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Communication

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Photoinduced Formation of Hybrid Aryl Pd-Radical Species Capable of 1,5-HAT: Selective Catalytic Oxidation of Silyl Ethers into Silyl Enol Ethers

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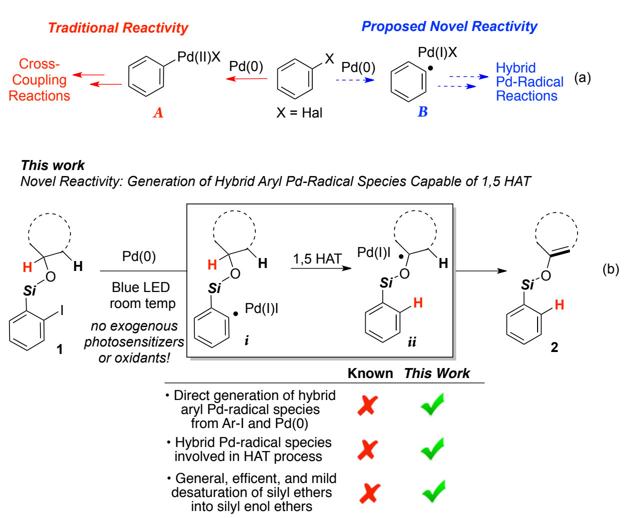
Supporting Information Placeholder

ABSTRACT: A direct visible light-induced generation of a hybrid aryl Pd-radical species from aryl iodide and Pd(0) is reported to enable an unprecedented (for hybrid Pd-radical species) hydrogen atom transfer (HAT) event. This approach allowed for efficient desaturation of readily available silyl ethers into synthetically valuable silyl enols. Moreover, this oxidation reaction proceeds at room temperature without the aid of exogenous photosensitizers or oxidants.

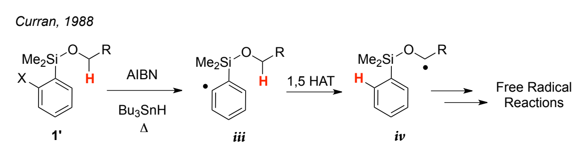
Aryl halides are vital starting materials for a variety of important Pd(0)-catalyzed C–C and C–heteroatom bond forming reactions, which usually involve Pd(II) intermediates **A**, formed via a two-electron oxidative addition process (Scheme 1, a).[1] Alternatively, if a hybrid aryl Pd-radical species **B**, possessing both traditional Pd and radical nature can be realized, it may exhibit novel reactivity.[2] Thus, if conditions for a direct conversion of easily available aryl halides into **B** will be found, it could trigger the development of an array of novel transformations. The work described herein features: (1) the first direct visible light-induced generation of a hybrid aryl Pd-radical species (***i***) from aryl iodide and

Scheme 1. Traditional and Proposed Novel Reactivity of Aryl Halides in Pd(0)-Catalyzed Reactions



Pd(0); (2) capability of the formed hybrid aryl Pd-radical species to undergo a 1,5-hydrogen atom transfer (HAT) process (***i***→***ii***); (3) a new method for general, efficient, and mild desaturation of silyl ethers (**1**) into silyl enol ethers (**2**) (Scheme 1, b).

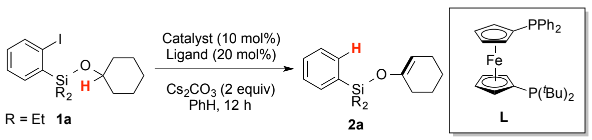
In his pioneering work, Curran reported a remote C–H functionalization of alcohols via a 1,5-HAT processes utilizing a halo-aryl silane tether (**1'**) (eq 1).[3a] Standard radical initiation of **1'** led to the aryl radical ***iii***, which underwent 1,5-HAT to produce alkyl radical ***iv*** capable of undergoing further useful free radical reactions.[3] We thought of developing an oxidative hybrid Pd-radical version of Curran's free radical chemistry as a potentially useful new method. Indeed, if a hybrid aryl Pd-radical complex ***i***, capable of HAT and a subsequent *β*-hydride elimination could be generated (Scheme 1b), it would allow for a direct oxidation of silyl ethers (**1**) into silyl enols (**2**).[4,5] Clearly, the success of this process hinges on the efficient generation of the hybrid aryl Pd-radical species (***i***) from aryl halides, and capability of the latter to undergo HAT, both of which, to the best of our knowledge, are unprecedented.[6,7] We envisioned that putative species ***i*** could possibly be generated either via thermal[6,8] or photochemical[9,10] activation of an aryl iodide in the presence of Pd(0) complex.



(1)

To this end, we first tested silyl-tethered alcohol **1a** under various thermal Pd-catalyzed conditions that have been developed for hybrid Pd-radical reactions of *alkyl halides* (Table 1).[2,6,11] However, employment of $Pd(PPh_3)_4$ or PEPPSI™-IPr complexes resulted in hydro-dehalogenation[12] of **1a** (entries 1, 2). The combination of $Pd(OAc)_2$ and bidentate ferrocene ligands were also incompetent (entries 3, 4). Evidently, other means of activation were needed to stimulate this process. We were intrigued by recent reports of beneficial effect of visible light on promoting radical-type transition metal-catalyzed transformations.[9]

Table 1. Optimization of the Reaction Conditions



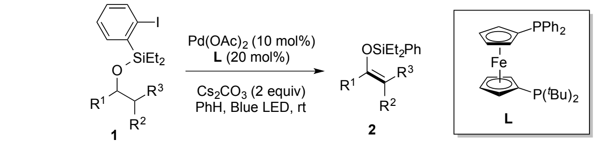
entry	Catalyst	Ligand	Conditions	Yield, %[a]
1	$Pd(PPh_3)_4$	-	120 °C	0[b]
2	PEPPSI™-IPr	-	120 °C	0[b,c]
3	$Pd(OAc)_2$	dppf	120 °C	0[b]
4	$Pd(OAc)_2$	**L**	120 °C	0[b]
5	$Pd(PPh_3)_4$	-	rt, Blue LED	72
6	$Pd(OAc)_2$	dppf	rt, Blue LED	67
7	**$Pd(OAc)_2$**	**L**	**rt, Blue LED**	**79 (79)**[d]
8	$Pd(OAc)_2$	**L**	rt, 23W CFL	49[e]
9	-	**L**	rt, Blue LED	NR

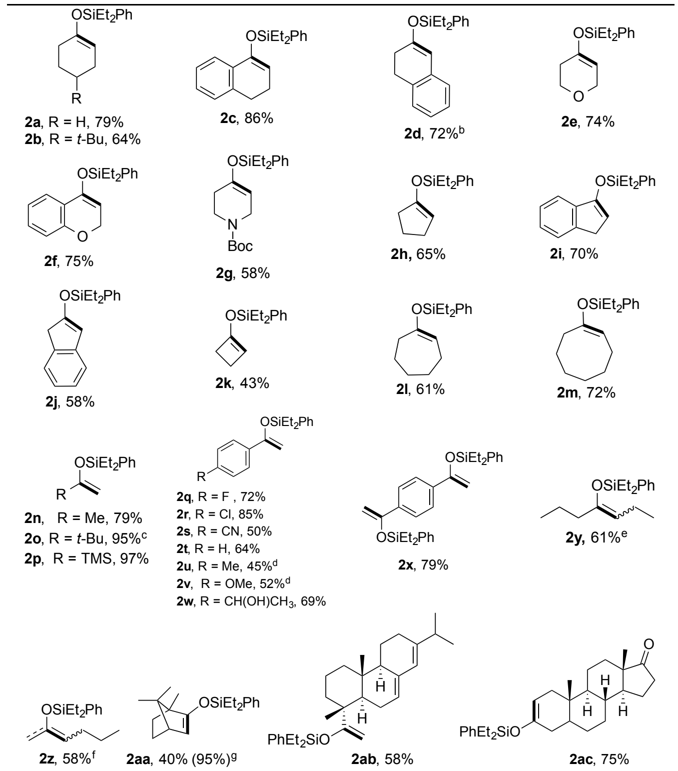
Standard Conditions: **1a** 0.05 mmol scale, PhH 0.1 M, 120 °C or 34W Blue LED. [a]NMR Yield. [b]14-35% of hydro-dehalogenation of **1a** was obtained. [c]5 mol% of catalyst was used. [d]Isolated yield. [e]51% conversion of **1a**.

Thus, we examined the reaction under irradiation of visible light (Blue LED). *Excitingly, product **2a** was obtained in 72% using $Pd(PPh_3)_4$ catalyst at room temperature (Table 1, entry 5). Remarkably, the reaction proceeded quite efficiently without the use of any exogenous photosensitizers.*[13] Next, bidentate phosphine ligand dppf with $Pd(OAc)_2$ was tried, although, it was less efficient (entry 6). Delightfully, 1-diphenylphosphino-1′-(di-tert-butylphosphino)ferrocene (**L**) was found to be the best ligand, producing desaturated product **2a** in 79% yield (entry 7). Notably, performing the reaction with a 23W CFL led to lower efficiency (entry 8). A control experiment indicated that the Pd-catalyst is crucial for this reaction (entry 9). It was also found that both dimethyl- and diisopropyl substituted substrates were less efficient.[14] Obviously, this novel desaturation protocol requires no external oxidants, which makes it milder compared to other desaturation methods.[4b,c,15]

With the optimized conditions in hand, the generality of this reaction was examined. Thus, cyclohexanol derivatives (**1b**-**d**) reacted smoothly to produce silyl enol ethers **2b**-**d** in good yields. Heterocycles, possessing 4-hydroxyltetrahydropyran (**1e**), 4-chromanol (**1f**), and 4-hydroxylpiperidine (**1g**) motifs, afforded products **2e**-**g** in good yields. Cyclopentanol derivatives **1h**-**j** were found to produce **2h**-**j** in reasonable yields. Moreover, cyclobutanol (**1k**) and medium sized cyclic-alcohol derivatives (**1l**-**m**) were found to be competent substrates as well, producing the corresponding products **2k**-**m** in moderate to good yields. Next, we tested this methodology on desaturation of acyclic ethers, which are known to react inefficiently in dehydrogenation reactions.[16] Hence, desaturation of 2-propanol derivative**1n** produced **2n** efficiently. Likewise, substrates

Table 2. Photoinduced Pd-Cat. Oxidation of Silyl Ethers[a]





Standard Conditions: **1** 0.2 mmol, $Pd(OAc)_2$ 0.02 mmol, **L** 0.04 mmol, Cs_2CO_3 0.4 mmol, PhH 0.1 M, 34W Blue LED, rt. [a]Isolated yields. [b]10:1 ratio, major isomer shown. [c]3 mmol scale = 99% isolated yield. [d]Yield based on NMR ratios. [e]Z:E = 3:1. [f]Z:E:terminal = 7:3:1. [g]Yield based on isolation of desilylated product, Camphor (55% isolated yield).

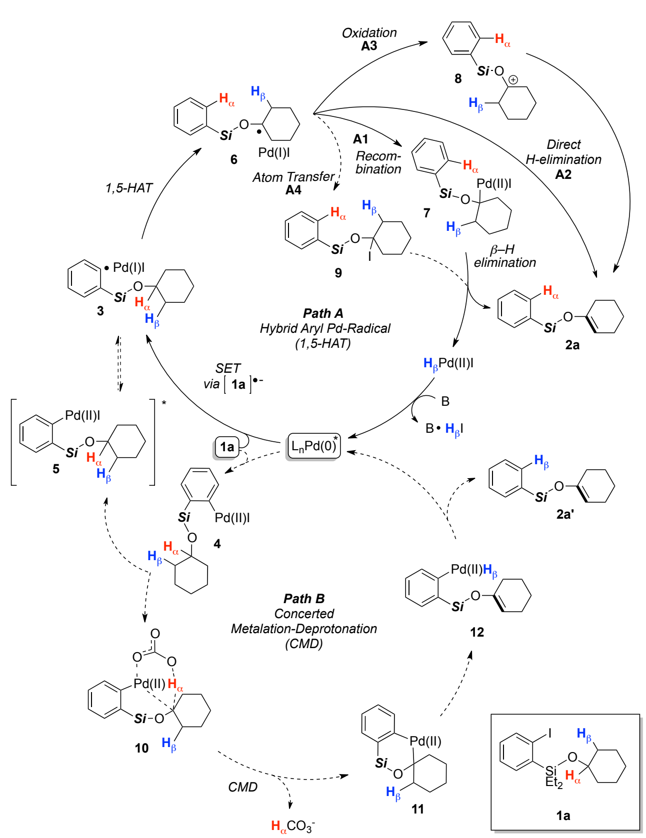
possessing bulky groups at the β-position, such as -*t*-Bu (**1o**) and -TMS (**1p**), provided **2o** and **2p** in 95% and 97% yields, respectively. The practicality of this method was supported by a scale-up experiment with 1.2 grams of **1o**, where the oxidation product **2o** was produced in nearly quantitative yield. Desaturation of 4-substituted benzylic alcohol derivatives **1q**-**w** containing different functionalities, including aryl chloride (**1r**), cyanide (**1s**) and unprotected 2°alcohol (**1w**), proceeded well, producing moderate to good yields of the corresponding silyl enol ethers. Moreover, a double-fold desaturation of diol derivative **1x** led to the dienol ether **2x** in good yield. This methodology also has proven to be efficient on challenging linear substrates, which are known to be unselective in HAT protocols.[3a,3d,17] Thus, 4-heptanol **1y** and 2-hexanol **1z,** selectively generated their respective α-β desaturated products (**2y, z**) in good yields, although as a mixture of stereoisomers.[18] Then, we investigated our technology towards functionalization of more complex molecules. Thus, terpenes **1aa** and **1ab** reacted well, though the former produced an unstable silyl enol (**2aa**) that resulted in 40% isolated yield along with 55% yield of desilylated ketone product (Camphor). Oxidation of steroid androstanone **1ac**, bearing multiple sites of desaturation, proceeded smoothly, producing **2ac** in 75% yield as a sole regioisomer.

We foresee two distinct mechanistic scenarios for this novel oxidation reaction, a radical pathway (***Path A***) and a concerted metalation deprotonation (CMD) protocol (***Path B***) (Scheme 2). First, under visible light (Blue LED), a direct SET[2,6,10,11] from excited Pd(0) complex to aryl iodide **1a** produces a hybrid Pd-radical intermediate **3** (***Path A***). In an alternative, though, less likely scenario,[19] the latter can form through a conventional oxidative addition of Pd(0) complex to **1a** to form the Pd(II) intermediate **4**, followed by its excitation into **5**[20] and a subsequent homolysis.[21] Then, **3** undergoes a 1,5-HAT of H_α to generate the hybrid alkyl Pd-radical complex **6,** which subsequently produces silyl enol **2a** either via recombination and successive *β*-hydride elimination of H_β (Path **A1**),[11] or via a direct H_β–atom elimination[22] with Pd(I)I (Path **A2**). Potentially, **6** can also be converted to **2a** either via oxidation by Pd(I)I into a cationic intermediate **8**, followed by its deprotonation (Path **A3**), or via an atom transfer/HI-elimination sequence (Path **A4**).[23,24] In the alternative pathway (***Path B***), intermediate **4** undergoes a CMD process[16a,25] of H_α (**4→10**) to produce palladacycle **11**. The following *β*-hydride (H_β) elimination of the latter occurs to generate the aryl Pd(II) silyl enol intermediate **12**. A subsequent reductive elimination yields **2a'** and regenerates the Pd(0) catalyst. However, the performed deuterium-labeling experiments disproved this mechanism (***Path B***).[14]

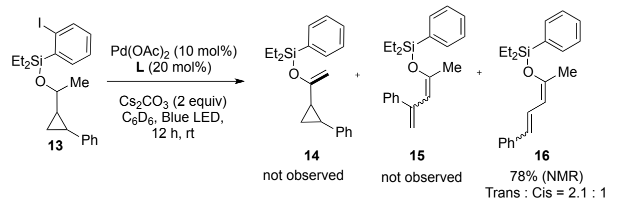
The intermediacy of radical species (***Path A***) was supported by the use of radical scavengers[11] and radical clock experiments.[14,26] Hence, it was found that employment of radical traps, such as galvinyloxy and TEMPO, completely suppressed the reaction.[14] It was also found that cyclopropyl-containing substrate **13** under standard reaction conditions underwent smooth ring opening of the cyclopropyl ring producing **16** as the major product (Scheme 3). Notably, formation of product **14** with preserved cyclopropyl unit and the *β*–C elimination product[27] **15** were not detected.

In conclusion, we demonstrated the first direct generation of a hybrid aryl Pd-radical species from aryl halides and Pd(0), and its capability of promoting 1,5-HAT process, which allowed for a general mild and efficient conversion of easily available silyl ethers into valuable silyl enol ethers. Notably, this photoinduced Pd-catalyzed reaction proceeds at room temperature without any exogenous photosensitizers or oxidants. We envision that this methodology can be applied for a late-stage desaturation of complex molecules.

Scheme 2. Possible Mechanisms



Scheme 3. Radical Clock Experiment



ASSOCIATED CONTENT

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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