

論文の内容の要旨

論文題目 Development of Catalytic Enantioselective Allylation of
Ketones and Ketoimines Using Chiral CuF Catalyst
(キラル CuF 触媒を用いたケトンおよびケトイミンに
対する触媒的不斉アリル化反応の開発)

Reiko Wada (和田 麗子)

Catalytic enantioselective construction of chiral tetrasubstituted carbons via the addition of organometallics to ketones or ketoimines is a long standing problem in organic synthesis. To synthesize a trisubstituted carbon, a nucleophile adds to a carbonyl carbon of which one of the 2 substituents is hydrogen. Tetrasubstituted carbon synthesis requires the carbon nucleophile to attack much more sterically hindered carbonyl carbon which has 2 carbon substituents, so either a strong nucleophile or harsh conditions are required for enough reactivity. To control the face selectivity is another difficult task because of the lesser steric dissimilarity between R^1 and R^2 .

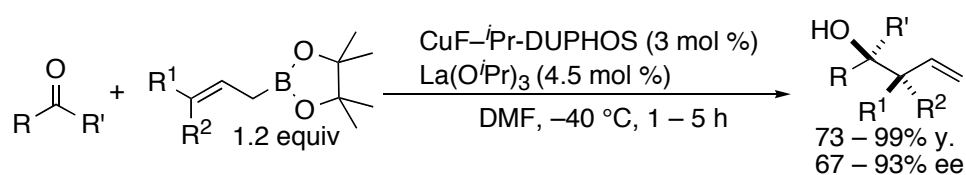
To be more specific, one of the most important carbon-carbon bond forming reactions to construct a chiral tetrasubstituted carbon is allylation of ketones. The product is homoallylic alcohol, a versatile chiral building block which can be easily converted, for example, to an ester by oxidative cleavage of the terminal olefin or to an internal olefin by olefin metathesis. There are highly stereoselective (enantioselective and diastereoselective) catalytic allylation and crotylation reactions using aldehydes as a substrate to produce chiral secondary homoallyl alcohols. There are far fewer successful examples, however, of targeting ketones as a substrate. Despite the importance of a chiral tertiary homoallyl alcohol as a chiral building block for biologically significant compounds, there is little synthetic methodology available due to the attenuated reactivity of ketones and the lesser steric dissimilarity of the two substituents on the carbonyl carbon compared to aldehydes.

The most frequently used allylmetals in organic synthesis are allylsilicons,

allylstannanes and allylborons. Allylstannanes are the most reactive of these, and by 2004, catalytic asymmetric allylation to ketones was only possible with these reagents. Allylsilicon and allylboron have advantages over other allylmetals for their low toxicity and stability under air and moisture. They can be handled easily and can be stored for a long period of time. If allylsilanes or allylborons could be catalytically activated by a chiral catalyst, then the best catalytic enantioselective allylation of ketones would be developed. With these objectives in mind, I started to develop a novel catalytic enantioselective allylation of ketones with allylsilanes or allylborons.

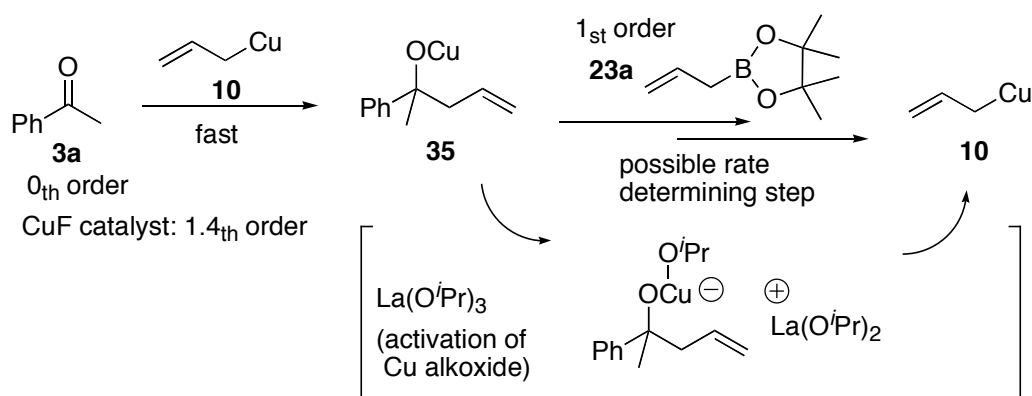
The chiral CuF-phosphine complex prepared from 1:2 mixture of $\text{CuF}_2 \cdot 2\text{H}_2\text{O}$ and chiral diphosphine ligand was found to catalyze enantioselective allylation of ketones using allyltrimethoxysilane. This is the first reaction that allylsilane is generally applied to catalytic enantioselective allylation of ketones. But limitations remain: high catalyst amount is required and reaction time is long; and enantioselectivities are still moderate.

After extensive investigations, I have developed a catalytic enantioselective allylboration and crotylboration of ketones using a combination of 3 mol % of chiral CuF-phosphine complex and 4.5 mol % of $\text{La}(\text{O}^i\text{Pr})_3$ as catalyst and commercially available allylboronic acid pinacol ester as an allylating reagent. The reaction proceeded at $-40\text{ }^\circ\text{C}$, and the product was obtained in good yield and up to 93% ee in short reaction time. This is the first example of catalytic enantioselective allylation of ketones that utilizes a chiral catalyst in a *truly* catalytic amount, and the use allylboronate in such reaction is unprecedented. Catalytic enantioselective crotylation of ketones is the first example using any allylmetals.



The mechanistic studies revealed that the active nucleophile in this reaction is allylcopper **10**, generated by the reaction of allylboronate and CuF. Kinetic studies clarified that the order dependency on the initial rate for substrate ketone, allylboronate, and CuF catalyst are 0, 1.0, and 1.4, respectively. Therefore, the addition step proceeds rapidly, and the rate determining step should be the regeneration of allylcopper after the addition step.

$\text{La}(\text{O}^i\text{Pr})_3$ has a rate accelerating effect without affecting the enantioselectivity of the product. From NMR studies, it was suggested that $\text{La}(\text{O}^i\text{Pr})_3$ accelerates the rate-determining catalyst regeneration step by activating copper alkoxide **35** which is generated after the addition of allylcopper to ketone.



Moreover, $\text{CuF}\text{-La}(\text{O}^i\text{Pr})_3$ catalyst was found to be effective in catalytic allylboration of *N*-benzyl ketoimines. This reaction is the first general catalytic allylation of ketoimines, and it was further extended to a catalytic enantioselective allylboration of ketoimines using 10 mol % of chiral CuF -phosphine complex and 15 mol % of LiO^iPr . Although improvements on catalytic amount and substrate generality are still needed, this is the first example of catalytic enantioselective allylation of ketoimines. Obtaining mechanistic information of this reaction in future will hopefully support to develop an even more efficient process, and easy access to the class of chiral α -tertiary alkyl substituted amines, now far from being a general method, should open a new entry into a series of useful synthetic methods.

