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Dearomatizing Spiroannulation Reagents: Direct Access to Spirocycles from Indoles and Dihalides

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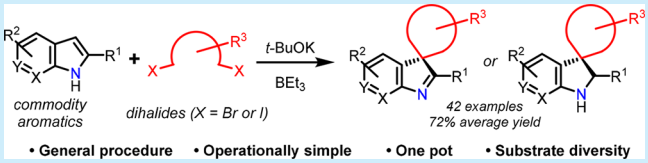
Supporting Information

ABSTRACT: Unfunctionalized indoles can be directly converted into 3,3′-spirocyclic indolenines and indolines upon reaction with electrophilic dihalides in the presence of *t*-BuOK/BEt_3. This double C−C bond forming reaction, which simultaneously generates a quaternary spirocyclic center, typically proceeds in high yield and has good functional group tolerance. In contrast to existing dearomatizing spirocyclization approaches, there is no need to prepare a prefunctionalized aromatic precursor, enabling faster access to valuable spirocyclic products from simple, commercially available aromatics in one step.



Spirocycles have been the focus of much research in recent years, in large part due to their utility in medicinal chemistry.[1] Spirocycles are typically rigid molecules with relatively predictable shapes, and often have a high "3D character", meaning that they can be used to probe regions of pharmaceutical space that historically have been underexplored.[2] In view of this, significant effort has gone into the development of effective ways to prepare diversely functionalized spirocycles, with dearomatization approaches among the most popular.[3] Existing dearomatizing spirocyclization methods almost always involve the preparation of a monosubstituted cyclization precursor, which then undergoes spriocyclization upon activation with a suitable reagent or catalyst (**1a** → **1b** → **1c**, Figure 1a).

Several efficient methods of this type have been reported, both by ourselves[4] and others,[5] but a drawback is that the preparation of the requisite starting materials (**1b**) is often not trivial, which can serve as a barrier to the uptake of the method. In this work, we describe a strategy by which this barrier can be removed, through the development of a series of simple, easily prepared bifunctional dearomatizing spiroannulation (DSA) reagents capable of undergoing two bond-forming reactions directly onto commercially available aromatics (Figure 1b).

To the best of our knowledge, there is remarkably little precedent for such an approach, even when all aromatic frameworks are considered. Taking indoles as an example, the only reported reactions that adhere to our design criteria[6] are summarized in Scheme 1.[7,8] Thus, Banerji et al. reported a double conjugate addition of indole **2a** with Michael acceptor **3**

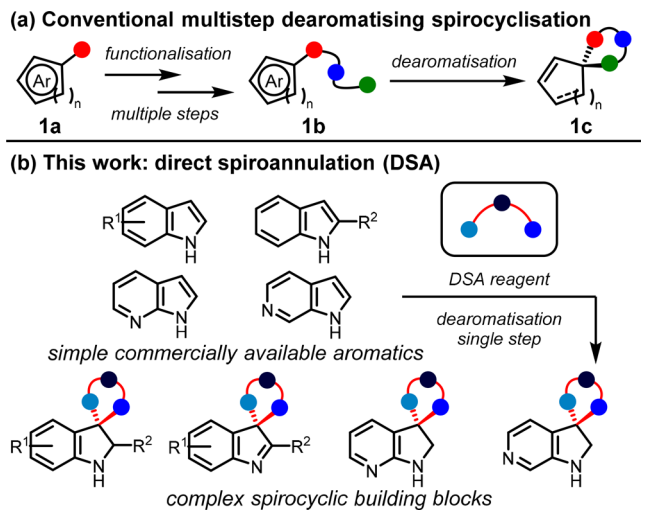
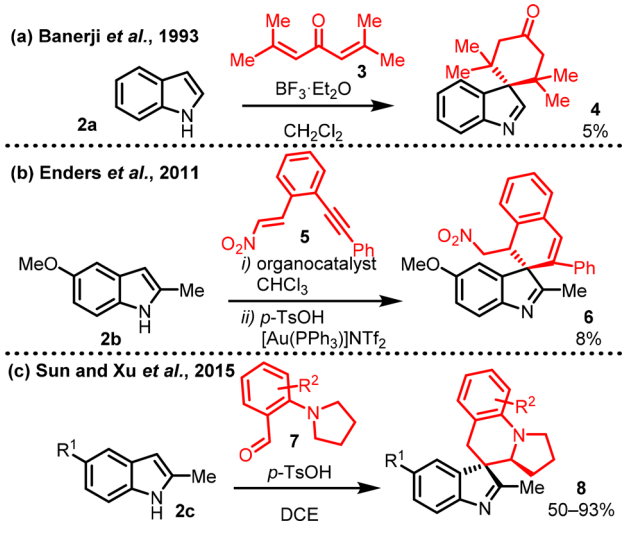


Figure 1. Spiroannulation strategies.

Scheme 1. Literature DSA-Type Approaches



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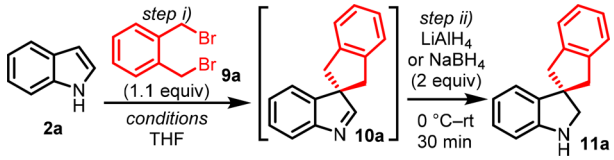
to form indolenine **4** (Scheme 1a),[7a] while Enders et al. isolated indolenine **6** from C2-substituted indole **2b** and bis-electrophile **5** (Scheme 1b).[7b] Both products were isolated in <10% yield, although it is important to stress that spirocycle synthesis was not the main objective in either of these studies. Arguably the best precedent is found in a 2015 report by Sun, Xu, and co-workers, who showed that spirocycles **8** could be prepared in good yields via a double C−C bond forming process using benzaldehyde derivatives **7** (Scheme 1c).[7c] Rare DSA-type reactions have also been reported for phenol derivatives,[9] but we were unable to find a precedent for similar approaches being adopted on any other class of aromatic system. Hence, this appears to be an underexplored area that could significantly expedite the synthesis of valuable spirocycles. The proof-of-concept results reported herein illustrate the potential value of this strategy through the development of a one-pot procedure for the direct spiroannulation of unfunctionalized indoles and azaindoles using simple dihalide reagents.

We decided to focus this proof-of-concept study on the use of simple, commercially available indole starting materials, in part due to our recent experience in the development of indole dearomatization methods.[10] Simplicity in the DSA reagents was a priority, which influenced our decision to use simple dihalide bis-electrophiles, all of which were either commercially available or easily prepared by short literature sequences (see Supporting Information (SI)). Our aim was to develop a dearomatizing spirocyclization procedure based on a one-pot, double alkylation process, starting with the reaction of commercially available 1,2-bis(bromomethyl)benzene **9a** and indole **2a** (Table 1). Note that because spiroindolenine product **10a** exists as an equilibrating mixture of monomer and trimeric compounds in solution,[11] a reductive quench was typically used (**10a** → **11a**; $LiAlH_4$ or $NaBH_4$) to simplify product isolation and characterization, as is commonly done in related processes.[12]

Table 1. Reaction of indole 2a with DSA reagent 9a



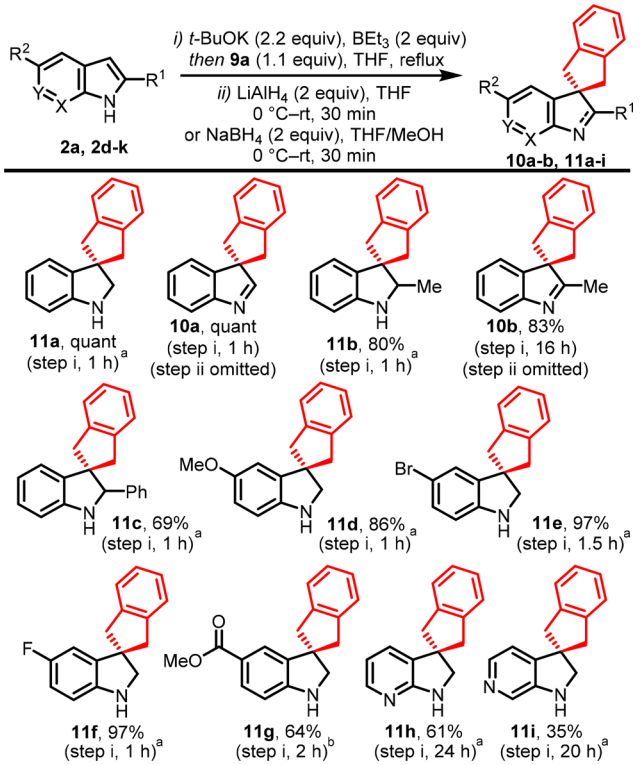
entry	conditions for step i	yield/%
i	*n*-BuLi, $ZnCl_2$, rt, 18 h[a]	0
ii	MeMgCl, rt, 18 h[a]	<63
iii	*t*-BuOK (2.0 equiv), rt, 18 h[a]	0
iv	*t*-BuOK (2.2 equiv), $BF_3{\cdot}Et_2O$ (2.0 equiv), rt, 18 h[a]	0
v	*t*-BuOK (1.1 equiv), BEt_3 (1.0 equiv), rt, 18 h[a]	70[c]
vi	*t*-BuOK (2.2 equiv), BEt_3 (1.0 equiv), rt, 18 h[a]	33[c]
vii	*t*-BuOK (1.1 equiv), BEt_3 (2.0 equiv), rt, 18 h[a]	76[c]
viii	*t*-BuOK (2.2 equiv), BEt_3 (2.0 equiv), rt, 18 h[a]	98
ix	*t*-BuOK (2.2 equiv), BEt_3 (2.0 equiv), reflux, 1 h[a]	quant
x	Conditions ix on gram scale[b]	99
xi	to isolate **10a**, conditions ix, then filtration (without reduction step (ii).	quant (10a)

[a]$LiAlH_4$ reduction. [b]$NaBH_4$ reduction. [c]In these cases, the quoted yield was based on the ratio of **2a**:**11a** in the ^1H NMR spectra of the unpurified reaction mixture.

Organometallic-based conditions for indole C3 alkylation (entries i–ii) either failed completely or provided a low yield of impure product.[13] Likewise, the use of *t*-BuOK, with or without BF_3, failed to provide the desired spirocycle (entries iii–iv). Pleasingly, switching to a *t*-BuOK/BEt_3 reaction system, adapted from conditions published by Yang and co-workers[14] (entries v–ix), enabled spirocycle **11a** to be formed in quantitative yield following a reductive quench. Using these optimized conditions (2.2 equiv *t*-BuOK, 2.0 equiv BEt_3, 1.1 equiv **9a**, THF, reflux, then $NaBH_4$ reduction) spirocyclic indoline **11a** was also prepared in 99% yield on gram scale (entry x). Finally, while a reductive quenching step was generally used, it is not essential; by omitting the reductive quench, indolenine **10a** was isolated in quantitative yield after filtration, concentration and column chromatography (entry xi). Mechanistically, the reaction likely proceeds through sequential inter- and intramolecular C-3 indole alkylation reactions, via the mechanism proposed by Yang and co-workers in their related study,[14] with the borane reagent helping to minimize competing N-1 and C-2 alkylation side reactions. Pleasingly, no C2 annulated products were detected in any of the unpurified reaction mixtures, which is notable, given the proclivity of 3,3-disubstituted indolenines to undergo 1,2-migration.[12,15]

With the optimized conditions in hand, we next examined the reaction of dibromide **9a** with other commercially available indole derivatives (Scheme 2). Thus, using the standard conditions (Table 1, conditions ix), both 2-methyl and 2-phenyl indole reacted to give the expected 2-alkyl indolines **11b** and **11c**, respectively, demonstrating that the C2 position can be unsubstituted or derivatized in our procedure (in contrast to Scheme 1c, in which all published examples have C-2 alkyl substituents).[7c] Likewise, both electron-rich (**11d**) and electron-poor (**11e**–**g**) functionalities were tolerated at the indole 5-position. Finally, electron-deficient aza-indole hetero-

Scheme 2. Spiroannulation with Dibromide 9a



[a]Step ii using $LiAlH_4$. [b]Step ii using $NaBH_4$.

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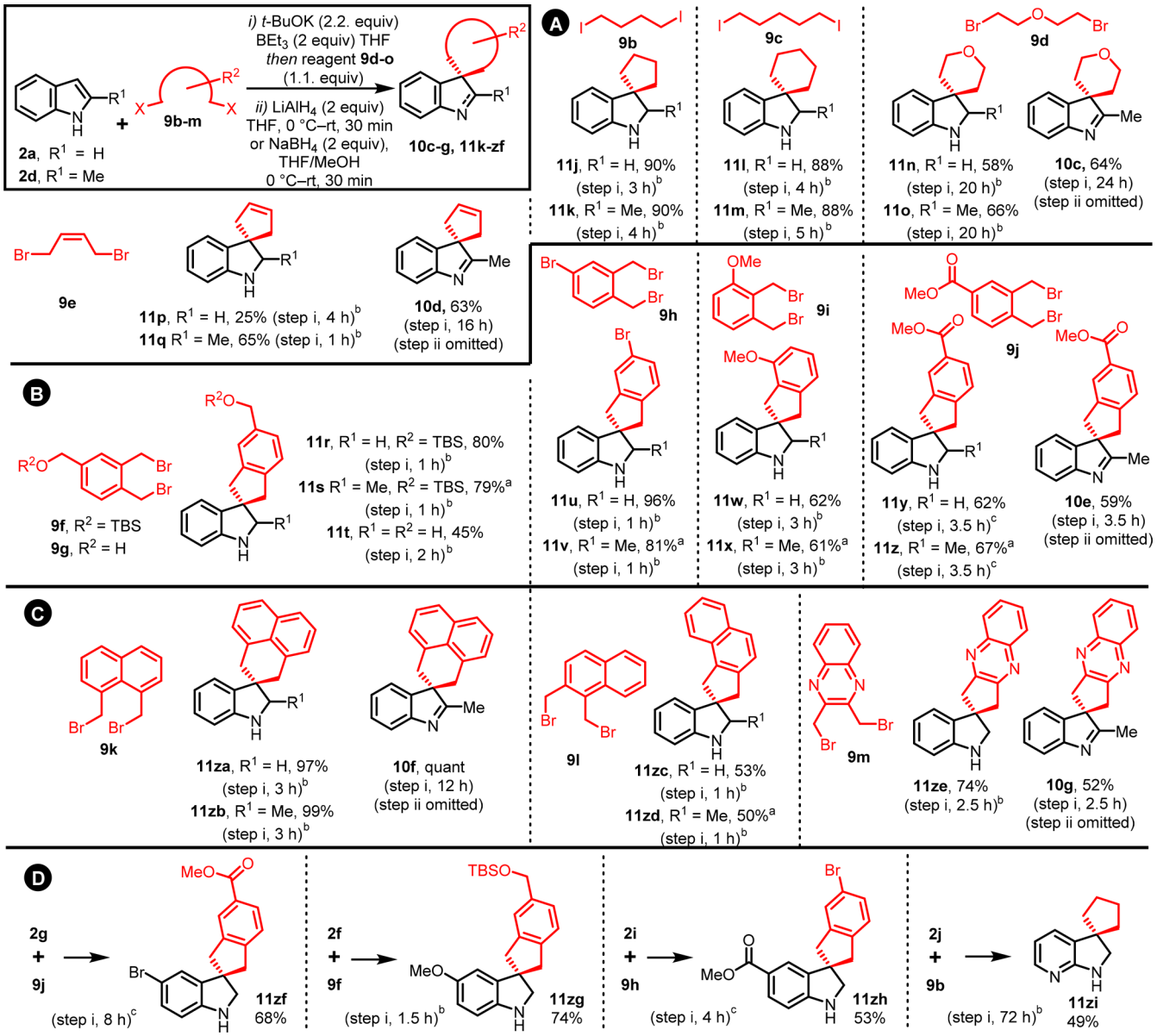
Scheme 3. Spiroannulation of Indoles 2a and 2d



[a]Formed in ~1:1 dr; [b]Step ii using $LiAlH_4$. [c]Step ii using $NaBH_4$.

cycles were found to give usable quantities of spiro-annulated product (**11h,i**), albeit in lower yields. As before, a reductive quench was preferred for ease of handling, but was not a requirement, as exemplified by the high yielding isolation of indolenines **10a** and **10b** when omitting the reduction step.

Next, we turned our attention to examining the scope with respect to the dihalide DSA reagent. Thus, a range of simple dihalides **9b–m** were tested, on both indole **2a** and 2-methylindole **2d**, to establish whether indoles with and without C2 substitution are compatible with each dihalide reagent (Scheme 3). First, simple alkyl halides **9b** and **9c** reacted with indole and 2-methylindole to provide cyclopentyl and cyclohexyl spirocycles **11j–m** in high yields (Scheme 3A). Remarkably, no competing elimination reactions or other side reactions were observed during the reactions of these unactivated bis-electrophiles. In addition, the use of 2-bromoethyl ether **9d** afforded tetrahydropyran derivatives **11n,o** in moderate yields, with both structures supported by X-ray crystallographic data.[16] While (*Z*)-1,4-dibromobut-2-ene **9e** reacted with 2-methylindole to provide cyclopentene **11q** in reasonable yield, the analogous reaction with indole **2a** was complicated by competing intermolecular S_N2' reactions, which led to product **11p** being obtained in a much lower yield of 25% (see SI for further details). Other benzannulated DSA reagents are well tolerated, and examples include substrates substituted with functional groups amenable to further derivatization, including protected benzylic alcohols, aryl bromides, anisoles, and aryl esters (**11r–z**, Scheme 3B). In addition, benzyl alcohol **11t** could be formed in a protecting group-free reaction from reagent **9g** directly. 1,8-Bis(bromomethyl)naphthalene **9k** reacted with both indole and 2-methylindole to form 6-carbon spirocycles **11za** and **11zb** in near quantitative yield (Scheme 3C). Spiroannulation was also possible with 1,2-bis(bromomethyl)naphthalene **9l**, although in a lower yield (50–53%), possibly due to the formation of orthoquinone dimethide decomposition products. Nitrogen

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heterocycle quinoxaline **9m** also reacted productively with both indole and 2-methylindole, despite incomplete starting indole consumption. While indoline **11ze** was formed in good yield, the 2-methyl analogue was best isolated as indolenine **10g** without reduction. Three bis-functionalized products were also prepared by combining orthogonally functionalized indoles and DSA reagents (Scheme 3D); 5-bromo-**2g**, 5-methoxy-**2f** and 5-carbomethoxy-indoles-**2i**, were combined with DSA reagents **9j**, **9f**, and **9h**, respectively, providing spirocycles with multiple possibilities for further derivatization (**11zf**−**zh**). In addition, the challenging 7-azaindole substrate **2j** was successfully spiroannulated with unactivated DSA reagent 1,4-diiodobutane **9k** to provide nitrogen-containing spirocycle **11zi**. Finally, to further exemplify the isolable nature of the indolenine intermediates, products **10c**−**f** were also isolated in comparable yields by omitting the reduction step.

In summary, a convenient method for the conversion of unfunctionalized, unprotected commercially available indoles and aza-indoles into spirocyclic indolenines and indolines is reported, via a simple, one-pot protocol. The ready availability of both coupling partners is a key feature, especially for the synthesis of new chemical entities for lead-identification in medicinal chemistry. In the future, it is our hope that this concept will be applied much more generally with other bifunctional reagents, which could lead to a step-change in the way dearomatizing spirocyclizsation reactions are carried out. Developing bifunctional reagents (including unsymmetrical systems) that are compatible with the conditions required to perform both the inter- and intramolecular bond-forming steps needed to achieve overall spiroannulation is challenging, but given the advantages in terms of synthetic efficiency and rapid access to useful spirocyclic products, we believe that this is an approach with much potential.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01248.

Experimental procedures, spectroscopic data and NMR spectra (PDF)

Accession Codes

CCDC 1555786−1555787 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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(16) CCDC 1555786 and 1555787 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.com.ac.uk/data_request/cif

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