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$ZnBr_2$-MEDIATED HIGHLY DIASTEREOSELECTIVE ADDITION OF GRIGNARD REAGENTS TO α-BENZYLOXY ALDEHYDES

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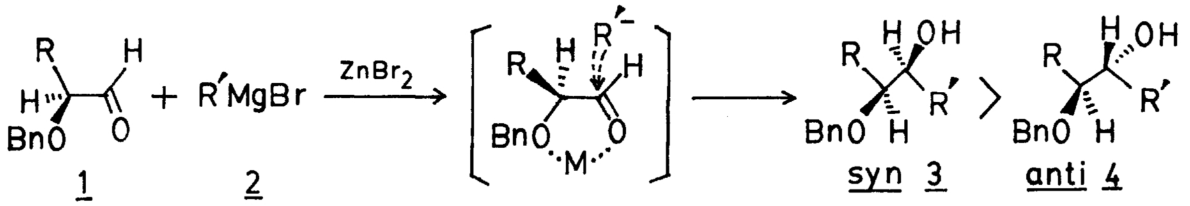
α-Benzyloxy aldehydes reacted with Grignard reagents in the presence of $ZnBr_2$ to afford vicinal syn-diol derivatives with high diastereoselectivity.

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 $ZnBr_2$ 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 $ZnBr_2$. It was found that 2-benzyloxy-3-heptanol was obtained with very high diastereoselectivity (syn:anti=71:1) in ether in the presence of $ZnBr_2$ 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 $ZnBr_2$ at 0 °C, and the results are summarized in Table 2.

A general experimental procedure is as follows; to the suspension of $ZnBr_2$ (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. NH_4Cl was added. The ethereal layer was washed successively with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced

Table 1. The Reaction of 2-Benzyloxypropanal and Butylmagnesium Bromide ($R=CH_3$, $R'=C_4H_9$)

Solvent	Temp / °C	Yield / %a)	*syn* 3	:	*anti* 4a),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 $ZnBr_2$ 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 debenzylation 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 $ZnBr_2$

Run	R	R'	Yield / %a)	*syn* 3	:	*anti* 4b),c)
1	CH_3	CH_3	72	29	:	1
2		C_4H_9	71	71	:	1
3		C_6H_{13}	70	>100	:	1
4		Ph	67	>30	:	1
5	$(CH_3)_2CH$	CH_3	81	47	:	1
6		C_4H_9	89	>100	:	1
7	Ph	CH_3	79	46	:	1
8		C_4H_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 debenzylation followed by comparison with authentic samples by gas chromatography (runs 2, 3, and 5), or comparison of ^{13}C 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 *J* (CH-OH, *syn*) > *J* (CH-OH, *anti*).6)

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

Although the actual role of $ZnBr_2$ is not clear at present, the highly diastereoselective addition of Grignard reagents to acyclic α-benzyloxy aldehydes was achieved in the presence of $ZnBr_2$ 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

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