OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Catalytic Asymmetric Synthesis of Cyclopentene-spirooxindoles Bearing Vinylsilanes Capable of Further Transformations

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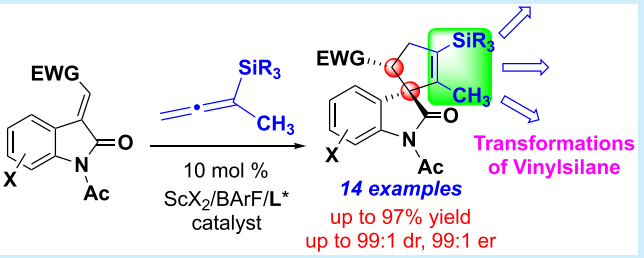
Supporting Information

ABSTRACT: We report a scandium-catalyzed [3 + 2] annulation of alkylideneoxindoles with allenylsilanes for the enantioselective formation of cyclopentene-spirooxindoles containing vinylsilanes. Using a $Sc(OTf)_2$/PyBOX/BArF complex, the spiroannulation of allenylsilanes affords products with >94:6 dr and >90:10 er. The effect of the counterion and ligand to control selectivity is discussed. The transformation of the vinylsilane is demonstrated using cross-coupling, epoxidation, and Tamao−Fleming oxidation reactions. A series of competition experiments provide a comparison of nucleophilicity between allyl- and allenylsilanes.

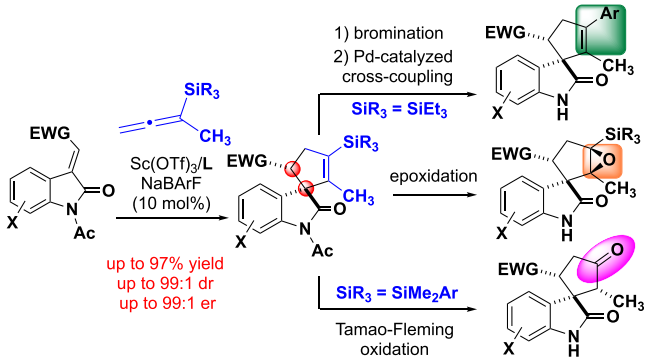


Spirooxindoles contain a privileged structural framework with a spirocycle at the C-3 position of the oxindole core.[1] In recent years, spirooxindoles have gained significant attention in medicinal chemistry and drug discovery with broad representation in alkaloid natural products and pharmaceutical lead compounds,[2] with therapeutic properties ranging from antiviral,[3] to anticancer,[4] to antimalarial.[5] Spirocycles and spirooxindoles exhibit stereospecific biological activity,[6] indicating the importance of diastereo- and enantioselective synthetic methods to prepare these scaffolds. Construction of the spirooxindole framework represents a challenge for selectively creating the congested spiro-quaternary carbon center and incorporating functional handles for further synthetic manipulation.[7a] Asymmetric synthetic methods often exploit chiral catalysts to differentiate facial selectivity of a prochiral substrate.[7b,c]

Our group has developed enantioselective methods to access spirooxindoles using an annulation strategy with allyl- and crotylsilane nucleophiles and prochiral, electrophilic oxindoles.[8,9] Based on the high yield and enantioselectivity we observed with allylsilanes, we envisioned using allenylsilanes, which have been much less explored as nucleophiles compared to allylsilanes. Allenylsilanes were first reported as 3-carbon synthons by Danheiser in a [3 + 2] annulation reaction involving Lewis-acid-activated α,β-unsaturated ketones to yield trialkylsilylcyclopentenes.[10] Evans also reported the catalytic enantioselective addition and corresponding annulation of allenylsilanes to access either homopropargylic alcohols or dihydrofurans from ethyl glyoxylate, depending on the size of the silyl group.[11]

Herein, we report a chiral Lewis-acid-catalyzed annulation with allenylsilanes and alkylidene oxindoles to access enantioenriched spirocyclopentene oxindoles **3** containing a vinylsilane available for further transformations (Scheme 1).[12] Vinylsilanes provide a functional handle for a variety of transformations,[13,14] including organometallic cross-coupling reactions,[15] C−Si oxidation to the corresponding ketone by the Fleming−Tamao processes,[16] and direct alkene reactions such as epoxidation. Considering the limited reports of allenylsilane annulations, we were also interested in directly comparing the relative nucleophilicity of allylsilanes vs allenylsilanes.

Scheme 1. Catalytic Asymmetric Annulation of Allenylsilanes for Novel Spirooxindoles

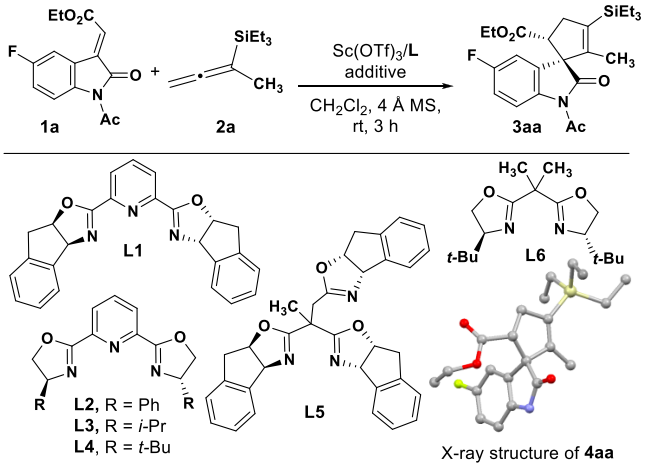


Our initial investigations determined that the mild nucleophilicity of allenylsilanes requires the use of an activated chiral scandium complex to catalyze the annulation reaction with alkylidene oxindole **1a** (Table 1). The use of both ligand and sodium tetrakis-[3,5-bis(trifluoromethyl)phenylborate (NaBArF) is required for high yields (Table 1, entries 1−2), which is attributed to the *in situ* formation of a discrete cationic scandium complex capable of high efficiency in this process.[17]

Received: August 12, 2019

DOI: 10.1021/acs.orglett.9b02852
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Screen of Ligands and Additives for Annulation[a]



entry	ligand	additive	conversion[b] (%)	dr[c]	er[d]
1	none	NaBArF	0	—	—
2	**L1**	NaBArF	100	90:10	82:12
3	**L2**	NaBArF	65	75:25	74:26
4	**L3**	NaBArF	100	93:7	95:5
5	**L4**	NaBArF	100	98:2	99:1
6	**L5**	NaBArF	0	--	--
7	**L6**	NaBArF	0	--	--
8	**L4**	$AgSbF_6$	25	nd	nd
9	**L4**	$NaSbF_6$	0	--	--
10	**L4**	$NaBF_4$	0	--	--
11	**L4**	none	0	--	--

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Sc(OTf)_3$ (10 mol %), ligand (11 mol %), NaBArF (10 mol %), CH_2Cl_2 (0.5 mL), and 4 Å MS (50 mg) under argon. See SI for solvent screening. [b]Determined using ^1H NMR analysis based on consumption of **1a** (product mixture includes **3aa** + varying amounts of deacylation **4aa**). [c]Determined using ^1H NMR analysis for unpurified **3aa**. [d]Determined using CSP-HPLC analysis after deacylation (i.e., for **4aa**). No erosion in yield or selectivity was observed at longer (i.e., 12−24 h) reaction times.

A series of chiral ligands were screened using scandium triflate to identify the optimal catalyst system to provide high selectivity for the formation of spirocyclopentene **3aa**. Using (*S*,*R*)-Inda-PyBOX (**L1**) provided high yield with moderate selectivity (entry 2), while (*S*)-phenyl-PyBOX (**L2**) afforded product in significantly lower yield and reduced enantioselectivity (entry 3).[11] Increasing the steric demand of the PyBOX ligand (**L3** and **L4**) improved the selectivity with (*S*)-*tert*-butyl-PyBOX (**L4**), affording the highest selectivity (entries 4 and 5).

Scorpionate Inda-TRISOX ligand (**L5**) and *tert*-butyl-BOX ligand (**L6**) were also explored, but no reactivity was observed (entries 6 and 7). The diastereomeric ratio was measured for **3aa**, while enantiomeric excess was determined after *N*-acyl deprotection (for the NH product **4aa**); *N*-acyl **3aa** was not separable on HPLC (see Supporting Information). Based on our initial ligand screen, we proceeded to utilize the $Sc(OTf)_3$/NaBArF/**L4** catalyst system as the optimal system for subsequent experiments. It is notable that all initial reaction conditions favored formation of the annulation product (**3aa**) with no addition (i.e., propargylation) product observed (vide infra).[18,19] The reaction proceeded with significantly reduced activity when other weakly coordinating anions were employed (entries 8−10).

High selectivity is observed for alkylidene oxindoles and allenylsilanes with varying electronic effects and steric bulk of the silyl group (Figure 1). Allenylsilanes with small ($SiMe_3$) to large ($Si(i\text{-}Pr)_3$) silyl groups all afford annulation products **4ba**, **4bb**, and **4bc** in good yields and selectivity (99:1 dr and ≥97:3 er).[20] Using aryl(dimethyl)silyl allene **2d**, which we envisioned could enable future derivatization,[21] afforded **4ad** with only a slight decrease in yield and diastereoselectivity but retained high enantioselectivity (95:5 er). Proceeding with allenylsilane **2a**, we explored the alkylidene substrate scope (**1b−i**) and observed that all reactions proceed with high selectivity (>90:10 er) and high yields (87−95%), except for cyano **1i** which has notably reduced activity, proceeding in only 38% yield for product **4ia** even after extended reaction times and higher catalyst loading.[22] Both electron-withdrawing and electron-donating substituents on the oxindole ring were well accepted. X-ray structure analysis of **4aa** confirms the absolute configuration of the annulation product as (1*R*,5*R*).[23]

Next, the versatility of the vinylsilane functional handle and transformation of the spirocyclopentene structure were demonstrated. Vinylsilane **4aa** was converted to vinyl bromide

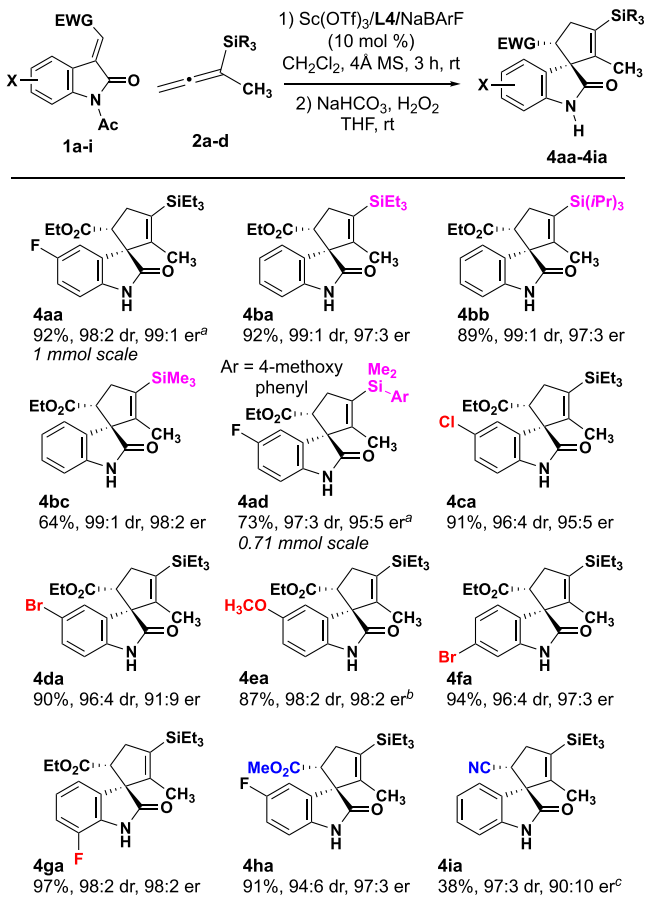


Figure 1. Scope of allenylsilane annulation reaction. Reaction conditions (unless otherwise indicated): **1** (0.1 mmol), **2** (0.2 mmol), $Sc(OTf)_3$ (10 mol %), **L4** (11 mol %), NaBArF (10 mol %), CH_2Cl_2 (0.5 mL), and 4 Å MS (50 mg) under argon. Diastereomeric ratio determined using ^1H NMR analysis for **3**. Isolated yields reported for **4** over two steps. Enantiomeric ratios determined using CSP-HPLC (AD-H column) for **4** (after deacylation prior to purification). [a]Reaction conducted on a larger scale, up to 1 mmol scale, as indicated. [b]Reaction time = 6 h. [c]Performed with 20 mol % catalyst loading; reaction time = 24 h.

DOI: 10.1021/acs.orglett.9b02852
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5 in 90% yield using *N*-bromosuccinamide in the presence of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) under light-free conditions.[13,15] Vinyl bromide **5** can be employed as an organometallic cross-coupling partner as demonstrated by the conversion to **6** using a Suzuki reaction which retains high stereochemical enrichment (Figure 2).[24] The vinylsilane also readily undergoes epoxidation with *m*-CPBA to afford tetracyclic spirooxindole **7** in 76% yield and 90:10 dr, retaining high enantioenrichment (97:3 er).[16b]

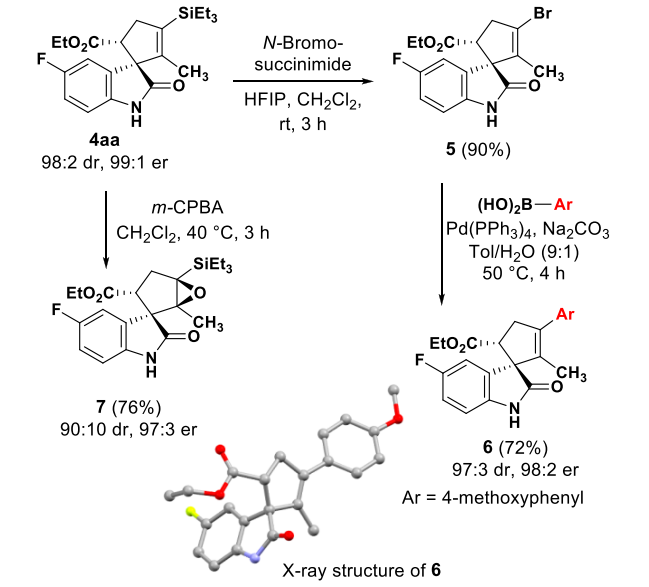


Figure 2. Transformation of vinylsilane-containing cyclopentene spirooxindoles.

The vinylsilane can also be transformed under Tamao–Fleming oxidation conditions to produce a cyclopentanone-spirooxindole (e.g., **10**).[16,25] Oxidation of the vinylsilane proceeds via protodesilylation of the *p*-methoxyphenyl and formation of silyl fluoride **8** (Figure 3). The best conditions for protodesilylation were identified by exposing vinylsilane **4ad** to BF_3·2AcOH to afford silyl fluoride **8**, which was isolated in quantitative yield.

For oxidation of the C–Si bond, silyl fluoride **8** requires further activation with excess fluoride to form a pentavalent silicon fluoride in the presence of peroxide.[26] Several common

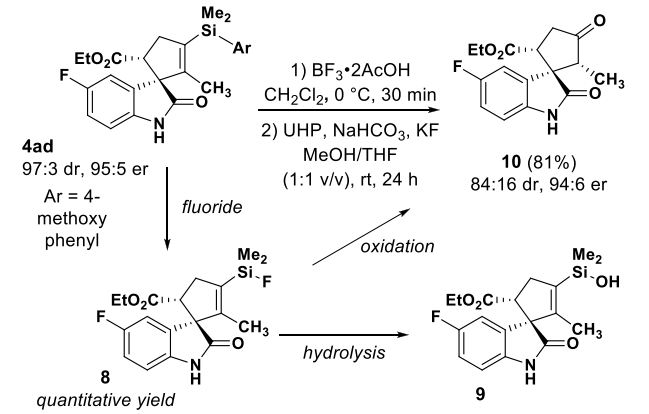
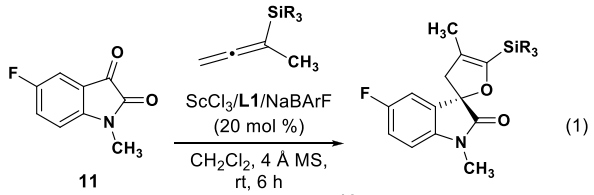


Figure 3. Tamao–Fleming oxidation of aryl-substituted vinyl-silane **4ad** for the synthesis of cyclopentanone-spirooxindole **10**.

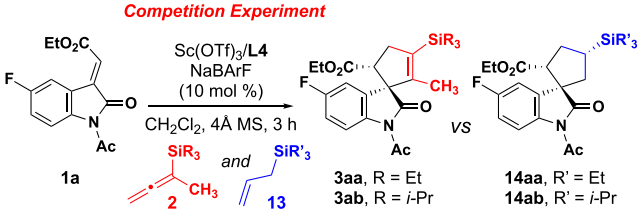
fluoride and peroxide sources were initially explored, but only low yields of the desired oxidation product were observed. Instead, the formation of silanol **9** (resulting from Si–F hydrolysis) was observed (Figure 3). To reduce the competing hydrolysis pathway and favor oxidation, we employed KF with an anhydrous peroxide source (H_2O_2·urea) in a MeOH/THF solution of the vinylsilane. The Tamao–Fleming product (an enol) tautomerizes to cyclopentanone-spirooxindole **10** which was isolated in 81% yield with retention of enantioselectivity at C1 (Figure 3). The diastereomer ratio was determined to be 84:16 based on ^{1}H NMR integration of the proton at the C2 position. A NOESY experiment was performed, and the relative stereochemistry of the major stereoisomer of **10** was determined to be (1*R*, 2*R*, 5*R*) based on the absolute confirmation determined for **4aa** by X-ray analysis.

To expand the application of this methodology, we also demonstrated conditions for the synthesis of dihydrofuran-spirooxindoles **12** (eq 1).[27] Annulation of isatin electrophile **11**



with allenylsilane **2a** was accomplished using $ScCl_2$/(*S*,*R*)-Inda-PyBOX/BArF (20 mol %) to afford **12a** in 44% yield with 95:5 er. When **2b** is employed, **12b** was formed in higher yield, albeit with a lower selectivity (87:3 er). Here our method also demonstrates notable selectivity for the annulation pathway (vs the elimination/propargylation), favoring exclusive formation of spirooxindole **12**. A competition experiment in the annulation reaction with **1a** was performed as the first direct comparison of allenylsilane and allylsilane nucleophilicity (Table 2).[28] Under the assumption that the annulation process

Table 2. Competition Experiments between Allenylsilane and Allylsilane Nucleophiles



experiment	allenyl [Si]	allyl [Si]	product ratio (**3**:**14**)
1	$SiEt_3$ (**2a**)	$SiEt_3$ (**13a**)	2.5:1 (**3aa**:**14aa**)
2	$SiEt_3$ (**2a**)	$Si(iPr)_3$ (**13b**)	1:2.4 (**3aa**:**14ab**)
3	$Si(iPr)_3$ (**2b**)	$Si(iPr)_3$ (**13b**)	1:2.8 (**3ab**:**14ab**)

is not reversible (see SI for conditions with yield and selectivity retained at longer reaction times), competition experiments with **1a** were utilized to extrapolate a kinetic analysis with the product distribution determined using ^{19}F NMR spectroscopy (integration of ^{19}F peaks was substantiated with ^{1}H NMR peak integration for known products). The first competition experiment comparing allenyl(triethyl)silane **2a** with allyl-(triethyl)silane **13a** under our standard reaction conditions indicated enhanced nucleophilicity of the allenylsilane, favoring

DOI: 10.1021/acs.orglett.9b02852
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the formation of spirocyclopentene **3aa** in a 2.5:1 ratio (Table 2, entry 1). Only the two annulation products (**3aa** and **14aa**) were observed as products in this competition reaction. Switching to allyl(tri-isopropyl)silane **13b**, a competition experiment with **2a** *reversed* selectivity with spirocyclopentane **14ab** produced at a faster rate in a 2.4:1 ratio (entry 2). The competition between allyl(tri-isopropyl)silane **13b** and allenyl-(tri-isopropyl)silane **2b** also indicated enhanced nucleophilicity for the allylsilane, with product **14ab** again forming at a faster rate than **3ab** in a 2.8:1 ratio (entry 3). The trend from these initial data suggests that an allenylsilane is more nucleophilic with a smaller silyl group ($SiEt_3$), while an allylsilane is more nucleophilic with a larger silyl group ($Si(i\text{-}Pr)_3$). Although not a large effect, the reversal in relative rates may suggest a different mechanistic pathway is followed for the allenylsilane and allylsilane in this reaction. While the allylsilane annulation proceeds via formation of a β-stabilized carbocation intermediate (via a 1,2-silyl shift),[29a−c] which is favored for large silyl groups,[29d] the allenylsilane annulation may proceed via a concerted cycloaddition that is more favorable for the smaller silyl group.[28]

In conclusion, we have shown the utility of allenylsilanes to access cyclopentene-spirooxindoles in high yield and selectivity with a chiral scandium catalyst. This methodology favors the annulation pathway (vs propargylation). Competition experiments comparing the nucleophilicity of allenylsilanes and allylsilanes demonstrate that both the π-system and the size of the silyl group affect the relative rate and product distribution for these annulation reactions and suggest that different mechanistic pathways may be operative. The vinylsilane affords a versatile functional group to further modify the spirooxindole scaffold for potential applications in medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02852.

Experimental procedures, reaction optimization, more experimental data, spectral data for all compounds, HPLC data, and X-ray crystal structure coordinates for compounds **4aa** and **6** (PDF)

Accession Codes

CCDC 1941096−1941097 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the American Chemical Society Petroleum Research Fund, ACS-PRF (49I8I-DNI1 and 56230-ND1), for partial support of this research. We acknowledge the National Science Foundation (DBIO/722538) for funding the 800 MHz NMR spectrometer.

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DOI: 10.1021/acs.orglett.9b02852
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