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Bioinspired Direct Access to Benzofuroindolines by Oxidative [3 + 2] Annulation of Phenols and Indoles

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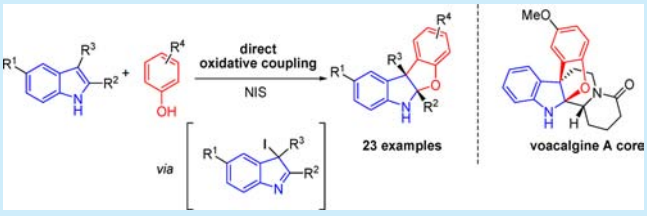
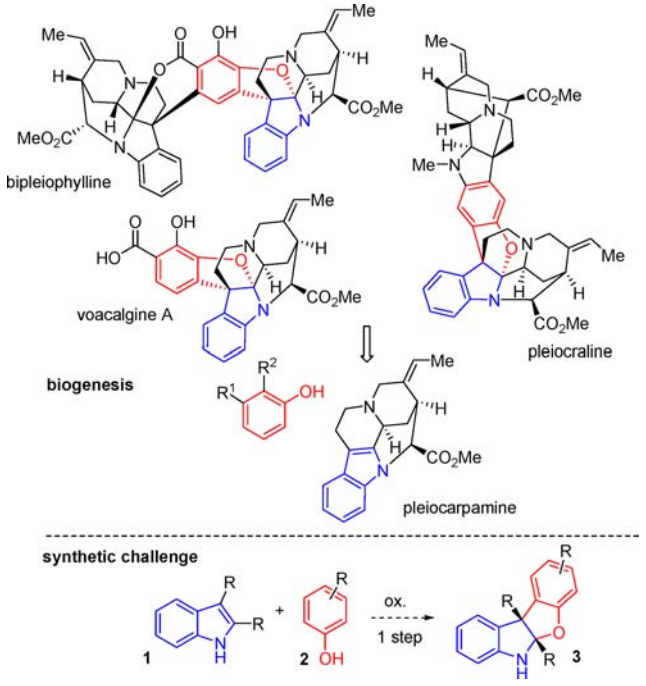
Supporting Information

ABSTRACT: The straightforward entry to benzofuroindoline containing natural product-like scaffolds has been achieved by a challenging [3 + 2] oxidative coupling between phenols and indoles. The reaction proceeds by NIS-oxidation of the indole followed by the trapping of the resulting electrophilic intermediate by phenol.



Bipleiophylline,[1] voacalgine A,[2] and pleiocraline[3] are natural products containing a benzofuro[2,3-*b*]indoline[4] substructure thought to be biogenetically produced by the oxidative coupling of the indole alkaloid pleiocarpamine and a phenol unit (Scheme 1).[1−3] Synthetically mimicking this transformation is known to be a particularly difficult endeavor because it involves the union of two nucleophilic entities.[5] We therefore set our goal to achieve a direct [3 + 2] annulation[6] between indoles and phenols, the biogenetic precursors of the benzofuroindoline natural products.

Scheme 1. Benzofuroindoline Containing Natural Products Derived from Pleiocarpamine



Pioneered by Harran et al., few direct syntheses of benzofuro[2,3-*b*]indolines via the oxidative coupling of indoles and phenols mediated by hypervalent-iodine(III) reagents or electrochemistry have been described.[7] This strategy is conceptually very attractive and elegant despite modest yields and its substrate specificity.[8] We have been recently interested in the union of indoles and phenols in order to construct the benzofuroindoline skeleton. In 2012, we reported a two-phase approach: the C3-regioselective addition of phenols to electrophilic N−Ac indoles activated by $FeCl_3$, followed by an oxidation which delivers the desired benzofuro[2,3-*b*]indolines.[9] More recently, we have uncovered the radical coupling of phenols with N−Ac indoles in the presence of DDQ and $FeCl_3$ leading to regioisomeric benzofuro[3,2-*b*]indolines.[10]

However, we found that none of these methods were suitable to access structures of the bipleiophylline/voacalgine A series. Therefore, to overcome these limitations, the design of an alternative strategy was required. In contrast to the mentioned methods, we planned to preoxidize the indole nucleus in order to generate an electrophilic species at C3 before realizing the coupling with a phenol.[11]

To meet this criterion, we turned our attention to 3-halogenoindolines **4** which have been described to be involved in reactions with nucleophiles,[7b,12−14] including arenes.[12a,b,13a−d] However, the C-addition of phenols to halogenoindoline derivatives is unreported. Two pathways may be envisioned for this coupling: the O-addition of the phenol **2** to the imine of **4** followed by an intramolecular nucleophilic substitution at C3 in **5** or the generation of a carbocation **6** in alpha to the imine which would react with the phenol to form a

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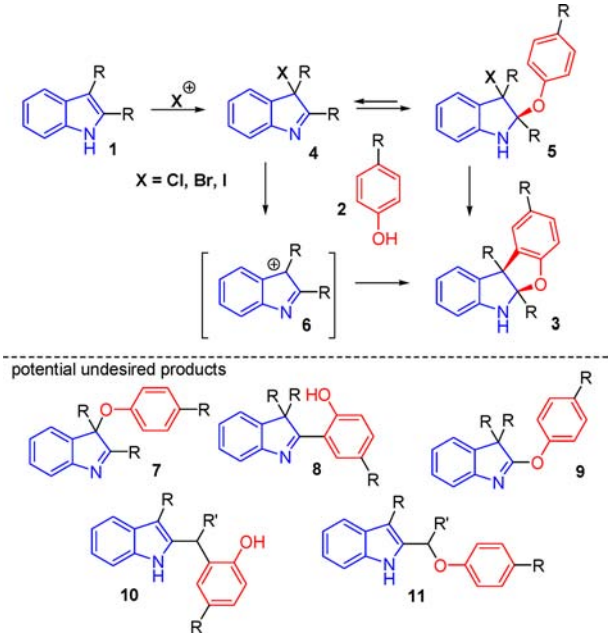
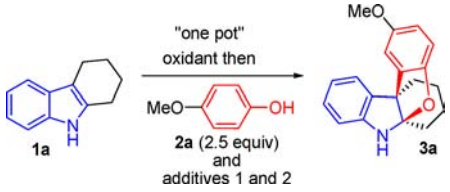
C−C bond (Scheme 2). The literature warned us against competition pathways from halogenoindolines **4** which would result in the formation of undesired products.[12c−h] O-Alkylation of phenol at C3 of the indoline could occur and lead to compound **7** which may rearrange into the undesired compound **8** through migration of the C2-substituent to the C3 position. Migration of the C2-substituent to the C3 position from **5** may also be expected and deliver **9**. Additions of arenes or alcohols on the C2-substituents of the halogenoindoline are also documented; therefore, isolation of indole **10** or **11** could be expected.

Scheme 2. Our Strategy via Preoxidation of Indoles



The investigation started by coupling tetrahydrocarbazole **1a** with 4-methoxyphenol **2a** (Table 1), although we had in mind that side reactions could be operative. Mixing the two partners with *N*-chloro- or *N*-bromosuccinimide (NCS and NBS) did not lead to any of the desired benzofuroindoline (entries 1, 2). Eventually, the reaction with *N*-iodosuccinimide (NIS) allowed us to isolate the expected annulated compound **3a** whether indole **1a**, phenol **2a**, and NIS were added at the same time (26%, entry 3) or the indole was first mixed with NIS to form the iodoindoline **4** before phenol was added (28%, entry 4). We reasoned that the addition of soluble silver salts to the preformed iodoindoline **4** will allow the formation of a carbocation such as **6**, which would be more reactive toward phenol **2a** and hopefully increase the yield of **3a**.[12a,b,13a−d] However, the addition of silver tetrafluoroborate disappointingly yielded only 33% of **3a** (entry 5). All the iodoindoline was consumed, but traces of **7**, which arose from the O-alkylation pathway, were observed as well as other unknown byproducts. In order to favor the C-alkylation, Lewis acids were screened with the idea to form a complex between the hydroxyl of the phenol and the Lewis acid. We observed that scandium triflate (entry 6) and tin chloride (entry 7) were efficient to deliver satisfactory yields (44% and 53%) of benzofuroindoline **3a**. The addition of sodium hydroxide in lieu of the Lewis acid was of similar efficiency (52%, entry 9). In the absence of the silver salt an important decrease in yield was noted with tin chloride alone or sodium hydroxide alone (entries 8, 10). In both cases, tetrahydrocarbazole **1a** was recovered, and in the former case, O-alkylation products were detected.

Table 1. Investigation of the Oxidative Coupling of Tetrahydrocarbazole 1a and 4-Methoxyphenol 2a

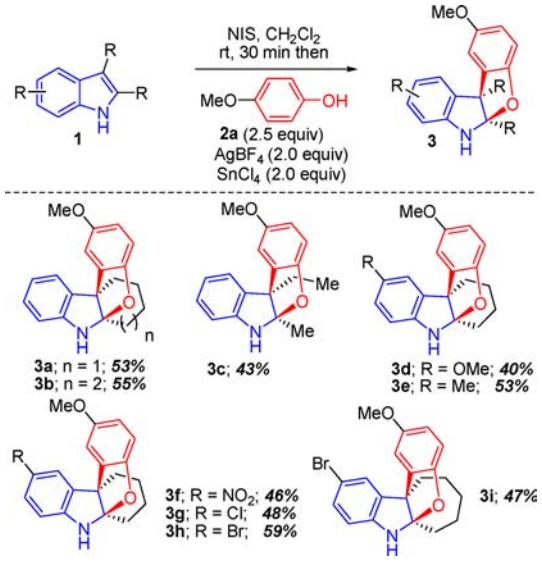


entry	oxidant	additive 1 (equiv)	additive 2 (equiv)	yield[a]
1	NCS	–	–	0%[b]
2	NBS	–	–	0%[b]
3	NIS	–	–	26%[b]
4	NIS	–	–	28%
5	NIS	$AgBF_4$ (2.0)	–	33%
6	NIS	$AgBF_4$ (2.0)	$Sc(OTf)_3$ (2.0)	43%
7	**NIS**	**$AgBF_4$ (2.0)**	**$SnCl_4$ (2.0)**	**53%**
8	NIS	–	$SnCl_4$ (2.0)	<5%
9	**NIS**	**$AgBF_4$ (2.0)**	**NaOH (5.0)**	**52%**
10	NIS	–	NaOH (5.0)	15%

[a]Isolated yields. [b]The oxidant and the phenol were added at the same time.

After the discovery of suitable conditions for the challenging direct oxidative merging of tetrahydrocarbazole **1a** and 4-methoxyphenol **2a**, we desired to explore in more detail the scope of this reaction. Keeping 4-methoxyphenol **2a** as a test nucleophile, we engaged several 2,3-disubstituted indoles in the NIS/$AgBF_4$/$SnCl_4$ conditions (Scheme 3). Changing the substitution of the 2 and 3 positions of the indole from tetrahydrocarbazole to cycloheptaindole resulted in benzofuroindoline **3b** in 55% yield; 2-methyl-3-ethylindole led to benzofuroindoline **3c** in 43% yield. The electronic effects on the benzene part of the indole nucleus were then evaluated. Pleasantly, electron-donating groups (OMe, **3d**, 40%; Me, **3e**,

Scheme 3. Oxidative Coupling between Phenols and Indoles; Scope of Indoles



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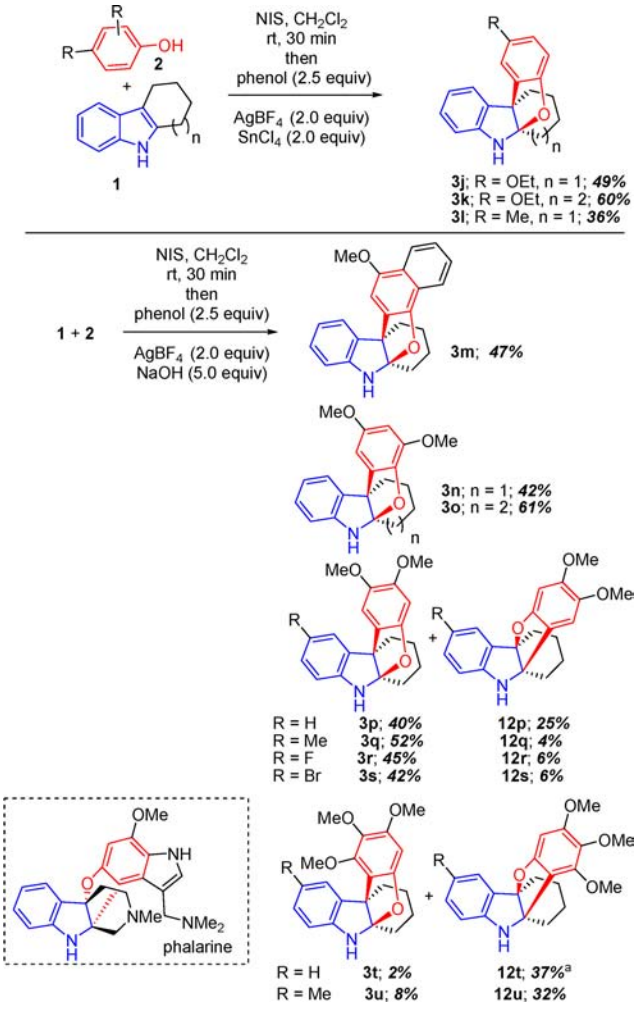
53%;), an electron-withdrawing group (NO_2, **3f**, 46%;), and halides (Cl, **3g**, 48%; Br, **3h**, 59%; **3i**, 47%) afforded the expected benzofuroindolines in appreciable yields given the complexity of the transformation.

We next investigated phenols susceptible to participating in the [3 + 2] annulation (Scheme 4). Indeed, 4-ethoxyphenol

Scheme 4. Oxidative Coupling between Phenols and Indoles; Scope of Phenols[a]



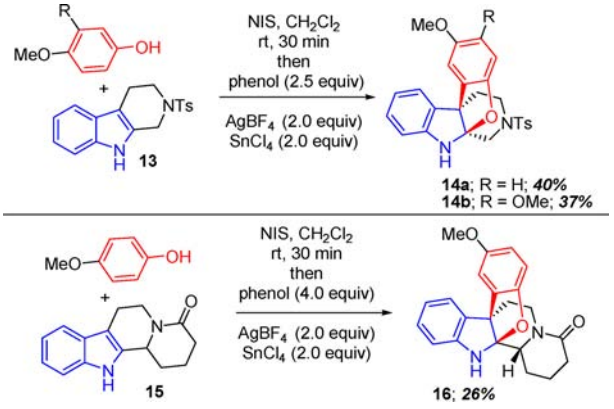
[a]K_2CO_3 was used instead of NaOH.

delivered the desired benzofuroindolines **3j** (49%) and **3k** (60%) from tetrahydrocarbazole and cycloheptaindole. Less electron-rich phenols were less reactive; however, 4-methylphenol allowed the synthesis of **3l** in 36% yield. Methoxynaphtol was also a suitable partner in the presence of NaOH, and **3m** was obtained (47%).

We then turned our attention to more electron-rich dimethoxy or trimethoxy phenols and found that basic conditions were more efficient than $SnCl_4$ to promote the reaction. We isolated benzofuroindolines **3n** and **3o** from 2,4-dimethoxyphenol in 42% and 61% yields, respectively. With 3,4-dimethoxyphenol, a different trend appeared: along with the expected benzofuro[2,3-*b*]indolines **3p** (R = H, 40%), **3q** (R = Me, 52%), **3r** (R = F, 45%), and **3s** (R = Br, 42%) as the major products, we observed the formation of the regioisomeric benzofuro[3,2-*b*]indolines **12p** (R = H, 25%), **12q** (R = Me, 4%), **12r** (R = F, 6%), **12s** (R = Br, 6%).[15] Increasing the electron density with 3,4,5-trimethoxyphenol resulted in the major formation of regioisomeric benzofuro[3,2-*b*]indolines **12t** (R = H, 37%) and **12u** (R = Me, 32%)[16] over the benzofuro[2,3-*b*]indolines **3t** (R = H, 2%) and **3u** (R = Me, 8%). In this unexpected case, the O-alkylation of the phenol by the indolenium ion **6** is probably predominant over the C-alkylation, and then intramolecular C−C bond formation between the C2 position of the indole and *ortho* position of the phenol should occur and deliver benzofuro[3,2-*b*]indolines **12**. The structure of the natural product phalarine very interestingly displays the benzofuro[3,2-*b*]indoline skeleton.[17]

Our oxidative coupling was then tested with tetrahydrocarboline **13**. The reaction with 4-methoxyphenol and 3,4-dimethoxyphenol afforded benzofuroindolines **14a** and **14b** (Scheme 5). Encouraged by this result, we increased the level of

Scheme 5. Oxidative Coupling from Tetrahydrocarboline Derivatives; Synthetic Approach to Voacalgine A



structural complexity and performed the reaction on the more challenging tetracycle **15**, which was synthesized in three steps. The hexacyclic core **16** of voacalgine A/bipleiophylline was thus obtained diastereoselectively in a very concise manner.[16]

In conclusion, we developed a method for direct access to the benzofuro[2,3-*b*]indoline scaffold, which is found in several natural products. The [3 + 2] oxidative coupling between nucleophilic phenols and indoles which we designed was inspired by the biogenesis of the benzofuroindoline containing natural products. This transformation from unprotected indoles and phenols is known to be a particularly difficult task. The preoxidation of the indole nucleus by NIS to form an electrophilic intermediate captured by phenol is the key to the success of this procedure. Our method is conceptually the reverse of the hypervalent iodine mediated coupling of indoles and phenols developed by Harran in which the phenol is oxidized before the coupling with the nucleophilic indole.[7] Our method features the bimolecular formation of a C−C bond which is a great added value. We believe that the scope of the reaction and the yields obtained complement the known hypervalent-iodine mediated reaction favorably.[7] Very interestingly, particularly electron-rich 3,4,5-trimethoxyphenol led to regioisomeric benzofuro[3,2-*b*]indolines, the scaffold of which is found in the natural product phalarine. Finally, we have achieved the straightforward synthesis (4 steps) of the hexacyclic skeleton of voacalgine A.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterizations, and ^{1}H and ^{13}C NMR spectra copies for all benzofuroindolines as well as X-ray crystallographic data for compounds **12u** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) CCDC 1015645 (**12u**) and 1015646 (**16**) 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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