New 2,5-diazabicyclo[2.2.1]heptanes and their application in the asymmetric addition of diethylzinc to benzaldehyde

Ulrich Jordis,*[a] Martin Kesselgruber,[a] Sven Nerdinger[a] and Kurt Mereiter[b]

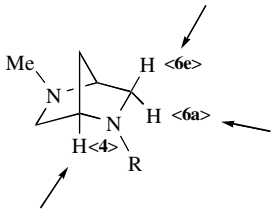
[a] *Institut für Organische Chemie der TU Wien, A-1060 Wien, Austria.*
Fax: +43 1 58801 15499; e-mail: ulrich.jordis@tuwien.ac.at
[b] *Institut für Mineralogie, Kristallographie und Strukturchemie der TU Wien, A-1060 Wien, Austria*

New (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane derivatives synthesised by directed ortho metalation result in enantioselectivities of up to 78% e.e. when used as catalysts in the addition of diethylzinc to benzaldehyde.

The addition of diethylzinc to prochiral aldehydes is a convenient model for testing chiral ligands as enantioselective catalysts for this fundamental carbon–carbon bond-forming reaction. Enantiopure -amino alcohols[1] often are used as catalysts for these reactions. Compounds structurally related to proline were found to be particularly efficient for the preparation of highly effective chiral ligands.[2–4]

Recently, Guijarro *et al.*[5] introduced a related class of catalysts using the 2-azabicyclo[2.2.1]heptane moiety which was prepared *via* a hetero Diels–Alder reaction. Here we report 2,5-diazabicyclo[2.2.1]heptane derivatives as a new class of chelating ligands for organozinc compounds.

N-Boc-substituted pyrrolidines are readily deprotonated by *sec*-butyllithium to yield -lithio amino synthetic equivalents.[6–8] The inclusion of (–)-sparteine as the chiral auxiliary[9] provides excellent stereochemical control. However, when an enantiopure compound, such as (1*S*,4*S*)-2-methyl-2,5-diazabicyclo[2.2.1]-heptane **1**, prepared by the 'chiral-pool' synthesis from *trans*-4-hydroxy-L-proline[10] is used as the starting material, the need for an additional chiral base is eliminated.

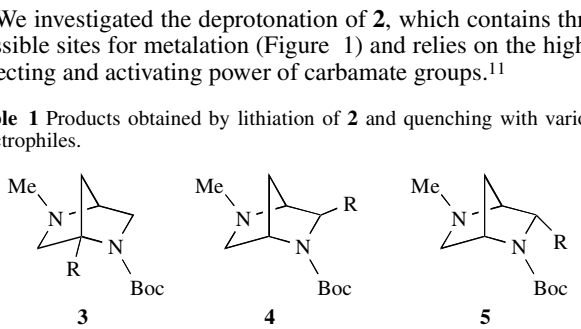


1 R = H
2 R = Boc

Figure 1 Deprotonation sites in **2**.

We investigated the deprotonation of **2**, which contains three possible sites for metalation (Figure 1) and relies on the highly directing and activating power of carbamate groups.[11]

Table 1 Products obtained by lithiation of **2** and quenching with various electrophiles.



3 **4** **5**

	Substituent R	Yield of **3** (%)[a]	Yield of **4** (%)[a]	Yield of **5** (%)[a]
a	Diphenylhydroxymethyl	27	—	16
b	[3,3′-Bis(trifluoromethyl)-diphenyl]hydroxymethyl	12	12	4
c	9-Hydroxy-9*H*-fluoren-9-yl	26	—	14
d	Phenylmercapto	31	—	32
e	9-hydroxy-9*H*-xanth-9-yl	24	—	—
f	*N*-Phenylaminocarbonyl	—	—	13

[a]Isolated yield after flash chromatography.

Compound **2** was prepared in five steps starting from (*S*,*trans*)-4-hydroxyproline.[10] However, the *N*-tosyl-*O*,*O*′-dimesyl-protected (*S*,*trans*)-4-hydroxy-2-pyrrolidinemethanol replaced the previously reported tritosyl-protected substance.[10] The deprotonations were performed using 1.7 equiv. of *sec*-butyllithium/TMEDA and the subsequent addition of a selected electrophile.† The reactivity depends on the choice of solvent, *e.g.*, the use of dry diethyl ether instead of THF enhances the regioselectivity but decreases the conversion and yield. For most electrophiles, substitution at the 4-position appears to be favoured over the 6-position; however, in the presence of benzophenone, 3,3′-bis-(trifluoromethyl)benzophenone or diphenyl disulfide, the 6-substituted products can be isolated by chromatography. On the basis of the structure determination of **4b** by X-ray diffraction (Figure 2),‡ it was possible to assign the configuration of all other products: as shown in Figure 2, the orientation of the substituent at the 6-position was found to be equatorial.

The sterically more hindered electrophiles (**c**, **e**) resulted in the substitution predominantly on the bridgehead (Table 1).

† *Preparation and analysis of* **3a** *and* **5a**. A solution of 882 mg (8.00 mmol) of TMEDA in 15 ml of dry THF was cooled to –78 °C and 6.2 ml of 1.3 M Bu^{s}Li in hexane (8.00 mmol; 1.7 equiv.) was added dropwise. After stirring for 30 min at this temperature, a solution of 1 g (4.70 mmol) of **2** in 10 ml of dry THF was added dropwise at –78 °C or below. The mixture was additionally stirred for 3 h at this temperature. 2.92 g (16.00 mmol) of benzophenone in 10 ml of dry THF was added. Then the mixture was warmed slowly to room temperature and quenched with 30 ml of saturated aqueous ammonium chloride. The layers were separated, and the aqueous phase was extracted with diethyl ether (3×30 ml). The organic layers were collected, dried over sodium sulfate and evaporated. The residue was purified by column chromatography (silica gel, light petroleum–ethyl acetate, 2:1). The two fractions (**3a** and **5a**) were recrystallised from diisopropyl ether yielding 500 mg of **3a** (27%) and 300 mg of **5a** (16%) as colourless crystals.

For **3a**: mp 125–126 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.21 (s, 9H, Boc–Me), 1.32 (d, 1H, H-7, *J* 11 Hz), 2.33 (s, 3H, NMe), 2.36 (d, 1H, H-7, *J* 11 Hz), 3.10 (d, 1H, H-3, *J* 10 Hz), 3.14 (d, 1H, H-3, *J* 10 Hz), 3.18–3.22 (m, 1H, H-1), 3.53 (d, 1H, H-6, *J* 12 Hz), 3.84 (d, 1H, H-6, *J* 12 Hz), 7.07–7.65 (m, 10H, aromatic H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 28.10, 41.32, 42.23, 54.60, 60.72, 61.73, 76.82, 77.91, 80.40, 126.37, 126.68, 127.21, 127.33, 127.70, 144.97, 146.88, 155.56. Found (%): C, 72.79; H, 7.78; N, 7.09. Calc. for $C_{24}H_{30}N_2O_3$ (%): C, 73.07; H, 7.66; N, 7.10.

For **5a**: mp 135–136 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.18 (s, 9H, Boc–Me), 1.39 (d, 1H, H-7, *J* 10 Hz), 1.67 (d, 1H, H-7, *J* 10 Hz), 2.15 (s, 3H, NMe), 2.35 (d, 1H, H-3, *J* 10 Hz), 3.30–3.34 (m, 1H, H-1), 3.67 (d, 1H, H-3, *J* 10 Hz), 4.38 (d, H-6, *J* 3 Hz), 4.68–4.72 (m, 1H, H-1), 7.10–7.80 (m, 10H, aromatic H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 27.73, 33.68, 42.95, 59.92, 63.26, 66.95, 68.27, 78.81, 79.78, 126.08, 126.51, 126.85, 127.15, 127.19, 127.88, 145.62, 146.96, 157.46. Found (%): C, 72.70; H, 7.68; N, 7.07. Calc. for $C_{24}H_{30}N_2O_3$ (%): C, 73.07; H, 7.66; N, 7.10.

‡ *Crystal data for* **4b**: $C_{26}H_{28}F_6N_2O_3$, orthorhombic, space group $P2_12_12_1$, a = 9.070(3) Å, b = 12.011(4) Å, c = 24.835(6) Å, V = 2705.5 Å^3, Z = 4, T = 297 K. Details of the crystal structure determination may be obtained from the Director of the Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge CB21EW (UK) quoting the reference number CCD-103148.

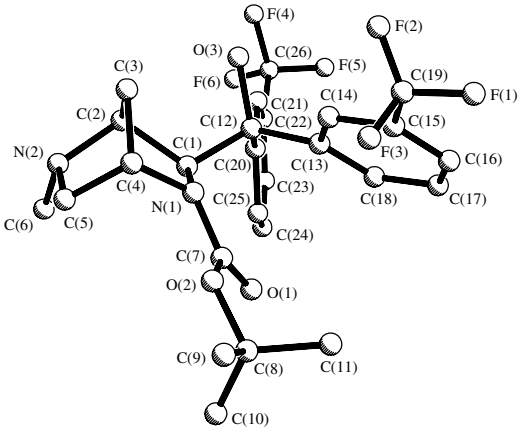


Figure 2 Structure of **4b** in the solid state. Selected bond lengths (Å): C(1)–C (2) 1.549, C(1)–C (12) 1.574, C(1)–N(1) 1.475, C(4)–N(1) 1.483, N(1)–C(7) 1.361, C(12)–O(3) 1.426; selected bond angles (°): N(1)–C (1)–C(12) 116.5, C(2)–C (1)–C(12) 114.4, N(1)–C(1)–C(2) 100.0; torsional angle C(12)–C (1)–C(2)–N(2) 164.4°.

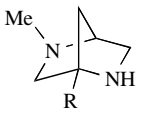
Cleavage of the Boc group was achieved in moderate to excellent yields either by using TFA or (in the case of **3a**, **5a** and **4b**) by refluxing with aqueous sodium hydroxide.[§] The resulting compounds were tested for their ability to direct chiral selectivity in the addition of diethylzinc to benzaldehyde.[§]

As summarised in Table 2, the highest enantiomeric excess was observed for ligand **6a**. Generally, the compounds with flexible phenyl substituents (**6a**, **6b** and **8a**) resulted in higher e.e. values than more rigid derivatives (**6c** and **6e**). The yields of the catalysed reactions were moderate giving up to 50% of benzyl alcohol as a by-product. When the reaction was conducted using catalyst **6a** in dry light petroleum instead of toluene, a decrease in the enantioselectivity from 78% to 38% e.e. was observed.

In summary, we have introduced a new class of chiral catalysts capable of inducing moderate-to-high e.e. values in the addition of diethylzinc to benzaldehyde with moderate yields. These catalysts are synthesised by directed lithiation of **2**, which can be produced in technical-scale amounts. Further studies investigating the effects of different catalyst ligand substituents on the stereoselectivity of this addition reaction are in progress.

[§] A solution of 15 mg (0.05 mmol) of **3a** in 2 ml of dry toluene was cooled to 0 °C and treated with 2.2 ml (2.2 mmol) of 1.0 M diethylzinc in hexane. After stirring for 30 min at this temperature, 0.1 ml of benzaldehyde (1.0 mmol) was added dropwise. The mixture was stirred at 0 °C for 24 h, quenched with 10 ml of saturated aqueous ammonium chloride and extracted with diethyl ether (3×10 ml). The organic layers were collected, dried over sodium sulfate and evaporated. The oily residue was filtered through silica gel (light petroleum–et hyl acetate, 9:1).

Table 2 Results of the asymmetric addition of diethylzinc to benzaldehyde.[a]



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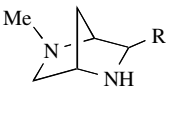

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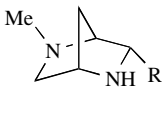

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	e.e.[b]	Configuration
6a	78	*R*
6a[c]	38	*R*
6b	37	*R*
6c	2	*R*
6d	10	*S*
6e	4	*S*
7b	11	*S*
8a	38	*R*
8f[d]	16	*R*

[a]Substituents R: see Table 1. [b]Enantiomeric excesses were determined by HPLC analysis using a chiral column (Daicel Chiralcel OD-H, 5% Pr^{i}OH–*n*-hexane, 0.5 ml min^{-1}, detection at 254 nm). [c]Boc-protected ligand. [d]Reaction conducted in dry light petroleum.

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