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Asymmetric Deprotonation of *N*-Boc Piperidine: React IR Monitoring and Mechanistic Aspects

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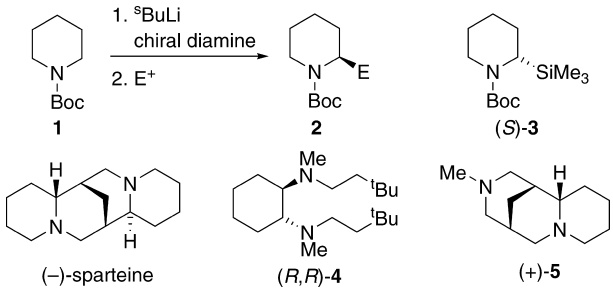
Piperidines are widespread subunits in biologically active natural products and pharmaceuticals. Indeed, 26 of the "Top 200 Brand-Name Drugs by Retail Dollars in 2008"[1] contain piperidine fragments. To provide ready access to molecules for exploring new aspects of 3-D pharmaceutical space, we have investigated the asymmetric synthesis of 2-substituted piperidines. One of the simplest routes to such piperidines is the asymmetric deprotonation-trapping of *N*-Boc-activated piperidine **1** (→ **2**) (Scheme 1) mediated by *s*-BuLi and chiral diamines (e.g., (−)-sparteine).[2,3] Although successful with *N*-Boc pyrrolidine,[2] extension to the 6-ring heterocycle is unsatisfactory.[3,4] For example, lithiation of *N*-Boc piperidine **1** using *s*-BuLi/(−)-sparteine (Et_2O, −78 °C, 16 h) and trapping with Me_3SiCl gave the Me_3Si-adduct (*S*)-**3** (87:13 er) in only 8.5% yield, despite the extended lithiation time. The best result to date was reported by us in 2007: lithiation of **1** with *s*-BuLi/(*R*,*R*)-**4** (Et_2O, −78 °C, 6 h) and reaction with Me_3SiCl gave adduct (*S*)-**3** in 13% yield and 90:10 er.[5] The main limitation with the asymmetric lithiation of *N*-Boc piperidine **1** is the low yield.

Scheme 1



In previous work, we have shown that the chiral base complex formed from *s*-BuLi and (+)-sparteine surrogate **5**[6] is more reactive than the corresponding (−)-sparteine complex.[7] Thus, use of diamine **5** in place of (−)-sparteine was explored in the lithation-trapping of *N*-Boc piperidine **1** (→ **2**) and a high-yielding protocol has been optimized. Herein, we report our results.

First, the known[3] low-yielding lithiation of *N*-Boc piperidine **1** with *s*-BuLi/(−)-sparteine was investigated using React IR (Figure 1a).[8] Thus, 1.05 equiv of (−)-sparteine and **1** were combined in TBME at −70 °C and a peak at 1695 cm^{-1} was observed (assigned to $\nu_{C=O}$ in **1**). Upon addition of 1.05 equiv of *s*-BuLi, an ∼50:50 mixture of peaks at 1695 and 1675 cm^{-1} was visible. As time progressed an additional peak at 1644 cm^{-1} appeared although, even

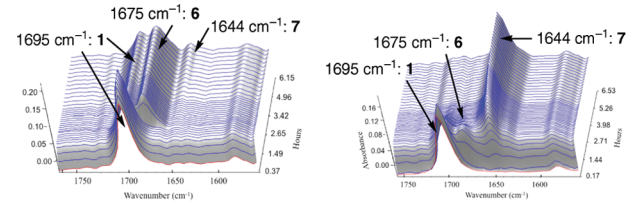
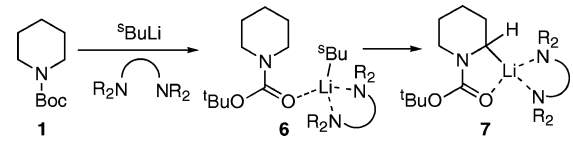


Figure 1. In situ React IR monitoring of the lithiation of *N*-Boc piperidine **1** using *s*-BuLi/diamine in TBME at −78 °C.

Scheme 2



after 6 h, this peak was a minor component (see Figure 1a). Based on a comparison with the lithiation of **1** using *s*-BuLi/TMEDA (see Supporting Information (SI)), we assigned $\nu_{C=O}$ = 1675 cm^{-1} to prelithiation complex **6** and $\nu_{C=O}$ = 1644 cm^{-1} to lithiated *N*-Boc piperidine **7** (Scheme 2). At the end of the lithiation (6 h), the mixture consisted of ∼45:45:10 of nonlithiated **1**, prelithiation complex **6**, and lithiated complex **7**. This is in line with Beak's 8.5% yield of the Me_3Si adduct under similar conditions.[3] Notably, this is the first direct observation of a prelithiation complex in the lithation of *N*-Boc heterocycles and is consistent with a kinetic study with *N*-Boc pyrrolidine.[9] In contrast, reaction of **1** with 1.05 equiv of *s*-BuLi/(+)-sparteine surrogate **5** led to rapid lithiation to give lithiated complex **7** (*via* prelithiation complex **6**) as the major component (Figure 1b). The higher reactivity of *s*-BuLi/**5** set the stage for high yielding asymmetric lithiation of *N*-Boc piperidine **1** (Table 1).

Lithiation of *N*-Boc piperidine **1** using 1.3 equiv of *s*-BuLi/**5** (Et_2O, −78 °C, 6 h) and trapping with Me_3SiCl gave adduct (*R*)-**3** (86:14 er) in 73% yield (Table 1, entry 1). Similarly, a high yield and ∼88:12 er were obtained with a range of electrophiles in Et_2O and TBME: Bu_3SnCl (→ (*R*)-**8**, entry 2), CO_2 (→ (*S*)-**9**, entries 3/4), and MeO_2CCl (→ (*S*)-**10**, entries 5/6). With each of these electrophiles, there is an ∼10-fold yield increase using *s*-BuLi/**5** compared to that obtained with *s*-BuLi/(−)-sparteine. An asymmetric deprotonation mechanistic pathway was confirmed for this process: tin−lithium exchange with stannane *rac*-**8** (*n*-BuLi, Et_2O, −78 °C, 2 h) followed by addition of diamine **5** (−78 °C, 2 h) and trapping with MeO_2CCl gave *racemic* adduct **10** (15% yield). This clearly demonstrated that enantiocontrol was not a result of a postlithiation asymmetric substitution.[10] Further investigation revealed that the lithiation time could be reduced to 3 h without a

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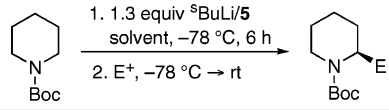
Table 1. Asymmetric Lithiation of *N*-Boc Piperidine **1** Using *s*-BuLi/**5**



entry[a]	solvent	E^+	product	E	yield (%)[b]	er[c]
1	Et_2O	Me_3SiCl	(*R*)-**3**	$SiMe_3$	73	86:14
2	Et_2O	Bu_3SnCl[d]	(*R*)-**8**	$SnBu_3$	82	88:12
3	Et_2O	CO_2	(*S*)-**9**	CO_2H	92	88:12
4	TBME	CO_2	(*S*)-**9**	CO_2H	85	88:12
5	Et_2O	MeO_2CCl	(*S*)-**10**	CO_2Me	78	88:12
6	TBME	MeO_2CCl	(*S*)-**10**	CO_2Me	68	88:12
7	Et_2O	MeO_2CCl	(*S*)-**10**	CO_2Me	83 (3 h[e])	87:13
8	Et_2O	MeO_2CCl	(*S*)-**10**	CO_2Me	24 (1 h[f])	86:14
9	Et_2O	$PhMe_2SiCl$	(*R*)-**11**	$SiMe_2Ph$	85	73:27
10	Et_2O	MeI[d]	(*R*)-**12**	Me	45	64:36
11	Et_2O	Me_2SO_4	(*R*)-**12**	Me	45	60:40
12	Et_2O	allyl-Br	(*R*)-**13**	allyl	45	57:43
13	Et_2O	allyl-Br[g]	(*R*)-**13**	allyl	75	75:25
14	Et_2O	Negishi[h]	(*S*)-**14**	3,4-$(MeO)_2C_6H_3$	33	82:18

[a] Reaction conditions: (i) 1.3 equiv of *s*-BuLi/**5**, Et_2O or TBME, −78 °C, 6 h; (ii) E^+, −78 °C → rt, 16 h. [b] Yield after chromatography. [c] Enantiomer ratio (er) determined by CSP GC or HPLC (see SI for details). [d] Electrophile precooled to −78 °C. [e] Lithiation for 3 h. [f] Lithiation for 1 h. [g] Reaction conditions: (i) 1.3 equiv of *s*-BuLi/**5**, Et_2O, −78 °C, 6 h; (ii) CuCN·2LiCl, THF, −78 °C, 40 min; (iii) allyl-Br, −78 °C → rt, 16 h. [h] Reaction conditions (Negishi): (i) 1.3 equiv of *s*-BuLi/**5**, Et_2O, −78 °C, 6 h; (ii) $ZnCl_2$, −78 °C, 30 min; (iii) −78 °C → rt, 35 min; (iv) 3,4-$(MeO)_2C_6H_3Br$, *t*-Bu_3PHBF_4, $Pd(OAc)_2$, rt, 16 h.

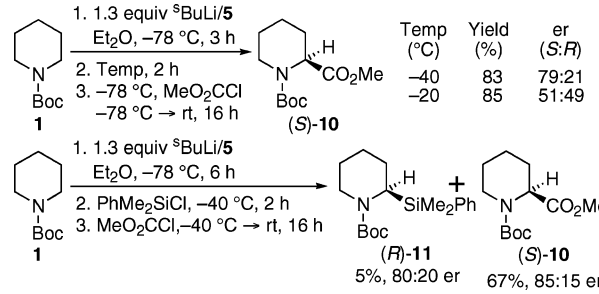
reduction in yield (entry 7). However, only a 24% yield of (*S*)-**10** (86:14 er) was isolated after a 1 h lithiation time (entry 8). An asymmetric Negishi coupling[11] was also carried out to give a 33% yield of arylated piperidine (*S*)-**14** (82:18 er) (entry 14).

Although the reactions using Me_3SiCl, Bu_3SnCl, CO_2, and MeO_2CCl all proceeded satisfactorily (entries 1−6), those with $PhMe_2SiCl$, MeI, Me_2SO_4, and allyl bromide gave lower enantioselectivity (57:43−73:27 er) (entries 9−12). The low er with allyl bromide (entry 12) is probably due to the intervention of a single electron transfer pathway;[12] higher enantioselectivity (75:25 er) was observed using Dieter-style[13] transmetalation to copper (entry 13). To explain the low ers with $PhMe_2SiCl$, MeI, and Me_2SO_4, we speculated that trapping of the lithiated complex **7** (Scheme 2) might not occur at −78 °C due to the steric bulk of the diamine ligand. Instead, as the solution warmed up from −78 °C to rt, trapping of **7** could occur at higher temperatures. In this scenario, lithiated complex **7** might be configurationally unstable[14] at the higher temperatures which could then account for the lower ers ultimately obtained.

To investigate the configurational stability of lithiated complex **7**, *N*-Boc piperidine **1** was lithiated using 1.3 equiv of *s*-BuLi/**5**, in Et_2O at −78 °C for 3 h, and then incubated at −40 or −20 °C for 2 h before trapping with MeO_2CCl at −78 °C. After 2 h at −40 °C, (*S*)-**10** of 79:21 er was obtained, indicating some configurational instability. In contrast, **7** was configurationally unstable at −20 °C: (*S*)-**10** of 51:49 er was formed after incubating at −20 °C for 2 h (Scheme 3). Presumably, trapping of lithiated complex **7** by $PhMe_2SiCl$, MeI, and Me_2SO_4 occurs at temperatures at which **7** is configurationally unstable thus accounting for the low ers of (*R*)-**11** and (*R*)-**12**.[15] The low rate of trapping of **7** by $PhMe_2SiCl$ at −40 °C was shown by attempted reaction of **7** with $PhMe_2SiCl$ over 2 h at −40 °C (→ (*R*)-**11**, 5% yield, 80:20 er) and subsequent addition of the more reactive electrophile, MeO_2CCl (→ (*S*)-**10**, 67% yield, 85:15 er) (Scheme 3).

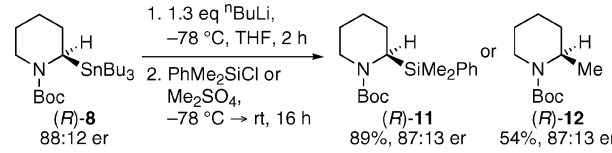
Finally, since we believed that the slow rate of trapping of lithiated complex **7** at −78 °C by $PhMe_2SiCl$, MeI, and Me_2SO_4 was due to the sterically hindered (+)-sparteine surrogate **5** ligand,

Scheme 3



a ligand-free route to adducts (*R*)-**11** and (*R*)-**12** was explored. Tin−lithium exchange of stannane (*R*)-**8** (88:12 er) using *n*-BuLi in THF at −78 °C gave a THF-complexed lithiated intermediate which was trapped separately with $PhMe_2SiCl$ (→ (*R*)-**11**, 87:13 er) and Me_2SO_4 (→ (*R*)-**12**, 87:13 er) in high er (Scheme 4).

Scheme 4



In conclusion, use of *s*-BuLi/(+)-sparteine surrogate **5** allows the first examples of high yielding asymmetric deprotonation-trapping of *N*-Boc piperidine **1**. Direct lithiation-trapping to enantioenriched 2-substituted piperidines is now possible.[16]

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Supporting Information Available: Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) A similar rationale has been noted for a related 6-ring *N*-Boc heterocycle (see ref 4b) and can explain the low er previously obtained by us in the lithiation trapping of *N*-Boc piperidine **1** using 1.4 equiv of *s*-BuLi and 2.4 equiv of (+)-sparteine surrogate **5** (see ref 7 and SI).
(16) For dynamic resolution approaches to piperidines, see: Coldham, I.; Raimbault, S.; Whittaker, D. T. E.; Chovatia, P. T.; Leonori, D.; Patel, J. J.; Sheikh, N. S. *Chem.—Eur. J.* **2010**, *16*, 4082.

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