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Oxygen-Promoted Palladium(II) Catalysis: Facile C(sp^2)–C(sp^2) Bond Formation via Cross-Coupling of Alkenylboronic Compounds and Olefins

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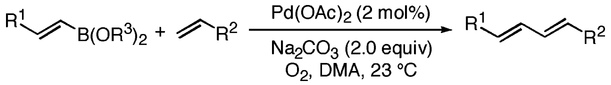
ABSTRACT



Oxygen-promoted Pd(II) catalysis facilitated the synthesis of conjugated dienes by cross-coupling of alkenylboronic compounds and various olefins including highly substituted alkenes and cyclohexenone. Under mild conditions, these versatile reactions were efficient and highly stereoselective.

In recent years, significant advances have been made in the molecular oxygen-promoted palladium catalysis for the use of oxidation of alcohols to carbonyl compounds.[1] However, there have been only a few reports on carbon−carbon bond formation,[2,3] and they have failed to offer a general synthetic method presumably due to poor understanding of the catalysis. We have pioneered novel C−C bond formation methods utilizing oxidative palladium catalysis to culminate in communications on the homocoupling protocol[4] and the first report on a cross-coupling method.[5]

Suzuki−Miyaura[6] and Stille reactions[7] have been utilized for the cross-coupling of alkenyl−alkenyl moieties to generate conjugated dienes. However, these reactions can be cumbersome since both coupling substrates should be stereoselectively prepared prior to coupling. The Heck reaction[8−10]

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[1] (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (b) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766. (c) Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188. (d) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725. (e) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475. (f) Brink, G. T.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636. (g) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185.

[2] For oxygen-promoted Pd-catalyzed homocoupling reactions, see: (a) Yoshida, H.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2003**, *44*, 1541. (b) Mukhopadhyay, S.; Rothenberg, G.; Lando, G.; Agbaria, K.; Kazanci, M.; Sasson, Y. *Adv. Synth. Catal.* **2001**, *343*, 455. (c) Hossain, K. M.; Kameyama, T.; Shibata, T.; Tagaki, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2415. (d) Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087. (e) Ohe, T.; Tanaka, T.; Kuroda, M.; Cho, C. S.; Uemura, S. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1851. (f) Smith, K. A.; Campi, E. M.; Jackson, W. R.; Marcuccio, S.; Maeslund, C. G. M.; Deacon, G. B. *Synlett* **1997**, 131.

[3] For oxygen-promoted Pd-catalyzed cross-coupling reactions, see: (a) Andappan, M. M. S.; Nilsson, P.; Larhed, M. *Chem. Commun.* **2004**, 218. (b) Zou, G.; Zhu, J.; Tang, J. *Tetrahedron Lett.* **2003**, *44*, 8709. (c) Dams, M.; De Vos, D. E.; Celen, S.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3512. (d) Matoba, K.; Motofusa, S.-I.; Cho, C. S.; Ohe, K.; Uemura, S. *J. Organomet. Chem.* **1999**, *574*, 3. (e) For Pd-catalyzed cross-coupling reactions with Cu(II) as an oxidant: Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A. *Org. Lett.* **2001**, *3*, 3313.

[4] (a) Parrish, J. P.; Jung, Y. C.; Floyd, R. J.; Jung, K. W. *Tetrahedron Lett.* **2002**, *43*, 7899. (b) Parrish, J. P.; Flanders, V. L.; Floyd, R. J.; Jung, K. W. *Tetrahedron Lett.* **2001**, *42*, 7729.

[5] (a) Jung, Y. C.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2231. (b) Parrish, J. P.; Jung, Y. C.; Shin, S. I.; Jung, K. W. *J. Org. Chem.* **2002**, *67*, 7127. For an application, see: (c) Furman, B.; Dziedzic, M. *Tetrahedron Lett.* **2003**, *44*, 8249.

[6] For reviews of the Suzuki−Miyaura reaction, see: (a) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

[7] For a review of the Stille reaction, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652.

[8] For reviews of the Heck reaction, see: (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (c) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449. (d) Gürtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107. (e) Kondolff, I.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2003**, *44*, 8487.

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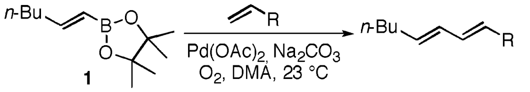
has been considered as the best alternative to avoid this problem. Due to inefficiency, poor selectivities, and harsh conditions, Heck coupling has been limited in use, especially with substituted olefins. Recently, Fu[9a] and Hartwig[9b] reported mild Heck conditions for the coupling of aryl halides with olefins. However, the reaction conditions require phosphine ligands and longer reaction times (20−77 h). In this account, we report a new synthetic method to address these shortcomings and offer a generally applicable protocol.

Just recently, we discovered a mild means of oxidative palladium catalysis, effecting carbon−carbon bond formation between alkenylboron compounds and various olefins. Monosubstituted olefins were facile in coupling, and the yields and stereoselectivities were generally high (Table 1).

Table 1. Coupling of Hexenyl Boronic Ester **1** with Various Alkenes



entry	R	product	yield[a] (%)
1	$CO_2{}^tBu$	**2**	A: 85
			B: 90
2	Ph	**3**	A: 82
			B: 92
3	CH_2OBn	**4**	A: 81[b]
			B: 91
4	CN	**5**[c]	A: 85

[a] A: one-pot condition with 10 mol% of Pd(OAc)$_2$, 3 h. B: slow addition protocol with 2 mol% of Pd(OAc)$_2$, 6 h. [b] 2 mol% of Pd(OAc)$_2$. [c] *E*/*Z* ratio is 3:2, as determined by ^{1}H NMR.

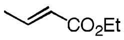
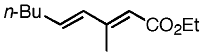
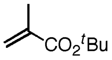
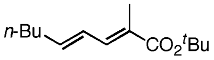
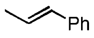
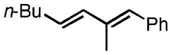
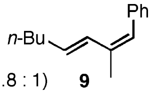
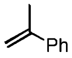
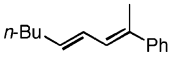
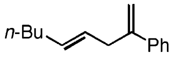
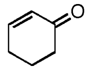
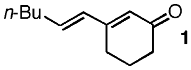
The reactions with *tert*-butyl acrylate and styrene afforded (*E*,*E*)-dienes **2** and **3**, respectively (entries 1 and 2). Furthermore, the reaction with unreactive allyl benzyl ether took place, successfully delivering (*E*,*E*)-diene **4** (entry 3). For comparison, we conducted the Heck reaction of *trans*-iodohexene with allyl benzyl ether under Jeffery conditions,[10] known as mild Heck reaction conditions, and confirmed that this method failed to afford any coupling product.[11] The coupling reaction with acrylonitrile provided an isomeric mixture of diene **5** in 85% yield (entry 4).[12]

Because homocoupling[4] was expected as the major side reaction, we employed two different conditions, where boron compounds were added in the beginning (condition A) and where slow addition of organoborons was utilized (condition B). It was envisioned that a low concentration of boronic ester would decrease the probability of the reaction between the boronic ester and the incipient alkenylpalladium intermediate, resulting in avoidance of homocoupling. Condition B averted homocoupling to offer higher yields and cleaner products, allowing for easy purification while the one-pot condition was convenient and pragmatic. The details of the conditions will be discussed in a separate full account.

Due to low yields and stereoselectivity, substituted olefins have been poor substrates for Heck reactions. Thus, the remedy for this chronic problem can be highly valuable, prompting us to probe the feasibility of oxygen-promoted Pd(II) catalysis (Table 2). At ambient temperatures, ethyl crotonate and *tert*-butyl methacrylate afforded the desired (*E*,*E*)-dienes **6** and **7** in high yields (entries 1 and 2). In the case of substituted styrenes, coupling proceeded smoothly at 50 °C (entries 3 and 4). With *trans*-*β*-methylstyrene, the mixture of (*E*,*E*)- and (*E*,*Z*)-dienes **8** and **9** was obtained in an 8.8:1 ratio in 88% overall yield. The reaction with α-methylstyrene furnished an inseparable mixture of **10** and **11** in 84% yield via two possible *β*-elimination pathways during the reaction cycle.[8b] Similarly to the previous examples, *E*-selectivity was high as expected.

Table 2. Coupling of Boronic Ester **1** with Highly Substituted Alkenes

$$\mathbf{1} \xrightarrow[\text{Na}_2\text{CO}_3\text{, DMA, O}_2\text{, 23 °C}]{\text{olefin, Pd(OAc)}_2} \text{product}$$

entry	olefin	product (yield)[a]
1		 **6** (79%)
2		 **7** (81%)
3[b, c]		 +  **8** (88%, 8.8 : 1) **9**
4[b, d]		 +  **10** (84%, 1 : 3.7) **11**
5		 **12** (76%)

[a] Condition B. [b] Reaction temperature: 50 °C. [c] *E*/*Z* ratio was determined by ^{1}H NMR. [d] Internal/terminal alkene ratio was determined by ^{1}H NMR.

Contrary to acyclic alkenes, Heck reactions of cyclohexenone with aryl halides afforded a mixture of Heck coupling product and conjugate addition product via a palladium enolate intermediate.[13] Recently, Myers reported a clever Heck-type arylation via decarboxylative palladation at high temperature (>80 °C).[14] According to these previous reports,

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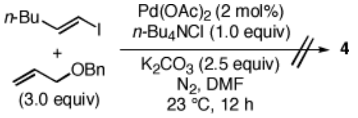
(9) (a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (b) Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677. (c) Berthiol, F.; Doucet, H.; Santelli, M. *Synlett* **2003**, 841.

(10) (a) Jeffery, T. *Tetrahedron Lett.* **1993**, *34*, 1925. (b) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667. (c) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1247.

(11)

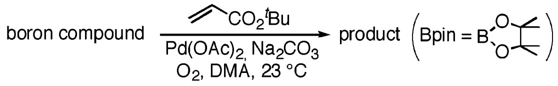


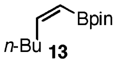
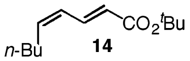
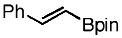
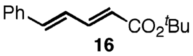
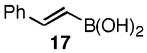
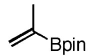
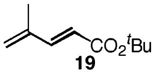
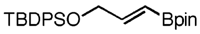
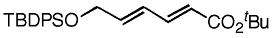
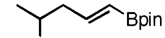
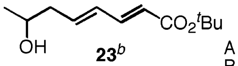
(12) In most cases, the Heck reaction of acrylonitrile afforded *E*- and *Z*-coupling isomers as a result of a small difference in the two transition states for concerted Pd−H syn-elimination of the migratory insertion intermediate due to its smaller size. See: (a) ref 8b. (b) Crisp, G. T.; Glink, P. T. *Tetrahedron* **1994**, *50*, 2623. (c) Kim, J.-I.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1981**, *46*, 1067.

Heck-type catalysis is challenging with cyclohexenone, and there is no successful case of alkenylation to the best of our knowledge. However, our protocol delivered the vinylated product **12** in 76% yield without the concomitant formation of the conjugate addition product (entry 5). The mildness of our oxidative catalysis is presumed to be responsible for its success, most likely through an alternate mechanism, which will be the target of a separate investigation in the future.

To further examine the scope and limitation of this method, we conducted coupling reactions between various alkenylboron compounds and *tert*-butyl acrylate (Table 3). Under both developed conditions, *cis*-hexenyl pinacolboronic ester[15] led to the stereoselective formation of (*E*,*Z*)-diene **14** (entry 1). These results implied retention of the geometry in alkenylboron compounds during the catalytic process. Pinacolboronic ester **15**[16] afforded (*E*,*E*)-diene **16** exclusively, whereas the corresponding boronic acid **17** gave 80−85% of **16** along with the homocoupling compound (entries 2 and 3). This finding indicated that alkenylboronic acids were less resistant to homocoupling as compared to the corresponding esters. Nonetheless, both boronic acids and esters were well-suited for oxidative Pd(II) catalysis in most cases.

Table 3. Coupling of Various Alkenylboron Compounds



entry	boron compound	product	yield (A, B)[a]
1	 **13**	 **14**	A: 86% B: 86%
2	 **15**	 **16**	A: 86% B: 89%
3	 **17**	**16**	A: 80% B: 85%
4	 **18**	 **19**	A: 86% B: 91%
5	 **20**	 **21**	A: 83% B: 87%
6	 **22**	 **23**[b]	A: 96% B: 91%

[a] A: one-pot condition with 10 mol% of Pd(OAc)$_2$, 3 h. B: slow addition protocol with 2 mol% of Pd(OAc)$_2$, 6 h. [b] TMS group was deprotected during column chromatography.

In addition, highly substituted alkenylboron compounds were compatible with this method. Reaction of sterically hindered 1-methylvinyl pinacolboronic ester (**18**)[17] took place efficiently to provide **19** exclusively and stereoselectively (entry 4). The boronic esters **20** and **22** containing alcohol functionalities also successfully gave rise to the corresponding (*E*,*E*)-dienes **21** and **23** in high yields (entries 5 and 6). Therefore, such highly functionalized boron compounds can be used for the introduction of versatile functional groups to the alkene compounds for further manipulation.

In conclusion, oxidative palladium(II) catalysis of vinyl boron compounds with various alkenes provided the corresponding conjugated dienes in good to excellent yields under mild reaction conditions. Furthermore, expensive ligands and additives are unnecessary, while oxygen finds utility as an environmentally benign, economical reoxidant of the palladium catalyst. Additionally, high stereoselectivity as well as functional group tolerance are worthy of note. This new protocol is advantageous over the conventional and modified Heck conditions and allows a wide array of substrates, otherwise found difficult or impossible to react smoothly. Due to its easy and convenient nature, this protocol is highly practical, holding great promise for wide use. Mechanistic insight and applications will be reported in due course.

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Supporting Information Available: Representative experimental procedures with spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Costa, A.; Najera, C.; Sansano, J. M. *J. Org. Chem.* **2002**, *67*, 5216. (b) Gelpke, A. E. S.; Veerman, J. J. N.; Goedheijt, M. S.; Kamer, P. C. J.; van Leeuwen, P. W. M. N.; Hiemstra, H. *Tetrahedron* **1999**, *55*, 6657. (c) Genet, J. P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715.

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(15) Ohmura, T.; Yamamoto, Y.; Miyaura, M. *J. Am. Chem. Soc.* **2000**, *122*, 4990.

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(17) (a) Molander, G. A.; Ribagorda, M. *J. Am. Chem. Soc.* **2003**, *125*, 11148. (b) Ueda, M.; Saitoh, A.; Miyaura, N. *J. Organomet. Chem.* **2002**, *642*, 145.