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Communication

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Catalyst-Controlled Regioselectivity in the Synthesis of Branched Conjugated Dienes via Aerobic Oxidative Heck Reactions

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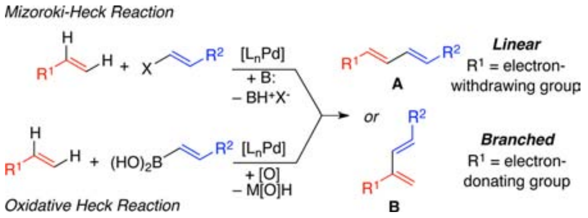
Supporting Information

ABSTRACT: Pd-catalyzed aerobic oxidative coupling of vinylboronic acids and electronically unbiased alkyl olefins provides regioselective access to 1,3-disubstituted conjugated dienes. Catalyst-controlled regioselectivity is achieved by using 2,9-dimethylphenanthroline as a ligand. The observed regioselectivity is opposite to that observed from a traditional (nonoxidative) Heck reaction between a vinyl bromide and an alkene. DFT computational studies reveal that steric effects of the 2,9-dimethylphenanthroline ligand promote C−C bond formation at the internal position of the alkene.

Heck-type coupling reactions provide a versatile strategy to convert vinylic C−H bonds into C−C bonds,[1] and one promising application of these methods is the synthesis of conjugated dienes via coupling of alkenes and vinyl halides or vinylboronic acids (Scheme 1). The scope of these reactions is severely limited, however, by challenges in controlling the product regioselectivity. The selectivity is typically under substrate control. The linear product (**A**) is obtained with electron-deficient alkenes, such as acrylates and styrenes,[2] and also can be favored through the use of coordinating directing groups in the substrate.[3] Selective formation of branched dienes (**B**) is rare and typically only observed with electron-rich alkenes, such as vinyl amides.[4,5] Ideally, selectivity could be established via catalyst control, thereby enabling electronically unbiased alkyl olefins to be used as effective substrate partners.[6] The groups of Sigman[7] and Zhou[8] recently demonstrated catalyst-controlled regioselectivity in the synthesis of styrenes via Heck-type coupling of alkenes with arylboronic acids (linear selectivity),[7a] aryl diazonium salts (linear selectivity),[7b] and aryl triflates (branched selectivity).[8−10] Here, we report a Pd^{II}-catalyzed method for aerobic oxidative coupling of vinylboronic acids and electronically unbiased alkenes to prepare 1,3-disubstituted dienes. These results represent the first general method for catalyst-controlled regioselectivity in Heck-type synthesis of dienes. Additional experimental studies and DFT calculations provide insights into the origin of the reaction selectivity.

Scheme 1. Regioisomeric Conjugated Dienes Potentially Accessible via Heck-Type Cross-Coupling Reactions



Several recent studies in our lab have focused on regioselective aerobic oxidative coupling reactions of alkenes and arenes with nitrogen-ligated Pd^{II} catalysts.[11] In this context, our attention was drawn to recent work by Larhed,[12] Jung,[13] and others,[14] highlighting the use of nitrogen ligands in Pd-catalyzed aerobic oxidative coupling of boronic acids and alkenes. Although these precedents were limited to examples of substrate-controlled regioselectivity (e.g., with acrylates as the alkene coupling partner), this work suggested that chelating nitrogen ligands could be used in the development of regioselective oxidative Heck reactions with electronically unbiased alkenes.

Our initial efforts focused on the reaction of (*E*)-styrenylboronic acid **1a** and 1-octene. Use of previously reported oxidative Heck conditions led to limited success (<40% yield of diene; see Supporting Information for full screening data), but variation of the Pd^{II} source, ancillary ligand, and solvent showed that good yields and regioselectivities could be achieved with Pd(nc)(TFA)$_2$ (TFA = trifluoroacetate, nc = neocuproine = 2,9-dimethyl-1,10-phenanthroline) as the catalyst and *N*-methylpyrrolidone as the solvent. The ligand effects depicted in Chart 1 provide useful insights. Bipyridine and phenanthroline, which have been used in other Pd-catalyzed aerobic oxidative Heck reactions,[2f,14a] led to very low yields and favored formation of the linear diene product, similar to the results obtained with Pd(TFA)$_2$ in the absence of an ancillary ligand. Improved yields and a preference for the branched diene isomer were observed upon using chelating ligands with substituents adjacent to the nitrogen atoms of the ligand (**L5**−**L10**). The best result was observed with neocuproine (**L8**); with this ligand, the branched diene was obtained in 90% yield with 20:1 selectivity over the linear isomer.[15]

To assess the generality of these catalytic conditions, we investigated the reaction of (*E*)-styrenylboronic acid with a number of different terminal olefins (Table 1). Good yields were observed with substrates bearing a wide range of functional groups, including ethers, ketones, esters, unprotected alcohols, silyl and silylether groups, and phthalimide.[16] Good-to-exclusive regioselectivities were observed in these reactions,

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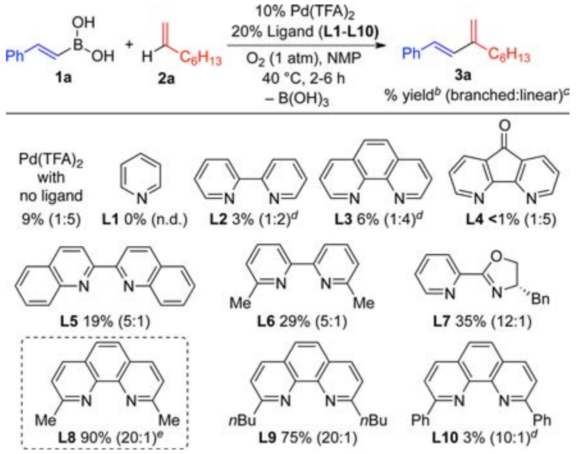
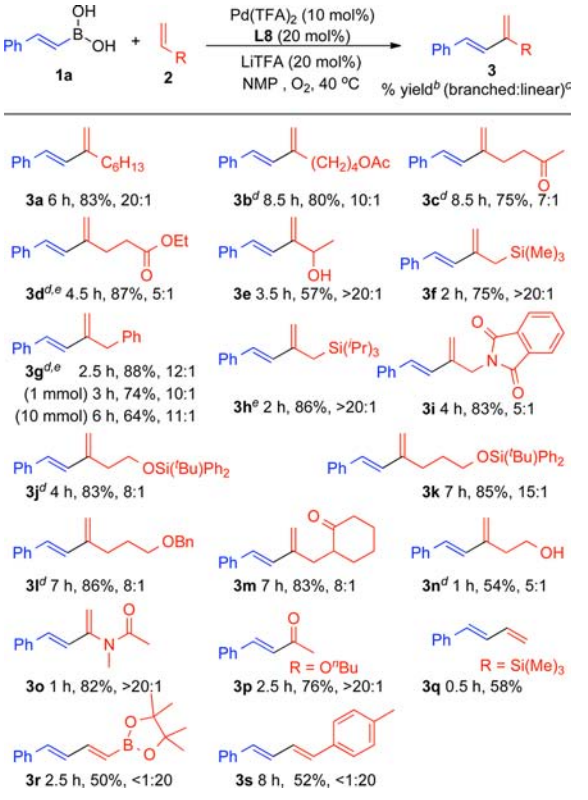
Chart 1. Ligand Effects on the Oxidative Heck Coupling of Styrenylboronic Acid and Octene[a]



[a] Reaction conditions: vinylboronic acid (1.5 equiv), alkene (0.2 mmol), NMP (0.5 mL). Reactions were monitored on GC using 4-methylanisole as the internal standard. [b] GC yield. [c] Determined by GC and ^{1}H NMR spectroscopy. [d] $Pd(TFA)_2$ (20 mol %) and ligand (40 mol %) were used. [e] LiTFA (0.2 equiv) was added.

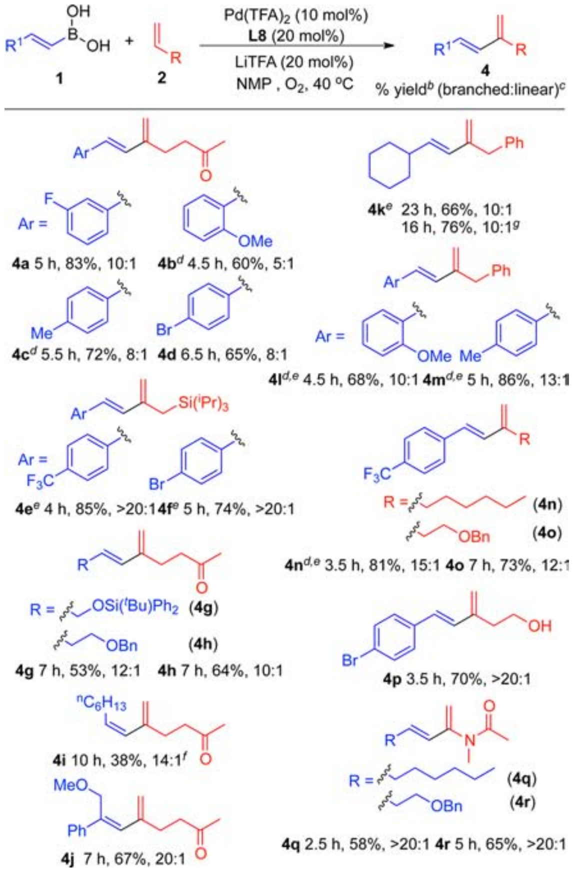
Table 1. Diene Synthesis via Oxidative Heck Coupling of (*E*)-Styrenylboronic Acid and Terminal Olefins[a]



[a] Reaction conditions: vinylboronic acid (1.5 equiv), alkene (0.2 mmol) in NMP (0.5 mL). [b] Isolated yields. [c] Branched:linear selectivity determined by GC and ^{1}H NMR spectroscopy. [d] Isolated as a mixture of branched and linear regioisomers. [e] Some isomerization of the diene (<5%) occurs during purification.

favoring formation of the branched diene product (**3a**–**3n**). As expected, the electron-rich vinyl ether and vinyl amide substrates undergo oxidative coupling to afford the branched diene products (**3o** and **3p**). The vinyl ether product hydrolyzes under the reaction conditions, resulting in the α,β-unsaturated methyl ketone.[17] Vinyltrimethylsilane represents a formal ethylene equivalent; oxidative Heck coupling of this alkene substrate results in loss of the TMS group to afford 1-phenylbutadiene (**3q**). Electron-deficient alkenes such as vinylboronic pinacol ester and styrene afford the linear products (**3r** and **3s**).

Table 2. Diene Synthesis via Oxidative Heck Coupling of Diverse Vinylboronic Acids and Terminal Olefins[a]

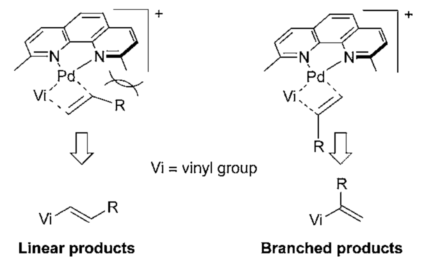


[a] The reactions were performed with vinylboronic acid (1.5 equiv), alkene (0.2 mmol) in NMP (0.5 mL) at 40 °C. [b] Isolated yields. [c] Branched:linear selectivity determined by GC and ^{1}H NMR spectroscopy. [d] Isolated as a mixture of the branched and linear regioisomers. [e] Some isomerization of the diene (<5%) occurs during purification. [f] *cis*-Octenylboronic acid used; (*Z*)-**4i**:(*E*)-**4i** = 3.5:1. [g] Catalyst/additive loading doubled.

One appeal of oxidative Heck reactions for the synthesis of dienes is the straightforward accessibility of the vinylboronic acids via hydroboration of alkynes. In this context, we evaluated reactions of a number of different vinylboronic acids with various alkene coupling partners (Table 2). Diverse substituted styrenylboronic acids were compatible with the reaction conditions and led to branched dienes in good-to-excellent yields and regioselectivities (products **4a**–**4f**, **4j**, **4l**–**4p**). Of particular note is the compatibility of aryl bromide substituents, which implies that Pd^0 reacts more rapidly with O_2 than the Ar–Br bond.[18,19] Products from *cis*-alkenyl- and β,β-disubstituted alkenylboronic acids were also obtained (**4i**, **4j**). Vinylboronic acids with aliphatic substitution on the vinyl group were somewhat less reactive than the styrenylboronic acids, but good yields and regioselectivities were still observed (products **4g–4i**, **4q–4r**). If needed, a modest improvement in the yield can be obtained with a higher catalyst loading (cf. product **4k**).

Factors that govern regioselectivity in Heck-type coupling reactions have been discussed extensively in the literature.[1g,20] Neutral bidentate ligands lead to cationic $[Pd^{II}(L_2)(aryl/vinyl)(alkene)]^+$ intermediates that exhibit higher selectivity for Markovnikov addition to the alkene, relative to neutral $Pd^{II}(L)(X)(aryl/vinyl)(alkene)$ intermediates formed with neutral monodentate ligands. Electronic effects are not sufficient to explain the present results, however, because several bidentate ligands favor the linear coupling product (see Chart 1). Steric effects undoubtedly play an important role in these reactions, and it seems reasonable to expect that the methyl groups of the neocuproine ligand disfavor the transition state leading to the linear product (Scheme 2).

Scheme 2. Steric Effects that Favor Formation of Branched Diene Products



DFT calculations of the insertion of allylbenzene into a neocuproine-ligated Pd^{II}–styrenyl species provide insights into the relative energies of pathways leading to the branched and linear dienes (Figure 1).[21] Multiple conformations of the intermediates and transition states associated with this step are possible, and the two prochiral faces of the alkene correspond to diastereomeric intermediates and transition states. The most favorable alkene insertion pathways are shown in Figure 1. The coordinated alkene in intermediates $I^{pro\text{-}S}$ and $I^{pro\text{-}R}$ orients perpendicular to the square plane of Pd^{II}. It then rotates into the plane as it proceeds through the subsequent alkene-insertion transition states, and the (pro-*R*)- and (pro-*S*)-isomers of $TS^{branched}$ and TS^{linear} show a preference for the branched pathway, particularly for the lower-energy *Si*-face insertion ($\Delta\Delta G^{\ddagger}$ = 4.9 kcal/mol). If exchange between $I^{pro\text{-}S}$ and $I^{pro\text{-}R}$ is facile, formation of the branched isomer is calculated to be favored over the linear isomer by 2.3 kcal/mol. For both pathways, alkene insertion is substantially downhill (≥9.7 kcal/mol) from $I^{pro\text{-}S}$ to form the resulting Pd^{II}–alkyl intermediate.

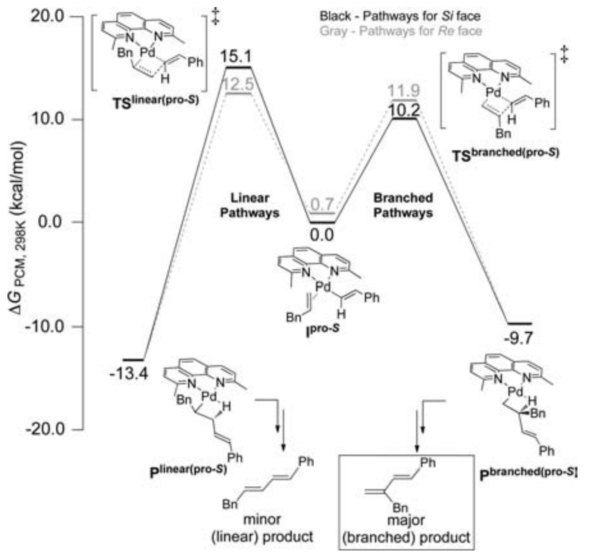
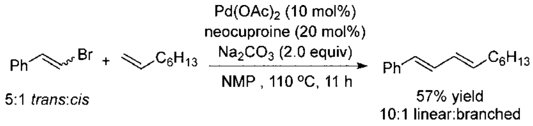


Figure 1. Energies for the two regioisomeric alkene insertion pathways involving the *Si*- and *Re*-face of the alkene. The chemical structures of the *Re*-face insertion pathway and the +1 charges on all structures are omitted for clarity. See Supporting Information for additional details.

The results described here are notable not only for the catalyst control over regioselectivity, but also for the ability to access the branched regioisomer. Precedents for Heck-type synthesis of dienes (including both traditional and oxidative methods) with electronically unbiased alkenes are rare, and essentially all known examples favor linear over branched products.[6] In light of precedents for use of phenanthroline ligands in traditional Heck coupling reactions,[22] we investigated whether neocuproine could control the regioselectivity of diene synthesis in a traditional Heck coupling reaction. The coupling of *β*-bromostyrene and octene with a $Pd(OAc)_2$/neocuproine catalyst system led to a 57% yield of diene (eq 1), but the *linear* regioisomer was strongly favored (10:1) over the branched product.[23] This outcome potentially could be rationalized by invoking a neutral pathway for alkene insertion [i.e., via a $Pd^{II}(\kappa^1\text{-nc})(Br)(styrenyl)(octene)$ intermediate], which may favor formation of the linear diene.[20] An alternative, perhaps more likely, explanation takes into account the high temperature required for this reaction: 110 °C, relative to 40 °C for the oxidative Heck reactions. Under the more-forcing conditions, the Pd catalyst could decompose into Pd nanoparticles that promote coupling via a "ligand-free" pathway.[24] Potential support for this hypothesis was obtained from dynamic light scattering data, which reveal that Pd nanoparticles, 200–400 nm in diameter, form under the Heck coupling conditions in eq 1. Furthermore, independently prepared nanoparticles are effective catalysts for the same reaction and afford the linear product in nearly identical yield.[25] No nanoparticles are detected from an oxidative Heck reaction with styrenylboronic acid and octene. These observations highlight the uniqueness of the oxidative Heck coupling conditions reported above.



(1)

In conclusion, we have developed highly regioselective oxidative Heck reactions that enable the preparation of synthetically useful branched 1,3-disubstituted conjugated dienes. The ability to achieve selectivity with electronically unbiased alkenes complements recent advances by others and significantly expands the scope and synthetic utility of Heck coupling reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full catalyst screening data, experimental procedures, product characterization data for all products, and computational data.

This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For reviews, see: (a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. (b) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed.* **1995**, *33*, 2379. (c) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (e) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (f) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (g) Nilsson, P.; Olofsson, K.; Larhed, M. In *The Mizoroki-Heck Reaction*; Oestreich, M., Ed.; John Wiley & Sons: Chichester, 2009; pp 133−162. (h) Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K.; Zamani, A. *Synthesis* **2010**, 1399. (i) Mc Cartney, D.; Guiry, P. J. *Chem. Soc. Rev.* **2011**, *40*, 5122.

(2) For example, see: (a) Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083. (b) Crisp, G. T.; Glink, P. T. *Tetrahedron* **1994**, *50*, 2623. (c) Berthiol, F.; Doucet, H.; Santelli, M. *Synlett* **2003**, 841. (d) Yoon, C. H.; Yoo, K. S.; Yi, S. W.; Mishra, R. K.; Jung, K. W. *Org. Lett.* **2004**, *6*, 4037. (e) Hansen, A. L.; Ebran, J. P.; Ahlquist, M.; Norrby, P. O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349. (f) Yoo, K. S.; Yoon, C. H.; Jung, K. W. *J. Am. Chem. Soc.* **2006**, *128*, 16384. (g) Ebran, J.-P.; Hansen, A. L.; Gøgsig, T. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2007**, *129*, 6931. (h) Lemhadri, M.; Battace, A.; Berthiol, F.; Zair, T.; Doucet, H.; Santelli, M. *Synthesis* **2008**, 1142.

(3) (a) Crisp, G. T.; Gebauer, M. G. *Tetrahedron* **1996**, *52*, 12465. (b) Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 11270. (c) Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4729. (d) Su, Y.; Jiao, N. *Org. Lett.* **2009**, *11*, 2980.

(4) (a) Vallin, K. S. A.; Zhang, Q. S.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **2003**, *68*, 6639. (b) Hansen, A. L.; Skrydstrup, T. *Org. Lett.* **2005**, *7*, 5585. (c) McConville, M.; Saidi, O.; Blacker, J.; Xiao, J. *J. Org. Chem.* **2009**, *74*, 2692.

(5) For leading references describing Heck-type reactions between *aryl* coupling partners and electron-rich alkenes, see: (a) Andappan, M. M. S.; Nilsson, P.; von Schenck, H.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 5212. (b) Ruan, J.; Xiao, J. *Acc. Chem. Res.* **2011**, *44*, 614 and the references cited.

(6) Only isolated examples of Heck-type synthesis of conjugated dienes with electronically unbiased alkenes have been reported in the literature. The examples that exist typically favor formation of the linear regioisomeric product (**A**, Scheme 1). See refs 2c, 2h, and the following: (a) Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 3898. (b) Kim, J.; Lee, J. T.; Yeo, K. D. *Bull. Korean Chem. Soc.* **1985**, *6*, 366. (c) Wang, G.; Mohan, S.; Negishi, E. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 11344.

(7) (a) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 13981. (b) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 9692.

(8) Qin, L. N.; Ren, X. F.; Lu, Y. P.; Li, Y. X.; Zhou, J. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 5915.

(9) A recent Ni-catalyzed Heck-type coupling of benzyl chlorides and alkenes exhibits selectivity for the branched isomer: Matsubara, R.; Gutierrez, A. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2011**, *133*, 19020.

(10) The use of ionic liquids as solvents can enhance the regioselectivity of certain Heck-type coupling reactions. See: (a) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, *127*, 751. (b) Mo, J.; Xu, L.; Ruan, J.; Liu, S.; Xiao, J. *Chem. Commun.* **2006**, 3591.

(11) (a) Campbell, A. N.; White, P. B.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 15116. (b) Izawa, Y.; Stahl, S. S. *Adv. Synth. Catal.* **2010**, *352*, 3223. (c) Campbell, A. N.; Meyer, E. B.; Stahl, S. S. *Chem. Commun.* **2011**, 10257.

(12) See ref 5a and the following: (a) Andappan, M. M. S.; Nilsson, P.; Larhed, M. *Chem. Commun.* **2004**, 218. (b) Enquist, P. A.; Lindh, J.; Nilsson, P.; Larhed, M. *Green Chem.* **2006**, *8*, 338. (c) Lindh, J.; Enquist, P. A.; Pilotti, Å.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2007**, *72*, 7957.

(13) See ref 2f and the following: Yoo, K. S.; Park, C. P.; Yoon, C. H.; Sakaguchi, S.; O'Neill, J.; Jung, K. W. *Org. Lett.* **2007**, *9*, 3933.

(14) (a) Park, C. P.; Kim, D.-P. *J. Am. Chem. Soc.* **2010**, *132*, 10102. (b) Gottumukkala, A. L.; Teichert, J. F.; Heijnen, D.; Eisink, N.; van Dijk, S.; Ferrer, C.; van den Hoogenband, A.; Minnaard, A. J. *J. Org. Chem.* **2011**, *76*, 3498.

(15) The beneficial effect of neocuproine as a ligand in substrate-controlled oxidative Heck reactions has been noted in a number of studies by Larhed and co-workers. See ref 12.

(16) Gas−liquid mixing can influence the outcome of the reaction. The majority of yields in Tables 1 and 2 were obtained by vortexing the reaction mixtures under 1 atm of O_2. Larger scale reactions were carried out in a round-bottom flask (cf. Table 1, **3g**).

(17) For related reactions of vinyl ethers with arylboronic acids, see refs 4c and 5a.

(18) Similar observations have been noted by Jung et al. in competition studies of Ar−I and O_2 substrates: Jung, Y. C.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2231.

(19) For fundamental studies of reactions of O_2 with Pd^0−alkene complexes bearing a dimethylphenanthroline ligand, see: (a) Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188. (b) Popp, B. V.; Morales, C. M.; Landis, C. R.; Stahl, S. S. *Inorg. Chem.* **2010**, *49*, 8200.

(20) Cabri, W.; Candiani, I.; Bedeschi, A. *J. Org. Chem.* **1993**, *58*, 7421.

(21) Final structures were optimized with the following method (*Gaussian 09*): B3LYP; Stuttgart RSC 1997 ECP basis sets for Pd; 6-311+G (d, p) basis sets on all other atoms; polarizable continuum solvation model (*N*,*N*-dimethylformamide); see Supporting Information for computational details.

(22) See ref 20 and the following: Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *Synlett* **1992**, 871.

(23) $Pd(OAc)_2$ was used rather than $Pd(TFA)_2$ in the Heck coupling reaction in eq 1 based on literature precedents (e.g., ref 6c). Control experiments with the oxidative Heck coupling show that, while $Pd(OAc)_2$ is not as effective as $Pd(TFA)_2$, good yields and high branched selectivity can be achieved. See Supporting Information for details.

(24) Control experiments show that the reaction in eq 1 does not proceed at 40 °C. See Supporting Information for details. Ligand-free/nanoparticle conditions for traditional Heck coupling reactions commonly employ polar solvents: (a) Reetz, M. T.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165. (b) de Vries, J. G. *Dalton Trans.* **2006**, 421. (c) Reetz, M. T.; de Vries, J. G. *Chem. Commun.* **2004**, 1559.

(25) See Supporting Information for details.