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Phenylaziridine as a 1,3-dipole. Application to the synthesis of functionalized pyrrolidines

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Abstract

Phenylaziridine **1** in the presence of an appropriate Lewis acid reacts as a 1,3-dipole. The cyclocondensation of **1** with DHP in the presence of $BF_3 \cdot Et_2O$ produced the azaoxa[3.2.0] cycloadducts **4a–4b**. The reactivity of the corresponding *N*-tosyliminium ions was explored.

In recent years, aziridines have become very popular in organic synthesis not only as building blocks but also as synthetic intermediates as emphasized by Tanner.[1] Their ability to undergo regioselective ring opening reactions with a wide range of nucleophilic reagents contributes largely to their synthetic value. Recently, Toshimitsu reported that homochiral phenylaziridine **1** is regioselectively opened at the benzylic carbon by using allylmagnesium bromide (charged nucleophile). Adduct **2** was obtained with an enantiomeric excess (ee) of 94%, when a large excess (4 equiv.) of Grignard reagent was used.[2] It was assumed that the excess of Grignard reagent interacts with the nitrogen lone-pair of the aziridine to favor a S_N2 reaction.[2–4] The high enantioselectivity of this process prompted us to study the behavior of aziridines in the presence of other non-charged nucleophiles, especially allylsilanes (in this case an external Lewis acid was necessary to activate the aziridine).[5,6]

Using trimethylallylsilane in presence of $BF_3 \cdot Et_2O$ for performing the reaction, we found that **2** is formed with an ee of 12% (Scheme 1(a)). For this process we suggest the following explanation: aziridine **1** in presence of $BF_3 \cdot OEt_2$ develops transiently a benzylic carbocation (loss of chirality) and a negatively charged nitrogen. This mechanism not only accounts for the poor enantioselectivity (loss of chirality), but also for the formation of the pyrrolidine **3** when dimethylphenylallylsilane was used (Scheme 1(b)).[5,6] (For differences of reactivity between trimethylallylsilane and dimethylphenylallylsilane, see Fleming and Langley.[7]) In this letter we present some new evidence that, in the presence of a Lewis acid and a properly chosen nucleophile, aziridine **1** has the reactivity of a 1,3-dipole (Scheme 1(c)).

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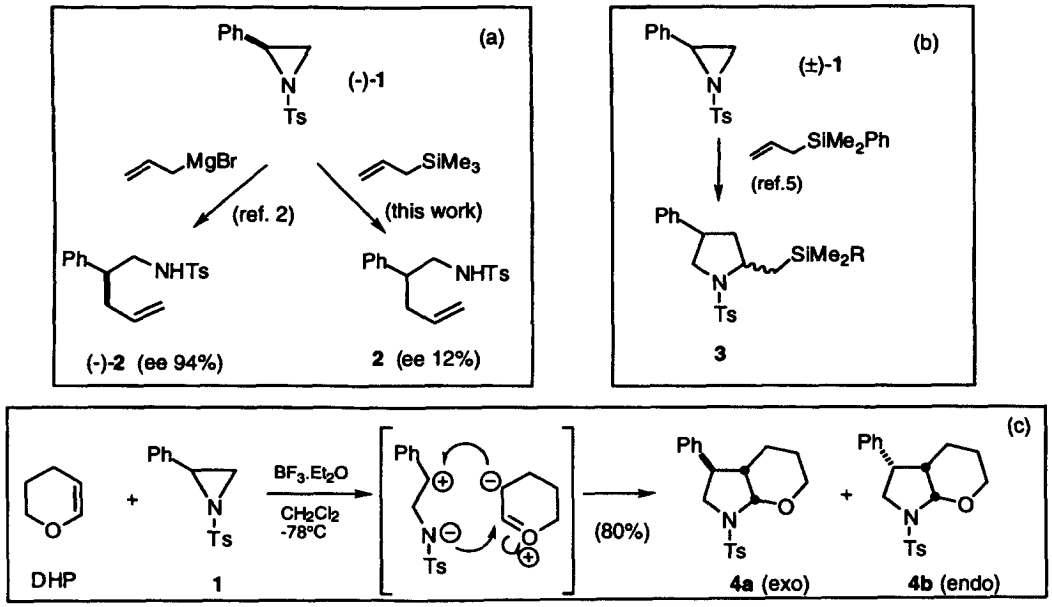
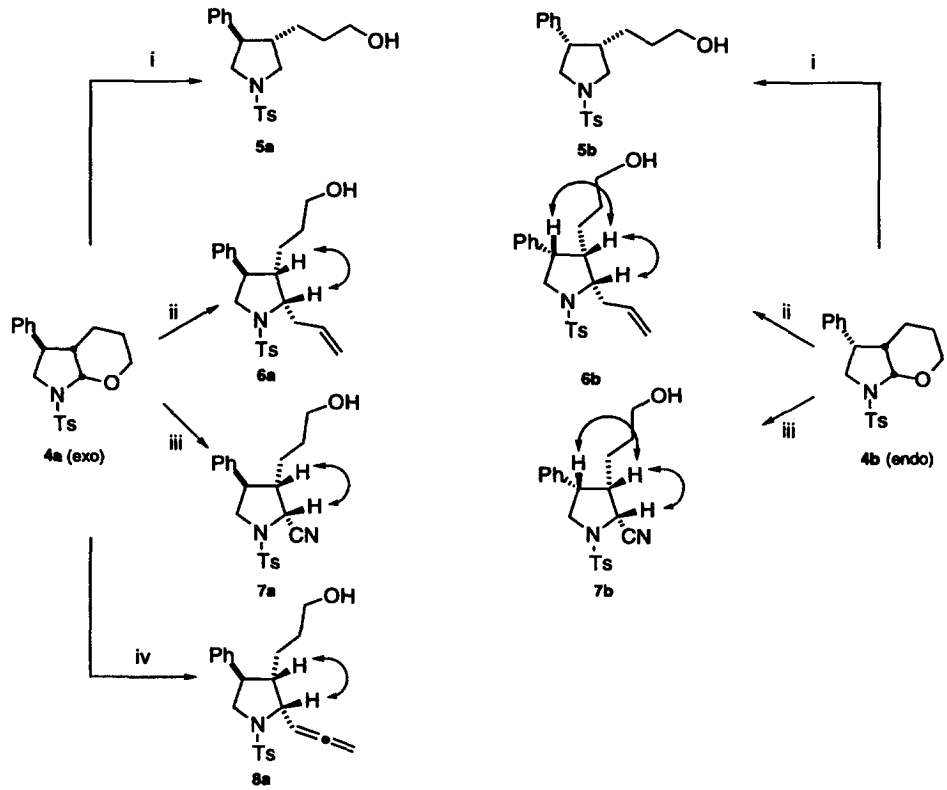


Scheme 1.

In order to validate our hypothesis, we searched for a suitable reagent complementary to the 1,3-dipole formed by activation of aziridine **1**. Since the double bonds in enol ethers could be expected to show the same type of reactivity as allylsilanes in the present reaction, we decided to use DHP as reaction partner for aziridine **1**. A literature survey revealed that there are several reports concerning the use of DHP in cycloadditions with isocyanate [2+2],[8,9] nitrone [3+2],[10,11] dienes [4+2],[12–15] and aminals [5+2].[16] In fact when a mixture of aziridine **1**, DHP and $BF_3 \cdot Et_2O$ in CH_2Cl_2 was stirred for 4 h at −78°C, we were pleased to notice the formation of two adducts. After purification by column chromatography on silica gel, the analysis of their NMR spectra was consistent with the azaoxa[3.2.0] bicyclic structures of compounds of **4a** and **4b** (Scheme 1(c)),[17] in a 1:1 ratio. The two compounds have a *cis* junction (J=4.9 Hz for **4a** and J=3.8 Hz for **4b**), and the phenyl ring is *exo* in **4a** and *endo* in **4b**. Finally, the assigned structures of **4a** and **4b** were verified by single-crystal X-ray analysis.[18] Later we found that the *exo* diastereomer can be obtained from the mixture by fractional crystallization. The formation of compounds **4a** and **4b** can be explained by a [3+2] polar cycloaddition between the aziridine and DHP: the Lewis acid is activating the *N*-tosyl group in aziridine **1**, the benzylic C–N bond breaks and the dipole is formed (Scheme 1(c)). The nucleophilic attack of carbon C(3) of DHP takes place and the formed oxonium ion is captured by the transient amide. The lack of facial selectivity which characterizes this process may be attributed to the rather flat geometry of the DHP molecule. In attempts to improve the yield and the selectivity of this reaction, we changed the temperature and the Lewis acid; however, above −50°C DHP polymerizes under our conditions, and some other Lewis acids [$TiCl_4$, $Mg(OTf)_2$, $Ti(OiPr)_4$, $B(OMe)_3$] proved to be ineffective. If one considers the rather simple structures of the starting material, a major increase in molecular complexity is achieved in one step. Furthermore, this new synthetic application of DHP and phenylaziridine opens the way for the preparation of functionalized pyrrolidines.

Indeed, compounds **4a–b** are direct precursors for the generation of cyclic *N*-tosyliminium ions studied by Somfai.[19,20] A series of nucleophiles including Et_3SiH, allylsilane, TMSCN and propargylsilane were allowed to react with **4a–b** in presence of $BF_3 \cdot OEt_2$ as Lewis acid (Scheme 2). In the case of Et_3SiH the expected reductive ring opening reaction was observed and compounds **5a** and **5b** were formed. With trimethylallylsilane the opening of the pyranyl ring was observed: the nucleophilic allylsilane

quenched the transient *N*-tosyliminium ion to realize the allylation at C(2) yielding **6a** and **6b** as single diastereomers. The stereochemistry of the newly formed carbon–carbon bond was assigned by using NOESY experiments (significant correlations are depicted on Scheme 2). It turns out that the configuration of the two adjacent stereocenters at C(2) and C(3) is *cis*! This result can be explained by invoking an anchimeric participation of the tosyl group: one of the oxygen atoms from the sulfonyl group may participate from the β-face and drives the nucleophile to the α-face producing **6a** and **6b** with global retention (a similar anchimeric assistance of the *N*-protective group of a substituted pyrrolidine has been disclosed by Seebach).[21] The reaction with TMSCN produced **7a**[22] and **7b**[23] as single diastereomers with the *cis* stereochemistry. The reaction with propargylsilane works only with the aminal **4a**, producing the allenyl adduct **8a** as a single *cis* adduct. Furthermore the obtained compounds **5a–8a** and **5b–7b** are highly functionalized pyrrolidines which can be transformed into interesting compounds in the dopamine field (owing to the presence of the phenethylamine motive)[24] or to substituted pyrrolidines related to the kainoids.[25]



Scheme 2. Reagents and conditions: (i) Et_3SiH, $BF_3 \cdot OEt_3$ in CH_2Cl_2: **5a** (95%) and **5b** (76%); (ii) allylsilane, $BF_3 \cdot OEt_3$ in CH_2Cl_2: **6a** (80%) and **6b** (78%); (iii) Me_3SiCN, $BF_3 \cdot OEt_3$ in CH_2Cl_2: **7a** (75%) and **7b** (85%); (iv) ≡–CH_2SiMe_3, $BF_3 \cdot OEt_3$ in CH_2Cl_2: **8a** (81%). (NOESY correlations are shown by double arrows)

In this work we have shown that phenylaziridine **1** reacts as a 1,3-dipole with DHP producing two azaoxobicycles **5a** and **5b**. These molecules give rise to highly functionalized pyrrolidines after nucleophilic opening of the pyranyl ring.

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17. Preparation of compounds **4a** and **4b**. A solution of phenylaziridine (1.93 g, 7 mmol) and dihydropyrane (0.9 g, 10.7 mmol, 1.5 equiv.) in CH_2Cl_2 (25 ml) was cooled to −78°C, under argon atmosphere and a solution of $BF_3{\cdot}OEt_2$ (0.2 ml, 1.6 mmol, 0.2 equiv.) in CH_2Cl_2 (2 ml) was slowly added over 30 min. Upon consumption of aziridine the reaction is quenched at −78°C with saturated aqueous ammonium chloride and diluted with CH_2Cl_2. The solution is allowed to warm to rt, and then extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with hexane:ether (1:1) to afford 2 g (80%) of a mixture of the two diastereoisomers **4a**:**4b**, in a 1:1 ratio. A second chromatography eluting with hexane:ether (9:1) was necessary to separate the two diastereoisomers. Physical data for **4a** (*exo*): mp 155–156°C (hex/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J*=8.3 Hz, 2H), 7.35 (d, *J*=8.3 Hz, 2H), 7.35–7.21 (m, 3H), 7.11–7.08 (m, 2H), 5.33 (d, *J*=4.9 Hz, 1H), 3.89 (d, *J*=8.5 Hz, 2H), 3.64–3.46 (m, 2H), 3.20 (dd, *J*=8.5 and 15 Hz, 1H), 2.46 (s, 3H), 2.40–2.32 (m, 1H) 1.49–1.11 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 139.2, 136.7, 129.7, 129.6, 128.9, 127.9, 127.5, 65.7, 53.6, 45.2, 43.8, 21.7, 20.2; IR (neat) cm^{-1} 3054, 2986, 1421, 1340, 1260, 1165. MS (EI): *m/z*=357.1 (M^+). Physical data for **4b** (*endo*): mp 122–124°C (hex/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J*=8.3 Hz, 2H), 7.35–7,22 (m, 5H), 7.20–7.15 (m, 2H), 5.33 (d, *J*=3.8 Hz, 1H), 3.97–3.92 (m, 1H), 3.71–3.42 (m, 4H), 2.45 (s, 3H), 2.22–2.15 (m, 1H), 1.81–1.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.7, 129.6, 128.9, 127.9, 127.5, 87.9, 65.7, 53.5, 45.2, 43.7, 21.7, 20.2; IR (neat) cm^{-1} 3054, 2986, 1599, 1496, 1345, 1269, 1167. MS (EI): *m/z*=357 (M^+).
18. The X-ray structures and coordinates for **4a** and **4b** have been submitted to the Cambridge Crystallographic Database under the following codes CCDC 121746 (**4b**) and CCDC 121747 (**4a**).
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22. Physical data for **6a** : ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J*=8.5 Hz, 2H), 7.41–7.14 (m, 5H), 4.98 (d, *J*=7.1 Hz, 1H), 3.67 (dd, *J*=8.5 and 9 Hz, 1H), 3.61–3.53 (m, 2H), 3.47 (dd, *J*=10 Hz, 1H), 3.19–3.08 (m, 1H), 2.48 (s, 3H), 2.48–2.38 (m, 1H), 1.61–1.39 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 139.2, 136.7, 129.6, 128.9, 127.9, 127.5, 88.0, 65.7, 53.6, 45.2, 43.8, 21.7, 20.2; IR (neat) cm^{-1} 3443, 2125, 2054. MS (EI): *m/z*=384 (M^+).
23. Physical data for **6b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J*=8.3 Hz, 2H), 7.43 (d, *J*=8.6 Hz, 2H), 7.30–7.14 (m, 5H), 4.77 (d, *J*=8.7 Hz, 1H), 3.78 (dd, *J*=6.8 and 9.8 Hz, 1H), 3.67 (dd, *J*=2.3 and 9.8 Hz, 1H), 3.65–3.55 (m, 3H), 2.50 (s, 3H), 2.81–2.60 (m, 1H), 1.61–1.22 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 138.7, 135.7, 128.5, 128.1, 127.9, 127.4, 127.2, 127.0, 88.9, 65.7, 50.2, 43.7, 39.9, 22.2, 20.8, 21.7; IR (neat) cm^{-1} 3452, 2150. MS (EI): *m/z*=384 (M^+).
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