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# Stereochemical course of the reductive spiroannulations of *N*-Boc and *N*-benzyl 2-cyanopiperidines

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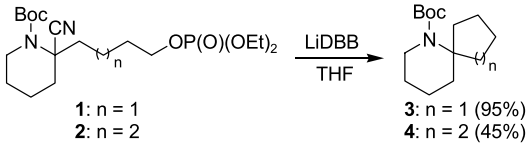
**Abstract**—The stereochemical outcome of spiroannulations of *N*-protected 2-lithiopiperidines (generated by lithium di-*tert*-butyl biphenylide (LiDBB) mediated reductive lithiation of 2-cyanopiperidines) was investigated using deuterium labeled side-chains containing phosphate leaving groups. High stereoselectivity was observed when benzyl (Bn) protected 2-cyanopiperidines were employed, while *tert*-butoxycarbonyl (Boc) protected 2-cyanopiperidines afforded lower selectivity. Models are proposed to rationalize the results of this study.

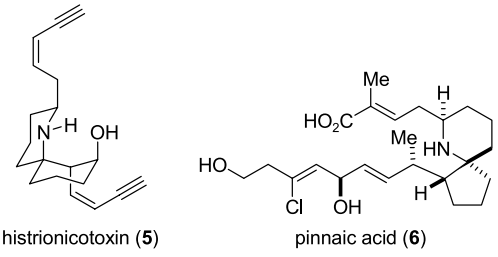

## 1. Introduction

Sequential nitrile alkylation and reductive decyanation/lithiation with subsequent intramolecular electrophile displacement ('reductive annulation') represents a powerful method for the synthesis of carbocyclic molecules.[1] Work in our laboratory has demonstrated the utility of this strategy in the stereoselective synthesis of complex spirocyclic tetrahydrofuran derivatives[2] and in an enantioselective synthesis of cyclopentane rings.[3] This approach is convergent and possesses the potential for the stereoselective generation of quaternary centers. As an extension of this chemistry, we have also applied this sequence towards 2-cyanopiperidines (Scheme 1).[4,5] The resulting 2-spiropiperidine ring systems can be found in a small but structurally and biologically interesting selection of naturally-occurring alkaloids such as histrionicotoxin[6] (**5**) and pinnaic acid[7] (**6**) (Fig. 1).




**Scheme 1.** Reductive spiroannulation approach to 2-spiropiperidines.

The efficiency of these spiroannulations, especially in forming the five-membered ring product **3**, encouraged further development of this approach in the context of the 2-spiropiperidine alkaloids. New stereocenters are not generated in the simple examples in Scheme 1. We chose to probe the stereoinduction imparted by additional stereocenters on the piperidine ring. At the onset of these studies, we recognized that the protecting group on nitrogen could have a profound effect in directing the resulting stereochemistry of the quaternary spiro center. For example, Husson[8] has shown that *N*-benzyl (benzyl = Bn) 2-cyanopiperidine **7** undergoes highly stereoselective reductive decyanation under dissolving metal conditions to produce **8** as a single diastereomer while Nagasaka[9] has revealed that under similar conditions, the related *N*-carbethoxy compound **9** produces decyanated products **10** and **11** with low stereoselectivity (Scheme 2).




histrionicotoxin (**5**) pinnaic acid (**6**)

**Figure 1.** Naturally-occurring 2-spiropiperidine alkaloids.

For our studies, we targeted *N*-benzyl and *N*-*tert*-butoxycarbonyl (Boc) protected cyanopiperidines **12** and **13**. Alkylation with deuterium labeled iodide **14** and reductive spiroannulation should produce the diastereomeric products *N*-benzyl *trans*/*cis*-**17** and *N*-Boc *trans*/*cis*-**18** (Scheme 3). The relative configuration of the generated quaternary spiro centers could then be determined using nuclear Overhauser effect (NOE) studies to establish the position of the

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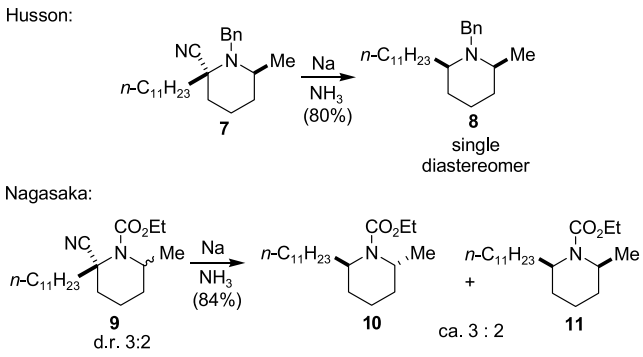
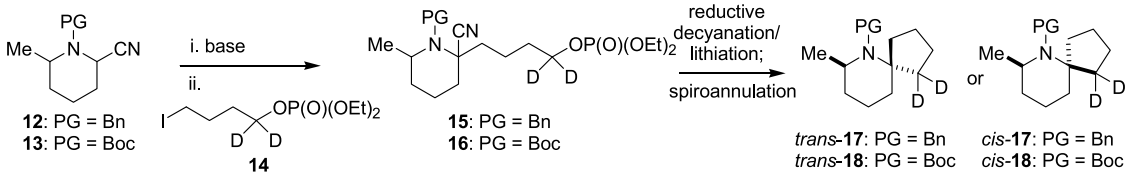



**Scheme 2.** Representative reductive decyanations.

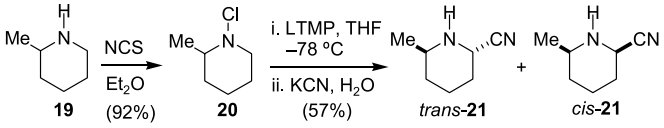
diastereomers following chromatographic purification. For ease of characterization, typically only *trans*-**21** was carried forward, although the relative stereochemistry at this stage was ultimately irrelevant.

Protection of the relatively unreactive 2-cyanopiperidines was accomplished by treatment with BnBr/KI/$Na_2CO_3$ in refluxing acetone or with neat di-*tert*-butyl dicarbonate ($Boc_2O$) at 60 °C for several hours to afford *N*-benzyl derivative *trans*-**12** and *N*-Boc derivative *trans*-**13**, respectively (Scheme 5).

The 2-cyanopiperidines *trans*-**12** and *trans*-**13** are readily alkylated by treatment with lithium diisopropylamide




**Scheme 3.** Proposed deuterium-labelled spiroannulations.




**Scheme 4.** Synthesis of unprotected 2-cyanopiperidines.

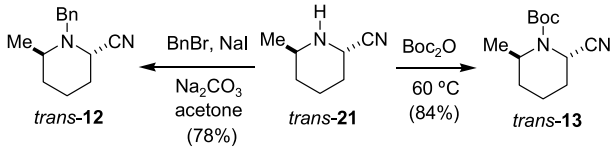
deuterium labels. This study would provide information regarding the stereoselectivity of the reductive lithiations and would indicate the most appropriate protecting group for more complex spiroannulations leading to the 2-spiropiperidine cores of histrionicotoxin and pinnaic acid.

## 2. Results and discussion

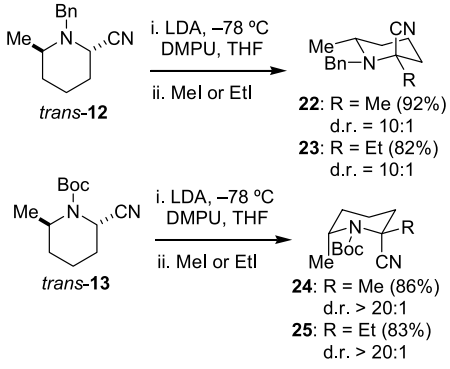
### 2.1. Synthesis of substrates

A flexible approach to either *N*-benzyl or *N*-Boc cyanopiperidines was desired. Our attention was drawn to work by Davis, who showed that imine formation by base-induced elimination of cyclic *N*-chloro amines could be rendered regioselective by choice of base.[10] Trapping of these cyclic imines with a nucleophilic cyanide source would produce the unprotected 2-cyanopiperidines.[11,12] Starting with 2-methylpiperidine (**19**), *N*-chlorination using *N*-chlorosuccinimide (NCS) produced *N*-chloro-2-methylpiperidine (**20**), which was reacted in unpurified form in a regioselective elimination mediated by lithium 2,2,6,6-tetramethylpiperidide (LTMP) (Scheme 4). Direct addition of an aqueous solution of KCN and gradual warming to room temperature produces diastereomeric 2-cyanopiperidines *trans*- and *cis*-**21** in 52% overall yield from **19**. Analysis of the crude products by $^1$H NMR indicates a diastereomer ratio of ca. 3:1 *trans*/*cis* (relative stereochemistry assigned by NOE studies), however facile epimerization on silica gel produces ratios on the order of 9:1 of the separable

(LDA) at −78 °C in the presence of *N*,*N*-dimethylpropyleneurea (DMPU) followed by addition of an alkyl iodide electrophile (Scheme 6). Alkylation of *N*-benzyl derivative *trans*-**12** with MeI or EtI affords axial nitriles **22** and **23** along with their minor diastereomers in a ratio of ca. 10:1. Relative configuration of the major diastereomer was



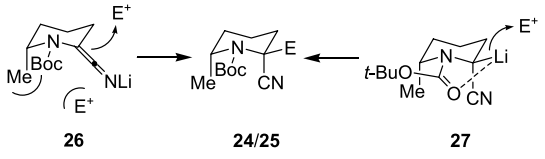

**Scheme 5.** Protection of 2-cyanopiperidine **21**.




**Scheme 6.** Alkylation of *N*-protected 2-cyanopiperidines.

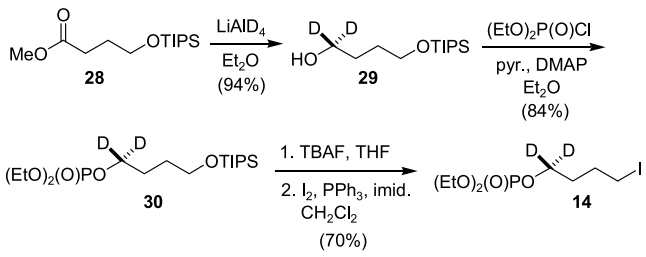
assigned based on the known anomeric-type effect in 2-cyanopiperidines.[13] *N*-Benzyl 2-alkyl-2-cyanopiperidines such as **22** and **23** are rather labile compounds and decompose in the presence of acid and on silica gel, presumably due to facile iminium ion formation and ensuing side reactions. Purification is best performed on basic alumina and long-term storage (>6 months) can be accomplished at low-temperature (−20 °C) in the presence of small amounts of triethylamine as an acid scavenger. Alkylation of *N*-Boc 2-cyanopiperidine *trans*-**13** under similar conditions produces single detectable diastereomers **24** and **25**. The relative configuration of **24** was assigned by X-ray crystallography and products from similar alkylations were assigned by analogy. In contrast to the *N*-benzyl compounds, *N*-Boc 2-alkyl-2-cyanopiperidines are very stable compounds, readily purified by silica gel chromatography and storable at room temperature for extended periods of time (>1 year).

The highly stereoselective alkylation of *N*-Boc 2-cyanopiperidine *trans*-**13** is a useful demonstration of a stereocontrol element found in amide and carbamate protected piperidines. The presence of such carbonyl groups on nitrogen forces substituents at the 2- or 6-positions to adopt axial dispositions to relieve severe $A^{1,3}$-strain.[14] This effect has been elegantly exploited by Beak in stereoselective lithiations of *N*-Boc piperidines.[15] While we are unsure of the precise nature of the intermediate involved in the *N*-Boc 2-cyanopiperidine alkylations, reasonable possibilities include 1) *N*-lithiated ketene iminate[16] **26**, where equatorial electrophile incorporation results due to blocking of the bottom face by the axial methyl group or 2) *C*-lithiated nitrile[17] **27**, stabilized by Boc–Li coordination, which undergoes electrophilic substitution with retention of configuration to afford equatorial products **24** and **25** (Scheme 7).



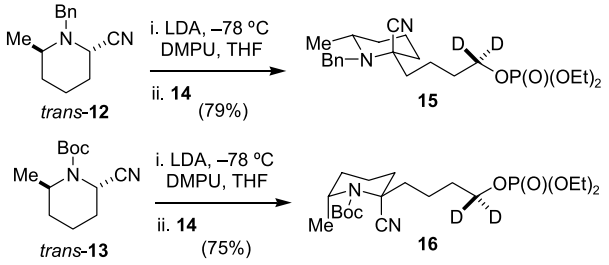

**Scheme 7.** Possible rationales for stereoselective nitrile alkylations.

The deuterium labeled bis-electrophile **14** was prepared starting with $LiAlD_4$ reduction of ester **28**. Phosphorylation, TIPS removal and iodination produced **14** in good overall yield (Scheme 8). Alkylation of *trans*-**12** and *trans*-**13** as described previously for **22**–**25** afforded the deuterium labeled cyclization precursors **15** (dr=ca. 9:1) and **16**




**Scheme 8.** Synthesis of deuterated bis-electrophile **14**.

(single diastereomer) without evidence of competing phosphate displacement (Scheme 9).

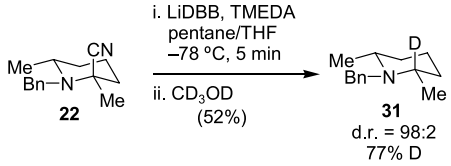



**Scheme 9.** Preparation of deuterium-labeled cyclization precursors.

## 2.2. Preliminary reductive lithiations

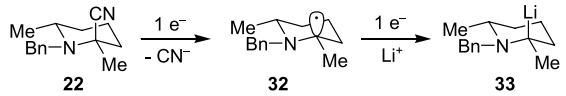
Prior to exploring the reductive spiroannulations of **15** and **16**, we conducted some preliminary reductive decyanation/lithiations on *N*-benzyl 2-cyanopiperidine **22** and *N*-Boc 2-cyanopiperidine **24** in order to explore the stereoselectivity of reductive lithiation in these simpler systems. The intermediate α-aminoorganolithiums were typically generated by addition of the cyanopiperidines to solutions of lithium di-*tert*-butylbiphenylide (LiDBB) in THF at low temperature. After a given time period, $CD_3OD$ was added and the reaction was worked up and crude mixtures were analyzed by GC to determine diastereomer ratios and $^1H$ NMR (for **22**) or GC–MS (for **24**) to determine deuterium incorporation.

The reductive lithiations of *N*-benzyl 2-cyanopiperidine **22** were problematic, with low crude yields and the presence of small amounts of several unidentified by-products. Additionally, deuterium incorporation was often low despite extensive efforts to exclude proton sources. These results are indicative of the high basicity of the α-aminoorganolithium derived from **22**, where THF is likely acting as a proton donor.[18] Efforts to utilize Cohen's THF-free conditions[19] (lithium 1-(dimethylamino)naphthalenide (LDMAN), $Me_2O$, −78 °C) produced no reduced product. Reasonably useful yields and deuterium incorporations were ultimately achieved using *N*,*N*,*N*′,*N*′-tetramethylethylene diamine (TMEDA) as an additive[20] in a pentane/THF (1:1) solvent system (Scheme 10). The reductive lithiations of **22** occur with high stereoselectivity (≥95:5) to produce *cis* piperidine **31**.[21] While higher temperatures are not conducive to the chemical stability of the intermediate α-aminoorganolithiums, they appear to be configurationally stable at −78 °C for at least 60 min.




**Scheme 10.** Reductive lithiation/deuteriation of **22**.

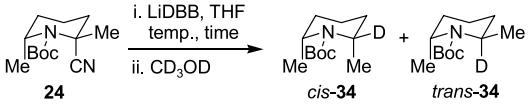
In accord with Husson's work, the major stereoisomer isolated from these reactions displays axial incorporation of the proton or electrophile. We interpret these results with the following explanation: (1) single-electron transfer to **22**




**Scheme 11.** Rationale for stereoselective reductive lithiation.

diastereomers *trans*/*cis*-**35** (Scheme 12).[24] These are presumed to be in rapid equilibrium due to a low-lying barrier to radical inversion.[22] A cursory inspection of the radical diastereomers suggests that a strong thermodynamic preference does not exist. Unlike the *N*-benzyl derivative,

**Table 1**. Reductive lithiation/deuteriation of **22**

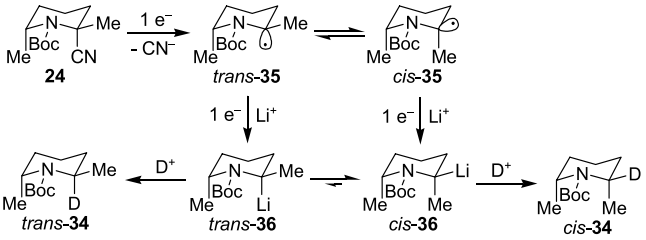



| Entry | Reduction temperature (°C) | Time | Ratio (*cis*-**34**: *trans*-**34**) | Total yield (%) |
|---|---|---|---|---|
| 1 | −78 | 5 min | 62 (91% D): 38 (89% D) | 88 |
| 2 | −78 | 12.5 h | 78 (92% D): 22 (79% D) | 83 |
| 3 | −40 | 5 min | 94 (84% D): 6 (72% D) | 67 |

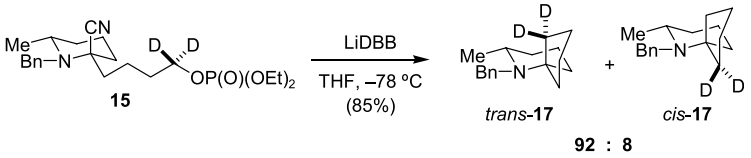
leads to carbon–CN bond cleavage, predominantly generating anomerically-stabilized axial radical[22] **32**; (2) subsequent single-electron transfer occurs with retention of configuration, leading to formally axial 2-lithiopiperidine **33**, which reacts with $CD_3OD$ with retention of configuration to produce **31** (Scheme 11). Attempts to utilize electrophiles other than $D^+$ (*i*-PrCHO, PhCHO, MeI and $Me_2SO_4$) produced complex reaction mixtures. While our work with this class (*N*-benzyl) of α-aminoorganolithiums has not demonstrated broad synthetic utility in intermolecular reactions with electrophiles, this route does provide a means of accessing axial 2-lithiopiperidines. Gawley has reported failed Sn–Li exchange in attempted generation of an axial *N*-methyl 2-lithiopiperidine from the corresponding axial 2-stannylpiperidine.[23]

Reductive lithiations of *N*-Boc 2-cyanopiperidine **24** initially proved to be less stereoselective than those of the *N*-benzyl derivative. However, several features of these reductive lithiations are noteworthy. The α-aminoorganolithiums derived from **24** were far more robust than the α-aminoorganolithium derived from **22**, as evidenced by generally high yields and levels of deuterium incorporation (Table 1). While rapid (<1 h) $CD_3OD$ quenches afforded low ratios of diastereomeric products *cis*/*trans*-**34** (entry 1), maintaining a solution of the α-aminoorganolithiums derived from **24** at −78 °C for extended time periods demonstrated slow equilibration of the intermediate diastereomeric organolithiums (entry 2). Conducting the reductive lithation at −40 °C provided superior diastereomer ratios, albeit at the expense of yield and deuterium incorporation (entry 3).

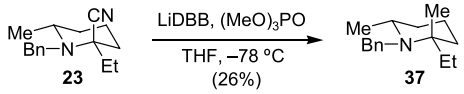
To account for these results, we suggest the following possibilities. Single-electron transfer produces radical anomeric stabilization of an axially disposed radical (*trans*-**35**) would be expected to be diminished due to significant delocalization of the nitrogen lone pair into the carbonyl moiety. Additionally, $A^{1,3}$-strain between the Boc group and the equatorial methyl group in *trans*-**35** serves to destabilize this conformation.[15] Further single-electron reduction of the diastereomeric radical intermediates leads to α-aminoorganolithiums *trans*/*cis*-**36**. *trans*-**36** is destabilized by the axial disposition of the carbon–lithium bond, a manifestation of an anti-anomeric (HOMO–HOMO) effect,[25] and by $A^{1,3}$-strain arising from interactions between the Boc group and the equatorial methyl group. This stereoelectronic interaction is absent in *cis*-**36**, which may also benefit from coordinative stabilization between the Boc group and the equatorial lithium.[15] These factors appear to override the 1,3-diaxial (Me–Me) interactions in *cis*-**36**.[15c] Deuterium incorporation with retention of configuration produces the observed products, *trans*/*cis*-**34**. Despite the presumed thermodynamic preference for *cis*-**36**, a substantial energy barrier still exists, resulting in slow equilibration at −78 °C. Computational work by Haeffner, Brandt and Gawley suggests an inversion barrier of ca. 16 kcal/mol for related *N*-Boc 2-lithiopyrrolidines.[26] At




**Scheme 12.** Possible rationale for stereoselectivity in reductive lithiation of **24**.



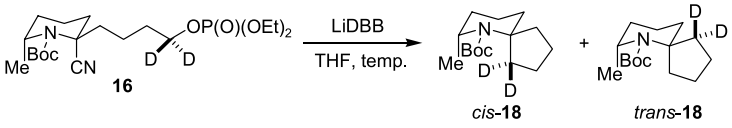

**Scheme 13.** Reductive spiroannulation of **15**.




**Scheme 14.** Intermolecular addition of a phosphate electrophile.

below). The cyclization of *N*-benzyl derivative **15** is presumably rapid enough to outcompete the side reactions which plagued the intermolecular reactions of **22**, leading to high yields of the spirocyclic products. From these results, we conclude that reductive lithiation generated a predominantly axially lithiated α-aminoorganolithium intermediate corresponding to **33** (Scheme 11). Cyclization with retention of configuration then produces the major diastereomer *trans*-**17**. Further evidence for retentive electrophilic addition was shown by conducting reductive lithiation on *N*-benzyl 2-cyanopiperidine **23** in the presence of a large excess (20 equiv) of trimethyl phosphate (Scheme 14). The sole detectable isomer (**37**) by GC–MS again displays axial incorporation of the electrophile as determined by NOESY.

**Table 2**. Reductive spiroannulation of **16**




| Entry | Reduction temperature (°C) | Ratio (*cis*-**34**: *trans*-**34**) | Total yield (%) |
|---|---|---|---|
| 1 | −78 | 72:28 | 85 |
| 2 | −40 | 74:26 | 90 |

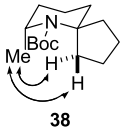
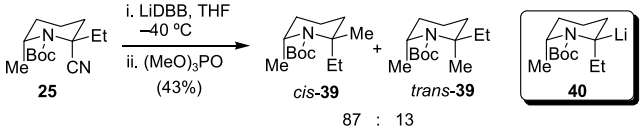



**Figure 2.** Relevant NOESY signals.



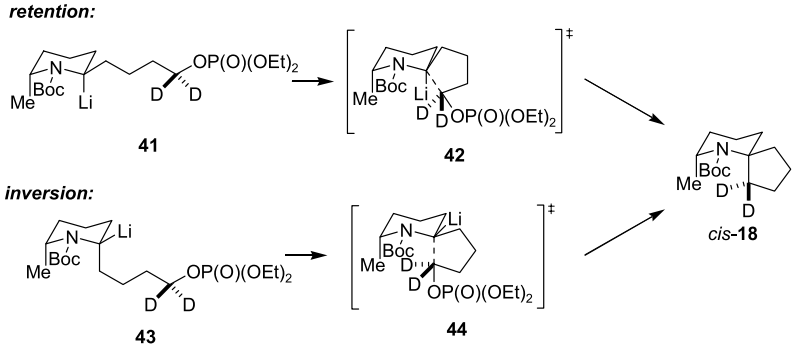

**Scheme 15.** Intermolecular addition of a phosphate electrophile to **25**.

−40 °C, we may be observing faster equilibration of these species, however the lower yield may indicate selective decomposition of the axially lithiated *trans*-**36**.

## 2.3. Reductive spiroannulations

With the above information in hand, cyclization precursors **15** and **16** were subjected to LiDBB in THF at −78 °C. As anticipated from our preliminary studies, the reductive spiroannulation of **15** was highly stereoselective producing *trans*/*cis*-**17** in a ratio of 92:8 (Scheme 13). Relative configurations of the diastereomeric products were assigned by conversion to the corresponding *N*-Boc compounds (see

As we had previously observed with *N*-Boc 2-cyanopiperidine **24**, reductive spiroannulation of **16** was not highly stereoselective (Table 2). Proton assignments of the non-deuterated compound **38** were assigned using COSY, HMQC and NOESY experiments (Fig. 2) and relative stereochemistry and diastereomeric ratios of the deuterated compounds *cis*/*trans*-**18** were made using $^1$H NMR. We also observed that spiroannulation stereoselectivity was independent of temperature, providing nearly identical results at −78 °C (entry 1) or −40 °C (entry 2). Whereas the major diastereomer from reductive lithiation/deuteration of **24** displayed equatorial electrophile incorporation (Table 1), the major spirocycle diastereomer (*cis*-**18**) results from axial electrophile incorporation. Subjecting *N*-Boc 2-cyanopiperidine **25** to reductive lithiation conditions at −40 °C, at which temperature the equatorially lithiated α-aminoorganolithium (**40**) is presumed to be present in excess, followed by addition of trimethyl phosphate affords *cis*/*trans*-**39** in a ratio of 87:13 (Scheme 15). As with $CD_3OD$, the phosphate electrophile is predominantly




**Scheme 16.** Possible raation pathways leading to *cis*-**18**.

incorporated equatorially, resulting in major diastereomer *cis*-**39**.

An explanation for the disparity in stereoselection between the reductive spiroannulations of *N*-Boc 2-cyanopiperidine **16** and the intermolecular reactions of **24** and **25** is not readily apparent. Fast deuterium quenches (Table 1, entry 1) indicate that a mixture of equatorially and axially lithiated intermediates are initially produced following single electron reduction of the radical intermediates. If the diastereomer ratios of *cis*/*trans*-**34** are representative of the diastereomer ratios of the lithiated intermediates through a retentive electrophilic addition pathway, an equatorially lithiated intermediate such as **43** would be expected to predominate. This scenario in the reductive spiroannulation of **16** would lead to *trans*-**18** as the major diastereomer, which is not the observed result. The major diastereomer, *cis*-**18**, may arise through retentive cyclization of an axially lithiated intermediate (**41**) or through an invertive cyclization of an equatorially lithiated intermediate (**43**) (Scheme 16). While retentive electrophilic addition occurs in the intermolecular cases, competing invertive electrophilic addition of the presumed major equatorially lithiated **43** may be responsible for the generation of *cis*-**18** as the major diastereomer. The constrained transition states that must be operative in these cyclizations (e.g., **42** and **44**) would appear to include a different set of interactions when compared to the intermolecular reactions.

## 3. Conclusion

Clearly, the missing piece of the puzzle in these reductive lithiations remains the exact structure and stereochemistry of the α-aminoorganolithium intermediates. Nevertheless, we have demonstrated several interesting features associated with this chemistry. As Gawley has reported with secondary *N*-methyl 2-lithiopiperidines, tertiary *N*-benzyl 2-lithiopiperidines such as **33** possess high configurational stability.[20,27] While chemical lability remains an issue for intermolecular reactions, the methods reported herein allow for their stereoselective generation and use in intramolecular electrophilic additions. The *N*-Boc 2-lithiopiperidines present an unresolved synthetic dichotomy. They possess superior chemical stability when compared to the *N*-benzyl derivatives. However, their generation in stereochemically homogenous form and understanding the stereoselectivity of their reactions with electrophiles require further study. Exploration of the fascinating chemistry and synthetic potential of these reactive intermediates will continue in our laboratory.[28]

## 4. Experimental

### 4.1. General experimental details

Unless otherwise noted, all reactions were carried out under positive argon pressure in flame- or oven-dried glassware using standard syringe/septum techniques. THF, $Et_2O$ and $CH_2Cl_2$ were degassed with argon and dried by vacuum filtration through activated alumina columns purchased from GlassContour, Laguna Beach, CA.[29] *n*-Butyllithium was used from freshly opened bottles following the indicated molarity or was titrated using *N*-benyzlbenzamide.[30] Diisopropylamine and 2,2,6,6-tetramethylpiperidine was distilled from $CaH_2$. DMPU was distilled from $CaH_2$ and stored over microwave-activated 4 Å molecular sieves. $d_4$-Methanol was utilized from freshly opened (<1 week old) bottles. Iodomethane and iodoethane were filtered through oven-dried basic alumina prior to use. Trimethylphosphate was vacuum-distilled from $CaH_2$ onto microwave-activated 4 Å molecular sieves. LiDBB was prepared as described previously.[4] All other reagents were used as received from commercial suppliers. Thin layer chromatography was performed on Whatman silica gel PE SIL G/UV (0.25 mm) plates. Flash chromatography was performed using the indicated solvent system on Sorbent Technologies 230–400 mesh silica gel. Melting points were determined using an Electrothermal apparatus and are reported uncorrected. Infrared spectra were recorded on a MIDAC Prospect FT-IR. NMR spectra were recorded on Bruker instruments. $^1$H NMR spectra are reported in ppm relative to tetramethylsilane or residual solvent ($CDCl_3$: δ 7.26 ppm; $C_6D_6$: δ 7.16 ppm). Data are presented as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, br=broad), coupling constant(s) in Hertz (Hz), and integration. $^{13}$C NMR spectra were reported in ppm relative to the solvent signal ($CDCl_3$: 77.2 ppm; $C_6D_6$: δ 128.0 ppm). Capillary GC analysis was performed on a Hewlett Packard Model 6890 instrument with a 30 m X 0.25 μM Alltech EC-5 (SE-54) or Restek RTX-1701 capillary column equipped with a flame ionization detector. Mass spectral data was obtained on a MicroMass Autospec E spectrometer or a MicroMass LCT Electrospray spectrometer. Combustion analyses were performed by M-H-W Laboratories (Phoenix, AZ).

**4.1.1. *trans*/*cis*-6-Methyl-piperidine-2-carbonitrile (21).** To a 0 °C suspension of *N*-chlorosuccinimide (14.8 g, 111 mmol) in $Et_2O$ (100 mL) was added 2-methylpiperidine (11.8 mL, 101 mmol) over 5 min. After 1.5 h, the reaction was diluted with hexanes (250 mL), washed with water (3x50 mL), satd aq NaCl (50 mL), dried ($MgSO_4$) and concentrated to afford 1-chloro-2-methylpiperidine[10] (12.5 g, 92%) as a pale yellow oil that was dissolved in THF (200 mL) and cooled to −78 °C. To a 0 °C solution of 2,2,6,6-tetramethylpiperidine (22.5 g, 159 mmol) in THF (100 mL) was added *n*-BuLi (2.50 M, 58.4 mL, 146 mmol) over 30 min. The cooling bath was removed and the orange solution was allowed to warm to room temperature at which time it was added to the 1-chloro-2-methylpiperidine solution via cannula over 1 h. After 30 min, a solution of KCN (17.3 g, 266 mmol) in MeOH (100 mL)/water (30 mL) was added over 10 min. The reaction was stirred for 14 h with gradual warming to room temperature. Water (500 mL) was added and the mixture was extracted with EtOAc (3×100 mL) and $CH_2Cl_2$ (3×100 mL). The combined organic phases were washed with satd aq NaCl (50 mL), dried ($Na_2SO_4$) and concentrated. $^1$H NMR revealed a diastereomeric ratio of ca. 5.5 *trans*-**21**: 1 *cis*-**21**. Flash chromatography (30–50% EtOAc/hexanes) afforded less polar cyanopiperidine *cis*-**21** (1.01 g, 6%) and more polar cyanopiperidine *trans*-**21** (8.43 g, 51%) as pale yellow oils.

*Analytical data for cis*-**21**. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 3.62 (dd, $J=11.6$, 2.6 Hz, 1H), 2.62 (dqd, $J=12.4$, 6.2, 2.5 Hz, 1H), 1.96 (m, 1H), 1.86 (m, 1H), 1.68–1.60 (m, 3H), 1.37 (qt, $J=13.2$, 3.8 Hz, 1H), 1.08 (d, $J=6.2$ Hz, 3H), 1.08 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 120.6, 52.4, 47.5, 33.2, 30.3, 23.9, 22.7.

*Analytical data for trans*-**21**. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.12 (m, 1H), 3.02 (dqd, $J=12.4$, 6.2, 2.5 Hz, 1H), 1.87–1.64 (m, 6H), 1.12 (m, 1H), 1.06 (d, $J=6.2$, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 120.4, 48.2, 46.9, 33.4, 28.2, 22.7, 21.2; IR (thin film) 3332, 2223 cm$^{-1}$; MS (CI) *m/z* 125 (M+H, 100%).

**4.1.2. *trans*-1-Benzyl-6-methyl-piperidine-2-carbonitrile (*trans*-12).** To a solution of *trans*-**21** (4.88 g, 39.3 mmol) in acetone (50 mL) was added NaI (5.89 g, 39.3 mmol) and $K_2CO_3$ (8.15 g, 59.0 mmol). Benzyl bromide (5.6 mL, 47 mmol) was added over 2 min and the mixture was heated at 50 °C for 9 h. The reaction was cooled to room temperature, diluted with water (250 mL) and extracted with $Et_2O$ (3×50 mL). The combined organic phases were washed with satd aq NaCl (25 mL), dried ($Na_2SO_4$) and concentrated. Flash chromatography (3% EtOAc/hexanes) afforded cyanopiperidine *trans*-**12** (6.70 g, 78%) as an orange oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.36–7.26 (m, 5H), 4.25 (d, $J=13.3$ Hz, 1H), 3.65 (m, 1H), 3.21 (d, $J=13.3$ Hz, 1H), 2.66 (dqd, $J=12.1$, 6.0, 2.5 Hz, 1H), 1.81–1.59 (m, 5H), 1.34 (m, 1H), 1.22 (d, $J=6.1$, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 138.0, 129.2, 128.8, 127.6, 117.5, 55.5, 53.6, 51.5, 34.7, 28.9, 21.3, 21.3; IR (thin film) 2937, 1454 cm$^{-1}$; HRMS (ESI) calcd for $C_{14}H_{19}N_2$ $[M+H]^+$ 215.1548, found 215.1553.

**4.1.3. *trans*/*cis*-2-Cyano-6-methyl-piperidine-1-carboxylic acid *tert*-butyl ester (*trans*/*cis*-13).** A mixture of diastereomers **21** (5.14 g, 41.4 mmol) and $Boc_2O$ (9.03 g, 41.4 mmol) was heated at 60 °C for 10 h. Flash chromatography (10% to 15% to 20% EtOAc/hexanes) afforded inseparable cyanopiperidines *trans*/*cis*-**13** (7.78 g, 84%) as a pale yellow oil.

*Analytical data for cis diastereomer*. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.05 (m, 1H), 4.33 (m, 1H), 2.01 (m, 1H), 1.90 (m, 1H), 1.71–1.61 (m, 4H), 1.48 (s, 9H), 1.33 (d, $J=7.0$, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 154.4, 120.5, 81.5, 47.1, 40.8, 29.4, 28.7, 28.5, 17.5, 15.3.

*Analytical data for trans diastereomer*. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.80 (app t, $J=4.2$ Hz, 1H), 4.00 (m, 1H), 2.10 (m, 1H), 2.04–2.00 (m, 2H), 1.88–1.73 (m, 2H), 1.64–1.57 (m, 1H), 1.48 (s, 9H), 1.24 (d, $J=6.7$, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 154.6, 119.8, 81.4, 48.3, 42.7, 28.5, 27.1, 25.7, 20.8, 14.6; IR (thin film) 1704 cm$^{-1}$; HRMS (ESI) calcd for $C_{12}H_{20}N_2O_2Na$ $[M+Na]^+$ 247.1420, found 247.1420.

**4.1.4. *cis*-1-Benzyl-2,6-dimethyl-piperidine-2-carbonitrile (22).** To a −78 °C solution of diisopropylamine (6.2 mL, 44 mmol) in THF (50 mL) was added *n*-BuLi (2.31 M, 16.2 mL, 37.4 mmol) over 10 min. After 30 min, DMPU (7.5 mL, 62 mmol) was added followed by dropwise addition of a solution of **12** (6.69 g, 31.2 mmol) in THF (15 mL) over 15 min. After 30 min, iodomethane (3.9 mL, 62 mmol) was added over 5 min and the solution was stirred for 1 h. Buffer solution (pH 7.0, 50 mL) was added and the reaction was warmed to room temperature and extracted with EtOAc (3×50 mL). The combined organic phases were washed with satd aq NaCl (50 mL), dried ($Na_2SO_4$) and concentrated. Flash chromatography (10% triethylamine/hexanes to 5% EtOAc/10% triethylamine/85% hexanes) afforded cyanopiperidine **22** (6.56 g, 92%) as an orange oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.38 (d, $J=7.3$ Hz, 2H), 7.30 (t, $J=7.7$ Hz, 2H), 7.20 (t, $J=7.3$ Hz, 1H), 3.95 (d, $J=17.7$ Hz, 1H), 3.77 (d, $J=17.7$ Hz, 1H), 2.72 (m, 1H), 1.95 (m, 1H), 1.76–1.56 (m, 5H), 1.40 (s, 3H), 1.35 (m, 1H), 0.99 (d, $J=6.1$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 142.6, 128.4, 126.8, 126.5, 120.9, 60.1, 56.8, 55.1, 38.9, 35.0, 28.1, 22.5, 21.7; IR (thin film) 2216 cm$^{-1}$; HRMS (ESI) calcd for $C_{14}H_{20}N$ $[M-CN]^+$ 202.1596, found 202.1591. Additional purification could be performed using flash chromatography on basic $Al_2O_3$ (30% $CH_2Cl_2$/hexanes). Long term storage (>24 h) was conducted by concentrating the cyanopiperidine down from $Al_2O_3$-filtered $NEt_3$ several times and low-temperature (−20 °C) storage under argon.

**4.1.5. *cis*-1-Benzyl-2-ethyl-6-methyl-piperidine-2-carbonitrile (23).** To a −78 °C solution of diisopropylamine (0.657 mL, 4.69 mmol) in THF (15.0 mL) was added *n*-BuLi (1.46 M, 2.98 mL, 4.36 mmol) over 5 min. After 15 min, DMPU (0.810 mL, 6.70 mmol) was added followed by dropwise addition of a solution of **12** (0.718 g, 3.35 mmol) in THF (3.0 mL) over 5 min. After 1 h, iodoethane (0.804 mL, 6.70 mmol) was added over 2 min and the solution was stirred for 1 h. Water (50 mL) was added and the reaction was warmed to room temperature and extracted with EtOAc (3×20 mL). The combined organic phases were washed with satd aq NaCl (10 mL), dried ($Na_2SO_4$) and concentrated. Flash chromatography (basic $Al_2O_3$, 30% $CH_2Cl_2$/hexanes) afforded cyanopiperidine **23** (0.667 g, 82%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.36 (d, $J=7.2$ Hz, 2H), 7.29 (t, $J=7.6$ Hz, 2H), 7.19 (t, $J=7.3$ Hz, 1H), 3.98 (d, $J=18.0$ Hz, 1H), 3.75 (d, $J=18.0$ Hz, 1H), 2.73 (dqd, $J=12.2$, 6.12, 2.74 Hz, 1H), 2.07 (ddd, $J=13.3$, 5.6, 3.1 Hz, 1H), 1.86 (dq, $J=14.9$, 7.5 Hz, 1H), 1.77–1.62 (m, 3H), 1.55–1.48 (m, 2H), 1.32 (m, 1H), 0.99 (d, $J=6.1$ Hz, 3H), 0.94 (t, $J=7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 142.5, 128.3, 126.8, 126.4, 120.3, 65.2, 57.2, 55.3, 35.0, 34.7, 32.6, 22.8, 21.3, 8.8; IR (thin film) 2216 cm$^{-1}$; HRMS (ESI) calcd for $C_{15}H_{22}N$ $[M-CN]^+$ 216.1752, found 216.1761. Long term storage (>24 h) was effected by concentrating the cyanopiperidine down from $Al_2O_3$-filtered $NEt_3$ several times and low-temperature (−20 °C) storage under argon.

**4.1.6. *trans*-2-Cyano-2,6-dimethyl-piperidine-1-carboxylic acid *tert*-butyl ester (24).** To a −78 °C solution of diisopropylamine (8.6 mL, 61 mmol) in THF (200 mL) was added *n*-BuLi (1.6 M, 35.6 mL, 57 mmol) over 10 min. After 30 min, DMPU (10.6 mL, 88 mmol) was added followed by dropwise addition of a solution of **13** (9.82 g, 43.8 mmol) in THF (50 mL) over 20 min. After 1.5 h, iodomethane (8.2 mL, 131 mmol) was added over 5 min and the solution was stirred for 1.5 h. Half-saturated $NH_4Cl$ solution (500 mL) was added and the reaction was warmed

to room temperature and extracted with $Et_2O$ (3×150 mL). The combined organic phases were washed with satd aq NaCl (100 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded cyanopiperidine **24** (9.03 g, 86%) as a pale yellow solid. Low-temperature (−20 °C) recrystallization from EtOH/MeOH/$H_2O$ provided crystals (colorless cubes) suitable for X-ray diffraction. Mp 38–40 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.34 (m, 1H), 4.00 (m, 1H), 2.21 (m, 1H), 1.94–1.84 (m, 1H), 1.81 (s, 3H), 1.79–1.59 (m, 5H), 1.52 (s, 9H), 1.24 (d, $J$=6.9, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.9, 122.8, 81.7, 49.8, 49.7, 38.9, 29.3, 29.0, 28.5, 18.8, 15.3; IR (thin film) 1708 cm$^{-1}$; HRMS (ESI) calcd for $C_{13}H_{22}N_2O_2Na$ $[M+Na]^+$ 261.1579, found 261.1580; Anal. calcd for $C_{13}H_{22}N_2O_2$: C 65.51, H 9.30, N 11.75; found C 65.70, H 9.23, N 11.93.

**4.1.7. *trans*-2-Cyano-2-ethyl-6-methyl-piperidine-1-carboxylic acid *tert*-butyl ester (25).** To a −78 °C solution of diisopropylamine (0.240 mL, 1.72 mmol) in THF (10.0 mL) was added *n*-BuLi (1.46 M, 1.09 mL, 1.59 mmol) over 5 min. After 15 min, DMPU (0.297 mL, 2.46 mmol) was added followed by dropwise addition of a solution of **13** (0.275 g, 1.23 mmol) in THF (1.0 mL +0.5 mL rinse) over 5 min. After 2 h, iodoethane (0.295 mL, 3.69 mmol) was added over 2 min and the solution was stirred for 2 h. Half-saturated $NH_4Cl$ solution (40 mL) was added and the reaction was warmed to room temperature and extracted with EtOAc (3×15 mL). The combined organic phases were washed with satd aq NaCl (10 mL), dried ($Na_2SO_4$) and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded cyanopiperidine **25** (0.257 g, 83%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.32 (m, 1H), 2.28 (dq, $J$=14.7, 7.4 Hz, 1H), 2.16–2.06 (m, 2H), 1.92–1.82 (m, 2H), 1.76–1.60 (m, 3H), 1.52 (s, 9H), 1.30 (d, $J$=6.9 Hz, 3H), 0.94 (t, $J$=7.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.5, 122.4, 81.5, 53.9, 49.4, 33.6, 32.2, 28.6, 28.5, 19.5, 14.6, 8.5; IR (thin film) 1708 cm$^{-1}$; HRMS (ESI) calcd for $C_{14}H_{24}N_2O_2Na$ $[M+Na]^+$ 275.1736, found 275.1725.

**4.1.8. 4-(Triisopropylsiloxy)butyric acid methyl ester (28).** To a solution of γ-hydroxybutyric acid methyl ester (4.30 g, 36.4 mmol (contaminated with 2.21 g of γ-butyrolactone)) in DMF (20 mL) was added imidazole (2.98 g, 43.7 mmol) followed by dropwise addition of TIPS-Cl (9.4 mL, 44 mmol) over 5 min. After 24 h, water (200 mL) was added and the mixture was extracted with $Et_2O$ (4×50 mL) and the combined organic phases were washed with satd aq NaCl (3×50 mL), dried ($MgSO_4$)- and concentrated. Flash chromatography (10% $Et_2O$/hexanes) afforded ester **28** (9.99 g, 100%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.71 (t, $J$=6.1 Hz, 2H), 3.66 (s, 3H), 2.43 (t, $J$=7.5 Hz, 2H), 1.85 (p, $J$=6.9 Hz, 2H), 1.03 (s, 21H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.8, 62.1, 51.4, 30.4, 28.0, 17.9, 11.8; IR (thin film) 1743 cm$^{-1}$; HRMS (CI/$NH_3$) calcd for $C_{15}H_{30}O_3Si$ $[M+H]^+$ 275.2042, found 275.2054.

**4.1.9. 1,1-Dideuterio-4-triisopropylsilanyloxybutan-1-ol (29).** To a 0 °C suspension of $LiAlD_4$ (0.576 g, 13.7 mmol) in $Et_2O$ (40 mL) was added a solution of ester **28** (5.02 g, 18.3 mmol) in $Et_2O$ (10 mL) over 15 min. After 30 min, satd aq NaCl (ca. 10 mL) was added dropwise and the resulting mixture was stirred vigorously for 15 min and then filtered through a thin Celite pad, washing with $Et_2O$ (ca. 200 mL). Concentration of the filtrate and flash chromatography (30% EtOAc/hexanes) afforded alcohol **29** (4.27 g, 94%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 3.74 (t, $J$=4.5 Hz, 2H), 2.55 (br s, 1H), 1.66 (m, 4H), 1.09 (s, 21H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 63.8, 30.3, 30.2, 18.4, 12.4; IR (thin film) 3337 cm$^{-1}$; HRMS (CI/$NH_3$) calcd for $C_{14}H_{28}D_2O_2Si$ $[M+H]^+$ 249.2217, found 249.2222.

**4.1.10. Phosphoric acid diethyl ester 1,1-dideuterio-4-triisopropylsilanyloxy-butyl ester (30).** To a 0 °C solution of alcohol **29** (2.01 g, 8.09 mmol) in $Et_2O$ (30 mL) was added pyridine (0.98 mL, 12 mmol) followed by dropwise addition of diethyl chlorophosphate (1.40 mL, 9.71 mmol) over 5 min. A catalytic amount of DMAP (5 crystals) was added and the reaction was allowed to stir at room temperature for 24 h. Water (100 mL) was added, the mixture was stirred for 15 min and the layers were separated. The aqueous phase was extracted with $Et_2O$ (2×30 mL) and the combined organic phases were washed with satd aq NaCl (3×20 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (gradient elution: 10 to 50% EtOAc/hexanes) afforded phosphate **30** (2.60 g, 84%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.09 (dp, $J$=7.2, 1.4 Hz, 4H), 3.70 (dt, $J$=6.2, 1.2 Hz, 2H), 1.74 (t, $J$=8.0 Hz, 2H), 1.60 (m, 2H), 1.32 (t, $J$=7.0 Hz, 6H), 1.04 (s, 21H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 64.0 ($J$=5.8 Hz), 63.2, 29.3, 27.2 ($J$=7.0 Hz), 18.4, 16.6 ($J$=6.8 Hz), 12.4; IR (thin film) 1281, 1035 cm$^{-1}$; HRMS (ESI) calcd for $C_{17}H_{37}D_2O_5PSiNa$ $[M+Na]^+$ 407.2326, found 407.2308.

**4.1.11. Phosphoric acid diethyl ester 1,1-dideuterio-4-iodo-butyl ester (14).** To a chilled (0 °C) flask containing phosphate **30** (1.96 g, 5.10 mmol) was added TBAF solution (1.0 M in THF, 5.6 mL, 5.6 mmol) and the solution was stirred for 30 min. The cooling bath was removed and the reaction was allowed to stir for an additional 30 min. Solvent was removed by rotary evaporation and the resulting pale brown oil was dissolved in $CH_2Cl_2$ (10 mL) and cooled to 0 °C. Imidazole (2.28 g, 33.5 mmol) was added followed by $PPh_3$ (8.00 g, 30.5 mmol) and the mixture was stirred until dissolution at which time iodine (7.74 g, 30.5 mmol) was added in portions over 5 min. After 1 h, $Et_2O$ (50 mL) was added and the mixture was washed with 1 M aq HCl (2×10 mL), satd aq $NaHCO_3$ (2×10 mL) and 10% aq $Na_2S_2O_3$ (2×10 mL). The combined aqueous phases were extracted with $Et_2O$ (3×10 mL) and the combined organic phases were then washed with satd aq NaCl (10 mL), dried ($Mg_2SO_4$) and concentrated. Flash chromatography ($Et_2O$) afforded iodide **14** (1.21 g, 70% over 2 steps) as a pale yellow oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.11 (m, 4H), 3.22 (t, $J$=6.8 Hz, 2H), 1.94 (m, 2H), 1.78 (t, $J$=8.1 Hz, 2H), 1.34 (dt, $J$=7.1, 0.95 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 64.2 ($J$=5.8 Hz), 31.3 ($J$=6.9 Hz), 29.8, 16.6 ($J$=6.6 Hz), 6.3; IR (thin film) 1267, 1030 cm$^{-1}$; HRMS (CI/$NH_3$) calcd for $C_8H_{16}D_2IO_4P$ 338.0111, found 338.0110. Comparison to the corresponding non-deuterated compound[4] confirmed the position of the deuterium labels. Deuterium incorporation was quantitative within the limits of $^1$H NMR.

**4.1.12. Phosphoric acid 3-(*cis*-1-benzyl-2-cyano-6-methyl-piperidin-2-yl)-1,1-dideuterio-propyl ester diethyl ester (15).** To a −78 °C solution of diisopropylamine (0.297 mL, 2.12 mmol) in THF (5.0 mL) was added *n*-BuLi (1.38 M, 1.42 mL, 1.96 mmol) over 2 min. After 15 min, DMPU (0.394 mL, 3.26 mmol) was added followed by dropwise addition of a solution of *trans*-**12** (0.350 g, 1.63 mmol) in THF (2.0 mL +0.5 mL flask rinse) over 10 min. After 1.5 h, a solution of **14** (0.552 g, 1.63 mmol) in THF (1.5 mL +0.5 mL rinse) was added over 2 min. After 1.5 h, water (15 mL) was added and the mixture was warmed to room temperature and extracted with EtOAc (3×8 mL). The combined organic extracts were washed with satd aq NaCl (2×5 mL), dried ($Na_2SO_4$) and concentrated. Flash chromatography (basic $Al_2O_3$, $CH_2Cl_2$ to 10% $Et_2O/CH_2Cl$-$_2$ to $Et_2O$ to 10% MeOH/$Et_2O$) afforded cyanopiperidine **15** (0.550 g, 79%) as a pale yellow oil. Additional chromatography (basic $Al_2O_3$, 50% EtOAc/hexanes to EtOAc) afforded an analytical sample: $^1$H NMR (500 MHz, $C_6D_6$) $\delta$ 7.22 (d, $J$=7.6 Hz, 2H), 7.16 (m, 2H), 7.05 (t, $J$=7.2 Hz, 1H), 3.94 (m, 4H), 3.89 (d, $J$=17.9 Hz, 1H), 3.55 (d, $J$=17.9 Hz, 1H), 2.58 (m, 1H), 1.65–1.49 (m, 4H), 1.36–1.27 (m, 5H), 1.24–1.09 (m, 3H), 1.05 (t, $J$=7.0 Hz, 6H), 1.00–0.92 (m, 2H), 0.78 (d, $J$=6.1 Hz, 3H); $^{13}$C NMR (125 MHz, $C_6D_6$) $\delta$ 142.6, 128.6, 127.0, 126.6, 119.9, 64.2, 63.4 (d, $J$=5.5 Hz), 57.0, 55.5, 39.0, 35.0, 34.8, 30.0 (d, $J$=6.7 Hz), 22.7, 21.4, 20.3, 16.2 (d, $J$=6.4 Hz); IR (thin film) 1275, 1031 cm$^{-1}$; HRMS (ESI) calcd for $C_{21}H_{33}D_2NO_4P$ $[M-CN]^+$ 398.2215, found 398.2208. Long term storage (>24 h) was effected by concentrating the cyanopiperidine down from $Al_2O_3$-filtered $NEt_3$ several times and low-temperature (−20 °C) storage under argon.

**4.1.13. *trans*-2-Cyano-2-[4-(diethoxy-phosphoryloxy)-4,4-dideuterio-butyl]-6-methyl-piperidine-1-carboxylic acid *tert*-butyl ester (16).** To a −78 °C solution of diisopropylamine (0.195 mL, 1.39 mmol) in THF (5.0 mL) was added *n*-BuLi (1.52 M, 0.845 mL, 1.28 mmol) over 2 min. After 15 min, DMPU (0.259 mL, 2.14 mmol) was added followed by dropwise addition of a solution of **13** (0.264 g, 1.18 mmol) in THF (1.0 mL) over 5 min. After 1 h, a solution of **14** (0.362 g, 1.07 mmol) in THF (1.0 mL) was added over 3 min. After 3 h, half-saturated aq $NH_4Cl$ (25 mL) was added and the mixture was warmed to room temperature and extracted with EtOAc (3×10 mL). The combined organic phases were washed with satd $Na_2S_2O_3$ (10 mL), brine (10 mL), dried ($Na_2SO_4$) and concentrated. Flash chromatography (25% hexanes/EtOAc) afforded cyanopiperidine **16** (0.349 g, 75%) as a pale yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.30 (m, 1H), 4.11 (m, 4H), 2.31 (td, $J$=12.5, 5.1 Hz, 1H), 2.17–2.12 (m, 1H), 2.04 (td, $J$=12.7, 4.3 Hz, 1H), 1.92–1.81 (m, 2H), 1.75–1.59 (m, 5H), 1.51 (s, 9H), 1.39 (m, 1H), 1.34 (m, 6H), 1.30 (d, $J$=6.9 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.5, 122.2, 81.6, 63.9 (d, $J$=6.2 Hz), 53.2, 49.5, 38.6, 34.4, 30.1 (d, $J$=6.8 Hz), 28.6, 28.5, 20.2, 19.4, 16.4 (d, $J$=6.7 Hz), 14.7; IR (thin film) 1705 cm$^{-1}$; HRMS (ESI) calcd for $C_{20}H_{36}N_2O_6PD_2$ $[M+H]^+$ 435.2595, found 435.2606.

**4.1.14. *cis*-1-Benzyl-2,6-dimethyl-piperidine (31).** To a −78 °C solution of **22** (0.0972 g, 0.426 mmol) in THF (0.5 mL)/pentane (0.5 mL) was added 3 drops of *n*-BuLi/hex. This solution was transferred over 15 s via cannula down the chilled wall of a flask containing a solution of LiDBB (1.05 mmol) and TMEDA (0.141 mL, 0.936 mmol) in THF (2.0 mL)/pentane (2.0 mL). After 5 min, $CD_3OD$ (0.3 mL) was added down the flask wall over 15 s. After 15 min, water (10 mL) was added and the mixture was extracted with EtOAc (3×5 mL). The combined organic phases were washed with satd aq NaCl solution (3 mL), dried ($Na_2SO_4$) and concentrated. GC analysis of the crude reaction mixture indicated a dr of 98:2 *cis*/*trans*. Flash chromatography (10% *i*-PrOH/$CH_2Cl_2$) afforded piperidine **31** (0.0457 g, 52%) as a pale brown oil. $^1$H NMR was consistent with literature data[21] and indicated 77% D.

**4.1.15. Representative reductive lithiation/deuterium quench (inverse addition).** To a −40 °C solution of **24** (0.0534 g, 0.224 mmol) and 1,10-phenanthroline (1 crystal) in THF (5.0 mL) was added *n*-BuLi/hexanes (2 drops) followed by addition of LiDBB solution (ca. 0.50 M, 0.986 mL, 0.493 mmol) over 15 s. After 5 min, $CD_3OD$ (0.3 mL) was added and the reaction was stirred for 5 min. Half-saturated $NH_4Cl$ (20 mL) was added and the mixture was extracted with EtOAc (3×5 mL). The combined organic extracts were washed with satd aq NaCl (3 mL), dried ($Na_2SO_4$). A sample was analyzed by GC, indicating a dr of 94:6 *cis*-**34**/*trans*-**34**. GC–MS (EI) analysis of a sample indicated deuterium incorporations of 84% D (*cis*-**34**) and 72% D (*trans*-**34**). Flash chromatography (20% $CH_2Cl_2$/hexanes to 10% $Et_2O$/hexanes) afforded an inseparable mixture of *cis*/*trans*-**34** (0.0321 g, 67%) as a colorless oil. $^1$H NMR was consistent with literature data.[15b,31]

**4.1.16. *trans*/*cis*-Dideuterio-6-benzyl-7-methyl-6-aza-spiro[4.5]decane (*trans*/*cis*-17).** To a 0 °C solution of **15** (0.0140 g, 0.0330 mmol) and 1,10-phenanthroline (1 crystal) in THF (0.25 mL) was added *n*-BuLi/hexanes (1 drop). This solution was added via syringe down the chilled flask wall over 1 min to a −78 °C solution of LiDBB solution (ca. 0.50 M, 0.165 mL, 0.0824 mmol) in THF (2.0 mL) followed by a syringe/flask rinse of THF (0.25 mL). After 1.5 h, MeOH (0.1 mL) was added followed by water (6 mL) and the mixture was warmed to room temperature and extracted with EtOAc (3×2 mL). The combined organic phases were washed with satd aq NaCl (1 mL), dried ($Na_2SO_4$) and concentrated. Flash chromatography (20% $CH_2Cl_2$/hexanes to 7.5% EtOAc/hexanes) afforded spirocycles *trans*/*cis*-**17** (0.0063 g, 85%) as a pale yellow oil: $^1$H NMR (500 MHz, $C_6D_6$) $\delta$ 7.42 (d, $J$=7.2 Hz, 2H), 7.27 (m, 2H), 7.15 (t, $J$=7.3 Hz, 1H), 3.79 (d, $J$=17.1 Hz, 1H), 3.50 (d, $J$=17.1 Hz, 1H), 2.75 (dqd, $J$=9.6, 6.5, 3.1 Hz, 1H), 1.71–1.19 (m, 12H), 0.81 (d, $J$=6.5 Hz, 3H); $^{13}$C NMR (125 MHz, $C_6D_6$) $\delta$ 145.4, 128.1, 127.2, 125.9, 67.9, 55.0, 51.5, 39.5, 36.7, 32.9, 25.6, 25.1, 22.0, 21.4; IR (thin film) 2930, 1453 cm$^{-1}$; HRMS (ESI) calcd for $C_{17}H_{24}D_2N$ $[M+H]^+$ 246.2189, found 246.2175. For correlation purposes, the product from a larger scale experiment (ca. 0.300 g) was transformed without purification to the corresponding *N*-Boc compounds (*cis*/*trans*-**18**) through the following sequence: (1) LiDBB, THF, −78 °C; (2) $Pd(OH)_2$/C, $H_2$ (1 atm), 1 N HCl/MeOH, 6 h and (3) $Boc_2O$, 60 °C, 48 h (34% yield, 3 steps). $^1$H NMR indicated a dr of 92:8 *trans*/*cis*-**18**.

**4.1.17. *cis*-1-Benzyl-2-ethyl-2,6-dimethyl-piperidine (37).** To a −78 °C solution of **23** (0.0799 g, 0.330 mmol), trimethyl phosphate (0.777 mL, 6.60 mmol) and 1,10-phenanthroline (1 crystal) in THF (1.0 mL) was added *n*-BuLi/hexanes (3 drops). This solution was transferred via cannula over 5 min down the chilled flask wall of an LiDBB solution (ca. 0.50 M, 2.64 mL, 1.32 mmol) in THF (4.0 mL) at −78 °C. The reaction was stirred for 15 h with gradual warming to room temperature at which time it was diluted with $Et_2O$ (25 mL) and extracted with 1 N HCl (3× 7.5 mL). The combined acidic aqueous phases were washed with $Et_2O$ (3×5 mL), basified to pH=12 with solid KOH and extracted with $Et_2O$ (3×5 mL). The combined organic phases were washed with satd aq NaCl (3 mL), dried ($K_2CO_3$) and concentrated. GC analysis of a sample indicated the presence of a single major component with several minor components. GC–MS (CI) confirmed the identity of the major component as **37** but failed to detect the minor components. Flash chromatography (5% EtOAc/hexanes) afforded **37** (0.0203 g, 26%) as a pale yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.43 (d, $J$=7.7 Hz, 2H), 7.25 (t, $J$=7.6 Hz, 2H), 7.14 (t, $J$=7.3 Hz, 1H), 3.99 (d, $J$=17.4 Hz, 1H), 3.34 (d, $J$=17.4 Hz, 1H), 2.69 (dqd, $J$=12.5, 6.2, 2.3 Hz, 1H), 1.59–1.43 (m, 8H), 1.26 (m, 2H), 0.99 (s, 3H), 0.81–0.78 (m, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 145.3, 127.9, 127.2, 125.7, 57.6, 54.5, 52.5, 36.6, 36.1, 35.4, 23.5, 20.4, 15.6, 8.7; IR (thin film) 2929, 1459 cm$^{-1}$; MS (CI) *m/z* 232 (M+H, 100%).

**4.1.18. *cis/trans*-Dideuterio-7-methyl-6-aza-spiro[4.5]-decane-6-carboxylic acid *tert*-butyl ester (*cis/trans*-18).** To a −78 °C solution of **16** (0.0522 g, 0.120 mmol) and 1,10-phenanthroline (1 crystal) in THF (0.5 mL) was added *n*-BuLi/hex (1 drop) to form a brown solution. This solution was transferred via syringe to a −78 °C solution of LiDBB solution (ca. 0.50 M in THF, 0.529 mL, 0.264 mmol) in THF (2.0 mL) down the chilled flask wall over 3 min followed by a flask/syringe rinse with THF (0.25 mL). After 2.5 h, half-saturated $NH_4Cl$ (10 mL) was added and the mixture was warmed to room temperature and extracted with EtOAc (3×4 mL). The combined organic phases were washed with satd aq NaCl (3 mL), dried ($Na_2SO_4$) and concentrated. Flash chromatography (20% $CH_2Cl_2$/hexanes to 5% $Et_2O$/hexanes) afforded diastereomers *cis/trans*-**18** (0.0236 mg, 77%) as a colorless oil. $^1$H NMR indicated a dr of 72:28 *cis/trans*-**18**; HRMS (ESI) calcd for $C_{15}H_{25}D_2NO_2Na$ $[M+Na]^+$ 278.2063, found 278.2061.

*Analytical data for non-deuterated compound.* $^1$H NMR (500 MHz, $C_6D_6$) $\delta$ 4.38 (m, 1H), 2.75 (ddd, $J$=13.0, 8.9, 4.6 Hz, 1H), 2.28–2.15 (m, 2H), 1.94 (dtt, $J$=11.1, 7.0, 3.4 Hz, 1H), 1.59–1.48 (m, 4H), 1.44 (s, 9H), 1.43–1.35 (m, 3H), 1.31–1.17 (m, 3H), 1.08 (d, $J$=6.8 Hz, 3H); $^{13}$C NMR (125 MHz, $C_6D_6$) $\delta$ 155.9, 78.8, 64.8, 49.2, 41.0, 39.8, 38.7, 30.1, 29.0, 27.3, 26.2, 21.5, 16.4; IR (thin film) 1698 cm$^{-1}$; HRMS (ESI) calcd for $C_{15}H_{27}NO_2Na$ $[M+Na]^+$ 276.1939, found 276.1949.

**4.1.19. *cis/trans*-2-Ethyl-2,6-dimethyl-piperidine-1-carboxylic acid *tert*-butyl ester (*cis/trans*-39).** To a −40 °C solution of **25** (0.104 g, 0.412 mmol) and 1,10-phenanthroline (1 crystal) in THF (5.0 mL) was added *n*-BuLi/hex (3 drops) to form a brown solution. To this solution was added LiDBB solution (ca. 0.50 M, 1.81 mL, 0.907 mmol) rapidly via syringe. After 5 min, the solution was cooled to −78 °C and trimethyl phosphate (0.970 mL, 8.24 mmol) was added over 2 min. The solution was allowed to stir for 15 h with gradual warming to room temperature. Satd aq $NH_4Cl$ (15 mL) was added and the mixture was extracted with EtOAc (3×5 mL). The combined organic phases were washed with satd aq NaCl (3 mL), dried ($Na_2SO_4$) and concentrated. GC analysis indicated a diastereomeric ratio of 87:13 *cis/trans*. Flash chromatography (20% $CH_2Cl_2$/hexanes to 2.5% EtOAc/hexanes) afforded a mixture of *cis/trans*-**39** (0.0370 mg, 37%) as a colorless oil.

*Analytical data for cis*-**39**. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.28 (m, 1H), 2.16 (dq, $J$=15.0, 7.5 Hz, 1H), 2.03 (ddd, $J$=14.3, 9.6, 6.9 Hz, 1H), 1.86 (m, 1H), 1.73–1.40 (m, 4H), 1.46 (s, 9H), 1.37 (s, 3H), 1.20 (m, 1H), 1.18 (d, $J$=7.0 Hz, 3H), 0.78 (d, $J$=7.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.8, 79.0, 57.0, 47.9, 33.1, 33.0, 28.8, 27.3, 26.9, 22.2, 14.2, 9.1; IR (thin film) 1688 cm$^{-1}$; MS (CI) *m/z* 242 (M+H, 100%).

## References and notes


1. For related methods, see: (a) Zeller, E.; Grierson, D. S. *Heterocycles* **1988**, *27*, 1575–1578. (b) Zeller, E.; Sajus, H.; Grierson, D. S. *Synlett* **1991**, 44–46. (c) Zeller, E.; Grierson, D. S. *Synlett* **1991**, 878–880. (d) Broka, C. S.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981–2984. (e) Deng, K.; Bensari, A.; Cohen, T. *J. Am. Chem. Soc.* **2002**, *124*, 12106–12107.
2. (a) Rychnovsky, S. D.; Hata, T.; Kim, A. I.; Buckmelter, A. J. *Org. Lett.* **2001**, *3*, 807–810. (b) Rychnovsky, S. D.; Takaoka, L. R. *Angew. Chem. Int. Ed.* **2003**, *42*, 818–820.
3. La Cruz, T. E.; Rychnovsky, S. D. *Chem. Commun.* **2004**, 168–169.
4. Wolckenhauer, S. A.; Rychnovsky, S. D. *Org. Lett.* **2004**, *6*, 2745–2748.
5. A conceptually similar approach can be found in the work of Husson: Ribeiro, C. M. R.; de Melo, S. J.; Bonin, M.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1994**, *35*, 7227–7230.
6. Daly, J. W.; Karle, I. L.; Myers, C. W.; Tokuyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U. S. A.* **1971**, *68*, 1870–1875.
7. Chou, T.; Kuramoto, M.; Otani, Y.; Skiano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871–3874.
8. Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1982**, *23*, 3369–3372.
9. Nagasaka, T.; Hayashi, H.; Kumakawa, M.; Sakamoto, M.; Mizuno, M.; Hamaguchi, F. *Heterocycles* **1989**, *29*, 2157–2166.
10. Davis, B. G.; Maughan, M. A. T.; Chapman, T. M.; Villard, R.; Courtney, S. *Org. Lett.* **2002**, *4*, 103–106.
11. Mulzer, J.; Meier, A.; Buschmann, J.; Luger, P. *Synthesis* **1996**, *1*, 123–132.
12. For an alternate synthesis of 2-cyanoamines using phenylseleninic anhydride mediated oxidation, see: Barton, D. H. R.; Billion, A.; Boivin, J. *Tetrahedron Lett.* **1985**, *26*, 1229–1232.
13. (a) Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1984**, *49*, 2392–2400. (b) Booth, H.; Dixon, J. M.; Khedhair, K. A. *Tetrahedron* **1992**, *48*, 6161–6174.

14. (a) Chow, Y. L.; Colon, C. J.; Tam, N. J. S. *Can. J. Chem.* **1968**, *46*, 2821–2825. (b) Fraser, R. R.; Grindley, T. B. *Tetrahedron Lett.* **1974**, *47*, 4169–4172.
15. (a) Beak, P.; Lee, W. K. *J. Org. Chem.* **1990**, *55*, 2578–2580. (b) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109–1117. (c) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000**, *2*, 155–158.
16. *N*-Lithiated ketene iminates have been isolated: Enders, D.; Kirchoff, J.; Gerdes, P.; Mannes, D.; Raabe, G.; Runsink, J.; Boche, G.; Marsch, M.; Ahlbrecht, H.; Sommer, H. *Eur. J. Org. Chem.* **1998**, *1*, 63–72.
17. *C*-Lithiated nitriles have previously been proposed as intermediates: Leclercq, S.; Thirionet, I.; Broeders, F.; Daloze, D.; Vander Meer, R.; Braekman, J. C. *Tetrahedron* **1994**, *50*, 8465–8478.
18. *tert*-Butyllithium itself has a half-life of approximately 6 h in THF at −40 °C. Stanetty, P.; Mihovilovic, M. D. *J. Org. Chem.* **1997**, *62*, 1514–1515.
19. Cohen, T.; Kreethadumrongdat, T.; Liu, X.; Kulkarni, V. *J. Am. Chem. Soc.* **2001**, *123*, 3478–3483.
20. Yields were typically higher in the presence of TMEDA ($\geq$2 equiv). Gawley has also observed an apparent stabilizing effect of TMEDA on *N*-alkyl α-aminoorganolithiums: Gawley, R. E.; Zhang, Q. *Tetrahedron* **1994**, *50*, 6077–6088.
21. Boga, C.; Manescalchi, F.; Savoia, D. *Tetrahedron* **1994**, *50*, 4709–4722.
22. Rychnovsky, S. D.; Powers, J. P.; LePage, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 8375–8384.
23. Chambournier, G.; Gawley, R. E. *Org. Lett.* **2000**, *2*, 1561–1564.
24. These conformations likely represent an oversimplification. Calculations at the B3LYP/6-31G* level indicate low energy gas-phase conformers having the depicted chair-like conformation and axial 6-methyl group, with very shallow pyramidalization at the radical center.
25. Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270–3276.
26. Haeffner, F.; Brandt, P.; Gawley, R. E. *Org. Lett.* **2002**, *4*, 2101–2104.
27. (a) Gawley, R. E.; Zhang, Q. *J. Am. Chem. Soc.* **1993**, *115*, 7515–7516. (b) Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763–5769. (c) Gawley, R. E.; Low, E.; Zhang, Q.; Harris, R. *J. Am. Chem. Soc.* **2000**, *122*, 3344–3350.
28. For additional examples of α-aminoorganolithium cyclizations, see: (a) Meyers, A. I.; Du, B.; Gonzalez, M. A. *J. Org. Chem.* **1990**, *55*, 4218–4220. (b) Beak, P.; Wu, S.; Yum, E. K.; Jun, Y. M. *J. Org. Chem.* **1994**, *59*, 276–277. (c) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *715*, 721. (d) Coldham, H. R.; Snowden, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5322–5323. (e) Serino, C.; Stehle, N.; Park, Y. S.; Florio, S.; Beak, P. *J. Org. Chem.* **1999**, *64*, 1160–1165. (f) Coldham, I.; Fernandez, J.-C.; Price, K. N.; Snowden, D. J. *J. Org. Chem.* **2000**, *65*, 3788–3795.
29. E-mail: glasscontour@cox.net
30. Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281–283.
31. Kim, S.; Lee, J. I.; Yi, K. K. *Bull. Chem. Soc. Jpn* **1985**, *58*, 3570–3575.