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Stitching Oxindoles and Ynones in a Domino Process: Access to Spirooxindoles and Application to a Short Synthesis of Spindomycin B

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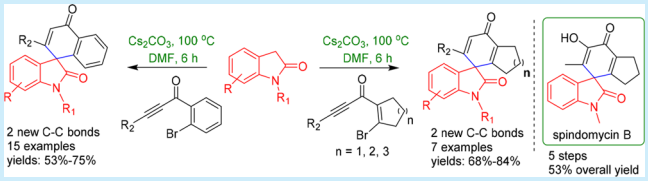
Supporting Information

ABSTRACT: A general, transition-metal-free, one-pot, domino Michael−S_NAr or Ad_NE substitution protocol was devised for spiroannulation of oxindoles with *ortho*-bromoaryl ynones, *β*-bromoalkenyl ynones, and *β*-bromoalkenyl enones in a convenient and efficient manner. As an application, a short synthesis of tetracyclic alkaloid spindomycin B was accomplished.



Spirooxindoles, embodying spiroannulation of a carbo- or heterocyclic rings at the 3-position of oxindoles, are generally perceived as privileged structures through their three-dimensional architecture with variegated and generous distribution of functionalities. They are found as core substructures in many bioactive natural products and pharmacologically relevant synthetic compounds.[1] Among the spirooxindoles, those with 3,3′-fused six-membered rings with additional appendages, both of natural and synthetic origin and displaying promising bioactivity attributes,[2] have drawn considerable interest from the synthetic organic and medicinal chemistry community.[3−10] Representative examples of natural products spindomycin A **1** and B **2** (tyrosine kinase inhibitor),[2a] gelsemine **3**, gelseverine **4** (antidepressant),[2d,c] maremycin F **5**[2d] and synthetic compounds satavaptan **6** (hyponatremia),[2e] **7** (MDM2-p53 inhibitor),[2f] and **8** (a progesterone receptor agonist)[2g] depicting the diversity among 3-spirocyclohexanyl-2-oxindole based scaffolds are displayed in Figure 1.

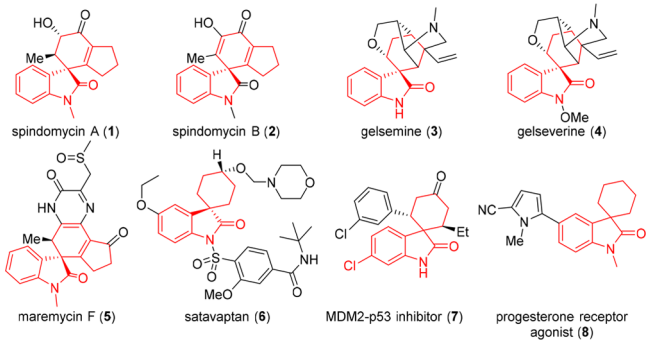


Figure 1. Representative six-membered spirooxindoles

A confluence of complex structural features and wide range bioactivities has aroused considerable interest in exploring chemical space around the 3-spirocyclohexanyl-2-oxindole scaffolds. Several methods developed in this context that involve Pd-catalyzed intramolecular Heck cyclization (**9** → **10**),[3] *α*-arylation (**11** → **12**),[4] C−H activation (**13** → **14**),[5a,b] Lewis acid mediated cyclizations (**15** → **16**),[6a,f] Diels−Alder cycloadditions (**17** → **18**),[7a,e] radical cyclizations (**19** → **20**),[8a,d] organocatalytic reactions (**21** → **22**),[9a,j] and other catalytic/domino processes (**23** → **24**),[10a,g] among many others, are captured in Figure 2.

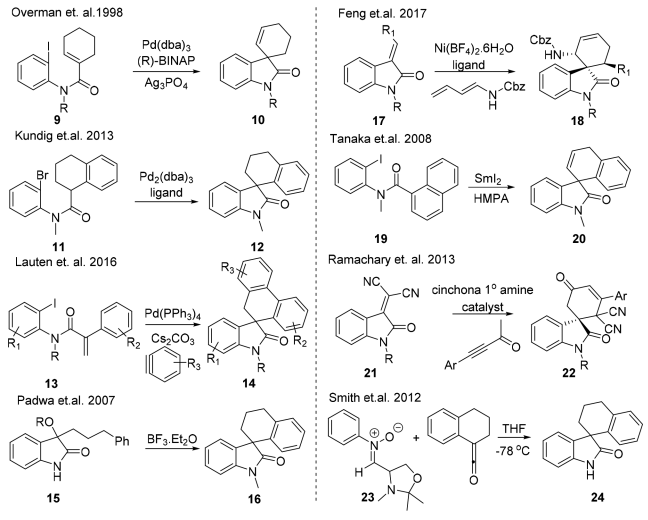


Figure 2. Previous approaches for six-membered spirooxindoles

Although the previous methods are useful in their own right, some require considerable effort toward the acquisition of precursors or deployment of metal catalysts and less accessible reagents, underscoring the need for a general, simple to execute

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approach employing readily available precursors to access these valuable pharmacophoric scaffolds. As part of our ongoing research,[11] we recently demonstrated an approach to 3,3′-cyclopentaspirooxindoles (**27**, **29**)[11a] through aryne **26** and ynone **28** insertion into 3-oxindole acetic acid ester **25** (Figure 3).

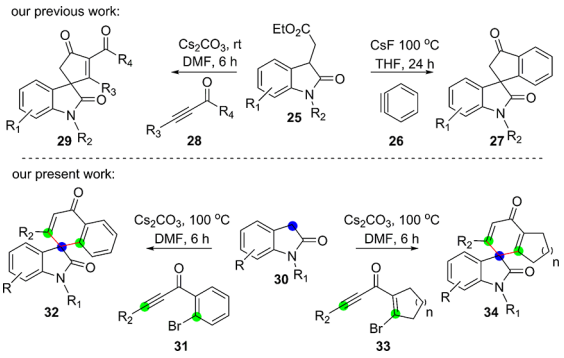
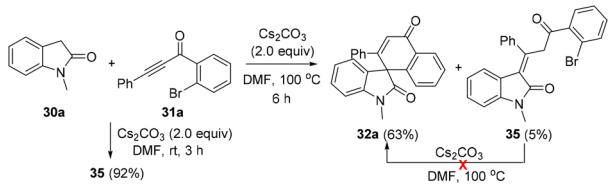


Figure 3. Our approach to carbocyclic spirooxindoles

We report here an interesting transition-metal-free, "one-pot" domino reaction between readily available oxindole **30** and *o*-bromoaryl ynones **31** and *β*-bromoalkenylynones **33** via domino Michael−S_NAr[12,13] or Ad_NE[14] reactions to deliver variously embellished 3-spirocyclohexanyl-2-oxindole scaffolds **32** and **34**, respectively (Figure 3). This conceptualization was successfully extended to accomplish the first total synthesis of bioactive alkaloid spindomycin B (**2**).

Reaction between *N*-methyl oxindole **30a** and 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one **31a** was probed. Under optimized conditions [Cs_2CO_3 (2.0 equiv), DMF, 100 °C, 6 h; see Supporting Information (SI)], **32a** and **35** (~13:1) were realized (Scheme 1). While the major spiroannulated product

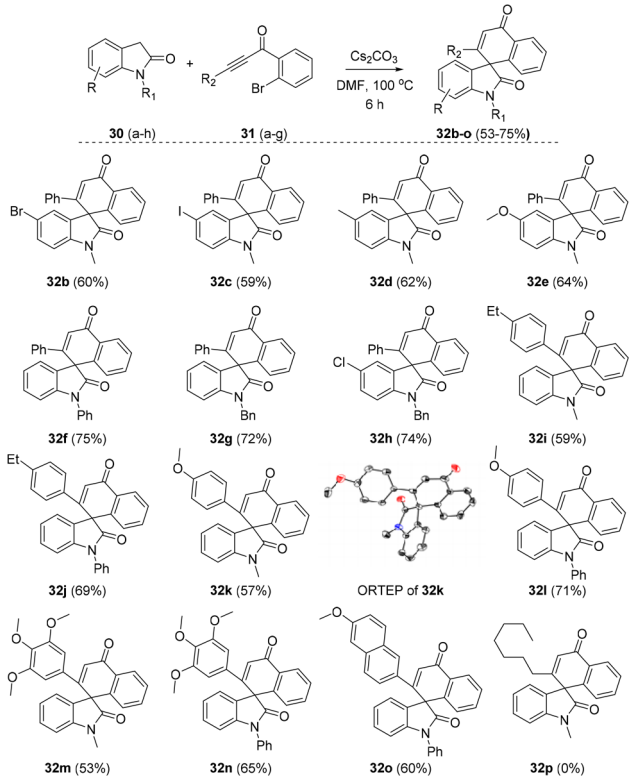
Scheme 1. Initial experiment



32a (63%) could be envisioned to arise through tandem Michael addition−nucleophilic aromatic substitution (S_NAr), the origin of the minor product **35** (5%) could be traced to Michael addition and base mediated double bond relocation (Scheme 3). When the reaction was conducted at ambient temperature, **35** was the only product observed. In a control experiment it was observed that **32a** and **35** originated independently, as **35** under the optimized reaction conditions remained unaltered (Scheme 1).

We proceeded to demonstrate the generality and scope of this domino Michael−S_NAr reaction employing various oxindoles and *o*-bromoaryl ynones under the optimized conditions. Reaction between ynone **31a** and various 5-substituted oxindoles (**30b−e**) led to the formation of spirooxindoles **32b−e**, respectively, as the main products with the minor products similar to **35** formed only in <5% yield and were not isolated (Scheme 2). Oxindoles with *N*-phenyl **30f** and *N*-benzyl **30g,h** also engaged ynone **31a** to furnish the corresponding spirooxindoles **32f−h**. It was also felt appropriate to investigate this domino process with diverse ynone partners **31b−e** which upon reaction with oxindole **30a**

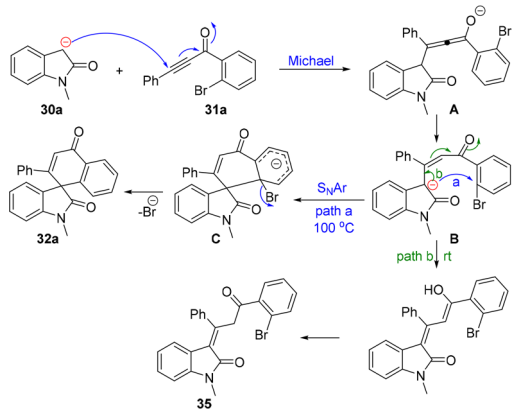
Scheme 2. Reaction of Various Substituted Oxindoles with *o*-Bromoaryl Ynones



and oxindole **30f** smoothly delivered the corresponding spirooxindoles **32i−o**, respectively, in moderate yields (Scheme 2). The formation of spirooxindoles **32a−o** was secured through consistent and complementary spectral data and single crystal X-ray structure determination of one of them (**32k**, Scheme 1 and 2). However, ynone **31f** bearing an alkyl substituent did not undergo spirocyclization to yield the desired **32p** but afforded only the Michael product **35a** (see SI).

Our experimental observations and scrutiny of related precedence, gleaned from the literature,[12,13] are suggestive of a plausible reaction mechanism (Scheme 3) for this domino

Scheme 3. Proposed Reaction Mechanism



process. It would be reasonable to assume that the oxindole derived anion **30a** adds to ynone **31a** in Michael fashion to afford intermediate **A** which tautomerizes to olefin **B**. At higher temperature (~100 °C) the anion derived from **B** displaces the

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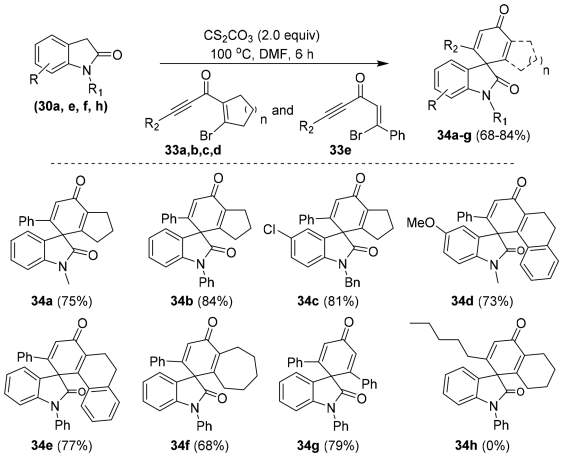
aromatic bromide in a nucleophilic aromatic substitution (S_NAr) reaction to deliver the spiro product **32a** via intermediate **C**. On the other hand, at ambient temperature the anion **B** only undergoes double bond isomerization to furnish alkylidene oxindole product **35**.

In this facile and apparently general S_NAr reaction of oxindoles with β-bromoaryl ynones, we were curious to find out if the similar protocol could be implemented on β-bromoalkenyl ynones to advance the potentiality of our domino reaction. Accordingly, when **30a** was engaged with readily obtainable 1-(2-bromocyclopent-1-en-1-yl)-3-phenylprop-2-yn-1-one **33a** (for the preparation of bromoalkenylynones **33a−d**, see SI) under optimized conditions (Cs_2CO_3, DMF, 100 °C), the reaction afforded the tetracyclic spirooxindole **34a** in 75% yield, along with the minor product **36** in <5% yield. Once again, it was observed that **34a** and **36** were formed independently and the latter did not convert to the former under the reaction regime. Furthermore, to demonstrate the generality and scope of this reaction, various substituted oxindoles (**30e/f/h**) readily engaged with diverse cyclic β-bromoalkenyl ynones **33a/b/c/e** to afford the corresponding tetracyclic spiroannulated compounds **34b−g**, respectively, in good yields, Scheme 4. However, the alkyl-substituted ynone **33d**

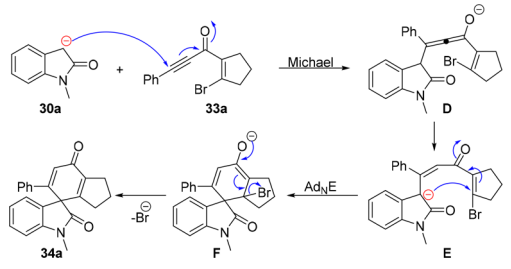
Scheme 4. Michael−Ad$_N$E Reaction of Oxindoles with β-Bromoalkenylynones



like **31f** (Scheme 2) did not lead to **34h** but provided only **36a** (see SI) under the reaction conditions.

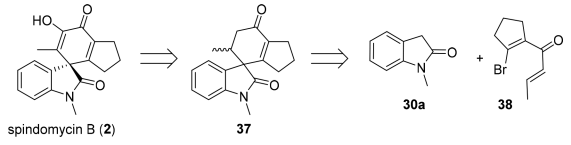
A plausible mechanism for the above transformation can be through a tandem Michael addition followed by addition−elimination (Ad$_N$E) reactions (D → E→F → **34a**), Scheme 5.

Scheme 5. Proposed Reaction Mechanism



To further evaluate the scope and efficacy of our one-pot β-bromoalkenyl ynone mediated oxindole spiroannulation methodology, we ventured to extend it to β-bromoalkenyl enones as partners for oxindole and target recently isolated natural products **1** and **2** as a total synthesis objective. These tetracyclic alkaloids were isolated from rhizosphere strain *Streptomyces*sp. xzqh-9, and their structures and absolute configurations were determined through 2D NMR and calculated electronic circular dichroism.[2a] Among the two sibling alkaloids, **2** displayed weak (30 μM) inhibitory activity against tyrosine kinase Bcr-Abl implicated in chronic myeloid leukemia and was chosen as the initial target. A retrosynthetic perspective aimed at a short synthesis of **2** is depicted in Scheme 6. Thus, a Michael−Ad$_N$E protocol between

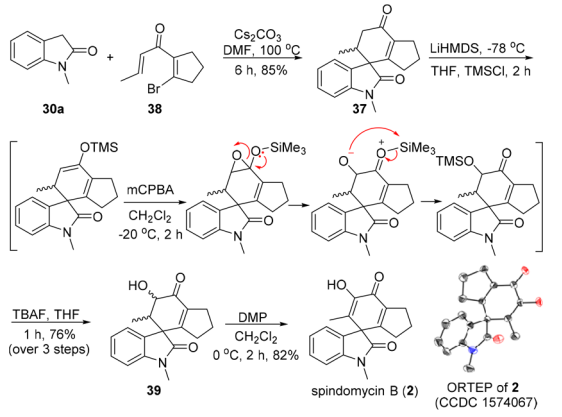
Scheme 6. Retrosynthetic Analysis of Spindomycin B



30a and **38** would deliver the tetracyclic framework **37**, well geared for functional group amplification to deliver the target natural product in a few steps.

The reaction between **30a** and cross-conjugated **38** under optimized conditions (Cs_2CO_3, DMF, 100 °C) afforded the expected spiroannulated tetracyclic oxindole **37** as a mixture of inseparable diastereomers and was elaborated to diastereomeric α-hydroxyketones **39** following the Rubottom oxidation protocol.[15] Thus, **37** with LiHMDS and TMSCl afforded silyl-enol ether, which upon further epoxidation with *m*CPBA and TBAF exposure led to **39** as a mixture of diastereomers. Dess-Martin periodinane[16] oxidation of **39** and concomitant enolization afforded **2** in 82% yield. The spectral data of the synthetic spindomycin B were found to be identical with those reported for the natural product. Moreover, we also determined its single crystal X-ray structure (Scheme 7).

Scheme 7. Total Synthesis of Alkaloid Spindomycin B (2)



In conclusion, we outlined a one-pot, metal-free spiroannulation strategy to conveniently access the 3-spirocyclohexanyl-2-oxindole motif from oxindoles and β-bromoaryl ynones and further extended this domino protocol to β-bromoalkenyl ynones and enones. As an application of this new method, the first synthesis of tetracyclic alkaloid spindomycin B was accomplished in five steps with an overall yield of 53%.

■ ASSOCIATED CONTENT

Supporting Information

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Detailed experimental procedures and spectral data for all new compounds (PDF)
Crystallographic data for compound **32k** (CIF)
Crystallographic data for compound **2** (CIF)

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Notes

The authors declare no competing financial interest.

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