Development of Unactivated Bond Cleavage and Its Application for the Removal of Directing Groups

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論　文　内　容　の　要　旨

The molecules having directing groups are designed to functionalize substrates with respect to reaction efficiency, selectivity, and scope. To enhance the utility of these functionalization reactions, the selective transformation of the directing groups into more useful functional groups is a critical issue. Therefore, the development of unactivated bond cleavage reactions under mild conditions offers an efficient approach for the functional group transformations and have found important applications in synthetic organic chemistry. This dissertation covers our recent development of practical methodologies to transform two important directing groups—8-aminoquinoline amides and 2-acylimidazoles.

1. Ni(II)-Catalyzed Direct Alcoholysis of Unactivated 8-Aminoquinoline Amides (My work focused on the alcohol scope and demonstration of advantages)

The 8-aminoquinoline amide is one of the most reliable directing groups for regioselective functionalization reactions. In most cases, however, cleavage of C–N bond of 8-aminoquinoline amide requires harsh reaction conditions, limiting the functional group compatibility. Another option is to attach an activating functionality such as a tert-butoxycarbonyl group before the cleavage, but such indirect methods require additional reaction steps, as well as additional reagents. Although the recent seminal contributions offer some solutions to cleave amide bonds, none of these strategies had been applied for the catalytic cleavage of directing group amides.

The reaction system was established very well, in which only 8-aminoquinoline amides, alcohols, and a commercially available, air-stable Ni(II) diketonate catalyst are used to give the desired esters with high chemoselectivity and broad functional group tolerance. I focused on the examination of alcohol scope. A one-pot, direct catalytic alcoholysis-catalytic transesterification reactions using nickel(II) and iron(III) catalysts was developed to broaden the applicability of alcohols. This C-N bond cleavage reaction has already been applied by

several research groups to transform their functionalized 8-aminoquinoline amides into esters effectively, demonstrating the practicality of our method.

2. Direct C–C Bond Cleavage of 2-Acylimidazoles

2-Acylimidazoles are widely used for a number of chemoselective and enantioselective reactions. Nevertheless, the transformation of 2-acylimidazoles requires pretreatment with highly reactive methylating reagents to generate an imidazolium salt which allows C–C bond cleavage via nucleophilic attack under basic conditions. This conventional method has several drawbacks, however, such as toxicity of the reagent, low step economy, waste formation, and limited functional group tolerance. Thus, the development of a more practical C–C bond cleavage method under mild conditions is greatly desired.

We discovered that such pretreatment is unnecessary and the C–C bond of 2-acylimidazoles can be cleaved directly with nucleophiles in the absence of any catalysts nor additional reagents. In the dissertation, I will show the effects of 2-acylimidazole structure on reactivity, substrate scope with broad functional group tolerance, chemoselective C–C bond cleavage, and preliminary mechanistic studies. In addition, applications to the reported functionalized and enantioenriched 2-acylimidazoles will also be demonstrated.

Catalytic reaction for transformation from 2-acylimidazole ketones into benzimidazole structures were also preliminarily developed. $Sc(OTf)_3$ effectively promoted imine formation, then C-C bond cleaved via intermolecular cyclization. Various 2-acylimidazoles as well as 2-acylpyrrole and 2-acylbenzothiozole were investigated to demonstrate the reaction efficiency and broad functional group tolerance.