Z 2020/11/25 M1 Yumeng Liao

Three-Component, Interrupted Radical Heck/Allylic Substitution Cascade Involving Unactivated Alkyl Bromides

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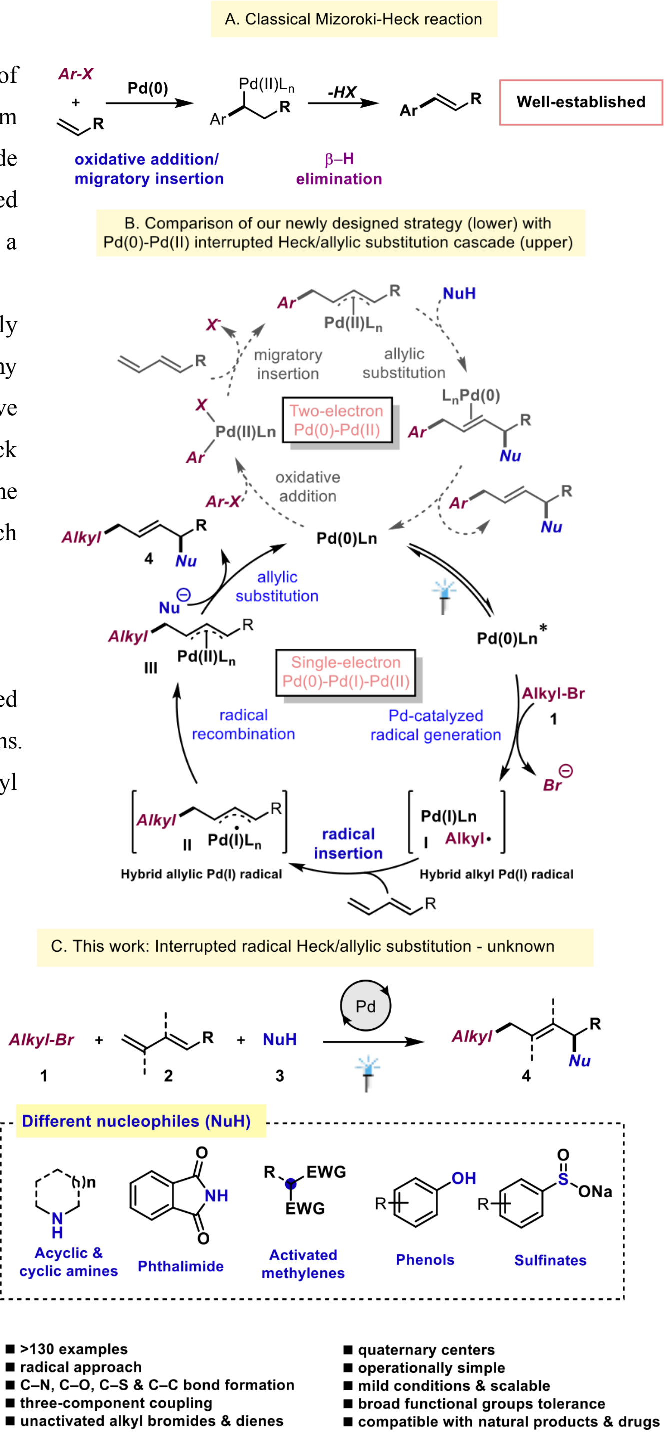
Introduction

A three-component Heck/allylic substitution coupling involving unactivated alkyl bromide has been reported as the first example. Such method allowed the construction of C_{sp3}–C_{sp3} and C–X (X = N, O, S) bonds with a broad scope (>130 examples) as well as excellent selectivity (>95:5 *E*/*Z*, >20:1 rr). Subsequent mechanistic studies indicated an unprecedented radical-promoted route in this reaction.

Previous Work

Mizoroki-Heck reaction plays an important role in the construction of carbon–carbon and carbon-heteroatom bonds. In the presence of palladium catalyst, substituted alkene was formed by the coupling between aryl halide (or triflate) and alkene (**Scheme 1A**). Meanwhile, palladium-catalyzed allylic substitution (e.g., the well-known Tsuji-Trost reaction) is also a frequently used method to achieve nucleophilic allylic functionalization.

Catalytic cascade reactions allow the single-step synthesis of structurally complex compounds from simply available precursors. Therefore, many groups have developed numerous examples of three-component arylative or vinylative allylic substitution of 1,3-dienes. Combination of the Heck reaction and allylic substitution becomes a unique strategy to achieve the difunctionalization of 1,3-dienes (**Scheme 1B, *up***). However, such cascades have been limited to activated aryl or vinyl electrophiles.



This Work

According to past reports, unactivated alkyl halides have been established well as widely used reagents in C–C bond forming cross-coupling reactions. Also, visible-light-driven Heck reactions which employed unactivated alkyl halides have also been achieved by several groups independently.

Inspired by those facts, the authors hypothesized a palladium-catalyzed reaction. Initially, light excitation formed Pd(0)* species. Then a Pd(I) radical intermediate **I** generated from alkyl bromides which could undergo radical addition into 1,3-dienes to form allylic Pd(I) intermediate **II**. After radical combination, formed Pd(II) intermediate **III** would be attacked by different nucleophiles to form the product **4** with regenerating the palladium(0) catalyst (**Scheme 1B, *below***).

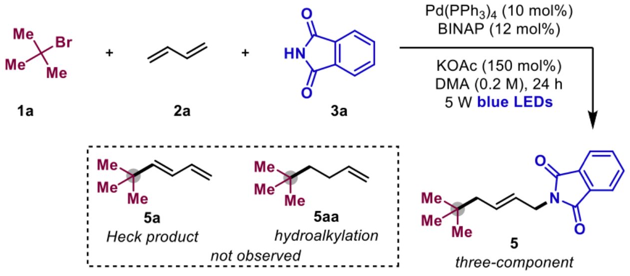
Herein, the authors developed a three-component Heck/allylic substitution cascade as the first example. Different nucleophiles including acyclic & cyclic amines, phtalimide, activated methylenes, phenols and sulfonates are applicable to this method to form C–N, C–C, C–O, and C–S bonds respectively with excellent yields and regio- & diastero- selectivities (**Scheme 1C**).

Optimization of Conditions (**Table 1**)

In the presence of Pd(PPh_3)$_4$, BINAP and KOAc, *t*-butyl bromide (**1a**), 1,3-butadiene (**2a**), and phthalimide (**3a**) were reacted for 24 h in DMA under irradiation with blue LEDs as the initial investigation. As a result:

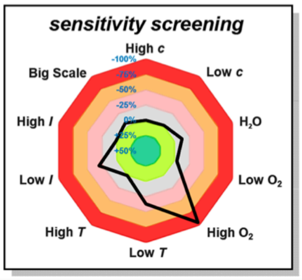
- BINAP is superior to DPEPhos and XantPhos as ligand.
- KOAc is the most suitable base rather than Na_2CO_3, $NaHCO_3$, and K_2HPO_4.
- Both base and ligand are essential to this reaction.
- A longer reaction time increased the yields.
- Less amount of catalyst/ligand slightly increased the yields.
- Palladium catalyst and blue LEDs are necessary for this reaction.
- High temperature under standard conditions decreased the yields.
- *Sensitivity screenings* were also conducted and shown that this reaction is highly sensitive to high O_2 concentration, low light intensity and low temperature.
- Delightfully, no Heck product or hydroalkylated product were detected.

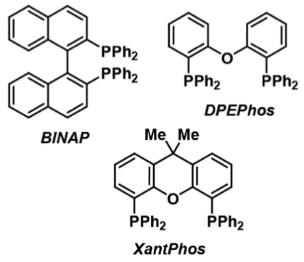
Table 1. Optimization of Three-Component Interrupted Radical Heck/Allylic Substitution Cascade[a]



entry	deviation from standard conditions	**5** (%)[b,c]
1	none	60
2	DPEPhos instead of BINAP	51
3	XantPhos instead of BINAP	17
4	Na_2CO_3, $NaHCO_3$, and K_2HPO_4 instead of KOAc	17 or 5 or 0
5	without BINAP	31
6	without BINAP and KOAc	0
7	48 h	91 (87)[d]
8	Pd(PPh_3)$_4$ (5 mol %)/BINAP (6 mol %), 48 h	73
9	without Pd(PPh_3)$_4$, 48 h	0
10	4-CzIPN (5 mol %) instead of Pd(PPh_3)$_4$, 48 h	0
11	without blue LEDs, 48 h	0
12	100 °C instead of blue LEDs, 48 h	<5

[a] **1a** (0.3 mmol), Pd(PPh_3)$_4$ (10 mol %), ligand (12 mol %), butadiene **2a** (0.3 mmol, 2 M in THF, 0.15 mL), DMA (0.85 mL), **3a** (0.2 mmol), base (0.3 mmol), RT, blue LEDs (5 W, 455 nm), 24 h, under argon. [b] Yield was determined by ^{1}H NMR spectroscopy analysis with 1,2-dibromoethane as internal standard. [c] >95:5 dr and >20:1 rr in all cases determined by ^{1}H NMR spectroscopy at the crude reaction mixture. [d] Isolated yields.


sensitivity screening



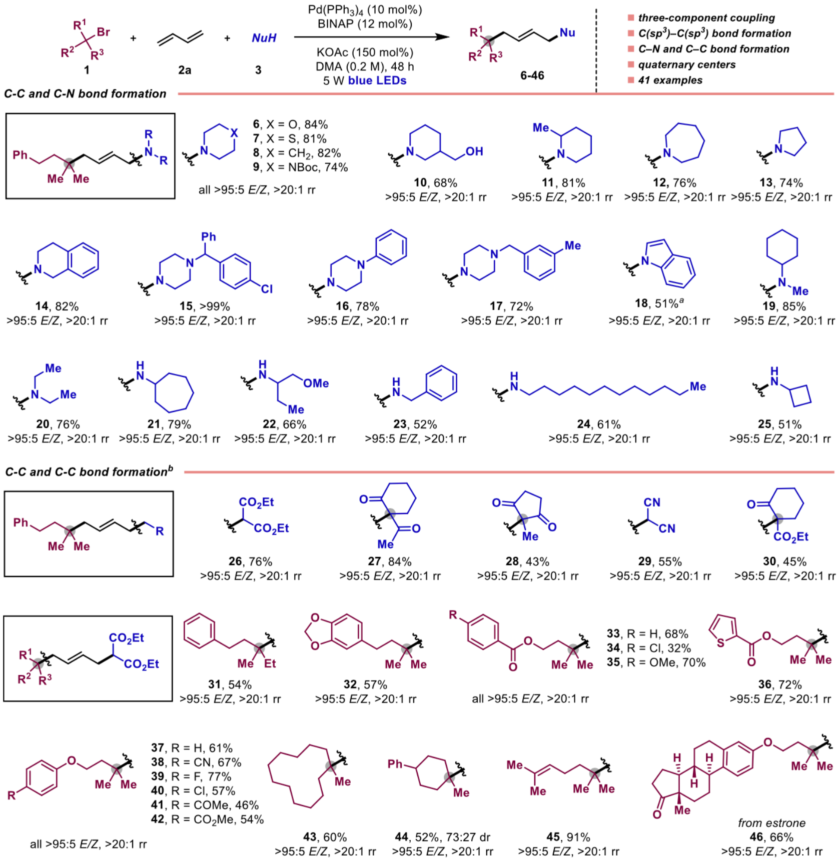
Substrate Scope with N- and C- Based Nucleophiles

a). C–C & C–N bond formation

- Various primary and secondary amines including their linear and cyclic heteroatomic derivatives were all tolerated with moderate to high yields and selectivity (**6-25**).

b). C–C & C–C bond formation

- Carbon-based nucleophiles could be employed in this reaction (**26-30**).
- When choosing diethyl malonate (**26**) as nucleophile, various linear and cyclic trialkyl bromides were investigated and all well-tolerated (**31-46**).



[a] NaOH (150 mol %) was used instead of KOAc. [b] **1** (0.2 mmol, 1.0 equiv), **3** (0.6 mmol, 3.0 equiv). [c] Reaction conditions: **1** (0.3 mmol), **3** (0.2 mmol), Pd(PPh_3)$_4$ (10 mol %), BINAP (12 mol %), butadiene **2a** (0.3 mmol, 2 M in THF, 0.15 mL), DMA (0.85 mL), KOAc (0.3 mmol), RT, blue LEDs (5 W, 455 nm), 48 h, under argon.

Substrate Scope with O- and S- Based Nucleophiles

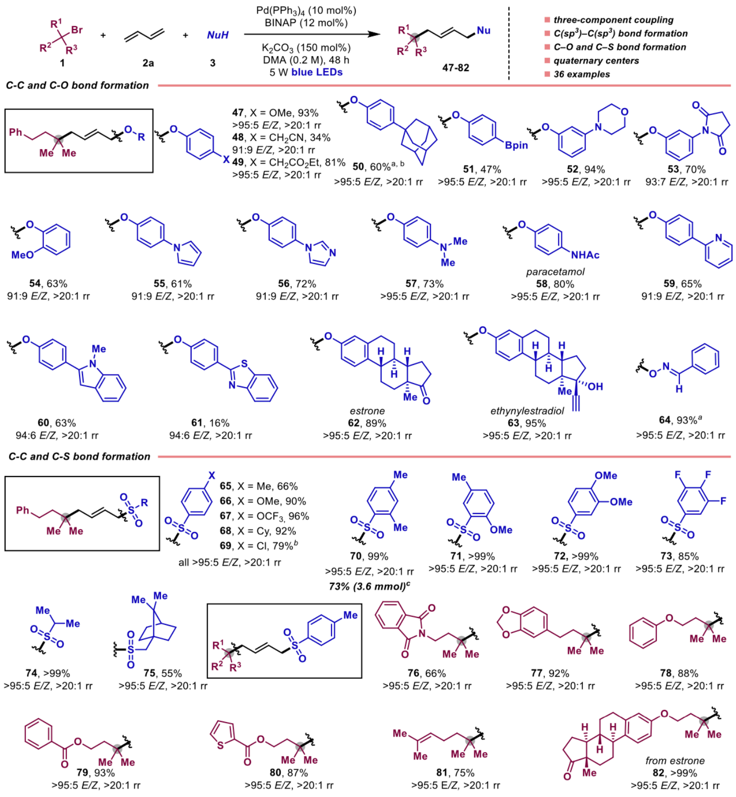
(*Variation from standard conditions*: **K_2CO_3** were used as base instead of **KOAc**)

c). C–C & C–O bond formation

- Hydroxy-containing nucleophiles with various substituents such as methoxy, nitrile and ester, as well as boron and nitrogen-containing heterocycle were all well-tolerated to give corresponding products (**47-62**). Moreover, natural products estrone and ethynylestradiol could be used (**62-63**). Oxime could also be employed (**64**).

d). C–C & C–S bond formation

- Sulfinates with different substituent all produced corresponding products with good yields (**65-75**).
- With using sulfinate nucleophile, various trialkyl bromides were also tolerated (**76-82**).



[a] $PhthCH_2CH_2(CH_3)_2Br$ was used. [b] Yield was determined by ^1H NMR spectroscopy analysis with 1,2-dibromoethane as the internal standard. [c] The conditions were modified as follows: **1b** (1.3 equiv), $Pd(PPh_3)_4$ (5 mol %), BINAP (6 mol %), 48 h. [d] Reaction conditions: **1** (0.3 mmol), **3** (0.2 mmol), $Pd(PPh_3)_4$ (10 mol %), BINAP (12 mol %), butadiene **2a** (0.3 mmol, 2 M in THF, 0.15 mL), DMA (0.85 mL), KOAc (0.3 mmol), RT, blue LEDs (5 W, 455 nm), 48 h, under argon.

Substrate Scope with Various Alkyl Bromides and 1,3-Dienes

e). Tertiary alkyl bromides as nucleophile

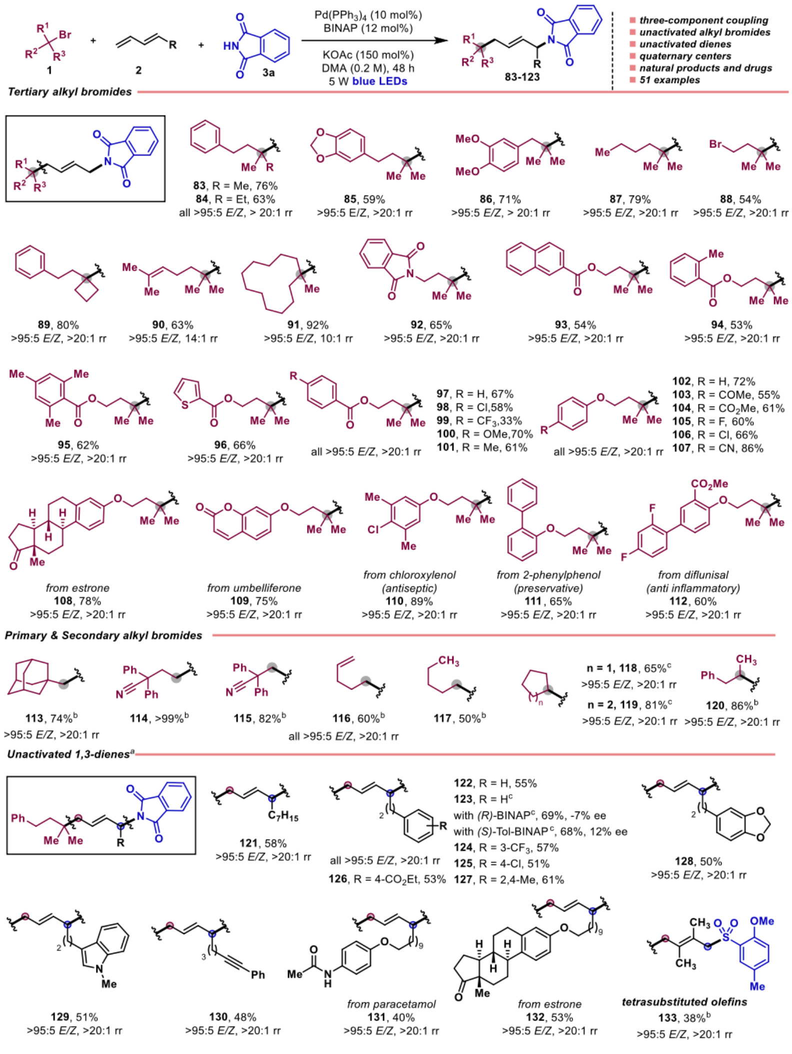
- With employing phthalimide (**3a**) as nucleophile, various unactivated trialkyl bromides even including some natural product derivatives were tolerated well (**83-112**).

f). Primary & Secondary alkyl bromides as nucleophile

- Primary (**113-117**) and secondary (**118-120**) alkyl bromides were all well-tolerated.

g). Unactivated 1,3-dienes as substitution scaffold

- Various substituted 1,3-dienes were tolerated with excellent regioselectivity (**121-132**).
- However, using enantiopure ligands gave minimal ee (**123**).
- By employing 2,3-disubstituted 1,3-diene has achieved the synthesis of tetrasubstituted olefin (**133**).

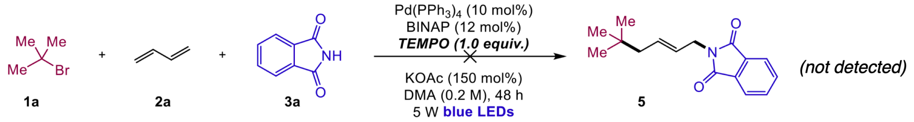


[a] The corresponding unactivated 1,3-diene **2** was used instead of **2a**. [b] Nucleophile **S3o** (1.0 equiv) was used, K_2CO_3 (1.5 equiv) as base. [c] Sodium 4-toluensulfinate (1.0 equiv) was used as nucleophile, K_2CO_3 (1.5 equiv) as base. [d] Reaction conditions: **1** (0.3 mmol), **3a** (0.2 mmol), $Pd(PPh_3)_4$ (10 mol %), BINAP (12 mol %), butadiene **2a** (0.3 mmol, 2 M in THF, 0.15 mL), DMA (0.85 mL), KOAc (0.3 mmol), RT, blue LEDs (5 W, 455 nm), 48 h, under argon.

Mechanistic Studies

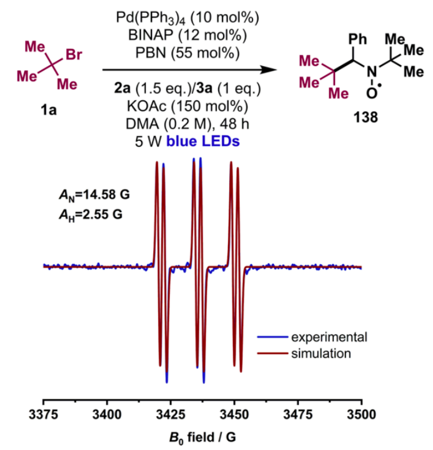
SI. TEMPO inhibition:

When reaction was performed in the presence of TEMPO, desired product **5** was not detected, indicating that this reaction may proceed via a radical route.



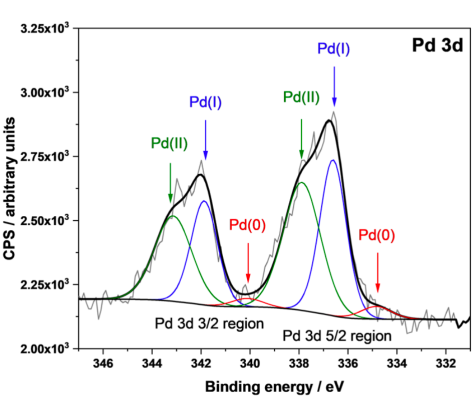
a. EPR experiment: By conducting EPR experiment, radical intermediate **138** was detected with the well-fitting EPR spectra between experimental and simulation which indicated the radical formation.

a. EPR experiment



b. XPS experiment: Through the X-ray photoelectron spectroscopy (XPS) measurement of reaction mixture, a Pd(II)-Pd(I)-Pd(0)-routing mechanism was indicated.

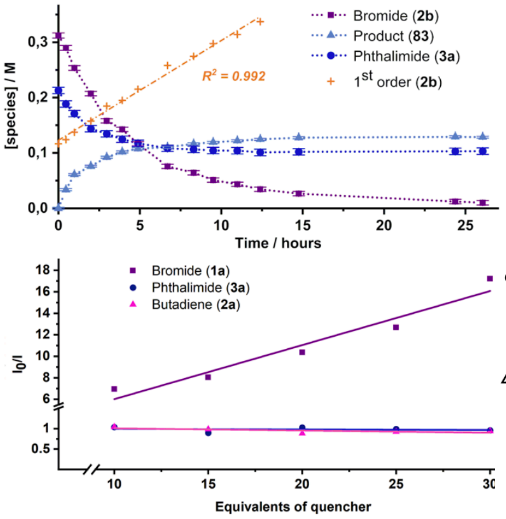
b. XPS experiment



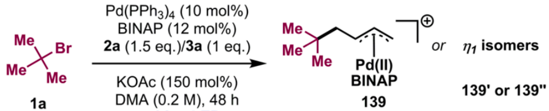
c. Kinetic profile / Stern-Volmer Analysis: Cleavage of **3a** follows the 1st order kinetics. However, which of **2b** has a faster rate than **3a**, shown that the nucleophilic attack may be the rate-determing step (***up***);

Stern-Volmer analysis shown that bromide **1a** was the only effective quencher to palladium species (***below***).

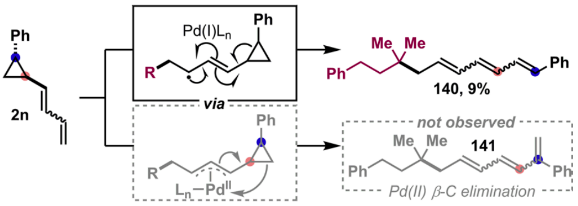
c. Kinetic profile and Stern-Volmer Analysis



d. ESI-MS analysis

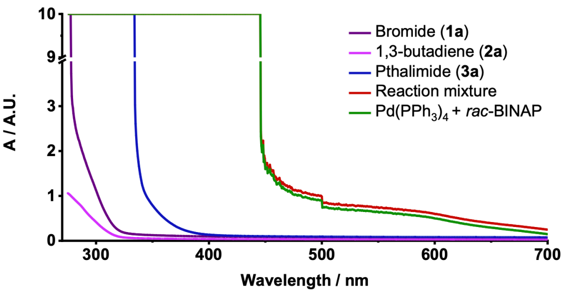


e. Radical probe experiment



d. ESI-MS: Allylpalladium complex **139** or **139'** or **139''** was detected by ESI-MS, indicated Pd(I) radical intermediate was trapped by 1,3-diene in this reaction.

e. Radical probe experiment: **140** Which generated via a radical addition to 1,3-diene, ring-opening of cyclopropane, ß-H elimination route was the only obtained product, which also indicated a radical addition of palladium species to 1,3-diene is happening.



SI. UV-vis absorption analysis: Palladium species shown the only absorption in the visible light reaction system (red/green curve).

Conclusion

A general and modular three-component radical Heck/allylic substitution cascade involving unactivated alkyl bromides has been developed for the first time. In this developed method, a wide substrate scope of nitrogen-, oxygen-, sulfur- and carbon-based nucleophiles, different substituted unactivated alkyl bromides and various 1,3-dienes which has demonstrated the excellent compatibility, and is expected to construct a diverse platform in synthetic chemistry and pharmaceutical chemistry.