

Palladium-Catalyzed 1,1-Difunctionalization of Ethylene

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Supporting Information

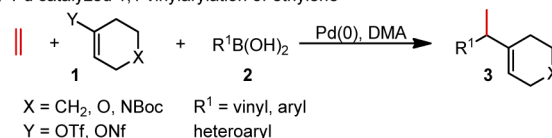
ABSTRACT: The 1,1-difunctionalization of ethylene, with aryl/vinyl/heteroaryl transmetalating agents and vinyl electrophiles, is reported. The reaction is high-yielding under a low pressure of ethylene, and regioselectivity is generally high for the 1,1-disubstituted product. The process is highlighted by the use of heteroaromatic cross-coupling reagents, which have not been competent reaction partners in previously reported efforts.

Ethylene is an industrial petrochemical and natural product with an annual production of >100 million tons. Additionally, up to 30% of all petroleum-based commodity chemicals are derived from ethylene, as suggested by it being the most abundant organic chemical produced globally by volume.¹ However, the utility and abundance of ethylene has not found frequent use in fine chemical and complex target synthesis, although notable exceptions include Heck reactions,² alkene hydrovinylation reactions pioneered by Rajanbabu,³ and enyne metathesis processes.⁴ Besides the general technical complexities of using a gas, the potential reason for the scarcity of reports exploiting ethylene for synthesis may arise from its inherent simplicity. That is, addition of one functional group to the ethylene framework (e.g., the Wacker oxidation⁵ or a Heck reaction²) results in molecules of modestly enhanced complexity. Therefore, we sought to develop new complexity-generating cross-coupling reactions involving ethylene. In this regard, we report herein a mild, three-component coupling of vinyl electrophiles, a diverse array of organometallic reagents, including heteroaromatic partners, and 15 psi pressure of ethylene to construct two C–C bonds at a terminal end of ethylene.

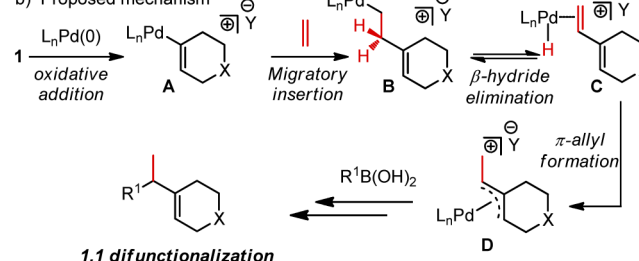
For the past several years, our group has been focused on the development of palladium-catalyzed alkene difunctionalization reactions that avoid Heck products resulting from β -hydride elimination.⁶ Conceptually, most of these reactions rely on the formation of stabilized Pd-alkyl intermediates. In the case of ethylene difunctionalization, we propose the use of a cyclic vinyl triflate, similar to our recently reported three-component coupling reaction of simple terminal alkenes,^{6a} to initiate the catalysis. This is due to the relative ease with which these reagents undergo oxidative addition to form intermediates of type A (Scheme 1). Additionally, the resultant Pd(II)-complex is electrophilic in nature due to the noncoordinating counterion, which should facilitate ethylene insertion to avoid the Suzuki cross-coupling pathway.⁷ The most intriguing mechanistic step is the Pd migration via β -hydride elimination of the Pd-alkyl B and reinsertion of the diene into the putative Pd–H

Scheme 1. Proposed 1,1-Difunctionalization of Ethylene with Vinyl Electrophiles and Boronic Acids

a) Pd catalyzed 1,1 vinylarylation of ethylene



b) Proposed mechanism



intermediate C, which is likely promoted by the formation of a π -allyl adduct D. Subsequent cross-coupling of a boronic acid with D completes the proposed catalytic cycle, furnishing the 1,1-ethylene difunctionalization product. It should be noted that reductive elimination⁸ can occur on either side of the π -allyl intermediate; as a consequence of this, the other regioisomer can be observed. Nevertheless, the regioselectivity is likely biased by the formation of the thermodynamically more favorable endocyclic double bond.

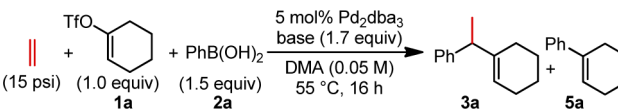
Ethylene was subjected to slightly modified optimal conditions previously reported by our group for the difunctionalization of terminal olefins (Table 1, entry 1).^{6a} Only a modest yield of the desired product was observed at 15 psi of ethylene, and conversion of the vinyl triflate 1a, which is the limiting reagent in this reaction, was incomplete. Increasing the pressure of ethylene to 30 psi did not improve the outcome (entry 2). To improve the conversion of the vinyl triflate, electron-rich phosphines were evaluated and, not surprisingly, a significant amount of the Suzuki product was observed consistent with faster transmetalation than ethylene insertion. More Suzuki product was observed as a function of the phosphine cone angle (entries 3–5).⁹ Considering the ineffectiveness of phosphines as well as solvent variation for improving yields (see Supporting Information), other ligands were considered. Specifically, dibenzylideneacetone (dba) was evaluated, as it was reasoned that this ligand would help stabilize Pd(0) intermediates from decomposition, but may not

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Table 1. Reaction Optimization



entry	ligand	base	yield of 3a (%) ^a	ratio 3a:5a
1	—	KF	30	3a only
2 ^b	—	KF	25	3a only
3	PPh ₃ (20 mol %)	K ₂ CO ₃	57	60:40
4	P(^t Bu) ₃ (20 mol %)	K ₂ CO ₃	0	5a only ^c
5	P(Cy) ₃ (20 mol %)	K ₂ CO ₃	19	30:70
6	dba (15 mol %)	K ₂ CO ₃	70	3a only
7	dba (15 mol %)	NaHCO ₃	82	3a only
8	—	NaHCO ₃	50	3a only
9	dba (15 mol %)	—	40	3a only
10 ^d	dba (15 mol %)	NaHCO ₃	90	3a only

^aDetermined by NMR using an internal standard. ^bReaction performed at 30 psi. ^cHeck product was observed in 21% yield. ^dThe reaction was performed at 0.1 M in 1a.

affect the electrophilic nature of the Pd(II) species presumably required for efficient reaction due to the electron-poor nature of this ligand.¹⁰ Indeed, addition of dba considerably enhanced the reaction outcome (entry 6). Further improvements were found by changing the base (entry 7) and increasing the concentration of the vinyl triflate (entry 10). Removal of either dba (entry 8) or the base (entry 9) resulted in significantly lower yields.

Using the optimized conditions, the scope of the three-component coupling was explored, where phenyl boronic acid yielded the desired product in high yield and selectivity (Table 2, 3a). Excitingly, the more stable and cost-effective nonaflates (ONf) are similarly effective electrophiles (3a).¹¹ Both vinyl

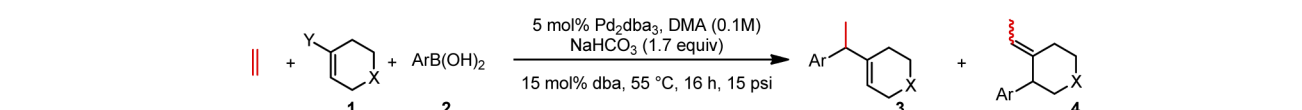
nonaflates and triflates were used interchangeably throughout these studies. Heterocyclic triflates containing oxygen (3j–3l) and Boc-protected nitrogen groups (3m–3q) performed well, although modest effects on regioselectivity were observed. As previously observed, linear vinyl triflates are effective coupling partners but a significant reduction in the ratio of 3 to 4 is observed.^{6a}

Functionalized phenyl boronic acids with electron-donating substituents such as methoxy and isopropoxy at the *para* position are excellent coupling partners with high regioselectivity observed (3c, 3d). Various phenyl boronic acids bearing common functional groups in synthesis are good substrates: an aldehyde (3e, 3k, 3q), an ester (3f), a ketone (3g, 3m), and a chloride (3l). Tertiary (3r), secondary (3h), and free amides (3i) were found to be compatible functional groups under these reaction conditions. Electron-withdrawing substrates, such as 4-trifluoromethyl (3j) and 4-fluoro (3o) phenyl boronic acids,¹² provided the three-component coupling products in good yields. The use of an arylboronic acid pinacol ester (Bpin) is also effective (3c) in comparable yields (87% for Bpin and 95% for B(OH)₂).

To further explore the scope, vinyl boronic acid derivatives were evaluated under the optimized conditions. In general, the reaction performs similarly to aryl boronic acid derivatives to yield skipped-diene products. For example, high yields using (*E*)- β -styryl (3s) and simple (*E*)-alkenyl boronic acids (3t) are observed but with significantly lower regioselectivity for formation of the *endo*- versus *exocyclic* products (Figure 1). The origin of this result is not currently understood. Cyclic vinyl boronic esters (Bpin) having heteroatoms such as oxygen and Boc protected nitrogen serve as effective coupling partners (3u, 3v).

To further examine and expand the scope of the reaction, the use of heteroaromatic organometallic reagents was considered,

Table 2. Scope (Yields Average of at Least Two Experiments)



3a, (OTf)=90% (ONf)=87% (20:1) ^a	3b, 82% (9:1)	3c ^b , 95% (9:1)	3d, 87% (9:1)	3e, 85% (20:1)	3f, 85% (14:1)
3g, 61% (14:1)	3h, 76% (14:1)	3i, 82% (13:1)	3j, 65% (3:1)	3k, 71% (10:1)	3l, 60% (4:1)
3m, 55% (10:1)	3n, 58% (3:1)	3o, 68% (4:1)	3p, 72% (5:1)	3q, 75% (6:1)	3r ^c , 60% (>20:1)

^aRepresents the regioselectivity of 3:4. Regioselectivity determined by ¹H NMR of the crude reaction mixture. ^b4-Methoxy phenylboronic acid pinacol ester yields the desired compound (3c) in 87% yield and similar regioselectivity. ^cBoronic acid pinacol ester was used. Note: (1) For 3b–3e, 3g, 3i, 3m–3q, vinyl triflates were used; for 3f, 3h–3l, 3r, vinyl nonaflates were used. (2) For products 3a–3i, yields are reported as a mixture of regioisomers. For products 3j–3r, yields are reported as only the desired three-component coupling product. (3) The products were accompanied by polyethylene as a contaminant (see Supporting Information for details).

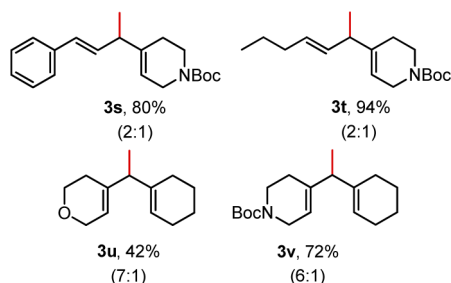
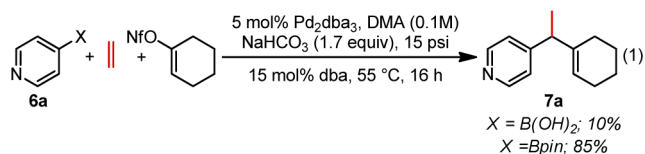


Figure 1. Scope of the three component coupling of ethylene, vinyl nonaflates, and vinyl boronic acids/esters. The regioselectivity of **3:4** is in parentheses. For **3s** and **3t**, boronic acid was used. For **3u** and **3v**, boronic acid pinacol ester was used. *Note:* (1) In the case of **3u** and **3v**, cyclohexenyl nonaflate was used as an electrophile. (2) Yields are reported as a mixture of regioisomers. (3) The products were accompanied by polyethylene as a contaminant.

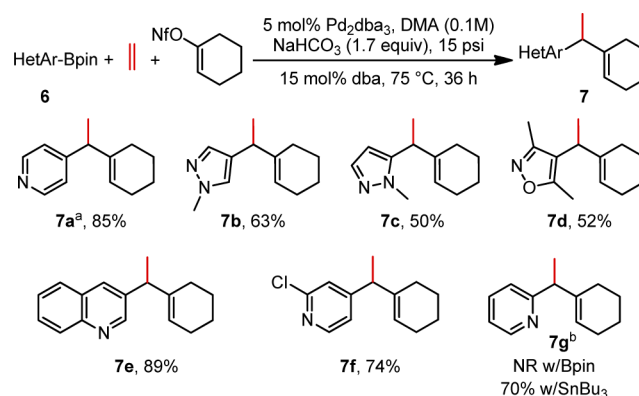
as they pose a greater challenge and allow access to considerably more structurally diverse products. Significant issues have been encountered in Suzuki reactions employing these reagents, as their Lewis basicity, slow rate of transmetalation, and ability to undergo protodeborylation all have been proposed to limit their successful coupling. Ligand-controlled solutions to some of these issues have been reported recently by the groups of Buchwald,¹³ Fu,¹⁴ Plenio,¹⁵ and others.¹⁶

Indeed, in our previous efforts with terminal alkene three-component couplings,^{6a} reactions of heteroaromatic boronic acids like **6a** fail to yield the desired product with low conversion of the vinyl triflate observed. Therefore, it was not surprising that a low yield of the ethylene difunctionalization reaction with **6a** was found (eq 1). However, a modest change



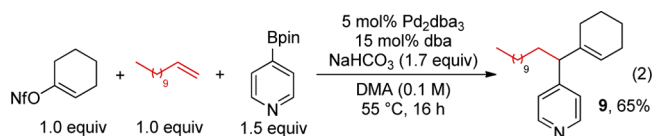
from the boronic acid to the pinacol ester (Bpin) led to the successful three component coupling of these reagents (eq 1), allowing for a significant expansion of the scope, as depicted in Table 3. Surprisingly, under these reaction conditions, only a single regioisomer is observed. Increasing the reaction time (36 h) and temperature (75 °C) allowed for enhanced yields. Various heterocyclic boronic esters perform well under these conditions as demonstrated by the use of five-membered heterocycles (**7b–7d**). In addition, the more challenging substrates 3-quinoline (**7e**) and a 2-substituted 4-pyridyl (**7f**) boronic ester gave excellent yields of the desired product. However, the reaction is sensitive to the nature of the nucleophile as the reaction of 3-pyridineboronic ester and 3-isoquinoline boronic ester produced low yields (<10%) of the desired three-component coupling products. Of interest, 2-pyridyl boronic acid derivatives have been found to be highly prone to protodeborylation¹⁷ and in the current system are not compatible with the reaction. However, replacement of the Bpin derivative with the Stille reagent led to an excellent yield of the three-component coupling of ethylene (**7g**). Finally, to explore if the changes in the reaction conditions can be extended to a simple terminal alkene, dodecene was evaluated with **6a**. Using only a single equivalent of the terminal alkene,

Table 3. Scope of Three-Component Coupling of Heteroaryl Boronic Acid Pinacol Ester, Vinyl Nonaflates, and Ethylene



^aReaction performed at 55 °C for 16 h. ^bReaction performed at 55 °C using CsF as base. ^cThe products were accompanied by polyethylene as a contaminant.

the reaction is now effective (eq 2). The overall success of this cross-coupling reaction in the absence of bulky, electron-rich



phosphine ligands is in great contrast with that which has been reported in the cross-coupling of heteroaromatic partners suggesting some unique mechanistic features of this reaction.

In summary, we have developed a catalytic method that utilizes ethylene as a substrate in a three-component cross-coupling reaction to rapidly access structurally unique compounds containing various pharmacophores under study in our laboratory.^{6c} In this vein, the scope of the reaction is broad, allowing for the vinylarylation and vinylvinylolation of ethylene, as well as the extension to heteroaromatic coupling partners by employing boronic ester derivatives. This advance not only clearly impacts a major limitation of our previous efforts in terms of scope but also opens up intriguing mechanistic questions. Considering this, future work is focused on expansion of the scope and understanding the underlying means by which this cross-coupling operates to facilitate this effort and the development of an enantioselective variant.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for new substances. 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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