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Flexible Strategy for Syntheses of Spirooxindoles using Palladium-Catalyzed Carbosilylation and Sakurai-Type Cyclization

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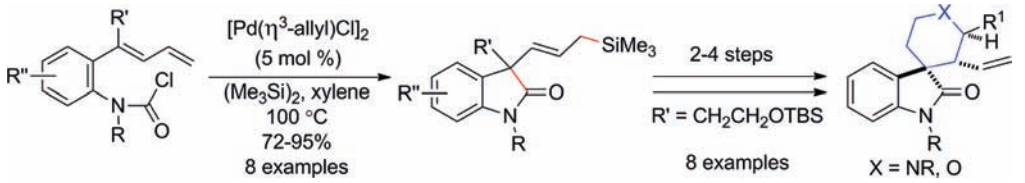
ABSTRACT



The intramolecular carbosilylation of *N*-[2-(1,3-butenyl)aryl]carbamoyl chloride has been investigated. The reaction with hexamethyldisilane proceeds smoothly in the presence of a catalytic amount of [Pd(η^3-allyl)Cl]$_2$ to give oxindoles with an allylsilane functional group in good yield. The subsequent subjection of the products to a Sakurai-type reaction provides more advanced tricyclic spirooxindoles by controlling the stereochemistry of three contiguous stereogenic centers.

The spirooxindole moiety is a core structure in many complex natural products; such natural products often possess interesting biological activities.[1] This structure has also drawn the attention of medicinal chemists because of its potential as an important pharmacophore.[2] Various spiro ring systems have been reported in spirooxindole natural products, for example, fused with pyrrolidine (alstonisine[3]), piperidine (tabernoxidine[4]), and five- and six-membered carbocycles (prosurgatoxine[5] and gelsemine[6]) (Figure 1). The development of new methods for

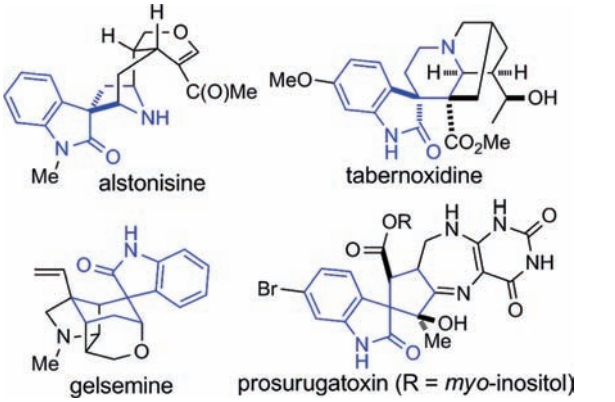


Figure 1. Spirooxindole natural products.

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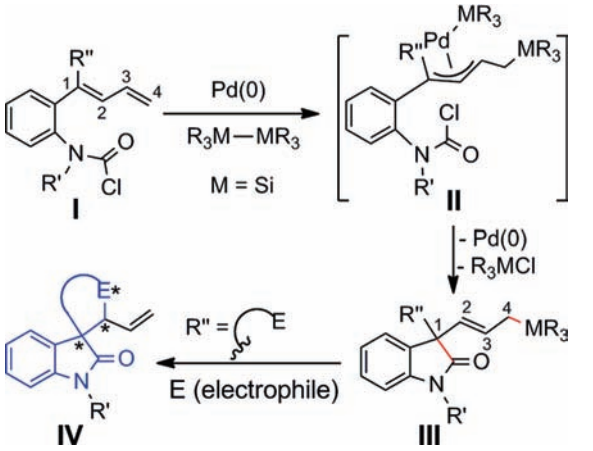
the synthesis of spirooxindoles has therefore evoked immense interest from both synthetic and biological standpoints. Various synthetic methods[1,7] have been reported in the literature, including oxidative rearrangement,[8] Heck reaction,[9] intramolecular Mannich reaction,[10] ring expansion,[11] and 1,3-dipolar cycloaddition.[12] Although the construction of spiro(pyrrolidine-3,3′-oxindole) has attracted many groups, including ours,[13] there has been no focus on devising a concise synthesis of spirooxindoles fused with various ring systems. A unified strategy for the synthesis of various spirooxindoles would be valuable because it could be applied not only to natural products synthesis but also to library synthesis in medicinal chemistry. In this paper, we report a new strategy for the synthesis of spirooxindoles fused with tetrahydropyran, piperidine, and a five-membered carbocycle, based on palladium-catalyzed carbosilylation followed by a Sakurai-type cyclization to construct three stereogenic centers.

Bismetalation of 1,3-dienes is a valuable process because the reaction product contains two carbon−metal bonds; these bonds could be used for further derivatization.[14] Mori et al. reported nickel-catalyzed bismetallative cyclization of 1,3-dienes bearing an aldehyde group.[15] The reaction with $Me_3SiSnBu_3$ gave a cyclized product containing an allylstannyl group. Yu et al. successfully extended this reaction for making two carbon−carbon bonds by sequential allylic transfer in one pot.[16] The nickel-catalyzed cyclization of 1,3-dienes bearing an aldehyde group with an external aldehyde and a diboronyl reagent proceeded diastereoselectively. Based on this bismetallative cyclization, we investigated carbosilylation for the synthesis of spirooxindoles. As shown in Scheme 1,

Scheme 1. Synthetic Strategy



treatment of 1,3-diene **I**, bearing a carbamoyl chloride unit, with a disilanyl reagent would give the π-allyl complex **II**, which would be converted into the disubstituted oxindole **III** by reaction with an internal carbamoyl chloride. By taking advantage of the allylic silanyl group in the product, spirooxindole **IV** could be readily accessed by the Sakurai-type reaction of a tethered electrophile (R″), with control of three contiguous stereocenters. So far, carbamoyl chloride and a 1,1-disubstituted diene have not been employed in bismetallative cyclization. It should be noted that the C1 position of the diene unit is converted to a quaternary carbon center.

In an initial survey, we examined the carbosilylation of 1,3-diene **1a** using hexamethyldisilane and 10 mol % of a palladium or rhodium catalyst in xylene (Table 1). Although $Rh(PPh_3)_3Cl$ did not afford the cyclized product **2a**, $[Rh(cod)Cl]_2$ gave **2a** in 43% yield as a mixture of (*E*)- and (*Z*)-isomers (entries 1 and 2).[17] Several palladium catalysts afforded the desired product **2a** in 22−75% yields (entries 3−7).[18] Addition of PPh_3 was not effective (entries 8 and 9). Finally, we found that $[Pd(\eta^3\text{-allyl})Cl]_2$ is an efficient catalyst for this transformation, and the reaction

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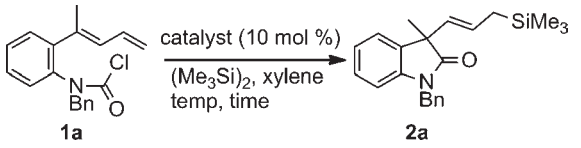
(18) Intermolecular carbometalation of dienes, see: (a) Obora, Y.; Tsuji, Y.; Kawamura, T. *J. Am. Chem. Soc.* **1993**, *115*, 10414. (b) Obora, Y.; Tsuji, Y.; Kawamura, T. *J. Am. Chem. Soc.* **1995**, *117*, 9814. (c) Yang, F.-Y.; Shanmugasundaram, M.; Chuang, S.-Y.; Ku, P.-J.; Wu, M.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 12576.

Table 1. Screening of Palladium and Rhodium Catalysts for Carbosilylation



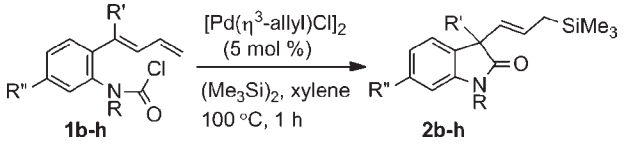
entry	catalyst	temp (°C)	time (h)	yield (%)
1	$[Rh(cod)Cl]_2$	130	10	43[a]
2	$Rh(PPh_3)_3Cl$	130	24	0
3	$Pd(TFA)_2$	100	24	22
4	$Pd(acac)_2$	100	8	32
5	$Pd(dba)_2$	100	24	75
6	$Pd(OAc)_2$	100	24	55
7	$PdCl_2(PhCN)_2$	100	24	48
8	$Pd(OAc)_2$, PPh_3	130	2	12[a]
9	$PdCl_2(PhCN)_2$, PPh_3	130	24	0
10	$[Pd(\eta^3\text{-allyl})Cl]_2$[b]	100	1	77

[a] .Mixture of isomers. [b] Catalyst (0.5 mol %) was used.

with 5 mol % catalyst was completed within 1 h to afford product **2a** in good yield (entry 10).

Next, we applied the optimized conditions to several substrates (Table 2). Treatment of carbamoyl chlorides **1b** and **1c**, which were prepared from Boc-protected 2-iodoaniline in 7 steps following our previous report,[13c] with 5 mol % of $[Pd(\eta^3\text{-allyl})Cl]_2$ and hexamethyldisilane gave the desired oxindoles **2b** and **2c** in 75 and 85% yields, respectively (entries 1 and 2). Carbosilylation of **1d**, possessing a Boc-protected aminoethyl group, proceeded smoothly to give **2d** in 95% yield (entry 3). Siloxyethyl or aminoethyl groups were essential for formation of the next spiro ring, but we have also examined the substrate scope without these side chains. A methoxyphenylmethyl (MPM) group could be employed as a nitrogen-protecting group (entry 4). The cyclization of substrates bearing a chlorine or methoxy group on the aromatic ring gave oxindoles **2f** and **2g** in good yields (entries 5 and 6). Studies of the reaction mechanism are now under way.[19]

Table 2. Scope of the Cyclization Reaction[a]

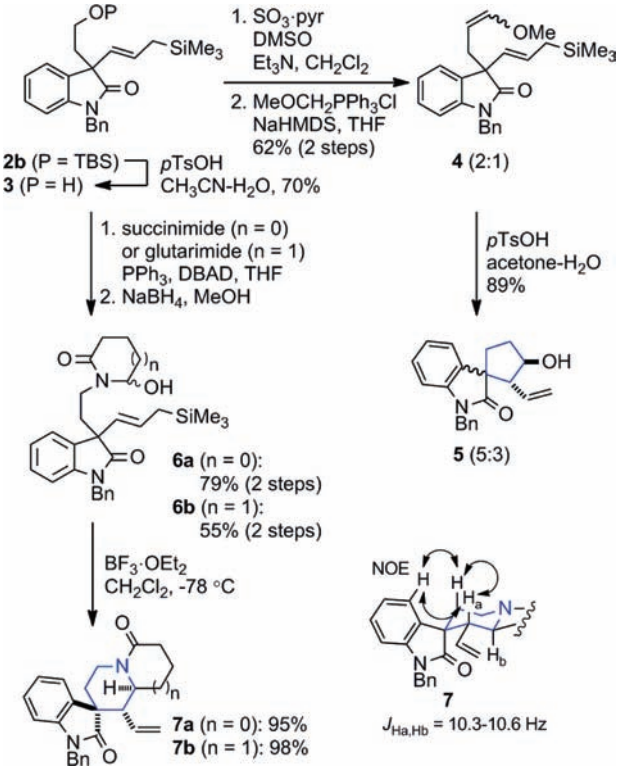


entry	starting material	R	R′	R″	product	yield (%)
1	**1b**	Bn	$(CH_2)_2OTBS$	H	**2b**	75
2	**1c**	Me	$(CH_2)_2OTBS$	H	**2c**	85
3	**1d**	Me	$(CH_2)_2NHBoc$	H	**2d**	95
4	**1e**	MPM	Me	H	**2e**	72
5	**1f**	Me	Me	Cl	**2f**	86
6	**1g**	Me	Me	OMe	**2g**	80

[a] TBS = *tert*-butyldimethylsilyl, Boc = *tert*-butoxycarbonyl.

With 3,3-disubstituted oxindoles containing an allylic silane in hand, the spirooxindoles fused with five-membered carbocycles were initially synthesized by a Sakurai-type reaction.[20] The TBS group of **2b** was removed under acidic conditions to give alcohol **3** (Scheme 2). Oxidation

Scheme 2. Synthesis of Spirooxindoles Fused with Piperidine and a Five-Membered Carbocycle



followed by Wittig olefination of the resultant aldehyde afforded vinyl ether **4** as a 2:1 mixture of *E*:*Z* isomers. After investigation of the cyclization conditions, it was found that treatment of compound **4** under the conditions of *p*-toluenesulfonic acid in acetone−water gave cyclization product **5** in 89% yield in a 5:3 mixture of diastereomers via hydrolysis to an aldehyde.[21] In contrast, formation of spirooxindoles fused with six-membered rings was accomplished with controlling stereoselectivity. A Mitsunobu reaction of compound **3** with succinimide and glutarimide

(19) The two plausible mechanisms are possible. One is shown in Scheme 1. The other plausible pathway commences with oxidative addition of a palladium catalyst to carbamoyl chloride. Insertion into the diene moiety was followed by transmetalation with $Me_3SiSiMe_3$ and reductive elimination to give the product. We previously reported (ref 13) that the addition of PPh_3 was beneficial for the oxidative addition of palladium to carbamoyl chloride, however, it hampered the present cyclization (Table 1, entries 8 and 9), thus we assume the bismetallative process in the reaction mechanism.

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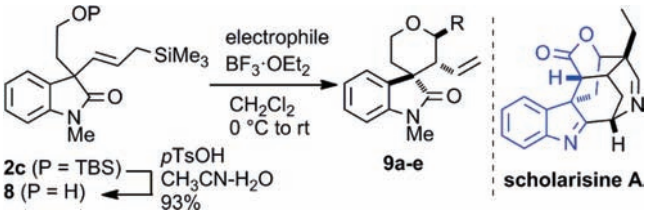
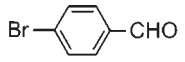
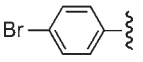
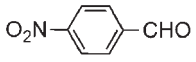
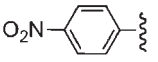
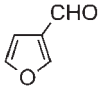
(21) A newly generated stereochemistry was determined by NOE experiments and derivatization, see Supporting Information.

was followed by reduction to give compounds **6a** and **6b**, respectively.[22] The Sakurai-type cyclization of compounds **6a** and **6b** with $BF_3 \cdot OEt_2$ proceeded smoothly to give compounds **7a** and **7b** in excellent yields and with excellent diastereoselectivity; the products had the same stereochemistry as the core structure of tabernoxidine (Figure 1).[21]

This stereoselective approach could be extended to the formation of other spiro ring systems. We selected oxindole fused with a tetrahydropyran ring to show that our strategy is useful. After deprotection of the TBS group in compound **2c**, treatment of alcohol **8** with trimethyl orthoformate and $BF_3 \cdot OEt_2$ afforded **9a** in 83% yield as a single diastereomer (Table 3, entry 1).[21] The Sakurai-type

Table 3. Synthesis of Spirooxindoles Fused with Tetrahydropyran



entry	electrophile	product	R	yield (%)
1	$CH(OMe)_3$	**9a**	OMe	83
2	PhCHO	**9b**	Ph	85
3		**9c**		89
4		**9d**		87
5		**9e**		78

cyclization of compound **8** with benzaldehyde also proceeded smoothly under the same conditions to give compound **9b** in 85% yield as a single diastereomer (entry 2). The reaction conditions were applied to either electron-rich or electron-poor aromatic aldehydes, such as *p*-bromobenzaldehyde, *p*-nitrobenzaldehyde, and 3-furancarboxaldehyde, to furnish the desired products as a single isomer in 78−89% yield (entries 3−5). Additionally, methyl acetal **9a** could be the valuable intermediates for synthesis of various indole alkaloids such as scholarisine A.[23]

In this cyclization, four chair-like transition states **A**−**D** would be possible via formation of oxonium cations (Figure 2). Because an aromatic ring is sterically bulkier

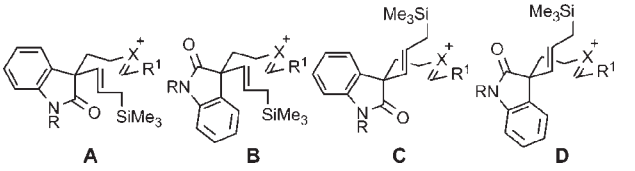


Figure 2. Transition states of Sakurai-type reaction (X = NR^2, O).

than an amide group,[24] transition state **A**, in which both the aromatic ring and the allylic silane group are in pseudo-equatorial positions, would be more favorable than the others, resulting in excellent diastereoselectivity.

In summary, we have developed a concise synthetic route to various spirooxindoles based on palladium-catalyzed carbosilylation of 1,3-dienes bearing carbamoyl chloride, and subsequent Sakurai-type cyclization. This is the first example of the construction of a quaternary stereocenter from a 1,1-disubstituted diene via a bismetallative process. Spiro ring systems fused with tetrahydropyran, piperidine, and five-membered carbocycles were constructed by a Sakurai-type cyclization with control of two or three contiguous stereocenters. This strategy would be a powerful tool for accessing various spirooxindole natural products. Further mechanistic studies as well as synthetic application are in progress.

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Supporting Information Available. Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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