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Three component condensation of a Betti-type – efficient tool for synthesis of chiral naphthoxazines and aminobenzylnaphthols for enantioselective diethylzinc addition to aldehydes

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2-Naphthol, formaldehyde and chiral amines have been applied in three component Betti-type condensation to provide chiral 1,3-naphthoxazines in excellent yields. The latter have been easily transformed to chiral N-methyl aminobenzylnaphthols through reaction with lithium aluminum hydride. The chiral aminobenzylnaphthols are active catalyst (ligands) for enantioselective diethylzinc addition to aldehydes providing secondary alcohols in good yields only up to a moderate degree of enantioselectivity.

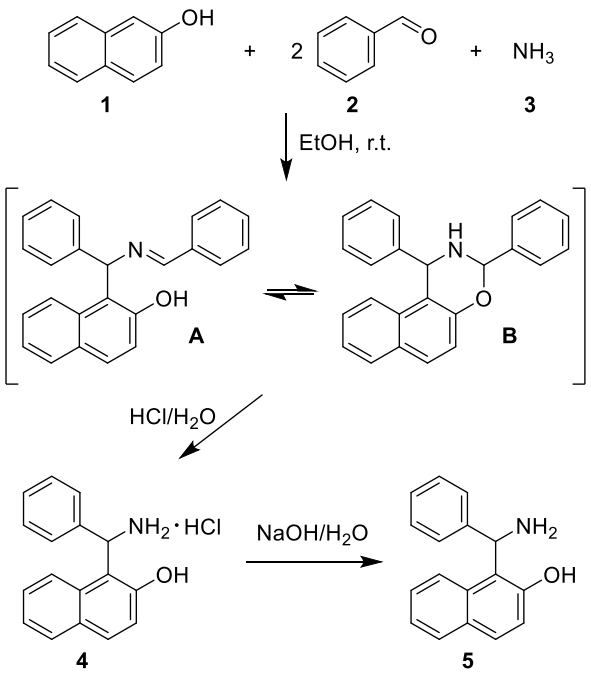
Keywords: oxazines, aminobenzylnaphthols, diethylzinc, enantioselectivity

INTRODUCTION

The three component condensation of 2-naphthol (**1**), benzaldehyde (**2**) and ammonia (**3**) was first realized by Mario Betti [1] and has been forgotten for a long time until the finding in recent years that the replacement of the ammonia used with chiral amines leads to a very potent approach for the synthesis of chiral aminobenzylnaphthols (Scheme 1). This relatively simple reaction, often referred to as modified Mannich condensation, forms in a first step equilibrating mixture of an imine **A** and 1,3-naphthoxazine **B**. Upon treatment with hydrochloric acid the aminonaphthol salt **4** is formed which treatment with sodium hydroxide then leads to aminonaphthol **5** (the so called "Betti base"). In recent years there is a growing interest in the synthesis of "Betti bases" due to the application of chiral analogues in asymmetric synthesis [2, 3]. The scope of the current knowledge about the synthesis and application of aminobenzylnaphthols of type "Betti base" has recently been demonstrated in review articles [4-6]. The most important achievement in the recent history of the "Betti bases" is the condensation of enantiopure amines with 2-naphthol and aldehydes leading to aminobenzylnaphthols of type **5** (Scheme 1) formed in high to excellent diastereoselectivity [7-10]. The aminonaphthols of type **5** form readily 1,3-oxazines with aldehydes, including formaldehyde [11-13].

Surprisingly, little attention has been directed to the condensation of 2-naphthol, formaldehyde and amines for the synthesis of 1,3-naphthoxazines [14-16]. There is only one report describing the synthesis of enantiopure 1,3-naphthoxazine by using formaldehyde and chiral amine [17].

The aim of the current work is the realization of three component condensation of 2-naphthol, formaldehyde and chiral amines with the purpose of using the targeted 1,3-naphthoxazines for further transformations to chiral aminobenzylnaphthols. The latter compounds can be applied as precatalysts in the enantioselective addition of diethylzinc to aldehydes.



Scheme 1. Condensation of 2-naphthol, benzaldehyde and ammonia (Betti condensation).

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EXPERIMENTAL

General

The reagents were commercial grade and used without further purification. 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 on a Bruker Avance II+ 600 spectrometer (600.13 MHz for ^{1}H, 150.92 MHz for ^{13}C NMR) in $CDCl_3$ 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. The assignment of the ^{1}H and ^{13}C NMR spectra was made on the basis of DEPT, COSY, HSQC, HMBC and NOESY experiments. All assignments marked with an asterisk are tentative. Mass spectra (MS) were recorded on a Thermo Scientific High Resolution Magnetic Sector MS DFS by electrospray ionization (ESI) and are reported as fragmentation in *m/z* with relative intensities (%) in parentheses. Gas chromatography (GC) was performed with a Shimadzu GC-17A. Elemental analyses were performed at the Microanalytical Service Laboratory of the Institute of Organic Chemistry, Bulgarian Academy of Sciences.

*(S)-2-(1-phenylethyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine **11***

To a mixture of 2-naphthol (**1**) (0.100 g, 0.694 mmol) and *S*-(-)-1-phenylethylamine (**6**) (0.088 g, 0.728 mmol) in EtOH (3 ml) 37% aq solution of formaldehyde (calculated to provide 3 equiv of formaldehyde) was added. The mixture was stirred at 50°C for 2h. After evaporation of the solvent, the crude product was chromatographed (petroleum ether/MTBE = 20:1) to give 0.192 g (96%) of **11**. $[\alpha]_D^{20}$ = +66 (c 1.04, $CHCl_3$). ^{1}H NMR: δ 1.50 (d, $J_{H,H}$ = 6.6 Hz, 3H, H-14), 4.04 (q, $J_{H,H}$ = 6.6 Hz, 1H, H-13), 4.17 (d, $J_{H,H}$ = 16.7 Hz, 1H, H-11), 4.41 (d, $J_{H,H}$ = 16.8 Hz, 1H, H-11), 4.92 (d, $J_{H,H}$ = 10.1 Hz, 1H, H-21), 5.17 (dd, $J_{H,H}$ = 10.1, 1.0 Hz, 1H, H-21), 7.05 (d, $J_{H,H}$ = 8.9 Hz, 1H, H-3), 7.25-7.29 (m, 1H, H-18), 7.30-7.37 (m, 5H, H-16, H-17, H-7, H-19, H-20), 7.38-7.42 (m, 1H, H-8), 7.46 (d, $J_{H,H}$ = 8.4 Hz, 1H, H-9), 7.64 (d, $J_{H,H}$ = 8.9 Hz, 1H, H-4), 7.76 (d, $J_{H,H}$ = 8.1 Hz, 1H, H-6) ppm. ^{13}C NMR: δ 21.62 (q, C-14), 46.12 (t, C-11), 58.21 (d, C-13), 79.91 (t, C-21), 112.14 (s, C-1), 118.48 (d, C-3), 121.03 (d, C-9), 123.34 (d, C-7), 126.39 (d, C-8), 127.23 (d, C-18), 127.30 (2d, C-16, C-20), 127.85 (d, C-4), 128.53 (2d, C-17, C-19), 128.57 (d, C-6), 128.90 (s, C-5), 131.82 (s, C-10), 144.70 (s, C-15), 152.55 (s, C-2) ppm. MS (ESI) *m/z* (rel int.) = 290 (100, $[M+H]^+$), 157 (17), 152 (10), 128 (30), 104 (40). Anal. Calcd for $C_{20}H_{19}NO$ (289.37): C 83.01, H 6.62, N 4.84; Found: C 83.24, H 6.54, N, 4.71.

*(S)-2-(1,2,3,4-tetrahydronaphthalen-1-yl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine **12***

To a mixture of 2-naphthol (**1**) (0.100 g, 0.694 mmol) and *S*-(+)-1,2,3,4-tetrahydro-1-naphthylamine (**7**) (0.107 g, 0.728 mmol) in EtOH (3 ml) 37% aq solution of formaldehyde (calculated to provide 3 equiv of formaldehyde) was added. The mixture was stirred at 50°C for 2h. After evaporation of the solvent, the crude product was chromatographed (petroleum ether/MTBE = 10:1) to give 0.209 g (95%) of **12**. $[\alpha]_D^{20}$ = +34.4 (c 0.975, $CHCl_3$). ^{1}H NMR: δ 1.63-1.73 (m, 2H, H-14, H-15), 1.87 (m, 1H, H-15), 2.07 (dt, $J_{H,H}$ = 11.4, 5.6, 1H, H-14), 2.65-2.78 (m, 2H, H-16), 4.12 (d, $J_{H,H}$ = 17.0 Hz, 1H, H-11), 4.28 (dd, $J_{H,H}$ = 8.8, 4.90, Hz, 1H, H-13), 4.38 (d, $J_{H,H}$ = 17.0 Hz, 1H, H-11), 5.05 (dd, $J_{H,H}$ = 10.0, 1.35, Hz, 1H, H-23), 5.14 (d, $J_{H,H}$ = 10.0 Hz, 1H, H-23), 7.04 (d, $J_{H,H}$ = 8.88 Hz, 1H, H-3), 7.07-7.11 (m, 1H, H-18), 7.16-7.22 (m, 2H, H-19, H-20), 7.30-7.35 (m, 1H, H-7), 7.39-7.43 (m, 1H, H-8), 7.53 (d, $J_{H,H}$ = 8.40 Hz, 1H, H-9), 7.63 (d, $J_{H,H}$ = 8.89 Hz, 1H, H-4), 7.66-7.69 (m, 1H, H-21), 7.75 (d, $J_{H,H}$ = 8.04 Hz, 1H, H-6) ppm. ^{13}C NMR: δ 21.25 (t, C-15), 27.91 (t, C-14), 29.19 (t, C-16), 43.58 (t, C-11), 62.64 (d, C-13), 82.35 (t, C-23), 114.38 (s, C-1), 118.99 (d, C-3), 121.14 (d, C-9), 123.32 (d, C-7), 125.81 (d, C-20), 126.33 (d, C-8), 126.80 (d, C-19), 127.66 (d, C-4), 128.39 (d, C-21), 128.54 (d, C-6), 128.74 (s, C-5), 129.10 (d, C-18), 131.16 (s, C-10), 137.48 (s, C-22), 138.44 (s, C-17), 152.96 (s, C-2) ppm. MS (ESI) *m/z* (rel int.) = 316 (100, $[M+H]^+$), 186.4(15), 157.4 (17), 131.1 (33). Anal. Calcd for $C_{22}H_{21}NO$ (315.41): C 83.78, H 6.71, N, 4.44; Found: C 83.82, H 6.82, N, 4.52.

*(S)-2-(1-(naphthalen-1-yl)ethyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine **13***

To a mixture of 2-naphthol (**1**) (0.200 g, 1.387 mmol) and *S*-(-)-1-(1-naphthyl)-ethylamine (**8**) (0.249 g, 1.456 mmol) in EtOH (3 ml) paraformaldehyde (0.104 g) was added. The mixture was stirred at 50°C for 4h. After evaporation of the solvent, the crude product was chromatographed (petroleum ether/MTBE = 10:1)

to give 0.461 g (98%) of **13**. $[\alpha]_D^{20}$ = + 104 (c 1.00, $CHCl_3$). ^{1}H NMR: δ 1.64 (d, $J_{H,H}$ = 6.7 Hz, 3H, H-14), 4.18 (d, $J_{H,H}$ = 16.9 Hz, 1H, H-11), 4.52 (d, $J_{H,H}$ = 16.9 Hz, 1H, H-11), 4.86 (q, $J_{H,H}$ = 6.6, Hz, 1H, H-13), 5.02 (d, $J_{H,H}$ = 10.2 Hz, 1H, H-25), 5.26 (dd, $J_{H,H}$ = 10.2, 1.4 Hz, 1H, H-25), 7.08 (d, $J_{H,H}$ = 8.9 Hz, 1H, H-3), 7.28-7.31 (m, 1H, H-7), 7.32-7.35 (m, 1H, H-8), 7.37-7.41 (m, 2H, H-9, H-19), 7.42-7.45 (m, 1H, H-18), 7.46-7.50 (m, 1H, H-23), 7.66 (d, $J_{H,H}$ = 8.9 Hz, 1H, H-4), 7.72-7.76 (m, 2H, H-6, H-24), 7.78 (d, $J_{H,H}$ =8.17 Hz, 1H, H-22), 7.86 (d, $J_{H,H}$ = 8.04 Hz, 1H, H-17), 8.17 (d, $J_{H,H}$ = 7.58 Hz, 1H, H-20) ppm. ^{13}C NMR: δ 20.69 (q, C-14, CH_3), 46.42 (t, C-11), 55.18 (d, C-13), 80.03 (t, C-25), 112.46 (s, C-1), 118.57 (d, C-3), 121.09 (d, C-9), 123.33 (d, C-7), 123.69 (d, C-20), 124.62 (d, C-24), 125.39 (d, C-18), 125.63 (d, C-23), 125.72 (d, C-19), 126.33 (d, C-8), 127.69 (d, C-22), 127.83 (d, C-4), 128.53 (d, C-6), 128.81 (d, C-17), 128.91 (s, C-5), 131.33 (s, C-16), 131.82 (s, C-10), 134.08 (s, C-21), 140.14 (s, C-15), 152.70 (s, C-2) ppm. MS (ESI) *m/z* (rel int.) = 340 (100, $[M+H]^+$), 155 (73). Anal. Calcd for $C_{24}H_{21}NO$ (339.43): C 84.92, H 6.24, N, 4.13; Found: C 85.19, H 6.17, N, 4.09.

*(S)-2-(1-(naphthalen-2-yl)ethyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine **14***

To a mixture of 2-naphthol (**1**) (0.200 g, 1.387 mmol) and *S*-(-)-1-(2-naphthyl)-ethylamine (**9**) (0.249 g, 1.456 mmol) in EtOH (3 ml) paraformaldehyde (0.104 g) was added. The mixture was stirred at 50°C for 3h. After evaporation of the solvent, the crude product was chromatographed (petroleum ether/MTBE = 10:1) to give 0.466 g (99%) of **14**. $[\alpha]_D^{20}$ = +25.6 (c 1.02, $CHCl_3$). ^{1}H NMR: δ 1.57 (d, $J_{H,H}$ = 6.6 Hz, 3H, H-14), 4.16-4.23 (m, 2H, H-11, H-13), 4.44 (d, $J_{H,H}$ = 16.9 Hz, 1H, H-11), 4.98 (d, $J_{H,H}$ = 10.1 Hz, 1H, H-25), 5.23 (dd, $J_{H,H}$ = 10.1, 1.30, Hz, 1H, H-25), 7.07 (d, $J_{H,H}$ = 8.9 Hz, 1H, H-3), 7.31 (ddd, $J_{H,H}$ = 10.2, 5.7, 2.4, Hz, 1H, H-7), 7.35 (ddd, $J_{H,H}$ = 8.3, 6.8, 1.4, Hz, 1H, H-8), 7.42 (d, $J_{H,H}$ = 8.3 Hz, 1H, H-9), 7.44-7.48 (m, 2H, H-19, H-20), 7.56 (dd, $J_{H,H}$ = 8.5, 1.64, Hz, 1H, H-24), 7.66 (d, $J_{H,H}$ = 8.9 Hz, 1H, H-4), 7.73-7.79 (m, 3H, H-6, H-16, H-18), 7.82-7.86 (m, 2H, H-23, H-21) ppm. ^{13}C NMR: δ 21.62 (q, C-14), 46.21 (t, C-11), 58.33 (d, C-13), 79.89 (t, C-25), 112.18 (s, C-1), 118.51 (d, C-3), 121.09 (d, C-9), 123.36 (d, C-7), 125.44 (d, C-24), 125.64* (d, C-19), 125.94* (d, C-20), 125.99* (d, C-16), 126.41 (d, C-8), 127.63* (d, C-18), 127.83 (d, C-4), 127.86* (d, C-21), 128.36* (d, C-23), 128.55 (d, C-6), 128.91 (s, C-5), 131.84 (s, C-10), 132.91 (s, C-22), 133.41 (s, C-17), 142.28 (s, C-15) 152.61 (s, C-2) ppm. MS (ESI) *m/z* (rel int.) = 340 (100, $[M+H]^+$), 155 (40). Anal. Calcd for $C_{24}H_{21}NO$ (339.43): C 84.92, H 6.24, N 4.13; Found: C 85.19, H 6.18, N, 4.05.

*(S)-2-(3,3-dimethylbutan-2-yl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine **15***

To a mixture of 2-naphthol (**1**) (0.200 g, 1.387 mmol) and *S*-(+)-3,3-dimethyl-2-butylamine (**10**) (0.147 g, 1.456 mmol) in EtOH (3 ml) paraformaldehyde (0.104 g) was added. The mixture was stirred at 50°C for 4h. After evaporation of the solvent, the crude product was chromatographed (petroleum ether/MTBE = 10:1) to give 0.329 g (88%) of **15**. $[\alpha]_D^{20}$ = –109.1 (c 1.00, $CHCl_3$). ^{1}H NMR: δ 0.95 (s, 9H, H-16, H-17, H-18), 1.00 (d, $J_{H,H}$ = 7.1 Hz, 3H, H-14), 2.81 (q, $J_{H,H}$ = 7.1 Hz, 1H, H-13), 4.29 (d, $J_{H,H}$ = 17.0 Hz, 1H, H-11), 4.40 (d, $J_{H,H}$ = 17.0 Hz, 1H, H-11), 4.91 (dd, $J_{H,H}$ = 10.0, 1.52 Hz, 1H, H-19), 5.02 (d, $J_{H,H}$ = 10.0 Hz, 1H, H-19), 7.00 (d, $J_{H,H}$ = 8.9 Hz, 1H, H-3), 7.31-7.36 (m, 1H, H-7), 7.46 (ddd, $J_{H,H}$ = 8.3, 6.9, 1.3 Hz, 1H, H-8), 7.62 (d, $J_{H,H}$ = 7.9 Hz, 1H, H-6), 7.61 (d, $J_{H,H}$ = 8.6 Hz, 1H, H-4), 7.75 (d, $J_{H,H}$ = 8.2 Hz 1H, H-9) ppm. ^{13}C NMR: δ 12.78 (q, C-14), 26.69 (3q, C-16, C-17, C-18), 36.59 (s, C-15), 45.61 (t, C-11), 67.25 (d, C-13), 84.83 (t, C-19), 114.96 (s, C-1), 119.07 (d, C-3), 120.88 (d, C-6), 123.22 (d, C-7), 126.33 (d, C-8), 127.56 (d, C-4), 128.59 (d, C-9), 128.67 (s, C-5), 131.11 (s, C-10), 153.20 (s, C-2) ppm. Anal. Calcd for $C_{18}H_{23}NO$ (269.38): C 80.26, H 8.61, N, 5.20; Found: C 80.18, H 8.75, N, 4.95.

General procedure for the reduction of the naphthoxazines with $LiAlH_4$

To a solution of the corresponding naphthoxazine (1 equiv) in dry THF (4 ml), $LiAlH_4$ (2.5 equiv) was added portion wise at 0°C and the mixture was stirred at rt for 3 h. The reaction mixture was quenched with water and the suspension was filtered through celite. The water phase was extracted with EtOAc and the organic phase was dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography (petroleum ether/MTBE = 5:1).

*(S)-1-((methyl(1-phenylethyl)amino)methyl)-naphthalene-2-ol **16***

According to the GP the reduction of **11** (0.160 g, 0.553 mmol) with $LiAlH_4$ (0.031 g, 0.830 mmol) afforded after column chromatography 0.126 g (78%) of **16**. $[\alpha]_D^{20}$ = -11 (c 1.00, $CHCl_3$). ^{1}H NMR:

δ 1.55 (d, $J_{H,H}$ = 6.9 Hz, 3H, H-14), 2.28 (s, 3H, H-21), 3.86 (q, $J_{H,H}$ = 6.9 Hz, 1H, H-13), 4.14 (br s, 2H, H-11), 7.10 (d, $J_{H,H}$ = 8.8 Hz, 1H, H-3), 7.26 (ddd, $J_{H,H}$ = 7.9, 6.8, 0.9 Hz, 1H, H-7), 7.28-7.31 (m, 1H, H-18), 7.33 (d, $J_{H,H}$ = 7.2 Hz, 2H, H-16, H-20), 7.35-7.38 (m, 2H, H-17, H-19), 7.38-7.42 (m, 1H, H-8), 7.67 (d, $J_{H,H}$ = 8.8, Hz, 1H, H-4), 7.71-7.76 (m, 2H, H-9, H-6) ppm. ^{13}C NMR: δ 17.68 (q, C-14), 37.61 (q, C-21), 53.29 (t, C-11), 62.79 (d, C-13), 111.26 (s, C-1), 119.14, (d, C-3), 120.87 (d, C-9), 122.29 (d, C-7), 126.19 (d, C-8), 127.69 (d, C-18), 128.06 (2d, C-16, C-20), 128.42 (s, C-5), 128.55 (2d, C-17, C-19), 128.85 (d, C-6), 129.01 (d, C-4), 132.49 (s, C-10), 140.42 (s, C-15) 156.72 (s, C-2) ppm. MS (ESI) *m/z* (rel int.) = 292 (70 $[M+H]^+$), 157 (73), 136 (32), 129 (93), 105 (100), 102 (18). Anal. Calcd for $C_{20}H_{21}NO$ (291.39): C 82.44, H 7.26, N 4.81; Found: C 82.23, H 7.35, N 4.58.

1-((methyl(1,2,3,4-tetrahydronaphthalen-1-yl)amino)methyl)naphthalene-2-ol ***17***

According to the GP the reduction of **12** (0.185 g, 0.587 mmol) with $LiAlH_4$ (0.056 g, 1.466 mmol) afforded after column chromatography 0.130 g (70%) of **17**. $[\alpha]_D^{20}$ = -23 (c 1.00, $CHCl_3$). ^{1}H NMR: δ 1.66-1.75 (m, 1H, H-15), 1.92-1.99 (m, 1H, H-14), 2.05 (m, 1H, H-15), 2.14 (m, 1H, H-14), 2.24 (s, 3H, H-23), 2.74 (dt, $J_{H,H}$ = 16.4, 4.5 Hz, 1H, H-16), 2.82 (m, 1H, H-16), 4.21 (dd, $J_{H,H}$ = 8.7, 6.5 Hz, 1H, H-13), 4.32-4.40 (m, 2H, H-11), 7.10 (d, $J_{H,H}$ = 7.5 Hz, 1H, H-18), 7.13 (d, $J_{H,H}$ = 8.8 Hz, 1H, H-3), 7.17 (t, $J_{H,H}$ =7.38, 1H, H-19), 7.23-7.26 (m, 1H, H-20), 7.28 (dd, $J_{H,H}$ = 7.9, 7.0 Hz, 1H, H-7), 7.43-7.46 (m, 1H, H-8), 7.53 (d, $J_{H,H}$ = 7.8 Hz, 1H, H-21), 7.69 (d, $J_{H,H}$ = 8.8 Hz, 1H, H-4), 7.76 (d, $J_{H,H}$ = 8.1 Hz, 1H, H-6), 7.86 (d, $J_{H,H}$ = 8.6 Hz, 1H, H-9) ppm. ^{13}C NMR: δ 21.07 (t, C-14), 21.51 (t, C-15), 29.82 (t, C-16), 35.86 (q, C-23), 52.84 (t, C-11), 61.04 (d, C-13), 111.18 (s, C-1), 119.00 (d, C-3), 120.81 (d, C-9), 122.31 (d, C-7), 126.28 (d, C-8), 126.48 (d, C-20), 126.90 (d, C-19), 128.12 (d, C-21), 128.46 (s, C-5), 128.93 (d, C-6), 129.19 (2d, C-4, C-18), 132.63 (s, C-10), 135.97 (s, C-22), 138.75(s, C-17), 156.76 (s, C-2). MS (ESI) *m/z* (rel int.) = 318 (43 $[M+H]^+$), 157 (70), 131 (100), 129 (55). Anal. Calcd for $C_{22}H_{23}NO$ (317.43): C 83.24, H 7.30, N 4.41; Found: C 83.10, H 7.21, N 4.33.

(S)-1-((methyl(1-(naphthalen-1-yl)ethyl)amino)methyl)naphtalen-2-ol ***18***

According to the GP the reduction of **13** (0.140 g, 0.410 mmol) with $LiAlH_4$ (0.040 g, 1.031 mmol) afforded after column chromatography 0.106 g (75%) of **18**. $[\alpha]_D^{20}$ = +187 (c 1.00, $CHCl_3$). ^{1}H NMR: δ 1.71 (d, $J_{H,H}$ = 6.7 Hz, 3H, H-14), 2.38 (s, 3H, H-25), 4.22 (d, $J_{H,H}$ =14.4, 1H, H-11), 4.29 (d, $J_{H,H}$ =14.5, 1H, H-11), 4.70-4.78 (m, 1H, H-13), 7.04 (d, $J_{H,H}$ = 8.8 Hz, 1H, H-3), 7.25 (dd, $J_{H,H}$ = 9.2, 5.6 Hz, 1H, H-7), 7.36-7.41 (m, 1H, H-8), 7.50 (d, $J_{H,H}$ = 8.6, Hz, 1H, H-19), 7.53 (d, $J_{H,H}$ = 8.5, Hz, 1H, H-23), 7.59 (t, $J_{H,H}$ = 7.6 Hz, 1H, H-18), 7.63 (d, $J_{H,H}$ = 8.8, 1H, H-4), 7.66 (d, $J_{H,H}$ = 7.2 Hz, 1H, H-24), 7.72 (d, $J_{H,H}$ = 8.1 Hz, 1H, H-6), 7.74 (d, $J_{H,H}$ = 8.5 Hz, 1H, H-9), 7.81 (d, $J_{H,H}$ = 8.1 Hz, 1H, H-22), 7.89 (d, $J_{H,H}$ = 8.1 Hz, 1H, H-20), 8.20 (d, $J_{H,H}$ = 8.53 Hz, 1H, H-17) ppm. ^{13}C NMR δ 16.51 (q, C-14), 38.71 (q, C-25), 53.42 (d, C-13), 59.14 (t, C-11), 111.24 (s, C-1), 119.11 (d, C-3), 120.89 (d, C-9), 122.30 (d, C-7), 122.81 (d, C-17), 124.69 (d, C-24), 125.33 (d, C-23), 125.75 (d, C-19), 126.15 (d, C-8), 126.46 (d, C-18), 128.26 (d, C-22), 128.41 (s, C-5), 128.82 (d, C-6), 128.96 (d, C-4), 129.14 (d, C-20), 131.51 (s, C-16), 132.54 (s, C-10), 134.07 (s, C-21), 137.73 (s, C-15), 156.24 (s, C-2) ppm. MS (ESI) *m/z* (rel int.) = 342 (10, $[M+H]^+$), 186 (40), 155 (100). Anal. Calcd for $C_{24}H_{23}NO$ (341.45): C 84.42, H 6.79, N 4.10; Found: C 84.24, H 6.52, N 4.29.

(S)-1-((methyl(1-naphthalen-2-yl)ethyl)amino)methyl)naphtalen-2-ol ***19***

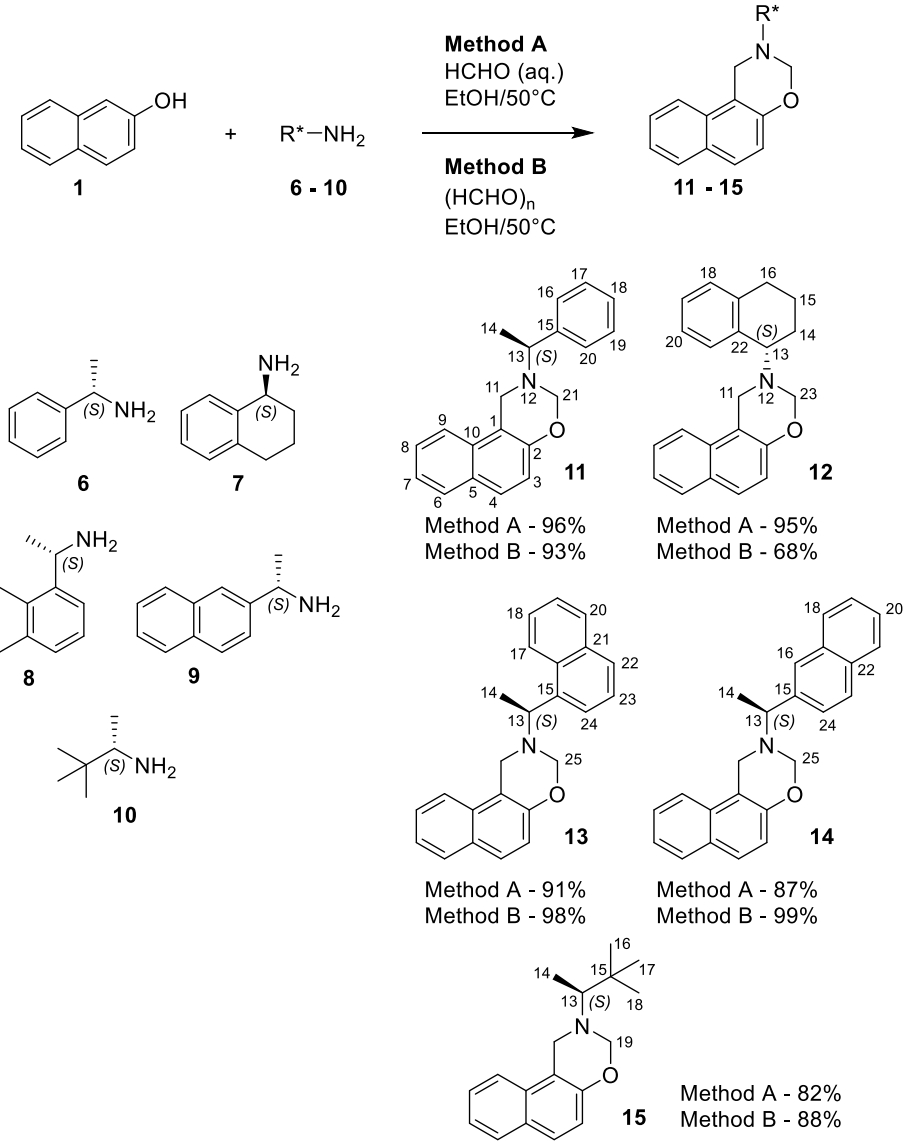
According to the GP the reduction of **14** (0.190 g, 0.560 mmol) with $LiAlH_4$ (0.053 g, 1.40 mmol) afforded after column chromatography 0.150 g (79%) of **19**. $[\alpha]_D^{20}$ = -49.3 (c 1.00, $CHCl_3$) ^{1}H NMR: δ 1.65 (d, $J_{H,H}$ = 6.8 Hz, 3H, H-14), 2.33 (s, 3H, H-25), 4.03 (q, $J_{H,H}$ = 6.8 Hz, 1H, H-13), 4.11-4.30 (m, 2H, H-11), 7.12 (d, $J_{H,H}$ = 8.8 Hz, 1H, H-3), 7.27 (t, $J_{H,H}$ = 7.4 Hz, 1H, H-7), 7.38-7.43 (m, 1H, H-8), 7.45-7.54 (m, 3H, H-19, H-20, H-24), 7.68 (d, $J_{H,H}$ = 8.8 Hz, 1H, H-4), 7.71 (s, 1H, H-16), 7.72-7.76 (m, 2H, H-6, H-9), 7.80-7.85 (m, 2H, H-21, H-18), 7.87 (d, $J_{H,H}$ = 8.5 Hz, 1H, H-23) ppm. ^{13}C NMR: δ 17.7 (q, C-14), 37.71 (q, C-25), 53.31 (t, C-11), 62.73 (d, C-13), 111.31 (s, C-1), 119.14 (d, C-3), 120.95 (d, C-9), 122.34 (d, C-7), 125.84 (d, C-20)*, 126.04 (d, C-19)*, 126.21 (d, C-24)*, 126.25 (d, C-8), 127.16 (d, C-16), 127.63 (d, C-18)*, 127.89 (d, C-21)*, 128.41 (d, C-23), 128.46 (s, C-5), 128.87 (d, C-6), 129.08 (d, C-4), 132.49 (s, C-10), 132.90 (s, C-22), 133.13 (s, C-17), 137.8 (s, C-15) 156.74 (s, C-2) ppm. MS (ESI) *m/z* (rel int.) = 342 (43, $[M+H]^+$), 155 (100), 153 (43), 129 (40). Anal. Calcd for $C_{24}H_{23}NO$ (341.45): C 84.42, H 6.79, N 4.10; Found: C 84.56, H 6.85, N 3.98.

*(S)-1-(((3,3-dimethylbutan-2-yl)(methyl)amino)methyl)naphthalene-2-ol **20***

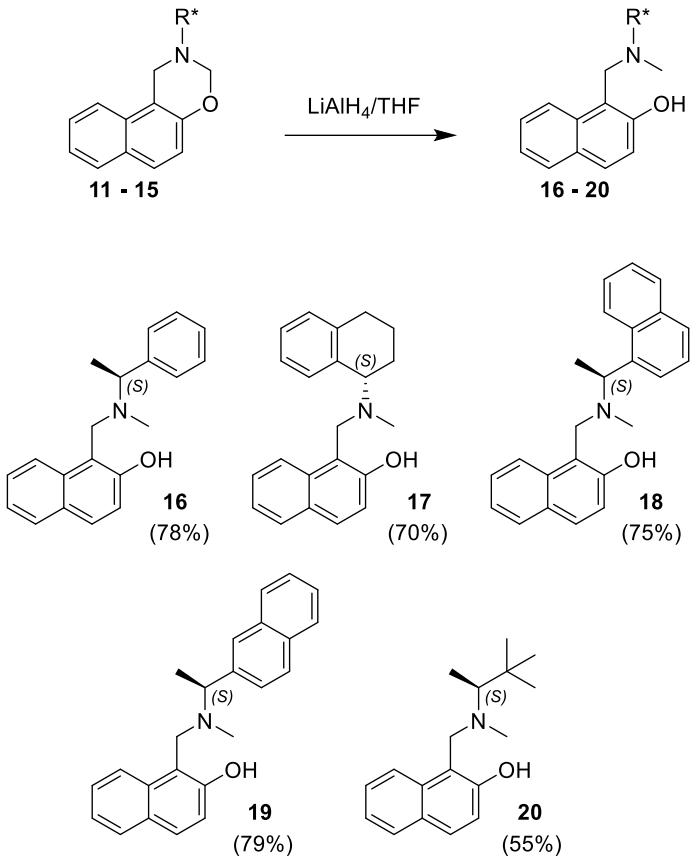
According to the GP the reduction of **15** (0.306 g, 1.136 mmol) with $LiAlH_4$ (0.108 g, 2.840 mmol) afforded after column chromatography 0.170 g (55%) of **20**. ^{1}H NMR: δ 1.04 (s, 9H, H-16, H-17, H-18), 1.17 (d, $J_{H,H}$ = 7.0 Hz, 3H, H-14), 2.30 (s, 3H, H-19), 2.69 (q, $J_{H,H}$ = 7.0 Hz, 1H, H-13), 4.06 (d, $J_{H,H}$ = 14.6 Hz, 1H, H-11), 4.35 (d, $J_{H,H}$ = 14.6 Hz, 1H, H-11), 7.09 (d, $J_{H,H}$ = 8.8, 1H, H-3), 7.21-7.32 (m, 1H, H-7), 7.42 (ddd, $J_{H,H}$ = 8.5, 6.8, 1.5 Hz, 1H, H-8), 7.67(d, $J_{H,H}$ = 8.8 Hz, 1H, H-4), 7.71-7.81 (m, 2H, H-6, H-9) ppm. ^{13}C NMR: δ 6.83 (q, C-14), 27.84 (3q, C-16, C-17, C-18), 35.50 (d, C-13), 55.22 (t, C-11), 68.29 (q, C-19), 110.91 (s, C-1), 119.16 (d, C-3), 120.71 (d, C-9), 122.21 (d, C-7), 126.19 (d, C-8), 128.38 (s, C-15), 128.57 (s, C-5), 128.90 (d, C-4), 129.04 (d, C-6), 132.70 (s, C-10), 156.73 (s, C-2) ppm.

General procedure for enantioselective addition of diethylzinc to aldehydes

To a solution of the corresponding ligand **16**-**20** (3 mol %) in hexane or toluene (4 ml) Et_2Zn (1.7 mmol, 1M solution in hexane) was added dropwise at 0°C in an Ar atmosphere. The mixture was stirred for 30 min at 0°C and then the corresponding aldehyde (1.0 mmol) was added at -20°C. The reaction mixture was stirred at 20°C and monitored by TLC (petroleum ether/MTBE = 5:1) until the aldehyde was consumed. 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/MTBE = 5:1).

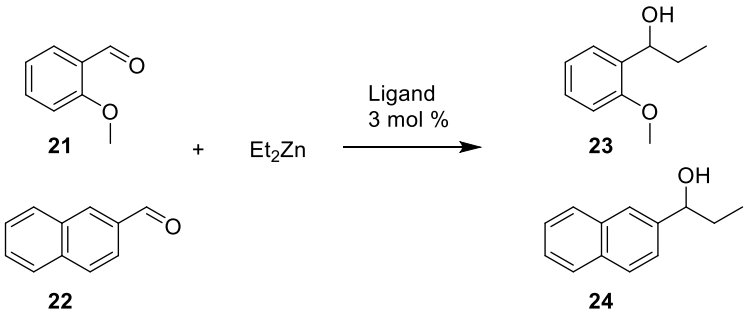


Scheme 2. Three component condensation of 2-naphthol, formaldehyde and chiral amines (the numbering of the C-atoms is presented to support the assignment of the NMR spectra.



Scheme 3. Reduction of the 1,3-oxazines **11-15** to the N-methyl derivatives **16-20**.

Table 1. Enantioselective addition of Et_2Zn to *o*-methoxybenzaldehyde (**21**) and 1-naphthaldehyde (**22**) catalyzed by chiral ligands **16**-**20**.



Ligand	Product **23**		Product **24**	
	Yield[a] %	ee %, (config.)[b]	Yield[a] %	ee %, (config.)[c]
16	68	0	54	3 *R*
17	69	14 *R*	34	0
18	86	47 *R*	57	2 *R*
19	64	24 *R*	36	14 *R*
20	56	8 *R*	56	3 *R*

[a]Isolated pure products after column chromatography; [b]Enantiomeric excess (ee) determined by GC analysis (FS-Cyclodex beta-I/P, 150 °C isothermal, 1 ml/min He, split 21:1, T_{det} = 230 °C, T_{inj} = 220 °C; retention time t_{minor} = 9.6 min, t_{major} = 10.1 min.); [c](FS-Cyclodex beta-I/P, 160 °C isothermal, 1 ml/min He, split 21:1, T_{det} = 230 °C, T_{inj} = 220 °C; retention time t_{minor} = 29.2 min, t_{major} = 30.0 min.).

RESULTS AND DISCUSSION

The condensation of 2-naphthol (**1**), formaldehyde and chiral amines was performed in ethanol at 50°C whereupon the formaldehyde was applied as formalin (37% aq. solution) or as paraformaldehyde, methods **A** or **B**, respectively (Scheme 2). Compounds **6**-**10**, were used as chiral amines that are readily available and relatively inexpensive. The yields of 1,3-naphthoxazines **11**-**15** were slightly better due to the use of Method **B** with the exception of product **12** (Method **A** provided better results). With respect to all the other reaction conditions results obtained, both methods are equally efficient. Naphthoxazines **11**-**15** are colorless amorphous solids, which are not stable when standing for long periods at room temperature. It seems that the compounds **11**, **13** and **14** bearing the aromatic amino moiety are somewhat more stable. For longer periods of time oxazines can be stored in flasks in an inert atmosphere in the refrigerator.

The naphthoxazines synthesized were reduced with lithium aluminum hydride in tetrahydrofuran as a solvent providing the N-methyl aminobenzylnaphthols **16**-**20** in good yields (Scheme 3). Aminobenzylnapthols **16**-**19** were stable while standing at room temperature for a couple of days in contrast to compound **20** which decomposes fast within hours after purification by column chromatography. This might be the reason for the lower yield of **20**.

With the aminobenzylnaphthols in hand we performed additional reactions of diethylzinc to the aromatic aldehydes **21** and **22** to test the activity of compounds **16**-**20** (3 mol %) as precatalysts (ligands). In all the cases the ligands studied were active catalysts that provide the additional reaction in relatively good yields. However, the enantioselectivity observed was very low. In some cases there was no selectivity or selectivity in error in the range (0 to 2 or 3% ee). Only in the case of ligand **18** a moderate enantioselectivity of product **23** formation could be realized. Comparing these result with our previous studies [11] and literature data [3, 7, 18] it is clear that an efficient ligand of the presented structural type would need substitution at the CH_2-carbon atom next to the nitrogen.

CONCLUSIONS

Efficient synthesis of 1,3-naphthoxazines applying three component Betti-type condensation of 2-naphthol, formaldehyde and chiral amines was demonstrated. The lithium aluminum hydride reduction of the naphthoxazines obtained provides chiral aminobenzylnaphthols, which were tested as precatalysts (ligands) for enantioselective addition of diethylzinc to aldehydes realizing good yields of secondary alcohols with low to moderate enantioselectivity. The synthesis of the chiral naphthoxazines and aminobenzylnaphthols could be extended to the synthesis of a structurally diverse series of analogues, which is important as these compounds are expected to possess biological activity.

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ТРИ КОМПОНЕНТНА КОНДЕНЗАЦИЯ ОТ БЕТИ ТИП – ЕФЕКТИВЕН ИНСТРУМЕНТ ЗА СИНТЕЗ НА ХИРАЛНИ НАФТОКСАЗИНИ И АМИНОБЕНЗИЛНАФТОЛИ ЗА ЕНАНТИОСЕЛЕКТИВНО ДИЕТИЛ ЦИНК ПРИСЪЕДИНЯВАНЕ КЪМ АЛДЕХИДИ

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(Резюме)

2-Нафтол, формалдехид и хирални амини са приложени в трикомпонентна кондензация от Бети тип за получаване на 1,3-нафтоксазини с отлични добиви. Последните са трансформирани лесно до хирални N-метил аминобензилнафтоли посредством реакция с литиевоалуминиев хидрид. Хиралните аминобензилнафтоли са активни катализатори (лиганди) за енантиоселективно диетил цинк присъединяване към алдехиди и получаване на вторични алкохоли с добри добиви с достигане на умерена енантиоселективност.