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Cu-Catalyzed Oxidation of C2 and C3 Alkyl-Substituted Indole via Acyl Nitroso Reagents

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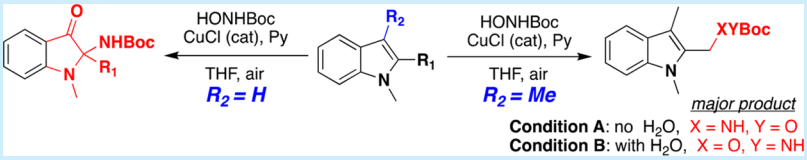
Supporting Information



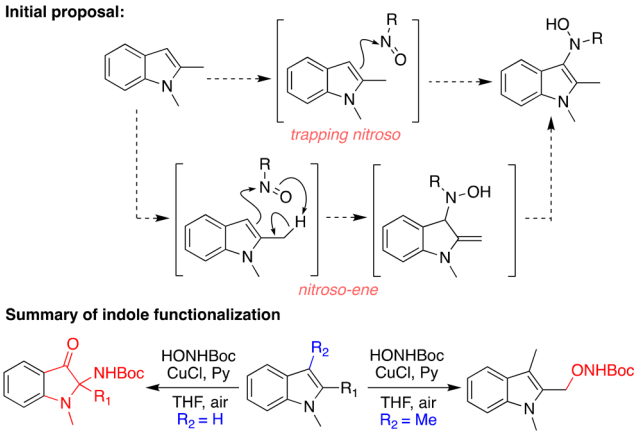
ABSTRACT: The selective oxidation of C2-alkyl-substituted indoles to 3-oxindole and the selective C−H oxygenation or amination of C2,C3-dialkyl-substituted indoles at C2 are reported under mild conditions. The position of the alkyl substitution on the indole directs the reaction to different pathways under similar conditions.

Functionalized indoles are privileged subunits that appear in a number of biologically active molecules, specifically indole alkaloids.[1] As a result, syntheses of functionalized indoles have received a great deal of attention, although synthetic challenges remain. Successful synthetic approaches have included the C−H activation of the ring,[2] construction of the indole core,[3] functionalization via aerobic dearomatization and oxidative coupling reactions,[4] among others. Nonetheless, these methods also come with limitations: direct C−H activation normally requires extra directing groups and specialized ligand/catalyst pairs, and strong oxidants and harsh conditions are needed for dearomatizations and oxidative coupling reactions. As such, a facile reaction to selectively functionalize specific regions in an indole ring is welcomed as a complementary approach to the existing strategies. In this report, we disclose reaction manifolds that can convert indoles to either 2-amino-substituted 3-oxindoles or partake in selective C−H activation of 3-methyl-substituted indoles with nitroso reagents.

Nitroso compounds are powerful reagents for classic ene-type reactions, enabling functionalization of the allylic position in a stereo- and regioselective manner.[5] Nonetheless, the use of the nitroso-ene reaction with aromatic compounds is not well explored. In fact, our initial proposal was to harness the reactivity of the nitroso functionality, as described above, for the amination of the indole ring at C3 by either trapping the nitroso as an electrophile or the nitroso ene reaction (Scheme 1). Although upon screening a variety of conditions the anticipated product was not observed, fortuitously and unexpectedly, the reaction of **1a** with *tert*-butyl nitrosoformate led to the isolation of the oxindole product **3a**. In contrast to other preparations of oxindoles, the formation of this product was accompanied by a novel N−O bond cleavage to form an aminal. Formation of this unexpected product piqued our curiosity to explore this unusual oxidation.

Intrigued by the initial results, screening and optimization of the reaction conditions were pursued (Table 1). The results

Scheme 1. Nitroso Functionalization of Indole



were benchmarked against those obtained from the reaction of **1a** with hydroxylamine (1 equiv) and CuCl (2 mol %) in THF under air (45% yield, Table 1, entry 1). The addition of 2 mol % of pyridine increased the yield of oxindole **3a** slightly (54%, Table 1, entry 2). Conversely, bipyridine, 2,6-di-*tert*-butyl-4-methylpyridine, and 1,10-phenanthroline resulted in lower yields (<35%, entries 3−5). Increasing the *tert*-butyl hydroxycarbamate **2** loading to 2 equiv, however, led to a substantial increase in yield (88%, entry 6), yet increasing the amount of pyridine was counterproductive (entry 7). It is noteworthy that other hydroxylamines (see the Supporting Information (SI) for details) afforded no desired product under the same conditions. Use of other Cu(I) or Cu(II) sources instead of CuCl failed to improve the reaction yield and, in fact, led to diminished production of **3a** (see entries 8−13). Similarly, the yield suffered when the reaction was

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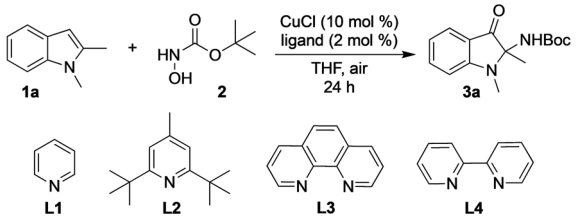
Table 1. Screen of Conditions for 3-Oxindole Formation



entry	catalyst	2 (equiv)	ligand	solvent	yield[a] (%)
1	CuCl	1		THF	45
2	CuCl	1	L1	THF	54
3	CuCl	2	L2	THF	33
4	CuCl	2	L3	THF	20
5	CuCl	2	L4	THF	28
6	**CuCl**	**2**	**L1**	**THF**	**88**
7[b]	CuCl	2	L1	THF	19
8	CuBr	2	L1	THF	35
9	CuI	1	L1	THF	0
10	$CuCl_2$	1	L1	THF	42
11	$Cu(OAc)_2$	1	L1	THF	0
12	Cu_2O	1	L1	THF	0
13	$Cu(ACN)_4PF_6$	1	L1	THF	16
14	CuCl	2	L1	DCE	26
15	CuCl	2	L1	ACN	3

[a]Determined by H NMR using an internal standard; all reactions were performed on a 0.1 mmol scale. [b]10 mol % ligand loading was used. Py = pyridine, DCE = dichloromethane, ACN = acetonitrile.

conducted in other solvents (ACN, DCE, entries 14 and 15). In this regard, we speculated that the combination of CuCl, pyridine, and THF promotes the formation of the transient active nitroso intermediate to avoid self-decomposition.[6] Indeed, the optimal conditions were found to be CuCl (10 mol %), pyridine (2 mol %), and 2 equiv of *tert*-butyl hydroxycarbamate in THF under air (Table 1, entry 6).

With the optimal indole oxidation conditions established, a range of indole substrates were screened (Figure 1). Substitution on positions C4−C7 of the indole were well tolerated to afford the desired oxindoles in good yields (**3a−o**, Figure 1). Generally, electron-donating substituents led to a faster reaction and higher yield, while electron-withdrawing substrates provided the product with lower efficiency. Notably, alkyl groups such as ethyl and *n*-butyl on the indole nitrogen atom were also tolerated in this reaction (**3p**, **3q**), although more bulky substituents were not so fortunate (see the SI). Nonetheless, switching the alkyl groups to other electron-withdrawing protecting groups on the indole nitrogen atom affords no product. Alkyl groups besides methyl, such as an ethyl group, on the C-2 position were also tolerated, yielding the corresponding product **3r** in moderate yield (49%). Interestingly, oxindole **3a** was isolated as a bright yellow fluorescent solid, exhibiting solvatochromic properties; namely, it exhibits different emission wavelengths in various solvents (see the SI for details).

Next, the reaction of C2,C3-bis-alkyl-substituted indoles was investigated with conditions that produced 3-oxindole with C2-alkyl-substituted indoles (Figure 2). Surprisingly, two different products were obtained as a result of the ambident reactivity of the nitroso reagent:[7] C−H oxygenation product **5a** and C−H amination product **5aa**, with a 2:1 $ar_{O:N}$ ratio, favoring the oxygenation pathway. We have taken the liberty to

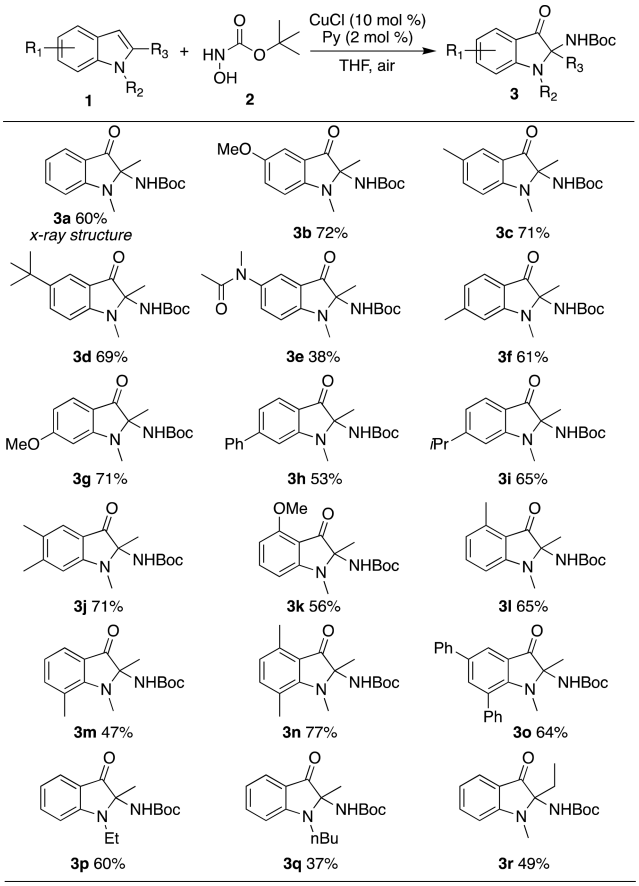


Figure 1. Substrate scope for 3-oxindole formation. Reactions were conducted on a 0.1 mmol scale (yields refer to isolated product). The reaction to produce **3a** was performed on a 1 mmol scale providing the product in 34% yield while returning 50% unreacted starting material (see the SI for details).

define *ar* as the ambident-selectivity ratio, denoting the distribution of products obtained from reaction at the oxygen atom relative to the nitrogen atom of the nitroso group. Crystal structures confirm the identity of both products. Notably, this allylic functionalization happens exclusively at C2 ($rr_{C2:C3}$ > 19:1) for the C2,C3-disubstituted systems. Various reaction conditions and additives were screened to favor specifically the N and O functionalization. Full details of these efforts are described in the SI; nonetheless, addition of water suppressed the aminated product, thus favoring the oxygenated product **5a**. With 20 equiv of water, a higher ambident reactivity for oxygenation vs amination was achieved (**5a**, $ar_{O:N}$ = 6.7:1). Alternatively, increased pyridine loading (12 mol %) reversed the selectivity from the C−H oxygenation to the C−H amination (**5aa**, $ar_{O:N}$ = 1:3.8). Further addition of pyridine led to suppression of the reaction. Use of other ligands was not fruitful and in most cases halted the reaction.

Figure 2 illustrates the substrate scope with various C2,C3-disubstituted indoles using the optimized conditions for oxygenation and amination. Replacing the methyl group on the nitrogen atom with a benzyl or ethyl group leads to a lower *ar* value for both oxygenation and amination reactions (**5b**/**5ba**-**5c**/**5ca**). The selectivity for C−H oxygenation was higher when C2 is an ethyl instead of a methyl group (**5l**, 53%, $ar_{O:N}$ = 13:1). For electron- poor indole substrates, C−H amination is highly favored (**5ia**, **5ja**, $ar_{O:N}$ < 1:10). On the other hand,

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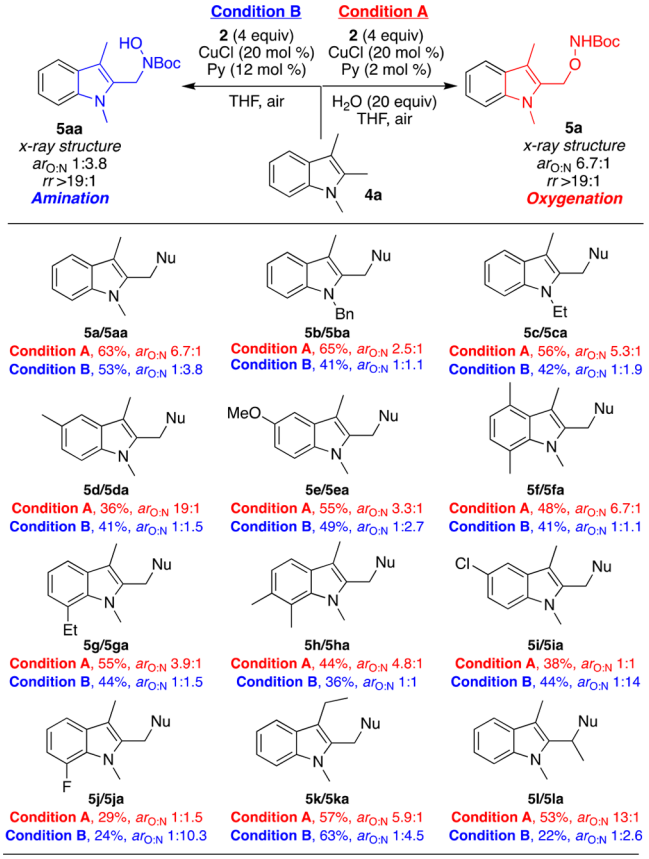


Figure 2. Substrate scope for C2,C3-bisalkyl indole oxygenation. Reactions were conducted on a 0.1 mmol scale in THF (with 20 equiv H_2O), and the yield was measured by NMR with internal standard. $ar_{O:N}$ is defined as the oxygenation to amination product ratio. Reaction to produce **5a** was performed on a 1 mmol scale providing the product in 47% yield (see the SI for details). Transformation under conditions B resulting in **5i**/**5ia** was conducted with 6 mol % of pyridine, while 4 mol % of pyridine was used for **5b**/**5ba** and **5j**/**5ja**.

electron-rich indoles yield a higher ratio favoring the hydroxylation product; even under the conditions that favor amination, there is no clear preference for amination vs oxygenation.

Results for expansion of this reaction to ring-fused indoles, which could find utility for the total synthesis of complex natural products, are depicted in Figure 3. Both 6- and 7-membered fused-ring substrates afforded good yield and regioselectivity (60% and 53% yields for **7a** and **7b**, $ar_{O:N}$ = 6:1). Unexpectedly, 5-membered ring indole substrates react to yield the indoline product, as depicted in the transformation of **6c** to **8c**. Presumably, this occurs via the dearomatization of the indole ring, leading to the hydroxylated indoline via the putative intermediates **A** and **B**. Likely, the strain of the 5-membered ring restricts the elimination of the allylic proton, thus affording **8c** as the product.

Mechanistic investigations of the transformations disclosed here are well beyond the scope of this manuscript and will require intense scrutiny. Nonetheless, based on anecdotal evidence observed during the course of our studies, literature precedence, and control experiments described below, postulated routes for the two class of products described are presented, with the caution that these are suggestions at best. To gain some mechanistic insight into these transformations, a set of control experiments was carried out. First, the presence

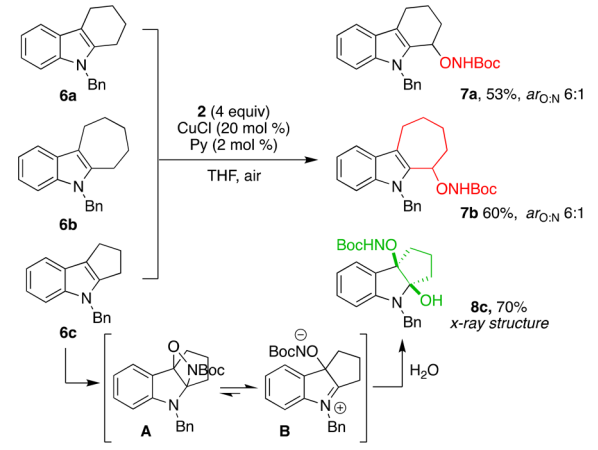
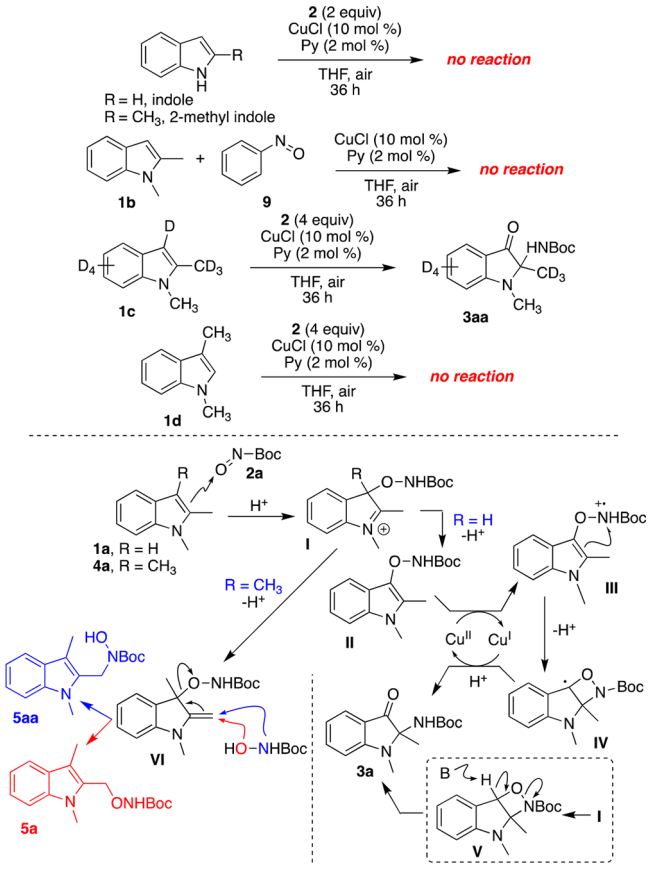


Figure 3. Oxygenation of cyclic indoles.

of the hydroxylamine is obligatory for oxidation, as no reaction was observed with CuCl and air. This agrees with the literature that strong heating or oxidative environment is required for similar transformations.[4a,f] Furthermore, at a minimum, both the indole nitrogen atom and C2 should be alkylated for the reaction to proceed. As depicted in Scheme 2, neither indole nor 2-methylindole led to oxidized products under conditions that led to the 3-oxindole product with **1b**, returning mostly the starting materials in both cases, save for traces of unidentified products. The nature of the hydroxylamine, which presumably is converted to the reactive nitroso

Scheme 2. Mechanistic Reactions for 3-Oxindole Formation along with CH Activation Pathway



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intermediate, was also critically important. Substitution of nitrosobenzene **9** instead of the *tert*-butyl hydroxycarbamate **2** did not yield any product but only resulted in slow decomposition of the nitrosobenzene. Interestingly, use of other hydroxylamines in lieu of **2** also did not lead to the desired product (see the SI). The use of *tert*-butyl nitrosoformate has been reported for the ene-type and Diels–Alder reactions.[8] The deuterated 1,2-dimethylindole **1c** was synthesized to examine the potential involvement of an ene process. Under the standard reaction conditions, no loss of the deuterium from the C2 methyl group was observed on the basis of ^{1}H NMR analysis, suggesting that an ene-type reaction of the *tert*-butyl nitrosoformate is likely not involved in this reaction. Furthermore, reaction of 1,3-dimethylindole **1d** under the same conditions also did not yield any product, returning the starting material intact. The 1,2-disubstitution pattern seems obligatory for the success of this reaction.

Based on the observations above, we propose a plausible mechanism for oxindole formation, as depicted in Scheme 2. Oxidation of *tert*-butyl hydroxycarbamate **2** to the corresponding nitroso **2a** in the presence of air and Cu(I) has been reported previously.[8a,9] Reaction of **1a** and **4a** with **2a** leads to the common intermediate **I**. Subsequent loss of a proton leads to either intermediate **II** or **VI**, the point at which the mechanism diverges. Intermediate **II** presumably can be oxidized to the radical cation **III** through the intermediacy of Cu(II). Intramolecular trap of the nitrogen-centered radical, concomitant with a proton loss, could lead to intermediate **IV**. Fragmentation of this intermediate along with one-electron reduction, mediated through Cu(I), yields the final product **3a**. Alternatively, intramolecular closure of **I** to the oxazetidine **V** (see dashed box), concomitant with deprotonation of C3, and cleavage of the NO bond to deliver **3a** cannot be excluded.[10] Returning to the point of divergence, nucleophilic attack of **VI** with hydroxylamine, either through the oxygen or nitrogen atom, leads to the oxygenated or aminated products **5a** or **5aa**, respectively. As discussed above, the ratio of oxygenated to aminated product is influenced with the amount of water added to the reaction. This is presumably as a result of the change in the acidity of NH and OH in the presence or absence of water, as has been discussed previously.[11]

In conclusion, we have developed a mild, tunable Cu(I)-catalyzed indole oxidation and a selective C–H functionalization method. This methodology features a new route to oxidize 1,2-dialkyl indoles to form oxindole frameworks. Furthermore, a new approach for the selective C–H functionalization of 1,2,3-trialkylindoles and cyclic indoles is disclosed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03185.

Experimental details and spectroscopic data (PDF)

Accession Codes

CCDC 1566683–1566686 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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