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Stereocontrolled Synthesis of Spirooxindoles Through Lewis Acid Promoted [5+2]-Annulation of Chiral Silylalcohols

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Abstract

The enantioselective synthesis of stereochemically and structurally diverse spirocyclic oxindoles by [5+2]-annulation of chiral crotylsilanes bearing a primary alcohol is described. The annulation products were further elaborated to polycyclic oxindoles by Pd (0) catalysis.

Spirooxindoles are commonly occurring heterocyclic ring systems found in many natural products and pharmaceuticals.¹ A range of biologically active compounds possessing the spiropyrrolidine framework is well documented.^{1a–c} For instance, coeruleosine (**1**), the simplest spirooxindole found in nature, displays a local anaesthetic effect.^{2a,b} Polycyclic

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Supporting Information Available Complete experimental procedures and compound characterization data including X-ray crystal structures for *cis*-**7a**, *trans*-**7a**, **7b** and **12**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

alkaloid pteropodine (**2**) has a long history for its medicinal applications.^{2c,d} The recent discovery of small-molecule MDM2 inhibitors MI-219 (**3**) and its analogs has led to their advanced preclinical development as cancer therapeutics^{1d,e} (Figure 1). Although azaspirooxindoles have been extensively studied, the corresponding oxaspirocyclic oxindoles remain underdeveloped.³ Recent approaches to oxaspirooxindoles include Lewis acid-promoted annulation,^{4a} oxidative cycloaddition,^{4b} RCM,^{4c} photocycloaddition,^{4d} base-catalyzed condensation^{4e} and dipolar cycloaddition.^{4f} However, very few examples demonstrate enantioselective preparation of these compounds. Herein, we describe an efficient protocol for accessing functionalized oxaspirooxindoles with high diastereo- and enantioselectivity by mild Lewis acid promoted [5+2]-annulation of chiral silylalcohols.⁵

As part of our ongoing investigations aimed at expanding the scope of organosilane reactivity, the [4+2]-annulations of crotylsilane **4** and its many structural and stereochemical counterparts have been previously documented.⁶ In that regard, we envisioned ring-expanded oxepene templates could be constructed *via* analogous [5+2]-annulations^{6d} of silylalcohol (*S*)-**5** (Scheme 1). Preliminary screening of electrophilic annulation partners identified *N*-methyl isatin dimethyl ketal **6a** (Table 1) as a potential substrate for this ring-forming process.^{4a} The stereoselective formation of a quaternary, spirocyclic center was especially intriguing and our efforts turned towards optimizing this transformation. It was eventually found that when treated with TMSOTf, silylalcohol (*S*)-**5** cyclized with **6a** to afford oxepenyl-spirooxindole **7a** in 37% yield as a 15:1 mixture of *trans*- and *cis*-isomers (Table 1, entry 1).

Further experiments revealed that *cis*-**7a** could be preferentially prepared under appropriate conditions (Table 1, entry 2). After 10 minutes at 0 °C, the *cis*-isomer could be isolated in 70% yield (dr = 15:1). It was also observed that prolonged reaction time or increased polarity of solvents correlated with increased amounts of *trans*-**7a** (Table 1, entry 3 and 4).

The presence of *trans*-**7a** as a function of time suggested that the *cis*-product may be epimerizing to the *trans*-isomer, possibly through a spiro-ring opening mechanism involving intermediates **I** and **II** (Scheme 2).

In support of this hypothesis, polar solvents such as THF, CH₃NO₂, and CH₃CN were found to yield preferentially *trans*-**7a** after 12 h at 0 °C as compared to the lower efficiency in CH₂Cl₂ (see Supporting Information). In fact, when reactions performed in dry CH₃CN at low temperatures, indolenium ion **I**⁷ is sufficiently stable and upon aqueous quenching gave rise to isolatable amounts of diol **8** (inset). Fortunately, exposure to silica gel during purification does not influence the diastereomer ratio. Microwave irradiation of *cis*-**7a** in the presence of BF₃•OEt₂ provided the most efficient means of interconverting the stereoisomers (Scheme 2).

The structure and stereochemistry of *cis*- and *trans*-**7a** were established by X-ray crystallography (Figure 2). Analysis reveals the interatomic distance between the carbonyl oxygen and H^a in *cis*-**7a** (2.388 Å) increases to 2.627 Å (O to H^b) in *trans*-**7a**. Orienting the isatin carbonyl away from the oxepene ring lowers ground-state energy of the *trans*-isomer by approximately 3.96 kcal/mol relative to the *cis*-product.⁸ This supports our observation that the *cis*-spirocycle is the kinetic product.

A plausible mechanistic rationale for the observed stereochemical outcome of the initial annulation reaction is illustrated in Scheme 3. Formation of the (*Z*)-oxonium intermediate is favored to avoid peri interaction associated with the corresponding (*E*)-oxonium intermediate. Designating the aryl ring as the larger steric contributor,⁹ orients the carbonyl pseudo-axial. Thus, transition state **IV** is preferred and leads to the formation of *cis*-**7a** as the major diastereomer under kinetic conditions.

At this juncture, we sought to expand this methodology to include additional isatin derivatives **6b–6e** (Table 2). HPLC analyses of the spirooxindole products indicated complete chirality transfer from the starting silyl alcohol (see Supporting Information). For all cases evaluated, both *cis* and *trans* diastereomers were readily obtained in useful yields and with excellent diastereoselectivities. 4-Bromoisatin **6b** proved an exception affording only the kinetic product *cis*-**7b** (Table 2, entry 2).¹⁰ Thermal promoted epimerization failed perhaps as the result of the sterically bulky bromine, destabilizing transition state **V** en route to the *trans*-isomer. Isatin dimethylketal **6e** also provided both kinetic and thermodynamic products, however, even prolonged reaction times afforded a 7:1 mixture of *trans*- and *cis*-**7e** (Table 2, entry 5).

In order to prepare more complex spirooxindoles, we prepared silyl alcohols **9a–d** using an established protocol.¹¹ Because of the increased steric congestion the original annulation conditions described above were unable to afford useful amounts of desired product. Reoptimization led to the use of 1.0 equivalent of $\text{BF}_3 \cdot \text{OEt}_2$ in refluxing CH_2Cl_2 to provide the desired products as single diastereomers (Table 3).¹² Unlike annulations with (*S*)-**5**, no products from spiro-ring opening and reclosure pathways were observed with these cases.

Additional skeletal complexity was achieved by diversification of the annulation products through intramolecular Heck cyclization. The cyclization of **10c** under standard conditions (cat. $\text{Pd}(\text{OAc})_2$, Et_3N , 120 °C) was highly regio- and stereoselective affording the pentacyclic oxindole **11** in 86% isolated yield as a single diastereomer (Scheme 4). Proton, COSY and n.O.e NMR experiments indicated *syn*-insertion of the aryl palladium occurred at the proximal olefin carbon. Subsequent elimination involved the only available *syn*- β -hydride (H^c) to form compound **11**. The methyl bearing stereocenter was reintroduced through catalytic hydrogenation, and the stereochemistry of product **12** was determined by X-ray crystal analysis.

Cyclization of spirocycle *cis*-**7b** was also achieved with excellent regio- and stereocontrol (Scheme 5). Initially, *cis*-**7b** was treated with similar conditions as **10c**, but the unexpected olefin isomer **14** was observed as the only product. However, by adding 1.0 equivalent of silver (I) nitrate,¹³ olefin isomerization was suppressed and compound **13** was isolated in 70% yield as a single diastereomer. The [4.2.1]-bicyclic structures of **13** and **14** were determined by 1D and 2D NMR experiments.¹⁴

In summary, we have developed a convenient approach for directly accessing spirooxindoles with excellent stereocontrol from enantiomerically enriched crotylsilanes. The complexity of the spirooxindoles can be enhanced by employing different combinations of functionalized silyl alcohols or substituted isatin reaction partners. Products were further converted into fused polycyclic ring systems utilizing intramolecular Heck cyclization, thereby demonstrating skeletal variation. The [5+2]-annulation strategy nicely expands the scope of the Prins cyclization in the construction of highly functionalized spirocyclic oxindoles.¹⁵ Application of this methodology towards library synthesis and subsequent biological evaluation of its members are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Biologically active spirocyclic oxindoles.

Figure 2.
X-ray structures of *trans*-7a and *cis*-7a.

Scheme 1.
Annulations of chiral crotylsilanes.

Scheme 2.
Epimerization of *cis*-**7a** to *trans*-**7a**.

Scheme 3.
Proposed transition state.

Scheme 4.
Formation of pentacyclic oxindole.

Scheme 5.
Formation of tetracyclic oxindole.

Table 1

Optimization of the annulation of (S)-**5** with **6a**.

entry ^a	solvent	temp (°C)	time	yield ^{b,c}	dr ^d <i>cis:trans</i>
1	CH ₂ Cl ₂	23	12 h	37%	1:15
2	CH ₂ Cl ₂	0	10 min	70%	15:1
3	CH ₂ Cl ₂	0	24 h	67%	1:2
4	CH ₃ CN	0	10 min	74%	10:1

^a All reactions performed at 0.1 M with 1.0 equiv of TMSOTf.

^b Isolated yields after purification over silica gel.

^c Inseparable mixture of diastereomers.

^d Product ratios were determined by HPLC and ¹H NMR analysis of the crude material.

Table 2

[5+2]-Annulations of isatin derivatives.

entry	isatin	R ¹	R ²	R ³	R ⁴	time A	yield ^a (<i>cis:trans</i>) ^b	time B	dr ^b <i>cis:trans</i>
1	6a	H	H	H	Me	10 min	70% (15:1)	30 min	1:15
2	6b	Br	H	H	Me	30 min	62% (>20:1)	-	-
3	6c	H	H	Br	Me	30 min	65% (14:1)	30 min	1:13
4	6d	H	OMe	H	Me	5 min	71% (15:1)	30 min	1:15
5	6e	H	H	H	H	10 min	76% (>20:1)	12 h ^c	1:7

Condition A: 1.0 equiv (*S*)-**5**, 1.0 equiv TMSOTf, 0.1 M in CH₂Cl₂, 0 °C. Condition B: 1.0 equiv BF₃•OEt₂, 0.1 M in CH₃CN, μ wave, 300 W, 40 °C.

^a Isolated yields after purification over silica gel.

^b Diastereomeric ratios were determined by ¹H NMR analysis.

^c Conventional heating at 60 °C.

Table 3

Accessing more complex spirooxindoles.

entry ^a	silane	R ¹	R ¹	time	product	yield ^b	dr ^c cis:trans
1	9a	Me	Me	2 h	10a	50	>20:1
2	9a	Me	H	1 h	10b	47	>20:1
3	9b	Me	Me	2 h	10c	45	>20:1
4	9b	Me	H	1 h	10d	45	>20:1
5	9c	<i>o</i> -Br-Bn	Me	3 h	10e	60	>20:1
6	9c	<i>o</i> -Br-Bn	H	3 h	10f	58	>20:1
7	9d	propargyl	Me	5 h	10g	42	>20:1
8	9d	propargyl	H	5 h	10h	36	>20:1

^a All reactions performed at 0.1 M with 1.0 equiv BF₃•OEt₂ in refluxing CH₂Cl₂.

^b Isolated yields after purification over silica gel.

^c Diastereomeric ratios were determined by ¹H NMR analysis.