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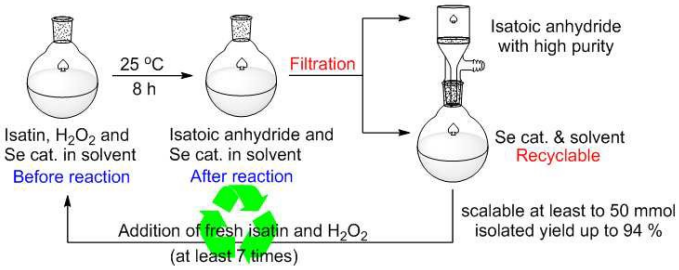
Recyclable $(PhSe)_2$-Catalyzed Selective Oxidation of Isatin by H_2O_2: A Practical and Waste-Free Access to Isatoic Anhydride under Mild and Neutral Conditions

Lei Yu,* Jianqing Ye, Xu Zhang, Yuanhua Ding and Qing Xu*



A practicle and waste-free synthesis of isatoic anhydride was reported. Besides the common advantages of organoselenium-catalyzed reactions such as the eco-friendly and recyclable catalyst, the clean procedures and the mild conditions, the feature of this methodology is the simple isolation procedure by filtration, which facilitates the direct recovery and reuse of both organoselenium catalyst and solvents.

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Recyclable $(PhSe)_2$-Catalyzed Selective Oxidation of Isatin by H_2O_2: A Practical and Waste-Free Access to Isatoic Anhydride under Mild and Neutral Conditions†

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After a series of careful conditional optimizations and catalyst screenings, the methodology to prepare isatoic anhydrides through the organoselenium-catalyzed selective oxidation of isatins by H_2O_2 under mild and neutral conditions was developed. The reactions were very practical because of the recyclable catalyst and solvent and the convenient isolation procedures of the products. This work reports the organoselenium-catalyzed oxidation of heterocycles that greatly expands the application scopes of the organoselenium catalysis. It also indicates that the organoselenium catalysts are robust to be recycled in industrial production if suitable isolation procedures are developed.

Introduction

Isatoic anhydrides (1*H*-benzo[*d*][1,3]oxazine-2,4-diones) are significant intermediates for the construction of many useful organic skeletons, such as quinolones,[1a-1b] 2,3-dihydroquinazolin-4(1*H*)-ones,[1c] benzodiazepinones,[1d] 2-aminobenzoic acid derivatives,[1e-1g] 1,2-dihydro-2-thioxo-4*H*-3,1-benzothiazin-4-ones[1h] and others.[1i] In addition, isatoic anhydrides are also abundantly employed compounds in herbicide production,[2] natural product synthesis[3] and medicine chemistry for the preparation of enzyme inhibitors, non-nucleoside inhibitors, antagonists *et. al*.[4] Therefore, synthesis of isatoic anhydrides is an important topic in synthetic organic chemistry research. Although isatoic anhydrides can be synthesized through a series of methodologies from smaller building blocks such as *N*-methylbenzenamines,[5a] 2-isocyanophenyl lithiums,[5b] indoles,[5c] 2-aminobenzoic acids,[5d-5f] *etc*., the oxidation of isatins should be a more concise and clean choice because isatins are cheap and accessible starting materials and this procedure does not require highly toxic and hazard chemicals for laboratory preparation. But the currently reported oxidations of isatins to isatoic anhydrides always employed oxidants that generated wastes, and required large amount of acids, which were harmful from industrial production view due to the corrosion of equipments.[6] In 2006, Deligeorgiev *et. al.* reported a nice work on the ultrasound-promoted oxidation of isatin to prepare isatoic anhydride using urea/H_2O_2.[7] But since generation of ultrasound requires special sonication equipment and consumes huge power energy and the oxidant urea/H_2O_2 inevitably leads to urea as the massive solid waste, this technology is still some far away from large scale production. In addition, the method also required acidic solvent such as acetic acid or formic acid along with drops of sulfuric acid.[7] Thus, developing practical and waste-free oxidations of isatins in neutral media are not only desirable but also timely for industrial applications.

On the other hand, selenium is an important and necessary trace element for human beings and has very wide applications in biochemistry, medicinal chemistry, organic synthesis and material science.[8] Recently, the eco-friendly aspects of organoselenium chemistry attract chemists much[9] and among reported works, organoselenium catalysis is an important topic because of its clean procedures, transition metal-free conditions and the metabolizable catalyst element that is safe to environment,[10] providing potential alternatives of transition-metal catalysts in medicine synthesis. Currently, people have reported a series of organoselenium-catalyzed reactions[11-13] and this field is still in rapid progress in recent years. During our continuous investigations on green organic reactions with industrial potential,[12, 14] we also found that the organoselenium compounds were very good catalysts for the reactions using H_2O_2 as the clean oxidant.[12] Thus, it is envisioned that isatoic anhydrides might be synthesized through the organoselenium-catalyzed clean oxidations under mild and neutral conditions as well. But this strategy faces tremendous challenges because of the multiple reaction points for the oxidations of C-C bonds (paths *a*-*b*)[6f] and the possible organoselenium-catalyzed oxidation of the amidogen N-H (path *c*), as reported in literature (Scheme 1).[13] Recently, after a series of careful conditional optimizations and catalyst screenings, we successfully overcome the above difficulties and developed the

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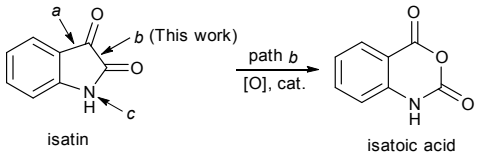
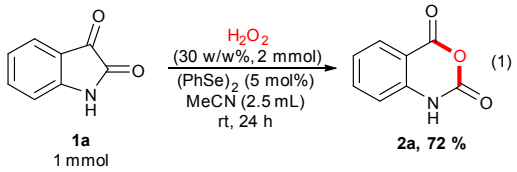
organoselenium-catalyzed selective oxidation of isatins to prepare isatoic anhydrides (Scheme 1, path *b*). Herein, we wish to report our findings.



Scheme 1 Possible oxidation sites of isatin

Results and Discussion

Based on our previous works,[12] we initially stirred isatin **1a** and H_2O_2 in MeCN in the presence of $(PhSe)_2$ at room temperature (25 °C). After 24 h, the expected product isatoic anhydride **2a** could be obtained in 72% yield after purification with column chromatography (*eq.* 1).



We then tried to optimize the reaction conditions. Solvent effect was first examined and parallel reactions were performed in a series of solvents such as MeCN, alcohols, water, DMF, NMP, DMSO and THF for comparison (Fig. 1). It was shown that alcohol solvents did not help to optimize the reaction (Fig. 1, runs 2-5 *vs.* 1) and water as solvent also resulted in very low product yield (run 6). Other polar solvents, such as DMF, NMP and DMSO were also tested (runs 7-9) and DMF was found to be the best one among them (run 7) while the other two led to the reduced product yield (run 8) or even completely restrained the reaction (run 9). Low-polar solvent, such as THF, was also employed but gave **2a** in very low yield (run 10).

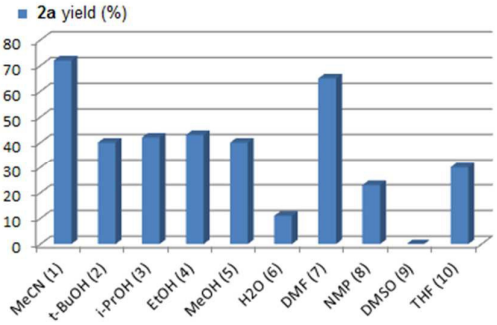


Fig. 1 Solvent effect test.[15]

It was noticed that although the reaction in DMF afforded product **2a** in lower yield than in MeCN, the starting material **1a** dissolved well in it. Therefore, for further optimizations, we then tried to increase starting material solubility by employing composite solvents of MeCN with DMF. Results of the reactions performed in solvents with different DMF/MeCN ratio were concluded in Fig. 2 and it was found that the product yield reached its peak at 88% when 9 *vol.* % of DMF/MeCN was employed (Fig. 2).

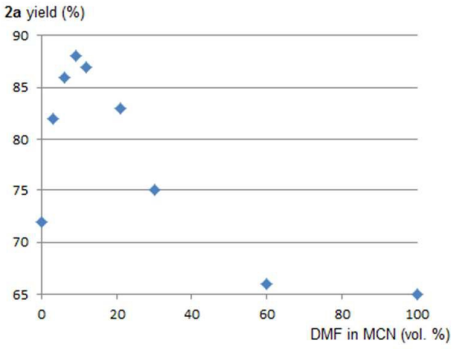


Fig. 2 DMF concentration effect test.[15]

Then, with the optimized solvent, reaction temperature effect was tested, showing that room temperature (25 °C) should be the most suitable condition. The product yield decreased gradually when higher temperature was employed, probably due to the decomposition of H_2O_2 or deep oxidation of product (Fig. 3).

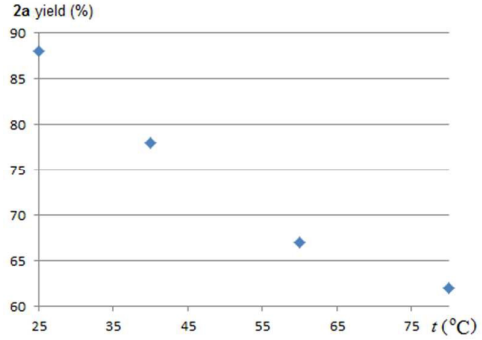


Fig. 3 Temperature effect test.[15]

Since the reactions could not complete and traces of starting material were always observed by TLC even after 24 h, a series of parallel experiments were carried out in 9 *vol.* % DMF/MeCN at 25°C and stopped at 4h, 6h, 8h, 12h and 24h to judge the termination of the reaction. Fig. 4 showed that the best reaction time should be 8 h and the product yield did not increase any more after then.

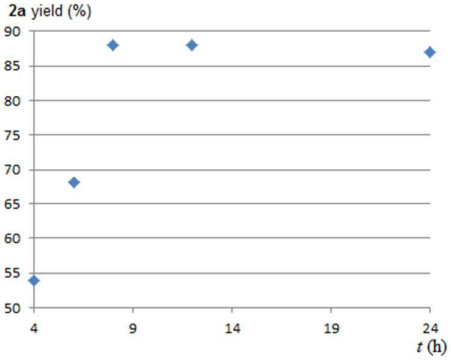


Fig. 4 Time effect test.[15]

The effect of H_2O_2 dosage was also examined. Using 50-300 mol % of H_2O_2, five parallel reactions were performed under the screened out conditions respectively and their results were concluded by Fig. 5. It was found that the product yield reached its peak when 200 mol % of H_2O_2 was employed and decreased with more H_2O_2, probably due to the deep oxidation of the product because a series of unidentified by-products were observed from TLC.

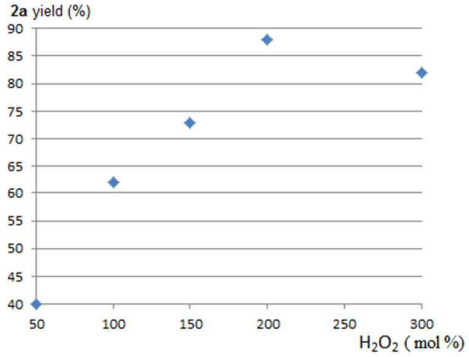


Fig. 5 H_2O_2 dosage effect test.[15]

Catalyst loading effects were also investigated. Fortunately, the best catalyst loading should be 5 mol % as employed initially. Lower catalyst loadings resulted in a reduced **2a** yield due to the slower reaction speed while the higher catalyst loading also gradually pulled down the product yield, probably due to the side reactions of the catalytic organoselenium species with starting material or product.

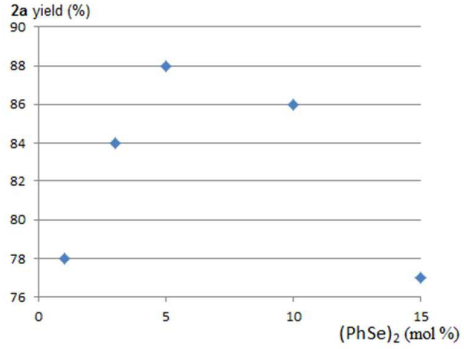


Fig. 6 $(PhSe)_2$ loading effect test.[15]

It was notable that unlike many reported organoselenium-catalyzed oxidations,[11-13] this reaction did not require special organoselenium catalysts and the cheapest and most available *pre*-catalyst $(PhSe)_2$ was screened out to be the best one (Fig. 7), probably due to the high activity of isatin which bears two carboxyl on the ring and insertion of an oxygen releases part of the ring tension. These phenomena were also observed during our previous research on 2-MCBones' Baeyer-Villiger oxidation.[12c] Catalyst screenings showed that with most diselenides as catalyst, the reaction proceeded smoothly and gave product **2a** in moderate to good yields (Fig. 7, runs 1-7). Diselenides with strong electron donation group {*e.g.* [*p*-$(CH_3)_2NC_6H_4Se]_2$, run 3} or strong electron withdrawing group {*e.g.* [*3,5*-$(CF_3)_2C_6H_3Se]_2$, run 7} both led to **2a** in reduced yields. The former was probably due to the lower reaction speed while the later was because of the too strong catalytic activity that caused over-oxidations because a series of unidentified by-products were observed by TLC. Selenides, such as EtSePh, *i*-PrSePh, *c*-C_6H_{11}SePh and PhSePh all resulted in decreased **2a** yields (runs 8-11). The former three was probably due to the delay of the catalytic species PhSe(O)OH generation through *syn*-selenoxide elimination with H_2O_2. For the example of PhSePh, although this compound cannot generate PhSe(O)OH via *syn*-selenoxide elimination, its oxidation product selenoxide also have some catalytic activities, as documented in literature.[11n] Our previous studies has disclosed that in the presence of H_2O_2, $(PhSe)_2$ was converted to PhSe(O)OH in two steps, showing that PhSe(O)OH was the real catalytic species.[12c] However, when PhSe(O)OH was directly used (run 12), **2a** yield was slightly reduced (run 12, 80% *vs.* run 1, 88%). This was because of the loading differences between these two catalysts, since 5 mol% of PhSe(O)OH was in equivalent to only 2.5 mol% of $(PhSe)_2$, resulting to **2a** yield similar to that of 3 mol% $(PhSe)_2$ case (84%, in Fig. 6). Similarly, PhSeBr, which can rapidly generate PhSe(O)OH also led to a reduced **2a** yield due to the half-cut of the real catalytic species (run 13). Inorganic selenium compound, such as SeO_2, only resulted in traces of product **2a** (run 14), showing that only organoselenium compounds are catalytic active for this reaction. Other chalcogen compounds, such as $(PhS)_2$ and $(PhTe)_2$, also showed some catalytic activities, but the yield of **2a** were very low (runs 15-16). Finally, a blank reaction confirmed that the reaction could not happen without catalyst (run 17).

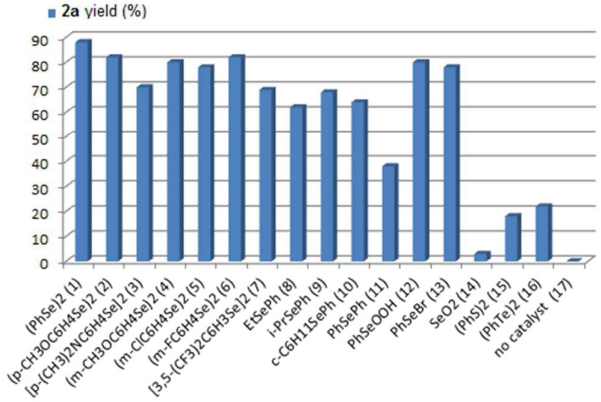
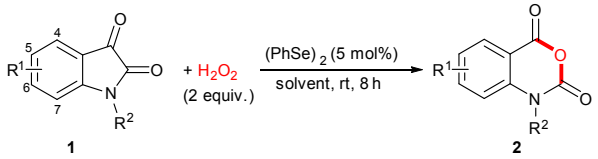


Fig. 7 Catalyst screenings.[15]

Under the optimized conditions (Table 1, entry 4), a series of isatins were employed, giving isatoic anhydrides in good yields (Table 2). This methodology has wide application scopes and isatins with different kinds of substitutes including electron-donation or electron withdrawing groups at different positions of aromatic ring or nitrogen were all successfully oxidized to give the corresponding isatoic anhydrides, affording a convenient methodology for isatoic anhydrides preparation. It was noticed that for reactions taken in 9 *vol.* % DMF/MeCN, nitrogen unsubstituted isatins generally afforded higher product yield than substituted ones (Table 2, entries 1- 10 *vs.* 11-17), probably due to the higher polar of substrates, which led to the higher solubility in DMF/MeCN. These phenomena inspired us to perform reactions of nitrogen substituted isatins in

lower polar solvent pure MeCN, giving higher product yields than before (Table 1, entries 18-24 *vs.* 11-17).

Table 1. Synthesis of isatoic anhydrides[a]

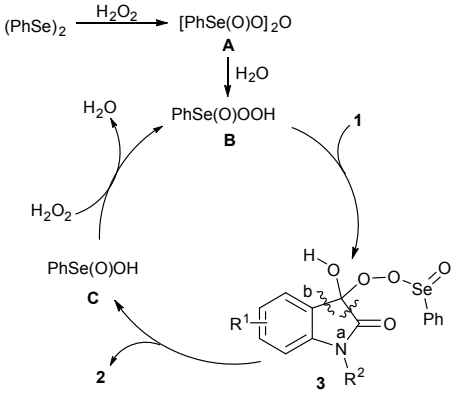


1 2

Entry	**1**: R^1, R^2	solvent	**2**%[b]
1	**1a**: H, H	9 vol. %DMF/MeCN	**2a**: 88
2	**1b**: 5-Me, H	9 vol. %DMF/MeCN	**2b**: 86
3	**1c**: 5-MeO, H	9 vol. %DMF/MeCN	**2c**: 85
4	**1d**: 5-F, H	9 vol. %DMF/MeCN	**2d**: 89
5	**1e**: 5-Cl, H	9 vol. %DMF/MeCN	**2e**: 80
6	**1f**: 7-Cl, H	9 vol. %DMF/MeCN	**2f**: 84
7	**1g**: 4-Br, H	9 vol. %DMF/MeCN	**2g**: 78
8	**1h**: 5-Br, H	9 vol. %DMF/MeCN	**2h**: 81
9	**1i**: 6-Br, H	9 vol. %DMF/MeCN	**2i**: 78
10	**1j**: 7-Br, H	9 vol. %DMF/MeCN	**2j**: 88
11	**1k**: H, Bn	9 vol. %DMF/MeCN	**2k**: 72
12	**1l**: 5-Me, Bn	9 vol. %DMF/MeCN	**2l**: 73
13	**1m**: 5-Me, Bu^n	9 vol. %DMF/MeCN	**2m**: 76
14	**1n**: 5-F, Bn	9 vol. %DMF/MeCN	**2n**: 72
15	**1o**: 5-F, Bu^n	9 vol. %DMF/MeCN	**2o**: 71
16	**1p**: 5-Cl, Bn	9 vol. %DMF/MeCN	**2p**: 71
17	**1q**: 5-Cl, Bu^n	9 vol. %DMF/MeCN	**2q**: 70
18	**1k**: H, Bn	MeCN	**2k**: 75
19	**1l**: 5-Me, Bn	MeCN	**2l**: 75
20	**1m**: 5-Me, Bu^n	MeCN	**2m**: 84
21	**1n**: 5-F, Bn	MeCN	**2n**: 76
22	**1o**: 5-F, Bu^n	MeCN	**2o**: 75
23	**1p**: 5-Cl, Bn	MeCN	**2p**: 80
24	**1q**: 5-Cl, Bu^n	MeCN	**2q**: 78

[a] 1mmol of **1**, 2 equiv. of H_2O_2, 0.05 mmol of $(PhSe)_2$. and 2.5 mL of solvent were stirred at rt (25 °C) for 8h. [b] Isolated yields.

On the basis of our previous studies as well as references,[11-13] a plausible mechanism of this reaction was given: As proved by ^{77}Se NMR studies in our previous works,[12c] $(PhSe)_2$ was initially oxidized by H_2O_2 to organoselenium species $[PhSe(O)O]_2O$ (**A**), which afforded benzeneseleninoperoxoic acid (**B**) after hydrolysis. Nucleophilic addition of isatin **1** with **B** afforded **3**. Then, a ring break happened[12c] in **3** and due to the higher activity of C-C bond adjacent to carboxyl, path *a* was preferred, giving final product isatoic anhydrides **2** and the selenium species **C**. Oxidation of **C** by H_2O_2 regenerated **B**, which took part in the next cycle of reaction (Scheme 2).



Scheme 2. Possible mechanisms.

To ensure that the methodology is practical for large-scale preparation, a magnified experiment for the oxidation of isatin **1a** in 50 mmol scale was performed in a 250 mL round bottom flask. It was noticed that the product precipitated at the bottom of the flask (Fig. 8). Thus, different from the previous small-scale preparations, the product could be easily isolated by a simple filtration.

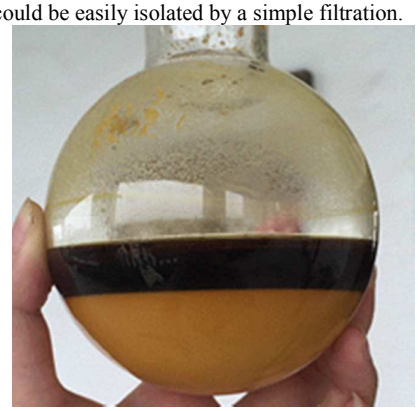
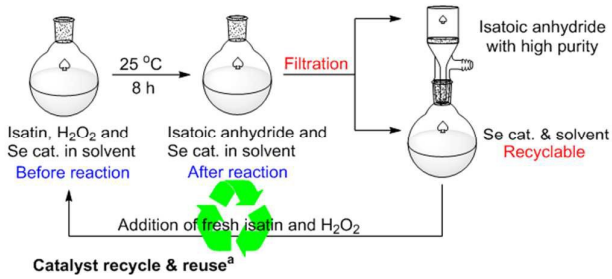


Fig. 8 The round bottom flask after reaction.

Because the organoselenium catalytic species were very stable and could be recycled and reused for many times in our previous works,[12a, 12b, 12d] we speculated that the mother liquid, which contained the organoselenium catalyst, could be **directly** reused in the next turn of reaction by adding fresh isatin **1a** and H_2O_2 (Fig. 9). It was shown that the recycled mother liquid resulted in even higher **2a** yield than its first use, possibly because of the fact that part of the product **2a** of the first turn experiment saturated the mother liquid and thus reduced the loss of product caused by its partial dissolution in next cycles. The product yield began to decrease after three times recycle of the mother liquid, possibly because that for each reaction, some water was introduced from aqueous H_2O_2 and the accumulated water finally changed the solvent properties and thus reduced the product yield. It was shown that the mother liquid could be reused for at least seven times with satisfied **2a** yield (77-94%) and high purity, which was confirmed by the ^1H NMR spectrum (Fig. 10).



Catalyst recycle & reuse[a]

Recycle NO.	0[b]	1	2	3	4	5	6	7
2a weight (g)	6.9	7.1	7.5	7.7	7.3	7.1	6.8	6.3
2a yield (%)[c]	84	87	92	94	89	87	83	77

[a] Reaction scale: 50 mmol; [b] First use; [c] Isolated yields based on isatin.

Fig. 9 Catalyst recycle & reuse.

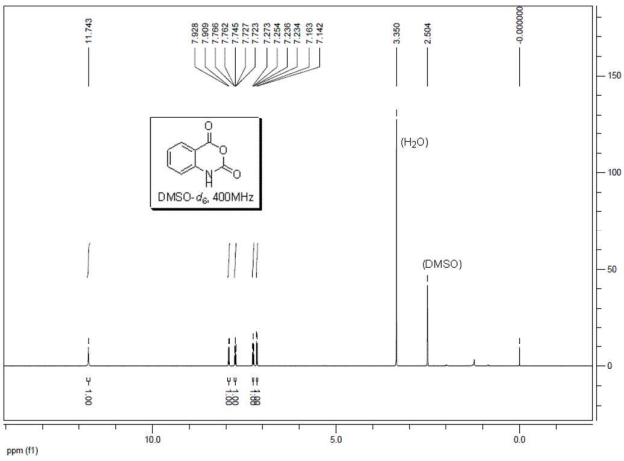


Fig. 10 Product ^{1}H NMR spectrum of the 7th catalyst recycle & reuse reaction.

Conclusions

In conclusion, we developed a concise method for the synthesis of isatoic anhydrides from the available isatins through the organoselenium-catalyzed oxidations. Compared with known methodologies, this method is waste-free and can be performed under mild and neutral conditions, which are more preferable for large-scale preparation. The reaction is metal-free and the catalytic element selenium is eco-friendly. In addition, the easily recyclable catalyst and solvent and the convenient isolation procedures made this method more practical than previously reported works on isatoic anhydride synthesis and organoselenium catalysis. To the best of our knowledge, this reaction is the first example of the organoselenium-catalyzed Baeyer-Villiger oxidation of heterocycles and expands the applications scopes of organoselenium catalysis. More researches on the applications of organoselenium catalysis are on the way in our laboratory.

Experimental Section

General methods

Isatins were purchased from reagent merchant with their purities more than 98% and were directly used as received. Organoselenium-catalysts were commercially available or prepared according to literature.[12d] Solvents were analytical pure (AR) and directly used without any special treatment. All reactions were carried out in open air in Schlenk tube and monitored by GC-MS and/or TLC. In small-scale experiments (1 mmol), products were all purified by column chromatography on silica gel using petroleum ether and ethyl acetate (ratio 2/1) as the eluent. Melting points were measured by WRS-2A digital instrument. IR spectra were measured on Bruker Tensor 27 Infrared spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 600/400 instrument (600 or 400 MHz for ^{1}H and 150 MHz for ^{13}C NMR spectroscopy) using $CDCl_3$ as the solvent and Me_4Si as the internal standard. Chemical shifts for ^{1}H and ^{13}C NMR were referred to internal Me_4Si (0 ppm) and *J*-values were shown in Hz. Mass spectra were measured on a Shimadzu GCMS-QP2010 Ultra spectrometer (EI). HRMS (ESI) analysis was measured on a Bruker microTOF-Q II instrument.

Typical procedure for the synthesis of 2a

1 mmol of **1a** (147.1 mg), 0.05 mmol of $(PhSe)_2$ (5 mol%, 15.6 mg) were added. A solution of 2 mmol H_2O_2 (30 w/w%, 226.0 mg) in 2.5 mL 9 *vol.* % DMF/MeCN was injected by syringe. The mixture was stirred at 25 °C for 8 h and solvent was evaporated by vacuum. The residue was purified by column chromatography (eluent: petroleum ether/EtOAc 2/1) to give 143.5 mg of **2a** (yield 88%). Other isatoic anhydrides **2** were prepared in similar way.

Detailed procedure for the large scale synthesis and the catalyst recycle and reuse

To a 250 mL round bottom flask, 7.35 g isatin **1a** (50 mmol), 0.78 g $(PhSe)_2$ (2.5 mmol), 91 mL MeCN and 9 mL DMF were added in order. 10.2 mL H_2O_2 (30 w/w%, d = 1.11 g/mL, 100 mmol) was then dropped in to the stirred solution. The mixture was stirred for 8 h at room temperature. The precipitated product isatoic anhydride **2a** and the mother liquid were isolated by a simple filtration. The product **2a** was washed with small amount of EtOH and dried in air. The mother liquid was directly reused as both solvent and catalyst in the next cycle. Detailed results were summarized in Fig. 9.

Characterization of the products

1*H*-benzo[*d*][1,3]oxazine-2,4-dione 2a. Yellow solid. m.p. 231.3-232.2 °C (*lit.* 233-234 °C). IR (KBr): 3240, 3104, 2939, 1767, 1617, 1513, 1487, 1438, 1362, 1327, 1264, 1152,1121, 1011, 904, 792, 763 cm^{-1}. ^{1}H NMR (600MHz, DMSO-*d*6) δ (ppm): 11.73 (s, 1H, NH), 7.92 (dd, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H, ArH), 7.74 (dt, *J* = 2.4 Hz, *J* = 7.2 Hz, 1H, ArH), 7.25 (dt, *J* = 2.4 Hz, *J* = 7.2 Hz, 1H, ArH), 7.16 (d, *J* = 7.8Hz, 1H, ArH). ^{13}C NMR (150MHz, DMSO-*d*6) δ (ppm): 159.8, 147.1, 141.4, 136.9, 128.9, 123.5,115.3, 110.2. MS

(EI, 70 eV): m/z (%) 163(22) [M^+], 119(100) [M^+-CO_2], 92(70). Known compound(118-48-9).[5b]

6-Methyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione 2b. Yellow solid. m.p. 248.6-249.8 °C (*lit.* 249-250 °C). IR (KBr): 3109, 2010, 1781, 1728, 1622, 1514, 1422, 1349, 1269, 1145, 1030, 1001,916, 825, 780, 728 cm^{-1}. ^1H NMR (600MHz, DMSO-*d*6) δ (ppm): 11.64 (s, 1H, NH), 7.71 (s, 1H, ArH), 7.56 (d, *J* = 8.4 Hz, 1H, ArH), 7.06 (d, *J* = 8.4 Hz, 1H, ArH), 2.33 (s, 3H, CH_3). ^{13}CNMR (150MHz, DMSO-*d*6) δ (ppm): 159.9, 147.1, 139.2, 137.9, 132.9, 128.3,115.3, 110.0, 20.0. MS (EI, 70 eV): m/z (%) 177(20) [M^+], 133(100), 104(58). Known compound(4692-99-3).[16a]

6-Methoxy-1*H*-benzo[*d*][1,3]oxazine-2,4-dione 2c. Yellow solid. m.p. 242.5-243.3 °C (*lit.* 242-244 °C). IR (KBr): 3246, 3183, 1782, 1733, 1623, 1507, 1422, 1360, 1334, 1257, 1157, 1016, 920, 838, 753 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.6 (s, 1H, NH), 7.38 (dd, *J* = 2.4 Hz, *J* = 9.0 Hz, 1H, ArH), 7.33 (d, J = 2.4 Hz, 1H, ArH), 7.11 (d, *J* = 9.0 Hz, 1H, ArH), 3.81 (s, 3H, OCH_3); ^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 159.8, 155.2, 146.9, 135.5, 125.7, 116.9, 110.6, 109.8, 55.7. MS (EI, 70 eV): m/z (%) 193(25) [M^+], 149(88), 106(100). Known compound(37795-77-0).[16b]

6-Fluoro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione 2d. Yellow solid. m.p. 263.7-264.6 °C (*lit.* 265-268 °C). IR (KBr): 3188, 2932, 1941, 1760, 1696, 1426, 1259, 1224, 1119, 1040, 1002, 933, 893,847, 735 cm^{-1}. ^1H NMR (600MHz, DMSO-*d*6) δ (ppm): 11.80 (s, 1H, NH), 7.70-7.64 (m, 2H, ArH), 7.20-7.17 (m, 1H, ArH). ^{13}C NMR (150MHz, DMSO-*d*6) δ (ppm): 159.2 (d, $J_{C\text{-}F}$ = 3.2 Hz), 157.5 (d, $J_{C\text{-}F}$ = 239.9 Hz), 146.8, 138.1, 124.8 (d, $J_{C\text{-}F}$ = 24.2 Hz), 117.5 (d, $J_{C\text{-}F}$ = 7.8 Hz), 114.0 (d, $J_{C\text{-}F}$ = 24.2 Hz), 111.4 (d, $J_{C\text{-}F}$ = 8.1 Hz). MS (EI, 70 eV): *m/z* (%) 181(22) [M^+], 137(100), 109(53). Known compound (321-69-7).[6f]

6-Chloro-1*H*-benzo[*d*][1,3]oxazine-2,4-dioneorange 2e. Yellow solid. m.p. 277.0-278.6 °C (*lit.* 278-281 °C). IR (KBr): 3098, 1772, 1698, 1619, 1495, 1419, 1343, 1272, 1243, 1186, 1038, 999, 909,846, 811, 751 cm^{-1}. ^1H NMR (600MHz, DMSO-*d*6) δ (ppm): 11.85 (s, 1H, NH), 7.86 (d, *J* = 8.4 Hz, 1H, ArH), 7.80-7.78 (m, 1H, ArH), 7.16 (d, *J* = 8.4 Hz, 1H, ArH). ^{13}C NMR (150MHz, DMSO-*d*6) δ (ppm): 158.9, 146.7, 140.3, 136.6, 127.6, 127.1,117.4, 112.0. MS (EI, 70 eV): m/z (%) 197(20) [M^+], 153(100), 125(35). Known compound(4743-17-3).[16c]

8-Chloro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione 2f. Yellow solid. m.p. 212.4-214.6 °C (*lit.* 210-215 °C). IR (KBr): 3482, 3368, 3058, 1796, 1670, 1608, 1586, 1548, 1455, 1420, 1338, 1312, 1272, 1251, 1164, 1077, 1014, 892, 752 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.74 (dd, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H, ArH), 7.48 (dd, *J* = 1.8 Hz, *J* = 7.2 Hz, 1H, ArH), 6.58 (t, *J* = 7.8 Hz, 1H, ArH); ^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 169.1, 146.9, 133.7, 130.3, 119.0, 115.1, 111.7. MS (EI, 70 eV): m/z (%) 197(13) [M^+], 153(88), 44(100). Known compound(63497-60-9).[6f, 16d]

5-Bromo-1*H*-benzo[*d*][1,3]oxazine-2,4-dione 2g. Yellow solid. m.p. 218.3-220.6 °C. IR (KBr): 3182, 3102, 2995, 2916, 1771, 1700, 1608, 1588, 1506, 1465, 1428, 1362, 1305, 1257, 1215, 1181, 1031, 801, 751 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.82 (s, 1H), 7.57-7.50 (m, 2H), 7.14 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 156.8, 146.5, 144.0, 136.7, 129.3, 123.3, 115.1, 109.2. MS (EI, 70 eV): m/z (%) 241(18) [M^+], 197(100), 170(50). Known compound (77603-45-3).[5e]

6-Bromo-1*H*-benzo[*d*][1,3]oxazine-2,4-dione. 2h. Yellow solid. m.p. 233.6-234.9 °C (*lit.* 235 °C). IR (KBr): 3491, 3240, 3179, 3094, 1772, 1701, 1615, 1496, 1474, 1417, 1340, 1272, 1184, 1138, 1035, 998, 907, 845, 764 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.85 (s, 1H), 7.99 (d, *J* = 2.4 Hz, 1H), 7.89 (dd, *J* = 2.4 Hz, *J* = 8.7 Hz, 1H), 7.10 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 158.8, 146.7, 140.6, 139.3, 130.6, 117.6, 114.6, 112.4. MS (EI, 70 eV): m/z (%) 241(19) [M^+], 197(100), 170(26). Known compound (4692-98-2).[16e]

7-Bromo-1*H*-benzo[*d*][1,3]oxazine-2,4-dione 2i. Yellow solid. m.p. 220.1-222.5 °C. IR (KBr): 3179, 3104, 1780, 1706, 1612, 1485, 1403, 1341, 1246, 1072, 1025, 922, 892, 785, 760 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.81 (s, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.42 (dd, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 159.3, 146.8, 142.4, 130.7, 130.3, 126.5, 117.7, 109.7. MS (EI, 70 eV): m/z (%) 241(20) [M+], 197(100), 170(56). Known compound (76561-16-5).[5e]

8-Bromo-1*H*-benzo[*d*][1,3]oxazine-2,4-dione 2j. Yellow solid. m.p. 191.8-193.0 °C (*lit.* 192-194 °C). IR (KBr): 3243, 3215, 3131, 1792, 1721, 1608, 1494, 1459, 1346, 1308, 1252, 1213, 1136, 1023, 815, 788, 745cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.07 (s, 1H), 8.02 (dd, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.95 (dd, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 159.1, 146.5, 140.1, 139.5, 128.6, 124.5, 112.9, 107.9. MS (EI, 70 eV): m/z (%) 241(17) [M^+], 197(100), 169(13). Known compound (331646-98-1).[16f]

1-Benzyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione 2k. Yellow solid, yield: 72%. m.p. 138.8-140.6 °C (*lit.* 139-141 °C). IR (KBr): 3028, 2921, 1662, 1575, 1516, 1440, 1410, 1362, 1324, 1279,1250, 1160, 1108, 1075, 1028, 898,834, 789 cm^{-1}. ^1H NMR (600MHz, $CDCl_3$) δ (ppm): 7.98 (d, *J* = 7.8Hz, 1H, ArH), 7.36-7.32 (m, 5H, ArH), 7.28-7.26(m, 1H, ArH), 6.64-6.61 (m, 2H, ArH), 4.49 (s, 2H, NCH_2). ^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 151.6, 138.7, 135.6, 132.6, 129.1, 128.7,128.2, 127.2, 127.0, 115.1, 111.9, 46,9. MS (EI, 70 eV): m/z (%) 253(35) [M^+], 180(85), 91(100). Known compound(35710-05-5).[1d]

1-Benzyl-6-methyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione 2l. Yellow solid. m.p. 147.3-148.8 °C. IR (KBr): 2917, 2861, 1780, 1619, 1574, 1445, 1384, 1317, 1280, 1063, 1048,912, 892, 808, 775cm^{-1}. ^1H NMR (600MHz, $CDCl_3$) δ (ppm): 7.96 (s, 1H, ArH), 7.43 (d, *J* = 9.0 Hz, 1H, ArH), 7.37-7.34 (m, 2H, ArH), 7.31-7.28 (m, 3H, ArH), 7.00 (d, *J* = 8.4 Hz, 1H, ArH), 5.29 (s, 2H, NCH_2), 2.37 (s, 3H, CH_3). ^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 158.5, 148.5, 139.2, 138.2, 134.6, 134.2, 130.5, 129.1, 128.1, 126.6, 114.7, 111.7, 48.5, 20.4. MS (EI, 70 eV): *m/z* (%) 267(27) [M^+], 194(59), 91(100). Known compound(35710-11-3).[16g]

1-Butyl-6-methyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione 2m. Yellow solid. m.p. 142.1-143.3 °C. IR (KBr): 2957, 2862, 2370, 1720, 1655, 1568,1512, 1476, 1440, 1406, 1383, 1221, 1162, 1126,801, 745 cm^{-1}. ^1H NMR (600MHz, CDCl3) δ (ppm): 7.96 (s, 1H, ArH), 7.55(dd, *J* = 1.2 Hz, *J* = 9.0 Hz, 1H, ArH), 7.06 (d, *J* = 8.4Hz, 1H, ArH), 4.04 (t, *J* = 7.8 Hz, 2H, NCH_2), 2.41 (s, 3H, CH_3), 1.76-1.71 (m, 2H,

CH_2), 1.48-1.45 (m, 2H, CH_2), 1.0 (t, J = 7.5Hz, 3H, CH_3). ^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 158.8, 147.8, 139.2, 138.3, 133.9, 130.5, 113.9, 111.6, 44.7, 28.9, 20.4, 19.9, 13.7. MS (EI, 70 eV): *m/z* (%) 233(22) [M^+], 146(100), 133(78). HRMS calcd. for $C_{13}H_{16}NO_3$ ([M+H]$^+$) : 234.1125 ; found: 234.1130.

1-Benzyl-6-fluoro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione 2n. Yellow solid. m.p. 136.6-138.3 °C. IR (KBr): 2917, 2600, 1669, 1581,1523, 1493, 1342, 1310, 1284,1260, 1226, 1145, 1025, 938, 886, 753 cm^{-1}. ^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.83 (dd, J = 3.0 Hz, J = 7.8 Hz, 1H, ArH), 7.37-7.28 (m, 6H, ArH), 7.10 (dd, J = 3.6 Hz, J = 9.0 Hz, 1H, ArH), 5.30 (s, 2H, NCH_2). ^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 158.5 (d, JC-F = 245.9 Hz), 157.5 (d, JC-F = 2.9 Hz), 148.1, 137.9, 134.1, 129.3, 128.3, 126.6, 125.0 (d, JC-F = 23.7 Hz), 117.0 (d, JC-F = 7.7 Hz), 116.3 (d, JC-F = 24.2 Hz), 113.2(d, JC-F = 8.0 Hz), 48.9. MS (EI, 70 eV): *m/z* (%) 271(20) [M^+], 198(43), 91(100). Known compound (749865-71-2).[16h]

1-Butyl-6-fluoro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione 2o. Yellow solid. m.p.129.6-131.2 °C. IR (KBr): 2923, 2858, 2724, 2547, 1659, 1579, 1518, 1388, 1306, 1224, 1146, 1021, 935, 807,768 cm^{-1}. ^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.66-7.64 (m, 1H, ArH), 7.17-7.14 (m, 1H, ArH), 6.65-6.63 (m, 1H, ArH), 3.19(t, J = 7.2 Hz, 2H, NCH_2), 1.69-1.65 (m, 2H, CH_2), 1.48-1.44 (m, 2H, CH_2), 0.98 (t, J = 7.5Hz, 3H, CH_3). ^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 151.8 (d, J_{C-F} = 231.6 Hz), 147.8, 127.2, 122.3 (d, J_{C-F} = 22.8 Hz), 116.4 (d, J_{C-F} = 23.0), 111.5 (d, J_{C-F} = 6.9 Hz), 107.3, 42.0, 30.2, 19.3, 12.9. MS (EI, 70 eV): *m/z* (%) 237(19) [M^+], 150(100), 137(79). HRMS calcd. for $C_{12}H_{12}FNNaO_3$ ([M+Na]$^+$): 260.0693; found: 260.0699.

1-Benzyl-6-chloro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione 2p. Yellow solid. m.p. 147.0-148.8 °C (*lit.* 147-149 °C). IR (KBr): 2922, 2852, 2541, 1668, 1571, 1443, 1338, 1312, 1280, 1228, 1158, 1117, 1024, 917, 894, 873 cm^{-1}. ^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 7.94 (d, J = 2.4 Hz, 1H, ArH), 7.36-7.32 (m, 4H, ArH), 7.29 (d, J = 5.4 Hz, 1H, ArH), 7.24 (d, J = 2.4 Hz, 1H, ArH), 6.58 (d, J = 9.0 Hz, 1H, ArH), 4.47 (s, 2H,NCH_2). ^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 150.1, 138.2, 135.5, 131.7, 129.0, 128.8, 128.2, 127.4, 126.9, 119.7, 113.4, 109.7, 47.0. MS (EI, 70 eV): m/z (%) 243 [(M-44) $^+$, 100], 288 [(M+1) $^+$, 30]. Known compound(57384-84-6).[16i]

1-Butyl-6-chloro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione 2q. Yellow solid. m.p. 140.8-142.2 °C. IR (KBr): 2956, 2924, 2854, 2389, 2318, 1654, 1566, 1383, 1307, 1216, 1157, 1017, 907, 871,772 cm^{-1}. ^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 8.12 (d, J = 2.4 Hz, 1H, ArH), 7.70 (dd, J = 2.4 Hz, J = 9.0Hz, 1H, ArH), 7.13 (d, J = 9.0 Hz, 1H, ArH), 4.05 (t, J = 7.8 Hz, 2H, NCH_2), 1.76-1.71 (m, 2H, CH_2), 1.50-1.44 (m, 2H, CH_2), 1.01 (t, J = 7.2Hz, 3H, CH_3). ^{13}C NMR (150MHz, $CDCl_3$) δ (ppm): 157.6, 147.3, 139.9, 137.3, 130.1, 129.6, 115.7, 113.0, 45.1, 28.9, 19.9, 13.8. MS (EI, 70 eV): m/z (%) 253(24) [M+], 166(100), 111(40). Known compound(144155-83-9).[16j]

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