Complete transfer of chirality in an intramolecular, thermal [2 + 2] cycloaddition of allene-ynes to form non-racemic spirooxindoles

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Abstract
A thermal [2 + 2] cycloaddition reaction of allene-ynes has been used to transform chiral non-racemic allenyl oxindoles into chiral non-racemic spirooxindoles containing an alkylidene cyclobutene moiety. The enantiomeric excesses were determined by chiral lanthanide shift NMR analysis and the transfer of chiral information from the allene to the spirooxindole was found to be greater than 95%.

Introduction
The [2 + 2] cycloaddition reaction of allenes and alkynes provides rapid entry into synthetically challenging alkylidene cyclobutene ring systems. We, along with others, have demonstrated the intramolecular variant of this reaction under thermal conditions [1,2]. This thermally forbidden process is believed to proceed via a biradical intermediate mechanism, a conclusion supported by both computational and experimental studies [3]. Recently, the scope of this method has been expanded to the synthesis of spirooxindole-containing skeletons 2 in a two-step one-pot process from propargyl acetates 1 [4] (Scheme 1). Inspired by this rapid entry into the molecularly complex substructure 2, and the structural similarity to welwitiindolinone A isonitrile (3), we became interested in the synthesis of chiral non-racemic spirooxindoles for application to natural product synthesis [5-7]. Herein, we disclose preliminary results demonstrating a complete transfer of chiral information from a chiral non-racemic allene-yne to form an enantiomerically enriched spirooxindole in a [2 + 2] cycloaddition reaction.

Findings
This study commenced with the preparation of the enantiopure propargyl acetate 7 [8]. Treatment of racemic propargyl alcohol 4 with the (R)-acid chloride 5, DMAP, and pyridine resulted in propargyl ester 6 as a separable 4:1 mixture of diastereomers.
Scheme 1: Conversion of propargyl acetate 1 to spirooxindole 2 containing the core framework of welwitindolinone A isonitrile (3).

Scheme 2: Preparation of enantiopure propargyl acetate 7 (R = Ac).

Saponification of the major diastereomer of 6, followed by acylation provided the propargyl acetate 7 in quantitative yield (Scheme 2).

The enantiomeric purity of propargyl acetate 7 was determined based on treatment of the compound with the chiral shift reagent (+)-Eu(hfc)₃. Figure 1 shows the ¹H NMR of the racemic as well as the enantiomerically enriched propargyl acetate upon treatment with the chiral shift reagent. Treating racemic acetate 7 with the chiral shift reagent enabled resolution of the resulting diastereomeric complexes, which was evidenced by the resonances for the aromatic proton labeled H₃ in the spectrum shown below. The spectrum of racemic acetate 7 contains two doublets at δ 7.54 and 7.52, while the spectrum of enantiomerically enriched 7 shows only a single doublet at δ 7.54. Based on this result, the enantiomeric excess of enantiomerically enriched acetate 7 is greater than 95%.

Next, the focus turned to the conversion of enantiomerically enriched propargyl acetate 7 to an enantiomerically enriched allene 8. It has been previously shown that delivery of an alkyl group from an organocuprate in an S₉₂’ fashion occurs with retention of chiral information in the resulting allene [9]; thus we began by screening cuprate conditions to form the desired allenyloxindole 8 (Table 1). In order to generate the allene, we examined various leaving groups (OMs, OMe, OAc), solvents (THF, Et₂O), and cuprates (lower and higher order cyanocuprates). The reaction incorporating a mesylate as a leaving group was problematic due to substrate instability issues, even at low temperatures (Table 1, entry 1) and the substrates containing –OMe and –OAc leaving groups were unreactive toward the lower order cuprates (Table 1, entries 2–5). The optimal conditions were found using the propargylic acetate and the higher order cuprate, t-Bu₂Cu(CN)Li₂ at –78 °C which gave compound 8 (R' = tert-butyl) in 49% yield (Table 1,
Table 1: Screening conditions for the formation of allenyloxindole 8.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Solvent</th>
<th>Temp</th>
<th>Cuprate</th>
<th>R'</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ms</td>
<td>THF</td>
<td>−45 °C</td>
<td>MeCu(CN)Li</td>
<td>Me</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Et₂O</td>
<td>0 to 35 °C</td>
<td>MeCu(CN)Li</td>
<td>Me</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>Ac</td>
<td>Et₂O</td>
<td>0 °C</td>
<td>MeCu(CN)Li</td>
<td>Me</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>Ac</td>
<td>THF</td>
<td>−78 °C to rt</td>
<td>MeCu(CN)Li</td>
<td>t-Bu</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>Ac</td>
<td>Et₂O</td>
<td>−78 °C</td>
<td>t-Bu₂Cu(CN)Li₂</td>
<td>t-Bu</td>
<td>49%</td>
</tr>
<tr>
<td>6</td>
<td>Ac</td>
<td>THF</td>
<td>−78 °C</td>
<td>t-Bu₂Cu(CN)Li₂</td>
<td>t-Bu</td>
<td></td>
</tr>
</tbody>
</table>

*Complete decomposition of the mesylate (generated in situ) was observed prior to cuprate addition. *Complete recovery of starting material. *Starting material was recovered in addition to the deacylation product. *The product of a second addition of the tert-butyl group to the central carbon of the allene was also isolated in 21% yield.
Spirooxindole 9 was purified by column chromatography and the transfer of chiral information was determined using chiral $^1$H NMR shift analysis. Our working hypothesis for the mechanism for transfer of chiral information from the allene to the spirooxindole-containing cyclobutene is that the reaction still proceeds through the thermally generated biradical intermediate, but the tert-butyl group hinders rotation around the carbon–carbon bond as shown in Figure 4, thus slowing racemization of the resulting radical containing carbon. This hypothesis is supported by a report by Pasto, where transfer of chiral information was incomplete in a thermal, intermolecular [2 + 2] cycloaddition reaction between 2,3-pentadiene and methyl propiolate [10].

In summary, there are only a few general methods to prepare carbocyclic spirooxindoles non-racemically [11-14]; we have demonstrated the first thermal, intramolecular [2 + 2] cycload-
dition reaction of an allene-yne that generates a chiral non-racemic spirooxindole from a chiral non-racemic allene. Furthermore, this reaction could also be applicable in the enantioselective synthesis of natural products that contain a spirooxindole core, such as welwitindolinone A isonitrile. We are currently working to expand the scope of this chirality transfer to other allenyl systems possessing less bulky and/or traceless groups.

Supporting Information

Supporting Information File 1
General methods, experimental and spectral data for all new compounds.
[[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-70-S1.pdf]]

Acknowledgements

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References

   For other examples of [2 + 2] cycloadditions involving allenes and the references within.
8. For the preparation of racemic 4 and 7 see the supporting information in reference [4].
   For a review of allene synthesis using organometallic reagents as well as generation of chiral allenes using organocuprates.

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