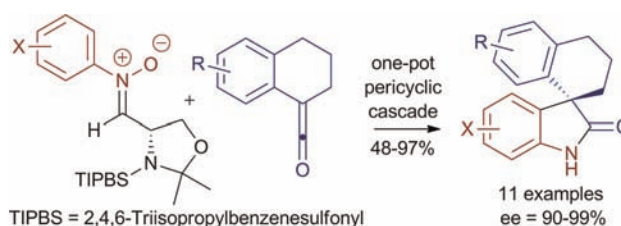


Asymmetric Pericyclic Cascade Approach
to Spirocyclic OxindolesEdward Richmond, Nicolas Duguet, Alexandra M. Z. Slawin, Tomáš Lébl, and
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ABSTRACT



The reaction of chiral *N*-arylnitrones with carbocyclic alkylarylketenes generates spirocyclic oxindoles in good yields and with excellent levels of enantioselectivity (90–99% ee) via a pericyclic cascade process.

Spirocyclic oxindoles are an important structural motif central to a variety of both natural products¹ and pharmaceutically relevant materials.² Synthetic routes to 3,3-disubstituted oxindoles bearing a spiro-heterocyclic framework (such as 3,3'-pyrrolidines) are relatively common.³ However, routes that access 3,3-spirocarbocyclic oxindoles, especially asymmetric strategies, are relatively less explored, with the alkaloid natural product gelsemine providing a major impetus for synthetic exploration.⁴

Prominent examples of approaches toward spirocarbocyclic oxindoles include Lewis acid mediated cyclizations,⁵ adaptations of classic Fischer indole chemistry and other [3,3]-sigmatropic rearrangements,⁶ radical cyclizations,⁷ catalytic asymmetric domino/tandem processes,⁸ as well as transition-metal- and organo-catalyzed asymmetric cycloadditions,⁹ among others.¹⁰ Overman's extensive

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intramolecular Heck studies have been used to great effect in the synthesis of both gelsemine¹¹ and spirotryprostatin B,¹² and epitomize the principal strategies employed in construction of these motifs. Much attention is now focused upon asymmetric variants of these reactions.¹³

We have previously developed an asymmetric route to 3,3-oxindoles (up to 91% ee) through treatment of isolable alkylarylketenes with Garner's aldehyde derived *N*-arylnitrones.¹⁴ A computational rationale and optimization of the observed stereoselectivity in this process, consistent with a pericyclic cascade comprising a [3 + 2]-cycloaddition followed by [3,3]-sigmatropic rearrangement, has been reported.¹⁵ Herein, we apply this methodology to the synthesis of a range of achiral and chiral 3,3-spirocarbocyclic oxindoles, while demonstrating the robustness of this process by using ketenes prepared in situ (Figure 1).

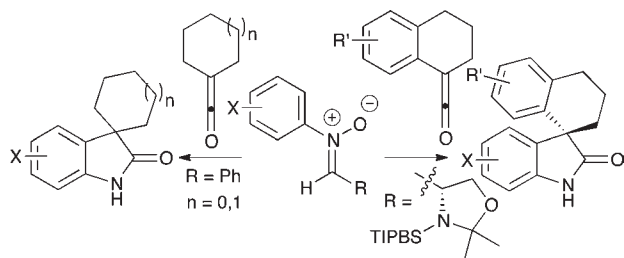


Figure 1. Proposed synthesis of spirocyclic oxindoles.

Initial proof of concept studies used zinc-mediated reduction of acyl bromide **1** to access pentamethyleneketene **2** in situ,¹⁶ with addition of nitron **3** giving oxindole **6** in 65% yield. Following this procedure, 5-substituted oxindoles **7** and **8** were prepared in 48 and 56% yield, respectively, from the corresponding 4-substituted *N*-arylnitrones (Figure 2).

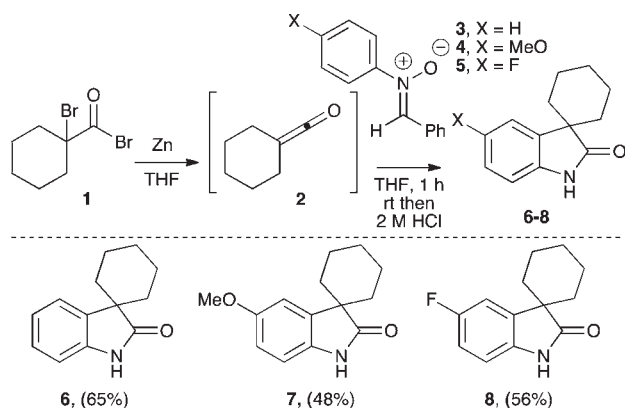


Figure 2. Initial proof of concept study.

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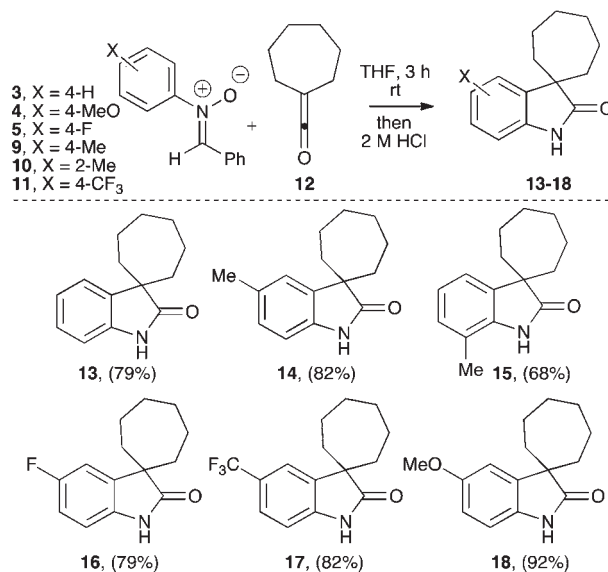
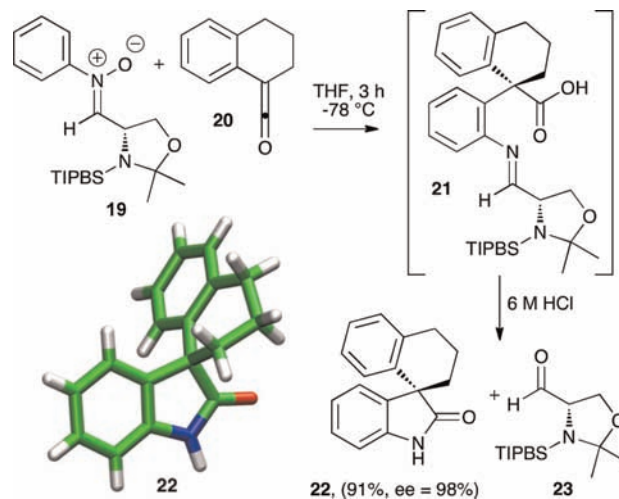


Figure 3. Synthesis of 3,3-spirocyclic oxindoles.

Scheme 1. Asymmetric Spirooxindole Formation and Molecular Representation of X-ray Structure of **22**



Further investigations used the known, stable hexamethyleneketene **12**¹⁷ in combination with a range of *N*-arylnitrones. In an optimized procedure, treatment of

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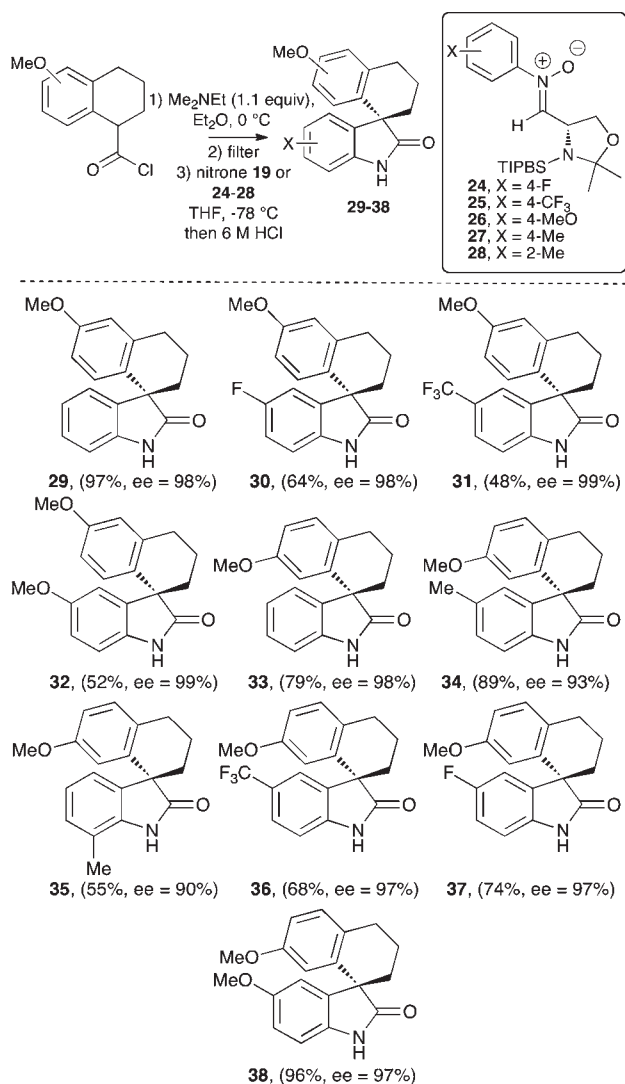


Figure 4. Asymmetric spirocyclic oxindole synthesis; scope.

nitron **3** with ketene **12** gave oxindole **13** in 79% isolated yield. Similar levels of reactivity were observed with a range of substituted *N*-arylnitrones incorporating both electron-donating and -withdrawing 4-substituents, as well as 2-substitution, giving selectively the respective 5- and 7-substituted oxindoles **14–18** that were isolated in good to excellent yields (68–92%) (Figure 3).

An asymmetric spirocyclic oxindole synthesis was next investigated using TIPBS = 2,4,6-triisopropylbenzenesulfonyl nitron **19** and known, isolable ketene **20**.¹⁸ In preliminary studies, low yields of the oxindole **22** were obtained, with intermediate imino acid **21** (99:1 dr) isolated as the major component of the crude reaction mixture.¹⁹ In contrast to our previous studies,¹⁴ spirocyclic imino acid **21** is stable to mild acidic hydrolysis and concomitant

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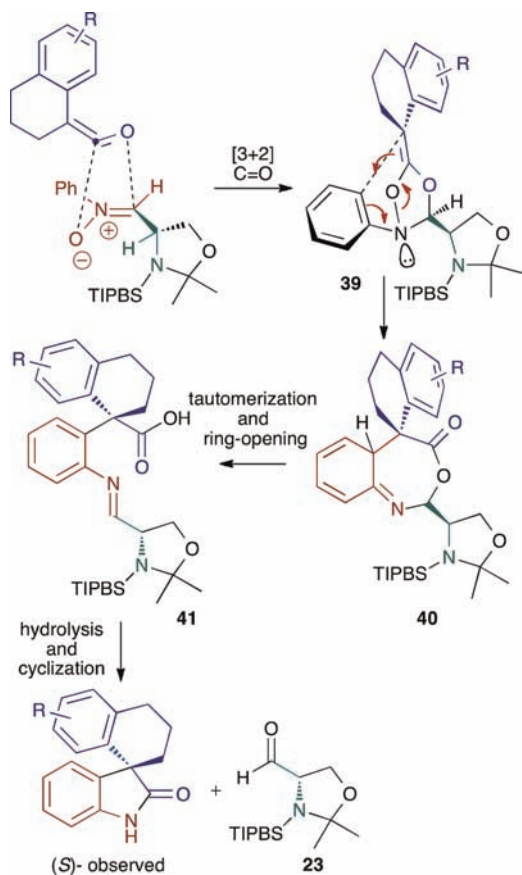


Figure 5. Proposed mechanism and rationalization of stereocontrol.

cyclization. However, the use of more forcing acidic conditions as a workup step (6 M HCl) ensured complete imine hydrolysis and cyclization to the desired oxindole (Scheme 1). In an optimized process, treatment of nitron **19** with ketene **20** gave, after aqueous workup, the desired asymmetric oxindole **22** in 91% yield and 98% ee (Scheme 1), with spectroscopic data in agreement with that previously reported for the racemate by Padwa.^{5a} The absolute configuration within (*S*)-**22** was confirmed by single-crystal X-ray diffraction,²⁰ with the observed sense of asymmetric induction consistent with our previous work using simple disubstituted alkylarylketenes.¹⁴

Having demonstrated in our initial studies that crude solutions of ketene are tolerated in this reaction process, the generality of this asymmetric process was investigated by treatment of a series of TIPBS-substituted *N*-arylnitrones **24–28** with in situ prepared carbocyclic alkylarylketenes. The desired ketenes were prepared via

(20) Crystallographic data for **22** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 871574.

(21) A one-pot preparation was also investigated; however, in the presence of base, the nitron and acid chloride form, through a rearrangement process, the amide rather than the ketene. For further details, see: Heine, H. W.; Zibuck, R.; VandenHeuvel, W. J. A. *J. Am. Chem. Soc.* **1982**, *104*, 3691–3694.

dehydrohalogenation of the corresponding acid chloride with Me₂NEt, readily synthesized from the requisite tetralone in a scalable, multigram procedure (see the Supporting Information), and were used as crude solutions in THF after filtration of Me₂NEt·HCl.²¹ This process is tolerant of 2- and 4-substitution within the *N*-aryl unit of the chiral nitron, allowing selective access to the corresponding 5- and 7-substituted oxindoles **29**–**38** that were isolated in good yield (48–97%) and excellent ee (90–99%) (Figure 4).²²

In congruence with the previous mechanistic elucidation of this transformation,¹⁵ the observed asymmetry can be rationalized through initial enantioselective [3 + 2] cycloaddition of nitron across the ketene C=O bond, with preferential *anti*-addition with respect to the aryl portion of the ketene. Facial selectivity in this cycloaddition is governed by 1,3-allylic strain in the nitron chiral auxiliary, generating

(22) The absolute configurations of **29**–**38** were assigned by analogy to that established for oxindole **22**.

(23) To demonstrate the recyclability of TIPBS nitron **19**, the following representative experiment was performed. TIPBS nitron **19** (0.075 g, 0.154 mmol) and ketene **20** (0.029 g, 0.185 mmol) gave, under standard reaction conditions (see the Supporting Information; general procedure **F**), oxindole **22** (0.035 g) in 90% yield and 98% ee with chiral aldehyde **23** (0.045 g) recovered in 74% yield. Aldehyde **23** (0.045 g, 0.114 mmol) was then treated with PhNHOH (0.015 g, 0.137 mmol), regenerating nitron **19** (0.055 g) in 99% yield after trituration with petroleum ether. The regenerated TIPBS nitron **19** (0.050 g, 0.103 mmol) and ketene **20** (0.020 g, 0.123 mmol) gave oxindole **22** (0.012 g) in 46% yield and 91% ee with chiral aldehyde **23** (0.025 g) once more recovered in 61% yield.

stereodefined cyclic intermediate **39**. Subsequent [3,3]-sigmatropic rearrangement yields further intermediate **40** that undergoes rearomatization and tautomerization to yield imino acid precursor **41**. Acidic hydrolysis and cyclization then yields the oxindole with excellent levels of enantiocontrol and also regenerates chiral aldehyde **23** (Figure 5).²³

In conclusion, we have extended the scope of this chiral auxiliary approach to the asymmetric synthesis of spirocyclic oxindoles (up to 99% ee). This methodology is robust, tolerating *in situ* generated crude ketene solutions without the need for their isolation, improving the versatility of this process and avoiding the need for ketene purification by distillation. Further extensions of this methodology including the development of a catalytic version of this transformation and applications in natural product synthesis are ongoing and will be reported in due course.

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Supporting Information Available. Experimental procedures and spectroscopic and HPLC data for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.