Letter

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Practical Intermolecular Hydroarylation of Diverse Alkenes via Reductive Heck Coupling

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ABSTRACT: The hydroarylation of alkenes is an attractive approach to construct carbon–carbon (C–C) bonds from abundant and structurally diverse starting materials. Herein we report a palladium-catalyzed reductive Heck hydroarylation of aliphatic and heteroatom-substituted terminal alkenes and select internal alkenes with an array of (hetero)aryl iodides. The reaction is anti-Markovnikov selective for terminal alkenes and tolerates a wide variety of functional groups on both the alkene and (hetero)aryl coupling partners. Additionally, applications of this method to complex molecule diversifications are demonstrated. Mechanistic experiments are consistent with a mechanism in which the key alkylpalladium(II) intermediate is intercepted with formate and undergoes a decarboxylation/C–H reductive elimination cascade to afford the saturated product and turn over the cycle.

KEYWORDS: reductive Heck, hydroarylation, palladium, alkene functionalization, regioselectivity

The Mizoroki–Heck coupling of aryl halides and alkenes is an effective means of forging C–C bonds to enable preparation of densely functionalized alkenes.[1] The broad functional group compatibility and vast scope of the Mizoroki–Heck reaction have allowed it to emerge as a staple transformation in complex-molecule synthesis. Mechanistically, the catalytic cycle involves oxidative addition of palladium(0) to an aryl halide followed by 1,2-migratory insertion to access a key alkylpalladium(II) intermediate. In the classical Mizoroki–Heck reaction, this intermediate succumbs to rapid β-hydride (β-H) elimination to deliver the functionalized alkene product, followed by HX reductive elimination to regenerate Pd(0), thereby closing the catalytic cycle. Alternatively, one could envision intercepting this intermediate with an additional reaction partner as a general strategy for programmed conversion of alkenes to various hydrofunctionalized or 1,2-difunctionalized products. Our laboratory has previously utilized chelation stabilization of organopalladium(II) intermediates to achieve hydroarylation of alkynes[2] and alkenes[3] via Heck-type nucleopalladation followed by protodepalladation. We thus became interested in exploring strategies for enabling similar modes of bond construction with organopalladium(II) intermediates in the absence of directing substituents. To this end, the goal of the present study was to develop a reductive Heck hydroarylation reaction of diverse aliphatic and heteroatom-substituted alkenes.

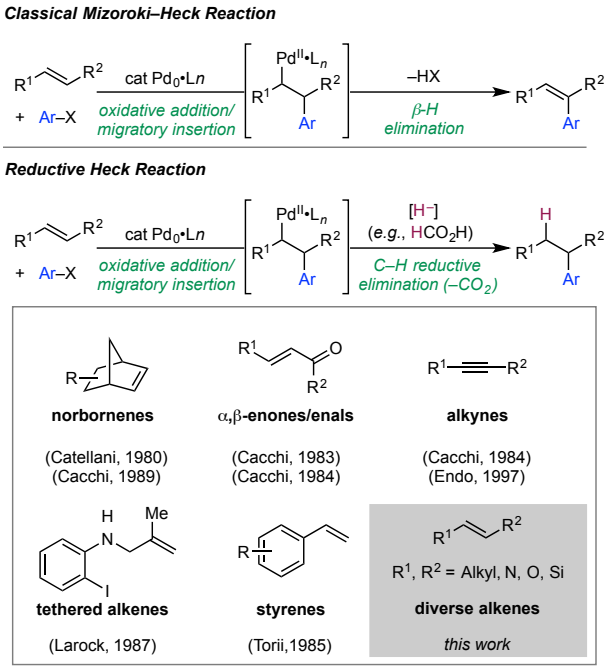


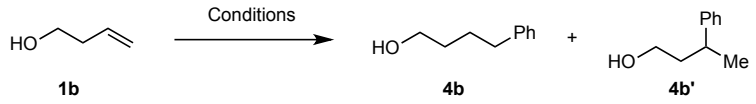
Figure 1. Strategy and early precedents for the reductive Heck reaction.

Reductive Heck hydroarylation involves intercepting the alkylpalladium(II) intermediate that is generated upon migratory insertion with a hydride source, most commonly formate. This transformation has been investigated since the early 1980s, and pioneering work by Cacchi[4] and others during this period led to effective protocols with several classes of C–C-π-bond-containing substrates that lack β-H atoms or that form stabilized π-allyl/π-

benzyl/enolate intermediates, including strained alkenes (*e.g.*, norbornene),[5] α,β-enones/enals,[6] alkynes,[7] tethered alkenes,[8] and styrenes[9] (Scheme 1).[10] In contrast, application of this mode of reactivity to aliphatic terminal alkenes is comparatively undeveloped, likely due to the rapid nature of the aforementioned β-H elimination step with such substrates. To circumvent this issue, alternative strategies for hydroarylation of terminal aliphatic alkenes have been developed.[11] In particular, Buchwald has described a CuH/Pd dual catalytic system for anti-Markovnikov hydroarylation of terminal alkenes with aryl bromides and electron-poor aryl chlorides.[11c] To complement this approach, we became interested in developing a general monometallic reductive Heck protocol that would be operationally simple, employ readily available reaction components, and exhibit broad functional group compatibility, which motivated the present study. While this manuscript was in preparation, related catalytic systems for reductive Heck coupling of alkenes with aryl bromides[12] and aryl triflates[13] were reported.

To initiate our study, we elected to use 3-buten-1-ol (**1b**) and iodobenzene as model reaction partners for optimization (Table 1). At the outset we hypothesized that two key aspects would be vital for achieving successful reductive Heck coupling. First, the palladium catalyst would need to be coordinatively saturated throughout the catalytic cycle to suppress β-H elimination from the alkylpalladium(II) intermediate. Second, the rates of decarboxylation (to form Pd–H) and C–H reductive elimination would need to be sufficiently fast such that C–H bond formation could outcompete β-H elimination. With these considerations in mind, we began examining potential reaction conditions, deliberately using a high molar ratio of triphenyl phosphine relative to palladium (10:1). With potassium formate as the hydride source in the presence of water and a phase transfer reagent ($TBABF_4$) as additives, we were pleased to observe reductive Heck hydroarylation with several different inorganic bases (entries 1–8). Moderately strong bases provided higher yields than weaker bases, and, among those tested, K_3PO_4 offered the best yield. An approximately 4:1 ratio of anti-Markovnikov to Markovnikov addition products was observed, and the regioisomeric ratio was roughly constant across different conditions, reflecting earlier literature precedent of migratory insertion under a neutral Heck-type mechanism.[14] Next, we investigated different formate sources (entries 9–12) and identified aqueous tetramethylammonium formate solution ($TMA{\bullet}HCO_2$) as a superior reductant that did not require additional water or tetraalkylammonium salts for high yield and selectivity. Lastly, we varied the palladium and phosphine loadings and found that 1 mol % $Pd_2(dba)_3$ with 20 mol % PPh_3 performed similarly to higher loadings (entries 13–19). Increasing or decreasing the phosphine:palladium ratio from 10:1 led to lower yield. Extending the reaction time from 1 h to 4 h led to full consumption of starting material with a combined product yield of 92% and 4:1 r.r. (entry 10). Notably, the optimized protocol is operationally convenient, as it does not require rigorous exclusion of air or moisture and can be conveniently performed on the benchtop without specialized equipment or glassware.

Table 1. Optimization of reaction conditions[a]



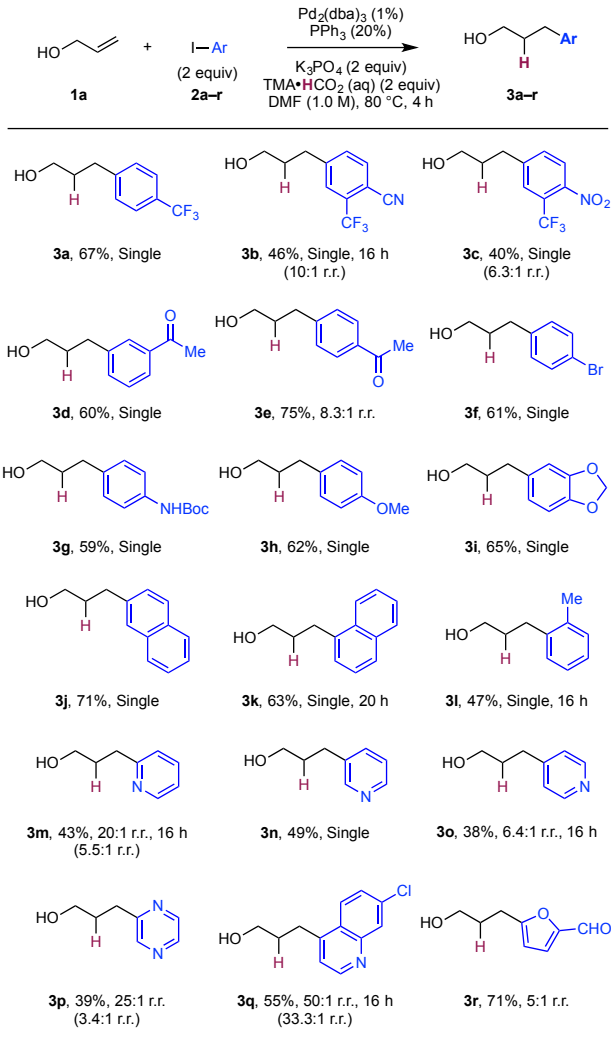
1b **4b** **4b'**

Entry	$Pd_2(dba)_3$ (%)	PPh_3 (%)	Base	Reductant/Additive	Yield **4b** + **4b'** (%)[b]	**4b**:**4b'**[c]	**1b** (%)
1	2.5	50	None	$KHCO_2/H_2O/TBABF_4$	24	3.8	58
2	2.5	50	KO^{t}Bu	$KHCO_2/H_2O/TBABF_4$	44	3.9:1	31
3	2.5	50	KOH	$KHCO_2/H_2O/TBABF_4$	51	4:1	33
4	2.5	50	K_2CO_3	$KHCO_2/H_2O/TBABF_4$	43	3.8:1	39
5	2.5	50	$KHCO_3$	$KHCO_2/H_2O/TBABF_4$	18	3.5:1	67
6	2.5	50	KH_2PO_4	$KHCO_2/H_2O/TBABF_4$	1	ND	79
7	2.5	50	K_2HPO_4	$KHCO_2/H_2O/TBABF_4$	23	3.6:1	62
8	2.5	50	K_3PO_4	$KHCO_2/H_2O/TBABF_4$	61	4.1:1	23
9	2.5	50	K_3PO_4	$NaHCO_2/H_2O/TBABF_4$	40	4:1	41
10	2.5	50	K_3PO_4	$CsHCO_2/H_2O/TBABF_4$	47	4.2:1	28
11	2.5	50	K_3PO_4	$NH_4HCO_2/H_2O/TBABF_4$	19	3.8:1	63
12	2.5	50	K_3PO_4	$TMA{\bullet}HCO_2$ (aq)/$TBABF_4$	79	3.9:1	7
13	2.5	50	K_3PO_4	$TMA{\bullet}HCO_2$ (aq)	89	3.5:1	6
14	2.5	25	K_3PO_4	$TMA{\bullet}HCO_2$ (aq)	81	3.8:1	1
15	2.5	10	K_3PO_4	$TMA{\bullet}HCO_2$ (aq)	67	4.1:1	ND
16	2.5	5	K_3PO_4	$TMA{\bullet}HCO_2$ (aq)	5	ND	ND
17	1	25	K_3PO_4	$TMA{\bullet}HCO_2$ (aq)	67	3.8:1	10
18	1	20	K_3PO_4	$TMA{\bullet}HCO_2$ (aq)	80	4:1	3
19	1	10	K_3PO_4	$TMA{\bullet}HCO_2$ (aq)	67	4.6:1	ND
20[d]	1	20	K_3PO_4	$TMA{\bullet}HCO_2$ (aq)	92	4:1	ND

[a] **1b** (1 equiv), $Pd_2(dba)_3$ (X mol %), PPh_3 (Y mol %), iodobenzene (2 equiv), base (2 equiv), H_2O (10 equiv), $TBABF_4$ (1 equiv), reductant (2 equiv), DMF (1.0 M), 80 °C, 1 h. $TBABF_4$ = tetrabutylammonium tetrafluoroborate, $TMA{\bullet}HCO_2$ (aq) = tetramethylammonium formate 30% w/w aqueous solution. [b] Yields were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. In many cases with poor mass balance, byproducts of 1-butanol, 4-phenylbutanal, and (*E*)-4-phenylbut-3-en-1-ol were observed in varying amounts. [c] The regioisomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture (ND = not determined). [d] 4 h.

Having identified optimal conditions, we next explored the aryl iodide scope using allyl alcohol (1a) as the alkene partner (Table 2). This choice was motivated by the potential versatility of the alcohol moiety in downstream functionalization and because of the high regioselectivity observed for this substrate (vide infra), which simplified purification and analysis in most cases. Both electron-deficient (**3a**–**3f**) and electron-rich (**3g**–**3i**) aryl iodides were competent coupling partners, affording the desired products in synthetically useful yields, even when multi-substituted (**3b**, **3c**, and **3i**) or sterically congested (**3k** and **3l**) aryl iodides were used. A variety of heteroaryl iodides were also suitable coupling partners for the reaction, including those containing pyridine (**3m**–**3o**), pyrazine (**3p**), quinoline (**3q**), or furan (**3r**) heterocycles. Additionally, the reaction was found to tolerate a range of functional groups that can serve as handles for further diversification, such as nitriles, ketones, halides, protected amines, and aldehydes. Notably, the regioselectivity of the insertion step appears to be influenced by the electronic nature of the aryl group, with electron-deficient aryl iodides giving lower regioisomeric ratios than electron-neutral or -rich aryl iodides.

Table 2. Aryl iodide scope.[a–c]



[a] **1a** (1 equiv), $Pd_2(dba)_3$ (1 mol %), PPh_3 (20 mol %), aryl iodide (2 equiv), K_3PO_4 (2 equiv), TMA•HCO_2 (aq) (2 equiv), DMF (1.0 M), 80 °C, 4–20 h. TMA•HCO_2 (aq) = tetramethylammonium formate 30% w/w aqueous solution. [b] Isolated yields. [c] The regioisomeric ratio of the isolated compound. The regioisomeric ratio of the crude reaction mixture as determined by ^{1}H NMR analysis is given in parenthesis if it differed from the ratio of the isolated material.

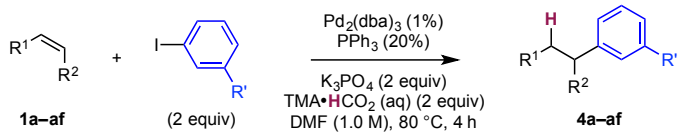
Next, we probed the alkene coupling partner scope using iodobenzene and 3'-iodoacetophenone as representative aryl iodides, with the latter facilitating product isolation with non-polar alkenes (Table 3). High yields of the hydroarylated products were obtained for alcohol-containing substrates of various chain lengths (**4a**–**4c**), and the reaction was ≥4:1 selective across this series of alkenes. Steric hindrance adjacent to the alkene could be accommodated (**4d**), although higher palladium and phosphine loadings and a longer reaction time were required. The reaction was amenable to scale-up, providing **4a** in 60% yield on a 15 mmol scale; in this case, extended reaction time was required to achieve high conversion. The tetrahydropyran acetal protecting group (**4e**) was tolerated under the reaction conditions, as were epoxides (**4f** and **4g**), affording moderate to high yields of the desired products. Additionally, thioethers (**4h**), protected amines (**4i**–**4l**), and silanes (**4m**) were found to be compatible functional groups for this transformation. Non-activated aliphatic alkene hydrocarbons were also suitable substrates in this reaction (**4n**–**4p**), highlighting the broad scope of alkenes tolerated by this method. Esters (**4q** and **4r**) and lactams (**4s**), which are known to undergo hydrolysis under basic conditions at elevated temperatures, were well tolerated under the conditions. Moreover, alkenes containing Lewis basic functional groups with the capacity for metal binding, namely an imidazole (**4t**) and a urea (**4u**), were compatible.

In addition to non-conjugated terminal alkenes, we discovered that heteroatom-substituted terminal alkenes were also competent substrates in this reaction. Specifically, we found that a vinyl ether (**4v**), a vinyl silane (**4w**), and *N*-vinyl-pyrrolidinone (**4x**) reacted to give predominantly the anti-Markovnikov hydroarylated products, albeit in modest yield in the last two cases. To underscore the synthetic utility of this transformation, we explored a variety of alkene-containing natural products and derivatives thereof. Quinine reacted smoothly to provide the anti-Markovnikov hydroarylation product as a single regioisomer in quantitative yield (**4y**), emphasizing the power of this transformation to provide expedited access to cinchona alkaloid derivatives, which are useful chiral ligands and organocatalysts. A variety of terpene derivatives, including the bicyclic diterpene sclareol (**4z**) and the linear monoterpenes linalool (**4aa**) and (+)-β-citronellene (**4ab**), were also viable substrates, providing moderate to high yields of the anti-Markovnikov hydroarylation products as single regioisomers. Of note, the reaction is chemoselective for terminal alkenes, evidenced by **4aa** and **4ab** where the trisubstituted alkene underwent neither the hydroarylation reaction nor reduction to the alkane.

Finally, we also tested several representative internal alkenes. For acyclic substrates, reactivity and regioselectivity were low, as illustrated by both *Z*- and *E*-3-hexen-1-ol (**4ac**). However, when cyclic substrates were employed, moderate yields were obtained. Specifically, cyclohexene resulted in 47% yield of the reductive Heck product **4ad**. 2,3-Dihydrofuran was a suitable substrate, though only modest regioselectivity of 1.6:1 was observed. Fortunately, the desired product **4ae** could be isolated in 47% as a single regioisomer. Additionally, a protected 3-pyrroline substrate yielded 71% of the desired product **4af**.

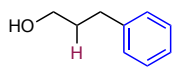
For all examples included in Tables 2 and 3, only trace amounts (<5%) of the corresponding Heck products were observed. However, competitive reduction of the alkene starting material was observed in several cases. Overall, this reductive Heck transformation is tolerant of a wide array of functional groups, including some that are potentially reductively labile, and it thus represents a powerful transformation to install aryl moieties over a diverse range of alkenes that complements existing methods.

Table 3. Alkene scope.[a–c]

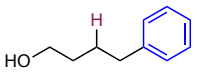


1a–af (2 equiv) **4a–af**

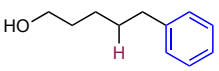
Non-Conjugated Terminal Alkenes



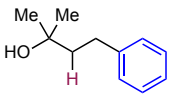
4a, 66%, Single
[15 mmol]: 60%, Single, 24 h



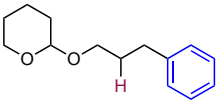
4b, 88%, 5:1 r.r.
(4:1 r.r.)



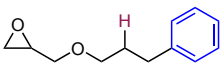
4c, 84%, 4.5:1 r.r.



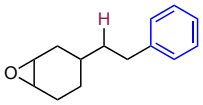
4d, 74%, Single, 16 h[d]



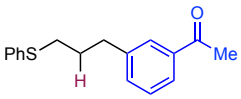
4e, 63%, Single



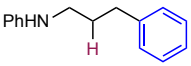
4f, 30%, 3:1 r.r.



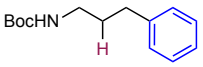
4g, 89%, Single, 1:1 d.r.[e]



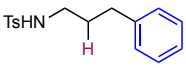
4h, 43%, Single
(5:1 r.r.)



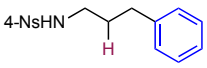
4i, 59%, Single
(20:1 r.r.)



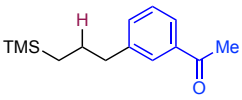
4j, 96%, 3.5:1 r.r.



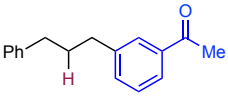
4k, 57%, 12.5:1 r.r.
(10:1 r.r.)



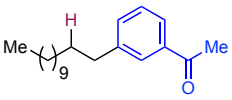
4l, 41%, Single[d]



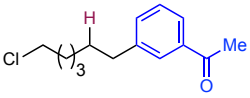
4m, 63%, 7.7:1 r.r.[f]



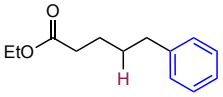
4n, 56%, 10:1 r.r.
(3:1 r.r.)



4o, 96%, 4:1 r.r.

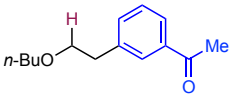


4p, 51%, 4:1 r.r.
(3:1 r.r.)

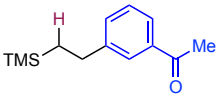


4q, 54%, 3:1 r.r.

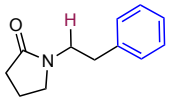
Heteroatom-Substituted Terminal Alkenes



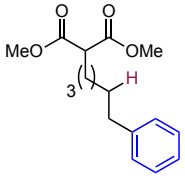
4v, 71%, Single
(5:1 r.r.)



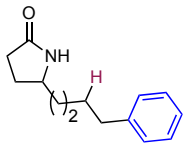
4w, 31%, 16.7:1 r.r.



4x, 36%, 25:1 r.r.
(2.5:1 r.r.)

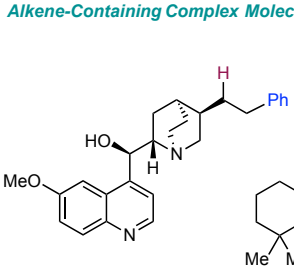


4r, 64%, 3.5:1 r.r.
(3.8:1 r.r.)

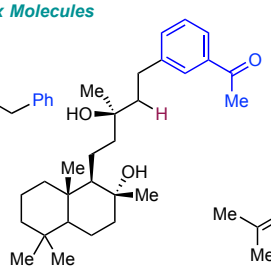


4s, 54%, 2.3:1 r.r.
(3.8:1 r.r.)

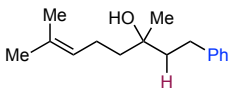
Alkene-Containing Complex Molecules



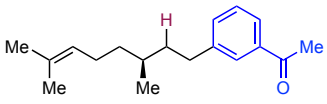
4y, 99%, Single
from quinine



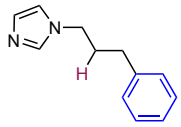
4z, 71%, Single, 16 h[d]
from sclareol



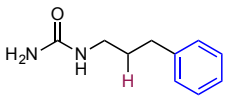
4aa, 64%, Single, 16 h[d]
from linalool



4ab, 86%, Single, 16 h[d]
from (+)-(β)-citronellene

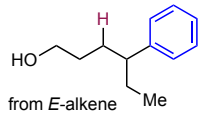


4t, 84%, 1.5:1 r.r., 24 h[d]

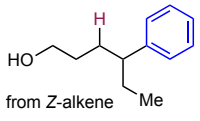


4u, 30%, Single
(4.2:1 r.r.)

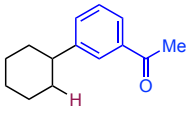
Internal Alkenes



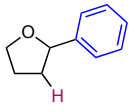
4ac, 17%, 1:1 r.r., 16 h[g]



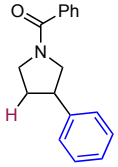
4ac, 23%, 1:1 r.r., 16 h[g]



4ad, 47%, 16 h



4ae, 47%, Single
(1.6:1 r.r.)



4af, 71%, 16 h

[a]Alkene (1 equiv), $Pd_2(dba)_3$ (1 mol %), PPh_3 (20 mol %), aryl iodide (2 equiv), K_3PO_4 (2 equiv), TMA•HCO_2 (aq) (2 equiv), DMF (1.0 M), 80 °C, 4–24 h. TMA•HCO_2 = tetramethylammonium formate 30% w/w aqueous solution. [b] Isolated yields unless otherwise specified. [c] The regioisomeric ratio of the isolated compound. The regioisomeric ratio of the crude reaction mixture as determined by ^{1}H NMR analysis is given in parenthesis if it differed from the ratio isolated. [d] $Pd_2(dba)_3$ (2.5 mol %) and PPh_3 (50 mol %). [e] The alkene starting material **3g** was a 1:1 mixture of diastereomers. [f] An additional constitutional isomer was formed and isolated together with the other two products. [g] Yield and regioisomeric ratio determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Regarding selectivity patterns, across the examples described above, the r.r. values ranged from 1.5:1 to >50:1, with the anti-Markovnikov product favored in all cases. Although many of the observed regioisomeric ratios are in accordance with literature precedents[14] for a neutral Heck mechanism with these substrates, a detailed description of the origins of the observed trends remains outside of the scope of the present study. Generally speaking, it appears that the steric and electronic properties of both the alkene and the migrating aryl group contribute to the activation energy of the product-determining step.

Based upon our results and literature precedents,[4–10] we propose the catalytic cycle in Figure 2A. The initial sequence of events follows that of the Mizoroki-Heck reaction: oxidative addition of the aryl iodide, alkene coordination, and migratory insertion of the aryl group to give the alkylpalladium(II) intermediate. At this stage, rather than undergoing β-H elimination (as in the Mizoroki-Heck reaction), this intermediate exchanges iodide for formate, at which point decarboxylation generates a Pd–H species. Upon C–H reductive elimination, the reductive Heck product is formed and Pd(0) is regenerated to close the catalytic cycle. To validate that formate is indeed the source of hydrogen in the product, we performed the reaction using sodium formate-d. As expected, full deuterium incorporation in the product with no deuterium scrambling was observed, supporting the proposed mechanism (Figure 2B). Lastly, to probe the viability of an alternative pathway involving classical Mizoroki–Heck arylation followed by styrene reduction, we preformed the control experiments in Figure 2C. When cinnamyl alcohol (**1ag**), a putative intermediate in this potential pathway, was subjected to the standard reaction conditions with and without iodobenzene, only a minimal amount of styrene reduction was observed. This indicates that this alternative mechanism is not the predominant pathway under these conditions.

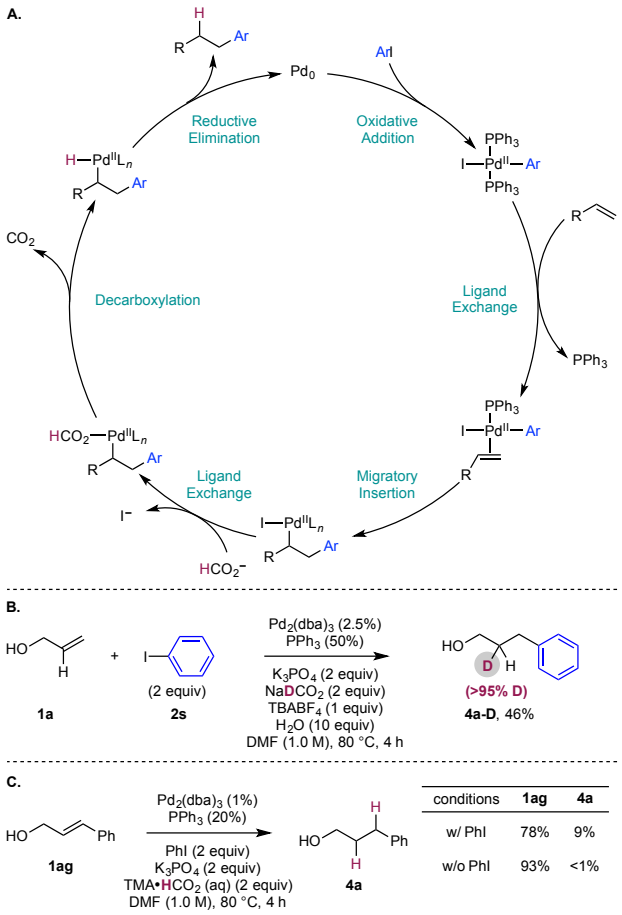


Figure 2. (A) Proposed catalytic cycle. (B) Deuterium-labeling experiment. (C) Control experiments testing potential involvement of a classical Mizoroki–Heck arylation/styrene reduction mechanism. Percentages were determined by ^{1}H NMR analysis of the crude reaction mixtures with 1,3,5-trimethoxybenzene as an internal standard.

In summary, we have developed a mild and operationally convenient palladium-catalyzed reductive Heck reaction of aliphatic and heteroatom-substituted terminal alkenes and select internal alkenes with (hetero)aryl iodides. Mechanistically, the catalytic cycle follows the same initial steps as the Mizoroki–Heck reaction to generate the alkylpalladium(II) intermediate, which then undergoes decarboxylation from a bound formate ligand followed by C–H reductive elimination to produce the hydroarylated product. With terminal alkenes, the reaction provides predominantly the anti-Markovnikov product. Notably, the transformation is compatible with a wide variety of synthetically important functional groups, including many that are reductively labile, and can accommodate heterocycles containing basic sp^2-hybridized nitrogen atoms. Furthermore, it can be used for complex molecule diversification. The procedure is scalable and requires only inexpensive, readily available components, highlighting its practicality as a synthetic tool. We anticipate that this method will find use in

both target-oriented and divergent synthesis and that the mechanistic implications of this study will stimulate the development of additional alkene functionalization reactions in the future.

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Notes

The authors declare no competing financial interest.

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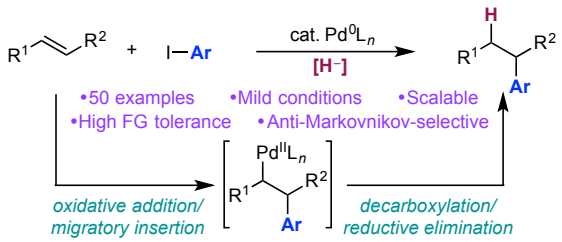
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•Scalable
•High FG tolerance
•Anti-Markovnikov-selective
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R1
R2
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oxidative addition/
migratory insertion
decarboxylation/
reductive elimination