

Visible Light-Induced Pd-Catalyzed Alkyl-Heck Reaction of Oximes

Nikita Kvasovs, Valeriia Iziumchenko, Vitalii Palchykov, and Vladimir Gevorgyan*

ABSTRACT: A visible light-induced palladium-catalyzed oxidative C–H alkylation of oximes has been developed. This mild protocol allows for an efficient atom economical C–C bond construction of alkyl-substituted oximes. Broad range of primary, secondary, and tertiary alkyl bromides and iodides, as well as a range of different formaldoximes, can efficiently undergo this transformation. The method features visible light-induced generation of nucleophilic hybrid alkyl Pd radical intermediates, which upon radical addition at the imine moiety and a subsequent β -hydrogen elimination deliver substituted imines.

KEYWORDS: oxime, alkylation, Heck reaction, palladium, light-induced, radical

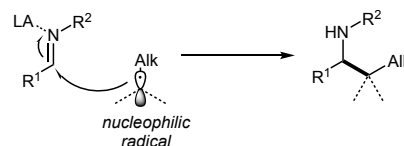
Addition of alkyl radicals to imines is an established strategy toward synthesis of multisubstituted amines.¹ Most often, these reactions rely on employment of stoichiometric radical mediators in combination with catalytic Lewis Acid, which is required for activation of imine moiety towards addition of nucleophilic radical (Scheme 1a).² With recent development of photoredox catalysis,³ as well as metal-catalyzed hydrogen atom transfer techniques,⁴ a number of catalytic versions of such transformations appeared in the literature. Nevertheless, these transformations remain overall reductive, which limits potential for further functionalization. In order to retain synthetically attractive imine group upon radical alkylations, an addition/elimination strategy has been developed (Scheme 1b).⁵ In 1996, Kim and co-workers introduced oxime **1'** bearing sulfonate as a suitable radical leaving group.^{5a} Major problems with such approach are the lengthy synthesis of starting materials (**1'**), and the poor atom economy, as the high molecular weight byproduct is produced. In addition, with the few exceptions,⁶ these methods rely on employment of stoichiometric tin reagents. Despite these synthetic drawbacks, the discussed protocols remain in demand due to the vast synthetic^{7,8} and biological⁹ relevance of oxime-containing molecules. In this light, the development of catalytic oxidative C–H functionalization of oximes **1** is warranted.^{10,11} Herein, we report mild and general visible light-induced Pd-catalyzed method for synthesis of substituted oximes **3** operating via a direct C–H Heck-type alkylation protocol (Scheme 1c).

In recent years, the visible light-induced photoexcited chemistry of palladium has become an emerging field of study.¹² Particularly, we¹³ and others¹⁴ have demonstrated a feasibility of visible light-induced palladium-catalyzed alkyl-Heck reaction of broad range of alkyl electrophiles proceeding via hybrid palladium C(sp³)-centered radical species. Encouraged by this novel mild protocol for generation of alkyl radicals,^{13,14} and motivated by the need of new synthetic methods toward substituted oximes,⁷ we aimed at the development of alkyl imino-Heck reaction. The feasibility of this transformation was supported by the effectiveness for generation of nucleophilic alkyl radicals under light-induced Pd-catalyzed conditions;¹² affinity of oximes toward nucleophilic alkyl radicals;¹⁵ and the propensity of palladium catalysis for the oxidative endgame.¹⁶

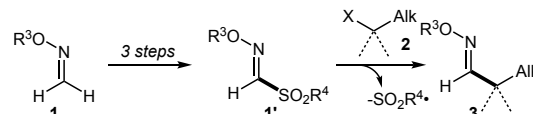
Toward this end, we investigated the reaction between formaldoxime (**1**) and iodocyclohexane (**2**) under our standard palladium(II) acetate/Xantphos catalytic system¹³ in the presence of indium(III) chloride additive. *Gratifyingly, it was found that*

Scheme 1. Radical Reactions of Imines

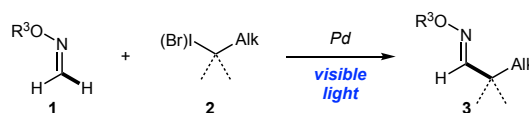
(a) Radical Reductive Alkylation of Imines



(b) Radical Alkylation of Oximes via Addition/Elimination



(c) This work: Heck-Type Alkylation of Oximes



under these conditions, the desired coupling product **3** was formed, albeit in the moderate yield (Table 1, entry 1). The combination of monodentate and bidentate phosphine ligands¹⁷ resulted in a significant improvement of the reaction efficiency (entry 2). Further optimization revealed indium(III) acetate to be superior additive with high reproducibility (entry 3). Control experiments demonstrated that thermal reaction (entry 4) is much less efficient, and Pd catalyst is essential for this transformation (entry 5). Notably, this reaction can proceed without Lewis acid additive, however with lower reproducibility (entry 6).

With the optimized conditions in hand, the scope of alkyl halides was examined first (Scheme 4). It was found that all linear alkyl halides tested, including those having distant functional groups, such as phenyl (**3b**), ester (**3c**), alkyl and aryl ethers (**3d**, **3e**), terminal alkene (**3g**), chloride (**3f**), cyano- (**3h**), and ketone (**3i**), proven to be capable substrates for this coupling reaction. Interestingly, compound **3j** having silicon atom beta to imine could also be

synthesized via this protocol. It is particularly surprising, considering silyl methyl radicals being more electrophilic compared to simple alkyl radicals.¹⁸ Notably, β -D-ribofuranoside derivative **3k**, as well as dipeptide derivative **3l**, could be accessed via this approach,

Table 1. Reaction Optimization

Entry	L1, L2	additive	Yield, % ^a
1	Xantphos	InCl ₃	37
2	Xantphos, PPh ₃	InCl ₃	68
3	Xantphos, PPh₃	In(OAc)₃	99^b
4 ^c	Xantphos, PPh ₃	In(OAc) ₃	27
5 ^d	Xantphos, PPh ₃	In(OAc) ₃	0
6	Xantphos, PPh ₃	none	90

^a GC-MS yield. ^b E/Z 1/1. ^c 80°C, no light. ^d No Pd(OAc)₂.

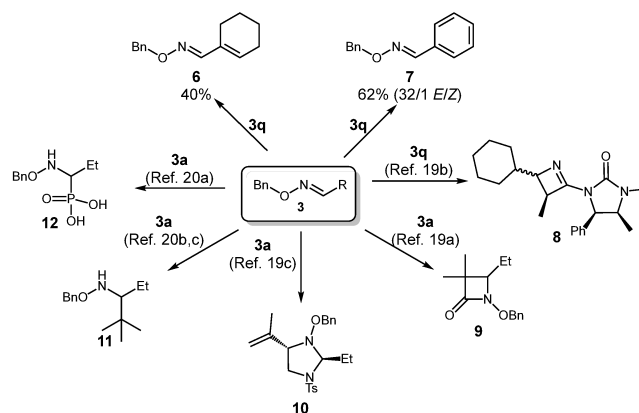
thus indicating applicability of this method to functionalization reactions in a more complex setting. Secondary alkyl halides were found to be the most effective coupling partners. Thus, oximes possessing acyclic substituents (**3m**, **n**), could be obtained in good yields. Oximes having varied size carbocycles (**3o-3s**) could also be efficiently synthesized. Oxime, possessing secondary adamantyl derivative (**3t**) was obtained in nearly quantitative yield. Saturated heterocyclic derivatives, such as oxetane (**3u**), tetrahydropyran (**3v**), and piperidine (**3w**) were also successfully obtained. Intriguingly, this reaction exhibited notable halide effect (**3p**, **q**). While efficiencies of processes for alkyl bromides and iodides were comparable, the use of iodides resulted in products with substantially higher Z isomer content. This counterion effect was observed throughout the entire scope of the reaction, where alkyl iodides in general resulted in products with higher amount of Z oxime. Tertiary alkyl halides **3x-3ab** are also capable coupling partners. In the reaction with tert-adamantyl iodide, however, a substantial amount of non-separable Friedel-Crafts arylation side product was observed. Accordingly, the product in reduced form (**3ac**) was isolated. A simple tert-butyl derivative **3x** was obtained in good yield from both respective iodide and bromide. As in the cases of primary and secondary alkyl halides, the reaction gave mixture of E/Z isomers. In this case, however, it is particularly surprising, as Z isomer containing bulky tertiary substituent is thermodynamically much less favorable. On the other hand, cyclobutene-containing product **3ab** formed with almost exclusive E selectivity.

Next, the scope of oxime in reaction with cyclohexyl bromide was tested. First, benzylic formaldoximes possessing different functional groups at the aryl group were examined. Overall, the process demonstrated outstanding efficiencies for these substrates (**4a-f**). Notably, styrene derivative **4g** could be synthesized in an excellent yield, despite a potential side addition of the alkyl radical at the double bond leading to a highly stabilized benzylic radical.^{13,14} Linear molecules possessing various distant functionalities, such as phenyl (**4h**), ester (**4i**), cyano- (**4j**), and protected primary amine

(**4k**), all worked well. Synthesis of formaldoximes bearing secondary alkoxy groups posed no problem either (**4l,m**). Gratifyingly, imines **4n** and **4o** having easily removable trimethylsilylethoxymethyl (SEM) and benzyloxymethyl (BOM) groups were synthesized with moderate to good yields, which opens access to O-unprotected oximes. At this point, attempts to perform this imine-Heck reaction on aldoximes resulted in reductive radical additions only. Obviously, the presence of additional substituent hampers the re-oxidation of amine into imine.

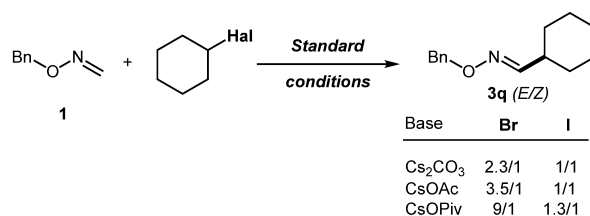
As discussed in the introduction, oximes enjoy vast synthetic applications.^{7,8} There is a number of reported protocols highlighting transformations of oximes **3** obtained via our alkyl Heck-type alkylation protocol and its derivatives (Scheme 2). Primarily, these feature the construction of different nitrogen containing heterocycles **8-10**.¹⁹ Diverse additions to electrophilic carbon of oxime are also well-established (**11**, **12**).²⁰ We have also found that **3** could undergo partial (**6**) or exhaustive (**7**) dehydrogenation upon exposure to different amounts of N-bromosuccinimide.

Scheme 2. Synthetic Utility of Obtained Products

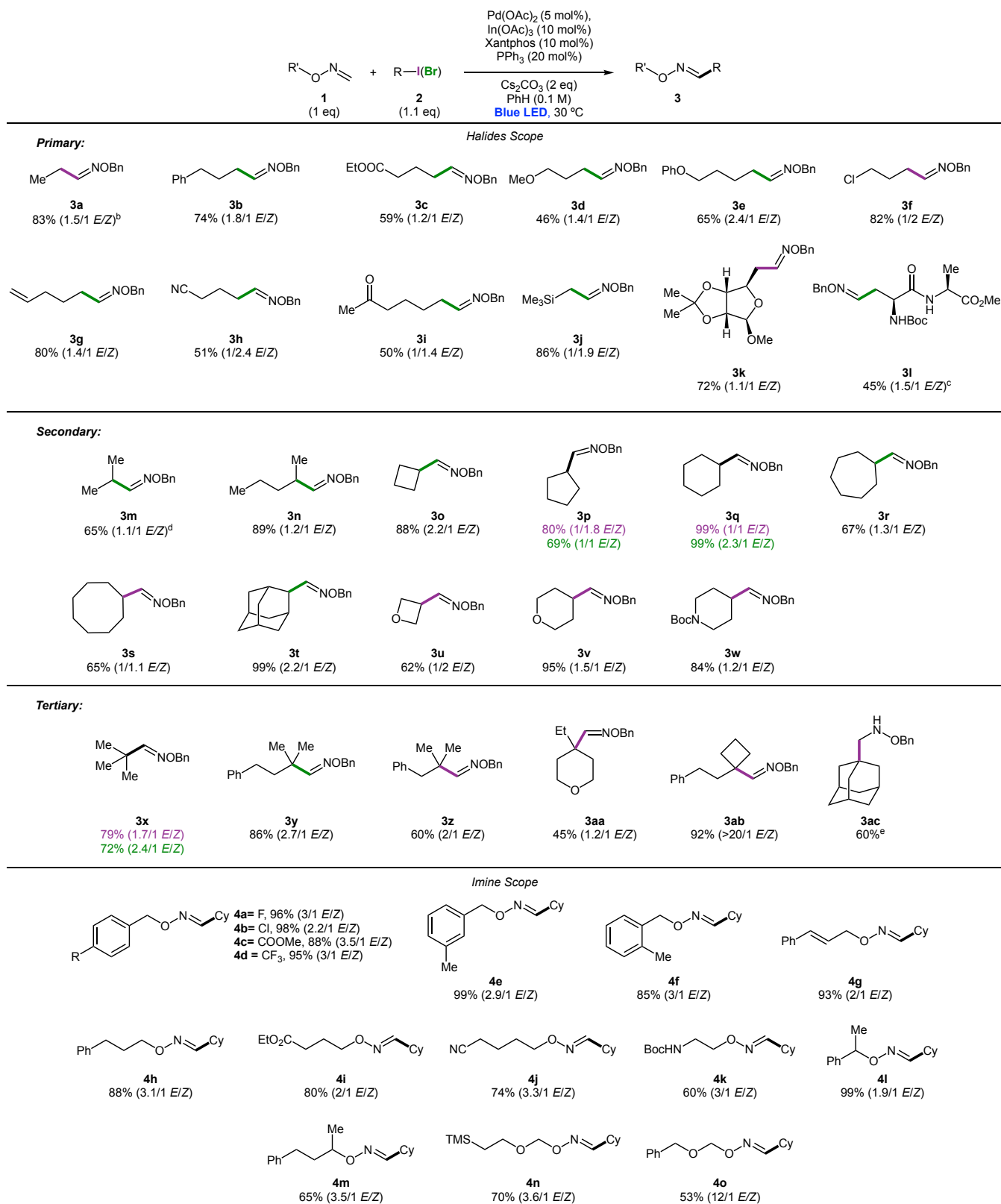


Notably, in contrast to the thermal²¹ and visible light-induced^{13,14} alkyl-Heck protocols, which exclusively or predominantly deliver the thermodynamically more stable E isomers, the alkyl-Heck reaction of oximes shows broadly varied stereoselectivity: from nearly exclusive E (**3ab**) to preferentially Z (**3u**). As alluded above, the stereochemistry depended on the halide used. In addition, it was found to be base-dependent (Scheme 3).²² It seems apparent that, in the case of alkyl bromides, the size of the base (c.f. CsOAc vs CsOPiv) rather than the basicity governs the stereochemical outcome of the reaction. This may imply that the classical β -hydride elimination process, where the base is only required for scavenging acid from HPdX for the catalyst regeneration,²³ is an unlikely end-game scenario in the alkylation of imines with alkyl bromides. Possibly, a base-assisted elimination takes place, which is responsible for the observed base-dependent selectivity. In contrast, this effect is muted for alkyl iodides, suggesting a potential switch of the mechanism.

Scheme 3. Impact of Base and Halide on E/Z Selectivity



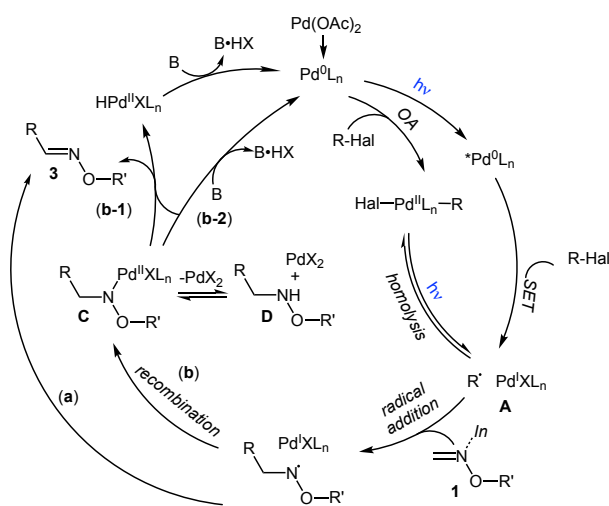
Scheme 4. Scope of Alkyl Heck-type Coupling of Oximes^a



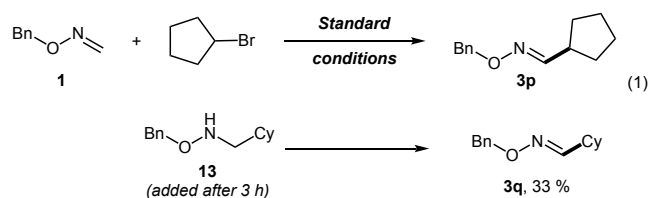
^a0.3 mmol scale, isolated yields. ^b3 eq of EtI. ^c3 eq of oxime. ^d0.5 mmol scale, 3 eq of i-PrBr. ^eYield after reduction with NaBH₃CN.

Based on the relevance to alkyl-Heck reaction of alkenes^{13,14} and above-mentioned observations, the following plausible mechanism is proposed for the novel alkyl-Heck reaction of imines (Scheme 5). First, a hybrid alkyl Pd-radical species **A** is formed either via a direct SET from the generated in situ photoexcited Pd(0) complex or via oxidative addition of alkyl halide with Pd(0) complex, followed by homolysis of the C–Pd bond. The radical nature of this transformation was supported by radical clock-, radical trapping-, and spin-trapping experiments.²⁴ Next, the well-established addition of alkyl radical to oxime takes place,¹⁵ resulting in the formation of the hybrid nitrogen centered radical **B**. A direct hydrogen atom transfer (HAT) by palladium would result in the formation of the reaction product **3** (path **a**). In alternative scenario (path **b**), the radical recombination would produce Pd(II) complex **C**, which could be in equilibrium with alkoxyamine **D** and PdX₂ salt. Pd(II) complex **C** may either undergo classical β -hydride- (path **b-1**) or base assisted elimination process via a classical bimolecular (E2) or a concerted ligand-assisted elimination path (path **b-2**).²⁵

Scheme 5. Proposed Mechanism



The feasibility of path **b** was supported by the observation of small amounts of intermediate **D** by early stage GC/MS analysis of the reaction mixtures. This was further validated by the test experiment, where benzyloxyamine **13** produced substantial amounts of oxime derivative **3q** under our standard alkyl-Heck reaction of oximes (**1**→**3p**, eq. 1). At this point, none of the proposed pathways can be reliably ruled out. It is likely that the reaction path is governed by the nature of counterion X at Pd, contingent to the choice of halide and base used. Obviously, more detailed studies are required to establish a concise mechanism for this novel alkyl imino-Heck reaction.²⁶



In conclusion, the first example of visible light-induced palladium-catalyzed Heck-type alkylation of oximes has been developed. In this transformation, the affinity of oximes to nucleophilic carbon-centered radicals, combined with the oxidative nature of palladium catalysts, allowed for new C–H functionalization protocol. It

is anticipated that this mild visible light-induced method will find application in synthesis and will stimulate development of new C–H functionalization methods.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at Experimental procedures; analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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