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Hydroarylation of terminal alkynes with arylboronic acids catalyzed by low loadings of palladium

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ABSTRACT

The hydroarylation reaction of terminal alkynes with arylboronic acids catalyzed by low (400 ppm) loadings of palladium has been developed. The reaction is broad in scope and high-yielding, even on multigram scale. It is suitable for the synthesis of alkenes labeled with deuterium, and for the late-stage modification of bioactive molecules.

The 1,1-disubstituted alkene motif is ubiquitous in natural [1,2] and synthetic products [3–11], and can be prepared by many methods, such as Wittig or Peterson olefinations [12,13], olefin metathesis [14,15], and hydroarylation of alkynes using organometallic reagents [16–21]. Several different classes of organometallic reagents including organolithiums, organozinc reagents, organoboron and Grignards reagents are compatible with this reaction, of which organoboron reagents have attracted significant attention due to their imperviousness to air and moisture, broad tolerance for various functional groups, ready availability, and minimal toxicity [22]. Hayashi [23] and Shirakaw [24] independently reported the first hydroarylation of alkynes with arylboronic acids using Rh/Ni catalysts in 2001, and Oh reported the first example of a Pd(0)-catalyzed version in 2003 [25], which relies on an acid additive (HOAc) [25–27]. Since then, palladium catalyzed versions using alkaline additives [28], as well as copper [29] and cobalt [30] catalyzed versions, have all been developed (Scheme 1A). However, despite this progress, these reactions are severely limited in that terminal alkynes are poorly compatible with almost all of them, a severe limitation given the ubiquity of the unsubstituted alkene motif [31]. Oh's conditions are suitable for terminal alkynes (Scheme 1B), but catalyst loadings of up to 3 mol% are needed — a major drawback due to dwindling supplies of economically accessible noble metals, sustainability concerns [32], and FDA regulation of metal impurities in pharmaceutical products [33,34]. Therefore, the ability to use ultra-low loadings ($\leq$1000 ppm) of homogeneous noble metal catalyst in cross-coupling reactions [35–40] would be greatly advantageous.

Herein, we report that the hydroarylation of terminal alkynes with arylboronic acids can be catalyzed by low loadings (400 ppm = 0.04 mol%) of Pd in the presence of an alkaline additive (Scheme 1C).

In preliminary studies, we screened a selection of Pd catalysts against the model substrates 4-ethynylaniline (**1**) and 4-(trimethy-lsilyl)phenyl)boronic acid (**2**) using KOAc as an additive (Table 1). As expected, the reaction yield was highly dependent on the nature of the Pd catalyst. When 400 ppm of $Pd(OAc)_2$, $PdCl_2$ or $Pd_2(dba)_3$ were used, the target product **3** could not be detected (entries 1–3). However, **3** was obtained in low yield (40% and 10%, respectively) using 400 ppm of $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ (entries 4 and 5). Using $Pd(OAc)_2$/PPh_3, $Pd(OAc)_2$/Davephos or $Pd(OAc)_2$/Ruphos (400 ppm/50,000 ppm), **3** was obtained in low yield (entries 7, 9 and 11). However, when $Pd(OAc)_2$/Binap, $Pd(OAc)_2$/tbuXphos or $Pd(OAc)_2$/1,10-Phen (400 ppm/50,000 ppm) were used, **3** was not detected at all (entries 8, 10 and 12). Notably, using 400 ppm of $Pd(PCy_3)_2Cl_2$, **3** was obtained in 80% yield (entry 13). Decreasing the amount of $Pd(PCy_3)_2Cl_2$ below 400 ppm decreased the yield of **3** (300 ppm, 75%, 200 ppm, 41%, 100 ppm, 15%, 50 ppm, 6%) (entries 14–17). Finally, several additives were also tested. PhCOOK, PivOK, AdOK, NaOAc all promoted the reaction, but were less effective than KOAc (entries 18–21) and inferior reaction yields were observed with CsF, K_2CO_3, TEA, DBU as the additives (entries 22–25). For the screening of the sol-

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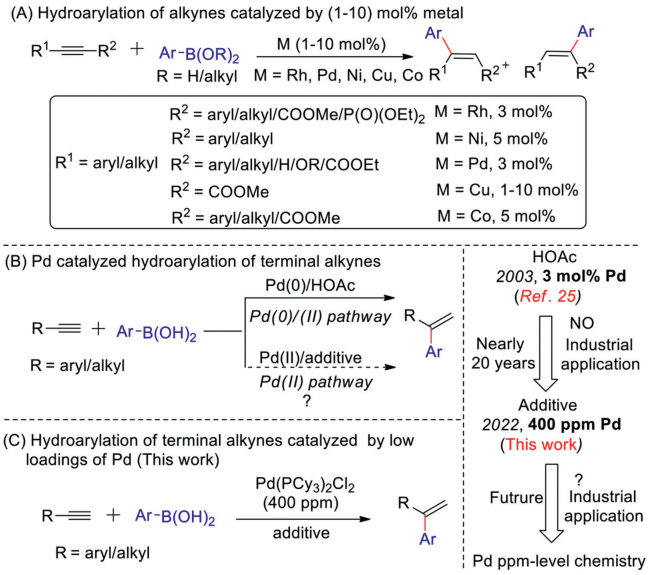
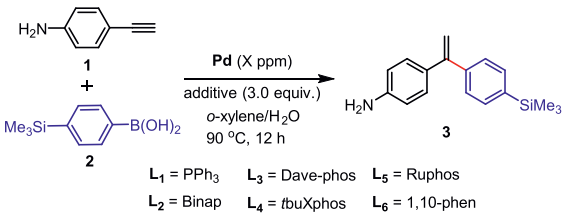


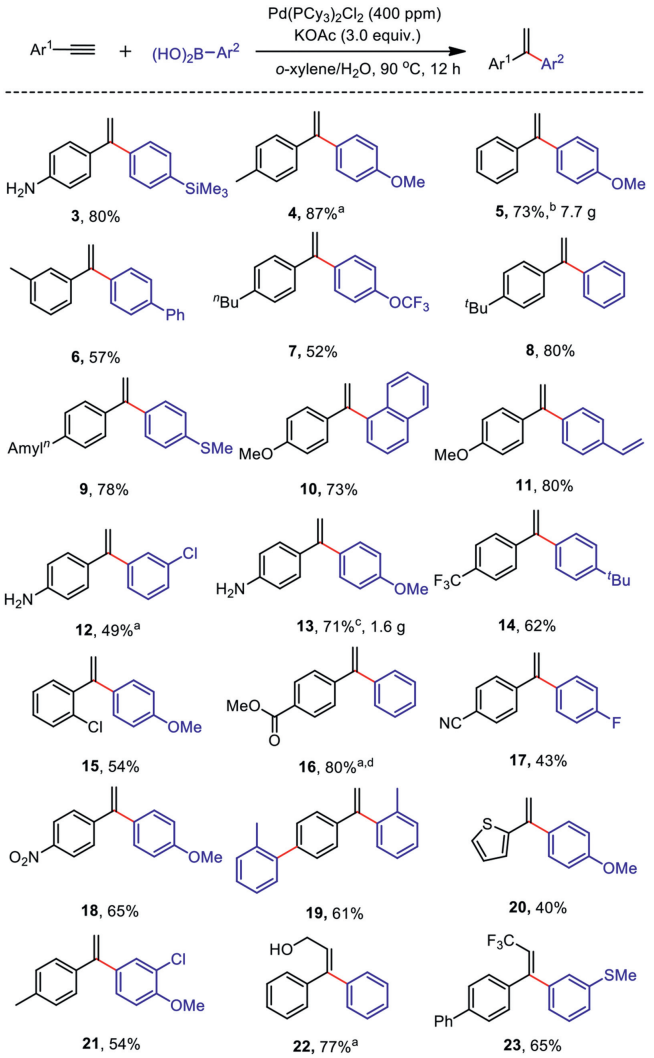
Scheme 1. Transition-metal-catalyzed hydroarylation of alkynes with arylboronic acids.

Table 1
Optimization of the reaction conditions.[a]



Entry	Pd	Loading	Additive	Yield (%)[b]
1	$Pd(OAc)_2$	400 ppm	KOAc	0
2	$PdCl_2$	400 ppm	KOAc	0
3	$Pd_2(dba)_3$	400 ppm	KOAc	0
4	$Pd(PPh_3)_2Cl_2$	400 ppm	KOAc	40
5	$Pd(PPh_3)_4$	400 ppm	KOAc	10
6	$Pd(dppf)Cl_2$	400 ppm	KOAc	0
7[c]	$Pd(OAc)_2/L_1$	400 ppm	KOAc	30
8[c]	$Pd(OAc)_2/L_2$	400 ppm	KOAc	0
9[c]	$Pd(OAc)_2/L_3$	400 ppm	KOAc	20
10[c]	$Pd(OAc)_2/L_4$	400 ppm	KOAc	0
11[c]	$Pd(OAc)_2/L_5$	400 ppm	KOAc	30
12[c]	$Pd(OAc)_2/L_6$	400 ppm	KOAc	0
13	$Pd(PCy_3)_2Cl_2$	400 ppm	KOAc	80
14	$Pd(PCy_3)_2Cl_2$	300 ppm	KOAc	75
15	$Pd(PCy_3)_2Cl_2$	200 ppm	KOAc	41
16	$Pd(PCy_3)_2Cl_2$	100 ppm	KOAc	15
17	$Pd(PCy_3)_2Cl_2$	50 ppm	KOAc	6
18	$Pd(PCy_3)_2Cl_2$	400 ppm	PhCOOK	72
19	$Pd(PCy_3)_2Cl_2$	400 ppm	AdOK	67
20	$Pd(PCy_3)_2Cl_2$	400 ppm	PivOK	78
21	$Pd(PCy_3)_2Cl_2$	400 ppm	NaOAc	70
22	$Pd(PCy_3)_2Cl_2$	400 ppm	CsF	5
23	$Pd(PCy_3)_2Cl_2$	400 ppm	K_2CO_3	trace
24	$Pd(PCy_3)_2Cl_2$	400 ppm	TEA	trace
25	$Pd(PCy_3)_2Cl_2$	400 ppm	DBU	0

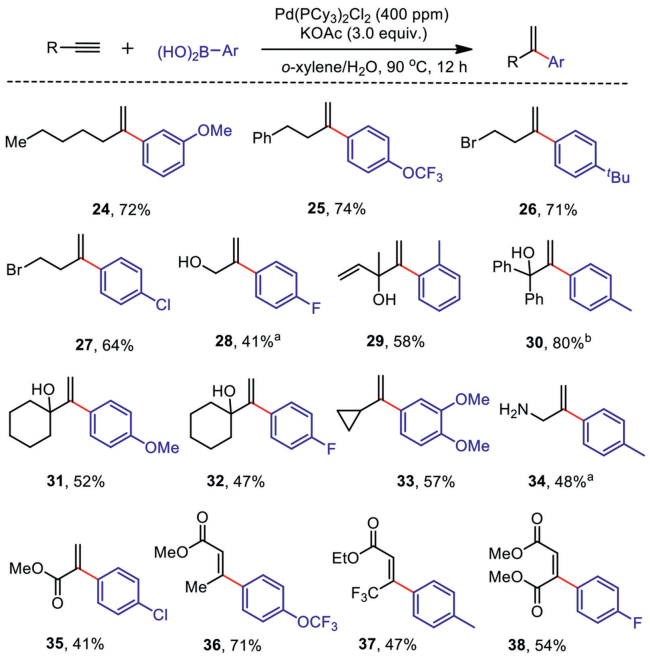
[a] Reaction conditions: **1** (0.20 mmol, 1.0 equiv.), **2** (0.40 mmol, 2.0 equiv.), additive (0.6 mmol, 3.0 equiv.), Pd (400 ppm = 0.04 mol%), *o*-xylene (3.0 mL), H_2O (1.0 mL) under argon at 90 °C for 12 h (oil bath), unless otherwise noted.
[b] Isolated yields.
[c] Ligand (5 mol%). $Pd(PCy_3)_2Cl_2$ (400 ppm catalyst for 0.2 mmol reaction): dissolve $Pd(PCy_3)_2Cl_2$ (3.0 mg, 0.02 equiv.) in 10 mL *o*-xylene, and then take 200 μL of the solution. PivOK = potassium pivalate; AdOK = potassium adamantane-1-carboxylate.



Scheme 2. Scope of aryl alkynes. Reaction conditions: alkyne (0.20 mmol, 1.0 equiv.), arylboronic acid (0.40 mmol, 2.0 equiv.), potassium acetate (0.6 mmol, 3.0 equiv.), $Pd(PCy_3)_2Cl_2$ (400 ppm), *o*-xylene (3.0 mL), H_2O (1.0 mL), under argon at 90 °C for 12 h (oil bath), isolated yields, unless otherwise noted. [a] $Pd(PCy_3)_2Cl_2$ (1000 ppm). [b] Aryl alkyne (50 mmol). [c] Aryl alkyne (10 mmol). [d] 110 °C for 12 h. 400 ppm = 0.04 mol%.

vents and proton sources, please the Tables S1 and S2 (Supporting information).

A range of aryl alkynes (Scheme 2) bearing different functional groups including electron-donating groups such as amino (**3**,**12**,**13**), alkyl (**6**–**9**), and methoxy (**10**,**11**) groups and electron-withdrawing groups such as halogen (**14**,**15**), carboxylate (**16**), cyano (**17**) and nitro (**18**) groups, as well as *ortho*-(**15**), *meta*-(**6**) and *para*-substituted (**9**,**11**–**14**) aromatic alkynes, heterocyclic aromatic alkynes (**20**), and disubstituted aromatic alkynes (**22**,**23**) were well tolerated. Notably, **5** was prepared from ethynylbenzene (5.1 g) and (4-methoxyphenyl) boronic acid (15.2 g) in 73% yield on a 50 mmol scale (7.7 g); and **13** was prepared from 4-ethynylaniline (1.17 g) and (4-methoxyphenyl)boronic acid (3.04 g) in 71% yield on a 10 mmol scale (1.6 g), establishing the suitability of this method for industrial applications. Alkyl substituted alkynes proved compatible with this system (Scheme 3), as did long-chain alkyl substituted alkynes such as 1-heptyne (**24**), 4-phenyl-1-butyne (**25**), 4–bromo-1-butyne (**26**,**27**), and substrates bearing hydroxyl groups including propargyl alcohol (**28**), allyl alcohol (**29**), benzyl alcohol



Scheme 3. Scope of alkyl substituted alkynes. Reaction conditions: alkyne (0.20 mmol, 1.0 equiv.), arylboronic acid (0.40 mmol, 2.0 equiv.), potassium acetate (0.6 mmol, 3.0 equiv.), $Pd(PCy_3)_2Cl_2$ (400 ppm), *o*-xylene (3.0 mL), H_2O (1.0 mL), under argon at 90 °C for 12 h (oil bath), isolated yields. [a] Alkyne (0.60 mmol, 3.0 equiv.), arylboronic acid (0.20 mmol, 1.0 equiv.). [b] $Pd(PCy_3)_2Cl_2$ (1000 ppm).

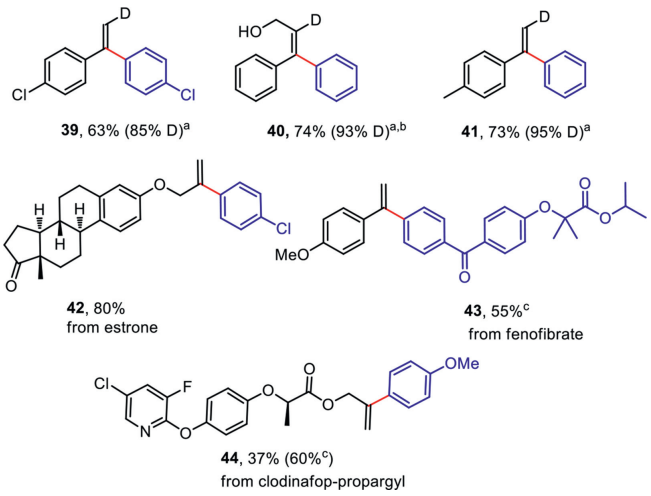


Fig. 1. Deuterium incorporation and late-stage modification of bioactive molecules. Reaction conditions: alkyne (0.20 mmol, 1.0 equiv.), arylboronic acid (0.40 mmol, 2.0 equiv.), potassium acetate (0.6 mmol, 3.0 equiv.), $Pd(PCy_3)_2Cl_2$ (400 ppm), *o*-xylene (3.0 mL), H_2O (1.0 mL), under argon at 90 °C for 12 h, isolated yields. [a] Arylboronic acid (0.30 mmol, 1.5 equiv.), *o*-xylene (2.0 mL, dry), D_2O (1.0 mL). [b] $Pd(PCy_3)_2Cl_2$ (1000 ppm). [c] $Pd(PCy_3)_2Cl_2$ (800 ppm).

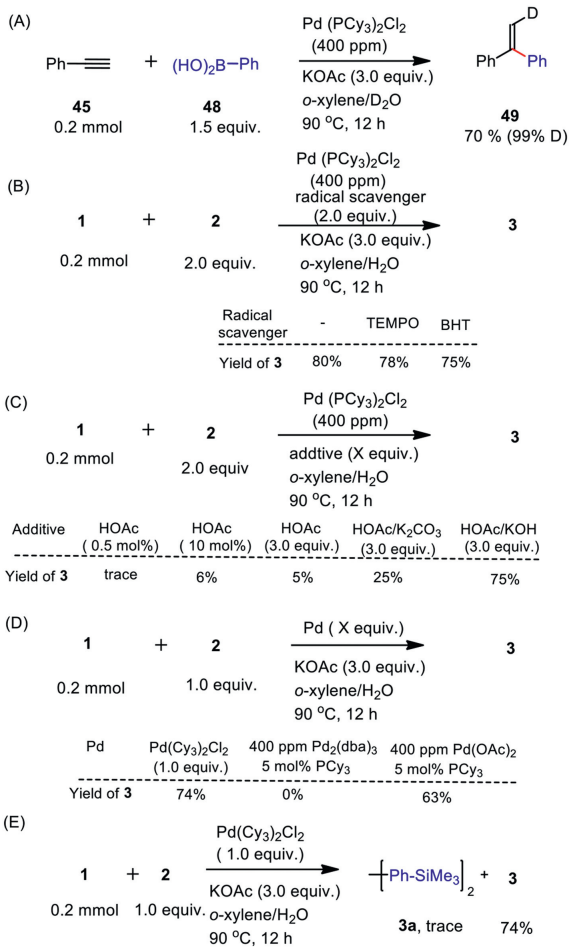
(**30**), and cyclohexanol (**31**,**32**). Substrates bearing three-(**33**) and six-(**32**) membered rings, an amino group (**34**), ester groups and various disubstituted alkynes (**36**–**38**) were all compatible as well. Therefore, this reaction significantly extends the overall synthetic utility of alkynes as platforms for molecular diversity.

The scope of the reaction with respect to the choice of arylboronic acid was also found to be broad (Schemes 2 and 3). Arylboronic acids bearing electron-donating trimethylsilyl (**3**), methoxy (**4**,**5**,**31**), phenyl (**6**), trifluoromethoxy (**7**), methylthio (**9**), 1-naphthyl (**10**), vinyl (**11**) groups; as well as those bearing electron-withdrawing halogens (**12**,**17**,**21**,**27**,**28**,**32**,**35**,**38**) were all well tolerated, as were *ortho*-(**19**,**29**), *meta*-(**12**,**24**), *para*-(**3**–**7**) and poly-(**21**,**33**) substituted aryl boronic acids.

Notably, this reaction also adequately tolerated groups such as trimethylsilyl (**3**), alkenyl (**11**), chlorine (**12**,**21**,**27**,**35**) and fluorine (**17**,**32**,**38**), which are used as handles in subsequent, sequential orthogonal cross-couplings. The scope of alkenyl boronic acids, please see Scheme S1 (Supporting information).

We also established that these optimized conditions could be used to synthesize deuterium-labeled alkenes with high deuteration yield (Fig. 1, **39-41**), and that they demonstrate sufficient functional group compatibility and chemoselectivity to be suitable for the synthesis of pharmaceutical and complex natural products. For example, derivatives (**42**–**44**) of estrone, fenofibrate and clodinafop-propargyl, respectively, could all be synthesized with this reaction. The residual Pd content of derivative **44** was 0.185 ppm, for details, see Table S3 (Supporting information).

Mechanistic studies were also conducted, to elucidate the mechanism of the reaction (Scheme 4). Isotope-labeling experiments established that the protons required for the transformation come from water (Scheme 4A), and the results of radical inhibition and capture experiments were inconsistent with the reaction being a radical process (Scheme 4B, radical clock experiment, see Scheme S2 in Supporting information) [41,42]. When acetic acid was used to replace the potassium acetate in the system, only a very low yield of product was obtained. However, the target product was formed in medium yield by addition of acetic acid and potassium hydroxide, which formed potassium acetate *in situ* (Scheme 4C). Use of one equivalent of $Pd(PCy_3)_2Cl_2$ as a



Scheme 4. Mechanistic probes.

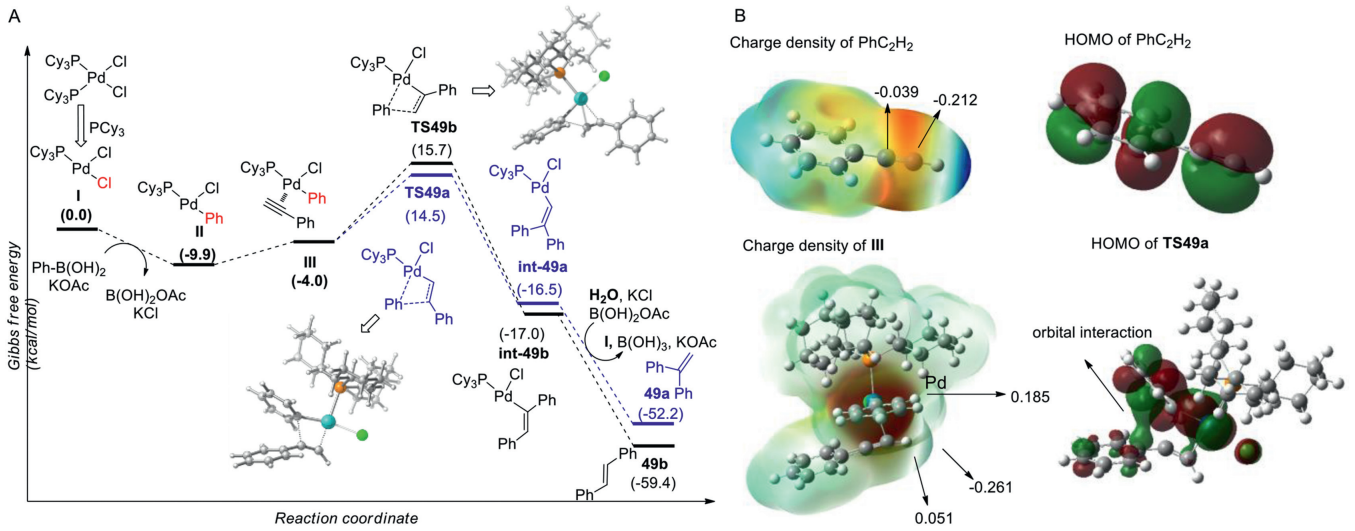


Fig. 2. DFT calculations and proposed mechanism.

pre-catalyst yielded **3** in 74% yield, along with a trace amount of biphenyl by-product **3a**. When a catalytic amount of $Pd(OAc)_2/PCy_3$ (400 ppm/50,000 ppm) was used, the yield of **3** was 63%. When $Pd_2(dba)_3/PCy_3$ (400 ppm/50,000 ppm) was used, **3** was not detected at all (Schemes 4D and E).

DFT calculations were conducted to rationalize the Markovnikov selectivity of the reaction (Figs. 2A and B). Intermediate **I** obtained by ligand dissociation first undergoes transmetalation to give **II**, lowering the free energy to −9.9 kcal/mol. **II** coordinates with the alkyne to give intermediate **III**, wherein the triple bond of the alkyne is perpendicular to the pH-Pd-Cl; the free energy increases to −4.0 kcal/mol. As shown in Fig. 2B, the NBO charges of the terminal C1 and internal C2 atoms are −0.261 and 0.051, respectively, and the C1 atoms interact more closely with the positive Pd metal center (NBO charge 0.185). Correspondingly, the distances between Pd-C1 and Pd-C2 are 2.319 Å and 2.588 Å, respectively, of which the former is significantly shorter. For the subsequent alkyne insertion, there are two possible transition states, **TS49a** and **TS49b**, where the pH is bonded to C2 and C1, respectively, and for which the free energies are 14.5 and 15.7 kcal/mol; **TS49a** is therefore more favorable. Note that, the NBO charges of the C1 and C2 atoms of the ethynylbenzene substrate are −0.212 and −0.039, which is consistent with the charge density in intermediate **III**. In addition, the HOMO of ethynylbenzene is predominantly comprised of C1. Therefore, the Pd metal center is closer to C1 than it is to C2. The HOMO orbital of **TS49a** was further investigated and it was found that π-π orbital interaction exists between the two benzene rings, which also contributes to the advantage of **TS49a**. The experimentally obtained product mixture (**49a**/**49b** = 92/8) is consistent with these DFT calculations.

Based on these results, as well as the mechanism of Engle reported in the literature [11], a possible catalytic cycle based on a Pd(II) nucleopalladation pathway is proposed. First, transmetalation between Pd(II) and the arylboronic acid occurs, followed by 1,2-migratory insertion of the alkyne and proto-depalladation to generate the 1,1-disubstituted alkene.

In conclusion, a hydroarylation reaction of alkynes with arylboronic acids and H_2O catalyzed by low loadings (400 ppm) of Pd has been developed. The reaction is tolerant of terminal alkynes and anticipated to be useful for synthesizing a range of 1,1-disubstituted and deuterium-labeled alkenes. The mechanism of the reaction is believed to entail a Pd(II) nucleopalladation pathway based on mechanistic experiments and DFT calculations.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.05.048.

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