主　論　文　の　要　約

論文題目　Rational Design of High-Performance Catalysts Based on Acid–Base Dual Activation: Amidation and Halocyclization
(酸塩基二重活性化に基づく高機能触媒の創製：アミド縮合反応とハロ環化反応)

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論　文　内　容　の　要　約

Chapter 1. Introduction (Amidation)

The amide bond plays a critical role in proteins, pharmacologically active compounds and various other materials (such as nylon, hydrogels and artificial silks). In fact, the amide unit is used in 2/3 of drug candidates and is present in 1/4 of all pharmaceuticals currently on the market. It has been estimated that “amidation” has been the most commonly used reaction in the synthesis of pharmaceuticals. A host of efficient methods employing dehydrating-activating reagents have been developed for direct coupling of carboxylic acids and amines. These reagents are highly effective, even for the industrial synthesis of peptides. Unfortunately, the process generally suffers from poor atom economy, complicated purification of the product and the use of environmentally harmful toxic reagents. Thus, catalytic condensation between carboxylic acids and amines should be one of the most ideal methods for amide synthesis, since the only byproduct is water.

Organoboron compounds have long been known to be effective Lewis acidic activators of the carbonyl group. Over the past two decades, organoboron-catalysis for direct condensation between carboxylic acids and amines has enjoyed great success with respect to both optimization of catalyst activity and understanding of the underlying mechanism. While the application of *ortho*-functionalized arylboronic acids has made it possible to use more practical and mild conditions involving simple and reactive carboxylic acids and amines, their performance with sterically demanding substrates, multifunctional substrates and amino acid residues has been far more appreciated. Moreover, to afford more practical alternatives, with particular emphasis on

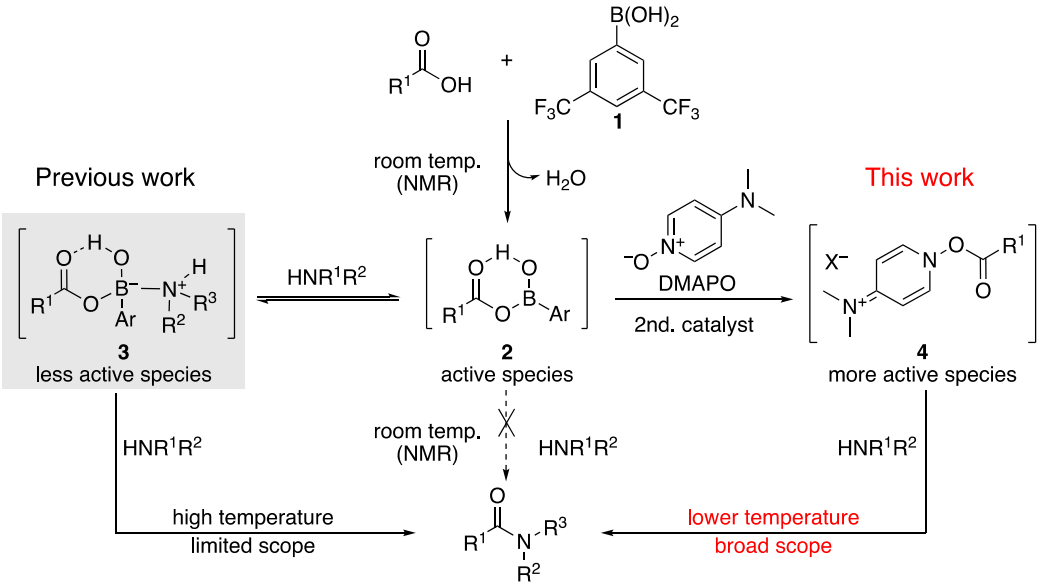
catalyst recovery and reuse, notable drawbacks of the current boronic acid catalysts: 1) They require relatively long steps to prepare, which would increase the cost of large-scale synthesis, and 2) Specific functional groups such as a pyridinyl group or a hydroxycarbonyl group on the boronic acids are needed to bind to the solid carriers; should be overcome.

Chapter 2 describes the boronic acid–nucleophilic base cooperative catalysis for dehydrative condensation between less reactive carboxylic acids and amines. Chapter 3 describes the design of simple boronic acid–base complexes as reusable homogeneous catalysts in direct amidation.

Chapter 2

Boronic acid **1** was previously reported to activate carboxylic acid through the generation of a mixed anhydride **2**. If the substrate amine directly attacks the acyl group of **2**, the corresponding amide should be obtained. However, amines can otherwise coordinate to the boron center of active species **2** to give a more stable tetrasubstituted boronate complex **3** (Scheme 1, left). It was anticipated that suppression of the generation of **3** might increase the chance for amide formation. Thus, a two-step activation of carboxylic acid using boronic acid–nucleophilic base cooperative catalysis was developed. In this catalysis, DMAPO was thought to promote amidation by the transformation of **2** to a more active cationic species **4** before the generation of less reactive **3** (Scheme 1, right).

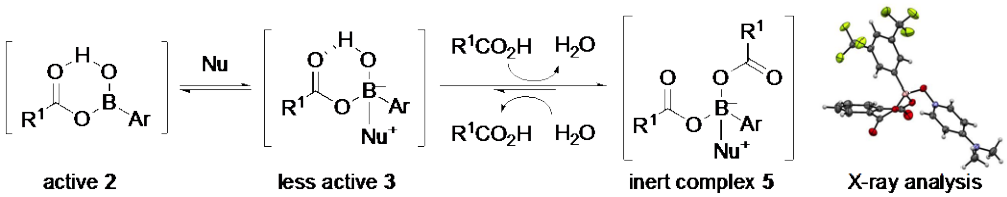
Scheme 1. Second activation of carboxylic acids with DMAPO



In the amidation of less hindered carboxylic acid, a relatively stable complex **5**, which is inert for amidation, was observed (Scheme 2). Through NMR study, the author found that weak Lewis acidic phenylboronic acid or *ortho*-substituted phenylboronic acid was effective for destabilizing the

inert species **5** and forcing the equilibrium to the active process. The results suggested that both the nucleophilicity of the additive and the Lewis acidity and steric effect of the boronic acid are important in the cooperative catalysis with an $ArB(OH)_2$–nucleophilic base. Through tuning the combinations, it was found that the cooperative use is much more effective than their individual use as catalysts, and chemoselectively promotes the amide condensation of (poly)conjugated carboxylic acids. The present method is practical and scalable, and has been applied to the synthesis of sitagliptin and a drug candidate.

Scheme 2. Generation of inert complex **5** for less hindered acid substrates



Chapter 3

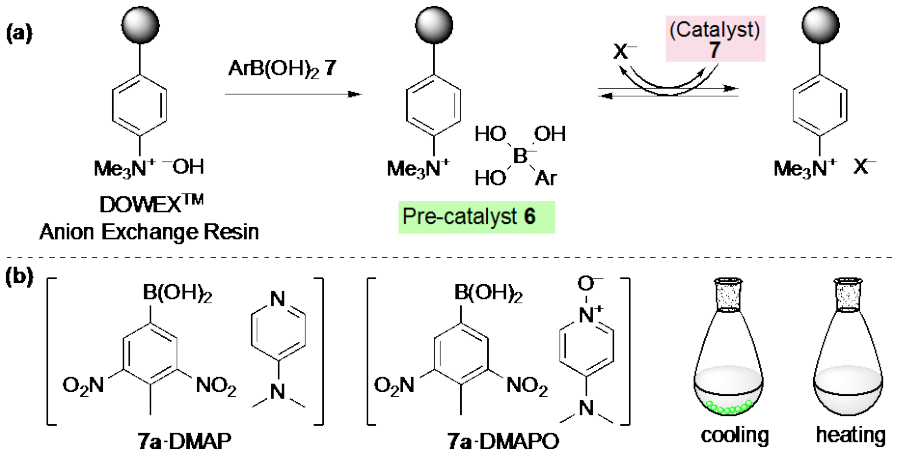


Figure 1. Novel boronic acid–base complexes as reusable homogeneous catalysts for amide condensation

To address the problems of current catalysts, two kinds of boron-containing acid–base complexes were developed as reusable catalysts for amide condensations between carboxylic acids and amines. First, resin-bound quaternary ammonium boronates **6** as precatalysts were prepared from DOWEX™ anion exchange resin and boronic acids **7**, which exhibited catalytic activities as high as their corresponding free boronic acid forms. Control experiments suggested that the trapped boronic acids **7** would be released through anion exchange *in situ* and the free boronic acids would act as the real catalysts for amidation reactions. Second, it was found that 3,5-dinitro-4-tolylboronic acid

(**7a**)–DMAP or DMAPO complexes are more efficient catalysts than boronic acid alone and can be recovered through simple decantation after cooling because of their poor solubility (Figure 1).

Chapter 4. Introduction (Halocyclization)

Enantioselective alkene halogenation is a powerful transformation for rapidly increasing the molecular complexity. Catalytic enantioselective alkene halogenation has been the subject of intense investigation over the past decade. Two major issues that have prevented progress with asymmetric alkene halogenations are the rapid racemization of chiral haliranium ions through olefin-to-olefin haliranium transfer, and the ring-opening of haliranium ions to β-halocarbenium ions.

Chiral nucleophilic base-catalyzed halofunctionalizations have been shown to be effective over the past decade because of the coordination effect. From the unstable phosphoramidite to stable BINOL-derived phosphate triester catalysts, our group has made great efforts toward the development of chiral catalysts for the halofunctionalization of alkenes (Figure 2). Although the catalyst efficiency has been greatly improved (from 100 mol % to 5 mol %), even greater progress has been made in the scope of suitable substrates.

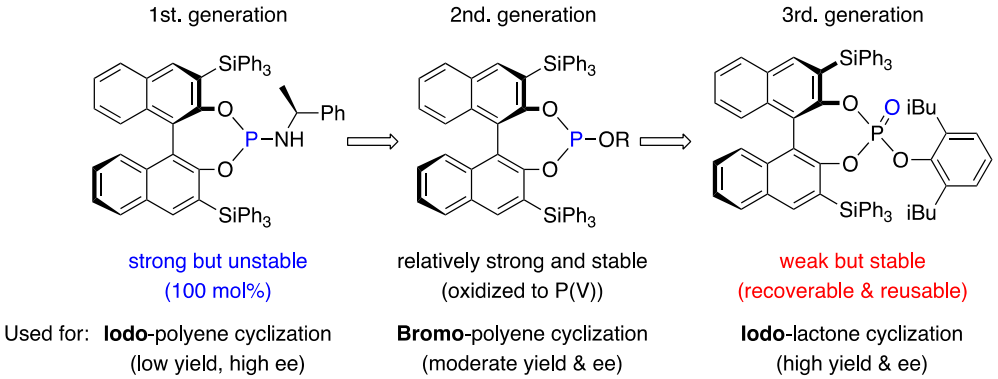


Figure 2. Approach for improving the catalytic efficiency of our BINOL-derived phosphine catalysts.

The third generation of catalyst has a total of five modifiable handles (Figure 3). For instance, 1) the size of the chiral pocket by using other commercially available C2-symmetric scaffolds (**A**) can be changed; 2) the shape of the chiral environment by turning the 3,3'-substituents (**B**) and side substituents (**C**) are modulated; and 3) the nucleophilicity by changing the combination of P=Y and P–Z moieties is adjusted.

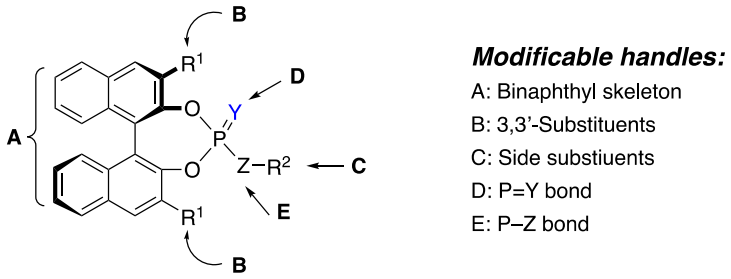


Figure 3. Modification of current third-generation catalyst

These new-designed catalysts show good catalytic activities in various halofunctionalizations through further modification. In addition, the current catalysts do not work equally well in different halogenations, which seems to be a common problem for most nucleophilic base-catalyzed halofunctionalizations. However, the reasons for this phenomenon remain unclear. Chapter 5 describes the factors that may influence the enantioselectivity and the principles for developing catalysts for different halogens.

Chapter 5.

Biologically active compounds with a chiral chroman skeleton are abundant in nature and synthetic analogues. In addition to the well-known Vitamin E family, small synthetic chiral chromans have also been shown to be effective against hyperpigmentation, metabolic disorders and cancers (Figure 4a). Asymmetric catalysis involving chiral catalysts has recently emerged as a powerful method for building the chiral chroman skeleton. In constructing chiral chromans, it is important to control the stereoselectivity at position 2. It was proposed that enantioselective halocyclizations of certain 2-alkenylphenols **8** could deliver chiral centers at position 2 (Figure 4b). Enantioselective alkene halogenation has been a subject of intense investigation over the past decade. Although enantioselective halolactonizations have been well-documented, enantioselective cyclizations of **8** are still limited to some polyene systems. One major issue in the development of catalytic asymmetric alkene halogenations is the rapid racemization of chiral haliranium ions through olefin-to-olefin haliranium transfer. Chiral nucleophilic base-catalyzed halofunctionalizations have been shown to be effective over the past decade because of the coordination effect. However, there are important differences between iodonium and bromonium ions: 1) The ionic radius of iodonium ion is much longer than that of bromonium ion; 2) Iodonium ion forms a stronger halogen bond with nucleophilic bases; 3) While both iodonium and bromonium ions can form haliranium ions with alkenes, their stabilities and reactivities are quite different, and thus the same nucleophilic catalysts do not work equally well in different halogenations. Here describes an efficient, enantioselective, and site-selective (in the presence of multiple olefins) iodo- and bromocycloetherification of **8** to construct chiral chromans using chiral nucleophilic

amidophosphate catalysts. Moreover, the broad applicability of this catalytic system for not only halocycloetherification but also haloazacyclization was demonstrated.

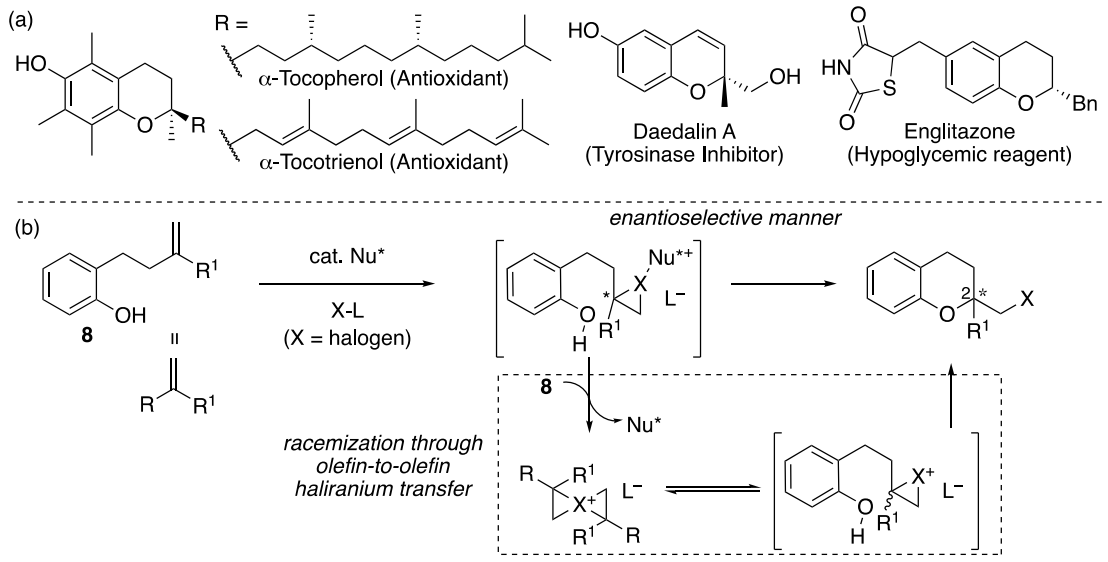


Figure 4. (a) Natural products or synthetic analogues containing chiral chromans. (b) Strategies for constructing chiral chromans through chiral nucleophilic base-catalyzed enantioselective halocycloetherifications.

Several natural products and key synthetic intermediates could be obtained through the easy transformation of halocyclic products (Figure 5). Experimental results and DFT calculations suggested that the nucleophilicity of the catalysts plays an important role in the enantioselectivity. Based on the results of NMR studies and control experiments, the author proposed a new highly reactive species from catalyst, IBr and NIS. Apparently, a deeper chiral cavity around the halonium ion is required to induce high enantioselectivity in bromocyclization compared to iodocyclization.

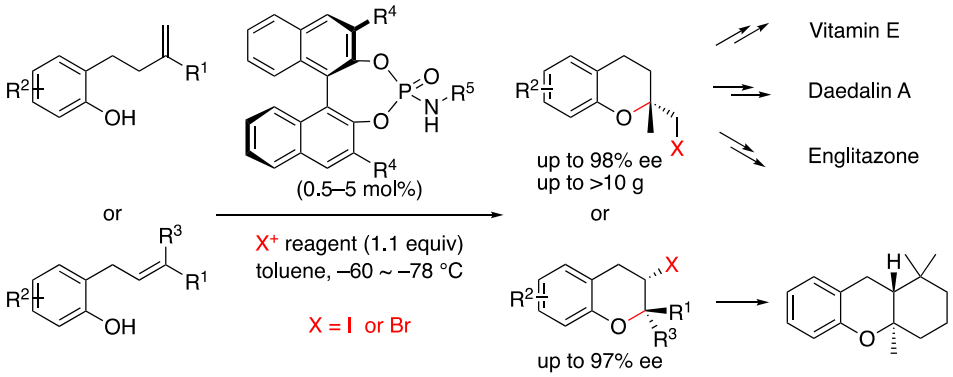


Figure 5. Summary of results for halocycloetherification