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Anionic Reactions of *N*-(*trans*-2,3-Diphenylaziridin-1-yl)imines and Their Use as 1,1-Dipoles in Anionic Cyclizations

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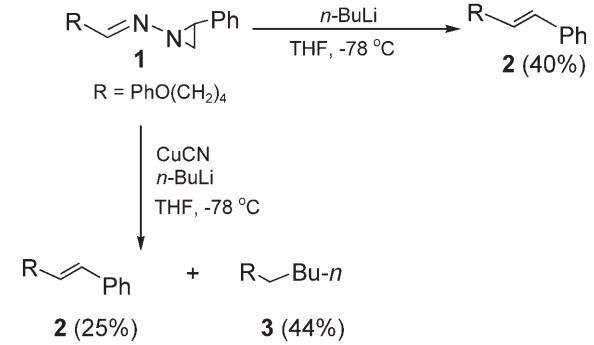
Abstract: Reaction of *N*-(*trans*-2,3-diphenylaziridin-1-yl)imines with alkyllithiums and organocuprates afforded the desired addition products after consecutive fragmentations along with liberation of stilbene and nitrogen gas, while the reaction of *N*-(2-phenylaziridin-1-yl)imines under similar conditions gave an anomalous by-product. Anionic cyclizations of *N*-(*trans*-2,3-diphenylaziridin-1-yl)imines using unactivated alkenes and alkynes as acceptors proceeded smoothly, yielding cyclized products in good yields.

Keywords: alkyllithiums; anionic cyclizations; aziridines; 1,1-dipoles; hydrazones; imines



Scheme 1. Anionic reactions of *N*-(2-phenylaziridin-1-yl)-imine **1**.

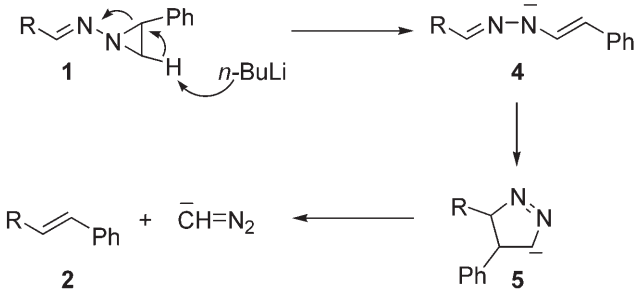


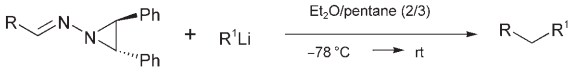
Figure 1. Possible mechanism for the formation of **2**.

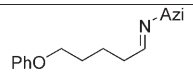
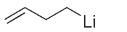
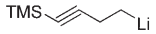
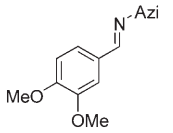
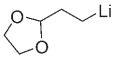
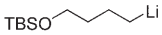
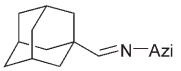
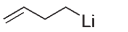
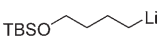
N-Aziridinylimines have found many useful synthetic applications as precursors of various reactive intermediates such as diazoalkanes, carbenes, and carbocations.[1] In addition, *N*-aziridinylimines have been utilized to generate geminal methylene radicals in radical cyclizations.[2]

We reported a novel anionic cyclization of *N*-aziridinylimines to provide an efficient route to carbocycles *via* a consecutive carbon-carbon bond formation approach.[3,4] It was known that *N*-(2-phenylaziridin-1-yl)-imines reacted with allyllithium, vinyllithium, allyl- and vinyl-Grignard reagents to give the addition products after liberation of styrene and nitrogen gas. However, we have found that the success of the reaction depended critically on the nature of the alkyllithiums. As shown in Scheme 1, treatment of *N*-(2-phenylaziridin-1-yl)-imine (**1**) with an alkyllithium like *n*-BuLi surprisingly resulted in the formation of alkene **2** in 40% yield together with several side products. There was no indication of the presence of the desired addition product **3**. The use of an organocuprate afforded a mixture of **2** and **3** in 25% and 44% yields, respectively. Although further studies are needed to clarify the mechanism for the formation of **2**, our assumption is depicted in Figure 1. It seems that *n*-BuLi might act as a base to provide intermediate **5** *via* intermediate **4**. Intermediate **5** might then undergo a retro-type anionic 1,3-dipolar cycloaddition reaction to provide the side product **2**. Previously, retro-1,3-anionic cycloadditions had been reported.[5]

To obviate the problem of the elimination by the alkyllithium, we have studied the possibility of using *N*-(*trans*-2,3-diphenylaziridin-1-yl)imines.[6] Treatment of **6** with *n*-BuLi in Et_2O/pentane at $-78\,^{\circ}C$ afforded a mixture of **7** and **8** in 52% and 15% yields, respectively. Apparently, **8** must be derived from the further addition of an intermediate carbanion onto **6**. As shown in Table 1, treatment of *N*-(*trans*-2,3-diphenylaziridin-1-yl)imines in Et_2O/pentane (2:3) with alkyllithiums[7] at $-78\,^{\circ}C$ for 1 h and the warm-up to room temperature for 0.5 h afforded the desired addition products. The reaction worked reasonably well with primary, secondary,

Table 1. Reaction of *N*-(*trans*-2,3-diphenylaziridin-1-yl)-imines with RLi.[a]



Entry	Substrate[b]	R¹Li	Isolated Yield [%]
1			70
2			69
3			67
4		*n*-BuLi	65
5		*s*-BuLi	60
6		*t*-BuLi	68
7			67
8			61
9			61
10		*n*BuLi	64
11			62
12			59

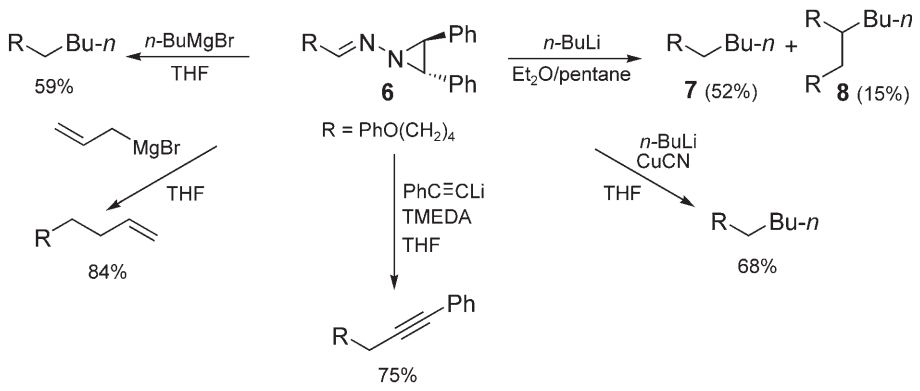
[a] *Reaction conditions:* alkyllithium (0.40 mmol) in Et_2O/pentane = 2/3 (4 mL), and *N*-(*trans*-2,3-diphenylaziridin-1-yl)imine (0.20 mmol) in Et_2O/pentane = 2/3 (2 mL) at −78 °C.

[b] Azi = *trans*-2,3-diphenylaziridin-1-yl.

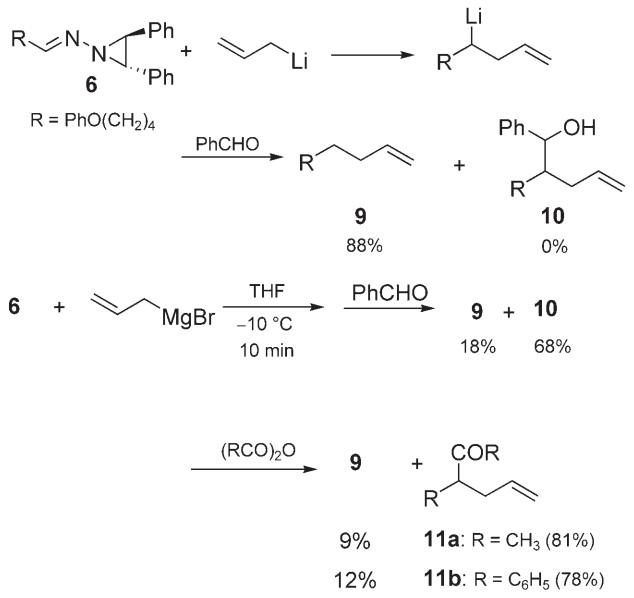
and tertiary alkyllithiums. It is noteworthy that alkyllithiums bearing functional groups such as an acetal and a *t*-butyldimethylsilyl ether group can be employed. Reactions with other organometallic reagents were also studied and the experimental results are summarized in Scheme 2. Organocuprates also worked equally well. Reaction of **6** with *n*-BuMgBr in THF at −20 °C for 1 h and at room temperature for an additional 7 h gave **7** in 59% yield, whereas *N*-(2-phenylaziridin-1-yl)imine (**1**) did not react with *n*-BuMgBr at room temperature. Furthermore, the reaction of **6** with lithium phenylacetylide was complete within 5 h at 0 °C but **1** required 5 h at 60 °C. Apparently, *N*-(*trans*-2,3-diphenylaziridin-1-yl)imine (**6**) turned out to be much more reactive than *N*-(2-phenylaziridin-1-yl)imine (**1**) towards organometallic reagents.

Our next interest was to use *N*-aziridinylimines as 1,1-dipoles by quenching a carbanion intermediate with electrophiles. Aldehyde arylsulfonylhydrazones have similar utilities to *N*-aziridinylimines in synthetic applications[8] but it was known that they failed to act as 1,1-dipoles, with the exception of one case.[9,10] Treatment of **6** with allyllithium in THF or in Et_2O at −78 °C for 2 h followed by quenching with benzaldehyde gave only the addition product **9** without giving any quenching product **10**. When we repeated the reaction in the presence of 2.2 equivs. of TMEDA or 10 equivs. of HMPA, the same results were observed without any quenching product. Similarly, the use of organocuprates was also unsuccessful. At present we do not know why carbanion intermediates do not react with electrophiles and where the proton comes from. However, our effort was partially successful with the allyl-Grignard reagent. After **6** had been treated with allylmagnesium bromide in THF at −10 °C for 10 min, and the reaction mixture was quenched with acetic anhydride, methyl ketone **11a** was isolated in 81% yield along with **9** (9%). When the reaction mixture was quenched with benzoic anhydride and benzaldehyde, **11b** and **10** were isolated in 78% and 68% yields, respectively, along with a small amount of **9** as shown in Scheme 3.

We have studied the possibility of anionic cyclization of the carbanion intermediate onto unactivated alkenes[11] and alkynes[12] as acceptors. As shown in Scheme 4, the addition of *n*-BuLi onto **12** should give carbanion intermediate **13** initially, which would cyclize to afford **14**. When **12** was treated with allyllithium (2.0 equivs.) and TMEDA (2.0 equivs.) in Et_2O/pentane (2:3) at 0 °C with warming to room temperature, **15b** was isolated in 73% yield. Similar results were obtained with *n*-butyllithium and 1-butenyllithium. Two features are noteworthy. First, *trans*-isomers were obtained ex-



Scheme 2. Anionic reactions of **6** with organometallic reagents.



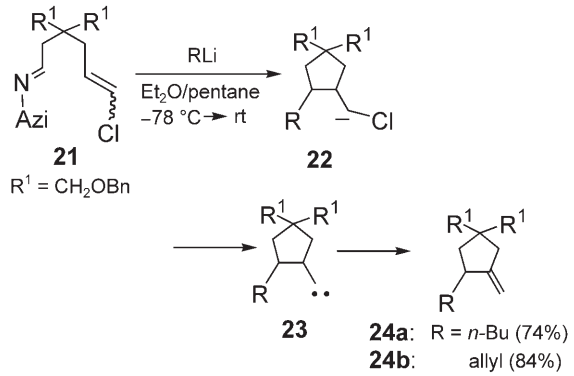
Scheme 3. Anionic reactions of **6** with allyllithium and allyl Grignard reagent followed by quenching with electrophiles.

clusively. A strong *trans* preference for the anionic cyclizations of 1-methyl-5-hexenyl and related systems was noted previously.[13] Second, our attempts to quench the resulting carbanion intermediate with electrophiles such as benzaldehyde and deuteromethanol were unsuccessful. However, the formation of carbanion intermediates seems to be evident. Treatment of **16** with *n*-BuLi in Et_2O/pentane (2:3) at $-78\,^{\circ}C$ and warming up to $-50\,^{\circ}C$ gave **18a** in 71% yield. Apparently, the methoxy group was eliminated from intermediate **17**. Furthermore, it is noteworthy that the reaction of **21** with allyllithium under similar conditions afforded **24b** in 84% yield. As shown in Scheme 5, apparently, intermediate **22b** underwent α-elimination to yield carbene intermediate **23**, from which a 1,2-H shift took place to produce the product **24b**.[14] Further studies on sequential anionic cyclization and subsequent generation of carbene intermediates are planned.

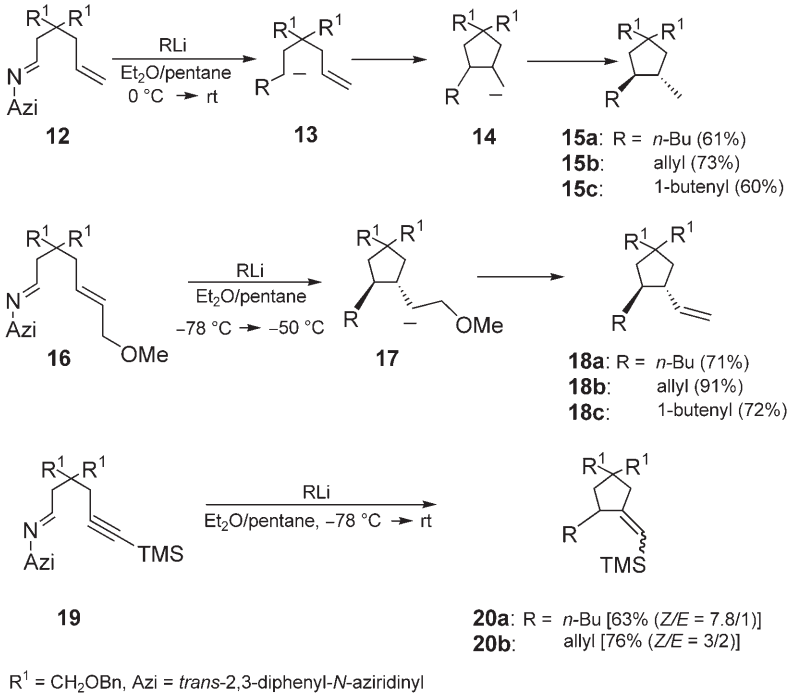
Experimental Section

General Remarks

All reactions were performed under an atmosphere of dry, oxygen-free nitrogen using standard syringe/cannula techniques,



Scheme 5. Anionic cyclization of *N*-aziridinylimine **21**.



Scheme 4. Anionic cyclization of *N*-(*trans*-2,3-diphenylaziridin-1-yl)imines.

and all reagents and solvents used for the preparation of alkyllithiums were freshly distilled under nitrogen immediately prior to use. The concentration of the solution of *t*-BuLi in pentane was determined by titration with *sec*-butyl alcohol in xylene with 1,10-phenanthroline as indicator.[15] The concentration of *n*-BuLi in hexane was corrected with anhydrous diphenylacetic acid as indicator in THF.

Reaction of *N*-(*trans*-2,3-Diphenylaziridin-1-yl)imines with Alkyllithiums; Typical Experimental Procedure

t-BuLi (518 μL, 0.88 mmol of a 1.7 M solution in pentane) was added dropwise to a solution of 4-iodo-1-butene (72.8 mg, 0.40 mmol) in Et_2O/pentane (2/3, 4 mL) at −78 °C. The reaction mixture was stirred for 5 min at −78 °C and then warmed to room temperature. A solution of *N*-(*trans*-2,3-diphenylaziridin-1-yl)imine (6; 74.0 mg, 0.20 mmol) in Et_2O/pentane (2/3, 2 mL) was added at −78 °C. The reaction mixture was stirred for 1 h at −78 °C. The mixture was allowed to warm to room temperature, quenched with saturated NH_4Cl solution, and extracted with Et_2O. The Et_2O extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (15/1) to give *1-(non-8-enyloxy)benzene* as a colorless oil; yield: 30.1 mg (69%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42–1.54 (m, 8H), 1.79–1.86 (m, 2H), 2.08–2.14 (q, *J* = 6.9 Hz, 2H), 3.98–4.02 (t, *J* = 6.6 Hz, 2H), 4.98–5.09 (m, 2H), 5.83–5.92 (m, 1H), 6.94–7.00 (m, 3H), 7.29–7.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.97, 28.81, 28.99, 29.19, 29.24, 33.71, 67.77, 114.15, 114.45, 120.39, 129.32, 139.01, 159.10; IR (NaCl): ν = 3041, 2937, 2857, 1601, 1497, 1491, 1246, 1098, 1037, 836, 752, 691 cm^{-1}; HR-MS $(M)^+$: calcd. for $C_{15}H_{22}O$: 218.1671; found: 218.1679.

Acknowledgements

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