

Simple Diastereoselectivity on Addition of α-Haloalkyl Grignard Reagents to Benzaldehyde

Volker Schulze, Peter G. Nell, Andrew Burton, and Reinhard W. Hoffmann*

Fachbereich Chemie der Philipps-Universität Marburg, Hans Meerwein Str. D-35032 Marburg, Germany

rwho@chemie.uni-marburg.de

Received January 31, 2003

Abstract: The addition of α -haloalkyl Grignard reagents to benzaldehyde occurs with simple diastereoselectivity substantially higher than that of the corresponding lithium reagents. Reaction in the presence of dimethyl-aluminum chloride suppresses subsequent Oppenauer oxidation of the resulting Mg-alkoxides by excess benzaldehyde.

The addition of a chiral organolithium compound (1) to an aldehyde is a stereogenic carbon-carbon bond forming reaction. Two diastereomeric products, syn-2 and anti-2, are generated, which could be used to prepare stereodefined epoxides 3 and 4 (Scheme 1). This approach to epoxides is hardly used, because simple diastereoselectivity¹ i.e., the ratio between *syn*-**2** and *anti*-**2**² is low.^{3,4} Seebach, when studying the reaction of 5 with benzaldehyde, showed⁵⁻⁷ that a change from an organolithium compound 5a to the corresponding organomagnesium compound **5b** led to high *syn/anti* selectivity in the formation of 6 (Scheme 2). We therefore surmised that a transmetalation of 1 to the corresponding magnesium reagents⁸ could lead to higher and, hence, useful levels of diastereoselectivities on addition to aldehydes. We report here on the simple diastereoselectivity on addition of chiral α -haloalkyl-magnesium reagents 7–9 to ben-

- (3) For a review, see: Hoppe, D. In *Houben-Weyl, Methods of Organic Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; G. Thieme: Stuttgart, 1995; Vol. E21b; pp 1341-1347
- (4) For further examples of diastereogenic addition of α -heterosubstituted organolithium compounds to aldehydes: α-nitrogensubstituted cases, see ref 20; α -oxygen-substituted cases, see refs 21 and 22; α-sulphur-substituted cases, see ref 23; α-selenium-substituted cases, see ref 24; for unexpected high diastereoselectivities in these reactions see refs 22 and 25
- (5) (a) Seebach, D.; Syfrig, M. A. Angew. Chem. **1984**, *96*, 235–236; Angew. Chem., Int. Ed. Engl. **1984**, *23*, 248. (b) Seebach, D.; Hansen, J.; Seiler, P.; Gromek, J. M. J. Organomet. Chem. **1985**, *285*, 1–13. (c) Seebach, D.; Huber, I. M. P.; Syfrig, M. A. Helv. Chim. Acta **1987**, *70*, 1977 (2027) 1357-1379. These findings on the system 5 have since been substantiated by others.

SCHEME 1



zaldehyde. These reactions had actually been studied with a different objective.⁹⁻¹² Here we focus on the attendant simple diastereoselectivity. The reagents 7-9 were generated from the 1-halo-1-iodo-2-phenyl-ethane in an iodine/lithium or iodine/magnesium exchange reaction using *n*-butyllithium or isopropyl-magnesium chloride,^{9,10} or by a sulfoxide/magnesium exchange reaction from α-haloalkyl sulfoxides and ethyl-magnesium chloride.¹¹ Depending on the workup procedure, halohydrins derived from 2 or epoxides 3 and 4 were obtained and analyzed for diastereomer composition by NMR spectroscopy. The simple diastereoselectivities recorded for the addition of the α -haloalkyl-metal reagents 7–9 to benzaldehyde are compiled in Table 1.

The data in the table show that a marked increase in simple diastereoselectivity results on going from the organolithium to the organomagnesium reagents 7 and 8. Moreover, high simple diastereoselectivity has been recorded for the addition of the Grignard reagents 9 and 10 to benzaldehyde. The presence of Me₂AlCl or of a bisoxazoline ligand has only small (beneficial) effects on simple diastereoselectivity.

It has been suggested by Gawley⁷ that organolithium and organomagnesium reagents react with benzaldehyde by different reaction mechanisms: Grignard reagents are postulated to add in a concerted polar process with a late transition state, which favors significant stereodifferentiation¹⁴ in the formation of the products. In the reaction of the more basic organolithium compounds SET may precede carbon-carbon bond formation, which then occurs with an early transition state by combination of a radical pair. Stereodifferentiation is accordingly low.

⁽¹⁾ Heathcock, C. H. In Asymmetric Synthesis; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3; pp 111-212.

⁽²⁾ A major part of this chemistry had been explored before the advent of high-field NMR spectroscopy. Hence, reactions that led to diastereomer mixtures had been avoided or diastereomer ratios have not been determined.

^{(6) (}a) Rein, K. S.; Gawley, R. E. J. Org. Chem. 1991, 56, 1564–1569. (b) Zhang, P.; Gawley, R. E. Tetrahedron Lett. 1992, 33, 2945–2948. (c) Gawley, R. E.; Zhang, P. J. Org. Chem. 1996, 61, 8103–8112. (7) Rein, K. S.; Chen, Z.-H.; Perumal, P. T.; Echegoyen, L.; Gawley,

R. E. Tetrahedron Lett. 1991, 32, 1941–1944.

⁽⁸⁾ The beneficial effect of transmetalation from lithium to magnesium on simple diastereoselectivity in the addition to aldehydes has been noted on several occasions. $^{\rm 26-30}$

⁽⁹⁾ Müller, M.; Stiasny, H.-C.; Brönstrup, M.; Burton, A.; Hoffmann, R. W. J. Chem. Soc., Perkin Trans. 2 1999, 731–736.

⁽¹⁰⁾ Schulze, V.; Hoffmann, R. W. Chem. Eur. J. 1999, 5, 337-344. (11) Hoffmann, R. W.; Nell, P.; Leo, R.; Harms, K. Chem. Eur. J. 2000, 6, 3359-3365.

⁽¹²⁾ Nell, P. G. New. J. Chem. 1999, 23, 973-975.

⁽¹³⁾ Köbrich, G.; Trapp, H. *Chem. Ber.* **1966**, *99*, 670–679.
(14) Bassindale, A. R.; Ellis, R. J.; Lau, J. C. Y.; Taylor, P. G. J. Chem. Soc., Chem. Commun. **1986**, 98–100.

Compound	Metal M =	Solvent	Temp. (°C)	Yield (%) of halohydrin 2 (H) or epoxides 3,4	Syn/anti of 2
7 ^{Ph} M	Li	Trapp ^{a)}	-110	E 80	52 : 48
	MgCl	THF	-78	E+H 65	83:17
	MgCl×Me ₂ AlCl	THF	-78	H 83	88:12
	MgL*×Me ₂ AlCl ^{b)}	THF	-78	H 96	96:4
8 Ph M	Li	Trapp ^{a)}	-110	E 94	68 : 32
	MgCl	THF	-78	H 69	96:4
	MgBr	THF	-78	H 82	92:8
	MgCl×Me ₂ AlCl	THF	-78	H 72	94 : 6
	MgL*×Me ₂ AlCl ^{b)}	THF	-78	H (33) ^{c)}	97: 3
9 ^{Ph} M	MgCl	THF	-78	H 87	88 : 12
	MgBr	THF	-78	H 57	85:15
	MgBr×Me ₂ AlCl	THF	-78	H 77	90:10
		THF	-50	H 62 H 78	96 : 4 88 : 12
		THF	-40	Н 5	83 :17
	MgCl×Me ₂ AlCl	THF	-50	H 69	90:10
	Mg ⁱ Pr×Me ₂ AlCl	THF	-50	H 83	84 : 16
SPh Ph 10 M	MgBr	THF	-78	Н 35	>98:<2

TABLE 1. Simple Diastereoselectivity on Reaction of α -Haloalkyl-metal Compounds 1 (R = Bn) with Benzaldehyde

^a Trapp = Trapp solvent mixture.¹³



 $^{\it c}$ Low conversion, because an excess of 1-bromo-1-iodo-2-phenyle-thane was used.

The absence of a SET process in the addition of simple Grignard reagents to benzaldehyde has been demonstrated.¹⁵

The Grignard addition of **7**(MgX) to excess benzaldehyde (especially with Mg^{*i*}Pr in nonpolar solvents and letting the reaction mixture warm to room temperature before quenching) was accompanied by considerable Oppenauer oxidation of **11** by benzaldehyde to the iodoketone **12**, resulting in lower yields of the halohydrins,¹⁰ cf. Scheme 3. This oxidation could affect the *syn/anti* ratio of the halohydrins obtained, if this oxidation is in any way diastereomer-selective. We have indeed indications that *syn-***11** is more readily oxidized than *anti-***11**.¹⁶

This annoying oxidation of the primary adducts **11** could be suppressed by carrying out the reaction in the presence of dimethyl-aluminum chloride.¹⁰ This procedure probably leads to the chloro-bridged¹⁷ alkoxide **14** as the primary adduct.¹⁸ When the chloro-bridged alkox-

SCHEME 3



ide **14** coordinates further benzaldehyde, it will do so as a bidentate Lewis acid¹⁹ in the μ -position. This could prevent subsequent reduction of the benzaldehyde, which possibly originates from a monodentate coordination of benzaldehyde by the magnesium cation via a monocyclic six-membered transition state.

Addition of dimethyl-aluminum chloride to the Grignard reagents 7-9 presumably generates initially a chloro-bridged reagent 13. As there is no substantial difference in the syn/anti ratio of the alkoxides 11 formed in the absence or presence of dimethyl-aluminum chloride, the chloro-bridged reagent 13 reacts apparently with a similar simple diastereoselectivity as the Grignard reagent 7(MgCl) (cf. 8 and 9). There are no obvious indications for a transmetalation of 7(MgCl) with dimethyl-aluminum chloride to an trialkyl-aluminum compound 15 under the conditions applied, as 15 should be less reactive toward benzaldehyde. Transmetalation of **7**(Li), though, with dimethyl-aluminum chloride to give **15** appears to proceed at -110 °C, as subsequently no addition occurred to benzaldehyde at the low temperature.10

(22) Barner, B. A.; Mani, R. *Tetrahedron Lett.* **1989**, *30*, 5413–5416.
(23) Johnson, C. R.; Nakanishi, A.; Nakanishi, N.; Tanaka, T. *Tetrahedron Lett* **1975**, 2865–2868.

(24) Sarkar, T. K.; Satapathi, T. K. Tetrahedron Lett. 1989, 30, 3333-3334.

(25) Katritzky, A. R.; Zhao, X.; Shcherbakova, V. J. Chem. Soc., Perkin Trans. 1 1991, 3295–3299.

(26) Seyferth, D.; Lefferts, J. L.; Lambert, R. L., Jr. J. Organomet. Chem. 1977, 142, 39.

(27) Perrier, H.; Huyer, G.; Young, R. N. Tetrahedron Lett. 1992, 33, 725-728.

(28) Hoffmann, R. W.; Julius, M.; Chemla, F.; Ruhland, T.; Frenzen, G. *Tetrahedron* **1994**, *50*, 6049–6060.

(29) Klute, W.; Krüger, M.; Hoffmann, R. W. *Chem. Ber.* **1996**, *129*, 633–638.

(30) Kise, N.; Urai, T.; Yoshida, J.-I. *Tetrahedron: Asymmetry* **1998**, *9*, 3125–3128.

^{(15) (}a) Gajewski, J. J.; Bocian, W. B.; Harris, N. J.; Olson, L. P.; Gajewski, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 326–334. (b) Hoffmann, R. W.; Hölzer, B. *Chem. Commun.* **2001**, 491–492.

 ⁽¹⁶⁾ Schulze, V. Ph.D. Dissertation, University Marburg, 1997.
 (17) Markies, P. R.; Akkerman. O. S.; Bickelhaupt, F.; Smeets, W.

⁽¹⁷⁾ Markies, P. R.; Akkerman, O. S.; Bickelhaupt, F.; Smeets, W J. J.; Spek, A. L. Adv. Organomet. Chem. **1991**, *32*, 147–226.

 ⁽¹⁸⁾ Yamazaki, S.; Yamabe, S. J. Org. Chem. 2002, 67, 9346–9353.
 (19) Ooi, T.; Miura, T.; Itagaki, Y.; Ichikawa, K. M.; Maruoka, K. Synthesis 2002, 279–291.

^{(20) (}a) Pearson, W. H.; Lundbeck, A. C. J. Org. Chem. 1989, 54, 5651–5655. (b) Barrett, A. G. M.; Flygare, J. A. F. J. Org. Chem. 1991, 56, 638–642. (c) Barrett, A. G. M.; Hill, J. M.; Wallace, E. M.; Flygare, J. A. F. Synlett 1991, 764–770. (d) Moody, C. J.; Rees, C. W.; Young, R. G. J. Chem. Soc., Perkin Trans. 1 1991, 323–327. (e) Tsunoda, T.; Fujiwara, K.; Yamamoto, Y.; Ito, S. Tetrahedron Lett. 1991, 31, 1975–1978.

⁽²¹⁾ Cohen, T.; Matz, J. R. J. Am. Chem. Soc. 1980, 102, 6900-6902.

JOC Note

Experimental Section

General Procedures. The preparation of the starting materials, the reactions and the products have been described before. $^{9-12}$

Reaction of Diisopropyl-magnesium with 1,1-Diiodo-2phenyl-ethane. A solution of diisopropyl-magnesium (0.59 M in diethyl ether, 1.01 mL, 0.60 mmol) was cooled under a nitrogen atmosphere to -78 °C. A solution of the diiodoalkane¹⁰ (0.5 M in THF, 2.00 mL, 1.00 mmol) was added slowly along the wall of the flask. After 2 h of stirring at -78 °C the deep yellow color had disappeared. THF (4.5 mL) and benzaldehyde (0.25 mL, 2.5 mmol) were added dropwise, and the mixture was allowed to reach room temperature over 15 h. Saturated aqueous NH₄Cl solution (20 mL), aqueous Na₂S₂O₃ solution (20%, 3 mL), and tert-butyl methyl ether (20 mL) were added. The layers were separated, and the aqueous layer was extracted with tert-butyl methyl ether (3 \times 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), and concentrated. p-Xylene (20.5 μ L) was added as internal standard, and the yields of the different products were determined by ¹H NMR spectroscopy (300 MHz). Flash chromatography with petroleum ether/ethyl acetate 30:1 furnished the epoxides 3, 4 (R = Bn)¹⁰ (57 mg, 27%) and 2-iodo-1,3-diphenyl-1-propanone 12 (160 mg, 47%). 10

Reaction of *n***-Butyllithium with 1,1-Diiodo-2-phenylethane.** A solution of *n*-butyllithium (1.55 M, 0.21 mL, 0.32 mmol) was added at -100 °C under a nitrogen atmosphere to a solution of 1,1-diiodo-2-phenyl-ethane¹⁰ (100 mg, 0.32 mmol) in THF (5 mL). After 10 min of stirring, benzaldehyde (31 μL) was added. The mixture was allowed to reach room temperature over 15 h. Saturated aqueous NH₄Cl solution (5 mL) was added, and the aqueous layer was extracted with diethyl ether (3 \times 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), and concentrated. Flash chromatography with petroleum ether/diethyl ether 10:1 furnished the epoxides **3**, **4** (1.1:1, R = Bn)¹⁰ (50 mg, 85%).

Reaction of *n***-Butyllithium with 1,1-Dibromo-2-phenylethane.** A solution of *n*-butyllithium (1.55 M, 0.21 mL, 0.32 mmol) was added at -100 °C under a nitrogen atmosphere to a solution of 1,1-dibromo-2-phenyl-ethane¹⁰ (200 mg, 0.76 mmol) in THF (5 mL). After 10 min of stirring, benzaldehyde (31 μ L) was added. The mixture was allowed to reach room temperature over 15 h. Saturated aqueous NH₄Cl solution (5 mL) was added, and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), and concentrated. Flash chromatography with petroleum ether/diethyl ether 10:1 furnished the epoxides **3**, **4** (1.5:1 R = Bn)¹⁰ (66 mg, 32%).

Acknowledgment. We are grateful to the Deutsche Forschungsgemeinschaft (SFB 260 and Graduierten-Kolleg "Metallorganische Chemie") as well as the Fonds der Chemischen Industrie for generous support of this study.

JO034138M