

論文の内容の要旨

Development of Novel Heterogeneous Nickel Catalysts Utilizing Mesoporous Silica as a Support Material for Enantioselective 1,4-Addition Reactions under Continuous-Flow Conditions

(連続フロー不斉 1,4-付加反応への適用を志向したメソポーラスシリカ担持新規不均一系ニッケル触媒の開発)

氏名 金井 敏

Although flow methods are very common in bulk chemical manufacturing, synthetic organic and process chemists have begun to pay much attention to the potential applications of flow methods for the synthesis of complex organic molecules since flow methods are safer to conduct, more efficient, and often generates less wastes compared to conventional batch methods. In particular, continuous-flow reactions with columns packed with heterogeneous catalysts represents the ideal flow reactor since the immobilized catalysts can facilitate organic transformations under mild conditions and in a selective manner, and will remain in the reactors so that multiple columns can be connected together for multi-step flow reactions without the fear of downstream catalyst contamination. Although flow processes taking advantage of heterogeneous catalysis is in high demand, relative narrow sets of highly active and selective heterogeneous catalyst are available for flow synthesis. For instance, enantioselective heterogeneous catalysis under continuous-flow condition is important since many specialty chemicals, such as drugs, are chiral. However, relatively limited number of chiral heterogeneous catalysts have been examined for fine flow synthesis. The most common approach of preparing chiral heterogeneous catalysts is through the attachment of catalytically active species on heterogeneous supports by utilizing a linker or spacer to mitigate undesirable influences from the support to the catalyst. However, these immobilized chiral catalysts are often inferior to their homogeneous counterparts, with respect to its reactivity and selectivity, and their preparation is often long and tedious. An alternative strategy for the immobilization of a chiral catalyst to a solid support is to utilize non-covalent bonding interactions, such as electrostatic or physiochemical absorption. Under flow conditions, a mobile phase including reactants penetrate into a static catalyst phase of a reactor along with close contact; thus, direct interaction between reactants with a catalyst phase through adsorption/desorption should be

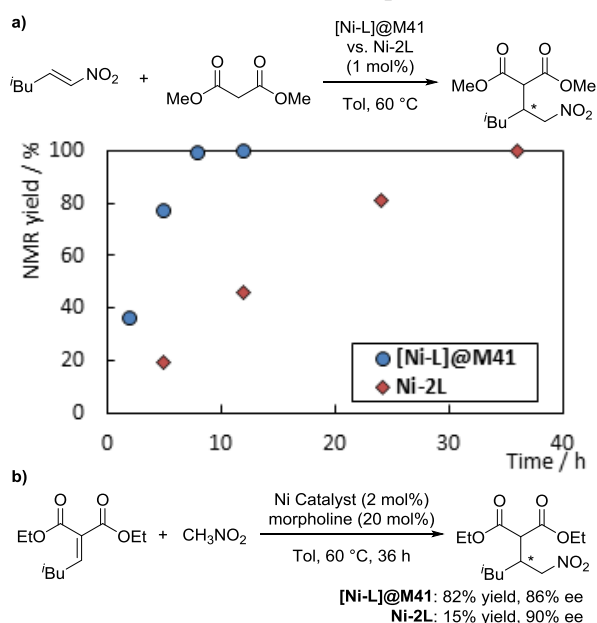
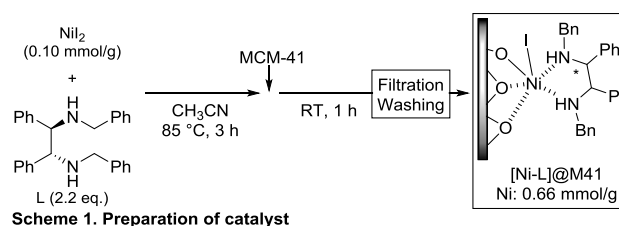
important. From these points of view, immobilization of chiral active sites directly onto supports by non-covalent bonding interactions is much suitable under flow conditions. However, a major challenge with this preparation method is the instability of these heterogeneous catalysts since non-covalent bonding is weaker than covalent bonding. It was hypothesized that mesoporous silica may represent an ideal support material for non-covalent immobilization of chiral metal complexes since the wide and uniform surface area and large pore space of these materials may provide a suitable environment that can efficiently immobilize the catalyst without diminishing its activity and selectivity. In this Ph.D. thesis, the utilization of chiral heterogeneous catalysts, generated through the impregnation of chiral metal complexes to mesoporous silica surface, for enantioselective reactions was examined.

In my master course study, the sequential-flow synthesis of racemic pregabalin, one of the world's top-selling drugs used for the treatment of various ailments, such as epilepsy, neuropathic pain, anxiety disorder, etc., was achieved. Since the actual drug is a chiral compound, I decided to establish an enantioselective flow synthesis of pregabalin with a chiral heterogeneous catalyst. For its synthesis, asymmetric 1,4-addition of a malonate to a nitroalkene is required to introduce chirality, and it was reported by Evans that a chiral nickel diamine complex was an effective catalysts for this organic transformation. I hypothesized that impregnation of the chiral nickel diamine catalyst to a mesoporous silica support would led to an efficient chiral heterogeneous catalyst. I found that a chiral complex prepared from nickel iodide and

chiral diamine could be immobilized on mesoporous silica, MCM-41 (Scheme 1). I demonstrated that this chiral composite worked well as a heterogeneous catalyst for 1,4-addition reactions of dimethyl malonate with nitroalkenes. To understand the nature of the

obtained heterogeneous catalyst, several experiments were performed. The nitrogen adsorption experiment indicated that the Brunauer-Emmett-Teller (BET) surface area and pore volume of the nickel-embedded sample decreased as the amount of nickel loaded on the support increased, while the external surface area was almost constant. This suggested that chiral nickel complexes were located inside of the MCM-41 mesopores. Quantitation

of nickel and iodine in the solid catalyst and amount of the chiral ligand recovered during the heterogeneous catalyst preparation revealed that the proportion of the newly formed nickel species was in the ratio of 1:1:1 for nickel, iodine, and ligand, respectively. This was supported by Ni K-edge EXAFS studies, and while the 1:1 complex is known to be unstable under homogeneous conditions, I hypothesized that the formation of nickel silicate bond may be key in stabilizing this nickel complex. I also found that the prepared heterogeneous catalyst showed better activity than the homogeneous chiral nickel complex when dimethyl malonate was used a substrate (Scheme 2a). On the other hand, the reaction rate was reversed when the larger dibenzyl malonate was employed as the nucleophile,

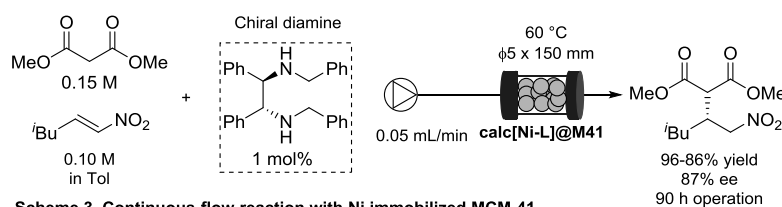


Scheme 2. Heterogeneous vs. homogeneous catalyst

and these results also supported my assertion that the chiral nickel diamine complex is located within the mesopores of the silica support. In addition, I found that the same catalyst provided the first successful examples of enantioselective 1,4-addition of nitromethane to alkylidene malonates with the assistance of a catalytic amount of morpholine (Scheme 2b). Although organic bases can decompose the homogeneous chiral Ni-diamine complex through ligand exchange, the supported Ni-diamine was compatible with the base, presumably due to the stabilizing effect of the support to the chiral metal complex.

I also applied the chiral mesoporous material as a catalyst for asymmetric continuous-flow synthesis. The [Ni-L]@M-41 powder could be easily packed in a stainless column reactor, and was used for the enantioselective 1,4-addition in flow. The desired product was obtained in a good yield and enantioselectivity. Although the catalyst lifetime was somewhat limited, I found that by co-feeding the chiral diamine (0.2 mol%) with the substrates enable the heterogeneous catalyst to be active for at least 1 day. Additionally, I demonstrated a two-step sequential-flow synthesis of (*S*)-pregabalin precursor by connecting the enantioselective addition reaction with a heterogeneous Pd-catalyzed hydrogenation reaction, and the desired γ -lactam was obtained in 89% yield with 87% ee.

In the previous part, I found that a new catalytic species was formed by treating a chiral Ni complex with mesoporous silica. However, single-site immobilization of the nickel species through I-Ni-O-Si bond led to a heterogenous catalyst with a relatively poor lifetime that was incompatible for long-term operation in flow. In this study, I tested another approach to generate a more robust heterogenous nickel catalyst through calcination. I used a surface modification technique with an achiral nickel diamine complex and MCM-41, and the obtained material was calcined at 450 °C in air to generate the desired nickel silicate bond and remove the achiral ligand. Asymmetric 1,4-addition of malonate to nitroalkene was used to evaluate the catalyst activity with external addition of a chiral diamine ligand. The continuous-flow reaction with the optimal calc[Ni-L]@M-41 and co-feeding 1 mol% chiral diamine ligand afforded the desired product in 86% yield with 87% ee for 90 h operation (Scheme 3). Compared with the typical impregnation method or template ion-exchange method, the present surface modification method provided a more robust catalyst.



In my Ph. D. studies, I developed various heterogeneous catalysts for enantioselective addition reactions by taking advantage of the features of mesoporous silica. In the first topic, a chiral Ni-diamine complex was directly immobilized on the mesoporous silica, and this led to a heterogeneous catalyst that possessed superior catalyst activity and stability compared to the homogeneous catalyst for asymmetric 1,4-addition reactions of malonates to nitroalkenes and nitromethane to alkylidene malonates. In the second topic, a more robust heterogeneous nickel material was prepared by calcination, and this solid catalyst, in conjunction with a chiral diamine ligand, was utilized for a continuous-flow asymmetric 1,4-addition reaction that could be operated for 90 hours without significant deactivation of the catalyst.