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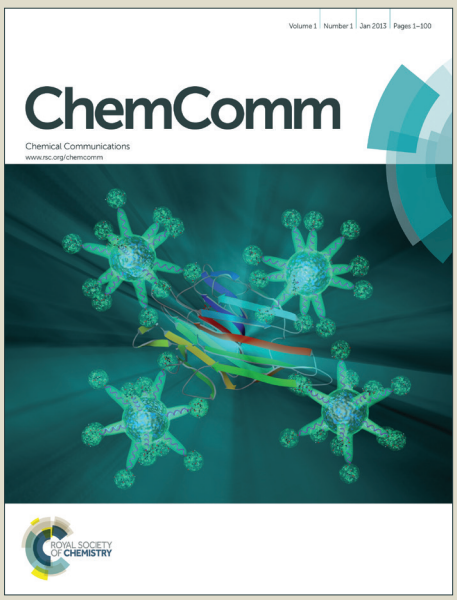

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Stereocontrolled Synthesis of Vicinally Functionalized Piperidines by Nucleophilic β-Addition of Alkyllithiums to α-Aryl Substituted Piperidine Enecarbamates

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Substituted piperidines are emerging as important medicinally-active structural motifs. Here, we report highly stereoselective carbolithiation reactions of α-aryl piperidine enecarbamates that offer direct access to vicinally-substituted piperidine compounds. We have also demonstrated that the carbanion intermediates can be trapped with a carbon electrophile

The lithiation chemistry of piperidines has been studied for over two decades following the seminal discovery by Beak that *N*-Boc piperidine can be deprotonated at the α position (i.e., C2 or C6, see **1** for numbering) by the action of *sec*-BuLi in the presence of a diamine.[1] This early discovery has led to a wealth of knowledge on α-lithiated piperidines in terms of both fundamental reactivity and synthetic applications.[2] The piperidine structural motif is found in a wide variety of biologically active natural products and pharmaceuticals (for selected examples see Figure 1).[3,4] As such, there continues to be sustained effort from the synthesis community to develop new methods to access substituted piperidines. Even though one of the most established methods for the functionalization of piperidines is using lithiation chemistry,[1] to date, all the reported lithiation methods for the functionalization of piperidines (which are significantly more challenging to deprotonate compared to pyrrolidines)[1b] have only achieved the introduction of a single substituent at the activated α-positions (i.e., C2 or C6)[5,6,7] or at the unactivated C3 position (through a metal-mediated 1,2-migration from an α-metalated precursor).[8] Given the well-established reactivity of benzylic lithiated piperidines,[6,7] we sought to develop methods involving lithiated intermediates that could achieve multiple functionalizations. We have been especially drawn to direct methods that would enable vicinal substitution on the piperidine structural motif, specifically at C2 and C3, given the prevalence of biologically active natural products (e.g., **4** and **5**) which possess this substitution pattern. Importantly, because of the emergence of C2-arylated piperidines with medicinal potential (e.g., piperidine **1** was identified as a lead compound in an NK1 receptor antagonist program at Merck laboratories)[9] we reasoned that the synthesis of C2/C3 vicinally substituted piperidines would expand the structural space for the discovery of novel compounds of medicinal value.

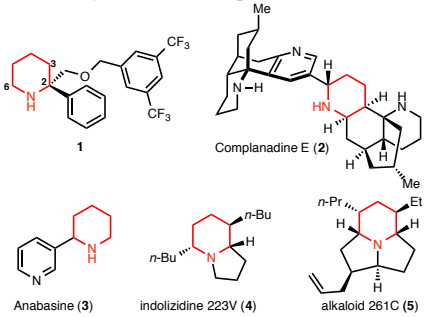
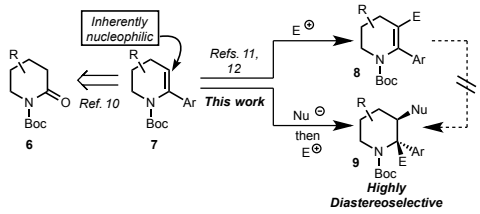


Figure 1. α-Aryl and vicinally-substituted piperidines.

In our view, α-arylated dehydro-piperidines (e.g., **7**, Scheme 1) could serve as versatile substrates for the purpose of building highly functionalized C3 substituted, α-arylated, piperidine derivatives. Owing to the ready availability of δ-lactams (e.g., **6**), we anticipated that they would be good starting points for the synthesis of dehydro-piperidines such as **7** (see Figure 2) using the method of Occhiato et al.[10] Given the inherent nucleophilicity of the C3 position of enamine derivatives related to **7**, numerous methods have been

developed for the introduction of *electrophiles* at C3. However, only strong electrophiles (e.g., formyl, or acylium ions using Vilsmeier-Haack formylations and Friedel-Crafts-type acylations) have been successful reacting partners.[11] To the best of our knowledge, the direct electrophilic installation of alkyl groups under transition metal-free conditions, which would be beneficial from a late-stage diversification standpoint, have not been reported nor have they been successful in our hands.[12] We envisioned an alternative approach to the C3-alkylation of enecarbamates, which would utilize alkyl *nucleophiles* in what is formally an 'umpolung' process.[13] The success of this type of addition would exploit the recognized stabilization of lithium carbanions at C2 of *N*-Boc piperidines by chelation of the lithium ion to the Boc group.[14] Several challenges had to be overcome in order for the addition of relatively basic alkyl nucleophiles to dehydropiperidines to be successful. These include: (1) the potential for allylic deprotonation at C4, (2) deprotonation at C6 and at C3 (i.e., directed ortho-lithiation of the enecarbamate[15]), (3) ortho-lithiation of the α-aryl substituent, or (4) the addition of the nucleophile into the Boc group. Finally, it was our goal to achieve highly diastereoselective vicinal difunctionalizations of piperidines. This latter goal is especially important given that only poor diastereoselectivity is observed in analogous processes attempted with the azepene homologue.[16]



Scheme 1. Diastereoselective vicinal functionalization of piperidine enecarbamates.

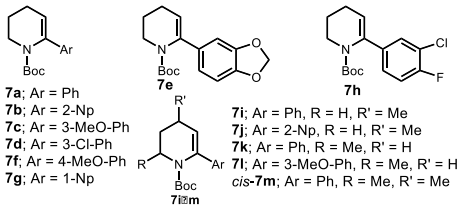


Figure 2. α-Aryl dehydro-piperidines utilized in this study**.**

We initiated our studies by investigating the addition of alkyl lithium nucleophiles to arylated enecarbamate **7a** (Figure 3A). *n*-BuLi was selected as the nucleophile because of its ready availability and the recognized superiority of lithium-based intermediates in carbolithiation chemistry.[14,17] Following a survey of several conditions, we were delighted to find that the reaction of **7a** with *n*-BuLi gives the product of carbolithiation (i.e., **9aA**, following a methanol quench) along with **10** (resulting from addition of *n*-BuLi into the Boc group). The carbolithiation process is highly diastereoselective, with the C2 aryl and the C3 alkyl groups *anti* (see Figure 3B). The nature of the aryl substituent has a marked effect on the extent of competing nucleophile addition into the Boc group. As illustrated in Figure 3B, phenyl, 2-naphthyl, *m*-methoxyphenyl and *m*-chloro phenyl enecarbamate substrates readily participate in the carbolithiation without competing ortho-lithiation[18] of the aryl group (e.g., in the case of **9cB**) or halogen-metal exchange (in the case of **9dC**). The use of *sec*-BuLi as a nucleophile resulted in excellent stereoselectivity with respect to the C2 and C3 positions (see **9aB** and **9cB**). However, no stereoselectivity was observed with respect to the stereocenter bearing the ethyl and methyl groups in these products. Unambiguous support for the nature of the alkylated products that are formed was obtained by X-ray crystallographic analysis of the *p*-nitro-benzoyl derivative of **9bC** (see CYLview[19] of **11**; most H's removed for clarity).

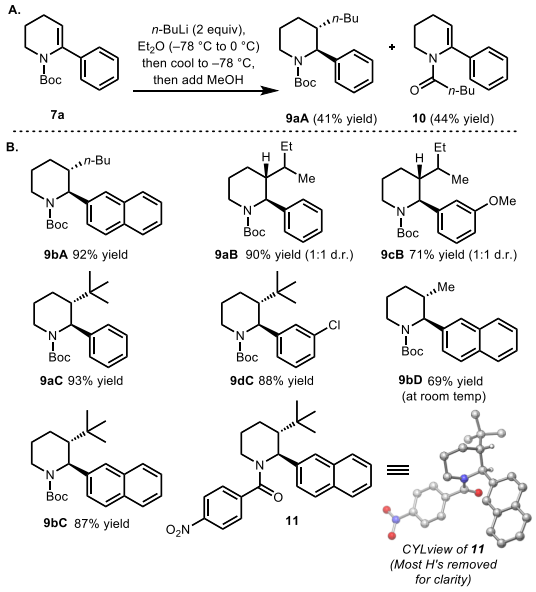


Figure 3. Scope of the carbolithiation/proton quench. (In the numbering, lowercase letter reflects enecarbamate substrate and upper case letter reflects alkyl nucleophile).

Not all piperidine enecarbamate substrates that we have examined undergo efficient carbolithiation. For example, enecarbamates **7e** and **7f** (see Figure 2), bearing electron-rich arenes, as well as sterically encumbered 1-naphthyl bearing **7g** mainly undergo addition of the alkyllithium into the Boc group, whereas **7h**, which possesses a fluorine group on the aryl substituent, yields a complex mixture (presumably arising from competing aryl ortho-lithiation/benzyne formation or dehalogenation).[20] In addition, contrary to the observations made in the carbolithiation of a single azepene enecarbamate example,[16] our studies on piperidine enecarbamates have revealed that in the latter substrates, aryl lithium nucleophiles do not add easily to C3. This observation highlights the significant reactivity differences in the lithiation chemistry of azacycles of different ring sizes.[21,1b]

We have also examined the diastereoselectivity of the piperidine enecarbamate carbolithiation processes in the presence of other substituents on the ring. For example, a C4 methyl group (see **7i**, Figure 4A) does not adversely impact the efficiency of the carbolithiation and instead leads (following a MeOD quench and Boc cleavage) to a 78% yield of **9iC** as a single diastereomer. Similarly, 2-naphthyl substituted enecarbamate **7j** provides carbolithiation product **9jC** in 79% yield over two steps. The stereochemical outcome of these carbolithiations was confirmed by single crystal X-ray crystallographic analysis of the *p*-nitrobenzoyl

derivative of **9jC** (see CYLview of **12**). C6-methyl substituted enecarbamates such as **7k** and **7l** also undergo highly diastereoselective carbolithiations to give alkylated adducts (e.g., **9kA**, obtained from **7k** and *n*-BuLi in 70% yield and **9lA**, which was obtained from **7l** in 86% yield over 2 steps). Furthermore, carbolithiation of enecarbamate **7m** bearing two methyl substituents at C4 and C6 yields **9mC** as a single diastereomer[22] when treated with *tert*-butyllithium.

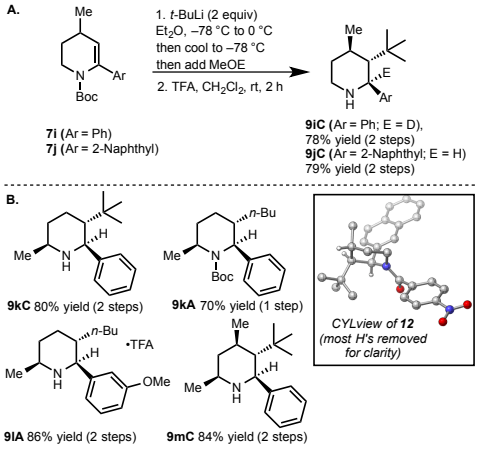
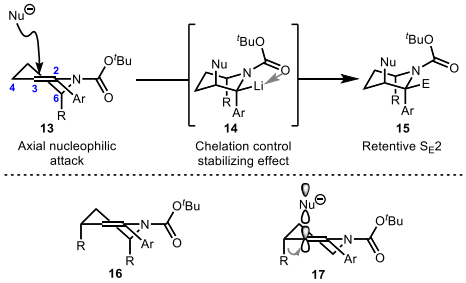


Figure 4. Substrate-controlled diastereoselective carbolithiation/proton quench substrate scope.

A DFT computational analysis performed at the B3LYP/6-31G(d) level of theory on the structures of the lithiated intermediates that arise upon carbolithiation (e.g., **14**, see Scheme 2) revealed that in all cases, the *syn* isomer (i.e., bearing the alkyl nucleophile, Nu, and the Li group on the same face) is ~8 kcal/mol more stable than the corresponding *anti* isomer.[23] Additionally, our computations support the pseudo-axial orientation of substituents at the C2 and C6 positions of the *N*-Boc piperidine intermediates (i.e., carbolithiations proceed via enecarbamate conformers similar to **13** and **16**, respectively). The surprising case is **7i/j**, where the stereochemical outcome appears to be governed by a pseudo-axial placement of the C4 methyl group (see R in **17**). In this case, a lower-lying transition state is presumably accessed by virtue of a stabilizing donor-acceptor interaction between the axially disposed C–C bond and the developing C–C σ* in accord with a Cieplak-type effect[24] and an unusual manifestation of the Fürst-Plattner rule.[25] This stabilizing effect likely overrides any developing *syn*-pentane interaction between the C4 and C6 substituents. Attempts to extend the carbolithiations from C2-*arylated* enecarbamate substrates to the C2-*alkyl* variants have been unsuccessful. We believe that the success of the carbolithiation in the α-arylated enecarbamate variants may be attributed to the added carbanion stabilization afforded by the aryl group. This assertion is supported by the correlation of the efficiency of carbolithiation with the electronics of the aryl moiety (e.g., electronic-rich aryl substrates **7e** and **7f** do not undergo efficient carbolithiation).



Scheme 2. Rationalization of the stereochemical outcome.

In the successful carbolithiation cases, the lithiated intermediate likely exists as an *ion pair* with stabilization of the carbanion by the electron deficient aryl substituents.[5b,26,27] This is supported by NBO analysis of **18a/b** (Figure 5) where C–Li bonding is not pronounced (see the Supporting Information for a full reaction coordinate/transition state analysis). In contrast, for the C2-methyl intermediate **19**, a highly covalent C2–Li bond was computed. For carbanion intermediates **18a/b** and **19**, computations indicate that the O–Li bond distance (1.843 Å, Ar = Ph) is shortened whereas the C–Li bond distance is lengthened (2.133 Å), consistent with significant interaction between the lithium and Boc carbonyl group.[5d,5e,28] During the course of the carbolithiation, reorganization of the coordination sphere is required as reflected in the Li–C2–C7 bond angle, which is compressed when electron-deficient aryl substituents are employed. The lower degree of distortion (as compared to the starting enecarbamate),[29,30], leads to a lower-lying transition state and to a lower energy barrier.[31]

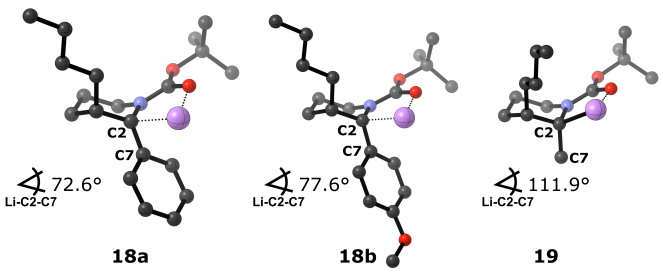
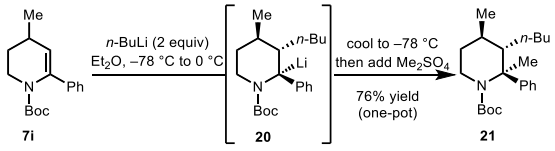


Figure 5. Computed carbanion intermediates (compounds **18a, b** and **19**). Color code: gray (C), blue (N), red (O) and purple (Li). H's removed for clarity.

Finally, in a preliminary study, we have demonstrated that the lithiated carbanion intermediate (e.g., **20**, Scheme 3) can be stereospecifically intercepted by other electrophiles such as dimethyl sulfate leading to a product (**21**) that possesses three contiguous stereocenters of which one (at C2) is tetra-substituted. In this single-step transformation, two C–C bonds are forged on vicinal carbons, thus, highlighting the power of the carbolithiation/trapping protocol described herein. The reactivity of benzylic lithio-carbanion intermediates such as **20** with other electrophiles is the focus of future studies.



Scheme 3. Diastereoselective carbolithiation/methyl electrophile trap.

Conclusions

In conclusion, we report the first examples of highly diastereoselective carbolithiations of α-arylated dehydropiperidine enecarbamates with alkyllithium nucleophiles.[32] This novel reactivity side-steps the challenge of the direct deprotonation of *N*-Boc piperidines and has led to the diastereoselective synthesis of piperidine derivatives bearing vicinal (C2, C3) substituents. This short, umpolung-type synthetic sequence provides a straightforward method to access alkylated piperidines that may be applied in the synthesis of compounds of medicinal and biological importance. Efforts to render this unusual umpolung-type coupling enantioselective as well as to extend the scope to include other α-substituted enecarbamates are underway.[33]

Acknowledgments

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Notes and references

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†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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