ORGANIC LETTERS

2004
Vol. 6, No. 16
2745−2748

Generation and Utility of Tertiary α-Aminoorganolithium Reagents

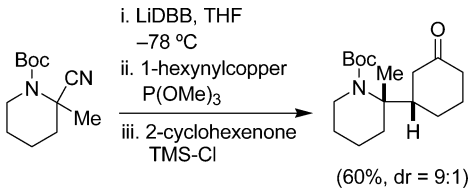
Scott A. Wolckenhauer and Scott D. Rychnovsky*

Department of Chemistry, 516 Rowland Hall, University of California−Irvine, Irvine, California 92697-2025

srychnov@uci.edu

Received May 24, 2004

ABSTRACT



A general approach to tertiary α-aminoorganolithium reagents by reductive lithiation of α-aminonitriles has been developed. This class of organolithium nucleophiles reacts efficiently with carbonyl electrophiles or in intramolecular cyclizations with tethered phosphate leaving groups. Transmetalation can be used to produce α-aminoorganocuprate reagents that react with alkyl halide electrophiles and in 1,4-additions with enones. These methods establish a new approach for the synthesis of quaternary centers adjacent to nitrogen.

Since Peterson's work on the generation of α-aminoorganolithium reagents,[1] the use of these intermediates in synthesis has been extensively explored.[2] Particular focus has been given to the development of enantioselective processes that take advantage of the high configurational stability associated with these species.[3] Frequently utilized methods for the preparation of primary and secondary α-aminoorganolithiums include (1) tin−lithium exchange and (2) deprotonation aided by the proximity of a coordinating functional group. The utility of these methods for the preparation of tertiary α-aminoorganolithiums has not been well demonstrated. To the best of our knowledge, no examples of tin−lithium exchange to generate a tertiary α-aminoorganolithium have been reported and deprotonation does not appear to be a general strategy.[4−6]

An alternate approach to tertiary α-aminoorganolithium reagents involves reductive lithiation of an aryl sulfide using lithium di-*tert*-butylbiphenylide (LiDBB).[7,8] In a similar manner, reductive decyanation of α-aminonitriles under traditional dissolving metal conditions (lithium or sodium in liquid ammonia) generates α-metalloamines, albeit as fleeting intermediates due to rapid protonation of the strongly basic tertiary organometallics.[9] Although α-aminonitriles are

(1) (a) Peterson, D. J. *J. Organomet. Chem.* **1970**, *21*, P63−64. (b) Peterson, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 4027−4031. (c) Peterson, D. J.; Ward, J. F. *J. Organomet. Chem.* **1974**, *66*, 209−217.

(2) Reviews: (a) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471−523. (b) Katritzky, A. R.; Qi, M. *Tetrahedron* **1998**, *54*, 2647−2668. (c) Gawley, R. E.; Coldham, I. α-Amino-organolithium Compounds. In *The Chemistry of Organolithium Compounds (Patai Series)*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2003; pp 997−1053.

(3) (a) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552−560. (b) Gawley, R. E.; Low, E.; Zhang, Q.; Harris, R. *J. Am. Chem. Soc.* **2000**, *122*, 3344−3350. (c) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Elmsford, NY, 2002; Vol. 23.

(4) Deprotonation/lithiation at a benzylic position: (a) Meyers, A. I.; Du, B.; Gonzalez, M. A. *J. Org. Chem.* **1990**, *55*, 4218−4220. (b) Meyers, A. I.; Guiles, J.; Warmus, J. S.; Gonzalez, M. A. *Tetrahedron Lett.* **1991**, *32*, 5505−5508. (c) Park, Y. S.; Boys, M. L.; Beak. P. *J. Am. Chem. Soc.* **1996**, *118*, 3757−3758. (d) Hara, O.; Ito, M.; Hamada, Y. *Tetrahedron Lett.* **1998**, *39*, 5537−5540.

(5) Deprotonation/lithiation at a cyclopropyl position: Beak, P.; Wu, S.; Yum, E. K.; Jun, Y. M. *J. Org. Chem.* **1994**, *59*, 276−277.

(6) Seebach has used the *N*-nitroso group to faciliate lithiation at a tertiary position; however, the potential carcinogenicity of *N*-nitrosoamines is likely responsible for lack of further development of this method. See: (a) Seebach, D.; Enders, D. *Angew. Chem., Int. Ed.* **1972**, *11*, 1101−1102. (b) Seebach, D.; Enders, D. *Angew. Chem., Int. Ed.* **1975**, *14*, 15−32.

(7) LiDBB is an arene radical anion reducing agent first described by Freeman: Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924−1930.

(8) (a) Tsunoda, T.; Fujiwara, K.; Yamamoto, Y.-I.; Ito, S. *Tetrahedron Lett.* **1991**, *32*, 1975−1978. (b) Florio, S.; Capriati, V.; Galio, A.; Cohen, T. *Tetrahedron Lett.* **1995**, *36*, 4463−4466.

(9) Husson has extensively developed this method. For a review of his elegant work, see: Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383−394.

10.1021/ol049039p CCC: $27.50
Published on Web 07/03/2004

readily accessed and elaborated[10] and would appear to be ideal precursors for this chemistry,[11] their use in generation of tertiary α-aminoorganolithiums under aprotic conditions is essentially unknown.[12−14] At the outset of our studies, we sought to develop a general preparative strategy toward tertiary α-aminoorganolithiums from α-aminonitriles as a means of accessing polysubstituted amines (Figure 1).

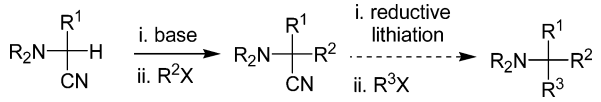
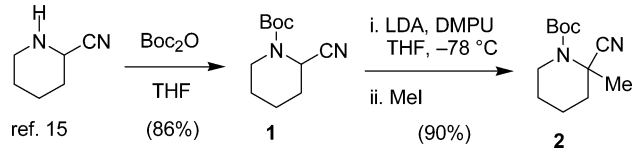


Figure 1. Polysubstituted Amines from α-Aminonitriles.

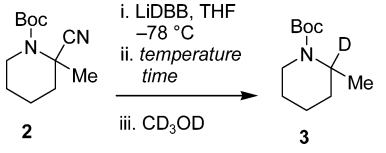
Importantly, the compatibility of these reactive intermediates with various common electrophiles would need to be addressed. Herein, we present initial results of our studies.

As a precursor for the bulk of our studies, we focused on α-aminonitrile **2**, synthesized in two steps from 2-cyanopiperidine[15] (Scheme 1). This compound undergoes rapid

Scheme 1. Synthesis of α-Aminonitrile **2**



reductive lithiation with LiDBB in THF at −78 °C to produce solutions of the desired lithiated piperidines,[16,17] which show good stability over a useful range of temperatures as demonstrated by deuterium quenching experiments (Figure 2).



temp. (°C)	*time* (h)	% D	% yield
–78	15	85	91
0	1	74	75

Figure 2. Deuterium Quenching Experiments.

The reductive lithiation/electrophilic addition protocol was next extended to carbonyl compounds. Carbon dioxide, methyl chloroformate, and a variety of aldehydes and ketones, including those with acidic α-protons, react efficiently with the organolithium reagent derived from α-aminonitrile **2** (Table 1). When aldehydes or ketones are employed, the intermediate lithium alkoxides undergo intramolecular cyclization upon warming to displace *tert*-butoxide and form the depicted bicyclic carbamates.[18] While low to moderate levels of diastereoselectivity were observed in most cases, addition of pivalaldehyde afforded a single detectable diastereomer (entry 5).

Direct addition of alkyl halides to the organolithium reagent derived from α-aminonitrile **2** is not an efficient reaction. For example, addition of methyl iodide provides desired addition product **14** in 13% yield along with side products **17** and **18** in yields of 20 and 18%, respectively (Table 2). These side products may arise from an intervening single-electron transfer (SET) pathway.[19] Meyers has found that transmetalation of an α-aminoorganolithium to the corresponding cuprate was effective in raising the yield of desired addition products by limiting SET.[19a,b] In a modification of this procedure, we have observed significantly increased yields by performing the reductive lithiation and then adding a solution of $P(OMe)_3$-solubilized 1-hexynylcopper[20] in THF prior to addition of an alkyl halide electrophile (Table 2).

The α-aminoorganocuprate reagents produced in this way also engage in 1,4-addition with enones. Methyl vinyl ketone

(10) (a) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207−3233. (b) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359−373. (c) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795−2827.

(11) Yus reported the first examples of reductive decyanation/lithiation mediated by LiDBB in non α-amino systems: Guijarro, D.; Yus, M. *Tetrahedron* **1994**, *50*, 3447−3452.

(12) The following reference contains a cyclization that may proceed through a tertiary α-aminoorganolithium reagent generated by LiDBB-mediated reductive lithiation of an α-aminonitrile: Ribeiro, C. M. R.; de Melo, S. J.; Bonin, M.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1994**, *35*, 7227−7230.

(13) Grierson has prepared secondary α-aminoorganolithium reagents by reductive metalation of α-aminonitriles: (a) Zeller, E.; Grierson, D. S. *Heterocycles* **1988**, *27*, 1575−1578. (b) Zeller, E.; Grierson, D. S. *Synlett* **1991**, 878−880.

(14) An additional, but relatively unexplored, method for the generation of tertiary α-aminoorganolithium reagents involves lithium naphthalenide-mediated reductive lithiation of imines: Guijarro, D.; Yus, M. *Tetrahedron* **1993**, *49*, 7761−7768.

(15) In a modification of De Kimpe's procedure, 2-cyanopiperidine was synthesized by adding KCN to 2,3,4,5-tetrahydropyridine, prepared using Rapoport's method. (a) Bender, D. R.; Bjeldanes, L. F.; Knapp, D. R.; Rapoport, H. *J. Org. Chem.* **1975**, *40*, 1264−1269. (b) De Kimpe, N.; Stevens, C. *J. Org. Chem.* **1993**, *58*, 2904−2906.

(16) **Representative Reductive Lithiation Procedure.** A solution of 100 mg (0.446 mmol) of α-aminonitrile **2** and 1 crystal of 1,10-phenanthroline in 5.0 mL of THF was cooled to −78 °C and treated with a few drops of *n*-butyllithium/hexanes solution to a brown endpoint (this procedure serves to quench adventitious proton sources). A solution of LiDBB (ca. 0.5 M) was added rapidly via a gastight syringe until the dark green color persisted, indicating a slight excess of reducing agent and complete consumption of the starting α-aminonitrile. The solution of α-aminoorganolithium was then treated with an appropriate electrophile. See Supporting Information for specific experimental details.

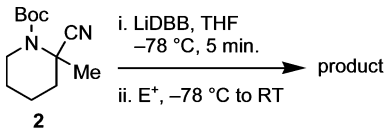
(17) By virtue of the Boc-protecting group, these intermediates fall under the classification of "stabilized" α-aminoorganolithiums. We are also studying the use of the reductive lithiation procedure to generate the related "nonstabilized" (*N*-alkyl) α-aminoorganolithiums.

(18) Beak has observed this behavior in similar systems: (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.

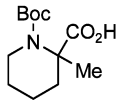
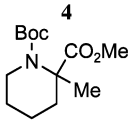
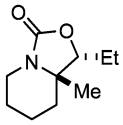
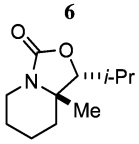
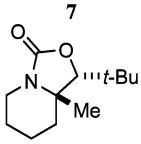
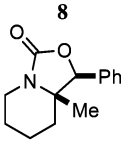
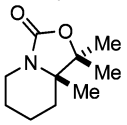
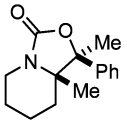
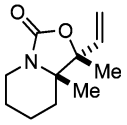
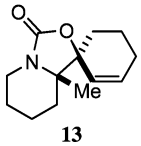
(19) Oxidation products similar to **18** have previously been observed in reactions of 2-lithiopiperidines with alkyl halides. *tert*-Butylformamidine-protected systems: (a) Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270−3276. (b) Meyers, A. I.; Milot, G. *J. Am. Chem. Soc.* **1993**, *115*, 6652−6660. Oxazoline-protected systems: (c) Gawley, R. E.; Hart, G. C.; Bartolotti, L. J. *J. Org. Chem.* **1989**, *54*, 175−181. Me-protected systems: (d) Chambournier, G.; Gawley, R. E. *Org. Lett.* **2000**, *2*, 1561−1564. Boc-protected systems: (e) Bertini Gross, K. M.; Beak, P. *J. Am. Chem. Soc.* **2001,** *123*, 315−321.

(20) Corey developed the use of alkynes as nontransferable ligands for cuprate chemistry: Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210−7211.

Table 1. Reductive Lithiation/Electrophilic Addition of Carbonyl Compounds

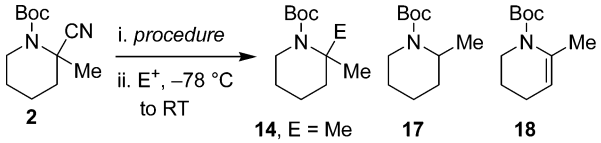


2

entry	E^+	product[a]	yield (%)	dr[b]
1	CO_2 (g)	 **4**	87	—
2	$ClCO_2Me$	 **5**	79	—
3	EtCHO	 **6**	75	4.5:1
4	*i*-PrCHO	 **7**	74	3.7:1
5	*t*-BuCHO	 **8**	59	—[c]
6	PhCHO	 **9**	82	1.5:1
7	MeC(O)Me	 **10**	68	—
8	PhC(O)Me	 **11**	61	3.3:1
9	CH_2=CHC(O)Me	 **12**	65	1.5:1
10	2-cyclohexenone	 **13**	84	2.2:1

[a] In cases where diastereomers were obtained, the major diastereomer is shown. See Supporting Information for details of stereochemistry assignment. [b] Determined by GC analysis of crude reaction mixtures. [c] Single diastereomer was obtained.

Table 2. Addition of Alkyl Halides to α-Aminoorganolithium and Cuprate Nucleophiles



2

14, E = Me **17** **18**
15, E = C_7H_{15}
16, E = allyl

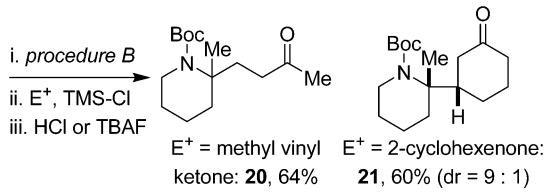
procedure A: LiDBB, THF, –78 °C, 5 min.
procedure B: LiDBB, THF, –78 °C, 5 min.; 1-hexynylcopper, $P(OMe)_3$, –78 °C, 30 min.

			yield (%)	
entry	E^+	product	via organolithium	via organocuprate
1	MeI	E = Me **14**	13	52
2	$C_7H_{15}I$	E = C_7H_{15} **15**	a	51
3	allylBr	E = allyl **16**	29	60

[a] 5-Chloro-1-iodopentane afforded a 13% yield.

and 2-cyclohexenone produce adducts **20** and **21** in yields of 64 and 60%, respectively (Scheme 2).[21] In neither case were the 1,2-addition products **12** or **13** observed. These appear to be the first reported examples of the generation and usage of tertiary α-aminoorganocuprate reagents.[22]

Scheme 2. 1,4-Addition Products

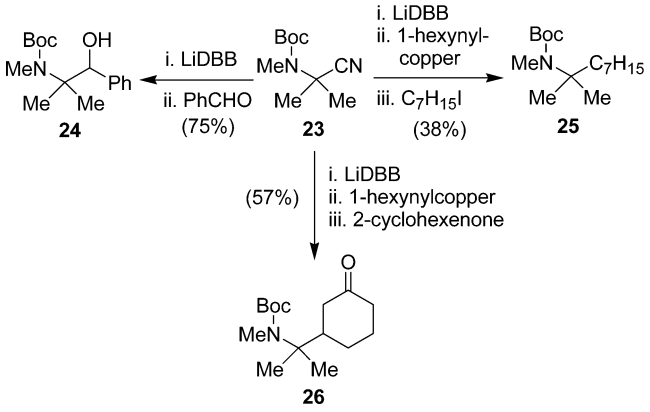


We have also extended this methodology to acyclic α-aminonitrile **23** (Scheme 3). Applying the procedures used for **2** afforded benzaldehyde addition product **24** in 75% yield via the corresponding α-aminoorganolithium reagent. The transmetalation protocol was also successful for aminonitrile **23**, providing products **25** and **26** in 38 and 57% yields by addition of *n*-iodoheptane or 2-cyclohexenone, respectively, to the α-aminoorganocuprate reagent.

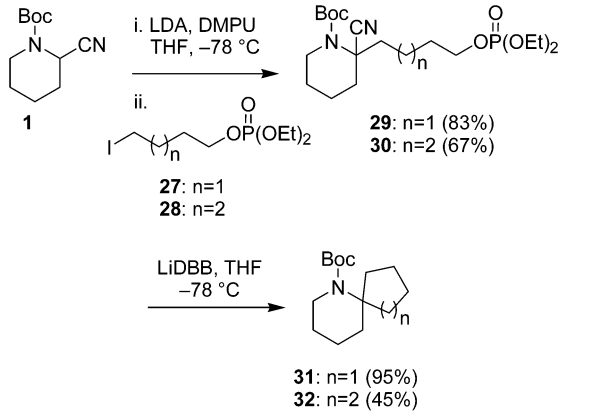
(21) TMS−Cl was used as an additive in each case. For the beneficial effect of TMS−Cl in cuprate 1,4-additions, see: (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015−6018. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019−6022.

(22) For a review of other applications of α-aminoorganocuprate chemistry, see: Dieter, R. K. Heteroatomcuprates and α-Heteroatomalkylcuprates in Organic Synthesis. In *Modern Organocopper Chemistry*; Krause, N., Ed.; John Wiley & Sons: New York, 2002; pp 114−122.

Scheme 3. Acyclic α-Aminonitrile **23** and Addition Products



Scheme 4. Synthesis of 2-Spiropiperidines



Finally, we have applied our reductive lithiation procedure toward the synthesis of simple 2-spiropiperidine ring systems similar to those found in naturally occurring alkaloids such as pinnaic acid[23] and histrionicotoxin.[24] Alkylation of aminonitrile **1** with iodides **27** or **28** produces cyclization precursors **29** and **30**, respectively, having pendant phosphate leaving groups (Scheme 4). Reductive lithiation and resultant cyclization produces the desired spiro[4.5] and [5.5] ring systems.[12,13,25]

In summary, we have developed a method for the generation of tertiary α-aminoorganolithium reagents from α-aminonitriles using LiDBB-mediated reductive lithiation. These intermediates react in good yield with carbonyl electrophiles or in spirocyclizations with tethered phosphate leaving groups. Transmetalation produces α-aminoorganocuprates that will react with alkyl halides and enones in 1,4-additions. Current efforts in our laboratory are focused on directing this chemistry toward enantio- and diastereoselective processes, with a particular interest in the synthesis of the spirocyclic cores of 2-spiropiperidine alkaloids.

Acknowledgment. This work was supported in part by the National Institutes of Health (GM-65338). S.A.W. acknowledges Amgen for a predoctoral fellowship. We are grateful to Drs. John Greaves and John Mudd for mass spectral analyses and Dr. Joe Ziller for determining the crystal structure of compound **21**.

Supporting Information Available: Preparation and characterization of the described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049039P

(23) Chou, T.; Kuramoto, M.; Otani, Y.; Skiano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871−3874.

(24) 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.

(25) For similar reductive cyclizations, see: Rychnovsky, S. D.; Takaoka, L. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 818−820.