ENANTIOSELECTIVE CONJUGATE ADDITION OF ORGANOMETALLIC REAGENTS TO CYCLOALKENONES BY THE AID OF CHIRAL LACTAM-PHOSPHINE LIGAND[1]

Kiyoshi Tomioka* and Yuichi Nakagawa

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

Abstract - The chiral lactam-phosphine ligand and copper salt mediated asymmetric conjugate addition reaction of butylmagnesium chloride and diethylzinc with cycloalkenones. Among phosphines examined, 5-((diphenylphosphino)methyl)-3,3-dimethylpyrrolidin-2-one (**1**) gave rise to good selectivity and high yield.

We have been engaged in the development of asymmetric conjugate addition reaction of organometallic reagents mediated by an external chiral ligand.[2] Stoichiometric and catalytic enantioselective reactions of organocopper reagents with cycloalkenones giving the corresponding 1,4-addition products have been developed.[3] Our strategy relies on activation and subsequent control of stereochemistry of organometallic species by the formation of a phosphine ligand-organocopper complex. However, excess of organometallic reagent in the catalytic reaction may destroy the chiral phosphine-organocopper complex and causes loss of enantioselectivity. To circumvent this drawback it is desirable to use tight complex of chiral phosphine and copper.[4] It may be reasonably assumed that a chiral lactam bearing a phosphine appendage should form the stable amidocopper species whose copper is intramolecularly coordinated by phosphine as shown in Figure 1. We describe herein that the asymmetric conjugate addition reaction of butylmagnesium chloride and diethylzinc[5] was catalyzed by the lactam-phosphine in the presence of copper salt to give the corresponding addition product in up to 64% ee.

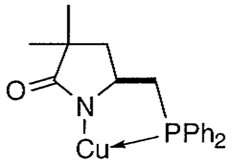
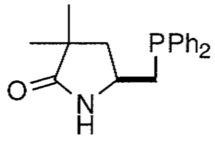


Figure 1



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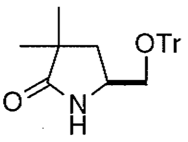

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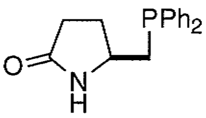

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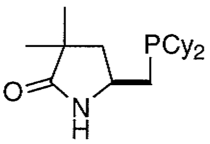

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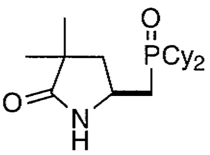

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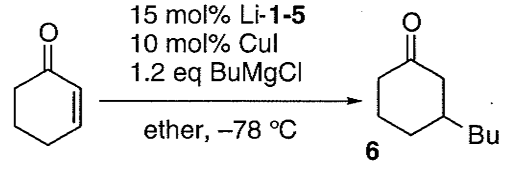
We examined chiral lactam-phosphines (**1**, **3**, **4**) that were prepared from L-glutamic acid according to the previously reported procedure.[6] At first, we examined the catalytic behavior of **1**. A solution of 15 mol% of lithiated **1**, generated by butyllithium in ether at 0 °C for 0.5 h, was added into a suspension of 10 mol% of copper(I) iodide in ether at room temperature. The mixture was stirred at room temperature for 1 h. Then, a solution of butylmagnesium chloride in ether was added at –78 °C and the mixture was stirred for additional 0.5 h at –78 °C. Finally, a solution of 2-cyclohexenone in ether was added at –78 °C. After 1 h stirring at the same temperature, usual workup and purification gave (*S*)-3-butylcyclohexenone (**6**) in 47% ee and 92% yield (Table 1).[7] The formation of the desired complex of copper amide is dependent on mixing conditions. Mixing of lithiated **1** and copper iodide at –78 °C was not satisfactory to afford after 1 h at 0 °C **6** in 12% ee and 22% yield. The amount of catalysts, lithiated **1** and copper iodide, was reduced to 7.5 and 5 mol% each to afford **6** in 44% ee and 90% yield. However, the reaction is highly sensitive to a solvent. Other solvents such as THF, toluene, hexane, methylene dichloride, and acetonitrile gave **6** in marginal ee's. Although copper bromide can be alternative to afford 23% ee, other copper salts such as copper chloride, cyanide, and triflate are not the choice to afford marginal selectivity.

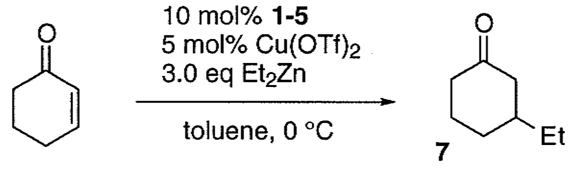
Since trityllactam (**2**) and phosphine oxide (**5**) gave **6** in only 4 and 2% ees, the importance of phosphorus atom is apparent (Table 1). Simple lactam-phosphine (**3**) gave **6** in only 2% ee, suggesting a directing effect of dimethyl substitution at the α-position of carbonyl group of **1**. It was disappointing that dicyclohexylphosphine (**4**) was expected to coordinate more tightly to copper than diphenylphosphine (**1**), however, gave rise to a similar level (40% ee).

Table 1. Asymmetric reaction using lithiated **1-5**.



entry	**1-5**	time/h	yield/%	ee/%	*R/S*
1	**1**	1	92	47	*S*
2	**2**	1.5	84	4	*R*
3	**3**	1	74	2	*R*
4	**4**	1	96	40	*S*
5	**5**	1	88	1	*R*

Table 2. Asymmetric reaction using **1-5**.



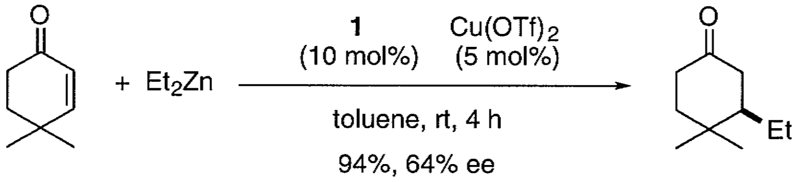
entry	**1-5**	time/min	yield/%	ee/%	*R/S*
1	**1**	20	84	35	*S*
2	**2**	180	76	6	*R*
3	**3**	30	82	19	*S*
4	**4**	10	93	31	*S*
5	**5**	420	73	9	*S*

Next, we examined the catalytic activity of lactam-phosphine-copper complexes using diethylzinc as a carbonucleophile. The reaction procedure is quite simple. A mixture of 10 mol% of **1** and 5 mol% of $Cu(OTf)_2$[8] in toluene was stirred at room temperature for 1 h. A solution of 3 equiv. of diethylzinc was added at 0 °C and the mixture was stirred for 15 min at 0 °C. To the reaction mixture was added a solution of 2-cyclohexenone in toluene and the whole was stirred for 20 min at 0 °C. Usual workup and purification gave (*S*)-3-ethylcyclohexanone (**7**) in 35% ee and 84% yield.[7] Toluene was the best solvent examined. Ether and THF gave marginal ee's. Enantioselectivity was affected significantly by the reaction temperature; for example, 19 and 27% ee at room temperature and at –40 °C, respectively. At a lower temperature below 0 °C, some reactive species giving poorer selectivity may be involved in the reaction.

The chiral lactam-phosphines exhibited similar trend of enantioselectivity to that observed for the reaction of butylmagnesium chloride (Table 2). The relatively higher 35 and 31% ee were obtained using **1** and **4**. The phosphine (**3**) gave 19% ee. Other lactams were unsatisfactory to afford low ee's.

The reactions of diethylzinc with cycloalkenones using **1** were examined. Ethyl group was introduced to cyclopentenone and cycloheptenone in 24 and 32% ees, and in high yields. It was remarkable to find that the reaction with 4,4-dimethylcyclohexenone gave the product in 64% ee and 94% yield after 4 h at room temperature (Scheme 1).[9]

Scheme 1



Further studies directed towards more sophisticated design of chiral copper species are in progress in our laboratories.[10]

REFERENCES AND NOTES

1. We dedicate this paper to Professor Teruaki Mukaiyama on the celebration of his 73rd birthday.
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