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Functionalized 2-Azabicyclo[3.3.0]octanes as Ligands in the Enantioselective Catalysis

Hans Günter Aurich*, Michael Soeberdt

Fachbereich Chemie der Philipps-Universität Marburg, D-35032 Marburg, Germany

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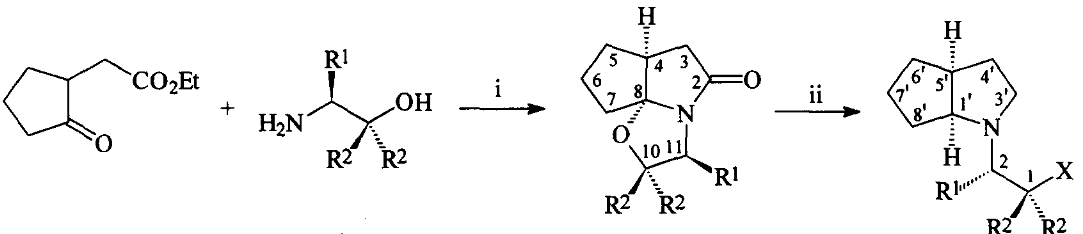
Abstract: Enantiopure compounds **4** were prepared by condensation of β-aminoalcohols **2** with ethyl (2-oxocyclopentyl)acetate **1** and subsequent reduction of intermediates **3**. Compound **4a** was converted to **6** via **5**. With compounds **4**, **5** or **6** as chiral ligands in the reaction of benzaldehyde with diethylzinc an enantiomeric excess between 14 and 84% was achieved.

The reaction of aldehydes with a dialkylzinc compound in the presence of chiral ligands that give rise to a catalytic process belongs to the frequently studied enantioselective reactions.[1] Among the various bicyclic compounds with a β-aminoalcohol group that are used as chiral ligands are only a few with a 2-azabicyclo-[3.3.0]octane backbone.[2] We synthesized enantiopure N-hydroxyalkylsubstituted 2-azabicyclo[3.3.0]octanes **4** and checked them as ligands in the enantioselective reaction of diethylzinc with benzaldehyde. Since β-aminothiols revealed sometimes a higher enantioselectivity compared to the corresponding β-aminoalcohols[3] it seemed reasonable to study also such compounds.

Condensation of γ-ketoester **1** with aminoalcohols **2** afforded 9-oxa-1-azatricyclo[6.3.0.0^{4,8}]undecan-2-ones **3** or ent-**3**[4] (for substitution pattern see Table 1). Reductive ring-opening either with lithium aluminium hydride (R^2 =H) or borane-tetrahydrofuran complex (R^2 = Ph) gave 2-azabicyclo[3.3.0]octanes **4** or ent-**4**, respectively. Aminoalcohol **4a** was converted to aminothiol **6** via compound **5**.[5] An analogous conversion of compound ent-**4g**, however, could not be achieved. Compounds **4**-**6** were obtained diastereomerically pure as was shown by their ^{1}H and ^{13}C NMR spectra. Since aminoalcohols **2** were enantiopure, this must be also true for the products **4**-**6**.[6]



1 **2** **3**

i: reflux in toluene, ii: $LiAlH_4$ in THF or BH_3- THF complex in THF,
iii: MsCl, NEt_3, iv: CH_3CO-SK, v: $LiAlH_4$

iii, iv
v
4: X = OH
5: X = S-$COCH_3$
6: X = SH

For substitution pattern R^1, R^2 see Table 1

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The reaction of diethylzinc with benzaldehyde was performed in the presence of 6 mol% of compounds **4**, **5** or **6** at 0°C hexane. The enantiomeric excess of the reaction was determined as described earlier.[7] The results are summarized in Table 1.

$$C_6H_5\text{-CHO} + (C_2H_5)_2Zn \longrightarrow C_6H_5\text{-}\overset{*}{C}H(OH)C_2H_5$$

Table 1.
Enantiomeric excess in the reaction of benzaldehyde with diethylzinc in the presence of compounds **4**-**6**[a]

Compound	R^1	R^2	Yield (%)	ee (%)	config.[f]
4a	Me	H	88[b]	32	R
4b	iPr	H	58[c]	34	R
4c	Bn	H	93	30	R
4d	Me	Ph	97[d]	46	R
4e	Bn	Ph	88[d]	74	R
ent-**4f**[e]	Ph	H	90[c]	14	S
ent-**4g**	Ph	Ph	100	78	S
5	-	-	100	82	R
6	-	-	100	84	R

[a] 150 mol% of Et_2Zn, 6 mol% of compounds **4**, **ent-4**, **5**, or **6** - [b] 8% of benzylalcohol were formed in addition to the 1-phenylpropanol-1 - [c] 10% of benzylalcohol were formed - [d] 3% of benzylalcohol were formed - [e] See reference 4a - [f] Configuration of the enantiomer formed in excess

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References and Notes

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5. The conversion of compound **4a** to **6** via **5** was performed according to the procedure described in ref. 3a.
6. Characterization of selected compounds: Compound **3a** (R^1 = Me, R^2 = H): Colourless oil, cc (SiO_2, AcOEt/ petroleum ether 1:1, $R_f = 0.10$); 85% yield. - $[\alpha]_D^{20} = +91.4$.- Selected signals: ^1H NMR (300 MHz, $CDCl_3$) 1.21 (d, 3H. CH_3), 2.29 (dd, 7-H), 2.53 (m, 8-H), 2.68 (dd, 7-H'), 3.53 (dd, 3-H), 4.07 (ddq, 4-H), 4.16 (dd, 3-H'). - ^{13}C NMR (75 MHz, $CDCl_3$): 50,3 (C-4), 73.6 (C-3), 110.1 (C-1), 179.5 (C-6). MS (EI): m/z (%) = 181 (24) [M^+]. - Compound **4a** (R^1 = Me, R^2 = H): Colourless oil, kugelrohrdistillation, 85% yield. - $[\alpha]_D^{20} = +44.3$. - Selected signals: ^1H NMR (300 MHz, $CDCl_3$) 0.84 (d, 3H, CH_3), 2.23 (dd, 3'-H), 2.43 (m, 5'-H) 2.58 (dd, 3'-H'), 2.88 (ddq, 2-H), 3.08 (dd, 1'-H), 3.15 (t, 1-H), 3.35 (dd, 1-H'). - ^{13}C NMR (75 MHz, $CDCl_3$): 41.6 (C-5'), 44.7 (C-3'), 54.4 (C-2), 63.5 (C-1), 65.2 (C-1'). - MS (FD): m/z (%) = 169 (100) [M^+]. - $C_{10}H_{19}NO$ (169.3) Calcd. C 70.95 H 11.31 N 8.27 Found C 71.12 H 11.42 N 8.31. - Compound **5**: Pale-yellow oil, cc (SiO_2; AcOEt/petroleum ether 1:1, $R_f = 0.25$), AcOEt (R_f = 0.23), 23% yield. - $[\alpha]_D^{25} = -29.6$. - Selected signals: ^1H NMR (300 MHz, $CDCl_3$): 0.99 (d, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.28 (ddd, 3'-H), 2.41 (m, 5'-H), 2.66-2.73 (m, 2H, 2-H and 3'-H'), 2.85 (dd, 1-H), 3.03 (m, 1'-H), 3.04 (dd, 1-H'). - ^{13}C NMR (75 MHz, $CDCl_3$): 35.2 (C-1), 42.1 (C-5'), 48.4 (C-3'), 55.2 (C-2), 66.2 (C-1'), 196.3 (CO). - MS (EI): m/z (%) = 138 (100) [$C_9H_{16}N^+$]. - $C_{12}H_{21}NOS$ (227.4) Calcd C 63.38 H 9.31 N 6.16 Found 62.82 H 9.41 H 6.36. - Compound **8**: Pale-yellow oil, cc (SiO_2; EtOH, R_f = 0.21), 61% yield, undergoes oxidation on air. - Selected signals: ^1H NMR (300 MHz, $CDCl_3$) 0.96 (d, CH_3), 2.22 (m, 3'-H), 2.34 (m, 5'-H), 2.53 (dd, 1-H), 2.64 (m, 3'-H'), 2.81 (m, 2-H), 2.86-3.11 (m, 1'-H), 3.04 (dd, 1-H'). - ^{13}C NMR (75 MHz, $CDCl_3$): 14.2 (CH_3), 42.3 (C-5'), 46.2 (C-1), 48.3 (C-3'), 55.3 (C-2), 66.0 (C-1'). - MS (FD): m/z (%) = 185 (70) [M^+], 368 (15) [$2M^+$-2 H, disulfide]. - MS (EI): m/z (%) = 138 (100) [$C_9H_{16}N^+$].
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