論文の内容の要旨

論文題目 **Development of Cu(I)–Catalyzed Asymmetric Construction of Chiral Tertiary Alcohols and Dihydropyranones**

(一価銅触媒による3級アルコールおよびジヒドロピラノン類の不斉合成)

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1. Development of New Modular Chiral Bisphosphine Ligands (ShrimP*): Design, Synthesis and Their Application in Cu(I)–Catalyzed Asymmetric Allylation and Propargylation of Ketones[1]

Chiral phosphines play crucial roles in asymmetric catalysis. Many privileged chiral phosphines have been developed. Continuous structural improvement and diversification are still necessary, however, to achieve high asymmetric induction in difficult-to-control C–C bond formations, such as tertiary alcohols constructions. Synthesis of chiral phosphines is generally laborious, which has hampered their intensive structural optimization. Modular approaches allowing for rapid synthesis and systematic optimization of ligand structure will facilitate the development of chiral phosphines. Herein, I report the development of new modular chiral bisphosphine ligands (ShrimP*, **Figure 1**) and their application in construction of two kinds of chiral tertiary alcohols.

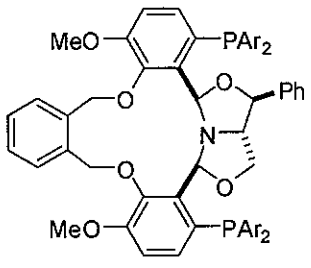


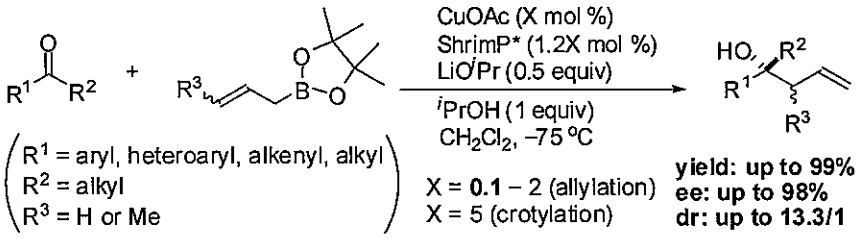
Figure 1. ShrimP*: Ar = *p*-F-Ph

(1) Development of ShrimP* and its Application in Cu(I)–Catalyzed Asymmetric Allylation of Ketones

Catalytic asymmetric allylation of ketones constructing chiral tertiary alcohols represents a challenging reaction. Although many efforts have been devoted to this reaction, there are still several drawbacks in the known methodologies, such as high catalyst loadings, narrow substrate generalities, and requirement of unstable allylating reagents. Our group previously developed the first asymmetric allylboration of ketones catalyzed by a CuF–^{i}Pr-DuPHOS complex[2]. Although the products were obtained in high yields, the enantioselectivity was not necessarily satisfactory, even after intensive screening of commercially available chiral phosphines. Therefore, efficient catalysts with excellent enantio-induction ability to facilitate the asymmetric allylation of ketones are in high demand.

With these considerations in mind, I started to develop original modular chiral phosphines. The intensive optimization of a series of readily synthesized phosphines in the catalytic enantioselective allylation of acetophenone led me to identify Shrimp* as the best ligand. ShrimP* was easily prepared in multigram scale in high yield *via* three facile transformations (*O*-alkylation, bisaminal formation, and phosphination) using commercially available reagents. Further optimization of reaction conditions revealed that the addition of co-catalyst LiO^{i}Pr and protonic additive isopropanol significantly improved the reactivity. As a result, the optimal reaction conditions were developed as shown in **Scheme 1**.

Scheme 1. CuOAc–ShrimP* complex catalyzed asymmetric allylation of ketones

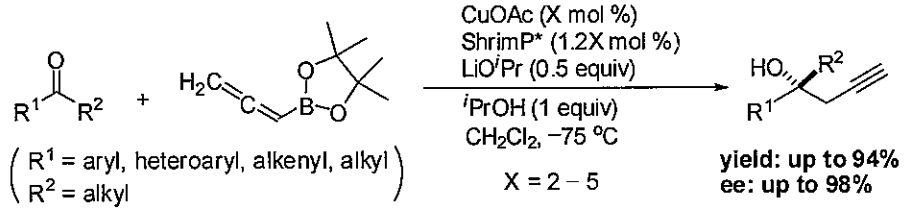


In general, the allylation reaction proceeded smoothly in the presence of 2 mol % of catalyst, affording the product in high yield and excellent enantioselectivity. Compared with our previous reaction using ^{i}Pr-DuPHOS[2], the enantioselectivity and catalyst activity were significantly improved. The crotylation reaction also proceeded with improved diastereo- and enantioselectivity. Notably, in the case of tetralone as substrate, using as low as 0.1 mol % of CuOAc–ShrimP* catalyst afforded the product in excellent enantioselectivity (95% ee) and high yield (85%). These facts clarified that Cu–ShrimP* possesses high activity and excellent enantio-control ability.

(2) Application of ShrimP* to the First Cu(I)–Catalyzed Asymmetric Propargylation of Ketones

To further demonstrate the utility of ShrimP*, I applied the CuOAc–ShrimP* catalyst to an enantioselective propargylation of ketones using allenylboronate (**Scheme 2**). Homopropargyl tertiary alcohols were produced with high enantioselectivity from a range of ketones, including aryl, heteroaryl, α,β-unsaturated and alkyl ketones. The reaction proceeded with perfect regioselectivity (γ-addition), and the corresponding allenyl alcohol isomers (α-adducts) were not detected in any case. Due to the synthetic versatility of terminal alkynes, various product conversions, such as Sonogashira coupling and one-pot propargylation–Huisgen cycloaddition, were successfully performed. Therefore, this reaction produces a synthetically independent family of chiral building blocks for allylation. It's noteworthy that this is the first catalytic enantioselective propargylation of ketones.

Scheme 2. CuOAc–ShrimP* complex catalyzed asymmetric propargylation of ketones



(3) Mechanistic Studies

To gain some insight into the origin of the high catalyst activity and enantioselectivity of the CuOAc–ShrimP* complex, I elucidated the X-ray crystal structure of the complex. The observed bite angle was extraordinarily wide ($\angle$PCuP = 137.8°), resulting in the stabilization of the catalytically active monomeric Cu complex. This hypothesis was confirmed by comparison of the catalytic activity and aggregation state of the Cu–bisphosphine (ShrimP*, ^{i}Pr-DuPHOS, and XantPHOS) complex. Furthermore, through DFT calculation for transition state structures of the allylation of acetophenone, it was observed that the carbonyl oxygen in acetophenone formed non-conventional C–H···O=C hydrogen bonds with the bisaminal protons (H_{19}, H_{28}) and aryl-H (H_{90}) on the phosphorous atom (**Figure 2**), leading to a distortion of the tetrahedral copper atom geometry. Therefore, I tentatively proposed that the significant stabilization by hydrogen bond network formation in the transition state, as well as the extraordinarily wide bite angle, is responsible for the high catalyst activity and enantioselectivity of the CuOAc–ShrimP* complex.

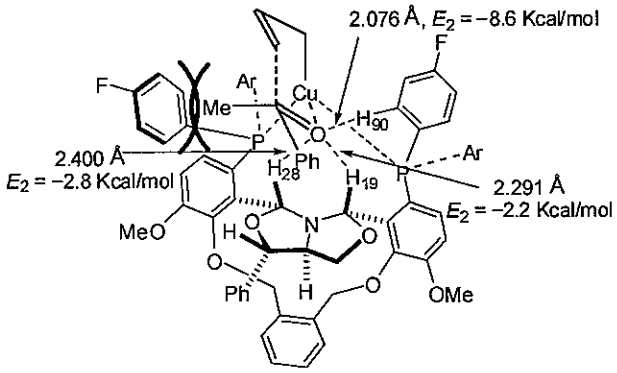


Figure 2. DFT calculation for transition state structure of the catalytic asymmetric allylation of acetophenone

2. Direct Asymmetric Synthesis of Dihydropyranones *via* a Soft Metal Catalyzed Sequential Aldol–oxy-Michael Reaction Using α,β-Unsaturated Ynones[6]

Chiral dihydropyranones are versatile skeletons of various biologically active molecules. Catalytic asymmetric hetero-Diels-Alder reactions between carbonyl compounds and activated dienes (typically, Danishefsky's dienes) is a conventional method to access them.[3, 4] However, preparation of labile dienes is a cumbersome process. Thus, I envisioned that an asymmetric hetero-Diels-Alder reaction to produce dihydropyanones *via* a sequential aldol–oxy-Michael reaction using enolates generated in situ by a chiral base catalyst from stable and easily available ynones will be advantageous.

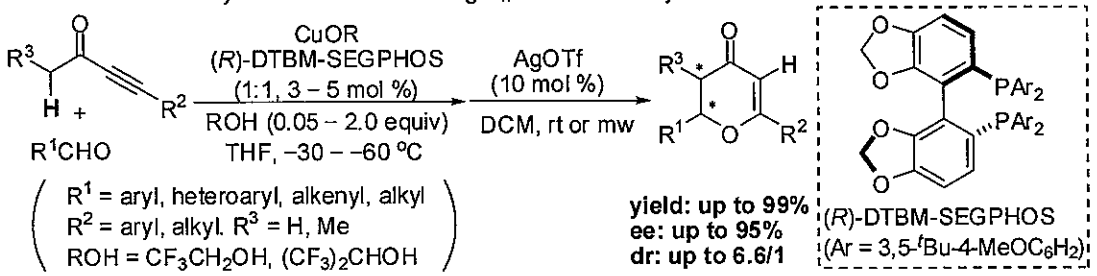
Despite the presumable fascinating efficiency, developing such a reaction is particularly challenging due to two reasons: 1) there are possible side reactions in a base-catalyzed direct aldol reaction, such as retro-aldol reaction, homo-aldol reaction of substrates, and dehydration of aldol adducts; 2) the corresponding intramolecular oxy-Michael reactions to ynones are not studied extensively.

To overcome these difficulties, I assumed a soft metal-conjugated base would facilitate the sequential aldol–oxy-Michael reaction. My designed process relies on two distinct soft metal–soft π electron interactions: 1) chemoselective deprotonative activation of ynones through soft metal–soft ynone interaction in the presence of (enolizable) aldehydes to promote the aldol reaction;[5] 2) electrophilic activation of thus-generated aldol adducts (β-hydroxyynones) *via* soft metal–soft ynone interaction to promote the oxy-Michael reaction. As expected, after intensive screening, I successfully developed a direct asymmetric synthesis of dihydropyanones *via* a sequential aldol–oxy-Michael reaction catalyzed by a Cu(I)–DTBM-SEGPHOS complex and AgOTf, respectively (**Scheme 3**).[6] Chiral 2,6-disubstituted dihydropyranones were produced in moderate to excellent enantioselectivity and good yields with high

substrate generality. One example for asymmetric synthesis of 2,3,6-trisubstituted dihydropyranones resulted in high diastereo- and enantioselectivity.

It's notable that the highly chemoselective deprotonative activation of ynones allows for a direct aldol-cyclization reaction of α-nonbranched aliphatic aldehydes, which are susceptible to self-condensation. Furthermore, a series of functional groups was compatible, such as ketone, ester and unprotected hydroxyl group. Expansion of substrate scope in the diastereoselective reaction, as well as application of the current methodology to a catalytic asymmetric synthesis of Relenza (an antiviral drug) is now ongoing.

Scheme 3. Direct asymmetric synthesis of dihydropyranones *via* a soft metal catalyzed sequential aldol–oxy-Michael reaction using α,β-unsaturated ynones



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