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Acetals as Chiral Ligands for Organomagnesium and Organolithium Compounds

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Summary. Five 2-alkoxyoctahydro-7,8,8-trimethyl-4,7-methanobenzofurans were tested as additives for the enantioselective addition of butyllithium and butylmagnesium bromide to benzaldehyde. The selectivity of the reaction was determined by GC, HPLC, and by measurement of the optical rotation of the obtained 1-phenyl-1-pentanol, and the stability of the ligands under the given reaction conditions was investigated. Upon reaction with benzaldehyde, the addition of octahydro-7,8,8-trimethyl-2-(2-(phenylmethoxy)ethoxy)-4,7-methanobenzofuran to butylmagnesium bromide yielded (*R*)-1-phenyl-1-pentanol with 47% *ee*.

Keywords: Acetals; Ligands, chiral; Carbonyl addition, stereoselective.

Acetale als chirale Liganden für organische Magnesium- und Lithiumverbindungen

Zusammenfassung. Fünf 2-Alkoxyoctahydro-7,8,8-trimethyl-4,7-methanobenzofurane wurden als Additive für die enantioselektive Addition von Butyllithium bzw. Butylmagnesiumbromid an Benzaldehyd getestet. Die Selektivität der Reaktion wurde mittels GC, HPLC und Messung der optischen Aktivität des erhaltenen 1-Phenyl-1-pentanols bestimmt. Die Stabilität der Liganden unter den gegebenen Reaktionsbedingungen wurde untersucht. Die Addition von Octahydro-7,8,8-trimethyl-2-(2-(phenylmethoxy)ethoxy)-4,7-methanobenzofuran an Butylmagnesiumbromid lieferte nach der Reaktion mit Benzaldehyd (*R*)-1-Phenyl-1-pentanol mit 47% *ee*.

Introduction

One of the fundamental methods to establish a carbon–carbon bond is the addition of organometallic reagents to compounds with a carbonyl functionality, *e.g.* a *Grignard* reaction. In most cases, a new stereogenic center is formed in this reaction. Therefore, attempts to perform this addition enantioselectively have been carried out early [1]. Since then, numerous approaches have been directed towards the synthesis of chiral non-racemic ligands for organometallic compounds, and their usefulness has been investigated. Some of them displayed high enantioselectivities, as *e.g.* zinc [2] and titanium [3] derivatives, but in general, applicability

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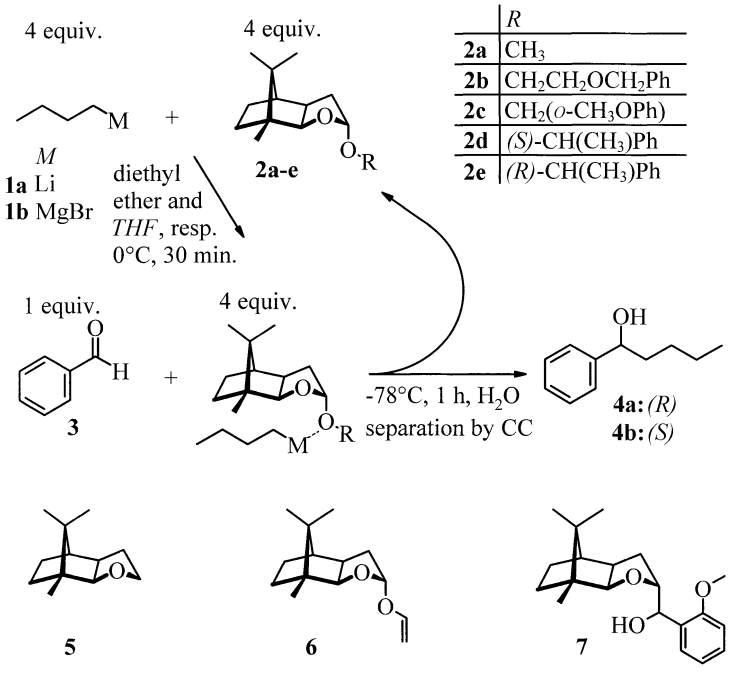
was limited to a few examples. For a recent overview of this topic, see Ref. [4] and literature quoted therein.

In the case of *Grignard* reagents, only the addition to ketones can be performed with high enantioselectivity in the presence of $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolan-4,5-dimethanols [5]. Some other ligands have been used for the addition to aldehydes with selectivities up to 75% *ee* [6]. One of these ligands, which showed some selectivity, was derived from carbohydrates [7].

This prompted us to test acetals of type **2** as additives. They had been used in stereoselective synthesis in a broad range of applications and had shown promising results in previous investigations, in which the acetal was a covalently bound part of the molecule which reacted with a *Grignard* reagent [8]. This type of acetals had never been tested as additives. For this reason we investigated the reaction of benzaldehyde (**3**) with butylmagnesium bromide (**1b**) and butyllithium (**1a**), resp., which were complexed with acetals **2**. These metals were chosen because of the very broad field of application and ready availability of their organic derivatives. Moreover, the highest selectivity reported for the *Grignard* reaction without modification, *e.g.* transmetalation, was 39% *ee* [9, 10].

Results and Discussion

For the sake of comparability we used the same conditions as were found in the literature dealing with this kind of experiments [9]. In detail, a solution of the acetal **2a**-**e** in *THF* and diethyl ether, resp., was cooled to 0°C before one equivalent of the organometallic component **1a**,**b** was added. The mixture was



Scheme 1. Principle reaction pathway of the selectivity experiments and by-products **5**–**7** obtained from **2b** and **2c**, resp., upon reaction with BuLi in *THF*

stirred for 30 min to complete complex formation, cooled to −78°C, and a solution of a quarter equivalent of **3** in the corresponding solvent was added dropwise. It was stirred for exactly 1 h keeping the temperature between −84 and −72°C, quenched with water, and worked up by extraction to give a mixture of recovered acetal **2a**-**e**, 1-phenyl-1-pentanol (**4**), and sometimes unreacted **3** and degradation products of the additive **5**–**7**, resp., which were all separated by chromatography.

The enantiomeric excess of **4** was determined by GC, HPLC, and measurement of $[\alpha]_D^{25}$. The gaschromatographic analyses were carried out directly with **4** on derivatized cyclodextrines. For HPLC, substituted cellulose was used as stationary phase.

One experiment only (**2b**, Et_2O, BuMgBr) out of 20 (5 ligands, 2 solvents, 2 organometallics) showed a considerable enantioselectivity; the (*R*)-enantiomer was formed with 47% *ee*. The reaction was very sensitive with regard to conditions; both the change from Et_2O (47% *ee*) to *THF* (1% *ee*) and from BuMgBr (47% *ee*) to BuLi (0% *ee* in Et_2O, 1% *ee* in *THF*) led to a complete loss of selectivity. The fact that with BuLi as organometallic compound no selectivity was observed may be attributed, on the one hand, to the degradation of **2b** by BuLi (*vide infra*), and, on the other hand, to the higher reactivity of BuLi.

Further evidence that Et_2O is essential for the observed enantioselectivity arises from an experiment carried out in toluene which is unable to coordinate to the organometallic species and in which the obtained alcohol showed only 9% *ee*. In all other investigated cases the selectivity was lower than 5% *ee*.

As far as the stability of the acetals was concerned, they were recovered in high yield (74–100%) in most of the experiments, which shows that they were stable under these reaction conditions. However, **2b** and **2c** gave some degradation products (about 40%) when used with BuLi. These products were identified as **5** and **6**, which can be formed by β-elimination, and **7**, which is the product of a base induced [1,2]-*Wittig* rearrangement of **2c** [11]. For more detailed information on yield, recovered ligand, and enantioselectivity see Table 1 in the experimental section.

Eventually, the different methods for determination of enantioselectivity used within this paper were compared. Considering the time necessary to conduct the analysis and from the separation factor point of view as well, HPLC was the method of choice. Unfortunately, especially in cases in which by-products originating from the ligand were observed, results from HPLC were not reliable, because by-products and product under investigation showed nearly the same retention time. Thus, it was obvious that measuring the optical rotation of products purified by chromatography would also give incorrect results. Taking all this into account we had to conclude that GC analysis was the most appropriate method in our study, although the separation factor was not as good and the analysis time was much longer than with HPLC.

Conclusion

Acetals of type **2** only exhibit a significant enantioselectivity as ligand for the addition of *butylmagnesium* bromide to benzaldehyde, if a further heteroatom is available for complex formation, *i.e.* if chelat formation is possible. The achieved

selectivity is still rather low compared with other reaction systems, but somewhat higher than the highest value reported so far for *Grignard* reagents [9,10].

Experimental

General techniques

All reactions were carried out under a nitrogen atmosphere in dry, freshly distilled solvents under anhydrous conditions unless otherwise stated. Tetrahydrofuran (*THF*) and diethyl ether (Et_2O) were distilled from sodium/benzophenone. Magnesium chippings were dried in a desiccator at 60 °C before use. Butyllithium was purchased from Aldrich as a 2.5 *M* solution in *n*-hexane and used immediately. All other reagents were purchased in standard commercial quality unless otherwise stated. Reactions were monitored by TLC carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as visualizing agent and 5% ethanolic phosphomolybdatic acid solution and heat as developing agents. For vacuum flash chromatography (VFC) and column chromatography (CC), the amount of silica gel 60 (Merck, 0.2–0.5 mm mesh size) and the eluent is given. Melting points were recorded according to Kofler and are uncorrected. Microanalyses were performed at the Institute of Physical Chemistry, University of Vienna, under the supervision of Mag. *J. Theiner*; their results agreed with the calculated values within experimental error. NMR spectra were recorded on a Bruker AC 200 instrument and calibrated using the solvent as internal standard. Optical rotations were recorded on a Perkin Elmer 241 polarimeter, and optical purity was based on the highest value of specific rotation ($[\alpha]_D^{25} = 37.6\,(c = 3;$ benzene)) [12]. HPLC separations of 1-phenyl-1-pentanol were performed on a Shimadzu system (LC-8A pump and SPD-6AV detector) using a Daicel column (Chiralcel OD) and 1% 2-propanol in *n*-hexane as eluent. UV light (254 nm) was used for detection. The signals were recorded and integrated with a DP 700 from Carlo Erba. GC analyses of 1-phenyl-1-pentanol were performed on a Carlo Erba HR-GC 5300 Mega Series using a 50 m Macherey-Nagel fused silica capillary column (FS-Lipodex/E) with an ID of 0.25 mm. Helium 5.0 was used as carrier gas with a flow rate of 4.3 ml/min (column pre-pessure: 210 kPa). The injector was heated to 220°C, and injected samples were splitted in a ratio of 1/73. The column was held at 100°C for 50 min; then the temperature was raised to 140°C in a rate of 1°C/min. Signals were detected with a FID (260°C), and chromatograms were recorded on a Carlo Erba SP4270 integrator and processed with LABNET2 software from Spectra Physics.

n-Butylmagnesium bromide (**1b**) was prepared in the appropriate solvent (Et_2O or *THF*, resp.) immediately before use. Compounds **2a**,**d**,**e** were prepared as described in Ref. [13].

(2R-(2α,3aα,4β,7β,7aα))-Octahydro-7,8,8-trimethyl-2-(2-(phenylmethoxy)ethoxy)-4,7-methanobenzofuran (**2b**; $C_{21}H_{30}O_3$)

A solution of 4.0 g (11.5 mmol) of (2*S*,2′*S*-(2α,2′α,3aα,3a′α,4β,4′β,7β,7′β,7aα,7a′α))-2,2′-oxy*bis*-(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran) (*MBE*)$_2$O), 6.5 g (42.7 mmol) of 2-(phenylmethoxy)ethanol, and 0.2 g (1.05 mmol) of 4-methylbenzenesulfonic acid monohydrate in 50 ml CH_2Cl_2 was stirred for 30 min. 2 g Na_2SO_4 were added, and stirring was continued for further 90 min. The mixture was washed with a saturated $NaHCO_3$ solution, dried over Na_2SO_4, and the solvent was evaporated. VFC (200 g, petroleum ether (*PE*)/Et_2O (20:1)) and *Kugelrohr* distillation gave 4.0 g (59%) of **2b** as a colorless oil.

B.p.: 70°C/1.3 Pa (*Kugelrohr*); $[\alpha]_D^{25} = -46.6$ ($c = 3$, benzene); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 7.42–7.22 (m, 5H, Ph-H), 5.16 (dd, 1H, 2-H), 4.58 (s, 2H, Ph-CH_2-O), 3.90 (d, $J = 6.6$ Hz, 1H, 7a-H), 3.86–3.50 (m, 4H, O-CH_2-CH_2-O), 2.4–0.8 (m, 17H, aliphatic H, therein: 1.00, 0.98, and 0.80 (3s; 9H, 3 CH_3) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 138.4 (s, C(ph)- 1), 128.3 (d, C(ph)-3, C(ph)-5), 127.6 (d, C(ph)-2, C(ph)-6), 127.5 (d, C(ph)-4), 105.1 (d, C-2), 91.1 (d, C-7a), 73.0 (t, Ph-CH_2-O),

69.4 (t, Ph-CH_2-O-*C*H_2), 65.8 (t, O-CH-O-*C*H_2), 48.4 (d, C-4), 47.5 (s, C-7), 47.0 (s, C-8), 45.9 (d, C-3a), 38.6 (t, C-3), 32.4 (t, C-6), 28.9 (t, C-5), 22.9, 20.4, and 11.6 (3q, 3 CH_3) ppm.

(2R-(2α,3aα,4β,7β,7aα))-Octahydro-2-((2-(methoxy)phenyl)methoxy)-7,8,8-trimethyl-4,7-methanobenzofuran (**2c**; $C_{20}H_{28}O_3$)

Prepared analogously to **2b** from 4.49 g (12.9 mmol) of $(MBE)_2O$ and 3.57 g (25.8 mmol) of 2-methoxybenzenemethanol [14]; yield after VFC (220 g, *PE*/Et_2O (50:1)) and *Kugelrohr* distillation: 4.75 g (58%) of **2c** as a colorless oil.

B.p.: 80°C/1.1 Pa (*Kugelrohr*); $[\alpha]_D^{25} = -90.8$ ($c = 1$, CH_2Cl_2); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 7.42–7.18, and 7.01–6.82 (2m, 4H, Ph-H), 5.25 (dd, 1H, 2-H), 4.71 and 4.51 (2d, $J = 13$ Hz, 2 H, Ph-CH_2-O) 3.97 (d, $J = 6.6$ Hz, 1H, 7a-H), 3.80 (s, 3H, OCH_3), 2.4–0.8 (m, 17H, aliphatic H, therein: 1.01, 0.98, and 0.80 (3s; 9H, 3 CH_3)) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 157.1 (s, C(ph)- 2), 128.7, 128.3 (2d, C(ph)-3, C(ph)-5), 127.1 (s, C(ph)-1), 120.3 (d, C(ph)-4), 110.2 (d, C(ph)-6), 104.5 (d, C-2), 91.1 (d, C-7a), 63.2 (t, Ph-CH_2-O), 55.3 (q, CH_3-OPh), 48.5 (d, C-4), 47.6 (s, C-7), 47.0 (s, C-8), 46.0 (d, C-3a), 38.6 (t, C-3), 32.5 (t, C-6), 28.9 (t, C-5), 22.9, 20.5, and 11.6 (3q, 3 CH_3) ppm.

General procedure of selectivity experiments

To a solution of 4 mmol of **2a–e** in 18 ml of anhydrous Et_2O and *THF*, resp., a solution of 4 mmol of the organometallic compound (BuMgBr and BuLi, resp.) was added at 0°C within 10 min. The mixture was stirred for 30 min, cooled to −78°C, a solution of 0.106 g (1 mmol) of benzaldehyde in the corresponding solvent was added within 10 min, and the mixture was stirred for 1 h. After adding 5 ml of water the mixture was allowed to reach room temp. When *THF* was used as solvent, the mixture was concentrated *in vacuo* and diluted with a mixture of Et_2O and water. If BuMgBr was used as organometallic component, ammonium chloride was added to dissolve the magnesium salts. The aqueous phase was separated and extracted twice with Et_2O. The combined organic layers were dried with sodium sulfate, and the solvent was evaporated. VFC (20–30 g, *PE*/Et_2O (50:1–4:1)) and CC (150–300 g, *PE*/Et_2O (20:1–4:1)), resp., yielded 1-phenyl-1-pentanol (**4**) and recovered **2a-e** which could be reused after *Kugelrohr* distillation. Additionally in experiments 5 and 6 (**2b**, BuLi, *THF*) and 10 (**2c**, BuLi, *THF*) larger amounts (about 40%) of by-products were obtained which were identified as enolether **5**, vinylacetal **6**, and alcohol **7**.

(3aS-(3aα,4β,7β,7aα))-3a,4,5,6,7,7a-Hexahydro-7,8,8-trimethyl-4,7-methanobenzofuran (**5**; $C_{12}H_{18}O$)[15]

Colorless oil; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 6.10–6.02 (m, 1H, 2-H), 5.15–5.05 (m, 1H, 3-H), 4.35 (d, $J = 9.9$ Hz, 1H, 7a-H), 2.86–2.74 (m, 1H, 3a-H), 1.8–0.75 (m, 14H, aliphatic H, therein: 1.11, 1.05, and 0.83 (3s, 9H, 3 CH_3)) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 146.6 (d, C-2), 105.6 (d,C-3), 93.6 (d, C-7a), 52.5 (d, C-3a), 48.6 (d, C-4), 47.6 (s, C-7), 46.1 (s, C-8), 32.6 (t, C-6), 28.1 (t, C-5), 23.3, 18.9, and 11.2 (3q, 3 CH_3) ppm; MS: $m/z = 178$ [M^+].

(2R-(2α,3aα, 4β, 7β, 7aα))-2-(Ethenyloxy)-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran (**6**; $C_{14}H_{22}O_2$)

Colorless oil; $[\alpha]_D^{25} = -103.3$ ($c = 1$, CH_2Cl_2); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 6.43 (dd, $J_1 = 20$ Hz, $J_2 = 6.6$ Hz, 1H, O-C*H*=CH_2), 5.40 (dd, 1H, 2-H), 4.41 (d, $J = 20$ Hz, 1H, O-CH=C*H*$_2$ *trans*), 4.09 (d, $J = 6.6$ Hz, 1H, O-CH=C*H*$_2$ *cis*), 3.98 (d, $J = 6.6$ Hz, 1H, 7a-H), 2.4–0.75 (m, 17H, aliphatic H, therein: 0.99, 0.96, and 0.80 (3s, 9H, 3 CH_3)) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 148.9 (d, O-*C*H=CH_2), 104.7 (d, C-2), 91.8 (d, C-7a), 90.5 (t, O-CH=*C*H_2), 48.4 (d, C-4), 47.6 (s, C-7), 47.0 (s, C-8), 45.5 (d, C-3a), 38.3 (t, C-3), 32.3 (t, C-6), 28.8 (t, C-5), 22.9, 20.4, and 11.5 (3q, 3 CH_3) ppm.

(2R-(2α(R),3aα,4β,7β,7aα))-Octahydro-α-(2-methoxyphenyl)-7,8,8-trimethyl-4,7-methanobenzofuran-2-methanol* (**7a**; $C_{20}H_{28}O_3$) and *(2R-(2α(S*),3aα,4β,7β,7aα))-Octahydro-α-(2-methoxyphenyl)-7,8,8-trimethyl-4,7-methanobenzofuran-2-methanol* (**7b**; $C_{20}H_{28}O_3$); mixture (3/2) [16]

Colorless crystals; m.p.: 73–90°C; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 7.47–7.36 and 7.30–7.18 (2m, 2H, 3(ph)-H, 5(ph)-H), 7.03–6.91 (m, 1H, 4(ph)-H), 6.87 (d, 0.6H, 6(ph)-H, **7a**), 6.83 (d, 0.4H, 6(ph)-H, **7b**), 5.07 (d, $J = 4.4$ Hz, 0.4H, C*H*OH, **7b**), 4.84 (d, $J = 9.6$ Hz, 0.6H C*H*OH, **7a**), 4.48–4.37 (m, 0.4H, 2-H, **7b**), 4.21–4.08 (m, 0.6H, 2-H, **7a**), 4.01 (d, $J = 7$ Hz, 0.4H, 7a-H, **7b**), 3.97 (d, $J = 7$ Hz, 0.6H, 7a-H, **7a**), 3.83 (s, 3H, OCH_3), 2.4–2.1 (m, 1H, 3a-H), 1.9–0.75 (m, 16H, aliphatic H, therein: 1.0, 0.95, and 0.8 (3s, 9H, 3 CH_3) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 157.0 (s, C(ph)-2, **7a**), 156.2 (s, C(ph)-2, **7b**), 129.3 (s, C(ph)-1, **7b**), 128.8 (s, C(ph)-1, **7a**), 128.6, 128.2, and 127.3 (3d, C(ph)-3, C(ph)-5), 120.9 (d, C(ph)-4, **7a**), 120.5 (d, C(ph)-4, **7b**), 110.5 (d, C(ph)-6, **7a**), 110.1 (d, C(ph)-6, **7b**), 93.8 (d, C-7a, **7b**), 91.1 (d, C-7a, **7a**), 84.7 (d, C-2, **7a**), 82.5 (d, C-2, **7b**), 73.1 (d, CHOH, **7b**), 68.4 (d, CHOH, **7a**), 55.4 (q, OCH_3, **7a**), 55.1 (q, OCH_3, **7b**), 49.2 (d, C-4, **7b**), 48.9 (d, C-4, **7a**), 48.7 (d, C-3a, **7b**), 48.4 (s, C-7, **7b**), 48.2 (s, C-7, **7a**), 47.9 (d, C-3a, **7a**), 46.8 (s, C-8, **7a**),

Table 1. Summary of the selectivity experiments: yield of **4** (% based on **3**), amount of recovered **2a-e** (% of added acetal), and enantiomeric excess (% *ee*) determined by different methods (GC, HPLC, $[\alpha]_D^{25}$) for different additives, solvents, and organometallic compounds

Exp. Nr	Add.	Solv.	Organometallic Component	Yield of **4** (%)	Rec. Add. (%)	%*ee* [b]		
						GC	HPLC	$[\alpha]_D^{25}$
1	**2a**	*THF*	BuLi	84	86	1	4	2
2	**2a**	*THF*	BuMgBr	77	93	1	1	2
3	**2a**	Et_2O	BuLi	79	98	–	–	0
4	**2a**	Et_2O	BuMgBr	93	93	5	3	3
5	**2b**	*THF*	BuLi	6	46	1	–	–
6	**2b**[a]	*THF*	BuLi	30	51	4	–	–
7	**2b**	*THF*	BuMgBr	81	80	1	1	1
8	**2b**	Et_2O	BuLi	94	45	0	–	–
9	**2b**	Et_2O	BuMgBr	36	83	47	44	45
10	**2b**	toluene	BuMgBr	98	-	9	–	–
11	**2c**	*THF*	BuLi	18	52	1	–	–
12	**2c**	*THF*	BuMgBr	72	100	1	2	0
13	**2c**	Et_2O	BuLi	88	89	5	4	4
14	**2c**	Et_2O	BuMgBr	85	97	1	2	0
15	**2d**	*THF*	BuLi	80	95	1	4	–
16	**2d**	*THF*	BuMgBr	66	97	1	4	1
17	**2d**	Et_2O	BuLi	91	100	1	5	1
18	**2d**	Et_2O	BuMgBr	82	98	1	5	2
19	**2e**	*THF*	BuLi	89	78	2	2	–
20	**2e**	*THF*	BuMgBr	85	74	1	3	1
21	**2e**	Et_2O	BuLi	97	94	1	1	0
22	**2e**	Et_2O	BuMgBr	42	83	1	3	1

[a] In alteration to the general procedure, in this experiment the complex formation between **1a** and **2b** was carried out at −46°C because the yield was very low under usual reaction conditions (see experiment 5); [b] □ main product **4b** (*S*-enantiomer), ▒ main product **4a** (*R*-enantiomer)

46.5 (s, C-8, **7b**), 32.5 (t, C-3, **7a**), 32.4 (t, C-3, **7b**), 32.3 (t, C-6, **7a**), 31.2 (t, C-6, **7b**), 28.8 (t, C-5, **7a**), 28.7 (t, C-5, **7b**), 22.7, 20.5, 20.2, and 11.7 (4q, 3 CH_3) ppm.

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