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

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### 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 (non-oxidative) 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,<sup>1</sup> 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,<sup>2</sup> and also can be favored through the use of coordinating directing groups in the substrate.<sup>3</sup> Selective formation of branched dienes (**B**) is rare and typically only observed with electron-rich alkenes, such as vinyl amides.<sup>4,5</sup> Ideally, selectivity could be established via catalyst control, thereby enabling electronically unbiased alkyl olefins to be used as effective substrate partners.<sup>6</sup> The groups of Sigman<sup>7</sup> and Zhou<sup>8</sup> recently demonstrated catalyst-controlled regioselectivity in the synthesis of styrenes via Heck-type coupling of alkenes with arylboronic acids (linear selectivity),<sup>7a</sup> aryl diazonium salts (linear selectivity)<sup>7b</sup> and aryl triflates (branched selectivity).<sup>8,9,10</sup> Here, we report a Pd<sup>II</sup>-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.

Several recent studies in our lab have focused on regioselective aerobic oxidative coupling reactions of alkenes and arenes with nitrogen-ligated Pd<sup>II</sup> catalysts.<sup>11</sup> In this context, our attention was drawn to recent work by Larhed,<sup>12</sup> Jung,<sup>13</sup> and others,<sup>14</sup> highlighting the use of nitrogen ligands in Pd-catalyzed aerobic oxidative coupling of boronic acids and alkenes. Although these reactions were limited to examples of substrate-controlled regioselectivity

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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>.

(e.g., with acrylates as the alkene coupling partner), this work suggested that chelating nitrogen ligands might enable 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 Supp. Info. for full screening data), but variation of the Pd<sup>II</sup> source, ancillary ligand and solvent showed that good yields and regioselectivity could be achieved with Pd(nc)(TFA)<sub>2</sub> (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,<sup>2f,14a</sup> led to very low yields and favored formation of the linear diene product, similar to the results obtained with Pd(TFA)<sub>2</sub> 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.<sup>15</sup>

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.<sup>16</sup> Good-to-exclusive regioselectivity was observed in these reactions, 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  $\alpha,\beta$ -unsaturated methyl ketone.<sup>17</sup> 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**).

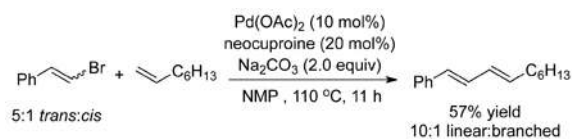
One appeal of oxidative Heck reactions for the synthesis of dienes is the straightforward accessibility of the vinylboronic acids via hydroboration of alkynes. In this context, we evaluated reactions of a number of different vinylboronic acids with various alkene coupling partners (Table 2). Diverse 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<sup>0</sup> reacts more rapidly with O<sub>2</sub> than the Ar–Br bond.<sup>18,19</sup> Products from *cis*-alkenyl- and  $\beta,\beta$ -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 higher catalyst loading (cf. product **4k**).

Factors that govern regioselectivity in Heck-type coupling reactions have been discussed extensively in the literature.<sup>1g,20</sup> Neutral bidentate ligands lead to cationic [Pd<sup>II</sup>(L<sub>2</sub>)(aryl/vinyl)-(alkene)]<sup>+</sup> intermediates that exhibit higher selectivity for Markovnikov addition to the alkene, relative to neutral Pd<sup>II</sup>(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 disfavors the transition state leading to the linear product (Scheme 2).

DFT calculations of the insertion of allylbenzene into a neocuproine-ligated Pd<sup>II</sup>-styrenyl species provide insights into the relative energies of pathways leading to the branched and linear dienes (Figure 1).<sup>21</sup> 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<sup>pro-S</sup>** and **I<sup>pro-R</sup>** orients perpendicular to the square plane of Pd<sup>II</sup>. 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<sup>branched</sup>** and **TS<sup>linear</sup>** 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<sup>pro-S</sup>** and **I<sup>pro-R</sup>** 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 ( $\geq 9.7$  kcal/mol) from **I<sup>pro-S</sup>** to form the resulting Pd<sup>II</sup>-alkyl intermediate.

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.<sup>6</sup> In light of precedents for use of phenanthroline ligands in traditional Heck coupling reactions,<sup>22</sup> we investigated whether neocuproine could control the regioselectivity of diene synthesis in a traditional Heck coupling reaction. The coupling of  $\beta$ -bromostyrene and octene with a Pd(OAc)<sub>2</sub>/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.<sup>23</sup> This outcome potentially could be rationalized by invoking a neutral pathway for alkene insertion [i.e., via a Pd<sup>II</sup>( $\kappa^1$ -nc)(Br)-(styrenyl)(octene) intermediate], which may favor formation of the linear diene.<sup>20</sup> An alternative, perhaps more likely, explanation takes into account the high temperatures 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.<sup>24</sup> 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.<sup>25</sup> 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 expanding the scope and synthetic utility of Heck coupling reactions.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

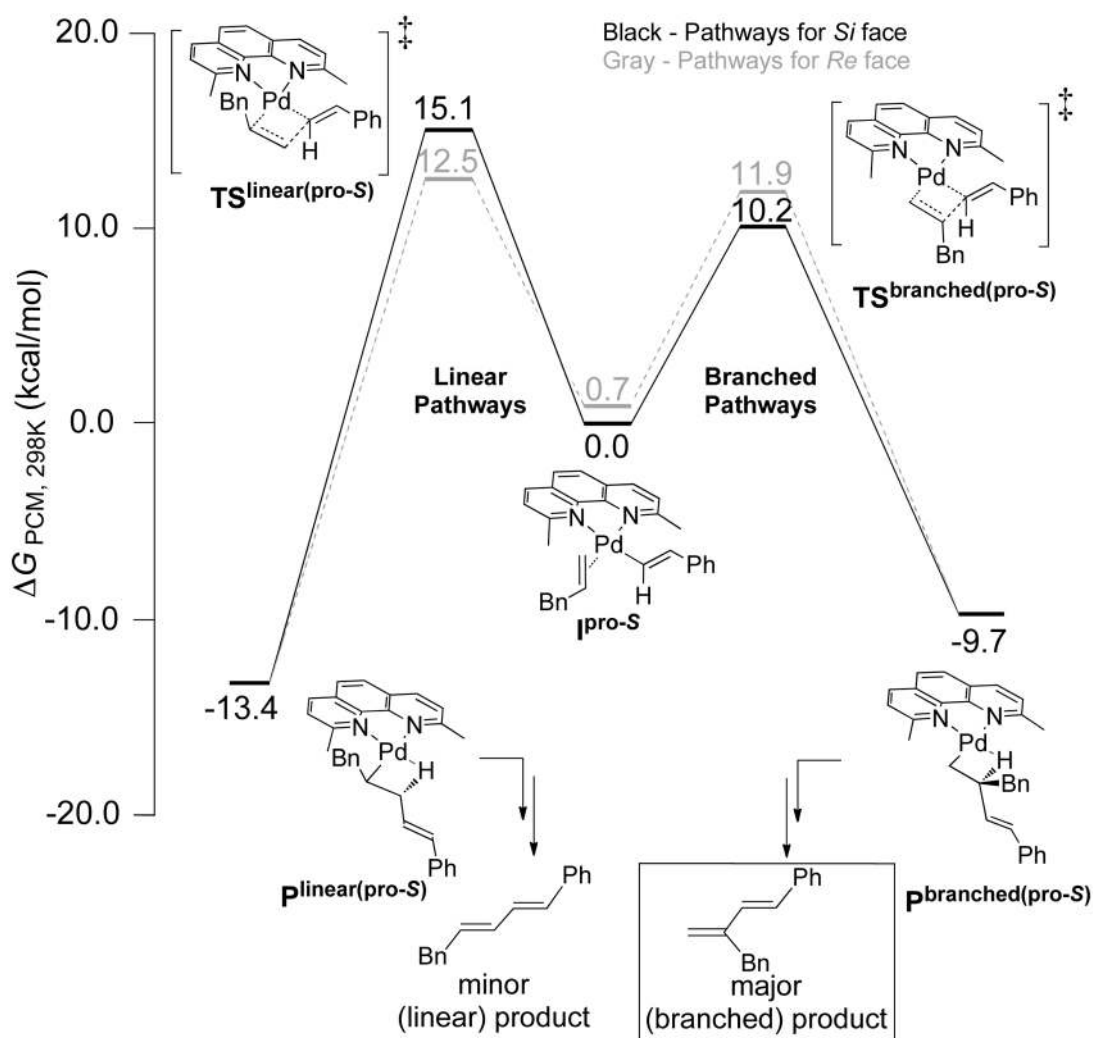
## Acknowledgments

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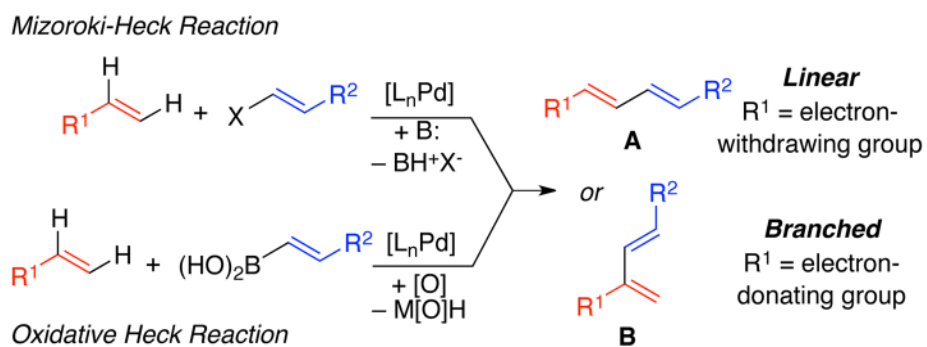
## References

1. For reviews, see: Heck RF. *Acc Chem Res.* 1979; 12:146. de Meijere A, Meyer FE. *Angew Chem Int Ed.* 1995; 33:2379. Cabri W, Candiani I. *Acc Chem Res.* 1995; 28:2. Beletskaya IP, Cheprakov AV. *Chem Rev.* 2000; 100:3009. [PubMed: 11749313] Dounay AB, Overman LE. *Chem Rev.* 2003; 103:2945. [PubMed: 12914487] Nicolaou KC, Bulger PG, Sarlah D. *Angew Chem Int Ed.* 2005; 44:4442. Nilsson P, Olofsson K, Larhed M, Oestreich M. The Mizoroki-Heck Reaction. John Wiley & Sons Chichester 2009:133–162. Karimi B, Behzadnia H, Elhamifar D, Akhavan PF, Esfahani FK, Zamani A. *Synthesis.* 2010:1399. Mc Cartney D, Guiry PJ. *Chem Soc Rev.* 2011; 40:5122. [PubMed: 21677934]
2. See, for example: Dieck HA, Heck RF. *J Org Chem.* 1975; 40:1983. Crisp GT, Glink PT. *Tetrahedron.* 1994; 50:2623. Berthiol F, Doucet H, Santelli M. *Synlett.* 2003:841. Yoon CH, Yoo KS, Yi SW, Mishra RK, Jung KW. *Org Lett.* 2004; 6:4037. [PubMed: 15496093] Hansen AL, Ebran JP, Ahlquist M, Norrby PO, Skrydstrup T. *Angew Chem Int Ed.* 2006; 45:3349. Yoo KS, Yoon CH, Jung KW. *J Am Chem Soc.* 2006; 128:16384. [PubMed: 17165795] Ebran JP, Hansen AL, Gøgsig TM, Skrydstrup T. *J Am Chem Soc.* 2007; 129:6931. [PubMed: 17474745] Lemhadri M, Battace A, Berthiol F, Zair T, Doucet H, Santelli M. *Synthesis.* 2008:1142.
3. (a) Crisp GT, Gebauer MG. *Tetrahedron.* 1996; 52:12465. (b) Delcamp JH, Brucks AP, White MC. *J Am Chem Soc.* 2008; 130:11270. [PubMed: 18671350] (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. [PubMed: 19534546]
4. (a) Vallin KSA, Zhang QS, Larhed M, Curran DP, Hallberg A. *J Org Chem.* 2003; 68:6639. [PubMed: 12919028] (b) Hansen AL, Skrydstrup T. *Org Lett.* 2005; 7:5585. [PubMed: 16320997] (c) McConville M, Saidi O, Blacker J, Xiao J. *J Org Chem.* 2009; 74:2692. [PubMed: 19323572]
5. For leading references describing Heck-type reactions between aryl coupling partners and electron-rich alkenes, see: Andappan MMS, Nilsson P, von Schenck H, Larhed M. *J Org Chem.* 2004; 69:5212. [PubMed: 15287763] Ruan J, Xiao J. *Acc Chem Res.* 2011; 44:614. and the references cited. [PubMed: 21612205]
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: Patel BA, Heck RF. *J Org Chem.* 1978; 43:3898. Kim J, Lee JT, Yeo KD. *Bull Korean Chem Soc.* 1985; 6:367. Wang G, Mohan S, Negishi E. *Proc Natl Acad Sci U S A.* 2011; 108:11344. [PubMed: 21709262]
7. (a) Werner EW, Sigman MS. *J Am Chem Soc.* 2010; 132:13981. [PubMed: 20858011] (b) Werner EW, Sigman MS. *J Am Chem Soc.* 2011; 133:9692. [PubMed: 21627305]
8. Qin LN, Ren XF, Lu YP, Li YX, Zhou JR. *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 AC, Jamison TF. *J Am Chem Soc.* 2011; 133:19020. [PubMed: 22066899]
10. The use of ionic liquids as solvents can enhance the regioselectivity of certain Heck-type coupling reactions. See: Mo J, Xu LJ, Xiao JL. *J Am Chem Soc.* 2005; 127:751. [PubMed: 15643901] Mo J, Xu L, Ruan J, Liu S, Xiao J. *Chem Commun.* 2006:3591.
11. (a) Campbell AN, White PB, Guzei IA, Stahl SS. *J Am Chem Soc.* 2010; 132:15116. [PubMed: 20929224] (b) Izawa Y, Stahl SS. *Adv Synth Catal.* 2010; 352:3223. [PubMed: 21399704] (c) Campbell AN, Meyer EB, Stahl SS. *Chem Commun.* 2011:10257.

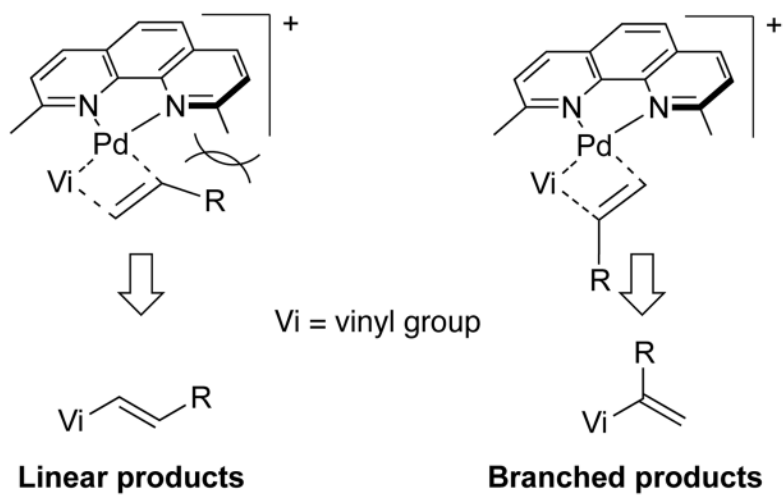
12. See ref. 5a and the following: Andappan MMS, Nilsson P, Larhed M. Chem Commun. 2004:218. Andappan MMS, Nilsson P, Schenck HV, Larhed M. J Org Chem. 2004; 69:5212. [PubMed: 15287763] Enquist PA, Lindh J, Nilsson P, Larhed M. Green Chem. 2006; 8:338. Lindh J, Enquist P, Pilotti Å, Nilsson P, Larhed M. J Org Chem. 2007; 72:7957. [PubMed: 17887706]
13. See ref. 2f and the following: Yoo KS, Park CP, Yoon CH, Sakaguchi S, O'Neill J, Jung KW. Org Lett. 2007; 9:3933. [PubMed: 17760452]
14. (a) Park CP, Kim DP. J Am Chem Soc. 2010; 132:10102. [PubMed: 20593807] (b) Gottumukkala AL, Teichert JF, Heijnen D, Eisink N, van Dijk S, Ferrer C, van den Hoogenband A, Minnaard AJ. J Org Chem. 2011; 76:3498. [PubMed: 21428446]
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 coworkers. 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 reactions mixtures under 1 atm O<sub>2</sub>. 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 12b.
18. Similar observations have been noted by Jung et al. in competition studies of Ar-I and O<sub>2</sub> substrates: Jung YC, Mishra RK, Yoon CH, Jung KW. Org Lett. 2003; 5:2231. [PubMed: 12816416]
19. For fundamental studies of reactions of O<sub>2</sub> with Pd<sup>0</sup>-alkene complexes bearing a dimethylphenanthroline ligand, see: Stahl SS, Thorman JL, Nelson RC, Kozee MA. J Am Chem Soc. 2001; 123:7188. [PubMed: 11459511] Popp BV, Morales CM, Landis CR, Stahl SS. Inorg Chem. 2010; 49:8200. [PubMed: 20604535]
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)<sub>2</sub> was used rather than Pd(TFA)<sub>2</sub> 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)<sub>2</sub> is not as effective as Pd(TFA)<sub>2</sub>, 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: Reetz MT, Westermann E. Angew Chem Int Ed. 2000; 39:165. de Vries JG. Dalton Trans. 2006:421. [PubMed: 16395440] Reetz MT, de Vries JG. Chem Commun. 2004:1559.
25. See Supporting Information for details.



**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 Supp. Info. for additional details.



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



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



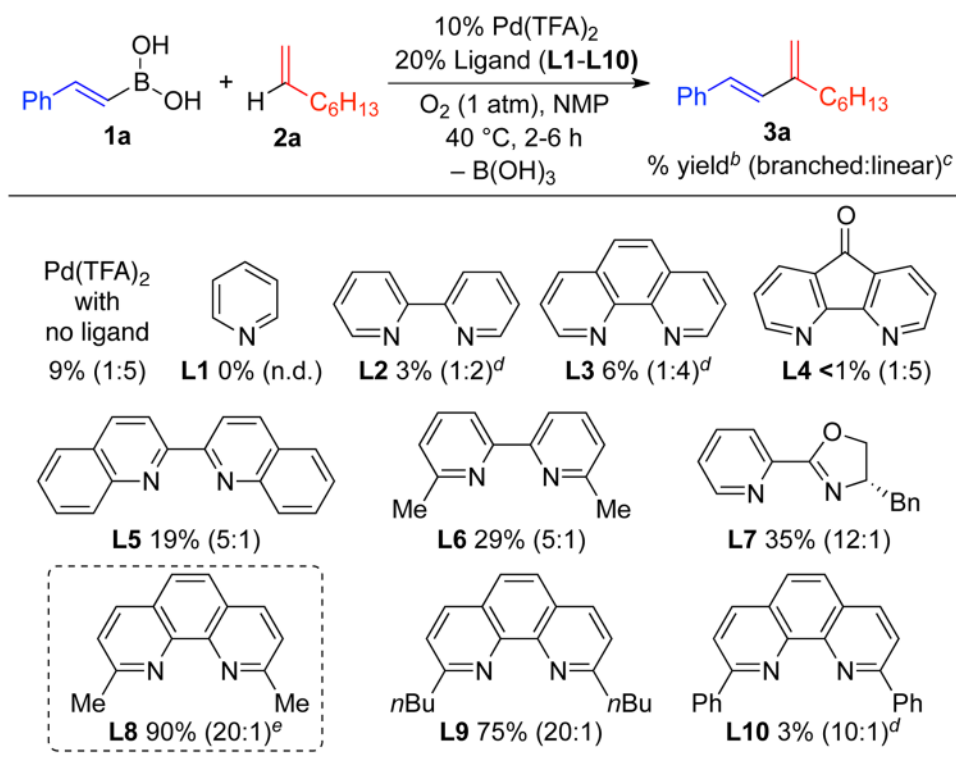
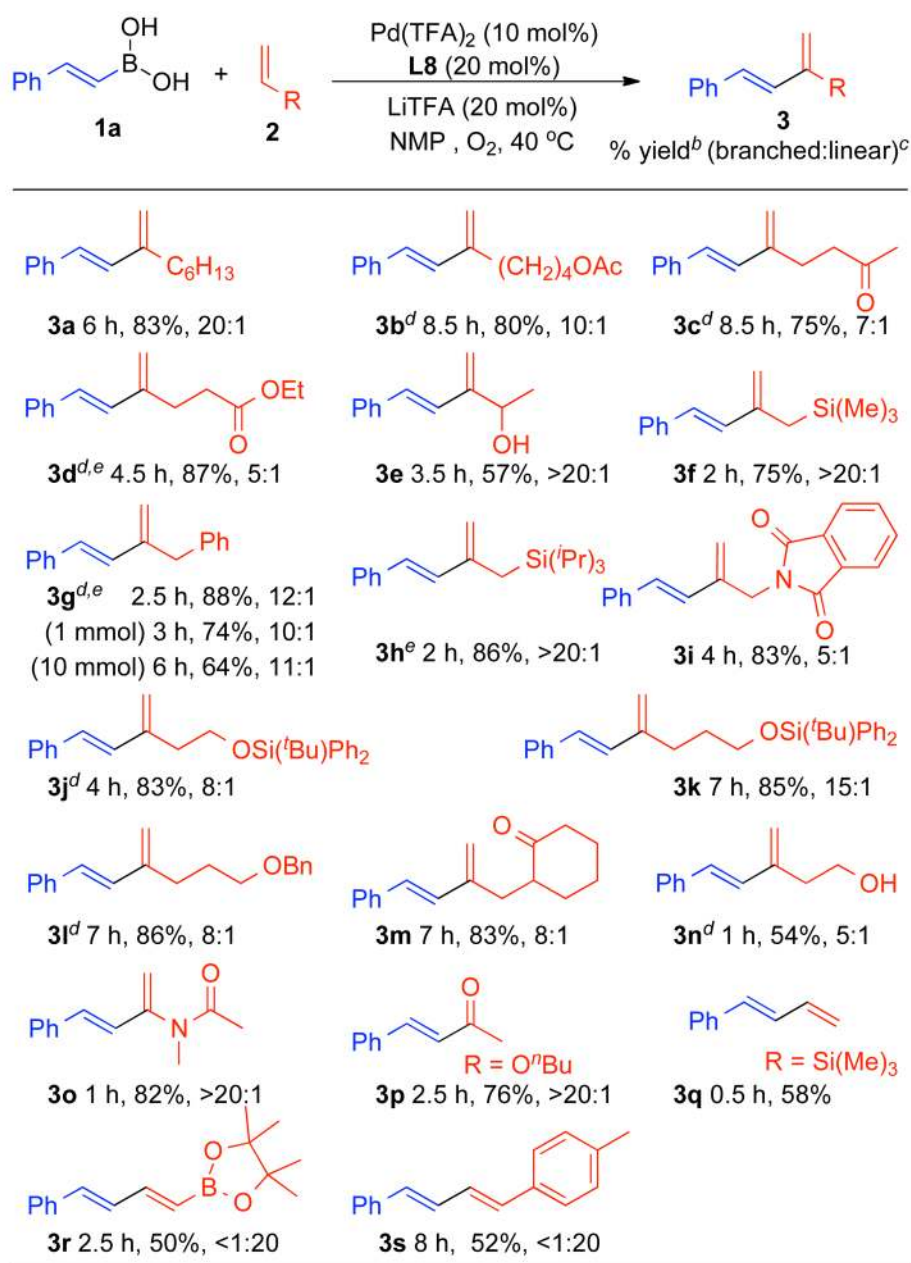
**Chart 1.**Ligand Effects on the Oxidative Heck Coupling of Styrenylboronic Acid and Octene<sup>a</sup><sup>a</sup> Reaction conditions: vinyl boronic acid (1.5 equiv), alkene (0.2 mmol), NMP (0.5 mL).Reactions were monitored on GC using 4-methylanisole as the internal standard. <sup>b</sup> GCyield. <sup>c</sup> Determined by GC and <sup>1</sup>H NMR. <sup>d</sup> Pd(TFA)<sub>2</sub> (20 mol%) and ligand (40 mol%)were used. <sup>e</sup> LiTFA (0.2 equiv) was added.

Table 1

Diene Synthesis via Oxidative Heck Coupling of (*E*)-Styrenylboronic Acid and Terminal Olefins.<sup>a</sup><sup>a</sup>Reaction conditions: vinyl boronic acid (1.5 equiv), alkene (0.2 mmol) in NMP (0.5 mL).<sup>b</sup>Isolated yields.<sup>c</sup>Branched:linear selectivity determined by GC and <sup>1</sup>H NMR spectroscopy.<sup>d</sup>Isolated as a mixture of branched and linear regioisomers.

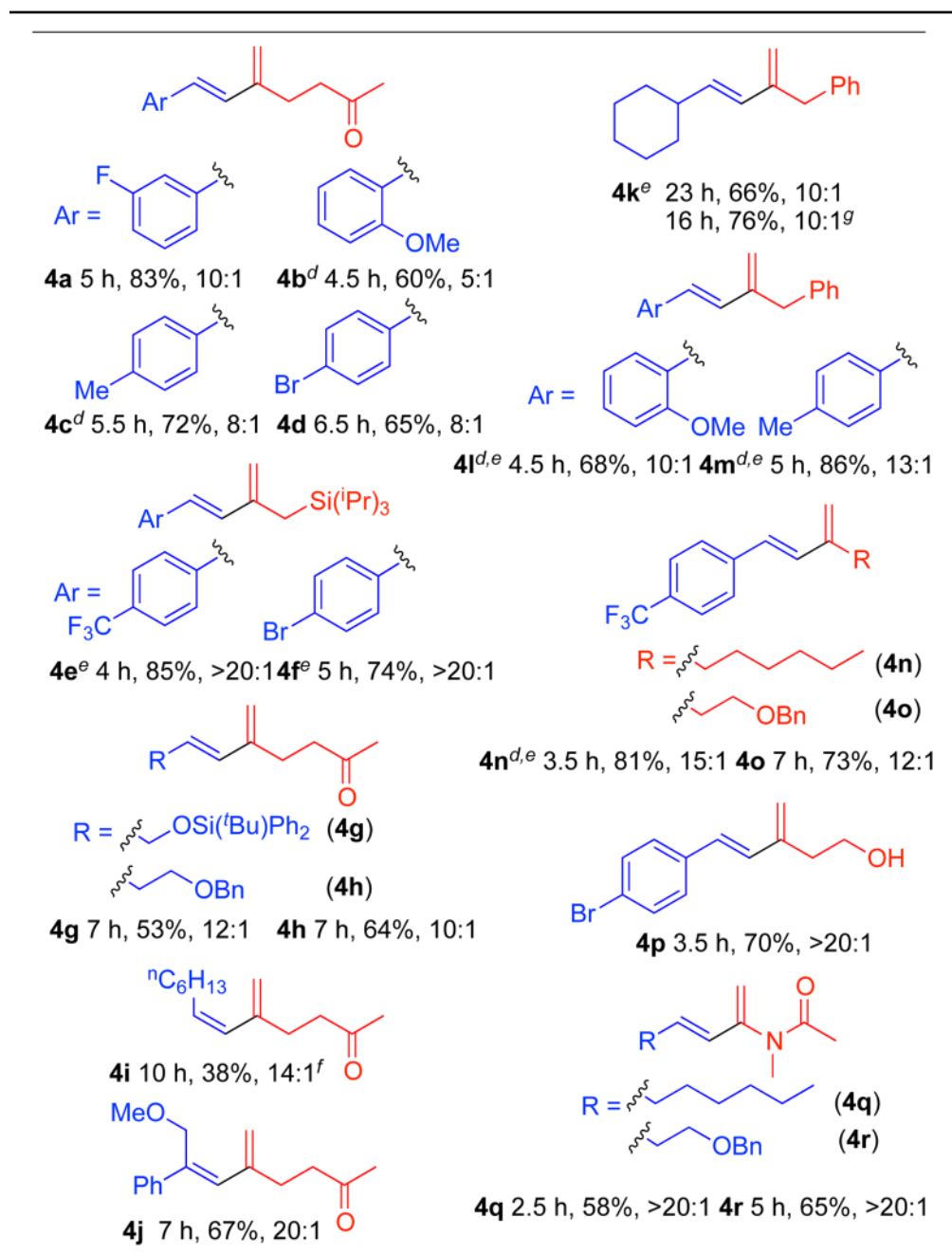
<sup>e</sup>Some isomerization of the diene (< 5%) occurs during purification.

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Table 2

Diene Synthesis via Oxidative Heck Coupling of Diverse Vinylboronic Acids and Terminal Olefins.<sup>a</sup><sup>a</sup>The reactions were performed with vinyl boronic acid (1.5 equiv), alkene (0.2 mmol) in NMP (0.5 mL) at 40 °C.<sup>b</sup>Isolated yields.<sup>c</sup>Branched:linear selectivity determined by GC and <sup>1</sup>H NMR spectroscopy.

<sup>d</sup>Isolated as a mixture of the branched and linear regioisomers.

<sup>e</sup>Some isomerization of the diene (< 5%) occurs during purification.

<sup>f</sup>*cis*-Octenylboronic acid used; (*Z*)-**4i**:(*E*)-**4i** = 3.5:1.

<sup>g</sup>Catalyst/additive loading doubled.

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