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Oxygen-Promoted Pd(II) Catalysis for the Coupling of Organoboron Compounds and Olefins

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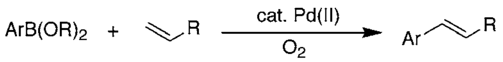
ABSTRACT



Reported herein is a mild and efficient Pd(II) catalysis, leading to the formation of carbon–carbon bonds between a broad spectrum of organoboron compounds and alkenes. Molecular oxygen was employed to reoxidize the resultant Pd(0) species back to Pd(II) during catalytic cycles. This oxygen protocol promoted the desired Pd(II) catalysis, whereas it retarded competing Pd(0) catalytic pathways such as Heck or Suzuki couplings.

The Heck reaction is one of the most widely used standard tools for carbon−carbon bond-forming reactions in organic synthesis.[1] In addition to the conventional Heck reaction of unsaturated compounds with organic halides and triflates as an electrophile, the use of nucleophilic organometallic reagents such as organosilanes,[2] organoantimony,[3] and organotins[4] have attracted much attention. Our group has also reported an improved method for the aryl−alkenyl coupling by utilizing arylstannanes via Pd(II) catalysis in the presence of oxygen or Cu(II) oxidants.[5] However, these organometallic reagents and their byproducts are highly toxic[6] and difficult to remove.[7] Comparatively, organoboron reagents are less toxic,[8] stable in air, and easily accessible; thus, it is worthwhile to explore their synthetic utility for the Heck-type reactions. Uemura reported a Pd(0)-catalyzed cross-coupling of boronic acids and alkenes via oxidative addition of Pd(0) to a carbon−boron bond.[9] In this case, the reactions required long reaction times (20−38 h) and acetic acid as a solvent. On the other hand, Mori reported a Pd(II)-catalyzed pathway for the reaction between organoboron reagents and alkenes in the presence of $Cu(OAc)_2$ as an oxidant, which involved transmetalation as the initial step in the catalytic cycle.[10] However, the reaction conditions remained harsh (100 °C, DMF) and excess Cu(II) reagent was utilized as an oxidant, generating a poisonous waste.[11]

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[1] For reviews, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Ikeda, M.; El Bialy, S. A. A.; Yakura, T. *Heterocycles* **1999**, *51*, 1957. (c) Shibasaki, M.; Boden, C. O. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371. (d) Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447. (e) Negishi, E.; Coperet, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (f) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (g) Heck, R. F. *Org. React.* **1982**, *27*, 345. (h) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146.

[2] (a) Hirabayashi, K.; Nishihara, Y.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, *39*, 7893. (b) Hirabayashi, K.; Kondo, T.; Toriyama, F.; Nishihara, Y.; Mori, A. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 749. (c) Hirabayashi, K.; Ando, J.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1409.

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[11] For toxicology studies, see; (a) Beritic, T.; Dimov, D. *Arhiv Za Higijenu Rada I Toksikologiju* **1970**, *21* (3), 285. (b) Grebennikov, E. P. *Sovetskaia Meditsina* **1969**, *32* (4), 94.

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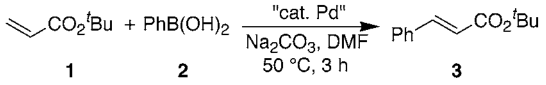
The use of molecular oxygen as a sole reoxidant has been reported in palladium-catalyzed methodologies, encompassing oxidation of alcohols to carbonyl compounds,[12] cyclization of olefinic compounds,[13] and synthesis of hydrogen peroxide.[14] Recently, arylzinc compounds,[15] triarylbismuthines,[16] and arylboronic acids[17] were reported to be dimerized in the presence of oxygen. Our group has also reported the use of oxygen for the oxidative homocouplings of aryl and akenylboronic acids.[18] The mechanistic aspect of aerobic oxidation of palladium catalysts via peroxopalladium(II) species has been well rationalized by Stahl.[19]

Described herein is the use of molecular oxygen as the catalyst oxidant in Pd(II)-catalyzed couplings of organoboron compounds and olefins. The presence of oxygen was critical for catalyst reoxidation as we reported earlier.[5,18] As shown in Table 1, a low yield of the product was obtained when the reaction was run under a nitrogen condition (entry 1). Under air and oxygen, the product was obtained in 44 and 87% yields, respectively (entries 2 and 3). In a further study, it was found that Pd(OAc)$_2$ was the choice of the catalyst and that Pd(0) catalyst was also effective in delivering the desired product in 85% yield in the presence of oxygen (entry 4), whereas no product was observed under nitrogen conditions (entry 5). Comparable results were obtained when 5 mol% Pd(OAc)$_2$ was used.[20] From these results, we inferred that molecular oxygen played a pivotal role in Pd(II)-catalyzed reaction through the reoxidation of Pd(0) species to Pd(II). Under these aerobic conditions, Na$_2$CO$_3$ proved to be the best, and several bases such as NaOAc, Cs$_2$CO$_3$, and K$_2$CO$_3$ were effective as well. DMF was the choice of the solvent, whereas protic solvents, including water and EtOH, delivered biaryls via homocoupling reaction exclusively.[17] Regarding temperature, optimal results were obtained at 50 °C, while longer reaction times (12−24 h) were required to complete the reactions at 23 °C; increased amounts of homocoupling products were produced at higher temperatures such as 100 °C. When arylboronic acids were utilized as coupling partners, phenols were sometimes observed as minor side products along with the aforementioned biaryls.[17c]

Table 1. Effect of Oxygen

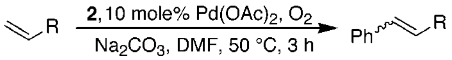


entry	Pd catalyst[a]	oxidant	yield
1	Pd(OAc)$_2$	none[b]	12%
2	Pd(OAc)$_2$	air	44%
3	Pd(OAc)$_2$	O$_2$	87%
4	Pd$_2$(dba)$_3$	O$_2$	85%
5	Pd$_2$(dba)$_3$	none[b]	0%

[a] Amount used = 10 mol%. [b] N$_2$ condition.

To examine substrate versatility, we first probed the effect of electron density on olefins as shown in Table 2. *tert*-Butyl acrylate (**1**), which is an electron-poor alkene, was converted smoothly to *tert*-butyl *trans*-cinnamate in 87% yield (entry 1). An electron-rich alkene, *n*-butyl vinyl ether (**4**) delivered 73% of β-butoxystyrene with an isomeric ratio of 2/1 at 23 °C after 10 h (entry 2). Styrene (**5**), an aromatic nonallylic alkene, reacted with phenylboronic acid to give 90% of *trans*-stilbene (entry 3). Allylbenzene (**6**) was converted to (*E*)-1,3-diphenylpropene smoothly in 86% yield (entry 4). This newly developed protocol was effective regardless of the electron density on olefins and was regioselective to provide an (*E*)-isomer exclusively except with an electron-rich alkene.

Table 2. Effect of Electron Density on Olefins



entry	R	yield	*E*/*Z* ratio
1	CO$_2$^{t}Bu (**1**)	87%	(*E*)-only
2	OBu (**4**)	73%[a]	2/1
3	Ph (**5**)	90%	(*E*)-only
4	CH$_2$Ph (**6**)	86%	(*E*)-only

[a] *n*-Butyl vinyl ether (2.0 equiv), 23 °C, 10 h. Yields were calculated on the basis of boronic acid.

After screening olefins, we investigated the scope and limitation of organoboron compounds as summarized in Table 3. 4-Methoxyphenylboronic acid (**7**), which has an electron-donating group, and 3-acetylphenylboronic acid (**8**), which has an electron-withdrawing group, showed similar reactivities, furnishing the desired arylated products in 79

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[12] (a) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766. (b) Brink, G. T.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636. (c) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185.

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[16] Ohe, T.; Tanaka, T.; Kuroda, M.; Cho, C. S.; Ohe, K.; Uemura, S. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1851.

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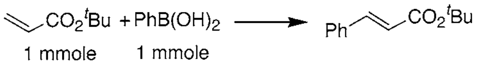
[18] Parrish, J. P.; Jung, Y. C.; Floyd. R. J.; Jung, K. W. *Tetrahedron Lett.* **2002**, *43*, 7899.

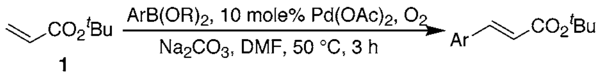
[19] (a) Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188. (b) Stahl, S. S.; Thorman, J. L.; de Silva, N.; Guzei, I. A.; Clark, R. W. *J. Am. Chem. Soc.* **2003**, *125*, 12.

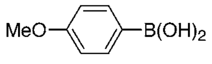
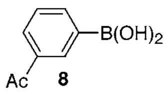
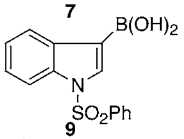
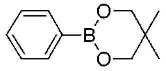
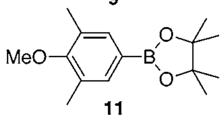
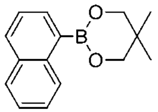
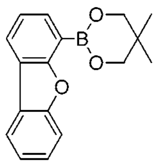
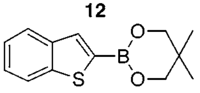
[20] Reaction conditions: O$_2$, Pd(OAc)$_2$, Na$_2$CO$_3$, DMF, 50 °C, 3 h.



Pd(OAc)$_2$	10 mole%	5 mole%	2.5 mole%	1 mole%
yield	81%	79%	66%	42%
time	3 h	5 h	24 h	24 h

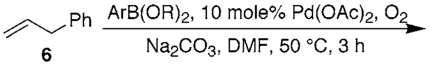
Table 3. Various Aryl Boronic Acids Coupled with *tert*-Butyl Acrylate



ArB(OR)2	yield	ArB(OR)2	yield
 **7**	79%	 **8**	78%
 **9**	75%	 **10**	92%
 **11**	79%	 **12**	85%
 **13**	77%	 **14**	52%

and 78% yields, respectively. Indole derivatization on the C-3 position was also possible by coupling 1-(phenylsulfonyl)-3-indoleboronic acid (**9**) with alkene **1** in good yield. We found that arylboronates functioned as benign coupling partners for this methodology, decreasing the formation of side products[17] such as biaryls and phenols.[21] 2,2-Dimethyl-1,3-propanediol benzeneboronate (**10**) was prepared from the corresponding arylboronic acids[22] and subjected to the Pd(II) catalysis, giving rise to the exclusive synthesis of *tert*-butyl *trans*-cinnamate. Likewise, 3,5-dimethyl-4-methoxybenzene catechol boronate (**11**) furnished the corresponding arylated product in 79% yield. No biphenyl product was observed at all. We were also interested in the reaction of fused aromatic and heterocyclic boronic acids. The arylboronates of 1-naphthaleneboronic acid (**12**) and 4-dibenzofuranboronic acid (**13**) afforded 85 and 77% yields of the desired arylated products, respectively. Next, the coupling with 2,2-dimethyl-1,3-propanediol boronate of thianaphthene-2-boronic acid (**14**) was smooth with moderate yield.

Table 4. Various Aryl Boron Reagents Coupled with Allylbenzene



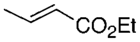
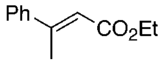
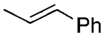
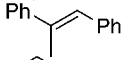
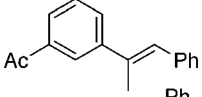
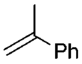
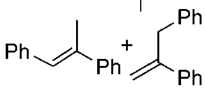
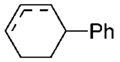
entry	ArB(OR)2	yield
1	**7**	80% (1/1.0)[a]
2	**8**	86% (1/1.6)[a]
3	**11**	83% (1/1.3)
4	**12**	85% (1/5.4)
5	**13**	82% (1/3.0)[a]

[a] Reaction solvent = CH_3CN.

Table 4 shows the reactions of allylbenzene (**6**) with various boron compounds. Various arylboron compounds were coupled with allylbenzene smoothly to deliver the mixture of the double-bond-migrated isomers. Electron density in arylboronic acids did not have a significant influence on the results, still giving the desired products in high yields (entries 1 and 2). Arylboronates containing bulky fused aromatic or heterocyclic groups were equally effective in this protocol to provide the regioisomeric mixtures (entries 3−5).

Table 5. Coupling with Highly Substituted Olefins

$$\text{Olefin} \xrightarrow[\text{Na}_2\text{CO}_3\text{, DMF, 50 °C, 3 h}]{\textbf{2}\text{, 10 mole\% Pd(OAc)}_2\text{, O}_2} \text{Product}$$

entry	olefins	products		yield
1	 (**15**)		(**19**)	70%
2	 (**16**)		(**20**)	82%
3	**16**		(**21**)	86%[a]
4	 (**17**)		(**22**)	69% (1/1.5)
5	 (**18**)		(**23**)	48% (1/2)

[a] 3-Acetylphenylboronic acid was used as a coupling partner.

Having obtained satisfactory results with monosubstituted alkenes, we then turned our attention to the arylation of a highly substituted system as depicted in Table 5. Ethyl *trans*-crotonate (**15**) reacted with phenylboronic acid to give 70% yield of ethyl *β*-methylcinnamate with exclusive (*E*)-configuration (entry 1). *trans*-*β*-Methylstyrene (**16**) reacted smoothly with both phenylboronic acid and 3-acetylphenylboronic acid to furnish the corresponding trans-α-methylstilbenes in high yields (entries 2 and 3). Conversely, α-methylstyrene (**17**) delivered an inseparable mixture of *trans*-α-methylstilbene and α-benzylstyrene in 69% yield in a ratio of 1/1.5 (entry 4). Cyclohexene (**18**), a cyclic disubstituted olefin, was also effective in our protocol to furnish a 1/2 mixture of 3-phenylcyclohexene and 4-phenyl-

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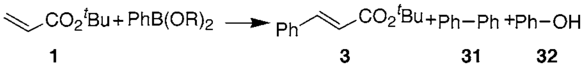
[21] Reaction conditions : O_2, 10 mol % $Pd(OAc)_2$, Na_2CO_3, DMF, 50 °C, 3 h.



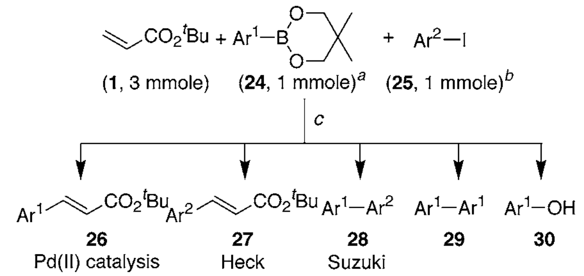
PhB(OR)2 (1.0 eq)	3	31	32
2	81%	7%	5%
10	90%	4%	trace

[22] Shi, B.; Boyle, R. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, *11*, 1397.

cyclohexene in 48% yield (entry 5). These data implied that this oxygen protocol could be applicable to most highly substituted olefin systems, resulting in outstanding (*E*)-selectivity.

To elucidate the catalytic pathway of this oxygen protocol, we conducted the competition reactions using *tert*-butyl acrylate (**1**, 3 mmol),[23] 2,2-dimethyl-1,3-propanediol boronate of 3-acetylphenylboronic acid (**24**, 1 mmol), and 2-iodoanisole (**25**, 1 mmol). As shown in Scheme 1, 71% of Pd(II) catalysis product **26** and 26% of Heck coupling product **27** were isolated using oxygen conditions, while only 18% of **26** was isolated together with Heck product as the major product using oxygen free conditions (argon atmosphere). The Suzuki coupling product[24] **28** was detected in low yield under both conditions. The side products,[17,21] **29** and **30**, were detected with oxygen conditions in 5 and 6% yields, respectively. From these results, we inferred that molecular oxygen promoted the desired Pd(II) catalysis and suppressed the competing Pd(0) catalytic pathways.

Scheme 1. Competition Reaction



	26 Pd(II) catalysis	27 Heck	28 Suzuki	29	30
O_2[d]	71%	26%	0.5%	5%	6%
Ar	18%	74%	1%	0%	0%

[a] Ar^1 = 3-acetylphenyl. [b] Ar^2 = 2-methoxyphenyl. [c] $Pd(OAc)_2$ (20 mol%), Na_2CO_3, DMF, 50 °C, 6 h. [d] Oxygen was delivered by bubbling into the reaction solution slowly.

Although the details are not yet known, we propose a mechanistic catalytic cycle as shown in Figure 1. Presumably, the Pd(II) works as the active species throughout the reaction as suggested by Mori.[10] As delineated in cycle I, transmetalation of arylboronic acid gives Ar−Pd−L, and migratory insertion of the olefin is followed by β-hydride elimination to produce the desired product and Pd(0) species. Molecular oxygen then oxidizes the Pd(0) to Pd(II) species, possibly via a peroxopalladium(II) complex.[19] The high efficiency of the Pd(0) complex, $Pd_2(dba)_3$, can be explained by this scheme involving the oxidation step of Pd(0) species by oxygen. The preference of our oxygen-promoted Pd(II) catalysis to the conventional Heck or Suzuki catalysis under an oxygen atmosphere can also be explained by this reaction scheme involving rapid oxidation of Pd(0) species. Therefore, Pd(0)-catalyzed oxidative addition of 2-iodoanisole can be suppressed to follow Heck or Suzuki pathways (cycle II).

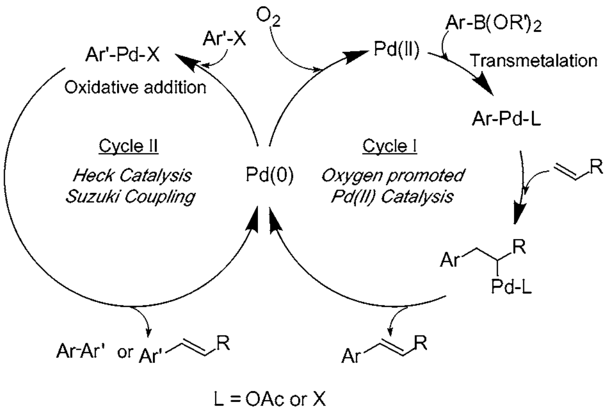


Figure 1. Reaction cycle.

In summary, we elaborated a mild and efficient Pd(II) catalysis, an organometallic variation of Heck reaction. Our newly developed protocol uses an environmentally friendly and inexpensive oxidant, molecular oxygen, and provides various aryl−alkenyl coupling products from a broad spectrum of olefins and arylboron compounds in good to excellent yields. This oxygen protocol demonstrates a new mechanistic concept that oxygen would promote the Pd(II) catalytic pathway and in turn suppress the competing Pd(0) catalysis encompassing Heck or Suzuki couplings.

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Supporting Information Available: Representative experimental procedure and copies of the spectral data for the representative products in schemes and tables are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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[23] Suzuki coupling product was detected in low yield from boron reagent and halide; thus, excess alkene was used to maximize the efficiency of the other reactions.

[24] In a separate Suzuki coupling reaction between **24** and **25**, the desired product **28** was isolated in 31% yield under oxygen and 71% yield under argon conditions (20 mol % $Pd(OAc)_2$, Na_2CO_3, DMF, 50 °C, 6 h).