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Oxidative Palladium(II) Catalysis: A Highly Efficient and Chemoselective Cross-Coupling Method for Carbon−Carbon Bond Formation under Base-Free and Nitrogenous-Ligand Conditions

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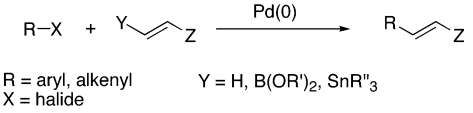
Abstract: We report herein the development of a general and mild protocol of oxygen-promoted Pd(II) catalysis resulting in the selective cross-couplings of alkenyl- and arylboron compounds with various olefins. Unlike most cross-coupling reactions, this new methodology works well even in the absence of bases, consequently averting undesired homo-couplings. Nitrogen-based ligands including dimethyl-phenanathroline enhance reactivities and offer a highly efficient and stereoselective methodology to overcome challenging substrate limitations. For instance, oxidative palladium(II) catalysis is effective with highly substituted alkenes and cyclic alkenes, which are known to be incompatible with other known catalytic conditions. Most examined reactions progressed smoothly to completion at low temperatures and in short times. These interesting results provide mechanistic insights and utilities for a new paradigm of palladium catalytic cycles without bases.

Introduction

Transition metal-catalyzed coupling reactions are extremely powerful tools for carbon−carbon bond formation and have been widely utilized in a great number of syntheses. In particular, palladium-catalyzed arylation and vinylation of alkenes known as Mizoroki−Heck (Y = H),[1] Suzuki−Miyaura (Y = B(OR′)$_2$),[2] and Stille (Y = SnR″$_3$)[3] reactions have become classical vehicles to various carbon−carbon bonds (Scheme 1). Among these methods, the Heck reaction has been considered the best choice presumably because Suzuki−Miyaura and Stille couplings often require stereoselective syntheses of both substrates prior to couplings. However, this methodology has been limited primarily to monosubstituted olefins due to inefficiency, low selectivity, and harsh reaction conditions when used for di- and trisubstituted olefins.

To overcome these limitations, two distinct approaches have been pursued by a number of research groups. In one approach, mild conditions have been sought by changing reaction parameters as seen in recent reports by Fu[4a] and Hartwig.[4b] On the contrary, other groups investigated alternative halide surrogates

Scheme 1



such as diazonium halide salt,[5] triflate,[6] acid chloride,[7] telluronium salt,[8] etc. These efforts to find new conditions have provided high efficiency under mild conditions; yet these methods are not widely used. Our group has pursued a combined strategy of aforementioned approaches by changing halides to boronic acids[9] and modifying the reaction parameters such as atmosphere.[10] This approach presents a novel paradigm for these types of coupling, which stems from a change in reaction mechanism, Pd(0) to Pd(II) catalysis under an oxygen atmosphere.

Recently, we reported early developments of an oxygen-promoted palladium(II) catalysis for the cross-coupling of

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

(2) For reviews of the Suzuki−Miyaura reaction, see: (a) Miyaura, N. *J. Organomet. Chem.* **2002**, *653*, *54*. (b) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, *11*. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, *147*. (d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

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

(4) (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.

(5) (a) Akiyama, F.; Miyazaki, H.; Kaneda, K.; Teranishi, S.; Fujiwara, Y. *J. Org. Chem.* **1980**, *45*, 2359. (b) Kikukara, K.; Nagira, K.; Wada, F.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31. (c) Sengupta, S.; Bhattacharyya, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1943.

(6) (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (b) Fu, X.; Thiruvengadam, T. K.; Zhang, F. *Tetrahedron Lett.* **2002**, *43*, 573. (c) Fu, X.; Zhang, S.; Yin, J.; Schumacher, D. P. *Tetrahedron Lett.* **2002**, *43*, 6673. (d) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704. (e) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 194. (f) Klapars, A.; Campos, K. R.; Chen, C.-Y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185. (g) Hanse, A. L.; Skrydstrup, T. *Org. Lett.* **2005**, *7*, 5585.

(7) (a) Blaser, H.-U.; Spencer, A. *J. Organomet. Chem.* **1982**, *233*, *267*. (b) Spencer, A. *J. Organomet. Chem.* **1983**, *247*, *117*. (c) Spencer, A. *J. Organomet. Chem.* **1984**, *270*, *115*.

(8) Zeni, G.; Lu, D. S.; Panatieri, R. B.; Braga, A. L. *Chem. Rev.* **2006**, *106*, 1032.

(9) As compared to the time when Heck discovered the original conditions, there are currently an astronomical number of commercially available boronic acids and esters.

10.1021/ja063710z CCC: $33.50

Scheme 2

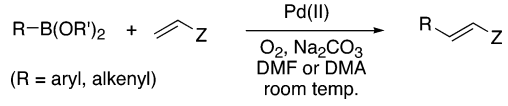
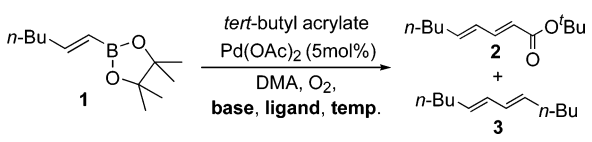


Table 1. Coupling of 1-Hexenyl Boronic Ester **1** with *tert*-Butyl Acrylate under Various Conditions



					yield (%)	
entry	base	ligand	temp (°C)	time (h)	**2**	**3**
1	Na_2CO_3		23	3	85	10
2			50	6	95	
3	-	phen[a]	50	2	98	

[a] phen = 1,10-phenanthroline.

organoboron compounds and alkenes to afford aryl−alkene and alkene−alkene compounds (Scheme 2).[11] In this carbon−carbon bond formation protocol, the most characteristic feature is utilization of molecular oxygen as a reoxidant of palladium(0) species.[13] Coupling reactions proceed smoothly with various substrates, and the reactions are highly efficient and stereoselective presumably due to mildness of the reaction conditions employed. In this definitive report, we offer general conditions for wide applications.

As representatively shown in Table 1, we have discovered benign conditions to enhance the desired cross-coupling process. Our early studies on oxidative Pd(II) catalysis exhibited superior activities and selectivities; however, these conditions accompanied homo-couplings to a small extent (entry 1).[14] Although these undesired homo-coupled products can be easily separated out by column chromatography, it would be ideal to avoid them for wide application, especially in library generation. In this context, we embarked on efforts to eliminate homo-coupling products by scrutinizing possible mechanisms and control elements.

(10) 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.

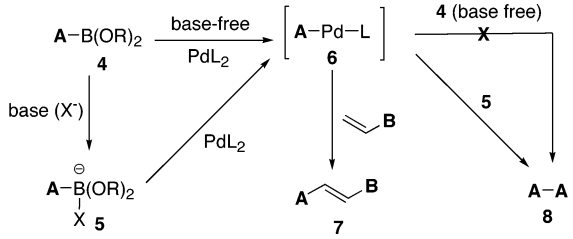
(11) (a) Yoon, C. H.; Yoo, K. S.; Yi, S. W.; Mishra, R. K.; Jung, K. W. *Org. Lett.* **2004**, *6*, 4037. (b) Jung, Y. C.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2231. (c) Parrish, J. P.; Jung, Y. C.; Shin, S. I.; Jung, K. W. *J. Org. Chem.* **2002**, *67*, 7127.

(12) (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.

(13) Adamo, C.; Amatore, C.; Ciofini, L.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829.

(14) 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.

Scheme 3



First, we considered the value of using bases. Reactions run in the absence of base consequently yielded cross-coupled compound **2** without any concomitant formation of **3** (entry 2). Despite the success, the base-free conditions needed a longer reaction time. Meanwhile, the palladium catalyst started to precipitate out. Therefore, we next pursued stabilizing the palladium catalysts and maximizing their catalytic efficiency. This goal was successfully achieved by adopting amine ligands such as 1,10-phenanthroline resulting in the exclusive formation of the desired cross-coupling product in just 2 h (entry 3).[15]

We believe that these newly developed methods can serve as the optimal conditions for these types of cross-coupling reactions. The current account addresses these control elements, the scope of each methodology, and mechanistic insights. On the basis of the observed results, a new mechanism is proposed herein to account for the desired catalytic cycle, avoidance of byproducts, base-free and ligand-present conditions, and most importantly the mildness and efficiency relative to known methodologies.

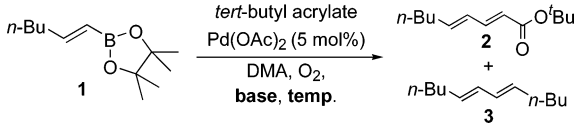
Results and Discussion

1. Cross-Coupling Reaction of Alkenylboron Compounds and Olefins. 1.1. Base Effect on the Cross-Coupling Reaction. Generally, bases are well known to be a pivotal component in palladium-catalyzed coupling reactions such as the Miyaura−Suzuki reaction.[2] The role of the bases in these reactions is to facilitate transmetallation of organoboron compounds via formation of organoborate salts resulting in the enhancement of coupling reactions. Likewise, in our protocol, the reactive borate salts **5** should accelerate the coupling processes as shown in Scheme 3. However, homo-coupled compounds **8** were concomitantly formed albeit in low yields due to the reactive borate salts **5**. Therefore, we anticipated exclusive cross-coupling by avoiding generation of reactive borate salts. On the basis of this assumption, we conducted oxidative Pd(II) cross-coupling reaction in the absence of bases, and the results are summarized in Table 2.

We examined the base effect on the cross-coupling of *trans*-1-hexenyl pinacolboron ester (**1**) and *tert*-butyl acrylate. The cross-coupling reaction in the presence of Na_2CO_3 as a base at room temperature provided 85% yield of conjugated diene compound **2** and 10% of homo-coupled compound **3** (entry 1). At a higher temperature, 50 °C, although reaction rate was accelerated, the yield of homo-coupled compound was also increased to 23% (entry 2). In the absence of a base, the reactivity was attenuated significantly to effect low conversion; however, the desired cross-coupling was observed exclusively (entry 3). Hence, an elevated temperature was required to

(15) Without amine ligands, the reaction mixture turned black, while the solution stayed clear in the presence of amine ligands.

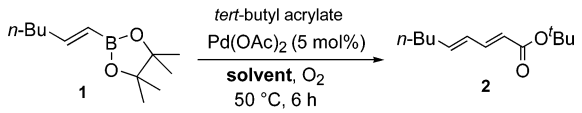
Table 2. Effect of Bases and Temperature on the Cross-Coupling Reactions of Alkenyl Boronic Ester with Alkene[a]



entry	base	temp (°C)	time (h)	yield (%) 2	3
1[b]	Na_2CO_3	23	3	85	10
2[b]	Na_2CO_3	50	1	75	23
3		23	6	17	
4		50	6	95	

[a] All reactions were carried out with **1** (0.5 mmol), *tert*-butyl acrylate (1.5 mmol), and $Pd(OAc)_2$ (5 mol %) in DMA (dimethylacetamide, 2.5 mL). [b] Na_2CO_3 (1.0 mmol).

Table 3. Effect of Solvents on the Cross-Coupling Reactions of Alkenyl Boronic Ester with Alkene under Base-Free Conditions



entry	solvent	yield (%)
1	**DMA**	**95**
2	CH_3CN	89
3	DMF	92
4	THF	12
5	toluene	17

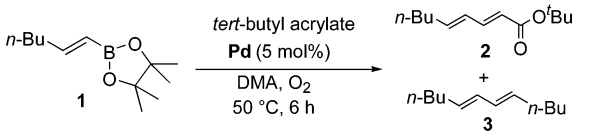
facilitate the catalysis. At 50 °C, the cross-coupling reaction proceeded smoothly to give 95% yield of the desired diene compound **2**, and no homo-coupled compound **3** was detected (entry 4). These results implied that the homo-coupled reaction should be prohibited under the base-free conditions due to the avoidance of the reactive borate salts as we hypothesized.

On the basis of these results, we screened the reaction conditions by varying solvents and palladium catalysts to determine optimal base-free conditions (Table 3). In the cases of THF and toluene, the reactions were incomplete even after 36 h, and the yields were very low (entries 4, 5). However, in polar solvents such as DMA, acetonitrile, and DMF, the desired (*E*,*E*)-conjugated diene **2** was obtained in excellent yields (entries 1−3). The homo-coupled product was not detected at all in any of those cases.

The effect of the palladium catalyst was investigated as demonstrated in Table 4. In the case of $PdCl_2$, the conversions were unsatisfactorily low (entry 2). With $Pd_2(dba)_3$, the reaction did not proceed at all. These results were contrary to our expectation because the cross-coupling reaction took place well in the presence of bases independent of palladium species described in our previous communications.

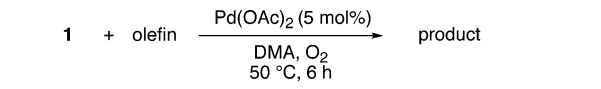
These phenomena can be rationalized by considering the reactivity of the oxo-palladium complex in-situ generated by reaction of PdL_2 (L = Cl, dba) with bases (OH^-, $R'O^-$, and RCO_2^-).[2a] The ligand (RO) on the oxo-palladium complex will coordinate to the boron atom, which can facilitate the transfer of the organic group on the boron atom to the palladium atom resulting in the enhancement of transmetallation. In the absence of bases, there would be no such oxo-palladium complex in

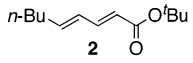
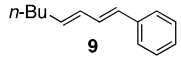
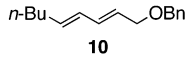
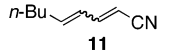
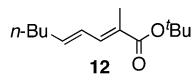
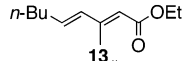
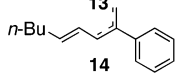
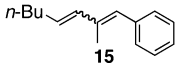
Table 4. Effect of Palladium Catalysts on the Cross-Coupling Reactions of Alkenyl Boronic Ester with Alkene under Base-Free Conditions



entry	catalyst	yield (%) 2	3
1	**$Pd(OAc)_2$**	**95**	
2	$PdCl_2$	21	
3	$Pd_2(dba)_3$	no reaction	
4	$Pd(PPh_3)_4$	46	51

Table 5. Cross-Coupling Reactions of Hexenyl Boronic Ester with Various Alkenes under Base-Free Conditions



entry	olefin	product	yield (%)[a]
1		 **2**	95
2		 **9**	88
3		 **10**	87
4		 **11**	78[b]
5		 **12**	90
6		 **13**	89
7		 **14**	50[c]
8		 **15**	52[d]

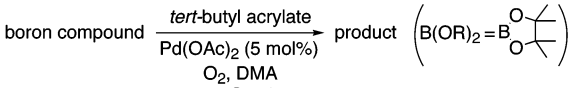
[a] Isolated yields. [b] *E*:*Z* = 3:2. [c] 1,4-Diene and 1,3-diene ratio is 2.8 to 1. [d] *EE* and *EZ* ratio is 6 to 1.

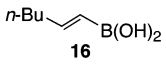
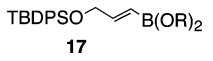
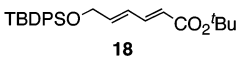
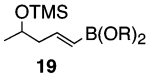
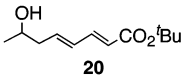
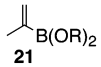
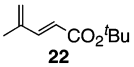
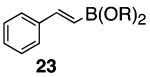
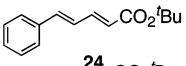
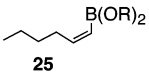
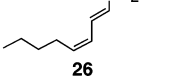
the cases of $PdCl_2$ and Pd_2dba_3, which may explain the low yield and no reaction. Interestingly, coupling reaction with $Pd(PPh_3)_4$ afforded homo-coupled compound **3** as the major product along with 46% of the desired compound **2**.[16] These results indicate that palladium ligands can play a key role in the coupling reactions under base-free conditions, which prompted us to investigate studies on the use of various ligands (vide infra).

Having established optimized conditions, various alkenes were examined for the feasibility of the methodology as shown in Table 5. Styrene reacted with hexenyl boronic ester efficiently to generate diene compound **9** in a high yield (entry 2). Furthermore, the unreactive allyl ether was subjected to coupling reaction to deliver product **10** in a good yield of 87% (entry 3). These couplings were highly stereoselective to furnish *E*,*E*-

(16) For an example of homocoupling with $Pd(OAc)_2$ in the presence of phosphine ligands, see: Yoshida, H.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2003**, *44*, 1541.

Table 6. Cross-Coupling Reactions of *tert*-Butyl Acrylate with Various Alkenyl Boron Compounds under Base-Free Conditions



entry	boron compound	product	yield (%)[a]
1	 **16**	**2 + 3**	64, 35
2	 **17**	 **18**	92
3[b]	 **19**	 **20**	81
4[c]	 **21**	 **22**	86
5	 **23**	 **24**	81
6[c]	 **25**	 **26**	91

[a] Isolated yields. [b] TMS group was deprotected during column chromatography. [c] The reaction time is 8 h.

isomers only. However, acrylonitrile furnished a mixture of *E*- and *Z*-isomers as expected, mainly due to the lack of steric presence (entry 4).[17] We examined a number of cases in addition to the reported ones here and came to a conclusion that the *E*-selectivity was prominent.

The reaction with disubstituted alkenes such as *tert*-butyl methacrylate and ethyl crotonate afforded the corresponding methyl-substituted diene products **12** and **13** in 90% and 89% yields, respectively, while exhibiting excellent *E*-selectivities (entries 5 and 6). Interestingly, in the case of α-methyl styrene, the coupling reactions provided the isomeric mixtures of diene compounds **14** due to the different pathways of *β*-hydride elimination during the reaction cycle (entry 7). The reaction with *cis*-*β*-methyl styrene also provided an isomeric mixture of coupling compound **15** in moderate yield (entry 8).

Regardless of the steric and electronic nature of the alkenes, the reaction under the base-free conditions delivered the corresponding cross-coupled products exclusively without homo-coupled products. To our delight, yields were generally desirably high due to excellent chemoselectivities, and stereoselective outcomes were outstandingly in favor of the *E*-isomer. In particular, *E*-selective preparation of trisubstituted alkenes should be of great value because of known difficulty in their stereoselective synthesis.

To further examine the method versatility, we carried out cross-coupling reactions of various alkenylboronic esters with *tert*-butyl acrylate (Table 6). The coupling reaction with boronic acids furnished considerable amounts of homo-coupled products because alkenylboronic acids are known to be more reactive than the corresponding boronic esters. However, the second transmetallation for the alkenylboronic esters may be slower than that for the corresponding acids due to the repulsion between the alkenylpalladium complex and the sterically hindered ketal group of alkenylboronic esters, averting the unwanted homo-couplings. For example, the cross-coupling reaction with hexenyl boronic acid (**16**) and *tert*-butyl acrylate afforded 64% of diene compound **2** along with 35% of homo-coupled product **3** even under base-free conditions (entry 1). For these reasons, we conducted the coupling reactions with boron ester compounds, which were easily prepared from the corresponding boronic acids in nearly quantitative yields.

Pinacol boron esters **17** and **19** containing the alcohol functional moieties were subjected to base-free oxidative Pd(II) catalysis, giving rise to the exclusive formation of (*E*,*E*)-dienes **18** and **20** in high yields, respectively. Highly substituted alkenylboron ester compounds were also compatible with this protocol. Isopropenyl pinacol boron ester (**21**) prepared from the corresponding bromide via Grignard reaction with the alkyl borate[18,25] reacted smoothly to offer diene compound **22** in 86% yield and with high selectivity. Aryl-substituted boronic ester **23** gave the corresponding (*E*,*E*)-dienoate **24** efficiently. Furthermore, palladium-catalyzed cross-coupling with *cis*-hexenyl pinacolboronic ester **25**[19] yielded (*E*,*Z*)-diene **26** with full retention of the olefin stereochemistry. Advantageously, highly functionalized structural groups can be incorporated for further manipulation utilizing this protocol.

On the basis of these results, we would like to suggest a plausible catalytic mechanism for base-free oxygen-promoted Pd(II) catalysis as follows (Figure 1): initial transmetallation should be feasible with an alkene boron compound even without activating it to an "ate" complex, giving the palladium(II) intermediate **I**; the second incorporation of an alkenyl group can be carried out by migratory insertion, which would be followed by *β*-hydride elimination to produce cross-coupling product **III** and Pd(0) species without the aid of bases; molecular oxygen would then oxidize the resulting Pd(0) to a peroxopalladium complex **V**,[12] which can react with another alkenylboron compound to regenerate alkene−Pd(II)−L complex **I**.[13] As we confirmed in previous work,[11] oxygen is crucial for the catalytic cycle, acting as an efficient Pd(0) reoxidant. The most notable feature of the proposed mechanism is that transmetallation takes place in the first alkenylation process, facilitating the whole catalysis under mild conditions. We believe that this transmetallation operation is facile due to lack of steric repulsion, which

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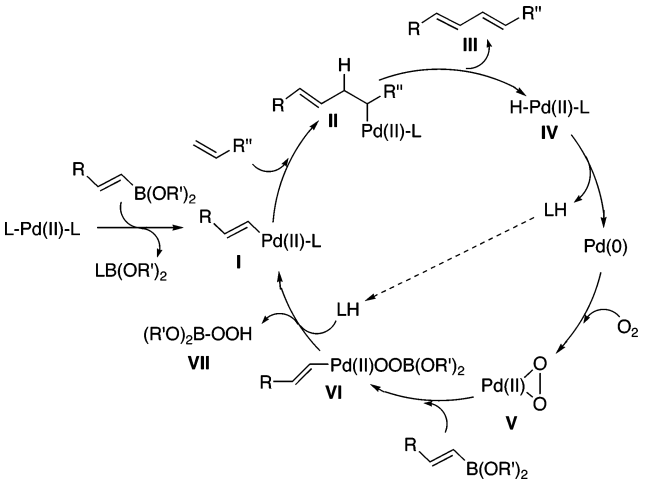


Figure 1. Proposed mechanism for the cross-coupling reactions under base-free conditions.

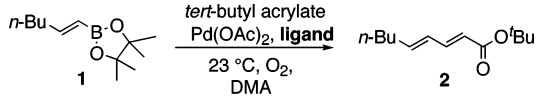
is prevalent in a number of organometallic reactions. Other known cross-coupling methods require transmetallation in the second alkenylation step after already adsorbing the first alkenyl group through Pd(0)-catalyzed oxidative addition. This is not the case with our newly developed methodology.

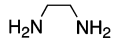
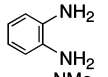
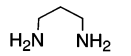
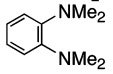
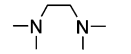
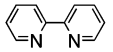
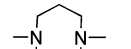
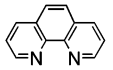
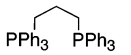
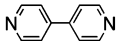
1.2. Ligand Effect on Cross-Coupling Reaction of Alkenylboron Compounds and Olefins. The Heck-type reaction is usually carried out in the presence of phosphine ligands, which stabilize the active Pd(0) species and accelerate the reaction rate.[1c,d] In our base-free reaction protocol, we found that palladium catalyst was quite easily precipitated and the coupling reaction was retarded. To stabilize and minimize the precipitation of palladium catalysts, we decided to employ organic ligands in our base-free conditions. The most suitable ligands for cross-couplings we found during this study were bidentated nitrogen ligands,[20] which have been known to facilitate the efficient redoxidation of Pd(0) by molecular oxygen and remain stable upon exposure to air and moisture unlike their phosphine counterparts. Many phosphine ligands are sensitive to air and moisture, and subsequently convert to phosphine oxide species upon exposure.

First, we examined the cross-coupling reaction of *trans*-1-hexenyl pinacolboron ester (**1**) and *tert*-butyl acrylate by screening with various bidentated aliphatic and aryl amines, pyridine, and phosphine ligands as shown in Table 7. The reactions with alkyl amines provided the cross-coupled compound **2** in low yields (entries 1−3), whereas tetra-*N*-methylpropyldiamine resulted in an excellent yield (entry 4). However, in the case of the phosphine analogue of tetra-*N*-methylpropyldiamine, the yield was dramatically reduced (entry 5). In general, phosphine ligands were observed to be incompatible with our coupling system. Aniline derivatives were similarly inefficient for the coupling reaction (entries 6, 7). However, reactions with 2,2′-bipyridine and 1,10-phenanthroline afforded the desired compound in excellent yields (entries 8, 9).

In none of these cases was the precipitation of palladium catalysts detected, which indicated stabilization of the Pd species by the bidentate ligands. However, all ligands did not enhance the coupling reaction. We envisioned the bidentate amine ligands should be located at two adjacent sites among the square chelating sites of palladium catalysts, leaving the other two sites open for the coupling reaction. Notably, cis-configuration of

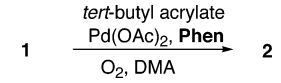
Table 7. Effect of Ligands on the Cross-Coupling Reactions under Base-Free Conditions



entry	ligand	yield (%)[a,b]	entry	ligand	yield (%)[a,b]
1		38	6		0
2		35	7		23
3		32	8		95
4		91	9		95
5		15	10		0

[a] All reactions were carried out with **1** (0.5 mmol), *tert*-butyl acrylate (1 mmol), and $Pd(OAc)_2$ (5 mol %) in DMA (dimethylacetamide, 2.5 mL). [b] Isolated yields.

Table 8. Effect of Pd(II) Catalyst Amount Employed on the Cross-Coupling Reactions in the Presence of Amine Ligands



entry	Pd/ligand	*T* (°C)	*t* (h)	yield (%)[a]
1	5 mol %	23	12	95
2	2 mol %	23	12	32
3	2 mol %	50	2	98
4	1 mol %	50	2	81
5	0.5 mol %	50	2	54

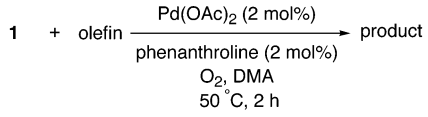
[a] Isolated yields.

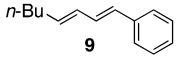
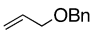
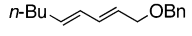
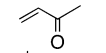
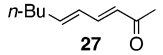
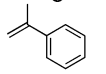
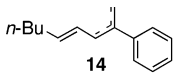
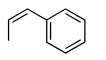
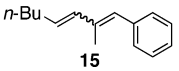
two ligand groups in the square-planar structure would be more favorable for the migratory insertion steps during the catalytic cycle, resulting in the enhancement of the coupling reaction.[21] This idea was supported by the reaction with 4,4′-bipyridine as a ligand (entry 10). Coupling reaction with 4,4′-bipyridine did not proceed, and the palladium catalyst precipitated early in the reaction presumably because 4,4′-bipyridine did not effectively form a Pd−nitrogen complex due to its linear structure.

These results indicate the coupling reactions are sensitive to the structure of the Pd−ligand complex: Pd−nitrogen chelating length, coordination angle, and steric environment. On the basis of these factors, phenanthroline was selected as the best choice for the coupling reaction.

Subsequently, we sought optimal conditions by screening various temperatures and Pd/ligand amounts. The results are summarized in Table 8. At room temperature, reduction of catalyst loading provided diminished yields (entry 2). However, at a higher temperature, the reaction proceeded well in shorter reaction time to afford the coupling compound in an excellent yield. Further reduction of catalyst loading at 50 °C provided slightly diminished yields. In conclusion, phenanthroline is the ligand of choice under the optimal coupling reaction conditions. These conditions are general and efficient to afford (*E*,*E*)-diene as the exclusive product in high yields, when the undesirable homo-coupled product is not observed. In particular, there is

Table 9. Cross-Coupling Reactions of Hexenyl Boronic Ester with Various Alkenes in the Presence of Ligand



entry	olefin	product	yield (%)[a]
1		 **9**	92
2		 **10**	89
3		 **27**	88
4		 **14**	87[b]
5		 **15**	91[c]

[a] Isolated yields. [b] The ratio of 1,4- and 1,3-diene was 6:1 by ^{1}H NMR analysis. [c] The ratio of *E* to *Z* isomer was 9:1 by ^{1}H NMR analysis.

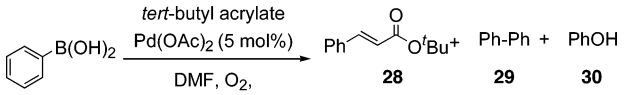
no need for base, and a minimal loading of catalyst is sufficient for high turnover up to 108.

By utilizing the optimized reaction conditions, we examined the cross-coupling reaction of alkenylboronic ester **1** with various olefins as shown in Table 9. All of the examined monosubstituted alkenes reacted smoothly, furnishing exclusively the corresponding conjugated dienes in excellent yields (entries 1−3). Regardless of substituents, cross-couplings were successful, and this protocol was generally applicable to a number of alkene systems.

Because of difficulty and low stereoselectivity, highly substituted olefins are poor substrates for Heck reaction as pointed out earlier. Therefore, a coupling reaction compatible with di- and trisubstituted olefins can be highly valuable, prompting us to probe the feasibility of Pd−nitrogen ligand catalysis. The reaction with α-methyl styrene (entry 4) furnished an inseparable mixture of 1,4- and 1,3-diene compound **14** in 87% yield via two possible *β*-elimination pathways during the reaction cycle. With *cis*-*β*-methyl styrene (entry 5), the 9:1 mixture of (*E*,*E*)- and (*E*,*Z*)-dienes was obtained in 91% overall yield. As compared to the previous results in the base-free and ligandless conditions (Table 5), the yields were dramatically increased and the reactions went to completion faster. We believe these reactivities and selectivities illustrate the efficiency and feasibility of our carbon−carbon bond forming protocol with palladium(II)−nitrogenous ligand complexes under oxidative and base-free conditions.

2. Cross-Coupling Reaction of Aryl Compounds and Olefins. 2.1. Base Effect on the Cross-Coupling Reaction of Aryl Compounds and Olefins. The base-free oxidative catalysis was next examined for the cross-coupling of arylboron compounds and alkenes. In our previous communication, we reported the development of an oxygen-promoted Pd(II)-catalyzed coupling of arylboronic acids and alkenes in the presence of bases. As with the alkenylboron compounds, the homo-coupled side product was also generated under the reaction conditions. In addition, phenol was unfortunately formed by oxidation of the corresponding arylboron compounds

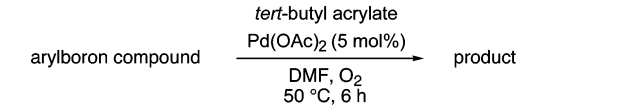
Table 10. Effect of Bases and Temperature on the Cross-Coupling Reactions of Aryl Boronic Acid with Alkene under Base-Free Conditions[a]

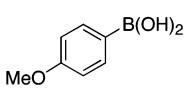
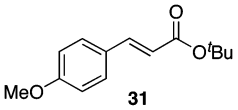
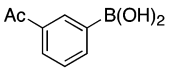
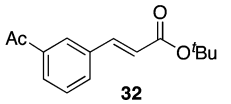


				yield (%)[b]		
entry	base	temp (°C)	*t* (h)	**28**	**29**	**30**
1[c]	Na_2CO_3	23	8	78	2	15
2[c]	Na_2CO_3	50	1	81	7	5
3[c]		23	>24[d]	28		10
4		50	>24[d]	35		11

[a] All reactions were carried out with phenylboronic acid (1 mmol), *tert*-butyl acrylate (1.5 mmol), and $Pd(OAc)_2$ (5 mol %) in DMF (2.5 mL). [b] Isolated yield. [c] Na_2CO_3 (2 mmol). [d] The reaction was incomplete after 24 h.

Table 11. Effect of Substituent on the Arylboron Compounds on the Cross-Coupling Reactions under Base-Free Conditions



entry	arylboron compound	product	yield (%)[a]
1		 **31**	37%
2		 **32**	41%

[a] Isolated yield.

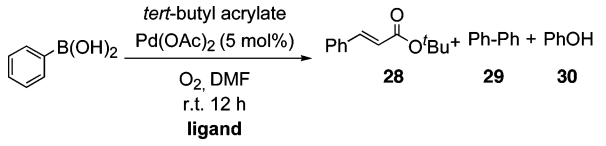
by boron peroxide, which was generated during the catalytic cycle.[22] To prevent homo-couplings, we attempted the coupling reaction of phenylboronic acid and *tert*-butyl acrylate in the absence of bases, adopting the same methodology.

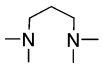
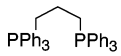
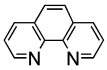
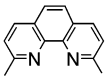
In the presence of Na_2CO_3 as a base, the reactions proceeded smoothly to afford the coupling product **28** in good yields along with homo-coupled compound **29** and phenol **30** at room temperature (entry 1, Table 10). At an elevated temperature, the reaction furnished the same products in similar yields, albeit in shorter reaction time (entry 2). Under base-free conditions, however, the coupling reaction did not proceed well despite longer reaction time and higher temperature. Interestingly, the homo-coupled products were not detected (entries 3 and 4).

We also examined coupling reactions with *p*-methoxy and *m*-acetyl phenyl boronic acids. The yields for these coupling reactions were 37% and 41%, respectively, indicating the electronic variation in arylboron compounds does not affect the coupling reaction under the base-free conditions (Table 11).

Based on these results, the bases seem to be a critical element in the coupling reaction between arylboronic compounds and alkenes contrary to the case of alkenylboron compounds. In consideration of reaction time and temperature under the same conditions, the rate of transmetallation for the aryl boron compounds was slower than that for alkenyl boron compounds. These results imply that transmetallation for aryl boron com-

Table 12. Effect of Ligands on the Cross-Coupling Reactions of Aryl Boronic Acid with Alkene under Base-Free Conditions[a]



entry	ligand	yield (%)[b] 28	29	30
1		13	44	17
2		10	60	5
3		76	-	23
4		84	-	13

[a] All reactions were carried out with phenylboronic acid (1 mmol), *tert*-butyl acrylate (1.5 mmol), and $Pd(OAc)_2$ (5 mol %) in DMF (2.5 mL). [b] Isolated yield.

pounds does not occur effectively and requires other elements under base-free condtions.

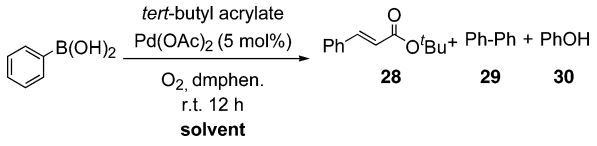
2.2. Ligand Effect on Cross-Coupling Reaction of Arylboron Compounds and Olefins. Shifting our attention to ligand effect on the cross-coupling reaction of arylboron compounds and olefins, we conducted the coupling reaction with phenyl boronic acid and *tert*-butyl acrylate using various ligands in the absence of bases at room temperature (Table 12).

Reaction with *N*,*N*,*N*′,*N*′-tetramethylpropylamine afforded only 13% of the desired product, 17% of phenol, and 44% of homo-coupled compound as the major product, which was contrary to the previous results for the coupling with alkenylboron compounds (entry 1). Using diphenylphosphonopropane as a ligand, homo-coupling was also predominant (entry 2). With 1,10-phenanthroline, the coupling reaction proceeded smoothly to give **28** in a good yield without homo-coupled compound **29**, resembling the case of alkylboron compounds (entry 3). Base-free conditions with 2,9-dimethyl-1,10-phenanthroline afforded better yields than 1,10-phenanthroline as representatively illustrated in entry 4, thus offering a general method of aryl−alkenyl couplings devoid of homo-coupling side pathways. In practice, phenolic side products are easily removed by washing away during the aqueous workup.

Using 2,9-dimethyl-1,10-phenanthroline as a palladium ligand, we screened various solvents in the absence of bases. Reactions performed in DMF, DMA, and NMP gave similarly satisfactory results (Table 13). However, the reaction in CH_3CN and THF afforded the desired coupling compound in low yields. Therefore, using 2,9-dimethyl-1,10-phenanthroline as a ligand and DMF as a solvent proved to be the best choice for the coupling reaction with arylboronic compounds.

With the optimized conditions in hand, we carried out the coupling reaction of various alkenes with phenylboronic acid. As shown in Table 14, *tert*-butyl acrylate was converted efficiently to (*E*)-*tert*-butyl cinnamate **28** in 87% yield (entry 1). The reaction with methyl vinyl ketone and acryl amine afforded (*E*)-4-phenyl-3-butene-2-one **33** and (*E*)-3-phenyl-2-

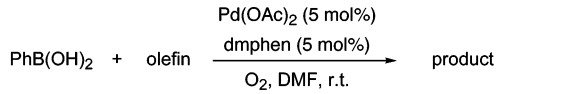
Table 13. Effect of Solvents on the Cross-Coupling Reactions of Aryl Boronic Acid with Alkene in the Presence of Ligand[a]

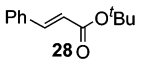
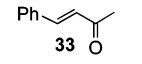
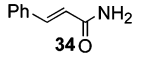
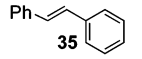
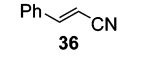
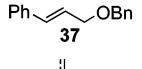
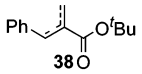
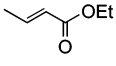
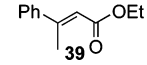


entry	solvent	yield (%)[b] 28	29	30
1	DMF	84		13
2	DMA	77		22
3	NMP	77		23
4	MeCN	63		37
5	THF	35	23	42

[a] All reactions were carried out with phenylboronic acid (1 mmol), *tert*-butyl acrylate (1.5 mmol), 1,10-dimethylphenanthroline (5 mol%), and $Pd(OAc)_2$ (5 mol %) in solvent (2.5 mL). [b] Isolated yield.

Table 14. Cross-Coupling Reactions of Phenyl Boronic Acid with Various Alkenes in the Presence of Ligand



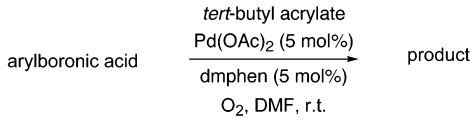
entry	olefin	product	yield (%)[a] A[b]	B[c]
1		 **28**	87	95
2		 **33**	71	-
3		 **34**	64	-
4		 **35**	85	93
5		 **36**	84	91
6		 **37**	78	-
7		 **38**	85[d]	95
8		 **39**	82	96

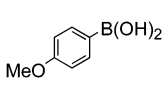
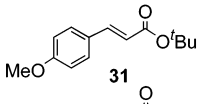
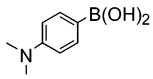
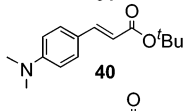
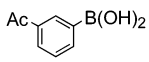
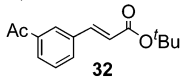
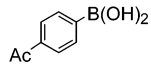
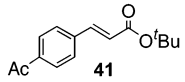
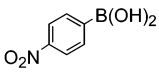
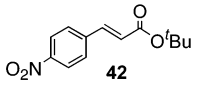
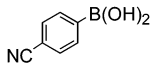
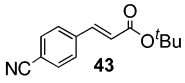
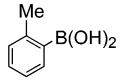
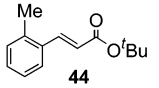
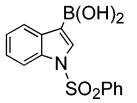
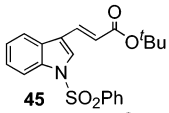
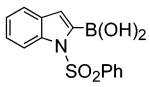
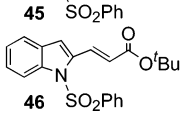
[a] Isolated yields. [b] The yield was calculated on the basis of phenylboronic acid. [c] The yield was calculated on the basis of olefin. [d] The ratio of Heck and migrated products was 1:1.4 by ^1H NMR analysis.

propenamide **34** in 71% and 64% yields, respectively (entries 2, 3). Furthermore, styrene and acrylonitrile reacted with phenylboronic acid to give 85% and 84% yields of (*E*)-stilbene **35** and (*E*)-3-phenyl-2-propenenitrile **36**, respectively (entries 4, 5). The coupling with unreactive allyl benzyl ether proceeded successfully, affording benzyl (*E*)-cinnamyl ether **37** in 78% yield (entry 6).

In the case of highly substituted alkenes, coupling reaction of *tert*-butyl methyl methacrylate with phenylbronic acid afforded a mixture of migrated product **38** along with α-methyl cinnamte. Ethyl crotonate delivered ethyl *β*-methyl cinnamate **39** with exclusive (*E*)-configuration in 82% yield. Because phenol was not factored in, the conversion yields based on

Table 15. Cross-Coupling Reactions of *tert*-Butyl Acrylate with Various Aryl Boron Compounds in the Presence of Ligand



entry	arylboron compound	product	yield (%)[a]
1		 **31**	61
2		 **40**	94
3		 **32**	72
4		 **41**	71
5		 **42**	57
6		 **43**	69
7		 **44**	84
8		 **45**	63
9		 **46**	49

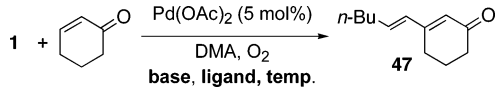
[a] Isolated yields.

alkenes were generally higher up to 96% (yield B) than those based on arylboron compounds (yield A), exhibiting excellent efficiency and selectivity.

To further investigate the scope and limitation of this methodology, we carried out cross-couplings of various arylboronic acids and *tert*-butyl acrylate as summarized in Table 15. Reactions of 4-methoxy phenyl boronic acid and *N*,*N*-dimethyl phenyl boronic acid, substituted with electron-donating groups, took place smoothly to provide the desired compounds, *tert*-butyl-(*E*)-4-methoxycinnamate **31** and *tert*-butyl-(*E*)-3-(4-dimethylamino) phenyl) acrylate **40** and in 61% and 94% yields, respectively (entries 1, 2). Also, the reactions with *meta*- and *para*-acetyl phenyl boronic acids, substituted with an electron-withdrawing group, afforded **32** and **41** in 72% and 71% yields, respectively (entries 3, 4). 4-Nitro phenyl boronic acid and 4-cyano phenyl boronic acid possessing highly electron-withdrawing groups reacted with *tert*-butyl acrylate to give arylated products **42** and **43** in 57% and 69% yields, respectively (entries 5, 6). The coupled reaction of sterically hindered 2-methyl phenyl boronic acid with *tert*-butyl acrylate afforded 84% yield of the desired product **44** (entry 7).

In addition, we examined the reaction of heterocyclic boronic acids. The coupling reaction involving 1-(phenylsulfonyl)-indol-3-boronic acid proceeded to afford the corresponding cross-coupling compound **45** in 63% yield (entry 8). Reactions with 1-(phenylsulfonyl)-indol-2-boronic acid gave the cross-coupling compound **46** in only moderate yields due to protodeboronation (entry 9). It is well known that heteroarylboronic acids bearing the boron atom ortho to the heteroatom are prone to protodeboronation.[23] Nontheless, this synthetic method appears to be applicable to the synthesis of heterocyclic templates used in medicinal chemistry. Overall, this oxidative palladium(II) catalysis offers an efficient method for aryl−alkenyl C−C bond formation under mild conditions.

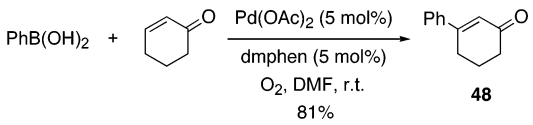
Table 16. Effect of Bases and Ligands on the Cross-Coupling Reaction of Cyclohexenone with Vinyl Boronic Compounds



entry	base	ligand	temp (°C)	time (h)	yield (%)
1	Na_2CO_3		23	6	76
2			50	6	37
3[a]		phen[b]	50	2	82

[a] Isolated yields. [b] TMS group was deprotected during column chromatography. [c] The reaction time is 8 h.

Scheme 4

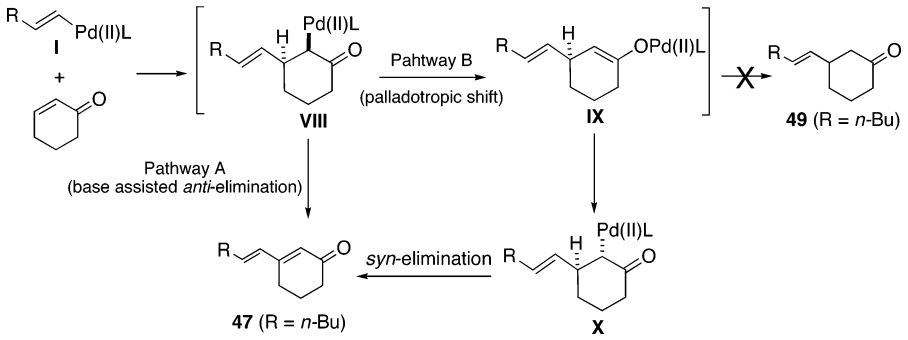


3. Oxidative Pd(II) Catalysis for Unusual Cycloalkenyl Substrates. During the catalytic cycle, β-elimination has been known to occur through concerted syn-elimination of Pd−H without aid of bases, which explained the high *E*-stereoselectivity of the Heck-type reaction. Nonetheless, the Pd−H was scavenged quickly by bases after the syn-elimination step, and bases seem to play a key role in the β-elimination step. Contrary to acyclic substrates, the base is found to be an important factor for the coupling reaction with cyclic substrates in our protocol as described below.

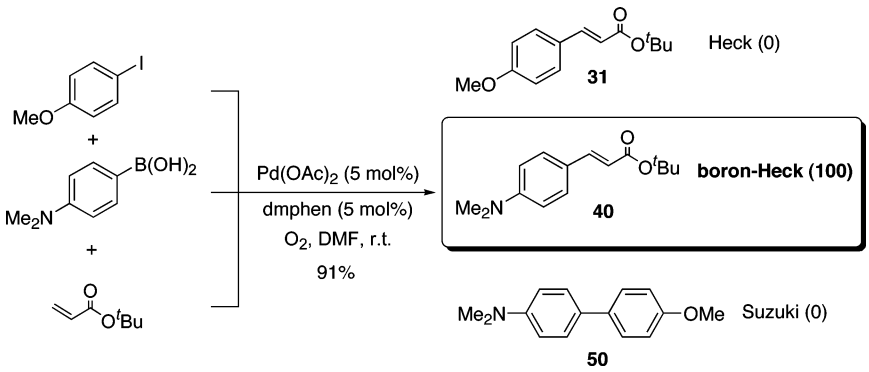
Although cyclohexenone has been known to be a difficult substrate for direct Heck-type conversion, we obtained the desired cross-coupling product **47** in a high yield along with the homo-coupled product in the presence of bases (Table 16, entry 1).[24] However, the same base-free reaction conditions for acyclic alkenes yielded diene compound **47** in a poor yield, implying that β-elimination was inefficient in the absence of a base (entry 2). However, when 1,10-phenanthroline was used as a palladium ligand, the catalysis was rapid, and the yield was increased to 82% without the homo-coupled product. Likewise, the cross-coupling reaction of cyclohexeneone with phenylboronic acid afforded the desired product **48** in a good yield (Scheme 4).

As shown in Scheme 5, we assumed two pathways for the coupling reaction with cyclohexenone: (i) base-catalyzed β-elimination via an E2-like mechanism (pathway A); and (ii) palladotropic shift followed by normal syn-elimination (pathway B).[1c] We thought that β-elimination in the presence of bases would take place in an anti-fashion from **VIII** in pathway A, because the syn-elimination in pathway B would not be affected to a great extent by the presence of bases. In addition, Michael addition product **49** was not observed at all, suggesting that

Scheme 5



Scheme 6



pathway B can be ruled out. Therefore, in the absence of bases, pathway A was very slow, resulting in low yields of the coupled product. These findings suggested a base-assisted β-elimination process should be considered in the mechanism for the Heck-type reaction with cyclic systems. Based on this assumption, phenanthroline would work as not only a palladium ligand but also a base participating in the β-elimination step.

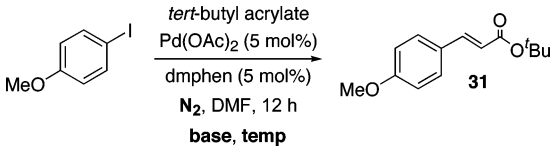
4. Competition Experiments. To understand kinetic and mechanistic differences, we studied intermolecular competition reaction using *p*-methoxyiodobenzene, *N*,*N*-dimethylaminophenyl boronic acid, and *tert*-butyl acrylate. As shown in Scheme 6, coupling reaction with an equimolar amount of each compound under the oxidative conditions afforded only boron Heck-type compound **40** without any other coupling compounds such as Heck and Suzuki coupling products.

This result implied that Heck reaction was suppressed under these coupling conditions due to lack of bases, relatively low temperature, or oxygen atmosphere. To confirm these assumptions, we conducted Heck coupling reaction of *p*-methoxyiodobenzene with *tert*-butyl acrylate under the same conditions except nitrogen atomosphere (Table 17).

Independent of bases, Heck coupling reaction was not efficient at room temperature (entries 1 and 2). Only at high temperature, the coupling reaction proceeded well to afford the coupling compound **31** with good yield in the presence of bases (entry 3). These results showed that oxidative boron Heck was more feasible than Heck reaction.

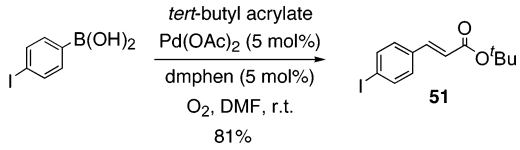
With these results, we undertook intramolecular competition experiment with 4-iodophenylboronic acid and *tert*-butyl acrylate (Scheme 7). As expected, boron Heck reaction product **51** was exclusively produced, and no other coupling products were obtained. This established high chemoselectivity would open the door to wide application.

Table 17. Bases and Temperature Effect on the Suzuki−Miyaura Reaction in the Presence of Ligand



entry	base	temp	yield
1		room temp	no reaction
2	Na_2CO_3	room temp	<10%
3	Na_2CO_3	50 °C	95%

Scheme 7



Conclusion

We have demonstrated the first example of oxygen-promoted palladium-catalyzed cross-coupling of alkenyl and aryl boron compounds with various alkenes in the absence of bases, which afford the corresponding conjugated diene compounds without homo-coupled products. While Heck- and Suzuki-type reactions require bases to facilitate coupling reactions, bases are not a requisite element for the oxidative palladium(II) catalysis, but useful in transmetallation and β-hydride elimination steps resulting in the enhancement of reaction rates. Additionally, base-free and bidentated nitrogen ligands stabilized palladium(II) species successfully catalyzed cross-coupling reactions to prevent precipiation of Pd(0) species and enhanced reactivity of palladium catalysts, resulting in the enhancement of yields

under milder reaction conditions. Therefore, our new synthetic protocol is advantageous over the conventional and modified Heck conditions and allows a wide array of substrates otherwise difficult or impossible to utilize. Because of its easy and convenient nature, this methodology for carbon−carbon bond formation is highly practical, holding great promise for wide use in organic and medicinal chemistry fields. Studies on asymmetric catalysis are currently in progress by using chiral amine ligands, and their successful results will be reported in due course.

Experimental Section

General Procedure A for the Coupling Reaction with Alkenyl Pinacolboronic Ester and Olefin in the Absence of Base (Base-Free Conditions). To a solution of olefin (1.5 mmol) in *N*,*N*-dimethylacetamide (2.5 mL, $C = 0.2$ M) were added pinacolboronic ester (0.5 mmol) followed by a single addition of $Pd(OAc)_2$ (0.025 mmol). The reaction flask was fitted with an oxygen balloon. The resulting reaction was stirred for 6 h at 50 °C, diluted with ethyl acetate (20 mL), and washed with water (2×10 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuo and subjected to flash chromatography, affording a cross-coupling compound.

General Procedure B for the Coupling Reaction with Alkenyl Pinacolboronic Ester and Olefin in the Presence of 1,10-Phenanthroline as a Ligand. To a premixed solution of palladium acetate (0.025 mol) and 1,10-phenanthroline as a ligand (0.028 mmol) in DMF (2.5 mL) for 30 min were added olefin (1.5 mmol) and pinacolboronic ester (0.5 mmol). The reaction flask was fitted with an oxygen balloon, and the reaction mixture was stirred at room temperature for 12 h, then diluted with ethyl acetate (20 mL), and washed with water and brine (2×10 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel to give a cross-coupled product.

General Procedure C for the Coupling Reaction with Arylboronic Acid and Olefin in the Presence of 2,9-Dimethyl-phenanthroline as a Ligand. To a premixed solution of palladium acetate (0.025 mol) and 2,9-dimethyl-phenanthroline as a ligand (0.028 mmol) in DMF (2.5 mL) for 30 min were added olefin (1.5 mmol) and arylboronic acid (0.5 mmol). The reaction flask was fitted with an oxygen balloon, and the reaction mixture was stirred at room temperature for 12 h, then diluted with ethyl acetate (20 mL), and washed with saturated aqueous $NaHCO_3$, water, and brine (2×10 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel to give a cross-coupled product.

Procedures for the Coupling of Cyclohexenone. (*1E*)-3-Hex-1-enyl-cyclohex-2-enone (47). Following the general procedure **A**, cross-coupling reaction of boronic ester **1** with cyclohexenone afforded diene **47** (37%). Following the general procedure **B**, cross-coupling reaction of boronic ester **1** with cyclohexenone afforded diene **47** for 2 h (82%). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 6.19$ (m, 2H), 5.85 (s, 1H), 2.41 (m, 4H), 2.16 (m, 2H), 2.00 (m, 2H), 1.35 (m, 4H), 0.89 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 200.5$, 157.7, 139.2, 131.3, 126.4, 37.7, 32.9, 31.0, 25.0, 22.3, 22.2, 13.9. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.82; H, 10.19.

(1*E*)-3-Phenyl-cyclohex-2-enone (48). Following the general procedure **C**, cross-coupling reaction of phenylboronic acid with cyclohexenone afforded **48** (81%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.52$ (m, 2H), 7.39 (m, 3H), 6.40 (s, 1H), 2.76 (t, $J = 5.6$ Hz, 2H), 2.47 (t, $J = 6.8$ Hz, 2H), 2.14 (q, $J = 6.8$ Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 199.9$, 159.8, 138.6, 130.0, 128.7, 126.0, 125.3, 115.4, 37.1, 28.0, 22.7. Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.69; H, 7.05.

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Supporting Information Available: Full experimental procedures and spectral data (^{1}H and ^{13}C NMR) for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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