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Generation of Aziridinyllithiums from Sulfinylaziridines by the Ligand Exchange Reaction of Sulfoxides with *tert*-Butyllithium: Their Properties and An Application to Asymmetric Synthesis of α-Dialkylamino Acid Ester

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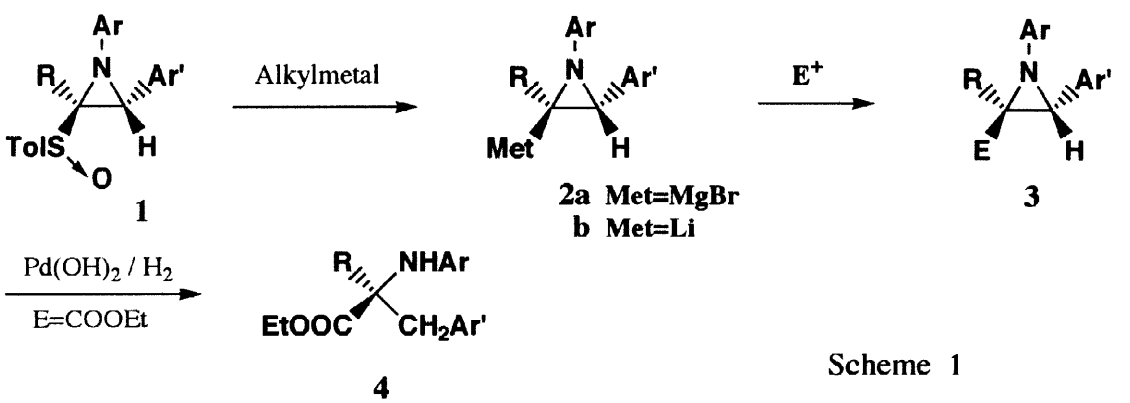
Abstract: Aziridinyllithiums were generated from sulfinylaziridines by the ligand exchange reaction of sulfoxides with *tert*-butyllithium. The aziridinyllithiums were found to be stable in THF at below -30 °C and reactive with several electrophiles such as carbonyl compounds. Synthesis of an optically active α-dialkylamino acid ester was realized via the aziridinyllithium starting from optically active chloromethyl *p*-tolyl sulfoxide.

Aziridines are widely recognized as being extremely versatile synthetic intermediates.[1] Attributable to ring strain, the reaction of aziridines with a variety of nucleophiles, including carbon nucleophiles, leads to ring opening with carbon-heteroatom or carbon-carbon bond-formation. In these reactions aziridines act as electrophiles. In contrast to this, only a very limited number of reactions in which aziridines act as nucleophiles have been reported to date.[2, 3]

We previously reported a method for generation of aziridine Grignard reagents **2a** from sulfinylaziridines **1** with EtMgBr[4] via the ligand exchange reaction of sulfoxides.[5] In continuation of our studies on the generation of aziridinyl anions and development of this chemistry to new synthetic methods, we report herein a new procedure for generation of aziridinyllithiums **2b** and some studies on their properties and reactivity. We also describe an application of this method to a synthesis of optically active α-dialkylamino acid ester **4** (Scheme 1).



Scheme 1

A THF solution of sulfinylaziridine **5**, which was synthesized from 1-chloroethyl *p*-tolyl sulfoxide and benzalaniline in high yield,[4b] was treated with 1.8 equivalents of *t*-BuLi at -78 °C. Compared to the reaction

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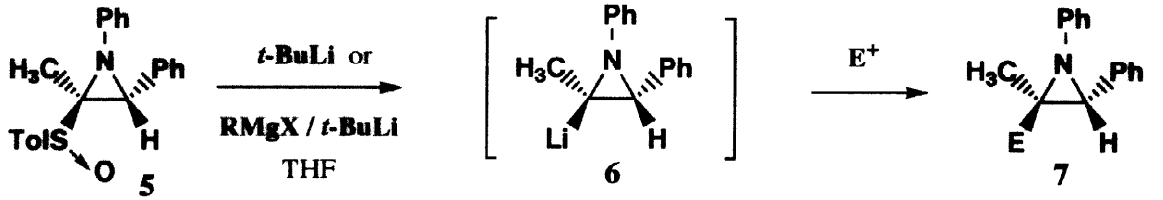
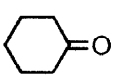
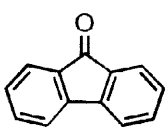
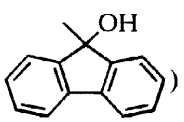
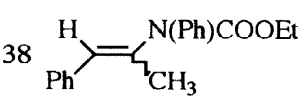
Table 1. Generation of Aziridinyllithium **6** from **5** and Its Reaction with Electrophiles



Entry	Alkylmetal (equiv.)	Temp (°C)	Electrophile	7 Yield/%[a]
1	*t*-BuLi (1.8)	-78	CD_3OD	99 (E=D; 67%[b])
2	*t*-BuLi (2)[c]	-78	CD_3OD	55 (E=D; 65%[b])
3	*t*-BuMgCl (1.5) / *t*-BuLi (1.5)	-70	CD_3OD	96 (E=D; 92%[b])
4	MeMgBr (1) / *t*-BuLi (1.5)	-70	CD_3OD	94 (E=D; 90%[b])
5	MeMgBr (1) / *t*-BuLi (1.5)	-70 to -30	CD_3OD	96 (E=D; 86%[b])
6	MeMgBr (1) / *t*-BuLi (1.5)	-70 to r. t.	CD_3OD	90 (E=H)
7	*t*-BuLi (1.8)	-78	CH_3CH_2CHO	70 (E=CH(OH)Et; L:P= 30:40[d])
8	*t*-BuMgCl (1.5) / *t*-BuLi (1.5)	-70	PhCHO	33 (E=CH(OH)Ph; L:P=18:15[d])
9	MeMgBr (1) / *t*-BuLi (1.2)	-100	PhCHO	70 (E=CH(OH)Ph; L:P=37:33[d])
10	MeMgBr (1) / *t*-BuLi (1.5)	-100	CH_3COCH_3	41 (E=C(OH)$(CH_3)_2$)
11	MeMgBr (1) / *t*-BuLi (1.5)	-100		38 (E= )
12	MeMgBr (1) / *t*-BuLi (2)	-68		35 (E= )
13	MeMgBr (1) / *t*-BuLi (1.5)	-70	ClCOOEt	47 (E=COOEt) 38 
14	MeMgBr (2) / *t*-BuLi (2)	-100	ClCOOEt	75 (E=COOEt)
15	MeMgBr (1) / *t*-BuLi (1.5)	-70 to -30	$(EtO)_2POCl$	43 (E=$PO(OEt)_2$)
16	MeMgBr (1) / *t*-BuLi (2)	-78 to -30	CH_3I / DMPU[e]	0[f]

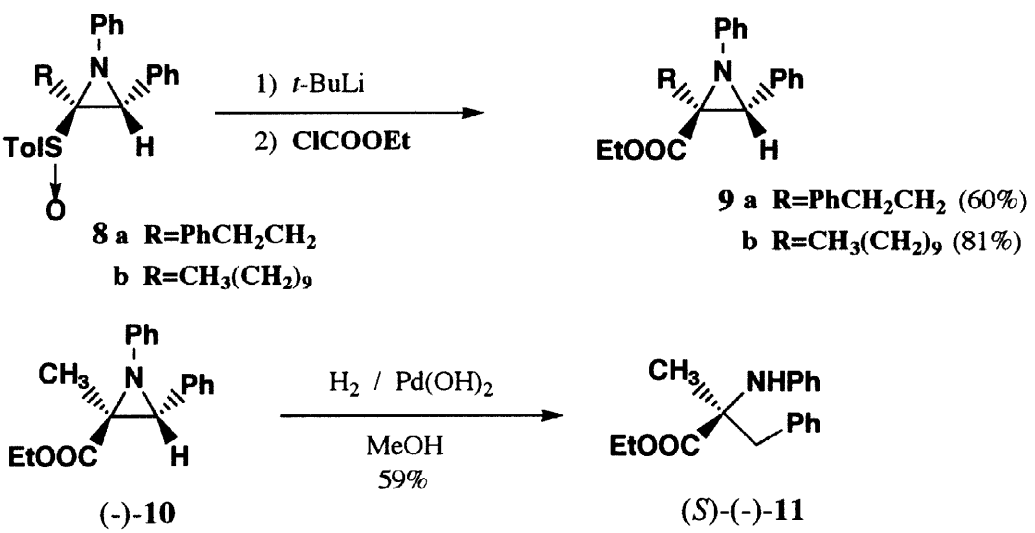
a) Isolated yield after silica gel column chromatography. b) The deuterium incorporation was measured from ^1H NMR. c) A solution of **5** in THF was added to a solution of *t*-BuLi (inverse addition). d) The letters L and P indicate the less polar isomer and more polar isomer on silica gel TLC, respectively. e) DMPU: *N,N*-dimethylpropyleneurea. f) This reaction gave **7** (E = H) in 95% yield.

with EtMgBr reported previously,[4b] this reaction was found to be very rapid, and after 1 min the reaction was quenched with CD_3OD to give desulfinylated aziridine in quantitative yield (Table 1, entry 1). Though special attention was paid to remove the proton source, the rate of deuterium incorporation was only less than 67%. Inverse addition (entry 2), which was very effective in the reaction with sulfinyloxiranes,[6] did not work in this case. It was considered that a trace of moisture in THF was the proton source.[7]

In our previous study we found that the sulfinylaziridine **1** did not react at all with *t*-BuMgCl and MeMgBr.[4] We tried to use these Grignard reagents for removing the moisture in THF. t-BuMgCl was added to a solution of **5** in THF at -70 °C and the reaction mixture was stirred for 10 min, then *t*-BuLi was added. After 1 min, the reaction was quenched with CD_3OD to afford **7** (E = D) in high yield with up to 92% D-content (entry 3). Entry 4 shows that MeMgBr works equally well. We usually use MeMgBr for this removal of the moisture in THF.

In order to know the properties of the aziridinyllithium generated by this method, the reaction mixture was gradually warmed to -30 °C and quenched with CD_3OD. The obtained product was deuterated aziridine (entry 5). This result shows that the aziridinyllithium **6** is stable at lower than -30 °C. Interestingly, the above-mentioned reaction was warmed to room temperature and quenched with CD_3OD to give desulfinylated aziridine **7**; however, no deuterium incorporation was observed (entry 6). This result implies that **6** is able to pick up a proton in the reaction medium, presumably from THF, at around room temperature.

Reactivity of the aziridinyllithium **6** with several electrophiles was investigated and the results are summarized in Table 1 (entries 7-16). Aldehydes reacted with **6** to give the adducts in 70% yield. Usually, lower reaction temperature gave better results (entries 8 and 9). The reaction with ketones gave also the adducts; however, the yields were about 40%. The reaction with ethyl chloroformate is interesting. The reaction at -70 °C gave the desired ester in 47% with a significant amount of ring-opened urethane (entry 13). The formation of the urethane was suppressed when the reaction was carried out at -100 °C (entry 14). Diethyl chlorophosphate reacted with **6** at about -40 °C; however, the yield was moderate (entry 15). Methylation of **6** was investigated under several conditions but it was not successful (entry 16).



Scheme 2

The aziridinyllithium could be generated from other sulfinylaziridines **8a** and **8b** in the same way as described above (Scheme 2). The generated aziridinyllithiums were treated with ethyl chloroformate at -90 °C to give **9a** and **9b**, respectively, in good yields.

In order to extend this reaction in organic synthesis, we investigated regioselective cleavage of the carbon-nitrogen bond to obtain α-dialkylamino acid derivatives from the aziridine having an ethoxycarbonyl group. The aziridine **10** (entry 14 in Table 1) was reduced under several conditions[8] and catalytic hydrogenation with $Pd(OH)_2$ in MeOH was found to be effective,[9] giving α-benzyl α-methyl α-amino acid ethylester **11** in moderate yield.

Further, the presented method was extended to an asymmetric synthesis of optically active **11**. Optically pure (-)-**5**, which was synthesized from (-)-chloromethyl *p*-tolyl sulfoxide,[4b] was treated with MeMgBr-*t*-BuLi followed by ethyl chloroformate to afford optically active **10** ($[\alpha]_D$ -94.3° (C = 0.2, acetone)). The catalytic hydrogenation of optically active **10** with $Pd(OH)_2$ in MeOH afforded optically active (*S*)-(-)-**11** (mp 93-94 °C; $[\alpha]_D$ -34.2° (C = 0.2, acetone)).[10]

We are continuing to study the scope and limitation of this chemistry.

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10. HPLC analysis of racemic **11** using a chiral column (Daisel Chiralpak AD, 10% 2-isopropanol in hexane, flow rate 0.5 ml/min) showed clear separation of both enantiomers. The enantiomeric purity of (-)-**11** was found to be over 99%.