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An Efficient and Reliable Catalyst System Using Hemilabile Aphos for *B*-Alkyl Suzuki–Miyaura Cross-Coupling Reaction with Alkenyl Halides

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The 9-methoxy-9-borabicyclo[3.3.1]nonane-based *B*-alkyl Suzuki–Miyaura cross-coupling reaction (the 9-MeO-9-BBN variant) has been efficiently performed by using the catalyst consisting of $Pd(OAc)_2$ and a hemilabile P,O-ligand, Aphos-Y, under mild reaction conditions ($K_3PO_4 \cdot 3H_2O$, THF/H_2O, room. temp.). For applications in the total synthesis of structurally complex natural products, the Johnson protocol commonly uses two ligands (dppf and Ph_3As) and two organic solvents (THF and DMF). In contrast, the new version reported here employs one ligand (Aphos-Y) and one organic solvent (THF). Moreover, the broad substrate scope and the excellent functional group tolerance of the $Pd(OAc)_2$–Aphos-Y catalyst have been demonstrated, providing a reliable and simple synthetic tool for fragment coupling in total synthesis through formation of a $C(sp^3)$–$C(sp^2)$ bond.

Introduction

The *B*-alkyl Suzuki–Miyaura cross-coupling reaction is a powerful tool for the formation of $C(sp^2)$–$C(sp^3)$ bonds and has widespread applications in the total synthesis of natural products.[1] Two main protocols have been established by using 9-alkyl-9-borabicyclo[3.3.1]nonane (9-alkyl-9-BBN)[1b] and the alkyl borinate derived from 9-methoxy-9-BBN and an alkyl iodide.[1f] In contrast to 9-alkyl-9-BBN formed by hydroboration of 1-alkenes with 9-BBN-H, the "9-MeO-9-BBN variant" tolerates a broader spectrum of functionalities, some of which might not survive under the hydroboration conditions. This distinct advantage renders the "9-MeO-9-BBN variant" an attractive protocol for coupling of densely functionalized fragments in the total synthesis.[1b,1e,1f,2] In general, a catalytic amount of $[Pd(dppf)Cl_2]$ and a mild base such as NaOH, K_2CO_3, or K_3PO_4 were used in aqueous DMF for promoting the *B*-alkyl Suzuki–Miyaura cross-coupling reaction.[1a,1b] In 1993, Johnson and Braun first reported the use of an additional ligand, Ph_3As, for achieving a higher turnover rate and a cleaner reaction.[3a] Since then, the Johnson protocol is popularly employed in total synthesis, and omission of Ph_3As has been reported to decrease the product yield significantly in some cases.[3b] We have recently demonstrated that the catalytic activity of aromatic amide-derived phosphanes (Aphos) such as **1** and **2** can be modified by the aryl group appended at the C4 (or C5) position of the benzamide core (Scheme 1). These Aphos ligands promoted Suzuki–Miyaura reactions of inactivated aryl chlorides with arylboronic acids at room temperature,[4a] reactions of benzyl halides with arylboronic acids at 60 °C,[4b] and *B*-alkyl Suzuki–Miyaura reactions of aryl and alkenyl halides under mild conditions.[4a,4c] In the latter case, addition of Ph_3As was not necessary, which implies that one hemilabile ligand **2**[5] can substitute for dppf and Ph_3As.[4c] We report here a detailed study on a simpler catalyst system consisting of $Pd(OAc)_2$ and Aphos-Y (**2**) in the presence of $K_3PO_4 \cdot 3H_2O$ and H_2O in THF at room temperature for catalyzing the "9-MeO-9-BBN variant" of the Suzuki–Miyaura cross-coupling reaction. Our emphasis focuses on the substrate scope and the practical applicability in the total synthesis of natural products.

Previously, we established by NMR spectroscopy that Aphos formed a P,O-chelating palladium(0) complex **Ia** (Ar = H) with $[Pd_2(dba)_3]$ in $[D_8]THF$ as the dominant species along with some detectable monoligated and P-monodentate complex **Ib** (Scheme 1).[4a] Both P,O-chelating and P-monodentate palladium(II) complexes and oxidative adducts **IIb** (Ar = H; X = Br, Cl, OAc; $R^1 = 4\text{-}t\text{Bu}C_6H_4$) were characterized by X-ray crystallographic analysis.[6] It was suggested that minor palladium complex **Ib** is the most reactive catalyst for oxidative addition[4a,7] and the initially formed adduct, **IIa**, should be equilibrated into **IIb**. Moreover, the above three complexes **IIb** exerted similar reactivity in the coupling reaction with $PhB(OH)_2$ [THF/H_2O (10:1), K_3PO_4, room temp., 1 h] to give the biaryl in yields of 90–95 %,[6] indicating that **IIb** might be converted into hydroxido complex **III** prior to transmetallation.[8] We envisioned two scenarios for the formation of intermediate **IV**

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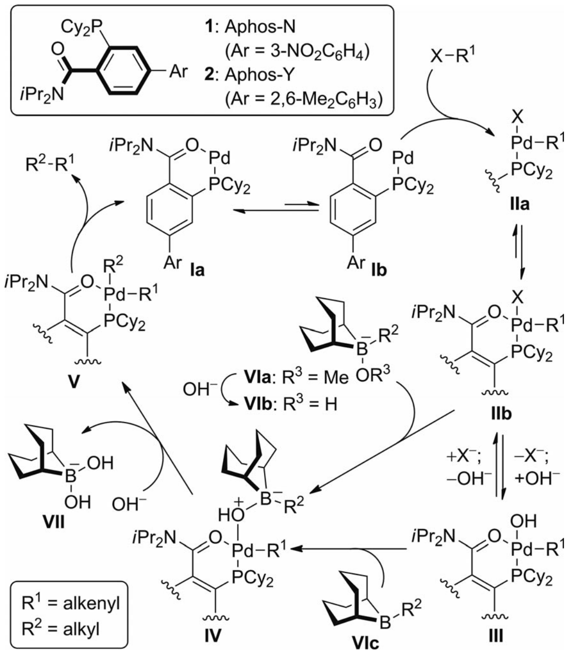
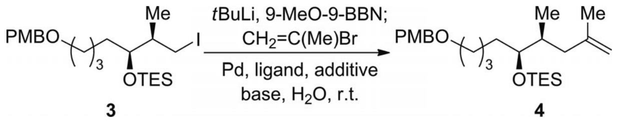


Scheme 1. Structures of Aphos **1** and **2** and the Pd–Aphos-promoted catalytic cycle for the *B*-alkyl Suzuki–Miyaura cross-coupling reaction.

responsible for the transmetallation.[8a–8g] One involves the reaction of halide complex **IIb** with hydroxy borinate **VIb**[8g] derived from the hydrolysis of MeO borinate species **VIa**. Alternatively, reaction of hydroxido complex **III**[8h–8k] with 9-alkyl-9-BBN **VIc**, which is formed by loss of MeO⁻ from **VIa**, should give **IV**. Both pathways were consistent in that K_3PO_4 and H_2O were required for the coupling reaction as the source of OH⁻ anion[8k] (vide infra). Transmetallation within **IV** was proposed to occur through a four-centered hydroxido μ_2-bridged transition state (TS)[8g] or via a three-centered TS as in the reaction of arylboronic acids.[8e,8i–8k] One remarkable feature of the hemilabile Aphos in complex **IV** is the higher *trans* effect of the phosphorus atom, which weakens the $Pd^{II}–O^{+}(H)B^{-}(R_3)$ bond and renders the transmetallation easier. Finally, reductive elimination from *cis*-R^1PdR^2(Aphos) (**V**) without assistance of OH⁻ anion[8i–8k] should furnish the $R^1–R^2$ product with regeneration of **Ia**,**b**. It should be emphasized that the details of the above-proposed mechanism, in particular the transmetallation processes, need further investigation. Our current work focuses on the practical application of the $Pd(OAc)_2$–Aphos-Y catalyst.

We first compared the $Pd(OAc)_2$–Aphos-Y catalyst with the Johnson protocol[9] in the coupling reaction of 2-bromoprop-1-ene with the alkyl iodide **3** (Table 1). With 5 mol-% each of $PdCl_2$ and dppf, product **4**[10] was formed in yields of 77–80% in the presence of 9 equiv. of H_2O and with or without 10 mol-% Ph_3As (entries 1 and 3, Table 1). In the absence of H_2O, the coupling did occur in DMF, but a much lower yield of **4** was observed (entry 2, Table 1). By using $Pd(OAc)_2$–Aphos-Y, **4** was formed in THF in 86% yield in the presence of K_3PO_4 and H_2O, but no reaction took place once the base was omitted (entry 5 vs. entry 4, Table 1). These results demonstrate that the $Pd(OAc)_2$–Aphos-Y catalyst is as efficient as the Johnson protocol.

Table 1. Effects of ligand(s), base, and water on the coupling of alkyl iodide **3** with 2-bromoprop-1-ene.[a]



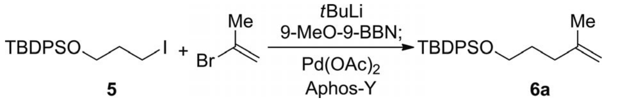
Entry	Pd[b]	Ligand (mol-%)	Base	Additive[c]	*t* [h]	Yield [%][e]
1	$PdCl_2$	dppf (5)	K_3PO_4	–	12	77
2[d]	$PdCl_2$	dppf (5)	Cs_2CO_3	Ph_3As	12	46
3	$PdCl_2$	dppf (5)	K_3PO_4	Ph_3As	12	80
4	$Pd(OAc)_2$	**2** (7.5)	–	–	20	0
5	$Pd(OAc)_2$	**2** (7.5)	K_3PO_4	–	16	86

[a] Reaction conditions: 0.2 mmol alkyl iodide **3**, 4 equiv. *t*BuLi, 4 equiv. 9-MeO-9-BBN, 2 mL each of Et_2O and THF, –78 °C to room temp., 1.5 h; then Pd, ligand, additive, 3 equiv. base, 5.5 equiv. 2-bromoprop-1-ene, 9 equiv. H_2O, 2 mL DMF (entries 1–3) or THF (entries 4 and 5), room temp. The long reaction times and large excess of 2-bromoprop-1-ene were purposely used here for maximizing the conversion. [b] 5 mol-%. [c] 10 mol-% Ph_3As was added. [d] H_2O not added. [e] Isolated yield of **4** based on alkyl iodide **3**. PMB = *para*-methoxybenzyl, TES = triethylsilyl.

As the effect of H_2O is profound, a detailed investigation was followed (Table 2). Under the Johnson protocol, the reaction of alkyl iodide **5** with 1.5 equiv. of 2-bromoprop-1-ene in the presence of 19 equiv. of H_2O proceeded smoothly in a mixture of THF/DMF to afford **6a** in 91% yield (entry 1, Table 2). Similarly, the same coupling catalyzed by $Pd(OAc)_2$–Aphos-Y in the presence of 9 equiv. of H_2O in THF furnished **6a** in 97% yield (entry 2, Table 2). When $K_3PO_4·3H_2O$ was used, the coupling did not occur without extra added H_2O. It was interesting to note that **6a** could be formed once extra H_2O was added (entry 3 vs. entry 4, Table 2). In the presence of H_2O, similar results were obtained regardless of whether $K_3PO_4·3H_2O$ or K_3PO_4 was used (entry 5 vs. entry 2, Table 2). Moreover, the palladium loading could be reduced to 1 mol-% without deteriorating the yield, albeit at the expense of prolonged reaction time (entry 6, Table 2). Therefore, the $Pd(OAc)_2$–Aphos-Y catalyst could efficiently catalyze the coupling reaction with inexpensive $K_3PO_4·3H_2O$ as the base in THF and without using Ph_3As and DMF.

With the coupling protocol established above, making use of $Pd(OAc)_2$–Aphos-Y, the scope of substituted alkenyl bromides in the reactions with alkyl iodide **5** was examined (Table 3). Di-, tri-, and tetrasubstituted alkenes **6a**–**d** were prepared in good to excellent yields (entries 1–4, Table 3). A correlation of the reaction time and product yield with the steric bulkiness of the alkenyl bromide is noted. Steric hindrance should be the main reason for the lower yield of **6e** in which the phenyl group (R^3 = Ph) and the alkyl group carried over from **5** are *cis* to each other (entry 5, Table 3).

Table 2. Effect of water on the coupling of **5** with 2-bromoprop-1-ene.[a]



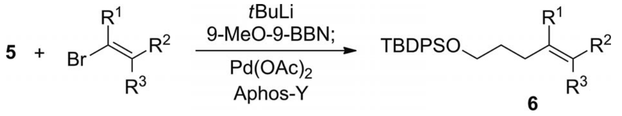
5 **6a**

Entry	Base[b]	H_2O [equiv.]	Solvent(s)	*t* [h]	Yield [%][c]
1	Cs_2CO_3	19	THF/DMF	1.5	91
2	K_3PO_4	9	THF	1.5	97
3	$K_3PO_4\cdot 3H_2O$	–	THF	16	0
4	$K_3PO_4\cdot 3H_2O$	9[d]	THF	12 + 3	45
5	$K_3PO_4\cdot 3H_2O$	9	THF	2	93
6[e]	$K_3PO_4\cdot 3H_2O$	9	THF	10	90

[a] Reaction conditions are found in the Experimental Section. The Johnson protocol [5 mol-% $Pd(dppf)Cl_2$, 10 mol-% Ph_3As] was used in entry 1. [b] 3 equiv. [c] Isolated yield of **6a** based on alkyl iodide **5**. [d] H_2O was added after 12 h of reaction, and the reaction was continued for another 3 h. [e] 1 mol-% $Pd(OAc)_2$ and 1.5 mol-% Aphos-Y were used. TBDPS = *tert*-butyldiphenylsilyl.

Nevertheless, the $Pd(OAc)_2$–Aphos-Y catalyst system is applicable for the preparation of all types of substituted alkenes in synthetically useful yields.

Table 3. Coupling reactions of alkyl iodide **5** with various alkenyl bromides.[a]



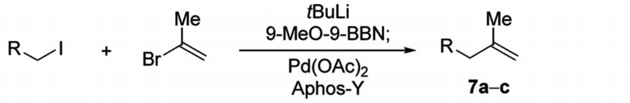
6

Entry	R^1	R^2	R^3	*t* [h]	Yield [%][b]
1[c]	Me	H	H	1.5	**6a**: 97
2	Me	Me	H	3	**6b**: 85
3	Me	Me	Me	6	**6c**: 81
4	Ph	H	H	2	**6d**: 92
5	CHO	H	Ph	15	**6e**: 64

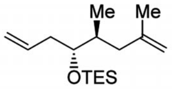
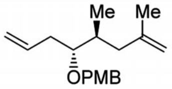
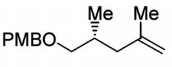
[a] Reaction conditions are found in the Experimental Section. [b] Isolated yield based on **6**. [c] Data taken from entry 2 of Table 2.

In the total synthesis of polyketide natural products, the requisite fragments often possess *syn*- and *anti*-aldol subunits as well as different protecting groups such as the *para*-methoxybenzyl (PMB) and various bulky silyl groups. Synthesis of alkene **4** with the TES-protected *syn*-aldol moiety is given in Table 1. The results of reactions of other representative chiral alkyl iodides are summarized in Table 4. Alkene **7a** with a TES-protected *anti*-aldol moiety could be synthesized in 90% yield (entry 1, Table 4). It was found that the PMB group, if close to the coupling reaction site (i.e. in 1,3-relationship to the iodine atom), might interfere with the reaction. While the yield of **7b** (85%) is slightly lower than that of the TES-protected analogue **7a** (90%) (entry 2 vs. entry 1, Table 4), a significantly diminished yield of 65% was obtained for **7c**, and extension of the reaction time could not improve the yield (entry 3, Table 4). Chelation of the PMBO group appended at the primary carbon with boron would retard the reaction.

Table 4. Coupling reactions of various alkyl iodides with 2-bromoprop-1-ene.[a]



7a–c

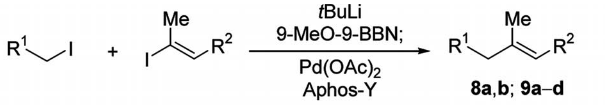
Entry	Alkene Product	*t* [h]	Yield [%][b]
1		3	**7a**: 90
2		4	**7b**: 85
3		12	**7c**: 65
		24	**7c**: 60

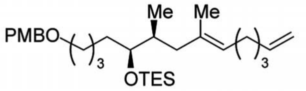
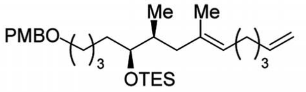
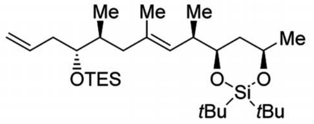
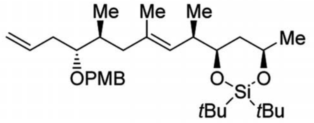
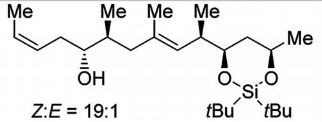
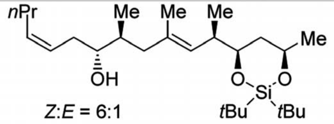
[a] Reaction conditions are found in the Experimental Section. [b] Isolated yield of **7** based on the alkyl iodides.

Trisubstituted alkenes with multiple functionalities are useful fragments for total synthesis of natural products, and yet their synthesis is often challenging.[10–13] To demonstrate the practical applicability of the $Pd(OAc)_2$–Aphos-Y catalyst, Table 5 highlights the highly functionalized trisubstituted alkenes synthesized. Compounds **8a**,**b**, obtained in 85% yield each, feature an additional double bond and a free hydroxy group,[3b] respectively (entries 1 and 2, Table 5). The cyclic silyl protecting group for chiral 1,3-diols has been proven to be beneficial in highly stereoselective ketone aldol reactions and has been utilized in the total synthesis of the plecomacrolides.[14] This protecting group was also found to be critically important in Altmann's synthesis of the mycolactone core via the "9-MeO-9-BBN variant" under the Johnson protocol, presumably due to reduced steric hindrance as compared to the bis(TBS) ether analogue.[9,10b] We used the same cyclic silyl-protected alkenyl iodide in entries 3–6 of Table 5. Although the alkyl iodide with the TES-protected *anti*-aldol unit underwent the coupling reaction with 2-bromoprop-1-ene (entry 1, Table 4), it nearly failed to form product **9a** (entry 3, Table 5).[11b] Fortunately, the less sterically demanding PMB ether greatly enhanced the coupling efficiency, furnishing **9b** in 90% yield (entry 4, Table 5). In addition, analogous products **9c**,**d** were synthesized under the same catalytic conditions in 83 and 80% overall yields, respectively, after cleavage of the PMB group (entries 5 and 6, Table 5).

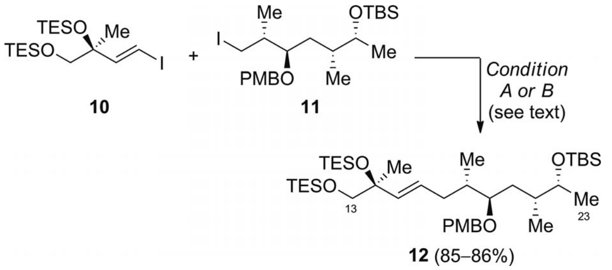
Finally, we prepared the C13–C23 fragment **12** designed for the synthesis of iriomoteolide-1a diastereomers according to our previously established strategy (Scheme 2).[2] The same type of reaction has been used by others in the total synthesis of the proposed structure of iriomoteolide-1a.[15] Under the Johnson protocol (*Condition A*) **12** was isolated in 85% yield. It was pleasing to find that the $Pd(OAc)_2$–Aphos-Y catalyst (*Condition B*) performed equally well, affording product **12** in 86% yield.

Table 5. Synthesis of densely functionalized trisubstituted alkenes by $Pd(OAc)_2$–Aphos-Y-catalyzed C(sp^3)–C(sp^2) coupling reactions.[a]



Entry	Alkene product	*t* [h]	Yield [%][b]
1		6 2[c]	**8a**: 85 **8a**: 84
2		2[c]	**8b**: 85
3		20	**9a**: 7[d]
4		2	**9b**: 90
5	 *Z*:*E* = 19:1	2	**9c**: 83[e]
6	 *Z*:*E* = 6:1	2	**9d**: 80[e]

[a] Reaction conditions are found in the Experimental Section. [b] Isolated yield based on the alkenyl iodides. [c] With 18 equiv. H_2O. [d] 75% of the alkenyl iodide was recovered. [e] Overall yield for the coupling and cleavage of the PMB group.



Scheme 2. Synthesis of the C13–C23 fragment of iriomoteolide-1a. *Condition A*: 1.6 equiv. **11**, 4 equiv. *t*BuLi, 6 equiv. 9-MeO-9-BBN, Et_2O/THF, –78 °C to room temp., 1.5 h; then 1 equiv. **10**, 6 mol-% $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, 18 mol-% Ph_3As, 4 equiv. Cs_2CO_3, 25 equiv. H_2O, DMF, room temp., 1 h (85%). *Condition B*: 1.2 equiv. **11**, 2.8 equiv. *t*BuLi, 3 equiv. 9-MeO-9-BBN, Et_2O/THF, –78 °C to room temp., 1.5 h; then 1 equiv. **10**, 5 mol-% $Pd(OAc)_2$, 7.5 mol-% Aphos-Y, 3 equiv. K_3PO_4, 18 equiv. H_2O, THF, room temp., 1 h (86%).

Conclusions

In summary, we have developed a general and efficient catalyst system consisting of $Pd(OAc)_2$–Aphos-Y[4a,4c] for the *B*-alkyl Suzuki–Miyaura cross-coupling reaction using 9-alkyl-9-BBN[1b] and the "9-MeO-9-BBN variant".[1f] The catalyst system functions under mild conditions in THF with K_3PO_4 or $K_3PO_4 \cdot 3H_2O$ as the base and without the use of an additional ligand (such as Ph_3As) or solvent (such as DMF). As exemplified by the analogous fragments used in the total synthesis of mycolactone[10b] and iriomoteolide-1a,[2,15] di- and trisubstituted alkenes **8**, **9**, and **12** possessing dense functionalities, such as double bonds, free hydroxy groups, *syn*- and *anti*-aldol subunits, or PMB and silyl protecting groups, can be synthesized at room temperature in good to excellent yields. The hemilability of Aphos-Y[4a] enables its efficient role in the catalytic cycle as dppf and Ph_3As do under the Johnson protocol, resulting in an efficient and reliable tool for the construction of the C(sp^3)–C(sp^2) bond. Application of the $Pd(OAc)_2$–Aphos-Y catalyst system in the total synthesis of natural products is in progress in our laboratories.

Experimental Section

Formation of the Alkyl Borinate: A flame-dried two-neck flask of 10 mL capacity was charged with the alkyl iodide (0.20 mmol) and was then evacuated and backfilled with argon (5 times). 9-MeO-9-BBN (1 M in hexanes, 0.60 mL, 0.60 mmol) and freshly distilled dry Et_2O (2 mL) were added with a syringe at room temperature. The colorless solution was cooled to –78 °C in a dry ice/acetone bath. After stirring for 5 min, *t*BuLi (1.6 M in heptane, 0.35 mL, 0.56 mmol) was rapidly added with a syringe in one portion at –78 °C. The resulting milky suspension was stirred for 10 min at the same temperature, and freshly distilled dry THF (2 mL) was added. The mixture turned clear, and the cooling bath was removed after stirring for 10 min. The mixture was stirred at room temperature for another 1.5 h to form a homogeneous pale yellow solution of the alkyl borinate.

Cross-Coupling Reaction: A 10 mL process vial was charged with $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), Aphos-Y (7.6 mg, 0.015 mmol), and K_3PO_4 (127.4 mg, 0.60 mmol) or $K_3PO_4 \cdot 3H_2O$ (159.8 mg, 0.60 mmol). The loaded vial was sealed with a cap containing a silicon septum and was evacuated and backfilled with argon (5 times) through a needle. A solution of the alkenyl halide (5.5 equiv. for Table 1 and 1.5 equiv. for Tables 2, 3, and 4) in degassed THF (2 mL) was added with a syringe, followed by the addition of H_2O (33 µL, 1.8 mmol or 66 µL, 3.6 mmol). The mixture was stirred at room temperature for 5 min, and then the alkyl borinate prepared as described above was transferred with a syringe. After being stirring at room temperature for the indicated time, the reaction mixture was filtered off through a plug of Celite and rinsed with EtOAc. The combined organic layer was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluting with EtOAc/hexane) to give the coupling product. For Table 5, 1.1–1.5 equiv. of the alkyl borinate were used per equiv. of alkenyl iodide.

Supporting Information (see footnote on the first page of this article): Representative procedures reported in the literature, product characterization data, images of the reaction mixture at various stages, and copies of NMR spectra.

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