Reaction of Grignard Reagents with Benzaldehyde, 2,2-Dimethylpropanal and Cinnamates of Chiral Alcohols in Chiral Solvents

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The asymmetric induction in a Grignard reaction carried out in (−)-1-isopropyl-2-methoxy-4-methylcyclohexane was higher than in the reaction carried out in (+)-1-methoxy-2-methylbutane. The chirality of the solvent contributed more than that of the reagent to the stereodifferentiation in the reaction of (+)-2-methylbutylmagnesium bromide with benzaldehyde in (+)-1-methoxy-2-methylbutane.

The asymmetric addition of benzylmagnesium chloride to chiral cinnamates has been examined by Kawana and Emoto.[1] They found that the addition of cuprous chloride to the reactions did not significantly change the stereoselectivity. However, the addition of cuprous chloride to the

reactions of phenylmagnesium bromide with chiral crotonates caused a significant increase in stereoselectivity, even reversing the sign of rotation of the product.[1,2] Other asymmetric Grignard reactions [3,4,5] as well as reactions with lithium diorganocuprates [5,6,7,8] have later been extensively investigated. Partial stereoselective syntheses have also been accomplished with the Simmons-Smith reagent and chiral cinnamates.[9]

The purpose of the present study was to examine the contribution of chiral substrates, reagents and solvents to the stereoselectivity in the reactions of some Grignard reagents with cinnamates (Scheme 1) and two aldehydes (Scheme 2).

(+)-1-Methoxy-2-methylbutane and (−)-1-isopropyl-2-methoxy-4-methylcyclohexane were
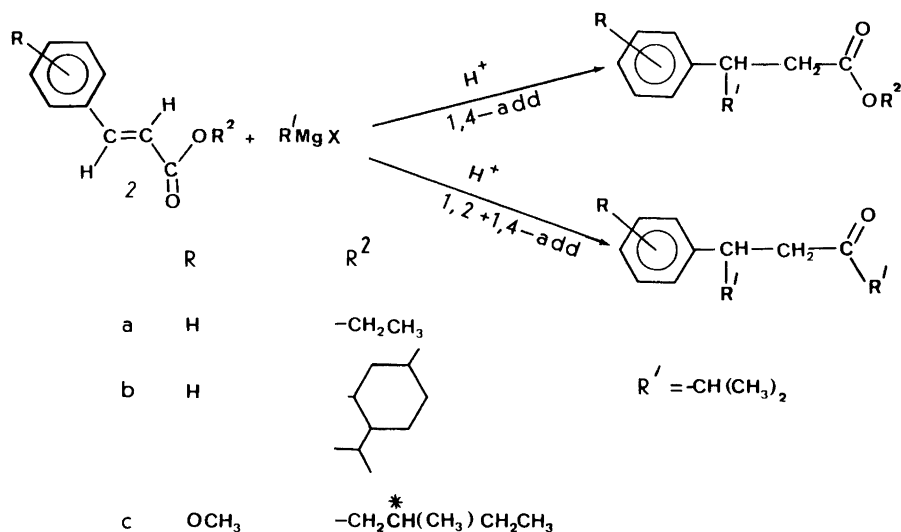
Scheme 1.
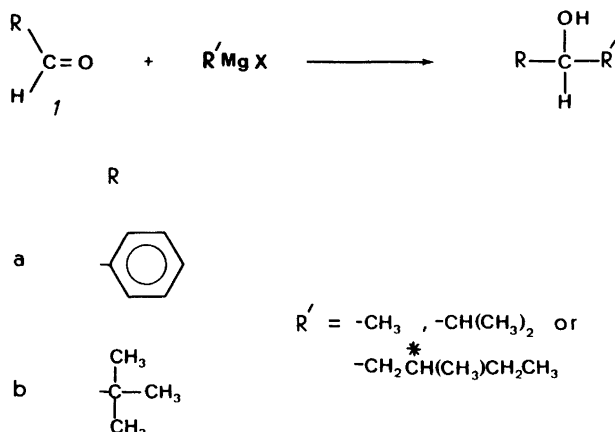
Scheme 2.

used as chiral solvents. The asymmetric induction was generally somewhat higher in the latter solvent (reactions 3, 5, 9 and 10; Table 1) but the total yield was lower. The efficiency of the asymmetric induction in the reactions of benzaldehyde increased as the steric bulk of the Grignard reagents was increased (reactions 1, 2, 3 and 5). The results of reactions 3 and 4 show that the chirality of the reagent does not contribute to the stereodifferentiation in these reactions. The d.e. in the reaction of the chiral reagent in (+)-1-methoxy-2-methylbutane and (−)-methyl menthyl ether was 5.28 and 5.4% respectively. The asymmetric induction, according to GLC was reversed in (−)-methyl menthyl ether compared with that in (+)-1-methoxy-2-methylbutane. The diastereomers were almost completely separated on a 50 m SP-1000 capillary GLC column. Although the capillary GLC analyses did not provide information of the sign of optical rotation, GLC appeared to be an excellent method for determining the diastereomeric excess of these reaction products in small quantities and without isolating the diastereomers.

Table 1. Addition of R^1MgX to some aldehydes and alkyl 3-phenylpropenoates according to Scheme 1 and 2, (d) in (+)-1-methoxy-2-methylbutane, (e) in (±)-1-methoxy-2-methylbutane and (f) in (−)-1-isopropanol-2-methoxy-4-methylcyclohexane. $R^* = (+)$-2-methylbutyl.

Reaction No.	Substrate	Reagent	Solvent	1,4-add. ratio/%	1,2+1,4-add. ratio/%	Total GLC yield/%	$[\alpha]_D^{20}$ (°)	c g ml^{-1} (benzene)	e.e./%
1	1a	MeMgI	d			92	+0.06	0.085	0.11
2	1a	i-PrMgBr	d			72	+0.11	0.22	0.24
3	1a	R*MgBr	d			67			5.28[a]
4	1a	R*MgBr	e			69			−
5	1a	R*MgBr	f			58			5.40[a]
6	1b	PhMgBr	f			78	−5.04	0.17	19.4
7	2a	i-PrMgBr	d	67		69	+0.008[b]	0.25	0.026
					33		−0.09	0.088	
8	2c	i-PrMgBr	d	72		72	−0.24[c]	0.49	0.72
					28		+0.023	0.13	
9	2b	i-PrMgBr	d	99		72	+0.72[c]	0.55	2.15
10	2b	i-PrMgBr	f	100		65	+1.19[c]	0.043	3.56

[a] Determined by GLC. [b] Measured as ethyl ester. [c] Measured as methyl ester.

The highest asymmetric induction (e.e. 19.4%) was achieved in the reaction of 2,2-dimethylpropanal with phenylmagnesium bromide in chiral methyl menthyl ether. An enantiomeric excess of 11% has earlier been achieved in the same reaction carried out in (+)-2-methyltetrahydrofuran.[10]

The reaction of ethyl and (+)-2-methylbutyl cinnamate with isopropylmagnesium bromide gave besides the 1,4-addition product a ketone *(10)* resulting from diaddition (1,2 + 1,4-addition). The diaddition was almost completely suppressed when the alcohol components above were replaced by the bulkier menthyl or *tert*-butyl[11] group. The asymmetric induction was somewhat higher in chiral methyl menthyl ether than in (+)-1-methoxy-2-methylbutane. But the chiral solvent alone exerted a poor asymmetric induction. The highest stereodifferentiation on the cinnamates was achieved with (−)-menthyl cinnamate in chiral methyl menthyl ether (3.56%).

EXPERIMENTAL

A Varian 2400 gas chromatograph equipped with a 30 m × 0.2 mm glass capillary column (stationary phase SP 1000) was used for GLC analyses. Mass spectra were recorded at 70 eV on an LKB 9000 instrument equipped with the same capillary column GLC system. ^{1}H NMR spectra were obtained on a Perkin-Elmer R 12 A spectrometer at 60 MHz. The Grignard reactions were carried out under purified nitrogen. The chiral solvents were distilled from sodium prior to use. The concentration of Grignard reagents were determined by standard titration. The magnesium turnings were synthetical grade.

Preparation of chiral substances

(+)-1-Methoxy-2-methylbutane (d) was prepared from (−)-2-methyl-1-butanol and methyl iodide in the presence of sodium by the method of Williamsson.[12] Distillation of the crude product over sodium gave 63% of *d* b.p. 85−90 °C, $[\alpha]_D^{20}$ +0.37°, Lit.[13] $[\alpha]_D^{20}$ +0.34°.

(+)-1-methoxy-2-methylbutane (e) was prepared in the same way from (±)-2-methyl-1-butanol.

(+)-1-Bromo-2-methylbutane[14] (4) was synthesized from (−)-2-methyl-1-butanol (0.5 mol), concentrated hydrobromic acid (0.625 mol) and concentrated sulfuric acid (0.25 mol). Distillation at 120 °C gave 55% of *4* $[\alpha]_D^{20}$ +3.2°. Lit.[14] $[\alpha]_D^{20}$ +3.68°, which corresponds to 87% optical purity.

(±)-1-Bromo-2-methylbutane was synthesized in the same way from (±)-2-methyl-1-butanol.

(+)-2-Methylbutyl 3-(2-methoxyphenyl)propenoate (2c) was prepared by refluxing 3-(2-methoxyphenyl)propenoic acid (0.25 mol) and (−)-2-methyl-1-butanol (0.3 mol) in the presence of a cation-exchange resin (Dowex 50 W × 8, 5.55 g) and benzene (0.75 mol) for 48 h. Distillation at 189−191 °C/1.2 kPa gave 55% of *2c* $[\alpha]_D^{20}$ +8.

(±)-2-Methylbutyl 3-(2-methoxyphenyl)propenoate was prepared in the same way from 3-(methoxyphenyl)propenoic acid and (±)-2-methyl-1-butanol.

(−)-Menthyl 3-phenylpropenoate[15] (2b) was prepared by the reaction of 3-phenylpropenoyl chloride with one equivalent (−)-menthol at 140 °C. The yield of the product boiling at 229−232 °C/3.6 kPa was 54% and $[\alpha]_D^{20}$ −77°, lit.[15] $[\alpha]_D^{20}$ −77°.

(−)-1-Isopropyl-2-methoxy-4-methylcyclohexane (f). (−)-Menthol (1 mol) was reacted with sodium (2 mol) for 56 h and then with methyl iodide. Distillation of the crude product from sodium gave 59% of *f*, b.p. 60 °C/2.7 kPa, $[\alpha]_D^{20}$ −95.2°, lit.[16] $[\alpha]_D^{20}$ −95.7°.

2,2-Dimethylpropanal[10] (8). t-BuMgCl (0.75 mol) in diethyl ether was reacted with N,N-dimethylformamide (1.5 mol) at 0 °C. After reflux for 16 h and normal work-up, *8* was isolated as a bisulphite addition complex. Distillation at 75 °C gave 31% of *8*.

General procedure for the Grignard reactions in chiral solvents. The Grignard reagents were prepared from Mg turnings (0.03 mol) and the appropriate alkyl or aryl halide (0.025 mol) in 15 ml of the chiral ether. The Grignard reactions were carried out by adding dropwise the substrates to the Grignard reagents in the proportion one to three at 0 °C. The reactions were followed by GLC until complete conversion. The reaction mixtures were decomposed with 5 M cold hydrochloric acid, extracted with diethyl ether, neutralized with NaHCO₃ and dried with Na₂SO₄.

Benzaldehyde and methylmagnesium iodide in (+)-1-methoxy-2-methylbutane. The main reaction product was (+)-1-phenylethanol b.p. 85 °C/1.9 kPa. The specific rotation was $[\alpha]_D^{20}$ +0.006° (c 0.085 benzene) and e.e. = 0.11%.

Benzaldehyde and isopropylmagnesium bromide in (+)-1-methoxy-2-methylbutane. The main reaction product was 2-methyl-1-phenylpropanol, b.p. 92−93 °C/1.3 kPa. The specific rotation was $[\alpha]_D^{20}$ +0.11° (c 0.22, benzene) and the optical purity 0.24%. Small amounts (<1%) of phenylmethanol and 2-methyl-1-phenyl-1-propenone were also formed according to GLC-MS analyses.

Benzaldehyde and (+)-2-methyl-1-butylmagnesium

bromide in (+)-1-methoxy-2-methylbutane. The diastereomers of 3-methyl-1-phenylpentan-1-ol were formed almost exclusively according to GLC-MS. The same reaction was also carried out with (a) the chiral reagent in racemic ether and (b) with the racemic reagent in racemic ether in order to check the influence of the chiral reagent on the asymmetric induction. The separation of the diasteromers was almost complete on a 30 m capillary column (SP-1000). The proportions of the diastereomers in reactions a and b were the same, which shows that the chiral reagent does not have a discernable asymmetric induction in this reaction. The integrated areas of the slightly overlapping peaks gave the same diastereomer proportion *i.e.* 50.48 to 49.52 %. The correction factor Δ because of overlapping peaks is then 0.96 %.

The reaction with the chiral reagent and the chiral ether gave the diastereomers in the proportion 53.12 to 46.88 %. The e.e. after correction is then 5.28 %. The results show that the asymmetric induction (measurably by GLC) in this reaction is only dependent on the chiral ether.

Ethyl 3-phenylpropenoate and isopropylmagnesium bromide in (+)-1-methoxy-2-methylbutane. The reaction was performed with isopropylmagnesium bromide (0.1 mol) and ethyl 3-phenylpropenoate (0.03 mol) in 30 cm^3 of the chiral ether. The reaction time was 10 h at 20 °C. After ordinary work-up, ethyl 4-methyl-3-phenylpentanoate *(9)* and 2,6-dimethyl-5-phenylheptane-3-one *(10)* were identified by GLC-MS. The ketone *(10)* was separated by alkaline hydrolysis and distillation at 120 − 125 °C/1.3 kPa. The specific rotation $[\alpha]_D^{20}$ was − 0.09° (c 0.088, benzene). Anal. $C_{15}H_{22}O$:C, H. ^{1}H NMR (60 MHz, CDCl$_3$): δ 0.7 (3H, d, J 6.5 Hz), 0.8 (3H, d, J 6.5 Hz), 0.9 (6H, d, J 6.5 Hz), 1.8 (1H, m), 2.3 (1H, sep. J 6.5 Hz), a multiplet with the highest signal at 2.7 (3H, m), 7.0 (5H, s).

MS [IP 70 eV; *m/e* (% rel. int.)]: 218 (2, M), 175 [7,M − CH(CH$_3$)$_2$], 133 (90), 132 (98), 105 (25), 104 (23), 91 (91), 71 (73), 43 (100).

Ethyl 4-methyl-3-phenylpentanoate (9) was distilled at 94 − 96 °C/0.5 kPa, $[\alpha]_D^{20}$ + 0.008° (c 0.25, benzene). Anal. $C_{14}H_{20}O_2$: C, H. ^{1}H NMR (60 MHz, CDCl$_3$): δ 0.7 (3H, d, J 6.5 Hz), 0.9 (3H, d, J 6.5 Hz), 0.95 (3H, t, J 7.2 Hz), 1.8 (1H, m), a multiplet with the highest signal at 2.7 (3H, m), 3.8 (2H, q, J 7.2 Hz), 7.0 (5H, s).

MS [IP 70 eV; *m/e* (% rel. int.)]: 220 (18, M), 175 (7, M − OC$_2$H$_5$), 135 (100, PhCHOC$_2$H$_5$) 133 [68, PhCHCH(CH$_3$)$_2$], 132 (67), 105 (77), 104 (50), 91 (77).

(+)-2-Methylbutyl   3-(2-methoxyphenyl)propenoate and isopropylmagnesium bromide in (+)-1-methoxy-2-methylbutane. The reaction gave 1,4- and 1,2 + 1,4-addition products in the ratio 3 to 1. The ester *(11)* was separated from the ketone *(12)*

by alkaline hydrolysis. After acidification and methylation with diazomethane *methyl 4-methyl-3-(2-methoxyphenyl)pentanoate (11)* was distilled at 160 °C/2.7 kPa, $[\alpha]_D^{20}$ − 0.24° (c 0.49, benzene).

^{1}H NMR (60 MHz, CDCl$_3$): δ 0.7 (3H, d, J 6.5 Hz), 0.9 (3H, d, J 6.5 Hz), 1.8 (1H, m), a multiplet with the highest signal at 2.6 (3H, m), 3.4 (3H, s), 3.7 (3H, s), 6.5 − 7.1 (4H, aromatic).

MS [IP 70 eV; *m/e* (% rel. int.)]: 236 (29, M), 193 [49,   M − CH(CH$_3$)$_2$], 163 (17), 151 (100, CH$_3$OPhCHOCH$_3$), 121 (90, CH$_3$OPhCH$_2$), 91 (28).

2,6-Dimethyl-5-(2-methoxyphenyl)-heptan-3-one (12) was distilled at 126 − 128 °C/2.7 kPa, $[\alpha]_D^{20}$ + 0.023° (c 0.16, benzene).

^{1}H NMR (60 MHz, CDCl$_3$): δ 0.7 (3H, d, J 7.0 Hz), 0.85 (3H, d, J 7.0 Hz), 9.0 (6H, d, J 7.0 Hz), 1.8 (1H, m), 2.3 (1H, m), a multiplet with the highest signal at 2.8 (3H, m), 3.8 (3H, s), 6.4 − 7.0 (4H, aromatic).

MS [IP 70 eV; *m/e* (% rel. int.)]: 248 (32, M), 205 (27, M − C$_3$H$_7$), 164 (70), 163 (78), 121 (77, CH$_3$OPhCH$_2$), 91 (70), 71 (36), 43 (100).

(−)-Menthyl 3-phenylpropenoate and isopropylmagnesium   bromide   in   (+)-1-methoxy-2-methylbutane. The ratio of 1,4- and 1,2 + 1,4-addition products was 99 to 1 %. The ester was submitted to alkaline hydrolysis and the acid was methylated with diazomethane. Methyl 4-methyl-3-phenylpentanoate *(13)* was distilled at 133 − 135 °C/2.6 kPa, $[\alpha]_D^{20}$ + 0.72° (c 0.55, benzene).

^{1}H NMR (60 MHz, CDCl$_3$): δ 0.7 (3H, d, J 6.5 Hz), 0.9 (3H, d, J 6.5 Hz), 1.8 (1H, m), a multiplet with the highest signal at 2.6 (3H, m), 3.3 (3H, s), 7.0 (5H, s).

MS [IP 70 eV; *m/e* (% rel. int.)]: 206 (18, M), 164 (10), 163 (9, M − C$_3$H$_7$), 132 (35), 121 (100, PhCHOCH$_3$), 104 (48, PhCHCH$_2$), 91 (28), 77 (10), 59 (10).

Benzaldehyde and (+)-2-methyl-1-butylmagnesium   bromide   in   (−)-1-isopropyl-2-methoxy-4-methylcyclohexane. The diastereomers of 3-methyl-1-phenylpentane-1-ol was formed in the ratio 52.7 to 47.3 % as measured by capillary GLC. The e.e. is then 5.4 %. The asymmetric induction is the opposite to the one observed when the reaction was carried out in (+)-1-methoxy-2-methylbutane.

(−)-1-Methyl 3-phenylpropenoate and isopropyl-magnesium bromide in (−)-1-isopropyl-2-methoxy-4-methylcyclohexane. The only reaction product formed was the 1,4-addition product, which was isolated as *methyl 4-methyl-3-phenylpropenoate* at 133 − 135 °C/2.6 kPa, $[\alpha]_D^{20}$ + 1.19° (c 0.43, benzene).

2,2-Dimethylpropanal and phenylmagnesium bromide in (−)-1-isopropyl-2-methoxy-4-methylcyclohexane. The main reaction product was 2,2-

dimethyl-1-phenylpropanol which was isolated by preparative GLC (6 m × 1.2 cm metal column, SE-30 15 %). $[\alpha]_D^{20}$ − 5.04° (c 0.17, benzene) e.e. 19.4 %.

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