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Efficient Selenium-Catalyzed Selective C(sp^3)−H Oxidation of Benzylpyridines with Molecular Oxygen

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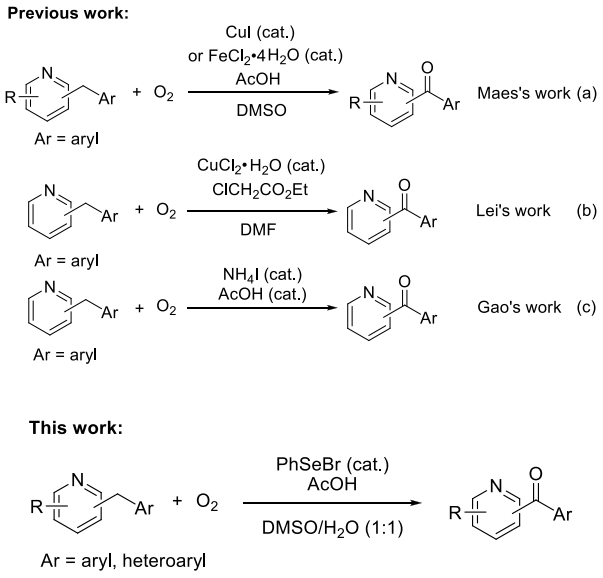
Abstract. An efficient selenium-catalyzed direct oxidation of benzylpyridines in aqueous DMSO has been successfully developed by using molecular oxygen as the oxidant. A variety of benzoylpyridines with broad functional group tolerance were obtained in modest to excellent yields and with exclusive chemoselectivity.

Keywords: selenium catalysis; heterocycles; C—H oxidation; molecular oxygen

Direct oxidation of inert sp^3 C—H bonds to the corresponding carbonyl groups is one of the most prevailing and reliable approaches for the construction of ketone building blocks.[1] Benzoylpyridines are a class of significant architectures in light of their potential applications in pharmaceutical industry[2,3] organic transformations[4] and coordination chemistry.[5] Many traditional synthetic methods for these compounds have been established with the aid of transition metal catalysts[6] and stoichiometric quantities of toxic oxidants.[7] In catalytic asymmetric hydrogenation of N-heteroaromatic compounds, brønsted acids and organic halides were introduced as activators to interact with N-containing substrates in order to destroy the aromaticity partially and activate the substrates.[8] The use of molecular oxygen as the oxidant is always a long-term goal in organic synthesis because molecular oxygen is one of the most inexpensive, available and eco-friendly oxidants.[9] In recent years, some impressive progress with molecular oxygen as oxidants has been made in the direct oxidation of methylene sp^3 C—H bonds.[10-13] In 2012, Maes group reported a Cu and Fe-catalyzed oxidation protocol for benzylpyridines based on AcOH as the promoter and O_2 as the stoichiometric oxidant (Scheme 1a).[10a] Lei et al. extended the similar idea to chloroacetate as the activator (Scheme 1b).[11] Miura also mentioned one special substrate without activators in their work on copper-catalyzed α–methylenation of benzylpyridines in air.[12] Recently, Gao and co-workers disclosed the first nonmetallic catalytic oxidation of the sp^3 C—H bonds of benzylpyridines with the synergistic H_4NI−AcOH catalyst and molecular oxygen (Scheme 1c).[13] Although several remarkable reports have been achieved in this area, there is still meaningful to search some more diverse catalytic system especially exploiting new catalysts.

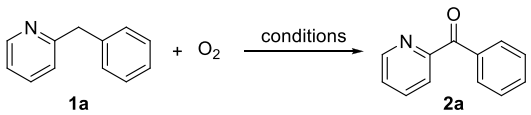


Scheme 1. Versatile oxidation routes of benzylpyridines with molecular oxygen to benzoylpyridines.

Over the past several years, organoselenium catalysis has emerged as a new and helpful force in the methodology development of non-metallic catalytic organic reactions.[14] For example, some reports on the synthesis of N- and O-heterocyclic compounds via selenium-catalyzed direct C—H amination and acyloxylation have been well documented separately in Zhao[15] and Breder[16] groups. Meanwhile, organoselenium chemistry has also received increasing attention from applied chemists because of its significance for sustainable chemistry and industrial potential.[17] A representative

green oxidation procedure using the polymer resin-supported hexavalent Se species as the recyclable heterogeneous catalyst has been successfully established very recently by Yu et al.[17a] As part of our continued effort on C—H activation and selenium chemistry,[18] we report herein our preliminary studies on selenium-catalyzed direct oxidation of methylene sp^3 C—H bonds to form the ketones with molecular oxygen as the oxidant (Scheme 1).

Table 1. Optimization of the reaction conditions.[a]



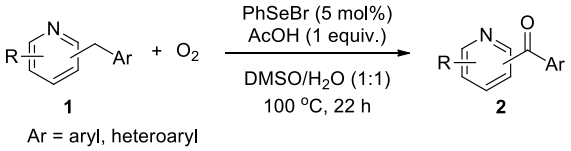
1a 2a

Entry	[Se]/ (mol%)	Additive (equiv.)	Solvent	Conv. (%)[b,c]
1	N-PSP (10)	AcOH (1)	DMSO	81
2	PhSeCl (10)	AcOH (1)	DMSO	89
3	PhSeBr (10)	AcOH (1)	DMSO	100
4	$(PhSe)_2$ (5)	AcOH (1)	DMSO	25
5	PhSeH (10)	AcOH (1)	DMSO	21
6	PhSeBr (5)	AcOH (1)	DMSO	100
7	PhSeBr (3)	AcOH (1)	DMSO	39
8[d]	PhSeBr (5)	AcOH (1)	DMSO	18
9	PhSeBr (5)	TFA (1)	DMSO	100
10	PhSeBr (5)	$TsOH·H_2O$ (1)	DMSO	100
11	PhSeBr (5)	PivOH (1)	DMSO	48
12	PhSeBr (5)	1-AdOH (1)	DMSO	61
13	PhSeBr (5)	AcOH (0.5)	DMSO	63
14	PhSeBr (5)	AcOH (1)	dioxane	27
15	PhSeBr (5)	AcOH (1)	toluene	31
16	PhSeBr (5)	AcOH (1)	DMF	53
17	PhSeBr (5)	AcOH (1)	H_2O	85
18	PhSeBr (5)	AcOH (1)	CF_3CH_2OH	9
19	**PhSeBr (5)**	**AcOH (1)**	**DMSO/ H_2O**	**100 (91)**
20	PhSeBr (0)	AcOH (1)	DMSO	6
21	PhSeBr (5)	AcOH (0)	DMSO	18
22	PhSeBr (0)	AcOH (0)	DMSO	1

[a] *Reaction conditions*: **1a** (0.5 mmol), [Se] catalyst, additive, solvent (0.5 mL), O_2 balloon, 100 °C, 22 h.
[b] Determined by ^1H NMR analysis.
[c] Isolated yields in parentheses.
[d] 80 °C.

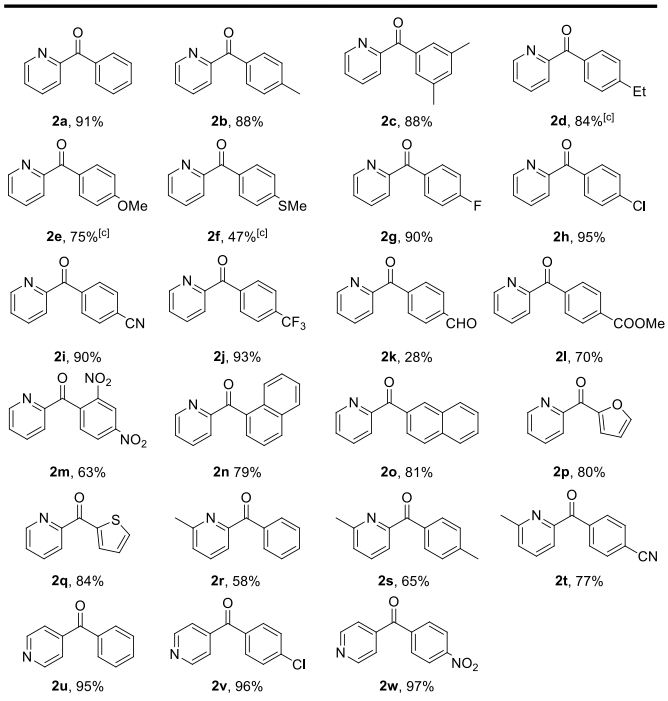
Initially, we selected AcOH as the additive to activate the sp^3 C—H bond of the model substrate 2-benzylpyridine (**1a**) in the presence of 1 atm O_2 as the oxidant. It was found that various organic selenium catalysts could participate in this reaction in different levels (Table 1, entries 1-5), only PhSeBr produced the desired product **2a** in quantitative conversion. Decreasing the amount of catalyst to 5 mol%, no adverse effect was observed to the conversion (Table 1, entry 6). Further lowering the catalyst loading to 3 mol% or reducing the reaction temperature to 80 °C result in an obvious detrimental influence on the catalytic activity (Table 1, entries 7 and 8). A systematic screening of other Brønsted acids showed that TFA and $TsOH·H_2O$ can also catalyze the model reaction in completely ways (Table 1, entries 9-12). Considering the low price and easy handling, we fixed the acetic acid as the best activating agent. The optimal loading of AcOH was 1 equivalent (Table 1, entry 13). Intriguingly, **1a** showed quite good reactivity in pure water to yield the corresponding product **2a** in 85% conversion (Table 1, entries 14-18). By carefully regulating the ratio of DMSO/H_2O to 1:1 as the mixed solvents, we got the best conditions and prepared the target product **2a** in 91% isolated yield (Table 1, entry 19 and Table S1, entries 33-37). Blank experiments showed that the catalyst PhSeBr and the activator AcOH both were indispensable in order to achieve the higher conversions (Table 1, entries 20-22). Based on the literature report,[8,11] we also test the possibility of using organic halides as the activator. Although the comparative conversions could be achieved, only the modest isolated yields were obtained probably due to the strong covalent bonds between the activating groups and substrates (see the Supporting Information, Table S2).

Table 2. Substrate scope of the benzylpyridines.[a,b]



1 2

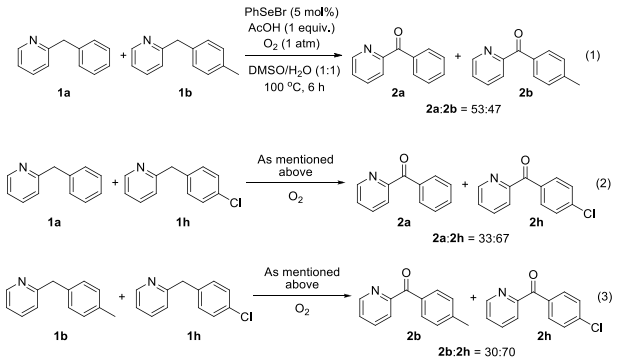
Ar = aryl, heteroaryl



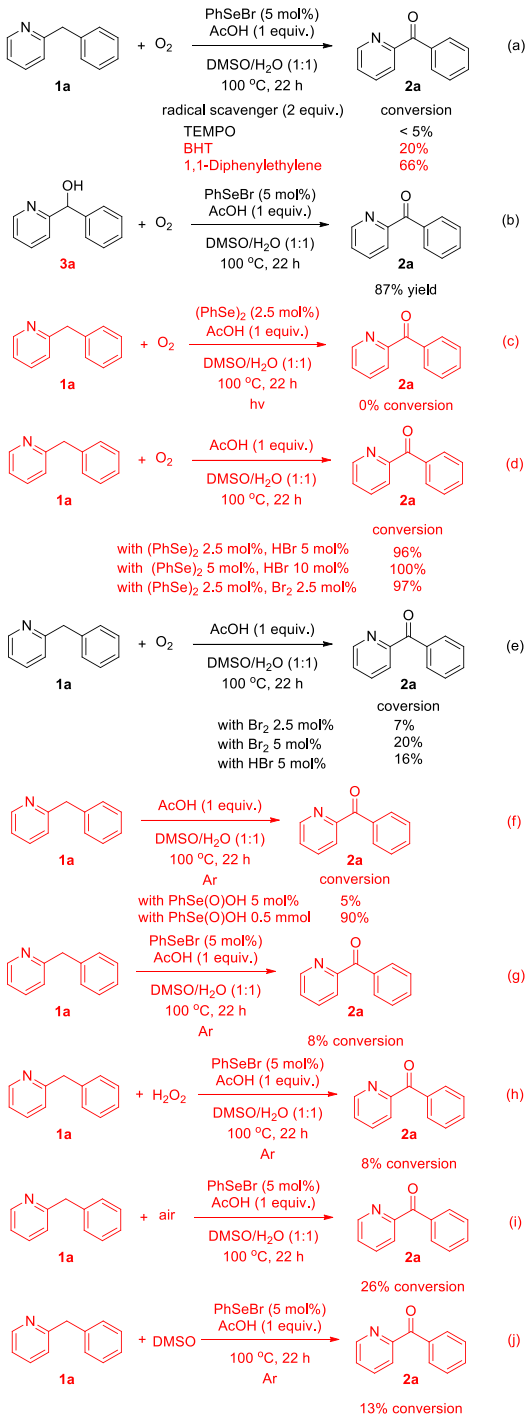
[a] *Reaction conditions*: **1a** (0.5 mmol), PhSeBr (5 mol%), AcOH (0.5 mmol), DMSO/H_2O (v/v = 1:1, 0.5 mL), O_2 balloon, 100 °C, 22 h.
[b] Isolated yield.
[c] 10 mol% PhSeBr was used.

With the optimized conditions in hand, the scope of the substrates was then investigated to probe the generality of this methodology (Table 2). A wide variety of 2 or 4-substituted benzylpyridines bearing either electron-donating (Me, Et, MeO and MeS) and electron-withdrawing groups (F, Cl, CN, CF_3, CHO, COOMe and NO_2) at the aromatic rings were introduced to give the desired product **2** in modest to good yields (**2a**-**o**, **2r**-**t** and **2u**-**w**). The electronic effect of the functional groups on the phenyl ring had notable influence on the reaction efficiency [Eqs. (1)-(3)]. For examples, in order to get the satisfactory yields of products **2d-f**, 10 mol% PhSeBr was necessary. Starting materials that contain two or three different methylene reaction sites (**2b-d**) were involved in this reaction, no any aldehyde or diketone by-products were detected, this highlights the exclusive chemoselectivity of this method. The introduce of a methyl group on the pyridine moiety also allowed the oxidation reaction to smoothly furnish the products **2r-t** in 58-77% yields. Surprisingly, this protocol was able to be extended to 2-(furan-2-ylmethyl)pyridine **1p** and 2-(thiophen-2-ylmethyl)pyridine **1q**, forming the corresponding products **2p** and **2q** in 80% and 84% yields, respectively. In particular, the structures of **2g, 2m** and **2w** were confirmed by single X-ray structure analysis (see the Supporting Information).

In order to investigate the reactivity and electronic effect of the substrates, three competition experiments were executed. A 1:1 mixture of **1a** and **1b** reacted with O_2 under typical conditions to afford the oxidative products **2a** and **2b** in a 53: 47 M ratio [Eq. (1)]. When using **1a** and **1h** as the starting materials, the products **2a** and **2h** were obtained in a 33:67 M ratio [Eq. (2)]. A similar trend was observed in Eq. (3). These results showed that the electron-withdrawing group (EWG) in phenyl rings apparently facilitated the oxidation process because of their contribution to the formation of the stable free radical intermediates during the catalytic cycle.

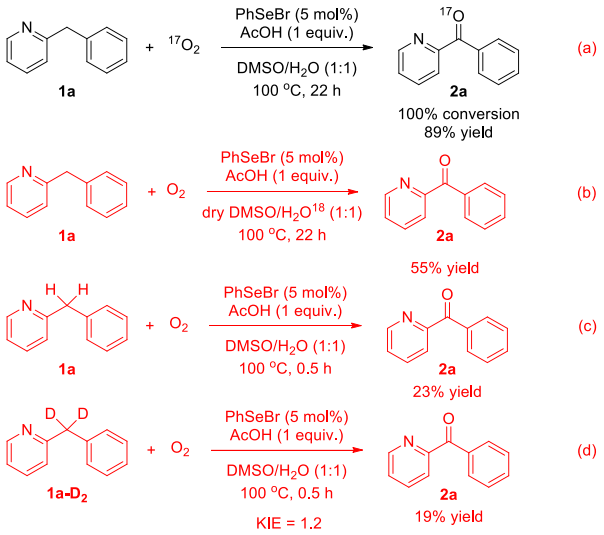


To elucidate the details of the mechanism, a variety of control experiments were performed. The model reaction was apparently suppressed at various levels when two equivalents of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), BHT (2,6-di-tertbutyl-4-methylphenol) or 1,1-diphenylethylene were added as the radical scavengers, demonstrating that an organic radical process may be involved in the catalytic cycle (Scheme 2a). Futhermore, no simple interaction between TEMPO and PhSeBr was detected by TLC and GC-MS analysis. Under standard conditions, the substrate phenyl(pyridin-2-yl)methanol (**3a)** was converted to the ketone **2a** in 87% isolated yield, which declared that the benzyl alcohol may be an intermediate during this reaction (Scheme 2b). In an attempt to elucidate this further, we attempted to make the substrate 2-(phenyl(phenylselanyl)methyl)pyridine **3b.** However despite following several synthetic routes from literature, we have been unsuccessful.[19] Hence, the formation of this as a possible precursor for the reaction cannot be excluded completely, although there is no literature reported examples. Upon using Diphenyl diselenide as a catalyst, no product was evidenced even under visible light irradiation (Scheme 2c).[20] However, when Diphenyl diselenide was combined with catalytic amounts of HBr or Br_2 as the additives, it formed the desired product **2a** in almost quantitative conversions (Scheme 2d). We believe, the reason to this is due to the function of Br_2 or HBr, which causes the $(PhSe)_2$ to be easily transformed to PhSeBr.[21] As mentioned above, iodide can catalyze the oxidation of sp^3 C—H bond of benzylpyridines.[13] Therefore, control experiments were conducted in the presence of Br_2 or HBr as the catalysts, this resulted in very low conversions (7-20%) of the product. (Scheme 2e). These results further demonstrated that the PhSeBr is the real catalyst behind this catalytic system. Our control experiments using $(PhSe)_2$, Br_2 or HBr supports the inefficiently of these as catalysts in the reaction (Scheme 2c-e). Finally, we investigated the possibility of PhSe(O)OHs as a catalyst which can be formed by hydration through moisture and oxidized by O_2. Our studies found that this was a good oxidant but not a good catalyst for the model reaction (Scheme 2f). Considering the fact that only 5mol% PhSeBr was used as the catalyst in our method, these experiments excluded the possible mechanism involving PhSe(O)OH as the active catalytic specie.[17c] Our studies also showed that molecular oxygen was critical in the system to ensure the oxidation reaction to proceed smoothly, by contrast, the oxidative ability of H_2O_2, air and DMSO was insufficient (Scheme 2g-j).[22]



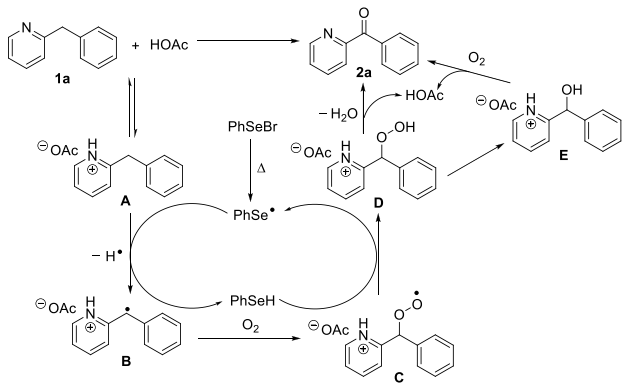
Scheme 2. Control experiments.

Isotope labeling technique was also used to trace the origin of the oxygen atom in the final product to support our mechanism. The model reaction was carried out under standard conditions in the presence of 1 atm $^{17}O_2$ or H_2O^{18}, respectively. The ^{17}O-labeled product **2a** was isolated in 89% yield and no ^{18}O-labeled product was formed by GC-MS analysis, thus manifesting that O_2 is the oxygen source of the carbonyl group in the product 2-benzoylpyridine (Scheme 3a-b). An intermolecular secondary kinetic isotope effect (KIE) of 1.2 was obtained, thus manifesting that the cleavage of the methylene sp^3 C—H bond may not be involved in the rate-determining step in this oxidation reaction (Scheme 3c-d).



Scheme 3. Isotope labeling experiments and kinetic isotope effect study.

A plausible mechanism is proposed based upon our above mentioned experimental results and related literature reports[8,11-12,14] (Scheme 4). We infered that the reaction is initiated by the formation of 2-benzylpyridinium salt **A** through the interaction of 2-benzylpyridine **1a** with HOAc. Then, **A** reacted with PhSe radical which come from the homolytic cleavage of PhSeBr to form the key free radical intermediate **B**. Oxidation of **B** with molecular oxygen leads to another peroxy radical intermediate **C** followed by protonation producing the hydroperoxidate intermediate **D**. Finally, releasing of the HOAc gives the target product **2a** as well as a molecule of water. The intermediate **D** may also be transformed into the benzyl alcohol derivate **E**, which under further oxidation tranforms to the ketone **2a**.[23]



Scheme 4. A proposed mechanism.

Consequently, we have developed an efficient selenium-catalyzed direct oxidation of methylene sp^3 C—H bonds to form the ketones with molecular oxygen as the oxidant. HOAc was used as the promoter to activate the starting materials. A number of benzoylpyridines with broad functional groups compatibility were obtained in good to excellent yields and with exclusive chemoselectivity. A tentative organic free radical procedure was proposed as the mechanism. Further studies are now in progress in our laboratory to expand this strategy to other useful heterocyclic compounds.

Experimental Section

Typical procedure for the synthesis of 3 and 4: synthesis of 3a

A mixture of 2-benzylpyridine **1a** (85 mg, 0.50 mmol), PhSeBr (6 mg, 0.025 mmol), AcOH (30 mg, 0.50 mmol), DMSO (0.25 mL) and H_2O (0.25 mL) was added to a 25 mL Schlenk tube. The reaction tube was flushed with O_2 for 1.5 minutes and then equipped with a O_2 balloon. The reaction was stirred at 100 °C for 22 h. After cooling to ambient temperature, the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and all the volatiles were evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether (35-60 °C)/Et_2O = 10:1, v/v) to afford the desired product **2a** in 91% yield.

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