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Practical Intermolecular Hydroarylation of Terminal 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 palladiumcatalyzed reductive Heck hydroarylation of unactivated and heteroatom-substituted terminal alkenes with an array of (hetero)aryl iodides. The reaction is anti-Markovnikov selective 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 were demonstrated. Deuteriumlabeling 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

alkenes; Heck reaction; hydroarylation; palladium; 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 complexmolecule 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 terminal aliphatic and heteroatom-substituted alkenes.

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, a related catalytic system for reductive Heck coupling of alkenes with aryl bromides was reported.^[12]

To initiate our study, we elected to use 3-buten-1-ol 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 (TBABF₄) 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, K₃PO₄ 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.^[13] Next, we investigated different formate sources (entries 9–12) and identified aqueous tetramethylammonium formate solution (TMA•HCO₂) 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% Pd₂(dba)₃ with 20% PPh₃ 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.

Having identified optimal conditions, we next explored the aryl iodide scope using allyl alcohol 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 multisubstituted (**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.

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. Nonactivated 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. Finally, 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. 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.

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^[13] 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, we propose the catalytic cycle in Scheme 2. 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 was 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 our proposed mechanism (Equation 1).

(1)

In summary, we have developed a mild and operationally convenient palladium-catalyzed reductive Heck reaction of aliphatic and heteroatom-substituted terminal 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. The reaction provides predominantly the anti-Markovnikov product and is compatible with a wide variety of synthetically important functional groups, including many that are reductively labile. Notably, the transformation accommodates heterocycles, including those containing basic sp^2 -hybridized nitrogen

atoms, and 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.

Experimental Details.

To a 1-Dram (4 mL) vial equipped with a magnetic stir bar were added Pd₂(dba)₃ (1.8 mg, 0.002 mmol), triphenylphosphine (10.5 mg, 0.04 mmol), K₃PO₄ (84.9 mg, 0.4 mmol), alkene (0.2 mmol), aryl iodide (0.4 mmol), TMA•HCO₂ (30% w/w aqueous solution) (0.16 mL, 0.4 mmol), and DMF (0.2 mL). The vial was sealed with a solid screw cap and placed in a heating block that was pre-heated to 80 °C. After the designated reaction time, the reaction mixture was diluted with water (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic layers were dried over Na₂SO₄, concentrated *in vacuo*, and purified by column chromatography.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Reductive Heck Reaction

Scheme 1.

Strategy and early precedents for the reductive Heck reaction.

Scheme 2.
Proposed catalytic cycle.

Table 1.

Optimization of reaction conditions.^[a]

Entry	Pd ₂ (dba) ₃ (%)	PPh ₃ (%)	Base	Reductant/Additive	Yield 4b + 4b' (%) ^[b]	4b:4b' ^[c]	SM (%)
1	2.5	50	None	KHCO ₂ /H ₂ O/TBABF ₄	24	3.8	58
2	2.5	50	KO ^t Bu	KHCO ₂ /H ₂ O/TBABF ₄	44	3.9:1	31
3	2.5	50	KOH	KHCO ₂ /H ₂ O/TBABF ₄	51	4:1	33
4	2.5	50	K ₂ CO ₃	KHCO ₂ /H ₂ O/TBABF ₄	43	3.8:1	39
5	2.5	50	KHCO ₃	KHCO ₂ /H ₂ O/TBABF ₄	18	3.5:1	67
6	2.5	50	KH ₂ PO ₄	KHCO ₂ /H ₂ O/TBABF ₄	1	ND	79
7	2.5	50	K ₂ HPO ₄	KHCO ₂ /H ₂ O/TBABF ₄	23	3.6:1	62
8	2.5	50	K ₃ PO ₄	KHCO ₂ /H ₂ O/TBABF ₄	61	4.1:1	23
9	2.5	50	K ₃ PO ₄	NaHCO ₂ /H ₂ O/TBABF ₄	40	4:1	41
10	2.5	50	K ₃ PO ₄	CsHCO ₂ /H ₂ O/TBABF ₄	47	4.2:1	28
11	2.5	50	K ₃ PO ₄	NH ₄ HCO ₂ /H ₂ O/TBABF ₄	19	3.8:1	63
12	2.5	50	K ₃ PO ₄	TMA•HCO ₂ (aq)/TBABF ₄	79	3.9:1	7
13	2.5	50	K ₃ PO ₄	TMA•HCO ₂ (aq)	89	3.5:1	6
14	2.5	25	K ₃ PO ₄	TMA•HCO ₂ (aq)	81	3.8:1	1
15	2.5	10	K ₃ PO ₄	TMA•HCO ₂ (aq)	67	4.1:1	ND
16	2.5	5	K ₃ PO ₄	TMA•HCO ₂ (aq)	5	ND	ND
17	1	25	K ₃ PO ₄	TMA•HCO ₂ (aq)	67	3.8:1	10
18	1	20	K ₃ PO ₄	TMA•HCO ₂ (aq)	80	4:1	3
19	1	10	K ₃ PO ₄	TMA•HCO ₂ (aq)	67	4.6:1	ND
20 ^[d]	1	20	K ₃ PO ₄	TMA•HCO ₂ (aq)	92	4:1	ND

^[a] **1b** (1 equiv), Pd₂(dba)₃ (X%), PPh₃ (Y%), iodobenzene (2 equiv), base (2 equiv), H₂O (10 equiv), TBABF₄ (1 equiv), reductant (2 equiv), DMF (1.0 M), 80 °C, 1 h.

^[b] Yields were determined by ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

^[c] The regioisomeric ratio was determined by ¹H NMR analysis of the crude reaction mixture (ND = not determined).

^[d] 4 h. TBABF₄ = tetrabutylammonium tetrafluoroborate, TMA•HCO₂ (aq) = tetramethylammonium formate 30% w/w aqueous solution.

Table 2.

Aryl iodide scope.^[a-c]

^[a] **1a** (1 equiv), Pd₂(dba)₃ (1%), PPh₃ (20%), aryl iodide (2 equiv), K₃PO₄ (2 equiv), TMA•HCO₂ (aq) (2 equiv), DMF (1.0 M), 80 °C, 4–20 h.

^[b] Isolated yields.

^[c] The regioisomeric ratio of the isolated compound. The regioisomeric ratio of the crude reaction mixture as determined by ¹H NMR analysis is given in parenthesis if it differs from the ratio of the isolated material. TMA•HCO₂ (aq) = tetramethylammonium formate 30% w/w aqueous solution.

Table 3.

Alkene scope.^[a-c]

^[a] Alkene (1 equiv), Pd₂(dba)₃ (1%), PPh₃ (20%), aryl iodide (2 equiv), K₃PO₄ (2 equiv), TMA•HCO₂ (aq) (2 equiv), DMF (1.0 M), 80 °C, 4–24 h.

^[b] Isolated yields.

^[c]The regioisomeric ratio of the isolated compound. The regioisomeric ratio of the crude reaction mixture as determined by ¹H NMR analysis is given in parenthesis if it differs from the ratio isolated.

^[d]2.5% Pd₂(dba)₃ and 50% PPh₃.

^[e]The alkene starting material **3g** was a 1:1 mixture of diastereomers.

^[f]Contaminated with a constitutional isomer. TMA•HCO₂ = tetramethylammonium formate 30% w/w aqueous solution.