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Studying the Morita-Baylis-Hillman Reaction in Continuous Flow Using Packed Bed Reactors

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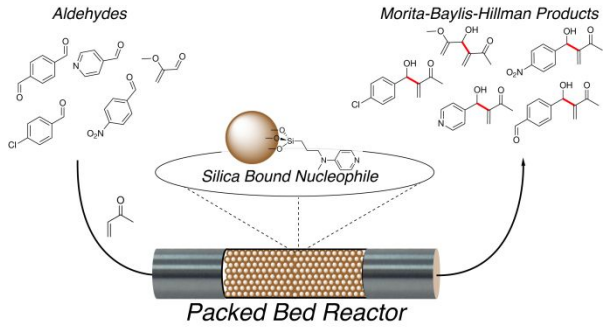


Abstract

Conditions for the Morita-Baylis-Hillman reaction have been developed under continuous flow using a packed bed reactor carrying DMAP immobilized on silica. High reaction rates were obtained as the packed bed reactor mimics super-stoichiometric catalyst loadings for the passing reaction mixture. Catalyst deactivation was circumvented by avoiding acrylate esters as the reaction partners. The developed flow protocol provided all desired Morita-Baylis-Hillman products in yields attaining 95% with typical retention times between just 30-60 minutes. Precise control of the retention time proved imperative for one example, in which optimal yield was attained in just 10 minutes, while outpacing sideproduct formation. Finally, a scale-out study was performed proving high stability of the packed bed reactor setup and catalyst for more than 20 hours of operation.

Keywords

Morita-Baylis-Hillman, Continuous Flow, Packed Bed Reactor, DMAP Catalysis, Scale-Out

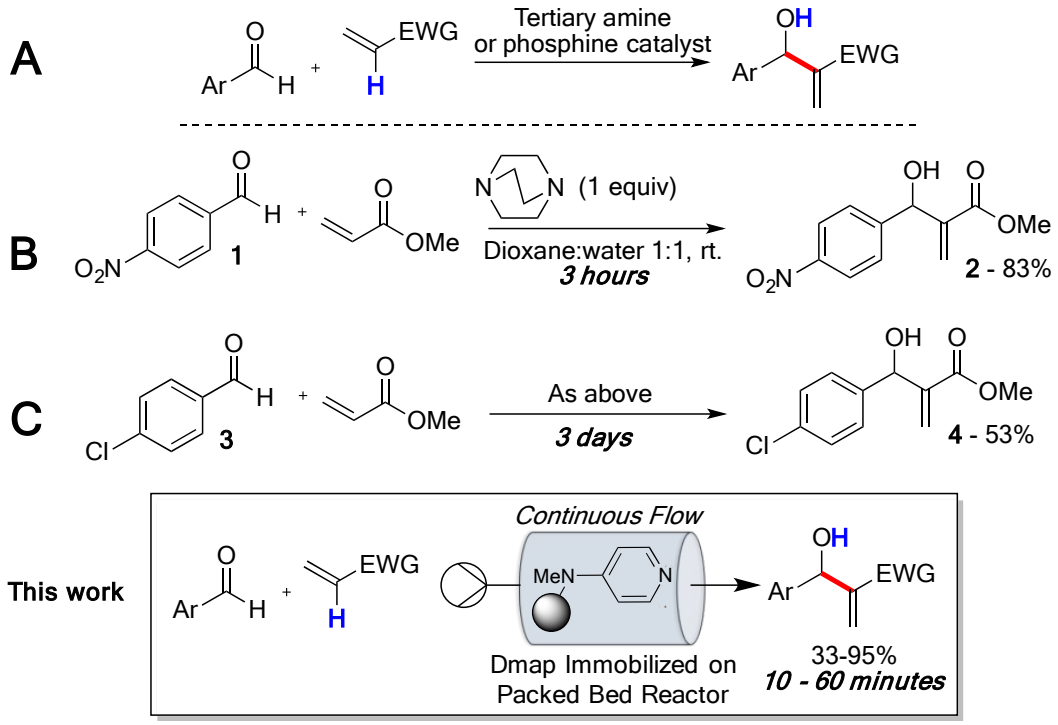
Introduction

The Morita-Baylis-Hillman (MBH) reaction is the coupling of an electron deficient olefin with an aldehyde, ketone or imine, typically catalyzed by a tertiary amine.[1,2] The transformation was initially named the Baylis-Hillman reaction by the group of Roos et. al., based on a patent filed by Baylis and Hillman in 1972.[3] However, the reaction was originally reported by Morita et. al. in 1968 using tertiary phosphines as catalysts.3[a]

MBH reactions are known for their mild reaction conditions, allowing the products thereof, to be decorated with a vide variety of functional groups. A carbon-carbon bond is formed during the MBH reaction and the transformation runs with complete atom efficiency as shown with the generic example depicted in Scheme 1A.

Despite its simple appearance, an interesting feature to the MBH reaction is its fairly complex reaction kinetics and multiple competitive reaction pathways.[4] Reaction times in the MBH reaction range from hours to days, and it has been shown that electron-deficient aldehydes reacts at higher rates than their more electron rich

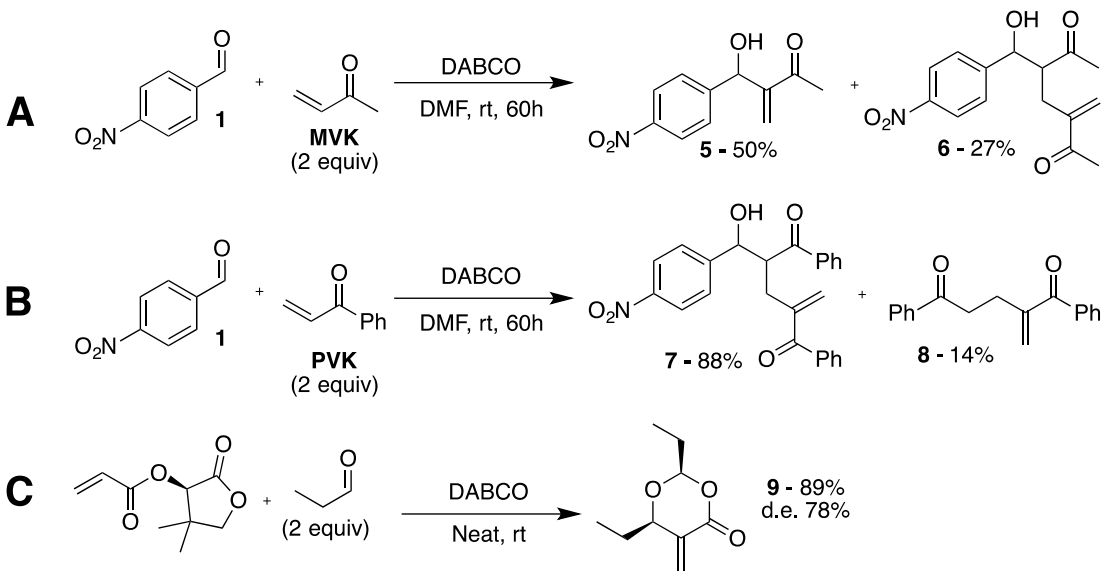
counterparts. Reaction of methyl acrylate with *p*-nitrobenzaldehyde (**1**) affords **2** in 83% in just three hours. In comparison the similar reaction with the more electron rich *p*-chlorobenzaldehyde (**3**) takes three days to yield **4** in 53% under identical conditions. (Scheme 1 – B and C, respectively).[5]



Scheme 1. A) General Morita-Baylis-Hillman reaction of an aromatic aldehyde with an electron deficient olefin. B) MBH reaction with electron-deficient aldehyde. C) MBH reaction with electron rich aldehyde.

The reaction kinetics of the MBH reaction are dependent on all reaction components including, carbonyl derivative, olefin, catalyst, etc. and combined reaction orders of up to 4 have been reported.[6] Furthermore, alcohols and protic solvents have been

shown to play the important role of facilitating proton transfer, resulting in an increased reaction rate.[7] Whereas long reaction times of multiple days clearly define a drawback to the MBH reaction, another set of problems emerges with increasing electrophilicity of the olefin.[8] Examples of this are provided in Scheme 2, where the olefin has reacted with the formed MBH product. Hence, both the desired product **5** and sideproduct **6** are formed in 50% and 27%, respectively, when methyl vinyl ketone (**MVK**) is applied as the olefin (Scheme 2A). Turning to phenyl vinyl ketone (**PVK**) only the product **7**, from double olefin addition, is observed after 60 hours at room temperature (Scheme 2B). In this example the authors also isolated the product **8** derived from dimerization of **PVK**. When acrylates are used as the reacting olefin the formation of 1,3-dioxan-4-ones, such as compound **9**, are also observed amongst the sideproducts of the Morita-Baylis-Hillman transformation (Scheme 2C). It is important to note that the catalyst for the MBH reaction also catalyzes the formation of the in Scheme 2 mentioned sideproducts. Hence, if the reaction kinetics favor formation of the target MBH product, precise control of the reaction time would lead to improve yields by inhibiting these secondary reaction events.



Scheme 2. Potential by-products formed during the MBH reaction with electrophilic olefins.

As part of an ongoing project in our laboratory, access to a set of different MBH substrates were needed, and furthermore, some of these substrates were required in a +20 gram scale.[9] Hence, focus was directed towards their preparation in continuous flow, as scale-out would allow the MBH-products to be prepared in practical any scale.[10] Despite the numerous reports on the MBH reaction, a detailed search through the literature only revealed few previous examples of the transformation being performed in continuous flow. One report by Acke and Stevens studies the MBH reaction between 4-nitrobenzaldehyde and methyl acrylate in a plug-flow microreactor setup.[11] Despite the improved mass transfer and temperature control obtained by the microreactor setup, only a reduction of 30% in reaction time was observed. Prof. Baxendale reported on the MBH reaction between isobutyraldehyde and acrylonitrile in continuous stirred tank reactors

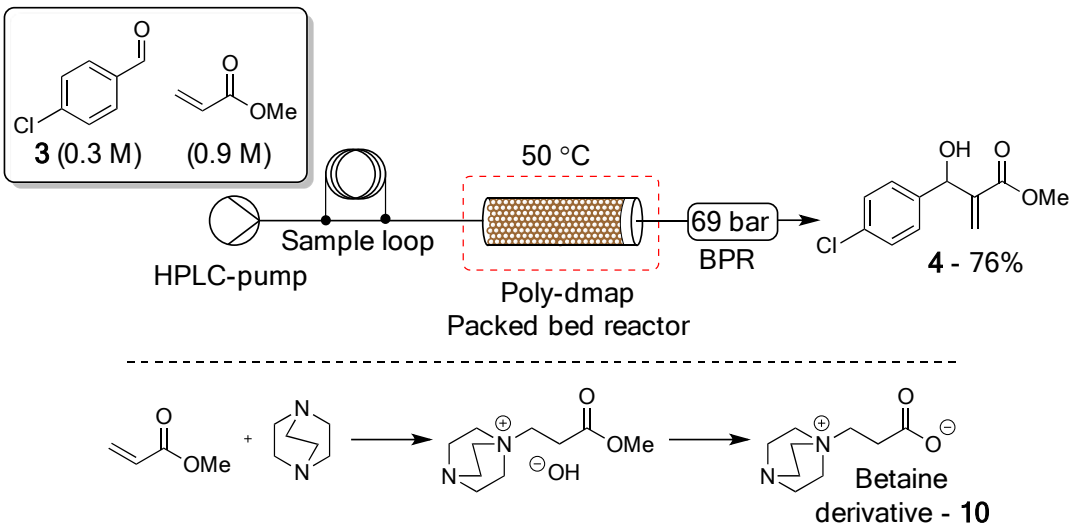
(CSTR). [12] The setup was devised by aligning 6 x 100 mL CSTR´s in series thereby allowing an impressive +200 mmol/h of reactants to be processed when running all reactors at 65 °C. Finally, Ishitani et. al. devised a packed bed reactor (PBR) loaded with DMAP immobilized on silica for the reaction between *β*-styrene with ethyl glyoxalate in toluene at room temperature.[13,14] This setup initially provided Ishitani with a high ^{1}H-NMR yield, however, catalyst degradation led to depletion in conversion rates to approx. 50% within 48 hours of operation.

As discussed above, it has been shown that the loading of nucleophilic catalyst affects the overall reaction rate of the MBH reaction by an order of one.6 Hence, addition of an organo-catalyst, such as DABCO or DMAP, in super-stoichiometric loadings should reduce the total reaction time of the MBH transformation. However, the same high loading of catalyst also catalyzes the formation of undesired by-products (Scheme 2). From these observations, we concluded that a similar approach to that of Ishitani and co-workers would provide a setup with a two-fold benefit. Firstly, a PBR carrying an immobilized amine catalyst would increase the MBH reaction rate, as the *on-reactor* reaction mixture experiences super-stoichiometric catalyst loadings. Secondly, precise control of the reaction time becomes possible as the catalyst is retained in the PBR upon reaction mixture exit. The latter being relevant for combinations of highly reactive substrates, where the secondary reaction events described in Scheme 2, quickly leads to deterioration of the overall reaction yield. Finally, work by Lin and co-workers indicates that application of immobilized catalysts inhibits sideproduct formation in MBH reactions.[15]

In this manuscript we wish to report on the development of the Morita-Baylis-Hillman reaction in continuous flow using dimethylaminopyridine, immobilized on silica particles, as the catalyst in a packed bed reactor (Scheme 1 – *This work*). In particular, the combination of methyl vinyl ketone as the vinylic reaction partner in 1-butanol, as the solvent, led to fast reaction rates and improved catalyst stability. Furthermore, precise control of the reaction time for highly reactive combinations of MBH reagents led to significantly improved isolated yields of the desired products. Finally, a scale-out experiment proved the stability of both the reactor and catalyst with no loss of reactivity during 20 hours of operation.

Results and Discussion

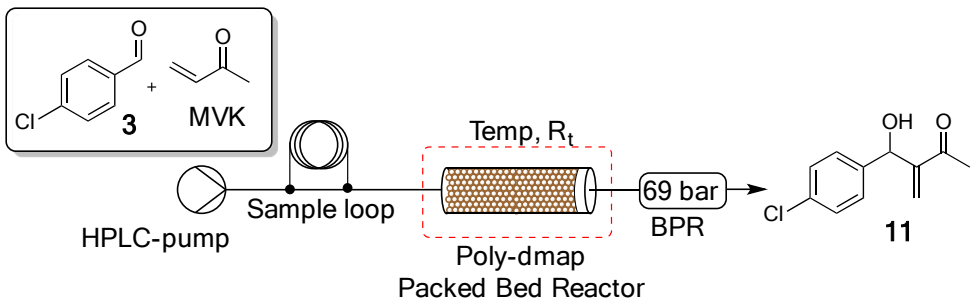
Initially, the MBH reaction between 4-chlorobenzaldehyde (**3**) and methyl acrylate was chosen as the test reaction. A small screening of reaction conditions in batch revealed commercially available polymer bound 4-(dimethylamino)pyridine (polyDMAP, 3 mmol/g) as the catalyst combined with 1-butanol as the solvent to be an efficient system (results not shown).[7,16] Next, a packed bed reactor (PBR) was constructed by loading polyDMAP into an empty HPLC column (ID = 5.0 mm, L = 130 mm) which was placed in an oil bath heated to 50 °C (See Experimental Section for details). A stock solution of **3** (0.3 M) and methyl acrylate (0.9 M) dissolved in 1-butanol was loaded onto a sample loop (10 mL) and pumped through the reactor using 1-butanol as the background solvent (See Scheme 3 - a). Combined with a retention time of 20 minutes this setup provided the desired MBH product **4** in a good 76% isolated yield after column chromatography.



Scheme 3. Continuous flow MBH reaction using a polyDMAP packed bed reactor. Below: Catalyst deactivation with formation of **10**.

Although polyDMAP provided good results for the MBH reaction the catalytic activity dropped rapidly in sequential runs. This deactivation of the catalyst was ascribed to a similar observation made by Hu and Stevens, who both reported the formation of an inactive betaine species **10** upon mixing of acrylates with DABCO (Scheme 3 – bottom).[11, 5a] Speculating that the same reaction could occur for DMAP in the presence of methyl acrylates, it was decided to substitute methyl acrylate for methyl vinyl ketone (**MVK**) for further optimization (Table 1).

Table 1. Optimization of the MBH-Reaction using poly-DMAP as catalyst in Continuous Flow.[a]

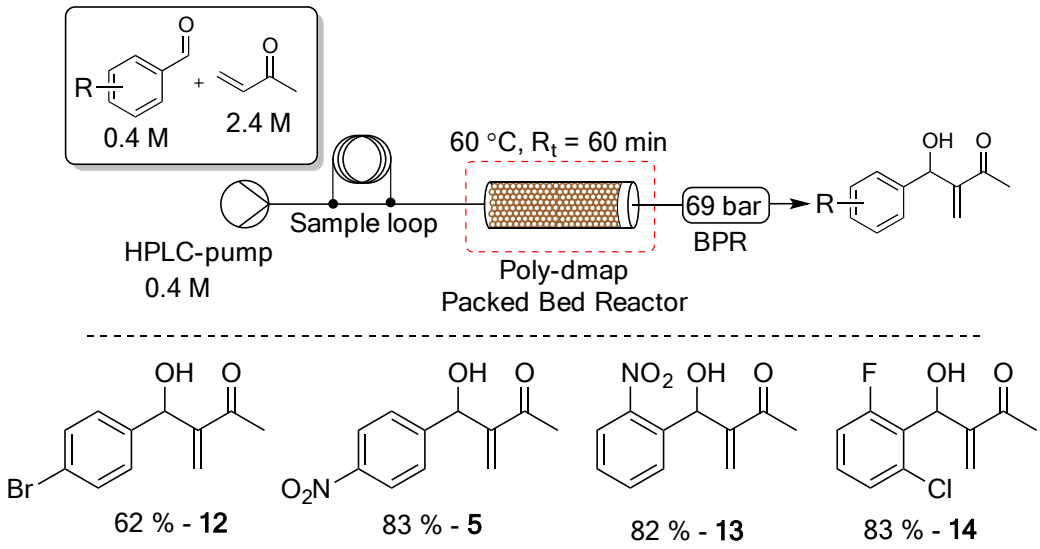


Entry	3 (mmol)	MVK (Molar)	Temp. (°C)	R_t (min)	Poly-DMAP[b] (mmol)	Yield (%)
1	0.2 M	0.3 M	60	30	3	12 %
2	0.4 M	1.2 M	50	30	3	32 %
3	0.4 M	2.4 M	50	30	3	43 %
4	0.4 M	3.6 M	50	30	3	45 %
5	0.4 M	2.4 M	60	30	3	50 %
6	0.4 M	2.4 M	60	45	3	56 %
7	0.4 M	2.4 M	60	30	6	59 %
8	0.4 M	2.4 M	70	30	6	51 %
9	0.8 M	4.8 M	60	30	6	56 %
10	0.4 M	2.4 M	60	60	6	72 % (61%)[c]

[a] A stock solution of 4-chlorobenzaldehyde (**3**) and **MVK** in 1-butanol (2 mL) was loaded onto the sample-loop. The reaction mixture was then pumped through the PBR at the temperature and retention time given in the table, using 1-butanol as the background solvent. Sample collection was continued for 2,5 times the retention time. The crude reaction mixture was concentrated under reduced pressure and the yield determined by ^{1}H-NMR analysis using dimethyl terephthalate as the internal standard. [b] Reactor 1 contained 0.5 g polymer bound DMAP (6 mmol/g), reactor 2 contained 1.0 g polymer bound DMAP (6 mmol/g). [c] Yield in brackets is isolated yield after column chromatography.

A stock solution of **3** (0.2 M) and **MVK** (0.3 M) was prepared using 1-butanol as the solvent. The stock solution (2 mL) was loaded onto a sample loop and passed through the packed bed reactor at 60 °C with a retention time of 30 min. This resulted in a disappointing ^{1}H-NMR yield of only 12% of **11**, the remaining material being unreacted **3** and **MVK** (Table 1, entry 1). Increasing the concentrations of **3** to 0.4 M and **MVK** to 1.2 M at 50 °C afforded an improved yield of 32% (Entry 2). Further increases in the concentration of **MVK** to 2.4 M and 3.6 M provided **11** in 43 % and 45 %, respectively (entries 3 and 4). Performing the reaction at 60 °C and prolonging the retention time to 45 minutes resulted in an increase in the ^{1}H-NMR yield to 56% (entries 5 and 6). Importantly, loss of catalytic activity was no longer observed when applying **MVK** as the olefinic reaction partner. At this stage it was decided to double the polyDMAP loading of the packed bed reactor from 3 mmol to 6 mmol. Gratifyingly, the presence of additional catalyst afforded **11** in a good 59% yield after only 30 minutes on the reactor at 60 °C (entry 7). Higher temperatures or increased **MVK** concentrations did not lead to any improvements in yield (entries 8 and 9). Finally, doubling the retention time from 30 to 60 minutes led to a satisfactory ^{1}H-NMR yield of 72% with a 61% isolated yield of **11** after column chromatography (Entry 10).

Satisfied with the developed conditions, the scope of the reaction was next investigated, a few results of which are depicted in Scheme 4.



Scheme 4. MBH Reactions using poly-DMAP in Continuous Flow. See supporting information for reaction details.

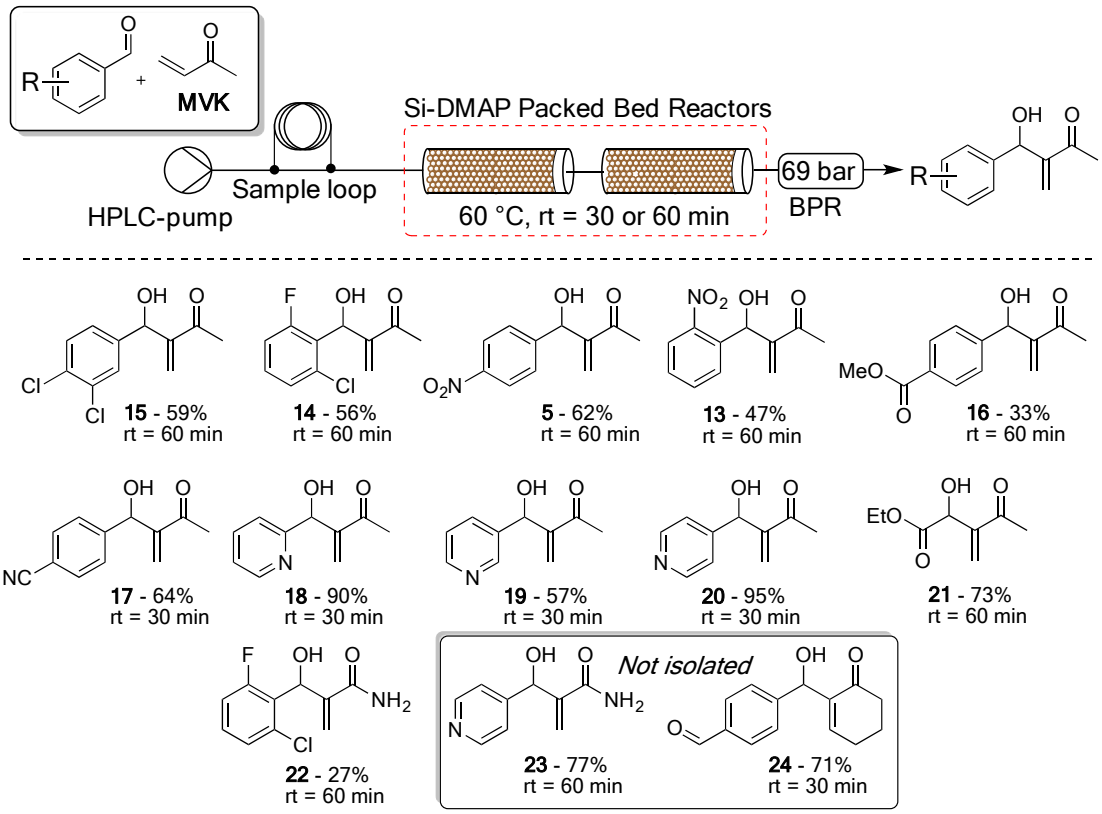
Substitution of chlorine for bromine provided **12** in 62% isolated yield. The electron poor aldehydes 4- and 2-nitrobenzaldehyde afforded **5** and **13** in 83% and 82% isolated yields, respectively. Finally, when 2-chloro-6-fluorobenzaldehyde was tested **14** was obtained in an excellent 83% isolated yield after only 60 minutes on the PBR.

Although the devised reactor setup initially provided promising results, the pressure drop over the PBR steadily increased as a function of time. The commercially available polyDMAP beads used in this study are crosslinked using 2 w/w% divinyl benzene. The observed increase in pressure drop is most likely related to the swelling of the polyDMAP beads, inside the reactor, leading to clogging. Examination of the packed bed reactor content after several runs also indicated the column material to have become tightly packed. The group of Steven

Ley has previously reported that application of beads with higher degrees of crosslinking leads to decreased swelling, and hence, increased packed bed reactor stability.[17] Following this concept, it was decided to change the solid reactor material to DMAP bound on silica particles (Si-DMAP).[13,15,18] The Si-DMAP particles sizes range between 40-63 μm and has a DMAP loading of 0.53 mmol/g.

The new continuous flow setup was constructed by serial connection of two HPLC-columns (ID = 4,6 mm, L = 250 mm) loaded with Si-DMAP (See Scheme 5 for schematic diagram).[19] The applied silica-DMAP PBRs had average combined DMAP loadings of 4.25 mmol and average void volumes of 3.92 mL (see Experimental Section for details). The Si-DMAP reactor setup carries a reduced average catalyst loading of 4.25 mmol, compared to the poly-DMAP system, with 6 mmol DMAP/reactor. This effect of this resulted in a decreased yield of 20% of **11** when tested under the conditions developed in Table 1 – entry 10 (results not shown). However, the silica matrix provided a packed bed reactor performing with a completely stabilized pressure drop. Hence, no further optimization studies were performed at this stage and the scope of the MBH reacted was investigated using Si-DMAP as the matrix-bound catalyst (Scheme 5). Some of the reactions required the addition of CH_2Cl_2 as a co-solvent in order to fully solubilize the starting aldehyde in the stock solution.[20,21] The retention time was optimized for each entry with an upper limit of 60 minutes. Halogenated aldehydes afforded the **15** and **14** in 59% and 56% isolated yields. Interestingly, the normally highly reactive nitrated aromatic aldehydes only afforded compounds **5** and **13** in 62% and 47% isolated yields, respectively. The presence of a *p*-cyano substituent provided **17** in a good

64% isolated yield after only 30 minutes on the reactor, whereas the presence of a methyl ester deteriorated the yield to 33% of compound **16**. Next, the 2,3 and 4-pyridinecarboxaldehydes were tested.



Scheme 5. Morita-Baylis-Hillman reaction in Continuous Flow using a Si-DMAP Catalyst.

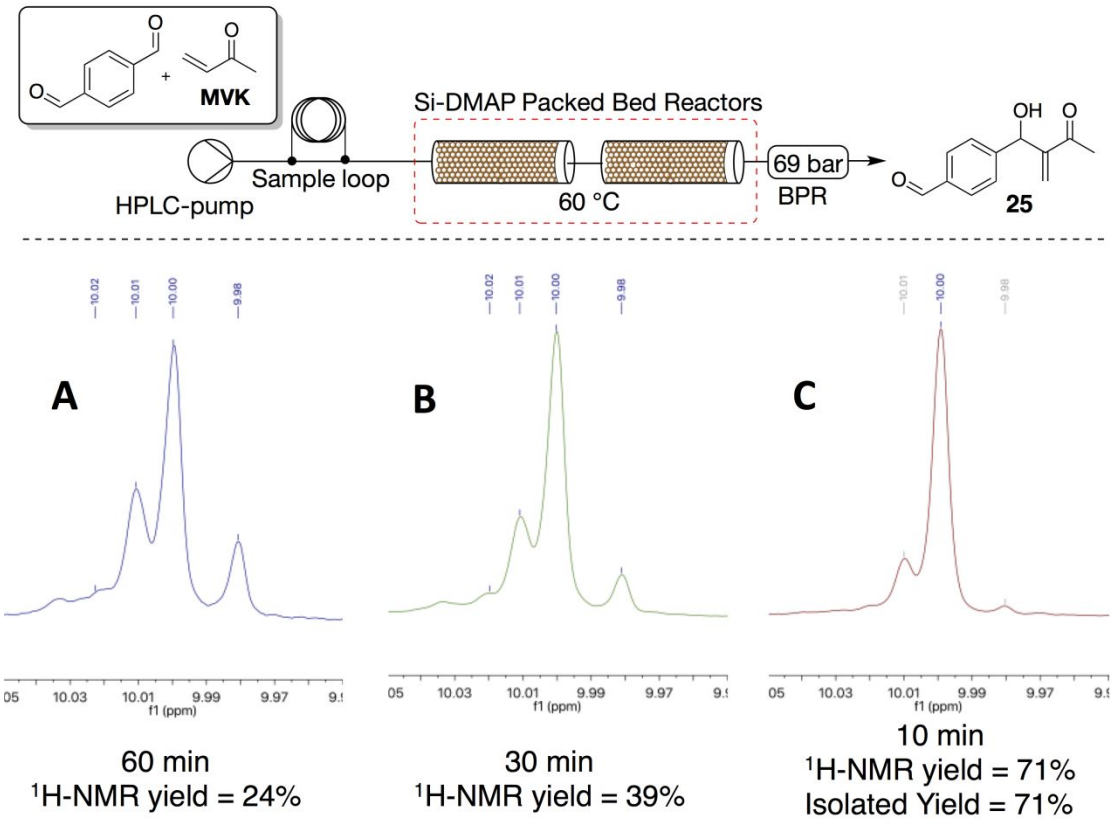
All proved highly reactive and afforded compounds **18**, **19**, **20** in yields attaining 95% with a retention time of only 30 minutes. When ethyl glyoxalate was used the desired MBH-product **21** was obtained in a good 73% isolated yield, again with only 30 minutes on the reactor. Finally, the less reactive acrylamide was tested instead of **MVK**. However, ^{1}H-NMR analysis of the crude reaction mixtures showed formation of several sideproducts. These impurities severely hampered isolation by column

chromatography and only a mere 27% of **22** was secured in its pure form. Despite these isolation problems both acrylamide and 2-cyclobutenone proved reactive under the developed conditions affording the MBH products **23** and **24** in 77% and 71% ^{1}H-NMR yields. Importantly, opposed to the observations made by Ishitani et. al. the Si-DMAP catalyst seemed to operate without loss of activity under the developed conditions.13

Attention was next turned towards terephthalaldehyde as substrate. Terephthalaldehyde was chosen to test if the reaction of the second aldehyde functionality could be prevented, thereby leading to the desymmetrized MBH-product. However, significant overreactions of the MBH adduct with **MVK** occurred during the reaction (Figure 1). The formation of sideproducts is clearly visible from the presence of several additional aldehyde peaks in the ^{1}H-NMR of the crude reaction mixture (see SI for full spectrum).[22] Hence, when performing this reaction with a retention time of 60 minutes only a meager ^{1}H-NMR yield of 24% of **25** was obtained. Interestingly, reducing the retention time to 30 minutes provided a lower conversion of terephthalaldehyde, however, this was counterbalanced by small increase in product selectivity and **25** was present in a ^{1}H-NMR yield of 39%. Finally, application of a retention time of *only 10 minutes* nearly outpaced the formation of overacted sideproducts, and **25** was secured in a good 71% isolated yield after column chromatography. Notably, the majority of remaining material was unreacted terephthalaldehyde and the side reaction of **MVK** with butanol was also suppressed (See the Experimental Section). Further reductions in retention time did not lead to any further improvements. The reaction of terephthalaldehyde with

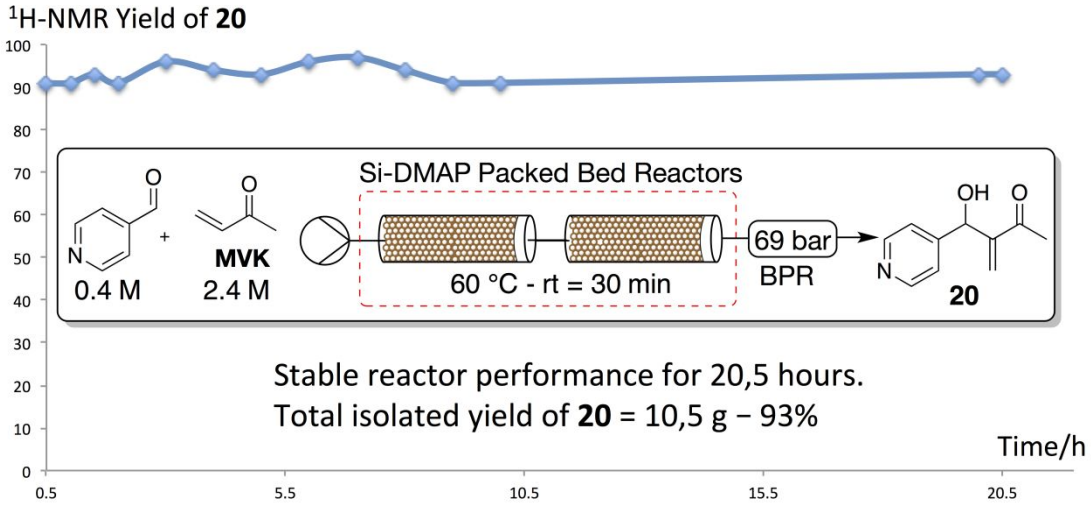
MVK exemplifies the importance of precision reaction time control obtained when performing the MBH transformation in continuous flow.

Figure 1. Elimination of sideproduct formation in the MBH reaction by precise time control.



As the final part of this study, it was decided to test the PBR catalyst stability by a scale-out experiment (Scheme 6). Towards this purpose the MBH reaction between 4-pyridinecarboxaldehyde and **MVK,** using a retention time of 30 minutes, was chosen (See Scheme 5, compound **20**). The flow setup was allowed to run for 45

minutes before sample collection was initiated, in order to secure steady state operation in the packed bed reactor. Samples were collected every 30 or 60 minutes for the first ten hours and analyzed by ^{1}H-NMR using dimethyl terephthalate as internal standard. The setup continuously afforded **20** in a >90% yield. The setup was then allowed to run overnight, and before termination of the experiment, one final 30-minute sample was collected.



Scheme 6. 20 hour Scale-out experiment affording **20**.

Both the overnight run and the final sample contained **20** in 93% ^{1}H-NMR yield, thereby proving the high stability of the catalyst in the PBR. All samples were combined and **20** was isolated in an excellent 93% yield (10.5 grams, 59.3 mmol). With a total PBR loading of 4.19 mmol of Si-DMAP this corresponds to a TON of more than 14 without loss of activity.

Conclusions

In conclusion, reaction conditions for the Morita-Baylis-Hillman reaction have been developed in continuous flow using DMAP immobilized on silica in a packed bed reactor setup. DMAP catalyst deactivation was overcome by avoiding methyl acrylate as the olefin. This setup allowed for the repeated use of the same PBR-catalyst to generate a library of MBH adducts using retention times of 30 or 60 minutes for all entries. The conditions provided all desired MBH products in yields ranging from 33% to 95%. The ability to control the reaction time with great precision was exemplified by the reaction between terephthalaldehyde and **MVK**. Here sideproduct formation was suppressed by only subjecting the reaction mixture to the catalyst for 10 minutes while affording the target product in 71% isolated yield. Finally, a scale-out experiment was performed to investigate the catalyst and reactor stability. Gratifyingly, running the continuous flow system for 20.5 hours afforded the desired product in an excellent 93% isolated yield. Importantly, no sign of catalyst deactivation was observed throughout the entire scale-out experiment.

Experimental section

General

All solvents were HPLC-graded quality and were used without further treatment unless otherwise stated. All chemicals were used as received. DMAP-MS was obtained from silicycle (product nr: R75630B, lot: 104492, 0.98 mol/g). Physical properties of DMAP-MS (particle size = 40 - 63 μm, surface area = 480-550 m^2/g, pore diameter = 60 Å). Concentration *in vacuo* was conducted using a rotary evaporator with a water bath set to 40 ^oC - 55 ^oC . Flash column chromatography

was conducted with silica gel (230-400 mesh particle sizes, 60 Å pore size) as the stationary phase. TLC was conducted using silica coated alumina plates (Kieselgel 60 F254). The TLC plates were visualized using UV light. ^{1}H-NMR spectra were recorded at 400 MHz, ^{13}C-NMR were recorded at 101 MHz spectroscopy and ^{19}F NMR were carried out at 376 MHz on a 400 MHz spectrometer. ^{1}H NMR and ^{13}C NMR spectra are reported in ppm and correlated to their respective solvent residual peak[23]. High-resolution mass spectra were conducted on a LC TOF (ES) apparatus, with positive electrospray ionization. Masses were calibrated using internal standards from sodium formate clusters. Melting points (mp) were obtained on a capillary melting point apparatus and are uncorrected. Quantitative NMR was conducted with dimethyl terephthalate as the internal standard.

General Methods

General Continuous Flow Reactor Setup

A HPLC pump was used to pump the stock solution through the flow setup. A back-pressure regulator (69 bar) was connected to prevent boiling of solvents and reagents. All stainless steel tubing (1/16'' OD x 0.75 mm ID) and reactors were connected using HPLC fittings (T-pieces, unions etc. all with 0.75 mm ID). The packed bed reactors were heated in an oil bath (scheme-1, fig.1). Important: All parts of the continuous flow setup, i.e. tubing, columns, fittings, connectors, back-pressure regulator, etc, are constructed using HPLC-components. This is done to ensure a high level of security during operation at high pressures.

Determination of Internal Volume:

The void volume of the PBR was determined by weighing the newly prepared PBR's

$$V_{void} = \frac{m_2 - m_1}{\rho_{Solvent}}$$

(m_1). Then 1-butanol was pumped through the reactor to fill the reactor void with solvent and the PBR was weighed again (m_2). The total reactor void volume, V_{void}, was determined by:

Eq(1)

MBH Reactions Using Poly-DMAP in Continuous Flow

The aldehyde (0.4 M, 1 equiv.) and the activated alkene (2.4 M, 6 equiv.) were dissolved in n-butanol in a measuring flask (10 mL). 2.0 mL of the stock-solution was loaded into the sample loop and pumped through the packed bed reactor containing DMAP (1.0 g, 6 mmol/g, 200-400 mesh, 2 % cross-linked) and silica gel with a flow rate of 0.019 mL/min corresponding to a residence time of 60 min at 60 °C. The product was collected for 5.5 hours, concentrated under reduced pressure and purified by flash column chromatography.

Packed bed reactor

An empty HPLC column (13 cm length, 0.5 cm ID) was filled with a mixture of polystyrene-bound DMAP (1 g, 6 mmol/g, 200-400 mesh, 2% cross-linked) and silica gel. Both ends of the column were fitted with a small piece of cotton (~20 mg).

4-Hydroxy-4-(4-chlorophenyl)-3-methylenebutan-2-one (4): The crude product was obtained using the general method for MBH reaction in continuous flow. The title compound was purified using flash column chromatography eluting with EtOAc/pentane (1/7) and obtained as a colorless oil (103 mg, 0.49 mmol, 61 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (s, 4H), 6.19 (s, 1H), 5.98 (s, 1H), 5.56 (s, 1H), 3.27 (bs, 1H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.4, 149.8, 140.2, 133.5, 128.6, 128.0, 127.0, 72.2, 26.6. The title product (**11**) was also produced in a

one pot fashion. The reaction was conducted in a one chamber reaction flask in 24 hours at 60 degree celcius (table 1).

4-Hydroxy-4-(4-bromophenyl)-3-methylenebutan-2-one (12): The crude product was obtained using the general method for MBH reaction in continuous flow. The title compound was purified using flash column chromatography eluting with EtOAc/pentane (1/5) and obtained as a colorless oil (127 mg, 0.50 mmol, 62 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.40 Hz, 2H), 7.22 (d, *J* = 8.40 Hz, 2H), 6.19 (s, 1H), 5.97 (s, 1H), 5.55 (s, 1H), 3.22 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.3, 149.6, 140.6, 131.5, 128.3, 127.0, 121.6, 72.3, 26.5. HRMS (m/z): Calculated $C_{11}H_{12}BrO_2$ $[M+H]_+$ 255.0015 found 255.0000.

4-Hydroxy-4-(4-nitrophenyl)-3-methylenebutan-2-one (5):[24] The crude product was obtained using the general method for MBH reaction in continuous flow. The reagents were dissolved in DCM (2 mL) and the measuring flask was filled with *n*-butanol). The title compound was purified using flash column chromatography eluting with EtOAc/pentane (2/3) and obtained as a white solid (147 mg, 0.66 mmol, 83 % yield). Mp: 74.5 - 76.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 6.26 (s, 1H), 6.03 (s, 1H), 5.67 (d, *J* = 5.60 Hz, 1H), 3.32 (d, *J* = 5.60 Hz, 1H), 2.35 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.2, 149.1, 149.0, 147.5, 127.9, 127.4, 123.7, 72.4, 26.5. HRMS (m/z): Calculated $C_{11}H_{11}NO_4$ $[M+H]_+$ 222.0761 found 222.0745.

4-hydroxy-4-(2-nitrophenyl)-3-methylenebutan-2-one (13):[25] The crude product was obtained using the general method for MBH reaction in continuous flow. The title compound was purified using flash column chromatography eluting

with EtOAc/pentane (1/3) and obtained as a white solid (145 mg, 0.65 mmol, 82 % yield). Mp: 71.4 - 74.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 6.22 (d, *J* = 3.80 Hz, 1H) 6.17 (s, 1H), 5.79 (s, 1H), 3.52 (d, *J* = 3.80, 1H), 2.37 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.0, 149.0, 148.2, 136.6, 133.6, 129.0, 128.6, 126.7, 124.8, 67.7, 26.2. HRMS (m/z): Calculated $C_{11}H_{11}NO_4$ $[M+H]_+$ 222.0761 found 222.0741.

4-Hydroxy-4-(2-chloro-6-fluoro-phenyl)-3-methylenebutan-2-one (14): The crude product was obtained using the general method for MBH reaction in continuous flow. The title compound was purified using flash column chromatography eluting with EtOAc/pentane (1/5) and obtained as a yellow oil (152 mg, 0.66 mmol, 83 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (m, 2H), 6.97 (m, 1H), 6.24 (s, 1H), 6.13 (d, *J* = 6.20 Hz, 1H), 6.01 (s, 1H), 3.23 (d, *J* = 6.20 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.8, 163.0, 160.5, 147.8, 134.7 (d, *J* = 6.2 Hz), 129.8 (d, *J* = 10 Hz), 126.9 (d, *J* = 14.4 Hz), 126.0 (d, *J* = 26.2 Hz), 126.0 (d, *J* = 22.4 Hz) 115.3 (d, *J* = 23.0 Hz), 67.6, 26.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ -111.24 - -111.28 (m).

HRMS (m/z): Calculated $C_{11}H_{10}ClFO_2$ $[M+H]_+$ 229.0426 found 229.0431.

Morita-Baylis-Hillman reaction in Continuous Flow using a Si-DMAP Catalyst

General continuous flow procedure A: The packed bed reactor setup was flushed with 1-butanol:CH_2Cl_2 (3:1) prior to the reaction. The aldehyde (10 mmol, 1 equiv.) and MVK (60mmol, 6 equiv.) were mixed in a measuring flask (25 mL) filed with 1-butanol:CH_2Cl_2 (3:1). Prior to sample collection the reaction was run for two times the residence times to reach steady state (se individual entries for flow rates). The

crude reaction mixture was collected for one residence time in a round-bottomed flask. Conversion was determined by quantitative ^{1}H-NMR analysis using dimethyl terephthalate as internal standard.

General continuous flow procedure B: The packed bed reactors setup were flushed with MeOH:H_2O (2:1) prior to the reaction. The aldehyde (2.4 mmol, 1 equiv.) and Acrylamide (60mmol, 6 equiv.) were mixed in a measuring flask (25 mL) filed with MeOH:H_2O (2:1). Prior to sample collection the reaction was run for two times the residence times to reach steady state (se individual entries for flow rates). The crude reaction mixture was collected for one residence time in a round-bottomed flask. 1 mL internal standard (see individual entry for concentrations) was added to the crude reaction and the yield was determined by quantitative ^{1}H-NMR analysis.

Packed Bed Reactor

Two empty HPLC columns (25 cm length, 0.46 cm ID) were fitted with a small ball of cotton in one of the ends which was compressed with a metal rod. The columns were each filled with DMAP-MS (0.98 mmol/g). Four reactor setups were used in total for this study, and in the following reactor(**letter**) refers to the specific dual-PBR setup with total silica-DMAP loading and void volume. **ReactorA**: Loading of 4.45 mmol DMAP, void volume = 4.09 mL. **ReactorB**: Loading of 4.17 mmol DMAP, void volume = 3.98 mL. **ReactorC**: Loading of 4.15 mmol DMAP, void volume = 3.69 mL. **ReactorD:** Loading of 4.19 mmol DMAP, void volume = 3.90 mL.

Extraction method A: The crude mixture was suspended in H_2O (50 mL) and poured into a separation funnel. The aqueous phase was extracted with Et_2O (30

mL). The organic phase was re-extracted with H_2O (50 mL). The aqueous phases were combined and evaporated *in vacuo*.

3-(Hydroxy(4-nitrophenyl)methyl)but-3-en-2-one (5):24 The reaction was performed using general method **A** on reactor**B** with 4-nitrobenzaldehyde (10 mmol, 0.4 M, 1 equiv.), MVK (60 mmol, 2.4 M, 6 equiv.). Flowrate = 0.068 mL·min^{-1} giving a residence time t_R = 60 min. The crude mixture was concentrated *in vacuo* and conversion was determined using dimethyl terephthalate as internal standard. The title compound was purified using flash chromatography eluting with toluene:MeOH (99.5:0.5), and was obtained as an yellow oil (0.216 mg, 0.98 mmol, 62 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 6.26 (s, 1H), 6.03 (s, 1H), 5.68 (d, *J* = 5.6 Hz, 1H), 3.33 (d, *J* = 5.7 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.2, 149.1, 149.1, 147.5, 127.9, 127.4 (2C), 123.7 (2C), 72.4, 26.5. HRMS (m/z): Calculated $C_{11}H_{12}NO_4$ $[M+H]^+$ 222.0761 found 222.0756

3-(Hydroxy(2-nitrophenyl)methyl)but-3-en-2-one (13):[25] The reaction was performed using general method **A** on reactor**A** with 2-nitrobenzaldehyde ((10 mmol, 0.4 M, 1 equiv.), MVK (60 mmol, 2.4 M, 6 equiv.). Flowrate = 0.068 mL·min^{-1} giving a residence time t_R = 60 min. The crude mixture was concentrated *in vacuo* and conversion was determined using dimethyl terephthalate as internal standard. The title compound was purified using flash chromatography eluting with CH_2Cl_2, and was obtained as a brown solid (0.170 mg, 0.77 mmol, 47 %). Mp: 72.5 °C - 75.0 °C , lit 75 °C .[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 8.2 Hz, 1H), 6.23 (d, *J* = 4.3 Hz, 1H), 6.17 (s,

1H), 5.79 (s, 1H), 3.47 (s, 1H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.0, 149.0, 141.0, 136.5, 133.7, 129.0, 128.7, 126.7, 124.8, 67.8, 26.2. HRMS (m/z): Calculated $C_{11}H_{12}NO_4$ $[M+H]^+$ 222.0761 found 222.0756.

3-((2-Chloro-6-fluorophenyl)(hydroxy)methyl)but-3-en-2-one (14): The reaction was performed using general method **A** on reactor**B** with 2-chloro-6-fluoro-benzaldehyde (10 mmol, 0.4 M, 1 equiv.), MVK (60 mmol, 2.4 M, 6 equiv.). Flowrate = 0.066 mL·min^{-1} giving a residence time t_R = 60 min. The crude mixture was concentrated *in vacuo* and conversion was determined using dimethyl terephthalate as internal standard. The title compound was purified using flash chromatography eluting with pentane:CH_2Cl_2 (1:4), and was obtained as an yellow oil (0.204 mg, 0.89 mmol, 56 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (m, 2H), 6.97 (m, 1H), 6.24 (s, 1H), 6.14 (d, *J* = 6.6 Hz, 1H), 6.01 (s, 1H), 3.21 (s, 1H), 2.37 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.8, 163.1 (d, *J* = 251.7 Hz), 147.8, 134.8 (d, *J* = 6.5 Hz), 129.9 (d, *J* = 10.1 Hz), 126.9 (d, *J* = 14.3 Hz), 126.3 (d, *J* = 2.1 Hz), 126.0 (d, *J* = 3.4 Hz), 115.3 (d, *J* = 23.2 Hz), 67.7, 26.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ -111.24 - -111.28 (m) HRMS (m/z): Calculated $C_{11}H_{11}ClFO_2$ $[M+H]^+$ 229.0426 found 229.0424.

3-((3,4-Dichlorophenyl)(hydroxy)methyl)but-3-en-2-one (15): The reaction was performed using general method **A** on reactor**A** with 3,4-dichlorobenzaldehyde (10 mmol, 0.4 M, 1 equiv.), MVK (60 mmol, 2.4 M, 6 equiv.). Flowrate = 0.068 mL·min^{-1} giving a residence time t_R = 60 min. The crude mixture was concentrated *in vacuo* and conversion was determined using dimethyl terephthalate as internal standard. The title compound was purified using flash chromatography eluting with pentane:CH_2Cl_2 (1:4), and was obtained as an yellow oil (0.235 mg, 0.96 mmol, 59

%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 6.22 (s, 1H), 6.01 (s, 1H), 5.53 (d, *J* = 5.4 Hz, 1H), 3.30 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.2, 149.2, 142.1, 132.6, 131.7, 130.4, 128.6, 127.5, 126.0, 71.9, 26.5. HRMS (m/z): Calculated $C_{11}H_{11}Cl_2O_2$ $[M+H]^+$ 266.9950 found 266.9947.

Methyl 4-(1-hydroxy-2-methylene-3-oxobutyl)benzoate (16): The crude mixture was obtained using general method **A** on reactor**C** with methyl 4-formylbenzoate (10 mmol, 0.4 M, 1 equiv.), MVK (60 mmol, 2.4 M, 6 equiv.). Flowrate = 0.061 mL·min^{-1} giving a residence time t_R = 60 min. The crude mixture was concentrated *in vacuo* and conversion was determined using dimethyl terephthalate as internal standard. The title compound was purified using flash chromatography eluting with pentane:EtOAc (6:1), and was obtained as a colorless oil (0.114 mg, 0.49 mmol, 33 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 6.22 (s, 1H), 5.96 (s, 1H), 5.66 (d, *J* = 5.6 Hz, 1H), 3.91(s, 3H), 3.23 (d, *J* = 5.6 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.4, 167.0, 149.6, 146.7, 129.9, 129.6, 127.5, 126.6, 72.8, 52.3, 26.6. HRMS (m/z): Calculated $C_{13}H_{15}O_4$ $[M+H]^+$ 235.0965 found 235.0962.

4-(1-Hydroxy-2-methylene-3-oxobutyl)benzonitrile (17):[26] The reaction was performed using general method **A** on reactor**C** with 4-cyanobenzaldehyde (7.5 mmol, 0.3 M, 1 equiv.), MVK (45 mmol, 1.8 M, 6 equiv.). Flowrate = 0.123 mL·min^{-1} giving a residence time t_R = 30 min. The crude mixture was concentrated *in vacuo* and conversion was determined using dimethyl terephthalate as internal standard. The title compound was purified using flash chromatography eluting with CH_2Cl_2,

and was obtained as a light red oil (0.182 mg, 0.71 mmol, 64 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 6.25 (s, 1H), 6.01 (s, 1H), 5.63 (d, *J* = 5.6,1H), 3.24 (d, *J* = 5.7, 1H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.2, 149.2, 147.1, 132.4 (2C), 127.8, 127.3 (2C), 118.9, 111.6, 72.6, 26.5. HRMS (m/z): Calculated $C_{12}H_{12}NO_2$ $[M+H]^+$ 202.0863 found 202.0860.

3-(Hydroxy(pyridin-2-yl)methyl)but-3-en-2-one (18):[27] The reaction was performed using general method **A** on reactor**B** with 2-pyridinecarboxaldehyde (10 mmol, 0.4 M, 1 equiv.), MVK (60 mmol, 2.4 M, 6 equiv.). Flowrate = 0.123 mL·min^{-1} giving a residence time t_R = 30 min. The crude mixture was concentrated *in vacuo* and conversion was determined using dimethyl terephthalate as internal standard. The title product was purified by extraction method A, and was obtained as an yellow oil (0.235 mg, 1.33 mmol, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, *J* = 4.0 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 5 Hz, 1H), 6.21 (s, 1H), 6.15 (s, 1H), 5.70 (s, 1H), 4.78 (s, 1H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.9, 160.0, 149.9, 148.3, 137.0, 127.2, 122.7, 121.6, 71.3, 26.6. HRMS (m/z): Calculated $C_{10}H_{12}NO_2$ $[M+H]^+$ 178.0863 found 178.0863.

3-(Hydroxy(pyridin-3-yl)methyl)but-3-en-2-one (19):24 The reaction was performed using general method **A** on reactor**A** with 3-pyridinecarboxaldehyde (10 mmol, 0.4 M, 1 equiv.), MVK (60 mmol, 2.4 M, 6 equiv.). Flowrate = 0.068 mL·min^{-1} giving a residence time t_R = 60 min. The crude mixture was concentrated *in vacuo* and conversion was determined using dimethyl terephthalate as internal standard. The title product was purified by extraction method **A**, and was obtained as an yellow solid (0.161 mg, 0.91 mmol, 57 %). Mp: 69.0 °C - 71.1 °C , lit: 85 °C .[24] ^{1}H

NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.52 (d, *J* = 5.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 5.0 Hz, 1H), 6.25 (s, 1H), 6.03 (s, 1H), 5.64 (s, 1H), 3.26 (d, 1H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.2, 149.4, 149.2, 148.5, 137.2, 134.4, 127.4, 123.5, 71.2, 26.5. HRMS (m/z): Calculated $C_{10}H_{12}NO_2$ $[M+H]^+$ 178.0863 found 178.0867.

3-(Hydroxy(pyridin-4-yl)methyl)but-3-en-2-one (20):[28] The reaction was performed using general method **B** on reactor**A** with 4-pyridinecarboxaldehyde (10 mmol, 0.4 M, 1 equiv.), MVK (60 mmol, 2.4 M, 6 equiv.). Flowrate = 0.133 mL·min^{-1} giving a residence time t_R = 30 min. The crude mixture was concentrated *in vacuo* and conversion was determined using dimethyl terephthalate as internal standard. The title product was purified by extraction method **A**, and was obtained as a red solid. (0.268 mg, 1.51 mmol, 95 %). Mp: 93.1 °C - 97.1 °C , lit 103 °C .[26] ^1H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, *J* = 6.0 Hz, 2H), 7.30 (d, *J* = 6.0 Hz, 2H,), 6.25 (s, 1H), 6.02 (s, 1H), 5.56 (s, 1H), 2.36 (s, 3H), 1.25 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.3 150.8, 150.0 (2C), 149.0, 127.9, 121.4 (2C), 72.1, 26.5. HRMS (m/z): Calculated $C_{10}H_{12}NO_2$ $[M+H]^+$ 178.0863 found 178.0864.

Ethyl 2-hydroxy-3-methylene-4-oxopentanoate (21):[29] The crude mixture was obtained using general method **A** on reactor**D** with ethyl glyoxalate ((10 mmol, 0.4 M, 1 equiv.), MVK (60 mmol, 2.4 M, 6 equiv.). Flowrate = 0.065 mL·min^{-1} giving a residence time t_R = 60 min. The crude mixture was concentrated *in vacuo* and conversion was determined using dimethyl terephthalate as internal standard. The title compound was purified using flash chromatography eluting with pentane:EtOAc (2:1), and was obtained as a colorless oil (0.1951 mg, 1.13 mmol, 73

%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.21 (s, 1H), 6.12 (s, 1H), 4.82 (d, *J* = 6.10 ,1H), 4.22 (q, *J* = 7.2, 2H), 3.44 (d, *J* = 6.30 ,1H), 2.36 (s, 3H), 1.24 (t, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.5, 172.6, 146.2, 128.8, 71.1, 62.2, 26.1, 14.2. HRMS (m/z): Calculated $C_8H_{12}O_4$ $[M+H]^+$ 173.0808 found 173.0807.

2-((2-Chloro-6-fluorophenyl)(hydroxy)methyl)acrylamide (22): The crude mixture was obtained using general method **B** on reactor**B** with 2-chloro-6-fluorobenzaldehyde (10 mmol, 0.4 M, 1 equiv.), acrylamide (60 mmol, 2.4 M, 6 equiv.). Flowrate = 0.066 mL·min^{-1} giving a residence time t_R = 60 min. The crude mixture was concentrated *in vacuo* and conversion was determined using dimethyl terephthalate as internal standard. The title compound was purified using flash chromatography eluting with pentane:Et_2O (1:2), and was obtained as a white solid (0.097 mg, 0.42 mmol, 27 %). Mp: 79.0 °C - 81.5 °C. ^{1}H NMR (400 MHz, D_2O): δ 7.44-7.39 (m, 1H), 7.36-7.34 (m, 1H), 7.22-7.18 (m, 1H), 6.97 (s, 1H), 6.37-6.21(m, 3H), 5.84 (d, 2H). ^{13}C NMR (101 MHz, DMSO): δ 166.4, 163.8, 162.41 (d, *J* = 251.7 Hz), 132.6 (d, *J* = 7.2 Hz), 132.0 (d, *J* = 67.9 Hz), 130.5 (d, *J* = 9.9 Hz), 127.3 (d, *J* = 15.7 Hz), 126.3 (d, *J* = 77.9 Hz), 115.6 (d, *J* = 22.1 Hz), 70.3. ^{19}F NMR (376 MHz, D_2O) δ -113.99 - -114.04 (m) HRMS (m/z): Calculated $C_{10}H_9ClFNNaO_2$ $[M+Na]^+$ 252.0198 found 252.0202.

4-(1-Hydroxy-2-methylene-3-oxobutyl)benzaldehyde (25): The reaction was performed using general method **A** on reactor**C** with terephthalaldehyde (10 mmol, 0.4 M, 1 equiv.), MVK (60 mmol, 2.4 M, 6 equiv.). Flowrate = 0.369 mL·min^{-1} giving a residence time t_R = 10 min. The crude mixture was concentrated *in vacuo* and conversion was determined using dimethyl terephthalate as internal standard. The

title compound was purified using flash chromatography eluting with pentane:EtOAc (6:1), and was obtained as a colorless oil (0.214 mg, 1.05 mmol, 71 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 6.24 (s, 1H), 6.01 (s, 1H), 5.67 (d, *J* = 5.6 Hz, 1H), 3.32 (d, *J* = 5.6 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.3, 192.0, 149.4, 148.6, 135.9, 130.0 (2C), 127.6, 127.2 (2C), 72.8, 26.5. HRMS (m/z): Calculated $C_{12}H_{13}O_3$ $[M+H]^+$ 205.0859 found 205.0852.

In same instance following sideproduct was isolated:

4-Butoxybutan-2-one:[30] The title compound was purified using flash chromatography eluting with pentane:EtOAc (3:1), and was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 3.67 (t, *J* = 6.3 Hz, 1H), 3.42 (t, *J* = 6.6 Hz, 1H), 2.67 (t, *J* = 6.3 Hz, 1H), 2.18 (s, 3H), 1.53 (pent, *J* = 8.0 Hz, 2H), 1.35 (sekt, *J* = 7.6 Hz, 1H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): 207.7, 71.2, 65.9, 44.0, 31.8, 30.7, 19.5, 14.1. HRMS (m/z): Calculated $C_8H_{17}O_2$ $[M+H]^+$ 145.1223 found 145.1222.

Scale-out Experiment

3-(Hydroxy(pyridin-4-yl)methyl)but-3-en-2-one (20):28 The crude mixture was obtained from the scale-out experiment on reactor**D** with 4-pyridinecarboxaldehyde (70 mmol, 0.4 M, 1 equiv.) and Methyl vinyl ketone (420 mmol, 2.4 M, 6 equiv.). Flowrate = 0.133 mL·min^{-1} giving a residence time t_R = 30 min for 20.5 h. conversion was determined using dimethyl terephthalate as internal standard. The crude mixture was concentrated *in vacuo* and purified by dissolving the crude mixture in Et_2O (200 mL) and toluene (50 mL) the organic phase was washed with H_2O (300 mL) followed by five washes with H_2O (100 mL each). The aqueous phase was

combined and concentrated *in vacuo*. The obtained mixture was re-suspended in Et_2O (60 mL) then extracted with H_2O (100 mL). The organic phase was extracted with H_2O (100 mL) and the aqueous phases were combined and concentrated *in vacuo*. The title compound was obtained as a red solid (10.53 g, 59 mmol, 93 %). Mp: 83.2 °C - 86.1 °C , lit 103 °C .[26] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, *J* = 6.0 Hz, 2H), 7.30 (d, *J* = 6.0 Hz, 2H), 6.25 (s, 1H), 6.04 (s, 1H), 5.57 (s, 1H), 3.48 (s, 1H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.2, 151.0, 149.8 (2C), 149.0, 127.8, 121.5 (2C), 71.9, 26.5. HRMS (m/z): Calculated $C_{10}H_{12}NO_2$ $[M+H]^+$ 178.0863 found 178.0866.

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Supporting Information

^{1}H NMR, ^{19}F-NMR, ^{31}P NMR and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[19] A setup of two PBR´s was chosen to compensate for the lowered DMAP loading on silica (0.53 mmol/gram) when compared to polyDMAP (6 mmol/gram).

[20] The addition of CH_2Cl_2 had a negative impact on the conversion of the MBH reaction of **1** with **MVK**. See Supporting Information

[21] See supporting information for spicific reaction details for each entry.

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