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A catalytic, mild and efficient protocol for the C-3 aerial hydroxylation of oxindoles

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ABSTRACT

A mild, high yielding approach to C-3 hydroxylated oxindoles using catalytic quantities of tetrabutylammonium fluoride and air as the stoicheiometric oxidant is reported over a wide range of substitution patterns.

Methods for functionalization of the oxindole nucleus are of significant value in medicinal chemistry and natural product synthesis.[1] Due to their unprecedented structural diversity, biological activity and structural challenge, oxindoles continue to attract the interest of chemists and biologists alike. For example, the convolutamydines,[2] and the 3-hydroxywelwitindolinones are part of a growing list of biologically active 3-hydroxyoxindoles (Fig. 1).[3] 3-Hydroxyoxindoles with a quaternary benzylic centre are a useful class of compounds also found in several drug candidates, including the potent, orally active growth hormone secretagogue SM-130686,[4] a drug that currently is under investigation for the treatment of growth hormone deficiency and other medical conditions (Fig. 1).[5]

There are a number of reports on the enantioselective formation of quaternary carbon centres at the 3-position of oxindoles.[6] For example, Hartwig first reported the palladium-catalysed synthesis of oxindoles by amide α-arylation with ees of up to 67%.[7] This was later improved upon by Kündig using modified *N*-heterocyclic carbenes[8] and Marsden has reported several methods for the synthesis of 3-hydroxy- and 3-amino-oxindoles.[9]

Copper-mediated processes have also recently been employed to prepare quaternary C-3 oxindoles by both the Kündig[10] and Taylor groups.[11] Also of note are the recent reports by Franz,[12] who has reported the asymmetric direct addition of nucleophiles to isatins using chiral Lewis acids, and Shibata and Toru who have reported the asymmetric C-3 hydroxylation of oxindoles also using chiral

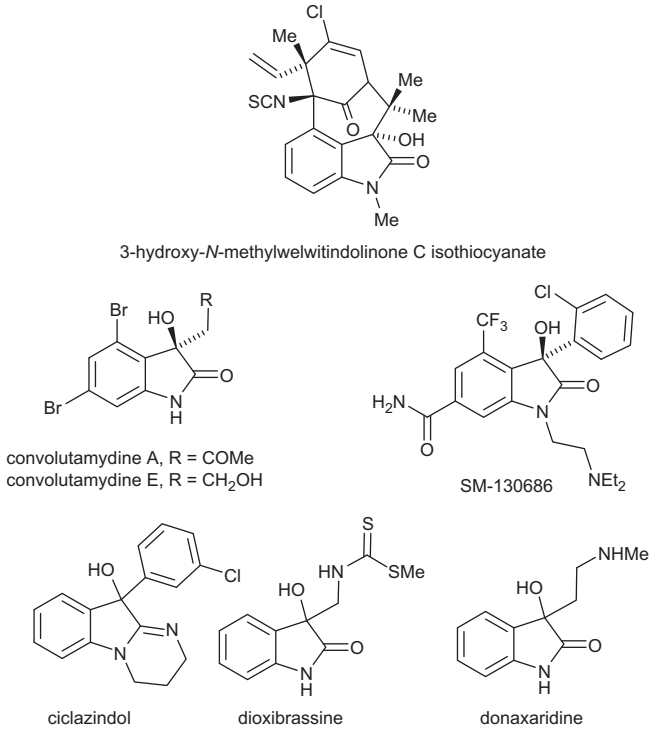

Figure 1. Exemplar biologically active C-3 hydroxy oxindoles and a related compound.

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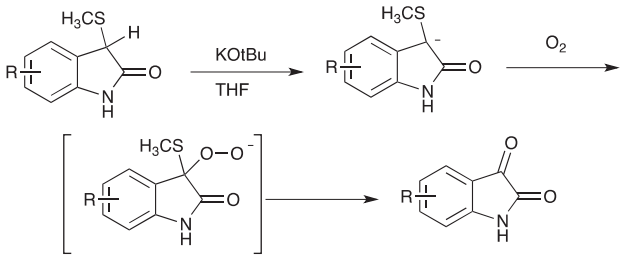
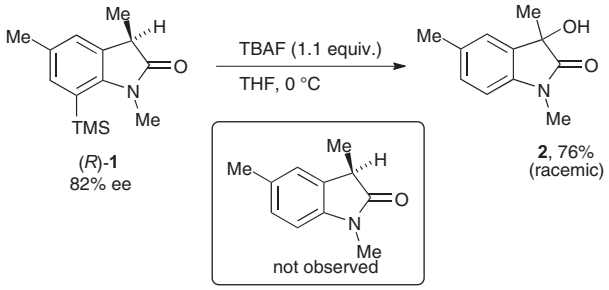


Scheme 1. Gassman's and Halweg's route to isatins.



Scheme 2. Curran's attempted removal of the trimethylsilyl group from **1**.

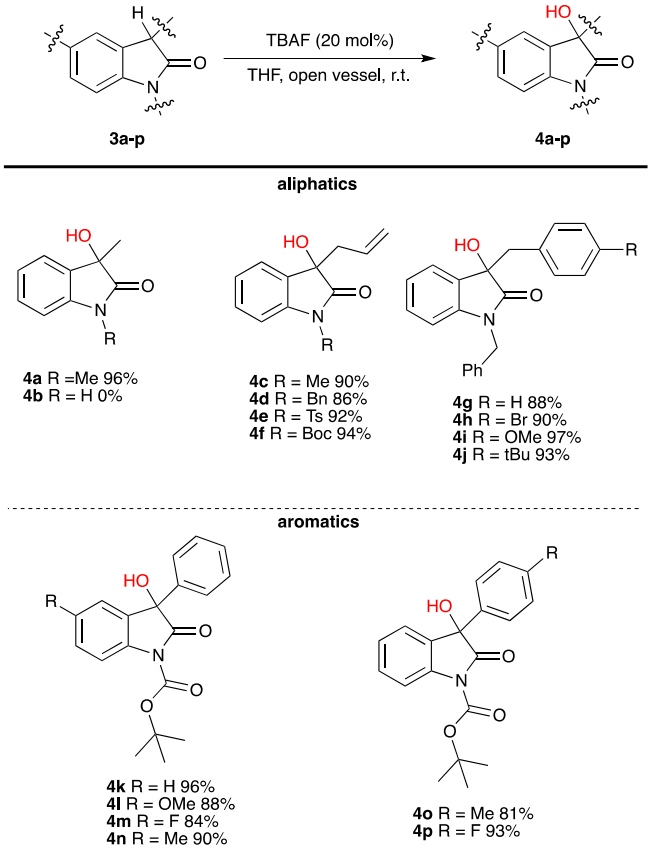
Lewis acids, with an oxaziridine as the stoicheiometric oxidant.[13] Thus owing to the significance of the oxindole structural motif, the development of catalytic methods for the synthesis of oxindoles bearing a C-3 hydroxy quaternary centre is highly desirable.

Gassman and Halweg reported the air oxidation of oxindoles to isatins (Scheme 1) through treatment of 3-methylthiooxindoles with a strong stoicheiometric base and air; strict anhydrous conditions were required in order to prevent degradation of the isatin to the corresponding anthranilic acid.[14] We also noted the recent report from Curran and co-workers,[15] where the attempted removal of the trimethylsilyl (TMS) group from **1** resulted in 3-hydroxy-1,3-dihydroindol-2-one **2** being the sole product of the reaction (Scheme 2). Careful investigation of Curran's reaction conditions revealed the use of 1.1 equiv of tetrabutylammonium fluoride (TBAF); as 1.0 equiv was required to fully desilylate the aryl ring we postulated that in order for 3-hydroxy-1,3-dihydroindol-2-one to be the sole product of the reaction, base-catalysed aerial oxidation must occur. We believed that this interesting unwanted side reaction could be a practical, mild solution to the synthesis of 3-hydroxyoxindoles using a readily available organocatalyst (TBAF) and a benign oxidant (air). This is even more important when one considers that from both an economic and environmental viewpoint there is currently an urgent need for more atom efficient systems that employ environmentally benign oxidants such as H_2O_2, or more preferably, O_2.[16]

We started our investigation by looking at the aerial oxidation of 1,3-dimethyl-1,3-dihydroindol-2-one (**3a**) using varying equivalents of TBAF in tetrahydrofuran as the solvent.[17] We were delighted to find that the reaction was extremely rapid at room temperature and excellent yields of the hydroxylated oxindole **4a** were observed with catalyst loadings as low as 10 mol %. Below this level we observed a poor conversion into the desired product perhaps due to the breakdown of catalyst–counterion pairs at a low catalyst concentration.[18]

Using our optimized conditions (THF, 20 mol % TBAF)[19] we screened a range of 3-alkyloxindoles, and again we were delighted to find that excellent yields of the corresponding 3-hydroxyoxindoles **4c**–**4j** were achieved (Table 1). We were also interested to see if our system was able to oxidize 3-aryl oxindoles as this motif

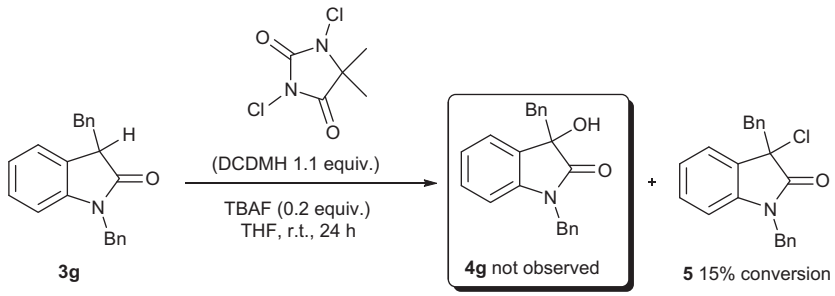
Table 1
Application to a range of substrates[a,b]



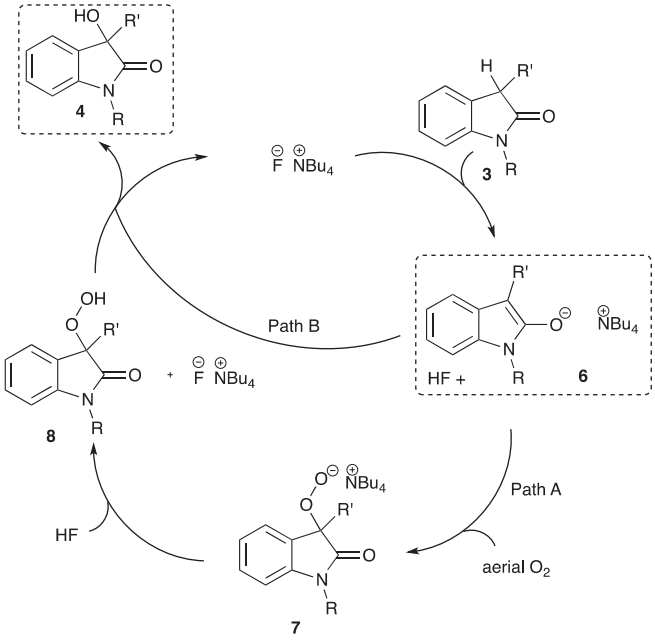
[a] General conditions: TBAF (1 M in THF, 0.2 equiv), THF (2 mL), open vessel, rt, 24 h.[19]
[b] Percentage yields shown refer to the isolated yield after chromatography.

is present in a variety of natural products and biologically important molecules (see Fig. 1 for example); again we observed an excellent conversion into the hydroxylated products **4k**–**4p**. These results are important when considering the recent report in which Itoh and co-workers described the asymmetric aerial phase-transfer oxidation of oxindoles (using aq KOH as a stoicheiometric base): they noted that benzyl protected oxindoles gave poor yields of C-3 hydroxylated products, also that the Boc protecting group was not tolerated under their reaction conditions; further they did not report the oxidation of oxindoles with aromatic groups at C-3.[20] Jiang and Tan have also reported the molecular oxygen oxidation of oxindoles employing a stoicheiometric base and a chiral pentadinium salt, but the substrate screen was narrow with the only group at nitrogen studied being *p*-methoxybenzyl.[21] Our procedure appears quite general with the protecting group on nitrogen having little influence on the reaction, however, a group at nitrogen is essential for the reaction to occur (see **4b**, Table 1 for example, this is presumably due to deprotonation of the nitrogen in preference to enolate formation).

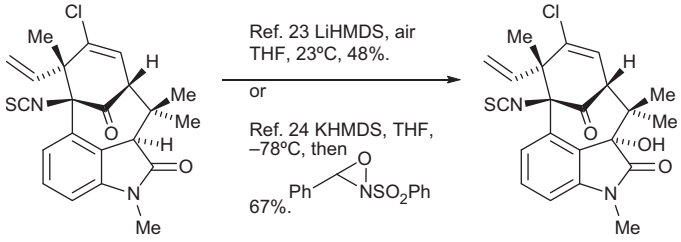
Intrigued by these findings we also carried out a competition experiment through the addition of an electrophile to the reaction. For example, when **3g** is treated with TBAF (0.2 equiv) in THF the oxidized oxindole **4g** is the sole product (Table 1), however, if 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) is added prior to the addition of TBAF then chlorination at C-3 is observed (to afford **5** along with recovered starting material **3g**, Scheme 3), with no C-3 hydroxylated product **4g** being detectable by ^{1}H NMR spectroscopy or TLC analysis. Suggesting that quenching of the enolate with



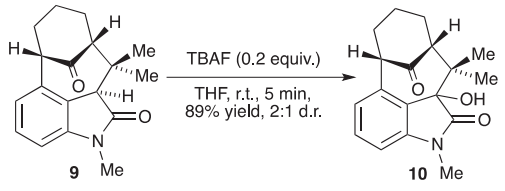
Scheme 3. Competition experiment by addition of DCDMH to the reaction.



Scheme 4. Proposed catalytic cycle.



Scheme 5. Garg and Rawal's independent routes to 3-hydroxywelwitindoline.



Scheme 6. Application towards 3-hydroxywelwitindolines.

an electrophile other than O_2 is more facile and that the reagent used inhibits formation of the enolate after 1 turnover of the system, thus only 15% of the chlorinated product is observed from the use of 20 mol % TBAF. When 1 equiv of TBAF is employed complete conversion into **5** is observed.

A proposed catalytic cycle is outlined in Scheme 4. Treatment of oxindole **3** with TBAF affords tetrabutylammonium enolate **6** plus HF, following Path A addition of O_2 affords peroxide anion **7** and recombination with a molecule of HF affords peroxide **8** plus TBAF which can re-enter the catalytic cycle.[22] In order to break down peroxide **8** we propose that another molecule of enolate **6** intercepts **8** (Path B) and affords two molecules of the hydroxylated product **4** plus another molecule of TBAF.

Recently Garg and co-workers[23] and Rawal and co-workers[24] both independently described their routes to (−)-3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate employing a strong base, and in the case of Garg, air and Rawal an oxaziridine as oxygen sources for the C-3 hydroxylation reaction (Scheme 5). Employing our TBAF conditions to a model substrate **9**, shown in Scheme 6, which was prepared by analogy to that reported previously by Garg and co-workers,[17,25] we were able to establish that an excellent yield of the C-3 hydroxylated product **10** could be achieved.

In conclusion, we have developed a mild catalytic process for the hydroxylation of oxindoles at the C-3 position using an environmentally benign terminal oxidant that appears to be of general use to a wide range of protected oxindoles. The protocol is also effective for hindered substrates such as the welwitindolinone model **9**. In addition stoicheiometric TBAF is an effective base for halogenation at the C-3 position of oxindoles.

Acknowledgments

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Supplementary data

Supplementary data (synthetic details along with ^{1}H and ^{13}C NMR spectra for all novel compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.083.

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19. Representative method for the C-3 hydroxylation of oxindoles: 3-hydroxy-1,3-dimethylindolin-2-one (**4a**):
To a solution of **3a** (0.16 g; 1.0 mmol) in THF (10 mL) was added TBAF (0.2 mL; 1 M in THF; 0.20 mmol) in a Carousel 12 reaction vial. The reaction was followed by TLC analysis. Once complete the reaction mixture was quenched with a saturated solution of NH_4Cl (5 mL) and extracted with Et_2O (3×30 mL). The organic layer was washed with brine (2×10 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Flash chromatography on silica gel (light petroleum/EtOAc; 10:1) afforded the title compound as a colorless oil (0.17 g, 96%) with almost identical spectroscopic data to that reported in the literature, see: Thomson, J. E.; Kyle, A. F.; Gallagher, K. A.; Lenden, P.; Concellón, C.; Morrill, L. C.; Miller, A. J.; Joannesse, C.; Slawin, A. M. Z.; Smith, A. D. *Synthesis* **2008**, 2805.
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