

Ambient temperature zincation of *N*-Boc pyrrolidine and its solvent dependency[†]

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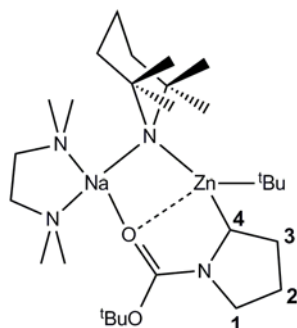
Experimental Section

General Methods

General: All reactions were performed under a protective argon atmosphere using standard Schlenk techniques. Hexane and toluene were dried by heating to reflux over sodium benzophenone ketyl and distilled under nitrogen prior to use. Butylsodium¹ and di-*t*-butylzinc² were prepared according to literature methods. NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer, operating at 400.03 MHz for ¹H and 100.60 MHz for ¹³C.

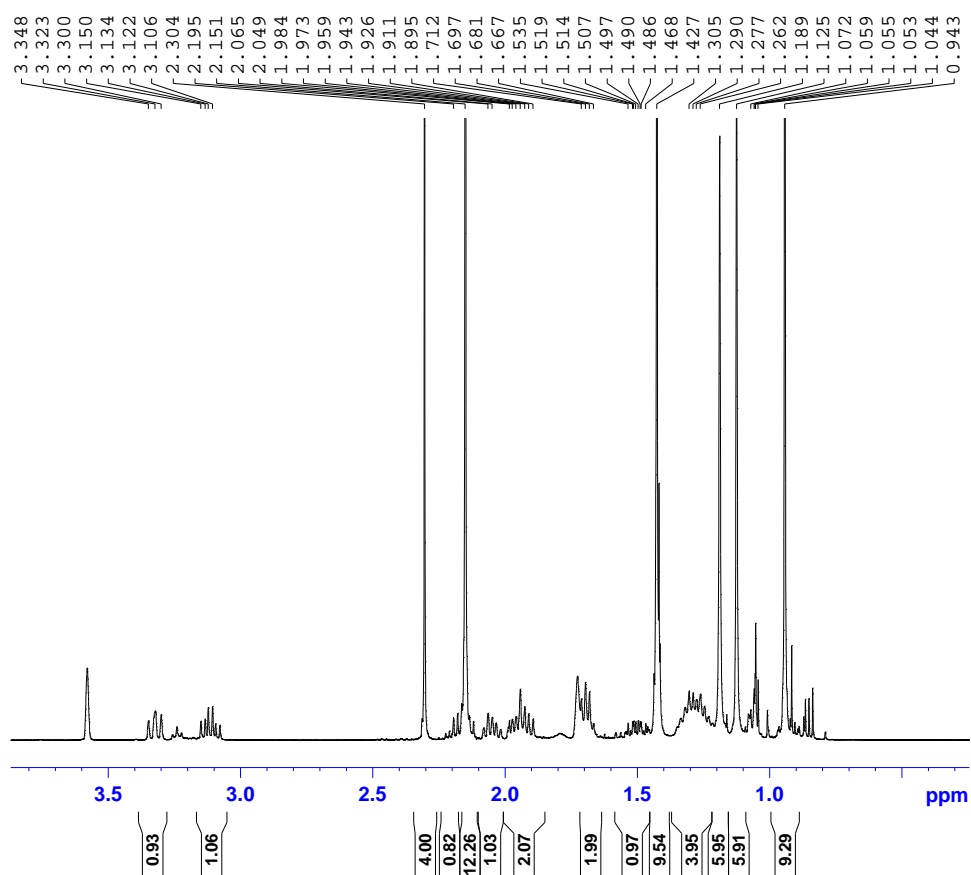
Synthesis of [(TMEDA)Na(μ -TMP)(μ -Boc-NC₄H₇)Zn(^tBu)] (2)

TMPH (0.17 mL, 1 mmol) was transferred *via* syringe to a suspension of freshly prepared ⁿBuNa (0.08 g, 1 mmol) in hexane (5 mL). The colourless suspension was allowed to stir for 1 hour at ambient temperature. A solution of ^tBu₂Zn (0.18 g in 5 mL hexane, 1 mmol) was transferred to the reaction mixture *via* cannula, followed by TMEDA (0.15 mL, 1 mmol). Gentle heating produced a pale yellow solution, to which *N*-Boc pyrrolidine (0.18 mL, 1 mmol) was added *via* syringe to form a brown oil. The reaction mixture was transferred to the freezer at -70°C and colourless crystals were obtained after 4 h (0.37 g, 65% yield).

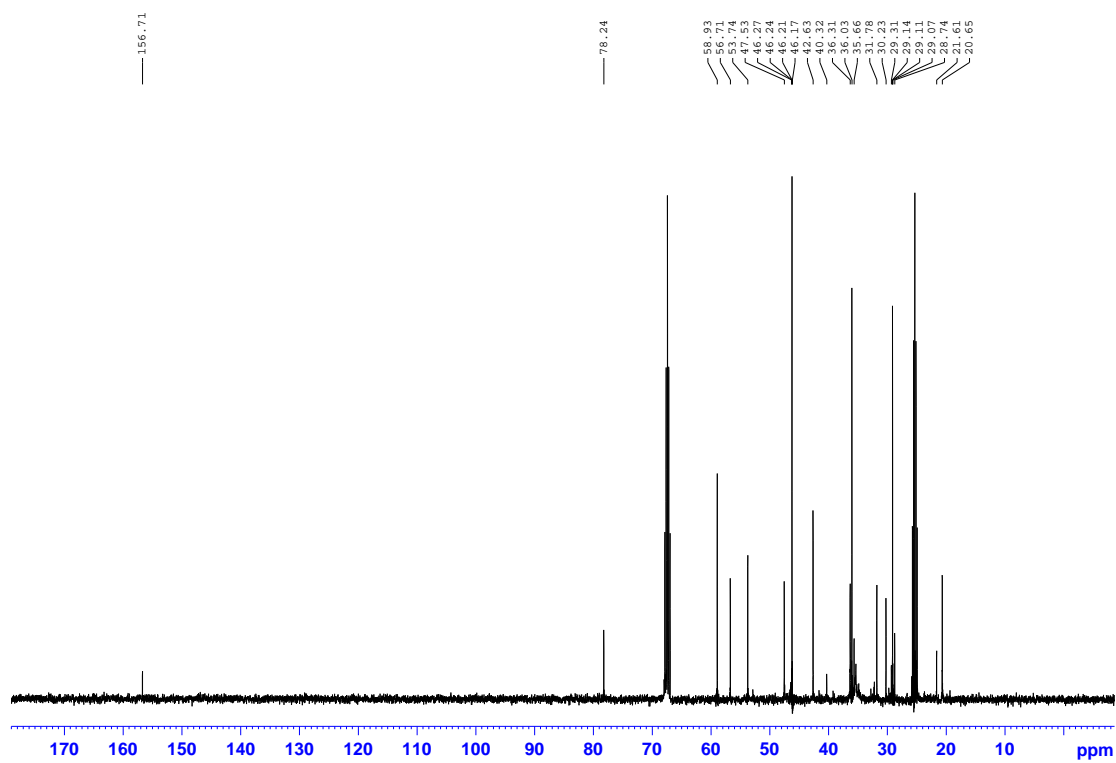


¹H NMR (25°C, 400.03 MHz, *d*₈-THF) δ = 3.32 (m, 1H, 1-NC₄H₇) 3.12 (m, 1H, 1-NC₄H₇) 2.30 (s, 4H, CH₂-TMEDA) 2.19 (m, 1H, 3-NC₄H₇) 2.15 (s, CH₃-TMEDA) 2.05 (m, 1H, 3-NC₄H₇) 1.94 (m, 2H, overlapping signals for 2-NC₄H₇ and 4-NC₄H₇) 1.69 (m, 2H, γ -TMP) 1.51 (m, 1H, 2-NC₄H₇) 1.43 (s, 9H, O^tBu) 1.28 (m, 4H, β -TMP) 1.19 and 1.13 (s, 6H, CH₃-TMP) 0.94 (s, 9H, ^tBu); ¹³C NMR (25°C, 100.60 MHz, *d*₈-THF) δ = 156.71 (s, CO) 78.24 (O^tBu quaternary) 58.93 (s, CH₂-TMEDA) 56.71 (s, 4-NC₄H₇) 53.74 (s, α -TMP quaternary) 47.53 (1-NC₄H₇) 46.17 (s, CH₃-TMEDA) 42.63 (s, β -TMP) 36.31 (br s, CH₃-TMP) 36.00 (s, ^tBu) 31.78 (s, 3-NC₄H₇) 30.78 2-NC₄H₇) 29.14 (s, O^tBu) 21.61 (s, ^tBu quaternary) 20.65 (s, γ -TMP).

^1H NMR Spectrum of **2**



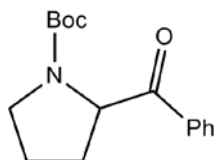
^{13}C NMR Spectrum of **2**



Reaction of **2** with benzoylchloride: synthesis of 2-benzoylpyrrolidine-1-carboxylic acid *t*-butyl ester

To a suspension of NaTMP, prepared from freshly prepared ⁿBuNa (0.16 g, 2 mmol) and TMPH (0.34 mL, 2 mmol) in hexane (10 mL), a solution of ^tBu₂Zn (0.36 g, 2 mmol in 10 mL hexane) was added. Addition of TMEDA (0.30 mL, 2 mmol) to the colourless precipitate produced a pale yellow solution upon gentle heating. Crystalline sodium zincate [(TMEDA)Na(μ-TMP)(μ-^tBu)Zn(^tBu)] (**1**) was deposited after 1 hour upon cooling the solution to -28°C. Crystalline **1** (0.46 g, 1 mmol) was dissolved in hexane (10 mL) and *N*-Boc pyrrolidine (0.18 mL, 1 mmol) was added to the pale yellow solution. The reaction was allowed to stir at ambient temperature for 24 hours. All volatiles were then removed *in vacuo*, THF (10 mL) was added and the resultant solution was cooled to 0°C. CuCl (0.05 g, 0.5 mmol) was added and the black solution formed was allowed to stir for 5 mins. Following this, benzoylchloride (0.48 mL, 4 mmol) was added slowly under stirring.³ After 30 minutes the ice bath was removed and after a further 30 minutes, deionised water (20 mL) and hexane (20 mL) were added. The organic layer was separated from the aqueous layer and the aqueous layer was washed with hexane (3 x 10 mL). Magnesium sulphate was used to dry the combined organic layers. Solvent was removed *in vacuo* and the resultant colourless oil was purified using flash column chromatography on silica with a 19:1 hexane-EtOAc eluent (increased to pure EtOAc over a period of 35 minutes). 2-Benzoylpyrrolidine-1-carboxylic acid *t*-butyl ester (0.21 g, 76.3 %) was obtained as a colourless oil; R_F 4:1 (hexane-EtOAc) 0.4.

When a crystalline sample of **2** was dissolved in THF (10 mL) and immediately used in a similar reaction, an improved yield of 2-benzoylpyrrolidine-1-carboxylic acid *t*-butyl ester (0.24 g, 87.2 %) was achieved.



2-benzoylpyrrolidine-1-carboxylic acid *t*-butyl ester

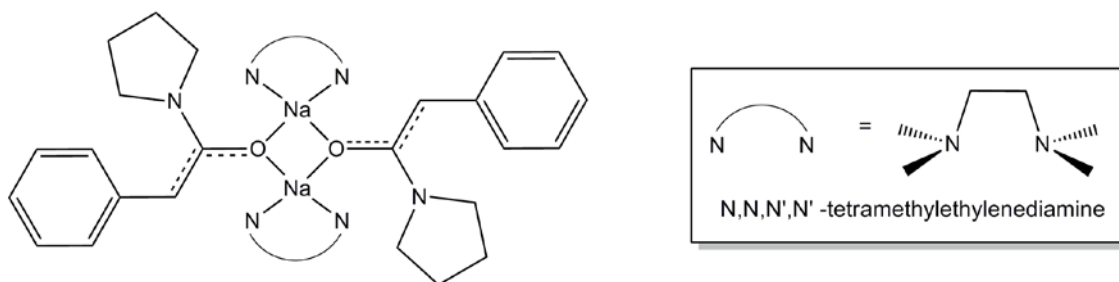
Supporting Information

^1H NMR (25°C, 400.03 MHz, CDCl_3) (60:40 mixture of rotamers) δ 8.01-7.95 (m, 2H, *m*-Ph), 7.59-7.54 (m, 1H, *p*-Ph), 7.51-7.44 (m, 2H, *o*-Ph), 5.35 (dd, $J = 9.4, 3.4$ Hz, 0.4H, NCH) 5.19 (dd, $J = 8.8, 3.9$ Hz, 0.6H, NCH), 3.70-3.50 (m, 2H, NCH_2), 2.34-2.30 (m, 1H, CH_2), 1.97-1.91 (m, 3H, CH_2) 1.48 (s, 3.9H, CMe_3) 1.27 (s, 5.6H, CMe_3); ^{13}C NMR (25°C, 100.60 MHz, CDCl_3) (rotamers) δ 198.9 (PhC=O), 198.4 (PhC=O), 154.5 (C=O, Boc) 153.8 (C=O, Boc) 135.3 (*ipso*-Ph), 135.1 (*ipso*-Ph) 128.7 (Ph), 128.6 (Ph) 128.6 (Ph), 128.5 (Ph), 128.2 (Ph), 79.8 (CMe_3), 79.6 (CMe_3), 61.4 (NCH), 61.1 (NCH), 46.8 (NCH_2), 46.6 (NCH_2), 30.9 (CH_2), 29.7 (CH_2), 28.5 (CMe_3), 28.2 (CMe_3), 24.2 (CH_2), 23.6 (CH_2). Spectroscopic data are consistent with those reported in the literature.⁴

Synthesis of $[(\text{TMEDA})\text{Na}[\text{OC}(\text{NC}_4\text{H}_8)\text{CHPh}]]_2$, (3)

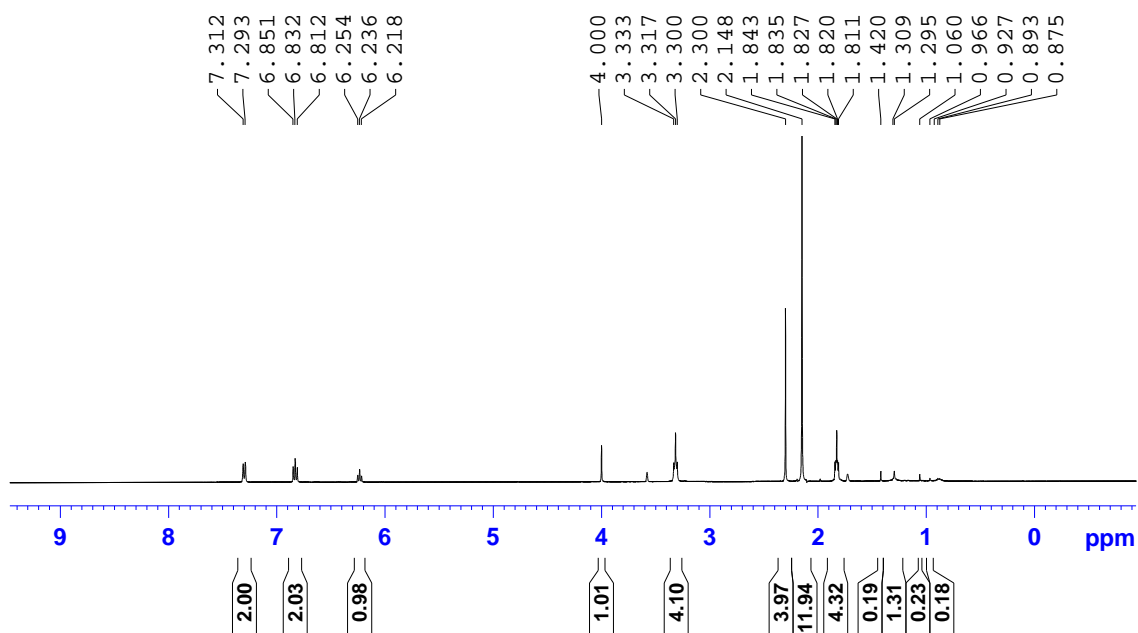
The heterotrianiionic zincate $[(\text{TMEDA})\text{Na}(\mu\text{-TMP})(\mu\text{-Boc-NC}_4\text{H}_7)\text{Zn}(\text{tBu})]$ (2) was prepared on a 2 mmol scale *via* the preparation method detailed above. Toluene (10 mL) was subsequently added, producing a yellow-brown solution that was allowed to stir for 10 minutes at ambient temperature. The resultant solution was transferred to the refrigerator (at 4°C) and pale yellow crystals (0.12 g, 18%) were obtained after 24 h.

Alternative rational synthesis – *N*-Boc pyrrolidine (0.35 mL, 2 mmol) was transferred *via* syringe to an orange suspension of benzyl sodium (0.23 g, 2 mmol) in hexane (10 mL), producing a pale brown solution. TMEDA (0.3 mL, 2 mmol) was subsequently added *via* syringe to the mixture, forming an orange suspension. Toluene (10 mL) was added and the reaction mixture was heated, producing an orange solution that was transferred to the refrigerator (at 4°C). A crop of pale yellow crystals (0.10 g, 15%) was deposited after 72 h.

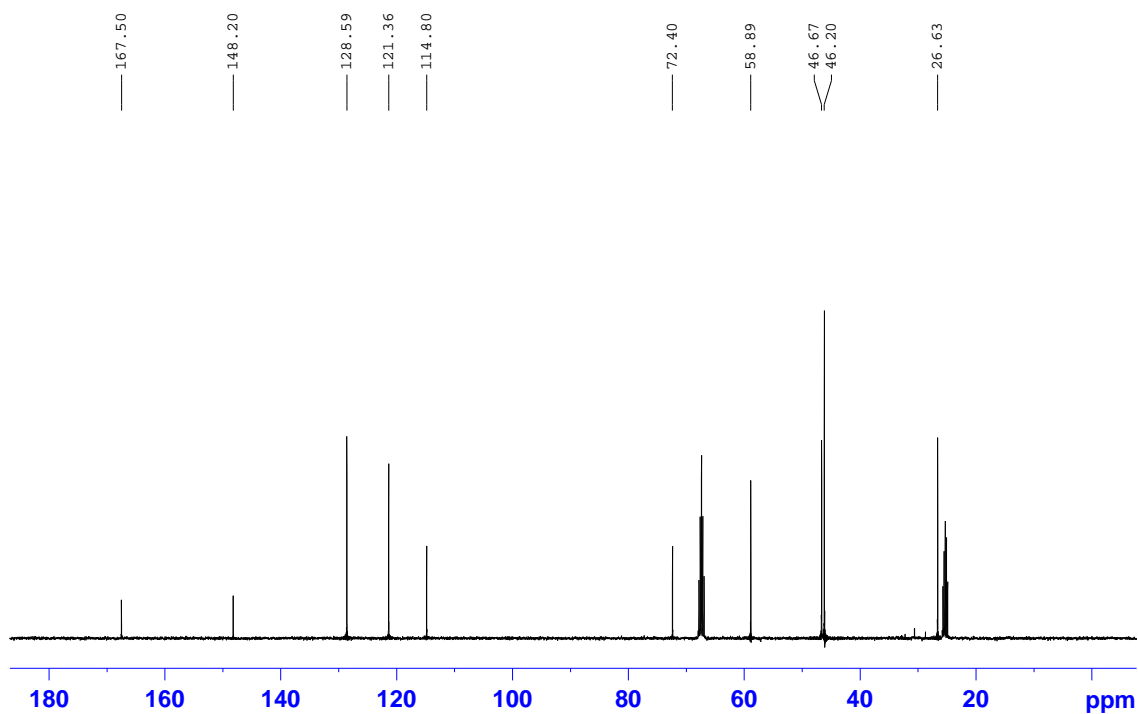


^1H NMR (25°C, 400.03 MHz, C_6D_6) δ = 7.30 (d, J = 7.1 Hz, 2H, *o*- C_6H_5) 6.83 (apparent t, J = 7.7 Hz, 1H, *p*- C_6H_5) 6.23 (t, J = 7.1 Hz, 2H, *m*- C_6H_5) 4.00 (s, 1H, =CH) 3.31 (t, 4H, $\alpha\text{-NC}_4\text{H}_8$) 2.30 (s, 4H, CH_2 TMEDA) 2.15 (s, 12H, CH_3 TMEDA) 8.20 (t, 4H $\beta\text{-NC}_4\text{H}_8$); ^{13}C NMR (25°C, 100.60 MHz, C_6D_6) δ = 167.5 (s, CO) 148.20 (s, *i*- C_6H_5) 128.6 (s, *m*- C_6H_5) 121.3 (s, *o*- C_6H_5) 114.8 (s, *p*- C_6H_5) 72.4 (s, =CH) 58.9 (s, CH_2 TMEDA) 46.7 (s, $\alpha\text{-NC}_4\text{H}_8$) 46.2 (s, CH_3 TMEDA) 26.6 (s, $\beta\text{-NC}_4\text{H}_8$).

^1H NMR Spectrum of 3



^{13}C NMR Spectrum of 3



Control Reaction between *N*-Boc pyrrolidine and ^tBu₂Zn

TMEDA (0.05 mL, 0.3 mmol) was added to a colourless solution of ^tBu₂Zn (0.12 g, 0.3 mmol) in hexane (5 mL). *N*-Boc pyrrolidine (0.06 mL, 0.3 mmol) was subsequently added and the reaction mixture was allowed to stir for 15 minutes prior to transfer to the freezer at -28°C. After 1 week, the colourless solution was analysed via ¹H NMR spectroscopy, which revealed signals corresponding to free *N*-Boc pyrrolidine, free TMEDA and hexane. The dialkylzinc compound ^tBu₂Zn is highly volatile and is thought to have been removed under vacuum.

References

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