Heck Reaction of Electronically Diverse Tertiary Alkyl Halides

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Abstract

The efficient Pd-catalyzed Heck reaction of diverse tertiary alkyl halides with alkenes has been developed. Unactivated tertiary alkyl halides efficiently react at room temperature under visible light irradiation with no exogenous photosensitizers required. For activated tertiary alkyl halides, the same catalytic system works well without light. These methods offer a general access to electronically diverse alkenes possessing quaternary and functionalized tertiary allylic carbon centers. The substituents at these centers include alkyl-, carbalkoxy-, tosyl-, phosphonyl-, and boronate groups. It was also shown that the end-game mechanism of this transformation may vary depending on the type of the substrates used.

Graphical Abstract
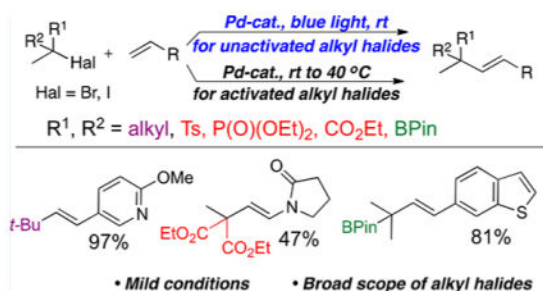
The Mizoroki–Heck reaction[1] is a fundamental transformation in organic chemistry that is traditionally used for coupling of aryl and vinyl halides/pseudohalides with alkenes.[2] Originally, employment of alkyl halides in this reaction was not straightforward due to premature β-hydrogen elimination[3] and slow oxidative addition rates.[4] Although there were numerous reports on the Heck reaction of activated[5] and perfluorinated[6] alkyl halides, employment of unactivated alkyl halides became possible only after seminal works by Fu[7] and Alexanian.[8] Due to the above-mentioned reasons, employment of tertiary alkyl halides

in Heck reactions is even more problematic. For activated tertiary alkyl halides, the solution was found by Lei,[9] Thomas,[10] and Nishikata[11] employing Ni-, Fe-, and Cu catalysts, respectively (Scheme 1a). Still, these methods either require high temperatures or are limited in scope. All these transformations were proposed to occur via generation of alkyl radical species stabilized by adjacent electron-withdrawing groups. This may be a reason for the underutilization of unactivated tertiary alkyl halides in Heck-type reactions for a long time. In 2002, Oshima reported the Co-catalyzed Heck-type coupling of 1°, 2°, and 3° alkyl halides with styrenes promoted by Me_3SiCH_2MgCl (Scheme 1b). Obviously, the requisite Grignard reagent limits the scope of this method.[12] Recently, Hashmi reported a single example of coupling between *tert*-butyl bromide and 1,1-diphenyl ethene under light-induced, Au-catalyzed Heck-type reaction (Scheme 1c).[13a] A single report by deMeijere disclosed a moderately efficient Pd-catalyzed Heck reaction of unactivated tertiary halides (Scheme 1d).[14] However, it is limited to employment of adamantyl bromide, a substrate not disposed to β-hydrogen elimination.

Evidently, the development of a method that would feature mild reaction conditions and broad substrate scope, including both activated and unactivated tertiary alkyl halides, is highly warranted. Very recently, our group introduced the *first visible light-induced*[15] Pd-catalyzed Heck reaction, which allows activated and unactivated primary and secondary alkyl electrophiles to react with vinylarenes in a highly efficient and stereoselective manner (Scheme 1e).[16] Herein, we report general *room temperature, visible light-induced,*[17] *exogenous photosensitizer-free*[18] Pd-catalyzed Heck reaction of a wide range of tertiary alkyl halides with alkenes to produce electronically neutral,[19] electrophilic, and nucleophilic allylic systems possessing quaternary and functionalized tertiary carbon center (Scheme 1f).

Aiming at the elaboration of the Heck reaction with unactivated tertiary alkyl halides, we commenced our studies with *tert*-butyl iodide **1a**. First, the reaction of **1a** with styrene **2a** was tested under the reported palladium-based thermal conditions;[8b,20] however, only decomposition of the starting materials was observed (Table 1, entries 1 and 2). *Switching to our previously found conditions for visible-light-induced Heck reaction of primary and secondary alkyl halides*[16] *led to formation of **3aa** in 87% yield (entry 3)!* Other catalyst/ligand combinations, such as $Pd(PPh_3)_4$, and $Pd(OAc)_2$ with DPEphos, *t*-Bu-Xantphos, **L**, [18b,c] or DPPE were much less efficient (entries 4–7). Control experiments indicated that both light and the Pd catalyst are essential for this transformation (entries 8 and 9). Naturally, we were eager to verify if this method could also be used for reactions of *activated tertiary alkyl halides*. It was found that activated tertiary alkyl halides of different electronic nature, such as **1d** and **1h**, were incompatible with the standard thermal palladium-based conditions, reported for alkyl Heck reaction[8b] (entries 10 and 13). However, under the developed blue light conditions, satisfactory yields of the corresponding products were obtained (entries 11 and 14). Further optimization under blue light led to significant improvement of the reaction efficiency for **1h** (entry 13). Remarkably, the control experiments for both activated substrates (**1d** and **1h**) indicated that these reactions proceed efficiently without light to produce **3da** and **3ha** at room temperature and at 40 °C, respectively (entries 12 and 16).

With the optimized conditions in hand, the generality of visible-light-induced reaction of unactivated tertiary alkyl halides was investigated first (Scheme 2). Reaction of *tert*-butyl

iodide **1a** with both electron-rich and electron-deficient para-substituted styrenes[21] proceeded very efficiently, leading to alkene products in excellent yields (**3aa–af**). Reactions with *meta*-and *ortho*-substituted styrenes proceeded uneventfully, as well (**3ag–aj**). Importantly, sensitive functional groups such as primary alcohol (**3ah**) and aldehyde (**3ai**) were tolerated under these reaction conditions. Moreover, vinyl heteroarenes were found to be competent substrates in this reaction to produce heterocyclic derivatives **3ak–am** in good to excellent yields. Other unactivated tertiary iodides reacted well with styrene and acrylonitrile to produce alkenes possessing quaternary allylic carbon centers (**3ba**, **3ca**, **3cn**).

Next, the scope of activated tertiary alkyl halides under the newly developed thermal Heck reaction conditions was examined (Scheme 3). It was found that a variety of electron-deficient alkyl halides underwent smooth Heck reaction to produce electrophilic alkenes, possessing carbethoxydimethyl-(**3da**), phosphonyldimethyl- (**3ea**), tosyldimethyl- (**3fa**), and dicarbethoxymethyl- (**3gb–gp**) moieties in good to nearly quantitative yields. Motivated by the great synthetic usefulness of allylboronates,[22,23] we attempted approaching this important motif via Heck reaction of pinacolboronyldimethyl methyl iodide (**1h**). Gratifyingly, it was found that a wide range of electronically different styrenes, as well as vinyl heteroarenes, underwent a smooth reaction with **1h**, resulting in useful[22] tertiary allylic boronates (**3ha–hl**) in excellent yields.

Upon investigating the scope of this transformation, it was found that the reaction of tertiary alkyl bromide **1g** with phenyl vinyl ether (**2s**) did not produce the expected Heck product. However, in the presence of *O*-nucleophiles, the carboxyalkoxylation and alkoxyalkylation adducts, mixed acetals **4a** and **4b**, were selectively obtained (Scheme 4). It is apparent that in contrast to the previously reported reactions involving aryl-(**18b**) and alkyl Pd-radical hybrid species,[16,18,19] this transformation proceeds through cationic intermediates (vide infra).

On the basis of the observations above (Scheme 4) and our initial mechanistic studies, including radical clock experiments, radical trapping, and Stern–Volmer quenching experiments,[24] as well as literature precedents for Heck reactions of alkyl halides,[8,16,19] the following hybrid-Pd radical mechanism is proposed for this transformation (Scheme 5). First, the in situ generated Pd(0) species undergoes visible-light excitation to produce the active Pd(0) complex **A**. Next, it undergoes an SET with alkyl halide **1** to produce the putative alkyl Pd–hybrid radical species **B**.[25] Addition of the latter to alkene **2** produces a new alkyl radical intermediate **C**. A subsequent β-H-elimination delivers Heck product **3** and closes the catalytic cycle (**D → A**). Alternatively, in the reaction with electron-rich aryl vinyl ether (**2s**, Scheme 4), the Pd(I) species oxidizes intermediate **C**[26] into the stabilized cation **E**, which is then trapped by a nucleophile to give the double-addition product, acetal **4**.

In conclusion, we developed the first general, efficient, and mild Heck reaction of tertiary alkyl halides. This visible light-induced Pd-catalyzed method, which works well with unactivated tertiary alkyl halides, operates at room temperature and does not require employment of exogenous photosensitizers. For activated tertiary alkyl halides, the same catalytic system does not require light for a successful Heck coupling. Employment of an

array of alkyl halides allows synthesis of valuable electronically diverse allylic products, including neutral alkenes possessing quaternary carbon centers, electron-deficient alkenes having carbalkoxy- and tosyl groups, as well as nucleophilic allylboronates. Importantly, for the reactions of electronically different alkenes, a mechanistic dichotomy was discovered. Thus, in contrast to the reactions with electron-neutral and electron-deficient alkenes, operating via hybrid Pd-radical mechanism, the reactions with electron-rich alkenes proceed through a hybrid radical/cationic pathway leading to mixed acetals, the products of the double-addition process.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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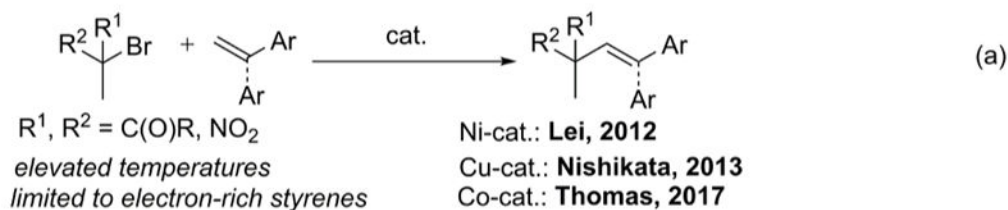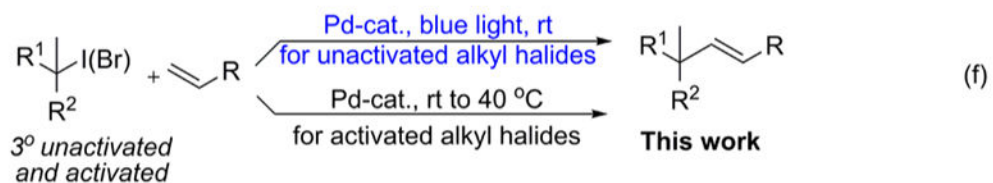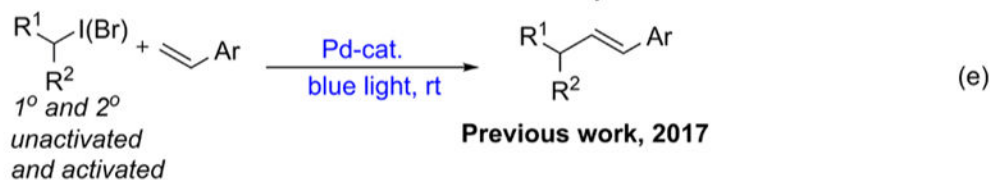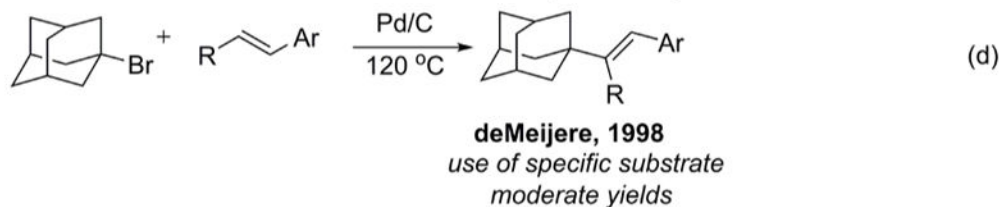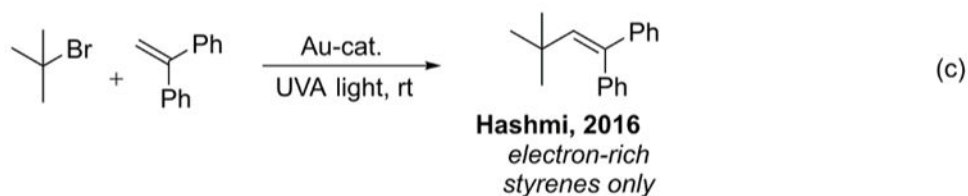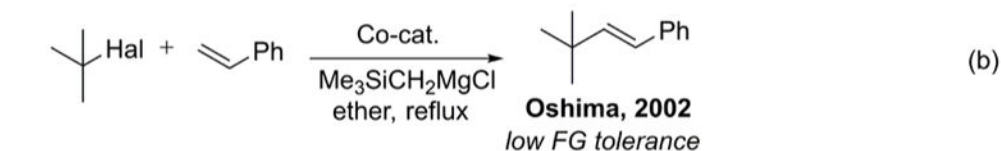
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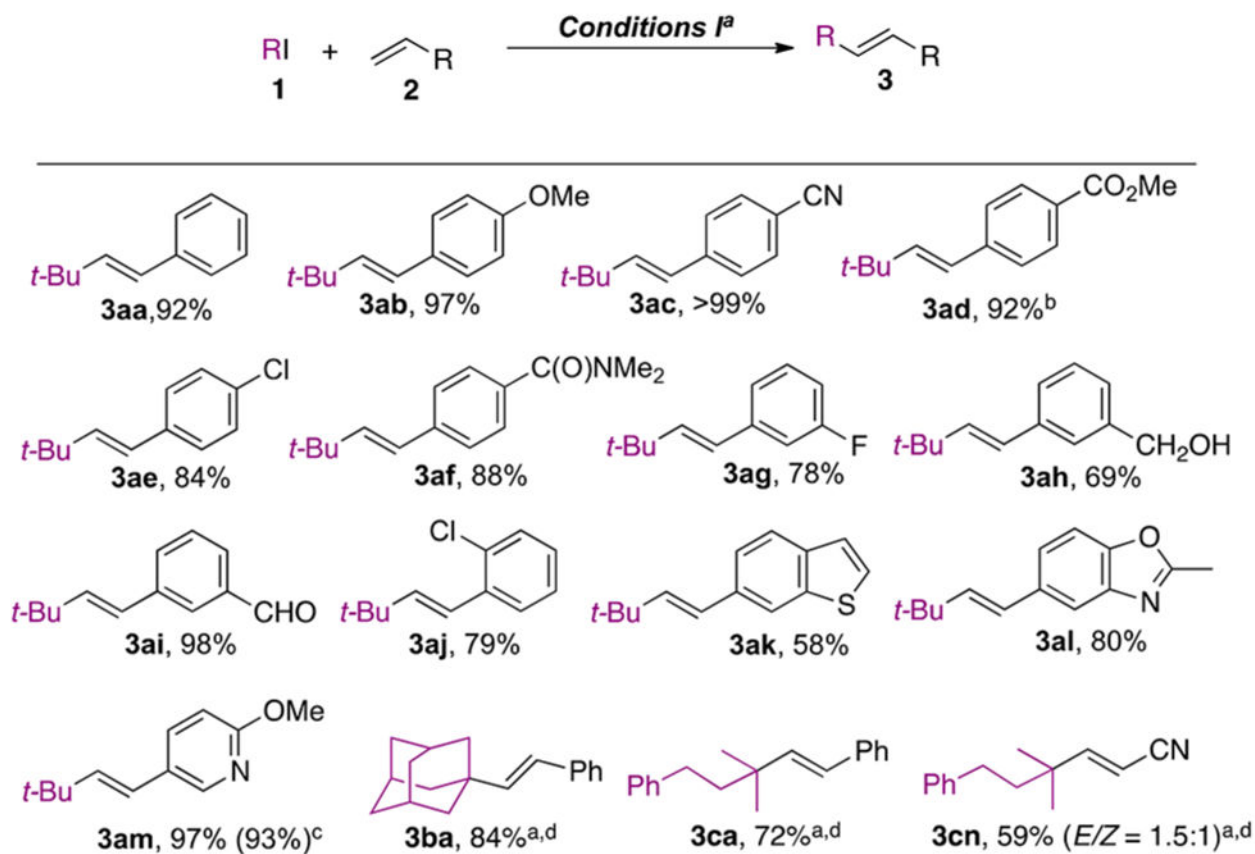**Employment of Activated Tertiary Alkyl Halides:**

$R^1, R^2 = C(O)R, NO_2$
elevated temperatures
limited to electron-rich styrenes

Ni-cat.: **Lei, 2012**
Cu-cat.: **Nishikata, 2013**
Co-cat.: **Thomas, 2017**

(a)

Employment of Unactivated Tertiary Alkyl Halides:

Co-cat.
Me_3SiCH_2MgCl
ether, reflux

Oshima, 2002
low FG tolerance

(b)

Au-cat.
UVA light, rt

Hashmi, 2016
electron-rich styrenes only

(c)

Pd/C
120 °C

deMeijere, 1998
use of specific substrate moderate yields

(d)

1° and 2°
unactivated and activated

Pd-cat.
blue light, rt

Previous work, 2017

(e)

3° *unactivated and activated*

Pd-cat., blue light, rt
for unactivated alkyl halides

Pd-cat., rt to 40 °C
for activated alkyl halides

This work

(f)

Scheme 1.
Heck Reaction of Tertiary Alkyl Halides

Scheme 2. Scope of Unactivated Tertiary Alkyl Iodides
[a]Conditions I: **1a** 1.0 mmol, **2** 0.5 mmol, Pd(OAc)$_2$ 0.05 mmol, Xantphos 0.1 mmol, Cs$_2$CO$_3$ 1 mmol, PhH 0.5 M, 34 W blue LED, rt, 12 h. [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 an additional 6 h. [c]Yield for a 1 mmol scale reaction. [d]**1** (0.25 mmol) and **2** (0.5 mmol) were used.
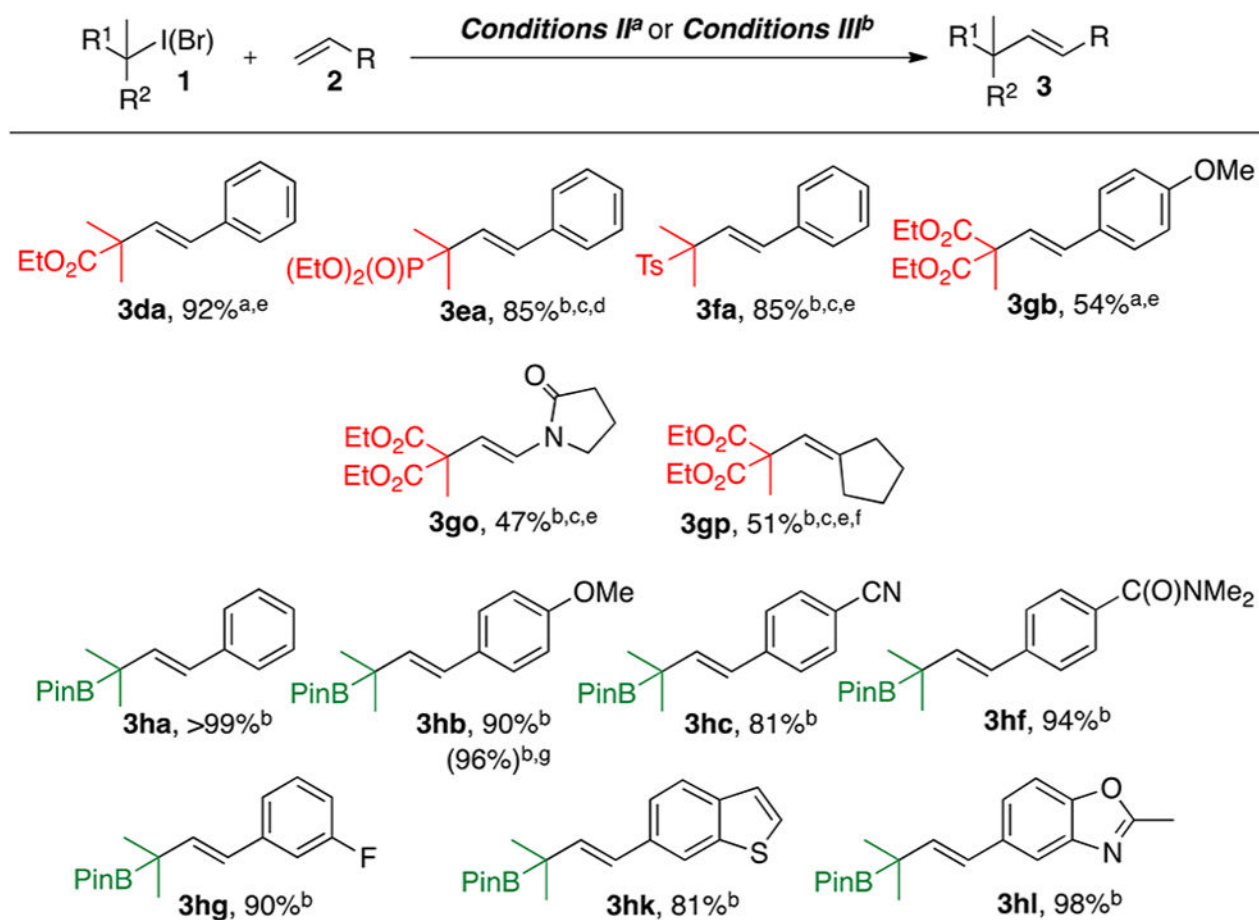
**Scheme 3. Scope of Activated Tertiary Alkyl Halides[a,b]**
[a]Conditions II: 1 (0.25 mmol), 2 (5 mmol), Pd(OAc)$_2$ (0.025 mmol), Xantphos (0.05 mmol), Cs$_2$CO$_3$ (0.5 mmol), PhH (0.5 mL), rt, 12 h. [b]Conditions III: 1a (0.375 mmol), 2 (0.25 mmol), Xantphos Pd G3 (0.025 mmol), iPr$_2$NEt (0.5 mmol), PhH (0.5 mL), 40 °C, 12 h. [c]1 (0.25 mmol) and **2** (0.5 mmol) were used. [d]5 mol % of Xantphos Pd G3 was used. [e]Alkyl bromide was used. [f]Reaction required 45 °C and 24 h for completion. [g]Yield for a 1 mmol scale reaction.
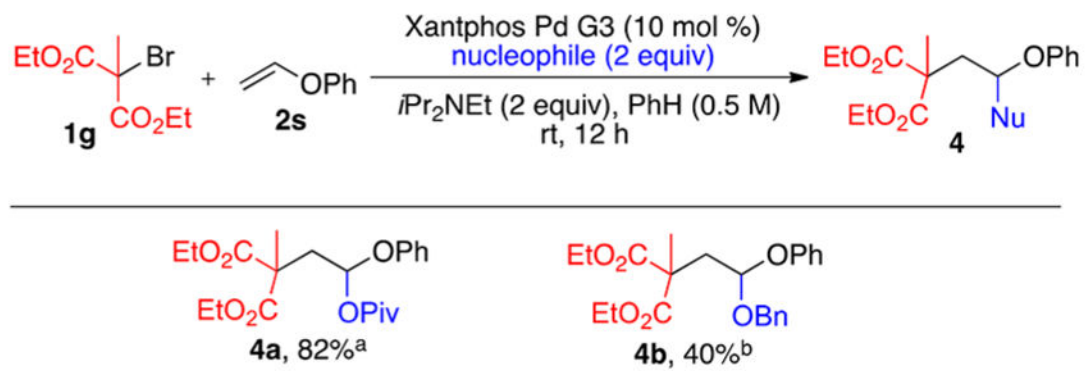
Scheme 4.
Carboxyloxy- and Alkoxyalkylation of Aryl Vinyl Ether
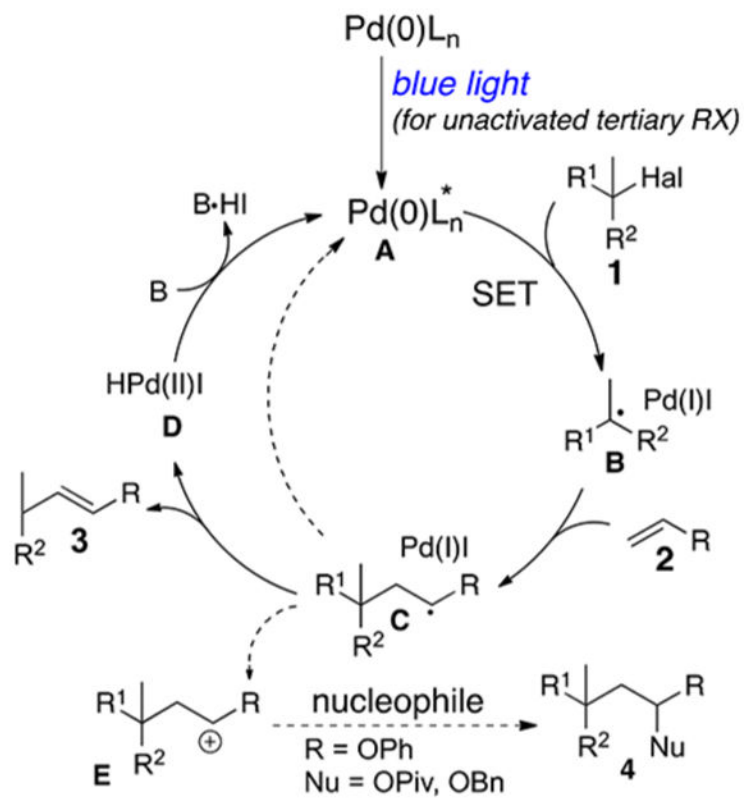
Scheme 5.
Proposed Reaction Mechanism

Table 1

Optimization[a]

no	1	cat.	ligand	base	deviation from standard conditions	Yield of 3a[b] (%)
1	1a	Pd(PPh₃)₄	-	Cs₂CO₃	toluene, 50 °C	dec.
2	1a	Pd(dppf)Cl₂	-	Cy₂NMe	PhCF₃, 110 °C	dec.
3	**1a**	**Pd(OAc)₂**	**Xantphos**	**Cs₂CO₃**	-	**87**
4	1a	Pd(PPh₃)₄	-	Cs₂CO₃	THF	14
5	1a	Pd(OAc)₂	DPEPhos	Cs₂CO₃	-	7
6	1a	Pd(OAc)₂	t-Bu-Xantphos	Cs₂CO₃	-	0
7	1a	Pd(OAc)₂	L	Cs₂CO₃	-	7
8	1a	Pd(OAc)₂	Xantphos	Cs₂CO₃	no light, 40 °C	traces
9	1a	-	Xantphos	Cs₂CO₃	-	0
10	1d	Pd(dppf)Cl₂	-	Cy₂NMe	PhCF₃, 110 °C	dec.
11	1d	Pd(OAc)₂	Xantphos	Cs₂CO₃	-	67
12	**1d**	**Pd(OAc)₂**	**Xantphos**	**Cs₂CO₃**	**no light, rt**	**88**
13	1h	Pd(dppf)Cl₂	-	Cy₂NMe	PhCF₃, 110 °C	dec.
14	1h	Pd(OAc)₂	Xantphos	Cs₂CO₃	-	30
15	1h	Xantphos Pd G3	-	iPr₂NEt	-	86
16	**1h**	**Xantphos Pd G3**	-	**iPr₂NEt**	**no light, 40 °C**	**96**

^{b}GC–MS yield.