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Heck Coupling Using a Vinyliodo-MIDA Boronate: An Efficient and Modular Access to Polyene Frameworks

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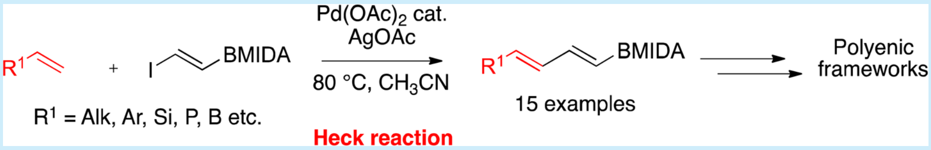
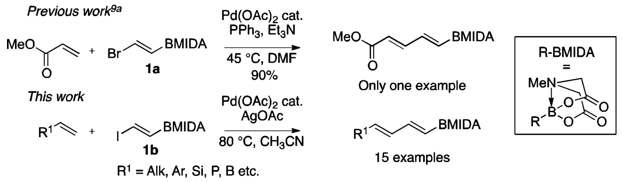
Ⓢ *Supporting Information*



ABSTRACT: A simple Heck coupling between an alkenyl iodo-boronate and a variety of terminal olefins is disclosed. This method gives access to a wide range of dienic moieties including valuable bis-functionalized dienes. The synthetic potential of the coupling reaction is demonstrated by a short and modular preparation of several tetraenic compounds.

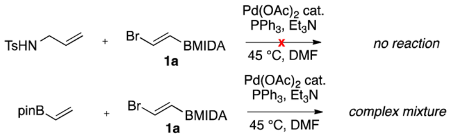
Myriad natural products incorporating a conjugated polyenic motif have been isolated.[1] They generally display attractive properties, and some of them have been used as drugs, pigments, or fluorescent probes. Thus, the synthesis of polyenic moieties still represents a significant challenge for organic chemists. Traditional olefination methods such as the Wittig,[2] the Horner–Wadsworth–Emmons,[3] and the Julia[4] reactions have been widely applied to the preparation of conjugated polyenes, but the lack of stereocontrol as well as troublesome purifications remain a major obstacle to their use in total synthesis of complex molecules. Metal-catalyzed sp^2–sp^2 cross-couplings overcome this difficulty, allowing the construction of polyenic fragments in a stereospecific fashion.[5] Hence, Suzuki, Negishi, Stille, or Heck cross-couplings recently emerged as privileged strategies for the assembly of polyene moieties.[6] However, the preparation, the potential toxicity, as well as the instability of the alkenyl metal reagents prevent these reactions from becoming the universal method for the stereoselective construction of polyenes. Burke et al. partly solved this problem by focusing on *N*-methyliminoacetic acid (MIDA) boronates which have several advantages over boronic acids or other surrogates: they are bench-stable, compatible with silica gel chromatography, crystalline, inert toward a range of reaction conditions, and in addition, easy to cleave.[7,8] Thus, bis-functionalized alkenyl building-blocks incorporating both an halide atom (I, Br) and a MIDA boronate have been synthesized and successfully involved in several Pd-catalyzed cross-couplings including Suzuki, Stille, or Negishi reactions, allowing the modular synthesis of a large variety of polyenic natural products.[9,10] However, the preparation of alkenyl metal reagents is still necessary to perform such cross-couplings, and the Heck reaction, which requires simple olefins, could appear as a very attractive alternative.[11] Surprisingly, only one example of Heck coupling involving the protected haloboronic acid **1a** and the reactive methyl acrylate has been reported.[9a,c,12] Herein, we disclose a Pd-catalyzed Heck reaction between the iodoalkenyl boronate **1b** and a broad range of olefins including functionalized alkenes (Scheme 1). The great potential of this method is highlighted by the short synthesis of several polyenic units.

Scheme 1. Heck Reaction with Halogenoalkenyl Boronates



We first tried to generalize the reported Burke et al. conditions [$Pd(OAc)_2$, PPh_3, and Et_3N] for the Heck coupling between **1a** and several alkenes (Scheme 2). However, when the bromo boronate **1a** was treated with *N*-tosylallylamine, no reaction

Scheme 2. Limitations of the Heck Coupling under Burke et al.'s Reported Conditions



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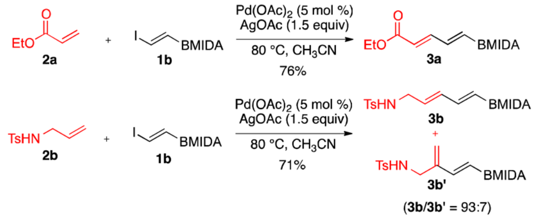
occurred. In addition, when vinylpinacolborane was used as the olefinic partner, a complex mixture of products was formed.

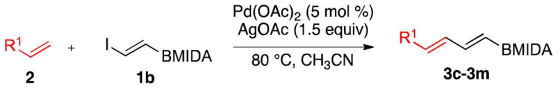
In order to overcome these limitations, we switched to the more reactive iodoboronate **1b**, and after the reaction conditions were tuned, Pd(OAc)$_2$ (5 mol %) and AgOAc (1.5 equiv) were found to afford the coupling products with both ethyl acrylate and *N*-tosylallylamine in good yields (76% and 71%, respectively) in a regioselective fashion (100:0 and 93:7 linear/branched ratio) (Scheme 3).[13]

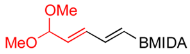
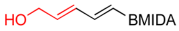
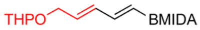
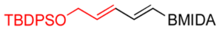
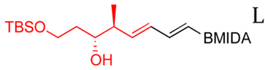
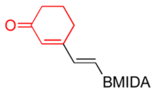
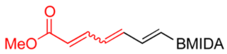
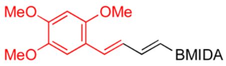
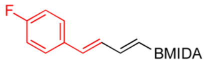
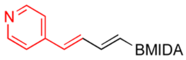
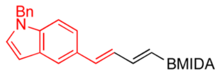
Scheme 3. Heck Coupling Involving Iodoboronate 1b



With these conditions in hand, the scope and limitations of the Heck coupling involving iodo boronate **1b** were explored. Pleasingly, the reaction appeared quite general, and several functional groups such as an acetal were well tolerated when present in the olefinic partner (Table 1, entry 1). Allyl alcohol derivatives were also suitable under the reaction conditions, and the protection of the hydroxyl group as a silyl ether proved to be beneficial (Table 1, entries 2–4). In all cases, a satisfactory regioselectivity of about 90:10 in favor of the linear isomer was observed. An enantiopure alcohol was successfully used to produce **3g** (65% yield, 85% purity) without epimerization of the stereocenters, thus highlighting the synthetic value of the method (Table 1, entry 5). Unfortunately, the coupling did not proceed with disubstituted olefins such as cyclohexenone (Table 1, entry 6). In contrast, a triene was formed when **1b** was reacted with methylpenta-2,4-dienoate **2i** (76%) albeit in a 80:10:10 mixture of isomers (Table 1, entry 7).[14] Styrenic partners exhibited good reactivity under the coupling conditions whatever the electronic nature of the substituents on the aryl moiety, and the expected products were isolated in good yields and high regioselectivities (Table 1, entries 8 and 9). Interestingly, the presence of heteroaromatics such as pyridine or indole was not detrimental to the reaction as **3l** and **3m** were isolated in good yields (Table 1, entries 10 and 11).

Table 1. Scope and Limitations of the Heck Coupling

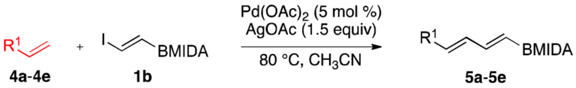


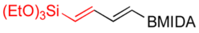
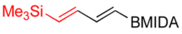
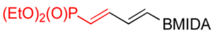
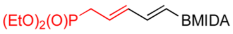
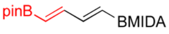
entry	3	product	L/B or L/I[a]	yield[b]
1	**3c**		L/I = 85:15	75%
2	**3d**		L/B = 88:12	58%
3	**3e**		L/B = 87:13	63%
4	**3f**		L/B = 90:10	74%
5	**3g**		L/I = 85:15	65%
6	**3h**		-	0%
7	**3i**[c]		80:10:10[d]	76%
8	**3j**		L/I = 95:5	77%
9	**3k**		L/I = 95:5	68%
10	**3l**		L/I = 95:5	75%
11	**3m**		L/I = 95:5	74%

[a] L/B: linear/branched. In some cases, the impurity (I) could not be identified undoubtedly as the branched isomer. The isomers were not separable. [b] The yield was calculated on the L/B or L/I mixture. [c] Purchased as a 95:5 mixture of (*E*)/(*Z*) isomers. [d] Mixture of isomers.

These promising results prompted us to examine the reactivity of functionalized alkene partners in order to access bifunctional dienes which are highly valuable building blocks in polyene synthesis.[15,16] Bis-functionalized Si–B dienes **5a** and **5b** were efficiently prepared from iodo-boronate **1b** (60% and 89% yield, respectively) (Table 2, entries 1 and 2). Vinyl and allyl phosphonates **4c** and **4d** were reacted with iodoboronate **1b** delivering the bifunctional dienes **5c** and **5d** in good yields (66% and 60%, respectively) (Table 2, entries 3 and 4). To the best of our knowledge, these dienes are unprecedented in the literature and could be involved subsequent transformations such as metal-catalyzed cross-couplings or HWE reaction. Gratifyingly, the bis-borylated diene **5e** was formed with an excellent yield of 90% (Table 2, entry 5). Thus, it is worth noting that this attractive building block was obtained in a one-step procedure from commercially available compounds, using a Heck coupling.[17,18]

Table 2. Access to Bifunctionalized Dienes



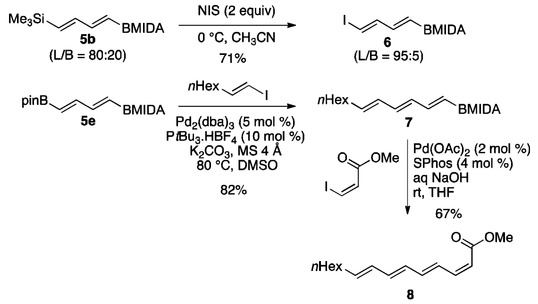
entry	5	product	L/B or L/I[a]	yield
1	**5a**		L/I = 95:5	60%
2	**5b**		L/B = 80:20	89%
3	**5c**		L/I = 95:5	66%
4	**5d**		L/B = 85:15	60%
5	**5e**		L/I = 90:10	90%

[a] L/B: linear/branched. In some cases, the impurity (I) could not be identified undoubtedly as the branched isomer.

An iodo desilylation was performed on **5b**, thus achieving a short synthesis of the dienic iodo boronate **6** which could be involved in an iterative Heck coupling (Scheme 4).[19] The synthetic utility of **5e** was well illustrated by performing two consecutive Suzuki cross-couplings that allowed the efficient and stereospecific formation of the (*E,E,E,Z*)-tetraene **8**.[20]

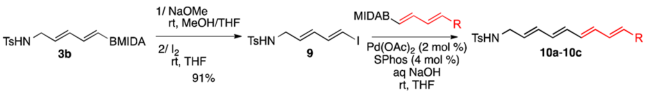
In order to demonstrate the high synthetic potential of the method, the MIDA boronate **3b** was transformed into the corresponding alkenyl iodide **9**, which was then submitted to a Suzuki cross-coupling with a range of MIDA boronates (Table

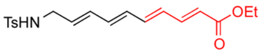
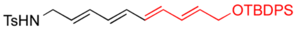
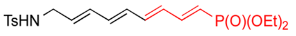
Scheme 4. Transformations of Dienes 5b and 5e



3). It is worth noting that these boronate partners were previously obtained by a Heck coupling. Only a few combinations among all possible are depicted here showing that this short sequence of reactions provides an easy and modular access to a large variety of polyenic frameworks.

Table 3. Synthesis of Tetraenes 10a−c

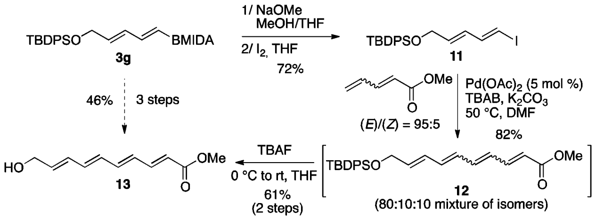


entry	product	purity	**10** (yield)
1		92%	**10a** (74%)
2		84%	**10b** (77%)
3		93%	**10c** (75%)

[a]The isomeric purity was evaluated on the ^{1}H NMR spectrum after purification.

During the course of our studies toward the synthesis of the macrolactam mirabalin, we were interested in the preparation of tetraene **13** (Scheme 5).[21] Starting from the Heck product **3g**, the targeted compound could be prepared in 3 steps with a satisfying global yield of 46%.[22] This straightforward synthesis advantageously competes with those already reported in the literature to access the same tetraenic motif.[23,24]

Scheme 5. Straightforward Synthesis of Tetraene 13



In conclusion, a simple, general and chemoselective Heck coupling involving an alkenyl iodoboronate is reported. A wide range of alkenes was compatible with the conditions, providing a library of dienic compounds. The stereoselective method gave a straightforward access to bis-functionalized building blocks, which could be easily transformed into polyenic frameworks. The use of simple olefins as the coupling partner makes the reaction easy-to-run even on highly advanced synthetic intermediates as no preparation of alkenyl metal is required. As such, this modular strategy should rapidly enter into the chemist toolbox for the construction of polyenic natural and non-natural products.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for all new compounds are provided. 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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(1) (b) Madden, K. S.; Mosa, F.; Whiting, A. *Org. Biomol. Chem.* **2014**, *12*, 7877. (a) Whiting, A.; Thirsk, C. *J. Chem. Soc., Perkin Trans. 1* **2002**, *8*, 999.

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(4) (a) Blakemore, P. R. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563. (b) Aïssa, C. *Eur. J. Org. Chem.* **2009**, 1831. (c) Markó, I. E.; Pospíšil, J. In *Science of Synthesis, Vol 47a: Alkenes*; de Meijere, A., Ed.; George Thieme Verlag: Stuttgart, 2009, 105.

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7645. (e) Lightfoot, A. P.; Twiddle, S. J. R.; Whiting, A. *Org. Biomol. Chem.* **2005**, *3*, 3167. (f) Batsanov, A. S.; Knowles, J. P.; Whiting, A. *J. Org. Chem.* **2007**, *72*, 2525. (g) Sakai, M.; Guan, T.; Hara, S. *J. Fluor. Chem.* **2007**, *128*, 1444. (h) Batsanov, A. S.; Knowles, J. P.; Samsam, B.; Whiting, A. *Adv. Synth. Catal.* **2008**, *350*, 227. (i) Uno, B. E.; Gillis, E. P.; Burke, M. D. *Tetrahedron* **2009**, *65*, 3130. (j) Delcamp, J. H.; Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 8460. (k) Szudkowska-Frątczak, J.; Ryba, A.; Franczyk, A.; Walkowiak, J.; Kubicki, M.; Pawluć, P. *Appl. Organomet. Chem.* **2014**, *28*, 137.

(13) See the Supporting Information for details.

(14) The (*E,E*)-diene was the major isomer, and the other isomers could not be identified without a doubt.

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(16) For selected examples of other bis-functionalized dienes and trienes, see: (a) Lipshutz, B. H.; Lindsley, C. *J. Am. Chem. Soc.* **1997**, *119*, 4555. (b) Denmark, S. E.; Tymonko, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 8004. (c) Coleman, R. S.; Lu, X.; Modolo, I. *J. Am. Chem. Soc.* **2007**, *129*, 3826. (d) Coleman, R. S.; Walczak, M. C. *Org. Lett.* **2005**, *7*, 2289. (e) Badubri, F.; Fiandanese, V.; Marchese, G.; Naso, F. *J. Chem. Soc., Chem. Commun.* **1991**, 237. (f) Badubri, F.; Fiandanese, V.; Naso, F.; Punzi, A. *Tetrahedron Lett.* **1994**, *35*, 2067. (g) Singidi, R. R.; RajanBabu, T. V. *Org. Lett.* **2010**, *12*, 2622.

(17) As a comparison, Burke et al. prepared the same building block in five steps; see ref 15f.

(18) The Heck cross-coupling was performed on gram scale, and a batch of 2 g of **5e** was prepared without erosion of the yield.

(19) For other methods to access dienic halogeno-boronates, see: (a) Woerly, E. M.; Cherney, A. H.; Davis, E. K.; Burke, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 6941. (b) Singidi, R. R.; Kutney, A. M.; Galluci, J. C.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2010**, *132*, 13078. (c) Gillis, E. P.; Lee, S. J.; Gray, K.; Burke, M. D.; Knapp, D. M. WO US84156, 2007. (d) Sakai, M.; Guan, T.; Hara, S. *J. Fluorine Chem.* **2007**, *178*, 1444.

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(22) In **12**, the major isomer was the (*E,E,E,E*)-tetraene. After a purification by flash chromatography on silica gel, **13** was isolated as a single (*E,E,E,E*)-isomer.

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(24) A 200 mg portion of the tetraenic fragment **13** could be obtained through this sequence of reactions.

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