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# Ring-closing metathesis as a tool for the efficient preparation of chiral spirocyclic ethers from homoallylic alcohols

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ABSTRACT

The preparation of chiral spirocyclic ethers via allylic etherification/olefin metathesis of homoallylic alcohols is investigated. This reaction sequence transforms the enantiopure substrate alcohols, synthesized by a one-pot asymmetric rhodium-catalyzed conjugate addition/metal-mediated allylation procedure, into the desired spiro ethers with full conversions and in excellent isolated yields. The synthetic sequence provides an efficient means for a rapid construction of functionalized spiro ethers in a stereoselective manner.



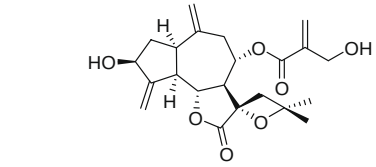
The frequent occurrence of the spiro framework in naturally occurring and pharmaceutically active substances has made their stereoselective preparation an important area of investigation in organic synthesis.[1] One of the commonly encountered members of this family of compounds are spirocyclic ethers,[2] exemplified by natural products such as clementein (**1**),[3] clerocidin (**2**),[4] and theaspirone (**3**)[5] (Fig. 1).

As reported by us previously, the combination of enantioselective Rh-catalyzed conjugate addition of arylboronic acids to enones, in the presence of the monodentate phosphoramidite ligand **L**,[6] followed by Barbier-type indium-mediated allylation[7] as the second step in a one-pot sequence, in aqueous medium, afforded 1,3-disubstituted cyclic alcohols in excellent diastereoselectivities and high yields (Scheme 1).[8]

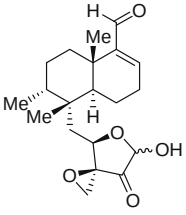
In our earlier work, the potential for further derivatization of the product alcohols was briefly explored by allylic etherification/ring-closing metathesis (RCM) of a single compound to afford the corresponding spiro ether in moderate yield.[8]

Here, we report optimized conditions for the conversion of diastereomerically pure homoallylic alcohols, prepared via the one-pot conjugate addition/allylation sequence (Scheme 1), into chiral spirocyclic ethers via allylic etherification/RCM, quantitatively, and in excellent isolated yields. The product spiro ethers can be functionalized by, for example, dihydroxylation, as is also exemplified in the present work.

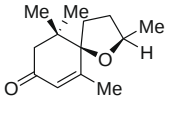
Conversion of the homoallylic alcohols **1a–f** into the spiro ethers commenced by reaction with sodium hydride and allyl bromide to afford the corresponding allyl ethers **2a–f** (step 1, Table 1).[9] As the deprotonation with sodium hydride and the subsequent reaction with excess allyl bromide at room temperature provided quantitative conversions, the allyl ethers **2a–f** were used for the next reaction step without further purification. Thus, on treating degassed dichloromethane solutions of **2a–f** with Grubbś second generation ruthenium catalyst at room temperature, chiral spirocyclic ethers **3a–f** were obtained in excellent isolated yields (step




clementein (**1**)




clerocidin (**2**)




theaspirone (**3**)

**Figure 1.** Naturally occurring spirocyclic ethers.

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*E-mail address:* reko.leino@abo.fi (R. Leino).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
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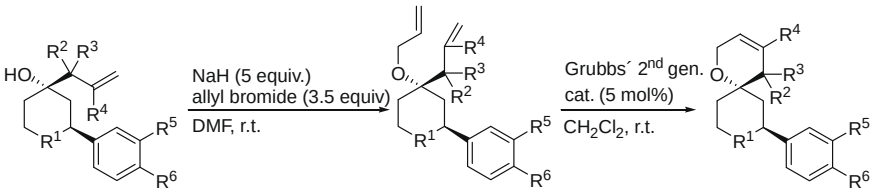
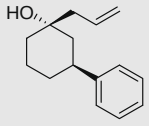
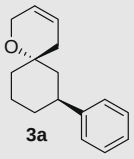
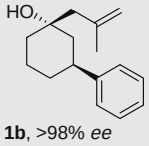
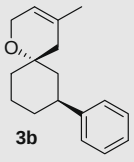
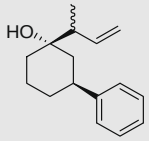
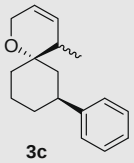
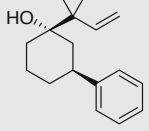
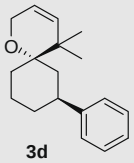
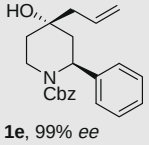
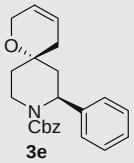
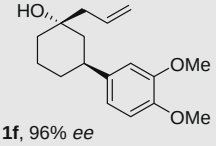
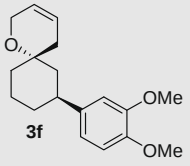
**Table 1**
Synthesis of chiral spiro ethers **3a**–**f** by allylation/RCM of **1a**–**f**[a]



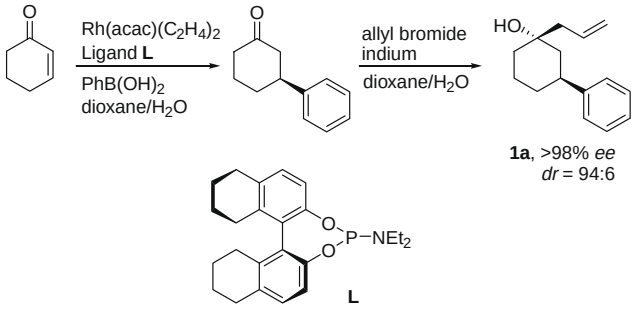

**1a**, $R^1 = CH_2$, $R^2 = R^3 = R^4 = R^5 = R^6 = H$ **2a-f** **3a-f**
**1b**, $R^1 = CH_2$, $R^2 = R^3 = R^5 = R^6 = H$, $R^4 = Me$
**1c**, $R^1 = CH_2$, $R^2 = Me$, $R^3 = R^4 = R^5 = R^6 = H$
**1d**, $R^1 = CH_2$, $R^2 = R^3 = Me$, $R^4 = R^5 = R^6 = H$
**1e**, $R^1 = NCbz$, $R^2 = R^3 = R^4 = R^5 = R^6 = H$
**1f**, $R^1 = CH_2$, $R^2 = R^3 = R^4 = H$, $R^5 = R^6 = OMe$

| Entry | Substrate[b] | Product | Yield[c] (%) |
|---|---|---|---|
| 1 |  **1a**, >98% *ee* *dr* = 94:6 (a/b) |  **3a** | 90 |
| 2 |  **1b**, >98% *ee* *dr* = 95:5 (a/b) |  **3b** | 89 |
| 3 |  **1c**, >98% *ee* *dr* = 98:2 (a/b) |  **3c** | 89 |
| 4 |  **1d**, >98% *ee* *dr* = >99:<1 (a/b) |  **3d** | 95 |
| 5 |  **1e**, 99% *ee* *dr* = 73:27 (a/b) |  **3e** | 80 |
| 6 |  **1f**, 96% *ee* *dr* = >99:<1 (a/b) |  **3f** | 84 |

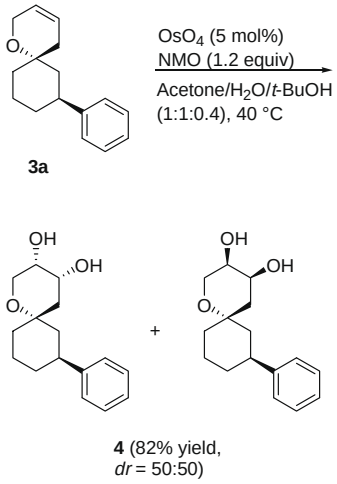
[a] Allylations were performed at rt on 0.10–0.20 mmol scale with 5 equiv of NaH and 3.5 equiv of allyl bromide, respectively. RCM was performed at rt with 5 mol % of Grubbś second generation catalyst.
[b] *ee* Values were determined by chiral HPLC. *dr* Values were determined by GC or $^1H$ NMR spectroscopy (a: axial OH group; b: equatorial OH group). Pure single diastereoisomers were used for further derivatization by allylation/RCM.
[c] Isolated yields based on substrates **1a**–**f**.

2, Table 1).[10,11] The stereochemistry of the substrate alcohols **1a**–**f** was, in our earlier work, ascertained by NMR and, in the case of **1a**, also by single-crystal X-ray analysis.[8]

To demonstrate an example of further derivatization of the double bond in the chiral spirocyclic ether products **3a**–**f**, we reacted the spiro ether **3a** with osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO) in an acetone, water, and *t*-butanol solvent mixture (1:1:0.4) at 40 °C. The highly functionalized dihydroxyspiro ether **4** was obtained in 82% isolated yield as a 1:1 mixture of cis-dihydroxy diastereoisomers (Scheme 2).[12,13] In 2008, Carroll




**Scheme 1.**




**Scheme 2.**

and co-workers reported the dihydroxylation of a similar unsaturated spiro ether using a Sharpless one-pot procedure which afforded the corresponding diol product in 74% yield and 1:4 cis/trans selectivity.[14]

To summarize, we have shown that enantiopure homoallylic alcohols, obtained by one-pot conjugate addition/allylation, are easily converted into chiral spirocyclic ethers in excellent isolated yields via an allylation/RCM reaction sequence. Furthermore, we have shown that the obtained spiro ethers may be further utilized for the preparation of highly functionalized spiro building blocks, resembling spiroglycosides,[15] by subsequent cis-dihydroxylation.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.136.

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10. Standard procedure (Table 1): A Schlenk tube flushed with argon was charged with NaH (16.8 mg, 0.70 mmol) and anhydrous DMF (0.4 mL) and cooled in an ice bath. To this slurry was added a solution of **1a** (31.1 mg, 0.14 mmol) in anhydrous DMF (0.2 mL). The reaction mixture was allowed to warm to rt over the course of 1 h and then recooled in an ice bath and treated with freshly purified allyl bromide (42 μL, 0.49 mmol, filtered through a basic alumina column). The reaction mixture was stirred at rt overnight. After 15 h the mixture was again cooled using an ice bath and was quenched by slow addition of water. The resulting mixture was extracted with diethyl ether, washed with water and brine, and the combined organics were dried over $MgSO_4$. Filtration through a pad of silica gel followed by concentration in vacuo gave **2a** (100% conversion) as a colorless liquid.
In the second step, a Schlenk tube flushed with argon was charged with a solution of **2a** (35.0 mg, 0.14 mmol) in anhydrous $CH_2Cl_2$ (0.7 mL) and degassed using three evacuation/argon-fill cycles. In a separate tube a degassed solution of Grubbś second generation catalyst (5.9 mg, 7 μmol) in anhydrous $CH_2Cl_2$ (0.3 mL) was prepared. The solution of **2a** was cooled in an ice bath and treated dropwise with the solution of catalyst over approximately 5 min. The reaction mixture was then removed from the ice bath, allowed to warm to rt and stirred overnight. After 12 h, the reaction product was purified by flash chromatography by passing the reaction mixture, as such, through a silica gel column affording **3a** (28.7 mg, 90% from **1a**) as a light yellow oil. For analytical data, see Supplementary data.
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12. (a) *Compound* **3a** (22.8 mg, 0.10 mmol) was dissolved in a mixture of acetone, water, and *t*-butanol (1:1:0.4, 1.10 mL), after which $NMO{\cdot}H_2O$ (14.1 mg, 0.12 mmol) and $OsO_4$ (1.6 μL, 5 μmol) were added. The resulting mixture was stirred for 16 h at 40 °C, then treated with $Na_2S_2O_5$ (22.8 mg, 0.12 mmol) and stirring was continued for an additional 1 h. Finally, the mixture was extracted with EtOAc and the organic extracts were washed with 1 N HCl, water, and brine, and dried over $Na_2SO_4$. After evaporation, the crude product was purified by silica gel flash chromatography (eluent:EtOAc) giving **4** (21.4 mg, 82%) as a colorless oil. For analytical data, see Supplementary data. (b) Asymmetric dihydroxylation of **3a** under Sharpless conditions using AD-mix-α was also investigated providing only marginal diastereoselectivity and yielding the cis-dihydroxy diastereoisomers **4a** and **4b** in a 1.5:1 ratio as ascertained by NMR analysis.
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