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Irradiation-Induced Heck Reaction of Unactivated Alkyl Halides at Room Temperature

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Supporting Information Placeholder

ABSTRACT: The palladium-catalyzed Mizoroki–Heck reaction is arguably one of the most significant carbon–carbon bond-construction reactions to be discovered in the last 50 years, with a tremendous number of applications in the production of chemicals. This Nobel-Prize-winning transformation has yet to overcome the obstacle of its general application in a range of alkyl electrophiles, especially tertiary alkyl halides that possess eliminable β-hydrogen atoms. Whereas most palladium-catalyzed cross-coupling reactions utilize the ground-state reactivity of palladium complexes under thermal conditions and generally apply a single ligand system, we report that the palladium-catalyzed Heck reaction proceeds smoothly at room temperature with a variety of tertiary, secondary, and primary alkyl bromides upon irradiation with blue light-emitting diodes in the presence of a dual phosphine ligand system. We rationalize that this unprecedented transformation is achieved by utilizing the photoexcited-state reactivity of the palladium complex to enhance oxidative addition and suppress undesired β-hydride elimination.

1.INTRODUCTION

Palladium-catalyzed cross-couplings constitute a fundamental carbon–carbon bond-formation methodology in modern organic synthesis.[1] These reactions have proven to be highly efficient for the coupling of unsaturated carbon electrophiles and nucleophiles to meet the requirements of various synthetic tasks.[2] Although palladium-catalyzed cross-coupling reactions are highly advanced, work has mainly focused on the development and application of the ground-state reactivity of palladium species through the Pd(0)-Pd(II) catalytic cycle.[3] While these reactions are highly efficient for coupling C(sp^2)-hybridized carbon electrophiles, couplings with a C(sp^3)-hybridized electrophile[4] are less efficient because of the inherent instability of alkyl palladium species,[5] interference of β-hydride (β-H) elimination,[6] and difficulties associated with the oxidative addition of the alkyl electrophile (Fig. 1a).[7] Elegant contributions have been presented that use alkyl electrophiles as amenable substrates in various palladium-catalyzed cross-couplings by suppressing undesired β-H elimination through the application of new ligand designs,[8] or through the use of first-row-transition metals, such as nickel, which is less likely to induce β-H elimination.[9] Although being developed for years, Heck reactions on an sp^3-hybridized C-X center remains challenging because, unlike other cross-coupling reactions, β-H elimination is required as an elementary step in the Heck reaction.[10] Thus, simply suppressing β-H elimination in alkyl Heck reaction by ligand design is less feasible. Pd-catalyzed Heck reactions have been established by using unactivated primary and second alkyl halides by Fu,[11] Alexanian,[12] and Zhou;[13] however, the scope remains limited. No precedent has been achieved for tertiary alkyl halides possessing eliminable β-H. This lack of progress stems from the difficulty in reconciling suppression of β-H elimination after oxidative addition of alkyl halides, while necessarily utilizing β-H

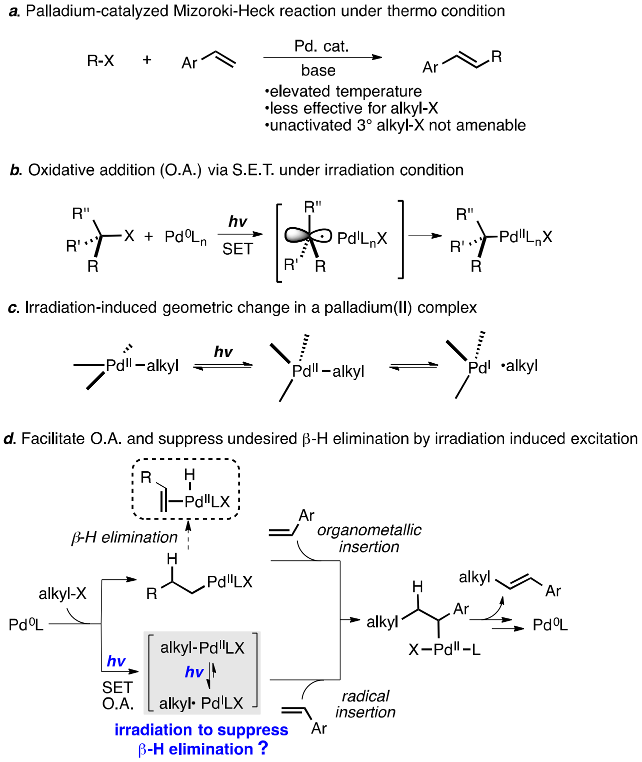


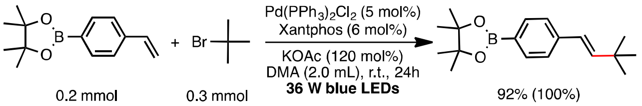
Figure 1. Problems facing the palladium-catalyzed Heck reaction under thermal conditions and a hypothetical solution. a, The Heck reaction developed under thermal conditions was found to be less effective for coupling alkyl electrophiles possessing eliminable β-hydrogen, especially for tertiary alkyl electrophiles. b, Irradiation facilitated oxidative addition of alkyl electrophiles with a Pd(0) complex through single-electron transfer (SET). c, Geometric change of a Pd(II) complex reported under irradiation with destabilization to induce radical reactivity. d, Possible solution that could enable efficient Heck reaction using alkyl electrophiles by merging radical and organometallic reactivity of palladium species under irradiation excited conditions

elimination as a productive step to deliver the desired olefin product. We envisioned that photoirradiation of a Pd(0) complex mayfacilitate a single-electron-transfer process to activate alkyl halides (Fig. 1b). The use of irradiation with a xenon lamp to facilitate radical-type oxidative addition has been reported by Ryu et al.[14] In addition, Pd(II) complexes can undergo geometric exchange from square planar to tetrahedron under irradiation.[15] This geometric change is caused by the formation of an excited-state Pd(II) complex involving outer orbitals that possess higher energy and may induce radical reactivity of the alkyl-Pd(II) species (Fig. 1c).[16] This photoexcitation effect may suppress undesired β-H elimination by preventing bonding of the alkyl radical to palladium, especially for tertiary alkyl radicals with large steric bulkiness. Thus, the following steps will proceed through a radical insertion process, in contrast to a pure organometallic insertion pathway, to generate an insertion product, which then undergoes β-H elimination (Fig. 1d). With this hypothesis in mind, we tested palladium-catalyzed Heck reactions of unactivated alkyl halides under various irradiation conditions. Herein, we reveal that, by using blue light-emitting diodes (LEDs) irradiation[17] and applying a dual phosphine ligand system, palladium-catalyzed Heck reactions of unactivated tertiary, secondary, and primary alkyl bromides with styrene-type substrates proceeds efficiently at room temperature. The discovery solves the long-standing problem of using unactivated tertiary alkyl halides in palladium-catalyzed Heck reactions, and makes it feasible to construct a quaternary carbon center connected to a double bond, which is easily functionalized for complex molecule synthesis. Although palladium catalysis has been studied for decades, most of the contributions have been restricted to the framework of ground-state reactivity. This discovery reveals that screening of irradiation sources (such as LEDs) as a parameter in palladium catalysis enables access to excited-state reactivity,[18] offers new opportunities to discover novel reactions, and can help solve challenging problems that remain in traditional ground-state palladium-catalyzed cross-coupling reactions.

2.RESULT AND DISCUSSION

The optimized reaction conditions used to cross-couple 4,4,5,5-tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane with *tert*-butyl bromide are shown in Table 1. *tert*-Butyl bromide is one of the most challenging substrates for transition-metal-catalyzed cross-couplings because it contains an abundance of hydrogen atoms that can easily undergo β-elimination and because its high steric bulk hinders oxidative addition reactions. Nevertheless, this substrate has recently been applied in nickel-catalyzed Kumada couplings[19] and Suzuki couplings,[20] wherein β-H elimination was suppressed because of the intrinsically lower electronegativity of the Ni(II) compared with that of the Pd(II).[9] The use of *tert*-butyl bromide as a coupling partner in palladium-catalyzed Heck coupling is unprecedented. The optimized reaction shows that a simple catalytic system composed of commercially available $Pd(PPh_3)_2Cl_2$ (5 mol%), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 6 mol%), and a mild inorganic base (potassium acetate), under irradiation with blue LEDs at room temperature enables efficient Heck coupling regio- and stereoselectively. Under the optimized conditions, we did not detect any product of Suzuki coupling or oxidative Heck reaction of aryl boronate.[21] The reaction conditions resemble those of widely applied Pd-catalyzed Heck reactions with the only difference being irradiation with blue LEDs.

Table 1. Irradiation-induced Palladium-catalyzed Mizoroki–Heck Reaction Using *tert*-Butyl Bromide orthogonal with Suzuki–Miyaura coupling and studies on reaction parameters[a]

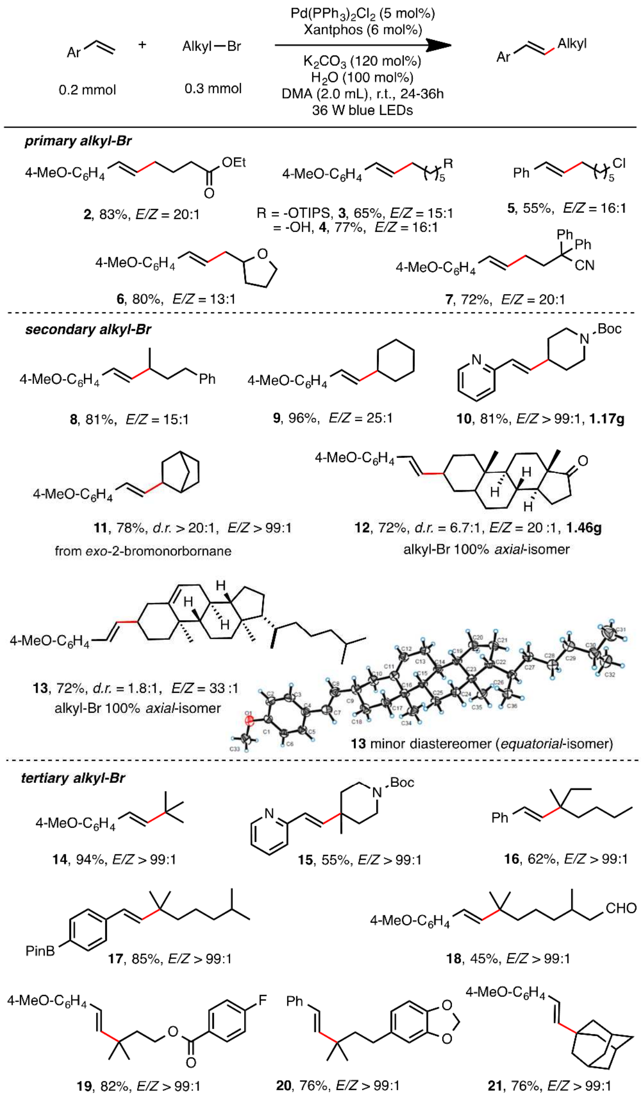


entry	variation from standard conditions	yield [%] (conversion [%])
1	$Pd(PPh_3)_4$ instead of $Pd(PPh_3)_2Cl_2$	82% (92%)
2	$Pd_2(dba)_3$ instead of $Pd(PPh_3)_2Cl_2$	0% (<5%)
3	$PdCl_2$ instead of $Pd(PPh_3)_2Cl_2$	0% (<5%)
4	$Pd(OAc)_2$ instead of $Pd(PPh_3)_2Cl_2$	0% (<5%)
5	$Pd(dppf)Cl_2$ instead of $Pd(PPh_3)_2Cl_2$	0% (<5%)
6	$PdCl_2/PCy_3$ (1:2) instead of $Pd(PPh_3)_2Cl_2$	38% (55%)
7	$PdCl_2/P(2\text{-furanyl})_3$ (1:2) instead of $Pd(PPh_3)_2Cl_2$	0% (<5%)
8	without Xantphos	0% (<5%)
9	CyXantphos instead of Xantphos	9% (15%)
10	NiXantphos instead of Xantphos	81% (90%)
11	dppp instead of Xantphos	<5% (<10%)
12	BINAP instead of Xantphos	<5% (<10%)
13	dtbpy instead of Xantphos	38% (56%)
14	reaction carried at 100 °C without irradiation	0% (<5%)
15	without irradiation	0% (<5%)
16	36 W green LEDs instead of blue LEDs	19% (25%)
17	36 W white LEDs instead of blue LEDs	21% (30%)
18	36 W purple LEDs instead of blue LEDs	82% (87%)
19	15 W UV (254 nm) instead of blue LEDs	0% (85%)
20	under air	0% (<5%)
21	using *tert*-butyl iodide	26%
22	using *tert*-butyl chloride	0%

a. Yields and conversions determined by GC analysis using an internal standard. dba = ((*1E*,*4E*)-1,5-diphenylpenta-1,4-dien-3-one), dppf = (1,1-bis(diphenyphosphino)ferrocene), Xantphos = (9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene), CyXantphos = ((9,9-dimethyl-9H-xanthene-4,5-diyl)bis(dicyclohexylphosphine)), NiXantphos = (4,6-bis(diphenylphosphino)phenoxazine), dppp = (1,3-bis(diphenylphosphino)propane), BINAP = (2,2-bis(diphenylphosphino)-1,1-binaphthyl), dtbpy = (4,4-di- tert-butyl-2,2-bipyridine).

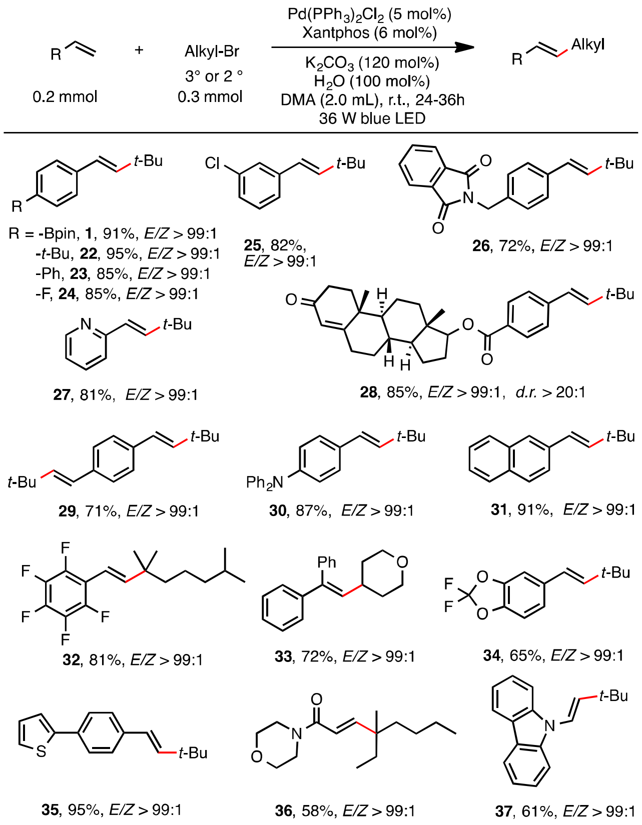
Studies of the reaction parameters revealed that the alkyl Heck reaction under irradiation conditions has distinct controlling factors compared with the reaction conducted under thermal conditions. The outcome of the reaction is highly dependent on the palladium source, with only $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$ being effective. Other palladium sources such as $Pd_2(dba)_3$, $PdCl_2$, $Pd(OAc)_2$, and $Pd(dppf)Cl_2$ were entirely ineffective (entry 2–5). It was soon realized that the PPh_3 and Xantphos both play an essential role in this reaction. The use of PCy_3 significantly reduced the yield of the desired product and no reaction occurred when tri(2-furanyl) phosphine, with an adjacent coordinating oxygen, was used (entries 6 and 7). From these results we can conclude that the monodentate phosphine ligand is not just a sacrificial reagent to reduce Pd(II) because the use of PCy_3, which has a higher reducing ability, gave poor performance. Testing triphenylphosphine in combination with other bidentate phosphine ligands revealed that the structure of the bidentate ligand also significantly affects the efficiency of the reaction. The reaction did not proceed at all in the absence of Xantphos (entry 8). Only bisphosphine ligands with a conjugated backbone similar to that of Xantphos were effective (entries 9–13). Although the reasons for the observed ligand dependence are not clear at present, we speculate that the conjugated backbone of the bisphosphine ligand influences the degree of photoexcitation and thus the reactivity on the palladium center. The essential role of irradiation was established in further control experiments (entries 14 and 15) in which the same reaction system did not deliver any detectable product under thermal conditions at 100 °C. One intriguing aspect of this reaction is that the blue LEDs used had a wavelength of only around 460 nm. We wondered whether the energy of the light source would significantly affect the outcome of the reaction and therefore applied other light sources with different irradiation wavelength. The use of 36 W green LEDs (wavelength 520–525 nm) of lower excitation energy instead of blue LEDs resulted in a clear drop in yield (entry 16). Purple LEDs (wavelength 395–405 nm), with higher irradiation energy, were also effective (entry 18), but the use of high-energy ultraviolet (UV) light (254 nm) converted the styrene into other byproducts (e.g., oligomerization or polymerization) without giving the desired product. White LEDs were much less effective (entry 17). The reaction stopped completely when it was exposed to ambient air (entry 20). Testing a range of alkyl electrophiles showed that alkyl iodide was less effective because of the occurrence of side reactions, and alkyl chloride was not activated (entries 21 and 22). We also tested several photoredox catalysts,[22] for this reaction instead of the palladium/phosphine system. Under these conditions, none of the desired product was detected, which shows that a catalytic cycle of single-electron redox is less feasible (see Supporting Information, S-12, for detailed parameter studies). Using K_2CO_3 as base with one equivalent amount of water showed comparable efficiency with KOAc. The additional one equivalent amount of water in amide solvent is supposed to facilitate reduction of Pd(II) precatalyst to Pd(0) (see Supporting Information for detailed optimization of bases).

Table 2. Reaction Scope with Respect to Alkyl Bromide[a]



a. Yields of isolated products. Ratio of stereoisomers was determined by ^{1}H-NMR analysis. The reactions were conducted in front of a cooling fan in a room of constant temperature (T = 30 ± 2 ° C).

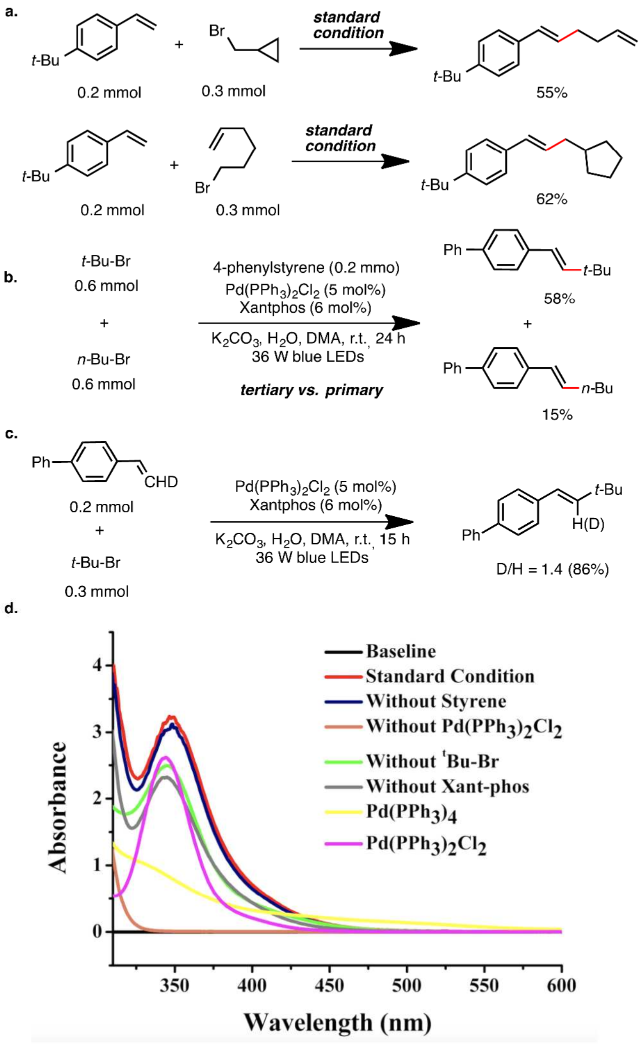
Table 3. Reaction Scope with Respect to Alkenes[a]



a. Yields of isolated products. Ratio of stereoisomers was determined by ^{1}H-NMR analysis. The reactions were conducted in front of a cooling fan in a room of constant temperature (T = 30 ± 2 ° C).

Subsequent studies revealed that the scope of the reaction with respect to the alkyl bromide is very broad (Table 2). Besides unprecedented coupling partners of tertiary alkyl bromides, primary and secondary alkyl bromides were also amenable to the reaction at room temperature. Alkyl bromides derived from complex nature products are suitable substrates under mild reaction conditions, as demonstrated by the use of epiandrosterone (**12**), cholesterol (**13**), and testosterone (**28**). It is notable that although the stereoisomerically pure axial alkyl bromide was used (compounds **12** and **13**), the reaction delivered a diastereomeric mixture of olefination at both axial and equatorial positions on the cyclohexyl ring, which suggests that the alkyl radical is formed. For cholesterol substrate **13**, the minor diastereoisomer was isolated and crystallized to obtain a single crystal. X-ray diffraction analysis (CCDC-1560078) unambiguously confirmed its stereostructure. The mild reaction conditions enabled a broad range of functional groups to be tolerated, including ester (**1**, **19**), silyl ether (**3**), alcohol (**4**), alkyl chloride (**5**), ether (**6**), cyano (**7**), amide (**10**), ketone (**12**), boronate (**17**), aldehyde (**18**), and acetal (**20**) groups. All reactions delivered the products with excellent *E*-stereoselectivity, as commonly observed for palladium-catalyzed aryl Heck reactions under thermal conditions. In previous reports by Alexanian[12] and Zhou[13] of palladium-catalyzed intermolecular Heck reactions under thermal conditions, only primary and secondary alkyl halides could be applied, and the reactions delivered the olefin product as a mixture of *Z/E* isomers. The stereoselectivity of this reaction using tertiary alkyl bromide is remarkable because only the *E*-isomer was observed in all cases. Although it is not yet clear whether this stereoselectivity is related to the irradiation, it is reasonable to expect that the very mild reaction conditions may contribute to the high stereoselectivity in the β-H elimination step to deliver the thermodynamically favored stereoisomer. The reaction can be performed on a gram scale, as demonstrated for compounds **10** and **12** (Table 2). Notably, the pyridine group in **10** was tolerated under the reaction conditions, which suggests that the formation of a carbonium ion is unlikely in this reaction (Table 2). The basic nitrogen atom would be expected to react with a carbonium ion to disturb the desired reaction.

Scheme 1. Mechanistic studies



a, Radical clock experiments revealed the radical properties of the alkyl-metal species. b, Kinetic experiments between tertiary and primary alkyl bromides. c, An intramolecular kinetic isotope experiment. d, UV/Vis absorption spectrum of the reaction mixture, Pd(II), and Pd(0) phosphine complexes. Standard conditions: $Pd(PPh_3)_2Cl_2$ (1.0 equiv.), Xantphos (1.0 equiv.), t-BuBr (1.0 equiv.), and styrene (1.0 equiv.) in DMA after 2 h under argon atmosphere at room temperature.

The scope of the reaction with respect to styrene-coupling partner is summarized in Table 3. Both electron-deficient styrene (**1**, **24**, **27**, **32**) and electron-rich styrene (**22**, **30**) derivatives are amenable substrates. Notably, 2-vinylpyridine also reacted with *tert*-butyl bromide efficiently (**27**). Pentafluorostyrene also reacted as an amenable substrate (**32**). The good reactivity of these electron-deficient substrates suggests that a mechanism that proceeds through generation of a benzylic carbenium ion followed byproton elimination is not likely, and supports a β-H elimination pathway. 4-Diphenylaminostyrene (**30**) and 1,1-diphenylethene (**33**), which are often used as radical scavengers in free-radical processes, also reacted well. The alkyl radical may thus only exist as a palladium-intercepted radical, and not as a free alkyl radical. Styrene substrates, acrylamide substrate (**36**), and 9-vinyl-9*H*-carbazole (**37**) also reacted with tertiary alkyl bromide to deliver the desired products in moderate yields. For reasons that are not yet clear, the reaction was not effective with acrylate esters. We also substantially tested other alkene substrates, such as α-aliphatic alkene, internal alkene, and 1,3-diene. However, these alkene substrates gave either very low yield (<10%) or were unreactive under the optimized reaction condition.

As noted in our working hypothesis, the reaction may proceed through a single-electron-transfer oxidative addition to generate a palladium-intercepted alkyl radical under irradiation, and the irradiation may excite the palladium complex to prevent recombination of the alkyl radical to form a Pd(II)-alkyl complex that undergoes β-H elimination.[23] We conducted radical clock experiments,[24] which are often used to probe the radical reactivity of metal alkyl species (Scheme. 1a). The results showed that radical rearranged products were formed exclusively and confirmed that the oxidative addition under irradiation forms an alkyl palladium species with distinct radical properties. In addition, competition experiments between primary and tertiary alkyl bromide examining the kinetics of oxidative addition were conducted (Scheme. 1b). The results clearly demonstrated that oxidative addition of alkyl halides to deliver the thermodynamically more stable alkyl radical proceeds faster. The results of the competition experiment also supports the conclusion that oxidative addition under blue LEDs irradiation proceeds through a single-electron-transfer mechanism to cleave the C–Br bond. Previous studies have shown that for S_N2-type oxidative addition of alkyl bromide to a phosphine-ligated Pd(0) complex,[25] the rate of secondary alkyl oxidative addition is much slower than for a primary alkyl bromide, and the oxidative addition does not proceed with tertiary alkyl halides because of steric hindrance.[26] We also conducted intramolecular kinetic isotope effect (KIE) experiments using β-D-styrene as substrate (Scheme. 1c). The small observed KIE (1.4) suggests that a mass-transfer process to form the benzylic brominated product followed by E2 elimination to deliver the alkene product is unlikely because this would be expected to result in a large KIE.[27] Furthermore, the introduction of benzyl bromide poisons the reaction system. The addition of 50 mol% (1-bromoethyl) benzene stopped the desired reaction completely. Combined with the observed insensitivity of the reaction towards the electronic nature of the styrene, these results support the conclusion that a β-H elimination mechanism delivers the product instead of an ionic or mass-transfer mechanism. To gain information on the valance state of the palladium species in this catalytic system, X-ray photoelectron spectroscopy (XPS) measurements (Figure S1) were also conducted. XPS measurements of the reaction mixture revealed three peaks corresponding to Pd(II), Pd(I), and Pd(0), suggesting the reaction proceeds through a Pd(0)-Pd(I)-Pd(II) mechanism. Given that the reaction proceeds through Pd(I), which is prone to dimerize in the presence of a bisphosphine ligand,[28] the beneficial effect of the monophosphine ligand may originate in its coordination to Pd(I), thereby preventing the formation of the dimer complex with consequent disruption of the catalytic cycle. Furthermore, we cannot rule out the possibility that the PPh_3 contributes to facilitate oxidative addition and to suppress β-H elimination through its labile coordination with the palladium intermediate. Beside the dual phosphine ligand system, the essential irradiation effect that is sensitive to the energy of incident light was also very intriguing. The reaction entirely stopped after the irradiation source was removed. We can exclude the possibility that irradiation just initiates a radical chain process. UV/Vis measurements were conducted with a mixture of stoichiometric amounts of palladium salts and ligands (Scheme. 1d). It was observed that the reaction mixture exhibits a clear absorption peak centered at 350 nm with absorption onset that overlaps with the blue LEDs wavelength (460 nm). This absorption onset explains the best performance of the blue LEDs among other irradiation sources. Removing styrene from the reaction mixture did not change the absorption wavelength or intensity, whereas removing *tert*-butyl bromide and removing Xantphos caused a reduction in the absorption intensity and a hypsochromic shift of about 5 nm. An important observation is that when $Pd(PPh_3)_2Cl_2$ was removed from the reaction mixture, the absorption peak at around 350 nm disappeared, revealing that the absorption peak of $\lambda_{max\,=}$ 350 nm with an onset around 460 nm originates from the palladium intermediate form in the reaction mixture. To verify this conclusion, we also measured the absorption spectrum of $Pd(PPh_3)_2Cl_2$ and an absorption peak around 350 nm was observed. The measurement of UV/Vis absorption of $Pd(PPh_3)_4$ gives a broadened absorption band extending from the visible region to the UV region, revealing that irradiation by blue LEDs can also excite the Pd(0) phosphine complex, which may facilitate single-electron oxidative addition. Irradiation with suitable wavelengths is crucial for the reaction as demonstrated in optimization studies because low-energy irradiation (such as green LEDs) does not excite the palladium complex, and higher energy irradiation (in the UV region) may cause decomposition of the intermediate and destroy the desired reaction process. We may conceive that an irradiation wavelength between that of purple and blue light may offer the best efficiency for this reaction, although this is currently limited by the irradiation sources available. Based on the absorption spectrum, these studies suggest that irradiation at different wavelengths should be considered as a parameter when optimizing palladium-catalyzed reactions induced by irradiation.

3.CONCLUSION

Since the palladium-catalyzed Mizoroki–Heck reaction was discovered nearly half a century ago, tremendous efforts have been made to optimize the catalyst system as well as to expand the scope of the reaction. However, expanding the range of amenable substrates to encompass the full spectrum of alkyl halides, including tertiary alkyl halides with eliminable β-H hydrogen atoms, has not been achieved by utilizing the ground-state reactivity of palladium complexes. In this report, we revealed that, upon irradiation with a suitable source (blue LEDs), the palladium species in an excited state may exhibit a blend of both radical and organometallic reactivity, suppress undesired β-H elimination, and even achieve the unprecedented Heck reaction on an unactivated tertiary $C(sp^3)$-X center at room temperature. The use of a dual phosphine ligand system is also crucial for the success of this transformation. This discovery may further expand the scope of palladium-catalyzed cross-coupling methodologies to include the use of unactivated alkyl electrophiles and may inspire future studies on catalysis by palladium in its excited state[29] to discover its untapped reactivity.

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.

Experimental details and characterization data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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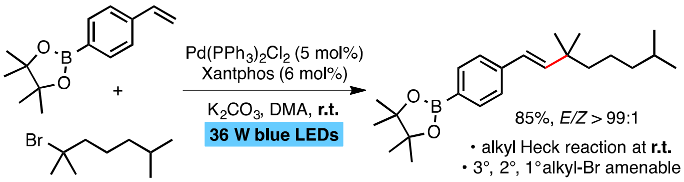
TOC


+
Br
Pd(PPh$_3$)$_2$Cl$_2$ (5 mol%)
Xantphos (6 mol%)
K$_2$CO$_3$, DMA, **r.t.**
36 W blue LEDs
O
B
O
85%, *E/Z* > 99:1
• alkyl Heck reaction at **r.t.**
• 3°, 2°, 1°alkyl-Br amenable