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Unified Approach for Fused and Spirocyclic Oxindoles *via* Lewis Acid Promoted Opening of Spiro-epoxyoxindoles with Allylsilanes: Application to Formal Synthesis of (±)-Physovenine

Brijesh M. Sharma[a, b], Mahesh Yadav[a], Rajesh G. Gonnade[b, c] and Pradeep Kumar *[a, b]

Abstract: A protocol for the construction of oxindoles bearing all-carbon quaternary centers in a highly regioselective manner has been developed. The reaction involves opening of spiro-epoxyoxindoles with allylsilanes to give Hosomi-Sakurai type products as well as novel silicon containing spirocyclic oxindoles. A formal synthesis of (±) physovenine is accomplished in short steps using this protocol.

Introduction

Oxindoles with a C3-quaternary framework have found a renewed synthetic interest due to its ubiquitous existence in natural products. [1] Among such oxindole derivatives, 3-allyl-3-(hydroxymethyl)-oxindole **1** containing an all-carbon quaternary centre is at the core of several pharmaceutically and naturally important alkaloids such as physovenine, physostigmine and oxaline (Figure 1), having a wide spectrum of biological activites. [2] At the same time, spirooxindole moiety **2** has been recognized as the key structural skeleton in a wide array of biologically active compounds such as aspergillines A-B and XEN402. [3] The unnatural spirooxindoles containing silane in their structure have also been found to exhibit excellent anti-tumour activity by Schreiber *et al.* [4] (Figure 1).

Smith and co-workers have accomplished the synthesis of alkaloids belonging to this class (example, (±)-coerulescine and (±)-Horsfiline) through **1** as a key intermediate. [5] The challenge for synthesizing 2-oxindoles, which contain all-carbon quaternary at C3 position, continues to inspire ingenious bond forming solution. Several synthetic approaches have been proposed so far in the literature. Few notable among them are: (i) Pd-catalyzed asymmetric allylic alkylation, [6] (ii) Black rearrangement approach, [7] (iii) PET-catalyzed [3+2] reactions, [8] (iv) Cu- and Pd-catalyzed Claisen rearrangement of allyloxy- and propargyloxy-indoles, [9] (v) Intramolecular-dehydrogenative coupling, [10] (vi) Nd^{III}-N,N'-dioxide mediated synthesis, [11] (vii) Ni catalyzed Heck cyclization approach, [12] (viii) Ru-catalyzed C-H functionalization, [13] (ix) Dearomatization approach [14] and so on.

Further, generation of all carbon quaternary by Lewis acid activation of spiro-epoxyoxindoles has been shown to be achieved initially by Hajra *et al.* and later by Wei *et al.* [15] Furthermore, generation of quaternary carbon by means of allylsilanes *via* Hosomi-Sakurai reaction [16] and [3+2] annulation reactions, [17] have been traversed for the synthesis of number of biologically active compounds in recent years. [18] Thus, Lewis acid catalyzed C-C bond formation using allylsilane reagents for accessing fused and spirocyclic oxindole framework with an all carbon quaternary centre has been proposed and demonstrated to be a new & promising route towards the synthesis of this class of alkaloids.

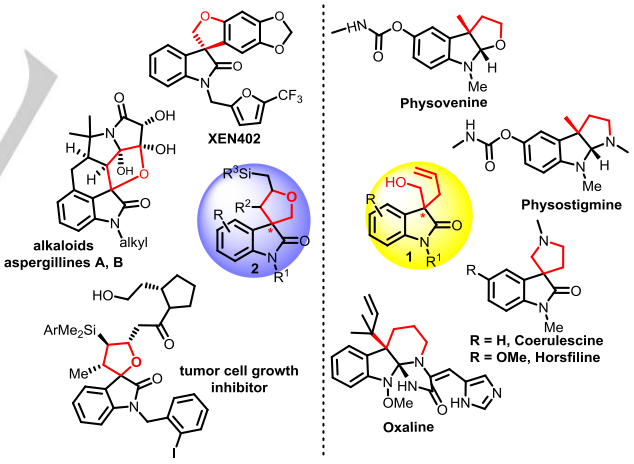

Figure 1. A schematic representation of natural and unnatural oxindole compounds.

The existing literature suggests that Lewis acid mediated annulation reaction of allylsilanes often favours the competing allylation pathway, due to stereoelectronic environment of different silyl groups. [19] As per our knowledge till date, effect of allylic substituents of allylsilanes in determining product selectivity (annulations vs. allylation) is not yet explored. Herein, we report Lewis acid mediated reactions of spiro-epoxyoxindoles employing allylsilanes as the nucleophilic source to afford either allylation **1** or annulation [3+2] product **2** exclusively, depending on reaction conditions & stoichiometry employed (Scheme 1). Stability of highly substituted annulated product towards Lewis

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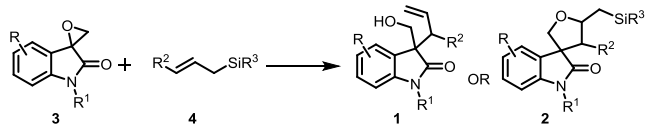
acid and fluoride source is also been demonstrated. The synthetic potential of the aforementioned route has been demonstrated by its successful application to the formal synthesis of (±)-physovenine.

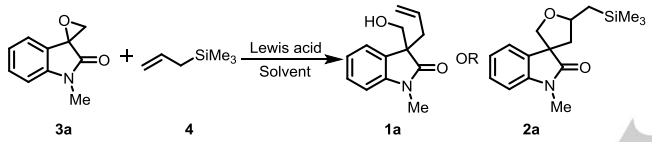


Scheme 1. Proposed concept: To generate quaternary carbon.

Results and Discussion

To validate our proposed design, we started our investigation by exploring various Lewis acids for regioselective ring opening of N-methyl spiro-epoxyoxindoles **3a** and allyltrimethylsilane **4** as a model substrate (Table 1).

Table 1. Optimization studies[a]



Entry	Lewis Acid	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	
					1a	**2a**
1	$Sc(OTf)_3$	DCE	0 °C	1	–	65
2	$Sc(OTf)_3$	CH_2Cl_2	0 °C	1	15	55
3	$Sc(OTf)_3$	CH_2Cl_2	25 °C	8	25	45
4	$Cu(OTf)_3$	CH_2Cl_2	25 °C	8	10	60
5	$Bi(OTf)_3$	CH_2Cl_2	25 °C	8	20	40
6	$FeCl_3$	CH_2Cl_2	0 °C	1	10	50
7	**$BF_3.OEt_2$**	**CH_2Cl_2**	**0 °C**	**0.5**	**–**	**72**[c]
8	$BF_3.OEt_2$	CH_2Cl_2	rt	24	10	65
9[d]	$BF_3.OEt_2$	CH_2Cl_2	0 °C	5 min	–	70
10[d]	$BF_3.OEt_2$	CH_2Cl_2	rt	25	58	20
11[e]	**$BF_3.OEt_2$**	**CH_2Cl_2**	**0 °C**	**2**	**75**	**–**
12[e, f]	$BF_3.OEt_2$	THF	rt	6	N.R	N.R
13[e]	$BF_3.OEt_2$	Toluene	0 °C	2	30	–
14[e]	$BF_3.OEt_2$	DCE	rt	8	15	52

[a] N-Methyl spiro-epoxyoxindole **3a** (0.28 mmol), Trimethylallylsilane **4** (0.56 mmol), and Lewis acid (20 mol%) in solvent (1 mL) were stirred at specified temperature.

[b] Isolated yield.

[c] *dr* determined by ^{1}H NMR analysis.

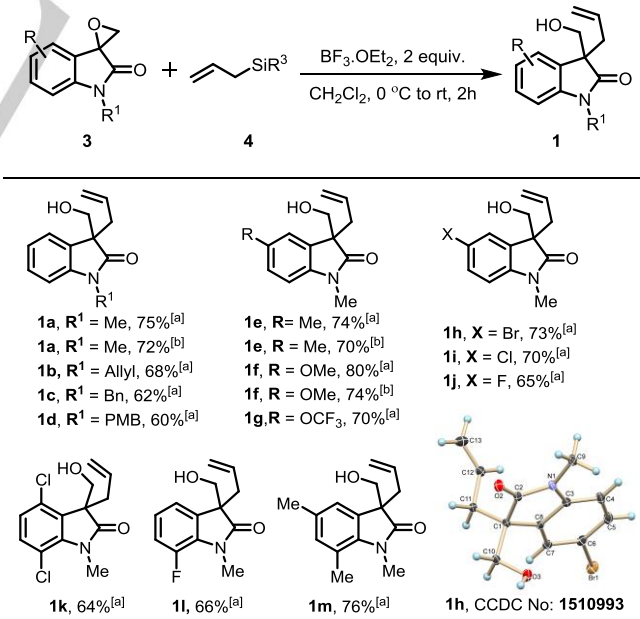
[d] 1 equiv. of $BF_3.OEt_2$ was used.

[e] 2 equiv. of $BF_3.OEt_2$ was used.

[f] 5 equiv. of $BF_3.OEt_2$, decomposition of **3a** was observed. NR: No reaction.

When the reaction was performed with 20 mol% of $Sc(OTf)_3$ in dichloroethane at 0 °C, the spiro annulated product **2a** was obtained in 65% yield (entry 1). On the other hand, when CH_2Cl_2 was used as solvent at 0 °C, the reaction afforded **2a** in 55% yield and allylated product **1a** in 15% yield (entry 2). 3-Allyl-3-(hydroxymethyl)-oxindole **1a** formed was an outcome of Hosomi-Sakurai type reaction, whereas spirooxindole **2a** formation proceeded through a trapping of transient *β*-silyl stabilized carbocation. [20] Even after prolonging the reaction time for 8 h at rt, the yield or selectivity of **1a** and **2a** (entry 3) could not be improved.

Next, we endeavored to optimize allylation **1a/** spiro-annulation **2a** products in a stepwise manner. Screening of different Lewis acids like $Cu(OTf)_2$, $Bi(OTf)_3$, and $FeCl_3$ didn't prove to be effective in terms of product selectivity (entries 4–6). Eventually the use of $BF_3.OEt_2$ resulted in the exclusive formation of spirooxindole **2a** with 72% yield at 0 °C in just about 30 mins (entry 7). Subsequently, the above results prompted us to monitor the reaction for longer time under similar reaction conditions, but spirooxindole **2a** was still observed as one of the major product (entry 8). Gratifyingly, when the reaction was carried out using 1 equivalent of $BF_3.OEt_2$, switch in the selectivity was observed (entry 10) furnishing allyloxindole product **1a** in 58% yield. Interestingly, when 2 equivalents of $BF_3.OEt_2$ were employed at 0 °C, 3-allyl-3-(hydroxymethyl)-oxindole was obtained exclusively in 75% yield (entry 11). Thus, slight modification in stoichiometry of $BF_3.OEt_2$ resulted in the tuning of product selectivity. Screening of solvents indicated that CH_2Cl_2 was optimal compared to toluene and DCE (entries 13–14), whereas no reaction was observed in THF (entry 12).

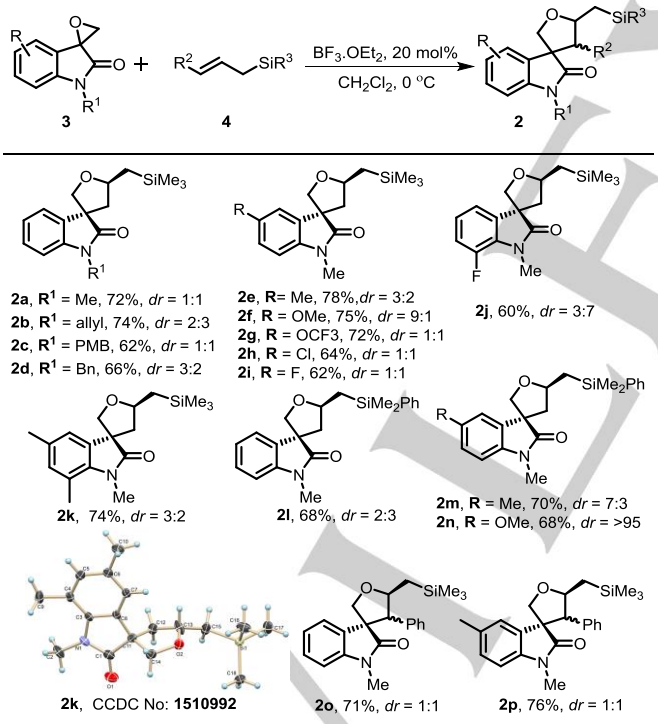


[a] Yields using (-$SiMe_3$) allylsilane and [b] Yields using (-$SiMe_2Ph$) allylsilane.

Scheme 2. Allylation reaction: Scope of spiro-epoxyoxindoles and allylsilanes.

The generality and scope of this method for allylation and spiro annulation reaction was explored using the optimized reaction conditions with an array of spiro-epoxyoxindoles **3** and allylsilanes **4**. First, we evaluated the scope of allylation reaction (Scheme 2) with a series of spiro-epoxyoxindoles bearing, N-methyl, N-*para*methoxybenzyl, N-benzyl and N-allyl substituents. These substrates were found compatible with the reaction condition, and reacted smoothly with allyltrimethylsilane to provide the desired Hosomi-Sakurai type of products **1a–m** in good to excellent yields (60–80%). Electronic influence of substituents at C5 and C7 of spiro-epoxyoxindoles has little or no impact on yields for electron donating and withdrawing substituents. The structural confirmation in the case of product **1h** was carried out using single-crystal X-ray analysis. Then, we studied the scope of the reaction with allyldimethylphenylsilane (–$SiMe_2Ph$) which worked equally well and underwent Hosomi-Sakurai type reaction, furnishing the expected product in good yields.

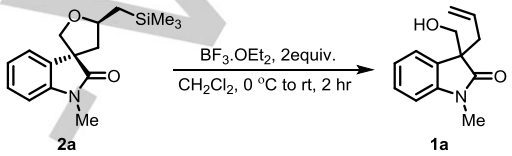
Further, the scope of spiro-annulation using substituted and unsubstituted allylsilanes **4** with spiro-epoxyoxindoles **3** was examined (Scheme 3) in order to determine the influence of the silyl group on yield and diastereoselectivity of products. With this aim, we screened different allylsilanes that favor the annulation pathway and also contain an oxidizable silane group with different steric and electronic properties.



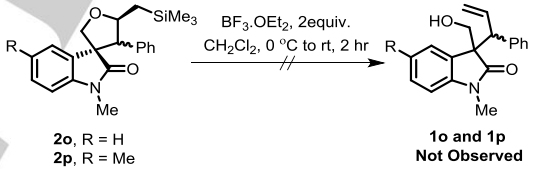
Scheme 3. Spirocyclization reaction: Scope of spiro-epoxyoxindoles and allylsilanes.

Under $BF_3.OEt_2$ catalyzed conditions, electronically dissimilar allylsilanes with different substitution patterns at silane motif (–$SiMe_3$, –$SiMe_2Ph$), added smoothly to spiro-epoxyoxindoles to afford the novel silicon containing spirocyclic oxindoles, as diastereomeric mixture in appreciable yields (60–78%). In case of substituted allylsilanes, three contiguous stereocenters (entry no **2o**-**2p**) are generated with a diastereomeric ratio of 1:1. The structure of spirocyclic oxindoles **2k** was further confirmed by single crystal X-ray crystallography.

To gain mechanistic insight of this transformation, we performed control experiments on few spirocyclic oxindoles **2a, 2o and 2p** as shown in scheme 4. The spirooxindole **2a** on treatment with $BF_3.OEt_2$ (2 equiv.) gave the desired allylated product **1a** (scheme 4a). On the other hand spirooxindole **2o** on treatment with $BF_3.OEt_2$ (2 to 5 equiv.) did not afford the allyl product **1o** but resulted either in recovery or decomposition of starting material. Even desilylation failed to occur in the presence of 4 equiv. of TBAF. Similar set of results were obtained when 5-methyl analogue of spirooxindole **2p** was used (Scheme 4b).



Scheme 4a. Control experiment using unsubstituted spirocyclic oxindole.

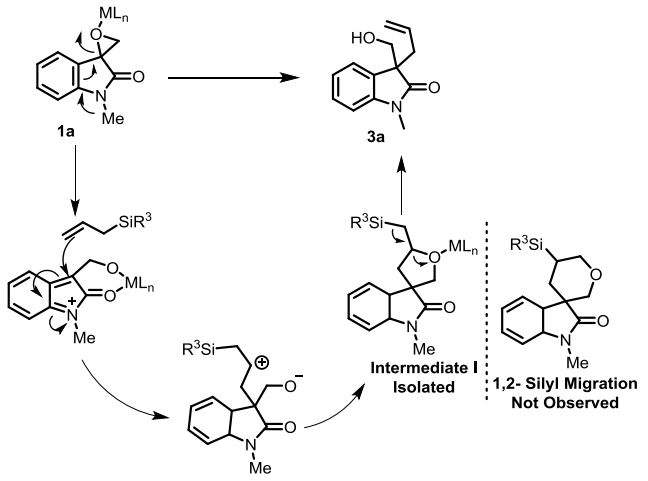


Scheme 4b. Control experiment using C3 substituted spirocyclic oxindoles.

Thus the spiro-annulated compound (**2a**) without any substituent at C3 position of THF ring easily underwent ring opening reaction as depicted in scheme 4a. But when a substituent is placed at C3 position,(**2o** & **2p**) it was difficult to eliminate the silyl group even in the presence of excess of Lewis acid and fluoride source (scheme 4b), suggesting the role of phenyl substituent in stabilizing *β*-carbocation. However, the exact role of the C3 substituent is not clear at this stage and further investigations are under progress.

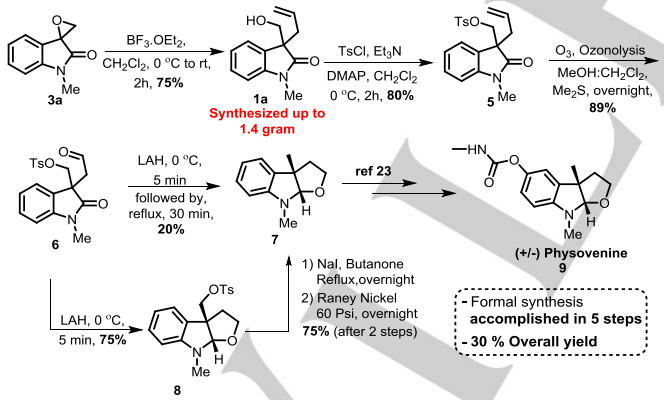
Based on the above results, a plausible mechanism for Lewis acid mediated opening of spiro-epoxyoxindole is given in (Scheme 5). Hosomi-Sakurai type reaction of spiroepoxide **3** with allylsilanes **4** could be triggered by chelation with Lewis acid $BF_3.OEt_2$, thus increasing the electrophilicity of the spiro-epoxyoxindole towards attack by allylsilane. The addition may lead to the formation of *β*-silyl stabilized carbocation as perceived through classical silicon chemistry. Although elimination of the silyl group from the carbocation would afford allylation product **1** in the classical cascade, it was observed that

the cation was intercepted by the nucleophilic oxygen [21] to afford spirocyclic-oxindole intermediate I. This intermediate was isolated and the structure of its 5,7-dimethyl analogue **2k** was conclusively established by single crystal X-ray**.** The annulation reaction, according to literature precedence; should proceed through 1,2-silyl migration [22] in the presence of bulky silyl groups. We observed no 1,2-silyl migration even with bulky (–$SiMe_2Ph$) silyl group.



Scheme 5. Plausible mechanism of Lewis acid-catalyzed spiro-epoxyoxindoles ring opening.

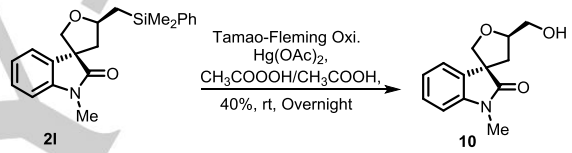
The synthetic potential and utility of this method was further demonstrated by formal synthesis of (±)-physovenine (Scheme 6).



Scheme 6. Formal synthesis of (±) physovenine.

Our synthetic journey commenced from gram scale opening of racemic spiro-epoxyoxindole **3a** and allylsilane **4a**, in presence of $BF_3.OEt_2$ to give Hosomi-Sakurai type product, **1a** in 75% yield with high regioselectivity. Tosylation of primary hydroxyl group furnished compound **5** in 80% yield, which was then subjected under ozonolysis conditions to give the key precursor spirooxindole aldehyde **6** in 89% yield. Finally, cyclization followed by displacement of tosyl group in one pot using LAH under reflux provided intermediate **7** in 20% yield. In order to improve the yield of **7,** we conceptualized a stepwise transformation. In this regard compound **6** was treated with 4 equivalents of LAH at 0 °C to give fused compound **8** in 75% yield. Displacement of tosylate using NaI, under reflux in butanone gave iodo compound, which was further subjected to hydrogenation without any purification to give final intermediate **7** in 75% yield after 2 steps. In two additional steps, the intermediate **7** could be transformed to (±)-physovenine, [23] thus completing the formal synthesis of target molecule **9** in 5 steps with an overall yield of **30**% starting from spiro-epoxyoxindole **3a**

Silicon containing spirocyclic oxindoles serve as potential synthon to various biological active compounds. To demonstrate the synthetic utility derived from oxidation of the C–Si bond, [24] an interesting organic transformations using Tamao-Fleming oxidation was carried out to functionalize silyl group (i.e., to access the corresponding alcohol **10**) using compound **2l** as shown in (Scheme 7) which can serve as important building block. [25]



Scheme 7. Synthetic utility of spiro-annulated silyl product.

Conclusions

In summary, we have developed a versatile and highly regioselective strategy for the synthesis of 3-allyl-3-(hydroxymethyl)-oxindoles as well as novel silicon containing spirocyclic oxindoles *via* Lewis acid mediated ring opening of spiro-epoxy oxindoles with allylsilanes. Allylated and annulated product are solely dependent on the stoichiometry of Lewis acid used. Substituted allylsilanes give access to spirocyclic oxindoles, having three contiguous stereocenters and show unusual stability towards Lewis acid, which is one of the important key findings of our method. A formal synthesis of (±)-physovenine is achieved in **5** steps starting from cheap and easily accessible spiro-epoxy oxindole **3a**.

Experimental Section

General Experimental Methods

All reactions were carried out under anhydrous conditions, using flame-dried glassware under a positive pressure of argon unless otherwise mentioned. Dichloroethane, CH_2Cl_2, Et_3N, and *i*-Pr_2NEt were distilled from CaH_2; Et_2O, Toluene and THF were distilled from Na/benzophenone. Other reagents were obtained from commercial suppliers and used as received. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa.

Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm precoated silica gel plates (60 F254). Visualization was accomplished with either UV light, iodine adsorbed on silica gel, or by immersion in ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde, or KMnO4 followed by heating with a heat gun for ~15 s. Flash chromatography was performed on silica gel (230−400 mesh). All ^{1}H NMR and ^{13}C NMR spectra were obtained using a 200, 400, or 500 MHz spectrometer in $CDCl_3$. Coupling constants were measured in Hertz. All chemical shifts were quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet and br = broad. HRMS (ESI^+) were recorded on an ORBITRAP mass analyzer. Infrared (IR) spectra were recorded on a FT-IR spectrometer as thin films using NaCl plates, wave numbers are indicated in cm^{-1}. Optical rotations were measured using a polarimeter with a 1 dm path length. Chemical nomenclature was generated using Chem Bio Draw Ultra 14.0.

General procedure for allylation reaction of spiro–epoxyoxindoles with allylsilanes

General procedure A: To a stirred solution of spiro-epoxyoxindoles **3** (0.28 mmol, 1.0 eq.) and allyllsilane **4** (0.56 mmol, 2.0 eq.) in CH_2Cl_2 (1.0 mL) at 0 °C was added $BF_3.OEt_2$ (0.56 mmol, 2 eq.) dropwise and the reaction was stirred for 2 h at rt. After completion as monitored by TLC, the reaction was quenched with water and the reaction mixture was sequentially washed with brine (2 mL), sat. aq. $NaHCO_3$ (2 x 2 mL), extracted with CH_2Cl_2 (3×5 mL), dried over $NaSO_4$ and concentrated in vacuo. Purification by flash column chromatography using petroleum ether/ethyl acetate gave product **1a-m**.

General procedure for annulation reaction of spiro–epoxyoxindoles with allylsilanes

General procedure B: A mixture of spiro-epoxyoxindole **3** (0.28 mmol, 1.0 eq.), allylsilane **4** (0.56 mmol, 2.0 eq.) and $BF_3.OEt_2$ (0.056 mmol, 20 mol %) in CH_2Cl_2 (1.0 mL) was stirred at 0 °C for 0.5 h. The reaction was monitored by TLC until consumption of spiro-epoxyoxindole **3**, and then the reaction mixture was directly loaded onto a silica gel column and purified using ethyl acetate/petroleum ether as eluents to give product **2a-p.**

Formal synthesis of (±)–physovenine

(3-Allyl-1-methyl-2-oxoindolin-3-yl)methyl4-methylbenzenesulfonate (5). Compound **1a** (1 g, 4.60 mmol) was dissolved in dry CH_2Cl_2 (10 mL) under argon, and the solution was treated with TsCl (1.1 g, 5.52 mmol), Et_3N (1.6 mL, 11.51 mmol) and catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 2 h and then quenched with water. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were washed with brine, concentrated, and the residue was purified by flash column chromatography (pet. ether/ethyl acetate = 4:1) to afford **5** (1.370 g, 80%) as a pale yellow solid; mp = 83 ºC; *Rf* = 0.63 (pet. ether/ethyl acetate = 3:2); IR ($CHCl_3$): ν_{max} = 3423, 3017, 2936, 1718, 1612, 1469, 1359, 1181, 1096, 984, 837, 754 cm^{-1}; ^{1}H NMR (400 MHz , $CDCl_3$) δ = 7.63 (d, *J* = 8.2 Hz, 2 H), 7.33 - 7.28 (m, 3 H), 7.19 (dd, *J* = 0.9, 7.8 Hz, 1 H), 7.04 (ddd, *J* = 0.9, 7.8, 7.8 Hz, 1 H), 6.82 (d, *J* = 7.8 Hz, 1 H), 5.32 (dddd, *J* = 6.9, 7.8, 10.1, 16.9 Hz, 1 H), 5.01 - 4.95 (m, 1 H), 4.93 - 4.89 (m, 1 H), 4.28 (d, *J* = 9.2 Hz, 1 H), 4.14 (d, *J* = 9.2 Hz, 1 H), 3.16 (s, 3 H), 2.56 (dd, *J* = 6.9, 13.7 Hz, 1 H), 2.51 - 2.45 (m, 1 H), 2.45 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.6, 144.9, 143.7, 132.3, 130.5, 129.8, 128.7, 128.1, 127.9, 123.9, 122.7, 119.7, 108.2, 72.0, 52.1, 37.8, 26.2, 21.6; HRMS (ESI^+) calcd for $C_{20}H_{21}NO_4S$ $[M+H]^+$ 372.1256, found 372.1264.

(1-Methyl-2-oxo-3-(2-oxoethyl)indolin-3-yl)methyl 4-methyl benzenesulfonate (6). Ozone was bubbled through a solution of **5** (1 g, 2.69 mmol) in CH_2Cl_2 (50 mL) and MeOH (50 ml) at -78 °C until the solution colour turned to violet. Oxygen gas was bubbled into the reaction mixture for 5 min. After Me_2S (0.5 mL, 6.73 mmol) was added, the mixture was warmed to room temperature, stirred overnight, and then concentrated. The remaining solvents were removed using rotavapour under reduced pressure to afford the crude aldehyde, which was purified through flash silica gel column chromatography using (pet. ether/ethyl acetate = 3:2) to afford compound **6** (895 mg, 89%) as a colourless solid; mp = 110 ºC; *Rf* = 0.32 (pet. ether/ethyl acetate = 1:1); IR ($CHCl_3$): ν_{max} = 3424, 3022, 1714, 1617, 1494, 1372, 1217, 988, 760 cm^{-1}; ^{1}H NMR (400 MHz , $CDCl_3$) δ = 9.40 (s, 1 H), 7.61 (d, *J* = 7.9 Hz, 2 H), 7.30 - 7.21 (m, 3 H), 7.16 (d, *J* = 7.3 Hz, 1 H), 6.97 (t, *J* = 7.3 Hz, 1 H), 6.82 (d, *J* = 7.3 Hz, 1 H), 4.23 (d, *J* = 9.8 Hz, 1 H), 3.93 (d, *J* = 9.2 Hz, 1 H), 3.18 (s, 3 H), 3.13 (d, *J* = 18.3 Hz, 1 H), 2.95 (d, *J* = 18.3 Hz, 1 H), 2.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.9, 175.0, 145.2, 143.8, 132.1, 129.9, 129.2, 127.9, 127.7, 123.8, 122.9, 108.6, 72.2, 48.6, 46.3, 26.6, 21.6; HRMS (ESI^+) calcd for $C_{19}H_{19}NO_5S$ $[M+H]^+$ 374.1052, found 374.1057.

3a,8-Dimethyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole (7). To a solution of aldehyde **6** (500 mg, 1.34 mmol) in THF (10 mL) at 0 ºC was added solid $LiAlH_4$ (255 mg, 6.69 mmol). After completion of reaction as indicated by TLC after 5 min, the same reaction mixture was further heated at reflux for 2 h. After cooling to room temperature, excess hydride was decomposed by adding EtOAc (15 mL) dropwise. Saturated aqueous $NaHCO_3$ (15 mL) was added, the phases were separated, the aqueous layer was extracted with EtOAc (2 × 15 mL), and the combined organic extracts were washed with brine (14 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash column chromatography using (pet. ether/ethyl acetate = 98:2) gave fused compound **7** (50 mg, 20%) as a pale yellow liquid; *Rf* = 0.41 (pet. ether/ethyl acetate = 95:5); IR ($CHCl_3$): ν_{max} = 3447, 3052, 2959, 1608, 1494, 1388, 1300, 1123, 1013, 918, 740 cm^{-1}; ^{1}H NMR (500 MHz , $CDCl_3$) δ = 7.11 (ddd, *J* = 1.1, 7.6, 7.6 Hz, 1 H), 7.05 (dd, *J* = 1.1, 7.3 Hz, 1 H), 6.69 (ddd, *J* = 1.1, 7.3, 7.3 Hz, 1 H), 6.38 (d, *J* = 7.6 Hz, 1 H), 5.08 (s, 1 H), 3.96 (ddd, *J* = 1.5, 7.3, 8.7 Hz, 1 H), 3.47 (ddd, *J* = 5.3, 8.7, 11.4 Hz, 1 H), 2.93 (s, 3 H), 2.14 (ddd, *J* = 1.5, 5.3, 11.8 Hz, 1 H), 2.06 (ddd, *J* = 7.3, 11.8, 11.8 Hz, 1 H), 1.47 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 150.4, 134.5, 128.1, 122.4, 117.3, 105.0, 104.8, 67.3, 52.3, 41.7, 30.9, 24.7; HRMS (ESI^+) calcd for $C_{12}H_{15}NO$ $[M+H]^+$ 190.1225, found 190.1226.

(8-Methyl-2,3,8,8a-tetrahydro-3aH-furo[2,3-b]indol-3a-yl)methyl 4-methylbenzenesulfonate (8). To a 50 mL two neck round bottom flask containing a solution of compound **6** (200 g, 0.54 mmol) in THF (5 mL) was cooled to 0 °C. LAH (0.082 g, 2.14 mmol) was added to the reaction mixture under an Ar-atmosphere and was stirred at 0 °C for 5 min. EtOAc (10 mL) followed by a sat. NaCl (aq) (5 mL) were added. The organic layers were washed with water and brine solution, dried over Na_2SO_4 and concentrated. The resultant crude product was purified by flash column chromatography (pet. ether/ethyl acetate = 85:15) to produce **8** (144 mg, 75%) as a colourless liquid; *Rf* = 0.23 (pet. ether/ethyl acetate = 4:1); IR ($CHCl_3$): ν_{max} = 3449, 3053, 2941, 1606, 1495, 1361, 1179, 1020, 853, 747 cm^{-1}; ^{1}H NMR (200 MHz , $CDCl_3$) δ = 7.65 (d, *J* = 8.3 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 7.05 (ddd, *J* = 1.3, 7.6, 7.6 Hz, 1 H), 6.88 (dd, *J* = 0.9, 7.3, 7.3 Hz, 1 H), 6.54 (ddd, *J* = 0.9, 7.3, 7.3 Hz, 1 H), 6.28 (d, *J* = 7.8 Hz, 1 H), 5.12 (s, 1 H), 4.14 (d, *J* = 9.6 Hz, 1 H), 4.02 (d, *J* = 9.7 Hz, 1 H), 3.89 (ddd, *J* = 1.5, 7.5, 8.7 Hz, 1 H), 3.41 (ddd, *J* = 5.3, 8.7, 11.0 Hz, 1 H), 2.80 (s, 3 H), 2.38 (s, 3 H), 2.17 (ddd, *J* = 7.5, 11.0, 11.0 Hz, 1 H), 1.95 (ddd, *J* = 1.5, 5.3, 11.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 151.0, 144.9, 132.6, 129.9, 129.3, 128.1, 127.9, 123.4, 117.4, 105.3, 100.4,

71.8, 66.8, 56.3, 36.4, 30.7, 21.6; HRMS (ESI^+) calcd for $C_{19}H_{21}NO_4S$ $[M+H]^+$ 360.1264, found 360.1264.

3a,8-Dimethyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole (7). The tosylate **8** (100 mg, 0.278 mmol) was treated with sodium iodide (0.417 g, 2.782 mmol) in refluxing 2-butanone (10 mL) for 6h. After completion of reaction, the cooled mixture was filtered through the pad of celite. Concentration of the filtrate under reduced pressure afforded crude iodo compound in 88%yield.

To a crude solution of iodo compound and triethylamine (590 mg, 58.4 mmol) in dry methanol was added freshly prepared Raney nickel (0.05 g) and the reaction mixture was stirred under an atmosphere of H_2 (60 psi) overnight at 25 °C. After the completion of the reaction (monitored by TLC), the reaction mixture was filtered over celite and the filtrate was concentrated under reduced pressure to provide the reduced compound, which was purified by flash column chromatography using (pet. ether/ethyl acetate 98:2) to give fused compound **7** (39 mg, 75% over 2 steps) as a pale yellow liquid; *Rf* = 0.41 (pet. ether/ethyl acetate = 95:5).

Synthetic utility of product

5-(Hydroxymethyl)-1'-methyl-4,5-dihydro-2H-spiro[furan-3,3'-indolin]-2'-one (10). Mercuric acetate (27 mg, 0.085 mmol) was added to a stirred solution of the compound **2l** (20 mg, 0.27 mmol) in peracetic acid (0.72 ml of a 15% solution in acetic acid, containing 1% sulphuric acid, 1.482 mmol), and the mixture kept for 8 h at room temperature. Ether (5 ml) was added and the solution washed with sodium thiosulphate solution, water, sodium hydrogen carbonate solution, and brine, dried ($MgSO_4$), and evaporated in vacuo. The resulting oil was purified by flash silica gel column chromatography eluting with (pet. ether/ethyl acetate = 30:70) to give the compound **10** (5 mg, 40%, *dr* ~ 1:1 by NMR) as a colourless liquid; *Rf* = 0.52 (ethyl acetate); IR ($CHCl_3$): ν_{max} = 3426, 2924, 2855, 1697, 1613, 1469, 1353, 1257, 1110, 756 cm^{-1}; ^1H NMR (400 MHz , $CDCl_3$) δ = 7.37 - 7.27 (m, 2 H), 7.17 - 7.06 (q, *J* = 7.9 Hz, 1 H), 6.86 (dd, *J* = 7.9, 13.4 Hz, 1 H), 4.61 - 4.53 (m, 0.5 H), 4.53 - 4.44 (m, 0.5 H), 4.19 – 3.88 (m, 3 H), 3.83 - 3.72 (m, 1 H), 3.24 (d, *J* = 3.7 Hz, 3 H), 2.44 (ddd, *J* = 4.8, 7.3, 12.2 Hz, 1 H), 2.20 (dd, *J* = 7.3, 12.8 Hz, 1 H), 2.11 (dd, *J* = 9.2, 12.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 178.6, 178.3, 143.1, 143.0, 133.5, 132.1, 128.4, 128.2, 123.1, 122.7, 122.6, 108.3, 108.0, 80.9, 80.8, 77.2, 76.1, 64.1, 63.8, 54.7, 54.6, 39.4, 38.5, 26.5, 26.4; HRMS (ESI^+) calcd for $C_{13}H_{15}NO_3$ $[M+H]^+$ 234.1125, found 234.1125.

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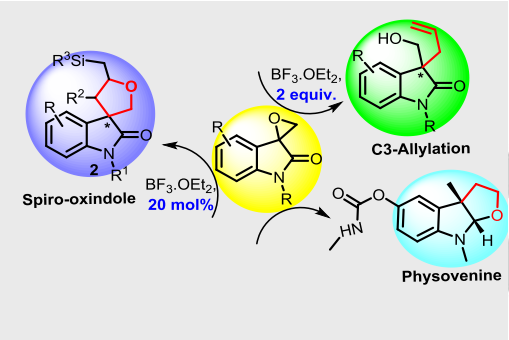
Entry for the Table of Contents

FULL PAPER

Lewis acid switch: C3-functionalization of 2-oxindoles *via* Lewis acid promoted opening of spiro-epoxyoxindoles with allylsilanes to give Hosomi-Sakurai type products as well as spirocyclic oxindoles with all-carbon quaternary has been developed. A formal synthesis of (±) physovenine is accomplished in 5 steps using this protocol.



*Brijesh M. Sharma, Mahesh Yadav, Rajesh G. Gonnade and Pradeep Kumar**

Unified Approach for Fused and Spirocyclic Oxindoles via Lewis Acid Promoted Opening of Spiro-epoxyoxindoles with Allylsilanes: Application to Formal Synthesis of (±)-Physovenine