acetonitrile at 90 °C under 5 atm pressure. The formation of 2-benzylidene malononitrile (**7**) was calculated based on the increase in the absorption at 306 nm. The molar absorptivity of **7** is ε_{306}=21,080/(M cm). The k_{obs} values were calculated by fitting the experimental data with the following equation: [**7**]=[**5**]$_0$×(1-exp (−k_{obs}·t)) using a least-squares fit by keeping the [**5**]$_0$ constant and optimizing the k_{obs}. The experimental errors in these measurements are ±5%.

4.6. Catalytic Reactions Inside Microreactor

4.6.1. Knoevenagel Condensation Reaction. The Knoevenagel condensation reaction of salicylaldehyde (**8**, 50 μM) and 4-nitrobenzaldehyde (**9**, 50 μM) with malononitrile (**6**, 60 mM) (Table 1, entries 1 and 2) was carried out in a catalytic microreactor using similar conditions mentioned above. The formation of the products was determined by following the increase in the extinction of the products (2-hydroxybenzylidene)malononitrile (**13**, ε_{292}=8100/(M cm)) and 2-(4-nitrobenzylidene) malononitrile (**14**, ε_{302}=32,640/(M cm)) at 292 nm and 302 nm, respectively.

4.6.2. Coumarin Derivatives. 3-Cyanocoumarin (**15**) and 3-(ethoxycarbonyl)coumarin (**16**) (Table 1, entries 3 and 4) were prepared by reacting salicylaldehyde (**8**, 50 μM) with ethyl cyanoacetate (**10**, 125 mM) and diethyl malonate (**11**, 125 mM), respectively, using the same reaction conditions as above, but with a residence time of 52 min. The formation of **15** and **16** was determined based on the extinction at 295 nm (ε_{295}=14,940/(M cm)) and 289 nm (ε_{289}=12,880/(M cm)), respectively.

4.6.3. Nitroaldol Condensation Reaction. The nitroaldol condensation reaction between 4-nitrobenzaldehyde (**9**, 50 μM) and nitromethane (**12**, 30 mM) was also carried out under similar conditions mentioned above. The formation of the product *trans*-4-nitro-β-nitrostyrene (**17**) was determined based on the increase in the extinction of the product at 309 nm (ε_{309}=19,580/(M cm)).

4.6.4. Titration with Picric Acid. The number of catalytically active sites was estimated using Gisin's acid–base titration procedure [29]. First, the catalytic device was rinsed with a solution of 5% diisopropylethylamine in acetonitrile for 15 min and washed thoroughly with acetonitrile. Subsequently, a 50-mM solution of picric acid in acetonitrile was flowed into the microchannel for 15 min, whereupon it was thoroughly washed with acetonitrile for 30 min. Finally, the picric acid was eluted from the microreactor with a solution of 5% diisopropylethylamine in acetonitrile and collected in a volumetric flask and was analyzed using UV-vis spectroscopy. The molar absorptivity of picric acid is ε_{375}=16,040/(M cm).

Acknowledgement. The financial support from NanoNext NL is gratefully acknowledged.

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