# 論文の内容の要旨

## Development of Copper(I)-Catalyzed Asymmetric Construction of Tetrasubstituted Carbons from Ketones and β-Disubstituted Enones
## 一価銅触媒を用いるケトンとβ−二置換エノンに対する不斉四置換炭素構築反応の開発

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Catalytic asymmetric synthesis of molecules containing tetrasubstitued carbons is an important topic in organic synthesis.[1] These molecules can be important precursors of complex molecules or pharmaceutical leads. Among various methodologies, catalytic asymmetric addition of versatile nucleophiles to ketones and β-disubstituted enones are direct methods toward the construction of chiral tetrasubstituted carbons. I would like to present my achievement about the construction of tetrasubstituted carbons through chiral copper(I)-catalysis.

### 1. Copper(I)-Catalyzed Hetero-Diels-Alder Reaction between Danishefsky-Type Siloxy Dienes and Ketones.[2]

Dihydropyranones are versatile skeletons of various biologically active compounds. A direct method for the synthesis of dihydropyranones is the hetero-Diels-Alder reaction between Danishefsky's siloxy diene and carbonyl compounds. Various chiral catalysts have been developed for this reaction, but the substrate scope was limited to aldehydes and α-ketoesters. The corresponding development using simple ketones to synthesize dihydropyranones containing tetrasubstituted carbons was still unsatisfactory due to the attenuated reactivity of simple ketones compared with aldehydes and α-ketoesters. Therefore, it is a challenging task to achieve the catalytic hetero-Diels-Alder reaction with simple ketones even in a racemic system.

Based on our previous investigation and realization of copper(I)-catalyzed aldol reaction of simple ketones,[3] we hypothesized that a copper-dienolate species would be generated in situ through transmetalation between copper(I) complex and Danishefsky's diene (Figure 1). This copper dienolate, furthermore, would be reactive enough to achieve the synthesis of dihydropyranones containing tetrasubstituted carbons by using simple ketones. The results showed high substrate generality and proved that our concept was vaible (Scheme 1).

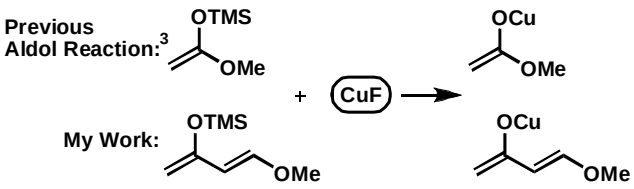
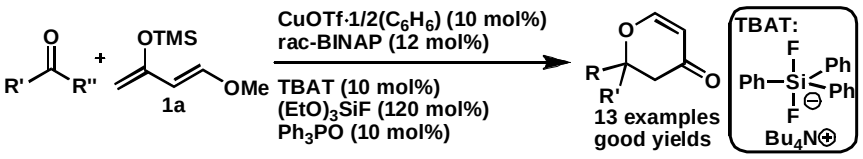


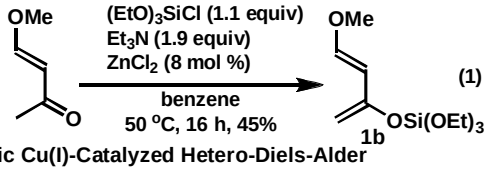

**Figure 1. Hypothesis for the generation of copper dienolate based on the previous aldol reaction.**

**Scheme 1. Cu(I)-Catalyzed Hetero-Diels-Alder Reaction of Ketones**




At this stage, I was still unsatisfied with the consumption of a stoichiometric amount of $(EtO)_3SiF$ from the aspect of atom economy, so another type of siloxyl diene, **1b**, was designed based on the reaction mechanism. New diene **1b** was prepared in gram

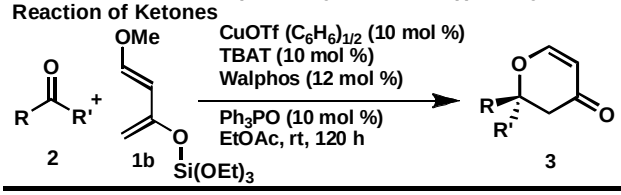
scale by the similar procedure of Danishefsky's diene **1a** (eq. 1). The copper(I)-catalyzed hetero-Diels-Alder reaction between ketones and **1b** proceeded smoothly in the absence of $(EtO)_3SiF$ without losing any reactivity.

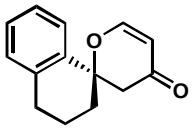



(1)

Then we extended this platform to develop an asymmetric version. Screening of chiral phosphines led us to identify Walphos type diphosphines as the optimized chiral ligand. Use of ethyl acetate as a solvent afforded better results than THF. By using these conditions, various tetra-hydropyranones were obtained with high to moderate selectivities, Table 1. In conclusion, this is the first example of catalytic asymmetric hetero-Diels-Alder reaction between Danishefsky-type diene and simple ketones.

**Table 1. Substrate Scope of Asymmetric Cu(I)-Catalyzed Hetero-Diels-Alder Reaction of Ketones**




| Product | Walphos | Yield | ee |
|---|---|---|---|
| R = H | 5 | 80 | 85 |
| R = 4-Me | 5 | 67 | 78 |
| R = 4-Ph | 4 | 87 | 76 |
| R = 4-Vinyl | 4 | 80 | 74 |
| R = 4-F | 4 | 87 | 70 |
| R = 2-Napthyl | 4 | 84 | 70 |
|  | 4 | 41 | 65 |

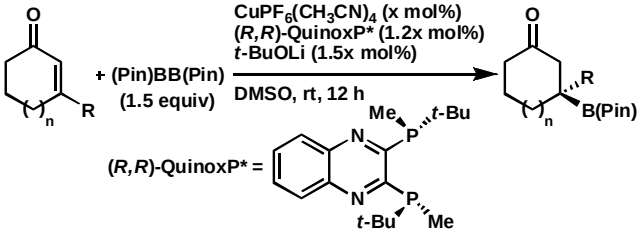
## 2. Catalytic Asymmetric Synthesis of Chiral Tertiary Organoboronic Esters through Conjugate Boration of $\beta$–Disubstituted Cyclic Enones.[4]

Conjugate addition is a fundamental method to establish a stereocenter at the $\beta$-position of electron-withdrawing groups. Although various catalytic asymmetric conjugate additions for $\beta$–monosubstituted substrates have been well developed, addition to $\beta$-disubstituted unsaturated electron-poor olefins for the construction of tetrasubstituted chiral centers was still limited. Two important reasons are that the reaction is difficult to promote due to great steric hindrance, and that the enantioselectivity is hardly controlled by the small steric difference between two substituents at the $\beta$-position in the addition step.

Recently, chiral organoboronic acids exhibiting unique biological activities are identified, in addition to the fact that organoboron compounds are versatile synthetic intermediates. Catalytic asymmetric synthesis of chiral tertiary organoboron compounds had not been developed yet. We hence focused on the catalytic asymmetric synthesis of chiral tertiary organoboronic esters through conjugate addition to $\beta$-disubstituted cyclic enones.

In the initial study, the conditions developed by Yun's group[5] for the reactions of $\beta$-monosubstitued

**Table 2. Catalytic Enanotioselective Conjugate Boration of $\beta$-Disubstituted Cyclic Enones**



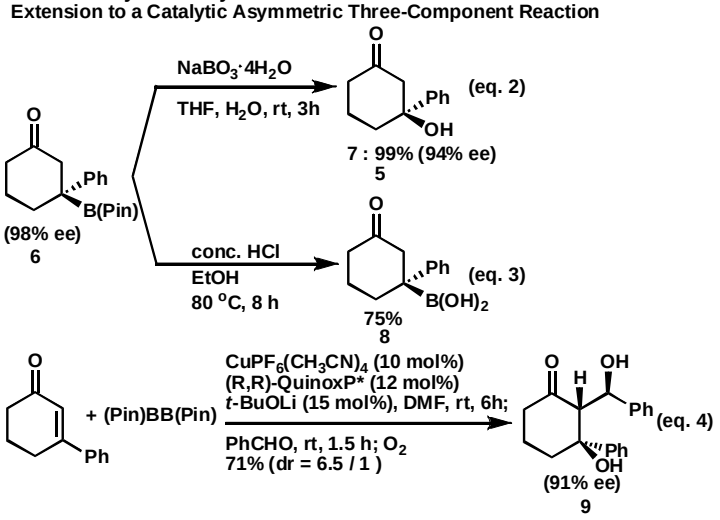

| entry | substrate | x | yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | R = Ph, n = 1 | 5 | 88 | 98 |
| 2 | R = *p*-MeO-$C_6H_4$, n = 1 | 10 | 84 | 93 |
| 3 | R = *p*-Me-$C_6H_4$, n = 1 | 10 | 86 | 95 |
| 4 | R = *p*-F-$C_6H_4$, n = 1 | 5 | 80 | 93 |
| 5 | R = *m*-MeO-$C_6H_4$, n = 1 | 10 | 83 | 95 |
| 6 | R = *m*-Me-$C_6H_4$, n = 1 | 10 | 89 | 98 |
| 7[a] | R = Me, n = 1 | 5 | 91 | 81 |
| 8 | R = *i*-Pr, n = 1 | 10 | 91 | 94 |
| 9 | R = *i*-Bu, n = 1 | 10 | 92 | 85 |
| 10 | R = Ph, n = 0 | 10 | 85 | 98 |
| 11 | R = *i*-Bu, n = 0 | 10 | 94 | 70 |
| 12 | R = Ph, n = 2 | 10 | 99 | 98 |

[a] NaO*t*-Bu was used instead of LiO*t*-Bu.

substrates was employed for 3-phenylcyclohexenone, but it just afforded the desired chiral organoboronic ester in low yield. I then optimized the reaction conditions. Use of polar solvent such as DMSO and lithium alkoxide as copper(I) alkoxide catalyst generating reagent gave better yields for this reaction. QuinoxP* containing P-chirality was the best ligand to afford excellent reaction yield and enantioselectivity. The investigation of substrate scope was then conducted as shown in Table 2. Excellent enatioselectivities were obtained with $\beta$–aromatic-substutied enones, and stereoselectivities were almost not influenced by substituents on the aromatic rings. $\beta$ – Alkyl-substituted substrates also afforded highly enantiomerically-enriched products. Moreover, $\beta$ -substituted-5 and 7-membered cyclic enones produced synthetically useful enantioselectivity.

This reaction is a useful platform for the synthesis of various chiral building blocks that are otherwise difficult to access (Scheme 2). Interesting $\beta$–hydroxy ketone **7** containing a tetrasubstituted carbon was easily obtained almost without losing enantioselectivity through the oxidation by sodium perborate (eq. 2). Chiral tertiary organoboronic acid **8** was produced through acid hydrolysis (eq. 3). This reaction system was extended to a catalytic asymmetric cascade three-component reaction. In situ generated chiral boron enolate was treated with benzaldehyde before quenching, and the resulting product was oxidized in one pot. Under these conditions, chiral diol **9** involving three contiguous stereogenic centers was obtained with good diastereoselectivity and enantioselectivity (eq. 4).

**Scheme 2. Synthetically Useful Conversions of the Products and Extension to a Catalytic Asymmetric Three-Component Reaction**




To this stage, the copper(I)-catalyzed conjugate boration of $\beta$-disubstituted cyclic enones was well developed. However, linear $\beta$-disubstituted enones did not produce good results by using the same conditions, affording desired product just with low enantioselectivity. The development of copper(I)-catalyzed conjugate boration of linear $\beta$-disubstituted enones would be a challenging topic, and related investigation is ongoing.

## References:


(1) (a) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (c) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873.

(2) Chen, I.-H.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 5151.

(3) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164.

(4) Chen, I.-H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *133*, 11664.

(5) Mun, S.; Lee, J.; Yun, J. *Org. Lett.* **2006**, *8*, 4887.