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An α-Metalloamine Synthetic Equivalent from N-Boc-Allylamine

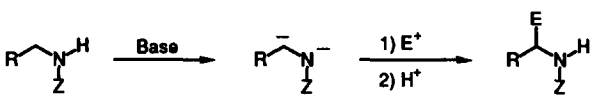
James E. Resek and Peter Beak*

Department of Chemistry, Roger Adams Laboratory
University of Illinois, Urbana-Champaign, Urbana, IL 61801 USA

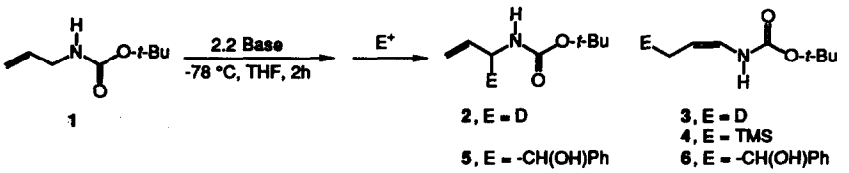
Abstract: Treatment of N-Boc-allylamine (**1**) with 2 equivalents of *sec*-butyllithium followed by 1 equivalent of $ZnCl_2$ provides a reagent that reacts readily with aldehydes and ketones at the α-position to form N-Boc-2-amino-3-buten-1-ol derivatives (**7**).

An important method of amine synthesis involves α-lithioamine synthetic equivalents.[1] The general strategy involves addition of an activating group to nitrogen of a given amine, followed by α-lithiation, trapping and removal of the activating group to give the α-substituted amine. This methodology has been used successfully for the elaboration of many secondary amines, and a variety of activating groups (Z) have been reported.[1] Scheme 1 illustrates an analogous, yet largely undeveloped strategy for the substitution of activated primary amines involving a dianionic derivative of the amine.[2] Greene and coworkers have recently reported successful use of this approach for substitution of N-Boc-benzylamine, and dilithiations of N-Boc-methallylamine and of N-allylcarboxamides have been reported by Kempf and by Tischler and Tischler.[3-5] We wish to report the application of the strategy described by Scheme 1 to N-Boc-allylamine (**1**).[6]

Scheme 1



Treatment of **1** with 2.2 equivalents of *sec*-BuLi or *sec*-BuLi/TMEDA results in formation of a dianion, as evidenced by the incorporation of deuterium in the allylic moiety upon addition of MeOD. The products **2** and **3** are formed in 80% combined yield for *sec*-BuLi and 94% yield for *sec*-BuLi/TMEDA. In both cases reaction of the electrophile is favored at the γ-position, with **2**/**3** formed in a 1/10 ratio. Reaction of the same formal dianion from *sec*-BuLi/TMEDA with chlorotrimethylsilane produces the Boc protected enamine **4** as the only substitution product in 64% yield.[5,7] Use of benzaldehyde as an electrophile provides products **5** and **6** in a 1/1 ratio in 30% overall yield. The carbon-carbon double bonds in **3** and **4** are assigned the *Z* configuration based upon the coupling constant of the adjacent olefinic protons (J = 9 Hz).



Since the regioselectivity of this reaction is unsuitable for elaboration of allylamine in the α-position, we investigated the effect of a change in the counterion on the α/γ selectivity.[7,8] Treatment of the lithium dianion of **1** formed from *sec*-BuLi with 1.1 equivalent of $ZnCl_2$ provides a reagent that reacts readily with aldehydes and ketones in the α-position to provide the N-Boc-2-amino-3-buten-1-ol derivatives **7** in 56-82% yield. Several examples of this reaction are displayed in Table 1. The reaction is successful for a wide variety of aldehydes and ketones, including those that are easily enolized. The diastereoselectivity of the reaction improves modestly with increasing steric bulk of the aldehyde (entries 4-7), yet benzaldehyde provides the best selectivity (entry 8). The reagent reacts rapidly with carbonyl compounds at -98 °C and -120 °C (entries 9-10), although solubility problems become significant at these temperatures.

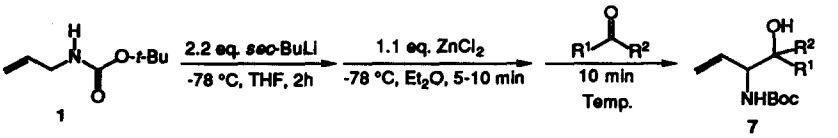
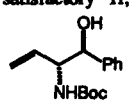


Table 1. N-Boc-2-amino-3-buten-1-ols 7 from the α-Substitution of N-Boc-allylamine 1.[a]

Entry	R^1	R^2	Temp.	Yield of 7	Diastereoselectivity
1	$-(CH_2)_5-$		-78 °C	82%	
2	$-(CH_2)_4-$		"	60%	
3	Me	Me	"	75%	
4	*t*-Bu	H	"	60%	72:28
5	*i*-Pr	H	"	70%	70:30
6	Et	H	"	74%	60:40
7	Me	H	"	56%	60:40
8	Ph	H	"	70%	85:15[b]
9	Ph	H	-98 °C	77%	94:6[b]
10	Ph	H	-120 °C	70%	97:3[b]

[a] All products have satisfactory ^1H, ^{13}C, and mass spectra. Yields are based on the isolated mass of pure **7**.

[b] The *anti* isomer,  is the major product.

The relative stereochemistry of the two diastereomeric products has been assigned for 2-(N-Boc-amino)-1-phenyl-3-buten-1-ol (entries 8-10). The two diastereomers were separated, cyclized to the corresponding *cis* and *trans* oxazolidinones by treatment with NaH in THF, and the NOEs between the ring protons were measured. This analysis allowed assignment of relative configurations at these centers, and indicates that the *anti* isomer is formed preferentially in this reaction.

In summary, the sequence described provides a simple route to 2-amino-3-buten-1-ol derivatives **7** in good yields and with experimental convenience from N-Boc-allylamine **1**.[9] Further work to elaborate **7** and define the reaction pathway is in progress.

Representative Experimental Procedure

1-(N-Boc-1-aminoallyl)cyclohexanol. N-Boc-allylamine (103 mg, 0.66 mmol), in a 0.5 M THF solution (1.3 mL) is cooled to -78 °C and treated with *sec*-butyllithium[10] (1.31 M in cyclohexane, 1.10 mL, 1.44 mmol, 2.2 eq). The resulting yellow solution is stirred at -78 °C for 2 h, after which $ZnCl_2$[11] (1.1 M in Et_2O, 0.64 mL, 0.72 mmol, 1.1 eq) is added, and the solution is stirred for 5-10 min.[12] To the colorless solution is added cyclohexanone (141 mg, 1.44 mmol, 0.15 mL, 2.2 eq), and the mixture is stirred at -78 °C for 10 min. The reaction is quenched at -78 °C with acetic acid (0.5 mL), the mixture is poured into 0.5 M H_3PO_4 (5 mL), and extracted with ether (5 x 5 mL). The combined ether extracts are washed with sat. $NaHCO_3$ (25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (15% EtOAc/hexane) followed by Kugelrohr distillation (1 mm Hg, 160 °C) provides the product (138 mg, 82%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 9H, tBu), 1.2-1.6 (m, 10H, cHex ring), 1.81 (br, 1H, OH), 4.03 (br, 1H, NH), 5.03 (m, 1H, allylic H), 5.17-5.24 (m, 2H, terminal vinyl), 5.83 (m, 1H, internal vinyl). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 21.8, 25.5, 28.3, 34.4, 35.1, 60.0, 73.0, 79.2, 117.2, 134.6, 155.8. GC/MS: 199(1, M^+-C_4H_8), 182(2), 157(3), 101(63), 99(100), 81(47), 57(83). Anal. Calc'd for $C_{14}H_{25}NO_3$: C 65.85; H 9.87; N 5.49. Found: C 65.86; H 9.93; N 5.56.

Acknowledgment. We are grateful to the National Institutes of Health and the National Science Foundation for support of this work.

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(12) Occasionally at this point a viscous precipitate forms that prevents stirring. If this occurs, the flask should be removed from the -78 °C bath for *ca.* 15-20 s and held over a stir plate such that stirring is restored and a color change from yellow to colorless is observed. The flask is then replaced in the -78 °C bath. The duration of the warming period must be minimized because the dianionic species is susceptible to decomposition at elevated temperatures.

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