Indole Oxidation

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Oxaziridine-Mediated Oxyamination of Indoles: An Approach to 3-Aminoindoles and Enantiomerically Enriched 3-Aminopyrroloindolines**

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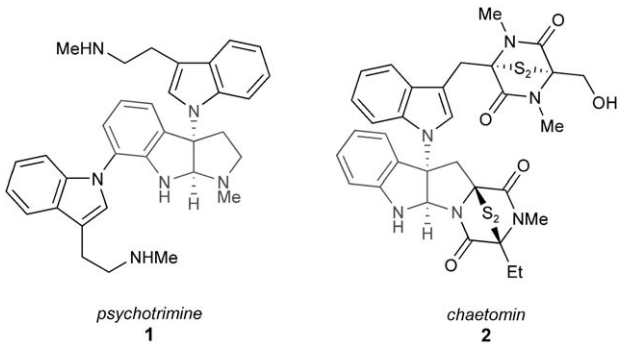
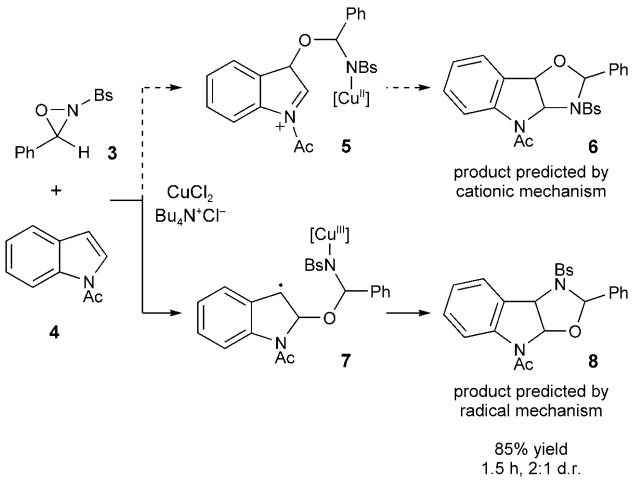
Pyrroloindoline natural products have attracted considerable interest because of both their biological activity and their unique structures.[1] Nature presumably produces these architecturally fascinating compounds through electrophilic cyclization cascades involving appropriately functionalized tryptamine and tryptophan precursors. In the laboratory, the use of chemical oxidants (e.g., *m*-chloroperbenzoic acid, dioxirane, *N*-bromosuccinimide) to trigger similar cascades has been a common strategy for the total synthesis of these target molecules.[2] Recently, several research groups have become interested in the synthesis of a subclass of pyrroloindoline alkaloids, such as psychotrimine (**1**)[3] and chaetomin (**2**; Scheme 1),[4] which feature a carbon–nitrogen bond at



Scheme 1. 3-Aminopyrroloindoline natural products.

the 3-position of the oxidized indole.[5] However, only a limited number of methods for the direct electrophilic introduction of a nitrogen atom at this position have been developed,[5b,d,g,6] and thus the synthesis of aminated indole alkaloids, especially in an enantioselective fashion, remains a formidable synthetic challenge.

For the past several years, we have been investigating the oxidative functionalization of alkenes with *N*-sulfonyloxaziridines[7] ("Davis oxaziridines", e.g., **3**) in the presence of copper(II) catalysts.[8] Much of our effort has been focused on elucidating the mechanism for the formation of the 1,3-oxazolidine products of this highly regioselective olefin oxyamination. We recently summarized our accumulated evidence, which suggests that the cationic mechanism we originally proposed is not operational, and that the reaction instead involves a radical intermediate.[9] As a further test of this conclusion, we elected to study the reactivity of indoles under the oxaziridine-mediated oxyamination conditions we have developed (Scheme 2). The regiochemistry of electrophilic addition to indoles is well-established. Preferential attack at the 3-position occurs as a result of the stability of the intermediate iminium cation (e.g., **5**). This analysis suggests that a cationic mechanism would result in the formation of regioisomer **6** with the oxygen atom attached to C3. Indeed, Dmitrienko and co-workers observed the formation of this regioisomer in the uncatalyzed reaction between oxaziridine **3** and electron-rich indoles and suggested a similar cationic intermediate to account for its formation.[10] On the other hand, the addition of radicals to indoles has also been the subject of extensive investigation, and the regiochemistry of these reactions prefers initial attack at C2 as a result of the



Scheme 2. Oxyamination of indoles as a regiochemical mechanistic probe. Bs = benzenesulfonyl.

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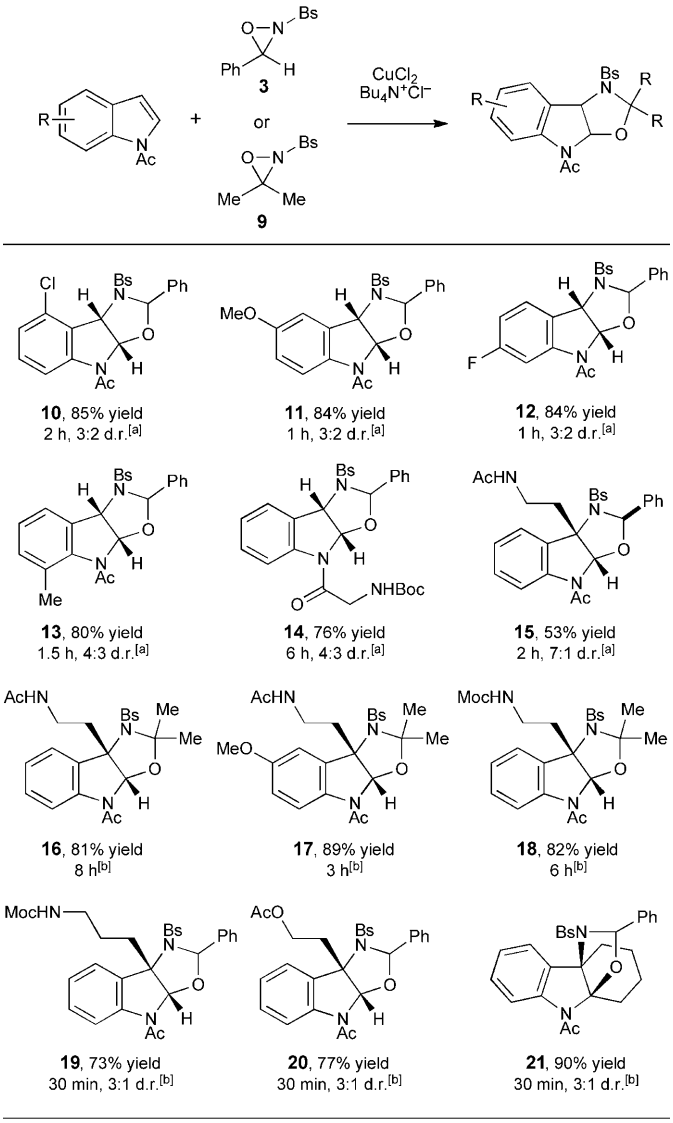
stability of the intermediate benzylic radical (e.g., **7**).[11] A radical mechanism for the copper-catalyzed oxyamination would therefore result in the formation of regioisomer **8**.

Our investigation began with an examination of the reaction between oxaziridine **3** and indoles in the presence of copper(II) catalysts. Under these strongly oxidizing conditions, we found that electron-rich *N*-alkyl indoles underwent rapid and exothermic decomposition to an intractable mixture of products. On the other hand, the reaction of *N*-acetylindole (**4**) proceeded smoothly within 1.5 h in 85% yield and with 2:1 diastereoselectivity. Importantly, both diastereomers of the oxyaminated product **8** corresponded to the benzylic amine regioisomer that would be predicted on the basis of a radical mechanism.[12] This outcome provides further evidence against the cationic mechanism we originally proposed.

Exclusive formation of the C3 aminated regioisomer was observed in the oxyamination of all indole substrates that we have examined to date. A range of structurally varied *N*-acyl indoles were suitable substrates for oxyamination, including substrates with electron-donating and electron-withdrawing substituents at various positions on the indole (products **10**–**13**) and more complex *N*-acyl groups (product **14**; Scheme 3). The reaction of tryptamines and other indoles substituted at C3 afforded the corresponding products in somewhat lower yields under these conditions (e.g., product **15**), which we speculate might be attributable to unproductive side oxidations of these more electron-rich substrates. After some optimization, we found that the yield could be improved by performing the reaction in acetone with a higher loading of the copper(II) catalyst and with the less reactive 3,3-dimethyloxaziridine **9** as the terminal oxidant (product **16**). This modification enabled the oxyamination of a variety of more electron-rich indoles with alkyl substituents on the indole olefin (products **17**–**21**). The functional group compatibility of this process is quite good: aryl halides, ethers, esters, amides, and carbamates are all tolerated well under both sets of reaction conditions.

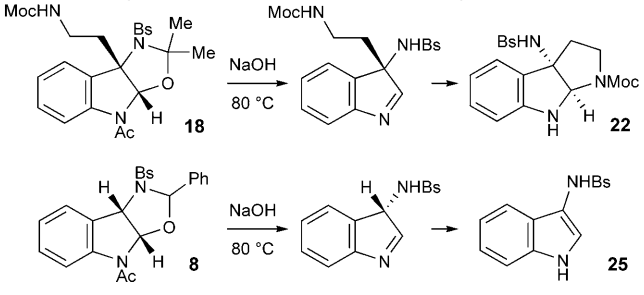
Although the initial impetus for this study was to provide additional evidence for a radical mechanism, we quickly recognized that the aminal products could serve as synthetically valuable precursors to a variety of heterocyclic systems found in bioactive compounds, including pyrroloindoline natural products such as **1** and **2**. Indeed, treatment of the tryptamine-derived aminal **18** with NaOH resulted in facile cleavage of the *N*-acetyl group with concomitant elimination of acetone; under the basic conditions of this hydrolysis, the *N*-Moc carbamate underwent spontaneous cyclization onto the imine intermediate to produce pyrroloindoline **22** in 85% yield (Table 1, entry 1). The cyclization of the homotryptamine-derived aminal **19** to α-carboline **23** also proceeded in good yield (Table 1, entry 2). This cyclization cascade can also be terminated with oxygen nucleophiles; the latent alcohol of *O*-acyl tryptophol derived aminal **20** was revealed under the basic reaction conditions, and furoindoline **24** was obtained in excellent yield (Table 1, entry 3). Substrates without an internal nucleophile were also subjected to these reaction conditions. The imine intermediate resulting from the hydrolysis of **8** undergoes rearomatization to afford 3-aminoindole **25** (Table 1, entry 4).[13] The rearomatization of substituted indolines was also successful (Table 1, entries 5 and 6).

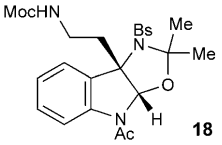
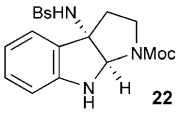
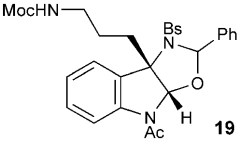
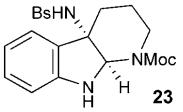
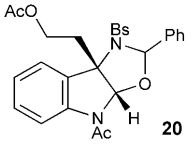
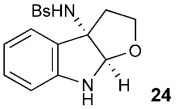
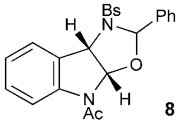
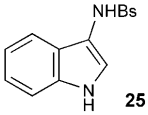
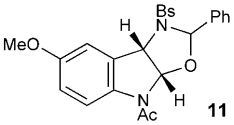
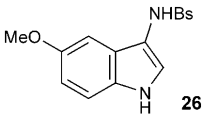
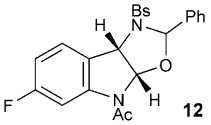
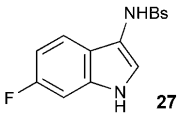


Scheme 3. Scope of the indole oxyamination. The average yield of the isolated product from two experiments is given in each case. [a] Reaction conditions: $CuCl_2$ (2 mol%), $Bu_4N^+Cl^-$ (2 mol%), oxaziridine (2 equiv), CH_2Cl_2, 23 °C. [b] Reaction conditions: $CuCl_2$ (10 mol%), $Bu_4N^+Cl^-$ (10 mol%), oxaziridine (2 equiv), acetone, 23 °C. Boc = *tert*-butoxycarbonyl, Moc = methoxycarbonyl.

The challenge of the enantioselective synthesis of pyrroloindolines has been addressed by several methods, including asymmetric Heck cyclizations,[14] organocatalytic cascade cyclizations of tryptamines,[15] and electrophilic cyclizations of enantiomerically pure tryptophan derivatives.[16] We wondered if an asymmetric version of this copper-catalyzed oxyamination might also serve as a platform for the enantioselective synthesis of pyrroloindolines with an amino substituent at C3, as exemplified by psychotrimine (**1**). Our strategy took advantage of two key observations. First, we found that a variety of acyl groups are tolerated on the indole nitrogen atom, including amino acid derivatives (e.g., in **14**).

Table 1: Base-promoted transformations of aminal products.[a]



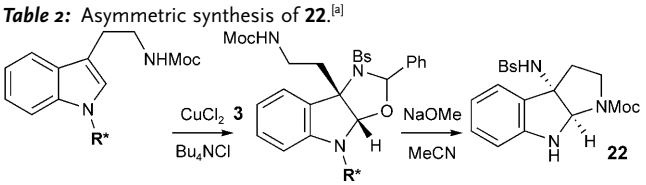
Entry	Aminal	Product	*t* [h]	Yield [%][b]
1			7	85
2			7	75
3			14	95
4			14	88
5			26	87
6			14	93

[a] Reaction conditions: 6 M NaOH, dioxane, 80 °C. [b] Average yield of the isolated product from two experiments.

Second, on the basis of our mechanistic hypothesis, the initial stereodetermining step of the oxyamination process should occur at the C2 position of the indole, proximal to the *N*-acyl moiety. We therefore wondered whether the use of a chiral amino acid auxiliary on the indole nitrogen atom could influence the stereochemical outcome of the initial C–O bond-forming step.

Thus, we prepared a variety of tryptamines modified at N1 with *N*-Boc-protected aminoacyl groups, which could be installed in one step in excellent yield (see the Supporting Information for details), and examined these substrates in a two-step oxyamination–cyclization sequence (Table 2).[17] Surprisingly, we found that the enantiomeric purity of the pyrroloindoline product increased as the steric demand of the amino acid auxiliary decreased (Table 2, entries 1–5). Of the auxiliaries screened, *N*-Boc-protected proline provided the highest enantioselectivity and afforded **22** with 73% *ee* (Table 2, entry 6). The identity of the protecting group on the nitrogen atom of the prolyl moiety proved to be critical;

Table 2: Asymmetric synthesis of **22**.[a]

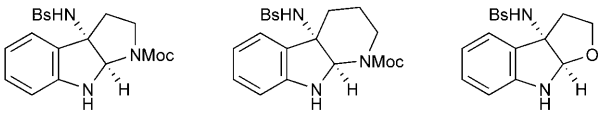


Entry	R*[b]	Solvent	*T* [°C]	*t* [h]	*ee* [%][c]
1	L-Boc-*t*Leu	acetone	23	6	<5
2	L-Boc-Phg	acetone	23	6	<5
3	L-Boc-Val	acetone	23	6	20
4	L-Boc-Phe	acetone	23	6	36
5	L-Boc-Ala	acetone	23	6	57
6	L-Boc-Pro	acetone	23	1	73
7	L-Cbz-Pro	acetone	23	2	48
8	L-Boc-Pro	$CHCl_3$	23	2	86
9	**L-Boc-Pro**	**$CHCl_3$**	**−30**	**24**	**91**

[a] Oxyamination conditions: $CuCl_2$ (10 mol%), $Bu_4N^+Cl^-$ (10 mol%), **3** (2 equiv); cyclization conditions: NaOMe, MeCN, 23 °C. [b] *t*Leu = *tert*-leucine, Phg = phenylglycine. [c] The *ee* value was determined by supercritical fluid chromatography on a chiral phase. Cbz = carbobenzyloxy.

smaller carbamates, such as Cbz, provided significantly lower enantioselectivities (Table 2, entry 7). When the reaction was performed in chloroform, a marked increase in enantioselectivity was observed (Table 2, entry 8). Finally, the enantioselectivity of the process could be further improved to 91% *ee* by conducting the reaction at −30 °C, although a longer reaction time was required (Table 2, entry 9). In an initial exploration of the generality of this two-step sequence, we found that a variety of enantiomerically enriched indole derivatives could be prepared with 86–91% *ee* (Scheme 4).[18]

The ground-state conformation of the *N*-prolylindole **28**, as predicted by molecular mechanics energy minimization (Figure 1), suggests a possible rationale for the absolute sense of stereoinduction in this process. This model is consistent with the known propensity of *N*-acyl indoles to strongly prefer a *Z* conformation about the N–acyl bond.[19] Furthermore, the prolyl moiety adopts a conformation that minimizes the pseudo-A(1,3) strain between its α stereogenic center and the 2-position of the indole. The bulky *N*-Boc group is thus placed in an orientation that shields the *Re* face of the indole and



Scheme 4. Enantiomerically enriched oxidized-indole derivatives (see the Supporting Information for experimental details).

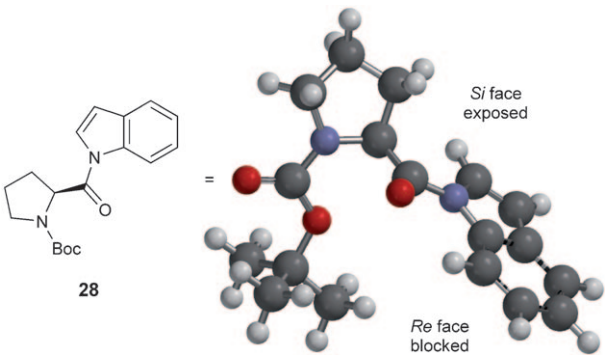


Figure 1. Ground-state conformation of **28** predicted by computational minimization (Sybyl force field, Spartan).

leaves the *Si* face open to attack by the oxaziridine. This model is consistent with the absolute sense of stereoinduction observed in this transformation. It is also consistent with the observations that the enantioselectivity increases with decreasing steric bulk of the aminoacyl side chain (Table 2, entries 1–6) and that smaller protecting groups on the prolyl nitrogen atom are less effective at differentiating the prochiral faces of the indole (Table 2, entry 7).

In summary, we have demonstrated that the copper(II)-catalyzed oxyamination of indoles affords aminals in high yields and with excellent regioselectivity. The regiochemical outcome of this process is consistent with a radical intermediate and thus further corroborates our recently revised mechanistic model. The aminal products can be transformed readily into 3-aminoindoles, α-carbolines, pyrroloindolines, and other synthetically valuable heterocyclic structures. Finally, we used our understanding of this process to design a chiral-auxiliary-controlled asymmetric oxyamination of tryptamines. This transformation enables the enantioselective construction of 3-aminopyrroloindolines, which may be useful in the synthesis of oxidized-indole natural products. In future studies we will apply this method to the total synthesis of psychotrimine.

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[12] The regiochemistry of both diastereomers was determined unambiguously by single-crystal X-ray diffraction. CCDC 785147, 785148 (for each diastereomer of **8**), and 785149 (**24**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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