SYNTHETIC APPROACHES TO SPIRO-OXINDOLES AND IMINOINDOLINES BASED ON FORMATION OF C2–C3 BOND

Chihiro Tsukano and Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto, 606-8501, Japan, Takemoto@pharm.kyoto-u.ac.jp

Abstract – Spirooxindole and iminoindoline structures can be found in a wide range of complex natural products, and compounds containing these groups invariably display interesting biological activities. Considering their interesting biological properties and complex architecture, significant research efforts have been directed towards developing new synthetic methods for constructing these structures. This review summarizes our studies towards developing novel synthetic strategies capable of accessing these structures, as well as the applications of these methods to synthesizing natural products, including elacomine and dehaloperophoramidine.

CONTENTS

1. SPIROOXINDOLE

The spirooxindole structure (**1**) is found in many complex natural products, and several compounds containing a spirooxindole moiety have been reported to possess interesting biological properties (Figure 1).[1] For example, prosurugatoxin (**2**),[2] alstonisine (**3**)[3] and spirotryprostatin A (**4**),[4] which are complex pentacyclic indole alkaloids bearing contiguous stereocenters, have been reported to exhibit anti-nicotinic, moderate in vitro antiplasmodial, and antimitotic activities, respectively. The related compounds scholarisine A (**5**) and arbophylline (**6**), however, have not been reported to possess any interesting biological properties,[5,6] although these molecules have captured the attention of synthetic chemists all over the world because of their unusual cage-like structures. Interestingly, various spiro-ring systems have been reported in spirooxindole natural products, such as those fused with pyrrolidine [e.g., alstonisine (**3**), spirotryprostatin A (**4**), and elacomine (**7**)[7]], piperidine [e.g., tabernoxidine (**9**)[8]], five- and six-membered carbocycles [e.g., prosurgatoxin (**2**) and gelsemine (**10**)[9]], and six-membered oxacycles [e.g., scholarisine A (**5**) and arbophylline (**6**)]. The spirooxindole structure is also an important pharmacophore in medicinal chemistry,[10] and structures of this type can also be used as intermediates for synthesizing other indole alkaloids. Considering their numerous applications and interesting properties, there has been significant interest in developing new methods for the construction of spirooxindoles from researchers working in both synthetic and medicinal chemistry.
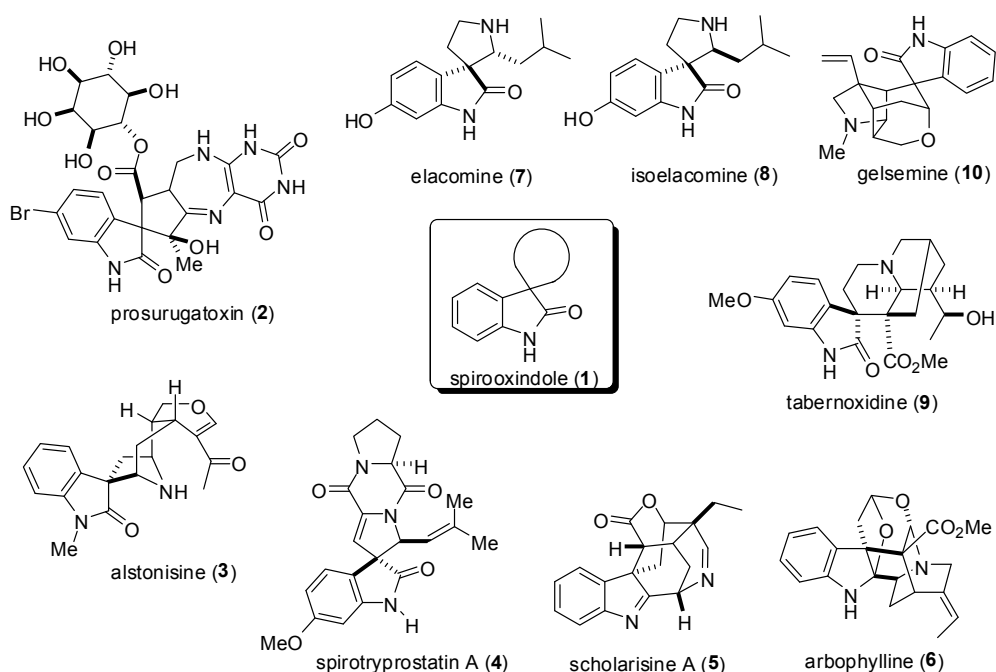

Figure 1. 3,3′-Pyrrolidinyl-spirooxindole-type natural products

## 1-1. REPORTED SYNTHETIC METHODS FOR SPIROOXINDOLE BY FORMING C2–C3 BOND

A variety of methods have been reported for synthesizing spirooxindoles,[11] and these methods can be divided into two categories, including (i) stepwise synthesis involving the formation of the oxindole ring followed by the construction of the spiro-ring system, and (ii) direct synthesis involving the simultaneous construction of the two rings making up the spiro-ring system. 3,3-Disubstituted oxindoles are quite often employed as synthetic intermediates for the stepwise synthesis of spirooxindoles because a variety of methods, including asymmetric procedures, have been developed for the synthesis of these compounds. However, the development of a direct method for the simultaneous construction of a spiro-center and an oxindole skeleton would be desirable from the perspective of synthetic efficiency. Murphy[12] and Overman[13] reported the development of an elegant one-step procedure for synthesizing the spiro[indoline-3,3′-pyrrolidine] skeleton using a radical-mediated or palladium-catalyzed tandem cyclization and intramolecular trapping reaction. Several other methods have also been reported for constructing spirooxindole structures in a single step, including oxidative rearrangement,[14] Heck,[15] intramolecular Mannich,[16] ring expansion,[17] and 1,3-dipolar cycloaddition[18] reactions. Despite the large number of methods that have been reported in this area, research towards developing new methods for constructing spirooxindoles continues to attract considerable attention.

1-2. OUR SYNTHETIC STRATEGIES

We developed a cyanoamidation process for synthesizing 3,3-disubstituted oxindoles, which involved the formation of the C2−C3 bond (Scheme 1).[19] The reaction of compound **11** with Pd(PPh$_3$)$_4$ in xylene at 130 °C proceeded regioselectively to give 3,3-disubstituted oxindole **12** without any of the six membered lactam.[19a,b] We also developed an enantioselective version of this cyanoamidation process using Pd(dba)$_2$ with the chiral phosphoramidite **13** and *N,N*-dimethylpropylene urea (DMPU).[19c,d] It was envisaged that several new approaches could be developed for constructing the spirooxindole skeleton by extending the idea of the cyanoamidation reaction used for the formation of the C2−C3 bond, including (i) a domino reaction for the construction of the spiro-ring system; and (ii) a stepwise reaction for constructing various spiro-ring systems (Scheme 2). The first half of this review has been focused on our most recent research efforts that explore these two strategies and their application to the synthesis of natural products.[20-22]
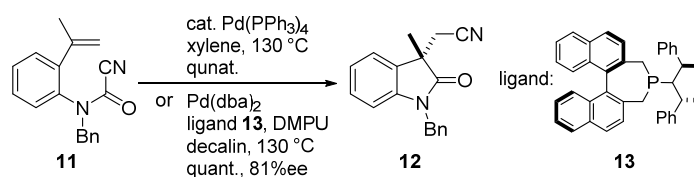

Scheme 1. Synthesis of 3,3-disubstituted oxindole by cyanoamidation
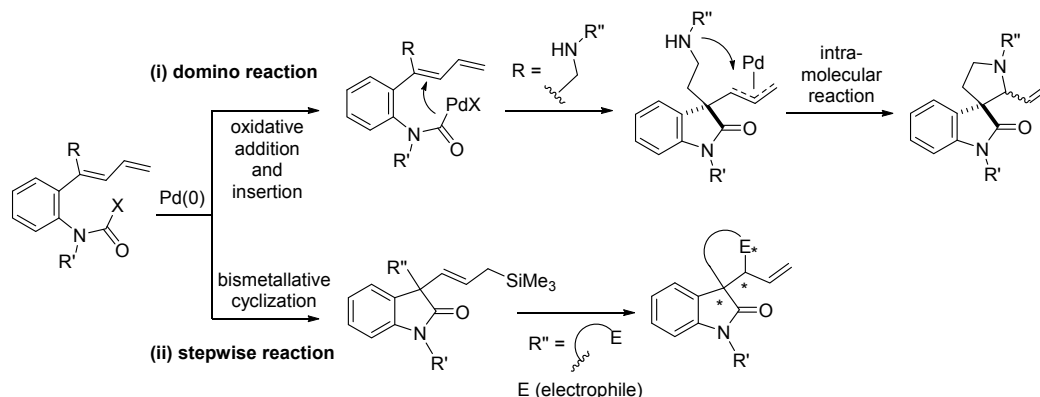
Scheme 2. Synthetic strategy for spirooxindoles

1-3. CONSTRUCTION OF SPIROOXINDOLE SKELETON BY DOMINO CYCLIZATION

When we started our research towards developing of a novel domino reaction strategy for constructing spirooxindole skeletons, we had already developed a palladium catalyzed cyanoamidation process for constructing 3,3-disubstituted oxindoles from 2-(alkenyl)phenylcarbamoyl cyanide **11**, as described above (Scheme 1).[19] However, this cyanoamidation reaction only worked for substrates bearing a terminal olefin, which represented a major limitation for this transformation. It was envisaged that the use of a diene instead of a terminal olefin would allow **13** to react to give the π-allylpalladium intermediate **17**,[23] which could be converted to the spirooxindole **18** by a trapping reaction involving an intramolecular nucleophile (Scheme 3).[24] With this in mind, we focused our initial efforts on the development of a palladium catalyzed cyclization reaction for carbamoyl chlorides such as **13** (X = Cl) bearing a 1,3-diene moiety.[25]
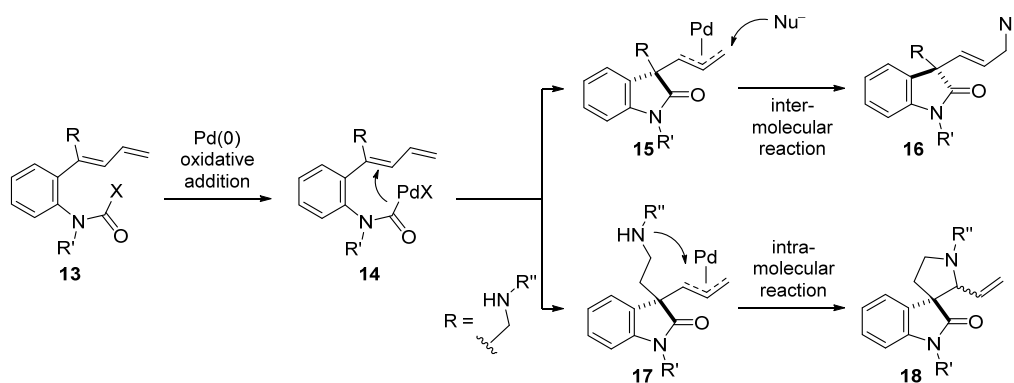
Scheme 3. Synthetic strategy for constructing the contiguous stereogenic centers of spirocyclic compounds

We initially examined an intermolecular reaction to determine the most appropriate nucleophiles for the effective trapping of the π-allylpalladium intermediate. The treatment of carbamoyl chlorides **19** bearing a diene moiety with a catalytic amount of palladium acetate (Pd(OAc)$_2$), triphenylphosphine (PPh$_3$) and cesium carbonate (Cs$_2$CO$_3$) gave the corresponding π-allylpalladium intermediates, which were trapped

with several nucleophiles (Table 1). As expected, the reaction with *p*-NsNH$_2$ proceeded smoothly to give the 1,4-adduct **20a** via the corresponding π-allylpalladium intermediate, with none of the 1,2-adducts observed (Table 1, entry 1). Two other sulfonamides, TsNH$_2$ and TfNH$_2$, were also used as nucleophiles the reaction, resulting in the formation of oxindoles **20b** and **20c** (Table 1, entries 2 and 3). Although the reactions of **19** with morpholine and aniline gave the corresponding ureas **21d** and **21e** instead of the cyclized products **20d** and **20e**, the use of indole as a nitrogen nucleophile resulted in the successful formation of the cyclized product **20f** (Table 1, entries 4−6). Interestingly, the π-allylpalladium intermediate also reacted with phenol and benzoic acid, which are both only weakly nucleophilic, to give the corresponding oxindoles **20g** and **20h** in 81% and 74% yields, respectively (Table 1, entries 7 and 8). Furthermore, the π-allylpalladium intermediate could be trapped with organoboronic acids under the same reaction conditions to give the corresponding arylated and alkenylated adducts **20i** and **20j** (Table 1, 9 and 10).

Table 1. Synthesis of 3,3-disubstituted oxindole by palladium(0)-catalyzed amidation

entry	Nu-H	time (h)	yield (%)
1	*p*-NsNH$_2$	2	**20a**: 51[a]
2	*p*-TsNH$_2$	0.5	**20b**: 73
3	TfNH$_2$	3	**20c**: 94
4	morpholine	1	**20d**: 0
5	aniline	24	**20e**: 0
6	indole	8	**20f**: 62
7	phenol	0.5	**20g**: 81[b]
8	benzoic acid	0.5	**20h**: 74
9	PhB(OH)$_2$	0.5	**20i**: 58
10	PhCH=CHB(OH)$_2$	24	**20j**: >37

[a] A doubly alkylated product was obtained in 29% yield as a by-product. [b] A carbamate was obtained in 10% yield.

Following on from our successful synthesis of several 3,3-disubstituted oxindoles via the trapping of a π-allylpalladium intermediate with a range of nucleophiles, we proceeded to investigate the direct

synthesis of spirooxindoles based on an extension of this approach. This extended approach involved sequential palladium(0)-catalyzed amidation and intramolecular nucleophilic addition reactions, which were conducted in a single pot (Scheme 4). Carbamoyl chloride **26** was prepared from aryl iodide **22** via a six-step linear sequence, including a Stille coupling with trimethylstannyl-1,3-hexadiene **23**,[26] as well as the introduction of a nitrogen unit using TfNH$_2$. The domino cyclization of **26** was conducted in the presence of 10 mol% Pd(OAc)$_2$, 20 mol% PPh$_3$ 1.2 equiv. of Cs$_2$CO$_3$ (1.2 equiv) at 130 °C, and gave the desired spirocyclic products **27a** and **27b** in a combined yield of 71% as a 63:37 mixture of two diastereomers. The newly generated stereochemistry was determined by extensive 2D NMR measurements, including NOE experiments. Notably, the major product **27a** possessed the same configuration as spirotryprostatin A (**4**) and elacomine (**7**) (Figure 1).
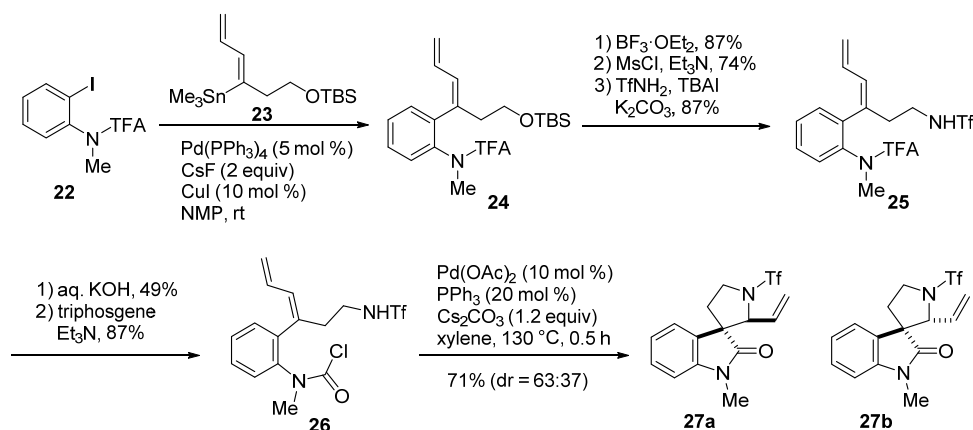
Scheme 4. Application of the palladium(0)-catalyzed amidation for spiro-ring formation

A novel domino palladium-catalyzed method was developed by our group for the direct synthesis of spirooxindole **27** from carbamoyl chloride **26** bearing a terminal 1,3-diene moiety.[20] Although the selectivity of the spiro-ring formation was poor, we proceeded to investigate the application of this palladium-catalyzed spirooxindole formation to the formal synthesis of elacomine (**7**) and isoelacomine (**8**).

1-4. FORMAL SYNTHESIS OF ELACOMINE BY THE DOMINO PALLADIUM(0)-CATALYZED SPIROOXINDOLE FORMATION

Elacomine (**7**, Figure 1) is a hemiterpene spirooxindole alkaloid, which was first isolated from the shrub *Elaeagnus commutata* in 1968 by Slywka et al.[7a] The structure of elacomine was determined by X-ray crystallography by James and Williams.[7b] Borschberg et al.[27] later reported that **7** occurred naturally in its racemic form following a series of re-isolation studies. The first enantioselective total synthesis of **7** and

its diastereomer **8**, which is known as isoelacomine and was isolated from the same species, was described by Borschberg in the same paper, and proceeded via the oxidative rearrangement of β-carboline. The authors of this particular study also reported that elacomine and isoelacomine could be interconverted and undergo racemization under mild conditions. Although compounds **7** and **8** have not been reported to exhibit any biological activity, these molecules are regarded by many researchers as important synthetic targets and benchmark compounds, because they contain a simple spiro(pyrrolidine-3,3-oxindole) skeleton that is often found in spirooxindole natural products. In 2004, Horne et al.[28] reported the total synthesis of **7** and **8** based on a stereoselective intramolecular iminium ion spirocyclization method. White et al.[29] developed a tandem intramolecular photocycloaddition retro-Mannich fragmentation strategy and applied it to the diastereoselective synthesis of **7**. Notably, tryptamine derivatives were selected as starting materials in all three of these total syntheses, with the main focus of each approach being the construction of the spiro-center.

We envisioned that the application of our newly developed domino reaction to an internal 1,3-diene would allow for the efficient construction of the spirooxindole skeleton of elacomine (**7**) and isoelacomine (**8**) from carbamoyl chloride **29**, which would act as a cyclization precursor (Scheme 5). Oxidative addition and insertion into the 1,3-diene would give the π-allylpalladium complexes **30a** and **30b** as well as the oxindole. Intramolecular nucleophilic attack to the π-allylpalladium moiety would give compound **28**. Considering the acidity required to generate a suitably nucleophilic nitrogen-based nucleophile and the feasibility of the subsequent deprotection, a methoxy carbamate was chosen as an internal nitrogen-based nucleophile (i.e., R^2 = Me). Carbamoyl chloride **29** could be synthesized in several steps, including the Heck reaction of iodoaniline **31** and dihydro-2*H*-pyranone **32** followed by the ring-opening of the dihydro-2*H*-pyranone moiety to allow for the introduction of the nitrogen and isoprenyl units, and the formation of the carbamoyl chloride.

Practical work towards realizing this strategy was initially focused on the intermolecular Heck reaction of dihydro-2*H*-pyranone **32**, because the reaction of this species had not been reported in the same way as the intermolecular Heck reaction of cyclic enones.[30] Screening experiments revealed that **31a** could be coupled to **32** using Pd(OAc)$_2$, PPh$_3$, *i*Pr$_2$NEt and tetrabutylammonium bromide (Bu$_4$NBr) in dimethylformamide (DMF) at 100 °C followed by deprotection of the *t*-butoxycarbonyl (Boc) group to give lactone **33** in a 52% yield over the two steps (Scheme 6). The diene unit was introduced by the half-reduction of lactone **33** using diisobutylaluminum hydride (DIBAL-H) followed by a Wittig reaction. Trifluoroacetylation of the aniline moiety followed by mesylation of the primary alcohol gave **35**, which was treated with NaN$_3$ to give the corresponding azide **36**. Reduction of the azide followed by the protection of the resulting amine as a methoxy carbamate gave compound **37**, which was treated with KOH to allow for the deprotection of the trifluoroacetyl group. The resulting secondary amine **38** was

treated with a mixture of triphosgene and pyridine in CH_2Cl_2 at -78 °C to give carbamoyl chloride **29a**, which could be used as a cyclization precursor.
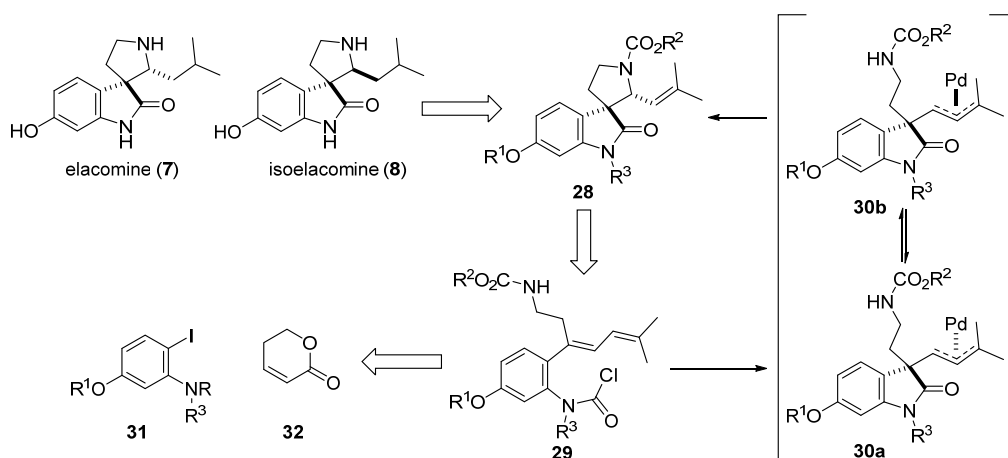
Scheme 5. Retrosynthetic analysis of elacomine (**7**) and isoelacomine (**8**)
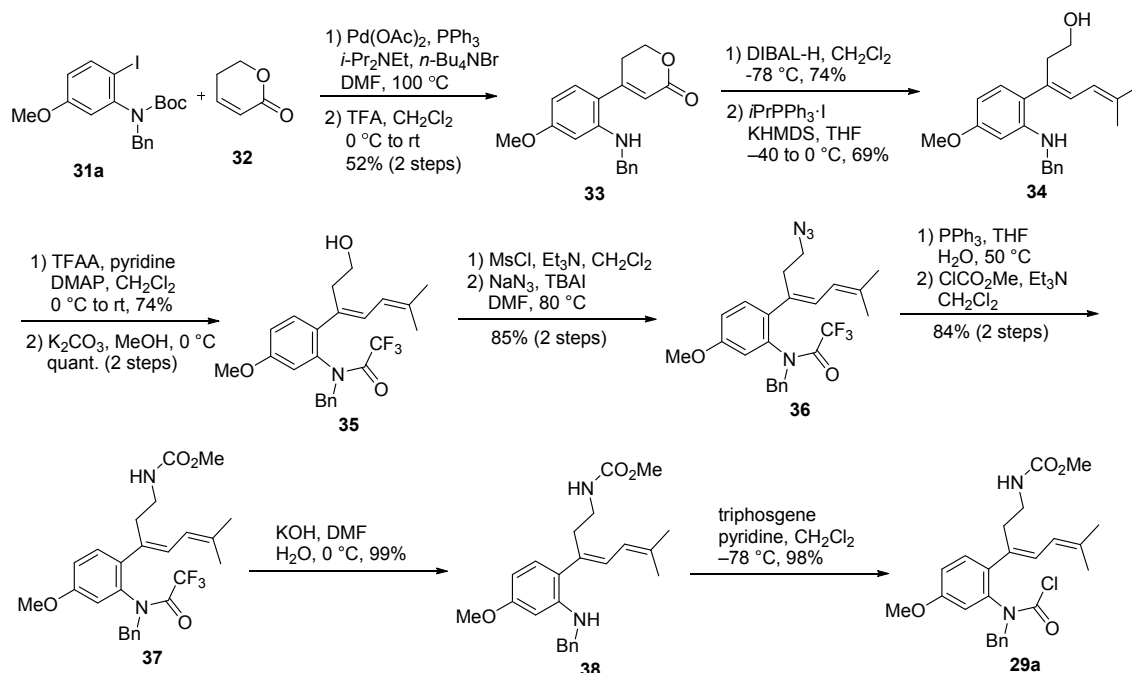
Scheme 6. Synthesis of carbamoyl chloride **29a**

We subsequently investigated the domino palladium-catalyzed spirooxindole formation of carbamoyl chloride **29a** bearing an internal diene moiety. Compound **29a** was initially subjected to a set of conditions that had been optimized for terminal dienes, such as those shown in Scheme 4.[20] Unfortunately, however, the treatment of **29a** with Pd(OAc)$_2$, PPh$_3$ and Cs$_2$CO$_3$ in xylene at 130 °C gave compound **39** in a 86% yield, which was most likely produced by the β-elimination of the π-allylpalladium complex

instead of the nucleophilic addition of the nitrogen atom (Table 2, entry 1). Several additives and ligands were screened in an attempt to suppress the undesired β-elimination. Disappointingly, the use of diphenylphosphinoferrocene (dppf) as a ligand or Bu_4NPF_6 as an additive in the presence of Cs_2CO_3 or Ag_2CO_3 proved to be unsuccessful, whereas the addition of Bu_4NI led to the formation of **28** in only 11% yield with no diastereoselectivity (Table 2, entries 2−5). Interestingly, the reaction proceeded smoothly to give the desired spirooxindole **28** as the major product when it was conducted without a base such as Cs_2CO_3 (Table 2, entry 6). Given that the undesired β-elimination step could potentially be suppressed under acidic conditions, we investigated the addition of several acids to the reaction mixture, including TfOH, $Hf(OTf)_4$ and $Bi(OTf)_3$ (Table 2, entries 7−9). The results of these experiments revealed that $Bi(OTf)_3$ was an effective additive for this domino palladium-catalyzed spirooxindole formation (Table 2, entry 9). The resulting spirooxindole **28** was isolated as a 1:1 mixture of diastereomers in all cases because the inversion of the π-allylpalladium intermediates **30a** and **30b** would occur prior to the nucleophilic addition of the nitrogen atom (Scheme 5).

**Table 2.** Palladium-catalyzed spirooxindole formation of carbamoyl chloride **29a**
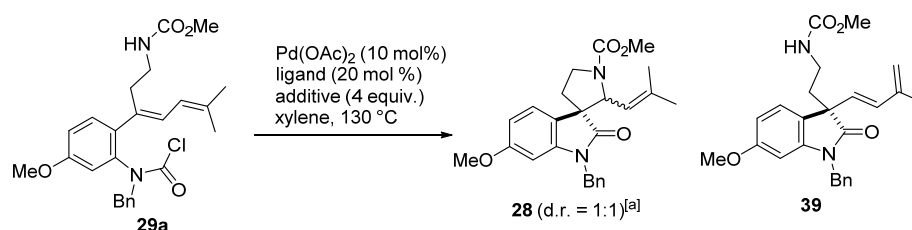
entry	ligand	additives	yield (%) of **28**	yield (%) of **39**
1	PPh₃	Cs_2CO_3	0	86
2	PPh₃	Cs_2CO_3, Bu_4NPF_6	0	66
3	PPh₃	Cs_2CO_3, Bu_4NI	11	28
4	Dppf	Cs_2CO_3	0	84
5	Dppf	Ag_2CO_3	0	74
6	Dppf[b]	none	37	17
7	Dppf	TfOH[c]	17	0
8	Dppf	$Hf(OTf)_4$	33	0
9	Dppf	$Bi(OTf)_3$	52	0

[a] The ratio was estimated by ^{1}H NMR. [b] $Pd(TFA)_2$ was used instead of $Pd(OAc)_2$. [c] 50 mol% was used.

The Lewis acid catalyzed intramolecular hydroamination of **39** was investigated to determine whether diene **39** was formed as an intermediate in the domino cyclization reaction described above. The

treatment of **39** with a Bi(OTf)$_3$ or Hf(OTf)$_4$ catalyst in xylene at 130 °C according to the conditions described above for the domino cyclization reaction, except for the absence of the palladium catalyst and ligand, gave spirooxindole **28** as a mixture of diastereomers in 49 and 41% yields, respectively (Table 3, entries 1 and 2). The use of Shibasaki's conditions,[31] which involved the use of a PF$_6$ salt and Bi(OTf)$_3$, Hf(OTf)$_4$ or Sc(OTf)$_3$, led significant improvements in the yield, with a combination of Bi(OTf)$_3$ and KPF$_6$ being especially effective (Table 3, entries 3−6).[32] In contrast, the use of Zn(OTf)$_2$ did not afford any of the cyclized products (Table 3, entry 7). The diastereoselectivity of the cyclization was found to be 1:3 under almost all of the conditions tested, and therefore different to the results observed in the domino cyclization process. These results therefore indicated that **39** was not an intermediate in the domino cyclization reaction. A comparison of these results with those from the hydroamination reaction suggested that nucleophilic addition to the π-allylpalladium complex would be preferred to the hydroamination pathway in the domino reaction.

Table 3. Hydroamination of diene **39**
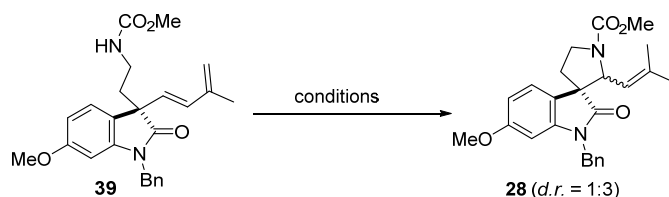
entry	conditions	solvent	temp (°C)	yield (%)
1	Bi(OTf)$_3$	xylene	130	49
2	Hf(OTf)$_4$	xylene	130	41[a]
3	Bi(OTf)$_3$, Cu(MeCN)$_4$PF$_6$	1,4-dioxane	50	66
4	Bi(OTf)$_3$, KPF$_6$	1,4-dioxane	50	80
5	Hf(OTf)$_4$, KPF$_6$	1,4-dioxane	50	57
6	Sc(OTf)$_3$, KPF$_6$	1,4-dioxane	50	58
7	Zn(OTf)$_2$, KPF$_6$	1,4-dioxane	50	0

[a] mixture of 1:2 diastereomers.

Having successfully synthesized spirooxindole **28**, which possessed the same carbon skeleton as elacomine (**7**) and isoelacomine (**8**), we turned our attention to the final stage of the synthesis. The hydrogenation of **28** under high pressure conditions gave diastereomers **40a** and **40b**, which were separated by column chromatography over silica gel (Scheme 7). Finally, the formal synthesis of elacomine and isoelacomine was achieved by the removal of the benzyl group from the nitrogen atom of

the isoxazole ring with lithium di-*t*-butylbiphenyl (LiDBB). The spectral data for the key intermediates **41a** and **41b** were in agreement with those reported by Horne et al.[28]
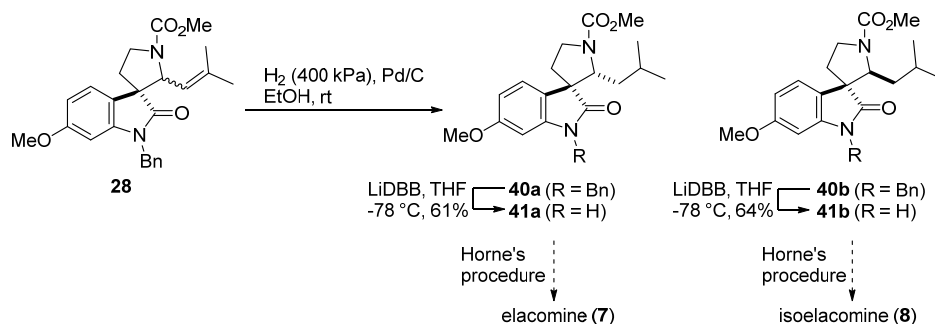

Scheme 7. Formal synthesis of elacomine (**7**) and isoelacomine (**8**)

This newly developed domino palladium-catalyzed spirooxindole formation was successfully applied to the formal synthesis of elacomine (**7**) and isoelacomine (**8**). It is noteworthy that terminal and internal dienes could both be employed in this domino cyclization.[21]

## 1-5. SYNTHESIS OF SPIROOXINDOLES USING SILYL AMIDATION

The focus of our research subsequently shifted to synthesizing spirooxindoles fused with tetrahydropyran, piperidine, and five-membered carbocycle ring systems. Developing a unified synthetic strategy capable of providing access to various spirooxindoles would be of considerable value to synthetic and medicinal chemists because it could be applied to the synthesis of natural products as well as compound libraries for use in drug discovery. The domino cyclization reaction described above[20,21] is a convenient method for constructing spiro-ring systems fused with pyrrolidine, although the scope of this reaction has been limited by its requirement for strong nucleophiles to allow for the intramolecular trapping of the π-allylpalladium intermediate. For this reason, the domino cyclization reaction could be unsuitable for the synthesis of other spiro-ring systems. To develop a comprehensive method capable of providing access to various spirooxindole systems, we turned our attention to the bismetallation of 1,3-dienes, which provides products containing two carbon–metal bonds that could be subjected to further transformations.[33] Mori et al.[34] developed a nickel-catalyzed process for the bismetallative cyclization of 1,3-dienes with an aldehyde on their side chain. Furthermore, the same reaction with $Me_3SiSnBu_3$ gave a cyclized product containing an allylstannyl group. This reaction was extended to include the formation of two carbon–carbon bonds by sequential allylic transfer reactions in one pot by Yu.[35] The nickel-catalyzed cyclization of 1,3-dienes with internal and external aldehydes in the presence of a diboronyl reagent proceeded in high levels of diastereoselectivity. Based on this bismetallative cyclization process, we

became interested in developing a carbosilylation strategy for constructing various spirooxindole ring systems. We envisioned that the treatment of 1,3-diene **13** bearing a carbamoyl chloride with a catalytic amount of palladium catalyst and hexamethyldisilane would give the disubstituted oxindole **42** via the reaction of the π-allyl complex **41** with the internal carbamoyl chloride (Scheme 8). The C1 position of the diene unit would be converted to a quaternary carbon center and the resulting oxindole **42**, bearing an allylic silanyl group, could be readily converted to spirooxindole **43** by the Sakurai-type reaction of the tethered electrophile (R"), which would allow for a high level of control over the three contiguous stereocenters. Although the realization of this strategy would mean that the spirooxindole ring would have to be formed in a stepwise manner, various spiro-ring systems could be accessed from this intermediate by the nucleophilic attack of the allyl metal species on the electrophile in the side chain. Conceptually, this idea is effectively the reverse of that described above for the domino cyclization reaction in terms of the nucleo- and electro-philicity of the allyl metal intermediate derived from the diene.
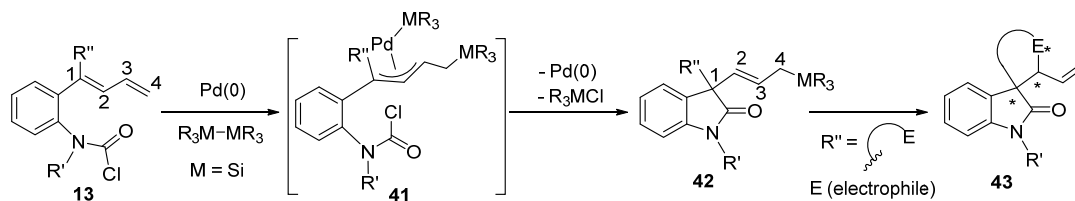
Scheme 8. Synthetic strategy for spirooxindole fused with various rings

When we started our work in this area, there had been no reports in the literature pertaining to the palladium-catalyzed bismetallative cyclization of a carbamoyl chloride with a 1,1-disubstituted diene. In the absence of any related examples to guide our research, our initial efforts focused on the carbosilylation of 1,3-diene **19** using hexamethyldisilane and 10 mol% of a palladium or rhodium catalyst in xylene (Table 4). Although the use of Rh(PPh$_3$)$_3$Cl as a catalyst resulted in none of the desired cyclization product, the use of the chloro(1,5-cyclooctadiene)rhodium(I) dimer ([Rh(cod)Cl]$_2$) gave **44** in 43% yield as a mixture of (*E*)- and (*Z*)-isomers (Table 4, entries 1 and 2).[36] Several palladium catalysts were screened against this reaction and performed effectively in the cyclization to give the desired product **44** in 22%–75% yields (Table 4, entries 3–7).[37] Interestingly, however, the addition of PPh$_3$ hampered the cyclization reaction (Table 4, entries 8 and 9). Finally, we found that the allylpalladium(II) chloride dimer [Pd(η^3-allyl)Cl]$_2$ was an efficient catalyst for this transformation, with 5 mol% catalyst allowing the reaction to proceed to completion within 1 h to afford the desired product **44** in 77% yield (Table 4, entry 10).

Table 4. Screening of palladium and rhodium catalysts for the carbosilylation reaction
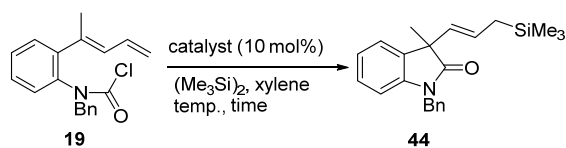

entry	catalyst	temp (°C)	time (h)	yield (%)
1	[Rh(cod)Cl]$_2$	130	10	43[a]
2	Rh(PPh$_3$)$_3$Cl	130	24	0
3	Pd(TFA)$_2$	100	24	22
4	Pd(acac)$_2$	100	8	32
5	Pd(dba)$_2$	100	24	75
6	Pd(OAc)$_2$	100	24	55
7	PdCl$_2$(PhCN)$_2$	100	24	48
8	Pd(OAc)$_2$, PPh$_3$	130	2	12[a]
9	PdCl$_2$(PhCN)$_2$, PPh$_3$	130	24	0
10	[Pd(η^3-allyl)Cl]$_2$[b]	100	1	77

[a] Mixture of isomers. [b] 5 mol% catalyst was used.

The optimal conditions were subsequently applied to a variety of substrates to assess the scope of this reaction (Table 5). Carbamoyl chlorides **45a–c** were prepared from Boc-protected 2-iodoaniline, because the presence of a siloxyethyl or aminoethyl group was essential for the formation of the spiro-ring. Compounds **45a–c** were subsequently converted to the desired oxindoles **46a–c** in 75%−95% yields using 5 mol% [Pd(η^3-allyl)Cl]$_2$ and hexamethyldisilane. The substrate scope of this reaction was also investigated using carbamoyl chlorides without a siloxyethyl or aminoethyl side chain (i.e., **45d–f**). A *p*-methoxybenzyl (PMB) group was tolerated under the cyclization conditions, with the PMB substituted product **46d** being isolated in good yield. Substrates bearing a chlorine or methoxy group on their aromatic ring also reacted smoothly to give oxindoles **46e** and **46f** in 86% and 80% yields, respectively. Spirooxindoles fused with a five-membered carbocycle were synthesized by a Sakurai-type reaction[38] using the 3,3-disubstituted oxindole described above (Scheme 9). The removal of the *t*-butyldimethylsilyl (TBS) group from **46a** under acidic conditions gave alcohol **47**, which was converted to enol ether **48** following sequential oxidation and Wittig reactions. Enol ether **48**, which existed as a 2:1 mixture of *E:Z* isomers, was converted to spirooxindole **49** under acidic conditions in 89% yield as a 5:3 mixture of diastereomers. The formation of spirooxindoles fused with a six-membered piperidine ring was also achieved with excellent diastereoselectivity. The Mitsunobu reactions of compound **47** with succinimide and glutarimide gave the corresponding addition products, which were reduced with NaBH$_4$ to give the

cyclization precursors **50a** and **50b**, respectively. Treatment of compounds **50a** and **50b** with $BF_3 \cdot OEt_2$ gave compounds **51a** and **51b** in 95% and 98% yields, respectively, with excellent diastereoselectivity, and the newly generated stereochemistry was confirmed by 2D NMR analyses, including NOESY experiments. Notably, these products possessed the same relative configuration as the core structure of tabernoxidine (**9**) (Figure 1).[8]

Table 5. Scope of the cyclization reaction[a]
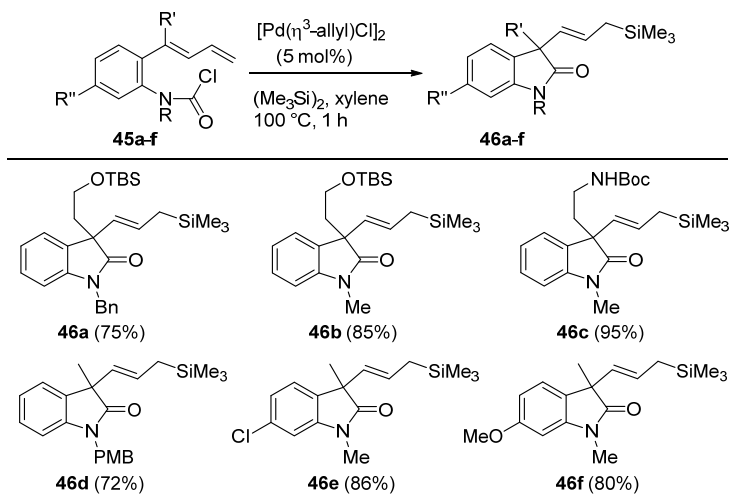
[a] TBS = *tert*-butyldimethylsilyl, Boc = *tert*-butoxycarbonyl
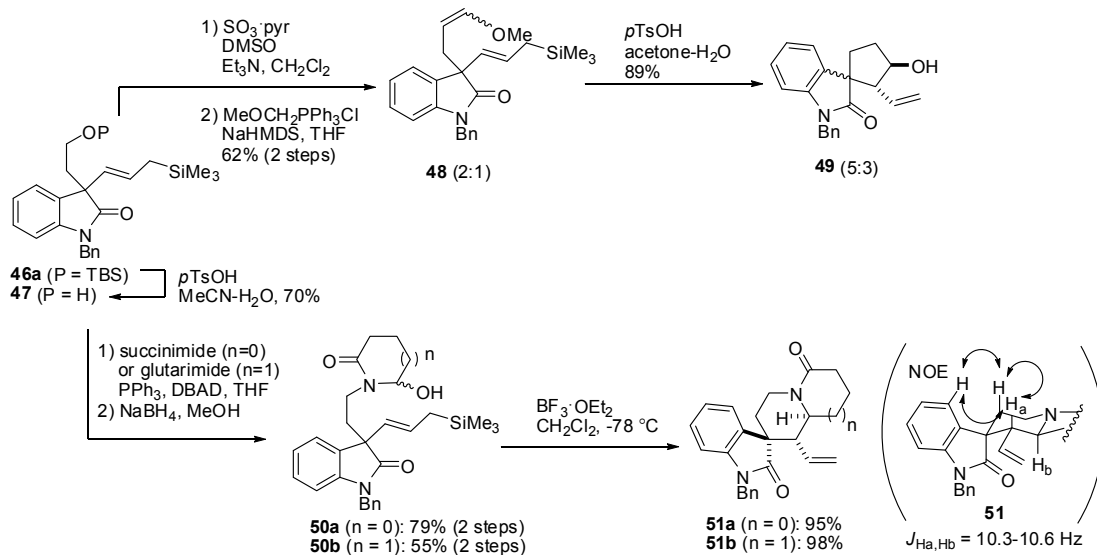
**Scheme 9.** Synthesis of spirooxindoles fused with piperidine and a five-membered carbocycle

The 3,3-disubstitued oxindole **46c** was used to synthesize a series of spirooxindoles fused with a tetrahydropyran ring using a Sakurai-type cyclization. Deprotection of the TBS group in compound **46c** gave the corresponding alcohol **52**, which was treated with trimethyl orthoformate or an aryl aldehyde in

the presence of BF$_3$·OEt$_2$ to give the spirooxindoles **53a–e** in high yields (Table 6). The reaction with trimethyl orthoformate gave **53a** in 83% yield as a single diastereomer, and several other aldehydes, including electron-rich or electron-deficient aromatic aldehydes, reacted smoothly to give the desired products **53b–e** as single isomers in 78%–89% yields.

Table 6. Synthesis of spirooxindoles fused with tetrahydropyran
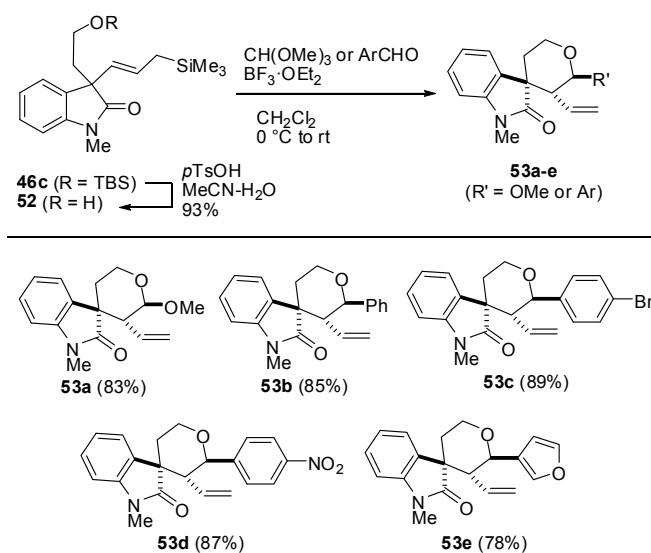
The excellent diastereoselectivity observed in this cyclization can be rationally explained as follows: It would be possible for the 3,3-disubstitued oxindole substrates to adopt four chair-like transition states **A–D** via the formation of an oxonium cation (Figure 2). Given that an aromatic ring is more sterically encumbered than an amide group,[39] transition state **A**, where the aromatic ring and allylic silane group are both sitting in pseudo-equatorial positions, would be energetically more favorable than transition states **B–D**.
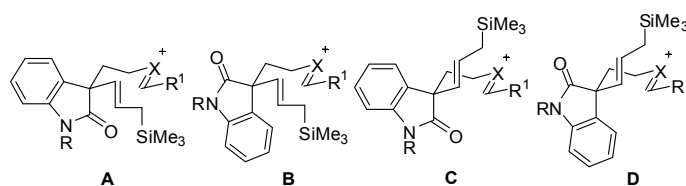

Figure 2. Transition states of Sakurai-type reaction (X = NR^2, O)

The examples shown above provide a good illustration of the powerful and concise nature of this newly developed method for constructing various spirooxindoles via the palladium-catalyzed carbosilylation of 1,3-dienes bearing a carbamoyl chloride moiety followed by a Sakurai-type cyclization.[22] Spiro-ring systems fused with tetrahydropyran, piperidine, and five-membered carbocycles can be constructed according to this method with a high level of control over two or three contiguous stereocenters.

Furthermore, the work described here was the first reported example of the construction of a quaternary stereocenter from the 1,1-disubstituted diene via a bismetallation strategy.[40]

Using this methodology, it is now possible to access spirooxindole systems fused with pyrrolidine, piperidine, five-membered carbocycle and six-membered lactone rings based on the originally developed method. These two synthetic strategies could therefore not only be useful for synthesizing natural spirooxindoles but could also be used to synthesize the intermediates of indole alkaloids.

2. SYNTHETIC STUDIES ON 2-IMINOINDOLINE

During the course of our synthetic studies of spirooxindoles, we became interested in synthesizing 2-iminoindolines (**54a**), 2-aminoindolenines (**54b**) and 2-aminoindolines (**55**) (Figure 3). In some cases, **54a** and **54b** could be tautomers of each other. The class of natural products containing these structures is very similar to that of spirooxindoles, and several interesting examples from this class have been reported in the literature, including communesin F (**56**),[41] perophoramidine (**57**),[42] flustramine C (**58**),[43] quinadoline B (**59**)[44] and neoxaline (**60**)[45] (Figure 4). These compounds often exhibit interesting biological activities, and communesin F (**56**), perophoramidine (**57**) and neoxaline (**60**), for example, have been reported to be cytotoxic. Flustramine C (**58**) shows moderate antibiofilm activity against *Acinetobacter baumannii*, *Escherichia coli* and methicillin resistant *Staphylococcus aureus* (MRSA);[46] and quinadoline B (**59**) has been reported as a moderate inhibitor of lipid droplet synthesis in mouse macrophages. The synthesis of these compounds, however, is challenging because of their complex structural architecture. In the latter half of this review, we will focus in detail on our synthetic efforts towards developing a robust strategy for constructing 2-iminoindolines.[47,48]
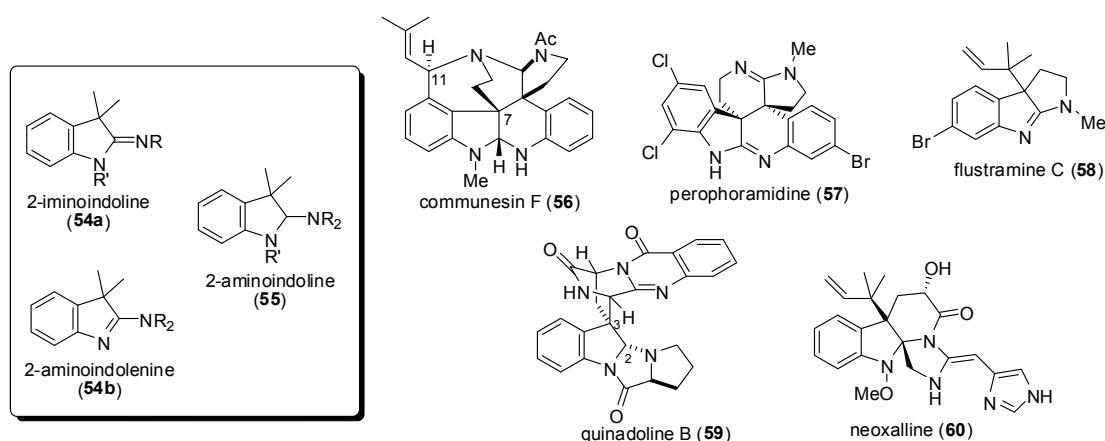

Figure. 3. Natural products containing 2-iminoindoline and 2-aminoindoles

2-1. REPORTED SYNTHETIC METHODS FOR CONSTRUCTING 2-IMINOINDOLINES AND RELATED COMPOUNDS

Various methods have been reported in the literature for synthesizing 2-iminoindolines and related compounds. Most of the reported methods involve the tether-dependent condensation of oxindole derivatives[49a–d] and the oxidative cyclization of indoles.[49e] Several other synthetic strategies have also been developed to provide access to these systems, including aza-Pauson–Khand-type reactions,[50] heteroannulation of *N*-alkynylanilines,[51] ring enlargement of aminoazirines,[52] addition of azides to indoles,[53] oxidation of aminals,[54] and amidination of aryl halides.[55] Despite several methods being available for constructing these compounds, the development of mild and selective synthetic methods is still highly desired.

2-2. SmI$_2$-MEDIATED REDUCTIVE CYCLIZATION OF CARBODIIMIDES FOR SYNTHESIS OF SPIRO-2-IMINOINDOLINES

For the synthesis of spiro-2-iminoindolines **61**, we envisioned a retrosynthetic disconnection of the C2−C3 bond because we had already developed a synthetic method for constructing spirooxindoles by forming the C2−C3 bond (Scheme 10). Compound **62** bearing an unsaturated carbonyl group and a carbodiimide moiety was therefore identified as a suitable synthetic precursor for the cyclization reaction. Carbodiimides are often employed as synthetic precursors for amidines for their reactions with various organometallic species.[56] However reports pertaining to their use as radical acceptors have been scarce.[57]
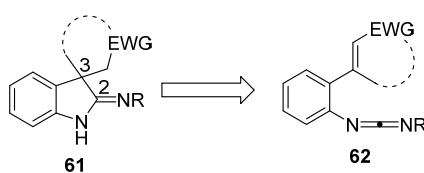
Scheme 10

SmI$_2$, which was first introduced as a reagent for synthetic chemistry in 1977 by Kagan, is a powerful single-electron reductant.[58,59] SmI$_2$ exhibits excellent functional group selectivity and is regularly used to affect the formation of carbon–carbon bonds and selective reduction reactions in synthesizing complex natural products.[60] Although various reductive homo-/hetero-coupling reactions have been reported involving the reaction of SmI$_2$ with substrates bearing electron-withdrawing groups,[61] there have, to the best of our knowledge, been no reports to date pertaining to the development of similar reactions involving carbodiimides.[62]

Before we started this project, a report appeared in the literature describing the synthesis of oxindoles based on the SmI_2-promoted intramolecular cyclization of aryl isocyanates bearing a cyclohexenone moiety as part of a synthetic study towards welwitindolinone A isonitrile.[61g] Inspired by these results, it was envisioned that a quaternary-carbon center and an imine carbon bond could be constructed via a reductive cyclization reaction involving SmI_2, an α,β-unsaturated carbonyl moiety and carbodiimide. According to this strategy, the radical or anionic species generated from the reaction of SmI_2 with an unsaturated carbonyl group would attack the central carbon atom of the carbodiimide species, or vice versa. Although tandem nucleophilic addition and 6π electrocyclic reactions have been reported for the related carbodiimides **62**, which gave the corresponding dihydroquinazolines **63** and 2-aminoquinoline **64**, respectively,[63,64] there have been no reports concerning similar cyclization reactions for **62** to give quaternary-carbon centers (Scheme 11).
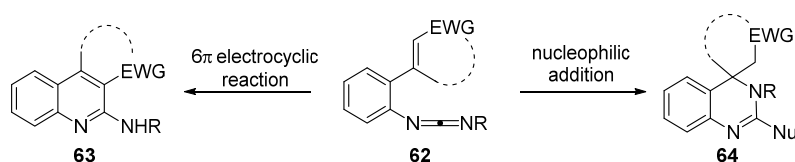

Scheme 11. Nucleophilic addition and 6π electrocyclic reaction of the related carbodiimides **62**

Compound **65** was selected as a simple model substrate to establish suitable conditions for the reductive cyclization reaction. Treatment of THF solution of **65** with SmI_2 at −78 °C resulted in no reaction (Table 7, entry 1), although the desired reaction did proceed at room temperature to give the cyclized product **66** exclusively (Table 7, entry 2). The addition of an additive to the reaction was also investigated, with hexamethylphosphoramide (HMPA)[65] and *t*-butanol (^tBuOH) providing similar enhancements in the yield of the cyclized product (Table 7, entries 3 and 4). In contrast, the addition of several other additives, including $LiCl$[66a] and NiI_2[66b] did not lead to any significant improvements in the yield (Table 7, entries 5 and 6). The structure of iminoindoline **66** was unambiguously determined by the X-ray crystallographic analysis of **67**, which was prepared by the Boc protection of **66** (Figure 4).

The scope and limitations of this SmI_2-mediated reductive cyclization reaction were evaluated using a series of carbodiimides, and the results are shown in Table 8. Some of the cyclized products were found to be unstable, and the cyclization yields were therefore determined following the regioselective Boc protection of amidine. Under the optimal reaction conditions (method A), both electron-donating and electron-withdrawing functionalities were well tolerated on the phenyl ring to the left-hand side of the carbodiimide, including chlorine, methyl and methoxy groups, which gave the spirocyclic products **69a–d**

in 62% to 87% yields. It is noteworthy that compound **68a**, bearing a conformationally restricting substituent at the 3-position of its aromatic ring, reacted smoothly to give the desired product in good yield. When substrates **68e−i** bearing substituents on the phenyl ring to the right-hand side of the carbodiimides were used in the reaction, the optimized conditions (method A) gave lower yields of the cyclized products as well as several unidentified byproducts. Further experimental work concerning substrates **68e−i** revealed that the use of an inverse addition and changes to the amounts of SmI_2 and *t*-butanol to the reaction (Table 8, condition B) led to much higher yields with fewer byproducts. In the case of **68e**, a small amount of byproduct was formed from a 6π electrocyclic reaction, which most likely occurred as a result of Lewis acid-promoted acceleration through a chelated Sm species.

Table 7. Optimization of reaction conditions[a]
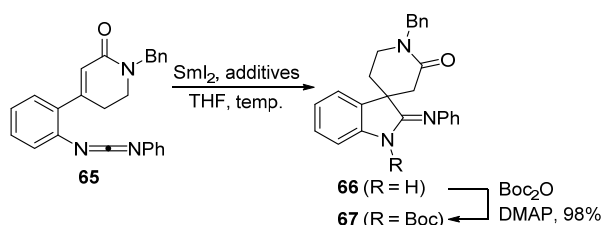
entry	temp.	additives	yield (%) of **66**
1	−78 °C	none	N.R.
2	rt	none	55
3	rt	HMPA[b]	78
4	rt	*t*BuOH[c]	83
5	rt	*t*BuOH*c* + LiCl[d]	68
6	rt	*t*BuOH*c* + NiI$_2$[e]	79

[a] Substrate solutions were added to 0.1 M SmI_2 solutions (2.4 equiv.). [b] 10% vol in SmI_2 solution. [c] 2.2 equiv. [d] 10 equiv. [e] 5 mol%.
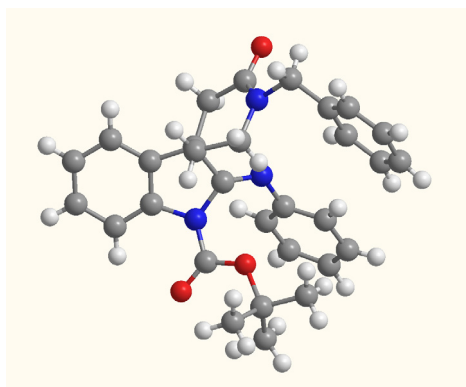

Figure 4. X-Ray structure of **67**

When the acyclic unsaturated ester **68j** and lactone **68k** were subjected to the optimal reaction conditions (condition B) they gave the desired products **69j** and **69k** in 76% and 83% yields, respectively (Table 8). In sharp contrast, the reaction of the corresponding ethyl cinnamate **68l** resulted in a complex mixture. Analysis of this mixture by mass spectroscopy revealed the presence of dimerized and trimerized products. These results therefore indicated that the β,β-disubstituted carbonyl moiety was essential to the success of the reaction.

Table 8. Scope and limitations of the reductive cyclization[a]
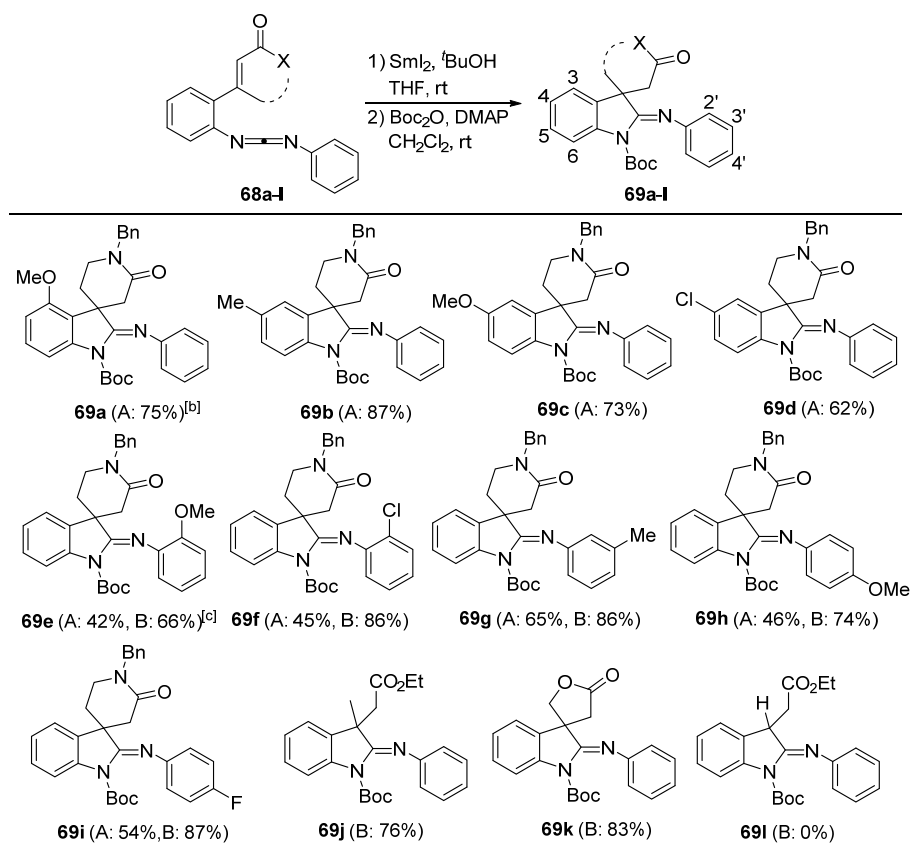
[a] All of these reactions were carried out on a 0.100 mmol scale. [b] A indicates the yield from condition A: A THF solution of the substrate and ^{t}BuOH (2.2 equiv.) was added to a THF solution of SmI$_2$ (2.4 equiv.). [c] B indicates the yield from condition B: A THF solution of SmI$_2$ (2.1–2.2 equiv.) was added to a THF solution of substrate and ^{t}BuOH (10 equiv.).

A possible mechanism for this reductive cyclization reaction is shown in Scheme 12. The carbonyl oxygen of compound **68** would initially coordinate to SmI$_2$. The subsequent reduction of the unsaturated carbonyl group would produce a radical anion **70** that would attack the carbon of the carbodiimide at a faster rate than the samarium enolate. Further reduction by a second equiv. of SmI$_2$ would provide the Sm amidinate **71**. Given that cyclized product was formed in the absence of *t*-butanol, dianion **71** would be

generated without the assistance of a proton source (Table 7, entry 2). Finally, protonation of **71** would give the reductively cyclized iminoindoline **69**. However, it remains unclear whether the formation of the carbon–carbon bond is promoted by chelation between a carbodiimide moiety and SmI$_2$ prior to the cyclization. The reported instability and difficulties associated with the generation of nitrogen-centered radical species[57] suggest that dianion **71** could be formed from a chelated complex.
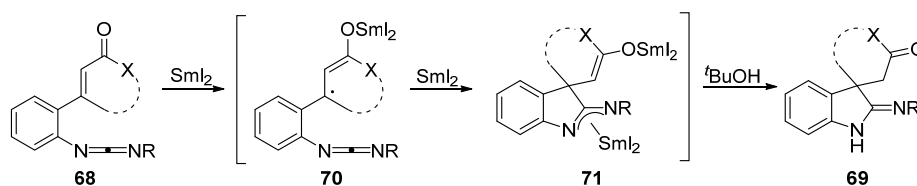
Scheme 12. Possible mechanism for the SmI$_2$-promoted intramolecular reductive cyclization of carbodiimides

The SmI$_2$-promoted intramolecular reductive cyclization reaction of carbodiimides bearing unsaturated carbonyl moieties was developed for the synthesis 2-iminoindolines bearing quaternary-carbon centers at their C3 position.[47] We considered this newly developed synthetic method is a powerful tool for the construction of 2-iminoindolines, and consequently applied this strategy to synthesize the core structure of perophoramidine (**57**).

2-3. SYNTHETIC STUDIES OF PEROPHORAMIDINE

Perophoramidine (**57**) was isolated from an extract of Philippine ascidian *Perophora namei* by Ireland et al.[42] in 2002 (Figure 3). The structure of this compound is characterized by a pentacyclic alkaloid bearing two contiguous quaternary carbon stereocenters, and was determined following extensive spectroscopic analyses, including a series of 2D NMR experiments. Perophoramidine (**57**) has been reported to induce apoptosis via PARP cleavage as well as being cytotoxic towards HCT116 colon carcinoma cells, with an IC$_{50}$ of 60 μM. Significant research efforts have been directed towards the synthesis of this natural product because of its highly complex polycyclic structure and interesting biological activities.[67-75] In 2004, Funk et al.[67a] accomplished the first total synthesis of (±)-perophoramidine, and its absolute configuration was confirmed by Qin in 2010 following his total synthesis of (+)-perophoramidine.[68a] The key step in all of these syntheses was the Diels‑Alder reaction of an indole with an *ortho*-quinone methide imine, which was inspired by the proposed biosynthetic pathway.[69a] Rainier also described a synthesis of (±)-dehaloperophoramidine **72**,[71] and Wang recently reported the total synthesis of (+)-perophoramidine, which involved the catalytic asymmetric alkylation reaction of a 3-bromooxindole

as a key step.[75] We also became interested in the total synthesis of perophoramidine because we had developed a synthetic method for constructing 2-iminoindolines.

Dehaloperophoramidine **72** was selected as our initial target, because this compound can be synthesized from the pentacyclic compound **73** according to an existing procedure (Scheme 13).[71] The key features of our retrosynthesis can be summarized as follows: (i) palladium-catalyzed intramolecular C−N bond formation between the amidine nitrogen and the aryl chloride in spiro-2-iminoindoline **74**; and (ii) the SmI$_2$-mediated reductive cyclization of carbodiimide **75** bearing an electron-deficient tetrasubstituted olefin. This strategy was reliant on the aryl chloride moiety of **75** remaining intact throughout the SmI$_2$-mediated reductive cyclization reaction so that it could then be used in the palladium-catalyzed cyclization. Our strategy for this compound was unique in terms of the way in which we planned to assemble the 3,3-disubstituted 2-iminoindoline during the initial stage of the process. In contrast, Funk, Qin, Rainier, and Wang had all employed indoles and their oxidized intermediates during the latter stages of their respective processes for constructing the core structure.
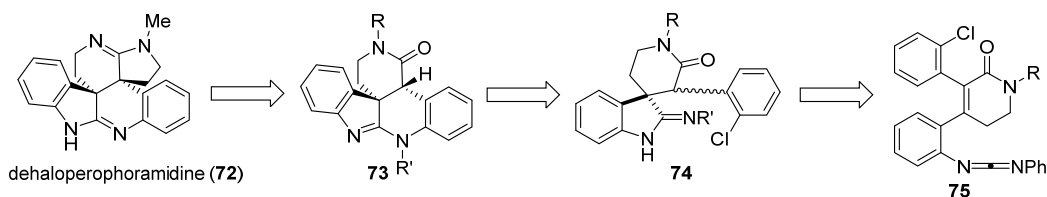
Scheme 13. Retrosynthesis of dehaloperophoramidine (**72**)

Carbodiimide **75**, which contains a tetrasubstituted olefin, was synthesized from the commercially available ethyl *N*-(benzylamino)propionate (**76**) (Scheme 14). The introduction of the ethyl malonyl moiety followed by the Dieckmann condensation of the resulting amide gave lactam **77**, which was converted to β-keto-lactam **78** via a one-pot hydrolysis decarboxylation reaction. Treatment of **78** with *N*-phenyl trifluoromethanesulfonimide (Tf$_2$NPh) and Et$_3$N gave the corresponding vinyl triflate **79**. The Suzuki coupling reaction of triflate **79** with boronic acid **80**[76] gave the biaryl product **81**, which was sequentially brominated and trityl (Tr)-protected to give **82**. The second Suzuki coupling of lactam **82** with 2-chlorophenyl boronic acid **83** proceeded smoothly to give the tetrasubstituted olefin, which was treated with trifluoroacetic acid to give aniline **84** in 50% yield from **82**. Two carbodiimides (**75a** and **75b**) bearing a *p*-methoxyphenyl (PMP) or *p*-methoxybenzyl (PMB) group were synthesized to determine the effect of different protecting groups on the palladium-catalyzed intramolecular C–N bond forming reaction. These carbodiimides were prepared by the treatment of compound **84** with an appropriate aryl

isocyanate followed by the dehydration of the resulting urea with triphenylphosphine and carbon tetrabromide. The resulting carbodiimides **75a** and **75b** were found to be stable at room temperature, whereas carbodiimide **65**, which did not possess an α-substituent on its α,β-unsaturated lactam, was gradually converted to 2-aminoquinoline through an undesired 6π electrocyclic reaction under the same conditions (Scheme 11 and Table 7).[64]
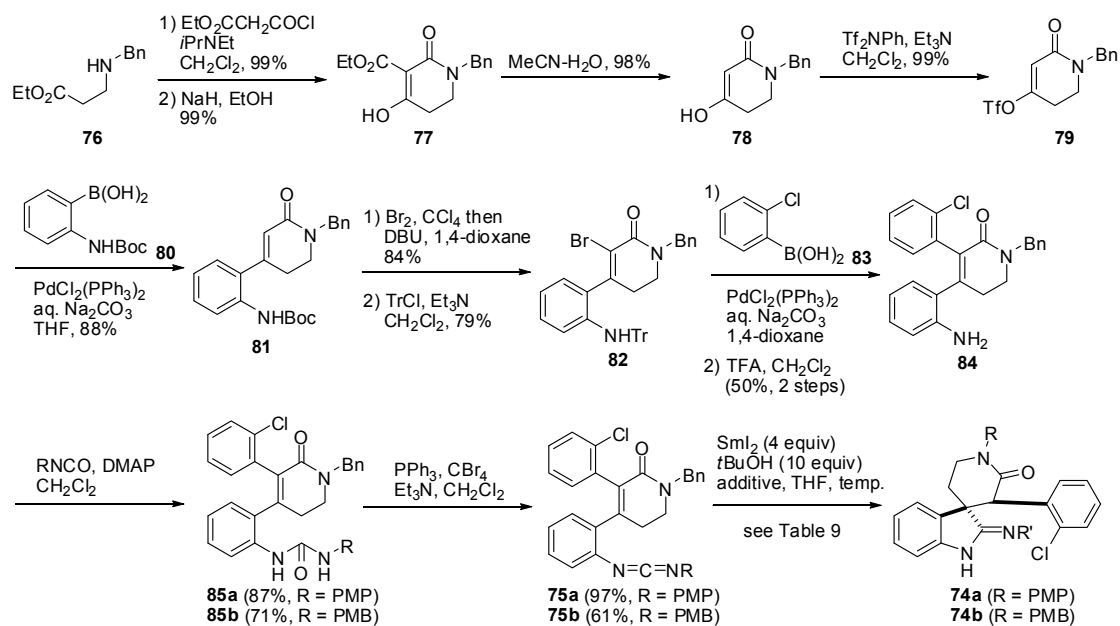

Scheme 14. Synthesis of spiro-2-iminoindolines **74a** and **74b**

With carbodiimides **75a** and **75b** bearing tetrasubstituted olefins in hand, we proceeded to investigate their performance in the SmI$_2$-mediated reductive cyclization. The reductive cyclization of the *N*-PMP carbodiimide **75a** with SmI$_2$ in the presence of *t*-butanol at room temperature proceeded smoothly to give spiro-2-iminoindoline **74a** in 86% yield (Scheme 14 and Table 9, entry 1). ^{1}H NMR and X-ray crystallography indicated that **74a** existed as a mixture of amidine-tautomers, with the ratio of the tautomers depending on the solvent. X-Ray crystallographic analysis of **74a** also revealed that the two aryl groups on the 2-piperidinone ring were in a *syn* configuration (Figure 5, left). The stereoselectivity of this reaction was attributed to the selective protonation of the samarium enolate **85** from the same side as the PMP-imine moiety, which was less sterically hindered (Figure 5, right). We also investigated the reductive cyclization of *N*-PMB carbodiimide **75b** under the optimal conditions. Unfortunately, the reaction did not proceed at room temperature or 60 °C, with the starting material **75b** being recovered in both cases (Table 9, entries 2 and 3). Pleasingly, the use of HMPA as a co-solvent, which is generally used to increase the reduction potential of SmI$_2$,[65] allowed for the desired cyclization reaction to proceed at room temperature to give iminoindoline **74b** in 90% yield (Table 9, entry 4).

Table 9. Reductive cyclization of carbodiimide **75a** and **75b**

| entry	substrate	additives	temp	results
1	**75a**	none	rt	86%[a]
2	**75b**	none	rt	no reaction
3	**75b**	none	60 °C	no reaction
4	**75b**	HMPA (10%vol)	rt	90%

[a] 2.8 equiv of SmI$_2$ was used.
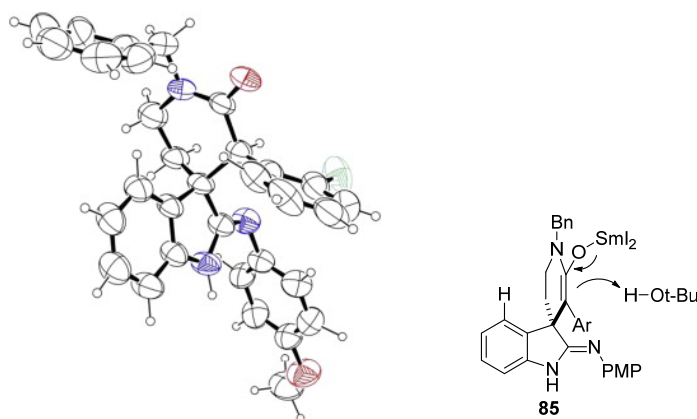
Figure 5. X-Ray structure of **74a** (left) and the protonation of samarium enolate **85** (right)

The epimerization of the α-position of the lactam was investigated prior to evaluating the intramolecular palladium-catalyzed aryl amidination[77] because the spiro-2-iminoindolines **74a** and **74b** were much less likely than the other diastereomers to undergo the cyclization based on their conformation. Treatment of spiro-2-iminoindoline **74a** with sodium *t*-butoxide in DMA at room temperature resulted in no reaction, whereas **74c** was obtained by epimerization after 2 h at 60 °C, which was observed by ^{1}H NMR analysis (Scheme 15). Surprisingly, the desired cyclization reaction occurred to give the pentacyclic compound **73a** when the material was heated at 120 °C for 24 h (Table 10, entry 1). While we did not extensively investigate these transition-metal-free conditions, we suspected a involvement of a trace amount of palladium catalyst under these conditions. Several alkylphosphine ligands were screened to develop a concise cyclization reaction for the palladium catalyzed amidination of compound **74a**. Although the use of Ad$_2$PBu in the presence of Pd(OAc)$_2$ did not give satisfactory results (Table 10, entry 2), *t*Bu$_3$P· HBF$_4$, CyJohnPhos, DavePhos, and tricyclohexylphosphine (Cy$_3$P) led to improvements in the yield up to 78% (Table 10, entries 3−6). Notably, Cy$_3$P, which was identified as the best ligand for the reaction, also led to a significant increase in the reaction rate (17 h, 78% yield) (Table 10, entry 6). Decreasing the amounts of palladium catalyst and Cy$_3$P led to an increase in the yield up to 86% (Table 10, entry 7). The newly generated stereochemistry in pentacycle **73a** was determined by 2D NMR analyses, including NOESY

experiments (**Figure 6**). In sharp contrast, the application of these optimized conditions to the *N*-PMB-protected iminoindoline **74b** did not give the cyclized product. In this particular case, the starting material was recovered unchanged, and the differences in the reactivities of the two substrates were attributed to differences in the electronic properties. However, it is important to mention that a detailed mechanism for this cyclization reaction has not yet been determined.

The pentacyclic skeleton of perophoramidine (**57**) was successfully constructed by the SmI_2-mediated reductive cyclization of carbodiimide **75a** bearing a tetrasubstituted olefin followed by a palladium-catalyzed intramolecular C−N bond formation.[48] The resulting pentacyclic compound **73a** was synthetically equivalent to Rainier's pentacyclic amidine, which was used as an intermediate for dehaloperophoramidine.[71] This newly developed and unique strategy provided a novel platform for synthesizing natural products containing an amidine moiety.
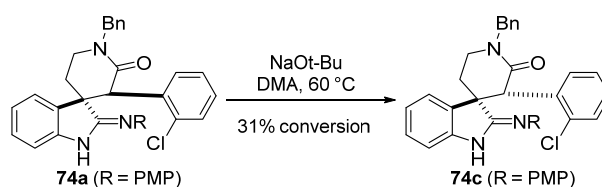
Scheme 15. Isomerization of iminoindoline **74a**

Table 10. Intramolecular aryl amidination of iminoindoline **73a**
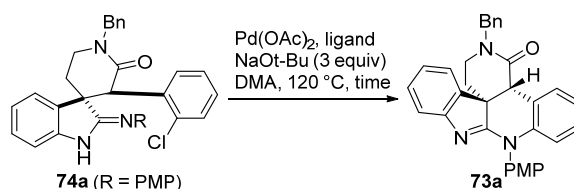
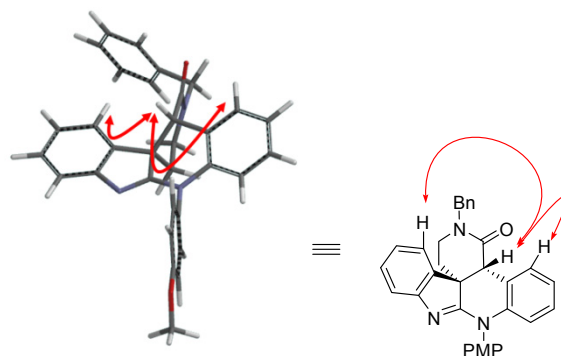| entry	Pd(OAc)$_2$	ligand (mol%)	Time (h)	Yield (%)
1	none	none	24	27
2	10 mol%	Ad$_2$PnBu (20)	24	31
3	10 mol%	tBu$_3$P· HBF$_4$ (20)	24	63
4	10 mol%	Cyclohexyl JohnPhos (20)	24	66
5	10 mol%	Davephos (20)	24	70
6	10 mol%	Cy$_3$P· HBF$_4$ (20)	17	78
7	5 mol%	Cy$_3$P· HBF$_4$ (10)	17	86

Figure 6. NOESY correlation of pentacycle **73a**

3. SUMMARY

We have been heavily involved in developing novel synthetic strategies for constructing spirooxindoles based on the formation of the C2−C3 bond. Our work in this area has led to the development of a palladium-catalyzed domino reaction for the formation of spirooxindoles, as well as an alternative strategy involving the palladium-catalyzed carbosilylation of carbamoyl chlorides bearing a 1,3-diene moiety. Using the former method, we successfully completed a formal synthesis of elacomine and isoelacomine. The combination of our newly developed domino palladium-catalyzed carbosilylation of 1,3-dienes with a Sakurai-type cyclization reaction allowed for the successful construction of spirooxindoles fused with tetrahydropyran, piperidine, and five-membered carbocycles, with control over two or three contiguous stereocenters.

Inspired by these newly developed methods for constructing spirooxindoles, we also established a SmI_2-mediated process involving the intramolecular reductive cyclization of carbodiimides, which allowed for the synthesis of 2-iminoindolines bearing a quaternary-carbon center at their C3 position. This unique synthetic method was combined with a palladium-catalyzed intramolecular C−N bond formation reaction to allow for the effective construction of the core structure of perophoramidine, which is a hexacyclic alkaloid.

We believe that these synthetic strategies represent a powerful addition to the plethora of synthetic transformations already available to synthetic chemists, and could be readily applied to the synthesis of complex spirooxindole- and iminoindoline-containing natural products. Further work towards the application of these reactions is currently underway in our laboratory and will be reported in due course.[78]

Scientists (B) (C.T.), and Young Scientists (Start-up) (Y.Y.), "Targeted Proteins Research Program" and "Platform for Drug Design, Discovery and Development" from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and JSPS Research Fellowship for Young Scientists (T.I.).

REFERENCES (AND NOTES)

1. For selected reviews on natural products containing indoles and related skeletons, see: (a) J. S. Bindra, 'The Alkaloids', Vol. 14, ed. by R. H. F. Manske, Academic Press, Inc., New York, 1973, pp.84-121; (b) M. Ishikura and K. Yamada, *Nat. Prod. Rep.*, 2009, **26**, 803; (c) A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489.

2. T. Kosuge, K. Tsuji, K. Hirai, T. Fukuyama, H. Nukaya, and H. Ishida, *Chem. Pharm. Bull.*, 1985, **33**, 2890.

3. (a) R. C. Elderfield and R. E. Gilman, *Phytochemistry*, 1972, **11**, 339; (b) S. Cheenpracha, T. Ritthiwigrom, and S. Laphookhieo, *J. Nat. Prod.*, 2013, **76**, 723.

4. C.-B. Cui, H. Kakeya, and H. Osada, *Tetrahedron*, 1996, **52**, 12651.

5. X.-H. Cai, Q.-G. Tan, Y.-P. Liu, T. Feng, Z.-Z. Du, W.-Q. Li, and X.-D. Luo, *Org. Lett.*, 2008, **10**, 577.

6. K.-H. Lim and T.-S. Kam, *Tetrahedron Lett.*, 2006, **47**, 8653.

7. (a) G. W. A. Slywka, Ph. D. Thesis, The University of Alberta, Edmonton (1969); (b) M. N. G. James and G. J. B. Williams, *Can. J. Chem.*, 1972, **50**, 2407.

8. B. S. Joshi, P. G. Rao, D. Rogers, B. P. Singri, and D. J. Williams, *Indian J. Chem. Sect. B*, 1984, **23B**, 101.

9. (a) T. G. Wormley, *Am. J. Pharm.*, 1870, **42**, 1; (b) F. M. Lovell, R. Pepinsky and A. J. C. Wilson, *Tetrahedron Lett.*, 1959, **1**, 1; (c) H. Conroy and J. K. Chakrabarti, *Tetrahedron Lett.*, 1959, **1**, 6.

10. For recent examples, see: (a) A. Fensome, W. R. Adams, A. L. Adams, T. J. Berrodin, J. Cohen, C. Huselton, A. Illenberger, J. C. Kern, V. A. Hudak, M. A. Marella, E. G. Melenski, C. C. McComas, C. A. Mugford, O. D. Slayden, M. Yudt, Z. Zhang, P. Zhang, Y. Zhu, R. C. Winneker, and J. E. Wrobel, *J. Med. Chem.,* 2008, **51**, 1861; (b) N. Teno, K. Masuya, T. Ehara, T. Kosaka, T. Miyake, O. Irie, Y. Hitomi, N. Matsuura, I. Umemura, G. Iwasaki, H. Fukaya, K. Toriyama, N. Uchiyama, K. Nonomura, I. Sugiyama, and M. Kometani, *J. Med. Chem.,* 2008, **51**, 5459.

11. (a) A. B. Dounay and L. E. Overman, *Chem. Rev.,* 2003, **103**, 2945; (b) H. Lin and S. J. Danishefsky, *Angew. Chem. Int. Ed.,* 2003, **42**, 36; (c) C. Marti and E. M. Carreira, *Eur. J. Org. Chem.,* 2003, 2209; (d) A. Steven and L. E. Overman, *Angew. Chem. Int. Ed.*, 2007, **46**, 5488; (e) C. V. Galliford and K. A. Scheidt, *Angew. Chem. Int. Ed.,* 2007, **46**, 8748; (f) B. M. Trost and M. K. Brennan, *Synthesis,* 2009, 3003; (g) F. Zhou, Y.-L. Liu, and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**,

1381; (h) R. Dalpozzo, G. Bartoli, and G. Bencivenni, *Chem. Soc. Rev.*, 2012, **41**, 7247; (i) N. R. Ball-Jones, J. J. Badillo, and A. K. Franz, *Org. Biomol. Chem.*, 2012, **10**, 5165.

12. D. Lizos, R. Tripoli, and J. A. Murphy, *Chem. Commun.*, 2001, 2732.

13. (a) L. E. Overman and M. D. Rosen, *Angew. Chem. Int. Ed.*, 2000, **39**, 4596; (b) L. E. Overman and M. D. Rosen, *Tetrahedron,* 2010, **66**, 6514.

14. S. D. Edmondson and S. J. Danishefsky, *Angew. Chem. Int. Ed.*, 1998, **37**, 1138.

15. (a) W. G. B. van Henugouwen, R. M. Fieseler, F. P. J. T. Rutjes, and H. Hiemstra, *Angew. Chem. Int. Ed.*, 1999, **38**, 2214; (b) W. G. B. van Henugouwen, R. M. Fieseler, F. P. J. T. Rutjes, and H. Hiemstra, *J. Org. Chem.*, 2000, **65**, 8317.

16. F. Von Nussbaum and S. J. Danishefsky, *Angew. Chem. Int. Ed.*, 2000, **39**, 2178.

17. P. B. Alper, C. Meyers, A. Lerchner, D. R. Siegel, and E. M. Carreira, *Angew. Chem. Int. Ed.*, 1999, **38**, 3186.

18. P. R. Sebahar and R. M. Williams, *J. Am. Chem. Soc.*, 2000, **122**, 5666.

19. (a) Y. Kobayashi, H. Kamisaki, R. Yanada, and Y. Takemoto, *Org. Lett.*, 2006, **8**, 2711; (b) Y. Kobayashi, H. Kamisaki, H. Takeda, Y. Yasui, R. Yanada, and Y. Takemoto, *Tetrahedron,* 2007, **63**, 2978; (c) Y. Yasui, H. Kamisaki, and Y. Takemoto, *Org. Lett.*, 2008, **10**, 3303; (d) Y. Yasui, H. Kamisaki, T. Ishida, and Y. Takemoto, *Tetrahedron*, 2010, **66**, 1980.

20. H. Kamisaki, Y. Yasui, and Y. Takemoto, *Tetrahedron. Lett.*, 2009, **50**, 2589.

21. H. Kamisaki, T. Nanjo, C. Tsukano, and Y. Takemoto, *Chem. Eur. J.*, 2011, **17**, 626.

22. S. M. Hande, M. Nakajima, H. Kamisaki, C. Tsukano, and Y. Takemoto, *Org. Lett.*, 2011, **13**, 1828.

23. (a) R. F. Heck, *J. Am. Chem. Soc.*, 1963, **85**, 3381; (b) S. D. Robinson and B. L. Shaw, *J. Chem. Soc.*, 1963, 4806; (c) R. M. Rowe and D. A. White, *J. Chem. Soc.,* 1967, 1451.

24. For reports concerning the addition of nitrogen-based nucleophiles to conjugated dienes catalyzed by palladium(0), see: (a) B. A. Patel, J. E. Dickerson, and R. F. Heck, *J. Org. Chem.*, 1978, **43**, 5018; (b) F. G. Stakem and R. F. Heck, *J. Org. Chem.*, 1980, **45**, 3584.

25. The carbamoyl chloride was employed by Grigg and co-workers in their synthesis of 3,3-disubstituted oxindoles using palladium catalyst, see: (a) M. R. Fielding, R. Grigg, and C. J. Urch, *Chem. Commun.*, 2000, 2239; (b) J. Anwar, M. R. Fielding, R. Grigg, V. Sridharan, and C. J. Urch, *J. Organomet. Chem.*, 2006, **691**, 1476

26. E. Piers and R. D. Tillyer, *Can. J. Chem.*, 1996, **74**, 2048.

27. C. Pellegrim, M. Eber, and H.-J. Borschberg, *Helv. Chim. Acta*, 1996, **79**, 151.

28. F. Y. Miyake, K. Yakushijin, and D. A. Horne, *Org. Lett.*, 2004, **6**, 711.

29. J. D. White, Y. Li, and D. C. Ihle, *J. Org. Chem.*, 2010, **75**, 3569.

30. For reviews of the Heck reaction, see: (a) W. Cabri and I. Candiani, *Acc. Chem. Res.*, 1995, **28**, 2;

(b) I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009; (c) J. T. Link *Org. React.*, 2002, **60**, 157.

31. (a) H. Qin, N. Yamagiwa, S. Matsunaga, and M. Shibasaki, *J. Am. Chem. Soc.*, 2006, **128**, 1611; (b) H. Qin, N. Yamagiwa, S. Matsunaga, and M. Shibasaki *Chem. Asian J.*, 2007, **2**, 150.

32. (a) H. Wei, G. Qian, Y. Xia, K. Li, Y. Li, and W. Li, *Eur. J. Org. Chem.*, 2007, 4471; (b) X. Cheng, Y. Xia, H. Wei, B. Xu, C. Zhang, Y. Li, G. Qian, X. Zhang, K. Li, and W. Li, *Eur. J. Org. Chem.*, 2008, 1929.

33. I. Beletskaya and C. Moberg, *Chem. Rev.*, 2006, **106**, 2320.

34. (a) Y. Sato, N. Saito, and M. Mori, *Chem. Lett.*, 2002, **38**, 18; (b) N. Saito, M. Mori, and Y. Sato, *J. Organomet. Chem.*, 2007, **692**, 460.

35. C.-M. Yu, J. Youn, S.-K. Yoon, and Y.-T. Hong, *Org. Lett.*, 2005, **7**, 4507.

36. Rh catalysts were employed for the silylation of aryl and alkenyl cyanides and the borylative cyclization of alkynylaryl isocyanates involving the cleavage of Si–Si or B–B bonds, see: (a) M. Tobisu, Y. Kita, and N. Chatani, *J. Am. Chem. Soc.*, 2006, **128**, 8152; (b) T. Miura, Y. Takahashi, and M. Murakami, *Org. Lett.*, 2008, **9**, 1743.

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

38. For related reviews, see: (a) D. R. Adams and S. P. Bhatnagar, *Synthesis*, 1977, 661; (b) T. Mukaiyama and M. Murakami, *Synthesis*, 1987, 1043.

39. L. E. Overman and D. A. Watson, *J. Org. Chem.*, 2006, **71**, 2587.

40. While the mechanism of the palladium-catalyzed carbosilylation has not been disclosed, we assumed the two plausible mechanisms. One is shown in Scheme 8. The other plausible pathway would commence with the oxidative addition of the carbamoyl chloride to a palladium catalyst. Insertion into the diene moiety would be followed by transmetallation with $Me_3SiSiMe_3$ and reductive elimination to give the product. We previously reported (refs. 19d, 20 and 21) that the addition of PPh_3 was beneficial for the oxidative addition of the carbamoyl chloride to palladium, however, the addition of PPh_3 in this case proved to be detrimental to the cyclization (Table 4, entries 8 and 9), and it was therefore assumed that the reaction proceeded via a bismetallative process.

41. (a) A. Numata, C. Takahashi, Y. Ito, T. Takada, K. Kawai, Y. Usami, E. Matsumura, M. Imachi, T. Ito, and T. Hasegawa, *Tetrahedron Lett.*, 1993, **34**, 2355; (b) H. Hayashi, H. Matsumoto, and K. Akiyama, *Biosci. Biotechnol. Biochem.*, 2004, **68**, 753; (c) R. Jadulco, R. A. Edrada, R. Ebel, A.

Berg, K. Schaumann, V. Wray, K. Steube, and P. Proksch, *J. Nat. Prod.*, 2004, **67**, 78; (d) P. W. Dalsgaard, J. W. Blunt, M. H. G. Munro, J. C. Frisvad, and C. Christophersen, *J. Nat. Prod.*, 2005, **68**, 258; (e) B. Andersen, J. Smedsgaard, and J. C. Frisvad, *J. Agric. Food Chem.*, 2004, **52**, 2421; (f) L. J. Wigley, P. G. Mantle, and D. A. Perry, *Phytochemistry*, 2006, **67**, 561.

42.   S. M. Verbitski, C. L. Mayne, R. A. Davis, G. P. Concepcion, and C. M. Ireland, *J. Org. Chem.*, 2002, **67**, 7124.

43.   J. S. Carlé and C. Christophersen, *J. Org. Chem.*, 1981, **46**, 3440

44.   N. Koyama, Y. Inoue, M. Sekine, Y. Hayakawa, H. Homma, S. Ōmura, and H. Tomoda, *Org. Lett.*, 2008, **10**, 5273.

45.   A. Hirano, Y. Iwai, R. Masuma, K. Tei, and S. Ōmura, *J. Antibiot.*, 1979, **32**, 781.

46.   C. Bunders, J. Cavanagh, and C. Melander, *Org. Biomol. Chem.*, 2011, **9**, 5476.

47.   T. Ishida, C. Tsukano, and Y. Takemoto, *Chem. Lett.*, 2012, **41**, 44.

48.   T. Ishida and Y. Takemoto, *Tetrahedron*, 2013, **69**, 4517.

49.   (a) T. Kawasaki, R. Terashima, K. Sakaguchi, H. Sekiguchi, and M. Sakamoto, *Tetrahedron Lett.*, 1996, **37**, 7525; (b) Y. Jiang, J. Zhao, and L. Hu, *Tetrahedron Lett.*, 2002, **43**, 4589; (c) Y. A. O. Barbosa, D. J. Hart, and N. A. Magomedov, *Tetrahedron*, 2006, **62**, 8748; (d) A. Sabahi, A. Novikov, and J. D. Rainier, *Angew. Chem. Int. Ed.*, 2006, **45**, 4317; (e) M. Ohno, T. F. Spande, and B. Witkop, *J. Am. Chem. Soc.*, 1968, **90**, 6521.

50.   D. Aburano, T. Yoshida, N. Miyakoshi, and C. Mukai, *J. Org. Chem.*, 2007, **72**, 6878.

51.   B. Witulski, C. Alayrac, and L. Tevzadze-Saeftel, *Angew. Chem. Int. Ed.*, 2003, **42**, 4257.

52.   M. K. G. Mekhael and H. Heimgartner, *Helv. Chim. Acta*, 2003, **86**, 2805.

53.   D. Dhanak, S. Neidle, and C. B. Reese, *Tetrahedron Lett.*, 1985, **26**, 2017.

54.   J. R. Fuchs and R. L. Funk, *J. Am. Chem. Soc.*, 2004, **126**, 5068.

55.   Y. Matsuda, M. Kitajima, and H. Takayama, *Org. Lett.*, 2008, **10**, 125.

56.   A. Williams and I. T. Ibrahim, *Chem. Rev.*, 1981, **81**, 589.

57.   (a) W. Ahrens and A. Berndt, *Tetrahedron Lett.*, 1974, **15**, 3741; (b) G. Brunton, J. F. Taylor, and K. U. Ingold, *J. Am. Chem. Soc.*, 1976, **98**, 4879.

58.   J. L. Namy, P. Girard, and H. B. Kagan, *New J. Chem.*, 1977, **1**, 5.

59.   For reviews concerning SmI$_2$ mediated reactions, see: (a) G. A. Molander and C. R. Harris, *Chem. Rev.*, 1996, **96**, 307; (b) K. Gopalaiah and H. B. Kagan, *New J. Chem.*, 2008, **32**, 607.

60.   (a) D. J. Edmonds, D. Johnston, and D. J. Procter, *Chem. Rev.*, 2004, **104**, 3371; (b) K. C. Nicolaou, S. P. Ellery, and J. S. Chen, *Angew. Chem. Int. Ed.*, 2009, **48**, 7140.

61.   (a) J. L. Namy, J. Souppe, and H. B. Kagan, *Tetrahedron Lett.*, 1983, **24**, 765; (b) S. Fukuzawa, A. Nakanishi, T. Fujinami, and S. Sakai, *Chem. Commun.*, 1986, 624; (c) T. Imamoto and S.

Nishimura, *Chem. Lett.*, 1990, **19**, 1141; (d) J. Inanaga, Y. Handa, T. Tabuchi, K. Otsubo, M. Yamaguchi, and T. Hanamoto, *Tetrahedron Lett.*, 1991, **32**, 6557; (e) N. Taniguchi T. Hata, and M. Uemura, *Angew. Chem. Int. Ed.*, 1999, **38**, 1232; (f) Y. H. Kim, H. S. Park, and D. W. Kwon, *Synth. Commun.*, 1998, **28**, 4517; (g) J. M. Ready, S. E. Reisman, M. Hirata, M. M. Weiss, K. Tamaki, T. V. Ovaska, and J. L. Wood, *Angew. Chem. Int. Ed.*, 2004, **43**, 1270.

62. For a report concerning the dimerization of carbodiimide by samarocene, see: M. Deng, Y. Yao, Y. Zhang, and Q. Shen, *Chem. Commun.*, 2004, 2742.

63. T. Saito, K. Tsuda, and Y. Saito, *Tetrahedron Lett.*, 1996, **37**, 209.

64. (a) T. Saito, H. Ohmori, E. Furuno, and S. Motoki, *Chem. Commun.*, 1992, 22; (b) P. Molina, M. Alajarín, A. Vidal, and P. Sánchez-Andrada, *J. Org. Chem.*, 1992, **57**, 929.

65. J. Inanaga, M. Ishikawa, and M. Yamaguchi, *Chem. Lett.*, 1987, **16**,1485.

66. (a) R. S. Miller, J. M. Sealy, M. Shabangi, M. L. Kuhlman, J. R. Fuchs, and R. A. Flowers II, *J. Am. Chem. Soc.*, 2000, **122**, 7718; (b) F. Machrouhi, B. Hmann, J. L. Namy, and H. B. Kagan, *Synlett*, 1996, 633.

67. (a) J. R. Fuchs and R. L. Funk, *J. Am. Chem. Soc.*, 2004, **126**, 5068; (b) S. L. Crawley and R. L. Funk, *Org. Lett.*, 2003, **5**, 3169.

68. (a) H. Wu, F. Xue, X. Xiao, and Y. Qin, *J. Am. Chem. Soc.*, 2010, **132**, 14052; (b) J. Yang, H. Song, X. Xiao, J. Wang, and Y. Qin, *Org. Lett.*, 2006, **8**, 2187; (c) H. Wu, X. Xiao, and Y. Qin, *Synlett*, 2011, 907.

69. (a) J. A. May, R. K. Zeidan, and B. M. Stoltz, *Tetrahedron Lett.*, 2003, **44**, 1203; (b) S.-J. Han, F. Vogt, S. Krishnan, J. A. May, M. Gatti, S. C. Virgil, and B. M. Stoltz, *Org. Lett.*, 2014, **16**, 3316.

70. (a) G. D. Artman III and S. M. Weinreb, *Org. Lett.*, 2003, **5**, 1523; (b) J. H. Seo, G. D. Artman III, and S. M. Weinreb, *J. Org. Chem.*, 2006, **71**, 8891; (c) M. A. Evans, J. R. Sacher, and S. M. Weinreb, *Tetrahedron*, 2009, **65**, 6712.

71. A. Sabahi, A. Novikov, and J. D. Rainier, *Angew. Chem. Int. Ed.*, 2006, **45**, 4317.

72. B. M. Trost and Y. Zhang, *Chem. Eur. J.*, 2011, **17**, 2916.

73. Y. Du, H. Wu, H. Song, Y. Qin, and D. Zhang, *Chin. J. Chem.*, 2012, **30**, 1970.

74. A. W. Schammel, G. Chiou, and N. K. Garg, *Org. Lett.*, 2012, **14**, 4556.

75. H. Zhang, L. Hong, H. Kang, and R. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 14098.

76. M. J. Sharp and V. Snieckus, *Tetrahedron Lett.*, 1985, **26**, 5997.

77. (a) C. B. Brain and T. Brunton, *Tetrahedron Lett.*, 2002, **43**, 1893; (b) M. A. McGowan, C. Z. McAvoy, and S. L. Buchwald, *Org. Lett.*, 2012, **14**, 3800.

78. For our most recent papers concerning the synthesis of indoles, oxindoles and iminoindolines, see: (a) C. Tsukano, M. Okuno, and Y. Takemoto, *Angew. Chem. Int. Ed.*, 2012, **51**, 2763; (b) T. Nanjo,

C. Tsukano, and Y. Takemoto, *Org. Lett.*, 2012, **14**, 4270; (c) C. Tsukano, M. Okuno, and Y. Takemoto, *Chem. Lett.*, 2013, **42**, 753; (d) T. Nanjo, S. Yamamoto, C. Tsukano, and Y. Takemoto, *Org. Lett.*, 2013, **15**, 3754; (e) T. Ishida, H. Ikota, K. Kurahashi, C. Tsukano, and Y. Takemoto, *Angew. Chem. Int. Ed.*, 2013, **52**, 10204; (f) T. Nanjo, C. Tsukano, and Y. Takemoto, *Synlett*, 2014, **25**, 1473; (g) C. Tsukano, M. Okuno, H. Nishiguchi, and Y. Takemoto, *Adv. Synth. Catal.*, 2014, **356**, 1533.
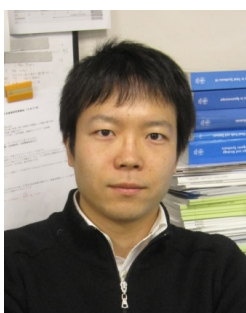
Chihiro Tsukano studied chemistry at the Department of Chemistry at Tokyo University under the guidance by Prof. Kazuo Tachibana. After received B.Sc and M.Sc. degrees, he moved to Tohoku University and received his Ph. D. in 2006 under the guidance by Prof. Makoto Sasaki. After postdoctoral studies (2006-2008 under Prof. Samuel J. Danishefsky, Memorial Sloan-Kettering Cancer Center, New York), he joined the Department of Chemistry at Tohoku University and worked in the laboratory of Prof. Masahiro Hirama. In 2009 he moved to Graduate School of Pharmaceutical Sciences, Kyoto University and worked with Prof. Yoshiji Takemoto as Assistant Professor. In 2014 he promoted to Lecturer in the same group. His research interests center on the area of development synthetic methodology and natural product synthesis.

Yoshiji Takemoto is a professor at the Graduate School of Pharmaceutical Sciences, Kyoto University. He received his B.S. (1983), M.S. (1985), and Ph.D. (1988) degrees from Osaka University. He worked as a postdoctoral fellow with Prof. R. A. Holton at Florida State University for 1 year from 1988, and with Dr. S. Terashima at Sagami Chemical Research Center for 1 year from 1989. He joined the Faculty of Pharmaceutical Sciences, Osaka University, as an assistant professor in 1990. He moved to the Graduate School of Pharmaceutical Sciences, Kyoto University, as an associate professor in 1998 and was promoted to professor in 2000. His research interests are in the areas of synthetic organic chemistry, transition metal chemistry, organocatalyst chemistry, and total synthesis of natural products.