

Communication

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Palladium-Catalyzed Intermolecular Dehydrogenative Aminohalogenation of Alkenes under Molecular Oxygen: An Approach to Brominated Enamines

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Supporting Information Placeholder

ABSTRACT: A novel and efficient palladium-catalyzed dehydrogenative aminohalogenation of alkenes with molecular oxygen as the sole oxidant has been developed. This protocol provides a valuable synthetic tool for the assembly of a wide range of brominated enamines under mild conditions, with unprecedented stereoselectivity and exceptional functional group tolerance. This attractive route for the synthesis of brominated enamines is of great significance due to the products' versatile reactivity for further transformations.

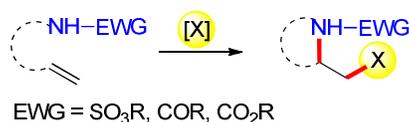
Alkene difunctionalization, involving the formation of two new vicinal chemical bonds, exemplifies a class of reactions with significant synthetic potential to rapidly increase molecular complexity.¹⁻³ Among them, the aminohalogenation of alkenes has attracted intensive attention over the years particularly in developing regio- and stereoselective reaction systems to provide multifunctional alkane products (Scheme 1a).⁴⁻⁸ Despite of the overall efficiency and versatility of this transformation, significant limitations still exist. For instance, the nitrogen sources have been limited to sulfonamides,⁶ amides⁷ and carbamates⁸ so far. Simple aromatic amines have not been successfully used as the nitrogen source in such transformations yet.⁹

On the other hand, as for the final products compared with traditional aminohalogenation of alkenes, dehydrogenative aminohalogenation would be of great significance to yield synthetically useful halogenated enamines, which are versatile building blocks in organic synthesis and medicinal chemistry, as well as valuable intermediates in the construction of biologically active natural products. To the best of our knowledge, there are no reported examples dedicated to dehydrogenative difunctionalization of alkenes to afford multifunctional olefins. Herein we disclose the first example of a highly regio- and stereoselective Pd-catalyzed dehydrogenative aminohalogenation of activated alkenes with molecular oxygen as the sole oxidant (Scheme 1b).¹⁰ The present protocol directly employs simple aromatic amines as the

nitrogen sources and more importantly provides highly convenient access to halogenated enamine scaffold which was difficult to prepare by traditional methodologies.¹¹

Scheme 1. Difunctionalization and Dehydrogenative Difunctionalization of Alkenes with Amines and Halogens

(a) Aminohalogenation of alkene (previous reports)



(b) Dehydrogenative aminohalogenation of alkene (this work)

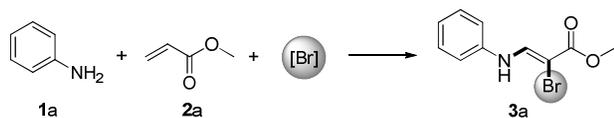


We commenced our study by investigating the Pd-catalyzed reaction of aniline **1a** and methyl acrylate **2a** in the presence of bromine source with O₂ as the oxidant (Table 1). Fortunately, the desired product (*Z*)-**3a** was obtained in 62% GC yield with LiBr¹² (4 equiv) as bromine source and PdCl₂ as catalyst in acetonitrile under 5 atm O₂ (entry 1). The use of Pd(OAc)₂ as the catalyst resulted in a decent boost in the yield of (*Z*)-**3a**, while Pd(PPh₃)₂Cl₂ and Pd(PPh₃)₄ gave decreased yields (entries 2-4). Further optimization showed that the bromine source was critical for the success of this reaction, and the desired product (*Z*)-**3a** was hardly obtained with TBAB or NBS (entries 5-6). Screening of different solvents revealed that using THF as solvent led to further increase in the yield of (*Z*)-**3a** with excellent stereoselectivity (>20:1) (entries 7-8). The reaction hardly proceeded to give the desired product under 1 atm O₂ (entry 9). Notably, no reaction was observed using stoichiometric Pd(OAc)₂ under nitrogen atmosphere, suggesting that O₂ is likely to be involved in the product forming step rather than reoxidation of Pd(o) (entry 10).

We next evaluated the substrate scope of this transformation. The optimized reaction conditions were found to be applicable to a broad range of substrates (Scheme 1). As for the aniline partner, various valuable functional groups such as methoxyl, fluoro, chloro, bromo, ester, methyl, cyanide, mesyl, and trifluoromethyl were reasonably well tolerated in *meta* and *para* positions of the aromatic ring, providing ample opportunity for further derivatization of the products (3a-3k). The structure of 3j was further characterized by X-ray crystal diffraction measurement.^{13,14} Besides, α -naphthylamine and β -naphthylamine proceeded smoothly to give the corresponding products in excellent yields (3p-3q). The *ortho* substituted anilines retarded the reaction, possibly due to the steric interference. Gratifyingly, good results were obtained with longer reaction times. It is noteworthy that coumarin 151 was also productive, leading to product 3r in excellent yield. Unfortunately, benzylamine and *N*-methylaniline could not undergo this dehydrogenative aminohalogenation of alkenes in current reaction system.

On the other hand, acrylates with various functional groups, such as cyclohexyl, tetrahydrofuran, and trifluoromethyl, were successfully transformed into desired products in good to excellent yields (3s-3w). Intriguingly, hydroxyl was also tolerated well in this reaction system, with 3x obtained in 80% yield. Other alkenes with electron-withdrawing groups, including acrylamide and acrylonitrile, gave the corresponding products in good yields (3y-3z).

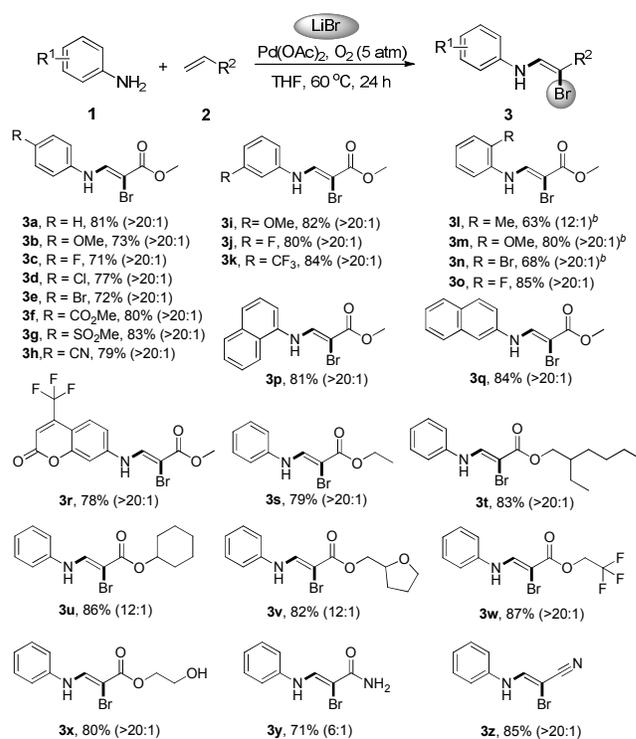
Table 1. Optimization of the Reaction Conditions^a



entry	[Br] source	catalyst	solvent	yield(%) ^b
1	LiBr	PdCl ₂	CH ₃ CN	62
2	LiBr	Pd(OAc) ₂	CH ₃ CN	79
3	LiBr	Pd(PPh ₃) ₂ Cl ₂	CH ₃ CN	43
4	LiBr	Pd(PPh ₃) ₄	CH ₃ CN	trace
5	TBAB	Pd(OAc) ₂	CH ₃ CN	trace
6	NBS	Pd(OAc) ₂	CH ₃ CN	-
7	LiBr	Pd(OAc) ₂	DMF	57
8	LiBr	Pd(OAc) ₂	THF	87 ^c
9 ^d	LiBr	Pd(OAc) ₂	THF	trace
10 ^e	LiBr	Pd(OAc) ₂	THF	-

^aReaction conditions: aniline 1a (0.5 mmol), methyl acrylate 2a (0.8 mmol), [Br] Source (4 equiv), catalyst (10 mol %), 2 mL solvent, under 5 atm O₂, 60 °C for 24 h. ^bGC yield based on 1a. ^cZ/E ratio >20:1. ^dThe reaction proceeded with an oxygen balloon. ^eWith Pd(OAc)₂ (1 equiv), under N₂ atmosphere.

Scheme 2. Pd-Catalyzed Dehydrogenative Aminohalogenation of Alkenes^a



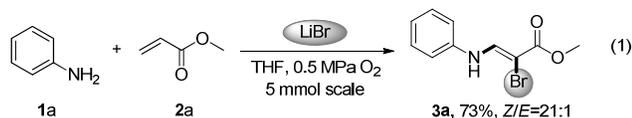
^aReaction conditions: aromatic amine 1 (0.5 mmol), alkene 2 (0.8 mmol), LiBr (4 equiv), Pd(OAc)₂ (10 mol %), 2 mL THF, under 5 atm O₂, 60 °C for 24 h. Yields of isolated products are reported, Z/E ratio is reported in parentheses. ^bThe reaction time was prolonged to 60 h.

The vinyl halide functionality and the free NH functionality in the product molecules enable them to be attractive and versatile synthetic building blocks in a variety of chemical transformations, leading to more complicated organic architectures by the formation of new C-C, C-N, etc. bonds. Thus to demonstrate the synthetic utility of this protocol, the newly formed brominated enamines were employed for further transformations to prepare a series of functionalized products (Scheme 3). The Suzuki-Miyaura cross-coupling reactions of 3a and 3b with phenylboronic acid delivered arylated compounds 4a and 4b, respectively, in excellent yields.¹⁵ Brominated enamine 3a was successfully reduced to methyl 2-bromo-3-(phenylamino) propanoate (5) by NaBH₄ (3 equiv) in 91% yield.¹⁶ Intriguingly, 3a and 3d gave rise to the formation of tertiary amine 6a and 6d, respectively, in excellent yields with excessive NaBH₄ (8 equiv) and prolonged reaction time, probably resulting from the further reduction of the corresponding amide compounds formed *in situ* from alkylamines and acetic acid.

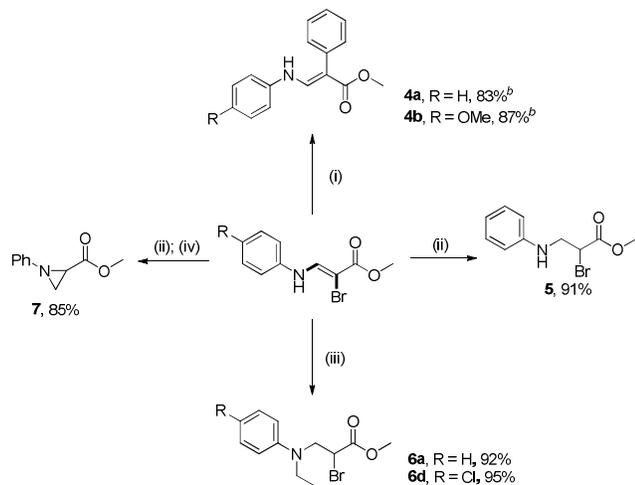
Moreover, 3a was efficiently transformed into aziridine compound 7 in 85% overall yield via a reduction/intramolecular formation of C-N bond sequence without purification of the reduced product 5. Aziridine compounds have become useful synthons in organic synthesis due to their diverse reactivities. Especially, the activated aziridine compounds, such as aziridine-2-carboxylic acid derivatives, have been widely investigated in ring-opening reactions to produce a large number of functionalized products that are not easily accessible by other means.¹⁷ Thus, this method also provides a novel and efficient access to the

aziridine compounds from readily available starting materials under mild conditions.

The reaction is scalable and practical since a satisfactory yield (73%) with excellent stereoselectivity ($Z/E=21:1$) was obtained in the presence of just 0.5 mol % $\text{Pd}(\text{OAc})_2$ when the reaction was performed on 5 mmol scale (eq 1).¹⁴

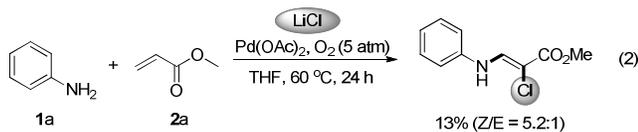


Scheme 3. Selected Transformations of Brominated Enamines^{a,14}



^aReaction conditions: (i) $\text{Pd}(\text{OAc})_2$ (5 mol %), Xphos (10 mol %), $\text{PhB}(\text{OH})_2$ (3.0 equiv), K_3PO_4 (3.0 equiv), toluene, 110 °C, 10 h. (ii) NaBH_4 (3 equiv), AcOH, rt, 2 h. (iii) NaBH_4 (8 equiv), AcOH, rt, 8 h. (iv) K_3PO_4 , toluene, 70 °C, 36 h. ^bThe stereoselectivity was 6:1.

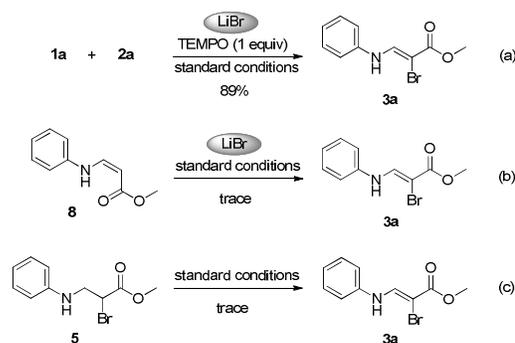
To further highlight the versatility of this strategy, we next attempted to other halide ions. A preliminary experiment showed that the addition of 4 equiv of LiCl instead of LiBr results in the expected chlorinated enamine product in 13% GC yield under analogous conditions, with a stereoselectivity (Z/E) of 5.2/1 (eq 2). This result provides extremely promising precedent that palladium-catalyzed intermolecular dehydrogenative aminochlorination of alkenes can be realized to give chlorinated enamines under molecular oxygen.



To gain insight into the mechanism of the dehydrogenative aminohalogenation process, several controlled experiments were conducted. First, when the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO; 1 equiv) was added under the standard conditions, the reaction afforded **3a** in 89% yield (Scheme 4a), indicating the transformation might not proceed via a free-radical pathway. Subsequently, methyl 3-(phenylamino) acrylate (**8**), a side product in some cases, when treated with 4 equiv LiBr under the standard

conditions, gave a trace amount of **3a** (Scheme 4b), indicating that **3a** was not derived from simple bromination of **8**. We speculated that **3a** might be formed through the oxidation of methyl 2-bromo-3-(phenylamino) propanoate (**5**). However, only trace **3a** was detected by GC-MS when **5** was subjected to the standard conditions (Scheme 4c). These results described above suggested that neither **8** nor **5** was possible intermediate of the transformation. Combining with the fact that N-methylaniline could not undergo this transformation, we speculated that the NH in the alkyl palladium intermediate, formed by nucleopalladation of an alkene, played an important role in the formation of the final product.

Scheme 4. Mechanistic Investigations of the dehydrogenative aminohalogenation process



In summary, we have developed a novel and efficient palladium-catalyzed dehydrogenative aminohalogenation of activated alkenes with molecular oxygen as the oxidant, with unprecedented stereoselectivity and exceptional functional group tolerance. It represents an unprecedented example of the dehydrogenative difunctionalization of alkenes to our knowledge. In addition, this protocol provides a valuable synthetic tool for the assembly of a wide range of brominated enamines under mild conditions, which are expected to be useful intermediates for the preparation of pharmaceutically and biologically active compounds as well as functional materials. Moreover, the use of inexpensive and readily available starting materials, as well as the environmentally benign oxidant, makes this practical and atom-economy approach particularly attractive. Further investigations toward the scope of the reaction, a detailed mechanism, and applications in organic synthesis are currently ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data and spectra of products, and X-ray crystal structures of **3j**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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