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Asymmetric aziridination with chiral allyl aminosulfoxonium ylides: synthesis of alkenyl aziridine carboxylates and palladium-catalyzed *E*,trans/*E*,cis-isomerization of an alkenyl aziridine

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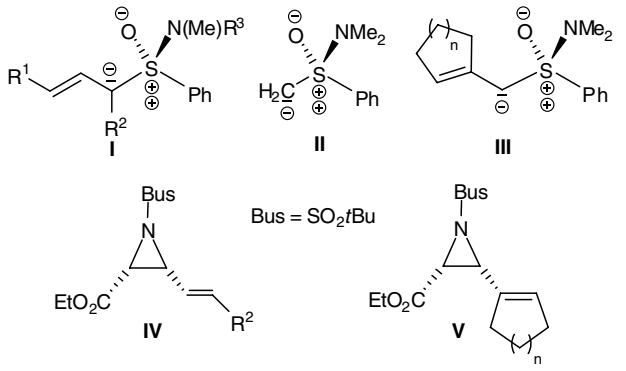
Abstract—Chiral cyclic and acyclic allyl aminosulfoxonium ylides have been generated from aminosulfoxonium-substituted β,γ-unsaturated α-amino acids (method A) and 1-alkenyl aminosulfoxonium salts (method B) upon treatment with DBU. Their application to the asymmetric aziridination of *N*-*tert*-butyl-sulfonyl imino ester, generated either in situ (method A) or externally added (method B), gave the corresponding alkenyl aziridine carboxylates with medium to high diastereoselectivity and enantioselectivity. A highly stereoselective Pd(0)-catalyzed isomerization of an *E*,trans-configured alkenyl aziridine methanol derivative to its *E*-cis-isomer is described, which proceeded with retention of the double bond configuration.

We had recently described the synthesis, structure, and reactivity of chiral *N*-titanium allyl aminosulfoxonium ylides of type **I**, $R^2 = H$, $R^3 = Ti(NEt_2)_3$ (Scheme 1).[1] The investigations of **I** were supplemented by ab initio calculations of allyl aminosulfoxonium ylide **I**, $R^1 = R^3 = Me$, $R^2 = H$ and parent ylide **II**. The ylides exhibit a polar S–O single bond and are stabilized by electrostatic and n_C–σ^*_{SO} interaction. A further important mode of stabilization of allyl ylide **I** is n_C–π^* interaction.



Scheme 1. Aminosulfoxonium ylides and alkenyl aziridine carboxylates.

The hitherto unknown chiral allyl *S*-ylides of type **I**, $R^3 = Me$, and **III** should be of considerable synthetic interest since a number of useful transformations of these ylides can be envisioned based on the chemistry of **II**.[2,3] Although chiral alkylidene *S*-ylides are well established reagents,[3] only a few examples of chiral conjugated allyl *S*-ylides had been described.[4] Thus, we have developed an interest in the synthesis and reactivity of ylides of type **I** and **III**, which are expected to be configurationally stable.[2] Here, we describe the generation of the conjugated cyclic and acyclic allyl aminosulfoxonium ylides **I** and **III** and their application to the asymmetric aziridination of *N*-*tert*-butylsulfonyl imino ester, which gave enantioenriched alkenyl and cycloalkenyl aziridine carboxylates of type **IV** and **V**, respectively, for which only a few asymmetric syntheses had been described.[5] In particular methods for the asymmetric synthesis of cycloalkenyl aziridine carboxylates of type **V** are scarce.[5b] Because of the rich chemistry of alkenyl

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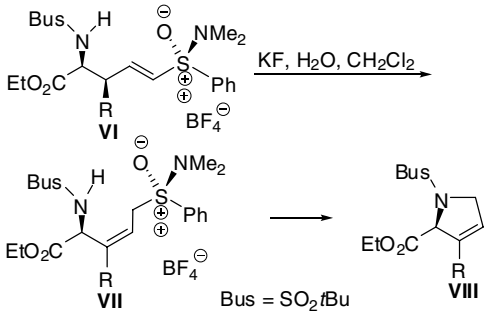
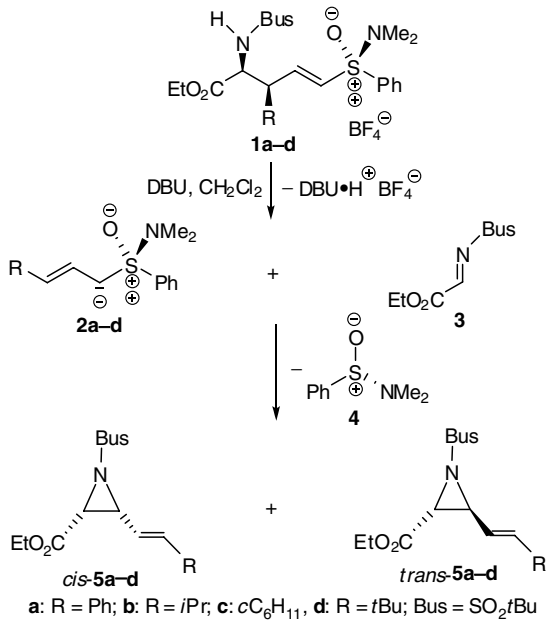
aziridines and aziridine carboxylates, alkenyl aziridine carboxylates **IV** and **V** should make valuable synthetic building blocks.[3] Although the parent methylene aminosulfoxonium ylide **II** and its *C*-alkyl derivatives have been much studied in asymmetric epoxidation and cyclopropanation, nothing is known about their reactivity in the aziridination of imines.[2,3]

We had previously reported the facile migratory cyclization of the aminosulfoxonium-substituted unsaturated amino acids **VI** with formation of 3,4-dihydro prolines



Scheme 2. Migratory cyclization of aminosulfoxonium-substituted unsaturated amino acids.[6]



Scheme 3. Generation of acyclic allyl aminosulfoxonium ylides from aminosulfoxonium-substituted amino acids and aziridination of **3**.

VIII upon treatment with KF in H_2O/CH_2Cl_2 (Scheme 2).[6] This transformation most likely involves allyl aminosulfoxonium salts **VII** as intermediates, which are generated in the two-phasic system through an F^--catalyzed isomerization of **VI**. In order to generate the corresponding allyl ylides of type **I**, $R^2 = H$, $R^3 = Me$, from **VII** 1-alkenyl aminosulfoxonium salts **1a–d** (Scheme 3) were treated with DBU. Surprisingly, salts **1a–d** afforded the alkenyl aziridine carboxylates *cis*-**5a–d** and *trans*-**5a–d** in high yields with good diastereoselectivities and medium to high enantioselectivities (Table 1). The enantioselectivity of the synthesis of the cis-configured aziridines is significantly higher than that of the trans-configured isomers. Preparative HPLC of the cis/trans-mixtures afforded the pure *cis*- and *trans*-aziridines except in the case of **5d**.[7] In addition to aziridines *cis*-**5a–d** and *trans*-**5a–d**, *S*-configured sulfinamide **4** of ⩾98% ee was isolated in high yields. It is proposed that salts **1a–d** reacted with DBU under deprotonation at the N-atom followed by a fragmentation of the corresponding anions to give conjugated allyl aminosulfoxonium ylides **2a–d** and imino ester **3**.[8] Then ylides **2a–d** combined with **3** under aziridination to afford aziridines and the sulfinamide. The opposite reactivity of **1a–d** toward F^- and DBU may be due to the different reaction conditions and the differences in basicity and size of the bases.

The synthesis of amino acids **8a–d**, used as the starting material in the synthesis of salts **1a–d**, was carried out as previously described (Scheme 4).[9] Isomerization of enantiopure 1-alkenyl sulfoximines **6a–d** with DBU gave allyl sulfoximines **7a–d**. Their successive treatment with *n*-BuLi, $ClTi(OiPr)_3$ and **3** afforded the unsaturated amino acid derivatives **8a–d** with high regio- and diastereoselectivities in high yields, the methylation of which furnished salts **1a–d** in practically quantitative yields.

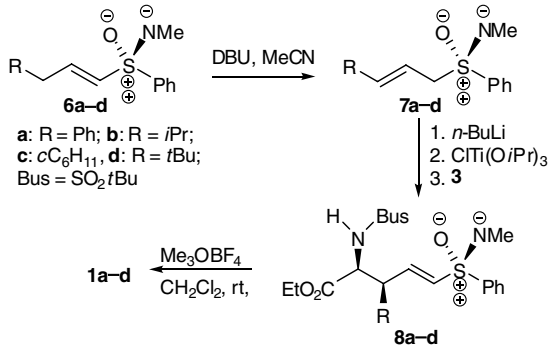
The aziridination of **3** with cyclic allyl aminosulfoxonium ylides of type **II** generated through deprotonation of the corresponding cyclic aminosulfoxonium-substituted unsaturated amino acids has not yet been investigated in detail. Its feasibility is demonstrated, however, by the following result. Treatment of aminosulfoxonium salt **9**[1] with DBU afforded ylide **10c** and imine **3**, which reacted with each other and gave cycloalkenyl aziridine carboxylates *cis*-**11c** and *trans*-**11c** in a ratio of 2:1 in 82% yield (Scheme 5).

The formation of aziridines *cis*-**5a–d** and *trans*-**5a–d** in the reaction of aminosulfoxonium salts **1a–d** with DBU suggested an alternative entry to the aziridines starting from 1-alkenyl aminosulfoxonium salts **12b**,

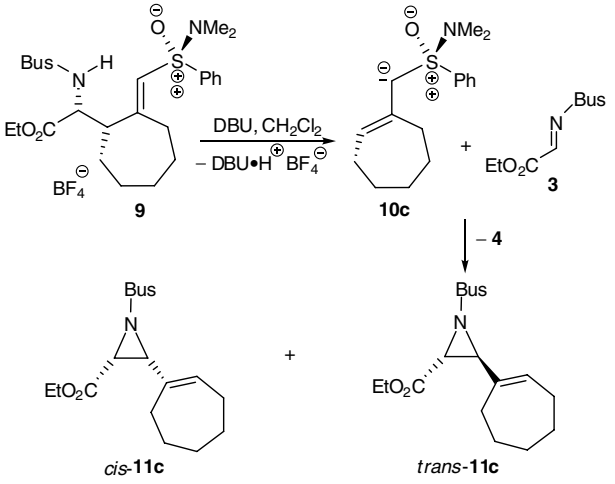
Table 1. Synthesis of alkenyl aziridine carboxylates from aminosulfoxonium-substituted unsaturated amino acids

1	R	**5** Cis:trans	Yield (%)	Cis		Trans		**4** Yield (%)
				ee[a] (%)	Yield (%)	ee[a] (%)	Yield (%)	
a	Ph	93:7	94	⩾98	82	30	5	79
b	*i*Pr	91:9	91	92	76	26	6	71
c	cC_6H_{11}	90:10	93	71	75	48	9	70
d	*t*Bu	91:9[b]	94	50	—	5	—	71

[a] Determined by HPLC. Compound **5a**: Chiralpack-AD; **5b** and **5d**: Chiracel OD-H; **5c**: Chiralpack-IA.
[b] Inseparable mixture.

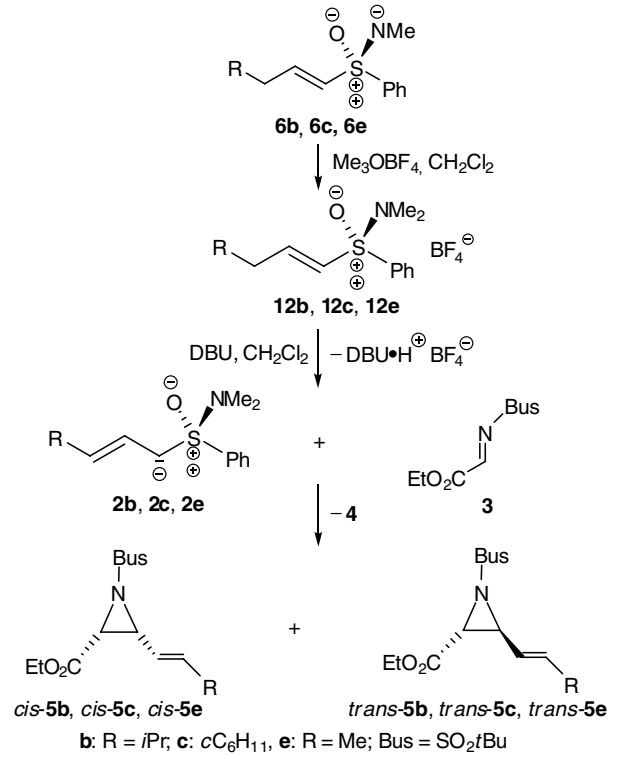


Scheme 4. Asymmetric synthesis of sulfoximine-substituted unsaturated amino acids.[9]



Scheme 5. Generation of a cyclic allyl aminosulfoxonium ylide from the aminosulfoxonium-substituted amino acid and aziridination of **3**.

12c, and **12e** and **3** (Scheme 6). Methylation of 1-alkenyl sulfoximines **6b**, **6c**, and **6e**, which are readily available from (*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine and the corresponding aldehydes following a one-pot procedure,[10] gave aminosulfoxonium salts **12b**, **12c**, and **12e** (98% yield), respectively. The successive treatment of salts **12b**, **12c**, and **12e** with imino ester **3** and DBU indeed furnished aziridines *cis*-**5b**, *cis*-**5c**, and *cis*-**5e** together with *trans*-**5b**, *trans*-**5c**, and *trans*-**5e**, respectively, in good yields (Table 2). Thus, DBU presumably caused a deprotonation of 1-alkenyl salts **12b**, **12c**, and **12e** at the γ-position with formation of trans-configured allyl ylides **2b**, **2c**, and **2e**, respectively, which reacted with **3** to give aziridines. In addition to aziridines, sulfinamide **4** of ⩾98% ee was isolated in high yields. It should be noted that the stereoselective conversion of **4** to (*S*)-



Scheme 6. Generation of acyclic allyl aminosulfoxonium ylides from 1-alkenyl aminosulfoxonium salts and aziridination of **3**.

N,*S*-dimethyl-*S*-phenylsulfoximine, the starting material for the synthesis of **6a**–**d** and **8a**–**d**, had already been described.[11]

The diastereo- and enantioselectivities of the formation of aziridines from 1-alkenyl salts **12** differ significantly from those starting from the amino acid derivatives **1**. The major difference between the two pathways is the concentration of **3**. While in the case of **1** imine **3** is generated in situ and thus present only in low concentration, it is there in excess in the case of **12**. However, a rationalization of the different selectivity is difficult at present because of the lack of further mechanistic information. For example, it is not known whether the addition of **2** to **3** is reversible or not.

Because of the high reactivity of α-unsubstituted ylides **2a**–**d** toward **3**, it was of interest to see whether a substituted allyl ylide of type **II**, R^2 = alkyl, can be generated and what its reactivity would be. Thus, methyl-substituted 1-alkenyl sulfoximine **14** was prepared starting from 1-alkenyl sulfoximine **6b** via lithiation at the α-position[12] with formation of alkenyllithium derivative **13**,

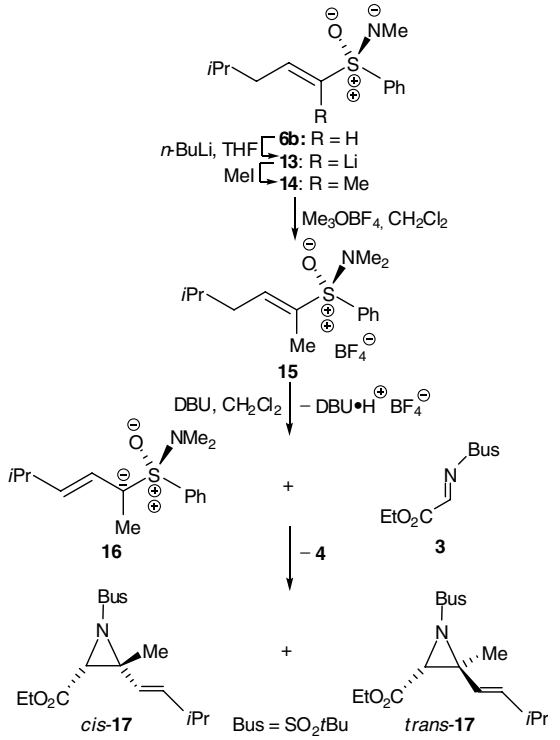
Table 2. Synthesis of alkenyl aziridine carboxylates from 1-alkenyl aminosulfoxonium salts and the imino ester

6	R	**5** Cis:trans	Yield (%)	Cis ee (%)[a]	Trans ee (%)[a]	**4** Yield (%)
b	*i*Pr	64:36	70	76	49	92
c	cC_6H_{11}	70:30	68	47	45	90
e	Me	60:40[b]	65	65	—[c]	90

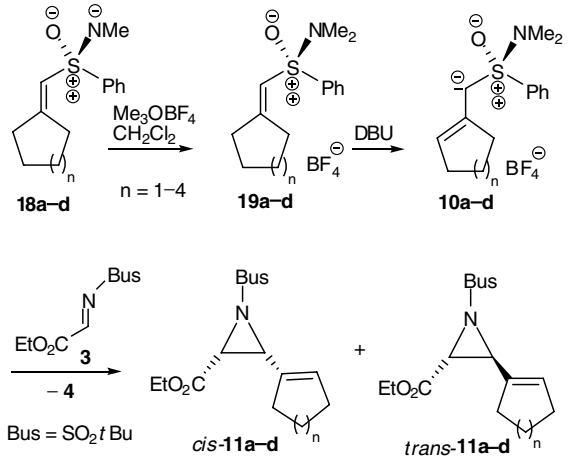
[a] Determined by HPLC, Chiralpack-IA.
[b] Inseparable mixture.
[c] Could not be determined.

which upon treatment with MeI gave sulfoximine **14** in 95% overall yield based on **6b** (Scheme 7). Methylation of sulfoximine **14** afforded aminosulfoxonim salt **15** (98% yield). The treatment of salt **15** with DBU in the presence of **3** furnished methyl-substituted allyl aminosulfoxonium ylide **16**, which readily reacted with **3** and gave aziridines *cis*-**17** and *trans*-**17** in a ratio of 60:40 in 81% yield. Interestingly, aziridine *cis*-**17**, which was separated by HPLC, had only 28% ee. Thus, the substituted ylide **16** reacted with **3** with a much lower enantioselectivity than the corresponding unsubstituted ylide **2b**.

Having recorded a facile synthesis of acyclic aziridines from the corresponding acyclic 1-alkenyl aminosulfoxonium salts **12** and **3**, it was of interest to see whether this method could also be applied to the generation of cyclic allyl aminosulfoxonium ylides and thus to the synthesis of cycloalkenyl aziridine carboxylates. Methylation of cyclic 1-alkenyl sulfoximines **18a–d**, which are readily available in high yield from (*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine and the corresponding cycloalkanones,[10] furnished the cyclic 1-alkenyl aminosulfoxonium salts



Scheme 7. Generation of a α-methyl-substituted allyl aminosulfoxonium ylide and aziridination of **3**.



Scheme 8. Generation of cyclic allyl aminosulfoxonium ylides cyclic 1-alkenyl aminosulfoxonium salts and aziridination of **3**.

19a–d (98% yield) (Scheme 8). The successive treatment of salts **19a–d** with DBU and **3** afforded cycloalkenyl aziridine carboxylates *cis*-**11a–d** and *trans*-**11a–d** with low diastereoselectivities and medium to high enantioselectivities in good yields (Table 3).

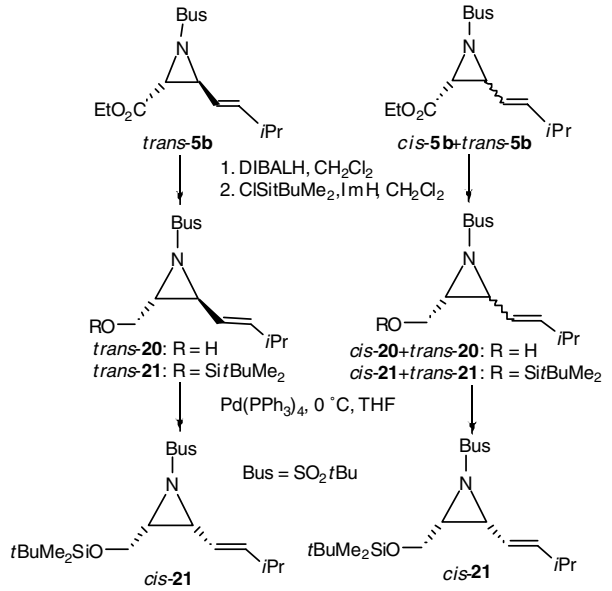
Because of the attainment of mixtures of *cis*- and *trans*-aziridines, a convergent conversion of the cis/trans-mixtures of the corresponding aziridine methanol derivatives to their cis-configured isomers was thought, which should be interesting substrates, for example, for an aza-Payne rearrangement.[13] Thus, reduction of ester *trans*-**5b** gave alcohol *trans*-**20** (90%), which was protected as silyl ether *trans*-**21** (89%) (Scheme 9). The Pd-catalyzed isomerization[14] of *E*,trans-configured alkenyl aziridine *trans*-**21** proceeded with high diastereo-selectivities and afforded *E*,cis-configured isomer *cis*-**21** with de's ⩾98% in 84% yield. Similarly, a mixture of *cis*-**5b**/*trans*-**5b** was converted via *cis*-**20**/*trans*-**20** and *cis*-**21**/*trans*-**21** to *cis*-**21** with de's ⩾98% in 81% overall yield.

Surprisingly, the Pd(0)-catalyzed isomerization of *trans*-**21** to *cis*-**21** proceeded with complete retention of the configuration of the double bond.[14b] The reaction of aziridine *trans*-**21** with $Pd(PPh_3)_4$ is expected to afford π-allyl–Pd(II) complex **22** (Scheme 10), which has to undergo an inversion of configuration at Cβ en route to *cis*-**21**. A typical π–σ–π-isomerization of **22** would furnish complex **23**,[15] the intramolecular substitution of which should give, however, *Z*-configured aziridine *cis*-**24** and not *E*-configured aziridine *cis*-**21**. This shows,

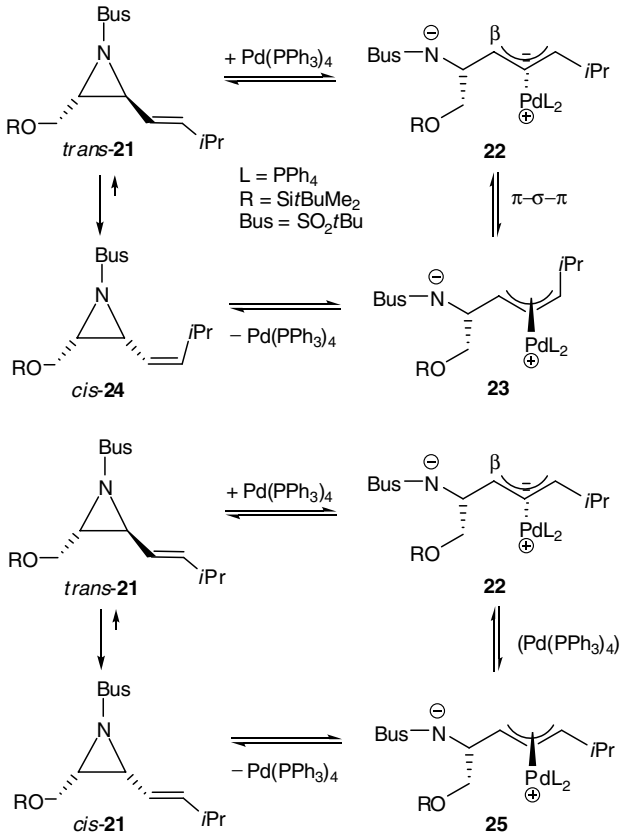
Table 3. Synthesis of cycloalkenyl aziridine carboxylates from cyclic 1-alkenyl aminosulfoxonium salts and the imino ester

18	*n*	**11** Cis:trans	Yield (%)	Cis		Trans		**4** Yield (%)
				ee[a] (%)	Yield (%)	ee[a] (%)	Yield (%)	
a	1	60:40[b]	70	79	—	90	—	80
b	2	60:40	73	76	42	56	28	81
c	3	60:40	71	78	41	57	26	76
d	4	50:50	66	70	29	25	30	70

[a] Determined by HPLC, Chiralpack-IA.
[b] Inseparable mixture.



Scheme 9. Palladium(0)-catalyzed stereoselective isomerization of an *E*-alkenyl *trans*-aziridine methanol derivative to its *E*-cis-isomer.



Scheme 10. Mechanistic rationalization of the Pd(0)-catalyzed isomerization of *trans*-**21** to *cis*-**21**.

that a different reaction pathway had prevailed. Either an intramolecular *syn* attack of the N-atom at the allyl moiety of **22**[15] had occurred or an isomerization of **22** had taken place with formation of π-allyl–Pd(II) complex **25**,[15] the intramolecular substitution of which gave *cis*-**21**. Such an isomerization could be accomplished by a nucleophilic substitution of **22** by $Pd(PPh_3)_4$ via an *anti*-attack of the Pd(0)-complex at the allyl moiety.[16,17] Thus, the reaction of $Pd(PPh_3)_4$ with *trans*-**21** and *cis*-**21** perhaps resulted in the establishment of an equilibrium in which *E*,cis-configured aziridine *cis*-**21** dominated because of its higher stability.[14]

Acknowledgments

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