An unusual thermodynamic preference of chiral *N*-arylsulfonyl *cis*-3-alkyl-2-vinylaziridines over their *trans*-isomers: palladium(0)-catalysed equilibration reactions

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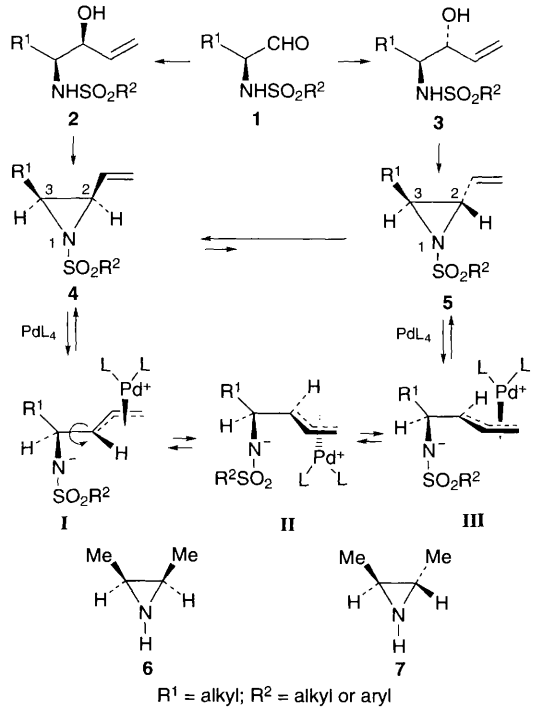
Palladium (0)-catalysed reactions of *N*-alkylsulfonyl- or *N*-arylsulfonyl-3-alkyl-2-vinylaziridines reveal that 2,3-*cis*-isomers are more stable than the corresponding 2,3-*trans*-isomers in accord with *ab initio* calculations.

Activated chiral aziridines,[1] notably 2-vinylaziridines[2] and their derivatives,[3] are versatile synthetic intermediates for the synthesis of biologically important compounds. Recently we,[4] Merck[5] and Dupont Merck[6] groups, and Panek[7] have reported that peptides containing (*E*)-alkene dipeptide isosteres show potent biological activity. As part of an ongoing project aimed at the synthesis of biologically active peptides containing (*E*)-alkene isosteres[8] we required a reliable method for the preparation of activated *cis*-3-alkyl-2-vinylaziridines **4**, key synthetic intermediates in the synthesis of these isosteres.

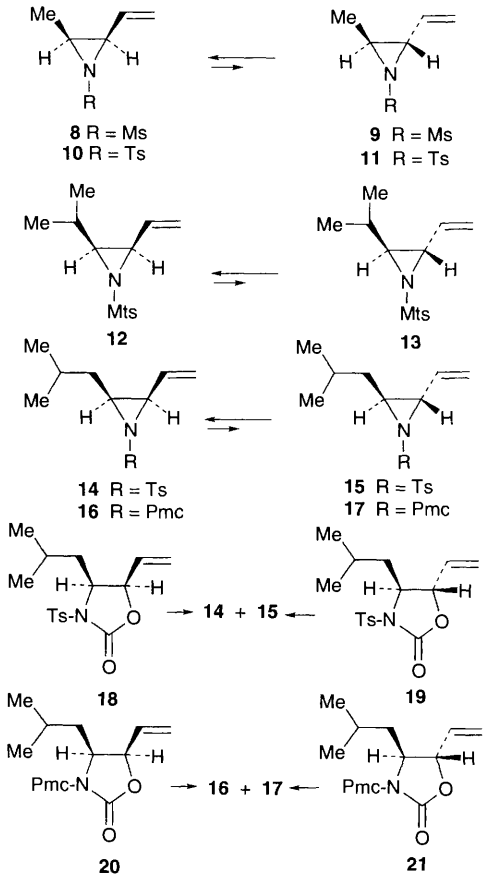
Chiral activated 3-alkyl-2-vinylaziridines **4** and **5** could be derived from a homochiral *N*-protected amino aldehyde **1** *via* amino alcohols **2** and **3**. However, the highly stereoselective synthesis of either *syn*- or *anti*-amino alcohols **2** or **3** and hence 2,3-*cis*- or 2,3-*trans*-3-alkyl-2-vinylaziridines **4** or **5** from an amino aldehyde **1** has hitherto been difficult.

It was expected that the palladium(0)-catalysed isomerization of 2,3-*trans*-3-alkyl-2-vinylaziridines **5** into the corresponding desired *cis*-isomers **4** could occur *via* π-allyl palladium complexes **I**, **II** and **III**. In spite of their synthetic utility, the relative themodynamic stabilities of activated *cis*- and *trans*-2,3-disubstituted aziridines are still poorly understood. Here we describe a study involving the palladium(0)-catalysed equilibration of various activated 3-alkyl- 2-vinylaziridines.

At the outset, we were apprehensive as to the possible success of palladium(0)-catalysed isomerizations (*e.g.* **9** → **8**, Scheme 2) because *trans*-2,3-disubstituted aziridines are usually believed to be more stable than their *cis*-isomers.[9] In order to gain an understanding of the relative thermodynamic stabilities of *cis*-2,3-dimethylaziridine **6** and the *trans*-isomer **7**, as well as



Scheme 1



Scheme 2

N-methanesulfonyl-*cis*-3-methyl-2-vinylaziridine **8** and the *trans*-isomer **9**, we undertook *ab initio* calculations involving full optimizations using the GAUSSIAN 92 quantum mechanical package (Revision C).†

As one might expect, the calculations suggest that the energy minimum of *trans*-2,3-dimethylaziridine is favoured by 3.167 KJ mol^{-1} over the energy minimum of the *cis*-isomer at the MP2/ 6–31G** level.

On the contrary, *N*-methanesulfonyl (mesyl)-*cis*-3-methyl-2-vinylaziridine **8** and the *trans*-isomer **9** gave different results. It became apparent that the energy minimum of *N*-mesyl-*cis*-3-methyl-2-vinylaziridine **8** was predicted to be *ca.* 6 KJ mol^{-1} lower than the energy minimum of the *trans*-isomer **9** at the RHF/6–31G** level. Accordingly, an unusual predominant formation of 2,3-*cis*-aziridine **8** could be expected by exposure of 2,3-*trans*-aziridine **9** to palladium (0) catalysts in appropriate solvents.

In good agreement with the computational prediction, *N*-mesyl-*trans*-3-methyl-2-vinylaziridine **9**, prepared from (*R*)-*allo*-threonine, did give a 98:2 mixture of *N*-mesyl-*cis*-3-methyl-2-vinylaziridine **8** and its *trans*-isomer **9** in 97% isolated yield upon treatment with 5 mol% of $Pd(PPh_3)_4$ in THF at 0 °C for 18 h. An essentially identical result was obtained following treatment of *N*-mesyl-*cis*-3-methyl-2-vinylaziridine **8** under the same reaction conditions (Scheme 2 and Table 1 entries 1 and 2).

The other requisite activated *cis*-3-alkyl-2-vinylaziridines (**10, 12, 14** and **16**) and their *trans*-isomers (**11, 13, 15** and **17**) were prepared from chiral amino acids *via* routine sequences of reactions.

Results obtained by exposure to the palladium (0) catalyst(s) for the other eight different activated aziridines (**10-17**) are summarized in Table 1 (entries 4–13). In the presence of PPh_3, tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] could be used equally well (entries 3, 5 and 7, Table 1). However, dibenzylideneacetone was found to hinder product purification by silica gel flash chromatography. Space restrictions prevent detailed descriptions of all results for these experiments, however, it is readily apparent that the equilibrated reactions give very satisfactory results. Changing the steric bulk of the *N*-protecting group and the alkyl group at the C-3 position presumably shifted the equilibrium. Interestingly, as can be seen from Table 1, neither the bulk of the *N*-protecting group (Ms, Ts, Mts or Pmc) nor the 3-alkyl group (Me, isopropyl or isobutyl) exerts any significant influence on the *cis–trans* ratios of the reaction at equilibrium. It should be clearly noted that although we usually stir reaction mixtures for 15–18 h, all reactions described above generally attained equilibrium at 0 °C in THF within a few minutes.

Table 1 Palladium(0)-catalysed equilibration reactions of *N*-activated 3-alkyl-2-vinylaziridines **8–17** and *N*-protected 4-alkyl-5-vinyloxazolidin-2-ones **18–21**[a]

Entry	Reactant	Catalyst[b] (mol%)	Conditions	Product ratio[c]	Yield (%)
1	**8**	A (5)	0 °C, 18 h	**8**:**9** = 98:2	97
2	**9**	A (5)	0 °C, 48 h	**8**:**9** = 98:2	95
3	**9**	B (4)	0 °C, 18 h	**8**:**9** = 98:2	75
4	**10**	A (2)	0 °C, 18 h	**10**:**11** = 96:4	97
5	**10**	B (4)	0 °C, 18 h	**10**:**11** = 95:5	80
6	**11**	A (2)	0 °C, 18 h	**10**:**11** = 96:4	95
7	**11**	B (4)	0 °C, 18 h	**10**:**11** = 95:5	74
8	**12**	A (4)	0 °C, 24 h	**12**:**13** = 96:4	95
9	**13**	A (4)	0 °C, 24 h	**12**:**13** = 95:5	97
10	**14**	A (5)	0 °C, 18 h	**14**:**15** = 97:3	96
11	**15**	A (5)	0 °C, 18 h	**14**:**15** = 96:4	97
12	**16**	A (4)	0 °C, 18 h	**16**:**17** = 96:4	99
13	**17**	A (4)	0 °C, 18 h	**16**:**17** = 97:3	99
14	**18**	A (5)	0 °C, 18 h	**14**:**15** = 97:3	87
15	**19**	A (5)	0 °C, 18 h	**14**:**15** = 97:3	86
16	**20**	A (4)	rt, 7 h	**16**:**17** = 95:5	84
17	**21**	A (4)	0 °C, 15 h	**16**:**17** = 95:5	79

[a] All reactions were carried out in THF (*ca.* 0.05 molar solution) under a positive pressure of argon. [b] A = $Pd(PPh_3)_4$; B = $Pd_2(dba)_3{\cdot}CHCl_3$: PPh_3 = 1:8. [c] Product ratios for entries 1–3 and 4–17 were determined by capillary gas chromartography (0.2 mm × 50 m) and reverse phase HPLC, respectively.

Having established useful conditions for the equilibrated reactions of *cis*- and *trans*-3-alkyl-2-vinylaziridines, the reaction of five membered heterocycles **18–21** with $Pd(PPh_3)_4$ was briefly investigated. The required four homochiral oxazolidin-2-ones **18–21** were readily prepared in high yields from (*S*)-leucine *via* routine sequences of reactions. As expected, when either the 4,5-*cis*-oxazolidin-2-one **18** or the 4,5-*trans*-isomer **19** was treated with 5 mol% of $Pd(PPh_3)_4$, a 97 : 3 mixture of the *cis*-3-isobutyl-2-vinylaziridine **14** and its *trans*-isomer **15** were formed in good yield *via* a decarboxylative ring closure (Table 1, entries 14 and 15). A similar trend was noted for the reaction of oxazolidin-2-ones **20** and **21** (Table 1, entries 16 and 17).

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Footnote

† All *ab initio* calculations were performed on a CRAY Y-MP2E/264 at the Supercomputer Laboratory, Institute for Chemical Research, Kyoto University.

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