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Synthesis of 3,3-disubstituted oxindoles through Pd-catalyzed intramolecular cyanoamidation

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ABSTRACT

The cyanoamidation of olefins was achieved. When *N*-(2-vinylphenyl)cyanoformamides were treated with palladium catalyst, intramolecular cyanoamidation took place to give corresponding 3,3-disubstituted oxindoles. P(*t*-Bu)$_3$ showed a remarkable effect on this reaction. When it was used with Pd(dba)$_2$, the reaction was completed in 15 min at 100 °C for many substrates. Furthermore, the enantioselective cyanoamidation was accomplished with Pd(dba)$_2$ and an optically active phosphoramidite to provide optically active 3,3-disubstituted oxindoles. Manipulation of the resulting oxindoles has been studied.

1. Introduction

Compounds possessing the 3,3-disubstituted oxindole substructure have received considerable pharmacological attention, and have frequently been used as synthetic intermediates for indole alkaloid synthesis.[1] To obtain optically active 3,3-disubstituted oxindoles, various classes of enantioselective methodologies have been applied. These can be classified on the basis of retrosynthetic disconnection (Fig. 1). Formation of the bond between C(3) and the benzene ring (path **a**), represents an enantioselective Heck reaction pioneered by Overman et al.[2] Recently, this strategy has been expanded to an arylpalladation–cyanation cascade.[3] Alternatively, the same bond was constructed through palladium-catalyzed enantioselective intramolecular α-arylation of acetanilide derivatives.[4] The strategies starting from 3-monosubstituted oxindole (path **b**) have also been extensively studied; namely, optically active pyridine-catalyzed acyl migrations,[5] palladium- or molybdenum-catalyzed allylations,[6] palladium-catalyzed trimethylenemethane [3+2]-cycloadditions,[7] cinchona-alkaloid-catalyzed enantioselective aldol-type reactions,[8] palladium-catalyzed enantioselective arylations and vinylations,[9] organocatalytic Mannich reactions,[10] and enantioselective Claisen rearrangements.[11,12] In this project, we studied the synthesis of optically active 3,3-disubstituted oxindoles by bond formation between an amide carbonyl and C(3) (path **c**), which has not been explored previously.

Recently, we have been interested in developing lactam formation through intramolecular insertion of carbamoyl transition-metal complexes (Fig. 2).[13] The catalytic process starts with the oxidative addition of formamide derivatives to low valent transition-metal species to generate carbamoyl complex **A**. This complex undergoes ring closure via amidometalation. Either reductive elimination or β-hydride elimination leads to the final product. The advantages of our strategy are: (i) providing access to highly functionalized and substituted lactams, (ii) in a single step, (iii) from readily available starting materials, and (iv) under neutral conditions.

In line with this reaction design, several lactam forming methods were developed (Fig. 3). Alkylidene lactams were synthesized from alkynyl formamides through rhodium-catalyzed

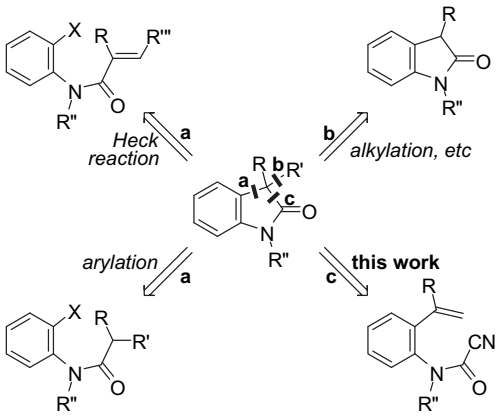

Figure 1. Enantioselective synthesis of 3,3-disubstituted oxindoles.

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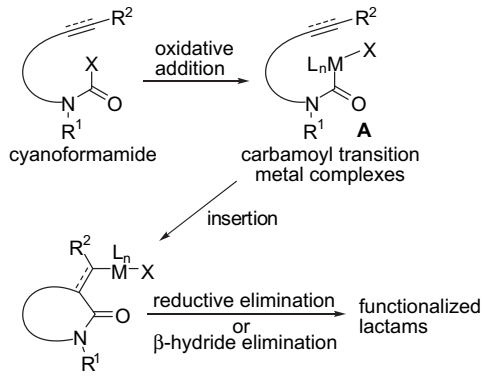


Figure 2. Synthesis of lactams through carbamoyl transition-metal complexes.

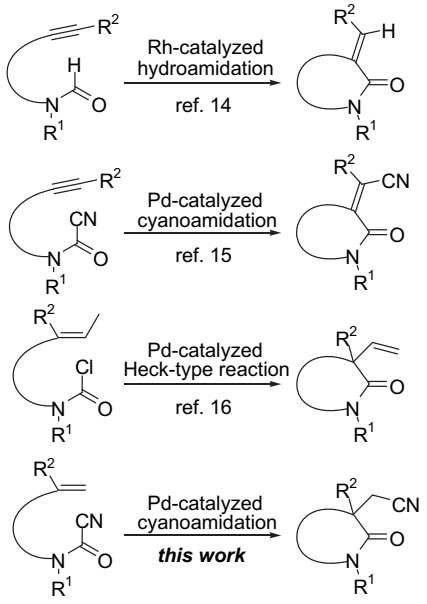


Figure 3. Transition-metal-catalyzed lactam formations studied in our group.

hydroamidation[14] and palladium-catalyzed cyanoamidation.[15] Replacement of the alkyne with an alkene led to the formation of α,α-disubstituted lactams: a palladium-catalyzed Heck-type reaction proceeded from alkenyl chloroformamides to give α-vinyl lactams.[16] As part of these studies, the reaction of alkenyl cyanoformamides with palladium catalyst was found to give α-cyanomethyl lactams. This reaction was applied to the synthesis of 3,3-disubstituted oxindoles and other α,α-disubstituted lactams and was expanded to enantioselective transformation. Details of this intramolecular cyanoamidation of alkenes are described herein.[17]

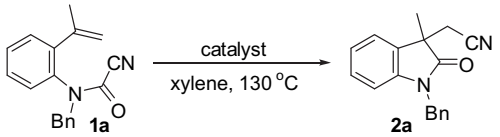
During the period when we were studying cyanoamidation, other carbocyanation reactions were developed extensively.[18] Nishihara's group and Hiyama's group reported cyanoesterification of norbornenes and allenes.[19,20] Hiyama also achieved a series of carbocyanation reactions through C–CN bond activation of aryl,[21] alkynyl,[22] allyl,[23] and alkyl[21b] cyanides. Recently, intramolecular enantioselective arylcyanation has been achieved.[24]

2. Results and discussion

2.1. Pd-catalyzed intramolecular cyanoamidation of olefins

Cyanoformamide **1a**[25] derived from commercially available 2-isopropenylaniline was treated with palladium catalyst in xylene at 130 °C (Table 1). Treatment of 10 mol % $Pd(PPh_3)_4$, under similar

Table 1
Pd-catalyzed intramolecular cyanoamidation of olefins

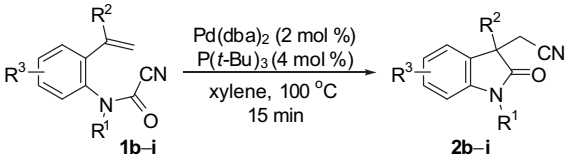


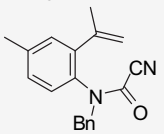
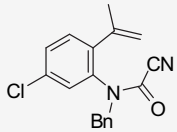
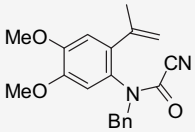
Entry	Catalyst (mol %)	Time (h)	Yield[a] (%)
1	$Pd(PPh_3)_4$ (10)	0.25	98
2	$Pd(PPh_3)_4$ (2)	6	quant
3	$Pd(dba)_2$ (2), PPh_3 (4)	2	97
4[b]	$Pd(dba)_2$ (2), P(*t*-Bu)$_3$ (4)[c]	0.25	98
5[d]	$Pd(dba)_2$ (2), P(*t*-Bu)$_3$ (4)[c]	69	74 (16)
6	$Pd(dba)_2$ (2), P(2-furyl)$_3$ (4)	24	66 (33)
7	$Pd(dba)_2$ (2), P(OPh)$_3$ (4)	24	58 (42)
8	$Pd(dba)_2$ (2), (*t*-BuO)$_2$PN(*i*-Pr)$_2$ (4)	24	16 (63)
9	$Pd(dba)_2$ (2), BINAP (2)	24	6 (91)
10	$Pd(dba)_2$ (2), dppb (4)	24	44 (45)
11	$Pd(dba)_2$ (2), dppp (4)	24	11 (78)
12	$Pd(dba)_2$ (2), dppf (4)	24	78 (21)

[a] The values in parentheses show the yield of recovered starting materials.
[b] Reaction was performed at 100 °C.
[c] P(*t*-Bu)$_3$ was generated from HBF_4·P(*t*-Bu)$_3$ and Et_3N in situ.[26]
[d] Reaction was performed at 80 °C.

reaction conditions to these investigated for the intramolecular cyanoamidation of alkynes,[15] gave the desired 3-cyanomethyl-3-methyloxindole **2a** in quantitative yield after 15 min (entry 1). When the catalyst loading was reduced to 2 mol %, the reaction took 6 h to reach completion (entry 2). Interest in the reactivity profile of the ligand prompted us to test a variety of phosphine and phosphorus ligands in combination with 2 mol % $Pd(dba)_2$. As

Table 2
Synthesis of 3,3-disubstituted oxindoles



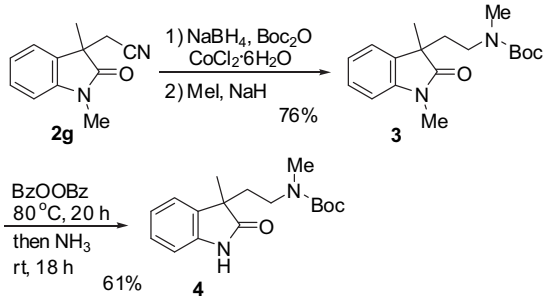
Entry	Substrate	R^1	R^2	R^3	Yield (%)
1	**1b**	Bn	*n*-Pr	H	96
2	**1c**	Bn	*i*-Pr	H	90
3	**1d**	Bn	Ph	H	quant
4[a]	**1e**	Bn	CH_2OTBS	H	74
5[b]	**1e**	Bn	CH_2OTBS	H	90
6	**1f**	Me	CH_2CH_2OTBS	H	98
7	**1g**	Me	Me	H	94
8	**1h**				97
9	**1i**				86
10	**1j**				97

[a] The reaction was allowed to run for 60 h and 12% of **1e** was recovered.
[b] The reaction was performed at 130 °C for 6 h.

a result, it was found that the catalyst generated from P(*t*-Bu)$_3$ was extremely reactive. The cyanoformamide **1a** was converted to oxindole **2a** in 98% yield after 15 min even at 100 °C (entry 4). Further decrease of the temperature to 80 °C led to incomplete conversion (entry 5). In contrast to those relatively strongly donating monophosphorus ligands, such as PPh_3 and P(*t*-Bu)$_3$, the conditions using weaker donating ligands (entries 6–8) and bisphosphorus ligands (entries 9–12) resulted in poor conversion.

A variety of oxindoles were synthesized using 2 mol % Pd(dba)$_2$ and 4 mol % P(*t*-Bu)$_3$ at 100 °C (Table 2). Most of the cyanoformamides were converted to the corresponding oxindoles in 15 min. The substituent R^2 on the vinyl group did not affect the reaction significantly, so a variety of oxindoles possessing different types of side chains has been made available (entries 1–7). An exception was the reaction of cyanoformamide **1e** that required higher temperature and longer reaction time (entries 4 and 5). In particular, among the products, oxindoles **2e** and **2f** with two distinct functionalized side chains, namely cyanomethyl and silyloxyalkyl, possess high utility as synthetic intermediates for natural and synthetic targets. Indeed, a compound related to oxindole **2f** was used as a key intermediate for synthetic studies on vincorine by our group.[27] This reaction also tolerated substitution on the aromatic ring, which is considered to be crucial for medicinal studies (entries 8–10).

At present, the substituent on the amide nitrogen is limited to alkyl groups due to the low stability of the corresponding primary cyanoformamides and difficulty in the synthesis of other derivatives. However, it is worth noting that a methyl group on oxindole nitrogen is known to be cleaved under oxidative conditions.[28] Thus, oxindoles not substituted on the amide nitrogen are available through cyanoamidation of *N*-methyl cyanoformamides followed by sequential demethylation (Scheme 1).[29]



Scheme 1. Oxidative demethylation of the cyclized product.[29]

This intramolecular cyanoamidation was not limited to oxindole formation (Table 3). When pyridine derivative **5** was treated with 10 mol % Pd(PPh$_3$)$_4$ (conditions A), azaoxindole **6** was isolated in 97% yield after 1 h (entry 1). Conditions B using P(*t*-Bu)$_3$ unexpectedly did not enable this transformation; cyclized product **6** was obtained in only 7% yield even after 24 h, and 71% of the starting material was recovered (entry 2). It is apparent that under both conditions cyanoformamide **5** reacted more slowly than **1a**. This difference likely comes from the presence of the nitrogen attached closely to the reaction site. Although such nitrogen atoms are known to promote some transition-metal-catalyzed reactions by functioning as a directing group,[30] negative effects showed up in the case of **5**. All the substrates tested had a rigid aromatic framework that brings the two reaction sites close. Next, *N*-butenyl cyanoformamide **7** with a flexible framework was tested. As a result, **7** gave the corresponding cyanomethyl-γ-lactam **8** in 95% yield by treatment of 10 mol % Pd(PPh$_3$)$_4$ (entry 3). The catalyst generated with P(*t*-Bu)$_3$ gave no product (entry 4). Furthermore, six-membered lactam **10** and seven-membered lactam **12** were obtained from the reaction with 10 mol % Pd(PPh$_3$)$_4$ (entries 5 and 7). Obviously, the Pd(dba)$_2$–P(*t*-Bu)$_3$ system (conditions B) was not effective for all the compounds in Table 3. We hypothesize that this system generates reactive but unstable catalytic species with short lifetimes, which are sensitive to neighboring heteroatoms (for **5**) or are not sufficiently stable to promote the cyclization of the substrates that require large conformational changes (for **7**, **9**, and **11**). Nevertheless, this intramolecular cyanoamidation strategy is not limited to 3,3-disubstituted oxindoles but is also effective for the synthesis of other α,α-disubstituted lactam.

2.2. Enantioselective synthesis of 3,3-disubstituted oxindoles

Next, we studied the enantioselective version of this intramolecular cyanoamidation (Table 4). We started the investigation with optically active monophosphorus ligands according to the results shown in Table 1. Initial attempts were made with well-known phosphine derivatives such as NMDPP (**L1**)[31] and MOP (**L2**)[32] with 2 mol % Pd(dba)$_2$ in xylene at 130 °C (entries 1 and 2). As expected, these electron rich ligands promoted the reaction efficiently to give oxindole **2a** in quantitative yields after 15 min, but only slight enantioselectivity was observed. Phosphonite **L3**[33] and phosphonic diamide **L4**[34] promoted the reaction poorly, and no enantioselectivity was detected (entries 3 and 4). However, the reaction with phosphoramidite **L5**[35] synthesized from BINOL and dimethylamine gave (*S*)-oxindole **2a** in 80% isolated yield and 16% ee (entry 5). It was found that the size of the amino group significantly affected the enantioselectivity. The selectivity increased from 16 to 26% ee when dimethylamine was changed to morpholine (entry 6).[36] Phosphoramidite **L7**[36] derived from bulkier diisopropylamine gave 46% ee, and finally phosphoramidite **L8**[37] with the bis[(*R*)-1-phenylethyl]amino group resulted in 69% ee with 96% isolated yield (entries 7 and 8). Changing the configuration of BINOL from *R* to *S* gave (*R*)-**2a** as a major product with lower selectivity and yield (entry 10). Phosphoramidites **L9**,[37] **L11**,[38] **L12**,[39] and **L13**[40] derived from dimethyl BINOL, biphenol, spirobiindane diol, and TADDOL, respectively, unexpectedly resulted in higher reactivity than **L8** but poorer selectivity (entries 9, 11–13). Bisphosphorus ligands **L14**, **L15**,[41] and **L16**[42] gave poor conversion and selectivity (entries 14–16). The effects

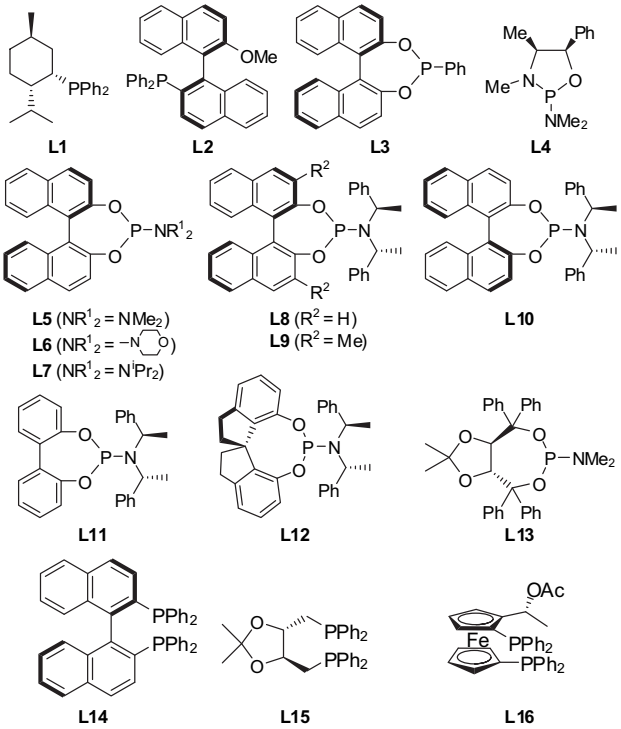
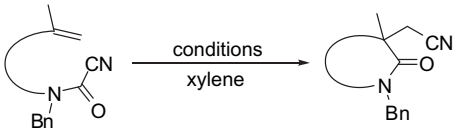
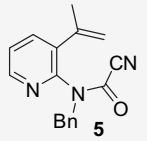
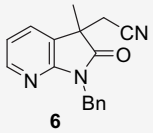
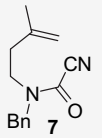
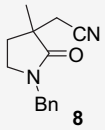
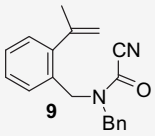
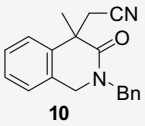
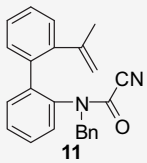
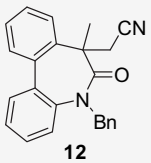


Table 3
Synthesis of α,α-disubstituted lactams through intramolecular cyanoamidation

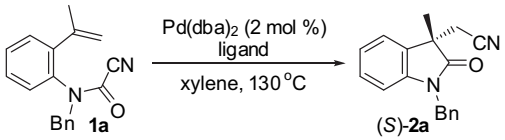


Entry	Substrate	Product	Conditions[a]	Time (h)	Yield (%)	Recovery of SM (%)
1	 **5**	 **6**	A	1	97	—
2			B	24	7	71
3	 **7**	 **8**	A	0.25	95	—
4			B	24	0	89
5	 **9**	 **10**	A	24	45	38
6			B	24	0	92
7	 **11**	 **12**	A	10	quant	—
8			B	24	0	94

[a] Conditions A: $Pd(PPh_3)_4$ (10 mol %) at 130 °C; Conditions B: $Pd(dba)_2$ (2 mol %), P(*t*-Bu)$_3$ (4 mol %), at 100 °C.

of solvents and additives were examined with using 2 mol % $Pd(dba)_2$ and 8 mol % phosphoramidite **L8** (Table 5). When polar *N*-methyl-2-pyrrolidone (NMP) was used as the solvent, the reaction rate was markedly increased so that it reached completion in 15 min, but the selectivity dropped to 56% ee (entry 2). The reaction in less-polar decalin gave better selectivity but poorer conversion (entry 3). To achieve good selectivity and conversion, a polar additive was employed in the reaction in decalin. Addition of 100 mol % of NMP resulted in completion of the reaction in 2 h to give quantitative yield and 78% ee (entry 4). The amount of NMP was reduced to 8 mol % and 2 mol % but the effect remained comparable (entries 5 and 6). Next, the reaction temperature was reduced to 100 °C in the hope of enhancing the stereoselectivity. However, the reaction was not completed in 24 h even with 100 mol % of NMP (entry 7). The more donating 1,3-dimethyl-2-imidazolidinone (DMI) was found to bring the reaction to completion (entry 8), and at the end, addition of *N*,*N*-dimethylpropylene urea (DMPU) gave quantitative yield and 81% ee (entry 9). It is worth noting that other Lewis bases, such as 4-(*N*,*N*-dimethylamino)pyridine (DMAP) or hexamethylphosphorus triamide (HMPT) had no activation effect at all. Several possibilities for the effects of additive can be suggested: for example, (i) accelerating formation of the reactive complex from $Pd(dba)_2$ and phosphoramidite, and (ii) stabilizing the coordinatively unsaturated species during the catalytic cycle. Additionally, we wish to propose other roles by noting the structural similarity of the effective additives and the reaction product: both have an amide or a urea functionality. After reductive elimination, the product must be cleaved from the palladium complex to induce the next catalytic cycle. However, the cyanomethyl oxindole should complex tightly to palladium, particularly in nonpolar solvents. Lewis base additives may promote this decomplexation.[43]

Table 4
Intramolecular enantioselective cyanoamidation of olefins

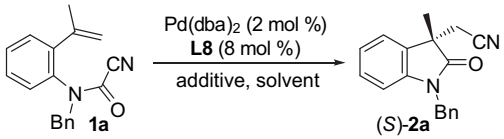


Entry	Ligand (mol %)	Time (h)	Yield[a] (%)	ee (%)
1	**L1** (4)	0.25	98	7 (*R*)
2	**L2** (4)	0.25	quant	9 (*R*)
3	**L3** (4)	24	26 (70)	0
4	**L4** (4)	24	4 (87)	0
5	**L5** (4)	24	80	16 (*S*)
6	**L6** (4)	8	97	26 (*S*)
7	**L7** (4)	24	65	46 (*S*)
8	**L8** (8)	6	96	69 (*S*)
9	**L9** (8)	0.25	quant	16 (*S*)
10	**L10** (8)	24	76	25 (*R*)
11	**L11** (8)	0.25	93	15 (*S*)
12	**L12** (8)	0.25	97	44 (*S*)
13	**L13** (2)	3	95	32 (*S*)
14	**L14** (2)	24	6 (91)	0
15	**L15** (2)	48	33 (58)	5 (*S*)
16	**L16** (2)	48	51 (38)	31 (*S*)

[a] The values in parentheses show the yield of recovered starting materials.

Optically active 3,3-disubstituted oxindoles were synthesized under the conditions determined (Table 6). The substituent R^2 on the vinyl group did not affect the reaction rate and yield in these

Table 5
Effect of solvent and additive

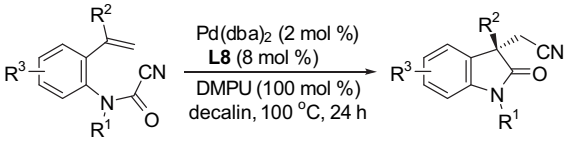


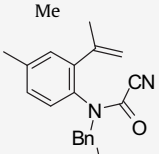
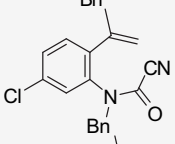
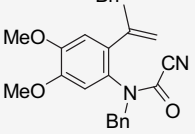
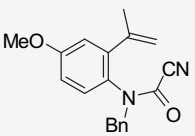
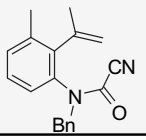
Entry	Solvent	Additive (mol %)	Temp (°C)	Time (h)	Yield (%)	ee[a] (%)	Recovery of SM (%)
1	Xylene	—	130	6	96	69	—
2	NMP	—	130	0.25	97	56	—
3	Decalin	—	130	24	83	74	10
4	Decalin	NMP (100)	130	2	quant	78	—
5	Decalin	NMP (8)	130	3	98	76	—
6	Decalin	NMP (2)	130	3	97	76	—
7	Decalin	NMP (100)	100	24	85	80	15
8	Decalin	DMI (100)	100	24	97	79	—
9	Decalin	DMPU (100)	100	24	quant	81	—

[a] The major enantiomer was the *S*-isomer in all reactions.

enantioselective reactions but did affect their stereoselectivity (entries 1–5). An increase in bulkiness (Me<*n*-Pr<CH_2OTBS<*i*-Pr≈Ph) resulted in a decrease in selectivity. *N*-Methyl cyanoformamide **1g** gave slightly lower selectivity than **1a** (entry 6).

Table 6
Synthesis of optically active 3,3-disubstituted oxindoles

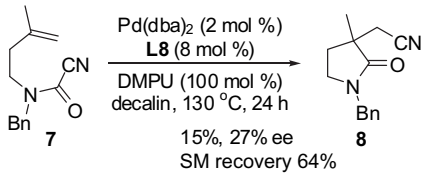


Entry	Substrate				Yield (%)	ee (%)
		R^1	R^2	R^3		
1	**1a**	Bn	Me	H	quant	81
2	**1b**	Bn	*n*-Pr	H	quant	72
3	**1c**	Bn	*i*-Pr	H	96	60
4	**1d**	Bn	Ph	H	quant	61
5	**1e**	Bn	CH_2-OTBS	H	72	68
6	**1g**	Me	Me	H	88	75
7	**1h**				94	74
8	**1i**				quant	82
9[a]	**1j**				91	82
10[a]	**1k**				94	78
11[b]	**1l**				44	86

[a] $Pd(dba)_2$ (5 mol %) and **L8** (20 mol %) was used.
[b] $Pd(dba)_2$ (5 mol %) and **L8** (10 mol %) was used.

Substitution on the aromatic ring did not affect enantioselectivity but unexpectedly changed the reactivity. An increased amount of catalyst was required to complete the reaction of **1j** and **1k** that have methoxy groups (entries 9, 10). The reaction of cyanoformamide **1l** with a substituent close to the vinyl group was not completed even with an increased amount of catalyst (entry 11).

The conditions described were applied to the cyclization of aliphatic cyanoformamide **7** without modification (Scheme 2). Unfortunately, the starting material was not consumed completely after 24 h even at 130 °C, and its selectivity was only 27% ee. Better conditions for enantioselective access to α,α-disubstituted lactams are being explored.



Scheme 2. Enantioselective cyclization of cyanoformamide **7**.

2.3. Mechanistic considerations

Although not much information is available on the reaction mechanism, we believe that the reaction proceeds through oxidative addition of the CO–CN bond to palladium(0), followed by amidopalladation and reductive elimination (Fig. 4). The alternative cyanopalladation pathway (**C**→**E**), which may give the same final product, has been excluded by previous studies.[15] We propose that the oxidative addition of the CO–CN bond forms the four-coordinate intermediate **C** prior to insertion. Other pathways through the five-coordinate complex **F** or cationic complex **G** are unlikely, because the reaction is catalyzed effectively by large unidentate ligands and not by bidentate ligands. There are clear contrasts in terms of effective ligands between this reaction and other related enantioselective 3,3-disubstituted oxindole and indoline formations starting from allyl amine derivatives **H**. These reactions proceed efficiently in the presence of optically active bidentate ligands. For example, the palladium-catalyzed enantioselective Heck reaction studied by Overman et al. gave the best result with BINAP, and the reaction pathway containing a five-coordinate complex and a cationic complex like **F** and **G** were proposed.[2b] More recently, enantioselective arylation–cyanation reactions[3] and nickel catalyzed enantioselective intramolecular cyanoarylations[24a] have been reported to give the best result with optically active bidentate ligands.

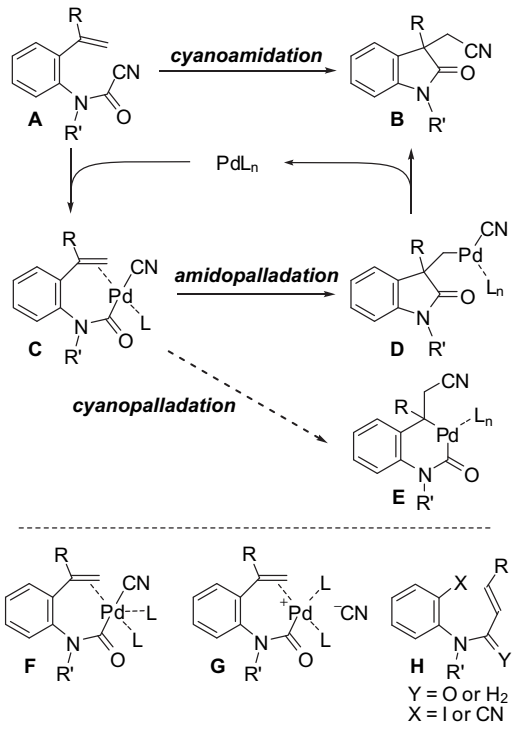


Figure 4. Plausible mechanism.

2.4. Synthetic manipulations of 3,3-disubstituted oxindoles

With the highly substituted oxindoles in hand, we studied synthetic manipulations of this class of compounds with the aim of providing drug-like structural motifs and realizing efficient access to natural products. Our approach illustrated in Figure 5 takes advantage of the presence of the cyano group incorporated by the cyanoamidation. Connection between the cyano group and substituent R^2 on the quaternary carbon gives spirooxindole **A**. On the other hand, ring formation between the cyano group and the amide carbonyl provides fused indoline derivatives **B** with quaternary stereocenters at the ring junctions.

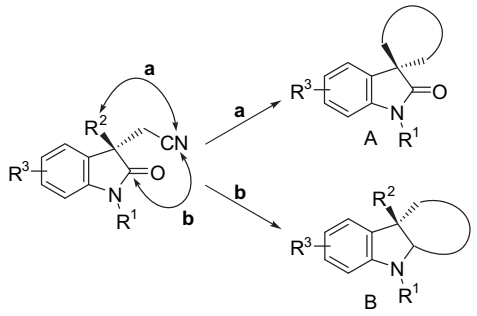
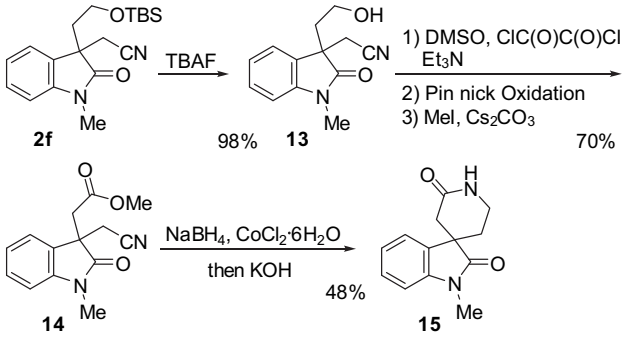


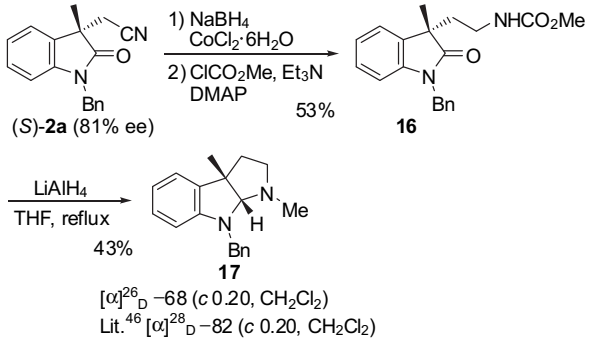
Figure 5. Strategy for the access to higher-ordered structures.

The first example is the synthesis of spirolactam **15** (Scheme 3). Starting from oxindole **2f**, removal of the TBS group followed by sequential oxidation and methylation gave cyanoester **14**. This compound was cyclized through selective reduction of the cyano group by $CoCl_2 \cdot 6H_2O$ and $NaBH_4$, followed by treatment with KOH.[44] Two distinct amides (*N*-methyl and *N*–H) in spirolactam **15** provide easy further manipulations.



Scheme 3. Synthesis of spirolactam **15**.

On the other hand, pyrroloindole **17** can also be formed in simple steps from oxindole **2a** (Scheme 4). Again the selective reduction of the cyano group was achieved by $CoCl_2 \cdot 6H_2O$ and $NaBH_4$. Subsequent methoxycarbonylation gave carbonate **16**. This compound was reductively cyclized to give pyrroloindole **17**.[45] Comparison of the optical rotation of **17** with that reported in the literature showed that oxindole **2a** has the *S*-configuration.[46]



Scheme 4. Synthesis of pyrroloindole **17**.

3. Conclusions

The palladium-catalyzed intramolecular cyanoamidation of olefins was reported and shown to be an efficient strategy toward the synthesis of 3,3-disubstituted oxindoles as well as other α,α-disubstituted lactams. Electron rich phosphine ligands were found to promote this reaction smoothly. In particular, the catalyst generated from $Pd(dba)_2$ and P(*t*-Bu)$_3$ gave desired oxindoles in 15 min at 100 °C. On the other hand, $Pd(PPh_3)_4$ provided better results for the synthesis of other α,α-disubstituted lactams. Efforts to expand this reaction to enantioselective conversions resulted in the finding that a catalytic amount of $Pd(dba)_2$ and the phosphoramidite derived from (*R*)-BINOL and bis[(*R*)-1-phenylethyl]amine gave high yields and high enantioselectivity. The addition of DMPU was crucial to achieve the best results. This progress enables quick access to a variety of oxindoles and related compounds in a convenient manner.

4. Experimental section

4.1. General

Unless otherwise noted, all reactions were performed under argon. $Pd(PPh_3)_4$ was prepared by using the reported protocol.[47] $Pd(dba)_2$ was purchased from Tokyo Chemical Industry Co., Ltd. *N*,*N*′-Dimethyl propylene urea (DMPU) was distilled from CaH_2. **L8** and other optically active phosphoramidite ligands were prepared according to the literature procedure.[48] Silica gel column chromatography was performed with Kanto silica gel 60 (particle size,

63–210 μm). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL JNM-LA 500 at 500 MHz or a JEOL JNM-AL 400 at 400 MHz. Chemical shifts are reported relative to Me_4Si (δ 0.00). Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL JNM-LA 500 at 126 MHz or a JEOL JNM-AL 400 at 100 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0). Infrared spectra were recorded on a FT/IR-4100 (JASCO) equipped with an attenuated total reflection (ATR) attachment or on a FT/IR-410 (JASCO) as a thin film on NaCl plate (thin film) or as a KBr pellet (KBr) or as a $CHCl_3$ solution ($CHCl_3$). Optical rotations were measured with a JASCO DIP-360 digital polarimeter. Enantiomer ratios were determined by chiral HPLC using a Shimadzu SPD-10A with Daicel Chemical Industries, LTD. Chiralpak AD-H (0.46 cm×25 cm), Chiralpak OJ-H (0.46 cm×25 cm), Chiralpak OD-H (0.46 cm×25 cm), or Chiralpak AS-H (0.46 cm×25 cm).

4.2. Preparation of cyanoformamides[49]

*4.2.1. Cyanoformamide **1a**.* To a solution of *N*-benzyl-2-(prop-1-en-2-yl)aniline (3.20 g, 14.6 mmol) in CH_2Cl_2 (30 mL) was added pyridine (1.77 mL, 21.9 mmol) followed by triphosgene (1.51 g, 5.10 mmol) at −78 °C. The reaction mixture was warmed to room temperature, diluted with $CHCl_3$, and washed with 1 M HCl and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude chloroformamide. To a solution of this crude chloroformamide in MeCN (25 mL) and *t*-BuOH (5.0 mL) were added 18-crown-6 (392 mg, 1.46 mmol) and KCN (1.43 g, 21.9 mmol), and the resulting mixture was stirred at 60 °C for 2 h. After removal of the solvents, water was added, and the mixture was extracted with $CHCl_3$. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue obtained was purified by silica gel column chromatography (hexane/EtOAc=95/5) to give oxindole **1a** (3.83 g, 95% over two steps) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.40 (dd, 1H, J_1=J_2=7.6 Hz), 7.37 (dd, 1H, J_1=1.5, J_2=7.6 Hz), 7.31–7.25 (m, 3H), 7.19 (dd, 1H, J_1=J_2=7.6 Hz), 7.15–7.13 (m, 2H), 6.75 (d, 1H, J=7.6 Hz), 6.66* (d, J=7.7 Hz), 5.50 (d, 1H, J=14.3 Hz), 5.35 (s, 1H), 5.26* (s), 5.08 (s, 1H), 4.96* (s), 4.09 (d, 1H, J=14.3 Hz), 2.12 (s, 3H), 2.05* (s); ^{13}C NMR (126 MHz, $CDCl_3$, δ) 145.7, 142.4, 142.2, 135.1, 134.8, 130.7, 130.6, 130.5, 130.0*, 129.5, 129.3*, 129.1*, 128.9, 128.6, 128.5, 118.4, 116.8*, 111.0, 52.4, 23.7; IR ($CHCl_3$) 2231, 1677 cm^{-1}; MS (EI) m/z=276 (M^+). Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.35; H, 5.91; N, 10.02. (*denotes peaks of minor rotamer).

4.3. General procedure for Pd-catalyzed cyanoamidation

4.3.1. Conditions using 10 mol% Pd(PPh$_3$)$_4$ (Table 1, entry 1). A solution of cyanoformamide **1a** (100 mg, 0.362 mmol) and $Pd(PPh_3)_4$ (41.8 mg, 0.0362 mmol) in xylene (3.6 mL) was stirred at 130 °C for 0.25 h. The mixture was subjected directly to silica gel column chromatography (hexane/EtOAc=10/0→8/2) to give the oxindole **2a** (98.2 mg, 98%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.48 (d, 1H, J=7.6 Hz), 7.34–7.25 (m, 5H), 7.23 (dd, 1H, J_1=J_2=7.6 Hz), 7.09 (dd, 1H, J_1=J_2=7.6 Hz), 6.78 (d, 1H, J=7.6 Hz), 4.95 (d, 1H, J=16.5 Hz), 4.92 (d, 1H, J=16.5 Hz), 2.91 (d, 1H, J=16.8 Hz), 2.64 (d, 1H, J=16.8 Hz), 1.57 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, δ) 177.9, 142.0, 135.5, 131.2, 129.3, 129.1, 128.0, 127.4, 123.5, 123.4, 116.8, 109.9, 45.1, 44.1, 26.4, 22.6; IR ($CHCl_3$) 1714 cm^{-1}; MS (EI) m/z=276 (M^+). Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.18; H, 6.06; N, 10.12.

4.3.2. Conditions using 2 mol% Pd(dba)$_2$ and 4 mol% P(t-Bu$_3$) (Table 1, entry 4). A solution of cyanoformamide **1a** (100 mg, 0.362 mmol), $Pd(dba)_2$ (4.16 mg, 0.00724 mmol), P(*t*-Bu$_3$)·HBF$_4$ (4.20 mg, 0.0145 mmol), and Et_3N (5.08 μL, 0.0362 mmol) in xylene (3.6 mL) was stirred at 100 °C for 0.25 h. The mixture was subjected directly to silica gel column chromatography (hexane/EtOAc=10/0→8/2) to give the oxindole **2a** (98.4 mg, 98%).

4.3.3. Enantioselective cyanoamidation (Table 5, entry 9). A solution of cyanoformamide **1a** (100 mg, 0.362 mmol), **L8** (15.6 mg, 0.0290 mmol), DMPU (0.043 mL, 0.36 mmol), and $Pd(dba)_2$ (4.2 mg, 0.0072 mmol) in decalin (3.6 mL) was stirred at 100 °C for 24 h. The mixture was subjected directly to silica gel column chromatography (hexane/EtOAc=10/0→8/2) to give the oxindole **2a** (99.4 mg, quant). HPLC [Chiralcel OD-H, hexane/2-propanol=90/10, 1.0 mL/min, λ=210 nm, retention times: (minor) 14.3 min, (major) 17.5 min]; $[\alpha]_D^{26}$ 26.9 (*c* 0.90, $CHCl_3$, 81% ee).

*4.3.4. Oxindole **2b**.* Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.42 (dd, 1H, J_1=0.9 Hz, J_2=7.6 Hz), 7.33–7.25 (m, 5H), 7.23 (dd, 1H, J_1=J_2=7.6 Hz), 7.10 (ddd, 1H, J_1=0.9 Hz, J_2=J_3=7.6 Hz), 6.78 (d, 1H, J=7.6 Hz), 4.96 (d, 1H, J=15.6 Hz), 4.90 (d, 1H, J=15.6 Hz), 2.87 (d, 1H, J=16.8 Hz), 2.65 (d, 1H, J=16.8 Hz), 2.02 (ddd, 1H, J_1=5.2 Hz, J_2=10.7 Hz, J_3=13.1 Hz), 1.98 (ddd, 1H, J_1=5.2 Hz, J_2=10.7 Hz, J_3=13.1 Hz), 1.08 (m, 1H), 0.90 (m, 1H), 0.82 (dd, 3H, J_1=J_2=7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$, δ) 177.4, 142.8, 135.6, 129.5, 129.2, 129.0, 128.0, 127.5, 123.44, 123.41, 116.7, 109.8, 49.3, 44.2, 38.7, 26.3, 17.6, 14.0; IR (thin film) 1712 cm^{-1}; MS (EI) m/z=304 (M^+); HPLC [Chiralcel OD-H, hexane/2-propanol=90/10, 1.0 mL/min, λ=210 nm, retention times: (minor) 10.5 min, (major) 13.1 min]; $[\alpha]_D^{26}$ 26.7 (*c* 0.78, $CHCl_3$, 72% ee).

*4.3.5. Oxindole **2c**.* Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.37 (dd, 1H, J_1=0.9, J_2=7.7 Hz), 7.33–7.25 (m, 5H), 7.24 (ddd, 1H, J_1=1.2 Hz, J_2=J_3=7.7 Hz), 7.08 (ddd, 1H, J_1=0.9 Hz, J_2=J_3=7.7 Hz), 6.78 (d, 1H, J=7.6 Hz), 4.98 (d, 1H, J=15.5 Hz), 4.88 (d, 1H, J=15.5 Hz), 2.98 (d, 1H, J=16.4 Hz), 2.74 (d, 1H, J=16.4 Hz), 2.44–2.31 (m, 1H), 0.97 (d, 3H, J=7.1 Hz), 0.92 (d, 3H, J=7.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$, δ) 176.9, 143.0, 135.4, 129.0, 128.9, 128.8, 127.7, 127.3, 123.5, 122.9, 116.6, 109.4, 52.1, 43.9, 34.4, 23.9, 17.1, 16.8; IR (thin film) 2360, 1711 cm^{-1}; MS (EI) m/z=304 (M^+). Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.66; H, 6.52; N, 9.24; HPLC [Chiralcel OD-H, hexane/2-propanol=90/10, 1.0 mL/min, λ=210 nm, retention times: (minor) 12.0 min, (major) 16.0 min, 60% ee].

*4.3.6. Oxindole **2d**.* Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.41 (d, 1H, J=7.7 Hz), 7.28–7.13 (m, 11H), 7.07 (ddd, 1H, J_1=1.0, J_2=J_3=7.7 Hz), 6.75 (d, 1H, J=7.7 Hz), 4.82 (d, 1H, J=15.9 Hz), 4.86 (d, 1H, J=15.9 Hz), 3.33 (d, 1H, J=16.5 Hz), 3.05 (d, 1H, J=16.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$, δ) 176.0, 142.7, 136.7, 135.1, 129.6, 129.0, 128.9, 128.4, 127.8, 127.1, 126.7, 125.2, 123.4, 116.4, 110.1, 52.7, 44.1, 26.1; IR (ATR) 2353, 1716 cm^{-1}; MS (EI) m/z=338 (M^+). Anal. Calcd for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28. Found: C, 81.43; H, 5.49; N, 8.01; HPLC [Chiralcel OD-H, hexane/2-propanol=70/30, 1.0 mL/min, λ=210 nm, retention times: (minor) 9.3 min, (major) 13.4 min, 61% ee].

*4.3.7. Oxindole **2e**.* Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.53 (d, 1H, J=7.7 Hz), 7.38–7.32 (m, 5H), 7.28 (dd, 1H, J_1=J_2=7.7 Hz), 7.14 (dd, 1H, J_1=J_2=7.7 Hz), 6.81 (d, 1H, J=7.7 Hz), 5.02 (d, 1H, J=16.7 Hz), 4.98 (d, 1H, J=16.7 Hz), 4.07 (d, 1H, J=9.5 Hz), 3.93 (d, 1H, J=9.5 Hz), 3.10 (d, 1H, J=16.5 Hz), 2.86 (d, 1H, J=16.5 Hz), 0.87 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 175.7, 143.1, 135.4, 129.4, 129.0, 128.5, 127.9, 127.3, 124.3, 123.1, 116.6, 109.7, 66.8, 51.2, 44.1, 25.7, 21.8, 18.2, −5.5, −5.7; IR (thin film) 2353, 1716 cm^{-1}; MS (EI) m/z=406 (M^+). Anal. Calcd for $C_{24}H_{30}N_2O_2Si$: C, 70.90; H, 7.44; N, 6.89. Found: C, 70.61; H, 7.46; N, 6.78; HPLC [Chiralcel OD-H,

hexane/2-propanol=90/10, 1.0 mL/min, λ=210 nm, retention times: (minor) 6.7 min, (major) 8.2 min]; $[\alpha]_D^{26}$ −5.2 (*c* 0.83, $CHCl_3$, 68% ee).

4.3.8. Oxindole ***2f***. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, δ); 7.43 (d, 1H, *J*=7.8 Hz), 7.36 (dd, 1H, J_1=J_2=7.8 Hz), 7.13 (dd, 1H, J_1=J_2=7.8 Hz), 6.89 (d, 1H, *J*=7.8 Hz), 3.51–3.39 (m, 2H), 3.22 (s, 3H), 2.92 (d, 1H, *J*=16.6 Hz), 2.58 (d, 1H, *J*=16.6 Hz), 2.32–2.25 (m, 1H), 2.20–2.15 (m, 1H), 0.77 (s, 9H), −0.12 (s, 3H), −0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 177.1, 143.8, 129.4, 128.9, 123.9, 123.1, 116.9, 108.8, 59.2, 47.5, 37.9, 26.8, 26.6, 25.9, 18.3, −5.64; IR ($CHCl_3$) 2251, 1719 cm^{-1}; MS (FAB) *m*/*z*=345 ($M+H^+$). Anal. Calcd for $C_{19}H_{28}N_2O_2Si$: C, 66.24; H, 8.19; N, 8.13. Found: C, 65.91; H, 8.19; N, 8.04.

4.3.9. Oxindole ***2g***. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.48 (d, 1H, *J*=8.0 Hz), 7.36 (dd, 1H, J_1=J_2=8.0 Hz), 7.14 (dd, 1H, J_1=J_2=8.0 Hz), 6.92 (d, 1H, *J*=8.0 Hz), 3.25 (s, 3H), 2.85 (d, 1H, *J*=16.4 Hz), 2.58 (d, 1H, *J*=16.4 Hz), 1.53 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, δ) 177.7, 142.9, 131.2, 129.3, 123.4, 123.3, 116.8, 108.8, 44.9, 26.6, 26.3, 22.2; IR (thin film) 1715 cm^{-1}; MS (EI) *m*/*z*=200 (M^+). Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.70; H, 6.08; N, 13.85; HPLC [Chiralcel AD-H, hexane/2-propanol=90/10, 1.0 mL/min, λ=210 nm, retention times: (minor) 8.4 min, (major) 9.6 min]; $[\alpha]_D^{26}$ 63.6 (*c* 0.93, $CHCl_3$, 75% ee).

4.3.10. Oxindole ***2h***. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.32–7.23 (m, 6H), 7.01 (d, 1H, *J*=7.8 Hz), 6.66 (d, 1H, *J*=7.8 Hz), 4.91 (s, 2H), 2.88 (d, 1H, *J*=16.5 Hz), 2.63 (d, 1H, *J*=16.5 Hz), 2.32 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 177.8, 139.6, 135.6, 133.1, 131.2, 129.5, 129.0, 127.9, 127.3, 124.1, 116.8, 109.6, 45.0, 44.0, 26.3, 22.6, 21.1; IR (thin film) 1712 cm^{-1}; MS (EI) *m*/*z*=290 (M^+). Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.55; H, 6.41; N, 9.53; HPLC [Chiralcel OD-H, hexane/2-propanol=90/10, 1.0 mL/min, λ=210 nm, retention times: (minor) 11.4 min, (major) 15.1 min]; $[\alpha]_D^{26}$ 22.9 (*c* 1.38, $CHCl_3$, 74% ee).

4.3.11. Oxindole ***2i***. Colorless solid; mp 96.5–97.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.39 (d, 1H, *J*=7.8 Hz), 7.37–7.28 (m, 5H), 7.08 (dd, 1H, J_1=1.7 Hz, J_2=7.8 Hz), 6.78 (d, 1H, *J*=1.7 Hz), 4.90 (s, 2H), 2.89 (d, 1H, *J*=16.6 Hz), 2.63 (d, 1H, *J*=16.6 Hz), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 177.9, 143.3, 135.3, 135.0, 129.5, 129.3, 128.3, 127.4, 124.4, 123.5, 116.5, 110.6, 44.9, 44.2, 26.4, 22.6; IR (KBr) 1680 cm^{-1}; MS (EI) *m*/*z*=310 (M^+). Anal. Calcd for $C_{18}H_{15}ClN_2O$: C, 69.57; H, 4.86; N, 9.01. Found: C, 69.58; H, 5.10; N, 9.14; HPLC [Chiralcel OD-H, hexane/2-propanol=90/10, 1.0 mL/min, λ=210 nm, retention times: (minor) 16.7 min, (major) 22.4 min]; $[\alpha]_D^{26}$ 12.2 (*c* 0.17, $CHCl_3$, 82% ee).

4.3.12. Oxindole ***2j***. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.35–7.27 (m, 5H), 7.07 (s, 1H), 6.36 (s, 1H), 4.92 (s, 2H), 3.87 (s, 3H), 3.74 (s, 3H), 2.89 (d, 1H, *J*=16.6 Hz), 2.61 (d, 1H, *J*=16.6 Hz), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 178.3, 150.4, 146.0, 135.7, 129.18, 129.17, 128.1, 127.4, 121.9, 117.0, 108.3, 96.1, 57.0, 56.4, 45.3, 44.2, 26.7, 22.7; IR (thin film) 1710 cm^{-1}; MS (EI) *m*/*z*=336 (M^+). Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.18; H, 6.03; N, 8.27; HPLC [Chiralcel AS-H, hexane/2-propanol=90/10, 1.0 mL/min, λ=210 nm, retention times: (minor) 40.2 min, (major) 47.3 min]; $[\alpha]_D^{26}$ 36.4 (*c* 0.98, $CHCl_3$, 82% ee).

4.3.13. Oxindole ***2k***. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.33–7.26 (m, 5H), 7.08 (d, 1H, *J*=2.5 Hz), 6.74 (dd, 1H, J_1=2.5 Hz, J_2=8.5 Hz), 6.67 (d, 1H, *J*=8.5 Hz), 4.90 (s, 2H), 3.77 (s, 3H), 2.89 (d, 1H, *J*=16.6 Hz), 2.65 (d, 1H, *J*=16.6 Hz), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 177.6, 156.7, 135.6, 135.3, 132.5, 129.1, 128.0, 127.4, 116.7, 113.7, 110.7, 110.4, 55.9, 45.4, 44.1, 26.4, 22.6; IR (thin film) 1712 cm^{-1}; MS (EI) *m*/*z*=306 (M^+); HPLC [Chiralcel AD-H, hexane/2-propanol=90/10, 1.0 mL/min, λ=210 nm, retention times: (minor) 16.7 min, (major) 19.1 min]; $[\alpha]_D^{26}$ 13.7 (*c* 1.11, $CHCl_3$, 78% ee).

4.3.14. Oxindole ***2l***. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.24–7.17 (m, 5H), 7.03 (dd, 1H, J_1=J_2=7.8 Hz), 6.77 (d, 1H, *J*=7.8 Hz), 6.54 (d, 1H, *J*=7.8 Hz), 4.91 (d, 1H, *J*=15.8 Hz), 4.84 (d, 1H, *J*=15.8 Hz), 2.98 (d, 1H, *J*=16.8 Hz), 2.91 (d, 1H, *J*=16.8 Hz), 2.34 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 178.0, 142.8, 135.5, 134.6, 129.1, 129.0, 127.9, 127.3, 125.9, 116.30, 116.29, 107.9, 46.8, 44.1, 24.7, 21.6, 18.4; IR (thin film) 1713 cm^{-1}; MS (EI) *m*/*z*=290 (M^+). Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.32; H, 6.39; N, 9.53; HPLC [Chiralcel OD-H, hexane/2-propanol=90/10, 1.0 mL/min, λ=210 nm, retention times: (minor) 15.1 min, (major) 19.6 min]; $[\alpha]_D^{26}$ −37.5 (*c* 0.88, $CHCl_3$, 86% ee).

4.3.15. Lactam ***6***. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.25 (dd, 1H, J_1=1.7 Hz, J_2=5.3 Hz), 7.73 (dd, 1H, J_1=1.7 Hz, J_2=7.3 Hz), 7.44–7.42 (m, 2H), 7.32–7.24 (m, 3H), 7.02 (dd, 1H, J_1=5.3 Hz, J_2=7.3 Hz), 5.01 (s, 2H), 2.89 (d, 1H, *J*=16.6 Hz), 2.53 (d, 1H, *J*=16.6 Hz), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 177.0, 155.6, 148.2, 136.2, 131.0, 128.6, 128.2, 127.7, 125.2, 118.8, 116.3, 44.3, 42.8, 25.6, 21.7; IR (ATR) 1722 cm^{-1}; MS (EI) *m*/*z*=277 (M^+). Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.78; H, 5.67; N, 15.02.

4.3.16. Lactam ***8***. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.35–7.27 (m, 3H), 7.22–7.21 (m, 2H), 4.49 (d, 1H, *J*=14.6 Hz), 4.43 (d, 1H, *J*=14.6 Hz), 3.24–3.21 (m, 2H), 2.61 (d, 1H, *J*=16.8 Hz), 2.57 (d, 1H, *J*=16.8 Hz), 2.12 (ddd, 1H, J_1=J_2=8.2 Hz, J_3=13.1 Hz), 1.96 (ddd, 1H, J_1=5.2 Hz, J_2=6.4 Hz, J_3=13.1 Hz), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 175.3, 135.8, 128.7, 127.9, 127.6, 117.3, 46.7, 42.7, 42.5, 30.7, 26.2, 22.1; IR (thin film) 1689 cm^{-1}; MS (EI) *m*/*z*=228 (M^+). Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.47; H, 7.22; N, 11.99.

4.3.17. Lactam ***10***. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.39–7.25 (m, 8H), 7.09 (d, 1H, *J*=7.6 Hz), 4.86 (d, 1H, *J*=14.6 Hz), 4.74 (d, 1H, *J*=14.6 Hz), 4.48 (d, 1H, *J*=16.3 Hz), 4.41 (d, 1H, *J*=16.3 Hz), 3.28 (d, 1H, *J*=16.4 Hz), 2.96 (d, 1H, *J*=16.4 Hz), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 170.6, 136.5, 136.2, 130.1, 128.9, 128.3, 127.9, 127.8, 127.5, 125.9, 124.9, 117.6, 50.8, 49.2, 44.6, 27.4, 26.2; IR (thin film) 2248, 1642 cm^{-1}; MS (EI) *m*/*z*=290 (M^+). Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.72; H, 6.24; N, 9.63.

4.3.18. Lactam ***12***. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.57–6.88 (m, 13H), 5.12 (d, 1H, *J*=15.8 Hz), 5.02 (d, 1H, *J*=15.8 Hz), 3.41 (d, 1H, *J*=16.1 Hz), 3.24 (d, 1H, *J*=16.1 Hz), 2.45* (d, *J*=16.1 Hz), 2.34* (d, *J*=16.1 Hz), 2.02* (s), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 171.4, 170.2*, 140.1, 139.9*, 139.4, 138.7*, 137.4*, 137.3, 136.5, 136.4*, 135.6, 135.0*, 130.7, 130.3*, 130.2, 130.0, 129.5*, 129.2*, 129.1, 129.0, 128.9*, 128.6, 128.5*, 127.2, 126.8*, 126.6, 126.5*, 126.2, 126.0*, 124.1, 123.1*, 122.5, 119.1, 117.0*, 54.6*, 54.2, 49.0, 48.2*, 28.1, 24.1*, 24.0*, 20.3; IR (thin film) 1648, 2360 cm^{-1}; MS (EI) *m*/*z*=352 (M^+). Anal. Calcd for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.54; H, 5.63; N, 7.83. (*denotes peaks of minor atropisomer).

4.4. Synthesis of spirolactam 15

4.4.1. Alcohol ***13***. To a solution of compound **2f** (148 mg, 430 μmol) in THF (15 mL) was added 1 M TBAF solution in THF (970 μL, 970 μmol) at 0 °C. After stirring at the same temperature for 30 min, water was added, and the mixture was extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=9/1 → 6/4) to give **13** (96.8 mg, 98%) as a white solid; mp 85.5–85.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ); 7.46 (d, 1H, *J*=7.3 Hz), 7.39 (dd, 1H, J_1=7.8 Hz, J_2=7.5 Hz), 7.16 (dd, 1H, J_1=7.6 Hz, J_2=7.5 Hz), 6.93 (d, 1H,

J=7.8 Hz), 3.68–3.61 (m, 1H), 3.50–3.42 (m, 1H), 3.25 (s, 3H), 2.95 (d, 1H, J=16.6 Hz), 2.62 (d, 1H, J=16.6 Hz), 2.37–2.31 (m, 1H), 2.24–2.18 (m, 1H), 1.72 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ); 177.9, 143.5, 129.7, 129.1, 123.7, 123.6, 116.6, 109.1, 59.0, 47.6, 38.1, 26.8, 26.1; IR ($CHCl_3$) 3347, 2251, 1707, 1613 cm^{-1}; MS (FAB) m/z=231 ($M+H^+$). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.64; H, 6.22; N, 12.00.

4.4.2. Ester ***14***. To a solution of oxalyl chloride (177 mg, 1.39 mmol) in CH_2Cl_2 (2 mL) was added DMSO (191 mg, 2.44 mmol) in CH_2Cl_2 (2 mL) at −78 °C. After stirring for 10 min, a solution of **13** (112 mg, 0.487 mmol) in CH_2Cl_2 (2 mL) was added at the same temperature. After stirring for 15 min, Et_3N (680 μl, 4.88 mmol) was added, and the reaction mixture was warmed to room temperature. After stirring for 30 min, the reaction mixture was quenched with 1 M HCl and brine. The mixture was extracted with $CHCl_3$. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in *t*-BuOH (6 mL) and 2-methyl-2-butene (3 mL). To this solution was added $NaClO_2$ (385 mg, 3.41 mmol) in NaH_2PO_4 buffer solution (1 mM in water, 3.5 mL). After stirring for 30 min, organic solvents were concentrated under reduced pressure. The obtained residue was diluted with water and then washed with hexane. The aqueous layer was acidified with 1 M HCl to pH2 and extracted with $CHCl_3$. Combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. To the residue was added CH_3CN (1.5 mL), Cs_2CO_3 (170 mg, 0.522 mmol) and MeI (54.4 μL, 0.873 mmol) at room temperature. After stirring for 11 h, the reaction mixture was diluted with $CHCl_3$ and filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc=9/1→6/4) to give **14** (87.9 mg, 70% over three steps) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, δ); 7.44 (d, 1H, J=7.6 Hz), 7.38 (dd, 1H, J_1=J_2=7.8 Hz), 7.12 (dd, 1H, J_1=7.6 Hz, J_2=7.5 Hz), 6.93 (d, 1H, J=7.8 Hz), 3.53 (s, 3H), 3.28 (s, 3H), 3.13–2.96 (m, 3H), 2.62 (d, 1H, J=16.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ); 176.4, 169.5, 143.9, 129.9, 128.5, 123.4, 116.1, 109.0, 52.1, 46.1, 39.2, 26.8, 25.9; IR ($CHCl_3$) 2341, 1715 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{14}H_{15}N_2O_3$: 259.1083. Found: 259.1082.

4.4.3. Lactam ***15***. To a solution of **14** (18.1 mg, 70.2 μmol) and $CoCl_2\cdot 6H_2O$ (33.3 mg, 140 μmol) in MeOH (3 mL) was added $NaBH_4$ (20.8 mg, 550 μmol) in five portions over 2 h. After stirring for 15 min, 10% w/v KOH in MeOH solution (1 mL) was added. After stirring for 3 h, 1 M HCl and brine were added, and the mixture was extracted with $CHCl_3$. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=97/3→95/5) to give **15** (7.8 mg, 48%); mp 198.9–199.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ); 7.34 (dd, 1H, J_1=7.8 Hz, J_2=7.5 Hz), 7.27 (d, 1H, J=7.1 Hz), 7.10 (dd, 1H, J_1=7.5 Hz, J_2=7.6 Hz), 6.91 (d, 1H, J=7.6 Hz), 6.39 (br, 1H), 3.75–3.69 (m, 1H), 3.64–3.57 (m, 1H), 3.25 (s, 3H), 2.82 (d, 1H, J=17.6 Hz), 2.37 (d, 1H, J=17.7 Hz), 2.24–2.17 (m, 1H), 1.82–1.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ); 178.3, 170.3, 143.0, 131.7, 129.0, 123.6, 123.2, 108.8, 46.1, 38.7, 37.7, 29.5, 26.6; IR (KBr) 3179, 1709, 1659 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{13}H_{15}N_2O_2$: 231.1134. Found: 231.1129.

4.5. Synthesis of pyrroloindole 17

4.5.1. Carbamate ***16***. To a solution of (*S*)-**2a** (81% ee) (326 mg, 1.81 mmol) in MeOH (18 mL) was added $CoCl_2\cdot 6H_2O$ (702 mg, 2.95 mmol) at 0 °C, and the mixture was stirred for 15 min at the same temperature. $NaBH_4$ (342 mg, 9.05 mmol) was added and stirring was continued at room temperature for 2 h. After adding 2 M HCl at 0 °C and neutralizing with saturated aqueous $NaHCO_3$, the mixture was extracted with EtOAc. The combined organic extracts were washed with saturated aqueous potassium sodium tartrate, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. To a solution of the residue in pyridine (10 mL) was added 4-(*N*,*N*-dimethylamino)pyridine (12.5 mg, 0.102 mmol) and methylchloroformate (0.40 mL, 5.1 mmol) at 0 °C. After stirring at room temperature overnight, saturated aqueous NH_4Cl was added, and the mixture was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by silica gel column chromatography (hexane/EtOAc=9/1→7/3) to give carbamate **16** (182 mg, 53% over two steps) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.33–7.20 (m, 6H), 7.15 (ddd, 1H, J_1=1.2 Hz, J_2=J_3=7.8 Hz), 7.04 (ddd, 1H, J_1=1.2 Hz, J_2=J_3=7.8 Hz), 6.74 (d, 1H, J=7.8 Hz), 4.95 (d, 1H, J=15.8 Hz), 4.87 (d, 1H, J=15.8 Hz), 4.85 (br, 1H), 3.58 (s, 3H), 3.02–2.91 (m, 2H), 2.21–2.14 (m, 1H), 2.10–2.03 (m, 1H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 180.7, 157.0, 142.2, 136.1, 133.5, 129.0, 128.2, 127.8, 127.4, 123.0, 122.9, 109.4, 52.0, 47.1, 43.8, 37.7, 37.5, 24.4; IR ($CHCl_3$) 1708, 1611 cm^{-1}; MS (FAB) m/z=339 ($M+H^+$).

4.5.2. Pyrroloindole ***17***. To solution of carbamate **16** (52.1 mg, 0.154 mmol) in THF was added $LiAlH_4$ (36.5 mg, 0.770 mmol) at 0 °C. After stirring at room temperature for 1.5 h and at reflux for 10 min, $Na_2SO_4\cdot 10H_2O$ was added at 0 °C. After stirring for 1 h at room temperature, the inorganic solid was removed by filtration. The filtrate was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by silica gel column chromatography ($CHCl_3$/MeOH=95/5) to give pyrroloindole **17** (18.3 mg, 43%) as a colorless oil. Spectra were identical to those reported previously[46]; $[\alpha]_D^{26}$ −68 (*c* 0.20, CH_2Cl_2).

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Supplementary data

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