

Development of Heterogeneous Catalysts for Continuous-Flow Synthesis of Chiral Compounds

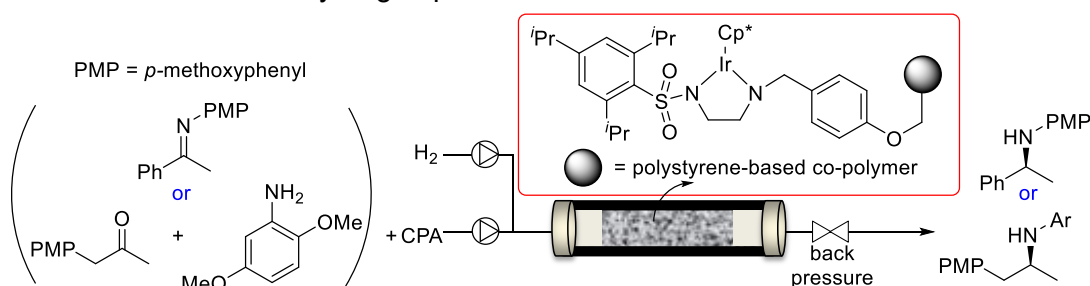
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Development of heterogeneous catalysts for asymmetric synthesis has lagged far behind that of homogeneous catalysts. One reason is that the advantages of heterogeneous catalysts, such as ease of separation and reusability, have not been valued compared to the high catalytic turnover of homogeneous catalysts. However, in recent years, toward the realization of a sustainable society, heterogeneous catalysts that can be used for continuous synthesis by the flow methods have been attracting attention. To accomplish such systems, the development of heterogeneous catalysts that can effectively produce useful chiral molecules and have a long lifetime is necessary. In this talk, the latest methodology to achieve efficient asymmetric synthesis by flow methods using heterogeneous catalysts will be discussed.

(1) Immobilized Ir complex catalysts for asymmetric hydrogenation in flow

Flow hydrogenation using heterogeneous catalysts is expected to show superior reactivity to conventional batch hydrogenation because of efficient mixing of the three phases (solid, liquid and gas).¹⁾ We developed heterogeneous iridium complex catalysts from polystyrene-immobilized chiral diamine ligands. Asymmetric hydrogenation of aromatic imines and reductive asymmetric amination of aliphatic ketones proceeded smoothly in the presence of these catalysts and chiral phosphoric acid co-catalyst (CPA).²⁾ When the catalyst system was applied to the flow method, continuous operation for more than 30-50 hours was possible and high activity could be maintained at lower hydrogen pressures than that in a batch method.

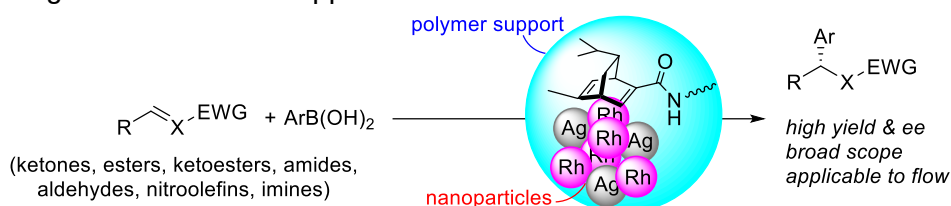


(2) Chiral Rh nanoparticle (NP) catalyzed asymmetric arylation reactions

Chiral ligands modified metal NP catalysts have a great potential to construct robust heterogeneous catalysts for asymmetric synthesis because NPs are easily immobilized with high stability. However, their applications to asymmetric C–C bond

forming reactions were very limited.³⁾

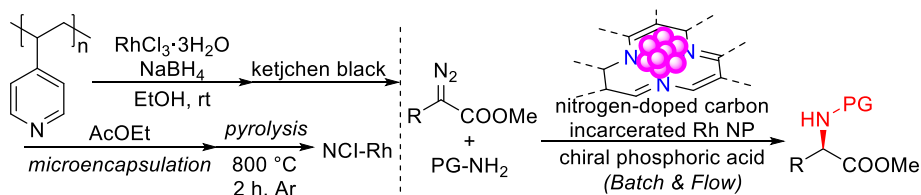
Rh/Ag bimetallic NP catalysts immobilized on polystyrene-based polymers and activated carbon as composite supports were developed. Asymmetric arylation of various electron-deficient double bonds using arylboronic acids proceeded in high yields with high enantioselectivity in the presence of these catalysts and chiral diene ligands.⁴⁾ The catalysts could be reused without metal leaching and loss of activity. Furthermore, Rh/Ag NP catalysts supported on chiral diene ligand-immobilized polymers were developed. They enabled the simultaneous recovery of both the metal and the ligand and could be applied to flow reactions.⁵⁾



(3) Nitrogen-doped carbon incarcerated Rh NP catalyzed asymmetric insertion of carbenoids to amines

To expand scope of metal NP catalysis, nitrogen-doped carbon as a support that can activate metals by a strong coordination was focused on. We developed nitrogen-doped carbon incarcerated metal NP catalysts (NCI-M) prepared by pyrolysis of metal NPs encapsulated by poly-4-vinylpyridine. They showed high activity for several oxidation reactions that hardly proceeded without dopants.⁶⁾

Encouraged by these results, nitrogen-doped carbon supported Rh NPs were developed and applied for the asymmetric insertion of amines into diazo esters in the presence of chiral phosphoric acid as a co-catalyst. The reaction proceeded only in the presence of nitrogen dopant and showed high yields and enantioselectivities without metal leaching. The catalytic system was also applicable to a flow reaction, and succeeded in maintaining high activity and selectivity for more than 65 h.



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