Pergamon

Tetrahedron Letters, Vol. 35, No. 6, pp. 895-898, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

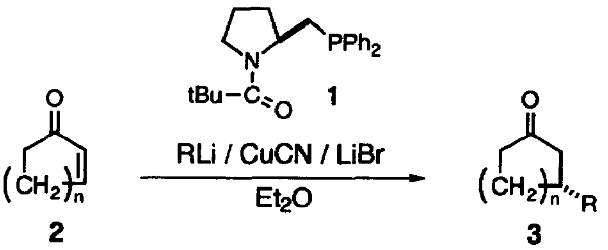
0040-4039(93)E0336-I

Asymmetric Conjugate Addition of Organocopper-Amidophosphine Reagents to Cycloalkenones

Motomu Kanai and Kiyoshi Tomioka*
The Institute of Scientific and Industrial Research, Osaka University,
Ibaraki, Osaka 567, Japan

Abstract: *Mediated by a noncovalently bound chiral amidophosphine ligand 1, reaction of organocoppers with cycloalkenones 2 afforded the corresponding 3-substituted cycloalkanones 3 in 95-68% ee.*

Conjugate addition of organocopper reagents to α,β-unsaturated carbonyl compounds is one of the most reliable carbon-carbon bond forming reactions.[1] Asymmetric modifications have been realized by the three major methods[2] using (1) carbonyl compounds as substrates having covalently bound chiral auxiliaries,[3] (2) metal amides and thiolates as chiral components of heterocuprates,[4] and (3) noncovalently bound chiral ligands for organocuprates and organocoppers.[5,6] The latter two methods are challenging and practical in terms of reagent control and some suggestive recipes have been described in the representative reports.[4-6] We have recently been involved in an enantioselective reaction of organometallics controlled by an external chiral ligand[7] and found chiral amidophosphines as such ligands for homocuprates in the addition to chalcone.[8] We describe herein a highly efficient enantioselective conjugate addition of organocoppers to 2-cycloalkenones 2 in the presence of 1 giving 3-substituted cycloalkanones 3.



Typical reaction procedure is as follows (Table I, entry 14): To a solution of copper cyanide (1.52 mmol) and lithium bromide (12.1 mmol) in ether (32 mL) was added butyllithium (1.51 mmol) in hexane at -78 °C, and the resulting pink solution was stirred for 20 min at the same temperature. A solution of 1 (4.55 mmol) in ether (16 mL) was added to the solution, whereupon the solution immediately turned to yellow. The solution was stirred for 15 min at -78 °C. A solution of 2-cyclohexenone 2 (n=2)(1.01 mmol) in ether (4 mL) was added and the whole was stirred for 30 min at -78 °C. Usual workup and purification by silica gel column chromatography (CH_2Cl_2 / hexane 4:1) followed by short path distillation afforded (*R*)-3-butylcyclohexanone 3 (n=2, R=Bu) ($[\alpha]_D^{23}$ +7.21 °(c 1.04, toluene))[9] in 97% isolated yield. The ee was determined to be 90% by ^{13}C NMR analysis of the corresponding diastereomeric ketals prepared with (*R*,*R*)-2,3-butanediol (*p*-TsOH in benzene at reflux, 98% yield).[10] The ligand 1 was recovered in 93% yield for reuse without any racemization.

Table I. Asymmetric Conjugate Addition of RCu-1 to Cycloalkenone 2 Giving 3[a]

entry	n	RLi	CuX and added salt	1/eq	solvent	temp/°C	ee/%	yield/%
1	2	MeLi	CuI + 8LiBr	2	Et_2O	-20	56	61
2	2	MeLi	CuCN	2	Et_2O	-20	4	47[b]
3	2	MeLi	CuCN + 8LiBr	3	Et_2O	-20	76	99
4	2	MeLi	CuCN + 8LiBr + 2TMSCl	3	Et_2O-HMPA[c]	-78	92	66
5	2	MeLi	CuSCN + 8LiBr + 2TMSCl	3	Et_2O-HMPA[c]	-10	41	45
6	2	MeLi	CuBr + 8LiBr + 2TMSCl	3	Et_2O-HMPA[c]	-45	45	53
7	2	MeLi	CuCN + 8LiBr + 2TMSCl	3	THF-HMPA[c]	-78	0	99
8	2	EtLi	CuCN + 8LiBr + 2TMSCl	3	Et_2O-HMPA[c]	-78	67	48
9	2	EtLi	CuCN + 8LiBr	3	Et_2O	-78	91	89
10	2	EtLi	CuCN + 8LiCl	3	Et_2O	-78	41	77
11	2	EtLi	CuCN + 8LiI	3	Et_2O	-78	14	80
12	2	EtLi	CuCN + 8LiCN	3	Et_2O	-78	86	38
13	2	EtLi	CuCN + 8Bu_4NBr	3	Et_2O	-78	60	46
14	2	BuLi	CuCN + 8LiBr	3	Et_2O	-78	90	97
15	1	EtLi	CuCN + 8LiBr	3	Et_2O	-78	94	90
16	1	BuLi	CuCN + 8LiBr	3	Et_2O	-78	95	99
17	3	MeLi	CuCN + 8LiBr + 2TMSCl	3	Et_2O-HMPA[c]	-78	68	46
18	3	BuLi	CuCN + 8LiBr	3	Et_2O	-78	74	92[d]

(a) Reaction was run as described in the text. Molar ratio of RLi:CuX:LiY:1:(TMSCl):cycloalkenone=1.5:1.5:12:3 or 4.5:(3):1. (b) (*S*)-3 (n=2, R=Me) was obtained. (c) HMPA (2 equivalents toward CuX) was used. (d) Absolute configuration was not determined.

We began our studies with finding dramatic effects of copper sources and lithium bromide on enantioselectivity in reaction of methylcopper with 2-cyclohexenone 2 (n=2). Reaction of lithium dimethylcuprate, prepared from methyllithium (2 equivalents) and copper iodide, in ether in the presence of 1 proceeded at -78 °C to give (*R*)-3-methylcyclohexanone 3 (n=2, R=Me) in only 16% ee (63% isolated yield). The reaction of methylcopper, prepared from copper iodide, did not proceed at -78 °C, but did at -20 °C in the presence of two equivalents of 1 to give 3 in 26% ee. An addition of lithium bromide to the latter reaction had a beneficial effect on enantioselectivity and that of eight equivalents of lithium bromide gave 3 in the maximum ee of 56% (entry 1).[6] The lithium bromide effect was prominent in the reaction of methylcopper prepared from copper cyanide as a copper source as shown in entries 2 and 3. The ee was dramatically increased to 76% from only 4%.

The equivalence of the ligand 1 is important and 3 of 24, 69, 76, and 80% ee were obtained, respectively, along with increasing equivalence of 1 from 1, 2, 3, and 6.[11] Addition of TMSCl[12] in the reaction also exerted a profound effect to promote the reaction at the lower temperature -78 °C affording 3 in 92% ee and 66% isolated yield (entry 4).[13,14] A selection of copper source is quite important; 3 of 41, 45, and 92% ee were obtained using copper thiocyanate, bromide, and cyanide, respectively (entries 4-6). A selection of solvent is also important; the reaction in THF provided racemic 3, while in ether the reaction gave 3 in 92% ee (entries 4 and 7).

The effect of TMSCl is not always operative. The reaction of organocopper with higher reactivity gave 3 in higher ee in the absence of TMSCl; ethylcopper is reactive enough to give 3 (n=2, R=Et) in 91% ee without aid of TMSCl and in 67% ee in the presence of TMSCl at -78 °C (entries 8 and 9). It is also worthwhile to show that lithium bromide and lithium cyanide both exerted beneficial effect on enantioselectivity, while lithium chloride, iodide, and ammonium bromide did not (entries 9-13).

In conclusion, fine tuning of the reaction conditions for enantioselective conjugate addition of organocopper to cycloalkenone was realized with respect to copper source, added lithium salt, TMSCl, and solvent. As shown in entries 4, 9, 14-18, methyl, ethyl, and butyl groups were introduced in cyclopentenone, cyclohexenone, and cycloheptenone to afford the corresponding 3-substituted cycloalkanones in 95-68% ee.

The present study revealed that fine condition tuning is still essential in realizing high efficiency and much more efforts are needed to propose some useful guidances on structure-enantioselectivity relationships in developing a chiral ligand mediated asymmetric reaction of organocopper species.[15]

References and Notes

1. Lipshutz, B. H., Ed. Recent Developments in Organocopper Chemistry, *Tetrahedron* **1989**, *45*, No.2, 349; Normant, J. F. *Pure Appl. Chem.* **1978**, *50*, 709; Posner, G. H. *Org. Reaction* **1972**, *19*, 1
2. Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771; Tomioka, K. *Synthesis* **1990**, 541; Tomioka, K.; Koga, K. in Asymmetric Synthesis, Vol. II, Academic Press, New York, 1983, chapter 7.
3. Tomioka, K.; Suenaga, T.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 369.
4. Imamoto, T.; Mukaiyama, T. *Chem. Lett.* **1980**, 45; Bertz, S. H.; Dabbagh, G.; Sundararajan, G. *J. Org. Chem.* **1986**, *51*, 4953; Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114; Tanaka, K.; Ushio, H; Suzuki, H. *J. Chem. Soc., Chem. Commun.* **1990**, 795; Dieter, R. K.; Lagu, B.; Deo, N.; Dieter, J. W. *Tetrahedron Lett.* **1990**, *31*, 4105; Ahn, K.-H.; Klassen, R. B.; Lippard, S. J. *Organometallics* **1990**, *9*, 3178; Lambert, F.; Knotter, D. M.; Janssen, M. D.; van Klaveren, M.; Boersma, J.; van Koten, G. *Tetrahedron Asymmetry* **1991**, *2*, 1097; Rossiter, B. E.; Eguchi, M.; Miao, G.; Swingle, N. M.; Hernandez, A. E.; Vickers, D.; Fluckiger, E.; Patterson, R. G.; Reddy, K. V. *Tetrahedron* **1993**, *49*, 965.
5. Leyendecker, F.; Laucher, D. *Tetrahedron Lett.* **1983**, *24*, 3517; *Idem, Nouv. J. Chim.* **1985**, *9*, 13.
6. Alexakis, A.; Mutti, S.; Normant, J. F. *J. Am. Chem. Soc.* **1991**, *113*, 6332.
7. Shindo, M.; Koga, K.; Tomioka; K. *J. Am. Chem. Soc.* **1992**, *114*, 8732.
8. Kanai, M.; Koga, K.; Tomioka, K. *Tetrahedron Lett.* **1992**, *33*, 7193; *Idem, J. Chem. Soc., Chem. Commun.* **1993**, 1248.
9. The absolute configuration of **3** was determined by optical rotation. Cyclopentanones (3-ethyl: Posner, G. H.; Frye, L. L.; Hulce, M. *Tetrahedron* **1984**, *40*, 1401; 3-butyl: Taura, Y.; Tanaka, M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* **1989**, *30*, 6349), Cyclohexanones (3-methyl: Leyendecker, F.; Jesser, F.; Ruhland, B. *Tetrahedron Lett.* **1981**, *22*, 3601; 3-ethyl: Posner, G. H.; Frye, L. L. *Isr. J. Chem.* **1984**, *24*, 88; 3-butyl: See the paper reported by Corey et al. in reference 4), 3-Methylcycloheptanone: Djerassi, C.; Burrows, B. F.; Overberger, C. G.; Takekoshi, T.; Gutsche, C. D.; Chang, C. T. *J. Am. Chem. Soc.* **1963**, *85*, 949.
10. Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183.
11. The reactivity of organocopper complexed with phosphine ligand has been discussed: Suzuki, M.; Suzuki, T.; Kawagishi, T.; Morita, Y.; Noyori, R. *Isr. J. Chem.* **1984**, *24*, 118.
12. Two equivalent of TMSCl was added together with two equivalents of HMPA. In the absence of HMPA, the ee of **3** (n=2, R=Me) was 86%.
13. Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27; Alexakis, A.; Sedrani, R.; Mangeney, P. *Tetrahedron Lett.* **1990**, *31*, 345.
14. However, the reaction condition is not successfully applicable for the homocuprate. The reaction of lithium dimethylcuprate, prepared from copper iodide, in the presence of lithium bromide and TMSCl-HMPA proceeded at -78 °C to afford **3** in only 14% ee.

15. We are grateful to The Research Foundation for Optically Active Compounds, The Fugaku Trust for Medicinal Research, Ono Pharmaceutical Company Ltd., and Grant-in-Aid for Scientific Research, Ministry of Education, Science and Culture, Japan, for partial support of this work. We are also grateful to the Material Analysis Center of ISIR for NMR measurements.

(*Received in Japan* 7 *September* 1993; *accepted* 1 *November* 1993)