### **Toward Efficient Asymmetric Carbon–Carbon Bond Formation: Continuous** Flow with Chiral Heterogeneous Catalysts

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Preparation of optically active compounds, which are often observed in pharmaceuticals, liquid crystals, agrochemicals, etc., is among the most important tasks in synthetic organic chemistry.<sup>[1]</sup> Catalytic asymmetric synthesis provides one of the most efficient methods for their preparation, because desired optically active compounds are obtained by using small amounts of chiral sources.<sup>[2]</sup> Accordingly, while many chiral catalysts for asymmetric reactions have been developed in the past two decades, the efficiency of the catalysts has also been intensively pursued because it is a key factor for applications in industry. For example, turnover number (TON) is an index to evaluate efficiency of catalysts. Whereas high TONs have been attained in some reactions such as asymmetric hydrogenation,<sup>[3]</sup> TONs of asymmetric C-C bond forming reactions, which construct basic carbon skeletons of target molecules, are generally lower.<sup>[4]</sup> To achieve high TONs, not only are fast catalytic cycles required, but also issues of catalyst destruction and product inhibition have to be addressed. To prevent the catalyst destruction, development of robust catalysts that are tolerant of both water and oxygen is required. As for product inhibition, we thought that the issue might be solved by using continuous flow with chiral heterogeneous catalysts, if the inhibition occurred under coordination equilibrium. Herein, we describe the development of robust catalysts and their use in continuous flow systems using chiral calcium (Ca)-catalyzed asymmetric 1,4-addition of malonates to nitroalkenes as examples.

Asymmetric 1,4-addition of 1,3-dicarbonyl compounds to nitroalkenes is one of the most important methods for the preparation of chiral y-nitro compounds, which can be converted to chiral  $\gamma$ -amino acids and other derivatives.<sup>[5]</sup> We have recently reported chiral calcium alkoxide (phenoxide) (Ca(OR)<sub>2</sub>)-pyridinebisoxazoline (Pybox) complex-catalyzed asymmetric 1,4-addition reactions of 1,3-dicarbonyl compounds with nitroalkenes to afford the desired adducts in high yields with high enantioselectivities (ees).<sup>[6]</sup> In these reactions, TONs were around nine in most cases (Table 1, en-

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Table 1. 1,4-Addition reaction catalyzed by Pybox-Ca(OR)2 and air-stable Pybox-CaCl<sub>2</sub>.



[a] Reaction was conducted under Ar. [b] Reaction was conducted under air. Ar = p-MeOC<sub>6</sub>H<sub>4</sub>

tries 1, 2).<sup>[7]</sup> The Ca(OR)<sub>2</sub> catalysts were relatively unstable under air (moisture) because of hydrolysis. In addition, product inhibition occurred in this asymmetric 1,4-addition because starting materials and products have 1,3-dicarbonyl and nitro functional groups.<sup>[8]</sup> To address these issues, we first focused on calcium chloride (CaCl<sub>2</sub>). CaCl<sub>2</sub> is a common and abundant salt; it has low toxicity and is moisture tolerant and inexpensive. It is familiar as a desiccant, as a deicing and freezing point depressing agent, and as an additive to food and medicines. Although CaCl<sub>2</sub> is also a very common compound in laboratories and is employed as a drying agent for liquid or gas materials in desiccators or drying tubes, use of CaCl<sub>2</sub> as a reagent, in particular as a catalyst in organic synthesis, is very rare.<sup>[9]</sup> After screening several reaction conditions, it was found that CaCl<sub>2</sub> with an amine worked quite well for the reaction of methyl malonate (1a) with  $\beta$ -trans-nitrostyrene (2a) under air. At this stage, TONs were increased to around 18 (Table 1, entries 3, 4). It is noted that the CaCl<sub>2</sub>-Pybox complex is more stable than the Ca(OR)<sub>2</sub> catalysts and can be handled in air. Furthermore, this is the first example of a CaCl<sub>2</sub> complex with a chiral ligand being successfully used as a chiral catalyst.

Next, we examined an application of the chiral CaCl<sub>2</sub> system to continuous flow with a chiral heterogeneous catalyst to address the product inhibition issue and to further in-

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crease the TON. Continuous flow systems have several advantages over batch systems in terms of space, energy and time savings, and facility and safety in large-scale synthesis.<sup>[10]</sup> Furthermore, in continuous flow with a heterogeneous catalyst, a product is removed from a catalyst if a productcatalyst interaction occurs under coordination equilibrium; that is, inhibition of catalytic turnover by a product may be avoided to attain a higher TON compared with that in a batch system. From this point of view, continuous flow with chiral heterogeneous catalysts is a promising method to realize high performance of chiral catalysts; indeed, several investigations have been conducted for over 10 years in laboratory-scale experiments,<sup>[11]</sup> successful examples are limited. In chiral metal complex-catalyzed continuous flow reactions, a serious problem, especially in pharmaceuticals, is the leaching of precious metals, leading not only to loss of expensive metals but also to contamination of metals in products.<sup>[12]</sup> Because of this, use of ubiquitous and nontoxic metals such as Ca is highly desirable.<sup>[13]</sup>

Because chiral heterogeneous catalysts are needed for the flow systems, we then synthesized polymer-supported Pybox (PS-Pybox, loading of Pybox:  $0.72-0.85 \text{ mmol g}^{-1}$ ) according to conventional transformations.<sup>[14]</sup> PS-Pvbox was first tested in the reaction of 1a with 2a in a batch reactor. When  $Ca(OiPr)_2$  was used, the desired product was obtained in high yield with good enantioselectivity (88%, 74% ee, Table 2, entry 1). In addition, the desired 1,4-addition reaction pro-







Entry	Ca	Et <sub>3</sub> N [mol%]	Yield [%]	ee [%]	TON	
1	$Ca(OiPr)_2$	0	88	74	17.6	
2	$CaCl_2 \cdot 2H_2O$	5	91	91	18.2	



Figure 1. 1,4-Addition reaction using a flow reactor.

ceeded smoothly using 5 mol % of CaCl<sub>2</sub>·2H<sub>2</sub>O with PS-Pybox (5 mol %) and triethylamine (5 mol %) to afford the product in higher yield with higher enantioselectivity (Table 2, entry 2).

Encouraged by these results, we then tried the 1,4-addition reaction using a flow reactor (Figure 1).<sup>[15]</sup> Two glass columns  $(\phi \ 1.0 \ \text{cm} \times 10 \ \text{cm})^{[16]}$  were filled with a mixed catalyst powder, which contained PS-Pybox (750 mg, loading of Pybox:  $0.72-0.85 \text{ mmol g}^{-1}$ ), CaCl<sub>2</sub>·2H<sub>2</sub>O (375 mg), and Celite (1.4 g) in each column. A precolumn ( $\phi$  0.5 cm x 5.0 cm) containing activated MS 4 A (500 mg) was attached to dry the substrate solution.<sup>[17]</sup> The substrate toluene solution (1a: 0.25 M, 2a: 0.30 M (1.2 equiv), Et<sub>3</sub>N: 0.005 M (0.02 equiv)) was passed through the system. Initially, the flow rate was 50  $\mu$ Lmin<sup>-1</sup> (3 mLh<sup>-1</sup>), and it was found that a lower temperature showed better enantioselectivity (Table 3, entries 1-3), although the yield was moderate at -20°C. To increase the flow rate, we chose 0°C, and conducted this flow reaction at the rate of 100 µLmin<sup>-1</sup>  $(6 \text{ mLh}^{-1})$  at 0°C (Table 3, entry 4). After stabilizing the flow system (12 h), fractions each corresponding to 30 min

Table 3. 1,4-Addition reaction using a flow reactor.

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	1a + -	Flow system PS-Pybox CaCl <sub>2</sub> •2H <sub>2</sub> O		9-	
	о.25 м 0.3	zа - 30 м	Et <sub>3</sub> N (0.005 м), Toluene Flow Rate, Temp.	Ja	
Entry	Flow rate [µL min <sup>-1</sup> ]	Temp [°C]	Duration of experiment [h]	Yield [%]	ee [%]
1	50	RT	13	95–96	85-87
2	50	0	13	93–96	92–93
3	50	-20	13	69–71	94
4	100	0	61	91_93	92-93

of flow (theoretically 0.75 mmol of the product included in each fraction) were collected; each fraction was quenched with solid  $NH_4Cl$  and diluted with dichloromethane. After filtration, the filtrate was evaporated to remove the solvents under reduced pressure, and the crude product was purified

by preparative TLC. We monitored 12 fractions during the 61 h-continuous flow. In each fraction, the desired 1,4-addition product was obtained in high yield (av. 92.4%) with high enantioselectivity (av. 92.8% ee), and minimal deactivation of the flow system was observed during 12-61 h. Under these conditions, we obtained a total amount of 67.9 mmol of the product and the TON was 62.6. Then, we further prolonged the reaction time. During analysis of 11 fractions, we found no deactivation of the catalyst after 216 h. The product was obtained in high yield with high enantioselectivity (av. 95.5% yield, 92.0% ee) during 204 h (8.5 days). The total amount of the product was 291.4 mmol and the TON reached 228 (Table 4). When we stopped the system after 216 h, the catalyst was not deactivated (the catalyst was still "living"). Furthermore, when the flow rate was increased to  $200 \,\mu \text{Lmin}^{-1}$  (12 mLh<sup>-1</sup>), high yield and high enantioselectivity were still obtained (86-90%, 91% ee).

#### Table 4. Long-period experiment.

10 + 20			Flow system PS-Pybox CaCl <sub>2</sub> •2H <sub>2</sub> O	► 3a	
та + 2а 0.25 м 0.30 м		Et <sub>3</sub> N (0.005 м) Toluene, 0 °С 100 µL min <sup>-1</sup> TON: 228			
Time [h]	Yield [%]	ee [%]	Time [h]	Yield [%]	ee [%]
12-12.5	88	93	132-132.5	98	92
24-24.5	91	93	156-156.5	96	92
36-36.5	97	92	180-180.5	97	92
60-60.5	98	92	204-204.5	95	91
84-84.5	97	92	216-216.5	95	91
108-108.5	98	92			

Finally, the substrate scope of the 1,4-addition reaction using the continuous flow system was surveyed. Several substituted nitroalkenes bearing either electron-withdrawing or electron-donating groups and heteroaromatic and aliphatic nitroalkenes were examined. The collection, isolation, and analysis were conducted the same as in the previous experiments. We monitored the reactor from 12 h to 18 h for each substrate (Scheme 1). For nitroalkenes with p-, m-tolyl, and p-anisyl groups, high yields and high enantioselectivities were obtained (3b, 3c, 3d). In particular, the m-tolyl substrate gave the highest enantioselectivity (3c). p-Bromoand p-fluoro-substituted aromatic nitroalkenes also reacted smoothly to afford the desired compounds (3e, 3f) in high yields with high enantioselectivities. Nitroalkenes bearing heteroaromatics were also good substrates for this flow system (3g, 3h). For a nonaromatic nitroalkene, the yield was lower while good enantioselectivity was obtained (3i). We also examined a nonsubstituted  $\beta$ -ketoester, which afforded the desired product 3i in high yield with high enantioselectivity. It should also be noted that wide substrate generality was confirmed in this system, and that this is the

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Scheme 1. Substrate scope of the 1,4-addition reactions using a flow reactor. [a] Malonate (0.1 M) was used. [b] Malonate (0.5 M) was used. Flow rate was 50  $\mu$ Lmin<sup>-1</sup>. Yields were determined by <sup>1</sup>H NMR spectroscopy using an internal standard.

first successful example of asymmetric 1,4-addition reactions of 1,3-dicarbonyl compounds with nitroalkenes using a continuous flow system and a chiral heterogeneous catalyst.

In summary, we have developed an asymmetric 1,4-addition of 1,3-dicarbonyl compounds to nitroalkenes affording the synthetically useful y-nitro carbonyl compounds in high yields with high enantioselectivities by using a chiral Ca catalyst based on CaCl<sub>2</sub> with a chiral ligand that is tolerant of moisture and can be handled in air. The catalyst is more robust than the previous Ca(OR)<sub>2</sub> catalysts, and the TON of the catalyst was improved from about 9 to about 18. Moreover, the catalyst was applied to continuous flow with a chiral heterogeneous catalyst to solve the issue of product inhibition. A polymer-supported Pybox was synthesized and was successfully used in a flow system, which worked well for 8.5 days without loss of activity. The TON reached 228, the catalyst was still "living," and wide substrate scope of this continuous flow system was shown. Thus, it has been demonstrated that development of robust catalysts and continuous flow with chiral heterogeneous catalysts is effective in increasing TONs of the catalyst. Further investigations to develop more efficient chiral catalysts for asymmetric C-C bond forming reactions are now in progress.

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#### **Experimental Section**

Catalytic asymmetric 1,4-addition reaction of malonate with trans-\beta-nitrostyrene in a flow system: Two glass columns ( $\phi$  1.0 cm × 10 cm) were used. Celite (1.4 g), calcium chloride dihydrate (375 mg), and polymersupported Pybox (0.85 mmol g<sup>-1</sup>, 750 mg) were charged into each column. For drying substrates and Et<sub>3</sub>N solution, a precolumn ( $\phi$  0.5 cm × 5 cm), which contained dried activated MS 4 A (500 mg), was connected between an HPLC pump and the reaction columns. Malonic acid methyl ester (1a, 0.25 mol L<sup>-1</sup>), *trans*- $\beta$ -nitroalkene (2a, 0.30 mol L<sup>-1</sup>) and  $Et_3N$  (0.005 mol L<sup>-1</sup>) in toluene was passed through the reaction columns (flow rate:  $100 \,\mu L \,min^{-1}$ ) at 0 °C. After 12 h, several fractions (Table 4) were collected during flow of the substrate solution, which contained theoretically 0.75 mmol of the product in each fraction. The solid NH<sub>4</sub>Cl was added to the fraction and the mixture was diluted with CH2Cl2 and was filtered. The obtained solution was evaporated under vacuum and purified by preparative TLC. The enantioselectivity of the obtained product was determined by HPLC analysis.

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- [17] To avoid the loss CaCl<sub>2</sub>, we passed the mixture through a precolumn (MS 4 A), although we could obtain the products without using a precolumn.

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#### Asymmetric Catalysis -

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Carbon Bond Formation: Continuous Flow with Chiral Heterogeneous Catalysts



A chiral Ca catalyst based on CaCl<sub>2</sub> with a chiral ligand was developed and applied to the asymmetric 1,4-addition of 1,3-dicarbonyl compounds to nitroalkenes as a model system. To address product inhibition issues, the Ca catalyst was applied to continuous flow with a chiral heterogeneous catalyst. The continuous flow system using a newly synthesized, polymer-supported Pybox was successfully employed, and the TON was improved 25-fold compared with those of the previous  $Ca(OR)_2$  catalysts.