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Translating the Enantioselective Michael Reaction to a Continuous Flow Paradigm with an Immobilized, Fluorinated Organocatalyst

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ABSTRACT: A novel polymer-supported fluorinated organocatalyst has been prepared and benchmarked in the enantioselective Michael addition of aldehydes to nitroalkenes. The system has proven to be highly efficient and displays excellent selectivities (er and dr) with a wide variety of substrates. Detailed deactivation studies have given valuable insights thus allowing the lifespan of this immobilized aminocatalyst to be significantly extended. These data have facilitated the implementation of enantioselective, continuous flow processes allowing either the multigram synthesis of a single Michael adduct over a 13 h period, or the sequential generation

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3 of a library of enantiopure Michael adducts from different combinations of substrates (13
4 examples, 16 runs, 18.5 h total operation). A customized in-line aqueous work-up, followed by
5 liquid-liquid separation in flow, allows for product isolation without the need of chromatography
6 or other separation techniques.
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14 **KEYWORDS:** fluorinated organocatalyst • continuous flow • polystyrene-supported catalysts •
15 enantioselective catalysis • Michael reaction
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19 20 1. INTRODUCTION 21

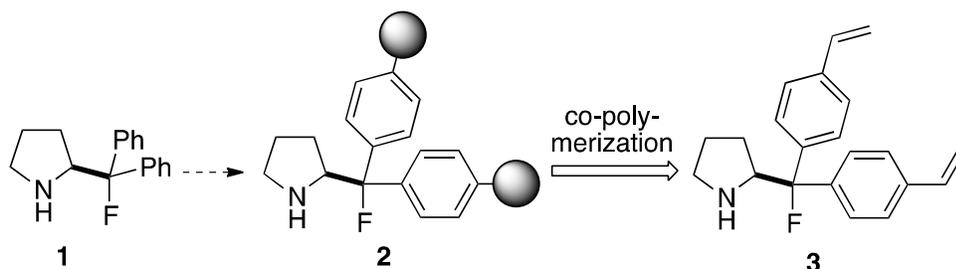
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23 Sustainability concerns have resulted in a change of paradigm where not only cost reduction,
24 but also waste minimization and catalyst recovery are crucial issues in process design. In this
25 context, continuous flow chemistry is one of the technologies expected to facilitate process
26 intensification, reducing the footprint of chemical plants whilst increasing their productivity,
27 modularity and flexibility.¹ Despite the potential of immobilized catalysts for enantioselective
28 flow processes, the fine chemical industry still shows some reluctance to apply these techniques
29 due to the often limited lifespan of the reference homogeneous species. Designing more stable
30 homogeneous catalysts and successfully translating their corresponding batch processes to an
31 immobilized platform is therefore essential to further validate the potential of this approach.
32 Consequently, the preparation of supported catalysts with high activity and improved stability
33 holds great potential for both the industrial and academic chemical communities.
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50 Since the pioneering reports by List, Lerner, Barbas² and MacMillan³ laid the foundations of
51 modern organocatalysis, efforts to develop effective metal-free small molecule catalysts have
52 intensified.⁴ One of the most successful organocatalysts is the diarylprolinol trimethylsilyl ether,
53 commonly known as the Jørgensen-Hayashi catalyst.⁵ Given the versatility of this species,
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3 which is able to exploit both the enamine and iminium ion activation mode, several groups have
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5 tried to harness its potential by developing immobilized analogues.⁶ With the aim of enhancing
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7 the sustainability profile of this catalyst, this laboratory has reported the preparation of a set of
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9 solid-supported derivatives⁷ whose robustness was established through recycling and
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11 implementation of enantioselective continuous flow processes.⁸ These studies revealed that the
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13 reusability of the catalyst was often compromised by the lability of the trimethylsilyl ether; this
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15 has also been investigated spectroscopically in the homogeneous paradigm.⁹ Several approaches
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17 have been employed to address this issue. First, it was demonstrated that re-silylation is indeed
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19 possible,^{7a} although this has obvious drawbacks from an operational point of view and it
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21 precludes continuous flow applications. The analogous methyl ether¹⁰ (rather than silyl) was also
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23 prepared, but the polymer-supported version proved to be less active and selective than the
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25 parent system.^{7b} Whilst catalysts with bulkier silyl ethers display increased stability,^{7d,e}
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27 significant structural changes can compromise reactivity and they tend to deactivate over time.
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29 With these data in hand, efforts to immobilize the fluorinated compound **1**,¹¹ were initiated; this
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31 system was introduced in asymmetric organocatalysis by Gilmour *et al.* in 2009.¹² The
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33 pyrrolidine derivative, designed to validate the *gauche*-effect hypothesis for molecular pre-
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35 organization,¹³ has proven to be highly effective in the enantioselective epoxidations,^{12a,14} and
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37 aziridinations¹⁵ of enals with great success, outperforming the Jørgensen-Hayashi catalyst in
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39 some cases.¹⁶ Moreover, the low steric demand of the fluorine substituent, coupled with the
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41 reactively inert C-F bond, ensures that any concerns regarding stability of this site are mitigated.
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52 It was therefore envisaged that compound **2**, a polymer-supported analog of **1**, would display
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54 increased robustness when compared to the structurally related silyl ethers. In addition, since the
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56 active site of **1** (the pyrrolidine moiety) is not involved in the polymerization of **3** and the
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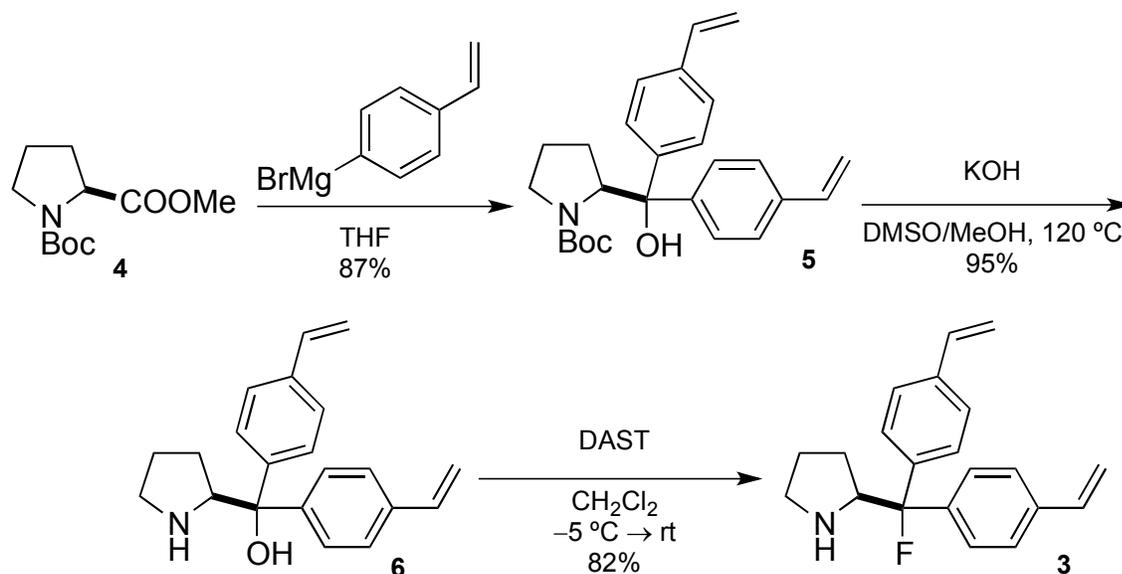
pyrrolidine moiety can freely rotate in polymer **2**, we anticipated that the performance of **1** would be preserved in the polymer. To test the validity of this hypothesis, compound **2** was prepared by co-polymerization of the divinylated derivative **3** with styrene (Scheme 1).



Scheme 1. Strategy for the preparation of a polymer-supported analog of **1**.

2. RESULTS AND DISCUSSION

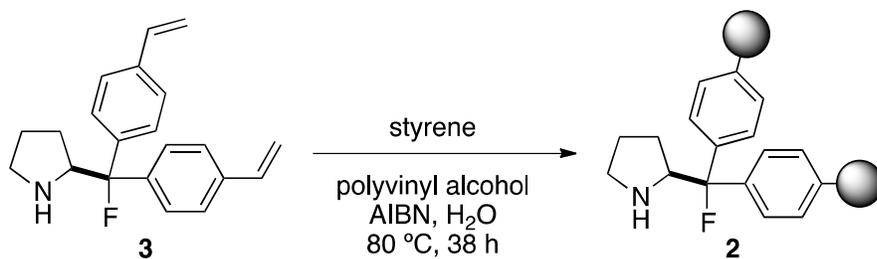
The synthesis of the target catalyst (Scheme 2) started with the addition of 4-vinylphenyl magnesium bromide (prepared *in situ*) to the proline derivative **4**,¹⁷ which furnished **5** in 87% yield.¹⁸ The Boc group was then cleaved in basic media, presumably via the corresponding oxazolidinone, to generate amino alcohol **6**.¹⁹ Deoxyfluorination of this amino alcohol, achieved by treatment with diethylaminosulfur trifluoride²⁰ (DAST), provided **3** in a concise three-step sequence and 68% overall yield. Immediate fluorination of compound **6** was essential to avoid spontaneous self-polymerization.



Scheme 2. Preparation of the monomer **3**.

Polymer **2** was obtained by suspension polymerization of the chiral monomer **3** with styrene in water, following a modification of the procedure reported by Itsuno for the related amino alcohol²¹ (Scheme 3). Since the monomeric species has two vinyl units, a cross-linking agent (e.g. DVB) was not required. Up to 65% of the functional monomer was incorporated to the polymer, giving rise to resin batches with functionalization levels ranging between 0.80-1.15 mmol g⁻¹. This polymer was characterized by IR, elemental analysis and SEM (see Supporting Information for details). Moreover, it was possible to confirm the presence of the fluorine substituent at the surface of the catalyst by EDX analysis

To characterize the behavior of this polymer further, the swelling ability with different solvents was determined in CH₂Cl₂, toluene and water. As expected for a polystyrene derivative, greater swelling was observed in CH₂Cl₂ than in water, whereas toluene led to an average result (see Supporting Information for details).

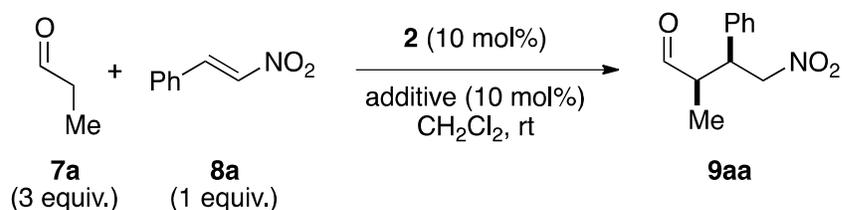


14 **Scheme 3.** Preparation of resin **2** by co-polymerization of **3**.

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18 To evaluate the catalytic activity and recyclability of this system, the well-established catalytic
19 addition of aldehydes to nitroalkenes²² was selected as the benchmark reaction for this study. It is
20 worth mentioning that there are no reports of **1** acting as a catalyst for this reaction. Indeed, this
21 study constitutes the first report of its application in the enamine activation mode.
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28 As a model substrate set, propanal and (*E*)- β -nitrostyrene were selected. An initial screening of
29 the addition reaction catalyzed by **2** is summarized in Tables 1 and 2. Gratifyingly, the reaction
30 in CH₂Cl₂ without any additives was complete within 11 h and gave excellent stereoselectivities
31 in CH₂Cl₂ without any additives was complete within 11 h and gave excellent stereoselectivities
32 (entry 1). Consistent with literature reports on the homogeneous reaction, the addition of organic
33 acids increased the reaction rate,²³ while maintaining the high levels of enantioselectivity (entries
34 2-8). As illustrated in Table 1, relatively strong acids such as TFA proved detrimental (entry 2),
35 whilst several carboxylic acids were tested with good results. Finally, it was observed that 4-
36 nitrophenol (the weakest of the acids examined) as an additive^{23,23a,d} provided the desired product
37 with excellent levels of enantioselectivity (95% *ee*) within 1.5 h. Good levels of diastereocontrol
38 (up to 96:4 *syn/anti*) were observed throughout this optimization process.
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53 **Table 1.** Effect of additives for the addition of propanal to β -nitrostyrene.^a

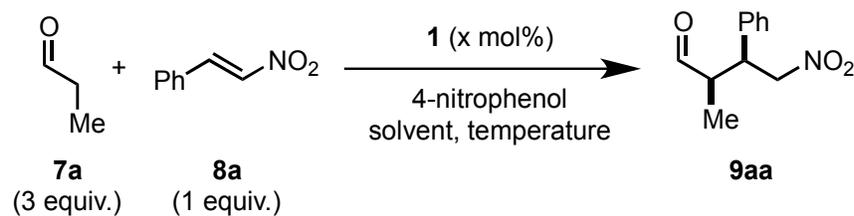


entry	additive	pK _a in H ₂ O ^b	t [h]	Conv. ^c (yield ^d)	dr ^c	ee ^e [%]
1	–	–	11	100 (99)	96:4	94
2	CF ₃ COOH	0.52	5	14 (n.d.)	67:33	–
3	2-FC ₆ H ₄ COOH	3.27	3.5	100 (97)	93:7	95
4	(<i>R</i>)-mandelic acid	3.37	5	81 (n.d.)	85:15	94
5	(<i>S</i>)-mandelic acid	3.37	5	81 (n.d.)	83:17	94
6	PhCOOH	4.20	3.5	100 (98)	95:5	94
7	CH ₃ CH ₂ COOH	4.887	4	98 (n.d.)	96:4	94
8	4-nitrophenol	7.15	1.5	100 (99)	95:5	95

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^aGeneral conditions: (*E*)-β-nitrostyrene (22.4 mg, 0.15 mmol), propanal (33 μL, 0.45 mmol), catalyst **2** (10 mol%), additive (10 mol%) in 300 μL of CH₂Cl₂ at room temperature. ^bpK_a values taken from literature sources.²⁴ ^cConversion (%) and diastereomeric ratio (dr) determined by ¹H NMR spectroscopy of the crude reaction mixture. ^dIsolated yield. ^eDetermined by chiral HPLC analysis using a Chiralpak IC column.

The organocatalytic Michael addition reaction was then optimized in batch mode using catalyst **1** to provide a data set for comparison with the immobilized system (Table 2). The initial reaction in CH₂Cl₂ reached completion in only 1 h furnishing the desired product **9aa** in quantitative yield and with excellent levels of both diastereo- and enantioselectivity (dr 97:3 *syn/anti* and *ee* 97%. Table 2, entry 1). Indeed, the selectivity of the transformation was essentially unaffected by changes in reaction medium (entries 4-7), and temperature variations (entries 2 and 3).

Table 2. The organocatalytic Michael addition in batch mode.^a

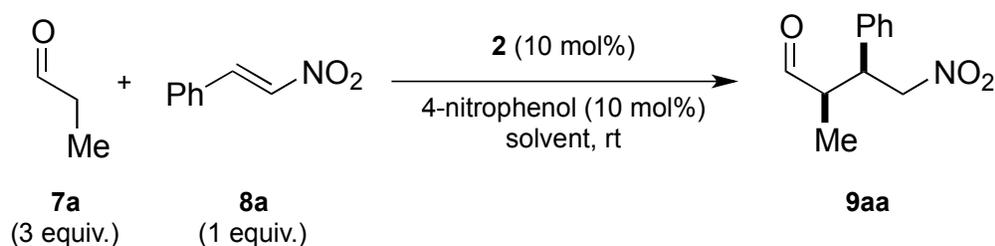
entry	catalyst/ additive (mol%)	solvent	t [h]	conv. ^b (yield ^c) [%]	dr ^b	ee ^d [%]
1	10	CH ₂ Cl ₂	1	>99 (99)	96:4	95
2	10	CH ₂ Cl ₂ ^e	3	>99 (98)	97:3	95
3	10	CH ₂ Cl ₂ ^f	0.5	>99 (97)	84:16	97
4	10	CH ₂ Cl ₂ (dry) ^g	1	>99 (98)	96:4	96
5	10	Toluene	2.5	>99 (95)	95:5	95
6	10	EtOAc	16	>99 (97)	94:6	92
7	10	THF	24	93(86)	94:6	90
8	5	CH ₂ Cl ₂	1.5	>99 (98)	96:4	95
9	5	Toluene	8	>99 (95)	96:4	95

^aGeneral conditions: (*E*)-β-nitrostyrene (22.4 mg, 0.15 mmol), propanal (33 μl, 0.45 mmol), catalyst **1** and 4-nitrophenol in 300 μl of solvent at room temperature. ^bConversion (%) and diastereomeric ratio (dr) determined by ¹H NMR spectroscopy of the crude reaction mixture. ^cIsolated yield (%). ^dDetermined by chiral HPLC analysis. ^eReaction temperature: 0 °C. ^fReaction temperature: 40 °C. ^gDry solvent, stored over 4 Å molecular sieves.

Next, the influence of reaction medium on the organocatalytic Michael reaction with resin **2** was examined using several solvents whilst retaining 4-nitrophenol as an additive. In all cases, excellent diastereo- and enantioselectivities were recorded (up to 95:5 and 96%, respectively; see Table 3). Of the organic solvents investigated, CH₂Cl₂ proved to be beneficial in terms of reaction rate, leading to full conversions in less than 1.5 h (Table 3, entry 1). Use of toluene also

led to efficient reactions (5 h, entry 2), whereas EtOAc and THF resulted in more sluggish processes (entries 3 and 4). To our delight, the reaction worked well in water (entry 5), affording the desired compound in only 1.5 h and with enantioselectivities that were comparable to those in CH₂Cl₂, irrespective of the low swelling ability of **2** in this solvent. Finally, lowering the catalyst loading to only 5 mol% was well tolerated, and the reaction reached completion in 5 h (entry 6).

Table 3. Examining the effect of solvent on the addition of propanal to β-nitrostyrene in the presence of 4-nitrophenol and catalyst **2**.^a

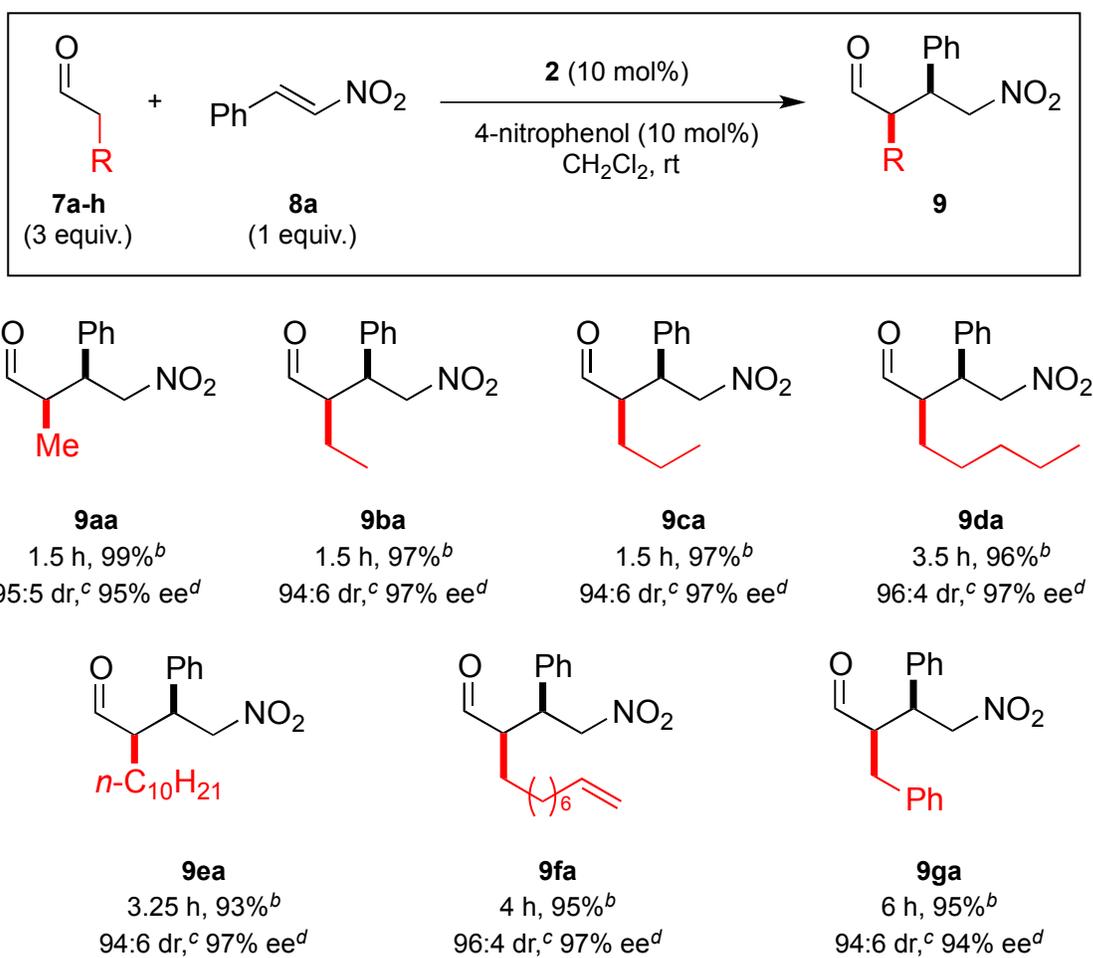


entry	solvent	t [h]	Conv. ^b (yield ^c)	dr ^b	ee ^d [%]
1	CH ₂ Cl ₂	1.5	100 (99)	95:5	95
2	Toluene	5	100 (98)	95:5	96
3	EtOAc	16	99 (n.d.)	95:5	93
4	THF	16	65 (n.d.)	93:7	92
5	H ₂ O	1.5	100 (99)	95:5	95
6	CH ₂ Cl ₂ ^e	5	100 (98)	95:5	95

^aGeneral conditions: (*E*)-β-nitrostyrene (22.4 mg, 0.15 mmol), propanal (33 μL, 0.45 mmol), catalyst **2** (10 mol%), 4-nitrophenol (10 mol%) in 300 μL of solvent at room temperature.

^bConversion (%) and diastereomeric ratio (dr) determined by ¹H NMR spectroscopy of the crude reaction mixture. ^cIsolated yield. ^dDetermined by chiral HPLC analysis using a Chiralpak IC column. ^e5 mol% of catalyst **2** and 5 mol% of 4-nitrophenol were used.

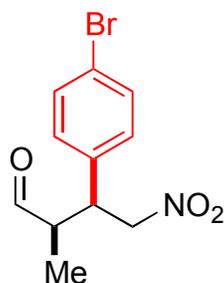
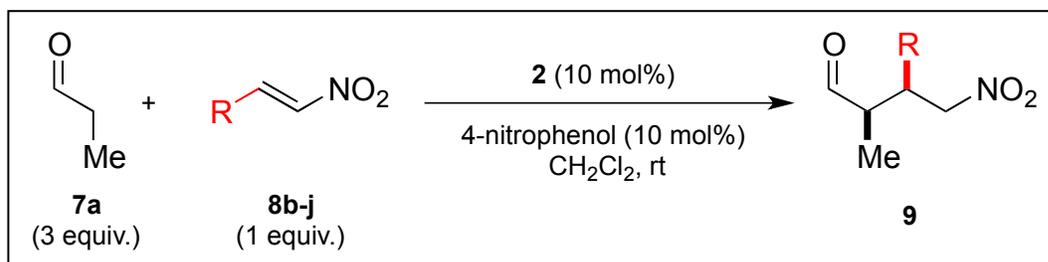
An important conclusion of these studies is that immobilization of **1** (in polymer **2**) does not lead to any decrease in catalytic performance under the optimized set of reaction conditions. This being secured, the scope of the reaction was next studied. Initially, variation of the donor quickly revealed that a wide variety of aldehydes reacted smoothly with β -nitrostyrene (Scheme 4). This result sharply contrasts with a similar catalytic resin previously prepared in our group,^{77a} which was extremely selective in the case of propanal.²⁵ Using catalyst **2**, linear aldehydes bearing longer alkyl chains gave rise to the corresponding Michael adducts in short reaction times with excellent enantioselectivities (**9aa-9fa**). In the case of 3-phenylpropionaldehyde, longer reaction times were required to drive the reaction to completion (**9ga**).



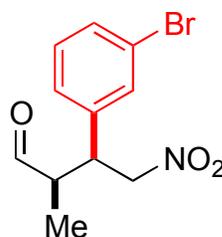
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3 **Scheme 4.** Scope of the aldehyde reaction partner.^a
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7 ^aGeneral conditions: (*E*)- β -nitrostyrene (22.4 mg, 0.15 mmol), aldehyde (0.45 mmol), catalyst
8 **2** (10 mol%), 4-nitrophenol (10 mol%) in 300 μ L of CH₂Cl₂ at room temperature. ^bIsolated yield
9 (%). ^cDiastereomeric ratio (dr) determined by ¹H NMR spectroscopy of the crude reaction
10 mixture. ^dDetermined by chiral HPLC analysis.
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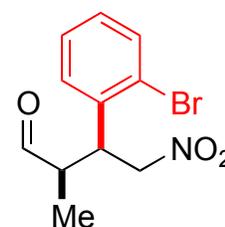
12 Variation of the nitroalkene partner was then investigated (Scheme 5). It was generally noted
13 that using aromatic nitro olefins (**9ab-9ag**) led to short reaction times, regardless of the nature of
14 the substituents (< 2.5 h). Nitroalkenes with heterocyclic aromatic groups, such as the 2-furyl or
15 2-thienyl systems proved to be excellent Michael acceptors for this reaction, providing the
16 desired compounds in 1 h (**9ah-9ai**). Employing nitro olefins with an aliphatic side chain (adduct
17 **9aj**) led to longer reaction times (5.5 h), and whilst the dr slightly decreased, high
18 enantioselectivities were recorded (97%). The characteristically high yields obtained throughout
19 (95-99%) are due to the simplified isolation procedure, made possible by the immobilization of
20 the catalyst: filtration, washing with 0.1 M NaOH to remove the additive and evaporation
21 rendered the pure products. Michael adduct **9ag** is the sole exception to this, where the phenol-
22 containing product had to be further purified by flash chromatography on silica gel.
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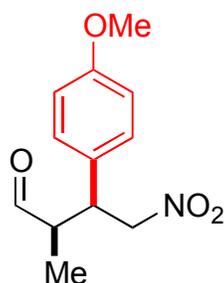
1.25 h, 98%^b
97:3 dr,^c 96% ee^d



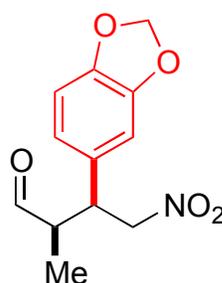
1.5 h, 98%^b
96:4 dr,^c 94% ee^d



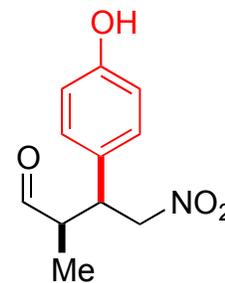
1.5 h, 98%^b
94:6 dr,^c 94% ee^d



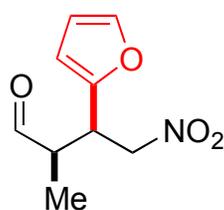
2.25 h, >99%^b
95:5 dr,^c 95% ee^d



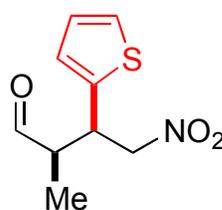
2.25 h, >99%^b
95:5 dr,^c 95% ee^d



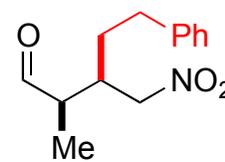
1 h, 97%^b
93:7 dr,^c 96% ee^d



1 h, 95%^b
93:7 dr,^c 95% ee^d



1 h, >99%^b
94:6 dr,^c 93% ee^d



5.5 h, 97%^b
85:15 dr,^c 97% ee^d

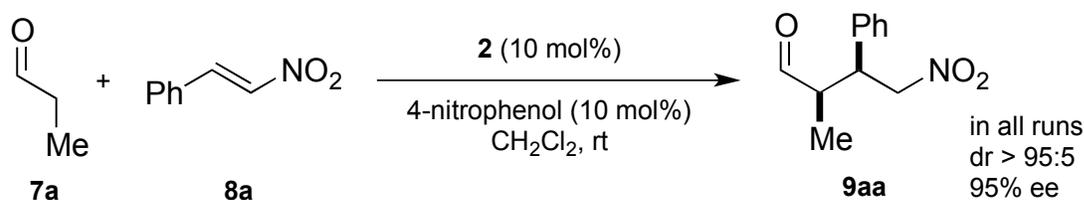
Scheme 5. Scope of the nitroalkene.^a

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3 ^aGeneral conditions: nitroalkene (0.15 mmol), propanal (33 μ L, 0.45 mmol), catalyst **2** (10
4 mol%), 4-nitrophenol (10 mol%) in 300 μ L of CH₂Cl₂ at room temperature. ^bIsolated yield (%).
5 ^cDiastereomeric ratio (dr) determined by ¹H NMR spectroscopy of the crude reaction mixture.
6 ^dDetermined by chiral HPLC analysis (GC for **9ag**).
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12 To further establish the scope and limitations of the present methodology, catalytic reactions of
13 more challenging substrates mediated by **2** were also examined (Scheme 6). To this end, we
14 started with the β -branched donor isovaleraldehyde. Although the reaction proved to be sluggish,
15 full conversions resulting in the formation of **9ha** were observed after 20 h using the standard
16 conditions (10 mol% **2**, 10 mol% 4-nitrophenol). Whereas doubling the amount of additive had a
17 remarkable effect on the reaction rate, the optimal results were obtained with 20 mol% catalyst
18 loading in the presence of 20 mol% benzoic acid. Isovaleraldehyde was also found to react
19 smoothly with both 2-bromo- and 4-bromonitrostyrene. After fine-tuning the reaction conditions,
20 the desired products **9hb** and **9hc** were obtained in quantitative yield after simple extraction with
21 0.1 M NaOH or saturated NaHCO₃ without additional purification. As for α -branched aldehydes,
22 it was found that isobutyraldehyde can be employed as the Michael donor with nitrostyrene and
23 4-bromonitrostyrene, giving rise to products **9ia** and **9ib**, respectively, which bear quaternary
24 centers. Despite the severe steric hindrance of the corresponding trisubstituted enamine, full
25 conversions were achieved after 28 h using 30 mol% catalyst and 60 mol% of 4-nitrophenol.
26 Extraction with 0.1 M NaOH gave the Michael adducts in good yields, but with moderate
27 enantioselectivities (66 and 72% ee, respectively). Unfortunately, trisubstituted nitroalkenes such
28 as α -methylnitrostyrene or β -ethoxycarbonylnitrostyrene proved unreactive, even after 42 h with
29 20 mol% catalyst and 4-nitrophenol.
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last cycles. Despite this, even in the eighth run the desired Michael adduct could be obtained in 68% isolated yield after 24 h. Importantly, the stereoselectivity remained constant throughout the whole process.

Table 4. Recycling experiments.^a



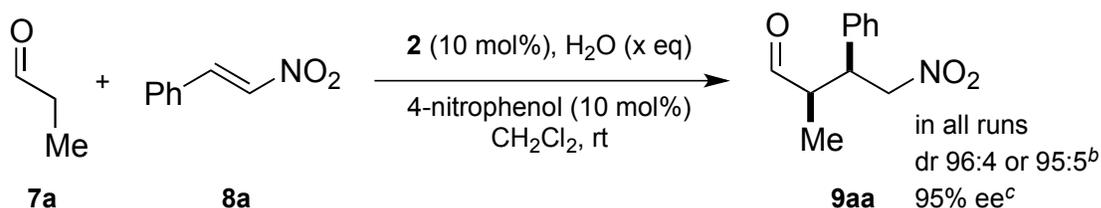
run	t [h]	Conv ^b [%]	Yield ^c [%]
1	1.5	100	99
2	2	100	98
3	2.5	100	97
4	4	100	98
5	6	100	97
6	12	84	83
7	24	100	97
8	24	70	68

^aGeneral conditions: (*E*)-β-nitrostyrene (41.0 mg, 0.275 mmol), propanal (60 μL, 0.83 mmol), catalyst **2** (10 mol%), additive (10 mol%) in 550 μL of CH₂Cl₂ at room temperature. ^bConversion (%) and diastereomeric ratio (dr) determined by ¹H NMR spectroscopy of the crude reaction mixture. ^cIsolated yield (%).

As outlined in the introduction, the major contributing factor to the deactivation of the Jørgensen-Hayashi catalyst (i.e. desilylation) is no longer a risk owing to the installation of the C-F unit. Consequently the slow decay observed in reaction efficiency can be attributed to several factors, including mechanical degradation of the polymer or irreversible oxidation of

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3 reaction intermediates as demonstrated by Zlotin *et al.*²⁶ Based on these precedents, a series of
4 recycling experiments were carried out under glovebox conditions to study the effect of oxygen
5 exclusion on catalyst stability. It was quickly noted that, after only a few reaction cycles in the
6 glovebox, the catalytic activity decreased. However, performing another run with the same
7 immobilized catalyst outside the glovebox immediately led to improved performance. This
8 suggests that the absence of water results in sluggish reactions. Three additional recycling
9 experiments were carried out to gain further insight into the factors responsible for catalyst
10 deactivation: performing the reaction under a nitrogen atmosphere (oxygen exclusion with 0.5
11 and 2.0 equivalents of water) and under air with 2.0 equivalents of water; in these experiments,
12 dry CH₂Cl₂ was used. The results indicate that trace amounts of water are beneficial for catalyst
13 turnover, whereas oxygen is detrimental (Table 5).
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30 **Table 5.** Recycling experiments in the presence of water.^a



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run	t [h]	Conv. ^b [%] (under N ₂ , 0.5 equiv. H ₂ O)	Conv. ^b [%] (under N ₂ , 2.0 equiv. H ₂ O)	Conv. ^b [%] (under air, 2.0 equiv. H ₂ O)
1	1.5	100	100	93
2	2	94	96	89
3	2	79	81	80

53 ^aGeneral procedure: (*E*)-β-nitrostyrene (41.0 mg, 0.275 mmol),
54 propanal (60 μL, 0.83 mmol), catalyst **2** (10 mol%), additive (10
55 mol%) in 550 μL of CH₂Cl₂ at room temperature. ^bConversion (%) and
56 diastereomeric ratio (dr) determined by ¹H NMR spectroscopy of the
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crude reaction mixture. ⁶Determined by chiral HPLC analysis.

These conditions that have allowed catalytic activity to be retained for longer periods of time were then translated into a continuous flow process.²⁷ An overview of the set-up used, where 500 mg of resin **2** were packed in a glass column (1 cm diameter), is shown in Figure 1.

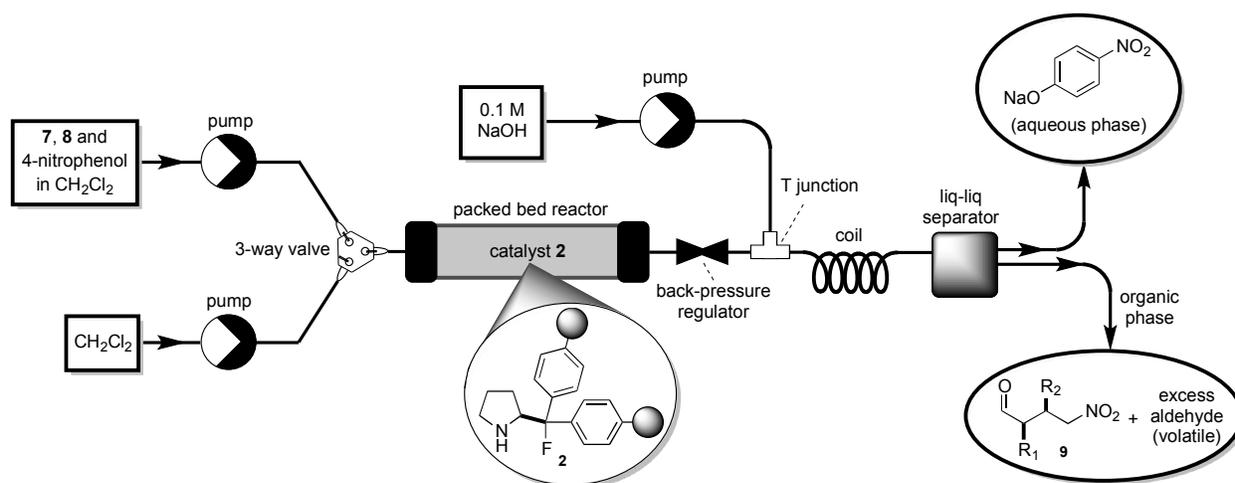


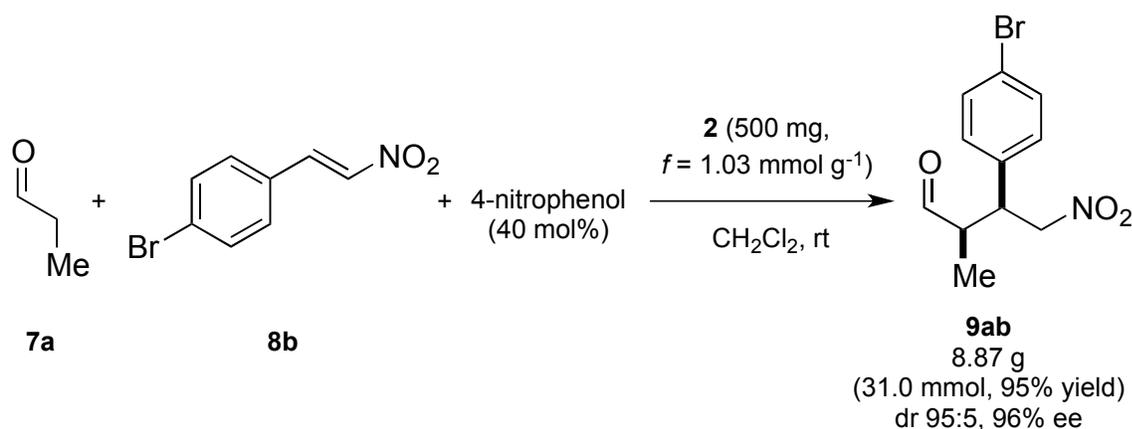
Figure 1. Continuous flow set-up.

Upstream of the column, two channels were connected to a three-way valve that determined which one would feed the catalytic column. Through the first channel dry, degassed CH_2Cl_2 was passed through, its purpose being to swell the resin prior to the reaction and also to rinse any remaining organic material from the column when the reagents have passed through. The second channel was fed with a solution of 4-bromonitrostyrene, propanal and 4-nitrophenol in dry, degassed CH_2Cl_2 with 2.0 equivalents of water.

Downstream, a back-pressure regulator was mounted to avoid bubble formation with volatile solvents such as CH_2Cl_2 , and then further a third pump with 0.1 M NaOH was assembled to

allow for the aqueous work-up and removal of 4-nitrophenol. The biphasic mixture was then separated in-line using a Zaiput liquid-liquid separator, which gave rise to a yellow aqueous phase (due to the presence of 4-nitrophenolate) and an organic phase with the desired Michael adduct and excess aldehyde (plus remaining nitrostyrene if the conversions were not complete). In most cases simply evaporating the organic outstream furnished pure product where no further purification was necessary.

Using this set-up, full conversions were obtained during the first 10 h running the flow process at $100 \mu\text{L min}^{-1}$ (Figure 2). Over the following 3 h, a slight decrease in conversion was observed, but remained above 97%. Overall, the desired Michael adduct was obtained in 95% yield and the effective catalyst loading for the whole operation period was determined to be 1.6%; this corresponds to an overall turnover number (TON) slightly above 60. The turnover frequency (TOF) remained essentially constant at 4.6 h^{-1} over the considered 13 h operation period.



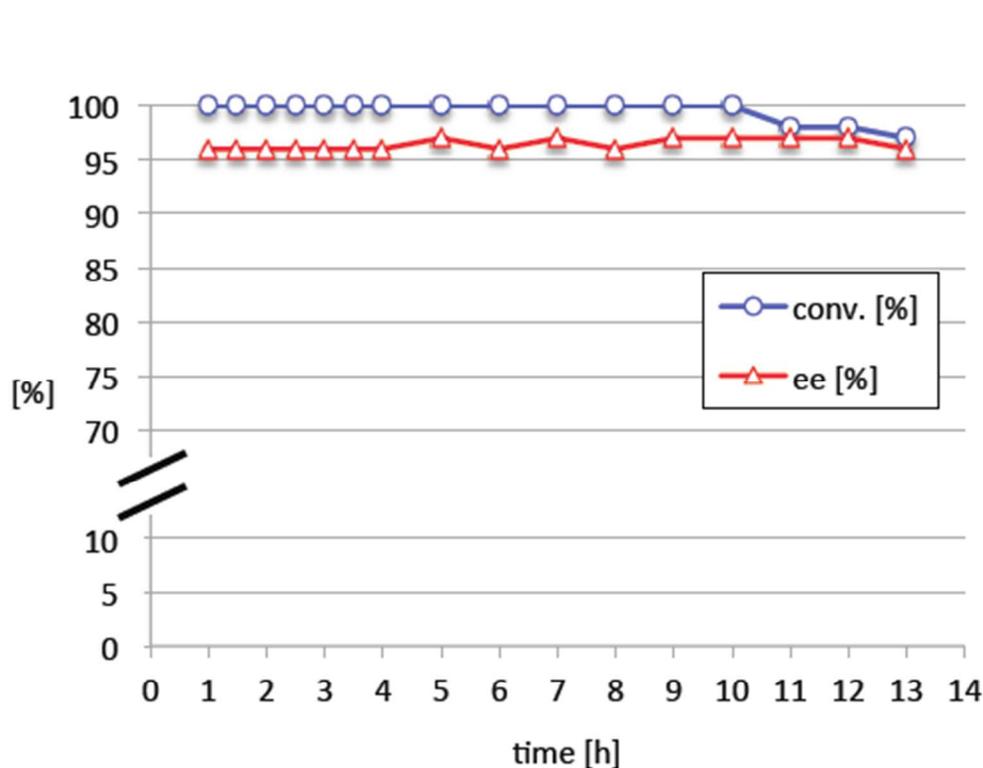


Figure 2. Continuous flow process for polymer-supported catalyst in the formation of **9ab**.

The importance of correctly handling the packed catalyst columns is illustrated by the following fact: when a still fully active column used in a flow experiment was dried, stored in contact with the atmosphere and then attempted to recycle after re-swelling, it was found that catalytic activity was lost to a high degree. This behavior can be easily understood when the conditions of use of the catalytic column in flow are considered. Since an excess of aldehyde reactant is employed, when flow is arrested most of the active sites in the column will be in the active, enamine form. If the column is then dried and allowed to be in contact with air, oxidation of the labile enamine units²⁶ will lead to irreversible deactivation. As shown below, simply keeping the catalytic column wet with dichloromethane when not in use efficiently suppresses this problem.

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3 The possibility of using this continuous flow set-up to generate a library of compounds was
4 then explored. With a new batch of catalyst, a similar flow process was run with different reagent
5 combinations. Each pair of starting materials was circulated through the system for 30 min,
6 rinsing with solvent for 1 h afterwards. At the end of each day, and to avoid catalyst deactivation,
7 CH_2Cl_2 was passed at a rate of $25 \mu\text{l min}^{-1}$ before continuing the flow experiments the next day.
8 Eight different combinations were run the first day and five more the second. On the third day
9 the first three examples were re-run for 4 h each, thus demonstrating that the catalytic activity
10 was retained after several changes of substrates and an extended operation time. The compounds
11 synthesized and the results obtained during the generation of this library are summarized in
12 Figure 3. In total, 16 consecutive runs were carried out, with high yields and stereoselectivities
13 observed in all cases. Remarkably, the last run produced the desired Michael adduct in 90%
14 conversion, thus demonstrating the robustness of the catalyst. The overall TON for this set of
15 experiments was 72.
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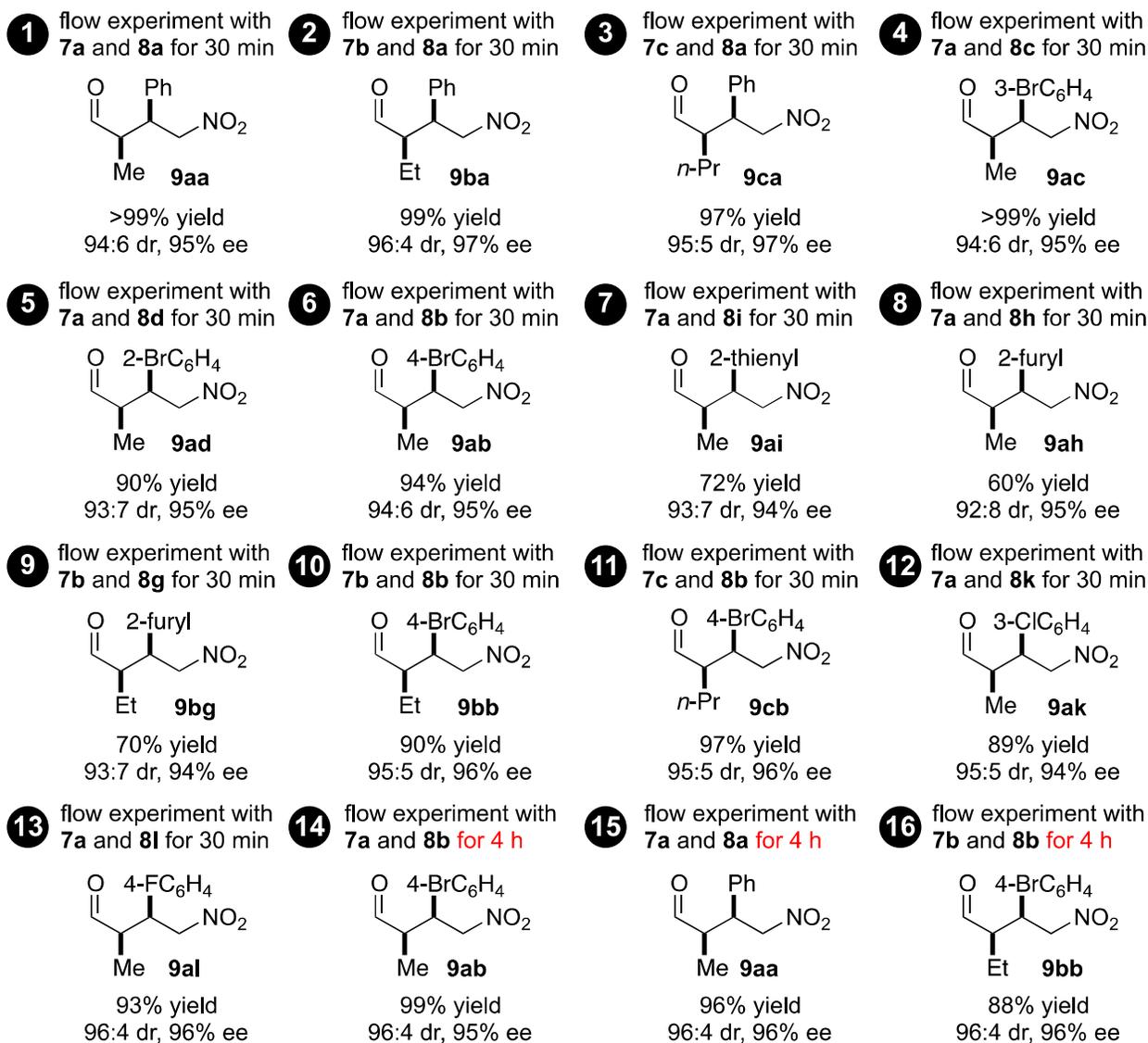
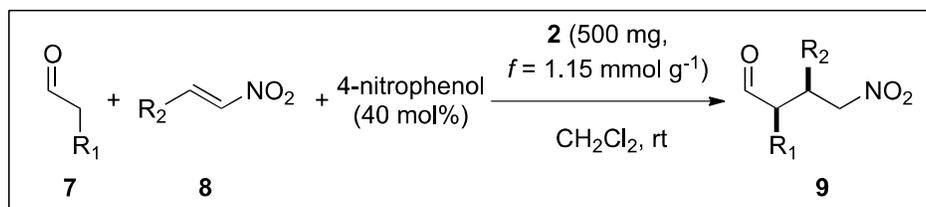
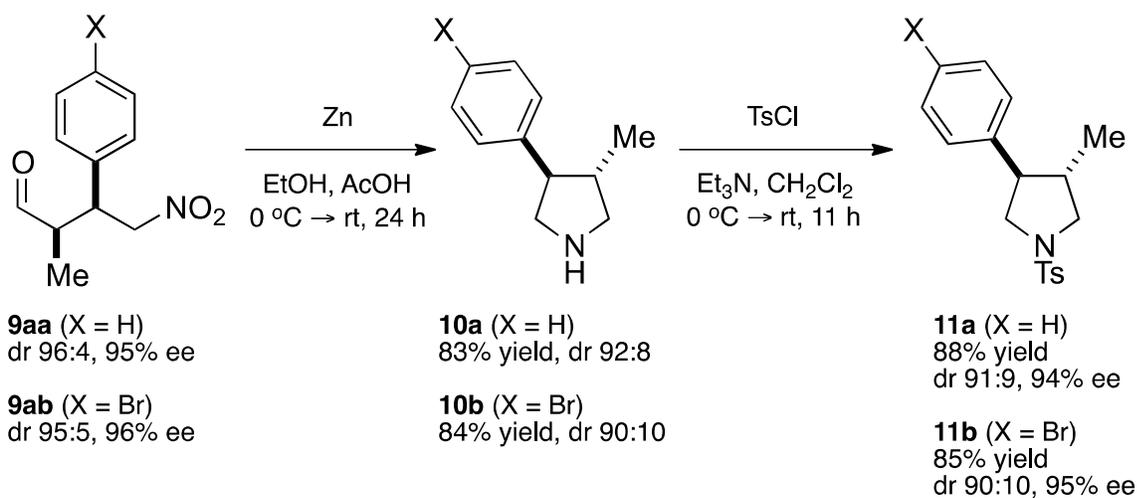


Figure 3. Continuous flow process with polymer-supported catalyst **2** applied to the preparation of a compound library.

To demonstrate the synthetic utility of the process, two different Michael adducts were further derivatized to the corresponding 3,4-disubstituted pyrrolidines **10** by a one-pot operation involving reduction of the nitro group and reductive amination of the corresponding amino aldehyde²⁸ (Scheme 7). The process was carried out on a gram scale and the corresponding products were transformed into the *N*-tosylated derivatives **11** before determining the optical purity. Excellent yields were obtained in both reactions for the two Michael adducts tested.



Scheme 7. Derivatization of the adducts **9aa** and **9ab** to pyrrolidines **10**.

3. CONCLUSIONS

In summary, an immobilized analog of the fluorinated aminocatalyst **1** has been developed and showcased in a model transformation. Key to the success of this approach has been a polymer design that does not affect the active site in **1** and, hence, maintains its catalytic performance. The catalytic resin **2** shows great potential for the Michael addition of aldehydes to nitroalkenes in batch and flow: this is the first example of this catalytic system in enamine activation. Catalyst

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3 deactivation studies have delineated the conditions responsible for degradation, thus allowing the
4 process to be streamlined to extend the lifespan of the catalyst. Applying this resin in a carefully
5 designed continuous flow set-up has allowed for the facile isolation of the desired Michael
6 adducts without chromatographic purification. This catalyst system has proved to be extremely
7 active, both in experiments that were run for extended periods of time and in the preparation of a
8 complex library of analogs. Importantly, the immobilized system shows comparable activity with
9 the batch process. This, together with the stability profile of this novel polymer-supported
10 catalyst, is a powerful endorsement for the use of flow chemistry as an enabling synthesis
11 technology. Application of this catalytic resin to other synthetically valuable transformations is
12 in progress and will be reported in due course.
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27 28 **ASSOCIATED CONTENT**

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31 **Supporting Information.** Experimental procedures, compound and polymer characterization,
32 NMR spectra and HPLC chromatograms. This material is available free of charge via the
33 Internet at <http://pubs.acs.org>.
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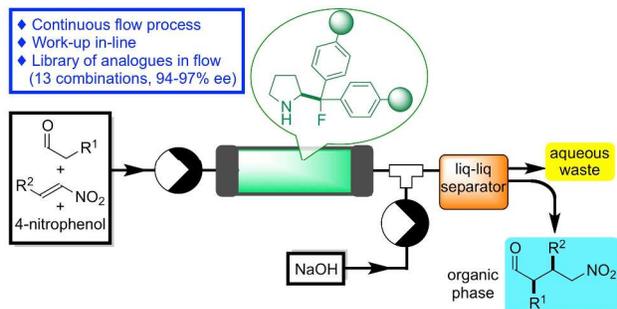
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Table of Contents Graphic and Synopsis



A polystyrene-supported fluorinated organocatalyst has been prepared by co-polymerization and showcased in the asymmetric Michael addition of aldehydes to nitroalkenes. High catalytic activity and enantioselectivity were observed throughout. This immobilized aminocatalyst has been implemented in a continuous flow design employed in the generation of a compound library.