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One-pot synthesis of 2,3,4,5,6-pentasubstituted tetrahydropyrans using lithiation-borylation, allylation and Prins cyclisation reactions

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One-pot synthesis of 2,3,4,5,6-pentasubstituted tetrahydropyranas using lithiation-borylation, allylation and Prins cyclisation reactions

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ABSTRACT

2,3,4,5,6-Pentasubstituted tetrahydropyrans have been prepared in good yield (42-57%) with excellent $dr (>95:5)$ and $er (>95:5)$ using a one-pot lithiation-borylation, allylation and Prins cyclisation reaction.

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Substituted tetrahydropyrans (THPs) are ubiquitous in nature. They show great diversity in structure and complexity, from the relatively simple tri-substituted THP (−)-diospongion A to the highly complex polyketide marine metabolites clavosolide A and (−)-kendomycin with penta-substituted THP cores (Figure 1). One of the most efficient strategies for their construction involves the Prins cyclisation, as demonstrated by numerous research groups. Indeed, the acid-catalysed Prins cyclisation of an in situ generated oxocarbenium ion has been extensively used for the stereoselective synthesis of diverse functionalised THPs. Although allyltin and allylsilyl reagents have been used in this context, to the best of our knowledge, there is only a single report of allylboron reagents being used for the stereoselective synthesis of racemic THPs using a tandem allylation and Prins cyclisation.

Figure 1. THP containing natural products.

We recently reported the enantioselective synthesis of α-substituted allylic boron reagents which could be reacted with aldehydes to give homoallylic alcohols with control of all elements of stereochemistry (syn/anti; E/Z). We recognised that if these products could be used in a subsequent Lewis acid-catalysed Prins cyclisation we would have the ability to form highly substituted THPs with excellent diastereoselectivity and enantioselectivity.

We postulated that if the allylation products, 6 or 7 formed via an initial allylation with the first equivalent of aldehyde, could be trapped by a second aldehyde in the presence of a Lewis acid, a Prins cyclisation should ensue (8–10 or 9–11) to give highly substituted THPs (Figure 2). The diastereoselectivity would be set in the lithiation-borylation reaction (>98:2 er) and the diastereoselectivity would be set in the allylation reaction (>95:5 dr), and subsequent Prins cyclisation.

Significantly, the substituents on boron could be exploited to favour one of two transition-state structures (TS) 4 and 5 in the initial allylation reaction with the first aldehyde. Large substituents on boron (eg 9-BBN) would cause a steric clash between R1 and the boron substituents, thereby favouring the allylation product arising from TS 4. This would give the (Z)-alkene which, after Prins cyclisation, would give the 3,5-anti-THP 12 after work-up. Use of small boron substituents (eg (OCH2)2CMe2) reduces the steric clash between R1 and the boron substituents and now TS 5 bearing the equatorial substituent would be favoured due to competing A1,3 strain in TS 4. This would lead to the (E)-alkene which, following Prins cyclisation and trapping by water, would give the all equatorial substituted THP 13, with the 3,5-syn arrangement.

Furthermore, the sequential nature of our proposed THP synthesis presents the possibility for a one-pot synthesis of fully differential THPs from the addition of two different aldehydes. The 3- and 5-substituents arise from the carbamate 1 and boron reagent 2 and the 2- and 6-substituents from the aldehydes used in the allylation and Prins reactions, respectively.

Figure 2. Proposed synthesis of highly substituted THPs using lithiation-borylation, allylation and Prins cyclisation.

Our studies began by targeting the all equatorial substituted THPs 13 (Table 1, entries 1-6). To favour TS 5, neopentylglycol boronic esters were used along with a similar allylation protocol to that which we had previously used with great success. Thus, deprotonation of ethyl carbamate 1 with t-BuLi in the presence of (−)-sparteine followed by addition of vinyl boronic ester 2 gave an intermediate ate complex. To promote 1,2-metallate rearrangement, and thus formation of the allylboronic ester 3 (X = (OCH2)2CMe2) a solvent exchange was carried out from Et2O to CH2Cl2 and BF3.OEt2 was added. Subsequent addition of an
excess of either cyclohexylcarboxaldehyde or benzaldehyde (these were used as representative aldehydes) and further addition of BF₃·OEt₂ followed by aqueous workup gave the THPs in moderate yield but very high enantioselectivity and very high diastereoselectivity. In the one-pot process 3 C-C bonds, and 2 C-O bonds have been formed and 5 stereogenic centres have been controlled. The use of a variety of boronic esters was examined including Me- (entries 1,2), Bu- (entries 3,4) and H- (entries 5,6). In all cases excellent stereocontrol was observed even with the parent unsubstituted vinylboronic ester (R² = H, entries 5,6). Interestingly, no addition of fluoride was observed in the 4-position as might be expected when using BF₃ in the absence of a fluoride trap.15,16

The use of two different aldehydes in the sequential allylation, Prins cyclisation was also explored as this would lead to a fully differentially substituted THP, a significantly greater challenge.17 However, by simply adding the two different aldehydes in sequence we were able to obtain the 2,6-differentially substituted THPs in good yield and excellent dr and er (table 1, entry 7-10). In one case (table 1, entry 9), when cyclohexylcarboxaldehyde was used as the first aldehyde (followed by benzaldehyde), we observed a significant amount the bis-cyclohexyl substituted THP. In contrast, use of benzaldehyde as the first aldehyde followed by cyclohexylcarboxaldehyde gave the required THP with complete control over the substitution at each THP-carbon (entry 8). Presumably, the lower selectivity of former reaction can be explained by the decreased reactivity of benzaldehyde compared to cyclohexylcarboxaldehyde.

Table 1. Synthesis of 2,3,4,5,6-pentasubstituted THPs using neopentylglycolic boronic esters.15,16

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield (%)</th>
<th>dr</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
<td>54</td>
<td>&gt;95:5</td>
<td>96:4</td>
</tr>
<tr>
<td>2a</td>
<td>Me</td>
<td>Cy</td>
<td>Cy</td>
<td>51</td>
<td>&gt;95:5</td>
<td>-</td>
</tr>
<tr>
<td>3a</td>
<td>Bu</td>
<td>Ph</td>
<td>Ph</td>
<td>52</td>
<td>&gt;95:5</td>
<td>98:2</td>
</tr>
<tr>
<td>4a</td>
<td>Bu</td>
<td>Cy</td>
<td>Cy</td>
<td>57</td>
<td>99:1</td>
<td>-</td>
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<tr>
<td>5a</td>
<td>H</td>
<td>Ph</td>
<td>Ph</td>
<td>45</td>
<td>&gt;95:5</td>
<td>98:2</td>
</tr>
<tr>
<td>6a</td>
<td>H</td>
<td>Cy</td>
<td>Cy</td>
<td>49</td>
<td>&gt;95:5</td>
<td>-</td>
</tr>
<tr>
<td>7b</td>
<td>Bu</td>
<td>Cy</td>
<td>Ph</td>
<td>50</td>
<td>&gt;95:5</td>
<td>96:4</td>
</tr>
<tr>
<td>8b</td>
<td>Bu</td>
<td>Ph</td>
<td>Cy</td>
<td>48</td>
<td>&gt;95:5</td>
<td>95:5</td>
</tr>
<tr>
<td>9b</td>
<td>Me</td>
<td>Cy</td>
<td>Ph</td>
<td>54a</td>
<td>&gt;95:5</td>
<td>97:3</td>
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<tr>
<td>10b</td>
<td>H</td>
<td>Cy</td>
<td>Ph</td>
<td>44</td>
<td>&gt;95:5</td>
<td>97:3</td>
</tr>
</tbody>
</table>

Table 2. Synthesis of 2,3,4,5,6-pentasubstituted THPs using B-9-BBN boranes.15,16

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
<th>dr</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Ph</td>
<td>Ph</td>
<td>48</td>
<td>&gt;95:5</td>
<td>95:5</td>
</tr>
<tr>
<td>2a</td>
<td>Cy</td>
<td>Cy</td>
<td>45</td>
<td>&gt;95:5</td>
<td>-</td>
</tr>
<tr>
<td>3b</td>
<td>Cy</td>
<td>Ph</td>
<td>42b</td>
<td>&gt;95:5</td>
<td>97:3</td>
</tr>
</tbody>
</table>

Isolated as a 2:1 mixture of 2-Ph-6-c.Hex- and 2,6-di-c.Hex-THP.

We next turned our attention to the synthesis of the diastereomeric 3,5-anti-THPs 12 (Table 2). To favour TS 4, a bulky substituent at boron was required and the B-9-BBN group was selected. Furthermore, the increased reactivity of boranes in the lithiation-borylation reaction17 negated the need for Lewis acids to trigger 1,2-metallate rearrangement, although a solvent exchange to CH₂Cl₂ was still needed to effect efficient Prins cyclisation.

Thus, deprotonation of ethyl carbamate 1 with s-BuLi in the presence of sparteine followed by addition of B-vinyl-9-BBN gave an intermediate ate complex which underwent rapid 1,2-metallate rearrangement at low temperature. Solvent exchange from Et₂O to CH₂Cl₂ followed by addition of an excess of either cyclohexylcarboxaldehyde or benzaldehyde, followed by further addition of BF₃·OEt₂ gave the THPs in moderate yield but very high enantioselectivity and diastereoselectivity. Once again, excellent levels of stereocontrol were observed using both aryl- and alkyl aldehydes giving excellent dr and er (entries 1-2) and the sequential addition of two different aldehydes could be used to differentiate the 2- and 6-positions with excellent dr and er (entry 3). The use of the B-9-BBN reagents giving the highest levels of diastereoselectivity reported herein. Presumably the large 9-BBN group significantly shifts the TS equilibrium towards 4 in the allylation reaction and increased reactivity of the intermediate boronic esters increases the rate of aldehyde exchange and Prins cyclisation.

In summary we have developed a one-pot synthesis of functionalised tetrahydroxans using a sequential lithiation-borylation, allylation and Prins cyclisation reaction. The protocol has been successfully applied to the highly diastereo- and enantioselective syntheses of 2,3,4,5,6- and 2,3,4,5,6-substituted THPs.
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2. References


