Catalytic enantioselective alkylation of imines is one of the most efficient methods to access optically active propargylamines. Conventional methods to realize the reactions mostly rely on the use of stoichiometric amounts of organometallic reagents. A rational approach to developing a much greener protocol would be in situ catalytic activation of unmodified terminal alkynes without pre-activation of alkynes under proton-transfer conditions. This direct approach is successful for aldmines, but reactions with ketimines, which provide chiral propargylamines with tetrasubstituted carbon stereocenters, are quite limited in the literature because of the reduced reactivity and difficulty in obtaining enantioselectivity for ketimines. Based on our previous report on direct catalytic enantioselective alkylation of ethyl trifluoroacetate, 2 we achieved direct enantioselective alkylation of both aryl- and alkyl-substituted terminal alkynes α-ketiminoester catalyzed by diacetato-Rh-Phebox complex. 3 This reaction provided α-trifluoromethyl α-amino acid derivatives with tetrasubstituted carbon stereocenter in high yield and enantioselectivity. Furthermore, application to the enantioselective synthesis of α-trifluoromethyl thalidomide analog was realized.

Limited reactivity of diacetato Rh complex, however, prevented further application to other ketimines. To improve the reactivity of Rh catalysts, we performed detailed mechanistic studies and found that alkynyl-Rh complex is catalytically active species in the alkylation and coordination of terminal alkynes to Rh is the turnover-limiting step. In fact, the reaction with this alkynyl-Rh complex was more than 20 times faster than that with diacetato-Rh complex. Based on these mechanistic studies, we synthesized trimethylsilylalkynyl-Rh complex as a general precatalyst for alkylation, and the use of this precatalyst allowed us to perform reactions with reduced catalyst loading without affecting yield and enantioselectivity. Enhanced reactivity also allowed us to obtain alkylation products of less-reactive α-ketimino phosphonate and cyclic N-sulfonyl-α-ketiminoesters.

REFERENCES

Date: 12th December 2014 (Friday)
Time: 11:00am–12:30pm
Venue: NTU SPMS CBC Building Level 2, Conference Room
Host: Assoc Professor Shunsuke Chiba