Silyloxy Carbanions

On the Configurational Stability and Reactivity of Tertiary Silyloxy Carbanions Derived from Stereoselective Brook Rearrangement

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Abstract: Here we report a stereospecific Brook rearrangement/trapping sequence, initiated by the formation of a zinc alkoxide from an enantioenriched (hydroxyallyl) silane. The chiral carbanion resulting from the Brook rearrangement is trapped intermolecularly by carbonyl electrophiles with complete transfer of chirality. A concerted mechanism is proposed to rationalize the stereospecificity observed in the reaction sequence.

Introduction

Enantioselective formation of chiral organometallic species, followed by stereospecific trapping with an electrophile, is a powerful strategy for asymmetric carbon–carbon bond-forming reactions. An important prerequisite for this strategy is the configurational stability of chiral carbanions. Configurational instability can be overcome by trapping the chiral carbanions at very low temperatures or by introducing a carbamoyloxy group, for instance in the case of α-oxygen- or α-nitrogen-substituted chiral organolithium compounds.[1]

A common strategy for generating carbanions is the [1,2]-Brook rearrangement.[2] This reversible transformation from α-
silyl oxyanions to α-silyloxy carbanions has found many implementations in organic synthesis. However, enantiospecific variants of the [1,2]-Brook rearrangement/trapping processes are rare and often proceed through configurationally stable chiral allene intermediates. We recently reported the synthesis of chiral (α-hydroxyallyl)silanes 2 by enantioselective catalytic addition of Grignard reagents to acylsilanes 1 (Scheme 1c). The scope of products obtained in this study included chiral allylic systems, which are excellent substrates to study the configurational stability and reactivity of the chiral tertiary carbanions formed after Brook rearrangement. The Brook rearrangement of chiral (hydroxyallyl)silanes (Scheme 1a) has been studied for specific substrates that allow intramolecular trapping. More challenging, intermolecular trapping has been achieved almost exclusively via allenyl intermediates. The only example of intermolecular trapping, in which allenyl species are not involved, was reported by Takeda et al.. In this case, thermodynamically stabilized and configurationally labile α-cyano, phosphono or sulfonyl carbanions, could trap protons by formal SE2 reaction with a remarkable level of chirality transfer (77%, 96%, and 97% ee, respectively), while benzyl bromide was trapped by an α-cyano carbanion with 39% ee (Scheme 1b). The presence of the carbamoyl moiety in the substrates was necessary for the configurational stabilization of the stereolabile carbanion intermediates.

Here, we report our preliminary results on a stereospecific Brook rearrangement/trapping sequence, initiated by the formation of a zinc alkoxide from an enantioenriched (hydroxyallyl)silane, followed by intermolecular trapping with a carbonyl electophile (Scheme 1c). A remarkable feature of this reaction sequence is the complete transfer of chirality from the zinc alkoxide to the final product, namely a C-tertiary alcohol. Also noteworthy, no electron-withdrawing or configuration-stabilizing group in the substrate, nor a pathway via an allenyl species is required for the sequence to occur.

Results and Discussion

We set out to investigate the conditions for the Brook rearrangement of (α-hydroxyallyl)silane 2, prepared according to our previously developed catalytic asymmetric addition reaction of iBuMgBr to acylsilane 1. The thermodynamic and configurational stability of the chiral carbanion formed upon rearrangement is uncertain a priori. Furthermore, whether it can be trapped by a carbon electophile and, most importantly, whether this will proceed with complete transfer of chirality, are question marks. When (hydroxyallyl)silanes undergo Brook rearrangement, the chemoselectivity of the trapping of the rearranged product (either the α- or the γ-position) is an additional concern.

To assess the thermodynamic stability of the rearranged product and the chemoselectivity of the trapping process, a racemic experiment was carried out initially. Performing a one-pot sequence consisting of the addition of iBuMgBr to acylsilane 1, followed by quenching of the reaction with water or benzyol chloride (BzCl) at −78 °C, led only to the recovery of the product 2. Since no Brook rearrangement occurred at −78 °C, the reaction mixture was warmed up to room temperature. Unfortunately, also in this case only the addition product 2 or its O-benzyolated adduct were recovered. This result was not surprising, as the Brook rearrangement is typically a reversible process between the α-silyl oxanion and the α-silyloxy carbanion (Scheme 1a). The equilibrium is heavily affected by (i) the presence of a carbanion-stabilizing group, which is absent in our system, (ii) the nature of the counterion (Mg in this case), and (iii) the reaction solvent.

To study the effect of the counterion and the solvent on the overall process, we decided to explore the Brook rearrangement of isolated, racemic (α-hydroxyallyl)silane 2. A variety of metal bases were evaluated in THF. Addition of MeMgBr to 2 at −78 °C, followed by addition of benzyl chloride and warming up to 45 °C in THF, led to undesired product 4 (Table 1, Entry 1). Similarly, no conversion to the desired product 3a was observed when adding nBuLi; instead, a complex mixture of decomposition products was detected (Table 1, Entry 2). This observation indicates that with both the Mg and the Li counterion the equilibrium of the Brook rearrangement lies predominantly on the side of α-silyl oxyanions rather than on the side of the corresponding α-silyloxy organomagnesium or organolithium species, most likely due to their low thermodynamic stability. Next, we studied the effect of a Zn base. We were pleased to see that replacement of the Mg or Li base by Et2Zn finally led to the desired product 3a, derived from Brook rearrangement and subsequent trapping with BzCl at the α-position (Table 1, Entry 3). Intriguingly, we found that if the benzyl chloride was added after warming up to 45 °C, rather than shortly after the deprotonation, decomposition product 4 was again predominant. This result indicates that the electrophile must be in the media from the beginning of the reaction for the complete sequence to take place. Keeping this in mind, we then focused on optimizing the reaction with Et2Zn.

Table 1. Selected optimization results.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal base</th>
<th>Solvent</th>
<th>Conversion [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeMgBr</td>
<td>THF</td>
<td>0.100</td>
</tr>
<tr>
<td>2</td>
<td>nBuLi</td>
<td>THF</td>
<td>0.000†</td>
</tr>
<tr>
<td>3</td>
<td>Et2Zn</td>
<td>THF</td>
<td>55.0†</td>
</tr>
<tr>
<td>4</td>
<td>Et2Zn</td>
<td>MeCN</td>
<td>100.0</td>
</tr>
</tbody>
</table>

[a] Determined by 1H NMR spectroscopy. [b] Decomposition products were observed regardless of the electrophile. [c] 45% of starting material was recovered together with side product derived from the attack of THF on benzoyl chloride.

Together with the desired product 3a, the reaction with Et2Zn also furnished a considerable amount of a side product derived from the attack of THF on benzoyl chloride (Table 1, Entry 3). In order to suppress this side reaction, different solvents were tested. The closely related 2-Me-THF did not give
any product, and starting material was recovered together with other side products. In apolar toluene, as well as in dimethoxyethane and tert-butyl methyl ether, many side reactions took place. However, when conducting the reaction in acetonitrile (Table 1, Entry 4) all side reactions were effectively suppressed, and product 3a was obtained exclusively. The positive outcome when using THF or acetonitrile can be explained by their destabilising effect on zinc alkoxides, thus shifting the Brook rearrangement equilibrium to the organozinc species.\(^3\)

Having established the optimal counterion and solvent for the Brook rearrangement/trapping sequence, the next important question to address was the stereoselectivity of the overall process. It has been shown earlier that unstabilized sp\(^3\) alkyl lithium and -magnesium reagents have a low configurational stability,\(^1,7\) that sp\(^3\) alkylzinc species are usually configurationally stable only at temperatures up to 25 °C,\(^8\) and that allenylzinc species are configurationally stable.\(^4k,9\) Although the configurational stability of allyl–Zn species is not known, we expected it to be low, especially under heating to 45 °C, because of the absence of typical stabilizing groups present in the molecule (e.g. carbamoyl).

To assess the stereoselectivity of the Brook rearrangement and trapping sequence, we performed the same experiments using enantioenriched 2 with an initial ee of 88 % (Scheme 2). Due to its highly apolar character, the silylated alcohol product 3a could not be separated by chiral HPLC, and thus deprotection using TBAF was carried out to furnish the corresponding deprotected alcohol in good yield. To our delight, performing the tandem reaction in acetonitrile furnished the product 5a with 71 % yield and 88 % ee, meaning full transfer of chirality. Absolute configuration of products are based on literature data.\(^10\) For ease of handling, the Brook rearrangement/trapping/deprotection sequence was also done as a one-pot procedure, providing product 5a with similar yield and the same enantioselectivity.

When an activated acyl chloride [4-(trifluoromethyl)benzoyl chloride] was used, the Brook rearrangement took place, and the subsequent trapping product 5b was isolated, again with full transfer of chirality. We were pleased to find that p-CF\(_3\)benzaldehyde was also an amenable substrate, and product 5c was obtained with full retention of enantioselectivity as a mixture of diastereoisomers (3:1). Activated ketones were also tested as electrophiles, but – unfortunately – they did not react, presumably due to increased steric hindrance. Ethyl chloroformate, on the other hand, was too reactive and gave many different products.

In the course of the submission of our work, Marek et al. reported similar results (with a broader substrate scope) including a mechanistic rationale based on computational and experimental data.\(^10\) The main differences between our and their reports consist of the reaction media and the proposed initial steps in the reaction sequence. In THF (the solvent used by Marek et al.), we were unable to obtain clean conversion of the substrate to the product, due to the side reaction derived from the attack of THF on benzoyl chloride. We could avoid the side product formation by using MeCN as a solvent. Furthermore, we found that with electrophiles not bearing a carbonyl moiety, such as iodine, allyl bromide or methyl iodide, no reaction takes place, and mainly the undesired product 4 was observed. These results cannot be understood when only the electrophilicity of the reagents is considered, and might indicate that a carbonyl moiety is needed to trigger the Brook rearrangement. Furthermore, as noted above, the carbonyl electrophile must be in the medium from the beginning of the Brook rearrangement for the complete sequence to take place. Thus, we hypothesize that carbonyl-based electrophiles are involved in the transition state by an activation of the silicon atom via penta- or hexacoordinate species (Scheme 3).\(^11\) In order to determine whether the presence of an external carbonyl group could facilitate the trapping of other electrophiles, DMF was added together with allyl...
bromide, Me₂SO₄ or tBuOH. This did not have the pursued effect, leading to decomposition products only.

To rationalize the experimental results we propose a concerted mechanism with three steps for our reaction sequence. First, the carbonyl electrophile triggers the Brook rearrangement by activation of the silicon atom (A; Scheme 3). Second, a migration of the Zn atom to the γ-position takes place (B; Scheme 3), which could be stabilized by coordination with the silyloxy moiety. Finally, trapping of the carbonyl electrophile at the α-position through a chair-like transition state (C; Scheme 3) gives rise to the chiral alcohol with quaternary stereocenter. In no case did we observe trapping in the γ-position (formal S₂Z₂ product). The product obtained in our reaction sequence can be regarded as the result of a formal S₂ pathway.

Conclusions

We have shown that (α-hydroxallyl)silanes, upon treatment with a Zn base, undergo stereospecific Brook rearrangement to form unprecedented, configurationally stable carbanions (allyl–Zn species). These can be trapped with several carbonyl electrophiles to form C-tertiary alcohols with full retention of the enantiomeric excess. A concerted mechanism involving the carbonyl electrophile in all stages is proposed as responsible for the total stereospecificity observed in the Brook rearrangement/trapping sequence.

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Keywords: Alcohols · Brook rearrangement · Carbanions · Chirality · Enantioselectivity · Hydroxysilanes · Trapping reactions


