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Preparation and Reactions of Indoleninyl Halides: Scaffolds for the Synthesis of Spirocyclic Indole Derivatives

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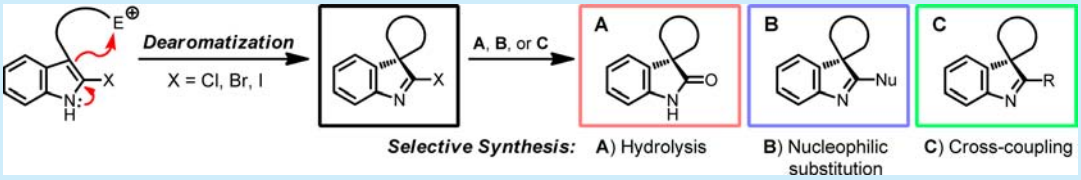
Supporting Information



ABSTRACT: The dearomatization of 2-haloindole precursors allows access to indoleninyl halides, a hitherto underexploited functional handle with broad synthetic utility. Indoleninyl iodides have been shown to react via three distinct modes: hydrolysis, nucleophilic substitution, and cross-coupling. This allows a broad array of functionalized spirocyclic indole derivatives to be generated from a common starting material. They are also useful precursors to functionalized quinolines following migratory rearrangement and subsequent derivatization reactions.

Structural motifs that pair high stability with versatile reactivity are of great value in organic synthesis. Moreover, such motifs are particularly useful if they are easy to prepare and can be incorporated into biologically significant frameworks, rendering them important in pharmaceutical and agrochemical research programs. Herein we detail the synthesis and subsequent reactions of indoleninyl halides **2**, a vastly underexploited functional handle for the synthesis of a broad array of spirocyclic indole derivatives. Simple dearomative methods[1] for their generation (**1** → **2**) and a series of procedures for their subsequent reaction (via three distinct reaction modes, **1** → **3**, **4**, or **5**) are outlined (Figure 1). In view of their ease of formation, high stability, and diverse reactivity, indoleninyl halides are expected to be of broad utility in synthesis.

Indoleninyl halides are surprisingly rare in the chemical literature, with very little reported about their stability and reactivity.[2] Initially, we postulated that indoleninyl halides **2** would behave similarly to acid chlorides and react readily with nucleophiles. This notion is supported by literature precedent;

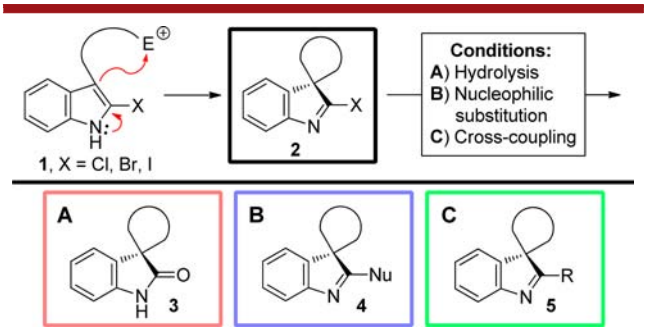
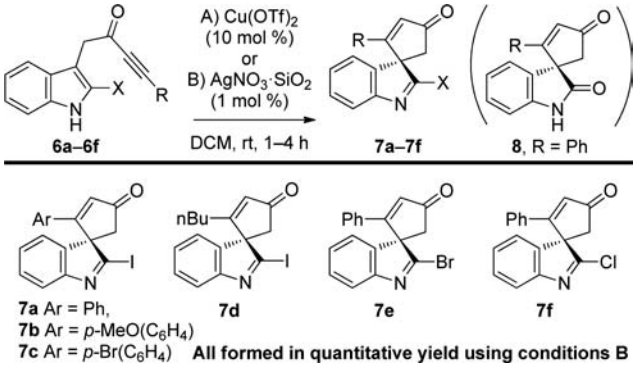


Figure 1. Preparation and reactions of indoleninyl halides.

indoleninyl chlorides and bromides have each been proposed as short-lived[3] or putative intermediates[4] in previous synthetic protocols and were found to hydrolyze readily in situ, generating oxindoles.[5] It was this precedent that prompted us to initiate the research program described herein, in which it was planned to react readily available 2-haloindole precursors of the form **6** with π-acidic catalysts in the expectation of promoting dearomatizing spirocyclization[6,7] and in situ hydrolysis to generate spirocyclic oxindoles (e.g., **6** → **7** → **8**; Scheme 1). However, when ynone **6a** (R = Ph) was reacted with 10 mol % $Cu(OTf)_2$ in DCM at rt, the only product isolated after workup and column chromatography was spirocyclic indolenine **7a** in quantitative yield. None of the expected oxindole **8** was isolated, and spirocycle **7a** proved to be surprisingly stable; it appears to be insensitive to air and

Scheme 1. Indoleninyl Halide Substrate Synthesis



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moisture and can be stored in a freezer for several months with no evidence of decomposition.

While this Cu(II)-mediated spirocyclization worked well, a brief examination of other catalysts revealed that $AgNO_3$·SiO_2 was an even more convenient catalyst system for this transformation, enabling spirocycle **7a** to be isolated in quantitative yield at just 1 mol % catalyst loading.[8] Indoleninyl iodides **7b**–**d**, as well as indoleninyl bromide **7e** and chloride **7f**, were also prepared in quantitative yield using the same procedure and were found to have comparable stability.

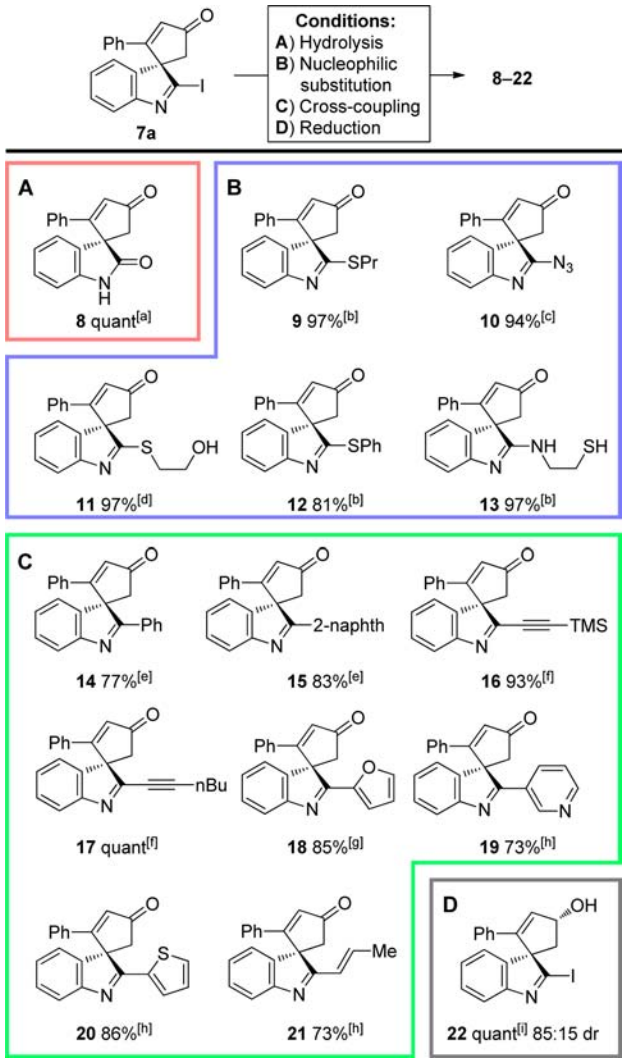
With a simple method to generate spirocyclic indoleninyl halides established, it was next decided to examine their reactivity. Indoleninyl iodide **7a**, an easy-to-handle solid product that could be readily prepared on a gram scale, was chosen as the main test substrate. Its reactivity with a range of nucleophilic reagents was investigated, with three distinct reaction modes [hydrolysis (**8**), nucleophilic substitution (**9**–**13**), and transition-metal-catalyzed cross-coupling (**14**–**21**)] all being demonstrated. These results are summarized in Scheme 2.

To begin, indoleninyl iodide **7a** was hydrolyzed using aqueous HCl in THF, affording spirocyclic oxindole **8** in quantitative yield (Scheme 2A). Next, a selection of nucleophilic substitution reactions were performed with sulfur and nitrogen nucleophiles, leading to the formation of indolenine derivatives **9**–**13** in high yields (Scheme 2B). With spirocycle **7a** acting as a vinyl halide surrogate, cross-coupling reactions were performed (Scheme 2C). Suzuki reactions using arylboronic acids afforded phenyl and 2-naphthyl derivatives **14** and **15** in good yields. Likewise, Sonogashira cross-couplings yielded alkyne derivatives **16** and **17**, and Stille coupling reactions allowed furan (**18**), pyridine (**19**), thiophene (**20**), and olefin groups (**21**) to be added at the indolenine 2-position, all in good yields. Finally, alcohol derivative **22** was prepared in quantitative yield with 85:15 dr following a chemo- and diastereoselective Luche reduction of the enone moiety of **7a**, leaving the indoleninyl halide moiety intact (Scheme 2D). In terms of the reduction step, hydride attack presumably occurs predominantly via the most accessible face of the molecule, i.e., anti to the indole unit.

Having successfully demonstrated the synthesis and utility of indoleninyl halides derived from ynone precursors, it was then decided to examine whether the same functional handle could be installed and used in a much broader range of indole systems. This was done by applying established indole dearomatization procedures to previously untested 2-halogenated starting materials, beginning with an enantioselective iridium-catalyzed allylic dearomatization procedure[10a] developed by You and co-workers.[10] Thus, 2-iodoindole precursor **23** was prepared and reacted with bis(1,5-cyclooctadiene)-diiridium(I) dichloride and commercially available chiral phosphoramidite ligand **27**.[10a] Pleasingly, indoleninyl iodide **24** was produced in near-quantitative yield with >9:1 dr and 86:14 er based on NMR and chiral HPLC data respectively, with its absolute stereochemistry assigned on the basis of comparison to literature precedent.[10a] Its subsequent derivatization was also achieved successfully, with both cross-coupling and nucleophilic substitution reactions being performed to produce spirocycles **25** and **26** in good yields (Scheme 3).

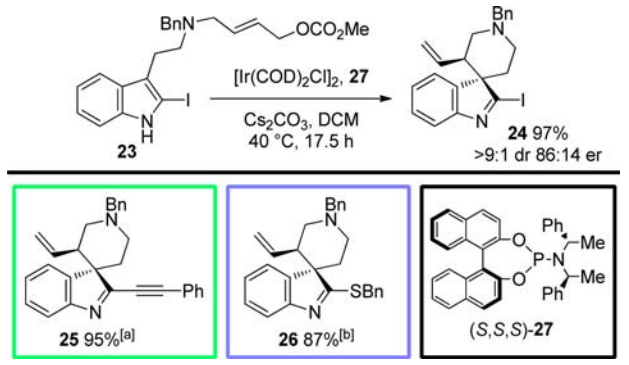
In another application, indoleninyl iodide **30** was prepared from imine **29** and indole **28**. These were treated with the peptide coupling agent T3P and iPr_2NEt at rt, using the direct imine acylation (DIA) method developed by our group,[11]

Scheme 2. Indoleninyl Iodide 7a Diversification



[a]10% HCl(aq), THF, rt, 4 h. [b]Thiol, Cs_2CO_3, MeCN, rt, 2–4 h. [c]NaN_3, DMF, 60 °C, 1.5 h. [d]2-Mercaptoethanol, Et_3N, MeCN, rt, 22 h. [e]Arylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, toluene/H_2O, 80 °C, 16–20 h. [f]RC≡CH, iPr_2NH, $PdCl_2(PPh_3)_2$, CuI, THF, rt, 1.5 h. [g]2-(Tributylstannyl)furan, $Pd(PPh_3)_4$, dioxane, 100 °C, 21 h. [h]Stannane, *trans*-PdBr(*N*-Succ)$(PPh_3)_2$,[9] toluene or dioxane, 100–130 °C, 17–48 h. [i]$CeCl_3$·$7H_2O$, $NaBH_4$, MeOH, rt, 90 min.

Scheme 3. Indoleninyl Iodide via Allylic Dearomatization



[a]**24**, phenylacetylene, iPr_2NH, $PdCl_2(PPh_3)$, CuI, THF, rt, 1.5 h. [b]**24**, benzyl mercaptan, Cs_2CO_3, MeCN, 1.5 h.

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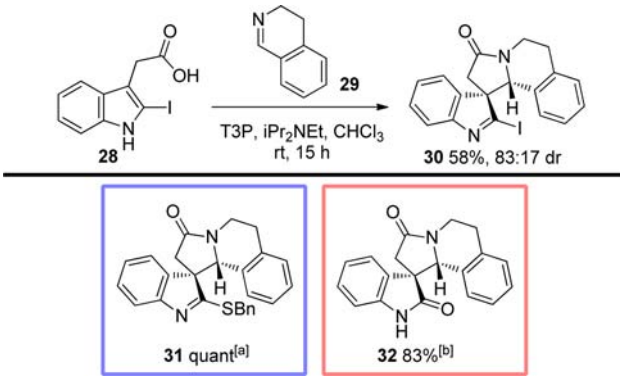
furnishing spirocycle **30** with 83:17 dr. The relative stereochemistry of **30** was assigned on the basis of analogy to related compounds.[11a] This scaffold was again amenable to additional functionalization either by nucleophilic substitution with benzyl mercaptan or by hydrolysis, forming products **31** and **32**, respectively (Scheme 4).

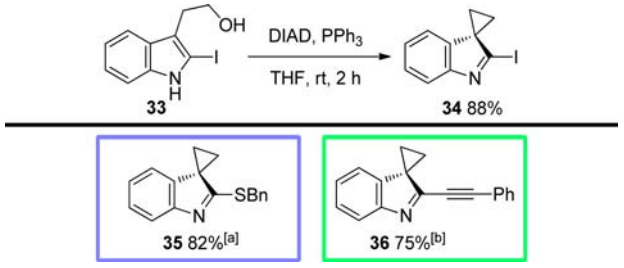
Scheme 4. Indoleninyl Iodide via Direct Imine Acylation



[a]**30**, benzyl mercaptan, Cs_2CO_3, MeCN, 3.5 h. [b]**30**, 10% HCl(aq), THF, rt, 3 h.

In addition, cyclopropyl substrate **34** was prepared in high yield by a Mitsunobu-type reaction of indole-tethered alcohol **33**. Functionalization by nucleophilic displacement (**35**) and cross-coupling (**36**) again demonstrated the synthetic utility of the indoleninyl iodide substructure (Scheme 5).

Scheme 5. Indoleninyl Iodide via a Mitsunobu Reaction

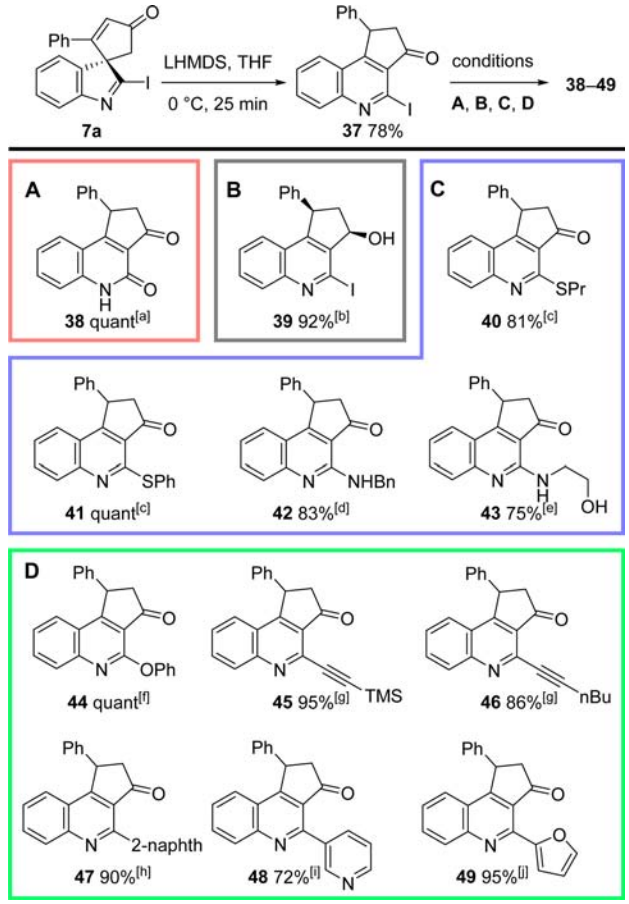


[a]**34**, benzyl mercaptan, Cs_2CO_3, MeCN, 3.5 h. [b]**34**, phenylacetylene, Cs_2CO_3, $PdCl_2(PPh_3)$, CuI, THF, rt, 5 h.

Finally, it was found that indoleninyl halide **7a** rearranges to form quinoline **37** under basic conditions. A related rearrangement reaction was reported by our group in a 2016 study, in which non-halogenated spirocyclic indolenines were shown to rearrange to form quinoline derivatives upon treatment with either strong base or Lewis acid.[6c] It was found that treating spirocyclic indolenine **7a** with LHMDS in THF at 0 °C promoted its conversion into 2-iodoquinoline **37** in 78% yield via a similar process (Scheme 6; for mechanistic speculation, see our earlier publication[6c]). Of course, 2-iodoquinolines are valuable, versatile building blocks in their own right, and to demonstrate this, derivatization reactions similar to those performed on indoleninyl iodide **7a** were also explored. These results are summarized in Scheme 6.

First, it was found that quinoline **37** could be hydrolyzed with aqueous HCl, affording 2-quinolone **38** in quantitative yield (Scheme 6A). A chemo- and diastereoselective reduction was also performed using $NaBH_4$ to yield alcohol **39** in good

Scheme 6. 2-Iodoquinoline 37 Diversification



[a]10% HCl(aq), 100 °C, 16 h. [b]$NaBH_4$, MeOH, rt, 3.5 h. [c]Thiol, Cs_2CO_3, MeCN, rt, 3–6 h. [d]Benzylamine, rt, 15 h. [e]2-Aminoethanol, rt, 5 h. [f]Phenol, *trans*-PdBr(*N*-Succ)$(PPh_3)_2$,[9] Cs_2CO_3, toluene, 100 °C, 2 h. [g]RC≡CH, Et_3N, $PdCl_2(PPh_3)$, CuI, DMF, rt, 2–3 h. [h]2-Naphthylboronic acid, $Pd(PPh_3)_4$, LiCl, Na_2CO_3, toluene/ethanol/H_2O, 80 °C, 16 h. [i]3-Pyridinylboronic acid, *trans*-PdBr(*N*-Succ)-$(PPh_3)_2$,[9] LiCl, Na_2CO_3, toluene/ethanol/H_2O, 100 °C, 24 h. [j]2-(Tributylstannyl)furan, $Pd(PPh_3)_4$, LiCl, THF, 85 °C, 16 h.

yield, with reduction presumably occurring anti to the adjacent phenyl substituent (Scheme 6B).[12] A selection of S_NAr derivatizations with sulfur (**40**–**41**) and amine nucleophiles (**42**–**43**) were also demonstrated (Scheme 6C). Finally, various cross-coupling protocols were also tested, with Buchwald–Hartwig (**44**), Sonogashira (**45**–**46**), Suzuki (**47**–**48**), and Stille (**49**) cross-coupling reactions all proceeding well in good yields (Scheme 6D).

In summary, we have demonstrated that indoleninyl iodides are readily accessible via the dearomatization of 2-iodoindole derivatives and that they can be used to synthesize a range of diverse spirocyclic indole derivatives. In view of their ability to react via three distinct reaction modes (hydrolysis, nucleophilic substitution, and cross-coupling), we expect indoleninyl iodides to quickly become established as valuable intermediates and reagents. Their utility as precursors to easily functionalized 2-iodoquinolines has also been demonstrated, further expanding their synthetic utility. Finally, while this work has focused largely on indoleninyl iodides, we have also demonstrated that indoleninyl bromide and chloride analogues can also be prepared using similar methods, and in future work the reactivity of these systems will also be examined.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03221.

Experimental procedures, spectroscopic data, NMR spectra, and further discussion of stereochemical assignments (PDF)

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Notes

The authors declare no competing financial interest.

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(12) For further information regarding the assignment of the stereochemistry of substrate **39**, see the Supporting Information.

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