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Copper sulfate-catalyzed asymmetric 1,4-addition of amidofunctionalized allylboronates to maleimides in water

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Abstract. A new application of amido-functionalized allylboronates to asymmetric 1,4-addition in water has been developed. Extremely high enantioselective 1,4-addition was achieved by employing *N*-mesityl maleimide as a substrate under CuSO₄/bis(oxazoline) catalysis, affording the adduct with >99% ee.

Water is an ideal reaction solvent for chemical production, which is non-hazardous, environmentally benign, and ubiquitous on the earth. Expansion of synthetic technology in aqueous media should be a priority issue in the organic chemistry field in order to reduce the environmental impact of organic synthesis. In this context, huge efforts have been devoted to the development of carbon-carbon bond formation in aqueous media.^[1] However, many reactions are still mainly performed in organic solvents because reagents and in situ generated reactive species are moisture sensitive or poor soluble in water. Therefore, development of water-stable materials is one of the most straightforward approaches for conducting reactions in water.

amide-functionalized Recently, we reported allylboronate 1 as a new type of carbonyl-conjugated allylating agent. which showed sufficient nucleophilicity toward isatin derivatives under the influence of a chiral zinc catalyst.^[2a] We also established allylation of N-carbonyl imides using 1 (Scheme 1).^[2b,c] In this case, the reaction proceeded in the presence of zinc bromide and potassium carbonate to furnish the 1,2-adducts which could be used as a common precursor for three types of spiro compounds. More recently, we focused on the remarkable air- and water-stability of 1 and developed enantioselective allylation of acetophenones catalyzed by a zinc-chiral aminophenol system in water.^[3] Although these results show the utility of 1 on allylation of carbonyl compounds not only in organic solvents but also in



Scheme 1. Utility of β -amido-functionalized allylboronates 1.

water, its synthetic application is still limited to 1,2addition to carbonyl groups. In this paper, we report a new copper-catalyzed enantioselective amidefunctionalized allylation of maleimide derivatives, which expand the utility of 1 to 1,4-addition.

As a preliminary investigation, we examined racemic 1,4-addition of **1** to *N*-phenylmaleimide (Table S1 in the Supporting Information). According to the previous works,^[4] we screened copper salts as a catalyst in water. Although no reaction occurred with CuCl or CuCl₂, the desired 1,4-adduct was modestly obtained in 22–38% yields in the presence of 10 mol % of Cu(acac)₂, Cu(OAc)₂, CuSO₄•5H₂O, or Cu(OH)₂. Then, we next explored promising chiral ligands for asymmetric induction (Scheme 2). Six types of chiral reagents **L1-6** were tested in the presence of 10 mol % of $Cu(OH)_2$, but reactions using L3-6 gave 3a with poor enantioselectivities (3-9% ee). On the other hand, low but encouraging levels of enantioselectivity were observed with L1 and L2, affording 3a in 36% and 44% yields with 27% and 28% ee, respectively. Both



Scheme 2. Preliminary screening of chiral ligands L for the 1,4-addition of **1a** to **2a** in the presence of $Cu(OH)_2$. The ee values were determined by chiral HPLC analysis using Daicel Chiralpak IC. *The reactions were carried out with $CuSO_4$ •5H₂O at 0 °C.

the product yield and enantioselectivity were drastically increased by performing the reactions with $CuSO_4 \cdot 5H_2O$ instead of $Cu(OH)_2$ at 0 °C, providing the desired adduct in 99% and 96% yields with 83% and 79% ee, respectively.

Encouraged by these results, we next tried to further improve the enantioselectivity by structural modification of the chiral ligands. At first, we evaluated the effect of substituents on the bis(oxazolinyl)pyridine (PyBOX) ligand (Figure 1). Not only alkyl derivatives L7,8 but also aryl ones L9-12 gave inferior results compared to that obtained with L1, although the chemical yields were almost satisfactory. A similar trend in selectivity was observed with bis(oxazoline) (BOX) ligand L13, which led to significantly decreased enantioselectivity. Therefore, we turned our focus to investigate the influence of the ligand bite angle^[5] on the enantioselectivity of this reaction. The BOX ligands with cyclopropyl and cyclohexyl substitution at the carbon bridging the oxazole moieties (L14 and L16) resulted in diminished enantioselectivities. Meanwhile, the reactions using the cyclopentyl and cycloheptyl derivatives (L15 and L17) proceeded with higher enantioselectivity to afford 3a in almost quantitative yields with 88% and 83% ee, respectively. Further attempt to optimize the ligand structure by preparing indane derivative L18 was tested. This example also gave an excellent result, but was slightly less than that of L15 in terms of chemical yield or stereoselectivity. Thus, the optimal conditions were determined using 10 mol% of CuSO₄•5H₂O and 11 mol% of L15 in water at 0 °C.

Having established optimal reaction conditions, we turned our focus to investigate versatility of this reaction (Figure 2).^[6] The facial selectivity was also observed on *N*-benzyl and *N*-methyl maleimides, providing **3b**,**c** with 91% and 78% ee, respectively. As for the phenyl substituents, 1,4-addition to *p*-

nitrophenylmaleimide resulted in moderate yield and enantioselectivity (**3h**, 75%, 61% ee), but this protocol can tolerate not only halogens but also electron donating groups at *para*-position, affording the corresponding adducts **3d–g,i** in excellent yields and high enantioselectivities (96–99%, 77–91% ee). The



Figure 1. Screening of (a) PyBOX ligands and (b) BOX ligands for the 1,4-addition of **1a** to **2a** in the presence of CuSO4•5H₂O at 0 °C. The ee values were determined by chiral HPLC analysis using Daicel Chiralpak IC.



Figure 2. Substrate scope of asymmetric 1,4-addition. The ee values were determined by chiral HPLC analysis using Daicel Chiralpaks IB, IC, and ID. The absolute configurations of the products were tentatively assigned to be R by analogy (see Figure S1).



Scheme 3. Effect of amide functionality on 1.

meta-substituents also had no significant effect on the enantioselectivity (**3j-l**, 82–91% ee). On the other hand, the substrate bearing an *ortho*-substituent gave the corresponding 1,4-adduct with higher enantiomeric excess (**3m**, 93% ee) than those obtained with the *meta*- or *para*-derivative **3g,k**. From these results, it is expected that higher stereoselectivity will be exhibited for substrates having substituents at the two *ortho* positions. After investigation of several compounds (**3n-p**) based on this assumption, as expected, substrates bearing a mesityl group gave the best result in terms of yield and enantioselectivity, affording the corresponding product **3p** in 99% yield with >99% ee.^[7]

Furthermore, we evaluated the effect of amide functionality on the allylboronate (Scheme 3). When the reaction was carried out with *para*-tolyl, *para-tert*-butylphenyl, or 1-naphthyl derivatives **1b-d**,^[8] the corresponding 1,4-adducts **3q-s** were given in excellent yields with complete enantioselectivities (>99% ee), indicating that the enantioselectivity is not influenced by the substituents on the amide group.

Among a series of enantioenriched 1,4-adducts 3, compound 3d could be further purified by recrystallization from ethanol /H₂O (99% ee) to afford X-ray quality crystals. The single-crystal X-ray diffraction analysis showed that the molecules adopt the orthorhombic space group $P2_12_12_1$ with the Flack parameter of 0.022(16). From these results, we could identify that the absolute configuration of the newly formed stereocenter should be *R* (Figure S1, Supporting Information)^[9,10]

Very interestingly, treatment of *N*-mesitylmaleimide with commercially available 2allyl-5,5-dimethyl-1,3,2-dioxaborinane resulted in the formation of a trace amount of the corresponding product (Scheme 3). This reaction behavior is aligned with that observed in the previous investigation,^[3] highlighting the importance of water-stability of the allylboronates **1** for not only 1,2-addition to carbonyl compounds but also 1,4-addition to α , β -unsaturated carbonyl compounds in water.

According to this line, a proposed reaction mechanism is illustrated in Scheme S1 in the Supporting Information. A bis(oxazoline) copper complex **A** should be initially formed in situ from $CuSO_4 \cdot 5H_2O$ and **L16**,^[11] which would generate an allyl copper species **B** after Cu-B transmetallation.^[4a]

The imide substrate could be activated through coordination of a carbonyl oxygen to the copper center. In this system, the *Si*-face of the β -carbon atom seems to be blocked by the phenyl group of the ligand, therefore, the nucleophilic attack proceeds from the *Re*-face, in agreement with the stereochemistry of the product.

In conclusion, we have developed an asymmetric 1,4-addition of allylboronates to maleimides in water. Our reaction system consists of water-stable amido allylboronate and CuSO₄-chiral bis(oxazoline) catalyst and gave the corresponding 1,4-adducts with up to >99% ee. The amide functionality on allylboronates was found to exhibit a significant influence on both the reaction efficiency and stereoselectivity in water media.

Experimental Section

General procedure for amide-functionalized allylation of maleimides

A suspension of CuSO₄•5H₂O (5.0 mg, 0.020 mmol, 0.10 equiv.) and L15 (7.9 mg, 0.0220 mmol, 0.11 equiv.) in water (0.50 mL) was stirred at room temperature for 1 hour. Then, 1 (0.300 mmol, 1.5 equiv.) and *N*-phenylmaleimide (0.200 mmol) were added to the resulting mixture at 0 °C. After stirring the mixture at the same temperature for 24 hours, the reaction was quenched by addition of saturated sodium hydrogen carbonate (1.0 mL). The resulting solution was extracted with dichloromethane (5.0 mL) and hydrochloric acid (3% w/w, 3.0 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to give a crude material. This material was purified by column chromatography to give **3**.

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Keywords: allylayion • bisoxazoline • boron • copper; maleimides

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