Microreactors

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Improving Solid-Supported Catalyst Productivity by Using Simplified Packed-Bed Microreactors**

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Catalysts supported on polymeric resins are readily synthesized and offer the promise of recycling and easy removal from reaction mixtures through filtration.[1] Often, however, such a support significantly diminishes a catalyst's activity.[2] Although homogeneous catalyst loadings in a batch reactor are simply increased by the addition of more catalyst, additional supported catalyst can hinder reagent mixing within a reaction vessel. These issues are circumvented by using continuous-flow systems. The use of flow is advantageous as the support does not need to be removed from the reaction mixture and continuous processing is also possible.[3] Our interest in microreactors prompted us to ask if supported catalysts would work when well packed into small channels.

Microreactors are a relatively new technology for performing safer, more-efficient, and more-selective reactions.[1a,4] The improved performance is attributed to faster heat transfer and mixing as a result of the increased surface-area-to-volume ratio.[4a] Despite the increasing body of literature on microreactors, few reports discuss the use of packed-bed microreactors applied to synthetic chemistry (Figure 1). What literature does exist concerning synthesis within these channels describes reactions performed by using solid-supported reagents that require regeneration.[5–7]

A major issue encountered in packing microchannels with supported-catalysts is the pressure drop across the channel caused by either the swelling or size of the packing material.[8–10] Common Merrifield-type and gel-like resins are not appropriate for microchannel packing as they clog the channels when swollen with solvent, leading to irreproducible flow.[8,9] Other than monolithic materials,[11] no material investigated so far permits facile flow through packed-bed microreactors in a wide range of solvents. Herein, we demonstrate that a commercially available resin works well as a catalyst support in a high throughput, packed-bed microreactor and that supported catalysts in flow systems yield greater productivity [Eq. (1)]. We limit this discussion to commercially available polymeric resins.

$$\text{productivity} = \frac{\text{moles product}}{\text{reactor volume} \times \text{time} \times \text{moles catalyst}} \qquad (1)$$

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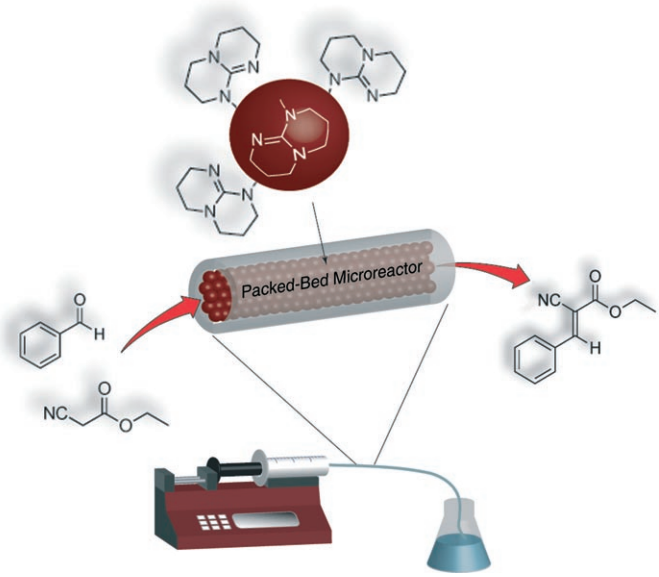


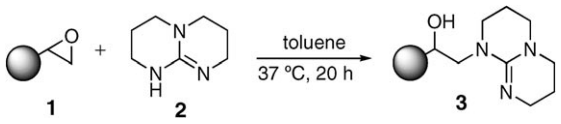
Figure 1. Flow reactions with a packed-bed microreactor.

Although the use of electroosmotic flow permits flow through a wider range of packing materials,[12] these systems are far more complex than pressure-driven systems and only work with polar solvents. We subsequently examined a wide range of resins to be used in a pressure-driven system by passing different solvents through a 10-cm packed bed and qualitatively assessing whether flow was free or constricted (see the Supporting Information). Typically, lightly cross-linked resins swell in certain solvents, which prohibits flow through the microchannels. Highly cross-linked or macroreticular resins and silicas, on the other hand, allow flow under nearly all solvent conditions as they do not swell. Numerous solid-supported catalysts have been reported in the literature, including analogues of the supported catalysts discussed herein.[1a] Nonetheless, our flow experiments showed that many polymeric resins do not permit flow in a wide array of solvents. A packing material that does not restrict flow is desired as higher flow rates and output can be attained.

Of the two supports that passed our flow tests (flow with no pressure drop), we favored the methacrylate-based Amberzyme Oxirane resin (AO, **1**), a macroreticular resin with a large, fixed pore volume and pendant epoxide groups designed for enzyme immobilization. Catalysts were attached to the resin by direct nucleophilic attack or by a Huisgen cycloaddition to an azide-modified AO. These catalysts showed excellent batch activity, but when they were used in

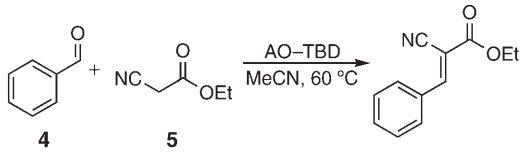
packed-bed microreactors, their productivity increased significantly [Eq. (1)].

We tethered organocatalysts containing nucleophilic groups to AO. As an example, we reacted 1,5,7-triazabicyclo-[4.4.0]undec-3-ene (TBD, **2**) with the epoxide (Scheme 1).



Scheme 1. Preparation of AO–TBD resin.

Solid-supported TBD has been shown to catalyze a number of reactions[1a,13] but had not yet been used in a pressure-driven flow system.[12,14] TBD on AO (AO–TBD, **3**, Scheme 1) is a highly active, Knoevenagel catalyst in batch systems but works significantly better in flow systems. We selected a Knoevenagel condensation between benzaldehyde (**4**) and ethyl cyanoacetate (**5**) as a demonstration (Scheme 2). All



Scheme 2. The Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate.

flow experiments were performed by using a simplified packed-bed microreactor based on a platform developed within our group and also by others (Figure 2).[15] The present device consisted of fluoroelastomeric tubing (1.6-mm inner diameter) packed with functionalized AO resins (Figure 2b).

For the flow Knoevenagel condensation experiments, a 30-cm segment of tubing was packed with AO–TBD and placed in an HPLC column oven set to 60 °C. A solution of benzaldehyde in acetonitrile was prepared, to which ethyl cyanoacetate was added prior to the flow experiment. At a flow rate of 50 μL min^{-1} (approximately 280 s residence time),

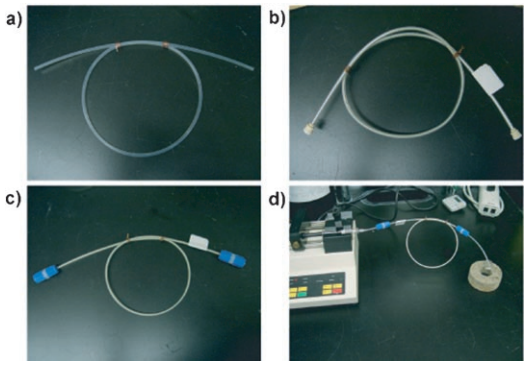


Figure 2. The simplified microreactor: empty tubing (a) filled with AO resin (b) with filter caps (c) and attached to syringe pumps (d).

a conversion of 93% was obtained (Figure 3). This flow rate gives over 200 mg of product per hour from a single channel. The device presented provides roughly forty times the output of previously reported flow devices.[11] The increased performance of a packed-bed microreactor is due to the small

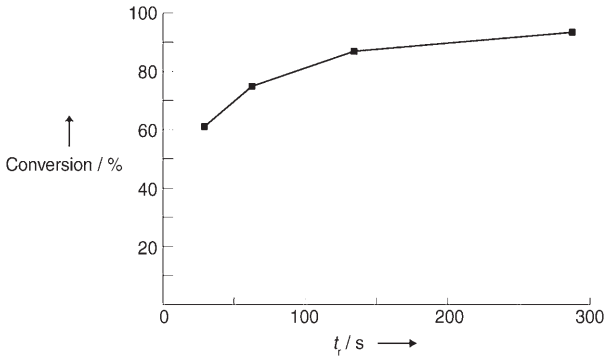


Figure 3. Conversion of flow Knoevenagel condensations as a function of residence time. t_r = residence time.

dimensions of the channel, allowing rapid and uniform heating. In addition, all packed-bed reactors benefit from flowing reagents over the catalyst-bound resin. This feature allows the catalyst loading to be maximized and for transfer of reagents and starting materials into and out of the beads.

As anticipated, increasing the flow rate (decreasing the residence time) gave lower conversions (Figure 3). The process of numbering up could be applied to acquire higher outputs since reactor conditions need not be changed upon reaction scaling.[16] The AO–TBD packed channel was used 30 times without apparent catalyst degradation. After each trial, the column was simply regenerated with aqueous ammonia and washed with acetonitrile to maintain activity.

Knoevenagel condensations were run on an identical scale and concentration in both the batch and flow experiments. In both cases, the resulting reaction-mixture volume and amount of AO–TBD catalyst were the same. A conversion of 90% was achieved in the flow system (at 50 μL min^{-1}, resulting in 3-mL total volume in one hour), and the reaction mixture could be concentrated under high vacuum to yield the product. Batch reactions, however, yielded only 69% conversion after one hour (reaction volume of 3 mL). The microreactor productivity for the flow reactions was 3.4 times greater than the batch reaction owing to the decreased dimensions of the reactor and better mixing (Table 1).

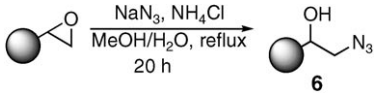
Increasing the scale of the reaction emphasizes the benefits of using the packed-bed reactor. By doubling the reaction size and maintaining a constant mass of AO–TBD, the productivity for batch reactions decreased by 2.5, whereas the productivity of the flow reactions changed very little. We propose that the microreactor performs better because the molar ratio of the starting material for AO–TBD remains constant in the microreactor as new reaction mixture is continuously introduced. The productivity at this larger scale is 5.8, which should increase as the scale of the reaction increases (Table 1).

Table 1: Flow reaction productivities.

Reaction	Flow productivity[a]	Batch productivity	Flow/batch productivity
TBD Knoevenagel	1.12	0.33	3.4
TBD Knoevenagel (double scale)	0.75	0.13	5.8
DMAP acylation[b]	3.2	1.0	3.2

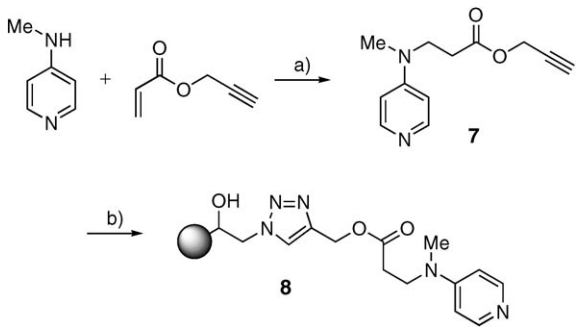
[a] Productivities are measured in mmol product mL^{-1} min^{-1} mmol catalyst^{-1}. [b] Batch reaction for the acylation run by using 10 mg of catalyst compared with 215 mg for the flow reaction.

We then prepared a packed-bed reactor by using immobilized 4-dimethylaminopyridine (DMAP), a catalyst that has been studied extensively on solid supports.[2,17] Azide-functionalized AO resin (AO-N_3, **6**) was prepared by treatment of AO with sodium azide (Scheme 3).[18] An acetylene-functionalized DMAP (**7**), synthesized by using a Michael addition,[19] was conjugated to AO–N_3, affording the DMAP-functionalized resin (AO–DMAP, **8**, Scheme 4). The acylation of *sec*-phenethyl alcohol (**9**) was used as a test reaction (Scheme 5).

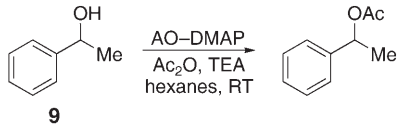


Scheme 3. Preparation of AO–N_3 resin.

Acetic anhydride was added to a stock solution of *sec*-phenethyl alcohol and triethylamine in hexanes and used immediately in the flow experiment. Full conversion was achieved at a flow rate of 0.5 mL min^{-1} (approximately 48 s residence time; Figure 4). At 0.5 mL min^{-1}, extrapolation of this output suggests that 1.6 g of product per hour could be obtained from a single 60-cm channel. Use of the highest flow rate of the syringe pump (3.9 mL min^{-1}) gave the highest throughput of the acylated product (50.5 mmol h^{-1}), albeit the lowest conversion (68.5 %).



Scheme 4. Preparation of AO–DMAP resin. Reagents and conditions: a) neat, 90 °C, 2 h (65 %); b) **6**, [$CuBr(PPh_3)_3$], DIPEA, THF, 50 °C, 3 days. DIPEA = diisopropylethylamine.



Scheme 5. The acylation of *sec*-phenethyl alcohol. TEA = triethanolamine.

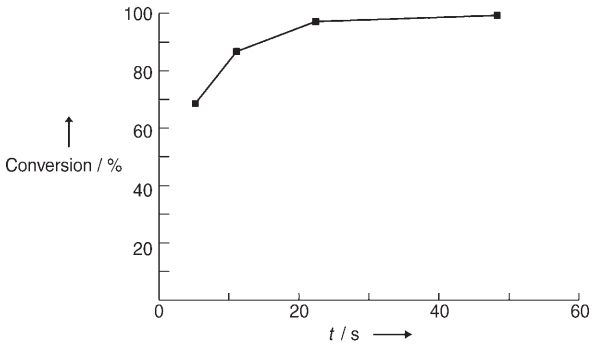


Figure 4. AO–DMAP-catalyzed flow acylation of *sec*-phenethyl alcohol.

As with the Knoevenagel condensation, the flow acylation was run in direct comparison with the batch reaction by using identical amounts of catalyst, reagent concentrations, and final reaction volumes (3 mL). In this case, the flow acylation was marginally superior to the batch reaction, generating 95 % conversion in flow experiments (at 50 μL min^{-1}, resulting in 3-mL total volume in one hour) versus 92 % conversion in one hour in batch experiments.

However, AO–DMAP catalyzed acylations were more productive in flow experiments compared with batch experiments (Table 1). Furthermore, the AO–DMAP packed columns were reusable, and each column could be used in 35 trials without showing any apparent loss in catalytic activity (no regeneration was required). For this reason the AO–DMAP packed-bed microreactor is again superior to the batch system, because in flow systems, the catalyst is left in place and does not have to be recovered from the reaction.

Aside from increased productivity and ease of use, packed-bed microreactors containing AO-modified resins are superior to batch reactions for other reasons. The resin within the reactor remains intact throughout the course of the flow reaction, whereas in batch systems, most resins, including AO, showed signs of structural damage.[11e] Flow reactions also increase mixing without destroying the packing material by splitting the substrate stream into smaller segments of flow, leading to turbulent mixing.[20]

Though monolithic packed beds may provide more efficient contact between reagents and starting materials, we feel that the use of resins has advantages; namely the resin's ease of modification and characterization prior to channel packing.

These materials showed remarkable activity when used in batch reactors, yet were even more productive in the continuous-flow system. The device also enables a facile method to run high-throughput processes compared with previous literature that used microreactors. Compared with batch reactors, both AO–TBD and AO–DMAP show increased productivity owing to the improved mixing and decreased dimensions of the channel. This simplified approach to continuous catalytic chemistry can be used to

couple multiple catalysts together for generating complex molecules in one flow-through process. The use of purely catalytic-flow reactors will provide higher throughput and efficiency relative to the groundbreaking continuous-flow systems that use both resin-bound catalysts and reagents.[5,6] Finally, the use of packed-bed microreactors instead of larger bore-flow reactors will allow much faster heating and heat removal. Consistent temperature across the channel will combine the advantages of microreactors with packed-bed reactors.

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