Copper Sulfate‐Catalyzed Asymmetric 1,4‐Addition of Amido‐Functionalized Allylboronates to Maleimides in Water

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

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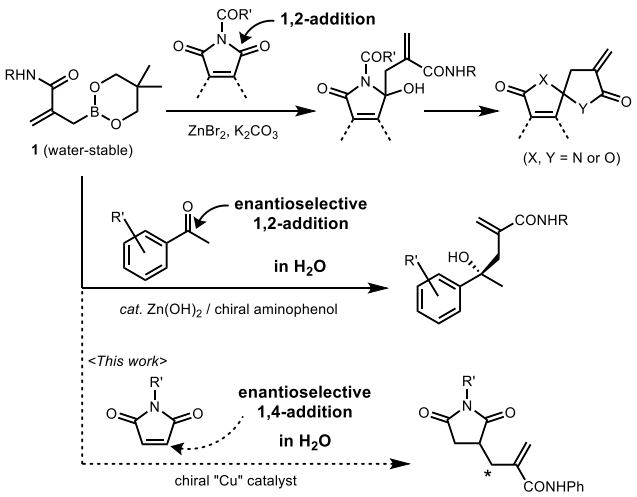
Abstract. A new application of amido-functionalized allylboronates to asymmetric 1,4-addition in water has been developed. Extremely high enantioselective 1,4-addition was achieved by employing *N*-mesityl maleimide as a substrate under $CuSO_4$/bis(oxazoline) catalysis, affording the adduct with >99% 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.

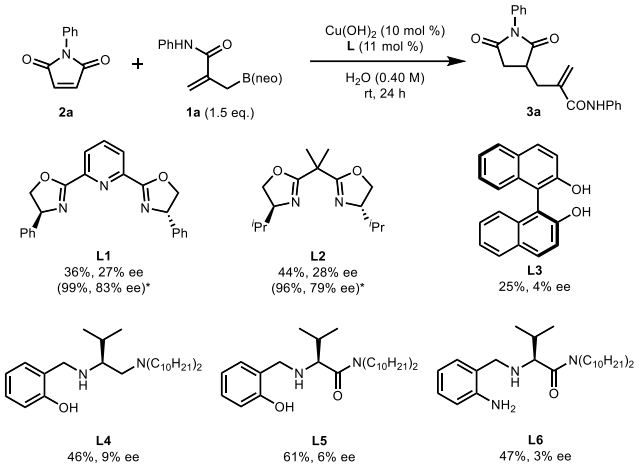
Recently, we reported amide-functionalized allylboronate **1** as a new type of carbonyl-conjugated allylating agent, which showed sufficient nucleophilicity toward isatin derivatives under the influence of a chiral zinc catalyst.[2a] We also established allylation of *N*-carbonyl imides using **1** (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 1,2-addition to carbonyl groups. In this paper, we report a new copper-catalyzed enantioselective amide-functionalized 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 $CuCl_2$, the desired 1,4-adduct was modestly obtained in 22–38% yields in the presence of 10 mol % of $Cu(acac)_2$, $Cu(OAc)_2$, $CuSO_4•5H_2O$, 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 $CuSO_4$•$5H_2O$ at 0 °C.

the product yield and enantioselectivity were drastically increased by performing the reactions with $CuSO_4$•$5H_2O$ 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 $CuSO_4$•$5H_2O$ 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

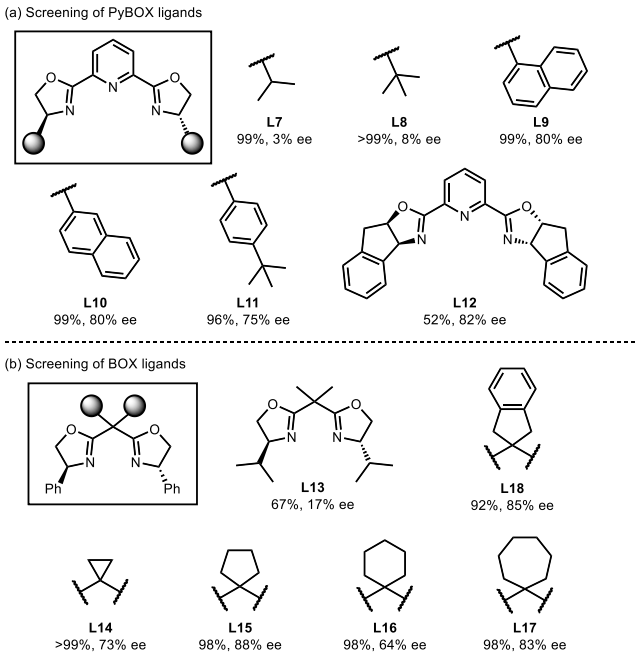


Figure 1. Screening of (a) PyBOX ligands and (b) BOX ligands for the 1,4-addition of **1a** to **2a** in the presence of $CuSO_4$•$5H_2O$ at 0 °C. The ee values were determined by chiral HPLC analysis using Daicel Chiralpak IC.

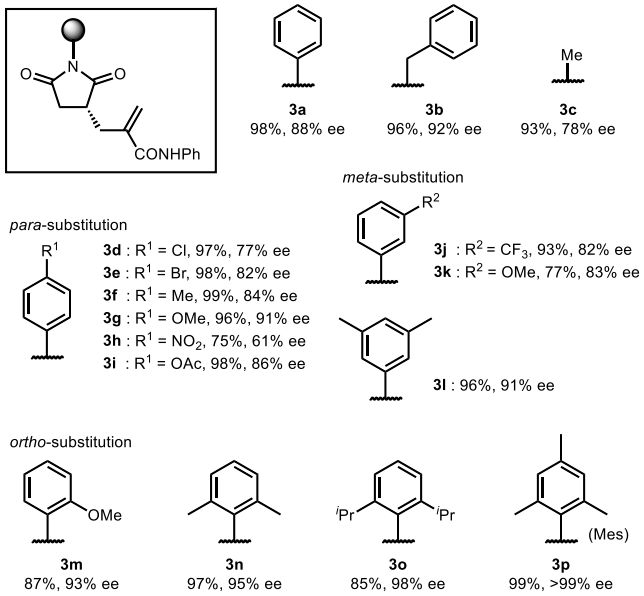
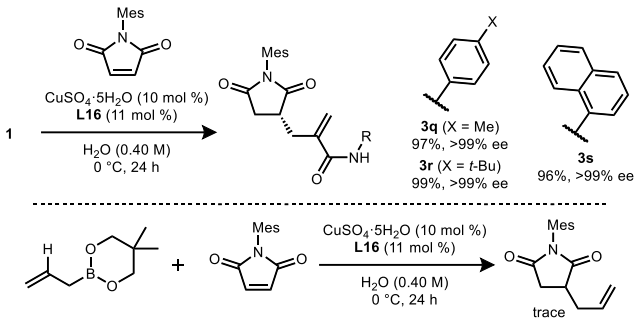


Figure 2. Substrate scope of asymmetric 1,4-addition. The ee values were determined by chiral HPLC analysis using Daicel Chiralpaks IB, IC, and ID. The absolute configurations of the products were tentatively assigned to be *R* by analogy (see Figure S1).



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 /H_2O (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 2-allyl-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 $CuSO_4$•$5H_2O$ 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 $CuSO_4$-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 $CuSO_4$•$5H_2O$ (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 ºC. 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 Na_2SO_4, filtered and concentrated in vacuo to give a crude material. This material was purified by column chromatography to give **3**.

Acknowledgements

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Keywords: allylayion • bisoxazoline • boron • copper; maleimides

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[6] As for 3,4-dimethyl-1-phenyl-1H-pyrrole-2,5-dione, the reaction failed to give any 1,4-adduct and the imide substrate remained intact. In this case, allylboronate **1a** was completely decomposed.

[7] Similar to our previously reported method in reference 3, we tried to simplify the work-up procedure by skipping the extraction step. However, **3p** was obtained with 30% ee, probably due to racemization during the isolation step.

[8] The scope of amide-functionalized allylboronate is limited to **1b**-**d** due to the synthetic difficulties. For details, see reference 2b.

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[10] Crystal data for **3d**: orthorhombic, space group $P2_12_12_1$, a = 5.92290(11) Å, b = 7.65280(16) Å, c = 40.4506(7) Å, V = 1833.68(6) Å^3, Z = 4, ρ = 1.401 Mgm^{-3}, μ(MoK$_\alpha$) = 0.238 mm^{-1}, T = 173 K; in the final least–squares refinement cycles on F^2, the model converge at R_1 = 0.0420 ($I > 2\sigma(I)$), wR_2 = 0.0979, , Flack parameter = 0.022(16), and GOF = 1.159 for 4970 reflections and 247 parameters (CCDC deposition number 2115550).

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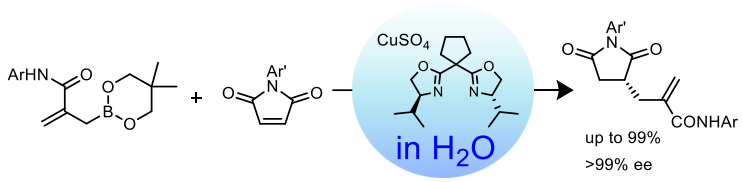
Entry for the Table of Contents



A new application of amido−functionalized allylboronates to asymmetric 1,4-addition in water has been developed. The reaction system consists of water-stable amido allylboronate and $CuSO_4$-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.