

## 論文の内容の要旨

### **Development of Heterogeneous Catalysts for Continuous-flow C–C Bond Formation and Hydrogenation Reactions for Multistep Synthesis of Fine Chemicals**

(不均一系触媒を用いる連続フロー炭素–炭素結合生成反応・水素化反応の開発及び多段階  
ファインケミカル合成への応用)

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#### **Introduction**

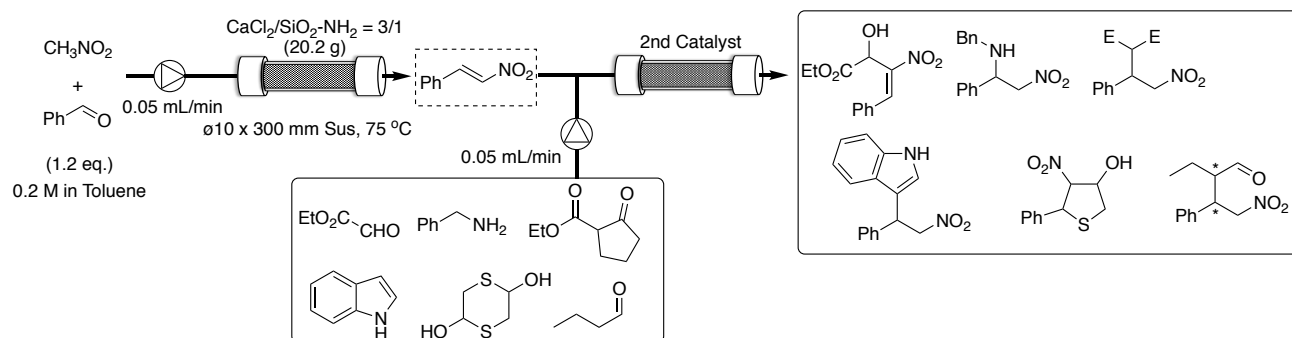
Continuous-flow synthesis has many advantages over conventional batch synthesis from the viewpoint of efficiency, safety, environmental friendliness and scalability. Among several types of continuous-flow methods, flow reactions using heterogeneous catalysts are the most attractive and efficient system for multistep chemical transformations, because the use of activated reagents can be avoided and catalysts can be easily separated from products and used continuously. However, the application of heterogeneous catalysts to continuous-flow reactions is still limited for single-step reactions, and it has been regarded as a great challenge to synthesize fine chemicals under continuous-flow conditions using heterogeneous catalysts. In general, active pharmaceutical ingredient (API) synthesis requires multistep chemical transformations. To realize continuous-flow synthesis of APIs with heterogeneous catalysts, each reaction has to be “clean” without generating byproducts for the next reaction. For this reason, the precise design of whole synthetic routes and the development of catalysts to enable each transformation are essential and challenging points. Previously, our group reported multistep continuous-flow synthesis of chiral API, Rolipram, without any quenching and purification operation. The whole process involves 6 chemical transformations through 4 kinds of heterogeneous catalysts. Although this example is the milestone of continuous-flow fine chemical synthesis, the scope of reactions and catalysts is still limited and needs to be expanded for future development of this field.

In my Ph.D. thesis, I decided to focus on C-C bond formation and hydrogenation, because these types of reactions generally take place with high atom economy and generate water as a sole byproduct, which can be easily removed. To achieve multistep continuous-flow synthesis, my strategy is construction of backbone of a target molecule at first by aldol-type reactions with substrates with high oxidation states, which can potentially act as nucleophile, followed by conversion the functional groups to final target by selective hydrogenation. I hypothesized that various kinds of fine chemicals can be synthesized by connecting of these two types of reactions under continuous-flow conditions.

#### **1. Synthesis of Nitro-Containing Compounds through Multistep Continuous-Flow**

Nitro alkenes are one of the most important, versatile, and frequently used intermediates in organic synthesis. In the first step, I investigated the effect of flow rates and concentrations on productivity and yield using nitro methane and benzaldehyde as substrates using amine functionalized silica with  $\text{CaCl}_2$  as catalyst under continuous-flow conditions. The reactions were performed with various flow rates between 0.05 to 1.0 mL/min at 0.1 M concentration. With 0.05 ml/min flow rate, the yield was kept >90% to supply 36 mmol of nitromethane. The yield was kept with 0.1 ml/min flow rate, resulting the increase of productivity by double. However, further increase of flow rate from 0.25 to 1.0 ml/min resulted in decrease of the yield. Next, concentrations were changed between 0.1 M to 1.0 M with 0.05 ml/min flow rate. Surprisingly, the yield was maintained >90% even with 1.0 M concentration, resulting in the increase of productivity by 10 times. These results clearly indicated that longer residence time was the key to achieve high productivity. Under optimized reaction conditions, scope of aldehyde

was examined. With 5 kinds of aromatic aldehydes, the yield was kept >80% to supply ~150 mmol of substrates. For the second step, I investigated various types of acid-base heterogeneous catalysts such as metal oxides, surface functionalized SiO<sub>2</sub>, and polystyrene immobilized catalysts. Metal oxides worked as heterogeneous base catalysts, and promoted 1,4-addition of benzyl amine and 1,3-ketoester under continuous-flow conditions. During investigation, I found that fresh preparation of catalysts was the key to achieve >80% yield and >48 h lifetime. DMAP immobilized silica was employed as heterogeneous Lewis base catalyst for Morita-Baylis-Hillman reaction. Although the catalyst was effective under single continuous-flow conditions, the catalyst deactivation was observed after 6 h when combined in the first nitro olefin synthesis. Such deactivation problem was solved by changing the dehydrating agent in the first column from CaCl<sub>2</sub> to MS 4A, indicating that the deactivation was caused by leached Ca species. Finally, I could synthesize 7 kinds of nitro-containing compounds in 2 steps under continuous-flow conditions without any workup and purification. (**Scheme 1**).

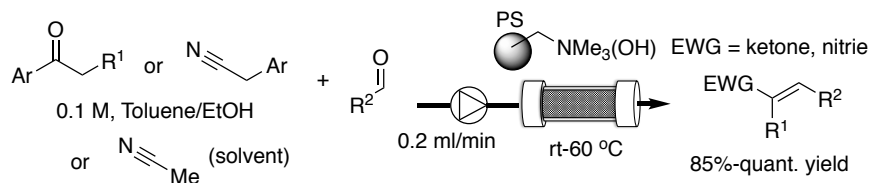


Scheme 1. 2-step synthesis of nitro-containing compounds

## 2. Anion Exchange Resins as Catalysts for Direct Aldol-type Reactions

To establish a general method of aldol condensations under continuous-flow conditions, I started the investigation of heterogeneous base catalysts. As a model reaction,  $\alpha$ -tetralone and benzaldehyde were used as substrates and various heterogeneous catalysts were evaluated under batch conditions. Amine-functionalized silica catalysts did not give any product, although they were effective for nitro alkene synthesis. Common solid bases such as metal oxides, hydrotalcite, and KF/Al<sub>2</sub>O<sub>3</sub> resulted in low conversion and yield presumably due to low basicity and deactivation by generated water. On the other hand, basic resin having ammonium hydroxide afforded the desired  $\alpha,\beta$ -unsaturated ketone in 90% yield. Because physical properties of these resins differ significantly depending on solvent, I decided to investigate the effect of solvent to catalyst activity. As a result, EtOH and Toluene gave superior results compared with THF. However, no conversion was observed using EtOAc or DCM as solvent. Although the origin of the solvent effect was still unclear, swelling of resins seemed to be the one key factor to achieve high catalyst activity. Interestingly, the aldol product could be obtained in >99% chemoselectivity by decreasing reaction temperature from rt to -40 °C using the same catalyst in moderate yield. The catalyst efficiently worked even under continuous-flow conditions to obtain the desired  $\alpha,\beta$ -unsaturated compounds in >80% yield with >99% selectivity for >48

h. Throughout the investigation of substrate scope, the catalyst was found to be effective for other kinds of nucleophiles such as benzyl nitriles, and even acetonitrile could be employed as nucleophile when using a solvent amount.



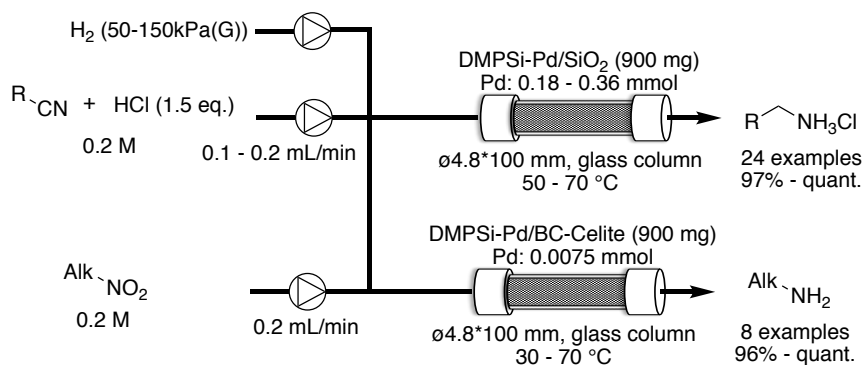
Scheme 2. Aldol-type reactions using basic resin catalysts

Interestingly, similar solvent effect was observed for other nucleophiles (**Scheme 2**).

## 3. Polysilane-Supported Pd Catalysts for Continuous-flow Hydrogenations

Previously, our laboratory reported polysilane-supported Pd/Al<sub>2</sub>O<sub>3</sub> catalysts for hydrogenation of alkenes and alkynes under continuous-flow conditions. I thought that changing support materials would affect property of the catalysts and could be applicable for hydrogenation of nitriles. I prepared polysilane-supported Pd catalysts with different inorganic supports, and evaluated using decanenitrile as a model substrate under continuous-flow conditions. Using Al<sub>2</sub>O<sub>3</sub> as support, the reaction proceeded to achieve 70% conversion under 1.5 bar of H<sub>2</sub>.

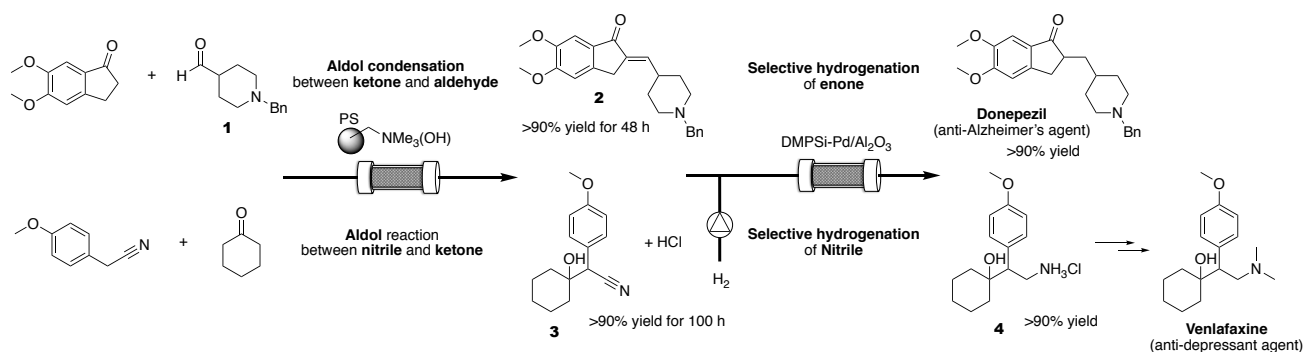
However, secondary amine was obtained as a side product. It was found that addition of 1.5 eq. of HCl improved conversion to 76% and selectivity to 96%. On the other hand, 100% selectivity was achieved using SiO<sub>2</sub> as catalyst support, although lower conversion was observed. By increasing the amount of catalyst and reaction temperature, >99% selectivity was maintained to achieve 89% yield. On the other hand, the selectivity was affected by concentration of substrate. When the concentration was decreased from 0.2 M to 0.1 M, selectivity was decreased to 89%. Decreasing the flow rate from 0.1 ml/min to 0.05 ml/min diminished selectivity to 88% as well. These results indicate that high concentration and short residence time are the key to prevent a non-catalyzed undesired side reaction. Very interestingly, when the reaction was performed under batch conditions, a complex mixture was obtained in low conversion. This result clearly indicates the advantage and uniqueness of the continuous-flow method. This method could be applicable for various kinds of aromatic, hetero aromatic and aliphatic nitriles. This catalyst kept its activity even after 120 h continuous-flow reaction and no Pd leaching was detected in the resulting solution. I also investigated the support effect in the hydrogenation of aliphatic nitro compounds. For this reaction, Bone charcoal was found to be an optimal support to give the desired compounds in excellent yields with selectivities. The catalyst could be applicable for various kinds of aliphatic nitro compounds including secondary and tertiary nitro compounds. In conclusion, I developed general methods to prepare primary amines from easily available starting materials under continuous-flow conditions (Scheme 3).



Scheme 3. Selective hydrogenations of nitriles and nitro compounds to primary amines

#### 4. Aldol-Type Reactions and Hydrogenations Mediated Continuous-Flow Synthesis of APIs

Next, I synthesized APIs and their intermediates under continuous-flow conditions. Donepezil and Venlafaxine were chosen as target compounds. I hypothesized that both molecules could be synthesized following common strategy using aldol reaction and hydrogenation. In the first step, two kinds of aldol-type reactions were investigated. For the Donepezil synthesis, the aldol condensation between indanone and aldehyde **1** was studied in detail. I found that addition of an alcohol as a second solvent was the key to achieve high activity with long lifetime. Under optimized reaction conditions, the unsaturated compound (**2**) was obtained in >90% yield for >48 h. On the other hand, the aldol reaction between benzyl nitrile and cyclohexanone was performed for the synthesis of Venlafaxine. Although there are several possible undesired side reactions such as dehydration and self-aldol reactions of the ketone, I found that precise control of temperature enabled to achieve both high yield and selectivity. Finally, the desired alcohol (**3**) was obtained in >90% yield for >100 h. In the second-step, selective hydrogenations of the enone **2** and nitrile **3** were studied. For the enone hydrogenation, de-benzylation was a major issue in the initial trial. I investigated several polysilane-Pd catalysts and found that the desired compound was obtained in excellent conversion with excellent selectivity for >50 h using Al<sub>2</sub>O<sub>3</sub> as support. Interestingly, undesired side reactions were significantly suppressed by performing the reaction under continuous-flow conditions. Finally, I performed the 2-step continuous-flow reaction and Donepezil was synthesized in excellent yield without any workup process. Al<sub>2</sub>O<sub>3</sub>-supported polysilane-Pd catalyst was also effective for the hydrogenation of nitrile **3** to amine HCl salt **4**. The desired compound was obtained in excellent yield without formation of a secondary amine. Following methylation of **4** under batch conditions gave Venlafaxine in excellent yield (Scheme 4).



Scheme 4. Continuous-flow synthesis of Donepezil and Venlafaxine

## Conclusion

In my Ph.D. study, I mainly focused on heterogeneously catalyzed C-C bond formation and hydrogenation under continuous-flow conditions. As for aldol-type reactions, I found that basic resin having ammonium hydroxide effectively catalyzed aldol condensations for broad range of nucleophiles. On the other hand, I have developed polysilane-supported Pd catalysts for hydrogenation of nitriles and nitro compounds under continuous-flow conditions. I found that inorganic supports affected both activity and selectivity significantly. The catalysts developed in this study were robust, active and have long lifetime. I also found the unique activity of the catalyst under continuous-flow conditions. Finally, Two kinds of APIs were synthesized under continuous-flow conditions using methods developed in this study.