Organocatalysis

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5-(Pyrrolidin-2-yl)tetrazole-Catalyzed Aldol and Mannich Reactions: Acceleration and Lower Catalyst Loading in a Continuous-Flow Reactor**

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Synthetic transformations involving chiral catalysts are attractive owing to their efficiency and atom economy.[1] Organocatalysis[2,3] is becoming increasingly popular as an alternative to catalysis by metal complexes.[4] Proline and some of its derivatives catalyze aldol reactions with selectivities typically observed only with enzymes.[5,6] Still, proline-catalyzed asymmetric aldol reactions and other transformations requiring amine catalysts suffer from long reaction times (sometimes several days) and high catalyst loading (typically 20–30 mol%). Accelerating organocatalytic reactions while at the same time lowering catalyst loadings would be an important step forward for this rapidly developing field.

Continuous-flow microreactors have been useful in accelerating a host of reactions and facilitating scale up. Microstructured continuous-flow reactors and chip-based microreactors are becoming an alternative to traditional batch reactors for synthetic chemistry.[7] Microreactors have been applied to many standard transformations in organic synthesis;[8,9] however, few examples of enantioselective reactions have been reported to date.[10] Reactions in microreactors are usually conducted at higher temperatures than batch reactions to decrease reaction time. In contrast, most asymmetric reactions are conducted at lower temperature to increase enantioselectivity.

Here, we report the first example of an organocatalytic asymmetric aldol reaction conducted in a microreactor; with the catalyst 5-(pyrrolidin-2-yl)tetrazole (**A**) reaction times were shortened dramatically and catalyst loading reduced (Figure 1). Readily available tetrazole **A**[11] was selected as the catalyst since it is more soluble in DMSO than is proline. Arvidsson,[11a] Ley,[11b] and Yamamoto et al.[11c] reported **A** to be more effective than proline for a number of organocatalytic transformations. The (pyrrolidin-2-yl)-tetrazole-catalyzed aldol reaction between 4-nitrobenzaldehyde and acetone was selected for an initial optimization study. A glass microreactor with an volume of 1.0 mL, a rectangular mixing zone (width 161 μm, depth 1240 μm, length 536 mm), and a rectangular residence channel (width 391 μm, depth 1240 μm, length 1844 mm) was used for this study.[12] Fluidic connections were made using 0.5 mm (inner diameter) polytetrafluoroethylene (PTFE) tubing (Figure 1). The reaction temperature was monitored using a sensor placed in close proximity to the reactor and remained constant during the experiments. Reagents were introduced separately through two inlets using a syringe pump. Initial screening (Table 1) revealed that reactions in the microreactor can be conducted at higher temperatures than batch reactions while maintaining yield and selectivity, owing to the better thermal profile in

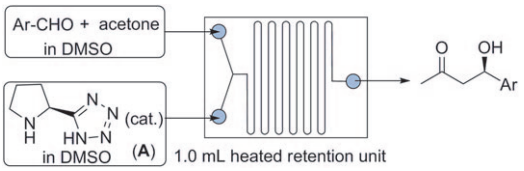
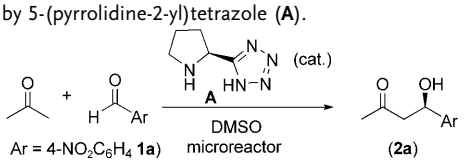


Figure 1. Experimental setup for the aldol and Mannich reactions.

Table 1: Aldol reaction between acetone and 4-nitrobenzaldehyde (**1a**) catalyzed by 5-(pyrrolidine-2-yl)tetrazole (**A**).



Entry	**A** [mol%]	*T* [°C]	*t*[b] [min]	Yield of **2a** [%]	*ee*[c] [%]
1	10	50	10	54[d]	76
2	10	60	10	73	77
3	10	70	10	72	70
4[e]	10	60	10	76	75
5[f]	10	60	10	79	76
6[f]	5	60	20	79	75
7[g]	5	RT	2400	77	74
8[h]	5	60	20	68	65
9[i]	5	50–60	20	72	70

[a] Reactions were conducted with **1a** (1 mmol), **A**, and 10 mL of DMSO/acetone mixture (4:1, v/v), effective concentration of [**1a**] = 0.1 M, conversion was >95% unless otherwise stated. [b] Residence time. [c] Determined by HPLC analysis using a Chiracel AS-H column. [d] **1a** was recovered in 10% yield. [e] Using 5.0 mL DMSO/acetone (3:1, v/v), effective concentration of [**1a**] = 0.2 M. [f] Using 2.0 mL DMSO/acetone (1:1, v/v), effective concentration of [**1a**] = 0.5 M. [g] Literature values for the reaction in flask from Ref. [13]. [h] Reaction in a flask. [i] Reaction using a microwave reactor.

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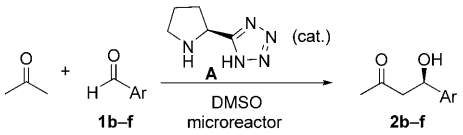
the microreactor. Increasing the reaction temperature from 50 °C to 60 °C improved the yield of the reaction but did not affect the enantioselectivity (Table 1, entries 1 and 2). A further temperature increase did not result in improved yields but rather lower enantioselectivity (Table 1, entry 3). Higher concentrations of starting materials improved the results to afford aldol product **2a** in 79% yield and 76% *ee* (Table 1, entry 5). The yields and enantioselectivities obtained in the microreactor compared well with the 81% yield and 79% *ee* that had been reported for the batch reaction using 20 mol% catalyst.[13] Further reduction of catalyst loading to 5 mol% in the microreactor resulted in complete conversion in 20 min (Table 1, entry 6), while yield and enantioselectivity were maintained. Strikingly, the same reaction in a flask takes 2400 min to reach completion at room temperature when 5 mol% catalyst was used.[13] We also performed the reaction using microwave irradiation,[14] under thermal conditions and in a flask; in both cases, the reaction was complete in 20 min using 5 mol% catalyst at 60 °C although the yield and enantioselectivity were slightly lower than that obtained in the microreactor (Table 1, entries 8 and 9). These initial results clearly demonstrate the potential microreactors offer for organocatalytic reactions.

We also tested a glass chip reactor with an volume of 250 μL and a PTFE tube reactor with a volume of 4.0 mL to study the effect of the channel size on the reaction.[12,15] The glass chip reactor, which had with a rectangular mixing zone (width 300 μm, depth 250 μm, length 532 mm) and a rectangular residence channel (width 400 μm, depth 250 μm, length 2509 mm), gave results similar to those obtained with the 1.0 mL glass reactor (75% yield and 76% *ee*). The same reaction in the tube reactor (4.0 mL volume, 1.0 mm inner diameter) gave slightly lower yield and selectivity (71% yield and 65% *ee*).

To investigate the scope and applicability of the method, aldol reactions between various aromatic aldehydes and acetone were explored (Table 2). Activated aromatic aldehydes such as 4-(trifluoromethyl)benzaldehyde and 4-cyanobenzaldehyde yielded the desired aldol products in good yields and enantioselectivities (68 and 70% *ee*, respectively) within 30 min using 5 mol% **A** (Table 2, entries 2 and 3). Similarly, 2-bromobenzaldehyde gave the aldol product in 78% yield and 75% *ee* (Table 2, entry 5). In the case of benzaldehyde, the aldol product was obtained in poor yield as a result of the competing dehydration. In this case, the batch process also gave the aldol product in poor yield (37%) along with the dehydration product (25% yield) when 20 mol% catalyst was employed (results not shown). High catalyst loading favored the dehydration reaction and the reaction was sensitive to catalyst loading as more catalyst resulted in increased side reactions (Table 2, entries 1,2, 4,5, and 6,7). Aldol reactions in the microreactor required lower catalyst loading and resulted in higher yields without compromising the enantioselectivity of the reaction.

Encouraged by these results, we embarked on the study of aldol reactions between aromatic aldehydes and cyclic ketones. The reaction of 4-cyanobenzaldehyde and an excess of cyclohexanone (9.6 equiv) was conducted in the microreactor using 10 mol% catalyst. The aldol product was

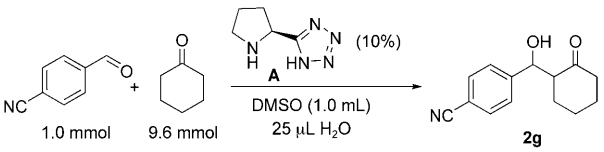
Table 2: Aldol reaction between acetone and various aromatic aldehyde acceptors.[a]



Entry	Ar	A [mol%]	t[b] [min]	Product; yield [%][c]	ee[d] [%]
1	4-$F_3CC_6H_4$ (**1b**)	10	20	**2b**; 71	74
2	**1b**	5	30	**2b**; 77	68
3	4-NCC_6H_4 (**1c**)	5	30	**2c**; 77	70
4	2-BrC_6H_4 (**1d**)	10	20	**2d**; 53	74
5	**1d**	5	30	**2d**; 78	75
6	C_6H_5 (**1e**)	15	30	**2e**; 36 (25)[e]	62
7	**1e**	10	30	**2e**; 38 (18)[e]	63
8	2-naphthyl (**1f**)	10	30	**2f**; 44 (19)[e]	57

[a] All reactions were conducted using the conditions described in Table 1, entry 5. [b] Reaction time. [c] Yields of purified product after column chromatography. [d] Determined by HPLC analysis using a Chiracel AS-H column. [e] Yield of the corresponding dehydration product, estimated from crude ^{1}H NMR spectra.

formed in 86% yield as 1:1 mixture of diastereomers with 77% *ee* for the *syn* isomer and 81% *ee* for *anti* isomer (Scheme 1). To clarify whether the poor diastereomeric ratio observed for this transformation was caused by heating in the



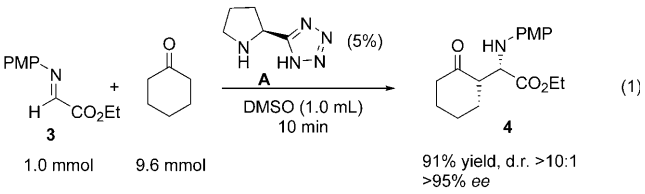
	t / min	T / °C	Yield / %	d.r. (*syn*/*anti*)	*ee*
In batch	540	RT	86	60:40	78 (*syn*)/59 (*anti*)
In microreactor	40	60	86	48:52	77 (*syn*)/81 (*anti*)

Scheme 1. Aldol reaction of cyclohexanone and 4-cyanobenzaldehyde.

microreactor or was an intrinsic feature of the tetrazole-catalyzed reaction, we conducted this reaction at room temperature as a batch process. The aldol product **2g** was obtained in identical 86% yield and a 1.5:1 ratio in favor of the *syn* isomer. The enantiomeric excess for the *anti* product obtained in the microreactor was higher than that obtained using the batch process (81% *ee* vs. 59% *ee*).

The scope of the organocatalyzed reactions in a continuous-flow reactor was further extended to Mannich reactions[16] using an α-iminoglyoxylate as a acceptor and cyclohexanone as a donor. After initial optimization, complete conversion of the two substrates was obtained within 10 min at 60 °C. In the presence of 5 mol% **A** β-amino ketone **4** was obtained in 91% yield and >95% *ee* [Eq. (1)].

We have demonstrated here the potential of continuous-flow microreactor systems to accelerate aldol and Mannich reactions, while simultaneously lowering the amount of organocatalyst required to facilitate the reactions. The enantioselectivity of the reaction was not compromised as lower catalyst loading increased yields in some cases since the



competing dehydration reaction was suppressed. Scale up of these organocatalytic reactions under the flow regime is straightforward—an important feature for developing asymmetric reactions for the pharmaceutical industry. The proof-of-principle results reported here are currently being extended to other organocatalyzed reactions.

Experimental Section

The aldol reaction between 4-nitrobenzaldehyde and acetone (Table 1, entry 6) was conducted in a glass reactor consisting of a 1.0 mL heated (60 °C) retention unit and two inlets. Reagents were introduced using a syringe pump. A 1.00 M solution of aldehyde (1.0 mmol) in acetone was introduced at one inlet at a flow rate of 25 $\mu L\,min^{-1}$, while a 0.05 M DMSO solution of catalyst was introduced from the other inlet at the same flow rate. Total output was 50 $\mu L\,min^{-1}$ (20 min of residence time). The products were collected over saturated NH_4Cl solution (5 mL) and extracted with ethyl acetate (3×10 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Residues were purified using silica gel column chromatography (cyclohexane/ethyl acetate 7:3) to afford the pure aldol product in 79% yield. The enantiomeric excess determined by HPLC (Diacel Chiralpak AS-H, *i*PrOH/hexane 30:70), UV absorption recorded at $\lambda = 254$ nm, flow rate 0.5 $mL\,min^{-1}$. *R* isomer: $t_r = 24.5$; *S* isomer: $t_r = 32.0$.

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