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# Stereochemical Outcomes in Reductive Cyclizations To Form Spirocyclic Heterocycles

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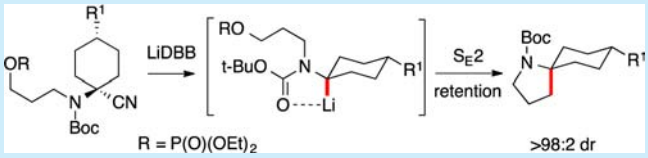
Supporting Information

**ABSTRACT:** Reductive lithiation and cyclization of *N*-Boc α-amino nitriles are often highly stereoselective. The alkyllithium intermediates are formed with varying levels of selectivity, but the alkyllithium geometry does not play a major role in the overall stereoselectivity. The final configuration is determined in the cyclization reaction, where both retention and inversion pathways are observed. Where strong thermodynamic preferences exist in the products, the kinetically controlled alkyllithium cyclization favors the more stable product.




Spirocyclic structures are common to many natural products,[1] and a wide variety of synthetic strategies have been developed for their synthesis.[2] Our group has developed a reductive cyclization strategy to assemble spirocycles in which the final step is the generation of an alkyllithium reagent from a nitrile, followed by cyclization onto a carbon electrophile. This method has been used to prepare a variety of spirocyclic ring systems, often with high stereoselectivity.[3] We have explored the use of *N*-Boc α-aminonitriles in reductive cyclization reactions.[3c,d,4] The stereochemical outcomes of these cyclizations can be surprising[3c] and are considered in detail in this report.

The three spirocycles in Figure 1 were prepared by reductive cyclization. Both compounds **1** and **2** were formed with high stereoselectivity.[5] The stereoselectivity in the former cyclization arises from the selective formation of the axial alkyllithium reagent, which is conformationally stable, and a stereospecific cyclization reaction with retention of configuration.[3a,6] In contrast, *N*-Boc spirocycle **2** arises from an alkyllithium reagent that appears to be configurationally stable but cyclizes with inversion of configuration.[3c] Spiropyrrolidine **3** is typical of the simple spirocycle formed by reductive cyclization and is generated as a racemate.[7] The reactivities of *N*-Boc α-aminoalkyllithium reagents are more promiscuous than α-alkoxy alkyllithium reagents and may react either with retention or inversion.[8] However, there are very few reactions reported with tertiary, unactivated *N*-Boc α-aminoalkyllithium reagents.[9] The investigations of a variety of spirocyclizations based on *N*-Boc α-aminonitiles are described herein.

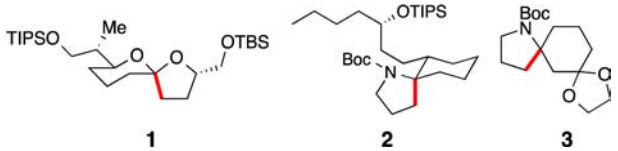



**Figure 1.** Spirocyclic structures prepared by reductive cyclizations are shown with the reductively formed bond highlighted in red. Cyclizations to produce compounds **1** and **2** are both highly stereoselective.[5]

The substrates for reductive cyclization were prepared through our previously described method.[7] Formation of the first ring proceeded through a double-alkylation reaction of an *N*-Boc α-aminonitrile **4** with dibromides **5** to give cyclic aminonitriles **6** as shown in Table 1. The alkylation and cyclization reactions were accomplished in moderate to good yields and variable diastereoselectivity. The silyl group was then replaced with a phosphate leaving group to enable the second cyclization step. Deprotection and phosphate formation proceeded in uniformly good yields. Several of the double-alkylation reactions generated mixtures of diastereomers. For each of the six-membered rings, the major diastereomer had the substituent equatorial and the nitrile axial.[10] In the case of nitriles **14** and **19**, the two diastereomers could be separated as the primary alcohols, and each alcohol diastereomer was taken on to the phosphate separately. The method was robust and produced cyclization substrates with three-, four-, five-, and six-membered rings with stereogenic centers positioned around the rings.

Reductive cyclization reactions of the *N*-Boc α-aminonitriles are presented in Table 2. The phosphates were cooled to −78 °C in THF and treated with an excess of freshly prepared LiDBB. The reactions were quenched at −78 °C, and the products were isolated by chromatography. The diastereomeric ratios were determined by GCMS, and the structure of the major diastereomer was determined by $^1$H NMR analysis and NOE.[11] Reductive cyclization of the cyclopropane **9** was expected to produce pyrrolidine **24**, but it was never detected. Instead, polar decomposition products were observed. All of the other cases produced the expected pyrrolidine rings.

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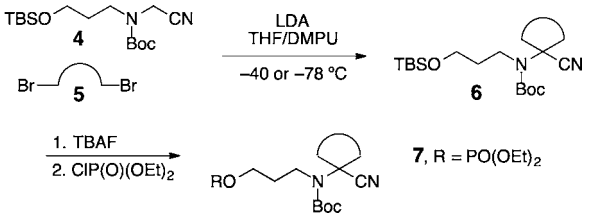
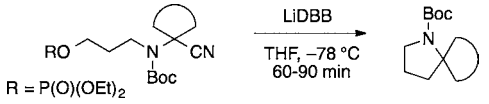
**Table 1. α-Aminonitrile Double-Alkylation Reactions**




| entry | alkylation (yield) | deprotect (yield) | phosphate (yield) |
|---|---|---|---|
| 1 | **8** 44% 2.6:1 dr | 77% | **9** 77% |
| 2 | **10** 55% 1.5:1 dr | 83% | **11** 83% |
| 3 | **12** 64% >95:5 dr[a] | quant[a] | **13** 93% |
| 4 | **14** 70% 1.9:1 dr | quant[a] (separated) | **15** 84% (major isomer); **16** 74% (minor isomer) |
| 5 | **17** 61% 22:1 dr | quant[a] | **18** 84% |
| 6 | **19** 97% 4.5:1 dr | 86% (separated) | **20** 72% (major isomer); **21** 92% (minor isomer) |
| 7 | **22** 91% 2.5:1 dr | quant[a] | **23** 82% |

[a]The mass of the intermediate alcohol was greater than 100%; the yield of phosphate **7** should be considered over two steps.

**Table 2. Stereoselective Spirocyclization of α-Aminonitrile Substrates**




| entry | phosphonate | cyclization product | yield and dr[a] |
|---|---|---|---|
| 1 | **9** | **24** | no product |
| 2 | **13** | **25** | 60% >99.9:0.1 dr |
| 3 | **15** | **26** | 52% >95:5 dr[b] |
| 4 | **16** | **26** | 43% >95:5 dr[b] |
| 5 | **15:16** 66:34 | **26** | 53% 99.9:0.1 dr |
| 6 | **18** | **27** | 66% 98.0:2.0 dr |
| 7 | **20** >95:5 major | **28** | 51% 98.2:1.8 dr |
| 8 | **21** <5:95 minor | **28** | 71% 98.7:1.3 dr |
| 9 | **20:21** 60:40 | **28** | 61% 98.5:1.5 dr |
| 10 | **23** | **29** | 53% >99.9:0.1 dr |

[a]Diastereomeric ratios were determined by GCMS analysis unless otherwise stated. [b]Diastereomeric ratio by $^1$H NMR analysis in which the minor isomer was not detected.

Most of the reductive cyclization reactions proceed with very high diastereoselectivity. Entries 2 and 10 (Table 2) lead to a single diastereomer to the limits of detection. All of the other cases lead to diastereomeric mixtures with ≤2% of the minor diastereomer. If we assume that the *N*-Boc group is larger than the methylene of the pyrrolidine, then the major product in each case is the more thermodynamically stable diastereomer. This outcome is surprising because the cyclization is clearly under kinetic control, vide infra. Entries 3–5 demonstrate that both epimers of the starting α-aminonitrile lead to the same major product. The case is more clearly made in entries 7–9, where both diastereomers of the *N*-Boc α-aminonitrile produce nearly identical ratios of the spiropyrrolidine product **28**. One interesting observation is the slightly higher yield with aminonitrile **21** than its epimer **20**. Compound **21** cyclizes with overall inversion of configuration. From these observations, we can formulate the simple prediction that reductive cyclization of *N*-Boc α-aminonitriles will lead to the thermodynamically favored product with high selectivity.



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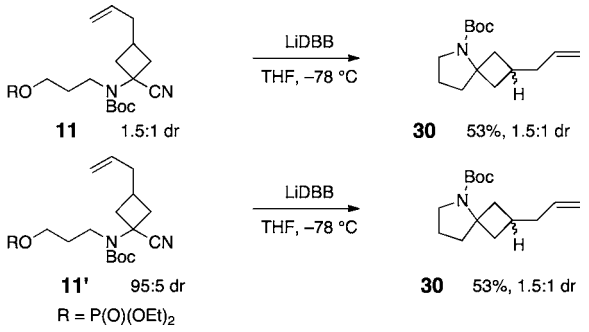
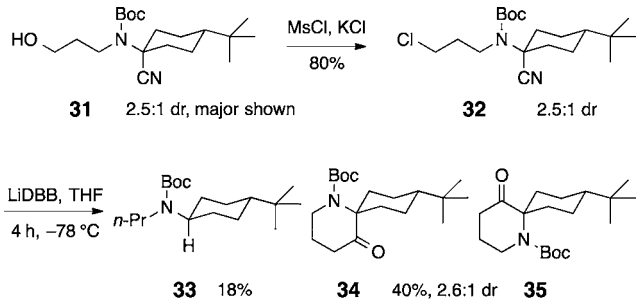
**Scheme 1. Stereoselectivity in the Spirocyclization of Cyclobutanes**




**Scheme 2. Unusual Reactions Observed in the Reductive Lithiation of Chloro Nitrile Substrate 32**

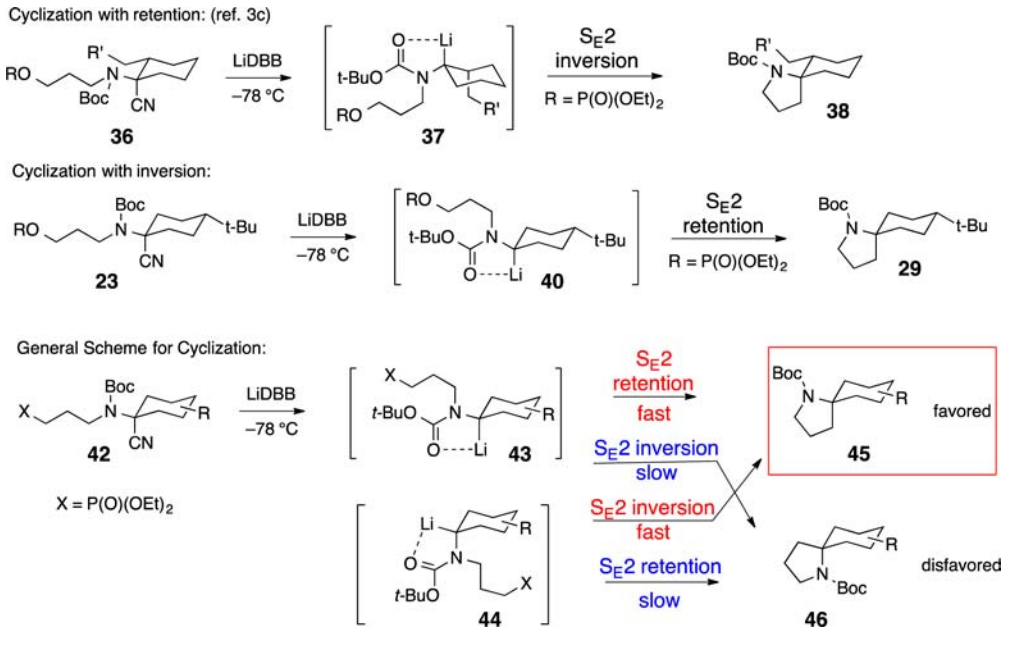



The cyclobutane $\alpha$-aminonitrile **11** was an exception to the prior generalization. In this case, reductive cyclization of a 1.5:1 dr of **11** led to a 1.5:1 dr of the spirocycle **30** in moderate yield, Scheme 1. The unusually low selectivity and similarity in diastereomeric ratio for starting material and product led us to postulate that this *N*-Boc aminonitrile might react stereospecifically. A sample of the diastereomerically enriched **11′** was prepared by HPLC and cyclized as before to produce the identical 1.5:1 dr of **30**. Our hypothesis was incorrect; the configuration of the *N*-Boc $\alpha$-aminonitrile is irrelevant and the cyclization simply proceeded with low stereoselectivity.

Although phosphates have been the most reliable electrophiles in these reductive cyclization reactions, alkyl chlorides have often been effective.[12] To examine the selectivity of an alkyl chloride in this type of cyclization, silyl ether **22** was deprotected to produce alcohol **31** as a 2.5:1 dr favoring the axial nitrile. Alcohol **31** was converted to the alkyl chloride **32** by mesylation and chloride displacement.[13] The reductive cyclization of **32** is presented in Scheme 2. None of the pyrrolidine product **29** was identified. Instead, lithiation at the chloride apparently takes place and leads to intramolecular addition to the nitrile. The diastereomeric ratio of the resulting amino ketones **34** and **35** closely matches the ratio of the starting material. The reductive dechlorination product **33** was also identified. The preferential reduction of an alkyl chloride in the presence of an *N*-Boc $\alpha$-aminonitrile has been observed[7] and should be the expected outcome with this additional data. The order of reduction with LiDBB for the following functional groups can be inferred as $\alpha$-dialkoxynitrile $\geq$ $\alpha$-alkoxynitrile > alkyl chloride > *N*-Boc $\alpha$-aminonitrile $\geq$ *N*-Bn $\alpha$-aminonitrile > alkyl phosphate. This reactivity scale should be useful in developing new reductive coupling reactions.

An explanation for the stereoselectivity of the reductive cyclization reactions is presented in Scheme 3.[14] When an adjacent substituent is present, as in structure **37**, lithiation tends to proceed with inversion, as shown by the protonation of alkyllithium **37** (R = TBS) to give the corresponding protonated product.[3c,15] The cyclization generates **38** by an inversion pathway. Pyrrolidine **27** (Table 2), which includes an adjacent methyl group, is probably produced by an analogous pathway. On the other hand, lithiation of *tert*-butyl aminonitrile **23** generates the intermediate alkyllithium **40** (R = TBS), which is protonated to produce a 5:1 dr favoring the axial hydrogen.[15,16] This outcome implies that alkyllithium **40** has the configuration shown and that the lithiation took place with retention. Surprisingly, the cyclization step now proceeds with retention to generate **29**. These results demonstrate that the

**Scheme 3. Alternative Pathways for Stereoselective Reductive Decyanations and Cyclizations**



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cyclization of *N*-Boc α-amino alkyllithium reagents can take place either with $S_E2$ retention or $S_E2$ inversion.[8]

We present a general pathway for the reductive cyclization events with *N*-Boc α-aminonitriles at the bottom of Scheme 3. Reduction with LiDBB generates a mixture of alkyllithium reagents **43** and **44** (based on the stability of the intermediate radical, which is discussed elsewhere).[4,17] The stereochemistry is set in the cyclization event, and the key conclusion is that the $S_E2$ retention and $S_E2$ inversion pathways have very similar intrinsic rates (i.e., $S_E2$ retention ~ $S_E2$ inversion). When there is a strong conformational preference, as would be expected with substituents on a six-membered ring, that preference funnels both the inversion and retention pathway to the thermodynamically preferred product (i.e., $S_E2$ retention and $S_E2$ inversion > $S_E2$ retention and $S_E2$ inversion). Extension of this idea to the cyclopentane substrate **13** or the cyclobutane substrate **11** is less obvious because the thermodynamic preferences in the products are expected to be modest. At least for the six-membered ring examples, the similar intrinsic rates for $S_E2$ retention and $S_E2$ inversion pathways account for the generation of thermodynamic products from a kinetically controlled cyclization event.

The reductive decyanation and cyclization reactions of *N*-Boc α-aminonitriles often show very high stereoselectivity in the formation of spirocyclic products. Given the wide occurrence of spirocyclic amines in alkaloid structures, these observations will be of interest to synthetic chemists.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and characterization data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01422.

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### Notes

The authors declare no competing financial interest.

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(5) Cyclization products **1** (ref 3a) and **3** (ref 3c) were both reported as single diastereomers (by NMR analysis).

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(11) In several cases the Boc group was removed or reduced to aid in the structural assignment. Details of the structural assignments are included in the Supporting Information.

(12) Examples of alkyl chlorides in successful cyclizations: (a) Takaoka, L. R.; Buckmelter, A. J.; LaCruz, T. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 528−529. (b) Reference 3a.

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(14) The conformations shown for alkyllithium reagents **37** and **40** are expected to be the most stable ones. The same is true for alkyllithium **43**, but alkyllithium **44** is shown in the less stable conformation (*N*-Boc axial) to keep the presentation of the generic substituent consistent.

(15) Protonation reactions are generally expected to proceed with retention of configuration. Thus, the configuration of the protonated product can be used to estimate the configuration of the alkyllithium reagent (ref 8). Details of these protonation experiments may be found in the Supporting Information.

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