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Published on Web 05/13/2006

Functionalized Chiral Vinyl Aminosulfoxonium Salts: Asymmetric Synthesis and Application to the Synthesis of Enantiopure Unsaturated Prolines, β,γ-Dehydro Amino Acids, and Cyclopentanoid Keto Aminosulfoxonium Ylides

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Abstract: Methylation of the enantiopure functionalized vinyl sulfoximines **5a**−**e** and **14a**−**d** followed by a F^- ion or DBU-mediated isomerization of the vinyl aminosulfoxonium salts **7a**−**e** and **15a**−**d**, respectively, gave the allyl aminosulfoxonium salts **10a**−**e** and **17a**−**d**, respectively. A concomitant intramolecular substitution of the aminosulfoxonium group of **10a**−**e** and **17a**−**d** by the amino group afforded the unsaturated prolines **8a**−**e** and **18a**−**d**, respectively. The starting vinyl sulfoximines are accessible through a highly selective and stereo-complementary aminoalkylation of the corresponding sulfonimidoyl-substituted mono- and bis(allyl)titanium complexes with the imino ester **4**. The vinyl aminosulfoxonium salts **34**, **7a**−**d**, and *E*-**15c** experienced upon treatment with the Cl^- ion a migratory substitution with formation of the δ-chloro-β,γ-dehydro amino acids **36**, *E/Z*-**37a**−**d**, and **38**, respectively. A migratory substitution of the hydroxy-substituted vinyl aminosulfoxonium salts **46a** and **46b** furnished the δ-chloro allyl alcohols *E/Z*-**48a** and *E*-**48b**, respectively. A facile one-pot conversion of the vinyl sulfoximines **31b**, **5c** and **45a** to the allyl chlorides **36**, *E/Z*-**37c** and *E/Z*-**48a**, respectively, was achieved upon treatment with a chloroformiate. A tandem cyclization of the vinyl aminosulfoxonium salts **7b**, Al-**7b** and **57** with LiN(H)*t*Bu yielded the cyclopentanoid keto aminosulfoxonium ylides **54**, Al-**54**, **59**, **60** and **61**, respectively. The structure of the tricyclic keto aminosulfoxonium ylide Al-**54** has been determined by X-ray crystal structure analysis. Ab initio calculations and a NBO analysis of the tricyclic keto aminosulfoxonium ylide **XXIII** show a polar structure stabilized by electrostatic interactions between the ylidic C atom and both the carbonyl C atom and the S atom.

Introduction

α-Amino acids and in particular proline derivatives have received much attention in recent years.[1] Peptide mimetics containing modified prolines are interesting probes for receptor studies and for the development of new drugs. In particular, 3-substituted prolines are being currently considered as conformationally restricted arginine, norleucine, phenylalanine, tyrosine, aspartic acid, and glutamic acid analogues[2] for the development of small molecule drugs. Therefore, the synthesis and biological activity of mono-[2−7] and bicyclic[8] prolines are being intensively studied.

Of special interest are 3,4-disubstituted prolines because of the occurrence of this substitution pattern in the kainoid amino acids.[9] Because of their ability to function as conformationally restricted L-glutamic acid analogues, the kanoid amino acids show neuroexcitatory properties and are, as such, interesting

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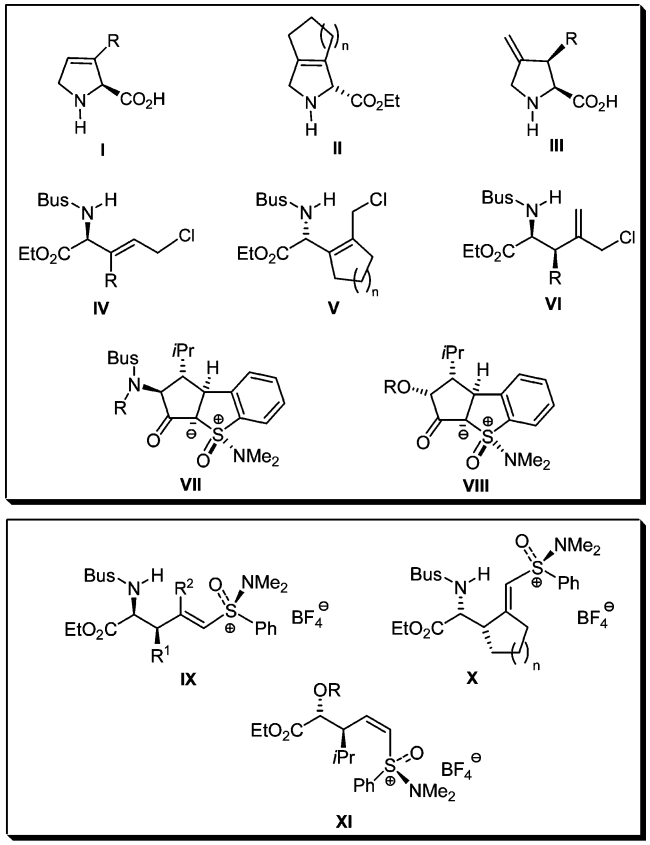

Figure 1. Unsaturated prolines, δ-chloro-β,γ-dehydro amino acids, cyclopentanoid keto aminosulfoxonium ylides and chiral functionalized vinyl aminosulfoxonium salts.

probes for a study of neurological disorder including Alzheimer's disease.[10] Despite the considerable synthetic activity in the field of proline derivatives, there is a lack of methods for the enantioselective synthesis of mono- and bicyclic 3,4-unsaturated prolines of type **I** and **II**, respectively and of 4-methylene prolines of type **III** (Figure 1).[7] Proline derivatives of this type should be interesting starting materials for the synthesis of monocyclic 3-mono- and 3,4-disubstituted prolines,[2−7] bicyclic prolines,[8] and kanoid amino acids.[9] We had recently observed that the amino-substituted cyclic vinyl aminosulfoxonium salts **XII** undergo upon treatment with diazabicyclo[5,4,0]-undec-7-ene (DBU) a migratory cyclization with formation of the unsaturated bicyclic prolines **XIV** (Figure 2).[11]

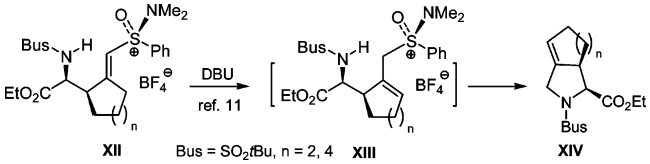

Figure 2. Migratory cyclization of cyclic amino-substituted vinyl aminosulfoxonium salts.

Key to the facile conversion of the vinyl aminosulfoxonium salts **XII** via the allyl aminosulfoxonium salt **XIII** to prolines **XIV** is the ability of the aminosulfoxonium group to act as both a powerful carbanion-stabilizer and an excellent nucleofuge.[12−14] These features make the aminosulfoxonium group a synthetically very interesting one, the potential of which has, however, not been fully explored.[12] In particular vinyl aminosulfoxonium salts have received only little attention.[12b] For example, it was only recently that the facile α-elimination of chiral hydroxy-substituted vinyl aminosulfoxonium salts with formation of substituted alkylidene carbenes has been recognized, a feature which led to the development of enantioselective syntheses of 2,3-dihydrofurans[13] and homopropargyl alcohols.[14]

We now describe an asymmetric synthesis of monocyclic 3,4-unsaturated prolines of type **I** and 4-methylene prolines of type **III**[15] through a F^- ion mediated migratory cyclization of the functionalized vinyl aminosulfoxonium salts of type **IX**. In addition, a complementary migratory substitution of aminosulfoxonium salts of type **IX** and **X** by the Cl^- ion is described, which enables an asymmetric synthesis of δ-chloro-β,γ-dehydro α-amino acids of type **IV**−**VI**. The dehydro amino acids **IV**−**VI** are expected to be useful starting materials for the enantioselective synthesis of substituted β,γ-dehydro α-amino acids[16] which are of considerable interest because of their natural occurrence and their ability to act as irreversible inhibitors of pyridoxal phosphate-dependent enzymes. The intramolecular substitution of chlorides of type **V** allows an enantioselective synthesis of bicyclic 3,4-unsaturated proline of type **II**, the regioisomers of prolines **XIV**.

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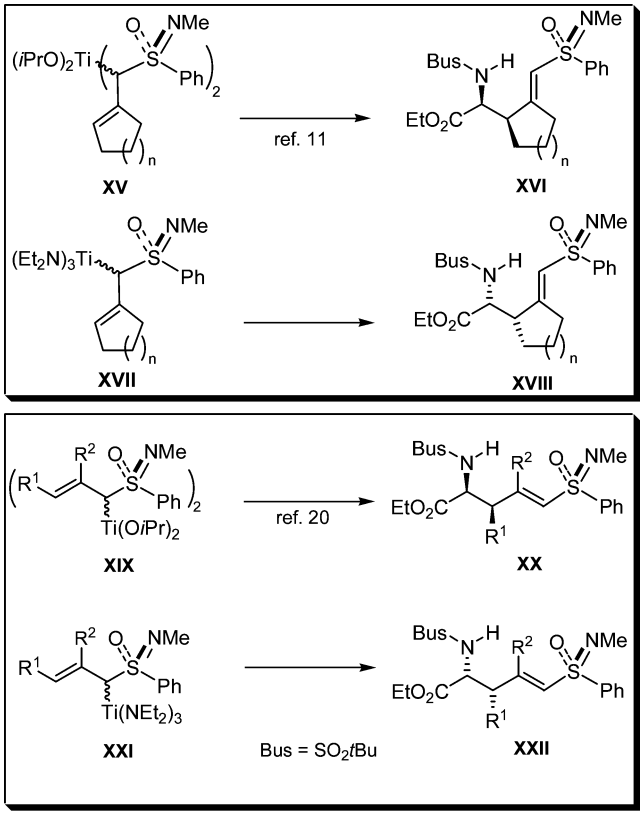
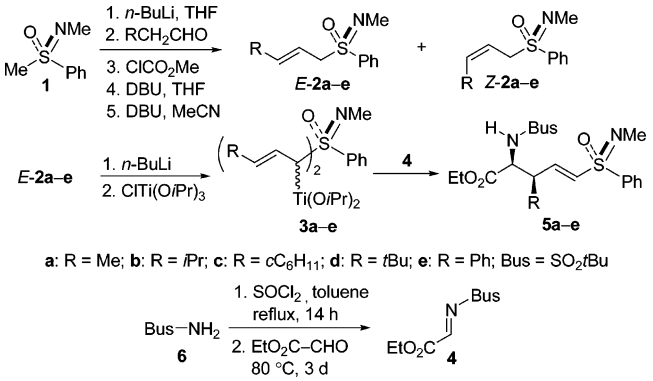


Figure 3. Chiral sulfonimidoyl-substituted allyl titanium complexes and chiral amino-substituted vinyl sulfoximines.

As a last example of the diverse reactivity of vinyl aminosulfoxonium salts of type **IX** and **XI** we describe their tandem cyclization with lithium *tert*-butylamide, which leads to the formation of the novel enantio- and diastereopure tricyclic cyclopentanoid aminosulfoxonium ylides **VII** and **VIII**, respectively, the structure of which has been studied by X-ray crystal structure analysis and ab initio calculations. Cyclopentanoid ylides of this type could perhaps serve as starting material for the asymmetric synthesis of highly substituted amino- and hydroxy cyclopentanones[17] through a ring-opening epoxidation reaction with aldehydes at the C−S bond.[12c,g]

The enantio- and diastereopure functionalized vinyl sulfoximines **XVI** and **XX**, required as starting material for the synthesis of the aminosulfoxonium salts **XII** and **IX**, respectively, are prepared, as previously reported,[15,18−20] through a highly regio− and diastereoselective aminoalkylation of chiral bis(allyl)titanium complexes of type **XV** and **XIX**, respectively, with *N*-*tert*-butylsulfonyl imino ester (Figure 3). We now describe a stereo-complementary γ-aminoalkylation of chiral mono(allyl)titanium complexes of type **XVII** and **XXI** giving the functionalized vinyl sulfoximines **XVIII** and **XXII**, respectively, the C atoms of which have the opposite configuration. Both the bis(allyl)titanium complexes and the mono(allyl)-titanium complexes are readily accessible from the corresponding (*S*)-configured lithiated allyl sulfoximines simply by using $ClTi(OiPr)_3$ and $ClTi(NEt_2)_3$ as titanation reagents.[21,22]

Scheme 1. Synthesis of Functionalized Vinyl Sulfoximines



Results and Discussion

I. Unsaturated Prolines. I.a. 3,4-Dehydro Prolines. Treatment of the sulfonimidoyl-substituted bis(allyl)titanium(IV) complexes **3a**−**e**,[21] which were prepared from the corresponding enantiomerically pure allyl sulfoximines *E*-**2a**−**e** through titanation following lithiation, with the *N*-Bus imino ester **4**[19] afforded the corresponding functionalized vinyl sulfoximines **5a**−**e**, respectively, with high regio- and diastereoselectivities in good yields as described previously (Scheme 1).[20] The α-imino ester **4** was prepared from sulfonamide **6**, using a modified version of our previously reported procedure,[19] which allowed an increase of the yield by 30% to 93%.

Gratifyingly, the new *tert*-butyl-substituted titanium complex **3d**, which was obtained in a similar way from the allyl sulfoximine *E*-**2d**, also reacted with **4** with high regio- and diastereoselectivities (≥98% de) and furnished the *tert*-butyl-substituted vinyl sulfoximine **5d** in 84% yield. The *tert*-butyl-substituted allyl sulfoximine **2d** in turn has been obtained as a single *E*-isomer in 86% yield starting from (*S*)-sulfoximine **1**[23] and 3,3-dimethylbutanal following the one-pot addition−elimination−isomerization (AEI) route.[21] The allyl sulfoximines **2a**−**c** and **2e** were synthesized, as described previously, by the AEI route starting from **1** and the corresponding aldehydes.[21] While **2e** was formed as a single *E*-isomer, **2a**, **2b**, and **2c** had been obtained as *E*/*Z*-mixtures in ratios of 70:30, 88:12, and 92:8, respectively. The respective *E*- and *Z*-isomers were separated by chromatography, and the *Z*-isomers were recycled through treatment with DBU in MeCN to again afford a mixture of the corresponding *E*/*Z*-isomers which were separated.

The synthesis of the 3,4-dehydro prolines **8a**−**e** started with the activation of the corresponding vinyl sulfoximines **5a**−**e** through methylation at the N atom upon treatment with Me_3OBF_4 (1.1 equiv) in CH_2Cl_2 at room temperature for 2 h (Scheme 2). The thus obtained vinyl aminosulfoxonium salts **7a**−**e** (≥95% yield) were then subjected to a treatment with KF (5−10 equiv) and a small amount of water in CH_2Cl_2 at room temperature under heterogeneous conditions, which afforded the corresponding proline derivatives **8a**−**e** with ≥98% ee in good yields (Table 1).

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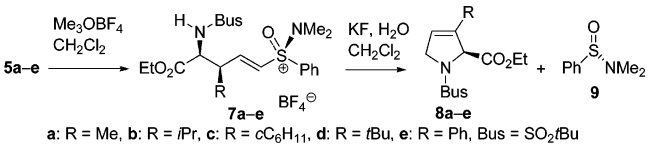
Scheme 2. Synthesis of 3,4-Dehydro Prolines



a: R = Me, **b**: R = *i*Pr, **c**: R = *c*C_6H_{11}, **d**: R = *t*Bu, **e**: R = Ph, Bus = SO_2*t*Bu

Table 1. Synthesis of 3,4-Dehydro Prolines

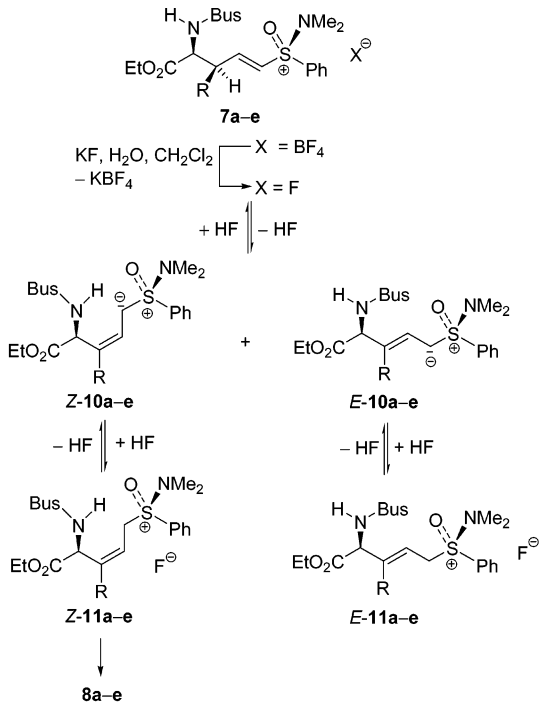
entry	derivative	R	*t* (h)	**8**, yield (%)	**9**, yield (%)
1	**a**	Me	3	51	83
2	**b**	*i*Pr	1	89	96
3	**c**	*c*C_6H_{11}	2	86	90
4	**d**	*t*Bu	1	92	96
5	**e**	Ph	0.75	66	84

The conversion of **5a**−**e** to **8a**−**e**, respectively, has also been carried out with similar results without isolation of **7a**−**e**. It is noteworthy that the yields were particularly good in the case of the proline derivatives **8b**−**d** which carry a sterically demanding substituent at the β-position (entries 2, 3, and 4). The moderate yield of the methyl-substituted proline derivative **8a** (entry 1) seems to be due to a competing fluoride ion-mediated deprotonation of the aminosulfoxonium salt **7a** at the N atom, leading to a generation of **4** and the corresponding allyl aminosulfoxonium salt (vide infra), which both in turn react with formation of the corresponding vinyl aziridine ester derivative.[24] In addition to the proline derivatives **8a**−**e** the sulfinamide **9** with ≥98% ee was isolated in each case in high yield. Conversion of sulfinamide **9** to (*S*)-sulfoximine **1**[23] of ≥98% ee, the starting material for the synthesis of *E*-**2a**−**e**, had already been described.[13]

Because of the high solubility of the vinyl aminosulfoxonium salts **7a**−**e** in CH_2Cl_2, it is assumed that in the three-phase system composed of solid KF, water, and CH_2Cl_2 an anion exchange between **7a**−**e** and KF occurs with formation of the ion pairs **7a**−**e** containing the F^- ion as counterion (Scheme 3).[25] The F^- ion which ought to be a reasonably strong base in CH_2Cl_2 then could cause a deprotonation of the aminosulfoxonium salts **7a**−**e** at the γ-position with formation of the corresponding allyl aminosulfoxonium ylides *Z*-**10a**−**e**.[11,13] A protonation of the ylides at the α-position would give the thermodynamically more stable allyl aminosulfoxonium salts *Z*-**11a**−**e**. Because of the high nucleofugacity of the allylic aminosulfoxonium group,[11,13] salts *Z*-**11a**−**e** could undergo a cyclization following a deprotonation of the sulfonamide group by the F^- ion with formation of the corresponding prolines **8a**−**e** and sulfinamide **9**. There is evidence (vide infra) suggesting that the reaction of **7a**−**e** with the F^- ion could also give to a minor extent the isomeric allyl aminosulfoxonium ylides *E*-**10a**−**e** and subsequently the allyl aminosulfoxonium salts *E*-**11a**−**e**. Salts *E*-**11a**−**e**, which cannot cyclize, may be, however, in equilibrium with *Z*-**11a**−**e**.

I.b. 4-Methylene Prolines. Having accomplished a synthesis of unsaturated prolines of type **I**, a perhaps facile synthesis of 4-methylene prolines of type **III** (cf. Figure 1) was envisioned starting from the functionalized β-methyl vinyl sulfoximines **14** (Scheme 4). It was speculated that the methyl-substituted vinyl aminosulfoxonium salts *E*-**15a**−**c** (Scheme 5, vide infra)

Scheme 3. Rationalization of the Formation of the 3,4-Dehydro Prolines



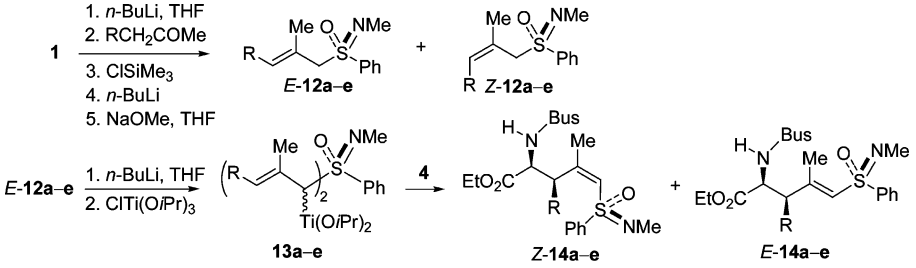
a: R = Me, **b**: R = *i*Pr; **c**: R = *c*C_6H_{11}, **d**: R = *t*Bu; **e**: R = Ph, Bus = SO_2*t*Bu

would experience a regioselective F^--catalyzed isomerization to the allyl aminosulfoxonium salts **17a**−**c**, leaving the stereogenic center at the γ-position intact, via the intermediate formation of the allyl aminosulfoxonium ylides **16a**−**c**. Deprotonation at the methyl group should be preferred over a deprotonation at the γ-position because of statistical reasons and the higher kinetic acidity of methyl hydrogen atoms. Cyclization of **17a**−**c** should afford the proline derivatives **18a**−**c**. Prerequisite to the successful realization of such a synthesis of **18a**−**c** would be a highly stereoselective reaction of the methyl-substituted titanium complexes **13a**−**c** with **4**. Aside of this objective it was of interest to see whether the methyl group of complexes **13a**−**c** would have any influence on the stereoselectivity of the reaction with **4**.

The enantiomerically pure allyl sulfoximines **12a**, **12b**,[13] **12c**, **12d**, and **12e**[26] were obtained from (*S*)-sulfoximine **1**[23] and the corresponding methyl ketones by the one-pot AEI-route in 68%, 75%, 72%, 61%, and 73% yield, respectively, including a separation and recycling of the *Z*-isomer.[27] The reaction sequence includes a deprotonation of sulfoximine **1** with *n*-BuLi followed by the addition of the lithiated sulfoximine to the ketone with formation of the corresponding lithium alcoholate (not shown in Scheme 4). Silylation of the lithium alcoholates with $ClSiMe_3$ and elimination of the corresponding silyl ethers with *n*-BuLi in THF at room temperature gave the corresponding vinyl sulfoximines (not shown in Scheme 4) as mixtures of isomers.[21] The crude vinyl sulfoximines were subjected to a NaOMe-catalyzed isomerization in THF to afford mixtures of the allyl sulfoximines *E*-**12a**−**e** and *Z*-**12a**−**e**, which were separated by preparative HPLC.[27] The configuration of the

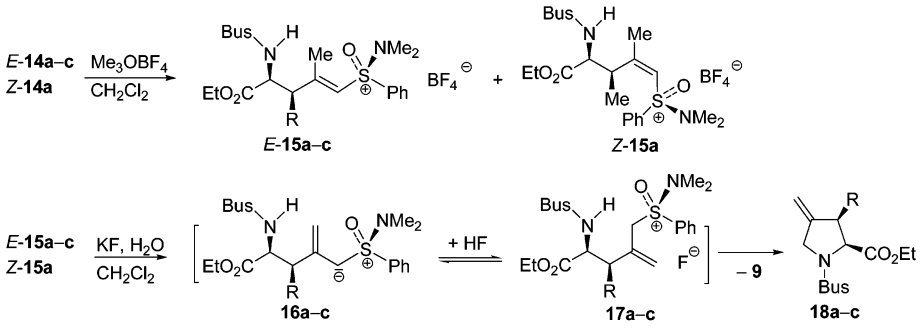
(24) Iska, V. B. R.; Tiwar, S. K.; Gais, H.-J.; Babu, G. S.; Adrien, A. Unpublished results.
(25) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429−452.
(26) Scommoda, M.; Gais, H.-J.; Bosshammer, S.; Raabe, G. *J. Org. Chem.* **1996**, *61*, 4379−4390.
(27) Gais, H.-J.; Müller, H.; Bund, J.; Scommoda, M.; Brandt, J.; Raabe, G. *J. Am. Chem. Soc.* **1995**, *117*, 2453−2466.

Scheme 4. Synthesis of Functionalized β-Methyl Vinyl Sulfoximines



a: R = Me, **b**: R = *i*Pr, **c**: R = *c*C_6H_{11}, **d**: R = $(CH_2)_2OSitBuMe_2$, **e**: R = Ph, Bus = SO_2tBu

Scheme 5. Synthesis of 4-Methylene Prolines with KF



a: R = Me, **b**: R = *i*Pr, **c**: R = *c*C_6H_{11}, Bus = SO_2tBu

Table 2. Synthesis of Functionalized β-Methyl Vinyl Sulfoximines

entry	derivative	R	*E*-**14**, yield (%)	*Z*-**14**, yield (%)
1	**a**	Me	33	38
2	**b**	*i*Pr	64	10
3	**c**	*c*C_6H_{11}	45	16
4	**d**	$(CH_2)_2OSitBuMe_2$	14[a]	36
5	**e**	Ph	58	–

[a] The allyl sulfoximine **12d** was recovered in 12% yield.

Table 3. Synthesis of 4-Methylene Prolines with KF

entry	derivative	R	**18**, yield (%)	**9**, yield (%)
1	**a**	Me[a]	63	98
2	**a**	Me[b]	54	97
3	**b**	*i*Pr	77	94
4	**c**	*c*C_6H_{11}	72	84

[a] Starting from *E*-**14a**°. [b] Starting from *Z*-**14a**.

double bonds of *E*-**12a**−**e** and *Z*-**12a**−**e** was assigned by ^{1}H NOE experiments. Isomerization of the minor isomers *Z*-**12a**−**e** with NaOMe in THF again delivered a mixture of *E*-**12a**−**e** and *Z*-**12a**−**e** which were separated. Lithiation of the enantiomerically pure *E*-configured allyl sulfoximines *E*-**12a**−**e** with *n*-BuLi (1.1 equiv) at −78 °C in THF followed by a titanation with ClTi(*i*OPr)$_3$ (2.1 equiv) gave the corresponding bis(allyl)-titanium(IV) complexes **13a**−**e** which were, however, not isolated. Gratifyingly, the reaction of complexes **13a**−**e** with **4**[19] (1.1 equiv) also proceeded with high regio- and diastereoselectivities and afforded the corresponding functionalized β-methyl-vinyl sulfoximines *E*-**14a**−**e** and *Z*-**14a**−**e** in good yields (Table 2).

The *E*- and *Z*-isomers of **14a**−**e** were each formed with ≥98% de. Because of the further synthetic studies, the *E*- and *Z*-isomers of **14a**−**e** were separated by preparative HPLC. Thus, both the methyl-substituted titanium complexes **13a**−**e** and the unsubstituted titanium complexes **3a**−**e** exhibit in the reaction with **4** similar high syn diastereoselectivities. However, the methyl group of **13a**−**e** causes the reaction to be of low *E*/*Z*-selectivity in regard to the double bond. Such a difference in the *E*/*Z*-selectivity between **13a**−**e** and **3a**−**e** was not observed in their reactions with aldehydes.[28] Interestingly, the reaction of the phenyl-substituted titanium complex **13e** with **4** was highly *E*-selective. The configurations of the double bonds of *E*-**14a**−**e** and *Z*-**14a**−**e** were assigned by ^{1}H NOE experiments. A final proof for the configuration of all stereogenic elements of *E*-**14b** was provided by an X-ray crystal structure analysis (Figure 4). The configuration of *Z*-**14a** was secured by conversion of both *E*-**14a** and *Z*-**14a** to proline **18a** (vide infra).

Methylation of the vinyl sulfoximines *E*/*Z*-**14a**−**c** through treatment with Me_3OBF_4 (1.1 equiv) in CH_2Cl_2 afforded the corresponding aminosulfoxonium salts *E*/*Z*-**15a**−**c**, respectively, in high yields (≥95%) (Scheme 5). Isomerization of *E*/*Z*-**15a**−**c** and cyclization of **17a**−**c** both proceeded readily upon treatment of the former salts with KF (5−10 equiv) and a small amount of water in CH_2Cl_2 under heterogeneous conditions and furnished the corresponding *cis*-configured 3-substituted 4-methylene prolines **18a**−**c**, respectively, with ≥98% ee and ≥98% de in medium to good yields (Table 3).

Both isomers *Z*-**15a** and *E*-**15a** afforded the proline derivative **18a**. Thus, a separation of the *E*- and *Z*-isomers is not required for the synthesis of **18a** and presumably also not for that of **18b** and **18c**. The conversion of *E*/*Z*-**14a**−**c** to **18a**−**c**, respectively, has been carried out with the same results without isolation of *E*/*Z*-**15a**−**c**. In addition to the proline derivatives **18a**−**c** sulfinamide **9** with ≥98% ee was isolated in each case in high yield.

The facile cyclization of the allyl aminosulfoxonium salts **17a**−**c** with formation of **18a**−**c**, respectively, prompted us to study the cyclization of a derivative of **17**, the double bond of

(28) Gais, H.-J.; Loo, R.; Roder, D.; Das, P.; Raabe, G. *Eur. J. Org. Chem.* **2003**, 1500−1526.

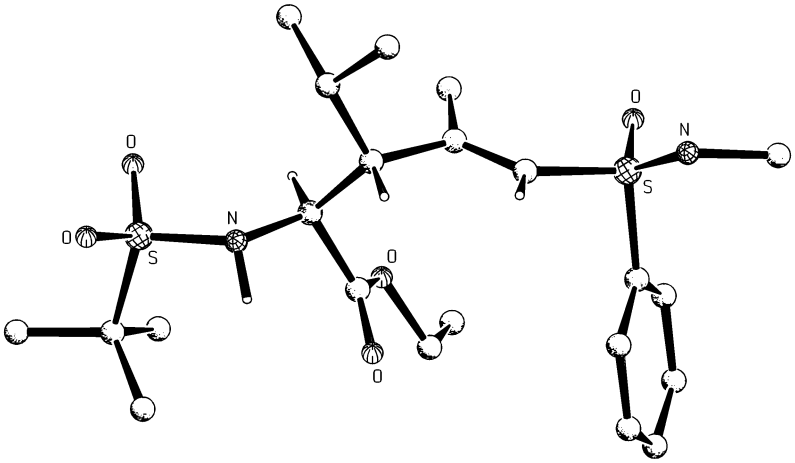
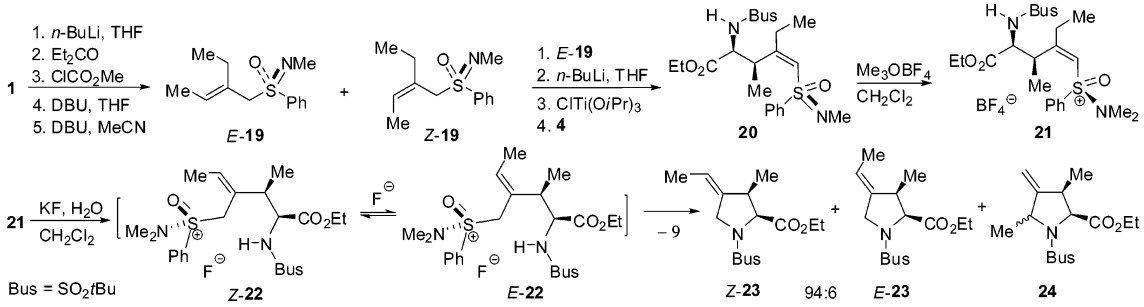


Figure 4. Structure of the functionalized β-methyl vinyl sulfoximine *E*-**14b** in the crystal.

Scheme 6. Synthesis of 4-Ethylidene Prolines



which carries an additional substituent. It was hoped to obtain information whether the cyclization involves a S_N or S_N' reaction. The corresponding allyl sulfoximine **19** was prepared as an *E*/*Z*-mixture starting from sulfoximine **1** and diethyl ketone by the AEI-route (Scheme 6). Chromatographic separation of the isomers and recycling of the *Z*-isomer *Z*-**19** afforded the enantiomerically pure *E*-isomer in 53% yield.

The aminoalkylation of *E*-**19** with **4** following lithiation and titanation of the sulfoximine gave with high regio- and diastereoselectivity the Z-configured functionalized β-ethyl vinyl sulfoximine **20** in 60% yield. Activation of sulfoximine **20** through methylation with Me_3OBF_4 furnished the vinyl aminosulfoxonium salt **21** which upon treatment with KF and a small amount of water in CH_2Cl_2 afforded a mixture of prolines *Z*-**23** and *E*-**23** in a ratio of 94:6 in 46% yield based on **20** and the α-methylated proline **24**, the configuration of which was not determined, in 5% yield based on **20**.

The configuration of *Z*-**23** was revealed by X-ray structure analysis (Figure 5). Besides prolines *Z*/*E*-**23** sulfinamide **9** was isolated in 84% yield. This result shows that the intermediate allyl aminosulfoxonium salts *Z*-**22** and *E*-**22** preferentially cyclize through a S_N reaction. Noteworthy is the high *Z*-selectivity of the cyclization. This may be ascribed to (1) an unselective formation of the allyl aminosulfoxonium salts *Z*-**22** and *E*-**22**, (2) a fast F^--catalyzed equilibration of *Z*-**22** and *E*-**22**, and (3) a cyclization of *Z*-**22** being faster than that of *E*-**22** because of less 1,3-allylic strain in the transition state, leading to *Z*-**23**. Alternatively, the preferential formation of *Z*-**23** could be rationalized by proposing a highly selective isomerization of **21** to *Z*-**22** being configurationally stable.

The synthesis of the substituted proline derivative **18d** (Scheme 7), a potential starting material for the synthesis of kainoid amino acids, from the aminosulfoxonium salt *Z*-**15d** could not be accomplished by using KF/H_2O for the migratory cyclization of because of a concomitant desilylation. However, treatment of the vinyl aminosulfoxonium salt *Z*-**15d** with DBU in CH_2Cl_2 caused a facile migratory cyclization and gave the proline derivative **18d** in 78% yield besides sulfonamide **9** (81%). Similarly, reaction of the vinyl aminosulfoxonium salt *E*-**15b** with DBU afforded proline **18b** in 83% yield and **9** in 94% yield (cf. Scheme 5). The vinyl salts *E*-**15b** and *Z*-**15d** are most likely converted by DBU via the allyl ylides **16b** and **16d**, respectively, to the allyl aminosulfoxonium salts **17b** and **17d**, respectively, which suffer a DBU-assisted cyclication with formation of the corresponding prolines.

I.c. Deprotection of the Unsaturated Prolines. The final step of the synthesis of the unsaturated prolines of type **I** and

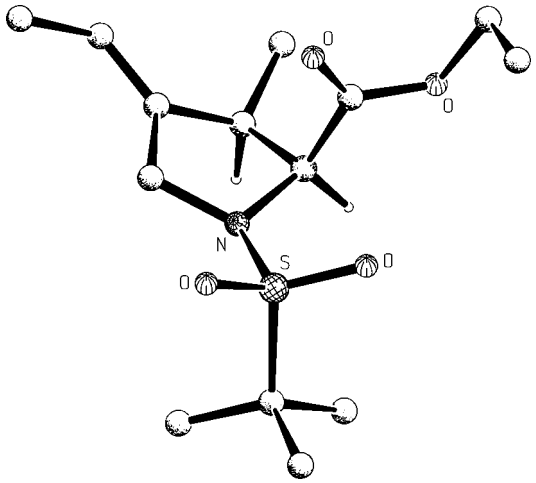
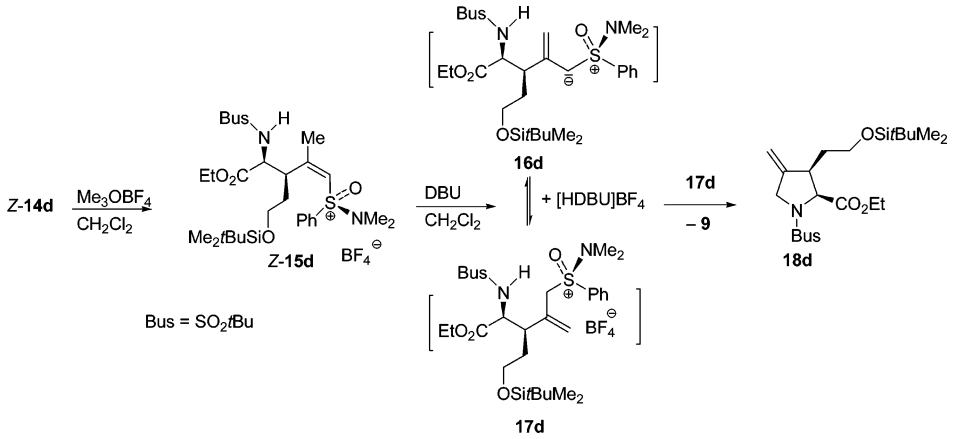
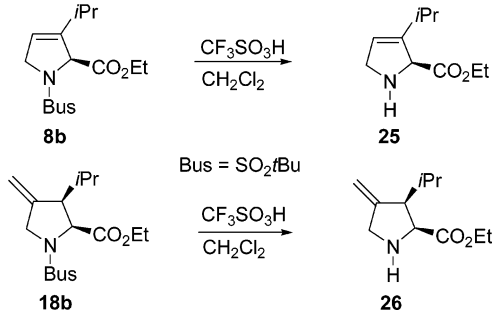


Figure 5. Structure of the 4-ethylidene proline *Z*-**23** in the crystal.

Scheme 7. Synthesis of a Functionalized 4-Methylene Proline with DBU



Scheme 8. Deprotection of Unsaturated *N*-Bus Prolines



III is the deprotection of the N atom of **8** and **18**. Because of the deliberate selection of the Bus group, this transformation should be possible by applying a water-free acid.[29] Indeed, treatment of the proline derivatives **8b** and **18b** with CF_3SO_3H in CH_2Cl_2 (0.05−0.1 M) afforded the proline esters **25** in 80% yield and **26** in 76% yield, respectively (Scheme 8).

Care had to be taken in the case of the isolation of **25** and **26** from the acidic reaction mixture. Workup was carried out by the addition of water and extraction with CH_2Cl_2 following the adjustment of the pH of the mixture to a value of 6.8 by the addition of 0.1 M NaOH. The adjustment of the pH to a value of 9 prior to the extraction of **26** surprisingly caused a partial epimerization at C2 and the formation of a mixture of **26** and its trans diastereomer. A partial epimerization of **26** was also observed upon treatment of the ester with NaOMe, NEt_3, and DBU. Interestingly, an epimerization of the protected proline ester **18b** was not observed with the later bases.

II. Stereo-Complementary Aminoalkylation of Sulfonimidoyl-Substituted Mono(allyl)titanium Complexes. We had previously shown that the bis(allyl)titanium complexes **28a**−**d**, which are derived from the corresponding cyclic allyl sulfoximines **27a**−**d** through lithiation and titanation with $ClTi(OiPr)_3$, react with the α-imino ester **4** with high regio- and diastereoselectivities at the γ-position to give *E*-*syn*- and *Z*-*syn*-configured functionalized vinyl sulfoximines *E*-**29a**−**d** and *Z*-**29a**−**d**, respectively, both with very high diastereoselectivities in ratios of 1.4:1, 5:1, 1:3, and 1:12, respectively (Scheme 9).[20] Similarly the titanium complexes **28a**−**d** react with aldehydes with high regio- and diastereoselectivities at the γ-position to afford the corresponding *anti*-configured homoallyl alcohols having, however, a *Z*-configured vinylic sulfoximine.[21] In contrast it was found that the mono(allyl)titanium complexes **30a**−**d**, which are also readily available from **27a**−**d** through lithiation and titanation with $ClTi(NEt_2)_3$, react with aldehydes with high regio- and diastereoselectivities at the α-position to furnish the corresponding allyl sulfoximines.[21,22,30] It was thus of interest to study the reactions of **30a**−**d** with **4** to see whether the mono(allyl)titanium complexes show a similar reactivity toward the imino ester.

Table 4. Synthesis of Functionalized Cyclic Vinyl Sulfoximines

				E-**31**		*E*-**29**	
entry	derivative	*n*	*E*-**31**:*E*-**29**	yield (%)	de (%)	yield (%)	de (%)
1	**a**	1	6:1	70	≥98	14	≥98
2	**b**	2	10:1	69	≥98	8	≥98
3	**c**	3	24:1	82	≥98	4	≥98
4	**d**	4	46:1	87	≥98	2	≥98

Surprisingly, the mono(allyl)titanium complexes **30a**−**d** reacted with **4** also at the γ-position and gave the corresponding functionalized cyclic vinyl sulfoximines **31a**−**d** and **29a**−**d** in ratios ranging from 6:1 to 46:1 (Table 4), both with very high diastereoselctivities. The ratio of the two diastereomers is strongly dependent on the ring size of the allyl sulfoximine, being the highest for the eight-membered cyclic derivative **30d** (entry 4). It is interesting to note that the major diastereomers, **31a**−**d**, derived from the mono(allyl)titanium complexes **30a**−**d** and the major diastereomers obtained from the bis(allyl)titanium complexes, **28a**−**d**, have the opposite configuration at the two stereogenic C atoms. Thus, both enantiomers of a given target molecule derived from **29** and **31** after substitution of the sulfoximine group (vide infra) are accessible from one enantiomer of the corresponding allyl sulfoximine, **27**, merely by choice of the titanation reagent $ClTi(NEt_2)_3$ and $ClTi(OiPr)_3$.

The configuration of the seven-membered sulfoximine **31c** was determined by X-ray crystal structure analysis (Figure 6).[31]

The observation of a stereo-complementary aminoalkylation of the cyclic titanium complexes **28a**−**d** and **30a**−**d** with **4** led us to investigate whether the acyclic titanium complexes **32a** and **32d** (Scheme 10) also show a reactivity toward **4** being

(29) Sun, P.; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 8604−8608.

(30) Gais, H.-J.; Babu, G. S.; Günter, M.; Das, P. *Eur. J. Org. Chem.* **2004**, 1464−1473.

(31) Only crystals of minor quality could be obtained from compound **31c**. Although the diffraction data collected at 150 K were sufficient for a solution of the structure, they did not allow a complete anisotropic refinement of the structure. Thus, the molecule shown in Figure 5 is the result of an isotropic refinement and merely a proof of the three-dimensional connection of the atoms in space.

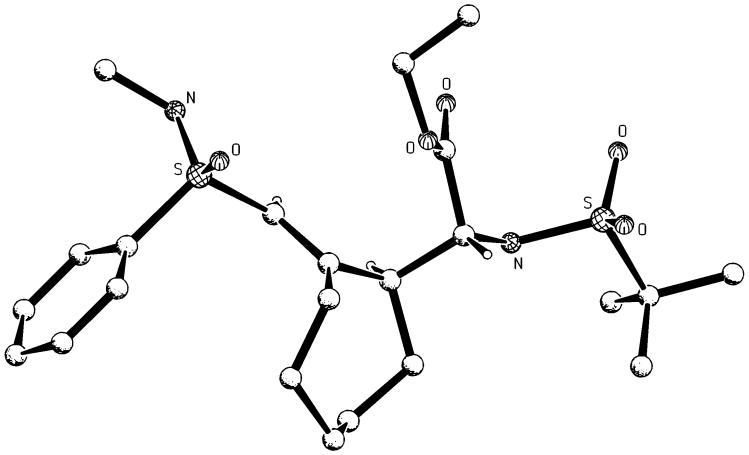
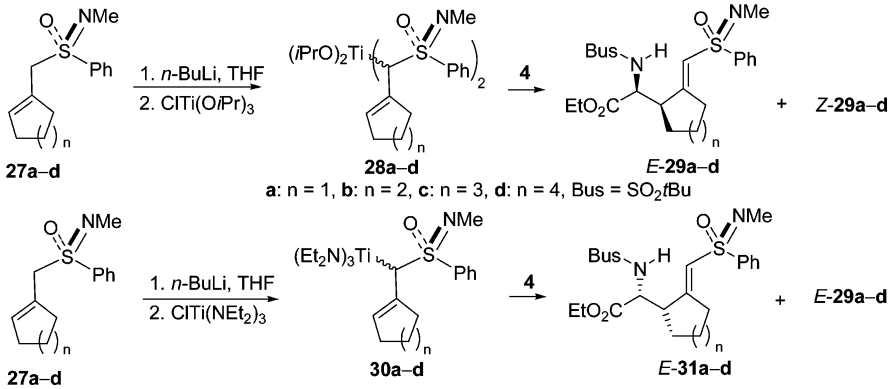


Figure 6. Structure of the functionalized cyclic vinyl sulfoximine **31c** in the crystal.

Scheme 9. Stereo-Complementary Aminoalkylation of Cyclic Sulfonimidoyl-Substituted Allyl Titanium Complexes



Scheme 10. Aminoalkylation of Acyclic Sulfonimidoyl-Substituted Mono(allyl)titanium Complexes

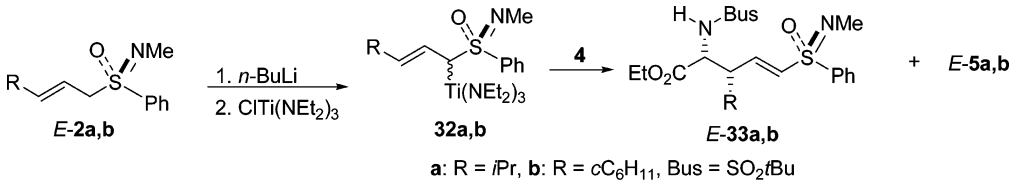


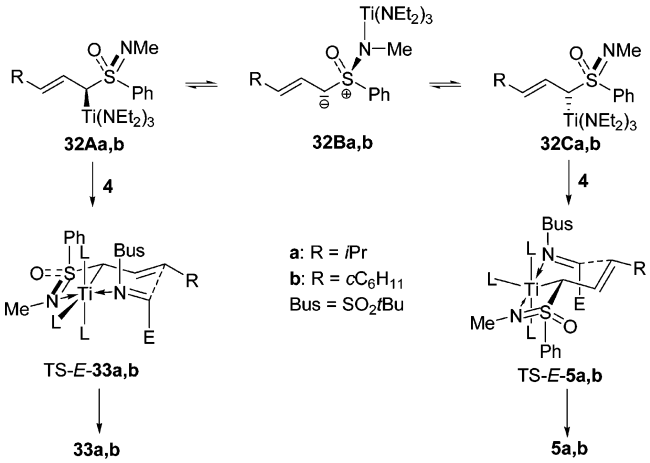
Table 5. Synthesis of Functionalized Acyclic Vinyl Sulfoximines

		33		5	
derivative	**33**:**5**	yield (%)	de (%)	yield (%)	de (%)
a	6:1	56	≥98	10	≥98
b	2:1	58	≥98	32	≥98

stereo-complementary to that of the corresponding bis(allyl)-titanium complexes **3a** and **3d**. Treatment of **32a** and **32b** with **4** afforded the corresponding functionalized acyclic vinyl sulfoximines **33a**,**b** and **5a**,**b** (Table 5), both with very high diastereoselectivities.

A NMR spectroscopic investigation of the structure of the acyclic mono(allyl)titanium complexes **32a** and **32b** had revealed a low configurational stability of the Cα atom and a fast Cα,N-shift of the titanium atom leading to the formation of an equilibrium mixture of complexes **32A**−**C** in ratios of 84:13:3 and 86:12:2, respectively (Scheme 11).[21,22] The formation of the *syn*-configured diastereomers **33** and **5** in the reaction of **32** with **4** can thus be rationalized, on the assumption of the operation of the Curtin-Hammett principle,[32] by proposing a stereo- and regioselective reaction of the ($S_{C\alpha}$)-configured

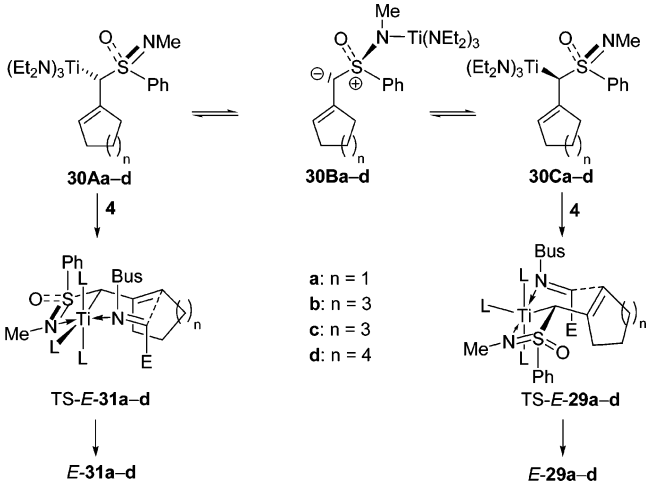
Scheme 11. Reactivity Model for the Aminoalkylation of the Acyclic Allyl Titanium Complexes **30a**−**d** with the α-Imino Ester **4**



complex **32A** with **4** through a six-membered cyclic transition state of type TS-*E*-**33** giving **33** and of the ($R_{C\alpha}$)-configured

(32) Seeman, J. L. *Chem. Rev.* **1983**, *83*, 83−134.

Scheme 12. Reactivity Model for the Aminoalkylation of the Cyclic Allyl Titanium Complexes **32a**,**b** with the α-Imino Ester **4**



complex **32C** with **4** through TS-*E*-**5** leading to **5**. The preferential formation of the *E*,$R_{C\alpha}$,$S_{C\beta}$-configured vinyl sulfoximine *E*-**33** points to a higher reactivity of the ($S_{C\alpha}$)-configured complex **32A**.

The similarity in the reactivity between the acyclic complexes **32a**,**b** and the cyclic complexes **30a**−**d** toward **4** gives strong support to the notion of the existence of a similar fast equilibrium between the complexes **A**−**C** also in the case of **30** (Scheme 12). Here the ($S_{C\alpha}$)-configured complex **30A** is proposed to react through a six-membered cyclic transition state of type TS-**31** to afford *E*-**31** and the ($R_{C\alpha}$)-configured complex **30C** with **4** through TS-***E***-**29** with formation of *E*-**29**. The preferential formation of the *E*,$R_{C\alpha}$,$S_{C\beta}$-configured vinyl sulfoximine *E*-**33** points to a higher reactivity of the ($S_{C\alpha}$)-configured complex **30A**.

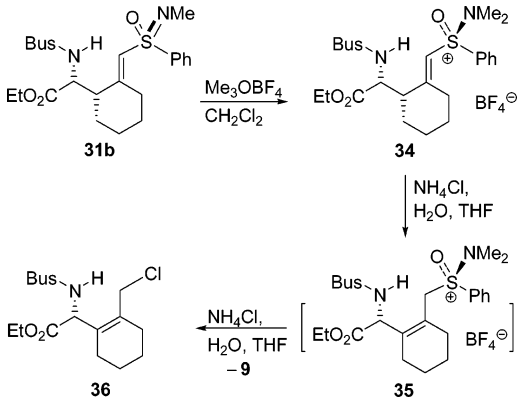
III. δ-Chloro-β,γ-Dehydro Amino Acids, δ-Chloro Allyl Alcohols and Bicyclic Prolines. III.a. *δ*-Chloro-*β*,*γ*-Dehydro Amino Acids. The synthesis of the 3,4-unsaturated proline derivatives **8a**−**e** from the acyclic vinyl aminosulfoxonium salts **7a**−**e**, respectively, led us to investigate the possibility of a similar synthesis of the bicyclic prolines of type **II** from the cyclic vinyl aminosulfoxonium salts **XVIII** (cf. Figures 1 and 3) by using KF as base. We had already observed that the migratory cyclization of the diastereomeric vinyl aminosulfoxonium salt **XII** with DBU gives the regioisomeric bicyclic prolines of type **XIV** (cf. Figure 2). Thus, it would synthetically be attractive to open an access to both regioisomers from the same starting material.

Activation of the cyclic vinyl sulfoximine **31b** through methylation with Me_3OBF_4 delivered the aminosulfoxonium salt **34** (Scheme 13). Surprisingly, an inadvertent treatment of salt **34** with NH_4Cl instead of KF in THF/water resulted in both a facile isomerization to the allyl aminosulfoxonium salt **35** and its concomitant substitution by the Cl^- ion and gave the allyl chloride **36** in 64% yield and sulfinamide **9** in 92% yield.

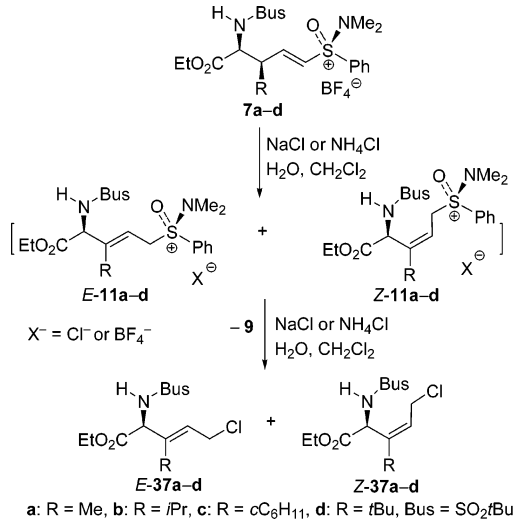
The unexpected facile migratory substitution of the vinyl aminosulfoxonium salt **34** by the Cl^- ion prompted a study of the acyclic vinyl aminosulfoxonium salts **7a**−**d** (Scheme 14) and *E*-**15c** (Scheme 15) to see whether this is a reactivity typical for vinyl and allyl aminosulfoxonium salts.

Treatment of the vinyl aminosulfoxonium salts **7a**−**d** either with NaCl or NH_4Cl and water in CH_2Cl_2 furnished a mixture

Scheme 13. Synthesis of a Cyclic δ-Chloro-β,γ-Dehydro Amino Acid



Scheme 14. Synthesis of Acyclic δ-Chloro-β,γ-Dehydro Amino Acids

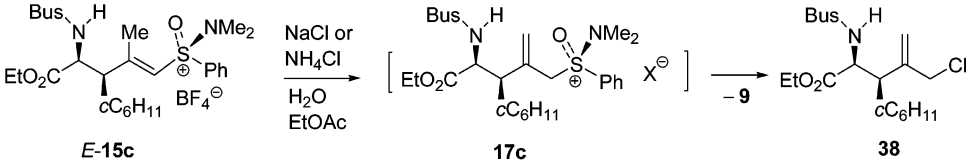


of the allyl chlorides *E*-**37a**−**d** and *Z*-**37a**−**d**, respectively, which were separated by chromatography, in good yields (Table 6). Surprisingly, the *tert*-butyl-substituted salt **7d** afforded only the *Z*-configured chloride *Z*-**37d**. Similarly, treatment of the methyl-substituted vinyl aminosulfoxonium salt *E*-**15c** with NaCl or NH_4Cl in water and ethyl acetate gave the allyl chloride **38** in 63% yield.

The vinyl aminosulfoxonium salts **34**, **7a**−**d**, and *E*-**15c** perhaps suffer a Cl^- ion-mediated isomerization to the allyl aminosulfoxonium salts **35**, *E*/*Z*-**11a**−**d**, and **17c**, respectively, which then experience an allylic substitution by the Cl^- ion with formation of the corresponding allyl chlorides and sulfinamide **9**. The vinyl aminosulfoxonium salts most likely form ion pairs in CH_2Cl_2 and EtOAc containing the Cl^- ion as the counterion. The Cl^- ion acts as a base in a way similar to that of the F^- ion to form the corresponding allyl aminosulfoxonium ylides, the protonation of which gives the thermodynamically more stable allyl aminosulfoxonium salts (cf. Scheme 3). In the case of unsaturated sulfones and sulfoximines the allyl isomer is strongly favored over the vinyl isomer in the equilibrium.[13,21,26,33] Because of the similarities in the structure of the sulfonimidoyl group and the aminosulfoxonium group which is, however, much more carbanion-stabilizing, it is to

(33) Lee, P. S.; Du, W.; Boger, D. L.; Jorgensen, W. L. *J. Org. Chem.* **2004**, *69*, 5448−5453.

Scheme 15. Synthesis of an Acyclic δ-Chloro γ-Methylene Amino Acid



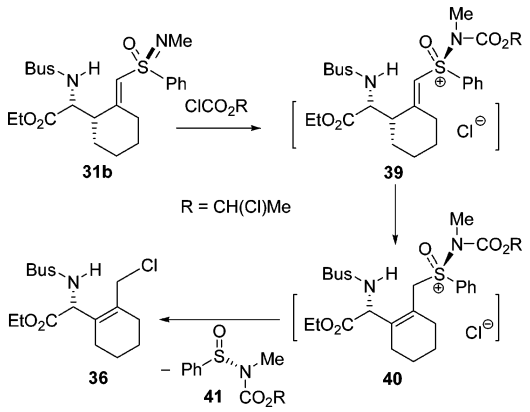
E-**15c** **17c** **38**

$X^- = Cl^-$ or BF_4^-, Bus = SO_2tBu

Table 6. Synthesis of Acyclic δ-Chloro-β,γ-Dehydro Amino Acids

derivative	R	*t* (d)	**37**, yield (%)	*E*:*Z*	**9**, yield (%)
a	Me	2.5	82	88:12	81
b	*i*Pr	3	93	80:20	94
c	cC_6H_{11}	2.5	89	66:34	80
d	*t*Bu	3	82	1:100	76

Scheme 16. One-Pot Synthesis of a Cyclic δ-Chloro-β,γ-Dehydro Amino Acid



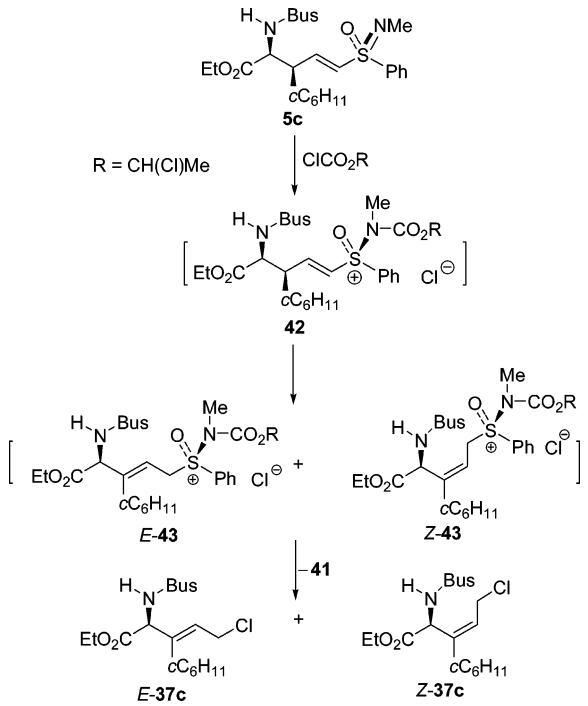
be expected that the aminosulfoxonium group also favors the allyl isomer. The difference in reactivity of the allyl aminosulfoxonium salts toward the Cl^- and the F^- ions, i.e., intermolecular substitution versus cyclization (vide supra), can be related to the differences in nucleophilicity and basisicity of the two anions. In the case of the migratory substitution of salts **34**, **7a**−**d**, and *E*-**15c** with NH_4Cl in the presence of water it could also be NH_3 which causes the isomerization.

Most interestingly, the allyl chloride **36** can also be obtained starting from the vinyl sulfoximine **31b** in a one-pot sequence by using a chloroformiate for the activation and migratory substitution (Scheme 16). Thus, treatment of **31b** with $ClCO_2$-CH(Cl)Me gave chloride **36** in 86% yield. In addition sulfinamide **41**[30,34] with >98% ee was isolated in 93% yield. Conversion of sulfinamide **41** to (*S*)-sulfoximine **1**[23] of ≥98% ee had already been described.[34]

The acyclic allyl chlorides of type **37** can also be obtained by the one-pot sequence starting from the vinyl sulfoximine **5** and using the chloroformiate (Scheme 17). Thus, treatment of **5c** with $ClCO_2CH(Cl)Me$ gave the allyl chloride **37c** as a *E*/*Z*-mixture in a ratio of 30:70 in 92% yield. In addition sulfinamide **41**[30,34] with >98% ee was isolated in 93% yield. Most likely sulfoximines **31b** and **5c** react with the chloroformiate with formation of the aminosulfoxonium salts **39** and **42**, respectively, which suffer a Cl^- ion-mediated isomerization to give the corresponding allyl aminosulfoxonium salts **40** and *E*/*Z*-**43**, respectively. Their substitution by the Cl^- ion yields chlorides

(34) Gais, H.-J.; Loo, R.; Roder, D.; Das, P.; Raabe, G. *Eur. J. Org. Chem.* **2003**, 1500−1526.

Scheme 17. One-Pot Synthesis of an Acyclic δ-Chloro-β,γ-Dehydro Amino Acid

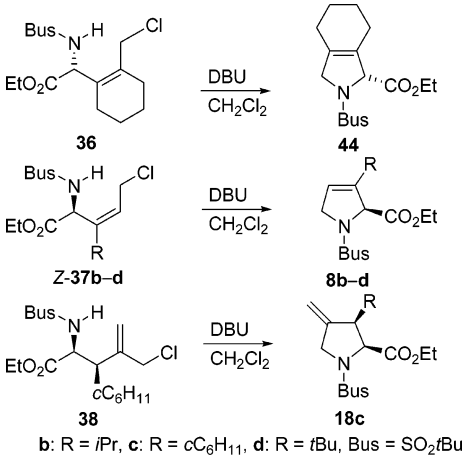


36 and *E*/*Z*-**37c**, respectively. Support for this mechanistic rationalization comes from a previous investigation in which we showed that allyl sulfoximines are readily converted to the corresponding chlorides and sulfinamide **41** upon reaction with the chloroformiate.[30,34] Interestingly, the *E*/*Z*-selectivities of the formation of chlorides *E*/*Z*-**37c** from the aminosulfoxonium salt **7c** and **42** are almost opposite.

III.b. Cyclization of δ-Chloro-β,γ-Dehydro Amino Acids. Treatment of chlorides **36**, *Z*-**37b**−**d**, and **38** with DBU gave the corresponding proline derivatives **44**, **8b**−**d**, and **18c**, respectively, in practically quantitative yields except **18c** which was obtained in only 66% yield (Scheme 18).

III.c. δ-Chloro Allyl Alcohols. Because of the ready availability of the hydroxy-substituted vinyl sulfoximines **45a** and **45b** (Scheme 19) from the corresponding bis(allyl)titanium complexes **XIV** (cf. Figure 2) and aldehydes, it was of interest to see whether the corresponding vinyl aminosulfoxonium salts **46a** and **46b** would also undergo a migratory substitution. Treatment of the vinyl aminosulfoxonium salt **46a**, which was obtained from sulfoximine **45a** through methylation,[13] first with DBU and then with saturated aqueous NH_4Cl in CH_2Cl_2 gave after a short reaction time a mixture of the allyl chlorides *E*-**48a** and *Z*-**48a** in a ratio of 92:8 in high yield (Table 7). A similar experiment with salt **46b**, which was prepared through methylation of **45b**,[13] afforded the allyl chloride *E*-**48b** as a single isomer in almost quantitative yield. The treatment of **45a** and **45b** with DBU most likely caused a facile isomerization to the

Scheme 18. Cyclization of δ-Chloro-β,γ-Dehydro Amino Acids



Scheme 19. Synthesis of δ-Chloro Allyl Alcohols

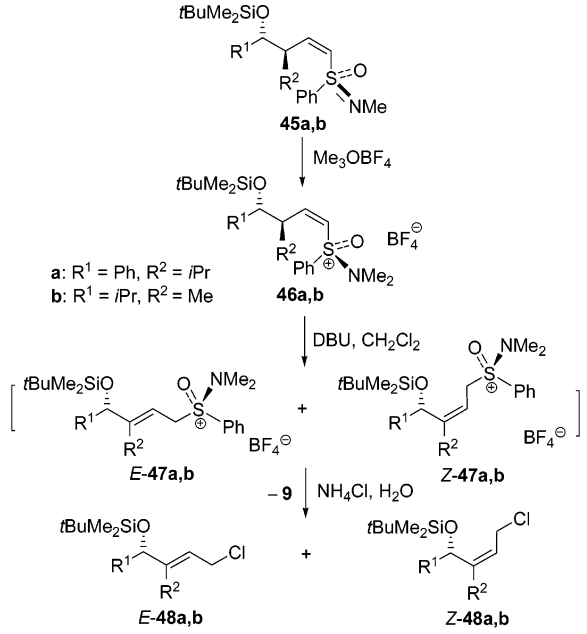


Table 7. Synthesis of δ-Chloro Allyl Alcohols

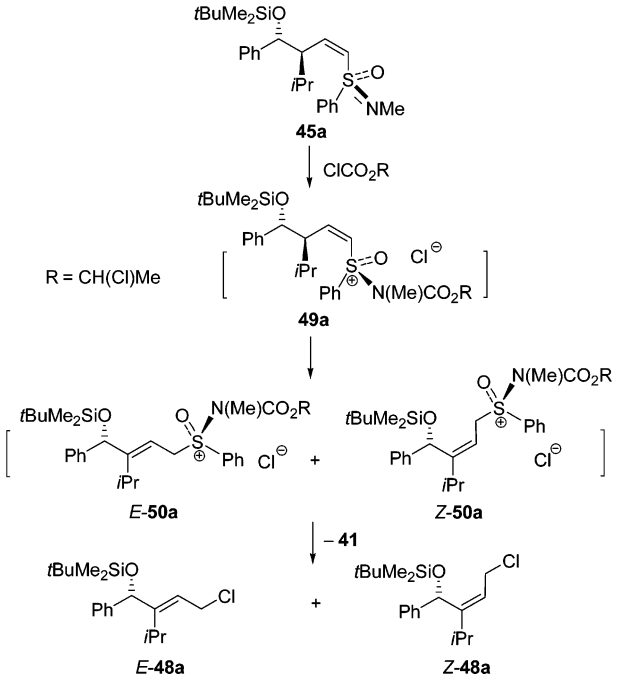
48	R^1	R^2	yield (%)	E:Z
a[a]	Ph	*i*Pr	89	92:8
a[b]	Ph	*i*Pr	81	90:10
b[c]	*i*Pr	Me	98	≥100:1

[a] From **46a**. [b] One-pot synthesis from **45a** and $ClCO_2CH(Cl)Me$. [c] From **46b**.

allyl aminosulfoxonium salts *E*/*Z*-**47a** and *E*/*Z*-**47b**, which suffered a similarly facile substitution by the Cl^- ion.

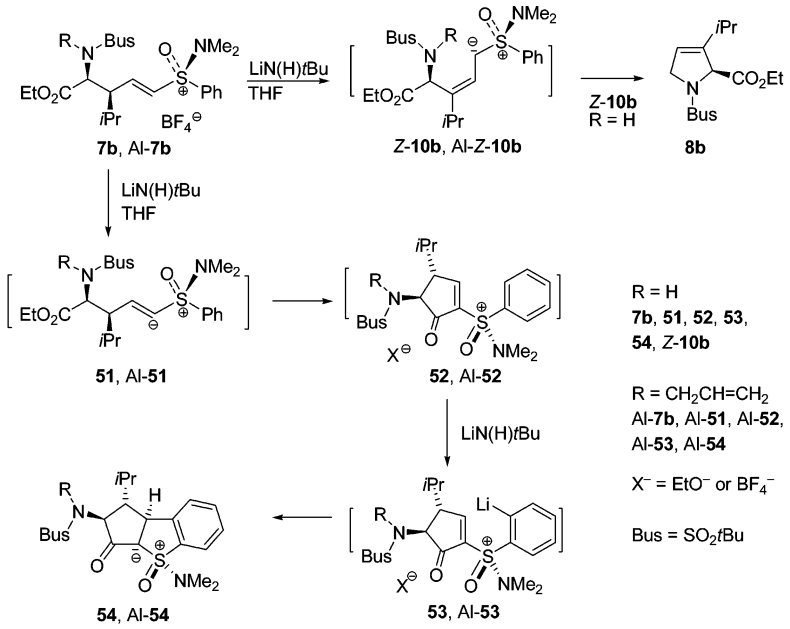
Allyl chlorides of type **48** can also be obtained by the one-pot sequence starting from the corresponding vinyl sulfoximine **45** and using the chloroformiate (Scheme 20). For example, treatment of **45a** with $ClCO_2CH(Cl)Me$ gave a mixture of the allyl chlorides *E*-**48a** and *Z*-**48a** in a ratio of 90:10 in 81% yield. In addition sulfinamide **41**[30,34] was isolated in 93% yield. Most likely sulfoximine **45a** reacts with the chloroformiate with formation of the aminosulfoxonium salt **49a** which suffers a Cl^- ion-mediated isomerization to give the corresponding allyl isomer *E*/*Z*-**50a**, the substitution of which by the Cl^- ion gives chlorides *E*/*Z*-**48a**.

Scheme 20. One-Pot Synthesis of a δ-Chloro Allyl Alcohol



IV. Cyclopentanoid Aminosulfoxonium Ylides. IV.a. Synthesis of Amino-Substituted Tricyclic Ylides. The facile isomerization of vinyl aminosulfoxonium salts of type **7** to the corresponding allyl aminosulfoxonium salts by the Cl^- and F^- ions led us to explore the possibility of generation and isolation of the intermediate allyl aminosulfoxonium ylides of type **10** (cf. Scheme 3) by using a strong base. Previously, we had studied the structure of ylides of type **10** by ab initio calculation,[22] and their isolation would also permit further structural investigations. Therefore, the vinyl aminosulfoxonium salt **7b** was treated with LiN(H)*t*-Bu (2−3 equiv) in THF at low temperatures. Surprisingly, the tricyclic keto aminosulfoxonium ylide **54** was isolated in 39% yield as a single diastereomer besides the proline derivative **8b** in 32% yield (Scheme 21). A similar reaction of the *N*-allyl vinyl aminosulfoxonium salt Al-**7b** afforded only the keto ylide Al-**54** in 49% yield as a single diastereomer. Formation of the tricyclic ylides can perhaps be rationalized as follows. We had previously observed that vinyl aminosulfoxonium salts of type **46** (cf. Scheme 18) are deprotonated by strong bases at the α-position to the aminosulfoxonium group with formation of the corresponding vinyl aminosulfoxonium ylides.[13,14] These ylides are stable at low temperatures but decompose at higher temperatures with formation of the corresponding alkylidene carbenes. Thus, it seems reasonable to assume that **7b** and Al-**7b** are deprotonated by the lithium amide to give the vinyl ylides **51** and Al-**51**, respectively. Subsequently the ylides suffer a cyclization through attack of the ylidic C atom at the ethoxycarbonyl group with formation of the cyclopentenone derivatives **52** and Al-**52**, respectively, the double bond and the phenyl group of which are both activated by the aminosulfoxonium group.[12b,g] Therefore, the phenylsulfoxonium derivatives **52** and Al-**52** react with the lithium amide through ortho lithiation of the phenyl group to generate the lithiophenyl derivatives **53** and Al-**53**, respectively, which undergo a highly stereoselective intramolecular enone addition of the phenyl group[35] with formation of ylides

Scheme 21. Synthesis of Amino-Substituted Tricyclic Ylides



54 and Al-**54**, respectively.[36] It has been shown that the ortho lithiation of phenylsulfoximines with lithium amides is a facile process[37−41] and that of the phenylaminosulfoxonium salts **52** and Al-**52** should be even more facile because of the powerful carbanion-stabilizing effect of the aminosulfoxonium group.[12a,b,g,14]

The formation of the proline derivative **8b** in the reaction of **7b** with the base can be ascribed to a competing deprotonation of the vinyl aminosulfoxonium salt at the Cγ atom with formation of the allyl ylide *Z*-**10b** which cyclizes following a proton transfer from the *N*-sulfonyl group to the Cα atom of the ylide. While the N-protected ylide Al-*Z*-**10b** may have also been formed, it cannot cyclize.

The novel tricyclic ylides **54** and Al-**54** should make interesting starting materials for the synthesis of highly substituted cyclopentanone derivatives, as for example, through a ring-opening reaction of the aminosulfoxonium ylide moiety with aldehydes at the Cα−S bond.[12c,g]

IV.b. Experimental and Calculated Structures of Tricyclic Keto Aminosulfoxonium Ylides. Besides the determination of the relative configuration of Al-**54**, the knowledge of the bonding parameters of the keto aminosulfoxonium ylide structural element was also of interest. Although aminosulfoxonium ylides are valuable reagents in stereoselective synthesis, we are unaware of any crystal structure analysis of such an ylide.[42]

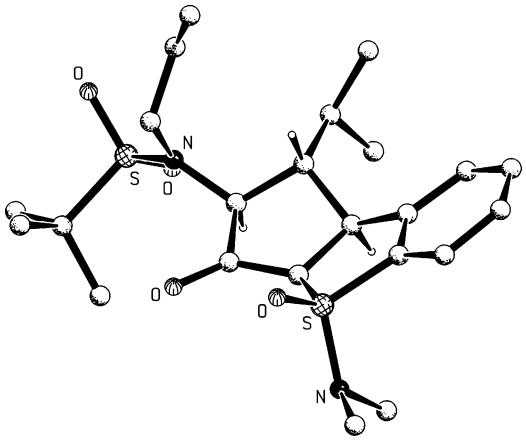


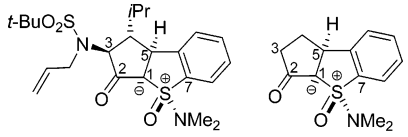
Figure 7. Structure of the keto aminosulfoxonium ylide Al-**54** in the crystal.

Thus, X-ray crystal structure analysis of ylide Al-**54** (Figure 7) was carried out.

Compared with the average value of 1.208(7) Å obtained from 155 solid-state structures of cyclopentanones[43] the carbonyl bond of Al-**54** (1.227(3) Å) (Table 8) appears to be somewhat elongated, indicating a weak enolic character of this bond. However, an ab initio structure optimization of the model ylide **XXIII** (Figure 8) at the MP2 level employing the 6-31+G* basis set and the Gaussian 03 suite of quantum-chemical routines[44] resulted in a CO bond length of 1.236 Å, which is only slightly longer than that of cyclopentanone (1.227 Å) obtained at the same level of theory. This indicates that the experimental average value for the cyclopentanones[43] is probably too small. At an experimental value of 1.409(3) Å the C1−C2 bond is quite short. The calculated value for the model ylide **XXIII** is 1.447 Å. According to both the X-ray structure determination and calculation, the carbonyl carbon atom C2 is planar. Moreover, at a sum of bond angles of 352.4(2)° carbon

(35) Piers, E.; Harrison, C. L.; Zetina-Rocha, C. *Org. Lett.* **2001**, *3*, 3245−3247.
(36) Acyclic keto aminosulfoxonium ylides had previously been obtained through acylation of (dimethylamino)sulfoxonium methylides: (a) Johnson, C. R.; Haake, M.; Schroeck, C. W. *J. Am. Chem. Soc.* **1970**, *92*, 6594−6598. (b) Johnson, C. R.; Rogers, P. E. *J. Org. Chem.* **1973**, *38*, 1798−1903. (c) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 2630−2634.
(37) Reggelin, M. Ph.D. Thesis, Universität Kiel, 1989.
(38) Müller, J. Ph.D. Thesis, Universität Basel, 1993.
(39) Müller, J. F. K.; Neuburger, M.; Zehnder, M. *Helv. Chim. Acta* **1997**, *80*, 2182−2190.
(40) (a) Bosshammer, S. Ph.D. Thesis, RWTH Aachen, 1998. (b) Wessels, M. Ph.D. Thesis, RWTH Aachen, 2002.
(41) (a) Levacher, V.; Eriksen, B. L.; Begtrup, M.; Dupas, G.; Quéguiner, G.; Duflos, J.; Bourguignon, J. *Tetrahedron Lett.* **1999**, *40*, 1665−1668. (b) Gaillard, S.; Papamicaël, C.; Dupas, G.; Marsais, F.; Levacher, V. *Tetrahedron* **2005**, *61*, 8138−8147.
(42) A search in the Cambridge crystallographic data files revealed no entry for an acyclic or cyclic aminosulfoxonium ylide of type Al-**54**.
(43) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. II* **1987**, S1.
(44) Frisch, M. J.; et al. *Gaussian 03*, Revision C.02; Gaussian, Inc., Wallingford CT, 2004.

Table 8. Bond Lengths (Å) and Dihedral Angles (deg) of the Keto Ylides Al-**54** (experimental) and **XXIII** (calculated)



Al-**54** **XXIII**

bond	Al-**54**	**XXIII**	angle	Al-**54**	**XXIII**
S−O	1.442(1)	1.478	C1−S−N−Me	−174.1(2)	−179.7
S−N	1.645(2)	1.696	C1−S−N−Me	49.6(2)	46.3
C1−S	1.661(2)	1.650	N−S−C1−C2	100.9(2)	106.8
C7−S	1.758(2)	1.781	N−S−C1−C5	−111.7(2)	−107.2
C1−C2	1.409(3)	1.447	O−S−C1−C2	−22.5(2)	−18.7
C1−C5	1.531(3)	1.510	O−S−C1−C5	124.9(1)	127.3
C2−C3	1.559(3)	1.541			
C2−O	1.227(3)	1.236			

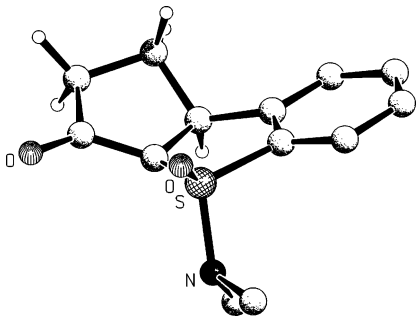
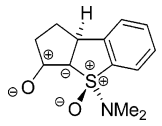


Figure 8. Calculated structure of the keto aminosulfoxonium ylide **XXIII**.

atom C1 is distinctly pyramidalized. The perpendicular distance of C1 from the plane defined by S1, C2, and C5 is 0.245(2) Å. Within its standard deviation this value coincides with the one from the ab initio calculation (351.9°).

A natural bond orbital (NBO) analysis[45] of the bonding in the model ylide **XXIII** revealed the following interesting features. (i) There is no double bond between the carbonyl C atom C2 and the neighboring tri-coordinate carbon atom C1. The atoms are bonded by a single bond between a $sp^{1.89}$ hybrid at the carbonyl C and a $sp^{1.73}$ hybrid at the neighboring carbon atom C1. The latter atom carries a lone pair with about 98% *p* character and an occupancy of 1.59 which strongly interacts with an only weakly occupied *p* orbital (occupancy 0.67) at the carbonyl C atom resulting in a stabilization energy[43b,46] of $\Delta E_2 = -157$ kcal/mol. At stabilization energies of −13 and −33 kcal/mol the interactions of the lone pair at C1 with the σ_{SO}* and σ_{SN}* bonds, respectively, are of minor importance. (ii) The CO bond is also a single bond between a $sp^{2.02}$ hybrid at the C atom and a $sp^{1.40}$ hybrid at the O atom. The O atom carries three lone pairs, one with about 58% *s*- and 42% *p* character and two essentially pure *p* orbitals. One of these *p* lone pairs gives a strong second-order stabilization energy ($\Delta E_2 = -365$ kcal/mol) with the above-mentioned weakly occupied *p* orbital at the carbonyl C atom. (iii) Although it is significantly shorter than a typical S−C single bond (1.811 Å in Me-S−NH_2, MP2/6-31+G*), the C1−S linkage is not a double bond. It is formed as a single bond between a $sp^{2.22}$ hybrid at the S atom and a $sp^{2.53}$ hybrid at C1. There are no significant interactions between the lone pair at C1 and the empty orbitals at the S atom. (iv) The natural atomic charges at S, C1, and C2 are +2.23, −0.76, and +0.67 e, respectively. Electrostatic interactions, therefore, contribute significantly to the shortening of the bonds between C1 and C2 on the one and between C1 and S on the other hand relative to the values of the corresponding typical single bonds. (v) According to the NBO analysis the S−O bond is not a double bond as depicted in the structural formulas. This bond is a single bond between a $sp^{2.64}$ hybrid at the S atom and a $sp^{2.87}$ hybrid at the O atom.[47] There are three lone pairs at the O atom, two of the orbitals of which are essentially *p* orbitals while the third one has about 74% *s* and 26% *p* character. The natural atomic charge at the O atom is −1.0 e. (vi) The lengths of the S−N bond is 1.696 Å and, therefore, only slightly shorter than a typical S−N single bond (1.722 Å in Ph-S−NH_2 at the same level of theory). The natural atomic charge of the N atom is −0.80 e, and its lone pair has about 87% *p* and 13% *s* character. The charge distribution can be expressed in a first approximation through the conventional polarized structure **XXIIIA**.[48] Stabilization of ylides Al-**54** and **XXIII** is thus mainly provided by electrostatic interactions.



XXIIIA

Ylide Al-**54** and the model ylide **XXIII** adopt a C1−S conformation in which the lone pair at C1 and the S−N bond are approximately in a syn/planar position. According to an ab initio calculation of (dimethylamino)phenylsulfoxonium methylide this conformation allows for a stabilizing $n_C-\sigma^*_{SN}$ hyperconjugative interaction (vide supra).[22] Furthermore the methylene ylide adopts, according to the calculations, S−N and C−S conformations in which the lone pairs at the C atom and N atom are in an almost orthogonal position. Thereby, a destabilizing interaction between both lone pairs is avoided that results when they are in a planar position.[22] Ylide Al-**54** and the model ylide **XXIII** adopt similar S−N and C−S conformations.

IV.c. Synthesis of Hydroxy-Substituted Mono- and Tricyclic Ylides. Having observed a facile tandem cyclization of the amino-substituted salts **7b** and Al-**7b**, it was of interest to see whether a hydroxy-substituted vinyl aminosulfoxonium salt of type **57** is also able to undergo such a series of transformations, giving the tricyclic ylide **59** (Scheme 22). The required functionalized vinyl aminosulfoxonium salt **56** was synthesized by a highly selective reaction of the bis(allyl)titanium complex **3b** with ethyl glyoxylate, which gave the substitute vinyl sulfoximine **55** as a single diastereomer in 36% yield. Protection of the hydroxy group of **55** afforded the silyl ether **56** in 92% yield. The treatment of the vinyl aminosulfoxonium salt **57**, which was obtained through methylation of the vinyl sulfox-

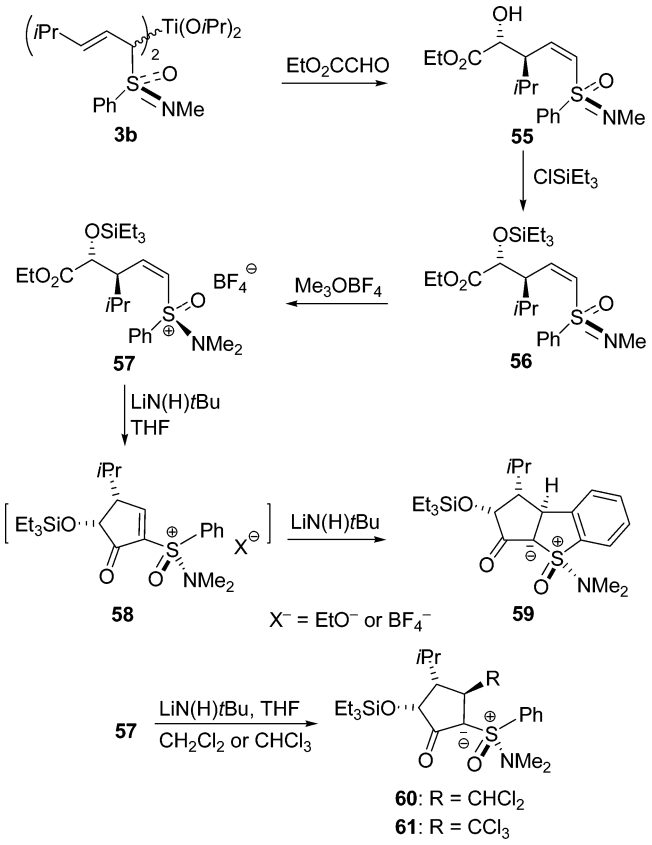
(45) (a) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899. (b) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. NBO 3.0 Program Manual, Theoretical Chemistry Institute and Department of Chemistry: University of Wisconsin, Madison, Wisconsin 53706, U.S.A.

(46) $\Delta E_2 = -q_{do}\langle do|\mathcal{F}|ac\rangle^2/(\epsilon_{ac}-\epsilon_{do})$, where $\mathcal{F}$ is the Fock operator of the molecule, q_{do} the occupation number of the donor orbital. ϵ_{ac} and ϵ_{do} are the NBO orbital energies of the acceptor and the donor orbital, respectively.

(47) (a) Chesnut, D. B.; Quin, L. D. *J. Comput. Chem.* **2004**, *25*, 734−738. (b) Glendening, E. D.; Shrout, A. L. *J. Phys. Chem. A* **2005**, *109*, 4966−4972. (c) Müller, J. F. K.; Batra, R. *J. Organomet. Chem.* **1999**, *584*, 27−32. (d) Kumar, P. S.; Bharatam, P. V. *Tetrahedron* **2005**, *61*, 5633−5639.

(48) For a discussion of the importance of polarized structures of this type in the case of enolate ions, see: Wiberg, K. B.; Ochterski, J.; Streitwieser, A. *J. Am. Chem. Soc.* **1996**, *118*, 8291−8299.

Scheme 22. Synthesis of Hydroxy-Substituted Cyclic Ylides



imine **55** in practically quantitative yield, with the lithium amide furnished the tricyclic keto ylide **59** in 30% yield as a single diastereomer. It is assumed that the formation of **59** from **57** takes a similar course as that of **54** from **7b** except for the additional requirement of a *Z/E*-isomerization of the vinyl ylide derived from salt **57**. Support for this notion came from reactions of **57**, samples of which were inadvertently admixed with CH_2Cl_2 or $CHCl_3$, with the lithium amide. Here the monocyclic ylides **60** and **61**, respectively, were isolated each in 22% yield, respectively, as single diastereomers. Formation of the ylides can be explained by the stereoselective addition of $LiCCl_3$ and $LiCHCl_2$[49] to the cyclopentenone derivative **58**, being derived from **57** through deprotonation and cyclization. The isolation of **60** and **61** gives support to the postulated formation of the cyclopentenone derivatives **52**, Al-**52**, and **58** as intermediates in the formation of the tricyclic ylides.

Conclusion

Chiral amino-substituted vinyl aminosulfoxonium salts are versatile starting materials for the asymmetric synthesis of unsaturated mono- and bicyclic prolines and δ-chloro-β,γ-dehydro amino acids. The strong carbanion-stabilizing effect and the high nucleofugacity of the aminosulfoxonium group are the key factors responsible for the facile migratory intra- and intermolecular substitution reactions of the vinyl and allyl aminosulfoxonium salts. Particularly illustrative is the one-pot activation and migratory substitution of the amino- and hydroxy-substituted vinyl sulfoximines with formation of the corresponding allyl chlorides upon treatment with a chloroformiate. The facile conversion of the hydroxy-substituted vinyl aminosulfoxonium salts to the corresponding allyl chlorides gives further proof for the generality of the migratory substitution of vinyl aminosulfoxonium salts. The proline derivatives and δ-chloro-β,γ-dehydro amino acids should make interesting building blocks for the enantioselective synthesis of nonnatural amino acids.

A further example for the high reactivity of the functionalized vinyl aminosulfoxonium salts is provided by the stereoselective conversion of the ethoxycarbonyl-substituted aminophenylsulfoxonium salts **7b**, Al-**7b**, and **57** to the corresponding highly substituted tricyclic keto aminosulfoxonium ylides **54**, Al-**54**, and **59**, respectively, upon treatment with a strong base. Although the yields of the ylides are only moderate at present, their tricyclic structure and the four-step reaction sequence leading to their formation are remarkable, and an optimization of the reaction conditions may perhaps lead to higher yields. The structure of the keto aminosulfoxonium ylide Al-**54** in the crystal shows some remarkable features including a CO bond which is only slightly longer than that of cyclopentanones. Ab initio calculations of the model ylide showed a good correlation between theoretical and experimental bonding parameters. An NBO analysis of the model keto aminosulfoxonium ylide **XXIII** revealed within the framework of the model interesting structural features including the absence of CO, CS, CC, and SO double bonds in the keto aminosulfoxonium unit and pointed to the importance of a polar structure of type **XXIIIA**.

The key step in the synthesis of the functionalized cyclic and acyclic vinyl sulfoximines is the highly regio- and stereoselective aminoalkylation of the sulfonimidoyl-substituted bis(allyl)-titanium complexes with the *N*-Bus imino ester. A similar aminoalkylation of the mono(allyl)titanium complexes, which are accessible from the same lithiated allyl sulfoximine used in the synthesis of the bis(allyl)titanium complexes, permits in the case of cyclic allyl sulfoximines a highly selective stereocomplementary synthesis of the corresponding functionalized cyclic vinyl sulfoximines of opposite configurations at the C atoms.

Acknowledgment. Financial support of this work by the Grünenthal GmbH, Aachen, and the Deutsche Forschungsgemeinschaft (Collaborative Research Center "Asymmetric Synthesis with Chemical and Biological Methods" SFB 380) is gratefully acknowledged. We thank Dr. Jan Runsink for NOE experiments, Dr. Christian W. Lehmann, MPI Mülheim, for the data set of Al-**54**, Cornelia Vermeeren for the HPLC separations, and Dominique J. Hahne for experimental assistance.

Supporting Information Available: General, experimental procedures and characterization for all new compounds described in this work, crystallographic data for the reported structures (CIF format), and complete ref 44. This material is available free of charge via the Internet at http://pubs.acs.org.

JA061152I

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