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Monolithic Silica Support for Immobilized Catalysis in Continuous Flow

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Abstract. Monolithic and packed-bed reactors featuring immobilized catalysts are well-precedented in continuous flow synthesis, but can suffer from adverse pressure drops due to the small pore sizes and/or structural changes of the support (e.g. swelling, deformation, movement of beads, etc.) during operation. Herein, we overcome this challenge with the synthesis of a structurally robust silica-based monolith featuring pore sizes on the millimeter scale. The 3-dimensional solid support structure is constructed from a removable polystyrene foam-based template and features a functional group handle that can be modified to display a reactive catalyst. Here we functionalize the support with palladium(0) for hydrogenation reactions and a modified proline catalyst for the alpha functionalization of aldehydes. Both reactors showed good activity and excellent catalytic longevity when utilized under continuous flow conditions.

Keywords: continuous flow; heterogeneous catalysis; hydrogenation; immobilization; organocatalysis

The use of immobilized catalysts in continuous flow synthesis is well-precedented in the literature, but not without its challenges.^[1-5] For example, functionalized beads within a traditional packed-bed reactor (Figure 1A) are randomly packed and there can be movement and changes to these beads during use. This can reduce the catalytic surface area in contact with the substrate solution, lead to poor mass transfer properties, restrict solution flow and cause an adverse pressure drop throughout the reactor. Channels may form, leading to rate differences across the bed.^[1,6]

As an alternative to packed-bed reactors, researchers have prepared monolithic solids via polymerization processes to support various catalysts (Figure 1B).^[1, 2, 6-9] In many cases, these materials have pore sizes in the range of 1 μm - 100 μm and are comprised of inorganic polymers such as silica, or organic polymers such as polystyrene. While the use of such monoliths offers many advantages^[1] including

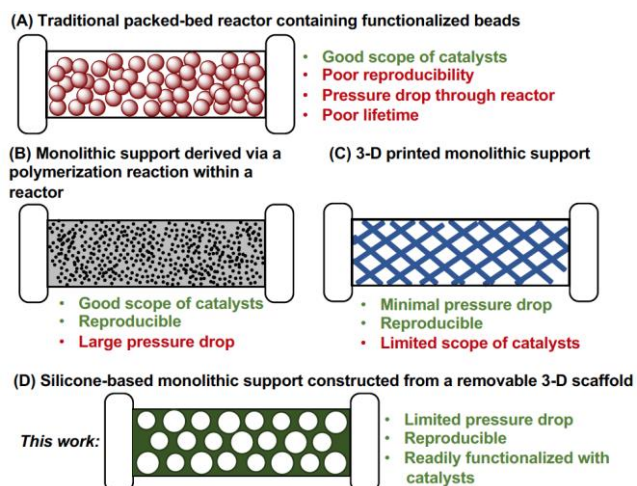


Figure 1. (A) Packed-bed comprised of functionalized beads. (B) Monolith support resulting from a polymerization reaction with the catalytically active material inside a reactor.^[2,6-9] (C) Monolith support derived from a 3-dimensional printed structure that can be plated with metal zero catalysts.^[10,11] (D) In this work, a silica-based support that can be functionalized post synthesis is constructed from a removable 3-dimensional scaffold.

a large surface area of catalyst in contact with the substrate fluid, they can be characterized with having high flow resistance due to polymer swelling and/or small pore sizes. Recently, a 3-dimensional-printed monolith was reported that is coated with ground state metal (Figure 1C).^[10,11] Although a minimal pressure drop was observed while using this monolith, the method is only applicable for ground state metal catalysis.

Herein, we envisioned the design of a silica-based monolithic support that features pore sizes on the millimeter scale (Figure 1D). By constructing the solid

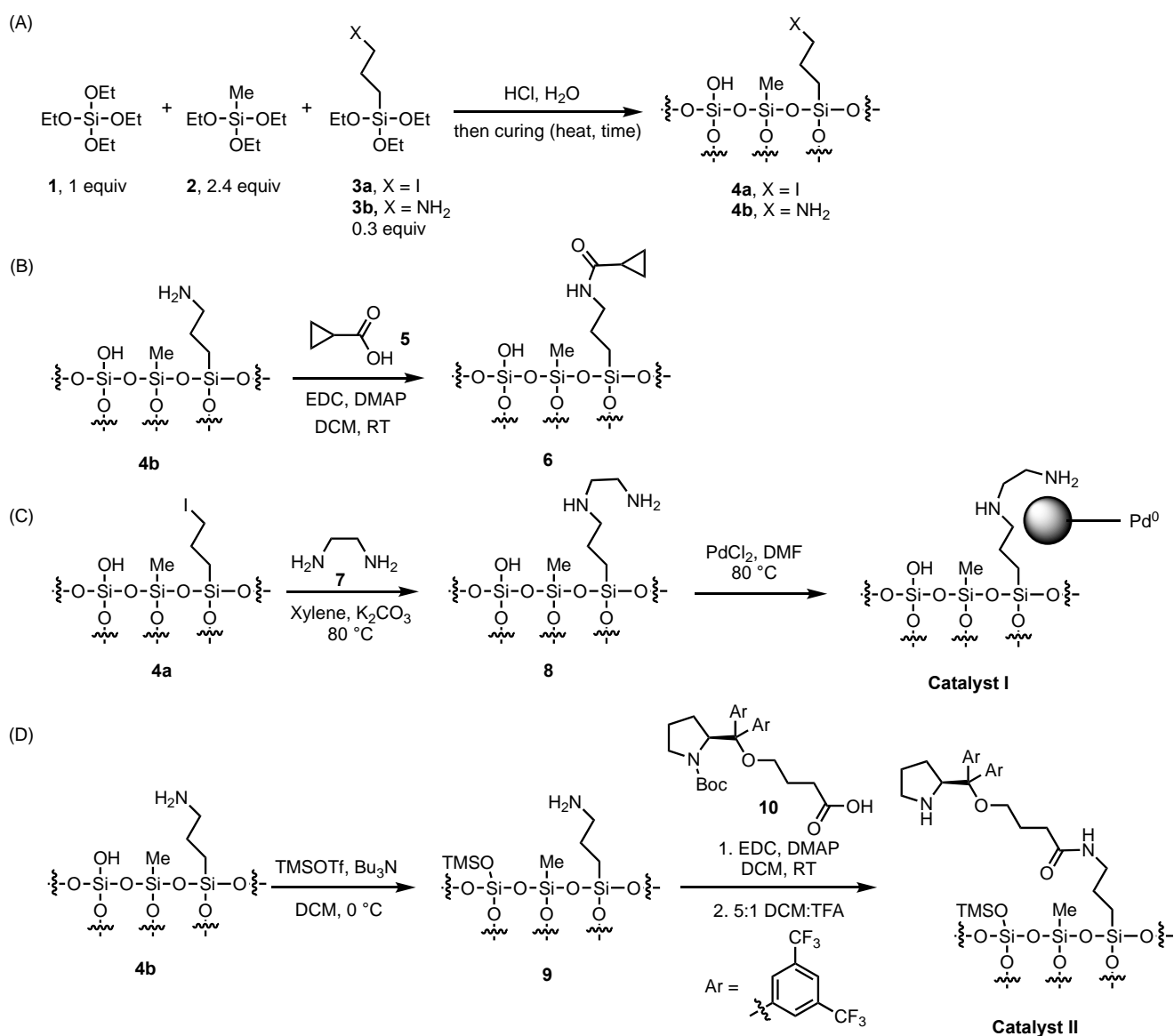


Figure 2. (A) Synthesis of **4a** and **4b** using tetraethyl orthosilicate (TEOS, **1**), methyl triethoxysilane (MTES, **2**) and **3a** or **3b**. (B) Synthesis of **6** from the silica-based support **4b**. (C) Synthesis of **Catalyst I** from the silica-based support **4a**. (D) Synthesis of **Catalyst II** reactor from **4b**. In this case, support **4b** was constructed using polystyrene foam beads 0.4 - 0.8 mm in diameter and modified equivalents of **2** and **3b** (see SI for details).

support to have larger pore sizes than mentioned above,^[2,6-9] we hypothesized that the reactor would have a limited pressure drop during operation. The use of silica for the support structure offers the benefit of resistance to swelling in many organic solvents and tolerance to acidic reaction conditions and oxidative environments. A silica surface can also be readily functionalized using well-precedented chemistry.

Our approach to the design of the silica-based monolithic support was to fill an empty stainless steel reactor with commercially available polymer beads (diameter of ~ 1 mm), prior to the addition of hydrolyzed silane monomers, including those that feature a handle for further functionalization. Following curing and removal of the beads, the 3-dimensional monolithic support would be provided that could be modified on the surface to generate the desired final catalyst system.

Since known procedures to synthesize silicas generally focus on making finely controlled mesoporous particles or thin films,^[12-15] we focused our initial efforts in developing reaction conditions to prepare a simple solid structure. We began by investigating the copolymerization of tetraethyl orthosilicate (TEOS (**1**), Figure 2A) and methyl triethoxysilane (MTES (**2**), Figure 2A) at varying molar ratios in an attempt to form a solid material with minimal cracks through visual inspection. Such flaws formed during the curing process would render the resulting structure more prone to collapse under continuous flow conditions. In general, conducting the reaction under acidic aqueous conditions (HCl) led to the formation of a solid material, whereas utilization of basic aqueous conditions (NH₄OH) resulted in flaky particles. Notably, the use of 2 - 5 equivalents of MTES (**2**) relative to TEOS (**1**) slowed the rate of

polymerization to 24 hours or more, which greatly reduced visible cracks within the resulting solid.^[16]

As shown in Figure 2A, we next investigated the copolymerization of **1** and **2** in the presence of silane **3** in order to enable surface functionalization after the curing process. Both (3-iodopropyl) triethoxysilane (**3a**) and (3-aminopropyl) triethoxysilane (APTES) (**3b**) were investigated to allow for functionalization via nucleophilic substitution and amidation reactions, respectively. The resulting solids **4a** and **4b** that were synthesized using the optimized equivalents of the respective monomers (Figure 2A) displayed minimal cracks and appeared similar to the solid produced in the absence of **3** under otherwise identical reaction conditions.

We subsequently constructed the 3-dimensional structure of the monolithic supports **4a** and **4b** by filling a stainless steel reactor (2 inches length, ¼ inch diameter) with polystyrene foam beads (1.0 - 1.5 mm diameter) prior to the addition of the aqueous acidic solution of **1**, **2** and **3a** or **3b** (Figure 2A). This solution was added from the bottom of the reactor until all of the air was displaced. Silica curing next proceeded for 24 hours at room temperature to prevent the beads from dissolving. After this initial 24 h period, we observed greater bead stability and thus the curing temperature was raised to 60 °C for an additional 24 h. The final phase of the curing process was performed at 160 °C for 2 h to ensure the removal of water and ethanol. Finally, removal of the beads to provide the silica supports **4a** and **4b** was accomplished using a simple acetone wash. It is important to note that when hard polyethylene beads were used instead of the soft foam beads, numerous stress fractures were produced during the curing process. Additionally, a high temperature (500 °C) was required to burn out (i.e. remove) the hard beads overnight, which would have

limited the types of functional groups on **3** that could be used. Overall, **4a** and **4b** had similar architectures from batch to batch due to the fairly consistent packing patterns of relatively large foam beads. The general structure of the support can be seen in the optical image of **6** (Figure 2B) viewed end-on under both light (Figure 3A) and UV-light (Figure 3B) as well as along the length under UV-light (Figure 3C). Monolith **6** was prepared from **4b** via a 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) mediated coupling reaction with cyclopropane carboxylic acid (**5**) (Figure 2B). Importantly, assessment of **4a** and **4b** under continuous flow conditions revealed the stability of the 3-dimensional structure and no detectable pressure drop at flow rates as high as 1 mL/min.

Having successfully constructed the silica support, we next prepared **Catalyst I** featuring Pd(0) for hydrogenation reactions by first functionalizing **4a** with ethylenediamine (**7**) (Figure 2C). A solution of PdCl₂ in DMF was then passed over **8** at 80 °C for 48 hours, followed by washing with 15 mL DMF (Figure 2B). The surface of **Catalyst I** was visualized using SEM imaging (Figure 3D-F) and revealed the deposition of well-dispersed Pd(0) on the surface of the solid support (Figure 3E). Elemental analysis was also performed and indicated the presence of 0.045 mmol of palladium within the 2-inch reactor.

The catalytic activity of **Catalyst I** was next screened via a series of continuous flow hydrogenation reactions (Figure 4). A 1:1 mixture of ethanol:ethyl acetate was used to ensure hydrogen gas and substrate solubility. Temperature was varied to optimize selectivity and product yield. As summarized in Figure 4, aryl nitro groups, alkenes, alkynes and imines were successfully reduced to the corresponding products

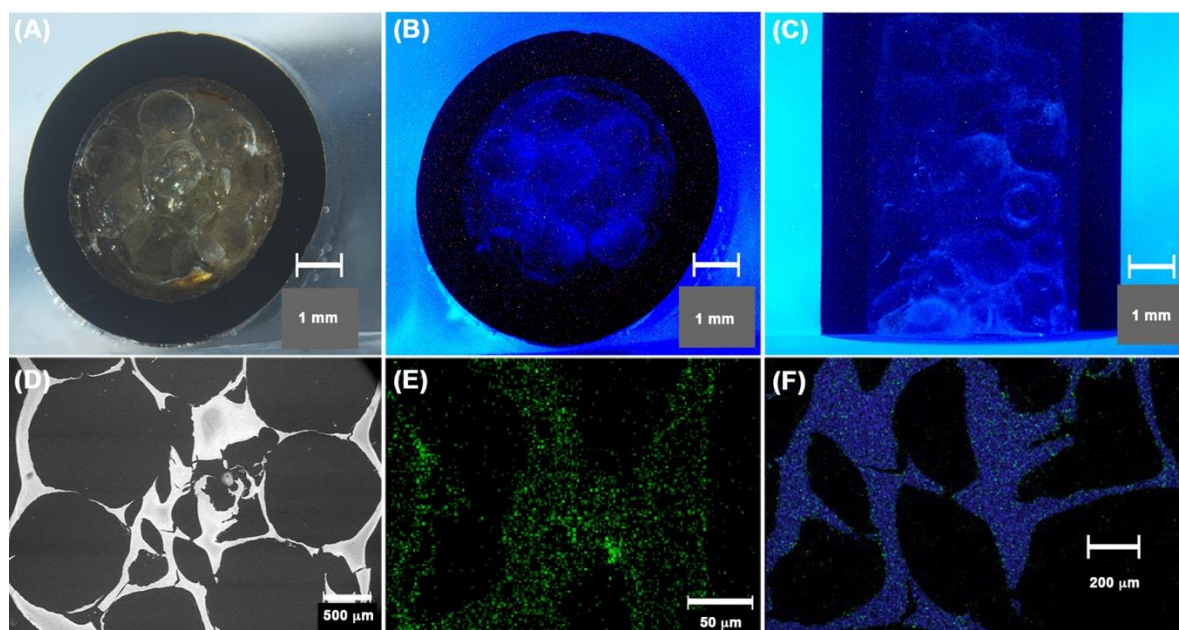


Figure 3. (A) Optical image of **6** (end view). Optical image of **6** under UV light (298 nm) viewed from the (B) end and (C) along the length of the reactor. (D) SEM image of **Catalyst I**. (E and F) SEM image of **Catalyst I** with energy dispersive x-ray analysis showing Pd(0) (green) and the silica-based monolithic support (blue), respectively.

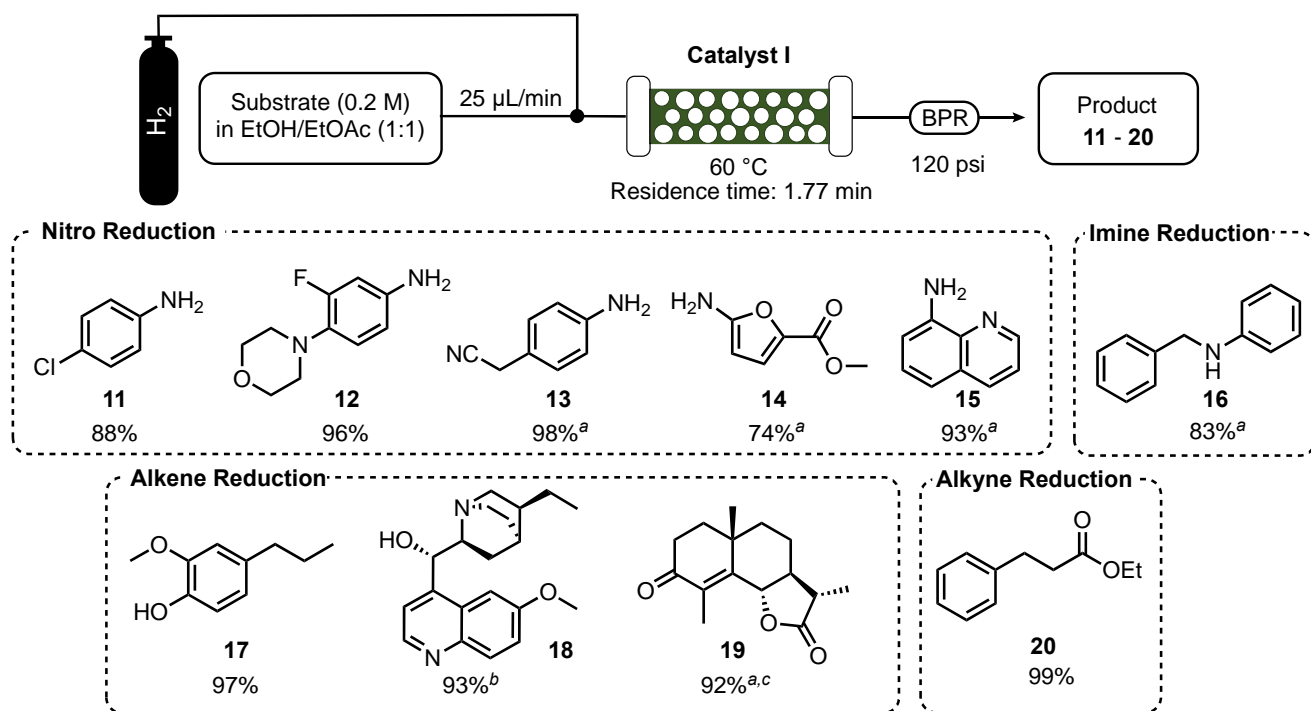


Figure 4. Scope of hydrogenation reactions using **Catalyst I** functionalized with Pd(0). Yields presented are isolated yields. Collection time = 100 minutes or 0.5 mmol. ^aReaction performed at 100 °C. ^bReaction performed at 120 °C. ^c0.1 M in EtOH/EtOAc (1:1). BPR = back pressure regulator.

11 - 20 in 74% - 99% isolated yield within a residence time of 1.77 min. [5,10,11,17,18] Challenging nitro groups^[19] which normally require long reaction times and often result in low yields of the amine product, were successfully reduced as demonstrated with the formation of **14** in 74% yield. While the reduction of compound **11** required a temperature of 60 °C to suppress dehalogenation, a higher temperature of 120 °C was necessary to achieve full conversion of quinine to compound **18**.

A longevity study was performed using the **Catalyst I** reactor by monitoring the reduction of eugenol (**21**) to **17** over a period of 113 hours (Figure 5).^[20] In general, excellent and consistent yields of **17** were observed by ¹H NMR spectroscopy with the exception of four data points shown in grey during hour ten (69% yield) to hour fifteen (90% yield). During that time period, there was a small leak in the system at the point of the back pressure regulator (BPR, 120 psi) and thus not related to the silica-based monolithic support. Notably, a single reactor was utilized for this longevity study as well as for the substrate scope shown in Figure 4. Between substrates, **Catalyst I** was washed with 5 mL of the reaction solvent (1:1 mixture of ethanol:ethyl acetate) to prevent cross-contamination.

As shown in Figure 2D, we also prepared **Catalyst II** featuring a modified Jørgensen catalyst **10**.^[21,22] In this case, support **4b** was constructed to feature a larger surface area via the use of smaller polystyrene foam beads (0.4 - 0.8 mm in diameter) so that sufficient catalyst would be covalently attached on the surface of the reactor (see Supporting Information for

details). When an EDC mediated amide coupling between **10** and **4b** was initially attempted, we observed rapid consumption of the activated carboxylic acid by FlowIR and only 10% of the expected conversion to the amide product. This suggested the participation of OH groups and possibly water molecules present on the surface of the support.

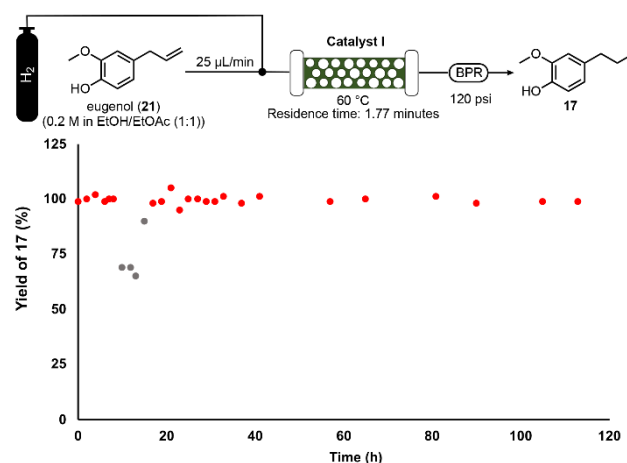


Figure 5. Continuous flow reduction of eugenol (**21**) to **17** using **Catalyst I** over 113 hours. Yields were measured using ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as an external standard. The four data points showed in grey were due to a leak in the system at the point of the BPR (back pressure regulator).

In order to remedy this undesired reactivity, the surface was treated with TMSOTf and tributylamine at 0 °C prior to performing the amide coupling reaction (Figure 2D). Finally, the active **Catalyst II** was generated by passing a 5:1 mixture of DCM:trifluoroacetic acid over the reactor for 2 hours at room temperature followed by rinsing with DCM and a 5:1 mixture of DCM and triethylamine. Elemental analysis was performed and revealed the presence of 0.0083 mmol of catalyst within the 2-inch reactor.

The catalytic activity of **Catalyst II** was examined by performing a Mannich reaction using a preformed imine and an aldehyde partner (Figure 6).^[22,23] DMF was determined to be the most suitable solvent in combination with 20% *N,N*-diphenylthiourea as an additive to activate the imine electrophile.^[23] The desired products **22** - **25** were obtained in modest isolated yields (40% - 63%) and diastereoselectivity with excellent enantioselectivity as observed by chiral HPLC. These results are generally comparable to the yields (63% - 83%) and enantioselectivities (94% -

98% ee) obtained of similar or identical products under batch conditions as described in the literature.^[21] Notably, **Catalyst II** performed reliably without any observable decrease in activity or selectivity over more than 110 experiments or 170 mmol of substrate passed over the reactor.

In conclusion, a new and practical monolithic silica-based support for the immobilization of catalysts has been developed. We have demonstrated the functionalization of the support with Pd(0) for hydrogenation reactions as well as a modified proline catalyst for the alpha functionalization of aldehydes. Both reactors displayed good activity and longevity under continuous flow conditions. Overall, these preliminary results allude to the potential for functionalizing the silica-based support with a broad range of catalysts and this will be the focus of future investigations within our laboratory.

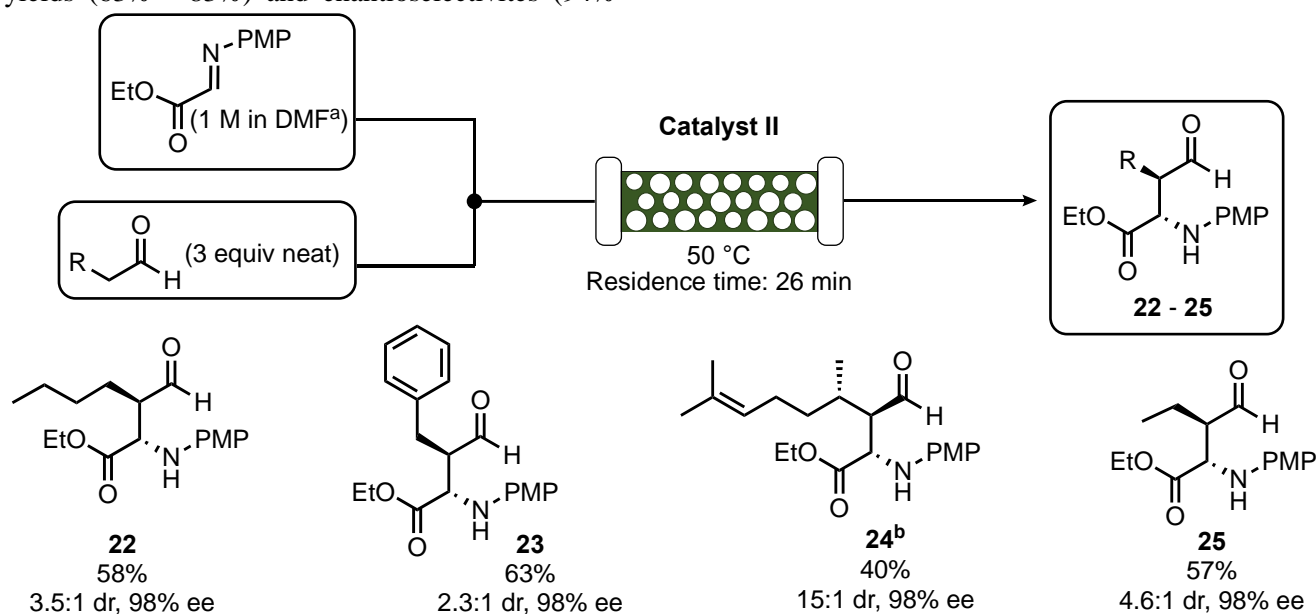


Figure 6. Scope of the alpha functionalization of aldehydes using **Catalyst II**. Collection = 0.5 mmol. Flow rate modified to achieve residence time and stoichiometry. PMP = *p*-methoxyphenyl. ^a 20% of *N,N*-diphenylthiourea added to this stream. ^b C3 stereocenter is a racemic mixture.

Experimental Section

General Method for Reactor Synthesis

TEOS (**1**) (1 equiv), MTES (**2**) (2.4 equiv) and **3a** or **3b** (0.3 equiv) were premixed and treated with 1M aqueous HCl (0.25 mL) at room temperature. The biphasic solution was stirred for approximately 5 minutes until clear and homogeneous.

A fitting was placed on the bottom end of a stainless steel tube (2 inches in length, ¼ inch in diameter). Polystyrene foam beads (1.0 - 1.5 mm) loaded into folded weighing paper with static removed were then tapped into the stainless steel tube. The homogeneous silane solution was added to the reactor from the bottom to push air bubbles out. The open end of the reactor was then plugged with folded

parafilm, inverted and the fitting where the solution was added was removed. After curing for several hours at room temperature, additional silane solution was added to the top of the reactor. After a total of 24 hours at room temperature, the reactor was subjected to a temperature of 60 °C for 24 hours, followed by 160 °C for 2-3 hours. The beads were then removed upon cooling to room temperature via rinsing with 10 mL of acetone to provide **4a** or **4b**.

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References

- [1] G. Jas, A. Kirschning, *Chem. - A Eur. J.* **2003**, *9*, 5708–5723.
- [2] A. Tanimu, S. Jaenicke, K. Alhooshani, *Chem. Eng. J.* **2017**, *327*, 792–821.
- [3] R. Porta, M. Benaglia, A. Puglisi, *Org. Process Res. Dev.* **2016**, *20*, 2–25.
- [4] D. Cantillo, C. O. Kappe, *ChemCatChem* **2015**, *6*, 3286–3305.
- [5] M. Irfan, T. N. Glasnov, C. O. Kappe, *ChemSusChem* **2011**, *4*, 300–316.
- [6] M. I. Burguete, A. Cornejo, E. García-Verdugo, M. J. Gil, S. V Luis, J. A. Mayoral, V. Martínez-Merino, M. Sokolova, *J. Org. Chem.* **2007**, *72*, 4344–4350.
- [7] N. Hird, I. Hughes, D. Hunter, M. G. J. T. Morrison, D. C. Sherrington, L. Stevenson, *Tetrahedron* **1999**, *55*, 9575–9584.
- [8] E. C. Peters, F. Svec, J. M. J. Fréchet, *Adv. Mater.* **1999**, *11*, 1169–1181.
- [9] A. Gömann, J. A. Deverell, K. F. Munting, R. C. Jones, T. Rodemann, A. J. Canty, J. A. Smith, R. M. Guijt, *Tetrahedron* **2009**, *65*, 1450–1454.
- [10] C. Genet, X. Nguyen, B. Bayatsarmadi, M. D. Horne, J. Gardiner, C. H. Hornung, *J. Flow Chem.* **2018**, *8*, 81–88.
- [11] C. H. Hornung, X. Nguyen, A. Carafa, J. Gardiner, A. Urban, D. Fraser, M. D. Horne, D. R. Gunasegaram, J. Tsanaktsidis, *Org. Process Res. Dev.* **2017**, *21*, 1311–1319.
- [12] T. S. Glazneva, E. V. Rebrov, J. C. Schouten, E. A. Paukshtis, Z. R. Ismagilov, *Thin Solid Films* **2007**, *515*, 6391–6394.
- [13] J. E. Martin, M. T. Anderson, J. Odinek, P. Newcomer, *Langmuir* **1997**, *13*, 4133–4141.
- [14] K. S. Rao, K. El-Hami, T. Kodaki, K. Matsushige, K. Makino, *J. Colloid Interface Sci.* **2005**, *289*, 125–131.
- [15] I. A. Rahman, V. Padavettan, *J. Nanomater.* **2012**, *2012*, 1–15.
- [16] E. J. Kappert, D. Pavlenko, J. Malzbender, A. Nijmeijer, N. E. Benes, P. A. Tsai, *Soft Matter* **2015**, *11*, 882–888.
- [17] A. K. Rathi, M. B. Gawande, V. Ranc, J. Pechousek, M. Petr, K. Cepe, R. S. Varma, R. Zboril, *Catal. Sci. Technol.* **2016**, *6*, 152–160.
- [18] C. J. Mallia, I. R. Baxendale, *Org. Process Res. Dev.* **2016**, *20*, 327–360.
- [19] A. Padwa, M. Dimitroff, A. G. Waterson, T. Wu, *J. Org. Chem.* **1997**, *62*, 4088–4096.
- [20] A. B. Xia, C. Zhang, Y. P. Zhang, Y. J. Guo, X. L. Zhang, Z. B. Li, D. Q. Xu, *Org. Biomol. Chem.* **2015**, *13*, 9593–9599.
- [21] See the Supporting Information for further details.
- [22] J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304.
- [23] H. Kuroda, I. Tomita, T. Endo, *Polymer (Guildf)*. **1997**, *38*, 6049–6054.

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