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Diastereoselective addition of functionalized organolithium compounds to (-)-menthone – synthesis of chiral ligands for enantioselective addition of diethylzinc to aldehydes

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Dedicated to Acad. Bogdan Kurtev on the occasion of his 100th birth anniversary

The addition of N- and S-functionalized organolithium compounds to (-)-menthone was studied and a series of new chiral substituted neomenthol derivatives has been isolated. The new chiral compounds have been applied as precatalysts for addition of diethylzinc to aldehydes and enantioselectivity of up to 80% ee was achieved.

Key words: (-)-menthone; organolithium compounds; diethylzinc; enantioselectivity

INTRODUCTION

The enantioselective addition of dialkylzinc compounds to aldehydes catalyzed by different types of chiral ligands has attracted in recent years significant interest because the resulting enantiomerically pure or enriched alcohols are important intermediates for the synthesis of bioactive compounds and natural products [1–4]. Aminoalcohols have been shown to act as highly efficient chiral ligands in this reaction and therefore a large number of aminoalcohols has been synthesized and tested as ligands [1, 2, 5–12]. One of the most potent ligand applied by Noyori as a catalyst is the dimethylamino-isoborneol Noyori prepared from camphor [13–19]. Considering the variety of the aminoalcohols synthesized so far, it is important to note that most commonly natural sources of chirality (*e.g.* terpenoids, aminoacids and alkaloids) have been used for their synthesis. The natural ketone (-)-menthone has been successfully used to prepare chiral aminoalcohols applied in the asymmetric addition of organozinc reagents to carbonyl compounds [20–26]. In our previous studies a series of aminoalcohols has been synthesized and applied as ligands through the highly diastereoselective addition of functionalized organolithium compounds to natural terpenoid ketons as chirality sources [27–30].

In this work we are describing the synthesis of set of neomenthol derivatives bearing N- and S-heteroatom functionalities, which are able to serve as chiral ligands for enantioselective addition of dialkylzinc reagents to aldehydes. The key step in the synthetic approach is the highly selective equatorial addition of N- and S-functionalized organolithium reagents to (-)-menthone leading to aminoalcohols and sulfur containing structural analogues.

EXPERIMENTAL

General

The reactions with air and moisture sensitive reagents were carried out in flame-dried Schlenk flasks under an argon atmosphere. The solvents were dried (sodium/benzophenone for ether and THF; $Na[Et_4Al]$ for toluene and hexane) and distilled under an argon atmosphere prior to use. Thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with silica gel 60 F_{254} (Merck). Flash column chromatography was carried out using silica gel 60 (230–400 mesh, Merck). Optical rotations ($[\alpha]_D^{20}$) were measured on a Perkin Elmer 241 polarimeter. The NMR spectra were recorded in $CDCl_3$ on a Bruker DRX 250 (250.13 MHz for ^{1}H NMR, 62.9 MHz for ^{13}C NMR) spectrometer with TMS as the internal standard for chemical shifts (δ, ppm). ^{1}H and ^{13}C NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration, and identification. C-multiplicities were assigned by DEPT techniques.

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EI-MS (70 eV) were recorded on a Hewlett Packard 6890/5973 and reported as fragmentation in *m/z* with relative intensities (%) in parentheses. High performance liquid chromatography (HPLC) separations were performed with an Agilent 1100 System fitted with a diode array detector and a manual injector with a 20 μL injection loop. Gas chromatography (GC) was performed with a Shimadzu GC-17A. Elemental analyses were performed by the Microanalytical Service Laboratory of the Institute of Organic Chemistry, Bulgarian Academy of Sciences.

The following starting materials were used (commercially available or prepared according to the literature): (-)-menthone, N,N-dimethylbenzylamine, N,N-dimethylaniline, TMEDA, *n*-BuLi (1.6 M or 2.5 M in hexane, *Fluka*), Et_2Zn (1 M in hexane or heptane, *Fluka*), anhydrous $CeCl_3$.

(1S,2S,5R)-2-isopropyl-5-methyl-1-(thiophen-2-yl)cyclohexan-1-ol ***7***

To a solution of thiophene (0.21 ml, 2.605 mmol) in THF (2 ml) *n*-BuLi (1.3 ml, 2.084 mmol, 1.6 M solution in hexane) was added at -10 °C under Ar atmosphere. The reaction mixture was stirred for 1 h at 20 °C and then (-)-menthone (0.3 ml, 1.74 mmol) was added. After 24 h the reaction mixture was hydrolyzed with water, extracted with Et_2O and the organic layer was dried (Na_2SO_4). After evaporation of the solvent, the crude product was chromatographed (∅ = 18 mm, *h* = 540 mm, 24 g silica gel, PE:Et_2O = 100:1). Compound **7** was isolated (0.333 g, 80%) as colorless oil. Compound **7** was additionally purified by Kugelrohr-distillation (120 °C, 0.001 Torr). $[\alpha]_D^{20}$ = -11.80 (c 1.00, $CHCl_3$). ^{1}H NMR: δ 0.71 (d, *J* = 6.8, 3H, CH_3), 0.78 (d, *J* = 6.8, 3H, CH_3), 0.80 (d, *J* = 6.1, 3H, CH_3), 1.82–1.25 (m, 8H), 1.04–0.88 (m, 1H), 1.86 (s, 1H, OH), 6.79 (dd, *J* = 3.4, 1.2, 1H, H-3'), 6.86 (dd, *J* = 5.1, 3.4, 1H, H-4'), 7.05 (dd, *J* = 5.1, 1.2, 1H, H-5'). ^{13}C NMR: 18.25 (q, CH_3), 21.14 (t, CH_2), 22.00 (q, CH_3), 23.71 (q, CH_3), 26.69 (d, CH), 28.38 (d, CH), 34.88 (t, CH_2), 51.77 (d, C-2), 52.86 (t, C-6), 78.20 (s, C-1), 121.28* (d, C-4'), 122.80* (d, C-3'), 126.68 (d, C-5'), 154.82 (s, C-2'). MS (EI): 238 (M^+, >1), 225 (13), 183 (3), 167 (3), 153 (100), 139 (5), 126 (19), 111 (23), 97 (7), 69 (11), 55 (11). Anal. Calcd for $C_{14}H_{22}OS$ (238.39): C 70.54, H 9.30, S 13.45; Found: C 70.60, H 9.29, S 13.26.

(1S,2S,5R)-2-isopropyl-5-methyl-1-(5-(trimethylsilyl)thiophen-2-yl)cyclohexan-1-ol ***8***

To a solution of trimethyl(thiophen-2-yl)silane (0.56 ml, 3.490 mmol) in THF (2 ml) *n*-BuLi (1.1 ml, 2.792 mmol, 2.5 M solution in hexane) was added at -10 °C under Ar atmosphere. The reaction mixture was stirred for 1 h at 20 °C and then (-)-menthone (0.4 ml, 2.327 mmol) was added. After 24 h the reaction mixture was hydrolyzed with water, extracted with Et_2O and the organic layer was dried (Na_2SO_4). After evaporation of the solvent, the crude product was chromatographed (∅ = 17 mm, *h* = 550 mm, 51 g silica gel, PE:Et_2O = 20:1). It were isolated 0.051 g (14%) unreacted (-)-menthone (**1**) and 0.529 g (73%) of pure product **8** as colorless oil. The product was additionally purified by Kugelrohr-distillation (120 °C, 0.001 Torr). $[\alpha]_D^{20}$ = -11.60 (c 1.00, $CHCl_3$). ^{1}H NMR: δ 0.30 (s, 9H, $Si(CH_3)_3$), 0.81 (d, *J* = 6.8 z, 3H, CH_3), 0.87 (d, *J* = 6.8, 3H, CH_3), 0.89 (d, *J* = 6.1, 3H, CH_3), 1.92–1.37 (m, 10H), 6.93* (d, *J* = 3.4, 1H, H-4'), 7.10* (d, *J* = 3.4, 1H, H-3'). ^{13}C NMR: -0.01 (3q, $Si(CH_3)_3$), 18.34 (q, CH_3), 21.20 (t, CH_2), 22.05 (q, CH_3), 23.80 (q, CH_3), 26.76 (d, CH), 28.51 (d, CH), 34.95 (t, CH_2), 51.61 (d, C-2), 53.10 (t, C-6), 78.61 (s, C-1), 122.80* (d, C-4'), 133.82* (d, C-3'), 137.43 (s, C-5'), 160.28 (s, C-2'). MS (EI): 310 (M^+, 31), 295 (18), 277 (5), 237 (4), 225 (100), 198 (29), 183 (34), 167 (3), 141 (4), 115 (4), 91 (4), 73 (23), 55 (6). Anal. Calcd for $C_{17}H_{30}OSSi$ (310.57): C 65.74, H 9.74, S 10.32, Si 9.04; Found: C 66.18, H 9.86, S 10.22, Si 9.49.

(1S,2S,5R)-1-(2-((dimethylamino)methyl)phenyl)-2-isopropyl-5-methylcyclohexan-1-ol ***9***

Procedure A: To a solution of N,N-dimethylbenzylamine (0.58 ml, 3.890 mmol) in Et_2O (15 ml) *n*-BuLi (1.24 ml, 3.112 mmol, 2.5 M solution in hexane) was added at 20 °C under Ar atmosphere. The reaction mixture was refluxed for 4.5 h. After cooling to 20 °C (-)-menthone (0.45 ml, 2.593 mmol) was added, the reaction mixture was stirred for 96 h and then was hydrolyzed with water, extracted with Et_2O, and the organic layer was dried (Na_2SO_4). After evaporation of the solvent, the crude product was chromatographed (∅ = 23 mm, *h* = 580 mm, 95g silica gel, CH_2Cl_2:CH_3OH:NH_4OH = 100:0.5:0.05). It were isolated 0.184 g (46%) unreacted (-)-menthone (**1**) and 0.160 g (21%) of pure product **9** as colorless oil. The product was purified by Kugelrohr-distillation (120 °C, 0.001 Torr).

Procedure B: To a solution of N,N-dimethylbenzylamine (0.58 ml, 3.890 mmol) in

Et_2O (17 ml) *n*-BuLi (1.24 ml, 3.112 mmol, 2.5 M solution in hexane) was added at 20 °C under Ar atmosphere. The reaction mixture was refluxed for 4.5 h. Activation of (-)-menthone (**1**) was performed separately as follows. To a suspension of anhydrous $CeCl_3$ (0.640 g, 2.593 mmol) in THF (10 ml) (-)-menthone (**1**) (0.45 ml, 2.593 mmol) was added and the mixture was stirred at room temperature until a yellow gel-like suspension was formed (40 min). The *in situ* prepared organolithium reagent **4** was added to the activated (-)-menthone and the mixture was stirred for a further 96 h at 20 °C under Ar atmosphere. The reaction mixture was hydrolyzed with saturated NH_4Cl solution, extracted with Et_2O, washed with water and the organic layer was dried (Na_2SO_4). After evaporation of the solvent, the crude product was chromatographed (∅ = 17 mm, *h* = 550 mm, 54g silica gel, CH_2Cl_2:CH_3OH:NH_4OH = 100:0.5:0.05). It was isolated 0.513 g (68%) of pure product **9** as colorless oil. The product was additionally purified by Kugelrohr-distillation (120 °C, 0.001 Torr). $[\alpha]_D^{20}$ = -3.90 (c 1.00, $CHCl_3$). ^{1}H NMR: δ 0.71 (d, *J* = 6.8, 3H, CH_3), 0.86 (d, *J* = 6.6, 3H, CH_3), 0.88 (d, *J* = 6.8, 3H, CH_3), 0.94–1.11 (m, 1H), 1.40–2.06 (m, 8H), 2.22 (2s, 6H, $(H_3C)_2N$), 3.65 (bs, 2H, H_2C-N), 7.02–7.14 (m, 2H, Ph), 7.23–7.30 (m, 2H, Ph). ^{13}C NMR: 18.40 (q, CH_3), 21.24 (t, CH_2), 22.39 (q, CH_3), 23.98 (q, CH_3), 27.34 (d, CH), 28.00 (d, CH), 35.48 (t, CH_2), 43.97 (2q, $N(CH_3)_2$), 51.42 (d, C-2), 53.18 (t, C-6), 65.46 (t, N-CH_2), 80.82 (s, C-1), 125.44 (d, Ph), 127.74 (d, Ph), 127.79 (d, Ph), 132.78 (d, Ph), 135.17 (s, C-2'), 148.71 (s, C-1'). MS (EI): 289 (M^+, 21), 274 (21), 225 (34), 204 (100), 183 (19), 159 (40), 145 (16), 119 (32), 105 (9), 91 (33), 69 (19), 58 (29), 46 (18). Anal. Calcd for $C_{19}H_{31}NO$ (289.463): C 78.84, H 10.79, N 4.84; Found: C 78.74, H 10.83, N, 4.68.

(1S,2S,5R)-1-(2-((dimethylamino)methyl)-3-(trimethylsilyl)phenyl)-2-isopropyl-5-methylcyclohexan-1-ol ***10***

To a solution of N,N-dimethyl-1-(2-trimethylsilyl)phenyl)methanamine (0.807 g, 3.890 mmol) in Et_2O (18 ml) *n*-BuLi (1.24 ml, 3.112 mmol, 2.5 M solution in hexane) was added at 20 °C under Ar atmosphere. The reaction mixture was refluxed for 4.5 h. After cooling to 20 °C (-)-menthone (0.45 ml, 2.593 mmol) was added. After 48 h the reaction mixture was hydrolyzed with water, extracted with Et_2O and the organic layer was dried (Na_2SO_4). After evaporation of the solvent, the crude product was chromatographed (∅ = 24 mm, *h* = 520 mm, 85g silica gel, CH_2Cl_2:CH_3OH:NH_4OH = 100:0.5:0.05). It were isolated 0.170 g (43%) unreacted (-)-menthone (**1**) and 0.426 g (45%) of pure product **10** as colorless oil. The product was purified by Kugelrohr-distillation (50–120 °C, 0.001 Torr). $[\alpha]_D^{20}$ = +7.30 (c 1.00, $CHCl_3$). ^{1}H NMR: δ 0.35 (s, 9H, $(H_3C)_3Si$), 0.71 (d, *J* = 7.1, 3H, CH_3), 0.85 (d, *J* = 6.4, 3H, CH_3), 0.86 (d, *J* = 6.8, 3H, CH_3), 0.90–1.00 (m, 1H), 1.40–2.10 (m, 8H), 2.22 (s, 6H, $(H_3C)_2N$), 3.88 (d, *J* = 12.2, 1H, HC-N), 3.96 (d, *J* = 12.2, 1H, HC-N), 7.18–7.25 (m, 1H, Ph), 7.31–7.38 (m, 2H, Ph), 8.57 (br s, 1H, OH). ^{13}C NMR: 2.01 (3q, $Si(CH_3)_3$), 18.45 (q, CH_3), 21.42 (t, CH_2), 22.46 (q, CH_3), 24.03 (q, CH_3), 27.45 (d, CH), 28.14 (d, CH), 35.58 (t, CH_2), 43.35 (2q, $(N(CH_3)_2)$, 51.63 (d, C-2), 53.38 (t, C-6), 63.18 (t, N-CH_2), 81.05 (s, C-1), 126.60 (d, Ph), 129.58 (d, Ph), 132.52 (d, Ph), 140.87* (s, C-3'), 141.45* (s, C-2'), 148.66 (s, C-1'). MS (EI): 361 (M^+, 24), 346 (31), 318 (10), 304 (26), 276 (100), 243 (13), 231 (21), 206 (17), 191 (35), 147 (9), 73 (50), 58 (20), 46 (10). Anal. Calcd for $C_{22}H_{39}NOSi$ (361.645): C 73.07, H 10.87, N 3.87, Si 7.77; Found: C 72.96, H 11.07, N 3.65, Si 7.92.

(1S,2S,5R)-1-(2-(dimethylamino)phenyl)-2-isopropyl-5-methylcyclohexan-1-ol ***11***

Procedure A: To a solution of *n*-BuLi (1.55 ml, 3.889 mmol, 2.5 M solution in hexane) TMEDA (0.58 ml, 3.889 mmol) was added in one portion at 0 °C under Ar atmosphere. The reaction mixture was stirred for 30 min at 20 °C and then N,N-dimethylaniline (0.62 ml, 4.862 mmol) was added. The reaction mixture was refluxed for 4.5 h. After cooling to 0 °C (-)-menthone (**1**) (0.56 ml, 3.241 mmol) was added, the reaction mixture was stirred at 20 °C for 96 h and it was hydrolyzed with water, extracted with Et_2O, and dried (Na_2SO_4). After evaporation of the solvent, the crude product was chromatographed (∅ = 30 mm, *h* = 577 mm, 80 g silica gel, petroleum ether/Et_2O = 100:1). It were isolated 0.142 g (28%) unreacted (-)-menthone and 0.262 g (29%) of pure product **11** as colorless crystals. Mp 117–118 °C (methanol). $[\alpha]_D^{20}$ = -19.70 (c 1.00, $CHCl_3$).

Procedure B: To a solution of *n*-BuLi (1.55 ml, 3.889 mmol, 2.5 M solution in hexane) TMEDA (0.58 ml, 3.889 mmol) was added in one portion at 0 °C under Ar atmosphere. The reaction mixture was stirred for 30 min at 20 °C and then N,N-

dimethylaniline (0.62 ml, 4.862 mmol) was added and it was refluxed for 4.5 h. Activation of the (-)-menthone (**1**) was performed separately as follows. To a suspension of anhydrous $CeCl_3$ (0.800 g, 3.241 mmol) in THF (10 ml) (-)- menthone (**1**) (0.56 ml, 3.241 mmol) was added and the reaction mixture was stirred at room temperature until a yellow gel-like suspension was formed (40 min). The *in situ* prepared organolithium reagent **6** was added to the activated (-)-menthone and the mixture was stirred for further 96 h at 20 °C under Ar atmosphere. It was hydrolyzed with saturated NH_4Cl solution, extracted with Et_2O, washed with water and the organic layer was dried (Na_2SO_4). After evaporation of the solvent, the crude product was chromatographed (∅ = 30 mm, *h* = 577 mm, 57g silica gel, petroleum ether/Et_2O = 100:1; 20:1; 5:1). It were isolated 0.009 g (2%) unreacted (-)-menthone and 0.315 g (35%) pure product as colorless crystals. Mp 117–118 °C (methanol). $[\alpha]_D^{20}$ = -19.70 (c 1.00, $CHCl_3$). ^{1}H NMR: δ 0.73 (d, *J* = 7.1, 3H, CH_3), 0.88 (d, *J* = 6.6, 3H, CH_3), 0.86–1.05 (m, 1H), 0.91 (d, *J* = 7.1, 3H, CH_3), 1.45–2.08 (m, 8H), 2.67 (s, 3H, H_3C-N), 2.68 (s, 3H, H_3C-N), 7.14–7.36 (m, 4H, Ph), 10.40 (s, 1H, OH). ^{13}C NMR: 18.40 (q, CH_3), 21.14 (t, CH_2), 22.44 (q, CH_3), 23.79 (q, CH_3), 27.58 (d, CH), 28.16 (d, CH), 35.50 (t, CH_2), 45.84 (q, N-CH_3), 46.89 (q, N-CH_3), 50.96 (d, C-2), 53.54 (t, C-6), 81.15 (s, C-1), 123.31 (d, Ph), 126.20 (d, Ph), 127.12 (d, Ph), 127.37 (d, Ph), 142.63 (s, C-1'), 151.74 (s, C-2'). MS (EI): 275 (M^+, 31), 260 (17), 232 (8), 214 (30), 204 (5), 190 (100), 160 (9), 148 (87), 134 (18), 120 (22), 106 (10), 91 (11), 77 (13), 55 (13). Anal.calcd for $C_{18}H_{29}NO$ (275.436): C 78.49, H 10.61, N, 5.09; Found: C 78.26, H 10.76, N, 4.99.

General procedure for enantioselective addition of diethylzinc to aldehydes

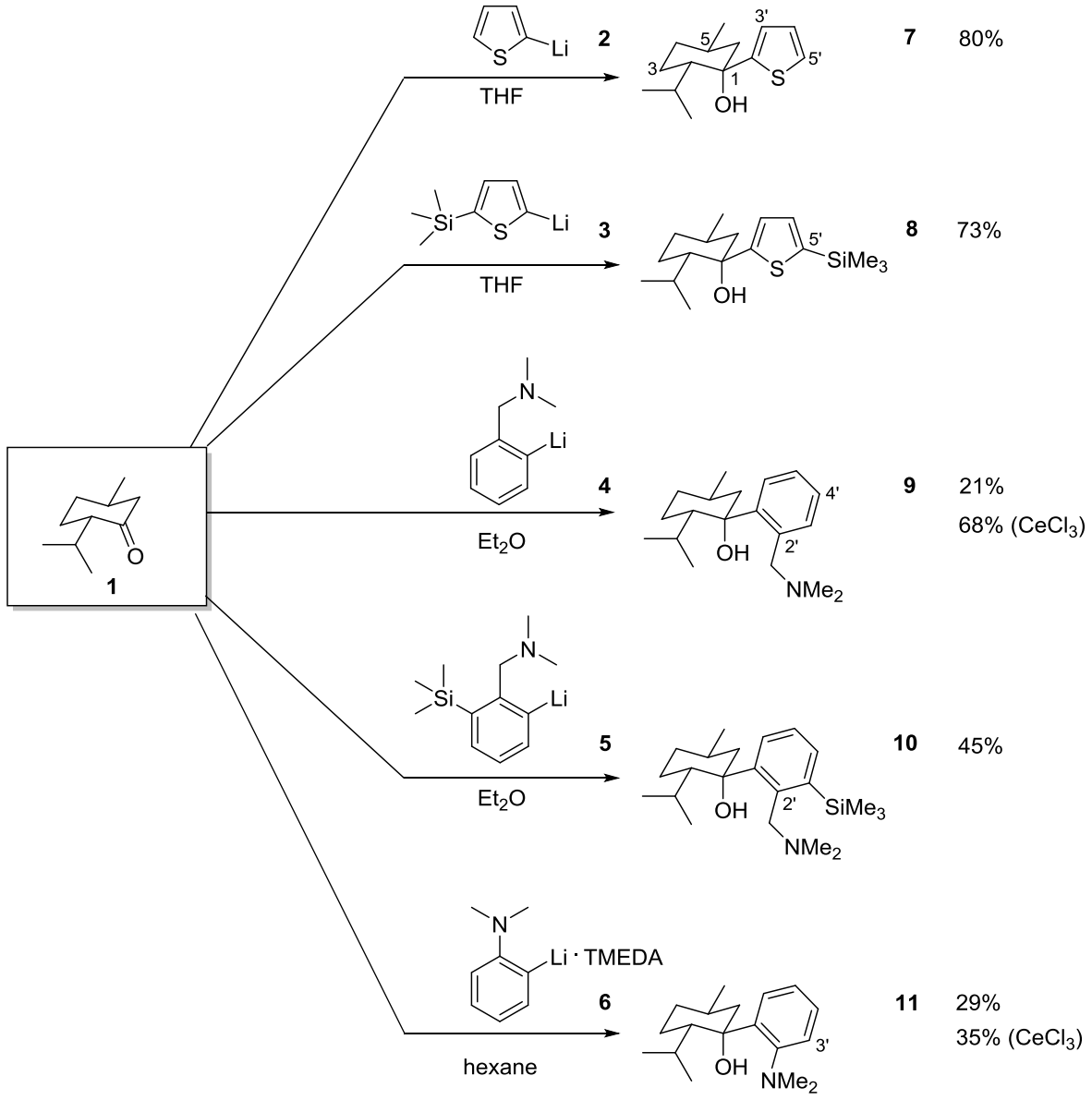
To a solution of the corresponding ligand **7**–**11** (3 mol %) in hexane or toluene (10 ml) Et_2Zn (1.7 mmol, 1 M solution in hexane) was added dropwise at 0 °C under Ar atmosphere. The mixture was stirred for 30 min at 0 °C and then the corresponding aldehyde (1 mmol) was added at -20 °C. The reaction mixture was stirred at the appropriate temperature (see Table 1) and monitored by TLC (petroleum ether/Et_2O = 4:1) until the aldehyde was consumed or no further consumption was observed. The mixture was quenched (aq. NH_4Cl), extracted with Et_2O and dried (Na_2SO_4). After evaporation of the solvent, the crude product was purified by column chromatography (petroleum ether/Et_2O = 20:1 or 10:1).

RESULTS AND DISCUSSION

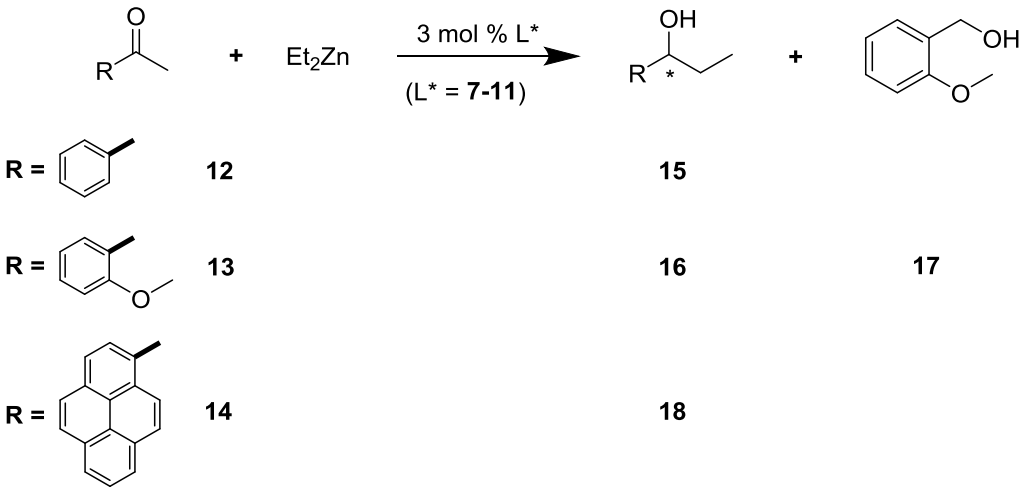
For the synthesis of neomenthol derivatives bearing N- and S-heteroatom functionalities, a set of lithium reagents was selected, which are based on the thiophene and amino-substituted phenyl moieties. The addition of the lithium reagents **2**–**6** (Scheme 1) was performed according previous experience [31]. The reagents **2** and **3** were chosen with the purpose to synthesize sulfur analogues of aminoalcohols, in which the bulky trimethylsilyl-group modifies in the case of **3** the stereochemical environment next to the sulfur coordinating center. With the reagents **4** and **5** was aimed to prepare δ-aminoalcohols, which incorporate the aromatic phenyl group in the side chain and in addition to study the sterical influence of the trimethylsilyl-group as in the case of **5**. The reagent **6** possess the dimethylamino group directly attached to the aromatic moiety and was planned to provide for comparison γ-aminoalcohol after the addition to (-)-menthone.

The addition of *in situ* generated thiophen-2-yl-lithium (**2**) [32] to (-)-menthone occurred readily at room temperature in THF as a solvent and the thiophene substituted neomenthyl derivative was isolated in excellent yield (80%) after purification by column chromatography. The analogous 5-trimethylsilyl-thiophen-2-yl-lithium (**3**) [32] was reacted with (-)-menthone under the same conditions as in the above case providing after hydrolytic work up and column chromatography product **8** in 73% yield and 14% unreacted menthone.

The formation of reagent **4** from N,N-dimethylbenzylamine with *n*-BuLi is known to proceed in THF *in situ* highly efficient [33]. Menthone was added to the generated solution of **4** and the mixture was stirred for 4 days at room temperature, monitored by TLC. The reaction was slow and incomplete. After hydrolytic work up and column chromatography the desired δ-aminoalcohol **9** was isolated in low yield (21%) together with 46% unreacted (-)-menthone. With the purpose to realize higher yield the own procedure [34–36] for activation of the ketone with anhydrous $CeCl_3$ in THF was applied. The addition of reagent **4** to the activated (-)-menthone occurred in this case in 68% yield (19% unreacted menthone was also recovered).



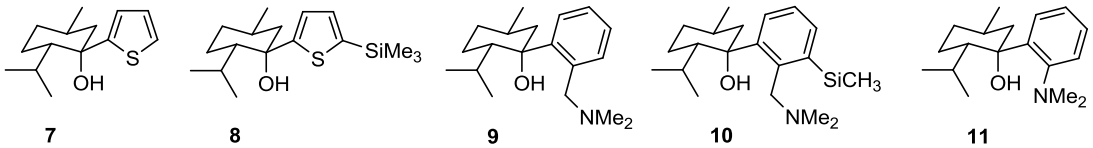
Scheme 1 Addition of organolithium reagents to (-)-mentone (**1**).



Scheme 2. Enantioselective addition of diethylzinc to the aldehydes **12, 13** and **14** catalyzed by chiral ligands **7**–**11**.

Table 1. Enantioselective addition of Et_2Zn to the aldehydes **12, 13** and **14** catalyzed by chiral ligands (L*) **7**–**11**.

Ligands L*:



7 **8** **9** **10** **11**

№	Ligand	Aldehyde	Solvent	Reaction time [h]	Reaction temp. [°C]	Yield[a] [%]	ee[b] [%]	Yield[a] 17 [%]
1	**7**	**12**	Hexane	168	20	70 (**15**)	0	-
2	**8**	**12**	Hexane	216	20	18 (**15**)	0	-
3	**9**	**12**	Hexane	45	20	92 (**15**)	66 (*S*)	-
4	**9**	**12**	Toluene	5	20	73 (**15**)	68 (*S*)	-
5	**9**	**12**	Toluene	5	60	83 (**15**)	58 (*S*)	-
6	**9**	**12**	Toluene	2	100	71 (**15**)	42 (*S*)	-
7	**10**	**12**	Hexane	24	20	83 (**15**)	18 (*S*)	-
8	**11**	**12**	Hexane	24	20	83 (**15**)	60 (*S*)	-
9	**11**	**12**	Toluene	5	20	68 (**15**)	80 (*S*)	-
10	**11**	**12**	Toluene	5	60	66 (**15**)	74 (*S*)	-
11	**11**	**12**	Toluene	5	100	64 (**15**)	66 (*S*)	-
12	**7**	**13**	Hexane	240	20	6 (**16**)	0	24
13	**7**	**13**	Toluene	72	20	73 (**16**)	0	9
14	**8**	**13**	Hexane	240	20	6 (**16**)	0	28
15	**8**	**13**	Toluene	48	20	62 (**16**)	0	6
16	**9**	**13**	Hexane	216	20	5 (**16**)	28 (*S*)	32
17	**9**	**13**	Toluene	48	20	81 (**16**)	46 (*S*)	4
18	**9**	**13**	Toluene	4	60	74 (**16**)	56 (*S*)	6
19	**9**	**13**	Toluene	2	100	75 (**16**)	38 (*S*)	10
20	**10**	**13**	Hexane	24	20	83 (**16**)	26 (*S*)	2
21	**11**	**13**	Hexane	24	20	82 (**16**)	54 (*S*)	5
22	**11**	**13**	Toluene	5	20	61 (**16**)	74 (*S*)	-
23	**11**	**13**	Toluene	3	60	69 (**16**)	62 (*S*)	7
24	**11**	**13**	Toluene	2	100	71 (**16**)	45 (*S*)	15
25	**9**	**14**	Hexane	24	20	84 (**18**)	68[c]	-
26	**9**	**14**	Toluene	6	60	68 (**18**)	52[c]	-
27	**11**	**14**	Hexane	24	20	74 (**18**)	60[c]	-
28	**11**	**14**	Toluene	4	60	60 (**18**)	64[c]	-

[a]Yields are given after column chromatography. [b]Enantiomeric excess of **15** determined by GC analysis (Hydrodex-β-TBDAc column, 122 ºC isothermal, 1 ml/min He, split 21, T_{det} = 230 °C, T_{inj} = 220 °C); retention times: t_{minor} (*R*) = 9.4 min and t_{major} (*S*) = 9.8 min; enantiomeric excess of **16** determined by HPLC with chiral column (Nucleodex β PM column, 0.8 ml/min, acetonitrile/water = 20:80 to acetonitrile/water = 43:57, for 17 min; 205 nm DAD detector); retention times: t_{major} = 11.3 min and t_{minor} = 12 min. [c]Optical purity determined by polarimetry based on the maximum values for the specific rotations of the corresponding enantiomer for **18** $[\alpha]_D^{20}$ = -60.1 (c 0.72, $CHCl_3$) for 95% ee of unknown configuration [38].

The trimethylsilyl-substituted lithium reagent **5** was formed and applied using the same conditions as in the case of reagent **4**. The δ-aminoalcohol **10** was isolated in 45% yield after chromatography purification. This yield was sufficient to obtain enough quantity for the further experiment and therefore it was abandoned to perform further optimization. For the synthesis of γ-aminoalcohol **11** the formation of lithium reagent **6** was performed from N,N-dimethylaniline and *n*-

BuLi·TMEDA in THF, refluxing the mixture within 4.5 h [32]. The addition of **6** to (-)-menthone occurred in low yield (29%) by using the standard conditions. After activation of the ketone with anhydrous $CeCl_3$ in THF the yield could be enhanced to 35%.

The newly synthesized aminoalcohols and sulfur containing analogues **7**–**11** were applied as ligands, in catalytic quantities (3 mol%), for enantioselective addition of diethylzinc (Scheme 2) to benzaldehyde (**12**), *o*-methoxybenzaldehyde (**13**) and pyrencarbaldehyde (**14**). In almost all cases the ligands studied were active catalysts that provide the additional reaction in good to high yields (Table 1). The sulfur containing ligands **7** and **8** were poor catalysts in respect of both providing chemical yields and enantioselectivity, although the reaction with benzaldehyde (in the case of **7**) realized acceptable yields (entries 1 *vs.* 12 and 14). Similar results were obtained with ligand **9** for the addition of Et_2Zn to aldehyde **13** in hexane as solvent (entry 16). Changing the solvent from hexane to toluene improved significantly the addition of Et_2Zn to *o*-methoxybenzaldehyde (**13**) in the case of ligand **9** (entries 16, 17), but also in the case of ligands **7** and **8** (entries 12, 13 and 14, 15). It should be pointed out that in the course of the Et_2Zn addition to *o*-methoxybenzaldehyde a competing reduction reaction takes place with formation of product **17**. This reaction may occur if prolonged reaction times are applied [14, 37] and in the case of aldehyde **13** the coordinating ability of the methoxy group provides favourable conditions. In most other cases suitable conditions have been optimized to obtain the corresponding secondary alcohols **15, 16** and **18** in good yields.

In respect of the enantioselectivity in general the best results were obtained with ligand **11**, considering the additions to aldehydes **12**–**14** – enantioselectivities between 45 and 80% ee. Ligand **9** provided acceptable degree of enantioselectivity compared with the poor result of **10** bearing the bulky trimethylsilyl group. It is interesting to note that increasing the reaction temperature from 20 °C to 60 °C and 100 °C brought shortening of the reaction time, but in general moderate change of yields and lowering of the enantioselectivity. In all studied cases the configuration of the predominant enantiomer of **15, 16** and **18** was *S*.

CONCLUSION

A series of aminoalcohols and sulfur containing analogues has been synthesized by addition of functionalized organolithium compounds to (-)-menthone. The new chiral compounds have been applied as precatalysts in the enantioselective addition of diethylzinc to aldehydes. Moderate enantioselectivity was observed and in some cases acceptable degrees of enantioselectivity could be achieved (up to 80% ee).

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ДИАСТЕРЕОСЕЛЕКТИВНО ПРИСЪЕДИНЯВАНЕ НА ФУНКЦИОНАЛИЗИРАНИ ОРГАНОЛИТИЕВИ СЪЕДИНЕНИЯ КЪМ (-)-МЕНТОН – СИНТЕЗ НА ХИРАЛНИ ЛИГАНДИ ЗА ЕНАНТИОСЕЛЕКТИВНО ПРИСЪЕДИНЯВАНЕ НА ДИЕТИЛЦИНК КЪМ АЛДЕХИДИ

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(Резюме)

Изучено е присъединяването на N- и S-функционализирани органолитиеви съединения към (-)-ментон и е синтезирана серия от хирални заместени неоментолови производни. Новите хирални съединения са приложени като пре-катализатори за присъединяване на диетилцинк към алдехиди и е постигната енантиоселективност до 80% ее.