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Spiroannulation of Oxindoles via Aryne and Alkyne Incorporation: Substituent-Diverted, Transition-Metal-Free, One-Pot Access to Spirooxindoles

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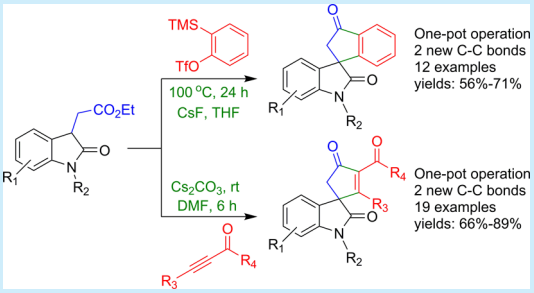
Supporting Information

ABSTRACT: A "product control via substrate design" strategy has been conceptualized and implemented to harness the potential of aryne and activated alkyne insertions into oxindoles to readily and efficiently furnish pharmacophoric indano- and cyclopentannulated spirooxindole scaffolds in an operationally straightforward, one-pot, transition-metal-free protocol.



Spirooxindoles, constituted through a spiro-fusion of a carbocyclic or heterocyclic ring at the 3-position of an oxindole, are well-recognized, privileged, three-dimensional structural motifs, frequently encountered in diverse natural products and pharmaceutically relevant entities.[1−3] Representative examples of natural and unnatural spirooxindoles **1**−**8** are collected in Figure 1 to capture their framework and functional

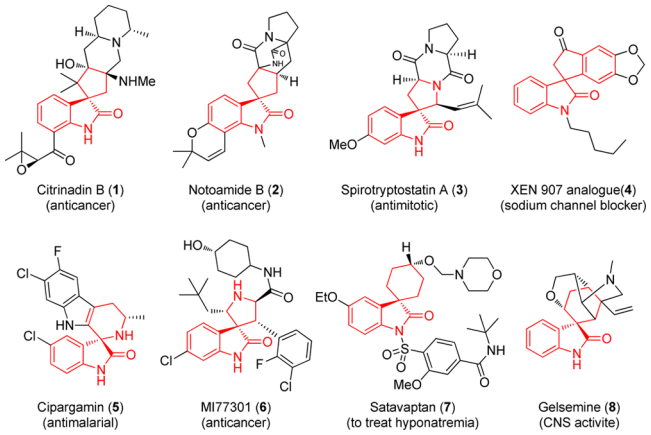


Figure 1. Representative examples for bioactive spirooxindole natural products and synthetic compounds.

diversity and complexity.[2] These spirooxindole-based constructs display an exceptionally broad range of biological activities that include anticancer,[1a,c] antiviral,[1b] antifungal, contraceptive, antimalarial, and antimigrane activity, to name a few. It is hardly surprising, therefore, that several drug discovery programs in industry and academia are anchored around a spirooxindole scaffold, and compounds such as cipargamin (**5**) (for malaria), MI77301 (**6**) (for endocrine-resistant breast cancer), satavaptan (**7**) (for hyponatremia), and gelsemine (**8**) (for CNS disorders) are in various stages of clinical development. Consequently, there is a widespread topical interest among synthetic organic and medicinal chemists toward devising new and efficient methods for accessing variegated spirooxindoles in order to explore the chemical diversity space around this scaffold.[3]

While numerous synthetic approaches to access 3,3-heterocycle-fused spirooxindole motifs have been devised,[3] contemporaneous efforts toward accessing 3,3-carbocycle-fused spirooxindoles are relatively few and of recent vintage.[4−10] In this context, metal-mediated activations/cyclizations on precrafted advanced precursors have been a commonly pursued approach toward 3,3-carbocycle-fused spirooxindoles. Notable examples that have surfaced in recent years are Pd-mediated tandem Heck reaction and C(sp^3)−H bond activation (**9** → **10**),[4] Pd-catalyzed α-arylation of amides (**11** → **12**),[5] Ni-catalyzed intramolecular Heck cyclization (**13** → **14**),[6] and Pd-catalyzed remote C−H alkylation (**15** → **16**)[7] (Figure 2). In addition, cationic rearrangements (**17** → **18**)[8] have also been harnessed to generate the spirooxindole framework, among others.[9] More recently, organocatalytic protocols[3b] have been employed for 3,3-cyclopentaannulation (**19** → **20**, **21** → **22**, and **23** → **24**) and 3,3-cyclohexannulation of oxindoles to access spirooxindoles (Figure 2).[10]

Although the aforementioned existing methods have met with varying degrees of success, they necessitate use of either metal catalyst or exotic organocatalyst and entail multistep substrate acquisition, which is self-limiting. Thus, new, efficient approaches

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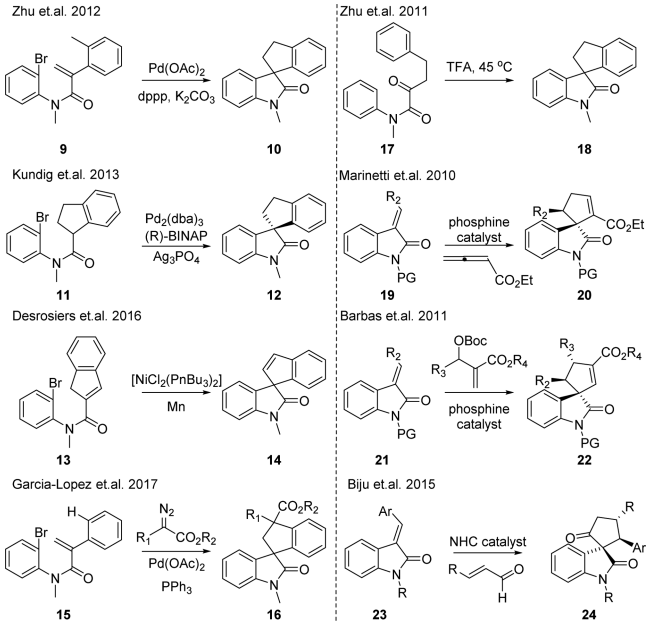
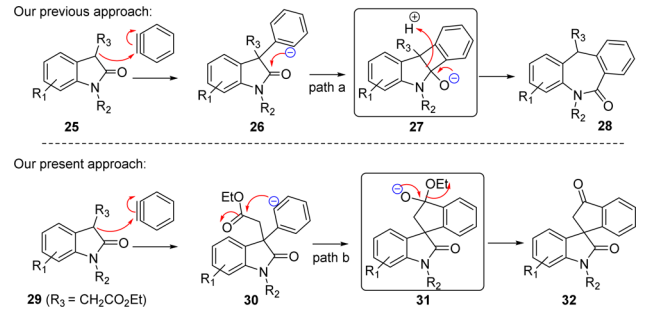


Figure 2. Representative recent approaches for accessing 3,3-carbocycle-fused spirooxindoles.

using readily available substrates with minimal processing maneuvers should be a welcome addition to the repertoire of methods for the synthesis of these valuable pharmacophoric scaffolds. In this paper, we disclose a transition-metal-free, one-pot access to 3,3-carbocylic spirooxindoles through incorporation of arynes and activated alkynes (as alkynones) into strategically crafted oxindoles bearing an opportunistic substituent to efficiently access a diverse range of spirooxindoles.

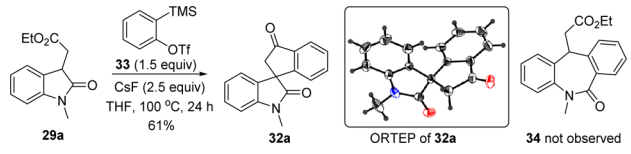
In the preceding decade, aryne chemistry has re-emerged as a powerful synthetic tool for generating complex and diverse chemical entities.[11,12] Our own recent efforts in the area have led to some new opportunities through multiple aryne insertions[13] that include reaction with oxindoles **25** to furnish diverse dibenzoazepinones **28** (Scheme 1).[13a] This transformation

Scheme 1. Evolution of Aryne Approach to Spirooxindoles

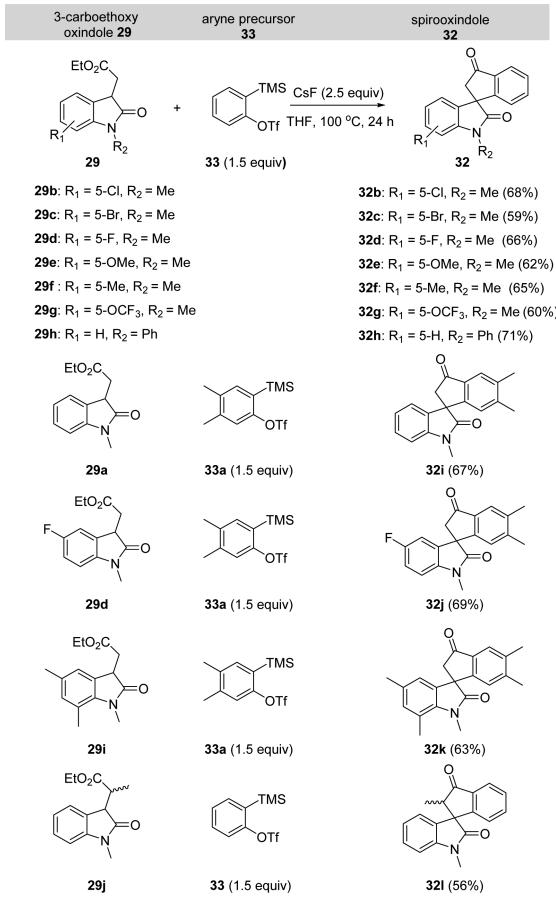


proceeds through initial aryne C(sp^3)–H insertion to oxindole to form anion **26**, which adds to the amide carbonyl to form a strained cyclobutenoid intermediate **27** and further fragments to deliver dibenzoazepinones **28** (path a) (Scheme 1). We reasoned that anion **26** is well poised for exploring an alternate reaction path by engaging a favorably and strategically positioned electrophilic ester substituent to eventuate in useful framework diversification. This conceptualization is depicted for **29** bearing an acetic acid side arm at the 3-postion (Scheme 1). Anion **30** formed through initial aryne C(sp^3)–H insertion now has a better option to engage the ester group **31** (path b) and lead to much desired spiroannulated oxindole **32** (Scheme 1). Many variants of this conceptualization could be imagined, but initially, we proceeded to test and demonstrate its validity with a few diverse substituents as depicted in Schemes 2 and 3.

Scheme 2. Initial Experiment



Scheme 3. Reaction of various Substituted Oxindoles with Arynes



In the event, reaction between an acetic acid side chain bearing 3-(carbethoxymethyl)oxindole **29a** and aryne generated in situ from Kobayashi[14] precursor **33** under optimized conditions (CsF, 2.5 equiv in THF, sealed tube at 100 °C for 24 h, Table 1, Supporting Information) led to the formation of the projected spirocyclized product **32a** in 61% yield, Scheme 2. The structure of 3,3-annulated spirooxindole **32a** was confirmed unambiguously through a single-crystal X-ray analysis (Scheme 2). Gratifyingly, there was no trace of the ring-expanded dibenzoazepinone **34**, and only path b was operational.

Following this encouraging outcome, generality of the spirocyclization protocol was demonstrated. Accordingly, various 5-substituted *N*-methyl-3-(carbethoxymethyl)oxindoles (**29b–g**) were reacted with aryne precursor **33** under optimized conditions to furnish the respective spirooxindoles (**32b–g**) in

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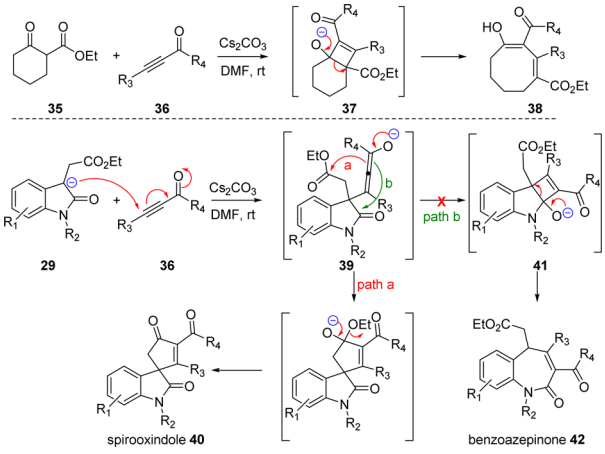
decent yields. It is to be noted that even *N*-aryl-substituted oxindole **29h** reacted likewise to deliver the spirooxindole **32h** in 71% yield. It was also considered useful to demonstrate the spiroannulation with a substituted Kobayshi-type aryne precursor **33a**. Reaction of **33a** with oxindole partners **29a**, **29d**, and **29i** proceeded smoothly to result in spirooxindoles**32i**, **32j**, and **32k**, respectively (Scheme 3). A substrate **29j** with a methyl substituent at the methylene group of **29a** also readily engaged the aryne **33** to furnish an inseparable mixture (1:1) of spiroannulated diastereomers **32l** in 56% yield (Scheme 3). Thus, the substitution on the methylene group is well tolerated, but the outcome is nonstereoselective.

In the backdrop of the successful spiroannulation of oxindoles through aryne incorporation, it was natural to ponder over the question whether such substitutent diverted annulations could be replicated by employing alkyne partners for oxindoles. An encouraging cue in this regard emerged from the recent work of Li et al.,[15] who showed that activated alkynes like the *α,β*-unsaturated alkynone **36** insert into the C−C bond of *β*-keto esters like **35** in the presence of Cs_2CO_3 to deliver ring-expanded product **38** via the intermediacy of cyclobutene intermediate **37** (Scheme 4). This outcome, reminiscent of the response of

Scheme 4. Alkynone Reactivity with Activated Carbonyl Compounds and Our Hypothesis

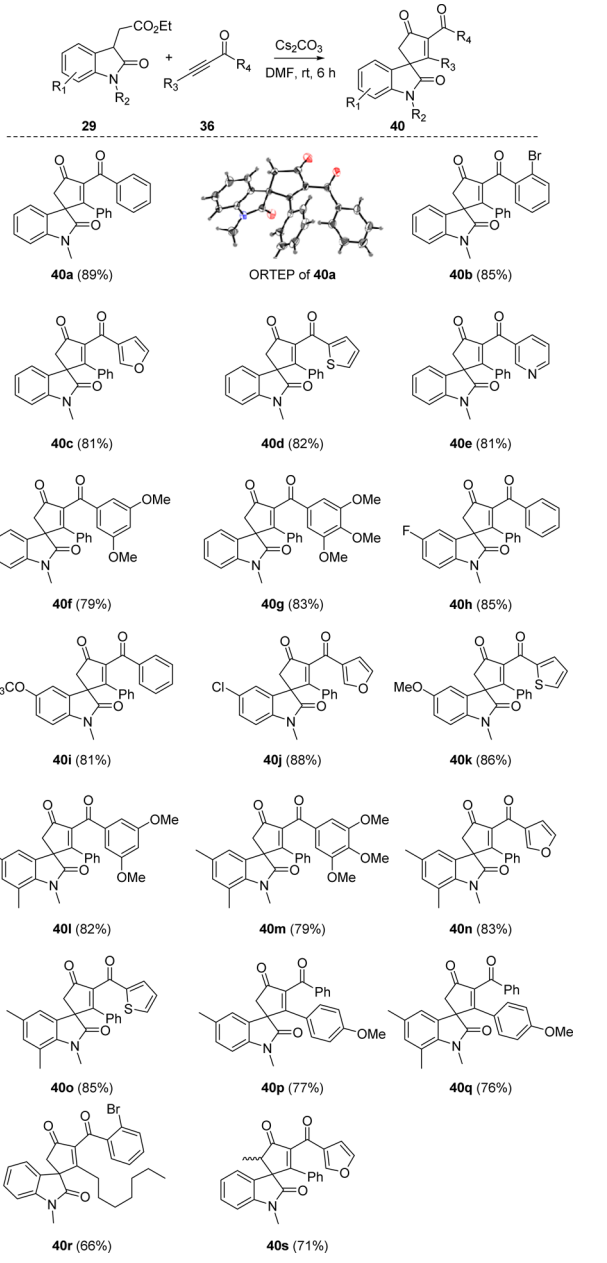


oxindole without a substituent in 3-position (Scheme 1), indicated that a 3-carbethoxymethyl group in **29** could be leveraged to induce diversion to **40** in the intermediate **39** (path a) obtained through initial Michael addition and thus circumvent the formation of benzoazepinone **42** via cyclobutene intermediate **41** (path b) (Scheme 4).

To validate this proposition, a reaction between 3-(carbethoxymethyl)oxindole **29a** and *α,β*-unsaturated alkynone **36a** (1,3-diphenylprop-2-yn-1-one) was performed using Cs_2CO_3 as base in DMF at room temperature. Pleasingly, exclusive formation of cyclopenteno-annulated spirooxindole **40a** was observed in very good yield (89%).The structure of **40a** was secured by a single-crystal X-ray structure determination (Scheme 5). As we had contemplated, the bystander 3-substituent steered the reaction between oxindole **29** and alkynone **36** along the preferred pathway b (Scheme 4), and no leakage to benzoazepinone **42** could be detected. Spiroannulated **40** is endowed with an interesting enedione moiety suitable for further elaboration of this interesting pharmacophoric scaffold.

Given such utilitarian prospects of **40**, it was of interest to demonstrate the generality of the one-pot spiro-cyclopentannulation of oxindoles through reaction between diverse *α,β*-unsaturated alkynones and 3-(carbethxymethyl)oxindoles. Indeed, reactions between various *α,β*-unsaturated alkynone **36a−i** (readily prepared from the corresponding aldehydes via TMS-acetylene addition and oxidation) were treated with 3-(carbethoxymethyl)oxindoles **29**. The *o*-bromo-substituted alkynone (**36b**), heterocyclic alkynones (**36c**, **36d**, **36e**), and methoxy-substituted alkynones (**36f**, **36g**, **36h**) reacted smoothly with 3-(carbethoxymethyl)oxindoles **29** under the optimized reaction conditions and provided the corresponding substituted spirooxindoles (**40a−q**) in excellent yields (Scheme 5). Alkyl-substituted ynone **36i** also smoothly reacted with oxindole **29a** to furnish the spiroannulated product **40r**. The ynone **36h** reacted with oxindole **29j** bearing a methyl substituent at the *α*-position to ester to furnish the spiroannulated **40s** (diastereomeric mixture)(Scheme 5).

Scheme 5. Synthesis of Cyclopentane-Fused Spirooxindoles from Various Substituted Oxindoles and Alkynones



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In summary, a "product control via substrate design" strategy in which a tactically placed 3-carbethoxymethyl group on the oxindole framework steers and deviates the reaction course of aryne and activated alkyne incorporation into oxindoles to furnish indano- and cyclopentannulated spirooxyindoles in a one-pot, transition-metal-free operation has been developed. The generality of this protocol and its efficacy in creating diversity have been demonstrated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01233.

Detailed experimental procedures and spectral data for all new compounds (PDF)
Crystallographic data for compounds **32a** (CIF)
Crystallographic data for compounds **40a** (CIF)

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Notes

The authors declare no competing financial interest.

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