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Enhanced Excited-State Hydricity of Pd−H Allows for Unusual Head-to-Tail Hydroalkenylation of Alkenes

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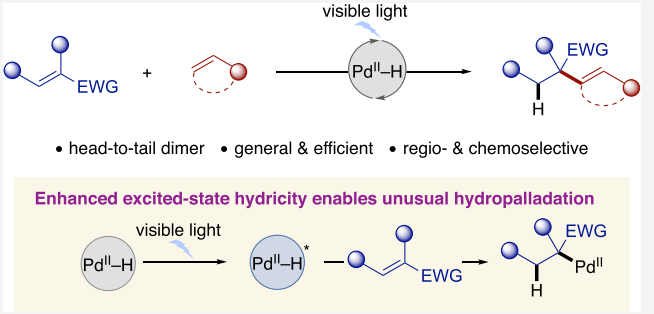
ABSTRACT: Photoinduced enhancement of hydricity of palladium hydride species enables unprecedented hydride addition-like ("hydridic") hydropalladation of electron-deficient alkenes, which allows for chemoselective head-to-tail cross-hydroalkenylation of electron-deficient and electron-rich alkenes. This mild and general protocol works with a wide range of densely functionalized and complex alkenes. Notably, this approach also allows for highly challenging cross-dimerization of electronically diverse vinyl arenes and heteroarenes.



INTRODUCTION

Catalytic cross-dimerization of feedstock olefins is one of the most powerful direct and atom- and step-economical approaches toward value-added alkenylated products.[1] Despite substantial developments in homodimerization methods, more significant cross-dimerization protocols of substituted alkenes remain underdeveloped.[1] One traditional approach involves Brønsted- and Lewis acid-catalyzed protonation or Lewis acid activation of alkenes (via intermediate **A**, Scheme 1a), providing cross-dimerization of vinyl arenes, albeit with limited scope.[2] For example, the employment of electron-rich alkenes, such as 4-methoxystyrene, in this method leads to polymerization, whereas electron-deficient heteroaryl arenes remain unreactive.[2a,b] Existing transition-metal-catalyzed hydroalkenylation approaches provide a partial solution to this problem.[1] These methods typically operate via protonation-like ("protic") hydrometallation (intermediate **B**, Scheme 1b) of electron-rich or electron-neutral terminal vinyl arenes, dienes, or strained alkenes with cationic hydrido complexes of transition metals, such as Ni, Pd, Ru, Co, and Fe.[3] Therefore, hydrometallation of electron-deficient alkenes in the presence of electron-rich alkenes is unfeasible. The existing examples of protic hydrometallation of electron-deficient methyl acrylate, which is achieved via coordination-assisted β-metalation (intermediate **C**, Scheme 1b), lead to regioisomeric mixtures of the head-to-head homodimerization products.[4,5] In general, the transition-metal-catalyzed approach often requires high temperatures (up to 160 °C) and employment of strong Lewis acid additives, which limit the functional group tolerance.[1c] Thus, the development of a mild, Lewis acid-free protocol engaging hydridic hydrometallation of electron-deficient alkenes, followed by coupling with electron-rich or electron-neutral alkenes, which would unlock a new chemical space in cross-dimerization and allow hydroalkenylation of densely functionalized and complex alkenes, is highly warranted.

Herein, we demonstrate visible light-induced hydricity enhancement of Pd−H species, which enables hydridic hydropalladation of electron-deficient alkenes (via intermediate **D**, Scheme 1c). Using this approach, various Michael acceptors are efficiently alkenylated with electron-rich and electron-neutral alkenes, such as vinyl arene, heteroarene, and enyne, in a highly regio- and chemoselective fashion. Notably, this approach also enables previously inaccessible chemoselective cross-dimerization of electronically diverse vinyl arenes and heteroarenes.

REACTION DESIGN

As discussed above, transition-metal-catalyzed hydroalkenylation relies on protic hydrometallation, which is favorable for the electron-rich or electron-neutral alkenes or dienes over their electron-deficient counterparts. Apparently, in order to change the chemoselectivity of the hydrometallation step, it would require accessing more hydridic metal-hydride species. Recently, visible light-excited palladium catalysis became an emerging area.[6] Our group and others have shown that visible light-induced homolysis of C(sp^3)−Pd bond leads to the generation of palladium(I) hybrid radical species, which are capable of undergoing alkyl Heck-type transformations.[7,8]

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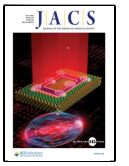

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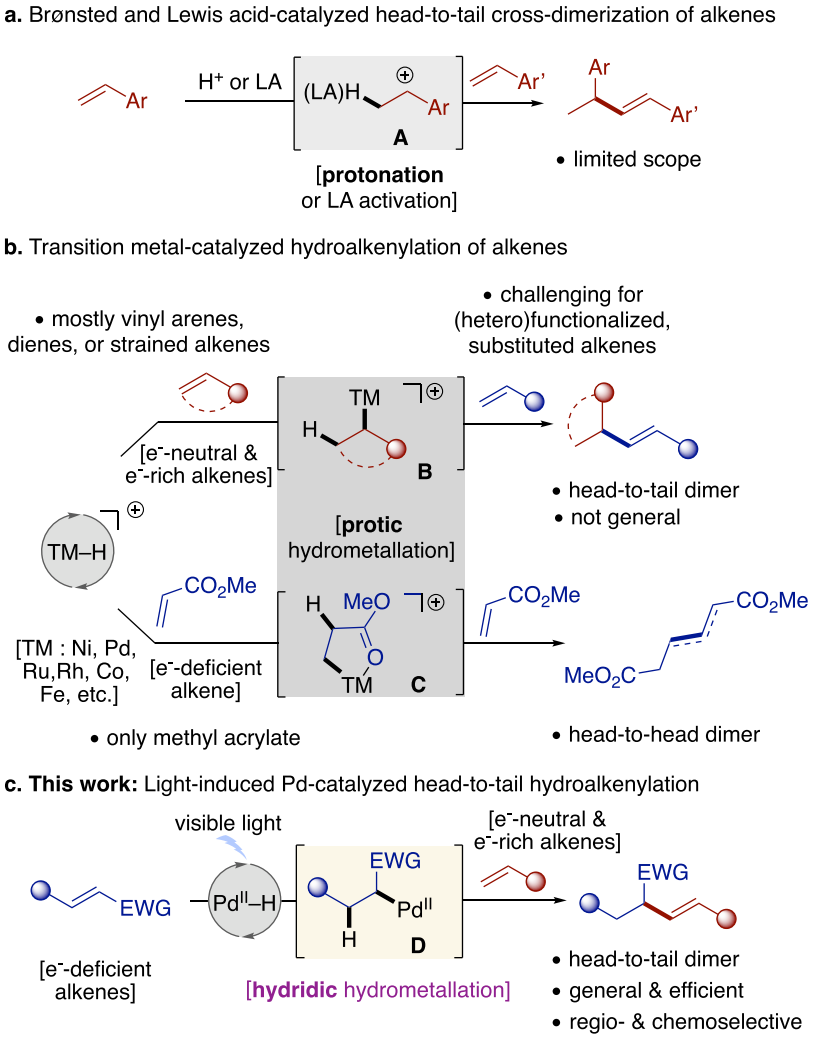
Scheme 1. Hydroalkenylation of Alkenes



Moreover, it was shown that palladium(I) hybrid radical species could be generated upon the addition of palladium hydride across diazocompounds[7a] or strained systems[7b] and a subsequent homolysis. However, neither the involvement of light in the hydropalladation step nor the change of the nature of the Pd−H species in this transformation has been validated. Previously, the Miller group has shown dramatic hydricity enhancement of $[Cp^*Ir(bpy)(H)]^+$ complex upon visible light excitation, which resulted in a striking rate enhancement of hydride transfer to *N*-methylpyridinium species (Scheme 2a).[9]

Accordingly, we wondered whether photoexcitation can enhance the hydricity of a phosphine-ligated palladium hydride complex. If successful, it would allow us to switch the protic hydropalladation of the ground-state Pd−H species with electron-rich alkenes (**E**, Scheme 2b) to the hydridic hydropalladation of the excited-state Pd−H with electron-deficient alkenes (**D**, Scheme 2b). Thus, the anticipated electrophilic[10] hybrid radical species[11] **F** is expected to undergo chemoselective radical addition to the electron-rich alkenes over the electron-deficient alkenes due to the polarity matching,[8] thus leading to the previously inaccessible head-to-tail cross-hydroalkenylation chemoisomers. The success of this design hinges on overcoming several potential pitfalls, such as uncontrolled regio- (**G**, Scheme 2b) and chemoselectivity (**H**) of hydropalladation, as well as isomerization and polymerization (**I**) via further hydropalladation of the alkenylation product. Moreover, uncontrolled radical reactivity could lead to HAT reduction, homodimerization, or chain polymerization (**J**).

RESULTS AND DISCUSSION

Reaction Optimization. First, cross-hydroalkenylation of ethyl acrylate (**1a**) with styrene (**1b**) under photoinduced Pd-catalyzed conditions in the presence of a Brønsted acid has been examined (Table 1).[12] Optimization studies indicated the commonly employed palladium(II) precatalyst with xantphos ligand to be the most efficient catalytic system (Table 1, entries 1−4).[13] It was found that a combination of pivalic acid and *N*,*N*-dicyclohexylmethylamine (NCy_2Me) as a proton source and tetrabutylammonium iodide (TBAI) as an additive was crucial for achieving highly selective and efficient hydroalkenylation (entries 5−7).[14,15] Under altered conditions, the formation of notable amounts of several side products was observed.[12] Thus, the employment of a more polar reaction media (entry 8) led to substantial isomerization of the product (**1c**), whereas the use of an equimolar ratio of reactants (entry 9) produced detectable amounts of oligomerization products (**1d**). Expectedly, under thermal conditions, the reaction was not efficient, producing small amounts of styrene homodimer **1e** (entry 10). Control experiments indicated that both

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Scheme 2. Reaction Design

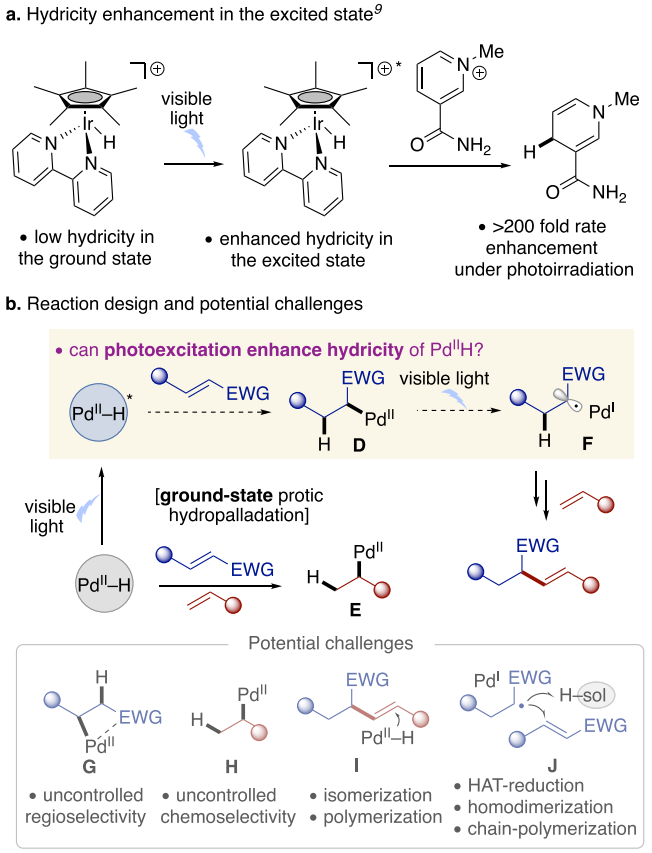
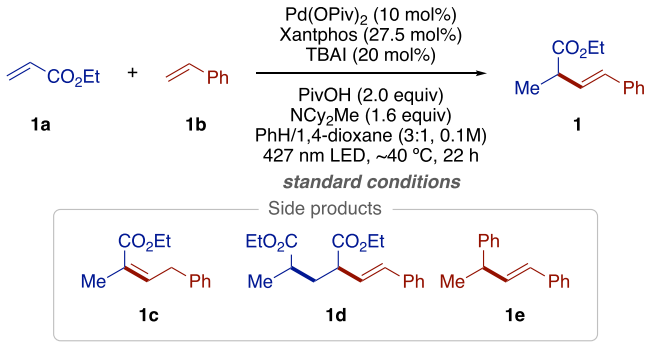


Table 1. Optimization of Reaction Conditions[a]



entry	deviation from standard conditions	yield of 1 (%)[b]
1	none	99(95)[c]
2	$Pd(OPiv)_2$ (5 mol %) Xantphos (14 mol %)	91
3	DPEPhos as a ligand	6
4	dtbdppf as a ligand	0
5	without PivOH	32
6	without TBAI	83
7	without NCy_2Me	81
8	PhH/DMA (3:1)	42[d]
9	**1a**:**1b** = 1:1	70[e]
10	no light, up to 160 °C	0[f]
11	without $Pd(OPiv)_2$ or Xantphos	0

[a]0.2 mmol scale, **1a**:**1b** = 1:2, **1**:**1c** > 20:1.[12] [b]GC-MS yields. [c]Isolated yield. [d]**1**:**1c** = 1.3:1. [e]14% of **1d** was formed. [f]10% of **1e** was formed.

palladium catalyst and ligand were essential for this transformation (entry 11).

Hydroalkenylation of Alkenes. With the optimized conditions in hand, the generality of the hydroalkenylation protocol, starting with the scope of the electron-deficient alkenes, has been examined (Table 2). Differently substituted Michael acceptors were found to be suitable substrates for this transformation. Thus, terminal acrylates with different functional groups, including the free hydroxyl group, reacted efficiently with vinyl arenes to deliver hydroalkenylation products **2**−**7** in a highly chemo- and regioselective manner. Likewise, tertiary acrylamides provided good yields of cross-dimerization products (**8**−**11**). More importantly, secondary (**12**) and primary (**13**) acrylamides underwent this hydroalkenylation tolerating unprotected amide groups, which is quite unusual for traditional palladium catalysis. Acrylonitrile afforded the head-to-tail cross-dimerization product **14** in reasonable yield. 1,1-Disubstituted electron-deficient olefins, including acrylate, acrylamide, and *α*,*β*-unsaturated lactone, were also efficient in this reaction, providing the corresponding hydroalkenylation products **15**−**23** in moderate to good yields. Expectedly, due to polarity mismatch, electron-rich vinyl ether moiety did not interfere with the hydridic hydropalladation step (**17**). Notably, the successful employment of this acid-sensitive alkene, as well as precursor for **20** possessing an allylic alcohol moiety, highlights the mildness of this Lewis acid-free method. Additionally, this protocol can also be applied for double alkenylation reaction (**24**). Markedly, more challenging internal alkenes, including dimethyl fumarate, diethyl maleate, and crotononitrile, underwent smooth hydroalkenylation with vinyl arenes (**25**−**36**).[12] Moreover, trisubstituted endo- and exocyclic acrylates (**37**−**39**) were found to be capable substrates for this hydroalkenylation reaction. It is worth mentioning that due to the low availability of the corresponding halides,[16] accessing many of these highly functionalized alkenylated products via the established alkyl Heck-type transformations[7,8] would be problematic.

Next, the scope of the electron-rich cross-dimerization partner was evaluated. Differently substituted vinyl arenes were found to be suitable substrates for hydroalkenylation with acrylates. Thus, *ortho*-, *meta*-, or *para*-substituted vinyl arenes (**40**−**44**) containing electron-donating groups underwent smooth hydroalkenylation reaction, including the reaction at a larger scale (**40**). It deserves mentioning that this method tolerated various functionalities at the vinyl arene, including pyrazole (**45**), free amide (**46**), and free benzyl alcohol (**47**). Notably, a chemoselective cross-dimerization of electron-deficient vinyl arenes with electron-deficient acrylates also proved viable. Thus, differently substituted vinyl arenes, containing chloro (**48**, **49**), trifluoromethyl (**50**), and pinacolboronate (**51**) groups, afforded hydroalkenylation products **48**−**51** in moderate to good yields. Vinyl pyridine derivative (**52**) also reacted well. Furthermore, 1,1-disubstituted vinyl arenes afforded cross-dimerization products (**53**−**56**) in good yields. More challenging internal alkenes including flavoring agent anethole delivered hydroalkenylation products **57**−**60** in moderate to good yields. Importantly, electron-rich olefins beyond vinyl arenes can also be employed. Thus, enyne (**61**), *N*-vinyl pyrazole (**62**), and even unactivated alkene (**63**) all underwent chemoselective cross-dimerization reaction, albeit in moderate efficiency.

Heterodimerization of Vinyl Arenes and Heteroarenes. Next, the feasibility of a more challenging cross-

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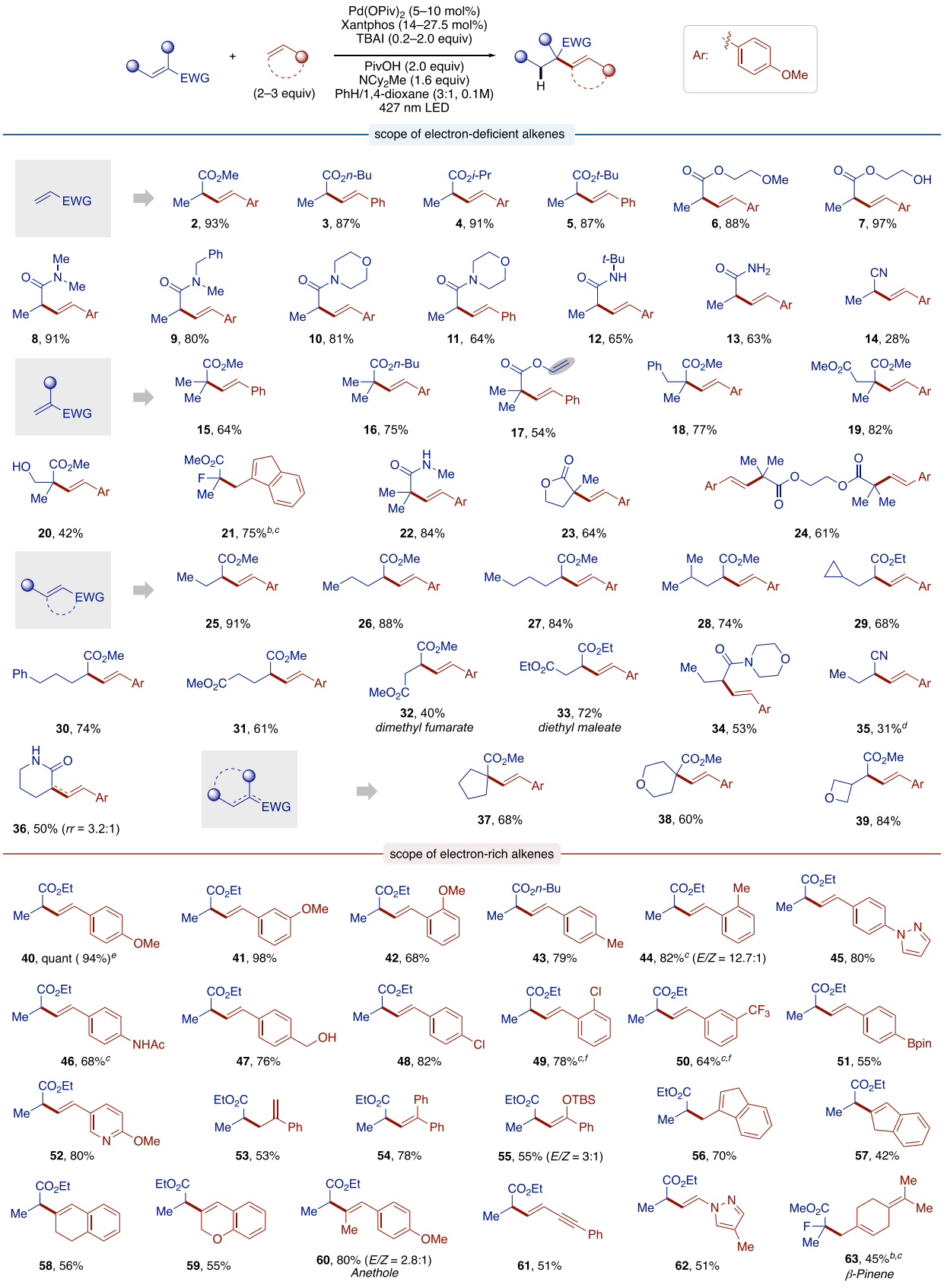
Table 2. Cross-Hydroalkenylation Alkenes[a]



[a]0.2 mmol scale, isolated yields, unless otherwise mentioned E/Z.[12] [b]3−5 equiv of alkene coupling partner was used; THF was used as a solvent. [c]No NCy_2Me. [d]Crotononitrile/4-vinylanisole (3:1), 0.25 (M) in PhH/1,4-dioxane. [e]Conducted on a 1 mmol scale. [f]0.11 (M) in PhH/1,4-dioxane (5:1).

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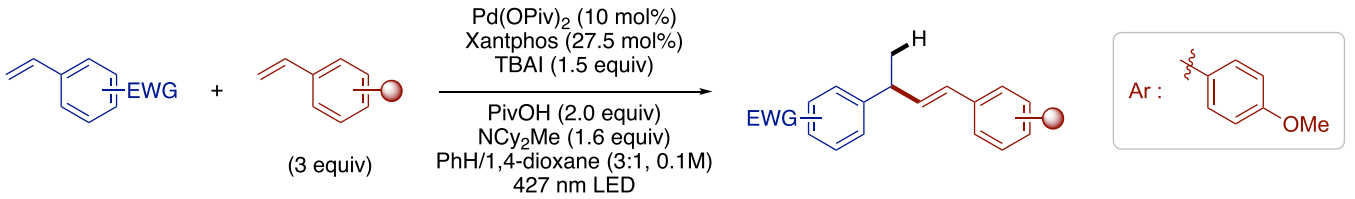
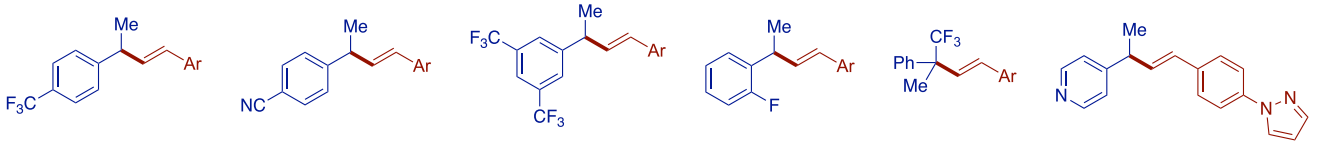
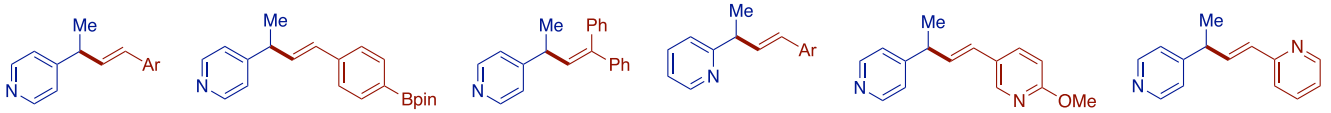
Table 3. Heterodimerization of Vinyl Arenes(Heteroarenes)[a]





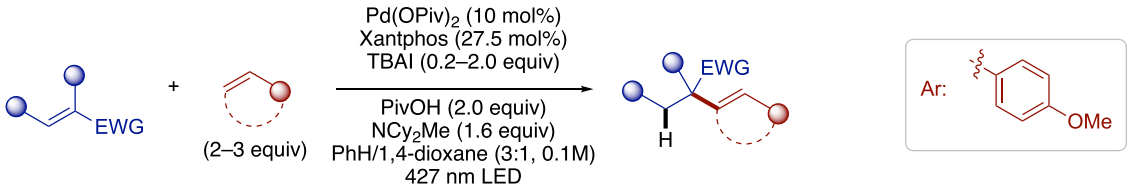
64, 49% **65**, 42% **66**, 60% **67**, 33% **68**, 55% **69**, 70%

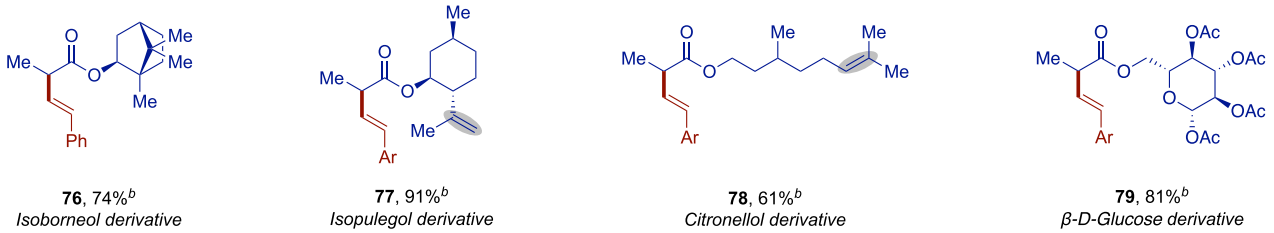


70, 67% **71**, 30% **72**, 40% **73**, 43% **74**, 55% **75**, 55%

[a]0.2 mmol scale, isolated yields, unless otherwise mentioned, E/Z > 20:1.[12]

Table 4. Cross-Hydroalkenylation of Complex Alkenes[a]



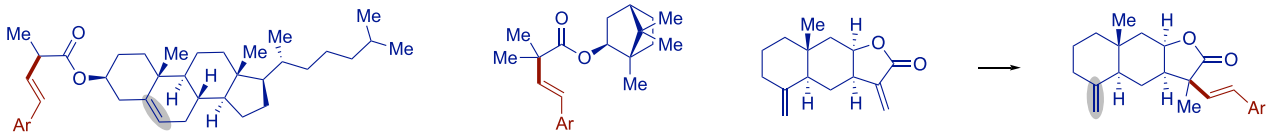


76, 74%[b] *Isoborneol derivative*

77, 91%[b] *Isopulegol derivative*

78, 61%[b] *Citronellol derivative*

79, 81%[b] *β-D-Glucose derivative*

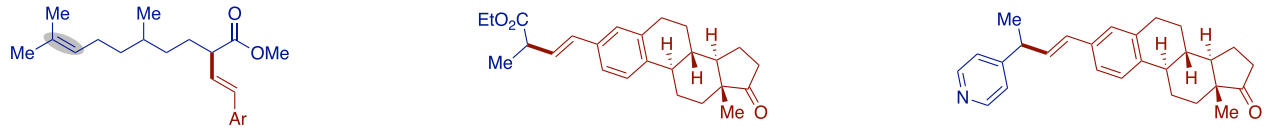


80, 80%[b] *Cholesterol derivative*

81, 87% *Isoborneol derivative*

Isoalantalactone

82, 67%[c]

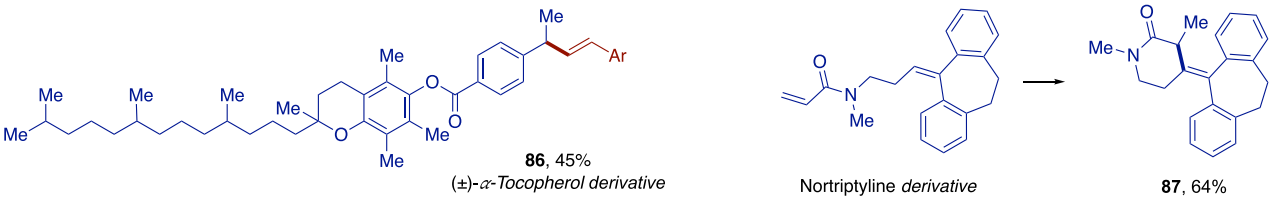


83, 55%[b] *Citronellal derivative*

84, 91%[b]

Estrone derivative

85, 48%[b]



86, 45% *(±)-α-Tocopherol derivative*

Nortriptyline *derivative*

87, 64%

[a]0.2 mmol scale, isolated yields, unless otherwise mentioned, E/Z > 20:1.[12] [b]dr = 1:1. [c]dr > 20:1.

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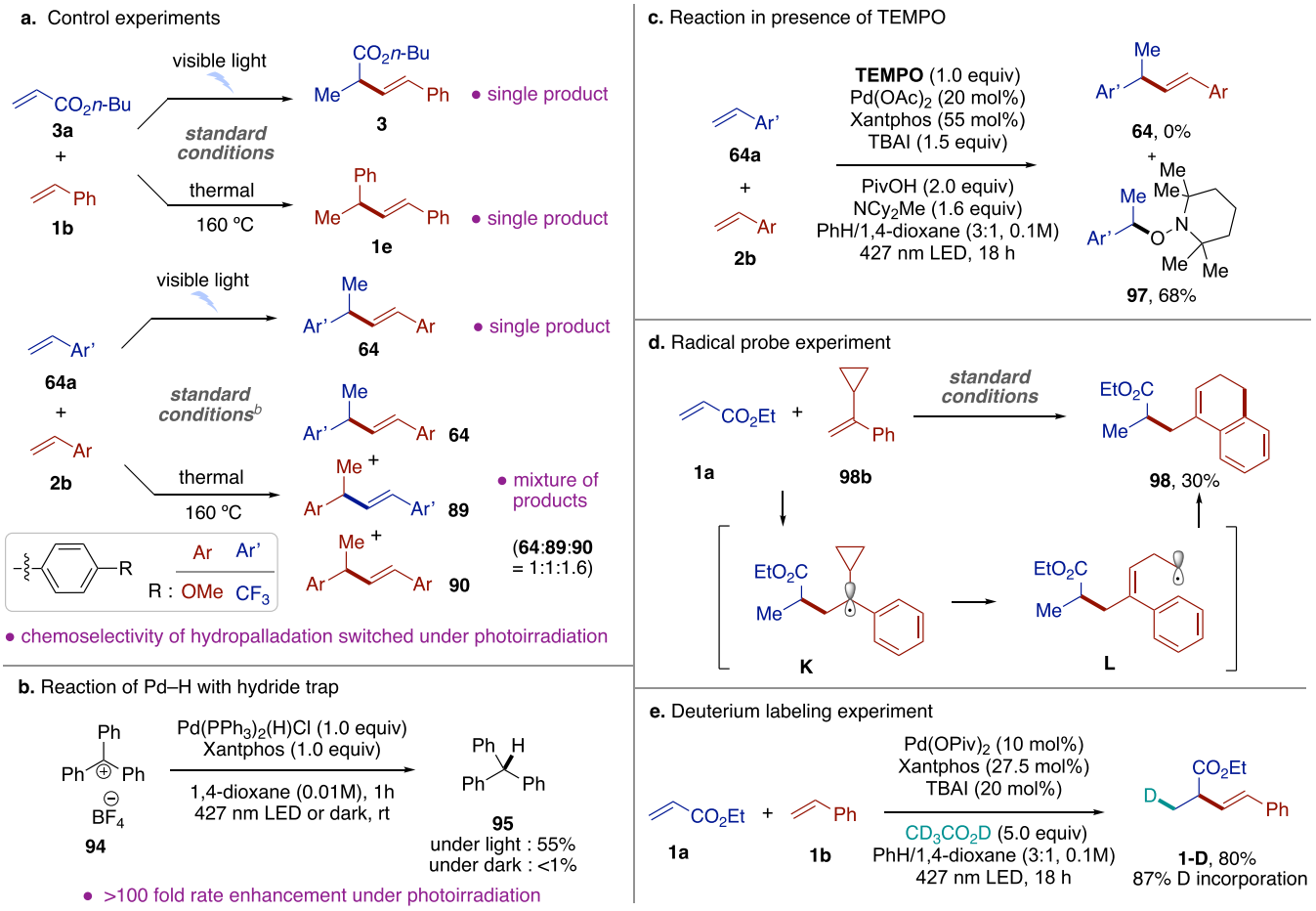
Scheme 3. Mechanistic Studies[a]



[a]Standard conditions: $Pd(OPiv)_2$ (10 mol %), Xantphos (27.5 mol %), TBAI (20 mol %), PivOH (2.0 equiv), NCy_2Me (1.6 equiv), PhH/1,4-dioxane (3:1, 0.1 M), 427 nm LED, 12−18 h; 0.2 mmol scale.[12] [b]1.5 equiv of TBAI was used.

hydroalkenylation of electron-rich and electron-deficient vinyl arenes (heteroarenes) has been examined (Table 3). Gratifyingly, it was found that this light-induced methodology can also be applied toward highly chemoselective heterodimerization of vinyl arenes (**64**−**68**). Moreover, vinyl heteroarenes, such as vinyl pyridine derivatives, were capable substrates in this cross-dimerization reaction with differently substituted vinyl arenes (**69**−**73**). Remarkably, a highly chemoselective cross-dimerization of two different vinyl pyridines is also feasible (**74**, **75**). Importantly, most of the vinyl arenes-(heteroarenes) employed in this protocol are either incompatible or unreactive under traditional Brønsted- and Lewis acid-catalyzed methods (vide supra).[2a,b]

Hydroalkenylation of Complex Alkenes. Further, the generality of this photoinduced hydroalkenylation protocol was tested under a more complex setting (Table 4). Thus, acrylates containing terpene (**76**, **77**, **81**), terpenoid (**78**), carbohydrate (**79**), and steroid (**80**) derivatives furnished hydroalkenylation products **76**−**81** in moderate to good yields. Due to the involvement of the highly chemoselective hydridic hydropalladation process, terminal and internal alkenes in isopulegol (**77**), citronellol (**78**), and cholesterol (**80**) were all tolerated in this reaction. Besides, glucoside derivative **79** was also tolerated under this mild protocol. Analogously, sesquiterpene natural product isoalantalactone (**82**), terpenoid citronellal derivative (**83**), estrone derivatives (**84**, **85**), and α-tocopherol derivative (**86**) were also capable substrates. Besides, intramolecular hydroalkenylation of nortriptyline derivative led to tetrasubstituted alkene **87** in reasonable yield.

Mechanistic Studies and Proposed Mechanism. Involvement of hydridic hydropalladation via excited-state hydricity enhancement was supported by the following experiments (Scheme 3a).[12] In the reaction of butyl acrylate **3a** with styrene **1b**, switching from light-induced to thermal conditions led to a complete switch from the cross-alkenylation (**3**) to homodimerization of styrene (**1e**) product. A dramatic switch of chemoselectivity of hydropalladation, and hence of dimerization reaction, was also observed in the reactions of electronically distinct vinyl arenes **64a** and **2b**. The reaction under light-induced conditions led to exclusive cross-hydroalkenylation product **64** via the excited-state hydridic hydropalladation of electron-deficient vinyl arene **64a**, whereas thermal hydroalkenylation proceeding mostly via the ground-state protic hydropalladation of electron-rich vinyl arene **2b** led to a chemoisomeric mixture of **64**, **89**, and **90**. The hydridic nature of the excited-state palladium hydride species was further supported by its trapping with trityl cation (**94**) (Scheme 3b).[17] Thus, under light irradiation, a dramatic rate enhancement of the hydride transfer (**94** → **95**) was observed.[4] Involvement of radical intermediates in this transformation was supported by the radical trapping and radical probe experiments. Thus, the employment of TEMPO

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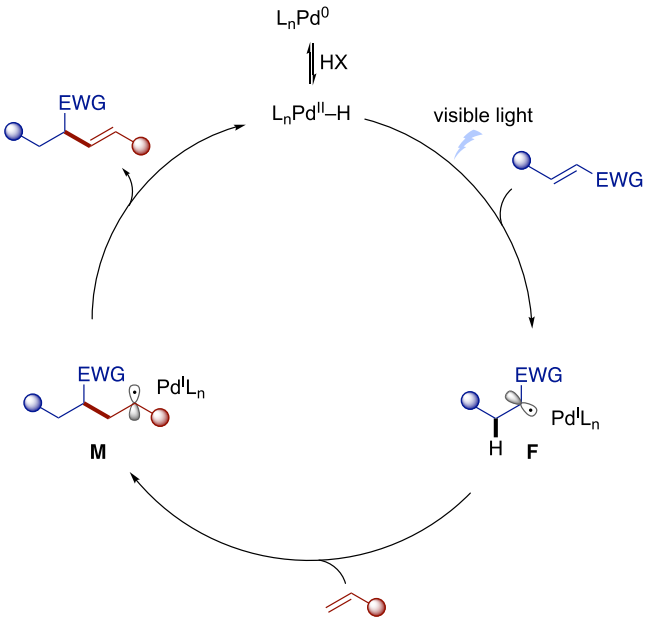
completely shut down the hydroalkenylation process to afford the TEMPO-trapping adduct **97** in good yield (Scheme 3c).[18] In the radical probe experiment, cross-hydroalkenylation of acrylate **1a** with cyclopropane-containing vinyl arene **98b** led to dehydronaphthalene **98** apparently via the radical rearrangement cascade (**K** → **L** → **98**) (Scheme 3d). Finally, the deuterium labeling experiments identified Brønsted acid as the primary proton source for the formation of Pd−H species (Scheme 3e).

Based on the results of the mechanistic studies[12] and literature precedents,[7,8] the following mechanism for this cross-hydroalkenylation reaction is proposed (Scheme 4). First, Pd−H species is generated upon the oxidative addition of Pd(0) species[19] with Brønsted acid (HX). Upon visible light irradiation, the excited-state hydricity enhancement enables chemoselective hydridic hydropalladation of electron-deficient alkene, followed by the Pd−C bond homolysis, to form hybrid Pd(I) alkyl radical species **F**. A subsequent selective polarity-matched radical addition to electron-rich alkene generates translocated radical species **M**, which upon β-H loss affords the head-to-tail dimerization product and regenerates Pd−H species.

Scheme 4. Proposed Mechanism



CONCLUSIONS

In conclusion, we report the novel head-to-tail cross-hydroalkenylation of electronically different alkenes. The unusual chemoselectivity of this transformation relies on the umpolung of the palladium hydride species, achieved by the visible light-induced excited-state hydricity enhancement. This mild, Lewis acid-free, chemo- and regioselective method exhibits broad functional group compatibility and can be employed for cross-hydroalkenylation of diversely substituted and complex alkenes. Notably, this approach also allows for highly chemoselective cross-hydroalkenylation of electronically diverse vinyl arenes(heteroarenes).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c02410.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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