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Synthesis of 3,3-Spiroindolines via $FeCl_3$-Mediated Cyclization of Aryl- or Alkene-Containing 3-Substituted N–Ac Indoles

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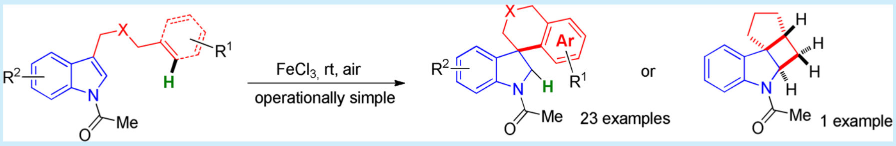
Supporting Information



ABSTRACT: We report the cyclization of 3-substituted *N*-acetylindoles for the straightforward synthesis of 3,3-spiroindolines via the Friedel–Crafts reaction of an appended aryl group or the formal [2 + 2] cycloaddition of an appended alkene. Our strategy involves an Umpolung of the C2═C3 bond of the indole nucleus during $FeCl_3$-mediated hydroarylation or annulation reactions.

The 3,3-spiroindoline motif is found in several biologically active natural products[1] such as spiroindimicin B or vindoline, and it is a privileged scaffold for the design of medicinally relevant compounds (Figure 1).[2] For example, NITD609 is an antimalaria agent,[2a] XEN907 is a promising compound for the treatment of pain,[2b] and SYN351 is an insecticidal[2c] (Figure 1).

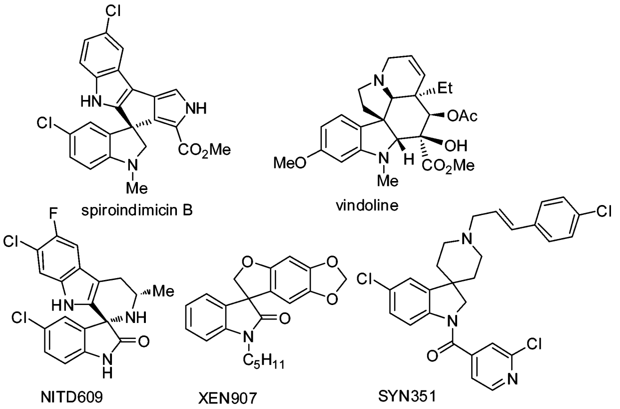
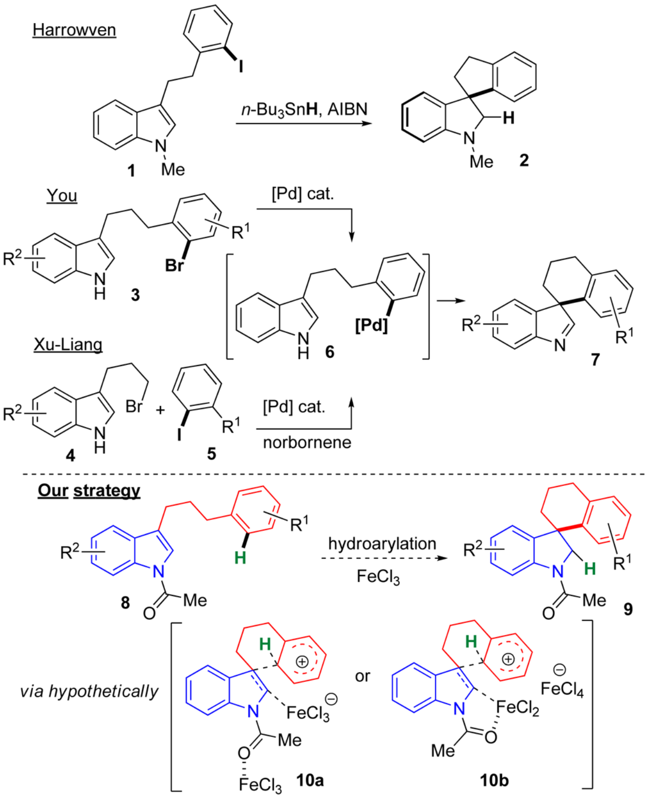


Figure 1. 3,3-Spiroindolines of interest.

Various methods to access 3,3-spiroindolines have been reported[3] including dearomative cyclization of indoles.[4−8] However, the access to 3-aryl-containing spiroindolines is less encountered.[9,2b] In particular spirocyclization by 3-arylative dearomatization of indole is uncommon (Scheme 1).[10] Harrowven reported one example of a radical spirocylization of a 2-iodoaryl-containing 3-substitued indole **1** mediated by tin hydride to give spiroindoline **2**.[11]

The group of You[12] and the group of Xu and Liang[13] reported a palladium catalyzed cyclization process from bromo or iodoarenes **3**–**5** involving the intramolecular nucleophilic attack of the C3 position of indole into an aryl palladium complex **6**, which led to 3,3-spiroindolenines **7**.

Scheme 1. Strategies for the Spiroarylation of Indoles



Given our interest in arylative functionalization of indoles,[14] we propose a mechanistically distinct approach to the synthesis of arylated 3,3-spiroindolines.

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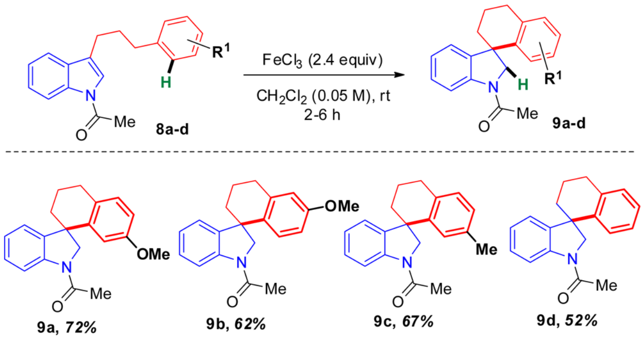
To access the spiroindoline framework **9** from substrates **8** (Scheme 1), we intend to deploy the $FeCl_3$-mediated hydroarylation reaction of the C3═C2 bond of N−Ac indoles that we developed and reported recently in the intermolecular mode.[14a,b,15] We believe that this reaction proceeds via both the activation of the acetyl and the C2═C3 bond of indole in intermediates **10a** or **10b**, which would be electrophilic to trigger a Friedel−Crafts type reaction and would indeed result in the transformation of a C−H bond into a C−C bond.[16]

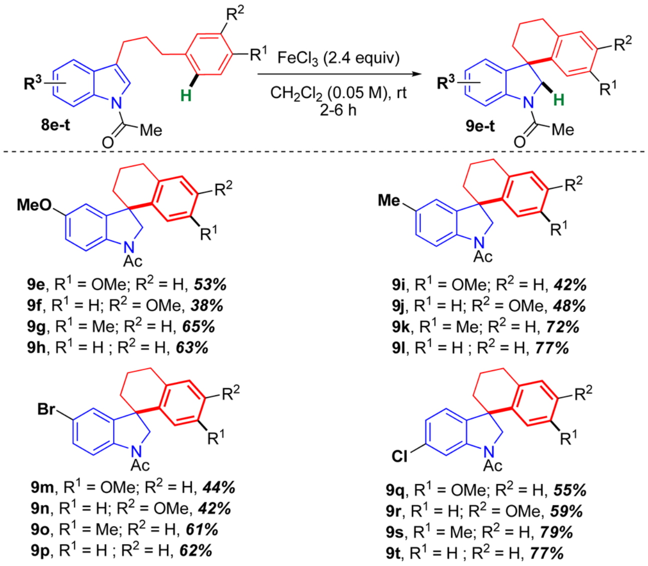
The hydroarylation cyclization proved to best proceed with 2.4 equiv of anhydrous $FeCl_3$ in dichloromethane in dilute conditions (0.05 M) at room temperature in air. The generality of the reaction was evaluated, and we found that *para*- and *meta*-methoxyphenyl as well as *para*-tolyl or phenyl substituents on the C3-chain of the indole led efficiently to the desired spiroindolines **9a−d** (Scheme 2).

Scheme 2. Spirocyclization via Hydroarylation of N−Ac Indoles: Substitution of the Aryl Group



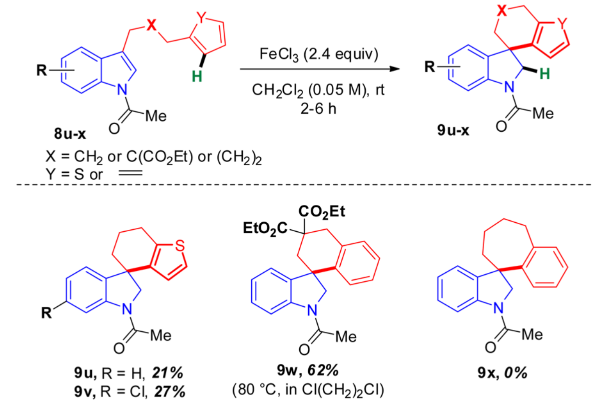
We then studied the substitution of the benzene part of the indole (Scheme 3). We noticed that electrondonating methoxy and methyl groups were well tolerated at the C5-position and led to the respective formation of spiroindolines **9e−h** and **9i−l**. Halogens were also tolerated since the 5-bromo-3,3-spiroindolines **9m−p** and the 6-chloro-3,3-spiroindolines **9q−t** were obtained.

Scheme 3. Spirocyclization via Hydroarylation of N−Ac Indoles: Substitution of the Indole Nucleus



We then found that it is also possible to use a heterocyclic substituent such as a thienyl to obtain heteroarylspiroindolines **9u,v** in moderate yields (Scheme 4).

Scheme 4. Spirocyclization via Hydroarylation of N−Ac Indoles: Use of a Heteroaryl and Substitution of the Tether



Finally, we also introduced a *gem*-diester on the tether between the indole and the phenyl parts (Scheme 4). We observed that the conversion was incomplete at room temperature probably due to sequestration of iron chloride by the ester groups. However, performing the reaction at 80 °C in 1,2-dichloroethane resulted in complete conversion of the starting indole and isolation of the spiroindoline **9w** in 62% yield. Unfortunately, no conversion of **8x**, the precursor of the 7-membered ring **9x**, was observed.[17]

X-ray crystallography of crystals of spiroindolines **9a**, **9d**, and **9u** allowed us to unambiguously assign their structures (Figure 2).[18]

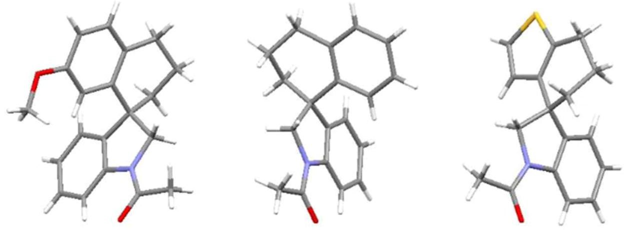
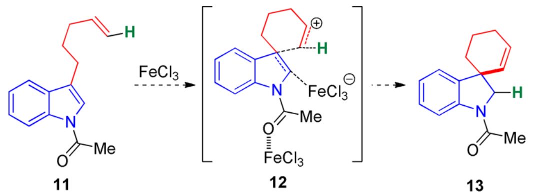


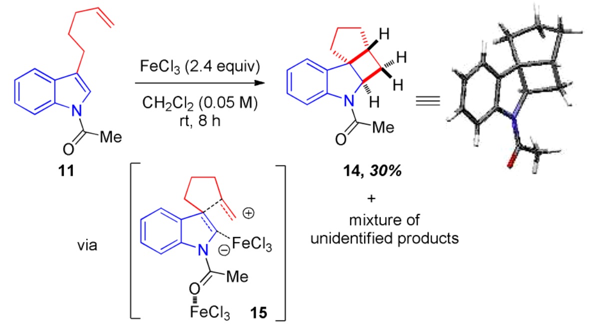
Figure 2. X-ray structures of spiroindolines **9a**, **9d**, and **9u**.

We next wished to evaluate other π nucleophiles to access the spiroindoline framework. Therefore, we replaced the aryl group on the C3-side chain by a terminal alkene. We believed that activation of the C2═C3 bond of indole **11** by $FeCl_3$ would trigger the addition of the alkene at C3 via intermediate **12** to form a 3,3-spirocyclic compound **13** bearing an *endo*-cyclic double bond (Scheme 5).[9a]

Scheme 5. Planned 3-Spirocyclization of an N−Ac Indole by Intramolecular Addition of a Terminal Alkene



Scheme 6. Spirocyclization via a Formal [2 + 2] Cycloaddition



However, when we performed the reaction of **11** with FeCl$_3$, we obtained a different 3,3-spirocyclic indoline **14** (Scheme 6). The terminal alkene and the C2═C3 bond of indole have been involved in a dearomative [2 + 2] annulation, which led to the formation of a cyclobuta[*b*]indoline framework fused with a cyclopentane, as determined by X-ray analysis.[18] Few dearomative [2 + 2] cycloaddition between indoles and alkenes are known, which are photoinduced, in contrast with our reaction.[7d,e,19−21] We can postulate that upon activation of the C2═C3 bond of the indole, the alkene adds onto the electrophilic C3 position of the indole by its more substituted carbon. It is also possible that FeCl$_3$ only activates the carbonyl group to promote a [2 + 2] cycloaddition.[22]

This result proves that the activation of *N*-acyl indole by FeCl$_3$ is not limited to induce C3-regioselective hydroarylation. Other dearomative reactions of indole could be promoted by this mode of activation such as a formal [2 + 2] cycloaddition.

In conclusion, we report a straightforward access to spiroindoline derivatives via the intramolecular hydroarylation of N−Ac indoles mediated by FeCl$_3$. This Friedel−Crafts reaction of the appended aryl leads to the concomitant C3-regioselective formation of a quaternary carbon center and dearomatization of the indole nucleus. This reaction is operationally simple and proceeds at room temperature in air with a cheap and nontoxic promoter. Moreover, in the presence of a terminal alkene on the C3-side chain of the indole, iron trichloride mediates a rare nonphotoinduced dearomative [2 + 2] annulation, which led to a constrained cyclopenta[2,3]cyclobuta[1,2-*b*]indoline holding also a spirocyclic structure.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00174.

Additional experiment, experimental procedures, characterizations, and ^{1}H and ^{13}C NMR spectra copies of all new compounds (PDF)
Compound **9a**(CIF)
Compound **9d**(CIF)
Compound **9u**(CIF)
Compound **14**(CIF)

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Notes

The authors declare no competing financial interest.

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(18) CCDC 1446909−1446912 (**9a**, **9d**, **9u**, and **14**) 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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(22) When we replaced the terminal monosubstituted alkene by a trisubstituted alkene, we did not obtain the desired cyclobutane but a tetrahydrocarbazole, see the Supporting Information.

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