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Synthetic Methods

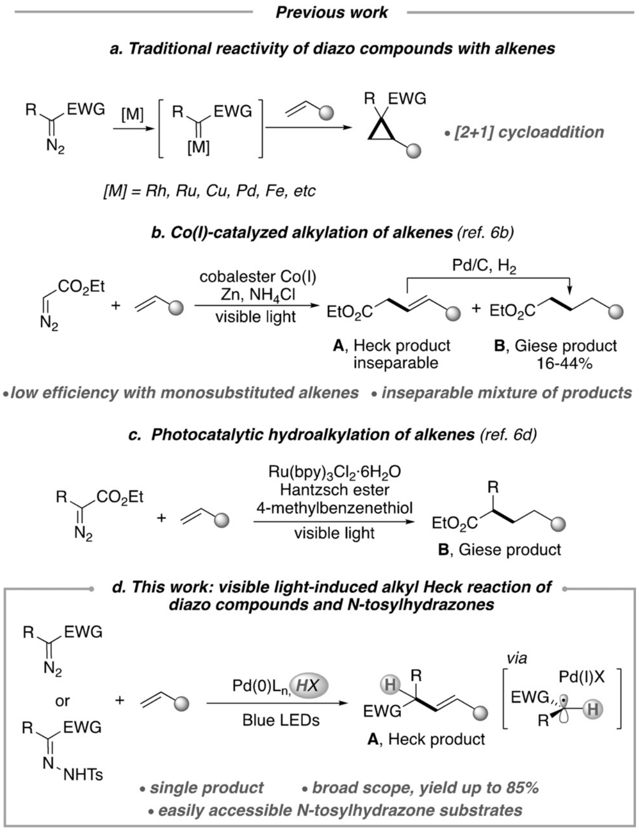
Visible Light Induced Brønsted Acid Assisted Pd-Catalyzed Alkyl Heck Reaction of Diazo Compounds and *N*-Tosylhydrazones

*Ziyan Zhang, Nikita Kvasovs, Anastasiia Dubrovina, and Vladimir Gevorgyan**

Abstract: *A mild visible light-induced palladium-catalyzed alkyl Heck reaction of diazo compounds and N-tosylhydrazones is reported. A broad range of vinyl arenes and heteroarenes with high functional group tolerance, as well as a range of different diazo compounds, can efficiently undergo this transformation. This method features Brønsted acid-assisted generation of hybrid palladium C(sp^3)-centered radical intermediate, which allowed for new selective C−H functionalization protocol.*

Since the first publication on synthesis of ethyl diazoacetate by Curtius in 1883,[1] diazo compounds have been recognized among the most versatile reagents in organic synthesis.[2] One of the most common reactions of diazo compounds is cyclopropanation of alkenes, which occurs through metal-carbene complex[3] or free carbene intermediates (Scheme 1 a).[4] In addition, the formation of carbon-centered radicals from diazo compounds with release of dinitrogen has been reported, but most processes still exhibit carbene-like reactivity, producing cyclopropanes in reactions with alkenes.[5] Their ability to generate free radical intermediate for alternative functionalizations with alkenes has rarely been explored.[6] In 2016, Gryko and co-workers pioneered light-induced cobalt(I)-catalyzed alkylation of alkenes with diazoacetate (Scheme 1 b).[6b] This method is efficient for Heck-type (**A**) alkylation of disubstituted electron-rich alkenes. However, in reactions with monosubstituted alkenes, substantial amounts of inseparable Giese-type reduced product **B** is produced, which limits synthetic usefulness of the method. Later, Doyle group reported that the product **B** can selectively be produced via Ru-photocatalysis (Scheme 1 c).[6d] To date, no methods exist for selective Heck-type C−H alkylation of synthetically important monosubstituted alkenes with diazo compounds. Herein, we report a mild, selective, and general visible light-induced Pd-catalyzed Brønsted acid-assisted Heck reaction of diazo compounds and their convenient precursors, *N*-tosylhydrazones, with vinyl arenes and heteroarenes, which proceeds via hybrid palladium C(sp^3)-centered radical intermediate (Scheme 1 d).

Recently, the photoinduced palladium catalysis has become an emerging field of study.[7] Thus, we[8] and others[9] have established mild and efficient methods for visible light-induced palladium-catalyzed alkyl-Heck reaction of various alkyl electrophiles, proceeding via hybrid palladium C(sp^3)-centered radical species. In our ongoing search for new precursors for hybrid Pd radical species,[8] we aimed at engaging diazo compounds in this chemistry, which would allow for a substantial broadening of the scope of electrophiles in alkyl Heck reaction.



Scheme 1. The reactivity of diazo compounds with alkenes.

To this end, we examined reaction of ethyl diazoacetate (**1a**) with styrene (**2a**) under our standard palladium(II) acetate/Xantphos catalytic system[8] with Cs_2CO_3.

However, no desired Heck product **3a** was observed under these conditions (Table 1, entry 1). To our surprise, 15% of product **3a** was formed when base additive was removed (entry 2). We hypothesized that the formation of traces amount of acetic acid from palladium acetate is crucial for the reaction to occur, which was later validated using $Pd(PPh_3)_4$ as catalyst with and without exogenous acetic acid (entries 4, 5). The addition of triphenylphosphine as monodentate ligand[10] further improved reaction efficiency

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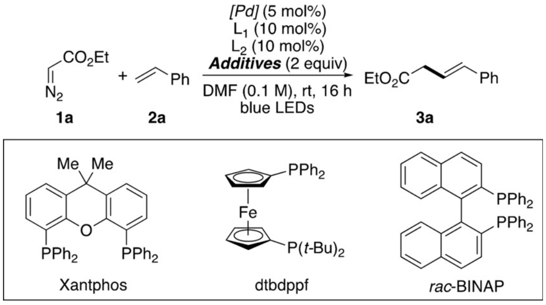
Table 1: Reaction optimization for Heck reaction with diazo compounds.



Entry	[Pd]	L_1, L_2	**Additives**	Yield [%][a]
1	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	0
2	$Pd(OAc)_2$	Xantphos	–	15
3	$Pd(OAc)_2$	Xantphos, PPh_3	–	21
4	$Pd(PPh_3)_4$	Xantphos	–	traces
5	$Pd(PPh_3)_4$	Xantphos	AcOH (10 mol%)	26
6	$Pd(OAc)_2$	Xantphos, PPh_3	NH_4Cl	56
7	**$Pd(OAc)_2$**	**Xantphos, PPh_3**	**4-Chloro-piperidine hydrochloride**	**80[b]**
8	$Pd(OAc)_2$	dtbdppf, PPh_3	4-Chloro-piperidine hydrochloride	0
9	$Pd(OAc)_2$	*rac*-BINAP, PPh_3	4-Chloro-piperidine hydrochloride	0
10	-	Xantphos, PPh_3	4-Chloro-piperidine hydrochloride	0
11	$Pd(OAc)_2$	-	4-Chloro-piperidine hydrochloride	traces
12	$Pd(OAc)_2$	Xantphos, PPh_3	4-Chloro-piperidine hydrochloride	traces[c]

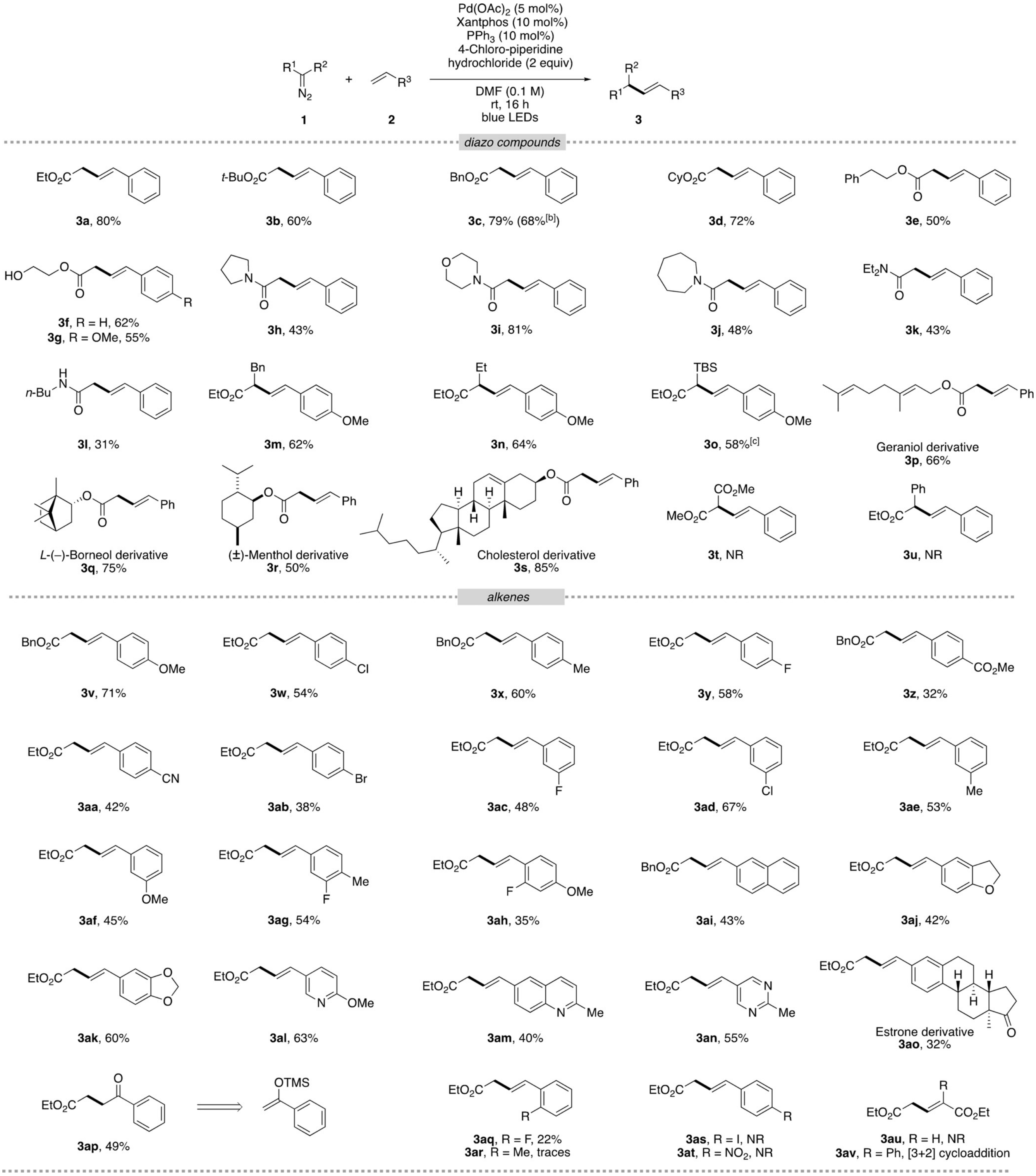
[a] 0.1 mmol scale; **1a**:**2a** = 1:2. Determined by GC/MS using pentadecane as internal standard. [b] 0.25 mmol scale, isolated yields. Standard condition A. [c] 50, 80 or 120 °C, no light.

(entry 3). Encouraged by these results, we began optimizing this novel visible light-induced Brønsted acid-assisted alkyl Heck reaction of diazo compounds by screening different additives.[11] In the turnover-enabling step of the Heck reaction, an exogenous base (e.g., Et_3N, Cs_2CO_3) is typically employed to convert H-Pd^{II}-X back to the active Pd^0 catalyst while simultaneously forming an equivalent of the base·HX waste.[12] Considering this sequence in reverse, we envisioned that base·HX species could be used as practical Brønsted acid surrogate, which would serve as hydrogen donor in the reduction with diazo compounds. This would then promote both, the generation of hybrid palladium C(sp^3)-centered radical species, and a catalytic turnover. Thus, different base·HX precursors were extensively tested (entries 6, 7). Various ammonium halides were identified to be superior additives. Among them, more soluble and inexpensive 4-chloro-piperidine hydrochloride produced the desired coupling product **3a** in 80 % yield (entry 7). Control experiments demonstrated both Pd catalyst and Xantphos ligand are essential for this transformation (entries 8–11), and thermal reaction under dark gave only traces of product (entry 12).

With the optimized conditions in hand, the scope of diazo compounds was examined first (Scheme 2). It was found that monosubstituted diazo esters (**3a**-**3g**), including bulky ester, such as *tert*-butyl (**3b**), proven to be capable substrates for this coupling reaction. A diverse array of diazo amides was fully compatible with the present protocol, providing the corresponding products **3h**-**3l** in moderate to high yields. Notably, sensitive protic functional groups such as primary alcohol (**3f**-**3g**) and secondary amide (**3l**) were tolerated under these reaction conditions, without formation of potential competing X−H insertion product. In addition, selected donor/acceptor substituted diazo esters (**3m**-**3n**) gave good yields without formation of cyclopropane or carbene dimer products. Importantly, silylated diazo ester also proved to be a viable substrate to produce allylsilane **3o**. Finally, we were pleased to find that the present Heck coupling was compatible with various natural alcohol derivatives (**3p**-**3s**), highlighting the broad applicability and the potential utility of this protocol in late-stage functionalization.

Next, the generality of alkenes in this methodology was examined. *Para*-substituted styrenes with a broad range of functional groups were readily tolerated, providing the corresponding products **3v**-**3aa** in moderate to good yields. *Meta*- and *ortho*-substituted styrenes also gave the corresponding products **3ac**-**3ah** with good efficiency. Heck reactions with vinyl heteroarenes proceeded uneventfully, efficiently producing alkenes possessing naphthalene (**3ai**), dihydrobenzofuran (**3aj**), benzodioxole (**3ak**), pyridine (**3al**), quinoline (**3am**), and pyrimidine (**3an**) rings. In addition, reaction of **1a** with vinyl derivative of estrone generated product **3ao**, highlighting the applicability of this visible light-induced Heck reaction protocol in complex settings. Finally, silyl enol ether also proved to be capable coupling partner, affording the ketone product **3ap**[10c] upon the in situ hydrolysis of the formed alkylated silyl enol ether. However, acrylates (**3au**-**3aw**) were unreactive under current conditions, presumably due to electronic mismatch with electrophilic radicals generated from diazo compounds, while 2-phenylacrylic ester (**3av**) gave pyrazoline, as a result of [3+2] cycloaddition,[13] instead of Heck product.

Motivated by the successful employment of diazo compounds in the Heck reaction, we sought of more practical precursors for this transformation. Thus, we turned attention to *N*-tosylhydrazones,[14] which can be easily accessed from simple ketones. Upon exposure to a base, *N*-tosylhydrazones could in situ be transformed into diazo compounds, thus serving as their convenient surrogates.[15] We rationalized that the required base·HX species under basic conditions can be generated through deprotonation of *N*-tosylhydrazones in the presence of exogenous halide counterion[16] additive. After extensive screening of reaction parameters,[11] we were delighted to find conditions, which allowed to efficiently perform alkyl Heck reaction of *N*-tosylhydrazone **4a** with **2a** (Table 2, entry 1). Control experiments indicated that both visible light irradiation and Pd catalyst were necessary (entries 2, 3). The reaction efficiency was substantially lower in the absence of base or iodide additive (entries 4, 5). Reactions in the presence of tetrabutylammonium bromide

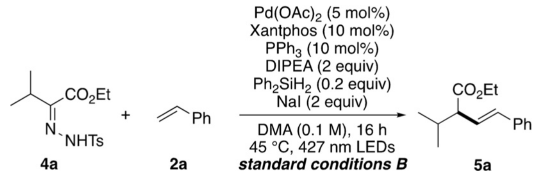


Scheme 2. Scope of Heck reaction of diazo compounds with alkenes.[a] [a] 0.2 mmol scale, isolated yields. **1**:**2** = 1:2. [b] Reaction was performed in 1 mmol scale. [c] 0.2 equivalent of $PhMeSiH_2$ was used. NR: no reaction.

(entry 6), or in absence of diphenylsilane (entry 7) were also less efficient.

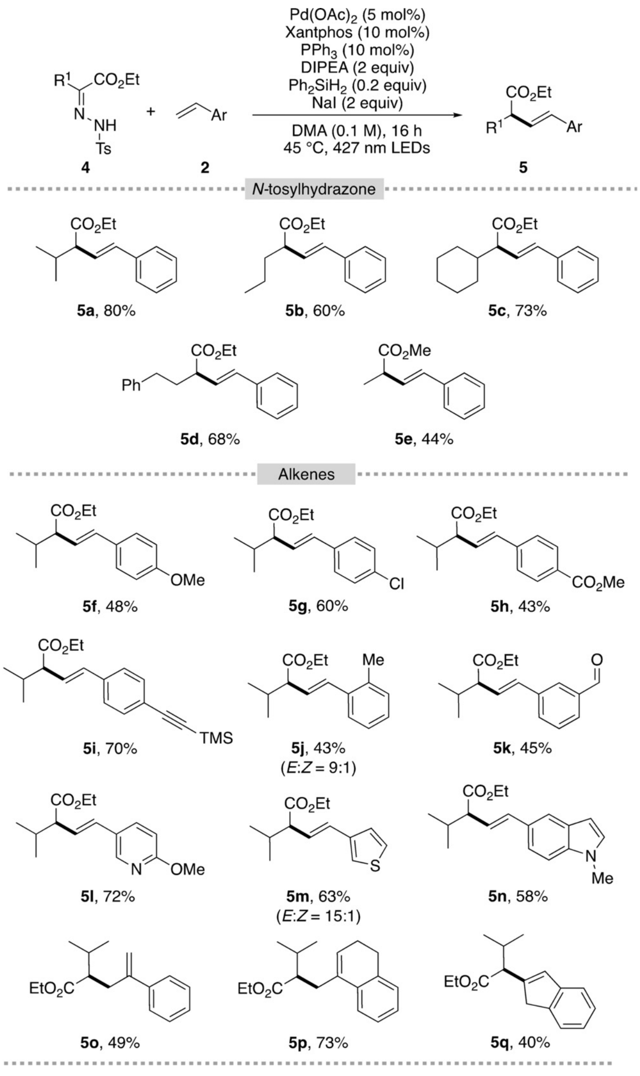
Next, the scope of alkyl Heck reaction of *N*-tosylhydrazones with alkenes was investigated (Scheme 3). Thus, *N*-tosylhydrazones possessing various primary and secondary alkyl substituents proved to be capable substrates for this reaction (**5a**-**5e**). Reactions with styrenes bearing electron-rich and electron-poor substituents at the *para*-, *ortho*-, and *meta*-positions on the aromatic ring furnished products **5f**-**5k** in moderate to good yield. Heteroaryl groups were also

Table 2: Reaction optimization for Heck reaction with *N*-tosylhydrazones.



Entry	Deviation from standard conditions	Yield [%][a]
1	None	80[b]
2	Without $Pd(OAc)_2$	0
3	Dark	traces
4	Without DIPEA	19
5	Without NaI	traces
6	NBu_4Br (2 equiv)	58
7	Without Ph_2SiH_2	45

[a] 0.1 mmol scale; **4a**:**2a** = 1:1.1. Determined by GC/MS using pentadecane as internal standard. [b] 0.25 mmol scale, isolated yields.



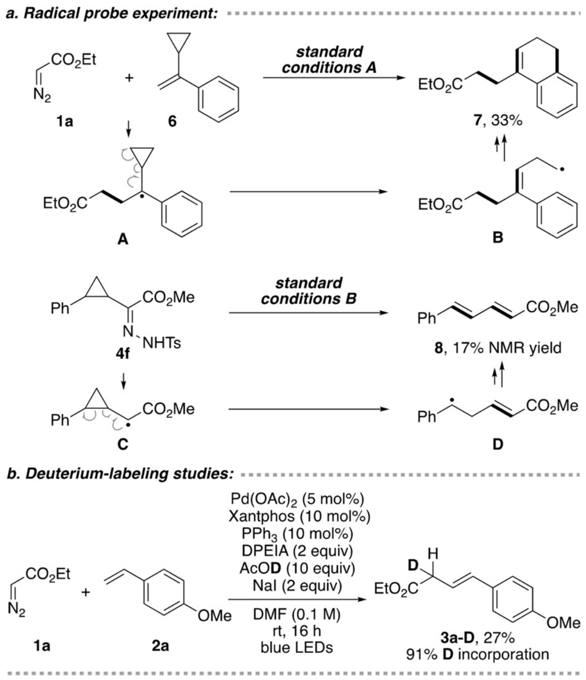
Scheme 3. Scope of Heck reaction of *N*-tosylhydrazones with alkenes.[a] [a] 0.2 mmol scale, isolated yields. **4**:**2** = 1:1.1.

amenable to this catalytic process, affording the corresponding products **5l**-**5n** in good yields. Notably, α-substituted styrenes, as well as indene, were reactive in this Heck coupling process (**5o**-**5q**).

Then, a series of mechanistic experiments were performed. The radical nature of this transformation was confirmed by employment of radical clock and radical traps (Scheme 4). Thus, reaction of ethyl diazoacetate **1a** with **6**, possessing a cyclopropyl substituent,[17] produced bicyclic product **7**, as a result of ring opening of methylenecyclopropyl radical **A** into a homoallylic radical **B** and its subsequent cyclization at the aryl ring. Likewise, methylenecyclopropyl radical intermediate **C**, generated from *N*-tosylhydrazone **4f**, upon visible light irradiation, rearranged into benzylic radical **D**, which upon β-hydrogen loss produced linear diene **8** in 17% yield. It was also shown that both modes of this reaction (with **1a** and **4a**) were inhibited in the presence of radical traps, such as TEMPO.[11]

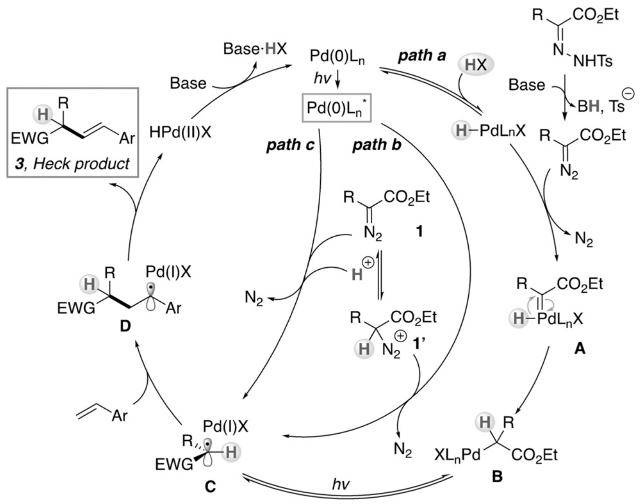
The performed isotope-labeling experiments with deuterated Brønsted acid, $DPd(PPh_3)_2Cl$, and *N*-deuterated tosylhydrazone unambiguously supported these to be the hydrogen sources in this alkyl Heck reaction.[11] A potential mechanism operating via cyclopropanation followed by ring opening was ruled out by independent synthesis of the corresponding cyclopropane and resubjecting it to the standard reaction conditions, under which no product was formed.[11]

Based on the above mechanistic studies and literature reports,[8,9] the following plausible mechanism is proposed for this novel alkyl-Heck reaction of diazo compounds and *N*-tosylhydrazones (Scheme 5). ***Path a*** begins with an oxidative addition of HX with Pd^0 to generate active $HPdXL_2$ species,[18] which via a denitrogenative reaction with diazo compound produces Pd-carbene intermediate **A**. A subse-



Scheme 4. Mechanistic studies.

quent hydride shift yields palladium species **B**, which upon light induced homolysis of the C−Pd bond results in a hybrid alkyl Pd-radical species **C**. Alternatively, the latter could be formed either via a single electron transfer (SET) to diazonium ions **1′**, a protonated form of diazo compound (***path b***),[19] or proton coupled electron transfer (PCET) directly from diazo compounds (***path c***).[6d] Next, the addition of alkyl radical **C** to a styrene takes place, resulting in the hybrid benzylic radical **D**. The endgame follows the classical Heck reaction mechanism, including β-H-elimination to produce the reaction product and reduction of HPd(II)X with the base to close the catalytic cycle.[8,9] It should be mentioned that the isotope-labelling studies cannot rule out any of these scenarios. Accordingly, at this point, all these pathways for hybrid alkyl Pd-radical species **C** generation considered feasible. Evidently, more detailed mechanistic studies are required to set a precise mechanism for this novel transformation.



Scheme 5. Proposed mechanism.

In conclusion, we developed a visible light-induced palladium-catalyzed Heck reaction of diazo compounds and *N*-tosylhydrazones, with vinyl arenes and heteroarenes, leading to synthetically valuable allylic products. The mechanistic studies support the Brønsted acid-assisted generation of hybrid palladium C(sp^3)-centered radical intermediate, thus expanding the boundaries of direct functionalization of alkenes using diazo compounds and *N*-tosylhydrazones. This method substantially expands the scope of substrates for alkyl Heck reaction. It is anticipated that this mild visible light-induced protocol will find use in synthesis and will stimulate development of new C−H functionalization methods.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: diazo compounds · Heck reaction · palladium · radicals · reaction mechanisms

[1] T. Curtius, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2230–2231.
[2] a) D. M. Hodgson, F. Y. T. M. Pierard, P. A. Stupple, *Chem. Soc. Rev.* **2001**, *30*, 50–61; b) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417–424; c) H. M. L. Davies, J. R. Denton, *Chem. Soc. Rev.* **2009**, *38*, 3061–3071; d) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857–1869; e) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981–10080; f) Q.-Q. Cheng, Y. Deng, M. Lankelma, M. P. Doyle, *Chem. Soc. Rev.* **2017**, *46*, 5425–5443; g) Y. Xia, D. Qiu, J. Wang, *Chem. Rev.* **2017**, *117*, 13810–13889; h) Ł. W. Ciszewski, K. Rybicka-Jasińska, D. Gryko, *Org. Biomol. Chem.* **2019**, *17*, 432–448; i) D. Zhu, L. Chen, H. Fan, Q. Yao, S. Zhu, *Chem. Soc. Rev.* **2020**, *49*, 908–950; j) Z. Yang, M. L. Stivanin, I. D. Jurberg, R. M. Koenigs, *Chem. Soc. Rev.* **2020**, *49*, 6833–6847.
[3] a) M. P. Doyle, M. N. Protopopova, *Tetrahedron* **1998**, *54*, 7919–7946; b) G. Maas, *Chem. Soc. Rev.* **2004**, *33*, 183–190; c) S. E. Reisman, R. R. Nani, S. Levin, *Synlett* **2011**, *2011*, 2437–2442; d) L. Liu, J. Zhang, *Chem. Soc. Rev.* **2016**, *45*, 506–516; e) S. Chanthamath, S. Iwasa, *Acc. Chem. Res.* **2016**, *49*, 2080–2090; f) C. Ebner, E. M. Carreira, *Chem. Rev.* **2017**, *117*, 11651–11679.
[4] a) I. D. Jurberg, H. M. L. Davies, *Chem. Sci.* **2018**, *9*, 5112–5118; b) Z. Zhang, D. Yadagiri, V. Gevorgyan, *Chem. Sci.* **2019**, *10*, 8399–8404.
[5] a) Y. Chen, X. P. Zhang, *J. Org. Chem.* **2004**, *69*, 2431–2435; b) W. I. Dzik, X. P. Zhang, B. de Bruin, *Inorg. Chem.* **2011**, *50*, 9896–9903; c) P. Li, J. Zhao, L. Shi, J. Wang, X. Shi, F. Li, *Nat. Commun.* **2018**, *9*, 1972; d) W.-C. C. Lee, D.-S. Wang, C. Zhang, J. Xie, B. Li, X. P. Zhang, *Chem* **2021**, *7*, 1588–1601.
[6] a) J. Jiang, J. Liu, L. Yang, Y. Shao, J. Cheng, X. Bao, X. Wan, *Chem. Commun.* **2015**, *51*, 14728–14731; b) M. Giedyk, K. Goliszewska, K. ó Proinsias, D. Gryko, *Chem. Commun.* **2016**, *52*, 1389–1392; c) C. te Grotenhuis, N. van den Heuvel, J. I. van der Vlugt, B. de Bruin, *Angew. Chem. Int. Ed.* **2018**, *57*, 140–145; *Angew. Chem.* **2018**, *130*, 146–151; d) Y.-L. Su, G.-X. Liu, J.-W. Liu, L. Tram, H. Qiu, M. P. Doyle, *J. Am. Chem. Soc.* **2020**, *142*, 13846–13855; e) J. Zhao, P. Li, Y. Xu, Y. Shi, F. Li, *Org. Lett.* **2019**, *21*, 9386–9390.
[7] a) P. Chuentragool, D. Kurandina, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2019**, *58*, 11586–11598; *Angew. Chem.* **2019**, *131*, 11808–11812; b) D. Kurandina, P. Chuentragool, V. Gevorgyan, *Synthesis* **2019**, *51*, 985–1005; c) W.-J. Zhou, G.-M. Cao, Z.-P. Zhang, D.-G. Yu, *Chem. Lett.* **2019**, *48*, 181–191; d) R. Kancherla, K. Muralirajan, A. Sagadevan, M. Rueping, *Trends Chem.* **2019**, *1*, 510–523; e) W.-M. Cheng, R. Shang, *ACS Catal.* **2020**, *10*, 9170–9196; f) K. P. S. Cheung, D. Kurandina, T. Yata, V. Gevorgyan, *J. Am. Chem. Soc.* **2020**, *142*, 9932–9937; g) H.-M. Huang, P. Bellotti, P. M. Pflüger, J. L. Schwarz, B. Heidrich, F. Glorius, *J. Am. Chem. Soc.* **2020**, *142*, 10173–10183; h) P. Bellotti, M. Koy, C. Gutheil, S. Heuvel, F. Glorius, *Chem. Sci.* **2021**, *12*, 1810–1817.
[8] a) D. Kurandina, M. Parasram, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2017**, *56*, 14212–14216; *Angew. Chem.* **2017**, *129*, 14400–14404; b) D. Kurandina, M. Rivas, M. Radzhabov, V. Gevorgyan, *Org. Lett.* **2018**, *20*, 357–360; c) P. Chuentragool, D. Yadagiri, T. Morita, S. Sarkar, M. Parasram, Y. Wang, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2019**, *58*, 1794–1798; *Angew. Chem.* **2019**, *131*, 1808–1812.

[9] a) G.-Z. Wang, R. Shang, W.-M. Cheng, Y. Fu, *J. Am. Chem. Soc.* **2017**, *139*, 18307 – 18312; b) G.-Z. Wang, R. Shang, Y. Fu, *Org. Lett.* **2018**, *20*, 888 – 891; c) M. Koy, F. Sandfort, A. Tlahuext-Aca, L. Quach, C. G. Daniliuc, F. Glorius, *Chem. Eur. J.* **2018**, *24*, 4552 – 4555; d) M. Koy, P. Bellotti, F. Katzenburg, C. G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed.* **2020**, *59*, 2375 – 2379; *Angew. Chem.* **2020**, *132*, 2395 – 2399; e) G. S. Lee, D. Kim, S. H. Hong, *Nat. Commun.* **2021**, *12*, 991.

[10] a) N. Kvasovs, V. Iziumchenko, V. Palchykov, V. Gevorgyan, *ACS Catal.* **2021**, *11*, 3749 – 3754; b) W.-M. Cheng, R. Shang, Y. Fu, *Nat. Commun.* **2018**, *9*, 5215; c) B. Zhao, R. Shang, G.-Z. Wang, S. Wang, H. Chen, Y. Fu, *ACS Catal.* **2020**, *10*, 1334 – 1343.

[11] See Supporting Information for details.

[12] a) R. F. Heck, *Acc. Chem. Res.* **1979**, *12*, 146 – 151; b) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009 – 3066; c) I. D. Hills, G. C. Fu, *J. Am. Chem. Soc.* **2004**, *126*, 13178 – 13179.

[13] Y. Shao, J. Tong, Y. Zhao, H. Zheng, L. Ma, M. Ma, X. Wan, *Org. Biomol. Chem.* **2016**, *14*, 8486 – 8492.

[14] a) Y. Xia, J. Wang, *Chem. Soc. Rev.* **2017**, *46*, 2306 – 2362; b) Y. Xia, J. Wang, *J. Am. Chem. Soc.* **2020**, *142*, 10592 – 10605.

[15] W. R. Bamford, T. S. Stevens, *J. Chem. Soc.* **1952**, 4735 – 4740.

[16] M. Ratushnyy, N. Kvasovs, S. Sarkar, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2020**, *59*, 10316 – 10320; *Angew. Chem.* **2020**, *132*, 10402 – 10406.

[17] a) M. Newcomb, P. H. Toy, *Acc. Chem. Res.* **2000**, *33*, 449 – 455; b) J. E. Baldwin, *Chem. Rev.* **2003**, *103*, 1197 – 1212.

[18] a) D. A. Petrone, I. Franzoni, J. Ye, J. F. Rodríguez, A. I. Poblador-Bahamonde, M. Lautens, *J. Am. Chem. Soc.* **2017**, *139*, 3546 – 3557; b) Y. Hu, Z. Shen, H. Huang, *ACS Catal.* **2016**, *6*, 6785 – 6789; c) R. W. Armbruster, M. M. Morgan, J. L. Schmidt, C. M. Lau, R. M. Riley, D. L. Zabrowsky, H. A. Dieck, *Organometallics* **1986**, *5*, 234 – 237.

[19] a) X. Huang, R. D. Webster, K. Harms, E. Meggers, *J. Am. Chem. Soc.* **2016**, *138*, 12636 – 12642; b) Ł. W. Ciszewski, J. Durka, D. Gryko, *Org. Lett.* **2019**, *21*, 7028 – 7032.

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