Trapping of carbolithiation-derived tertiary benzylic α-lithio piperidines with carbon electrophiles: Controlling the formation of α-amino quaternary and vicinal stereocenters

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The interception of carbolithiation-derived tertiary benzylic α-lithio piperidines with carbon electrophiles, under HMPA-mediated conditions, has led to the diastereoselective synthesis of vicinally functionalized piperidines bearing α-amino quaternary stereocenters.

One of the most succinct and atom economical approaches to substituted piperidines bearing at least one α-substituent (see Fig. 1 for numbering) is to functionalize the α-amino C-H bond of the parent azaheterocycle by employing a directed lithiation/trapping protocol; a strategy first introduced by Beak and Lee.[1] Over the last three decades, several researchers have extended the Beak methodology to include sequential α-functionalizations en route to accessing polysubstituted nitrogen- and oxygen-containing heterocycles.[2-9] For example, in 2012, Coldham/O'Brien[10] and Gawley[11] disclosed that enantioenriched *N*-Boc-2-aryl-2-lithiopiperidines (and pyrrolidines) can be functionalized at the α-position with maintenance of configurational stability at low temperatures.[10, 11] Recently, Coldham also reported that benzannulated piperidine derivatives such as tetrahydroisoquinolines display similar characteristics.[12] The ability for these dipole-stabilized tertiary benzylic α-amino organolithiums to exhibit configurational stability at ambient temperature[11] is truly remarkable since benzylic organolithiums that are configurationally stable, even at –78 °C, are relatively rare.[13-16] As a result, most approaches to stereoselective lithiation/alkylation sequences at benzylic sites typically employ chiral auxiliaries[17-19] or chiral ligands[20-23] to either impose configurational stability in the ground state or diastereomeric bias in the transition state.

The ever-increasing need for the development of expedient and efficient strategies for the construction and functionalization of privileged (from the standpoint of drug discovery) motifs such as the piperidine motif is supported by their prevalence in many alkaloid natural products and pharmaceuticals (Fig. 1). Accordingly, our interest in these functionalized azaheterocycles[11, 24-31] recently led us to the discovery that α'-lithiation/trapping of α-alkyl-α-aryl disubstituted piperidines such as **1** (Fig. 2A) proceeds satisfactorily to afford the corresponding trisubstituted products (*i.e.*, **2**), in good to excellent diastereoselectivities.[32] Additionally, we and Sarpong have revealed that the addition of organolithium nucleophiles to the β-position of α-arylated piperidine enecarbamates such as **3** followed by protonation of the resulting intermediate tertiary organolithium, is possible, under additive-free conditions (see **4**, Fig. 2B).[33] In that report, it was noted that incipient attempts at methylating the benzylic organolithium generated from enecarbamate **3a** were quite promising (see **5a**, Fig 2C). In this umpolung (nucleophile-nucleophile) mode of reactivity, two C-C bonds are forged in one step (*i.e.*, at the α- and β-positions). The stereoselectivity of the process is presumably governed by stereoelectronic effects[34] as well as by Cieplak's hypothesis.[35]

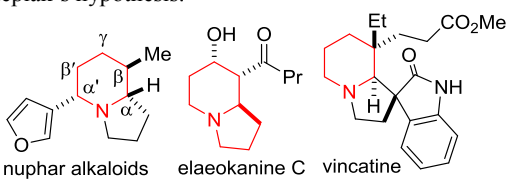


Fig. 1 Selected examples of vicinally functionalized piperidine alkaloids

Desiring an expedient and practical approach for accessing vicinally difunctionalized piperidines bearing an *α-amino benzylic quaternary stereocenter*, we sought to build on the aforementioned lone methylation example by examining the scope of carbolithiation/trapping of α-arylated enecarbamates with carbon electrophiles (Fig. 2D). If suitable conditions for transmetalation of the benzylic organolithium intermediate to other versatile organometallic species such as cuprates and zincates are identified, it is surmised that the synthetic potential of the methodology would be stupendously amplified. We anticipate that the repertoire of compounds assembled through the planned strategy would beneficially expand the structural space for the discovery of new bioactive piperidine derivatives. It is however recognized that the ability to mitigate the regioselectivity of the lithiation as well as the steric course of the alkylation/allylation/arylation would be paramount. Herein, efforts toward the elicitation of the proposed plan are described.

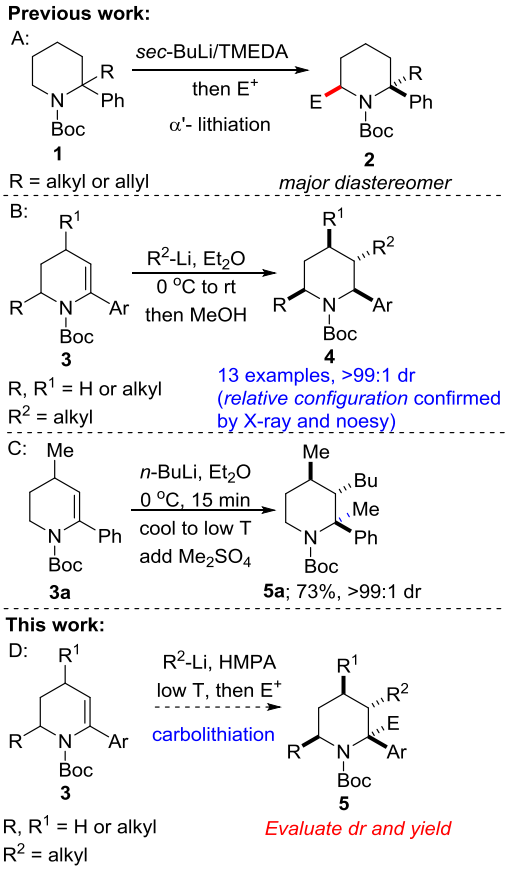


Fig. 2. Proposed plan for the synthesis of α-tetrasubstituted benzylic piperidines

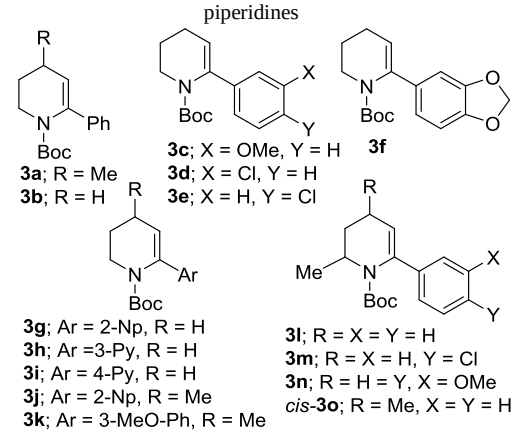
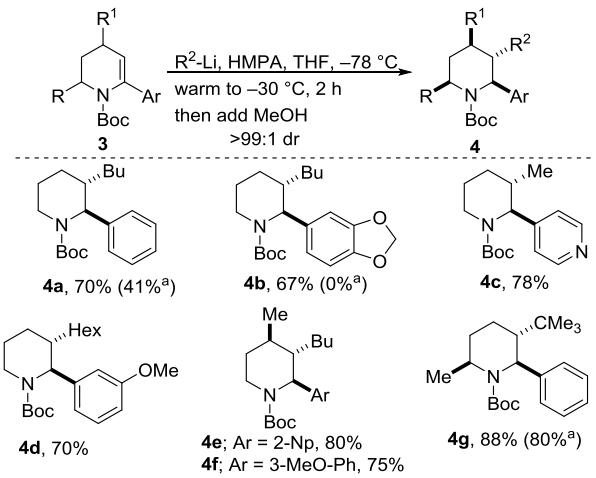


Fig. 3. Examples of α-arylated piperidine enecarbamates

During our previous attempts at β-regioselective alkylation of α-substituted enecarbamates such as those depicted in Fig. 3 with organolithium nucleophiles, under additive-free conditions (see Fig. 2B),[33] a few setbacks were encountered. Specifically, attack on the Boc-group by strongly nucleophilic organolithiums such as *n*-BuLi was competitive with β-alkylation. Thus, prior to examining the scope of carbolithiation/trapping of aryl enecarbamates with carbon electrophiles, it was of interest to seek ways to side-step the previously encountered shortcomings. We reasoned that the presence of an appropriate additive could aid in mediating an otherwise recalcitrant reaction, thus, increasing the chances of performing the reaction at a temperature where attack on the Boc-group is minimal. This is all the more important since we have found that other possible directing groups on nitrogen (e.g., formyl, pivaloyl, or tosyl) are inferior to the Boc-group in this reaction manifold. Pleasingly, when the carbolithiation is performed at −30 °C (after introduction of the organolithium nucleophile at −78 °C) in the presence of hexamethylphosphoramide (*i.e.*, HMPA), the desired vicinally functionalized piperidines are obtained in synthetically useful yields (Scheme 1, see **4a–g**). The diastereomeric ratios were determined by GC- or LC-MS analysis of the crude mixtures and the relative configuration of the products was assigned by analogy to those prepared using our previously reported approach (see Fig. 3A/B).[33] Enecarbamates bearing stereoelectronically diverse aryl substituents, including π-deficient heteroaryl motifs (e.g., **3i**) are tolerated in this transformation. The ability to prepare products such as **4b** (harboring the same aryl substituent that is resident in pharmaceuticals such as Cialis®) under these modified conditions is noteworthy since our previous attempts[33] were futile.

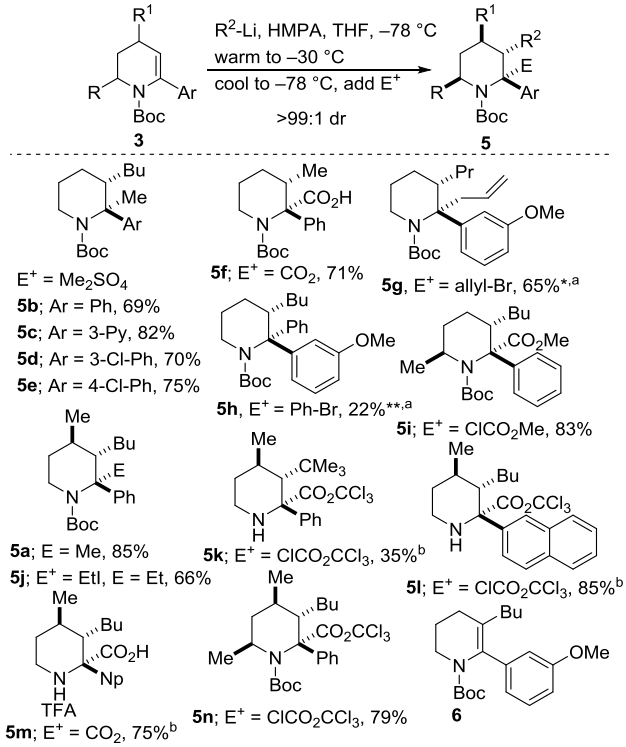


[a]yield obtained using the HMPA-free conditions described in *ref. 33*

Scheme 1. Carbolithiation/protonation of α-arylated piperidine enecarbamates under HMPA-mediated conditions

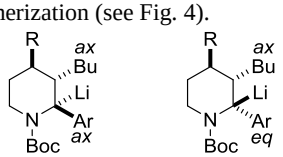
With sumptuous conditions for accessing vicinally functionalized piperidines in hand, we next sought to fully explore the possibility of intercepting the intermediate tertiary α-amino benzylic organolithium with carbon electrophiles. In the event, we were elated to find that carbolithiation of several α-arylated enecarbamates with *n*-BuLi followed by cooling of the mixture to –78 °C, then trapping with dimethyl sulfate, affords the α,α,β-trisubstituted piperidine derivatives in good yields (Scheme 2, see **5b–e**). Additionally, quaternary pipecolic acid derivatives are affordable when dry ice is employed as the electrophile (see **5f**). When TMEDA-mediated carbolithiation of enecarbamate **3c** is accompanied by transmetalation of the tertiary benzylic organolithium to the corresponding organozinc species (using $ZnCl_2$), subsequent copper-mediated allylation[10, 11] affords piperidine **5g** in acceptable yield. It is anticipated that the ability to prepare allylated piperidine derivatives such as **5g** would further endear this methodology to the synthesis community since the allyl motif offers several possibilities for late-stage diversification. For example, the double bond can be reduced,[26, 36, 37] oxidized,[26, 37-40] engaged in metathesis reactions,[41] carbolithiated,[42-45] or serve as a pyrrolidine surrogate when hydrozirconated.[46] Primarily due to steric congestion, carbolithiation of **3c** followed by transmetalation and palladium-catalyzed coupling with bromobenzene (using a $Pd_2(dba)_3$/*t*-$Bu_3P{\cdot}HBF_4$ catalyst system[11, 47, 48]) furnishes arylated piperidine **5h** in low yield. The remaining mass balance in this example is mostly accounted for by dehydropiperidine **6**, which probably arises from β-hydride elimination. In a finding of great significance, particularly within the context of accessing a *new*

family of indolizidine- and quinolizidine-type alkaloids bearing an α-aryl substituent, we find that carbolithiation/acylation of α,α'-disubstituted enecarbamate **3l** proceeds efficiently to afford quaternary pipecolinate **5i**. The studies conducted herein have audaciously revealed that 2,4-disubstituted dehydropiperidines such as **3a** undergo vicinal carbo-difunctionalization following carbolithiation/methylation, ethylation, esterification, or carboxylation to afford saturated piperidine derivatives bearing three *contiguous* stereocenters (see **5a**, **5j**–**m**). Since carbolithiation with *tert*-BuLi followed by protonation proceeds in high efficacy (see **4g**, Scheme 1), the low yield obtained during the preparation of **5k** is probably due to the combined steric encumbrance imposed by both the *tert*-butyl and acyl substituents. We have found that 2,4,6-trisubstituted enecarbamate *cis*-**3o** undergoes diastereospecific carbolithiation/acylation to afford tetrasubstituted piperidine **5n**.



Scheme 2. Carbolithiation/alkylation/arylation of α-arylated piperidine enecarbamates

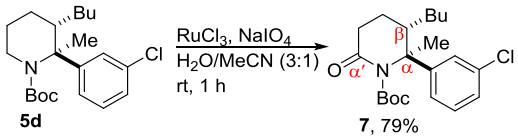
The results in Scheme 2 indicate that the influence of the α-aryl substituent on the diastereoselectivity of carbolithiation/alkylation is negligible. Indeed, DFT calculations performed at the B3LYP/6-31G(d) level of theory on the lithiated intermediates reveal almost identical barriers to epimerization (see Fig. 4).



	E_{rel} (kcal/mol)	
Ar = Ph, R = H	0	+3.5
Ar = 3-Py, R = H	0	+3.6
Ar = 3-MeO-Ph, R = H	0	+3.4
Ar = 4-Cl-Ph, R = H	0	+3.6
Ar = Ph, R = Me	0	+2.7

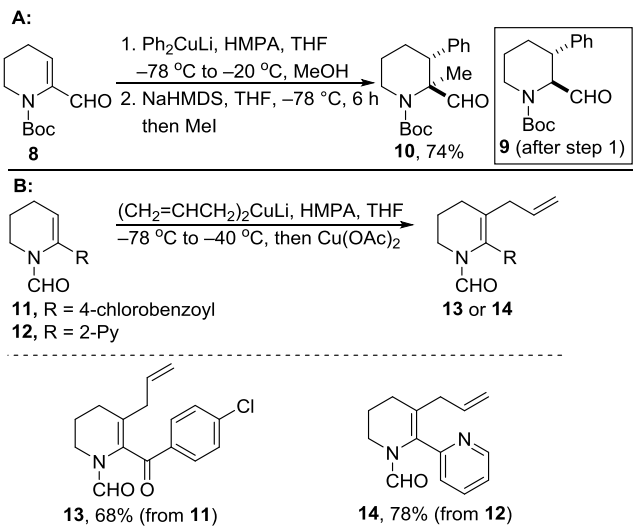
Fig. 4. Comparison of relative energies of *syn*-specific to *anti*-specific carbolithiation of α-aryl enecarbamates

Further elaboration of the quaternary piperidines depicted in Schemes 2 to other versatile synthetic intermediates is possible. For example, piperidine **5d** smoothly undergoes site-selective, α'-C–H oxidation, under Ru-catalysis to afford versatile chiral racemic lactam **7** in reasonable yield (Scheme 3).



Scheme 3. Ruthenium-catalyzed α'-oxidation of piperidine **5d**

Seeking to further expand the scope of the vicinal carbo-difunctionalization strategy described herein, dehydropiperidines bearing non-aryl or heteroaryl substituents at the α-position have also been evaluated. Thus, treatment of α-formyl dehydropiperidine **8** with lithium diphenyl cuprate followed by protonation affords the corresponding crude aldehyde **9**, which upon enolization with NaHMDS and trapping with methyl iodide, delectably affords quaternary pipecolinal **10** as a single diastereomer (Scheme 4A). Of note, diastereoselective α-alkylation of complementary α'-substituted pipecolinates have previously been reported.[49] When acylated eneformamide **11** is treated with lithium diallyl cuprate, subsequent $Cu(OAc)_2$-mediated oxidation affords fully substituted dehydropiperidine **13** (Scheme 4B). Cognizant of reports that the electron-withdrawing ability of a 2-pyridyl group makes vinyl pyridines reasonable Michael acceptors,[50] π-deficient eneformamide **12** was subjected to conjugate addition under the conditions described in Scheme 4B. Encouragingly, β-allylated dehydropiperidine **14** is obtained in acceptable yield following conjugate allylation/oxidation. It is worth pointing out that the poor diastereoselectivity (~50:50 dr) observed following protonation of the respective organometallic intermediates in these two examples is primarily what prompted us to induce a $Cu(OAc)_2$-mediated oxidation. This further highlights the importance of the Boc-group in controlling the stereoselectivity of these carbometalations and lends credence to the thought that the more commonly invoked *syn*-stereospecific carbometalation is not solely responsible for the high dr's obtained when enecarbamate substrates are employed.



Scheme 4. Copper-mediated conjugate addition

Conclusions

In summary, piperidine-derived tertiary benzylic organolithiums generated by carbolithiation have been successfully trapped with several carbon electrophiles, under HMPA-mediated conditions. Additionally, the benzylic organolithiums are amenable to transmetalation and cross-coupling under copper- or palladium-catalysis. Furthermore, several α-substituted eneformamides have been β-allylated via a conjugate addition/oxidation sequence. These short synthetic sequences have led to the assembly of a small library of vicinally functionalized and potentially bioactive piperidine derivatives bearing α-amino quaternary stereocenters and up to three contiguous stereocenters in some cases. Efforts to convert these tertiary benzylic organolithium intermediates to other established coupling partners (*e.g.*, stannanes and silanes) through trapping of the former with hetero-electrophiles will be reported in due course.

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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental procedures and spectroscopic data. See DOI: 10.1039/c000000x/

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