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

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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 (4*R**,5*R**)-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 chloromethylithium being the active chain-extending species rather than a chiral sulfurane intermediate.

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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.¹ Ostensibly, this reaction proceeds via sulfoxide-lithium exchange from the α -chloroalkyl sulfoxide **2** with the resulting α -chloroalkyllithium **5** 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 **3** 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.²

The exchange of carbanionic ligands about the tricoordinate sulfur-atom in sulfoxides has been long known³ 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,^{3f} but it is typically applied today as a means to access organometallics.⁴ 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 $\text{S}_{\text{N}}2$ displacement but more likely are pathways involving sulfurane intermediates.⁵ In this regard, two routes based on a principle of apical-in/apical-out substitution are

Scheme 1. Organolithium initiated stereospecific reagent-controlled homologation (StReCH) of boronic esters using α -chloroalkylsulfoxides.

Scheme 2. Putative pathways for sulfoxide-metal (/ligand) exchange.

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Scheme 3. Experiment to probe nature of chain-extending species in StReCH.

reasonable: (1) an S_N2 -like trajectory via sulfurane **9** wherein the incoming carbanion (R^{in}) adds opposite the outgoing nucleofuge (R^{out}), and (2) a more complex pathway involving apical addition of the incoming carbanion to a site opposite the S–O bond to give a sulfurane intermediate (**11**) which must experience a pair of pseudorotations (with R^{out} the pivot ligand for the first event and then R^{in} the pivot ligand for the second pseudorotation)⁶ to arrive at another sulfurane (**12**) that allows ejection of the nucleofuge in manner that is the exact reverse of the initial addition step (i.e., apical-out, opposite the S–O bond).

To glean the nature of the chain-extending species in StReCH, be it an α -chloroalkyllithium or one of the sulfurane isomers as described above (**9** or **12**), the following experiment using kinetic resolution as a reporter of chirality of the carbenoid was designed (Scheme 3). Thus, homologation of a racemic chiral boronic ester (**13**) by enantioenriched chloromethyl sulfoxide **14** is conducted by addition of some RLi ($R \neq Ph$) to the pair of compounds. The reaction is not run to complete conversion and the homologation product (**15**) and unconverted starting material (**13**) are analyzed for %ee. Realization of kinetic resolution (%ee $\neq 0$) would reveal that the chain-extending agent is a scalemic species and therefore chloromethyl lithium (**19**), which is achiral, is ruled out. In this scenario, sulfuranes **17** (of type **9**) and **18** (of type **12**) and the chloromethyl lithium•sulfurane 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 $\neq 0$) infers that this intermediate (**17**) and not **18** or **19•16** is the chain-extender. If %ee becomes zero upon changing from RLi ($R \neq Ph$) to PhLi, then the active carbenoid is sulfurane **18** or the organolithium sulfoxide complex **19•16**. To distinguish between these final two possibilities, the experiment is repeated with RLi ($R \neq Ph$) with wholly racemic substrates [(±)-**13** and (±)-**14**] but in the presence of scalemic **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 ($R \neq Ph$) is suggestive, but does not emphatically prove, that chloromethyl lithium (**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 carbenoid precursor, chloromethyl phenyl sulfoxide (**14**), was prepared in scalemic form by catalytic enantioselective sulfoxidation of thioanisole (**20**) using the Bolm-Ellman-Jackson protocol,⁷ followed by stereoinvertive chlorination of the product

Scheme 4. Synthesis of (S)-**14** and (±)-**14**.

Table 1. Evaluation of homologation efficacy using chloromethyl phenyl sulfoxide (**14**) as carbenoid precursor under various reaction conditions.

Entry	R ⁰	13	RLi	Solvent	Yield 15 ^a	Yield 16
1 ^b	BnCH ₂	13a	<i>n</i> -BuLi	THF	13%	7%
2 ^b	BnCH ₂	13a	<i>t</i> -BuLi	PhMe	19%	28%
3 ^b	BnCH ₂	13a	PhLi	THF	18%	41%
4 ^c	Ph	13b	<i>n</i> -BuLi	THF	0%	13%
5 ^c	Ph	13b	<i>t</i> -BuLi	PhMe	< 3%	33%
6 ^c	<i>c</i> -C ₆ H ₁₁	13c	<i>n</i> -BuLi	THF	11%	11%
7 ^c	<i>c</i> -C ₆ H ₁₁	13c	<i>t</i> -BuLi	PhMe	6%	16%

^aThe pair of **13** and **15** were isolated as a two component mixture by SiO₂ chromatography of the reaction residue, the effective yield for **15** is based on mass determination for this mixture and ¹H NMR analysis. ^bStoichiometry of **13**:**14**:RLi = 2:1:1. ^cStoichiometry of **13**:**14**:RLi = 1:1:1.

sulfoxide (**22**) with *N*-chlorosuccinimide (NCS) conducted in the presence of potassium carbonate to minimize racemization.^{8,1e} The same chlorosulfoxide was prepared in racemic form more expediently by oxidation of **20** by H₂O₂–MeOH followed by NCS mediated chlorination (Scheme 4). The requisite (4*R**,5*R**)-4,5-diphenyl-1,3,2-dioxaborolanes (±)-**13** ($R^0 = \text{BnCH}_2, \text{Ph}, c\text{-C}_6\text{H}_{11}$) 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 behavior was realized from the *B*-phenethyl boronate **13a** which was successfully homologated by chlorosulfoxide **14** using three different organolithium initiators (entries 1–3). Unfortunately, the boronate substrate **13a** and its homologue **15a** were too close in 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-diphenylethan-1,2-diol obtained by boronate hydrolysis. No more than a trace of homologue **15b** could be obtained from the *B*-phenyl boronate **13b** because an apparent sensitivity to oxidation precluded its isolation (entries 4–5). The *B*-cyclohexyl boronate **13c** was found to possess the

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

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 reactions conditions for chain extension identified, the key experiment was performed using scalemic chlorosulfoxide (S)-**14** (73% ee). An equimolar mixture of *B*-cyclohexyl 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 SiO_2 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-diphenylethan-1,2-diol (**23**) was liberated from both 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 $\leq 0.7\%$ 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 carbenoid species generated in situ from chlorosulfoxide (S)-**14** and *n*-BuLi does not occur.

Conclusion

Failure to detect a significant level of kinetic resolution in the experiment described above is consistent with the active chain-extender being chloromethylolithium (**19**), an intrinsically achiral species. However, given the nature of the experiment conducted, the possibility that some chiral carbenoid 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 sulfurane intermediates was not uncovered in this study, 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.

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Supplementary data

Supplementary data (full experimental procedures, characterization data, and ^1H and ^{13}C 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.###.###>.

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