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Highly enantioselective immobilized prolinamide-catalyzed aldol reactions in continuous-flow systems: effect of water on the catalyst lifetime and application in the synthesis of a chiral fenpentadiol analogue†

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Catalytic enantioselective aldol reactions of trifluoroacetophenones with ketones under continuous-flow conditions have been developed for the first time by using polystyrene-supported prolinamides. The robustness of the flow system was demonstrated by the continuous synthesis of a variety of trifluoromethyl carbinols in high yields with high enantioselectivities. The unusually long lifetimes (>195 h) of this flow process were achieved by facilitating H_2O-promoted hydrolysis of iminium intermediates on the polymer. Mechanistic study revealed a racemization phenomenon and an inherent reversible property of the aldol reactions in a conventional batch system, both of which were suppressed under continuous-flow conditions. The synthetic utility of this flow process was further demonstrated by the formal continuous-flow synthesis of a chiral fenpentadiol analogue.

Chiral secondary amines such as proline and its derivatives are commonly employed, reliable chiral organocatalysts for the synthesis of optically active carbonyl compounds.[1] These catalysts are generally stable and easily handled, and several types of chiral secondary amines have been developed and applied for catalytic asymmetric reactions. On the other hand, although immobilization of active catalysts on heterogeneous supports to enable their recovery and reuse has been extensively investigated,[2] the development of heterogeneous chiral secondary amines immobilized on supports has been problematic because immobilized catalysts are sometimes easily deactivated during asymmetric reactions, and their recovery and reuse is generally difficult.[3] Moreover, their application in continuous-flow reactions[4] has not been successful, mainly due to the short catalyst lifetime.

Since chiral trifluoromethylated tertiary alcohols are prevalent motifs in various natural products and biologically and pharmaceutically relevant molecules,[5] the development of efficient strategies to access enantioenriched trifluoromethylated tertiary alcohols is of great interest. Chiral secondary amine-catalyzed aldol reactions have been recognized as one of the most powerful carbon–carbon bond-formation methods for the synthesis of chiral secondary or tertiary alcohols.[6] Although a few catalytic systems have been developed for the synthesis of trifluoromethylated tertiary alcohols using aldol reactions with high enantioselectivities,[7] there are some serious issues to be resolved in their practical synthesis: (1) long reaction times and high catalyst loadings are generally required because of difficulties arising from the construction of quaternary carbon centers and (2) chiral trifluoromethylated tertiary alcohols easily undergo racemization in the presence of weak acids, protic solvents, and high catalyst loadings and sometimes during extended reaction times. One of the solutions that can be used to address these issues is a continuous-flow reaction system using an immobilized chiral secondary amine. There are many general advantages of continuous-flow systems over conventional batch systems with respect to efficiency, safety, and environmental compatibility.[8] Furthermore, under continuous-flow conditions, it is possible to realize high local catalyst loadings for reactions while avoiding prolonged contact of the catalysts with the chiral products, thereby reducing the extent of racemization. However, deactivation of immobilized secondary amines[9] under continuous-flow conditions is generally problematic, as described.[4] To overcome these challenging issues, we herein present for the first time a simple but efficient continuous-flow enantioselective aldol reaction system for the synthesis of enantioenriched trifluoromethylated tertiary alcohols using an immobilized chiral secondary amine catalyst and an additional small amount of water (Scheme 1).

For the target aldol reaction, we selected one of Singh's chiral prolinamide catalysts because of its high reactivity.[10] Inspired by the previous related reports on continuous-flow reactions by the group of Pericàs[4] and by our group,[11] we employed a copolymerization strategy and prepared three

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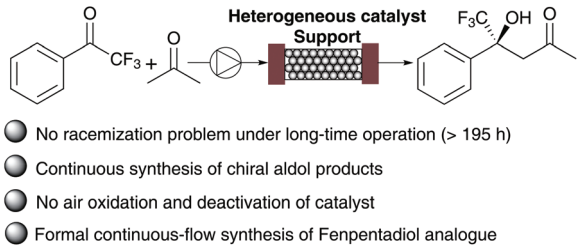


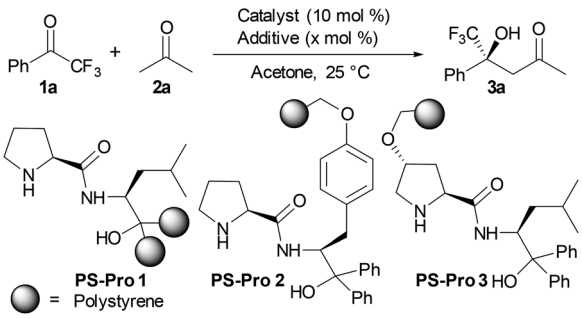
Scheme 1 This work: continuous-flow enantioselective aldol reaction for the synthesis of chiral trifluoromethylated tertiary alcohols.

different immobilized prolinamides by grafting styrene linkers to small molecular catalysts and further copolymerization with styrene and divinylbenzene (see Schemes S1–3 in the ESI†). The activities of the prepared polymer catalysts were compared in the aldol reaction of acetone (**2a**) with trifluoroacetophenone (**1a**) in a batch system. **PS-Pro 1** gave the highest efficiency, albeit with decreased enantioselectivity (Table 1, entry 1). The reduction in the enantioselectivity might result from emerging diastereomers of the catalyst in the copolymerization step.[12] **PS-Pro 2** gave a slightly decreased enantioselectivity and a longer reaction time was needed compared to the previous homogeneous report (Table 1, entry 2). **PS-Pro 3** was selected as the optimal catalyst for this aldol reaction because it exhibited the highest degree of enantiocontrol (Table 1, entry 3).[13] A range of acidic additives[14] were screened to improve the efficiency (TOF) of the aldol reaction[15] (Table 1, entries 4–6); however, no better results were obtained, with similar racemization tendency to that of the homogeneous cases being observed (entries 5 and 6).[7b,16] The lower levels of enantiocontrol may arise either from product decomposition or from an overreaction. The recovery and reuse of the catalyst **PS-Pro 3** was investigated to examine the stability of the catalyst in the batch system. Interestingly, the catalyst remained reactive after eight runs and prolonged reaction times (14 to 35 h) (see Tables S4–5 and Scheme S4 in the ESI†).

We then investigated the aldol reaction under continuous-flow conditions. In the continuous-flow experiment, fresh polymer (676 mg) and Celite (4.1 g) were packed into a flow column reactor (10 × 100 mm) and toluene was introduced to stabilize the flow system at 1 mL min^{-1} for 1 h in advance. The catalyst lifetime in this case was 65 h. The column reactor size was then reduced to 10 × 50 mm and the column was packed with the recovered polymer from the above column (polymer 676 mg and Celite 1.4 g). Under these conditions, the lifetime was 45 h. In contrast to the batch system, high enantioselectivities of the flow system were achieved in all cases. The deactivated polymer was recovered and subjected to fluorine elemental analysis and IR analysis (see Schemes S5 and 6 in the ESI†). The analysis of the obtained spectra, which indicated the presence of the fluorine atom, led us to speculate that the deactivation of the flow process might arise from a reduced rate of hydrolysis of the iminium intermediates on the polymer due to the loss of water in the catalytic cycle (Scheme 2).

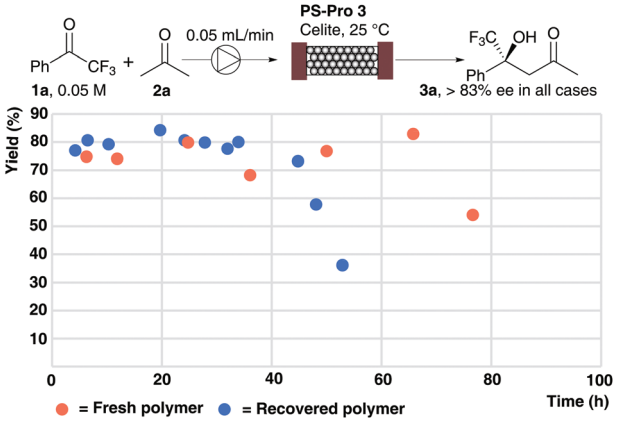
To overcome these issues, a range of additives, such as water, 4-nitrophenol, and HFIP, were introduced into the flow system in an attempt to increase the efficiency and lifetime of the catalyst (see Tables S6–S8 in the ESI,† also see Tables S1–S3† for the additive effect in a batch system). It was found that the inclusion of an additional 1 equivalent of H_2O was the key to success. In contrast to the batch system, H_2O generated *in situ* was not reusable in a flow reactor, which led to deactivation of the catalyst. An extended-time flow reaction (195 h) was conducted to evaluate the catalyst activity in the flow system and, in all cases, high enantioselectivities were obtained (≥87% ee). Interestingly, high isolated yields were still obtained even after 190 h. The high catalytic activity of the

Table 1 Activity evaluation of polystyrene-supported prolinamides (**PS-Pro**) in a batch system[a]



Entry	PS-Pro	Additive/pK_a in DMSO	Time (h)	Yield (%)	ee (%)
1	**1**	—	4	91	82
2	**2**	—	9	93	86
3	**3**	—	7	89	90
4[b]	**3**	H_2O/31.4	6.5	84	86
5[c]	**3**	PhCOOH/11.1	4	72	78
6[c]	**3**	4-Nitrophenol/10.8	2	87	82

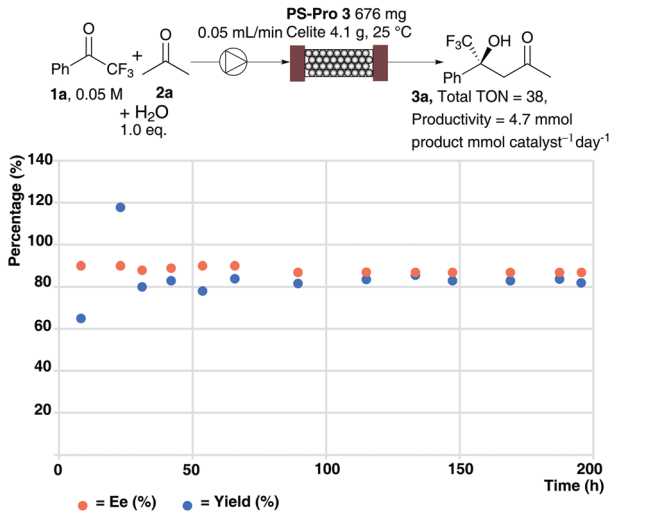
[a] Reaction conditions: **1a** (0.2 mmol), catalyst (10 mol%), **2a** (0.5 mL), room temperature. [b] H_2O (1 equiv). [c] Additive (0.1 equiv).



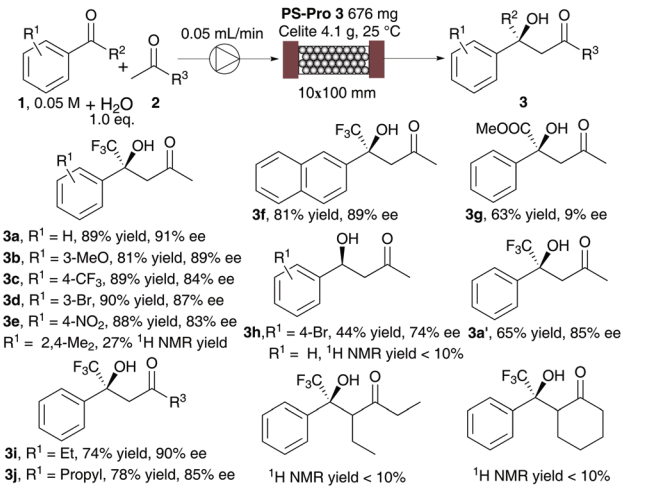
Scheme 2 Screenings of conditions for continuous flow. (a) A 10 × 100 mm column was used for the fresh polymer and (b) a 10 × 50 mm column was used for the recovered polymer.

flow system benefits from the H_2O-promoted hydrolysis of the iminium intermediate of the catalyst. In addition, a short residence time might avoid overreactions and side reactions in the flow reactor. The total TON was 38, five times higher than that of the previously reported reaction in batch systems. The productivity was 4.7 mmol product per mmol catalyst per day (Scheme 3).

The substrate scope was investigated under the optimized conditions using **PS-Pro 3** for the continuous-flow aldol reactions (Scheme 4). From **3a** to **3h** and **3a′**, the reactions of all samples were performed for 10 h. An acetone/H_2O mixture was introduced to rinse the flow system at 1 mL min^{-1} for 30 min between the reactions of two different samples. The reactions



Scheme 3 Long-time flow reactions in the presence of 1 equivalent of H_2O.

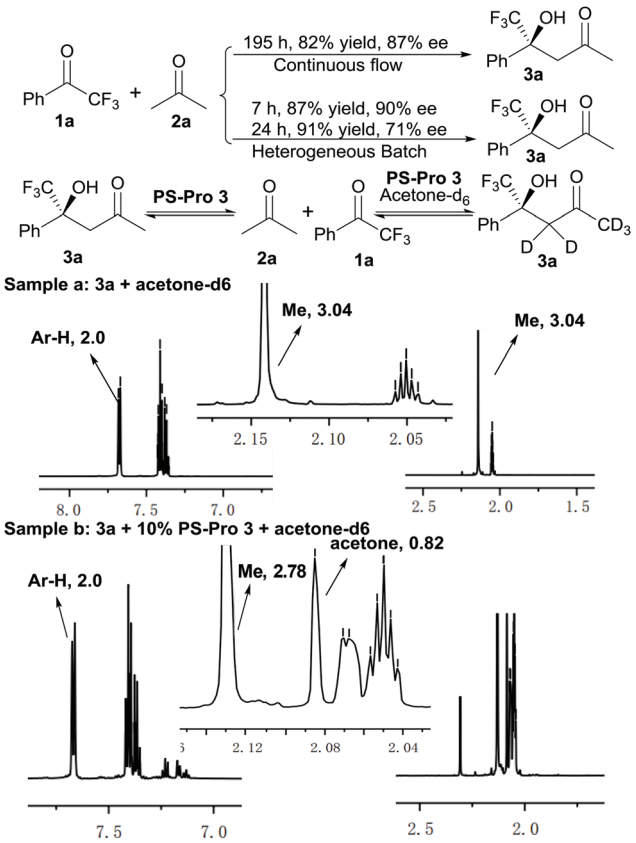


Scheme 4 Substrate scope of the sequential aldol reactions in continuous flow. (a) From **3a** to **3h** and **3a′**, a freshly prepared polymer was packed into a flow reactor. (b) From **3i** to **3j**, the recovered polymer was used.

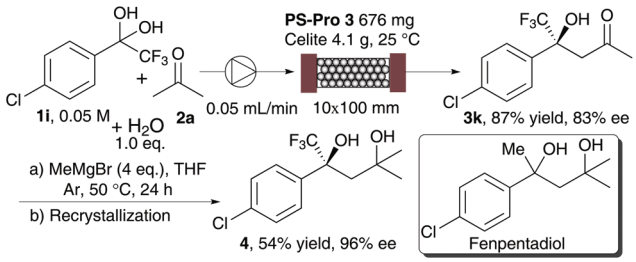
of **3i** and **3j** were performed for 5 h. Between running the two samples, a THF/H_2O mixture was introduced at 1 mL min^{-1} for 30 min and a toluene/H_2O mixture for another 30 min to wash the flow system. The flow rate was set as 0.05 mL min^{-1}, and the concentration was 0.05 mmol mL^{-1}. Degassing the organic solvents using an ultrasonic instrument for 10 min effectively prevented blockages caused by bubbles gathering in the flow pipe. Notably, only one batch of the polymer was used during the investigation of the substrate scope. The efficiency of the flow reactions slightly dropped with respect to yields and ee values between the beginning **3a** and the end **3a′**. Noting this deactivation, we recovered and reactivated the polymer and Celite by washing with HCOOH, 1 M NaOH, H_2O, methanol, and DCM. The reactivated catalyst was repacked into the flow reactor for use with asymmetric ketones and symmetric ketones. In accordance with previous reports, methyl ketones could smoothly react with trifluoroacetophenone, but others could not.[7] In addition, not easily accessible ketones or solid ketones that could not serve as solvents were intolerable to this flow system. Notably, high enantioselectivities could be achieved even after 100 hours.

In conventional batch systems, chiral products tend to racemize over a prolonged reaction time. In contrast, these continuous-flow systems automatically separate the product and catalyst, guaranteeing high enantioselectivity even after 100 h. This interesting phenomenon stimulated us to explore the reason why the flow system could present such an advantage over the batch system. *In situ* ^{1}H NMR study was conducted to identify the possible by-products or intermediates that were generated in the batch system. Thus, the optically active product **3a** was dissolved in acetone-d_6 and subjected to ^{1}H NMR analysis (sample (a)). The spectrum showed that the relative integral value of the methyl group of **3a** was 3.04, and no acetone peak was observed. To sample (a) was added 10 mol% of **PS-Pro 3** and, after 24 h of stirring at room temperature, the mixture was filtered and the filtrate was subjected to ^{1}H NMR analysis (sample (b)). This spectrum showed that the relative integral value of the methyl group of **3a** was 2.78 and the integral value of the formed acetone peak was 0.82. The reduction in the relative integral value of the methyl peak in sample (b) indicated that about 9% of the product **3a** was deuterated in acetone-d_6 in the presence of 10 mol% of **PS-Pro 3** after 24 h of stirring. Moreover, the appearance of the acetone peak (0.82) in sample (b) directly revealed that the reverse reaction occurred over a longer reaction time (Scheme 5). These ^{1}H NMR data provided solid experimental support for the reverse catalytic cycle and racemization mechanism.

Based on the ^{1}H NMR study and fluorine elemental analysis, we proposed a reasonable catalytic cycle for this aldol reaction (Scheme 6). The ^{1}H NMR study revealed the existence of a reverse catalytic cycle in which the chiral product **3a** could further react with **PS-Pro 3** and slowly produce **1a** and **2a** at the same time. This reverse catalytic cycle explained the racemization mechanism. In the flow process, deactivation of **PS-Pro 3** was observed in the absence of the H_2O additive. Intermediate **C** shown in Scheme 6 was proposed to explain the deactivation



Scheme 5 ^{1}H NMR study revealing the advantage of continuous flow over a heterogeneous batch system.

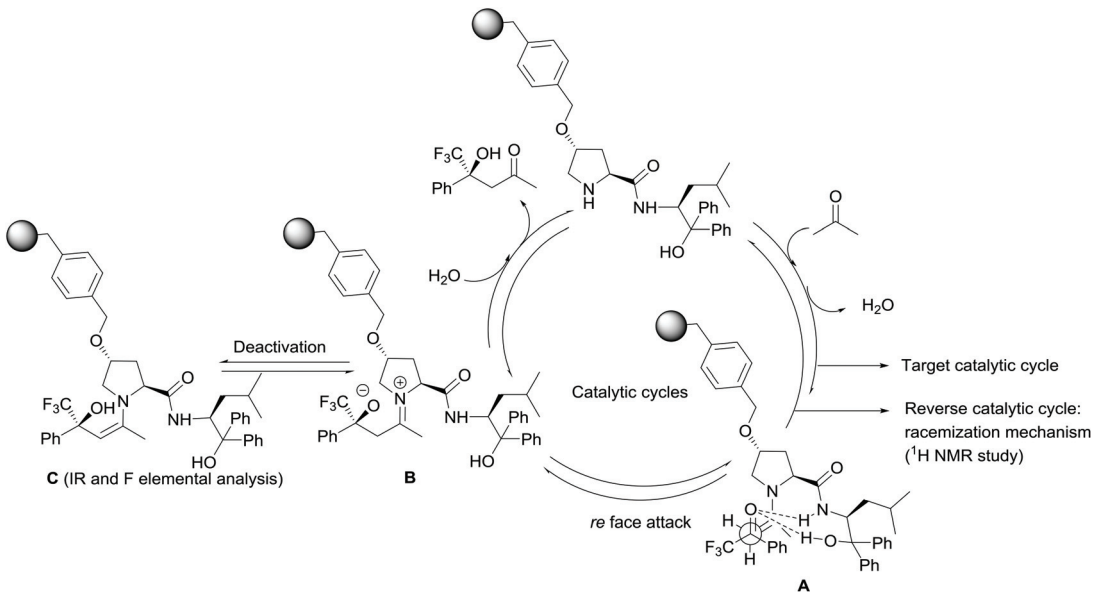


Scheme 7 Formal continuous-flow synthesis of chiral fenpentadiol analogue **4**.

pathway, which could be further suppressed by the addition of 1 equivalent of H_2O. The structure of intermediate **C** was supported by IR analysis and by fluorine elemental analysis (see Schemes S5 and 6†). A more detailed description of the transition states is shown in Scheme S11.†

The synthetic utility of this continuous-flow process is further demonstrated by the semiautomated synthesis of chiral fenpentadiol analogue **4**[17] (Scheme 7). The chiral precursor **3k** was obtained in a high yield with high enantioselectivity by using the developed continuous-flow system. The subsequent Grignard reaction with methyl magnesium bromide smoothly delivered the desired fenpentadiol analogue **4**, possessing potential antidepressant activity.[18]

In summary, we have developed highly enantioselective aldol reactions of trifluoroacetophenones with ketones in a continuous-flow system for the first time using **PS-Pro** catalysts and a small amount of water as an additive. The efficiency of the flow system over the batch system was demonstrated by the continuous synthesis of a variety of chiral trifluoromethyl carbinols in high yields with high enantioselectivities. This flow process highlighted the long-term stability (>195 h) that was achieved by the addition of 1 equivalent of H_2O. Fluorine elemental analysis and IR analysis provided experimental evidence for the deactivated polymer. *In situ* ^{1}H NMR study



Scheme 6 Catalytic cycles including the catalyst deactivation pathway and racemization mechanism.

revealed the existence of the reverse catalytic cycle. The synthetic utility of the system was documented by the formal continuous-flow synthesis of chiral fenpentadiol analogue **4**. This flow system is anticipated to become an important component of modular organic synthesis to access natural products, bioactive molecules, and materials.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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