

Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

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

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XXXXXX 20XX, Accepted Xth XXXXXXXXXXXX 20XX

DOI: 10.1039/b000000x

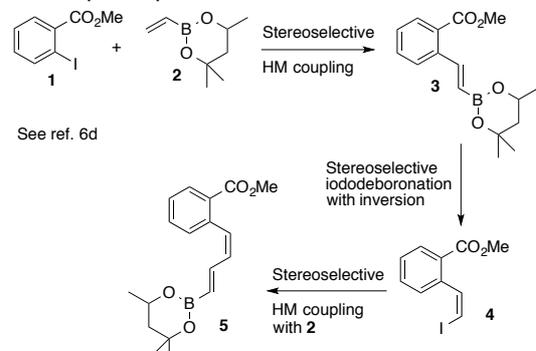
Vinyl iodide reacts chemoselectively under Heck-Mizoroki conditions with terminal alkenes, including vinylboronate esters, to give dienes. The resulting dienylboronates undergo Suzuki-Miyaura coupling with aryl, heteroaryl and alkenyl halides to access dienes and trienes.

Polyenes occur widely in natural products, many with medicinal properties.¹ Whilst there are strategies by which polyenes can be synthesised,² new robust and reliable protocols, which deliver both high yields and stereocontrol are still required. Terminal, unsubstituted polyenes have been accessed by hydrazone formation, elimination and metal-mediated couplings,³ 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 sequence⁴ in polyene synthesis.⁵ Related approaches have subsequently been employed for a number of stereoselective applications.⁶

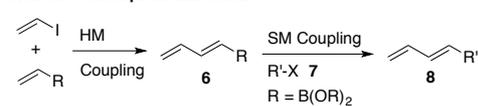
application in polyene synthesis. Also, when synthesising polyenes using ICC, protecting groups are generally required that prevent direct coupling on the growing chain. For example, Scheme 1 shows an iterative Heck-Mizoroki cross-coupling, iododeboronation strategy (as used by us⁸) to interconvert a boronate ester **2** stereoselectively to an iodide **4** 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 vinyl iodide could be employed in Heck-Mizoroki couplings directly on an alkene to access a diene **6** (Scheme 1). Vinyl iodide seems to have been almost completely overlooked in such couplings, except one report from Heck *et al.* in 1975⁹ of a palladium-mediated reaction with methyl acrylate; the resulting diene was trapped *via* a Diels-Alder reaction without isolation.⁹ We hoped that by applying the mild, chemoselective coupling conditions developed for vinylboronate Heck-Mizoroki coupling⁴ would allow vinyl iodide to be as used 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 vinyl iodide with vinylboronate **2** (Eq. 1).

ICC example from previous work

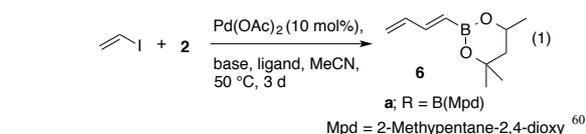


New ICC concept for this work



Scheme 1. An example of a highly stereoselective ICC strategy to access a triene system.⁸

Because the Heck-Mizoroki coupling can deliver complex and stereodefined polyenes⁷ and requires only one activated coupling partner (such as an alkenyl halide) [unlike the Suzuki-Miyaura (SM) coupling which requires two^{7a}], it is a powerful method for



The combination of silver(I) acetate and tri-*ortho*-tolylphosphine (as optimised for previous vinylboronate-electron deficient iodoalkene reactions, as in Scheme 1⁶) 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 vinyl iodide, 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 vinyl iodide with a range of other alkenes (Eq. 2, Table 1), with differing stereoelectronic demands and functional groups.

Table 1. HM coupling using vinyl iodide with different alkenes^a

Entry	Alkene	Product (Conversion) [Isolated yield]/% ^b
1	2	6a (100) [73] ^c
2	H ₂ C=CHBpin	6b R = B(Pin) (91) [72] ^c
3	H ₂ C=CHCO ₂ Me	6c R = CO ₂ Me (42)
4	H ₂ C=CHCO ₂ Bu	6d R = CO ₂ Bu (46) [28]
5	H ₂ C=CHCOMe	6e R = COMe (68)
6	H ₂ C=CHSi(OMe) ₃	6f R = Si(OMe) ₃ (42)
7	H ₂ C=CHSi(OEt) ₃	6g R = Si(OEt) ₃ (50)
8	H ₂ C=CHSO ₂ Me	6h R = SO ₂ Me (18)
9	H ₂ C=CHPO(OMe) ₂	6i R = PO(OMe) ₂ (15)
10	H ₂ C=CHSnBu ₃	(0) ^d

^aReaction conditions: See ESI. ^bConversions determined by ¹H NMR. ^c1:1 ratio of vinyl iodide to alkene used. ^dStille product formed exclusively.

Under the 1:1 ratio of vinyl iodide 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). Vinyltri-*n*-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 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 alkenyl halides, including vinyl iodide. It was, however, successfully applied in Suzuki-Miyaura couplings, where it reacted with a range of aryl and alkenyl 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].

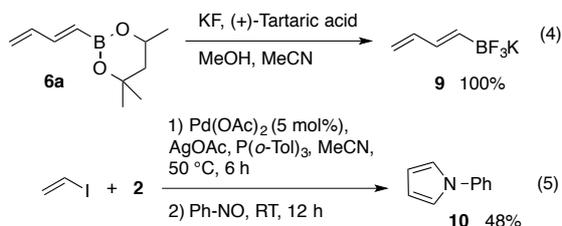
Table 2. Suzuki-Miyaura coupling using dienylboronate **6a**^a

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

^aSee ESI for reaction conditions. Yields determined by ¹H NMR and GC on crude product isolated after work up. ^bAg₂O base used.

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-iodopyridine 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.^{10c} Hence, the

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 ¹H 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 prepared¹² in quantitative yield (Eq. 4), resulting in an air stable, crystalline salt which may prove useful for Suzuki-Miyaura coupling.¹³ In addition, a one-pot formation of **6a**, followed by *in situ* nitroso-Diels-Alder trapping (followed by spontaneous rearrangement and elimination)¹⁴ 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 unsubstituted 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^{7d} 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 chelational 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^{6f} 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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We thank the EPSRC UK National Mass Spectroscopy Facility at Swansea University and the EPSRC for a DTG award (to KSM).

† Electronic Supplementary Information (ESI) available: Experimental details. See DOI: 10.1039/b000000x/

- a) K. S. Madden, F. A. Mosa, A. Whiting, *Org. Biomol. Chem.*, 2014, **12**, 7877-7899. (b) A. Whiting, C. Thirsk, *J. Am. Chem. Soc. Perkin Transactions I*, 2002, **8**, 999-1023.
- a) Kajikawa, T.; Okumura, S.; Iwashita, T.; Kosumi, D.; Hashimoto, H.; Katsumara, S., *Org. Lett.*, 2012, **14**, 808-811. (b) Zhao, Y.; Loh, T., *Tetrahedron*, 2008, **64**, 4972-4978. (c) Pattenden, G.; Plowright, A. T.; Tornos, J. A.; Ye, T., *Tetrahedron Lett.*, 1998, **39**, 6099-6102. (d) Clough, J. M.; Pattenden, G., *Tetrahedron Lett.*, 1978, **43**, 4159-4162. (e) Pattenden, G.; Weedon, B. C. L.; Garbers, C. F.; Schneider, D. F.; van der Merwe, J. P., *Chem. Commun. (London)*, 1965, **15**, 347-349.
- a) Campbell, N. E.; Sammis, G. M., *Angew. Chem. Int. Ed.*, 2014, **53**, 6228-6231. (b) Chatterjee, T.; Dey, R.; Ranu, B. C., *New J. Chem.*, 2011, **35**, 1103-1110. (c) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C., *Adv. Synth. Catal.*, 2010, **352**, 3235-3240. (d) McNulty, J.; Das, P., *Tetrahedron Lett.*, 2009, **50**, 5737-5740. (e) Mundal, D. A.; Lutz, K. E.; Thomson, R. J., *Org. Lett.*, 2009, **11**, 465-468. (f) Hattori, H.; Katsukawa, M.; Kobayashi, Y., *Tetrahedron Lett.*, 2005, **46**, 5871-5875. (g) Barluenga, J.; Rodríguez, F.; Álvarez-Rodrigo, L.; Fañanás, F., *Chem. Eur. J.*, 2004, **10**, 101-108.
- a) A. R. Hunt, S. K. Stewart, A. Whiting, *Tetrahedron Lett.*, 1993, **34**, 3599-3602. (b) S. K. Stewart, A. Whiting, *J. Organomet. Chem.*, 1994, **482**, 293-300. (c) S. K. Stewart, A. Whiting, *Tetrahedron Lett.*, 1995, **36**, 3929-3932. (d) A. P. Lightfoot, G. Maw, C. Thirsk, S. Twiddle, A. Whiting, *Tetrahedron Lett.*, 2003, **44**, 7645-7648.
- a) S. K. Stewart, A. Whiting, *Tetrahedron Lett.*, 1995, **36**, 3925-3928. (b) A. P. Lightfoot, S. J. R. Twiddle, A. Whiting, *Org. Biomol. Chem.*, 2005, **3**, 3167-3172.
- For examples of ICC in polyene synthesis: (a) Fujii, S.; Chang, S. Y.; Burke, M. D., *Angew. Chem. Int. Ed.*, 2011, **50**, 7862-7864. (b) Lee, S.; Anderson, T. M.; Burke, M. D., *Angew. Chem. Int. Ed.*, 2010, **49**, 8860-8863. (c) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D., *J. Am. Chem. Soc.*, 2008, **130**, 466-468. For examples of more generalized ICC strategies: (d) Liu, G.; Kong, L.; Shen, J.; Zhu, G., *Org. Biomol. Chem.*, 2014, **12**, 2310-2321. (e) Grob, J. E.; Dechantsreiter, M. A.; Tichkule, R. B.; Connolly, M. K.; Honda, A.; Tomlinson, R. C.; Hamann, L. G., *Org. Lett.*, 2012, **14**, 5578-5581. (f) Fallon, T.; Willis, A. C.; Rae, A. D.; Paddon-Row, M. N.; Sherburn, M. S., *Chem. Sci.*, 2012, **3**, 2133-2137. (g) Martínez, M. M.; Peña-López, M.; Sestelo, J. P.; Sarandeses, L. A., *Org. Biomol. Chem.*, 2012, **10**, 3892-3898. (h) Nakao, Y.; Chen, J.; Tanaka, M.; Hiayama, T., *J. Am. Chem. Soc.*, 2007, **129**, 11694-11695.
- a) Delcamp, J. H.; Gormisky, P. E.; White, M. C., *J. Am. Chem. Soc.*, 2013, **135**, 8460-8463. (b) Knowles, J. P.; O'Connor, V. E.; Whiting, A., *Org. Biomol. Chem.*, 2011, **9**, 1876-1886. (c) Sakai, M.; Guan, T.; Hara, S., *J. Fluorine Chem.*, 2007, **128**, 1444-1448.
- a) A. N. Hénaff, A. Whiting, *Org. Lett.*, 1999, **1**, 1137-1139. (b) A. N. Hénaff, A. Whiting, *Tetrahedron*, 2000, **56**, 5193-5204. (c) Knowles, J. P.; O'Connor, V. E.; Whiting, A., *Org. Biomol. Chem.*, 2011, **9**, 1876-1886. (d) Batsanov, A. S.; Knowles, J. P.; Whiting, A., *J. Org. Chem.*, 2007, **72**, 2525-2532. (e) G. Clemens, K. R. Flower, P. Gardner, A. P. Henderson, J. P. Knowles, T. B. Marder, A. Whiting, S. A. Przyborski, *Mol. BioSyst.*, 2013, 3124-3134.
- Heck, R. F.; Dieck, H. A., *J. Org. Chem.*, 1975, **40**, 1083-1090.
- a) Lightfoot, A. P.; Maw, G.; Thirsk, C.; Twiddle, S. J. R.; Whiting, A., *Tetrahedron Lett.*, 2003, **44**, 7645-7648. (b) Lightfoot, A. P.; Twiddle, S. J. R.; Whiting, A., *Org. Biomol. Chem.*, 2005, **3**, 3167-3172. (c) Lightfoot, A. P.; Twiddle, S. J. R.; Whiting, A., *Synlett*, 2005, 529-531.
- T. Li, J. Li and H. Li, *J. Chromatogr. A*, 1995, **715**, 372-375.
- A. J. J. Lennox and G. C. Lloyd-Jones, *Angew. Chem. Int. Ed.* 2012, **51**, 9385-9388.
- K. M. Traister, G. A. Molander, "Synthesis and Application of Organoboron Compounds," E. Fernández and A. Whiting, Eds., Springer, 2015.
- F. Tripoteau, L. Eberlin, M. A. Fox, B. Carboni and A. Whiting, *Chem. Commun.*, 2013, **49**, 5414-5416.

Graphical abstract

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