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Stereochemistry of Halogen-Metal Exchange Reaction of Vinyl Halide with Grignard Reagent

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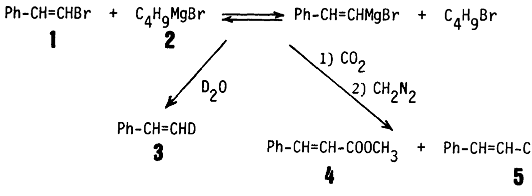
Synopsis. Halogen-magnesium exchange was confirmed to proceed with stereospecific retention of configuration in the reaction of β-bromostyrene and butylmagnesium bromide.

Vinyl Grignard reagents were formed with retention of configuration from the corresponding vinyl halides. The stereospecificities of their formation reaction, however, were widely diversed. Yoshino and his coworkers reported that *cis*- and *trans*-styrylmagnesium bromides were formed in THF with 95 and 91% retention of configuration, respectively, but the stereospecificities were lowered to 69 and 59% in diethyl ether.[1] In the formation of aliphatically substituted vinyl Grignard reagents, various degrees of configurational retention, 60—90%, depending on the substituens, were observed.[2,3] To discuss these discrete experimental results, it is necessary to confirm the stereochemistry of the halogen-metal exchange of vinyl halides with Grignard reagents. Zakharkin and his co-workers have made extensive studies on the halogen-metal exchange reactions involving Grignard reagents with ordinary alkyl and aryl halides. They concluded that the mechanism of halogen-metal exchange reaction is the same for both organomagnesium and organolithium compounds.[4] This would imply that the halogen-magnesium exchange proceeds with retention of configuration. Although there are some reports which suggest that the halogen-magnesium exchange reaction proceeds with retention of configration,[5] the exact experimental results on the stereochemistry of exchange seem to be unavailable. In this paper, we wish to report that the halogen-magnesium exchange between β-bromostyrene (**1**) and butylmagnesium bromide (**2**) does proceed with stereospecific retention of configuration.



Scheme 1.

(*E*)-**1** was treated with **2** in 1,2-dimethoxyethane (DME) at ambient temperature for 2 h. The reaction mixture was then quenched by D_2O. The isomer ratios of the resulted styrene-*β*-d_1 (**3**) are summarized in Table 1. As a reference experiment, the same reaction was carried out using butyllithium instead of **2**, since halogen-lithium exchange was known to proceed with complete retention of configuration.[6] The isomer ratios of **3** resulting from the halogen-magnesium and halogen-lithium exchange reactions are almost the same value. These results suggest that the halogen-magnesium exchange proceeds with highly stereospecific retention of configuration, rather like the halogen-lithium exchange does.

It has already been pointed out that an unignorable amount of hydrocarbon is also produced during the formation of Grignard reagents.[5] If undeuterated styrene was produced prior to the D_2O treatment, it should be estimated as the (*Z*)-**3** in the present analytical method. Unfortunately, the exchange reaction of (*Z*)-**1** gave only 8% of styrene, which failed to be isolated purely enough for NMR analysis, and the isomer ratio could not be determined.

Carbonation of the resulting Grignard mixture was, therefore, examined in order to obtain unequivocal results. Yields and isomer ratios of the products resulting from the exchange and carbonation reactions are summarized in Table 1. As the carbonation of Grignard reagents proceeds with complete retention of configration,[2,7] the results of these experiments clearly demonstrate that the halogen-magnesium exchange proceeds with highly stereospecific retention of configuration. (*Z*)-**1** afforded methyl (*Z*)-cinnamate (**4**) with complete retention of configuration, but the exchange of (*E*)-**1** proceeded less stereospecifically. It should be noted that the degree of configurational retention of the vinylic Grignard reagents formation usually falls upon going from *cis*- to *trans*-isomer.

TABLE 1. HALOGEN-METAL EXCHANGE REACTION OF β-BROMOSTYRENE WITH BUTYLMAGNESIUM BROMIDE

1	**2**	Product yield/%				Recovered
(mmol)	(mmol)	**3** (*Z*/*E*)	**4** (*Z*/*E*)	**5** (*ZZ*/*EE*)	**6**[a]	**1**
Hydrolysis with D_2O						
E (10)	40	20 (21/79)			16	54
E (10)	40	22 (33/67)			21	33
Z (10)	30	8			13	67
E (10)	40[b]	32 (29/71)			—[c]	—[c]
Carbonation						
Z (21)	42		2.0 (97/3)	7.5 (84/16)	19	52
Z (28)	84		2.7 (100/0)	20.0 (62/38)	36	11
E (21)	42		1.6 (15/85)	29.5 (0/100)	—[c]	—[c]

a) 1-Phenyl-1-hexene. b) Butyllithium hexane solution instead of **2** was used. c) Not determined.

1,4-Diphenyl-1,3-butadiene (**5**) obtained from (*E*)-**1** was (*E,E*)-isomer alone, which certainly resulted from the halogen-magnesium exchange reaction followed by the coupling with the unreacted **1**. In contrast to the (*E*)-isomer, (*Z*)-**1** gave a mixture of (*Z,Z*)- and (*E,E*)-5, although the former predominated. The coupling reaction of Grignard reagents with vinyl halides appears not to be stereospecific, since the alkylations of 1-halo-1-alkenes with Grignard reagents gave mixtures of *cis*- and *trans*-alkenes.[8] In the present case, the coupling reaction of (*Z*)-**1** with (*Z*)-stytylmagnesium bromide, formed stereospecifically from (*Z*)-**1**, may afford (*E,Z*)-**5** as well as its (*Z,Z*)-isomer. The formation of (*E,Z*)-**5** could not, however, be confirmed in the present experiments. The (*E,Z*)-isomer might be isomerised to (*E,E*)-**5** during the reaction or in the isolation process due to its instability.[9]

In THF solution, the halogen-magnesium exchange could not be observed, though it was examined in various conditions.

Experimental

All melting points and boiling points are uncorrected. IR spectra were measured with a Hitachi EPI-G2 spectrometer. ^{1}H-NMR spectra were obtained with a JEOL PMX-60 spectrometer in $CDCl_3$ using TMS as the internal standard. GLC analyses were conducted by a Hitachi 163 gas chromatograph using a 2 m column packed with PEG-20M 20% on Chromosorb-W.

Materials. The solvents were freshly distilled over lithium aluminum hydride under argon before use. (*E*)-**1** was commercially available, and (*Z*)-**1** was synthesized by the reported method.[10] Each isomer was purified by recrystallization from pentane,[1] and was confirmed to be isomerically pure by its IR and ^{1}H-NMR spectra.

Halogen-Magnesium Exchange of β-Bromostyrene with Butylmagnesium Bromide and Hydrolysis with Deuterium Oxide. A solution of **2** was prepared as usual from butyl bromide (22.5 g, 0.164 mol) and magnesium (4.0 g, 0.165 mol) in 82 ml of THF. The solution was filtered through a sintered glass funnel in order to separate it from the remaining metal, and the Grignard reagent solution prepared was used for the subsequent reactions after it was standardized by the method of Watson and Eastham.[11] To a solution of (*E*)-**1** (2.0 g, 11 mmol) in 50 ml of DME, 30 ml of the solution of **2** (40 mmol) was added. The mixture was stirred at ambient temperature for 2 h. All these procedures were carried out under argon atmosphere. The reaction mixture was quenched with 2 ml of D_2O. The mixture was then treated with aqueous ammonium chloride, extracted with ether, and distilled using a Kugelrohr apparatus to give **3**, bp 55—65 °C/30 mmHg (oven temperature; 1 mmHg≈133.322 Pa). Yield of **3**, 20.3%, was determined by GLC. The isomer ratio of the resulting 3 was estimated as E:Z=79:21 by peak integrals of the doublets at δ 5.19 (J=9 Hz: *cis*-β-H of (*Z*)-**3**) and at 5.62 (J=18 Hz: *trans*-β-H of (*E*)-**3**).[1]

Carbonation of the Exchange Reaction Mixture. To a stirred solution of (*Z*)-**1** (3.48 g, 21 mmol) in 100 ml of DME, 30 ml of the solution of **2** (42 mmol) was added. The mixture was stirred at ambient temperature in dark under argon for 20 h. The reaction mixture was poured onto a slurry of freshly powdered Dry Ice and ether with vigorous stirring. The carbonated solution was poured into a mixture of ice and hydrochloric acid and the ether layer was separated. The aqueous layer was extracted with ether and the combined ether solutions were extracted with a saturated sodium hydrogencarbonate solution. The alkaline extracts were acidified and extracted with ether. To the ether extracts, an ether solution of diazomethane was added until the mixture turned slightly yellow. After removal of the solvent, the products were submitted to GLC analysis. The ether layer of the alkaline extract was washed with saturated sodium chloride and dried. After removal of the solvent, the residual products were analyzed by GLC. The yields of the products estimated by GLC were as follows: **4**, 2.0% (Z:E=97:3); methyl 3-phenylpropionate, 0.8%; styrene, 2.4%; unreacted (*Z*)-**1**, 52.2%; **5**, 7.5% (*ZZ*:*EE*=84:16); (*Z*)-1-phenyl-1-hexene (**6**), 19.4%. The products other than **5** were identified by the comparison of their GLC retention times, IR and/or ^{1}H-NMR spectra with those of authentic samples. **5** was isolated from the product mixture and identified by its spectral data. (*Z,Z*)-**5**: mp 62.5—63.5°C (lit,[8] mp 70.5°C); its IR spectrum was superimposable with the reported one.[11] (*E,E*)-**5**: mp 142—144°C; its IR and ^{1}H-NMR spectra were completely identical with Sadtler's standard spectra.

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