

Palladium-Catalyzed Allylic Alkylation via Photocatalytic Nucleophile Generation

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KEYWORDS: allylic alkylation, hydrogen atom transfer, C-H functionalization, palladium catalysis, combined catalysis

alladium-catalyzed allylic alkylation reactions are known to be powerful carbon-carbon bond-forming methods¹ by merging π -allylpalladium electrophiles and carbon nucleophiles in a predictably chemo-, regio-, and stereoselective fashion.² In the past several decades, a wide range of stabilized and nonstabilized carbon nucleophiles have been used in allylation reactions;³ however, most nonstabilized carbon nucleophiles are preformed metal enolates based on the use of highly basic conditions for the enolization of substrates;⁴ therefore, a stoichiometric amount of metal salt waste is unavoidably generated (Scheme 1A). To avoid the use of highly basic reagents, decarboxylation⁵ and deacylation⁶ strategies have been utilized as alternative methods for the in situ generation of nonstabilized carbon nucleophiles (Scheme 1A), albeit with slightly eroded atom economy. Therefore, it is highly desirable to develop atom-economic and environmentally friendly methods for the generation of nonstabilized nucleophiles from easily accessible starting materials under mild conditions.

nonstabilized nucleophile for transition-metal catalysis.

Very recently, our group has described an asymmetric photocatalytic $C(sp^3)$ -H bond addition to electrophilic alkenes⁷ by using the combination of a hydrogen atom transfer (HAT) photocatalyst⁸ and a chiral phosphoric acid,⁹ and the key enantiodetermining step is the protonation of an in situ photogenerated nonstabilized enol intermediate. On the basis of this finding, we posit that this photocatalytic strategy (Scheme 1A), the in situ generation of a nonstabilized nucleophile through $C(sp^3)$ -H bond addition to an electron-poor alkene with nearly complete atom economy, might be viable in a Pd-catalyzed allylic alkylation reaction.¹⁰

Our design plan for the Pd-catalyzed allylic alkylation via photocatalytic nucleophile generation is outlined in Scheme

Scheme 1. Design Plan for Pd-Catalyzed Allylic Alkylation via Photocatalytic Nucleophile Generation



1B. The homolytic cleavage of an inert $C(sp^3)$ -H bond by a HAT photocatalyst would initially give rise to an alkyl radical

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and a reducing photocatalyst. The alkyl radical would undergo Giese radical addition¹¹ to an electron-poor alkene to give an electron-deficient radical, which would be readily reduced by the reducing photocatalyst to furnish a nonstabilized carbanionic nucleophile.¹² This carbanionic species would then react with a catalytically generated π -allylpalladium intermediate, ultimately leading to the desired allylation product. Nevertheless, this three-component coupling reaction with a combined catalytic system^{13,14} still faces several challenging issues. For instance, the compatibility of a photoredox HAT and a palladium catalyst shall be the first to bear the brunt.¹⁵ In addition, a competing protonation of the carbanionic species may be unavoidable when providing a Giese addition product.^{7a} In regard to the allylation mechanism, a direct coupling of the carbon-centered radical and the π -allylpalladium intermediate through a single-electron allylation pathway¹⁶ cannot be fully abandoned.

The initial investigation focused on a three-component coupling reaction of benzyl 2-phenyl acrylate (1), cyclohexane (2), and allyl methyl carbonate (3) under near-ultraviolet irradiation by using tetrabutylammonium decatungstate $(TBADT)^{17}$ as a HAT photocatalyst and $Pd_2(dba)_3/PPh_3$ as a palladium catalyst, and to our delight, these two catalysts showed good compatibility to provide the desired allylation product (4) in 27% yield (Table 1, entry 1). The variation of TBADT to 5,7,12,14-pentacenetetrone (PT),¹⁸ a commercially available visible-light organophotocatalyst, was able to give an enhanced yield (entry 2). The examination of solvents suggested that the use of 1,2-dichloroethane could dramatically improve the efficiency (entries 3–5). Then, a variety of

Table 1. Optin	nization of	Reaction	Conditions ^{<i>a</i>}
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Ph	⊥CO₂Bn -	+ + 2	- >OCO2M 3	Pd ₂ (dba) ₃ (2.5 mol%) L (6 mol%) HAT (5 mol%) e solvent, <i>hv</i> , RT, 24 h	Cy Ph 4
e	ntry	HAT	solvent	ligand	yield (%) ^b
	1 ^c	TBADT	MeCN	PPh ₃	27
2	2	PT	MeCN	PPh ₃	36
3	3	PT	THF	PPh ₃	27
4	4	РТ	DCM	PPh ₃	61
:	5	PT	DCE	PPh ₃	72
(5	PT	DCE	$P(2-MeC_6H_4)_3$	55
	7	PT	DCE	$P(3-ClC_6H_4)_3$	24
8	8	PT	DCE	$P(3-MeC_6H_4)_3$	80
9	Ð	PT	DCE	$P(3,5-Me_2C_6H_3)_3$	91 (89 ^d)
	10	PT	DCE	DPPE	55
	11	PT	DCE	DPPP	45
	12	PT	DCE	Xantphos	37
	13	PT	DCE		<1
	14 ^e	PT	DCE	$P(3,5-Me_2C_6H_3)_3$	<1
	15 ^f	PT	DCE	$P(3,5-Me_2C_6H_3)_3$	<1

^{*a*}Reaction conditions: **1** (0.1 mmol), **2** (2 mmol), **3** (0.2 mmol), Pd₂(dba)₃ (2.5 mol %), ligand (6 mol %), HAT catalyst (5 mol %), solvent (1 mL), 10 W LEDs (λ_{max} = 420 nm), under N₂, room temperature, 24 h. ^{*b*}Determined by ¹H NMR analysis using trimethyl 1,3,5-benzenetricarboxylate as an internal standard. ^c6 W LEDs (λ_{max} = 390 nm) were used. ^{*d*}Isolated yield. ^cWithout Pd₂(dba)₃. ^{*f*}Without PT (5 mol %). PT, 5,7,12,14-pentacenetetrone. TBADT, tetrabutylammonium decatungstate. DPPE, 1,2-bis(diphenylphosphino)ethane. DPPP, 1,3-bis(diphenylphosphino)propane. Xantphos, 4,5bis(diphenylphosphino)-9,9-dimethylxanthene. monophosphine ligands were evaluated (entries 6–9), and $P(3,5-Me_2C_6H_3)_3$ turned out to be superior to afford product 4 in 91% yield. In contrast, the use of bisphosphine ligands, including 1,2-1,2-bis(diphenylphosphino)ethane (DPPE), 1,3-bis(diphenylphosphino)propane (DPPP), and Xantphos, all resulted in much diminished results (entries 10–12). A wide range of chiral phosphine ligands were also tested, but no enantiomeric excess was obtained. (See the Supporting Information for details.) In addition, the control experiments confirmed that phosphine ligand, $Pd_2(dba)_3$, and HAT photocatalyst were essential to this three-component coupling reaction (entries 13–15).

Under the optimal reaction conditions, a variety of terminal alkenes were first evaluated (Scheme 2). Either electron-

Scheme 2. Scope of Terminal Alkenes^a



^{*a*}Reaction conditions: alkene (0.1 mmol), **2** (2 mmol), **3** (0.2 mmol), Pd₂(dba)₃ (2.5 mol %), P(3,5-Me₂C₆H₃)₃ (6 mol %), PT (5 mol %), DCE (1 mL), 6 W LEDs (λ_{max} = 420 nm), under N₂, room temperature, 24 h. ^{*b*}Run for 48 h. ^{*c*}Run for 36 h.

donating or electron-withdrawing substituents at the ortho, meta, or para position on the phenyl ring were tolerated to furnish the corresponding allylation products (5-11) in moderate to high yields. Heterocyclic moiety was also able to participate in this protocol to give the corresponding product (12) in useful efficiency. The variation of the ester moiety did not significantly affect the reaction performance (13), and in particular, the furan moiety (14), a highly sensitive functional group under photoredox conditions, was nicely tolerated. Moreover, α -alkylacrylic esters were capable of delivering the desired products (15 and 16) in moderate yields. In addition, acrylophenone, α -substituted acrylophenones and α -arylacrylaldehyde were able to serve as effective substrates (17-20), highlighting the high level of functional group tolerance of this protocol. Notably, styrene was proven to be compatible with this protocol, giving rise to the allylation product (21) in a synthetically acceptable yield.

With respect to the aliphatic $C(sp^3)$ -H coupling partners, both hydrocarbons and α -heteroatom $C(sp^3)$ -H bonds were suitable for this three-component coupling reaction (Scheme 3). For instance, five-, seven- and eight-membered cycloalkanes were capable of delivering the desired allylation products (22-

Scheme 3. Scope of Aliphatic C(sp³)-H Coupling Partners^a



^{*a*}Reaction conditions: 1 (0.1 mmol), hydrocarbon (2 mmol), 3 (0.2 mmol), Pd₂(dba)₃ (2.5 mol %), P(3,5-Me₂C₆H₃)₃ (6 mol %), PT (5 mol %), DCE (1 mL), 6 W LEDs (λ_{max} = 420 nm), under N₂, room temperature, 24 h. ^{*b*}Run for 36 h. ^{*c*}7:1 r/r. ^{*d*}Run for 48 h. ^{*e*}Run for 96 h. ^{*f*}1.3:1 dr. ^{*g*}2.3:1 dr.

24) in high yields. Interestingly, adamantane underwent functionalization predominantly at the sterically hindered bridgehead position with 7:1 site selectivity (25), presumably due to the relatively low bond dissociation energies (BDEs) of the tertiary $C(sp^3)$ -H bonds. Similarly, 2,3-dimethylbutane and 5-methylhexan-2-one were functionalized at the tertiary position with high levels of site selectivity (26 and 27). Toluene and methylarenes bearing various synthetic valuable functional groups, such as ether, borate, ketone, and ester, all proceeded smoothly to provide the corresponding products (28-32). Notably, 2-methylthiophene could be converted to the corresponding product (33) in 42% yield. Moreover, ethylbenzene, 2-propylbenzene, and cyclohexylbenzene also underwent site-selective benzylic C-H functionalization to provide the corresponding products (34-36) in moderate yields, albeit with 1.3:1 diastereoselectivity for ethylbenzene. In addition, methyl tert-butyl ether, 1,4-dioxane, and 1,3benzodioxole were viable to afford the α -oxy functionalized products (37-39) in good yields. Intriguingly, cyclopentyl methyl ether was specifically functionalized at the tertiary position adjacent to the oxygen, leading to a sterically hindered ether in good yield (40). It was noteworthy that Nmethyldiphenylamine and tert-butyl dimethylcarbamate were suitable for the reaction to generate the desired products (41 and 42) in good yields.

As for the allylating agents, a range of substituted allyl carbonates were proven to be competent for this protocol (Scheme 4). Both 2-alkyl- and 2-aryl-substituted allyl carbonates were successfully employed to provide the corresponding products (43-47) in moderate to good yields. Interestingly, the reaction with 1-phenylallyl carbonate resulted in the generation of the allylation product (48) as a 5:1 E/Z isomeric mixture, in which the thermodynamically less stable Z isomer might be raised from a photochemical isomerization.¹⁹

Scheme 4. Scope of Allylating Agents^a



^{*a*}Reaction conditions: 1 (0.1 mmol), 2 (2 mmol), allylating agent (0.2 mmol), Pd₂(dba)₃ (2.5 mol %), P(3,5-Me₂C₆H₃)₃ (6 mol %), PT (5 mol %), DCE (1 mL), 6 W LEDs (λ_{max} = 420 nm), under N₂, room temperature, 36 h. ^{*b*}Run for 48 h. ^{*c*}5:1 E/Z. VEC, vinyl ethylene carbonate. EB, 1,2-epoxybutene.

Furthermore, vinyl ethylene carbonate and 1,2-epoxybutene were also found to be applicable in this protocol to yield the same allylation product containing an allylic alcohol moiety, thus providing a useful handle for further functionalization.

To understand the reaction mechanism, a series of mechanistic studies were performed. A radical trapping experiment showed that the addition of TEMPO to the model reaction completely inhibited the formation of the desired product (Scheme 5A). The Stern–Volmer quenching experiments revealed that only C-H coupling partners, such as toluene and cyclohexane, were capable of quenching the excited state of PT (Scheme 5B). In addition, kinetic studies established a first-order dependence of the initial rate on the amount of both the palladium catalyst and HAT photocatalyst (Scheme 5C), indicating that these two catalysts might function in a synergistic manner^{20,13a,c} and be relevant to the rate-determining step of this binary catalysis. Moreover, the treatment of a potential Giese addition product 50 and methyl allyl carbonate 3 with 2.5 mol % $Pd_2(dba)_3$ and 6 mol % P(3,5- $Me_2C_6H_3$)₃ was unable to generate the desired allylation product 4, and nearly complete starting material 50 was recovered (Scheme 5D). In addition, the Giese addition product 50 was not observed in the progress curve under the optimized conditions (Scheme 5D). These results suggested that the Giese addition product 50 had extremely low reactivity under the optimized condition; therefore, a sequential reaction of Giese addition/Pd-catalyzed allylic alkylation by using a Giese addition product as a key intermediate was unfeasible. Notably, a series of control experiments using hexafluoroisopropanol (HFIP) as an additive showed that the increasing amount of HFIP as an additive could significantly inhibit the formation of the desired allylation product 4; meanwhile, the generation of the Giese addition product 50 was gradually increased (Scheme 5D). In particular, the presence of 60 mol % HFIP resulted in the complete formation of the Giese addition product 50. These results were in accordance with a two-electron allylation pathway, where a carbanionic species served as a key intermediate for nucleophile attack on the π allylpalladium intermediate; therefore, the presence of HFIP as a proton-transfer shuttle²¹ would enhance the competing protonation to provide the Giese addition product. On the contrary, a single-electron allylation pathway was conducted

Scheme 5. Mechanistic Studies



through a direct coupling of the carbon-centered radical and the π -allylpalladium intermediate, most probably being unaffected in the absence or presence of HFIP.

To demonstrate the synthetic utility of this three-component coupling protocol, we performed a concise formal synthesis of mesembrine (Scheme 6). The reaction of 2-aryl acrylate 51, *tert*-butyl dimethylcarbamate 52, and allyl methyl carbonate 3 was conducted with 5 mol % PT, 2.5 mol % Pd₂(dba)₃, and 6





mol % P(3,5-Me₂C₆H₃)₃ under visible-light irradiation, and the desired allylation product **53** was smoothly generated in 59% yield. Through an anti-Markovnikov Wacker oxidation of olefin to aldehyde,²² **53** was converted to **54** in 64% yield. The exposure of **54** to AlMe₃ resulted in a methyl addition to aldehyde, followed by oxidation with Dess–Martin periodinane (DMP). Methylketone **55** was generated in 89% yield in two steps. The treatment of **55** with MeONa gave 1,3-cyclohexanedione **56**, and the exposure of **56** to trifluoroacetic acid and MgSO₄ resulted in the formation of cyclohexenone **57** in 68% yield in two steps, which was actually a key intermediate for the synthesis of (±)-mesembrine **58** by following the procedure reported by Zhang.²³

In summary, we have developed a Pd-catalyzed allylic alkylation reaction by using a HAT photocatalyst-mediated nucleophile generation strategy, enabling the rapid assembly of an easily accessible terminal alkene, an aliphatic $C(sp^3)-H$ coupling partner, and allyl carbonate under mild conditions. This protocol showcases an atom-economic and environmentally friendly method to generate nonstabilized nucleophile through aliphatic $C(sp^3)$ -H bond addition to the terminal alkene, effectively complementing the established methodology for the transition-metal-catalyzed allylic substitution reaction. More significantly, the synthetic utility of this strategy is embodied by the concise synthesis of (\pm) -mesembrine. Mechanistic studies suggest that this three-component coupling protocol proceeds via a radical/ionic relay process, and a carbanionic species serves as a key intermediate for nucleophile attack on π -allylpalladium through a classic twoelectron allylation pathway. We anticipate that this Letter will facilitate the merging of the photocatalytic one-electron reaction and the transition-metal-catalyzed classical twoelectron reaction in the future development.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c01500.

General information, experimental section, compound characterization, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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