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Flow fine synthesis with heterogeneous catalysts

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ABSTRACT

In the past few decades, organic reactions under flow conditions have attracted increasing attention. Flow reactions have a number of advantages over batch reactions in terms of environmental compatibility, efficiency, and safety. In particular, flow reactions with heterogeneous catalysts that yield desired products without significant levels of by-product formation can enable purification processes to be avoided. This feature can allow flow reactions to be assembled in a multi-step and continuous manner for the synthesis of complex molecules. These new techniques have opened up new approaches to the synthesis of fine chemicals and are expected to play a prominent role in future chemical manufacturing processes. In this context, this review aims to summarize recent developments in continuous-flow reactions with heterogeneous catalysts for synthesis of fine chemicals.

Contents

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1. Introduction

The methodologies used in synthetic organic chemistry have been undergoing development for more than a century, and have for a long time traditionally relied on batch reactors, even in the industrial field. Glassware and other equipment used in modern laboratories are well designed for synthesis, but conceptually they are no different from 150 years ago. Meanwhile, in the field of petrochemicals and related bulk chemistry, products are treated continuously in flow-through systems optimized for high performance, cost efficiency, safety, and automatic operation for large-scale production. In recent decades, chemists in both academia and industry have been giving more consideration to flow-through type synthesis. In this technique, reagents/reactants are continuously injected into a confined reaction area using a mechanical setup so that only a limited amount of reagents react at a given time. These characteristics are advantageous to creating more efficient and safe reaction systems: reagents are mixed well by rapid diffusion in a narrow reaction area, reaction heat is easily removed from the large surface area of a reactor, treatment of chemicals in a closed system enables safe handling of hazardous chemicals, and a mechanical system setup ensures high reproducibility. In addition, the mechanical setup of a reaction system allows full automation of a process and rapid system evaluation. With respect to industrial applications, these characteristics offer great potential for reducing the cost of production.

Generally, flow synthesis can be classified into four types[1] (Fig. 1). **Type I**: In the simplest case, a stoichiometric reaction of A with B is promoted by simple mixing in a reactor (column or hollow tube) under specified conditions (heated, pressurized, etc.). As the reaction proceeds in the reactor, the concentration of each component decreases to diminish the reactivity, and sometimes unreacted reagents are obtained with a product. **Type II**: One of the reagents (B) is supported in a column and reacted with a flowing reagent A. The immobilization of an excess amount of B means that the reaction easily reaches full conversion and contamination of A or B is avoided, although overreaction(s) may occur. **Type III**: Reagents A and B are reacted in the presence of a homogeneous catalyst under continuous flow. Contamination by the catalyst cannot be avoided, and further separation or purification of the product is required. **Type IV**: A catalytic reaction of A with B is promoted by a heterogeneous catalyst in the reactor. If full conversion is achieved, no further purification of the product is necessary.

Based on the concept of green sustainable chemistry, catalytic reactions (Types III and IV) are preferable because they generally require less energy and produce less waste. Flow reactions of Type IV especially, with heterogeneous catalysts as a stationary phase, can obviate the need for both separation of catalysts and workup procedures after the flow; therefore, such systems are regarded as the most desirable way to produce organic substances. In an ideal "catalytic" continuous-flow reaction, all starting materials and reactants are consumed and only the desired material is obtained at the end of the flow. The obtained products can be applied directly in the next reaction without further treatment. By connecting such a "fine" flow synthesis in a multi-step way, it is possible to construct high-complexity molecules within a short reaction time, in a limited space in a laboratory, and in an "on demand" manner.

Type IV flow reactions, with heterogeneous catalysts, can be further classified based on the constitution of reactors and style of catalyst immobilization[2] (Fig. 2):

- Catalytic capillary

Narrow tubes, channels, or capillary-type reactors are coated with catalysts in their interior, and the reaction occurs in a very narrow space passing through the center. In the confined space, substrates diffuse easily and contact the catalytic surface, thereby promoting the reaction with high efficiency. Catalysts are usually immobilized onto the wall of the reactor using chemical methods.

- Packed-bed reactor

Heterogeneous catalyst particles, or powder, are simply packed

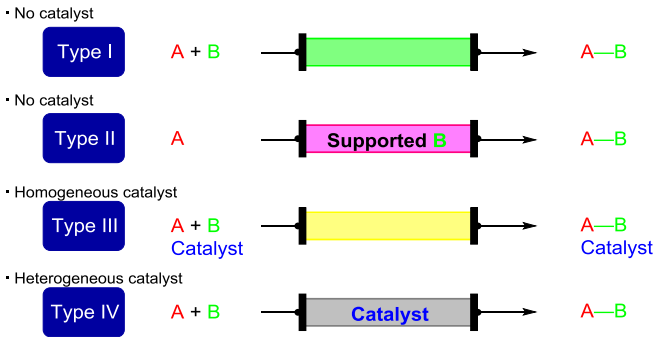

Fig. 1. Four types of flow reaction.[1]

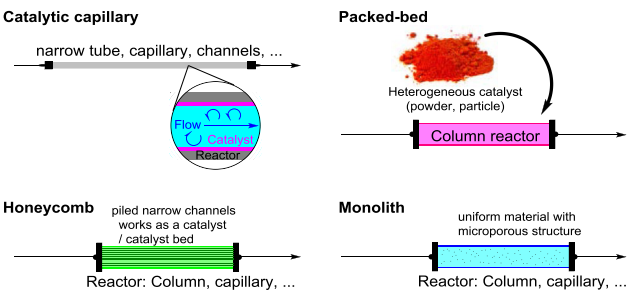

Fig. 2. Classification of heterogeneous catalysts in flow systems.