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Modular Asymmetric Synthesis of Functionalized Azaspirocycles Based on the Sulfoximine Auxiliary

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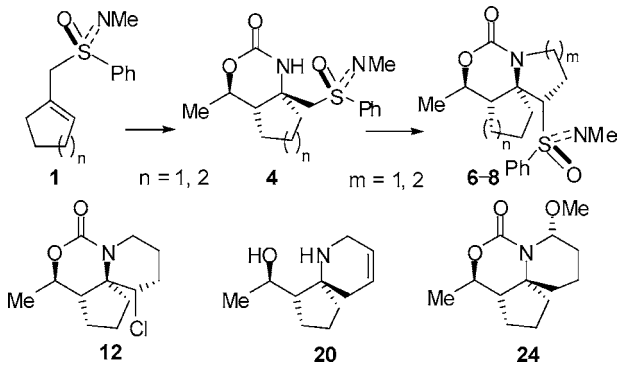
ABSTRACT



A modular asymmetric synthesis of the functionalized azaspirocycles 6 (*m* = 2, *n* = 1), 7 (*m* = 1, *n* = 2), 8 (*m* = *n* = 2), 12, 20, and 24 from the cyclic allylic sulfoximines 1 is described. The synthetic strategy is based on the stereoselective construction of the carbocycle 4 containing the amino-substituted tertiary C atom from 1 followed by the generation of the azaspirocycle. Three different routes have been followed for the synthesis of the heterocyclic ring: N,C-dianion cycloalkylation, ring-closing metathesis, and *N*-acyl iminium ion formation.

Azaspirocycles of type **I** (Figure 1) are found as structural motifs in a number of highly interesting natural products,

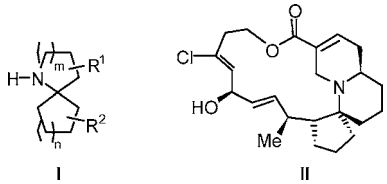


Figure 1. Azaspirocycles **I** and halichlorine **II**.

such as histrionicotoxin,[1] cephalotaxine,[2] cylindricine A,[3] lepadiformine,[3] halichlorine (**II**),[4] and pinnaic acid.[4] In particular, the marine alkaloid **II** containing a 6-azaspiro-[4.5]decane framework has received much attention in recent years because of its interesting biological activities and intricate structure.[4] A number of methods have been developed for the construction of **I**,[5] especially within the context of total syntheses or synthetic approaches to the aforementioned and other related target molecules. Although most of these primarily target-molecule-orientated methods are imaginative and high yielding, there is still an interest in the development of a more general method for the enantiose-

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(2) Jilal Miah, M. A.; Hudlicky, T.; Redd, J. W. In *The Alkaloids*; Cordell, G. A., Ed.; Academic: San Diego, CA, 1998; Vol. 51, pp 199−269.
(3) Weinreb, S. M. *Chem. Rev.* **2006**, *106*, 2531−2549.
(4) Clive, D. L. J.; Yu, M.; Wang, J.; Yeh, V. S. C.; Kang, S. *Chem. Rev.* **2005**, *105*, 4483−4514.
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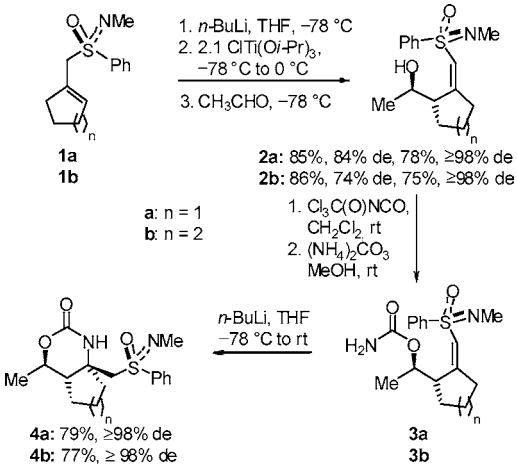
lective construction of **I**. Here, we describe a modular asymmetric synthesis of functionalized 1-azaspiro[4.5]decanes (**I**, $m = 1$, $n = 2$), 1-azaspiro[5.5]-undecanes (**I**, $m = 2$, $n = 2$), and 6-azaspiro[4.5]decanes (**I**, $m = 2$, $n = 1$) based on the sulfoximine auxiliary by exploiting its special features, including chirality, carbanion stabilization, and nucleofugacity.[6]

Our synthetic approach to azaspirocycles is based on a two-step strategy in which the carbocycle with the tertiary C atom bearing the amino group is constructed followed by formation of the heterocycle to generate the spiro-ring system. The asymmetric synthesis of the amino-substituted carbocycle takes advantage of the methods developed in our laboratories for the synthesis of β-amino acids from sulfoximines.[7]

The starting *R*-configured cyclic allylic sulfoximines **1a** and **1b** (Scheme 1) were prepared as described previously

Scheme 1. Synthesis of Carbocycles Having an Amino-Substituted Tertiary C Atom

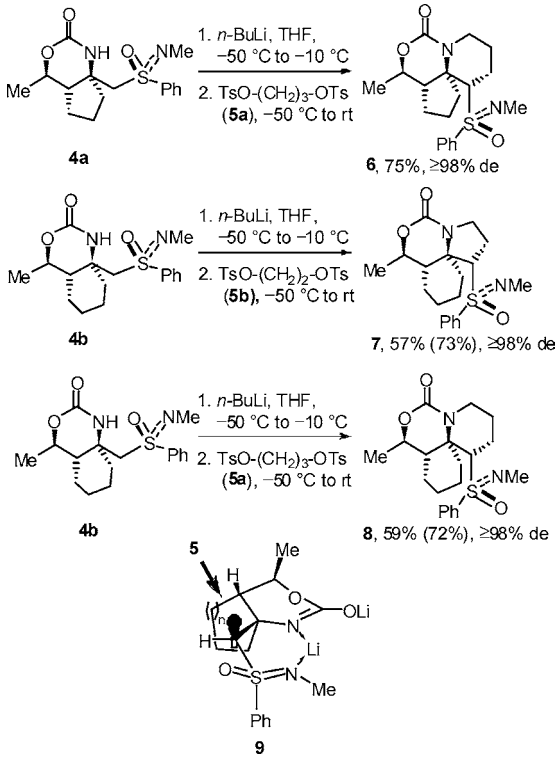


by the addition−elimination−isomerization route from (*R*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (≥98% ee)[8] and the corresponding cycloalkanones.[9] Lithiation of **1a** and **1b** followed by the treatment of the lithiated allyl sulfoximines with 2.1 equiv of ClTi(O*i*-Pr)$_3$ furnished the corresponding bis(allyl)-titanium complexes admixed with ClTi(O*i*-Pr)$_3$[9] which reacted with acetaldehyde with high regioselectivities (≥95%) and good diastereoselectivities at the γ-position and afforded the homoallylic alcohols **2a** and **2b**, respectively. HPLC and crystallization of the mixtures of diastereomers gave the diastereomerically pure alcohols **2a** and **2b** in 78 and 75% yield, respectively. Treatment of alcohols **2a** and **2b** with trichloroacetyl isocyanate and the subsequent hydrolysis of the corresponding *N*-trichloroacetyl carbamates with $(NH_4)_2CO_3$ in MeOH furnished carbamates **3a** and **3b**,[10] respectively. The crude carbamates **3a** and **3b** were subjected to a treatment with 1.3 equiv of *n*-BuLi, which gave the oxazinones **4a** and **4b**, respectively, with high diastereoselectivities in 79 and 77% overall yields, respectively, based on the starting alcohols **2a** and **2b**.[10] The configuration of oxazinone **4a** was determined by X-ray crystal structure analysis.

Having achieved an efficient synthesis of the functionalized carbocycles **4a** and **4b**, which carry three contiguous stereogenic C atoms, we focused on the construction of the heterocyclic ring starting from **4a** and **4b**. Three different routes were followed, including (1) the cycloalkylation of a carbamate−sulfoximine dianion, (2) a ring-closing metathesis, and (3) an *N*-acyl iminium ion formation.

First, the synthesis of the heterocyclic ring through cycloalkylation of the C,N-dianions of **4a** and **4b** with ditosylates was studied.[11] Thus, treatment of the five-membered cyclic sulfoximine **4a** with 2.2 equiv of *n*-BuLi in THF at low temperatures generated the corresponding N,C-dianion[11] which was stable in solution and gave upon treatment with the C$_3$-ditosylate **5a** tricycle **6** having a 6-azaspiro[4.5]decane skeleton with high diastereoselectivity in 75% yield (Scheme 2). The configuration of sulfoximine

Scheme 2. Synthesis of Azaspirocycles by C,N-Dianion Cycloalkylation



6 was determined by X-ray crystal structure analysis. Double deprotonation of the six-membered cyclic sulfoximine **5b** and treatment of the corresponding N,C-dianion with the

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(7) Gais, H.-J.; Loo, R.; Roder, D.; Das, P.; Raabe, G. *Eur. J. Org. Chem.* **2003**, 1500−1526.
(8) Brandt, J.; Gais, H.-J. *Tetrahedron: Asymmetry* **1997**, *8*, 909−912.
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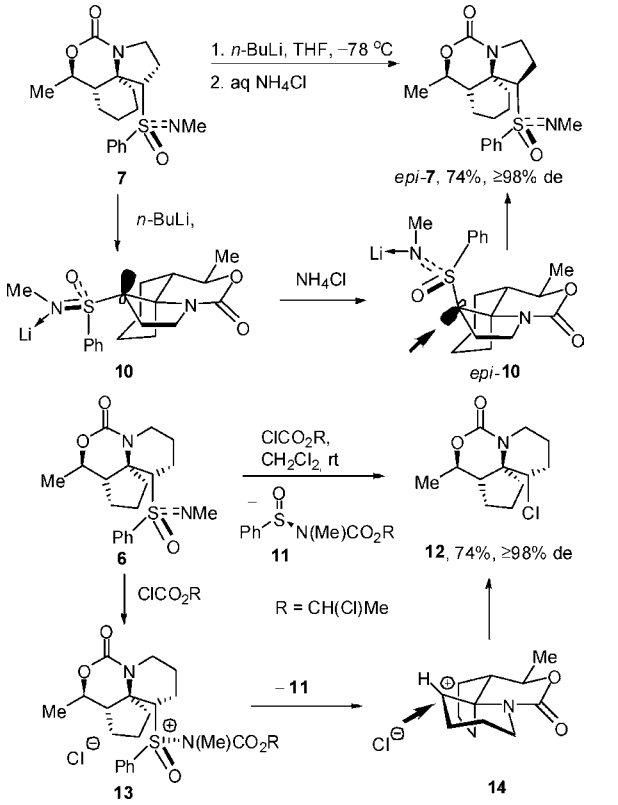
(10) Carbamate **3b** was obtained as a *Z*/*E* mixture (88:12). However, both isomers afforded oxazinone **4b** with high diastereoselectivity.

C_2-ditosylate **5b** afforded tricycle **7** having a 1-azaspiro[4.5]-decane skeleton with high selectivity in 57% isolated yield (73% based on conversion). Finally, reaction of the N,C-dianion derived from the six-membered cyclic sulfoximine **4b** with **5a** furnished tricycle **8** having a 1-azaspiro[5.5]-undecane skeleton with high diastereoselectivity in 59% isolated yield (72% based on conversion). The high diastereoselectivities of the cycloalkylation of the N,C-dianions derived from **4a** and **4b** are noteworthy. The selective formation of the *S*-configured tricycles can be rationalized by assuming a chelate structure of type **9** for the C,N-dianions[12] and a preferential attack of the ditosylate at the *Si* side of the Cα atom followed by a cyclization.

Interestingly, the successive treatment of sulfoximine **7** with *n*-BuLi and aqueous NH_4Cl afforded the epimeric sulfoximine *epi*-**7** with high diastereoselectivity in good yield (Scheme 3). Deprotonation of **7** should afford carbanion **10**,

Scheme 3. Stereoselective Epimerization and Cl Substitution of Sulfoximines



which is most likely endowed with a pyramidalized Cα atom, a Cα−S conformation as depicted, and a N−Li bond.[12] α-Sulfonimidoyl carbanions are configurationally labile,[12] and thus, carbanion **10** is expected to undergo an isomerization with formation of the epimeric carbanion *epi*-**10**. The epimer should be thermodynamically preferred over **10** because of the relief of steric interaction between the sulfoximine group and the carbocycle. Finally, protonation of **10** preferentially occurs from the direction of pyramidalization and gives *epi*-**7**. The selective synthesis of *epi*-**7** from **7** points to the possibility of the realization of highly stereoselective reactions of the α-sulfonimidoyl carbanions derived from the tricyclic sulfoximines **6**−**8** with electrophiles.

The application of tricycles **6**−**8** to the synthesis of azaspirocyclic natural products requires a substitution of the sulfoximine group. This was accomplished, for example, by the treatment of sulfoximine **6** with $ClCO_2CH(Cl)Me$, which gave chloride **12** with high diastereoselectivity in good yield and sulfinamide **11**. The configuration of **12** was determined by a combination of TOCSY and NOE experiments. Thus, the substitution of sulfoximine **6** had occurred with retention of configuration. We had previously shown that sulfinamide **11** is formed in such reactions with complete retention of configuration at the S atom and can not only be isolated in high yield but also recycled for the synthesis of **1**.[13] The mechanism of the substitution of sulfoximines with chloroformates is not known.[7,13] Previously, both retention and inversion of configuration had been observed in the substitution of secondary sulfoximines. The available evidence including the formation of **11** suggests an acylation of sulfoximine **6** at the N atom with formation of the aminosulfoxonium salt **13**. The formation of chloride **12** from **13** with complete retention of configuration could be the result of two yet unidentified S_N2 reactions or a S_N1 reaction with the intermediate formation of the carbenium ion **14**. However, it is difficult to see why the carbenium ion **14** should be attacked by the Cl^- ion with high selectivity from that side which seems to be the sterically more hindered one.

The alternative ring-closing metathesis route for the construction of the heterocyclic ring required the synthesis of suitable dienes from sulfoximines **4a** and **4b** via a substitution of the sulfoximine group by a nucleophilic and H atom at the N atom by an electrophilic reagent (Scheme 4). Therefore, sulfoximine **4a** was treated with a mixture of $ClCO_2CH(Cl)Me$ and NaI, which gave iodide **15** (Scheme 4) in good yield. The reaction of iodide **15** with 1-propenylmagnesium bromide (*Z*/*E* mixture) in the presence of CuI furnished alkene **16** (*Z*/*E* = 2:1) in good yield. Attachment of an unsaturated substituent at the N atom was accomplished upon treatment of carbamate **16** with allyl bromide, which afforded diene **17** (*Z*/*E* = 2:1) in good yield. The treatment of diene **17** with 5 mol % of catalyst **18**[14] gave alkene **19** having a 6-azaspiro[4.5]decane skeleton in high yield. Finally, the hydrolysis of oxazinone **19** with CsOH furnished the azaspirocycle **20** in good yield. This route could perhaps also open an access to azaspirocycles having a medium or large sized heterocyclic ring.

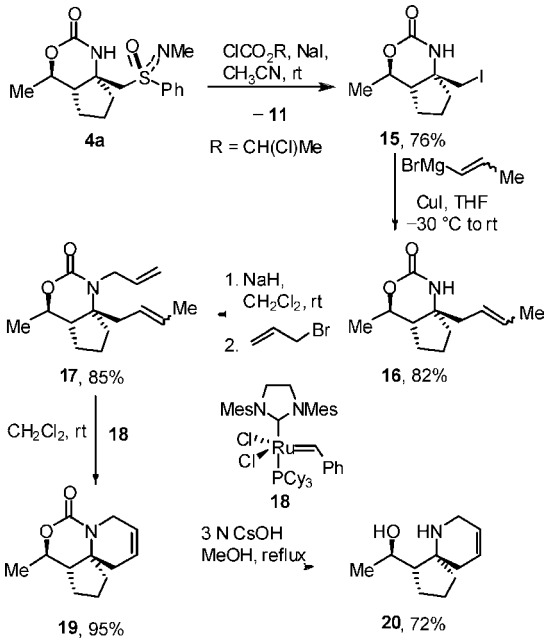
(11) For the cycloalkylation of C,N-dianions, see: (a) Costa, A.; Nájera, C.; Sansano, J. M. *Tetrahedron: Asymmetry* **2001**, *12*, 2205−2211.

(12) Gais, H.-J.; Erdelmeier, I.; Lindner, H. J.; Vollhardt, J. *Angew. Chem.* **1986**, *98*, 914−915; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 938−939. (b) Gais, H.-J.; Dingerdissen, U.; Krüger, C.; Angermund, K. *J. Am. Chem. Soc.* **1987**, *109*, 3775−3776. (c) Gais, H.-J.; Lenz, D.; Raabe, G. *Tetrahedron Lett.* **1995**, *36*, 7437−7440.

(13) (a) Gais, H.-J.; Babu, G. S.; Günter, M.; Das, P. *Eur. J. Org. Chem.* **2004**, 1464−1473. (b) Tiwari, S. K.; Gais, H.-J.; Lindenmaier, A.; Babu, G. S.; Raabe, G.; Reddy, L. R.; Köhler, F.; Günter, M.; Koep, S.; Iska, V. B. R. *J. Am. Chem. Soc.* **2006**, *128*, 7360−7373. (c) Loo, R. Ph.D. Thesis, RWTH Aachen, 1999.

(14) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117−7140.

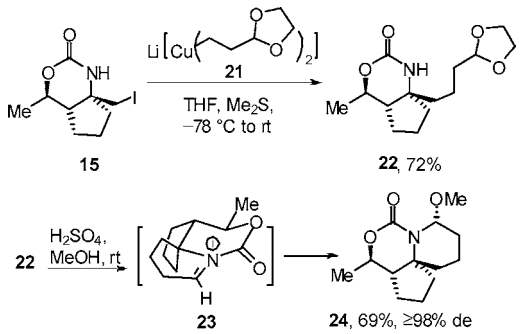
Scheme 4. Synthesis of Azaspirocycles by Ring-Closing Metathesis Reaction



Having realized syntheses of azaspirocycles with functional groups in the δ-, γ-, and β-position to the N atom of the heterocyclic ring, it was of interest to see whether an access to azaspirocycles carrying a functional group at the α-position could also be opened. Therefore, iodide **15** was treated with the functionalized cuprate **21**,[15] which gave acetal **22** in good yield (Scheme 5). Acetal **22** was submitted to a treatment with H_2SO_4 in methanol, which furnished, perhaps with the intermediate formation of the *N*-acyl iminium ion **23**, the tricyclic acetal **24** having a 6-azaspiro-[4.5]decane skeleton with high diastereoselectivity in good overall yield. The configuration of **24** was determined through a combination of TOCSY and NOE experiments.

(15) Brandaenge, S.; Dahlman, O.; Lindqvist, B.; Maahlen, A.; Moerch, L. *Acta Chem. Scand. B* **1984**, *B38*, 837−844.

Scheme 5. Synthesis of Azaspirocycles by *N*-Acyl Iminium Ion Formation



The stereoselectivity of the formation of acetal **24** is noteworthy. It is not known at present whether the exclusive formation of **24** is the result of a thermodynamic or kinetic control. Acetal **24** should allow a further functionalization at the α-position to the N atom via the formation of **23**.[16]

In summary, we have developed a modular asymmetric synthesis of azaspirocycles, the heterocyclic and carbocyclic rings of which carry different functional groups, from cyclic allyl sulfoximines. The use of ring-substituted cyclic allylic sulfoximines[17] as starting material should permit an access to azaspirocycles, the carbocyclic ring of which has two functional groups.

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Supporting Information Available: Experimental procedures for **4a**, **6**, **12**, and **24**, and copies of the NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Rajender, A.; Gais, H.-J. *Org. Lett.* **2007**, *9*, 579−582.