Reactivity series for *s*-BuLi/diamine-mediated lithiation of *N*-Boc pyrrolidine: applications in catalysis and lithiation of *N*-Boc piperidine

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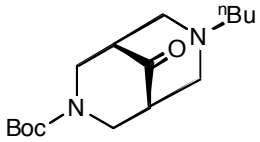
Supporting Information:

Representative experimental procedures for results in Tables 1/2 and Scheme 3, and information on ligand synthesis.

N-Boc pyrrolidine **1**[1] and *N*-Boc piperidine **11**[2] were prepared according to the literature procedures.

Diamines *rac*-TMCDA,[3] **5**,[4] **7**-**9**[5] and **10**[6] were prepared according to the literature procedures.

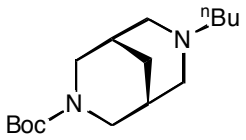
*Diamine **6** was prepared by the following three-step route:*



***tert*-Butyl 7-butyl-9-oxo-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxylate**

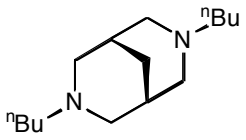
A solution of 1-Boc-4-piperidone (8.0 g, 40.0 mmol), *n*-butylamine (4.0 cm^3, 40.0 mmol), AcOH (2.2 cm^3, 40.0 mmol) and paraformaldehyde (3.6 g, 120.0 mmol) in MeOH (50 cm^3) was stirred and heated at reflux for 16 h. After allowing the solution to cool to rt, the solvent was evaporated under reduced pressure. The residue was treated with 1 M $KOH_{(aq)}$ (40 cm^3) and extracted with Et_2O (3 × 100 cm^3). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography using petrol-Et_2O (7:3) as eluent gave the title compound (6.2 g, 52%) as a colourless oil, R_F(7:3 petrol-Et_2O) 0.2; ν_{max}($CHCl_3$)/cm^{-1} 2935, 2871, 1730 (C=O, ketone) and 1688 (C=O, Boc); δ_H(400 MHz; $CDCl_3$) rotamers 4.62 (1 H, d, *J* 13.5, CHNBoc), 4.45 (1 H, d, *J* 13.5, CHNBoc), 3.34-3.12 (4 H, m), 2.67 (1 H, br dd, *J* 11.0 and 3.0), 2.58 (1 H, br dd, *J* 11.0 and 3.0), 2.41 (1 H, br s, CH), 2.37 (1 H, br s, CH), 2.34-2.16 (2 H, m), 1.49 (9 H, s, CMe_3), 1.50-1.39 (2 H, m), 1.29 (2 H, sextet, *J* 7.5) and 1.49 (3 H, t, *J* 7.5, Me); δ_C(100.6 MHz; $CDCl_3$) rotamers 213.9 (C=O, ketone), 154.9 (C=O, Boc), 79.7 (*C*Me_3), 59.6 (NCH_2), 58.5 (NCH_2), 57.2 (NCH_2), 50.6 (NCH_2), 49.8 (NCH_2), 48.1

(CH), 48.0 (CH), 29.1 (CH_2), 28.4 (C*Me*$_3$), 20.6 (CH_2) and 14.0 (Me); *m/z* (CI, NH_3) 297 [100%, $(M + H)^+$][Found: $(M + H)^+$, 297.2176. $C_{16}H_{28}N_2O_3$ requires *M* + H, 297.2178].



tert-Butyl 7-butyl-9-oxo-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxylate

$TsNHNH_2$ (2.4 g, 13.0 mmol) was added in one portion to a stirred solution of *tert*-butyl 7-butyl-9-oxo-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxylate (3.19 g 10.75 mmol) in EtOH (100 cm^3) at rt under N_2. The resulting solution was stirred and heated at reflux for 3 h. Then, the solvent was evaporated under reduced pressure to give the crude product as a yellow foam. To a stirred solution of the crude product in 9:1 THF-water (50 cm^3) was added $NaBH_4$ (4.0 g, 105.75 mmol) in portions over 1 h. The resulting solution was stirred at rt for 16 h. Then, the solution was stirred and heated at reflux for 2 h. After being allowed to cool to rt, water (50 cm^3) was added and the mixture was extracted with Et_2O (3 × 100 cm^3). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography using 7:3 petrol-Et_2O as eluent gave the title compound (1.37 g, 45%) as a colourless oil, R_F(7:3 petrol-Et_2O) 0.2; $\nu_{max}(CHCl_3)/cm^{-1}$ 2959, 2930, 2870 and 1678 (C=O); δ_H(400 MHz; $CDCl_3$) rotamers 4.15 (1 H, d, *J* 13.5, CHNBoc), 4.03 (1 H, d, *J* 13.5, CHNBoc), 3.08-2.85 (4 H, m), 2.15-2.09 (4 H, m), 1.85-1.61 (4 H, m), 1.47 (9 H, s, CMe_3), 1.46-1.20 (4 H, m) and 0.88 (3 H, t, *J* 7.0, Me); δ_C(100.6 MHz; $CDCl_3$) rotamers 155.1 (C=O), 78.4 (*C*Me_3), 60.0 (NCH_2), 58.9 (NCH_2), 58.6 (NCH_2), 48.7 (NCH_2), 47.7 (NCH_2), 31.7 (CH_2), 29.3 (CH), 29.2 (CH), 29.0 (CH_2), 28.6 (C*Me*$_3$), 20.5 (CH_2) and 14.1 (Me); *m/z* (CI, NH_3) 283 [100%, $(M + H)^+$], 227 (15) and 183 (30)[Found: $(M + H)^+$, 283.2387. $C_{16}H_{30}N_2O_2$ requires *M* + H, 283.2386].



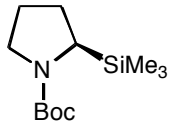
6

3-Butyl-7-butyl-3,7-diaza-bicyclo[3.3.1]nonane 6

TFA (8.0 cm^3, 104.2 mmol) was added dropwise to a stirred solution of *tert*-butyl 7-butyl-9-oxo-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxylate (1.37 g, 4.8 mmol) in CH_2Cl_2 (20 cm^3) at 0 °C under N_2. The resulting solution was stirred at rt for 16 h and the solvent was evaporated under reduced pressure. Then, the residue was dissolved in MeCN (20 cm^3) and K_2CO_3 (3.0 g, 21.7 mmol) and *n*-butyl bromide (0.8 cm^3, 7.45 mmol) were added. The resulting suspension was stirred and heated at reflux for 16 h. After being

allowed to cool to rt, the solids were removed by filtration and washed with Et_2O (20 cm^3). The filtrate was evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave diamine **6** (506 mg, 44%) as a colourless oil, bp 150-180 °C/2 mm Hg (lit.,[7] 115 °C/0.08 mbar); δ_H(400 MHz, $CDCl_3$) 2.83-2.63 (4 H, m), 2.42-2.15 (8 H, m), 1.94 (2 H, br s), 1.60-1.25 (10 H, m), 0.89 (6 H, t, *J* 7.0, Me). Spectroscopic data identical to that reported previously.[7]

Representative procedure for the competition experiments presented in Table 1:



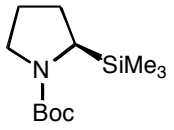
(*R*)-**4**

(*R*)-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine (*R*)-4 (Table 1, entry 4)

s-BuLi (3.55 cm^3 of a 1.23 M solution in cyclohexane, 4.36 mmol, 2.6 equiv.) was added dropwise to a stirred solution of (–)-sparteine (511 mg, 2.18 mmol, 1.3 equiv.) and diamine **5** (424 mg, 2.18 mmol, 1.3 equiv.) in Et_2O (20 cm^3) at –78 °C under Ar. After stirring at –78 °C for 10 min, a solution of *N*-Boc pyrrolidine **1** (287 mg, 2.68 mmol, 1.0 equiv.) in Et_2O (5 cm^3) was added dropwise over 10 min *via* a cannula and the resulting solution was stirred at –78 °C for 5 h. Then, Me_3SiCl (0.59 cm^3, 4.68 mmol, 2.8 equiv.) was added dropwise and the solution was allowed to warm to rt over 16 h. 5% $H_3PO_{4(aq)}$ (10 cm^3) was added and the solution was stirred for 20 min. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 cm^3). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography with 19:1 petrol-EtOAc as eluent gave adduct (*R*)-**4** (252 mg, 62%, 90:10 er by chiral GC) as a colourless oil, $[\alpha]_D$ –59.6 (*c* 1.18 in $CHCl_3$)(lit.,[8] $[\alpha]_D$ +69.4 (*c* 2.2 in $CHCl_3$) for (*S*)-**4** of 97:3 er); GC: Chiraldex G-PN 20 m × 0.25 mm i.d. (γ-cyclodextrin, propionyl derivative in the 3 position), t_R: 27.3 min [(*R*)-**4**]; 28.2 min [(*S*)-**4**]. Spectroscopic data identical to that reported previously.[8]

All other competition experiments reported in Table 1 were carried out in the same way.

Representative procedure for the catalysis experiments presented in Table 2:

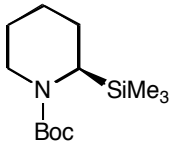


(*R*)-**4**

(*R*)-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine (*R*)-4 (Table 2, entry 6)

s-BuLi (3.1 cm^3 of a 1.2 M solution in cyclohexanes, 3.70 mmol, 1.3 equiv.) was added dropwise to a stirred solution of diamine **5** (167 mg, 0.86 mmol, 0.3 equiv.) and bispidine **10** (598 mg, 2.85 mmol, 1.0 equiv.) in Et_2O (10 cm^3) at –78 °C under Ar. After stirring at –78 °C for 10 min, a solution of *N*-Boc pyrrolidine **1** (488 mg, 2.85 mmol, 1.0 equiv.) in Et_2O (5 cm^3) was added dropwise over 10 min *via* a cannula and the resulting solution was stirred at –78 °C for 5 h. Then, Me_3SiCl (0.47 cm^3, 3.70 mmol, 1.3 equiv.) was added dropwise and the solution was allowed to warm to rt over 16 h. 5% $H_3PO_{4(aq)}$ (10 cm^3) was added and the solution was stirred for 20 min. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 cm^3). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography with 19:1 petrol-EtOAc as eluent gave adduct (*R*)-**4** (540 mg, 78 %, 94:6 er by chiral GC) as a colourless oil, $[\alpha]_D$ –61.9 (*c* 1.0 in $CHCl_3$)(lit.,[8] $[\alpha]_D$ +69.4 (*c* 2.2 in $CHCl_3$) for (*S*)-**4** of 97:3 er); GC: Betadex 120 30 m × 0.25 mm i.d. (β-cyclodextrin) T 92 °C isothermal, He carrier gas at 14 psi constant pressure t_R: 106.7 min [(*S*)-**4**] 108.6 min [(*R*)-**4**]. Spectroscopic data identical to that reported previously.[8]

All other catalysis experiments reported in Table 2 were carried out in the same way.



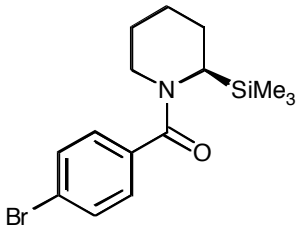
(*R*)-**12**

(*R*)-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpiperidine (*R*)-12 (Scheme 3)

s-BuLi (1.33 cm^3 of a 1.25 M solution in cyclohexanes, 1.65 mmol, 1.4 equiv.) was added dropwise to a stirred solution of diamine **5** (511 mg, 2.84 mmol, 2.4 equiv.) in Et_2O (4 cm^3) at –78 °C under N_2. After stirring at –78 °C for 10 min, a solution of *N*-Boc piperidine **11** (219 mg, 1.18 mmol, 1.0 equiv.) in Et_2O (2 cm^3) was added dropwise over 10 min *via* a cannula and the resulting solution was stirred at –78 °C for 6 h. Then, Me_3SiCl (0.24 cm^3, 1.81 mmol, 1.6 equiv.) was added dropwise and the solution was allowed to

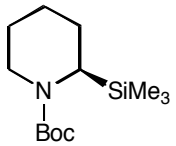
warm to rt over 16 h. 5% $H_3PO_{4(aq)}$ (5 cm^3) was added and the solution was stirred for 20 min. The layers were separated. The organic layer was washed with 5% $H_3PO_{4(aq)}$ (5 cm^3) and the combined aqueous layers were extracted with Et_2O (2 × 10 cm^3). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography with 97:3 petrol-EtOAc as eluent gave adduct (*R*)-**12** (86 mg, 28% of 73:27 er by chiral HPLC of the *p*-bromobenzamide) as a colourless oil, $[\alpha]_D$ –16.0 (*c* 1.16 in $CHCl_3$). Spectroscopic data identical to that reported previously.[9]

Method for the determination of the er of adduct (*R*)-12:



4-Bromophenyl-(2-trimethylsilanyl-piperidin-1-yl)-methanone

TFA (0.24 cm^3, 3.11 mmol) was added dropwise to a stirred solution of adduct (*R*)-**12** (80 mg, 0.31 mmol) in CH_2Cl_2 (10 cm^3) at 0 °C under N_2. The resulting solution was stirred at rt for 3 h and the solvent was evaporated under reduced pressure. Then, the residue was dissolved in CH_2Cl_2 (10 cm^3) and Et_3N (0.25 cm^3, 1.86 mmol) and *p*-bromobenzoyl chloride (270 mg, 1.8 mmol) were added. The resulting suspension was stirred and heated at reflux for 16 h. Water (10 cm^3) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 cm^3) and the combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography using 7:3 hexane- Et_2O as eluent gave the title compound (54 mg, 49%, 73:27 er by chiral HPLC) as a yellow oil, HPLC: Chiralcel OD 0.5 cm^3 min^{-1}, 330:1 v/v hexane/*i*-PrOH, 254 nm, 24.4 min (*R*); 26.2 min (*S*). Spectroscopic data identical with that reported previously.[9]



(*R*)-**12**

(*R*)-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpiperidine (*R*)-12 (Scheme 3)

s-BuLi (1.38 cm^3 of a 1.20 M solution in cyclohexanes, 1.65 mmol, 1.4 equiv.) was added dropwise to a stirred solution of (*R*,R)-TMCDA (484 mg, 2.84 mmol, 2.4 equiv.) in Et_2O (10 cm^3) at –78 °C under N_2.

After stirring at –78 °C for 10 min, a solution of *N*-Boc piperidine **11** (219 mg, 1.18 mmol, 1.0 equiv.) in Et_2O (2 cm^3) was added dropwise over 10 min *via* a cannula and the resulting solution was stirred at –78 °C for 6 h. Then, Me_3SiCl (0.24 cm^3, 1.81 mmol, 1.6 equiv.) was added dropwise and the solution was allowed to warm to rt over 16 h. 5% $H_3PO_{4(aq)}$ (5 cm^3) was added and the solution was stirred for 20 min. The layers were separated. The organic layer was washed with 5% $H_3PO_{4(aq)}$ (5 cm^3) and the combined aqueous layers were extracted with Et_2O (3 × 10 cm^3). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography with 97:3 petrol-EtOAc as eluent gave adduct (*R*)-**12** (110 mg, 36%, 55:45 er by chiral GC) as a colourless oil, $[\alpha]_D$ –1.4 (*c* 1.01 in $CHCl_3$); GC: Betadex 120 30 m × 0.25 mm i.d. (β-cyclodextrin) T 92 °C isothermal, He carrier gas at 14 psi constant pressure t_R: 123.9 min [(*S*)-**12**] 125.6 min [(*R*)-**12**]. Spectroscopic data identical to that reported previously.[9]

References for Supporting Information

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