

Communication

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Palladium-Catalyzed Regiocontrollable Reductive Heck Reaction of Unactivated Aliphatic Alkenes

Chengdong Wang,[†] Guanlin Xiao,[†] Tao Guo,[†] Yalan Ding,[†] Xiaojin Wu^{†*} and Teck-Peng Loh^{†‡*}

[†] Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Jiangsu National Synergetic Innovation Center for Advanced Materials, Nanjing Tech University, Nanjing 211816, P. R. China

[‡] Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637616

Supporting Information Placeholder

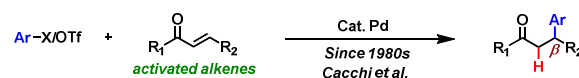
ABSTRACT: A general Pd-catalyzed intermolecular reductive Heck reaction of both terminal and internal unactivated aliphatic alkenes has been firstly developed. This method affords γ - and δ -arylated alkyl carboxylic acid derivatives in high yields with complete *anti*-Markovnikov selectivity. Notably, the coupling process is stereoretentive for the alkyl chain. Mechanistically, alkyl palladacycle intermediates stabilized by directing group and ligand, hydride species multi-generated from PS/TFA reductant, are two key factors that successfully promote the reaction and regioselectivity.

Regioselective Heck reaction of aliphatic alkenes has been extensively exploited and applied for the synthesis of many pharmaceuticals and natural products.¹ In comparison, the development of reductive Heck reaction, which produces alternative alkylarenes in the presence of hydride species, has met with less success.² Since its initial disclosure by Cacchi group,³ the intramolecular reductive Heck cyclization of alkenes has been well-exploited.⁴ Recently, the challenging enantioselective cyclization has also been developed by the groups of Buchwald,⁵ Jia,⁶ Zhou,⁷ Minnaard⁸ and Zhu.⁹ In contrast to the significant progress in intramolecular transformations, the development of an intermolecular reductive Heck reaction is mainly inhibited by the regioselectivity problem and competitive Heck reaction. The intermolecular reactions have been primarily limited to cyclic olefins. For example, specific *bi*- and oligocyclic alkenes like norbornenes are ideal substrates.¹⁰ The rigidity of the carbocyclic framework in these substrates does not allow the alkyl palladium intermediate to undergo rotation to form the usual Heck product, thus the intermediate reacts with the hydride donor instead. As for acyclic aliphatic olefins, only activated conjugated alkenes such as enones have been successfully reported (Figure 1A).¹¹ In 1983, Cacchi et al. reported the first palladium-catalyzed reductive Heck reactions of aryl iodides with α,β -unsaturated ketones.³ Since then, number of groups including Minnaard,^{11a,b} de Vries,^{11a,b} Reek,^{11b} Hagiwara,^{11c} Ornstein,^{11d} and others^{11e,f} have extended the substrate scope of this intermolecular reaction. Most of these examples exploited the electronic difference of the two olefinic sites to control the regioselectivity. In summary, although the reductive Heck reaction has been widely investigated since early 1980s, the intermolecular reductive Heck reaction of unactivated aliphatic alkenes is still unprecedented and remains a highly challenging task.

We envisioned that the selectivity of intermolecular reductive Heck reaction involving unactivated aliphatic alkenes could be addressed by utilizing a suitable directing group to regioselectively control the formation of the stable palladacycle intermediate and utilizing an efficient hydride source to promote the reductive elimination. Herein, we report the first example of a palladium-catalyzed regiocontrolled intermolecular reductive Heck reaction of unactivated aliphatic alkenes and organotriflates to provide γ or δ -functionalized alkyl carboxylic acid derivatives (Figure 1B).

These compounds that feature remote aryl substituents on their skeletons are widespread among important pharmaceuticals such as Ezetimibe,¹² Trandolapril,¹³ Delapril¹⁴ and Cilazapril.¹⁵

A. Previous Works: intermolecular reductive Heck reaction of *activated* aliphatic alkenes



B. This Work: regioselective reductive Heck reaction of *unactivated* aliphatic alkenes

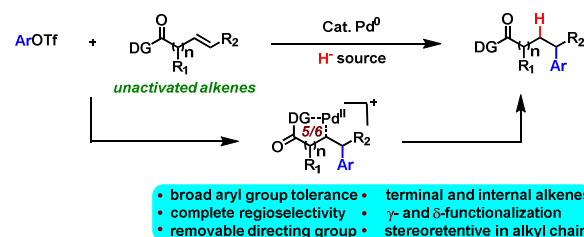


Figure 1. Development of Intermolecular Reductive Heck Reaction of Aliphatic Alkenes.

Initially, 3-butenic acid derivative bearing 8-aminoquinoline (AQ) directing group¹⁶ (**2a**) and *p*-tolyl triflate (**1a**) were chosen to evaluate the feasibility of our approach. Through extensive screening of reaction conditions, a catalytic system consisting of Pd₂(dba)₃, 2-(dicyclohexylphosphino)biphenyl (**Cy-JohnPhos**), 1,8-bis(dimethylamino)naphthalene (**Proton Sponge** or **PS**), trifluoroacetic acid (**TFA**) and 1,3-dimethyl-propyleneurea (**DMPU**) was found to promote the reaction at 130 °C, affording *N*-(quinolin-8-yl)-4-(*p*-tolyl)butanamide (**3a**) in 95% yield with exclusive *anti*-Markovnikov regioselectivity (Table S1 in Supporting Information, entry 1). Replacement of Cy-JohnPhos with other monophosphines led to lower yield albeit with good regioselectivity (Table S1, entries 2–20). Biphosphines were found to be catalytically inactive (Table S1, entries 21–25). When the ligand was omitted, Pd₂(dba)₃ alone showed no catalytic activity (Table S1, entry 26).

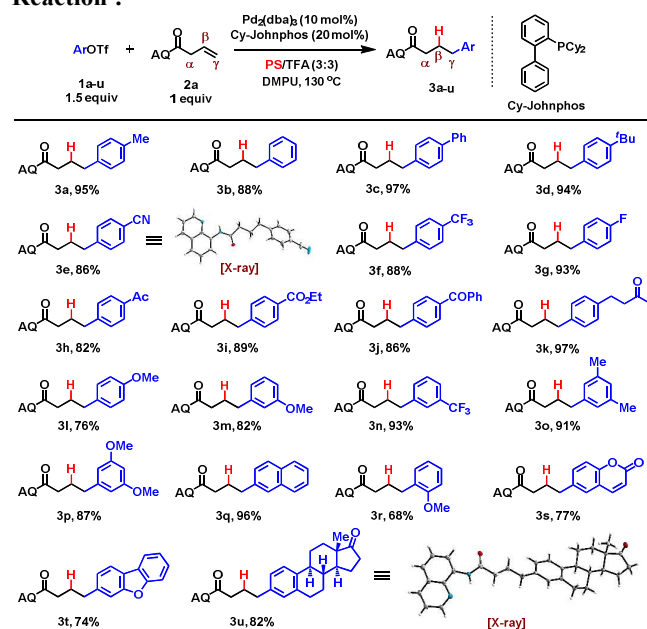
Notably, the catalyst loading and ratio of Pd/Ligand were crucial for the chemoselectivity and reactivity (Table S2 and S3), lower catalyst loading generated more Heck byproduct, and when the ratio of Pd₂(dba)₃/Cy-Johnphos¹⁷ was increased to 1:2, the competitive Heck reaction was completely omitted. These results indicated that high loading of Pd complex played an important role in efficient hydride generation to promote reductive elimination, while an optimized Pd/Ligand ratio favored the stable palladacycle formation to inhibit competitive β -H elimination side reaction.

The choice of suitable hydride source was also critical. Since the combination of amine/acid has been reported to act as an effective reductant in Pd-catalyzed reactions,^{7,10,11} several combinations of amine (Et₃N, ^tPr₂NEt and etc.) and TFA were examined (Table S4). Eventually, PS/TFA was identified to be the optimal reductant. Without the assistance of TFA, only 17% yield of reductive

Heck product was obtained even though PS was previously reported as an excellent hydride source (Table S5, entry 1).⁵ For other reaction condition optimizations, see the Supporting Information.

Under the optimal reaction conditions, we first investigated the aryl scope in the intermolecular reductive Heck reaction of unactivated terminal alkene (2a). The *para* substituents on the aromatic rings could be either electron-donating or electron-withdrawing, affording the corresponding γ -arylated products in good to excellent yields with complete *anti*-Markovnikov selectivity (Table 1, 3e–i). As expected, the reactivity and regioselectivity were not influenced by the steric hindrance at the *para* position (Table 1, 3a–d). The electronic effect at the *meta* position also remained minimal, the desired arylated products bearing both *mono*- and *di*-substituents were obtained in high yields and exclusive regioselectivity (Table 1, 3m–p). Moreover, slightly lower yield was observed for strong steric hindered substrate carrying an *ortho*-OMe group (Table 1, 3r). Notably, 2-naphthyl and heteroaryl groups also performed well (Table 1, 3q, 3s and 3t). The biologically relevant molecule 3-estrone functionalized product was also afforded in 82% yield (Table 1, 3u). The absolute configuration of both 3e and 3u were confirmed by X-ray crystallography¹⁸ while all other products were assigned based on NMR similarities. In summary, this reductive Heck reaction of unactivated aliphatic alkenes has a fairly broad aryl scope.

Table 1. Aryl Scope of Intermolecular Reductive Heck Reaction^a.

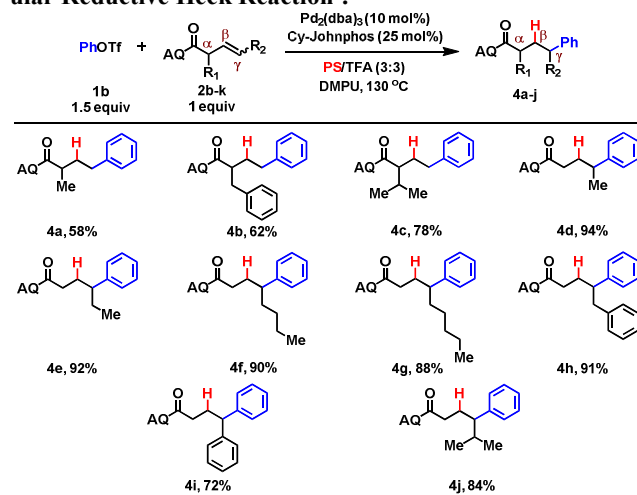


^aReactions were run on a 0.3 mmol scale. Percentages represent isolated yields.

To further explore the scope of this reaction, we next evaluated various aliphatic alkenes in the γ -selective reductive Heck reaction by using phenyl triflate (1b) as a representative aryl reagent. Several sterically hindered *non*-conjugated α -alkyl substituted terminal alkenes were tested, the corresponding linear arylated products were afforded in moderate yields with complete *anti*-Markovnikov selectivity (Table 2, 4a–c). To our gratification, this approach was also highly effective with unactivated internal alkenes. An array of alkyl-substituted internal alkenes proceeded well to provide branch reductive Heck products in excellent yields and exclusive regioselectivity (Table 2, 4d–j). The steric difference in the alkyl groups (from Me to 'Pr) has no obvious effect on the reactivity of relative internal alkenes. Collectively, we reasoned that exclusive regioselectivity and reactivity for γ -addition of terminal or internal alkenes were favored by efficient

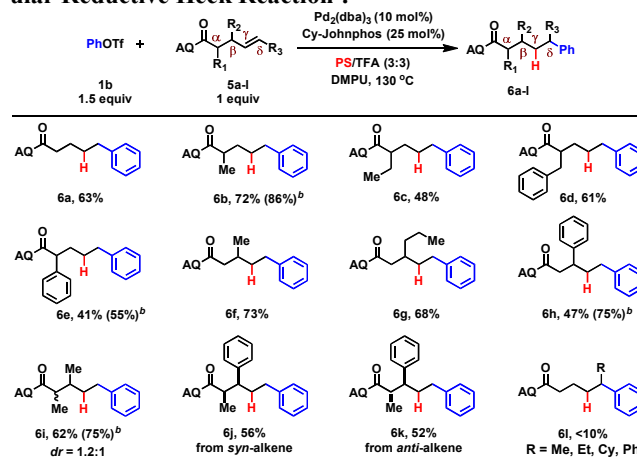
formation of the directing group controlled 5-membered palladacycle in our reductive Heck catalytic systems.¹⁹

Table 2. Aliphatic Alkene Scope in γ -Selective Intermolecular Reductive Heck Reaction^a.



^aReactions were run on a 0.3 mmol scale. Percentages represent isolated yields.

Table 3. Aliphatic Alkene Scope in δ -Selective Intermolecular Reductive Heck Reaction^a.



^aReactions were run on a 0.3 mmol scale. Percentages represent isolated yields.

^b20 mol% $\text{Pd}_2(\text{dba})_3$ and 40 mol% Cy-Johnphos .

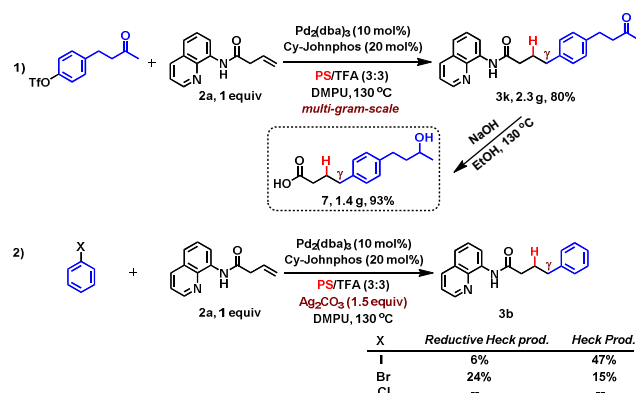
In contrast to the highly preferred formation of the rigid 5-membered alkyl palladacycles in AQ-directed reaction, the flexible 6-membered alkyl palladacycles were not easily established probably due to facile β -H elimination, which has made the δ -arylation more challenging.¹⁹ In order to assess the potential limitations of our reaction, 4-pentenoic acid derivative masked with the same directing group AQ (5a) was examined. Gratifyingly, the reaction produced the complete δ -selective addition product in 63% yield (Table 3, 6a). As expected, various terminal alkene substrates bearing an alkyl group at either α - or β -position of the amide also performed well (Table 3, 6b–h). Moderate to good yield of the exclusive δ -selective adduct was obtained in consistent with the relative steric effect of alkyl substituents. While increased catalyst loading, higher yield of corresponding product could be achieved. Encouraged by the results, more sterically hindered α , β -dimethyl substituted alkene was then tested, a mixture of two unseparated diastereomers was obtained in 75% yields (Table 3, 6i). Subsequently, geometrically pure *syn* or *anti*-alkene²⁰ (5j or 5k) was also subjected to the reaction conditions, they performed similarly and afforded the stereoretentive products in 56% and 52% yield respectively (Table 3, 6j and 6k). Therefore, we proposed that this coupling process was stereoretentive during the alkyl

palladacycle formation. As for the challenging internal alkenes, only trace amount of the desired products was observed from GC analysis (**Table 3**, **6l**), which is resulted from the fact that more substituted distal olefin is too sterically hindered to form stable 6-membered palladacycle intermediate.¹⁹

In order to demonstrate the synthetic practicality of this intermolecular reductive Heck reaction of unactivated aliphatic alkenes, a multi-gram scale reaction was conducted to afford the exclusive γ -arylated product (**3k**) in 80% yield. As shown in **Scheme 1**, eq 1, removing the directing group provided the long-chained carboxylic acid (**7**) in 93% yield, meanwhile, the ketone substituent was also reduced to the corresponding secondary alcohol under this basic condition.²¹ The product (**7**) is a potentially useful intermediate for the synthesis of various biological active compounds.²² Further studies on the coupling of commercially available aryl halides were conducted by adding Ag_2CO_3 as halide abstracter, both phenyl iodide and bromide showed moderate reactivity with poor chemoselectivity (**Scheme 1**, eq 2).

The unique reductive Heck reactivity enabled by this AQ-directed reaction system has supported our hypothesis. Further investigation on how the hydride is generated from the efficient PS/TFA reductant will offer deeper understanding of this reaction system. Initially, three deuterium-labelling experiments were conducted to determine the hydride sources (**Scheme 2**, eq 1). The reaction using $\text{CF}_3\text{CO}_2\text{D}$ produced the desired product (**3i**) in 85% yield with no deuterium atoms at the β -CH₂ proton, which clearly excluded the possibility of proton depalladation as the termination step. The reaction using d_7 -DMF produced the desired product (**3i**) in 65% yield with no deuterium atoms at the β -CH₂ proton, which ruled out DMF as the hydride source. Surprisingly, no reductive Heck product (**3i**) was detected in the reaction using d_{12} -PS, the Heck product was obtained in 88% yield instead. We proposed that the reductive Heck reaction was inhibited probably because of the more difficult β -D elimination of Pd complex in d_{12} -PS.²³ During our studies, we always observed an unexpected byproduct **Cy-PS** in addition to our desired products (**Scheme 2**, eq 2). Notably, replacing PS/TFA reductant with **Cy-PS**, the desired arylated product (**3i**) was also obtained in about 25% yield (**Scheme 2**, eq 3). This result showed that **Cy-PS** might also function as the hydride source.

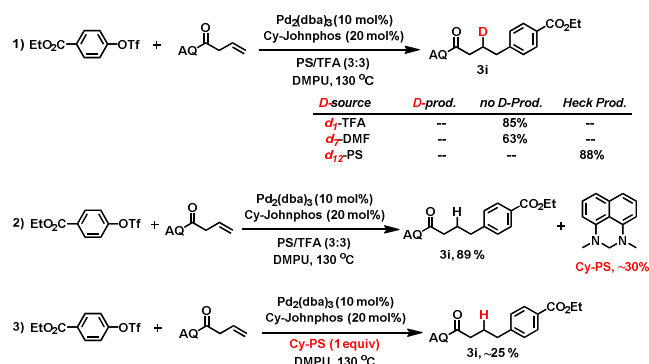
Scheme 1. Synthetic Practicality and Reaction Expansion.



On the basis of these observations and previously reported studies on the transformation of Proton Sponge,^{5,24} we proposed an explanation on how the PS/TFA reductant provided the hydride species for the reaction (**Figure 2**). Demethylation of Proton Sponge occurred under the acidic condition to produce **PS-1**.²⁴ This step was confirmed in our TFA/DMPU conditions (See Supporting Information). Subsequently, the hydride was generated under the Pd-catalyzed β -H elimination of **PS-1**, meanwhile, **Cy-PS** was formed to act as another hydride source. Given that there are more than one hydride-generation pathways operating concur-

rently sheds light on the high efficiency of the PS/TFA reductant in this challenging reductive Heck reaction. This also explained that high catalyst loading is necessary to generate adequate amount of the metal hydride species to promote the reductive elimination.

Scheme 2. Study on Generation of Hydride Species.



Based on the preceding results and literature studies on the reductive Heck reaction and palladacycle formation,^{5-11,16-19} we propose a possible catalytic cycle as depicted in **Figure 3**. Initially, oxidative addition to aryl triflate is conducted by *in situ* generated active $(\text{Cy-JohnPhos})_2\text{Pd}^0$ catalyst. The resulting cationic ArPd^{II} complex then coordinates with the alkene and undergoes regioselective 1, 2-migratory insertion to form the key cationic 5- or 6-membered alkyl palladacycle intermediate **A**, which is stabilized by AQ directing group and **Cy-JohnPhos** ligand. Subsequently, the hydride species are generated from PS/TFA reductant system to furnish the neutral palladacycle complex **B**. Finally, reductive elimination of complex **B** affords the desired γ - or δ -arylated product with concurrent regeneration of the active $(\text{Cy-JohnPhos})_2\text{Pd}^0$ catalyst.

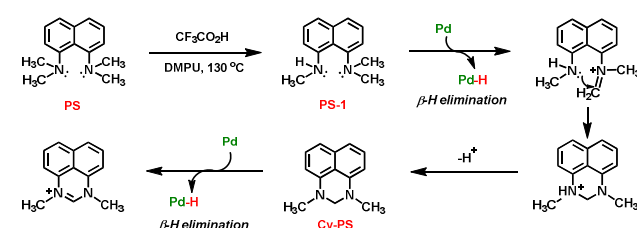


Figure 2. Proposed Reaction Route for Hydride Generation.

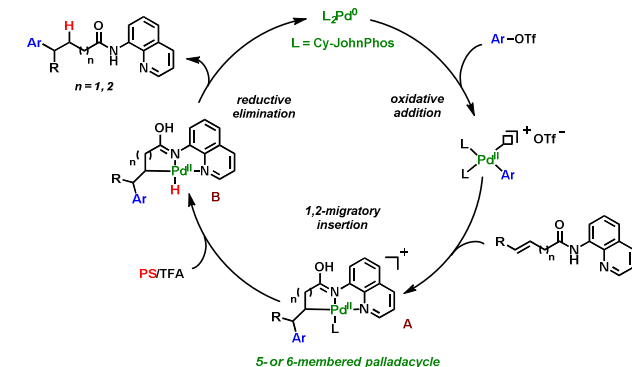


Figure 3. Proposed Catalytic Cycle for Reductive Heck Reaction.

In conclusion, we have developed the first Pd-catalyzed regiocontrollable intermolecular reductive Heck reaction of unactivated aliphatic alkenes. The hydroarylation approach proceeded well with a broad range of aryl groups and tolerated both terminal and internal unactivated aliphatic alkenes. Without modification of the AQ directing group, both γ - and δ -arylated

alkyl carboxylic acid derivatives were obtained in good yields with complete *anti*-Markovnikov selectivity. Mechanistically, by utilizing the chelation control of the AQ directing group and coordination assistance of ligand, the putative cationic 5- and 6-membered Pd^{II} complex intermediates were stabilized to enable reductive elimination under highly efficient hydride source (PS/TFA). Notably, the coupling process was found to be stereoretentive with regard to the olefin stereochemistry in the substrate. The easily removal of AQ directing group also illustrates the potential synthetic application of this methodology. Further study on the detailed mechanism and asymmetric version of this reaction are currently in progress and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Authors

*iamxiaojinwu@njtech.edu.cn; *teckpeng@ntu.edu.sg.

Notes

The authors declare no competing financial interests.

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