

Doctoral Dissertation (Censored)
博士論文（要約）

Continuous-flow C–N Bond Forming Reactions with Heterogeneous Catalysts
and Application for API Synthesis
(不均一系触媒を用いる連続フローC–N 結合形成反応と医薬品原体合成への展
開)

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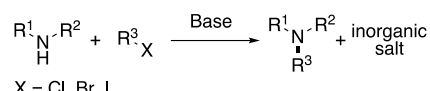
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Abstract

Introduction

Continuous-flow synthesis has several advantages in terms of environmental compatibility, safety, and efficiency compared with traditional batch synthesis. Judging from the demand for green sustainable chemistry (GSC) all over the world, catalytic reactions are preferred and continuous-flow reactions with heterogeneous catalysts are regarded as ideal methods.

C–N bond is the most abundant functional structure in organic chemistry, and many currently used Active Pharmaceutical Ingredients (APIs) have at least one C–N bond in their structures. For the construction of C–N bonds,



Scheme 1. Substitution Reactions with Alkyl Halides

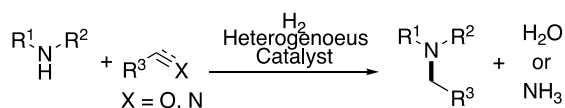
substitution reactions with alkyl halides are the most common ways; however, the formation of inorganic salts cannot be suppressed (Scheme 1). For flow reactions, such insoluble byproducts may cause clogging. Moreover, overalkylation may occur to afford tertiary amines, when primary amines are used as starting materials. To achieve continuous-flow fine chemical synthesis, the development of C–N bond forming reactions with less byproduct is highly desired.

In my Ph.D. thesis, I have focused on reductive aminations and aminolysis of epoxides and aziridines as suitable synthetic methods for flow reactions because the atom economy of those reactions is almost 100%. To realize those continuous-flow reactions, I have developed highly active heterogeneous catalysts.

Results and Discussion

1. Continuous-flow Reductive Amination and Application to API Synthesis

Reductive amination of carbonyl groups or nitriles using hydrogen gas is one of the most powerful tools for C–N bond construction because water or ammonia is a sole byproduct

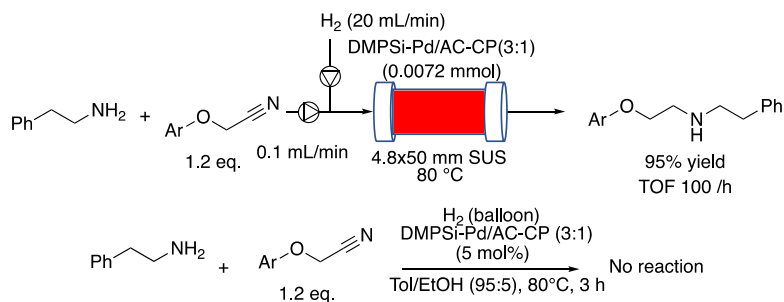


Scheme 2. Reductive Amination

(Scheme 2). Williams *et al.* and Kobayashi *et al.* respectively reported continuous-flow reductive amination utilizing a commercially available Pt/C catalyst with hydrogen. Those reactions afforded the N-alkylated products in excellent yields; however, more efficient heterogeneous catalysts are in high demand for challenging substrates.

1.1 Reductive Amination with Nitriles

Through screening of catalysts, it was found that dimethylpolysilane-modified Pd on activated carbon-calcium phosphate (3:1) (DMPSi-Pd/AC-CP(3:1)) showed high activity and durability for reductive amination of



Scheme 3. Comparison of continuous-flow and batch reaction

nitriles. In the presence of DMPSi and CP, the catalyst was stabilized, which avoided aggregation of

Pd nanoparticles. The investigation of substrate scope revealed that the reactions with phenoxy nitriles gave products with 100/h TOF. On the other hand, the lack of the α -oxygen atom and the phenyl group decreased the reactivity significantly. It was assumed that there was interaction between the electron-rich aromatic ring and Pd, which might improve the

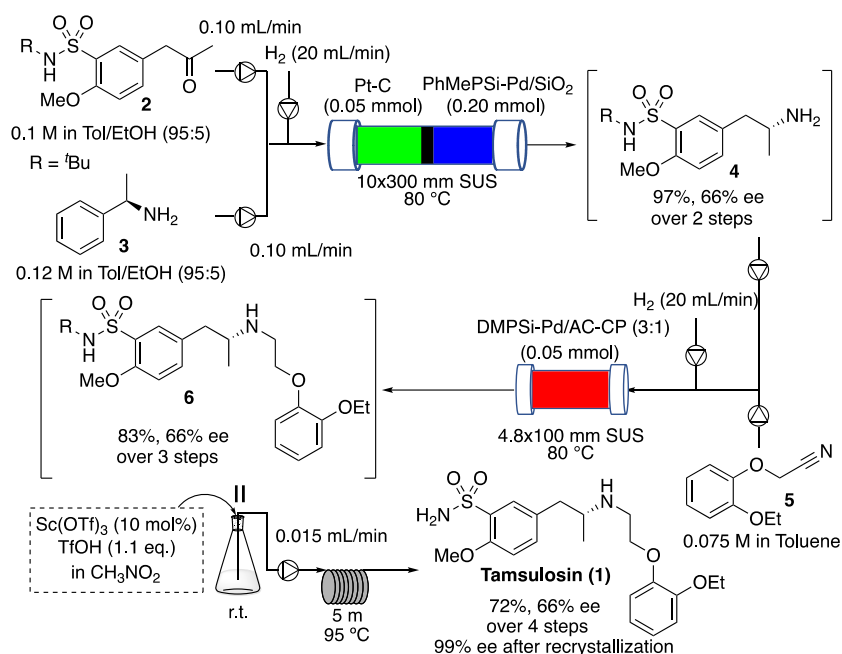


Figure 1. Overall scheme for Tamsulosin synthesis

substrate activity. Furthermore, in batch reactions with a hydrogen balloon, this reaction didn't proceed at all (Scheme 3). It was found that for this reaction, continuous-flow reaction was much more effective due to the enhanced solid-gas interaction.

1.2 Sequential-flow Synthesis of Tamsulosin

The reaction was applied to an API synthesis, Tamsulosin (Figure 1). Tamsulosin is one of the therapeutic drugs for dysuria associated with urinary stones and benign prostatic hyperplasia. In the first reaction, reductive amination of ketone (**2**) with (*R*)-phenylethylamine (**3**) was performed with Pt/C catalyst to afford a secondary amine in quantitative yield. Second, the removal of the phenethyl group was performed with PeMePSi-Pd/SiO₂ catalyst to afford chiral primary amine (**4**) in quantitative yield. Third, the key step, reductive amination with a nitrile (**5**) was conducted. Those consecutive three steps could be conducted without any isolation of intermediates and solvent exchange. Finally, the combination of Sc(OTf)₃ and TfOH in nitromethane deprotected the sulfonamide part to yield (*R*)-Tamsulosin. Enantiomeric excess was increased to 99% by 3 times recrystallization.

1.3 Domiphen Bromide and Carvedilol Synthesis

To

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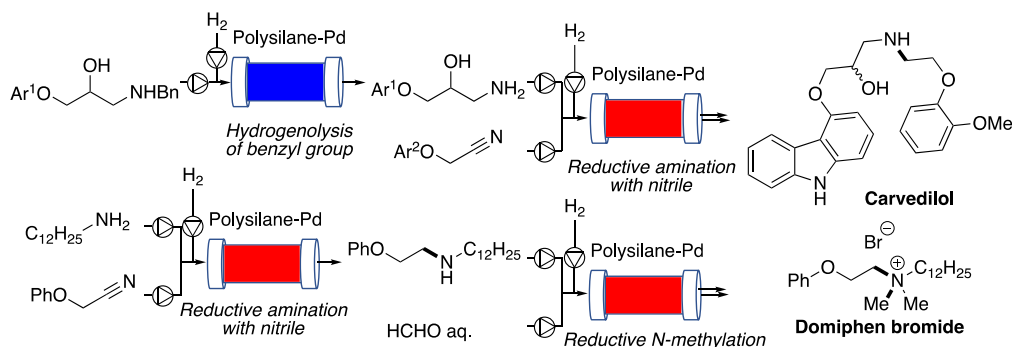


Figure 2. Domiphen bromide and Carvedilol

reductive amination with nitriles, I decided to conduct sequential-flow syntheses of the other APIs, such as Domiphen bromide and Carvedilol, which are also important APIs for stomatitis and high blood pressure (Figure 2). As well as Tamsulosin synthesis, those syntheses were performed in sequential-flow methods in high yields. In Domiphen Bromide synthesis, a reductive N-methylation reaction was developed.

2. Solid-Acid Catalyzed Continuous-flow Aminolysis of Epoxides and Application for Rivaroxaban Synthesis

β -Amino alcohols are versatile intermediates in fine chemicals and are often seen in the field of ligands, agricultural and pharmaceutical compounds. To synthesize β -amino alcohols, aminolysis of epoxides, which are epoxides opening reactions by amines, is one of the most accessible pathways. There has been only one example of aminolysis of epoxides with heterogeneous catalysts. In 2018, Luis *et al.* reported polystyrene immobilized scandium catalyzed aminolysis of cyclohexene oxide by aniline to afford the corresponding β -amino alcohol in quantitative yield. However, expensive rare-earth, scandium was used, and productivity was quite low (0.06 mmol/g·h). Therefore, there is plenty of room for improvement in developing highly active inexpensive heterogeneous catalysts.

Through numerous studies, I revealed that titania-zirconia-supported molybdenum oxide catalyst ($\text{MoO}_3/\text{TiO}_2\text{-ZrO}_2$) was the optimal catalyst. The productivity of the continuous-flow reaction reached 4.9 mmol/g·h, which was 80 times higher than the previous work. Moreover, sequential-flow synthesis of an API precursor,

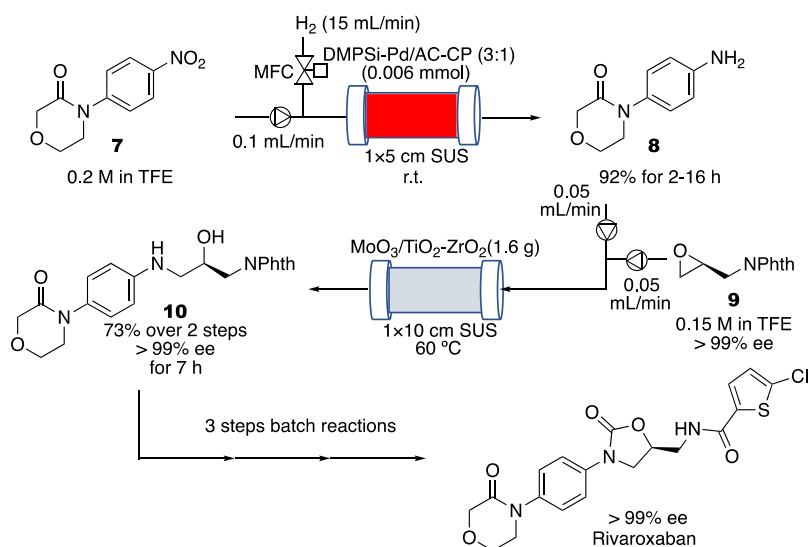
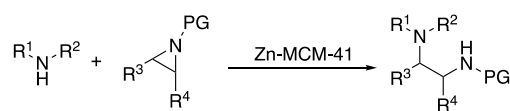


Figure 3. Overall Scheme for Rivaroxaban Synthesis

Rivaroxaban, which is an oral anticoagulant, was conducted (Figure 3). In the first step, hydrogenation of a nitro group was performed by using the polysilane-Pd catalyst to afford aniline (**8**) in an excellent yield. Then, the key step, aminolysis of epoxide (**9**) was conducted with $\text{MoO}_3/\text{TiO}_2\text{-ZrO}_2$ to give amino alcohol (**10**) in 73% yield over 2 steps without any isolation of any intermediate. Finally, 3 steps of batch reactions yielded Rivaroxaban without any loss of enantioselectivity.

3. Solid-Acid Catalyzed Continuous-flow Aminolysis of Aziridines

Aminolysis of aziridines yields 1,2 diamines, which are also a very important structure. As well as the aminolysis of epoxides, the 100% atom economy is ideal for sequential-flow reactions. However, due to



Scheme 4. Aminolysis of Aziridines

the low reactivity of aziridines compared with epoxides, substrates are mostly limited to activated aziridines such as N-tosyl-protected ones. This limitation not only decrease usefulness but also makes

deprotection steps difficult. I decided to try aminolysis of *N*-benzyl aziridines by the use of highly active catalysts. These aziridines are less reactive but easily deprotected. Finally, it was found that zinc immobilized mesoporous silica MCM-41 catalyst showed high activity (Scheme 3). Various substrates were tolerated in this reaction to afford the corresponding 1,2-diamine products in high yields.

Abbreviation

Ac	Acetyl	PDMSi	Dimethylpolysilane
AC	Activated Carbon	PhMePSi	Phenylmethylpolysilane
APIs	Activated Pharmaceutical Ingredients	Pr	Propyl
		PSi	Polysilane
Aq	Aqueous	Quant.	Quantitative
BC	Bone Charcoal	STEM	Scanning Transmission Electron Microscope
Bn	Benzyl		
Boc	<i>Tertiary</i> -butoxy carbonyl group	<i>t</i>	<i>Tertiary</i>
BPR	Back Pressure Regulator	TBAF	Tetrabutylammonium Fluoride
Bu	Butyl	TES	Triethylsilyl
CDI	1,1'-Carbonyldiimidazole	Tf	Trifluoromethanesulfonic
Conv	Conversion	TOF	Turnover Frequency
CP	Calcium Phosphate	Tol	Toluene
CSA	10-camphorsulfonic acid	TON	Turnover Number
DCC	N,N'- Dicyclohexylcarbodiimide	Ts	Tosyl
DCM	Dichloromethane	WHSV	Weight Hourly Space Velocity
DMF	N, N-dimethylformamide		
DMAP	4-dimethylamino pyridine		
DMPSi	Dimethylpolysilane		
DMS	Dimethyl sulfide		
DMSO	Dimethyl sulfoxide		
Diglyme	Diethylene glycol dimethyl ether		
<i>Dr</i>	<i>Diastereomeric ratio</i>		
EDS	Energy Dispersive X-ray Spectroscopy		
<i>Ee</i>	<i>Enantiomeric Excess</i>		
Eq	Equivalent		
Et	Ethyl		
GC	Gas Chromatography		
ICP	Inductive Coupled Plasma		
IPA	Isopropanol		
Me	Methyl		
Ms	Methanesulfonic		
Ns	Nesyl		
Organocat.	Organocatalyst		

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Chapter I : GENERAL INTRODUCTION

1. Batch Method vs Flow Method

Recently, the reshoring of factories has progressed. The reasons why global companies in Japan deploy their manufacturing base overseas are reducing manufacturing costs, gathering human resources, and saving delivery time, etc. However, in 2020, COVID-19 hit the world and things have changed completely. The pandemic stopped factories from operating, and a stable system has been pursued. Moreover, the yen is losing its value compared to the others since 2022; employees in Japan need less money than those in the foreign countries. Furthermore, the geopolitical risk cannot be ignored. Those problems facilitate the reshoring of factories while Japan's land area is small and limited. There is a need for manufacturing in smaller spaces.

Chemical synthesis is currently conducted in either a batch or a flow method (Figure 1.1).^{1,2}

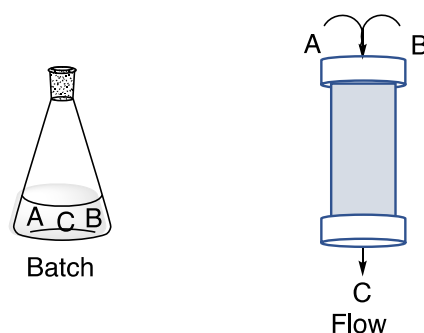


Figure 1.1. Batch Reaction vs Flow Reaction

In the batch methods, all reactants, including starting materials, reagents, catalysts, and solvents, are charged into a flask before initiating the reaction. Following the reaction, a work-up, evaporation, and purification process are typically employed to isolate the desired product. Batch synthesis remains the most widely used approach in both academic and industrial laboratories for organic synthesis. In contrast, flow methods involve the continuous introduction of starting materials through a column or a hollow loop, with the product continuously collected on the opposite side. Chemical companies have extensively employed flow methods for the large-scale synthesis of basic chemicals, exemplified by the Haber-Bosch process. However, the utilization of flow chemistry in the synthesis of fine chemicals has been somewhat limited thus far.³ Recent advancements in microfluidic reactors and flow chemistry techniques have demonstrated significant potential for fine chemical synthesis due to advantages such as significantly shorter reaction times, which can minimize undesired side reactions and improve product selectivity. One challenge still facing flow chemistry is scalability, as transitioning from small-scale microreactors to larger production volumes can be difficult.

Continuous-flow synthesis offers several advantages over batch reactions in terms of

environmental compatibility, efficiency, and safety.^{1,2} Moreover, a large-size batch reactor is not needed in industry to save space; it is much more suitable for manufacturing in Japan. The Food and Drug Administration (FDA) in the USA advocates for continuous manufacturing of pharmaceuticals, and, in 2011, suggested replacing chemical batch syntheses with flow syntheses within the next 25 years.⁵ Flow systems have widespread application in petrochemical and bulk chemical fields. However, a key difference lies in fine chemical flow synthesis, where minimizing byproducts is crucial to ensure human safety. While one-step continuous-flow reactions are becoming increasingly common, applying them to the multistep synthesis of complex molecules like active pharmaceutical ingredients (APIs) remains a significant challenge.⁶

In sequential-flow synthesis, two or more columns are connected in series (Figure 1.2). This enables consecutive reactions to be conducted in a streamlined manner, making it an efficient method for the synthesis of complex structures such as APIs. However, if byproducts are formed in the initial steps, they may carry over to subsequent steps, and potentially interfere with downstream reactions. Therefore, to mitigate this issue, the development of reactions that generate minimal byproducts is crucial.

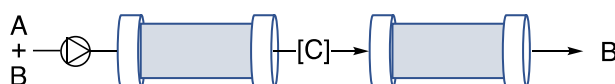


Figure 1.2. Sequential-flow reaction

2. Classification of Continuous-flow Reactions

Continuous-flow synthesis can be classified into 4 types of reactions (Figure 1.3).² Here, I explain each type and give an example of each.

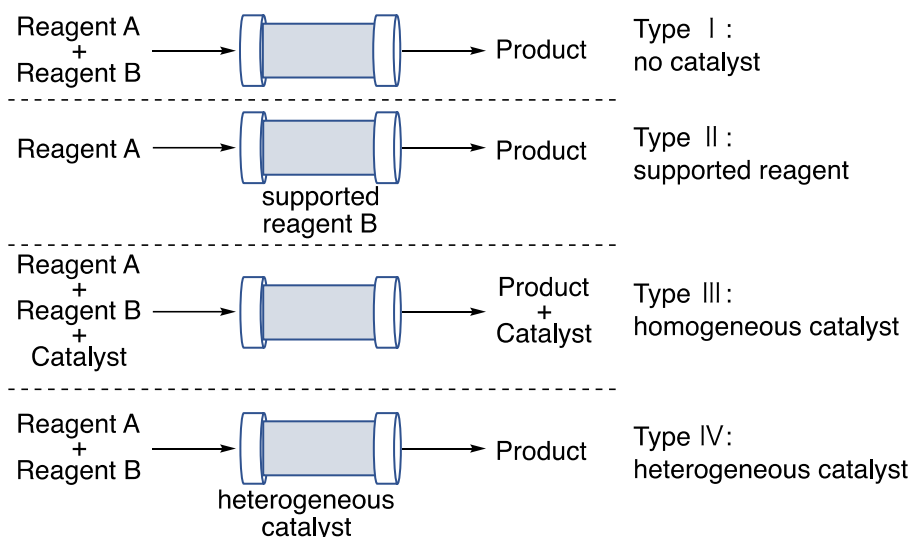
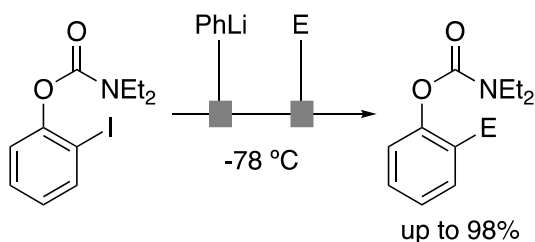


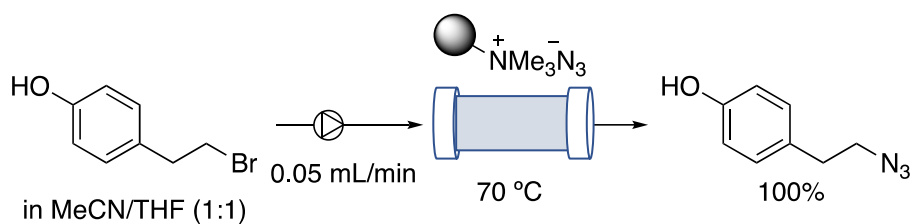
Figure 1.3. Classification of flow reactions

One of the simplest reactions involves the continuous introduction of all reagents into a flow reactor, with the product continuously collected from the opposite side (Type I). Yoshida reported the lithiation of aryl iodide compounds followed by nucleophilic addition (Scheme 1.1).⁴ This flow process offers high selectivity, a significant advantage over batch reactions, where Fries rearrangement is difficult to be suppressed due to longer reaction times.



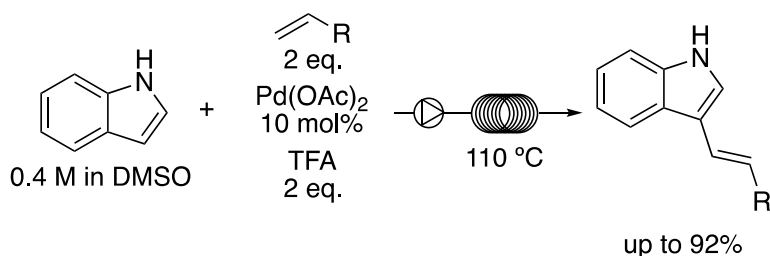
Scheme 1.1. An Example of Type I Flow Reaction

The use of supported reagents packed into the flow reactors (Type II) has gained attraction in recent years. In 2006, a polystyrene-immobilized azide exchange resin enabled the quantitative aziridination of alkyl bromide (Scheme 1.2).⁷ This commercially available reagent Syrris AFRICA facilitated a multistep synthesis of (\pm)-oxomaritidine in this study. However, replacing the column when the packed reagent is exhausted disrupts continuous flow, presenting a practical challenge.



Scheme 1.2. An Example of Type II Flow Reaction

Judging from the principles of green sustainable chemistry, catalytic reactions are preferable to stoichiometric ones due to their efficiency and reduced waste generation. Consequently, continuous-flow reactions employing either homogeneous catalysts (Type III) or heterogeneous catalysts (Type IV) have attracted significant research interest. In 2014, Noël reported a homogeneous Pd(OAc)₂-catalyzed aerobic C–H olefination of indoles through a cross-dehydrogenative coupling in a continuous flow system (Scheme 1.3).⁸ Notably, the transition from batch to flow processing enabled a significant reduction in reaction time from 4 hours to mere minutes, highlighting the superior mass transfer of continuous-flow reactions. However, for continuous production, Type IV reactions with heterogeneous catalysts offer distinct advantages in terms of catalyst separation and reusability. Unlike Type III reactions, where catalysts are dissolved in the reaction mixture and lead to laborious separation, Type IV reactions retain the immobilized catalysts within the reactor column, eliminating the need for post-reaction separation. This attribute makes Type IV reactions advantageous for streamlined, multi-step syntheses in a sustainable manner.



Scheme 1.3. An Example of Type III Flow Reaction

The challenge with Type IV lies in the lower activity of the heterogeneous catalysts compared to their homogeneous catalysts, as the reactions occur solely on the surface of the catalysts.⁹ Type IV flow reactions often encounter issues with the short lifetime of the catalysts (refer to the main content in this thesis). To enhance productivity, there is a critical need for heterogeneous catalysts that exhibit both high activity and durability.

Type IV reactions are exactly suitable for the sequential-flow synthesis of API. In 2015, Kobayashi reported an example of the sequential-flow synthesis of an API, Rolipram (Figure 1.4).¹⁰ This is the first report of the sequential-flow synthesis of an API consisting of only Type IV reactions. Since this report, several successful reports on sequential-flow

syntheses of APIs have been reported utilizing Type IV reactions, and most of them consist of C–C bond-forming reactions or function group conversion such as aldol condensation and hydrogenation to construct the structures.^{11,12,13,14}

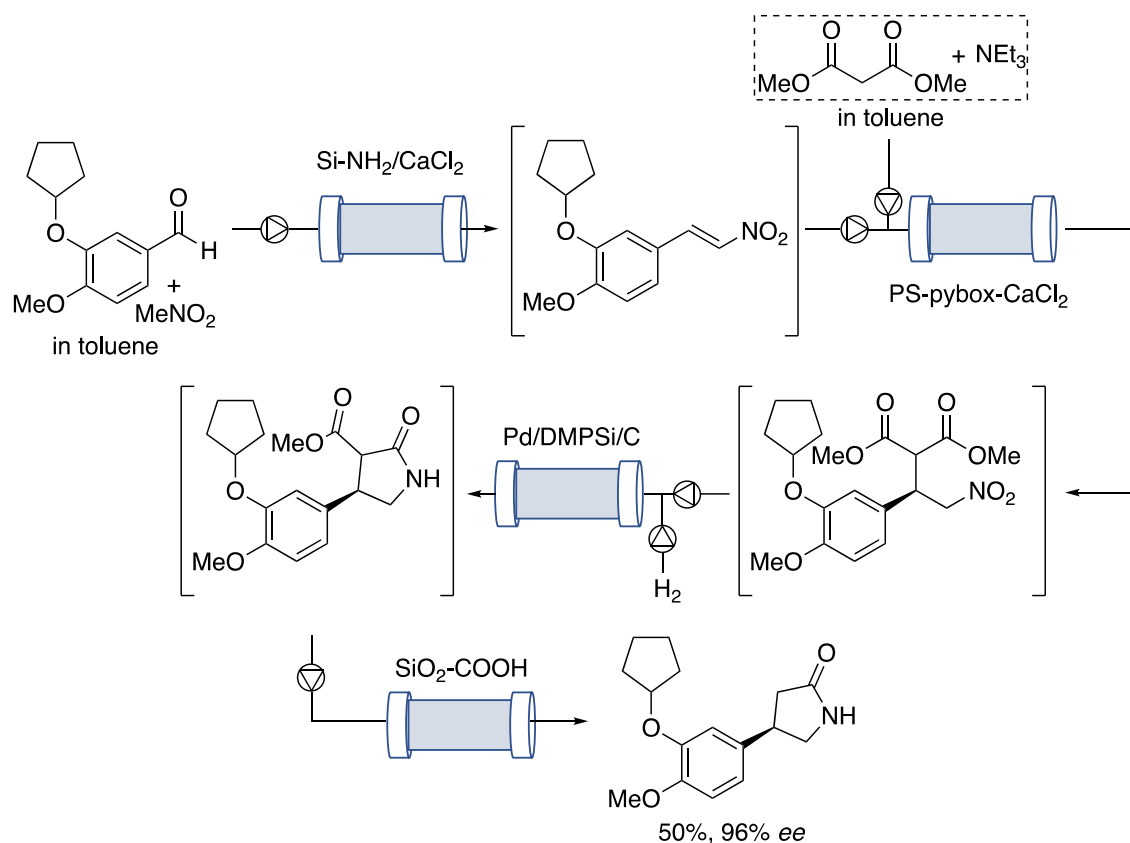
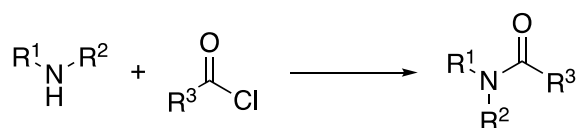


Figure 1.4. Sequential-flow Synthesis of (*R*)- and (*S*)-Rolipram

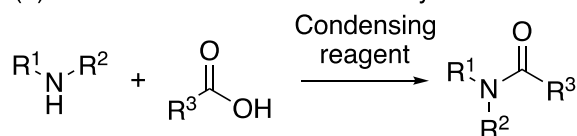
3. C–N Bond Forming Reactions

The C–N bond is one of the most abundant functional groups in organic chemistry. Over 80% of currently used APIs contain at least one C–N bond.¹⁵ This prevalence is due, in part, to the versatility of the C–N bond, which can participate in a wide range of reaction types. For example, amides can be readily synthesized from acid chlorides and amines through nucleophilic acyl substitution. Additionally, the direct conversion of carboxylic acids and amines to amides is possible using condensation reagents like DCC (Scheme 1.4).

(1) Amide Formation from Acid Chloride

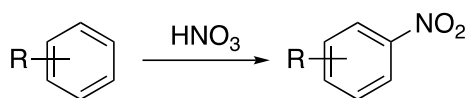


(2) Amide Formation from Carboxylic acid



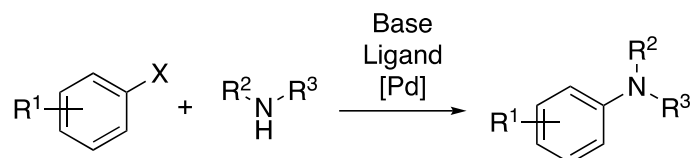
Scheme 1.4. Amides Formation

Another useful reaction for forming C–N bonds is the nitration of aromatic compounds. Well-developed methods exist for both stoichiometric reactions in acidic solvents and catalytic reactions under milder conditions (Scheme 1.5). The lower reactivity of the product compared to the starting material allows for easier control of the reaction, preventing overreactions. Additionally, the nitro group can be readily converted to the corresponding amine through hydrogenation.¹⁶



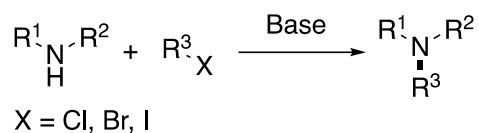
Scheme 1.5. Nitration of Aromatic Compounds

Pd-catalyzed Buchwald-Hartwig cross-coupling is also a well-studied reaction (Scheme 1.6). Although expensive Pd catalysts are required, it is one of the most powerful tools for C(sp²)–N bond formation.^{17,18}



Scheme 1.6. Buchwald Hartwig Cross Coupling

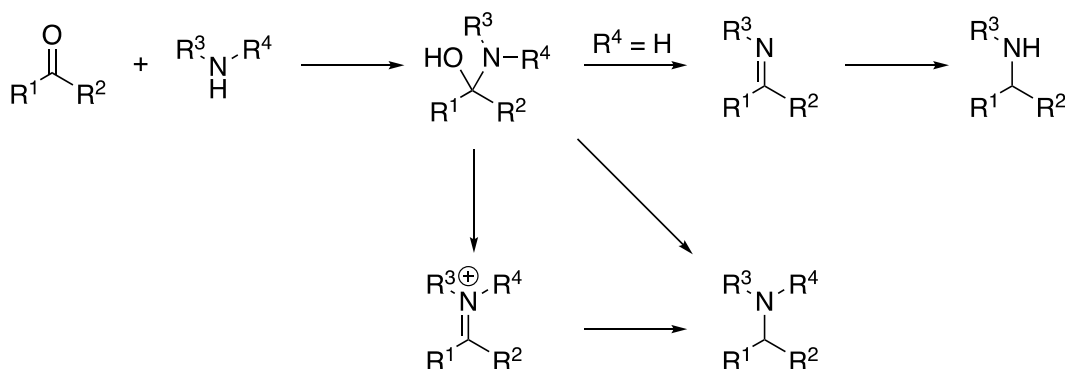
To construct C–N bonds, substitution reactions with alkyl halides are one of the most common pathways (Scheme 1.7). However, this approach has two drawbacks: (1) the formation of inorganic salts as byproducts, which can cause clogging, and (2) overalkylation when using primary amines as starting materials.¹⁹ Therefore, the development of C–N bond-forming reactions with minimal byproduct formation and utilizing heterogeneous catalysts is highly desirable.



Scheme 1.7. Substitution Reactions with Alkyl Halides

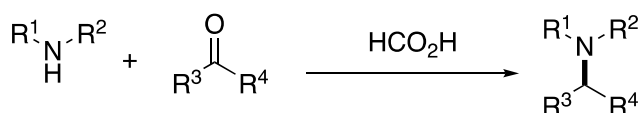
4. Reductive Amination Reactions

Reductive amination is a powerful tool for C–N bond formation, with over 20% of such reactions in the pharmaceutical industry utilizing this method.²⁰ The mechanism is shown in Scheme 1.8. Firstly, an amine attacks the carbonyl group to form a hemiaminal compound. When a primary amine is used, an imine intermediate is immediately reduced to an amine product. Similarly, a secondary amine forms an iminium ion intermediate that readily reacts with a reductant. Additionally, hemiaminal reduction also occurs.²¹

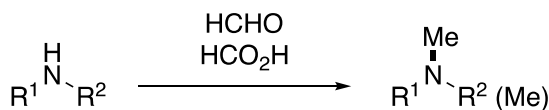


Scheme 1.8. Mechanism of Reductive Amination

The Leuckart reaction, one of the oldest reductive amination reactions, allows for the formation of a new C–N bond (Scheme 1.9).²² Here, formic acid serves as the reductant. The Escheweiler-Clarke reaction, a modification of the Leuckart reaction, yields N-methylated compounds (Scheme 1.10).²³ Formaldehyde acts as the C1 source in this reaction.

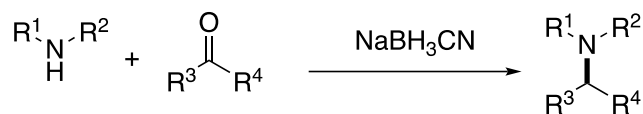


Scheme 1.9. Leuckart Reaction



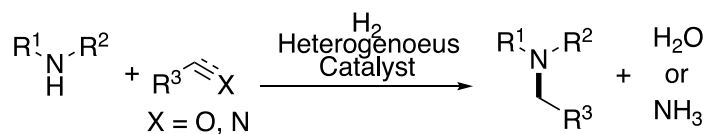
Scheme 1.10. Escheweiler-Clarke Reaction

In modern science, sodium cyanoborohydride is commonly used as a reducing agent for reductive amination (Scheme 1.11).²⁴ Although sodium cyanoborohydride is toxic and relatively expensive, it is a very useful reaction that can tolerate a wide range of substrates.



Scheme 1.11. Reductive Amination with Sodium Cyanoborohydride

Catalytic reductive amination can be achieved with transition metals and hydrogen as reductants.²⁵ In this process, the only byproducts are water or ammonia, which are unlikely to cause clogging or affect the following reaction in a sequential-flow system (Scheme 1.12).



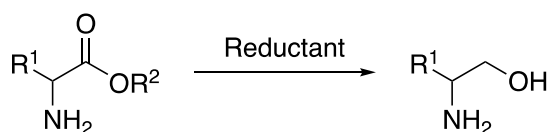
Scheme 1.12 Reductive Amination with Heterogeneous Catalyst and H₂

Due to this advantage, there is a vast amount of literature on reductive amination using a variety of heterogeneous transition metal catalysts and hydrogen.

5. Aminolysis Reactions

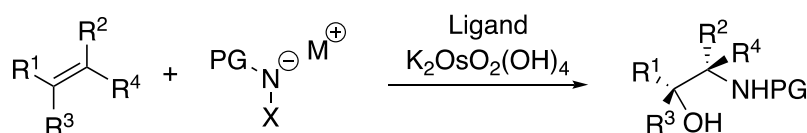
Aminolysis of Epoxides

β -Amino alcohols are crucial intermediates employed in numerous APIs and ligands due to their versatility.^{26,27} Various synthetic pathways lead to their production, with the reduction of α -amino acid or amino acid ether carbonyl compounds by metal hydrides standing out as a promising method (Scheme 1.13).



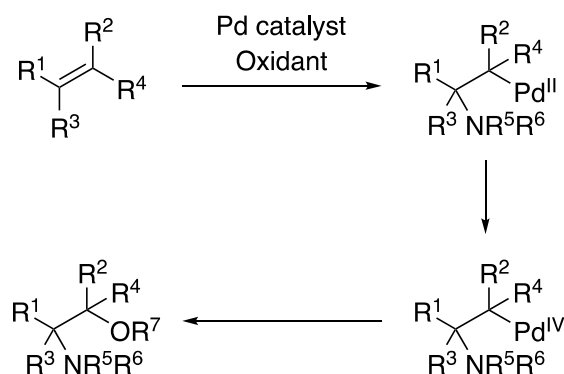
Scheme 1.13. Reduction of Amino Acids and Their Derivatives

Aminohydroxylation of alkenes offers a direct and efficient method for accessing β -amino alcohols. Among these methods, Sharpless aminohydroxylation is distinguished as a pioneering and versatile method (Scheme 1.14).²⁸ While the osmium catalyst raises concerns for large-scale applications due to its toxicity, this excellent transformation remains widely used in research and development.²⁹



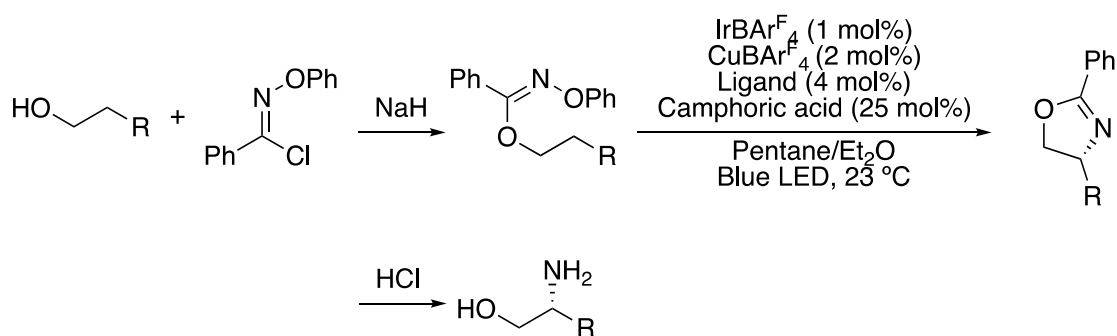
Scheme 1.14. Sharpless Asymmetric Aminohydroxylation

Recently, Pd-catalyzed oxidative difunctionalizations of alkenes have been intensively studied. Scheme 1.15 outlines the proposed Pd(II)/Pd(IV) cycle for this reaction. The carbon-carbon double bond first coordinates to Pd(II), followed by a nucleophilic attack by a specific nucleophile to generate an alkene-Pd(II) intermediate. Subsequently, palladium undergoes oxidation from Pd(II) to Pd(IV), which facilitates a second nucleophilic attack by another nucleophile.³⁰



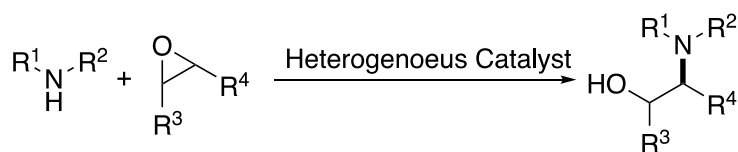
Scheme 1.15. Oxidative Difunctionalization of Alkenes

In 2020, Nagib reported an enantioselective radical C–H amination of alcohols to afford β -amino alcohols (Scheme 1.16).³¹ Regioselective hydrogen atom transfer (HAT) is a key step in this reaction.



Scheme 1.16. Enantioselective Radical C–H Amination

Aminolysis of epoxides, the ring-opening reaction with amines, is a key method for accessing β -amino alcohol APIs (Scheme 1.17). Its 100% atom economy makes it ideal for flow reactions. However, traditional methods often require harsh conditions like high temperatures, long reaction times, or microwave irradiation.^{32,33} Catalytic aminolysis with various homogeneous Lewis acid catalysts like ZnCl_2 , $\text{Sc}(\text{OTf})_3$, and CuBF_4 have emerged as an effective alternative under milder conditions.^{34,35,36,37,38,39,40,41,42} Heterogeneous solid-acid catalysts have also been developed, but their high activity often relies on water or neat conditions, limiting their utility to batch reactions.^{43,44,45} Therefore, the development of more efficient heterogeneous catalysts that function beyond these restrictive conditions remains a vital research area.

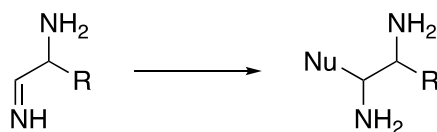


Scheme 1.17. Aminolysis of Epoxides

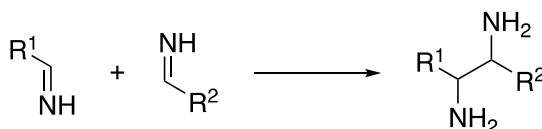
Aminolysis of Aziridines

1,2-Diamines are important building blocks found in numerous medicinal agents, ligands, and natural products. The diverse applications of these materials have been a key driving force behind the development of various synthetic methods. (Scheme 1.18). For instance, nucleophilic addition to α -amino imine intermediates has been well-studied (Scheme 1.18-1). Imine-imine cross-coupling reactions offer an efficient approach to prepare 1,2-diamines (Scheme 1.18-2). Notably, most of these reactions proceed via a radical pathway. Finally, ammonia addition to alkenes presents another viable strategy (Scheme 1.18-3).

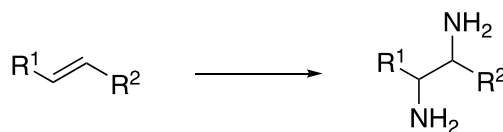
(1) addition reaction to α -amino imine



(2) imine-imine cross coupling

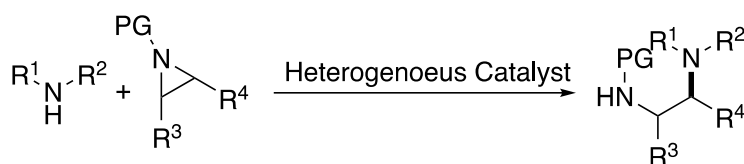


(3) ammonia addition to alkenes



Scheme 1.18. 1,2-Diamine Synthesis

Aminolysis of aziridine, the ring-opening reaction with amines, is a highly promising and versatile method for synthesizing 1,2-diamine compounds (Scheme 1.19). Like the aminolysis of epoxides, the complete atom economy makes it ideal for continuous-flow systems.



Scheme 1.19. Aminolysis of Aziridines

The key aspect of this reaction is the use of a protecting group. Aziridines can be divided into two categories: those with electron-withdrawing groups on the nitrogen atom, known as activated aziridines (e.g., N-Ts, Ns, Ac), and those with electron-donating groups, known as nonactivated aziridines. While activated aziridines readily undergo substitution reactions with amines under milder conditions, nonactivated aziridines typically require activation with acids for these reactions.

The challenging aspect of this research is the choice of catalysts. In reductive amination, amines and ammonia can coordinate with metals due to the strong donor character on NH moieties, deactivating the metal catalysts.⁴⁶ The heterogeneous catalysts with high durability are preferable for continuous-flow reactions. In aminolysis of epoxides and aziridines, it is known that Lewis acid catalysts can promote the reactions well while Brønsted acid catalysts make salts with amines, which interrupts activating the electrophiles. On the other hand, heterogeneous catalysts, and solid-acid catalysts hardly control the acid nature properly. In this thesis, I turned the metals which possess the proper acid, activating the electrophiles. Moreover, catalyst characterization was done to reveal the mechanisms.

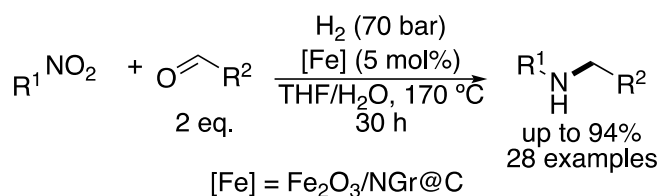
This thesis explores the potential of continuous-flow reactions for the synthesis of valuable pharmaceuticals and their intermediates (APIs and precursors). Chapter II details a novel continuous-flow method for reductive amination with nitriles, showcasing its utility in the synthesis of Tamsulosin, Carvedilol, and Domiphen Bromide. Chapter III demonstrates the application of continuous-flow aminolysis of epoxides, culminating in a sequential-flow process for the preparation of a Rivaroxaban precursor. Finally, Chapter IV investigates continuous-flow aziridine opening reactions with amines.

Chapter II : Continuous-flow Reductive Amination and Application for API Synthesis

1. Introduction

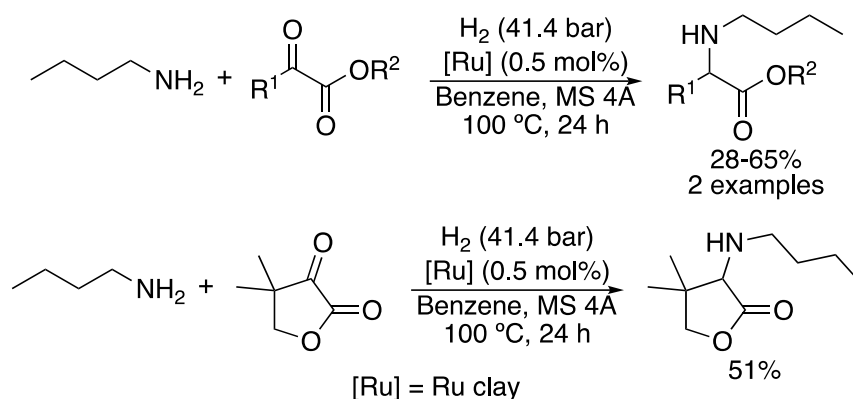
While hydrogenation reactions utilizing heterogeneous catalysts in batch systems have been extensively studied and hold promise, their three-phase (gas, liquid, and solid) mixing can be inefficient and lead to limitations in reaction control. Additionally, dissolving hydrogen gas into organic solvents often requires high pressures, raising safety concerns. In contrast, continuous-flow hydrogenation offers several advantages. Improved mass transfer rates due to enhanced gas-liquid-solid interaction allow for operation at ambient pressure, reducing carbon emissions and enhancing safety. Furthermore, studies have shown that continuous-flow systems can achieve significantly faster reaction rates (higher turnover frequencies, TOFs) compared to batch processes.^{47,48}

A substantial body of research exists on reductive amination utilizing various heterogeneous transition metal catalysts. Examples of different metals are illustrated below. In 2014, nanostructured Fe₂O₃/NGr@C (nitrogen-enriched graphene-type layers) was utilized for the reductive amination of nitroarenes with aldehydes (Scheme 2.1).⁴⁹ The authors immobilized an iron complex on commercially available carbon as a support, and the condensation step involved in situ generation of aryl amines from nitroarenes. The catalyst could be reused 5 times.



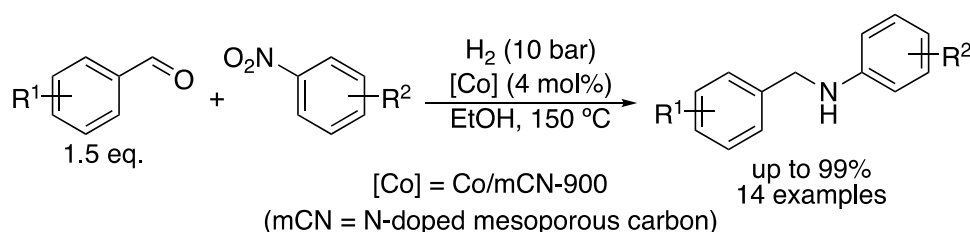
Scheme 2.1. Fe Catalyzed Reductive Amination between Nitroarenes and Aldehydes

Maschmeyer reported that the K10-supported Ru(III) complex effectively catalyzes the reductive amination of both noncyclic and cyclic α -keto esters (Scheme 2.2).⁵⁰ The reaction was facilitated by the addition of MS 4A (molecular sieves 4A), which efficiently removed water and accelerated the condensation step.



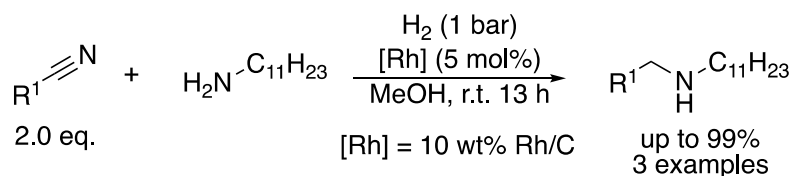
Scheme 2.2. Ru Catalyzed Reductive Amination of α -Keto Esters

In 2017, a novel approach for the reductive amination of aldehydes with nitro compounds was reported using Co nanoparticles supported on N-doped carbon (Co/mCN-900) (Scheme 2.3).⁵¹ The catalyst was prepared by pyrolysis of cobalt nitrate with melamine and polyacrylonitrile at 900 °C and employed for the reaction under harsh conditions of 150 °C and 10 bar.



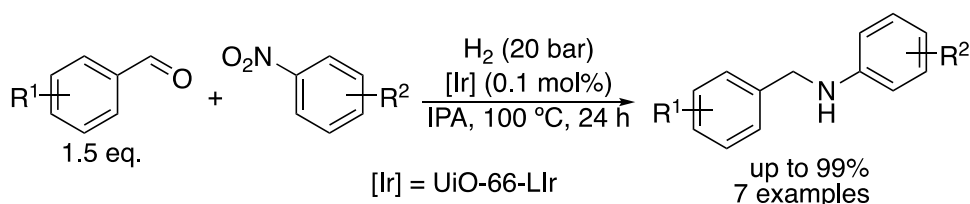
Scheme 2.3. Co Catalyzed Reductive Amination between Nitro Compounds and Aldehydes

In 2004, Sajiki et reported the *N*-alkylation of amines with nitriles as coupling partners using a commercially available Rh/C catalyst (Scheme 2.4).⁵² Amines were selectively mono-alkylated at ambient temperature. Only three substrates were tested.



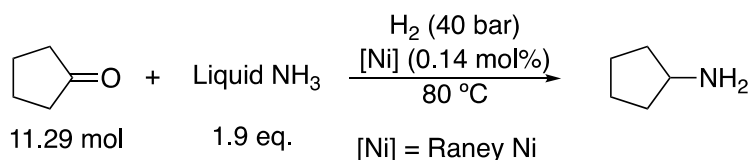
Scheme 2.4. Rh Catalyzed Reductive *N*-alkylation of Amines with Nitriles

Iridium-catalyzed reductive amination was also reported. In 2013, the reductive amination of aldehydes using nitroarenes was performed with Ir-modified UiO-66 (UiO = University of Oslo) (Scheme 2.5).⁵³ UiO-66 is a kind of MOF with high surface area and thermal stability. The cascade reaction proceeded quantitatively.



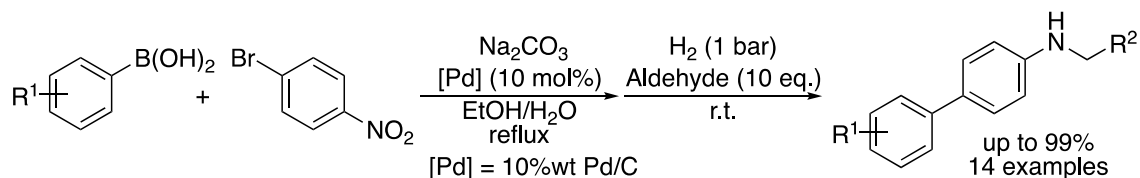
Scheme 2.5. Ir Catalyzed Reductive Amination of Aldehydes with Nitro Compounds

There have been several reports of Raney Ni-catalyzed reductive amination reactions. In 2005, a large-scale reductive amination of cyclopentanone with liquid ammonia was realized (Scheme 2.6).⁵⁴ In the presence of 0.14 mol% Raney Ni, 11.29 mol cyclopentanone was converted to cyclohexylamine.



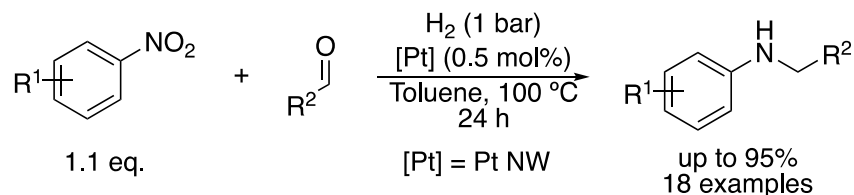
Scheme 2.6. Raney Ni Catalyzed Reductive Amination of Cyclopentanone with Ammonia

Suzuki-Miyaura cross-coupling followed by reductive amination of nitroarenes with aldehydes was achieved using a commercially available Pd/C catalyst (Scheme 2.7).⁵⁵ In this one-pot transformation, 14 types of boronic acids were tolerated with good to high yields. However, relatively high amounts of aldehydes were necessary.



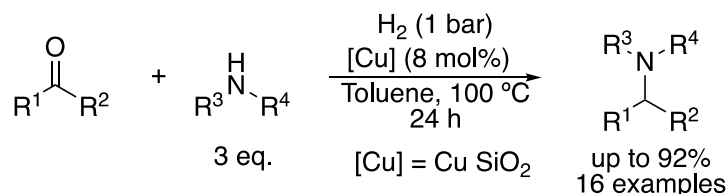
Scheme 2.7. Pd Catalyzed Suzuki-Miyaura Cross Coupling and Reductive Amination

Platinum is also a well-known reductive amination catalyst. In 2011, a reductive amination of aldehydes utilizing nitro compounds was reported (Scheme 2.8).⁵⁶ Pt NWs (ultrathin nanowires) were used as a catalyst, and *N*-alkylated products were obtained in high yield.



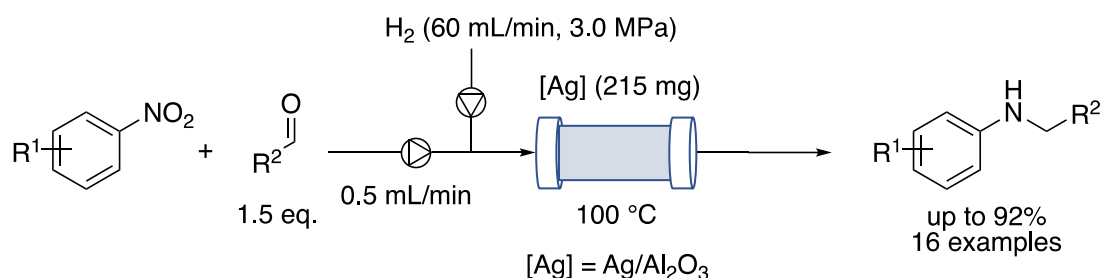
Scheme 2.8. Pt Catalyzed Reductive Amination of Aldehydes with Nitro Compounds

The reductive amination of carbonyl groups with amines was reported (Scheme 2.9).⁵⁷ The reaction proceeded with a high yield, and the authors explained that the acidic silica support might promote the condensation step.



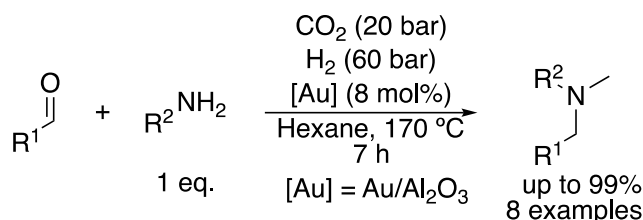
Scheme 2.9. Cu Catalyzed Reductive Amination of Carbonyl Group with Amines

In 2017, a continuous-flow system was used to perform the reductive amination of aldehydes with nitroarenes using Ag/Al₂O₃ (Scheme 2.10).⁵⁸ The catalyst was prepared by impregnating silver nitrate onto alumina and showed high activity for this reaction.



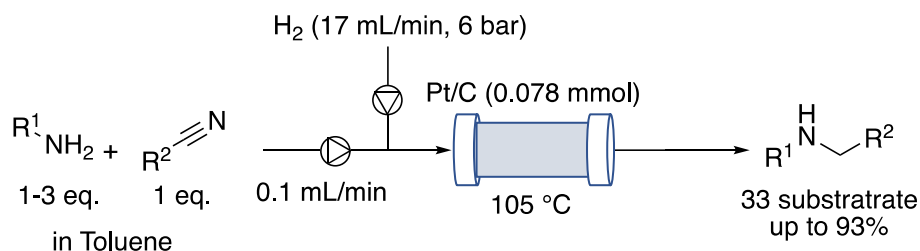
Scheme 2.10. Ag Catalyzed Reductive Amination of Aldehydes with Nitro Compounds in Continuous-flow

Reductive amination catalyzed by Au/SiO₂ was reported in 2015 (Scheme 2.11).⁵⁹ Aldehydes and CO₂ were used as electrophiles, and different substituted tertiary amines were formed.



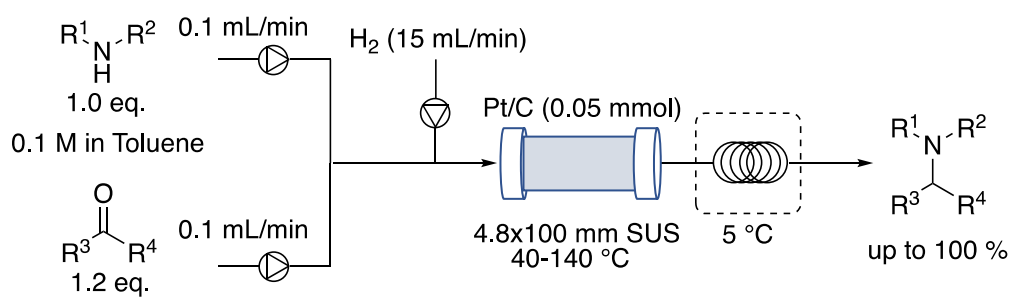
Scheme 2.11. Au Catalyzed Reductive Amination of Aldehydes with Amines and CO₂

In 2013, Williams demonstrated commercially available Pt/C-catalyzed reductive amination with nitriles in a continuous-flow process (Scheme 2.12).⁶⁰ This approach successfully converted a broad range of primary amines and nitriles to secondary amines in high yields, although requiring excess amine and pressure within a specific range.



Scheme 2.12. Pt-C Catalyzed Reductive Amination Reaction with Nitriles in Continuous-flow System

In 2019, Kobayashi achieved direct reductive amination of carbonyl compounds using a Pt/C catalyst in a continuous-flow method (Scheme 2.13).¹⁹ This reaction tolerated a variety of amines and ketones or aldehydes in high yield.



Scheme 2.13. Direct Reductive Amination in Continuous-flow Method

In both continuous-flow reactions (Schemes 2.13 and 2.14), more functionalized substrates were not tested. Additionally, *N*-methylation was not achieved due to the difficulty of using gas (formaldehyde). More efficient heterogeneous catalysts are in demand for overcoming these problems.

Numerous supported metal nanoparticle (NP) catalysts exist globally. However, our research group has recently shifted its focus to metal NPs immobilized on polysilane support materials. Polysilane's intriguing electronic properties have prompted extensive research over the years. The weak but manifold interactions between polysilane and metal NPs render the resulting catalyst both robust and highly active, surpassing the performance of commercially available counterparts.^{61,62,,48,63,64}

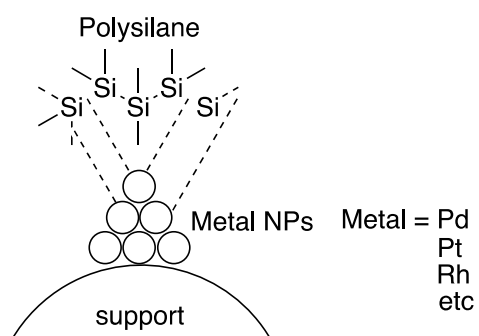


Figure 2.1. Polysilane-Metal Nanoparticles/Support Catalysts

I expected that highly active polysilane-metal complexes would be suitable for reductive amination with functionalized substrates.

2. Results and Discussion

2.1 Reductive Amination with Nitriles

Initially, 2-phenylethylamine (**1**) and butyronitrile (**2**) were chosen as model substrates for optimization of the catalyst and solvent (Table 2.1). Entry 3 with DMPSi-Pd/AC-CP (3:1)¹³ (dimethylpolysilane-Pd supported on activated carbon-calcium phosphate (3:1)) in a toluene/ethanol co-solvent system exhibited a higher yield than entries 1 and 2 using toluene or ethanol alone. Although using a high amount of ethanol resulted in the formation of a tertiary amine product, which might act as a catalyst poison, DMPSi-Pd/AC-CP (3:1) maintained superior activity compared to other Pd catalysts in entries 4-7. Furthermore, Pd demonstrated greater activity than other tested metals like Pt and Rh. With Rh/C, hydrogenation of the aromatic ring occurred concurrently. Pd was identified as the best metal in terms of activity and selectivity because Pd can take in the much amount of hydrogen.

Table 2.1 Optimization of the Reaction Conditions in Batch System

PhCH2CH2NH2 (**1**) + CCC#N (**2**, 1.2 eq.) $\xrightarrow[\text{Solvent, 80 } ^\circ\text{C, 15 h}]{\text{H}_2 (5 \text{ atg}), \text{Catalyst (5 mol\%)}}$ PhCH2CH2NCCC (**3**)

Entry	Catalyst	Solvent	Yield (%) ^a
1	DMPSi-Pd/AC-CP (3:1)	EtOH	21
2	DMPSi-Pd/AC-CP (3:1)	Toluene	31
3	DMPSi-Pd/AC-CP (3:1)	Toluene/EtOH (95:5)	59
4	PhMePSi-Pd/SiO ₂	Toluene/EtOH (95:5)	50
5	PdZAc	Toluene/EtOH (95:5)	33
6	PdZeoβ	Toluene/EtOH (95:5)	18
7	Pd-Lindlar	Toluene/EtOH (95:5)	17
8	Pt/C	Toluene/EtOH (95:5)	18
9	PhMePSi-Pt/SiO ₂	Toluene/EtOH (95:5)	23
10	Rh/C	Toluene/EtOH (95:5)	59

^a Determined by GC analysis

Since I had secured the optimal conditions for the batch reactions, I explored the substrate scope of the reaction in a continuous-flow system (Table 2.2). Yields varied significantly with the nitrile structure. Phenoxy-type nitriles afforded products in high yields (entry 1), while the absence of α -oxygen atoms significantly reduced reactivity (entry 2). Aliphatic nitriles lacking aromatic rings exhibited lower reactivity (entries 3, 4). This suggests an interaction between the Pd center and the phenyl ring, which may

enhance substrate activity. Consequently, electron-rich phenoxy nitriles demonstrate higher reactivity.

Table 2.2. Substrate Scope for The Reductive Amination with Nitriles

Entry	Nitrile	Yield (%) ^a	Conv. (CN) (%) ^a	TOF (/h) ^d
1		94-96	Full	0.63
2		87-90	79-83	0.53
3		64-66	- ^c	0.43
4		47-60 ^b	57-60 ^b	0.36

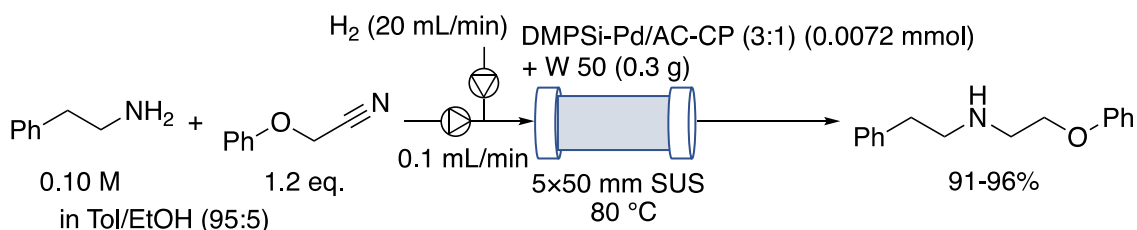
^a Determined by ¹H NMR analysis

^b Determined by GC analysis

^c Not calculated due to the volatility of the nitrile

^d Calculated based on the yield

Given the saturated conversion in entry 1, I attempted phenoxy nitrile reactions under milder conditions (Scheme 2.14). Using lower catalyst loading without backpressure, I achieved TOFs as high as 80 /h.



Scheme 2.14. Substrate Scope for The Reductive Amination with Nitriles in Milder Conditions

To further probe the impact of continuous-flow processing, I investigated the substrate scope of this reaction using a batch system (Table 2.3). Notably, under a hydrogen atmosphere, the reaction did not proceed at all in the batch setup. This observation

suggests that, compared to the continuous-flow system, the batch reaction necessitates a significantly higher pressure for completion. In essence, the continuous-flow approach demonstrably enhances the efficiency and viability of this particular reaction.

Table 2.3 Substrate Scope for The Reductive Amination with Nitriles in Batch Reactions

Entry	Nitrile	Yield (%) ^a
1		N.R.
2		N.R.
3		N.R.
4		N.R.

^a Determined by ¹H NMR analysis

While the reductive amination method was limited to phenoxy-type nitriles, its continuous-flow implementation proved highly valuable. Moreover, the corresponding aldehydes are highly unstable and unsuitable for flow systems. Therefore, I aimed to leverage this efficient transformation for sequential-flow API synthesis.

2.2 Sequential-flow Synthesis of (*R*)-Tamsulosin Precursor

Tamsulosin (Figure 2.2) is an API, used by men to treat the symptoms of an enlarged prostate. It does not shrink the prostate, but it works by relaxing the muscles in the prostate and the bladder. The commercial name of Tamsulosin hydrochloride is “Harnal” and its sales exceed 50 billion yen. Given that the patent has expired, the development of a generic drug is desired.

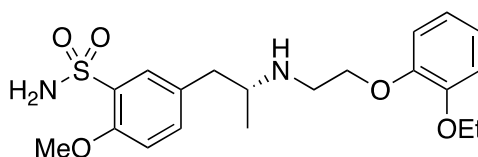
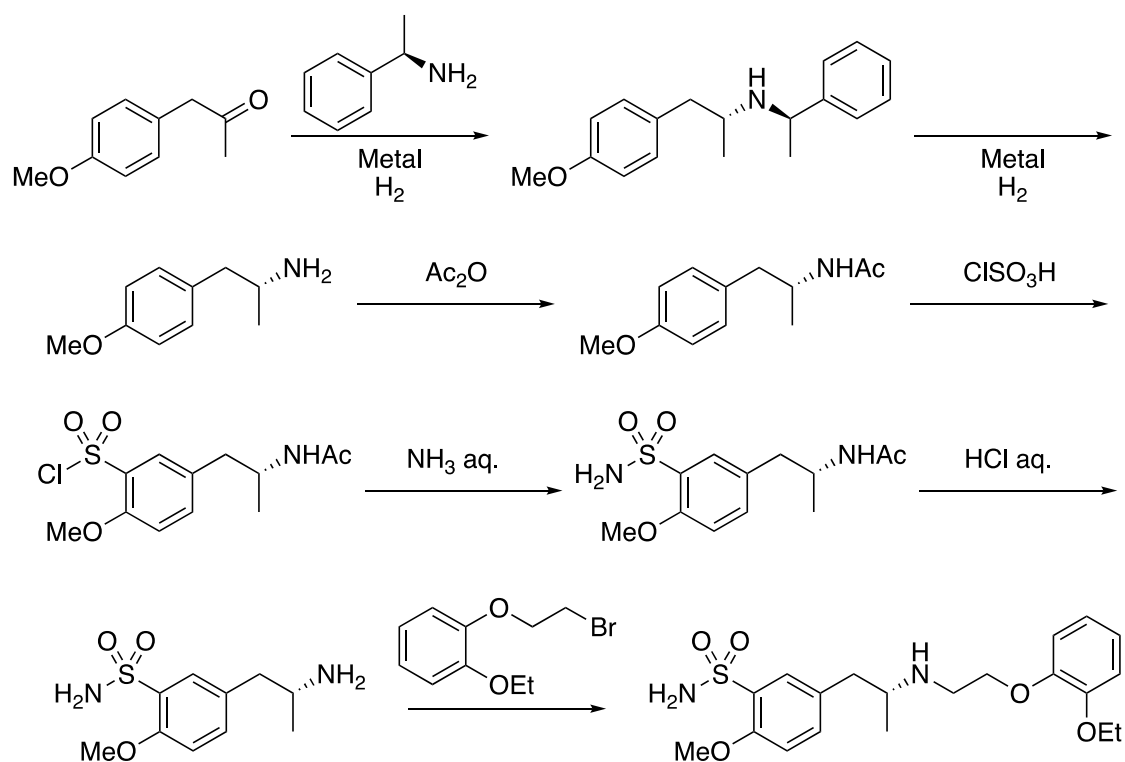


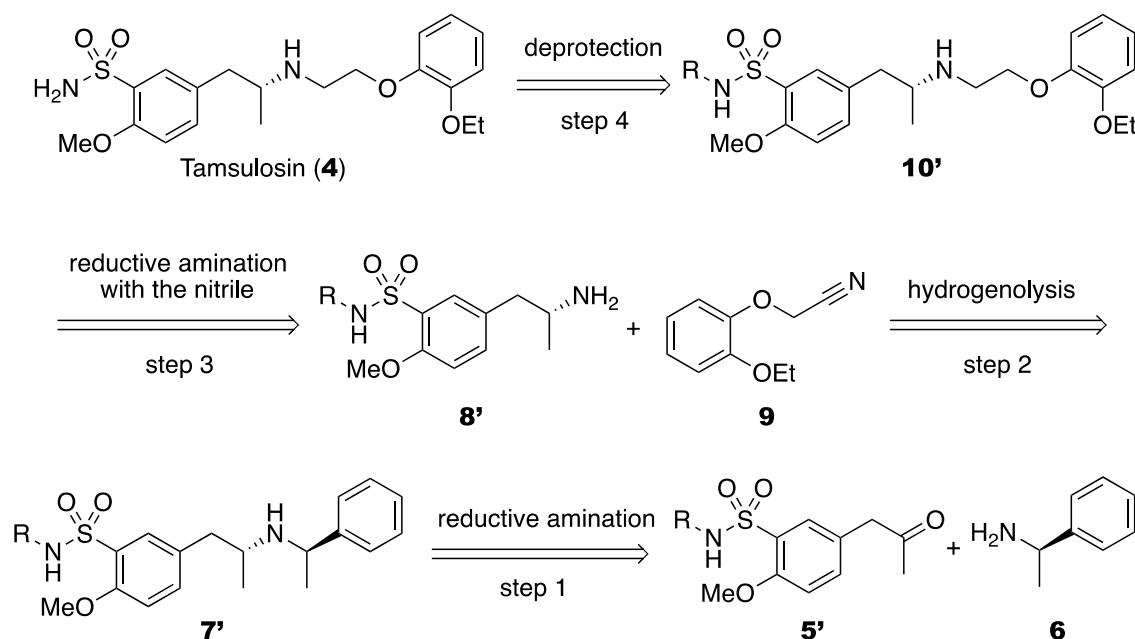
Figure 2.2. Tamsulosin

The proposed industrial synthetic route of Tamsulosin is shown here (Scheme 2.15).⁶⁵ Initially, diastereoselective reductive amination with metal and hydrogen is employed, facilitated by (*R*)-phenylethylamine as a diastereoselective authority, to generate a secondary amine. Subsequently, deprotection of the amine is conducted with a metal catalyst and hydrogen, yielding a chiral amine. Following the introduction of the sulfonamide part, an S_N2 reaction with an alkyl bromide leads to the formation of Tamsulosin. However, this synthesis faces the challenge that the final reaction may result in an overreaction, producing a tertiary amine as an uncontrollable byproduct. Moreover, the entire process is conducted in a batch system, requiring substantial effort and time, and generating significant waste. Considering these disadvantages, a sequential-flow synthesis of Tamsulosin utilizing reductive amination reactions in C–N bond formation steps was contemplated as a potential solution.



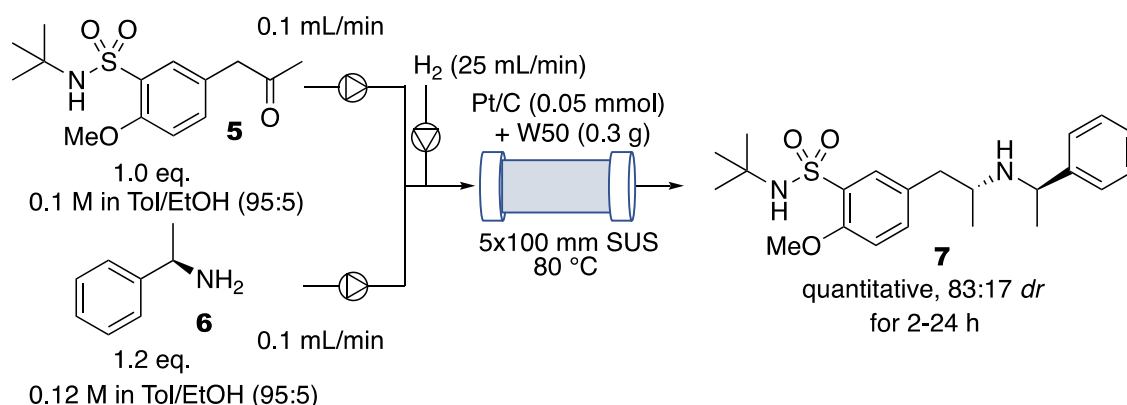
Scheme 2.15. Assumed Synthetic Route of Tamsulosin in Industry

Employing hydrogenation reactions in multi-steps, the synthetic route for Tamsulosin in late-stage sequential-flow methods was designed (Scheme 2.16). In consideration of the substrate solubility, the sulfonamide part needed protection. Secondary amine (**10**) was formed by reductive amination with nitrile (**9**). Hydrogenolysis and reductive amination with the amine (**6**) were proposed. After several investigations, it was found that using the ^tBu group as a protecting group could enhance solubility.



Scheme 2.16. Retrosynthetic Synthetic Analogy for Tamsulosin

Firstly, I conducted a continuous-flow reductive amination reaction of ketone (**5**) with amine (**6**) following our previous work (Scheme 2.17).¹⁹ To facilitate the dissolution of substrates, a toluene/EtOH (95:5) solvent system was chosen, and an increased ratio of EtOH was found to decrease diastereoselectivity. The desired amine (**7**) was obtained in quantitative yield with 83:17 *dr* for 24 hours. This reaction did not require any isolation, since the only byproduct was water, allowing the reaction to proceed quantitatively. Additionally, the presence of 20 mol% amine (**6**) did not negatively impact the next step.

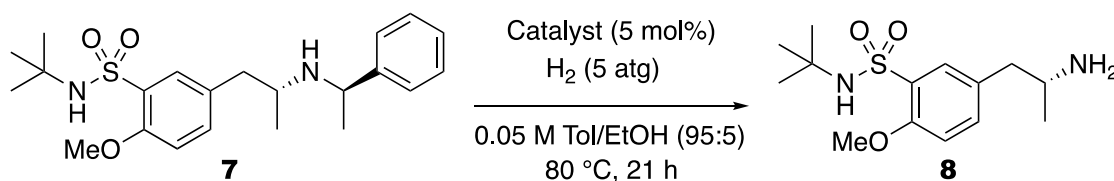


Scheme 2.17. Reductive Amination of Ketone **5** with Amine **6**

Moving on to the second step, the hydrogenolysis of the phenethyl group, I examined the reaction with different metal catalysts first (Table 2.4). To ensure a fair comparison of catalyst activity, compound (**7**) was used after isolation in this stage. While I initially expected a commercially available Pd/C catalyst to afford high yields, the installation of

the sulfonamide part resulted in suppressed catalyst activity (entry 1). However, it was discovered that Pd nanoparticles immobilized on a polysilane-activated carbon/calcium phosphate (3:1) catalyst exhibited high activity (entry 2). The activity was slightly decreased in the absence of calcium phosphate (CP), suggesting that CP might donate electrons to the Pd center. Moreover, the AC:CP co-support was more effective than alumina support. The other metals showed no activity (entries 5-7).

Table 2.4. Hydrogenolysis with Different Catalysts in Batch System

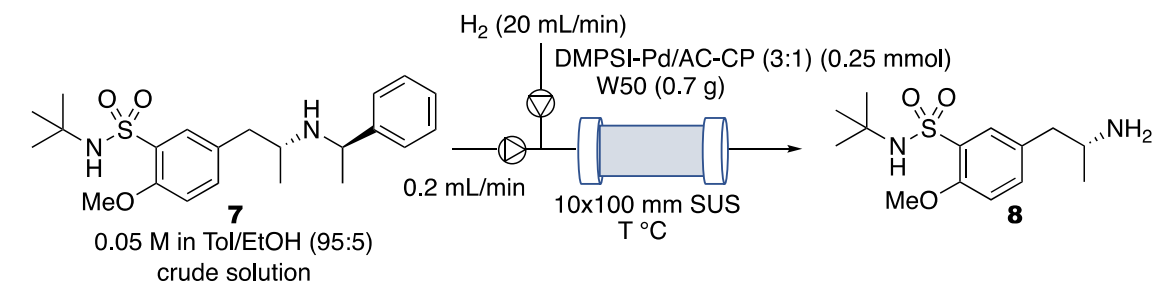


Entry	Catalyst	Yield (%) ^a
1	Pd/C	58
2	DMPSi-Pd/AC-CP (3:1)	88
3	DMPSi-Pd/AC	81
4	DMPSi-Pd/Al ₂ O ₃	12
5	DMPSi-Pt/AC-CP (3:1)	0
6	Ru/C	0
7	Rh/C	0

^a Determined by ¹H NMR analysis

Then, I examined this reaction with DMPSi-Pd/AC-CP (3:1) catalyst under different conditions in continuous-flow reactions (Table 2.5, Figure 2.3). In the early stages of the reaction, the product was obtained in almost quantitative yield while the yields decreased over time, indicating catalyst deactivation (entry 1). This phenomenon persisted even under high pressurized conditions (entry 2). Neither the polar solvent system nor the lower temperature showed a positive effect on this reaction (entries 3,4).

Table 2.5. Hydrogenolysis in Different Condition in Flow System



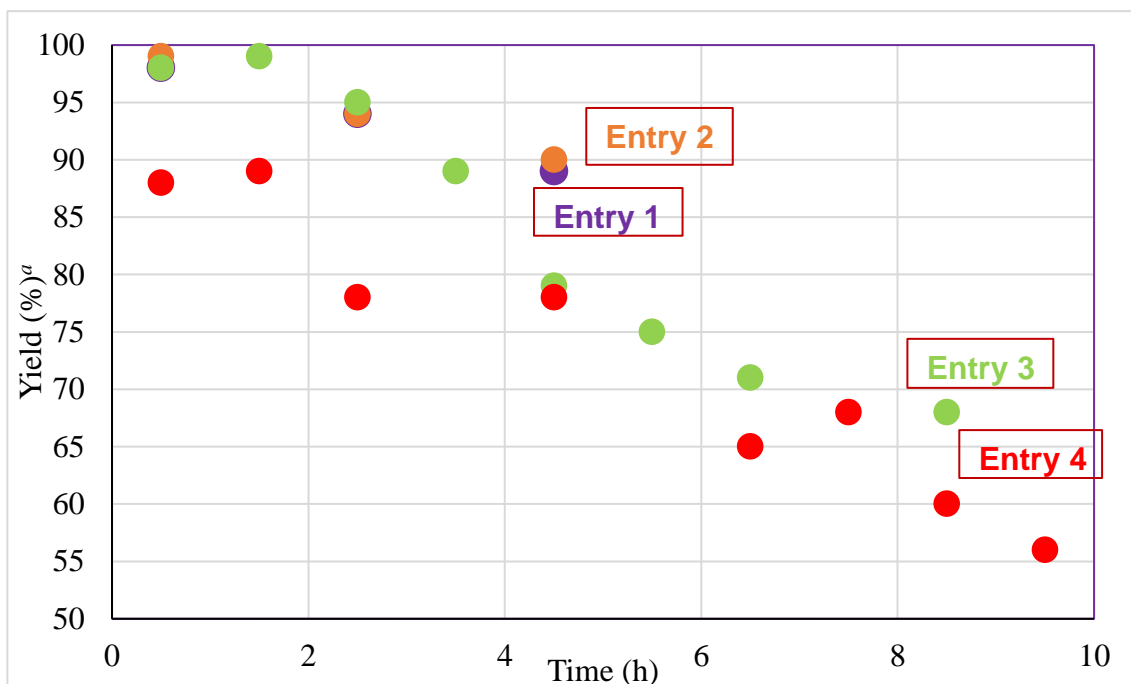
Entry	Time (h)	T (°C)	Yield (%) ^a
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1	9	80	98-88
2 ^b	8	80	100-90
3 ^c	12	80	98-68
4	11	60	88-56

^a Determined by ¹H NMR analysis

^b Back pressure 5 atg

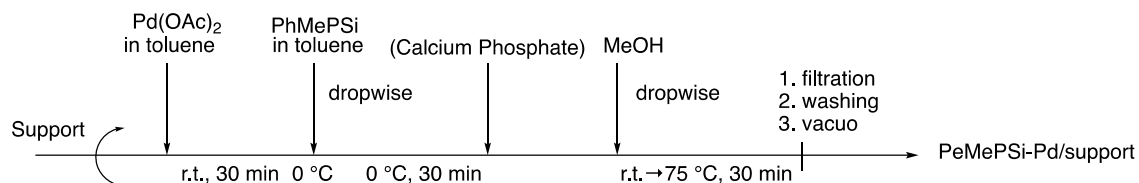
^c Toluene/EtOH = 90/10



^a Over 2 steps yield determined by ¹H NMR analysis

Figure 2.3. Hydrogenolysis in Different Conditions in Continuous-flow System

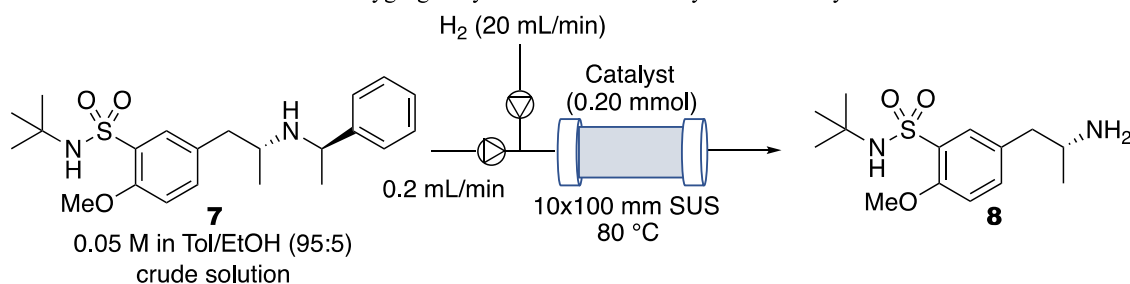
To address the deactivation problem, I tried to prepare more robust catalysts. Different types of polysilane-supported Pd catalysts were synthesized (Scheme 2.18). To a mixture of support and Pd(OAc)₂, phenylmethylpolysilane (PhMePSi) was added and stirred. PhMePSi also worked as a reductant. Then, the reaction temperature was increased to 75 °C and stirred for another 30 minutes after methanol was added dropwise. After the filtration, washing, and drying, PhMePSi-Pd/support catalysts were obtained. It is noteworthy that PhMePSi is soluble in organic solvent unlike DMPSi; however, it remains in the catalyst (See above).



Scheme 2.18. Preparation of PhMePSi-Pd/support

With the new catalyst in hand, a screening of catalysts in continuous-flow methods was conducted (Table 2.5, Figure 2.4). Three different types of dimethylpolysilane-Pd catalysts and two types of phenylmethylpolysilane-Pd catalysts were deactivated as well (entries 1-5), while PhMePSi-Pd/SiO₂ catalyst maintained its activity over 11 hours. Consequently, this catalyst was considered the most suitable for the reaction (Figure 2.4).

Table 2.6. Hydrogenolysis in Different Catalysts in Flow System



Entry	Catalyst	Time (h)	Yield (%) ^a	Reductant
1	DMPSi-Pd/AC-CP (3:1)	9	98-88	NaBH ₄
2	DMPSi-Pd/SiO ₂	11	49-40	NaBH ₄
3	DMPSi-Pd/SiO ₂	11	78-59	PCS
4	PhMePSi-Pd/AC-CP (3:1)	12	82-66	PhMePSi
5	PeMePSi-Pd/Al ₂ O ₃	12	100-78	PhMePSi
6	PhMePSi-Pd/SiO ₂	11	96-98	PhMePSi

^a Over 2 steps yield determined by ¹H NMR analysis

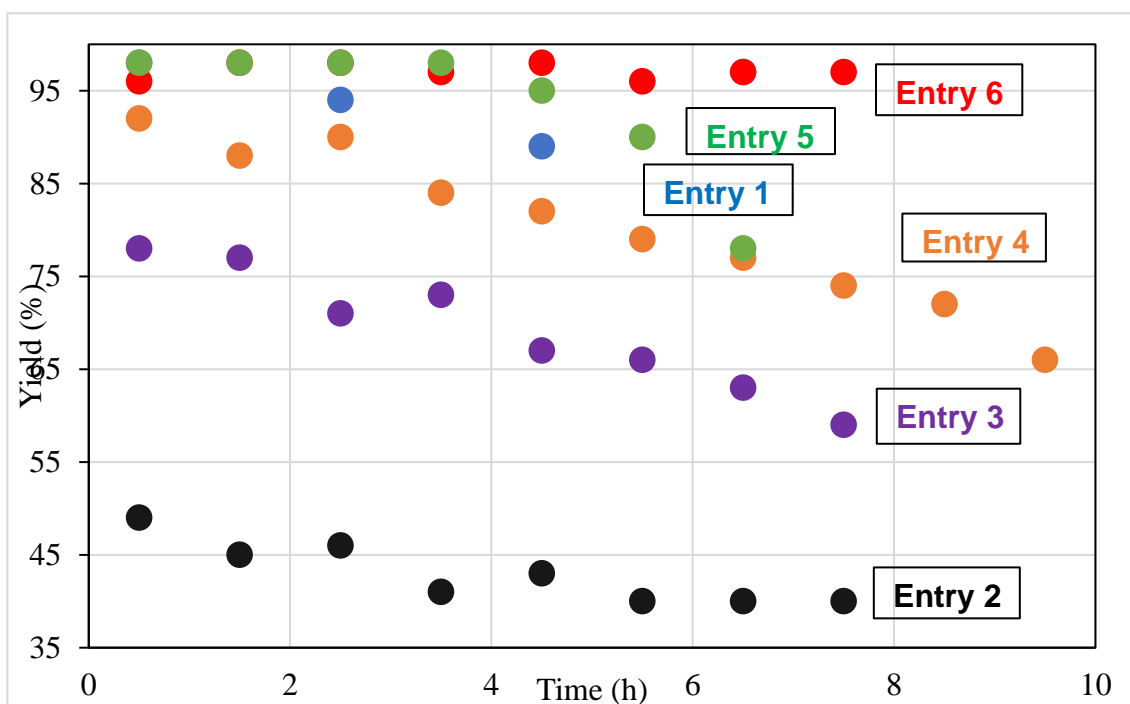
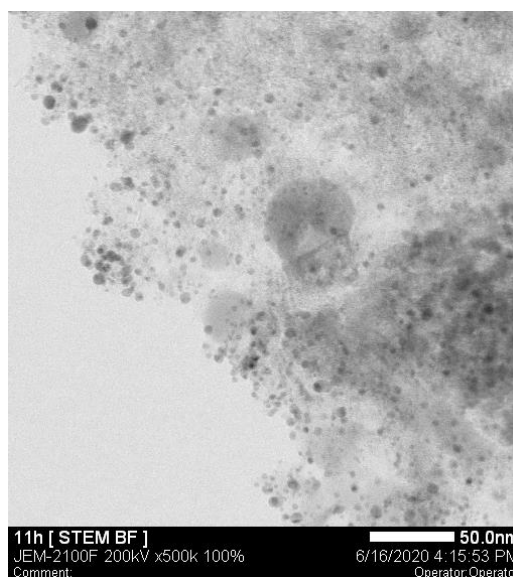
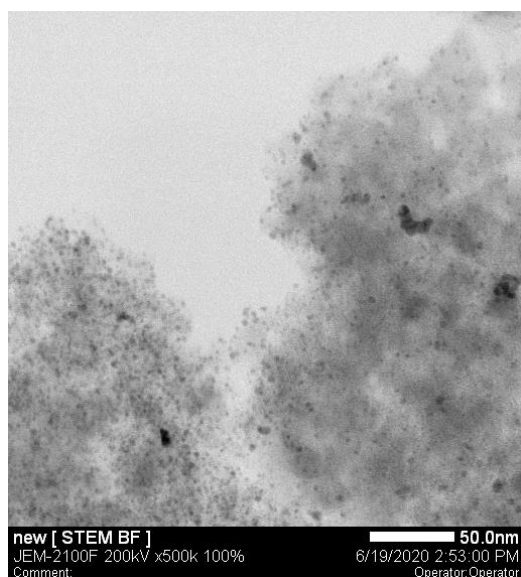


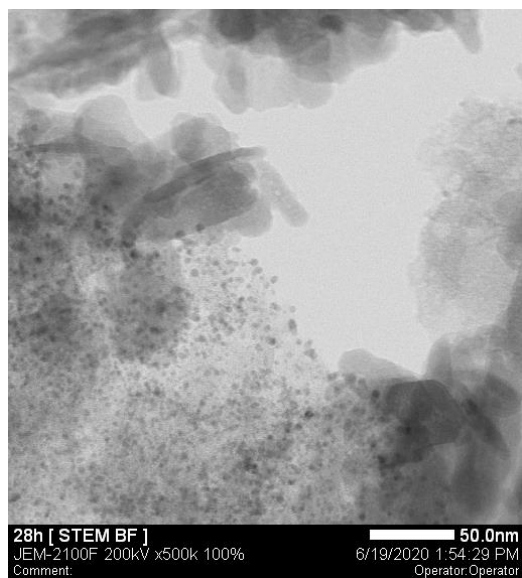
Figure 2.4. Hydrogenolysis with Different Catalysts in Continuous-flow System

To uncover the cause of the catalyst deactivation, the catalysts after the reaction proceeded for 11 hours and 28 hours were analyzed by STEM, revealing that some parts of the Pd particles aggregated to form larger particles (Figure 2.5 (a)-(c)). Furthermore, after the reaction, a sulfur atom was observed on the catalyst, and both changes might be contributing factors to the deactivation. The sulfur atom appeared due to the absorption of the starting material or the product (Figure 2.5 (d)-(f)).

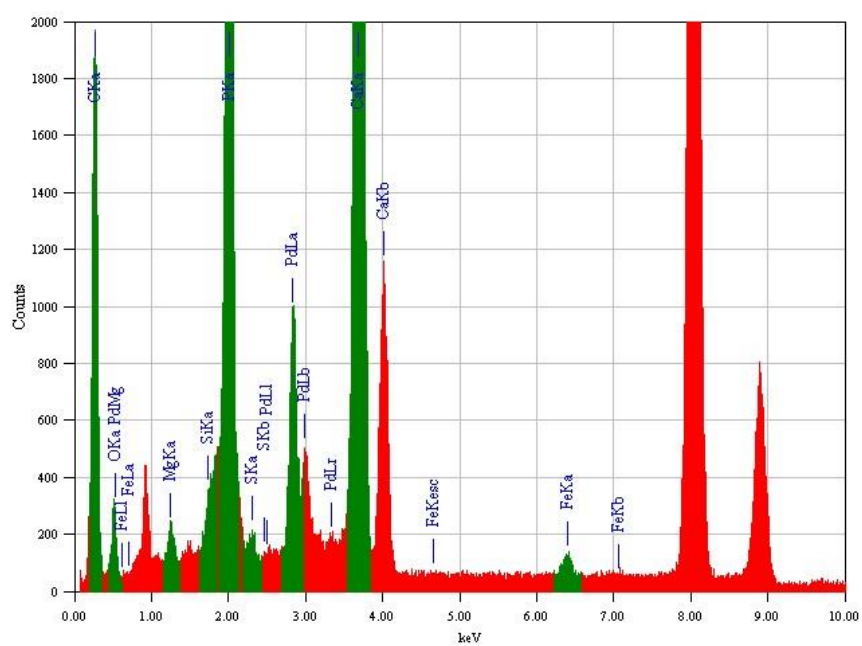
(a) DMPSi-Pd/AC-CP (3:1) before usage (b) DMPSi-Pd/AC-CP (3:1) after 11 h



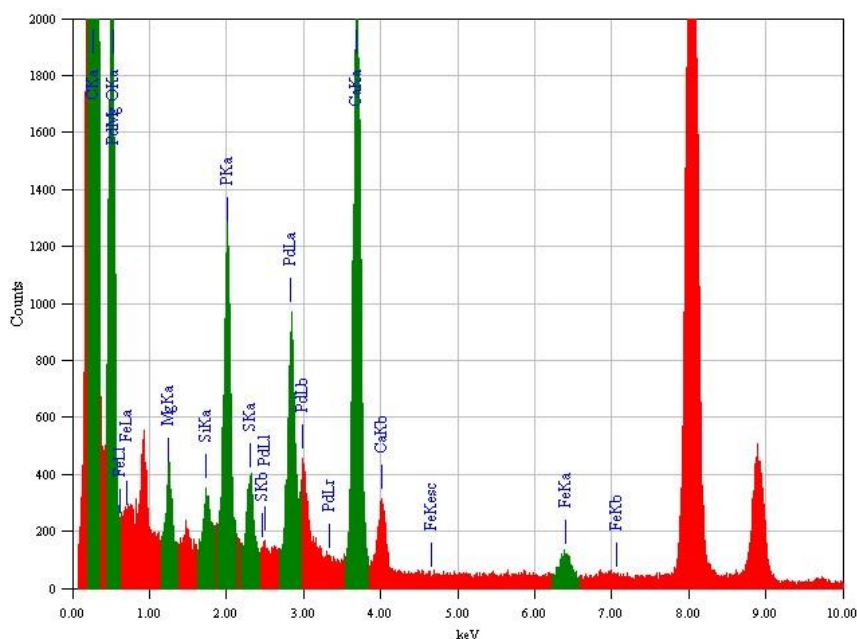
(c) DMPSi-Pd/AC-CP (3:1) after 28 h



(d) Area of DMPSi-Pd/AC-CP (3:1) before usage



(e) Area of DMPSi-Pd/AC-CP (3:1) after 11 h



(f) Area of DMPSi-Pd/AC-CP (3:1) after 28 h

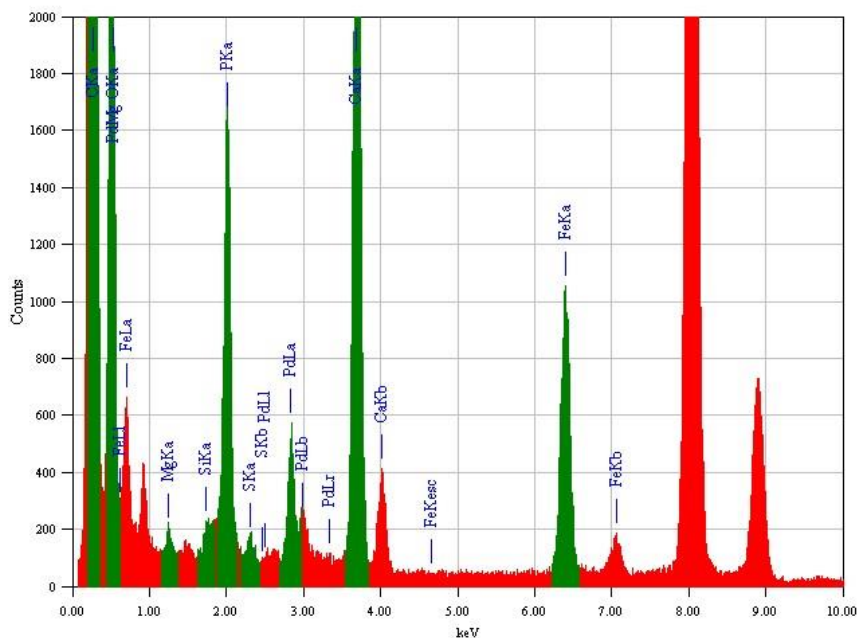


Figure 2.5. STEM Area Analysis of Catalysts Before and After

And, in the STEM image, PhMePSi-Pd/SiO₂ catalyst showed a better dispersion of Pd over DMPSi-Pd/AC-CP (3:1) catalyst (Figure 2.6), and the formation of Pd NPs with 5~10 nm particle size. Most of the Pd NPs maintained their particle size and no significant

aggregation was observed after 11 h of continuous-flow reaction (Figure S4). In preparation, Pd(OAc)₂ was absorbed on silica before the reduction by PhMePSi, probably contributing to the high Pd dispersion. On the other hand, some aggregation of Pd NPs were observed for other inferior catalysts such as DMPSi-Pd/AC-CP (3:1) (Figure 2.5). Therefore, it is likely that the deactivation was caused by aggregation of Pd NPs during flow reaction and SiO₂ support prevent it. The EDS mapping showed the broad distribution and overlap of SiO₂, PhMePSi, and Pd on the support (Figure S6). Therefore, a part of PhMePSi covers not only Pd but also SiO₂ support, although it dissolves in organic solvent. This observation is further supported by STEM area analysis (Figure S5). Co-existence of both PhMePSi and SiO₂ can be observed in Pd rich area. It seems that Pd NPs were supported by SiO₂ and the surface of Pd NPs is covered by PhMePSi.

(a) PhMePSi-Pd/SiO₂ before usage

(b) PhMePSi-Pd/SiO₂ after 11 h

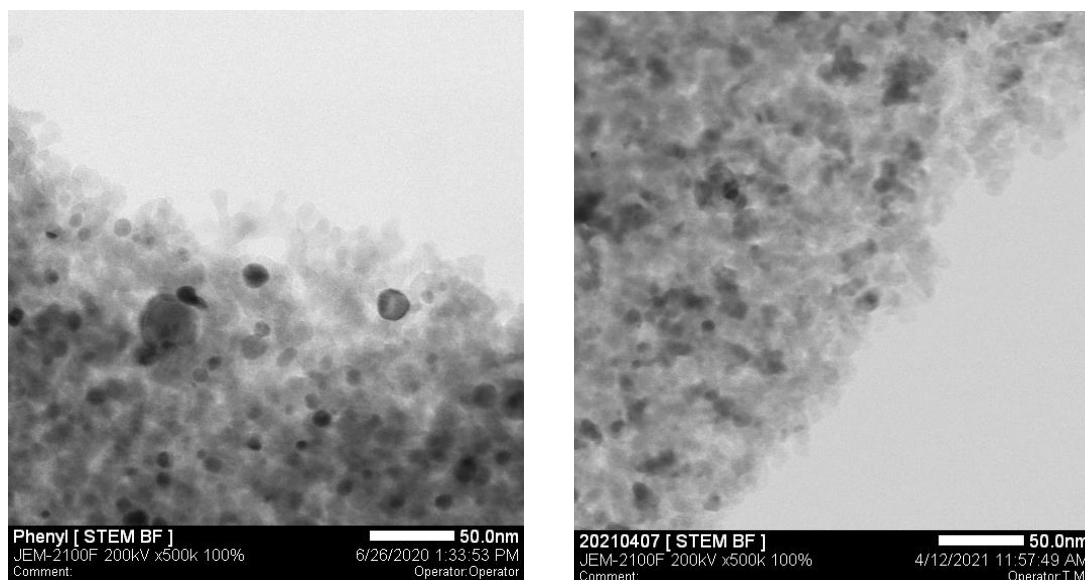
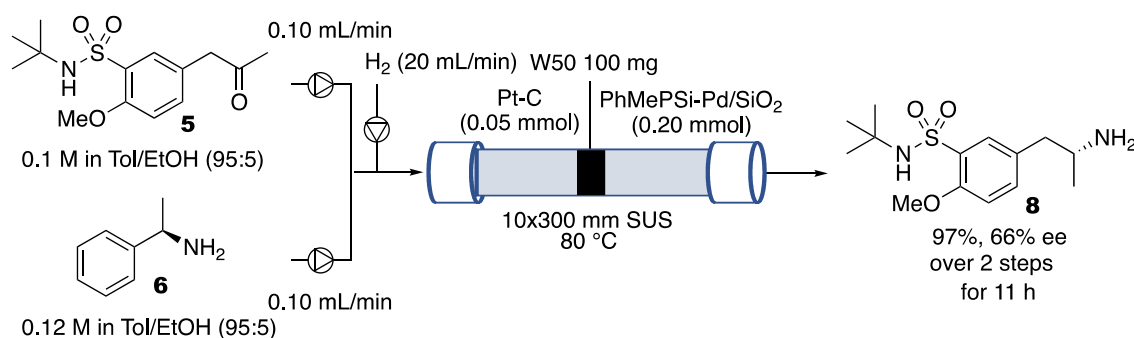


Figure 2.6. STEM Image of PhMePSi-Pd/SiO₂ Catalyst

In this reaction, no isolation was required since the byproduct of this reaction is only ethylbenzene. The reaction proceeded quantitatively, and the remaining 20 mol% of amine (**6**) was also converted to ammonia and ethylbenzene in the following step.

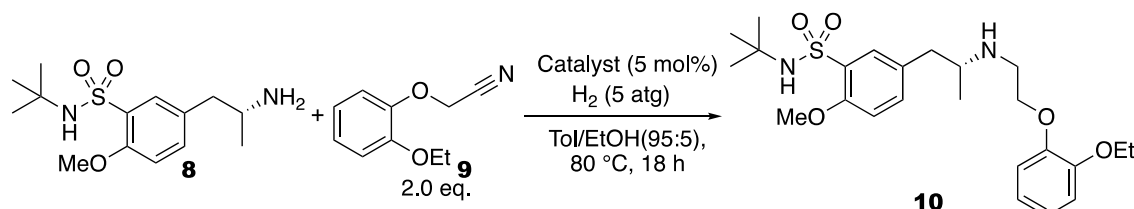
Subsequently, a two-step sequential-flow synthesis of compound (**8**) was conducted (Scheme 2.19). The reaction temperature for both the first and second reactions was 80 °C, allowing the sequential-flow reaction to be performed in a column packed with two catalysts. Amine (**8**) was obtained in 97% yield with 66% *ee*, and the catalysts kept their activities for more than 11 h.



Scheme 2.19. Sequential-flow Synthesis of Amine **8**

The third reaction involves the reductive amination reaction with the nitrile (**9**). Firstly, I examined this reaction with different catalysts (Table 2.7). To ensure a fair comparison of the catalyst activity, compound (**8**) was used after isolation by column chromatography in this stage. As mentioned in the introduction chapter, Pt/C catalyst catalyzed reductive amination with nitriles in a continuous-flow system was reported; however, the Pt/C catalyst gave the compound (**10**) in only 20% yield (entry 1). This low yield was mainly attributed to the installation of the sulfonamide part. Commercially available Rh/C catalyst, Ru/C catalyst, and Pd Lindlar catalyst did not perform well (entries 2-4), while the polysilane-Pd catalyst exhibited high activity in this reaction (entry 5).

Table 2.7. Reductive Amination with The Nitrile with Different Catalysts in Batch System



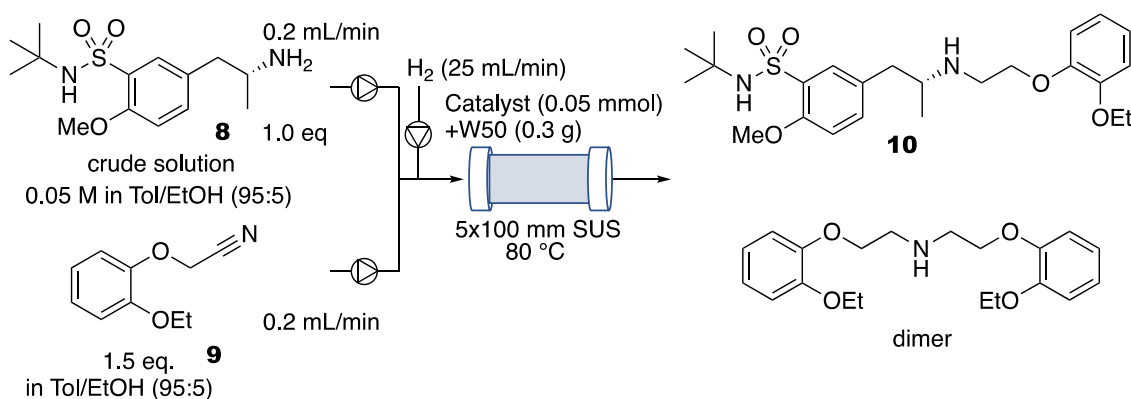
Entry	Catalyst	Yield (%) ^a
1	Pt/C	20
2	Rh/C	0
3	Ru/C	9
4	Pd Lindlar	trace
5	DMPSi-Pd/AC-CP (3:1)	45

^a Determined by ¹H NMR analysis

Then, I examined this reaction with different polysilane-Pd catalysts and a Pt/C catalyst in a continuous-flow system (Table 2.8, Figure 2.7). In this reaction, a dimer compound of the nitrile was formed as a byproduct, so even though the conversion of the nitrile was full, the product yields were not quantitative. Additionally, catalyst deactivation posed a significant issue. Two types of DMPSi-Pd/SiO₂ catalysts and Pt/C catalysts experienced

deactivation over time, while the DMPSi-Pd/AC-CP (3:1) catalyst and PhMePSi-Pd/SiO₂ catalyst maintained their activity. Considering both conversion and selectivity, the DMPSi-Pd/AC-CP (3:1) catalyst was identified as the optimal one for this reaction (entry 1).

Table 2.8. Reductive Amination with The Nitrile with Different Catalysts in Flow System



Entry	Catalyst	Yield (%) ^a	Dimer (%)	Reductant
1	DMPSi-Pd/AC-CP (3:1)	83-85	29-31	NaBH ₄
2	DMPSi-Pd/SiO ₂	83-74	20-11	NaBH ₄
3	DMPSi-Pd/SiO ₂	85-58	24-18	PCS
4	PhMePSi-Pd/SiO ₂	78-76	23-20	PhMePSi
5	Pt-C	55-52	25-35	-

^a Over 3 steps yield determined by ¹H NMR analysis

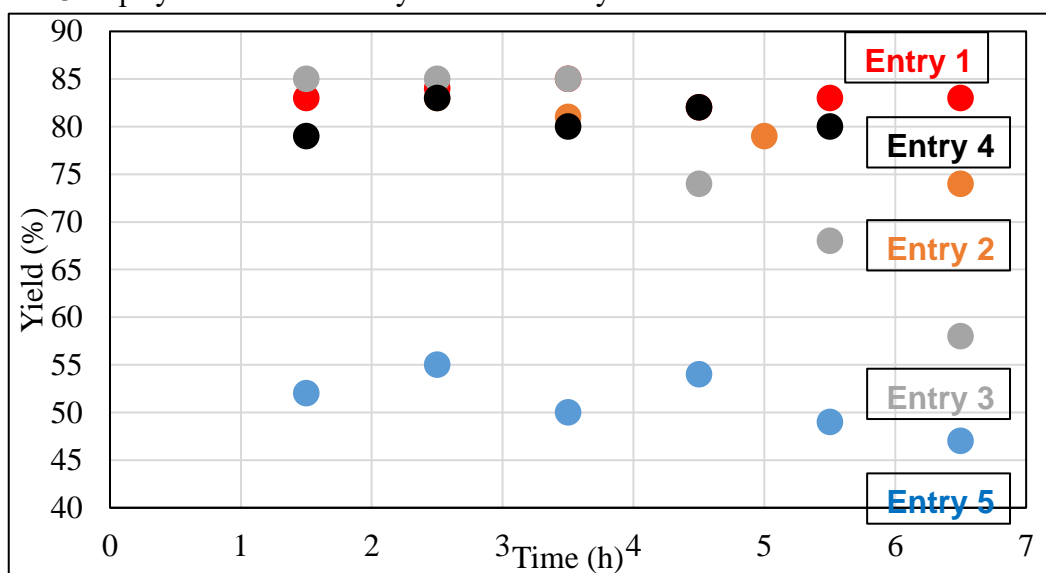
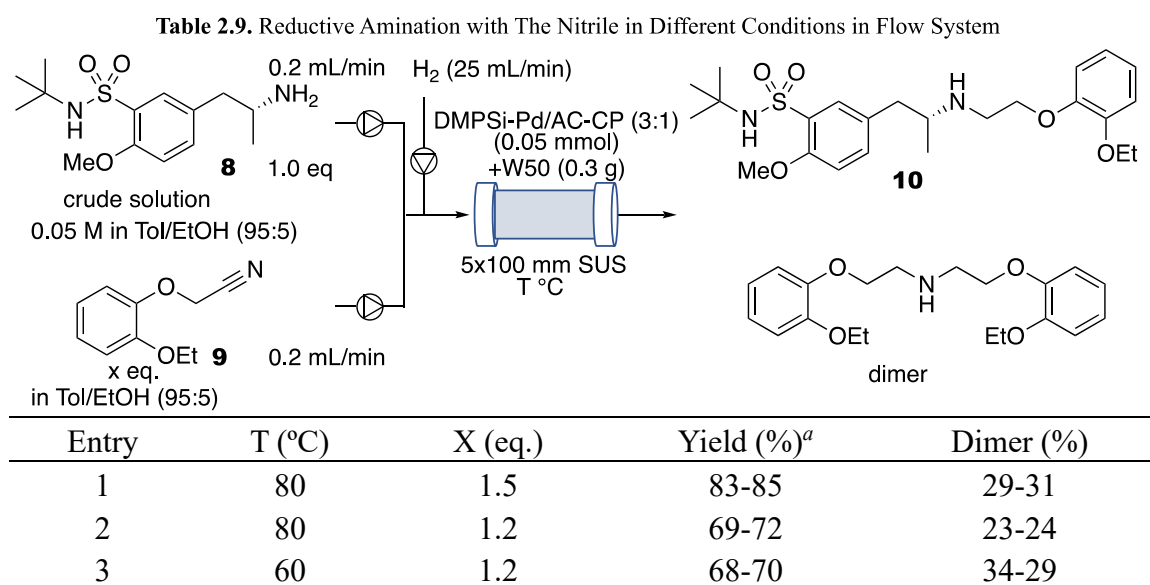


Figure 2.7. Reductive Amination with The Nitrile with Different Catalysts in Flow System

Then, I tried this reaction under different conditions in a continuous-flow system (Table 2.9, Figure 2.8). The decrease in the amount of nitrile resulted in a lower yield (entry 2). To suppress the byproduct formation, the reduced temperature was employed, however, it did not affect the yield and conversion of the nitrile so much (entry 3).



^a Over 3 steps yield determined by ¹H NMR analysis

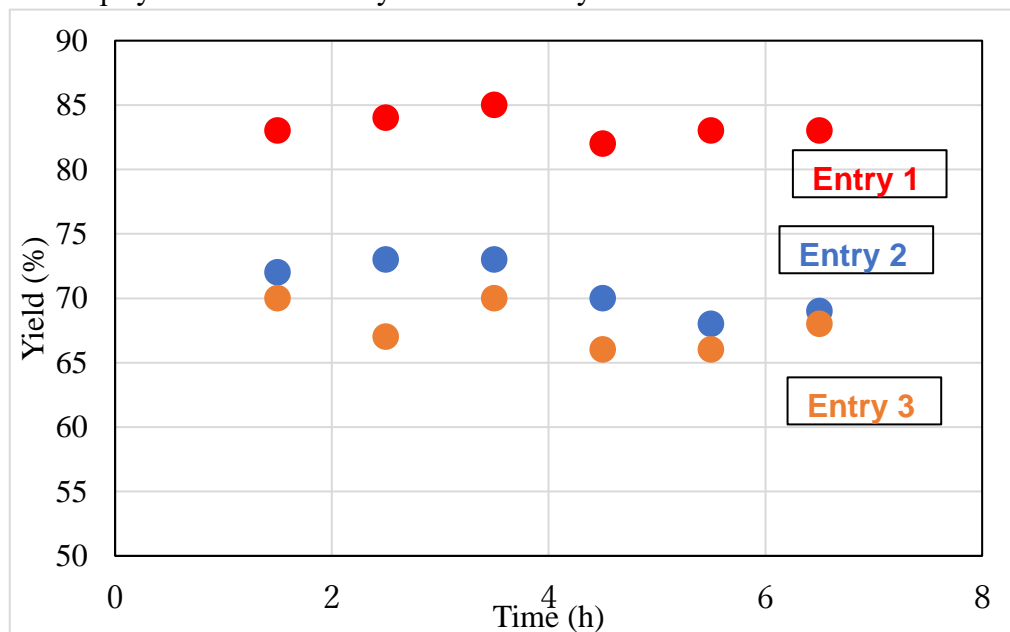
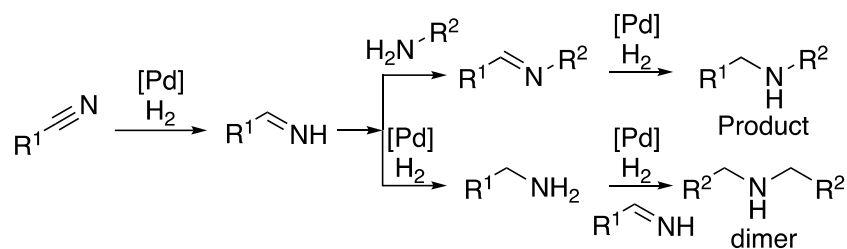


Figure 2.8. Reductive Amination with The Nitrile in Different Conditions in a Flow System

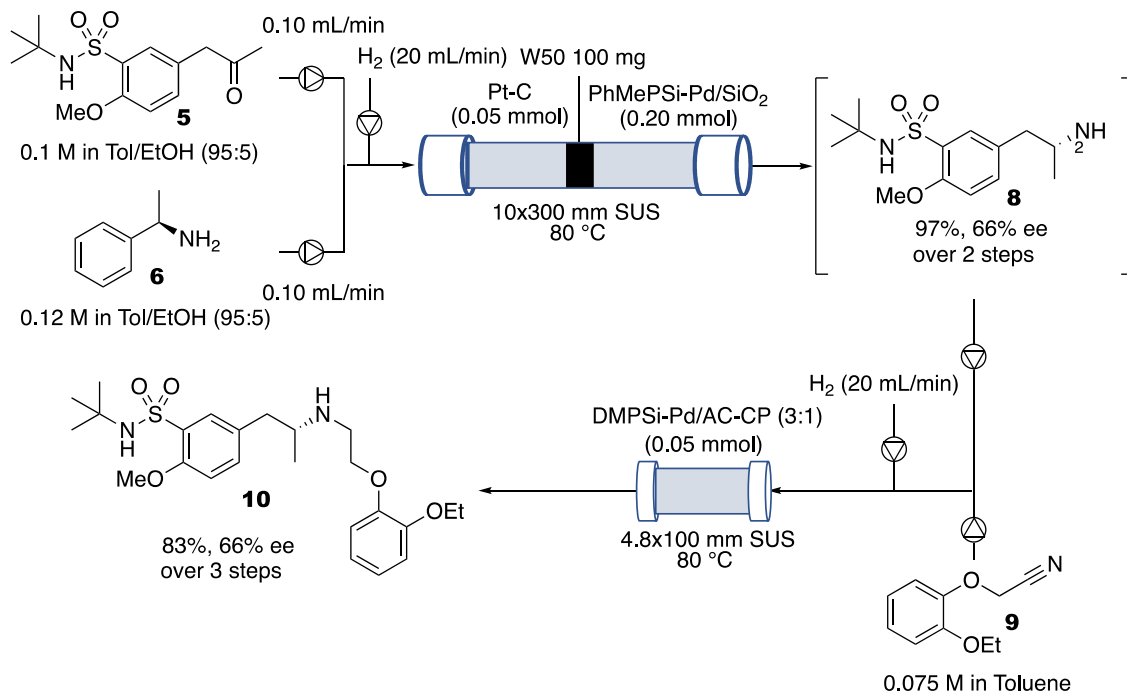
The proposed reaction mechanism for reductive amination with nitriles is shown here

(Scheme 2.20). At first, a nitrile is reduced to the imine, and then imine exchange with amine proceeds. Finally, newly formed imine undergoes reduction to afford the desired product. However, full reduction of the nitrile to primary amine also occurs, which reacts with the imine intermediate to form the dimer byproduct. According to Table 2.8, the amount of the dimer was constant even though the conversion of the amine (**8**) was low. I hypothesized that the simply active catalysts could reduce the nitrile, leading to a high yield.



Scheme 2.20. Proposed Reaction Mechanism of Reductive Amination with Nitriles

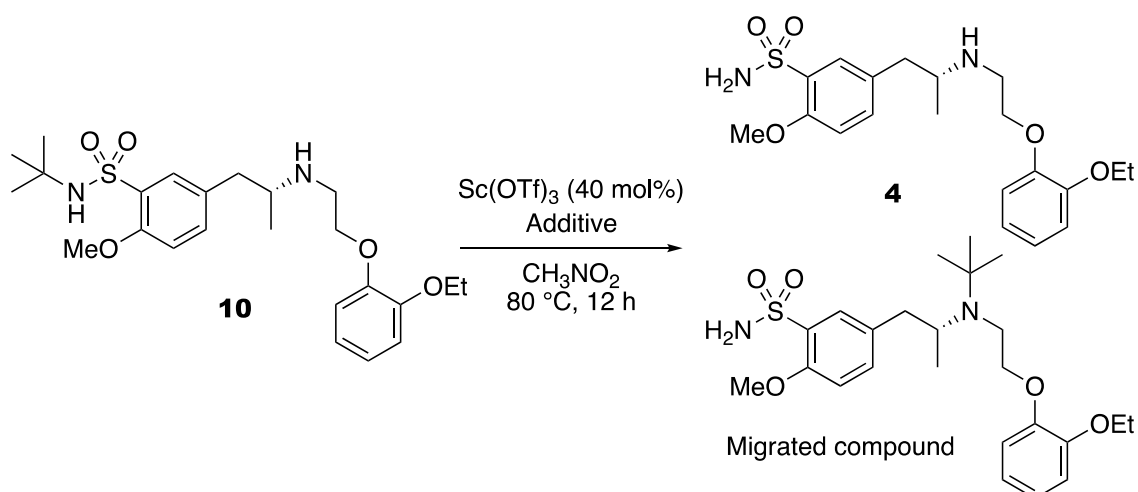
Having obtained the optimized conditions under continuous-flow methods, a three-step sequential-flow synthesis of compound (**10**) was carried out (Scheme 2.21). After the formation of amine (**8**) and H₂ output, reductive amination with nitrile (**9**) was performed without any isolation of intermediates, resulting in the production of compound (**10**) in 83% yield and 66% *ee*.



Scheme 2.21. Sequential-flow synthesis of amine **10**

Previously, $\text{Sc}(\text{OTf})_3$ -catalyzed deprotection of the sulfonamide group was reported.⁶⁶ However, the reaction under these conditions gave a migrated compound (Table 2.10, entry 1). To suppress the nucleophilicity of the secondary amine part, MsOH was used, leading to the product in 92% yield (entry 2). In this stage, an isolated compound (**10**) was used. The reaction did not proceed at all in the absence of the catalyst (entry 3). Thus, both Lewis acid and Brønsted acid are necessary to get the desired product.

Table 2.10. Deprotection of sulfonamide part using isolated solution

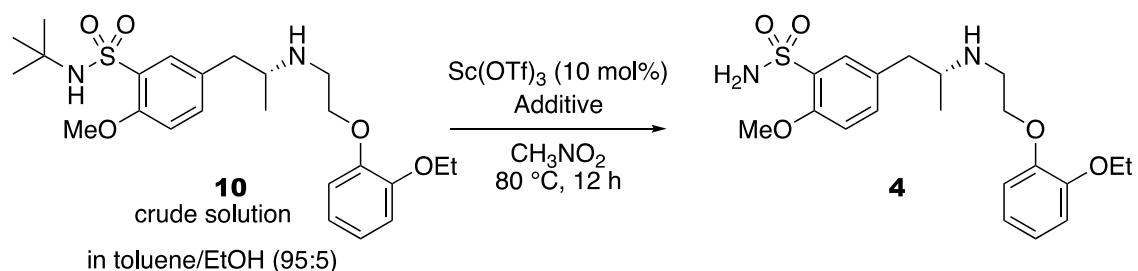


Entry	Additive	Yield (%)	Comment
1	-	0	Migration
2	MsOH (1.1 eq.)	92	
3	MsOH (1.1 eq.)	N.R.	Without $\text{Sc}(\text{OTf})_3$

^a Determined by ^1H NMR analysis

Then, I attempted this reaction using the crude solution (Table 2.11). The reaction with MsOH provided Tamsulosin in 67% yield over 3 steps yield (entry 1). In terms of the reaction time and Sc loading, TfOH was the most efficient acid (entry 3). After the column chromatography, Tamsulosin was obtained in 60% yield over 4 steps.

Table 2.11. Deprotection of sulfonamide part using crude solution



Entry	Additive	Reaction time (h)	Yield (%) ^a
1 ^b	MsOH (1.1 eq.)	12	67
2	MsOH (1.1 eq.)	3	5
3	TfOH (1.1 eq.)	3	72 (60) ^c

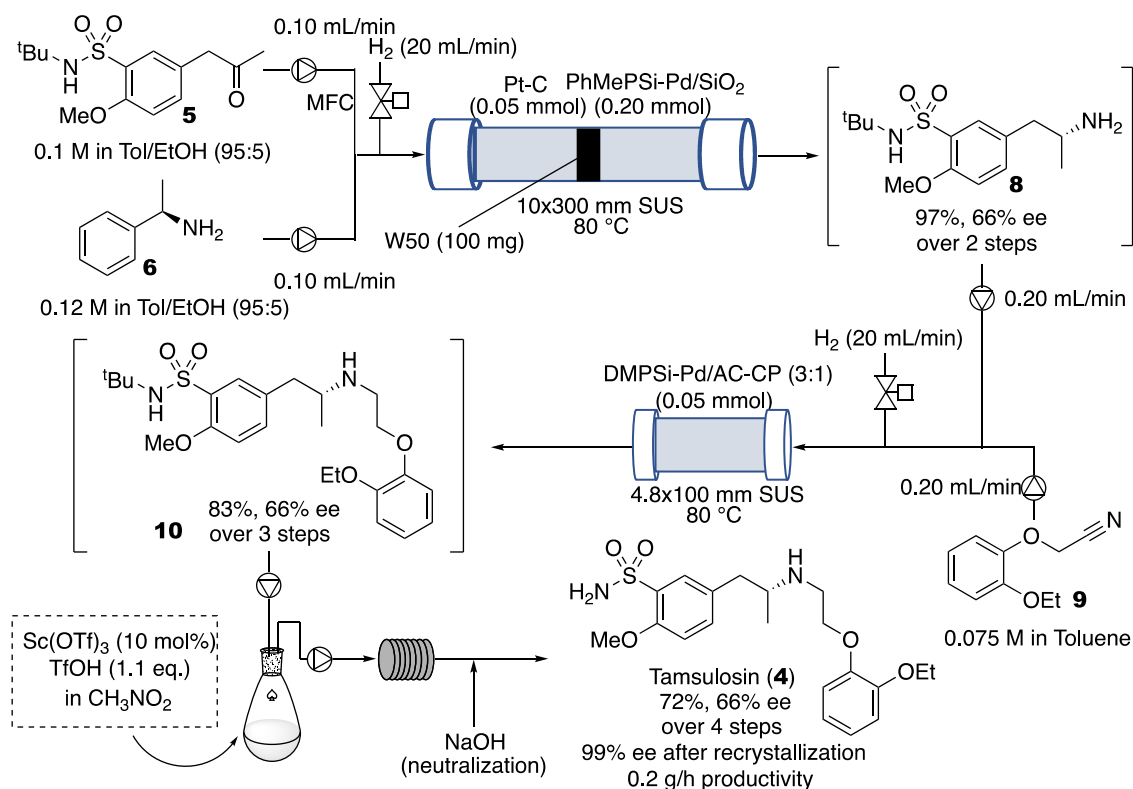
^a Over 4 steps yield determined by ¹H NMR analysis

^b 40 mol% Sc was used

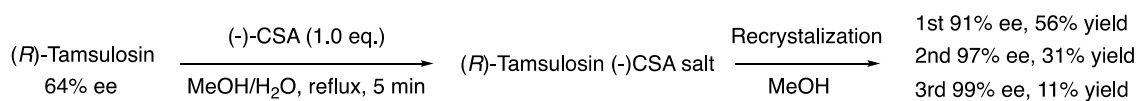
^c Isolated yield over 4 steps

A four-step sequential-flow synthesis of Tamsulosin was conducted (Scheme 2.22). After amine (**7**) was obtained, the crude solution was treated with Sc(OTf)₃ and TfOH in CH₃NO₂. The amount of these reagents was determined by estimating the concentration of amine (**7**). The substrate solution was flowed to a five meters coil reactor heated at 95 °C to afford Tamsulosin in 72% yield with 66% *ee*.

Making diastereomeric salt increased *ee* to 99% through 3 times recrystallization (Scheme 2.23).



Scheme 2.22. Sequential-flow Synthesis of Tamsulosin



Scheme 2.23. Recrystallization using (*R*)-Tamsulosin (-)-CSA salt

2.3 Sequential-flow Synthesis of Carvedilol Precursor

Carvedilol is an API utilized to treat high blood pressure and heart failure (Figure 2.9). It is also employed after a heart attack to improve the chance of survival if a human's heart is not pumping well. In this work, I decided to try sequential-flow synthesis of racemic Carvedilol.

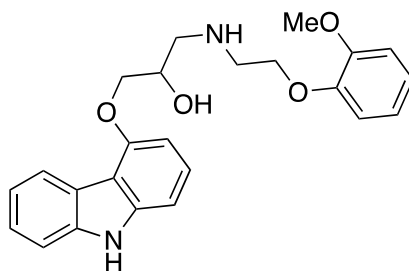
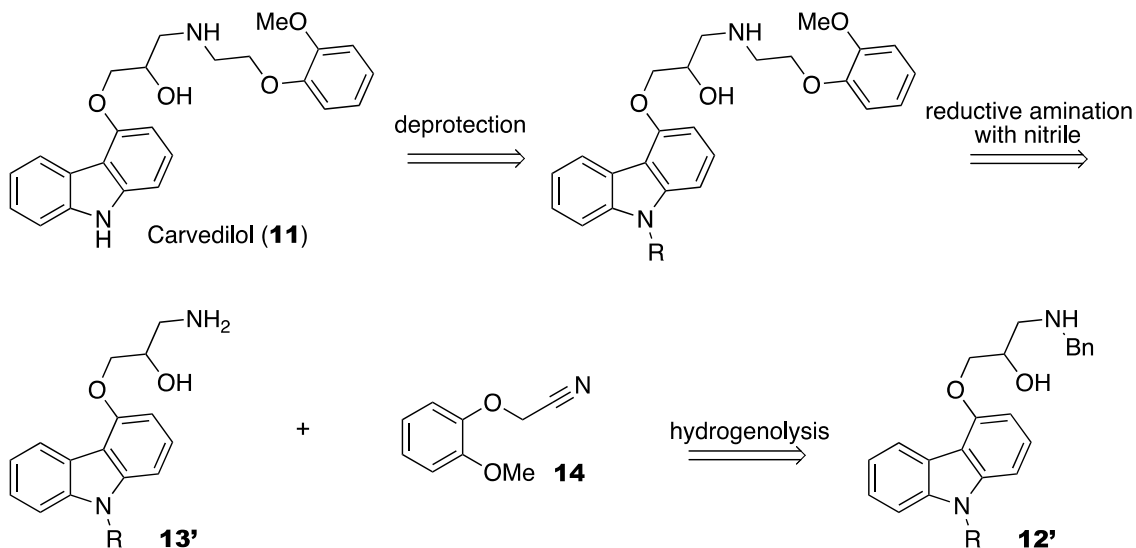


Figure 2.9. Carvedilol

I designed a retrosynthetic analogy for Carvedilol using a hydrogenolysis reaction and reductive amination with a nitrile reaction (Scheme 2.24). To increase the solubility of the substrates, the N-atom of the carbazole group needed to be protected. A compound (**15'**) could be formed by reductive amination with nitrile (**14**). A hydrogenolysis reaction would give a primary amine (**13'**) from an amine (**12'**). As a result, the Boc group was employed as a protecting group.

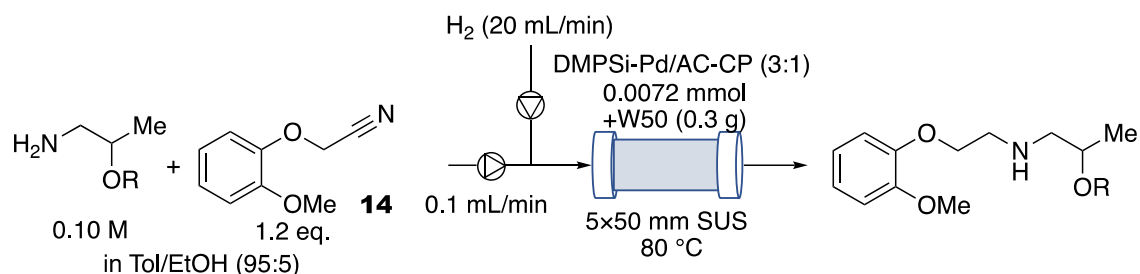


Scheme 2.24. Retrosynthetic Analogy for Carvedilol

Before starting the synthesis of Carvedilol, the coupling reaction of protected or non-protected α -amino alcohol and nitrile (**16**) was used in a model reaction (Table 2.12, Figure 2.10). Under optimized conditions, the presence of free alcohol decreased

reactivity (entry 1). This was mainly due to the byproduct formation. The alcohol might attack the imine intermediate, which can form an unstable five-membered ring intermediate. TMS-protected amino alcohol did not work well due to O–Si bond cleavage (entry 2). Finally, I found that TES-protected amino alcohol was tolerated in this reaction (entry 3).

Table 2.12. Reductive Amination with Amino Alcohol



Entry	R	Yield (%) ^a
1	H	43-45
2	TMS	20-51
3	TES	84-86

^a Determined by ¹H NMR analysis

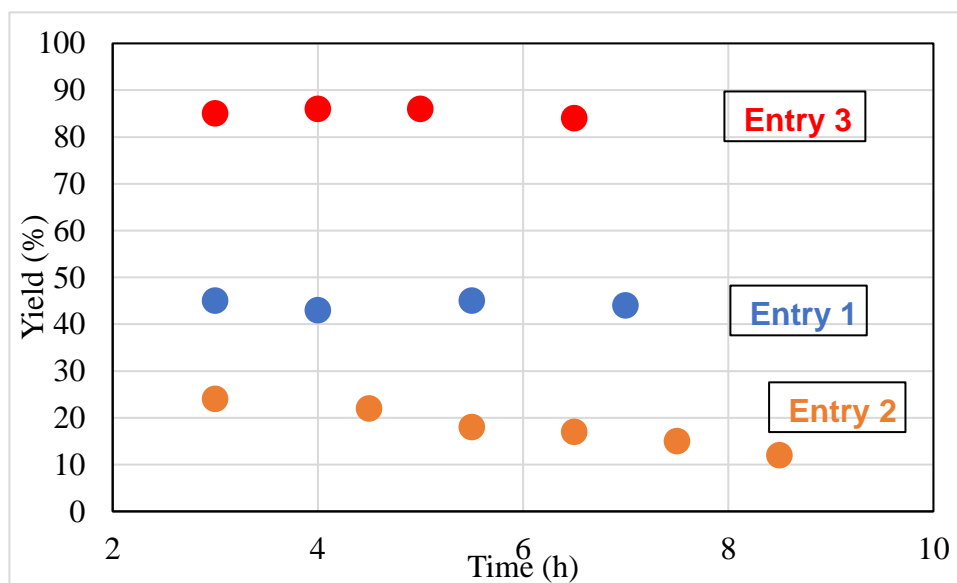
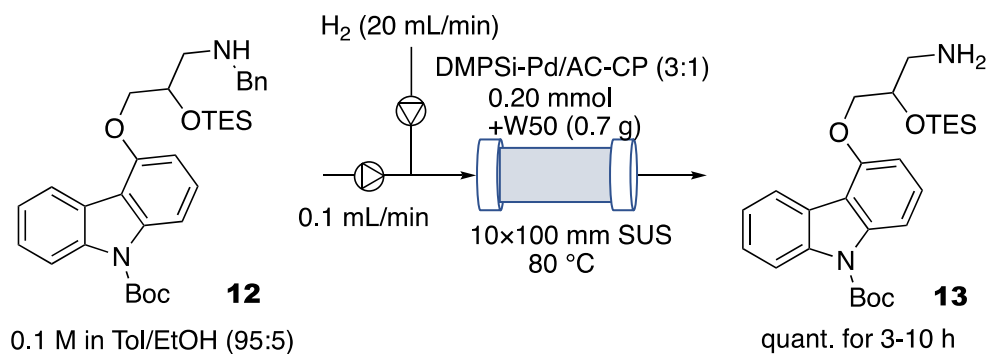


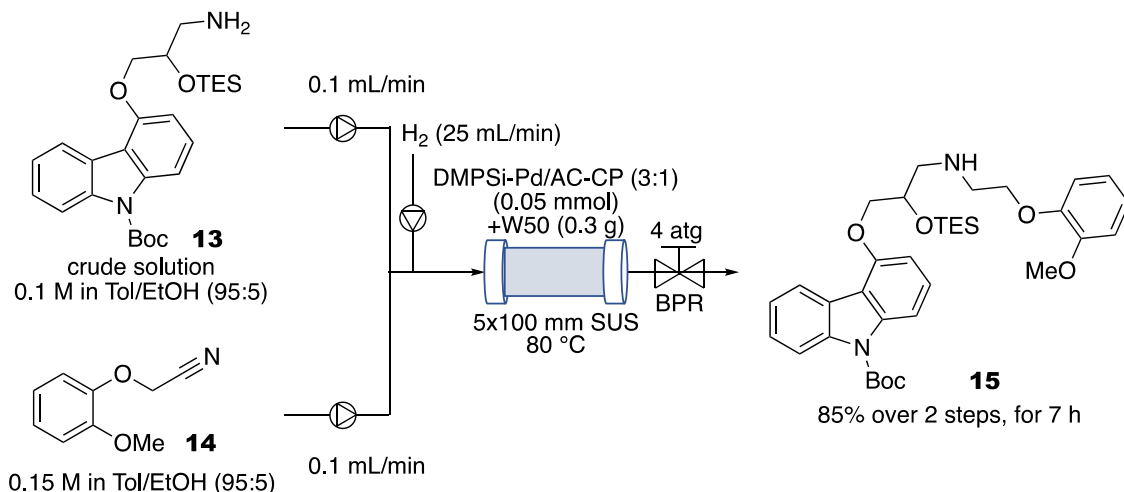
Figure 2.10. Reductive Amination with Amino Alcohol

From the results of the model reactions, I modified the synthetic route, and after compound (13) was obtained, I conducted a hydrogenolysis reaction in continuous-flow methods (Scheme 2.25). The PhMePSi-Pd/SiO₂ catalyst, which was the best in Tamsulosin synthesis, resulted in the removal of the Boc group at the same time due to

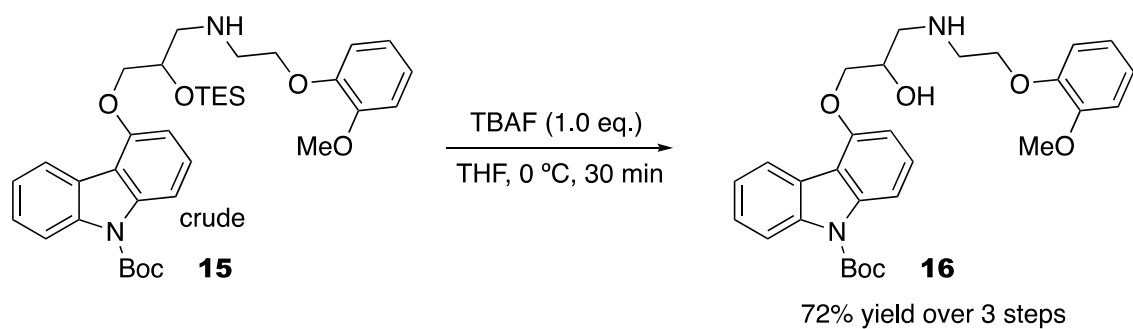
its surface acidity. The mechanism how the acidity was realized in PhMePSi-Pd/SiO₂ catalyst is still unclear. On the other hand, DMPSi-Pd/AC-CP (3:1) catalyst afforded the desired compound (**13**) in quantitative yield for 10 h.



In the second step, reductive amination with nitrile (**14**) was conducted in a continuous-flow method using the crude solution (Scheme 2.26). Although high pressure and a significant catalyst loading were necessary because the carbazole group worked as a catalyst poison, sequential-flow synthesis of compound (**15**) was achieved in 85% over a two-step yield.

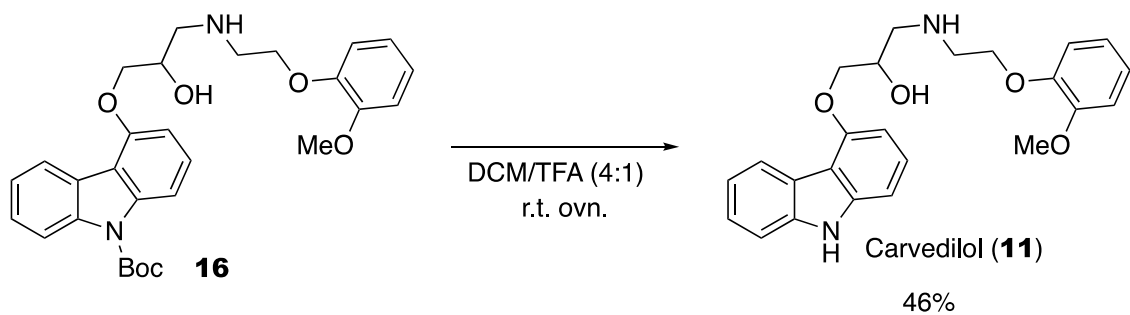


Since I obtained compound (**15**), I tried two-step deprotection reactions. Firstly, alcohol deprotection by TBAF was tried using crude starting material, and the desired compound (**16**) was obtained in 72% yield over 3 steps (Scheme 2.27).



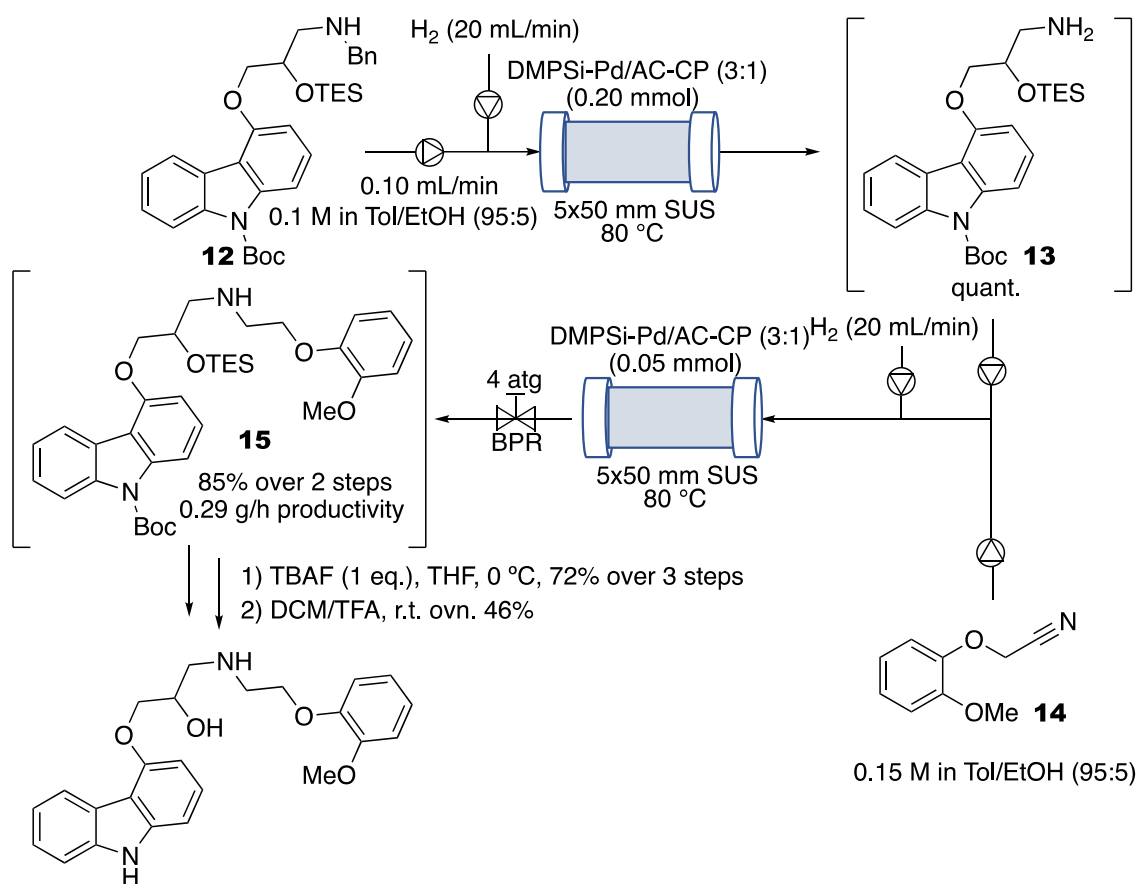
Scheme 2.27. Deprotection of Alcohol

After isolation, deprotection of amine was performed in DCM/TFA conditions to afford Carvedilol in 46% yield (Scheme 2.28).



Scheme 2.28. Deprotection of Amine

In summary with this synthesis, I achieved a sequential-flow synthesis of Carvedilol precursor (**15**) containing hydrogenolysis and reductive amination with a nitrile without any isolation of intermediates. Moreover, Carvedilol was obtained by performing two steps of deprotection in a batch system (Scheme 2.29).



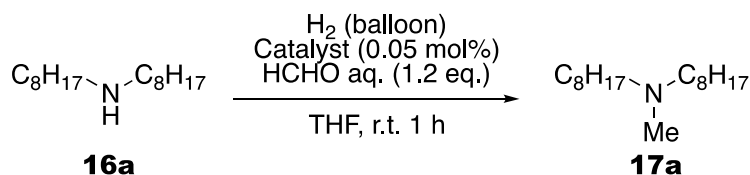
Scheme 2.29. Sequential-flow Synthesis of Carvedilol Synthesis

2.4 Reductive N-Methylation of Amines

Recently, advancements have been made in catalytic N-methylation, utilizing various species as C1 sources, including carbon dioxide, methanol, and DMSO.^{67,68} However, the reported reactions using these species have typically demanded high temperatures, elevated pressure, UV irradiation, and the inclusion of stoichiometric amounts of additives such as base or reductant. In contrast, N-methylation with formaldehyde presents a promising avenue due to its potential for milder reaction conditions compared to other electrophiles. So far, there are a few examples of heterogeneous catalysts, which enabled N-methylation with formaldehyde.^{69,70,71,72} However, high temperature and pressure are still required, and all the reactions were performed in batch conditions. I hypothesized that the use of highly active heterogeneous catalysts would achieve continuous-flow reductive N-methylation with formaldehyde in milder conditions.

At first, I screened the catalysts for reductive N-methylation of amines with formaldehyde and hydrogen. Formalin aqueous solution was chosen as the formaldehyde source due to its solubility in organic solvents, unlike paraformaldehyde, and its higher reactivity compared to 1,3,5-trioxane. Among the metals tested on carbon, the Pd/C catalyst exhibited a 36% product yield, whereas Pt, Rh, Ru, and Ir on carbon did not produce the desired outcome. (Table 2.13, entries 1-5). Then, I used DMPSi-Pd/AC-CP (3:1) catalyst, and the yield was increased to 48% (entry 6). It was found that both metal and support were important (entries 7,8). Finally, 89% product yield was obtained when the reaction time was prolonged to 5 hours.

Table 2.13. Catalyst Evaluation for Reductive N-Methylation under Batch Conditions



Entry	Catalyst	Yield (%) ^a
1	Pd/C	36
2	Pt/C	< 5
3	Rh/C	< 5
4	Ru/C	N.D.
5	Ir/C	N.D.
6	DMPSi-Pd/AC-CP (3:1)	48
7	DMPSi-Pt/AC-CP (3:1)	13
8	PhMePSi-Pd/SiO ₂	8
9 ^b	DMPSi-Pd/AC-CP (3:1)	89

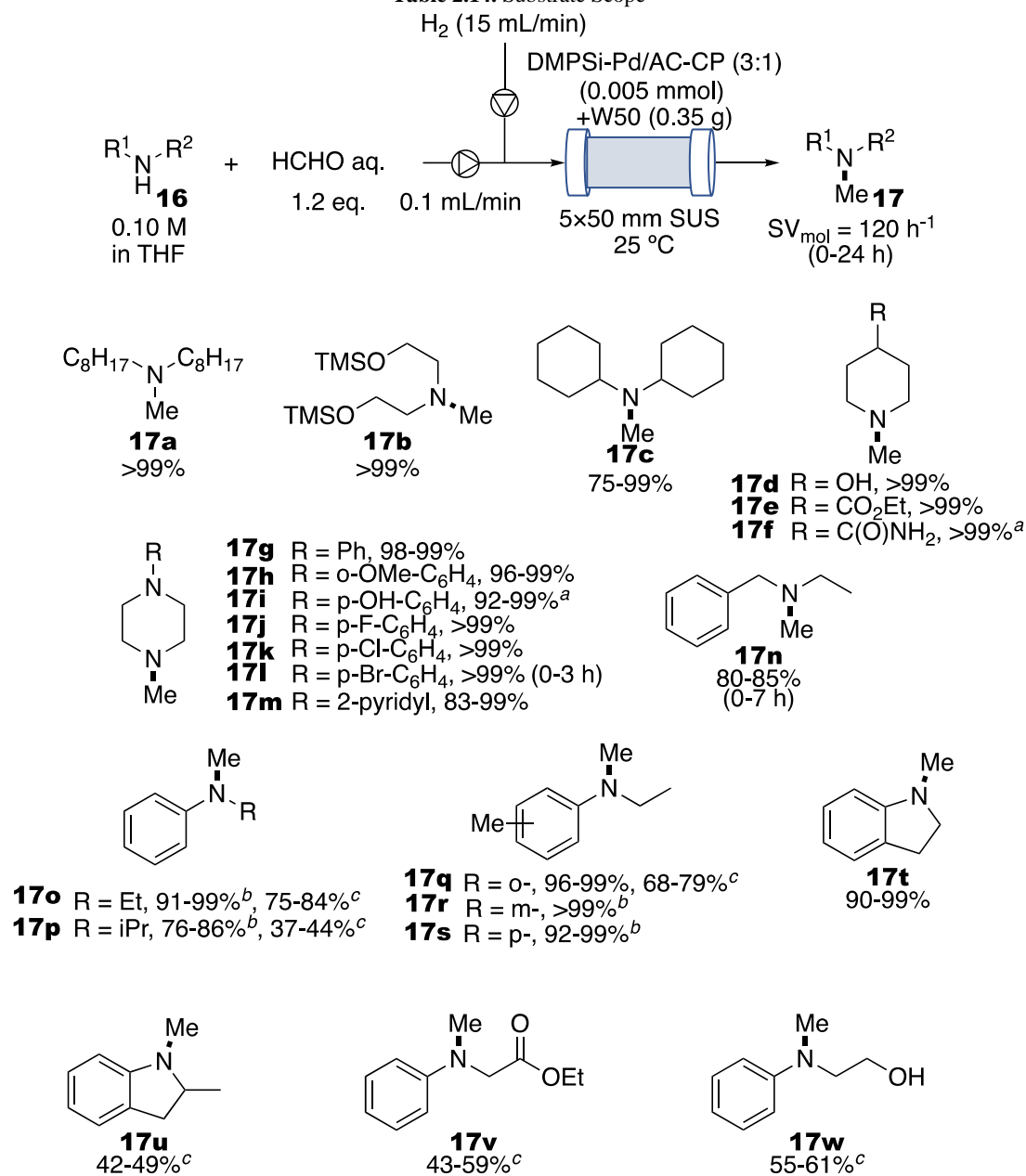
^a Determined by ¹H NMR analysis

^b Reaction was performed for 5 h

After obtaining the optimized conditions in hand, substrate generality was examined in a batch system (Table 2.14). First, a variety of aliphatic amines were tested. Amine (**16a**) and TMS ether (**16b**) were tolerated in this reaction to give the corresponding compound in quantitative yield. Sterically hindered amine (**16c**) was converted to a tertiary amine (**17c**) in relatively low yield due to the difficulty of the hydrogenation step. Then, cyclic amines were also tested. 4-substituted piperidines (**17d-f**) were afforded quantitatively. In addition, 4-substituted piperazine (**16g-m**) was successfully methylated in excellent yield. To my delight, N-ethylbenzyl amine (**16n**) was tolerated in this reaction without hydrogenolysis of the benzyl group.

I investigated aniline derivatives for this flow reaction. Although 50 °C was necessary due to the low nucleophilicity of anilines, N-ethyl aniline (**16o**) smoothly reacted, and **17o** was afforded. On the other hand, sterically hindered ⁱPr substituted amine (**17p**) was less active than **16o**. The methyl substitution on the phenyl part did not change the reactivity in **17q-s**. Indoline derivative (**16t**) was also tested and the corresponding product (**17t**) was yielded in quantitative yield, while the yield of amine (**17u**) was moderate due to the neighboring methyl substituent. The anilines that have other functional groups such as ether and alcohol (**16v-w**) were applicable to give the products (**17v-w**) in moderate yield.

Table 2.14. Substrate Scope



^a THF/MeOH (1:1)

^b 50 °C,

^c 0.05 M, SV_{mol} = 60 h⁻¹

2.5 Sequential-flow Synthesis of Domiphen Bromide Precursor

Domiphen Bromide is a quaternary ammonium compound (Figure 2.11), which is used as a chemical antiseptic. It has the functions of disinfecting and sterilizing the oral cavity and the throat.

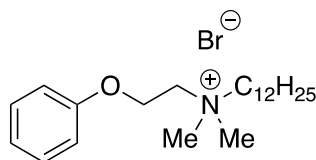
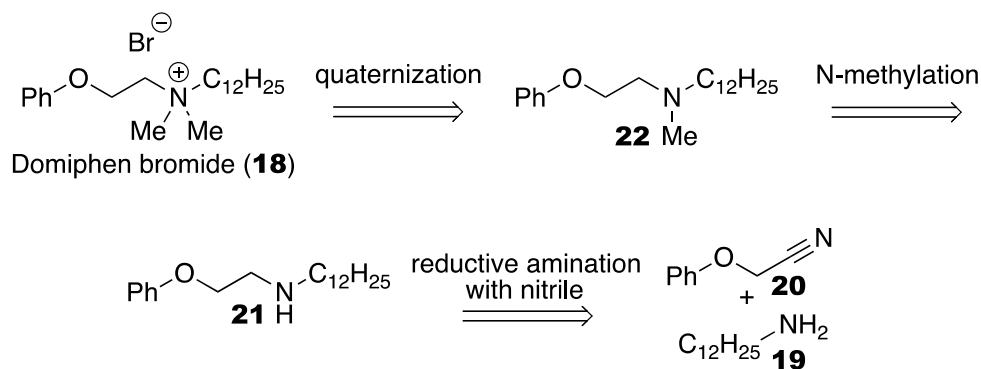


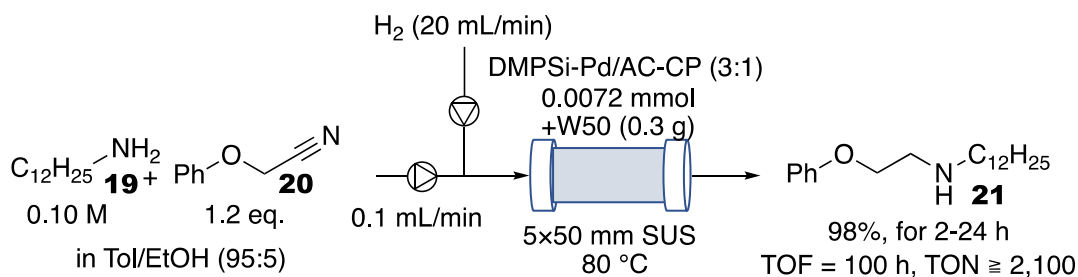
Figure 2.11. Domiphen Bromide

I designed a retrosynthetic analogy for Domiphen Bromide employing two different types of reductive amination (alkylation) reactions (Scheme 2.30). Quaternization could be performed by S_N2 reaction with bromomethane. Compound (**22**) would be obtained by reductive N-methylation with formaldehyde. Reductive amination with nitrile (**20**) would give compound (**21**). Direct conversion from compound (**21**) to (**18**) might be possible because the secondary amine has enough nucleophilicity, however, to avoid the use of an inorganic base, this route was designed.



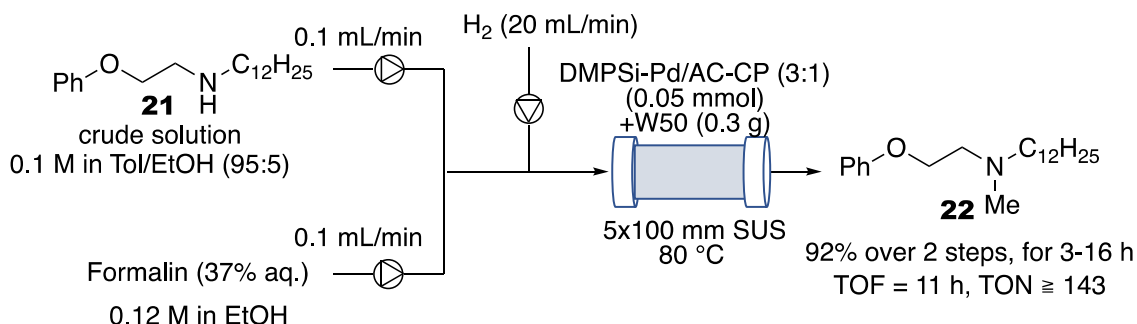
Scheme 2.30. Retrosynthetic Analogy for Domiphen Bromide

In the first step, I conducted the reductive amination reaction with nitrile (**20**) to obtain the secondary amine (**21**) in 98% yield for 24 h (Scheme 2.31). TOF and TON got to 100 /h and 2,100, respectively.



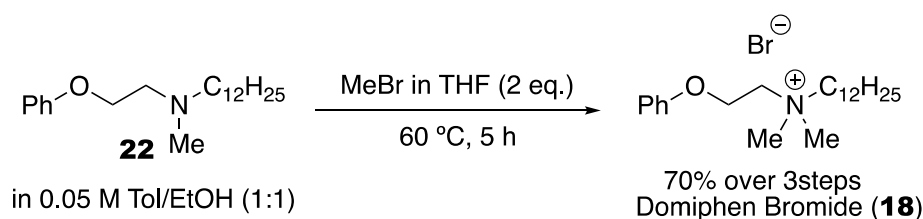
Scheme 2.31. Reductive Amination with Nitrile **20**

Then, this reaction was applied to a continuous-flow system to afford the product in 92% over 2 steps yield for 16 h, and TOF and TON reached 11 /h and 143, respectively (Scheme 2.32).



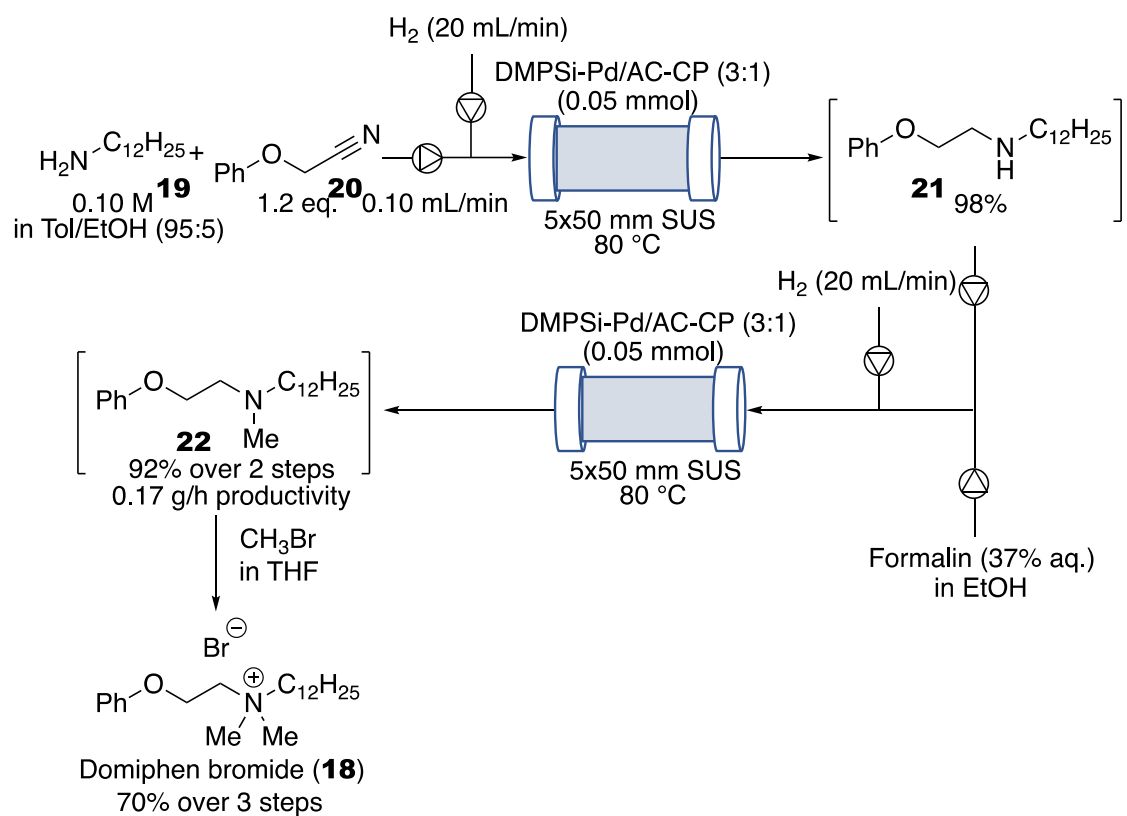
Scheme 2.32. Reductive N-Methylation of Amine **21** with Aqueous Formalin in Continuous-flow Methods

Finally, quaternization was performed by mixing solution (**22**) and bromomethane to give Domiphen Bromide in 70% over 3 steps yield using the crude solution (Scheme 2.33).



Scheme 2.33. Quaternization of amine **22** to Domiphen Bromide **18**

In summary of this synthesis, I could achieve a sequential-flow synthesis of Domiphen Bromide containing 2 steps of different types of reductive amination reactions without any isolation of intermediates (Scheme 2.34).



Scheme 2.34. Sequential-flow Synthesis of Domiphen Bromide

3. Conclusion

In summary, I have developed an efficient reductive amination reaction with nitriles in a continuous-flow system with DMPSi-Pd/AC-CP (3:1) identified as a highly active and robust catalyst. Dimethylpolysilane (DMPSi) can increase the activity and durability of the Pd nanoparticles due to the multiple interactions between nanoparticles and DMPSi. On the other hand, the effect of co-support was unclear in this thesis. The reaction exhibited substrate-dependence rates, with phenoxy-substituted nitriles demonstrating the highest yields. To showcase the versatility of the reaction, sequential-flow syntheses of three types of APIs were carried out.

For Tamsulosin synthesis, a four-step sequential-flow reaction was achieved without any isolation of intermediates including reductive amination with a ketone, hydrogenolysis of a phenethyl group, reductive amination with a nitrile, and deprotection of a sulfonamide. In the first step, reductive amination of the ketone with (*R*)-phenylethylamine as a chiral auxiliary was performed with Pt/C catalyst quantitatively. The second step, hydrogenolysis of a phenethyl group was the most challenging reaction in Tamsulosin synthesis. DMPSi-Pd/AC-CP (3:1) catalyst was deactivated in the early stage of the reaction. It was found that the newly developed PhMePSi-Pd/SiO₂ catalyst showed the highest durability, keeping its activity for more than 11 hours. The pre-mixing of Pd(OAc)₂ with silica support followed by the reduction by PhMePSi in preparation afforded the high Pd dispersion. Judging from the STEM analysis and EDS mapping, Pd NPs in PhMePSi-Pd/SiO₂ were supported by SiO₂, and the surface of Pd NPs was covered by PhMePSi, contributing to the high durability. In the third reaction, the reported Pt/C conditions for reductive amination with nitrile proved ineffective, whereas DMPSi-Pd/AC-CP (3:1) provided high yields. Tamsulosin with 99% *ee* was obtained after recrystallization.

In Carvedilol synthesis, two-step sequential-flow reactions were achieved utilizing hydrogenolysis of benzylamine and reductive amination with a nitrile.

For Domiphen Bromide synthesis, a two-step sequential-flow reaction includes reductive amination with a nitrile and reductive N-methylation. The combination of DMPSi-Pd/AC-CP (3:1) and an aqueous formalin solution proved effective for reductive N-methylation.

Chapter III : Solid-Acid Catalyzed Continuous-Flow Aminolysis of Epoxides and Application for Rivaroxaban Synthesis

本章については、5年以内に雑誌等で刊行予定のため、非公開。

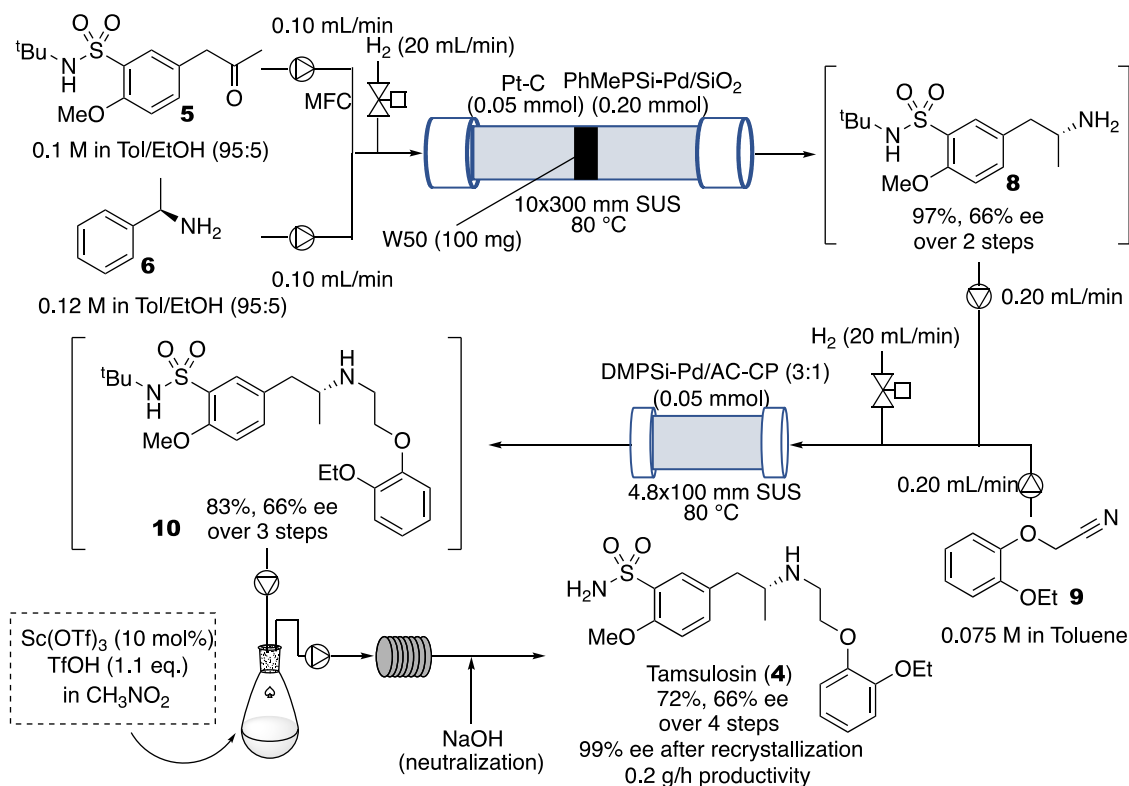
Chapter IV : Solid-Acid Catalyzed Continuous-Flow Aminolysis of Aziridines

本章については、5年以内に雑誌等で刊行予定のため、非公開。

Chapter V: CONCLUSION

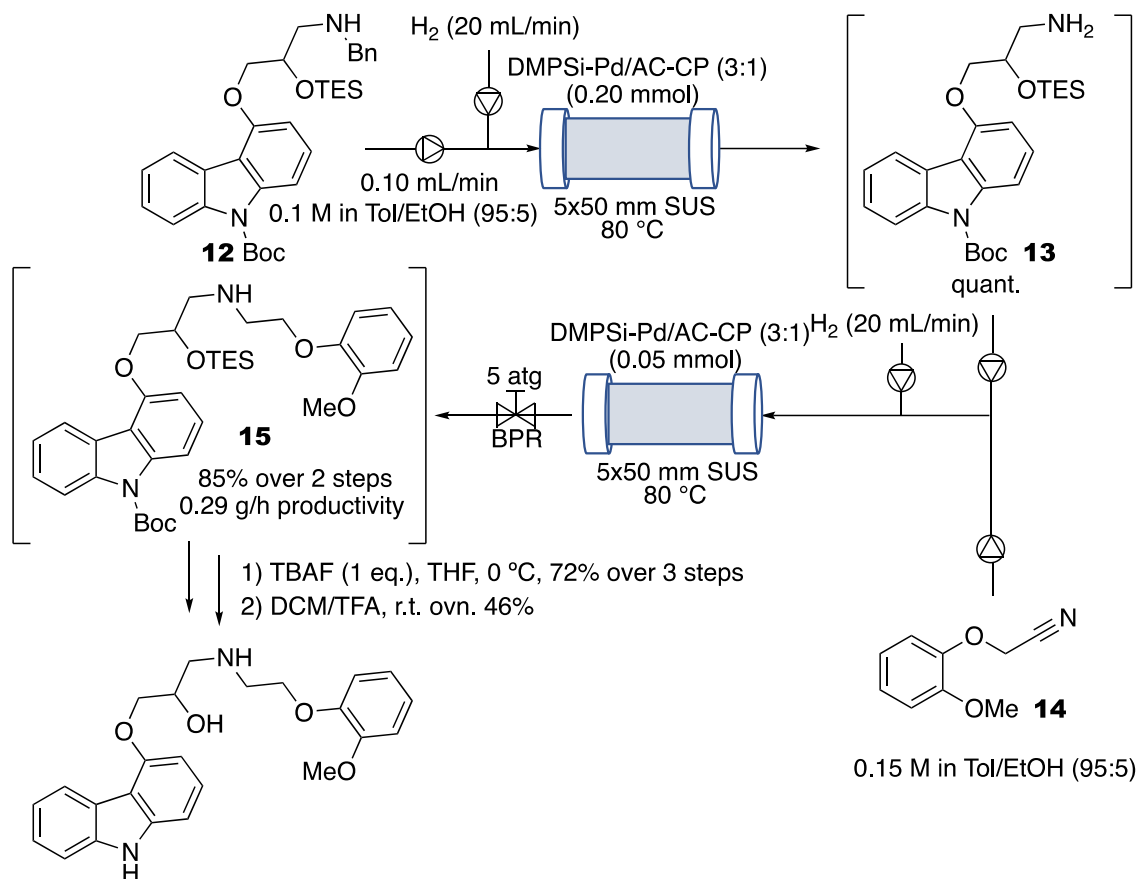
In this thesis, I developed C–N bond-forming reactions utilizing heterogeneous catalysts in a continuous-flow system. Focusing on reductive amination with nitriles, I sought a catalyst offering high yields and a clean reaction profile. Dimethyl-polysilane-palladium supported by activated carbon-calcium phosphate (3:1) outperformed both alternative metals (e.g., Pd/Al₂O₃, Rh/C) and other polysilane-type catalysts in terms of activity and selectivity. Notably, substrate scope studies in the flow system revealed a strong dependence of reactivity on nitrile structure: the absence of an α -oxygen atom and the presence of a phenyl group significantly decreased reaction rates. Recognizing the potential of highly reactive phenoxy nitriles to access α -amino ether motifs prevalent in APIs, I further explored sequential-flow syntheses of Tamsulosin, Domiphen Bromide, and Carvedilol using this reductive amination as a key step. These successful syntheses demonstrate the applicability of this continuous-flow methodology for efficient production of complex APIs.

Tamsulosin was successfully synthesized in a sequential flow process without the need to isolate intermediates (Scheme 5.1). The synthesis involved three sequential hydrogenation reactions and a deprotection reaction. After recrystallization, the enantiomeric excess (ee) was increased to 99%.



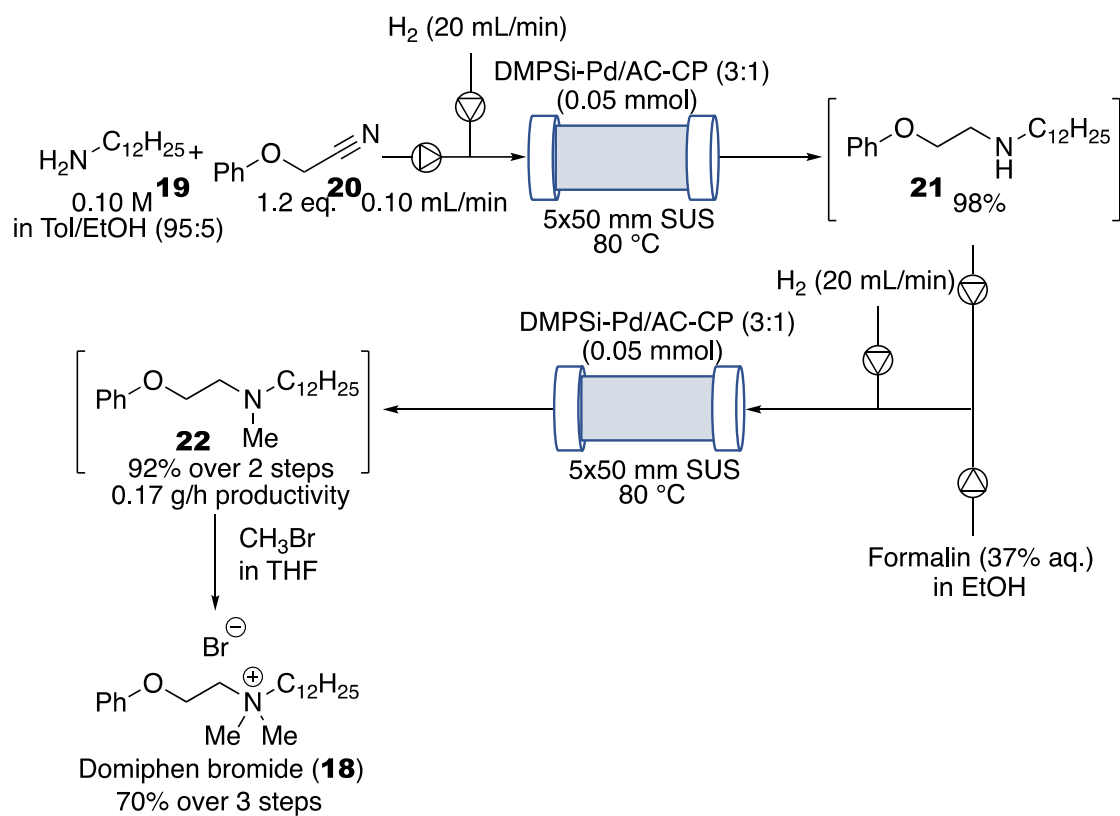
Scheme 5.1. Sequential-flow Synthesis of Tamsulosin

Carvedilol itself was difficult to synthesize in a sequential-flow process. Instead, the synthesis of its precursor was achieved (Scheme 5.2).



Scheme 5.2. Sequential-flow Synthesis of Carvedilol Synthesis

In the Domiphen Bromide synthesis, the reaction tolerated the presence of an amine with a long alkyl chain (Scheme 5.3). I have also developed a continuous-flow method for N-methylation of an amine with an aqueous formalin solution.



Scheme 5.3. Sequential-flow Synthesis of Domiphen Bromide

Chapter VI: EXPERIMENTAL DATA

General

- JEOL JNM-ECZ500R/M3 or ECX 600 spectrometers were used for NMR measurement. Tetramethyl silane (TMS) was used as an internal standard for ^1H -NMR ($\delta = 0$ ppm), and Deuterated chloroform was used for ^{13}C -NMR ($\delta = 77.36$ ppm). In NMR analysis using DMSO- d_6 as a solvent, DMSO served as an internal standard for ^{13}C NMR ($\delta = 40.4$ ppm). Structures of known compounds were confirmed by comparing them with data shown in literatures.
- IR spectra were measured using JASCO FT/IR-610 spectrometer.
- TG measurements were taken with a Thermoplus EVO2 TG-DTA8122.
- HPLC analysis was performed on Shimadzu LC-20AB, SPD-M20A, and DGU-20A3 with chiral columns from DAICEL Corporation.
- GC analysis was performed on a Shimadzu GC-2030 apparatus. Dodecan was used as an internal standard.
- TPD analysis was conducted with a Microtrac BETCAT II. Catalyst samples (ca. 50 mg) were pretreated at 200 °C for 3 h and cooled to room temperature under inert gas.
- The XRD patterns were recorded on a Rigaku Miniflex 300/600 diffractometer with Cu Ka ($\lambda = 0.15406$ nm) radiation at 40 kV and 40 mA.
- STEM/EDS images were obtained using a JEOL JEM-2100F instrument operated at 200 kV. All STEM specimens were prepared by placing a catalyst directly on carbon-coated copper grids.
- DART mass spectra were recorded on JEOL JMS-T100TD mass spectrometer.
- Preparative thin-layer chromatography was carried out using Wakogel B-5F.
- Solvents were purchased in anhydrous grade from Wako Pure Chemical Company. All the solvent was degassed by Freeze-Pump-Thaw cycle just before use.
- Plunger pump (Dual Pumps KP-22, Flom Inc.) and each size SUS column were used for flow reactions. All tubing were consisted of PTFE (ID 1.0 mm, OD 1/16 in.) tubes and appropriate fittings.
- CARiACT-Q10 was purchased from Fuji Silysia Chemical Ltd.
- Acetic anhydride, Activated carbon, Pt/C (5%), Calcium phosphate, and Ammonium Molybdate Tetrahydrate, 17% TiCl aqueous solution, $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$, and ammonium molybdate tetrahydrate were purchased from FUJIFILM Wako Pure Chemical Company.
- Dimethylpolysilane was purchased from Nippon Soda Co. Ltd.
- Phenylmethylpolysilane was purchased from Nippon Paint Co.
- Boc anhydride was purchased from Watanabe Chemical Industries. Ltd.
- 9H-Carbazol-4-ol was purchased from BLD pharm.
- 1-(2-pyridyl) piperazine was purchased from Oakwood Products Inc.
- 37% aqueous Formalin solution was purchased from Kokusan Chemical Co. Ltd.
- Scandium triflate was prepared according to the literature.⁹²

- Aziridines were prepared according to the literature.^{93,94}
- 2,2,2-Trifluoroethanol (TFE) was purchased from Apollo Scientific Ltd.
- All reagents, unless otherwise noted, were purchased from Tokyo Chemical Industry Co. Ltd.
- All commercially-available reagents, unless otherwise stated, were used without further purification.
- All reactions, unless otherwise stated, were carried out under argon atmosphere.

1. Experimental section in SECTION II

Catalyst preparation

Preparation of DMPSi-Pd/AC-CP (3:1)

To the mixture of activated carbon (3.38 g) and NaBH_4 (95.1 mg) in toluene (75 mL) and diglyme (7.5 mL), $\text{Pd}(\text{OAc})_2$ (0.1177 g) solution in THF (20 mL) was added dropwise at 0 °C. The resulting suspension stirred at room temperature for 30 min. Calcium phosphate (1.13 g) was added to the mixture and kept stirring for 30 min. 0.51 g of dimethylpolysilane was added to the mixture and the mixture was stirred another 30 min. 25 mL of methanol was added to the resulting mixture and the mixture was heated at 75 °C for 30 min. After the completion of the above operation, the mixture was filtered, and the resulting black powder was washed with acetone and water. Finally, the obtained material was dried under reduced pressure at 80 °C to get dimethylpolysilane-Pd on AC-CP catalyst (DMPSi-Pd/AC-CP).

Preparation of PhMePSi-Pd/SiO₂

To the solution of $\text{Pd}(\text{OAc})_2$ (0.1145 g) in toluene (75 mL), CARiACT Q-10 (4.487 g) was added. The resulting suspension stirred at room temperature for 30 min (until the liquid gets colorless). Phenylmethylpolysilane (0.499 g) in toluene (10 mL) was added dropwise to the mixture at 0 °C and kept stirring for 30 min at 0 °C. 25 mL of methanol was added dropwise to the resulting mixture and the mixture was heated at 75 °C for 30 min. After the completion of the above operation, the mixture was filtered, and the resulting black powder was washed with acetone and water. Finally, the obtained material was dried under reduced pressure at 80 °C to get phenylmethylpolysilane-Pd on SiO₂ catalyst (PhMePSi-Pd/SiO₂).

STEM and EDS mapping images of catalysts

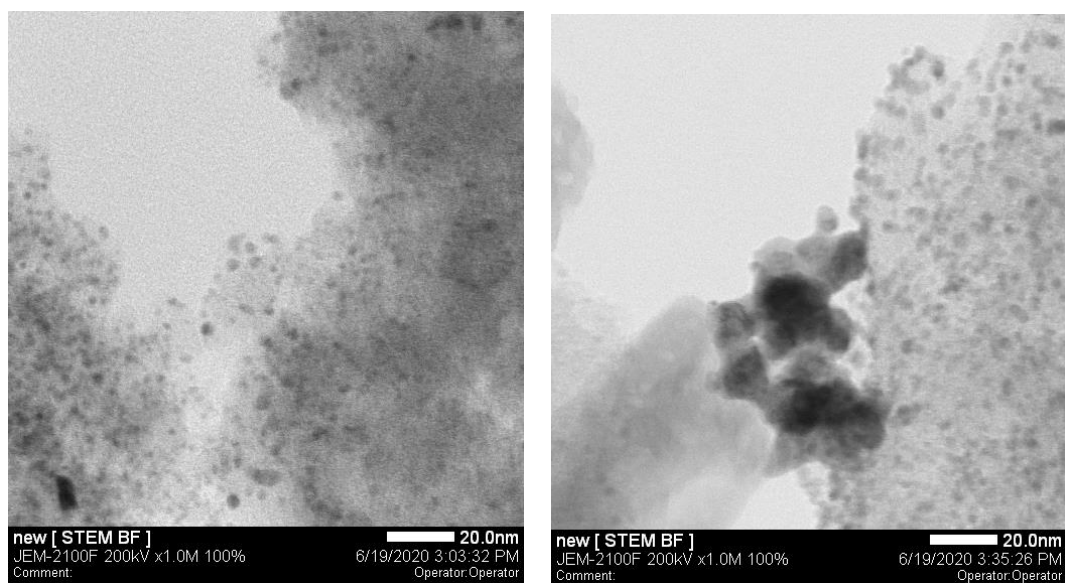


Figure S1. STEM images of DMPSi-Pd/AC-CP (3:1, two parts)

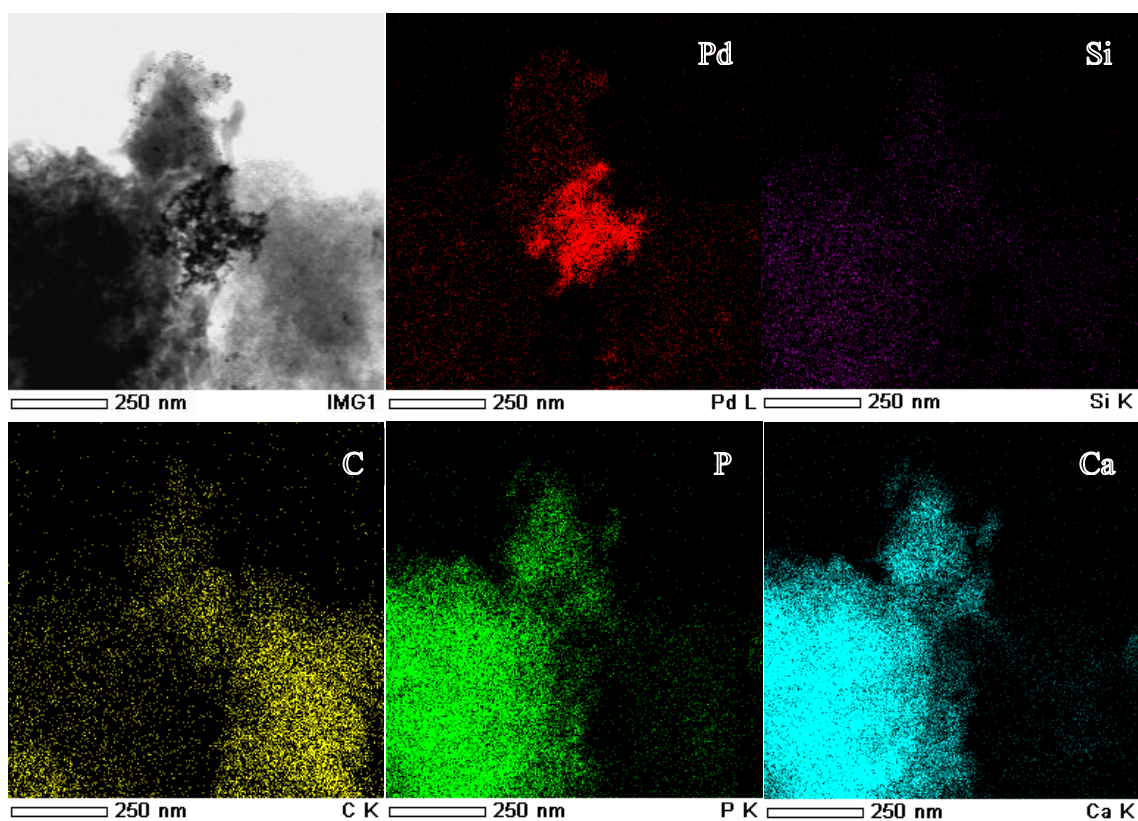


Figure S2. EDS mapping image of DMPSi-Pd/AC-CP (3:1)

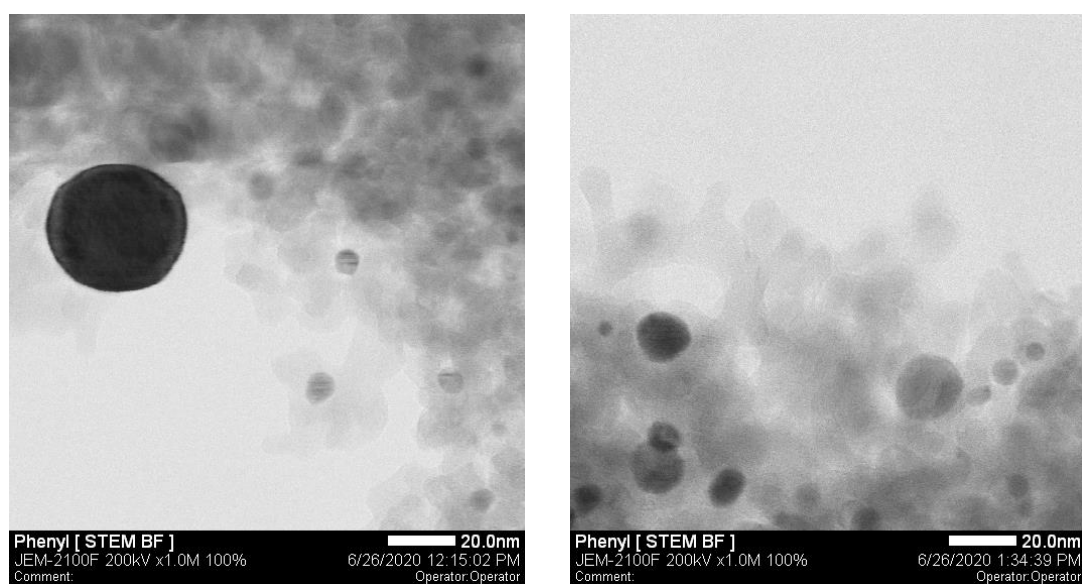


Figure S3. STEM images of PhMePSi-Pd/SiO₂ (two parts)

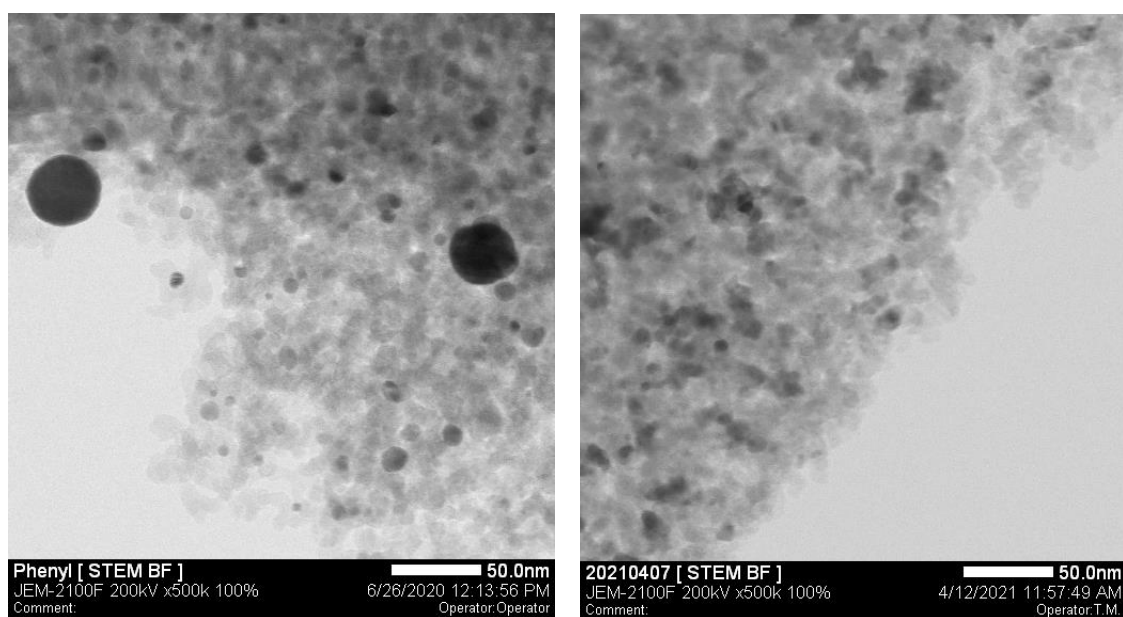
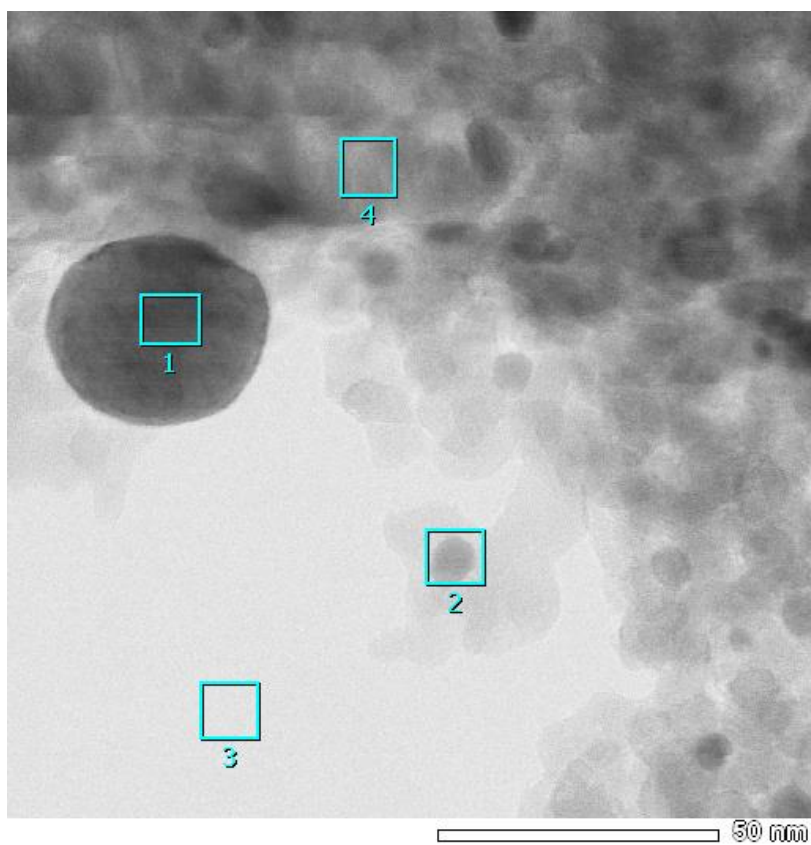
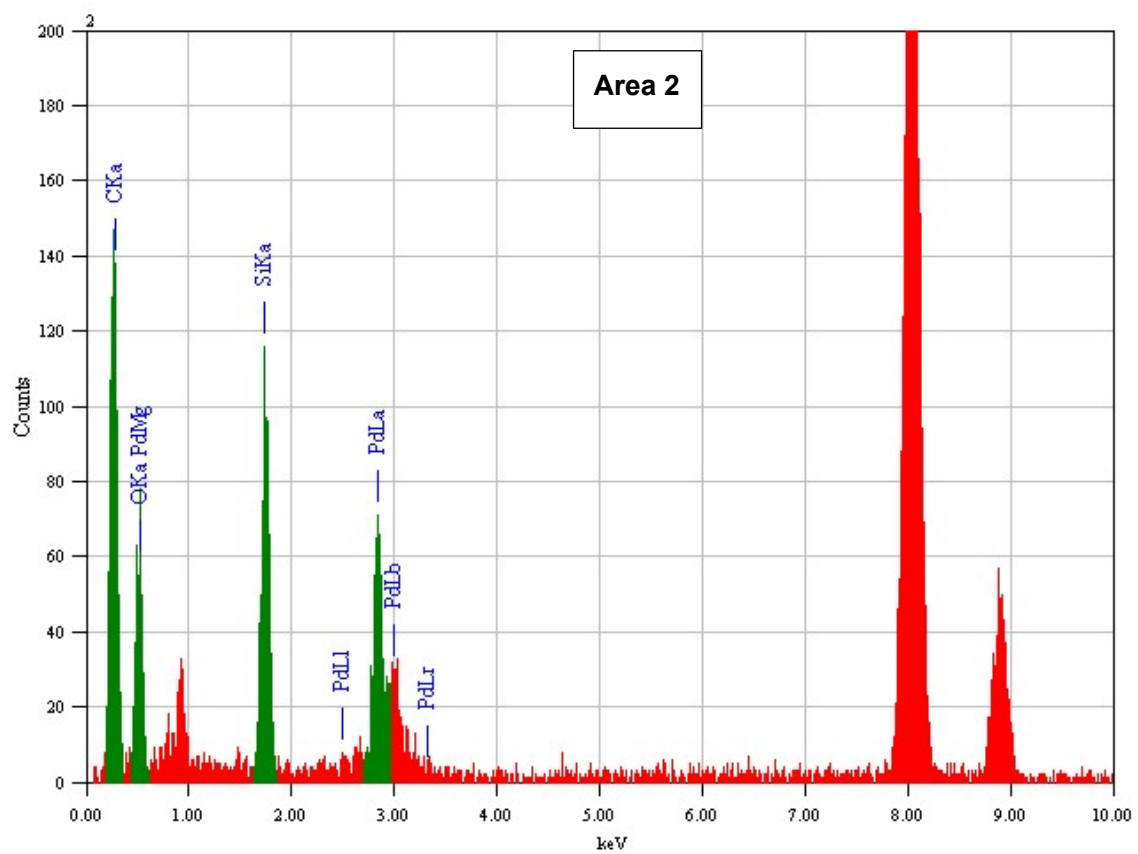
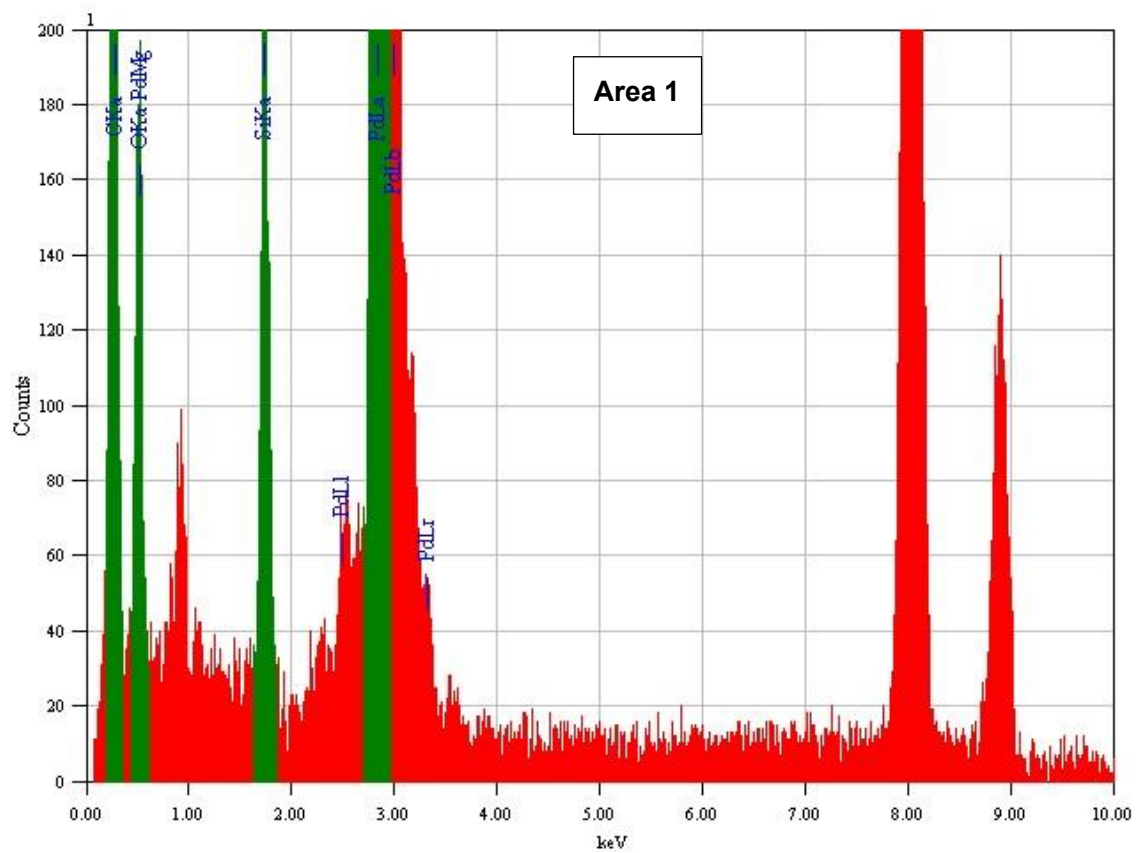


Figure S4. STEM images of PhMePSi-Pd/SiO₂ (the best catalyst for hydrogenolysis before usage (left) and after the flow reaction for 11h (right))





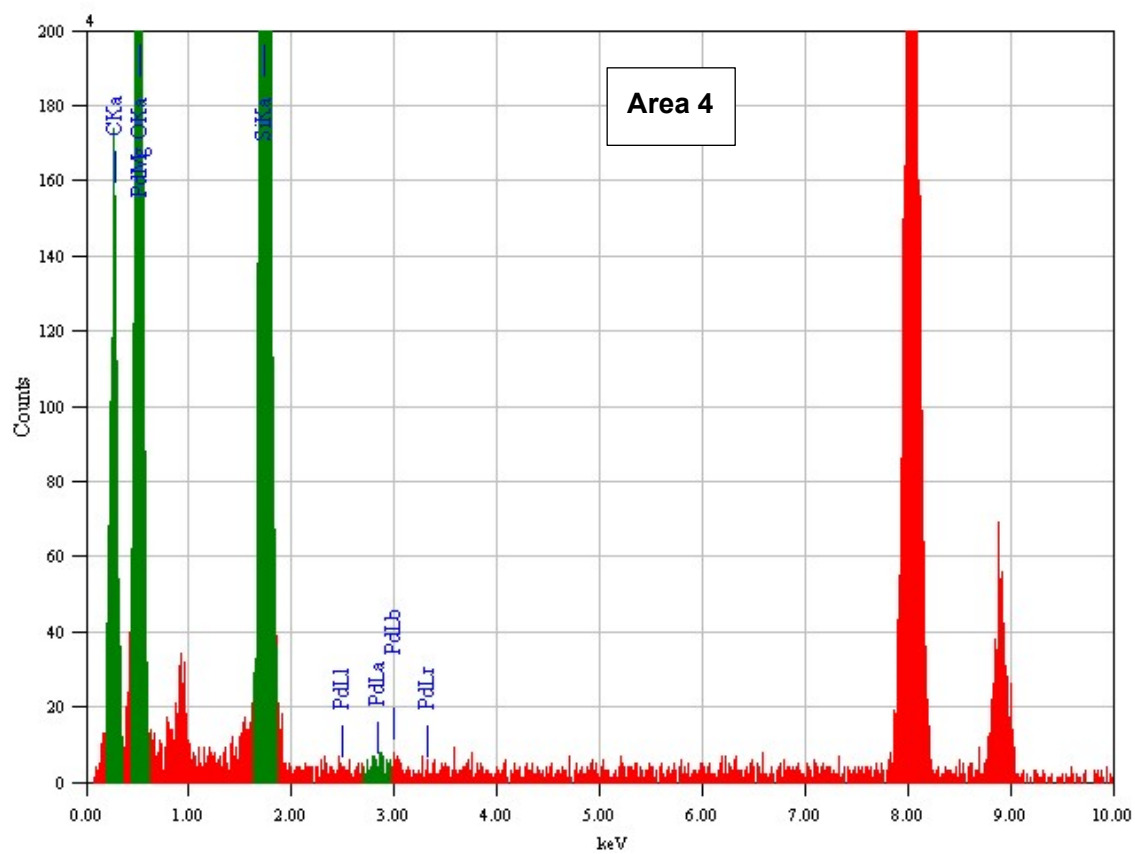
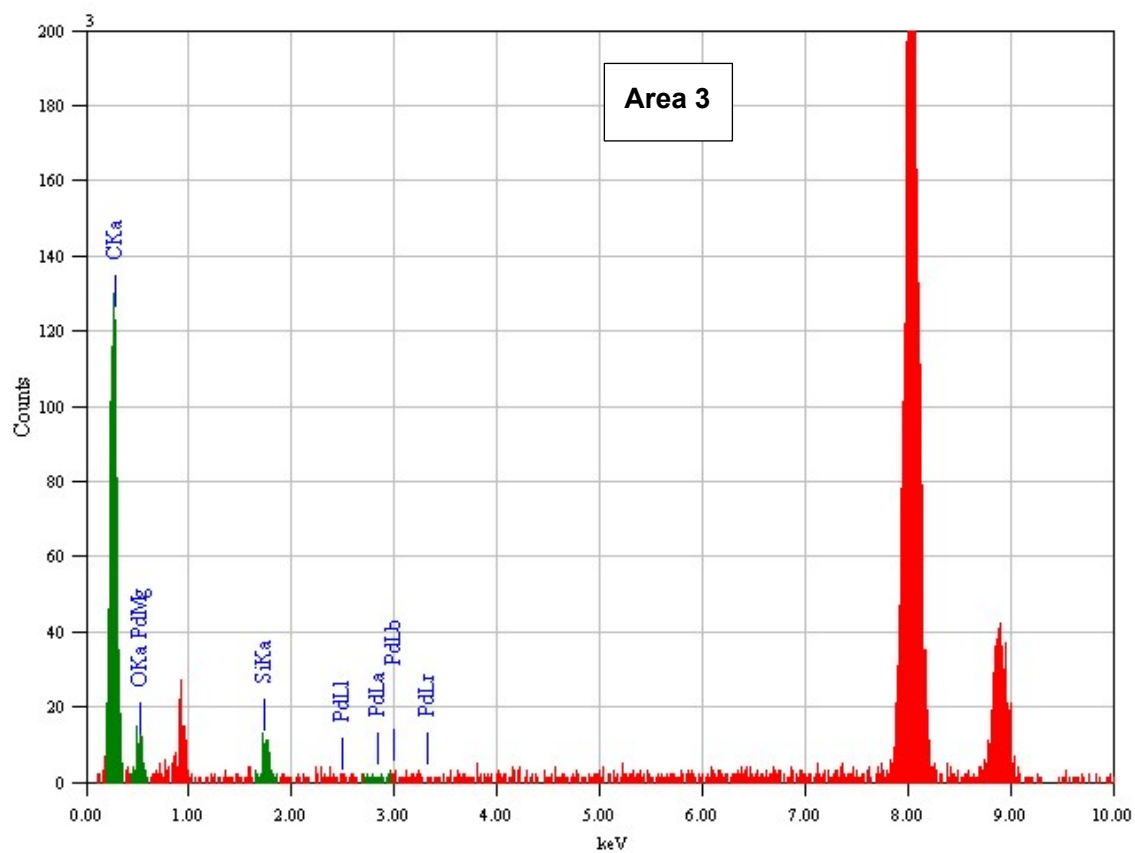


Figure S5. STEM Area Analysis of PhMePSi-Pd/SiO₂

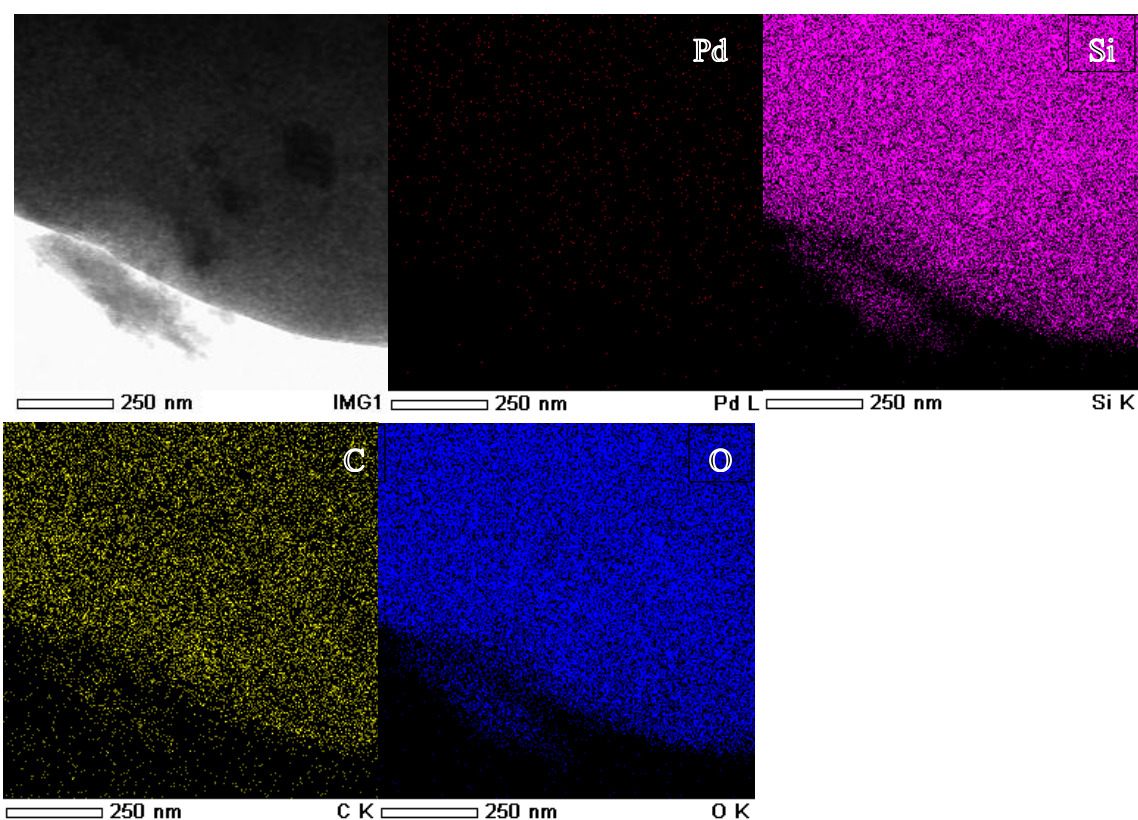
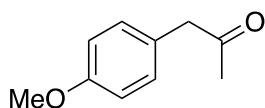


Figure S6. EDS mapping image of PhMePSi-Pd/SiO₂

A general procedure of synthesizing starting material

1-(4-Methoxyphenyl)propan-2-one⁹⁵

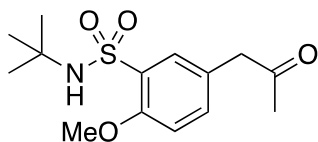


To a dried round bottom flask, 4-Methoxyphenylacetic acid (24.9 g, 150 mmol) was added and the flask was capped with a septum, connected to a vacuum line, then an Ar balloon was equipped. Acetic anhydride (76.6 g, 750 mmol) was added to the flask and the solution was stirred for 10 minutes at room temperature. Then, N-methylimidazole (6.2 g, 75 mmol) was added and the reaction mixture was stirred for 10 h. Then, the flask was kept at 0 °C and water was added portionwise. The layers were separated and the aqueous layer was extracted with ethyl acetate. The extracts combined and washed with saturated potassium carbonate solution followed by water, then dried over Na₂SO₄.

Removing the solvent by rotary evaporation gave the crude product as a liquid. The crude mixture was purified by distillation to afford the pure product (18.8 g, 77%) as a

pale yellow liquid. Spectra were identical to data found in the literature.

N-(*Tert*-butyl)-2-methoxy-5-(2-oxopropyl)benzenesulfonamide



Chlorosulfonic acid (93.6 g, 803 mmol) was added dropwise onto 1-(4-Methoxyphenyl)propan-2-one (18.8 g, 115 mmol) in DCM (115 mL, 1 M) at 0 °C under argon atmosphere. The resulting reaction mixture was stirred at room temperature for 2 h, before being transferred to cold water portionwise. Once the reaction mixture was fully quenched, the resulting solution was extracted with DCM, washed with water, and the organic layer was dried over Na₂SO₄. Concentration of the resulting mixture afforded this compound as a brown solid (15.7 g, 52%), which was used without further purification for the next step.

Onto a solution of *Tert*-butylamine (6.57 g, 89.8 mmol) and triethylamine (12.1 g, 120 mmol) in DCM (300 mL, 0.2 M), the crude solid (15.7 g, 59.8 mmol) in DCM was added by portion at 0 °C. The ice bath was removed and the reaction mixture was stirred overnight at room temperature. The crude reaction mixture was washed with a saturated aqueous solution of K₂CO₃, brine, and dried over Na₂SO₄. After concentration under rotary evaporator, the resulting crude material was purified by column chromatography on silica gel (eluent 95:5 DCM/EtOAc) followed by recrystallization in toluene to afford the product as a white solid (11.3 g, 63%).

¹H NMR (600 MHz, CDCl₃) δ(ppm): 7.75 (1H, d, *J* = 2.0 Hz), 7.34 (1H, dd, *J* = 2.0, 8.3 Hz), 6.99 (1H, d, *J* = 8.3 Hz), 4.91 (1H, brs), 3.98 (3H, s), 3.70 (2H, s), 2.17 (3H, s), 1.19 (9H, s).

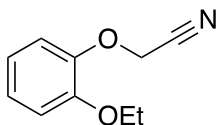
¹³C NMR (150 MHz, CDCl₃) δ(ppm): 205.4, 154.9, 134.7, 131.2, 130.0, 126.8, 112.4, 56.3, 54.4, 49.3, 29.9, 29.3.

IR (KBr, cm⁻¹) 3274, 1713, 1497, 1318, 1285, 1075, 1005.

HRMS (DART) calculated for C₁₄H₂₁NO₄S [2M+H]: 599.24608; found 599.24249.

Melting point 126 °C

2-(2-Ethoxyphenoxy)acetonitrile



To a solution of potassium carbonate (16.6 g, 120 mmol) in acetone,

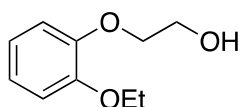
chloroacetonitrile (8.31 g, 110 mmol) and 2-ethoxyphenol (13.8 g, 100 mmol) were added under argon atmosphere. The mixture was kept stirring for 24 h at reflux conditions. Then, the crude reaction mixture was extracted with ethyl acetate, brine, and dried over Na₂SO₄. After concentration under rotary evaporator, the resulting crude material was purified by column chromatography on silica gel (eluent 90:10 Hex/EtOAc) to afford the product as a white solid (14.9 g, 84%).

¹H NMR (600 MHz, CDCl₃) δ(ppm): 7.24-7.04 (1H, m), 6.95-6.80 (1H, m), 4.75 (2H, s), 4.06 (2H, q, *J* = 6.8 Hz), 1.43 (2H, t, *J* = 6.8 Hz).

¹³C NMR (150 MHz, CDCl₃) δ(ppm): 149.8, 145.7, 124.7, 120.8, 118.1, 115.5, 113.5, 64.2, 55.6, 14.6.

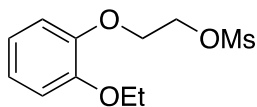
A general procedure of synthesizing racemic Tamsulosin

2-(2-Ethoxyphenoxy)ethan-1-ol³



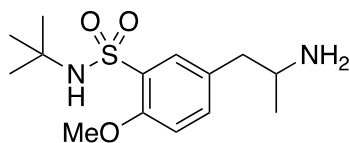
To the mixture of potassium carbonate (3.04 g, 22 mmol), and ethylene carbonate (1.76 g, 20 mmol), DMF (14 mL, 0.73 M) was added under argon atmosphere. Then, 2-ethoxyphenol (1.38 g, 10 mmol) was added and the reaction mixture was stirred at 140 °C for 24 h. After that, a crude reaction mixture was extracted with ethyl acetate and water, brine, and dried over Na₂SO₄. After concentration under rotary evaporator, the resulting crude material was purified by column chromatography on silica gel (eluent 20:80 Hex/EtOAc) to afford the product as an oil (1.31 g, 72%).

2-(2-Ethoxyphenoxy)ethyl methanesulfonate⁹⁶



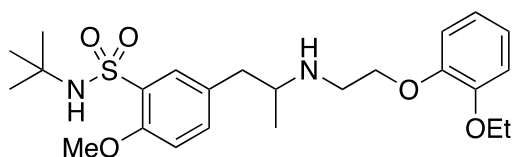
To 2-(2-Ethoxyphenoxy)ethan-1-ol, pyridine (24 mL, 0.3 M) was added. Methanesulfonyl chloride (1.36 g, 11.9 mmol) was added dropwise at 0 °C under argon atmosphere. The reaction mixture kept stirring at room temperature for 10 min. Then, the reaction mixture was added to the cold water with ice and the mixture was stirred for a few minutes. The solution was removed by filtration to give the product as a white solid (1.89 g, quant.), which was used without further purification for the next step.

5-(2-Aminopropyl)-*N*-(*tert*-butyl)-2-methoxybenzenesulfonamide



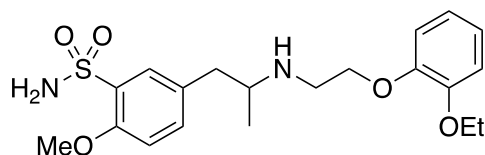
To dried flask, N-(*Tert*-butyl)-2-methoxy-5-(2-oxopropyl)benzenesulfonamide (1.48 g, 5 mmol), ammonium acetate (3.85 g, 50 mmol) and methanol (25 mL, 0.2 M) were added. Then, the reaction mixture was stirred for 10 min at room temperature. Sodiumcyanoborohydride (943 mg, 15 mmol) was added and the mixture was kept stirring overnight at room temperature. 1 M aqueous HCl was added until the bubble no longer appeared. The crude reaction mixture was extracted with ester and water, then into water layer, an aqueous NaOH solution was added until pH got to 7. The mixture was extracted with DCM and water, brine, and dried over Na₂SO₄. After concentration under rotary evaporator, the resulting crude material was purified by column chromatography on silica gel (eluent 90:10 DCM/MeOH) to afford the product as a white solid (1.48 g, 73%).

N-(*Tert*-butyl)-5-(2-((2-(2-ethoxyphenoxy)ethyl)amino)propyl)-2-methoxybenzenesulfonamide



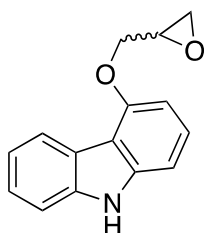
5-(2-Aminopropyl)-N-(*tert*-butyl)-2-methoxybenzenesulfonamide (448 mg, 1.49 mmol), 2-(2-ethoxyphenoxy)ethyl methanesulfonate (427 mg, 1.64 mmol), sodium bicarbonate (138 mg, 1.64 mmol) and potassium iodide (247 mg, 1.49 mmol), acetonitrile (15 mL, 0.1 M) were added under argon atmosphere. The reaction mixture stirred overnight at 80 °C. Then, water was added, the crude reaction mixture was extracted with DCM, washed with brine, and dried over Na₂SO₄. After concentration under rotary evaporator, the resulting crude material was purified by column chromatography on silica gel (eluent 95:5 DCM/MeOH) to afford the product as a white solid (339 mg, 49%).

5-(2-((2-(2-Ethoxyphenoxy)ethyl)amino)propyl)-2-methoxybenzenesulfonamide (Racemic Tamsulosin)⁹⁷



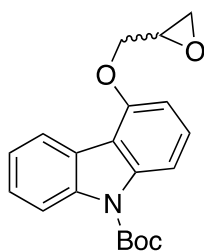
To the mixture of *N*-(*Tert*-butyl)-5-(2-((2-(2-ethoxyphenoxy)ethyl)amino)propyl)-2-methoxybenzenesulfonamide (139 mg, 0.3 mmol) in nitromethane (5 mL, 0.06 M), $\text{Sc}(\text{OTf})_3$ (14.8 mg, 0.03 mmol) and TfOH (49.5 mg, 0.33 mmol) were added. The reaction mixture stirred for 3 h at 95 °C. Then, the solvent was removed under reduced pressure, and an aqueous sodium hydroxide solution was added. The organic layer was extracted with ethyl acetate, then washed with brine, and dried over Na_2SO_4 . After concentration under rotary evaporator, the resulting crude material was purified by column chromatography on silica gel (eluent 90:10 DCM/MeOH) to afford the product as a white solid (113 mg, 92%).

4-(Oxiran-2-ylmethoxy)-9H-carbazole



The titled compound was obtained as a white solid (3.55 g, 30%) following the literature.⁹⁸

Tert-butyl 4-(oxiran-2-ylmethoxy)-9H-carbazole-9-carboxylate



To a dried round bottom flask, 4-(Oxiran-2-ylmethoxy)-9H-carbazole (3.55 g, 14.8 mmol), acetonitrile (74 mL, 0.2 M), and Boc anhydride (4.85 g, 22.3 mmol) were added and stirred. To the mixture, DMAP (181 mg, 1.48 mmol) was added in one portion at 0 °C, then stirred overnight at room temperature. Then, the solvent was removed under reduced pressure, and water was added. The layers were separated and the aqueous layer was extracted with ethyl acetate. The extracts combined and washed with brine, then dried

over Na₂SO₄. Removing the solvent by rotary evaporation gave the crude product as an oil (5.35g, quantitative). The crude mixture was used for the next step without any isolation.

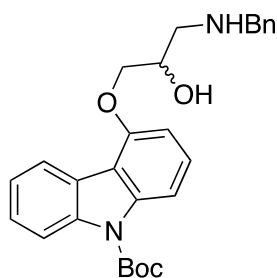
¹H NMR (500 MHz, CDCl₃) δ(ppm): 8.33 (1H, d, *J* = 7.5 Hz), 8.29 (1H, d, *J* = 8.6 Hz), 7.96 (1H, d, *J* = 8.6 Hz), 7.46-7.34 (3H, m), 6.80 (1H, d, *J* = 8.6 Hz), 4.46 (1H, dd, *J* = 3.5, 10.9 Hz), 4.20 (1H, dd, *J* = 5.7, 10.9 Hz), 3.55-3.52 (1H, m), 3.00-2.98 (1H, m), 2.87-2.85 (1H, m), 1.76 (9H, s).

¹³C NMR (125 MHz, CDCl₃) δ(ppm): 154.3, 151.1, 139.9, 137.8, 127.5, 126.2, 124.8, 123.1, 123.0, 115.6, 115.0, 109.4, 105.1, 83.9, 69.0, 50.2, 44.7, 28.3.

IR (KBr, cm⁻¹) 2890, 2178, 2028, 1718, 1589, 1431, 1368, 1320, 1274, 1212, 1150, 1025, 787, 715, 480.

HRMS (DART) calculated for C₂₀H₂₁NO₄ [M+H]: 340.15488; found 340.15140.

***Tert*-butyl 4-(3-(benzylamino)-2-hydroxypropoxy)-9H-carbazole-9-carboxylate**



To a dried round bottom flask, *tert*-butyl 4-(Oxiran-2-ylmethoxy)-9H-carbazole-9-carboxylate (4.69 g, 13.8 mmol), water (15 mL, 1 M), and benzylamine (7.4 g, 69.2 mmol) were added, then stirred overnight at 60 °C. Then, the solvent was removed under reduced pressure and, water was added. The layers were separated and the aqueous layer was extracted with dichloromethane. The extracts combined and washed with brine, then dried over Na₂SO₄. Removing the solvent by rotary evaporation gave the crude product as an oil. The crude mixture was purified by column chromatography on silica gel (eluent 95:5 DCM/MeOH) to afford the product as an oil (4.045 g, 65%).

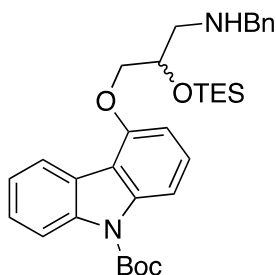
¹H NMR (500 MHz, CDCl₃) δ(ppm): 8.28 (1H, d, *J* = 8.0 Hz), 8.21 (1H, d, *J* = 7.5 Hz), 7.93 (1H, d, *J* = 8.6 Hz), 7.43-7.24 (8H, m), 6.78 (1H, d, *J* = 8.0 Hz), 4.32-4.17 (3H, m), 3.93-3.86 (2H, m), 3.33 (2H, brs), 3.07-3.04 (1H, m), 2.97-2.93 (1H, m), 1.75 (9H, s).

¹³C NMR (125 MHz, CDCl₃) δ(ppm): 154.4, 151.1, 139.8, 137.8, 128.5, 128.2, 127.6, 127.3, 126.1, 124.9, 123.1, 122.7, 115.6, 114.8, 109.2, 105.0, 83.9, 70.5, 68.2, 53.6, 51.3, 28.3.

IR (KBr, cm⁻¹) 2168, 1718, 1654, 1559, 1541, 1507, 1448, 1431, 1368, 1320, 1274, 1212, 1151, 1125, 1028, 907, 787.

HRMS (DART) calculated for C₂₇H₃₀N₂O₄ [M+H]: 447.22838; found 447.22572.

***Tert*-butyl 4-(3-(benzylamino)-2-((triethylsilyl)oxy)propoxy)-9H-carbazole-9-carboxylate**



To a dried round bottom flask, *Tert*-butyl 4-(3-(benzylamino)-2-hydroxypropoxy)-9H-carbazole-9-carboxylate (4.05 g, 9.06 mmol), dichloromethane (45 mL, 0.2 M), and imidazole (1.85 g, 27.2 mmol) were added, and then triethylsilylchloride (2.87g, 19.0 mmol) was added dropwise at 0 °C. The mixture was stirred overnight at room temperature, and an aqueous sodium bicarbonate solution was added. The layers were separated and the aqueous layer was extracted with dichloromethane. The extracts combined and washed with brine, then dried over Na₂SO₄. Removing the solvent by rotary evaporation gave the crude product as an oil. The crude mixture was purified by column chromatography on silica gel (eluent 95:5 DCM/MeOH) to afford the product as an oil (4.62 g, 91%).

¹H NMR (500 MHz, CDCl₃) δ(ppm): 8.29-8.25 (2H, m), 7.93 (1H, d, *J* = 8.6 Hz), 7.44-7.19 (8H, m), 6.84 (1H, d, *J* = 8.6 Hz), 4.40-4.37 (1H, m), 4.28-4.23 (2H, m), 3.90-3.83 (2H, m), 3.03 (1H, dd, *J* = 3.5, 12 Hz), 2.94 (1H, dd, *J* = 6.3, 12 Hz), 1.76 (9H, s), 0.96 (9H, t, *J* = 8.0 Hz), 0.67 (6H, q, *J* = 8.0 Hz).

¹³C NMR (125 MHz, CDCl₃) δ(ppm): 154.6, 137.8, 128.4, 128.0, 127.5, 126.9, 126.0, 123.0, 115.5, 114.9, 109.0, 105.1, 83.9, 70.5, 70.4, 54.0, 52.7, 28.4, 6.8, 5.0.

IR (KBr, cm⁻¹) 2953, 2875, 1725, 1589, 1447, 1431, 1394, 1368, 1342, 1320, 1274, 1212, 1152, 1124, 1110, 1047, 1030, 1003, 890, 819, 787, 717, 697, 534.

HRMS (DART) calculated for C₃₃H₄₄N₂O₄Si [M+H]: 561.31486; found 561.31803.

Experimental Procedure

Experimental Procedure for the reductive amination with a nitrile under batch conditions

A microwave tube was filled with 5 mol% of the selected catalyst, the amine (0.3 mmol, 1eq.), the nitrile (0.6 mmol, 2eq.), and a magnetic stirring bar. The tube was sealed with a septum, evacuated, and filled with argon via an argon balloon. Afterward, 2 mL solvent was injected into the microwave tube. The tube was placed into the autoclave with a syringe needle stuck into the septum. The autoclave was heated at 80 °C, and flushed two times with hydrogen, and run for 21 h. Afterward, the autoclave was removed from the heating block to cool down to ambient temperature, then hydrogen was released from the autoclave and disconnected from the hydrogen pipe. The resulting mixture was filtered, and the solution was evaporated and analyzed by ¹H NMR to determine the yield with 1,3,5-trimethoxybenzene as an internal standard.

Experimental Procedure for the reductive amination with a nitrile under continuous-flow conditions

A SUS column with column ends equipped with filters was used for a container of a trickle-bed reactor. One of the column ends was mounted a two-way unlet tube. A PETE tube was used to connect the pump with the column. the catalyst was weighed and mixed well with W 50, then packed into the column. Toluene flowed into the column by the pump (0.2 mL/min) for at least 30 minutes. The column was then pre-heated at the target temperature. After heating the column, hydrogen gas was introduced to the column at 25 mL/min flow rate. Then, toluene/EtOH (95:5) solution of the substrate was introduced to the column at 0.1 mL/min flow rate. The resulting solution (2.0 mL) in an appropriate time was evaporated and analyzed by ¹H NMR with 1,3,5-trimethoxybenzene as an internal standard or GC with dodecane as an internal standard to determine the yield.

Tamsulosin

Experimental Procedure for the reductive amination of ketone (5) with amine (6) under continuous-flow conditions

A SUS column (ID 5 mm × 100 mm) with column ends equipped with filters was used for a container of a trickle-bed reactor. One of the column ends was mounted a two-way unlet tube. A PETE tube was used to connect the pump with the column. 195 mg 5% Pt/C catalyst was weighed and mixed well with 0.3 g of W 50, then packed into the column. Toluene flowed into the column by the pump (0.2 mL/min) for at least 30 minutes. The column was then pre-heated at 80 °C. After heating the column, hydrogen gas was introduced to the column at 25 mL/min flow rate. Then, 0.1 M toluene/EtOH (95:5) solution of compound 5 and 0.12 M toluene/EtOH (95:5) solution of compound 6 were introduced to PETE tubes at 0.1 mL/min flow rate, respectively, and mixed with T-shape

mixer. And the mixed solution of 0.20 mL/min total flow rate was introduced to the column. The resulting solution (2.0 mL) in an appropriate time was evaporated and analyzed by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard to determine the yield (quantitative, for 2-24 h).

Experimental Procedure for the hydrogenolysis of amine (7) under batch conditions

A microwave tube was filled with 5 mol% of the selected catalyst, the amine (0.3 mmol, 1eq.), and a magnetic stirring bar. The tube was sealed with a septum, evacuated, and filled with argon via an argon balloon. Afterward, 2 mL Toluene/EtOH (95:5) was injected into the microwave tube. The tube was placed into the autoclave with a syringe needle stuck into the septum. The autoclave was heated at 80 °C, and flushed two times with hydrogen, and run for 21 h. Afterward, the autoclave was removed from the heating block to cool down to ambient temperature, then hydrogen was released from the autoclave and disconnected from the hydrogen pipe. The resulting mixture was filtered, and the solution was evaporated and analyzed by ^1H NMR to determine the yield with 1,3,5-trimethoxybenzene as an internal standard.

Experimental Procedure for the hydrogenolysis of amine (7) under continuous-flow conditions

A SUS column (ID 10 mm \times 100 mm) with column ends equipped with filters was used for a container of a trickle-bed reactor. One of the column ends was mounted a two-way unlet tube. A PETE tube was used to connect the pump with the column. the catalyst was weighed and mixed well with 0.7 g of W 50, then packed into the column. Toluene flowed into the column by the pump (0.2 mL/min) for at least 30 minutes. The column was then pre-heated at 80 °C. After heating the column, hydrogen gas was introduced to the column at 25 mL/min flow rate. Then, the crude solution of the substrate 7 was introduced to the column at 0.2 mL/min flow rate. The resulting solution (2.0 mL) in an appropriate time was evaporated and analyzed by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard to determine the yield (97%, for 3-11 h).

Experimental Procedure for the reductive amination with nitrile (9) under batch conditions

A microwave tube was filled with 5 mol% of the selected catalyst, the amine (0.3 mmol, 1eq.), the nitrile (0.6 mmol, 2eq.) and a magnetic stirring bar. The tube was sealed with a septum, evacuated, and filled with argon via an argon balloon. Afterward, 2 mL Toluene/EtOH (95:5) was injected into the microwave tube. The tube was placed into the autoclave with a syringe needle stuck into the septum. The autoclave was heated at 80 °C, and flushed two times with hydrogen and run for 21 h. Afterward, the autoclave was removed from the heating block to cool down to ambient temperature, then hydrogen was released from the autoclave and disconnected from the hydrogen pipe. The resulting

mixture was filtered, and the solution was evaporated and analyzed by ^1H NMR to determine the yield with 1,3,5-trimethoxybenzene as an internal standard.

Experimental Procedure for the reductive amination with nitrile (9) under continuous-flow conditions

A SUS column (ID 5 mm \times 100 mm) with column ends equipped with filters was used for a container of a trickle-bed reactor. One of the column ends was mounted a two-way unlet tube. A PETE tube was used to connect the pump with the column. the catalyst was weighed and mixed well with 0.3 g of W 50, then packed into the column. Toluene flowed into the column by the pump (0.2 mL/min) for at least 30 minutes. The column was then pre-heated at the target temperature. After heating the column, hydrogen gas was introduced to the column at 25 mL/min flow rate. Then, to the crude solution of the substrate 8, the same mass amount of toluene/EtOH (95:5) solution of the substrate 9 was added, and the well-mixed solution was introduced to the column at 0.4 mL/min flow rate. The resulting solution (2.0 mL) in an appropriate time was evaporated and analyzed by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard to determine the yield (85%, for 2-7 h).

Experimental Procedure for the deprotection of substrate (10) under batch conditions

To the dried flask, the crude solution of substrate 10 (4 mL) was added, and then the solvent was removed under reduced pressure. Then, nitromethane (1.7 mL, 0.06 M), $\text{Sc}(\text{OTf})_3$ (4.9 mg, 0.01 mmol) and TfOH (16.5 mg, 0.11 mmol) were added. The reaction mixture stirred for 3 h at 95 $^\circ\text{C}$. Then, the solvent was removed under reduced pressure, and aqueous sodium hydroxide solution was added. The organic layer was extracted with ethyl acetate, then washed with brine, and dried over Na_2SO_4 . After concentration under rotary evaporator, the resulting crude material was analyzed by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard to determine the yield.

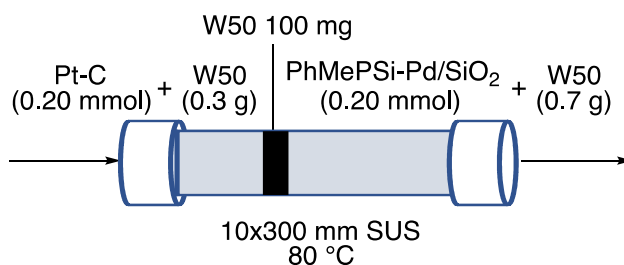
Experimental Procedure for the deprotection of substrate (10) under continuous-flow conditions

To the crude solution of substrate 10, TfOH (1.1 eq.), $\text{Sc}(\text{OTf})_3$ (10 mol%), and nitromethane (0.1 M) were added. Then the solution flowed into the pre-heated 5 m SUS tube at 0.015 mL/min flow rate. Then, the solvent was removed under reduced pressure, and an aqueous sodium hydroxide solution was added. The organic layer was extracted with ethyl acetate, then washed with brine, and dried over Na_2SO_4 . After concentration under rotary evaporator, the resulting crude material was purified by column chromatography on silica gel (eluent 95:5 DCM/MeOH) to afford the product as a white solid (60%).

Experimental Procedure for the recrystallization of substrate (4)

To a flask, Tamsulosin (1.0 eq.) and methanol (0.9 M) were added, and then the flask was heated and stirred at reflux conditions. Then, (1R)-(-)-10-Camphorsulfonic acid (1.0 eq.) in water (0.9 M) was added, then the mixture was stirred at room temperature for 5 h. After the filtration, the obtained solid was recrystallized in methanol. To the obtained solid, an aqueous sodium hydroxide solution was added, and extracted with ethyl acetate, and then washed with brine, and dried over Na₂SO₄. After concentration under rotary evaporator, the resulting material was analyzed by HPLC to determine *ee*.

Experimental Procedure for sequential-flow synthesis of Tamsulosin



Scheme S1. Column I

A solution of the ketone 5 and amine 6 were combined with T-shape mixture and introduced the pre-heated Column I (SUS column (ID 10 mm × 300 mm) packed with the mixture of Pt/C catalyst (195 mg) and W 50 (0.3 g), 0.1 g of W50 as separation, and the mixture of PhMePSi-Pd/SiO₂ (2.0 g, 0.20 mmol) and W 50 (0.7 g), at total 0.2 mL/min flow rate. The resulted solution was collected in a flask to remove hydrogen at once. The solution and a solution of the substrate 8 were mixed at 0.2 mL/min, respectively with T-shape mixture, and introduced into the pre-heated Column II packed with the mixture of DMPSi-Pd/AC-CP (3:1) (500 mg, 0.05 mmol) and W 50 (0.3 g) at 0.4 mL/min total flow rate. To the resulted solution, TfOH (1.1 eq.), Sc(OTf)₃ (10 mol%), and nitromethane (0.1 M) were added. Then the solution flowed into the pre-heated 5 m SUS tube at 0.015 mL/min flow rate. Then, the solvent was removed under reduced pressure, and an aqueous sodium hydroxide solution was added. The organic layer was extracted with ethyl acetate, then washed with brine, and dried over Na₂SO₄. After concentration under rotary evaporator, the resulting crude material was purified by column chromatography on silica gel (eluent 95:5 DCM/MeOH) to afford the product as a white solid.

Carvedilol

Experimental Procedure for the hydrogenolysis of amine (12) under continuous-flow conditions

A SUS column (ID 10 mm × 100 mm) with column ends equipped with filters was used for a container of a trickle-bed reactor. One of the column ends was mounted a two-way

unlet tube. A PETE tube was used to connect the pump with the column. PhMePSi-Pd/SiO₂ (2.0 g, 0.20 mmol) was weighed and mixed well with 0.7 g of W 50, then packed into the column. Toluene flowed into the column by the pump (0.2 mL) for at least 30 minutes. The column was then pre-heated at 80 °C. After heating the column, hydrogen gas was introduced to the column at 20 mL/min flow rate. Then, the solution of the substrate 12 was introduced to the column at 0.1 mL/min flow rate. The resulting solution (2.0 mL) in an appropriate time was evaporated and analyzed by ¹H NMR with 1,3,5-trimethoxybenzene as an internal standard to determine the yield (quantitative, for 3-10 h).

Experimental Procedure for the reductive amination with nitrile 14 under continuous-flow conditions

A SUS column (ID 5 mm × 100 mm) with column ends equipped with filters was used for a container of a trickle-bed reactor. One of the column ends was mounted a two-way unlet tube. A PETE tube was used to connect the pump with the column. DMPSi-Pd/AC-CP (3:1) (500 mg, 0.05 mmol) was weighed and mixed well with 0.3 g of W 50, then packed into the column. Toluene flowed into the column by the pump (0.2 mL/min) for at least 30 minutes. The column was then pre-heated at the target temperature. After heating the column, hydrogen gas was introduced to the column at 20 mL/min flow rate. Then, to the crude solution of the substrate 13, toluene/EtOH (95:5) solution of the substrate 14 was added, and the well-mixed solution was introduced to the column at 0.2 mL/min flow rate. The resulting solution (2.0 mL) in an appropriate time was evaporated and analyzed by ¹H NMR with 1,3,5-trimethoxybenzene as an internal standard to determine the yield (85%, for 2-7 h).

Experimental Procedure for sequential-flow synthesis of Carvedilol precursor 15

A solution of the amine (**20**) was introduced to the pre-heated Column I (SUS column (ID 10 mm × 100 mm) packed with the mixture of DMPSi-Pd/AC-CP (3:1) (2.0 g, 0.20 mmol) and W 50 (0.7 g), at 0.1 mL/min. The solution was collected in a flask to remove hydrogen at once. The resulting solution and a solution of the nitrile (**16**) were mixed with T-shape mixer, and introduced into the pre-heated Column II packed with the mixture of DMPSi-Pd/AC-CP (3:1) (500 mg, 0.05 mmol) and W 50 (0.3 g) at 0.2 mL/min total flow rate. The resulting solution (2.0 mL) in an appropriate time was evaporated and analyzed by ¹H NMR with 1,3,5-trimethoxybenzene as an internal standard to determine the yield (85%, for 2-7 h).

Reductive N-Methylation of Amines

Experimental Procedure for N-methylation reaction under batch conditions

DMPSi-Pd/AC-CP (3:1) (total quantity of Pd: 0.0005 mmol, Pd: 0.25 mol%, 5.0 mg) and a magnetic stirring bar were added to a flask. The flask was sealed with a septum,

evacuated, and filled with argon via an argon balloon. Afterward, THF (2 mL), di-n-octylamine (0.2 mmol, 1 eq. 48.1 mg) and formalin (0.24 mmol, 1.2 eq. 19.5 mg) were injected into the flask. A hydrogen balloon was equipped to the flask and the reaction mixture was stirred for 1 h at room temperature. After the reaction, the resulting mixture was filtered. After concentration under rotary evaporator, the resulting crude material was analyzed by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard to determine the yield.

Experimental Procedure for N-methylation reaction under flow conditions

A SUS column (ID 5 mm \times 50 mm) with column ends equipped with filters was used for a container of trickle-bed reactor. One of the column ends was mounted a two-way inlet tube. A PETE tube was used to connect the pump with the column. DMPSi-Pd/AC-CP (3:1) (total quantity of Pd: 0.005 mmol, 50 mg) mixed well with W50 cellulose (0.35 g) was packed into the column. THF flowed into the column by the pump (0.3 mL/min) for over 30 minutes. After that, hydrogen gas was introduced to the column at 15 mL/min flow rate. Then, the substrate solution (0.1 M, HCHO aq.: 0.12 M in THF and 1,3,5-trimethoxybenzene as an internal standard: 0.89 mmol, 150 mg) was introduced to the column at 0.1 mL/min flow rate. The resulting solution in an appropriate time was collected (1 mL). After concentration under rotary evaporator, the resulting crude material was analyzed by ^1H NMR to determine the yield.

Domiphen Bromide

Experimental Procedure for the reductive amination with the nitrile 2o under continuous-flow conditions

A SUS column (ID 5 mm \times 50 mm) with column ends equipped with filters was used for a container of a trickle-bed reactor. One of the column ends was mounted a two-way inlet tube. A PETE tube was used to connect the pump with the column. the catalyst was weighed and mixed well with W 50, then packed into the column. Toluene flowed into the column by the pump (0.2 mL/min) for at least 30 minutes. The column was then pre-heated at the target temperature. After heating the column, hydrogen gas was introduced to the column at 25 mL/min flow rate. Then, toluene/EtOH (95:5) solution of the substrate was introduced to the column at 0.1 mL/min flow rate. The resulting solution (2.0 mL) in an appropriate time was evaporated and analyzed by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard or GC with dodecane as an internal standard to determine the yield (98%, for 2-24 h).

Experimental Procedure for N-methylation of amine 21 with aqueous formalin solution under continuous-flow conditions

A SUS column (ID 5 mm \times 100 mm) with column ends equipped with filters was used for a container of a trickle-bed reactor. One of the column ends was mounted a two-way

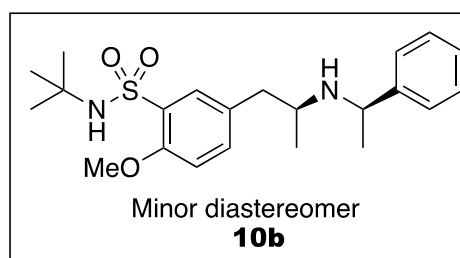
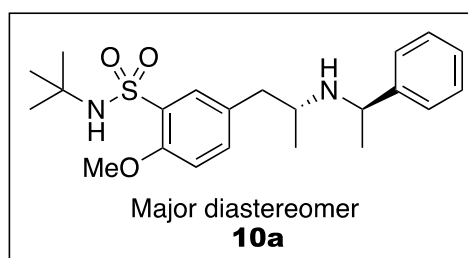
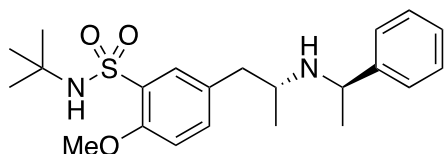
unlet tube. A PETE tube was used to connect the pump with the column. DMPSi-Pd/AC-CP (3:1) (500 mg, 0.05 mmol) was weighed and mixed well with 0.3 g of W 50, then packed into the column. Toluene flowed into the column by the pump (0.2 mL/min) for at least 30 minutes. The column was then pre-heated at the target temperature. After heating the column, hydrogen gas was introduced to the column at 20 mL/min flow rate. Then, to the crude solution of the substrate 21, EtOH solution of the formalin was added and well-mixed solution was introduced to the column at 0.2 mL/min flow rate. The resulting solution (2.0 mL) in an appropriate time was evaporated and analyzed by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard to determine the yield (92%, for 3-16 h).

Experimental Procedure for sequential-flow synthesis of Domiphen Bromide 18

A solution containing the amine (**9**) and the nitrile (**10**) was introduced to the pre-heated Column I (SUS column (ID 5 mm \times 50 mm) packed with the mixture of DMPSi-Pd/AC-CP (3:1) (72 mg, 0.0072 mmol) and W 50 (0.3 g), at 0.1 mL/min. The solution was collected in a flask to remove hydrogen at once. The solution and a solution of formalin were mixed with T-shape mixer, and introduced into the pre-heated Column II (SUS column (ID 5 mm \times 100 mm) packed with the mixture of DMPSi-Pd/AC-CP (3:1) (500 mg, 0.05 mmol) and W 50 (0.3 g) at 0.2 mL/min total flow rate. To the crude solution, bromomethane in THF (2 eq.) was added. Then the solution was stirred for 5 h at 60 °C. Then, the solvent was removed under reduced pressure to afford the product as a white solid. The yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard (70%).

Spectroscopic Information of the Products

N-(*Tert*-butyl)-2-methoxy-5-((*R*)-2-(((*R*)-1-phenylethyl)amino)propyl)benzenesulfonamide (Compound 10)



(7a) ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.69 (1H, d, $J = 1.8$ Hz), 7.40-7.15 (6H, m), 6.91 (1H, d, $J = 8.6$ Hz), 4.95 (1H, brs), 4.00-3.95 (4H, m), 2.78-2.51 (3H, m), 1.30 (3H, d, $J = 6.9$ Hz), 1.17 (9H, s), 0.88 (3H, d, $J = 6.3$ Hz).

(7b, isolable peaks of the minor product) ^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.77 (1H, d, $J = 2.3$ Hz), 6.96 (1H, d, $J = 8.6$ Hz), 1.02 (3H, d, $J = 6.3$ Hz).

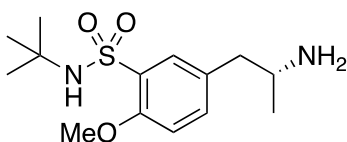
^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 154.2, 134.6, 132.2, 130.7, 129.8, 128.4, 126.8, 126.4, 111.9, 56.2, 56.2, 55.3, 54.2, 29.9, 24.4, 20.8.

IR (KBr, cm^{-1}) 3290, 2970, 1681, 1595, 1492, 1454, 1392, 1367, 1315, 1274, 1068, 1921, 997, 814, 761, 701, 691.

HRMS (DART) calculated for $\text{C}_{22}\text{H}_{32}\text{N}_2\text{O}_3\text{S}$ [2M+H]: 405.22119; found 405.21989.

Melting point 108 $^\circ\text{C}$

(*R*)-5-(2-Aminopropyl)-N-(*tert*-butyl)-2-methoxybenzenesulfonamide (Compound 8)



^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.74 (1H, d, $J = 1.4$ Hz), 7.33 (1H, dd, $J = 1.4, 8.9$ Hz), 6.96 (1H, d, $J = 8.9$ Hz), 4.93 (1H, brs), 4.01 (3H, s), 3.97 (3H, s), 3.16-3.11 (1H, m), 2.67 (1H, dd, $J = 5.5, 13.9$ Hz), 2.54 (1H, dd, $J = 7.6, 13.9$ Hz), 1.18 (9H, s), 1.08 (3H, d, $J = 6.8$ Hz).

^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 154.3, 134.5, 132.4, 131.0, 129.5, 112.1, 56.3, 54.3, 48.4, 45.5, 30.0, 23.2.

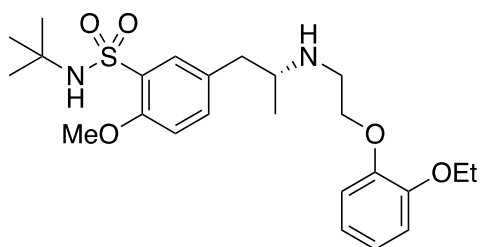
Enantiomeric excess was determined by using derivatized compound **5'**.

IR (KBr, cm^{-1}) 1734, 1718, 1701, 1684, 1654, 1647, 1637, 1600, 1541, 1534, 1521, 1507, 1497, 1486, 1472, 1457, 1437, 1420, 457, 418.

HRMS (DART) calculated for $\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$ $[2\text{M}+\text{H}]$: 601.30935; found 601.31119.

Melting point 134 °C

(*R*)-*N*-(*Tert*-butyl)-5-(2-((2-(2-ethoxyphenoxy)ethyl)amino)propyl)-2-methoxybenzenesulfonamide (Compound 10)



^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.74 (1H, d, $J = 2.0$ Hz), 7.34 (1H, dd, $J = 2.0, 8.9$ Hz), 6.93-6.87 (5H, m), 4.92 (1H, brs), 4.10 (2H, t, $J = 5.5$ Hz), 4.06 (2H, q, $J = 6.8$ Hz), 3.96 (3H, s), 3.09-2.94 (3H, m), 2.85 (1H, dd, $J = 5.5, 13.0$ Hz), 2.56 (1H, dd, $J = 7.6, 13.0$ Hz), 2.17 (3H, s), 1.42 (3H, t, $J = 6.8$ Hz), 1.17 (9H, s), 1.03 (3H, d, $J = 6.2$ Hz).

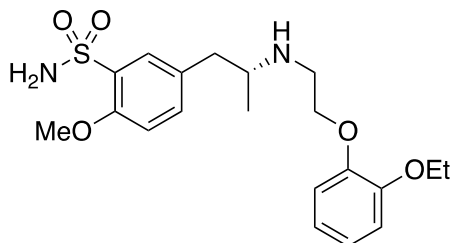
^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 154.3, 149.2, 148.6, 134.6, 132.2, 130.9, 129.6, 121.8, 121.0, 115.2, 113.8, 112.1, 69.3, 64.4, 56.2, 54.5, 54.3, 46.4, 42.3, 29.9, 19.8, 14.9.

IR (KBr, cm^{-1}) 2376, 2361, 2322, 1718, 1684, 1654, 1637, 1541, 1465, 1472, 1457.

HRMS (DART) calculated for $\text{C}_{24}\text{H}_{36}\text{N}_2\text{O}_5\text{S}$ $[\text{M}+\text{H}]$: 465.24232; found 465.24440.

Melting point 116 °C

(*R*)-5-(2-((2-(2-Ethoxyphenoxy)ethyl)amino)propyl)-2-methoxybenzenesulfonamide (Tamsulosin) (Compound 4)⁴



^1H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.55 (1H, d, $J = 2.3$ Hz), 7.38 (1H, dd, $J = 2.3, 8.6$ Hz), 7.09 (1H, d, $J = 8.6$ Hz), 7.00-6.84 (6H, m), 4.00-3.96 (4H, m), 3.86 (3H, s), 2.95-2.82 (3H, m), 2.75 (1H, dd, $J = 5.7, 13.7$ Hz), 2.47 (1H, dd, $J = 5.7, 13.7$ Hz), 1.29 (3H, t, $J = 6.9$ Hz), 0.92 (3H, d, $J = 6.3$ Hz).

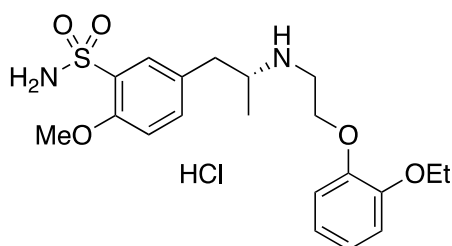
^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 154.3, 148.6, 148.3, 134.3, 131.1, 130.8, 128.1,

121.3, 120.9, 114.5, 113.9, 112.4, 68.9, 63.8, 56.0, 54.0, 45.6, 41.6, 19.7, 14.8.

Enantiomeric excess (64%) was determined by HPLC analysis with a Chiralpak AD-3 column (hexane:*i*PrOH= 17:3, 1.0 mL/min, 205 nm); major enantiomer *t*R = 65.5 min, minor enantiomer *t*R = 56.0 min.

Enantiomeric excess (99% after recrystallization) was determined by HPLC analysis with a Chiralpak AD-3 column (hexane:*i*PrOH= 17:3, 1.0 mL/min, 206 nm); major enantiomer *t*R = 63.6 min, minor enantiomer *t*R = 55.3 min.

(*R*)-5-(2-((2-(2-Ethoxyphenoxy)ethyl)amino)propyl)-2-methoxybenzenesulfonamide hydrochloride (Tamsulosin hydrochloride)⁹⁹

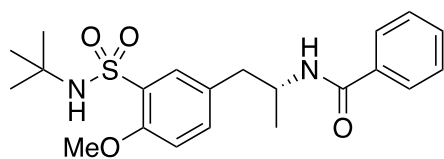


¹H NMR (600 MHz, DMSO-*d*₆) δ(ppm): 9.79-9.74 (2H, br), 7.62 (1H, s), 7.46 (1H, d, *J* = 7.6 Hz), 7.18 (1H, d, *J* = 7.6 Hz), 7.09-7.07 (3H, m), 7.00-6.89 (3H, m), 4.37 (2H, t, *J* = 5.5 Hz), 4.00 (2H, q, *J* = 6.8 Hz), 3.89 (3H, s), 3.53 (3H, m), 2.74-2.70 (1H, m), 2.09 (2H, s), 1.25 (3H, t, *J* = 8.4 Hz), 1.17 (3H, d, *J* = 6.2 Hz).

¹³C NMR (150 MHz, DMSO-*d*₆) δ(ppm): 154.8, 148.7, 147.3, 134.4, 131.2, 128.4, 128.1, 122.2, 120.7, 115.2, 113.6, 112.9, 64.9, 63.7, 56.1, 54.6, 42.8, 37.2, 14.7, 14.6.

[α]_D²⁰ = - 4.8 (c = 0.35 in methanol).⁵

(*R*)-N-(1-(3-(*N*-(*Tert*-butyl)sulfamoyl)-4-methoxyphenyl)propan-2-yl)benzamide (Compound 8')



To the mixture of (*R*)-5-(2-Aminopropyl)-*N*-(*tert*-butyl)-2-methoxybenzenesulfonamide (90.1 mg, 0.3 mmol), dichloromethane (3 mL, 0.1 M), and triethylamine (45.5 mg, 0.45 mmol), benzoyl chloride was added at 0 °C. The reaction mixture was stirred overnight at room temperature. Then, water was added, and the organic layer was extracted with dichloromethane, then washed with brine, and dried over Na₂SO₄. After concentration under rotary evaporator, the resulting crude material was purified by column chromatography on silica gel (eluent 90:10 DCM/EtOAc) to afford the product as a white solid (105 mg, 86%).

^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.69-7.65 (3H, m), 7.40-7.30 (4H, m), 6.88 (1H, d, $J = 8.3$ Hz), 6.15 (1H, s), 4.89 (1H, brs), 4.37-4.32 (1H, m), 3.87 (3H, s), 2.85 (1H, dd, $J = 6.2, 7.3$ Hz), 2.74 (1H, dd, $J = 6.2, 7.3$ Hz), 1.12 (3H, d, $J = 6.2$ Hz), 1.03 (9H, s).

^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 166.7, 154.5, 134.6, 134.5, 131.3, 130.9, 130.7, 129.8, 128.4, 126.8, 112.4, 56.2, 54.3, 46.6, 41.3, 29.9, 25.3, 20.0.

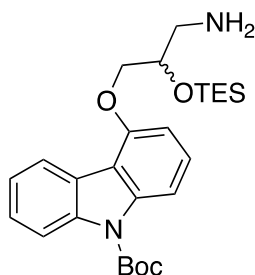
Enantiomeric excess (66%) was determined by HPLC analysis with a Chiralpak AD-3 column (hexane:*i*PrOH= 17:3, 1.0 mL/min, 250 nm); major enantiomer $t_R = 21.0$ min, minor enantiomer $t_R = 30.5$ min.

IR (KBr, cm^{-1}) 3854, 3736, 3676, 3650, 1734, 1718, 1701, 1684, 1654, 1637, 1559, 1541, 1507, 1490, 1472, 1457, 1437, 1148, 418.

HRMS (DART) calculated for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]$: 405.18480; found 405.18411.

Melting point 99 $^\circ\text{C}$

***Tert*-butyl 4-(3-amino-2-((triethylsilyl)oxy)propoxy)-9*H*-carbazole-9-carboxylate (Compound 13)**



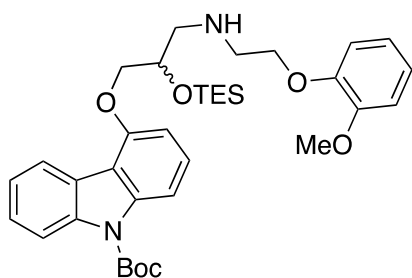
^1H NMR (500 MHz, CDCl_3) δ (ppm): 8.29-8.27 (2H, m), 7.94 (1H, d, $J = 8.6$ Hz), 7.44-7.32 (3H, m), 6.83 (1H, d, $J = 8.6$ Hz), 4.25-4.16 (3H, m), 3.14-3.04 (2H, m), 1.77 (9H, s), 0.99 (9H, t, $J = 8.1$ Hz), 0.68 (6H, q, $J = 8.1$ Hz).

^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 154.5, 151.1, 139.9, 137.8, 127.5, 126.1, 124.9, 123.0, 122.9, 115.6, 114.8, 109.1, 105.0, 83.9, 71.8, 69.5, 45.7, 28.3, 6.8, 5.0.

IR (KBr, cm^{-1}) 2953, 2875, 1723, 1617, 1589, 1447, 1431, 1394, 1368, 1342, 1320, 1274, 1214, 1152, 1124, 1110, 1047, 1030, 1004, 887, 840, 820, 787, 745, 717, 534.

HRMS (DART) calculated for $\text{C}_{26}\text{H}_{38}\text{N}_2\text{O}_4\text{Si}$ $[\text{M}+\text{H}]$: 471.26791; found 471.26896.

***Tert*-butyl 4-(3-((2-(2-methoxyphenoxy)ethyl)amino)-2-((triethylsilyl)oxy)propoxy)-9*H*-carbazole-9-carboxylate (Compound 15)**



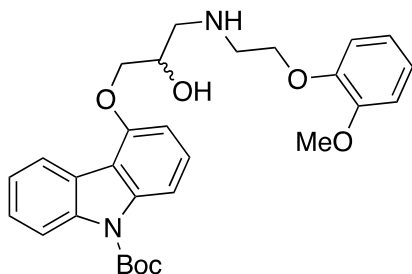
^1H NMR (500 MHz, CDCl_3) δ (ppm): 8.32 (1H, d, $J = 8.1$ Hz), 8.28 (1H, d, $J = 8.1$ Hz), 7.93 (1H, d, $J = 8.6$ Hz), 7.43-7.30 (3H, m), 6.92-6.83 (5H, m), 4.40-4.38 (1H, m), 4.25 (2H, d, $J = 5.7$ Hz), 4.12 (2H, t, $J = 5.2$ Hz), 3.80 (3H, s), 3.11-2.98 (4H, m), 1.76 (9H, s), 0.97 (9H, t, $J = 8.0$ Hz), 0.67 (6H, q, $J = 8.0$ Hz).

^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 154.6, 149.7, 139.9, 137.8, 127.5, 126.0, 125.0, 123.0, 121.4, 120.8, 115.5, 114.9, 113.9, 111.7, 109.0, 105.1, 83.9, 70.5, 68.6, 55.7, 53.4, 49.1, 28.4, 6.8, 4.9.

IR (KBr, cm^{-1}) 2876, 1724, 1591, 1507, 1447, 1431, 1394, 1368, 1320, 1275, 1252, 1214, 1152, 1124, 1110, 1045, 1030, 1002, 788, 738, 718, 534.

HRMS (DART) calculated for $\text{C}_{35}\text{H}_{48}\text{N}_2\text{O}_6\text{Si}$ $[\text{M}+\text{H}]^+$: 621.33599; found 621.33535.

***Tert*-butyl 4-(2-hydroxy-3-((2-(2-methoxyphenoxy)ethyl)amino)propoxy)-9H-carbazole-9-carboxylate**



To a dried round bottom flask, the crude solution of *Tert*-butyl 4-(3-((2-(2-methoxyphenoxy)ethyl)amino)-2-((triethylsilyl)oxy)propoxy)-9H-carbazole-9-carboxylate (27.5 mL, 0.05 M) was added, and the solvent was removed under reduced pressure. THF (1.5 mL, 1 M) was added, and then 1 M TBAF THF solution (1.375 mL) was added at 0 °C. The mixture was stirred for 30 minutes at 0 °C, and saturated NH_4Cl solution was added. The layers were separated and the aqueous layer was extracted with dichloromethane. The extracts combined and washed with brine, then dried over Na_2SO_4 . Removing the solvent by rotary evaporation gave the crude product as a solid. The crude mixture was purified by column chromatography on silica gel (eluent 95:5 DCM/MeOH) to afford the product as a solid (501 mg, 72%).

^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.28-8.27 (2H, m), 7.93 (1H, d, $J = 8.3$ Hz), 7.42-

7.29 (3H, m), 6.93-6.78 (5H, m), 4.32-4.12 (5H, m), 3.78 (3H, s), 3.35 (2H, brs), 3.14-3.10 (3H, m), 3.01-2.97 (1H, m), 1.75 (9H, s).

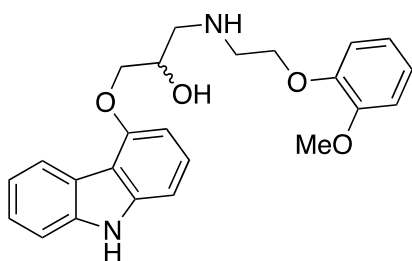
^{13}C NMR (150 MHz, CDCl_3) $\delta(\text{ppm})$: 154.4, 151.1, 149.6, 148.0, 139.8, 137.7, 127.5, 126.1, 124.9, 123.1, 122.8, 121.7, 120.8, 115.6, 114.8, 114.2, 111.8, 109.1, 105.0, 83.9, 70.5, 70.5, 68.5, 68.1, 55.7, 51.9, 48.6, 28.3.

IR (KBr, cm^{-1}) 2929, 1701, 1589, 1507, 1447, 1431, 1394, 1320, 1275, 1251, 1214, 1151, 1122, 1025, 838, 818, 788, 741, 718.

HRMS (DART) calculated for $\text{C}_{29}\text{H}_{34}\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]$: 507.24951; found 507.25026.

Melting point 42 °C

**1-((9H-Carbazol-4-yl)oxy)-3-((2-(2-methoxyphenoxy)ethyl)amino)propan-2-ol
(Carvedilol)¹⁰⁰**

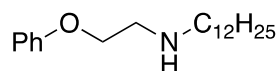


To a dried round bottom flask, *Tert*-butyl 4-(2-hydroxy-3-((2-(2-methoxyphenoxy)ethyl)amino)propoxy)-9H-carbazole-9-carboxylate (501 mg, 0.99 mmol), DCM (24 mL), and TFA (6 mL) were added, and the mixture was stirred overnight at room temperature. Then to the resulting mixture, an aqueous NaOH solution was added, and the layers were separated and the aqueous layer was extracted with dichloromethane. The extracts combined and washed with brine, then dried over Na_2SO_4 . Removing the solvent by rotary evaporation gave the crude product as a solid. The crude mixture was purified by column chromatography on silica gel (eluent 90:10 DCM/MeOH) to afford the product as a solid (185 mg, 46%).

^1H NMR (500 MHz, CDCl_3) $\delta(\text{ppm})$: 8.33 (1H, brs), 8.22 (1H, d, $J = 7.5$ Hz), 7.32-7.15 (4H, m), 6.98-6.82 (5H, m), 6.57 (1H, d, $J = 8.1$ Hz), 4.19-4.07 (5H, m), 3.77 (3H, s), 3.05-2.85 (6H, m).

^{13}C NMR (125 MHz, CDCl_3) $\delta(\text{ppm})$: 155.1, 149.5, 148.1, 140.1, 138.7, 126.6, 124.9, 122.9, 122.4, 121.6, 120.9, 119.6, 114.0, 112.6, 111.8, 110.0, 103.8, 101.1, 70.2, 68.6, 68.3, 55.7, 51.9, 48.6.

N-(2-Phenoxyethyl)dodecan-1-amine (Compound 21)



^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.25-7.22 (2H, m), 6.92-6.87 (3H, m), 4.04 (2H, t, $J = 5.5$ Hz), 2.96 (2H, t, $J = 5.5$ Hz), 2.63 (2H, t, $J = 7.6$ Hz), 1.49-1.22 (20H, m), 0.84 (3H, t, $J = 6.9$ Hz).

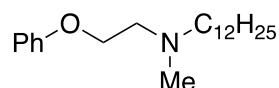
^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 158.9, 129.4, 120.8, 114.5, 67.3, 49.9, 48.9, 31.9, 30.2, 29.7, 29.6, 29.6, 29.6, 29.3, 27.3, 22.7, 14.1.

IR (KBr, cm^{-1}) 2923, 2852, 1601, 1588, 1559, 1497, 1457, 1300, 1242, 1171, 1078, 1038, 879, 804, 751, 721, 690, 508, 418.

HRMS (DART) calculated for $\text{C}_{20}\text{H}_{35}\text{NO}$ $[\text{M}+\text{H}]$: 306.27969; found 306.27845.

Melting point 37 $^{\circ}\text{C}$

N-Methyl-N-(2-phenoxyethyl)dodecan-1-amine (Compound 22)



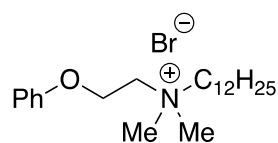
^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.28-7.26 (2H, m), 6.94-6.90 (3H, m), 4.07 (2H, t, $J = 6.2$ Hz), 2.80 (2H, t, $J = 6.2$ Hz), 2.44 (2H, t, $J = 7.6$ Hz), 2.34 (3H, s), 1.49 (2H, m), 1.29-1.26 (18H, m), 0.88 (3H, t, $J = 6.8$ Hz).

^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 158.8, 129.4, 120.6, 114.5, 66.0, 58.3, 56.1, 43.0, 31.9, 29.7, 29.6, 29.6, 29.6, 29.3, 27.5, 27.2, 22.7, 14.1.

IR (KBr, cm^{-1}) 2917, 2849, 1255, 1185, 1155, 1131, 1050, 1034, 773, 750, 718, 691. 418.

HRMS (DART) calculated for $\text{C}_{21}\text{H}_{37}\text{NO}$ $[\text{M}+\text{H}]$: 320.29534; found 320.29255.

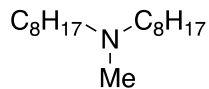
N,N-Dimethyl-N-(2-phenoxyethyl)dodecan-1-aminium (Domiphen Bromide 18)



^1H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.35-7.32 (2H, m), 7.01-6.99 (3H, m), 4.45 (2H, m), 3.79 (2H, m), 3.42-3.38 (2H, m), 3.16 (6H, s), 1.71 (2H, m), 1.25 (18H, m), 0.86 (3H, t, $J = 6.3$ Hz).

^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 157.3, 129.5, 121.3, 114.6, 63.9, 61.8, 61.3, 50.8, 31.3, 30.7, 29.0, 28.9, 28.8, 28.7, 28.5, 25.8, 22.1, 21.8, 13.9.

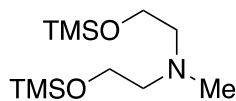
N-Methyl-di-n-octylamine (17a)



^1H NMR (600 MHz, CDCl_3): $\delta(\text{ppm})$: 2.31 (t, 4H, $J = 7.56$ Hz), 2.21 (s, 3H), 1.48-1.40 (m, 4H), 1.32-1.18 (m, 20H), 0.88 (t, 6H, $J = 6.87$ Hz);

^{13}C NMR (150 MHz, CDCl_3): $\delta(\text{ppm})$: 57.9, 42.3, 31.8, 29.6, 29.3, 27.6, 27.2, 22.6, 14.1.

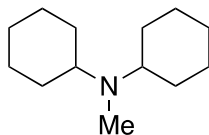
N-Methyl-bis[2-(trimethylsilyloxy)ethyl]amine (17b)



^1H NMR (600 MHz, CDCl_3): $\delta(\text{ppm})$: 3.56 (t, 4H, $J = 6.53$ Hz), 2.46 (t, 4H, $J = 6.53$ Hz), 2.20 (s, 3H), 0.00 (s, 18H)

^{13}C NMR (150 MHz, CDCl_3): $\delta(\text{ppm})$: 61.2, 60.5, 44.2, 0.2.

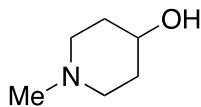
N-Methyl-dicyclohexylamine (17c)



^1H NMR (600 MHz, CDCl_3): $\delta(\text{ppm})$: 2.57-2.47 (m, 2H), 2.24 (s, 3H), 1.77-1.70 (m, 8H), 1.61-1.60 (m, 2H), 1.26-1.21 (m, 8H), 1.15-1.03 (m, 2H)

^{13}C NMR (150 MHz, CDCl_3): $\delta(\text{ppm})$: 59.2, 32.8, 30.5, 26.2, 26.1.

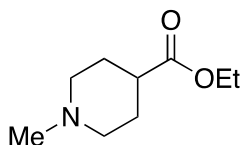
N-Methyl-4-hydroxypiperidine (17d)



^1H NMR (600 MHz, CDCl_3): $\delta(\text{ppm})$: 3.63-3.57 (m, 1H), 2.71-2.61 (m, 2H), 2.21 (s, 3H), 2.10-2.02 (m, 2H), 1.86-1.80 (m, 2H), 1.59-1.51 (m, 2H)

^{13}C NMR (150 MHz, CDCl_3): $\delta(\text{ppm})$: 66.6, 53.1, 45.8, 34.2.

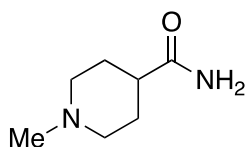
Ethyl N-methyl-4-piperidinecarboxylate (17e)



^1H NMR (600 MHz, CDCl_3): $\delta(\text{ppm})$: 4.13 (q, 2H, $J = 7.10$ Hz), 2.83-2.82 (m, 2H), 2.29-2.22 (m, 4H), 2.02-2.01 (m, 2H), 1.93-1.90 (m, 2H), 1.80-1.76 (m, 2H), 1.25 (t, 3H, $J = 6.87$ Hz)

^{13}C NMR (150 MHz, CDCl_3): $\delta(\text{ppm})$: 174.9, 60.2, 54.8, 46.2, 40.3, 28.0, 14.1.

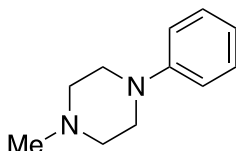
N-Methyl-4-piperidinecarboxamide (17f)



^1H NMR (600 MHz, CDCl_3): $\delta(\text{ppm})$: 7.19 (s, 1H), 6.70 (s, 1H), 2.73 (d, 2H, $J = 11.00$ Hz), 2.11 (s, 3H), 1.99-1.95 (m, 1H), 1.78 (t, 2H, $J = 11.00$ Hz), 1.66-1.62 (m, 2H), 1.54-1.39 (m, 2H)

^{13}C NMR (150 MHz, CDCl_3): $\delta(\text{ppm})$: 176.6, 54.9, 46.2, 41.1, 28.5.

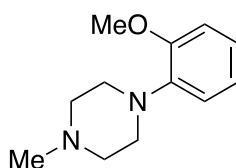
N-Methyl-N'-phenylpiperazine (17g)



^1H NMR (600 MHz, CDCl_3): $\delta(\text{ppm})$: 7.25-7.23 (m, 2H), 6.93-6.91 (m, 2H), 6.85-6.84 (m, 1H), 3.20 (t, 4H, $J = 5.15$ Hz), 2.56 (t, 4H, $J = 5.15$ Hz), 2.33 (s, 3H)

^{13}C NMR (150 MHz, CDCl_3): $\delta(\text{ppm})$: 151.1, 128.9, 119.5, 115.9, 55.0, 48.9, 46.0.

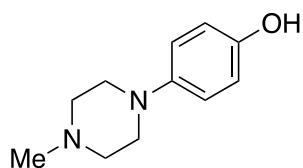
N-Methyl-N'-(2-methoxyphenyl) piperazine (17h)



^1H NMR (600 MHz, CDCl_3): $\delta(\text{ppm})$: 6.93-6.80 (m, 3H), 6.78-6.75 (m, 1H), 3.78 (s, 3H), 3.09-2.96 (m, 4H), 2.58-2.51 (m, 4H), 2.28(s,3H)

^{13}C NMR (150 MHz, CDCl_3): $\delta(\text{ppm})$: 152.1, 141.2, 122.7, 120.8, 118.1, 111.0, 55.23, 55.19, 50.5, 46.1.

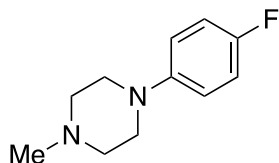
N-Methyl-N'-(4-hydroxyphenyl) piperazine (17i)



^1H NMR (600 MHz, CDCl_3): δ (ppm): 8.79 (br s, 1 H), 6.75 (d, 2H, $J = 7.56$ Hz), 6.63 (d, 2H, $J = 8.25$ Hz), 2.94-2.92 (m, 4H), 2.44-2.40 (m, 4H), 2.19 (s, 3H)

^{13}C NMR (150 MHz, CDCl_3): δ (ppm): 150.8, 144.2, 117.6, 115.4, 54.8, 49.8, 45.7.

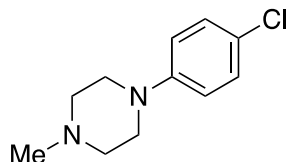
N-Methyl-N'-(4-fluorophenyl) piperazine (17j)



^1H NMR (600 MHz, CDCl_3): δ (ppm): 6.94-6.89 (m, 2H), 6.86-6.82 (m, 2H), 3.09 (t, 4H, $J = 4.81$ Hz), 2.53 (t, 4H, $J = 4.81$ Hz), 2.31 (s, 3H)

^{13}C NMR (150 MHz, CDCl_3): δ (ppm): 157.9, 156.3, 147.9, 117.7 (d, $J = 28.7$ Hz), 115.4 (d, $J = 86.2$ Hz), 55.1, 50.1, 46.1.

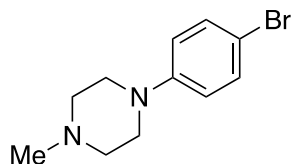
N-Methyl-N'-(4-chlorophenyl) piperazine (17k)



^1H NMR (600 MHz, CDCl_3): δ (ppm): 7.13 (d, 2H, $J = 8.50$ Hz), 6.77 (d, 2H, $J = 8.50$ Hz), 3.10 (t, 4H, $J = 4.12$ Hz), 2.50 (t, 4H, $J = 4.47$ Hz), 2.28 (s, 3H)

^{13}C NMR (150 MHz, CDCl_3): δ (ppm): 149.8, 128.9, 124.5, 117.2, 54.9, 49.0, 46.0.

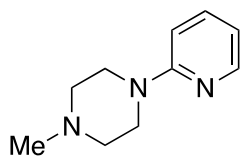
N-Methyl-N'-(4-bromophenyl) piperazine (17l)



^1H NMR (600 MHz, CDCl_3): δ (ppm): 7.25 (d, 2H, $J = 8.25$ Hz), 6.70 (d, 2H, $J = 8.25$ Hz), 3.09 (t, 4H, $J = 4.47$ Hz), 2.47 (t, 4H, $J = 4.81$ Hz), 2.26 (s, 3H)

^{13}C NMR (150 MHz, CDCl_3): δ (ppm): 150.3, 131.8, 117.6, 111.7, 54.9, 48.9, 46.1.

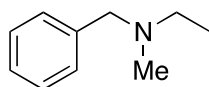
N-Methyl-N'-(2-pyridyl) piperazine (17m)



^1H NMR (600 MHz, CDCl_3): δ (ppm): 8.20- 8.18 (m, 1H), 7.47 (ddd, 1H, $J = 8.90, 7.10, 2.00$ Hz), 6.66-6.60 (m, 2H), 3.56 (t, 4H, $J = 5.15$ Hz), 2.52 (t, 4H, $J = 5.15$ Hz), 2.34 (s, 3H)

^{13}C NMR (150 MHz, CDCl_3): δ (ppm): 159.5, 147.9, 137.3, 113.2, 107.0, 54.8, 46.2, 45.1.

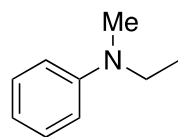
N-Methyl-N-ethyl-benzylamine (17n)



^1H NMR (600 MHz, CDCl_3): δ (ppm): 7.26-7.22(m, 4H), 7.19-7.15 (m, 1H), 3.41 (s, 2H), 2.38 (q, 2H, $J = 7.10$ Hz), 2.12 (s, 3H), 1.03 (t, 3H, $J = 7.22$ Hz)

^{13}C NMR (150 MHz, CDCl_3): δ (ppm): 139.1, 129.0, 128.1, 126.8, 61.9, 51.1, 41.6, 12.4.

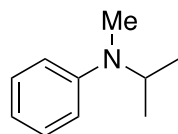
N-Methyl-N-ethylaniline (17o)



^1H NMR (600 MHz, CDCl_3): δ (ppm): 7.25-7.22 (m, 2H), 6.74-6.69 (m, 3H), 3.40 (q, 2H, $J = 7.10$ Hz), 2.90 (s, 3H), 1.12 (t, 3H, $J = 7.10$ Hz)

^{13}C NMR (150 MHz, CDCl_3): δ (ppm): 148.9, 129.1, 116.1, 112.4, 46.7, 37.4, 11.1.

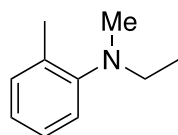
N-methyl-N-isopropylanilin (17p)



^1H NMR (600 MHz, CDCl_3): δ (ppm): 7.25-7.22 (m, 2H), 6.81 (d, 2H, $J = 7.56$ Hz), 6.71 (t, 1H, $J = 7.22$ Hz), 4.12-4.09 (m, 2H), 2.74 (s, 3H), 1.17(d,6H, $J=6.19$ Hz)

^{13}C NMR (150 MHz, CDCl_3): δ (ppm): 150.1,129.0,116.4,113.3, 48.9, 29.7, 19.2.

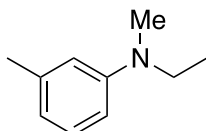
N-Methyl-N-ethyl-o-toluidine (17q)



^1H NMR (600 MHz, CDCl_3): $\delta(\text{ppm})$: 7.16 (q, 2H, $J = 7.56$ Hz), 7.04 (d, 1H, $J = 8.25$ Hz), 6.95 (t, 1H, $J = 7.22$ Hz), 2.91 (q, 2H, $J = 7.10$ Hz), 2.68 (s, 3H), 2.31 (s, 3H), 1.10 (t, 3H, $J = 7.22$ Hz)

^{13}C NMR (150 MHz, CDCl_3): $\delta(\text{ppm})$: 152.2, 133.1, 131.0, 126.2, 122.6, 119.8, 50.4, 40.9, 18.3, 12.8.

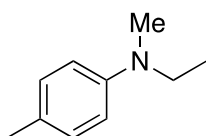
N-Methyl-N-ethyl-m-toluidine (17r)



^1H NMR (600 MHz, CDCl_3): $\delta(\text{ppm})$: 7.19-7.16 (m, 1H), 6.60-6.58 (m, 3H), 3.43 (q, 2H, $J = 7.10$ Hz), 2.93 (s, 3H), 2.37 (s, 3H), 1.16 (t, 3H, $J = 7.10$ Hz)

^{13}C NMR (150 MHz, CDCl_3): $\delta(\text{ppm})$: 149.1, 138.7, 129.0, 117.1, 113.2, 109.7, 46.8, 37.4, 21.9, 11.2.

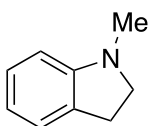
N-Methyl-N-ethyl-p-toluidine (17s)



^1H NMR (600 MHz, CDCl_3): $\delta(\text{ppm})$: 6.96 (d, 2H, $J = 8.25$ Hz), 6.61-6.57 (m, 2H), 3.28 (q, 2H, $J = 7.10$ Hz), 2.78 (s, 3H), 2.18 (s, 3H), 1.01 (t, 3H, $J = 7.10$ Hz)

^{13}C NMR (150 MHz, CDCl_3): $\delta(\text{ppm})$: 147.1, 129.6, 125.4, 112.9, 47.1, 37.6, 20.1, 11.0.

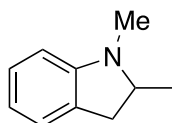
1-Methylindoline (17t)



^1H NMR (600 MHz, CDCl_3): $\delta(\text{ppm})$: 7.09-7.06 (m, 2H), 6.66 (t, 1H, $J = 7.22$ Hz), 6.48 (d, 1H, $J = 8.25$ Hz), 3.28 (t, 2H, $J = 8.25$ Hz), 2.93 (t, 2H, $J = 7.90$ Hz), 2.75 (s, 3H)

^{13}C NMR (150 MHz, CDCl_3): $\delta(\text{ppm})$: 153.4, 130.3, 127.3, 124.2, 117.7, 107.2, 56.1, 36.2, 28.7.

1,2-Dimethylindoline (17u)

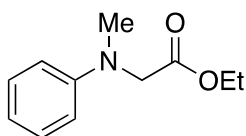


^1H NMR (600 MHz, CDCl_3): $\delta(\text{ppm})$: 7.08-7.03 (m, 2H), 6.65 (t, 1H, $J = 7.22$ Hz), 6.44 (d,

1H, J = 8.25 Hz), 3.42-3.36 (m, 1H), 3.07 (q, 1H, J = 7.79 Hz), 2.70 (s, 3H), 2.59 (dd, 1H, J = 15.12, 10.31 Hz), 1.32 (d, 3H, J = 6.19 Hz)

¹³C NMR (150 MHz, CDCl₃): δ(ppm): 153.5, 129.2, 127.3, 124.0, 117.8, 107.1, 62.8, 37.3, 33.7, 18.7.

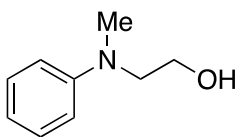
N-Methyl-N-phenylglycine ethyl ester (17v)



¹H NMR (600 MHz, CDCl₃): δ(ppm): 7.22 (m t, 2H, J = 7.90 Hz), 6.74 (t, 1H, J = 7.22 Hz), 6.68 (d, 2H, J = 8.25 Hz), 4.16 (q, 2H, J = 7.10 Hz), 4.05 (s, 2H), 3.06 (s, 3H), 1.23 (t, 3H, J = 6.87 Hz)

¹³C NMR (150 MHz, CDCl₃): δ(ppm): 170.9, 148.8, 129.0, 117.2, 112.2, 60.7, 54.4, 39.4, 14.1.

2-(N-Methylanilino)-ethanol (17w)



¹H NMR (600 MHz, CDCl₃): δ(ppm): 7.24 (t, 2H, J = 7.90 Hz), 6.83-6.72 (m, 3H), 3.78 (t, 2H, J = 5.50 Hz), 3.45 (t, 2H, J = 5.84 Hz), 2.95 (s, 3H), 2.04 (brs, 1H)

¹³C NMR (150 MHz, CDCl₃): δ(ppm): 149.8, 129.1, 117.0, 112.8, 59.8, 55.2, 38.6.

2. Experimental section in SECTION III

本章については、5年以内に雑誌等で刊行予定のため、非公開。

3. Experimental section in SECTION IV

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。

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