Monatshefte für Chemie 131, 867–877 (2000)

Monatshefte für Chemie
Chemical Monthly

[1,2]-*Wittig* Rearrangement of Acetals III [1]. New 1,2-Alkoxyalcohols, 1,2-Alkoxyamines and 1,2-Dialkoxy Compounds as Chiral Ligands for Organomagnesium and Organolithium Compounds and for Lithium Aluminum Hydride

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Summary. Eight O-substituted 1,2-diols and one O,N-substituted 1,2-aminoalcohol derived from 2-alkoxyoctahydro-7,8,8-trimethyl-4,7-methanobenzofurans *via* a [1,2]-*Witting* rearrangement and subsequent substitution were synthesized and tested as additives for the enantioselective addition of butyllithium and butylmagnesium chloride to benzaldehyde and for the reduction of acetophenone with lithium aluminum hydride. The selectivity of the reactions was determined by GC of the obtained 1-phenyl-1-pentanol and 1-phenylethanol on a chiral phase. Best results with regard to selectivity (52% *ee* and 94% *ee*, resp.) were achieved in the formation of 1-phenyl-1-pentanol by addition of the substituted 1,2-aminoalcohol to the organometallic reagent and in the reduction of acetophenone using an α-alkoxyalcohol (62% *ee*).

Keywords. Acetals; [1,2]-*Wittig* rearrangement; Ligands, chiral; Carbonyl addition, stereoselective.

Introduction

The enantioselective addition of organometallic reagents to aldehydes and the reduction of asymmetric ketones are two fundamental synthetic procedures to obtain stereoselectively chiral secondary alcohols [2–4]. This structural feature is part of many natural products or can serve as an important synthetic intermediate for various other functionalities, *e.g.* halide, amine, ester, and ether and is therefore a valuable target. A frequently used method to achieve this enantioselective addition and reduction is to perform the reaction in the presence of a chiral ligand. This is often a bifunctional compound capable of forming a chelate such as an alkoxy or amino alcohol [5]. Many chiral ligands have already been synthesized and tested in this type of reaction, some of them being highly selective [3, 4]. However, effort in the development of new ligands is still ongoing [6–10]. Recently, we have described the

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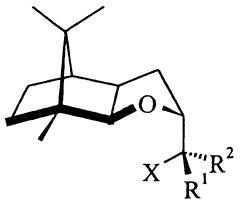
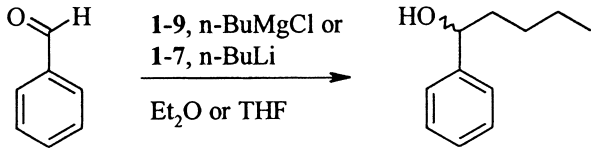
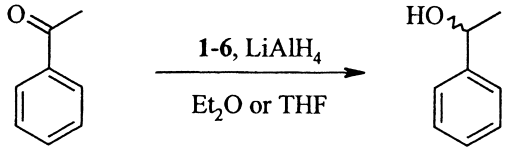


	X	R^1	R^2
1	OH	phenyl	H
2	OH	H	phenyl
3	OH	methyl	phenyl
4	OH	phenyl	methyl
5	OH	phenyl	phenyl
6	OH	phenyl	2-hydroxyphenyl
7	$N\text{-}(CH_2)_3\text{-}CH_3$	phenyl	H
8	OCH_3	H	phenyl
9	OCH_3	Phenyl	phenyl

Fig. 1. α-Alkoxyalcohols **1–6** and derivatives **7–9** of these



Scheme 1. Selective alkylation experiments with chiral additives



Scheme 2. Selective reduction experiments with alcohols **1–6** as chiral additives

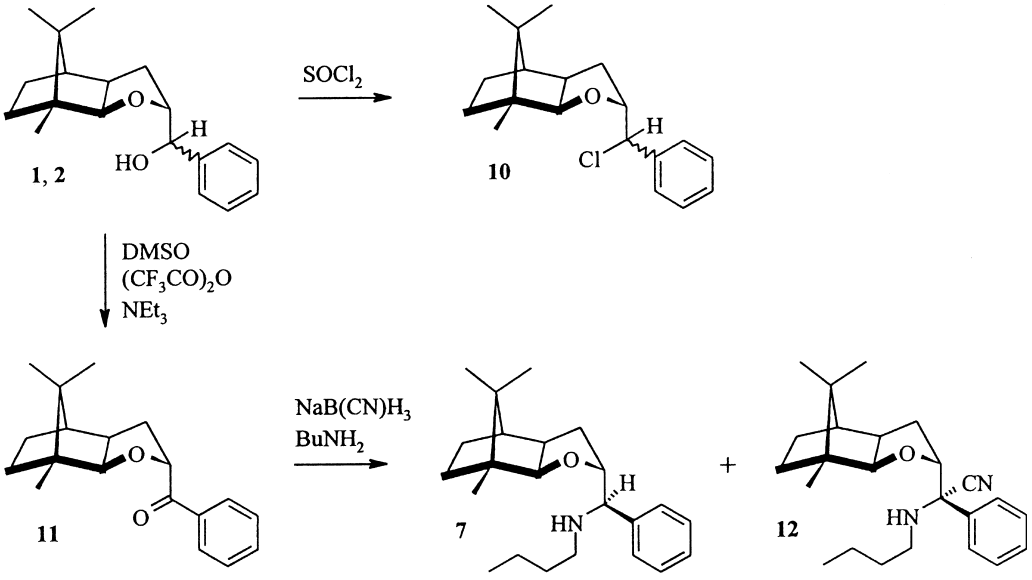
facile synthesis of six new α-alkoxyalcohols (**1–6**) from acetals by a simple [1,2]-*Wittig* rearrangement [1, 11]. The fact that many ligands used so far have 1,2-functionalities [12] prompted us – in continuation of our efforts searching for new chiral ligands [13, 14] – to test **1–6** and their derivatives **7–9** as additives.

In the present communication, results of the application of **1–9** in the reaction of butylmagnesium chloride and butyllithium with benzaldehyde (Scheme 1) and in the reduction of acetophenone with lithium aluminum hydride (Scheme 2) are reported.

Results and Discussion

Synthesis of derivatives **7–9**

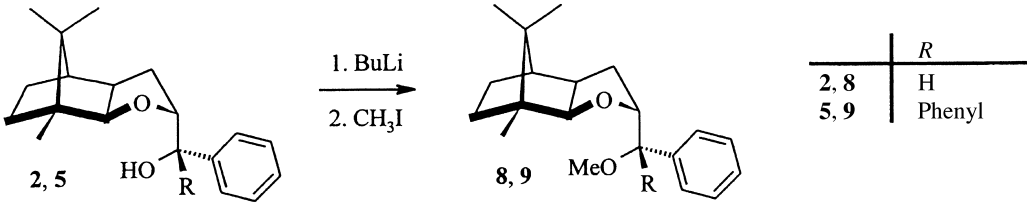
α-Alkoxyamine **7** was prepared from a mixture of **1** and **2** by *Swern* oxidation [15] and subsequent reductive amination [16]. Starting with a diastereomeric mixture was obviously without consequence, the center of chirality being destroyed in the oxidation step. The reduction of the intermediate imine was highly selective,



Scheme 3. Synthesis of α-alkoxyamine **7**

furnishing **7** as the single stereoisomer. Unexpectedly, aminonitrile **12** was formed as a by-product in this reaction, but it was also afforded in a highly selective way. The absolute configuration of the amine carbon atom was assigned based on the coupling constant between the vicinal hydrogens bound to the ether carbon and the amine center. For α-alkoxyalcohols it is well known that this value is bigger for products with *syn*-configuration like **1** ($J = 9.4$ Hz) than for *anti*-isomers like **2** ($J = 3.8$ Hz) [17]. Compound **7** exhibited a coupling constant of 9.0 Hz which is similar to the value observed for **1**. Thus, it is likely that α-alkoxyamine **7** has also *syn*-configuration which should be formed under non-chelating conditions according to the *Felkin-Anh* model [18]. For aminonitrile **12** no such coupling exists, because the carbon under question is quaternary, but considering that the nitrile just replaces the hydride in attacking the imine carbon the newly formed chiral center should be of *S*-configuration. It is worth mentioning that an approach *via* chloride **10** which was obtained as a diastereomeric mixture after treatment of **1** and **2** with thionyl chloride and subsequent *Hofmann* alkylation with diethylamine was not successful. Whereas **10** was obtained quantitatively, no reaction occurred with the amine which is probably due to the high steric hindrance at this carbon. A further indication for this assumption was given by the reaction of **1** and **2** with 4-methylbenzenesulfonyl chloride. This did not afford the expected tosylates but instead also yielded **10**. The formation of chloro derivatives *via* tosylates is not unprecedented and usually assisted by a neighboring group [19] which in our system could be the α-alkoxy substituent. However, the driving force for this transformation should be the steric requirement of the large tosyl group compared with the small chloride atom.

Ethers **8** and **9** were synthesized from alcohols **2** and **5** by deprotonation with *n*-butyllithium and O-alkylation with methyl iodide. Whereas **8** was obtained in excellent yield, the conversion of **5** was poor. This seems also to be a result of pronounced steric hindrance in **5** compared with **2**.



Scheme 4. Synthesis of ethers **8** and **9**

Selectivity experiments with benzaldehyde

The reactions with butylmagnesium chloride and butyllithium were carried out in diethyl ether as well as in tetrahydrofuran, because it is known that these solvents form complexes with the organometallic reagent; in addition, we have observed a strong influence of the solvent on enantioselectivity in earlier investigations [13]. For reasons of comparability and to exclude any reaction of an organometallic species without a chiral ligand we chose the same reaction conditions as described earlier [13]. Thus, since one equivalent of the organometallic reagent is consumed by each acidic proton of the additive, the reaction was carried out at −78°C using the following ratios: benzaldehyde:organometallic reagent: **8**,**9** = 1:4.7:5.2, benzaldehyde: organometallic reagent: **1**–**5**,**7** = 1:9.2:5.2, and benzaldehyde:organometallic reagent: **6** = 1:14.4:5.2. Due to the low temperature the reaction mixtures were heterogeneous

Table 1. Yield and enantiomeric excesses of 1-phenyl-1-pentanol in the alkylation of benzaldehyde by *n*-BuMgCl and *n*-BuLi in the presence of additives **1**–**9** and **1**–**7**

	Organometallic Compound	Additive	Solvent	Yield %	% *ee* (abs. conf.)
1	*n*-BuMgCl	**2**	Et_2O	97	48 (*R*)
2	*n*-BuMgCl	**2**	*THF*	71	13 (*R*)
3	*n*-BuMgCl	**3**	Et_2O	62	8 (*R*)
4	*n*-BuMgCl	**3**	*THF*	73	43 (*S*)
5	*n*-BuMgCl	**4**	Et_2O	50	18 (*S*)
6	*n*-BuMgCl	**5**	Et_2O	89	9 (*R*)
7	*n*-BuMgCl	**5**	*THF*	80	10 (*S*)
8	*n*-BuMgCl	**6**	Et_2O	24	49 (*S*)
9	*n*-BuMgCl	**6**	*THF*	3	–
10	*n*-BuMgCl	**7**	Et_2O	38	52 (*R*)
11	*n*-BuMgCl	**8**	Et_2O	68	8 (*R*)
12	*n*-BuMgCl	**8**	*THF*	41	1 (*S*)
13	*n*-BuMgCl	**9**	*THF*	< 1	4 (*R*)
14	*n*-BuLi	**1**	*THF*	< 1	1 (*R*)
15	*n*-BuLi	**2**	Et_2O	93	1 (*R*)
16	*n*-BuLi	**2**	*THF*	99	1 (*R*)
17	*n*-BuLi	**6**	*THF*	1.1	33 (*R*)
18	*n*-BuLi	**7**	Et_2O	< 1	94 (*R*)

with some ligands. However, this fact obviously is of no fundamental influence on the results, since even in heterogeneous systems high selectivities can be achieved [8].

In Table 1 the results of those experiments are summarized which yielded at least some 1-phenyl-1-pentanol under the reaction conditions defined above. All other experiments have been omitted from the table, but they are included in the discussion as well. Ligand **1** was not tested in Et_2O, and **7** was not used in *THF*. Reactions with *n*-BuLi have not been carried out with **8** and **9**, because results with *n*-BuMgCl were not promising at all.

As can be seen from Table 1, experiments in which additives **1**, **5**, **8**, and **9** were used did not show any significant selectivity. Enantiomeric excess in these cases was lower than 10% *ee*. For ligands **2**, **3**, **6**, and **7** at least the *Grignard* addition in one of the solvents (Et_2O for **2**, **6**, and **7**, *THF* for **3**) showed a moderate selectivity (>43% *ee*). The configuration of the alcohol formed in excess not only switched depending on the ligand (*R*: **2**, **7**; *S*: **3**, **6**), but also for the same ligand (**3**, **5**, **8**) in different solvents as was observed already in earlier investigations [13]. Surprisingly, reactions with *n*-BuLi gave only low conversions in most cases. Only if **2** was used as an additive the yield was good, but the reaction was nearly non-selective. On the other hand, if α-alkoxyamine **7** was added as chiral ligand the selectivity was 94% *ee*, but the yield was very small. To see whether a change of the reaction temperature would effect the conversion in the experiments with *n*-BuLi positively, the reaction with ligand **4** was also performed at 0°C. However, no product was obtained under these conditions, too.

Selectivity experiments with acetophenone

For the same reasons as already mentioned above the reactions with lithium aluminum hydride were also carried out in both solvents. In detail, a solution of two equivalents of the additive **1**–**6** in *THF* and diethyl ether was cooled to 0°C before one molar equivalent of lithium aluminum hydride was added. For **6** with its two acidic protons a second equivalent of $LiA1H_4$ was used. The mixture was stirred for 30 min to complete the complex formation, cooled to −78°C, and a solution of 0.8 equivalents of acetophenone in the corresponding solvent was added dropwise. After stirring for exactly 1 h keeping the temperature between −83 and −73°C, the reaction was quenched with 2 *N* hydrochloric acid and worked up by extraction to give a crude product which was analyzed by gas chromatography to determine yield and enantioselectivity.

Again, selectivities were heavily influenced by the solvent used, resulting in the predominant formation of the other enantiomer of 1-phenylethanol in the case of **1**, **2**, and **6**. However, enantiomeric excesses for the products were only low (**1**, **2**) to moderate (**3**, **5**, **6**). Only using additive **4** in Et_2O resulted in a product with 62% *ee* which dropped to 27% *ee* if the reaction was performed in *THF*.

With the best ligand in this series (**4**) we carried out two additional experiments with the intention of further improving the selectivity. In the first one we added one equivalent of N-methylaniline to the lithium aluminum hydride complex prior to the reduction. Although this addition of an achiral amine has been described to improve the selectivity for other auxiliaries significantly [20], we obtained 1-

Table 2. Yield and enantiomeric excesses of 1-phenylethanol in the reduction of acetophenone by $LiAlH_4$ in the presence of additives **1–6**

	Additive	Solvent	Yield (%)	% *ee* (abs. conf.)
1	**1**	Et_2O	84	13 (*R*)
2	**1**	*THF*	54	5 (*S*)
3	**2**	Et_2O	15	17 (*S*)
4	**2**	*THF*	40	8 (*R*)
5	**3**	Et_2O	42	15 (*S*)
6	**3**	*THF*	71	37 (*S*)
7	**4**	Et_2O	> 99	62 (*S*)
8	**4**	*THF*	60	27 (*S*)
9	**5**	Et_2O	39	43 (*S*)
10	**5**	*THF*	20	9 (*S*)
11	**6**	Et_2O	96	14 (*S*)
12	**6**	*THF*	92	42 (*R*)

phenylethanol with only 20% *ee*. In the second one, $LiAlH_4$ was replaced by $NaBH_4$ which resulted in a non-selective reaction (1.5% *ee*).

Conclusions

Some of the alcohols obtained *via* [1,2]-*Wittig* rearrangement of acetals of octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-ol and derivative **7** exhibit moderate enantioselectivities as ligands for the addition of butylmagnesium chloride to benzaldehyde and the reduction of acetophenone with lithium aluminum hydride. Ethers **8** and **9** showed no selectivity at all. The addition of butyllithium to benzaldehyde in diethyl ether was highly selective in the presence of **7**. However, in this case the question of the low conversion has still to be addressed and will be the issue of further investigations. In none of the reaction systems a general preference was found with regard to absolute configuration of the enantiomer formed in excess or to a solvent in which higher selectivities could be achieved. A so-called magic effect of the diarylhydroxymethyl-group [21] which is present in **5** and **6** was not observed in our investigation. These two ligands exhibited no significant better selectivity compared to the other additives.

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. *n*-Butyllithium and *n*-butylmagnesium chloride were purchased from Aldrich as 2.5 *M* solution in *n*-hexane and 2 *M* solution in Et_2O and *THF* and used immediately. The content of *n*-butyllithium in *n*-hexane was determined by titration with *t*-butanol using 1,10-phenanthroline as indicator. All other reagents were purchased in standard commerical quality unless otherwise stated. Reactions were monitored by TLC carried out on 0.25 mm Merck silica gel plates

(60F-254) using UV light for visualizing and molybdato phosphoric acid (5% in ethanol) 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 are 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 resonance as internal standard. Optical rotations were recorded on a Perkin Elmer 241 polarimeter. GC analyses 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 Helium 5.0 was used as carrier gas with a flow rate of 4.3 cm^3/min (column pre-pressure: 210 kPa). The injector was heated to 220°C, and injected samples were splitted in a ratio of 1:73. For 1-phenyl-1-pentanol the column temperature was held at 100°C for 50 min and then raised to 140°C at a rate of 1°C/min. 1-Phenylethanol was analyzed isothermal with a column temperature of 100°C. Compounds were detected in both cases with a FID (260°C), and chromatograms were recorded on a Carlo Erba SP4270 integrator and processed with LABNET2 software from Spectra Physics. R_t benzaldehyde 7.3 min, (*R*)-1-phenyl-1-pentanol 63.7 min, (*S*)-1-phenyl-1-pentanol 64.3 min, acetophenone 12.5 min, (*S*)-1-phenyl-1-ethanol 16.5 min, (*R*)-1-phenyl-1-ethanol 17 min. The absolute configuration of the major isomer was based on retention times of reference samples prepared via acetal formation between racemic alcohol and (2*S*,2′*S*-(2α2′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), separation of the diastereomers, and acid catalyzed cleavage with methanol [13, 22]. Compounds **1**–**6** were prepared as described in Refs. [1, 11]. Abbreviations used: *PE* = petroleum ether.

(2R-(2α(R),3aα,4β,7β,7aα))-N-Butyl-octahydro-7,8,8-trimethyl-α-phenyl-4,7-methanobenzofuran-2-methanamine* (**7**; $C_{23}H_{35}NO$)

A mixture of 0.419 g (1.48 mmol) of **11**, 0.70 cm^3 (6.91 mmol) of *n*-butanamine, 0.085 g (1.40 mmol) of sodium cyanoborohydride, 0.35 cm^3 (6.21 mmol) of glacial acetic acid, and 0.66 g of $MgSO_4$ in 13 cm^3 of ethanol was stirred for 48 h at room temperature. 14 cm^3 of a 1 *N* aqueous NaOH solution and 140 cm^3 of brine were added, the aqueous phase was extracted thoroughly with ethyl acetate, the combined organic layers were dried over Na_2SO_4, and the solvent was evaporated. Column chromatography (50 g, *PE*:Et_2O:NEt_3 = 300:30:1 to 400:100:1 to 0:20:1) afforded 0.149 g (30%) of **7** and 0.099 g (20%) of **12**.

7: Colorless oil; $[\alpha]_D^{23} = -47.1$ ($c = 1.42$, CH_2Cl_2); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 7.36-7.18 (m, 5H, Ph-H), 4.18-4.03 (m, 1H, 2-H), 3.80 (d, 1H, 7a-H), 3.41 (d, 1H, C*H*NH*R*), 2.46-0.74 (m, 27H, aliphatic H and NH, therein: 1.00, 0.98 and 0.79 (3s, 9H, 3 CH_3))ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 141.7 (s, C(ph)-1), 128.6, 128.2 (2d, C(ph)-2, C(ph)-6, C(ph)-3, C(ph)-5), 127.3 (d, C(ph)-4), 91.1 (d, C-7a), 84.1 (d, C-2), 66.3 (d, CHNH*R*), 48.9, 47.6 (2d, C-3a, C-4), 48.2, 46.7 (2s, C-7, C-8), 47.3 (t, N-CH_2), 33.1, 32.4, 32.2 (3t, C-3, C-6, NCH_2CH_2), 28.9 (t, C-5), 22.8, 20.4 (2q, 2 CH_3), 20.4 (t, $NCH_2CH_2CH_2$), 14.0 (q, butyl-CH_3), 11.7 (q, CH_3) ppm.

(2R-(2α(S),3aα,4β,7β,7aα))-α-Butylamino-octahydro-7,8,8-trimethyl-α-phenyl-4,7-methanobenzofuran-2-acetonitrile* (**12**; $C_{24}H_{34}N_2O$)

Yellow oil; $[\alpha]_D^{23} = -23.8$ ($c = 2.19$, CH_2Cl_2); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 7.65-7.22 (m, 5H, Ph-H), 4.32 (d, 1H, 7a-H), 4.18 (dd, 1H, 2-H), 2.78-0.74 (m, 27H, aliphatic H and NH, therein: 1.00, 0.88 and 0.79 (3s, 9H, 3 CH_3))ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 136.2 (s, C(ph)-1), 128.7, (d, C(ph)-3, C(ph)-4, C(ph)-5), 127.1 (d, C(ph)-2, C(ph)-6), 120.4 (s, CN), 94.1 (d, C-7a), 88.7 (d, C-2), 69.7, (s, CNH*R*), 49.4, 47.6 (2d, C-3a, C-4), 48.7, 46.7 (2s, C-7, C-8), 44.2 (t, N-CH_2), 33.1, 32.2,

32.0 (3t, C-3, C-6, NCH_2CH_2), 28.5 (t, C-5), 22.6, 19.8 (2q, 2 CH_3), 20.3 (t, $NCH_2CH_2CH_2$), 13.9 (q, butyl-CH_3), 11.6 (q, CH_3) ppm.

(2R-(2α(S),3aα,4β,7β,7aα))-Octahydro-2-(methoxyphenylmethyl)-7,8,8-trimethyl-4,7-methanobenzofuran* (**8**; $C_{20}H_{28}O_2$)

0.46 cm^3 (1.2 mmol) of a solution of butyllithium in *THF* were added to a solution of 0.267 g (0.93 mmol) of **2** in 16 cm^3 of *THF*. The solution was stirred for 90 min at room temperature, and subsequently 1.72 g (12 mmol) of methyl iodide were added. The solution was stirred for 15 h at room temperature, concentrated under vacuum, and the, residue was distributed between H_2O and Et_2O. The aqueous phase was extracted twice with Et_2O, the combined organic layers were dried over Na_2SO_4, and the solvent was evaporated. VFC (10 g, *PE*:Et_2O = 10:1) gave 0.247 g (88%) of **8** as colorless crystals.

M.p.: 67–69°C; $[\alpha]_D^{20} = +42.6$ ($c = 1$, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 7.42-7.18 (m, 5H, Ph-H), 4.30-4.13 (m, 2H, 2-H, therein: 4.26 (d, 1H, C*H*OCH_3)), 3.92 (d, 1H, 7a-H), 3.32 (s, 3H, OCH_3) 2.38-0.72 (m, 17H, aliphatic H, therein: 0.96, 0.92 and 0.78 (3s, 9H, 3 CH_3)) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 139.2 (s, C(ph)-1), 128.2 (d, C(ph)-3, C(ph)-5), 127.3 (d C(ph)-4), 126.8 (d, C(ph)-2, C(ph)-6), 93.5 (d, C-7a), 87.1 (d, *C*$HOCH_3$) 84.1 (d, C-2), 57.3 (q, OCH_3), 49.1, 48.4 (2d, C-3a, C-4), 48.2, 46.6 (2s, C-7, C-8), 32.3 (t, C-3), 31.5 (t, C-6), 28.7 (t, C-5), 22.8, 20.2, 11.7 (3q, 3 CH_3) ppm.

(2R-(2α,3aα,4β,7β,7aα))-Octahydro-2-(methoxydiphenylmethyl)-7,8,8-trimethyl-4,7-methanobenzofuran (**9**; $C_{26}H_{32}O_2$)

Prepared analogously to **8** from 1.969 g (5.43 mmol) of **5**, 2.76 cm^3 (7.2 mmol) of butyllithium solution, and 9.97 g (71 mmol) of methyl iodide; yield after VFC (40 g silica gel, *PE*:Et_2O = 1:0 to 30:1): 0.353 g (17%) of **9** as a colorless oil.

$[\alpha]_D^{20} = -66.7$ ($c = 0.86$, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 7.53 (dd, 2H, 2 4(ph)-H), 7.43-7.18 (m, 8H, Ph-H), 5.15 (m, 1H, 2-H), 3.09 (d, 1H, 7a-H), 3.07 (s, 3H, OCH_3), 2.50-2.28 (m, 1H, 3a-H), 2.11-1.92 (m, 1H, 4-H), 1.63-0.47 (m, 15H, aliphatic H, therein: 1.04, 0.91 and 0.75 (3s, 9H, 3 CH_3) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 143.1, 142.3 (2s, 2 C(ph)-1), 129.4, 129.4 (2d, 2 C(ph)-3, 2 C(ph)-5), 127.6, 127.2 (2d, 2 C(ph)-2, 2 C(ph)-6), 127.0, 126.9 (2d, 2 C(ph)-4), 94.0 (d, C-7a), 84.6 (d, *C*OCH_3), 83.6 (d, C-2), 51.5 (q, OCH_3), 49.4, 48.2 (2d, C-3a, C-4), 48.5, 45.9 (2s, C-7, C-8), 32.9 (t, C-3), 32.0 (t, C-6), 28.5 (t, C-5), 22.7, 20.0, 11.6 (3q, 3 CH_3) ppm.

(2R-(2α,3aα,4β, 7β,7aα))-2-Chlorphenylmethyl-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran (**10**; $C_{19}H_{25}ClO$)

A solution of 0.1 g (0.35 mmol) of a diastereomeric mixture of **1** and **2** and 0.09 cm^3 (1.24 mmol) of $SOCl_2$ in 10 cm^3 of Et_2O was stirred for 4 h at room temperature, quenched with water, and extracted exhaustively with Et_2O. The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated to furnish 0.11 g (100%) of **10** as a diastereomeric mixture.

Colorless oil; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 7.49-7.22 (m, 10H, Ph-H), 5.02 (d, 1H, CHCl, A), 4.81 (d, 1H, CHCl, *B*), 4.60-4.47 (m, 2H, 2-H), 4.08 (d, 1H, 7a-H, *A*), 3.82 (d, 1H, 7a-H, *B*), 2.50-0.77 (m, 34H, aliphatic H, therein: 0.96, 0.95 and 0.81 (3s, 18H, 6 CH_3)) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 139.1, (s, C(ph)-1), *B*), 138.6 (s, C(ph)-1), A), 128.4, 128.4, 128.2, 128.0, 127.5 (5d, C(ph)-3, C(ph)-5), C(ph)-2, C(ph)-6, C(ph)-4), 93.5 (d, C-7a, *A*), 92.8 (d, C-7a, *B*) 84.5 (d, C-2, *A*), 83.9 (d, C-2, *B*), 67.2 (d, CHCl, *A*), 65.5 (d, CHCl, *B*), 49.1, 48.2 (2d, C-4, C-3a, A), 48.9, 47.6 (2d, C-4, C-3a, B), 48.4, 46.5 (2s, C-7, C-8, *A*), 48.3, 46.5 (2s, C-7, C-8, *B*), 34.2 (t, C-3, *B*), 33.3 (t, C-3, *A*), 32.2 (t, C-6), 28.7 (t, C-5), 22.7, 20.3, 20.2 and 11.5 (4q, 6 CH_3) ppm.

(2R-(2α,3aα,4β,7β,7aα))-(Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)-phenylmethanon (**11**; $C_{19}H_{24}O_2$)

A solution of 0.68 cm^3 (4.85 mmol) of trifluoroacetic acid anhydride in 1.62 cm^3 of CH_2Cl_2 was added to a mixture of 0.46 cm^3 (6.46 mmol of *DMSO* and 3.2 cm^3 of CH_2Cl_2 at −50°C, and the mixture was stirred for 20 min. A solution of 0.923 g (3.22 mmol) of a diastereomeric mixture of **1** and **2** in 3.2 cm^3 of CH_2Cl_2 was added, and Stirring was continued for further 30 min. 1.29 cm^3 anhydrous triethylamine was added dropwise, and the mixture was allowed to warm to room temperature. It was quenched with H_2O, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated. VFC (40 g, *PE*:Et_2O = 30:1) afforded 0.524 g (57%) of **11** as a colorless oil.

$[\alpha]_D^{23} = -19.9$ ($c = 3.17$, CH_2Cl_2); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 7.95 (d, 2H, 2(ph)-H, 6(ph)-H, 6(ph)-H), 7.62-7.38 (m, 3H, 3(ph)-H, 4(ph)-H, 5(ph)-H), 5.44 (dd, 1H, 2-H), 4.08 (d, 1H, 7a-H), 2.41-0.72 (m, 17H, aliphatic H, therein: 1.10, 1.03 and 0.82 (3s, 9H, 3 CH_3)) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 199.8 (s, C=O), 134.7 (s, C(ph)-1), 133.1 d, C(ph)-4), 128.6, 128.5 (2d, C(ph)-2, C(ph)-6, C(ph)-3, C(ph)-5, 93.2 (d, C-7a), 80.4 (d, C-2), 48.7, 47.3 (2d, C-3a, C-4), 48.3, 46.9 (2s, C-7, C-8), 34.7, 32.0 (2t, C-3, C-6), 28.7 (t, C-5), 22.7, 20.6, 11.5 (3q, 3 CH_3))ppm.

Reaction of benzaldehyde with n-butyllithium and n-butylmagnesium chloride using protic additives **1–7**

A solution of 0.35 mmol of *n*-BuMgCl or *n*-BuLi was added to a solution of 0.2 mmol of **1–5** or **7** in 0.88 cm^3 of *THF* or Et_2O at 0°C. In the case of **6**, 0.55 mmol of the organometallic compound were used. The mixture was stirred for 30 min at this temperature and then cooled to −78°C. A solution of 0.38 mmol of benzaldehyde in 0.77 cm^3 of the corresponding solvent was added, and the mixture was stirred at −78±5°C After 1 h the reaction mixture was quenched with H_2O, allowed to reach room temperature, and 0.1 cm^3 of the organic layer were diluted with 0.9 cm^3 *n*-hexane and dried over Na_2SO_4. If *n*-BuMgCl was used, the mixture was treated with solid NH_4Cl prior to the dilution sequence. The solution was filtered through an Anotop 10 membrane filter and analyzed without any further treatment by gas chromatography. Enantiomeric excess and yield were determined from signal areas after recalculation considering response factors determined by calibration solutions.

Reaction of benzaldehyde with n-butylmagnesium chloride using aprotic additive **8–9**

The reaction was carried out as described for protic additives, only the amount of *n*-BuMgCl was reduced to 0.18 mmol for 0.2 mmol of additive.

Reduction of acetophenone with lithium aluminum hydride using protic additives **1–6**

A solution of 0.1 mmol of $LiAlH_4$ was added to a solution of 0.2 mmol of **1–5** in 0.88 cm^3 of *THF* or Et_2O at 0°C. In case of additive **6**, 0.2 cm^3 of $LiAlH_4$ were used. The mixture was stirred for 30 min at 0°C, cooled to −78°C, and a solution of 0.08 mmol of acetophenone in 0.1 cm^3 of the corresponding solvent was added. The mixture was stirred for 1 h at −78±5°C, quenched with H_2O and allowed to reach room temperature. After treatment with 2 *N* hydrochloric acid, 0.1 cm^3 of the organic layer were diluted with 0.9 cm^3 of *n*-hexane and dried over Na_2SO_4 This solution was filtered through an Anotop 10 membrane filter and analyzed directly by gas chromatography. Enantiomeric excess and yield were determined from signal areas after recalculation considering response factors determined by calibration solutions. When additive **1** was used in a tenfold larger scale, the whole amount of product was isolated by column chromatography, and the enantiomeric excess was determined as usual by gas chromatography.

Reduction of acetophenone with lithium aluminum hydride/N-methylaniline using additive **4**

Following the above procedure for the reduction of acetophenone, 0.2 mmol **4** in 0.88 cm^3 Et_2O were treated with 0.1 mmol of $LiAlH_4$. A solution of 0.1 mmol of N-methylaniline in 0.33 cm^3 of Et_2O was added to this mixture. After cooling to −78°C, 0.08 mmol of acetophenone were added. All other steps were performed as described above.

Reduction of acetophenone with sodium borohydride using additive **4**

Following the above procedure for the reduction of acetophenone, 0.2 mmol of **4** in 0.88 cm^3 of Et_2O were treated with 0.1 mmol of $NaBH_4$. After cooling to −78°C, 0.08 mmol of acetophenone were added. All other steps were performed as described above.

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Received March 10, 2000. Accepted March 23, 2000