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Palladium Hydride-Enabled Hydroalkenylation of Strained Molecules

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Cite This: J. Am. Chem. Soc. 2022, 144, 20875−20883
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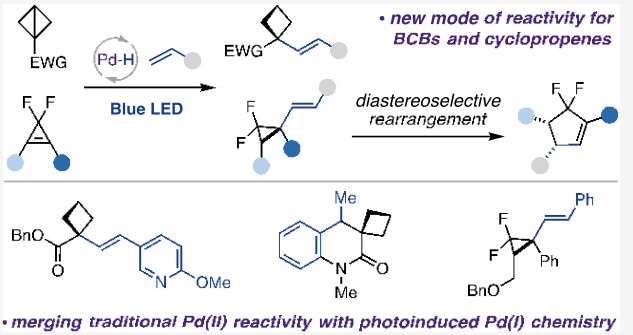
ABSTRACT: We report the first palladium hydride enabled hydroalkenylation of strained molecules. This new mild protocol proceeds via a regio- and chemoselective hydropalladation step, followed by a photoinduced radical alkyl Heck reaction. This methodology represents a new reactivity mode for strained molecules and opens new avenues for photoinduced palladium catalysis. The reaction is compatible with a wide range of functional groups and can be applied to complex structures, delivering a diverse array of highly valuable and modifiable alkenylated cyclobutanes and cyclopropanes. A hydroalkenylation/diastereoselective rearrangement cascade toward a cyclopentene scaffold has also been demonstrated.



1. INTRODUCTION

In recent years, 3- and 4-membered strained carbocycles have attracted significant attention in synthesis[1] and bioconjugation.[2] They serve as unusual bioisosteres[3] in the development of pharmaceuticals,[4] owing to their unique chemical and physical properties. One appealing and atom economical approach toward these molecules is from precursors with even higher energies, thus harnessing a thermodynamically favored strain-release process[5] (Scheme 1A). Among these, bicyclo[1.1.0]butanes (BCBs) A and cyclopropenes B display remarkable ring strain,[6] which enable them to undergo transformations that are challenging or unfeasible for non-strained ring systems. A particularly attractive strategy toward incorporation of small ring systems in organic molecules is a C−C bond formation between strained carbocycles and alkenes. Along this line, Gryko and co-workers disclosed an elegant Co-catalyzed addition of BCBs to a wide range of Michael acceptors. This transformation proceeds via the generation of alkyl radical intermediates, which upon Giese-type addition deliver disubstituted cyclobutanes C (Scheme 1B).[5i] In addition, the groups of Glorius, Brown, and Procter independently reported eficient [2 + 2] cycloaddition of BCBs with alkenes enabled by thioxanthone (TXT)-photosensitized energy transfer[5j,k] or SmI_2-catalysis,[5l] thus delivering bicyclo[2.1.1]hexanes D. Due to the inherent nature of these catalytic systems, however, all these transformations offer access to reduced products C or D, and thus a valuable and modifiable alkene moiety is sacrificed. Accordingly, the development of a new protocol that would preserve synthetically important olefin functionality is highly desirable. Likewise, it would be extremely appealing to develop the analogous alkenylation method for a cyclopropene core, which is another ideal candidate for strain-release transformations.[1b,7]

Herein, we report the first palladium hydride enabled hydroalkenylation approach of strained molecules, BCBs and cyclopropenes, with vinyl arenes and heteroarenes, which proceeds via a sequential regio- and chemoselective hydropalladation of strained C−C bonds, followed by a photoinduced generation of hybrid palladium C(sp^3)-centered radicals, and a Heck-type coupling reaction (Scheme 1C). Furthermore, this report also outlines our preliminary findings on diastereoselective rearrangement of vinyl cyclopropanes into cyclopentenes.

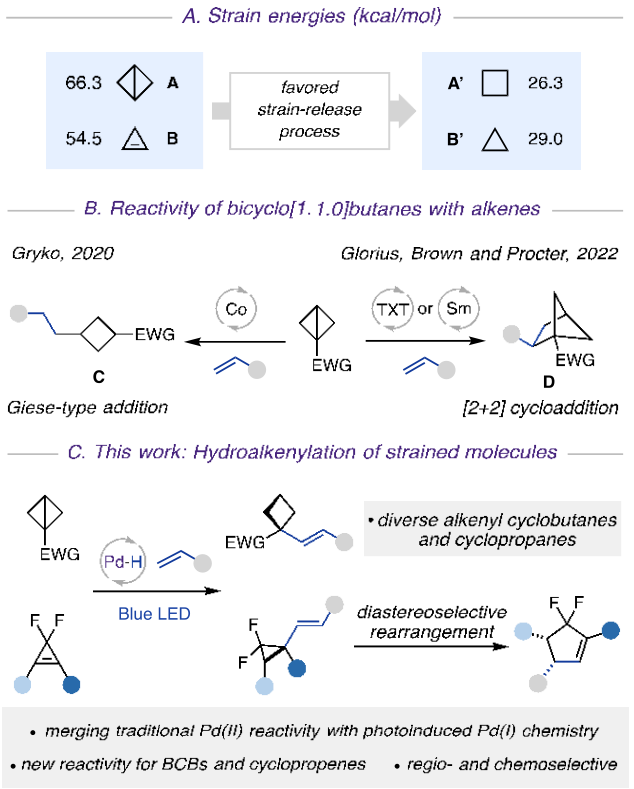
2. REACTION DESIGN

To achieve alkenylation of small rings, we sought a palladium catalysis known for its facile oxidative end-game.[8] Recently, photoinduced palladium catalysis has become an emerging field of study.[9] We and others have established mild and eficient generation of carbon-centered radicals from (pseudo) halides or redox-active esters via single electron transfer (SET) from photoexcited Pd^0 catalysts. Apparently, such an activation mode is not applicable to BCBs and cyclopropenes. Hence, we searched for generation of radicals from strained molecules via an alternative Pd-catalyzed strategy. In our recently developed method for a photoinduced Pd-catalyzed Heck reaction of

Received: August 24, 2022
Published: October 31, 2022

https://doi.org/10.1021/jacs.2c09045
J. Am. Chem. Soc. 2022, 144, 20875−20883

Scheme 1. Reactivity of Strained Molecules with Alkenes[a]

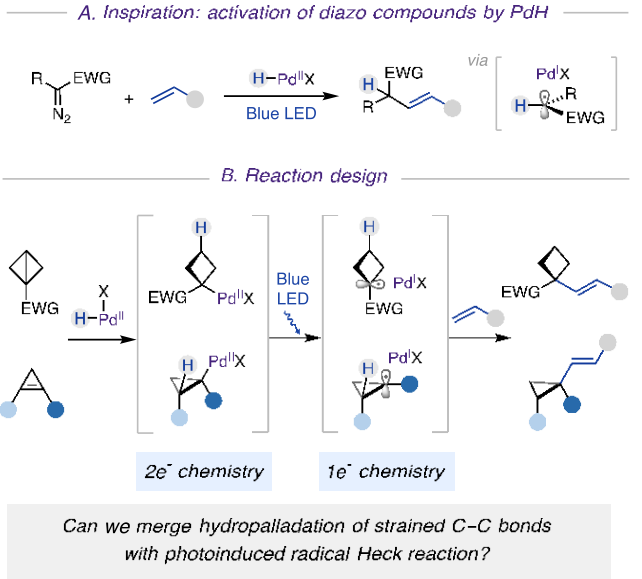


[a](A) Strained energies (kcal/mol). (B) The reactivity of bicyclo[1.1.0] butanes with alkenes. (C) This work: hydroalkenylation of strained molecules.

diazo compounds,[10] we suggested that the generation of alkyl radicals may proceed through a denitrogenative reaction between palladium hydride (PdH) and a diazo compound (Scheme 2A). Accordingly, we hypothesized that the desired cycloalkyl radicals could be accessed from highly reactive strained molecules with the aid of putative PdH species.

We envisioned achieving hydroalkenylation of strained molecules with alkenes via the design plan depicted in Scheme 2B, which combines traditional Pd(II) reactivity with photoinduced Pd(I) chemistry. Since two types of (pseudo) alkene substrates would be involved in the reaction, they must be differentiated in order to achieve the desired coupling reaction. As a design principle, we recognized that a π-like central C−C bond of BCBs or a strained double bond of cyclopropenes should be more reactive toward hydropalladation with PdH compared to that of its nonstrained counterpart. Therefore, the *in situ* generated PdH species is expected to add onto strained molecules in a chemoselective manner. The resulting alkyl Pd(II) complex, upon visible-light-induced homolysis of the Pd−C bond, would then generate hybrid Pd(I) cyclobutyl or cyclopropyl radical species. The capture of these key intermediates with an alkene and a successive facile β-H elimination would lead to the formation of aimed vinylcyclobutane and vinylcyclopropane products. If successful, this approach would represent a new reaction profile of the photoinduced Pd 0/I/II manifold, by introducing a hydropalladation process and encompassing a new class of substrates. Moreover, the ability to directly couple strained molecules with easily accessible alkenes would facilitate a practical synthesis of small rings with valuable alkenyl functionality.[11]

Scheme 2. Viability of Photoinduced Palladium Hydride Catalytic System[a]



[a](A) Inspiration: activation of diazo compounds with PdH. (B) Reaction design.

3. RESULTS AND DISCUSSION

3.1. Reaction Optimization. We commenced our studies with examining a model reaction between *gem*-difluorocyclopropene[12] 1a and styrene 2a under standard visible light/Pd conditions (Table 1). Consistently with our previous studies,[10,13] the combination of $Pd(OAc)_2$ and bidentate Xantphos proved to be the most eficient catalytic system. An extensive evaluation[14] of monodentate additive ligand[10,13e,15] indicated $P(2\text{-Furyl})_3$ as a superior ligand. Evidently, we recognized the need for additives to promote the *in situ* generation of PdH species. Therefore, in contrast to the previously developed basic conditions for photoinduced Heck reactions,[10,13,16] we introduced an acidic environment, where acetic acid was identified as the key beneficial hydrogen donor, operating with dimethylphenylsilane as a hydride codonor. It was also found that employment of tetrabutylammonium bromide (TBAB), an exogenous halide counterion source, was crucial for further improvement of the reaction eficiency.[17] Gratifyingly, under these conditions, the desired hydroalkenylation product 3a was formed in 80% yield (condition A, entry 1). Reaction was less eficient in the absence of hydrosilane (entry 2). Reactions with other bidentate phosphines failed to provide any product (entries 3 and 4). Control experiments demonstrated that both Pd catalyst and HX precursors were essential for this transformation (entries 5, 6). Likewise, thermal reactions under dark conditions did not lead to any product (entry 7).

Motivated by the successful employment of cyclopropenes in the hydroalkenylation reaction, we then turned our attention to BCBs. After re-evaluation of initial reaction parameters,[14] we found modified conditions, which allowed hydroalkenylation reaction of BCB 4a with styrene 2a to be eficiently performed (condition B, entry 8). Employment of substochiometric amounts of hydrosilane hampered the reaction

https://doi.org/10.1021/jacs.2c09045
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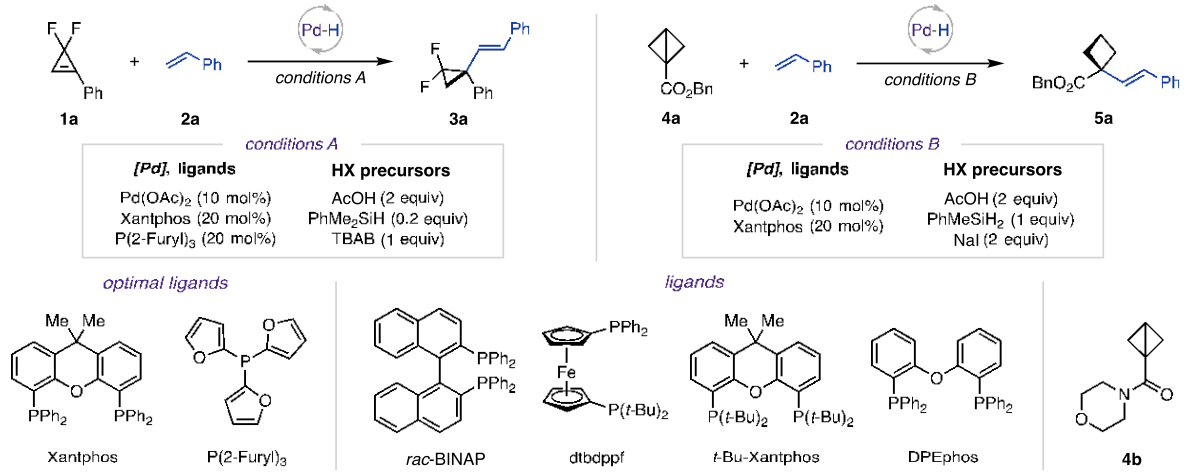
Table 1. Reaction Optimization and Control Experiments[a]



entry	deviation from *conditions A*	yield of **3a** (%)[b]
1	none	80[c]
2	Without $PhMe_2SiH$	64
3	dtbdppf instead of Xantphos	0
4	*rac*-BINAP instead of Xantphos	0
5	Without $Pd(OAc)_2$	0
6	Without AcOH, $PhMe_2SiH$, and TBAB	traces
7	Without light (rt, 40 °C or 100 °C)	0

entry	deviation from *conditions B*	yield of **5a** (%)[b]
8	none	68
9	$PhMeSiH_2$ (0.2 equiv)	40
10	*t*-Bu-Xantphos instead of Xantphos	0
11	DPEphos instead of Xantphos	47
12	40 °C, no light instead of blue LED	75
13	**4b** instead of **4a**	48
14	**4b**, 40 °C, no light	0

[a]0.1 mmol scale; 1a:2a = 1:2. 4a:2a = 1:2. Conditions A: $Pd(OAc)_2$ (10 mol %), Xantphos (20 mol %), $P(2\text{-Furyl})_3$ (20 mol %), acetic acid (2 equiv), $PhMe_2SiH$ (0.2 equiv), TBAB (1 equiv), 1,4-dioxane (0.15 M), blue LED (40 W, 427 nm), 16 h. Conditions B: $Pd(OAc)_2$ (10 mol %), Xantphos (20 mol %), acetic acid (2 equiv), $PhMeSiH_2$ (1 equiv), NaI (2 equiv), DCE (0.15 M), blue LED (40 W, 427 nm), 16 h. [b]Yields were determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. [c]0.15 mmol scale, isolated yields.

performance (entry 9). Similarly to the reactions with cyclopropenes, employment of other bidentate phosphine ligands resulted in diminished yields (entries 10, 11). Lastly, control experiments revealed that certain BCB substrates, such as strained ester 4a, engaged in the reaction in the absence of light[13b] (entry 12), whereas amide 4b was completely unreactive under such conditions (entries 13, 14).

3.2. Substrate Scope. With the optimized conditions in hand, the scope of strained molecules in reactions with styrene and derivatives was examined first (Table 2). It was found that *gem*-difluorocyclopropenes possessing different aryl substituents (3b and 3c) are all capable partners. Moreover, 1,2-disubstituted *gem*-difluorocyclopropenes proved to be viable substrates, delivering hydroalkenylation products 3d−3g with good diastereoselectivity. Notably, 3d was obtained with excellent regiocontrol.[18] Likewise, various BCBs, including ester 4a, amide 4b, and nitrile 4c, were competent radical precursors. This reaction can also be performed in an intramolecular fashion. Thus, 6-*exo*-*trig* cyclization of 4d furnished an interesting spiro-cyclobutyl benzolactam 5g in reasonable yield.

Next, the generality of alkenes was evaluated. Various *para*-substituted styrenes, including methyl, methoxy, fluoro, boronic ester, amine, and thioether groups, reacted smoothly to provide the corresponding products 3h−3m in moderate to good yields. Analogously, *meta*- and *ortho*-substituted styrenes furnished vinyl difluorocyclopropane 3n−3q in reasonable yields. Disubstituted substrates also showed good reactivity (3r and 3s). Hydroalkenylation reaction with vinyl heteroarenes proceeded uneventfully, producing targeted vinyl difluorocyclopropanes possessing dihydrobenzofuran (3t), benzodioxole (3u), pyridine (3v), pyrimidine (3w), and indole (3x) rings. Notably, indene (3y), as well as α-substituted alkenes (3z−3ab), reacted well in this hydroalkenylation process. In addition, TBS-enol ether was proven to be a capable coupling partner, affording cyclopropyl silyl enol ether 3ac. Finally, the reaction of 1a with a vinyl derivative of ferrocene and estrone generated product 3ad and 3ae, highlighting the applicability of this photoinduced hydroalkenylation protocol in a complex setting. While all reactions were run until full conversion of substrates, in some cases, formation of notable amounts of the reduced cyclopropane side products was observed.

Interestingly, during the investigation of the cyclopropene scope, we discovered a hydroalkenylation/diastereoselective rearrangement cascade toward the difluorocyclopentene scaffold (Table 3). Preliminary study of the scope of this transformation indicated that *gem*-difluorocyclopropenes possessing two phenyl groups at C1, 2 (1b) or phenyl and thioether substituent (1c) underwent hydroalkenylation reaction with alkenes 2, followed by a facile ring-expansion cycloisomerization to produce cyclopentenes 6. Using this strategy, tricyclic products 6c and 6e were smoothly obtained from indene. Notably, this rearrangement is highly diastereoselective, producing *cis*-substituted cyclopentenes exclusively.

3.3. Scalability and Diverse Transformations. The developed hydroalkenylation platform proved to be easily scalable. Thus, reaction on a 1 mmol scale was performed

https://doi.org/10.1021/jacs.2c09045
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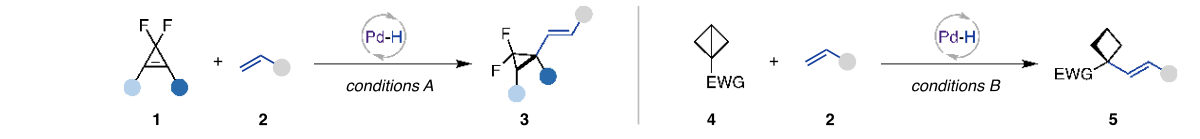
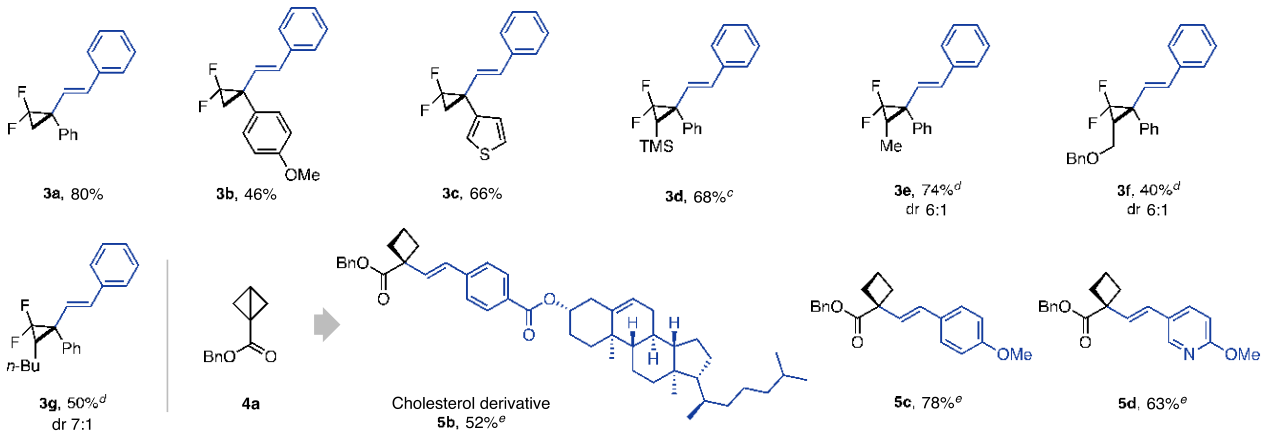
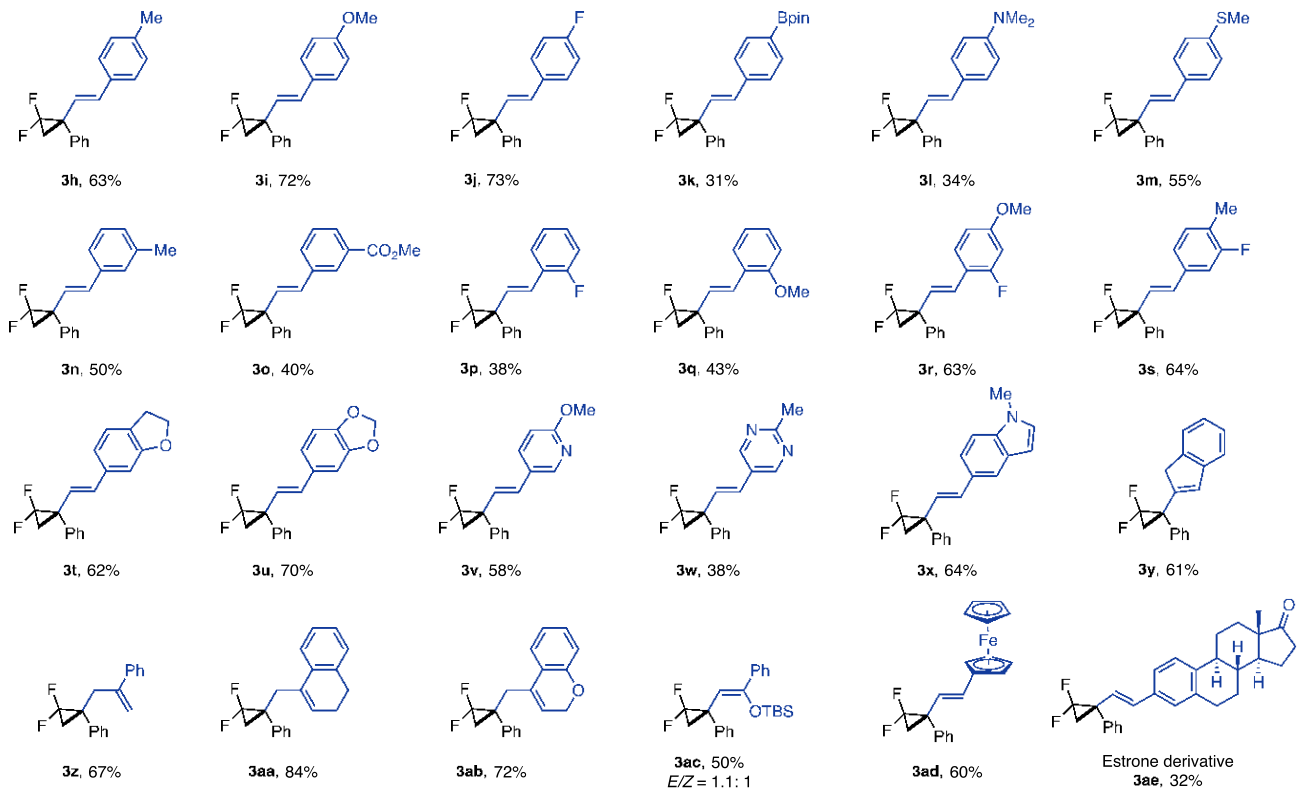
Table 2. Substrate Scope[a,b]



cyclopropenes and BCBs



alkenes



[a]0.15 mmol scale, 1:2 = 1:2, 4:2 = 1:2, isolated yields. [b]Diastereomeric ratio (dr) and *E*/*Z* ratio was determined by ^{1}H NMR analysis of crude reaction mixtures, using CH_2Br_2 as an internal standard. [c]Single diastereomer. [d]Xantphos Pd G3 (10 mol %) was used as a catalyst, and 1 equiv of $PhMe_2SiH$ was used. Xantphos Pd G3: [(4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate. [e]Reaction was performed at 40 °C without light. [f]Styrene was not added.

https://doi.org/10.1021/jacs.2c09045
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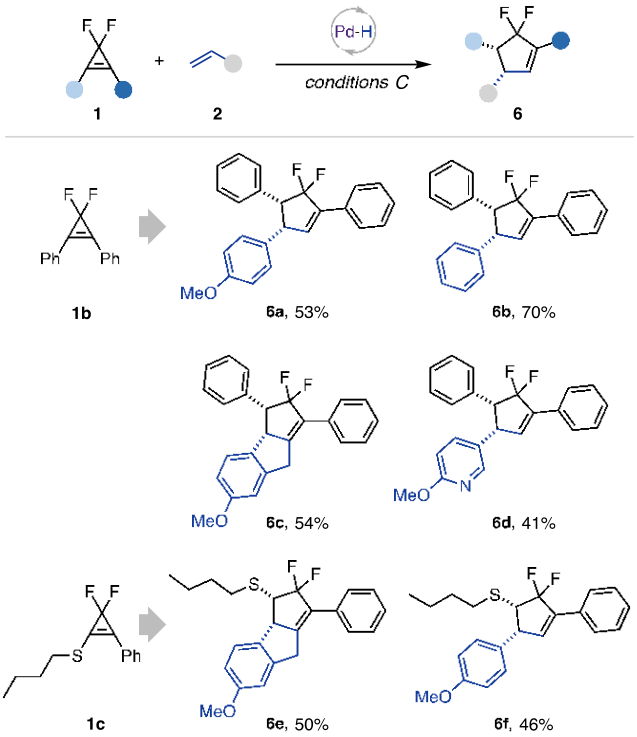
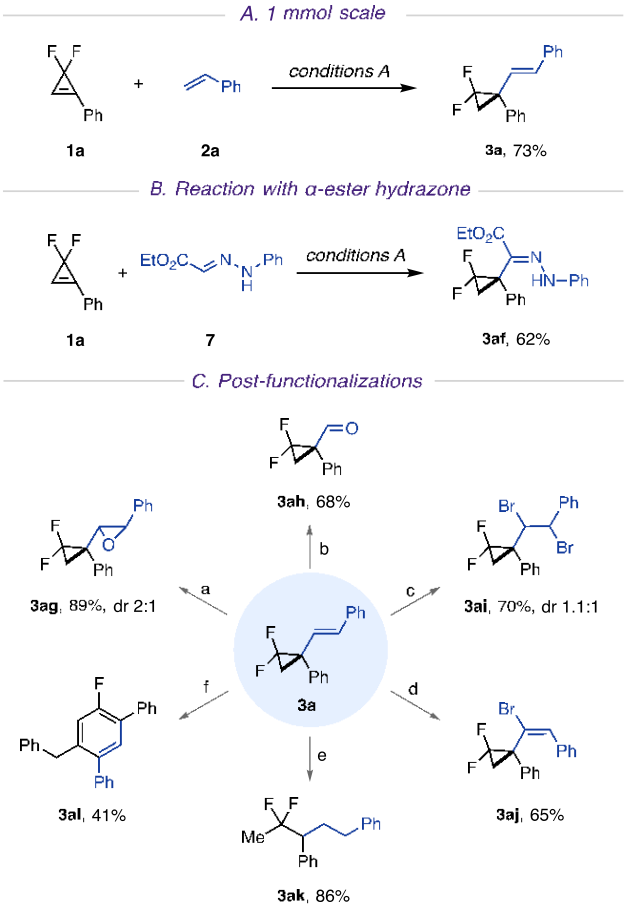
Table 3. Hydroalkenylation/Diastereoselective Rearrangement Cascade[a]



[a]0.15 mmol scale, 1:2 = 1:2, isolated yields. Conditions C: Xantphos Pd G3 (10 mol %), Xantphos (20 mol %), acetic acid (4 equiv), Et_3SiH (2 equiv), TBAB (1 equiv), 1,4-dioxane/toluene (0.15 M), blue LED (40 W, 427 nm), 16 h.

Scheme 3. Scalability and Diverse Transformations[a]



[a](A) 1 mmol scale. (B) Reaction with α-ester hydrazone. (C) Postfunctionalizations. Reaction conditions: (a) *m*-CPBA (1.5 equiv), DCM (0.1 M), rt, 24 h; (b) 4-nitrobenzonitrile (1.5 equiv), MeCN (0.1 M), rt, 390 nm LED, 16 h; (c) LiBr (2 equiv), $NaIO_4$ (0.5 equiv), H_2SO_4 (0.3 equiv), MeCN (0.05 M), rt, 24 h; (d) Br_2 (1.2 equiv), DCM (0.05 M), 0 °C, 2 h, then KOH (2 equiv), THF/MeOH (1/1), 80 °C, 3 h. (e) Pd/C (10 mol %), H_2 (1 atm), EtOAc (0.1 M), rt, 2 h; (f) phenylacetylene (2 equiv), $Pd(TFA)_2$ (10 mol %), P(*t*-Bu)$_3$·HBF_4 (12 mol %), Cs_2CO_3 (2 equiv), THF (0.2 M), 60 °C, 18 h. *m*-CPBA: *meta*-chloroperoxybenzoic acid. $Pd(TFA)_2$: palladium(II) trifluoroacetate.

without any additional optimization, furnishing product 3a in 73% yield (Scheme 3A). In addition, in a nonoptimized experiment, it was found that this reaction can also be applied to hydrazones[13g] to deliver cyclopropyl-containing hydrazone 3af in reasonable yield (Scheme 3B).

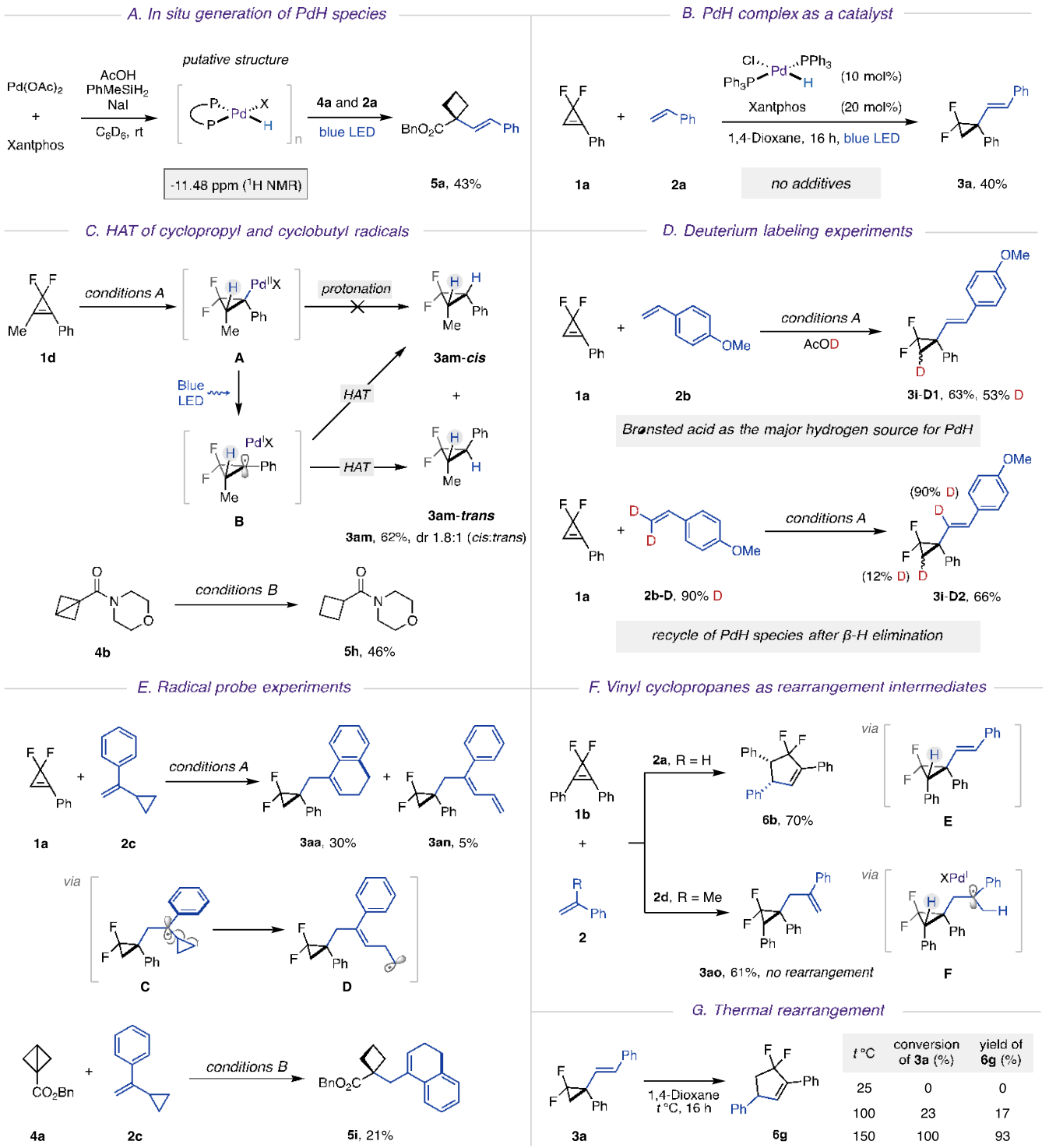
Synthetic usefulness of the obtained alkenylated *gem*-difluorocyclopropanes was highlighted by the following transformations (Scheme 3C). Epoxidation and photoinduced oxidative cleavage[19] of the alkene proceeded smoothly, furnishing epoxide 3ag and aldehyde 3ah, respectively. Dibromination[20] of the olefin provided product 3ai in good yield with two new functionalizable reaction sites. Additionally, a semi-one-pot dibromination/dehydrobromination of 3a delivered alkenyl bromide 3aj. Expectedly, hydrogenation of an alkene together with regioselective hydrogenolysis[21] of the distal C2−C3 bond of cyclopropane ring produced difluoropentane 3ak. Finally, alkenylated *gem*-difluorocyclopropane 3a was successfully employed in the Pd-catalyzed C−C bond activation/F elimination process,[22] followed by alkynylation with phenylacetylene and cycloisomerization, to deliver aryl fluoride 3al in reasonable yield.

3.4. Mechanistic Investigations and Proposed Mechanism. Naturally, we were eager to elucidate the mechanism of this novel two-component coupling reaction (Scheme 4). The involvement of a key PdH species was unambiguously supported by the following experiments. First, the reaction of $Pd(OAc)_2$, phosphine ligands, and additives was monitored by ^{1}H NMR (Scheme 4A). The appearance of a new resonance signal in the high-field region (−11.48 ppm) was detected in ^{1}H NMR spectra, which was attributed to the newly formed palladium hydride complex.[17] Upon addition of BCB 4a and styrene 2a to this reaction mixture, the expected hydroalkenylation product 5a was produced in 43% yield. Next, upon addition of the independently synthesized palladium(II) hydride complex,[17c] $HPdCl(PPh_3)_2$, to cyclopropene 1a and styrene 2a, the hydroalkenylation reaction proceeded smoothly without any exogenous additives (Scheme 4B).

To validate the radical nature of this transformation, we examined the reaction of cyclopropene 1d in the absence of styrene under otherwise identical catalytic conditions (Scheme 4C). It was expected that upon hydropalladation of 1d (A) and a subsequent photoinduced homolysis, the hybrid palladium cyclopropyl radical B could be produced, which would be capable of intermolecular hydrogen atom transfer (HAT) from either face. Indeed, a diastereomeric mixture of reduced products cyclopropane 3am-*cis* and 3am-*trans* (62%, *cis*:*trans* = 1.8:1) was formed, which provided additional support for the radical pathway for this transformation. It should be noted that no conversion of the starting material was observed in the

https://doi.org/10.1021/jacs.2c09045
J. Am. Chem. Soc. 2022, 144, 20875−20883

Scheme 4. Mechanistic Studies[a]



[a](A) *In situ* generation of PdH species. (B) PdH complex as a catalyst. (C) HAT of cyclopropyl and cyclobutyl radicals. (D) Deuterium labeling experiments. (E) Radical probe experiments. (F) Vinyl cyclopropanes as rearrangement intermediates. (G) Thermal rearrangement

absence of light, thus indicating that a direct protonation of alkyl palladium intermediate A, derived from *syn* hydropalladation, is unlikely. Analogously, when BCB 4b was tested under alkene-free conditions, the reduced product, cyclobutane 5h, was obtained.

Then, we performed a series of deuterium labeling experiments to reveal the H-source in this reaction (Scheme 4D). Thus, AcOD was used in the experiment of 1a with 2b. The D-incorporation of product 3i-D1 at the *β* position to the vinyl group, clearly suggested the Brønsted acid as the major hydrogen source for the formation of PdH species. Furthermore, when deuterium-labeled alkene 2b-D was subjected to the reaction, hydroalkenylation product 3i-D2 was obtained with minor deuterium incorporation at the cyclopropyl ring, which indicated the recycle of PdH species after the *β*-H elimination step.

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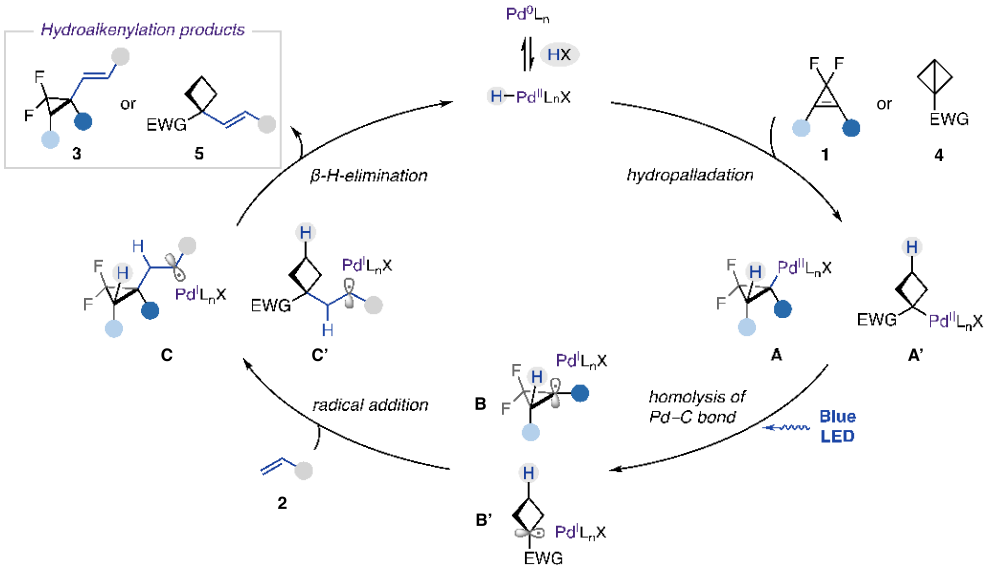
Scheme 5. Proposed Mechanism



The employment of radical probes and radical traps further confirmed the radical nature of this transformation. Hence, reaction of *gem*-difluorocyclopropene 1a with 2c, possessing a cyclopropyl substituent, underwent ring-opening of methyl-enecyclopropyl radical C into a homoallylic radical D. Its subsequent cyclization at the aryl ring produced bicyclic product 3aa, whereas competing *β*-hydrogen loss delivered linear diene 3an (Scheme 4E). Likewise, a radical probe experiment of BCB 4a delivered bicyclic product 5i. It was also shown that reactions of both substrates 1a and 4a were inhibited in the presence of radical traps, such as (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO).[14]

Lastly, a pathway of a hydroalkenylation/diastereoselective rearrangement cascade was investigated. As mentioned above, the reaction of 1,2-diphenyl cyclopropene 1b with styrene 2a delivered cyclopentene 6b (Scheme 4F). Thermal ring expansion of difluorinated alkenyl cyclopropanes containing an electron-withdrawing group is documented.[23] Accordingly, we presumed that the cascade reaction is likely to proceed via intermediacy of vinyl cyclopropane E. To validate this assumption, we subjected the same substrate 1b to the reaction with *α*-methylstyrene 2d. It was anticipated that hybrid Pd(I) tertiary alkyl radical F would undergo *β*-H elimination from a less substituted site, thus delivering an allyl cyclopropane product not capable of cycloisomerization. Indeed, the experiment indicated formation of allyl cyclopropane 3ao, as a single reaction product. Additional evidence was obtained by resubjecting the isolated, *β*-nonsubstituted vinyl cyclopropane 3a to thermal reactions (Scheme 4G). It was found that elevated temperatures (150 °C) were required to initiate its ring expansion, whereas *β*-phenyl-substituted akenyl difluorocyclopropane E, likely due to lower activation barriers,[23] underwent spontaneous rearrangement at room temperature.

Based on the above mechanistic studies, the following mechanism for photoinduced PdH-catalyzed hydroalkenylation of strained molecules is proposed (Scheme 5). Upon an oxidative addition of Pd(0) into HX precursor, the catalytically active H−Pd(II)−X species (X = Br^- or I^-) is formed. A following regio- and chemoselective migratory insertion of PdH into the double bond of cyclopropenes or *π*-like central C−C bond of BCBs provides alkyl−Pd(II)−X complex A or A′. A subsequent homolysis of the Pd−C bond under light irradiation generates the key hybrid Pd(I) cyclobutyl or cyclopropyl radical species B or B′. Addition of the latter at the alkene produces a benzylic radical intermediate C or C′. Finally, *β*-H-elimination delivers hydroalkenylation product 3 or 5, while the resulting H−Pd(II)−X complex returns to the catalytic cycle.

4. CONCLUSION

In summary, we developed the first light-induced Pd-catalyzed hydroalkenylation reaction of strained molecules, which allows for expedient synthesis of alkenylated cyclobutanes and cyclopropanes. Notably, this transformation highlights the merger of a traditional two-electron hydropalladation process and photoinduced hybrid Pd-radical chemistry, as intermediacy of both PdH and radical species were confirmed by mechanistic studies. This transformation demonstrates broad functional group tolerance and is amenable to late-stage functionalization of complex molecules. It is anticipated that this mild method would find broad applications in synthesis and would inspire development of new transformations.

ASSOCIATED CONTENT

*** Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c09045.

Additional experimental details, materials, methods, and characterization data for all new compounds. (PDF)

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https://doi.org/10.1021/jacs.2c09045
J. Am. Chem. Soc. 2022, 144, 20875−20883

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the National Institutes of Health (GM120281), National Science Foundation (CHE-1955663), and Welch Foundation (Chair, AT-0041) for financial support.

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