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Reversal of Selectivity in C3-Allylation and Formal [3 + 2]-Cycloaddition of Spiro-epoxyoxindole: Unified Synthesis of Spiro-furanooxindole, (±)-*N*-Methylcoerulescine, (±)-Physovenine, and 3a-Allylhexahydropyrrolo[2,3-*b*]indole

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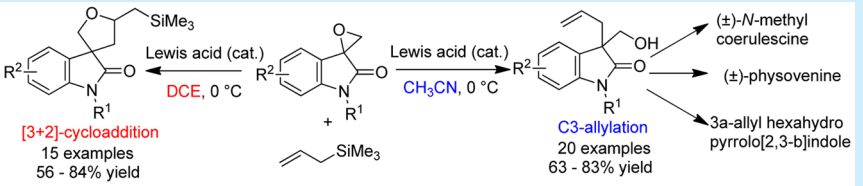
Supporting Information



ABSTRACT: An effective Lewis acid catalyzed regioselective C3-allylation and a formal [3 + 2]-annulation reaction of spiro-epoxyoxindoles have been developed and can be accessed simply by changing the reaction conditions. This method has been successfully employed for the synthesis of spiro(pyrrolidinyloxindole), 3a-allylhexahydropyrrolo[2,3-*b*]indole, and furanoindoline.

The construction of small molecules bearing an all-carbon quaternary center at the C3-position of oxindole has garnered considerable research interest in recent years because of the remarkable prevalence of such molecules in innumerable natural products.[1] The synthesis of spiro(pyrrolidinyloxindole) alkaloids, namely, horsfiline[2] and coerulescine,[3] has attracted the attention of synthetic chemists due to their intriguing molecular architecture and their broad range of pharmacological properties, which include anticancer, antimigraine, and contraceptive activities. On the other hand, hexahydropyrrolo[2,3-*b*]indole (HPI) ring systems with a carbon atom at the pseudobenzylic site of oxindole are found in a wide range of biologically active indole alkaloids[4] such as physostigmine. In particular, HPI rings with C3-3,3-dimethyl allyl substituents are present in natural products such as flustramine B, the pseudophrynamines, and mollenine A. Analogously, the C3-1,1-dimethyl allyl motif is also present in indole alkaloids such as brevicompanine B and flustramines A and C. All of these molecules[5] feature 3a-allylhexahydropyrrolo-[2,3-*b*]indole as a subunit (Figure 1).

The paramount clinical significance and the unique structural array of these molecules have inspired us to find a unified strategy to synthesize them or their congeners from a common precursor. A number of synthetic strategies toward the construction of an all-carbon quaternary center, followed by the synthesis of the aforementioned molecules, have been reported thus far in the literature.[6] The examples of (i) the Pd[6b]- and Mo[6c]-catalyzed allylic alkylation by Trost et al., (ii) catalytic allylation of 3-aryloxindoles by merging Pd-catalysis and H-bond catalysis by the Xiao group,[6d] (iii) catalytic Meerwein−Eschenmoser Claisen

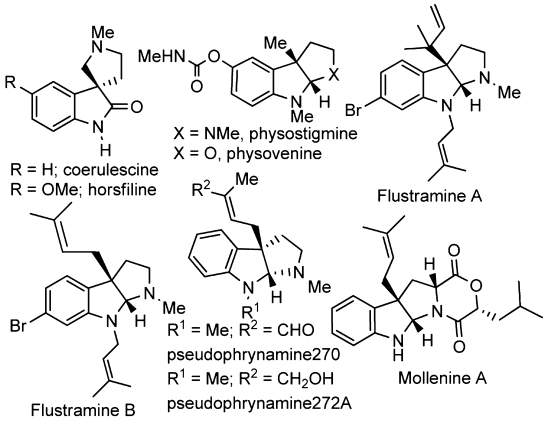


Figure 1. Several representative spiro(pyrrolidinyloxindole) and hexahydropyrrolo[2,3-*b*]indole alkaloids.

rearrangement by Kozlowski,[6e] (iv) double C−H activation for the synthesis of 3,3′-disubstituted oxindoles by Taylor et al.,[6f] (v) Cu-catalyzed intramolecular arylation-alkylation for the synthesis of HPIs by Zhang,[6g] (vi) thiourea-catalyzed aldol reactions with paraformaldehyde for the synthesis of HPIs and spiro-(pyrrolidinyloxindole) by the Bisai group,[6h] and (vii) the combination of Ru-catalyzed C−H functionalization with Pd-

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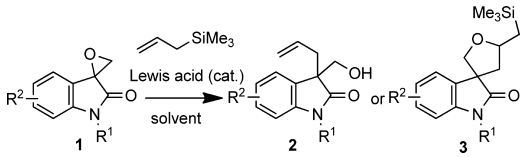
catalyzed allylic alkylation by Lautens et al.[6i] are worthy of attention.

Scrutinizing all of these literature reports, one can recognize C3-allyl oxindole−methanol or the corresponding ester as a versatile antecedent. To the best of our knowledge, literature reports of the Hosomi−Sakurai allylation of epoxides[7] are sparse; moreover, we know of no reports on the allylation of spiro-epoxyoxindole. The result of the regioselective ring opening of spiro-epoxyoxindole with nucleophiles such as indoles and arenes by our group[8] and later by Wei et al.[9] encouraged us to explore the regioselective allylation of spiro-epoxyoxindole with a potent nucleophile such as allyltrimethylsilane. When the reaction was performed using our previously developed method,[8] only a small amount of the desired 3a-allyloxindole−methanol product was obtained; however, a substantial amount of an unexpected [3 + 2]-annulated product was obtained. The existing literature confirmed the identity of this cycloadduct.[11] Interestingly, this annulated spirofuranooxindole moiety is also an important framework because it is present as a fundamental structural unit in XEN907 and XEN402, which are in phase IIb clinical trials for the treatment of chronic pain.[10] Therefore, the development of a method for the synthesis of both functionalities with appreciative selectivity is highly desirable. Herein, we describe a solvent-dependent, Lewis acid catalyzed, and highly regioselective Hosomi−Sakurai allylation as well as a formal [3 + 2]-cycloaddition of spiro-epoxyoxindole (Scheme 1). This

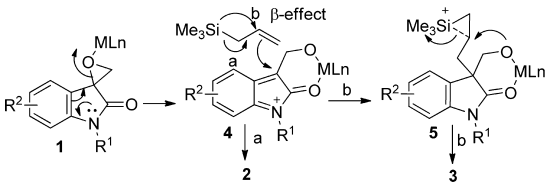
Scheme 1. Reaction of Spiro-epoxyoxindole 1 with Allylsilane



method also provides direct access to 3-allyl-3-(hydroxymethyl)-oxindole, which was effectively utilized in the synthesis of spiro(pyrrolidinyloxindole), 3a-allylhexahydropyrrolo[2,3-*b*]-indole, and furanoindoline.

If we deeply explore a plausible mechanism for the Hosomi−Sakurai allylation and the [3 + 2]-annulation reaction, the result can be rationalized through the addition of allylsilane to reactive 2*H*-indol-2-one intermediate **4**, formed upon treatment of spiro-epoxyoxindole with a Lewis acid (Scheme 2). Path a in Scheme 2

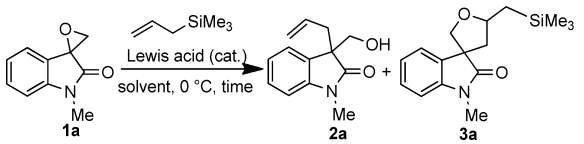
Scheme 2. Plausible Mechanism for C3-Allylation and [3 + 2]-Annulation Reaction



shows the allylation reaction proceeding through the direct addition of the allyl group to indolone intermediate **4** as a consequence of C−Si bond cleavage; by contrast, path b leads to the formation of a spiro-oxindole type annulated product, which can be explained by the well-known *β*-silicon effect. Consequently, both the solvent and the Lewis acid may strongly affect the course of the reaction.

We therefore commenced our investigation on the regioselective ring opening of model substrate *N*-methyl spiro-epoxyoxindole **1a** with allyltrimethylsilane by varying the Lewis acid and solvent (Table 1; for details, see the SI). As previously

Table 1. Optimization of Reaction Conditions[a]



				yield[b] (%)	
entry	Lewis acid	solvent	time (h)	**2a**	**3a**
1	**Sc(OTf)$_3$**	**DCE**	**1**	**22**	**65**
2	In(OTf)$_3$	DCE	1	20	56
3	Cu(OTf)$_2$	DCE	1.5	23	55
4	BF$_3$·OEt$_2$	DCE	1	18	63
5	Y(OTf)$_3$	DCE	1.5	<5	49
6	Sc(OTf)$_3$	CH_2Cl_2	1	21	56
7	Y(OTf)$_3$	CH_2Cl_2	6	10	45
8	Y(OTf)$_3$	$CHCl_3$	6	9	34
9	**Sc(OTf)$_3$**	**CH_3CN**	**1**	**78**	**<5**
10	In(OTf)$_3$	CH_3CN	1	72	10
11	Cu(OTf)$_2$	CH_3CN	1.5	70	15
12	Y(OTf)$_3$	CH_3CN	6	24	<5
13	BF$_3$·OEt$_2$	CH_3CN	6	26	10

[a]*N*-Methyl spiro-epoxyoxindole **1a** (0.57 mmol), trimethylallylsilane (1.7 mmol), and Lewis acid (10 mol %) in solvent (4 mL) were stirred at 0 °C. [b]Isolated yield.

described, when the initial attempt was performed in DCE at 0 °C using 10 mol % of Sc(OTf)$_3$, only 22% of 3-allyl-3-(hydroxymethyl)oxindole **2a** was obtained along with 65% of [3 + 2]-cycloadduct **3a** within 1 h (entry 1). Changing the Lewis acid to In(OTf)$_3$, Cu(OTf)$_2$, Bi(OTf)$_3$, Yb(OTf)$_3$, Zn(OTf)$_2$, and BF$_3$·OEt$_2$ in DCE and CH_2Cl_2 did not improve the product distribution. However, the cycloadduct **3a** was obtained almost exclusively using 10 mol % of Y(OTf)$_3$ within 1.5 h, but the yield was not satisfactory since a significant amount of undesired as well as uncharacterized products was formed (entry 5). With this promising result, we further applied Y(OTf)$_3$ in other chlorinated solvents like CH_2Cl_2 and $CHCl_3$ but ended up with unsatisfactory results (entry 7 and 8).

However, to our delight, after the solvent was changed from DCE to the more polar acetonitrile, we obtained the C3-allylated product **2a** almost exclusively in the presence of 10 mol % of Sc(OTf)$_3$ (entry 9). With the aforementioned encouraging result in hand, we screened different Lewis acids in acetonitrile. Whereas In(OTf)$_3$, Cu(OTf)$_2$, and Bi(OTf)$_3$ displayed comparable results, BF$_3$·OEt$_2$, Yb(OTf)$_3$, Y(OTf)$_3$, and Zn(OTf)$_2$ were not as successful. The reaction in THF with Sc(OTf)$_3$ was sluggish, whereas almost no reaction was observed in toluene. Thus, DCE was shown to be the best solvent for annulation, whereas the Hosomi−Sakurai allylation reaction was favored in acetonitrile.

On the basis of the aforementioned optimization, we further explored the substrate scope of the annulation and that of the allylation reaction with an array of spiro-epoxyoxindoles and allyltrimethylsilane. First, we executed the regioselective Hosomi−Sakurai allylation reaction with spiro-epoxyoxindoles bearing different protecting groups in acetonitrile (Figure 2). All *N*-methyl, *N*-benzyl, *N*-allyl, and *N*-prenyl epoxides smoothly

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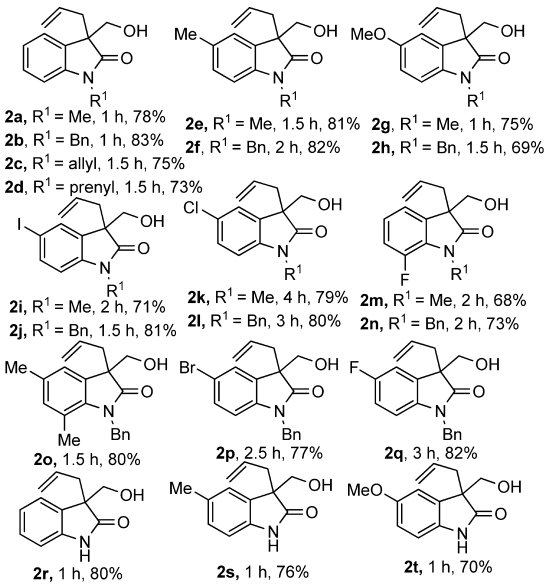


Figure 2. Substrate scope for the C3-allylation reaction.

underwent the allylation reaction with excellent regioselectivity under the optimized conditions to give the corresponding product in good to excellent yield (69−83%). Substituents on the spiro-epoxyoxindoles had little effect on the rate of the reactions. Whereas electron-donating substituents accelerated the allylation reactions, causing them to be completed within 1−2 h, electron-withdrawing substituents on the spiro-epoxyoxindoles prolonged the reaction time to 4 h. The reaction was also evaluated with unprotected spiro-epoxyoxindoles. $Cu(OTf)_2$ in acetonitrile was found to be the highest yielding catalyst, flawlessly furnishing the allylation product **2r−t** with excellent selectivity.

Next, the scope of the [3 + 2]-annulation reaction employing allyltrimethylsilane and different spiro-epoxyoxindoles was investigated in DCE (Figure 3). $Sc(OTf)_3$ (10 mol %) was optimal for all *N*-methyl and *N*-allyl spiro-epoxyoxindoles, whereas 10 mol % of $BF_3{\cdot}OEt_2$ was found to be the best catalyst in terms of the yield and feasibility of the annulation reaction for all

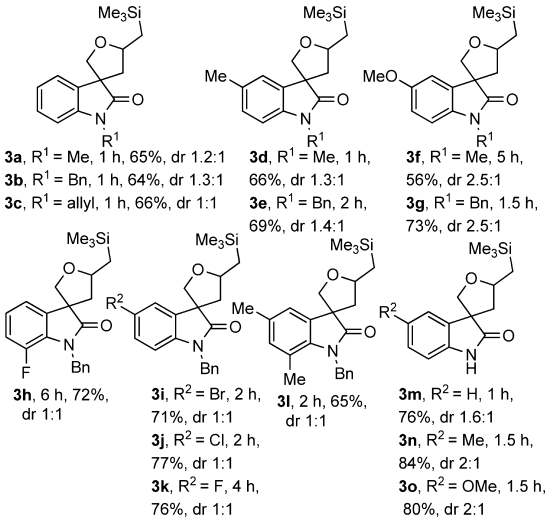
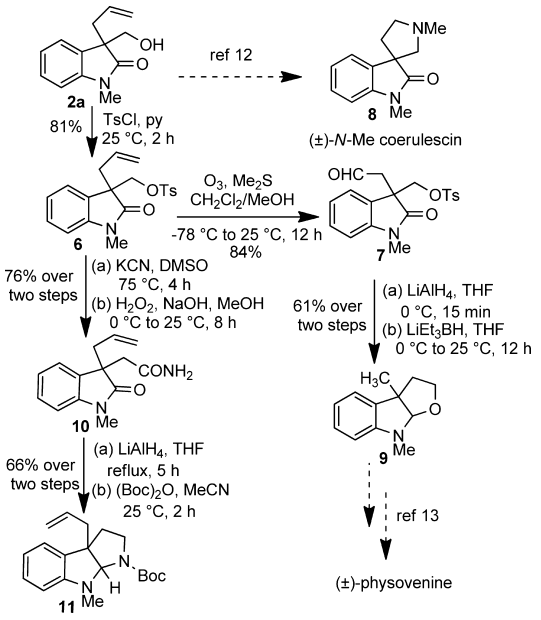


Figure 3. Substrate scope for the [3 + 2]-annulation reaction (10−22% of the C3-allylation product was obtained in the case of **3a−l**; **3m−o** were obtained almost exclusively (>95%)).

N-benzyl spiro-epoxyoxindoles. However, a fine-tuning of the Lewis acid to $In(OTf)_3$ afforded almost exclusively the product of the annulation reaction in good yield for unprotected spiro-epoxyoxindoles. A number of these spirocyclic oxindoles were obtained with a diastereomeric ratio of 1:1, although some of them exhibited better selectivity. It was also noteworthy that the cycloadduct **3a** was partly converted to allylated product **2a** when treated with an excess of $Sc(OTf)_3$ in acetonitrile at ambient temperature, but the same was not observed in DCE. This result validated our presumption that a polar solvent facilitated the C−Si bond cleavage, whereas the β-silicon effect was predominant in nonpolar solvent.

As previously mentioned, we were interested in 3-allyl-3-(hydroxymethyl)oxindole moieties because they are key precursors in the synthesis of a large variety of bioactive natural products and pharmaceuticals. As an application of this reaction, an initial effort was devoted to the synthesis of spiro-(pyrrolidinyloxindole) (Scheme 3). This 3-allyl-3-(hydroxy-

Scheme 3. Synthesis of (±)-*N*-Methylcoerulescine, (±)-Physovenine, and 3a-Allylic Pyrroloindole from 2a



methyl)oxindole **2a** could be converted to (±)-*N*-methylcoerulescine **8**, applying a previously reported procedure.[12] Again, tosylation of the primary hydroxyl group in 3-allyl-3-(hydroxymethyl)oxindole **2a** followed by ozonolysis provided another relevant intermediate, aldehyde **7**. Furthermore, aldehyde **7** was efficiently transformed into furanoindole when treated with $LiAlH_4$ at 0 °C. Expulsion of the −OTs group with the assistance of superhydride ($LiEt_3BH$) provided another advanced intermediate **9** in satisfactory yield that could be easily converted into the furanoindoline alkaloid (±)-physovenine via a reported literature procedure.[13] The synthetic potential and effectiveness of this method were further elaborated through the synthesis of 3a-allylhexahydropyrrolo[2,3-*b*]indole. Cyanation of tosylated compound **6** by vigilant use of potassium cyanide afforded oxindole cyanide. Partial hydrolysis of this crude cyanide compound using hydrogen peroxide with sodium hydroxide in methanol furnished amide **10** in good yield. This reaction was followed by reductive cyclization accomplished by applying $LiAlH_4$ in boiling THF to furnish C3-allyl pyrroloindole. Boc

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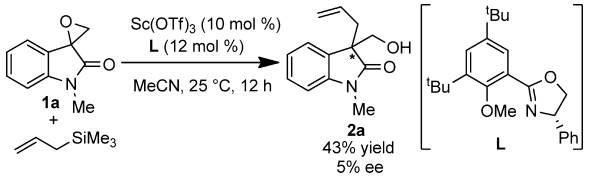
protection of this compound simplified its purification. This Boc-protected 3a-allylhexahydropyrrolo[2,3-*b*] indole **11** could be converted into the corresponding aldehyde compound, a formidable intermediate for the synthesis of the pseudophrynamine family of 3a-prenylated hexahydropyrrolo[2,3-*b*]indole alkaloids through the application of a previously reported procedure.[6h]

Finally, we extended our strategy toward the asymmetric ring-opening reaction of spiro-epoxyoxindole using several chiral ligands but hardly found any encouraging results (for details, see the SI). Only the chiral ligand L with $Sc(OTf)_3$ furnished the product **2a** with very low enantioselectivity (5% ee, Scheme 4).

Scheme 4. Asymmetric Version of C3-Allylation Reaction



In conclusion, we have accomplished a convenient, versatile, Lewis acid-catalyzed and highly selective C3-allylation as well as a formal [3 + 2]-annulation reaction of spiro-epoxyoxindoles that can be accessed simply by manipulating the reaction conditions. Whereas the annulation reactions furnished silicon-containing spiro-furanooxindoles, the Hosomi−Sakurai allylation of the spiro-epoxyoxindoles provided facile access to 3-allyl-3-(hydroxymethyl)oxindole, a useful intermediate for the synthesis of (±)-*N*-methylcoerulescine and the formal synthesis of (±)-physovenine. As a related application, 3-allyl-3-(hydroxymethyl)oxindole **2a** has been neatly transformed into 3a-allylhexahydropyrrolo[2,3-*b*]indole, a subunit of a large number of members of the HPI-alkaloid family. Further studies on the utility of spiro-epoxyoxindoles and their applications, including asymmetric ring-opening reactions, are currently being investigated in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00420.

Experimental details, characterization data and spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to Prof. Dipakranjan Mal (IIT Kharagpur) on the occasion of his 65th birthday.

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