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Sterically Congested Chiral Activated Aziridines: Synthesis of Both 2,3-*Cis*- and 2,3-*Trans*-2-Alkenyl-3-alkylaziridines from Common Intermediates

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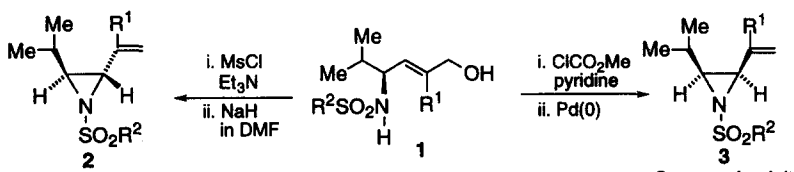
Abstract: Whereas treatment of the allylic mesylates of *N*-protected 2-alkyl-4-amino-(*E*)-2-alken-1-ols with sodium hydride in DMF yields exclusively the corresponding 2,3-*trans*-2-alkenyl-3-alkylaziridines, exposure of the methyl carbonates of *N*-protected 2-alkyl-4-amino-(*E*)-2-alken-1-ols to $Pd(PPh_3)_4$ (5-20 mol%) in THF or 1,4-dioxane affords predominantly the corresponding 2,3-*cis*-2-alkenyl-3-alkylaziridines. These reactions can be used to synthesize either of two diastereomers from single common intermediates.

Keywords: Aziridines; Palladium and compounds; Stereocontrol; Conformation.

The *N*-activated or *N*-unactivated aziridines form a peculiar class of strained azacyclic compounds, with remarkable synthetic potential.[1-6] Currently, aziridines bearing an alkenyl group on one of the aziridine-ring carbon atoms have proven to be extremely useful intermediates for various types of natural and synthetic compounds.[7-8]

In connection with a general programme directed towards the synthesis of bioactive compounds, we required a simple route to both 2,3-*cis*- and 2,3-*trans*-2-alkenylaziridines. Recently, we reported a method for synthesizing sterically non-congested 2,3-*cis*-2-vinyl-3-alkylaziridines from methyl carbonates as well as mesylates of *N*-protected 4-amino-(*E*)-2-alken-1-ols.[9a] Most recently, Olivo and co-workers have reported a synthetic route to activated vinylaziridines from *N*-substituted 1,4-amino alcohols using Mitsunobu conditions.[9b] However, scanning the literature revealed that there have been no reports describing an efficient and simple method for synthesizing sterically congested 2,3-*cis*- and 2,3-*trans*-2-alkenylaziridines from common intermediates.



Scheme 1 R^1 = Me or Et; R^2 = Me or aryl

This report describes the highly stereoselective conversion of methyl carbonates and mesylates, which can be readily synthesized from common intermediates **1**, into the sterically congested 2,3-*trans* and 2,3-*cis*-alkenylaziridines **2** and **3** (Scheme 1). Particularly notable is that the mode of the stereoselection can be changed from 2,3-*cis*- to 2,3-*trans* simply by switching the reaction condition and the leaving group from the allylic methyl carbonate to the mesylate.

The requisite substrates for the present study were readily prepared in synthetically acceptable yields from natural (*S*)-α-amino acids. In these substrates, the amino group was protected with the methanesulfonyl (Ms) or 2,4,6-trimethylbenzenesulfonyl (Mts) group, which can withstand a wide range of chemical manipulations.

As shown in Scheme 2, the methyl carbonates **4**, **5** and **6** bearing an alkyl group (Me or Et) on the double bond gave the corresponding 2,3-*cis*-aziridines **9**, **10**, and **11** in very high diastereoselectivities by treatment with a catalytic amount of $Pd(PPh_3)_4$ under equilibrated conditions.[9a,10,11] Surprisingly, the methyl carbonates **7**

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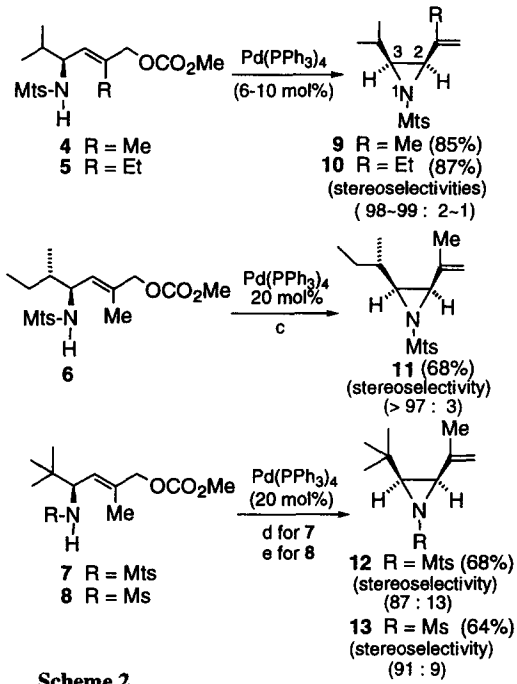
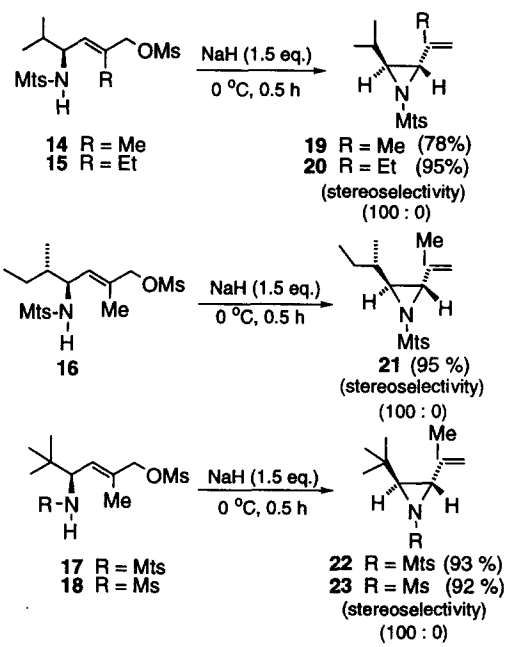
and **8** bearing a *tert*-butyl group also gave the corresponding sterically highly congested 2,3-*cis*-aziridines **12** and **13** as the major products.

The 2,3-*cis*- and 2,3-*trans*-stereochemistries were readily established from ^{1}H NMR analyses. The 2,3-*cis*-aziridines (**9**-**13**) show the $JH_{2,3}$ value (J = *ca.* 7.0 Hz) larger than that (J = *ca.* 4.2 Hz) of the corresponding 2,3-*trans*-isomers (**19**-**23**). The data are in good agreement with ^{1}H NMR data for related compounds.[10b,12]

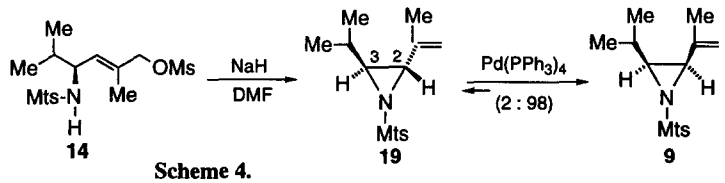


Scheme 2.
Reaction conditions: a. 65 °C, 4 h, in THF; b. reflux in dioxane, 15 min; c. reflux in dioxane, 0.5 h; d. reflux in dioxane, 2 h; e. reflux in dioxane, 2.5 h.



Scheme 3.

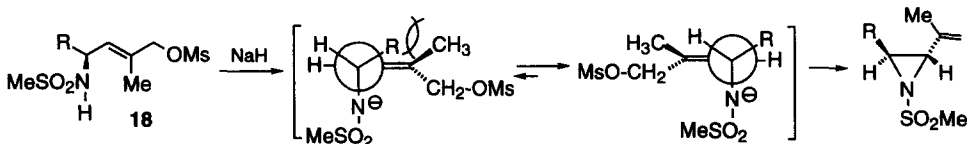
It has been reported that aziridination of certain mesylates of *N*-protected 4-amino-2-alken-1-ols gave a mixture of 2,3-*cis* and 2,3-*trans*-aziridines upon treatment with sodium hydride.[7c,9a] In sharp contrast, exposure of the mesylates **14**, **15**, **16**, **17**, and **18** *bearing an alkyl group on the double bond* to sodium hydride in DMF at 0 °C gave exclusively the corresponding 2,3-*trans*-aziridines **19**, **20**, **21**, **22**, and **23** in very high isolated yields. The diastereoselection of the products (**19**-**23**) is over 99.9% judging from reverse-phase HPLC, and we were unable to detect any of the corresponding 2,3-*cis*-isomer. It is apparent that the alkyl group on the double bond in the mesylates plays an important role for the very high 2,3-*trans*-aziridination.



Scheme 4.

Thus, sterically congested 2,3-*cis*- or 2,3-*trans*-2-alkenylaziridines could be obtained selectively by the use of methyl carbonates or the mesylates. It should be clearly noted that the 2,3-*trans*-2-alkenylaziridines are thermodynamically less stable than the corresponding 2,3-*cis*-isomers as reported previously.[9a,10,11] For example, as shown in Scheme 4, 2,3-*trans*-aziridine **19**, obtained by exposure of the mesylate **14** to sodium hydride, was stirred with 4 mol% of $Pd(PPh_3)_4$ for 12 h at 0 °C to yield a 2:98 equilibrated mixture of 2,3-*trans*-**19** and 2,3-*cis*-**9** in 96% combined isolated yield. This equilibrated reaction indicates that **9** is estimated to be *ca.* 2.0 kcal mol^{-1} more stable than **19**.

Although the ground state and the reactive conformer are not necessarily the same, the ground state conformations of various olefinic molecules containing the propene moiety play an important role in the stereochemical outcome of π-facial selectivity.[13] The exclusive formation of 2,3-*trans*-aziridine **23** from the mesylate **18** may be rationalized by assuming two aza-anionic intermediates **24** and **25**. Conformer **24**, which would lead to 2,3-*cis*-aziridine **13** with 2,3-stereochemistry opposite to what was observed experimentally, may be highly destabilized in comparison with conformer **25** owing to unfavorable interactions (allylic 1,3-strain) between the bulky R group and the methyl group. In conformer **25**, the allylic 1,3-strain may be minimized. In fact, semiempirical calculations (AM1) suggest that the conformer **25** is favored by 10 kcal mol^{-1} over the conformer **24**.[14] Accordingly, treatment of mesylate **18** with sodium hydride yields exclusively the 2,3-*trans*-aziridine **23** most probably *via* the conformer **25**.



Scheme 5. R = *tert*-Butyl

In vinylcyclopropane, it has been well documented that the stable conformation has the $CH{=}CH_2$ group synperiplanar to the cyclopropyl hydrogen on the adjacent carbon atom.[15] The explanation may be found in the Walsh picture of cyclopropyl bonding,[16] which ascribes a near sp^2 character to the cyclopropyl hydrogen atoms and places *p* orbitals in the plane of the cyclopropyl ring and at right angles to the plane of the H-C-H or (exo-C)-C-H bonds. Similarly, in simple non-congested 2,3-*cis*- and 2,3-*trans*-*N*-mesyl-2-vinyl-3-methylaziridines, the C(2)-H bond of the aziridine ring was predicted by *ab initio* calculations to be near-eclipsed with the $-C{=}CH_2$ group. In fact, solid conformation of 2,3-*trans*-*N*-mesyl-2-vinyl-3-methylaziridine has the $C{=}CH_2$ group rotated only less than 9° away from perfect eclipsing (synperiplanar arrangement).[10]

In sharp contrast, in sterically congested aziridine **12**, the hydrogen atom at the C(2)-position of the aziridine ring and the CH_2 group of the alkenyl are shown to be anticlinal from both X-ray analysis and ^{1}H-NMR spectral investigations as shown in **12-B** in Figure 1.[17] The synplanar arrangement **12-A** would be highly destabilized in comparison with conformer **12-B** owing to unfavorable interactions between the bulky *tert*-butyl group and the methyl group. Similarly, the preferred conformation **22-B** of 2,3-*trans*-aziridine **22** can be deduced from X-ray and ^{1}H-NMR analyses (Figure 1).

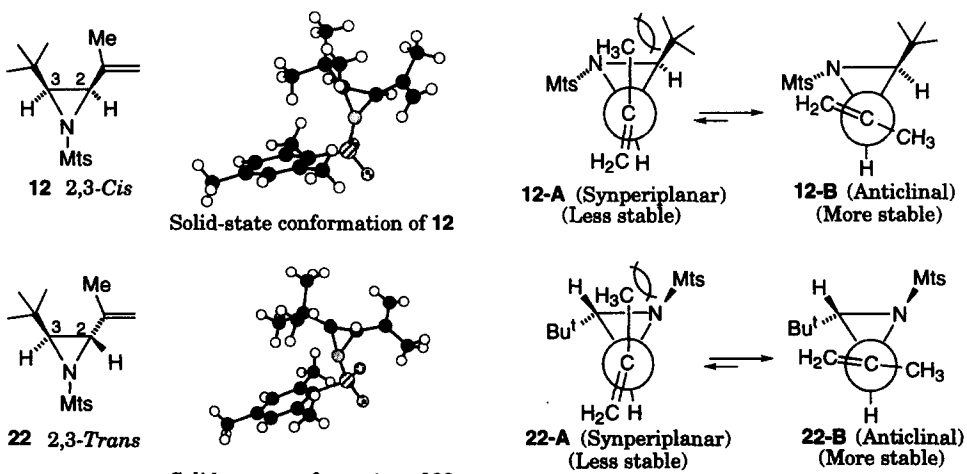


Figure 1.

In summary, whereas treatment of the allylic mesylates of *N*-protected 2-alkyl-4-amino-(*E*)-2-alken-1-ols with sodium hydride in DMF yields exclusively the corresponding 2,3-*trans*-2-alkenyl-3-alkylaziridines, exposure of

the methyl carbonates of *N*-protected 2-alkyl-4-amino-(*E*)-2-alken-1-ols to $Pd(PPh_3)_4$ (5-20 mol%) in THF or 1,4-dioxane affords predominantly the corresponding 2,3-*cis*-2-alkenyl-3-alkylaziridines. These reactions can be used to synthesize either of two diastereomers from single common intermediates.

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