Benzylic Boron Reagents Behaving as Allylic Boron Reagents towards Aldehydes: A New Asymmetric Reaction Leading to Homoallylic Alcohols with Concomitant Dearomatisation

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Dedicated to Professor José Barluenga on the occasion of his 70th birthday

The dearomatisation of an aromatic ring represents a powerful synthetic strategy as the aromatic ring can be easily carried through a number of synthetic manipulations and, following dearomatisation, a highly functionalised six-membered ring is created, primed for further transformations.[3] The Birch reduction is the best known example of this and has been used extensively.[3] Other methods for dearomatisation include metal-promoted nucleophilic and electrophilic addition to aromatic systems,[3] oxidation, reduction and radical cyclisation reactions.[4]

During the course of certain mechanistic studies (see later) we have discovered a new dearomatisation reaction in which benzylic boron substrates essentially behave as allylic boron reagents in reactions with aldehydes leading to cyclohexenones in high d.r. and e.r. In this paper we describe the optimisation of this novel process together with its asymmetric variant.

We recently reported the rhodium-catalysed 1,2-addition of chiral secondary and tertiary benzyl potassium trifluoroborate salts to aldehydes.[5] We proposed two possible mechanisms for this addition reaction: i) transmetallation of B → Rh followed by addition of the organometallic or ii) a cyclic mechanism in which [Rh–OH] activated both the boron and aldehyde substrates promoting the reaction (Scheme 1). In the latter mechanism Rh was essentially acting as a Lewis acid.[6] In order to distinguish between these two mechanisms we have now tested alternative, water-stable and more standard Lewis acids. Using Sc(OTf)₃ in the same solvent led to the same product, albeit in lower yield and with some erosion of e.r., nevertheless, implicating that the second mechanism was likely to be operating [Scheme 2, Eq. (1)].

However, a minor change in the substrate (p-MeOCH₃ in place of Ph) led to a completely different product [Scheme 2, Eq. (2)]. Cyclohexenones (Z/E)-2ba (3:1, Z/E) were now obtained with complete diastereoselectivity at the new sp³ centres.[7] A possible mechanism for the formation of the Z isomer is shown in Scheme 2. Conversion of the trifluoroborate salt to the difluoroborane would lead to a strongly electrophilic borane which could react with the aldehyde as if it was an allyl borane.[8] The high diastereoselectivity would arise from the closed six-membered ring TS which is often associated with allyl boron reactions with aldehydes.[8] Subsequent hydrolysis of the intermediate enol ether would give the product cyclohexenone. Presumably, the E isomer results from reaction through the alternate ortho position which places the substituents (Ar/Me) in slightly different steric environments.

Similar results were obtained using alternative water-stable Lewis acids such as Gd(OTf)₃, In(OTf)₃, Y(OTf)₃.
and Yb(OTf)₃ (Table 1, entries 2–6). Control experiments without Lewis acid (entry 1) or with TfOH (entry 7) showed that the lanthanide Lewis acids were critical to the success of the reaction. Using BF₃·OEt₂ or SiCl₄ in anhydrous CH₂Cl₂ at low temperature also led to adduct formation with dearomatisation, although with markedly different outcomes. SiCl₄ led to the E isomer (E)₂bA being the major product instead of the Z isomer (entry 8) whilst BF₃·OEt₂ led to formation of the furans 3bA/3*bA (entry 9).

Treatment of our isolated 3:1 Z/E olefin mixture of (Z/C₆)₂bA with one equivalent of BF₃·OEt₂ in anhydrous CH₂Cl₂ at −78°C led to the same mixture of furans 3bA/3*bA. The reaction of the ortho- or meta-methoxy analogues of the tri-fluoroborate salts 1c, 1d did not show the same reactivity. The ortho-methoxy salt 1c gave the alkene 6 as the major product as a result of dehydroboration, whilst the meta-methoxy salt 1d showed similar reactivity to the phenyl substrate, resulting in predominantly 1,2-addition (Scheme 3).

Further surprises emerged when we studied the reaction of enantioenriched 1b (97:3 e.r.) with p-nitrobenzaldehyde in the presence of Sc(OTf)₃ (Scheme 4). The E and Z isomers of 2bA were formed with markedly different e.r. values: the major Z isomer was formed with 96:4 e.r. (essentially complete stereoretention) whilst the minor E isomer was formed with only 36:64 e.r. Furthermore, from single crystal X-ray analyses of the major enantiomers of the Z- and E-cyclohexenones 2bA[10] it was found that they both had R,R configuration at the newly created sp³ centres. This implies that the Z isomer of 2bA had been formed via a closed TS and that the E isomer of 2bA had been formed via an open TS (Scheme 5).[11] The high e.r. observed in the formation of the Z isomer indicates that the closed TS d is strongly favoured over the open TS b. In contrast, the low e.r. observed for the E isomer indicates that the reaction

Table 1. Investigation of the effect of Lewis acid, solvent and temperature on course of reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (10 mol%)</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>Yield [%] 2bA (Z/E)</th>
<th>Yield [%] 3bA/3*bA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>1,4-dioxane/H₂O 6:1</td>
<td>65</td>
<td>81 (3:1)</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Sc(OTf)₃</td>
<td>1,4-dioxane/H₂O 6:1</td>
<td>65</td>
<td>34 (3:1)</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Gd(OTf)₃</td>
<td>1,4-dioxane/H₂O 6:1</td>
<td>65</td>
<td>60 (3:1)</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>In(OTf)₃</td>
<td>1,4-dioxane/H₂O 6:1</td>
<td>65</td>
<td>42 (3:1)</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>Y(OTf)₃</td>
<td>1,4-dioxane/H₂O 6:1</td>
<td>65</td>
<td>68 (3:1)</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>Yb(OTf)₃</td>
<td>1,4-dioxane/H₂O 6:1</td>
<td>65</td>
<td>52 (1:4)</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>TiOH</td>
<td>1,4-dioxane/H₂O 6:1</td>
<td>65</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>ScCl₃</td>
<td>anhydrous CH₂Cl₂</td>
<td>−78 → RT</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>BF₃·OEt₂</td>
<td>anhydrous CH₂Cl₂</td>
<td>−78 → RT</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

[a] A mixture of p-nitrobenzaldehyde (0.3 mmol), (±)-1b (0.45 mmol) and Lewis acid (10% mol) in deoxygenated 1,4-dioxiane/H₂O 6:1 (1.65 mL) was stirred at 65°C until consumption of aldehyde by TLC. With water-sensitive Lewis acids (ScCl₃ and BF₃·OEt₂), anhydrous CH₂Cl₂ (3 mL) was used and the Lewis acid addition was carried out at −78°C → RT. [b] Isolated yield. The Z/E ratio was determined by ¹H NMR of the crude. [c] Isolated yield. The 3 and 3* refer to the two diastereomers at the quaternary centre. The ratio was determined by ¹H NMR of the crude.
occurs via both open and closed TSs a and c, but now with the open TS a being marginally favoured over the closed TS c (~2:1).

In order to enhance the e.r. of the E isomer of 2bA we needed to shut down one of the two competing open and closed TSs a and c and sought to eliminate the open TS a as this would not impact negatively on the e.r. of the major Z isomer formed. We believed that this could be achieved by either i) converting more of the RBF3K salt into the neutral difluoroborane to promote the closed TS or ii) using a weaker external LA to limit the extent of the open TS, or both. Brønsted acids were expected to fulfil both roles. We therefore tested triflic acid and were delighted to find that it was highly effective, leading to adducts in good yield and without significant erosion of e.r. in both E and Z isomers (Table 2, entry 1). These new conditions were general for a range of aldehydes and benzyl trifluoroborate substrates (Table 2). The reaction with the less activated aldehyde, PhCHO B (entry 2), gave cyclohexenones (E/Z)-2bB in good yield but with a small degree of erosion in e.r. (<5%) in the E isomer. Under the same conditions cyclohexanecarboxaldehyde C gave the furan derivatives 3/3*bC by intramolecular 1,6-addition, rather than the free alcohol 2bC (entry 3). Small amounts of the 1,6-addition adducts 3bA and 3bB were also observed with aromatic aldehydes with/when using longer reaction times (entries 1–2). A mixture of products 2/3eA and 2/3eB were obtained when the salt (S)-1e was used with aromatic aldehydes (A and B, entries 4 and 6), but treatment of the crude reaction mixtures with 20 mol% BF3·OEt2 in anhydrous CH2Cl2 (Method B, see Supporting Information) converted them into the furans 3/3*eA and 3/3*eB (entries 5 and 7). With cyclohexanecarboxaldehyde (entry 8) the furan derivatives 3/3*eC were obtained exclusively and with complete stereoretention.

Having successfully demonstrated that the reactions of enantioenriched diarylalkyl trifluoroborate salts 1b and 1e with aromatic and aliphatic aldehydes occurred with almost complete transfer of stereochemical information, we considered the extension of the methodology to tertiary dialkylaryl and secondary arylalkyl trifluoroborate salts 1f–g. The tertiary trifluoroborate salt 1f reacted with aromatic and aliphatic aldehydes (A–C) giving the separable furan derivatives 3fA–fC and 3*fA–fC in good yields and again with almost complete retention of stereochemistry (entries 9–11). When similar conditions were applied to the secondary alkyl trifluoroborate salt 1g (entry 12), considerable erosion of e.r. (71:29) was observed for the minor (Z)-2gA isomer. However, by decreasing the amount of TfOH to 5 mol% this erosion of e.r. was markedly improved (entry 13) to give 85:15 e.r. and 95:5 e.r. for (Z)-2gA and (E)-2gA (major isomer), respectively.

Scheme 4. Reaction of enantioenriched (R)-1b with p-nitrobenzaldehyde (major enantiomers drawn).

Scheme 5. Proposed reaction pathways leading to the observed isomers of adducts.
In summary, we have discovered a new reaction manifold for benzylic trifluoroborate salts which react with aldehydes in the presence of Lewis or Brønsted acids to give homocyclic alcohols. The reactions are accompanied by deaeromatization of the aromatic ring which is especially synthetically useful since it leads to more functionalized products. The reactions show broad substrate scope in terms of both the benzylic trifluoroborate salts, which can be primary, secondary or tertiary, and the aldehydes employed (aromatic/alkiphatic). The use of enantioenriched benzylic trifluoroborate salts, which are easily accessible through the lithiation-borylation reaction, leads to adducts with almost complete retention of stereochemistry in most cases. This new reaction manifold extends the synthetic utility of benzylic boron reagents and the lithiation-borylation reactions that produce them.

### Experimental Section

Typical procedure for (1R,3S,3aS)-3′FA and (1R,3R,3aR)-3′FA (Table 2, entry 9): A dried Schlenk tube was charged with the potassium trifluoroborate salt (5) 12 mg (0.45 mmol) and the corresponding aldehyde (45 mg, 0.3 mmol). After cycles of vacum/VacN 2 (three cycles), deoxygenated dry CH2Cl2 (3 mL) and H2O (0.6 mmol, 11 mL) were added. The reaction mixture was cooled to ~78°C and TIOH (20% mol, 5.4 μL) was added. The dry ice-acetone bath was removed and the reaction mixture was stirred at room temperature until starting aldehyde is consumed by TLC (6 h). Saturated NH4Cl solution was then added and the mixture was extracted with EtOAc. The combined organic layers were dried over MgSO4 (anhy). Concentration and purification through silica gel column chromatography (petroleum ether 40–60°/EtOAc 6:1–1:1) gave (1R,3S,3aS)-3′FA (first fraction, 27 mg, 30%) and (1R,3R,3aR)-3′FA (second fraction, 49 mg, 54%) as yellow viscous oils. (1R,3S,3aS)-3′FA: 

[a] Method A: A mixture of aldehyde (0.3 mmol), [(−)-1b (0.45 mmol), H2O (0.6 mmol, 11 μL) and TIOH (20% mol, 5.4 μL) in deoxygenated and anhydrous CH2Cl2 (3 mL) was stirred at ~78°C until complete consumption of aldehyde was observed by TLC. [b] Isolated yield. [c] Determined by chiral HPLC or GC (see Supporting Information). [d] Isolated yield after partial recrystallisation. [e] The 3′b-3′BB adducts were formed in small amounts with longer reaction times. [f] Inseparable Z/E mixture. The yield was estimated by 1H NMR in the isolated mixture. [g] Method A followed by work up and treatment with BF3•OEt2 in anhydrous CH2Cl2 (see Supporting Information). Direct reaction of the salt and aldehyde with BF3•OEt2 gave lower yields of furan adducts due to formation of side-products derived from dehydroboration. [h] The furan enantiomers were not separable by GC using α, β, or γ-DEX columns. See Supporting Information for further details. [i] The reaction was carried out with 5% mol of TIOH.
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[7] Oxidation of the 3:1 mixture of isomers gave a 3:1 mixture of ketones indicating that the diastereomeric mixture was due to E and Z alkenes.


[10] X-ray analyses were achieved on the major enantiomer of the (Z)-p-nitrobenzaldehyde adduct and the major and minor enantiomers of the E benzaldehyde adducts which were more readily separable. See the Supporting Information.


[12] A primary 4-methoxybenzyl Grignard reagent has also been reported to react with certain aldehydes through the aromatic ring with concomitant dearomatisation. See: a) G. A. Kraus, I. Kim, S. Kesan van, Tetrahedron Lett. 2004, 45, 6839; b) For Pd-catalysed allylative dearomatisation of benzylic chlorides see reference [3]; c) Hoppe observed that hindered benzyl lithiums react with CO through the aromatic ring followed by rapid rearomatisation. See: J. G. Peters, M. Seppi, R. Fröhlich, B. Wibbeling, D. Hoppe, Synthesis 2002, 381.

The primary p-methoxybenzyl trifluoroborate salt was also tested and gave the corresponding homocyclic alcohol related to 2 in 36 % yield (unoptimized). See the Supporting Information for details.

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