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An Experimental and in Situ IR Spectroscopic Study of the Lithiation–Substitution of *N*-Boc-2-phenylpyrrolidine and -piperidine: Controlling the Formation of Quaternary Stereocenters

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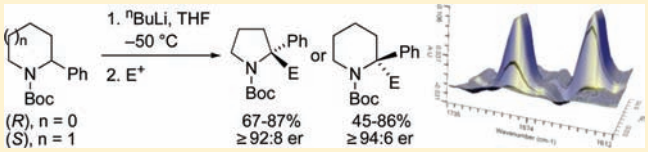
Supporting Information

ABSTRACT: A general and enantioselective synthesis of 2-substituted 2-phenylpyrrolidines and -piperidines, an important class of pharmaceutically relevant compounds that contain a quaternary stereocenter, has been developed. The approach involves lithiation–substitution of enantioenriched *N*-Boc-2-phenylpyrrolidine or -piperidine (prepared by asymmetric Negishi arylation or catalytic asymmetric reduction, respectively). The combined use of synthetic experiments and in situ IR spectroscopic monitoring allowed optimum lithiation conditions to be identified: *n*-BuLi in THF at −50 °C for 5–30 min. Monitoring of the lithiation using in situ IR spectroscopy indicated that the rotation of the *tert*-butoxycarbonyl (Boc) group is slower in a 2-lithiated pyrrolidine than a 2-lithiated piperidine; low yields for the lithiation–substitution of *N*-Boc-2-phenylpyrrolidine at −78 °C can be ascribed to this slow rotation. For *N*-Boc-2-phenylpyrrolidine and -piperidine, the barriers to rotation of the Boc group were determined using density functional theory calculations and variable-temperature ^{1}H NMR spectroscopy. For the pyrrolidine, the half-life ($t_{1/2}$) for rotation of the Boc group was found to be ∼10 h at −78 °C and ∼3.5 min at −50 °C. In contrast, for the piperidine, $t_{1/2}$ was determined to be ∼4 s at −78 °C.



INTRODUCTION

2,2-Disubstituted pyrrolidines and piperidines containing at least one aryl substituent represent an important class of pharmaceutically relevant compounds. For example, veliparib (ABT-888) (**1**),[1] a poly(ADP–ribose) polymerase (PARP) inhibitor, is currently in clinical trials for the treatment of cancer, and piperidine **2** was a lead compound in a search for orally active NK_1 receptor antagonists[2] (Figure 1). Despite the advances in methodology for the enantioselective formation of quaternary stereocenters,[3] the asymmetric synthesis of compounds such as **1** and **2** containing a quaternary stereogenic center in a nitrogen heterocycle presents a significant synthetic challenge. Indeed, there have been only a limited number of reports on enantioselective approaches to such 2,2-disubstituted nitrogen heterocycles. For example, the different approaches to enantioenriched α-phenylproline derivatives have included pig liver esterase-mediated kinetic resolution,[4] Sommelet–Hauser rearrangement,[5] catalytic asymmetric phase-transfer alkylation,[6] and rearrangement of *N*-sulfonylprolines.[7] In 2011, two approaches to 2,2-disubstituted nitrogen heterocycles with non-carboxylate substituents were described: a catalytic asymmetric bromoaminocyclization reaction (to give pyrrolidines)[8] and a stereoselective lithiation–borylation–amination process (to give a piperidine).[9]

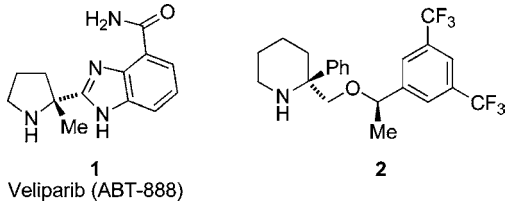


Figure 1. Biologically active 2-aryl-2-alkyl nitrogen heterocycles.

In all of the previous enantioselective approaches to 2,2-disubstituted nitrogen heterocycles with at least one aryl substituent, only isolated examples of each strategy were reported, and none represents a general approach to this class of compound. To address such limitations, we set out to develop a general method for the enantioselective synthesis of (*R*)- or (*S*)-2-substituted-2-aryl pyrrolidines and -piperidines containing a range of substituents. Our two-step approach is summarized in Scheme 1 for one enantiomeric series. The first step involved preparation of (*R*)-*N*-Boc-2-phenylpyrrolidine [(*R*)-**5**] and -piperidine [(*R*)-**6**] via established methods (see below). Then, in the second step, the lithiation–substitution of (*R*)-**5** and (*R*)-**6** were investigated as a route for preparing a

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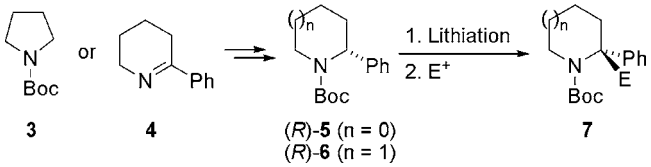
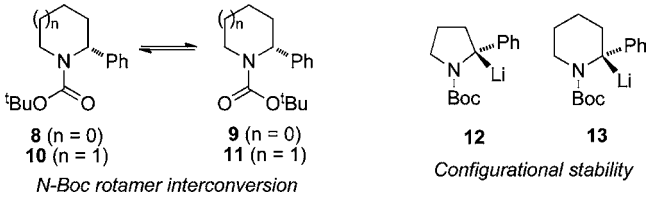
Scheme 1. Two-Step Approach to 2-Aryl-2-alkylpyrrolidines and -piperidines



variety of 2,2-disubstituted pyrrolidines and piperidines (**7**). This should enable the preparation of a small library of 2-phenyl-2-substituted heterocycles.[10,11]

To optimize the lithiation conditions for the apparently simple transformations of (*R*)-**5** and (*R*)-**6** into **7**, two aspects had to be considered (Scheme 2). First, since (*R*)-**5** and (*R*)-**6**

Scheme 2. Key Considerations in the Lithiation Step



are nonsymmetrical and lithiations of this type are directed by the C=O moiety of the Boc group,[12] the yield of the desired product **7** is adversely affected if the *N*-Boc rotamers **8**/**9** and **10**/**11** do not interconvert.[13] Second, a high enantiomeric ratio (er) in the products can be achieved only if the lithiated intermediates **12** and **13** are configurationally stable (and react stereospecifically with retention or inversion of configuration).[14] These features are temperature-dependent, and typically, the use of low temperatures such as −78 °C slows the rate of rotamer interconversion but gives a configurationally stable organolithium intermediate.

In this paper, we describe the optimization of the lithiation conditions in the conversion of (*R*)-**5** and (*S*)-**6** into **7** using a combination of typical synthetic experiments and in situ IR spectroscopic monitoring of the lithiation step at different temperatures. In addition, the interconversion of the *N*-Boc rotamers was studied by variable-temperature NMR spectroscopy and density functional theory (DFT) calculations. Notably, in situ IR spectroscopy provided specific information on the time required for the lithiation and on the interconversion of *N*-Boc rotamers **8**/**9** and **10**/**11**. In this way, a simple and effective method for the high-yielding lithiation−substitution of (*R*)-**5** and (*S*)-**6** was developed. This provides the first general synthesis of enantioenriched 2,2-disubstituted pyrrolidines and piperidines such as **7** (≥92:8 er).

RESULTS AND DISCUSSION

Optimization of the Lithiation−Substitution of *N*-Boc-2-phenylpyrrolidine (*rac*-5) and -piperidine (*rac*-6). *N*-Boc-2-phenylpyrrolidine (*rac*-**5**) was prepared using the previously reported diamine-free lithiation−Negishi coupling of *N*-Boc-pyrrolidine (**3**).[15,16] Previously, Xiao and co-workers had reported that lithiation−substitution of *rac*-**5** and *rac*-**6** using *n*-BuLi/TMEDA (THF, −78 °C, 1 h) gave the substituted products *rac*-**7** in 33−61% yield.[2a] Hence, our initial efforts focused on an in situ IR spectroscopic study of the lithiation of *rac*-**5** using *n*-BuLi in THF at −78 °C.[17] A solution of *rac*-**5** in THF at −78 °C exhibited a $\nu_{C=O}$ peak at 1696 cm^{-1}. Upon addition of *n*-BuLi, lithiation of *rac*-**5** ensued, as shown by the formation of a new peak at 1644 cm^{-1} (assigned to $\nu_{C=O}$ in lithiated intermediate **12**) (Figure 2a). Initial partial lithiation

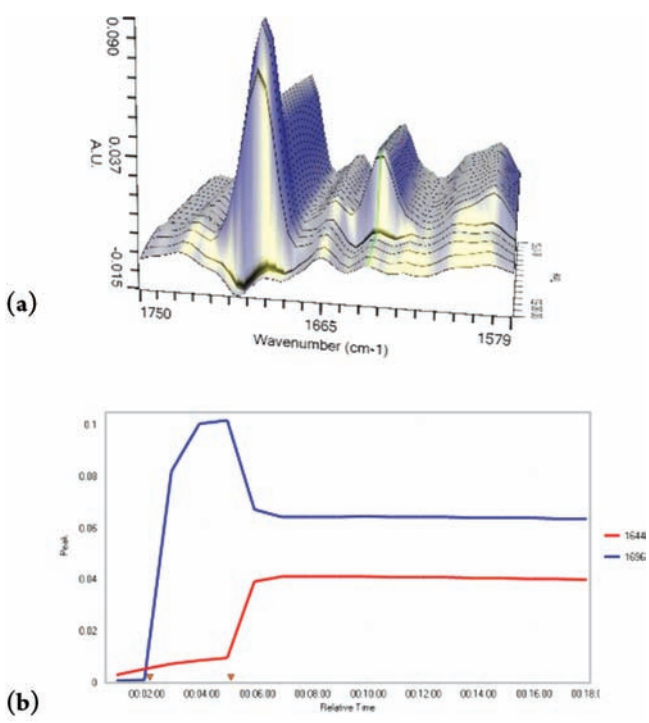


Figure 2. Investigation of the lithiation of *rac*-**5** using *n*-BuLi in THF at −78 °C by in situ IR spectroscopy. (a) 3D plot showing changes in the absorption spectrum with time. (b) 2D plot showing the time evolution of the *rac*-**5** peak at 1696 cm^{-1} (blue) and the lithiated intermediate **12** peak at 1644 cm^{-1}(red). The first and second red triangles indicate the additions of *rac*-**5** and *n*-BuLi, respectively.

was fast (complete in 2 min), but no further lithiation took place thereafter. This can be most clearly seen in the two-dimensional plot (Figure 2b), which shows the evolution of the peaks at 1696 cm^{-1} (*rac*-**5**, blue line) and 1644 cm^{-1} (organolithium **12**, red line).

It is apparent that at −78 °C, *N*-Boc rotamers **8** and **9** do not interconvert or interconvert very slowly, and ∼40% lithiation occurs from the reactive *N*-Boc rotamer **8**. Unsurprisingly, *n*-BuLi in THF at −78 °C is not reactive enough to lithiate *N*-Boc rotamer **9**. To facilitate rotamer interconversion, the reaction was carried out at 0 °C and monitored by IR spectroscopy (Figure 3). In this case, *rac*-**5** ($\nu_{C=O}$ 1701 cm^{-1}) was fully converted into lithiated intermediate **12** ($\nu_{C=O}$ 1643 cm^{-1}) after *n*-BuLi was added. Complete lithiation was achieved in just 2 min (Figure 3b), clearly demonstrating the importance of *N*-Boc rotamers **8** and **9** and the temperature dependence of their interconversion.

To complement the results obtained using in situ IR spectroscopy, ^{1}H NMR spectroscopic studies of *rac*-**5** in THF-d_8 were conducted. The rotamers **8** and **9** could clearly be distinguished by ^{1}H NMR spectroscopy. For example, at −72 °C, the benzylic CH signals appeared at ∼5.0 and ∼4.8 ppm in a ratio of 34:66 (Figure 4e). Addition of *n*-BuLi at −72 °C caused immediate loss of the minor rotameric signal at 5.0 ppm (Figure 4c), indicating that the minor rotamer has the carbonyl oxygen pointing toward the benzylic CH. This allowed the

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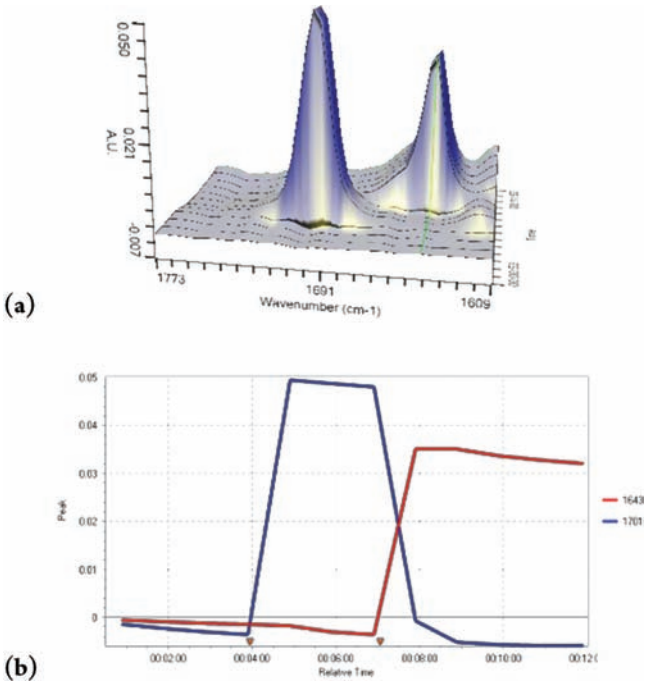

Figure 3. Investigation of the lithiation of *rac*-**5** using *n*-BuLi in THF at 0 °C by in situ IR spectroscopy. (a) 3D plot showing changes in the absorption spectrum with time. (b) 2D plot showing the time evolution of the *rac*-**5** peak at 1701 cm^{-1} (blue) and the lithiated intermediate **12** peak at 1643 cm^{-1}(red). The first and second red triangles indicate the additions of *rac*-**5** and *n*-BuLi, respectively.

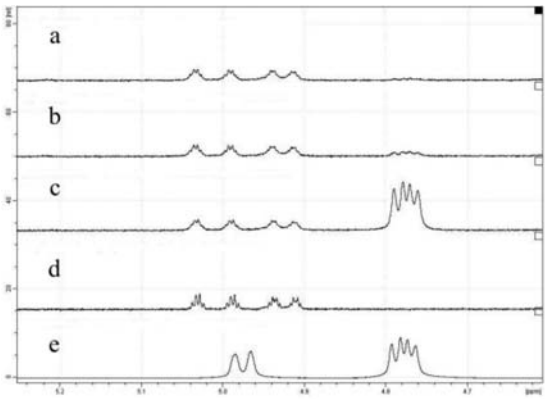

Figure 4. Investigation of the lithiation of *rac*-**5** using *n*-BuLi in THF-d_8 by ^{1}H NMR spectroscopy: (e) *rac*-**5** at −72 °C; (d) *n*-BuLi in THF-d_8 at −63 °C; (c) *rac*-**5** + *n*-BuLi at −72 °C; (b) *rac*-**5** + *n*-BuLi after warming to −58 °C; (a) *rac*-**5** + *n*-BuLi at −58 °C after 20 min.

assignment of the minor rotamer as **8** and the major rotamer as **9**. Two new double-quartet signals at 4.92 and 5.02 ppm are also present in Figure 4c. These signals, which are characteristic of a terminal alkene, were also observed in the ^{1}H NMR spectrum of *n*-BuLi in THF-d_8 (Figure 4d). Since these signals were also present in the ^{1}H NMR spectrum of *n*-BuLi in benzene-d_6, they cannot be due to lithium but-3-ene-1-oxide[18] (a THF breakdown product[19]). Thus, we conclude that they are likely due to an impurity in the commercial *n*-BuLi solution. When the reaction mixture was warmed to −58 °C (Figure 4b), the signal for the major rotamer **9** slowly disappeared, and this was complete after ∼20 min (Figure 4a).

In a separate experiment, a sample of *rac*-**5** in THF-d_8 was warmed to observe the coalescence of the benzylic CH signals, which occurred at ∼46 °C (see the Supporting Information). These signals were 79.2 Hz apart at low temperature, so this corresponds to a barrier of ∼64.5 kJ/mol for rotation of the Boc group. This value suggests that the half-life ($t_{1/2}$) for rotation of the Boc group in **5** is ∼10 h at −78 °C. However, $t_{1/2}$ is ∼3.5 min at −50 °C and ∼0.3 s at 0 °C. The $t_{1/2}$ values at −78 and 0 °C are fully consistent with the in situ IR spectroscopic results presented in Figures 2 and 3 and are also in accord with the synthetic experiments outlined below.

Synthetic experiments were carried out under different lithiation conditions, and the lithiated intermediate in each case was trapped with methyl chloroformate (Table 1). At −78 °C, *n*-BuLi was preferred to *s*-BuLi, and after a lithiation time of 3 h, a 39% yield of *rac*-**14** was obtained (entries 1−3). The remaining mass balance was recovered *rac*-**5** (entries 2 and 3). With *s*-BuLi, we established that competitive lithiation on the non-benzylic side in the major rotamer **9** occurred, giving *trans*- and *cis*-**15**:[20] after chromatography, a 40% yield of a 72:14:14 mixture (by ^{1}H NMR spectroscopy) of *rac*-**14**, *trans*-**15**, and *cis*-**15** was obtained (entry 1). In a separate experiment, careful chromatography gave a 17% yield of *rac*-**14**. The additive tetramethylethylenediamine (TMEDA) had no effect on the yield of *rac*-**14** (entries 4 and 5). As anticipated from the IR spectroscopy and variable-temperature NMR spectroscopy results, reactions at 0 °C led to higher yields (72−77%; entries 6−7) with short lithiation times (5 or 10 min). A reaction at 20 °C was lower-yielding (41%; entry 8), possibly as a result of competitive lithiation of THF at this elevated temperature. The highest yield of *rac*-**14** obtained at −78 °C (39%) and the improved yield of 77% obtained at 0 °C (lithiation time: 5 min) are fully consistent with the in situ IR spectroscopic observations (Figures 2 and 3).

After *n*-BuLi/THF at 0 °C for 5 min had been identified as a suitable set of lithiation conditions, a range of electrophiles was explored, and 2,2-disubstituted pyrrolidines *rac*-**14** and *rac*-**16**−**23** were obtained in 65−98% yield (Scheme 3). In the last case, using benzophenone, the intermediate alkoxide was cyclized to give oxazolidinone **23** in 84% yield.

Next, our attention switched to *N*-Boc-2-phenylpiperidine (*rac*-**6**), which was prepared as outlined in Scheme 4. Treatment of 5-bromovaleronitrile with PhLi (in toluene rather than benzene) followed by reduction of the resulting cyclic

Scheme 3. Lithiation−Substitution of *rac*-5

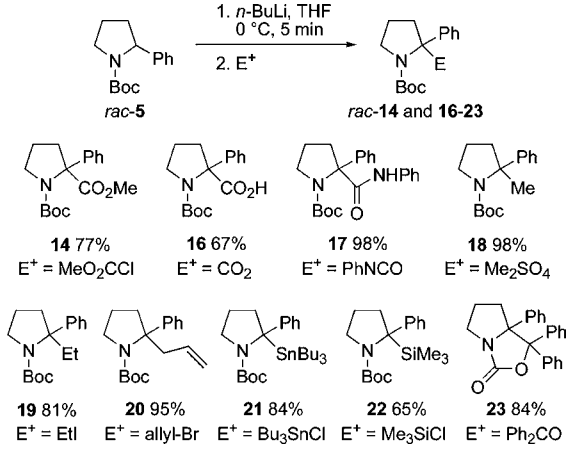

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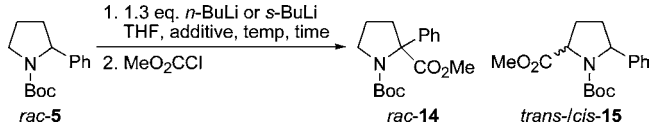
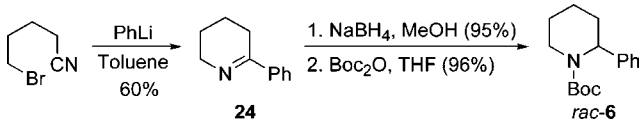
Table 1. Lithiation−Substitution of *rac*-5 under Different Lithiation Conditions



entry	base	temp (°C)	additive	time (min)	yield of *rac*-**14** (%)[a]
1	*s*-BuLi	−78	–	30	40[b]
2	*n*-BuLi	−78	–	60	33[c]
3	*n*-BuLi	−78	–	180	39[d]
4	*n*-BuLi	−78	TMEDA	60	31[e]
5	*n*-BuLi	−78	TMEDA	180	33[f]
6	*n*-BuLi	0	–	10	72
7	*n*-BuLi	0	–	5	77
8	*n*-BuLi	20	–	5	41

[a]Yields after chromatography. [b]A 40% yield of a 72:14:14 mixture (by ^{1}H NMR spectroscopy) of *rac*-**14**, *trans*-**15** and *cis*-**15** was obtained; after careful chromatography, a 17% yield of *rac*-**14** was obtained (see the Supporting Information). [c]66% yield of recovered *rac*-**5**. [d]52% yield of recovered *rac*-**5**. [e]65% yield of recovered *rac*-**5**. [f]49% yield of recovered *rac*-**5**.

Scheme 4. Preparation of *rac*-6



imine **24** with $NaBH_4$ gave 2-phenylpiperidine.[21] Subsequent protection using Boc_2O in THF delivered *rac*-**6**. Initially, the lithiation of *rac*-**6** using *n*-BuLi in THF at −78 °C was investigated by in situ IR spectroscopy (Figure 5). A solution of *rac*-**6** in THF at −78 °C gave a $\nu_{C=O}$ peak at 1694 cm^{-1}. After addition of *n*-BuLi, a new peak at 1644 cm^{-1} was observed, which was assigned to $\nu_{C=O}$ in lithiated intermediate **13** (Figure 5a). Notably, in stark contrast to the corresponding *N*-Boc 2-phenylpyrrolidine *rac*-**5**, *complete* lithiation of *rac*-**6** occurred within 2 min (Figure 5b). Clearly, the piperidine *N*-Boc rotamers **10** and **11** readily interconvert even at −78 °C.

With *rac*-**6**, it was found that TMEDA was not needed for the lithiation, and suitable conditions for lithiation−substitution involved lithiation using *n*-BuLi in THF at −40 °C for 30 min. A selection of electrophiles was explored under these conditions, and 2,2-disubstituted piperidines *rac*-**25**−**32** were obtained in good to excellent yields (75−91%) (Scheme 5).

The electrophile MeI gave the methylated product *rac*-**25**, and single-crystal X-ray analysis showed that the phenyl group is located in the equatorial position (see the Supporting Information). Unactivated (bromobutane) and activated (methoxymethyl chloride, prenyl bromide) electrophiles were suitable, giving alkylated products *rac*-**26**−**28**, respectively. The electrophilic quench with prenyl bromide proceeded by direct S_N2 reaction rather than S_N2' reaction.[22] Stannylation gave the products *rac*-**29** and *rac*-**30**. Carbonyl electrophiles were also successful, with methyl chloroformate giving the ester *rac*-**31** and benzaldehyde giving a separable mixture of diastereoisomeric oxazolidinones *rac*-**32** in high yield.

A sample of *rac*-**6** in THF-d_8 was cooled to −63 °C, and the ratio of the rotamers was measured as 51:49 using the benzylic CH signals in the ^{1}H NMR spectrum. Coalescence of these signals occurred at −28 °C (see the Supporting Information), and the barrier to rotation of the Boc group was estimated to be ~50.0 kJ/mol. This value suggests that the half-life for rotation of the Boc group in *N*-Boc 2-phenylpiperidine **6** is $t_{1/2} \approx 4$ s at −78 °C. Hence, the NMR spectroscopic studies are in

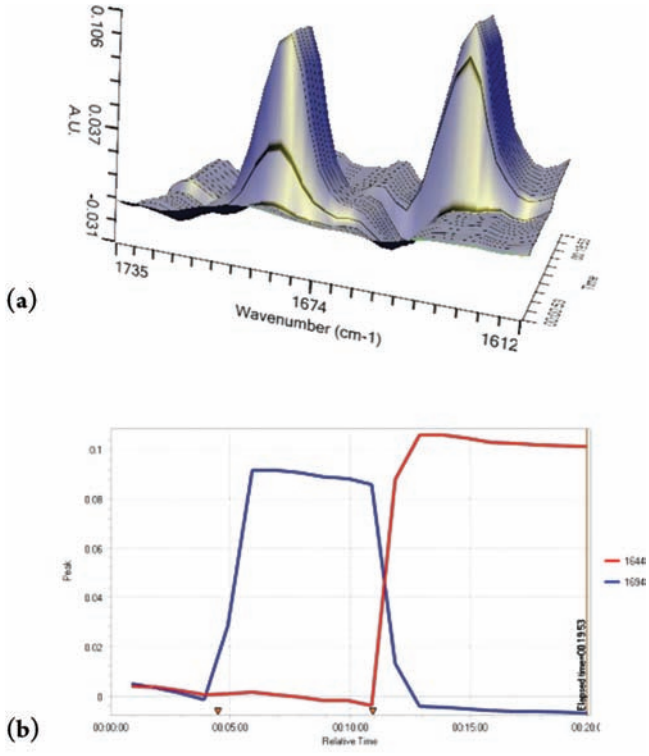


Figure 5. Investigation of the lithiation of *rac*-**6** using *n*-BuLi in THF at −78 °C by in situ IR spectroscopy.(a) 3D plot showing changes in the absorption spectrum with time. (b) 2D plot showing the time evolution of the *rac*-**6** peak at 1694 cm^{-1} (blue) and the lithiated intermediate **13** peak at 1644 cm^{-1} (red). The first and second red triangles indicate the additions of *rac*-**6** and *n*-BuLi, respectively.

agreement with the in situ IR spectroscopy results and the experiments showed that rotation of the Boc group is fast for the piperidine, affording high yields of the substituted products **25**−**32** even at low temperature.

The difference in the barriers for rotation of the Boc group in *N*-Boc-2-phenylpyrrolidine **5** and -piperidine **6** was also explored using DFT calculations (see the Supporting Information for full details). For **5**, the minimum-energy structures for rotamers **9** and **8** are shown in Figure 6a,c, respectively. The difference in energy between these structures is 848 J/mol, and if Boltzmann statistics is assumed, this

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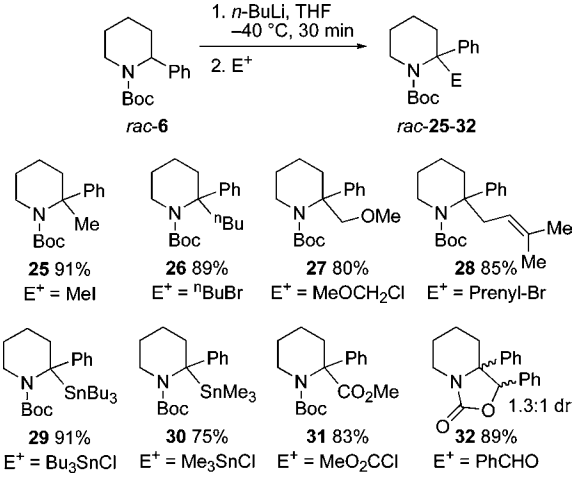
Scheme 5. Lithiation–Substitution of *rac*-6



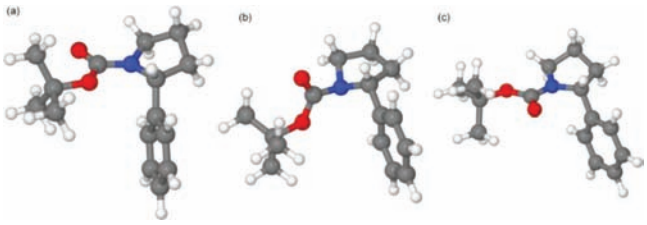


Figure 6. Geometries of **5** in THF solution: (a) and (c) are the minimum-energy structures, and (b) is the lowest transition state between (a) and (c).

corresponds to a 62:38 ratio of rotamers **9** and **8** at −72 °C, which is qualitatively comparable to the 66:34 ratio of **9** and **8** determined by ^{1}H NMR spectroscopy at −72 °C. Figure 6b depicts the structure of the lower of two possible transition states, corresponding to a clockwise rotation of the Boc group from rotamer **9** (Figure 6a) to rotamer **8** (Figure 6c). This calculated transition state is 63.1 kJ/mol higher in energy than the starting rotamer **9** (Figure 6a), in good agreement with the barrier of 64.5 kJ/mol for Boc rotation determined by variable-temperature ^{1}H NMR spectroscopy.

N-Boc-2-phenylpiperidine **6** was subjected to a similar analysis. In this case, two different conformations, corresponding to an axial phenyl group (Figure 7) and an equatorial

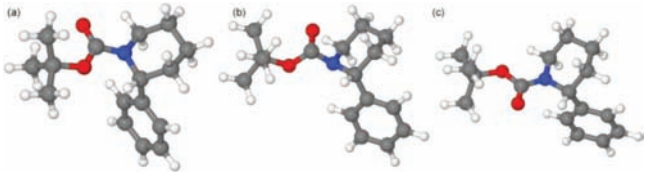


Figure 7. Geometries of **6** in THF solution with the phenyl group in the axial position: (a) and (c) are the minimum-energy structures, and (b) is the lowest transition state between (a) and (c).

phenyl group (Figure 8), were considered. As expected on the basis of $A_{1,3}$ strain considerations, rotamers **10** and **11** with an axial phenyl group were lower in energy than those with an equatorial phenyl group by 17.9 and 16.3 kJ/mol, respectively. The minimum-energy structures for rotamers **11** and **10** with the axial phenyl group are shown in Figure 7a,c, respectively. The difference in energy is only 184 J/mol, which corresponds to a 56:44 ratio of rotamers **11** and **10**, in agreement with the

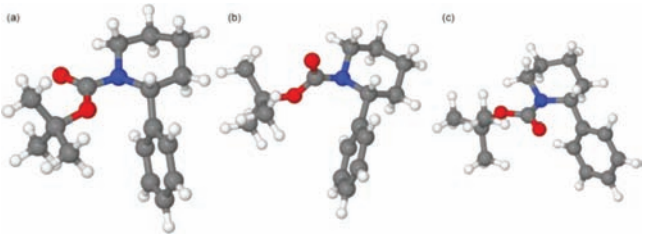


Figure 8. Geometries of **6** solution with the phenyl group in the equatorial position: (a) and (c) are the minimum-energy structures, and (b) is the lowest transition state between (a) and (c).

51:49 ratio determined by ^{1}H NMR spectroscopy at −63 °C. Although the axial phenyl conformation (Figure 7) is lower in energy, we found that the barrier for rotation of the Boc group was lower for the equatorial phenyl group. In the case of the axial phenyl group, the transition state (Figure 7b) for counterclockwise rotation of the Boc group from rotamer **11** (Figure 7a) to rotamer **10** (Figure 7c) is 70.0 kJ/mol higher in energy than the starting rotamer **11**. In contrast, when the phenyl substituent is in the equatorial position, the transition state (Figure 8b) from rotamer **11** (Figure 8a) to rotamer **10** (Figure 8c) is only 51.4 kJ/mol higher in energy than the starting rotamer **11**. This latter value matches well with the barrier for Boc rotation determined by variable-temperature ^{1}H NMR spectroscopy (50.0 kJ/mol) and suggests that the fast rotation of the Boc group in **6** at −78 °C actually proceeds via the *minor* conformation with an equatorial phenyl group. This analysis assumes that the rate of ring flipping (to interchange the phenyl group between the axial and equatorial positions) is fast at −78 °C.

Synthesis of Enantioenriched 2,2-Disubstituted Pyrrolidines and Piperidines. We next wanted to extend the chemistry to the enantioenriched substrates, (*R*)-*N*-Boc-2-phenylpyrrolidine [(*R*)-**5**] and (*S*)-*N*-Boc-2-phenylpiperidine [(*S*)-**6**]. For this to be successful, the organolithium species **12** and **13** had to be configurationally stable at the temperature used for the lithiation and subsequent electrophilic quench. One method for probing the hybridization of the carbanion that involves ^{13}C NMR spectroscopy of lithiated benzylic compounds has been reported by Beak and co-workers.[23] A difference of ∼35 ppm in the chemical shifts of the benzylic center of the unreacted starting material and the corresponding organolithium is indicative of a planar carbanion, while a shift of ∼8 ppm is expected for a pyramidalized carbanion. Diagnostic shifts are also expected for the ipso aromatic carbon, which shifts approximately 10 ppm for the sp^3 carbanion and −5 ppm for the sp^2 carbanion. In the case of *rac*-**6**, direct ^{13}C NMR spectroscopic analysis of its organolithium derivative **13** in toluene-d_8 resulted in a $\Delta\delta$ values of 6.4 ppm for the ipso carbon and 1.6 ppm for the benzylic center (tentatively assigned at 49.8 ppm) (see the Supporting Information). These results suggested that the lithium-bearing carbon atom has sp^3 character.

With confidence that the organolithium carbon center is pyramidal and could potentially maintain its configuration at sufficiently low temperatures, we set about preparing enantioenriched (*R*)-**5** and (*S*)-**6** and investigating their lithiation–substitution. Pyrrolidine (*R*)-**5** was prepared in 97:3 er using the *s*-BuLi/(−)-sparteine-mediated asymmetric lithiation of *N*-Boc-pyrrolidine **3** and subsequent transmetalation–Negishi coupling.[16] In contrast, piperidine (*S*)-**6**

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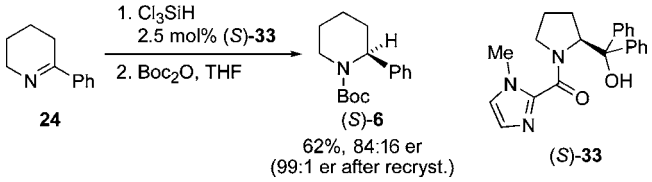
was prepared using asymmetric reduction of imine **24** in the presence of trichlorosilane and catalyst (*S*)-**33**, which is precedented for structurally related imines.[24] After Boc protection, this gave (*S*)-**6** in 84:16 er (by chiral-stationary-phase HPLC), and recrystallization provided (*S*)-**6** in 99:1 er (Scheme 6).

Scheme 6. Preparation of (*S*)-6



We initially established that for both (*R*)-**5** and (*S*)-**6**, the corresponding lithiated intermediates **12** and **13** had a high degree of configurational stability at −78 °C. Thus, (*R*)-**5** (97:3 er) and (*S*)-**6** (99:1 er) were lithiated using *n*-BuLi in THF at −78 °C and then trapped with methyl chloroformate and methyl iodide, respectively. Starting with pyrrolidine (*R*)-**5**, the product (*R*)-**14** was formed in 97:3 er (1 h lithiation time) but in only 31% yield since the *N*-Boc rotamers **8** and **9** do not interconvert at this low temperature. For piperidine (*S*)-**6**, the product (*S*)-**25** was formed in 60% yield and high er (99:1) using a 30 min lithiation time.

Lithiation−substitution of pyrrolidine (*R*)-**5** at −78 °C would not be ideal because of the incomplete lithiation and resulting low yield of the substituted products. Therefore, we turned to in situ IR spectroscopic monitoring to identify a temperature that would provide a synthetically useful amount of lithiation (higher temperatures would favor interconversion of rotamers **8** and **9**) but would also provide a useful level of configurational stability (lower temperatures would increase the degree of configurational stability). Results for the lithiation of *rac*-**5** at −78, −60, −50, −40, −30, and 0 °C are summarized in Figure 9.

The IR spectroscopy results presented in Figure 9 fall into three distinct categories. At −78 °C (Figure 9a), rotamers **8** and **9** interconvert very slowly, and the lithiation essentially proceeded only to ∼40%. At −60, −50, and −40 °C (Figure 9b−d), the profile has two distinct areas: (i) rapid initial lithiation of the reactive rotamer **8** and then (ii) slower lithiation, as the rate is limited by the rate of rotamer interconversion. At −60 °C, this second lithiation was rather slow, and complete conversion was not reached even after 30 min (Figure 9b). In contrast, complete conversion was reached after 5 min at −40 °C (Figure 9d). Finally, at −30 or 0 °C (Figure 9e,f), complete lithiation occurred in <5 min, as rotamers **8** and **9** readily interconvert at these higher temperatures.

At this point, it was still necessary to establish the degree of configurational stability of lithiated pyrrolidine **12** at the different temperatures. This was accomplished using lithiation−trapping of (*R*)-**5** (with methyl chloroformate) at −78, −50, −40, −30, and 0 °C (Table 2). Lithiation at −50 °C for 10 min gave (*R*)-**14** in 74% yield and 90:10 er (entry 2), indicating some configurational instability. Reducing the lithiation time to just 5 min at −50 °C led to higher er (94:6 er; entry 3) and good yield (78%), as expected on the basis of the IR spectroscopy results (Figure 9c). In comparison, higher temperatures, even for short lithiation times, led to reduced

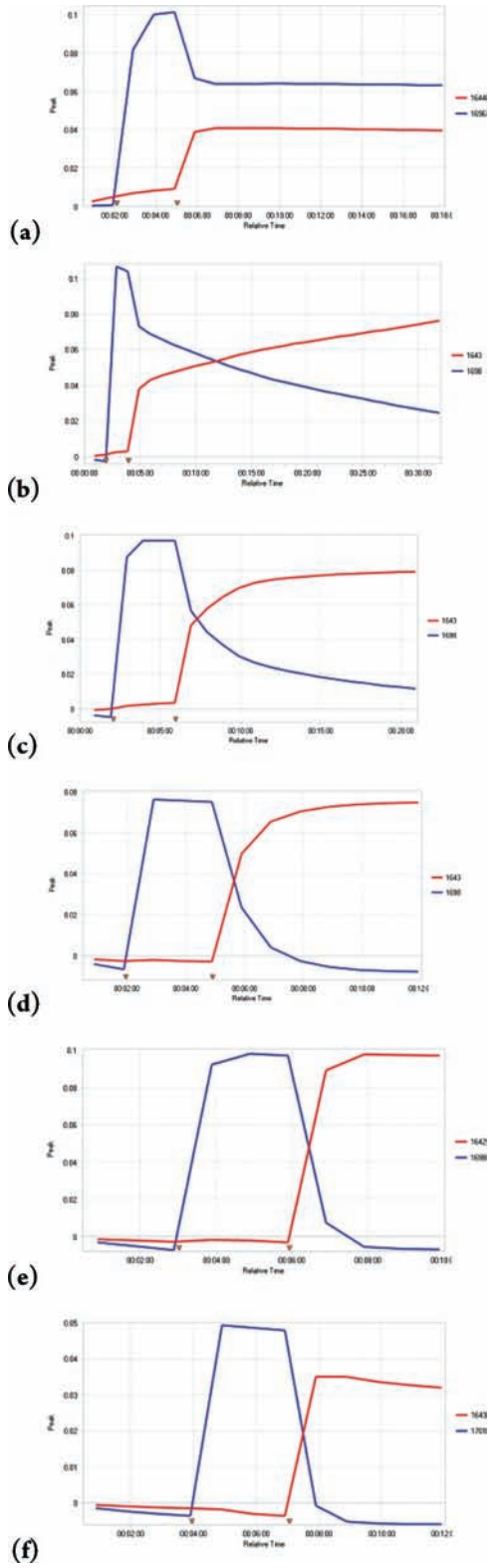


Figure 9. Investigation of the lithiation of *rac*-**5** using *n*-BuLi in THF by in situ IR spectroscopy at (a) −78, (b) −60, (c) −50, (d) −40, (e) −30, and (f) 0 °C. In each panel, the first and second red triangles indicate the additions of *rac*-**6** and *n*-BuLi, respectively.

er (entries 4−6). Not surprisingly, lithiation−substitution at 0 °C delivered *rac*-**14** (82% yield; entry 6). From the combination of these results and those from the IR spectroscopy study, we identified the optimum lithiation conditions as

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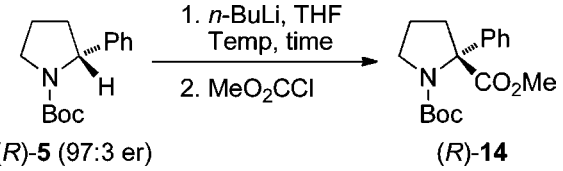
Table 2. Lithiation–Substitution of (*R*)-5 (of 97:3 er) at Different Temperatures



entry	temp (°C)	time (min)	yield of (*R*)-**14** (%)[a]	er of **14** (*R*:*S*)[b]
1	−78	60	31	97:3[c]
2	−50	10	74	90:10
3	−50	5	78	94:6
4	−40	5	69	85:15
5	−30	5	79	65:35
6	0	5	82	50:50

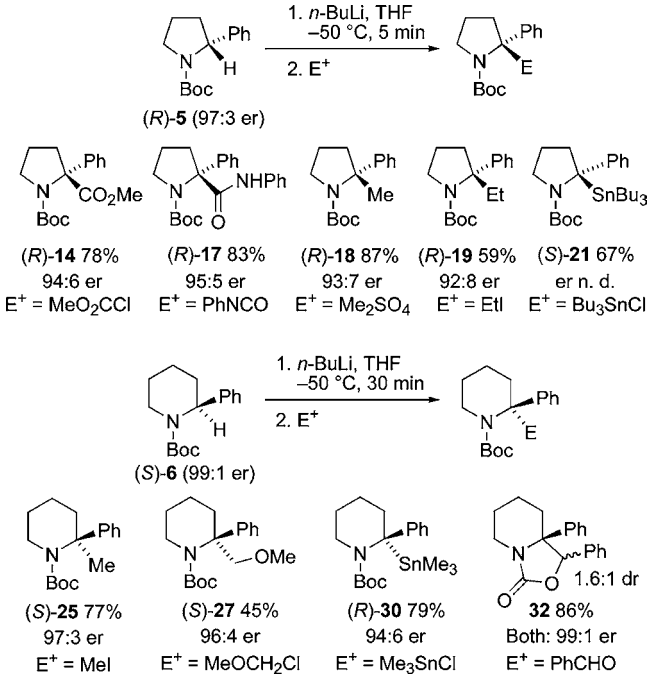
[a]Yields after chromatography. [b]Determined by chiral-stationary-phase HPLC. [c]62% yield of recovered (*R*)-**5**.

n-BuLi/THF at −50 °C for 5 min (entry 3). For piperidine (*S*)-**6**, we found that these conditions were suitable for lithiation–substitution, although a 30 min lithiation time gave the best yields. Using methyl iodide, we obtained methylpiperidine (*S*)-**25** in 97:3 er after 30 min at −50 °C. Lower temperatures (e.g., −78 °C) can alternatively be used with (*S*)-**6** because of the higher rate of rotamer interconversion. However, as expected, temperatures above −50 °C resulted in some configurational instability: at −40 °C for 30 min, (*S*)-**25** was formed with 85:15 er.

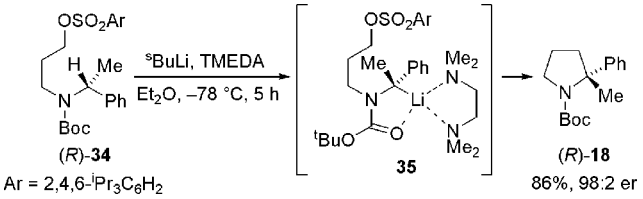
After the optimum lithiation conditions had been identified, a range of electrophiles was explored, and the results are shown in Scheme 7. In each case, the 2,2-disubstituted pyrrolidines and piperidines were obtained in good yields and high er (≥92:8 er). Notably, ethyl iodide (which can be considered as a slow-reacting electrophile) trapped the THF-solvated organolithium **12** efficiently, giving (*R*)-**19** in 92:8 er. The absolute configurations of (*R*)-**14**, (*R*)-**17**, (*S*)-**25**, and (*R*)-**30** were established unequivocally in the following way. Ester (*R*)-**14** was reduced to the primary alcohol, mesylated, and, after Boc deprotection, cyclized to a known (*R*)-bicyclic aziridine.[8] Saponification of ester (*R*)-**14** gave the acid, which was reacted with aniline under standard amide coupling conditions to give (*R*)-**17**. Removal of the Boc group in (*S*)-**25** using trimethylsilyl iodide gave the unprotected (*S*)-piperidine, for which the sign of rotation {$[\alpha]_D^{21}$ +16.0 (0.5, CH_2Cl_2)} was opposite to that reported for the (*R*)-piperidine {$[\alpha]_D^{22}$ −18.0 (0.33, CH_2Cl_2)}.[9] The configuration of (*R*)-**30** was established by tin–lithium exchange (*n*-BuLi, THF, −78 °C) and electrophilic trapping (with the assumption of retention of configuration for the tin–lithium exchange). Full details are described in the Supporting Information. The configurations of the remaining examples in Scheme 7 were assigned by analogy. Hence, it appears that lithiation–substitution occurs with retention of configuration for methyl chloroformate, phenyl isocyanate, dimethyl sulfate, methyl and ethyl iodide, R_3SnCl, methoxymethyl chloride, and benzaldehyde.

An alternative synthesis of 2,2-disubstituted pyrrolidine (*R*)-**18** was also developed (Scheme 8). The approach was based on Beak's synthesis of (*S*)-*N*-Boc-2-phenylpyrrolidine [(*S*)-**5**] via the lithiation–cyclization of an *N*-Boc-*N*-benzylchloroamine.[25] In our case, we started with (*R*)-*α*-methylbenzylamine and converted it in three steps to *N*-Boc sulfonate (*R*)-**34**. Treatment of (*R*)-**34** with *s*-BuLi/TMEDA in Et_2O at −78 °C for 5 h gave 2,2-disubstituted pyrrolidine (*R*)-**18** in 86% yield and 98:2 er. We believe that (*R*)-**34** is lithiated with retention of configuration to give **35**, which cyclizes with inversion of configuration at the carbanion center to give (*R*)-**18**. Trapping of a tertiary lithiated *N*-Boc-benzylamine with allyl triflate is known to occur with inversion,[26] and in our case, if **35** maintains chelation of the lithium to the Boc group, then cyclization is possible only via invertive trapping. This mechanistic interpretation is fully consistent with the formation of (*R*)-**18** in this reaction (Scheme 8) and also in the lithiation–methylation of (*R*)-**5** shown in Scheme 7.

Scheme 7. Lithiation–Substitution of (*R*)-5 and (*S*)-6 at −50 °C



Scheme 8. Lithiation–Cyclization of (*R*)-34 to (*R*)-18



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CONCLUSION

In conclusion, we have developed a general and enantioselective synthesis of 2,2-disubstituted pyrrolidines or piperidines containing quaternary stereocenters by simple lithiation−substitution of *N*-Boc-2-phenylpyrrolidine or -piperidine. The combined use of synthetic experiments and in situ IR spectroscopic monitoring allowed optimum reaction conditions to be identified. In situ IR spectroscopy allows real-time monitoring of rotamer interconversion, which is a crucial requirement for high-yielding lithiation. The Boc rotamer interconversion was also studied by ^{1}H NMR spectroscopy and DFT calculations. By studies at different temperatures, an indication of the propensity for enantiomerization of these organolithiums was gained. For the pyrrolidine series, the products were obtained via two separate lithiations. First, deprotonation of *N*-Boc-pyrrolidine with *s*-BuLi/(−)-sparteine and Negishi coupling gave (*R*)-*N*-Boc-2-phenylpyrrolidine [(*R*)-**5**], which was deprotonated with *n*-BuLi. Electrophilic quenches provided the 2,2-disubstituted products with retention of configuration. For the piperidine series, a catalytic asymmetric reduction led to (*S*)-*N*-Boc-2-phenylpiperidine [(*S*)-**6**], which could be lithiated with *n*-BuLi. Electrophilic trapping occurred with retention of configuration. During the course of this study, an interesting difference between the five- and six-membered rings was discovered: for lithiated *N*-Boc-2-phenylpyrrolidine, the rotamers **8** and **9** do not interconvert at −78 °C, whereas the corresponding piperidine rotamers **10** and **11** readily interconvert at this temperature. This was confirmed by the ^{1}H NMR spectroscopy study. For *N*-Boc-2-phenylpyrrolidine **5**, the half-life ($t_{1/2}$) for rotation of the Boc group was ∼10 h at −78 °C, ∼3.5 min at −50 °C, and ∼0.3 s at 0 °C, while for *N*-Boc-2-phenylpiperidine **6**, $t_{1/2}$ was determined to be ∼4 s at −78 °C. Therefore, higher temperatures are required for yields above 40% for the pyrrolidine series. As a result of this work, it should now prove possible to construct small libraries of 2-substituted 2-arylpyrrolidines and -piperidines for evaluation of their pharmaceutical properties.

ASSOCIATED CONTENT

Supporting Information

Full experimental procedures and spectroscopic data, together with copies of NMR spectra, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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