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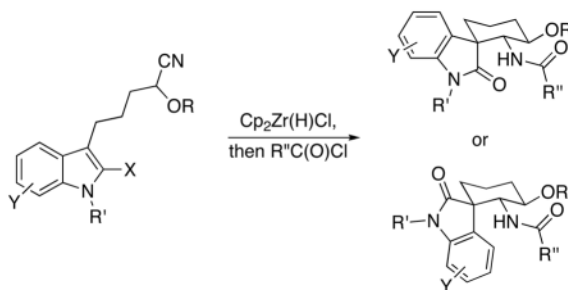
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## Stereoselective Synthesis of Spirooxindole Amides through Nitrile Hydrozirconation

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### Abstract



Spirooxindole amides can be prepared by the intramolecular addition of functionalized indoles into acyliminium ions that are accessed from nitriles by hydrozirconation and acylation. The stereochemical outcome at the quaternary center was controlled by the steric bulk of the substituent at the 2-position of the indole unit. The products are well-suited for diversification to prepare libraries.

The spirooxindole unit is earning the status of “privileged structure” in synthetic and medicinal chemistry, as evidenced by a number of recent reviews<sup>1</sup> and the rapid development of new methods for their synthesis.<sup>2</sup> The biological activity that a number of spirooxindoles exhibit has spawned library syntheses<sup>3</sup> that led to the identification of potent MDM2 inhibitors,<sup>4</sup> adjuvants of the actin polymerization inhibitor latrunculin B,<sup>3a</sup> and antimalarial agents.<sup>5</sup> We have developed a new protocol for stereoselective spirooxindole synthesis in accord with our interest in preparing structurally diverse amides through nucleophilic addition reactions to acylimines. These acylimines derive from nitriles via a sequence of nitrile hydrozirconation followed by acylation.<sup>6</sup> The oxindole preparation proceeds (Scheme 1) through the generation of indolyl acylimines (**1**) to form stereoisomeric spirooxindoles **2** or **3** through a Friedel-Crafts alkylation reaction, with the configuration of the quaternary stereocenter being controlled by the steric bulk of the substituent at the 2-position of the indole. The products of this sequence are structurally unique and contain multiple sites for diversification, making the route well-suited for applications in diversity-oriented synthesis.

Chloroindoles, shown by Horne and co-workers<sup>7</sup> to be effective oxindole enolate surrogates, and silyloxyindoles served as the nucleophilic components for the cyclization reactions in this study. A representative route for their preparation is shown in Scheme 2. Aldehyde **4**, prepared through a known<sup>8</sup> periodate mediated cleavage of commercially-available 7-

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 Supporting Information Available. Experimental protocols and spectral characterization of all new products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

octene-1,2-diol, was converted to cyanohydrin ether **5** through a one-pot sequential acetalization reaction with BnOTMS and BiBr<sub>3</sub> followed by TMSCN addition.<sup>9</sup> Ozonolysis and Fischer indole synthesis with benzyl phenylhydrazine provided **6**. Cyclization substrate **7** was prepared by chlorination with NCS. The corresponding silyloxyindole **8** was prepared by oxidizing **6** with DMSO and HCl through a variation on an established<sup>10</sup> protocol to form the oxindole followed by silylation by TIPSOTf and Et<sub>3</sub>N.<sup>11</sup>

Spirooxindole formation was demonstrated (Scheme 3) by subjecting **7** to Cp<sub>2</sub>Zr(H)Cl<sub>12</sub> followed by acylation with hydrocinnamyl chloride to form an acylimine<sup>13</sup> that folds preferentially into a reactive conformation (**9**) in which the benzyloxy and acylimine groups adopt pseudoequatorial orientations and the C2-center of the indole occupies a pseudoaxial orientation. The minor conformation (**10**) places the indole C2 in a pseudoequatorial orientation. Addition at the 3-position of the indole followed by hydrolysis of the chloroiminium ion intermediate provided spirooxindoles **11** and **12** in 73% and 10% yields respectively. The structures of the products were assigned based on extensive analyses of their NOESY spectra. This selectivity indicates that the aryl group is sterically more demanding<sup>14</sup> than the chlorine substituent in the transition states.

The scope of the reactions with the 2-chloroindoles is shown in Table 1. Aliphatic, branched aliphatic,  $\alpha$ ,  $\beta$ -unsaturated, and heteroatom-functionalized acid chlorides serve as suitable electrophiles for the transformation. *N*-Methoxymethylindoles are effective substrates (entries 4–9), though they are less reactive than the *N*-benzylindoles and in some cases require the addition of a Sc(OTf)<sub>3</sub> to promote the cyclization (entries 6 and 7). This reactivity difference can be ascribed to the inductive attenuation of indole nucleophilicity by the methoxy group. When Sc(OTf)<sub>3</sub> is used to promote the cyclization the stereoisomer that has a *cis*-relationship between the amide and benzyloxy groups forms as a minor product, presumably as a result of a competing chelation-controlled transition state. Aromatic acid chlorides can be used as electrophiles for this transformation, though product yields were <25% (not shown). Chlorination at the indole 4- and 6-positions, in anticipation of further structural manipulations of the spirooxindole products, is compatible with the reaction conditions (entries 8 and 9). These substrates reacted somewhat less efficiently than the corresponding non-halogenated substrate due to inductive deactivation by the chloro group and, in the case of **21**, steric interactions in the transition state, but useful quantities of the products could be isolated.

In accord with our interest<sup>15</sup> in exploring the impact of stereochemical diversity<sup>16</sup> in library synthesis, we sought to devise a protocol for preparing spirooxindoles in which the quaternary carbon is inverted. This can be achieved by changing the chloro substituent at the 2-position of the indole structure to a group that is more sterically demanding than the arene ring. Utilizing silyloxyindole substrate **8** in the cyclization reactions accomplished this objective (Table 2). Several issues related to these transformations are noteworthy. The overall yield of spirooxindole products from these reactions is comparable to the yields from the chloroindole substrates, indicating that the potentially labile enolsilane moiety is compatible with the reaction conditions. The reactions of **8** are slower than the reactions of the chloroindole substrates and require a full equivalent of Lewis acid despite the presence strongly electron donating silyloxy group. We attribute this effect to the steric demands in the cyclization transition states. Control of the quaternary center is good to excellent, though the *trans*:*cis* ratio between the alkoxy and amide groups is lower than what was observed for the chloroindole substrates. The *trans* and *cis* stereoisomers were readily separable by flash chromatography, with the *cis*-isomer reproducibly being the less polar stereoisomer. Based on the unusually downfield <sup>1</sup>H NMR chemical shift of the C4 hydrogen in the *cis*-isomer, we postulate that the polarity arises from a hydrogen bond between the oxygen and the arene hydrogen. Changing the Lewis acid from Sc(OTf)<sub>3</sub> to ZnCl<sub>2</sub> results in the *cis*-isomer being

the major product (entry 5) as a result of chelation between the acylimine and the benzyloxy group.

The spirooxindole products have numerous points for structural diversification as a prelude to library synthesis. Several of these opportunities are shown in Scheme 4. Benzyl ether cleavage was effected through standard hydrogenolysis conditions to afford the corresponding alcohol, which can undergo subsequent acylation as seen in the conversion of **17** to **29**. The acrylamide products are very versatile, undergoing Heck reaction<sup>17</sup> to form **30**, thiolate addition<sup>18</sup> to form **31**, and cross metathesis<sup>19</sup> to form **32**. Regioselective oxindole bromination can be achieved with NBS, and the resulting aryl bromide engages in a Suzuki reaction,<sup>20</sup> as seen in the preparation of **33** from **11**.

We have shown that indolyl cyanohydrin ethers can be converted to spirooxindole amides through a sequence of hydrozirconation, acylation, and intramolecular nucleophilic addition. Three of the four possible relative stereochemical outcomes can be prepared as major products through this process. The quaternary stereocenter can be controlled by adjusting the steric bulk of the substituent at the 2-position of the indole, while the relative configuration between the amide and benzyloxy groups can be influenced by choosing a chelating or non-chelating Lewis acid to promote the cyclization. The capacity for stereochemical diversification, the abundant opportunities for functionalizing the products, and the wide range of biological activities that spirooxindoles effect make this method a very attractive entry to library synthesis.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

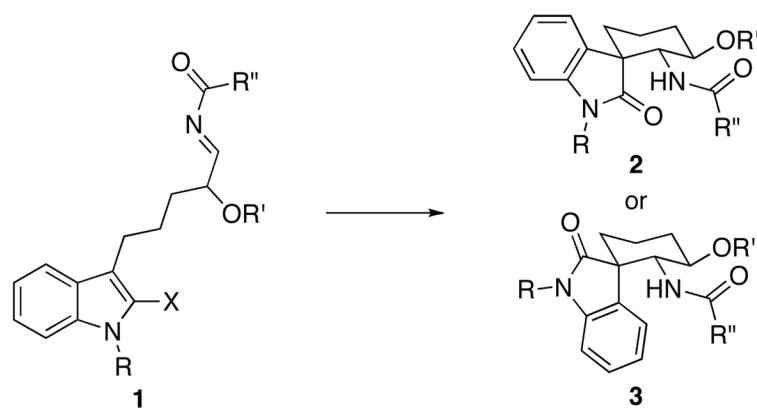
## Acknowledgments

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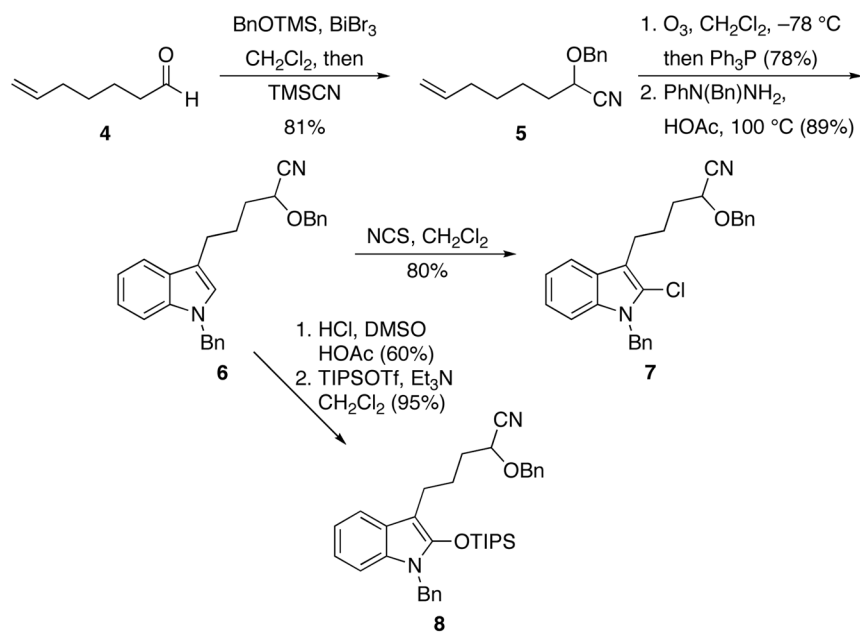
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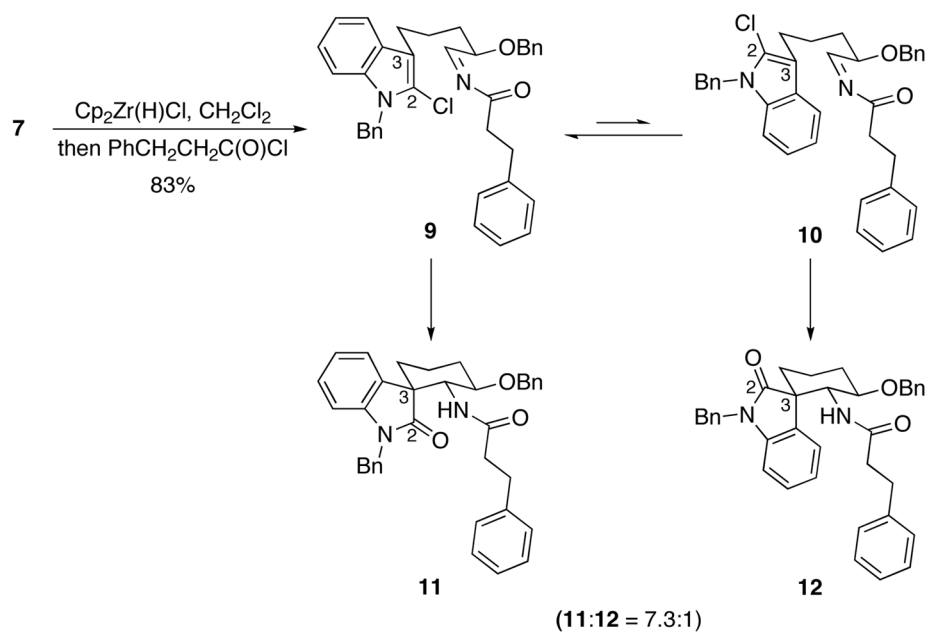
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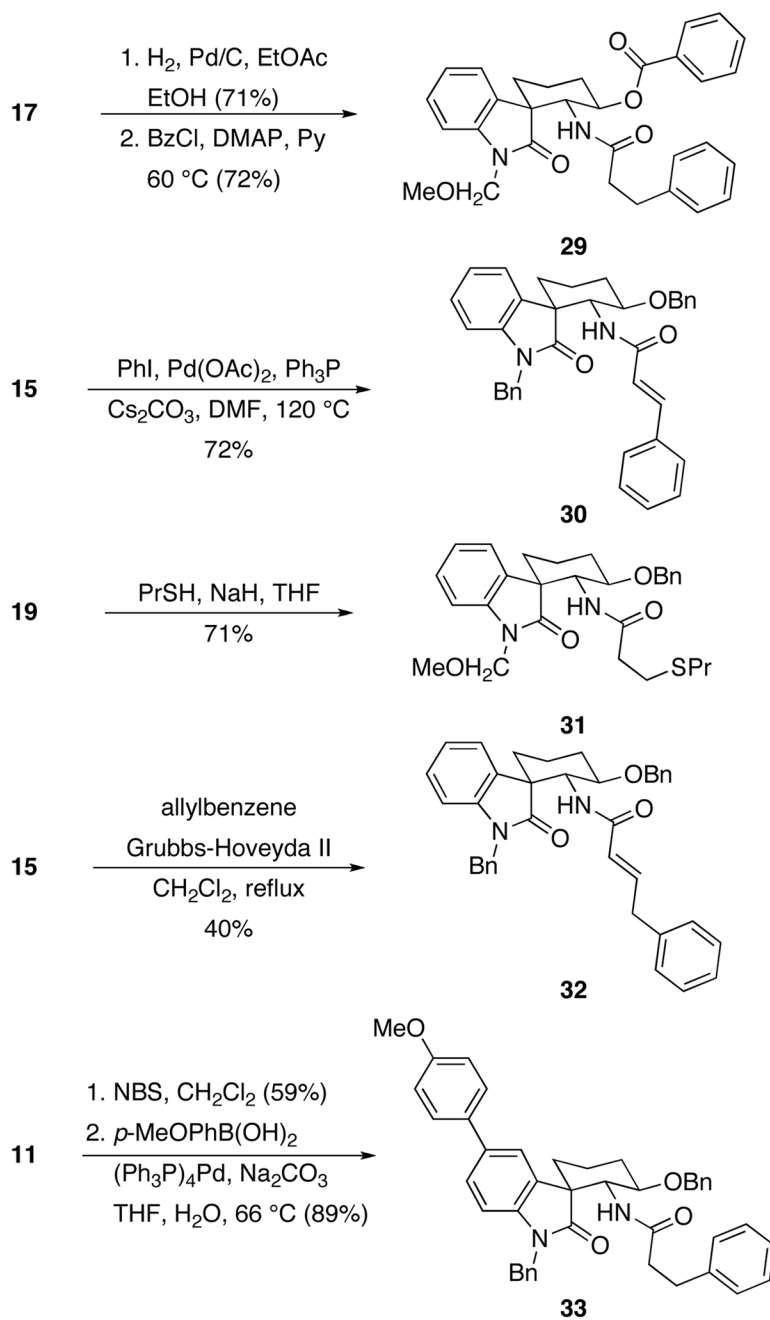
**Scheme 1.**  
Spirooxindole formation through acylimine addition.



**Scheme 2.**  
Substrate synthesis.



**Scheme 3.**  
Oxindole formation through nitrile hydrozirconation, acylation, and intramolecular addition.

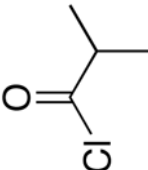
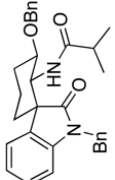
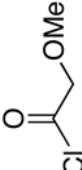
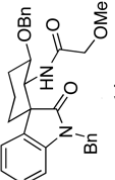
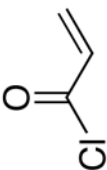
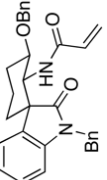
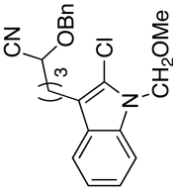
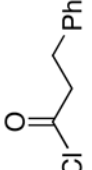
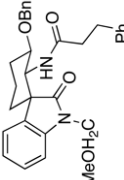
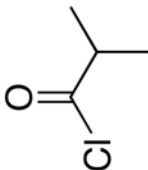
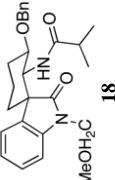
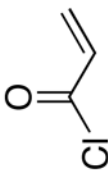
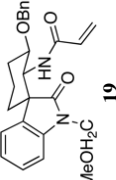


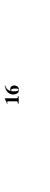
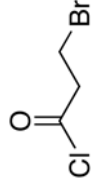
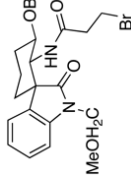
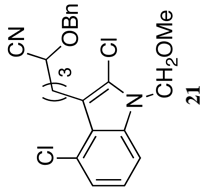
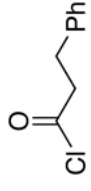
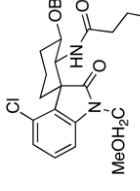
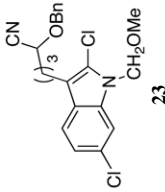
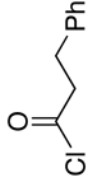
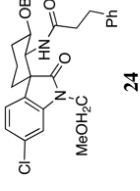
**Scheme 4.**  
Spirooxindole functionalizations.



Table 1

Chloroindole reaction scope.<sup>a</sup>

entry	substrate <sup>b</sup>	acid chloride	product	dr <sup>c</sup>	yield (%) <sup>d</sup>
1	7			3.6:1	87
2	7			9.1:1 <sup>e</sup>	46
3	7			20:1	53
4				15:1	64
5	16			11.8:1	51
6 <sup>f</sup>	16			8.2:1 <sup>e</sup>	46

entry	substrate <sup>b</sup>	acid chloride	product	dr <sup>c</sup>	yield (%) <sup>d</sup>
7 <sup>f</sup>				6.7:1 <sup>e</sup>	54
8				1:0	36
9				1:0	50

<sup>a</sup> Representative procedure: Cp<sub>2</sub>Zr(H)Cl (1.25 equiv) was added to a 0.1 M solution of the indole nitrile in CH<sub>2</sub>Cl<sub>2</sub> under Ar. After stirring at rt for 15 min the acid chloride was added. The mixture stirred overnight at rt.

<sup>b</sup> See the Supporting Information for substrate synthesis schemes.

<sup>c</sup> Ratio of isolated, purified diastereomers.

<sup>d</sup> Combined yield of diastereomers.

<sup>e</sup> Single isomer at the quaternary center - dr refers to the ratio of *trans* and *cis* amido ethers.

<sup>f</sup> Sc(OTf)<sub>3</sub> (0.1 equiv) was added to promote cyclization.

Table 2

Cyclizations with silyloxyindole substrates.<sup>a</sup>

entry	substrate	acid chloride	major product	dr <sup>b</sup>	yield(%) <sup>c</sup>
1	8			4.1:1 (2.1:1)	68 (46)
2	8			12:1 (1.7:1)	67 (42)
3	8			7.2:1 (3.7:1)	38 (30)
4	8			4.5:1 (2.4:1)	66 (47)
5 <sup>d</sup>	8			18:1 (1.8:1)	58 (37)

<sup>a</sup> Representative procedure: Cp<sup>\*</sup>Zr(H)Cl (1.25 equiv) was added to a 0.1 M solution of the indole nitrile in CH<sub>2</sub>Cl<sub>2</sub> under Ar. After stirring at rt for 15 min the acid chloride and Sc(OTf)<sub>3</sub> were added. The mixture stirred overnight at rt.

<sup>b</sup> The ratio refers to the quaternary center. The value in parentheses refers to the ratio of the major stereoisomer to all other stereoisomers.

<sup>c</sup> Combined yield of all stereoisomers. The yield of the major stereoisomer is in parentheses.

<sup>d</sup>ZnCl<sub>2</sub> was used instead of Sc(OTf)<sub>3</sub>.

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