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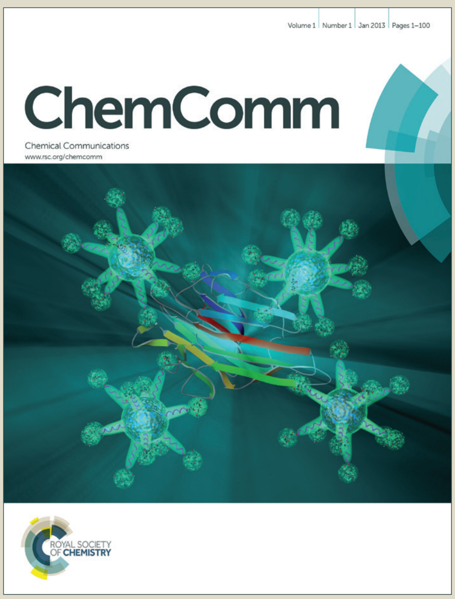

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Regioselective Aerobic Oxidative Heck Reactions with Electronically Unbiased Alkenes: Efficient Access to α-Alkyl Vinylarenes

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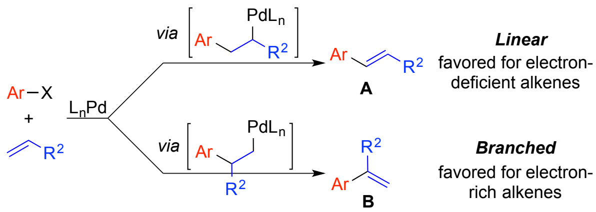
Branched-selective oxidative Heck coupling reactions have been developed between arylboronic acids and electronically unbiased terminal alkenes. The reactions exhibit high catalyst-controlled regioselectivity favoring the less common branched isomer. The reactions employ a catalyst composed of $Pd(TFA)_2$/dmphen (TFA = trifluoroacetate, dmphen = 2,9-dimethyl-1,10-phenanthroline) and proceed efficiently at 45-60 °C under 1 atm of O_2 without requiring other additives. A broad array of functional groups, including aryl halide, allyl silane and carboxylic acids are tolerated.

Mizoroki-Heck coupling reactions have found widespread use in organic synthesis[1] and are among the most versatile methods for selective functionalization of vinylic C–H bonds.[2] The ability to use unfunctionalized alkenes as substrates rather than vinyl halides represents a significant advantage over other cross-coupling methods for the synthesis of substituted alkenes. Several challenges, however, limit the scope of these reactions and prevent the advantages from being fully realized. Most precedents achieve regioselectivity by using substrates that have an intrinsic electronic bias (Scheme 1). Electron-deficient alkenes such as acrylates and styrenes favor coupling at the terminal position to give the linear products,[3] while electron-rich vinyl ethers and vinyl amides favor coupling adjacent to the heteroatom to give the branched products.[4] When electronically unbiased alkenes are used, the reaction often undergoes competitive reactions to afford different regioisomers with low selectivity, typically favoring the linear regioisomer. These issues were illustrated by Heck in 1974 in the reaction of bromobenzene with *n*-hexene, which under commonly used conditions afforded the linear phenylhexene as the major product, together with three other isomeric products.[5]

Recent developments have begun to address these limitations through the identification of appropriate substrate partners, reaction conditions and catalyst systems. For example, White[6a,b] and co-workers achieved substrate-controlled linear-selective



Scheme 1. Regioselectivity in Pd-catalyzed Heck coupling reactions.

product formation with electronically unbiased alkenes via the use of chelating functional groups in alkene substrate. Sigman[6c,d] et al. identified appropriate catalyst systems that could achieve linear-selective coupling of simple alkenes with arylboronic acids or aryl diazonium salts.

Branched-selective Heck coupling typically requires electron-rich substrates, as noted above,[4,7] but recent advances have led to catalysts capable of achieving branched selectivity with unbiased alkenes. Specifically, Zhou and co-workers reported Pd[0]-catalyzed Heck-coupling reactions between aliphatic olefins and aryl triflates using a bulky bisphosphine "dnpf" ligand [dnpf = 1,1'-bis[di(1-naphthyl)phosphino]-ferrocene].[8] Jamison and co-workers reported Ni-catalyzed Heck-type coupling reactions of aryl sulfonates and related substrates with terminal olefins that achieve high levels of branched selectivity.[9,10] Finally, in connection with our interest in Pd-catalyzed aerobic oxidative coupling reactions,[11] we recently developed a method for oxidative Heck coupling of vinylboronic acids and electronically unbiased alkenes that afford branched-selective 1,3-disubstituted conjugated dienes.[12] Here, we describe aerobic oxidative Heck reactions between arylboronic acids and electronically unbiased alkenes that proceed with high catalyst-controlled selectivity for the branched isomer. The sterically encumbered 2,9-dimethyl-1,10-phenanthroline (dmphen) ligand is crucial to control of the regioselectivity (Scheme 2).[13] The resulting α-alkyl vinylarenes are important precursors to chiral building blocks (via asymmetric hydrogenation and other transformations) and intermediates in the synthesis of bioactive natural products. The stability of α-branched styrenes relative to the conjugated dienes obtained in our previous study enables the reactions to proceed with improved efficiency. Furthermore, the mild air- and moisture-tolerant conditions allow the reactions to tolerate aryl

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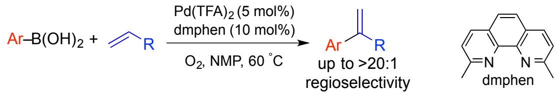
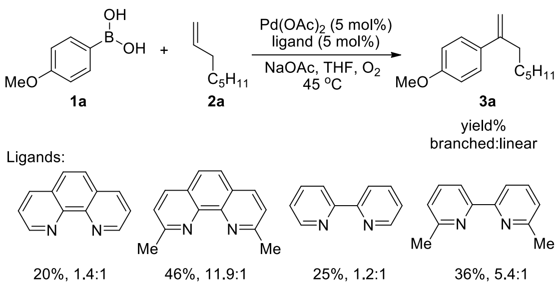
halide and allyl silane substrates that are often not compatible with traditional cross-coupling conditions (including the branched-selective Heck reactions noted above).



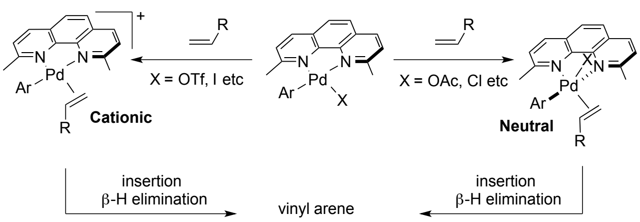
Scheme 2. Branched-selective aerobic oxidative Heck reactions with electronically unbiased alkenes

Our initial studies focused on assessing ligand effects on Pd(OAc)$_2$-catalyzed coupling of 4-methoxyphenylboronic acid (**1a**) and 1-octene (**2a**) in tetrahydrofuran (THF). Reactions with monodentate pyridine ligands such as pyridine and 2-fluoropyridine exhibited a slight preference for linear product formation, albeit with low yields (<10% yield). Improved results were obtained with bidentate nitrogen ligands (Scheme 3). Improved yields were observed with 2,9-dimethyl-1,10-phenanthroline (dmphen) and 6,6'-dimethyl-2,2'-bipyridine which bear two methyl groups adjacent to the nitrogen. The branched product was favored in both of these reactions, with branched:linear selectivity up to ~12:1 when the dmphen ligand was used. Related substituted-phen and -bpy ligands have been used previously in traditional and oxidative Heck-type coupling reactions; however, these precedents typically feature electronically biased substrates (e.g., vinyl amides or acrylates) in which the reactions exhibit product regioselectivity consistent with the substrate electronic effects.[13]



Scheme 3. Preliminary ligand screening showing the influence of ligands on regioselectivity

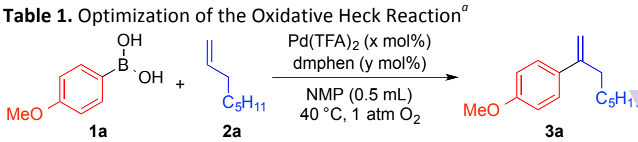
Cabri and co-workers have shown that Heck reactions that proceed via a "cationic pathway" exhibit enhanced selectivity for branched product formation with electron-rich alkenes owing to increased charge build-up in the alkene-insertion transition state.[13b] The cationic pathway can be favored over a less regioselective five-coordinate neutral pathway by using less basic counterions and/or more polar solvent to facilitate dissociation of the anionic ligand (Scheme 4).



Scheme 4. Cationic versus neutral, five-coordinate pathways.

These considerations prompted us to test alternative counterions and solvents for the oxidative coupling of **1a** and **2a**. Selected results are summarized in Table 1. Up to 71% yield of the branched styrene product was obtained by replacing Pd(OAc)$_2$ with Pd(TFA)$_2$ and by changing the solvent from THF to *N*-methylpyrrolidone (NMP) (cf. entry 3, Table 1). The best results were obtained by using a 2:1 dmphen:Pd ratio, possible arising from catalyst decomposition, which results in lower reaction yields at a 1:1 ligand:Pd ratio (cf. entry 4). All reactions with Pd(TFA)$_2$ as the Pd source exhibited high regioselectivity (>15:1), consistent with the involvement of the Cabri-like cationic pathway. The reactions performed in different solvents exhibited high regioselectivities in the presence of the Pd(TFA)$_2$/dmphen catalyst system (entries 1-3). Assessment of acidic and basic additives (e.g., entries 5-7) did not improve the reaction outcome. Standard reaction conditions employed 1.5 equiv of the boronic acid to account for the small amount of homocoupling side reaction; however, good product yields were also obtained by using the arylboronic acid as the limiting reagent with excess alkene (2 equiv) (72% yield; cf. entries 8 and 9). Increasing the reaction temperature to 60 °C led to a slight improvement in the yield (entry 10).

Table 1. Optimization of the Oxidative Heck Reaction[a]

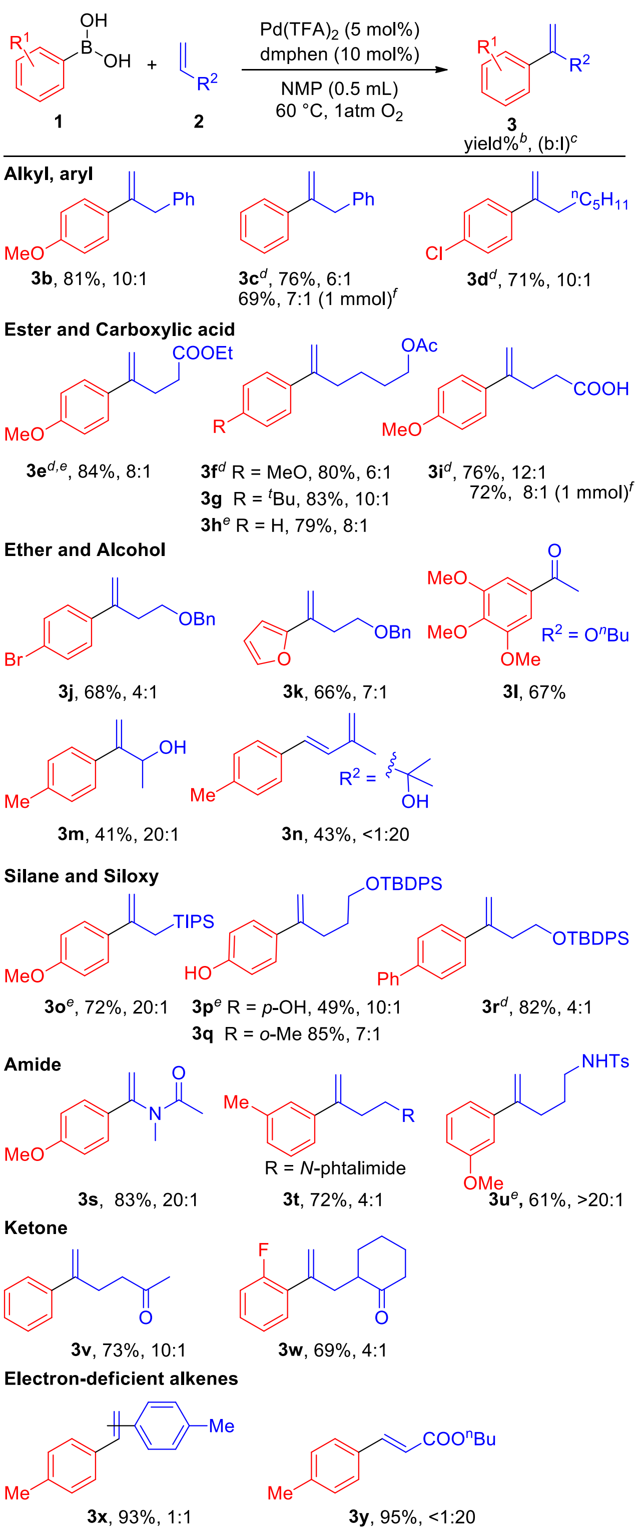


Entry	Pd/dmphen (x/y mol %)	additive[b]	solvent	yield (%)[c]
1	5/10	-	Dioxane	55
2	5/10	-	CH_3CN	13
3	5/10	-	NMP	71
4	10/10	-	NMP	43
5	5/10	KF	NMP	57
6	5/10	$PhCO_2H$	NMP	62
7	5/10	NMM	NMP	60
8[d]	5/10	-	NMP	60
9[e]	5/10	-	NMP	72
10[e,f]	5/10	-	NMP	75 (70)

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), NMP (0.5 mL), 6 h. [b] y mol% of the additives used. [c]GC yield based on **2a** (or limiting reagent). Regioselectivity (branched:linear) >15:1. [d] **1a/2a** = 0.2 mmol/0.2 mmol. [e]**1a/2a** = 0.2 mmol/0.4 mmol. [f]Reaction performed at 60 °C. NMM = *N*-methyl morpholine. NMP = *N*-methyl pyrrolidone.

The additive-free reaction conditions identified above were then used to explore the substrate scope. Before performing test with a broad substrate scope, several substrate partners were tested at different ratios between the arylboronic acid and alkene (1.5:1, 1:1, and 0.5:1). In general, the results at 1.5:1 substrate ratio afforded the best product yields, owing to the formation of small amounts of homocoupled biaryls from the boronic acid substrate (see Table S1 in the ESI† for details). The reactivities of a variety of arylboronic acids were tested with diverse alkenes, and the products are displayed in Table 2 according to the different functional groups present in the alkene. Except where indicated otherwise, the

Table 2. General Scope with a Variety of Arylboronic Acids and Olefins.[a]



[a]Reaction conditions: Pd(TFA)2 (0.01 mmol), dmphen (0.02 mmol), NMP (0.5 mL), 60 °C, 6 h. For **3b**, **3e-3f**, **3o**: **1/2** = 0.2 mmol/0.4mmol. For other substrates: **1/2** = 0.3 mmol/0.2 mmol. [b]Isolated yield. [c]Ratio of branched:linear was determined by ^{1}H NMR spectroscopy analysis of crude reaction mixture. [d]Isolated as a mixture of branched and linear (~10%) regioisomers. [e] Isomerization (~10%) to the internal alkenes occurred during purification. [f]Reaction in a round-bottom flask under O_2 balloon.

reactions were performed with 1.5 equiv of boronic acid relative the alkene. All of the yields were obtained following isolation ar purification, and two of the products (**3c** and **3i**) were prepared c 1 mmol scale to confirm the reliability of the reactions.

The alkyl and phenyl containing alkenes reacted effectively wi phenylboronic acids bearing *p*-MeO, -H, and -Cl substituents (**3a-3d**), with regioselectivity ranging from 6:1 (**3c**) to 15:1 (**3a**). Alken with ester moieties were even more effective, with yields typically above 80% (**3e-3g**). A free carboxylic acid was also well-tolerated this reaction (**3i**). Three olefins with ether functionality, including *tert*-butyl vinyl ether, were demonstrated with electron deficient (*p*-bromophenyl) and electron-rich (2-furanyl, and 3,4,5-trimethoxyphenyl) boronic acids (**3j-3l**). It is worth noting that t bromide substituent derived from the arylboronic acid in **3j** (similar to the aryl chloride in **3d**) is tolerated owing to the mildness of t reaction conditions relative to typical Pd(0)-catalyzed reactions. The electron-rich *tert*-butyl vinyl ether substrate reacts exclusively "branched" selectivity, as expected, and the resulting product t hydrolyzes in situ to give the aryl methyl ketone **3l**.[16] Two alkenes with free alcohol groups proceed in modest yields (**3m** and **3n**). In the case of the tertiary alcohol 2-methyl-3-buten-2-ol, the produ t derives from linear-selective alkene functionalization, following by spontaneous dehydration to afford the conjugated diene **3n**. Th switch in regioselectivity probably arises primarily from a steric effect of the fully substituted carbon center adjacent to the alken. In contrast, an allyl silane with the sterically hindere triisopropylsilyl substituent (TIPS) proceeds in good yield (72%, **3o**) and excellent regioselectivity (20:1). In this case, the electro donating beta-silicon effect, which should promote branched selectivity, presumably overrides any steric effect favoring th linear insertion product. This reactivity is quite appealing in light of the synthetic utility of substituted allyl silanes. Good results we also obtained with alkenes bearing remote siloxy groups (**3p-3r**), although the presence of the free phenol in the boronic acid u to afford **3p** appears to attentuate the product yield. An electronically biased vinyl amide affords the branched product **3s** in very good yield and regioselectivity, as expected, and remot phthalimide and secondary sulfonamide substituents were we tolerated (**3t**, **3u**). Alkenes with pendant ketones (a methyl keton and cyclohexanone) also were effective substrates (**3v**, **3w**), and di not appear to be complicated by Pd-enolate formation (e.g., whic could lead to dehydrodrogenation[17]). Styrene and butyl acrylate a electronically biased alkenes that typically favor linear product formation. The linear product remains strongly preferred with o catalyst system in the case of butyl acrylate (**3y**: 95% yield with >20:1 regioselectivity), but styrene affords a 1:1 mixture of regioisomeric products (**3x**).

Factors that govern regioselectivity in Heck-type couplir reactions have been discussed extensively in the literature.[2c,1] Bidentate ligands lead to cationic $[Pd^{II}(L_2)(aryl)(alkene)]^{+}$ intermediates that exhibit higher branched selectivity relativ neutral $Pd^{II}(L)(X)(aryl)(alkene)$ intermediates formed wit monodentate ligands. The cationic charge enhances charge build-u in the alkene-insertion transition state, thereby favoring

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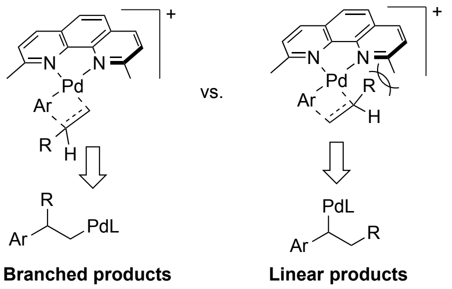
branched (Markovnikov) product. Access to the cationic intermediate noted in Scheme 4 is facilitated by use of the trifluoroactate anion, which may be readily displaced by an alkene.[18] Electronic effects are not sufficient to explain the present results, however, because bidentate ligands lacking the methyl groups exhibit little selectivity for the branched product (cf. Scheme 3). Thus, the high regioselectivity is best rationalized by synergistic electronic and steric effects, whereby the methyl groups in the dmphen ligand sterically inhibit formation of the linear coupling product, as depicted in Scheme 5.



Scheme 5. Transition state structures showing the steric contributions to branched vs. linear product formation.

In this study, we have identified a readily accessible Pd^{II} catalyst system for aerobic oxidative coupling of arylboronic acids and electronically unbiased alkenes. The catalyst enables highly regioselective formation of α-substituted vinylarenes with substrates bearing diverse functional groups. The ease of operation and broad substrate scope make this method readily accessible and highly appealing for synthetic applications.

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