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Rapid Oxidation Indoles into 2-Oxindoles Mediated by PIFA in Combination with *n*-$Bu_4NCl·H_2O$

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Abstract. We report the development of a rapid approach for directly converting indoles into 2-oxindoles promoted by HOCl formed in situ from the combination of (bis(trifluoroacetoxy) iodo)benzene (PIFA) and *n*-$Bu_4NCl·H_2O$. The procedure is widely functional group tolerant and provides 2-oxindoles in up to 94% yield within 5 min. The potential applications of the developed methodology are demonstrated by the gram-scale preparation of 3-methyl-2-oxindole (**11a**), the one-pot two-step syntheses of spiro-oxindoles **26a** and **26b**, and the formal synthesis of (-)-folicanthine (**2**).

Keywords: 2-Oxindole; Hypervalent iodine, Halide species; Spiro-oxindoles

Introduction

The 3-substituted 2-oxindole motif is a versatile synthetic building block for the total syntheses of biologically active indole-based natural products.[1] Selected examples include trigolute B (**1**),[2a] (-)-folicanthine (**2**),[2b] desoxyeseroline (**3**),[2c-2e] esermethole (**4**),[2f] (±)-corynoxine (**5**) (Figure 1).[2g] This framework is also present in a host of natural products and pharmaceutical molecules, such as the p53 inhibitor 6,[3a] SM-130686 (**7**),[3b] and maremycin (**8**).[3c] In this context, the development of a general, mild, and direct method for the transformation indoles into oxindoles is highly desired. Indeed, continual development has led to the development of a wide range of oxidation strategies (Figure 2A).[4] Among these, the DMSO/HCl(aq) system reported by Fontana et al. in 1977 remains a robust and frequently employed method, despite its inherent shortcomings, including its narrow functional-group tolerance under strong acidic conditions.[5] In addition, the treatment of indoles with *N*-bromosuccinimide (NBS) under aqueous conditions can also lead to the formation of 2-oxindoles; however, the amount of NBS needs to be

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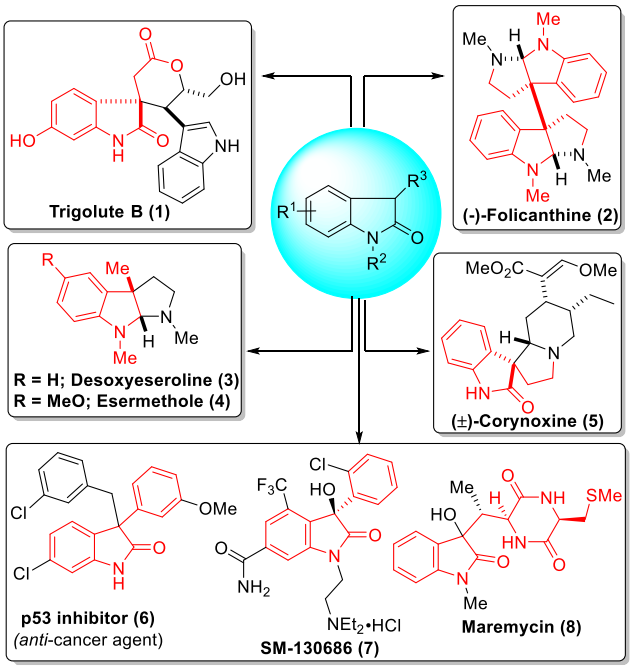

Figure 1. Selected applications and biologically active compounds containing the 3-substituted 2-oxindole subunit.

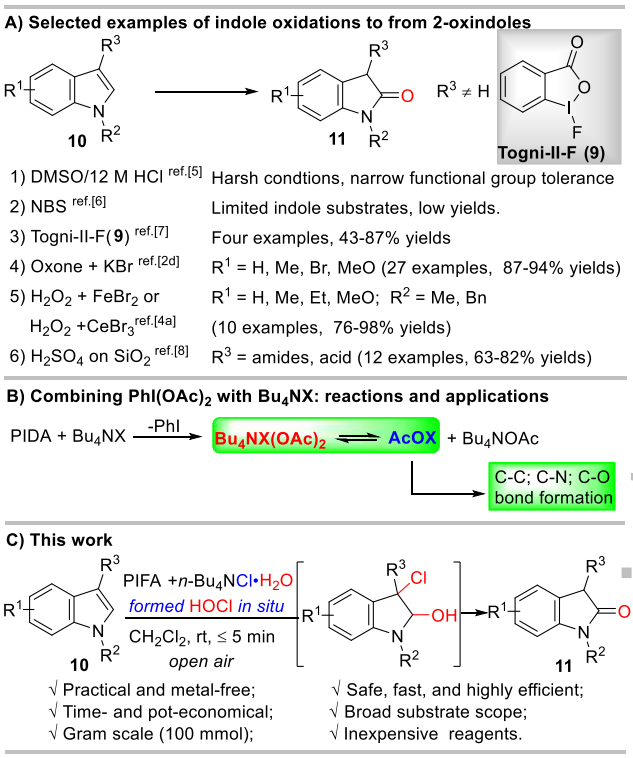

Figure 2. Selected examples of direct oxidations of indoles at their 2-positions and the application of the $PhI(OAc)_2$/halide combination.

carefully controlled to reduce the formation of 3-bromo-2-oxindole by-products, while limited scope and low yields render this method less important.[6] An elegant synthetic procedure based on the use of cyclic hypervalent iodine(III) **9** as an activating agent was developed in 2018 for the oxidation of indoles.[7] The method generally provides 3-unsubstituted 2-oxindoles in high yields, while 3-substitued indoles only afforded the corresponding products in moderate yields with limited scope (four examples, 43–87% yields).

A breakthrough was very recently reported by the Tong's group,[2d, 4a] in which different types of oxidized indole were prepared in a mild and green manner that included converting the indole into the 2-oxindole, [2d, 4a] oxidative rearrangement[2d, 4a] and Witkop oxidation[2d] using oxone[2d] or H_2O_2[4a] as the terminal oxidant. Although often effective, this process suffers from limited benzene-ring functional-group tolerance (only Me, Br, and MeO substituents were investigated) and long reaction times (up to 4 h). Very recently, Argade et al. used SiO_2/H_2SO_4 to oxidize indole;[8] however, this reaction is limited only to indoles devoid of substituents on the nitrogen atom and with an amide substituent at the 3-position, with yields ranging from 63% to 82% after stirring at room temperature for 12–24 h.

Treating hypervalent iodine compounds, such as $PhI(OAc)_2$ (PIDA), with halides is well-known to generate diacetoxyiodate(I) anions or acetyl hypoiodites that can react with double bonds or activated methylene groups to deliver a range of unusual C-C, C-O, or C-N bond-forming reactions (Figure 2B).[9, 10] Considering the above-mentioned limitations for the construction of 3-substituted 2-oxindoles and our continued interest in the development of mild conditions for the functionalization of heterocyclic compounds,[11] we believed that an alternative protocol that rapidly transforms indoles into 2-oxindoles under mild conditions with broad functional group tolerance represents a practical advantage. In particular, we wished to pursue an efficient way of generating HOX in situ, which would chlorohydroxylate the indole and then rapidly eliminate HX to generate the 2-oxindole product. Herein, we report a metal-free and efficient approach that converts indoles into 3-substituted 2-oxindoles, which involves forming HOCl in situ by combining (bis(trifluoroacetoxy) iodo)benzene (PIFA) and *n*-$Bu_4NCl•H_2O$ (Figure 2C).

Results and Discussion

Preliminary screening was performed using 3-methyl-1*H*-indole (**10a**), PIDA, and *n*-Bu_4NI in CH_2Cl_2 at room temperature (Table 1, Entry 1). Although **10a** was entirely consumed, the reaction gave a complex mixture. Surprisingly, the desired 2-

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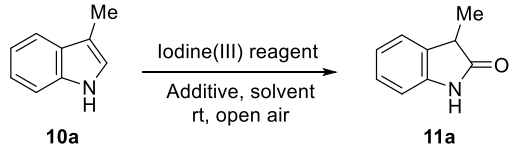
oxindole **11a** was isolated in 25% yield using PIFA instead of PIDA (Entry 2). The reaction conditions were further optimized by examining different halogen sources, which revealed that *n*-$Bu_4NCl{\bullet}H_2O$ was most efficient among NaI, NaCl, *n*-$Bu_4NF{\bullet}6H_2O$, *n*-$Bu_4NCl{\bullet}H_2O$, and *n*-Bu_4NBr (Entries 3–7). After a series of trials, **11a** was isolated in 94% yield when the reaction was carried out with 1.1 equiv. of both PIFA and *n*-$Bu_4NCl{\bullet}H_2O$ in CH_2Cl_2 at room temperature (entry 12).

Table 1. Screening the reaction conditions.[a]

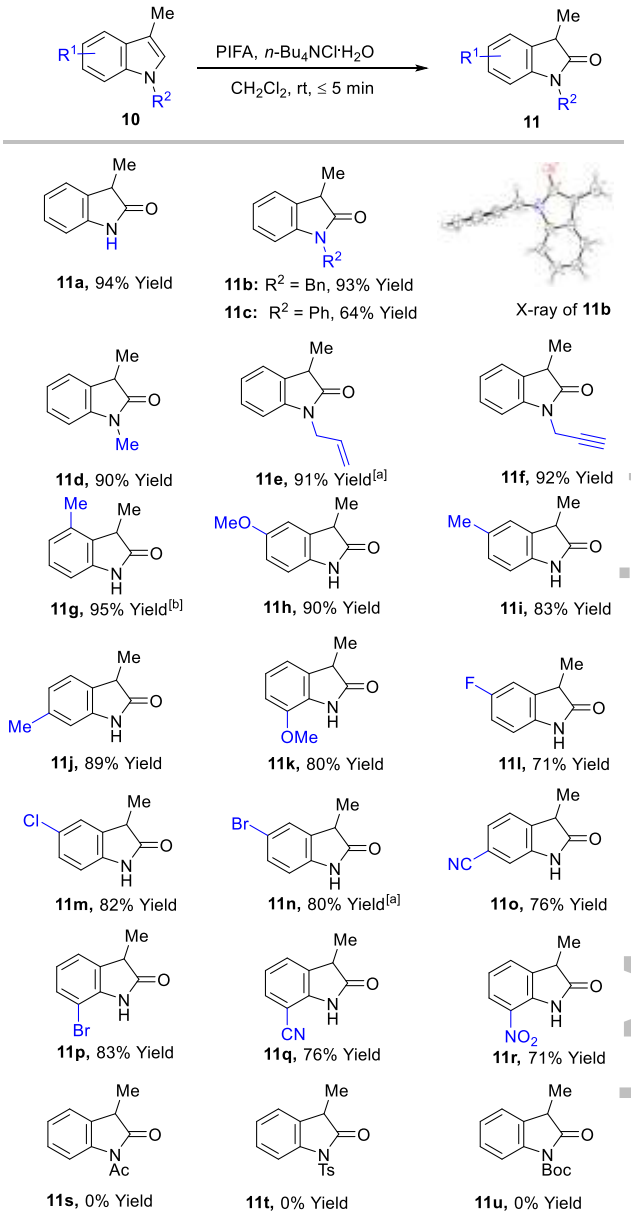


Entry	Oxidant	Additive	Solvent	Yield (%)[b]
1	PIDA	*n*-Bu_4NI	CH_2Cl_2	Complex
2	PIFA	*n*-Bu_4NI	CH_2Cl_2	25
3	PIFA	NaI	CH_2Cl_2	32
4	PIFA	NaCl	CH_2Cl_2	60
5	PIFA	*n*-$Bu_4NF{\bullet}6H_2O$	CH_2Cl_2	Complex
6	PIFA	*n*-$Bu_4NCl{\bullet}H_2O$	CH_2Cl_2	94
7[c]	PIFA	*n*-Bu_4NBr	CH_2Cl_2	48
8	PIFA	*n*-$Bu_4NCl{\bullet}H_2O$	DCE	90
9	PIFA	*n*-$Bu_4NCl{\bullet}H_2O$	CH_3CN	61
10	PIFA	*n*-$Bu_4NCl{\bullet}H_2O$	THF	37
11	PIFA	*n*-$Bu_4NCl{\bullet}H_2O$	toluene	83
12[d]	PIFA	*n*-$Bu_4NCl{\bullet}H_2O$	CH_2Cl_2	94

[a] Reaction conditions: **10a** (0.2 mmol), oxidant (0.22 mmol), H_2O (0.22 mmol), and additive (0.22 mmol) in 1.0 mL solvent ($H_2O \leq 500$ ppm) at room temperature for 5 min.
[b] Isolated yield.
[c] Standard conditions, with 0.42 mmol of H_2O.
[d] Without the addition of H_2O.

With the optimal conditions in hand, we next examined the scope of the substituents on the benzene ring and the nitrogen atom of the indole, the results of which are summarized in Table 2. Substrates **10b–10f**, in which benzyl, aryl, methyl, allyl and propargyl groups were installed on the nitrogen atom, provided the corresponding oxindole products **11b–11f** in yields of 64–93% in only 5 min. We then examined the reactivities of 3-methyl-1*H*-indoles with various substituents on the benzene ring. Oxidation proceeded effectively when electron-rich substituents, such as

Table 2. Substituent scope on the benzene ring and the nitrogen atom of indole.[a]



[a] Standard conditions except that 80 °C was used instead of 25 °C and DCM was replaced with DCE.
[b] Standard conditions except that −40 °C was used instead of 25 °C.

methyl or methoxy, were used, to afford the corresponding 2-oxindoles **11g–11k** in excellent yields in only 5 min. Substrates with electron-withdrawing groups, such as CN and NO_2, on the benzene ring provided products in very short times and with little variation in yield (76% and 71%, respectively). In addition, the reaction was found to be insensitive to the position of the substituent of the on the benzene ring, with all reactions complete in less than 5 min (**11l–11r**). A current limitation of the procedure is that the indoles with an electron withdrawing group on nitrogen atom did not provide the oxidative products as evidenced by substrates **11s-11u**.

To further expand the scope of this transformation, we subjected a wide range of 3-substituted indoles to

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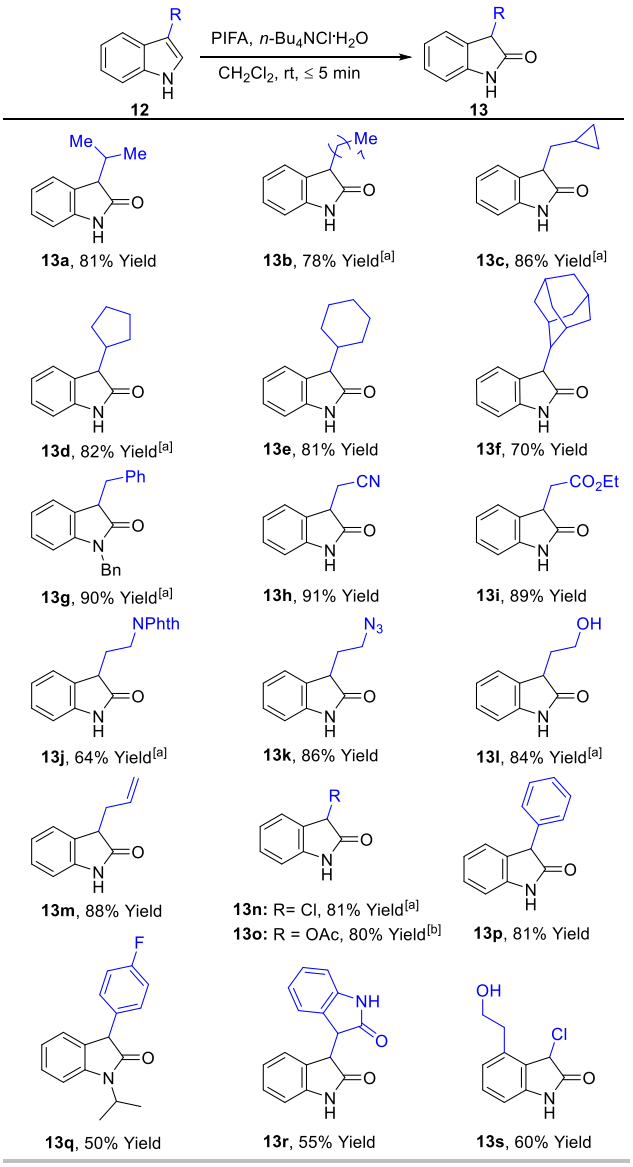
the standard the reaction conditions. As shown in Table 3, each examined indole substrate was

Table 3. Scope of the indole 3-substituent.[a]

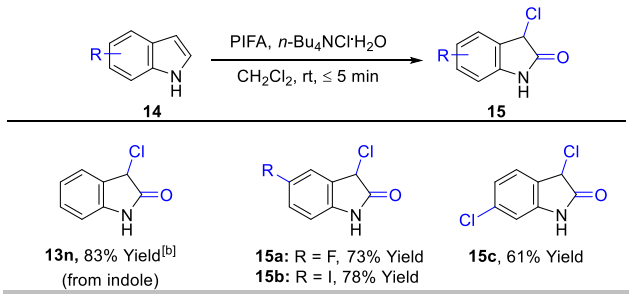


[a] Standard condition except that −40 °C was used instead of 25 °C.
[b] Standard condition except that 80 °C was used instead of 25 °C and DCM was replaced with DCE.

effectively converted into the corresponding oxindole within 5 min. Long-chain and sterically demanding alkyl groups were found to be suitable substrates for this transformation and afforded oxindoles **13a–13f** in moderate-to-good yields. Furthermore, various functional groups, including benzyl, cyano, ester, and azido groups, are well tolerated in this oxidation reaction (**13g–13k**). It is worth noting that substrates with hydroxyl groups and double bonds were smoothly transformed into the corresponding 2-oxindoles **13l** and **13m**. In addition, 3-Ar-, 3-OAc-, and 3-Cl-substituted 2-oxindoles **13n–13r** were obtained in yields of 80–82% from the corresponding 3-substituted indoles. Lastly, more complex products, such as [3,3'-biindoline]-2,2'-dione (**13s**) and 3-chloro-4-(2-hydroxyethyl)indolin-2-one (**13t**) were also efficiently prepared using our methodology.

Interestingly, when indole was subjected to the standard reaction conditions in table 3, we detected a complex reaction mixture, with the isolation of 3-chlorinated 2-oxindole **13n** in about 50% yield, however, a slight change of the reaction conditions by adding 2.2 equiv of both PIFA and *n*-$Bu_4NCl{\bullet}H_2O$ led to the formation of **13n** directly from indole in 83% yield. The new conditions were thus used to convert some other indoles without a substituted group at 3-position into corresponding 3-chloro-2-oxindoles, (**15a-15c**), which were obtained in 61-78% yield (Table 4).

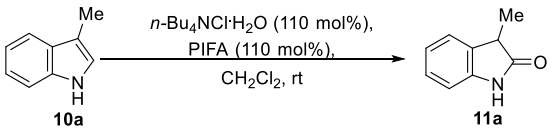
Table 4. Scope of chlorination-oxidation indoles into 3-Cl-2-oxindoles. [a]



[a] Reaction conditions: **14** (0.2 mmol), PIFA (0.44 mmol), and *n*-$Bu_4NCl{\bullet}H_2O$ (0.44 mmol) in 1.0 mL CH_2Cl_2 ($H_2O \leq$ 500 ppm) at room temperature for 5 min.
[b] Run at −40 °C.

A series of control experiments was carried out to gain additional information on the mechanism of our oxidation process (Table 5). Only trace amounts of product **11a** or no 2-oxindole product was formed when PIFA was replaced with PIDA or in the absence of PIFA (entries 2 and 3). The yield of **11a** was dramatically lower (approximately 30%) in the absence of *n*-$Bu_4NCl{\bullet}H_2O$ or with only 20 mol% *n*-$Bu_4NCl{\bullet}H_2O$ (entries 4 and 5). The 2-oxindole product was also produced, albeit in very low yield (18%), when *n*-Bu_4NHSO_4 was used (entry 6). Thus, we conclude that the *n*-$Bu_4NCl{\bullet}H_2O$/PIFA combination is required to successfully transform an indole into the

Table 5. Control experiments.



Entry	Variations from standard conditions	Yield of **11a**
1	none	94%
2	PIDA instead of PIFA, 12 h	< 10%

3	without PIFA	0%
4	without *n*-$Bu_4NCl•H_2O$, H_2O (110 mol%) was added, 12 h	29%
5	*n*-$Bu_4NCl•H_2O$ (20 mol%) + H_2O (100 mol%), 12 h	32%
6	*n*-Bu_4NHSO_4 (110 mol%) + H_2O (110 mol%) instead of *n*-$Bu_4NCl•H_2O$, 5 min	18%
7	PIFA + *n*-Bu_4NCl, 5 min, in glovebox	decomposed
8	PIFA + *n*-Bu_4NCl + $H_2{}^{18}O$, 5 min, in glovebox	11a + 11a-^{18}O 90%
9	BHT (100 mol%) was added, 5 min	91%

corresponding 2-oxindole. Furthermore, **10a** decomposed rapidly when it was stirred in a glovebox with PIFA and *n*-Bu_4NCl under the optimized conditions, and product **11a** was not detected by HRMS (entry 7). However, the introduction of 1.2 equiv. of $H_2{}^{18}O$ under the identified conditions in a glovebox led to the formation of ^{18}O-labeled TFA in the reaction mixture, as confirmed by HRMS, along with oxindole products **11a** and **11a-^{18}O** (Table 5, entry 8). Therefore, H_2O appears to play a pivotal role in this reaction. We believe that a radical process is not involved because the 2-oxindole product was isolated in similar yield (91%) when 2,6-di-tert-butyl-4-methylphenol (BHT, a radical inhibitor) was added to the reaction mixture under the identified conditions (Table 5, entry 9).

We attempted to prepare the ammonium-complexed halogen(I) species following the procedure reported by Toth,[10a] but a UV-absorbing yellow solid was obtained; its structure is proposed to be **16** or its polymer (Figure 3A) based on NMR spectroscopy, HRMS, and its ability to chlorinate a monoterpenoid[10o] (Figure 3B) and indole (Figure 3C, left). When PIFA and *n*-$Bu_4NCl•H_2O$ were replaced with **16**, oxindole product **11a** was produced in 73% yield under otherwise standard conditions (Figure 3C, right).

Based on the above observations, we propose a plausible mechanism for our transformation, as shown in Figure 4. Initially, *n*-$Bu_4NCl•H_2O$ reacts with PIFA to generate highly active intermediate **16**, which then

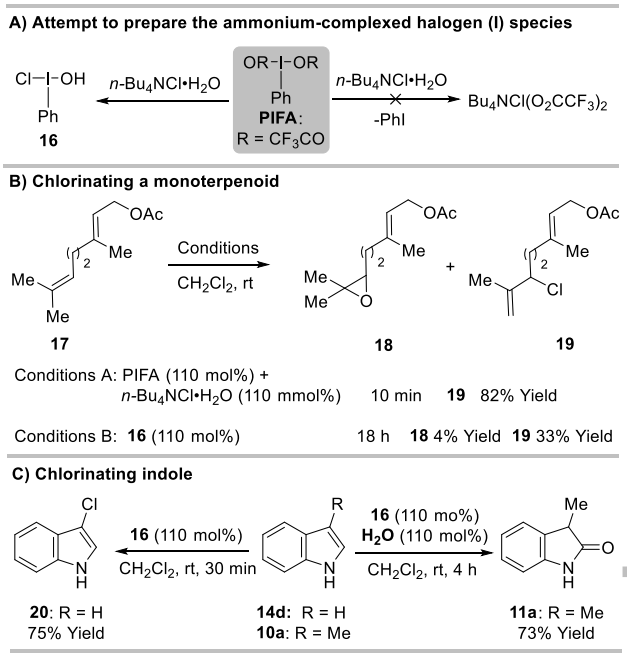


Figure 3. Confirming the structure of the intermediate.

forms Cl-OH after reductive elimination.[12] The indole then nucleophilically attacks **16** or Cl-OH to produce intermediate **21**, which then adds hydroxide (Path A) or trifluoroacetate anion (Path B) to form hemiacetal **22** or **23,** respectively (we assume that hydrolysis of **23** can also form **22**).[13] Subsequent elimination of HCl from **22** or HCl and TFA from **23** provides indole **24.** Finally, keto-enol tautomerism affords the desired product **11a**. We prefer this proposed mechanism even though intermediate **22** or chloronium-intermediate **21'** can also be produced directly by the reaction of intermediate **16** or Cl-OH with the C=C of indole, followed by reaction with

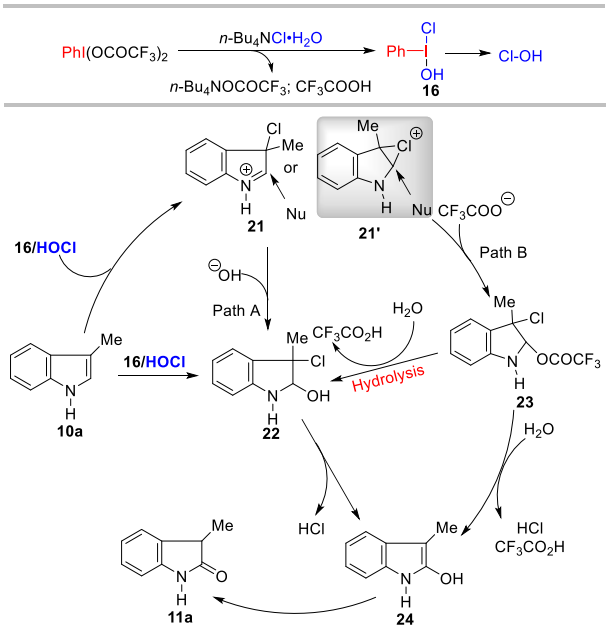


Figure 4. A plausible reaction mechanism for the PIFA-mediated oxidation of indole.

hydroxide or trifluoroacetate to generate **22** or **23**, respectively; however, this alternative cannot be ruled out at this stage.

A key feature of this transformation is its high efficiency; all examined reactions were complete in less than 5 min with good-to-excellent yields of the corresponding products, which means that it can be used when needed. To examine the potential application of our method, we oxidized **10a** on the gram scale (13.1 g, 100 mmol) under the standard reaction conditions with stirring for only 10 min, from which we obtained 13.4 g (91% yield) of **11a** (Figure 5A). Moreover, the reaction is always very clean, with no work-up necessary; once PIFA has been completely added, the solvent is simply removed and the crude reaction mixture is purified by chromatography or can be used in the next step without further purification. For example, spiro-oxindoles **26a** and **26b** were prepared in yields of 84% and 45%, respectively, using one-pot two-step processes from 3-substituted indoles **25a** and **25b** (Figure 5B). Alternatively, if necessary, following oxidation, a simple work-up provides the crude mixture, which can be also used in the next step. As shown in Figure 5C, treatment of **27** under standard conditions afforded **28** as a crude mixture, which was then transformed into **29** through double substitution in 42% yield over two steps. It is noteworthy that many compounds obtained by this methodology, including **11d**, **13i**, **13l**, and **26**, are key intermediates in the total syntheses of complex indole alkaloids, including those shown in Figure 1.

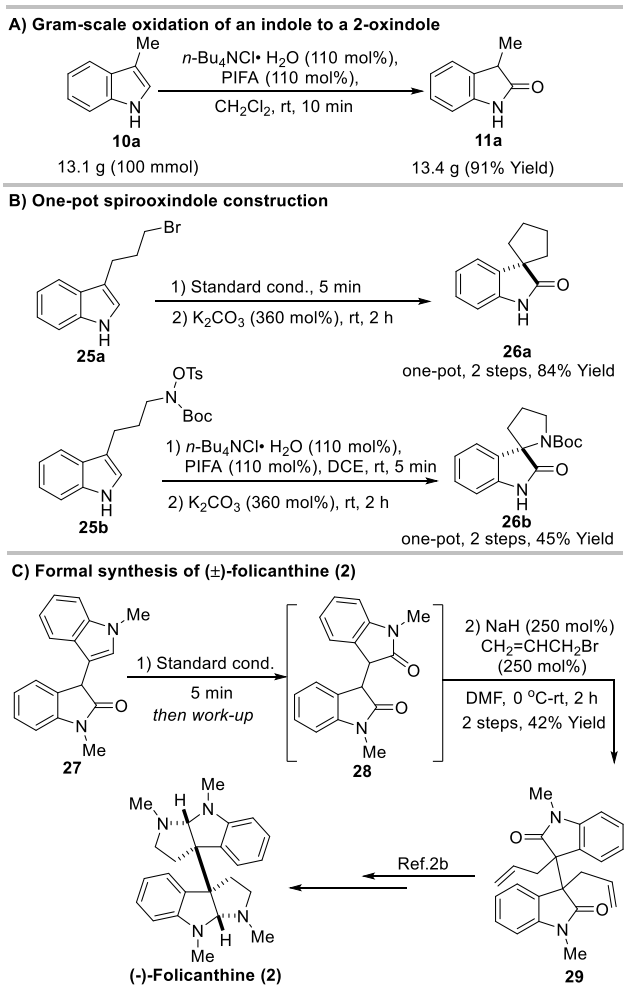


Figure 5. Applications of the PIFA mediated indole oxidation.

Conclusion

We developed a mild and rapid protocol for the synthesis of 3-substituted 2-oxindoles from indoles that is promoted by the combination of PIFA and *n*-$Bu_4NCl•H_2O$. The method has a number of advantages, including the use of inexpensive reagents, broad substrate scope, very short reaction times (less than 5 min), and good isolated yields. Mechanistic studies revealed that oxidation may take place through an in-situ-generated HOCl species. The applications of our protocol were demonstrated by the preparation of **11a** on a 13.4 g scale and the one-pot two-step syntheses of spirooxindoles **26a** and **26b**, and the formal synthesis of (-)-folicanthine (**2**).

Experimental Section

General Procedure for the Oxidation Indoles into 2-Oxindoles:

$PhI(OTFA)_2$ (0.22 mmol, 110 mol%) was added dropwise to a solution of the indole (0.2 mmol, 100 mol%) and *n*-$Bu_4NCl•H_2O$ (0.22 mmol, 110 mol%) in CH_2Cl_2 (1.0 mL) with stirring at open air listed in Tables 1–3 (between -40 and 80 °C). The resulting solution was stirred for further 1–5 min. Water (30 mL) was added to the reaction mixture once the starting material had been completely consumed as determined by TLC, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford the oxindole.

General Procedure for the Chlorination-Oxidation Indoles into 3-Cl-2-Oxindoles：

$PhI(OTFA)_2$ (0.44 mmol, 220 mol%) was added dropwise to a solution of the indole (0.2 mmol, 100 mol%) and *n*-$Bu_4NCl•H_2O$ (0.44 mmol, 220 mol%) in DCM (1 mL) at -40 ˚C or at room temperature. The resulting solution was stirred for further 1–5 min. Water (30 mL) was added to the reaction mixture once the starting material had been completely consumed as determined by TLC, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford the oxindole**.**

CCDC-1867773 contains the supplementary crystallographic data for compound **11b**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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FULL PAPER

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