ORGANIC LETTERS

2007
Vol. 9, No. 4
579−582

Asymmetric Synthesis of Substituted Homoallyl Alcohols, Halomethyl Tetrahydrofurans, and Chloro-amino Sulfones from Allyltitanium Sulfoximines and α-Hetero Aldehydes

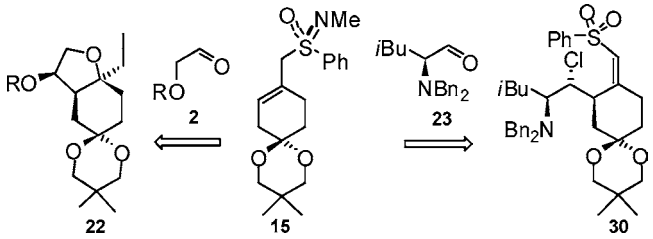
A. Rajender and Hans-Joachim Gais*

Institut für Organische Chemie der Rheinisch-Westfälischen Technischen Hochschule (RWTH) Aachen, Landoltweg 1, 52074 Aachen, Germany

gais@rwth-aachen.de

Received November 13, 2006

ABSTRACT



Asymmetric syntheses of the iodomethyl-substituted bicyclic tetrahydrofuran 22 and the chloro-amino sulfone 30 from the allylic sulfoximine 15 and the α-hetero aldehydes 2 and 23, respectively, are described. Further examples for the asymmetric synthesis of chloromethyl tetrahydrofurans and chloro-amino sulfones are given. The synthesis of 30 features as key step the stereoselective Cl-substitution of a hydroxy group under neighboring group participation by an aminosulfoxonium group which is converted to a sulfonyl group.

The asymmetric synthesis of tetrahydrofurans[1,2] and β-amino alcohols[3,4] has attracted considerable attention. Tetrahydrofurans[5] and β-amino alcohols[6] occur as structural motives in a large number of natural products, and β-amino alcohols have found application in the synthesis of chiral ligands and auxiliaries.[7] We describe in this paper asymmetric syntheses of mono- and bicyclic halomethyl tetrahydrofurans of type **C** and unsaturated chloro-amino sulfones of type **A** (Figure 1). While halomethyl tetrahydrofurans of type **C** are of interest as starting materials for the synthesis of both new muscarine analogs for the treatment of Alzheimer's disease[8] and tetrahydrofuran-containing macrocycles,[5] halides **A** should give access not only to the corresponding β-amino alcohols but also to a number of other synthetically interest-

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10.1021/ol0627606 CCC: $37.00
Published on Web 01/17/2007

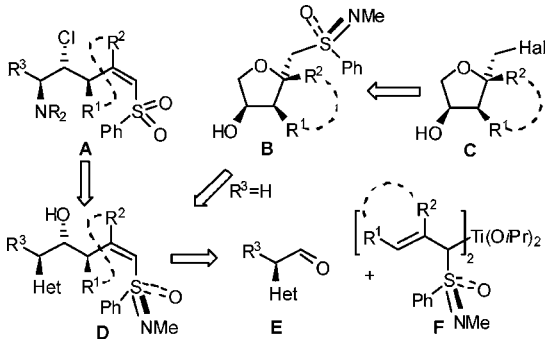

Figure 1. Asymmetric synthesis of halomethyl tetrahydrofurans and unsaturated chloro-amino sulfones.

ing derivatives. Key steps of the syntheses of **A** and **C** are (1) a highly regio- and diastereoselective γ-hydroxyalkylation of the allyltitanium sulfoximines **F**[9] with α-hydroxy and α-amino aldehydes of type **E**, (2) a highly diastereoselective cyclization of homoallyl alcohols of type **D** (Het = OH) with formation of tetrahydrofurans of type **B**, (3) a substitution of sulfoximines **B** with formation of halides **C**, and (4) a novel one-pot stereoselective conversion of the hydroxy sulfoximines **D** to chloro sulfones of type **A**. Although sulfoximine-substituted tetrahydrofurans of type **B**, carrying a functionalized chiral substituent at the N-atom, have been previously prepared with high selectivity by a similar route, their substitution with formation of halomethyl tetrahydrofurans of type **C** or other functionalized tetrahydrofurans proved not to be feasible.[10]

The allyl sulfoximines **1**, **7**, **8**, and **15** (Scheme 1) were prepared by the one-pot **a**ddition-**e**limination-**i**somerization (AEI) route starting from the corresponding ketones and enantiopure (*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine in 78%, 86%, 83%, and 91% overall yield, respectively, as described previously.[9] The acyclic sulfoximine **1** was obtained as a single *E*-isomer. Reaction of the allyltitanium sulfoximines (cf. Figure 1) derived from sulfoximines **1**, **7**, **8**, and **15** with 1.4 equiv of aldehyde **2** occurred with high diastereoselectivity and furnished the silyloxy-substituted homoallylic alcohols **3**, **9**, **10**, and **16**, respectively, in high overall yields. The complete conversion of the intermediate allyltitanium sulfoximines derived from **1**, **7**, **8**, and **15** required the presence of an additional 1 equiv of ClTi(O*i*Pr)$_3$.[9a,b] Therefore it was gratifying to see that the presence of the Lewis acid did not noticeably interfere in the reaction of the acetal-substituted allyl sulfoximine **15**. A similar situation was encountered in the reaction of the acetal-protected chiral aldehyde **19** with the titanium complexes derived from the allyl sulfoximines **7** and **8** in the presence of an additional 1 equiv of ClTi(O*i*Pr)$_3$, which proceeded with high diastereoselectivity and gave the homoallylic alcohols **20** and **21**, respectively, in high overall yields. Next the cyclization of the silyloxy-substituted homoallyl alcohols of type **D** with formation of tetrahydrofurans of type **B** was investigated. Treatment of the silyl ether **3** with either HF·pyridine in THF or Bu_4NF in THF led to a cleavage of the silyl group followed by a highly diastereoselective cyclization, which gave the tetrahydrofuran **4a** in high yield. A similar treatment of the cyclic silyloxy-substituted vinyl sulfoximines **9**, **10**, and **16** resulted in a similarly highly diastereoselective cyclication and afforded the bicyclic tetrahydrofurans **11a**, **12a**, and **17a**, respectively, in high yields. The configuration of **11a** was determined by X-ray crystal structure analysis. The application of sulfoximine-substituted tetrahydrofurans of type **B** in, for example, the synthesis of muscarine agonists requires the replacement of the sulfoximine group by a halogen atom and their conversion to **C**. We had previously shown that *S*-alkyl-*N*-methyl sulfoximines are readily converted to the corresponding alkyl chlorides upon reaction with a chloroformate.[11] Thus treatment of the acyclic sulfoximine **4b**, which was obtained through silylation of alcohol **4a** (91%), with $ClCO_2CH(Cl)Me$ in CH_2Cl_2 at room temperature cleanly afforded chloride **6** in good yield. Similarly, reaction of the cyclic sulfoximines **11b** and **12b**, obtained through silylation of alcohols **11a** (98%) and **12a** (86%), respectively, with the chloroformate furnished the bicyclic chloromethyl tetrahydrofurans **13** and **14**, respectively, in good yields. Finally, the reactivity of the functionalized sulfoximine **17b**, which was prepared through silylation of alcohol **17a** (89%), was probed in order to get information about the functional group tolerance of this substitution. Treatment of sulfoximine **17b** with the chloroformate gave chloride **18** in high yield. Eventually it was found that iodides are also directly accessible from alkyl sulfoximines.[12] Treatment of sulfoximine **17b** with phenyl iodoformate[13] in MeCN afforded iodide **22** in good yield. The conversion of sulfoximines **4b**, **11b**, **12b**, and **17b** into the corresponding halides upon reaction with a haloformate involves an acyclation at the N-atom with formation of the corresponding aminosulfoxonium salts carrying a methyl and an ester group at the N-atom, followed by a nucleophilic substitution of the aminosulfoxonium group by the halide ion with formation of the corresponding halides and sulfinamides **5a** and **5b**, respectively. Sulfinamides **5a** and **5b** were isolated in high yields. Since sulfinamide **5a** of ≥98% ee had already been converted to (*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine of ≥98% ee with good yield,[11] recycling of the chiral auxiliary is guaranteed.

Favorable results having been recorded in the hydroxyalkylation of complexes **F** with α-hydroxy aldehydes, their reaction with α-amino aldehydes was studied. Treatment of the allyltitanium sulfoximines derived from the allyl sulfox-

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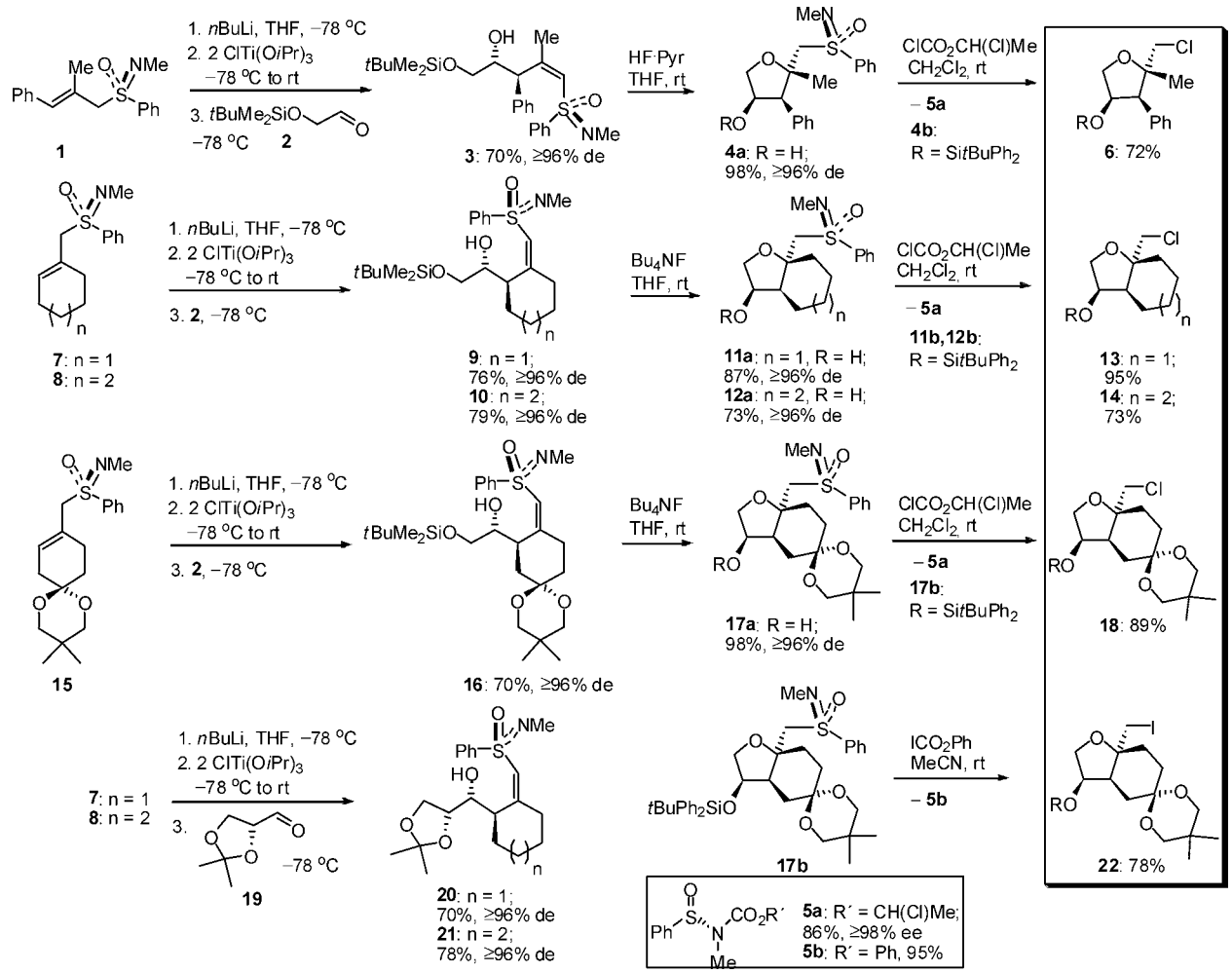
Scheme 1. Reaction of Allyltitanium Sulfoximines with α-Hydroxy Aldehydes and Asymmetric Synthesis of Tetrahydrofurans



imines **1**, **8**, and **15** with aldehyde **23** in the presence of an additional 1 equiv of $ClTi(OiPr)_3$ proceeded with high diastereoselectivity and gave the diastereopure homoallylamino alcohols **24**, **27**, and **29**, respectively, in high overall yields (Scheme 2). Because of synthetic and mechanistic reasons, the reactivity of aldehyde **31** and its enantiomer *ent*-**31** was also studied. Gratifyingly, reaction of the allyltitanium sulfoximine derived from the seven-membered cyclic allyl sulfoximine **8** with aldehydes **31** and *ent*-**31** occurred in both cases with high diastereoselectivity and gave the homoallyl alcohols **32** and **34**, respectively, in high overall yields. Thus the chirality of the aldehyde has no influence upon the stereoselectivity of the hydroxyalkylation. The configuration of **32** was determined by X-ray crystal structure analysis.

We had previously found that sulfoximine-substituted homoallyl alcohols derived from **F** and unsubstituted aldehydes undergo upon reaction with a chloroformate an acylation at the N-atom followed by a vinyl-allyl isomerization and a subsequent substitution of the allylic aminosulfoxonium group by the Cl^- ion to give the corresponding allyl chloride.[14] This prompted a study of the reactivity of the amino-substituted homoallyl alcohols of type **D** (Het = NR_2) toward chloroformates. Surprisingly, treatment of the acyclic sulfoximine **24** with $ClCO_2CH(Cl)Me$ gave *β*-chloroamine **26** carrying a sulfonyl group instead of the sulfoximine group with high diastereoselectivity in good yield. In addition to the chloro sulfone **26**, the carbamate **25** was isolated in similar yield. The generality of this novel transformation was demonstrated by the reaction of the cyclic sulfoximines **27**, **29**, and **32** with $ClCO_2CH(Cl)Me$, which gave with high diastereoselectivity the chloro-amino sulfones **28**, **30**, and **33**, respectively, in good yields. The configuration of the chloro sulfone **30** was determined by X-ray crystal structure analysis.

The stereoselective transformations of the two functional groups may be rationalized by the operation of a nucleophilic substitution cascade as exemplified for sulfoximine **29** (cf. Scheme 2). Sulfoximine **29** reacts with the chloroformate through acylation at the N-atom to give the hydroxy aminosulfoxonium salt **35**. An intramolecular nucleophilic attack of the hydroxy group of **35** at the S-atom is followed by an elimination of **25** to furnish the cyclic oxosulfoxonium

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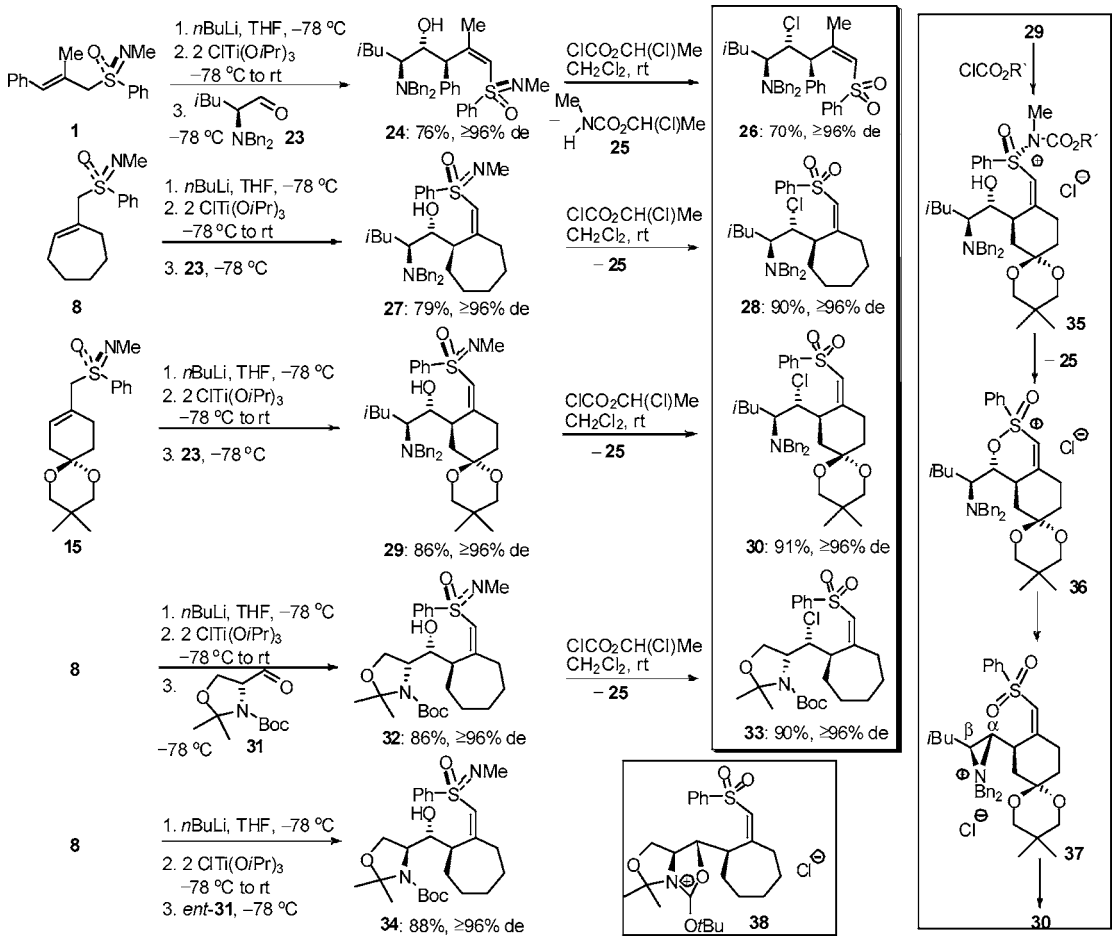
Scheme 2. Reaction of Allyltitanium Sulfoximines with α-Amino Aldehydes and Asymmetric Synthesis of δ-Chloro-ϵ-amino Sulfones



salt **36**. Salt **36** undergoes, as an O-alkylated sulfone, a facile intramolecular nucleophilic substitution by the amino group under inversion of configuration with formation of the aziridinum salt **37**. Then salt **37** reacts with the Cl^- ion with inversion of configuration[15] to deliver the chloro-amino sulfone **30**. According to molecular model analyses the high regioselectivity of the ring opening of **37** and the corresponding aziridinium ions derived from **24** and **27** seems to be primarily due to a shielding of the Cβ atom by the sulfonyl group. In the case of the hydroxy sulfoximine **32**, the Boc group could exert a similar neighboring group effect leading to the intermediate formation of the oxazolium salt **38**. In summary, we have developed asymmetric syntheses of halomethyl-substituted mono- and bicyclic tetrahydrofurans and unsaturated chloro-amino-substituted sulfones, a key step of which is the highly selective hydroxyalkylation of allylsulfoximines with α-hydroxy and α-amino aldehydes. The synthesis of the unsaturated chloro-amino-substituted sulfones involves the stereoselective substitution of a hydroxy group by the Cl^- ion under neighboring group participation by an aminosulfoxonium group which in turn is converted to a sulfonyl group.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (SFB 380 and GK 440).

Supporting Information Available: Experimental procedures and characterization data for compounds **15**, **16**, **17a**, **17b**, **18**, **29**, and **30** and copies of the ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0627606

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