

Highly Enantioselective One-Pot Synthesis of Spirocyclopentaneoxindoles Containing the Oxime Group by Organocatalyzed Michael Addition/ISOC/Fragmentation Sequence

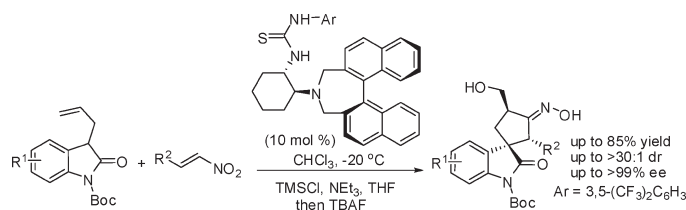
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ABSTRACT



A highly diastereo- and enantioselective organocatalytic protocol for the synthesis of biologically important spirocyclopentaneoxindoles containing the oxime functional group from easily accessible 3-allyl-substituted oxindoles and nitroolefins has been developed by a one-pot Michael addition/ISOC/fragmentation sequence.

The spirocyclic oxindole scaffold is featured in a large number of natural products and medicinally

relevant compounds.^{1–5} Thus, considerable efforts have been devoted toward the development of enantioselective methods to construct these spiroheterocyclic systems. Remarkable advances have been made on the enantioselective synthesis of pyrrolidinyl-spirooxindole compounds and analogues¹ as well as six-membered spirocyclic oxindole derivatives.² Quite recently enantioselective syntheses of spirocyclic 2-oxindoles bearing a cyclopentene motif have also been developed via tertiary phosphine or amine catalyzed [3 + 2] cycloaddition reactions.³ In contrast, efficient methodologies for the direct catalytic asymmetric construction of the spirocyclopentaneoxindole scaffold have been rarely disclosed.

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The 3-spirocyclopentane-2-oxindoles represent an important class of substructures which are widely encountered in a number of biologically active natural alkaloids⁴ (Figure 1) and drug candidates.⁵ However, the *direct* catalytic enantioselective construction of these molecules remains a daunting task. Generally their asymmetric syntheses rely on chiral substrate-controlled methods. To the best of our knowledge, so far there are only two general reports concerning the catalytic enantioselective synthesis of spirocyclopentaneoxindole scaffolds. Trost and co-workers reported an elegant Pd-catalyzed asymmetric [3 + 2] cycloaddition of methyleneindolinones for the synthesis of spirocyclopentaneoxindoles.⁶ During the course of our current investigations, Barbas and co-workers represented the only organocatalytic highly enantioselective synthesis of bispirocyclic oxindole derivatives through a cascade Michael-aldol reaction.⁷ However, the use of activated methyleneindolinones connected to a ketone or ester moiety as highly reactive Michael acceptors was required in this cascade process wherein the cascade reaction with methyleneindolinones connected to an aromatic group did not proceed at all.⁷ Additionally, the diastereoselectivity of the cascade reaction displayed a dependence on the structure of 3-substituted oxindole substrates. For example, the diastereoselectivity was high for reactions with aryl 3-substituted oxindoles, whereas it became moderate with alkyl 3-substituted oxindoles.⁷ Therefore, it is highly desirable to develop a new and efficient direct catalytic asymmetric method to synthesize structurally diverse spirocyclopentaneoxindoles.

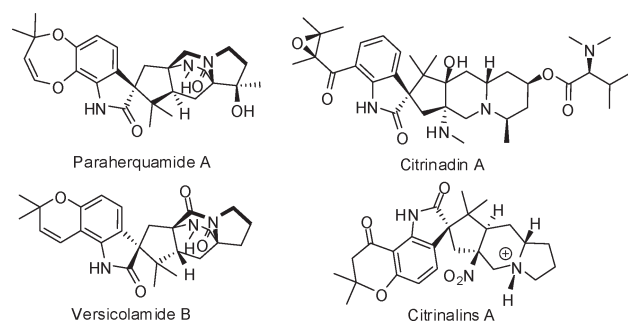


Figure 1. Representative natural products containing the spirocyclopentaneoxindole scaffold.

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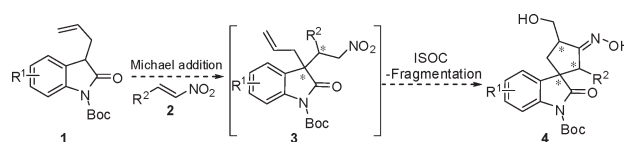
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Recently asymmetric organocatalytic multistep one-pot reactions have emerged as a powerful tool to efficiently and stereoselectively construct complex molecules from readily available simple starting materials in a single operation.⁸ As part of our research interest in developing novel catalytic asymmetric reactions,⁹ we herein describe a one-pot, organocatalyzed enantioselective intermolecular Michael addition (ISOC)/intramolecular silyl nitronate-olefin cycloaddition (ISOC)/fragmentation reaction which provided biologically important spirocyclopentaneoxindoles containing the oxime functional group with three stereocenters including one spiroquaternary stereocenter in good yields (up to 85%) with excellent diastereoselectivity (up to >30:1 dr) and enantioselectivity (up to >99% ee) (Scheme 1).

Although there have been several reports of intramolecular silyl nitronate-olefin cycloaddition (ISOC),¹⁰ to our knowledge, no processes have been described that employ ISOC to catalytic asymmetric syntheses of spirocyclic oxindoles.

Scheme 1. Strategy for the One-Pot Organocatalytic Asymmetric Synthesis of Spirocyclopentaneoxindoles



Logically, a highly diastereo- and enantioselective Michael addition of 3-allyl-substituted oxindoles to nitroolefins would be one critical element for an organocatalyzed enantioselective one-pot intermolecular Michael addition/ISOC/fragmentation sequence to the optically active spirocyclopentaneoxindoles. Despite the potential utility of this reaction due to the versatile transformations of olefin and nitro groups, to our knowledge, there is only one report concerning the organocatalytic asymmetric Michael addition of 3-allyl-substituted oxindole to nitroolefins.^{11c} The reaction diastereoselectivity is still modest for various aromatic nitroolefin substrates (3:1–9:1 dr).^{11c} Both good enantioselectivity and high diastereoselectivity (>10:1) for 3-allyl-substituted oxindoles to aromatic nitroolefins have not been achieved so far. Therefore, it is highly desirable to develop a highly diastereo- and enantioselective organocatalytic Michael addition of 3-allyl-substituted oxindoles to nitroolefins.

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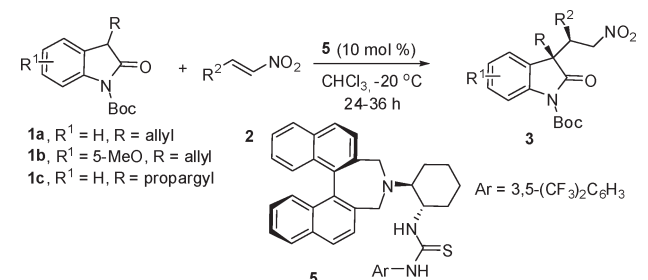
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Recently, we reported a new class of bifunctional thiourea catalysts bearing central and axial chiral elements, which showed good performance in the catalytic asymmetric addition of 1,3-dicarbonyl compounds to nitroolefins.^{12,13} To extend the interest of these bifunctional organocatalysts in asymmetric catalysis, we set out to determine if these catalysts could exhibit high diastereo- and enantioselectivity in the catalytic asymmetric Michael addition of 3-allyl-substituted oxindoles to nitroolefins. Also, we hoped to expand the application of these organocatalysts for new substrates and new types of asymmetric reactions.

Gratifyingly, with our bifunctional thiourea catalyst **5**, a significant improvement in dr was observed. Moreover, an improvement in ee was observed (entries 1–5, Table 1). Absolute configurations of **3a–d** were determined by comparing the HPLC retention times of products with those of literature data.^{11c} Given the importance of functionalized 1,6-dienes for the synthesis of various carbocycles,¹⁴ we tested the Michael addition of 3-allyl oxindole **1a** to 1-nitro-4-phenyl butadiene **2e**. We found that the desired chiral 1,6-diene **3e** was obtained in good dr and ee values (entry 6). It is noteworthy that no 1,6-addition was observed.¹⁵ The substituted 3-allyl oxindole was also tested, giving the desired product **3f** in 85% yield with 20:1 dr and >99% ee values (entry 7). Due to the rich chemistry involved with the alkynyl group, we also investigated the Michael addition of a previously unexplored 3-propargyl-substituted oxindole **1c** in the presence of catalyst **5**. The 3-propargyl-substituted oxindole **1c** was also shown to be a highly efficient substrate in this process (98–99% ee, 8:1–30:1 dr, entries 8–12). Notably, the optically active 1,6-enyne **3k** could be obtained with a complete regioselectivity in 10:1 dr and 99% ee (entry 12). Transition-metal-catalyzed cycloisomerization reactions of 1,6-enynes have appeared as highly attractive and unique tools for the synthesis of

various types of cyclic compounds.¹⁶ The stereochemically well-defined 1,6-enyne obtained from this methodology might potentially have applications in the construction of complex polycyclic molecules.

Table 1. Organocatalytic Asymmetric Michael Addition of 3-Allyl- and 3-Propargyl Substituted Oxindoles to Nitroolefins^a



entry	1	2 (R ²)	yield (%) ^b	dr ^c	ee (%) ^d
1 ^e	1a	Ph	87	>30:1	97
2	1a	Ph	90	>30:1 (6:1) ^f	>99 (94) ^f
3	1a	4-Br-C ₆ H ₄	89	>30:1 (6:1) ^f	94 (91) ^f
4	1a	4-MeO-C ₆ H ₄	96	>30:1 (5:1) ^f	94 (90) ^f
5	1a	<i>n</i> -C ₇ H ₁₅	92	20:1 (>20:1) ^f	98 (94) ^f
6	1a	(<i>E</i>)-PhCH=CH	90	12:1	93
7	1b	Ph	85	20:1	>99
8	1c	Ph	84	17:1	98
9	1c	4-MeO-C ₆ H ₄	80	8:1	>99
10	1c	4-CF ₃ O-C ₆ H ₄	90	14:1	99
11	1c	4-CF ₃ -C ₆ H ₄	90	30:1	>99
12	1c	(<i>E</i>)-PhCH=CH	86	10:1	>99

^aThe reactions were performed with oxindoles **1** (0.1 mmol) with nitroolefins **2** (1.1 equiv) in the presence of 10 mol % catalyst **5** in 0.3 mL of solvent at –20 °C. ^bIsolated yields. ^cDetermined by ¹H NMR analysis. ^dThe ee of major diastereoisomer determined by HPLC analysis using a chiral stationary phase. ^eCH₂Cl₂ was used as solvent. ^fThe results in parentheses are those of Barbas' report (see ref 11c).

Having proved excellent stereocontrol performance of the organocatalyst **5**, we next turned our attention to investigate sequential one-pot Michael addition/ISOC/fragmentation. Despite the potential of ISOC, there is no report on the employment of this method to the asymmetric synthesis of spirocyclic oxindoles. To explore the feasibility of such a strategy, we initially examined the diastereoselective ISOC/fragmentation sequence with compound **3a** obtained through the Michael addition above as the building block. Pleasingly, the desired ISOC/fragmentation proceeded smoothly to afford the optically active spirocyclopentaneoxindole **4a** in 84% yield and >99% ee (eq 1). The complete transfer of chirality in this reaction could be explained through the preferred

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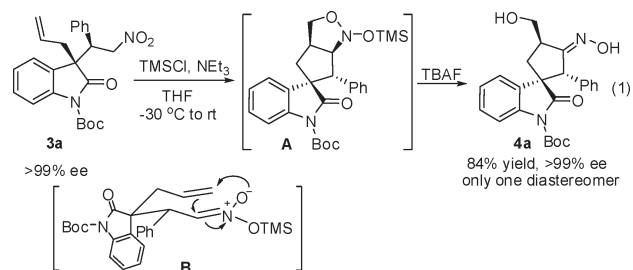
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nitronate conformation **B**¹⁷ driven by a 1,3-allylic strain which provided the transient isoxazolidine **A** in a highly diastereoselective manner. Surprisingly, the ISOC/fragmentation reaction with 3-propargyl-substituted Michael adduct **3g** gave a complex and inseparable mixture.



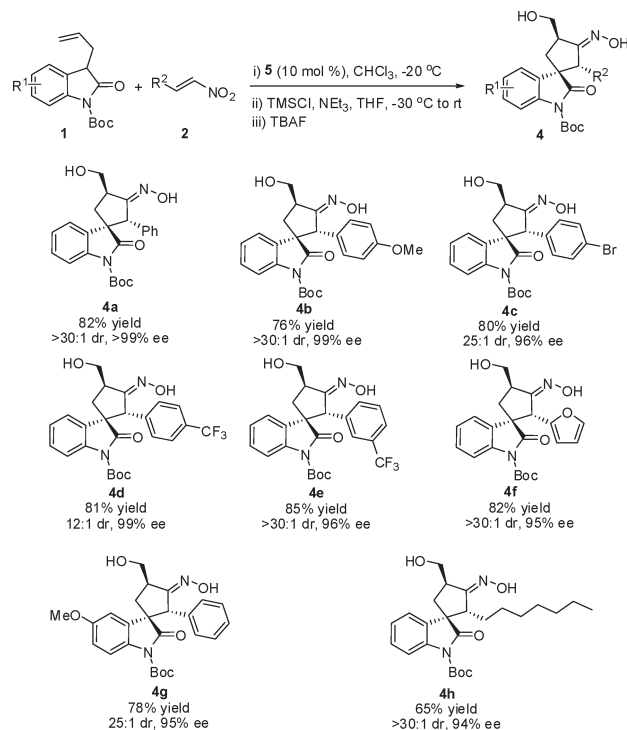
Then we investigated a one-pot organocatalyzed intermolecular Michael addition/ISOC/fragmentation sequence. As shown in Scheme 2, with our organocatalyst **5**, a wide variety of spirocyclopentaneoxindoles containing an oxime functional group were obtained in good yields with high diastereo- (12:1→30:1 dr) and enantioselectivities (94→99% ee). Oximes represent an important class of compounds with potential pharmaceutical properties¹⁸ and are also a versatile functional group since they can be easily transformed into various functional groups. Thus, this would make these newly synthesized spirocyclopentaneoxindole derivatives attractive candidates for drug discovery.

In summary, a highly diastereo- and enantioselective organocatalytic protocol for the synthesis of biologically important spirocyclopentaneoxindoles containing the oxime functional group from easily accessible 3-allyl-substituted oxindoles and nitroolefins has been developed by a one-pot Michael addition/ISOC/fragmentation sequence. Moreover, we have developed a highly syn-selective (up to > 30:1 dr) and enantioselective (up to > 99% ee) Michael addition of 3-allyl- and 3-propargyl substituted oxindoles to nitroolefins catalyzed by a novel bifunctional thiourea

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Scheme 2. One-Pot Organocatalytic Asymmetric Synthesis of Spirocyclopentaneoxindoles by Michael Addition/ISOC/Fragmentation



organocatalyst with central and axial chiral elements recently developed by our group.

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Supporting Information Available. Representative experimental procedure, compound characterization data, and copies of spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.