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Asymmetric synthesis of 3-substituted unsaturated prolines from chiral sulfoximine substituted allyl titanium(IV) complexes

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Abstract—An asymmetric synthesis of the 3-substituted $\Delta^{3,4}$-unsaturated prolines **7a**–**e** and 3-substituted 4-methylene prolines **14a**–**c** starting from the corresponding γ,δ-unsaturated α-amino acids **4a**–**e** and **11a**–**c**, respectively, is described. Amino acid derivatives **4a**–**e** and **11a**–**d** were obtained through aminoalkylation of the corresponding sulfoximine substituted allyl titanium(IV) complexes **2a**–**e** and **10a**–**d**, respectively, with the *N-tert*-butylsulfonyl imino ester **3**. Activation of sulfoximines **4a**–**e** and **11a**–**c** through methylation of the sulfoximine group followed by a KF mediated isomerization of the vinyl aminosulfoxonium salts **5a**–**e** and **12a**–**c**, respectively, to the corresponding allyl aminosulfoxonium salt **6a**–**e** and **13a**–**c**, respectively, and a subsequent intramolecular nucleophilic substitution of the allylic aminosulfoxonium group afforded the enantio- and diastereomerically pure proline derivatives in medium to high yields.

Cyclic α-amino acids and especially proline derivatives have gained much attention in recent years.[1] Incorporation of proline derivatives into peptides has been shown to provide interesting mimetics that can serve as new drugs and probes for receptor studies. In addition, proline derivatives are of interest as small molecule drugs. For example, 3-substituted prolines are being currently considered as conformationally restricted arginine, norleucine, phenylalanine, tyrosine, aspartic acid, and glutamic acid analogues.[2] This has led to intensive studies of proline derivatives in regard to biological activity and synthetic methodology.[2–6] Particularly interesting are prolines that carry substituents at both the 3- and 4-position. This substitution pattern offers not only new possibilities for the attainment of conformationally restricted peptide mimetics but can also be found as core structure in the kainoid amino acids,[7] which show neuroexcitatory properties. Because of their function as conformationally restricted L-glutamic acid analogues the kanoids and their derivatives are interesting probes for the study of neurological disorder as for example Alzheimerás disease.[8] Despite the considerable interest in proline derivatives, there is still a lack of methods for the asymmetric synthesis of 3-substituted $\Delta^{3,4}$-unsaturated[5] and 3-substituted 4-methylene prolines,[6] which should make excellent starting materials for the synthesis of 3-monosubstituted and 3,4-disubstituted prolines.[3,4] We have recently described an asymmetric synthesis of unsaturated bicyclic prolines[9] and amino acids[10] based on sulfoximine substituted cyclic and acyclic allyl titanium(IV) complexes.[11] We now describe a flexible asymmetric synthesis of substituted endocyclic and exocyclic unsaturated prolines based on sulfoximine substituted acyclic allyl titanium(IV) complexes.

Treatment of the sulfoximine substituted allyl titanium(IV) complexes **2a**–**e**,[11] which were prepared from the corresponding enantiomerically pure allyl sulfoximines **1a**–**e** through titanation following lithiation, with the imino ester **3**[12] afforded the corresponding amino acid derivatives **4a**–**e** with high regio- and diastereoselectivities as described previously (Scheme 1).[13] Gratifyingly, the new *tert*-butyl substituted titanium complex **2d**, which was obtained in a similar way from the allylic sulfoximine **1d**,[14] also reacted with **3** with high regio- and diastereoselectivities (⩾98% de) and furnished the *tert*-butyl substituted amino acid derivative **4d** in 84% yield. The synthesis of the $\Delta^{3,4}$-unsaturated prolines **7a**–**e** started with the activation of the corresponding sulfoximines **4a**–**e** through methylation at the N-atom upon treatment with Me_3OBF_4 (1.1 equiv) in CH_2Cl_2

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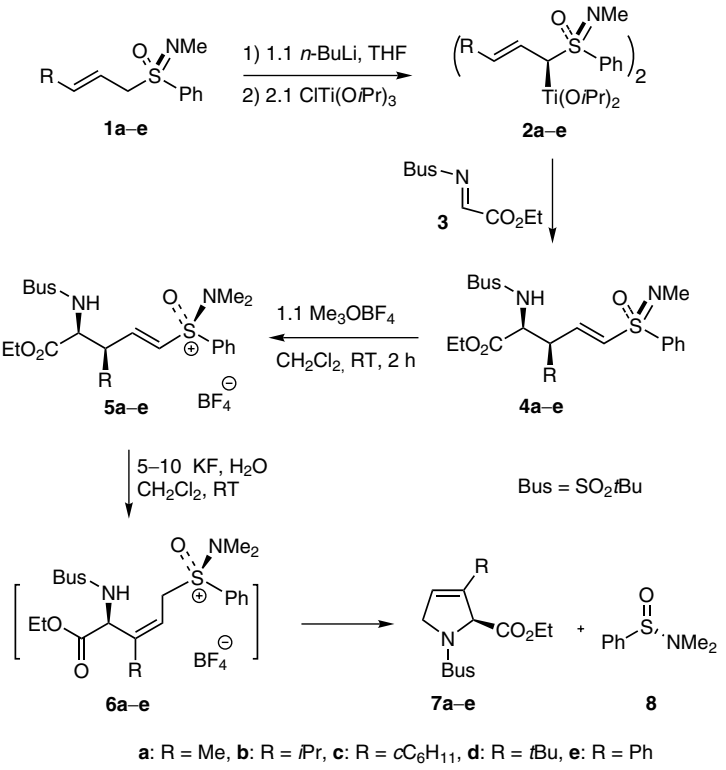


Scheme 1. Synthesis of $\Delta^{3,4}$-unsaturated prolines **7a**–**e**.

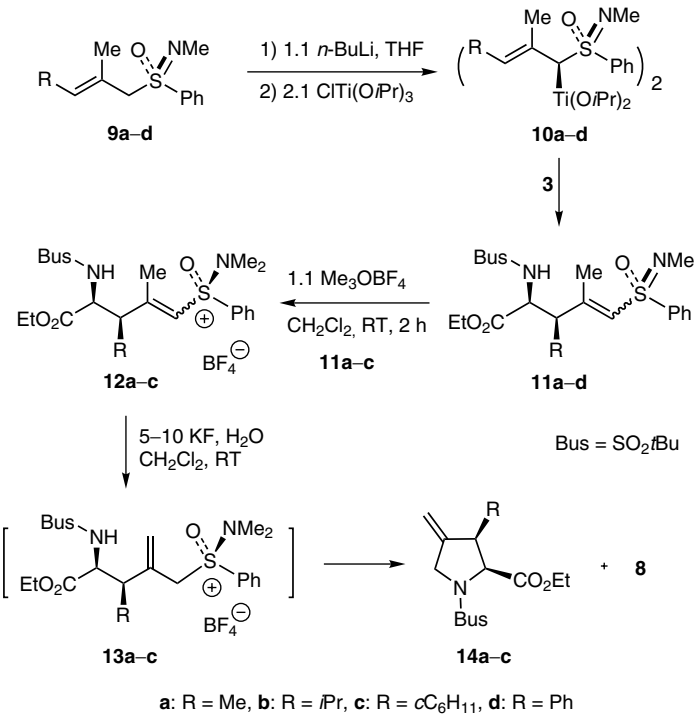
Table 1. Synthesis of $\Delta^{3,4}$-unsaturated prolines **7a**–**e**

Entry	Compd	R	*t* (h)	Yield (%) **7**	Yield (%) **8**
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

at room temperature for 2 h. The thus obtained aminosulfoxonium salts **5a**–**e** (⩾95% yield) were then subjected to a treatment with aqueous KF (5–10 equiv) in CH_2Cl_2 at room temperature, which afforded the corresponding prolines **7a**–**e** with ⩾98% ee in medium to high yields (Table 1). The conversion of **4a**–**e** into **7a**–**e**, respectively, can be carried out with the same results without isolation of any intermediate. It is noteworthy that the yields of **7** were especially good with amino acid derivatives **4** carrying a sterically demanding substituent at the β-position (entries 2–4). The moderate yield of the methyl substituted proline derivative **7a** (entry 1) seems to be due to a competing reaction of the aminosulfoxonium salt **5a** with KF at the sulfonamide group with formation of **3** and the corresponding allyl aminosulfoxonium salt. In addition to the proline derivatives **7a**–**e** sulfinamide **8** with ⩾98% ee was isolated in high yields. Conversion of sulfinamide **8** to (*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine[15] of ⩾98% ee, the starting material for the synthesis of **1a**–**e**, has already been described.[16]

It is assumed that the vinyl aminosulfoxonium salts **5a**–**e** suffer a F^--catalyzed isomerization with formation of the corresponding allyl aminosulfoxonium salts **6a**–**e**.[9,16] Because of the high nucleofugacity of the allylic aminosulfoxonium group[9,16] salts **6a**–**e** undergo a facile cyclization with formation of the corresponding prolines **7a**–**e**. After having accomplished a synthesis of prolines **7a**–**e**, a perhaps facile synthesis of the 3-substituted 4-methylene prolines **14** was envisioned starting from the methyl substituted amino acid derivatives **11** (Scheme 2).

It was speculated that the methyl substituted vinyl aminosulfoxonium salts **12** would experience a regioselective F^--catalyzed isomerization to the allyl aminosulfoxonium salts **13**, leaving the stereogenic center at the β-position intact. Prerequisite to a successful realization of such a synthesis of **14** would be a highly stereoselective reaction of the methyl substituted titanium complexes **10** with **3**. Aside from the present objective it was of interest to see whether the methyl group of complexes **11** would have any influence on the stereoselectivity of the reaction with **3**. Lithiation of the enantiomerically pure allylic sulfoximines **9a**, **9b**,[16] **9c**, and **9d**,[17] which were obtained from (*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine[15] and the corresponding ketones by the one-pot addition–elimination–isomerization route including a chromatographic separation of the *E*/*Z*-isomers,[18] with *n*-BuLi (1.1 equiv) at −78 °C in THF followed by a titanation with $ClTi(i\text{-}OPr)_3$ (2.1 equiv) gave the corresponding allyl titanium(IV) complexes **10a**–**d**. Gratifyingly, reaction of complexes **10a**–**d** with **3**[9] (1.1 equiv) in THF at −78 °C for 12 h also proceeded with high regio- and diastereoselectivities and afforded the corresponding amino acid derivatives *E*-**11a**–**d** and *Z*-**11a**–**c** in good yields (Table 2).



Scheme 2. Synthesis of 4-methylene prolines **14a**–**c**.

Table 2. Synthesis of α-amino acid derivatives **11a**–**d**

Entry	Compd	R	Yield (%) *E*-**11**	Yield (%) *Z*-**11**
1	**a**	Me	33	38
2	**b**	*i*-Pr	64	10
3	**c**	*c*-C_6H_{11}	45	16
4	**d**	Ph	58	—

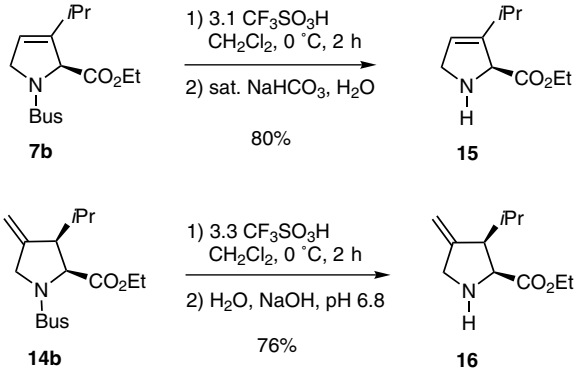
Table 3. Synthesis of 4-methylene prolines **14a**–**c**

Entry	Compd	R	Yield (%) **14**	Yield (%) **8**
1	**a**	Me (*E*-**11**)	63	98
2	**a**	Me (*Z*-**11**)	54	52
3	**b**	*i*-Pr	77	94
4	**c**	*c*-C_6H_{11}	72	84

The *E*- and *Z*-isomers were each formed with ⩾98% de. Because of the further synthetic studies the *E*- and *Z*-isomers of **11a**–**d** were separated by preparative HPLC. Thus both the methyl substituted complexes **10** and the unsubstituted complexes **2** exhibit in the reaction with **3** similar high *syn* diastereoselectivities. However, the methyl group of **10** causes the reaction to be of low *E*/*Z*-selectivity in regard to the double bond. Such a difference in *E*/*Z*-selectivity between **10** and **2** was not observed in their reactions with aldehydes.[19] Interestingly, the reaction of the phenyl substituted complex **10d** with **3** was highly *E*-selective.

Methylation of sulfoximines **11a**–**c** through treatment with Me_3OBF_4 (1.1 equiv) in CH_2Cl_2 afforded the corresponding aminosulfoxonium salts **12a**–**c** in high yields (⩾95%). Isomerization of **12a**–**c** and cyclization of **13a**–**c** both proceeded readily upon treatment of the former salts with aqueous KF (5–10 equiv) in CH_2Cl_2 and furnished the corresponding *cis*-configured 3-substituted 4-methylene prolines **14a**–**c** with ⩾98% ee and ⩾98% de in medium to good yields (Table 3). Both isomers *Z*-**11a** and *E*-**11a** afforded the proline derivative **14a**. Thus a separation of the *E*- and *Z*-isomers is not required for the synthesis of **14a** and presumably also not for that of **14b** and **14c**. The conversion of **11a**–**c** into **14a**–**c**, respectively, can be carried out with the same results without isolation of any intermediate. In addition to the proline derivatives **14a**–**c** sulfinamide **8** with ⩾98% ee was isolated in high yields.

Finally, deprotection of the proline derivatives **7b** and **14b** upon treatment with CF_3SO_3H in CH_2Cl_2 (0.05–0.1 M)[20] afforded the proline esters **15** and **16**, respectively, in good yields (Scheme 3).[21]



Scheme 3. Deprotection of the unsaturated prolines **7b** and **14b**.

Conclusion: We have developed a new asymmetric synthesis of 3-substituted $\Delta^{3,4}$-unsaturated prolines and *cis*-configured 3-substituted 4-methylene prolines both carrying various substituents at the 3-position including sterically demanding ones. This method should give access to proline derivatives that were previously not or only difficultly accessible.

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