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Development of New Methods for Asymmetric Synthesis Based on Sulfoximines

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ABSTRACT: *Sulfoximine-substituted bis(allyl)titanium complexes, which are configurationally labile at the Cα-atoms, have emerged as valuable reagents in asymmetric synthesis. Their highly selective reactions with aldehydes and N-sulfonyl imino esters allow the attainment of enantio- and diastereomerically pure sulfoximine-substituted homoallylic alcohols and homoallylic amines, respectively, which are valuable starting materials for the asymmetric synthesis of homopropargylic alcohols, 2,3-dihydrofurans, medium-sized carbocycles and lactones, unsaturated mono- and bicyclic prolines, β-amino acids, and vinyl oxiranes, respectively. The high synthetic versatility of the sulfoximine group stems from its ability to function as a chiral carbanion-stabilizing nucleofuge.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:472–481, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20331

INTRODUCTION

Heteroatom-substituted allylmetal compounds have gained considerable importance as reagents in organic synthesis [1]. Particularly interesting is the synthesis of chiral heteroatom-substituted allylmetal compounds and their application in asymmetric synthesis [2]. Some time ago we developed an interest in the synthesis, structure, and utilization of chiral sulfoximine-substituted allyltitanium complexes of type **I** (Scheme 1) in asymmetric synthesis [3–5]. For the synthesis of complexes of type **I** having an additional chiral substituent at the N-atom and their highly successful application in asymmetric synthesis, see [6].

We were particularly interested in the stereoselective synthesis of sulfoximine-substituted cyclic and acyclic homoallylic alcohols and homoallylic amines of type **II** and **III**, respectively, from **I** by using aldehydes and imines, respectively. The sulfoximine group is endowed with an almost unique combination of features including, besides a configurationally stable S atom, carbanion stabilization, nucleofugacity, and Lewis as well as Brønsted basicity [3,6–9]. A fine-tuning of most of these properties can be achieved by the proper choice of the substituent at the N-atom. Thus the sulfoximine-substituted homoallylic alcohol and homoallylic amine derivatives **II** and **III**, respectively, containing three stereogenic elements, besides the sulfoximine group, should be versatile building blocks for the asymmetric synthesis of natural and nonnatural products. According to the chemistry of sulfoximines developed in our laboratories and elsewhere [3,6–9], the following synthetic transformations of **II** and **III** can be envisioned: (1) a Michael addition to the activated double bond followed by a replacement of the sulfoximine group either by a H atom or a Cl atom; (2) a replacement of the sulfoximine group by an alkyl or aryl group through a Ni-catalyzed cross-coupling

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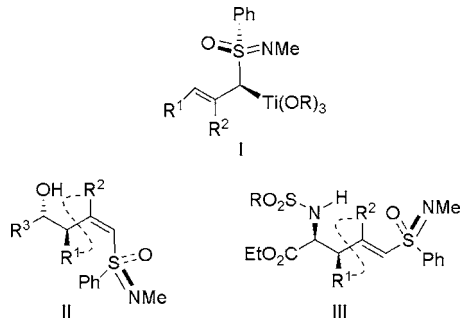


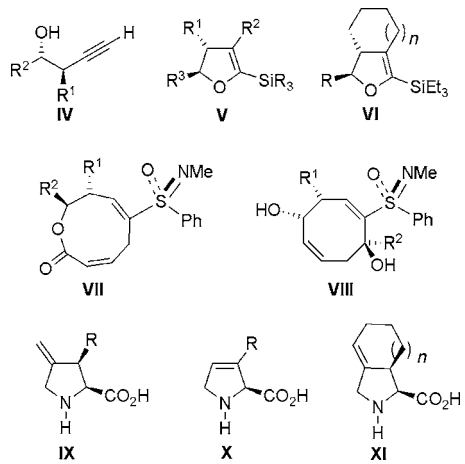
SCHEME 1 Sulfoximine-substituted allyltitanium complexes, homoallylic alcohols and homoallylic amines.

reaction; (3) a selective activation of the sulfoximine group through alkylation at the N atom; and (4) a lithiation at the α-position with formation of the corresponding alkenyllithium derivatives and their reaction with electrophiles. We became interested in the application of the sulfoximine-substituted homoallylic alcohols and homoallylic amines **II** and **III**, respectively, in the asymmetric synthesis of homopropargylic alcohols **IV**, dihydrofurans **V** and **VI**, medium-sized carbocycles and lactones **VII** and **VIII**, respectively, the unsaturated prolines **IX–XI** (Scheme 2), and further target molecules discussed elsewhere [3].

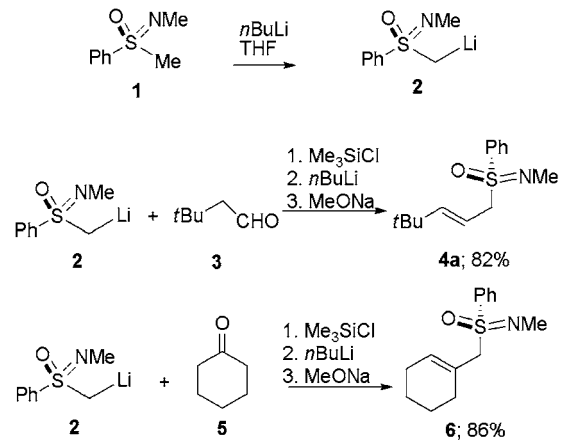
RESULTS AND DISCUSSION

Sulfoximine-Substituted Bis(allyl)titanium Complexes, Homoallylic Alcohols and Homoallylic Amines

The enantiopure allylic sulfoximines required for the synthesis of complexes of type **I** are readily acces-



SCHEME 2 Homopropargyl alcohols, 2,3-dihydrofurans, medium-sized carbocycles and lactones, and unsaturated prolines.

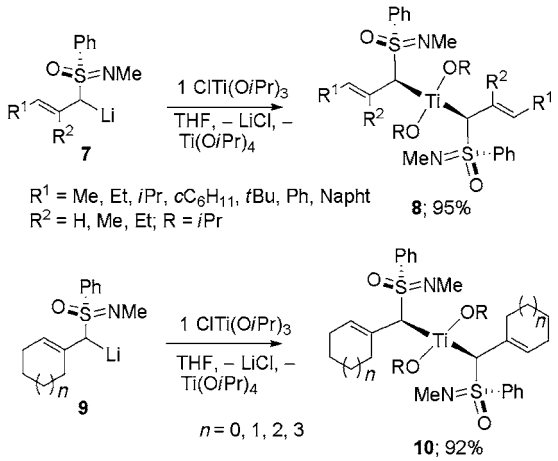


SCHEME 3 Synthesis of allylic sulfoximines.

sible from the *N*,*S*-dimethyl sulfoximine **1** and the corresponding aldehydes or ketones by the one-pot addition–elimination–isomerization (AEI) route depicted in Scheme 3 for the synthesis of **4a** and **6** from the lithiomethyl sulfoximine **2** and the carbonyl derivatives **3** and **5**, respectively [5,10].

Acyclic allylic sulfoximines are generally obtained as *E*/*Z* mixtures in ratios of 80:20 to 90:10 except the derivatives containing a *t*Bu or an aryl group, which are formed as single *E*-isomers. Separation by chromatography gives the pure *E*-isomers, and treatment of the *Z*-isomers with DBU again affords an *E*/*Z*-mixture. The starting sulfoximines **1** and *ent*-**1** are readily obtained enantiopure on a large scale through an efficient resolution of *rac*-**1** with ω-camphersulfonic acid by the method of half-quantities, that is the use of only 0.5 equivalents of the acid, which in the present case has the advantage that no recrystallization of the corresponding ammonium salt is required [11].

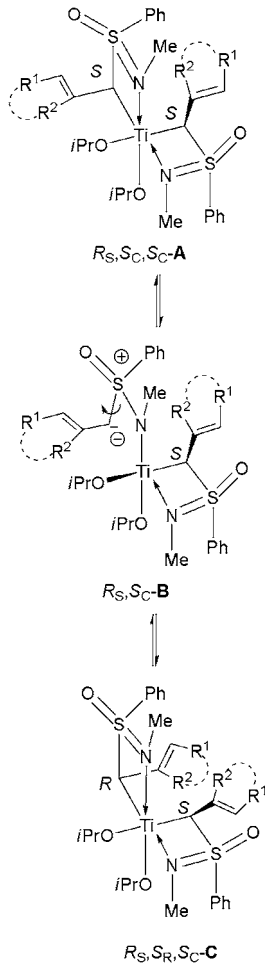
Treatment of the lithiated acyclic allylic sulfoximines **7** [12] with one equivalent of $ClTi(OiPr)_3$ in THF afforded the bis(allylsulfoximine)-titanium complexes **8** in high yield together with equimolar amounts of $Ti(OiPr)_4$ (Scheme 4) [9]. A similar lithium–titanium exchange of the lithiated cyclic allylic sulfoximines **9** gave the bis(allylsulfoximine)titanium complexes **10** also in high yield together with $Ti(OiPr)_4$. Thus, surprisingly titanation of **7** and **9** affords bis(allylsulfoximine)titanium complexes and not the corresponding mono(allylsulfoximine)titanium complexes of type **I** (cf. Scheme 1) [6]. Presumably reaction of the lithiated allylic sulfoximines with $ClTi(OiPr)_3$ primarily leads to complexes of type **I**, which suffer a disproportionation with formation of the bis(allylsulfoximine)titanium complexes and



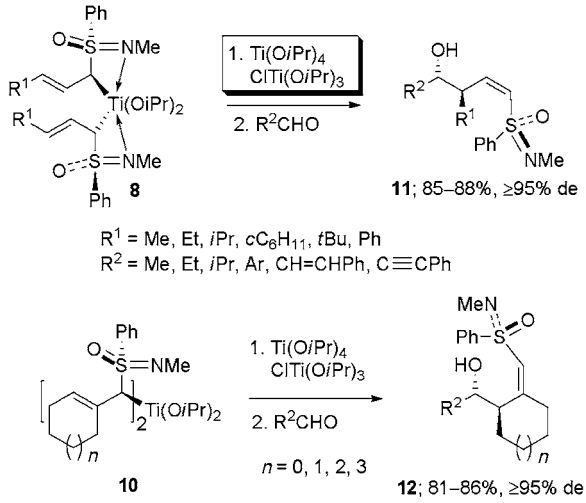
SCHEME 4 Synthesis of sulfoximine-substituted bis(allyl)titanium complexes.

$Ti(OiPr)_4$. According to X-ray crystal structure analysis and variable-temperature NMR spectroscopy, complexes **8** and **10** adopt a distorted octahedral structure characterized by a coordination of both allylsulfoximine moieties through their Cα atom and the N atom to the Ti atom [5]. The allylsulfoximine ligands and the isopropoxy groups undergo in solution a fast intramolecular topomerization perhaps by a pseudorotational mechanism. Complexes **8** and **10** are endowed with a low configurational stability of their Cα atoms. Diastereomerization of complex R_S,S_C,S_C-**A** with formation of complex R_S,R_C,S_C-**C** most likely involves a cleavage of the Cα—Ti bond with the intermediate formation of the allylic *N*-titanium aminosulfoxonium ylides R_S,S_C-**B** (Scheme 5), which undergo a Cα—S bond rotation followed by the formation of the Cα—Ti bond. Ab initio calculations of model ylides of type R_S,S_C-**B**, having a methyl instead of the titanium group at the N atom, revealed a low barrier toward Cα—S bond rotation [4]. NMR studies of sulfoximine-substituted mono(allyl)titanium complexes of type **I** carrying, however, three diethylamino groups at the Ti atom revealed the existence of such a diastereomerization pathway [4].

Gratifyingly, the reaction of the acyclic titanium complexes **8** with a broad range of aldehydes occurred with high regio- and diastereoselectivity in an *anti-Z*-fashion and gave the sulfoximine-substituted homoallylic alcohols **11** in good yields (Scheme 6) [9]. Similarly, the hydroxyalkylation of the cyclic titanium complexes **10** with aldehydes proceeded with high selectivities and furnished the *anti-Z*-configured homoallylic alcohols **12** in good yields. The hydroxyalkylation of the



SCHEME 5 Diastereomerization of sulfoximine-substituted bis(allyl)titanium complexes.



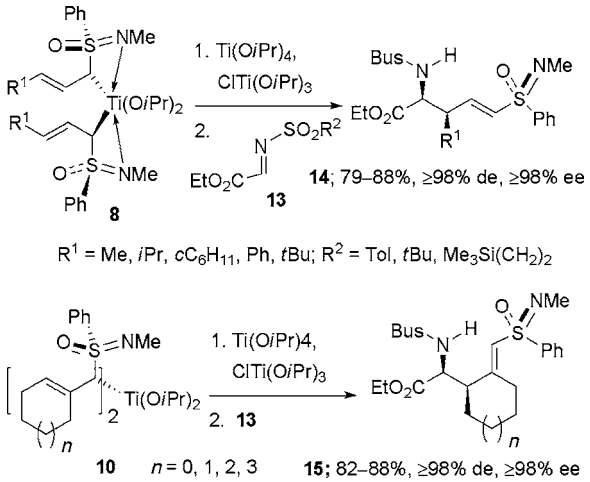
SCHEME 6 Synthesis of sulfoximine-substituted homoallylic alcohols.

bis(allylsulfoximine)titanium complexes occurs in a stepwise fashion. While the transfer of the first allylsulfoximine moiety to the aldehyde molecule requires the presence of $Ti(OiPr)_4$, that of the second one demands that of $ClTi(OiPr)_3$. Without the two Lewis acids at low temperatures no reaction takes place between **8** and **10** and the aldehydes. It is assumed that $Ti(OiPr)_4$ and $ClTi(OiPr)_3$ coordinate to a Cα-sulfoximine group of the bis(allylsulfoximine)titanium complexes and the intermediate mono(allysulfoximine)titanium complexes, thereby generating a free coordination site at the Ti atom for the aldehyde molecule, which after coordination reacts with the allylsulfoximine moiety, perhaps through a six-membered cyclic transition state, the sulfoximine group of which occupies a pseudo-axial position. According to these considerations, formation of the *anti-Z*-configured homoallylic alcohols **11** and **12** requires that out of the mixture of diastereomeric complexes of **8** and **10** the R_S,S_C,S_C-configured complex is the most reactive one.

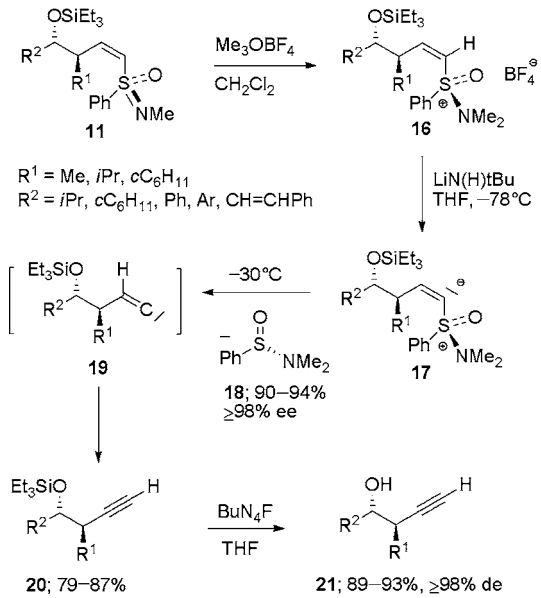
Having obtained favorable results in the reactions of the titanium complexes **8** and **10** with aldehydes, their reaction with *N*-sulfonyl imino esters was studied. Gratifyingly, the aminoalkylation of the acyclic titanium complexes **8** with the imino esters **13** in the presence of $Ti(OiPr)_4$ and $ClTi(OiPr)_3$ proceeded with high regio- and diastereoselectivity and gave the *syn-E*-configured sulfoximine-substituted homoallylic amines **14** in good yield (Scheme 7) [13,14]. It is noteworthy that even with sterically demanding substituents R^1 high selectivities were recorded. Similarly, reaction of the cyclic titanium complexes **10** with **13** occurred with high selectivities and yielded the *syn-E*-configured derivatives **15**. Besides the tolylsulfonyl imino ester **13a** the *tert*-butylsulfonyl derivative **13b** and the (trimethylsilylethyl)sulfonyl derivative **13c** were studied, which were prepared by the route described for the synthesis of **13a** [14]. While N-tolylsulfonamides are notoriously difficult to cleave, *tert*-butylsulfonamides and (trimethylsilylethyl)sulfonamides can readily be converted to the corresponding amines [15]. Formation of the *syn-E*-configured homoallylic amines **14** and **15** requires that (1) out of the mixture of the diastereomeric complexes of **8** and **10** the R_S,R_C,R_C-configured diastereomers are the most reactive one and (2) the sulfoximine group attains in the transition state a pseudo-equatorial position. Thus the diastereomers of complexes **8** and **10** show in reactions with aldehydes and *N*-sulfonyl imino esters the opposite reactivity.

Asymmetric Synthesis of Homopropargylic Alcohols

Homopropargylic alcohols of type **IV** (cf. Scheme 2) are valuable building blocks in natural product synthesis [16]. Existing methods for the asymmetric synthesis of **IV** are mainly confined to derivatives having sterically less demanding substituents R^1 and R^2 [17]. We envisioned a new and more flexible asymmetric synthesis of **IV** starting from the sulfoximine-substituted homoallylic alcohols **11** (Scheme 8) [18,19].



SCHEME 7 Synthesis of sulfoximine-substituted homoallylic amines.



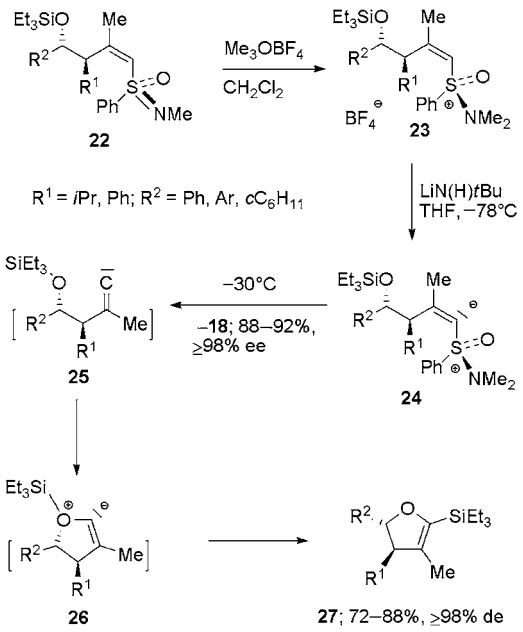
SCHEME 8 Asymmetric synthesis of homopropargylic alcohols.

The conversion of alkenes **11** to alkynes **21** requires an elimination of *N*-methylphenylsulfinamide. However, treatment of **11** with for example RLi leads to a lithiation at the α-position rather than an elimination (vide infra). Thus a selective activation of the sulfoximine group was sought in order to convert it to a better leaving group. Treatment of sulfoximine **11** with Meeerwein salt led to a methylation at the N atom and furnished the aminosulfoxonium salts **16** in a practically quantitative yield. Treatment of salts **16** with LiN(H)*t*Bu at low temperatures gave the novel vinylic aminosulfoxonium ylides **17**, which could be trapped with reactive electrophiles at low temperatures. However, at elevated temperatures ylides **17** gave, besides sulfinamide **18**, alkynes **20** in good yield. Presumably, ylides **17** experienced an elimination of **18** with formation of the alkylidene carbenes **19**, which underwent a 1,2-H-shift to give alkynes **20**. Deprotection of the silyl ethers **20** finally gave in good overall yield alcohols **21**. The synthesis of alkynes **21** from the sulfoximine-substituted homoallylic alcohols **11** involves a new method for the generation of alkylidene carbenes [20] and nicely exemplifies the synthetic versatility of the sulfoximine group.

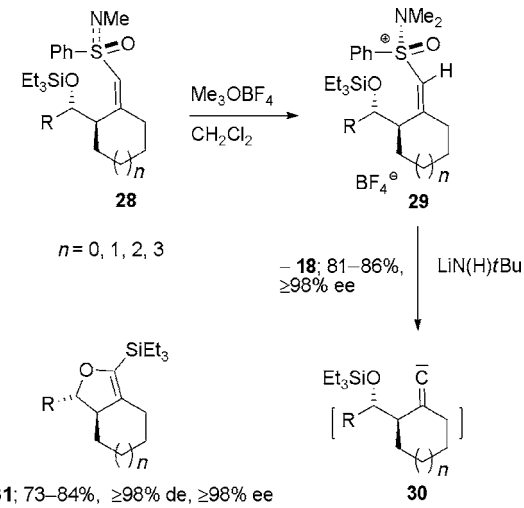
Asymmetric Synthesis of 2,3-Dihydrofurans

2,3-Dihydrofurans of type **V** and **VI** (cf. Scheme 2) should be interesting building blocks for the synthesis of natural product and in particular of those containing a substituted tetrahydrofuran ring as for example polyether antibiotics, lignans, and nucleosides [21]. Application of **V** and **VI** in natural product synthesis has been hampered, however, by a lack of suitable methods for their asymmetric synthesis [22]. It was therefore tempting to probe the generation of the silyloxy- and methyl-substituted alkylidene carbenes **25** from sulfoximines **22** (Scheme 9) [23] because of the following considerations. Since a 1,2-methyl-shift of alkylidene carbenes is slower than a 1,2-H-shift, carbenes **25** could perhaps undergo a 1,5-O,Si-bond insertion with formation of **27** rather than a 1,2-methyl shift to give the corresponding alkyne. Although the 1,5-O,Si-bond insertion of alkylidene carbenes was well documented at the beginning of our investigations [24], not much was known about the reactivity of carbenes of type **25** in regard to a competition among 1,2-methyl-shift, 1,5-O,Si-bond insertion, and 1,5-C,H-bond insertion.

Treatment of the aminosulfoxonium salts **23**, which were obtained through methylation of sulfoximines **22** in a practically quantitative yield, with LiN(H)*t*Bu gave 2,3-dihydrofurans **27** in good overall yield. Besides **27**, sulfinamide **18** with ≥98% ee was isolated in high yield. The conversion of sulfinamide **18** to sulfoximine **1** of ≥98% ee had already been accomplished [23]. Thus, a recycling of the chiral auxiliary is possible. Having obtained favorable results in the cyclization of acyclic aminosulfoxonium salts, the cyclic derivatives **29** were studied (Scheme 10). Treatment of salts **29**, which were prepared through methylation of sulfoximines **28**, with the lithium amide cleanly furnished the bicyclic 2,3-dihydrofurans **31** in good yield. It is assumed that salts **23** and **29** suffer upon treatment with



SCHEME 9 Asymmetric synthesis of 2,3-dihydrofurans.



SCHEME 10 Asymmetric synthesis of bicyclic 2,3-dihydrofurans.

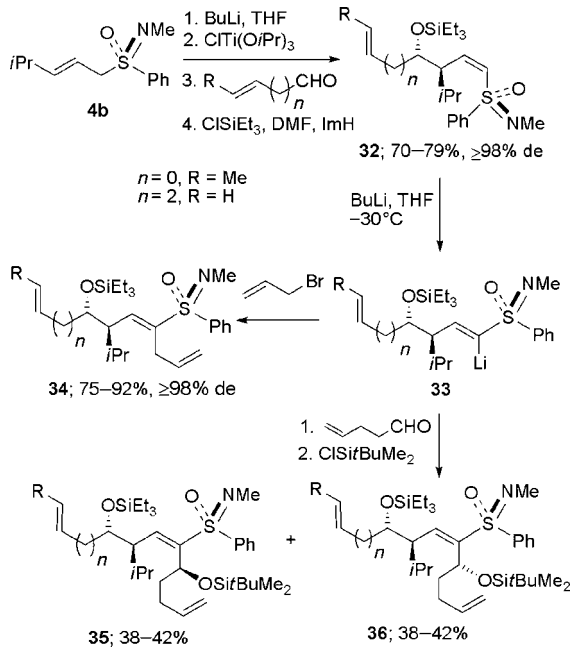
the lithium amide an α-elimination with formation of the alkylidene carbenes **25** and **30**, respectively. Subsequently, carbenes **25** and **30** undergo a 1,5-O,Si-bond insertion rather than a 1,2-alkyl-shift or 1,5-C,H-bond insertion. The 1,5-O,Si-bond insertion may occur in a concerted or nonconcerted fashion. In the later case, the oxonium ylides **26** should be formed as intermediates.

Asymmetric Synthesis of Medium-Sized Carbocycles and Lactones

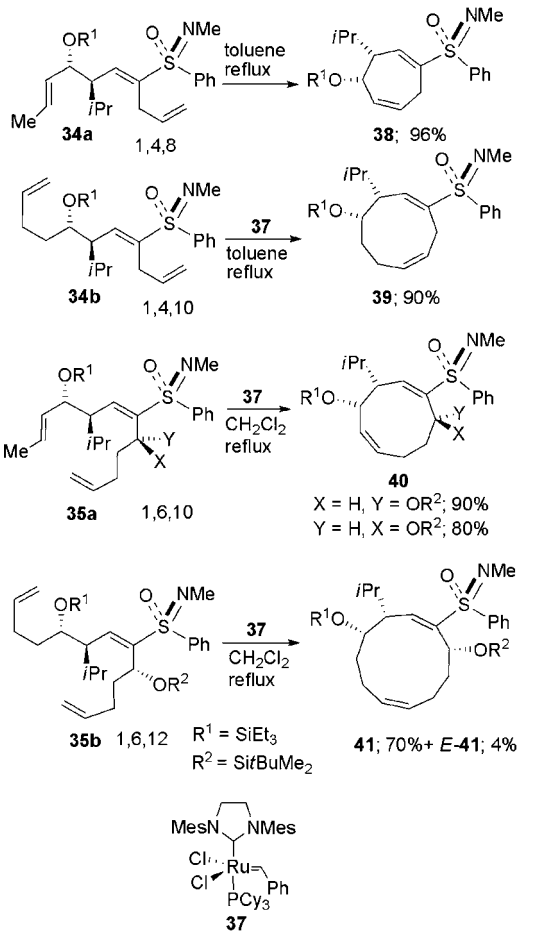
The asymmetric synthesis of medium-sized rings is a topic of considerable interest [25]. Medium-sized carbocycles and lactones for example are structural motifs of a large number of natural products [26]. Although several methods for the asymmetric synthesis of medium-sized rings have been described, those giving access to highly substituted derivatives are scarce [25]. We became interested in the development of a modular asymmetric synthesis of medium-sized rings starting from sulfoximine-substituted homoallylic alcohols and amines of type **II** and **III**, respectively, by using as key step a ring-closing metathesis reaction [25a,b,f,g] of sulfoximine-substituted trienes derived from **II** and **III** [27].

The reaction of the titanium complex derived from the allylic sulfoximine **4b** with but-2-enal and pent-4-enal afforded the diastereopure sulfoximine-substituted dienes **32** in good yield (Scheme 11). Treatment of the alkenyl sulfoximines **32** with *n*BuLi cleanly gave the *E*-configured alkenyllithium derivatives **33** via isomerization of the initially formed *Z*-configured alkenyllithium compounds [28]. Reaction of **33** with allyl bromide and 4-pentenal delivered the sulfoximine-substituted trienes **34**, **35**, and **36**, respectively, in good overall yields. The modular asymmetric synthesis of **34–36** from an allylic sulfoximine, two different unsaturated aldehydes or an allyl halide should allow a general access to sulfoximine substituted trienes. Treatment of 1,4,8-triene **34a**, 1,4,10-triene **34b**, 1,6,10-triene **35a** and 1,6,12-triene **35b** with the ruthenium catalyst **37** [25b] gave the carbocycles **38**, **39**, **40**, and **41**, respectively, with high diastereoselectivities and in good yields (Scheme 12).

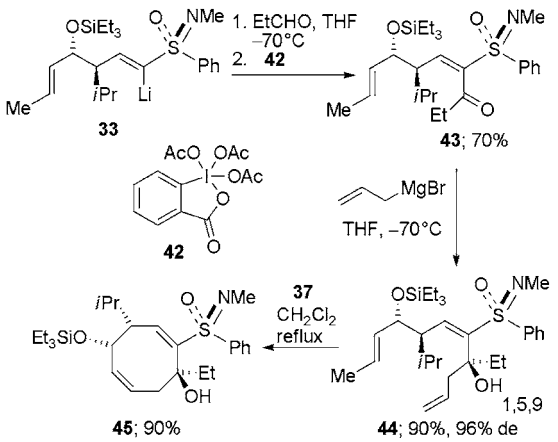
The hydroxyalkylation of the alkenyllithium derivatives **33** with 4-pentenal was unselective, giving a mixture of the diastereomeric trienes **35** and **36**. To solve this problem, an alternative and fully stereocontrolled synthesis of highly substituted sulfoximine-containing trienes was developed. Treatment of the alkenyllithium derivative **33** with propanal followed by the oxidation of the



SCHEME 11 Modular asymmetric synthesis of sulfoximine-substituted trienes.



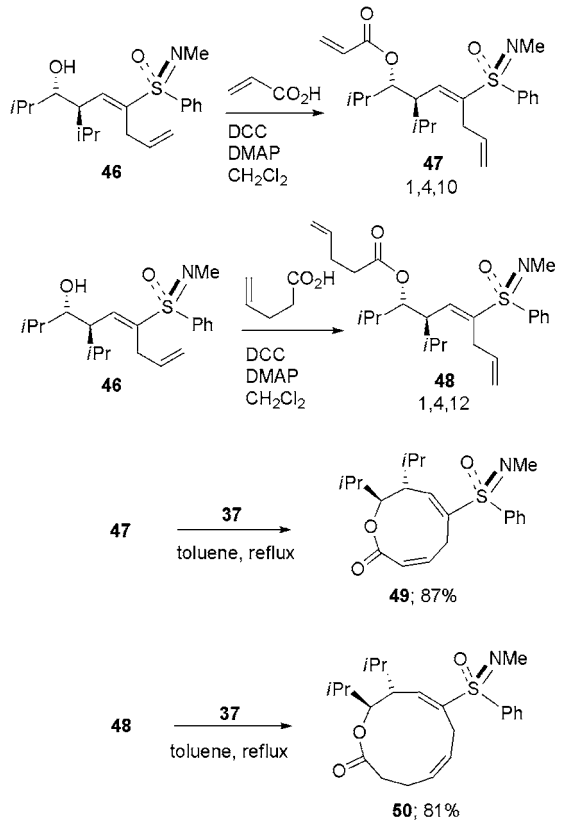
SCHEME 12 Ring-closing metathesis of sulfoximine-substituted trienes.



SCHEME 13 Fully stereocontrolled synthesis of an eight-membered carbocycle.

intermediate mixture of allylic alcohols with **42** gave enone **43** in good overall yield (Scheme 13). Reaction of enone **43** with allylmagnesium bromide proceeded with high diastereoselectivity and gave the tertiary alcohol **44**, the ring-closing metathesis (RCM) reaction of which with **37** furnished the highly substituted carbocycle **45** in high yield.

Finally the modular asymmetric synthesis of medium-sized lactones by the triensulfoximine-RCM route was probed. Esterification of alcohol **46** with acrylic acid and 4-pentenoic acid afforded esters **47** and **48**, respectively, in medium yield (Scheme 14). The RCM reaction of 1,4,10-triene **47** and 1,4,12-triene with **37** cleanly gave lactones **49** and **50**, respectively, with high stereoselectivity in good yield.

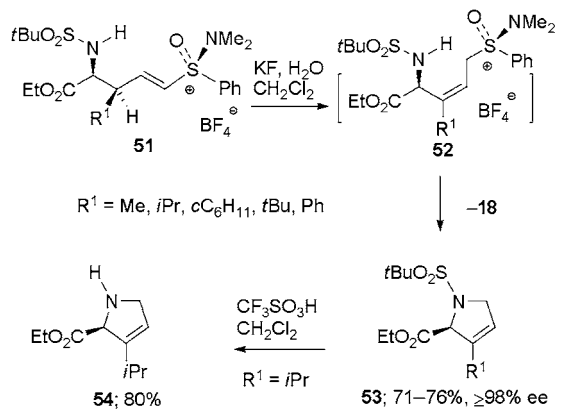


SCHEME 14 Modular asymmetric synthesis of medium-sized lactones.

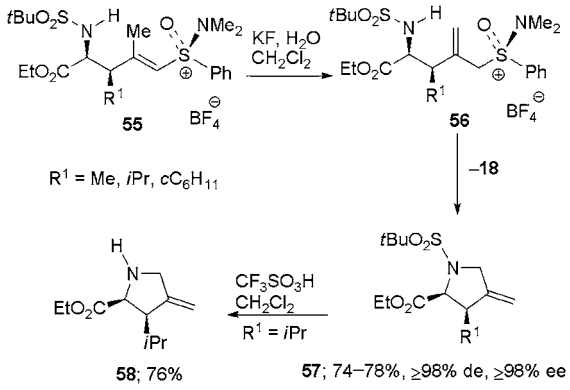
Asymmetric Synthesis of Unsaturated Prolines

Unsaturated prolines have gained considerable interest in recent years as starting material for the synthesis of conformationally fixed glutamic acid analogs as for example the kainoid amino acids [29]. The kainoid amino acids show neuroexcitatory properties and are as such interesting probes for a study of neurological disorder as for example Alzheimer's disease [30]. We have therefore developed an interest in the asymmetric synthesis of mono- and bicyclic unsaturated prolines of type **IX–XI** starting from sulfoximine-substituted homoallylic amines of type **III** (cf. Scheme 2) [31–33]. Although a number of asymmetric syntheses of proline derivatives have been described, there is a lack of methods for the asymmetric synthesis of unsaturated prolines of type **IX–XI** [34].

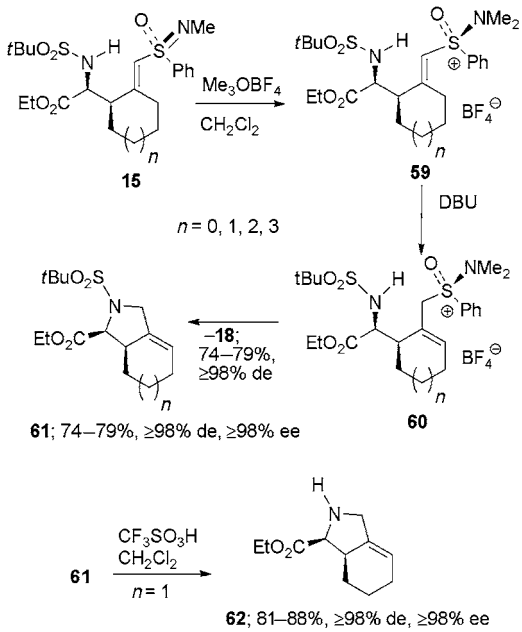
Treatment of the aminosulfoxonium salts **51**, which were synthesized through methylation of sulfoximines **14**, with KF in H_2O/CH_2Cl_2 afforded the proline derivatives **53** in good overall yield (Scheme 15). It is assumed that salts **51** suffer under the two-phase reaction conditions via a preceding anion exchange a vinyl/allyl isomerization catalyzed by the F^- ion leading to the formation of the allylic aminosulfoxonium salts **52** which undergo a cyclization mediated by the F^- ion to give **53**. Deprotection



SCHEME 15 Asymmetric synthesis of $\Delta^{3,4}$-unsaturated prolines.



SCHEME 16 Asymmetric synthesis of 3-methylene prolines.



SCHEME 17 Asymmetric synthesis of bicyclic unsaturated prolines.

of the *N-tert*-butylsulfonyl derivative **53** with CF_3SO_3H in CH_2Cl_2 gave the unprotected proline derivative **54** in good yield. A deprotection of the corresponding proline **53** carrying an *N*-tolylsulfonyl group proved not to be possible. This demonstrates the synthetic value of the imino ester **13b**.

It was speculated that a similar reaction of the methyl-substituted aminosulfoxonium salts **55** would perhaps provide access to the methylene proline derivatives **57** since a vinyl/allyl isomerization involving the methyl H atoms should be preferred because of statistic and kinetic reasons (Scheme 16). Treatment of salts **55** with KF in H_2O/CH_2Cl_2 indeed furnished the methylene derivatives **57** in good overall yield. Thus the vinyl/allyl isomerization preferentially proceeded with formation of the allylic aminosulfoxonium salts **56**, the F^--mediated cyclization of which gave **57**. Deprotection of **57** afforded the proline derivative **58** in good yield. The syntheses of **53** and **57** from the vinylic aminosulfoxonium salts **51** and **55**, respectively, clearly demonstrate the exceptional nucleofugacity of the allylic aminosulfoxonium group.

The successful synthesis of the proline derivatives **53** and **57** prompted a study of the reactivity of the cyclic aminosulfoxonium salts **59** (Scheme 17). Unsaturated bicyclic proline derivatives of type **61** should be interesting starting material for the synthesis of proline analogs and for the attainment of perhaps new catalysts [35]. Methylation of sulfoximines **15** afforded salts **59** in practically quantitative yield. Treatment of salts **59** with DBU gave the bicyclic proline derivatives **61** in good overall yield. Thus DBU most likely caused a kinetic vinyl/allyl isomerization of **59** with formation of the allylic aminosulfoxonium salts **60** which suffered a DBU-mediated cyclization. Deprotection of **61** furnished the proline derivative **62** in good yield [33].

In addition to the applications of the sulfoximine-substituted titanium complexes **8** and **10** described above the complexes have been successfully applied to the asymmetric synthesis of highly substituted β-amino acids [36] and bicyclic amino acids [37]. Complexes **8** and **10** have configurationally labile Cα-atoms, and only one of the possible diastereomers is depicted in the schemes. The sulfoximine group is depicted in the schemes for the sake of simplicity with SO and SN double bonds. However, ab initio calculation (References [4,31,38]) gave no evidence for the existence of a double bond composed of a σ-bond and of a π-bond of type $p_{N(O)}-d_S$. Thus a correct structural representation of the sulfoximine group would be the one containing SO and SN single bonds with two positive charges at the S atom and a negative charge at each O and N atom.

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