Studies on Regio- and Stereoselective Multicomponent Coupling Reaction *via* Nickelacycles

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Unsaturated hydrocarbons, such as alkenes and alkynes are very important constitutions for synthetic organic chemistry. However, owing to the high reactivity of C–C multiple bonds, the regio- and stereoselective control involving unsaturated hydrocarbons is quite difficult.

Metalacycles which are made from unsaturated hydrocarbon and transition metal complex catalyst are attractive and convenient intermediates for C–C bond formations and C–C bond cleavage reactions. Especially, novel catalytic reactions *via* nickelacycle have been developed in recent years, and oxanickelacycles and azanickelacycles serve as efficient activated species for C–C bond transformations.

Furthermore, multicomponent coupling reaction is one of the most convenient and versatile synthetic methods for C–C bond formations. This strategy often allows the construction of complicated molecules and a wide variety of fine chemicals from readily available small molecules in a single step. In this study, the regio- and stereoselective multicomponent coupling reactions are focused on the development of efficient organic synthesis using unsaturated hydrocarbons.

Chapter 1: Multicomponent Coupling Reaction *via* Oxanickelacycle; Stereoselective Coupling Reaction of Dimethylzinc and Alkyne toward Nickelacycles

The regio- and stereocontrolled three-component coupling reaction of alkynes, Me_2Zn, and vinyloxacyclopropane and vinylcyclopropane through oxanickelacycle intermediates to provide dienyl homoallylalcohols and α-dienyl malonates are described.

The reaction was readily conducted by exposing of Me_2Zn to a mixture of vinyloxacyclopropane and alkynes at room temperature under nitrogen atmosphere. In all cases, the alkynes tended to attack on the terminal carbon atom of the vinylic group to afford heptadienyl alcohol via methyl group transfer from Me_2Zn in a 3:1 ratio of *E* and *Z* isomers with respect to the C-2 olefin geometry.

Furthermore, the coupling reactions of alkynes, Me_2Zn, and vinylcyclopropane derived from dimethyl malonate and 1,4-dichloro-2-butene under similar catalytic conditions were investigated. In most cases, the reaction proceeded smoothly at room temperature within several hours and the coupling products were obtained with excellent *E*-stereoselectivities.

Chapter 2: Multicomponent Coupling Reaction *via* Azanickelacycle; Ni-Catalyzed Homoallylation of Polyhydroxy *N*,*O*-Acetals with Conjugated Dienes Promoted by Triethylborane

This chapter describes a reaction system involving a Ni catalyst and triethylborane that was extended successfully to the homoallylation of *N*,*O*-acetals prepared from cyclic hemiacetals and primary amines to provide ω-hydroxybishomoallylamines in high regio- and stereoselectivity. In similar catalytic reaction systems, *N*,*O*-acetals from carbohydrates with primary amines gave the polyhydroxybishomoallylamines as physiologically active molecules for development of medicinal and synthetic chemistry.

Chapter 3: Multicomponent Coupling Reaction *via* Nickelacycle; Efficient and Selective Formation of Unsaturated Carboxylic Acids and Phenylacetic Acids from Diketene

In this chapter, a Ni-catalyzed multicomponent coupling reaction of alkyne, dimethylzinc, and diketene (as butenoic acid equivalent) to provide 3-methylene-4-hexenoic acids in a single manipulation is described. In the presence of Ni catalyst, a formal [2+2+2] cycloaddition reaction with diketene and two equivalents of alkynes proceeded to give phenylacetic acid derivatives by use of $Et_2Al(OEt)$, instead of Me_2Zn. Furthermore, in the presence of Ni catalyst and PPh_3 under the similar catalytic conditions, the regio selectivity was changed dramatically to provide the symmetrical substituted phenylacetic acid as a single product *via* C–C double bond cleavage of diketene.

Ni-catalyzed oxidative cyclization of alkyne and diketene seems to form nickelacyclopentene intermediate. In the absence of phosphine ligand, the ring expansion reaction undergoes to form oxanickelacycle intermediate, whereas, in the presence of phosphine ligand, the active nickelacycle bearing PPh_3 ligand invokes C–C bond cleavage reaction *via* nickel carbene cyclopropane rearrangement.