Cyclization via Carbolithiation of α-Amino Alkyllithium Reagents

Robert J. Bahde and **Scott D. Rychnovsky**
Department of Chemistry, 1102 Natural Sciences II, University of California-Irvine, Irvine, California 92697

Abstract

R = (CH₂)₃-CH=CH₂

We report a new route to tertiary α-amino stereocenters by sequential alkylation of α-amino nitriles followed by reductive lithiation of the nitrile and cyclization onto an alkene. Reductive lithiation of α-amino nitriles using lithium 4,4′-di-*tert*-butylbiphenylide (LiDBB) and subsequent intramolecular carbolithiation proceeded with modest to high diastereoselectivity to deliver cyclic or spirocyclic ring systems. The stereoselectivity of these intramolecular carbolithiations was examined using density function calculations to evaluate plausible transition state models.

Tertiary α-amino stereogenic centers are found in many classes of alkaloids, including the cylindricines,[1] fasicularin,[2] and pinnaic acid,[3] and these stereogenic centers are often incorporated into rings. Previously we reported the reductive lithiation and cyclization of cyanohydrins to form spirocyclic ethers, often with high stereoselectivity.[4] A similar strategy might allow complex alkaloids skeletons to be rapidly assembled from α-amino nitriles. Nitriles can be deprotonated and these anions are excellent nucleophiles for alkylation.[5] Thus the α-amino nitriles substrates might be assembled using the facile alkylation adjacent to the nitrile, and subsequent reductive lithiation would trigger and intramolecular carbolithiation reaction. Herein we describe several model studies that delineate the scope of this reductive cyclization strategy.

Husson has studied the stereoselective reductive decyanation of α-amino nitriles extensively and applied this method very effectively in the synthesis of alkaloids.[6] Both Husson[7] and Grierson[8] have reported isolated examples of α-amino nitrile reduction and intramolecular alkylation, but they have not reported cyclization onto alkenes. Intramolecular cyclization of alkyllithium reagents onto unactivated alkenes has been extensively studied by Bailey[9] and by a number of other groups.[10] Wiberg and Bailey used computational methods to predict a four-centered transition state for insertion of an alkene into the organolithium bond.[11] The classic intramolecular carbolithiation of an α-amino alkyllithium reagent was reported by Coldham using an optically pure secondary α-amino stannane to generate the alkyllithium intermediate.[12] Transmetalation of stannanes is not an effective method for the preparation of tertiary alkyllithium reagents, however, and neither is the deprotonation method commonly used for carbamate-activated α-amino alkyllithium reagent generation.[13] The poor accessibility of these reagents means that intramolecular carbolithiation reactions using tertiary α-amino alkyllithium reagents are essentially unknown.

E-mail: srychnov@uci.edu.

Reduction of thiophenols and of nitriles with the powerful reducing agent lithium 4,4′-di-*tert*-butylbiphenylide (LiDBB)[14] in THF has proven to be a general route to many unusual and complex alkyllithium reagents.[15] We recently reported that the reductive lithiation of α-amino nitriles provides a facile, and in some cases stereoselective, route to tertiary α-amino alkyllithium reagents.[16] These nitrile reductive lithiation reactions provide an ideal entry into highly substituted carbolithiation precursors of interest in this study.

The piperidine substrates were assembled as outlined in Table 1. The starting material, *N*-benzyl-2-cyanopiperidine (**1**), was prepared in two steps from piperidine.[16a,17] Cyanopiperidine **1** was deprotonated with LDA and alkylated with a series of primary alkyl bromides and iodides (**2**-**8**) to give the substituted cyanopiperidines **9**-**15**. It is important to mention that the fully substituted nitriles demonstrated a propensity to undergo retro-Strecker reactions when exposed to mild acidic media, so care was taken during purification and characterization to minimize this side reaction.[18] Halides **2**, **3** and **6**-**8** were generated from commercially available alcohol precursors. Methoxy ethers **4** and **5** were readily prepared in high yield utilizing Grubbs' cross metathesis as a key step.[19] The alkene metathesis afforded *E*-alkenes in greater than a 20:1 ratio.[20]

Reductive decyanation of *N*-benzyl 2-cyanopiperidine **9** generated a tertiary α-amino organolithium species that underwent intramolecular carbolithiation to produce, after protonation, spiropiperidine diastereomer **16** with two new stereogenic centers with 20:1 selectivity (Table 2, entry 1). The configuration of **16** has the methyl group cis to the nitrogen atom and was assigned by NOE experiments.[20] Carbolithiation did not occur when cyanopiperidine **10** was subjected to the same conditions or upon warming. Reductive decyanation generated the tertiary organolithium species as shown by deuteration studies; however, the lithiated intermediate did not undergo cyclization. This result is consistent with Coldham's observation that temperature plays a key role in intramolecular carbolithiation reactions.[21] In order to overcome the entropic requirements to form a six-membered ring, prohibitively high temperatures were required that led to decomposition and protonation of the alkyllithium intermediate.[22]

Much like carbolithiation, spiroannulation onto allylic methoxy ethers occurred to form five-membered rings but not six-membered rings. Methyl ether **11** gave spirocycle **18** with a diastereomeric ratio of 2:1 (Table 2, entry 2).[20] The S_N' cyclization led to modest selectivity in contrast to the carbolithiation with substrates **9** and **10**. Surprisingly, cyclization of methyl ether **12** did not lead to the six-membered spirocycle,[4] but instead gave only the reduced product.

The alkyllithium cyclizations were also effective with alkynyl piperidine **15** (Table 2, entry 3). Selective ciscarbolithiation onto the TBS-alkyne at −78 °C produced the *E*-alkene **20** as the only isomer in modest yield. The configuration of the alkene was assigned by NOE analysis.[20]

Cyclizations with primary chlorides were explored as an alternative to previously reported spiroannulations with phosphate leaving groups.[4,7,8] Subtle differences in *N*-alkyl-2-cyanopiperidines can lead to different outcomes through competitive reduction between the primary chloride and the nitrile moiety.[7,8] We anticipated that the reductive decyanation of chloro nitriles **13** and **14** might produce a tertiary α-amino organolithium more rapidly than the potentially competitive halide reduction.[15] In the event, halide reduction occurred before reductive decyanation, and the intermediate alkyllithium reagent cyclized onto the nitrile to produce a spirocyclic ketone. Both the spirocyclic cyclohexanone **24** and the cycloheptanone **25** were formed in moderate yield under these conditions (Table 2, entry 4). Side products lacking both the nitrile and chloride were observed in both cases. Preferential reduction of the

alkyl chloride contrasts sharply with the result of cyanohydrins, where decyanation is the dominant pathway.[4]

N-Boc amino nitriles also generate tertiary α-amino alkyllithium reagents on reduction with LiDBB, and the intramolecular carbolithiation of a model compound was investigated.[16] The *N*-Boc piperidine was prepared by a route analogous to the synthesis of compound **9**, and it includes an efficient alkylation of the α-amino nitrile anion with bromide **2**.[20] Attempted cyclization of **23**, however, was not effective. Reductive decyanation produced the expected alkyllithium reagent, but no cyclized product was detected after 12 h at −78 °C. Attempted carbolithiation reactions at higher temperature (−45 °C) were also unsuccessful and only led to the protonated product **24**. One explanation for the lack of cyclization product is that the alkyllithium reagent produced from **23** is strongly coordinated with the *N*-Boc oxygen, and it may not be electrophilic enough to engage the alkene.

Pyrrolidines were also effective substrates in the spiroannulation reaction (Scheme 2). Synthesis of **26** was achieved by an intramolecular Strecker reaction.[23] Alkylation conditions from Table 1 were replicated and afforded cyclization precursor **26** in quantitative yield. Reductive lithiation with LiDBB in THF generated the cyclized spiropyrrolidine **27** in a 4:1 diastereomeric ratio in excellent yield. The methyl group of the major isomer **27** is cis to the nitrogen atom with respect to the newly formed cyclopentane ring.[20] The 2-cyano pyrrolidines are excellent substrates for reductive cyclization reactions.

The diastereoselectivity observed during the carbolithiation of nitriles **9** and **27** was rationalized by invoking coordination between the equatorial lone pair of the nitrogen atom and the lithium atom in the transition state (see below). A similar explanation for the selectivity in tetrahydropyranyl reductive cyclizations has been proposed.[4] Acyclic nitrile **30** was selected to probe this coordination effect. The synthesis of nitrile **30** began with cyanomethylation of dibenzylamine to produce the tertiary amine **28** as outlined in Scheme 3. Alkylation with primary bromide 2 produced the tertiary α-amino nitrile **30** in modest yield. As noted previously, some of these α-amino nitriles are prone to retro-Strecker reactions[18] and that accounts for the modest yield of compound **30** in the alkylation reaction.

Finally, reductive lithiation conditions of nitrile **30** induced an intramolecular carbolithiation reaction, but only in low yield. The cyclization led to a 1:1 mixture of diastereomers. The stereochemical outcome of this cyclization reaction is quite different from the examples with piperidine (**9**) and pyrrolidine (**27**) rings.

The spiroannulation reaction may also be applied to form pyrrolidine rings. An example of this strategy is presented in Scheme 4. The cyclization substrate **33** was assembled by sequential nitrogen and carbon alkylation reactions. Benzylamine was cleanly monoalkylated with chloroacetonitrile. The nitrile group reduces the nucleophilicity of the nitrogen atom, disfavoring over-alkylation.[24] The alkene side chain was introduced by alkylation with 4-bromobutene under more vigorous conditions. Deprotonation of the amino nitrile **32** and double alkylation with 1,5-diiodopentane gave the highly substituted amino nitrile **33**.[25] In theory the same product could be prepared by a Strecker reaction with cyclohexanone, but in practice such an approach is limited by the sometimes-unfavorable equilibrium found with ketone substrates in that process.

Reductive lithiation of amino nitrile **33** with LiDBB under standard conditions, followed by protonation of the alkyllithium product led to the spirocyclic pyrrolidine **34** in moderate yield. In this case there is only one isomer possible, and one would need to introduce a label into the cyclohexane ring to track the stereochemical course of the reaction.

Several of these spirocyclization reactions proceeded with high diastereoselectivity. On possible explanation for the selectivity is that coordination between the lithium and nitrogen atoms during carbolithiation of piperidine **9** (and pyrrolidine **27**) would favor the observed product. Heteroatom coordination of alkyllithium reagents has been invoked to explain the selectivity of intramolecular carbolithiation reactions, but the outcome is not always straightforward.[10c-e] This proposal was explored using DFT calculations.[26] The two lowest energy transition states are depicted in Figure 1. The atom distances present in these models closely match the transition states determined by Bailey and Wiberg for the intramolecular carbolithiation of 5-hexen-1-yllithium.[11] The favored transition state resembles a four-membered C-C-C-Li ring with the alkene inserting into the organolithium bond. The more stable transition state includes coordination between the nitrogen and lithium atoms (distance Li-N = 1.925 Å), and leads to the observed "cis" product. The geometry of the other transition state precludes lithium-nitrogen coordination (distance Li-N = 3.29 Å) and it is much higher in energy.[27]

We demonstrate that *tert*-α-amino alkyllithium reagents can be prepared by reductive lithiation of α-amino nitriles, and that in many cases these alkyllithium reagents will undergo intramolecular carbolithiation. These intramolecular carbolithiation reactions can be highly stereoselective, and lead to [4.4] and [4.5] spirocyclic structures. This new annulation reaction should be a useful tool in the synthesis of alkaloid structures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

References

1. aBlackman AJ, Li C, Hockless DCR, Skelton BW, White AH. Tetrahedron 1993;49:8645–8656.8656 bLi C, Blackman AJ. Aust. J. Chem 1994;47:1355–1361.1361 cLi C, Blackman AJ. Aust. J. Chem 1995;48:955–965.965 Review of synthetic work: dLiu J, Hsung RP. Chemtracts 2005;18:321–330.330.

2. aPatil AD, Freyer AJ, Reichwein R, Carte B, Killmer LB, Faucette L, Johnson RK. Tetrahedron Lett 1997;38:363–364.364 Review of synthetic work: bWeinreb SM. Chem. Rev 2006;106:2531–2549.2549 [PubMed: 16771458]. cSchar P, Cren S, Renaud P. Chimia 2006;60:131–141.141.

3. a Chou T, Kuramoto M, Otani Y, Shikano M, Yazawa K, Uemura D. Tetrahedron Lett 1996;37:3871–3874. b Arimoto H, Hayakawa I, Kuramoto M, Uemura D. Tetrahedron Lett 1998;39:861–862.

4. Rychnovsky SD, Takaoka LR. Angew. Chem. Int. Ed 2003;42:818–820.

5. For a recent review, see: Fleming FF, Zhang Z. Tetrahedron 2005;61:747–789.789.

6. a Husson H-P, Royer J. Chem. Soc. Rev 1999;28:383–394. b Bonin M, Romero JR, Grierson DS, Husson H-P. Tetrahedron Lett 1982;23:3369–3372.

7. a Ribeiro CMR, Sebastiao JM, Bonin M, Quirion J, Husson H-P. Tetrahedron Lett 1994;35:7227–7230. b Roulland E, Cecchin F, Husson HP. J. Org. Chem 2005;70:4474–4477. [PubMed: 15903327]

8. a Zeller E, Grierson DS. Heterocycles 1988;27:1575–1578. b Zeller E, Sajus H, Grierson D,S. Synlett 1991:44–46. c Zeller E, Grierson DS. Synlett 1991:878–880.

9. a Mealy MJ, Bailey WF. J. Organomet. Chem 2002;646:59–67. b Bailey WF, Jiang X. Tetrahedron 2005;61:3183–3194.

10. For leading references, see aChamberlin AR, Bloom SH, Cervini LA, Fotsch CH. J. Am. Chem. Soc 1988;110:4788–4796.4796 bBroka CA, Lee WJ, Shen T. J. Org. Chem 1988;53:1336–1338.1338 cMudryk B, Cohen T. J. Am. Chem. Soc 1993;115:3855–3865.3865 dDeng K, Bensari A, Cohen T.

J. Am. Chem. Soc 2002;124:12106–12107.12107 [PubMed: 12371845] eBailey WF, Jiang XL. Tetrahedron 2005;61:3183–3194.3194.

11. Bailey WF, Khanolkar AD, Gavaskar K, Ovaksa TV, Rossi K, Thiel Y, Wiberg K,B. J. Am. Chem. Soc 1991;113:5720–5727.

12. Coldham I, Hufton R, Snowden DJ. J. Am. Chem. Soc 1996;118:5322–5323.

13. a Beak P, Johnson TA, Kim DD, Lim SH. Top. Organomet. Chem 2003;5:139–176. b Beak P, Zajdel WJ, Reitz DB. Chem. Rev 1984;84:471–523.

14. Freeman's reagent: Freeman PK, Hutchinson LL. Tetrahedron Lett 1976;17:1849–1852.1852.

15. Reviews: aCohen T, Bhupathy M. Acc. Chem. Res 1989;22:152–161.161 bYus M. Chem. Soc. Rev 1996;25:155–161.161 Leading references: cScrettas CG, Micha-Screttas M. J. Org. Chem 1978;43:1064–1071.1071 dBoeckman RK, Enholm EJ, Demko DM, Charette AB. J. Org. Chem 1986;51:4743–4745.4745 eGuijarro D, Yus M. Tetrahedron 1994;50:3447–3452.3452 fFoubelo F, Gutierrez A, Yus M. Synthesis 1999:503–514.514.

16. a Wolckenhauer SA, Rychnovsky SD. Org. Lett 2004;6:2745–2748. [PubMed: 15281759] b Wolckenhauer SA, Rychnovsky SD. Tetrahedron 2005;61:3371–3381.

17. a De Kimpe N, Stevens CJ. J. Org. Chem 1993;58:2904–2906. b Davis BG, Maughan MAT, Chapman TM, Villard R, Courtney S. Org. Lett 2002;4:103–106. [PubMed: 11772101]

18. Only fully substituted α-aminonitrile compounds displayed a propensity to undergo a retro-Strecker reaction. In order to avoid decomposition, compounds were purified using basic aluminia flash chromatography and characterized in d_6-benzene.

19. a Morgan JP, Grubbs RH. Org. Lett 2000;2:3153–3155. [PubMed: 11009369] b Chatterjee AK, Choi TL, Sanders DP, Grubbs RH. J. Am. Chem. Soc 2003;125:11360–11370. [PubMed: 16220959]

20. Details are provided in the Supporting Information section.

21. a Oestreich M, Roland F, Hoppe D. Tetrahedron Lett 1998;39:1745–1748. b Ashweek NJ, Coldham I, Snowden DJ, Vennall GP. Chem. Eur. J 2002;8:195–207.

22. Alkyllithium intermediates deprotonating THF over extended periods of time. aDeng K, Bensari–Bouguerra A, Whetstone J, Cohen T. J. Org. Chem 2006;71:2360–2372.2372 [PubMed: 16526785] bStanetty P, Minovilovic MD. J. Org. Chem 1997;62:1514–1515.1515.

23. Bonnett R, Clark V, M. Giddey A, Todd A. J. Chem Soc 1959:2087–2093.

24. Tokuyama H, Kuboyama T, Amano A, Yamashita T, Fukuyama T. Synthesis 2000:1299–1304.

25. Guillaume D, Brum–Bousquet M, Aitken DJ, Husson H-P. Bull. Chim. Soc. Fr 1994;131:391–396.

26. Geometry optimizations were performed with B3LYP/6−31G* as implemented in Gaussian 03. Minima were characterized by their vibrational frequencies. The transition states were characterized by vibrational frequency calculations as well as internal reaction coordinate calculations. The energies reported are enthalpies without zero-point corrections. Transition state geometries and the full Gaussian 03 reference is included in the Supporting Information section.

27. The relative energy between the two transition states in Figure 1 is unreasonably large, but the actual values are unlikely to be very accurate because of the complete neglect of solvation in these calculations.

i. LiDBB, THF
−78 °C

ii.MeOH
(83%)

23   **24**

Scheme 1.
Reductive lithation of Boc aminonitrile **23** does not lead to cyclization

Scheme 2.
Carbolithiation of Pyrrolidine **27**

Scheme 3.
Sequential cyanomethylation and alkylation to prepare carbolithiation precursor **31**

Scheme 4.
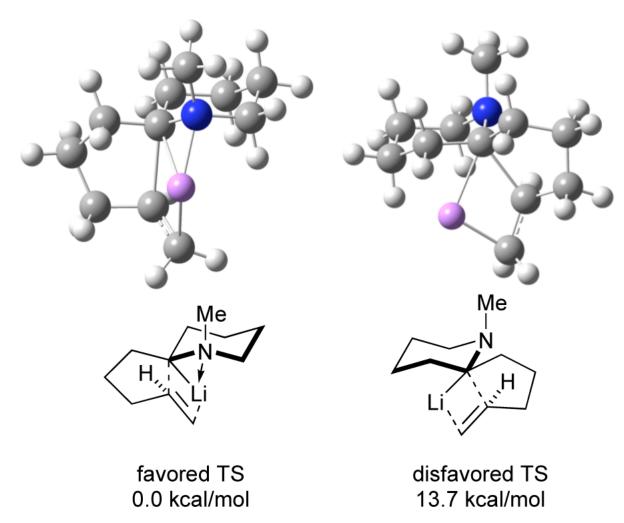Construction and spiroannulation of amino nitrile **29**

Figure 1.
B3LYP/6−31G(d) Transition states for the carbolithiation-cyclization of an *N*-methyl 2-lithiopiperidine.

Table 1

Alkylation of *N*-Benzyl-2-cyanopiperidine 1

entry	R-X	yiel
1	Br⌒⌒(⌒)ₙ⌒⫶ **2**, n = 1 **3**, n = 2	**9,** n = 98% n = 78%
2	I⌒⌒(⌒)ₙ⌒=⌒⌒O⌒ **4**, n = 2 **5**, n = 3	**11,** n 2, 90 **12,** n 3, 91

entry	R-X	yiel
3		**13**, n 1, 76 **14**, n 2, 72
4	**8**	**15**, 88

6, n = 1

7, n = 2

Table 2

Spiroannulation of *N*-Benzyl-2-cyanopiperidines.

entry	nitrile reagent	spirocyclic product	yield
1			**16**, n = 1, 67% (dr = 20:1) **17**, n = 2, 0%
2			**18**, n = 1, 60% (dr = 2:1) **19**, n = 2, 0%
3			**20**, 44%
4			**21**, n = 1, 45% **22**, n = 2, 46%