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Dynamic thermodynamic resolution of lithiated *N*-Boc-*N*′-alkylpiperazines

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Dedicated to Professor S. Florio on the occasion of his 70th birthday

ABSTRACT

Deprotonation of *N*-Boc-*N*′-alkylpiperazines with *sec*-BuLi in Et_2O–TMEDA gave the 2-lithio derivatives which were resolved in the presence of a chiral ligand. The best ligands for the asymmetric substitution were diamino-alkoxides that promoted a dynamic thermodynamic resolution (DTR) of the organolithium at −30 °C. Electrophilic quench gave enantiomerically enriched 2-substituted piperazines. Of a selection of piperazines, the *N*′-*t*-butyl derivative gave the best results, with the product *N*-Boc-*N*′-*t*-butyl-2-substituted piperazines being formed with enantiomer ratios up to 81:19.

α-Lithiation of an acyclic or cyclic *N*-Boc compound, followed by trapping with an electrophile, is an increasingly common strategy to access synthetically useful 2-substituted nitrogen-containing molecules.[1] Seminal work in this field was carried out by Beak and co-workers,[2] with important contributions from other research groups.[3,4]

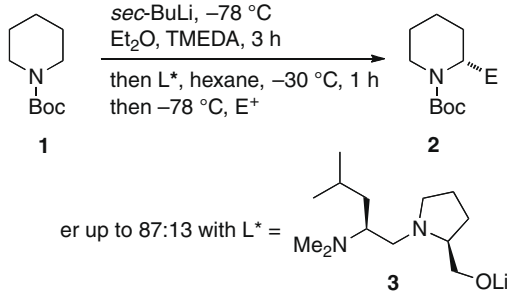
Typically, the base, *n*-BuLi or *sec*-BuLi in Et_2O and TMEDA, is used to deprotonate α- to the nitrogen atom. The chiral ligand (−)-sparteine, or other chiral ligands, can sometimes allow asymmetric deprotonation.[5] In contrast to asymmetric deprotonation, the configurational lability of the lithiated carbanion at temperatures above about −50 °C can allow a dynamic resolution to induce asymmetry.[6] In this chemistry, the chiral ligand complexes to the racemic organolithium, giving diastereomeric complexes that can be resolved under thermodynamic or kinetic control. In dynamic thermodynamic resolution (DTR), the electrophilic quench is normally carried out after cooling (to prevent further equilibration).

Recently, we successfully illustrated the application of DTR to the organolithium derived from deprotonation of *N*-Boc-piperidine (**1**) to give *N*-Boc-2-substituted piperidines **2** with good yields and with a good enantiomer ratio (er) (Scheme 1).[7] Diamino alkoxide ligands such as **3** were found to be among the best of those screened, leading to the products **2** with er up to 87:13.

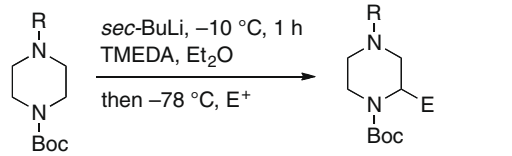
In contrast with *N*-Boc-piperidine, there are only a few reports of the α-lithiation of *N*-Boc-*N*′-alkylpiperazines, despite the synthetic and medicinal utility of such compounds. In 2005, van den Hoogenband, van Maarseveen and co-workers reported the racemic lithiation of *N*-Boc-*N*′-benzyl- and *N*-Boc-*N*′-methylpiperazines **4** and **5** followed by electrophilic quench (Scheme 2).[8] The electrophile TMSCl was more successful for the piperazine **4** (to give **6a**), but both substrates gave good yields of the products **6b** and **7b** with the electrophile Bu_3SnCl.

Recently, the piperazine **8** was treated with *sec*-BuLi in Et_2O and (−)-sparteine by McDermott et al. (Scheme 3).[9] Asymmetric deprotonation, followed by a CO_2 quench and coupling with *N*-benzylpiperazine, gave the enantioenriched product **9**.

The asymmetric synthesis of 2-substituted piperazines is important in medicinal chemistry.[10] We were therefore interested in studying the DTR of 2-lithiated piperazines and report here our initial attempts in this area.



Scheme 1. Dynamic resolution of *N*-Boc-2-lithiopiperidine.



Scheme 2. Racemic deprotonation–electrophilic quench.

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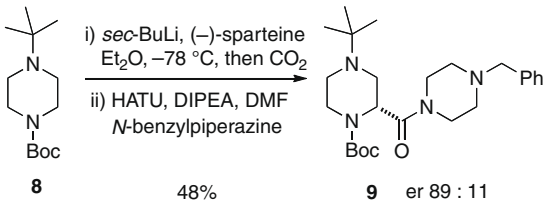


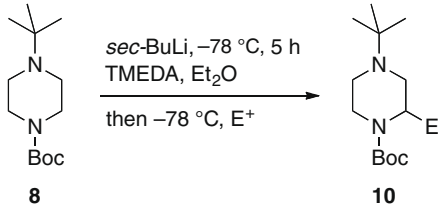
Scheme 3. Asymmetric deprotonation of piperazine **8**.

N-Boc-*N*′-benzyl- and *N*-Boc-*N*′-methylpiperazines **4** and **5** were prepared by treatment of commercially available 1-benzylpiperazine and 1-methylpiperazine with Boc_2O. *N*-Boc-*N*′-*t*-butylpiperazine **8** was prepared by mono-Boc protection of piperazine,[11] followed by treatment with KCN and acetone and then addition of MeMgBr according to the reported procedure.[9]

As the piperazine **8** has not been studied for lithiation, other than as shown in Scheme 3, we investigated the use of *sec*-BuLi in Et_2O and TMEDA followed by the addition of several electrophiles (Scheme 4, Table 1). The products **10** were formed in good yield. In each case the enantiomers could be resolved by chiral GC analysis.

Initial studies on the DTR of lithiated piperazines were conducted with *N*-Boc-*N*′-benzylpiperazine (**4**). Deprotonation of the piperazine **4** with *sec*-BuLi in Et_2O and TMEDA was followed by the addition of a chiral ligand (L*) at −78 °C and equilibration at elevated temperature (Scheme 5). The resolved diastereomeric complexes were quenched with TMSCl at −78 °C to give the product **6a**. The configuration of the major (*S*)-enantiomer was assigned on the basis of related chemistry with *N*-Boc-2-lithiopiperidine.[7] With the chiral ligand **3**, a good er was obtained after equilibration at −30 °C for 1 h or 1.5 h (Table 2, entries 1 and 2). Several other diamino-alkoxide ligands (**11**–**13**)[7] were also screened and gave similar levels of enantioselectivity. At higher temperatures, there was no improvement in the er suggesting that the thermodynamic ratio of the diastereomeric complexes had been achieved.

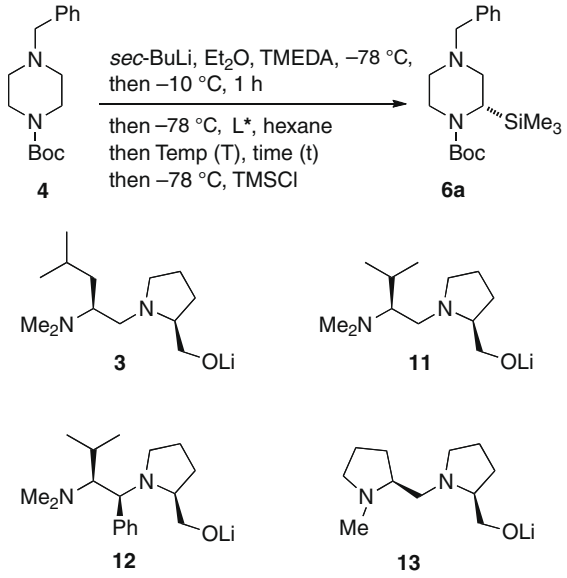
The yield of the silane product **6a** was reasonable (Scheme 6, Table 3, entry 1)[12] and so we opted to use these conditions for a selection of substrates and electrophiles. Unfortunately, we have not yet found a method suitable to determine the er of the products **6** from the electrophilic quench with MeI or Bu_3SnCl, so we turned to the DTR of the piperazine **5**. We anticipated that the piperazine **5** would give similar results and were pleased to find that deprotonation, then DTR with the chiral ligand **3** followed by electrophilic quench with MeI gave the product **7c**, E = Me with a reasonable enantioselectivity (Table 3, entry 2). However, addition of the electrophile Bu_3SnCl surprisingly gave a lower er (Table 3, entry 3). The use of DMF as the electrophile (Table 3, entry 4) resulted in a reasonable yield but poor er of the product **7d**, E = CHO. This is most likely due to racemization of the product as a result of enolization during work-up or purification (the GC of the crude product showed a higher er than that after column chromatography). The best substrate was *N*-Boc-*N*′-*t*-butylpiperazine **8**, which, under the optimized DTR conditions gave reasonable yields and



Scheme 4. Racemic deprotonation–electrophilic quench of **8**.

Table 1
Yields of products (±)-**10**

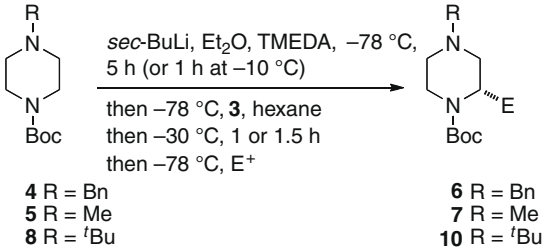
Entry	E^+	E	Product	Yield (%)
1	TMSCl	$SiMe_3$	**10a**	69
2	Bu_3SnCl	$SnBu_3$	**10b**	77
3	MeI	Me	**10c**	71
4	DMF	CHO	**10d**	66
5	CO_2	CO_2H	**10e**	65



Scheme 5. Initial DTR studies with the piperazine **4** and ligands **3** and **11**–**13**.

Table 2
Optimization of the DTR using piperazine **4**

Entry	Ligand	T (°C)	Time (h)	er **6a**
1	**3**	−30	1	80:20
2	**3**	−30	1.5	80:20
3	**11**	−30	1.5	80:20
4	**12**	−30	1.5	78:22
5	**13**	−10	1	77:23



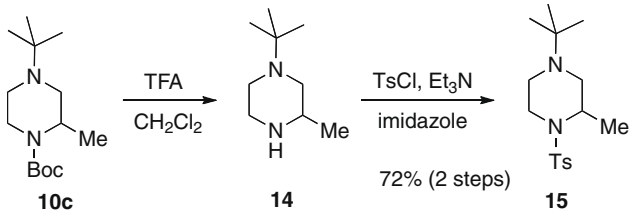
Scheme 6. General procedure for DTR of 2-lithiated piperazines.

enantioselectivities of products **10** after equilibration at −30 °C for 1.5 h (Table 3, entries 5–8).[13]

Substituted piperazines with differentially protected nitrogen atoms are likely to find use in medicinal drugs. Therefore we studied the removal of the *N*-Boc group from the racemic piperazine **10c** (Scheme 7). This was successful and gave the volatile piperazine **14** which was treated with *p*-toluenesulfonyl chloride to give the product **15**. As yet, we have not found conditions to remove the *N*-*t*-butyl group from the piperazines **14** or **15**.

Table 3
Yields and er for the DTR of lithiated piperazines with ligand **3**

Entry	R	E	Product	Yield (%)	er
1	Bn	$SiMe_3$	**6a**	48	80:20
2	Me	Me	**7c**	35	77:23
3	Me	$SnBu_3$	**7b**	34	65:35
4	Me	CHO	**7d**	57	60:40
5	^{t}Bu	$SiMe_3$	**10a**	64	77:23
6	^{t}Bu	$SnBu_3$	**10b**	75	76:24
7	^{t}Bu	Me	**10c**	52	80:20
8	^{t}Bu	CHO	**10d**	49	60:40
9	^{t}Bu	CO_2H	**10e**	30	81:19



Scheme 7. Removal of the *N*-Boc group from piperazine **10c**.

In summary, the first DTR reactions of various 2-lithiated piperazines are reported. Moderate yields and er values were obtained with a selection of *N*-Boc-*N′*-alkylpiperazines using deprotonation with *sec*-BuLi in Et_2O–TMEDA and resolution with the chiral ligand **3**. This has resulted in the synthesis of enantiomerically enriched 2-substituted piperazine products with er up to 81:19.

Acknowledgements

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12. *sec*-BuLi (0.67 mL, 1.3 M in hexanes) was added to piperazine **4** (100 mg, 0.36 mmol) and TMEDA (0.13 mL, 0.86 mmol) in Et_2O (0.8 mL) at −78 °C. The mixture was warmed to −10 °C for 1 h, then cooled to −78 °C and a solution of the ligand **3** [prepared by adding *sec*-BuLi (0.39 mL, 1.3 M in hexanes) to the alcohol precursor of **3**[7] (107 mg, 0.47 mmol) in Et_2O (0.8 mL)] and then hexane (0.39 mL) was added. The mixture was warmed to −30 °C for 1 h, then cooled to −78 °C and Me_3SiCl (0.16 mL, 1.27 mmol) was added. The mixture was allowed to warm to room temperature over 16 h then aqueous NH_4Cl (1 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol/EtOAc/NEt_3 (90:10:1), gave the piperazine **6a** (60 mg, 48%) as an oil; $[\alpha]_D^{21}$ +11.5 (0.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.22 (5H, m), 5.58 (1H, br s), 3.79 (1H, br s), 3.73 (1H, d, *J* 13.5 Hz), 3.45 (1H, d, *J* 13.5 Hz), 3.37 (1H, br td, *J* 12, 3 Hz), 2.89 (1H, br d, *J* 12 Hz), 2.82 (1H, br d, *J* 12 Hz), 2.18 (1H, td, *J* 12, 3 Hz), 2.08 (1H, dd, *J* 12, 2 Hz), 1.49 (9H, s), 0.13 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.0, 137.4, 129.1, 128.2, 127.1, 80.1, 62.5, 58.3, 52.6, 29.7, 28.4, 0.14; HRMS (ES) found 349.2308, $C_{19}H_{33}N_2O_2Si$ requires MH^+ 349.2311; HPLC analysis (Phenomenex Lux Amylose-2, 0.5% ^{i}PrOH in hexanes) showed the enantiomers eluting at 18.3 min (major) and 22.3 min (minor).
13. In the same way as that for the piperazine **6a**,[12] except that the deprotonation was maintained at −78 °C for 5 h (and not warmed to −10 °C), *sec*-BuLi (0.85 mL, 1.3 M in hexanes), piperazine **8** (200 mg, 0.83 mmol), TMEDA (0.16 mL, 1.08 mmol), the ligand **3** [prepared by adding *sec*-BuLi (0.89 mL, 1.3 M in hexanes) to the alcohol precursor of **3**[7] (247 mg, 1.08 mmol) in Et_2O (1.7 mL)], hexane (1.6 mL) and Me_3SiCl (0.32 mL, 2.5 mmol) gave, after purification by column chromatography, eluting with petrol/EtOAc (90:10), the piperazine **10a** (166 mg, 64%) as an oil; $[\alpha]_D^{21}$ +11.7 (1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.03 (1H, br s), 3.81 (1H, br s), 3.53 (1H, br s), 2.97 (1H, br s), 2.86 (1H, br s), 2.32 (1H, br s), 2.07 (1H, br s), 1.44 (9H, s), 1.02 (9H, s), 0.10 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 78.9, 53.6, 46.9, 46.2, 45.9, 42.3, 28.5, 25.9, −0.62; HRMS (ES) found 315.2468, $C_{16}H_{35}N_2O_2Si$ requires MH^+ 315.2474; GC analysis (β-cyclodextrin-permethylated, 125 °C) showed the enantiomers eluting at 16.6 min (minor) and 17.5 min (major).