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Selective benzylic lithiation of *N*-Boc-2-phenylpiperidine and pyrrolidine: expedient synthesis of a 2,2-disubstituted piperidine NK_1 antagonist

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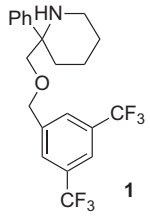
Dedicated to Professor Madeleine M. Joullié on the occasion of her birthday

Abstract—Unlike the lithiation of *N*-Boc-2-alkylpiperidines, which occurs at the 6-position, *N*-Boc-2-phenylpiperidine and *N*-Boc-2-phenylpyrrolidine can be lithiated exclusively at the 2-position. The tertiary carbanions can be trapped with a variety of electrophiles. This chemistry was used for the synthesis of a potent NK_1 ligand ($K_i = 0.3$ nM). The bioactive configuration at the piperidine quaternary center was determined by X-ray analysis to be (*S*).

In our recent medicinal chemistry efforts toward the discovery of orally active NK_1 receptor antagonists, we became interested in a series of 2,2-disubstituted piperidine compounds **1** initially described by a Merck group.[1] This compound showed good in vitro activity (IC_{50} $NK_1 = 1$ nM) as a racemate, but no absolute stereochemistry has been described. Subsequently, the same group also introduced a (*R*)-methyl group to the benzylic position of the bis-trifluoromethylbenzyl side chain in 2,3-disubstituted piperidine analogs such as **2**. This discovery resulted in increased binding potency and improved pharmacokinetic profiles over the desmethyl analogs.[2] Our previous NK_1 research program has been focused on a series of 4,4-disubstituted cyclic ureas such as **3**. We have demonstrated an efficient synthesis of lead analog **3** and showed the beneficial effect of incorporation of an (*R*)-methyl group on the side chain of the benzyl group.[3] As an extension of our continued interest in NK_1 antagonists, we decided to pursue the synthesis of compound **4** and determine the bioactive stereochemical configuration at the piperidine quaternary center.



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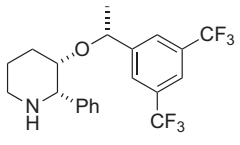

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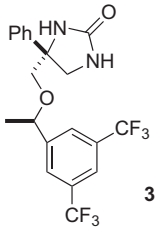

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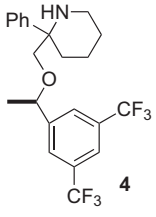

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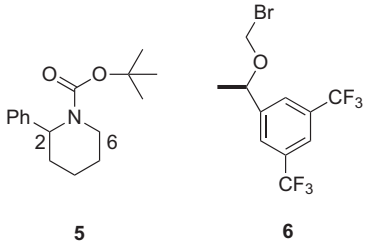
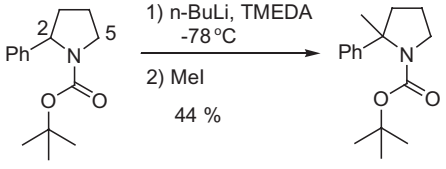
At the onset of the synthesis, it appeared that the original approach by the Merck group for accessing **1** was not suited to the addition of the chiral bis-trifluoromethylbenzyl group due to the difficulty of installation of the neopentyl ether moiety.[4] Although many options for piperidine synthesis are available,[5,6] we became intrigued by the possibility of using *N*-Boc-2-phenylpiperidine as the starting material, since it can be obtained by protection of commercial 2-phenylpiperidine. If **5** can be deprotonated at the benzylic position, then trapping the resulting carbanion with a suitable electrophile (such as **6**)[3] would produce *N*-Boc protected **4** as a mixture of diastereomers.

Formation of tertiary carbanions adjacent to nitrogen is reported to be difficult and substrate dependent.[7,8] However, nitrogen substituted benzylic lithiation has been demonstrated to be a useful synthetic method. Yet, the successful cases usually involved acyclic systems,[8–15] relatively planar fused tetrahydro/dihydroquinoline systems,[16–19] and in one case, a 2-phenyl aziridine system.[20] To the best of our knowledge, no work has been done in 2-phenylsubstituted piperidine systems. In piperidine systems, lithiation potentially can occur at the carbon adjacent to the nitrogen atom. The lithiation of 2-alkyl-*N*-Boc-piperidines is known to occur at C-6 position.[21,22] In the previously unknown 2-phenyl case, it is not certain whether the lithiation will occur at C-2 or C-6 and if the reaction will have enough selectivity to be synthetically useful.

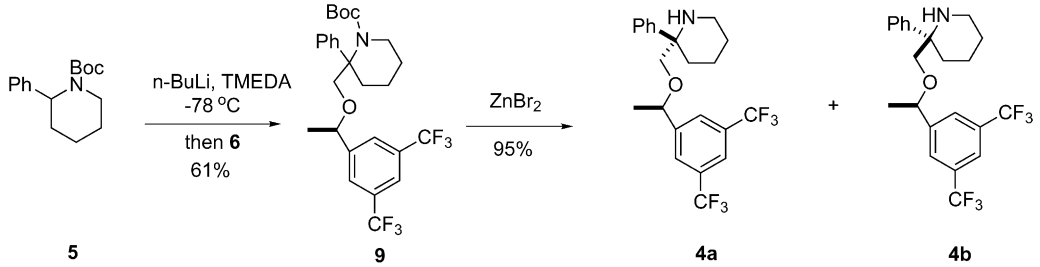
In order to determine the location of the lithiation, we decided to do a deuterium quenching experiment on the anion. When **5**[23] was treated with *n*-BuLi and TMEDA[22] at −78 °C for 2 h and quenched with CD_3OD at the same temperature, the product contained >98% D incorporation at C2 position and was obtained in 95% yield. Importantly, replacing TMEDA with (−)-sparteine resulted in no lithiation at either C2 or C6.[24] Because of the high degree of selectivity seen in the *N*-Boc-2-phenylpiperidine case, it also seemed appropriate to investigate the analogous reaction in the case of *N*-Boc-2-phenylpyrrolidine (**7**) as well. Previously, Beak and co-workers had treated **7** with *s*-butyl lithium in the presence of (−)-sparteine and found that it alkylated on the 5-position.[25] In order to investigate the site selectivity of lithiation chemistry, compound **7** was treated with *n*-butyl lithium/TMEDA. The resulting anion was quenched with methyl iodide to give the methylated compound **8**. Trapping occurred exclusively at the benzylic carbon. No C-5 trapping products were observed. This result, combined with observation in *N*-Boc-2-phenylpiperidine case, suggested that the site of lithiation might be largely influenced by the diamine ligand used.[26]



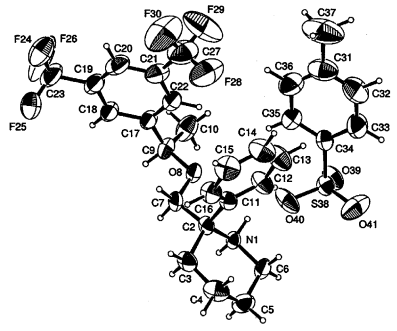
5 **6**



7 **8**



5 **9** **4a** **4b**



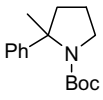
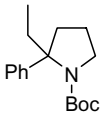
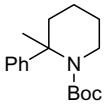
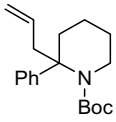
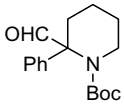
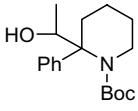
After securing the selectivity of the lithiation process with *n*-BuLi/TMEDA system, we further investigated the scope of this reaction by treating the anions with different electrophiles. As summarized in Table 1, the anions readily reacted with MeI, EtBr, and allyl bromide to form modest yields of alkylated products. The reactions of **5** with carbonyl electrophiles such as DMF and acetaldehyde also afforded useful yields of products.

For the proposed synthesis of NK_1 compound **4**, the lithiated *N*-Boc-2-phenylpiperidine **5** was treated with highly reactive bromomethylether **6**,[3] to obtain an inseparable mixture (1:1) of compounds **9** in 61% yield. No significant difference in the kinetics of alkylation between the two enantiomeric carbanions was detected. The mixture of **9** was further treated with $ZnBr_2$ in CH_2Cl_2 followed by preparative TLC on silica gel to obtain the desired two compounds **4a** and **4b**. An X-ray crystal structure analysis of the tosylate of **4a** unequivocally established the stereochemistry.

The HCl salt of **4a** has a K_i of 0.3 nM in the NK_1 binding assay while the HCl salt of **4b** is at least 50 times less active (>15 nM).[28] With this information, compound **4a** was determined to be the lead for further medicinal chemistry efforts.

In conclusion, we have studied the lithiation of *N*-Boc-2-phenylpiperidine and 2-phenylpyrrolidine. In each case, the lithiation occurred exclusively at the benzylic position under the conditions used.[27] The scope of this reaction was investigated and was found to be a useful synthetic method to make *gem*-disubstituted 2-phenylpiperidines and pyrrolidines. Further elaboration of this chemistry provided a rapid synthesis of **4** from which the bioactive configuration was established to be the same isomer as the 4,4-disubstituted cyclic urea **3**.

Table 1. Addition of electrophiles to tertiary anions of **5** and **7**

Entry	Reactants	Electrophiles	Products	Yields (%)
1	**7**	MeI		44
2	**7**	EtBr		33
3	**5**	MeI		51
4	**5**	AllylBr		43
5	**5**	DMF		52
6	**5**	CH_3CHO		59 (1.4:1)

Acknowledgments

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Supplementary data

Supplementary data includes, a representative lithiation procedure, spectroscopic data for alkylation products, and crystallographic data in CIF format for the tosylate salt of **4a**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.08.148.

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