On the nature of the chain-extending species in organolithium initiated stereospecific reagent-controlled homologation reactions using α-chloroalkyl aryl sulfoxides

Amanda L. Hoyt, Paul R. Blakemore*

Department of Chemistry, Oregon State University, Corvallis, OR 97331, USA

Abstract

The reaction of an organolithium with an α-chloroalkyl aryl sulfoxide ostensibly generates an α-chloroalkyllithium by sulfoxide–lithium exchange, but the actual identity of the chain-extending species in chlorosulfoxide-based StReCH reactions is not certain. To explore this issue, racemic 2-cyclohexyl (4R⁄5R, 5R⁄4S)-4,5-diphenyl-1,3,2-dioxaborolane was homologated by treatment with scalemic (S)-chloromethyl phenyl sulfoxide and n-BuLi (THF, −78 °C). The reaction proceeded without a detectable level of kinetic resolution, a finding consistent with chloromethylolithium being the active chain-extending species rather than a chiral sulfurane intermediate.

Keywords: Carbenoid Kinetic resolution Pseudorotation Sulfoxide–metal exchange Sulfurane

Introduction

The stereospecific reagent-controlled homologation (StReCH) of boronic esters using stereodefined carbenoids generated by the addition of organolithium reagents to α-chloroalkylsulfoxides has been successfully demonstrated for the preparation of a variety of stereochemically complex molecules. Ostensibly, this reaction proceeds via sulfoxide–lithium exchange from α-chloroalkyl sulfoxides with the resulting α-chloroalkyllithium going on to homologate the boronic ester by ate-complex formation followed by 1,2-metallate rearrangement (6 to 7) (pathway A, Scheme 1). In reality, however, it is not certain that an α-chloroalkyllithium is actually involved in the process since an intermediate sulfurane could equally well be responsible for loading the α-chloroalkyl moiety on the boronic ester (pathway B). Accordingly, we sought to design and execute an experiment capable of distinguishing between the two possibilities and that might also answer some questions about the sulfoxide–metal (ligand) exchange process (see Scheme 2).

The exchange of carbanionic ligands about the tricoordinate sulfur-atom in sulfoxides has been long known but it is a process that languished in comparative obscurity until quite recently. The transformation first came to prominence as a means to synthesize enantioenriched dialkyl sulfoxides, but it is typically applied today as a means to access organometallics. The mechanism for the ligand exchange is not certain; however, it is known that net stereochemical inversion occurs at sulfur. Consistent with this finding would be a direct $S_N2$ displacement but more likely are

* Corresponding author. Tel.: +1 541 737 6728; fax: +1 541 737 2062.
E-mail address: paul.blakemore@science.oregonstate.edu (P.R. Blakemore).
is the active chain-extending species. Failure to realize any kinetic resolution occurs under these conditions then [(±)-] is repeated with RLi (R
\[\text{distinguish between these final two possibilities, the experiment}
\]
sulfurane
\[\text{changing from RLi (R}
\[\text{not}
\]
kinetic resolution (%ee (R = Ph), only candidates. To decide between these alternatives, the experiment
\[\text{is still a chiral species and the observation of}
\]
chloromethyllithium (of type
\[\text{19)} \text{which is achiral, is ruled out.}
\]
in this scenario, sulfuranes 17 (of type 9) and 18 (of type 12) and chloromethyllithium-sulfoxide complex 19-16 remain potential candidates. To decide between these alternatives, the experiment is repeated with PhLi as the initiating organolithium. In this case (R = Ph), only 17 is still a chiral species and the observation of kinetic resolution (%ee ≠ 0) infers that this intermediate (17) and not 18 or 19-16 is the chain-extender. If %ee becomes zero upon changing from RLi (R ≠ Ph) to PhLi, then the active carbend is sulfurane 18 or organolithium-sulfoxide complex 19-16. To distinguish between these final two possibilities, the experiment is repeated with RLi (R = Ph) with wholly racemic substrates [(±)-13 and (±)-14] but in the presence of scaldemic 16; if kinetic resolution occurs under these conditions then 19-16 and not 18 is the active chain-extending species. Failure to realize any kinetic resolution with (S)-14 and RLi (R = Ph) is suggestive, but does not emphatically prove, that chloromethylolithium (19) is the relevant active chain-extending species. We now report execution of this experiment and observation of the last type of result.

**Results and discussion**

The key carbend precursor, chloromethyl phenyl sulfoxide (14), was prepared in scalcemic form by catalytic enantioselective sulfoxidation of thioanisole (20) using the Bolm–Ellman–Jackson protocol,\(^7\) followed by stereoeivertive chlorination of the product sulfoxide (22) with N-chlorosuccinimide (NCS) conducted in the presence of potassium carbonate to minimize racemization.\(^8,10\)

The same chlorosulfoxide was prepared in racemic form more expediently by oxidation of 20 by H\(_2\)O\(_2\)--MeOH followed by NCS mediated chlorination (Scheme 4). The requisite (4R\(^*,5R\(^*)\)-4,5-diphenyl-1,3,2-dioxaborolanes (±)-13 (R\(^0\) = BnCH\(_2\), Ph, c-C\(_6\)H\(_{11}\)) were typically prepared by esterification of commercial boronic acids with the diol [(±)-23] formed by dihydroxylation of trans-stilbene under standard conditions (see Supplementary data for details).

The basic efficacy of homologation using chlorosulfoxide 14 was evaluated using racemic material (Table 1). The process was found to be inefficient but this was not necessarily an issue since the occurrence of any kinetic resolution would be easy to detect in the chain extension product at low conversion. Good chemical behaviour was realized from B-phenethyl boronate 13a which was successfully homologated by chlorosulfoxide 14 using three different organolithium initiators (entries 1–3). Unfortunately, boronate substrate 13a and its homologue 15a were too close in

**Table 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R(^0)</th>
<th>13</th>
<th>RLi</th>
<th>Solvent</th>
<th>Yield (\text{(%)})</th>
<th>Yield (\text{(%)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^b)</td>
<td>BnCH(_2)</td>
<td>13a</td>
<td>n-BuLi</td>
<td>THF</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>2(^b)</td>
<td>BnCH(_2)</td>
<td>13a</td>
<td>t-BuLi</td>
<td>PhMe</td>
<td>19</td>
<td>28</td>
</tr>
<tr>
<td>3(^b)</td>
<td>BnCH(_2)</td>
<td>13a</td>
<td>PhLi</td>
<td>THF</td>
<td>18</td>
<td>41</td>
</tr>
<tr>
<td>4(^b)</td>
<td>Ph</td>
<td>13b</td>
<td>n-BuLi</td>
<td>THF</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>5(^b)</td>
<td>Ph</td>
<td>13b</td>
<td>t-BuLi</td>
<td>PhMe</td>
<td>&lt;3</td>
<td>33</td>
</tr>
<tr>
<td>6(^b)</td>
<td>c-C(<em>6)H(</em>{11})</td>
<td>13c</td>
<td>n-BuLi</td>
<td>THF</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>7(^b)</td>
<td>c-C(<em>6)H(</em>{11})</td>
<td>13c</td>
<td>t-BuLi</td>
<td>PhMe</td>
<td>6</td>
<td>16</td>
</tr>
</tbody>
</table>

\(^a\) The pair of 13 and 15 was isolated as a two component mixture by SiO\(_2\) chromatography of the reaction residue, the effective yield for 15 is based on mass determination for this mixture and \(^1\)H NMR analysis.

\(^b\) Stoichiometry of 13/14/RLi = 2:1:1.

\(^c\) Stoichiometry of 13/14/RLi = 1:1:1.
polarity to be separated; a necessity for later probing of kinetic resolution which was to be conducted via chiral stationary phase HPLC analysis of the syn-1,2-diphenylethyl-1,2-diol obtained by boronate hydrolysis. No more than a trace of homologue 15b could be obtained from β-phenyl boronate 13b because an apparent sensitivity to oxidation precluded its isolation (entries 4 and 5). β-cyclobexyl boronate 13c was found to possess the desired attributes for the key experiment: it could be successfully chain extended with 14 and the substrate and its homologue were separable by semi-preparative HPLC using an achiral column.

With an optimal boronate substrate and reaction conditions for chain extension identified, the key experiment was performed using scalemic chlorosulfoxide (S)-14 (73% ee). An equimolar mixture of β-cyclobexyl boronate 13c and chlorosulfoxide (S)-14 in THF solvent at −78 °C was treated with a single equivalent of n-BuLi (Scheme 5). After warming to room temperature and a work-up, boronates 13c and 15c were separated from other reaction mixture components using SiO₂ column chromatography and then these two non-polar materials were carefully separated from each other by semi-preparative HPLC on an achiral column. syn-1,2-Diphenylethyl-1,2-diol (23) was liberated from the recovered substrate 13c and the chain extended product 15c by oxidative hydrolysis and each sample was subjected to HPLC analysis on a chiral stationary phase. Neither sample exhibited a level of enantiomeric excess above the effective detection limit of the instrument (%ee < 0.7% from duplicated measurements) and the materials obtained were not differentiable from an authentic sample of racemic diol [(±)-23] when the same analysis method was applied. The experiment was repeated with essentially identical results and it was concluded that kinetic resolution of boronate (±)-13c by the carbeneoid species generated in situ from chlorosulfoxide (S)-14 and n-BuLi does not occur.

**Scheme 5.** Kinetic resolution not detected during chain extension of boronate (±)-13c by chlorosulfoxide (S)-14 (73% ee).

**Conclusion**

Failure to detect a significant level of kinetic resolution in the experiment described above is consistent with the active chain-extender being chloromethylithium (19), an intrinsically achiral species. However, given the nature of the experiment conducted, the possibility that some chiral carbeneoid species is involved, but that it fails to kinetically resolve the racemic boronate beyond a detectable limit, cannot be wholly discounted. Nonetheless, we extrapolate the findings herein to tentatively conclude that, in all likelihood, α-chloroalkyllithiums are the species responsible for the chain extension of boronic esters in organolithium initiated StReCH reactions using α-chloroalkyl sulfoxides. Although the direct intervention of sulfuran intermediates was not uncovered in this Letter, we believe that the kind of experiment described could prove useful in detecting their action and their character in other processes involving sulfoxide–metal (/ligand) exchange.

**Acknowledgments**

Support for this work by the National Science Foundation Grant CHE-0906409 is gratefully acknowledged. Drs. Selena Milicevic Sephton and Mark Sephton are thanked for helpful discussion.

**Supplementary data**

Supplementary data (full experimental procedures, characterization data, and 1H and 13C NMR spectra for all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.123.

**References and notes**


2. The process central to this work may be described equivalently as either sulfoxide–metal exchange or as sulfoxide–ligand exchange. The apposite term depends on viewpoint; the former term being most appropriate if the expelled nucleophile is of primary interest while the latter term is relevant if the sulfoxide product is the focus. For discourse on sulfoxide–metal (/ligand) exchange, see: (a) Blakemore, P. R.; Burge, M. S.; Sephton, M. A. Tetrahedron Lett. 2007, 48, 3999–4002; (b) Capozzi, M. A. M.; Cardellicchio, C.; Naso, F. Eur. J. Org. Chem. 2004, 1855–1861.


