JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

Photoinduced Palladium-Catalyzed Carbofunctionalization of Conjugated Dienes Proceeding via Radical-Polar Crossover Scenario: 1,2-Aminoalkylation and Beyond

Kelvin Pak Shing Cheung, Daria Kurandina, Tetsuji Yata, and Vladimir Gevorgyan*

Cite This: *J. Am. Chem. Soc.* 2020, 142, 9932−9937

Read Online

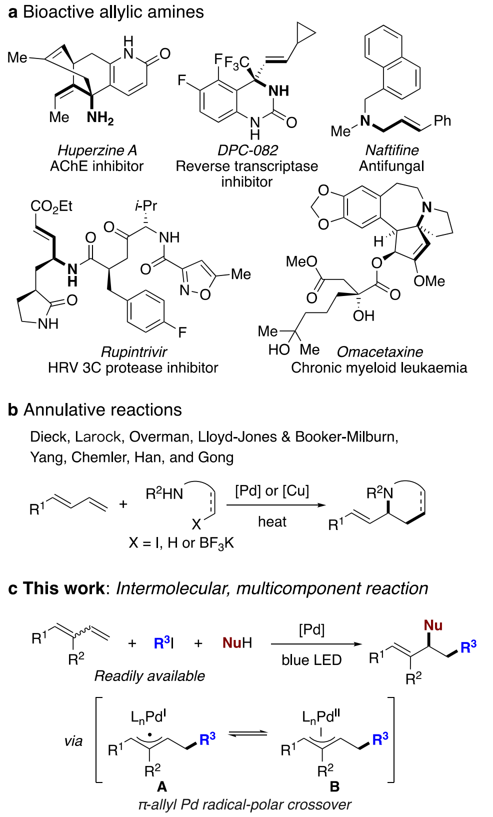
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A photoinduced palladium-catalyzed 1,2-carbofunctionalization of conjugated dienes has been developed. This mild modular approach, which does not require employment of exogeneous photosensitizers and external oxidants, allows for efficient and highly regio- and stereoselective synthesis of a broad range of allylic amines from readily available 1,3-dienes, alkyl iodides, and amines. Employment of O- and C-nucleophiles toward oxyalkylation and dialkylation products was also demonstrated. A putative π-allyl palladium radical-polar crossover path is proposed as a key event in this three-component coupling process. The utility of this protocol is highlighted by its application for derivatization of several amine-containing drugs.

1,3-Dienes are readily available versatile building blocks, which enjoy numerous applications in synthesis,[1] material science,[2] and medicinal chemistry.[3] Difunctionalization of 1,3-dienes enables rapid access to complex molecules in one step and is therefore highly sought after.[4] In particular, 1,2-carboamination of dienes represents an efficient synthetic route to allylic amines, which are valuable synthons,[5] as well as important motifs in bioactive molecules (Scheme 1a). However, only isolated examples have been reported to date, with the vast majority being two-component annulative reactions proceeding at elevated temperatures (Scheme 1b).[6] As a result, not only the choice of substrates but also the diversity of obtained products is limited. A multicomponent reaction (MCR) in which the carbon and nitrogen functionalities are introduced independently would therefore be an appealing method to address current limitations and allow for expedient synthesis of structurally diverse allylic amines. Herein, we report a light-induced palladium-catalyzed three-component coupling[7] of 1,3-dienes, alkyl iodides and amines that occurs under mild conditions (Scheme 1c). This transformation is proposed to involve a putative π-allyl hybrid palladium radical intermediate **A**. The latter, upon radical-polar crossover step, is converted into a "traditional" π-allyl palladium intermediate **B**,[8] which is then trapped with an amine to deliver the reaction products.

In recent years, the photoinduced palladium catalysis has become a highly emerging area of research.[9] It has been established by our group and others that hybrid palladium radical species can be generated via cleavage of C(sp^3)− and C(sp^2)−X (X = Cl, Br, I, CO_2NPhth, OTf) bonds in the presence of photoexcited palladium complexes. Formation of these species was crucial for achieving various processes, including remote desaturation,[10] alkyl Heck reactions,[11] and other transformations.[12] Keeping in mind a facile addition of hybrid alkyl radical palladium species across the double bond,[11] we envisioned that analogous addition at conjugated diene would also be feasible, thereby leading to a putative

Scheme 1. Background and Proposed 1,2-Carboamination of 1,3-Dienes



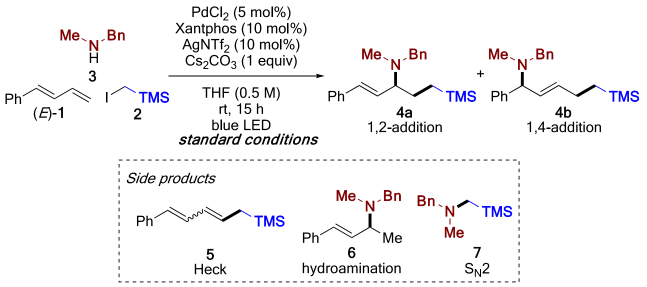
Received: April 12, 2020
Published: May 14, 2020

https://dx.doi.org/10.1021/jacs.0c03993

hybrid π-allyl palladium radical species **A** that would exist in equilibrium with the classical π-allyl complex **B**. The anticipated aminoalkylation product would be delivered upon nucleophilic attack by amine at the latter (Scheme 1c).

To this end, we commenced our study with examining the reaction of 1-phenylbutadiene (**1**), (trimethylsilyl)methyl iodide (**2**), and *N*-methylbenzylamine (**3**). Expectedly, the major challenge was to suppress the expected side reactions, including Heck reaction (**5**), hydroamination (**6**), and amine alkylation (**7**) processes. After extensive screening of reaction parameters,[13] we were delighted to obtain **4a** in 80% isolated yield (Table 1, entry 1). Similarly to our previous studies,[11a] the combination of Pd salt with Xantphos ligand proved to be the most efficient catalytic system. This reaction appeared to be insensitive to the stereochemistry of diene, as employment of a 1:1.2 mixture of (*E*)/(*Z*) isomers of **1** did not lead to a significant change of the yield (entry 2). Control experiments indicated that both visible light irradiation and palladium catalyst were necessary (entries 3, 4). Without silver triflimide (entry 5), the reaction was significantly less efficient due to the formation of substantial amounts of radical dimerization products (see Scheme 4b and discussion, therein). Likewise, the reaction efficiency was substantially lower in the absence of the base (entry 6). Employment of a bromo analog of **2** was much less efficient (24%), whereas the chloro counterpart did not react under these conditions at all.

Table 1. Optimization of Reaction Conditions[a]



Entry	Deviation from standard conditions	4:5:6:7[b]	Yield of 4a[c]
1	None	98:1:0.5:0.5	89% (80%)
2	(*E*)/(*Z*)-**1** (1:1.2)	96:1:1:2	83% (75%)
3	45 or 80 °C (dark)	8:0:0:92	Trace
4	Without $PdCl_2$	4:0:0:96	Trace
5	Without $AgNTf_2$	91:5:2:2	48%[d]
6	Without Cs_2CO_3	62:29:7:2	44%

[a] 0.2 mmol scale; (*E*)-**1**:**2**:**3** = 1:1.3:1.3. [b] Determined by GC/MS using pentadecane as internal standard; **4a**:**4b** > 20:1. [c] Determined by ^{1}H NMR using dibromomethane as internal standard; isolated yields given in parentheses. [d] Formation of substantial amounts of radical dimerization products was observed.

With the optimized conditions in hand, we examined the generality of this methodology (Table 2). First, the diene scope was tested. It was found that 1-aryl and hetaryl substituted dienes are all capable partners for this transformation. Thus, electron-rich dienes reacted smoothly to give the corresponding allyic amines in good yields (**8**−**12**). Notably, in the case of a phenol-containing moiety (**9**), the formation of a potential competing carboalkoxylation product was not observed, thus indicating high chemoselectivity of this reaction. Electron-deficient aryl groups were also tolerated, thus delivering the expected products in moderate to good yields (**13**−**15**). Alkyne and halide functionalities were also compatible with this transformation (**16**−**19**). Aminoalkylation of dienes possessing substituents at *meta*- and *ortho*-positions of the arene proceeded uneventfully producing the reaction products **20**−**24**. Ferrocenyl and heteroaryl groups were also amenable to this catalytic process, affording the corresponding products in moderate to good yields (**25**−**30**). Alkyl-substituted dienes were also reactive under these reaction conditions. Selective 1,2-addition was observed with a secondary alkyl substituent (**31**), whereas mixtures of 1,2- and 1,4-adducts were isolated for the primary counterparts (**32**−**33**), probably due to steric reasons. In addition, this MCR can be performed with trienes to obtain the corresponding dienamines **34**−**35**. A lower yield from diene ester (**36**) was obtained, presumably due to the electronic mismatch between the silylmethyl radical and electron-deficient diene ester. Importantly, 1,2-disubstituted butadiene also proved to be a viable substrate to produce trisubstituted alkenyl amine **37**. A higher catalyst loading, however, was required to achieve a reasonable yield for this substrate.

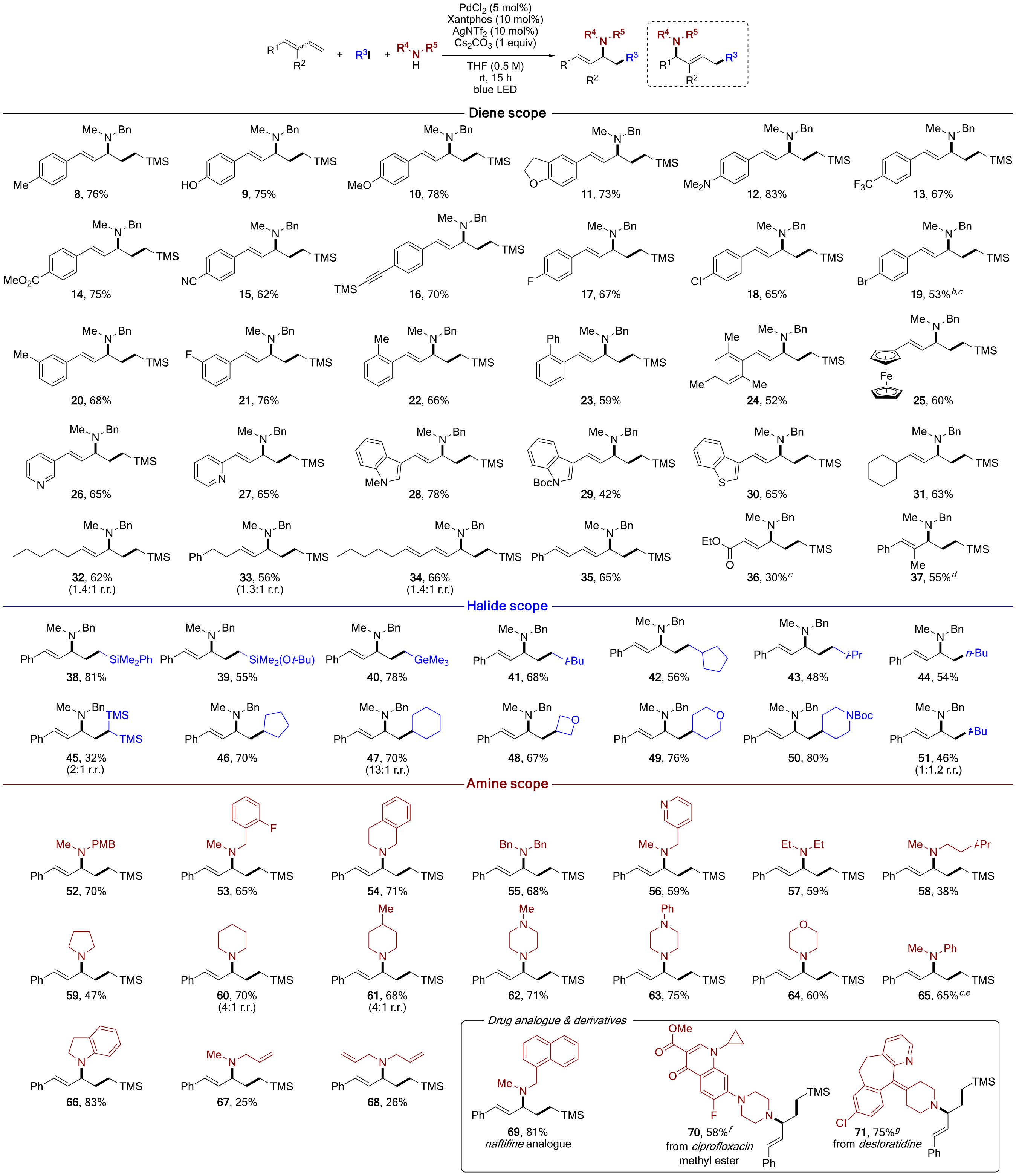
Next, the scope of alkyl iodides has been evaluated. Primary alkyl iodides bearing α-silyl or germyl substituents reacted efficiently to furnish the coupling products **38**−**40** in reasonable to good yields. Reactions employing primary alkyl iodides gave diminished yields (**41**−**44**), presumably due to the stronger C−I bond and thus lower reactivity,[14] as well as due to the competing alkylation reaction of the amine. In contrast, different secondary alkyl iodides reacted well producing the corresponding allylic amines **45**−**50** in good yields. Due to the steric reasons, employment of bulky *tert*-butyl iodide, however, produced a nearly equimolar mixture of 1,2- and 1,4-adducts (**51**). This reaction was found to be very general with the respect to the secondary amine used. Thus, benzylamines readily participated in this reaction, delivering the allylic amines **52**−**55** in moderate to good yields. An amine containing a picolyl moiety (**56**) was also found to be effective. Aliphatic acyclic amines also reacted, though with somewhat lower efficiency (**57**−**58**). Reactions with various amine heterocycles, including pyrrolidine, piperidine, piperazine, and morpholine, proceeded smoothly to furnish the target allylic amines in good yields (**59**−**64**), presumably due to higher nucleophilicity[15] in comparison to that of their acylic counterparts. Remarkably, reactions of less nucleophilic *N*-Me-aniline and indoline were successful, as well (**65**−**66**). Importantly, employment of allylic amines led to the corresponding di- and triallylamines, albeit in low yields (**67**−**68**). Notably, *N*-methyl-1-naphthyl amine underwent smooth reaction to give **69**, which represents an alkylated analogue of the drug naftifine. The scope of this transformation was also tested in a more complex setting. Hence, a secondary amine moiety of ciprofloxacin and desloratadine drugs was successfully converted into allylic amine functionality (**70**−**71**).

Importantly, 1,3-dienes containing substituents at C2 and/or C3 positions were also proven competent reaction partners. However, in these cases, 1,4-aminoalkylation products **73** and **75** were obtained selectively (Scheme 2).[16]

Moreover, the use of O- and C-nucleophiles, such as phenol (**76**) and malonate derivatives (**78**), respectively, led to the 1,2-carbofunctionalization products in reasonable yields (Scheme 3).

Naturally, we were eager to elucidate the mechanism of this novel transformation. We believe that under these reaction

Table 2. Scope of Three-Component 1,2-Carboamination of 1,3-Dienes[a]

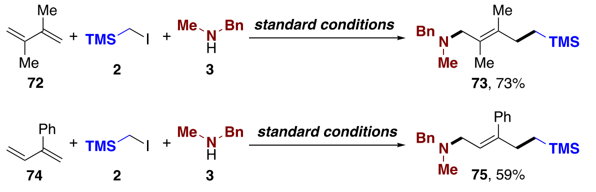


[a]0.4 mmol scale; isolated yields. [b]NMR yield. [c]0.2 mmol scale. [d]10 mol % $PdCl_2$, 20 mol % Xantphos and 20 mol % $AgNTf_2$ were used. [e]10 mol % $Pd(OAc)_2$, 20 mol % Xantphos and 20 mol % $AgNTf_2$ were used. [f]THF/MeOH = 1:1 (0.25 M). [g]THF/DCM = 2:1 (0.33 M).

conditions, an interplay between hybrid radical and ionic palladium intermediates takes place. The involvement of radical intermediates was unambiguously supported by the following experiments. Thus, initially formed alkyl radicals from alkyl iodide **2** were trapped by 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) in 22% yield (Scheme 4a, **80**[11a]). Next, the intermediacy of the allylic radicals was uncovered in the reaction performed without silver triflimide. In that case, the reaction produced a substantial amount of allylic radical dimerization[17] products **81** (Scheme 4b, Table 1,

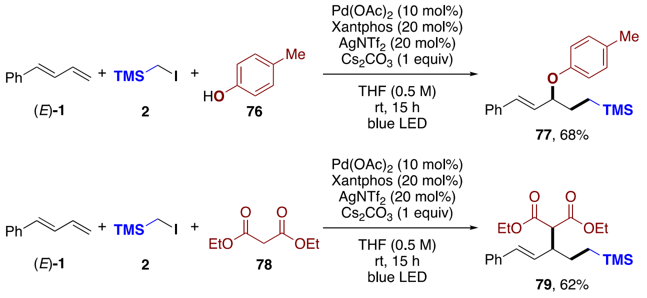
https://dx.doi.org/10.1021/jacs.0c03993
J. Am. Chem. Soc. 2020, 142, 9932−9937

Scheme 2. Examples of 1,4-Carboamination of 1,3-Dienes[a]



[a]0.4 mmol scale; isolated yields.

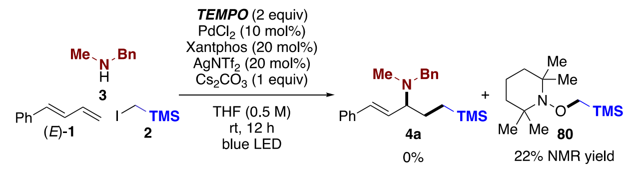
Scheme 3. Employment of O- and C-Nucleophiles[a]



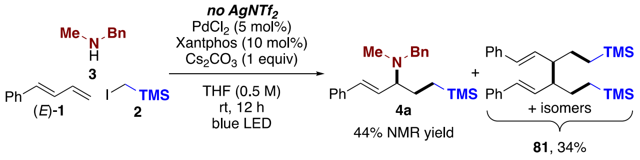
[a]0.2 mmol scale; isolated yields.

Scheme 4. Mechanistic Studies

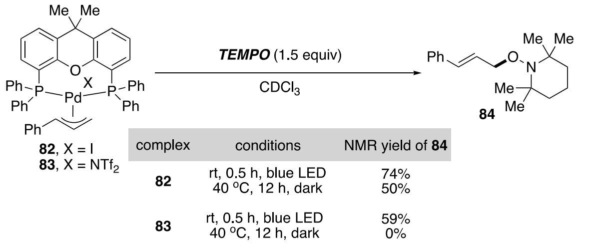
a Reaction in the presence of TEMPO



b Reaction without AgNTf$_2$



c Reactions of π-allyl Pd complexes with TEMPO

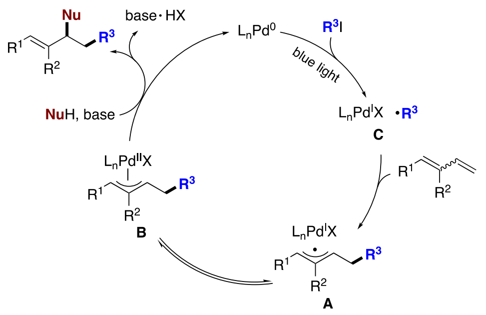


complex	conditions	NMR yield of 84
82	rt, 0.5 h, blue LED 40 °C, 12 h, dark	74% 50%
83	rt, 0.5 h, blue LED 40 °C, 12 h, dark	59% 0%

entry 5). A beneficial effect of accessing more electrophilic π-allyl palladium entities in reactions with nucleophiles by employing weakly coordinating anions is well documented.[18] Accordingly, we presumed that employment of triflimide would not only render the Pd-complex more electrophilic but also potentially shift the proposed equilibrium between π-allyl *radical*- and π-allyl *ionic* Pd entities to the right (cf. Scheme 1c, **A** ⇆ **B**). To validate this assumption, we synthesized model π-allyl palladium complexes bearing a Xantphos ligand[19] with iodide (**82**) and triflimide (**83**) counterions and subjected them to the reaction with TEMPO under blue light irradiation (Scheme 4c). In both cases,[20] the product of allyl radical trapping (**84**)[17c,21] was observed in good yields; however, the reaction of **83** occurred at a slower rate as compared to that of complex **82**.[13] Control experiments under the thermal conditions showed that the reaction of **82** with TEMPO still proceeded albeit much slower, while complex **83** was completely nonreactive under such conditions. These results support our hypothesis that a triflimide anion stabilizes the π-allyl Pd complex against homolysis upon irradiation with blue light or thermal conditions, thereby suppressing the undesired radical dimerization process.

Based on the results of the aforementioned studies, the following reaction mechanism is proposed (Scheme 5). First, photoexcited L$_n$Pd^0 undergoes a single electron transfer (SET) process with alkyl iodide to produce hybrid alkyl palladium radical species **C**,[11] which adds to the terminal position of diene to produce radical species **A** that exists in equilibrium with π-allyl complex **B**. In the presence of a triflimide anion, this equilibrium is shifted toward complex **B**. A subsequent attack of the amine at the latter delivers the carbofunctionalization product and regenerates the palladium catalyst.[22]

Scheme 5. Proposed Mechanism



In conclusion, the first visible-light-induced protocol for the intermolecular aminoalkylation, oxyalkylation, and dialkylation of 1,3-dienes has been developed. This mild multicomponent coupling reaction, which utilizes readily available reaction partners with broad functional group compatibility, does not require employment of exogeneous photosensitizers or external oxidants. It can be used for the late-stage derivatization of complex molecules and drugs. Preliminary mechanistic studies suggest that the radical-polar crossover path is crucial for the success of this reaction. It is expected that this modular, general, and mild method for synthesis of densely functionalized alkenes will find use in organic synthesis and drug discovery.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c03993.

Experimental procedures; analytical data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Vladimir Gevorgyan − *Department of Chemistry and Biochemistry, The University of Texas at Dallas, Richardson, Texas 75080-3021, United States;* orcid.org/0000-0002-7836-7596; Email: vlad@utdallas.edu

Authors

Kelvin Pak Shing Cheung − *Department of Chemistry and Biochemistry, The University of Texas at Dallas, Richardson, Texas 75080-3021, United States*

Daria Kurandina − *Department of Chemistry and Biochemistry, The University of Texas at Dallas, Richardson, Texas 75080-3021, United States*

Tetsuji Yata − *Department of Chemistry and Biochemistry, The University of Texas at Dallas, Richardson, Texas 75080-3021, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c03993

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Institutes of Health (GM120281), National Science Foundation (CHE-1936422), and Welch Foundation (Chair, AT-0041) for financial support.

■ REFERENCES

(1) (a) Büschleb, M.; Dorich, S.; Hanessian, S.; Tao, D.; Schenthal, K. B.; Overman, L. E. Synthetic Strategies toward Natural Products Containing Contiguous Stereogenic Quaternary Carbon Atoms. *Angew. Chem., Int. Ed.* **2016**, *55*, 4156−4186. (b) Holmes, M.; Schwartz, L. A.; Krische, M. J. Intermolecular Metal-Catalyzed Reductive Coupling of Dienes, Allenes, and Enynes with Carbonyl Compounds and Imines. *Chem. Rev.* **2018**, *118*, 6026−6052.

(2) (a) Valente, A.; Mortreux, A.; Visseaux, M.; Zinck, P. Coordinative Chain Transfer Polymerization. *Chem. Rev.* **2013**, *113*, 3836−3857. (b) Zaikov, G. E. Trends in Polymer Chemistry. In *Materials Chemistry: A Multidisciplinary Approach to Innovative Methods*; Friedrich, K., Zaikov, G. E.; Haghi, A. K., Eds.; CRS Press: Boca Raton, FL, 2016.

(3) (a) Paik, I. H.; Xie, S. J.; Shapiro, T. A.; Labonte, T.; Sarjeant, A. A. N.; Baege, A. C.; Posner, G. H. Second Generation, Orally Active, Antimalarial, Artemisinin-Derived Trioxane Dimers with High Stability, Efficacy, and Anticancer Activity. *J. Med. Chem.* **2006**, *49*, 2731−2734.

(4) For selected reviews on difunctionalization of 1,3-dienes, see: (a) Xiong, Y.; Sun, Y.; Zhang, G. Recent Advances on Catalytic Asymmetric Difunctionalization of 1,3-Dienes. *Tetrahedron Lett.* **2018**, *59*, 347−355. (b) Wu, X.; Gong, L.-Z. Palladium(0)-Catalyzed Difunctionalization of 1,3-Dienes: From Racemic to Enantioselective. *Synthesis* **2019**, *51*, 122−134.

(5) Skoda, E. M.; Davis, G. C.; Wipf, P. Allylic Amines as Key Building Blocks in the Synthesis of (*E*)-Alkene Peptide Isosteres. *Org. Process Res. Dev.* **2012**, *16*, 26−34.

(6) (a) O'Connor, J. M.; Stallman, B. J.; Clark, W. G.; Shu, A. Y. L.; Spada, R. E.; Stevenson, T. M.; Dieck, H. A. Some Aspects of Palladium-Catalyzed Reactions of Aryl and Vinylic Halides with Conjugated Dienes in the Presence of Mild Nucleophiles. *J. Org. Chem.* **1983**, *48*, 807−809. (b) Larock, R. C.; Berrios-Peña, N.; Narayanan, K. Palladium-Catalyzed Heteroannulation of 1,3-Dienes by Functionally Substituted Aryl Halides. *J. Org. Chem.* **1990**, *55*, 3447−3450. (c) Overman, L. E.; Rosen, M. D. Total Synthesis of (−)-Spirotryprostatin B and Three Stereoisomers. *Angew. Chem., Int. Ed.* **2000**, *39*, 4596−4599. (d) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. Distinct Reactivity of Pd(OTs)$_2$: The Intermolecular Pd(II)-Catalyzed 1,2-Carboamination of Dienes. *J. Am. Chem. Soc.* **2008**, *130*, 10066−10067. (e) Xing, D.; Yang, D. Pd(II)-Catalyzed Intramolecular 1,2-Aminoalkylation of Conjugated 1,3-Dienes for the Synthesis of Pyrrolizidines. *Org. Lett.* **2013**, *15*, 4370−4373. (f) Um, C.; Chemler, S. R. Synthesis of 2-Aryl and 2-Vinylpyrrolidines via Copper-Catalyzed Coupling of Styrenes and Dienes with Potassium β-Aminoethyl Trifluoroborates. *Org. Lett.* **2016**, *18*, 2515−2518. (g) Chen, S.-S.; Meng, J.; Li, Y.-H.; Han, Z.-Y. Palladium-Catalyzed Enantioselective Heteroannulation of 1,3-Dienes by Functionally Substituted Aryl Iodides. *J. Org. Chem.* **2016**, *81*, 9402−9408. (h) Chen, S.-S.; Wu, M.-S.; Han, Z.-Y. Palladium-Catalyzed Cascade sp^2 C−H Functionalization/Intramolecular Asymmetric Allylation: From Aryl Ureas and 1,3-Dienes to Chiral Indolines. *Angew. Chem., Int. Ed.* **2017**, *56*, 6641−6645. (i) Zhang, T.; Shen, H.-C.; Xu, J.-C.; Fan, T.; Han, Z.-Y.; Gong, L.-Z. Pd(II)-Catalyzed Asymmetric Oxidative Annulation of *N*-Alkoxyheteroaryl Amides and 1,3-Dienes. *Org. Lett.* **2019**, *21*, 2048−2051. For an example of non-annulative aminomethylamination reaction, see: (j) Liu, Y.; Xie, Y.; Wang, H.; Huang, H. Enantioselective Aminomethylamination of Conjugated Dienes with Aminals Enabled by Chiral Palladium Complex-Catalyzed C−N Bond Activation. *J. Am. Chem. Soc.* **2016**, *138*, 4314−4317. When this manuscript was under original submission, a related work on light-induced two-component aminoalkylation of dienes has been published: (k) Huang, H.-M.; Koy, M.; Serrano, E.; Pflüger, P. M.; Schwarz, J. L.; Glorius, F. Catalytic Radical Generation of π-Allylpalladium Complexes. *Nat. Catal.* **2020**, *3*, 393−400.

(7) For recent examples on radical-triggered three-component coupling reactions, see: (a) Gockel, S. N.; Buchanan, T. L.; Hull, K. L. Cu-Catalyzed Three-Component Carboamination of Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 58−61. (b) Buquoi, J. Q.; Lear, J. M.; Gu, X.; Nagib, D. A. Heteroarene Phosphinylalkylation via a Catalytic, Polarity-Reversing Radical Cascade. *ACS Catal.* **2019**, *9*, 5330−5335. (c) Lear, J. M.; Buquoi, J. Q.; Gu, X.; Pan, K.; Mustafa, D. N.; Nagib, D. A. Multi-Component Heteroarene Couplings via Polarity-Reversed Radical Cascades. *Chem. Commun.* **2019**, *55*, 8820−8823.

(8) For reactions involving addition of alkyl radicals to π-allyl Pd(II) species, see: (a) Lang, S. B.; O'Nele, K. M.; Tunge, J. A. Decarboxylative Allylation of Amino Alkanoic Acids and Esters via Dual Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 13606−13609. (b) Lang, S. B.; O'Nele, K. M.; Douglas, J. T.; Tunge, J. A. Dual Catalytic Decarboxylative Allylations of α-Amino Acids and Their Divergent Mechanisms. *Chem. - Eur. J.* **2015**, *21*, 18589−18593.

(9) For reviews, see: (a) Chuentragool, P.; Kurandina, D.; Gevorgyan, V. Catalysis by Visible Light Photoexcited Palladium Complexes. *Angew. Chem., Int. Ed.* **2019**, *58*, 11586−11598. (b) Kurandina, D.; Chuentragool, P.; Gevorgyan, V. Transition-Metal-Catalyzed Alkyl Heck-Type Reactions. *Synthesis* **2019**, *51*, 985−1005. (c) Kancherla, R.; Muralirajan, K.; Sagadevan, A.; Rueping, M. Visible Light-Induced Excited-State Transition-Metal Catalysis. *Trends Chem.* **2019**, *1*, 510−523. (d) Zhou, W.-J.; Cao, G.-M.; Zhang, Z.-P.; Yu, D.-G. Visible Light-Induced Palladium-Catalysis in Organic Synthesis. *Chem. Lett.* **2019**, *48*, 181−191.

(10) (a) Parasram, M.; Chuentragool, P.; Sarkar, D.; Gevorgyan, V. Photoinduced Formation of Hybrid Aryl Pd-Radical Species Capable of 1,5-HAT: Selective Catalytic Oxidation of Silyl Ethers into Silyl Enol Ethers. *J. Am. Chem. Soc.* **2016**, *138*, 6340−6343. (b) Parasram, M.; Chuentragool, P.; Wang, Y.; Shi, Y.; Gevorgyan, V. General, Auxiliary-Enabled Photoinduced Pd-Catalyzed Remote Desaturation of Aliphatic Alcohols. *J. Am. Chem. Soc.* **2017**, *139*, 14857−14860. (c) Chuentragool, P.; Parasram, M.; Shi, Y.; Gevorgyan, V. General, Mild, and Selective Method for Desaturation of Aliphatic Amines. *J. Am. Chem. Soc.* **2018**, *140*, 2465−2468.

(11) (a) Kurandina, D.; Parasram, M.; Gevorgyan, V. Visible Light-Induced Room-Temperature Heck Reaction of Functionalized Alkyl Halides with Vinyl Arenes/Heteroarenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 14212−14216. (b) Wang, G.-Z.; Shang, R.; Cheng, W.-M.; Fu, Y. Irradiation-Induced Heck Reaction of Unactivated Alkyl Halides at Room Temperature. *J. Am. Chem. Soc.* **2017**, *139*, 18307−18312. (c) Kurandina, D.; Rivas, M.; Radzhabov, M.; Gevorgyan, V. Heck Reaction of Electronically Diverse Tertiary Alkyl Halides. *Org. Lett.* **2018**, *20*, 357−360. (d) Wang, G.-Z.; Shang, R.; Fu, Y. Irradiation-Induced Palladium-Catalyzed Decarboxylative Heck Reaction of Aliphatic *N*-(Acyloxy)phthalimides at Room Temperature. *Org. Lett.* **2018**, *20*, 888−891. (e) Koy, M.; Sandfort, F.; Tlahuext-Aca, A.;

Quach, L.; Daniliuc, C. G.; Glorius, F. Palladium-Catalyzed Decarboxylative Heck-Type Coupling of Activated Aliphatic Carboxylic Acids Enabled by Visible Light. *Chem. - Eur. J.* **2018**, *24*, 4552−4555. (f) Kancherla, R.; Muralirajan, K.; Maity, B.; Zhu, C.; Krach, P. E.; Cavallo, L.; Rueping, M. Oxidative Addition to Palladium(0) Made Easy through Photoexcited-State Metal Catalysis: Experiment and Computation. *Angew. Chem., Int. Ed.* **2019**, *58*, 3412−3416. (g) Chuentragool, P.; Yadagiri, D.; Morita, T.; Sarkar, S.; Parasram, M.; Wang, Y.; Gevorgyan, V. Aliphatic Radical Relay Heck Reaction at Unactivated C(sp^3)−H Sites of Alcohols. *Angew. Chem., Int. Ed.* **2019**, *58*, 1794−1798.

(12) For selected examples, see: (a) Zhou, W.-J.; Cao, G.-M.; Shen, G.; Zhu, X.-Y.; Gui, Y.-Y.; Ye, J.-H.; Sun, L.; Liao, L.-L.; Li, J.; Yu, D.-G. Visible-Light-Driven Palladium-Catalyzed Radical Alkylation of C−H Bonds with Unactivated Alkyl Bromides. *Angew. Chem., Int. Ed.* **2017**, *56*, 15683−15687. (b) Ratushnyy, M.; Parasram, M.; Wang, Y.; Gevorgyan, V. Pd-Catalyzed Atom Transfer Radical Cyclization at Remote Unactivated C(sp^3)-H Sites Enabled by Hydrogen Atom Transfer of Hybrid Vinyl Pd-Radical Intermediates. *Angew. Chem., Int. Ed.* **2018**, *57*, 2712−2715. (c) Wang, G.-Z.; Shang, R.; Fu, Y. Irradiation-Induced Palladium-Catalyzed Direct C−H Alkylation of Heteroarenes with Tertiary and Secondary Alkyl Bromides. *Synthesis* **2018**, *50*, 2908−2914. (d) Cheng, W.-M.; Shang, R.; Fu, Y. Irradiation-Induced Palladium-Catalyzed Decarboxylative Desaturation Enabled by a Dual Ligand System. *Nat. Commun.* **2018**, *9*, 5215. (e) Koy, M.; Bellotti, P.; Katzenburg, F.; Daniliuc, C. G.; Glorius, F. Synthesis of All-Carbon Quaternary Centers by Palladium-Catalyzed Olefin Dicarbofunctionalization. *Angew. Chem., Int. Ed.* **2020**, *59*, 2375−2379. (f) Ratushnyy, M.; Kvasovs, N.; Sarkar, S.; Gevorgyan, V. Visible Light-Induced Palladium-Catalyzed Generation of Aryl Radicals from Aryl Triflates. *Angew. Chem., Int. Ed.* **2020**, DOI: 10.1002/anie.201915962.

(13) See Supporting Information for details.

(14) For some reductive potential of activated and inactivated primary alkyl halides, see: Isse, A. A.; Lin, C. Y.; Coote, M. L.; Gennaro, A. Estimation of Standard Reduction Potentials of Halogen Atoms and Alkyl Halides. *J. Phys. Chem. B* **2011**, *115*, 678−684.

(15) Kanzian, T.; Nigst, T. A.; Maier, A.; Pichl, S.; Mayr, H. Nucleophilic Reactivities of Primary and Secondary Amines in Acetonitrile. *Eur. J. Org. Chem.* **2009**, *2009*, 6379−6385.

(16) For a recent example of rhodium-catalyzed 1,4-carboamination, see: Pinkert, T.; Wegner, T.; Mondal, S.; Glorius, F. Intermolecular 1,4-Carboamination of Conjugated Dienes Enabled by Cp*Rh^{III}-Catalyzed C−H Activation. *Angew. Chem., Int. Ed.* **2019**, *58*, 15041−15045.

(17) For examples of dimerization of allyl radicals, see: (a) Sasaoka, S.; Yamamoto, T.; Kinoshita, H.; Inomata, K.; Kotake, H. Palladium-Catalyzed Coupling of Allylic Acetates with Zinc. *Chem. Lett.* **1985**, *14*, 315−318. (b) Millan, A.; Campana, A. G.; Bazdi, B.; Miguel, D.; Alvarez de Cienfuegos, L.; Echavarren, A. M.; Cuerva, J. M. Ti/Pd Bimetallic Systems for the Efficient Allylation of Carbonyl Compounds and Homocoupling Reactions. *Chem. - Eur. J.* **2011**, *17*, 3985−3994. (c) Xuan, J.; Zeng, T.-T.; Feng, Z.-J.; Deng, Q.-H.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J.; Alper, H. Redox-Neutral α-Allylation of Amines by Combining Palladium Catalysis and Visible-Light Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2015**, *54*, 1625−1628. For other Pd-catalyzed reactions of allyl radicals, see: (d) Campana, A. G.; Bazdi, B.; Fuentes, N.; Robles, R.; Cuerva, J. M.; Oltra, J. E.; Porcel, S.; Echavarren, A. M. Divergent Titanium-mediated Allylations with Modulation by Nickel or Palladium. *Angew. Chem., Int. Ed.* **2008**, *47*, 7515−7519. (e) Millan, A.; Martin-Lasanta, A.; Miguel, D.; Alvarez de Cienfuegos, L.; Cuerva, J. M. Ti/Pd-Promoted Intramolecular Michael-type Addition of Allylic Carboxylates to Activated Alkenes. *Chem. Commun.* **2011**, *47*, 10470−10472.

(18) (a) Åkermark, B.; Åkermark, G.; Hegedus, L. S.; Zetterberg, K. Amination of π-Allylpalladium Chloride Complexes. A Mechanistic Study. *J. Am. Chem. Soc.* **1981**, *103*, 3037−3040. (b) Cantat, T.; Genin, E.; Giroud, C.; Meyer, G.; Jutand, A. Structural and Kinetic Effects of Chloride Ions in the Palladium-Catalyzed Allylic Substitutions. *J. Organomet. Chem.* **2003**, *687*, 365−376. (c) Pratihar, S.; Marek, J.; Roy, S. Mono Cationic Palladium(II): Synthesis, Characterization and Catalytic Activity in Suzuki Coupling. *Inorg. Chim. Acta* **2011**, *372*, 362−366. (d) Cadu, A.; Tšupova, S.; Hashmi, A. S. K. Silver Triflimide. In *Encyclopedia of Reagents for Organic Synthesis*; Charette, A., Bode, J., Rovis, T., Shenvi, R., Eds.; John Wiley & Sons, Ltd.

(19) Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. A Highly Active Palladium Catalyst for Intermolecular Hydroamination. Factors that Control Reactivity and Additions of Functionalized Anilines to Dienes and Vinylarenes. *J. Am. Chem. Soc.* **2006**, *128*, 1828−1839.

(20) For examples of reactions of π-allyl palladium complexes under UVA light, see: (a) Muzart, J.; Pale, P.; Pete, J.-P. Preparation of Conjugated Carbonyl Compounds by Photolysis of η^3-Allylpalladium Complexes. *J. Chem. Soc., Chem. Commun.* **1981**, *0*, 668−669. (b) Vermeersch, G.; Marko, J. Photoreactivity of η^3-Allylpalladium Complexes Studied by CIDNP. *J. Chem. Soc., Perkin Trans. 2* **1986**, 383−389. (c) Crozet, M. P.; Muzart, J.; Pale, P.; Tordo, P. Photolyse des Complexes η^3−Allylpalladium: Étude Par Résonnance Paramagnétique Électronique des Nitroxydes Allyliques Formés en Présence de Nitrosodurène. *J. Organomet. Chem.* **1983**, *244*, 191−200.

(21) For examples of trapping cinnamyl radicals with TEMPO, see: (a) Song, F.; Wang, F.; Guo, L.; Feng, X.; Zhang, Y.; Chu, L. Visible-Light-Enabled Stereodivergent Synthesis of *E*- and *Z*- Configured 1,4-Dienes by Photoredox/Nickel Dual Catalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 177−181. (b) Yasu, Y.; Koike, T.; Akita, M. Visible Light-Induced Selective Generation of Radicals from Organoborates by Photoredox Catalysis. *Adv. Synth. Catal.* **2012**, *354*, 3414−3420. (c) Xu, B.; Troian-Gautier, L.; Dykstra, R.; Martin, R.; Gutierrez, O.; Tambar, U. K. Photocatalyzed Diastereoselective Isomerization of Cinnamyl Chlorides to Cyclopropanes. *J. Am. Chem. Soc.* **2020**, *142*, 6206−6215.

(22) Although generation of alkyl radicals by light irradiation of EDA complexes of alkyl halides with amines is known, the possibility of such a metal-free scenario for this transformation was ruled out based on the fact that the reaction did not proceed in the absence of a palladium catalyst (Table 1, entry 4). For light-induced radical generation from EDA complexes, see: (a) Sun, X.; Wang, W.; Li, Y.; Ma, J.; Yu, S. Halogen-Bond-Promoted Double Radical Isocyanide Insertion under Visible-Light Irradiation: Synthesis of 2-Fluoroalkylated Quinoxalines. *Org. Lett.* **2016**, *18*, 4638−4641. (b) Wang, Y.; Wang, J.; Li, G.-X.; He, G.; Chen, G. Halogen-Bond-Promoted Photoactivation of Perfluoroalkyl Iodides: A Photochemical Protocol for Perfluoroalkylation Reactions. *Org. Lett.* **2017**, *19*, 1442−1445. (c) Tang, X.; Studer, A. Alkene 1,2-Difunctionalization by Radical Alkenyl Migration. *Angew. Chem., Int. Ed.* **2018**, *57*, 814−817. (d) Herraiz, A. G.; Suero, M. G. A Transition-Metal-Free & Diazo-Free Styrene Cyclopropanation. *Chem. Sci.* **2019**, *10*, 9374−9379.