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Synthesis of Cyclopentadiindolyl Spirooxindoles via Palladium-catalyzed Intramolecular Oxidative Indole-Indole Coupling Reaction

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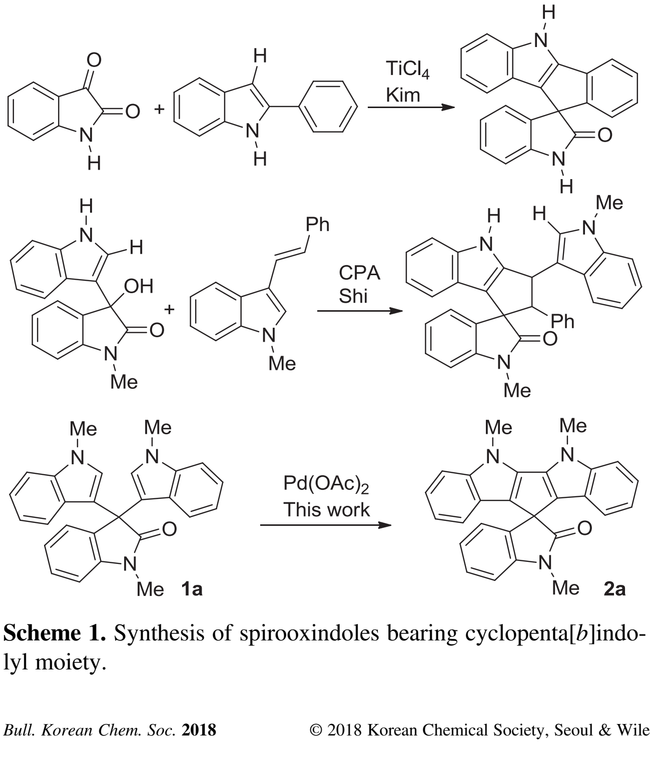
Spirooxindoles exist in a huge number of natural substances and pharmaceutically interesting compounds.[1] Thus, tremendous efforts have been devoted to development of efficient protocols to access these important motifs over the past years.[1–3] Recently, we reported the synthesis of various spirooxindoles[2] including spiroindeno[1,2-*b*]indolyloxindoles.[3] The spiroindeno[1,2-*b*]indolyloxindoles were synthesized from isatin and 2-arylindole in the presence of $TiCl_4$ via sequential inter- and intramolecular Friedel-Crafts reactions, as shown in Scheme 1.[3] Structurally similar spirocyclopenta[*b*]indolyl-2-oxindoles have been synthesized by Shi and co-workers from 3-indolyl-2-oxindoles and 3-vinylindoles via chiral phosphoric acid-catalyzed [3 + 2] cyclization (Scheme 1).[4a–c] Holz and co-workers also reported TfOH-catalyzed synthesis of spirocyclopenta[*b*]indolyl-2-oxindoles from isatin, indole, and styrene.[4d] In addition, Chen and co-workers reported the synthesis of similar polycyclic spirooxindoles by [3 + 2] annulations of Morita-Baylis-Hillman carbonates and 3-nitro-7-azaindoles.[4e] In these respects, we examined the synthesis of spirocyclopenta[2,1-*b*;3,4-*b'*]diindolyl-2-oxindole derivative **2a** by oxidative coupling reaction of 3,3-diindolyl-2-oxindole **1a**, as shown in Scheme 1.



Scheme 1. Synthesis of spirooxindoles bearing cyclopenta[*b*]indolyl moiety.

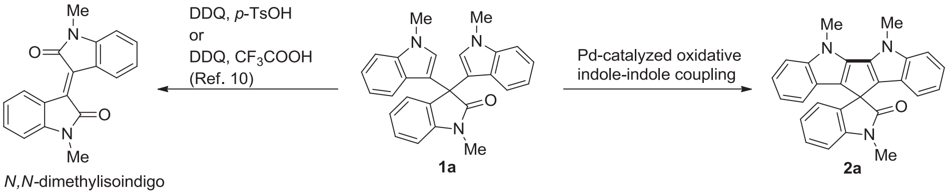
Similar intramolecular oxidative indole-indole coupling reactions have been carried out under various reaction conditions[5–9] including 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)/*p*-TsOH,[5] DDQ/CF_3COOH,[6] $K_3Fe(CN)_6$,[7] $Pd(OAc)_2$,[8] and other methods.[9] The reaction of **1a** under the reported intramolecular oxidative coupling reaction conditions employing DDQ/*p*-TsOH or DDQ/CF_3COOH afforded *N,N*-dimethylisoindigo in low yields (5–25%), unexpectedly,[10] as shown in Scheme 2.

We failed to obtain the desired compound **2a** in any trace amount. The reaction of **1a** in the presence of $K_3Fe(CN)_6$ in alkaline solution also did not produce **2a**. Thus, we examined the synthesis of **2a** by palladium-catalyzed oxidative arene-arene coupling reaction conditions.[8,11]

As shown in Table 1, the reaction of **1a** in the presence of $Pd(OAc)_2$, $Cu(OAc)_2$, and K_2CO_3 in *N,N*-dimethylacetamide (DMA) at 100 °C afforded **2a** in low yield (37%) for 18 h (entry 1).[8a] When we elevated the reaction temperature to 140 °C, the yield of **2a** decreased (entry 2).

To our delight, **2a** was obtained in good yield (88%) when we used AgOAc as an oxidant in pivalic acid (PivOH, entry 3) in short time (3 h).[11a–d] The use of Cs_2CO_3 (entry 4) afforded **2a** in better yield (90%). The yield was slightly lower by using cesium pivalate (entry 5), and the yield decreased slightly in the absence of a base (entry 6). With lesser amount of AgOAc (2.0 equiv), the yield decreased slightly (entry 7). When we carried out the reaction under O_2 balloon atmosphere, the yield was also reasonable (entry 8). However, the reaction was ineffective when we replaced pivalic acid with AcOH (entry 9), toluene (entry 10), and DMF (entry 11). The use of $Pd(TFA)_2$ (entry 12) afforded **2a** in good yield (90%). The use of $PdCl_2$ (entry 13) and $PdCl_2(PPh_3)_2$ (entry 14) were less effective. Among the examined conditions, we selected the condition of entry 4 based on the yield and clearness of the reaction.

Encouraged by the successful result, 3,3-diindolyl-2-oxindoles **1a-1j** were prepared from *N*-methylisatins and indoles according to the reported methods.[12] Various



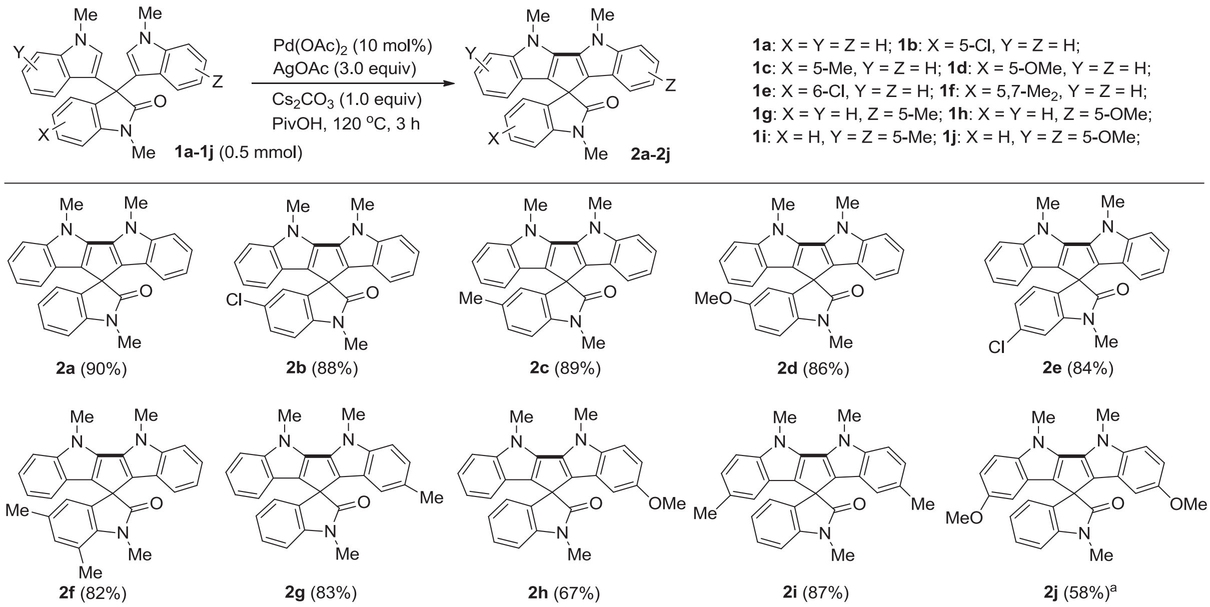
Scheme 2. Synthesis of spirooxindole **2a**.

Table 1. Optimization of reaction conditions for the synthesis of **2a**.[a]

Entry	Catalyst	Oxidant	Base	Solvent	Temp (°C)	Time (h)	Yield (%)
1	$Pd(OAc)_2$ (10 mol%)	$Cu(OAc)_2$ (3.0 equiv)	K_2CO_3 (1.0 equiv)	DMA	100	18	37
2	$Pd(OAc)_2$ (10 mol%)	$Cu(OAc)_2$ (3.0 equiv)	K_2CO_3 (1.0 equiv)	DMA	140	18	25
3	$Pd(OAc)_2$ (10 mol%)	AgOAc (3.0 equiv)	K_2CO_3 (1.0 equiv)	PivOH	120	3	88
4	**$Pd(OAc)_2$ (10 mol%)**	**AgOAc (3.0 equiv)**	**Cs_2CO_3 (1.0 equiv)**	**PivOH**	**120**	**3**	**90**
5	$Pd(OAc)_2$ (10 mol%)	AgOAc (3.0 equiv)	CsOPiv (3.0 equiv)	PivOH	120	3	78
6	$Pd(OAc)_2$ (10 mol%)	AgOAc (3.0 equiv)	no base	PivOH	120	3	84
7	$Pd(OAc)_2$ (10 mol%)	AgOAc (2.0 equiv)	K_2CO_3 (1.0 equiv)	PivOH	120	3	86
8	$Pd(OAc)_2$ (10 mol%)	O_2 balloon	K_2CO_3 (1.0 equiv)	PivOH	120	3	84
9	$Pd(OAc)_2$ (10 mol%)	AgOAc (3.0 equiv)	K_2CO_3 (1.0 equiv)	AcOH	reflux	3	<5[b]
10	$Pd(OAc)_2$ (10 mol%)	AgOAc (3.0 equiv)	K_2CO_3 (1.0 equiv)	toluene	reflux	18	<5[c]
11	$Pd(OAc)_2$ (10 mol%)	AgOAc (3.0 equiv)	K_2CO_3 (1.0 equiv)	DMF	120	18	<5[c]
12	$Pd(TFA)_2$ (5 mol%)	AgOAc (3.0 equiv)	K_2CO_3 (1.0 equiv)	PivOH	120	3	90
13	$PdCl_2$ (5 mol%)	AgOAc (3.0 equiv)	K_2CO_3 (1.0 equiv)	PivOH	120	3	70
14	$PdCl_2(PPh_3)_2$ (5 mol%)	AgOAc (3.0 equiv)	K_2CO_3 (1.0 equiv)	PivOH	120	3	76

[a] Substrate **1a** (0.5 mmol).
[b] Decomposition of **1a**.
[c] Most of **1a** was remained.

Table 2. Synthesis of cyclopentadiindolyl spirooxindoles.



[a] The reaction of **1j** was carried out at 80 °C (5 h).

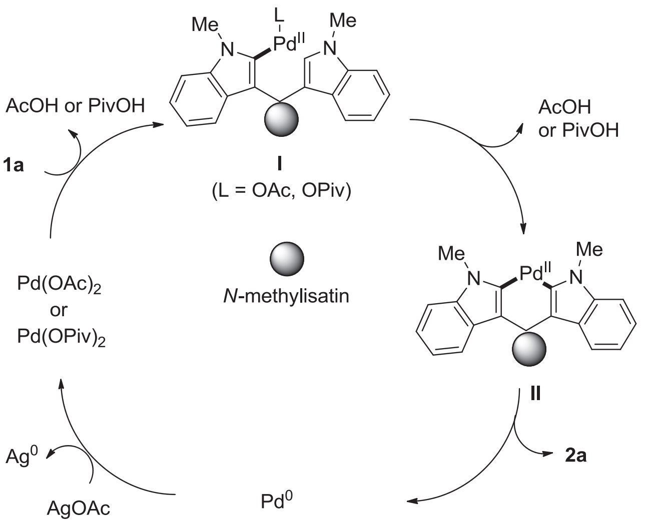
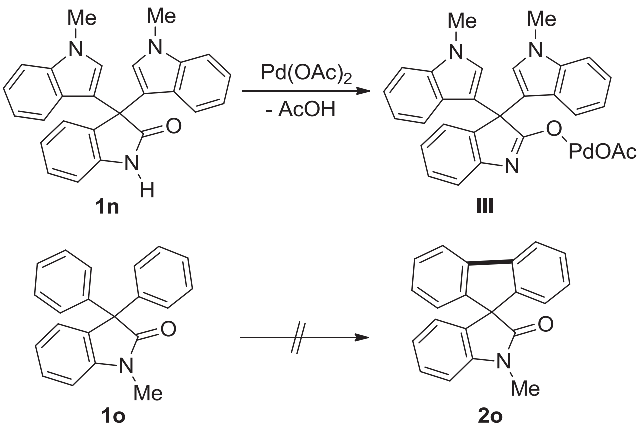


Figure 1. Possible reaction pathway.



Scheme 4. Failed substrates **1n** and **1o**.

cyclopentadiindolyl spirooxindoles **2a**-**2j** were synthesized under the optimized reaction condition (entry 4 in Table 1), and the results are summarized in Table 2. The reactions of 5-chloro-, 5-methyl-, 5-methoxy-, 6-chloro-, and 5,7-dimethylisatin derivatives **1b**-**1f** afforded **2b**-**2f** in good yields (82–89%). The reactions of 5-methyl- and 5-methoxyindole derivatives **1g**-**1j** also afforded **2g**-**2j** in good to moderate yields (58–87%). When the reaction of dimethoxy derivative **1j** was carried out at 120 °C, severe decomposition was observed. Thus, the reaction **1j** was carried out at 80 °C for a long time (5 h).

The reaction mechanism is proposed in Figure 1. An electrophilic palladation of **1a** with Pd(OAc)$_2$ or Pd(OPiv)$_2$ to form an intermediate **I**. A following intramolecular electrophilic palladation to form palladacycle **II**, and a following reductive elimination of palladium affords **2a**. The palladium is oxidized by AgOAc to generate a Pd^{II} species to finish the catalytic cycle.

In order to extend scope of the reaction, we examined the synthesis of spiroindeno[1,2-*b*]indolyloxindole **2k**,[3] as shown in Scheme 3. The required starting material **1k** was prepared from *N*-methylisatin by sequential introduction of phenyl group with phenylmagnesium bromide (83%) and *N*-methylindole in the presence of *p*-TsOH (88%).[12] The oxidative coupling reaction of **1k** was carried out under the standard condition to obtain **2k** in good yield (79%); however, somewhat longer reaction time (12 h) was required for the completion. Similarly, the reactions of **1l** and **1m** afforded **2l** (77%) and **2m** (80%) in good yields. The reaction might proceed via an initial electrophilic palladation toward more reactive indole moiety and a following intramolecular electrophilic palladation to benzene ring.

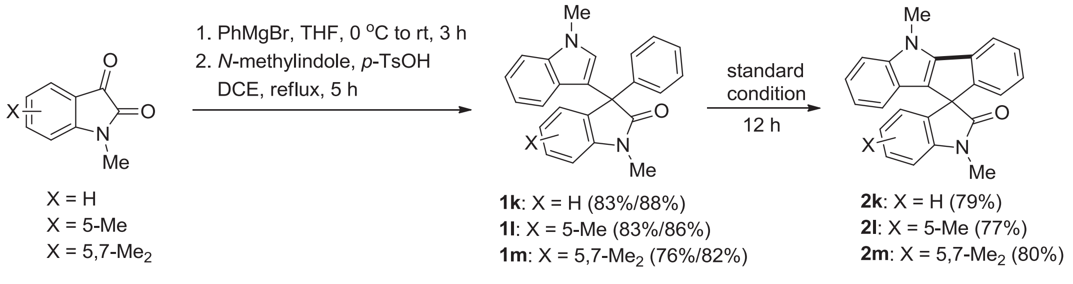
The oxidative coupling reaction of NH derivative **1n** failed, as we[2h] and other groups have already observed.[13]

The reason might be the formation of palladium intermediate **III**,[14] as shown in Scheme 4, instead of electrophilic palladation at the indole ring. Although the synthesis of spirofluorenyl-2-oxindoles has been reported by other methods,[15] we examined the synthesis of **2o** from **1o** by using our method. However, the reaction failed presumably due to less favorable electrophilic palladation at the benzene ring even at high temperature (160 °C).

In summary, various cyclopentadiindolyl spirooxindoles were synthesized in good yields by palladium-catalyzed intramolecular oxidative indole-indole coupling reaction. The coupling reaction could be also applied for the synthesis of spiroindeno[1,2-*b*]indolyloxindoles.

Experimental

Typical synthetic procedure of 2a. A mixture of **1a** (203 mg, 0.5 mmol), Pd(OAc)$_2$ (12 mg, 10 mol%), AgOAc (250 mg, 3.0 equiv), and Cs$_2$CO$_3$ (164 mg, 1.0 equiv) in PivOH (3.0 mL) was heated to 120 °C for 3 h under N$_2$ balloon atmosphere. The reaction mixture was diluted with



Scheme 3. Synthesis of **2k**-**2m**.

CH_2Cl_2 and filtered through a pad of Celite and washed with CH_2Cl_2. After usual aqueous extractive workup and column chromatographic purification process (*n*-hexane/EtOAc, 2:1), compound **2a** was isolated as a pale yellow solid, 182 mg (90%). Other compounds were synthesized similarly, and the selected spectroscopic data of **2a** are as follows.

Compound **2a**: 90%; pale yellow solid, mp 320–322 °C; IR (KBr) 1706, 1609, 1467, 1328 cm^{-1}; ^1H NMR (DMSO-d_6 + $CDCl_3$, 500 MHz) δ 3.40 (s, 3H), 4.19 (s, 6H), 6.62 (d, $J = 7.4$ Hz, 1H), 6.74 (d, $J = 7.8$ Hz, 2H), 6.81–6.91 (m, 3H), 7.05 (t, $J = 7.5$ Hz, 2H), 7.23 (d, $J = 7.7$ Hz, 1H), 7.33 (t, $J = 7.7$ Hz, 1H), 7.49 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (DMSO-d_6 + $CDCl_3$, 125 MHz) δ 27.2, 33.3, 54.9, 109.1, 111.2, 116.7, 120.5, 121.0, 122.79, 122.82, 123.1, 125.6, 128.7, 129.4, 139.7, 140.7, 144.9, 175.6; ESIMS *m/z* 404 $[M + H]^+$. Anal. Calcd for $C_{27}H_{21}N_3O$: C, 80.37; H, 5.25; N, 10.41. Found: C, 80.19; H, 5.54; N, 10.17.

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Supporting Information. Additional supporting information is available in the online version of this article.

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