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

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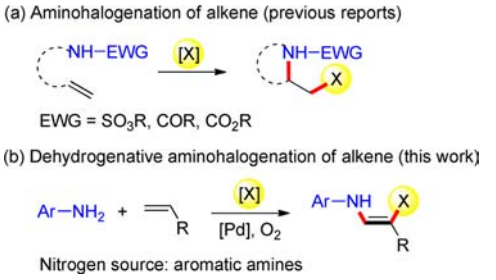
Supporting Information

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 attention over the years, particularly in developing regio- and stereoselective reaction systems to provide multifunctional alkane products (Scheme 1a).[4−8] Despite the overall efficiency and versatility of this transformation, significant limitations still exist. For instance, the nitrogen sources have been limited to sulfonamides,[6] amides,[7] and carbamates[8] so far. Simple aromatic amines have not yet been successfully used as the nitrogen source in such transformations.[9]

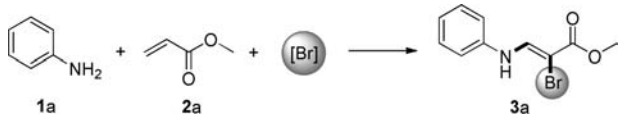
Scheme 1. Difunctionalization and Dehydrogenative Difunctionalization of Alkenes with Amines and Halogens



On the other hand, as for the final products compared with those of 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 a halogenated enamine scaffold which was difficult to prepare by traditional methodologies.[11]

We commenced our study by investigating the Pd-catalyzed reaction of aniline **1a** and methyl acrylate **2a** in the presence of a bromine source with O_2 as the oxidant (Table 1). Fortunately, the desired product (*Z*)-**3a** was obtained in 62% GC yield with LiBr[12] (4 equiv) as bromine source and $PdCl_2$ as catalyst in acetonitrile under 5 atm O_2 (entry 1). The use of $Pd(OAc)_2$ as the catalyst resulted in a decent boost in the yield of (*Z*)-**3a**, while $Pd(PPh_3)_2Cl_2$ and $Pd(PPh_3)_4$ gave decreased yields (entries 2−4). Further optimization showed that the bromine source was critical for the success of this reaction, and very little of the desired product, (*Z*)-**3a**, was obtained with TBAB or

Table 1. Optimization of the Reaction Conditions[a]



entry	[Br] source	catalyst	solvent	yield (%)[b]
1	LiBr	$PdCl_2$	CH_3CN	62
2	LiBr	$Pd(OAc)_2$	CH_3CN	79
3	LiBr	$Pd(PPh_3)_2Cl_2$	CH_3CN	43
4	LiBr	$Pd(PPh_3)_4$	CH_3CN	trace
5	TBAB	$Pd(OAc)_2$	CH_3CN	trace
6	NBS	$Pd(OAc)_2$	CH_3CN	–
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	–

[a]Reaction 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 O_2, 60 °C for 24 h. [b]GC yield based on **1a**. [c]*Z*/*E* ratio >20:1. [d]The reaction proceeded with an O_2 balloon. [e]With $Pd(OAc)_2$ (1 equiv), under N_2 atmosphere.

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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 (*Z*)-**3a**) under 1 atm O_2 (entry 9). Notably, no reaction was observed using stoichiometric $Pd(OAc)_2$ under N_2 atmosphere, suggesting that O_2 is likely to be involved in the product-forming step rather than reoxidation of Pd(0) (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] In addition, *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 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 the current reaction system.

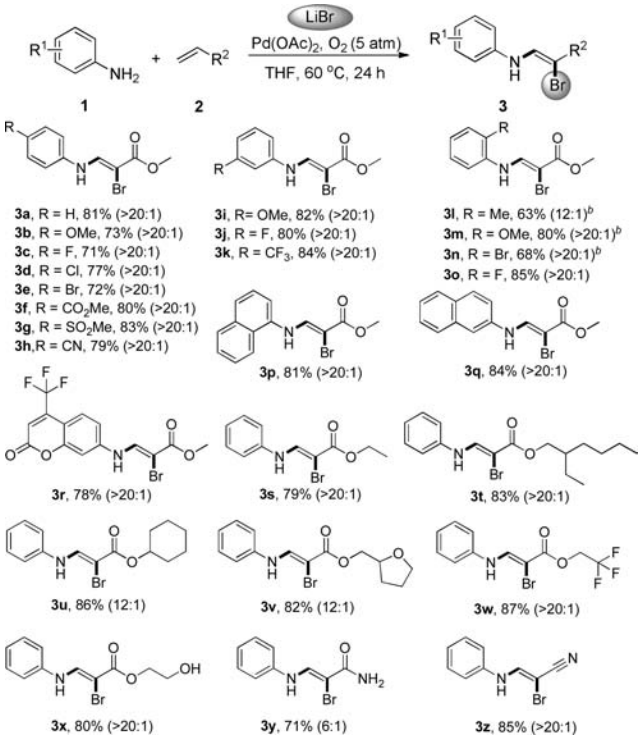
On the other hand, acrylates with various functional groups such as cyclohexyl, tetrahydrofuran, and trifluoromethyl were successfully transformed into desired products in good to excellent yields (**3s**−**3w**) (Scheme 2). Intriguingly, hydroxyl was also well tolerated in this reaction system, with **3x** obtained in 80% yield. Other alkenes with electron-withdrawing groups, including acrylamide and acrylonitrile, gave the corresponding products in good yields (**3y**, **3z**).

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 respectively delivered arylated compounds **4a** and **4b** in excellent yields.[15] Brominated enamine **3a** was successfully reduced to methyl 2-bromo-3-(phenylamino) propanoate (**5**) by $NaBH_4$ (3 equiv) in 91% yield.[16] **3a** and **3d** respectively gave rise to the formation of tertiary amines **6a** and **6d** in excellent yields with excessive $NaBH_4$ (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 a 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.

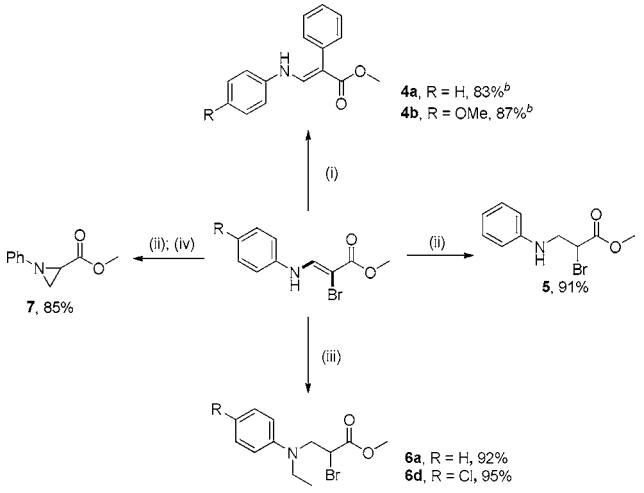
The reaction is scalable and practical since a satisfactory yield (73%) with excellent stereoselectivity (*Z*/*E* = 21:1) was

Scheme 2. Pd-Catalyzed Dehydrogenative Aminohalogenation of Alkenes[a]



[a]Reaction 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 O_2, 60 °C for 24 h. Yields of isolated products are reported, *Z*/*E* ratio is reported in parentheses. [b]The reaction time was 60 h.

Scheme 3. Selected Transformations of Brominated Enamines[a,14]



[a]Reaction conditions: (i) $Pd(OAc)_2$ (5 mol %), Xphos (10 mol %), $PhB(OH)_2$ (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. [b]The stereoselectivity was 6:1.

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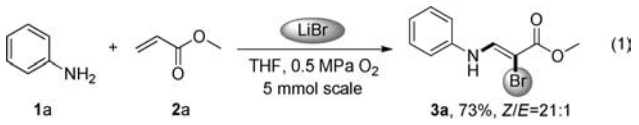
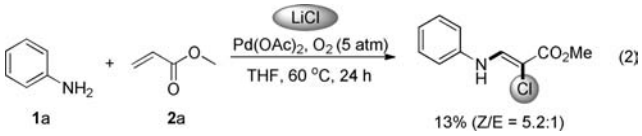
obtained in the presence of just 0.5 mol % $Pd(OAc)_2$ when the reaction was performed on 5 mmol scale (eq 1).[14]



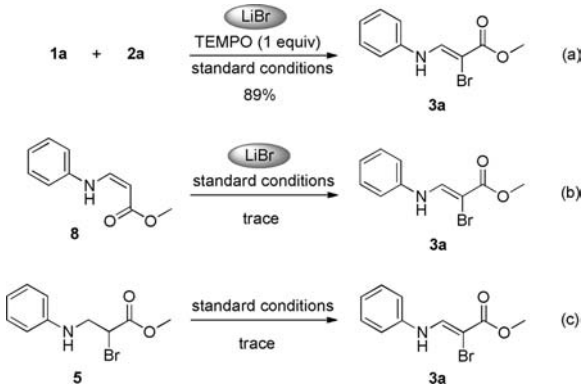
To further highlight the versatility of this strategy, we next attempted other halide ions. A preliminary experiment showed that the addition of 4 equiv of LiCl instead of LiBr resulted in the expected chlorinated enamine product in 13% GC yield under analogous conditions, with a stereoselectivity (Z/E) of 5.2/1 (eq 2). This result provided 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 that the transformation might not

Scheme 4. Mechanistic Investigations of the Dehydrogenative Aminohalogenation Process



proceed via a free-radical pathway. Subsequently, methyl 3-(phenylamino)acrylate (**8**) (a side product in some cases) gave a trace amount of **3a** (Scheme 4b) when treated with 4 equiv LiBr under the standard conditions, 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 standard conditions (Scheme 4c). These results described above suggested that neither **8** nor **5** was a possible intermediate of the transformation. When we saw 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 fomation of the final product.

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. To our knowledge, it represents an unprecedented example of the dehydrogenative difunctionalization of alkenes. In addition, this protocol provides a valuable synthetic tool for the assembly under mild conditions of a wide range of brominated enamines that 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-economical 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.

CCDC 875562 contains the supplementary crystallographic data for this paper. These data can be downloaded free of charge via www.ccdc.cam.ac.uk/conts/retrieving.hmtl.

■ 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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Notes

The authors declare no competing financial interest.

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(14) See the Supporting Information for details.

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