Synthetic Methods

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Catalytic Asymmetric [3+2] Annulation of Allylsilanes with Isatins: Synthesis of Spirooxindoles**

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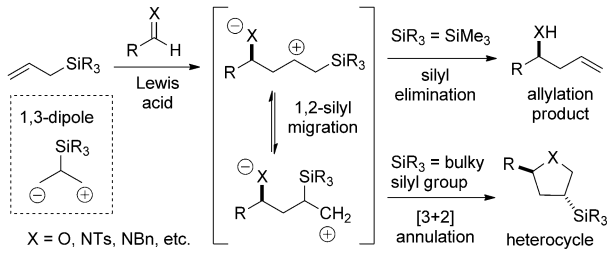
Allylsilanes are readily available, nontoxic, and versatile reagents for organic synthesis. Although fairly weak nucleophiles, allylsilanes exhibit a dynamic reactivity pattern that is dependent upon the electronic and steric properties of the silyl group, the electrophilic partner, and the reaction conditions.[1] Two primary pathways are known for the addition of an allylsilane to a C=X π electrophile in the presence of a Lewis acid: 1) an elimination pathway to afford allylation products (Hosomi–Sakurai reaction), and 2) a pathway wherein the allylsilane acts as a three-carbon unit in a [3+2] annulation reaction to afford cyclized products (Scheme 1).[2] The silyl group enhances the nucleophilicity of the alkene and stabilizes the β-carbocation, which is formed upon initial attack, through σ–p hyperconjugation (referred to as the β-silyl effect).[3] The [3+2] allylsilane annulation reaction represents a powerful method for efficient stereoselective synthesis of complex heterocycles and carbocycles; however, catalytic asymmetric variants have remained elusive.[4] In contrast, numerous methods have been reported that describe enantioselective allylation reactions with allylsilanes.[5] This enantioselective annulation represents a particular challenge because Lewis acid catalysts often favor the competing allylation pathway, and a balance of reactivity and product selectivity is required. Herein we report the first example of a catalytic asymmetric [3+2] annulation of allylsilanes and develop a method to access silyl- and hydroxy-substituted spirooxindoles with superb enantioselectivity.



Scheme 1. Mechanism of allylation versus annulation pathways. Bn = benyzl, Ts = 4-toluenesulfonyl.

We chose to study the catalytic asymmetric annulation of allylsilanes with isatin electrophiles as a route to access spirooxindoles because of the important biological activities of this class of compounds.[6,7] We examined a wide variety of chiral Lewis acid metal complexes (Pd, Cu, Ti, Sc, In, etc.) to find a catalyst that would provide sufficient activation of the electrophile to compensate for the relatively weak nucleophilicity of allylsilanes without favoring formation of the allylation product. On the basis of our previous studies investigating asymmetric additions to isatins, we envisioned that a scandium(III)/**L** complex[8,9] could be optimized for the annulation reaction with allyltriisopropylsilane (Table 1); however, several variations of the $Sc(OTf)_3$/**L** complex did not provide the necessary reactivity (entries 1, 2).

We proceeded to investigate additives to enhance the reactivity of the scandium(III) catalysts, and found that upon addition of both $AgSbF_6$ and TMSCl the annulation and allylation products (**3** and **4**, respectively) were observed in a ratio of 39:61, each with excellent enantioselectivity (Table 1, entries 3–5). By using a $ScCl_3$ complex in place of $Sc(OTf)_3$,[10] the annulation product was obtained as the major product in an 85:15 ratio using CH_2Cl_2 solvent (entry 8). The annulation product is obtained with a consistently high (95:5) diastereoselectivty. Although the counterion is essential for the desired reactivity, additional investigations demonstrated that increasing the amount of the counterion favors the competing allylation pathway, even with the bulky allyltriisopropylsilane (entries 8–10). Using $NaSbF_6$ demonstrated that there is no specific dependency on silver salts (entry 13).[11] Finally, other additives were also investigated (entries 7, 11, 14, and 15), but TMSCl was ideal for both rate enhancement and product ratio.[12,13] Through this screening process, it was established that: 1) a silyl chloride is an essential activator for this reaction, 2) the halide ligands and counterion of the scandium complex play a significant role in controlling the pathway selectivity between the competing annulation and allylation reactions, and 3) the diastereoselectivity and enantioselectivity for the annulation product are excellent under all reaction conditions.

With optimized reaction conditions for the selective formation of the spirocyclic annulation product **3** in hand, we explored the scope of isatins for this reaction (Table 2). In

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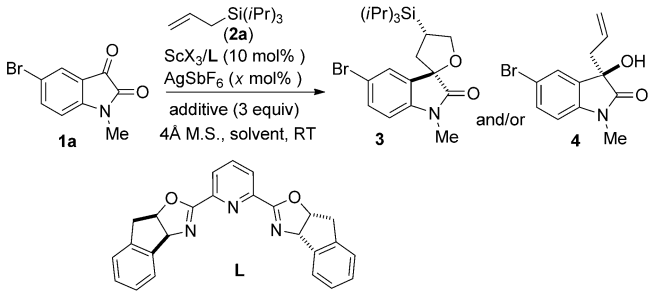
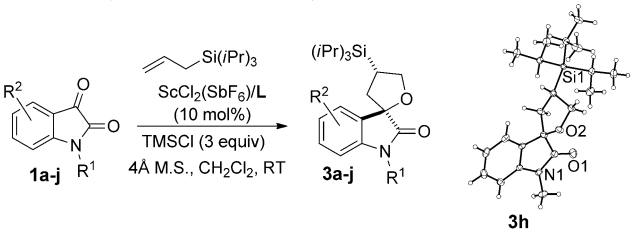
Table 1: Optimization of enantioselective allylsilane annulation.



Entry	X	Counterion source (mol%)	Additive	Solvent	**3**/**4**[a]	*ee* [%][b] (**3**)
1	OTf	–	–	CH_2Cl_2	n.r.	–
2	OTf	$AgSbF_6$ (10)	–	CH_2Cl_2	n.r.	–
3	OTf	–	TMSCl	CH_2Cl_2	n.r.	–
4	OTf	$AgSbF_6$ (10)	TMSCl	CH_2Cl_2	31:69	96[c]
5	OTf	$AgSbF_6$ (10)	TMSCl	CH_3CN	39:61	99
6	Cl	$AgSbF_6$ (10)	TMSCl	CH_3CN	58:42	99
7	Cl	$AgSbF_6$ (10)	$PhMe_2SiCl$	CH_3CN	47:53	99
8	Cl	$AgSbF_6$ (10)	TMSCl	CH_2Cl_2	85:15	99
9	Cl	$AgSbF_6$ (17)	TMSCl	CH_2Cl_2	68:32	99
10	Cl	$AgSbF_6$ (25)	TMSCl	CH_2Cl_2	48:52	99
11	Cl	$AgSbF_6$ (10)	TMSOTf	CH_3CN	0:100	–
12	Cl[d]	$AgSbF_6$ (10)	TMSCl	CH_2Cl_2	78:22	99
13	Cl[d]	$NaSbF_6$ (10)	TMSCl	CH_2Cl_2	82:18[e]	99
14	Cl[d]	$NaSbF_6$ (10)	$PhMe_2SiCl$	CH_2Cl_2	78:22	99
15	Cl[d]	$NaSbF_6$ (10)	PhCOCl	CH_2Cl_2	90:10[f]	99

[a] Product ratios were determined using ^{1}H NMR spectroscopy or HPLC analysis. [b] The *ee* value was determined by HPLC analysis using a chiral AD-H column. [c] Allylation proceeded with 90% *ee*. [d] Entries 6–11 were performed using $ScCl_3$, and entries 12–15 were performed using a $ScCl_3(THF)_3$ complex. [e] The product ratio is an average of five experiments. [f] PhCOCl provides rate enhancement, compared to conditions in entry 2, but only a 50% yield of **3** and with an 88:12 diastereomeric ratio (average of two experiments). **L** = 2,6-bis[(3a*S*,8a*R*)-3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazolin-2-yl]pyridine, n.r. = no reaction, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

Table 2: Scope of isatins for the allylsilane annulation.[a]



Entry	**1**	R^1	R^2	*t* [h]	**3**	Yield [%][b]	*ee* [%][c]
1	**1a**	CH_3	5-Br	24	**3a**	71	99
2	**1b**	CH_3	5-Cl	24	**3b**	74	99
3	**1c**	CH_3	4-Cl	24	**3c**	62[d]	97
4	**1d**	CH_3	5-F	48	**3d**	67	99
5	**1e**	CH_3	5-OCH_3	72	**3e**	47[e]	99
6	**1f**	Bn	5-OCF_3	48	**3f**	82	99
7	**1g**	PMB	5-F	48	**3g**	55	99
8	**1h**	CH_3	H	72	**3h**	47	99
9	**1i**	Ph	H	24	**3i**	81	97
10	**1j**	CH_2CCH	5-F	48	**3j**	72	97

[a] All reactions performed under argon with $ScCl_3(THF)_3$, $NaSbF_6$, and 3 equiv of the allylsilane **2a** with ligand **L**. Thermal ellipsoids of the X-ray structure of **3h** are shown at 50% probability. [b] Yield of isolated annulation product containing trace amounts of the minor diastereomer as determined by ^{1}H NMR spectroscopy. [c] The *ee* value was determined by HPLC analysis using an AD-H column. [d] A 71:29 mixture of diastereomers was isolated as determined by HPLC analysis; *ee* value is reported for the major diastereomer. [e] Reaction performed using $AgSbF_6$. PMB = *para*-methoxybenzyl.

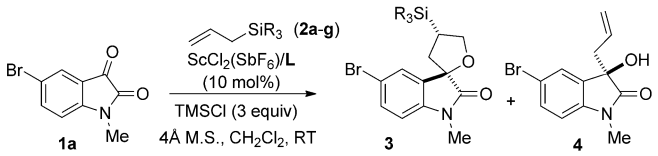
all cases, the annulation product is obtained as the major product with 97–99% *ee*, and the reported structures and absolute stereochemistry were confirmed by X-ray analysis of **3h**.[14] Asymmetric catalysis is often performed at low temperatures, so the consistently high enantioselectivity of this reaction at room temperature is noteworthy. The diastereoselectivity remained high for all isatins except for the case of 4-chloro-substituted isatin (**1c**), which afforded a 71:29 mixture of diastereomers while still maintaining a high 97% *ee* (entry 3). A decrease in reaction rate and yield was observed with more electron-donating substituents on isatin, such as a methoxy group (entry 5). Investigations of other pybox ligands confirmed that the indapybox ligand (**L**) provides superior enantioselectivity (99% *ee*); the isopropyl and norephedrine variants of the ligand still provide greater than 90% *ee*.

Silyl spirooxindoles and other organosilicon compounds are of interest for their potential biological activity,[15] as well as the added synthetic utility derived from oxidation of the C–Si bond. For greatest synthetic utility, the silyl group must be bulky enough to suppress the elimination pathway, while also containing a "removable" aromatic moiety so that the silyl group can be easily converted into a hydroxy group under mild oxidation conditions.[16] We screened several allylsilanes having different steric and electronic properties with the aim of identifying an allylsilane that favors the annulation pathway and also contains an oxidizable silane group (Table 3).[17] All annulation reactions maintained excellent enantioselectivity (99% *ee*) with these reaction conditions. Although we expected that various allylsilanes would favor the annulation product, the allylation pathway is remarkably persistent even for bulky silyl groups.[18] Even replacing one isopropyl group on the silicon with a *para*-anisole group led to a drop in the selectivity for the annulation product (entry 2). Overall, the benzhydryl allylsilane provided a balance for the desired reactivity and product ratio (entry 3), and was optimal given the ease of preparation.

Proceeding with the easily oxidizable benzhydryl silyl group, we demonstrated the Si–C oxidation and scope with respect to isatin for obtaining hydroxy-spirooxindoles **5** (Table 4). This reaction utilizes oxidation conditions with TBAF and hydrogen peroxide to achieve high yields.[17a] The conversion of the silyl group proceeds with retention of configuration as confirmed by X-ray structure analysis for the product **5d**,[14] and the high enantiomeric excess is preserved. The competing protodesilylation reaction with TBAF is minimized by maintaining the reaction at 0 °C and controlling the reaction time.[19]

In summary, we have demonstrated the first example of an asymmetric catalytic [3+2] annulation reaction of allylsilanes and an efficient enantioselective synthesis for 3′-silyl- and 3′-

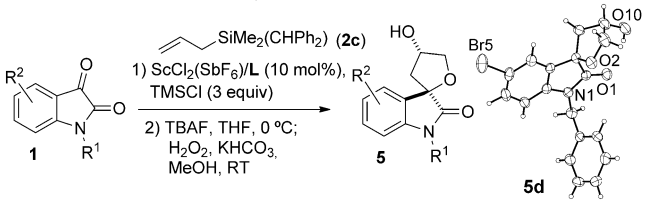
Table 3: Scope and annulation ratios for allylsilanes.[a]



Entry	SiR_3	*t* [h]	**3**/**4**	Yield of **3** [%][b]	*ee* of **3** [%][c]
1	$Si(iPr)_3$	24	82:18	71	99
2	$Si(iPr)_2(4\text{-}MeOC_6H_4)$	72	52:48	39	99
3	$SiMe_2(CHPh_2)$	72	66:34	51[d]	99
4	$SiMe_2(2\text{-}MeOC_6H_4)$	48	38:62	35	99
5	$SiMe_2(2,6\text{-}(MeO)_2C_6H_3)$	2	30:70	20[e]	99
6	$SiMe_2(1\text{-}Np)$	48	17:83	10[f]	99
7	$SiPh_3$	192	–	–	–

[a] All reactions performed under argon, using $ScCl_3(THF)_3$, $NaSbF_6$, with 3 equiv of allylsilane. [b] Yield of isolated annulation product. For entries 1–5, the annulation product is obtained with >95:5 diastereoselectivity as determined by ^1H NMR spectroscopy. [c] Determined by HPLC analysis using a chiral AD-H column. [d] Represents an average of four reactions. [e] The amount of annulation can vary because of the photosensitivity of the starting material under the reaction conditions; see Ref. [17b]. [f] An 85:15 mixture of diastereomers was isolated. Np = naphthyl.

Table 4: Enantioselective allylsilane annulation and C–Si oxidation.[a]



Entry	R^1	R^2	Yield of **3** [%][b]	**5**	Yield of **5** [%]	*ee* of **5** [%][c]
1	CH_3	5-Br	51[d]	**5a**	92	98
2	CH_3	5-Cl	53	**5b**	93	99
3	CH_3	5-F	53	**5c**	85	99
4	Bn	5-Br	55	**5d**	85	93

[a] All annulation reactions performed under argon, using $ScCl_3(THF)_3$, $NaSbF_6$, with 3 equiv of allylsilane **2c** for 72 h. Thermal ellipsoids of the X-ray structure of **3h** are shown at 50% probability. [b] Yield of isolated annulation product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Yield represents an average of four reactions. TBAF = tetra-*n*-butylammonium fluoride.

hydroxy-spirooxindoles. This reaction utilizes a chiral cationic $ScCl_2(SbF_6)$/**L** complex with TMSCl as an essential promoter, thus allowing the reaction to proceed with high enantioselectivity at room temperature. The role of TMSCl (and promoters such as ArCOCl) to enhance the reaction rate is currently under investigation. The optimization and scope of the enantioselective allylation of isatins with allylic silanes will be reported in a separate publication. Additional investigations into the scope of carbonyl electrophiles and substituted allylic silanes are underway.

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[12] Although we cannot comment on the exact role of TMSCl, several control experiments and NMR studies provide important insights. When addition of TMSCl to the $ScCl_2(SbF_6)$/**L** complex is monitored by ^1H NMR spectroscopy (in CD_2Cl_2), an overall broadening of the indapybox signals is observed. No interaction or complexation is observed upon mixing TMSCl with isatin. While the addition of TMSCl has a dramatic effect on the reaction rate, varying amounts of TMSCl does not affect the enantioselectivity. TMSCl also does not appear to be acting as a drying agent based on a series of control experiments regarding the effects of molecular sieves and water on the reaction rate and annulation ratio. Other additives (such as silyl-transfer agents HFIP and diisopropylphenol) were also investigated and do not enhance the rate of the reaction. Overall, this evidence supports a hypothesis that TMSCl interacts directly with the scandium complex by facilitating formation of the cationic catalyst or additionally enhancing the Lewis acidity of the scandium. See the Supporting Information for more details.

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[14] The structure and absolute stereochemistry was assigned and confirmed based on X-ray crystallography (anomalous dispersion method) of **3h** and **5d**. CCDC 832206 (**3h**) and CCDC 831210 (**5d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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