CHEMISTRY LETTERS, pp. 45-46, 1980.

ENANTIOFACE-DIFFERENTIATING 1,4-ADDITION OF METHYL GRIGNARD REAGENT TO 1,3-DIPHENYL-2-PROPEN-1-ONE

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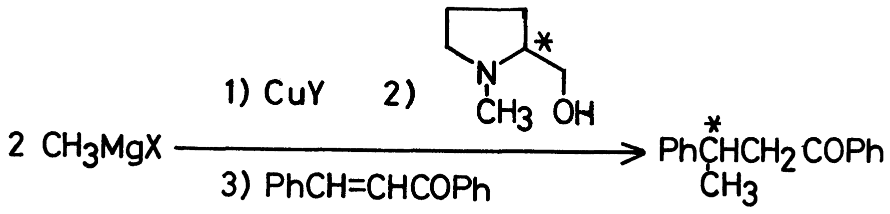
A good optical yield (68%) was achieved in the title reaction in the presence of (S)-1-methyl-2-hydroxymethylpyrrolidine as the chiral ligand.

The Michael-type addition of organocuprates or Grignard reagents to α,β-unsaturated carbonyl compounds is one of the most important methods for the formation of carbon-carbon bonds.[1] Therefore, the asymmetric induction in this reaction would provide a potential synthetic route to some important chiral compounds, and several methods were devised. Most of them were concerned with the diastereoface-differentiating reactions of the derivatives of optically active compounds, and high optical yields were achieved in some cases.[2-7] On the contrary, enantioface-differentiating 1,4-addition of organocuprates to prochiral α,β-unsaturated ketones has remained a difficult problem; a few attempts using chiral ligands such as (-)-sparteine and (-)-N-methylephedrine resulted in poor optical yields (2-6%) of the 1,4-addition products.[8,9]

In the previous papers,[10] we demonstrated that chiral pyrrolidine derivatives were effective in inducing highly enantioselective addition of organometallic reagents to carbonyl groups. Based on the results, asymmetric conjugate addition of methyl Grignard reagent to 1,3-diphenyl-2-propen-1-one was investigated by the use of (S)-1-methyl-2-hydroxymethylpyrrolidine and cuprous salt, as is shown in the following scheme.



A typical experimental procedure is as follows; to a suspension of freshly prepared cuprous bromide (572 mg, 4.0 mmol) in dry THF (7 ml) was added methylmagnesium bromide (7.8 ml of 1.13 M THF solution) at -30°C under argon, and the mixture was stirred at ice-bath temperature for 30 min. A solution of (S)-1-methyl-2-hydroxymethylpyrrolidine (664 mg, 5.6 mmol) in THF (2 ml) was then added, whereupon the color of the suspension immediately turned from white to orange. After stirring for 1 h at the same temperature, this suspension was cooled to -20°C and 1,3-diphenyl-2-propen-1-one (208 mg, 1.0 mmol) was added, and the mixture was stirred

Table The Reaction of PhCH=CHCOPh with RMgX in the Presence of (S)-1-Methyl-2-hydroxymethylpyrrolidine and CuY in THF.

Entry a,b)	RMgX	CuY	Temp(Time,h)	$\mathrm{Ph\overset{*}{\underset{CH_3}{C}}HCH_2COPh}$ Yield(%)	O.Y.(%) c)	$\mathrm{PhCH{=}CH\overset{*}{\underset{CH_3}{C}}(OH)Ph}$ Yield(%)	Recovery of PhCH=CHCOPh (%)
1	CH_3MgBr	CuBr	-20°C (1)	88	61 (S)	0	2
2 d)	CH_3MgBr	CuBr	-20°C (1)	35	40 (S)	0	27
3	CH_3MgBr	CuBr	-20°C (0.2)	79	64 (S)	0	15
4	CH_3MgBr	——	-78°C (2)	7	14 (R)	87 e)	3
5	CH_3MgBr	$CuBr.Bu_3P$	-20°C (0.1)	89	12 (S)	0	5
6	CH_3MgBr	CuI	-20°C (1)	82	48 (S)	0	2
7	CH_3MgI	CuI	-20°C (1) f)	84	14 (S)	0	0
8 g)	CH_3MgBr	CuBr	-20°C (0.2)	71	68 (S)	0	21 h)
9 g)	CH_3MgBr	CuBr	-20°C (0.08)	37	67 (S)	0	57 i)

a) (E)-PhCH=CHCOPh was used, unless otherwise noted. b) Molar ratio of [PhCH=CH-COPh]:[CH_3MgBr]:[CuY]:[Ligand] was 1:8.8:4:5.6, unless otherwise noted. c) Optical yield was calculated from optical rotation. See ref. 11). d) Molar ratio of [PhCH=CHCOPh]:[CH_3MgBr]:[CuBr]:[Ligand] was 1:2.8:1.3:1.8. e) $[\alpha]_D^{25}$ +10.6° (c 10, CCl_4). f) In THF-ether(2:1). g) (Z)-PhCH=CHCOPh was used. h) (Z):(E)=1:5. i) (Z):(E)=1:1.4.

for 1 h. The reaction was quenched with aqueous ammonium chloride solution, and usual work-up of the mixture afforded 1,3-diphenyl-1-butanone in 88% yield. This product was found to have a rotation corresponding to S configuration: $[\alpha]_D^{25}$ +8.96° (c 10, CCl_4) (i.e. 61% optical yield).11)

In a similar manner, this asymmetric reaction was examined changing the reaction conditions. The results are summarized in the above Table. The stereoselectivity in this asymmetric reaction remarkably depended on the nature of Grignard reagent and cuprous salt. The best result was obtained when the reaction was carried out within relatively short reaction time using large excess reagent prepared from methylmagnesium bromide and cuprous bromide.12)

References and Note

1) G. H. Posner, Organic Reactions, 19, 1 (1972). 2) S. Hashimoto, S. Yamada, and K. Koga, J. Am. Chem. Soc., 98, 7450 (1976). 3) A. I. Meyers and C. E. Whitten, ibid., 97, 6266 (1977). 4) A. I. Meyers and E. D. Mihelich, Angew. Chem. Int. Ed. Eng., 15, 270 (1976). 5) T. Mukaiyama, T. Takeda, and M. Osaki, Chem. Lett., 1977, 1165. 6) T. Mukaiyama, T. Takeda, and K. Fujimoto, Bull. Chem. Soc. Jpn., 51, 3368 (1978). 7) M. Asami and T. Mukaiyama, Chem. Lett., 1979, 569. 8) R. A. Kretchmer, J. Org. Chem., 37, 2744 (1972). 9) J. S. Zweig, L. L. Luche, E. Barreiro, and P. Crabbe, Tetrahedron Lett., 1975, 2355. 10) T. Mukaiyama, K. Soai, T. Sato, H. Shimizu, and K. Suzuki, J. Am. Chem. Soc., 101, 1455 (1979). 11) Optically pure (R)-1,3-diphenyl-1-butanone has $[\alpha]_D^{25}$ -14.6° (CCl_4) (T. J. Leitereg and D. J. Cram, J. Am. Chem. Soc., 90, 4011 (1968)). 12) It is noteworthy that the reaction of (Z)-isomer (Entry 8) afforded 1,4-addition product possessing the same absolute configuration (S) with similar optical purity as the reaction of (E)-isomer (Entry 3). These results suggest that both reactions involve the same radical anion intermediate generated by initial one-electron transfer from reagent cuprate to 1,3-diphenyl-2-propen-1-one.

(Received October 22, 1979)