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Aryl-to-alkyl radical relay Heck reaction of amides with vinyl arenes†

Yu-jia Du,‡ Xia-xin Sheng,‡ Jun-hua Li, Jia-ming Chen, Sen Yang* and Ming Chen *

A palladium-catalyzed aryl-to-alkyl radical relay Heck reaction of amides at α-C(sp^3)-H sites with vinyl arenes is described. This process displays a broad substrate scope with respect to both amide and alkene components and provides access to a diverse class of more complex molecules. The reaction is proposed to proceed *via* a hybrid palladium-radical mechanism. The core of the strategy is that the fast oxidative addition of aryl iodide and fast 1,5-HAT overcome the slow oxidative addition of alkyl halides, and the photoexcitation effect suppresses the undesired β-H elimination. It is anticipated that this approach would inspire the discovery of new palladium-catalyzed alkyl-Heck methods.

Introduction

The Nobel-Prize-winning Mizoroki–Heck reaction[1] is a fundamental synthetic transformation in chemical synthesis, enabling the direct cross coupling of aryl and vinyl halides (triflates or sulfonates) with simple alkenes.[2] The utility of the palladium-catalyzed Heck reaction with aryl/vinyl halide sites has been well demonstrated in synthesis.[2,3] However, the alkyl Heck reaction is less developed because of two main factors: the oxidative addition is slow with low-valent transition metals[4] and the resulting alkylmetal species can undergo premature β-hydride elimination which leads to side products[5] (Scheme 1A). To overcome these significant challenges, elegant contributions have been presented showing that β-hydride elimination can be suppressed through the use of first-row-transition metals, such as nickel, which is less likely to induce β-hydride elimination.[6] The application of new ligand designs[7] was also reported to be capable of constraining the β-hydride elimination. This, however, will lead to other adverse consequences as β-hydride elimination is eventually required as an elementary step in Heck reactions. To date, the Heck reaction of activated[8] and perfluorinated[9] alkyl halides has been established by Ni or Pd catalysis, and Pd-catalyzed Heck reactions of unactivated primary and secondary alkyl halides have been achieved by Fu,[10] Alexanian[11] and Zhou.[12] Recently, Gevorgyan[13] and Fu[14] separately developed a hybrid palladium radical species,[15] which has enabled a tertiary alkyl-Heck reaction to occur with high efficiency at room temperature.

Despite these developments, new strategies for alkyl-Heck reactions are still important. Inspired by Gevorgyan's seminal work on alkyl-to-alkyl radical relay Heck reactions using an easily installed/removed Si-based auxiliary through the selective I-atom/radical translocation pathway (Scheme 1B),[13b] we thus conceived the approach of merging a fast oxidative addition rate of aryl halides with a rapid 1,*n*-HAT (hydrogen atom transfer) to overcome the slow oxidative addition of alkyl halides.[16] Notably, the aryl-to-alkyl radical relay step was known in direct desaturation reactions, however, whether this step can happen in the presence of olefin is unpredictable, since the aryl Heck reaction is more favored. If feasible, the alkyl palladium species would be formed smoothly which subsequently underwent a photo-induced Heck reaction. The β-hydride elimination, on the other hand, can be suppressed by the photoexcitation effect (Scheme 1C).[14a] In 2022, our group developed a direct desaturation of amide by the cooperation of visible light and palladium catalysis (Scheme 1D).[16c] Herein, we disclose the first example of a palladium-catalyzed aryl-to-alkyl radical relay heck reaction of amide at α-C(sp^3)-H sites with vinyl arenes using aryl iodide as the alkyl-Heck coupling partner to construct α-alkenyl amides (Scheme 1E). To the best of our knowledge, alkyl-Heck reactions through such a process have not been realized, which became the motivation of this study. The success of this reaction faces several potential challenges, the first and greatest one is the premature Heck reaction on the aryl site (**S1**), which was well developed.[2,3] To compete with this, the 1,5-HAT rate has to be faster than the aryl-Heck reaction. Other possible pathways are the direct desaturation *via* β-hydride elimination[16c,17] (**S2**) and hydrodehalogenation (**S3**).

Results and discussion

To test this hypothesis, our investigation began by using *N*-(2-iodophenyl)-*N*-methylhexanamide **1a** and styrene as the

Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, School of Petrochemical Engineering, Changzhou University, 21 Gehu Road, Changzhou, 213164, China. E-mail: chenming0228@cczu.edu.cn

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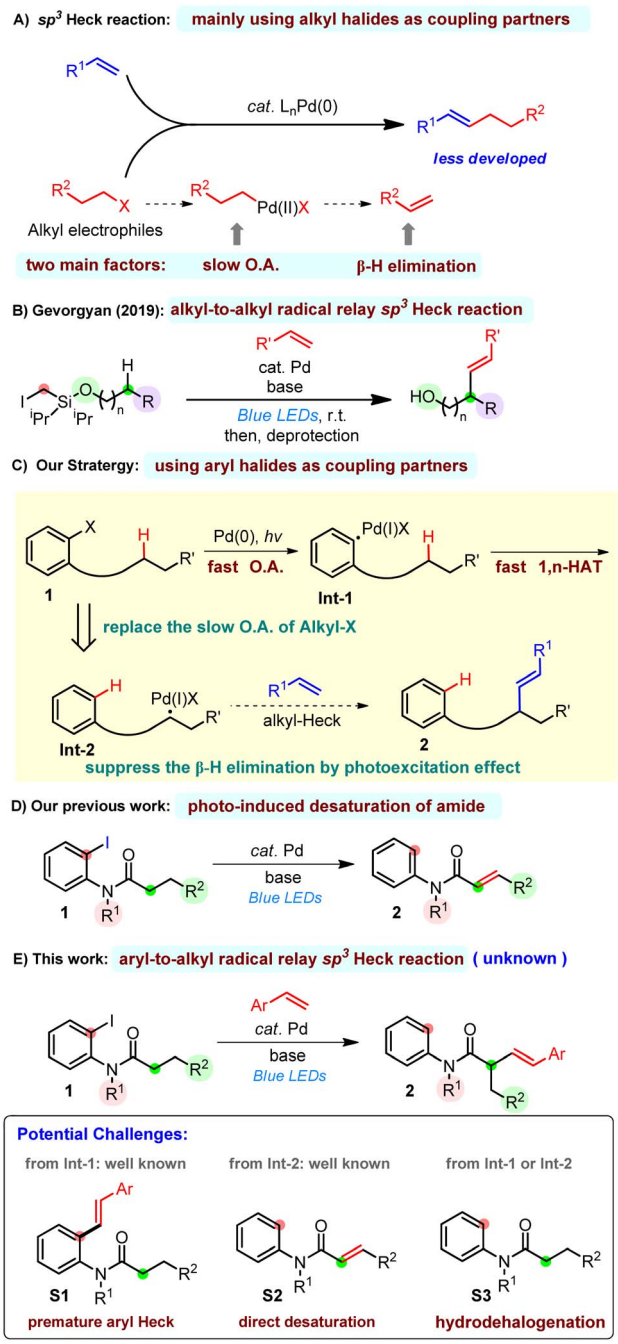
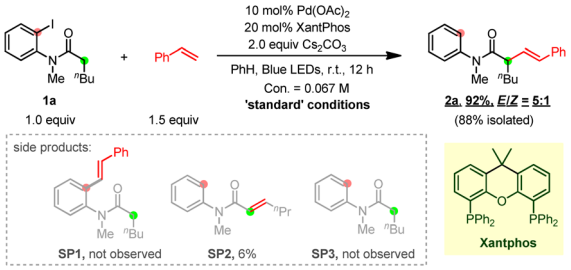
‡ These authors contributed equally to this work.

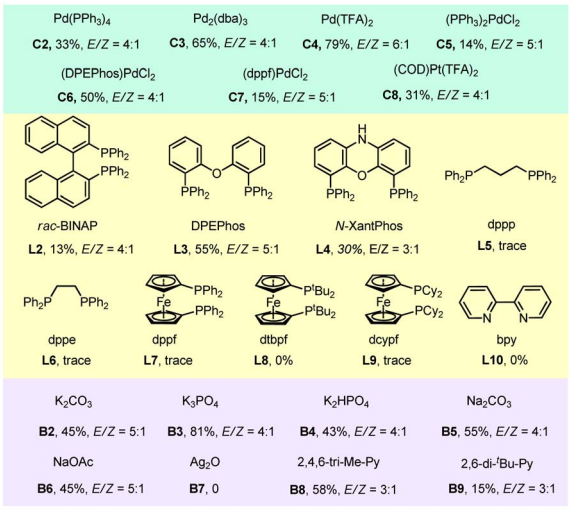


Scheme 1 Palladium-catalyzed alkyl-Heck reactions.

Table 1 Selected optimization studies[a,b]



Entry	Variation from 'standard' conditions	Yield [a](%) of **2a**
1	Without $Pd(OAc)_2$ (**C1**)	0
2	Without **XantPhos** (**L1**)	0
3	Without Cs_2CO_3 (**B1**)	16, E/Z = 4 : 1
4	Without blue LEDs	0
5	**C2–8** instead of $Pd(OAc)_2$	Listed below
6	**L2–10** instead of **XantPhos**	Listed below
7	**B2–9** instead of Cs_2CO_3	Listed below
8	Carried out in air	Trace
9	5 mol% $Pd(OAc)_2$/10 mol% **L1**, 24 h	33, E/Z = 4 : 1
10	Solvent = THF	73, E/Z = 3 : 1
11	Solvent = dioxane	90, E/Z = 4 : 1
12	Solvent = DCM	60, E/Z = 5 : 1
13	Solvent = $PhCF_3$	41, E/Z = 4 : 1
14	1.0 equiv. Cs_2CO_3	88, E/Z = 5 : 1
15	3.0 equiv. Cs_2CO_3	90, E/Z = 5 : 1
16	1.0 equiv. styrene	80, E/Z = 5 : 1
17	2.0 equiv. styrene	84, E/Z = 5 : 1



[a] Each reaction was run on a 0.1 mmol scale in a sealed 4 mL vial for 12 h. [b] Yields of **2a** and *trans*/*cis* ratios were determined by ^1H NMR using CH_2Br_2 as the internal standard. TFA = trifluoroacetate, COD = 1,5-cyclooctadiene, dba = dibenzylideneacetone, Py = pyridine.

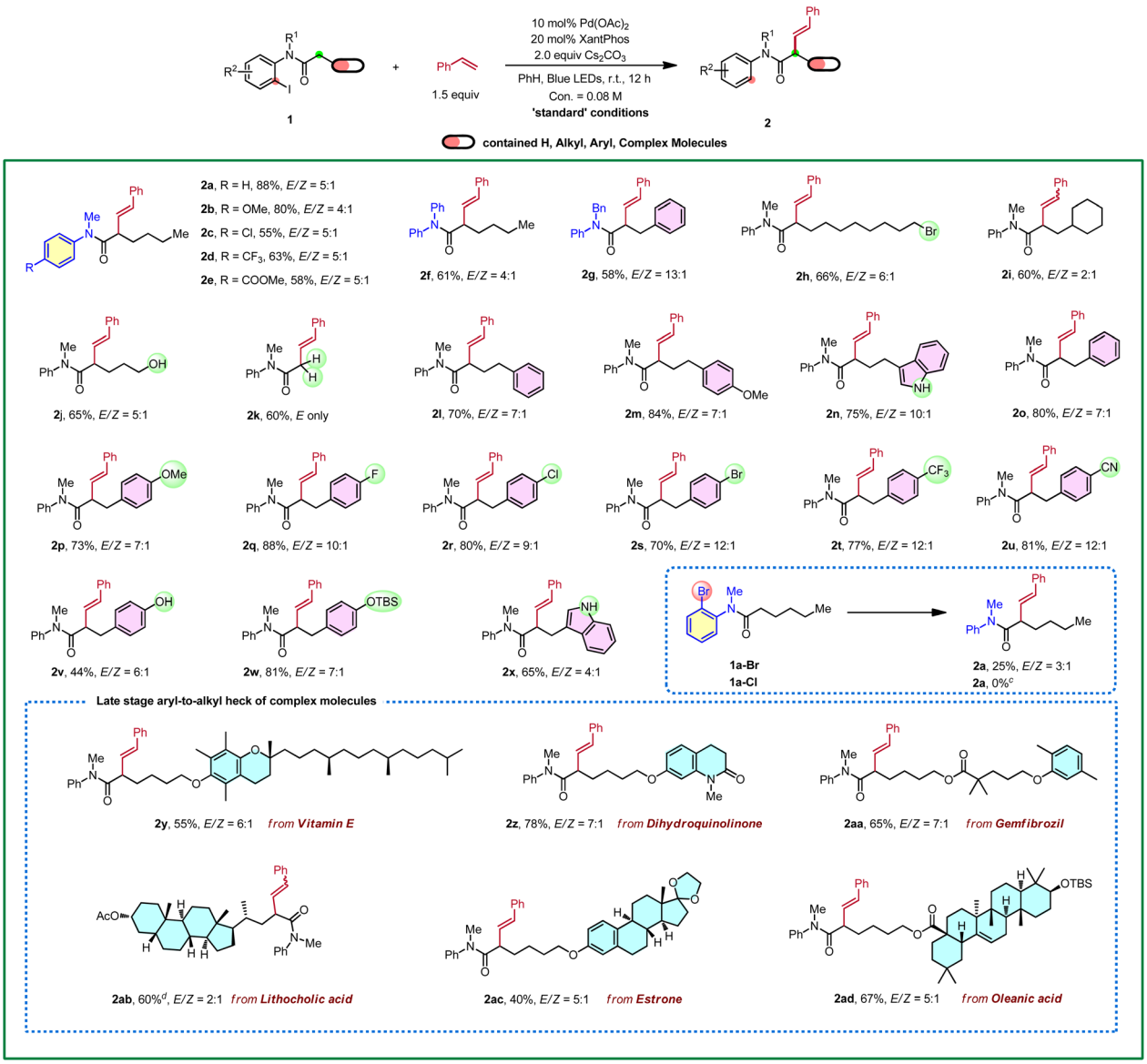
model substrates (Table 1). After extensive optimization, the desired Heck product **2a** was obtained in 88% isolated yield with a *trans*/*cis* (*E*/*Z*) selectivity of 5 : 1 at room temperature through an aryl-to-alkyl radical relay process when $Pd(OAc)_2$/4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos) was used as the metal/ligand combination and Cs_2CO_3 as the base. The direct desaturated **SP2** was isolated in 6% yield. Fortunately, both the premature ipso aryl-Heck product **SP1** and the hydrodehalogenated **SP3** were not obtained suggesting an excellent chemical selectivity of the current reaction. The necessity of each reactant was then explored through control experiments. Clearly, the palladium catalyst, the phosphine ligand, the base and blue light are all essential to this transformation (entries 1–4). Besides $Pd(OAc)_2$, a variety of other Pd(0) and Pd(II) complexes were also tested (entry 5). While $Pd_2(dba)_3$, $Pd(TFA)_2$ and $(DPEphos)PdCl_2$ also gave moderate to good yields, $Pd(PPh_3)_4$, $(PPh_3)_2PdCl_2$ and $(dppf)PdCl_2$ were much less efficient. Notably, the same group

Pt-catalyst $(COD)Pt(TFA)_2$ could also deliver the desired product in 31% yield. Next, a series of ligands have been examined (entry 6). Use of *rac*-BINAP, DPEPhos and *N*-XantPhos (**L2–L4**) proved less efficient, and other bidentate P/N ligands (**L5–L10**) gave none or trace desired product. Both inorganic (**B2–B6**) and organic bases (**B8–B9**) dramatically promoted the reaction, among which K_3PO_4 gave a comparative efficiency with Cs_2CO_3, while K_2CO_3, K_2HPO_4, Na_2CO_3, NaOAc and 2,4,6-tri-Me-pyridine produced moderate yields. Ag_2O totally shut down the reaction.

When the reaction was carried out in ambient air, only a trace amount of desired product was furnished indicating that oxygen may inhibit the reaction (entry 8). Attempts on reducing the catalyst/ligand loading remained unfruitful (entry 9). A survey of different solvents suggested benzene and dioxane to be optimal, though other solvents, such as dichloromethane, benzotrifluoride and more polar THF, also delivered the product in medium to good yields (entries 10–13). Varying the amount of Cs_2CO_3 had a negligible effect on this reaction (entries 14–15). Investigating the loading of styrene suggested that 1.5 equivalent was optimal (entries 16–17).

With the optimized conditions in hand, the substrate scope of amides was explored first (Table 2). Substitutions with both electron-withdrawing and electron-donating groups on the aniline moiety can all be tolerated with electron-rich arenes being more efficient (**2a–2e**). Then, substitutions at the nitrogen were explored, and the corresponding desired products were delivered in good yields (**2f** and **2g**). Gratifyingly, a wide range of functional groups were tolerated at the carbonyl fragment

Table 2 Substrate scope of amides with styrene[a,b,c,d]

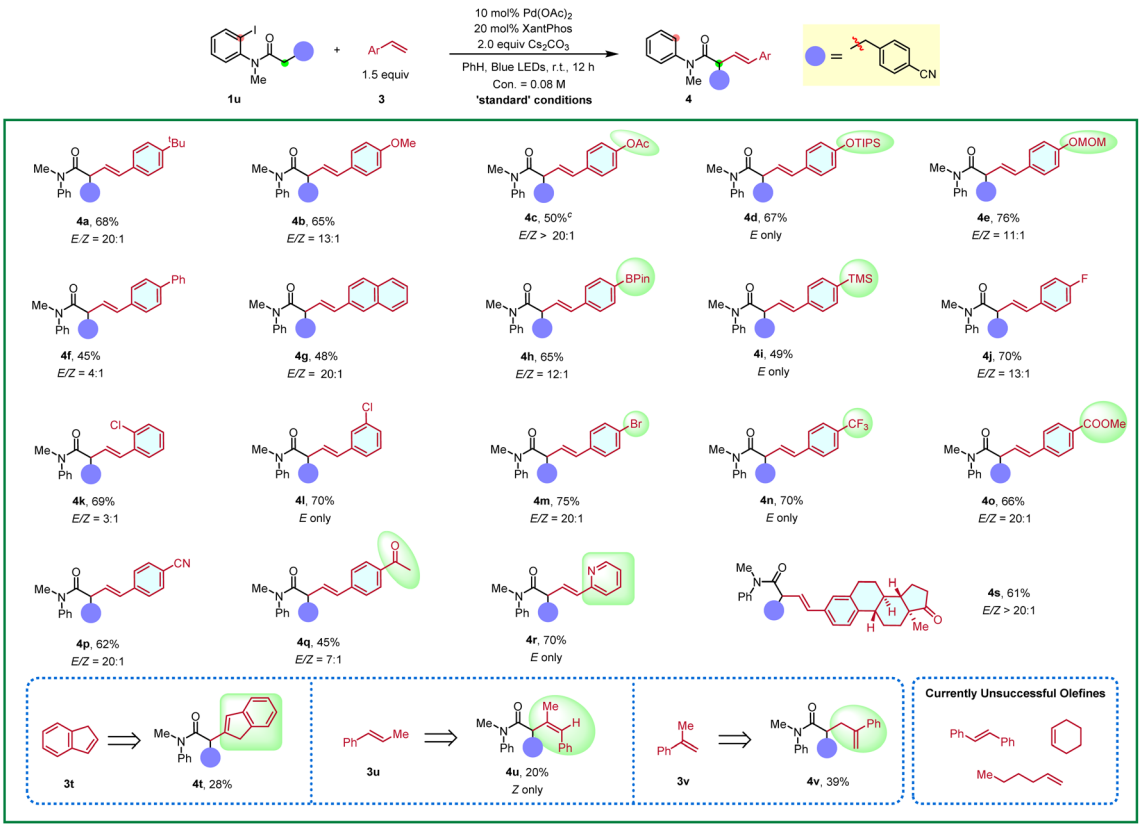


[a] Each reaction was run on a 0.2 mmol scale in a sealed 4 mL vial for 12 h; *trans*/*cis* (*E*/*Z*) ratios were determined by ^1H NMR. [b] Isolated yields. [c] 96% **1a-Cl** was remained. [d] Dioxane was used as the solvent.

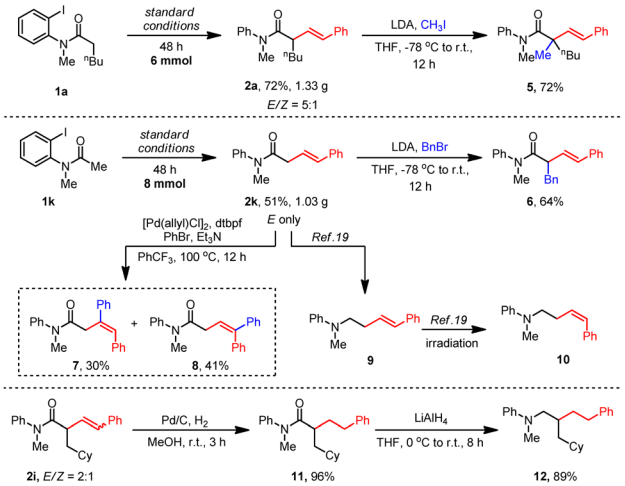
including acid-sensitive moieties, such as TBS ether (**2w** and **2ad**), ketal (**2ac**), and nucleophile/base sensitive moieties, such as alkyl halide (**2h**) and ester (**2aa**-**2ab**). In addition, free alcohol (**2j**), phenol (**2v**) and indol (**2n** and **2x**) were compatible. Remarkably, the substrate with the acetyl group gave a single *trans* isomer product **2k**. Moreover, common functional groups, such as methoxyl (**2m**, **2p**), fluoride (**2q**), chloride (**2r**), bromide (**2s**), trifluoromethyl (**2t**), nitrile (**2u**) and lactam (**2z**) remained intact. Bromo-analogue (**1a-Br**) was a potentially viable substrate which gave 25% yield of the product with a large amount of **1a-Br** remained. Chloro-analogue (**1a-Cl**) gave no desired product. Notably, late-stage modifications of biologically active molecules are often a key to identify medicinal agents. Amides derived from or tethered with bioactive natural products, such as vitamin E (**2y**), dihydroquinolinone (**2z**), gemfibrozil (**2aa**), lithocholic acid (**2ab**), estrone (**2ac**) and oleanic acid (**2ad**) all afforded the desired products in moderate to good yields. Next, 2-iodobenzamides **1ae** was employed as the substrate, on the basis of the above optimized conditions, and it only produced the corresponding enamide side product **S2-1ae** in 70% yield and no Heck-type desired product was observed.[18]

Furthermore, the substrate scope of styrene-type alkenes was examined in Table 3. Here, amide **1u** was employed as the coupling partner due to its good yields and high *trans*/*cis* selectivity. On the whole, styrenes with both electron-withdrawing and electron-donating substituents were well tolerated under the standard conditions, affording the alkyl Heck products in good yields with good to excellent *trans*/*cis* selectivity. A wide range of functional groups proved to be compatible, including methoxy (**4b**), acetoxyl (**4c**), silyl ether (**4d**), acetal (**4e**), pinacol boronate (**4h**), trimethylsilyl (**4i**), fluoro (**4j**), chloro (**4k** and **4l**), bromo (**4m**), trifluoromethyl (**4n**), ester (**4o**), cyano (**4p**), and ketone (**4q** and **4s**) groups. Note that substitutions at the *para*, *meta* or *ortho* position of styrenes all reacted smoothly (**4k**, **4l**). Extended aromatic rings, such as 4-vinyl-1,1′-biphenyl (**3f**), 2-vinylnaphthalene (**3g**), were also viable substrates. Notably, the reaction is compatible with 2-vinyl pyridine (**3r**) which has a good coordination ability, and the corresponding product was afforded in a good yield and excellent *trans*/*cis* selectivity (**4r**). An investigation of the substituents on the alkene moiety was also conducted. Both 1,2-disubstituted alkenes, such as 1*H*-indene (**3t**), (*E*)-prop-1-en-1-ylbenzene (**3u**) and 1,1-disubstituted, prop-1-en-2-ylbenzene (**3v**) were feasible substrates, albeit giving the corresponding products **4t**–**4v** in 20–40% yields but as the single isomer. Aliphatic alkenes, such as hex-1-ene and cyclohexene were unfruitful, which might undergo direct desaturation.

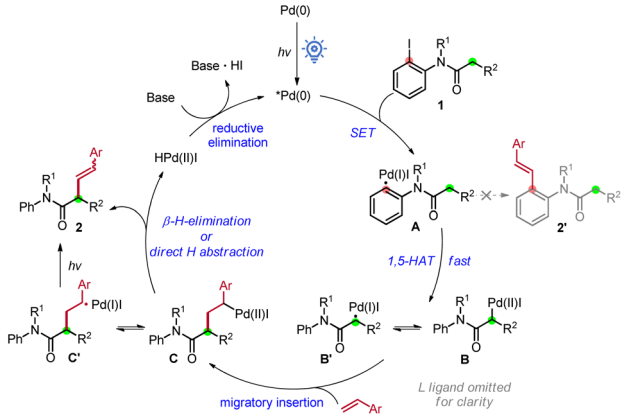
Table 3 Substrate scope of styrene-type alkenes[a,b,c]



[a] Each reaction was run on a 0.2 mmol scale in a sealed 4 mL vial for 12 h; *trans*/*cis* (*E*/*Z*) ratios were determined by ^{1}H NMR. [b] Isolated yields. [c] Separation of the pure product **4c** from the desaturation side product was difficult.



Scheme 2 Synthetic transformations.



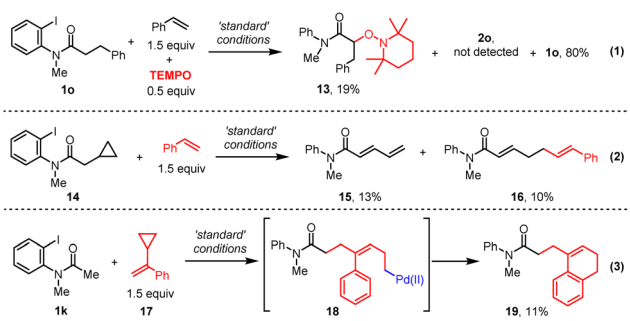
Scheme 4 Plausible mechanism.

(*E*)-1,2-diphenylethene also gave the direct desaturation side product.

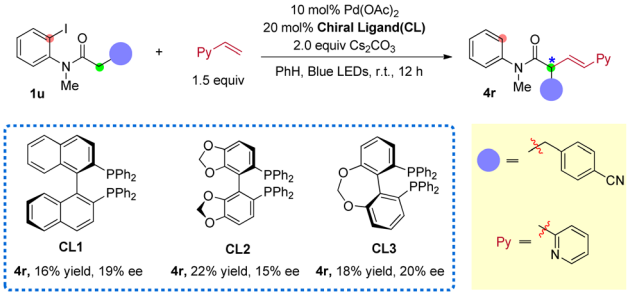
To test the practicality of this method, gram–scale reactions of **1a** and **1k** were carried out. More than one gram of the desired alkyl Heck products **2a** and **2k** were obtained with satisfactory yields (Scheme 2). Then, a variety of transformations were employed to extend the utility of this Heck reaction. First, α-alkylation occurred smoothly with methylation to give **5** and benzylation to form **6**. Interestingly, a further aryl-Heck reaction of **2k** with PhBr occurred at both olefine sides to produce **7** and **8**. The carbonyl group of amide **2k** could be reduced easily by $LiAlH_4$ to form an amine product **9** of which the *E* olefine could be transformed to a *Z* isomer **10** under irradiation.[19] Reduction of the olefine in **2i** gave **11** in 96% yield which was further reduced by $LiAlH_4$ to obtain an amine product **12**.

Based on the precedent literature for photo-induced palladium catalyzed alkyl-Heck reactions,[13a–c,14a] the mechanism is expected to be a hybrid Pd/radical pathway. A series of mechanistic studies were thus carried out. First, a radical-trapping experiment was conducted. In the presence of 50 mol% TEMPO, the α-radical was trapped by TEMPO to give **13** and no desired product was obtained (Scheme 3, eqn (1)). Next, the radical nature of this transformation was further confirmed by a radical-clock experiment with amide **14** and styrene, which produced both a ring-opening dienamide **15** and further a relay alkyl Heck product **16** [20](Scheme 3, eqn (2)). Finally, when cyclopropane substituted styrene was subjected to this Heck reaction, benzocyclohexene product **19** [20]was obtained through a ring-opening process followed by radical cyclization or electrophilic palladation of intermediate **18** (Scheme 3, eqn (3)). Altogether, these results provided evidence for the aryl-to-alkyl radical translocation process and radical nature of this relay Heck reaction.

The reaction mechanism is proposed in Scheme 4. First, the Pd(0) complex is excited using visible light to form its excited state species which abstract the iodide on **1** in a SET process to form the aryl hybrid Pd-radical intermediate **A**. Subsequently, the latter undergoes a fast 1,5-HAT event to generate translocated alkyl hybrid Pd-radical species **B′**. Premature aryl Heck product **2′** was not observed here. Note that C–I bond reductive elimination or the I-atom transfer product was not observed in our reaction system. The species **B**/**B′** then undergoes migratory insertion into the styrene to form the alkyl hybrid Pd-intermediate **C**/**C′**. The smooth occurrence of the reaction indicates that this step is much faster than β-H elimination of **B**. β-Hydride elimination of **C** or direct abstraction of a β-hydrogen atom by the Pd(I) species occurs of **C′** afterwards to produce the product **2** and regenerate the Pd catalyst *via* reductive elimination. The formation of *Z*-(**2**) may be from the direct H abstraction of intermediate **C′**, and another possibility is that *E*-(**2**) could be transformed to a *Z* isomer under irradiation.[19]



Scheme 3 Mechanistic studies.



Scheme 5 Investigation of an enantioselective radical relay Heck reaction.

Based on the reaction mechanism, an enantioselective aryl-to-alkyl radical relay Heck reaction was attempted using chiral ligands (Scheme 5). The reaction of amide **1u** with 2-vinyl pyridine was employed as the model reaction due to its good yields and high *trans*/*cis* selectivity. After screening of some chiral ligands, when BINAP-type chiral ligands (**CL1-3**) were employed as the ligands (instead of xantphos), 16–22% yield of the desired product **4r** was obtained with some extent of enantio-control (from 15% to 20% *ee*) (for screening of more chiral ligands, see ESI S54†). This indicates the feasibility of developing an enantioselective photo-induced aryl-to-alkyl radical relay sp^3 Heck reaction using chiral ligands. Efforts on improving both the enantioselectivity and conversion are ongoing.

Conclusions

In summary, a photo-induced palladium catalyzed aryl-to-alkyl radical relay Heck reaction at the α-C(sp^3)-H site of amide has been developed. This reaction escaped the shackles of traditional alkyl halides as alkyl Heck reagents, but adopted inexpensive and commercially more available aryl halides, which are also considered to be more active in Heck reactions. The tolerance of a large variety of functional groups makes this method attractive for use in the synthesis of complex bioactive molecules. This method is scalable and operationally simple under mild conditions at room temperature. Additionally, the promising preliminary results obtained in this study will motivate the development of an enantioselective radical relay sp^3 Heck reaction of amide. Mechanistic studies reveal a radical nature of this transformation. Development of intermolecular aryl-to-alkyl Heck reactions will be the focus of future work.

Data availability

The experiments data were provide in ESI,† and we did not have the computational data.

Author contributions

Y. D., X. S. and M. C. conceived the project and wrote the manuscript with feedback from the other authors. Y. D. and X. S. performed the experiments. M. C. and S. Y. supervised the project. All authors discussed the results and approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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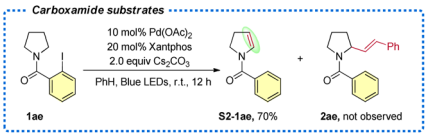

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