



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

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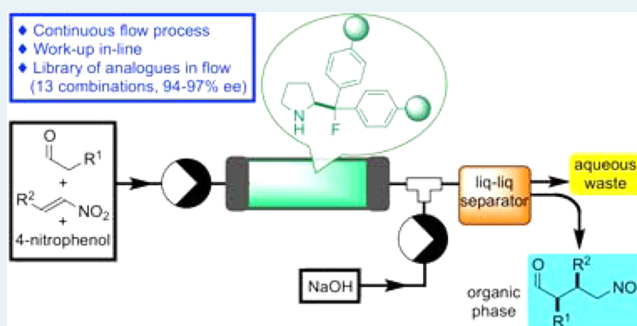
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S Supporting Information

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 of a library of enantiopure Michael adducts from different combinations of substrates (13 examples, 16 runs, 18.5 h total operation). A customized in-line aqueous workup, followed by liquid–liquid separation in flow, allows for product isolation without the need of chromatography or other separation techniques.

KEYWORDS: fluorinated organocatalyst, continuous flow, polystyrene-supported catalysts, enantioselective catalysis, Michael reaction



1. INTRODUCTION

Sustainability concerns have resulted in a change of paradigm in which not only cost reduction but also waste minimization and catalyst recovery are crucial issues in process design. In this context, continuous flow chemistry is one of the technologies expected to facilitate process intensification, reducing the footprint of chemical plants while increasing their productivity, modularity, and flexibility.¹ Despite the potential of immobilized catalysts for enantioselective flow processes, the fine chemical industry still shows some reluctance to apply these techniques because of the often limited lifespan of the reference homogeneous species. Designing more stable homogeneous catalysts and successfully translating their corresponding batch processes to an immobilized platform is therefore essential to further validate the potential of this approach. Consequently, the preparation of supported catalysts with high activity and improved stability holds great potential for both the industrial and academic chemical communities.

Since the pioneering reports by List, Lerner, Barbas,² and MacMillan³ laid the foundations of modern organocatalysis, efforts to develop effective metal-free small molecule catalysts have intensified.⁴ One of the most successful organocatalysts is the diarylprolinol trimethylsilyl ether, commonly known as the Jørgensen–Hayashi catalyst.⁵ Given the versatility of this

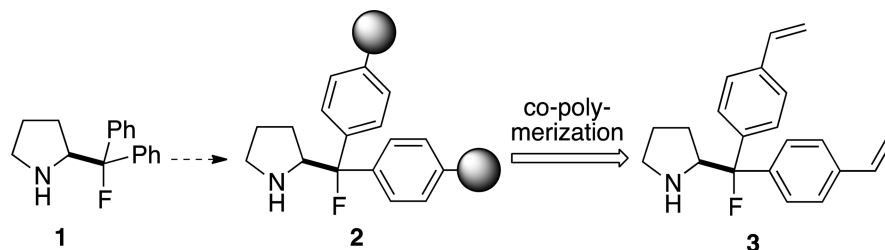
species, which is able to exploit both the enamine and iminium ion activation mode, several groups have tried to harness its potential by developing immobilized analogues.⁶ With the aim of enhancing the sustainability profile of this catalyst, this laboratory has reported the preparation of a set of solid-supported derivatives⁷ whose robustness was established through recycling and implementation of enantioselective continuous flow processes.⁸ These studies revealed that the reusability of the catalyst was often compromised by the lability of the trimethylsilyl ether; this has also been investigated spectroscopically in the homogeneous paradigm.⁹

Several approaches have been employed to address this issue. First, it was demonstrated that resilylation is indeed possible,^{7a} although this has obvious drawbacks from an operational point of view, and it precludes continuous flow applications. The analogous methyl ether¹⁰ (rather than silyl) was also prepared, but the polymer-supported version proved to be less active and selective than the parent system.^{7b} Although catalysts with bulkier silyl ethers display increased stability,^{7d,e} significant structural changes can compromise reactivity, and they tend to deactivate

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Scheme 1. Strategy for the Preparation of a Polymer-Supported Analog of 1

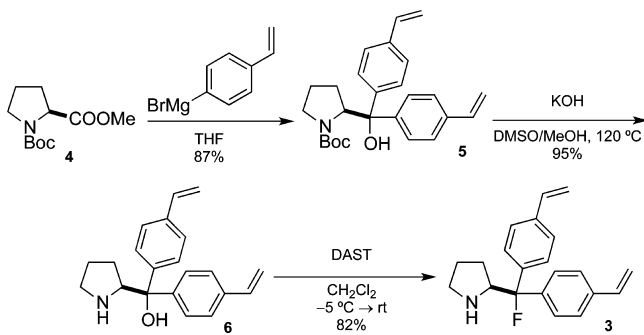


over time. With these data in hand, efforts to immobilize the fluorinated compound **1**¹¹ were initiated; this system was introduced in asymmetric organocatalysis by Gilmour et al. in 2009.¹² The pyrrolidine derivative, designed to validate the gauche effect hypothesis for molecular preorganization,¹³ has proven to be highly effective in the enantioselective epoxidations^{12a,14} and aziridinations¹⁵ of enals with great success, outperforming the Jørgensen–Hayashi catalyst in some cases.¹⁶ Moreover, the low steric demand of the fluorine substituent, coupled with the

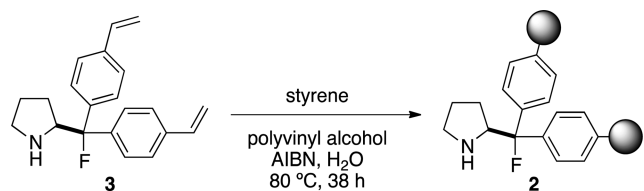
reactively inert C–F bond, ensures that any concerns regarding stability of this site are mitigated.

It was therefore envisaged that compound **2**, a polymer-supported analog of **1**, would display increased robustness when compared with the structurally related silyl ethers. In addition, because the active site of **1** (the pyrrolidine moiety) is not involved in the polymerization of **3** and the 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 copolymerization of the divinylated derivative **3** with styrene (Scheme 1).

Scheme 2. Preparation of the Monomer 3



Scheme 3. Preparation of Resin 2 by Copolymerization of 3



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.

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). Because 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

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	(R)-mandelic acid	3.37	5	81 (n.d.)	85:15	94
5	(S)-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

^aGeneral conditions: (*E*)- β -nitrostyrene (22.4 mg, 0.15 mmol), propanal (33 μ L, 0.45 mmol), catalyst **2** (10 mol %), additive (10 mol %) in 300 μ L 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.

ranging between 0.80 and 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).

Table 2. 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.

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.

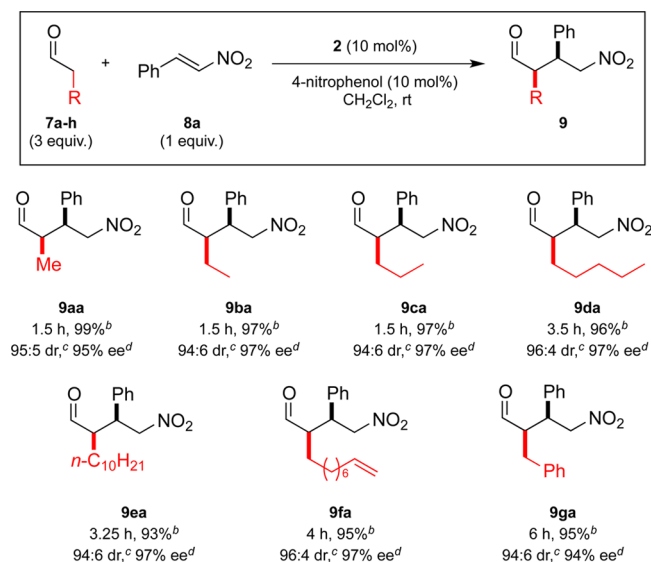
To evaluate the catalytic activity and recyclability of this system, the well-established catalytic addition of aldehydes to nitroalkenes²² was selected as the benchmark reaction for this study. It is worth mentioning that there are no reports of **1** acting as a catalyst for this reaction. Indeed, this study constitutes the first report of its application in the enamine activation mode.

As a model substrate set, propanal and (*E*)-β-nitrostyrene were selected. An initial screening of the addition reaction catalyzed by **2** is summarized in [Tables 1 and 2](#). Gratifyingly, the reaction in CH₂Cl₂ without any additives was complete within 11 h and gave excellent stereoselectivities (entry 1). Consistent with literature reports on the homogeneous reaction, the addition of organic acids increased the reaction rate²³ while maintaining the high levels of enantioselectivity (entries 2–8). As illustrated in [Table 1](#), relatively strong acids, such as TFA, proved detrimental (entry 2), but several carboxylic acids were tested with good results. Finally, it was observed that 4-nitrophenol (the weakest of the acids examined) as an additive^{23a,d} provided the desired product with excellent levels of enantioselectivity (95% ee) within 1.5 h. Good levels of diastereocontrol (up to 96:4 syn/anti) were observed throughout this optimization process.

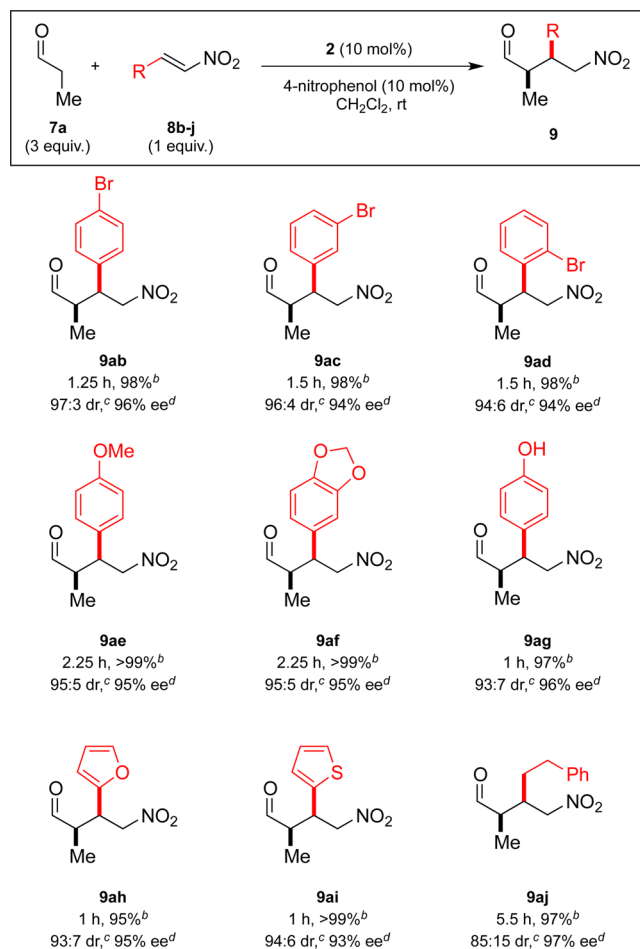
The organocatalytic Michael addition reaction was then optimized in batch mode using catalyst **1** to provide a data set for comparison with the immobilized system ([Table 2](#)). The initial reaction in CH₂Cl₂ reached completion in only 1 h furnishing the desired product **9aa** in quantitative yield 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).

Next, the influence of reaction medium on the organocatalytic Michael reaction with resin **2** was examined using several

Scheme 4. Scope of the Aldehyde Reaction Partner^a



^aGeneral conditions: (*E*)-β-nitrostyrene (22.4 mg, 0.15 mmol), aldehyde (0.45 mmol), catalyst **2** (10 mol %), 4-nitrophenol (10 mol %) in 300 μL of CH₂Cl₂ at room temperature. ^bIsolated yield (%). ^cDiastereomeric ratio (dr) determined by ¹H NMR spectroscopy of the crude reaction mixture. ^dDetermined by chiral HPLC analysis.

Scheme 5. Scope of the Nitroalkene^a

^aGeneral conditions: nitroalkene (0.15 mmol), propanal (33 μ L, 0.45 mmol), catalyst 2 (10 mol %), 4-nitrophenol (10 mol %) in 300 μ L of CH₂Cl₂ at room temperature. ^bIsolated yield (%). ^cDiastereomeric ratio (dr) determined by ¹H NMR spectroscopy of the crude reaction mixture. ^dDetermined by chiral HPLC analysis (GC for **9ag**).

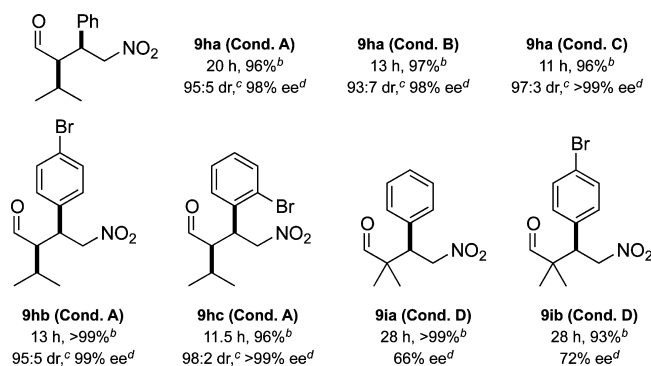
solvents while retaining 4-nitrophenol as an additive. In all cases, excellent diastereo- and enantioselectivities were recorded (up to 95:5 and 96%, respectively; see Table 3). Of the organic solvents investigated, CH₂Cl₂ proved to be beneficial in terms of reaction rate, leading to full conversions 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).

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,^{7a} 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**).

Variation of the nitroalkene partner was then investigated (Scheme 5). It was generally noted that using aromatic nitro olefins (**9ab–9ag**) led to short reaction times, regardless of the nature of the substituents (<2.5 h). Nitroalkenes with heterocyclic aromatic groups, such as the 2-furyl or 2-thienyl systems, proved to be excellent Michael acceptors for this reaction, providing the desired compounds in 1 h (**9ah–9ai**). Employing nitro olefins with an aliphatic side chain (adduct **9aj**) led to longer reaction times (5.5 h), and although the dr slightly decreased, high enantioselectivities were recorded (97%). The characteristically high yields obtained throughout (95–99%) are due to the simplified isolation procedure, made possible by the immobilization of the catalyst: filtration, washing with 0.1 M NaOH to remove the additive and evaporation rendered the pure products. Michael adduct **9ag** is the sole exception to this, in which the phenol-containing product had to be further purified by flash chromatography on silica gel.

To further establish the scope and limitations of the present methodology, catalytic reactions of more challenging substrates mediated by **2** were also examined (Scheme 6). To this end, we

Scheme 6. Scope of α - and β -Branched Aldehydes^a

^aConditions A: nitroalkene (0.15 mmol), isovaleraldehyde (45 μ L, 0.45 mmol), catalyst **2** (10 mol %), 4-nitrophenol (10 mol %) in 300 μ L of CH₂Cl₂ at room temperature. Conditions B: 20 mol % of 4-nitrophenol. Conditions C: 20 mol % of **2** and 20 mol % PhCOOH. Conditions D (for α -branched aldehydes): nitroalkene (0.21 mmol), isobutyraldehyde (96 μ L, 1.05 mmol), catalyst **2** (30 mol %), 4-nitrophenol (60 mol %) in 420 μ L of CH₂Cl₂ at room temperature. ^bIsolated yield (%). ^cDiastereomeric ratio (dr) determined by ¹H NMR spectroscopy of the crude reaction mixture. ^dDetermined by chiral HPLC analysis.

started with the β -branched donor isovaleraldehyde. Although the reaction proved to be sluggish, full conversions resulting in the formation of **9ha** were observed after 20 h using the standard conditions (10 mol % **2**, 10 mol % 4-nitrophenol). Whereas doubling the amount of additive had a remarkable effect on the reaction rate, the optimal results were obtained with 20 mol % catalyst loading in the presence of 20 mol % benzoic acid. Isovaleraldehyde was also found to react smoothly with both 2-bromo- and 4-bromonitrostyrene. After fine-tuning the reaction conditions, the desired products **9hb** and **9hc** were obtained in quantitative yield after simple extraction with 0.1 M NaOH or saturated NaHCO₃ without additional purification.

As for α -branched aldehydes, it was found that isobutyraldehyde can be employed as the Michael donor with nitrostyrene and 4-bromonitrostyrene, giving rise to products **9ia** and **9ib**, respectively, which bear quaternary centers. Despite the severe steric hindrance of the corresponding trisubstituted enamine, full conversions were achieved after 28 h using 30 mol % catalyst

Table 4. Recycling Experiments^a

run	<i>t</i> (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 μ L, 0.83 mmol), catalyst **2** (10 mol %), additive (10 mol %) in 550 μ L of CH₂Cl₂ at room temperature. ^bConversion (%) and diastereomeric ratio (dr) determined by ¹H NMR spectroscopy of the crude reaction mixture. ^cIsolated yield (%).

Table 5. Recycling Experiments in the Presence of Water^a

run	<i>t</i> (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

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

and 60 mol % of 4-nitrophenol. Extraction with 0.1 M NaOH gave the Michael adducts in good yields, but with moderate enantioselectivities (66 and 72% ee, respectively). Unfortunately, trisubstituted nitroalkenes such as α -methylnitrostyrene or β -ethoxycarbonylnitrostyrene proved unreactive, even after 42 h with 20 mol % catalyst and 4-nitrophenol.

Having established the generality of the reaction, it was essential to demonstrate the stability of the catalytic resin **2** upon reuse. To that end, a standard reaction was successively run in the presence of 4-nitrophenol, and after each cycle, the mixture was simply filtered off and washed to remove all of the soluble materials. The remaining material **2** was then dried and used in the subsequent cycle. The filtrate was extracted with 0.1 M NaOH, and provided pure compound when full conversions were achieved. We were pleased to find that this polymer remained active for at least eight runs (Table 4), although some progressive loss of activity was observed in the 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.

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

These conditions that have allowed catalytic activity to be retained for longer periods of time were then translated into a

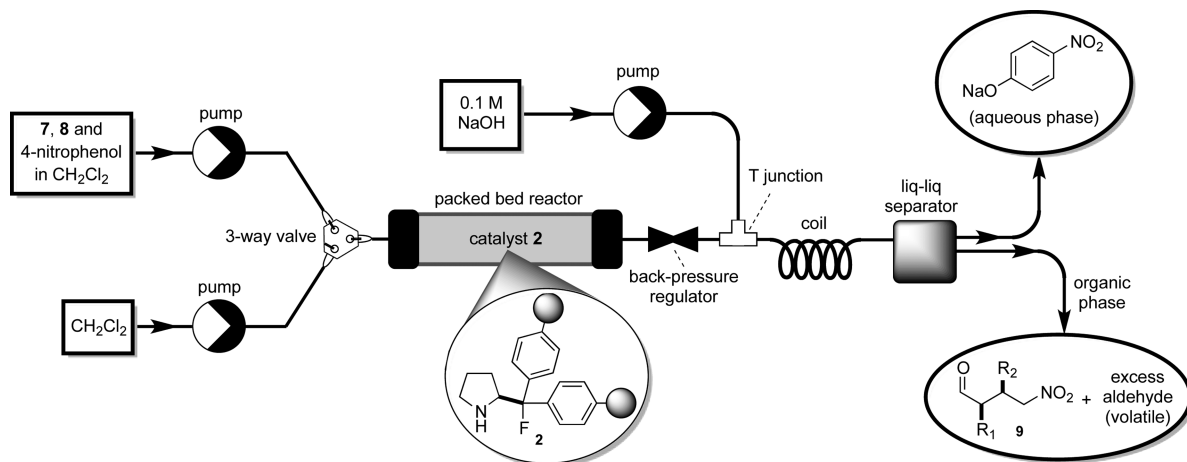


Figure 1. Continuous flow setup.

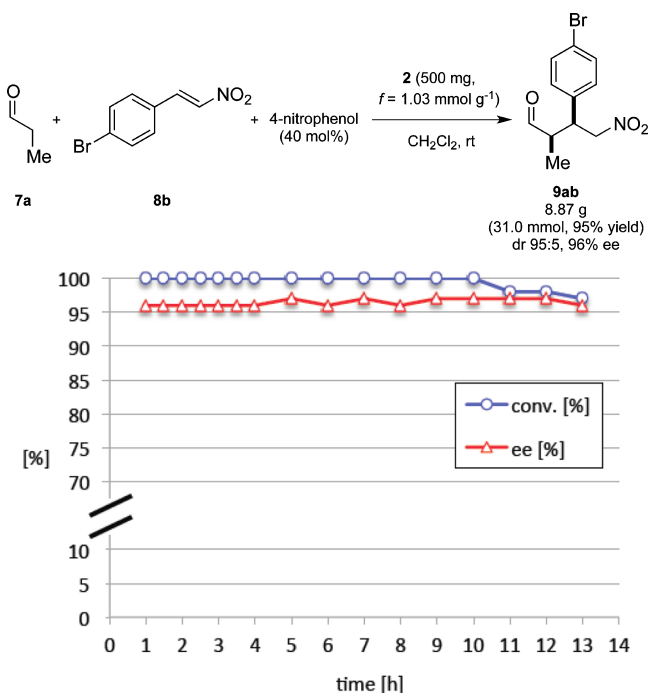


Figure 2. Continuous flow process for polymer-supported catalyst in the formation of **9ab**.

continuous flow process.²⁷ An overview of the setup used, in which 500 mg of resin **2** was packed in a glass column (1 cm diameter), is shown in Figure 1.

Upstream of the column, two channels were connected to a three-way valve that determined which one would feed the catalytic column. Dry, degassed CH_2Cl_2 was passed through the first channel, 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 equiv 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 workup 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 setup, full conversions were obtained during the first 10 h running the flow process at $100 \mu\text{L min}^{-1}$ (Figure 2).

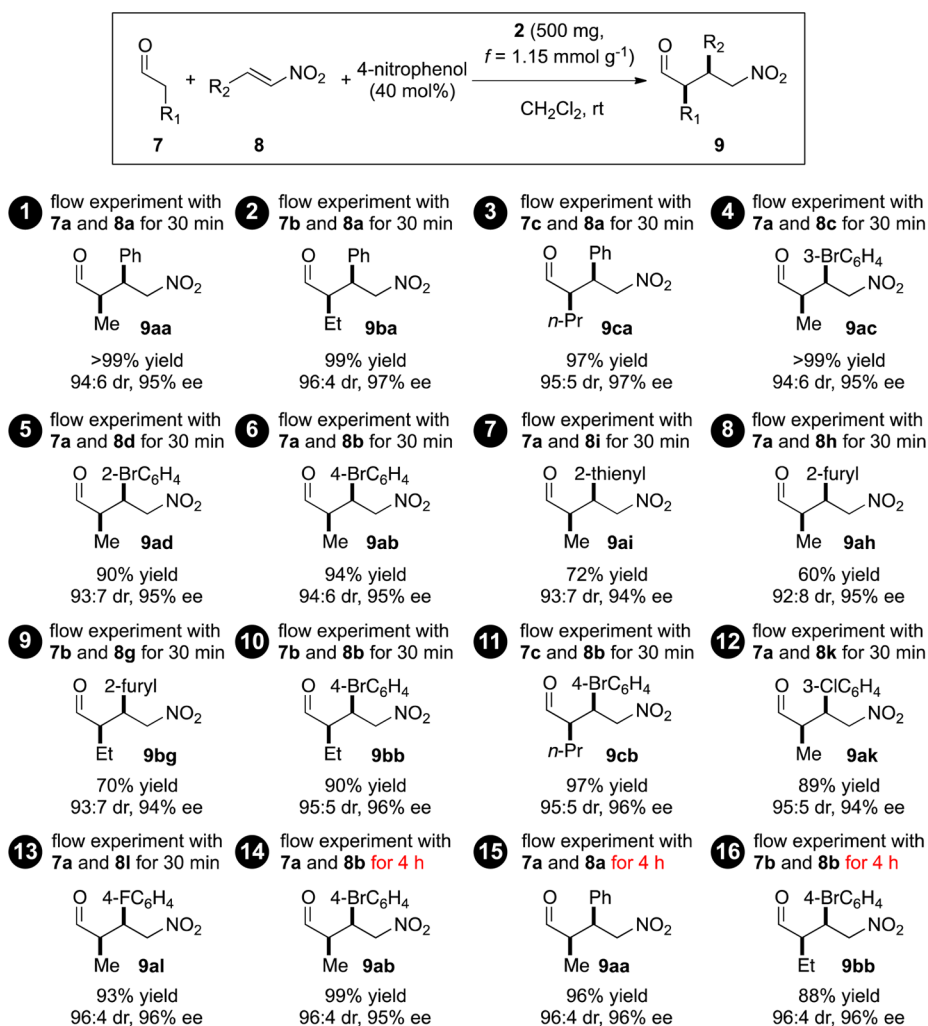


Figure 3. Continuous flow process with polymer-supported catalyst **2** applied to the preparation of a compound library.

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.

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 reswelling, 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. Because 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.

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

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.

3. CONCLUSIONS

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

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01746.

Experimental procedures, compound and polymer characterization, NMR spectra and HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

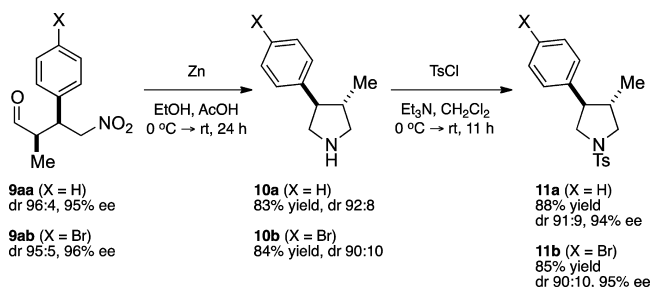
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Scheme 7. Derivatization of the Adducts 9aa and 9ab to Pyrrolidines 10



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