Application of Baldwin's Rules for the Preparation of Stable, β-Leaving Group-Bearing Organolithium Compounds

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A great deal of research has been devoted to the development of highly functionalized organometallic reagents.[1] Despite this interest, polar organometallic compounds possessing a leaving group (RO-, R_2N-, halogen) β to the anionic center remain notoriously elusive, due to their tendency to undergo elimination reactions to give alkenes.[2] Thus, *C*-lithioaziridines (**1**)[3] and α-acyloxy-β-aminoalkyl-lithiums (**2**, **3**)[4] are the only stable examples known of the potentially useful β-amino-alkyl-lithium reagents. The factors that prevent these β-amino-substituted lithiated species from undergoing elimination reactions have not been definitely established, but lithioaziridines **1** (and the analogous lithiooxiranes)[3b] may owe their stability to their cyclic nature, since electrocyclic ring-opening pathways should be inhibited by an enforced *syn* arrangement of the C−Li bond and the lone pair of the heteroatom,[3d] while the stability of **2** and **3** may arise from their dipole-stabilized nature.[4d]

In this communication we present our studies on the preparation and synthetic applications of the cyclic α-alkoxy-β-aminoalkyl-lithium compounds **4**, **5** (Figure 1). These species are of great interest from a mechanistic point of view, as well as for their great potential in organic synthesis.

We hypothesized that the relative stability of cyclic, β-functionalized organolithium compounds such as **4** and **5** could be predicted by using the principle of microscopic reversibility along with Baldwin's rules,[5] since their β-eliminative decompositions are in fact the reverse of *n-endo*-trig cyclizations.[6] If this were the case, the stability of these species would decrease with increasing ring size.[7]

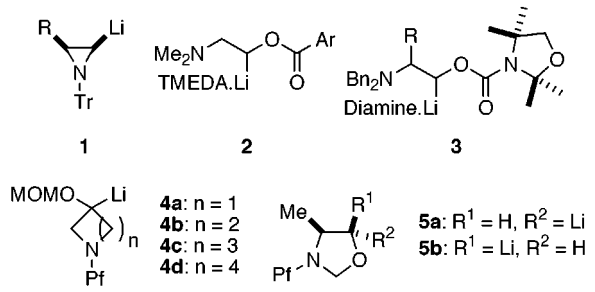
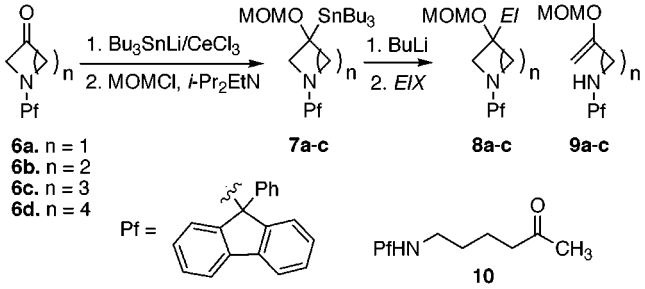


Figure 1.

Scheme 1



Entry	n	*ElX*	*El*	Solvent/T (°C)	Ratio 8/9	Yield
1	1	MeOD	D	THF/-78	100/0	95%[a]
2	1	PhCHO	PhCH(OH)	THF/-78	100/0	96%
3	1	MeOD	D	**DME/-50**	**100/0**	97%[a]
4	2	MeOH	H	THF/-78	17/1	95%[a]
5	2	MeOH	H	**DME/-50**	**2.4/1**	93%
6	3	MeOH	H	THF/-78	15/1	97%[b]
7	3	MeOH	H	**DME/-50**	**1/2.7**	94%

[a] **8** %D > 95%. [b] **8c** %D = 60%

To test this hypothesis we first prepared α-alkoxy-β-amino-stannanes **7**, as precursors of the corresponding organolithium reagents **4**. Cyclic β-aminoketones **6a**−**c** ($n = 1$ to 3) were reacted with $Bu_3SnLi/CeCl_3$ to provide the corresponding stannyl-alcohols,[8] which were straightforwardly protected (MOMCl/DIPEA) to provide the desired aminostannyl-acetals **7a**−**c** in good overall yields (50−60%). Reaction of the azepinone **6d** with the tin nucleophile gave only low yields of the desired alcohol, the main product being the *acyclic* ketone **10**.

Treatment of stannanes **7a**−**c** with 115 mol % of *n*-butyllithium in THF at −78 °C (for 2−80 min) resulted in tin−lithium exchange,[9] as evidenced by quenching experiments with the electrophiles shown in Scheme 1. The cyclic amines **8a**−**c**, which arise from the reaction of the organolithium intermediates with the corresponding electrophiles (entries 1, 2, 4, and 6), were isolated as the exclusive or very major reaction products. Only minute amounts of enol ethers **9b**,**c**, formed via β-elimination of the organolithium intermediates, were detected in the crude products of the reactions of the five- and six-membered ring stannanes **7b**,**c**. Azetidine **7a** afforded only substitution products (**8a**). The outcome of these experiments clearly showed that the cyclic α-alkoxy-β-aminoalkyl-lithium compounds **4a**−**c** are stable at −78 °C for extended periods.[10]

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(6) An analogous argument has already been put forward to explain the stability of β-alkoxy-substituted, four- and five-membered-ring cyclic enolates: Seebach, D.; Hungerbühler, E. *Modern Synthetic Methods*; Otto Salle Verlag: Frankfurt a. Main, 1980; Vol 2, p 91.

(7) 4- and 5-*endo*-trig cyclizations are disallowed, while 6- and 7-*endo*-trig processes are allowed. See ref 5c.

(8) In the absence of Ce(III) a large proportion of starting ketone was recovered after the reaction, presumably due to an enolization process. For a preparation of tributylstannyllithium, see ref 9c.

(9) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842 (b) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (c) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

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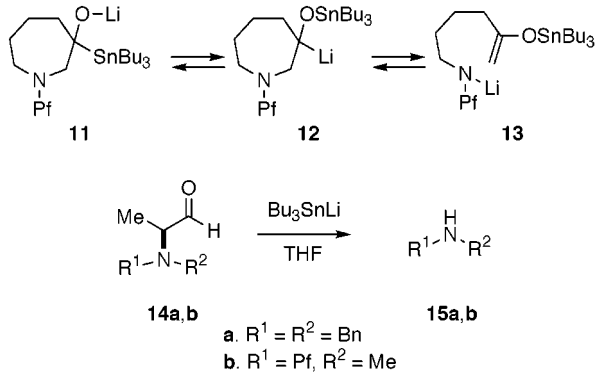
Scheme 2

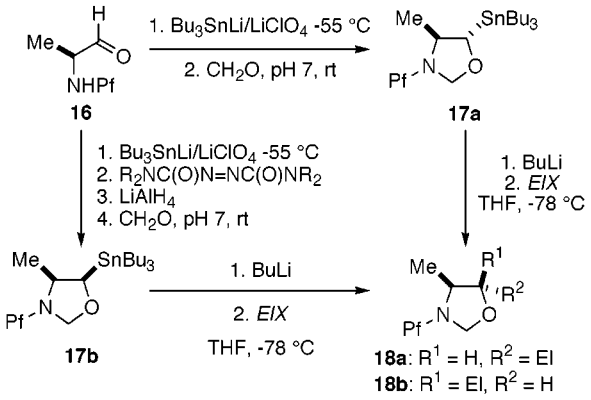


These results show the synthetic potential of this kind of *β*-amino-organolithium reagents, but they are somewhat surprising from the mechanistic standpoint, since Baldwin's rules predict that the decomposition of lithiopiperidine **4c** should be a facile process, contrary to its observed stability in THF at −78 °C.[7] The confirmation that Baldwin's rules correctly predict the *relative* stabilities of **4a**−**c** was obtained when the tin−lithium exchange experiments on **7a**−**c** were carried out in DME at −50 °C for 80 min (entries 3, 5, and 7). Lithioazetidine **4a** was found to be stable toward elimination under these conditions, but lithiopirrolidine **4b** and lithiopiperidine **4c** afforded noticeable amounts of elimination products **9b**,**c**, the six-membered ring compound undergoing elimination at a higher rate than the pyrrolidine analogue.

This trend of decreasing stability of **4a**−**c** with increasing ring size might explain first, the well-known stability of lithioaziridines **1** and the analogous lithioepoxides,[3] and second, why acyclic ketone **10** was the main product of the attempted stannylation of azepinone **6d**. The intermediate stannyl-alkoxide **11** could undergo the tin counterpart of a Brook rearrangement[11] to afford *C-lithio* azepine **12** which should rapidly undergo elimination to provide a tin enol ether that, on work up, should give rise to ketone **10**. We have observed that *N*-disubstituted *acyclic* α-amino aldehydes **14a**,**b** experience the same process when reacted with anionic tin nucleophiles (Scheme 2).

Once we had established the validity of our hypothesis, we studied its extension to the preparation of other types of cyclic *β*-amino-organolithium reagents that could show even greater synthetic potential than **4a**−**c**. We chose lithio-oxazolidines **5** as targets, as their reactions with electrophiles should give rise to a wide variety of synthetically and pharmacologically interesting *β*-amino alcohols. Scheme 3 summarizes the synthesis of **5a**,**b** and the results of their reactions with several representative electrophiles. Stannyl-oxazolidines **17a**,**b**, precursors of **5a**,**b**, were obtained from *N*-Pf-alaninal **16**.[12] Addition of tributylstannyl-lithium to **16** proceeded stereoselectively to give one sensitive stannyl-alcohol which was immediately cyclized to give oxazolidine **17a** (69% overall yield). NOE experiments performed on **17a** allowed us to establish its stereochemistry and showed that the addition to the aldehyde group of **16** had taken place under chelation control.

Scheme 3



Entry	St. Mat.	*EIX*	*El*	Yield
1	**17a**	D_2O	D	99%[a]
2	**17a**	PhCHO	PhCH(OH)	80%[b]
3	**17a**	*i*-BuCHO	*i*-BuCH(OH)	80%[c]
4	**17a**	Me_2CO	$Me_2C(OH)$	88%
5	**17a**	DMF	CHO	88%
6	**17a**	MeI	Me	70%
7	**17a**	DMA[d]	MeCO	57%
8	**17b**	D_2O	D	99%[a]
9	**17b**	Me_2CO	$Me_2C(OH)$	55%

[a] **17** %D > 95%. [b] dr = 2.6:1. [c] dr = 2.3:1. [d] DMA = Me–C(=O)–NMe2

The epimeric oxazolidine **17b** was obtained by oxidation of the alkoxide intermediate of the tin−lithium addition to **16** with 1,1′-(azodicarbonyl)dipiperazine (0 °C, 50% yield),[13] followed by reduction of the resulting stannyl-ketone with $LiAlH_4$. The mixture of alcohols obtained was cyclized to provide a mixture of **17a** and **17b** (2:1 ratio, 65% overall yield) which was resolved by HPLC.

Treatment of stannyl-oxazolidines **17a**,**b** with 115 mol % of BuLi (THF, −78 °C, 2−15 min) followed by addition of a variety of electrophiles (Scheme 3) afforded clean addition/substitution reactions to yield oxazolidines **18a**,**b**; no traces of byproducts coming from *β*-elimination reactions at the stage of the organolithium intermediates were detected.[14] Analysis of the products of the reactions of **5a**,**b** with D_2O and acetone (Scheme 3, entries 1, 4, 8, and 9) showed that the tin−lithium exchanges and the addition to the electrophiles had occurred with retention of configuration.[15]

We believe that the methodology presented herein can have wide application for the development of synthetically useful, highly functionalized organolithium reagents, previously inaccessible by other routes.

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(10) This kind of *tertiary* *β*-amino-organolithium compound cannot be prepared by deprotonation of the corresponding carbamates, since only *tertiary* hydrogens that are activated by an extra carbanion-stabilizing group can be abstracted using this methodology: (a) Derwing, C.; Hoppe, D. *Synthesis* **1996**, 149. (b) Paetow, M.; Kotthaus, M.; Grehl, M.; Fröhlich, R.; Hoppe, D. *Synlett* **1994**, 1034. (c) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097. (d) Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394. (e) Hoppe, D.; Carstens, A.; Krämer, T. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1424.

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(13) Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, *113*, 647 and references therein.

(14) Pf-NH_2 would be formed. The rest of the material was composed exclusively of protonated oxazolidine **18**, $R^1 = R^2 = H$.

(15) For removal of protecting groups in **18a**,**b** see: Fernández-Megía, E.; Paz, M. M.; Sardina, F. J. *J. Org. Chem.* **1994**, *59*, 7643.