Oxidation of indoles is a fundamental organic transformation to deliver a variety of synthetically and pharmaceutically valuable nitrogen-containing compounds. Prior methods require the use of either organic oxidants (meta-chloroperoxybenzoic acid, N-bromosuccinimide, t-BuOCl) or stoichiometric toxic transition metals [Pb(OAc)₄, OsO₄, CrO₃], which produced oxidant-derived by-products that are harmful to human health, pollute the environment and entail immediate purification. A general catalysis protocol using safer oxidants (H₂O₂, oxone, O₂) is highly desirable. Herein, we report a unified, efficient halide catalysis for three oxidation reactions of indoles using oxone as the terminal oxidant, namely oxidative rearrangement of tetrahydro-β-carbolines, indole oxidation to 2-oxindoles, and Witkop oxidation. This halide catalysis protocol represents a general, green oxidation method and is expected to be used widely due to several advantageous aspects including waste prevention, less hazardous chemical synthesis, and sustainable halide catalysis.
Chemical oxidation of indoles is a fundamental organic transformation to deliver a diverse array of versatile nitrogen-containing compounds, in particular 2-oxindoles, which have been used widely in organic synthesis and drug discovery. The electron-rich property of indoles allows the oxidation to occur under many oxidation conditions. However, a mixture of oxidation products is usually observed due to the competing oxidation of nitrogen, C2 and C3, as well as potential rearrangement and over-oxidation (Fig. 1a). The challenging chemo-selectivity and regio-selectivity requires not only a site-selective oxidant but also suitable substitutions at C2 and/or C3, as well as the protecting group on the nitrogen. Therefore, it is not surprising that only a small number of oxidants have been identified for only one or two of the three major types of the indole oxidation (Fig. 1a): (i) oxidative rearrangement of tetrahydro-β-carbolines to spirooxindoles, (ii) oxidation of C3-substituted indoles to 2-oxindoles, and (iii) oxidative cleavage of C2,C3-disubstituted indoles to 2-keto anilides (Witkop oxidation). Although these oxidants under the optimized conditions could solve the chemo-selectivity and regio-selectivity with high yields, their environmental and/or health impacts were not addressed, which is contrary to the rising concept and awareness of Green Chemistry. Oxone (KHSO₅-1/2KHSO₄-1/2K₂SO₄, MW 307) has been widely used as a green, cheap, and safe oxidant because it generates strong acid (HCl or HBr) or transition metal catalysis. Oxidative rearrangement with hydrogen peroxide or oxygen under either basic or even neutral conditions which is advantageous over related halide (e.g., bromide and chloride) oxidation under weakly acidic/cyclic spirooxindole core, in particular the spiro[pyrrolidine-3,3'-indolenine] can react with water (part of the solvent) to generate 3-halo-2-hydroxy indoline (II → III, Fig. 1c), which might undergo semi-pinacol rearrangement to provide spirooxindoles or 2-oxindoles. Alternatively, addition of potassium peroxymonosulfate (from excess of oxone) to indolenine (II) may generate hydroperoxysulfate intermediate IV (III → IV). Subsequent substitution of the halide with water triggers the C2-C3 bond cleavage of V to afford 2-keto anilides. In both scenarios, the halide is released and can be re-oxidized by oxone to generate the halogenating species. Therefore, halide is theoretically a catalyst for the oxone oxidation of indoles. This article presents the verification and implementation of this hypothesis, leading to the development of a unified green protocol for the oxidation of indoles to spirooxindoles, 2-oxindoles and 2-keto anilides (Fig. 1c). Our protocol (oxone-halide) can eliminate not only the use of hazardous oxidants (e.g., Pb(OAc)₄, CrO₃, OsO₄, t-BuOCl, NBS, and m-CPBA, etc) but also the production of organic byproducts or toxic heavy metals derived from oxidants to minimize the environmental and health impact of the indole oxidation.

Results
Oxidative rearrangement of tetrahydro-β-carbolines. The tricyclic spirooxindole core, in particular the spiro[pyrrolidine-3,3'-indolenine], is a privileged scaffold featured in a variety of medicinal agents (anti-tumor, anti-microbial, anti-viral, and anti-malarial, etc) and bioactive natural alkaloids (e.g., spirotryprostains, rhynchophylline, alstonine, horsfiline) to Oxidative rearrangement of tetrahydro-β-carbolines (THCs) to spirooxindoles was proposed as a biosynthetic process to account for the production of these metabolites and biogenesis connection with THC-type corynanthe alkaloids. It has been successfully mimicked as a key transformation in the total synthesis of many spirooxindole alkaloids and thus oxidative rearrangement becomes a major approach for the synthesis of spirooxindoles. However, the four identified stoichiometric oxidants: Pb(OAc)₄, OsO₄, t-BuOCl and N-bromosuccinimide (NBS) for the oxidative rearrangement are either unsafe to use or environmentally unfriendly. Pb(OAc)₄ and OsO₄ are extremely toxic heavy metal-based oxidants that pose a

Fig. 1 Oxidation of indoles and our hypothesis. a Prior methods for oxidation of indoles and some common side products; (b) Our previous work. (c) Hypothesis of oxone-halide oxidation of indoles. NBS N-Bromosuccinimide; m-CPBA meta-Chloroperoxybenzoic acid
significant threat to the human health and environment; while tBuOCl is an unstable, flammable, harmful liquid that usually requires fresh in-house preparation and appropriate titration.

In addition, tBuOCl required a subsequent acid treatment to complete the rearrangement (II → III, Fig. 2c). NBS was usually used in an acidic condition (AcOH–H2O) and inevitably produced the corresponding stoichiometric succinimide byproduct that required immediate elimination by column purification. Therefore, a green catalytic protocol is highly desirable.

In continuation of our interest in developing green oxone-halide protocols to replace N-halosuccinimides (NXS) and related halogenating reagents (e.g., Cl2, Br2, tBuOCl, etc.), we set out to explore the oxidative rearrangement of THCs using oxone-halide as a green alternative (Fig. 2b) to the widely used NBS and tBuOCl conditions. We believed such alternative was highly viable from the mechanistic perspective (Fig. 2c, d). The oxidative rearrangement of THCs involves a three-step sequence: oxidative halogenation, addition of water, and semi-pinacol rearrangement (Fig. 2c). We envisioned that oxone-halide (e.g., bromide) could deliver the reactive halogenating agent for the first step: oxidative halogenation. Small amount of water necessary for dissolving oxone as a co-solvent might add to β-bromo indolene (II); while the halide released in the semi-pinacol rearrangement of III could be re-oxidized by oxone to re-generate the halogenating agent for the next-cycle THC oxidation (Fig. 2d). In principle, catalytic amount of halide (e.g., KBr) in combination of stoichiometric oxone could be used for replacement of tBuOCl and NBS to achieve the goal of a green chemistry approach for the oxidative rearrangement of THCs to spirooxindoles.

To verify our hypothesis, we used THC 1a as our model compound to examine its oxidative rearrangement under various conditions (Table 1). We quickly found that the combination of oxone (1.2 eq) and KBr (5 mol%) in both THF/H2O (v/v = 1:1, 3:1, or 10:1) and MeCN/H2O (v/v = 1:1, 3:1, or 10:1) effected the oxidative rearrangement within 4 h in excellent yields (84–93%) (Table 1, entries 1 and 2). As compared to NBS-AcOH (83% yield) and tBuOCl-AcOH (79% yield), our protocol under optimal condition was higher yielding (93%). Other halides including tetrabutyl ammonium bromide (TRAB) (Table 1, entry 3), tetrabutyl ammonium iodide (TBAI) (Table 1, entry 4), tetrabutyl ammonium chloride (TBC) (Table 1, entry 5), KI (Table 1, entry 6), KC1 (Table 1, entry 7), NH4Cl (Table 1, entry 8) and NaCl (Table 1, entry 9), were also evaluated as the halide catalyst. We found that only TBAI was a competent halide catalyst without added advantage in terms of reaction time and yield. In the absence of halide (Table 1, entry 10), no rearranged product was observed in 24 h, which suggested that halide was the active catalyst for the oxidative rearrangement. In addition, other terminal oxidants including H2O2, K2S2O8, NaOCl, NaClO2, and tBuOOH were examined but they were inferior to oxone (entries 11–15) because they were either unable to oxidize bromide (H2O2 and tBuOOH, Table 1, entries 11 and 15) or unselective for oxidation of bromide and indole (K2S2O8, NaOCl, and NaClO2, Table 1, entries 12–14).

Next, we set out to examine the substrate scope (Table 2). It should be noted that, to the best of our knowledge, the substrate scope of this biomimetic oxidative rearrangement has not been studied systematically despite the fact that it was often used in the biomimetic total synthesis of spirooxindole alkaloids. We first investigated the electronic effect of the protecting group (N–R1 and N–R2) on the nitrogen (Table 2, entries 2a–2j). It was found that electron-donating group (EDG) including hydrogen, alkyl, and benzyl on the indole nitrogen (R1 = H, alkyl, Bn) was essential to the success of oxidative rearrangement (Table 2, entries 2a–2c). Interestingly, electron-withdrawing group (EWG, e.g., Ac, Ts, and Boc) on the indole nitrogen (N–R1) resulted in lower conversion (20–50%) and loss of EWG (2a was obtained instead of the expected 2d). The high chemoselectivity of indole oxidation via halide catalysis is hinged on that in situ generated halenium ion (c.f., Br+) as a catalyst reacts only with electron-rich indole (C2= C3) to form the corresponding indole halonium intermediate (I, Fig. 1c).

An electron-withdrawing group on the indole nitrogen (R1 = Ts, Boc) will substantially decrease the electron-density of indoles and consequently suppress the halenium-catalyzed indole oxidation, which is consistent with the result of 2d with 0% yield (R1 = Ts or Boc) in Table 2. On the other hand, the electronic property of protecting group on the piperidine (N–R2) is less significant to the electron density of indoles (not a conjugate system) and less influential to their oxidation under the halide catalysis, which is...
consistent with the higher yield (90–99%) with N-EWG (Table 2, entries 2e–2h: N-Boc, N-Ts, N-Cbz, and N-Ac). The low conversion (10–20%) for EDG (Table 2, entries 2i–2j: N-Me and N-Bn) under neutral condition might be attributed to preferentially oxidize the tertiary amine. It was later found that an acidic medium (THF/MeOH/H2O = 1:1:1) could substantially improve the conversion (>90%) and yield (60-74%). The lower isolated yield for electron-donating N-R3 (Table 2, entries 2k–2l) and N-Me (2m–2n) under neutral condition might be due to the difficult isolation/purification of tertiary amine products from our acid reaction medium. Two examples with electron-donating substituent (Me and OMe) on the THCs were selected to probe the possibly competing bromination on the benzene ring of THCs under our halogenating condition. Fortunately, the oxidative rearrangement occurred smoothly under our optimized condition (Table 2, entries 2k and 2l) and no aromatic bromination was detected. This finding was important to relevant total synthesis because such EDG substituents are found in a number of natural products (spirityprostacin A, horseline, and elacoline). Next, a variety of C1-substituted THCs were examined for their oxidative rearrangement (Table 2, entries 2m–2y). Except for C1-aryl THC (Table 2, entry 2v, 0%) that resulted in unexpected oxidative C1–N3 cleavage (see Supplementary Figs. 92 and 93 for the corresponding products), almost all C1-substituted THCs with various functional groups (alkene, CN, NO2, alkyn, and CO2Et) underwent smooth oxidative rearrangement to give the spirooxindole products in good to excellent yields with diastereoselectivity ranging from 1.5:1 to 3.8:1. Most of these diastereomers could be separated easily by column chromatography on silica gel and their relative stereochemistry was proposed according to the relative configuration of 2o (3R+/4S) and 2o′ (3R′/4R′), which were confirmed by X-ray diffraction analysis. It was to our surprise that 2u was obtained in 80% yield as a single diastereomer (dr = 20:1, 3R′/4S′). This remarkable high diastereoselectivity was in sharp contrast to those of tryptophan-derived THC 2z (dr = 4I). Interestingly, we found that C3-ester substitution enhanced the stereocontrol of C1-alkyl on the spirocenter from 1.5:1–3.8:1 (Table 2, entries 2m/m′–2t/t′) to 7/1–20/1 (Table 2, entries 2ac and 2ab). Another unexpected observation was that electron-donating group on the piperidine nitrogen (R3) appeared to reverse such diastereoselectivity, leading to isolation of the major products (Table 2, entries 2w and 2y) with different relative stereochemistry (3R′/4R′). The intriguing diastereoselectivity was not documented in the literature and our finding would be instrumental to the design and synthesis of spirooxindoles from THCs.

To showcase the utility of this protocol (Fig. 3c), we achieved the total synthesis of two popularly targeted spirooxindole natural products (±)-coerulescine (1.2 g, 2i) and (±)-horseline (3) from THC 1a (Fig. 3a)31,33–35. Reduction of THC 1a with LiAlH4 and oxidative rearrangement of the resulting THC 1i using our oxone-KBr under acidic condition (THF/MeOH/H2O = 1:1:1) furnished (±)-coerulescine (2i) with 1.2 g in two steps (overall yield: 39%). If the oxidative rearrangement of THC 1i was carried out with stoichiometric KBr and 2.4 equivalent of oxone, sequential one-pot oxidative rearrangement and bromination occurred to provide C5-bromo spirooxindole 2ad in 41% yield, which could be used for CuI-catalyzed Ullmann ether synthesis to furnish (±)-horseline (3) in 60% yield. Notably, this protocol allowed a one-pot sequential oxidative rearrangement and dibromination (1a → 2ae, 86% yield) when 2.1 equivalent of KBr and 3.6 equivalent of oxone were employed. This offered a compelling flexibility to access to a wide variety of spirooxindoles. Finally, we applied this protocol for the biomimetic oxidative rearrangement of natural alkaloid yohimbine and obtained the corresponding yohimbine oxindole 4 (Fig. 3b) in 56% yield, which apparently was superior to the reported three-step method38 with only 38% overall yield.

To further extend this interest, we were interested in the rarely-explored oxidative rearrangement of 1,3,4,9-tetrahydroxyano[3,4-b]indoles39,40 (THPIs, 5a–5e) to the oxa-spirooxindoles (Fig. 3d) because (i) oxa-spirooxindole is the structural core in many pharmacologically important molecules41,42 (Fig. 3c) and (ii) there are only a few synthetic methods33,44. To our delight, without further condition optimization all five THPIs underwent the expected oxidative rearrangement to provide the oxa-spirooxindoles 6a–6d in good to excellent yields, which constitutes the second examples of oxidative rearrangement of

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**Table 1 Selected conditions for oxidative rearrangement of THC 1a**

| Entry | Oxidant (1.2 eq) | MX (5 mol%) | Solvents (v/v, 10/1) | Conv. (%) | Yield (%) |
|-------|------------------|-------------|----------------------|-----------|-----------|
| 1     | Oxone            | KBr         | THF/H2O (1/1–10/1)   | 100       | 87–93     |
| 2     | Oxone            | KBr         | MeCN/H2O (1/1–10/1)  | 100       | 84–93     |
| 3     | Oxone            | TBAB        | MeCN/H2O             | 100       | 89        |
| 4     | Oxone            | TBAI        | MeCN/H2O             | 55        | 33        |
| 5     | Oxone            | TBAC        | MeCN/H2O             | 40        | 19        |
| 6     | Oxone            | KI          | MeCN/H2O             | 64        | 37        |
| 7     | Oxone            | KCl         | MeCN/H2O             | 28        | 19        |
| 8     | Oxone            | NH4Cl       | MeCN/H2O             | 30        | 17        |
| 9     | Oxone            | NaCl        | MeCN/H2O             | 32        | 16        |
| 10    | Oxone            | –            | MeCN/H2O             | 20        | 0         |
| 11    | H2O2             | KBr         | MeCN/H2O             | <10       | 0         |
| 12    | K2S2O8           | KBr         | MeCN/H2O             | 25        | 12        |
| 13    | NaClO            | KBr         | MeCN/H2O             | 75        | 54        |
| 14    | NaClO2           | KBr         | MeCN/H2O             | <10       | 0         |
| 15    | t-BuOOH          | KBr         | MeCN/H2O             | <10       | 0         |

*a yield was obtained by 1H-NMR analysis of the crude product using CH2Br2 as the internal reference. TBAB: tetrabutylammonium bromide; TBAC: tetrabutylammonium chloride; TBAI: tetrabutylammonium iodide.*
The reaction was carried out in THF/ACOH/H2O (1:1) at room temperature for 0.5-20 h. The minor diastereomer could not be obtained and the diastereomeric ratio was determined by 1H-NMR analysis of the crude reaction mixture. Additional 0.6 equivalent of oxone was added after 12 h reaction. Isolated diastereomeric ratio.

Oxidation of indoles to 2-oxindoles. The success of the green approach for the oxidative rearrangement of THCs/THPIs to (oxa-)spirooxindoles prompted us to explore the possibility of the o xo-halide oxidation of the simpler C3-substituted indoles to 2-oxindoles. 2-Cxindoles are not only important structural motifs in a number of biologically active alkaloid natural products and pharmaceutical molecules but also frequently used as the synthet ic building blocks in the synthesis of natural alkaloids and as the platform for development of synthetic methodologies. As shown in Fig. 4, the prior methods for direct oxidation of indoles to 2-oxindoles employed usually NBS or m-CPBA as the stoichiometric oxidant, even though electrophilic fluorinating agents such as selectfluor and Togni’s reagent were found to be ideal oxidants for some specific indoles that suffered from low yields when using NBS and m-CPBA. The DMSO-HCl (37%) condition was often limited to the oxidation of simple indoles without acid-labile functional groups. Apparently, there lacks of a green and efficient method for the indole oxidation to 2-oxindoles. We believed that the green o xo-halide oxidation system could be applicable to this case.

We chose 3-methylindole (skatole, 7a) as our model compound to examine the direct oxidation of indoles to 2-oxindoles. After quick screening of various solvents (Table 3, entries 1–9), three solvent systems: THF/H2O (20:1), MeCN/H2O (20:1), and t-BuOH/H2O (20:1), were identified to be an excellent reaction medium. We selected t-BuOH/H2O (20:1) for the best yield (91%) of 3-methyloxindole (8a) from the skatole oxidation. Notably, KBr was essential (Table 3, entry 13) and outperformed the corresponding KCl (58%) and KI (0%) (Table 3, entries 10 and 11), while the higher water ratio in the mixed solvent system

Table 2 Substrate scope of oxidative rearrangement of tetrahydro-β-carbolines

| Substrate | Oxone | KBr | Dr. | Product |
|-----------|-------|-----|-----|---------|
| 2a (93%) | 1.0 eq | | 20:1 | 93% |
| 2b (95%) | 1.0 eq | | 20:1 | 95% |
| 2c (95%) | 1.0 eq | | 20:1 | 95% |
| 2d (91%) | 1.0 eq | | 20:1 | 91% |
| 2e (94%) | 1.0 eq | | 20:1 | 94% |
| 2f (90%) | 1.0 eq | | 20:1 | 90% |
| 2g (99%) | 1.0 eq | | 20:1 | 99% |

THPIs. Remarkably, the diastereoselectivity (3R’/4R’) was unusually high and only a single diastereomer was isolated. The relative stereochemistry of 6a, 6c, and 6e was confirmed by X-ray diffraction. Notably, oxa-spirooxindole 6a possessed the same relative configuration as coixspirolactam C45 and could be used as a direct precursor for the synthesis of coixspirolactam C45.

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substrate scope led to some interesting examples of C3-substituted indoles (Fig. 5a). Our examination of the conditions for oxidation of indoles to 2-oxindoles (Table 2) showed that electron-donating substituents (e.g., R1 = Me, Bn, Allyl) were well tolerated in this mild oxidation condition, which outperformed prior methods regarding the functional group tolerance and efficiency.

This optimized condition was applied to oxidation of a variety of C3-substituted indoles (Fig. 5a). Our examination of the substrate scope led to some interesting findings. First of all, the electronic property of the protecting group on the indole nitrogen has a dominant influence on the oxidation: electron-donating groups including methyl, benzy1, ally1 (R1 = Me, Bn, Allyl) were favored (8b–8c, 90–92%), while electron-withdrawing group (e.g., R1 = Ts or Boc) completely suppressed the oxidation (8d′, 0%). Secondly, the electronic properties of C3 substituents (R2) is critical to the success of oxidation: C3-alkyl (electron-donating) indoles gave high yields while the parent indole, C3-phenylindole and C3-trifluoromethyl failed to deliver the corresponding 2-oxindoles (8a′, 8a″, and 8a‴ 0%). This finding was consistent with the observation that indole oxidation via halide catalysis required electron-rich indoles. The parent indole suffered from poor chemo-selectivity and regio-selectivity and gave a complex mixture, which was observed by m-CPBA. Thirdly, substitution at C5 and C7 of indoles (R3 = 7-Me, 5-Br, and 5-OMe) has little effect on the oxidation (8e–8g, 88–91%). Moreover, our oxone-KBr protocol was applicable to trypettamines (8j–8p), tryptophols (8r–8z), and their derivatives (8r–8v). In addition, the esters (8q–8s), carboxylic acids (8a, 8q), sulfonamides (8k–8l, 8n–8p), cyanide (8t–8v), and even free alcohol (8w–8z) were tolerated in this mild oxidation condition, which outperformed prior methods regarding the functional group tolerance and efficiency.

To showcase the scalability and utility of this oxone-KBr oxidation process (Fig. 5b), the catalytic oxidation of 7b and 7h on 2.0 mmol (2.62 g and 4.15 g, respectively) scales was carried out to provide the desired 2-oxindoles 8b and 8h in the excellent yield of 91% and 88%, respectively, which were used for the concise unified total syntheses of desoxyeseroline, physostigmin methyl ether, and esermethole. The availability of 2-oxindoles 8b and 8h with gram quantities enabled alkylation with two-carbon bromides to provide the 3,3-disubstituted 2-oxindoles (9a–9d). Reductive cyclization was employed for the construction of the key tricyclic hexahydropyrroloindolines (HP1s, 10c and 10d) and tetrahydrofurindolines (TFIs, 10a and 10b).
N-Methylation of the resulting hexahydropyrroloindoline furnished desoxyeseroline (10c) in 70% yield (46% overall yield for three steps). CuI-catalyzed Ulmann coupling of aryl bromide with NaOMe completed the synthesis of physovenol methyl ether (11a) and esermethole (11b) in 72% and 74%, respectively. Notably, physovenol methyl ether and esermethole were the 2-step precursor of respective phsyovenine and physostigmine.

In order to shed some light on the oxidation mechanism, we performed a small set of controlled experiments (Fig. 5c). 2-Deuterated 3-methylindole (D-7a, 72% D) was prepared and used for oxone-KBr oxidation. 49% Deuterium incorporation at C3 was observed in D-8a (90% yield). When D2O was used as a co-solvent, 85% deuterium at C3 was observed for the oxidation of un-deuterated substrate 7a. This seemingly contradictory result was attributed to the keto-enol tautomerism of 2-oxindole 8a under either neutral condition (THF/D2O, 14%D) or our standard condition (21%D), C2-Bromoindole (7aa) was not the intermediate for our oxone-KBr oxidation because it failed under our condition to provide 2-oxindole 8a. In addition, no 2-oxindole 8a was observed from the oxidation of 2-methylindole (7ab), which suggested that C3-alkyl substitution stabilized the developing positive charge at C3 in the course of bromide departure. All these results supported the proposed mechanism (Fig. 1c) that involved semi-pinacol rearrangement to provide the 2-oxindoles. However, we could not exclude the possible H–Br elimination over semi-pinacol rearrangement to afford 2-oxindoles when C2 was unsubstituted.

**Table 3** Selected conditions for oxone-KBr oxidation of skatole

| Entry | KX (10 mol%) | Solvents (v/v) | Time (h) | Yield (%) |
|-------|--------------|----------------|----------|-----------|
| 1     | KBr          | MeOH           | 2        | <5        |
| 2     | KBr          | tBuOH          | 2        | <5        |
| 3     | KBr          | CH2Cl2         | 2        | <5        |
| 4     | KBr          | DMF            | 2        | <5        |
| 5     | KBr          | H2O            | 2        | <5        |
| 6     | KBr          | DMSO           | 2        | <5        |
| 7     | KBr          | THF/H2O (20:1) | 87       |
| 8     | KBr          | MeCN/H2O (20:1)| 85       |
| 9     | KBr          | tBuOH/H2O (20:1)| 91       |
| 10    | KCI          | tBuOH/H2O (20:1)| 58       |
| 11    | KI           | tBuOH/H2O (10:1)| 0        |
| 12    | KBr          | BuOH/H2O (10:1)| 0        |
| 13    | -            | BuOH/H2O (20:1)| 0        |

*The reaction was carried out at room temperature with skatole (0.5 mmol), oxone (0.6 mmol), KX (10 mol%), solvent (5.0 mL). Isolated yield was obtained.

**Fig. 5** Oxone-Halide oxidation of indoles to 2-oxindoles. **a** Substrate scope for oxone-KBr oxidation of C3-substituted indoles to 2-oxindoles. **b** Total syntheses of (+)-desoxyeseroline, (+)-physovenol methyl ether and (+)-esermethole. **c** Controlled experiments for possible mechanism for the oxone-KBr oxidation of C3 substituted indoles to 2-oxindoles. TBAHS Tetrabutylammonium hydrogen sulfate

**Witkop oxidation of indoles to 2-keto acetanilides.** Oxidative cleavage of aromatic rings occurs frequently in Nature. In particular, the enzymatic oxidation of tryptophan to N-formylkynurenine is not only a major metabolic pathway of tryptophan but also the first key step of the biosynthesis of coenzyme NAD. The first chemical process of the corresponding oxidative cleavage of the C2–C3 double bond of indoles was reported in 1951 by Witkop, using Pt/O2 oxidation (Fig. 6b). Subsequently, various oxidants including peracids...
Notably, Winterfeldt found that NaH/O₂ and KO₃ were identified as effective systems for the commercial preparation of quinolones and for the Camps cyclization of indoles to 2-keto-acetanilides for the Camps cyclization

According to our model study, C₂-unsubstituted indoles were excellent substrates for Witkop oxidation with the oxone-halide system (~40%). Although C₂,C₃-disubstituted indoles were excellent substrates for Witkop oxidation with oxone-halide in HFIP/H₂O system, C₃-substitution was not critical (e.g., 12f and 12g; R₃ = Me). In the latter case, it should be noted that the oxone-KCl oxidation led to isolation of carboxylic acids 13f and 13g, instead of the expected aldehydes. Another interesting observation was that oxone-KCl oxidation of C₃-aldehydic indole 13h only resulted in 2-oxindole 13i, which might be arisen from decarboxylation.

We chose 2,3-dimethyl indole (12a) as the model compound to examine the viability of Witkop oxidation with the oxone-halide system. Surprisingly, the optimized conditions developed for oxone-halide oxidation of indoles to spirooxindoles and 2-oxindoles afforded only 14–34% yield of fragmentation product 13a (Table 4, entries 1–3). A large-scale screening of solvents (Table 4, entries 4–6) and halides (Table 4, entries 7–9) enabled us to identify a clean and efficient system: oxone-KCl in HFIP/H₂O (10:1) (Table 4, entry 8), which could deliver the desired Witkop product 13a in 74%. It was noted that the reaction time should be extended to 24 h, which was much longer than the time required for the oxidation of indoles to spirooxindoles and 2-oxindoles (1–4 h).

The success of Witkop oxidation with oxone-halide system in our model study prompted us to investigate the substrate scope (Fig. 6c). It was found electron-withdrawing group on the indole nitrogen (N-Ac or N-Boc) could not allow for the Witkop oxidation. One of our major findings in the course of expanding substrate scope was that C₂ substitution (R₂ = H) was necessary for the oxidative cleavage (12a–12o) as the C₂-unsubstituted indole 7w only resulted in 2-oxindole 8w (~40%). Although C₂,C₃-disubstituted indoles were excellent substrates for Witkop oxidation with oxone-halide in HFIP/H₂O system, C₃-substitution was not critical (e.g., 12f and 12g; R₃ = H). In the latter case, it should be noted that the oxone-KCl oxidation led to isolation of carboxylic acids 13f and 13g, instead of the expected aldehydes. Another interesting observation was that oxone-KCl oxidation of C₃-aldehydic indole 12i provided the unexpected carboxylic acid 13i, which might be arisen from an oxidation sequence involving C₂–C₃ cleavage, aldehyde

(3-MCPBA), periodic acid (NaIO₃), chromic acid, ozone and singlet oxygen, were identified for Witkop oxidation.65,66 Notably, Winterfeldt found that NaH/O₂ and KO₃Bu/O₂ could effect both Witkop oxidation and Camps cyclization to provide quinolones, which widely exist in many marketed drugs and bioactive molecules65 (Fig. 6a). The importance of Witkop oxidation of indoles to 2-keto-acetanilides for the Camps cyclization to quinolones and for the commercial preparation of benzodiazepines65,66 (drugs for treatment of insomnia and anxiety) aroused our interest in developing a green oxidation protocol for Witkop oxidation using the oxone-halide system (Fig. 6c).

We chose 2,3-dimethyl indole (12a) as the model compound to examine the viability of Witkop oxidation with the oxone-halide system. Surprisingly, the optimized conditions developed for oxone-halide oxidation of indoles to spirooxindoles and 2-oxindoles afforded only 14–34% yield of fragmentation product 13a (Table 4, entries 1–3). A large-scale screening of solvents (Table 4, entries 4–6) and halides (Table 4, entries 7–9) enabled us to identify a clean and efficient system: oxone-KCl in HFIP/H₂O (10:1) (Table 4, entry 8), which could deliver the desired Witkop product 13a in 74%. It was noted that the reaction time should be extended to 24 h, which was much longer than the time required for the oxidation of indoles to spirooxindoles and 2-oxindoles (1–4 h).

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Table 4 Selected conditions for Witkop oxidation with oxone-halide

| Entry | KX (10 mol%) | Solvents (v/v) | Time (h) | Yield (%) |
|-------|-------------|----------------|----------|-----------|
| 1     | KBr         | THF/H2O (10:1) | 24       | 20        |
| 2     | KBr         | MeCN/H2O (10:1) | 24       | 34        |
| 3     | KBr         | iBuOH/H2O (10:1) | 24       | 14        |
| 4     | KBr         | acetone/H2O (10:1) | 24       | 34        |
| 5     | KBr         | DMF            | 24       | <5        |
| 6     | KBr         | HFIP           | 24       | 47        |
| 7     | KBr         | HFIP/H2O (10:1) | 24       | 69        |
| 8     | KCl         | HFIP/H2O (10:1) | 24       | 74        |
| 9     | KI          | HFIP/H2O (10:1) | 24       | 13        |

The reaction was carried out with 12a (0.1 mmol, 1 eq), oxone (3.0 eq), KX (10 mol%), Solvent, rt. The residue was filtered, and concentrated under reduced pressure. The yield was determined by 1H-NMR analysis of the crude reaction mixture.

Discussion

We have developed a general halide catalysis for green oxidation of indoles to spiropinindoles, 2-oxindoles, 2-keto acetanilides. Our study demonstrated that oxone-halide could replace other organic halogenating agents (NBS, NCS, t-BuOCl etc) or peracids (mCPBA) in different types of oxidation of indoles, and thus eliminate the production of toxic organic byproducts derived from oxidants. As compared to prior methods, this protocol was usually more efficient partly due to the in situ generated halonium ion (X⁺) catalyst that has the appropriate concentration and reactivity towards the C2–C3 double bond of indoles and thus significantly suppressed other competing oxidations/rearrangements. In addition, no need to protect the indole nitrogen was advantageous since most previous methods required to mask the indole nitrogen with electron-withdrawing groups (e.g., N-Ts, N-Boc, N-Ac etc) for better chemo-selectivity and regio-selectivity. Achieving this oxone-halide oxidation of indoles was a milestone in the indole oxidation for its low-cost, safe/simple operation (open flask), and most importantly its greenness in several aspects of the 12 Green Chemistry Principles including (1) preventing waste, (2) less hazardous chemical synthesis, (3) safer chemicals, and (4) using catalysis. We believed that this oxone-halide system might be used for other types of indole oxidation that were not explored in this article. It is our expectation that this oxone-halide protocol for the indole oxidation will find wide applications in academia (organic synthesis) and industrial (pharmaceutical) communities.

Methods

Oxidative rearrangement of tetrahydro-β-carbolines. To a stirred solution of THF (1.0 eq) and KBr (5–10 mol%) in MeCN/H2O (10/1, 0.1 M) or in THF/H2O/AcOH (1/1/1, 0.1 M) at 0°C was added oxone (1.2 eq, MW = 307) in one batch. The reaction was stirred at room temperature for 24-h and then diluted with EtOAc. The resulting solution was filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give spiropinindoles.

Oxidation of C3-substituted indole to 2-oxindole. To a solution of C3-substituted indole (1.0 eq) and KBr (10 mol%) in iBuOH/H2O (20/1, 0.1 M) or in MeCN/H2O (10/1, 0.1 M) at rt was added oxone (1.2 eq, MW = 307), and stirred for 1–4 h. The reaction was quenched by addition of aq. sat. Na2SO3 and then diluted with EtOAc. The organic fractions were collected and the aqueous phase was extracted with EtOAc three times. The combined organic fractions were washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give 2-oxindoles.

Data availability

Experimental procedures and characterization data are available within this article and its Supplementary Information. Data are also available from the corresponding author on request. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Center (CCDC), under deposition numbers 1935503, 1935504, 1935506, 1935507, and 1935508. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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References

1. Norwood IV, V. M. & Hiugens III, R. W. Harnessing the chemistry of the indole heterocycle to drive discoveries in biology and medicine. ChemBioChem. https://doi.org/10.1002/cbic.201800768 (2019).
2. Zarrani, G. M., Gholamzadeh, P., Lasgari, N. & Hajiabassi, P. Oxindole as starting material in organic synthesis. Arkivoc 2013, 470–535 (2013).
3. Kaur, M., Singh, M., Chadha, N. & Silakari, O. Oxindole: a chemical prism and wide applications in academia and industrial (pharmaceutical) communities.
4. Van, D. D. Oxidative rearrangement of tetrahydro-β-carbolines. To a stirred solution of THF (1.0 eq) and KBr (5–10 mol%) in MeCN/H2O (10/1, 0.1 M) or in THF/H2O/AcOH (1/1/1, 0.1 M) at 0°C was added oxone (1.2 eq, MW = 307) in one batch. The reaction was stirred at room temperature for 24-h and then diluted with EtOAc. The reaction mixture was quenched by addition of aq. sat. Na2SO3 and then diluted with EtOAc. The organic fractions were collected and the aqueous phase was extracted with EtOAc three times. The combined organic fractions were washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give 2-oxindoles.
5. Hinman, R. L. & Bauman, C. P. Reactions of N-bromosuccinimide and CPBA in different types of oxidation of indoles, and thus eliminate the production of toxic organic byproducts derived from oxidants. As compared to prior methods, this protocol was usually more efficient partly due to the in situ generated halonium ion (X⁺) catalyst that has the appropriate concentration and reactivity towards the C2–C3 double bond of indoles and thus significantly suppressed other competing oxidations/rearrangements. In addition, no need to protect the indole nitrogen was advantageous since most previous methods required to mask the indole nitrogen with electron-withdrawing groups (e.g., N-Ts, N-Boc, N-Ac etc) for better chemo-selectivity and regio-selectivity. Achieving this oxone-halide oxidation of indoles was a milestone in the indole oxidation for its low-cost, safe/simple operation (open flask), and most importantly its greenness in several aspects of the 12 Green Chemistry Principles including (1) preventing waste, (2) less hazardous chemical synthesis, (3) safer chemicals, and (4) using catalysis. We believed that this oxone-halide system might be used for other types of indole oxidation that were not explored in this article. It is our expectation that this oxone-halide protocol for the indole oxidation will find wide applications in academia (organic synthesis) and industrial (pharmaceutical) communities.
6. Zhang, X. & Foote, C. S. Dimethyldioxirane oxidation of indole derivatives. J. Org. Chem. 29, 1206–1215 (1964).
7. Zhang, X. & Foote, C. S. Dimethyldioxirane oxidation of indole derivatives. J. Org. Chem. 29, 1206–1215 (1964).
8. Zhang, X. & Foote, C. S. Dimethyldioxirane oxidation of indole derivatives. J. Org. Chem. 29, 1206–1215 (1964).
9. Zhang, X. & Foote, C. S. Dimethyldioxirane oxidation of indole derivatives. J. Org. Chem. 29, 1206–1215 (1964).
of mitraphylline, rhynchophylline and corynoxeine. J. Am. Chem. Soc. 84, 3857–3863 (1962).

9. Finch, N. & Taylor, W. I. The Conversion of tetrahydro-β-carboline alkaloids into oxindoles. The structure and partial synthesis of mitraphylline and rhyynchophylline. J. Am. Chem. Soc. 84, 1318–1320 (1962).

10. Finch, N. et al. Oxidative transformations of indole alkaloids. III. pseudoxindols from yohimbinoindoids and their conversion to “inverted” yohimbane derivatives. J. Org. Chem. 27, 2229–2235 (1962).

11. Shavel, I. & Zinnes, H. Oxindole alkaloids. I. oxidative rearrangement of indole alkaloids to their oxindole analogues. J. Am. Chem. Soc. 84, 1320–1321 (1962).

12. Zinnes, H. & Shavel, I. Jr. Yohimbane derivatives. III. the oxidative rearrangement of indole alkaloids to their spirooxindole analogues. J. Org. Chem. 19, 3532–3536 (1954).

13. Hussain, H., Green, I. R. & Ahmed, I. Journey describing applications of spirooxindoles as antiviral agents. J. Org. Chem. Int. Ed. 57, 1725–17229 (2018).

14. Chung, C.-P. et al. Antiproliferative lactams and spiroenone from adlay bran in human breast cancer cell lines. J. Agric. Food Chem. 59, 1185–1194 (2011).

15. Ruiz-Sanchis, P., Savina, S. A., Albericio, F. & Álvarez, M. Structure, bioactivity and synthesis of natural products with hexahydropropylo[2,3-b]indole chemistry. J.Org. Chem. 73, 713–718 (1991).

16. Hussain, H., Green, I. R. & Ahmed, I. Journal describing applications of oxo in synthetic chemistry. Rev. Chem. 111, 3329–3371 (2013).

17. Noyori, R., Aoki, M. & Sato, K. Green oxidation with aqueous hydrogen peroxide. Chem. Commun. 16, 1977–1986 (2003).

18. Podgorsk, A., Zapan, M. & Iskra, J. Oxidative halogenation with “green” oxidants: oxygen and hydrogen peroxide. Angew. Chem. Int. Ed. 48, 8424–8450 (2009).

19. Ren, J. & Tong, R. Convenient in situ generation of various dichlorinating agents from oxo and chloride: diaireesserolec dichlorination of allylic and homoallylic alcohol derivatives. Org. Biomol. Chem. 11, 4312–4315 (2013).

20. Xu, J. & Tong, R. An environmentally friendly protocol for oxidative halocyclization of tryptamine and tryptophol derivatives. Green. Chem. 19, 2952–2956 (2017).

21. Song, Z. L., Fan, C. A. & Tu, Y.-Q. Semipinacol rearrangement in natural product synthesis. Chem. Rev. 111, 7532–7586 (2011).

22. Ye, N., Chen, H., Wold, E. A., Shi, P.-Y. & Zhou, J. Therapeutic potential of spirooxindoles as antiviral agents. ACS Infect. Dis. 2, 382–392 (2016).

23. Santos, M. M. M. Recent advances in the synthesis of biologically active spirooxindoles. Tetrahedron 70, 9735–9757 (2014).

24. Szabó, L. F. Rigorous biogenetic network for a group of indole alkaloids derived from strictosidine. Molecules 13, 1875–1896 (2008).

25. O'Connor, S. E. & Maresh, J. C. Chemistry and biology of monoterpene indole alkaloids: biosynthetic and biological significance. Nat. Prod. Rep. 23, 533–547 (2006).

26. Smith, J. M., Moreno, J., Boal, B. W. & Garg, N. K. Cascade reactions: a driving force in alkaamline alkaloid total synthesis. Angew. Chem. Int. Ed. 54, 400–412 (2015).

27. Trost, B. M. & Brennan, M. K. Asymmetric syntheses of oxindole and indole spirocyclic natural products. Synthesis 2009, 3003–3025 (2009).

28. Peterson, A. C. & Cook, J. M. Studies on the enantiospecific synthesis of oxindole alkaloids. Tetrahedron Lett. 35, 2651–2654 (1994).

29. Pellegrini, C., Strässler, C., Weber, M. & Borschberg, H. J. Synthesis of the oxindole alkaloid (=)-horisline. Tetrahedron Asymmetry 5, 1979–1992 (1994).

30. Mintz, M. J. & Walling, C. t-Butyl hypochlorite. Org. Synth. 49, 9–10 (1969).

31. Buev, E. M., Moskvin, V. S. & Sosnovskikh, V. Y. Nonstabilized azomethine ylides in the Mannich reaction: synthesis of 3, 3-disubstituted pyrrolidines, including oxindole alkaloids. J. Org. Chem. 82, 12827–12833 (2017).

32. Hirschlürser, G., Parker, J. S., Perry, M. W. D., Haddow, M. F. & Gallagher, T. Spiro-fused pyrrolidine, piperidine, and oxindole scaffolds from lactams. Org. Lett. 14, 4846–4849 (2012).

33. Ghosh, S. et al. Intramolecular dehydrogenative coupling of sp²-C-H and sp³-C-H bonds: an expedient route to 2-oxindoles. Org. Lett. 14, 5864–5867 (2012).

34. White, J. D., Li, Y. & Hie, D. C. Tandem intramolecular Photocyclodaddition Retro-Mannich fragmentation as a route to spiro[pyrroloindole-3,3′-oxindoles]: total synthesis of (±)-coerulene, (±)-horisline, (±)-elacoline, and (±)-6-deoxylacoline. J. Org. Chem. 75, 3569–3577 (2010).

35. Deppermann, N., Thomanek, H., Prentzel, A. H. G. P. & Maison, W. Pd-catalysed assembly of spirooxindole natural products: a short synthesis of horisline. J. Org. Chem. 75, 5994–6000 (2010).

36. Shavel, I. & Zinnes, H. Oxindole alkaloids. I. oxidative rearrangement of the yohimbane-type alkaloids, part B: formation of oxindol (±)-1,3-dihydro-2H-indol-2-one) derivatives. Helv. Chim. Acta 79, 1361–1378 (1996).
67. Huang, Y., Khoury, K., Chanas, T. & Dömling, A. Multicomponent synthesis of diverse 1, 4-benzodiazepine scaffolds. *Org. Lett.* **14**, 5916–5919 (2012).
68. Bunin, B. A. & Ellman, J. A. A general and expedient method for the solid-phase synthesis of 1, 4-benzodiazepine derivatives. *J. Am. Chem. Soc.* **114**, 10997–10998 (1992).

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**Author contributions**
J.X. and L.L. performed the experiments. H.Z. prepared some related substrates. Y.R.C. participated in discussing part of the experiments. R.T. conceptualized and directed the project, and drafted the paper with the assistance from all co-authors.

**Competing interests**
The authors declare no competing interests.

**Additional information**
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