学位論文(要約)

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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Abstract

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

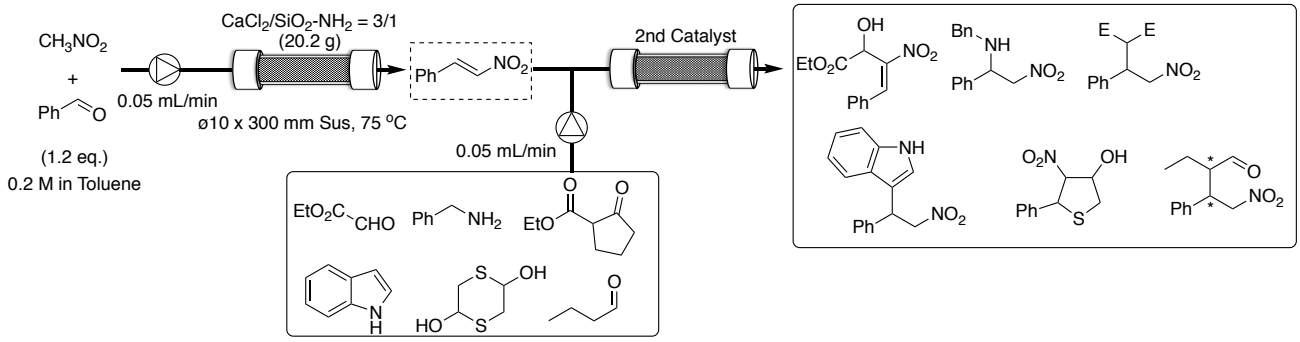
Introduction

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 $CaCl_2$ 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_2, 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 flesh 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 $CaCl_2$ 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**).



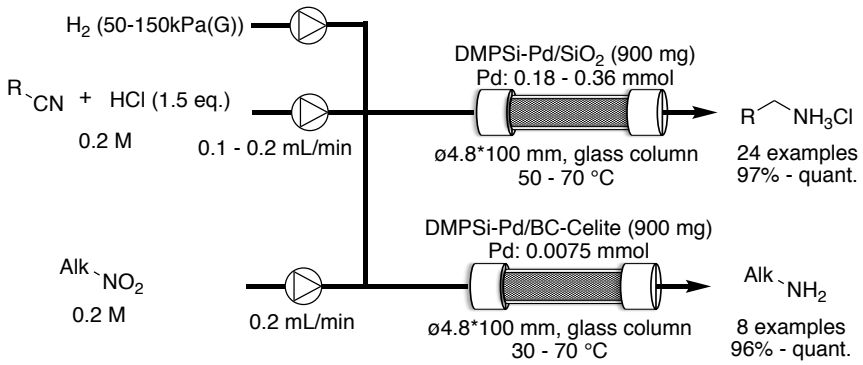
Scheme 1. 2-step synthesis of nitro-containing compounds

2.

本章については、5 年以内に雑誌等で刊行予定のため、非公開。

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

Previously, our laboratory reported polysilane-supported Pd/Al_2O_3 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_2O_3 as support, the reaction proceeded to achieve 70% conversion under 1.5 bar of H_2. 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_2 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.

本章については、5 年以内に雑誌等で刊行予定のため、非公開。

Conclusion

In my Ph.D. study, I mainly focused on heterogeneously catalyzed C-C bond formation and hydrogenation under continuous-flow conditions. 第二章の結論については、5 年以内に雑誌等で刊行予定のため、非公開。. 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.

Acknowledgement

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Table of Contents

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

Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
Alk	alkyl
Ar	aryl
API	active pharmaceutical ingredient
BC	bone charcoal
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DIEA	diisopropyl ethylamine
DMAP	N,N-dimethylamino pyridine
DMPSi	dimethylpolysilane
DMSO	dimethyl sulfoxide
dr	diastereomer ratio
EDS	energy dispersive X-ray spectrometry
ee	enantio excess
Et	ethyl
HT	hydrotalcite
HWE	Honer-Wadsworth-Emmons
i	iso
MBH	Morita-Baylis-Hillman
Me	methyl
Mes	mesityl
MS	molecular sieves
NP	nanoparticle
PDADMA	polydiallyl dimethyl ammonium
Ph	phenyl
PhMePSi	phenylmethylpolysilane
PMP	*para*-methoxy phenyl
Pr	propyl
PS	polystyrene
rt	room temperature
sc	supercritical
TBA	tetrabutyl ammonium
THF	tetrahydrofurane
TMS	tetramethylsilane

Tol	toluene
TON	turnover number
TOF	turnover frequency
Ts	tosyl
WHSV	Weight hourly space velocity

CHAPTER 1
Introduction and strategy

1-1. Continuous-flow synthesis

We, synthetic chemists, deeply rely on flasks as reaction environments. They have been used since the era of alchemy and most of the modern organic synthesis are still performed using conventional glassware. Such a manufacturing method is called as batch synthesis, where reagents, reactants, catalysts, and solvent are charged in a reaction vessel at once to perform target organic transformations. Because it is reliable and is a well-established method from a laboratory to industry, almost all fine chemicals such as active pharmaceutical ingredients (APIs), agrochemicals, and functional organic materials are synthesized by repeating this method. However, this method has several drawbacks, especially for the mass production.

At first, scaling up of a batch reaction is not always as simple as expected. Large-scale reactions quite often suffer from the limited heat and mass transfer during the reactions. It would cause poor reproducibility of the results in small-scale reactions and increase the risk of a chemical accident for exothermic reactions. Especially, for large-scale reactions, one chemical accident causes serious damages to our society and nature. That is why industry spends much time, costs, and efforts to establish large-scale synthesis. Second, there remained much room to be improved for efficiency. For the synthesis of complex molecules, multistep transformations are generally required. With batch synthesis, workup and purification are usually performed in every single step, which generates a large amount of waste (**Figure 1-1-1**). Indeed, E-factor, which is defined as an amount of waste divided amount of a product, for fine chemical synthesis is as high as 5 – 100. For these reasons, more efficient and easily scalable system is highly in demand to achieve a green sustainable chemistry.

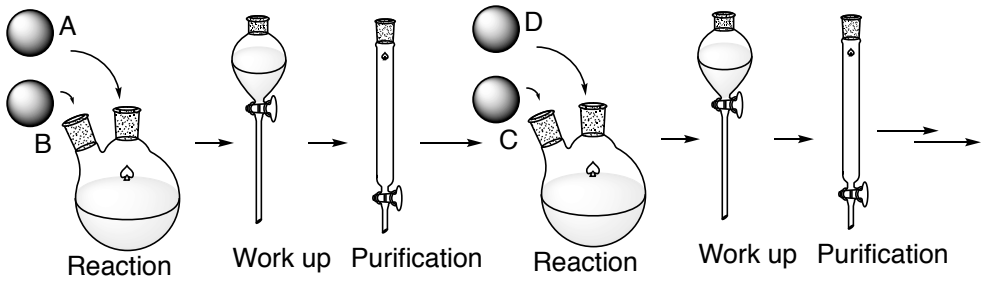


Figure 1-1-1. Multistep synthesis under batch conditions

On the other hand, recently, organic synthesis under continuous-flow conditions has gained much attention as a next generation in synthetic chemistry.[1] In the flow reaction, reagents and reactants are flowed into a column or tube continuously where a reaction

takes place during passing through (**Figure 1-1-2**). As a result, a product can be obtained continuously from the end of a reactor. It should be noted that there is principal difference between batch and flow methods for the definition the reaction time and productivity. For a batch reaction, reaction time corresponds to how long a substrate is exposed to reaction conditions. On the other hand, reaction time under flow conditions corresponds to residence time, which means how long a substrate stays in a reactor. Thus, size of the reactor and flow rate are key factors to determine it. In the same manner, productivity under batch condition is determined by reaction time and concentration, while under flow conditions it is determined by concentration and flow rate. Thus, flow rate, concentration, and size of a reactor are characteristic and important parameters for continuous-flow reactions.

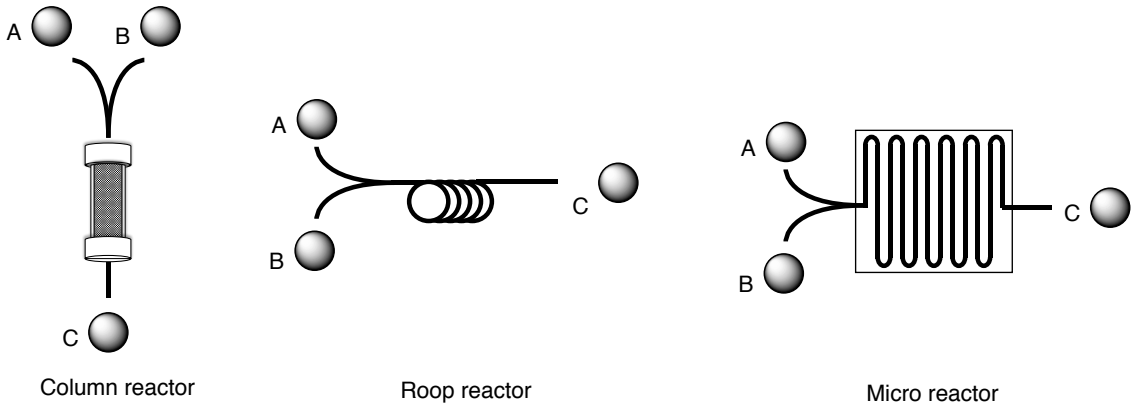


Figure 1-1-2. Continuous-flow reactors

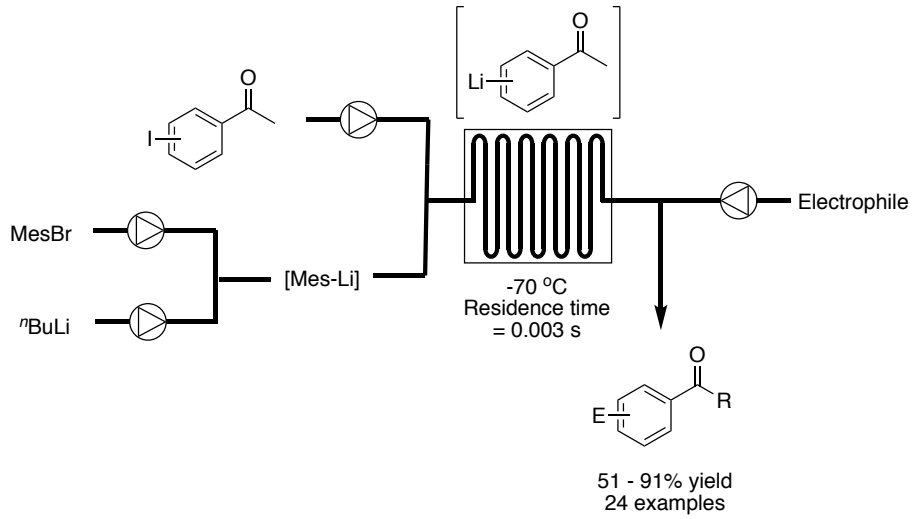
Flow synthesis has several advantages over conventional batch synthesis.[1a, e, i, l-n, 2] First, efficient organic synthesis can be achieved. Because even compact reactors can produce much amount of products by increasing flow rate and extending operation time, much space can be saved. Small reactors can also save energy to control reaction temperature, thanks to an efficient heat transfer. Furthermore, multistep continuous-flow synthesis can be achieved with precise design of synthesis and a reaction system, which can avoid workup and purification after each organic transformation. This point will be discussed in detail later. Second, a system can be easily scaled up. There are several methods to scale up a flow reaction. The most straightforward way is numbering up reactors. Because each reactor needs only small space, several times scaling up is reasonable without loss of its advantageous point. The second method is extending operation time. If enough lifetime of a system is ensured, much amount of compound can be produced within the same space. The third method is to increase flow rate and concentration by increasing column size. Although it may lose the advantage of microflow chemistry, it is the simplest way to improve productivity and a basic investigation in academic research can be directly transferred to an industrial investigation. By combining these methods, flow

synthesis can meet demands for industrial production of fine chemicals. Third, enhanced safety is expected. Thanks to the efficient heat transfer, a risk for a thermal runaway reaction can be significantly decreased. Also, a small reactor can minimize the damage of chemical accident even if it happens.

In an early stage of this field, flow methods were employed for gas phase reactions with heterogeneous catalysts. The most popular system is exhaust emission control in automobiles using three-way-catalyst. Vehicle emissions contain many air pollutants such as hydrocarbons, carbon monoxide, NO_x, and SO_x. Because they are highly toxic and cause serious environmental problems, the emissions from automobiles have to be strictly controlled. Such problematic chemicals can be decomposed by passing through the three-way-catalyst, which consists of Pt, Pd and Rh immobilized on solid support. This system can be considered as one of the continuous-flow reactions. Another famous example is ammonia synthesis by the Harber-Bosch process, where N_2 and H_2 are converted to NH_3 by passing through a heterogeneous Fe catalyst. Several bulk chemicals are also synthesized under continuous-flow conditions. However, until around 10 years ago, a flow method was rarely applied for the synthesis of fine chemicals. Only in recent years, it has gained much attention from both academia and industry, and various kinds of flow synthesis have been developed.

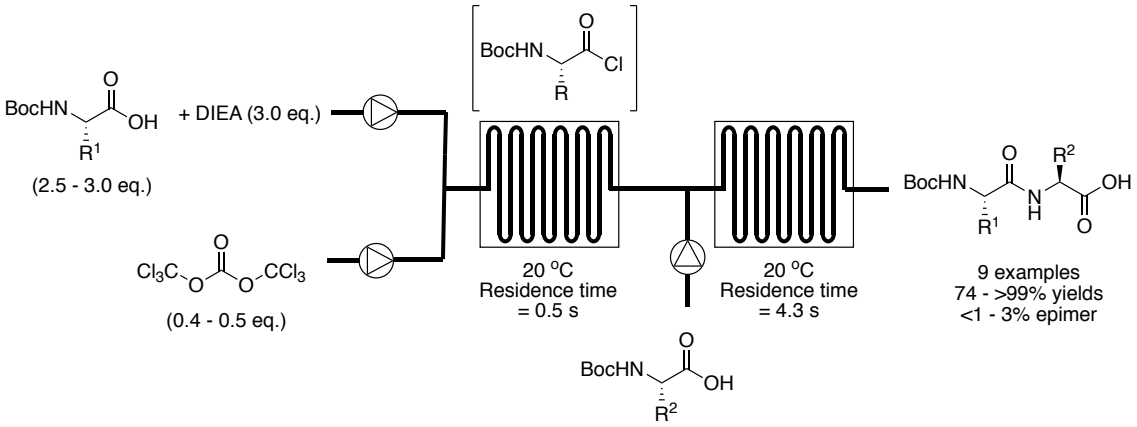
1-2. Four types of flow reactions

There are many examples of continuous-flow synthesis and Prof. S. Kobayashi categorized them into 4 groups.[2] The first group is named as Type I, where solutions of substrates are passed through a reactor and a reaction takes place just by mixing reagents or stimulating the reactor by light or electrolysis. These reactions are generally performed using μm size reactors to take advantage of flow reactions and called as microflow reactions. The main advantage of this type of reactions is the precise and exact control of residence time and reaction temperature. Prof. J. Yoshida is a pioneer in this field. He demonstrated that decomposition of unstable intermediates such as organometallic reagents with a reactive functional group can be suppressed by employing micro flow reactions. As a representative example, they developed a protecting group free synthesis using organolithium reagents (**Scheme 1-2-1**).[3a] In this paper, they generated aryl lithium reagents having carbonyl group under flow conditions. By the precise control of residence time of the halogen-metal exchange, the generated aryl lithium species was immediately reacted with electrophile before the reaction of its carbonyl part. They also applied this strategy for other types of short lifetime intermediates.[3]



Scheme 1-2-1. Protecting group free synthesis using organolithium reagents

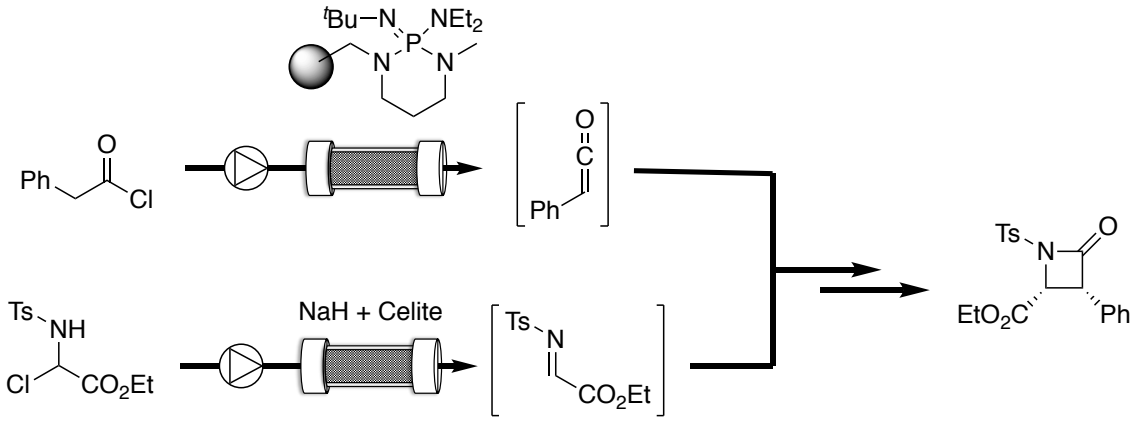
Another representative example is a condensation of amino acids under flow conditions reported by Fuse *et al.* in 2014 (**Scheme 1-2-2**).[4a] They established amide bond formation between amino acids under flow conditions without significant loss of enantiopurity. The key of their success was the use of a strongly activating reagent for the rapid formation of activated amino acids and precise control of residence time to prevent epimerization of activated intermediate. Later, they achieved a total synthesis of a natural peptide by employing this methodology. [4b]



Scheme 1-2-2. Peptide synthesis under flow conditions

Although these methods allow to perform chemical transformations that were impossible under batch conditions, over stoichiometric activated reagents have to be employed. Such reagents generate a significant amount of waste and they are not suitable for multistep sequential-flow synthesis. Another developing area is reactions promoted by external stimuli. The most frequently employed system is photochemical reactions.[5] Thanks to compact reaction environments, an efficient energy transfer is expected described in the Lambert-Beer law. In early examples, the scope was limited to conventional photo-induced reactions such [2+2] cycloadditions and rearrangements. More recently, the scope of reactions has been expanding to photocatalytic reactions and they will be discussed later.

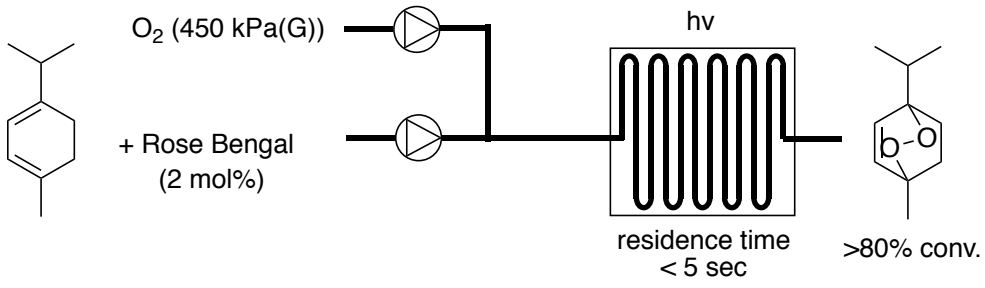
In the second group, one of the reagents is solid or immobilized on solid support and they are packed in a reactor column, which is called as type II flow reaction. With this system, the only product can be eluted, which makes the sequential-flow easier. One of the earliest and successful examples was reported by Lectka *et al.* in 2001 (**Scheme 1-2-3**).[7] They developed polystyrene-immobilized organobase for the formation of ketene from acid chloride under flow conditions. They also developed the flow system for the formation of glyoxyl imine from α-chloro glycine using NaH as a solid reactant. The resulting solutions of these unstable compounds were combined together and further transformations were performed without purification of each compound.



Scheme 1-2-3. PS-Immobilized organobase reagent and NaH + Celite solid base

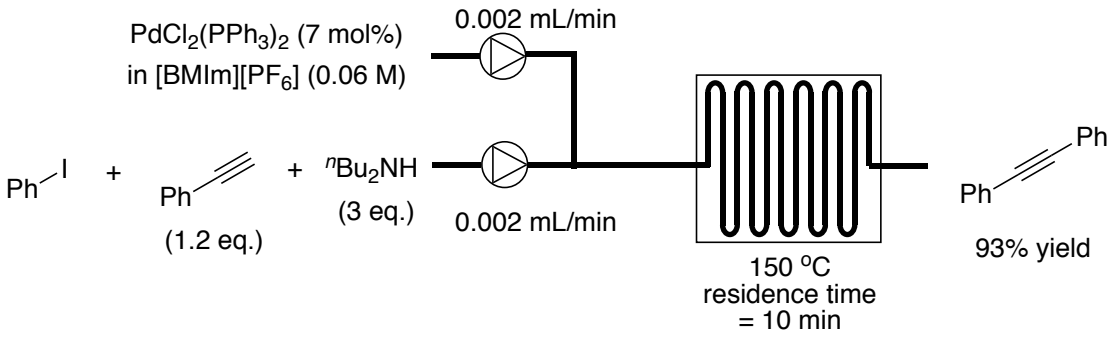
More recently, Prof. S. V. Ley's group have extensively studied this type of reactions and developed various kinds of solid and solid supported reagents for continuous-flow reactions.[1o] However, the major disadvantage of this type of reaction is that the reagent column has to be exchanged when the packed reagent is consumed. This makes it difficult for scale-up of the system and generate a stoichiometric amount of waste after the reaction.

The type III is defined as flow reactions using homogeneous catalysts. Because the residence time in flow reactions is generally much shorter than reaction time in batch reactions, only a few class of homogeneous catalysis has been applied for flow reaction. One of the most studied catalysis in this area is photocatalysis.[5] As described in the type II reaction, the significant advantage of flow photoreaction is the improved irradiation efficiency and photocatalysis also takes such advantage. An early example of flow photocatalysis is a reaction involving generation of singlet oxygen with photosensitizer as a catalyst. Organic dyes such as Rose Bengal and tetraphenylporphyrin were often used as catalysts. One of the first examples of flow reactions using singlet oxygen was developed by Mello *et al.* in 2002 (**Scheme 1-2-4**).[7] They efficiently adsorb light under flow conditions and much short reaction time was achieved for various singlet oxygen-mediated reactions under flow conditions as a result. This concept was further expanded to transition metal photoredox catalysis involving single electron transfer. Ru and Ir complexes are major players in this catalysis. Using these catalysts, several kinds of C–C and C–X bond formations were achieved.[5, 8]



Scheme 1-2-4. Generation of singlet oxygen under flow conditions

Another successful class of the type III reaction is Pd catalyzed cross-coupling reactions. Recent developments of highly active catalysts significantly increased TOF of a catalyst and it reached enough high level to be applicable for flow reactions. One potential problem for cross-coupling reaction is a formation of a stoichiometric amount of salt during the reaction. Because such side products are not soluble in common organic solvents, the solvent system has to be carefully examined to prevent clogging of flow. One of the earliest examples is copper-free flow Sonogashira coupling reaction reported by Ryu *et al.* in 2002 (**Scheme 1-2-5**).[9] The key point of their success is the use of ionic liquid as a solvent. It allowed to perform the catalysis in the absence of copper salt and increase the reaction temperature to 150 °C and dissolved all materials. Suzuki-Miyaura and Buchwald-Hartwig couplings were achieved by S. L. Buchwald *et al.*[10] More recently, Pd catalyzed C-H functionalization was also achieved by M. J. Gaunt *et al.* in 2015.[11] These methodologies expanded the scope of catalytic reactions under flow conditions. However, the significant disadvantage of type III reaction is that catalysts have to be introduced continuously and it is eluted together with a product. This makes it difficult to perform sequential flow reactions and causes the contamination of toxic metal into the final product.



Scheme 1-2-5. Continuous-flow Sonogashira coupling

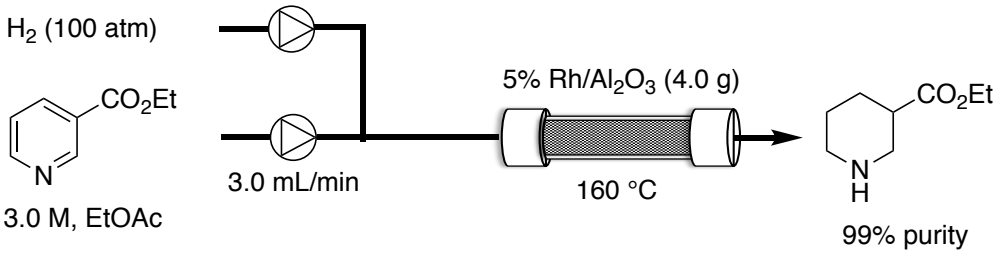
The 4th group, named as type IV, is the flow reactions using heterogeneous catalysts, and it will be discussed in detail in the next section.

1-3. Continuous-flow reactions using heterogeneous catalysts (Type IV)

There are several advantages in the type IV reactions among 4 types of flow reactions. First of all, the formation of problematic byproducts can be minimized because the use of activating reagents can be avoided. Second, contamination of catalysts can be avoided because they can be isolated by simple filtration. Third, a product can be obtained permanently simply by adding substrate continuously once the flow reaction is set, if the decomposition of heterogeneous catalysts is completely suppressed.

Another important and unique aspect of type IV reaction is reaction environments. As for the type III reaction, a molar ratio between catalyst and substrates in the reactor are reproducing the ratio under batch conditions. On the other hand, in the case of the type IV reactions, much amount of catalyst exists inside the reactor because the column is fully packed with heterogeneous catalyst. In some cases, the amount of a catalyst is higher than that of substrates. However, even in such cases, a catalytic process will be achieved because TON will increase with long operation time. This unique feature will allow not only to decrease residence time but also to achieve a unique chemical transformation, which cannot be achieved under batch conditions.

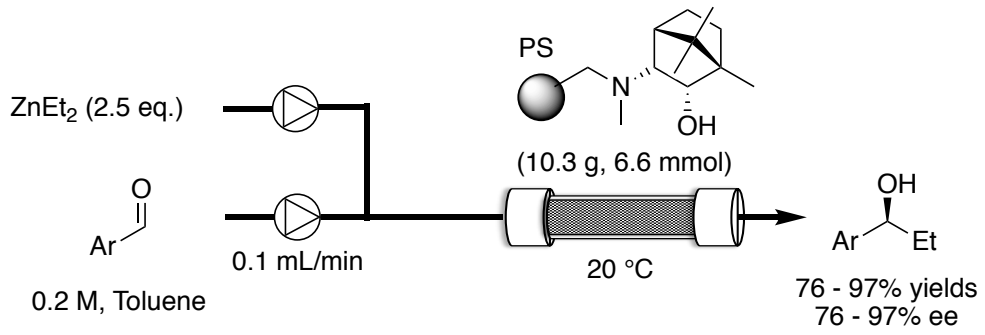
One of the most developed catalysis in this field is flow hydrogenation for several reasons.[12] First of all, hydrogenation is one of the most common organic transformations both in academia and industry. Therefore, flow hydrogenations are highly demanded. Second, various kinds of heterogeneous catalysts for hydrogenation have been developed and some of them are commercially available. Thus, they are easily evaluated under flow conditions. Third, flow reactions have an advantage for solid-liquid-gas triphasic reactions. Thanks to the efficient mixing and large interfacial area, hydrogenation can take place with much efficient mass transfer than that under batch conditions. Taking these advantages, many reports about flow hydrogenation have been published until recently. However, most of them are regarding with easy substrates such as olefins, alkynes, and aromatic nitro compounds. Several research groups developed hydrogenations of more difficult substrates such as carbonyl compounds and heteroaromatics. One of the recent successful examples was reported by S. V. Ley *et al.* in 2014 (**Scheme 1-3-1**).[13] They aimed to develop a flow hydrogenation system that can produce over a kg of product per a day in a research laboratory environment. The hydrogenation of ethyl nicotinate was chosen as a model reaction, and various catalysts and flow parameters were carefully examined. Under optimized reaction conditions, the target compound was obtained in excellent yield with 1959 gd^{-1} productivity although high reaction temperature and H_2 pressure were required. This report demonstrated the potential of flow hydrogenation for scaling up to meet industrial demand using a benchtop reactor.



Scheme 1-3-1. Flow hydrogenation of ethyl nicotinate

However, most of the reported examples employed commercially available catalysts, and there remained much chance to develop more efficient heterogeneous catalysts for flow hydrogenations.

Another mainstream is immobilization of ligands for transition metal catalysts and immobilization of organocatalysts, especially for asymmetric catalysis. Because such organic compounds can be relatively easily modified, they are immobilized on solid materials such as polystyrene and SiO_2 by covalent bonds. As for immobilization of chiral ligands, one of the earliest examples was reported by Hodge *et al.* in 1999.[14] They immobilized chiral amino alcohol onto polystyrene, and employed it for asymmetric addition of organozinc reagents under flow conditions. At an initial stage, the target compound was obtained in excellent yield and enantioselectivity. However, catalyst decomposition was observed after 275 h.

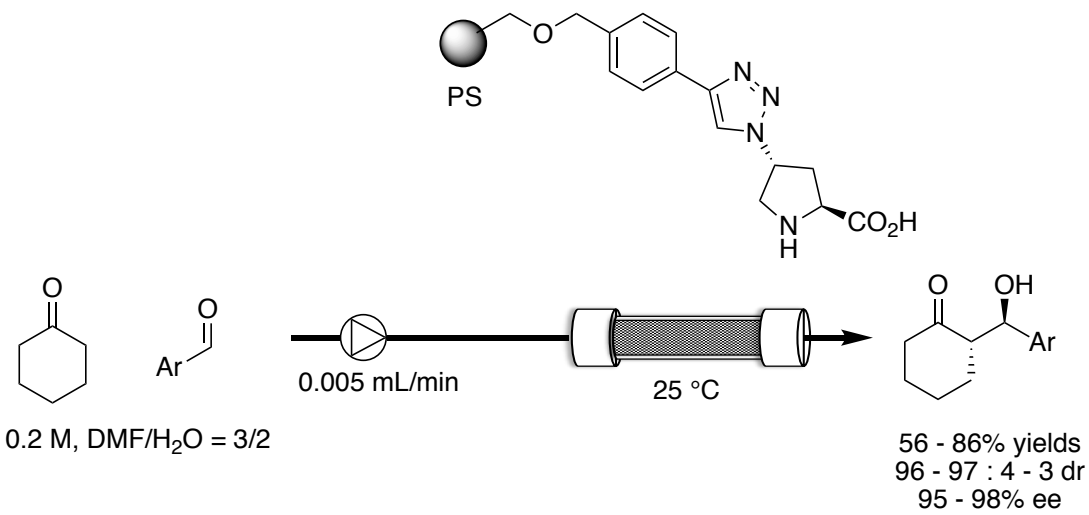


Scheme 1-3-2. Asymmetric diethylzinc addition under flow conditions

Since then several kinds of heterogeneous catalysts have been employed for asymmetric catalysis such as transfer hydrogenation, cyanidation, ene reaction, Michael addition, kinetic resolution of epoxide, and cycloaddition.[15] In most cases, excellent yields and comparable selectivities as batch conditions were achieved.

Similarly, chiral organocatalysts such as proline-based catalysts and cinchona alkaloid were immobilized on polystyrene and employed for flow reactions. One of the first examples of organocatalytic asymmetric aldol reaction under flow conditions were developed by Pericas *et al.* in 2012 (**Scheme 1-3-3**).[16] They immobilized proline moiety by Huisgen cyclization between polystyrene immobilized terminal alkyne and azide

substituted proline. The obtained heterogeneous catalysts showed excellent selectivity under flow conditions.[15b, 17]



Scheme 1-3-3. Asymmetric aldol reaction under flow conditions

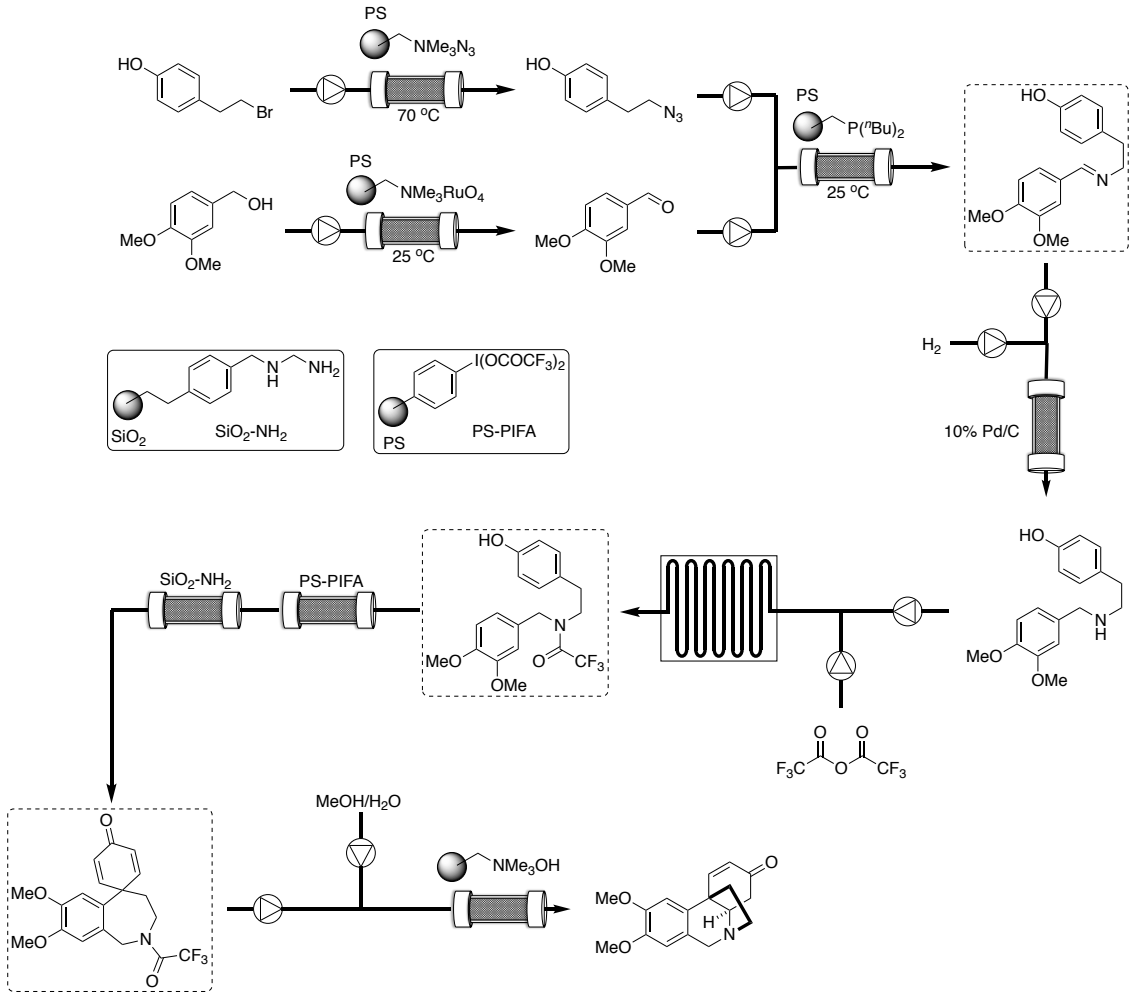
Other types of organocatalysis such as Michael additions and Diels-Alder reactions were also investigated.

These examples have provided efficient synthetic methods under flow conditions and demonstrated the potential application of type IV reactions for fine chemical synthesis. However, an application of these reactions for multistep flow synthesis is still limited.

1-4. Multistep continuous-flow synthesis of fine chemicals

As discussed in the first section, multistep synthesis of fine chemicals in large scale has been one of the big goals and challenges in flow chemistry. Although single flow reactions have been developed, there are limited examples for the application of them for fine chemical synthesis under sequential flow conditions. Obviously, there is a serious problem to connect two flow reactions. Especially, using type I or type III reactions, the resulting solution contains stoichiometric amounts of byproducts or homogeneous catalysts as well as desired products. Additionally, if the reaction was not efficient, it may contain remaining starting materials or side products for all types of flow reactions. Furthermore, if an excess amount of one reagent was used, an unreacted compound will be also contaminated. Because such impurities generally have a bad effect on the following reactions, in-line purification is required to achieve sequential flow reactions. Indeed, such in-line purification methods have been developed such as in-line liquid-liquid separation, evaporation, and scavenger columns.

One of the earliest successful examples was a total synthesis of Oxomaritidine reported by S. V. Ley *et al.* in 2006 (**Scheme 1-4-1**).[18] In the first step, alkyl azide was prepared from alkyl bromide by a nucleophilic substitution reaction with polystyrene immobilized ammonium azide. At the same time, aliphatic alcohol was oxidized by Ley-Griffith oxidation using a stoichiometric amount of Ru immobilized on polystyrene. These products were coupled by Staudinger reaction using a polystyrene immobilized phosphine reagent. The generated imine was hydrogenated to a secondary amine by Pd/C as catalyst without any purification. At this stage, a solvent switch was performed. After protection of the amine, an acidic side product was trapped by passing through amine-functionalized silica. Then, oxidative cyclization was performed using polystyrene supported hypervalent iodide. Final deprotection gave the target compound in good yields. Totally, one type I reaction, five type II reactions, and one type IV reaction were involved in the whole synthesis. The synthesis required no column chromatography or aqueous work up.



Scheme 1-4-1. Total synthesis of rac-Oxomaritidine

From the pioneering work by S. V. Ley, the number of examples of fine chemical synthesis under flow conditions increased especially in these 10 years especially using type I and II reactions (**Figure 1-4-1**).[19] However, there are only few examples of type III and IV reactions for the synthesis of complex molecules although they have a potential to decrease the amount of waste. Instead, in-line extraction and scavenger columns were employed to remove excess reagents and byproducts in some cases.

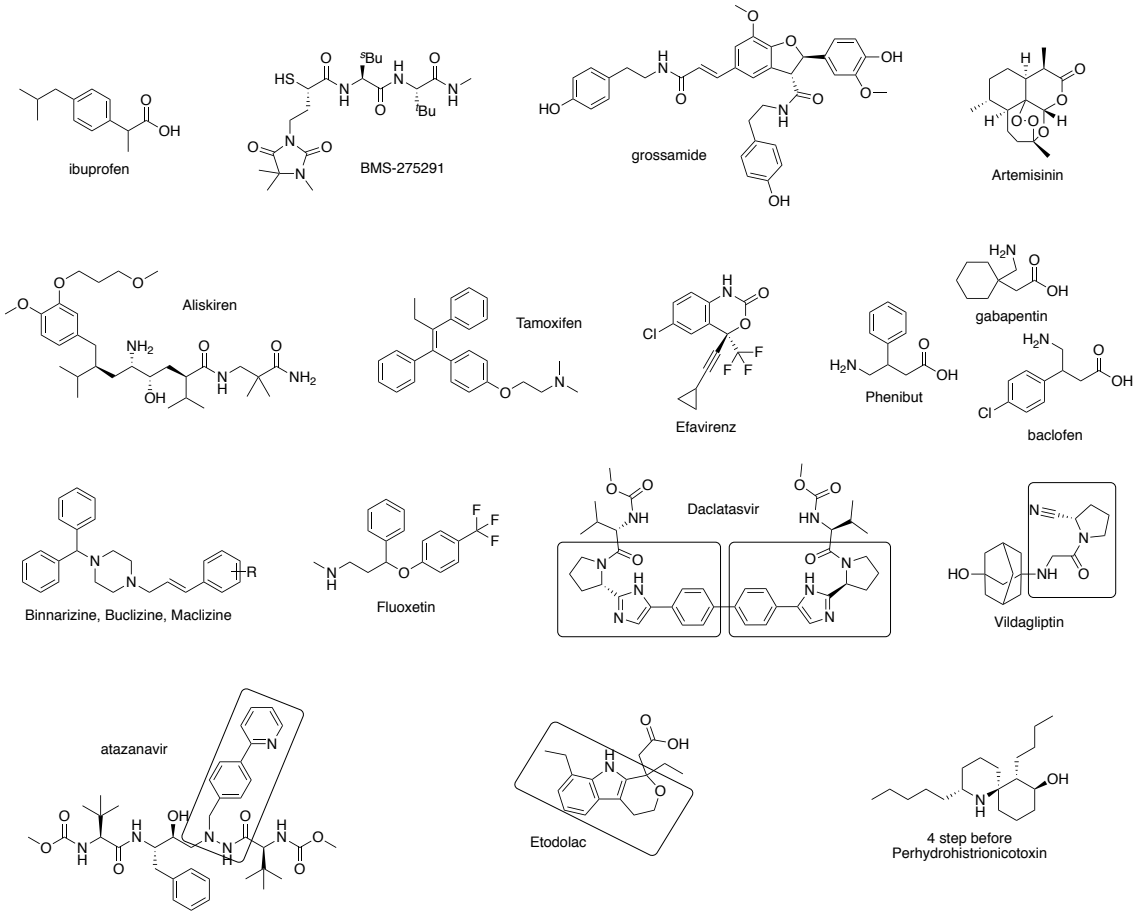
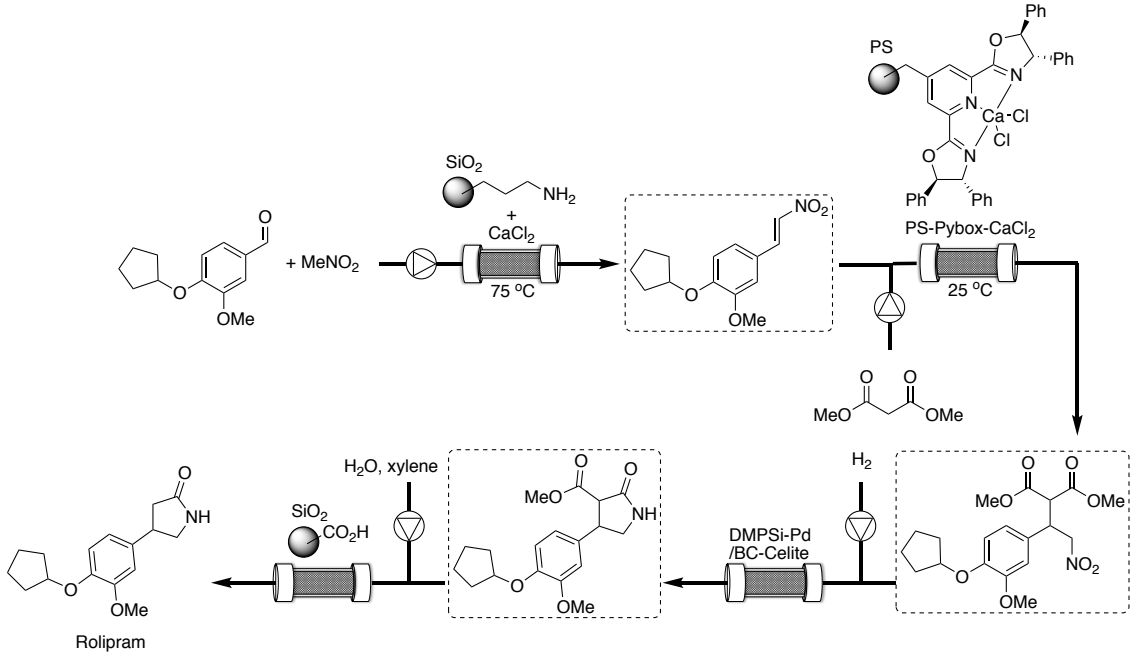


Figure 1-4-1. Fine chemicals synthesized through multistep flow reactions

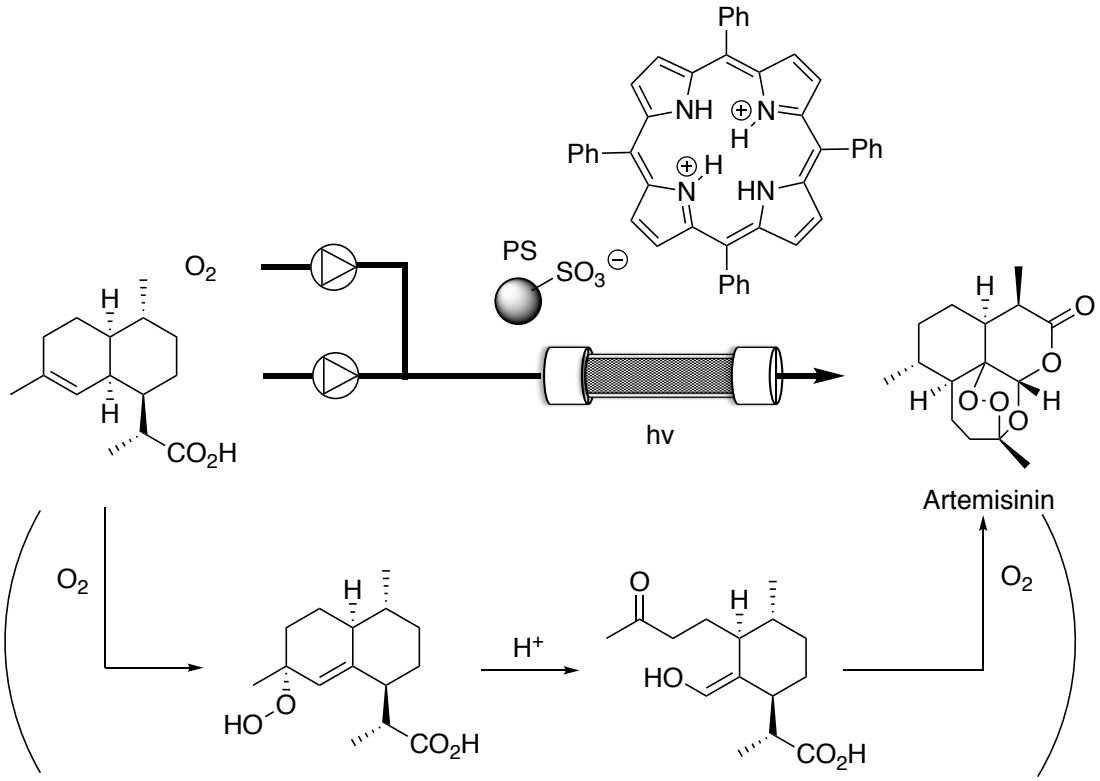
However, these kinds of purification are not always successful, and thus purification under batch conditions are required in most cases, which lose several advantages of flow reaction. Even if in-line purification is successful, it would cost additional energy, produce wastes, and decrease efficiency of the systems. Therefore, such purification protocols should be avoided as much as possible. In such context, development of multistep synthesis using type IV reactions is a promising way to go. It has been considered as extremely challenging. However, in 2015, our laboratory developed the asymmetric total synthesis of chiral Rolipram under multistep continuous flow reactions using only type IV reactions (**Scheme 1-4-2**).[20] In the first step, nitro olefin was synthesized from an aldehyde and nitromethane using amine-functionalized SiO_2 as a catalyst. Next, asymmetric 1,4-addition of malonate to a nitroolefin was performed with polystyrene immobilized Pybox-Ca catalyst. The generated nitroalkane was hydrogenated to a primary amine using supported Pd catalyst. The following intermolecular cyclization gave a lactam compound. Finally, hydrolysis and decarboxylation took place using a SiO_2 supported carboxylic acid catalyst to afford the target compound in excellent yield and selectivity. The whole synthesis involved 6 step

comical transformations using all type IV reactions. No in-line workup and purification were required, and the catalyst remained active at least for one week. The key of success was the design of synthetic route and detailed investigations of each step to minimize the equivalent of each reagent and to avoid the formation of problematic byproducts and side products.



Scheme 1-4-2. Total synthesis of chiral Rolipram using type IV reactions

Another example is the synthesis of Artemisinin reported by K. Rossan, M. Poliakoff, and M. W. George *et al.* in 2015 (**Scheme 1-4-3**).[21] Although this is a single flow reaction, three-step transformations were performed using a bifunctional heterogeneous catalyst. First, photosensitizer immobilized on polystyrene by ionic interaction generate singlet oxygen to perform allylic oxidation under irradiation of light. Generated hydroperoxide underwent an acid catalyzed ring opening process to form an enol. Finally, it reacted another oxygen to give target Artemisinin in good yield.



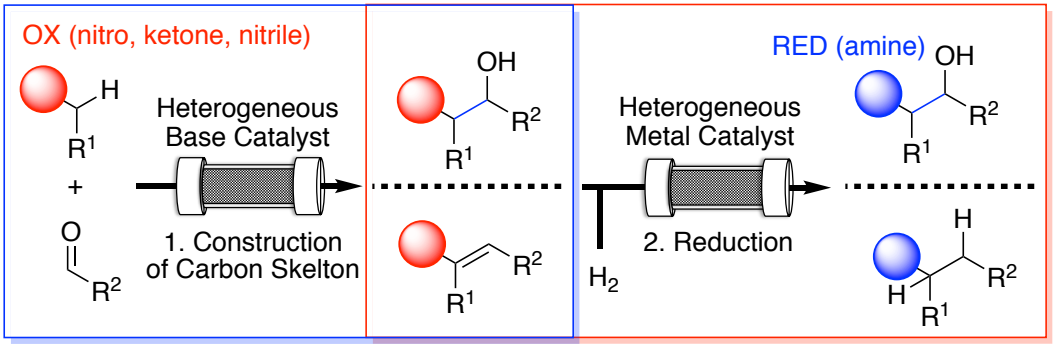
Scheme 1-4-3. Total synthesis of Artemisinin using type IV reactions

These examples are the proof of the concept of multistep flow synthesis of fine chemicals using only type IV flow reactions. However, examples were still very limited, and scope of catalytic reactions has to be expanded for future development in this field. Thus, first I rationalized key factors and proposed a general strategy to expand the applicability for other types of complex molecules.

1-5. Aldol-hydrogenation strategy

To establish the multistep synthesis of fine chemicals using type IV reactions, there are several important points for the design of the whole synthesis. First, use of organometallic reagents such as alkylzinc and boronic acid should be avoided. Although such reagents are frequently employed for asymmetric catalysis and transition metal catalysis, they generate stoichiometric amounts of metal salts as byproducts, and other heterogeneous catalysts are sometimes not compatible with such wastes. Similarly, use of silyl reagents and phosphine reagents such as silyl enol ethers and HWE ester should be avoided as well. Instead, catalysis with excellent atom economy is strongly preferred. Interestingly, this concept exactly matches with that of green sustainable chemistry.

To satisfy these requirements, I propose the aldol-hydrogenation strategy (**Scheme 1-5-1**). In this strategy, the carbon skeleton of a target molecule is constructed at first. For the C–C bond forming step, direct aldol-type reactions are chosen because this type of reactions proceed with 100% atom economy or generate 1 equivalent of water as a sole byproduct. Of course, simple amines or alcohols cannot be employed as substrates for this reaction because of low acidity and functional group tolerance of substrates, thus substrate scope seems to be limited. However, their oxidized form such as ketones and nitriles has relatively acidic proton at α-position and there is a chance to perform direct aldol-type reactions in a catalytic manner. The second step in my strategy is to convert functional group with high oxidation states to that with low oxidation states. In this functional group interconversion, hydrogenation is an ideal method because excellent atom economy and no byproduct formation are expected. Another advantage of this method is that C=C double bond generated by the first aldol condensation can be reduced to C–C single bond. As a result, this two-steps protocol can be considered as α-alkylation under flow conditions. It will provide a much more efficient method than conventional alkylation which employs stoichiometric amounts of strong bases and alkyl halides.



Scheme 1-5-1. Aldol-hydrogenation strategy

As described previously, each reaction has to be carefully optimized not only to achieve high yield and selectivity but also to minimize the equivalence of reagents. This is

because catalysts in the next step may get deactivated by remaining substrates in the first reaction. To achieve such reactions, development of efficient heterogeneous catalysts should be the key.

Based on this strategy, I developed two types of flow reactions using heterogeneous catalysts, and applied them for the synthesis of two kinds of APIs. In chapter 2, I examined the potential of simple and conventional heterogeneous catalysts for multistep flow reactions. In chapter 3, I developed heterogeneous Pd catalysts for the hydrogenation of functional groups in high oxidation states such as nitriles, imines, and ketones under flow conditions. In chapter 4, I developed heterogeneous base catalyzed aldol-type reactions. Finally, 2 kinds of APIs were synthesized by connecting 2 flow reactions developed in this study in the final chapter.

1-6. References

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CHAPTER 2

Synthesis of Nitro-containing Compounds through Multistep Continuous-flow with Heterogeneous Catalysts

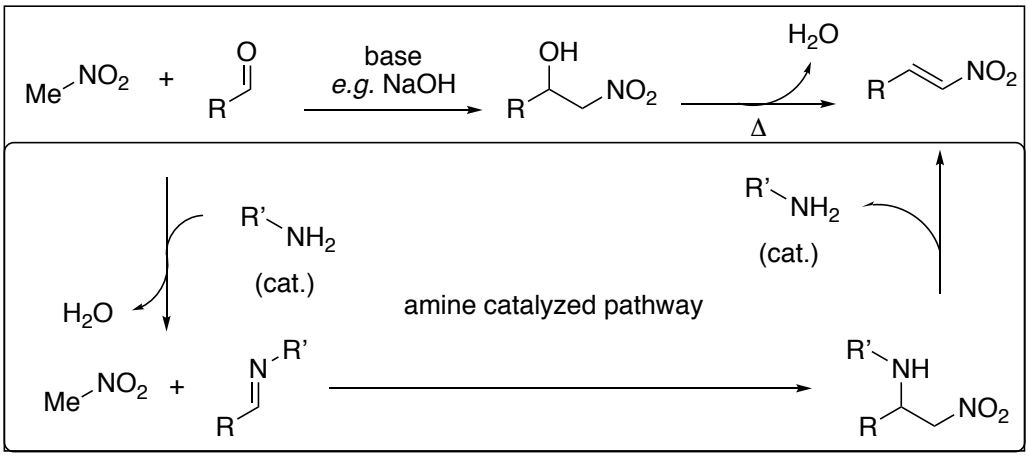
2-1. Background

Nitroalkene synthesis

Nitroalkenes are one of the most important, versatile, and frequently used intermediates in organic synthesis. Because of their strong electrophilicity, they can be readily employed in various kinds of pericyclic reactions and nucleophilic conjugate additions.[1] Nitro group can also be converted into useful functional groups such as primary amine by reduction or carbonyl group by Nef reaction.[2,3]

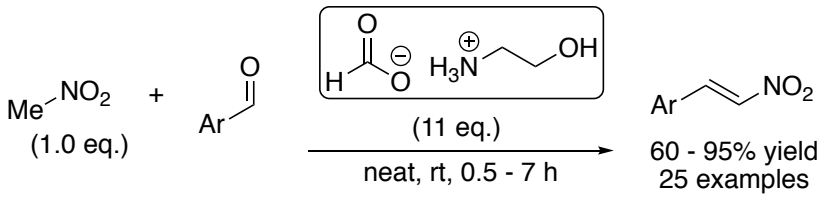
Among several methods to access these attractive compounds, a two-step protocol through nitroaldol (Henry) reaction followed by dehydration of resulting β-nitro alcohol is the most common and efficient method from the viewpoint of atom economy and availability of substrates. However, the present methods still suffer from several drawbacks such as excess reagents and harsh reaction conditions, especially in the second dehydration step. Conventionally, they are prepared from the reaction between an aldehyde and an excess amount of nitromethane in the presence of a large excess amount of NaOH and HCl.[4a] Improved reaction systems were developed by employing activation by microwave and ultrasound. Varma *et al* developed microwave-assisted nitroalkene synthesis in 1997. Under their reaction conditions, the amount of nitromethane was decreased to almost 1 equivalent to aldehyde, and various nitro alkenes were prepared in the presence of catalytic amount of ammonium acetate within 8 min.[4b] Within the same context, ultrasound promoted nitro alkene synthesis were reported by McNulty *et al* in 1998. They could decrease the amount of nitromethane to 1.5 equivalent to aldehyde and reactions could be performed at room temperature.[4c] However, these methods cannot be applied for large-scale synthesis due to the limitation of reaction systems.

To overcome these problems, several kinds of primary and secondary amine catalysts have been developed. With these catalysts, the reaction proceeds via imine formation, aza-Henry reaction, and followed by deamination, which enables the reaction conditions milder (**Scheme 2-1-1**).



Scheme 2-1-1. Amine catalyzed nitro alkene synthesis

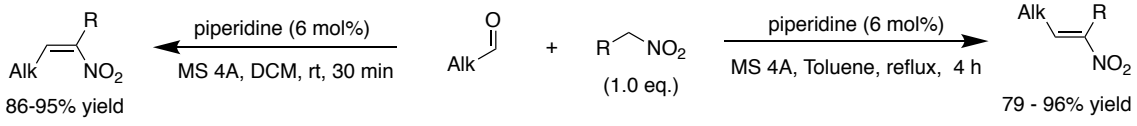
It should be noticed that immobilized amine catalysts show higher activity than homogeneous amine catalysts for this type of reaction. As a recent and representative example of homogeneous catalyst, Alizadeh and Khodaei *et al.* reported that primary ammonium formate can be used as a catalyst for reactions between various kinds of aliphatic aldehydes and nitromethane (**Scheme 2-1-2**).[5]



Scheme 2-1-2. Ammonium formate mediated nitro alkene synthesis

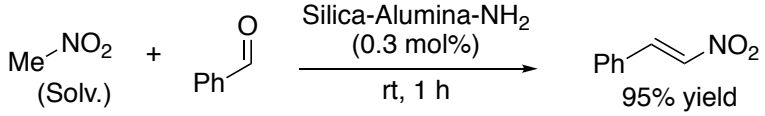
The target compounds could be obtained in high yields and selectivities. However, this method required over stoichiometric amount of catalyst although it could be recovered after the reaction.

Another interesting homogeneous catalyst system was reported by Fioravanti *et al.* in 2008. They found that simple piperidine mixed with MS 4A efficiently catalyzed the nitroalkene formation in excellent yield and selectivity. Furthermore, they could selectively synthesize (*E*)- and (*Z*)- alkene selectively by modifying reaction conditions. However, their protocol was applicable for only aliphatic aldehydes (**Scheme 2-1-3**).[6]



Scheme 2-1-3. Piperidine catalyzed nitro alkene synthesis

On the other hand, amorphous silica-alumina functionalized primary amine catalyst developed by Iwasawa *et al.* in 2007 is one of the most efficient heterogeneous catalysts ever reported (**Scheme 2-1-4**).[7]

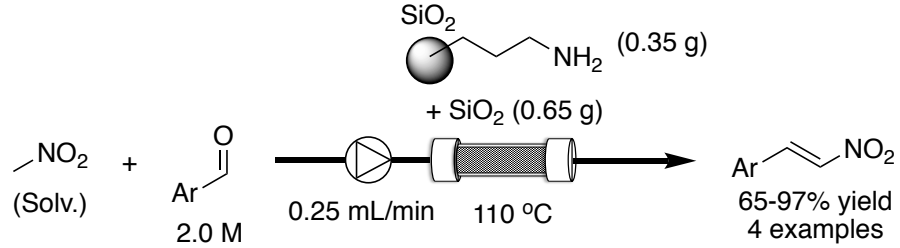


Scheme 2-1-4. Amine functionalized silica-alumina catalyzed nitrostyrene synthesis

The reaction took place even in the presence of 0.3 mol% of catalyst to give the desired compound in 99% yield, although a solvent amount of nitromethane was used. The outstanding high activity was explained as a result of cooperative catalysis between solid acid and functionalized amine.

Other research groups have developed heterogeneous primary amine catalysts immobilized on different supports such as mesoporous silica,[8,9] clay,[10] and hydrotalcite.[11] But all of them required an excess amount of nitromethane and the more efficient reaction system was highly demanded.

Considering the fact that nitromethane is an explosive chemical, a continuous-flow reaction is a promising method to decrease the risk of chemical accidents. There is one example of continuous-flow nitro alkene synthesis over heterogeneous amine catalyst. Satori *et al.* employed propyl amine-functionalized silica catalyst under continuous flow conditions for the reaction between benzaldehyde and nitromethane (**Scheme 2-1-5**).[12]



Scheme 2-1-5. Amine functionalized silica catalyst under continuous-flow conditions

The β-nitrostyrene was obtained in excellent yield with excellent selectivity. However, this method requires high reaction temperature and solvent amount of nitromethane. Therefore, an excess amount of nitromethane had to be removed to perform the following transformation.

Our laboratory has also developed propyl amine-functionalized silica catalyst under continuous flow conditions as the first step of Rolipram synthesis. It was found that packing $CaCl_2$ with amine functionalized catalyst could decrease the use of nitromethane

to almost 1 equivalent to an aldehyde. Therefore, following asymmetric 1,4-addition of malonate catalyzed by PS immobilized chiral Ca complex took place in excellent yield with excellent selectivity without any workup procedure. [13] Based on this report, I decided to investigate reaction conditions in detail under continuous flow conditions to achieve higher productivity and perform multistep transformation over different kinds of heterogeneous catalysts.

2-2. Nitro alkene synthesis from nitromethane and aldehydes

Aldol condensation between benzaldehyde **2a** and nitromethane **1** was chosen as a model reaction. At first, the effect of flow rate and concentration was examined under continuous-flow conditions using propyl amine-functionalized silica packed with $CaCl_2$ as heterogeneous catalysts. As standard conditions, a 0.1 M solution of nitromethane with 1.2 eq. of benzaldehyde was flowed into a catalyst column packed with 5 g of amine functionalized SiO_2 and 15 g of $CaCl_2$ heated at 75 °C using plunger pump at 0.25 mL/min flow rate. The resulting solution was collected and analyzed by GC. The results are shown in **Figure 2-2-1**.

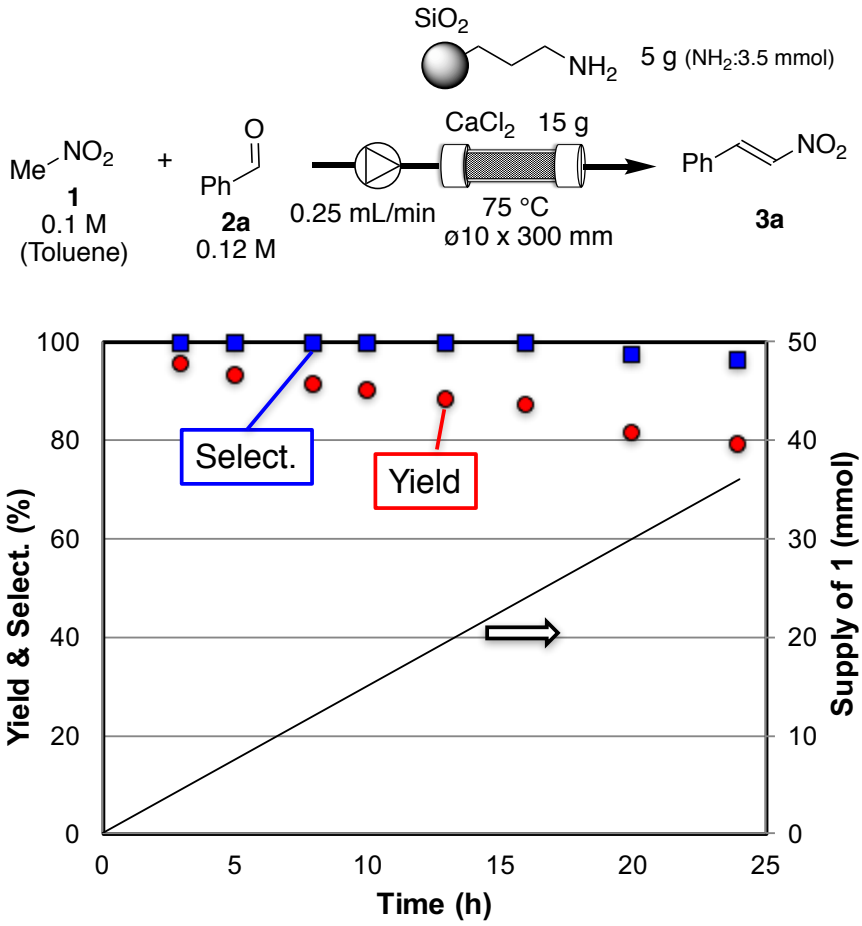


Figure 2-2-1. Continuous-flow reaction using amine functionalized silica and $CaCl_2$ catalysts

At the initial stage, the desired nitroalkene **3a** was obtained in >95% yield. The yield was gradually decreased as time passed, however, the yield was kept >80% yield for 24 h without significant loss of selectivity. At the stage of 24 h, 36 mmol of nitromethane was introduced to the system.

Next, to improve the productivity of this system, the effect of concentration and flow rate was examined with the same amount of catalyst and reaction temperature. The results are summarized in **Figure 2-2-2**. To evaluate the productivity, the x-axis refers to the time to supply 36 mmol of nitromethane and y-axis refers to average yield.

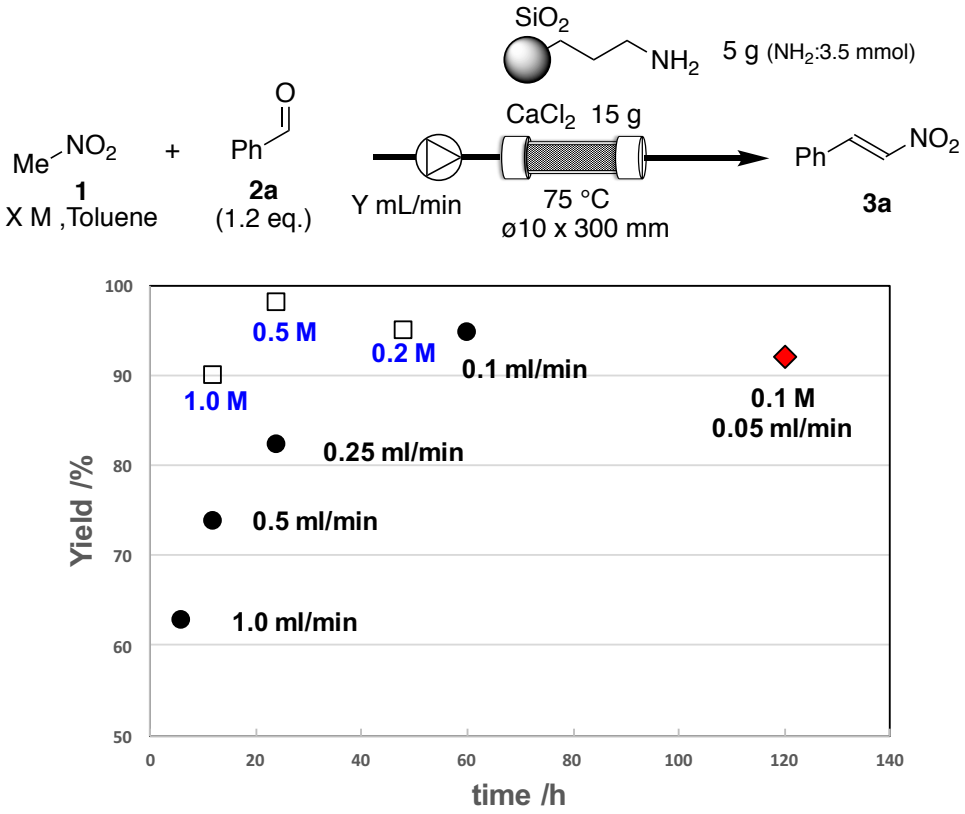


Figure 2-2-2. Effect of flow rate and concentration

The red diamond represents results of 0.1 M concentration with 0.05 mL/min flow rate. In these reaction conditions, it took 120 h to supply 36 mmol of substrate and yield was kept >90% for the whole period. At first, the flow rate was increased from 0.05 to 0.1 mL/min with 0.1 M concentration. With 0.1 mL/min, the yield was kept >90% resulting in the increase in productivity by double. On the other hand, further increase of flow rate from 0.25 to 1.0 ml/min decreased yield due to short residence time. Next, the concentration was increased from 0.1 to 1.0 M with 0.05 ml/min flow rate. As a result, the yield was maintained >90% even with 1.0 M concentration resulting in the increase in productivity by 10 times. These results clearly suggest that residence time is the key factor to determine the yield. Even with the same WHSV, the yield differs with concentration and flow rate. With proper residence time, the productivity can be increased by increasing concentration of substrate.

As it was found that the yield could be kept >95% with 0.05 ml/min flow rate and 0.5 M concentration, the scope of aldehydes was examined (**Figure 2-2-3**).

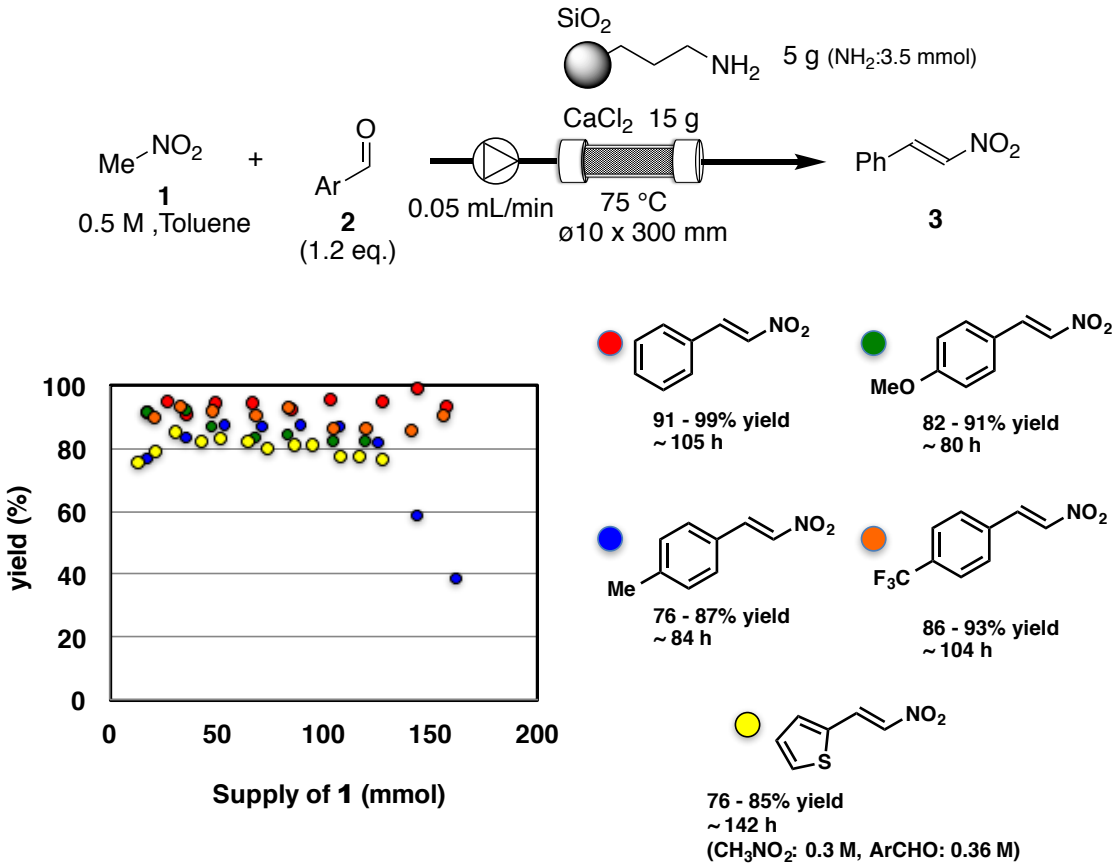


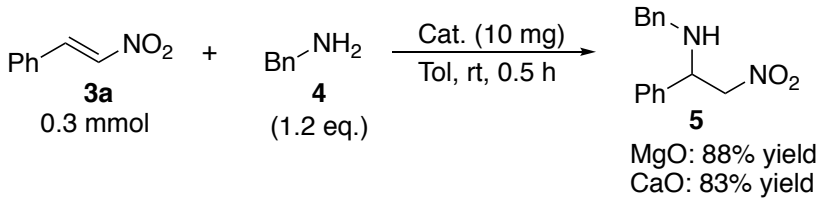
Figure 2-2-3. Substrate scope for aldehydes

The yield was plotted as a function of the supply of nitromethane. With 4-Me benzaldehyde, the deactivation of catalyst was observed after 84 h flow started. However, both 4-OMe and 4-CF_3 substituted benzaldehyde provided the desired nitroalkene in excellent yield for >80 h continuous-flow reactions indicating that electronic effect of aldehyde does not affect the reaction outcome significantly. 2- thiophencarboxyaldehyde could be also used as a substrate, although decreased concentration was required to achieve high yield.

2-3. Metal oxide-catalyzed conjugate additions to nitroalkenes

As the nitroalkene synthesis under continuous-flow conditions was established, transformations with a nitroalkene using heterogeneous catalysts were studied next. At first, basic metal oxides were determined to use as heterogeneous base catalysts. Indeed, alkali metal oxides are known to be effective solid bases for several kinds of organic transformations. However, there are few reports of their application for continuous-flow conditions.

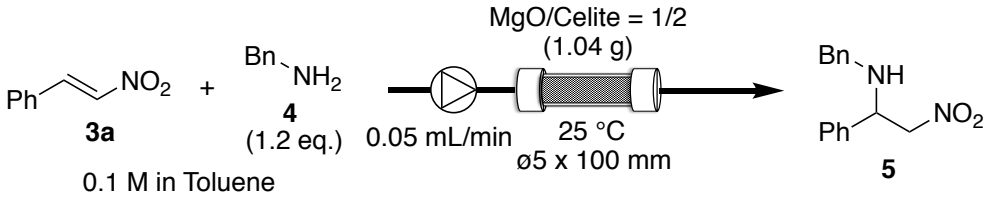
As an initial trial, conjugate addition of benzylamine **4** to nitrostyrene **3a** was examined using metal oxides as catalysts[14]. Fortunately, both MgO and CaO were found to be effective catalysts for this reaction to get aminated compound **5** under batch conditions (**Scheme 2-3-1**).



Scheme 2-3-1. Alkali metal oxide catalyzed amine conjugate addition

MgO diluted with Celite worked well even under single-flow conditions to afford >90% yield for 18 h without significant loss of activity (**Table 2-3-1**).

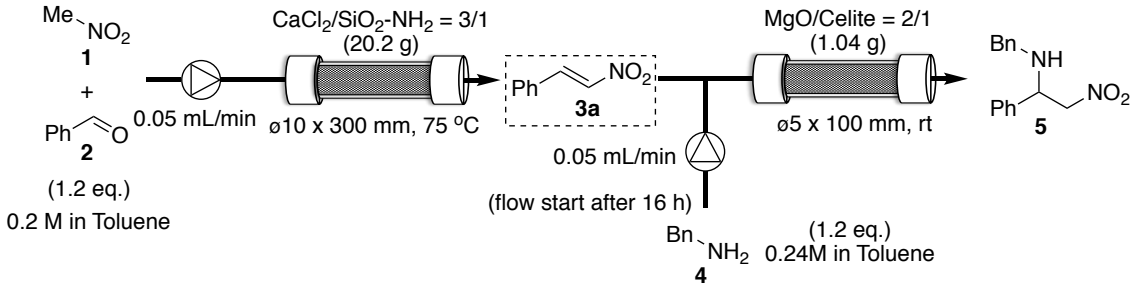
Table 2-3-1. Single flow reaction of MgO catalyzed amination



Time (h)	1	3	18
Yield (h)	93	90	90

Finally, the nitroalkene synthesis was connected to amine conjugate addition without any workup process to demonstrate 2-step flow reactions (**Table 2-3-2**). As a result, the target compound was obtained >85% yield for 50 h. Although there exists a small excess amount of aldehyde in the resulting solution from the 1st column, it did not affect the activity of the catalyst in the second column.

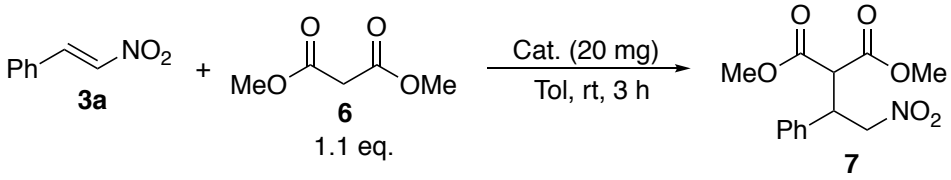
Table 2-3-2. 2-step flow reaction for amination of nitro styrene



Time (h)	6	10	22	27	30	35	46	50
Yield (%)	91	90	87	95	92	91	88	91

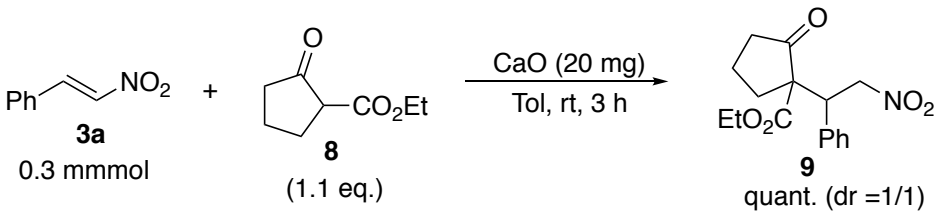
As another example of metal oxide catalysis, conjugate addition of 1,3-carbonyl compounds to nitrostyrene was examined. At first, dimethylmalonate **6** was used as a nucleophile and several kinds of metal oxides were evaluated (**Table 2-3-3**).[15] Unfortunately, MgO, which was an effective catalyst for amine conjugate addition, did not show catalyst activity for this reaction (Entry 1). However, CaO afforded the desired compound **7** in excellent yield (Entry 2). Other metal oxides such as Cu_2O and Ag_2O did not improve the result (Entries 3,4). As it is known that CaO is the strongest solid base among tested in this study, the basicity of the catalyst seems to be the key factor in this transformation.

Table 2-3-3. Metal oxides catalysts for conjugate addition of malonate



Entry	Catalyst	Yield (%)
1	MgO	Trace
2	CaO	87
3	Cu_2O	45
4	Ag_2O	N.R.

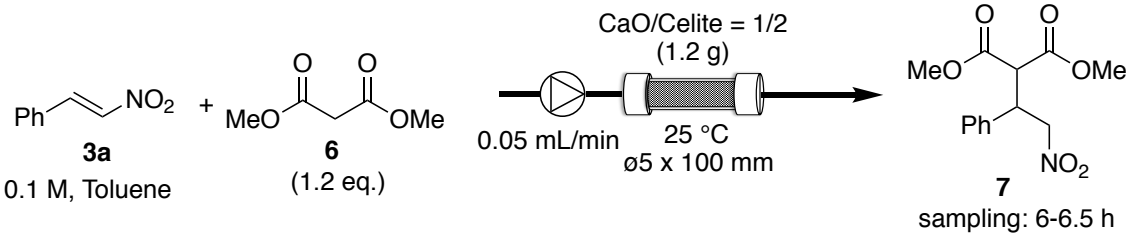
CaO catalyzed the conjugate addition of 1,3-keto ester **8** to nitroalkene as well (**Scheme 2-3-2**). Higher yield was obtained with 1,3-keto ester, indicating that deprotonation of nucleophile is the turnover-limiting step of these reactions.



Scheme 2-3-2. CaO catalyzed conjugate addition of 1,3-keto ester

Next, conjugate addition of malonate **6** was performed under continuous-flow conditions using CaO packed with Celite as catalyst (**Table 2-3-4**). Under standard conditions shown in the scheme, the desired compound **7** was obtained only trace amount (Entry 1). To increase the amount of catalyst, the column was fully packed with CaO. However, the yield of the desired compound did not improve (Entry 2). On the other hand, the decrease of flow rate to 0.01 mL/min resulted in the increase of yield to 11% indicating that residence time is an important factor to get the higher yield (Entry 3). Finally, the reaction temperature was increased to 75 °C, but the yield was only 17% (Entry 4).

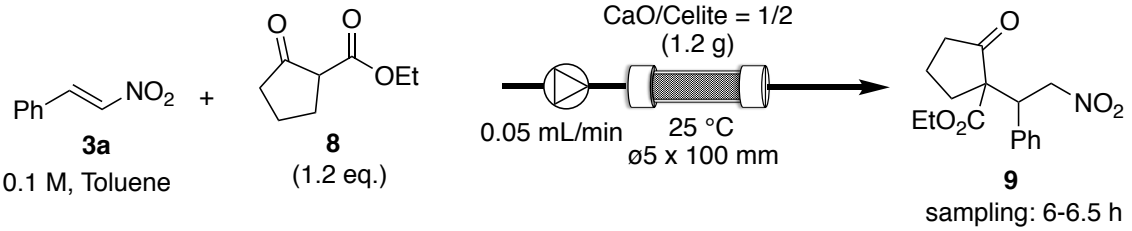
Table 2-3-4. Single-flow reaction of CaO catalyzed conjugate addition of malonate



Entry	Deviation from standard	Yield (%)
1	none	Trace
2	w/o Celite	Trace
3	0.01 mL/min flow rate	11
4	75 °C reaction temp.	17

On the other hand, the reaction took place smoothly when the nucleophile was changed to 1,3-keto ester (**Table 2-3-5**). Under standard conditions shown in the scheme, the desired compound was obtained in quantitative yield (entry 1). Decreasing amount of CaO by halt resulted in a decrease of yield to 68% (entry 2). On the other hand, the excellent yield was maintained with increasing the flow rate to 0.1 mL/min (entry 3).

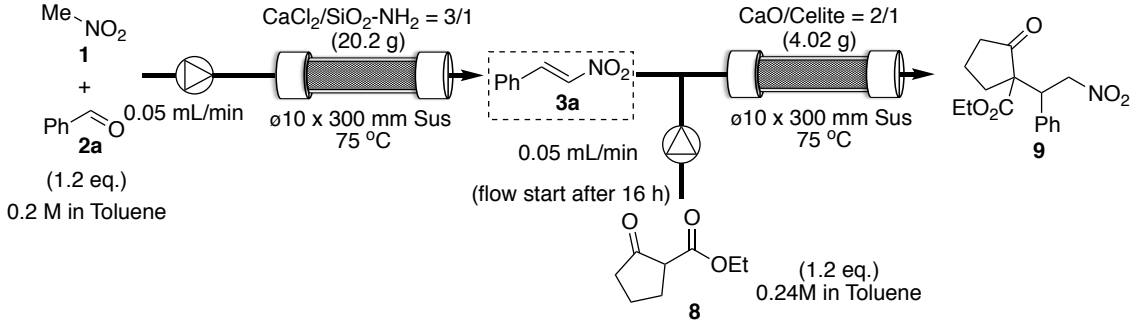
Table 2-3-5. Single-flow reaction of CaO catalyzed conjugate addition of 1,3- keto ester



Entry	Deviation from standard	Yield (%)	dr
1	none	Quant.	58/42
2	CaO/Celite = 1/2	68	58/42
3	0.1 mL/min flow rate	Quant.	58/24

With optimized reaction conditions for single-step continuous-flow reaction, a 2-step transformation was investigated (**Table 2-3-6**). In the first trial, CaO stored under ambient air was used as a catalyst. Although excellent yield was observed after 3 h, rapid catalyst deactivation was observed after 12 h. Finally, only intermediate **3a** was recovered after 24 h. In the second run, CaO was calcined at 600 °C for 3 h just before use to remove adsorbed water from the catalyst. As a result, the catalyst remained active for >40 h without significant loss of activity. However, a small decrease in yield was observed after 44 h. As it was confirmed that calcination of the catalyst was effective for a long lifetime, the deactivation in the second run seems to be originated from water generated in the first nitrostyrene synthesis.

Table 2-3-6. Two-step flow reaction for conjugate addition of 1,3-keto ester



1st run: CaO stored under ambient air			
Time (h)	3	12	24
Yield %)	98	43	Trace

2nd run: CaO calcined at 600 °C just before use								
Time (h)	5	15	19	24	28	40	44	48
Yield (%)	97	98	95	98	96	93	89	82

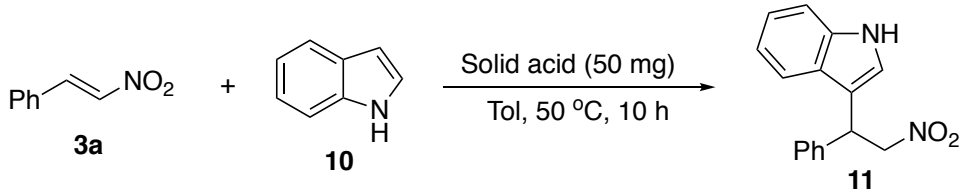
In this section, 2 kinds of alkali earth metal oxides were employed as solid base catalysts for nucleophilic conjugate additions. Although CaO was found to be sensitive to water, these solid bases efficiently worked as catalysts under continuous-flow conditions.

2-4. Solid acid-catalyzed nucleophilic addition of indole

In the previous section, the application of solid acids for continuous-flow reactions was described. Another important and reliable class of sold catalyst is solid acid catalysts. Thus, to demonstrate the utility of solid acid catalysts, nucleophilic addition of indole **10** toward nitro alkene **3a** catalyzed by Brønsted acid was chosen as model reaction.[17]

At first, the reaction was performed under batch conditions, and several kinds of solid acid catalysts were evaluated (**Table 2-4-1**). Al-doped MCM-41 and silica-alumina showed excellent catalyst activity for this reaction to afford desired compound **11** in quantitative yield (Entries 1,2). Carboxylic acid functionalized SiO_2 and sulfonic acid functionalized SiO_2 showed catalyst activity as well, however lower yields were observed (Entries 3,4).

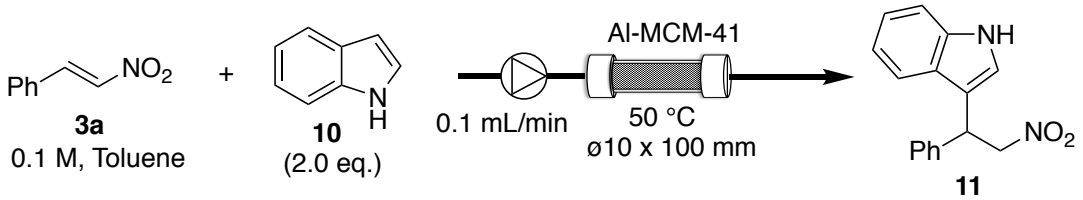
Table 2-4-1. Investigation of heterogeneous acid catalysts for indole addition



Entry	Catalyst	Yield (%)
1	Al-MCM-41	>99
2	SiO_2-Al_2O_3	>99
3	SiO_2-CO_2H	16
4	SiO_2-SO_3H	11

Using Al-doped MCM-41, single step flow reaction was performed. Fortunately, the catalyst efficiently worked even under continuous-flow conditions to afford indole adduct **11** in excellent yield for 18 h without any deactivation (**Table 2-4-2**).

Table 2-4-2. Investigation of heterogeneous acid catalysts for indole addition



Time (h)	3	6	15	18
Yield (%)	94	92	98	98

However, lower yield and short lifetime were observed when it was combined with nitroalkene synthesis to perform 2-step reaction (**Figure 2-4-1(a)**). Using 1.2 eq. of indole **10**, yield was decreased to <40% after 32 h flow started. It should be noticed that

recovered amount of nitroalkene **3a** kept almost same even after the decrease in yield of the desired compound **11**. This observation suggested that some undesired side reaction proceeded at the last stage of flow reaction. The lifetime of catalyst was improved by increasing the amount of indole **10** to 1.7 eq. The equivalence of indole was further examined in detail and found that >80% yield could be achieved using 1.5 eq. of indole without significant loss of activity even after 52 h flow started. Another important finding was that increasing the amount of catalyst significantly decreased the yield of the target compound. These results also indicated the existence of undesired reaction pathway.

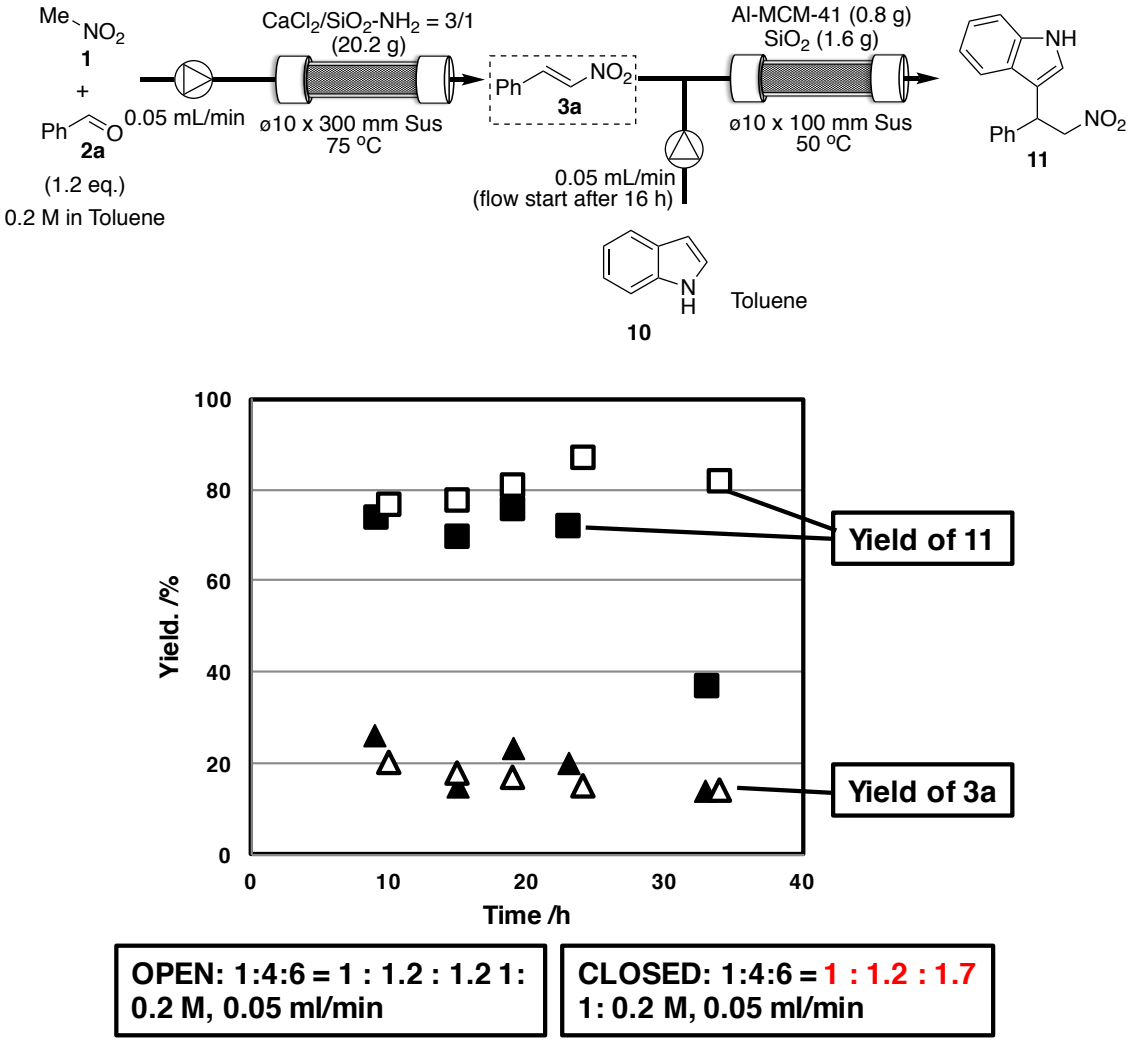


Figure 2-4-1(a) Two-step flow reaction for conjugate addition of indole

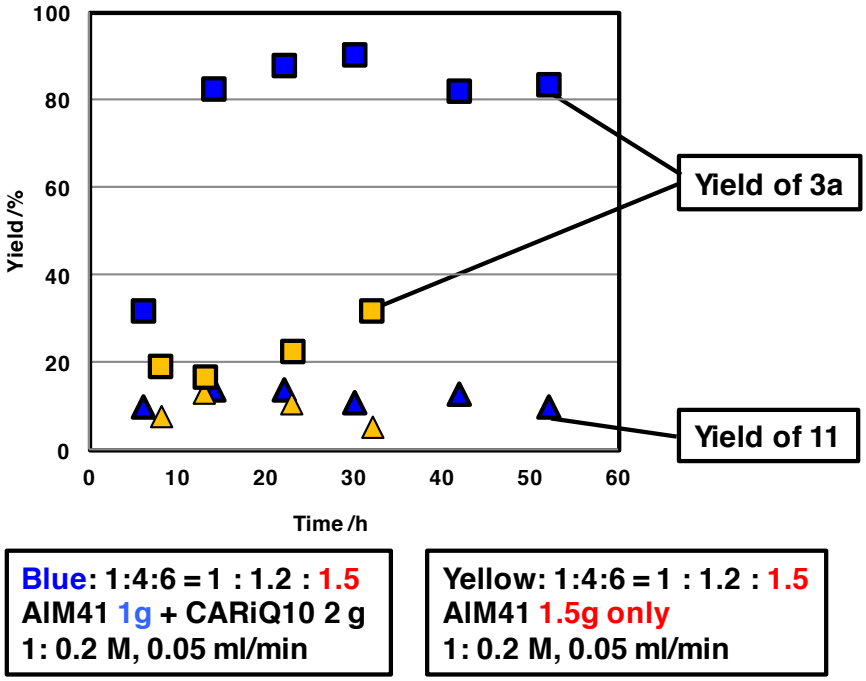
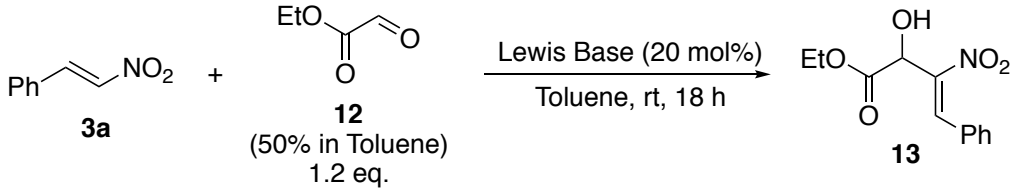


Figure 2-4-1(b) Two-step flow reaction for conjugate addition of indole

2-5. Silica immobilized DMAP catalyzed Morita-Baylis-Hillman reaction

Next, solid immobilized organocatalysts were determined to be investigated for different types of transformations of nitrostyrene. As a first study, Morita-Baylis-Hillman (MBH) reaction with ethyl glyoxylate was chosen as a target reaction. At first, several kinds of homogeneous Lewis bases were employed as catalysts under batch conditions (**Table 2-5-1**). As a result, among different types of Lewis bases, only DMAP could efficiently catalyze MBH reaction to afford target compound in good yield.

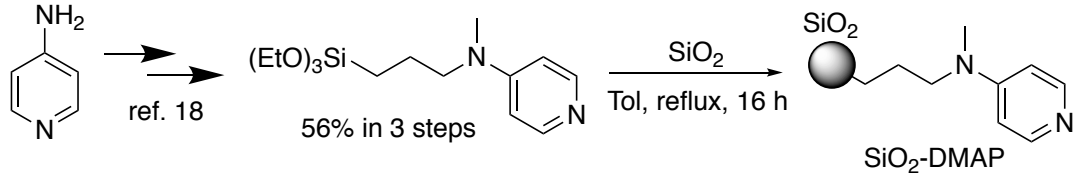
Table 2-5-1. Homogeneous Lewis base catalyzed MBH reaction



Entry	Lewis base	Yield (%)
1	DABCO	Trace
2	Imidazole	Trace
3*	DMAP	86
4	PPh_3	Trace

*reaction time = 3 h

To immobilize DMAP functionality on a solid support, surface functionalization of SiO_2 was employed because such method was well established and reliable. First silane coupling agent having DMAP moiety was synthesized following literature method.[18] Following surface functionalization was performed in toluene reflux conditions (**Scheme 2-5-1**). The solid material was collected by filtration and washed with toluene to remove remaining coupling agent to get heterogeneous catalysts with different concentration.

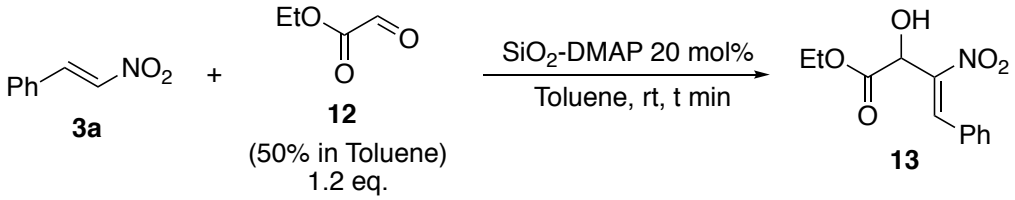


Scheme 2-5-1. Preparation of silica immobilized DMAP

Obtained catalysts were evaluated under batch conditions (**Table 2-5-2**). By using SiO_2-DMAP catalysts with 0.1 mmol/g loading, the desired compound was obtained in 26% yield for 3 h. The yield was significantly improved to quantitative by increase the concentration to 1.0 mmol/g. It should be noticed this catalyst showed higher activity than homogeneous DMAP catalyst. Considering the fact that higher concentration of DMAP

had higher activity, the high activity can be explained by the high concentration of active site on a solid support.

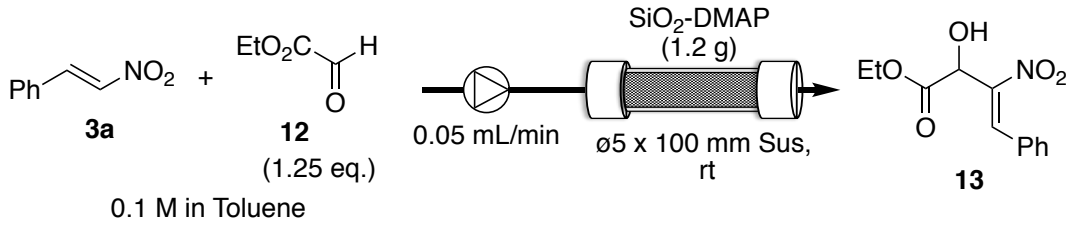
Table 2-5-2. SiO_2-DMAP catalyzed MBH reaction



Entry	Loading (mmol/g)	Time (min)	Yield (%)
1	0.1	180	26
2	1.0	80	Quant.

With successful result under batch conditions, the catalyst was evaluated single-step continuous-flow conditions. Fortunately, the target compound was obtained in excellent yield for 9 h with 1.2 g of catalyst (**Table 2-5-3**).

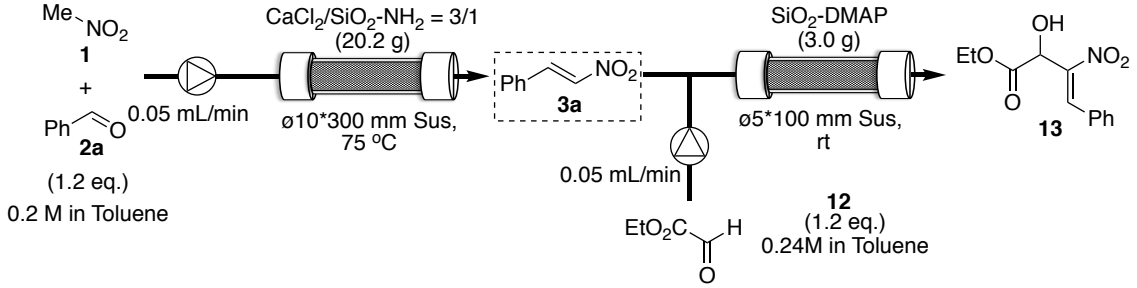
Table 2-5-3. Single-flow reaction of SiO_2-DMAP catalyzed MBH reaction



Time (h)	3	6	9
Yield (%)	Quant.	98	98

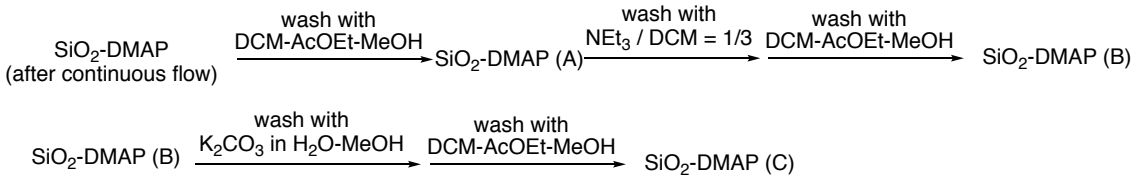
However, significant catalyst deactivation was observed when 2-step flow reaction was performed (**Table 2-5-4**). Under standard reaction conditions, the yield was decreased from quantitative to 40% after 6 h, and only a trace amount of the desired compound was obtained after 12 h (Run 1). Because the deactivation seemed to be caused by a small excess amount of benzaldehyde, a column packed with amine silica was introduced after 1st column to remove benzaldehyde. However, similar deactivation was observed after 6 and 12 h (Run 2). With the same purpose, the equivalence between nitromethane and benzaldehyde was changed from 1/1.2 to 1.2/1 in the 3rd run. Unfortunately, the same deactivation was observed as well. From these results, it was concluded that the cause of the deactivation is not originated from benzaldehyde remained in the solution.

Table 2-5-4. Two-step flow reaction of SiO_2-DMAP catalyzed MBH reaction



Run	Deviation from standard	Yield after 3 h (%)	Yield after 6 h (%)	Yield after 12 h (%)
1	None	Quant	40	Trace
2	SiO_2-NH_2 column after 1st-column	98	41	Trace
3	$MeNO_2$/PhCHO =1.2/1	96	52	Trace

To clarify the cause of deactivation in 2-step flow reaction, the deactivated catalyst was recovered and treated with several kinds conditions (**Scheme 2-5-2**). At first recovered catalyst was washed with organic solvents such as DCM, AcOEt and MeOH (SiO_2-DMAP(A)). It was further washed with NEt_3 to remove acidic compound adsorbed on DMAP moiety (SiO_2-DMAP(B)). Finally, it was further washed with K_2CO_3 in H_2O-MeOH solution (SiO_2-DMAP(C)).

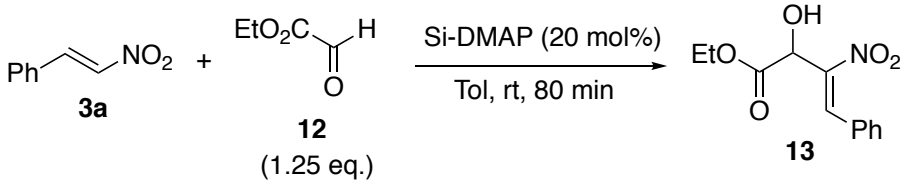


Scheme 2-5-2. Recovery and regeneration of deactivated SiO_2-DMAP

The activity of recovered and washed solid materials was examined under batch conditions (**Table 2-5-5**). At first, catalyst simply washed with organic solvent did not show any catalyst activity indicating that activity was completely lost (Entry 2). However, the catalyst further washed with NEt_3 afforded the target compound in 70% yield (Entry 3). Obviously, an acidic compound adsorbed on the catalyst is the cause of deactivation. The most likely poisoning agent was benzoic acid generated from oxidation of benzaldehyde. However, further washing with K_2CO_3 diminished the activity to 31% yield (Entry 4). This result clearly suggested that K_2CO_3 was a poison for this catalyst. Considering that DMAP is a strong Lewis base, one possible explanation is that potassium cation partially coordinated to DMAP and diminished the Lewis basic activity. Based on

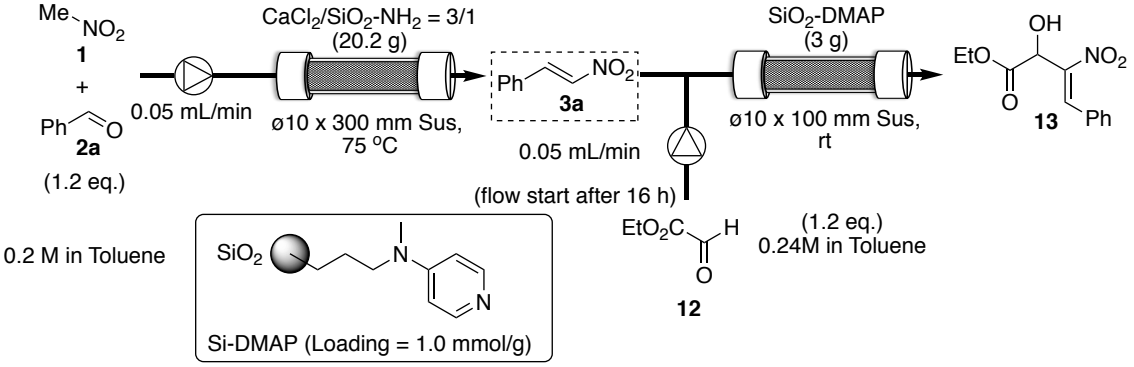
this consideration, it was hypothesized that the cause of deactivation in a 2-step reaction is leached out Ca salt from $CaCl_2$.

Table 2-5-5. Evaluation of recovered SiO2-DMAP catalysts



Entry	Cat.	Yield (%)
1	Original	Quant.
2	SiO_2-DMAP(A)	ND
3	SiO_2-DMAP(B)	70
4	SiO_2-DMAP(C)	31

To verify the hypothesis, the first column was modified and evaluated in 2-step flow reaction and results are summarized in **Figure 2-5-1**. Under standard conditions (conditions A), deactivation was observed even after 6 h. Such deactivation was significantly supressed simply by changing the first column from $CaCl_2$ to MS4A (conditions B). This result supported the hypothesis about deactivation, although still deactivation was observed after 12 h. The lifetime of the system could be prolonged by increasing the amount of catalyst (condition C). On the other hand, changing the equivalence between nitromethane and benzaldehyde resulted in decreased lifetime (conditions D).



Conditions	Deviation from standard
A	None
B	MS4A instead of $CaCl_2$
C	MS4A instead of $CaCl_2$, twice amount of catalyst
D	MS4A instead of $CaCl_2$, twice amount of catalyst, $MeNO_2$/PhCHO = 1.2/1

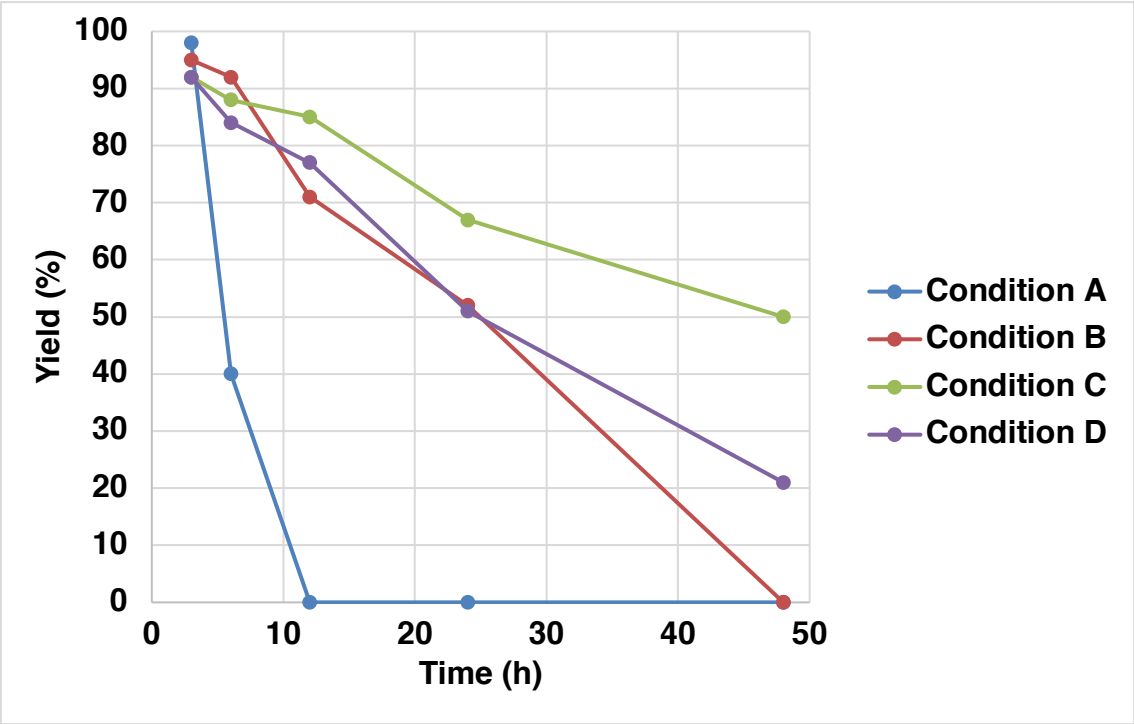


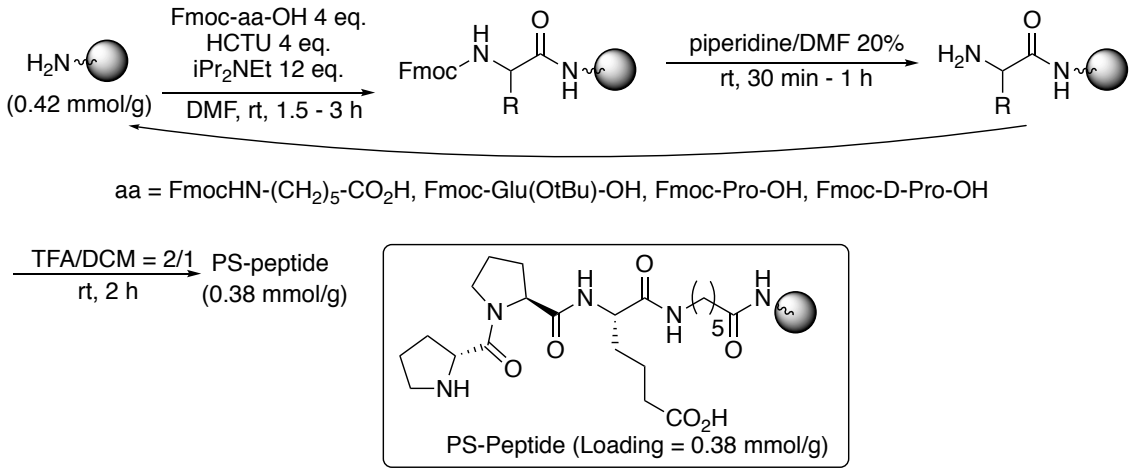
Figure 2-5-1. Modified 2-step flow reaction of SiO_2-DMAP catalyzed MBH reaction

In conclusion, silica immobilized DMAP catalyst was developed for MHB reaction between nitro styrene and ethyl glyoxylate under continuous-flow conditions. The activity was found to depend on the concentration of active site on silica, and optimized heterogeneous catalyst showed higher catalyst activity than homogeneous DMAP catalyst. The heterogeneous catalyst was active even single-step flow reaction to afforded desired compound in quantitative yield. Although catalyst deactivation was observed in 2-step flow reaction, it was suggested that Ca species leached out from 1st column was responsible for the deactivation. Finally, with proper tuning of 1st column, lifetime of the system could be prolonged to 48 h to afford desired compound in >50% yield.

2-6. Polystyrene immobilized peptide catalyzed conjugate addition of aldehyde

Polystyrene immobilized organocatalysts have been employed for various kinds of organic transformations under both batch and continuous-flow conditions. Especially, polystyrene immobilized proline derivatives are one of the most well studied heterogeneous asymmetric catalysts. This is not only because they can be applied for a wide range of organic transformations, but also because their proline-based structure allows to be immobilized on polystyrene by various kinds of covalent bonds. Among them, polystyrene immobilized chiral peptide catalysts developed by Wennemers *et al*. are one of the most efficient and reliable heterogeneous catalysts.[19] Their group has focused on proline-based peptide catalysis and has developed polystyrene immobilized catalysts for asymmetric aldol reaction and conjugate additions for nitrostyrene. Their catalysts demonstrated high activity and selectivity and could be applied for continuous-flow reactions. Additionally, they could be easily synthesized following well established solid phase peptide synthesis protocol.

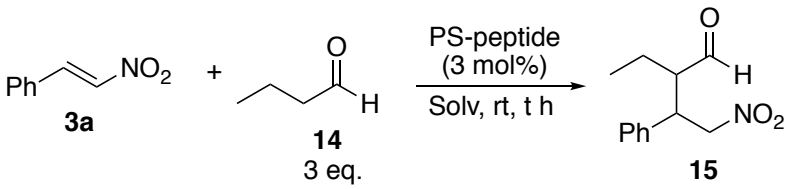
Then it was decided to employ their catalyst to this 2-step continuous-flow reactions. The catalyst was prepared from amino acids and commercially available amine functionalized polystyrene following literature method (**Scheme 2-6-1**).



Scheme 2-6-1. Preparation of polystyrene immobilized peptide catalyst

As the solvent of this reaction is restricted for toluene, first the activity of heterogeneous peptide catalyst was examined under batch conditions (**Table 2-6-1**). The results in original report were well reproducible under optimized reaction conditions (Entries 1,2). When the solvent was changed to toluene, almost same yield and dr were achieved although small decrease in ee was observed and longer reaction time was required (Entry 3).

Table 2-6-1 Asymmetric conjugate addition of aldehyde

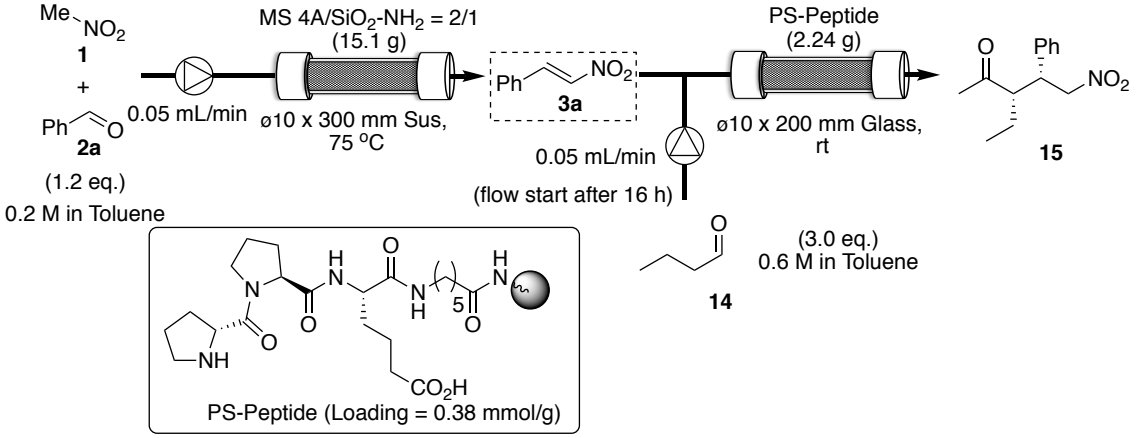


Entry	Solv.	Time (h)	Yield (%)	Dr	Ee (%)
1*	$CHCl_3$/IPA = 9/1	3	Quant.	97/3	95
2	$CHCl_3$/IPA = 9/1	3	95	97/3	96
3	Toluene	4.5	96	94/6	91

*date from original report

Because single-step flow reaction was already established in the original paper, 2-step flow reaction was studied (**Table 2-6-2**). At the initial stage, the desired compound was obtained in the excellent yield, dr, and ee. However, yield gradually decreased as time passed, and leached 58% yield after 25 h. On the other hand, dr and ee remained the same. These results indicated that a part of active site lost the activity, and the remaining part kept its active structure. Because one possible such deactivation is a formation of iminium salt by reaction with excess benzaldehyde, the equivalence of nitromethane and benzaldehyde was changed in the 2nd run. As expected, a lifetime of the catalyst was much improved and yield was kept >70% for 30 h without loss of dr and ee.

Table 2-6-2. 2-step flow reaction of PS-peptide catalyzed asymmetric conjugate addition



1st run: standard conditions					
Time (h)	4	6	9	21	25
Yield (%)	93	88	71	60	58
Dr	96/4	96/4	96/4	96/4	96/4
Ee (%)	-	91	-	91	-

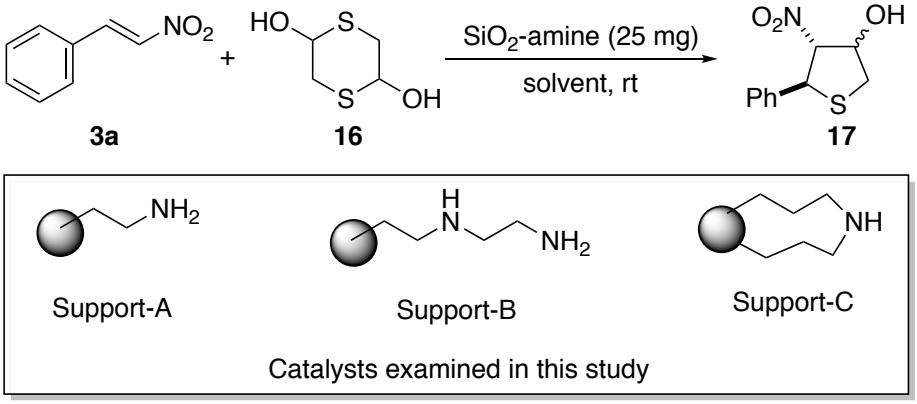
2nd run: $MeNO_2$ / PhCHO = 1.2 / 1								
Time (h)	4	6	9	21	25	30	42	48
Yield (%)	77	81	72	73	76	72	58	52
Dr	96/4	97/3	98/2	98/2	97/3	97/3	98/2	97/3
Ee (%)	89	89	-	88	-	89	-	88

2-7. Silica immobilized secondary amine catalyzed intermolecular cyclization with dithiane

Nitroalkenes can be also employed for intermolecular cyclization. In 2010, Southern *et al* developed intermolecular cyclization between nitroalkenes and 1,4-dithiane-2,5-diol **16** to prepare tetrahydrothiophene catalyzed by NEt_3.[20] Thus, I envisioned that I could employ silica immobilized amine as catalysts for this transformation.

Model reactions were performed using nitrostyrene **3a** and 1,4-dithiane-2,5-diol **16** as substrate and SiO_2 or Al-doped MCM-41 supported amine catalysts. 3 different kinds of amine were chosen as active sites. One has primary amine, another has both secondary and primary amines, the other one has cyclic secondary amines. Catalysis was performed at room temperature with 25 mg of catalyst (**Table 2-7-1**). Using SiO_2 supported primary amine catalyst, the desired compound was obtained in 14% yield (Entry 1). Introducing secondary amine to the catalyst significantly improve the activity (Entry 2). Using cyclic secondary amine further improve the activity and target compound was obtained in 93% yield (Entry 3). From these results, secondary amine seems to be essential to achieve high activity. The effect of support was also examined. As for the amine B as an active site, decreased activity was observed with Al-MCM-41 (Entry 4). On the other hand, with a cyclic amine as an active site, a small improvement in yield was observed and target compound was obtained in 99% yield (Entry 5).

Table 2-7-1. Investigation of SiO_2 functionalized amine catalysts for cyclization

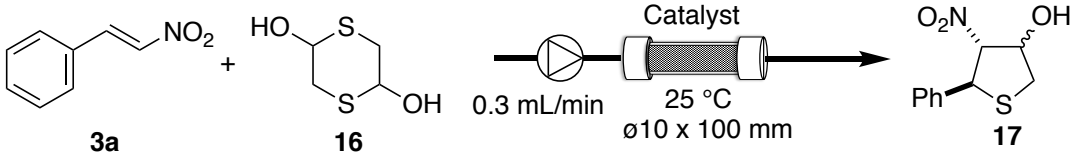


Entry	catalyst	Yield (%)
1	SiO_2-A	14
2	SiO_2-B	83
3	SiO_2-C	93
4	Al-MCM-41-B	47
5	Al-MCM-41-	99

	C	

With optimized catalyst in hand, a singles step continuous-flow reaction was examined (**Table 2-7-2**). It was found that main issue for this reaction is the solubility of the product. Using the best conditions under batch conditions resulted in clogging of flow (Entry 1). Changing the solvent to toluene/DMF co-solvent system slightly improve the solubility, however clogging was again observed after 4 h (Entry 2). Finally, a diluting catalyst with Celite was found to be effective to prevent clogging (Entry 3). Under these reaction conditions, cycloadduct was obtained in 97% yield.

Table 2-7-2. Single flow using Al-MCM-41 immobilized secondary amine catalyst

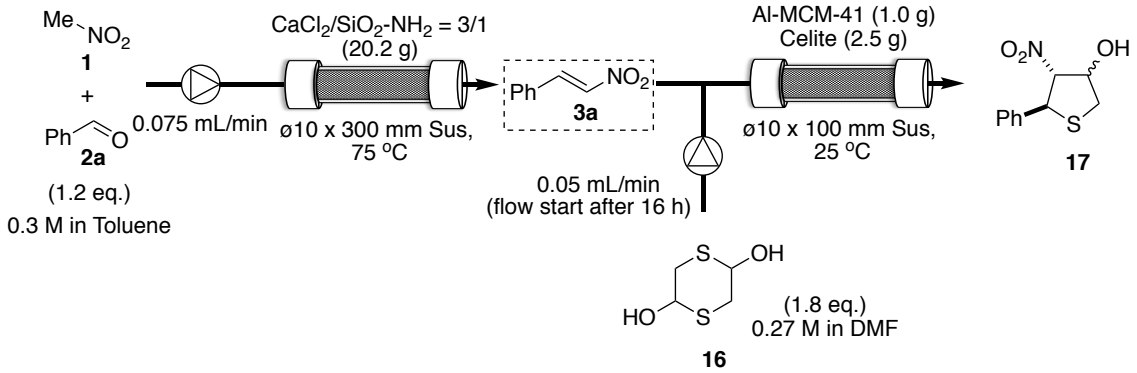


3a 0.067 M, Solv. **16** (1.2 eq.) **17**

Entry	Catalyst	Solvent system	Yield (%)
1	Al-MCM-41-C (1 g) + Celite (2 g)	Tol/THF/DMF =1/0.8/0.2	Clogged
2	Al-MCM-41-C (0.5 g)	Tol/DMF = 1/2	Clogged
3	Al-MCM-41-C (0.5 g) + Celite (2.5 g)	Tol/DMF = 1/2	97

As it was found the choice of solvent is important to achieve continuous-flow reactions, 2 step flow reaction was investigated employing the optimal solvent system for single flow reaction (**Table 2-7-3**). As expected, stable flow was achieved for 48 h. Although small catalyst deactivation was observed at the last stage of the reaction, the yield was kept >75% yield for 48 h operation.

Table 2-7-3. 2-step flow reaction for synthesis of tetrahydrothiophene

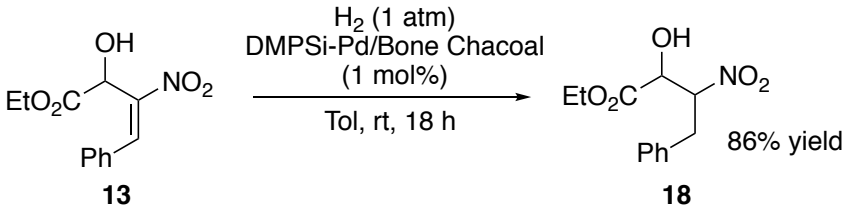


Time (h)	3	7	11	15	27	37	48
Yield (%)	72	93	94	86	89	81	75

2-8. Three-step transformation of nitro compounds

Until now, it was demonstrated that solid base catalysts and immobilized organocatalysts efficiently worked under 2-step flow reactions. Finally, it was determined to investigate 3-step flow reaction using other types of heterogeneous catalysts. Hydrogenation of MBH product was chosen as a model reaction because our laboratory previously developed heterogeneous Pd catalyst for continuous-flow hydrogenation of alkenes.[21]

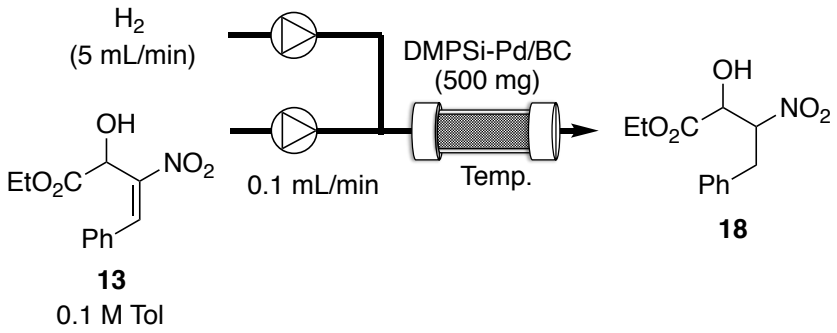
At first, hydrogenation of MBH alcohol using DMPSi-Pd/BC catalyst was performed under batch condition **(Scheme 2-8-1**). When the reaction was performed at room temperature, only alkene moiety was reduced to give nitro alkane compound in good yield.



Scheme 2-8-1. Hydrogenation of nitro alkene using heterogeneous

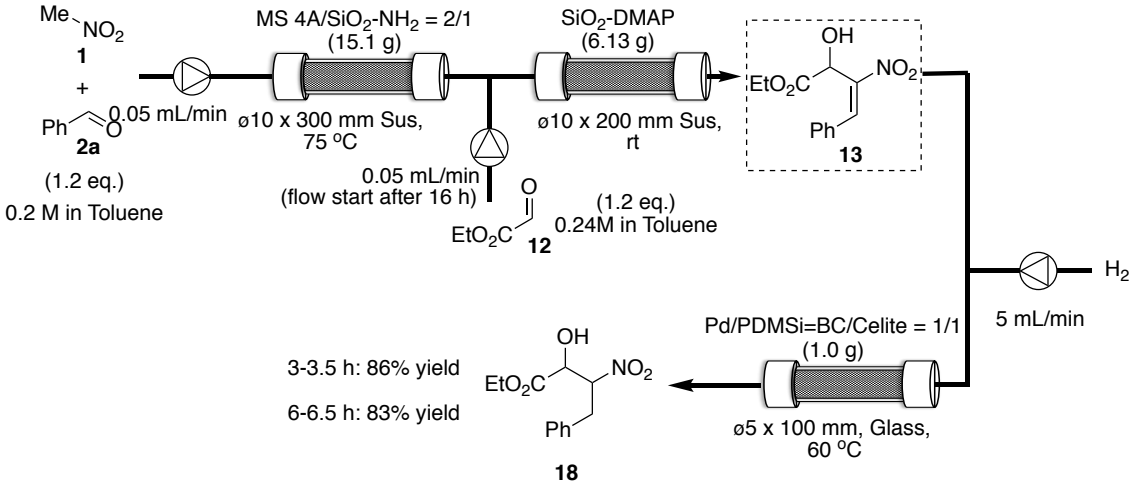
Next, single-step flow hydrogenation was investigated at different temperature (**Table 2-8-1**). When the hydrogenation was performed at 25 °C, the target compound was obtained in less than 20% yield (entry 1). To increase the yield, the reaction temperature was increased from 40 to 100 °C (entries 2-5). The highest yield was observed at 60 °C. It should be noticed that several undesired side product was observed due to the nucleophilic addition to nitroalkene and partial hydrogenation of nitro group when the temperature was higher than 80 °C.

Table 2-8-1. Single-flow hydrogenation of nitro alkene



Entry	Temp. (°C)	Yield (%)
1	25	<20
2	40	42
3	60	91
4	80	<75
5	100	Messy

As it was found that satisfying yield could be achieved with precise control of reaction temperature, 3-step continuous flow reaction consisting from nitro alkene formation-MBH reaction- hydrogenation of alkene was performed (**Scheme 2-8-2**). Fortunately, the final hydrogenation took place smoothly without any workup process. The final nitro alkane was obtained in >80% yield for 3-step transformations.



Scheme 2-8-2. Single-flow hydrogenation of nitro alkene

2-9. Conclusion

At first, amine functionalized silica catalyzed nitro alkene synthesis was studied under continuous-flow conditions. Investigation on flow rate and concentration revealed that longer residence time and high concentration was important to achieve high productivity. Under optimized reaction conditions, 5 kinds of nitro alkenes were synthesized under continuous-flow conditions in good to excellent yield.

Next, 2-step nitro alkene derivatizations were performed. As for conjugate addition reactions, alkali metal oxides, such as MgO and CaO, were found to be efficient heterogeneous solid base catalysts. Especially, basicity of metal oxides was the key factor for conjugate addition of 1,3-carbonyl compounds. On the other hand, solid immobilized catalysts such as DMAP immobilized SiO_2 and polystyrene immobilized peptide catalysts, efficiently promote MBH reactions and asymmetric enamine catalysis. For these reactions, proper modification of the first nitro alkene synthesis was important to achieve long lifetime of catalysts.

Finally, 3-step tranfromation of nitro compound was demonstrated by connecting nitro alkene synthesis, MHB reaction, and hydrogenation of alkene. In the hydrogenation reaction, chemoselective hydrogenation of alkene was achieved.

All transformations demonstrated in this study are environmentally benign, thus efficient methods to prepare various kinds of nitro compounds.

2-10. References

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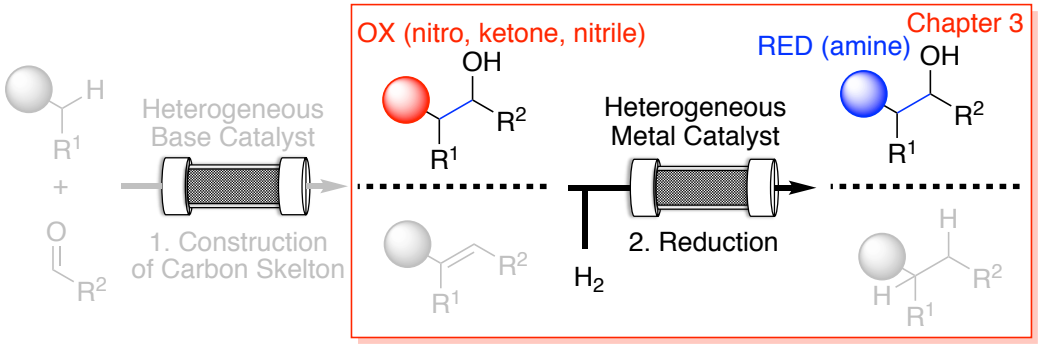
CHAPTER 3
Polysilane-Supported Pd Catalysts for Continuous-flow Hydrogenations

3-1. Background

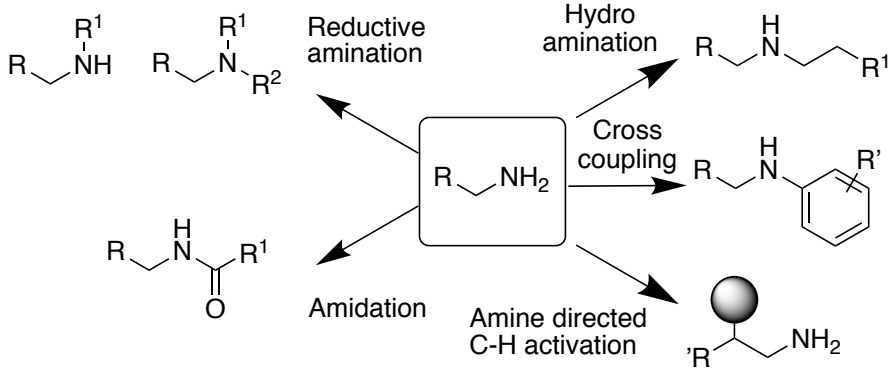
Continuous-flow hydrogenation is an important technology component to achieve multistep flow synthesis. Especially, hydrogenation of functional groups with high oxidation states such as nitrile, nitro, and carbonyl compounds are essential chemical transformations in my aldol-hydrogenation strategy (**Scheme 3-1-1**). To establish this method, I first focused on hydrogenation of nitriles to primary amines as a target reaction.



Scheme 3-1-1. Hydrogenation for multistep flow synthesis

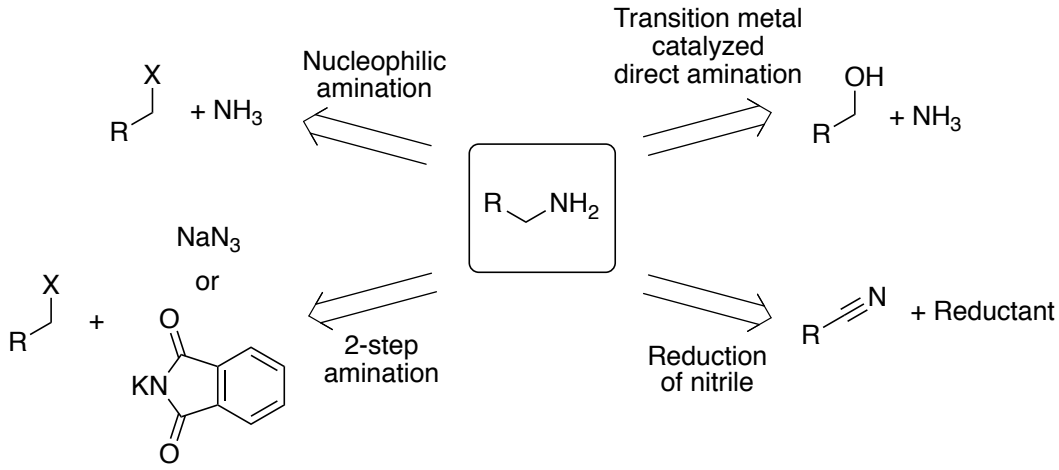
Hydrogenation of Nitriles

Primary amines are a significantly important class of organic compounds because many natural compounds possess their structure.[1] They can be easily converted into secondary and tertiary amines by reductive amination and amides by condensation with carboxylic acids, which are also very common structure in biologically active compounds. Some of the primary amines are manufactured in bulk scale in the industry for the synthesis of dyes and polymers as well.[2] The most famous compound is hexamethylene diamine, which is used as a monomer of 6,6-nylon. Furthermore, recent developments of transition metal catalysis with amines such as C–N coupling reactions, hydroamination, and amine-directed C–H functionalizations has been expanding the potential utilities of primary amines for the synthesis of complex molecules (**Scheme 3-1-2**).[3]



Scheme 3-1-2 Utility of primary amines

Because of the high demands for primary amines, various kinds of synthetic methods have been developed until recently (**Scheme 3-1-3**). Traditionally, they are prepared from ammonia and alkylating reagents such as halides and tosylates. However, such methods often suffer from low selectivity due to the higher reactivity of resulting amines than ammonia. Selectivity issue was overcome by changing nucleophile from ammonia to potassium phthalimide, knowns as Gabriel amine synthesis.[4] However, this protocol requires an additional step to remove phthalimide moiety to generate stoichiometric amounts of byproduct. Alternatively, primary amines can be synthesized by reduction of alkyl azide. Conversion of alkyl azide to primary amine generally takes place under mild hydrogenation conditions to generate nitrogen gas as a solo byproduct. However, stoichiometric amounts of metal waste are produced to synthesize alkyl azide, and hazardous metal azide has to be used. Recent development in transition metal catalysis allows the selective synthesis of primary amines from ammonia and alcohols as alkylating reagents. This method can be considered as an atom-economical process, but reactions have to be performed under harsh conditions, and expensive homogeneous transition metal catalysts have to be employed.[5]



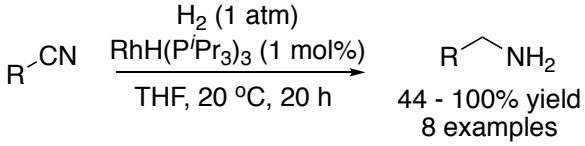
Scheme 3-1-3. Preparation of primary amines

Another reliable method for the preparation of primary amines is the reduction of nitriles. Strongly reducing reagents such as LAH are conventionally employed for this transformation. Milder reaction conditions are recently developed using hydrosilanes or $NaBH_4$ as a reductant with transition metal catalysts. However, these methods still suffer from low efficiency, use of hazardous chemicals, and production of over stoichiometric amount of metal salts as wastes.[6]

Alternatively, the use of H_2 gas as reductant would provide an ideal synthetic route for primary amines, because the reaction takes place with 100% atom economy using readily available substrates. Although much effort has been devoted to developing efficient

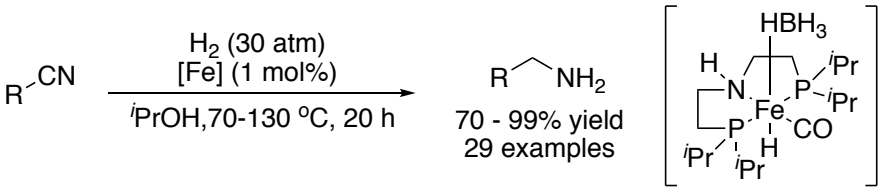
catalysts for this reaction, the present methods often suffer from several drawbacks such as limited substrate scope, harsh reaction conditions, and low selectivities. Especially, side products formation such as secondary and tertiary amines is a serious problem, because they are generally difficult to separate from desired primary amines.

As for the homogeneous catalysts, Ir, Rh and Ru complexes have been commonly employed as catalysts.[8] The first example of homogeneously catalyzed hydrogenation of nitriles to primary amines was achieved with rhodium hydride catalyst reported by Otsuka *et al.* in 1979. Although higher catalyst loading was required, the reaction took place in mild conditions to afford target primary amines in moderate to excellent yields (**Scheme 3-1-4**).

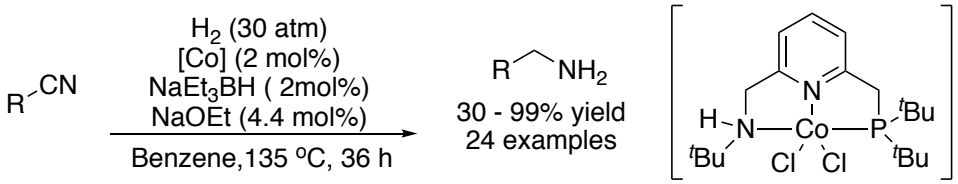


Scheme 3-1-4 Rh hydride catalyzed hydrogenation of nitriles

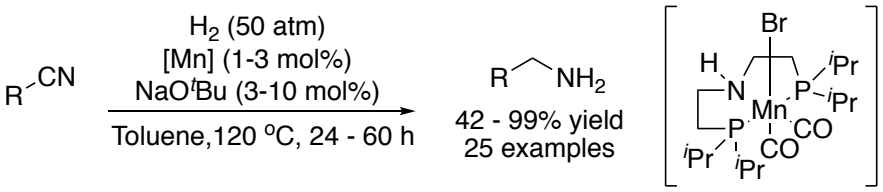
Since then, various kinds of efficient catalysts have been developed until recently mainly by a precise design of ligands for a metal center. However, such precious metals and complex ligands are difficult to recover after the reaction, and contamination of highly toxic metals into the products is another problem. Recently, Beller *et al.* and Milstein *et al.* independently developed the abundant and less toxic Co and Fe catalysts for the selective hydrogenation of nitriles to primary amines (**Scheme 3-1-5**).[9] In their reports, several kinds of nitriles were converted into primary amines in good to excellent yields, while high temperature and high pressure of H_2 were required and some of the heteroaromatic and aliphatic nitriles still suffered from the selectivity issue.



Scheme 3-1-5. (a) Fe catalyzed hydrogenation of nitriles

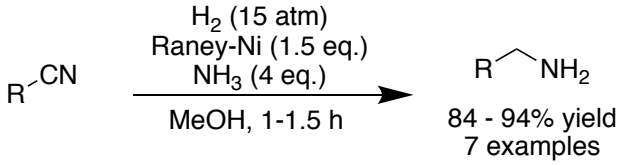


Scheme 3-1-5. (b) Co catalyzed hydrogenation of nitriles



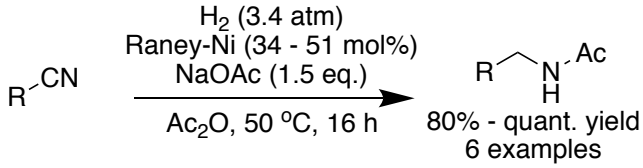
Scheme 3-1-5. (c) Mn catalyzed hydrogenation of nitriles

On the other hand, various kinds of heterogeneous catalysts have been developed for a long time for hydrogenation of nitriles.[10] In the early stage of the development in this field, Raney-Ni has been employed as a common catalyst. One of the early successful examples was reported by Huber in 1944 (**Scheme 3-1-6**).[10b] Although it required over stoichiometric amount of Ni and 15 atm of H_2, both aromatic and aliphatic nitriles could be reduced to primary amine in excellent yield. He found the addition of excess amount of ammonia was necessary to achieve high selectivity toward primary amines.



Scheme 3-1-6. Hydrogenation using stoichiometric amount of Raney-Ni

A catalytic process was achieved by Ferris *et al.* in 1960 although it is difficult to determine the exact amount of catalyst (**Scheme 3-1-7**).[10c] They could decrease the H_2 pressure to 3.4 atm as well. However, solvent amount of acetic anhydride had to be used to achieve high selectivity and a product was obtained as acetyl amide.

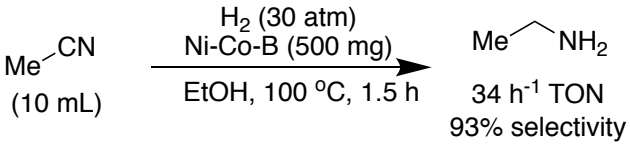


Scheme 3-1-7. Raney-Ni catalyzed hydrogenation of nitrile

Even until recently, several research groups continued to focus on the activity of Raney-alloy such as Raney-Ni or Raney-Co catalysts. However, still much amount of catalysts and high pressure of H_2 are necessary. Addition of excess amount ammonia or acylating reagents are crucial to achieve high selectivity.

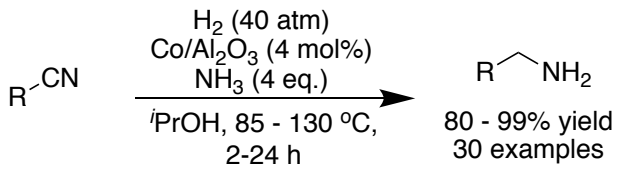
Raney-Ni was also employed for continuous flow hydrogenation for several nitriles despite the requirement of much catalyst amount and high H_2 pressure.[11] Although high yields were achieved using over stoichiometric amount of ammonia with 70 atm of H_2 pressure and 70 ^oC reaction temperature, there is no detailed discussion about a lifetime of catalyst and products were synthesized only in mg scale.

Because preliminary investigation of Raney-Ni suggested low valent Ni species are active catalysts for this transformation, several Ni alloy catalysts have been developed. One of the best alloy catalysts were reported by Li *et al.* in 2004. They demonstrated hydrogenation of acetonitrile to ethylamine using Ni-Co-B amorphous alloy catalyst (**Scheme 3-1-8**).[10o] Although harsh reactions such as 30 atm of H_2 and 100 ^oC reaction temperature were required, the reaction took place in high selectivity with 34 h^{-1} TON in the absence of any additive. However, the decrease of selectivity was observed at high conversion and substrate was limited to only acetonitrile. One possible reason for high selectivity can be the removal of the product from the solution because the boiling point of the product is much lower than reaction temperature at ambient pressure.



Scheme 3-1-8. Ni-Co-B catalyzed hydrogenation of nitrile

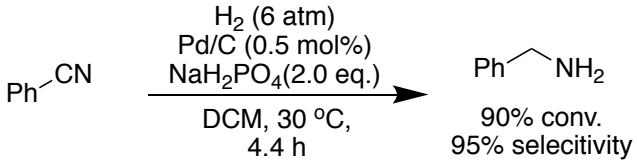
Supported Ni and Co catalysts were also developed for this transformation. However, most of them are applied for only gas phase hydrogenation of acetonitrile, thus they are only applicable for low boiling point substrates. One exception is Al_2O_3 supported Co catalyst reported by Beller *et al.* in 2016 (**Scheme 3-1-9**).[9d] They demonstrated broad substrate scope for both aromatic and aliphatic nitriles with high yields and selectivities using an excess amount of ammonia as an additive. However, still high H_2 pressure remained room to be improved.



Scheme 3-1-9. Co/Al_2O_3 catalyzed hydrogenation of nitrile

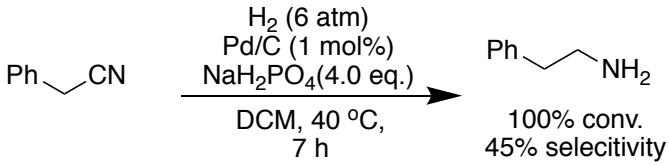
Another promising class of heterogeneous catalysts is supported Pd catalysts.[12] Although the activity of supported Pd for this reaction was discovered as early as in 1928, it has rarely employed for further investigation most likely due to their inferior selectivity

compared with Ni catalysts. Indeed, they are employed as secondary or even tertiary amine selective catalyst. However, recent investigations revealed that high selectivity and milder reaction conditions can be achieved with a proper choice of additives. One of the first successful examples were reported from Hegedus *et al* in 2005 using commercially available Pd/C as catalyst (**Scheme 3-1-10**).[12d] The key to their success is the use of NaH_2PO_4 as stoichiometric amount of additive. Under optimized reaction conditions, benzonitrile was converted to benzylamine in full conversion with 95% selectivity. The reaction could be performed with 6 atm pressure of H_2 and 30 ^oC reaction temperature, which is the mildest conditions ever reported.



Scheme 3-1-10. Pd/C catalyzed hydrogenation of benzylnitrile

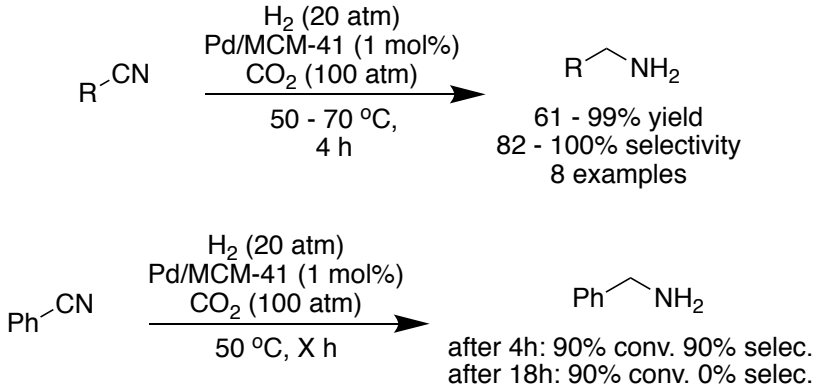
However, one serious disadvantage of their system is the limited substrate scope. In 2008, the same group reported the hydrogenation of benzyl cyanides under similar reaction conditions (**Scheme 3-1-11**).[12e] Surprisingly, the selectivity was significantly decreased to <50% simply by changing the substrate. Despite their efforts to improve the selectivity, the highest yield they could achieve was <50%.



Scheme 3-1-11. Pd/C catalyzed hydrogenation of alkyl nitrile

The scope of nitriles is somehow expanded by employing high-pressure CO_2 as reaction environment. Chatterjee and Kawanami *et al.* developed Pd/MCM-41 catalyzed selective hydrogenation toward primary amine under high pressure of CO_2 and H_2 conditions (**Scheme 3-1-12**).[12f] Under optimized reaction conditions, both aromatic and aliphatic nitriles were converted to primary amines with 75 – 100% selectivities. However, some of the substrates suffer from low conversions and 100 atm of CO_2 was required to achieve high selectivity. Another disadvantage of their system is that selectivity decreased with the increase of reaction time. Using benzonitrile as a substrate, conversion leached 90% after 4h with 90% selectivity toward primary amine. However, the increase of reaction time did not improve conversion and primary amine was completely converted

to the secondary amine.



Scheme 3-1-12. Pd/MCM-41 catalyzed hydrogenation of nitrile

High-pressure CO_2 was also employed with Pd/Al_2O_3 catalyst reported by Arai in 2013.[12h] Although the use of CO_2 significantly improved the selectivity, still 70 atm of CO_2 had to be employed and substrate was limited for only benzonitrile.

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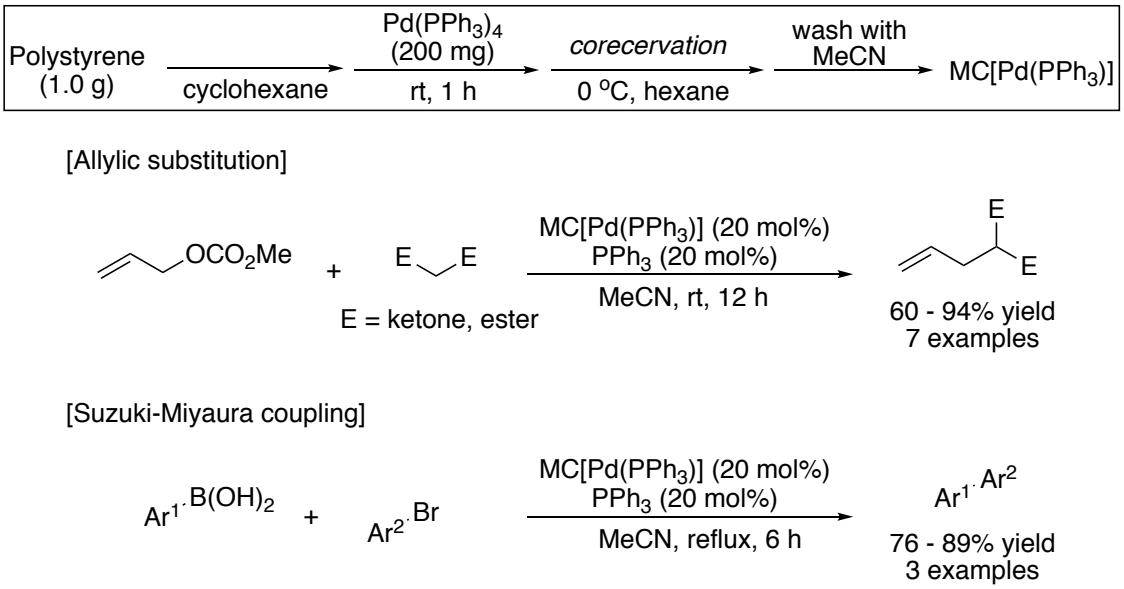
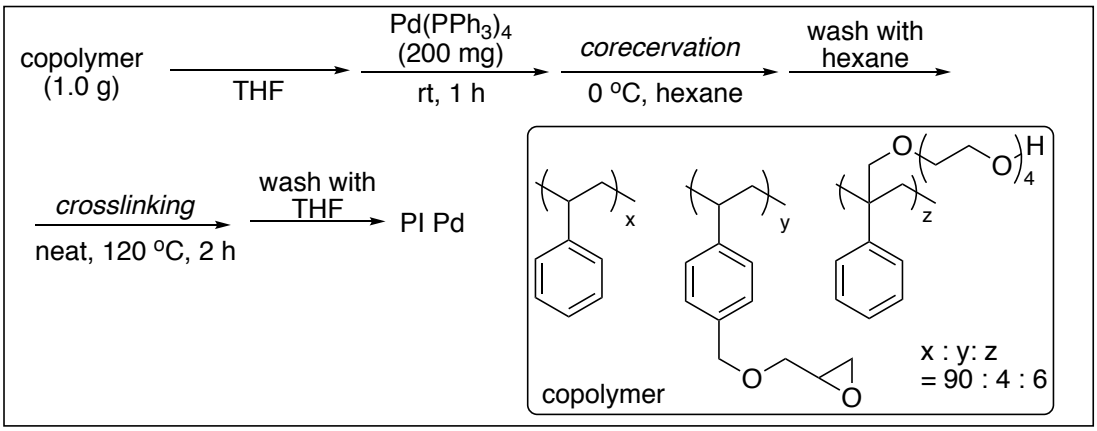
Polysilane-supported Pd Catalysts

Among several strategies to prepare supported Metal NP catalysts, our laboratory has focused on immobilization by a weak and multiple interaction between NPs and polymer.[13] In the preliminary report, $Pd(PPh_3)_4$ was reacted with polystyrene dissolved in a good solvent to form Pd NPs immobilized on polystyrene through metal-π interaction. The polymer was coacervated by addition of poor solvent and recovered as a solid material. This material was named as microencapsulated $Pd(PPh_3)$ (MC [$Pd(PPh_3)$]) and could be used as heterogeneous catalysts for allylic substitution reactions and Suzuki-Miyaura coupling reactions (**Scheme 3-1-12**).[14]

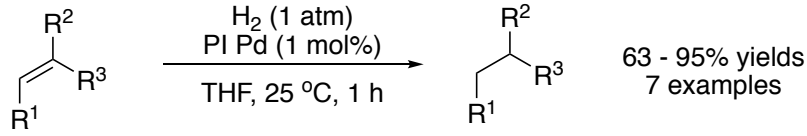


Scheme 3-1-12. MC[Pd(PPh$_3$)] catalyzed allylic substitutions and Suzuki-Miyaura coupling reactions

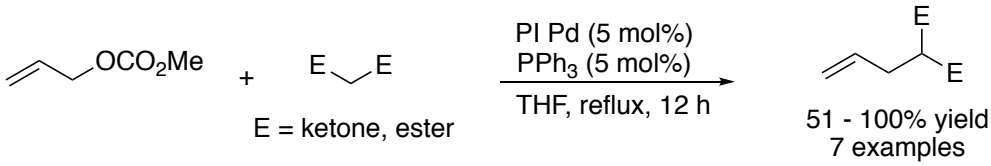
This MC method could be applicable for other metals and a wide range of catalytic reactions. The heterogeneous catalysts could be easily recovered and reused without significant loss of catalyst activity. However, in some cases, small leaching of metal species was observed due to the too much swelling of polystyrene. To overcome this leaching issue, a new method was developed by modification of polystyrene structure. The idea was to hold NPs inside the polymer caged by crosslinking after microencapsulation. Using polystyrene having epoxide and alcohol moiety, the catalyst was prepared with a similar manner as MC catalysts. On the other hand, after microencapsulation, the catalyst was heated at 120 °C to promote crosslinking between polymers by epoxide opening reaction. Catalysts prepared with this method were called as polymer incarcerated Pd catalysts (PI Pd catalysts). PI Pd showed excellent catalyst activity toward various kinds organic transformation such as hydrogenation, coupling reaction (**Scheme 3-1-12**).[15]



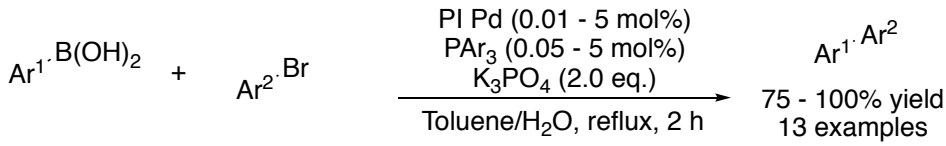
[Hydrogenations]



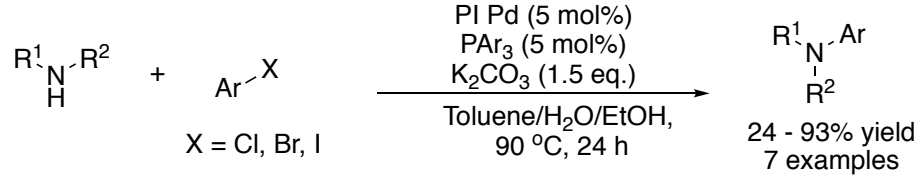
[Allylic substitution]



[Suzuki-Miyaura coupling]



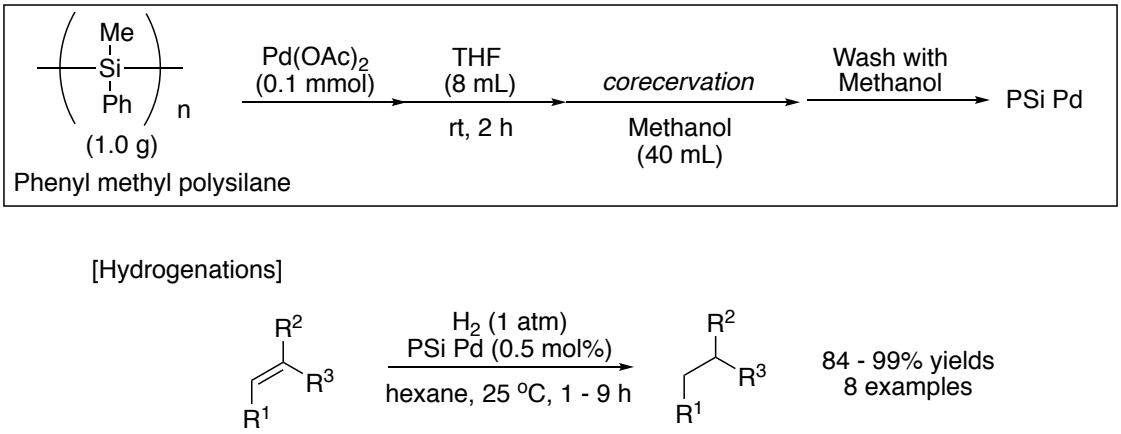
[Buchwald-Hartwig amination]



Scheme 3-1-12. PI Pd catalyzed hydrogenation, allylic substitution, and coupling reactions

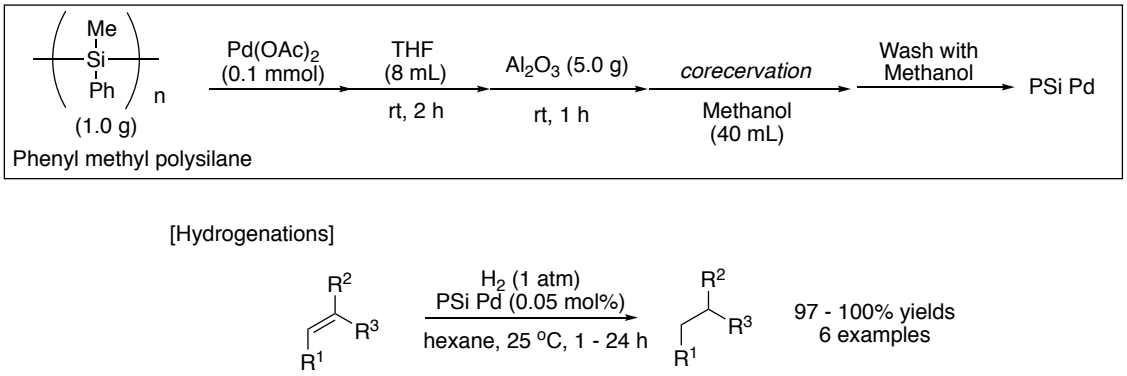
As another polymer material to support Pd NP, we recently have focused on polysilanes. Polysilane is a linear polymer having continuous Si-Si σ-bond and each Si has two alkyl or aryl substituents. They have been studied on its unique optical and electronic properties. In 2006, we first reported the phenyl-methyl-polysilane supported Pd catalysts for

hydrogenation of alkenes (**Scheme 3-1-13**). Phenyl-methyl-polysilane was chosen as a polymer material expecting phenyl substituent on Si atom to stabilize the Pd NPs. Polysilane supported Pd catalyst was prepared following the MC method and named as PSi/Pd. It was found that polysilane indeed worked as a stabilizer for Pd NP to achieve high catalyst activity. Another interesting finding during catalyst preparation was that $Pd(OAc)_2$ was reduced to Pd(0) NP in the absence of any external reductant. This result clearly indicated that polysilane also worked as a reductant of Pd(II).



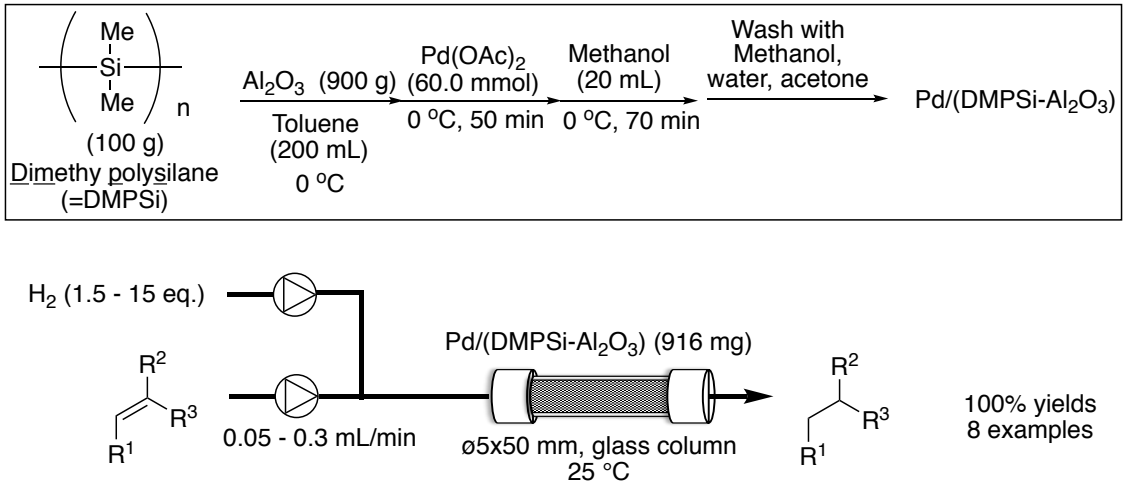
Scheme 3-1-13. PSi Pd catalyzed hydrogenation of olefin

Although polysilane supported Pd demonstrated excellent catalyst activity for hydrogenation, there were several drawbacks for this catalyst. First, due to good solubility of phenyl methyl polysilane, the reaction solvent was limited for a poor solvent such as hexane. Second, small leaching of Pd was detected using amine-containing compounds as substrates. To overcome these issues, inorganic support material was incorporated during catalyst preparation. After microencapsulation of Pd NP, the material was heated at 120 °C to promote the crosslinking between polysilane and inorganic support in similar manner as previous PI catalysts. Thus, the catalyst was named as PI Pd/PSi on a metal oxide. Among several examined metal oxides, Al_2O_3 showed the best activity for hydrogenation and efficient immobilization of Pd was achieved (**Scheme 3-1-14**). PI Pd/PSi on Al_2O_3 showed excellent catalyst activity for hydrogenation of a wide variety of olefins. It also allowed to use conventional organic solvents and to perform reaction under neat conditions without leaching of catalyst.[17]



Scheme 3-1-14. PI Pd/PSi on Al_2O_3 catalyzed hydrogenation of olefin

More recently, we also developed dimethyl polysilane supported Pd catalyst for hydrogenation of olefins under continuous-flow conditions. Dimethyl polysilane was employed as an alternative material of phenyl methyl polysilane. Interestingly Pd NPs were successfully immobilized on solid material even without aromatic rings on polymer structure. It was suggested that Si–Si σ-bond can coordinate to Pd NPs due to its narrow HOMO-LOMO gap originated from hyperconjugation. The new catalyst showed excellent activity even under continuous-flow conditions (**Scheme 3-1-15**).[18]

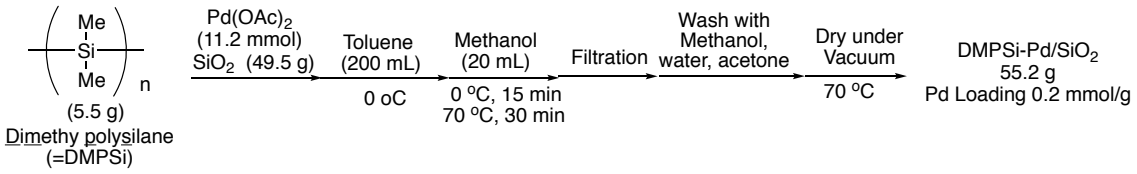


Scheme 3-1-15. Pd/(DMPSi-Al_2O_3) catalyzed continuous flow hydrogenation of olefin

Based on these previous results, I decided to start the investigation of nitrile hydrogenation under continuous-flow conditions using polysilane supported Pd catalyst. The purpose of this study is to establish the synthesis of primary amine based on nitrile at the late stage of multistep transformation.

3-2. Preparation of polysilane-supported Pd/SiO_2 catalysts

At first, polysilane-supported Pd catalyst was prepared using SiO_2 as inorganic support referring to the previously reported procedure (**Scheme 3-2-1**).



Scheme 3-2-1. Preparation of DMPSi-Pd/SiO_2

To a mixture of dimethyl polysilane, SiO_2, and $Pd(OAc)_2$ was added toluene at 0 °C. After stirring to get a dispersed solution, methanol was added dropwise and stirred for 15 minutes. Then the reaction temperature was increased to 70 °C and stirred for 30 minutes. During this period, the color of the mixture was turned from yellow to black, indicating that Pd(II) was reduced to Pd (0) particles. Following filtration, washing, and drying gave the heterogeneous Pd catalyst named as DMPSi-Pd/SiO_2 with 0.2 mmol/g loading of Pd. By changing the amount of $Pd(OAc)_2$, DMPSi-Pd/SiO_2 with different Pd loading was prepared as well. The prepared catalyst was characterized by a STEM and EDS mapping (**Figure 3-2-1**).

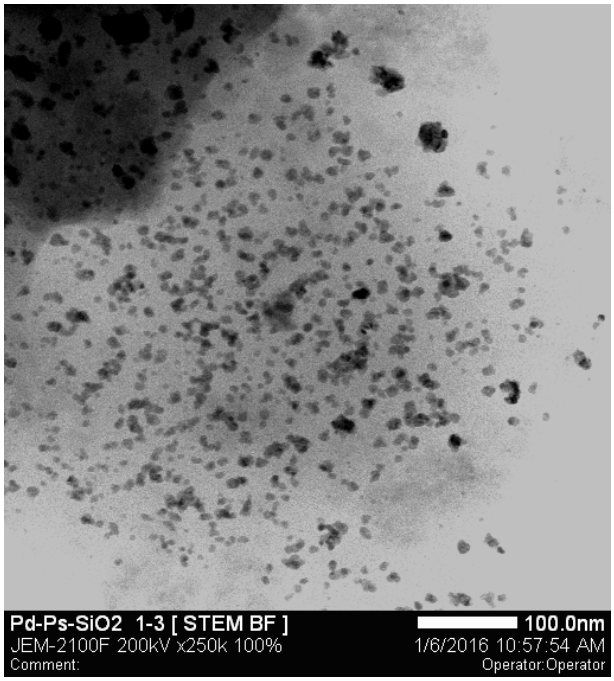


Figure 3-2-1-a. STEM image of DMPSi-Pd/SiO_2

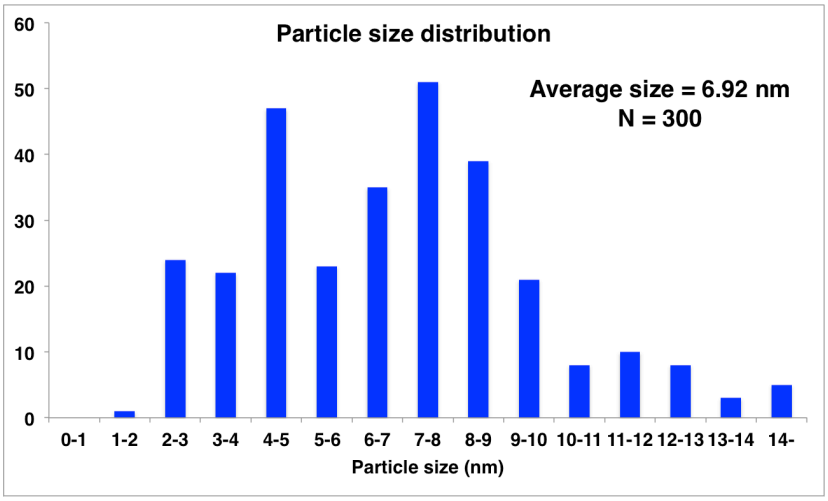


Figure 3-2-1-b. Size distribution of Pd NP

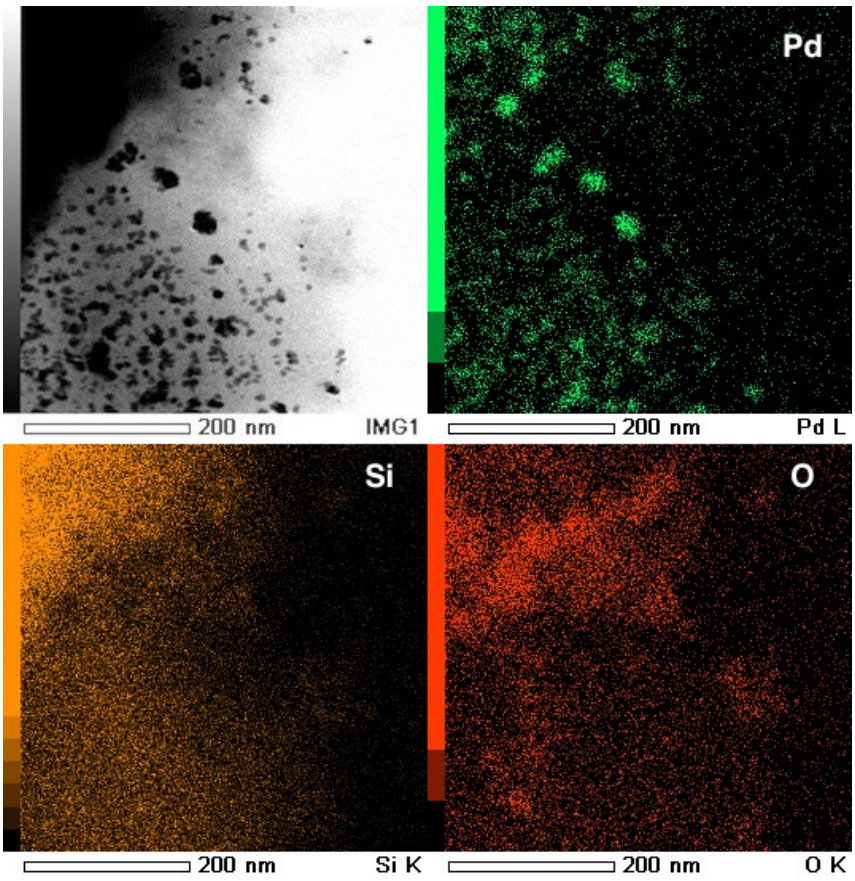


Figure 3-2-1-c. EDS mapping of DMPSi-Pd/SiO_2

The average size of Pd nanoparticle in DMPSi-Pd/SiO_2 is 6.92 nm, which is a little bit larger than DMPSi-Pd/Al_2O_3 as described in the previous report. However, size distribution histogram suggests that 2nd peak exists around 4-5 nm, which can be more

active species for the catalysis. Judging from the EDS mapping, the Pd nanoparticle exists in both Si-rich area and O-rich area. This observation suggests that Pd(II) was reduced to Pd (0) by polysilane and subsequently immobilized on the surface of SiO_2 to form nanoparticles. The Pd (0) particles are likely to be immobilized by Si-Pd covalent bonds or η^2 coordination of Si-Si single bonds.

3-3. Hydrogenation of decane nitrile using DMPSi-Pd/SiO_2 under continuous-flow conditions

The prepared catalysts were then evaluated in the hydrogenation of decanenitrile under continuous-flow conditions. As standard conditions, 0.2 M solution of decanenitrile **1a** and 1.5 eq. of HCl in 1-PrOH and H_2O was prepared. This mixed solvent system was chosen because of its homogeneity, high boiling point, and solubility of both substrate and products. The solution was flowed at 0.1 mL/min flow rate into a glass column packed with heterogeneous catalyst and SiO_2 heated at 60 °C together with 150 kPa(G) of H_2 flow. The resulting solution was collected after 18 h flow started and analyzed by ^{1}H NMR **(Figure 3-3-1)**.

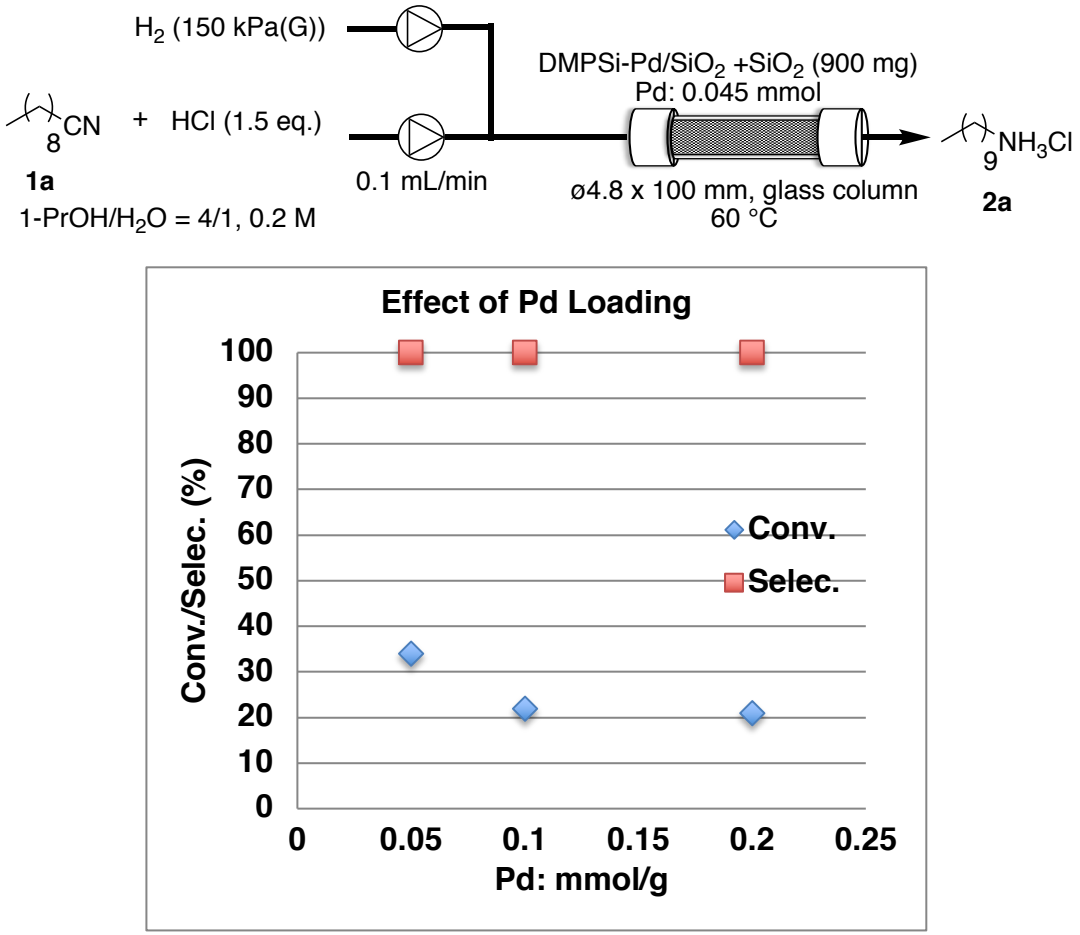


Figure 3-3-1. Hydrogenation of decanenitrile using DMPSi-Pd/SiO_2 with different concentration

At first, the effect of Pd concentration of catalyst was examined. The reaction took place in 23% conversion and >99% selectivity for desired primary ammonium salt **2a** with 0.2 mmol/g loading. When the loading was decreased to 0.1 mmol/g, the reaction proceeded with almost same conversion and selectivity. Further decrease of Pd loading

somehow improved the conversion to 34% without loss of selectivity. However, because lower concentration requires bigger catalyst column as well as much amount of SiO_2 thus decreases the space-time yield, the catalyst with 0.2 mmol/g loading was decided to be employed for further investigations.

Next, the effect of reaction temperature was investigated using the increased amount of Pd catalyst (**Figure 3-3-2**). When the reaction temperature was set at 60 °C, the desired compound was obtained in 65% conversion and >99% selectivity. The decrease of reaction temperature to 50 °C decreased the conversion to 46%. On the other hand, increasing the reaction temperature from 80 to 90 °C resulted in the increase of conversion. 95% conversion was achieved when the reaction was performed at 90 °C. It should be noticed that selectivity remained >99% even reaction under high reaction temperature.

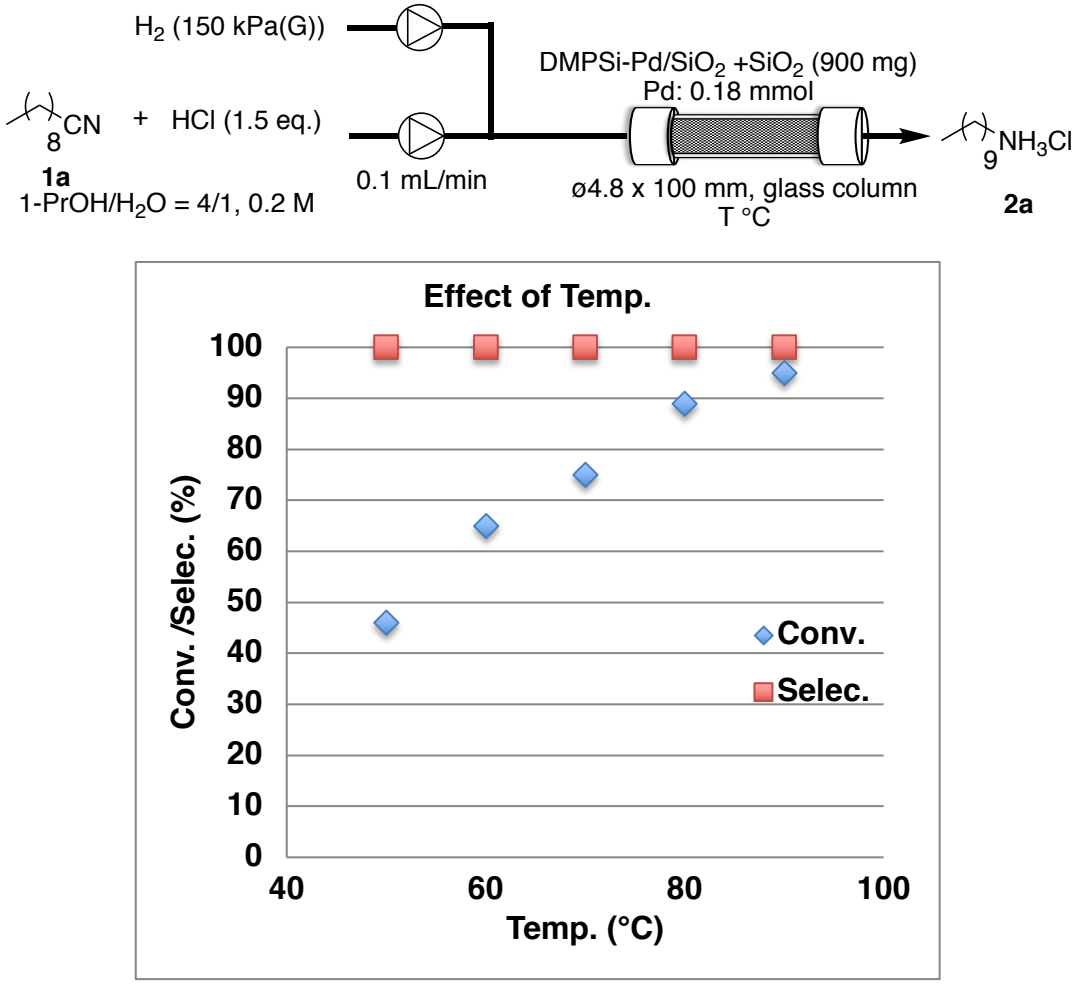


Figure 3-3-2. Effect of reaction temperature

As it was found that excellent conversion and selectivity could be achieved at the high reaction temperature, following investigations were focused on improving the productivity of the system. To improve the productivity, the effect of concentration was

investigated at first (**Figure 3-3-3**). When the concentration was increased from 0.2 to 0.3 M, decreased conversion was observed and the productivity was almost the same as 0.2 M. In contrast, decreased concentration resulted in the decrease of both productivity and selectivity. Reaction at low concentration gave secondary ammonium salt as a side product, which seemed to be generated from decomposition of imine intermediate. High concentration was found to be the key to suppress such undesired side reaction and to achieve high selectivity.

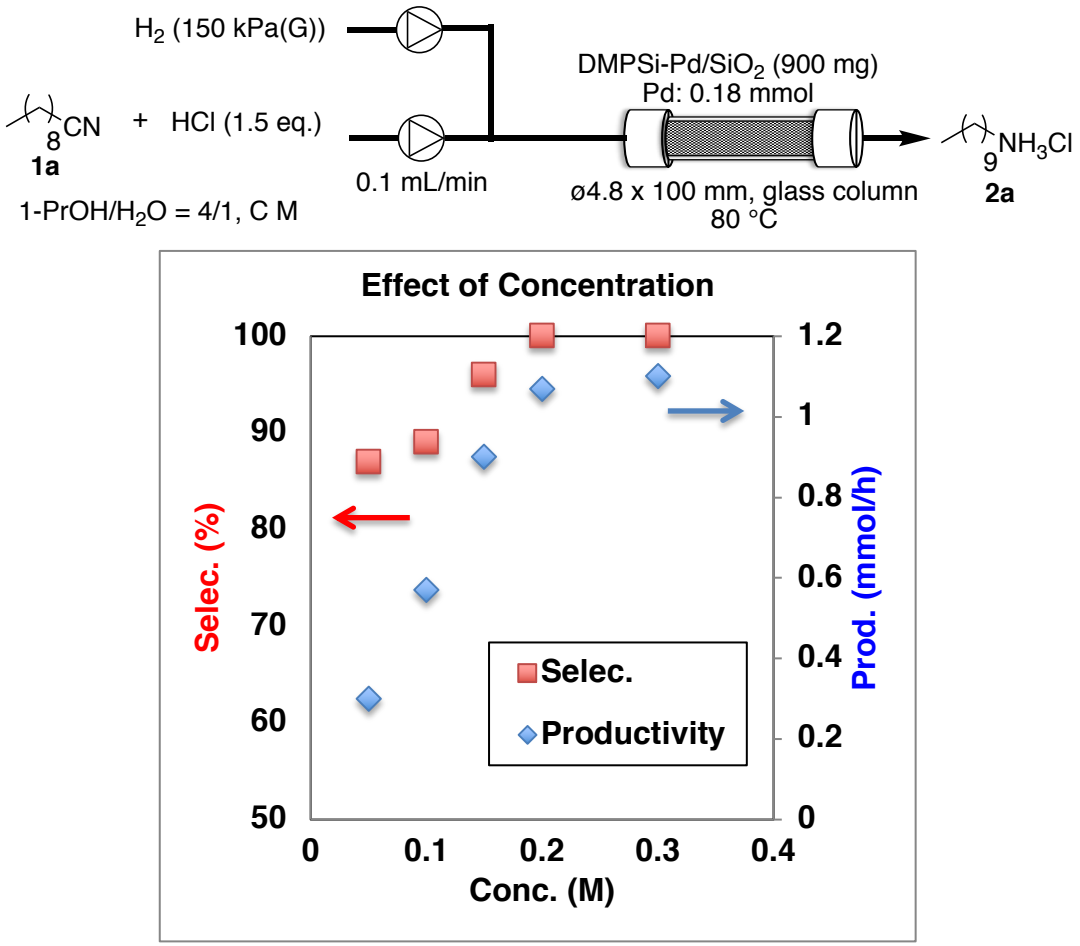


Figure 3-3-3. Effect of concentration

Next, the effect of the flow rate was investigated with 0.2 M concentration (**Figure 3-3-4**). As a result, a similar tendency was observed as the effect of concentration was examined. The increase of flow rate resulted in the decrease of conversion and productivity. The decrease of flow rate decreased productivity and selectivity as well. In these cases, secondary ammonium salt was obtained as a side product as well. These results indicated that less WHSV promoted undesired side reaction. Detailed reaction mechanism and effect of reaction parameters will be discussed in the following section.

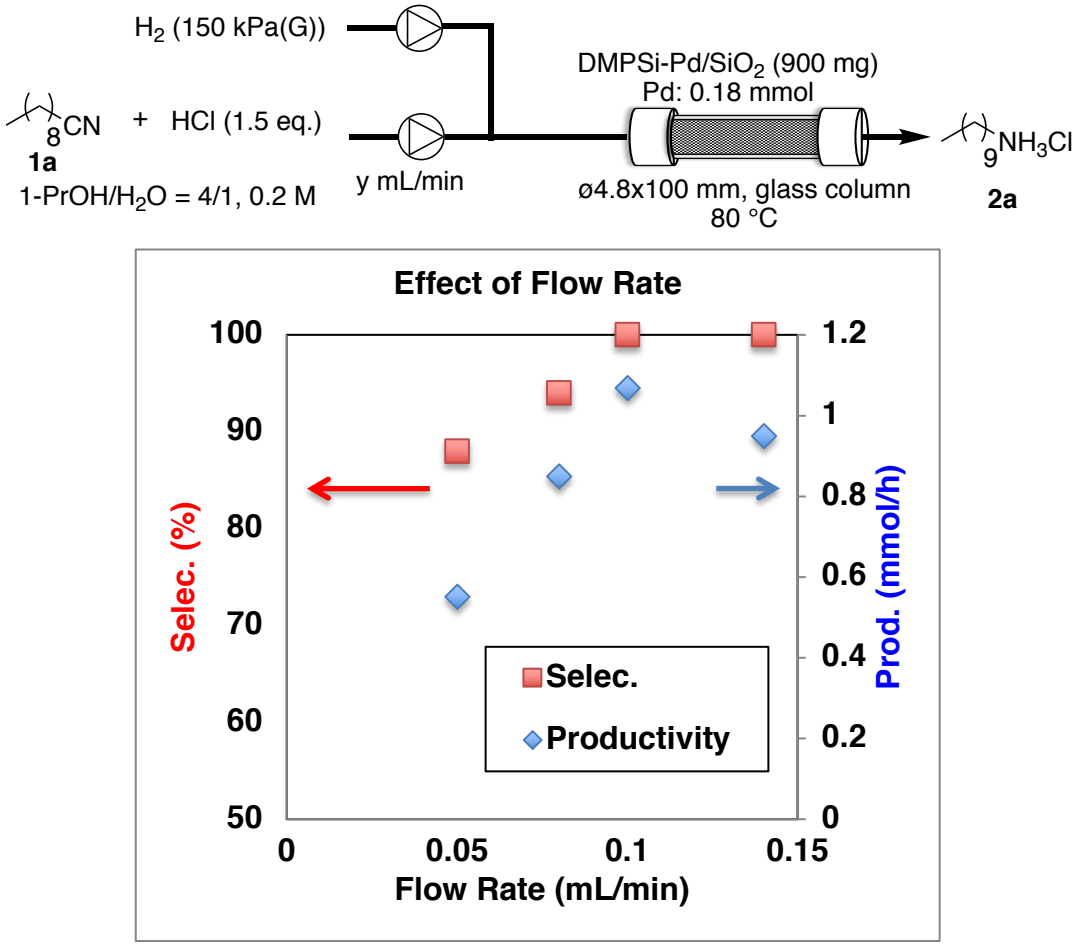
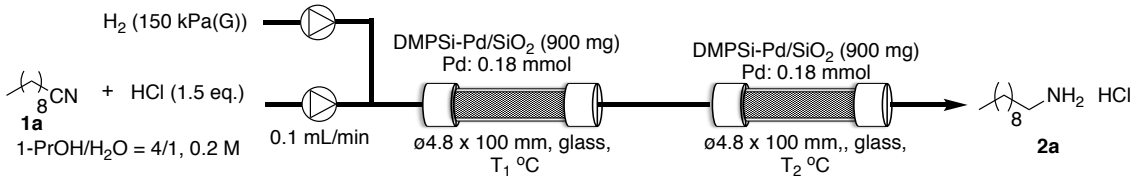


Figure 3-3-4. Effect of flow rate

Although excellent yield and selectivity were achieved under high reaction temperature, several attempts have been made with increased catalyst amount to make reaction conditions milder and to expand the substrate scope of nitriles which have low boiling points (**Table 3-3-1**). It was likely that undesired side product was formed by the reaction between primary amine product and intermediate. If it is true, such undesired side reaction would be accelerated at the last stage of the catalysis because of the high concentration of the product. Then, it was hypothesized that decreasing temperature of the column near exit point would be effective to achieve high selectivity. Thus, in this study, two catalyst columns were prepared, directly connected, and reaction temperature for each catalyst column was adjusted independently. When the both of catalyst column was heated at 90 °C, the desired compound was obtained in >99% conversion but 92% selectivity (Entry 1). To suppress undesired side reaction, the reaction temperature in the second column was decreased to 80 °C. As a result, a small improvement in selectivity was observed without loss of conversion (Entry 2). For further improvement of selectivity, the reaction temperature of both columns was decreased (Entries3-5). The best selectivity was achieved when the temperature was adjusted at 70 °C to 60 °C without significant loss of

conversion. Further decrease of reaction temperature resulted in decreased conversion (Entry 6). Under optimized reaction conditions, the target compound was obtained in 98% yield with >99% selectivity.

Table 3-3-1. reaction with two catalyst columns with different temperature

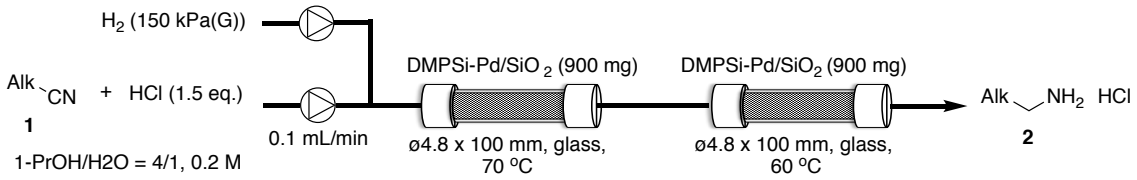


Entry	T_1	T_2	Conv. (%)	Selectivity (%)
1	90	90	99	92
2	90	80	99	93
3	80	80	99	97
4	70	70	99	99
5	70	60	98	>99
6	60	60	97	>99

3-4. Substrate scope for aliphatic and benzyl nitriles

Under optimized reaction conditions, the scope of aliphatic nitriles was investigated (**Table 3-4-1**). For the substrate scope, the flow reaction was continued for 18 h, and yield was determined at the stage of 3, 6, and 18 h. Under these reaction conditions, productivity was 1.2 mmol/g and TOF was 0.67 h^{-1}. First, several nitriles with different steric environments were employed for the flow reaction. β-branched nitrile **2n** gave a similar result as a model substrate to afford the desired compound in excellent yield (Entry 2). Next sterically more demanding α-branched nitriles were investigated. The reaction took place smoothly for both secondary and tertiary nitriles **2o** and **2p**, and the desired compounds were obtained in excellent yield (Entries 3,4). Thus, it was suggested the catalyst was not affected by a steric factor of substrates. Thanks to the low reaction temperature, even acetonitrile **2q** could be used as a substrate to afford ethyl ammonium salt in excellent yield (Entry 5). Functional group compatibility was examined using cyano ester **2r** as substrate. With this substrate, solvent system was changed to EtOH/Dioxane to suppress hydrolysis and transesterification. Under these reaction conditions, the desired ammonium salt was obtained in excellent yield without reduction of ester moiety nor lactam formation.

Table 3-4-1 substrate scope for aliphatic nitriles



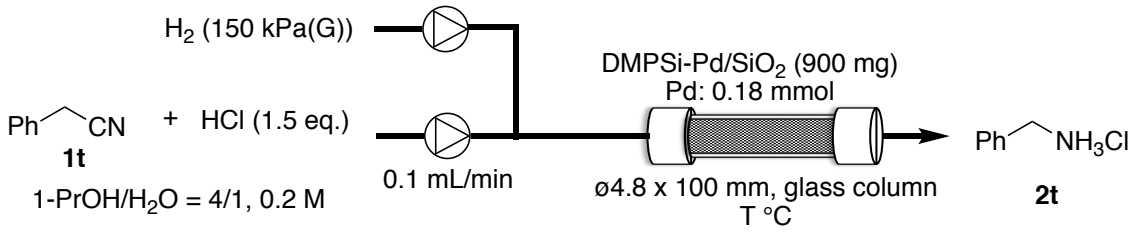
Entry	Alk	Yield (%)
1	$^{n}C_9H_{19}$ (**2a**)	98
2	Me_2CHCH_2 (**2n**)	98-99
3	^{i}Pr (**2o**)	98
4	^{t}Bu (**2p**)	quant.
5	Me (**2q**)	99 - quant.
6[a]	EtO_2CCH_2 (**2r**)	97

[a]EtOH/Dioxane was used as solvent

Next, benzyl cyanides were focused on. The product phenethylamine family is known to have biological activity. In that context, the establishment of the general and reliable preparation method would contribute to the drug synthesis. In the first trial, benzyl cyanide **1t** was employed as a substrate. Unfortunately, the only moderate yield for the desired compound was observed and the complex mixture was obtained under standard conditions for aliphatic nitriles (**Table 3-4-2**, Entry 1). It seems that phenyl substituent at α-position enhanced the formation of aza-enolate and promoted side reactions. Thus,

optimization of reaction conditions to suppress side reactions was performed. As expected, decreasing reaction temperature resulted in improved selectivity (Entry 2-5). On the other hand, the conversion was kept >99% even reaction at 50 °C unexpectedly. Comparing the low conversion of decane nitrile at a low reaction temperature, reactivity completely depends on the structure of the substrate. Finally, the concentration was decreased due to the low solubility of substrate and flow rate was increased to maintain the productivity (Entry 6). Fortunately, the desired compound was obtained in excellent yield with a small improvement of selectivity.

Table 3-4-2. Optimization for benzyl cyanide

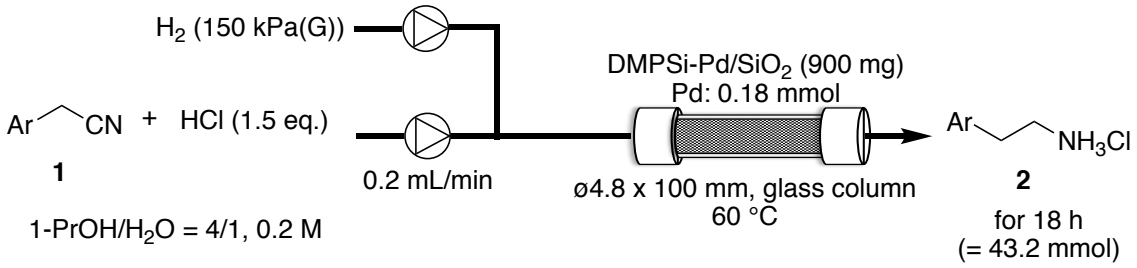


Entry	T (°C)	Conv. (%)	Selectivity (%)
1	90	>99	64
2	80	>99	71
3	70	>99	84
4	60	>99	90
5	50	>99	97
6[a]	50	>99	>99

[a] 0.1 M concentration and 0.2 mL/min flow rate

Under optimized reaction conditions for benzyl nitrile, substrate scope for substituent on phenyl ring was investigated (**Table 3-4-3**). The model substrate gave the desired phenylethylamine **1t** in excellent yield for 18 h (Entry 1). Both electron donating and withdrawing substituents did not affect the reactivity. A family of phenylethylamine was synthesized in excellent yields (Entries 2-4).

Table 3-4-3. substrate scope for benzyl nitriles

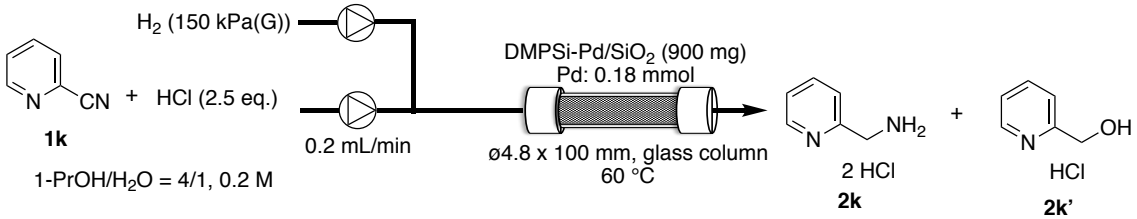


Entry	Ar	Yield (%)
1	Ph (**2t**)	99 - quant.
2	4-$OMeC_6H_4$ (**2u**)	quant.
3	3,4-$(OMe)_2C_6H_3$ (**2v**)	quant.
4	4-FC_6H_4 (**2w**)	quant.

3-5. Optimization for aromatic nitriles

Finally, substrate scope for aromatic nitriles was examined. As reported system frequently suffered from the low selectivity for heteroaromatic nitriles, 2-cyanopyridine **1k** was chosen as model substrate and reaction conditions were examined (**Table 3-5-1**). Under standard conditions for benzyl cyanide, the starting material was fully consumed. However, desired compound **2k** was obtained in only 62-66% yield for 18 h reaction, and a significant amount of alcohol **2k'** was obtained (Entry 1). As such side product seemed to be produced by the hydrolysis of intermediate, the reaction was performed in anhydrous conditions to prevent hydrolysis. Using 1PrOH/Dioxane co-solvent was not effective due to the low solubility of the desired product (Entry 2). Changing solvent MeOH/Dioxane improved the solubility issue, and reaction took place for the first 3 h to afford the desired compound in excellent yield (Entry 3). Under these conditions, the formation of alcohol was completely suppressed as expected. However, clogging was observed after 6 h flow started. To improve the solubility, the concentration was decreased to 0.1 M. Unfortunately, the over reduction of pyridine ring was observed due to the low WHSV, and yield of the desired compound was decreased to 56-66% yield (Entry 4). To suppress over reduction, the flow rate was increased to 0.4 mL/min, finally giving the desired compound in 99% yield for 18 h (Entry 5).

Table 3-5-1. Optimization for 2-cyanopyridine

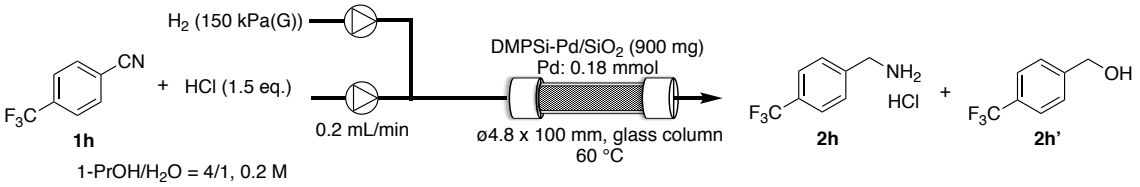


Entry	Deviation from standard	Conv. (%)	**2k** (%)	**2k'** (%)
1	none	100	62-66	33-41
2	1-PrOH/Dioxane = 9/1 as solvent	-	-	-
3	MeOH/Dioxane = 9/1 as solvent	-	-	-
4	MeOH/Dioxane = 9/1 as solvent, 0.1 M	100	56-66	<1
5	MeOH/Dioxane = 9/1 as solvent, 0.1 M, 0.4 ml/min flow rate	100	99	<1

A similar tendency was observed using *p*-CF_3 substituted benzonitrile **1h** as substrate (**Table 3-5-2**). Using 1-PrOH/H_2O as solvent system, alcohol was obtained in 13-16% yield together with desired ammonium salt (Entry 1). By changing the solvent system to 1-PrOH/Dioxane, the formation of alcohol was completely suppressed and the target compound was obtained in excellent yield (Entry 2). From the results obtained from 2-cyanopyridine and *p*-CF_3 benzonitrile, the anhydrous solvent system was determined to

be optimized conditions for electron deficient substrates.

Table 3-5-2. Optimization for *p*-CF_3 benzonitrile

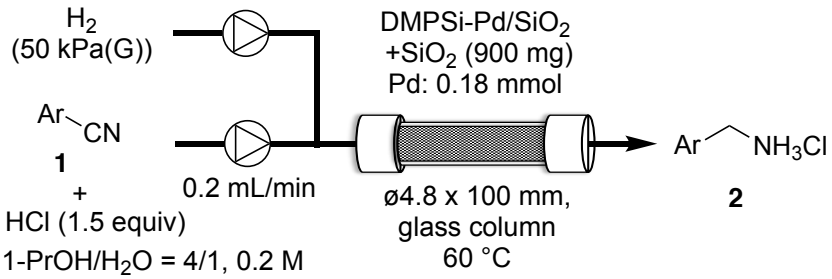


Entry	Deviation from standard	Conv. (%)	**2h** (%)	**2h'** (%)
1	none	100	62-66	13-16
2	1-PrOH/Dioxane = 9/1 as solvent	100	99	<1

3-6. Substrate scope for aromatic nitriles

With optimized condition for previously difficult substrates in hand, the scope of aromatic nitriles was examined (**Table 3-6-1**). Fortunately, benzonitrile **1b** was converted to benzyl ammonium salt **2b** under standard conditions for benzyl cyanide in quantitative yield (Entry 1). Undesired alcohol formation was suppressed probably due to the higher resistance of intermediate toward hydrolysis than that of electron deficient substrates. Similar results were obtained in *m*- and *p*-Me substituted benzonitriles (Entry 2-3). However, *o*-Me substituted benzonitrile required increased H_2 pressure to achieve full conversion (Entry 4). Lower reactivity of this substrate can be explained by the steric congestion around reaction site. Higher H_2 pressure was efficient for substrates with *p*-OMe and *p*-OH substituents as well (Entries 5-6). These results are good agreement with the general tendency that electron rich nitriles are more resistant toward reduction. As examined in the previous section, the anhydrous solvent system was effective for a wide range of electron deficient substrates (Entries 7-13). *p*-F substituent was tolerant under reaction conditions (Entry 8). Pyridine ring was not reduced regardless of the position of substituents (Entries 10, 11). Finally, the di-cyanide substrate was converted to di-ammonium salts in excellent yield (Entry 12).

Table 3-6-1 substrate scope for aromatic nitrile



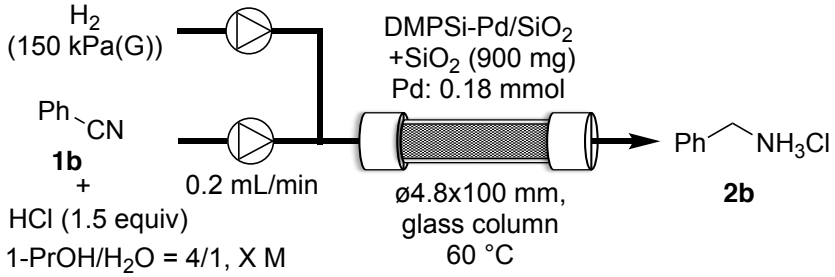
Entry	R	Yield (%)	Entry	R	Yield (%)
1	C_6H_5 (**2b**)	quant.	7[b]	*p*-$CF_3C_6H_4$ (**2h**)	quant.
2	*m*-MeC_6H_4 (**2c**)	99 – quant.	8[b]	*p*-FC_6H_4 (**2i**)	quant.
3	*p*-MeC_6H_4 (**2d**)	99 – quant.	9[b]	1-Naph (**2j**)	97 – 98
4[a]	*o*-MeC_6H_4 (**2e**)	quant.	10[c]	2-Py (**2k**)	99
5[a]	*p*-$OMeC_6H_4$ (**2f**)	99	11[c]	3-Py (**2l**)	99 – quant.
6[a]	*p*-OHC_6H_4 (**2g**)	97 – 98	12	*m*-CNC_6H_4 (**2m**)	99

[a] reaction was performed with 150 kPa(G) of H_2, [b] 1-PrOH/Dioxane as solvent,
[c] MeOH/Dioxane as solvent, 0.1 M concentration, 0.4 mL/min flow rate

3-7. Lifetime and reaching experiments

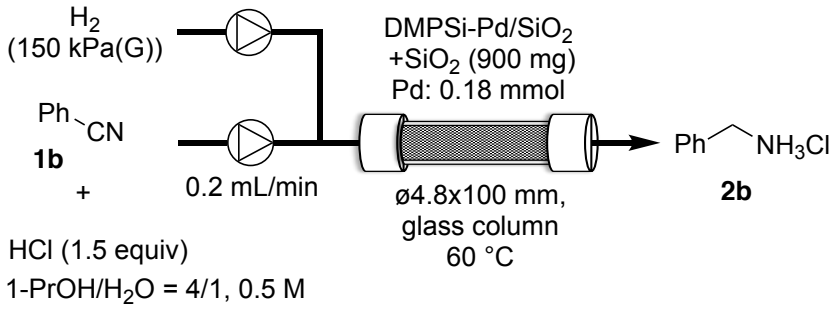
To examine the lifetime of DMPSi-Pd/SiO_2 catalyst, long time operation was performed using decanenitrile as a model substrate. Before starting long time experiment, the effect of concentration was investigated to improve the productivity of the system (**Table 3-7-1**). Increasing the concentration did not affect the conversion and selectivity, and the desired compound was obtained in quantitative yield (Entries 1,2). However, further increase of concentration to 1.0 M resulted in the clogging of flow due to the precipitation of product (Entry 3). Under optimized reaction conditions, the target compound can be produced with 6 mmol/h.

Table 3-7-1. Investigation to increase the productivity



Entry	Conc. (M)	Yield (%)
1	0.2	>99
2	0.5	>99
3	1.0	clogging

The longtime operation was performed with 0.5 M of substrate solution for 300 h (**Figure 3-7-1**). As a result, the target compound was obtained in quantitative yield over whole operation period. Finally, 1.80 mol of ammonium salt could be synthesized and TON value reached 10078. Leaching of Pd into the product was analyzed by ICP measurement of product. It was found that Pd leaching was under detection limit, indicating less than 7.44×10^{-5} mg of Pd existed in 1 g of product.



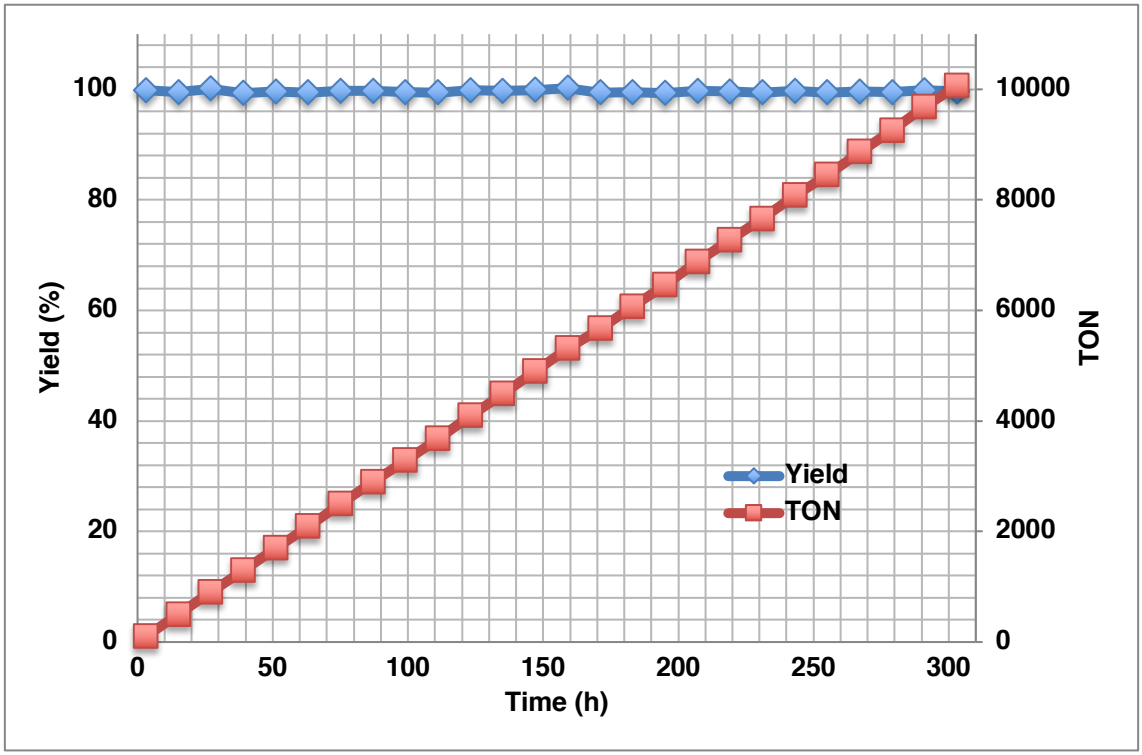
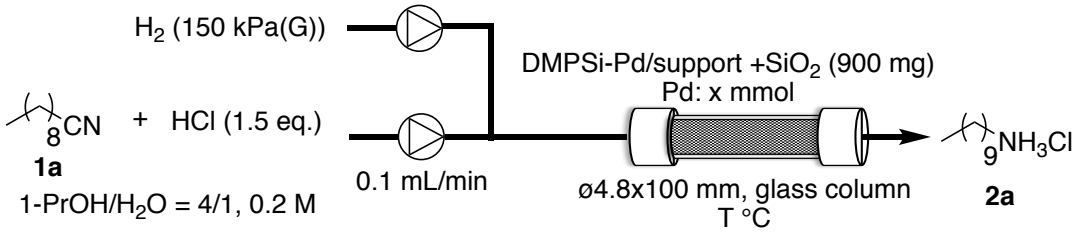


Figure 3-5-1. Lifetime experiment

3-8. Control experiments

Several control experiments were performed to clarify the effect of supports in this catalysis using decane nitrile model substrate (**Table 3-8-1**). First, the catalyst activity was compared with a small amount of catalyst and low reaction temperature. Under these reaction conditions, DMPSi-Pd/SiO_2 gave the desired compound in 23% conversion with >99% selectivity (Entry 1). By changing the inorganic support from SiO_2 to Al_2O_3, the significant increase of conversion was observed with small decrease of selectivity (Entry 2). From these results, it can be concluded that DMPSi-Pd/SiO_2 is less active but more selective than DMPSi-Pd/Al_2O_3. When commercially available Pd/C was used, high activity and excellent selectivity were observed after 3 h flow started. However, the significant decrease in conversion was observed after 18 h unlike former catalysts (Entry 3). Thus, decreased activity of Pd/C seemed to be caused by the deactivation of the catalyst. To observe the behavior of catalysts in higher conversion, flow reaction was performed with the increased amount of Pd catalyst and increased reaction temperature. As described in the previous section, the high reaction temperature was effective for DMPSi-Pd/SiO_2 to give target compound in 89% yield with >99% selectivity (Entry 4). However, when DMPSi-Pd/Al_2O_3 was used as a catalyst, the small improvement in conversion and the significant decrease in selectivity were observed (Entry 5). These results clearly emphasize the excellent selectivity of DMPSi-Pd/SiO_2 catalyst. Using Pd/C as catalyst, small decrease of selectivity was observed (Entry 6). More significantly, catalyst deactivation could not be suppressed even using the increased amount of catalyst. Finally, the catalysis was performed in the absence of HCl. Lower conversion and selectivity were observed. Therefore, HCl is crucial to get high activity and selectivity.

Table 3-8-1 Control experiments

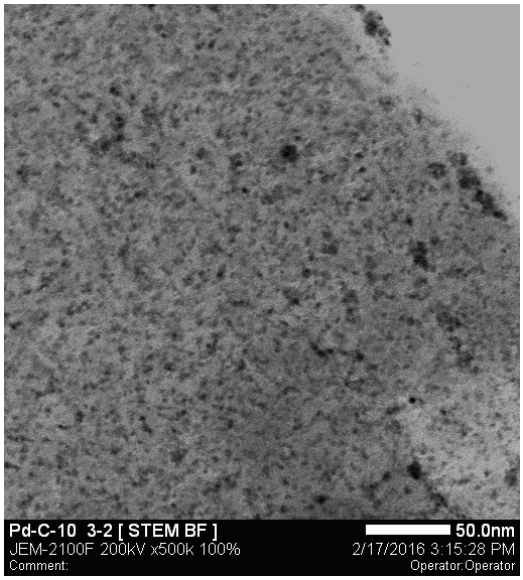


Entry	Cat.	Cond.	3-3.5 h		18-18.5 h	
			Conv. (%)	Selec. (%)	Conv. (%)	Selec. (%)
1	DMPSi-Pd/SiO_2	A	23	100	23	100
2	DMPSi-Pd/Al_2O_3	A	76	96	77	96
3	Pd/C	A	80	100	33	100
4	DMPSi-Pd/SiO_2	B	89	100	89	100
5	DMPSi-Pd/Al_2O_3	B	82	83	84	83
6	Pd/C	B	85	93	56	88
7	DMPSi-Pd/SiO_2	C	75	90	-	-

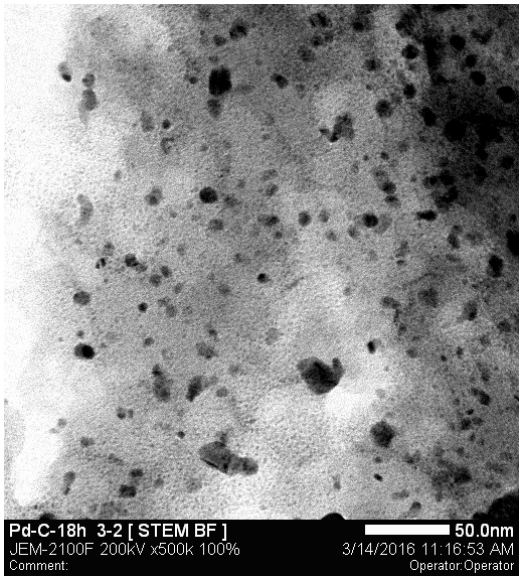
8	DMPSi-Pd/Al_2O_3	C	70	79	-	-

Cond. A 0.045 mmol of Pd was used, reaction was performed at 60 °C
Cond. B 0.18 mmol of Pd was used, reaction was performed at 80 °C
Cond. C 0.18 mmol of Pd was used, reaction was performed at 80 °C in the absence of HCl

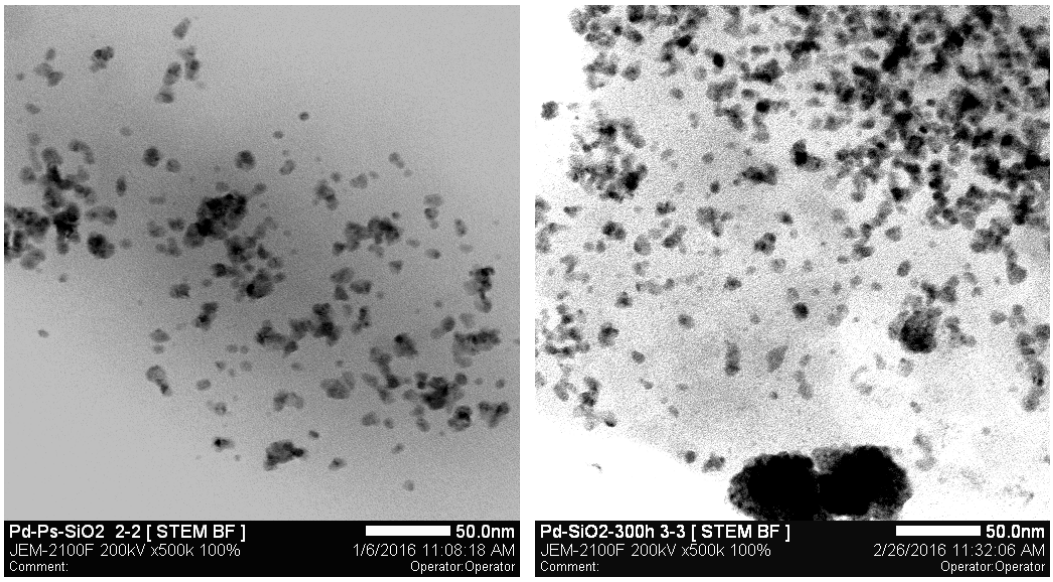
Next, to clarify the reason for long lifetime of DMPSi-Pd/SiO_2, catalysts recovered after the reaction was analyzed by the STEM images (**Figure 3-8-1**). As for Pd/C, 1-2 nm of Pd NPs were well dispersed on carbon black before catalysis. However, after hydrogenation, most of the small NPs get aggregated to form around 10 nm size NPs. On the other hand, DMPSi-Pd/SiO_2 kept its NP size even after the reaction, although a little aggregation was observed. From these results, it is likely that deactivation of the catalyst is originated from the aggregation of Pd NPs, and dimethylpolysilane is obviously effective to prevent aggregation.



(a) Pd/C before catalysis



(b) Pd/C after catalysis (18 h)



(c)DMPSi-Pd/SiO_2 before catalysis (d) DMPSi-Pd/SiO_2 after catalysis

Figure 3-8-1. STEM images of catalysts before and after catalysis

Finally, the effects of inorganic support and HCl for both conversion and selectivity were elucidated by considering the reaction mechanism to give side products. First, reaction mechanism in the absence of HCl is discussed to make it clear (**Figure 3-8-1**). First, nitrile **1** is deduced by 1 molecule of H_2 adsorbed on Pd to give NH imine **A** as the key intermediate. In the desired reaction pathway, NH imine again reacts with another H_2 adsorbed on Pd to give desired compound amine **2**. However, NH imine **A** can readily react with product amine **2** to give N-alkylated imine and ammonia in the absence of the catalyst. N-alkyl imine can be reduced as the same manner as NH imine by Pd catalyst to give secondary amine **B** as a side product. From this mechanism, it is obvious that smooth consumption of NH-imine **A** is crucial to achieve high selectivity. Considering the fact that DMPSi-Pd/SiO_2 is less active but more selective than DMPSi-Pd/Al_2O_3, it can be explained that lower activity can keep the concentration of NH imine low, and more active NH imine is selectively reduced by Pd catalyst in prior to undesired side reaction. Lower selectivity in the conditions of low concentration and low flow rate can be explained by the decreased chance of the intermediate to interact with the catalyst.

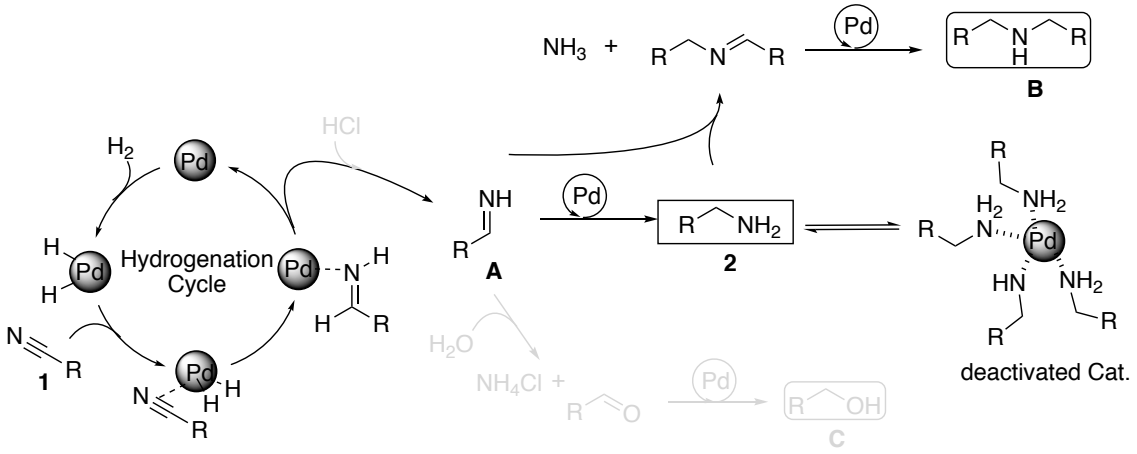


Figure 3-8-1. Reaction mechanism in the absence of HCl

In the presence of HCl, the reaction takes place as similar manner as described above (**Figure 3-8-2**). The difference in the structure of product and side reaction pathway. After second hydrogenation of NH imine, most of the product exists as ammonium salt due to the strong acidity of HCl. Thus, the product can no longer react with intermediate to form N-alkyl imine. On the other hand, solvent amount of H_2O readily reacts with intermediate **A** to form the aldehyde. Further hydrogenation of aldehyde gives the alcohol **C** as a side product. This consideration well agrees with the change of side product in the presence of HCl and experimental fact that anhydrous conditions were effective to achieve high selectivity for electron deficient substrates. Improved selectivity in the presence of HCl can be explained by the lower nucleophilicity of water or high reactivity of protonated intermediate. Another aspect of the HCl effect is the catalyst activity. It is well known that primary amines easily coordinate to Pd NPs, which may block the active site of Pd and resulted in decreased activity. Thus formation of ammonium salt would effective to prevent the formation of the inactive catalyst.

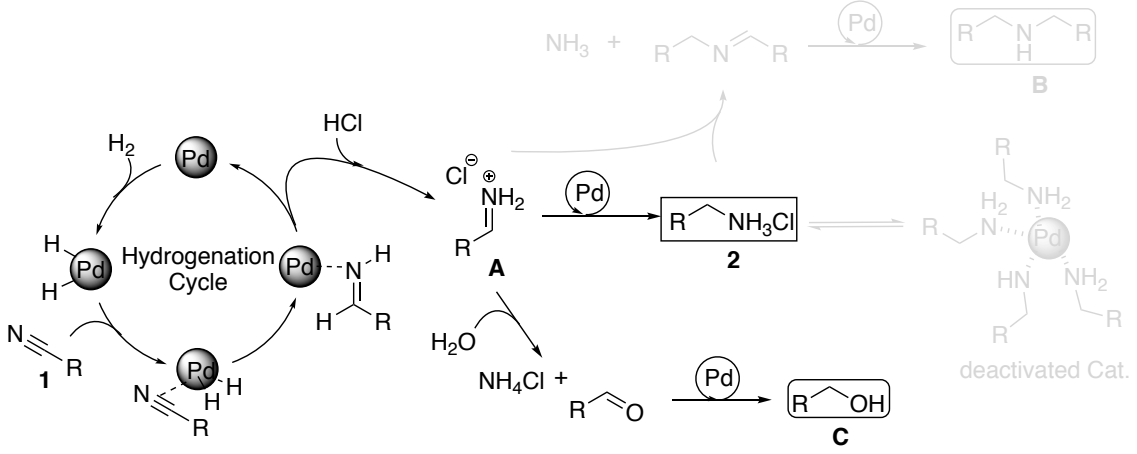


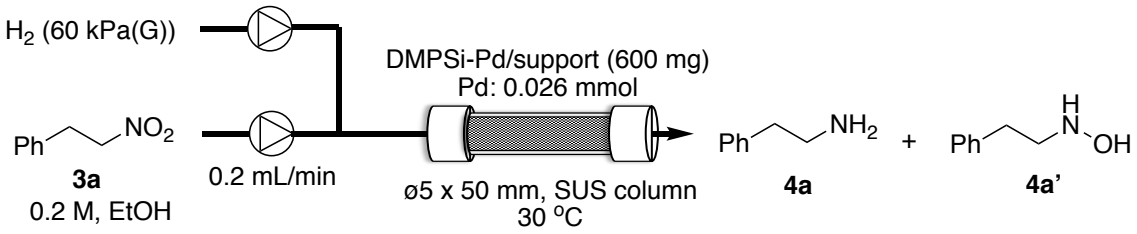
Figure 3-8-2. Reaction mechanism in the presence of HCl

3-9. Optimization for hydrogenation nitro compounds

As I established hydrogenation of nitriles to primary amines under continuous flow conditions, next I decided to focus on the hydrogenation of aliphatic nitro compounds under continuous flow conditions.

Through the investigation of nitrile hydrogenation, inorganic support significantly affected the inorganic support. Thus, the hydrogenation of aliphatic nitro compound was investigated using DMPSi-Pd catalysts immobilized on different inorganic supports. 1-nitro-2-phenyl ethane **3a** was used as a model substrate and flow-reaction was performed using 0.2 M solution of EtOH with 0.2 mL/min flow rate using 0.026 mmol of Pd catalyst packed in 5 x 50 mm column heated at 30 °C together with 80 kPa(G) of H_2 flow. The resulting solution was collected and analyzed after 3 h flow started (**Table 3-9-1**).

Table 3-9-1. Catalyst evaluation for hydrogenation of nitrile



Entry	Catalyst	Yield of **4a** (%)	Yield of **4a'** (%)
1	Pd/C	66	35
2	DMPSi-Pd/SiO_2	22	54
3	DMPSi-Pd/Al_2O_3	7	82
4	DMPSi-Pd/BC-Celite	78	21
5[a]	DMPSi-Pd/BC-Celite	>99	<1

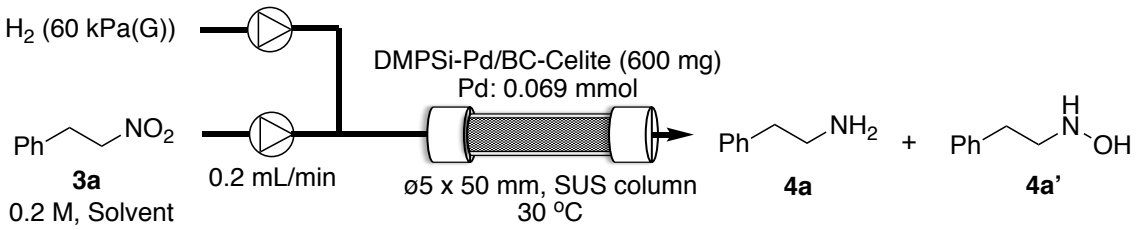
[a] using 0.069 mmol of Pd

At first, commercially available Pd/C was used as a catalyst to give the desired compound in 66% yield with 35% of hydroxylamine (Entry 1). To improve the selectivity toward amine, several kinds of polysilane-supported Pd catalysts were examined. Using DMPSi-Pd/SiO_2 as a catalyst, the yield of desired amine was decreased to 22%, but instead the yield of hydroxylamine was increased to 54% (Entry 2). The yield of amine was further decreased using Al_2O_3 as a catalyst and good selectivity toward hydroxylamine was observed (Entry 3). In contrast, using bone-charcoal and Celite (BC-Celite) as support, target amine was obtained in 78% yield (Entry 4). To improve the yield of amine, Pd amount was increased to 0.069 mmol. As a result, the desired compound was obtained in excellent yield. (Entry 5).

As DMPSi-Pd/BC-Celite was found to be the optimal catalyst for this hydrogenation, the effect of solvent was examined to improve the productivity (**Table 3-9-2**). Flow

reactions were performed with decreased H_2 pressure for easy comparison. Using EtOH as a solvent, the desired compound was obtained in 88% yield with 12% of hydroxylamine (Entry 1). However, changing the solvent to other aprotic solvent resulted in the decrease of both conversion and selectivity (Entries 2-4). Obviously, polar solvent gave better results.

Table 3-9-2. Solvent effect for hydrogenation of nitrile



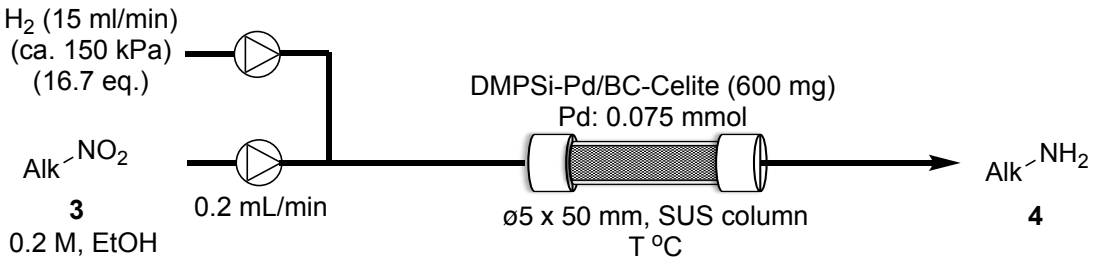
Entry	Solvent	Yield of **4a** (%)	Yield of **4a'** (%)
1	EtOH	88	12
2	AcOEt	51	31
3	THF	27	20
4	Toluene	<5	<5
5*	EtOH	>99	N.D.

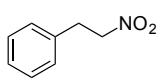
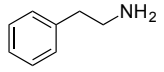
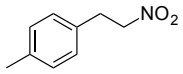
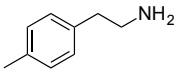
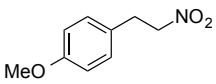
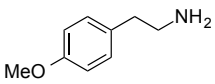
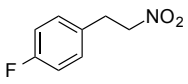
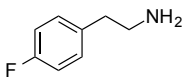
*0.075 mmol of Pd was used as catalyst

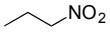
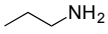
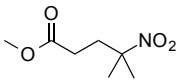
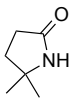
3-10. Substrate Scope for hydrogenation nitro compounds

With optimized reaction conditions in hand, the scope of aliphatic nitro compounds was examined (**Table 3-10-1**). For the substrate scope, flow reaction was performed for 15 h using 0.075 mmol of Pd catalyst. the yield was determined 3 h and 15 h after flow started. Model substrate gave the desired primary amine in excellent yield even after 15 h flow started (Entry 1). Next, the effect of substituents on benzene ring was examined (Entries 2-4). Both electron withdrawing and donating substituents did not affect the results. Desired compounds were obtained in >95% yield for 15 h reaction. Next, simple nitroalkenes were examined. Primary nitroalkenes were converted into primary amines in excellent yield under optimized reaction conditions for model substrate (Entry 5). On the other hand, secondary nitro alkene required higher reaction temperature to afford α-branched amine in excellent yield (Entry 7). Further elevation of reaction temperature was effective for tertiary nitro compound with ester functional group. Intramolecular cyclization took place under these reaction conditions, and lactam was obtained in excellent yield (Entry 7). In all cases, deactivation of catalyst was not observed at all.

Table 3-10-1. Substrate scope for aliphatic nitro compounds

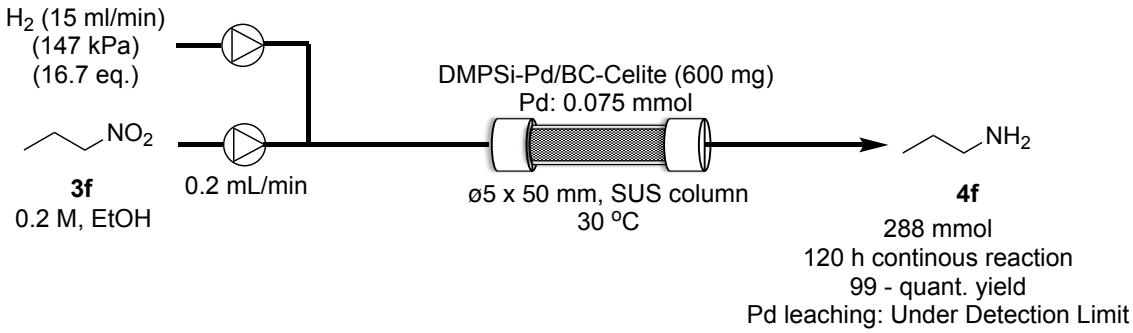


Entry	Substrate (**3**)	Product (**4**)	T (°C)	Yield after 3 h (%)	Yield after 15 h (%)
1			30	>99	99
2			30	99	99
3			30	>99	>99
4			30	96	97

5[a]			30	>99	>99
6[a]			30	>99	>99
7[a]			50	98	99
8			70	97	97

[a] Isolated as HCl salt

To examine the lifetime and leaching of Pd species, long time reaction was examined using nitropropane as a substrate (**Scheme 3-10-1**). The reaction was continued for 120 h to synthesize 288 mmol of product in excellent yield. At this stage, TON reached to 3400 and deactivation was not observed during all over the period. Contamination of Pd into the product was analyzed by ICP measurement, and Pd amount was under detection limit.



Scheme 3-10-1. Lifetime experiment

以下の部分については、5 年以内に雑誌等で刊行予定のため、非公開。

3-15. Summary

In this chapter, polysilane supported Pd catalysts were developed for hydrogenation reactions of various functional groups under continuous-flow conditions.

At first, hydrogenation of nitriles to primary ammonium salts was investigated using polydimethylsilane Pd/SiO_2 catalyst. DMPSi-Pd/SiO_2 showed high selectivity toward primary ammonium salt with proper tuning flow parameters such as flow rate and concentration. Under optimized reaction conditions, DMPSi-Pd/SiO_2 demonstrated wide substrate scope for nitriles, although proper tuning of reaction conditions was required depending on the structure of nitriles. As for benzyl cyanides, the lower reaction temperature was the key to prevent the formation of aza-enol. The anhydrous solvent system was suitable for electron deficient substrate to prevent the decomposition of key intermediate. The catalyst remained active even after 300 h to produce 1.8 mol of the target compound in quantitative yield without any leaching of Pd species.

Control experiments revealed the importance of SiO_2 support to achieve high selectivity to primary ammonium salts. The high selectivity could be explained by the controlled activity of the catalyst. Effect of polydimethylsilane for a long lifetime of catalysts was observed and clarified by comparison of STEM image. It was suggested that polysilane suppressed the aggregation of Pd NPs during the reaction. HCl was found to be important to achieve both high yield and selectivity. Formation of ammonium salts seems to be crucial to prevent the side reaction with intermediate and deactivation of catalyst by coordination. The unique activity of catalyst under continuous-flow conditions was observed as well.

In the second topic, hydrogenation of nitro compounds was studied focusing on the effect of inorganic supports. Indeed, bone charcoal support was important to promote the hydrogenation of hydroxylamine to amine efficiently.

以下の部分については、5 年以内に雑誌等で刊行予定のため、非公開。

3-16. References

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CHAPTER 4

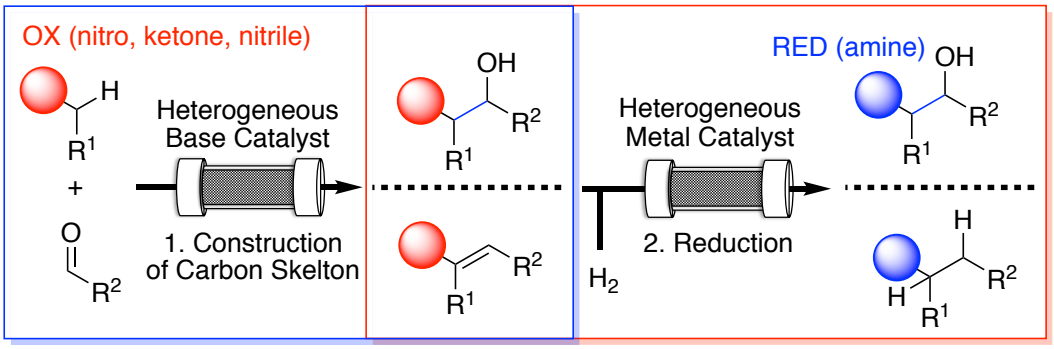
本章については、5 年以内に雑誌等で刊行予定のため、非公開。

CHAPTER 5

本章については、5 年以内に雑誌等で刊行予定のため、非公開。

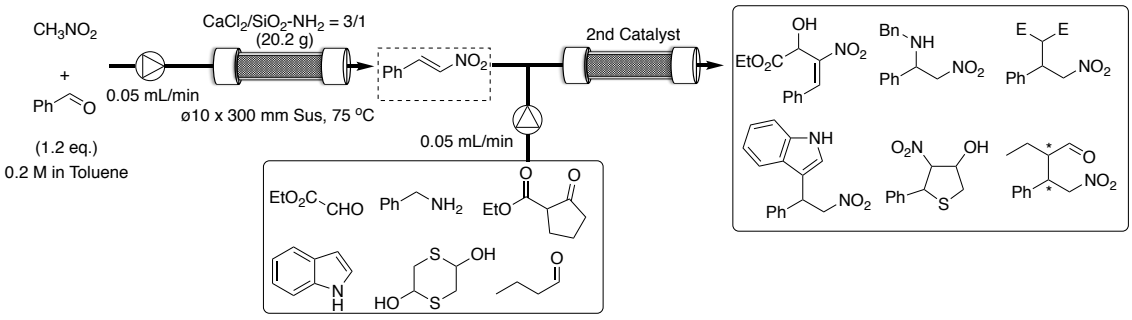
Summary

I have developed 2 kinds of continuous flow reactions using heterogeneous catalysts for multistep continuous-flow synthesis of fine chemicals. I designed aldol-hydrogenation strategy as a rational design for multistep flow synthesis and developed heterogeneous catalysts to enable target organic transformations (**Scheme 1**).



Scheme 1. Aldol-hydrogenation strategy

In chapter 2, I have investigated potential of simple and conventional heterogeneous catalysts for multistep flow reactions. Especially, I focused on preparation of nitro styrene and its derivatizations under flow conditions (**Scheme 2**). For the preparation of nitro styrene, primary amine functionalized SiO_2 and $CaCl_2$ were suitable catalysts and detailed investigations on reaction parameters could improve the productivity. For derivatization of nitro styrene various kinds of heterogeneous catalysts such as solid acids, solid bases, silica immobilized catalysts and polystyrene immobilized catalysts could be employed as effective heterogeneous catalysts with proper modification of reaction conditions. In this chapter, I succeeded multistep synthesis of nitro containing compounds under flow conditions using various kinds simple heterogeneous catalysts.



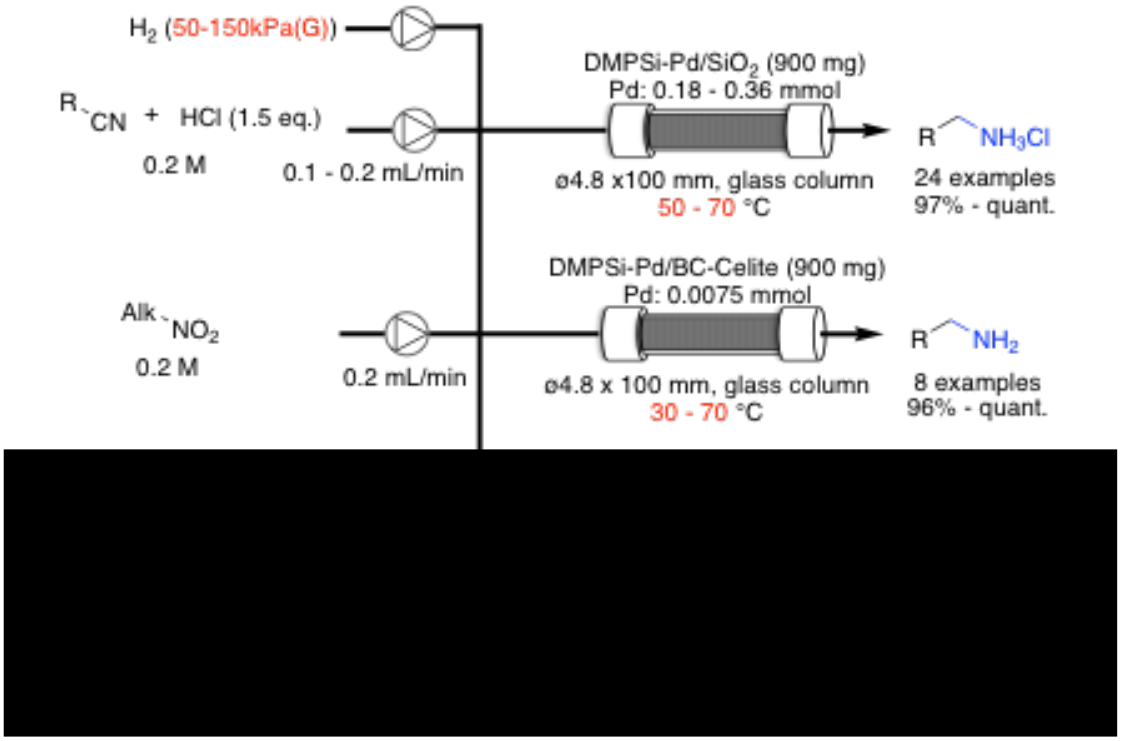
Scheme 2. Multistep flow synthesis of nitro containing compounds

In chapter 3, I have developed heterogeneous Pd catalysts for flow hydrogenation of high oxidation state functional groups. At first, selective hydrogenation of nitriles to primary amines were focused on. Using newly prepared DMPSi-Pd/SiO_2 as a catalyst, optimization was performed under flow conditions. It was found that precise control of flow parameters was the key to achieve high yields and selectivities. It was also revealed that optimal conditions were dependent on the structure of substrates. Under optimized reaction conditions, various nitriles including aliphatic, aromatic, and heteroaromatic nitriles were converted to primary ammonium salts in excellent yields and selectivities. Long operation of flow reaction revealed that this catalyst had >300 h lifetime without any deactivation and no leaching of Pd in solution. Control experiments suggested that inorganic support had impact on the selectivity of the reaction and polysilane was crucial to attain long lifetime. It should be emphasized that a reaction under batch conditions gave a complex mixture and a trace amount of desired product. This result clearly demonstrated the unique reactivity under flow conditions.

Effect of supports was also observed for the hydrogenation of aliphatic nitro compounds. In this reaction, polysilane supported Pd catalysts using SiO_2 or Al_2O_3 as support gave hydroxylamine as major product. On the other hand, a catalyst using bone charcoal-Celite as support gave the desired primary amine as a major product. Under optimized reaction conditions, several kinds of aliphatic nitro compounds including secondary and tertiary nitro compounds were converted to the corresponding primary amines in excellent yields.

この部分については、5 年以内に雑誌等で刊行予定のため、非公開。

As summary of this chapter, I have established flow hydrogenation of various functional groups under flow conditions (**Scheme 3**). Polysilane supported Pd catalyst showed excellent catalyst activity compared with conventional Pd catalysts.



Scheme 3. Flow hydrogenation of functional groups using polysilane supported Pd catalysts

In chapter 4, 以下の部分については、5 年以内に雑誌等で刊行予定のため、非公開。

In this thesis, I developed continuous-flow hydrogenations and aldol-type reactions using heterogeneous catalysts for the synthesis of fine chemicals. I revealed that even APIs could be synthesized through multistep flow reactions by connecting fundamental organic transformations. I believe that the key was the precise design of the whole synthetic route and the development of efficient heterogeneous catalysts. I hope further development of flow reactions using heterogeneous catalysts especially in asymmetric catalysis would enable to synthesize more complex and valuable molecules under multistep continuous-flow conditions.

Experimental Section –Chapter 2–

1. General

^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECX-600 and ECA-500 spectrometer spectrometer in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) and $CDCl_3$ served as an internal standard (δ = 0 and 7.24, respectively) for ^{1}H NMR, and $CDCl_3$ served as an internal standard (δ = 77.0) for ^{13}C NMR.

High-performance liquid chromatography was carried out using following apparatuses; SHIMAZU DGU-20A3, LC-20AB, SIL-20A, CBM-20A, SPD-M20A and CTO-20A. High resolution mass spectrometry was carried out using JEOL JMS-T100LP (AccuTOF LC-plus).

Preparative thin layer chromatography was carried out using glass plates with Wakogel B-5F (Wako Pure Chemical Industry Ltd.).

Calcium chloride (anhydrous) was purchased from Wako Pure Chemical Industry Ltd.

Amino silica gel (CHROMATOREX NH-DM1020) was purchased from Fuji Silysia Chemical Ltd., and the content of nitrogen was determined by elemental analysis (0.73 mmol/g).

Aldehydes, nitromethane, and the other reagents were purchased from Tokyo Chemical Industry Co., Ltd., Wako Pure Chemical Industry Ltd. or Sigma-Aldrich, and distilled before use.

Toluene and DMF were purchased from Wako Pure Chemical Industry Ltd. as a dried solvent and used directly.

Celite (Celite® 545) was purchased from Kokusan Chemical Co., Ltd.

Calcium chloride was purchased from Wako pure chemical.

For apparatuses for the flow systems, HPLC pump (SHIMADZU LC 20AT x 3, 20AD) or plunger pump (FROM Intelligent Pump Model AI-12 Series), tube pump (MCRP204 with a controller prepared by Tokyo Rikakikai Co., LTD. (EYLA)), oven (SHIMADZU LC CTO-20AC or EYLA) and cooling bath (EYLA PSL-1000) were used.

Details were mentioned in each section. EYLA Flow Master (CCR-1000G) was used for hydrogenation.

2. Experimental procedure and spectroscopic data

2.1. Experimental procedure for the synthesis of β-nitrostyrene 3[1]

A SUS (⌀ 10 mm x 300 mm) column with column ends equipped with a filter, an HPLC pump (SHIMADZU LC 20AT x 3, 20AD), and a column oven (SHIMADZU LC CTO-20AC or EYLA) were used for this system. A PETF tube (⌀ 0.8 mm) was used to connect the pump with the column. An aminopropyl-functionalized silica gel (CHROMATOREX NH-DM1020 (Fuji Silysia) 4.5 g, 0.73 mmol/g) and finely crushed calcium chloride (anhydrous, >95%, Wako pure chemical, 13.5 g) were well mixed and introduced into the column (column **A**). Toluene was flowed into the column by the pump (0.3 mL/min) for approx. 3 h. The column was then pre-heated at 75 °C. A toluene solution of nitromethane

(**1**), an aldehyde (**2,** 1.2 equiv. to **1**), and 1,3,5-trimethylbenzene (GC internal standard) with an appropriate concentration was prepared in a volumetric flask, and then this solution was flowed into the column (0.05 mL/min). The resulting solution (0.5 mL) was directly analyzed by GC in appropriate time.

2-Nitroethenylbenzene (3a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, 1H, *J* = 13.6 Hz), 7.52 (d, 1H, *J* = 13.6 Hz), 7.37-7.49 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 137.1, 132.1, 130.0, 129.4, 129.1.
1-Methoxy-4-(2-nitroethenyl)-benzene (3b): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, 1H, *J* = 13.8 Hz), 7.49-7.53 (m, 3H), 6.95 (d, 2H, *J* = 8.6 Hz), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 139.0, 135.0, 131.1, 122.5, 114.9, 55.5.
1-Methyl-4-(2-nitroethenyl)-benzene (3c): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, 1H, *J* = 13.8 Hz), 7.56 (d, 1H, *J* = 13.8 Hz), 7.44 (d, 2 H, *J* = 8.0 Hz), 7.25 (d, 2H, *J* = 8.0 Hz), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.1, 139.2, 136.3, 130.1, 129.2, 127.3, 21.7.
1-(2-Nitroethenyl)-4-trifluoromethyl-benzene (3d): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, 1H, *J* = 13.8 Hz), 7.72 (d, 2H, *J* = 8.1 Hz), 7.67 (d, 2H, *J* = 8.6 Hz), 7.62 (d, 1H, *J* = 13.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 137.1, 133.5, 133.3 (q, *J* = 32.2 Hz), 129.2, 126.7 (q, *J* = 3.6 Hz), 123.5 (q, *J* = 27.3 Hz).
2-(2-Nitroethenyl)-thiophene (3e): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, 1H, *J* = 13.8 Hz), 7.56 (d, 1H, *J* = 5.2 Hz), 7.45-7.48 (m, 2 H), 7.14 (dd, 1H, *J* = 4.3, 5.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.3, 134.6, 133.7, 132.0, 131.6, 128.8.

2.2. Experimental procedure for the synthesis of N-benzyl-2-nitro- 1-phenylethanamine (5) [2]

[batch conditions]

To 10 mL flask with magnetic stirring bar, heterogeneous catalyst (10 mg) was introduced. A solution of nitrostyrene **3a** (0.3 mmol, 44.8 mg) and amine **4** (0.36 mmol, 38.6 mg) in toluene (1 mL) was added to the reaction vessel. The mixture was stirred for 0.5 h at 25 ºC. Then, it was filtered through glass filter with Celite and filtrate was evaporated. The obtained material was analyzed by ^{1}H-NMR and crude material was purified by PTLC to obtain pure product.

[flow conditions]

MgO was prepared by the calcination of $Mg(OH)_2$ at 600 ℃ for 3 h. The prepared MgO (0.3 g) was well mixed with Celite (0.6 g) and introduced into a SUS (⌀5 x 100 mm) column (column **B1**) equipped with column ends and a filter. Toluene was flowed into the column **B1** by an HPLC pump (0.5 mL/min) for approx. 1 h. The toluene solution of benzylamine (0.24 M) was drawn up by the HPLC pump (0.05 mL/min). The stream of β-nitrostyrene prepared through column **A** (approx. 0.05 mL/min) and the stream of benzylamine (**4**) solution were both introduced into the column **B1** by using a Y-shape

connector. A resulting solution (5.0 mL) was evaporated and analyzed by NMR with durene as internal standard in appropriate time.

N-Benzyl-2-nitro-1-phenylethanamine (5): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.31 (m, 2H), 7.29-7.23 (m, 5H), 4.52 (dd, 1H, *J* = 12.7, 9.3 Hz), 4.42 (dd, 1H, *J* = 12.4, 4.8 Hz), 4.36 (q, 1H, *J* = 4.6 Hz), 3.66 (d, 1H, *J* = 13.1 Hz), 3.51 (d, 1H, *J* = 13.1 Hz), 1.89 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 138.1, 129.1, 128.5, 128.4, 128.0, 127.2, 80.8, 60.0, 50.9.

2.3. Experimental procedure for the synthesis of ketoester 9[3]

[batch conditions]

CaO was prepared by the calcination of $Ca(OH)_2$ at 600 ℃ for 3 h. To 10 mL flask with magnetic stirring bar, CaO (20 mg) was introduced. A solution of nitrostyrene **3a** (0.3 mmol, 44.8 mg) and ketoester **8** (0.36 mmol, 56.2 mg) in toluene (1 mL) was added to the reaction vessel. The mixture was stirred for 3 h at 25 ºC. Then, it was filtered through glass filter with Celite and filtrate was evaporated. The obtained material was analyzed by ^{1}H-NMR and crude material was purified by PTLC to obtain pure product.

[flow conditions]

CaO was prepared by the calcination of $Ca(OH)_2$ at 600 ℃ for 3 h. The prepared CaO (2.4 g) was well mixed with Celite (1.2 g) and introduced into a SUS (⌀10 x 100 mm) column (column **B2**) equipped with column ends and a filter. Toluene was flowed into the column **B2** by an HPLC pump (0.5 mL/min) for approx. 3 h. The toluene solution of ketoesrer (0.24 M) was drawn up by the HPLC pump (0.05 mL/min). The stream of β-nitrostyrene prepared through column **A** (approx. 0.05 mL/min) and the stream of the ketoester solution were both introduced into the column **B2** by using Y-shape connector. A resulting solution (5.0 mL) was evaporated and analyzed by NMR with internal standard in appropriate time. The product was obtained as a mixture of diastereomers (1:1).

Ethyl 1-(2-nitro-1-phenylethyl)-2-oxocyclopentane-1-carboxylate (**9**) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.18 (m, 7H), 7.12 (d, 2H, *J* = 7.4 Hz), 5.21 (dd, 1H, *J* = 11,3. 13.6 Hz), 5.10 (dd, 1H, *J* = 4.0, 13.6 Hz), 4.94 (dd, 1H, *J* = 11.3, 13.6 Hz), 4.77 (dd, 1H, *J* = 3.4, 13.6Hz), 4.20-4.10 (m, 5H), 4.00 (dd, 1H, *J* = 3.7, 11.1 Hz), 2.38-2.22 (m, 4H), 1.70-1.99 (m, 6H), 1.31-1.39 (m, 1H), 1.20 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ□171.0, 169.3, 135.5, 135.3, 129.3, 129.1, 129.0, 128.8, 128.4, 128.2, 76.7, 76.4, 62.4, 62.2, 47.2, 46.1, 39.5, 37.9, 33.5, 31.2, 19.6, 19.3, 14.0, 13.9.

2.4. Experimental procedure for the synthesis of 3-(2-nitro-1-phenylethyl) 1*H*-indole (11)[4]

[batch conditions]

To 10 mL flask with magnetic stirring bar, heterogeneous catalyst (50 mg) was introduced. A solution of nitrostyrene **3a** (0.3 mmol, 44.8 mg) and indole **10** (0.36 mmol, 42.2 mg) in toluene (1 mL) was added to the reaction vessel. The mixture was stirred for

10 h at 50 °C. Then, it was filtered through glass filter with Celite and filtrate was evaporated. The obtained material was analyzed by ^{1}H-NMR and crude material was purified by PTLC to obtain pure product.

[flow conditions]

Aluminum-containing mesoporous silica MCM-41 (1.0 g) was well mixed with silica gel (CARiACT Q10 (Fuji Silysia), 2.0 g) and introduced into a SUS (⌀10 x 100 mm) column (column **B3**) equipped with column ends and filter. The column **B3** was pre-heated at 50°C, and toluene was flowed into the column **B3** by an HPLC pump (0.3 mL/min) for approx. 3 h. The toluene solution of indole (0.3 M) was drawn up by the HPLC pump (0.05 mL/min). The stream of β-nitrostyrene including a GC internal standard prepared through column **A** (approx. 0.05 mL/min) and the stream of indole solution were both introduced into the column **B3** by using a Y-shape connector. The resulting solution (0.5 mL) was directly analyzed by GC in appropriate time.

3-(2-Nitro-1-phenylethyl)-1*H*-indole (11): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.93 (dd, 1H, 8,6 12.6 Hz), 7.43 (d, 1H, *J* = 8.0 Hz), 7.29-7.35 (m, 5H), 7.23-7.25 (m, 1H), 7.18 (t, 1H, *J* = 8.0 Hz), 7.06 (t, 1H, *J* = 7.5 Hz), 7.00 (s, 1H), 5,18 (dd, 1H, *J* = 8.0, 8.0 Hz), 5.05 (dd, 1H, *J* = 8.1, 12.9 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 139.3, 136.5, 128.9, 127.7, 127.5, 126.1, 122.7, 126.1, 122.7, 121.6, 119.9, 118.9, 114.5, 111.4, 79.5, 41.6.

2.5. Experimental procedure for the synthesis of ethyl 2-hydroxy-3-nitro- 4-phenyl-3-butenoate (13)[6]

[batch conditions]

A SiO_2-DMAP catalyst was prepared according to the literature procedure. To 10 mL flask with magnetic stirring bar, SiO_2-DMAP (60 mg) was introduced. A solution of nitrostyrene **3a** (0.3 mmol, 44.8 mg) and ethylglyoxylate **12** (0.36 mmol, 36.8 mg) in toluene (1 mL) was added to the reaction vessel. The mixture was stirred for 80 min at 25 °C. Then, it was filtered through glass filter with Celite and filtrate was evaporated. The obtained material was analyzed by ^{1}H-NMR and crude material was purified by PTLC to obtain pure product.

[flow conditions]

A SiO_2-DMAP catalyst was prepared according to the literature procedure. The prepared catalyst (6.0 g) was introduced into a SUS (⌀10 x 200 mm) column (column **B4**) equipped with column ends and a filter. Toluene was flowed into the column **B4** by an HPLC pump (0.5 mL/min) for approx. 3 h. The toluene solution of glyoxylate (0.60 M) was drawn up by the HPLC pump (0.05 mL/min). The stream of β-nitrostyrene prepared through column **A** (approx. 0.05 mL/min) and the stream of the glyoxylate solution were both introduced into the column **B4** by using a Y-shape connector. The resulting solution (5.0 mL) was evaporated and analyzed by NMR with an internal standard in appropriate time.

2-Hydroxy-3-nitro- 4-phenyl-3-butenoate (13) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.55 (dd, 2H, *J* = 2.6, 6.5 Hz), 7.46-7.48 (m, 3H), 5.21 (d, 1H, *J* = 6.2 Hz), 4.22-4.33 (m, 2H), 3.64 (d, 1H, *J* = 6.2 Hz), 1.25 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 147.8, 139.3, 131.1, 130.9, 129.8, 129.2, 65.9, 63.0, 14.0.

2.6. Experimental procedure for the synthesis of 2-ethyl-4-nitro-3-phenylbutanal (15)[5]

[batch conditions]

The PS-peptide catalyst was prepared according to the literature procedure. To 10 mL flask with magnetic stirring bar, heterogeneous catalyst (10 mg) was introduced. A solution of nitrostyrene **3a** (1.0 mmol, 149.2 mg) and aldehyde **14** (3.0 mmol, 216.3 mg) in toluene (1 mL) was added to the reaction vessel. The mixture was stirred for 4.5 h at 0 ^{o}C. Then, it was filtered through glass filter with Celite and filtrate was evaporated. The obtained material was analyzed by ^{1}H-NMR and crude material was purified by PTLC to obtain pure product.

[flow conditions]

The PS-peptide catalyst was prepared according to the literature procedure. The prepared catalyst (2.2 g) was introduced into a glass (⌀10 x 200 mm) column (column **B5**) equipped with column ends and a filter. Toluene was flowed into the column **B5** by an HPLC pump (0.5 mL/min) for approx. 3 h. A toluene solution of an aldehyde (0.60 M) was drawn up by the HPLC pump (0.05 mL/min). The stream of β-nitrostyrene prepared through column **A** (approx. 0.05 mL/min) and the stream of butylaldehyde solution were both introduced into the column **B5** by using a Y-shape connector. The resulting solution (5.0 mL) was evaporated and purified by flash column chromatography.

2-Ethyl-4-nitro-3-phenylbutanal (15) ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (d, 1H, *J* = 2.1 Hz), 7.25 (t, 2H, *J* = 7.0 Hz), 7.18- 7.22 (m, 1H), 7.09 (d, 2H, *J* = 5.0 Hz), 4.63 (q, 1H, *J* = 6.0 Hz), 4.54 (dd, 1H, *J* = 9.6, 12.4 Hz), 3.70 (dt, 1H, *J* = 3.8, 10.0 Hz), 2.57-2.61 (m, 1H), 1.38-1.44 (m, 2H), 0.74 (t, 3H, *J* = 7,56 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2, 136.8, 129.11. 129.08, 128.2, 128.1, 128.0, 78.5, 55.0, 42.7, 20.4, 10.7. The ee value was determined by HPLC analysis using Chiracel IA column (*n*-Hexane/*i*-PrOH = 98.5/1.5) at 0.4 ml/min, UV detection at 210 nm: t_R: (*syn*, minor) = 53.6 min, (*syn*, major) = 69.9 min.

2.7. Experimental procedure for the synthesis of 4-nitro-5-phenyltetrahydro-thiophen-3-ol (17)[7]

[batch conditions]

To 10 mL flask with magnetic stirring bar, heterogeneous catalyst (25 mg) was introduced. A solution of nitrostyrene **3a** (0.3 mmol, 44.8 mg) and dithiandiol **16** (0.6 mmol, 91.3 mg) in toluene (1 mL) was added to the reaction vessel. The mixture was stirred for 10 h at 25 ^{o}C. Then, it was filtered through glass filter with Celite and filtrate

was evaporated. The obtained material was analyzed by ^{1}H-NMR and Crude material was purified by PTLC to obtain pure product.

[flow conditions]

For the β-nitrostyrene preparation flow, 0.30 M and 0.36 M toluene solution of nitromethane and PhCHO was used. The flow rate for this flow was set to 0.075 ml/min. Dipropylamino-functionalized MCM-41 (1.0 g) was well mixed with Celite® (2.0 g), and introduced into a SUS (⌀10 x 100 mm) column (column **B6**) equipped with column ends and filter. Toluene was flowed into the column **B6** by HPLC pump (0.3 mL/min) for approx. 3 h. The DMF solution of 2,5-dihydroxy-1,4-dithiane (**16**, 0.27 M) was drawn up by the HPLC pump (0.05 mL/min). The stream of β-nitrostyrene including GC internal standard prepared through column **A** (approx. 0.075 mL/min) and the stream of **10** solution were both introduced into the column **B6** by using Y-shape connector. During the reaction, the column **B6** was kept at room temperature. A resulting solution (0.5 mL) was directly analyzed by GC in appropriate time.

4-nitro-5- phenyltetrahydro- thiophen-3-ol (17) ^{1}H NMR (500 MHz, $CDCl_3$) 1:1 mixture of 3,4-trans (*t*) and 3,4-cis adducts (*c*), δ 7.18-7.48 (m, 5H, *t* and *c*), 5.24 (d, 0.5 H, J = 10.3 Hz, *c*), 4.91-5.07 (m, 2.5H, *t* and *c*), 3.51 (dd, 0.5H, J = 4.6, 12.0 Hz, *c*), 3.31 (dd, 0.5 H, J = 6.6, 11.3 Hz, *t*), 3.17 (dd, 0.5 H, J = 8.1, 11.5 Hz), 3.08 (dd, 0.5H, J = 2.3, 12.1 Hz, *c*); ^{13}C NMR (125 MHz, $CDCl_3$) 1:1 mixture of 3,4-trans and 3,4-cis adducts, δ 136.8, 136.7, 129.0, 128.8, 128.5, 128.1, 127.7, 98.0, 95.5, 75.4, 49.5, 48.3, 36.6, 34.0.

2.8. Experimental procedure for the synthesis of compound 18[8]

[batch conditions]

To 10 mL flask with magnetic stirring bar, nitrostyrene **13** (0.3 mmol, 76.0 mg), Pd-PDMSi/Bone Chacoal (Pd amount: 0.003 mmol, Pd loading: 0.1 mmol/g, 30.0 mg) and toluene (1 mL) were added. Finally, H_2 balloon was equipped and stirred for 18 h at 25 ^{o}C. The mixture was filter by glass filter with Celite and evaporated. The obtained material was analyzed by ^{1}H-NMR and Crude material was purified by PTLC to obtain pure product.

[flow conditions]

Pd-PDMSi/Bone Chacoal (0.80 g) was well mixed with Celite (0.20 g) and packed in the glass column (⌀4.8 x 100 mm). The column was heated at 60 ^{o}C and toluene was flowed into the column by an HPLC pump (0.3 mL/min) for approx. 1 h. The Morita-Baylis-Hillman reaction under flow condition was performed following the same procedure described in SI **2.7** (with **column B4**). The stream contained alcohol **13** was introduced the column with H_2 gas (5.0 mL/min), and the column was heated at 60 ^{o}C. The resulting solution was collected (5.0 mL), evaporated and analyzed by ^{1}H-NMR with internal standard at appropriate time (86%). The desired compound **18** was isolated in 84% yield.

Ethyl 2-hydroxy-3-nitro-4-phenylbutanoate (18) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16-7.30 (m, 8H), 7.14 (d, 2H, J = 7.4 Hz), 4.91-4.99 (m, 2H), 4.61 (t, 1H, J = 3.7 Hz), 4.05-4.27 (m, 5H), 3.49 (q, 1H, J = 6.8 Hz), 3.42 (q, 1H, J = 7.6 Hz), 3.16-3.29 (m, 4H), 1.2-

1.24 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 170.6, 124.9, 129.3, 129.1, 129.0, 128.8, 127.6, 127.5, 90.0, 88.6, 70.5, 69.2, 63.1, 62.9, 35.1, 34.2, 13.98, 13.96.

3. References

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Experimental Section –Chapter 3–

1. General

For apparatuses for the flow systems, HPLC pump (SHIMADZU LC 20AT x 3, 20AD) or plunger pump (FROM Intelligent Pump Model AI-12 Series), tube pump (MCRP204 with a controller prepared by Tokyo Rikakikai Co., LTD. (EYLA)), oven (SHIMADZU LC CTO-20AC or EYLA) and cooling bath (EYLA PSL-1000) were used.

For apparatuses for the flow hydrogenation systems, EYELA Flow Master (CCR-1000G) was used.

Inductively coupled plasma-atomic emission spectrometry (ICP-AES) analysis was performed on Shimadzu ICPS-7510 equipment.

Preparative thin layer chromatography was carried out using glass plates with Wakogel B-5F (Wako Pure Chemical Industry Ltd.).

STEM/EDS images were obtained using a JEOL JEM-2100F instrument operated at 200 kV. All STEM specimens were prepared by placing a drop of the solution on carbon-coated copper grids and allowed to dry in air (without staining).

^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECX-600 and ECA-500 spectrometer spectrometer in $CDCl_3$ and DMSO-d_6 unless otherwise noted. Tetramethylsilane (TMS) and $CDCl_3$ served as an internal standard (δ = 0 and 7.24) for ^{1}H NMR, $CDCl_3$ served as an internal standard (δ = 77.0) for ^{13}C NMR. DMSO served as an internal standard (δ = 2.50) for ^{1}H NMR and an internal standard (δ = 39.5) for ^{13}C NMR. Structures of known compounds were confirmed by comparison with data shown in literature.

GC analysis was performed on Shimadzu GC-2010 apparatus.

Polysilanes and SiO_2 for catalyst preparation were purchased from Nippon Soda Co. Ltd. and JGC Catalysts and Chemicals Ltd. Polysilanes were passed through a sieve to get <250 μm particle before use.

$Pd(OAc)_2$, $NaBH_4$, and Et_3SiH was purchased from Sigma-Aldrich and Tokyo Chemical Industry Co., Ltd. and used directly.

Nitriles **1**, nitro alkane **3**, ketone **7**, and epoxide **9** were purchased from Tokyo Chemical Industry Co., Ltd., Wako Pure Chemical Industry Ltd., or Sigma-Aldrich, and used directly.

Imine **5** was prepared following literature procedure.[1]

Conc. HCl aq. and 4N HCl in 1,4-dioxane were purchased from Wako Pure Chemical Industry Ltd., and Watanabe Chemical Industries, Ltd. and used directly.

All solvents were purchased from Wako Pure Chemical Industry Ltd. as a dried solvent and used directly.

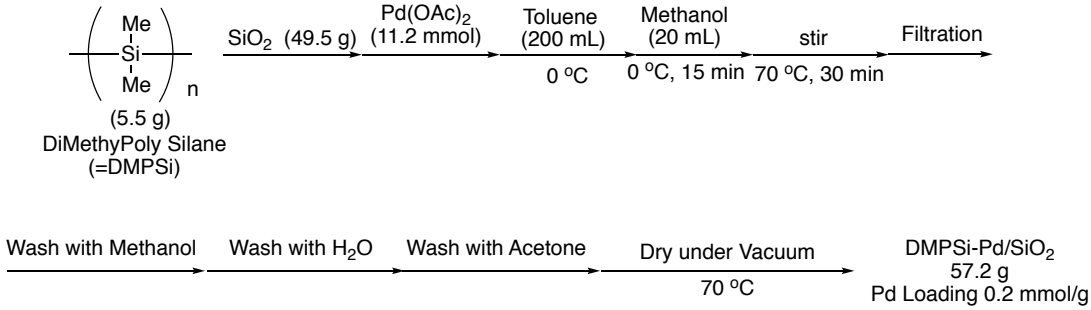
Pd/C (10%) was purchased from Wako Pure Chemical Industry Ltd. and used directly.

DMPSi-Pd/Al_2O_3 was prepared by following the literature.[2]

SiO_2 (CARiACT-Q10) for diluting catalyst was purchased from Fuji Silysia Co., Ltd., and used directly.

2. Catalyst preparation and STEM images for nitrile hydrogenation

2.1 Preparation of DMPSi-Pd/SiO_2



Scheme S1. Preparation of DMPSi-Pd/SiO_2

To the mixture of polydimethylsilane (5.5 g), SiO_2 (49.5 g) and $Pd(OAc)_2$ (2.51 g, 11.2 mmol) was added toluene (200 mL) and stirred at room temperature under Ar atmosphere. The mixture was put in the ice bath and methanol was added dropwise over 15 min. After the completion of the addition, the temperature was increased to 70 °C over 15 min and stirred for 30 min. The mixture was filtered and washed with methanol, water and acetone. Finally, the obtained solid material was dried under *vacuo* at 70 °C to get dimethylpolysilane-SiO_2 supported Pd catalyst (DMPSi-Pd/SiO_2).

DMPSi-Pd/Al_2O_3 was prepared by a similar method by following the literature [2].

2.2 STEM analysis of DMPSi-Pd/SiO_2

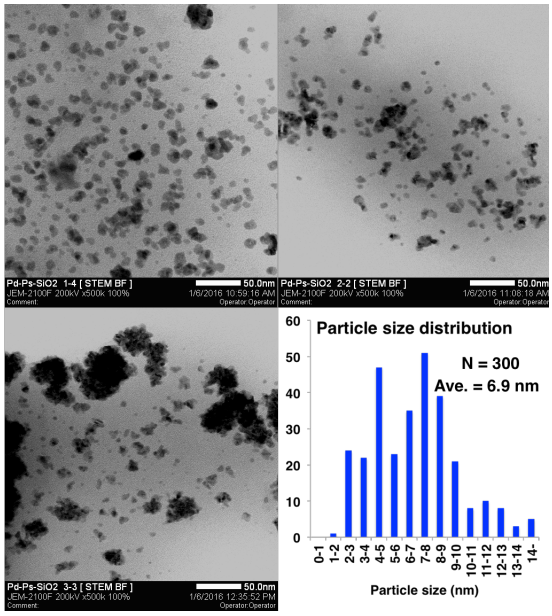


Figure S1. STEM Images of DMPSi-Pd/SiO_2

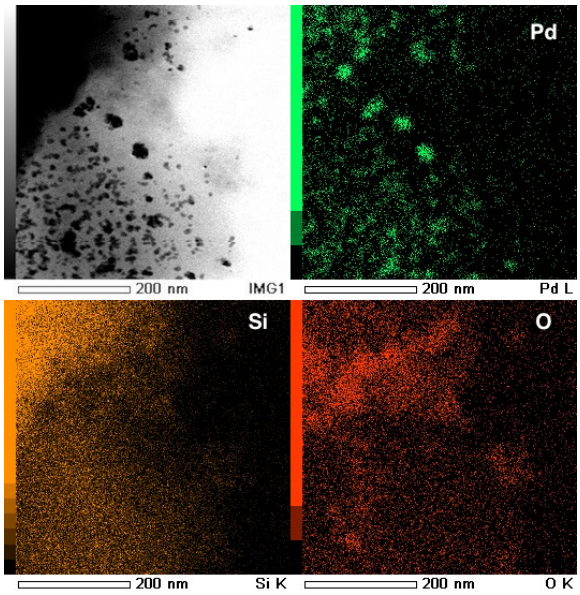


Figure S2. EDX mapping of DMPSi-Pd/SiO_2

3. General Procedure

3.1 Typical experimental procedure for the hydrogenation of decanenitrile 1a under flow condition: A glass column (⌀ 4.8 mm x 100 mm) with column ends equipped with filters was used for the catalysis. A PETF tube (⌀ 0.8 mm) was used to connect the pump with the column. First, heterogeneous Pd catalyst was weighed in appropriate amount to achieve regulated Pd amount calculated based on the loading of each catalyst. Pd catalyst was diluted with SiO_2 (CARiACT Q10 (Fuji Silysia)) up to 900 mg and was well mixed and then packed into the column. 1-PrOH/H_2O = 4/1 was flowed into the column by the pump (0.4 mL/min) for ca. 1 h. The column was then pre-heated at regulated temperature. After the heating of the column, H_2 gas was introduced to the column with 150 kPa(G) pressure at ca. 50 mL/min flow rate. Then, 0.3 M solution of HCl in 1-PrOH/H_2O = 4/1 was introduced to the column at 0.1 mL/min flow rate for 1 h. 0.2 M solution of decanenitrile (**1a**) in 1-PrOH/H_2O = 4/1 was prepared in a 100 mL volumetric flask, and finally this solution was flowed into the column (0.10 mL/min) under a concurrent flow of H_2 gas. The resulting solution (3.0 mL) was evaporated and analyzed by ^{1}H-NMR using MeOH-d_4 as solvent and 1,4-bis(trimethylsilyl)benzene as internal standard in appropriate time. The yield and conversion was determined by ^{1}H NMR analysis.

3.2 Experimental procedure for the hydrogenation of decanenitrile 1a under batch condition: To a test tube with magnetic stirring bar, decanenitrile (0.5 mmol, 76.6 mg), DMPSi-Pd/SiO_2 (Pd amount: 0.0125 mmol, Pd loading: 0.2 mmol/g, 6.25 mg) and 0.3 M of HCl in 1-PrOH/H_2O = 4/1 (2.5 mL) were added. Finally, H_2 balloon was equipped and heated at 90 ℃ and stirred for 3 h. After cooling the reaction mixture to room

temperature, the mixture was filter by glass filter with Celite and evaporated. The obtained oil was dissolved in MeOH-d_4 and analyzed by ^{1}H-NMR and GC-MS.

3.3 Typical experimental procedure for the substrate scope of nitriles under flow condition: A glass column (⌀ 4.8 mm x 100 mm) with column ends equipped with filters was used for the catalysis. A PETF tube (⌀ 0.8 mm) was used to connect the pump with the column. DMPSi-Pd/SiO_2 (0.2 mmol/g, 900 mg, 0.18 mmol of Pd) was introduced into the column. 1-PrOH/H_2O = 4/1 was flowed into the column by the pump (0.4 mL/min) for ca. 1 h. The column was then pre-heated at 60 ℃. H_2 gas was introduced to the column with 50 or 150 kPa(G) pressure at ca. 10 or 50 mL/min flow rate. Before the substrate solution was introduced, 0.3 M of HCl 1-PrOH/H_2O = 4/1 was introduced to the column at 0.1 mL/min flow rate for 1 h. Finally, 0.2 M solution of nitrile (**1**) in 1-PrOH/H_2O = 4/1 was prepared in a volumetric flask, and then this solution was flowed into the column (0.20 mL/min) under a concurrent flow of H_2 gas. The resulting solution (3.0 mL) was evaporated and analyzed by ^{1}H-NMR at the stage of 3, 6 and 18 h after flow started with 1,2-dimethoxyethane as internal standard. Basically, evaporating the resulting solution gave almost pure product. Further purification was performed by washing the product with hexane if necessary. The yield was calculated by both ^{1}H-NMR and weight of the product.

3.4 Experimental procedure for the lifetime and leaching experiment: A glass column (⌀ 4.8 mm x 100 mm) with column ends equipped with filters was used for the catalysis. A PETF tube (⌀ 0.8 mm) was used to connect the pump with the column. DMPSi-Pd/SiO_2 (900 mg) was introduced into the column. 1-PrOH/H_2O = 4/1 was flowed into the column by the pump (0.4 mL/min) for ca. 1 h. The column was then pre-heated at 60 ℃. H_2 gas was introduced to the column with 150 kPa(G) pressure at ca. 50 mL/min flow rate. Before the substrate solution was introduced, 0.75 M of HCl 1-PrOH/H_2O = 4/1 was introduced to the column at 0.1 mL/min flow rate for 1 h. Finally, 0.5 M solution of benzonitrile (**1**) in 1-PrOH/H_2O = 4/1 was prepared in a volumetric flask, and then this solution was flowed into the column (0.20 mL/min) under a concurrent flow of H_2 gas. The resulting solution (3.0 mL) was evaporated and analyzed by ^{1}H-NMR every 12 h after the flow started for totally 300 h. Yield was determined by both ^{1}H NMR and weight of the product after removing the solvent. At the same time, the resulting solution was evaporated every 24 h to get crude product. 1.0 g of product was placed on the ceramic plate and heated at 800 ^{o}C for 3 h under ambient atmosphere. The plate was washed with aqua regia (5 mL) and diluted to 25 mL using a volumetric flask. The resulting solution was used for ICP measurement to determine the contamination of the Pd into the product.

4. Spectroscopic information of the products

Decylamine hydrochloride (**2a**)[3]: ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.69 (t, *J* = 7.4 Hz, 2H), 1.60-1.45 (m, 2H), 1.36-1.08 (m, 14H), 0.84 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 39.0, 31.4, 29.1, 29.0. 28.9, 28.7, 27.4, 26.0, 22.3, 14.1

Benzylamine hydrochloride (**2b**)[4]: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (br, 3H), 7.51 (d, J = 6.8 Hz, 2H), 7.36 (m, 3H), 3.97 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 134.1, 128.9, 128.6, 128.4, 42.1.

3-Methyl-benzylamine hydrochloride (**2c**)[5]: ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.61 (br, 3H), 7.31-7.25 (m, 3H), 7.16 (d, J = 7.37 Hz, 1H), 3.93 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 137.7, 134.0, 129.6, 129.5, 128.9, 128.5, 126.0, 42.1, 21.0.

4-Methyl-benzylamine hydrochloride (**2d**)[4]: ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.60 (br, 3H), 7.38 (d, J = 6.2 Hz, 3H), 7.16 (d, J = 6.9 Hz, 1H), 3.92 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 137.7, 131.1, 129.02, 128.97, 41.8, 20.8.

2-Methyl-benzylamine hydrochloride (**2e**)[4]: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (d, *J* = 6.9 Hz, 1H), 7.12-7.06 (m, 3H), 3.76 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.0, 135.3, 130.1, 126.8, 126.7, 126.0, 44.0, 18.7.

4-Methoxyl-benzylamine hydrochloride (**2f**)[4]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 3.76 (s, 3H), 3.76 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 135.4, 128.1, 113.8, 55.1, 45.7.

4-Hrdoxyl-benzylamine hydrochloride (**2g**)[6]: ^{1}H NMR (500 MHz, CD_3OD) δ 7.27 (d, *J* = 7.9 Hz, 2H), 6.81 (d, *J* = 7.9 Hz, 2H), 4.96 (br, 4H), 3.97 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 130.54, 130.50, 124.1, 115.3, 55.1, 41.8.

4-Trifluoromethyl-benzylamine hydrochloride (**2h**)[4]: ^{1}H NMR (600 MHz, DMSO-d6) δ 8.72 (br, 3H), 7.78-7.73 (m, 4H), 4.10 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d6) δ 138.8, 129.8, 128.8, 125.4, 125.3, 41.5; ^{19}F NMR (466 MHz, DMSO-d6) δ 69.9.

4-Fluoro-benzylamine hydrochloride (**2i**)[4]: ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.38 (br, 3H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 9.1 Hz, 2H), 4.00 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.1, 133.2, 130.9, 117.9, 44.4; ^{19}F NMR (466 MHz, DMSO-d_6) δ 244.5

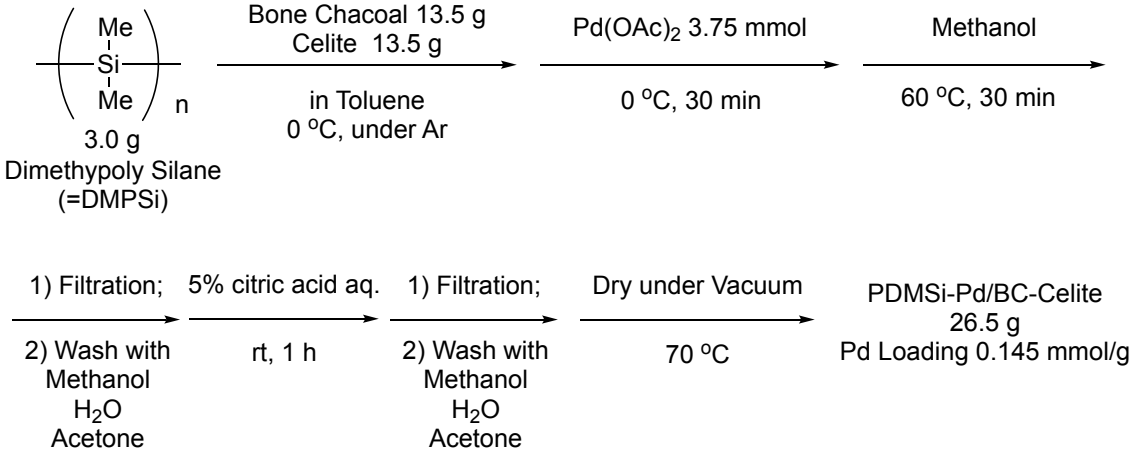
(α-Naphthylmethyl)ammonium chloride (**2j**)[4]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.5 Hz, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.54-7.41 (m, 4H), 4.32 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 133.8, 131.1, 128.8, 127.5, 126.1, 125.6, 125.5, 124.4, 123.1, 44.0.

3-(Aminomethyl)pyridine hydrochloride (**2k**)[7]: ^{1}H NMR (600 MHz, D_2O) δ 8.84 (s, 1H), 8.74 (d, *J* = 5.5 Hz, 1H), 8.62 (d, *J* = 7.6 Hz, 1H), 8.04 (dd, *J* = 5.5, 7.6 Hz, 1H), 4.36 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.6, 142.6, 142.4, 133.7, 128.7, 40.5.

2-(Aminomethyl)pyridine hydrochloride (**2l**)[4]: ^{1}H NMR (600 MHz, D_2O) δ 8.86 (d, *J* = 5.5 Hz, 1H), 8.57-8.54 (m, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 8.01 (t, *J* = 6.5 Hz, 1H), 4.60 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.1, 147.2, 143.6, 128.0, 127.6, 40.5.

1,3-Phenylenedimethanamine dihydrochloride (**2m**)[8]: ^{1}H NMR (500 MHz, CD_3OD) δ □(s, 1H), 7.55 - 7.52 (m, 3H), 4.18 (s, 4H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 135.3, 131.0, 130.8, 44.0.
Isoamylamine hydrochloride (**2n**) [4]: ^{1}H NMR (500 MHz, D_2O) δ 2.82 (t, *J* = 7.0 Hz, 2H), 1.49 - 1.45 (m, 1H), 1.35 (q, *J* = 7.6 Hz, 2H), 0.73 (d, *J* = 6.2 Hz, 6H) ; ^{13}C NMR (125 MHz, D_2O) δ 37.2, 35.7, 25.0, 22.3.
Isobutylamine hydrochloride (**2o**)[8]: ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.57 (d, *J* = 6.8 Hz, 2H), 1.91 - 1.83 (m, 1H), 0,90 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d6) δ 47.6, 26.6, 20.1.
Neopentylamine hydrochloride (**2p**)[8]: ^{1}H NMR (500 MHz, DMSO-d_6) δ 258 (s, 2H), 0.93 (s, 9H) ; ^{13}C NMR (125 MHz, D_2O) δ 49.7, 30.1, 26.9.
Ethylamine hydrochloride (**2q**)[9]: ^{1}H NMR (500 MHz, D_2O) δ 2.87□(d, *J* = 7.2 Hz, 2H), 1.10 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d6) δ 33.9, 12.4.
Ethyl β-alaninate hydrochloride (**2r**)[10]: ^{1}H NMR (500 MHz, D_2O) δ 4.04 (q, *J* = 7.0 Hz, 2H), 3.12 (t, *J* = 6.5 Hz, 2H), 2.64 (t, *J* = 6.5 Hz, 2H), 1.10 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, D_2O) δ 173.3, 62.9, 35.6, 31.8, 13.8.
Hexane-1,6-diamine dihydrochloride (**2s**) [4]: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (br, 3H), 2.72 (q, *J* = 6.6 Hz, 2H), 1.55 (t, *J* = 6.9 Hz, 2H), 1.29 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 38.5, 26.7, 25.3.
2-Phenylethylamine hydrochloride (**2t**) [4]: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.32□(br, 3H), 7.32-7.20 (m, 5H), 2.98 (t, *J* = 4.0 Hz, 2H), 2.92 (t, *J* = 4.0 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 137.5, 128.6, 126.7, 40.0, 32.9.
4-Methoxyphenethylamine hydrochloride (**2u**) [4]: ^{1}H NMR (500 MHz, CD_3OD) δ 7.10 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 3.67 (s, 3H), 3.03 (t, *J* = 7.9 Hz, 2H), 2.80 (t, *J* = 7.9 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 158.1, 129.7, 129.3, 114.0, 55.0, 40.1, 32.0.
3,4-Dimethoxyphenethylamine hydrochloride (**2v**)[11] : ^{1}H NMR (500 MHz, CD_3OD) δ 6.87 (s, 2H), 6.78 (d, *J* = 7.9 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.12 (t, *J* = 7.7 Hz, 2H), 2.87 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 150.7, 149.7, 130.6, 122.2, 113.6, 113.3, 56.5, 49.9, 42.1, 34.1.
4-Fluorophenethylamine hydrochloride (**2w**)[7] : ^{1}H NMR (500 MHz, CD_3OD) δ 7.32-7.30 (m, 2H), 7.06 (t, *J* = 8.5 Hz, 2H), 3.16 (t, *J* = 7.9 Hz, 2H), 2.97 (t, *J* = 7.9 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 163.4, 133.9, 131.6, 116.5, 42.0, 33.6, ^{19}F NMR (466 MHz, CD_3OD) δ −76.5.

5.1 Preparation of DMPSi-Pd/BC-Celite for nitro hydrogenation



Toluene (140 mL) was added to a mixture of bone charcoal (13.5 g), Celite (13.5 g), and dimethylpolysilane (3.0 g) under an Ar atmosphere. The mixture was cooled to 0 °C and a suspension of $Pd(OAc)_2$ (3.75 mmol) in toluene (10 mL) was slowly added. The resulting mixture was stirred for 30 min, then MeOH (15 mL) was added dropwise. After 5 min, the reaction temperature was increased to 60 °C and the mixture was stirred for 30 min. The mixture was then cooled to 0 °C and filtered. The resulting solid material was washed with toluene, MeOH, water, and acetone. The solid was poured into a 5% aqueous solution of citric acid (150 mL) and the mixture was stirred for 1 h at room temperature under an Ar atmosphere. The solid was filtered, washed, and dried at 70 °C under vacuo to give DMPSi-Pd/BC-Celite (26.5 g).

5.2 STEM and EDS Images of DMPSi-Pd/BC-Celite (0.145 mmol/g)

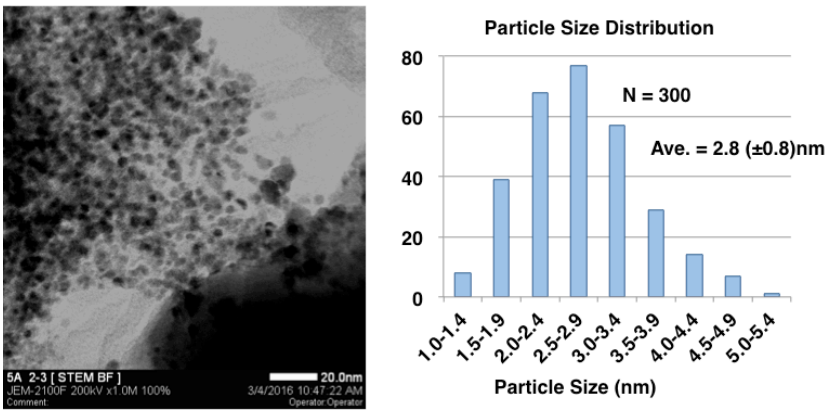


Figure S3. STEM image and size distribution of Pd NP

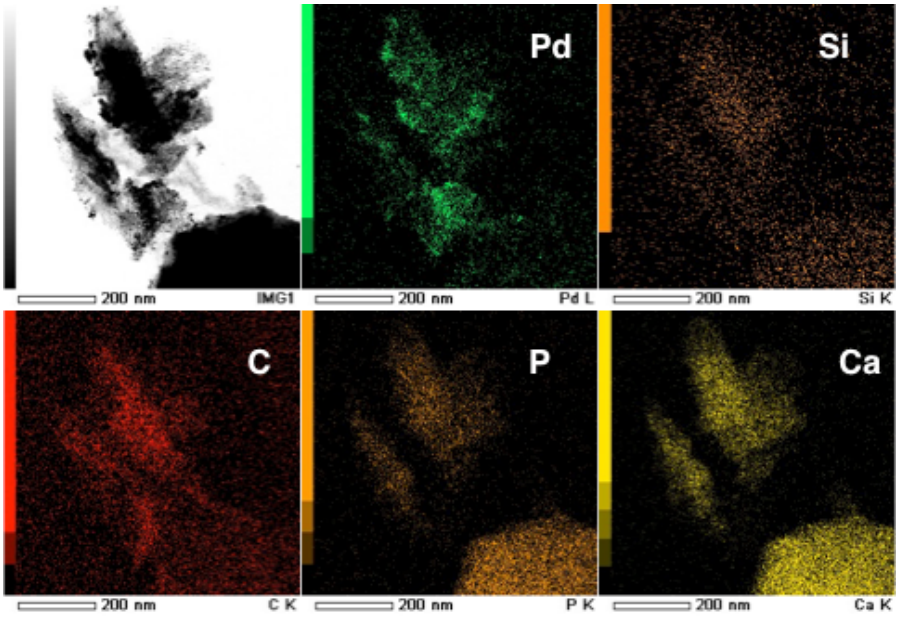


Figure S4. EDS mappimg

6. General Procedure

6.1 Experimental procedure for the hydrogenation of nitroalkane (3a) under flow conditions: A SUS column (⌀ 5 mm x 50 mm) with column ends equipped with a filter and EYELA Flow Master (CCR-1000G) were used. A PETF tube (⌀ 0.8 mm) was used to connect the pump with the column. Heterogeneous Pd catalyst was weighed so that a Pd amount would be an appropriate amount. Celite was added to the Pd catalyst so that total weight would be 900 mg, and the whole was mixed and packed in the column. EtOH was perfused into the column using a pump (0.4 mL/min) for ca. 1 h. The column was then pre-heated to 30 °C. Hydrogen gas was introduced to the column at 15 mL/min flow rate. Finally, an EtOH solution of nitroalkane (**1a**) with a concentration of 0.2 M was prepared in a volumetric flask, and this solution was then perfused into the column (0.20 mL/min) under a concurrent flow of hydrogen. The resulting solution (3.0 mL) was evaporated, and the residue was analyzed by ^{1}H-NMR 3 h after the flow started.

6.2 General procedure for the hydrogenation of aliphatic nitroalkanes under continuous-flow conditions: A SUS column (⌀5 mm x 50 mm) with column ends equipped with a filter and EYELA Flow Master (CCR-1000G) were used. A PETF tube (0.8 mm) was used to connect the pump with the column. DMPSi-Pd/BC-Celite (310 mg) and Celite (300 mg) were mixed and packed in the column. EtOH was perfused into the column using a pump (0.4 mL/min) for ca. 1 h. The column was then pre-heated to 30 C. Hydrogen gas was introduced to the column at 15 mL/min flow rate. Finally, an EtOH solution of nitroalkane **3** with a concentration of 0.2 M was prepared in a volumetric flask, and this solution was then perfused into the column (0.20 mL/min) under a concurrent flow of hydrogen. The resulting solution (3.0 mL) was evaporated, and the residue was

analyzed by ^{1}H NMR 3 and 15 h after the flow started. As for the nitroalkanes **3e**, **3f** and **3g**, the resulting solutions were added to a 1N HCl aqueous solution and the products were isolated as HCl salts due to their low boiling points.

6.3 Experimental procedure for the lifetime and leaching experiment

A SUS column (⌀ 5 mm x 50 mm) with column ends equipped with a filter and EYELA Flow Master (CCR-1000G) were used for. A PETF tube (⌀ 0.8 mm) was used to connect the pump with the column. DMPSi-Pd/BC-Celite (310 mg, 0.23 mmol/g) and Celite (600 mg) was mixed and packed into the column. EtOH was perfused into the column by a pump (0.4 mL/min) for ca. 1 h. The column was then pre-heated to appropriate temperature. Hydrogen gas was introduced to the column at 15 mL/min flow rate. Finally, an EtOH solution of nitroalkane **3** with a concentration of 0.2 M was prepared in a volumetric flask, and this solution was perfused into the column (0.20 mL/min) under a concurrent flow of hydrogen. The resulting solution (3.0 mL) was added to a 1N HCl aqueous solution, and the whole was evaporated and analyzed by ^{1}H-NMR every 12 h after the flow started for totally 120 h. At the same time, the resulting solution was added to a 1N HCl aqueous solution, and the whole was evaporated every 24 h to get a crude product. The product (1.0 g) was placed on a ceramic plate and was heated at 800 ^{o}C for 3 h under ambient atmosphere. The plate was washed with aqua regia (5 mL) and the solution was diluted to 25 mL using a volumetric flask. The resulting solution was used for ICP measurement to determine contamination of the Pd into the product.

7. Spectroscopic Information of the Products

Phenethylamine (**4a**)[12]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.29 (t, J = 8.9 Hz, 2H), 7.28-7.22 (m, 3H), 3.00 (t, J = 8.3 Hz, 2H), 2.78 (t, J = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.7, 128.8, 128.4, 126.2, 43.5, 40.0.

4-(Methylphenyl)-2-ethylamine (**4b**)[12]: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.10-7.06 (m, 4H), 2.92 (t, J = 6.9 Hz, 2H), 2.69 (t, J = 6.9 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.6, 135.6, 129.1, 128.7, 43.5, 39.5, 20.9.

4-(Methoxyphenyl)-2-ethylamine (**4c**)[13]: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.9 Hz, 2H), 3.73 (s, 3H), 2.90 (t, J = 6.8 Hz, 2H), 2.66 (t, J = 6.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.0, 131.8, 129.7, 113.9, 55.2, 43.7, 39.1.

4-(Fluorophenyl)-2-ethylamine (**4d**)[12]: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 (dd, J = 7.3, 5.5 Hz, 2H), 6.95 (t, J = 8.9 Hz, 2H), 2.92 (t, J = 6.9 Hz, 2H), 2.69 (t, J = 6.9 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.4, 135.4, 130.1, 115.1, 43.5, 39.1; ^{19}F NMR (466 MHz, $CDCl_3$) δ -130.6.

Ethylamine hydrochloride (**4e**)[14]: ^{1}H NMR (600 MHz, D_2O) δ 2.89 (q, J = 8.0 Hz, 2H), 1.11 (t, J = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, D_2O) δ 35.6, 12.5.

Propylamine hydrochloride (**4f**)[14]: ^{1}H NMR (600 MHz, D_2O) δ 2.75 (t, J = 7.3 Hz, 2H), 1.47 (tt, J = 7.3, 7.3 Hz, 2H), 0.76 (t, J = 7.3 Hz, 3H); ^{13}C NMR (600 MHz, D_2O) δ 41.8, 20.9, 10.8.

2-Propylamine hydrochloride (**4g**)[14]: ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.23-3.21 (m, 1H), 1.17 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 43.0, 20.4.
5,5-Dimethyl-2-pyrrolidone (**4h**)[15]: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.93 (br, 1H), 2.39 (t, *J* = 8.3 Hz, 2H), 1.91 (t, *J* = 7,5 Hz), 1.26 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.9, 56.5, 35.3, 30.6, 29.2.

以下の部分については、5 年以内に雑誌等で刊行予定のため、非公開。

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Experimental Section –Chapter 4–

本章については、5 年以内に雑誌等で刊行予定のため、非公開。

CHAPTER 5

本章については、5 年以内に雑誌等で刊行予定のため、非公開。