Multistep-flow Syntheses of APIs Utilizing Continuous-flow C–N Bonds Forming Reactions with Heterogeneous Catalysts

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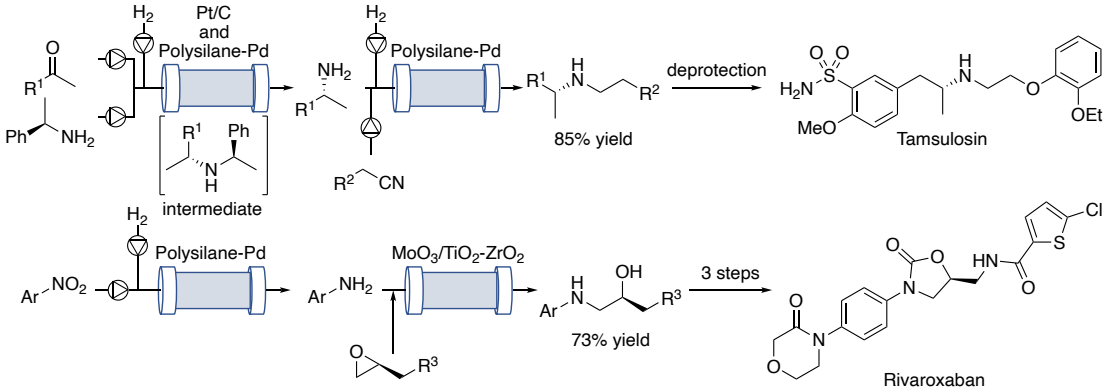
Multistep-flow synthesis is an efficient synthetic method to access complex structures such as active pharmaceutical ingredients (APIs). However, it's still challenging because byproduct formation disturbs consecutive reactions. C–N bond is one of the most abundant structures in fine chemicals, and most of the APIs have at least one C–N bond in their structures. Therefore, to achieve the multistep-flow synthesis of APIs, the development of continuous-flow C–N bond forming reactions with minimal amounts of byproducts is crucial. In this work, we investigated multistep-flow synthesis of APIs utilizing two types of continuous-flow C–N bond forming reactions with heterogeneous catalysts.

First, a Tamsulosin intermediate was synthesized via three-step sequential-flow reaction utilizing three different hydrogenation reactions. Of these, two types of polysilane-Pd catalysts were developed independently and used in the second and the third steps. An activated carbon-$Ca_3(PO_4)_2$-supported Pd catalyst and a silica-supported catalysts showed high activity and durability in reductive amination of a nitrile and hydrogenolysis of phenethyl group, respectively, and the overall yield was reached to 85%[1]. Second, a Rivaroxaban intermediate was synthesized in 73% yield via two-step reaction involving aminolysis of epoxide. In the aminolysis reaction, TiO_2-ZrO_2 supported molybdenum oxide catalyst exhibited high catalyst activity. Catalyst characterization revealed that acid density of the catalyst is one of important factors for the high activity. Both of the target compounds could be synthesized without any purification of intermediates and solvent exchange.



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