

学位論文 (要約)

Development of Tandem Oxidation Reactions and Arene
Hydrogenation/Dehydrogenation Reactions Facilitated by
Metal Nanoparticle Catalysts

(金属ナノ粒子触媒によるタンデム酸化反応および
芳香族化合物の水素化・脱水素化反応の開発)

平成 29 年 12 月博士 (理学) 申請

東京大学大学院理学系研究科

化学専攻

鈴木 綾

Table of Contents

Abstract.....	1
1. Introduction	8
2. Tandem oxidation processes (TOP) with metal NPs as heterogeneous catalysts for synthesis of chiral esters	29
3. 非公開	48
4. 非公開	102
5. 非公開	127
6. Overview	146
7. Experimental section	184
8. Acknowledgement	187

Abstract

1. Introduction

In organic syntheses, an efficient process to obtain a desired product with less waste is highly desired. Heterogeneous catalysts have attracted much attention because of their advantages such as reusability and simplification of separation from a product. On the other hand, a continuous-flow reaction using heterogeneous catalysts is attractive in terms of scalability, providing a large amount of desired product as pure form by simply feeding starting materials to columns packed with catalysts continuously. In addition, a sequential multistep reaction, which is a green process that omits purifications in each step, is realized by simply conducting several reactions sequentially in continuous-flow systems. For these reasons, a continuous-flow reaction with heterogeneous catalysts is one of ideal processes for organic syntheses. However, this process is sometimes difficult to apply to fine chemical synthesis because of a lack of activity and robustness of heterogeneous catalysts. In this context, I focused on metal nanoparticles (NPs)-immobilized heterogeneous catalysts, which have been of great interest for their high reactivity, unique selectivity and robustness. In my PhD studies, I have developed immobilized-metal NPs as heterogeneous catalysts for tandem oxidation processes including asymmetric C–C bond forming reactions, arene hydrogenation and dehydrogenation reactions, which are compatible with both batch and continuous-flow reactions.

2. Tandem oxidation processes (TOP) with metal NPs as heterogeneous catalysts for synthesis of chiral esters

TOP is a sequential multistep reaction, including oxidation and nucleophilic addition, which is an important method to construct complex molecules effectively. In my master course studies, I developed an integrated process of oxidation-olefination-asymmetric C–C bond formation catalyzed by polymer-supported metal NP catalysts under aerobic and aqueous conditions to form chiral esters, which are valuable synthetic precursors. However, the tandem oxidation-olefination did not give a satisfactory yield when aliphatic alcohols were used as starting materials, because they were suffered from over oxidation of intermediate aldehydes to give carboxylic acids.

To solve this problem, a base moiety was incorporated in the catalyst to accelerate olefination, suppressing the over oxidation. That is, a bifunctional catalyst of core-shell structure was prepared with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU)-immobilized polymer as a base and an immobilized-metal NP catalyst developed in our laboratory. It was found that a tandem oxidation-olefination process with benzyl alcohol was successfully accelerated.

1. Introduction

Heterogeneous catalysts for organic chemistry

Catalysts, which accelerate a reaction by reducing an energy of transition states and remain unchanged at the end of the reaction, play a significant role in various research fields. Needless to say, catalysts are necessary for organic chemistry; various valuable transformations which are difficult to achieve without them have been realized. The impact of catalysts is not only to facilitate the organic reactions themselves but also to make the reactions meet the criteria of “Green Chemistry”, which is an important conceptual guideline for organic chemistry.

Over a quite short period for a history of a universe, our lives have been improved dramatically thanks to a development of science; however, mass production, mass consumption, and mass disposal resulted in serious environmental problems which are difficult to solve. For this reason, a concept of Green Chemistry, whose aim is to reduce or eliminate the generation of hazardous compounds by changing from conventional processes to environmentally friendly ones, and also by replacing conventional chemical products with environmentally friendly or harmless ones, was established.^[1] Following this criteria, the importance of catalysts for chemistry is recognized.

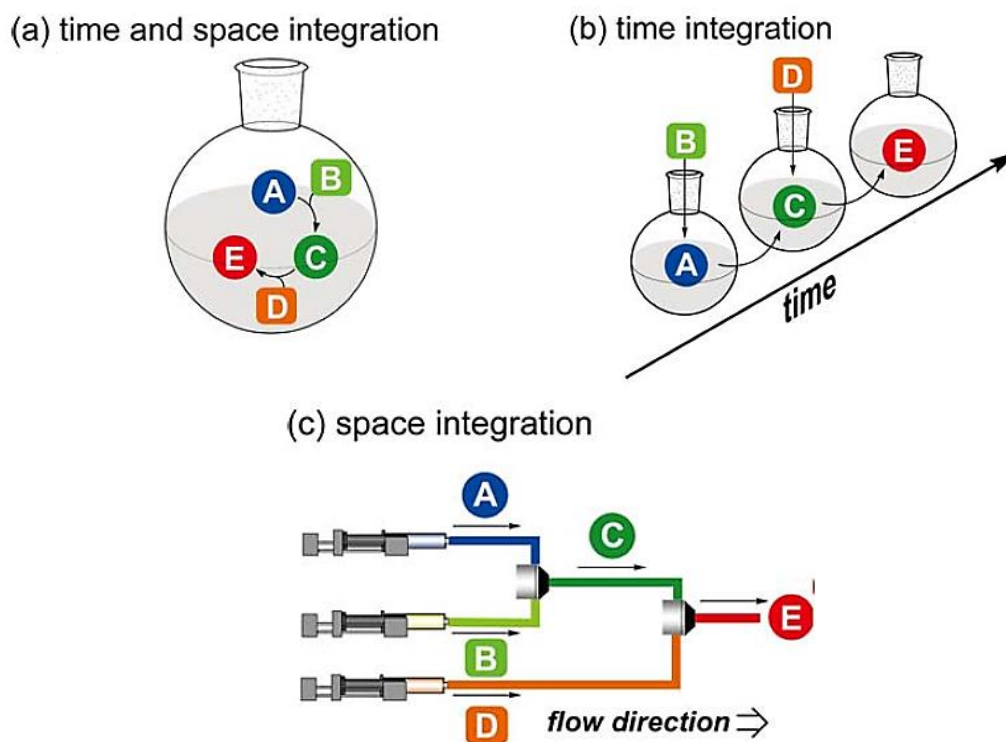
Synthetic organic chemistry, which is deeply related to environmental problems, especially has a duty to follow the concept of Green Chemistry. The requirement is to afford the target compounds efficiently with less waste generation, minimizing a consumption of finite and valuable resources. In this context, heterogeneous catalysts are an important key to achieve organic synthesis which meets the concept. Heterogeneous catalysts have great advantages over homogenous catalyst systems, represented by reusability. Except a special case such as organocatalysts, most of the practical catalysts for organic transformations contain precious metals, which are very difficult to be recovered and reused in a homogeneous catalyst system. As catalytic species are immobilized on solid support in heterogeneous catalysts, they can be recovered easily by simple filtration. Furthermore, they do not suffer from residual metals in the final products, which is a serious problem in a reaction with homogeneous catalysts including a pharmaceutical process.

Reaction integration

“Reaction integration” is another important aspect to achieve Green Chemistry, which was defined by Bard in 1994.^[2] A concept of reaction integration is to perform several reactions as a sequential multistep transformation. As this process does not require an isolation of intermediates, it has a lot of advantages: For example, a purification process, which is the most time- and cost-demanding and waste-producing operations in organic synthesis, can be omitted. Additionally, even toxic or unstable intermediates can be

generated and consumed immediately *in situ*, realizing more efficient and safe reaction.^[3] The concept of reaction integration was further categorized in detail by Yoshida.^[4] According to a classification he suggested, conventional methods for reaction integration performed in batch system, which is a reaction using a flask, is divided into two types: One is “time and space integration”, where all reagents and catalysts are mixed at once to perform a sequential reaction in one pot. The other is “time integration”, where a sequence of reactions is performed in one pot by adding the reaction components at intervals. Meanwhile, “space integration”, generally performed under continuous-flow condition with a microreactor, is a new method for reaction integration (Scheme 1-1).

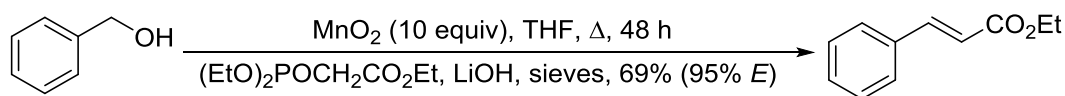
Scheme 1-1. Classification of reaction integration (ref. Yoshida *et al.*, *Synlett* **2011**, 9, 1189.)



<Time and space integration>

Tandem, domino, and cascade reactions are classified into this type. For example, In 2002, Taylor and co-workers reported tandem process of an oxidation of alcohols and Horner-Wadsworth-Emmons (HWE) reaction to provide α,β -unsaturated esters. In this reaction, all substrates and catalysts, which are alcohols, LiOH, MnO₂ as an oxidation catalyst, and triethyl phosphonacetate as a HWE reagent, were mixed at once from the beginning of the reaction, and the reaction proceeded sequentially in one-pot manner (Scheme 1-2).^[5]

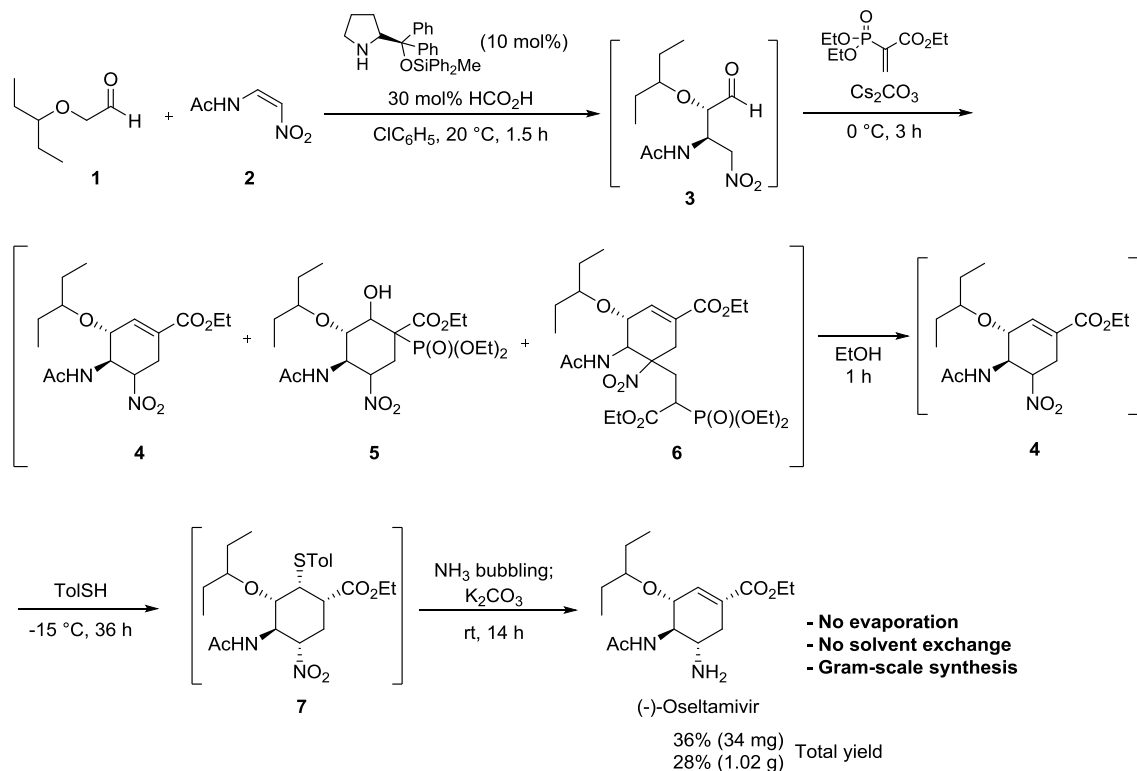
Scheme 1-2. Tandem oxidation process through “time-space integration”



<Time integration>

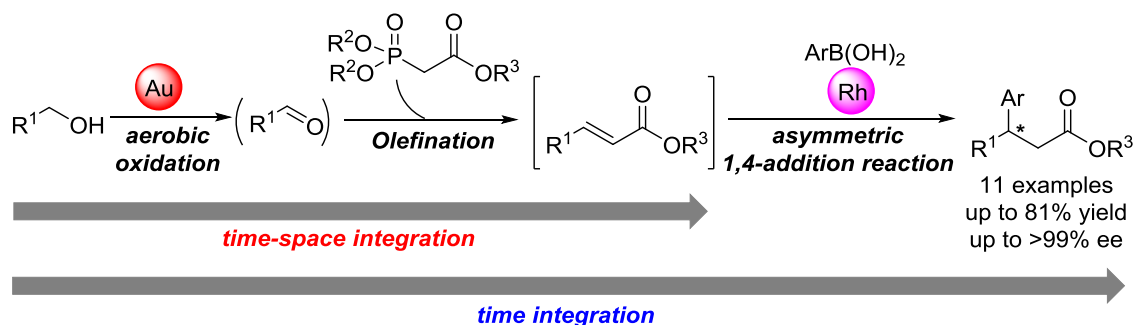
The other is “time integration”, where a sequence of reactions is performed in one pot by adding the reaction components at intervals. This reaction is called one-pot sequential reactions to distinguish from the first type reaction. Although these processes have merits mentioned above, undesired interactions between various catalysts, substrates, intermediates and products which are co-exist in the reaction system sometimes make it difficult to succeed. In 2013, Hayashi’s group succeeded one-pot sequential synthesis of (-)-Oseltamivir (Tamiflu), which is one of the most effective drugs for the treatment of influenza. In this process, asymmetric Michael addition reaction, Michael reaction and intermolecular HWE reaction, isomerization and further several transformations afforded the desired product by sequential addition of individual substrates without evaporation and solvent exchange (Scheme 1-3).^[6]

Scheme 1-3. Tamiflu synthesis through “time integration”



In my Master's course study, I have achieved an integrated process of oxidation–olefination–asymmetric 1,4-addition reactions under aerobic and aqueous conditions catalyzed by immobilized metal NPs. The first two step of tandem process is time and space integration of an aerobic oxidation of alcohols followed by olefination, and the second step is asymmetric 1,4-addition of boronic acid to α,β -unsaturated ester to afford chiral esters by sequential addition of reagent and the catalyst, which is the combination of time-space integration and time integration (Scheme 1-4).^[7]

Scheme 1-4. Integrated process of oxidation–olefination–asymmetric 1,4-addition reactions



<Space integration>

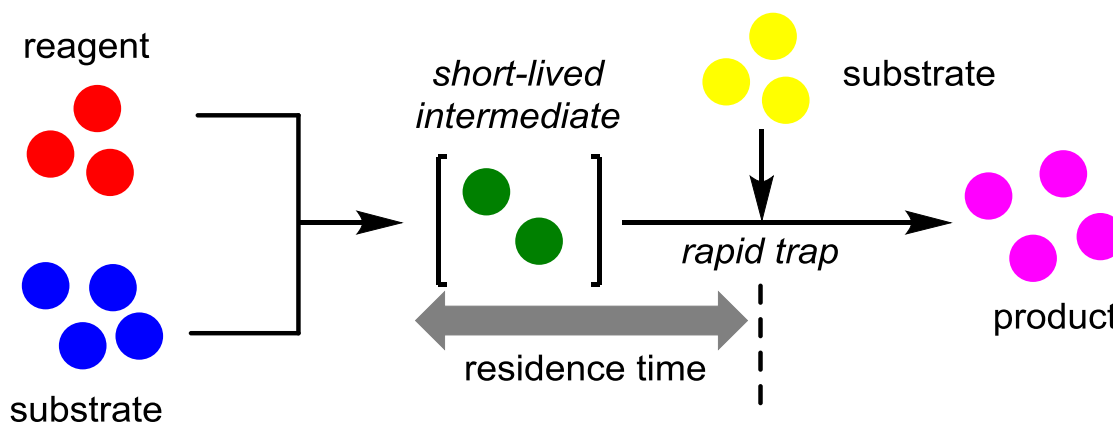
In the reaction classified into “space integration”, where several flow reactors which perform each reaction individually are connected to complete a target reaction, substrates introduced into flow reactors are transformed to the target products *via* several reactions while they are passing through the reactors; in other words, several sequential transformations on individual substrates which occur in independent reactors simultaneously are integrated to afford the final products. In common with integrated batch reactions, it is possible to add some reagents or catalysts during the course of the reaction.

Space integration under a microflow condition has several advantages over a batch method from the aspect of environmental compatibility, efficiency and safety. In general, a microflow process are more efficient than standard batch protocols and offer much higher through put per unit volume and per unite time with less waste. Starting materials are continuously fed to a column or a hollow loop and contact within a smaller reaction space, and removed quickly from there to provide the desired products continuously. As the reaction parameters such as temperature and reaction time can be controlled more precisely, the risk of side reactions is reduced. In addition, better heat transfer and mixing efficiency thanks to a smaller reaction space makes the reaction system more safety.

Furthermore, space integration realizes a new method for organic transformations utilizing highly unstable intermediates that cannot be treated in a conventional batch

system. For instance, quite short-lived species such as extremely reactive carbanion can immediately react with other substrates and reagents which co-exist in the reaction system before their decomposition. In the case of time and space integration, the design of the reaction is limited to some degree because the order of each reaction and the final product often depend on substrates or reagents. In the case of time integration, this issue is overcome thanks to the sequential addition of further reagents, which enables a control of the order of the reactions; however, a time interval of addition of individual reagents makes it technically impossible to employ an intermediate whose life time is significantly short such as less than milli-second. On the other hand, as a reaction is performed under continuous-flow condition in space integration, further reagents can be added immediately after generation of unstable intermediates. Recent flow microreactors enable active species whose life time is less than one second to be employed to the reaction without their decomposition. A rapid organic synthesis with flow microreactors utilizing short-lived active species is specifically called as Flash Chemistry, whose keyword is “controlling time by space”: Space integration based on Flash Chemistry realizes a molecular transformation of quite unstable intermediates by a precise control of residence time, which is impossible to achieve in a batch reaction (Scheme 1-5).^[4, 8]

Scheme 1-5. Utilization of short-lived active species through Flash Chemistry

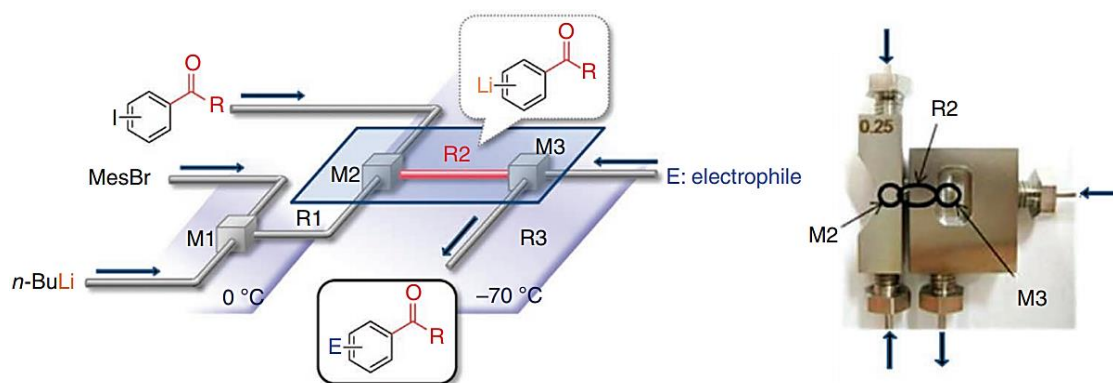
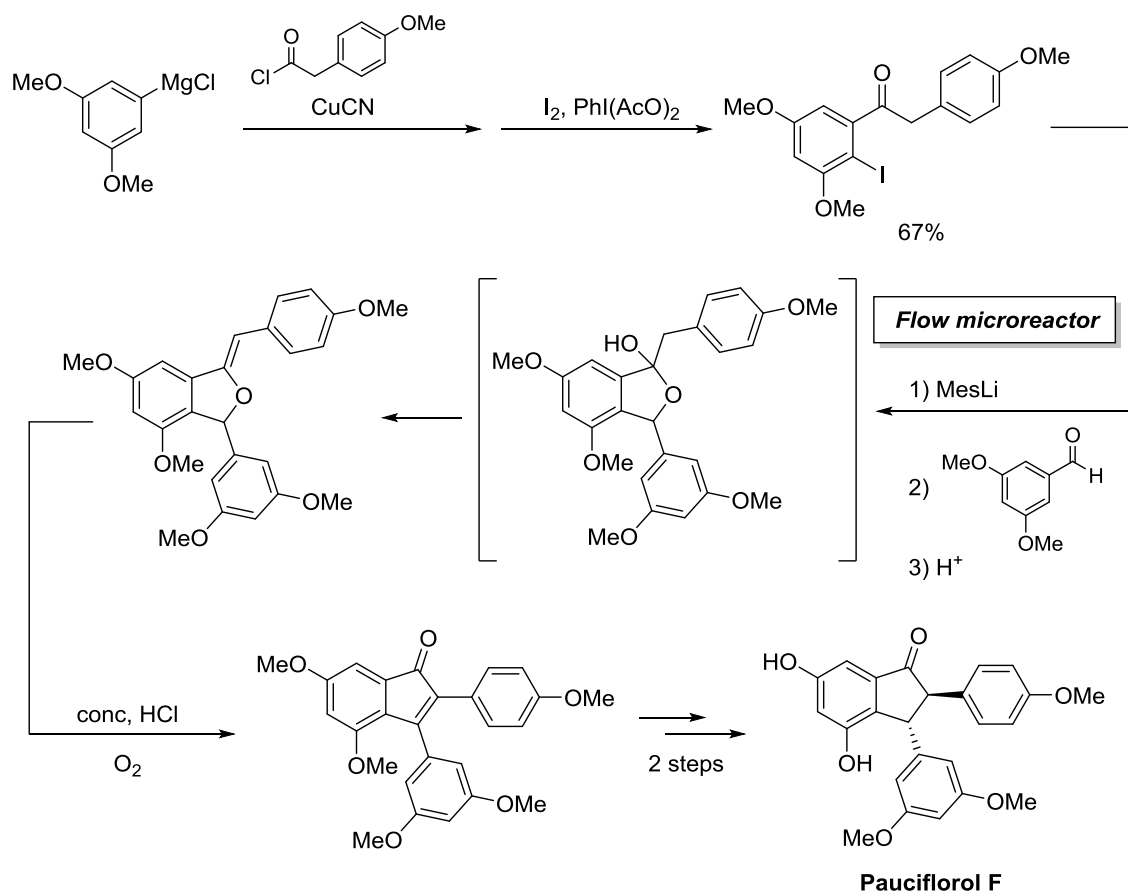


For example, Yoshida and co-workers succeeded to generate an organolithium intermediate without a protection of intramolecular carbonyl group followed by trapping it with an electrophile such as aldehyde; a formal total synthesis of bioactive natural polyphenol was achieved through this method (Scheme 1-6).^[9] This kind of process is expected to bring a new possibility of preparation of drugs or functional materials.

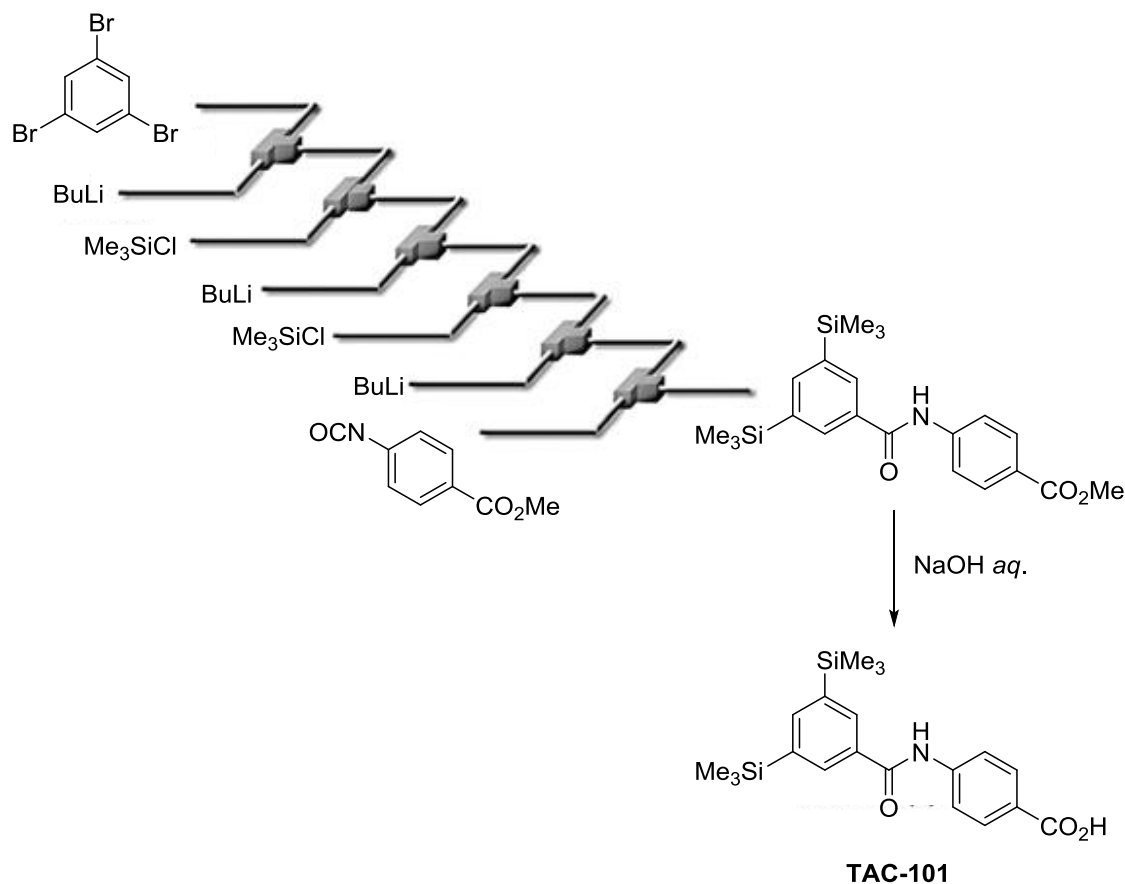
The concept of flash chemistry is also applicable to multi-step synthesis. In 2011, Yoshida's group achieved sequential introduction of three electrophiles into 1,3,5-tribromobenzene based on Br-Li exchange reaction using an integrated flow

microreactor system consisting of six micromixers and six microtube reactors. This method enables flash synthesis of methyl ester of TAC-101, which is a synthetic retinoid with selective binding affinity for RAR- α and its analogues in good yields. The total residence time of organolithium species was 0.003 s or less and that from 1,3,5-tribromobenzene to the ester was ca. 13 s, and the productivity of it was 100–200 mg/min (Scheme 1-7).^[8e]

Scheme 1-6. Organolithiation under microflow condition (ref. J.-i. Yoshida, *Nat. Commun.* **2011**, 2, 264.)



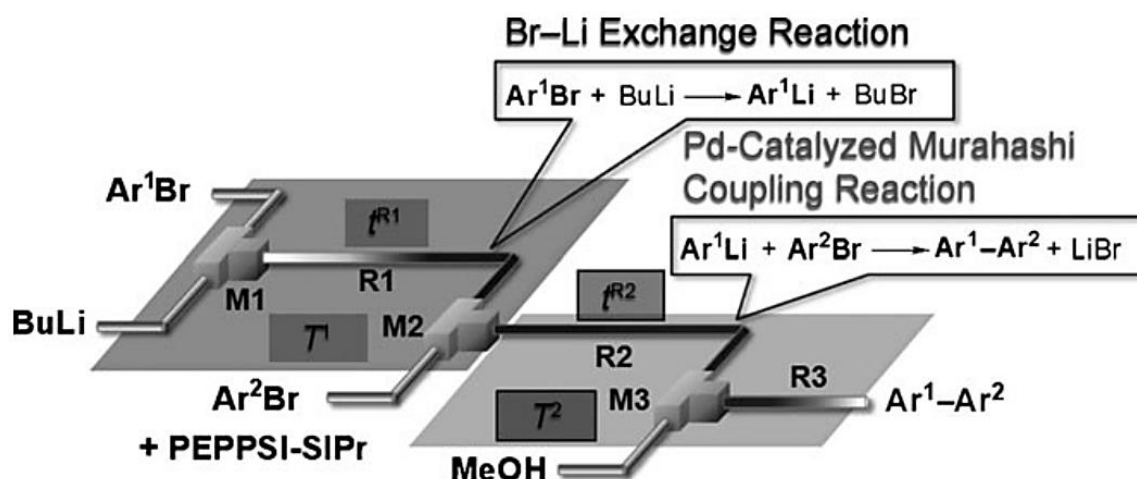
Scheme 1-7. Synthesis of TAC-101 using an integrated flow microreactor system



On the other hand, microflow strategy is suitable not only for the reactions with quite unstable species, but also for that with highly active reagents such as BuLi. In 2010, space integration of Br–Li exchange and Murahashi coupling under microflow condition for cross-coupling of two different aryl bromides (Ar¹–Br and Ar²–Br) was reported by Yoshida and co-workers. While Aryl–boron, aryl–silane, aryl–tin, aryl–zinc, and aryl–magnesium compounds are often used for cross-coupling reactions for their relative stability, the use of less stable but more reactive aryllithium compounds in cross-coupling has been rather limited. Until this Yoshida’s report, pioneering work by Murahashi in 1979 is only an example of the palladium-catalyzed cross-coupling of organolithium compounds with organic halides.^[10] One of the major reasons of less development of this type of reaction is X–Li exchange of ArX with BuLi leads to the formation of BuX, which consumes ArLi if desired subsequent coupling is slow. That is, the key for achieving this reaction might be a rapid reaction of generated ArLi with a coupling partner. In this context, they commenced an investigation of this space integration through microflow reaction. Eventually, it was found that the use of Pd catalyst (PEPPSI-SIPr) bearing a carbene ligand results in the Murahashi coupling being

much faster, enabling its integration with the Br–Li exchange of Ar¹Br with BuLi in a microflow reactor (Scheme 1-8).^[11]

Scheme 1-8. Integrated flow microreactor system for the cross-coupling (ref. J.-i. Yoshida *et al.*, *Angew. Chem. Int. Ed.* **2010**, *49*, 7543.)



As mentioned, “time control by space” strategy under microflow condition is desirable for a rapid reaction of highly active species; however, the requirement of a continuous flow of precious metals causes problems of an isolation issue and high cost. In this context, in the case of reactions using inactive compounds which require activation by catalysts, which take several minutes to hours to be completed, a simpler flow system with a column packed with immobilized-metal catalysts, which does not need isolation of the catalysts, is suitable.

Recently, a concept of flow “fine” synthesis, which is reactions and synthesis that attain high yields and high selectivities through a flow method, has been established by Kobayashi.^[12] Furthermore, as a characteristic of the flow method is that it is continuous, flow “fine” synthesis should construct multistep flow systems by combining individual flow reactions to synthesize structurally complex molecules. Flow “fine” synthesis has several advantages over conventional organic synthesis. (1) High energy productivity and energy saving compared with batch methods can be realized. (2) The compact nature of a reactor means that space saving can be realized in addition to energy saving. (3) The low-volume reaction space means that it is possible to suppress damage caused in the event of leakage even when high-risk substances are used; therefore, flow “fine” synthesis ensures high safety. (4) It is possible to adjust the quantity of production by controlling the rate of introduction of starting materials; such “just-in-time” production can reduce the amount of waste generated, which can lead to lower costs. (5) Automation is easier, and it is possible to minimize the exposure of operators to hazardous chemicals. (6) As discussed below, by using columns packed

with suitable catalysts, the separation of catalyst from the product is not required. In his review article, a classification of continuous-flow reactions into four types has been explained (Scheme 1-9).

Type I: Substrates (**A** and **B**) are passed through a column or hollow loop, etc. during which reactions occur. Although the product is obtained continuously, unreacted **A** or **B** or any byproduct(s) are also eluted as contaminants.

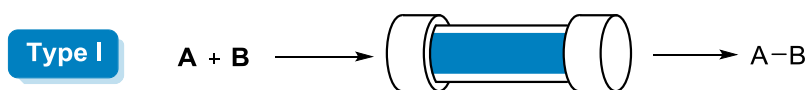
Type II: One of the substrates (**B**) is supported in a column. If an excess amount of **B** is used, the second substrate (**A**) is consumed. Although contamination of the product by unreacted **A** or **B** may be avoided, overreaction(s) may occur. In addition, once supported **B** is consumed, the column must be changed.

Type III: Substrate **A** reacts with **B** in the presence of a homogeneous catalyst. Although catalysis proceeds smoothly, the catalyst cannot be easily separated and it elutes as a contaminant in the product.

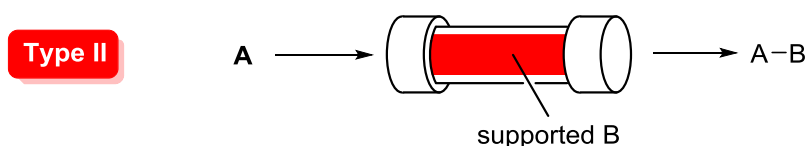
Type IV: Substrate **A** reacts with **B** in the presence of a heterogeneous catalyst. If catalysis proceeds smoothly, no separation of the catalyst from the product is required.

Scheme 1-9. Classification of continuous-flow reactions

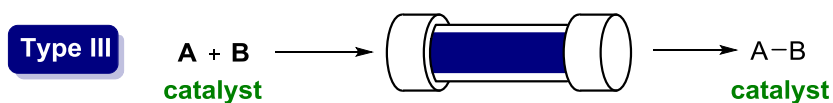
1) No catalyst



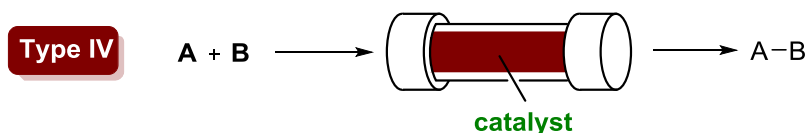
2) Supported reagent



3) Homogeneous catalyst



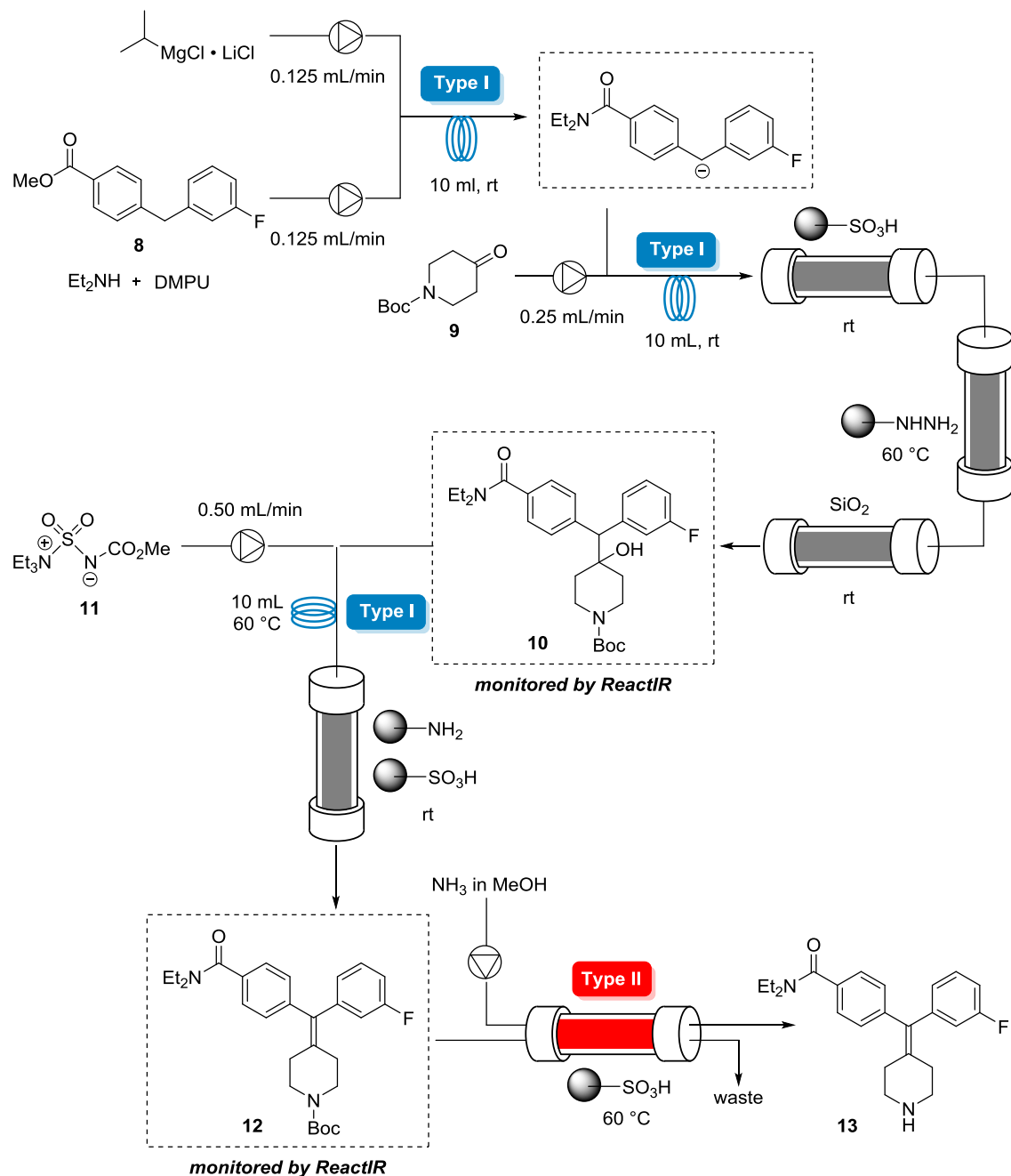
4) Heterogeneous catalyst



Following this definition, the microflow synthesis of TAC-101 and cross-coupling of arylbromides are classified into an integration of Type I reaction and an integration of I and III, respectively.

On the other hand, In 2010, Ley and co-worker achieved a 4-step continuous-flow reaction to synthesize *N,N*-Diethyl-4-(3-fluorophenylpiperidin-4-ylidenemethyl)benzamide **13**, which is a potent δ -opioid receptor agonist developed by AstraZeneca.^[13] A solution of *i*PrMgCl·LiCl in THF and a mixture of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), diethylamine, and ester **8** in THF were combined, and the resulting mixture was passed through a convection flow coil (CFC) reactor (10 mL, 25 °C) before being merged with a third flow of 1-Boc-4-piperidone **9**. The reaction stream was then directed through a second CFC (10 mL, 25 °C), followed by three scavenger columns containing, in order, supported-sulfonic acid, supported-TsNHNH₂, and silica gel to give tertiary alcohol **10**. The supported-sulfonic acid scavenged the residual amine starting material and the base, and the supported-TsNHNH₂ removed all the remaining piperidone **9**; the silica gel column trapped the magnesium salts generated during the process. Burgess reagent **11** then joined the main reaction stream of **10**. The reaction mixture was then pumped through a third CFC (10 mL, 60 °C) before entering into a column loaded with a mixture of supported-sulfonic acid and supported benzylamine to sequester the excess Burgess reagent and associated by-products, providing *N*-Boc-protected **12**. Finally, a heated column (60 °C) of supported-sulfonic acid was used to deprotect and catch the target molecule. Elution of the acidic column by using a solution of NH₃ in MeOH completed the synthesis in a continuous fashion, and gave the product **13** (Scheme 1-10). Four CFCs and one column were used, corresponding to 3 Type I and 1 Type II, and the four-step synthesis resulted in 35% overall yield of pure **13** (74 mg). It is noteworthy that ReactIR flow cell was utilized to know the appropriate time for the addition of followed reagent **11**; as soon as the indicative fingerprint signal of **10** was detected (i.e., IR stretching frequency 1690–1700 cm⁻¹), the following stream was started. The incorporation of in-line analysis into continuous-multistep-flow synthesis implies further development of this research field. The chief characteristic of this synthesis is the combination of Type I flow reactions and scavenger resins, which is for removal of unreacted starting materials, co-products, and by-products efficiently. Taking these problematic issues and the aspect of the recent regulations on Green Chemistry, continuous-flow reactions in Type IV are recommended to use. Continuous-flow reactions in Type IV are especially proper for flow “fine” chemistry.

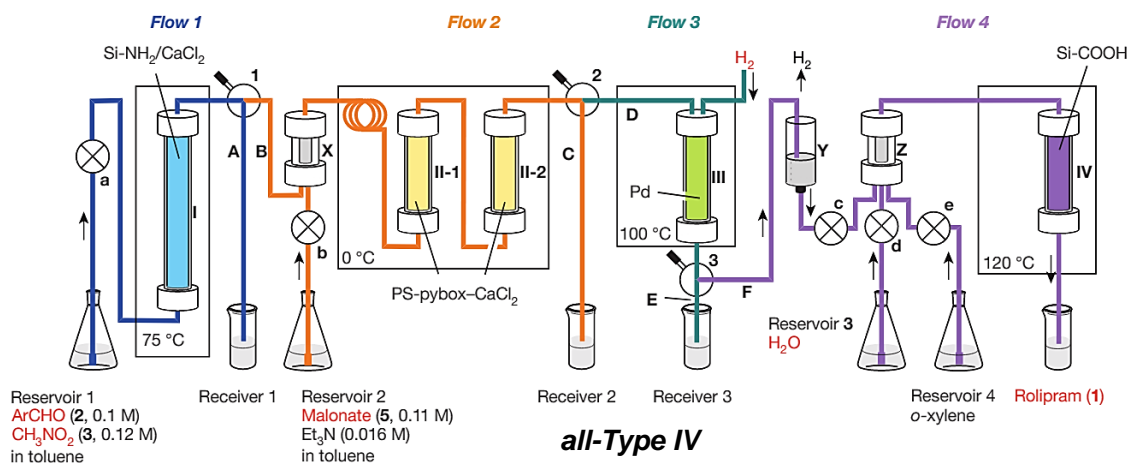
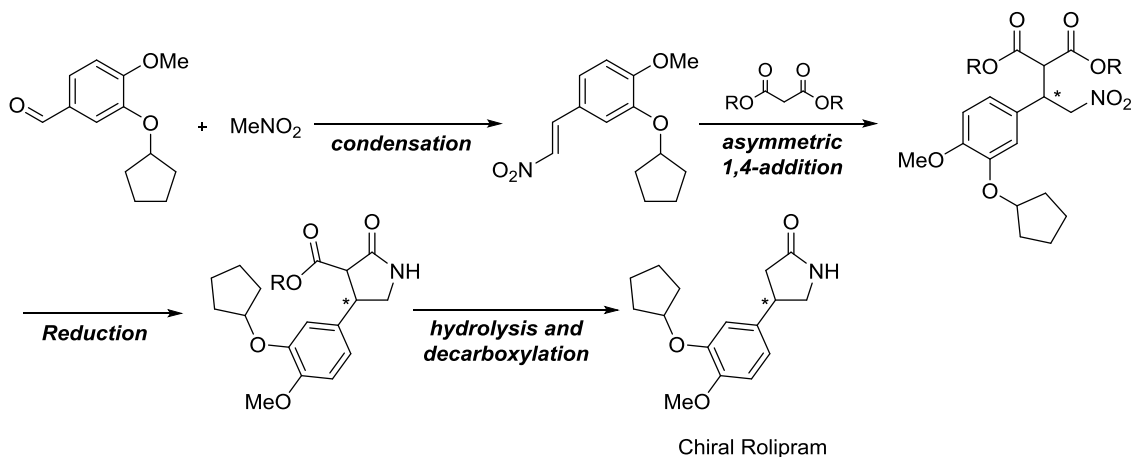
Scheme 1-10. Flow synthesis of δ -opioid receptor agonist **13**



In our laboratory, 4-step continuous-flow synthesis of (*R*)-Rolipram, which is an anti-inflammatory drug, has been achieved by the combination of all type IV reactions (Scheme 1-11).^[14] However, heterogeneous catalysts generally show lower activity than corresponding homogeneous counterparts due to a lower contact efficiency of solid catalysts and the substrates in a liquid phase. This makes an application of heterogeneous catalysts to a continuous-flow system difficult because the reactions

require to be completed within a short residence time in this system. In this context, metal nanoparticles, which show higher catalytic activity, are one of the solutions for this issue.

Scheme 1-11. Continuous-flow synthesis of chiral Rolipram

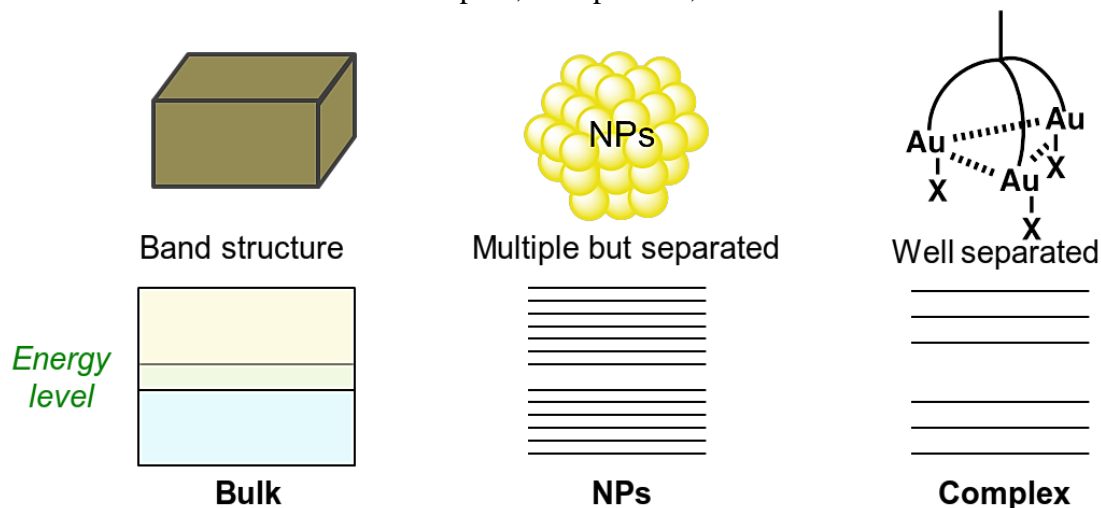


Immobilized-metal nanoparticles as heterogeneous catalysts

Metal nanoparticles (NPs), which are nanometer sized aggregates consisting of several tens to hundreds of metal atoms, have been of great interest in various research areas such as material science and biochemistry because of their unique physical properties, which are different from that of bulk metals or metal complexes. This unique property of metal NPs can be explained from a view point of their peculiar electron states. While metal complexes have energetically well-defined bonding and antibonding orbitals, bulk metals have typical consecutive band structures. Metal NPs possess a lot

of discrete energy levels and forms a small energy gap, in other words, the electronic states of metal NPs have a middle of those two natures (Scheme 1-12).^[15]

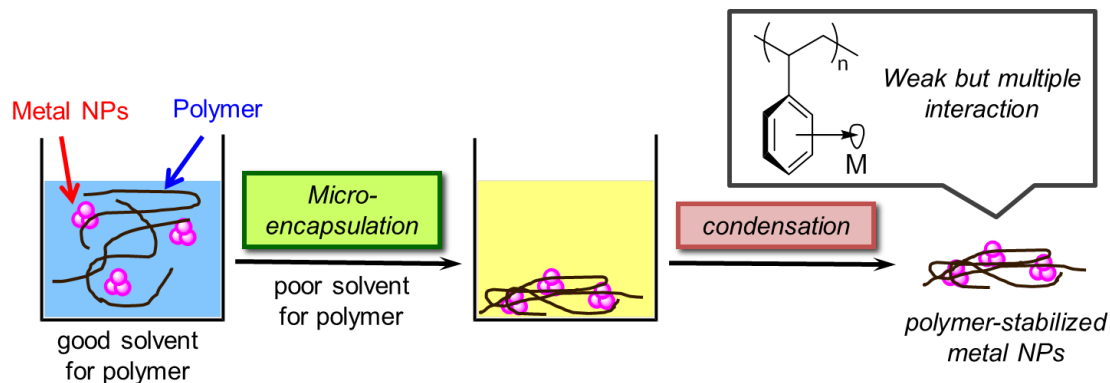
Scheme 1-12. Electron states in complex, nanoparticle, and bulk metals



In the field of synthetic organic chemistry, metal NPs have been attracted attention and showed high reactivity and unique selectivity as a catalyst. The example reported by Haruta and co-workers in 1987 is a representative of unique NP catalysis, which is totally different from bulk metals.^[16] Small gold NPs showed catalytic ability in aerobic oxidation of carbon monoxide to carbon dioxide at low temperature while no reaction was observed with bulk gold, demonstrating a characteristic nature of gold NPs as catalysts. Since this remarkable discovery, aerobic oxidation catalyzed by gold NPs has been extensively studied.

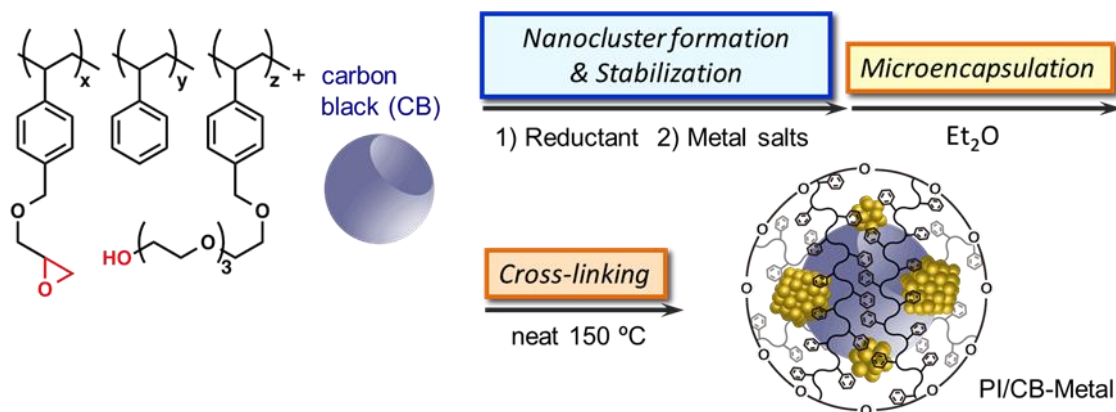
Because of lability of metal NPs, stabilizers such as small ligand molecules, inorganic or organic polymers are required for immobilization on supports. Microencapsulation (MC) of metal NPs is one of the methods to stabilize them keeping their activity. Our group has been succeeded to immobilize metal NPs by polystyrene-based polymers following this concept. The reduction of metal salts in a solution containing a polymer makes stabilized metal NPs, followed by the addition of poor solvent for the polymer which causes a precipitation of polymer encapsulated metal NPs. The immobilized metal NPs are obtained as a heterogeneous catalyst after separation from liquid phase. In this catalyst, metal NPs are physically enveloped and stabilized by polymer backbones through an interaction between vacant orbitals of the metals and π electrons of the benzene rings in polymer (Scheme 1-13). This immobilization manner of metal nanoparticles utilizing weak but multiple π -interactions realizes high activity of the catalysts. In addition, polystyrene-based polymer provides a suitable reaction field behaving like a solvent and facilitates the access of the substrates to metal NPs.^[17]

Scheme 1-13. Stabilization of metal NPs by MC technique



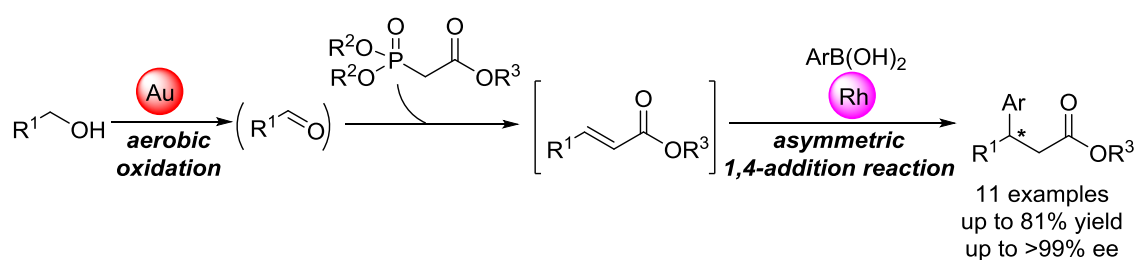
This method was further developed by a combination of two procedures of MC and cross-linking of the side chains of polymer to provide "Polymer-Incarcerated (PI) catalyst" (Scheme 1-14).^[17a, 18] Cross-linking reaction between epoxide and hydroxyl groups in the polymer resulted in solidier envelopment of metal NPs successfully prevented a leaching of metals from the catalyst. Additionally, incorporation of carbon black as a second support provides larger specific surface area of the catalyst, leading to higher catalytic activity (PI/CB catalyst). Furthermore, bimetallic NPs can be easily prepared by simultaneous reduction of both metal salts: Notably, catalytic activity and selectivity were enhanced by bimetallic NPs formation.^[18b, 19] The positive effect of bimetallic NPs formation is explained by mainly two factors^[20]: One is a "ligand effect", which electron transfer between two different metals changes an electronic state of the catalytically active center. The other is "ensemble effect", which several kinds of substrates are activated on each metal individually to accelerate the reaction at the interfaces of two metals.

Scheme 1-14. Preparation of PI/CB-metal catalysts



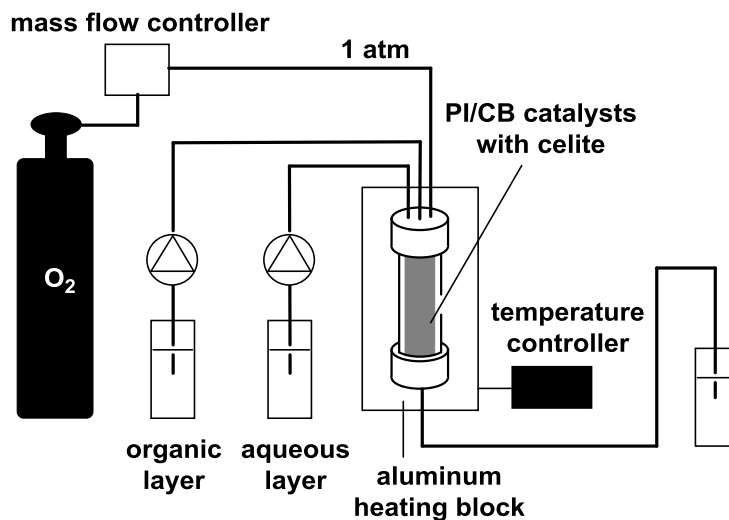
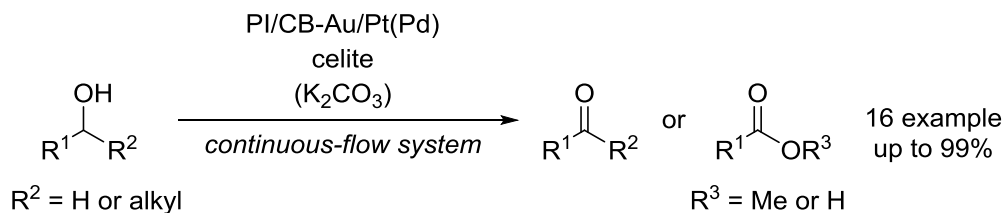
PI/CB-metal catalysts have been applied to various organic transformations such as aerobic oxidations^[18b, 19b, 21] and tandem oxidative processes for ester or amide formation.^[22] In addition, bimetallic NPs of Rh and Ag modified by chiral ligands, called chiral NPs, were applied to asymmetric 1,4-addition of arylboronic acid to α,β -unsaturated esters.^[7, 19a, 21a] In my master course study, I have achieved an integrated process of oxidation–olefination–asymmetric 1,4-addition reactions under aerobic and aqueous conditions catalyzed by immobilized metal NPs (Scheme 1-15).^[23]

Scheme 1-15. Integrated process of oxidation–olefination–asymmetric 1,4-addition reactions



Our laboratory has further applied gold-based bimetallic NPs to oxidation and oxidative esterification of alcohols under continuous-flow conditions.^[24] Organic layer with substrates and aqueous layer containing base were introduced into a glass column packed with PI/CB-metal catalyst with simultaneous flow of oxygen gas, which successfully achieved the gas-liquid-liquid-solid multiphase flow reaction (Scheme 1-16). However, this process required to pack certain amount of celite together with the catalyst; otherwise, the clogging of the system prevented the reaction mixture from passing through the column due to swelling of the catalyst by absorption of the solvent.

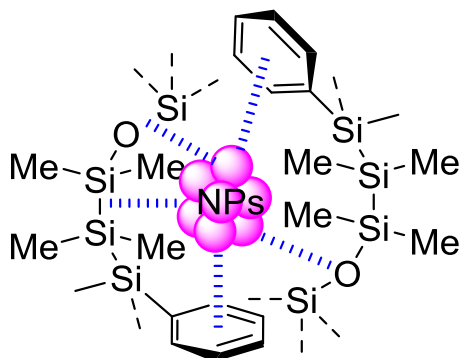
Scheme 1-16. Oxidative esterification of alcohols under continuous-flow conditions



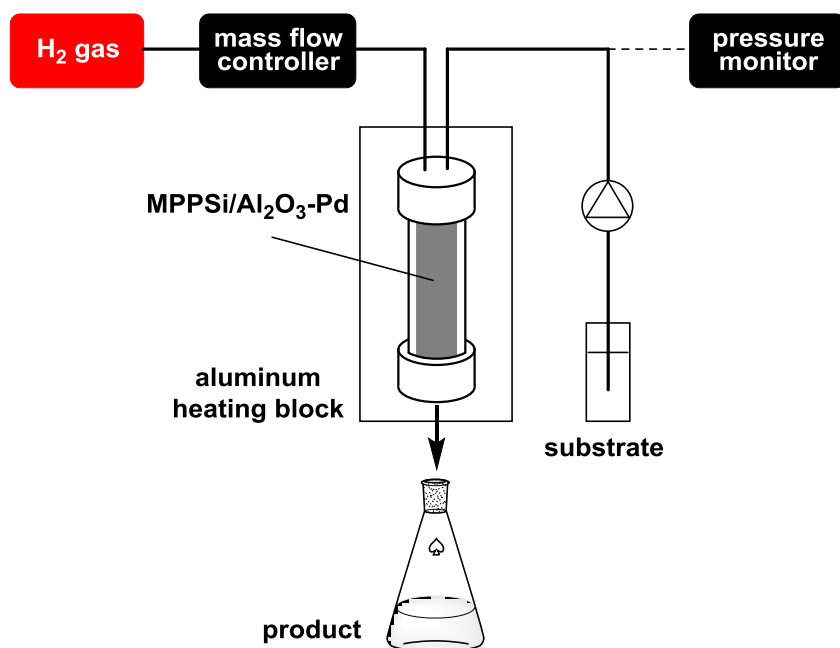
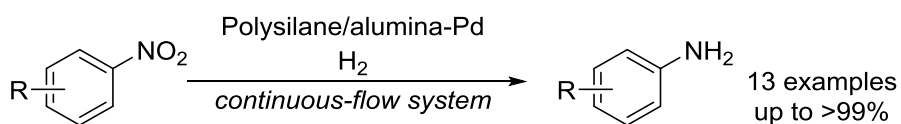
On the other hand, Polysilane-immobilized metal NPs catalyst, which developed in our laboratory,^[25] solved the problem of clogging of continuous-flow systems. Polysilanes are organosilicon polymers with the formula $(\text{R}_2\text{Si})_n$, which are synthesized by heating Na with R_2SiCl_2 , or obtained as an inexpensive industrial by-product from silicon wafer manufacturing.^[26] Polysilanes have been widely studied for their unique electronic properties, such as high hole mobility, photoconductivity, and nonlinear optical properties caused by σ -conjugation of the silicon backbones.^[27] The σ -conjugation stems from the low ionization energy of electrons in Si-Si bonds of the polymer backbones, compared to that of C-C σ -bonds. It was generally said that the delocalized electrons in the σ -conjugation of polysilanes could interact with the vacant orbitals of metals to immobilize the metals, which is the same manner as the π -electrons of the benzene rings in PI catalyst. Surely, polysilanes which have benzene rings in their structure such as methylphenylpolysilane would be able to stabilize NPs through π -metal interaction (Scheme 1-17). From the view point of availability and affordable price of them, the use of polysilanes as support of heterogeneous catalysts is advantageous to PI method, while co-polymer for PI catalysts requires tedious synthetic procedures. Recently, we have been achieved catalytic flow hydrogenation of aromatic nitro compounds with Pd NPs immobilized on nanocomposite of polysilane and alumina.^[28] This reaction did not suffer from clogging the column even without celite,

thanks to a property of polysilane which does not swell with organic solvents (Scheme 1-18).

Scheme 1-17. Stabilization of metal NPs by σ -conjugation of polysilane



Scheme 1-18. Hydrogenation with polysilane-immobilized heterogeneous catalyst

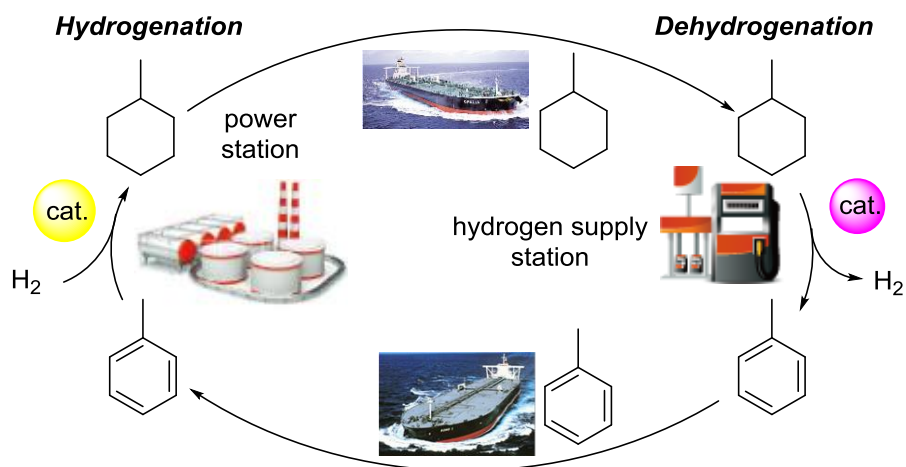


Hydrogen storage ^[29]

Another important role of heterogeneous catalysts is illustrated in a field of energy storage. Suffering from a depletion of fossil fuels, alternative energy resources are urgently desired. Wind-force, geometrical, and solar power generation can be a candidate; however, instability of an energy supply is one of the drawbacks of them. In this context, new system to compensate for such “unstable” energy resource has attracted attention.

Hydrogen, which generates water as a sole by-product in an energy production, has attracted much attention as a clean energy resource. In current method, hydrogen, which is a gas under ordinary temperature and pressure, is stored and transported as a liquid form or a compressed gas; however, it consumes significantly large amount of energy for compression and cooling the hydrogen gas. Furthermore, special containers for transportation are also required. Taking it into account that certain degree of loss of hydrogen during transportation additionally, this method should be regarded as a high-cost and low-efficiency process. For this reason, development of technique to provide hydrogen safely and simply to various applications such as power for automobiles and household power generation is highly desirable. In this context, liquid organic hydrides, such as methylcyclohexane (MCH) or decaline, have got much attention as a hydrogen transporter. In this process, hydrogen can be stored as organic hydrides through catalytic hydrogenation of aromatic compounds such as toluene, and can be regained by catalytic dehydrogenation of organic hydrides with regeneration of aromatics as reusable hydrogen transporters. The advantages of this process are higher hydrogen-storage ability of aromatics, easy operation of liquid aromatics and organic hydrides under ordinary temperature and pressure, and that it can utilize existing infrastructure for petroleum transportation, which enables not only hydrogen supply for interior area but also establishment of a massive network of hydrogen transportation connecting overseas (Scheme 1-19).

Scheme 1-19. Hydrogen storage technique utilizing organic hydrides



Calling it into account that mass treatment of hydrogen is required in industrial process to achieve future hydrogen society, continuous storage and production of hydrogen is desired; in this context, continuous-flow reaction using heterogeneous catalysts is suitable for hydrogen storage and extraction.

As represented by discussion above, heterogeneous catalyst for continuous-flow reactions are of great importance in future society. In this context, I had worked on development of heterogeneous catalysts which have high activity under milder conditions, wide substrate generality and robustness especially under continuous-flow conditions.

References

- [1] P. T. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2002**, 35, 686-694.
- [2] A. J. Bard, *Integrated Chemical Systems: A Chemical Approach to Nanotechnology*, Wiley, **1994**.
- [3] a) Ł. Albrecht, H. Jiang, K. A. Jørgensen, *Angew. Chem., Int. Ed.* **2011**, 50, 8492-8509; b) R. J. K. Taylor, M. Reid, J. Foot, S. A. Raw, *Acc. Chem. Res.* **2005**, 38, 851-869.
- [4] J.-i. Yoshida, K. Saito, T. Nokami, A. Nagaki, *Synlett* **2011**, 2011, 1189-1194.
- [5] L. Alcaraz, G. Macdonald, J. P. Ragot, N. Lewis, R. J. K. Taylor, *J. Org. Chem.* **1998**, 63, 3526-3527.
- [6] T. Mukaiyama, H. Ishikawa, H. Koshino, Y. Hayashi *Chem. Eur. J.* **2013**, 19, 17789-17800.
- [7] T. Yasukawa, A. Suzuki, H. Miyamura, K. Nishino, S. Kobayashi, *J. Am. Chem. Soc.* **2015**, 137, 6616-6623.
- [8] a) J.-i. Yoshida, *Chem. Commun.* **2005**, 4509-4516; b) J.-i. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, 14, 7450-7459; c) J.-I. Yoshida, *The Chemical Record* **2010**, 10, 332-341; d) J.-i. Yoshida, H. Kim, A. Nagaki, *ChemSusChem* **2011**, 4, 331-340; e) J.-i. Yoshida, Y. Takahashi, A. Nagaki, *Chem. Commun.* **2013**, 49, 9896-9904.
- [9] H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun.* **2011**, 2, 264.
- [10] S. Murahashi, M. Yamamura, K. Yanagisawa, N. Mita, K. Kondo, *J. Org. Chem.* **1979**, 44, 2408-2417.
- [11] A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi, J.-i. Yoshida, *Angew. Chem., Int. Ed.* **2010**, 49, 7543-7547.
- [12] S. Kobayashi, *Chemistry – An Asian Journal* **2016**, 11, 425-436.
- [13] Z. Qian, I. R. Baxendale, S. V. Ley, *Chem. Eur. J.* **2010**, 16, 12342-12348.
- [14] T. Tsubogo, H. Oyamada, S. Kobayashi, *Nature* **2015**, 520, 329.
- [15] G. Schmid, *Chem. Rev.* **1992**, 92, 1709-1727.
- [16] H. Masatake, K. Tetsuhiko, S. Hiroshi, Y. Nobumasa, *Chem. Lett.* **1987**, 16, 405-408.
- [17] a) S. Kobayashi, H. Miyamura, *Aldrichimica Acta* **2013**, 46, 3-19; b) S. Kobayashi, R. Akiyama, *Chem. Commun.* **2003**, 449-460.
- [18] a) S. Kobayashi, H. Miyamura, *The Chemical Record* **2010**, 10, 271-290; b) K. Kaizuka, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* **2010**, 132, 15096-15098.
- [19] a) T. Yasukawa, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* **2012**, 134, 16963-16966; b) H. Miyamura, R. Matsubara, S. Kobayashi, *Chem. Commun.* **2008**, 2031-2033.
- [20] P. Liu, J. K. Norskov, *Phys. Chem. Chem. Phys.* **2001**, 3, 3814-3818.

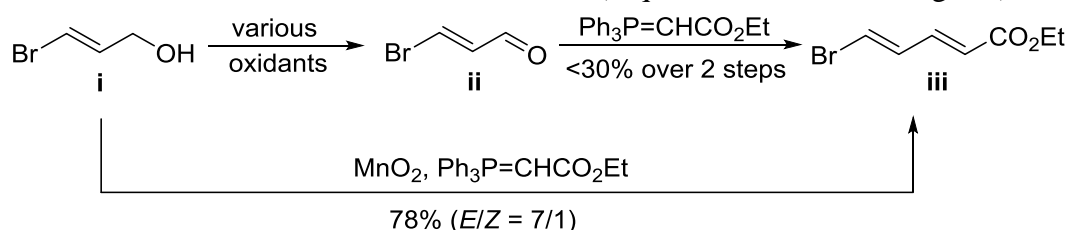
- [21] a) H. Miyamura, G. C. Y. Choo, T. Yasukawa, W.-J. Yoo, S. Kobayashi, *Chem. Commun.* **2013**, 49, 9917-9919; b) J.-F. Soulé, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* **2011**, 133, 18550-18553; c) H. Miyamura, T. Yasukawa, S. Kobayashi, *Green Chem.* **2010**, 12, 776-778; d) M. Hiroyuki, M. Masataka, I. Takeshi, K. Shū, *Bull. Chem. Soc. Jpn.* **2011**, 84, 588-599; e) N. Wang, T. Matsumoto, M. Ueno, H. Miyamura, S. Kobayashi, *Angew. Chem., Int. Ed.* **2009**, 48, 4744-4746; f) H. Miyamura, M. Shiramizu, R. Matsubara, S. Kobayashi, *Angew. Chem., Int. Ed.* **2008**, 47, 8093-8095; g) W.-J. Yoo, H. Yuan, H. Miyamura, S. Kobayashi, *Adv. Synth. Catal.* **2011**, 353, 3085-3089.
- [22] H. Miyamura, S. Kobayashi, *Acc. Chem. Res.* **2014**, 47, 1054-1066.
- [23] H. Miyamura, A. Suzuki, T. Yasukawa, S. Kobayashi, *Adv. Synth. Catal.* **2015**, 357, 3815-3819.
- [24] K. Kaizuka, K.-Y. Lee, H. Miyamura, S. Kobayashi, *Journal of Flow Chemistry* **2012**, 2, 1-4.
- [25] a) H. Oyamada, T. Naito, S. Miyamoto, R. Akiyama, H. Hagio, S. Kobayashi, *Org. Biomol. Chem.* **2008**, 6, 61-65; b) H. Oyamada, R. Akiyama, H. Hagio, T. Naito, S. Kobayashi, *Chem. Commun.* **2006**, 4297-4299.
- [26] C. A. Burkhard, *J. Am. Chem. Soc.* **1949**, 71, 963-964.
- [27] R. D. Miller, J. Michl, *Chem. Rev.* **1989**, 89, 1359-1410.
- [28] M. Ueno, Y. Morii, K. Uramoto, H. Oyamada, Y. Mori, S. Kobayashi, *Journal of Flow Chemistry* **2014**, 4, 160-163.
- [29] a) F. Alhumaidan, D. Cresswell, A. Garforth, *Energy Fuels* **2011**, 25, 4217-4234; b) D. Teichmann, W. Arlt, P. Wasserscheid, *Int. J. Hydrogen Energy* **2012**, 37, 18118-18132; c) Q. Lai, M. Paskevicius, D. A. Sheppard, C. E. Buckley, A. W. Thornton, M. R. Hill, Q. Gu, J. Mao, Z. Huang, H. K. Liu, Z. Guo, A. Banerjee, S. Chakraborty, R. Ahuja, K.-F. Aguey-Zinsou, *ChemSusChem* **2015**, 8, 2789-2825; d) Q.-L. Zhu, Q. Xu, *Energy & Environmental Science* **2015**, 8, 478-512.

2. Tandem oxidation processes (TOP) with metal NPs as heterogeneous catalysts for synthesis of chiral esters

Backgrounds

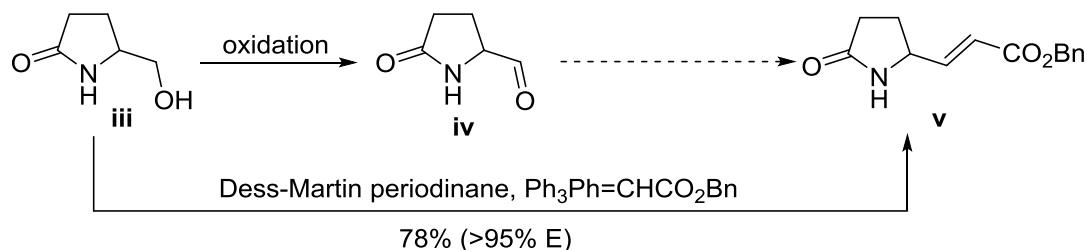
As described in general introduction, tandem reaction, a sequential multistep reaction has a lot of advantages, such as reduced number of purifications, and generation of toxic or unstable but highly reactive intermediates *in situ*, compared with stepwise processes involving the addition of various reagents, catalysts and temperature control. A tandem reaction involving oxidation, called as tandem oxidation process (TOP), matches with the criteria of Green Sustainable Chemistry.^[1] The first example of TOP was achieved during investigations to establish a synthetic method for the preparation of the manumycin family of antibiotics. 3-Bromopropenol **i** was oxidized to give aldehyde **ii** to convert conjugated ester **iii**, an intermediate of the synthesis. A range of oxidant was used, however, overall yield of **iii** was less than 30% because of lachrymatory and isomerization/origomerization of **ii** during isolation. Although Ireland tried to address this issue by a one-pot sequential Swern oxidation-Wittig trapping procedure, unstable nature of **ii** was still the problem.^[2] Finally, Xudong Wei performed this process by combining alcohol, MnO₂ as an oxidant, and a stabilized Wittig reagent in the same reaction vessel for immediate trap of *in situ* generated aldehyde **ii** and obtained the desired product **iii** in 78% yield (Scheme 2-1-1).^[3]

Scheme 2-1-1. The earliest achievement of TOP (sequential addition of reagents)



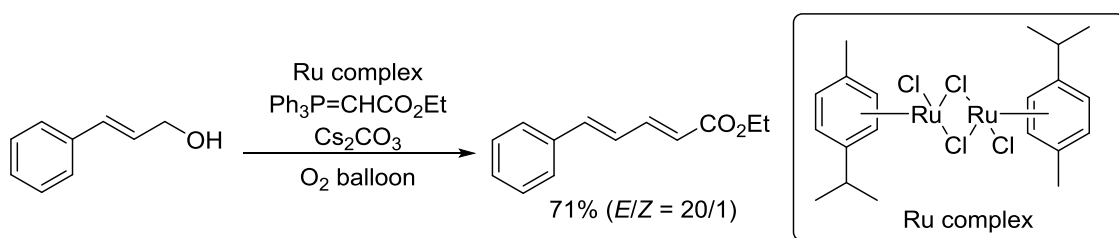
The first truly tandem oxidation–trapping sequence was reported by Huang in 1987. During the synthesis of carbon-14-labeled compound **v**, aldehyde **iv** could not obtain because of its lability; however, finally the desired product **v** was successfully obtained by Dess-Martin oxidation in the presence of a Wittig reagent (Scheme 2-1-2).

Scheme 2-1-2. First example of truly tandem oxidation-trapping sequence



Since this discovery, a large number of TOPs have been developed employing IBX^[4], PCC^[5], $\text{SO}_3 \cdot \text{Py}$ ^[6], TEMPO-BAIB^[7], which are homogeneous, and $\text{Ba}(\text{MnO}_4)_2$ ^[8], NBS (*N*-bromosuccinimide) or NIS (*N*-iodosuccinimide) in combination with MnO_2 , which are heterogeneous, as oxidants. However, stoichiometric or large excess amounts of oxidants were used in all these cases. Moreover, hazardous preparation of the Dess-Martin oxidant, toxicity of $\text{Ba}(\text{MnO}_4)_2$, and requirement of activation of a large excess amount of MnO_2 were serious problems. To address these issues, Kim and co-workers reported the *in situ* catalytic oxidation-Wittig reaction, which utilized aerobic oxidation catalyzed by a Ru complex although yields were highly substrate-dependent (Scheme 2-1-3).^[1] The use of molecular oxygen as the terminal oxidant has many advantages over the use of stoichiometric or excess amounts of typically used oxidants. Oxygen is abundant in air and the only byproduct formed is water after the oxidation.^[9]

Scheme 2-1-3. First example of one-pot oxidation-Wittig reaction utilizing aerobic oxidation



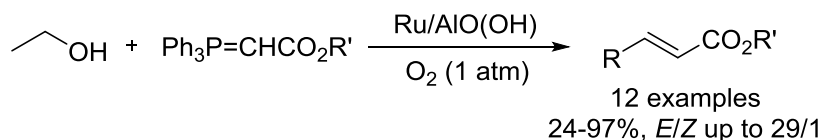
In 2009, Park and co-workers achieved Ru-complex catalyzed one-pot alcohol aerobic oxidation-Wittig reactions to give α,β -unsaturated esters.^[10] In this reaction, a primary alcohol is oxidized by molecular oxygen in a dehydrogenative fashion catalyzed by Ru NPs-embedded on aluminum oxyhydroxide (Scheme 2-1-4). Additionally, the similar tandem reaction utilizing aerobic oxidation catalyzed by manganese oxide octahedral molecular sieve (OMS) materials was reported by Suib and co-workers last year (Scheme 2-1-5).^[11] In all cases explained here, Wittig reaction was employed to form carbon-carbon double bond; however, Horner-Wadsworth-Emmons

reaction, called HWE reaction, is generally preferred to Wittig reaction because of its several advantages.

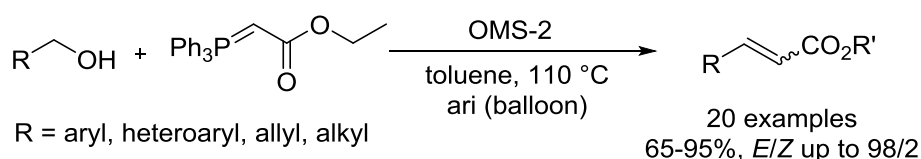
Horner-Wadsworth-Emmons reaction is one of the most useful methods to introduce carbon-carbon double bond to afford α,β -unsaturated carbonyl compounds.^[12] The procedure of this reaction is a modified procedure of Wittig reaction reported by Horner and co-workers in 1958.^[13] Wittig reaction is a reaction to obtain olefins from carbonyl compounds and phosphorus ylides and firstly reported by Wittig several years before Horner's report.^[14] The novel method reported by Horner, which used phosphine oxide stabilized carbanions as ylides, was further modified by Wadsworth and Emmons by employing phosphonates. Thereafter, so called 'Horner-Wadsworth-Emmons (HWE) reaction' has gained popularity and become a widespread tool for *de novo* carbon-carbon double bond formation.^[15] Compared with Wittig reaction, HWE reaction has a lot of advantages: 1) Preparation of alkylphosphonates is much easier and cheaper than phosphorus ylides, 2) Carbanions derived from alkylphosphonates have higher nucleophilicity, 3) HWE reaction proceeds under milder conditions, 4) strong bases such as $n\text{BuLi}$ are not required, which makes the reaction compatible to water, and 4) Products can be separated easily from the reaction mixture because dialkylsulfonates, co-product of HWE reaction, are easy to remove by washing with water due to its solubility in water while triphenylphosphine oxide, co-product of Wittig reaction, is not soluble in water.^[16]

As described above, HWE reaction is superior to Wittig reaction in terms of preparation of the reagent, reaction conditions, and easiness of removal of phosphonate co-products from the reaction mixture. To achieve more environmentally friendly process, TOP involving HWE reaction was reported by Taylor and co-workers in 2002. A range of alcohols were converted to α,β -unsaturated esters with triethyl phosphonacetate in the presence of lithium hydroxide/molecular sieves; however, this process had a drawback in the oxidant that a large excess amount of MnO_2 was required (Scheme 2-1-6). The most desired process, that is, one-pot oxidation-HWE reaction employing molecular oxygen as an oxidant, had not been achieved.

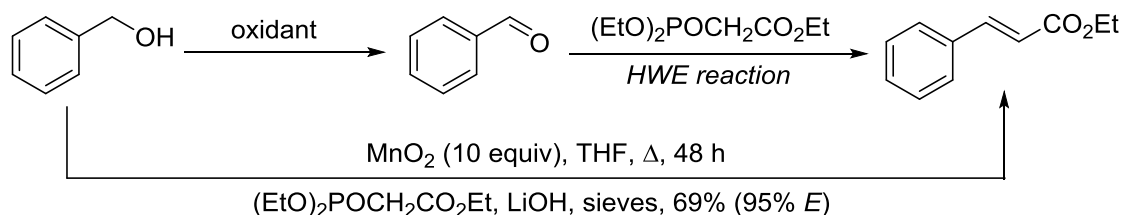
Scheme 2-1-4. Sequential aerobic oxidation-Wittig process



Scheme 2-1-5. Sequential aerobic oxidation-Wittig process

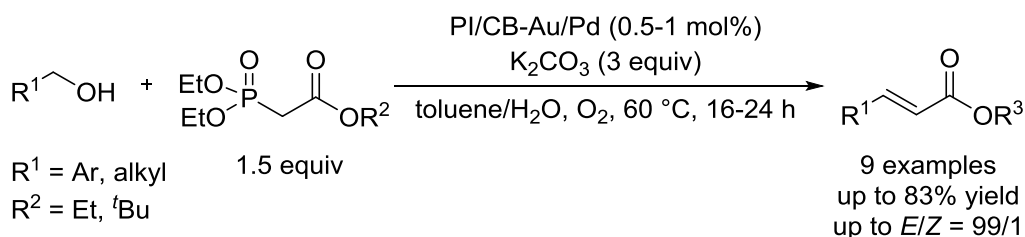


Scheme 2-1-6. TOP involving HWE reaction

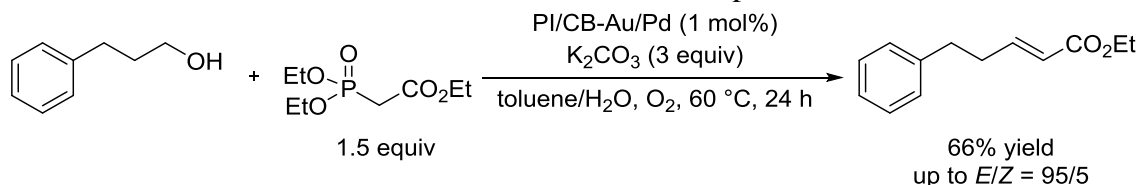


In this context, I have investigated tandem process of aerobic oxidation of alcohols and olefination through HWE reaction, which afforded α,β -unsaturated esters, which can be a precursor of bioactive chiral esters, in my master's course study. Eventually, the transformation proceeded smoothly under aerobic and aqueous conditions catalyzed by PI/CB-Au/Pd and gave the desired product in high yields with high *E/Z* selectivity (Scheme 2-1-7).^[17] However, it was challenging to obtain the product in more than 90% in this process; around 10% of aldehydes, which is an intermediate of an oxidation of alcohols, were further oxidized to corresponding carboxylic acids. In particular, this over oxidation is more significant in the reaction with aliphatic alcohols because of instability of aliphatic aldehydes, different from stabilized benzylic aldehydes (Scheme 2-1-8). In this context, acceleration of HWE process is one of the ideas to overcome this issue (Scheme 2-1-9).

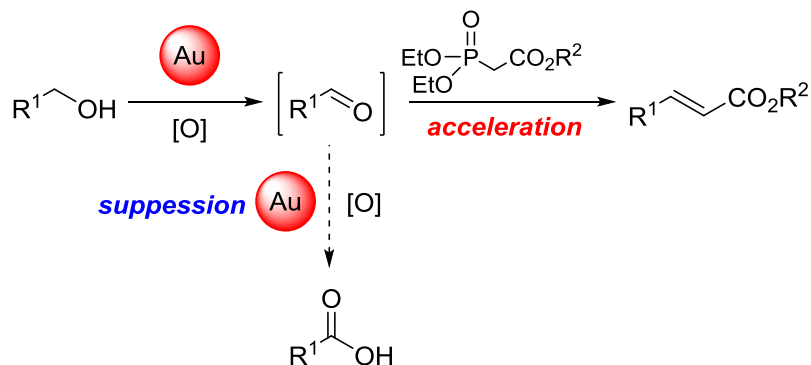
Scheme 2-1-7. Tandem oxidation/HWE process for α,β -unsaturated esters synthesis



Scheme 2-1-8. Tandem oxidation/HWE reaction with aliphatic alcohols

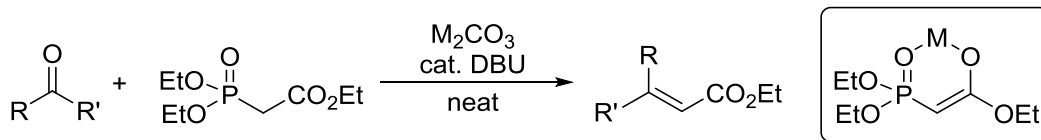


Scheme 2-1-9. Improvement of selectivity of desired reaction pathway



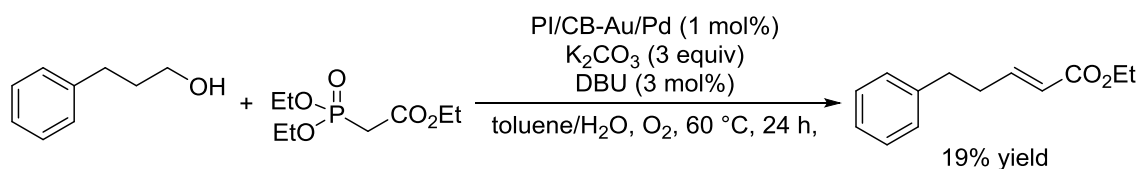
In 2011, Ando and co-workers reported that the catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) can accelerate HWE reaction in the presence of metal carbonate (Scheme 2-1-10); it is assumed that coordination of metal ion to both carbonyl groups in phosphonates facilitated deprotonation of phosphonates by DBU.^[18] Protonated DBU is then deprotonated by metal carbonate to regenerate the original form of DBU.

Scheme 2-1-10. HWE reaction catalyzed by DBU



On the bases of this report, it was expected that catalytic amount of DBU accelerates HWE reaction in our tandem oxidation/HWE process and affords the desired product selectivity, suppressing the over oxidation; however, the addition of DBU to this tandem process using 3-phenylpropanol as a substrate lowered the conversion of starting material, indicating that PI/CB-Au/Pd might be poisoned by strongly coordinative DBU (Scheme 2-1-11).

Scheme 2-1-11. Tandem oxidation/HWE reaction with DBU



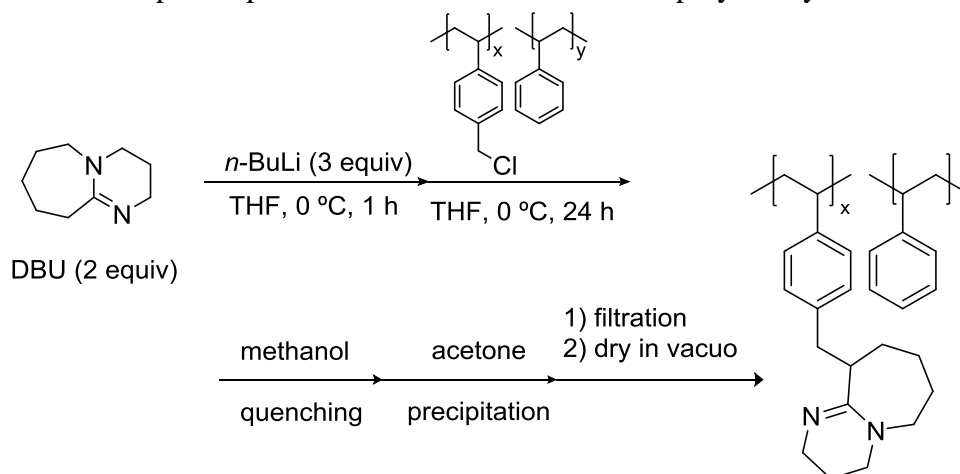
This result suggested that a newly designed catalyst is required to achieve high yield of the desired product. It is assumed that selective acceleration of HWE reaction suppressing an undesired interaction between both catalysts, which are the catalysts for oxidation of alcohols and HWE reaction, might be realized by keeping a spatial distance between these catalysts. To achieve this catalysis, an immobilization of each catalyst on individual support is one of the ideas. In this context, I started the preparation of DBU-containing polymer to employ it to the tandem process as a co-catalyst with PI/CB-Au/Pd.

Results and Discussion

Direct Olefination Catalyzed by Polymer-immobilized Metal nanoparticles and Polymer-immobilized Base

In 2007, Endo and co-workers reported the preparation of DBU-immobilized polymer by substitution of chloride in a styrene-based polymer^[19] (Scheme 2-2-1); however, the application of this polymer to organic synthesis has not been achieved. Based on this report, a preparation of DBU-immobilized polymer (DIP) has been started. Here, I targeted a cross-linked polymer to prepare heterogeneous catalyst which cannot dissolve in organic solvents, different from reported one.

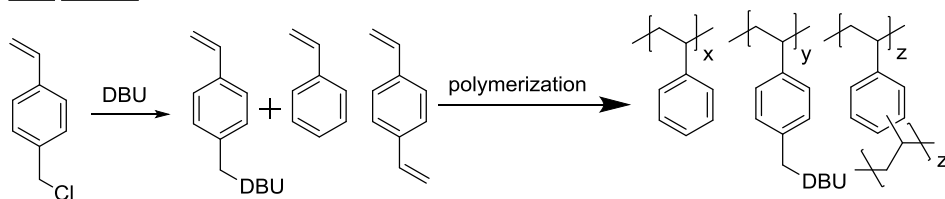
Scheme 2-2-1. Reported procedure for DBU-immobilized polymer synthesis



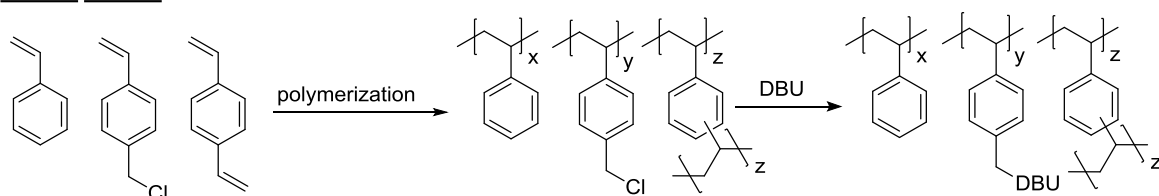
For the preparation of DIP, two strategies were planned; one is synthesis of DBU-substituted monomer followed by polymerization of this monomer, and another is polymerization of benzyl chloride-containing monomer followed by substitution of chloride by DBU (Scheme 2-2-2).

Scheme 2-2-2. Preparation of DIP

First method

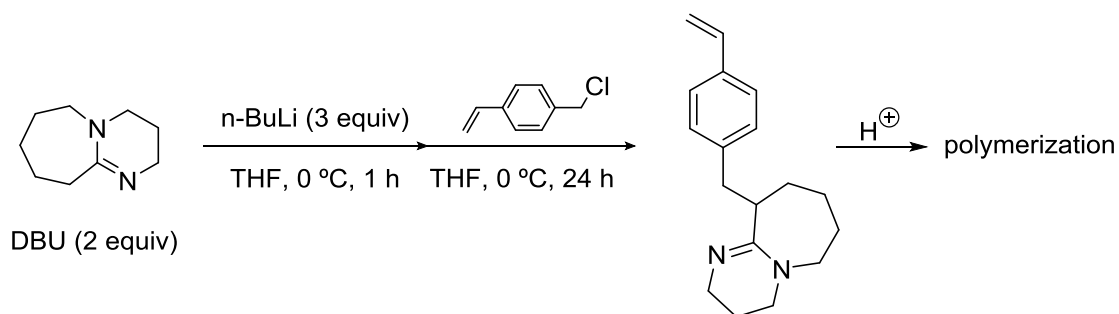


Second method

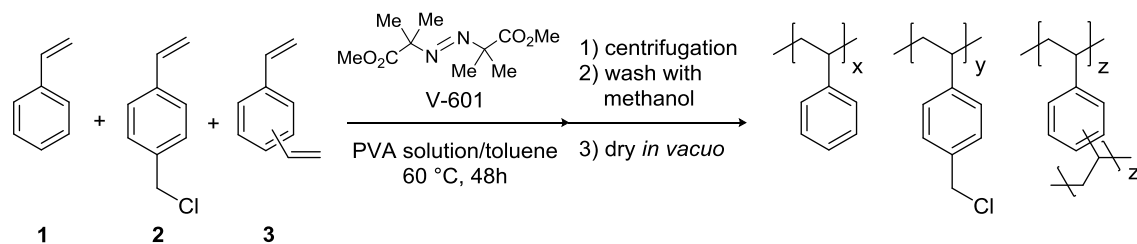


As the first strategy, a monomer containing DBU was prepared. After the reaction, the reaction mixture was acidified to obtain the product as a hydrochloric salt; however, it caused a rapid polymerization of the product (Scheme 2-2-3). To avoid this issue, the reaction mixture was neutralized (pH 7) after the reaction and concentrated. Unfortunately, it also resulted in a polymerization of the desired monomer.

Scheme 2-2-3. Synthesis of DBU-substituted monomer



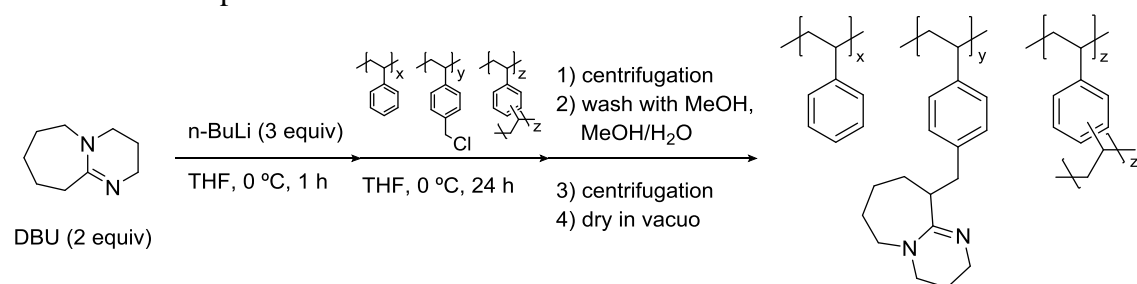
The second strategy, which is a substitution of pre-synthesized benzyl chloride-containing polymer by DBU, was then investigated. For a polymerization, suspension co-polymerization method, where a polymer is formed in monomer-solvent droplets in a continuous phase that is a non-solvent for both the monomer and the formed polymer, was applied because this process generally gives a cross-linked polymer with uniform particle size. In a solution of polyvinyl alcohol (PVA), polymerization of styrene, 4-chloromethylstyrene, and divinylbenzene as a cross-linking agent was conducted. Here, 3 different polymers P-1, P-2, and P-3 were prepared by varying the ratio of styrene and 4-chloromethylstyrene. According to an analysis of the prepared copolymer by ion chromatography, most of the 4-chloromethylbenzene used for the reaction was incorporated to the copolymer (Table 2-2-1).

Table 2-2-1. Preparation of copolymers

entry	polymer	1 (equiv)	2 (equiv)	3 (equiv)	yield (%)	Cl (desired)	Cl (wt%) ^a	Cl(act.)/ Cl(des.)
1	P-1	10.0	10.0	1.0	59	13.2	12.6	0.95
2	P-2	6.7	13.3	1.0	49	16.9	15.0	0.89
3	P-3	5.0	15.0	1.0	52	18.1	16.1	0.89

^a Determined by ion chromatography analysis.

With the chloride-containing copolymers, chloride in the polymer was substituted by DBU following the process for a synthesis of DBU-substituted monomer. The prepared copolymers, DIP-1, DIP-2, and DIP-3, were analyzed by an elemental analysis. Considering each DIP contained only 0.3% of Chloride, almost all of chloride contained in the polymers might be substituted by DBU, while an incorporation of DBU was estimated as 90% calculated on theoretical amount of nitrogen in the polymers. (Table 2-2-2).

Table 2-2-2. Preparation of DIPs

entry	DIP	C (%) ^a	H (%) ^a	N (desired)	N (%) ^a	N (act.)/ N (des.)	Cl (%) ^b	DBU (mmol/g) ^c
1	DIP-1	74.88	8.40	7.0	6.52	0.93	0.3	2.33
2	DIP-2	76.39	8.73	7.9	7.49	0.95	0.1	2.68
3	DIP-3	74.71	8.73	8.3	7.17	0.86	0.2	2.56

^a Determined by elementary analysis. ^b Determined by ion chromatography analysis.

^c Calculated based on the loading of nitrogen.

The activity of the prepared DIPs was evaluated through HWE reaction using *p*-tolaldehyde. Compared to the result obtained without DIPs, the yields of desired α,β -unsaturated ester were improved in the reactions with DIPs, demonstrating an acceleration of HWE reaction by DIPs (Table 2-2-3). DIP-2, which gave the best yield in the three, was used in further investigation.

Table 2-2-3. Activity check of DIPs through HWE reaction

entry	DIP	yield (%) ^a
1	—	68
2	DIP-1	76
3	DIP-2	81
4	DIP-3	78

^a Determined by ¹H NMR analysis.

The catalytic activity of DIP in tandem oxidation/HWE reaction was initially evaluated in the reaction with aromatic alcohol. Prior to it, PI/CB-Au/Pd was prepared following the reported procedure (Scheme 2-2-4). 4-Methylbenzyl alcohol and HWE reagent were reacted in the presence of PI/CB-Au/Pd, potassium carbonate, and DIP. An improvement in yield of the desired product was confirmed with 3 mol% of DIP, demonstrating the positive effect of DIP on HWE reaction in this tandem process (Table 2-2-4, entry 2). The amount of DIP was then further increased. It is noteworthy that the formation of carboxylic acid, which is a by-product, was decreased as the loading of DIP was increased, indicating the efficient acceleration of HWE reaction by DIP; however, higher loading of DIP also caused the transesterification of the product and the starting material (entries 3-5). These results showed that 5 mol% of DIP was suitable under this reaction conditions, which afforded the desired product in 87% isolated yield with 98:2 of *E/Z* selectivity (entry 3).

Scheme 2-2-4. Preparation of PI/CB-Au/Pd

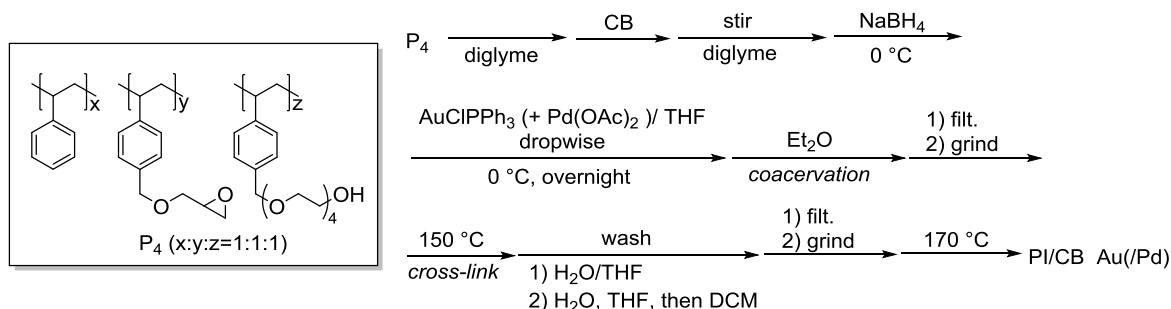
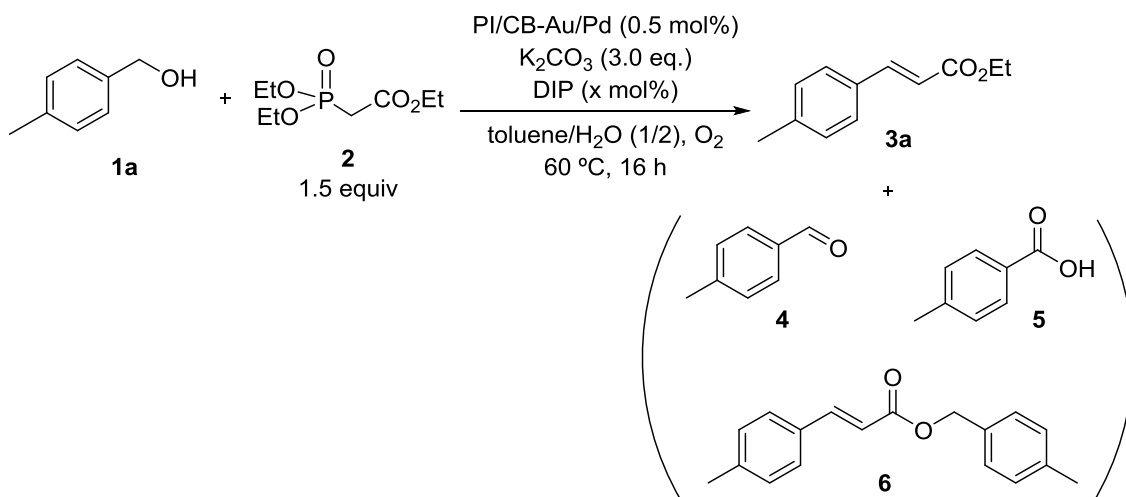


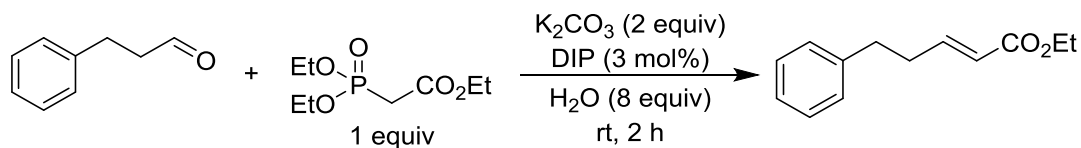
Table 2-2-4. Initial screening of DIP in tandem oxidation/HWE reaction



entry	x (mol %)	conv. (%) ^a	3a (%) ^b	4 (%) ^b	5 (%) ^b	6 (%) ^{b,c}
1	0	>99	78	<1	10	2 (4)
2	3	>99	84	<1	10	1 (2)
3	5	>99	87 (87) ^d	<1	7	1 (2)
4	10	>99	82	<1	4	2 (4)
5	20	>99	80	<1	2	5 (10)

^a Determined by GC analysis. ^b Determined by ¹H NMR analysis. ^c Corresponding value to conversion of alcohols in the parenthesis. ^d Isolated yield. *E:Z* = 98:2.

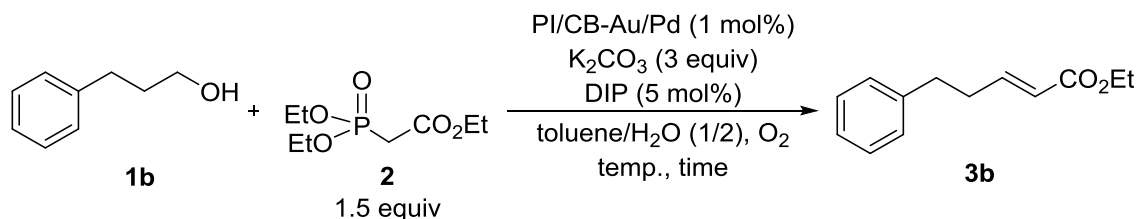
Next, this catalysis was applied to the reaction with aliphatic alcohol, which gave a moderate yield in the previous work. Initially, the catalytic ability of DIP was confirmed through HWE reaction using 3-phenylpropanal; however, the evaluation of the activity of DIP was difficult because the reaction proceeded rapidly regardless of the addition of DIP and afforded the product, suggesting the higher reactivity of 3-phenylpropanal than 4-methylbenzyl alcohol (Table 2-2-5).

Table 2-2-5. Activity check of DIP through HWE reaction with aliphatic alcohol

entry	DIP	yield (%) ^a
1	—	>99
2	+	>99

^a Determined by GC analysis.

In the investigation of tandem oxidation/HWE reaction using 3-phenylpropanol, the addition of DIP showed a slight improvement of the yield of the desired product (Table 2-2-6, entries 1 and 2). Here, a loss of the mass balance might be ascribed to the formation of corresponding carboxylic acid by *via* over oxidation of aldehyde considering the fact that no other by-product was observed. To suppress the over oxidation, the reaction was examined at lower temperature. The reaction at 40 °C afforded the product in 55% yield (entry 3), while that with DIP gave higher yield (entry 4). It is noteworthy that the formation of carboxylic acid is suppressed, suggesting the catalytic effect of DIP on HWE reaction is larger in the case of the reaction at lower temperature. As the starting material still remained in this reaction, the reaction time was prolonged; however, the yield of the product improved only 5%, while larger amount of carboxylic acid formed with a full consumption of the starting material (entry 5). This result indicates that the over oxidation proceeded prior to the desired HWE reaction in the latter part of the reaction because of almost full consumption of HWE reagent. Based on this result, a long-time reaction was performed with larger amount of HWE reagent; however, this resulted in a lower yield (entry 6). The reason of this negative result was assumed that larger amount of HWE reagent poisoned the catalyst and caused a slower oxidation of alcohol, which resulted in a transesterification due to a higher concentration of starting material or decomposition of HWE reagent by hydrolysis before HWE reaction occurred.

Table 2-2-6. Tandem oxidation/HWE reaction of aliphatic alcohols

entry	temp. (°C)	DIP	time (h)	conv. (%) ^a	yield (%) ^a	<i>E:Z</i> ^a	substrate loss (%)
1	60	—	24	>99	66	96:4	34
2	60	+	24	>99	68	97:3	32
3	40	—	24	75	55	97:3	20
4	40	+	24	75 (94) ^b	64	98:2	11
5	40	+	48	94	70	97:3	24
6 ^c	40	+	48	91	53	97:3	38

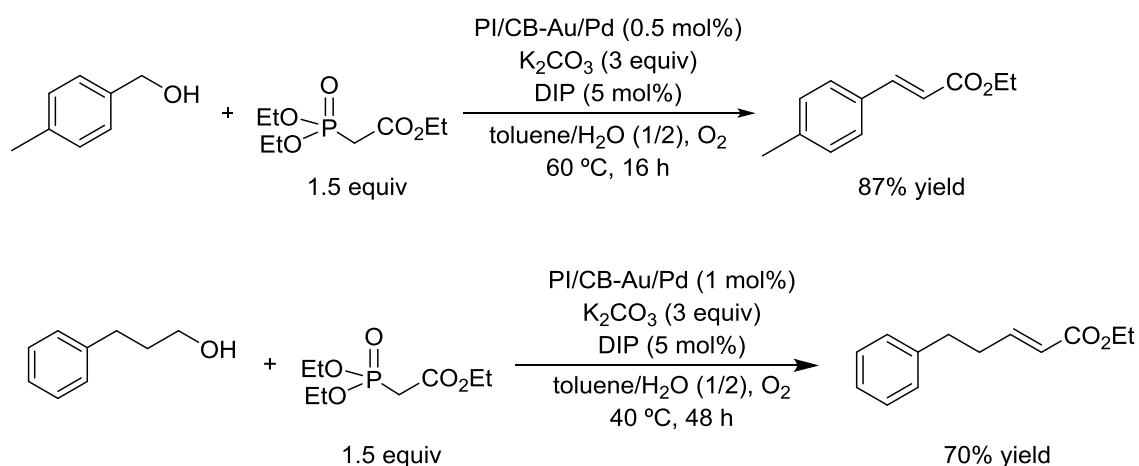
^a Determined by GC analysis. ^b Conversion of triethyl phosphonoacetate. ^c 2.0 equiv of HWE reagent was used.

As described, it is difficult to achieve high yield in this tandem oxidation/HWE process using aliphatic alcohols due to a higher reactivity of aliphatic aldehydes to form corresponding carboxylic acids through over oxidation. Furthermore, it is assumed that the catalytic ability of DIP might be lost by an acid-base reaction with formed carboxylic acids. To overcome this issue, another strategy to accelerate the tandem process suppressing the over oxidation is desired. In the next section, development of an effective catalysis which meets this requirement is targeted.

Direct Olefination with Integrated Catalyst of Polymer-immobilized Metal Nanoparticles and Base

As mentioned in the backgrounds section, acceleration of HWE reaction and suppression of competitive over oxidation to form corresponding carboxylic acids is a key for achievement of high yield in tandem oxidation/HWE reaction. Based on this concept, DBU-immobilized polymer has been developed as a heterogeneous catalyst for HWE reaction in the former section. What is important here is by keeping a special distance between two catalysts, which are for an oxidation and HWE reaction, to prevent an undesired interaction between them, which results in a deactivation of the oxidation catalyst. Although the co-catalytic system of PI/CB-Au/Pd and DIP showed positive effect in the tandem process with benzylic alcohols, it was still challenging to achieve high yield with aliphatic alcohols, which are more easily oxidized to carboxylic acids (Scheme 2-2-5).

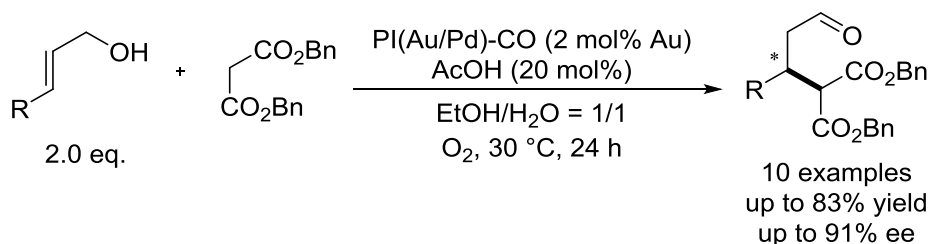
Scheme 2-2-5. Tandem oxidation/HWE reaction catalyzed by metal nanoparticles and DIP



In our laboratory, a tandem aerobic oxidation/asymmetric Michael addition reaction catalyzed by an integrated catalyst of metal nanoparticles and Hayashi-Jørgensen catalyst has been realized.^[20] These catalysts effectively accelerate an aerobic oxidation of alcohols and Michael addition of diethyl malonate to α,β -unsaturated esters, respectively; however, simultaneous use of these two catalysts in the reaction resulted in a deactivation of oxidation catalyst by amine-containing Hayashi-Jørgensen catalyst. For this reason, an integrated catalyst was developed by immobilizing these catalysts independently on the individual supports. The catalysts were immobilized in two methods: one is a coating of PI/CB-Au/Pd by polymer-immobilized Hayashi-Jørgensen catalyst, and the other is a coating of Hayashi-Jørgensen catalyst by PI/CB-Au/Pd.

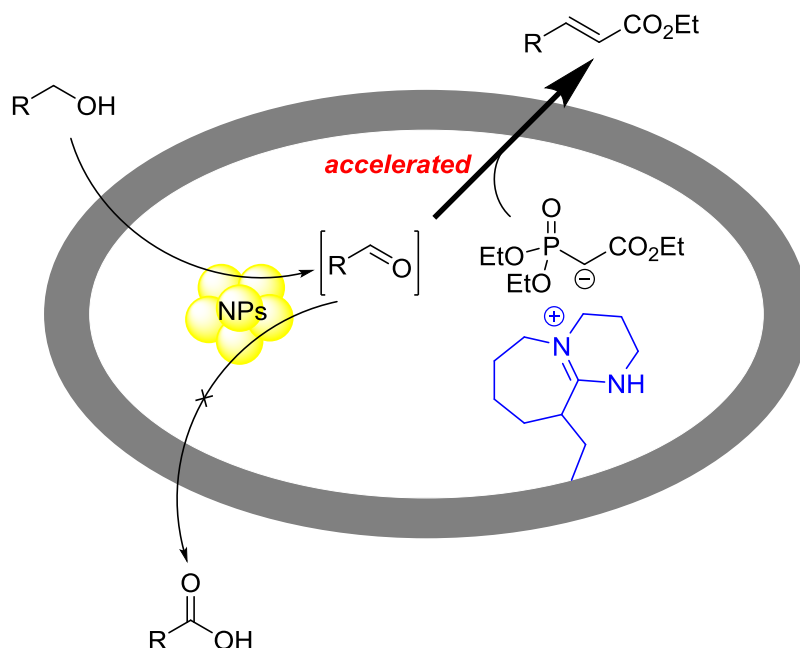
While the former still suffered from a deactivation, the latter afforded the desired 1,5-dicarbonyl compounds in high yields and enantioselectivity with wide substrate generality (Scheme 2-2-6).

Scheme 2-2-6. Tandem oxidation/asymmetric Michael addition reaction catalyzed by integrated catalyst

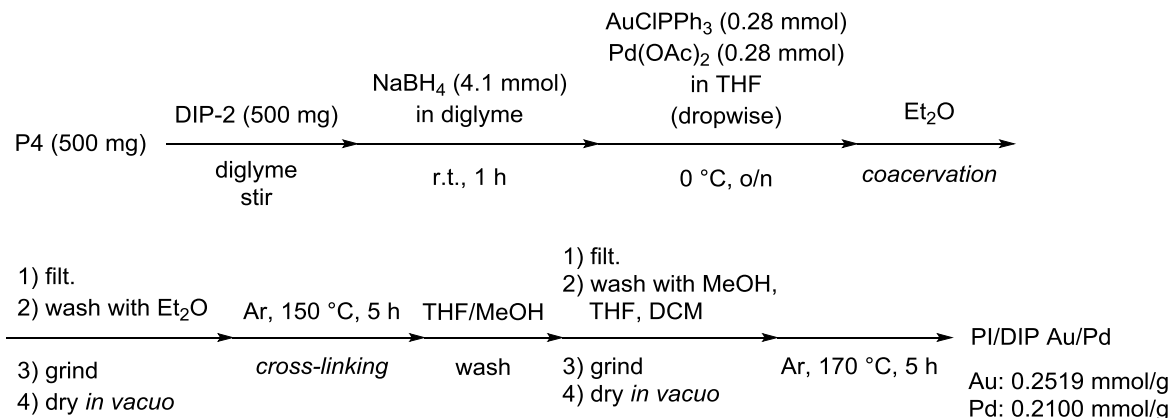


Inspired by this result, development of an integrated catalyst of PI/CB-Au/Pd and DIP (PI/DIP-Au/Pd), which is a bifunctional catalyst for an oxidation of alcohols and HWE reaction, was focused on. In this catalyst, it is assumed that *in situ* generated aldehydes by an oxidation of alcohols were rapidly trapped by proximal HWE reagent, which is deprotonated by DBU moiety in the catalyst, suppressing the over oxidation to form carboxylic acids through a kind of “inner-catalyst tandem process” (Scheme 2-2-7). On the basis of this hypothesis, an integrated catalyst of PI-Au/Pd and DIP (PI/DIP-Au/Pd) was prepared by coating of DIP by PI-Au/Pd, that is, DIP was used as a second support in a preparation of PI/CB-Au/Pd. To a suspension of P₄ polymer and DIP in diglyme containing sodium borohydride as a reductant, a solution of metal salts were added dropwise. After stirring the solution at 0 °C overnight, diethylether was added to precipitate the polymer with metal nanoparticles. The resulting suspension was filtered off and black solid was obtained. After drying, this solid was heated at 150 °C for a cross-linking, followed by wash with some solvents and further heating at 170 °C. The obtained catalyst was analyzed by ICP analysis (Scheme 2-2-8).

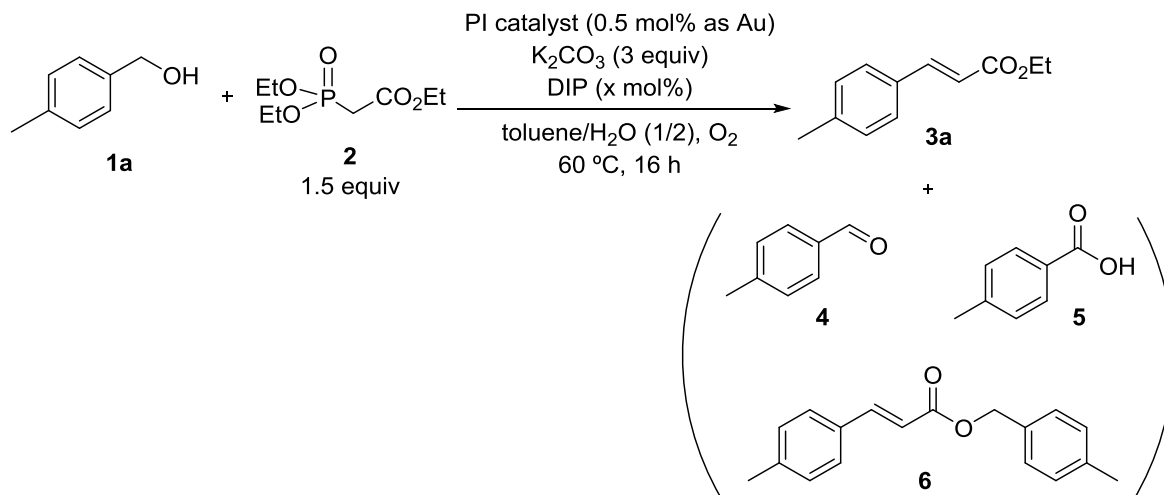
Scheme 2-2-7. Tandem oxidation/HWE reaction with an integrated catalyst



Scheme 2-2-8. Preparation of PI/DIP-Au/Pd



The prepared catalyst was examined in tandem oxidation/HWE reaction of 4-methylbenzyl alcohol. Compared to the result obtained in the reaction with an external addition of DIP, newly prepared PI/DIP-Au/Pd showed higher catalytic activity, demonstrating a suitable design of the catalyst (Table 2-2-7).

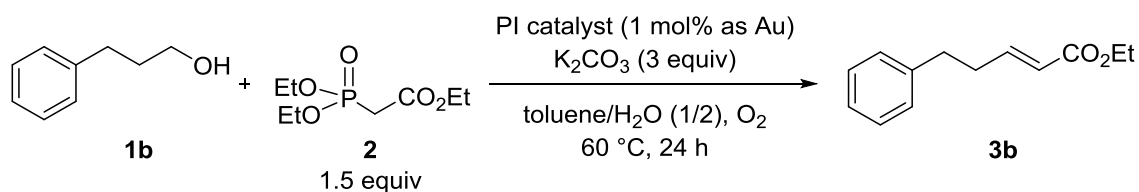
Table 2-2-7. First screening of PI/DIP-Au/Pd through tandem oxidation/HWE reaction

entry	PI catalyst	conv. (%) ^a	3a (%) ^b	4 (%) ^b	5 (%) ^b	6 (%) ^{b,d}
1	PI/CB Au/Pd	>99	78	>1	10	2 (4)
2 ^c	PI/CB Au/Pd	>99	87	>1	7	1 (2)
3	PI/DIP Au/Pd	>99	91	>1	6	1 (2)

^a Determined by GC analysis. ^b Determined by NMR analysis. ^c DIP (5 mol%) was added.

^d Corresponding value to conversion of alcohols in the parenthesis.

Finally, 3-phenylpropanol, which is more difficult substrate, was applied to the reaction in the presence of PI/DIP-Au/Pd (Table 2-2-8). Unfortunately, no improvement was confirmed; however, further optimization of the reaction conditions and composition of the catalyst such as the ratio of metal NPs and DBU moiety is expected to have a positive effect on this reaction.

Table 2-2-8. Tandem oxidation/HWE reaction

entry	PI catalyst	conv. (%) ^a	yield (%) ^a	<i>E:Z</i> ^a
1	PI/CB-Au/Pd	>99	66	96:4
2 ^b	PI/CB-Au/Pd	>99	68	97:3
3	PI/DIP-Au/Pd	>99	59	96:4

^a Determined by GC analysis. ^b DIP (5 mol%) was added.

Conclusion

In this chapter, development of a new catalysis was targeted for overcoming a problem, which is a competitive over oxidation of intermediate aldehydes to corresponding carboxylic acids, in tandem process of an oxidation of alcohols and HWE reaction. To suppress this side pathway, base catalyst to accelerate HWE reaction was introduced. Firstly, the polymer-immobilized DBU was externally added to the reaction system as a heterogeneous base catalyst and it successfully enhanced the rate of HWE reaction and gave higher yield in the reaction with aromatic alcohols. To achieve higher efficiency of the catalyst system, an integrated catalyst of metal nanoparticles and DBU-immobilized polymer was developed. In the reaction with this newly prepared catalyst, highly efficient acceleration of HWE reaction was expected for proximity of deprotonated HWE reagent and generated aldehydes through “inner-catalyst tandem manner”. While the catalyst gave a positive result in the reaction with aromatic alcohols, an improvement of the yield with aliphatic alcohols was still challenging. However, this strategy demonstrated a potential to overcome this problem, which is a lower selectivity of HWE reaction to rapid over oxidation, by further optimization of the reaction conditions including some parameters in the preparation of the catalyst.

References

- [1] R. J. K. Taylor, M. Reid, J. Foot, S. A. Raw, *Acc. Chem. Res.* **2005**, *38*, 851-869.
- [2] R. E. Ireland, D. W. Norbeck, *J. Org. Chem.* **1985**, *50*, 2198-2200.
- [3] a) L. Alcaraz, G. Macdonald, J. P. Ragot, N. Lewis, R. J. K. Taylor, *J. Org. Chem.* **1998**, *63*, 3526-3527; b) C. C. Huang, *Journal of Labelled Compounds and Radiopharmaceuticals* **1987**, *24*, 675-681; c) X. Wei, R. J. K. Taylor, *Tetrahedron Lett.* **1998**, *39*, 3815-3818.
- [4] A. Maiti, J. S. Yadav, *Synth. Commun.* **2001**, *31*, 1499-1506.
- [5] A. R. Bressette, L. C. Glover Iv, *Synlett* **2004**, *2004*, 738-740.
- [6] F. R. Pinacho Crisóstomo, R. Carrillo, T. Martín, F. García-Tellado, V. S. Martín, *J. Org. Chem.* **2005**, *70*, 10099-10101.
- [7] J.-M. Vatéle, *Tetrahedron Lett.* **2006**, *47*, 715-718.
- [8] S. Shuto, S. Niizuma, A. Matsuda, *J. Org. Chem.* **1998**, *63*, 4489-4493.
- [9] F. Cardona, C. Parmeggiani, Royal Society of Chemistry, **2014**.
- [10] E. Y. Lee, Y. Kim, J. S. Lee, J. Park, *Eur. J. Org. Chem.* **2009**, *2009*, 2943-2946.
- [11] a) J. R. Kona, C. K. King'ondou, A. R. Howell, S. L. Suib, *ChemCatChem* **2014**, *6*, 749-752; b) L. Blackburn, C. Pei, R. J. K. Taylor, *Synlett* **2002**, *2002*, 0215-0218.
- [12] J. A. Bisceglia, L. R. Orelli, *Curr. Org. Chem.* **2012**, *16*, 2206-2230.
- [13] L. Horner, H. Hoffmann, H. G. Wippel, *Chem. Ber.* **1958**, *91*, 61-63.
- [14] B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863-927.
- [15] P. J. Murphy, J. Brennan, *Chem. Soc. Rev.* **1988**, *17*, 1-30.
- [16] T. Takeda, *Wiley* **2006**.
- [17] H. Miyamura, A. Suzuki, T. Yasukawa, S. Kobayashi, *Adv. Synth. Catal.* **2015**, *357*, 3815-3819.
- [18] K. Ando, K. Yamada, *Green Chem.* **2011**, *13*, 1143-1146.
- [19] B. Ochiai, K. Yokota, A. Fujii, D. Nagai, T. Endo, *Macromolecules* **2008**, *41*, 1229-1236.
- [20] H. Miyamura, G. C. Y. Choo, T. Yasukawa, W.-J. Yoo, S. Kobayashi, *Chem. Commun.* **2013**, *49*, 9917-9919.

第3章

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。

第4章

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。

第5章

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。

7. Experimental section

General

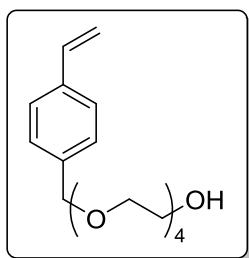
- JEOL JMN-LA400, 500 or 600 spectrometers were used for NMR measurement. Chloroform ($\delta = 7.24$) was used as an internal standard for ^1H NMR and CDCl_3 ($\delta = 77.0$) for ^{13}C NMR. Structures of known compounds were confirmed by comparison with commercially available compounds or data shown in literatures.
- IR spectra were measured on a JASCO FT/IR-610 spectrometer.
- Specific rotations were recorded with JASCO P-1010 or P-2100.
- Preparative thin-layer chromatography was carried out using Wakogel B-5F.
- ICP analysis was performed on Shimadzu ICPS-7510 equipment.
- GC analysis was performed on Shimadzu GC-2010 apparatus (Condition A : Column = GL Science, TCWAX, 0.25 mm ID, 0.25 μm , 60.0 m; Gas pressure: 214.2 kPa; Total flow: 90.6 mL/min; Column flow: 1.86 mL/min; Velocity: 30.8 cm/sec; Purge flow: 3.0 mL/min; Split ratio: 46.0; Injector: 250 $^\circ\text{C}$, FID: 250 $^\circ\text{C}$; Column program: starting from 50.0 $^\circ\text{C}$, 10 min hold, 10 $^\circ\text{C}/\text{min}$ to 220 $^\circ\text{C}$, 15 min hold) (Condition B : column = J & W SCIENTIFIC DB-1 0.25 mm ID, 0.25 μm , 60.0 m; Gas pressure: 157.5 kPa, Total flow: 41.3 mL/min, Column flow: 0.93 mL/min, Velocity: 21.1 cm/sec; Purge flow: 3.0 mL/min; Split ratio: 40.1; Injector: 300 $^\circ\text{C}$, FID: 300 $^\circ\text{C}$; Column program: starting from 100 $^\circ\text{C}$, 10 $^\circ\text{C}/\text{min}$ to 300 $^\circ\text{C}$, 10 min hold).
- HPLC analysis was performed on Shimadzu LC-20AB, SPD-M20A and DGU-20A₃.
- The absolute configuration of reported compounds was determined by comparison to literature and that of other products was assumed by analogy.
- 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 Cu grids and allowed to dry in air (without staining).
- AuPPh_3Cl was purchased from Strem Chemical Inc.
- $\text{Pd}(\text{OAc})_2$ was purchased from Sigma-Aldrich Co., Ltd.
- $[\text{Rh}(\text{OAc})_2]_2$ was purchased from Strem Chemical Inc.
- $\text{Na}_2\text{PtCl}_6 \cdot 6\text{H}_2\text{O}$ was purchased from Sigma-Aldrich Co., Ltd.
- Ru complexes were purchased from Strem Chemical Inc.
- Palladium 5% on Carbon (Pd/C) was purchased from N.E. CHEMCAT Co., Ltd.
- NaBH_4 was purchased from Wako Pure Chemical Industries. It was recrystallized from freshly distilled diglyme by heating according to the literature and stored in a glove box.^[1] During recrystallization, it is important to carry out all operations under Ar atmosphere. The activity and reproducibility are highly influenced by the purity and the condition of NaBH_4 during catalyst preparation.
- Ketjen black EC300J was purchased from Lion Corporation.

- SEM images of Ketjen black EC300J was described in W.-J. Yoo, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* **2011**, *133*, 3095-3103.^[2]
- Toluene was purchased in dried grade from Wako Pure Chemical Company and used without further purification.
- Deionized water from a MILLIPORE MilliQ machine (Gradient A 10) was used as solvent without further treatment.
- Other solvents were purchased in dried grade from Wako Pure Chemical Company and used without further purification.
- Alcohols were purchased from Tokyo Kasei Kogyo Co., Ltd.
- Arenes and primary amines were purchased from Tokyo Kasei Kogyo Co., Ltd.
- Organic hydrides were purchased from Tokyo Kasei Kogyo Co., Ltd.
- Asymmetric 1,4-addition reactions and other reactions in small scale (<1 mmol scale) were conducted with CarouselTM.
- 0.45 μm PTFE membrane filter (WhatmanTM cat. No. 6784-2504) was used for filtration of solid catalysts.

Chapter 2

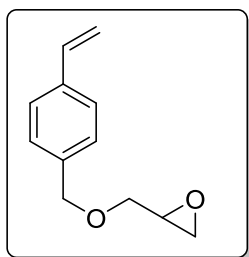
1-1. Preparation of PI/CB catalysts^[3]

Preparation of 2-(2-(2-(2-(4-vinylbenzyloxy)ethoxy)ethoxy)ethoxy)ethanol



To sodium hydride (55% in mineral oil, 5.7 g) suspended in THF (150 mL), tetraethyleneglycol (24.0 g) was added at 0 °C. After the reaction mixture was stirred for 20 min at room temperature, 1-(chloromethyl)-4-vinylbenzene (13.8 g) was added and the mixture was further stirred for 2 h. The mixture was cooled to 0 °C and diluted with diethyl ether. Saturated aqueous ammonium chloride was added to quench the reaction and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by column chromatography to afford 2-(2-(2-(2-(4-vinylbenzyloxy)ethoxy)ethoxy)ethoxy)ethanol ether (16.4 g, 43%); ¹H NMR (600 MHz, CDCl₃) δ 7.31-7.39 (m, 2H), 7.22-7.27 (m, 3H), 6.71 (dd, 1H, *J* = 11.0, 17.9 Hz), 5.53 (d, 1H, *J* = 18 Hz), 5.25 (d, 1H, *J* = 6.4 Hz), 4.55 (s, 2H), 3.59-3.73 (m, 16H), 2.55-2.59 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 138.0, 137.1, 136.0, 128.0, 126.3, 113.8, 73.0, 72.6, 70.74, 70.69, 70.5, 69.5, 61.8.

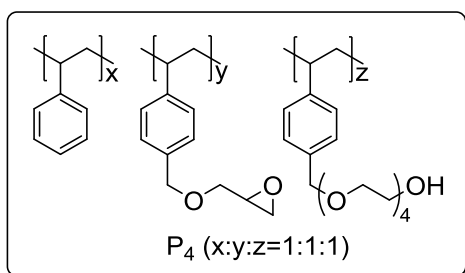
Preparation of 4-vinylbenzyl glycidyl ether



To sodium hydride (55% in mineral oil, 16.0 g) suspended in DMF (290 mL), glycidol (6.6 mL) was added at 0 °C. After the reaction mixture was stirred for 1 h at 0 °C, 1-(chloromethyl)-4-vinylbenzene (7 mL) was added and the mixture was further stirred for 5 h at room temperature. The mixture was cooled to 0 °C and diluted with diethyl ether. Saturated aqueous ammonium chloride was added to quench the reaction and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by column chromatography to afford 4-vinylbenzyl glycidyl ether (32 g, 82%).

¹H NMR (600 MHz, CDCl₃) δ 7.39 (d, 2H, *J* = 8.0 Hz), 7.30 (d, 2H, *J* = 8.0 Hz), 4.56 (dd, 2H, *J* = 10.8, 17.6 Hz), 3.74 (dd, 1H, *J* = 2.8, 11.2 Hz), 3.42 (dd, 1H, *J* = 5.6, 11.2 Hz), 3.17 (m, 1H), 2.78 (dd, 1H, *J* = 4.0, 4.8 Hz), 2.60 (dd, 1H, *J* = 2.8, 4.8 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 137.4, 137.0, 136.4, 127.9, 126.2, 113.8, 72.9, 70.7, 50.7, 40.2.

Preparation of copolymer



Styrene (2.1 g), 4-vinylbenzyl glycidyl ether (3.9 g), 2-(2-(2-(2-(4-vinylbenzyloxy)ethoxy)ethoxy)ethoxy)ethanol (6.3 g) and 2, 2'-azobis(4-methoxy)-2,4-dimethylvaleronitrile (V-70, 181.5 mg) were combined in chloroform (11.0 mL). The mixture was stirred for 48 h at room temperature. The resulting polymer solution was slowly poured into ether. Solvent was removed by decantation and remaining precipitated polymers were washed with ether several times. Polymers were dissolved in THF, repeated to precipitate for 2 times and dried *in vacuo* to afford the desired copolymer (6.86 g, 56 % yield). The molar ratio of the components was determined by ^1H NMR analysis ($x:y:z \doteq 1:1:1$). Obtained polymer should be stored in THF solution in refrigerator.

Preparation of PI/CB-Au/Pd (Scheme 2-2-4)

Copolymer (531 mg), ketjen black EC300J (531 mg) and NaBH_4 (169.4 mg, 4.2 mmol) were combined in diglyme (30 mL) at room temperature. To this solution was slowly added the solution of Chloro(triphenylphosphine)gold(I) (147.6 mg, 0.28 mmol) and Palladium(II) acetate (66.8 mg, 0.28 mmol) in THF (10 mL). The mixture was stirred overnight under air at 0°C and diethyl ether (200 mL) was slowly added to the mixture at room temperature. After the catalysts, which were black powders, were filtered and ground, they were washed with diethyl ether several times and dried *in vacuo*. The catalysts were heated at 150°C for 5 h without solvent and were stirred in 1:1 ratio of THF/water co-solvent overnight and were filtered, washed with water, THF and dichloromethane and dried *in vacuo* to afford black powder. This powder was heated at 170°C for 5 h without solvent to afford PI/CB-Au/Pd. PI/CB-Au/Pd (8 mg) was heated in the mixture of sulfuric acid and nitric acid at 200°C , and the mixture was cooled to room temperature. After the addition of aqua regia, the amount of metals in the resulting solution was measured by ICP analysis to determine the loading of metals (Au: 0.2619 mmol/g, Pd: 0.2507 mmol/g).

1-2. Preparation of DIP

Preparation of polymer P-1, P-2 and P-3 (P-x) (Table 2-2-1)

Total 32 mmol of Styrene/4-chloromethyl styrene (1/x), divinylbenzene (208.3 mg) and dimethyl 2, 2'-azobis(2-methylpropionate) (V-601, 85 mg) in toluene (9 mL) were slowly added into polyvinylalcohol solution (32 mL). The mixture was stirred for 48 h

at 60 °C. The resulting polymers were obtained by centrifugation. Polymers were washed with methanol, methanol/water and methanol again, which were removed by centrifugation. Polymers were dried *in vacuo* to afford the desired copolymer (about 50 % yield). The amount of including chloro-moiety was determined by ion chromatography analysis.

Preparation of DIP

To the mixture of DBU (3.04 g, 20 mmol) and THF (30 mL), *n*-BuLi (2.69 M in hexane, 11.15 mL) was slowly added at 0 °C. After the reaction mixture was stirred for 1 h, the polymer (Cl: 10 mmol) was added and stirred at 0 °C for 24 h. Then methanol was added for quenching. Resulting polymer was filtrated by suction, washed with diethyl ether, water, THF and dichloromethane and then dried *in vacuo*. Chemical composition of DIPs was determined by elemental analysis.

1-3. Preparation of PI/DIP-Au/Pd

P₄ (500 mg), DIP (500 mg) and NaBH₄ (158.8 mg, 4.1 mmol) were combined in diglyme (30 mL) at room temperature. To this solution was slowly added a solution of chloro(triphenylphosphine)gold(I) (138.6 mg, 0.28 mmol) and palladium(II) acetate (62.8 mg, 0.28 mmol) in THF (8 mL). The mixture was stirred overnight under air at 0 °C and diethyl ether (400 mL) was slowly added to the mixture at room temperature. After the catalysts, which were black powders, were filtered and ground, they were washed with diethyl ether several times and dried *in vacuo*. The catalysts were heated at 150 °C for 5 h without solvent and were stirred in 1:1 ratio of THF/methanol co-solvent overnight and were filtered, washed with methanol, THF and dichloromethane and dried *in vacuo* to afford black powder. This powder was heated at 170 °C for 5 h without solvent to afford PI/DIP-Au/Pd. PI/DIP-Au/Pd (10.03 mg) was heated in a mixture of sulfuric acid and nitric acid at 200 °C, and the mixture was cooled to room temperature. After the addition of aqua regia, the amount of metals in the resulting solution was measured by ICP analysis to determine the loading of metals (Au: 0.2519 mmol/g, Pd: 0.2100 mmol/g).

1-4. A typical procedure of HWE reactions of aldehyde with DIP (Table 2-2-3)

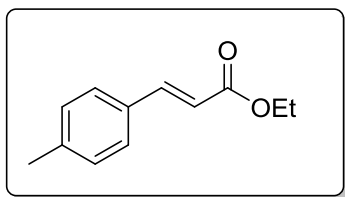
Benzaldehyde (1.0 mmol), ethyl 2-(diethoxyphosphoryl)acetate **2** (224.2 mg, 1.0 mmol), potassium carbonate (276.4 mg, 2.0 mmol), DIP (3 mol% as N) and water (144 µL) were combined in CarouselTM tube and the mixture was stirred for 2 h at 25 °C. Diethyl ether (5 mL) was added for quenching. An aliquot of the mixture was filtered through silica gel packed Pasteur pipette and washed with ethylacetate. The conversions of benzaldehyde and **2** and yield of the product **3a** were determined by GC analysis with reference to an internal standard (IS = ethylbenzene). The catalyst was removed by filtration using a funnel with a wrinkled filter paper and the filtrate was transferred to

separatory funnel. The aqueous layer was extracted with diethyl ether for several times. The combined organic layers were washed with brine and dried over sodium sulfate. After sodium sulfate was filtered and the solvent was removed *in vacuo*, the yields of the product **3a** was determined by ^1H NMR analysis of crude mixture with reference to an internal standard (IS = 1,1,2,2-tetrachloroethane).

1-5. A typical procedure of tandem aerobic oxidation/HWE reactions of alcohol **1a** (Table 2-2-4)

p-Tolylmethanol **1a** (48.9 mg, 0.4 mmol), ethyl 2-(diethoxyphosphoryl)acetate **2** (134.5 mg, 0.6 mmol), PI/CB Au/Pd (Au: 0.5 mol%), potassium carbonate (165.8 mg, 1.2 mmol), toluene (0.1 mL) and water (0.2 mL) were combined in CarouselTM tube and the mixture was stirred for 16 h under molecular oxygen atmosphere at 60 °C. Diethyl ether (5 mL) was added for quenching. An aliquot of the mixture was filtered through silica gel packed Pasteur pipette and washed with ethylacetate. The conversions of **1a** and **2** were determined by GC analysis with reference to an internal standard (IS = ethylbenzene). The catalyst was removed by filtration using a funnel with a wrinkled filter paper and the filtrate was transferred to separatory funnel. The aqueous layer was extracted with diethyl ether and acidified with 1M HCl_{aq}, then extracted with diethyl ether for several times. The combined organic layers were washed with brine and dried over sodium sulfate. After sodium sulfate was filtered and the solvent was removed *in vacuo*, the yields of the product **3a** and side-products **4**, **5** and **6** were determined by ^1H NMR analysis of crude mixture with reference to an internal standard (IS = 1,1,2,2-tetrachloroethane).

ethyl (*E*)-3-(*p*-tolyl)acrylate (**3a**)^[4]



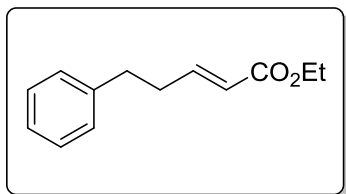
^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, 1H, J = 15.8 Hz), 7.40 (d, 2H, J = 8.2 Hz), 7.17 (d, 2H, J = 8.2 Hz), 6.39 (d, 1H, J = 15.8 Hz), 4.26 (q, 2H, J = 7.1 Hz), 2.35 (s, 3H), 1.33 (t, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 167.1, 144.5, 140.5, 131.6, 129.5, 128.0, 117.1, 60.3, 21.4, 14.3.

1-6. A typical procedure of tandem aerobic oxidation/HWE reactions of alcohol **1b** (Table 2-2-6)

3-Phenyl-1-propanol **1b** (54.5 mg, 0.4 mmol), ethyl 2-(diethoxyphosphoryl)acetate **2** (134.5 mg, 0.6 mmol), PI/CB Au/Pd (Au: 1 mol%), potassium carbonate (165.8 mg, 1.2 mmol), DIP, toluene (0.1 mL) and water (0.2 mL) were combined in CarouselTM tube and the mixture was stirred for 24 h under molecular oxygen atmosphere at 60 °C. Diethyl ether (5 mL) was added for quenching. An aliquot of the mixture was filtered through silica gel packed Pasteur pipette and washed with ethylacetate. The conversions

of **1b** and **2** and yield of the product **3b** were determined by GC analysis with reference to an internal standard (IS = ethylbenzene).

(E)-Ethyl 5-phenylpent-2-enoate (**3b**)^[5]



¹H NMR (600 Hz, CDCl₃) δ 7.27-7.30 (m, 2H), 7.17-7.21 (m, 3H), 7.00 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.83 (dt, *J* = 15.5, 2.0 Hz, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 2.76 (t, *J* = 8.0 Hz, 2H), 2.49-2.54 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 Hz, CDCl₃) δ 166.5, 148.0, 140.7, 128.4, 128.2, 126.1, 121.8, 60.1, 34.3, 33.9, 14.2.

1-7. A procedure to determine metal loadings by ICP analysis

Approximately 2-5 mg of catalyst was measured carefully (amount measured was recorded) and placed in test tube. 1 mL of sulfuric acid was added into this test tube. The test tube was heated at 200 °C and nitric acid was dropwise until all solid had dissolved and no more brown fumes were observed (3-5 days are required for this process because of less solubility of polysilane). The mixture was cooled to room temperature and aqua regia (1 mL) was added slowly. The resulting mixture was made up to 50 mL with water in a volumetric flask and the resulting solution was subjected to ICP analysis.

References

- [1] H. C. Brown, E. J. Mead, B. C. S. Rao, *J. Am. Chem. Soc.* **1955**, 77, 6209-6213.
- [2] W.-J. Yoo, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* **2011**, 133, 3095-3103.
- [3] H. Miyamura, A. Suzuki, T. Yasukawa, S. Kobayashi, *Advanced Synthesis & Catalysis* **2015**, 357, 3815-3819.
- [4] P. K. Hota, G. Vijaykumar, A. Pariyar, S. C. Sau, T. K. Sen, S. K. Mandal, *Advanced Synthesis & Catalysis* **2015**, 357, 3162-3170.
- [5] G. L. Hoang, Z.-D. Yang, S. M. Smith, R. Pal, J. L. Miska, D. E. Pérez, L. S. W. Pelter, X. C. Zeng, J. M. Takacs, *Organic Letters* **2015**, 17, 940-943.

Acknowledgement

I would like to express my sincere thanks Prof. Shū Kobayashi, The University of Tokyo, for his valuable suggestions, enthusiastic discussion and support ranging over many subjects throughout the course of this work.

I also gratefully thank Dr. Hiroyuki Miyamura for fruitful suggestions and helpful discussion, hands-on instructions and continuous encouragement throughout the course of this work.

Special mention goes to Mr. Noriaki Kuramitsu for electronic microscopy analysis.

I also thank Dr. Yasuhiro Yamashita, Dr. Harurou Ishitani, Dr. Woo-Jin Yoo, Dr. Tomohiro Yasukawa, Dr. Taku Kitanosono, and Dr. Koichiro Masuda for their beneficial advice and discussion.

I also thank the Japan Society for Promoting Science (JSPS) and Materials Education program for the future leaders in Research, Industry, and Technology (MERIT) for their financial support.

I am grateful to all the member of the synthetic organic chemistry laboratory for various help, discussion and motivation.

Finally, I would like to express my deepest gratitude to my mother for her warm emotional support. I could devote myself to research and enjoy it for five years with her help. Thanks a lot for everything you have done for me.

Aya SUZUKI
March, 2018