Solvent-Dependent Divergent Functions of Sc(OTf)$_3$ in Stereoselective Epoxide-Opening Spiroketalizations

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ABSTRACT: A stereocontrolled synthesis of benzannulated spiroketals has been developed using solvent-dependent Sc-(OTf)$_3$-mediated spirocyclizations of $\textit{exo}$-glycal epoxides having alcohol side chains. In THF, the reaction proceeds via Lewis acid catalysis under kinetic control with inversion of configuration at the anomeric carbon. In contrast, in CH$_2$Cl$_2$, Brønsted acid catalysis under thermodynamic control leads to retention of configuration. The reactions accommodate a variety of aryl substituents and ring sizes and provide stereochemically diverse spiroketals.

Benzannulated spiroketal natural products exhibit a broad array of biological activities. Examples include the matrix metalloproteinase inhibitor berkelic acid,$^2$ the fungal cell wall glucan synthase inhibitor papulacandins,$^3$ and the anti-inflammatory aquilarinoside A.$^4$ Bisbenzannulated spiroketals include the rubromycin family of human telomerase and HIV reverse transcriptase inhibitors,$^5$ the DNA helicase inhibitor heliquinomycin, and the antibiotic purpuromycin, which inhibits aminoacyl-tRNA synthesis by a novel mechanism involving direct binding to the tRNA substrate.$^6$ Notably, the benzannulated spiroketal core is essential for telomerase inhibition in the rubromycin family.$^7$ Numerous approaches to the synthesis of benzannulated spiroketals have been reported.$^8$,$^9$ Despite these notable advances, most strategies rely upon thermodynamically controlled reactions that often lead to stereoisomeric mixtures at the anomeric carbon.$^1$

We have previously developed stereocontrolled approaches to aliphatic spiroketals using stereocomplementary kinetic spirocyclization reactions of $\textit{endo}$-glycal epoxides that proceed with either inversion or retention of configuration at the anomeric carbon, independent of thermodynamic preferences.$^{10}$ We have also extended this approach to benzannulated spiroketals via incorporation of aromatic rings on the cyclizing side chain.$^{11}$ Unfortunately, this approach provides low diastereoselectivity in spirocyclization reactions with phenolic nucleophiles (45:55 to 58:42 dr).$^{11}$

Thus, the requisite benzannulated $\textit{exo}$-glycal epoxide substrates were synthesized from salicylaldehydes 1 via alkyn additions to form propargyl alcohols 2a–h (Figure 1).$^{15}$ Au(I)-mediated cycloisomerization, previously restricted to aromatic alkenes,$^{15}$ then afforded $\textit{exo}$-glycals 3a–h. Diastereoselective anti-epoxidation with dimethyldioxirane (DMDO)$^{17}$ provided $\textit{exo}$-glycal epoxides 6a–h. Interestingly, these epoxides were

Figure 1. Synthesis of $\textit{exo}$-glycal epoxide substrates 6a–h.

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stable upon warming to rt, in stark contrast to the corresponding endo-glycal epoxides, which cyclize spontaneously at −35 °C.18

We next explored spirocyclization reactions of benzannulated exo-glycal epoxide 6a (Table 1). Notably, 6a proved unreactive under our previously reported MeOH and Ti(O-i-Pr)4 spirocyclization conditions, as well as upon heating to 120 °C in toluene (entries 1–3). After investigating a wide range of Lewis acids,16 we were encouraged to find that Sc(OTf)3, favored the inversion product 7a (entry 4), which could be formed exclusively by changing the reaction solvent from CH2Cl2 to THF (entry 5). The diastereoselectivity decreased slightly with substoichiometric Sc(OTf)3 (entries 6 and 7). Other Lewis acids gave lower or even reversed diastereoselectivity.

In low-temperature 1H NMR experiments, we found that the Sc(OTf)3-mediated spirocyclization begins to occur at −35 °C.16 Complete selectivity for spirocyclization with inversion of configuration was maintained when the reaction was run at −20 °C (entry 8), but selectivity decreased at higher temperatures (entry 9), suggesting that the reaction proceeds under kinetic control between −35 and −20 °C.

Strikingly, when the room-temperature reaction was carried out in CH2Cl2 instead of THF, thermodynamic equilibration of an initially formed diastereomeric mixture afforded the retention product 8a with complete stereoselectivity (entries 10, 11).19 A structural rationale for the observed thermodynamic preference is nonobvious, due to the conformational flexibility of 5-membered rings,20 and remains a subject for further investigation. However, on the basis of these results, it is apparent that Sc(OTf)3 plays divergent roles in the spirocyclization reactions depending upon solvent selection (THF vs CH2Cl2, entry 9 vs 10).

It is known that metal triflates can serve as a mild source of triflic acid.21 Thus, we carried out mechanistic studies to differentiate between the Lewis and Brønsted acid activities of Sc(OTf)3. Inclusion of the noncoordinating Bronsted base, 2,6-di-tert-butyl-4-methylpyridine (DTBMP),21b in the reaction in THF did not affect diastereoselectivity (entry 8 vs 12). Treatment with ScCl3 at rt also led to complete stereoselectivity for the contrathermodynamic spiroketal 7a (entry 13). In contrast, spirocyclization with TFOH afforded a diastereomeric mixture favoring the retention product 8a (entry 14). Taken together, these results suggest that Sc(OTf)3 acts as a Lewis acid in THF at reduced temperatures, catalyzing formation of the contrathermodynamic spiroketal 7a under kinetic control.

We next carried out the analogous experiments in CH2Cl2 where, upon warming to rt, Sc(OTf)3 favors the retention product 8a (entry 11). In contrast, inclusion of DTBMP resulted in a diastereomeric mixture favoring the inversion product 7a (entry 15). However, spirocyclization with TFOH provided the retention product 8a exclusively (entry 16). Treatment with both TIOH and DTBMP afforded a diastereomeric mixture of spiroketal, similar to the result observed with Sc(OTf)3 and DTBMP (entry 17 vs 15). Collectively, these results suggest that Sc(OTf)3 acts as a mild source of Brønsted acid in CH2Cl2 at rt, catalyzing formation of the thermodynamically favored spiroketal 8a under equilibrium control.

We then investigated the scope of these stereocomplementary Sc(OTf)3-catalyzed spirocyclization reactions. Substrates with longer side chains (6b, 6c) and various aryl substituents (6d–h) were synthesized from the corresponding alkyne and salicylaldehyde precursors (Figure 1). The bromide intermediate 4h was also used to introduce other substituents (aryl, alkyne, azide, aldehyde, ester, imide) in 4i–n to examine the functional group tolerance of the spirocyclization reactions (Figure S2, Supporting Information).16 The exo-glycals 4i–n were then converted to the corresponding epoxide substrates 6i–n (Figure S2, Supporting Information).16

In the spirocyclization reactions, both diastereomers of the larger 6- and 7-membered ring spiroketal (7b,c and 8b,c) could be obtained with complete diastereoselectivity based on solvent selection (Figure 2). For 8b, equilibration with Sc(OTf)3 in CH2Cl2 required elevated temperature (60 °C). The 7-membered ring spiroketal 7c was obtained in somewhat lower yield due to an unexpected anti-Markovnikov 6-exo epoxide opening side reaction leading to a benzofuran product.16

Next, we investigated the electronic effects of various aryl substituents. A wide range of electron-withdrawing and donating groups were tolerated (7d–n, 8d–n), and high diastereoselectivities were maintained. Notably, the nitro-substituted substrate 6d was less reactive and required more forcing conditions (7d: rt; 8d: 6 h). Conversely, the methoxy-substituted substrate 6e was highly reactive, providing slightly decreased diastereoselectivity in the THF reaction (7e: 93:7 dr) and rapid equilibration in the CH2Cl2 reaction (8e: 1 h). These results are consistent with the expected electronic influence of these para substituents upon the reactive anomic spiroepoxide center.18

The reactions also tolerated other reactive functionalities including alkyne (7j, 8j), azide (7k, 8k), aldehyde (7l, 8l), ester (7m, 8m), and phthalimide (7n, 8n) groups. In the case of

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### Table 1. Spirocyclization Reactions of exo-Glycal Epoxide 6a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (equiv)</th>
<th>Solvent, temp (°C)</th>
<th>Product Ration</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH (excess)</td>
<td>MeOH, rt</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Ti(Oi-Pr)4 (2.0)</td>
<td>CH2Cl2, rt</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>Sc(OTf)3 (2.0)</td>
<td>CH2Cl2, −78 → 0</td>
<td>75:25</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Sc(OTf)3 (2.0)</td>
<td>THF, −78 → 0</td>
<td>&gt;98:2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Sc(OTf)3 (1.0)</td>
<td>THF, −78 → 0</td>
<td>&gt;98:2</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Sc(OTf)3 (0.1)</td>
<td>THF, −90</td>
<td>93:7</td>
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<tr>
<td>7</td>
<td>Sc(OTf)3 (1.0)</td>
<td>THF, −20</td>
<td>&gt;98:2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Sc(OTf)3 (1.0)</td>
<td>THF, rt</td>
<td>&lt;2.98</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Sc(OTf)3 (1.0)</td>
<td>CH2Cl2, 0 → rt</td>
<td>&lt;2.98</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Sc(OTf)3 (0.5)</td>
<td>CH2Cl2, 0 → rt</td>
<td>&lt;2.98</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Sc(OTf)3 (0.5)</td>
<td>CH2Cl2, 0 → rt</td>
<td>&lt;2.98</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Sc(OTf)3 + DTBMP (1.0 + 0.5)</td>
<td>THF, −20</td>
<td>&gt;98:2</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>ScCl3 (1.0)</td>
<td>THF, rt</td>
<td>&gt;98:2</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>TIOH (1.0)</td>
<td>THF, −20</td>
<td>30:70</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Sc(OTf)3 + DTBMP (0.5 + 0.5)</td>
<td>CH2Cl2, 0 → rt</td>
<td>75:25</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>TIOH (0.5)</td>
<td>CH2Cl2, 0 → rt</td>
<td>&lt;2.98</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>TIOH + DTBMP (0.5 + 0.5)</td>
<td>CH2Cl2, 0 → rt</td>
<td>51:49</td>
<td></td>
</tr>
</tbody>
</table>

*Product ratios determined by 1H NMR analysis of crude reaction products. NR = no reaction; DTBMP = 2,6-di-tert-butyl-4-methylpyridine. See the Supporting Information for the complete table.*
azide 8k, Sc(OTf)3 equilibration in CH2Cl2 required elevated temperature (60 °C).

In conclusion, we have developed novel, solvent-dependent Sc(OTf)3-mediated spirocyclizations of exo-glycal epoxides for the stereocontrolled synthesis of benzannulated spiroketals. This exo-glycal-based approach overcomes a key limitation of our previous endo-glycal-based approach and tolerates a wide range of functionalities. Applications to the diversity-oriented synthesis of stereochemically diverse spiroketal libraries are ongoing and will be reported in due course.

ASSOCIATED CONTENT

* Supporting Information
Detailed experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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REFERENCES


(16) See the Supporting Information for full details.


(19) A benzylidenedihydropyranone, presumed to arise from opening of the benzannulated ring followed by elimination of the C2-OTIPS group, was also recovered as a minor byproduct (Figure S1, Supporting Information).***


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