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Heck-Mizoroki Coupling of Vinyliodide and Applications in The Synthesis of Dienes and Trienes

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Vinyliodide reacts chemoselectively under Heck-Mizoroki conditions with terminal alkenes, including vinylboronate esters, to give dienes. The resulting dienylboronates undergo Suzuki-Miyaura coupling with aryl, heteroaryl and alkenyl halides to access dienes and trienes.

Polyenes occur widely in natural products, many with medicinal properties. Whilst there are strategies by which polyenes can be synthesised, new robust and reliable protocols, which deliver both high yields and stereocontrol are still required. Terminal, unsubstituted polyenes have been accessed by hydrazine formation, elimination and metal-mediated couplings, however, such methods are limited by substrate scope and stereoselectivity. More recently, we applied an iterative cross-coupling (ICC) approach using vinylboronate esters as dianion equivalents through a Heck-Mizoroki (HM), iododeboronation sequence in polyene synthesis. Related approaches have subsequently been employed for a number of stereoselective applications.

Scheme 1. An example of a highly stereoselective ICC strategy to access a triene system.

Because the Heck-Mizoroki coupling can deliver complex and stereodefined polyenes and requires only one activated coupling partner (such as an alkenyl halide) [unlike the Suzuki-Miyaura (SM) coupling which requires two], it is a powerful method for application in polynene synthesis. Also, when synthesising polyenes using ICC, protecting groups are generally required that prevent direct coupling on the growing chain. For example, Scheme 1 shows an iterative Heck-Mizoroki cross-coupling, iododeboronation strategy (as used by us) to interconvert a boronate ester stereoselectively to an iodide before the chain can be further elongated, e.g. to 5. However, it might be possible to reduce the number of such interconversions by using a more convergent strategy. Our question was whether vinyliodide could be employed in Heck-Mizoroki couplings directly on an alkene to access a diene (Scheme 1). Vinyliodide seems to have been almost completely overlooked in such couplings, except one report from Heck et al. in 1975 of a palladium-mediated reaction with methyl acrylate; the resulting diene was trapped via a Diels-Alder reaction without isolation. We hoped that by applying the mild, chemoselective coupling conditions developed for vinylboronate Heck-Mizoroki coupling would allow vinyliodide to be used as a coupling partner and enable isolation of the diene products. Herein, we report such a strategy (Scheme 1) and demonstrate some early-stage applications, particularly of using a dienylboronate for further coupling.

Preliminary examination of reaction conditions (see SI for full details of conditions screened) started with examining catalysts, bases and ligands for the reaction of vinyliodide with vinylboronate 2 (Eq. 1).

The combination of silver(I) acetate and tri-ortho-tolylphosphine (as optimised for previous vinylboronate-electron deficient iodoalkene reactions, as in Scheme 1) gave the best conversion for Eq. 1. The catalyst loading was further tuned, with the finding that 5 mol% catalyst and shorter reaction times gave better conversions and yields (Table 1, entry 1, i.e. a 100% conversion of vinylboronate 2 resulted in a 73% yield of dienylboronate 6a). Similarly, the vinylboronate pinacol ester (Table 1, entry 2) also showed good reactivity towards coupling with vinyliodide, with a conversion of 91% and an isolated yield of dienylboronate 6b of 72%. [Note: attempts to purify these products can cause polymerisation, and hence, ca. 3 ppm of 2,6-di-tert-butyl-4-methyl phenol (BHT) was employed in eluents. Also, prolonged...
air exposure of dienes 6a and b resulted in polymerisation, hence, storage under Ar at approx. 4°C was required with 20 ppm BHT. See ESI] These conditions were then employed in attempts to couple vinyliodide with a range of other alkenes (Eq. 2, Table 1), with differing stereoelectronic demands and functional groups.

Table 1. HM coupling using vinyliodide with different alkenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Product (Conversion) [Isolated yield] %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H=C=CHBpin</td>
<td>6b R = Br(Pin) (91) [72]</td>
</tr>
<tr>
<td>2</td>
<td>H=C=CHCO2Me</td>
<td>6c R = CO2Me (42)</td>
</tr>
<tr>
<td>3</td>
<td>H=C=CHCO2Bu</td>
<td>6d R = CO2Bu (46) [28]</td>
</tr>
<tr>
<td>4</td>
<td>H=C=CHCOMe</td>
<td>6e R = COMe (68)</td>
</tr>
<tr>
<td>5</td>
<td>H=C=CHSi(OMe)3</td>
<td>6f R = Si(OMe)3 (42)</td>
</tr>
<tr>
<td>6</td>
<td>H=C=CHSi(OEt)3</td>
<td>6g R = Si(OEt)3 (50)</td>
</tr>
<tr>
<td>7</td>
<td>H=C=CHSO(Me)2</td>
<td>6h R = SOMe (18)</td>
</tr>
<tr>
<td>8</td>
<td>H=C=CHPO(OMe)2</td>
<td>6i R = PO(OMe)2 (15)</td>
</tr>
<tr>
<td>9</td>
<td>H=C=CHSnBu</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>H=C=CHPh</td>
<td>0</td>
</tr>
</tbody>
</table>

3Reaction conditions: See ESI. 4Conversions determined by 1H NMR. 51:1 ratio of vinyliodide to alkene used. 6Stille product formed exclusively.

Under the 1:1 ratio of vinyliodide to alkene (vinylboronate) employed for the synthesis of dienylboronates 6a and b, poor conversions (under 10%) were observed. Increasing to two equivalents of alkene gave greatly increased conversions, with up to 68% for methyl vinyl ketone (Table 1, entry 5). Both electronic and steric factors appeared to have an effect on the extent of reaction; the poorest conversions being those of methyl vinylsulfone and dimethyl vinylphosphonate (Table 1, entries 8 and 9). Vinylnitr-butyltin underwent exclusive Stille coupling and no attempts were made to trap the butadiene produced. [Note: the high volatility of all the dienes 6, along with their potential to polymerise, made them difficult to isolate in many cases and excess alkene used proved difficult to separate from dienes 6 (see Table 1)].

Following the successful isolation of dienylboronate 6a, its utility as a four-carbon, butadienyl dianion equivalent was examined, in a manner analogous to the use of the vinylboronates, such as 2 as a two-carbon, vinyl dianion equivalent building blocks (as in Scheme 1, for example).4,10 However, dienylboronate 6a showed no reactivity towards further Heck-Mizoroki coupling when tested against a number of aryl and alkynyl halides, including vinyl iodide. It was, however, successfully applied in Suzuki-Miyaura couplings, where it reacted with a range of aryl and alkynyl halides, including both electron-rich and electron-deficient aryl halides, heteroaryl halides and a vinyl halide (see Table 2). Despite the high reactivity of the dienylboronate 6a (shown by high GC and 1H NMR conversions), there were issues with the isolation of the products 8, again, due to product stability. Indeed, the resulting terminally unsubstituted butadienyl analogues 8 were extremely sensitive towards polymerisation, and even more so than the starting dienylboronate 6a. In some cases, this resulted in lower product isolated yields (after silica gel chromatography) than suggested from crude 1H NMR and GC analysis [Approx. 3 ppm BHT was added to all solvents to minimise polymerisation (see ESI) which improved isolation].

Attempts to isolate the polyenes using silver nitrate-impregnated silica11 and other chromatographic supports did not lead to improved isolated yields. Despite this, the ability of dienylboronate 6a to undergo coupling was demonstrated on both electron-donating and electron-withdrawing aryl iodides (Table 2, entries 1, 5, 8 and 10). In the case of p-iodoanisole versus p-bromoanisole (Table 2, entries 1 and 2), there was a drop in reactivity of the bromide compared to the iodide. However, this was not observed for the tolyl derivatives (Table 2, entries 5 and 6), where the reactivity was comparable and these derivatives showed no appreciable difference in the reactivity of the o- versus p-aryl halides (Table 2, entries 6 and 7), though the anisole derivatives did show a significant drop in reactivity (Table 2, entries 1 and 3). Heterocyclic compounds were also coupled (Table 2, entries 11 and 12), with 3-iodoypyridine giving an isolated yield of 88%. Iodoacrylate 7m coupled, but gave undesired side-reactions (Table 2, entry 13), however, previous work also reported competitive HI elimination, and that this could be avoided through the use of silver-salt bases.12 Hence, the

Table 2. Suzuki-Miyaura coupling using dienylboronate 6a

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-X 7</th>
<th>Reaction time/hours</th>
<th>Product 8 crude (isolated) yields %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>4.5</td>
<td>76 (69)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>22</td>
<td>32 (28)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>23</td>
<td>33 (23)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>25</td>
<td>23 (22)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>6</td>
<td>91 (89)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>22</td>
<td>74 (72)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>25</td>
<td>70 (40)</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>6</td>
<td>65 (64)</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>23</td>
<td>33 (24)</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>22</td>
<td>73 (68)</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>24</td>
<td>88 (88)</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>23</td>
<td>61 (46)</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>4</td>
<td>0, 58 (53)</td>
</tr>
</tbody>
</table>

3See ESI for reaction conditions. Yields determined by 1H NMR and GC on crude product isolated after work up. 4Ag2O base used.
coupling between iodoacrylate 7m and diene 6a was attempted using both potassium tert-butoxide and silver(I) oxide. The difference between the two bases being apparent by $^{1}$H NMR of the two reaction mixtures; tert-butoxide resulted in no triene, whereas silver(I) oxide gave 58% crude yield. In order to circumvent stability issues of diene 6a, the corresponding trifluoroborate salt 9 was prepared in quantitative yield (Eq. 4), resulting in an air stable, crystalline salt which may prove useful for Suzuki-Miyaura coupling. In addition, a one-pot formation of dienes 6a, followed by in situ nitroso-Diels-Alder trapping (followed by spontaneous rearrangement and elimination) provided N-phenyl pyrrole 10 (Eq. 5) in 48% overall yield.

### Conclusions

Vinyl iodide can be employed in Heck-Mizoroki couplings to derive dienes. Vinylboronates are especially effectively giving dienylboronate 6a which can be applied for the synthesis of terminally substituted dienes and trienes. Hence, this type of ICC strategy provides an alternative to those currently used and delivers dienes and trienes in an efficient, stereoselective, atom economic manner. The facile formation of boronates 6a/b from (Table 1) using only 1 equivalent of alkene coupling partner contrasts with most alkenes which required 2 equivalents of alkene, yet still delivered variable conversions (despite many being considered good coupling partners). This clearly has mechanistic implications which are not clear at this point. However, we speculate that under the ambient Heck-Mizoroki coupling conditions necessary, the boronate group may coordinate (e.g. to an acetoxy ligand on palladium), resulting in kinetic assistance for the HM reaction. Previous kinetic studies on vinylboronate coupling did show that the rate determining step in such reactions was not oxidative addition, rather being either ligand exchange (e.g. acetate for iodide) or carbometallation. If acetate were involved as a palladium ligand, such chelatational assistance could intervene in these boronate systems, but would be absent in all the others examined, except potentially the vinyl siloxanes. Interestingly, the corresponding MIDA-vinylboronate was unreactive under the coupling conditions, potentially supporting this hypothesis and the need for an empty sp² hybridised orbital on boron. Further studies are underway.

### Notes and references

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2. Department of Chemistry, University of Bristol, Cantock's Close, Bristol, Avon BS8 1TS, UK.
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4. Electronic Supplementary Information (ESI) available: Experimental details. See DOI: 10.1039/b000000x

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