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Asymmetric β-Boration of α,β-Unsaturated *N*-Acyloxazolidinones by [2.2]Paracyclophane-Based Bifunctional Catalyst

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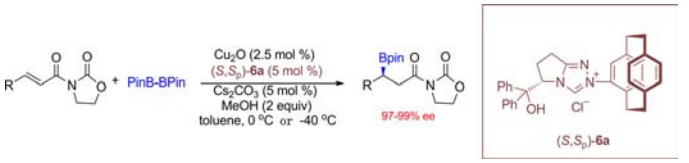
ABSTRACT



An efficient copper-catalyzed asymmetric conjugate boration has been achieved by exploiting a new planar and central chiral bicyclic triazolium ligand. This protocol was highly efficient and gave a variety of chiral secondary alkylboronates in 97−99% ee. A preliminary mechanistic study supports the bifunctional nature of the catalyst.

Optically active α-substituted organoboron derivatives are not only very important synthetic intermediates which can be transformed into various functional groups[1] but also useful chiral building blocks for many biologically active compounds.[2] In 1997, the Norman and Marder groups reported the first racemic work on the diboration of α,β-unsaturated carbonyl compounds which drives the development of the catalytic asymmetric variant of this reaction.[3] Recently, asymmetric conjugate addition of diboron reagents to α,β-unsaturated compounds through nucleophilic borylcopper species has attracted considerable interest.[4] Yet, although progress on Cu(I)-catalyzed asymmetric β-boration has been substantial, design and synthesis of new ligands to broaden the substrate scope and enhance the selectivity is still a challenge.

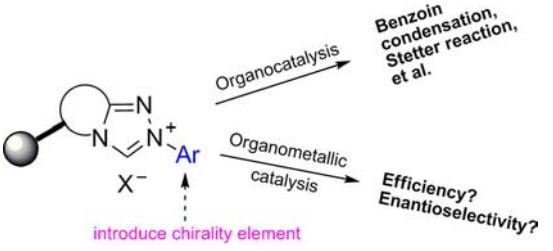


Figure 1. Design and application of triazolium salts.

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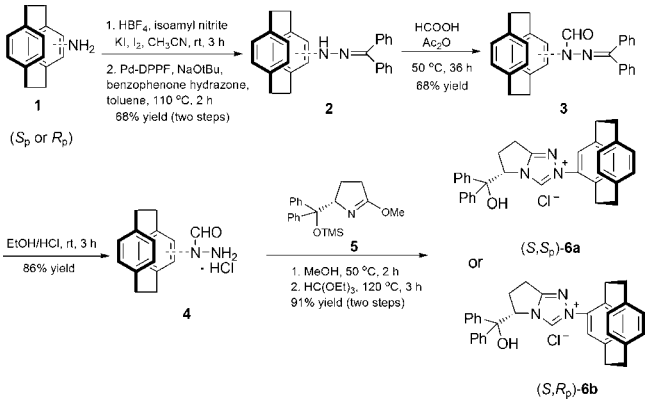
In recent years, chiral bicyclic 1,2,4-triazolium salts have been developed and successfully applied in asymmetric organocatalysis.[5] Their advantages arise from bicyclic restriction with the placement of the stereocenter and wide tunability of the triazolium backbone. Although these salts have been established, there are still limitations on their synthesis and application. For example, the chiral center is only derived from one side of the bicyclic backbone[6] and the bicyclic1,2,4-triazolium salts have not been reported in transition metal catalysis.[7] Based on these facts, we present two questions: (1) Can we introduce a chirality element on the triazolium skeleton in the N1 position? (2) Can the bicyclic 1,2,4-triazolium salts be applied in transition metal catalysis (Figure 1)?

As a chiral source, planar chiral [2.2]paracyclophane (PCP) has inspired great interest from researchers in asymmetric catalysis.[8] Recently our group and co-workers employed a series of planar chiral NHC precursors based on PCP and used them in asymmetric transition metal catalysis.[9] Herein, we report the synthesis of bicyclic 1,2,4-triazolium salts based on PCP and their applications in asymmetric Cu(I)-catalyzed β-boration of α,β-unsaturated *N*-acyloxazolidinones.

Our study began with the synthesis of planar chiral NHC precursors. On the basis of previous reports on synthesis of 1,2,4-triazolium salts,[10] the hydrazine hydrochloride salt based on PCP was synthesized first. Unfortunately, the hydrazine hydrochloride salt was unstable and difficult to isolate in pure form. Interestingly, the formyl-protected hydrazine hydrochloride salt **4** can be obtained in pure form by acid hydrolysis of the optically active **3** which was synthesized from readily available chiral 4-amine-[2.2]paracyclophane **1**[11] (Scheme 1). Triazolium salts **6a** and **6b** were then generated by treatment of **4** with imidate **5** in two steps, so the first triazolium salts derived from PCP were synthesized. Notably, this procedure also provides a new way to synthesize other kinds of triazolium salts with different aromatic groups in the N1 position, especially some unstable aromatic hydrazine compounds.

Scheme 1. Synthesis of NHC Precursors



With novel chiral triazolium salts in hand, we began to test whether our designed chiral triazolium salts **6** can act as chiral ligands in Cu(I)-catalyzed asymmetric β-boration. As a Michael acceptor, α,β-unsaturated *N*-acyloxazolidinone has been widely used in asymmetric conjugate addition reactions. The appeal of such an approach is that *N*-acyloxazolidinone can be easily removed and converted into a variety of carboxylic acids and their derivatives.[13] As a result, the addition of bis(pinacolato)diboron (B_2Pin_2) to *N*-cinnamoyloxazolidin-2-one **7a** was chosen as a model reaction: 5 mol % of Cu(NHC) complex was prepared from Cu_2O (2.5 mol %) and chiral triazolium salt (*S*,S_p)-**6a** (5 mol %) in THF, and then 5 mol % of Cs_2CO_3, 1.1 equiv of B_2Pin_2, 1.0 equiv of **7a**, and 2 equiv of MeOH were added (Table 1, entry 1). To our delight, the reaction was completed within 10 min at 0 °C, and product **8a** was obtained in good yield and enantioselectivity (93% yield, 94% ee). With this encouraging result, we screened different bases in place of Cs_2CO_3. Strong bases such as KO*t*Bu and NaO*t*Bu showed high reactivity, although the enantioselectivity decreased slightly, while weak bases CH_3COONa and CsF provided poorer reactivity and

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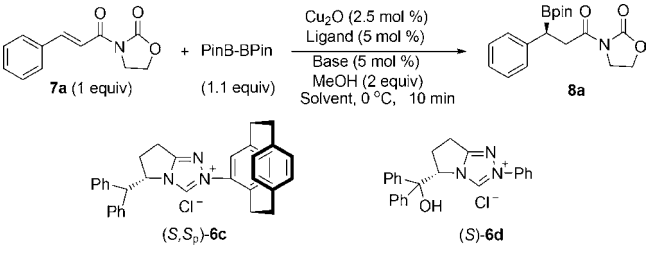
Table 1. Screening of Reaction Conditions[a]



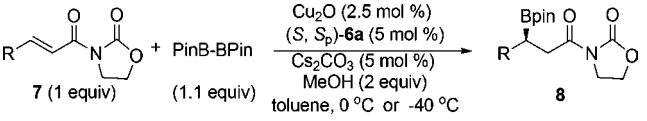
entry	ligand	base	solvent	yield (%)[b]	ee (%)[c]
1	**6a**	Cs_2CO_3	THF	93	94
2	**6a**	KO*t*Bu	THF	90	93
3	**6a**	NaO*t*Bu	THF	92	88
4[d]	**6a**	CH_3OONa	THF	48	72
5[e]	**6a**	CsF	THF	trace	–
6	**6a**	Cs_2CO_3	dioxane	91	94
7	**6a**	Cs_2CO_3	DME	84	82
8[f]	**6a**	Cs_2CO_3	*t*BuOH	74	90
9	**6a**	Cs_2CO_3	PhMe	94	99
10	**6a**	Cs_2CO_3	CH_2Cl_2	90	70
11	**6b**	Cs_2CO_3	PhMe	88	70
12	**6c**	Cs_2CO_3	PhMe	92	87
13	**6d**	Cs_2CO_3	PhMe	88	81
14[g]	**6a**	Cs_2CO_3	PhMe	92	97

[a] The reaction was carried out with ligand (5 mol %), Cu_2O (2.5 mol %), base (5 mol %), B_2Pin_2 (0.11 mmol), **7a** (0.1 mmol), and MeOH (0.2 mmol) in solvent (1 mL) at 0 °C for 10 min. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase (Chiralpak IA column). [d] Reaction for 4 h. [e] **7a** was consumed for 6 h; no product found. [f] Without adding MeOH. [g] The reaction was carried out with ligand (1 mol %), Cu_2O (0.5 mol %), base (1 mol %), B_2Pin_2 (1.40 g, 5.5 mmol), **7a** (1.08 g, 5.0 mmol), and MeOH (10 mmol) in toluene (20 mL) at 0 °C for 30 min.

enantioselectivity (Table 1, entries 2–5). Among the solvents screened (Table 1, entries 6–10), toluene gave the best yield (94% yield) and excellent enantioselectivity (99% ee) so it was chosen as the optimal solvent (Table 1, entry 9). Then, we tested chira triazolium salt (S,R_p)-**6b** as the ligand. The enantioselectivity dropped severely under the optimized conditions, but the absolute configuration was not changed (Table 1, entry 11). The results indicated that the diastereomers (S,R_p)-**6b** showed mismatched planar and central chirality while (S,S_p)-**6a** was matched. In addition, the absolute configuration was determined by the central chirality of the triazolium salts **6**. Interestingly, the chiral triazolium salt (S,S_p)-**6c** without hydroxyl afforded decreased enantioselectivity (Table 1, entry 12) which revealed that the hydroxyl group plays an important role in the catalytic process. The chiral triazolium salt (*S*)-**6d**, bearing only the element of central chirality, gave rise to the product in moderate enantioselectivity (Table 1, entry 13). Notably, asymmetric boration was conducted on a gram scale at a low catalyst loading (1 mol %), and the reaction completed within 30 min and gave the corresponding product in 92% yield and 97% ee (Table 1, entry 14).

Having identified the optimal set of reaction conditions, we then investigated the reactions with a variety of

Table 2. Substrate Scope of *N*-Acyloxazolidinones **7**[a]



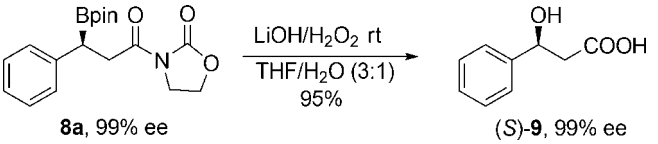
entry	**7**, R	*t* (°C)[b]	**8**	yield (%)[c]	ee (%)[d]
1	**7a**, Ph	−40	**8a**	95	99
2	**7b**, 4-MeC_6H_4	0	**8b**	92	99
3	**7c**, 2-MeC_6H_4	−40	**8c**	94	99
4	**7d**, 4-ClC_6H_4	−40	**8d**	93	99
5	**7e**, 4-BrC_6H_4	−40	**8e**	90	98
6	**7f**, 4-FC_6H_4	−40	**8f**	92	99
7	**7g**, 3-ClC_6H_4	0	**8g**	91	99
8	**7h**, 3-Cl,4-FC_6H_3	0	**8h**	87	99
9	**7i**, 4-MeOC_6H_4	0	**8i**	94	98
10	**7j**, 2-MeOC_6H_4	0	**8j**	96	98
11	**7k**, 3,4-$(MeO)_2C_6H_3$	0	**8k**	90	98
12	**7l**, 1-naphthyl	0	**8l**	90	99
13	**7m**, 2-naphthyl	0	**8m**	91	99
14	**7n**, 2-furyl	0	**8n**	84	98
15	**7o**, cyclohexyl	−40	**8o**	86	99
16	**7p**, Me	−40	**8p**	93	97
17	**7q**, *n*-propyl	−40	**8q**	88	99

[a] The reaction was carried out with ligand (5 mol %), Cu_2O (2.5 mol %), Cs_2CO_3 (5 mol %), B_2Pin_2 (0.11 mmol), **7** (0.1 mmol) and MeOH (0.2 mmol) in toluene (1 mL). [b] Reaction for 10 min at 0 °C, 2 h at −40 °C. [c] Yield of isolated product. [d] Determined by HPLC analysis using a chiral stationary phase (Chiralpak IA column).

α,β-unsaturated *N*-acyloxazolidinones. As summarized in Table 2, various β-substituted *N*-acyloxazolidinones including those bearing electron-withdrawing and -donating substituents at different positions on the aromatic ring, as well as heterocyclic groups, could be tolerated and gave the corresponding compounds **8a**–**n** in good yield (84–96%) and excellent enantioselectivity (98–99% ee). To gain excellent enantioselectivity we needed to lower the temperature to −40 °C for some substrates, because the enantioselectivity slightly decreased at 0 °C (**7c** in 98% ee, **7d**–**f** in 97% ee, not shown in Table 2). The scope was also extended to β-aliphatic-substituted *N*-acyloxazolidinones, which also gave the product in good yield and enantioselectivity (Table 2, entries 15–17). It is worth pointing out that the nature of the R substituents had a limited influence on the reactivity and enantioselectivity. The absolute configuration of the product was determined to be *S* from single-crystal X-ray analysis of the bromo-containing product **8e**. The configurations of other products were assigned to *S* by comparison with the CD spectra of **8a** and **8e** (see Supporting Information).

As we mentioned above, the boration products are versatile intermediates in organic synthesis and can be transformed into a number of valuable compounds. For example, treatment of **8a** with $LiOH/H_2O_2$ gave (*S*)-3-hydroxy-3-phenylpropanoic acid in one step without loss of enantiopurity (Scheme 2). The result is notable because chiral β-hydroxy carboxylic acids are important building blocks for pharmaceuticals and natural products.[12]

Scheme 2. Synthesis of Chiral 3-Hydroxy-3-Phenylpropanoic Acid



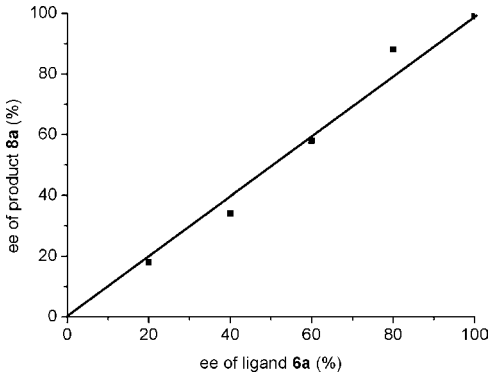


Figure 2. Relationship between the enantiomeric excess of ligand **6a** and that of the product **8a**.

For an in-depth understanding of the reaction mechanism, the relationship between the ligand **6a** and the product **8a** in enantioselectivity was examined. As shown in Figure 2, a clear linear effect was observed on this reaction. We therefore assumed that a single catalyst was involved in the activation of the α,β-unsaturated *N*-acyloxazolidinone.[14] To gain further insight into the correlation between **6a** and the substrate **7**, an α,β-unsaturated amide was also investigated in the β-boration reaction, and the boration product was only in 67% ee under the optimized conditions (Scheme 3). The poor enantiomeric excess indicates the possible coordination between the catalyst and **7**.

On the basis of these observations, two possible transition states are proposed in Figure 3. It is possible that the transition state is a bridged complex with two active centers in which the conformation of the substrate is fixed.

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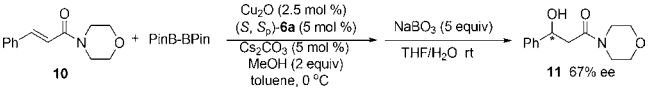
Scheme 3. Asymmetric β-Boration of α,β-Unsaturated Amide



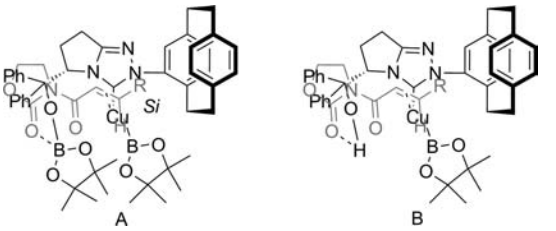


Figure 3. Proposed transition state model.

The big PCP group shields the *Re* face of the substrate; thus the Cu-Bpin could only attack from the *Si* face of the substrate, accounting for the absolute configuration of the final products. However, it is difficult to explain whether it is the boron that activates the carbonyl group or the H-bonding effect.[15] We think this is a new bifunctional catalyst in the asymmetric boration reaction, and such a powerful precatalyst might find utility in other metal-catalyzed asymmetric processes.

In conclusion, we have developed a series of new planar and central chiral bicyclic triazolium salts based on [2.2]paracyclophane and demonstrated their utilization in the Cu(I)-catalyzed asymmetric β-boration of α,β-unsaturated *N*-acyloxazolidinone. The procedure tolerates a relatively wide range of substrates and shows excellent selectivity (up to 99% ee) and high reactivity (up to 96% yield). Further investigations into other reaction variants in both organocatalysis and organometallic catalysis are currently underway in our laboratory.

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Supporting Information Available. Full experimental details and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.