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Diastereoselective synthesis of α,α,α′-trisubstituted pyrrolidines and piperidines by directed sequential lithiation/alkylation

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Dedicated to the memory of Professor Bob Gawley who passed on in March 2013. His mentorship forever will be appreciated

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ABSTRACT

The stereocontrolled synthesis of α,α,α′-trisubstituted pyrrolidines and piperidines has been accomplished through α′-lithiation/trapping of the corresponding α,α-disubstituted Boc-protected azaheterocycle with various electrophiles. The relative configuration of the major diastereomer has the α′-substituent *trans* to the α-aryl group in the pyrrolidines but *cis* to the α-aryl group in the piperidines. The diastereoselectivity of the lithiation/alkylation of pyrrolidines is unaffected by TMEDA but decreases in the presence of (−)-sparteine in diethyl ether.

The pyrrolidine and piperidine motifs are ubiquitous structural motifs in bioactive molecules, including alkaloid natural products and pharmaceuticals.[1] Furthermore, functionalized pyrrolidines and piperidines feature prominently as structural motifs in chiral organocatalysts[2] and chiral auxiliaries.[3] Additionally, the versatility of substituted pyrrolidines and piperidines in the synthesis has been amply demonstrated.[4–18]

In 1989, Beak disclosed that unsubstituted Boc-protected azaheterocycles may be effectively functionalized at the α-position through a lithiation/alkylation sequence.[19] Several researchers,[20–26] including one of us,[27,16] have since extended the Beak methodology to include sequential α-functionalizations en route to access α,α- and α,α′-disubstituted *N*-heterocycles, in both racemic and enantioenriched forms. It has been shown that the lithiation of phenyl pyrrolidine *S*-**1** (Fig. 1) of >99:1 er using *s*-BuLi/(−)-sparteine then trapping with Me_2SO_4 proceeds highly diastereoselectively, affording C-5 methylated pyrrolidine **2** in 45% yield and 93:7 dr (*cis*:*trans*).[24] In 2006, Campos and other scientists at Merck reported that lithiation of *R*-**1** of 96:4 er in the presence of (−)-sparteine followed by transmetalation and Pd-catalyzed coupling with phenyl bromide afforded enantiopure Boc-protected 2,5-diphenylpyrrolidine, *trans*-**3**, in 57% yield and 96:4 dr (*trans*:*cis*).[28] Later, O'Brien utilized a (+)-sparteine surrogate (i.e., **12**) to synthesize proline ester derivative **4** in >99:1 er and >95:5 dr (*cis*:*trans*), albeit in low yields as well.[20] Mechanistic studies conducted by Coldham and O'Brien have since revealed that the minor rotamer of **1** rotates extremely slowly at low temperatures (the half-life for rotation of the Boc-group was

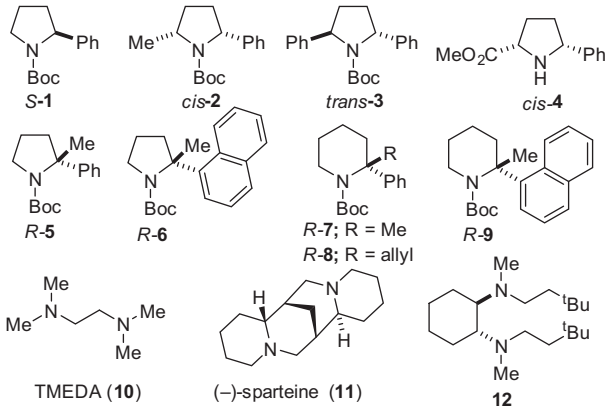

Figure 1. Selected examples of substituted pyrrolidines, piperidines, and diamine ligands.

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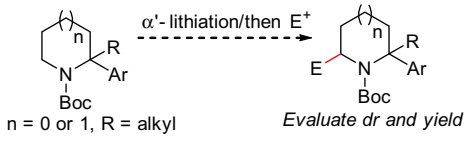
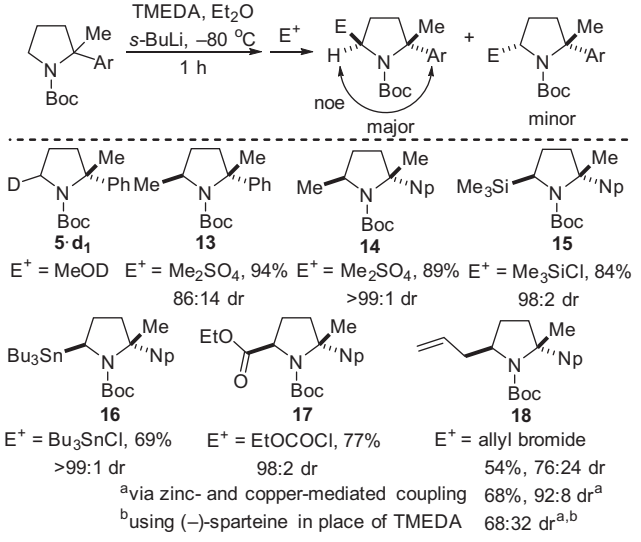


Figure 2. Proposed synthetic plan for α,α,α′-trisubstituted pyrrolidines and piperidines.

determined to be ~10 h at −80 °C).[21] It is thus likely that the modest yields obtained by Beak,[24] Campos,[28] and O'Brien[20] in the α′-lithiation/alkylation of **1** were due to the restricted mobility of the minor rotamer under their reaction conditions as well as due to competitive benzylic lithiation.

Benzylic organolithiums derived from enantioenriched *N*-Boc-2-aryl pyrrolidines[24,29,30,28] and piperidines[31–36,23] can now be functionalized at the 2-position with little or no loss of enantiopurity, via a S_E2ret[37] process.[27,21,38] Figure 1 illustrates several of the enantioenriched pyrrolidines and piperidines that have been prepared by this route (see **5**–**9**). As part of a program aimed at synthesizing cyclic amine derivatives through the intermediacy of functionalized organolithiums, and with a few α,α-disubstituted pyrrolidines and piperidines in hand, we sought to investigate the possibility of a third lithiation/alkylation sequence. An approach to 2,2,5-trisubstituted pyrrolidines and 2,2,6-trisubstituted piperidines was envisioned, whereby a diastereoselective α′-lithiation/alkylation of α,α-disubstituted azaheterocycles is implicated (Fig. 2). Efforts toward the implementation of the proposed plan are disclosed herein.

Starting with disubstituted pyrrolidine derivative *rac*-**5** (see Fig. 1), efficient conditions for lithiation/substitution at C-5 were investigated. Knowing that *N*-Boc-pyrrolidine undergoes complete and efficient lithiation under *s*-BuLi/TMEDA conditions at −80 °C but phenyl pyrrolidine **1** does not, it was of interest to understand the kinetics of deprotonation of **5**. Fortuitously, after 1 h of lithiation of a solution of *rac*-**5** in Et_2O at −80 °C using *s*-BuLi/TMEDA, trapping with MeOD and analysis of the sample by GC-MS revealed complete lithiation and **5** $\mathbf{d_1}$ was obtained (Scheme 1). The efficiency of the lithiation of disubstituted pyrrolidine **5** under these reaction conditions is noteworthy since, as previously mentioned,

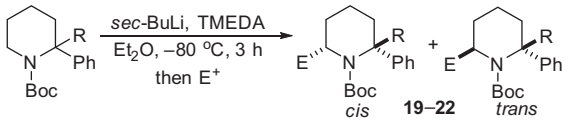


Scheme 1. Diastereoselective lithiation-substitution of *N*-Boc-2-aryl-2-methyl pyrrolidines.[40]

monosubstituted pyrrolidine **1** lithiated rather recalcitrantly.[21] Since the ^1H NMR spectrum of **5** shows ~70:30 ratio of rotamers, the fast and efficient lithiation of **5** suggests that the barrier to rotation at −80 °C is probably much lower than that of **1**.[21] Lithiation of *rac*-**5** followed by trapping with Me_2SO_4 affords C-5 methylated pyrrolidine **13** in high yield but in moderate dr (low dr's were also observed with other electrophiles such as Me_3SiCl and allyl bromide). Gratifyingly, when sterically encumbered, naphthyl-bearing **6** is lithiated and trapped with Me_2SO_4, a single diastereomer of trisubstituted pyrrolidine **14** is obtained. Additionally, silylation, stannylation, and acylation of 5-lithio-**6** proceed efficiently and highly diastereoselectively (see **15**–**17**). Whereas direct allylation of lithiated **6** using allyl bromide proceeds inefficiently and less selectively to afford **18** in 76:24 dr, copper-mediated allylation affords **18** in respectable yield and in high diastereoselectivity.

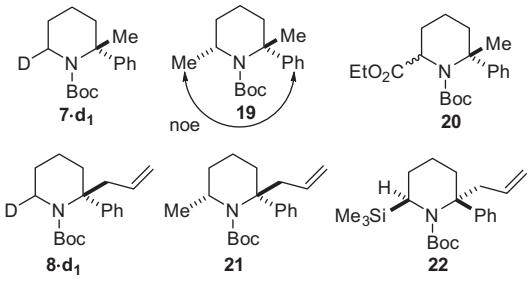
These studies have revealed that diamine-free lithiation[39] of **6** is possible when THF is employed as the solvent. Under this scenario, complete lithiation of **6** is observed after 2 h at −80 °C or after 1 h at −60 °C. Methylation and silylation of 5-lithio-**6** generated under these diamine-free conditions afford the C-5 substituted products with similar diastereoselectivities, suggesting that although the deprotonation of **6** is faster in the presence of TMEDA (in both Et_2O and THF), the steric course is unaltered. Intriguingly, when the lithiation of *rac*-**6** is carried out in the presence of *s*-BuLi/(−)-sparteine in Et_2O, ~75% lithiation is observed after 10 h at −80 °C. Trapping of the partially deprotonated mixture with Me_2SO_4 affords *trans*-**14** in 96:4 dr (68:32 er for the major diastereomer). Significantly, sparteine-mediated lithiation of **6** followed by transmetalation and copper-mediated allylation affords **18** in only 68:32 dr. The reason for the low diastereoselectivity under the *s*-BuLi/(−)-sparteine conditions is unclear at this point.

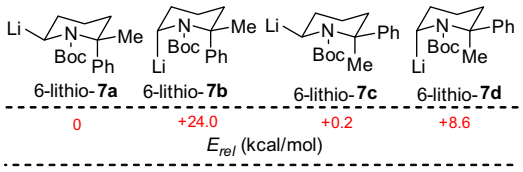
Table 1
Diastereoselective lithiation-substitution of *N*-Boc-2-phenyl-2-alkyl piperidines



Entry	R	E^+	Product	Yield (%)	dr (*cis*:*trans*)
1	R = Me	MeOD	**7**·$\mathbf{d_1}$	100[a]	nd[c]
2	R = Me	Me_2SO_4	**19**	85[b]	>99:1
3	R = Me	$EtCO_2Cl$	**20**	70[b]	60:40
4	R = allyl	MeOD	**8**·$\mathbf{d_1}$	100[a]	nd[c]
5	R = allyl	Me_2SO_4	**21**	81[b]	>99:1
6	R = allyl	Me_3SiCl	**22**	77[b]	>99:1

[a] GC yields.
[b] Isolated yields.
[c] nd stands for 'not determined'.





Scheme 2. Calculated relative energies of the conformers obtained from lithiation of α,α-disubstituted piperidine **7**.

NOESY (or ROESY) experiments were performed on **14**, **15**, and **16**. Each showed strong cross-peaks between the proton at C-5 and the aromatic protons of the aryl group at C-2, thereby revealing a *trans* arrangement of the aryl group and the C-5 substituent for these three examples. The others were assigned the same relative configuration by analogy.

After successful α′-lithiation/functionalization of α,α-disubstituted pyrrolidines, we sought to extend the methodology to the homologous piperidine heterocycle. After some optimization, we found that the lithiation of a solution of *rac*-**7** in Et_2O at −80 °C for 3 h, using *sec*-BuLi/TMEDA, is complete and efficient (see **7**·**d**$_1$, Table 1, entry 1). DFT calculations unsurprisingly indicate a preference for equatorial lithiation (Scheme 2, 6-lithio-**7a** vs 6-lithio-**7b** or 6-lithio-**7c** vs 6-lithio-**7d**). Interestingly, whereas the two equatorially lithiated epimers (i.e., **7a** and **7c**) are nearly isoenergetic, the diastereomers bearing an axially disposed lithium are about 15 kcal/mol apart in energy.

Trapping of 6-lithio-**7** with Me_2SO_4 affords **19** as a single diastereomer (Table 1, entry 2). NOESY experiments established the relative configuration as having the α-phenyl group and the α′-methyl group *cis*. Indeed, DFT calculations indicate that the *cis*-diaxial conformer is 4.7 kcal/mol more stable than the corresponding *cis*-diequatorial conformer. These results suggest that **19** arises from 6-lithio-**7c** following a ring flip. Lithiation/trapping with EtOCOCl affords acylated piperidine **20** in only 60:40 dr (entry 3), probably due to facile epimerization at C-6. Trapping of allyl-bearing 6-lithio-**8** with Me_2SO_4 also affords a single diastereomer of the trisubstituted piperidine (see **21**, entry 5). NOESY experiments again established the relative configuration as having the α-aryl group and the α′-methyl group *cis*. Analysis of coupling constants revealed that the C-6 proton in **21** is equatorial, indicating that the α-phenyl and α′-methyl groups are *cis*-diaxial. Silylation of 6-lithio-**8** with Me_3SiCl affords piperidine **22**, also as a single diastereomer (entry 6). However, in this example, although the *cis* relationship between the aryl group at C-2 and the newly introduced substituent at C-6 is preserved, the ^{1}H NMR of **22** shows a double doublet due to ^3J coupling between the proton at C-6 and both equatorial (J = 7 Hz) and axial (J = 13 Hz) protons at C-5, indicating that the C-6 proton is axial. Accordingly, NOESY experiments show cross-peaks between the C-6 proton and the α-allyl group. Calculations indicate a preference for equatorial dispensation of the TMS group, thus disfavoring the ring-flipped conformer.

Of note, a few activated arenes (e.g., methoxy-bearing and CF_3-containing arenes) were evaluated on both the pyrrolidine and piperidine heterocycles (see SI for details) but complications arising from competing aryl lithiation were encountered.

In summary, α,α,α′-trisubstituted pyrrolidines and piperidines are obtainable in good to excellent diastereoselectivity by directed lithiation/alkylation. The relative configuration of the major diastereomer has the α′-substituent *trans* to the α-aryl group in the pyrrolidines but *cis* to the α-aryl group in the piperidines. The current strategy sets the stage for the synthesis of enantioenriched trisubstituted pyrrolidines and piperidines since no racemization is anticipated during α′-lithiation/alkylation of the α,α-disubstituted enantioenriched precursors.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.031.

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40. Typical Procedure (Synthesis of **15**): To an oven-dried, septum-capped round bottom flask equipped with a stir bar, was added freshly distilled TMEDA (1.0 mL, 0.6 mmol, 1.2 equiv) and Et_2O (7.0 mL) under argon. The mixture was cooled to −80 °C and a solution of *s*-BuLi in cyclohexane (0.6 mL, 1.0 M, 1.2 equiv) was added via syringe. A precooled solution of pyrrolidine **6** (1.0 equiv) in Et_2O (3.0 mL) was added to the flask containing the TMEDA/*s*-BuLi mixture. After 1 h at this temperature, the mixture was trapped with Me_3SiCl (180 mg, 1.5 mmol, 3 equiv). After 4 h, MeOH was added and the mixture was stirred for 5 min. After warming to room temperature, 10% H_3PO_4 was added. Layers were separated and the aqueous layer was extracted with

Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated to obtain the crude product as an oil. Purification by flash chromatography on silica eluting with hexane–EtOAc (95:5) afforded 167 mg of **21** as an oil in 84% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 8.03–7.46 (m, 7H), 3.73 (dd, 1H), 2.72 (m, 2H), 2.15 (m, 2H), 1.90 (s, 3H), 0.80 (s, 9H), 0.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 143.0, 134.7, 130.3, 129.4, 127.7, 125.8, 124.8, 124.7, 124.2, 78.1, 66.5, 49.8, 42.5, 28.6, 27.6, 1.2. HRMS calcd for $C_{23}H_{33}NO_2Si$ 383.2281, found 383.2273.