

General, Auxiliary-Enabled Photoinduced Pd-Catalyzed Remote Desaturation of Aliphatic Alcohols

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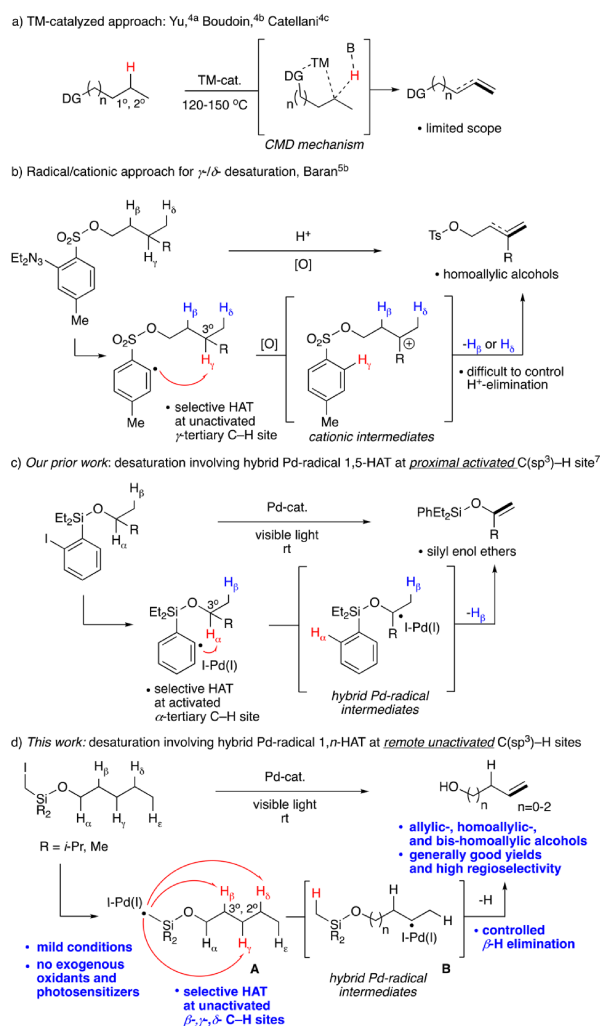
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Supporting Information

ABSTRACT: A general, efficient, and site-selective visible light-induced Pd-catalyzed remote desaturation of aliphatic alcohols into valuable allylic, homoallylic, and bis-homoallylic alcohols has been developed. This transformation operates via a hybrid Pd-radical mechanism, which synergistically combines the favorable features of radical approaches, such as a facile remote C–H HAT step, with that of transition-metal-catalyzed chemistry (selective β -hydrogen elimination step). This allows achieving superior degrees of regioselectivity and yields in the desaturation of alcohols compared to those obtained by the state-of-the-art desaturation methods. The HAT at unactivated $C(sp^3)$ –H sites is enabled by the easily installable/removable Si-auxiliaries. Formation of the key hybrid alkyl Pd-radical intermediates is efficiently induced by visible light from alkyl iodides and Pd(0) complexes. Notably, this method requires no exogenous photosensitizers or external oxidants.

Alkenes are one of the most widely used functional groups in organic synthesis, broadly found in a wide range of bioactive molecules and natural products.¹ Methods toward synthesis of these privileged motifs often involve nonuniversal strategies that require prefunctionalization of starting materials at the desired reaction site. Unfortunately, methods for synthesis of alkenes via direct desaturation of aliphatic chains are less explored. This is mainly attributed to the inherent difficulty of activating the kinetically inert $C(sp^3)$ –H bonds. Although, considerable progress has been made in converting unactivated C–H bonds into valuable C=C and C–heteroatom fragments via transition metal (TM) catalysis,² a synthetically appealing selective site-controlled desaturation of aliphatic systems into privileged olefins still remains underdeveloped. Modern TM-catalyzed approaches typically operate via a direct transfer-hydrogenation process³ or a directed concerted metalation–deprotonation (CMD) pathway.⁴ Between the two pathways, the latter approach is an attractive option owing to its site-controlled capability (Scheme 1a). Nevertheless, this method suffers from low selectivity and efficiency, limited substrate scope, and harsh reaction conditions. Moreover, the site of functionalization is often restricted based on formation of a favorable TM-cyclic intermediate and is limited to activation of 1° and 2° γ/δ -C–H bonds (Scheme 1a). To the best of our knowledge, there have been no reports on TM-catalyzed functionalization of unactivated 3° C–H bonds. Emerging radical strategies, however, have provided

Scheme 1. Desaturations Methods in Aliphatic Systems



solutions for 3° C–H bond functionalization.^{5,6} Thus, in Baran's pioneering work,^{5b} he showcased a guided C–H desaturation of aliphatic systems involving a tether possessing an aryl radical hydrogen abstracting group, which, due to geometrical constraints, favors γ -C–H HAT at the 3° site (Scheme 1b). Owing to the nature of this transformation, the translocated radical undergoes oxidation with an external oxidant, followed by elimination into the alkene moiety.

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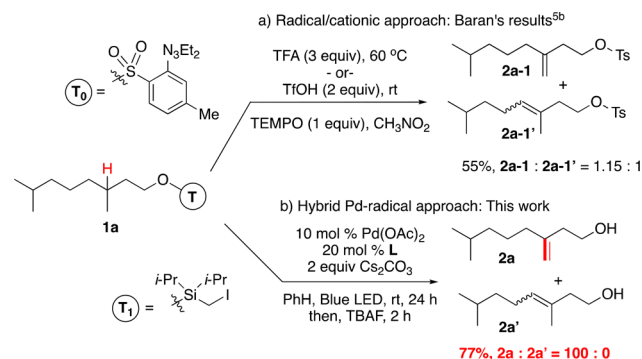
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While groundbreaking, in some cases, this approach suffers from regioselectivity issues due to a nonselective proton loss step from the formed cationic intermediate. Overall, both TM-catalyzed and radical approaches are complementary but still have certain limitations. We have recently reported visible light-induced formation of a hybrid aryl Pd-radical intermediate capable of the HAT process and a subsequent β -hydrogen elimination step to furnish an alkene moiety. Due to the favorable 1,5-HAT process of the aryl hydrogen-atom-abstracting group of the silicon tether, the H atom abstraction occurred exclusively at the proximal α -C–H site, thus resulting in the α -/ β -desaturation of silyl ethers into silyl enols (Scheme 1c).⁷ Herein, we report a general, efficient, selective, and mild visible light-induced⁸ Pd-catalyzed remote desaturation of aliphatic alcohols. This method involves an unprecedented, for alkyl hybrid Pd-radical species,⁹ HAT process at unactivated C(sp³)–H sites¹⁰ (Scheme 1d). The abstraction at β -, γ -, or δ -sites is enabled by employment of easily installable/removable Si-auxiliaries¹¹ (A). The formed transposed hybrid species B furnishes a remote alkene moiety upon a controlled β -hydrogen elimination step, thus resulting in desaturated alcohols with degrees of regioselectivity, unseen, for radical methods.

Based on our recent work on the formation of silyl methyl hybrid-Pd radicals from iodomethylsilanes,¹² we hypothesized that if this moiety (T₁, Scheme 2) could be engaged in a 1,6-

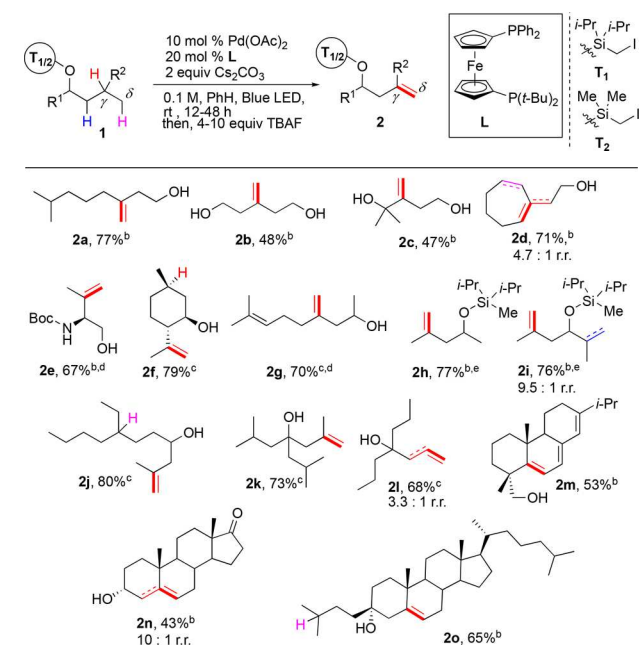
Scheme 2. Comparison Study



HAT event,^{13,14} it would subsequently enable γ -/ δ -desaturation toward important homoallylic alcohols.¹⁵ Furthermore, based on the usually selective β -hydride elimination step in the hybrid Pd-radical mechanism,^{9b,12} it was anticipated that the alkenol product would be formed with high degrees of regiocontrol. Accordingly, we were eager to validate this premise on desaturation of challenging alcohol derivative 1a, which under conditions of the reported radical/cationic protocol^{5b} resulted in a nearly equal mixture of regioisomeric alkenols (2a-1, 2a-1', Scheme 2a). We were pleased to find that exposure of T₁-tethered alcohol 1a-T₁ to our optimized¹⁶ photocatalytic conditions resulted in γ -/ δ -desaturation product 2a in 77% yield as a single regioisomer, thus fully supporting the above hypothesis! Notably, this outcome represents the first remote Pd-catalyzed 3 °C–H functionalization event under mild and neutral conditions. Finally, it deserves mentioning that this photochemical transformation does not require the employment of exogenous photosensitizers¹⁷ or external oxidants.

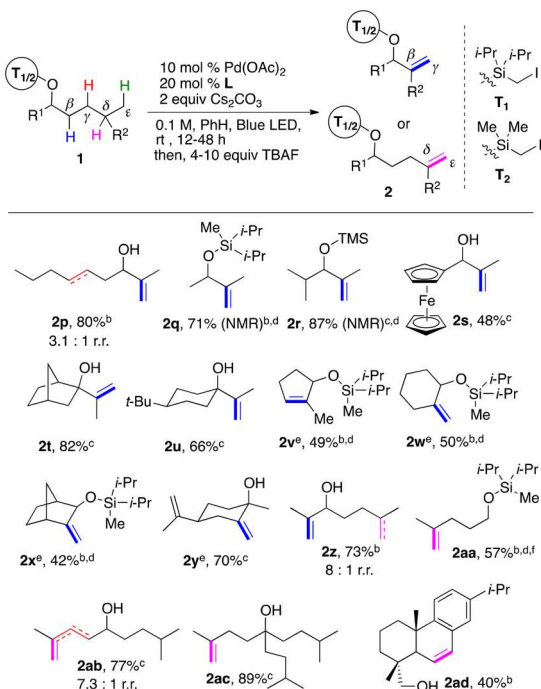
Next, the generality of the γ -/ δ -desaturation of aliphatic alcohols toward homoallylic alcohols was investigated (Table 1). After completion of the desaturation reaction, except for the cases with volatile low-molecular weight alkenols, the silyl-

Table 1. γ -/ δ -Desaturation of Alcohols^a



^aIsolated yields; r.r. = regioisomeric ratio. ^bT₁ was used. ^cT₂ was used. ^dContains minor amount of hydrodehalogenation byproduct. ^eThe desilylation step (TBAF) was omitted.

based tethers were, in one pot, routinely removed by treatment with TBAF. It was found that various primary alcohols, possessing functional groups such as alcohols (1b, c) and amides (1e), underwent smooth γ -/ δ -desaturation to generate their respective homoallylic derivatives (2b, c, e) in good yields. Then, desaturation of bulkier secondary alcohols was tested (1f–1j). For these cases, due to the relative ease of installation, we opted to employ sterically less hindered dimethyl-(iodomethyl)silane tether T₂ instead of bulkier T₁. Desaturation of naturally occurring (–)-menthol (1f), possessing two equally distant sites of functionalization, selectively furnished chiral building block (–)-isopulegol (2f) in 79% yield due to a favorable transition state for an HAT event at the isopropyl group.^{18,19} Endogenous alkene moiety 1g did not compromise the reaction, as diene 2g was formed efficiently. Desaturation of 1h proceeded uneventfully, producing alkene 2h in good yield. Notably, substrates 1i and 1j, which, along with H_γ, possess competitive H β and H δ sites of abstraction, reacted selectively at the γ -C–H sites, thus producing 2i and 2j in good yields and high regioselectivity. Based on these, as well as on the results of a direct competition between H β and H δ sites (*vide infra*, 2z using T₁) and the kinetic studies,¹⁶ the following reactivity preference order for silyl tethers T₁ and T₂ for HAT in substrates possessing 3 °C–H sites with similar BDEs²⁰ was revealed: 1,6 HAT of H γ > 1,5 HAT of H β > 1,7 HAT of H. Tertiary alcohols were also compatible with our desaturation protocol (2k, l). Importantly, HAT at challenging 2° C–H bonds of tertiary alcohol 1l was also achieved, producing 2l in good yield. Furthermore, this method proved competent for desaturation of complex natural products and derivatives. Thus, remote desaturation of abietol (1m) generated its dehydrogenated analog 2m in moderate yield. Moreover, γ -/ δ -desaturation of secondary *cis*-androsterone (1n) and tertiary cholestanol derivative (1o) worked well, furnishing 2n and 2o in reasonable yields.

Table 2. β -/ γ - and δ -/ ϵ -Desaturation of Alcohols^a

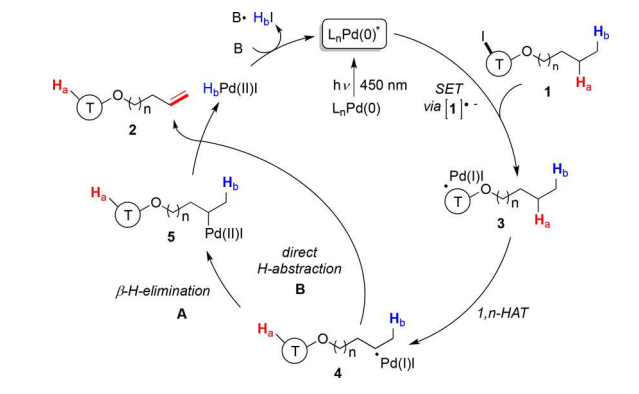
^aIsolated yields; r.r. = regioisomeric ratio. ^bT₁ was used. ^cT₂ was used.

^dThe desilylation step (TBAF) was omitted. ^eFor **1v–1y**, the trans precursor was used. ^fContains minor amount of hydrodehalogenation byproduct.

After developing an efficient method for γ -/ δ -desaturation of aliphatic alcohols into homoallylic alcohols, we aimed at extending this protocol toward formation of valuable allylic alcohols²¹ via the β -/ γ -desaturation process involving 1,5 HAT (Table 2). Delightfully, it was found that secondary and tertiary alcohols bearing an isopropyl unit underwent selective desaturation to generate the corresponding alcohols in a highly efficient manner (**2p–2u**). Subjecting five-membered cycloalkane **1v** to the reaction conditions unexpectedly resulted in the formation of the thermodynamically more stable *endo*-isomer **2v**. In contrast, six-membered β -methyl cycloalkanes produced the kinetic *exo*-methylene products **2w–x** in reasonable yields. Complex limonene derivative **1y** underwent β -/ γ -desaturation producing *exo*-alkene **2y** in 70% yield. Expectedly, based on the Si-tether reactivity preference for HAT (*vide supra*), desaturation of ambident substrate **1z**, possessing competing β -/ γ - and δ -/ ϵ -desaturation sites, preferably occurred at the former site, producing allylic alcohol **2z** in good yield. Finally, we examined the boundaries of this methodology toward δ -/ ϵ -desaturation of alcohols. Gratifyingly, primary (**1aa**), secondary (**1ab**), and tertiary alcohols (**1ac**) all produced the δ -C–H functionalized products in moderate to excellent yields! Likewise, desaturation of complex derivative dehydroabietol **1ad** resulted in δ -/ ϵ -desaturation product **2ad** in moderate yield.

The results of performed radical trap-, radical clock-, and isotope labeling studies¹⁶ supported the radical nature of this transformation. The UV–vis analysis revealed that the Pd(0) complex is the photoabsorbing species. Moreover, the Stern–Volmer studies supported quenching of the excited state of the Pd(0) catalyst by alkyl iodide **1f**.¹⁶ Based on the aforementioned studies, the following mechanism is proposed (Scheme 3).

Scheme 3. Proposed Mechanism



complex produces the active photoexcited Pd(0) complex, which engages in an SET process with alkyl iodide **1** to form alkyl hybrid intermediate **3**. Next, the formed radical species undergoes a rate-limiting 1,*n*-HAT event (for *n* = 5, k_H/k_D = 3.5¹⁶) to generate translocated alkyl hybrid Pd-radical species **4**. The latter, either via a recombination of **4** with the putative Pd(I) intermediate followed by a β -hydride elimination from **5** (path A) or via a direct abstraction of β -hydrogen atom²² by Pd(I) species (**4** $\rightarrow$ **2**, path B),²³ produces the alkene **2**²⁴ and regenerates the Pd catalyst.

In summary, we have developed a room temperature, auxiliary-enabled visible light-induced Pd-catalyzed remote β -/ γ -, γ -/ δ -, and δ -/ ϵ -desaturation of alcohols. The hybrid Pd-radical nature of this protocol enabled efficient functionalization of unactivated C–H sites. Moreover, the desaturation products were formed with superior degrees of regioselectivity compared to the state-of-the-art radical/cationic methods due to a better-controlled Pd-involved β -hydrogen elimination step. Overall, this transformation represents the first practical catalytic desaturation of aliphatic alcohols. We believe that this approach addresses the shortcomings of prior art and provides a new avenue for targeted aliphatic C–H functionalization under photoinduced transition metal catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b08459.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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