Communication

General, Mild, and Selective Method for Desaturation of Aliphatic Amines

Padon Chuentragool, Marvin Parasram, Yi Shi, and Vladimir Gevorgyan

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.8b00488 • Publication Date (Web): 05 Feb 2018

General, Mild, and Selective Method for Desaturation of Aliphatic Amines

Padon Chuentragool, Marvin Parasram, Yi Shi, and Vladimir Gevorgyan*

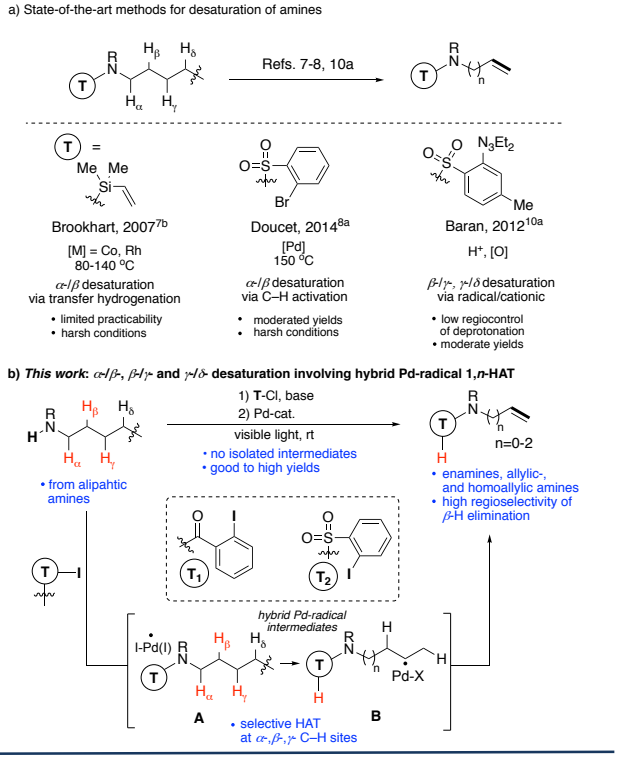
Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061, United States

Supporting Information Placeholder

ABSTRACT: A novel method for desaturation of aliphatic amines into enamines, allylic-, and homoallylic amines has been developed. This general protocol operates via putative aryl hybrid Pd-radical intermediates, which combine the signature features of radical chemistry, a hydrogen atom transfer (HAT) process, and transition metal chemistry, a selective β-hydride elimination step, to achieve efficient and selective desaturation of amines. These hybrid Pd-radical intermediates are efficiently generated under mild photoinduced conditions, and are capable of 1,*n*-HAT (*n*=5-7) event at C(sp^3)–H sites. The selectivity of HAT is tunable by varying different auxiliaries, which highlight the generality of this method. Remarkably, this desaturation method, which operates under mild conditions and does not require employment of exogenous photosensitizers or oxidants, can be performed in a practical scalable fashion from simple amines.

Unsaturated amines are common functional groups found in natural products, bioactive molecules, and are versatile synthetic building blocks.[1] Thus, not surprisingly, an array of methods toward these important motifs has been developed. Conventional approaches to enamines[2] involve condensations of carbonyl group,[2] cross-coupling reactions,[3] or hydroaminations of alkynes.[4] Main methods toward allylic- and homoallylic amines usually rely on alkylation of amines[5] and imines[6] with alkenyl halides. While most of the aforementioned methods are efficient, they all require prefunctionalized starting materials. It is apparent that straightforward conversion of cheap and abundant aliphatic amines into valuable alkenyl amines could serve as a more practical approach. However, methods for direct dehydrogenation of amines into unsaturated amines have not been broadly developed. One elegant strategy for converting amines into enamines employs non-directed[7a] or directed[7b] transfer-hydrogenation process (Scheme 1a). Nonetheless, these methods have limited practicability, as they work on

Scheme 1. Methods for Directed Desaturation of Amines



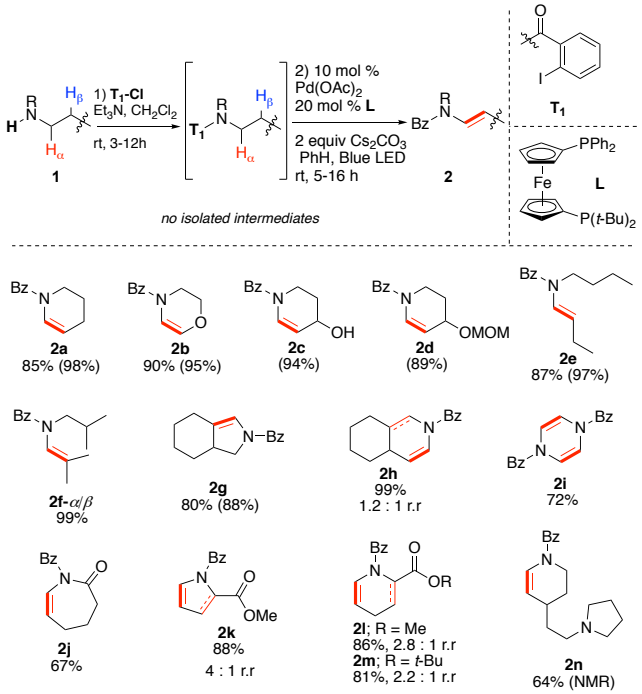
non-functionalizable tertiary alkyl amines[7a] or employ moisture-sensitive *N*-vinylsilane substrates.[7b] Another noteworthy, yet moderately efficient approach towards enamine by Doucet[8a] relies on conventional Pd-catalyzed C–H activation methodology. Both approaches suffer from harsh reaction conditions, and are limited to secondary α-/β-desaturation of amines due to restricted size and steric hindrance of transition metal (TM)-cyclic intermediates.[9] Conversely, radical strategies have shown exceptional capability for functionalization of unactivated tertiary and secondary C(sp^3)–H sites due to a facile HAT event.[10,11] The current state-of-the-art method for a remote desaturation of amines was developed by Baran,[10a] which follows a radical-polar crossover path (Scheme 1a). However, due to generation of cationic inter-

mediates, the end game of this protocol, the proton elimination step, in some cases, results in low regioselectivity of desaturation. Based on these limitations, the development of a practical and universal method for site-selective desaturation of aliphatic amines is highly desirable. Herein, we report a mild, practical, and general protocol for selective desaturation of aliphatic amines (Scheme 1b). This method employs simple aliphatic amines, which, under practical conditions, are selectively and efficiently transformed into enamines, allylic amines, and homoallylic amines. The high selectivity of desaturation is achieved via auxiliaries-controlled 1,5-, 1,6- and 1,7-HAT process of the photo-generated aryl hybrid Pd-radical intermediates[12] (Scheme 1b, **A**→**B**), and a subsequent Pd-involved β-H-elimination step.[13]

Recently, we developed Si-based auxiliaries for proximal and remote desaturation of aliphatic alcohols via photoinduced generation of hybrid aryl- and alkyl Pd-radical species.[14] Expectedly, due to the much lower hydrolytic stability of the N–Si bond compared to that of the O–Si bond,[15] employment of these Si-based tethers for desaturation of aliphatic amines was not feasible. Thus, we examined more practical amide-based tethers. Delightfully, it was found that piperidine **1a**, protected with commercially available *o*-iodobenzoyl chloride (tether $\mathbf{T_1}$), under our previously reported conditions[14] underwent efficient α-/β- desaturation via a facile 1,5-HAT[11] producing cyclic enamine **2a** in nearly quantitative yield (Table 1). This represents the first room temperature dehydrogenation of an amine into an enamine, which operates under visible light-induced[16] Pd-catalyzed conditions without employment of exogenous photosensitizers[17] or oxidants. Moreover, this method can efficiently be performed in a practical fashion without isolation of the tethered amine intermediate to produce enamine **2a** directly from amine **1a** in excellent yield over the two steps.

Next, the generality of the α-/β-desaturation of aliphatic amines was examined. Morpholine derivative **1b** found to be a competent substrate, producing dihydrooxazine **2b** in 95% yield. Piperidines, possessing an unprotected secondary alcohol moiety (**1c**) or a labile acetal group (**1d**), also reacted well, producing enamines **2c** and **2d** in high yields. These results represent the efficient synthesis of endocyclic enamines, which are difficult to access via traditional methods mentioned above.[2-4] Linear amines were also amenable, yielding almost quantitative yields of enamine products (**2e**, **2f**-α/β). It is worth mentioning that amine **1f** failed to react under reported C–H activation conditions.[8a] Gratifyingly, desaturation of pyrrolidine derivative and a bicyclic substrate produced the corresponding enamines in good yields (**2g**, **2h**). Interestingly, double-fold desaturation of piperazine, decorated with two reacting tethers, produced dehydropyrazine **2i** in good yield. Notably, caprolactam derivative was selectively desaturated at an unusual reaction site (**2j**).[18] Dehydrogenation of proline- and pipecolic esters (**1k**-**m**)

Table 1. α-β Desaturation of Amines with T_1[a]

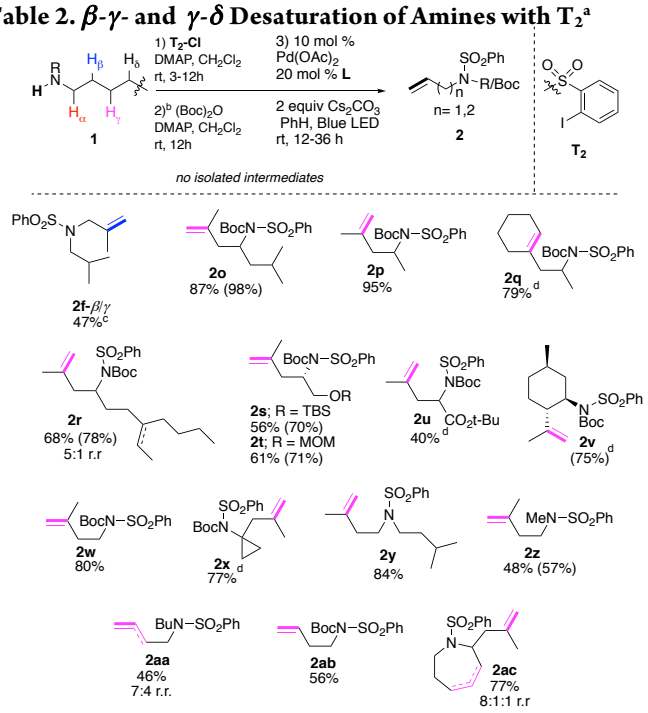


[a]Isolated yields for two steps (**1**→**2**) are shown. Yields for one-step desaturation (from amine protected with reactive tether) are shown in parenthesis. r.r, regiomeric ratio. Bz, benzoyl.

furnished separable mixtures (except for **2k**) of regioisomers, with the less substituted alkenes being the major products. Finally, desaturation of substrate **1n**, containing two amine moieties underwent selective directed reaction at the proximal site producing enamine **2n** in 64% NMR yield.

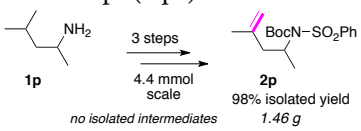
After establishing the scope of α-/β-desaturation, we turned our attention to remote desaturation of amines (Table 2). Apparently, for achieving this goal, the development of the tether capable of HAT at a more distant C–H site was necessary. Based on the efficient and selective remote HAT of Baran's tosyl triazene auxiliary (Scheme 1a),[10a] we assumed that the aryl iodide derivative of it could be an appropriate choice of tether ($\mathbf{T_2}$, Scheme 2). Indeed, this tether can easily be installed at the amine group using a commercially available *o*-iodobenzenesulfonyl chloride. Upon generation of the hybrid Pd-radical species, it expected to undergo 1,*n*-HAT (n=6,7) at an unactivated C(sp^3)–H site,[10a] followed by Pd-involved elimination to selectively furnish a remote alkene moiety. Remarkably, it was found that amine **1f**, now protected by $\mathbf{T_2}$ tether underwent efficient 1,6-HAT to produce β-/γ-desaturation product in 47% yield together with 31% of the cyclic sulfonamide, a product of cyclization of the formed alkyl radical at the aromatic ring of the arylsulfonyl group[19] (Table 2). On the other hand, the same amine (**1f**), while decorated with $\mathbf{T_1}$ tether (*vide supra*), underwent efficient α-/β-desaturation to produce enamine **2f**-$\boldsymbol{\alpha/\beta}$ (Table 1). These results, where two auxiliaries completely switched the regioselectivity of desaturation of

Table 2. β-γ- and γ-δ Desaturation of Amines with T_2[a]



[a]Isolated yields for two steps (**1**→**2**) are shown. Yields for one-step desaturation (from amine protected with reactive tether) are shown in parenthesis. r.r, regiomeric ratio. [b]The Boc installation was not applicable for secondary amines (**1f, 1y-1aa, 1ac**). [c]31% of HAT/cyclization at aromatic ring product was also isolated. [d]Contains minor amount of hydrodehalogenation by-product.

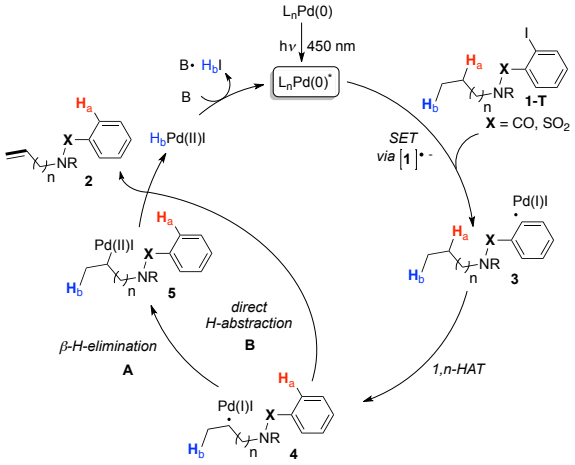
the same substrate,[20] clearly indicate the potential of this strategy toward development of auxiliaries-controlled site selective C–H functionalizations. Due to the observed competing cyclization of the formed β-alkyl radical at the arylsulfonyl group, at the moment, the attempts on further exploration of the β-/γ-desaturation of amines were halted; and we turned our attention to the γ-/δ-desaturation reaction. Delightfully, it was found that γ-/δ-desaturation of the amine **1o** via a three-step procedure (without isolation of the intermediates) produced **2o** as a sole product in excellent yield, which is superior, in both yield and regioselectivity, to those reported via the radical/cationic approach.[10a] Evidently, the observed highly regioselective outcome reflects the nature of the "controlled" β-Pd-H elimination step of the operative hybrid Pd-radical mechanism (*vide infra*). Desaturation of various aliphatic amines (**1p**-**1r**) proceeded uneventfully, resulting in the formation of homoallylic amines (**2p**-**2r**) in good yields. Particularly, acid-sensitive groups, such as primary TBS-ether (**1s**) or acetal groups (**1t**) which do not withstand the reported acidic conditions,[10a,19] were well-preserved in this reaction. Leucine ester (**1u**) and menthyl-amine (**1v**) were found to be competent substrates yielding the corresponding desaturation products **2u**-**2v** in reasonable yields. Amines bearing primary (**1w**) and tertiary (**1x**) alkyl carbon chains also provided high yields of the corresponding desaturation products. Notably, unprecedented remote desaturation of secondary amines **1y**, **1z** proceeded smoothly, furnishing the corresponding products (**2y**, **2z**) in good to excellent yields. Markedly, *functionalization of inert secondary C–H bonds occurred efficiently* (**1aa, 1ab**), resulting in homoallylic amines **2aa, 2ab** in respectable yields, where substrate possessing bulkier substituent at *N*-atom (**1ab**) resulted in better selectivity of the HAT event. A heterocyclic substrate, azepane derivative **1ac**, reacted efficiently to produce **2ac** in 77% yield. Importantly, under the reported conditions,[15] benzenesulfonyl group in homoallylic amine **2y** can easily be removed.[19] Finally, the practicality of this method was illustrated by a gram-scale desaturation of amine **1p** into homoallylic amine **2p** in nearly quantitative yield over the three steps (eq 1).



(1)

Based on the literature reports[13,14] and our initial mechanistic studies,[19] including the radical scavenger experiments, deuterium labeling studies, and Stern-Volmer quenching studies, the following mechanism for this remote desaturation reaction of amines is proposed (Scheme 2). The formed in situ Pd(0) complex undergoes excitation by the visible light to form the active Pd(0)* catalyst. The latter engages in an SET event with aryl iodide **1-T** to generate aryl hybrid Pd-radical species **3**, which via 1,*n*-HAT (*n*=5-7) produces alkyl hybrid Pd-radical species **4**. A subsequent β-hydrogen elimination (path **A**)[13] or a direct hydrogen abstraction (path **B**)[21] generates the desaturated product **2** and regenerates the catalyst.

Scheme 2. Proposed Mechanism



In summary, a general, mild, efficient, and selective method for desaturation of aliphatic amines has been developed. This method employs easily installable/removable[15,19] aryl iodide-containing tethers, which upon visible light irradiation/Pd-catalysis generate an aryl radical at the tether, which triggers an auxiliary-controlled 1,*n*-HAT event at the aliphatic amine moiety, followed by the Pd-assisted β-H

elimination step. It is expected that this operationally simple and easily scalable method, which does not require employment of exogenous photosensitizers or external oxidants, will find broad applications in synthesis.

ASSOCIATED CONTENT

Supporting Information

This Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedures and compound characterization data (PDF).

AUTHOR INFORMATION

Corresponding Author

*vlad@uic.edu

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank National Institutes of Health (GM120281) for financial support of this work. We also thank Dr. Yang Wang (Northwestern University) for helpful discussions.

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