

Generation and Utility of Tertiary  
 $\alpha$ -Aminoorganolithium Reagents

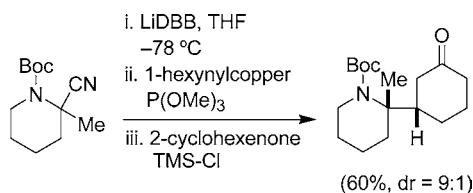
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## ABSTRACT



A general approach to tertiary  $\alpha$ -aminoorganolithium reagents by reductive lithiation of  $\alpha$ -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  $\alpha$ -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  $\alpha$ -aminoorgano-lithium reagents,<sup>1</sup> the use of these intermediates in synthesis has been extensively explored.<sup>2</sup> Particular focus has been given to the development of enantioselective processes that take advantage of the high configurational stability associated with these species.<sup>3</sup> Frequently utilized methods for the preparation of primary and secondary  $\alpha$ -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  $\alpha$ -aminoorganolithiums has not been well demonstrated. To the best of our knowledge, no examples of tin–lithium exchange to generate a tertiary  $\alpha$ -aminoorganolithium have been reported and deprotonation does not appear to be a general strategy.<sup>4–6</sup>

(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.  $\alpha$ -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.

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

(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.

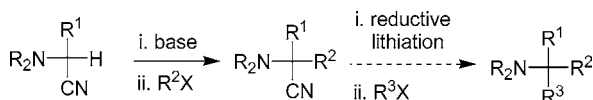
(6) Seebach has used the *N*-nitroso group to facilitate lithiation at a tertiary position; however, the potential carcinogenicity of *N*-nitrosoamines is likely responsible for lack of further development of this method. See: (a) Seebach, D.; Enders, D. *Angew. Chem., Int. Ed.* **1972**, *11*, 1101–1102.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

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

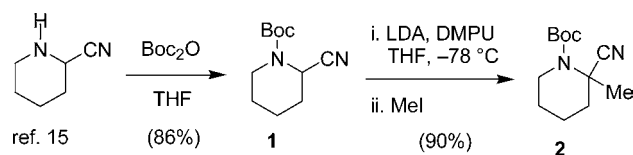


**Figure 1.** Polysubstituted Amines from  $\alpha$ -Aminonitriles.

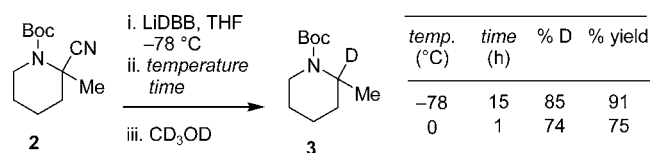
Importantly, the compatibility of these reactive intermediates with various common electrophiles would need to be addressed. Herein, we present initial results of our studies.

As a precursor for the bulk of our studies, we focused on  $\alpha$ -aminonitrile **2**, synthesized in two steps from 2-cyanopiperidine<sup>15</sup> (Scheme 1). This compound undergoes rapid

**Scheme 1.** Synthesis of  $\alpha$ -Aminonitrile **2**



reductive lithiation with LiDBB in THF at  $-78\text{ }^{\circ}\text{C}$  to produce solutions of the desired lithiated piperidines,<sup>16,17</sup> which show good stability over a useful range of temperatures as demonstrated by deuterium quenching experiments (Figure 2).



**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  $\alpha$ -protons, react efficiently with the organolithium reagent derived from  $\alpha$ -aminonitrile

(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  $\alpha$ -amino systems: Guijarro, D.; Yus, M. *Tetrahedron* **1994**, *50*, 3447–3452.

**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.<sup>18</sup> 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  $\alpha$ -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.<sup>19</sup> Meyers has found that transmetalation of an  $\alpha$ -aminoorganolithium to the corresponding cuprate was effective in raising the yield of desired addition products by limiting SET.<sup>19a,b</sup> In a modification of this procedure, we have observed significantly increased yields by performing the reductive lithiation and then adding a solution of  $\text{P(OMe)}_3$ -solubilized 1-hexynyl-copper<sup>20</sup> in THF prior to addition of an alkyl halide electrophile (Table 2).

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

(12) The following reference contains a cyclization that may proceed through a tertiary  $\alpha$ -aminoorganolithium reagent generated by LiDBB-mediated reductive lithiation of an  $\alpha$ -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  $\alpha$ -aminoorganolithium reagents by reductive metalation of  $\alpha$ -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  $\alpha$ -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  $\alpha$ -aminonitrile **2** and 1 crystal of 1,10-phenanthroline in 5.0 mL of THF was cooled to  $-78\text{ }^{\circ}\text{C}$  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  $\alpha$ -aminonitrile. The solution of  $\alpha$ -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"  $\alpha$ -aminoorganolithiums. We are also studying the use of the reductive lithiation procedure to generate the related "nonstabilized" (*N*-alkyl)  $\alpha$ -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*-Butylformamidinium-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.

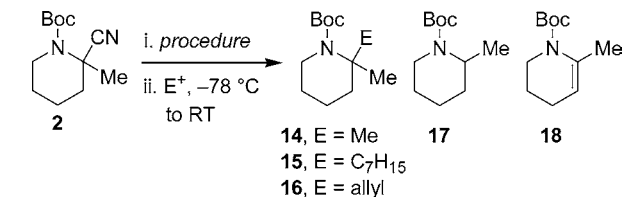
(20) Corey developed the use of alkynes as nontransferable ligands for cuprate chemistry: Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210–7211.

**Table 1.** Reductive Lithiation/Electrophilic Addition of Carbonyl Compounds

entry	E <sup>+</sup>	product <sup>a</sup>	yield (%)	dr <sup>b</sup>
1	CO <sub>2</sub> (g)		87	—
2	ClCO <sub>2</sub> Me		79	—
3	EtCHO		75	4.5:1
4	<i>i</i> -PrCHO		74	3.7:1
5	<i>t</i> -BuCHO		59	— <sup>c</sup>
6	PhCHO		82	1.5:1
7	MeC(O)Me		68	—
8	PhC(O)Me		61	3.3:1
9	CH <sub>2</sub> =CHC(O)Me		65	1.5:1
10	2-cyclohexenone		84	2.2:1

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

**Table 2.** Addition of Alkyl Halides to  $\alpha$ -Aminoorganolithium and Cuprate Nucleophiles



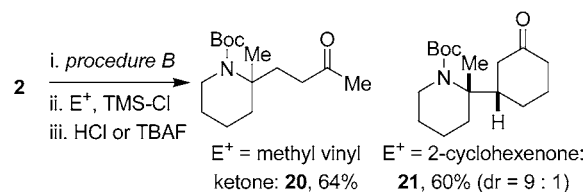
procedure A: LiDBB, THF, -78 °C, 5 min.  
procedure B: LiDBB, THF, -78 °C, 5 min.;  
1-hexynylcopper, P(OMe)<sub>3</sub>,  
-78 °C, 30 min.

entry	E <sup>+</sup>	product	yield (%)	
			via organolithium	via organocuprate
1	MeI	E = Me <b>14</b>	13	52
2	C <sub>7</sub> H <sub>15</sub> I	E = C <sub>7</sub> H <sub>15</sub> <b>15</b>	a	51
3	allylBr	E = allyl <b>16</b>	29	60

<sup>a</sup> 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).<sup>21</sup> 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  $\alpha$ -aminoorganocuprate reagents.<sup>22</sup>

**Scheme 2.** 1,4-Addition Products

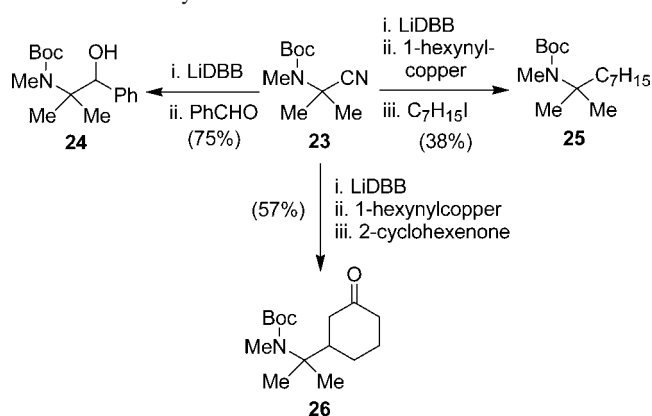


We have also extended this methodology to acyclic  $\alpha$ -aminonitrile **23** (Scheme 3). Applying the procedures used for **2** afforded benzaldehyde addition product **24** in 75% yield via the corresponding  $\alpha$ -aminoorganolithium reagent. The transmetalation protocol was also successful for aminonitrile **23**, providing products **25** and **26** in 38 and 57% yields by addition of *n*-iodoheptane or 2-cyclohexenone, respectively, to the  $\alpha$ -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  $\alpha$ -aminoorganocuprate chemistry, see: Dieter, R. K. *Heteroatomcuprates and  $\alpha$ -Heteroatomalkylcuprates in Organic Synthesis*. In *Modern Organocopper Chemistry*; Krause, N., Ed.; John Wiley & Sons: New York, 2002; pp 114–122.

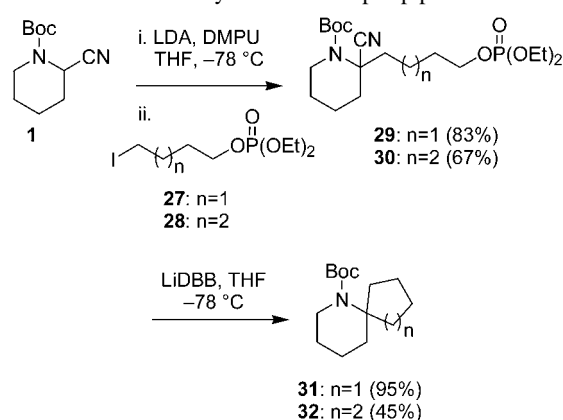
**Scheme 3.** Acyclic  $\alpha$ -Aminonitrile **23** and Addition Products



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<sup>23</sup> and histrionicotoxin.<sup>24</sup> 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.<sup>12,13,25</sup>

In summary, we have developed a method for the generation of tertiary  $\alpha$ -aminoorganolithium reagents from  $\alpha$ -aminonitriles using LiDBB-mediated reductive lithiation. These intermediates react in good yield with carbonyl

**Scheme 4.** Synthesis of 2-Spiropiperidines



electrophiles or in spirocyclizations with tethered phosphate leaving groups. Transmetalation produces  $\alpha$ -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.

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**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>.

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(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.