

ZnBr₂-MEDIATED HIGHLY DIASTEREOSELECTIVE ADDITION
OF GRIGNARD REAGENTS TO α -BENZYLOXY ALDEHYDES

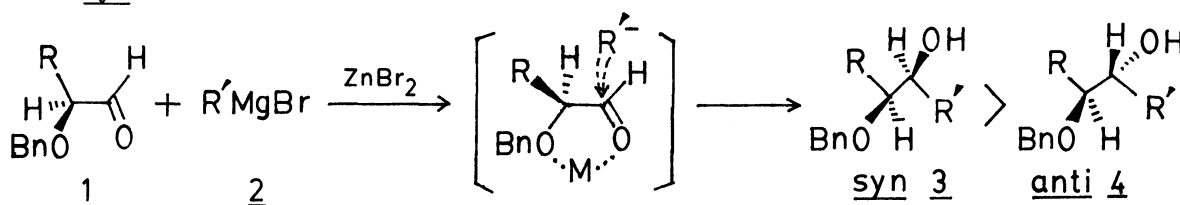
Masatoshi ASAMI* and Rieko KIMURA

Department of Chemistry, Faculty of Education,
Yokohama National University,
Tokiwadai, Hodogaya-ku, Yokohama 240

α -Benzyloxy aldehydes reacted with Grignard reagents in the presence of ZnBr₂ to afford vicinal syn-diol derivatives with high diastereoselectivity.

In recent years, many efforts have been made for the stereoselective addition of carbon nucleophiles to chiral carbonyl compounds to synthesize various complex molecules.¹⁾ As one successful example, Still et al. reported that Grignard reagents reacted with chiral α -alkoxy ketones in tetrahydrofuran (THF) with extremely high diastereoselectivity to give the product predicted by the chelation-controlled addition mechanism.²⁾ However, in case that α -alkoxy aldehyde was employed in place of α -alkoxy ketone, the diastereoselectivity became only 91:9 even when the reaction was carried out at very low temperature (-110 °C).^{3,4)}

In this paper, we wish to report the highly diastereoselective reaction of α -benzyloxy aldehydes with Grignard reagents in the presence of ZnBr₂ to afford vicinal syn-diol derivatives.



In the first place, the reaction of 2-benzyloxypropanal with butylmagnesium bromide was examined in ether or THF to estimate the effect of ZnBr₂. It was found that 2-benzyloxy-3-heptanol was obtained with very high diastereoselectivity (syn:anti=71:1) in ether in the presence of ZnBr₂ at 0 °C or -78 °C, as shown in Table 1. Then the reaction of various aldehydes with Grignard reagents were carried out in ether in the presence of ZnBr₂ at 0 °C, and the results are summarized in Table 2.

A general experimental procedure is as follows; to the suspension of ZnBr₂ (0.55 mmol) in ether (5 ml) was added α -benzyloxy aldehyde (1) (0.5 mmol) in ether (5 ml) at 0 °C under a nitrogen atmosphere. The Grignard reagent (2) (3 mmol) in ether was added to the vigorously stirred mixture at 0 °C. After stirring for 1-3 h, aq. NH₄Cl was added. The ethereal layer was washed successively with water and brine, and dried over anhydrous Na₂SO₄. The solvent was removed under reduced

Table 1. The Reaction of 2-Benzyloxypropanal and Butylmagnesium Bromide
(R=CH₃, R'=C₄H₉)

Solvent	Temp / °C	Yield / % ^{a)}	<u>syn</u> <u>3</u> :	<u>anti</u> <u>4</u> ^{a),b)}
THF	0	67 (80)	3	1 (2 : 1)
ether	0	71 (69)	71	1 (11 : 1)
	-78	67 (72)	71	1 (20 : 1)

a) The results obtained without ZnBr₂ are in parentheses. b) The diastereomer ratio was determined by capillary gas chromatography (PEG-HT). The stereochemistry was assigned by conversion of the adduct to 2,3-heptanediol by debenzoylation followed by comparison with an authentic sample by gas chromatography.

Table 2. The Diastereoselective Addition of Grignard Reagent
to α -Benzyloxy Aldehyde in the Presence of ZnBr₂

Run	R	R'	Yield / % ^{a)}	<u>syn</u> <u>3</u> :	<u>anti</u> <u>4</u> ^{b),c)}
1	CH ₃	CH ₃	72	29	1
2		C ₄ H ₉	71	71	1
3		C ₆ H ₁₃	70	>100	1
4		Ph	67	>30	1
5	(CH ₃) ₂ CH	CH ₃	81	47	1
6		C ₄ H ₉	89	>100	1
7	Ph	CH ₃	79	46	1
8		C ₄ H ₉	79	>100	1

a) All products gave satisfactory NMR and IR spectra. b) The diastereomer ratio was determined by capillary gas chromatography (PEG-HT). c) The stereochemistry was assigned by conversion of the adducts to the diols by debenzoylation followed by comparison with authentic samples by gas chromatography (runs 2, 3, and 5), or comparison of ¹³C NMR spectrum (run 1)⁵⁾ or ¹H NMR spectra (runs 4 and 7)⁶⁾ with the reported value. For runs 6 and 8, the stereochemistry was judged from ¹H NMR spectra of the diols based on the empirical rule of \underline{J} (CH-OH, syn) > \underline{J} (CH-OH, anti).⁶⁾

pressure to yield crude product, which was purified by preparative TLC.

Although the actual role of ZnBr₂ is not clear at present, the highly diastereoselective addition of Grignard reagents to acyclic α -benzyloxy aldehydes was achieved in the presence of ZnBr₂ at 0 °C via the chelation controlled addition mechanism. The present reaction would provide a convenient method for the stereoselective syntheses of vicinal syn-diols and their derivatives.

References

- 1) M. T. Reetz, *Angew. Chem.*, **96**, 542 (1984); S. Masamune, *ibid.*, **97**, 1 (1985).
- 2) W. C. Still and J. H. McDonald, III, *Tetrahedron Lett.*, **21**, 1031 (1980).
- 3) W. C. Still and J. A. Schneider, *Tetrahedron Lett.*, **21**, 1035 (1980).
- 4) For other stereoselective addition reaction of α -alkoxy aldehyde or its analog with carbon nucleophile, see Ref. 1, and K. Mead and T. L. Macdonald, *J. Org. Chem.*, **50**, 422 (1985) and references cited therein.
- 5) V. Schurig, B. Koppenhoefer, and W. Buerkle, *J. Org. Chem.*, **45**, 538 (1980).
- 6) C. Zioudrou and P. Chrysochou, *Tetrahedron*, **33**, 2103 (1977); M. Fujita and T. Hiyama, *J. Am. Chem. Soc.*, **106**, 4629 (1984).

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