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Palladium-Catalyzed Cross-Coupling Reaction of Bis(pinacolato)diboron with 1-Alkenyl Halides or Triflates: Convenient Synthesis of Unsymmetrical 1,3-Dienes via the Borylation-Coupling Sequence

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Abstract: The synthesis of 1-alkenylboronic acid pinacol esters via a palladium-catalyzed cross-coupling reaction of bis(pinacolato)diboron (pin$_2$B$_2$, pin = Me$_4$C$_2$O$_2$) with 1-alkenyl halides or triflates was carried out in toluene at 50 °C in the presence of KOPh (1.5 equiv) and PdCl$_2$(PPh$_3$)$_2$-2Ph$_3$P (3 mol %). The borylation of acyclic and cyclic 1-alkenyl bromides and triflates was achieved in high yields with complete retention of configuration of the double bonds. The method was applied to the one-pot synthesis of unsymmetrical 1,3-dienes via the borylation-coupling sequence.

Introduction

1-Alkenylboron derivatives are an important class of compounds as versatile intermediates in synthetic organic chemistry,[1] the utility of which has been amply demonstrated in the synthesis of natural products, biologically active compounds, and functional organic materials by application of numerous carbon−carbon bond forming reactions, such as Pd-catalyzed cross-coupling with organic electrophiles,[2] Rh-catalyzed addition to carbonyl substrates,[3] Matteson homologation,[4] and Petasis reaction with amine and carbonyl compounds.[5] Although 1-alkenylboron compounds have been generally prepared by hydroboration of alkynes or by transmetalation between trialkylborates and 1-alkenyllithium or -magnesium reagents, these methods have inherent limitations.[6] The hydroboration is known to proceed in an anti-Markovnikov manner; therefore, it is difficult to obtain 1-alken-2-ylboron compounds from 1-alkynes regioselectively. Also, the method cannot be applied to the synthesis of cyclic 1-alkenylboron compounds because of limited availability of the starting cycloalkynes. On the other hand, the

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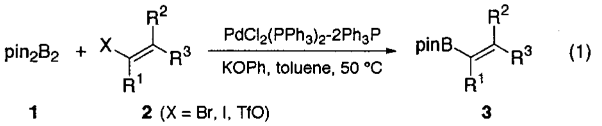
transmetalation protocol requires a tedious protection−deprotection process for preparing functionalized 1-alkenylboron compounds.

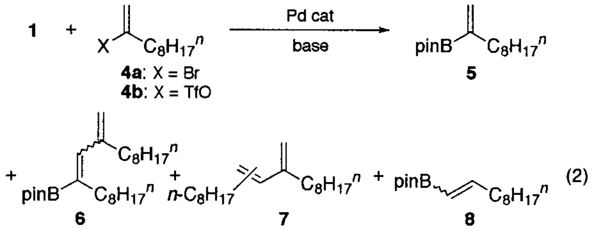
Transition metal-catalyzed cross-coupling reactions of metal nucleophiles with organic electrophiles have emerged as an efficient method for the synthesis of organometallic compounds because of the ready availability of various organic electrophiles. Extensive studies have been made on the silylation, stannylation, and germylation by using disilanes,[7] distannanes,[8] and digermanes[7c,9] as metal−anion equivalents; however, the corresponding reaction of boron has not been well developed. Recently, we have demonstrated that tetra(alkoxo)diborons such as bis(pinacolato)diboron are excellent boron nucleophiles which allow the palladium-catalyzed borylation of organic halides or triflates in the presence of a base.[10] Since the tetra(alkoxo)diborons highly tolerate various functional groups, the reaction provided variously functionalized arylboronates,[10,11] allylboronates,[10,12] and benzylboronates[10] from the corresponding organic electrophiles. Very recently, Masuda and Murata found that pinacolborane is an economical alternative for analogous palladium-catalyzed borylation of organic halides or triflates.[13] However, their method suffered from low yields, resulting in a complex mixture of several byproducts for the synthesis of 1-alkenylboronates.[13c]

In this paper, we report a palladium-catalyzed coupling reaction of bis(pinacolato)diboron (**1**, pin_2B_2, pin = $Me_4C_2O_2$) with 1-alkenyl halides or triflates (**2**), which provides a one-step procedure for the synthesis of pinacol 1-alkenylboronic esters (**3**) from 1-alkenyl electrophiles (eq 1).[14] The utility of the method was also demonstrated by a one-pot, two-step synthesis of unsymmetrical 1,3-dienes via the borylation-coupling sequence. Although similar borylation of **2** with **1** catalyzed by $PdCl_2(PhCN)_2$ or $PdCl_2(dppf)$ was reported by Marcuccio[15] and Eastwood,[16] respectively, the present method may have broader generality with respect to the range of applicable **2**.



Results and Discussion

Palladium-Catalyzed Cross-Coupling Reaction of Bis(pinacolato)diboron with 1-Alkenyl Halides or Triflates. Because the cross-coupling of the diboron **1** with 1-decen-2-yl bromide (**4a**) under the previous reaction conditions reported for the borylation of aryl,[10,11] allyl,[10] or benzyl[10] halides only gave a small amount of the expected 1-decen-2-ylboronate (**5**) together with a large amount of several byproducts (**6**−**8**) (eq 2), our initial efforts were focused on the reaction conditions selectively giving **5**.



A combination of $PdCl_2(dppf)$, KOAc, and DMSO used for the borylation of haloarenes[11a] resulted in a mixture of a desired boronate (**5**, 27%), a Heck coupling product between **4a** and **5** (**6**, <1%), a homo-coupling product (**7**, 20%), and a regioisomer of **5** (**8**, 6%). Probable processes for the formation of these products are shown in Scheme 1. The desired reaction to form **5** proceeds by a process involving oxidative addition of **4a** to Pd(0) to generate a 1-alkenylpalladium(II) bromide (**9**), transmetalation between **1** and **9** with the aid of the base to give a 1-alkenyl(boryl)palladium(II) species (**10**), and reductive elimination of **5** to regenerate Pd(0).[11a] The Heck coupling product **6** can be provided by insertion of the double bond of **5** into the C−Pd bond of **9** followed by β-hydride elimination.[17] On the other hand, two different processes can be operative to yield the homo-coupling products (**7a** and **7b**). The head-to-tail coupling product **7a** is obtained by an addition−elimination sequence involving formation and conversion of **11**, **6**, and **12**,

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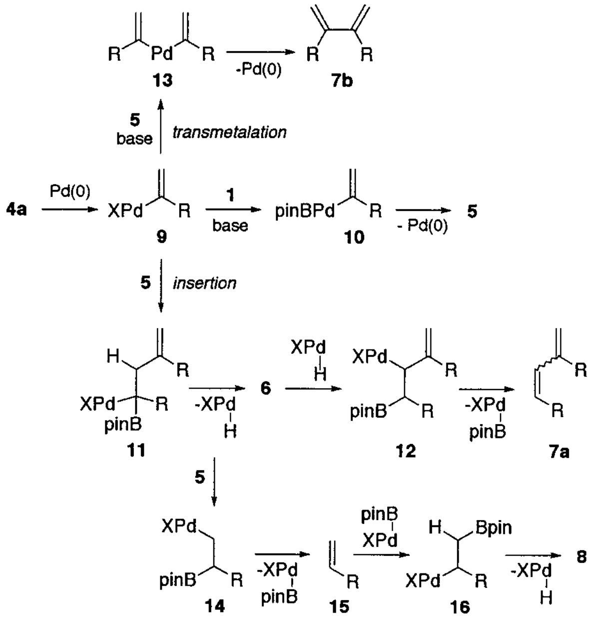
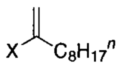
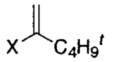
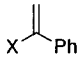
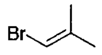
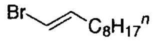
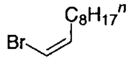
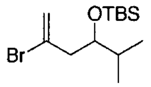
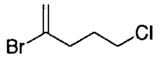
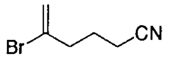
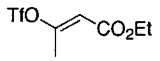
Scheme 1. Proposed Processes in the Reaction of **1** and **4a**



(R = *n*-C_8H_{17}, X = Br)

as was previously reported.[18] The reaction between **9** and **5** via a transmetalation process affords the head-to-head coupling product **7b** through an intermediate **13**.[19] Although the ratio of **7a** and **7b** depends on the reaction conditions, the coupling employing KOAc mainly yielded **7a**. The positional isomer **8** can be produced by an addition−elimination process through intermediates **14**, **15**, and **16**. The insertion of a C−C double bond into a B−Pd bond has been postulated in palladium-catalyzed diboration of allenes in the presence of a 1-alkenyl iodide.[20] Thus, the formation of all byproducts can be ascribed to the slow rate of the transmetalation between **1** and **9** compared with that of the insertion of **5** to **9**, suggesting the superiority of stronger bases which can accelerate the desired transmetalation process. Although changing KOAc to K_2CO_3 predominantly gave homo-coupling product **7b** arising from the transmetalation between **9** and **5**, use of a KOPh base effectively suppressed the formation of byproducts and improved the yield of desired **5**. The yield and selectivity were further increased when using less polar solvents such as toluene, mainly due to retardation of the transmetalation process to give **7b**. As for the ligands of palladium, Ph_3P resulted in a better yield and selectivity than dppf because bidentate ligands with large bite angle generally enhance the undesirable insertion process.[21] Electron-donating, electron-withdrawing, and sterically hindered triarylphosphines did not have significant influence on the reaction. On the other hand, the use of Ph_3As, which weakly coordinates to palladium, sufficiently decreased the yield and selectivity because of the ease of generating a coordinatively unsaturated palladium species facilitating the insertion process.[22] Finally, the best result could be obtained by using a catalyst comprised of $PdCl_2(PPh_3)_2$ and 2 equiv of PPh_3, which may prevent the formation of the coordinatively unsaturated palladium species. The reaction was completed within 5 h even at 50 °C to give desired **5** in 92% yield with 97% selectivity. Under analogous conditions, the coupling of the corresponding triflate (**4b**) was much more selective than that of the bromide and was completed within 1−2 h.

Table 1. Synthesis of Acyclic 1-Alkenylboronates (eq 1)[a]

entry	1-alkenyl halide or triflate		time/h	yield/%[b]
1		X = I	5	65[c]
2		X = Br	5	92
3		X = OTf	2	93
4		X = Br	5	69[d]
5		X = OTf	2	91
6		X = Br	5	88
7		X = OTf	4	99
8			5	57
9			5	47[e]
10			5	74
11			5	70
12			5	85
13			5	85
14			1	93

[a] A mixture of diboron **1** (1.1 mmol), 1-alkenyl halide or triflate (1.0 mmol), $PdCl_2(PPh_3)_2$−$2Ph_3P$ (0.03 mmol), KOPh (1.5 mmol), and toluene (6 mL) was stirred at 50 °C for the period shown in the table. [b] GC yields based on halides or triflates. [c] (*Z*)-1-Decenylboronate was also produced (3%). [d] (*E*)-3,3-Dimethyl-1-butenylboronate was also produced (7%). [e] 1-Decen-2-ylboronate was also produced (6%).

The scope and limitation in the synthesis of 1-alkenylboronates **3** by the cross-coupling of the diboron **1** with representative 1-alkenyl electrophiles **2** are summarized in Tables 1 and 2. The studies were mainly focused on the synthesis of **3**, which is not easily available by conventional methods such as hydroboration of alkynes.

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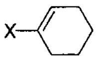
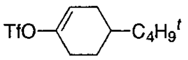
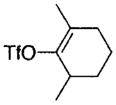
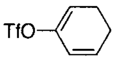
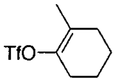
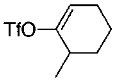
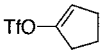
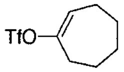
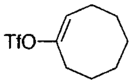
Table 2. Synthesis of Cyclic 1-Alkenylboronates (eq 1)[a]

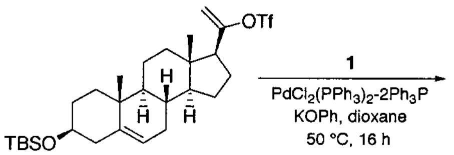
entry	1-alkenyl halide or triflate		time/h	yield/%[b]
1		X = I	16	49
2		X = Br	5	99
3		X = OTf	3	88
4			3	94
5			2	94
6			2	89
7			1	85
8			2	82
9			1	74[c]
10			2	60[c]
11			1	65[c]

[a] A mixture of diboron **1** (1.1 mmol), 1-alkenyl halide or triflate (1.0 mmol), $PdCl_2(PPh_3)_2-2Ph_3P$ (0.03 mmol), KOPh (1.5 mmol), and toluene (6 mL) was stirred at 50 °C for the period shown in the table. [b] GC yields based on halides or triflates. [c] The reactions were carried out in the presence of KBr (1.5 mmol).

Results of the borylation of acyclic 1-alkenyl halides and triflates are shown in Table 1. A series of coupling reactions with 1-decen-2-yl iodide, bromide, and triflate showed the superiority of the bromide and the triflate over the iodide (entries 1−3); however, the triflates can be better substrates than the bromides in achieving high yields and high selectivities, probably due to the lability of the Pd−OTf bond accelerating the desired transmetalation process (entries 4−7).[23] 2,2-Disubstituted 1-alkenylboronate was also obtained from the corresponding bromide without any difficulties because the side reactions shown in eq 2 were very slow for this substrate (entry 8). Although (*E*)-1-alkenylboronates have been synthesized by hydroboration of terminal alkynes[6] and (*Z*)-derivatives by a two-step procedure from 1-halo-1-alkynes,[24] the present borylation provided an alternative method for preparing both isomers with high stereoselectivities over 99% (entries 9 and 10). The reaction conditions with an insoluble KOPh base suspended in toluene can tolerate various functionalities, such as siloxy, chloro, cyano, and ester groups, in bromides and triflates (entries 11−14). Especially, 1-alkenyl triflates β-substituted by a carbonyl group are highly susceptible to nucleophilic S−O bond cleavage by a base because such an electron-withdrawing substituent makes the sulfur atom more electrophilic,[25] but the competitive formation of phenyl triflate and pinacol phenylboronate was not observed (entry 14). On the other hand, the corresponding borylation of β-halo-α,β-unsaturated carbonyl compounds, such as 3-iodo-3-penten-2-one and methyl 3-bromo-2-methylpropenoate, did not give the coupling products for an ambiguous reason. All attempts at the borylation of dihaloalkenes, such as (*E*)-1,2-diiodo-1-phenylethene and 2,2-dibromo-1-phenylethene, were also unsuccessful.

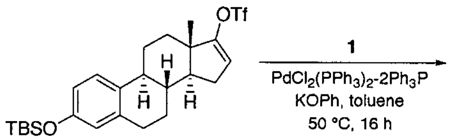
Table 2 represents results of the cross-coupling reaction of the diboron **1** with cyclic 1-alkenyl halides and triflates. The ready availability of the triflates from cyclic ketones offered a valuable method for the synthesis of cyclic 1-alkenylboronates.[26] A comparison of reactivities between 1-cyclohexenyl iodide, bromide, and triflate again revealed the superiority of the bromide and the triflate over the iodide (entries 1−3).[23] 1-Cyclohexenyl triflates bearing substituents and 1,3-cyclohexadien-2-yl triflate also underwent smooth reaction yielding the corresponding boronates in high yields (entries 4−6). An important aspect of the present borylation is the ability to prepare cyclic 1-alkenylboronates regioselectively from an unsymmetrical ketone by using either the kinetic or thermodynamic enolate,[27] and to couple the triflate with **1** to give only one regioisomeric product (entries 7 and 8). Isomerically pure 1-cyclopentenyl-, 1-cycloheptenyl-, and 1-cyclooctenylboronate were also produced by the borylation of the corresponding triflates. Although yields of these boronates were 20−30% lower than that of 1-cyclohexenylboronate under the conditions optimized above, satisfactory results could be obtained by using KBr as an additive (entries 9−11).[28]

The usefulness of the cross-coupling method was demonstrated by the borylation of a side chain of a steroid (eqs 3 and 4). Two triflates (**17** and **19**) were synthesized in high yields by treatment of a protected pregnenolone or estrone with LDA



17

18 75% (3)



19

20 86% (4)

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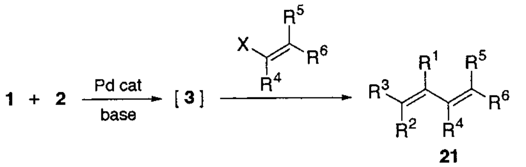
in THF followed by *N*-phenyltriflimide. The borylation with the diboron **1** at 50 °C yielded the corresponding 1-alkenylboronates (**18**, 75%, and **20**, 86%) which can be potential intermediates for elaborating a side chain of steroids. Although the reactions were carried out for 16 h, these may be completed within a shorter reaction time. The borylation of the triflate **17** was conducted in 1,4-dioxane because of its poor solubility in toluene.

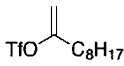
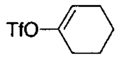
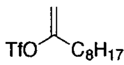
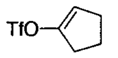
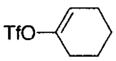
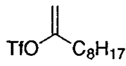
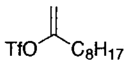
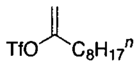
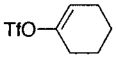
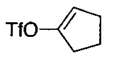
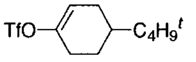
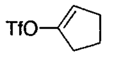
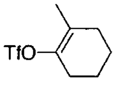
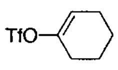
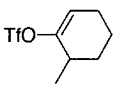
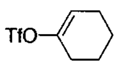
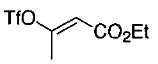
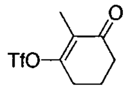
One-Pot Synthesis of Unsymmetrical 1,3-Dienes via the Borylation-Coupling Sequence. The regio- and stereospecific synthesis of 1,3-dienes is of great importance in synthetic organic chemistry due to the frequent occurrence of these fragments in biologically active natural products, as well as to their utilization in numerous transformations such as the Diels−Alder reaction.[29] Although a number of methods for preparing 1,3-dienes have been developed so far, the palladium-catalyzed cross-coupling reaction of 1-alkenylboron compounds with 1-alkenyl electrophiles has attracted recent attention due to its practical usefulness.[2] The present study now allows a one-pot, two-step procedure to access unsymmetrical 1,3-dienes (**21**) by sequential borylation of a 1-alkenyl electrophile and cross-coupling with a distinct 1-alkenyl electrophile, both of which were catalyzed by a common palladium catalyst (eq 5).



(5)

Because the borylation of 1-alkenyl triflates resulted in higher yields and selectivities than that of halides, 1-decen-2-ylboronate (**5**) in situ prepared from the corresponding triflate **4b** was directly subjected to the next cross-coupling with 1-cyclohexenyl triflate under modified reaction conditions. Although the reaction did not proceed at a detectable rate under the conditions used for the borylation even at 80 °C, the desired 1,3-diene could be obtained in almost quantitative yield (96%) when using a dppf ligand, a K_3PO_4 base, and a DMF solvent. The use of an additional ligand for palladium was indispensable to prevent catalyst decomposition. Addition of Ph_3P was also effective, resulting in 83% yield, but the reaction in the absence of an additional ligand significantly decreased the yield of the product. A strong base, K_3PO_4, was favorable for the present coupling rather than a weak base such as KOPh and K_2CO_3. The reaction was also affected by solvents and was effectively accelerated in polar solvents: e.g., DMF > 1,4-dioxane ≫ toluene.

Table 3. Synthesis of 1,3-Dienes via the Borylation-Coupling Reaction (eq 5)[a]

entry	1-alkenyl triflate (borylation/coupling)		yield/%[b]
1			(96)
2			81
3			(62)[c]
4			(99)[c]
5			74
6			77
7			81
8			79
9			76[d]

[a] Borylation of **2** (1.1 mmol) with diboron **1** (1.1 mmol) in toluene (4 mL) at 50 °C for 1−3 h in the presence of $PdCl_2(PPh_3)_2$−$2Ph_3P$ (0.03 mmol) and KOPh (1.5 mmol) was followed by cross-coupling with 1-alkenyl triflate (1.0 mmol) at 80 °C for 16 h by using dppf (0.03 mmol), K_3PO_4 (3.0 mmol), and DMF (4 mL). [b] Isolated yields based on 1-alkenyl triflates used for the second coupling; GC yields are in parentheses. [c] $PdCl_2$(dppf) (0.03 mmol) was used in place of dppf. [d] 1,4-Dioxane (4 mL) was uesd in place of DMF.

Representative results of the synthesis of 1,3-dienes **21** via the borylation−coupling sequence are summarized in Table 3. The present method provides a convenient and efficient route for preparing a variety of 1,3-dienes. Acyclic−cyclic (entries 1, 2, and 9), cyclic−acyclic (entry 3), acyclic−acyclic (entry 4), and cyclic−cyclic (entries 5−8) cross-coupling reactions all afforded the corresponding 1,3-dienes in high yields with excellent isomeric purities, while the cyclic−acyclic and acyclic−acyclic coupling required an addition of a fresh palladium catalyst, $PdCl_2$(dppf), to obtain acceptable yields (entries 3 and 4). Although the cross-coupling of 1-alkenylboronates β-substituted by a carbonyl group has not been reported before, the reaction also proceeded without any difficulties in 1,4-dioxane to give a functionalized 1,3-diene (entry 9).

Conclusions

The cross-coupling reaction of bis(pinacolato)diboron and 1-alkenyl halides or triflates in the presence of a palladium/triphenylphosphine catalyst and potassium phenoxide suspended in toluene afforded pinacol 1-alkenylboronates. The utility of the method was amply demonstrated by the one-pot synthesis of unsymmetrical 1,3-dienes via the borylation−coupling sequence. Now, aryl-, 1-alkenyl-, allyl-, and benzylboronic esters are accessible from the corresponding halides, triflates, or acetates via the palladium-catalyzed borylation with bis(pinacolato)diboron.

Experimental Section

The preparation of bis(pinacolato)diboron was reported previously.[30] 1-Alkenyl halides,[31] 1-alkenyl triflates,[26,32] and KOPh[33] were synthesized

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(29) (a) Fringuelli, F.; Taticchi, A. *Dienes in the Diels−Alder Reaction*; Wiley: New York, 1990. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, UK, 1990. (c) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, UK, 1991; Vol. 5, p 315. (d) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167. (e) Otto, S.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000**, *72*, 1365. (f) Kumar, A. *Chem. Rev.* **2001**, *101*, 1.

(30) (a) Nöth, H. *Z. Naturforsch.* **1984**, *39b*, 1463. (b) Ishiyama, T.; Murata, M.; Ahiko, T.-a.; Miyaura, N. *Org. Synth.* **2000**, *77*, 176.

by the reported procedures. Solvents were purified by distillation from appropriate drying agents. All of other compounds were used as received.

General Procedure for the Cross-Coupling Reaction of Bis(pinacolato)diboron with 1-Alkenyl Halides or Triflates (Tables 1 and 2 and Eqs 3 and 4). $PdCl_2(PPh_3)_2$ (0.021 g, 0.03 mmol), Ph_3P (0.016 g, 0.06 mmol), bis(pinacolato)diboron (0.279 g, 1.1 mmol), and KOPh (fine powder, 0.198 g, 1.5 mmol) were added to a flask equipped with a magnetic stirring bar, a septum inlet, and a condenser. The flask was flushed with nitrogen and then charged with toluene (6 mL) and a 1-alkenyl halide or 1-alkenyl triflate (1.0 mmol). The mixture was then stirred at 50 °C for the period shown in Tables 1 and 2 and eqs 3 and 4. The reaction mixture was treated with water (5 mL) at room temperature, extracted with benzene, washed with brine, and dried over $MgSO_4$. The products were isolated by chromatography over silica gel or Kugelrohr distillation in vacuo to give analytically pure samples. In general, pinacol 1-alkenylboronates are stable to water and chromatography over silica gel; however, the boronates β-substituted with a carbonyl group, such as the product of entry 14 in Table 1, are rather sensitive to protodeboronation.[34]

General Procedure for the One-Pot Synthesis of Unsymmetrical 1,3-Dienes via the Borylation−Coupling Sequence (Table 3). A flask equipped with a magnetic stirring bar, a septum inlet, and a condenser was charged with $PdCl_2(PPh_3)_2$ (0.03 mmol), Ph_3P (0.06 mmol), KOPh (1.5 mmol), bis(pinacolato)diboron (1.1 mmol), toluene (4 mL), and 1-alkenyl triflate (1.1 mmol) under nitrogen. The mixture was stirred at 50 °C for 1−3 h to give a solution of pinacol 1-alkenylboronate. To this solution were added dppf (0.017 g, 0.03 mmol), K_3PO_4 (0.637 g, 3.0 mmol), DMF (4 mL), and 1-alkenyl triflate (1.0 mmol), and the resulting mixture was then stirred at 80 °C for 16 h. The product was extracted with benzene, washed with water, and dried over $MgSO_4$. Column chromatography over silica gel provided analytically pure samples.

Supporting Information Available: Text describing experimental details and spectral and/or analytical data of the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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