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Enantioselective addition of organometallics to aldehydes using camphor derived chiral 1,4-aminoalcohols as ligands

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Abstract

(+)-Camphor derived enantiomerically pure 1,4-aminoalcohols have been used as ligands in the addition reactions of *n*-BuLi and *n*-BuMgBr to benzaldehyde and in the reaction of diethylzinc with benzaldehyde and hexanal. All chiral secondary alcohols were obtained in good chemical yields and enantioselectivities were up to 87% ee in the addition of diethylzinc.

1. Introduction

One of the most important and fundamental synthetic procedures to establish a new carbon–carbon bond stereoselectively is the enantioselective addition of organometallic reagents to aldehydes affording chiral secondary alcohols.[1,2] 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 is to perform the reaction in the presence of a chiral ligand such as an aminoalcohol.[3–5] Many chiral ligands have already been synthesized and tested in this type of reaction; however, mostly ligands with 1,2-functionalities have been used.[6] Besides a few examples[7–9] demonstrating the efficient use of γ-aminoalcohols, the synthesis and utilization of (+)-camphor and (−)-menthone derived 1,4-aminoalcohols as ligands for diethylzinc have been reported.[10–12] Recently, we described the synthesis of seven new 1,4-aminoalcohols **2a**–**g** from lactone **1** by a simple two-step procedure (Scheme 1).[13]

In the present communication, results of the application of **2a**–**g** as chiral additives in the reaction of different organometallic reagents with benzaldehyde and hexanal are reported (Scheme 2).

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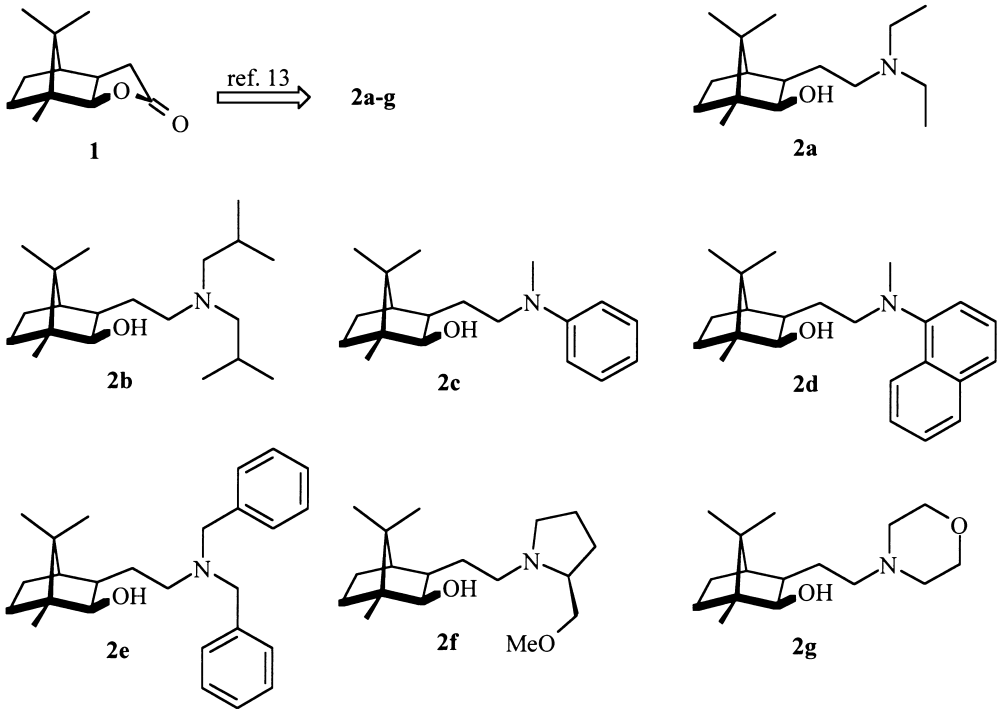
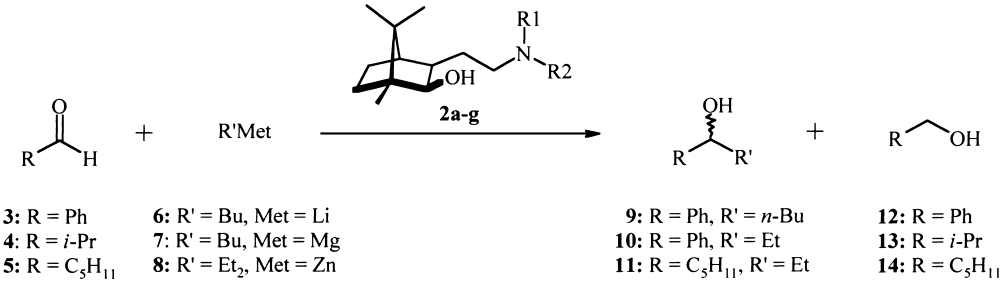


Scheme 1. Synthesis of the 1,4-aminoalcohols **2a**–**g**



Scheme 2. Selectivity experiments with the 1,4-aminoalcohols **2a**–**g** as chiral additives

2. Results and discussion

With alkyllithium and Grignard compounds being the most readily available and widely used organometallic reagents, we decided to test our ligands with these systems first. In this area many examples[14,15] have been described so far. Only recently, successful applications of 1,2-aminoalcohols as ligands for RLi[16] and the use of 1,4-diols of the TADDOL-type for RMgBr[17] have been reported.

The reactions with butylmagnesium bromide and butyllithium were carried out in diethylether as well as in tetrahydrofuran, because it is known that these solvents form complexes with the organometallic reagent and in earlier investigations[18] we have observed a strong influence of the solvent on the enantioselectivity. 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.[18] Thus, since one equivalent of the organometallic reagent is consumed by deprotonating the secondary hydroxy group of the ligand, the reaction was carried out using **3**:organometallic reagent:**1** in a molar ratio of 1:9.2:5.2 at a

Table 1
Enantiomeric excesses of 1-phenyl-1-pentanol **9** in the alkylation of benzaldehyde **3** by *n*-BuLi **6** and *n*-BuMgBr **7** in the presence of the aminoalcohols **2a**–**g**

Entry	R´Met	Solvent	**2a**[a]	**2b**[a]	**2c**[a]	**2d**[a]	**2e**[a]	**2f**[a]	**2g**[a]
1	**6**	Et_2O	15 (S)	15 (S)	23 (R)	25 (R)	32 (R)	23 (R)	14 (S)
2	**6**	THF	10 (R)	4 (R)	4 (R)	4 (R)	30 (R)	5 (R)	11 (R)
3	**7**	Et_2O	35 (S)	7 (S)	10 (S)	2 (S)	8 (S)	37 (R)	6 (S)
4	**7**	THF	5 (R)	30 (S)	37 (R)	18 (R)	7 (R)	2 (R)	1 (R)

[a] *Values in percent obtained by integration of HPLC peaks using a chiral stationary phase (Chiralcel OD).*

reaction temperature of −78°C. Due to the low temperature we had to accept that with some ligands the reaction mixtures were heterogeneous. But this fact should not have any fundamental influence on the results, because even in heterogeneous systems high selectivities can be achieved.[15c]

The results in Table 1 show that the enantioselectivities we obtained with our 1,4-aminoalcohols were only moderate (up to 37% ee), with no significance with regard to the solvent or the configuration of the preferably formed enantiomer. Thus, we changed the organometallic reagent to investigate the application of **2a**–**g** in the addition reaction of diethylzinc to aldehydes.[19] Because it is known that most of the catalysts reported are highly effective for aromatic and α-branched aliphatic aldehydes, we did our first experiments in this series with benzaldehyde **3** (cf. lit.,[1] pp. 1298–1299). Additionally, we were especially interested in testing the best of our reagent–ligand systems for an unhindered aliphatic aldehyde, for which only limited success has been achieved so far.[20–23] As a representative example of this group we chose the addition of diethylzinc to hexanal **5**. The reaction was carried out by the addition of 2 equiv. of **8** to **3** in the presence of 0.1 equiv. of the catalyst **2a**–**g** in toluene. For the experiments giving best results (yield 94%, 87% ee), the amount of aminoalcohol was reduced to 0.05 and 0.02 equiv., respectively, without affecting either the conversion or the enantioselectivity significantly. Only if the reaction was carried out with the best of our ligands **2g** at −30°C was the reaction rate reduced, and after 17 h only 58% of **3** had been converted. However, still no influence on the enantioselectivity was observed (entry 9). More detailed results are given in Table 2.

Next we used our best ligand **2g** in the alkylation of isobutyraldehyde **4** with diethylzinc, but unexpectedly we obtained only the corresponding primary alcohol **13**, which can be rationalized by the pronounced steric hindrance of the carbonyl-C in **4**. Finally, the four ligands **2a**,**b**,**f**,**g**, which gave the best results in the benzaldehyde series, were tested with hexanal **5** as the alkylation substrate, and the better catalysts **2a**,**g** yielded 3-octanol **11** with excellent chemical yield and good enantioselectivity (Table 3). This is in good accordance with a recently published paper about the advantageous use of morpholine as amino-partial structure in an aminoalcohol-ligand.[24] Remarkably, aminoalcohol **2f** gave a higher enantiomeric excess for 3-octanol **11** compared to 1-phenylpropanol **10** which is quite unusual (Table 3: entry 3 versus Table 2: entry 7) (cf. lit.,[1] p. 1314).

In contrast to the arylalkylcarbinol **10** we were not able to get two baseline resolved signals for the purely aliphatic alcohol **11** on our chiral stationary phase. Thus, we formed diastereomeric derivatives

Table 2
Distribution of products and enantiomeric excesses of 1-phenyl-1-propanol **10** in the alkylation of benzaldehyde **3** by diethylzinc catalyzed by one of the aminoalcohols **2a**–**g**

Entry	Catalyst	Mol % **2**[a]	**10**[c]	**12**[c]	**3**[c]	ee [%][d]	Config.[e]
1	**2a**	10	92	7	1	78	S
2	**2a**	5	86	13	1	70	S
3	**2b**	10	36	44	20	40	S
4	**2c**	10	28	49	23	21	S
5	**2d**	10	33	53	14	3	R
6	**2e**	10	29	43	28	20	S
7	**2f**	10	88	11	1	12	S
8	**2g**	10	94	5	1	87	S
9[b]	**2g**	10	53	5	42	86	S
10	**2g**	5	96	4	-	87	S
11	**2g**	2	94	6	-	85	S

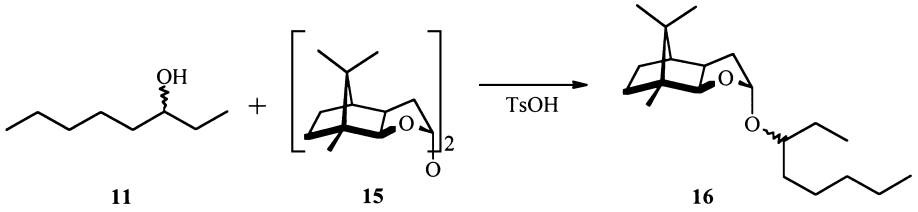
[a] Relative to benzaldehyde. [b] The reaction was carried out in toluene at -30°C. [c] Values in percent obtained by integration of GC peaks using an achiral stationary phase. [d] Values in percent obtained by integration of HPLC peaks using a chiral stationary phase. [e] Determined by the sign of optical rotation and the elution order of HPLC analysis.

Table 3
Distribution of products and enantiomeric excesses of 3-octanol **11** in the alkylation of hexanal **5** by diethylzinc catalyzed by one of the aminoalcohols **2a**,**b**,**f**,**g**

Entry	Catalyst	Mol % **2**[a]	**11**[b]	**14**[b]	**5**[b]	ee [%][c]	Config.[d]
1	**2a**	10	95	5	-	60	S
2	**2b**	10	26	48	26	17	S
3	**2f**	10	72	22	6	31	S
4	**2g**	10	98	2	-	60	S

*[a] Relative to hexanal. [b] Values in percent obtained by integration of GC peaks using an achiral stationary phase. [c] Values in percent obtained by integration of GC peaks of derivatives **16** of **11** using a chiral stationary phase. [d] Determined by the sign of optical rotation and the elution order of GC analysis.*

of **11** by reaction with excessive anhydrolactol **15**[25] in the presence of *p*-toluenesulfonic acid to obtain quantitatively acetals **16**, which could be separated very easily by gas chromatography (Scheme 3).



11 **15** **16**

Scheme 3. Acetal formation of 3-octanol **11** with the anhydrolactol **15** for determination of the enantiomeric excess of **11** by GC

Comparing the selectivities achieved with different alkoxide counterions there is little which can be generalized. In accordance with the literature,[26] diethylzinc gives better results in the non-coordinating solvent toluene than lithium- and Grignard-reagents in Et_2O or THF. Whereas lithium organic compounds (Table 1, entries 1 and 2) are more selective in ether solutions than in THF as solvent, no such dependence is observed for Grignard-reagents (Table 1, entries 3 and 4), which may be attributed to different solvent coordinating properties of the central metal. The question about 'matched' and 'mis-matched' pairs can be asked for ligand **2f**, which carries an additional stereogenic center derived from the amine component. From the fact that there is no significant difference in the observed selectivities between **2f** and the average value of the other ligands when used with lithium and magnesium, it may be assumed that there is almost no influence of this stereogenic chiral center. Nonetheless, it is worth mentioning that selectivities obtained with **2f** in Et_2O are amongst the better ones, whereas in THF both lithium- as well as Grignard-reagents are almost non-selective. In the case of diethylzinc **2f** was significantly less selective than the other ligands (with the exception of **2d**). Therefore, the possibility that **2f** represents the 'mis-matched' pair in this reaction should be considered.

In conclusion, we have shown that the camphor derived 1,4-aminoalcohols **2a**–**g** on the one hand exhibit only moderate chiral induction in the addition of *n*-BuLi and *n*-BuMgBr to benzaldehyde, but on the other hand, seem to be promising ligands in the addition of organozinc reagents to aldehydes, which will be further investigated.

3. Experimental

3.1. General

3.1.1. General procedure for the alkylation of benzaldehyde with n-*BuLi and* n-*BuMgBr*

To a solution of 5.2 mmol of the aminoalcohol **2a**–**g** in 23 ml of anhydrous solvent (ether, THF) was added 9.2 mmol of *n*-BuMgBr in 4 ml of ether (THF) with external cooling in a way that the temperature of the reaction mixture did not exceed 10°C. In the case of the addition of *n*-BuLi 3.68 ml of *n*-BuLi (9.2 mmol; 2.5 M solution in *n*-hexane) was added. After additional stirring at 0°C the mixture was cooled to −78°C and a solution of 106 mg (1 mmol) of benzaldehyde in 2 ml of solvent was added. The reaction mixture was stirred for 1 h at this temperature and quenched with 5 ml of H_2O. The organic layer was separated and the aqueous layer was extracted twice with ether. The combined organic layers were extracted with 2N HCl, washed with water, dried with Na_2SO_4, filtered and the solvent was evaporated. Yield: 79–100%, colorless oil, 1-phenyl-1-pentanol **9**, R_f (PE:Et_2O=3:1)=0.42. The ligands **2a**–**g** could be recovered quantitatively from the aqueous layer. Enantiomeric excess of **9** was determined directly

by HPLC (column: Chiralcel OD (25 cm, 4.6 mm ID; Daicel Chemical Industries); conditions: flow: 1.7 ml/min; eluent: 0.7% 2-propanol and 2% *t*-butylmethylether in *n*-hexane. R_t: *R*(+)-1-phenyl-1-pentanol 15.70 min, (*S*)-(−)-1-phenyl-1-pentanol 17.70 min).

3.1.2. General procedure for the alkylation of benzaldehyde, isobutyraldehyde and hexanal with diethylzinc

A 1.1 M solution of diethylzinc (2 ml, 2.2 mmol) in toluene was added dropwise at 0°C to an ice cooled solution of one of the aldehydes **3**–**5** (1 mmol) and one of the aminoalcohols **2a**–**g** in 6 ml of anhydrous toluene. After stirring at rt for 17 h, the reaction was quenched by addition of 5 ml of 2N HCl, and the aqueous layer was separated and extracted three times with 10 ml of diethylether. The combined organic phases were washed with a saturated solution of $NaHCO_3$, dried with sodium sulfate and concentrated to give the crude product which was analyzed by GC (**3**, **10**, **12**: column: Carbowax 57 CB (25 m, 0.22 mm ID; Chrompack); conditions: pre-pressure 80 kPa, isotherm at 120°C. R_t: **3** for 14.79 min, **10** for 14.65 min, **12** for 15.06 min; **5**, **11**, **14**: column: FS-LIPODEX-E (50 m, 0.25 mm ID; Macherey–Nagel); conditions: pre-pressure 100 kPa, isotherm at 60°C. R_t: **5** for 13.10 min, **11** for 53.48 min, **14** for 27.78 min) to determine the product composition. Enantiomeric excess of **10** was determined directly by HPLC (column: Chiralcel OD (25 cm, 4.6 mm ID; Daicel Chemical Industries); conditions: flow: 1.7 ml/min; eluent: 0.7% 2-propanol and 2% *t*-butylmethylether in *n*-hexane. R_t: (*R*)-(+)-1-phenyl-1-propanol for 17.00 min, (*S*)-(−)-1-phenyl-1-propanol for 20.77 min). The enantiomeric purity of **11** was determined after derivatization by GC analysis.

*3.1.3. Procedure for derivative formation of 3-octanol **11** with anhydrolactol **15***

The crude product (about 1 mmol) was treated with excessive anhydrolactol **15** (about 5 mmol) in the presence of catalytic amounts of *p*-toluenesulfonic acid in dichloromethane for 1 h. The reaction was stopped by addition of excessive sodium hydrogen carbonate, the solids were filtered off and the solution was directly analyzed by GC (column: FS-LIPODEX-E (50 m, 0.25 mm ID; Macherey–Nagel); conditions: pre-pressure 180 kPa, isotherm at 180°C. R_t: derivative of (*R*)-(+)-3-octanol for 17.21 min, derivative of (*S*)-(−)-3-octanol for 19.10 min).

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