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Visible Light-Induced Room Temperature Heck Reaction of Functionalized Alkyl Halides with Vinyl Arenes/Heteroarenes

Daria Kurandina, Marvin Parasram, and Vladimir Gevorgyan*

Abstract: *The first visible light-induced Pd-catalyzed Heck reaction of α-heteroatom substituted alkyl iodides and -bromides with vinyl arenes/heteroarenes has been developed. This transformation efficiently proceeds at room temperature and enables synthesis of valuable functionalized allylic systems, such as allylic silanes, -boronates, -germanes, -stannanes, -pivalates, -phosphonates, -phthalimides, and -tosylates from the corresponding α-substituted methyl iodides. Notably, synthesis of the latter substrates failed under existing thermally induced Pd-catalyzed conditions, which highlights the importance of visible light for this transformation.*

The Mizoroki-Heck reaction is a fundamental synthetic transformation that enables coupling of aryl and vinyl halides/pseudohalides with alkenes.[1] Recently, unactivated alkyl halides were found to be competent substrates for both intra- (Scheme 1, a) and intermolecular (Scheme 1, b) versions of this reaction. In his seminal work, Fu reported that employment of bulky NHC ligands promotes the intramolecular reaction of unactivated alkyl bromides and chlorides operating via classical Heck mechanism.[2] Later, in 2012, Alexanian introduced the first intramolecular alkyl Heck reaction of unactivated alkyl iodides, which occurred via formation of alkyl hybrid Pd-radical intermediates.[3,4] Very recently, Alexianan and Zhou independently reported an intermolecular version of this reaction. [3b, 5] Although these methods are highly innovative, challenges still remain. Currently, alkyl Heck reaction has been established for unactivated,[3,5] activated (possessing carbonyl group and equivalents at the β-position),[6] and perfluorinated[7] alkyl halide coupling partners. However, employment of α-heteroatom-substituted alkyl electrophiles toward synthesis of valuable allylic systems (*vide infra*) is unknown. Moreover, most alkyl Heck methods proceed at high temperatures, which often results in coupling products with low stereoselectivity.[5] Evidently, development of an alkyl Heck reaction that would feature milder reaction conditions and broader substrate scope are highly warranted. Herein, we report the first example of a *visible light-induced, exogenous photosensitizer free*[8] room temperature intermolecular Pd-catalyzed Heck reaction of α-heteroatom substituted electrophiles, such as silyl-, germyl-, tosyl-, phosphonyl-, phthalimidyl-, pinacolboronyl-, stannyl-, and pivaloyl methyl halides, with vinyl arenes/heteroarenes. This protocol allows for a facile and efficient formation of valuable diversely functionalized allylic synthons with high stereocontrol (Scheme 1, c).

Aiming at the development of α-heteroatom substituted alkyl Heck reaction, we commenced our studies with iodomethyl silyl electrophiles. We have previously reported the Pd-catalyzed *endo*-selective alkyl Heck reaction featuring this moiety.[9]

Scheme 1. Palladium-catalyzed alkyl-Heck reactions.

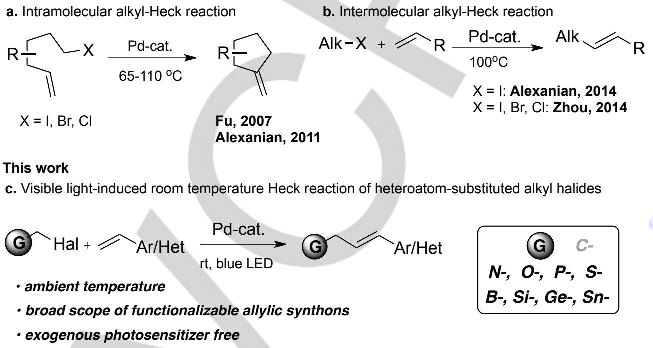
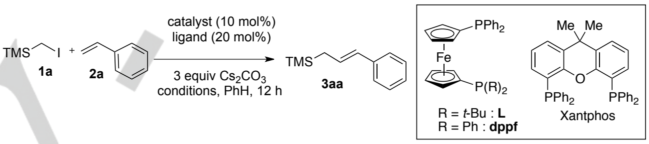


Table 1: Optimization of the reaction conditions.[a]



#	catalyst	ligand	base	cond.	yield,[b % (*E*:*Z*)
1[c]	$Pd(OAc)_2$	**L**	*i*Pr_2NEt	120 °C	traces
2[c]	$Pd(dppf)Cl_2$	-	Cy_2NMe	100 °C	35(5:1
3[d]	$Pd(PPh_3)_2Cl_2$ (5 mol%)	Xantphos (10 mol%)	Cs_2CO_3	100 °C	0
4[e]	$Pd(PPh_3)_4$ (35 mol%)	-	K_2CO_3	100 °C	10 (1:0
5	$Pd(PPh_3)_4$	-	Cs_2CO_3	rt, blue LED	35(56[f (30:1)
6	$Pd(dppf)Cl_2$	-	Cy_2NMe	rt, blue LED	traces
7	$Pd(OAc)_2$	dppf	*i*Pr_2NEt	rt, blue LED	traces
8	$Pd(OAc)_2$	**L**	*i*Pr_2NEt	rt, blue LED	traces
9	**$Pd(OAc)_2$**	**Xantphos**	**Cs_2CO_3**	**rt, blue LED**	**85 (49:1)**
10	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	Up to 110 °C	traces
11	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	rt, dark	traces
12	-	Xantphos	Cs_2CO_3	rt, blue LED	0

[a] Standard conditions: **1a** 0.1 mmol scale, PhH 0.25 M, 120 °C or 34W blue LED; [b] GC-MS yield and ratio; [c] $PhCF_3$ as solvent; [d] DCE as solvent; [e] PhMe as solvent; [f] THF as solvent.

Development of an intermolecular version of this reaction would be of synthetic interest, as it would provide facile access to valuable cinnamyl silanes.[10] Thus, reaction of iodomethyltrimethyl silane **1a** and styrene **2a** was tested (Table 1). However, employment of our previously developed reaction conditions provided only traces of allylic silane **3aa** (entry 1). Next, various reaction conditions, reported for the Pd-catalyzed alkyl Heck reactions by Alexanian[3](entry 2), Zhang[7a](entry 3), and Reutrakul[7c](entry 4), were tested, however, low yields and poor stereoselectivity of **3aa** were obtained. Apparently, other means of activation were required to promote this transformation. Our recent work[11] and reports from other groups[12] have illustrated the beneficial effect of visible light on TM-catalyzed transformations. Indeed, we were pleased to find that 35% yield of coupling adduct **3aa** was obtained under visible light irradiation (blue LED) at room temperature in the presence of

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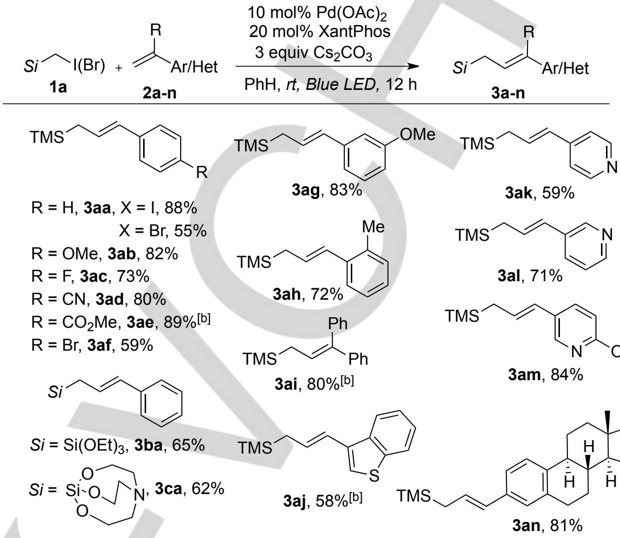
$Pd(PPh_3)_4$ catalyst (entry 5). Testing other catalyst/ligand combinations, such as $Pd(dppf)Cl_2$, and $Pd(OAc)_2$ with dppf or **L** under photoirradiation were less efficient (entries 6-8). Delightfully, employment of $Pd(OAc)_2$ and Xantphos catalytic system delivered 85% of **3aa** with excellent stereoselectivity (entry 9). It should be mentioned that attempts on promoting the reaction by thermal means were ineffective (entry 10). Also, control experiments indicated that both light and the Pd-catalyst are essential for this transformation (entries 11,12).

With the optimized reaction conditions in hand, the generality of this transformation with respect to the alkene component was investigated (Table 2). Reactions of **1a** with styrene derivatives (**2**),[13] possessing both electron-withdrawing and electron-donating groups at the *para*-position were found to be highly efficient (**3aa-3af**). Remarkably, this transformation is not only limited to alkyl iodides, as bromo-analogue of **1a** (X=Br) also participated in this reaction. It was also found that not only halomethyltrimethylsilanes (**1a**), but also its synthetically more appealing analogs, such as trialkoxysilyl-[14] (**1b**) and –silatranyl[15] (**1c**) derivatives, reacted well producing allylic silanes (**3ba, 3ca**) in reasonable yields. Styrenes containing substituents at either the *meta*- or *ortho*-positions reacted well, affording products **3ag** and **3ah** in 83% and 72% yield, respectively. Notably, 1,1-diphenylethylene, a challenging coupling partner for a related silyl-Heck reaction,[10] reacted smoothly with **1a** to produce **3ai** in high yield. Next, this methodology toward reaction of vinyl heteroarenes was examined. Coupling **1a** with 3-vinylbenzothiophene **3j**, and *p*- and *m*-vinyl pyridines (**3ak**, **3al**) proceeded uneventfully, producing the corresponding products in good yields (**3ak-3al**). Finally, reaction of **1a** with vinyl derivative of estrone **2n** generated product **3an** in 81% yield, highlighting the applicability of this *visible light-induced* Heck reaction protocol in complex settings.

Naturally, after developing this silyl methyl Heck reaction, we were eager to verify if this novel visible light-induced protocol is efficient for other α-heteroatom substituted methyl iodides, which, if successful, would provide expeditious access to valuable diversely functionalized allylic systems (Table 3). Accordingly, reactions of pinacolboronyl- (**1d**), trialkylstannyl- (**1e**), phthalimidyl- (**1f**), pivaloyl- (**1g**), phosphonyl- (**1h**), tosyl- (**1i**), and germyl- (**1j**) methyl iodides with **2a** were tested. *To our delight, all of these systems reacted efficiently, leading to privileged cinnamyl derivatives in good yields (**3da-3ja**).* Moreover, bromo-analogues of **1d**, **1f**, and **1i** ($PhSO_2CH_2Br$) were found to be competent coupling partners for this transformation. Coupling of electronically different vinyl arenes and heteroarenes, with selected α-heteroatom substituted methyl iodides all proceeded in a highly efficient manner (**3fc**, **3dd**, **3ig**, **3bb**, **3hm, 3ho**). Excitingly, reaction of **2a** with α,α-disubstituted methyl iodides possessing two trimethylsilyl groups (**1j**), as well as unsymmetrically disubstituted substrate possessing pinacolboronyl and dimethylphenyl silyl moieties (**1k**), proceeded well, producing dually functionalizable allylic systems **3ja** and **3ka** in 97% and 90% yields, respectively.

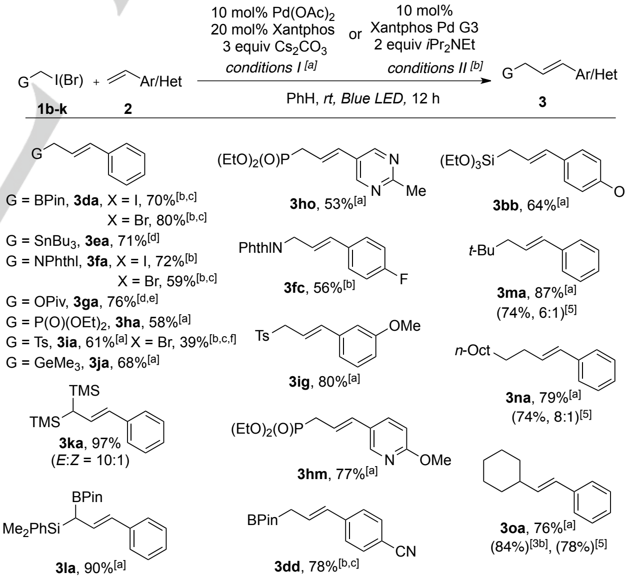
It deserves mentioning that α-heteroatom-substituted alkyl iodides, due to the lack of β-hydrogens, are seemingly "easy" substrates for an alkyl-Heck reaction. However, they showed much lower efficiency under reported thermal conditions.[16] In order to determine if visible light can provide any beneficial effects for established thermally induced alkyl Heck reactions,[3,5] known alkyl electrophiles **1m-o** possessing β-hydrogens were tested under our reaction conditions (Table 3). Remarkably, it was found that coupling of **1m-o** and styrene **2a** provided Heck

Table 2: Scope of alkenes.[a]



[a] Standard Conditions I: **1a** 0.75 mmol, **2** 0.5 mmol, $Pd(OAc)_2$ 0.05 mmol, Xantphos 0.1 mmol, Cs_2CO_3 1.5 mmol, PhH 0.25 M, 34W blue LED, rt. [b] $Pd(OAc)_2$ (2 mol%) and Xantphos (4 mol%) was added to the reaction mixture after 12 h, and the reaction was stirred for additional 6 h.

Table 3: Scope of alkyl iodides.[a,b]



[a] Standard Conditions I: **1a** 0.75 mmol, **2** 0.5 mmol, $Pd(OAc)_2$ 0.05 mmol, XantPhos 0.1 mmol, Cs_2CO_3 1.5 mmol, PhH 0.25 M, 34W blue LED, rt, isolated yields; [b] Standard Conditions II: **1a** 0.75 mmol, **2** 0.5 mmol, Xantphos Pd G3 0.05 mmol, *i*Pr_2NEt 1 mmol, PhH 0.25 M, 34W blue LED, rt, isolated yields; [c] NMR yield; [d] 0.25 mmol scale, **1a** 1 equiv, **2a** 4 equiv, Cs_2CO_3 6 equiv and PhH 0.0625 M, isolated yields; [e] The reaction requires 2 h for completion. [f] $PhSO_2CH_2Br$ was used.

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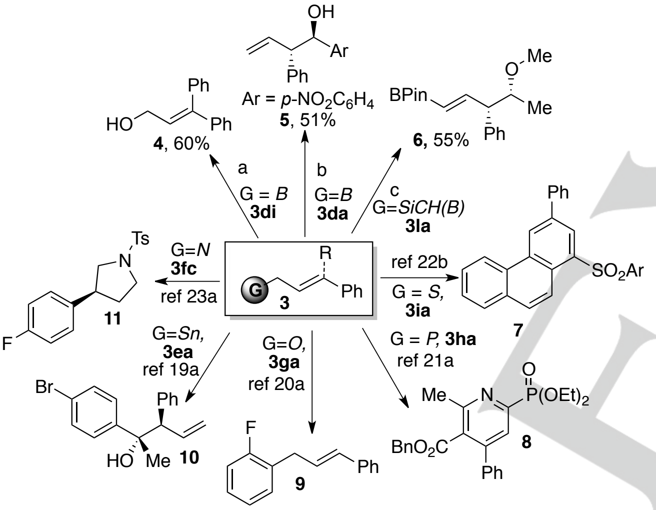
products **3ma-3oa** in yields comparable to these obtained under the previously reported thermal conditions,[3,5] however with superior stereocontrol (**3ma-3na**)! The observed phenomenon can be attributed to the milder reaction conditions of our method (room temperature), where a thermally-induced isomerization of the reaction products did not occur.[1,3,5]

The obtained diverse cinnamyl products (**3**) are useful synthetic intermediates,[17-23] widely used as reactive substrates toward further functionalization. However, depending on the nature of the cinnamyl products (possessing nucleophilic or electrophilic group G), methods toward these synthons involve different synthetic routes and starting materials. Conversely, our approach offers an attractive general method toward accessing these important fragments. Thus, after establishing the reaction scope, the synthetic applications of selected cinnamyl products were tested (Scheme 2). A sequential one-pot Heck reaction/oxidation procedure of **1g** with **2i** generated allylic alcohol **4** in good overall yield. Similarly, a one-pot reaction of **1g** with **2a**, followed by allylation of 4-nitrobenzenaldehyde furnished **5** in good yield and high diastereoselectivity. Finally, Hosomi-Sakurai reaction of dually functionalizable **3ka** with 1,1'-dimethoxyethane resulted in the selective formation of vinyl boronic ester **6** in respectable yield. Other nucleophilic synthons such as **3fa** and **3ha-ia**, as well as electrophilic allylic systems **3da-ea**, have been extensively featured in numerous reported synthetic transformations[17-23] (Scheme 2, **3**→**7-11**).

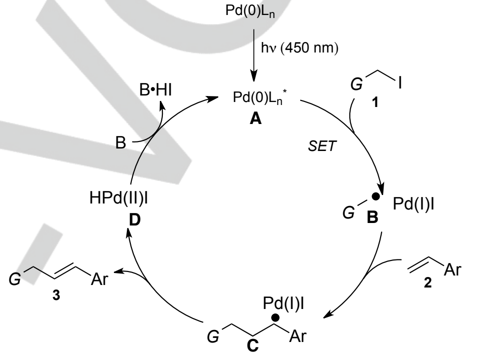
Scheme 2. Performed and reported transformations of obtained products.



Conditions: a) *One-pot reaction:* 1) Xantphos Pd G3 (10 mol%), N(i-Pr)$_2$Et (2.2 equiv), **1g** (1.5 equiv), **2i** (1 equiv), PhH, blue LED, rt, 12 h. 2) 30% H_2O_2, THF, rt; b) *One-pot reaction:* 1) Xantphos Pd G3 (10 mol%), N(i-Pr)$_2$Et (2.2 equiv), **1g** (1.5 equiv), **2a** (1 equiv), PhH, blue LED, rt, 12 h. 2) 4-Nitrobenzaldehyde (2 equiv), diphenyl phosphate (2 equiv), PhH, rt, 12 h; c) **3ka** (1 equiv), 1,1-dimethoxyethane (1.03 equiv), $TiCl_4$ (1.2 equiv), DCM, -78 °C, 15 min.

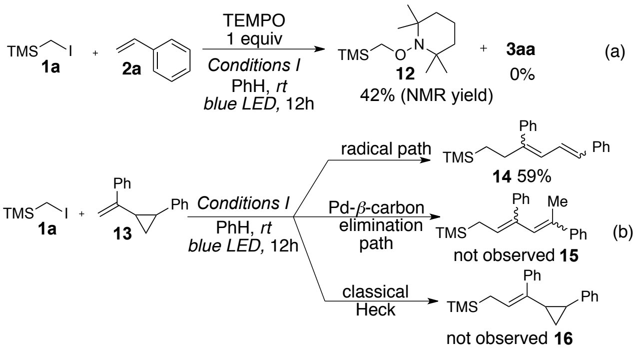
Based on the literature precedents on Heck reactions of alkyl iodides, a hybrid-Pd radical mechanism is proposed for this transformation (Scheme 3).[3,4,5,9] First, the active Pd(0) complex **A** is formed via an *in situ* reduction of Pd(II)OAc$_2$. Then, complex **A** undergoes an SET with alkyl halide **1** to generate the putative Pd(I) species and alkyl radical **B**. Addition of the latter to alkene **2** produces radical intermediate **C**. A subsequent β –H-elimination from the latter delivers allylic product **3** and closes the catalytic cycle. The radical nature of this transformation was confirmed by employment of radical traps[24] and radical clock[25] studies (Scheme 4). Thus, subjecting TEMPO to the reaction of **1a** and **2a** resulted in 42% NMR yield of TEMPO-trapped adduct **12** (Scheme 4, a). Next, reaction **1a** with a radical clock **13** resulted in regioselective radical-ring opening of the cyclopropyl unit **14** in 59% as a mixture of stereoisomers. Formation of a product of Pd-β-C elimination[26] of the cyclopropane component (**15**), or the coupling adduct possessing an intact cyclopropane unit (**16**), was not detected (Scheme 4, b).

Scheme 3. Plausible reaction mechanism.



At this stage, the origins of the visible light induction of this transformation are not fully understood. In 2009, Köhler studied an accelerating effect of visible light on classical thermal Heck reaction of aryl halides. In his studies,[27] the observed visible light acceleration effect was solely attributed to the facilitation of the initial off-cycle reduction step of the pre-catalyst Pd(II) into the active Pd(0) species. To test this possibility, Pd(II)OAc$_2$ was replaced with Pd(0) pre-catalyst, such as Pd$_2$dba$_3$[16] This resulted in comparable efficiency of the reaction compared to that in the presence of Pd(II)OAc$_2$, thus, disfavoring this scenario[27] for our visible light-induced Pd-catalyzed alkyl Heck reaction. Therefore, it is likely that visible light promotes photo excitation of the formed Pd(0) catalyst (Scheme 3, complex A),[29] which consequently undergoes SET with **1** and thus triggers the catalytic cycle. The control experiments including reactions performed in dark (Table 1, entry 11), light on/off tests,[28] UV/vis analysis of Pd(0) species,[29] as well as Stern-Volmer studies,[30] are in agreement with this mechanistic scenario.[16]

Scheme 4. Initial mechanistic studies



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In conclusion, we developed the first *visible light-induced* Pd-catalyzed room temperature Heck reaction of α-functionalized alkyl halides with vinyl arenes and heteroarenes leading to synthetically valuable allylic systems. Importantly, synthesis of these privileged synthons by reported thermal Heck protocols was ineffective, thus highlighting the benefits of employing visible light for this transformation. In addition, for unactivated alkyl halides, the obtained products were formed with higher stereoselectivity compared to the established thermally-induced methods.

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Keywords: Heck reaction • Visible light • Alkyl Radical • Palladium

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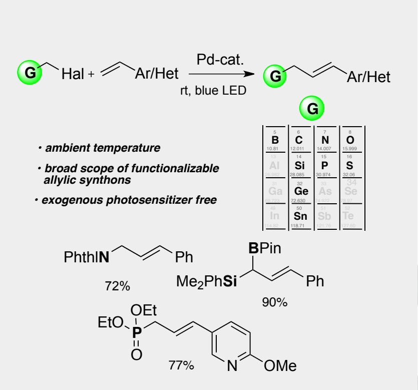
Entry for the Table of Contents

COMMUNICATION

The first room temperature visible light-induced Pd-catalyzed Heck reaction of α-heteroatom substituted alkyl halides with vinyl arenes/heteroarenes is reported. This transformation enables synthesis of valuable functionalized allylic systems, such as allylic silanes, -boronates, -germanes, stannanes, -pivalates, -phosphonates, -phthalimides, and -tosylates, from the corresponding α–substituted methyl halides in good yields.



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Page No. – Page No.

Visible Light-Induced Room Temperature Heck Reaction of Functionalized Alkyl Halides with Vinyl Arenes/Heteroarenes

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