論文の内容の要旨

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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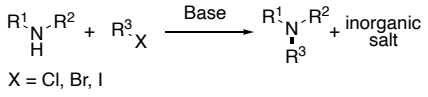
Introduction

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 all over the world, catalytic reactions are preferred and continuous-flow reactions with heterogeneous catalysts are regarded as ideal methods.[1]

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, 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.



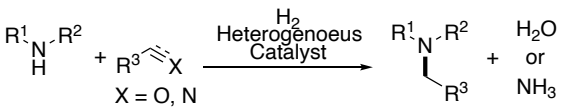
Scheme 1. Substitution Reactions with Alkyl Halides

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 solo byproduct

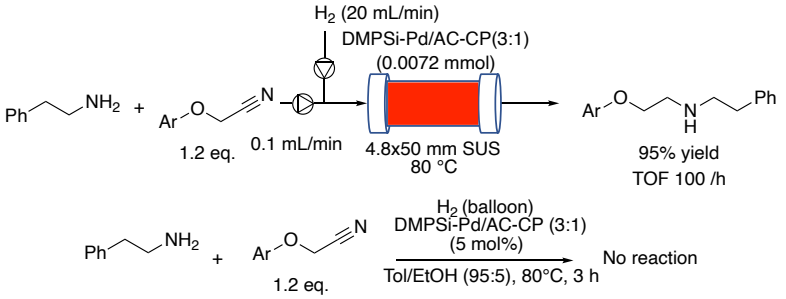


Scheme 2. Reductive Amination

(Scheme 2). Williams *et al*. and Kobayashi *et al.* respectively reported continuous-flow reductive amination utilizing a commercially available Pt/C catalyst with hydrogen.[2,3] 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))[4] showed high activity and durability for reductive amination of 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 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.



Scheme 3. Comparison of continuous-flow and batch reaction

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/SiO_2 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.

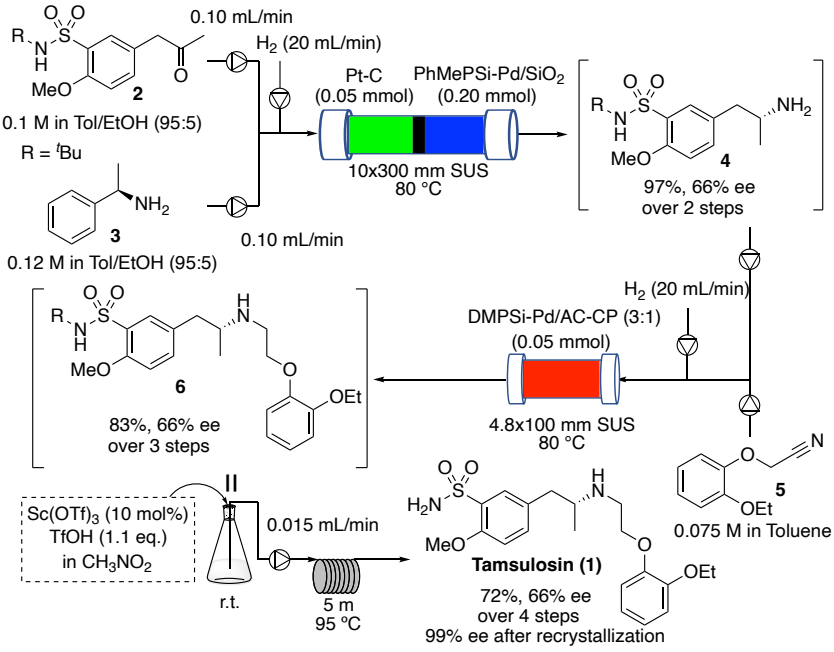


Figure 1. Overall scheme for Tamsulosin synthesis

1.3 Domiohen Bromide and Carvedilol Synthesis

To show the further utility of the 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.

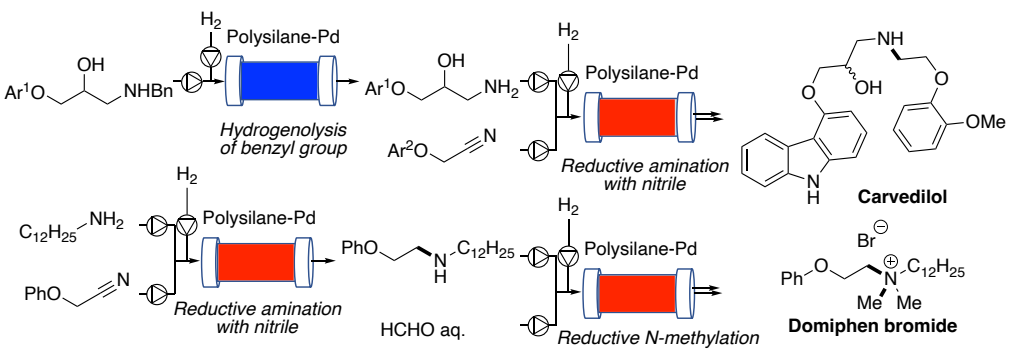


Figure 2. Domiphen bromide and Carvedilol

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.[5] 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 (MoO_3/TiO_2-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, 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 MoO_3/TiO_2-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.

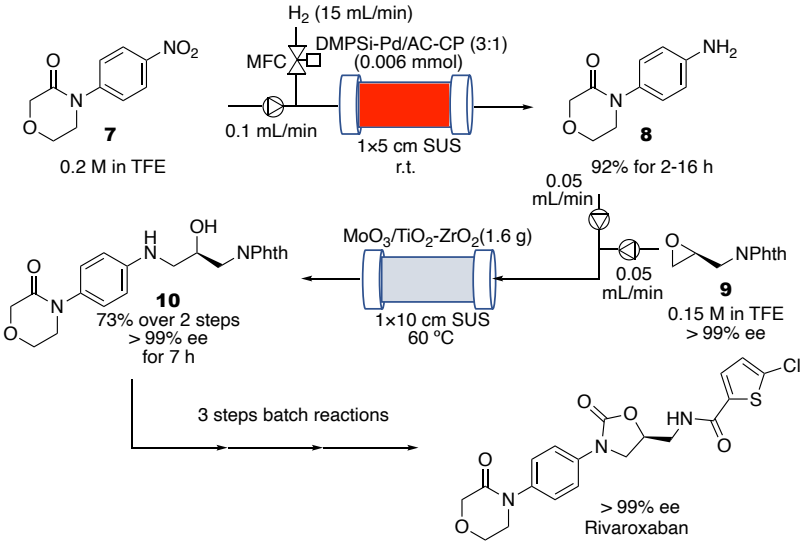
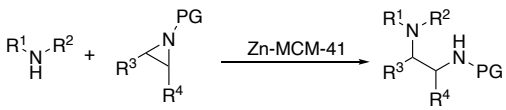


Figure 3. Overall Scheme for Rivaroxaban Synthesis

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



Scheme 4. Aminolysis of Aziridines

to the low reactivity of aziridines compared with epoxides, substrates are mostly limited to activated aziridines such as N-tosyl-protected ones. This limitation doesn't 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-doped 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.

Conclusion

I developed efficient C–N bond-forming reactions in continuous flow systems. First, reductive amination with nitriles was conducted with DMPSi-Pd/AC-CP(3:1) catalyst. To demonstrate the utility of the reaction, sequential-flow syntheses of APIs, Tamsulosin, Carvedilol, and Domiphen Bromide, were investigated. Also, a reductive N-methylation reaction was developed. Second, aminolysis of epoxides in continuous-flow system was described, and the reaction was utilized for sequential-flow synthesis of a Rivaroxaban precursor. From a viewpoint of catalyst cost and activity, MoO_3/TiO_2-ZrO_2 was found to be efficient. Finally, continuous-flow aziridine opening reaction by amine was studied, and it was found that the Zn-MCM-41 catalyst had optimal activity and durability.

References

[1] S. Kobayashi *et al. J. Org. Chem.* **2020**, *85*, 5132. [2] J. Williams *et al. Catal. Sci. Technol.* **2013**, *3*, 85.
[3] S. Kobayashi *et al. Adv. Synth. Catal.* **2018**, *360*, 4699. [4] S. Kobayashi *et al. Chem. Asian J.* **2020**, *15*, 1688.
[5] S.V. Luis *et al. React. Chem. Eng.* **2018**, *3*, 572.