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Stereocontrolled Synthesis of Spirooxindoles through Lewis Acid-Promoted [5 + 2]-Annulation of Chiral Silyl Alcohols

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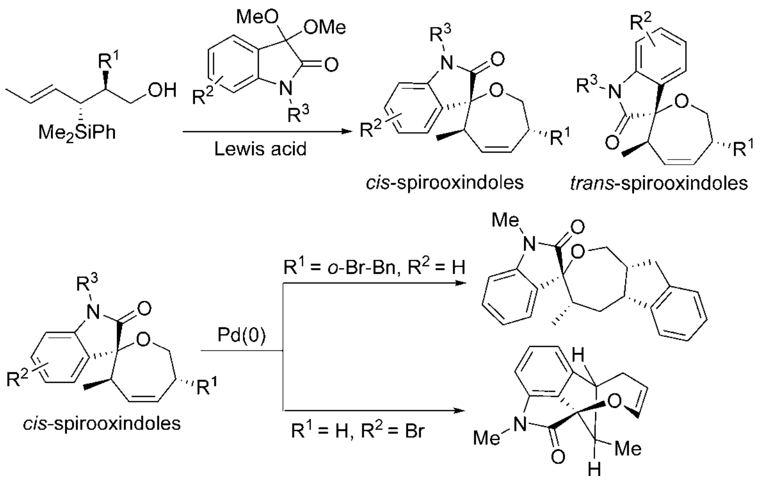
ABSTRACT



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, coerulescine (**1**), the simplest spirooxindole found in nature, displays a local anesthetic effect.[2a,b] Polycyclic alkaloid pteropodine (**2**) has a long history for its medicinal applications.[2c,d] The recent discovery of small-molecule MDM2 inhibitor MI-219 (**3**) and its analogues has led to their advanced preclinical development as cancer therapeutics[1d,e] (Figure 1). Although azaspirooxindoles have been extensively studied, the corresponding oxaspirocyclic

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(1) Recent reviews: (a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (b) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127. (c) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. Recent pharmaceuticals: (d) Shangary, S.; Wang, S. *Annu. Rev. Pharmacol. Toxicol.* **2009**, *49*, 223. (e) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Med. Chem.* **2006**, *49*, 3432.

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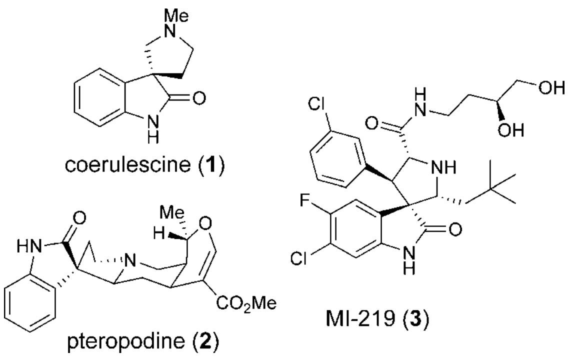
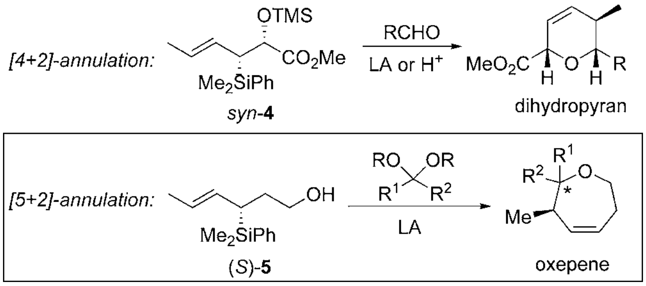


Figure 1. Biologically active spirocyclic oxindoles.

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 silyl alcohols.[5]

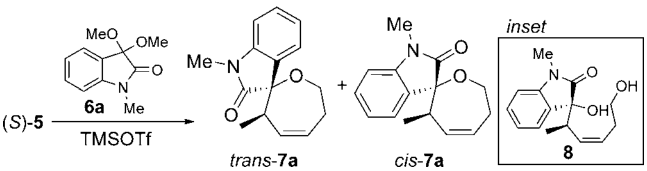
As part of our ongoing investigations aimed at expanding the scope of organosilane reactivity, the [4 + 2]-annulations of crotylsilane **4** and its many structural and stereochemical counterparts have been previously documented.[6] In that regard, we envisioned ring-expanded oxepene templates could be constructed via analogous [5 + 2]-annulations[6d] of silyl alcohol (*S*)-**5** (Scheme 1). Preliminary screening of electrophilic annulation partners identified *N*-methylisatin 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 toward optimizing this transformation. It was eventually found that when treated with TMSOTf, silyl alcohol (*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).

Scheme 1. Annulations of Chiral Crotylsilanes



Further experiments revealed that *cis*-**7a** could be preferentially prepared under appropriate conditions (Table 1, entry 2).

Table 1. Optimization of the Annulation of (*S*)-**5** with **6a**



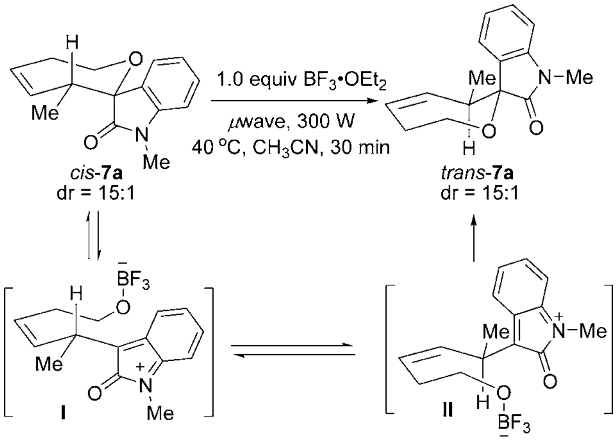
entry[a]	solvent	*T* (°C)	time	yield[b,c] (%)	dr[d] cis/trans
1	CH_2Cl_2	23	12 h	37	1:15
2	CH_2Cl_2	0	10 min	70	15:1
3	CH_2Cl_2	0	24 h	67	1:2
4	CH_3CN	0	10 min	74	10:1

[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.

After 10 min 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, CH_3NO_2, and CH_3CN were found to yield preferentially *trans*-**7a** after 12 h at 0 °C as compared to the lower efficiency in CH_2Cl_2 (see the Supporting Information). In fact, when reactions were performed in dry CH_3CN at low temperatures, indolenium ion **I**[7] was sufficiently stable and upon aqueous quenching gave rise to isolatable amounts of diol **8** (Table 1, inset). Fortunately, exposure to silica gel during purification does not influence the diastereomer ratio. Micro-

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



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(3) Recent pharmaceutial applications of oxaspirocylic oxindoles: Chafeev, M.; Chowdhury, S.; Fraser, R.; Fu, J.; Kamboj, R.; Hou, D.; Liu, S. ; Seid Bagherzadeh, M.; Sviridov, S.; Sun, S. ; Sun, J. ; Chakka, N.; Hsieh, T.; Raina, V. Use of spiro-oxindole compounds as therapeutic agents. WO 2008060789, May 22, 2008.

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wave irradiation of *cis*-**7a** in the presence of BF_3•OEt_2 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.

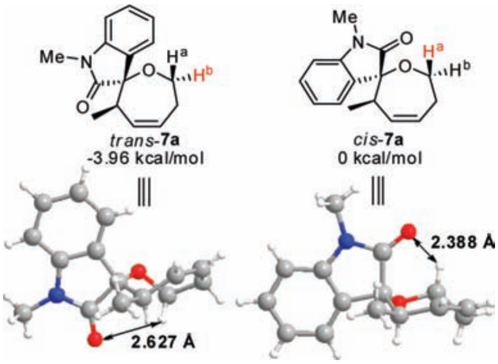


Figure 2. X-ray structures of *trans*-**7a** and *cis*-**7a**.

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-like interaction associated with the corresponding (*E*)-oxonium intermediate. Designating the aryl ring as the larger steric contributor[9] orients the carbonyl pseudoaxial. Thus, transition state **IV** is preferred and leads to the formation of *cis*-**7a** as the major diastereomer under kinetic conditions.

Scheme 3. Proposed Transition State

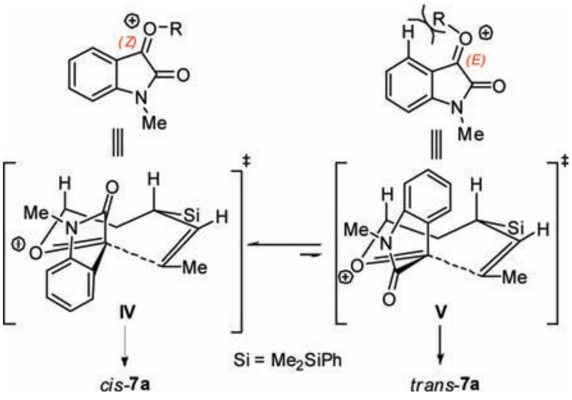
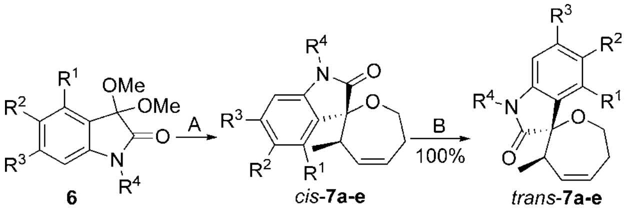


Table 2. [5 + 2]-Annulations of Isatin Derivatives*



entry	isatin	R^1	R^2	R^3	R^4	time A	yield[a] (cis/trans)[b]	time B	dr[b] cis/trans
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

* Conditions A: 1.0 equiv of (*S*)-**5**, 1.0 equiv of TMSOTf, 0.1 M in CH_2Cl_2, 0° C. Conditions B: 1.0 equiv of BF_3•OEt_2, 0.1 M in CH_3CN, microwave, 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.

At this juncture, we sought to expand this methodology to include additional isatin derivatives **6b**−**e** (Table 2). HPLC analyses of the spirooxindole products indicated complete chirality transfer from the starting silyl alcohol (see the Supporting Information). For all cases evaluated, both *cis* and *trans* diastereomers were readily obtained in useful yields and with exellent 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 dimethyl ketal **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

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(4) (a) Franz, A. K.; Dreyfuss, P. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 1020. (b) Savitha, G.; Niveditha, S. K.; Muralidharan, D.; Perumal, P. T *Tetrahedron Lett.* **2007**, *48*, 2943. (c) Alcaide, B.; Almendros, P.; Rodrguez-Acebes, R. *J. Org. Chem.* **2006**, *71*, 2346. (d) Wang, L; Zhang, Y; Hu, H-Y; Fun, H; Xu, Jian-H. *J. Org. Chem.* **2005**, *70*, 3850. (e) Smet, M.; Oosterwijck, C. V.; Hecke, K. V.; Meervelt, L. V.; Vandendriessche, A.; Dehaen, W. *Synlett.* **2004**, 2388. (f) Muthusamy, S.; Gunanathan, C.; Nethaji, M. *J. Org. Chem.* **2004**, *69*, 5631.

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(7) England, D. B; Merey, G.; Padwa, A. *Heterocycles* **2007**, *74*, 491.

(8) The calculated ground-state energy diffence is based on the RHF/3-21G (*) model of crystal structures *cis*-**7a** and *trans*-**7a**.

(9) Overman, L. E.; Watson, D. A. *J. Org. Chem.* **2006**, *71*, 2587.

(10) The absolute configuration of annulation products was confirmed by X-ray structure analysis of **6b**; see the Supporting Information.

(11) Panek, J. S.; Beresis, R.; Xu, F.; Y.; Yang, M. *J. Org. Chem.* **1991**, *56*, 7341.

(12) The absolute configuration of the spirocyclic carbon of products **10a**−**h** was confirmed by X-ray crystal structure analysis of **12**.

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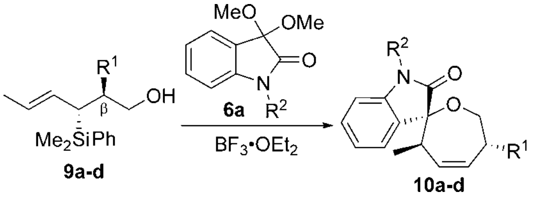
product. Reoptimization led to the use of 1.0 equiv of $BF_3{\cdot}OEt_2$ in refluxing CH_2Cl_2 to provide the desired products as single diastereomers (Table 3).[12] Unlike annulations with (*S*)-**5**, no products from spiro-ring-opening and reclosure pathways were observed with these cases.

Table 3. Accessing More Complex Spirooxindoles

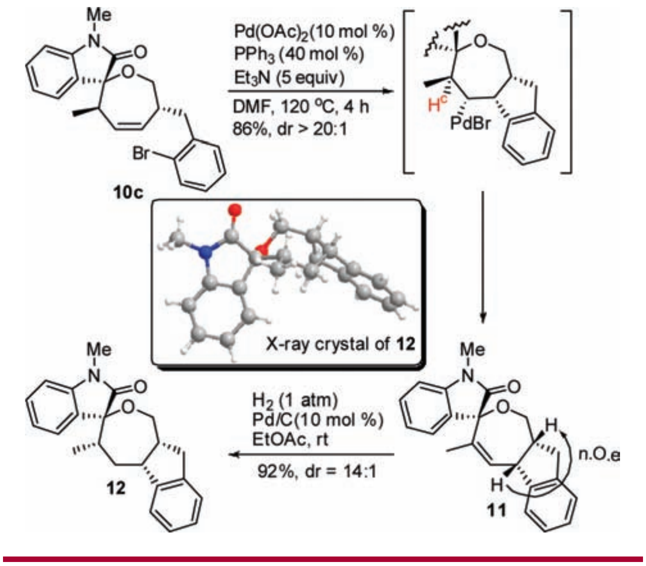


entry[a]	silane	R¹	R²	time (h)	product	yield[b] (%)	dr[c] cis:trans
1	**9a**	Me	Me	2	**10a**	50	>20:1
2	**9a**	Me	H	1	**10b**	47	>20:1
3	**9b**	Me	Me	2	**10c**	45	>20:1
4	**9b**	Me	H	1	**10d**	45	>20:1
5	**9c**	*o*-Br-Bn	Me	3	**10e**	60	>20:1
6	**9c**	*o*-Br-Bn	H	3	**10f**	58	>20:1
7	**9d**	propargyl	Me	5	**10g**	42	>20:1
8	**9d**	propargyl	H	5	**10h**	36	>20:1

[a] All reactions performed at 0.1 M with 1.0 equiv $BF_3{\cdot}OEt_2$ in refluxing CH_2Cl_2. [b] Isolated yields after purification over silica gel. [c] Diastereomeric ratios were determined by ^1H NMR analysis.

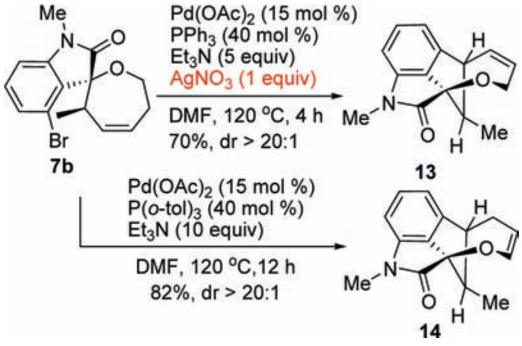
Additional skeletal complexity was achieved by diversification of the annulation products through intramolecular Heck cyclization. The cyclization of **10c** under standard conditions (cat. $Pd(OAc)_2$, Et_3N, 120 °C) was highly regio- and stereoselective, affording the pentacyclic oxindole **11** in 86% isolated yield as a single diastereomer (Scheme 4). Proton, COSY, and NOE NMR experiments indicated *syn*-insertion of the arylpalladium 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.

Scheme 4. Formation of Pentacyclic Oxindole



Cyclization of spirocycle *cis*-**7b** was also achieved with excellent regio- and stereocontrol (Scheme 5). Initially, *cis*-**7b** was treated under similar conditions as **10c**, but the unexpected olefin isomer **14** was observed as the only product. However, by adding 1.0 equiv 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]

Scheme 5. Formation of Tetracyclic Oxindole



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 toward library synthesis and subsequent biological evaluation of its members are underway.

Acknowledgment. Financial support from the NIGMS CMLD initiative (GM-067041) is gratefully acknowledged. We thank Professors John A. Porco Jr., Aaron B. Beeler, and Dr. Paola Castaldi (Boston University) for helpful discussions. We are endebted to Dr. Emil Lobkovsky (Cornell University) for X-ray crystal data.

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.

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(13) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.

(14) See the Supporting Information.

(15) Castaldi, P. M.; Troast, D. M.; Porco, J. A., Jr. *Org. Lett.* **2009**, *11*, (DOI 10.1021/ol901201k).