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A new chiral lithium amide based on (*S*)-2-[1-(3,3-dimethyl)pyrrolidinylmethyl]pyrrolidine — synthesis, NMR studies and use in the enantioselective deprotonation of cyclohexene oxide

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Abstract

A new chiral lithium amide has been designed starting from (*S*)-proline. This new chiral lithium amide has been used for asymmetric deprotonation/ring opening of cyclohexene oxide to give (*S*)-2-cyclohexen-1-ol in 88% yield and 78% enantiomeric excess. NMR studies of the lithium amide and the ligand–substrate complex are also presented.

1. Introduction

The enantioselective deprotonation of epoxides to allylic alcohols by chiral lithium amides have received much attention.[1–4] The resulting allylic alcohols are usually obtained in high enantiomeric excess (ee) and yield. Allylic alcohols of high enantiomeric purity are prospective starting materials for many drugs and natural products.[5–8] Most chiral lithium amides reported in the literature have been used either as deprotonating reagents and/or chiral ligands in lithiation reactions.[9,10] The most studied reagents are perhaps those obtained from (*S*)-proline and/or containing pyrrolidine rings. With the use of lithium (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidide **1** in THF as solvent, cyclohexene oxide **2** has been enantioselectively deprotonated to give (*S*)-2-cyclohexen-1-ol (*S*)-**3** in 84% yield and 80% ee (Scheme 1).[11–15] Recently we also reported the solvent induced isomerisation of 2-cyclohexen-1-ol to 3-cyclohexene-1-ol when the reaction was performed in 2,5-dimethyltetrahydrofuran under otherwise similar conditions.[16]

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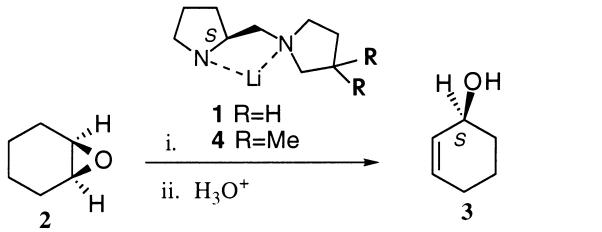


Scheme 1.

Attempts have been made to rationalise the stereochemical outcome of the deprotonation/ring opening reaction by employing the proposed transition state structure of complexes between **1** and **2** (Fig. 1, transition state complex **A** or **B**). It is believed that structure **B**, leading to product (*S*)-**3**, is responsible for the high enantioselectivity due to less steric hindrance than structure **A**.[4,12] However, concrete evidence is still to be found.

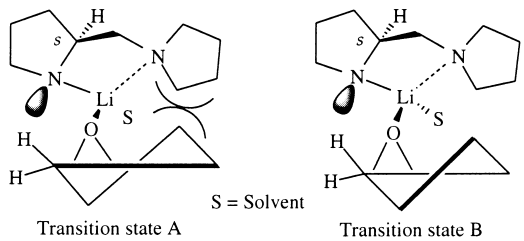
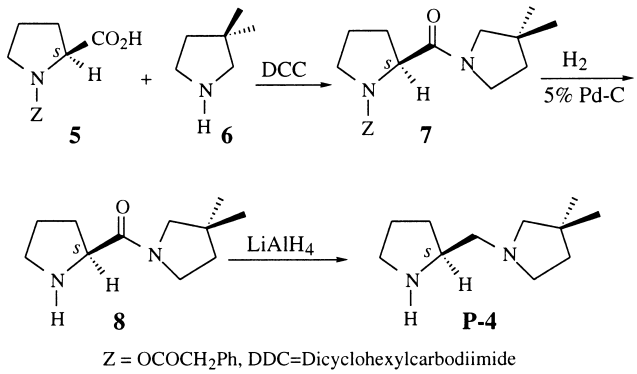


Fig. 1. Proposed transition state structures for the enantioselective deprotonation of **2** by **1**

We initiated NMR studies to obtain information about the solution state structure of **1** complexing **2** in the hope that this would reflect a possible transition state structure responsible for the enantioselectivity in the deprotonation/ring opening of **2**. However, our attempts were hampered in the absence of any suitable handles for the assignment of NMR signals in the overcrowded ^{1}H NMR spectrum. To overcome this problem without perturbing the demands of selectivity in the system, structural modifications were made in the pyrrolidine moiety. Two methyl groups were introduced at the 3 position of (*S*)-2-(1-pyrrolidinomethyl)pyrrolidine **P-1** precursor to **1**. From the NMR point of view, this new lithium amide, lithium (*S*)-2-[1-(3,3-dimethyl)pyrrolidinylmethyl]pyrrolidide **4**, contains the necessary handles for signal assignment and thereby it can be used for structural studies in solution by NMR. Frequent publications of new lithium amides in the literature[17–20] has prompted us to report the synthesis and efficiency of **4** in the enantioselective deprotonating of **2** and to present an account of the NMR solution studies of the complex between **2** and **4**.

2. Results and discussion

The precursor to **4**, (*S*)-2-[1-(3,3-dimethyl)pyrrolidinylmethyl]pyrrolidine **P-4** was synthesised by following the general method reported in the literature for the synthesis of **P-1**[11–15] by coupling 3,3-dimethylpyrrolidine **6**[21] with (*S*)-1-N-(benzyloxycarbonyl)proline **5** and following the other steps according to Scheme 2.



Scheme 2.

2.1. Enantioselective deprotonating efficiency of **4**

The enantioselective deprotonating efficiency of **4** was tested by performing the reaction with **2** in THF. Compound (*S*)-**3** was obtained in 88% yield (isolated) (GC yield >99%) and 78% ee. This compares to 84% yield (isolated) (GC yield >99%) and 80% ee when **1** was used under otherwise similar reaction conditions.

2.2. NMR studies

In order to determine the solution structure of **4**, ^{1}H–^{1}H-COSY, ^{1}H–^{1}H-NOESY and ^{6}Li NMR experiments were performed. The ^{1}H NMR spectra ($CDCl_3$ and THF-d8) of the precursor **P-4** gave a singlet for the 3′-methyls at the pyrrolidine rings at δ 1.04 despite the fact that the molecule possesses a stereogenic carbon (two singlets were expected). This shows that there is no rotational restriction between the two pyrrolidine moieties i.e. there is free rotation around the C(6)–N bond. However, the ^{1}H NMR of the corresponding amide **4** at −10°C in THF-d8 showed two separate 3′-methyl proton NMR signals at δ 1.05 and δ 1.12 indicating an element of rigidity in the structure due to a coordination of the lithium cation with both of the nitrogen atoms leaving two free places for the solvent or substrate molecule to occupy (Fig. 2). At 25°C these two 3′-methylproton signals coalesce into one 3′-methyl proton signal at δ 1.10.

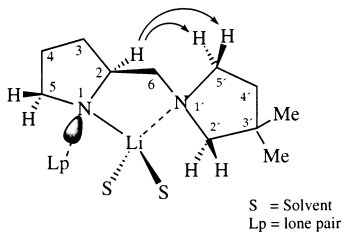


Fig. 2. The proposed structure of **4** monomer in THF. The NOE between H(2) and H(5′,5′) are shown

The ^{1}H–^{1}H-DQCOSY (optimised for H–C–C–H couplings) and ^{1}H–^{1}H-NOESY experiments were performed to assign the two H(2′,2′) signals in the proton spectra. The two H(2′,2′) signals were used as a starting point for the assignment of the 3D structure of **4** using NOEs. One of the H(2′,2′) protons at δ 2.17 shows a NOE effect with one of the 3′-methyl group proton signals at δ 1.05 whereas the other H(2′,2′) proton at δ 2.55 shows a NOE effect with one of the 3′-methyl group proton signals at δ 1.12 instead. In the case of H(4′,4′) protons, the proton appearing at δ 1.51 showed a correlation with the 3′-

Table 1
^{1}H NMR chemical shifts of **4** in THF-d8 at −10°C. The chemical shifts are arranged in two groups for each face of **4**, i.e. all the chemical shifts in the same column as H(2) are on the same side as H(2) in **4**

Proton#	δ	δ
H(2)	3.45	-
H(3,3)	1.60	0.84
H(4,4)	1.29	1.50
H(5,5)	3.10	3.10
H(6,6)	1.83	2.48
H(2',2')	2.17	2.55
H(3',3')-Me	1.05	1.12
H(4',4')	1.51	1.65
H(5',5')	2.15	3.23

methylgroup protons at δ 1.05 while the other H(4′,4′) proton appearing at δ 1.65 showed NOE effects with the 3′-methylgroup protons at δ 1.12. With the help of COSY and NOESY NMR experiments we were able to assign all the proton signals in the 3,3-dimethylpyrrolidine ring, see Table 1, Fig. 3.

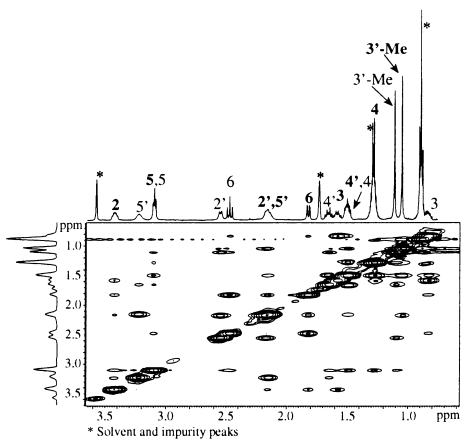


Fig. 3. A ^{1}H–^{1}H-NOESY of **4** in THF-d8 at −10°C. The protons that appear on the same face as H(2) are emboldened in the top proton NMR spectra

The orientation of two methyl groups at C(3′) (axial or equatorial) was determined by looking for NOE effects between H(2) at δ 3.45 of the (*S*)-proline ring and the H(6,6) at δ 1.83 and δ 2.48 in the methylene bridge and H(2′,2′)–H(6,6), H(5′,5′)–H(6,6) NOEs, respectively. A NOE effect between H(2) at δ 3.45 of the (*S*)-proline ring and H(5′,5′) at δ 2.17 and δ 3.23 of the pyrrolidine was observed (Fig. 2). On the basis of these observations, it can be interpreted that the methyl groups are pointing as shown in Fig. 2. It should be remembered that there is no rotation around the C(6)–N bond. The evidence of a locked structure was confirmed by the absence of cross peaks due to NOE's exchange, all the cross peaks observed showed opposite intensity compared to the diagonal peaks.[22]

On addition of **2** to **4**, a NOESY experiment of the complex was recorded at −10°C in THF-d8. Cyclohexene oxide protons, appearing at δ 1.20, 1.37, 1.74, 1.79 and 3.11, showed weak NOE correlations with the H(2,2′,4,5 and 6) protons in **4**. The NOE correlations between cyclohexene oxide and **4** are most pronounced for the pyrrolidide ring. However, we hasten to add that the observable

NOE only gives an average picture of the cyclohexene oxide·**4** complex in solution. The observed NOE correlations between cyclohexene oxide and **4** are in good agreement with results obtained for the deprotonation reaction of the cyclohexene oxide using analogues of the Asami reagent substituted at the pyrrolidinyl and pyrrolidide ring moieties. Substitutions at the pyrrolidinyl ring had no or opposite effect upon the ee in the above reaction.[12,15] However, substitution at the pyrrolidide ring resulted in a slight increase of the ee[18] These observations are in accordance with the observed NOE correlations described above.

3. Experimental

3.1. General

Glassware and syringes used for NMR and deprotonation reactions were dried at 50°C in a vacuum oven before transfer into a glove box (Mecaplex GB 80 equipped with a gas purification system that removes oxygen and moisture) containing a nitrogen atmosphere. Typical moisture content was less than 0.5 ppm. All manipulations concerning the deprotonation reactions were carried out in the glove box using gas-tight syringes. Etheral solvents, distilled under nitrogen from sodium and benzophenone, were kept over 4 Å molecular sieves in a septum sealed flask inside the glove box.

NMR spectra were recorded on a Varian Unity 400 MHz (1D spectra) or a Varian Unity 500 MHz (2D spectra) machine. Mass spectral analysis was done on a VG Analytical ZabSpec sector instrument. Chromatographic analyses were carried out using a Varian Star 3400 CX gas chromatograph using a chiral stationary phase column (heptakis (6-O-methyl-2,3-di-O-pentyl)-cyclodextrin).[23] All analyses were done at 85°C (injector 225°C, detector 250°C) using He (2 ml/min.) as a carrier gas. (*S*)-2-(1-Pyrrolidinylmethyl)pyrrolidine **P-1** used for comparison was synthesised according to literature methods.[11–15]

3.2. Preparation of (S)-3,3-dimethyl-1-[N-(benzyloxycarbonyl)prolyl]pyrrolidine 7

Dicyclohexylcarbodiimide (DCC, 2.92 g, 14.1 mmol) in 5 mL of CH_2Cl_2 was added to a solution of (*S*)-N-(benzyloxycarbonyl)proline **5** (3.52 g, 14.1 mmol) in 10 mL of CH_2Cl_2. After stirring the mixture for 30 min at 0°C, 3,3-dimethylpyrrolidine **6**[21] (1.4 g, 14.1 mmol) dissolved in 10 mL CH_2Cl_2 was added dropwise. The reaction temperature was then allowed to rise to room temperature and the mixture was stirred for 68 h. At the end of reaction (monitored by TLC on silica gel; eluent EtOAc:MeOH 4:1; R_f 0.5) the precipitate was filtered off. The slightly yellow CH_2Cl_2 layer was washed with 2% aqueous HCl solution (20 mL), 4% aqueous $NaHCO_3$ solution (20 mL), water (20 mL) and brine (20 mL) before drying over anhydrous Na_2SO_4. Filtration and evaporation of the solvent gave a pale yellow oil (3.9 g). The crude product was purified by flash chromatography on TLC grade silica gel using EtOAc:hexane (9:1) as an eluent (R_f 0.25) and increasing the solvent polarity with MeOH. Yield 2.4 g (52%); recrystallized from EtOAc:hexane (1:1); mp, 65–68°C; GC–(EI)MS: 330 (M^+, 17), 204 (62), 195 (11), 160 (86), 126 (6), 98 (52), 91 (100), 83 (6), 69 (7), 55 (9), 44 (19); HRMS: M^+ (found) 330.1924, calcd for $C_{19}H_{26}N_2O_3$=330.1943; $[\alpha]_D^{20}$=−6.70 (c=2.03, EtOH); ^{1}H NMR ($CDCl_3$): δ 0.88 (m, 6H), 1.43–2.16 (m, 6H), 3.14–3.70 (m, 6H), 4.36–4.54 (m, 1H), 5.02–5.21 (m, 2H), 7.30–7.40 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$): δ 24.63, 26.09, 26.24, 29.74, 37.52, 39.77, 47.42, 58.18, 58.39, 58.3, 67.06, 128–137, 154.5, 155.5, 171.5 and 171.9 ppm.

3.3. Preparation of (S)-2-[1-(3,3-dimethyl)pyrrolidinylmethyl]pyrrolidine **P-4**

Pd/C catalyst (10%, 69 mg) was added to a solution of (*S*)-3,3-dimethyl-1-[N-(benzyloxycarbonyl)prolyl]pyrrolidine **7** (1.55 g, 4.69 mmol) in 20 mL of dry methanol, and the mixture hydrogenated in a PARR-apparatus for 24 h. After removal of the catalyst by filtration over Celite, and the methanol by rotary evaporator, 960 mg of crude **8** was obtained as an oil. Both TLC and NMR indicated the desired product that was used in the next step without purification.

To a suspension of $LiAlH_4$ (0.9 g, 24 mmol) in 100 mL of dry THF cooled to 0°C and kept under a nitrogen atmosphere, was dropwise added crude **8** dissolved in 10 mL THF. The mixture was refluxed for 20 h and monitored by TLC. When the reaction was complete 2 mL of saturated Na_2SO_4 solution was carefully added. The solution was filtered under suction and THF removed on a rotary evaporator. The product was stripped twice with dry toluene to remove traces of water. The crude **P-4** as oil was purified by bulb-to-bulb distillation (bp 100°C/0.5 mbar) and obtained as a colourless oil. Yield 50% (430 mg, 2.36 mmol); GC–MS (CI): 183 (M+1, 7), 131 (10), 119 (6) 112 (100); HRMS: (M+1) found: 183.1857, calcd for $C_{11}H_{22}N_2$: 183.1861; $[\alpha]_D^{21}$=+14.2 (c=2.62, EtOH); ^{1}H NMR ($CDCl_3$): δ 1.04 (s, 6H), 1.30 (m, 1H), 1.52 (t, 2H), 1.69 (m, 2H), 1.82 (m, 1H), 2.23–2.28 (2H), 2.34–2.44 (2H), 2.57 (m, 2H), 2.82 (m, 1H), 2.93 (m, 1H), 3.14 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 25.16 (CH_2), 29.75 (CH_3), 30.07 (CH_2), 37.70 ($C(CH_3)_2$), 39.82 (CH_2), 46.18 (CH_2), 54.90 (CH_2), 57.29 (CH), 62.26 (CH_2), 68.88 (CH_2) ppm; UV (EtOH): 285 (2100).

3.4. Enantioselective deprotonation of **2** with **1** or **4**

To an ice cooled solution of diamine precursor (0.61 mmol) in 2 mL of THF was added 0.61 mmol of n-BuLi (1.7 M in hexane). The reaction mixture was kept at 0°C for 30 minutes. Cyclohexene oxide **2** (0.51 mmol) was added and reaction mixture was allowed to reach ambient temperature. At intervals, 10 mL of the sample was withdrawn and the reaction was quenched with 100 mL of sat. ammonium chloride solution, diluted with DEE, neutralised with 0.5 M HCl, washed with brine and water and dried over anhydrous sodium sulphate. The mixture was then analysed by GC with a chiral stationary phase column.

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