

# New World of Organic Synthesis Using Water

(水が拓く有機合成化学のニューワールド)

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## Introduction

Organic reactions are usually carried out in organic solvents in modern organic chemistry. It is very rare to use water as the reaction medium, while water is safe, benign, environmentally friendly, and inexpensive compared with organic solvents.<sup>1</sup> There are two major obstacles to be surmounted in organic reactions in aqueous media. First, many reactive substrates, reagents, and catalysts are decomposed or deactivated by water. Second, most organic substances are insoluble in water. Tremendous efforts have been made to address these issues.

On the other hand, we have investigated organic reactions in water from the standpoint that the most ideal reactions, enzymatic reactions *in vivo*, are carried out in water. Indeed, we have found unique reactivity and selectivity in aqueous media, which are not observed in organic solvents where water plays key roles. In this lecture, such examples where different reactivities and selectivities are observed in water compared with those in organic solvents will be discussed. It is noted that these are just examples and just the tip of the iceberg. We believe that many other examples may exist but have not yet been uncovered.<sup>2,3</sup>

## Heterogeneous *vs.* Homogeneous Copper(II) Catalysis in Enantioselective Boron Conjugate Additions in Water

Enantioenriched  $\alpha$ -chiral boron derivatives are an important class of compounds, and their C–B linkages can be transformed into C–O, C–N, as well as C–C bonds through 1,2-migration of intermediary ate complexes with appropriate nucleophiles retaining stereogenic centers.<sup>4</sup> Enantioselective boron conjugate addition to  $\alpha,\beta$ -unsaturated carbonyl and related compounds provides one of the most efficient routes to chiral organoboron compounds, and an incremental attraction toward enantioenriched organoboron compounds led to the emergence of a facile and straightforward methodology.<sup>5</sup> Based on seminal

independent reports of Cu(I)-catalyzed conjugate borylation by Hosomi *et al.*<sup>6</sup> and Miyaura *et al.*,<sup>7</sup> Yun *et al.* disclosed an enantioselective protocol for Cu(I)-catalyzed conjugate borylation, followed by several catalytic asymmetric boron conjugate additions using Cu(I) with chiral ligands.<sup>8</sup> Furthermore, other metal-catalyzed<sup>9</sup> and metal-free<sup>10</sup> enantioselective boron conjugate additions to  $\alpha,\beta$ -unsaturated carbonyl and related compounds have also been reported.<sup>11</sup>

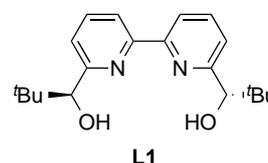
We have developed Cu(II)-catalyzed enantioselective boron conjugate additions to  $\alpha,\beta$ -unsaturated carbonyl compounds and  $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds in water.<sup>12</sup> In contrast to the Cu(I) catalysis reported previously in organic solvents, chiral Cu(II) catalysis was found to proceed efficiently in water.

Three catalyst systems have been exploited:

Cat 1: Cu(OH)<sub>2</sub> with chiral ligand **L1**;

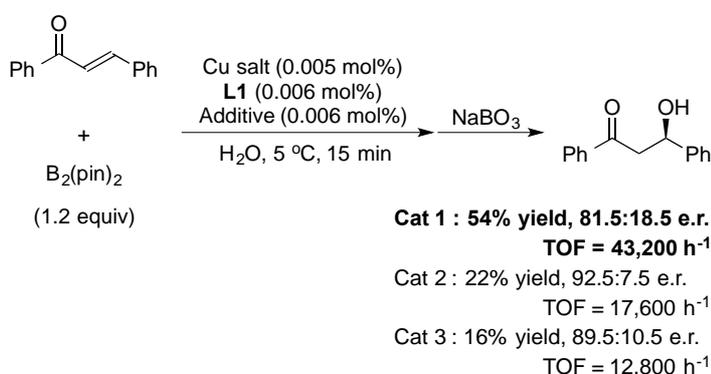
Cat 2: Cu(OH)<sub>2</sub> and acetic acid with **L1**;

Cat 3: Cu(OAc)<sub>2</sub> with **L1**.

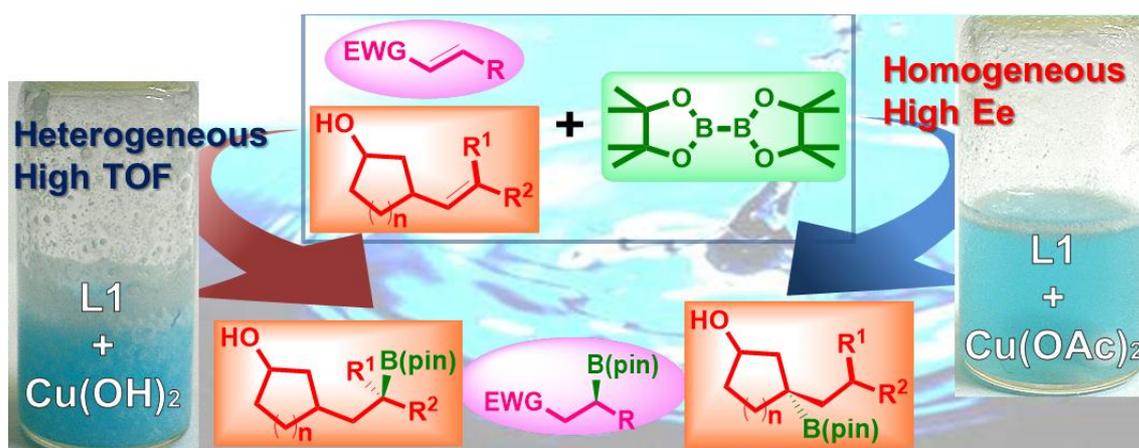


While Cat 1 is a heterogeneous system, Cat 2 and Cat 3 are homogeneous systems. We tested 27  $\alpha,\beta$ -unsaturated carbonyl compounds and an  $\alpha,\beta$ -unsaturated nitrile, including acyclic and cyclic  $\alpha,\beta$ -unsaturated ketones, acyclic and cyclic  $\beta,\beta$ -disubstituted enones, acyclic and cyclic  $\alpha,\beta$ -unsaturated esters including  $\beta,\beta$ -disubstituted forms, and acyclic  $\alpha,\beta$ -unsaturated amides including  $\beta,\beta$ -disubstituted forms. We found that Cat 2 and Cat 3 showed high yields and high enantioselectivities for almost all substrates; the TOF reached 17,600 h<sup>-1</sup> and 12,800 h<sup>-1</sup>, respectively. It is noted that *no catalysts that cover all these substrates with high yields and high enantioselectivities have ever been reported for boron conjugate addition reactions*. The heterogeneous Cat 1 also gave high yields and high enantioselectivities for some substrates, and the highest TOF (43,200 h<sup>-1</sup>) was achieved. In

some substrates, better yields and/or better enantioselectivities were obtained using Cat 1 than those obtained using Cat 2 or Cat 3; however, in general, the yields and the enantioselectivities were higher using Cat 2 or Cat 3 than when using Cat 1.



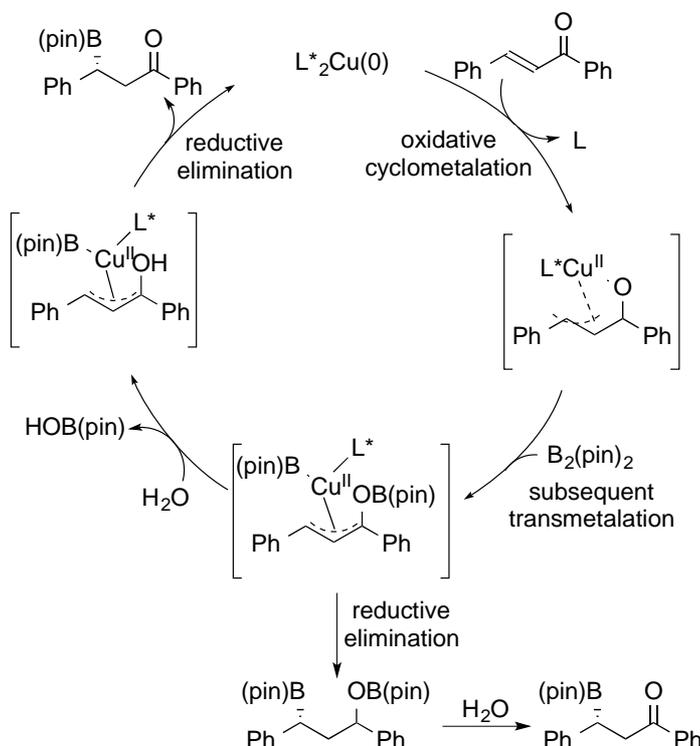
Moreover, the catalyst systems were also applicable to boron conjugate additions to  $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds, although such boron conjugate additions have been very limited previously in the literature even in organic solvents. 1,4-Addition products were obtained in high yields with high enantioselectivities in the reactions of acyclic  $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds with diboron **2** using Cat 1, Cat 2, or Cat 3. On the other hand, in the reactions of cyclic  $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds with **2**, while 1,4-addition products were obtained exclusively with Cat 2 or Cat 3, 1,6-addition products were produced exclusively with Cat 1. Similar unique reactivities and selectivities were also shown in the reactions of cyclic trienones. Finally, the reaction mechanism of these unique boron conjugate additions in water was investigated, and we proposed stereochemical models that were supported by X-ray crystallographic structure and ESI MS analysis. Although the role of water has not been completely revealed in this investigation, water is expected to be effective in the activation of a borylcopper(II) intermediate and a protonation event subsequent to a nucleophilic addition, leading to overwhelmingly high catalytic turnover.



### Catalytic Use of Cu(0) for Asymmetric Boron Conjugate Additions to Enones in Water

The use of copper(0) powder in water enabled chiral induction as well as high catalytic activity for the boron conjugate additions. Water plays a prominent role in determining both the catalytic activity and enantioselection. Elevated temperature is indispensable for the regular reaction pathway and an active species tends to aggregate after the completion of the reaction. Selective deuteration implies enantiofacial differentiation of the deuterium toward an *O*-enolate intermediate. Strict substrate specificity suggests the vital interaction between Cu(0) and an enone. The minute isotope effect is indicative of an instantaneous protonation. Accordingly, a redox copper cycle ( $0 \rightarrow II$ ) was tentatively proposed, in which

transmetalation of a cyclometalated enone with diboron would furnish a boron enolate, followed by hydrolysis and reductive elimination. However, a SET process cannot be excluded on the available evidence and a more detailed mechanistic study is under way.<sup>13</sup>



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