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Highly Diastereoselective One-Pot Synthesis of Spirocyclic Oxindoles through Intramolecular Ullmann Coupling and Claisen Rearrangement**

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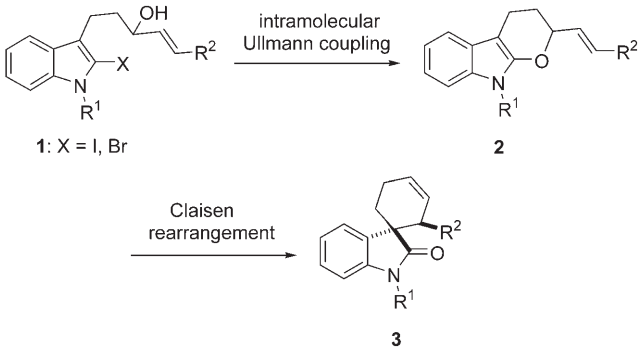
Oxindoles that incorporate a quaternary stereogenic center at C3 are attractive targets in organic synthesis because of their significant biological activities as well as wide-ranging utility as synthetic intermediates for alkaloids, drug candidates, and clinical pharmaceuticals.[1] Therefore, a number of synthetic methods have been developed in pursuit of this structure, including intermolecular alkylations,[2] palladium-catalyzed reactions,[1c,3] cycloadditions,[4] and sigmatropic rearrangements.[5] We recently developed the stereoselective synthesis of spiro[4.5]decane frameworks through a Claisen rearrangement of alkenyl bicyclic dihydropyrans.[6,7] On the basis of this result, we envisioned that a Claisen rearrangement of alkenyl pyranoindoles **2** would produce 3-spiro-2-oxindoles **3**, which are potential synthetic intermediates for indole alkaloids. Pyranoindoles **2** might, in turn, be prepared by an intramolecular Ullmann coupling (IUC) of haloindoles **1** bearing an allylic alcohol unit (Scheme 1).[8]



Scheme 1. General scheme for the construction of spirocyclic oxindoles **3**.

Herein we report an efficient and convenient method for the synthesis of spirocyclic oxindoles from haloindoles. The most striking feature of this approach is that it is a one-pot procedure in which the IUC of **1** and Claisen rearrangement of **2** proceed successively to provide 3-spiro-2-oxindoles **3** in good yields with high diastereoselectivities.[9]

To our knowledge, few general procedures are available for the preparation of **2**, and considering the reported properties of the unsubstituted pyranoindole, it was anticipated that **2** would be sensitive to acidic conditions.[10] Hence, we decided to examine the transition-metal-catalyzed intramolecular C–O coupling of **1** which is usually carried out under basic conditions. For C–O bond formation, the copper-mediated Ullmann-type reaction was chosen owing to its ease and lower cost.[11] Although several recent syntheses have involved IUC, these examples are much rarer than the intermolecular version.[12] As a preliminary survey, we compared several known procedures in which various 2-haloindoles **1** (R^1 = Me, SO_2Ph, R^2 = Me, *n*Bu) were employed. As a result, the Hauptman protocol (CuCl/2-aminopyridine, NaOMe)[13] was found to be effective and proceeds in moderate yield (up to 60%). However, direct application of the original Hauptman method to our indole substrates suffered from poor reproducibility. After many trials with **1a**, which can be readily prepared from commercially available *N*-methylindole by a three-step sequence,[14] we solved this problem with the following minor modifications: 1) Addition of a small amount of MeOH (≈2% *v*/*v*), and 2) more base (NaOMe). Under these optimized

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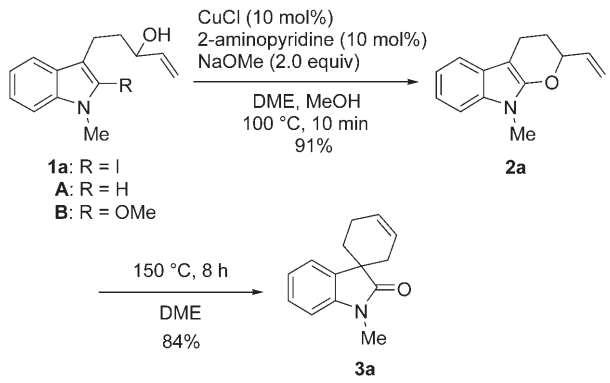
conditions, the yield of **2a** increased to 91% with good reproducibility (Scheme 2). The IUC of **1a** proceeded rapidly and was completed within 10 min. Interestingly, neither dehalogenated product **A** nor the product of cross-coupling

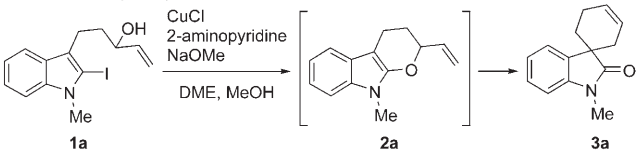


Scheme 2. Stepwise synthesis of oxindole **3a**. DME = 1,2-dimethoxyethane.

with NaOMe, **B**, was obtained. Finally, the isolated product **2a** underwent Claisen rearrangement, as expected, to afford the desired oxindole **3a** by heating in 1,2-dimethoxyethane (DME) at 150 °C.

As **2a** is relatively unstable, especially under acidic conditions, we next attempted a one-pot synthesis of **3a** (Table 1). When the reaction mixture was heated at 100 °C for 24 h, **3a** was obtained in 53% yield (Table 1, entry 1). On the other hand, when the reaction temperature was increased to 150 °C after complete formation of **2a** (100 °C, 10 min), the rearrangement of **2a** proceeded cleanly to afford **3a** in 84% yield (Table 1, entry 2). The IUC was completed with 5 mol% of CuCl and 2-aminopyridine, although a longer reaction time

Table 1: One-pot synthesis of oxindole **3a**.[a]



Entry	CuCl [mol%]	2-NH_2Py [mol%]	[**1a**] [mol L^{-1}]	Conditions	Yield of **3a** [%][b]
1	10	10	0.05	100 °C, 24 h	53[c]
2	10	10	0.05	100 °C, 10 min 150 °C, 12 h	84
3	5	5	0.05	100 °C, 3 h 150 °C, 12 h	80
4	10	10	0.10	100 °C, 10 min 150 °C, 12 h	72
5	0	0	0.05	100 °C, 24 h	6[d]

[a] Reaction conditions: indole **1a** (0.5 mmol), NaOMe/MeOH (25 wt%; 2.0 equiv), Ar, sealed tube. [b] Yield of isolated product. [c] **2a** was also obtained in 22% yield. [d] **1a** was recovered (74%) along with **2a** (10%).

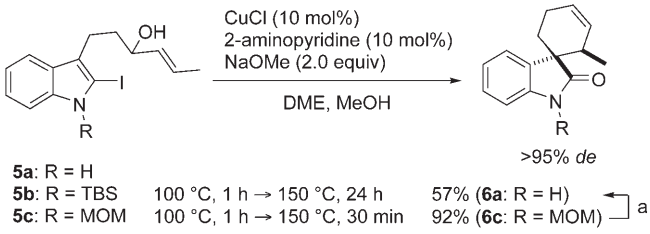
was required (Table 1, entry 3). An increase in the concentration of **1a** from 0.05 to 0.10 mol L^{-1} resulted in a slightly lower yield owing to side reactions during the IUC step (Table 1, entry 4). In the absence of CuCl and 2-aminopyridine, the IUC was sluggish; the yield of **3a** dropped to 6%, and 74% of **1a** was recovered (Table 1, entry 5). This result clearly indicates that CuCl and 2-aminopyridine efficiently catalyze the IUC.

To study the effect of substituents on the Claisen rearrangement, compounds **1** with a variety of substituents on the allylic alcohol unit were explored next (Table 2). Notably, all the indoles with *trans*-oriented substituents on the allylic double bond afforded the corresponding oxindoles as a single isomer, irrespective of the substituents (Table 2, entries 1, 2, 6–11).[15] The relative configuration was assigned on the basis of an X-ray crystal structure of oxindole **3h** and NOE experiments.[14] The configuration of these products indicates that the Claisen rearrangement proceeds through a boatlike transition state, analogously to previous results.[16] In contrast, the reaction of the *cis* isomer **1c** did not give the desired product; instead decomposition of the initially formed **2c** was observed (Table 2, entry 3). This result can be rationalized by considering the unfavorable transition state as a result of the steric repulsion between the *cis*-oriented methyl group and the hydrogen atoms of the dihydropyran ring.

The rate of the Claisen rearrangement is strongly dependent on the presence of substituents on the allylic double bond. The reaction of substrates with an alkyl or aryl substituent on the allylic double bond is fast (Table 2, entries 1, 6, 8–10). In contrast, substrates with no substituent on the allylic double bond react slowly (Table 1, entry 2).[7a]

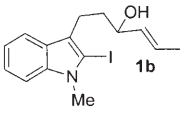
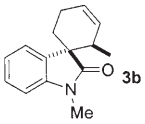
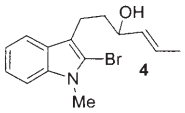
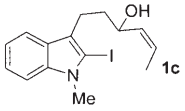
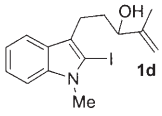
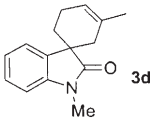
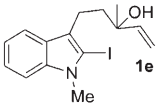
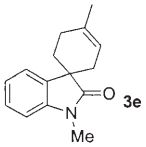
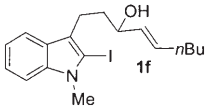
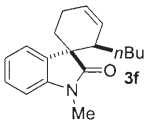
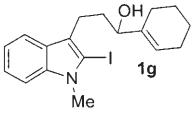
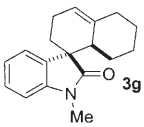
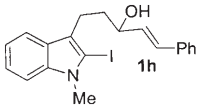
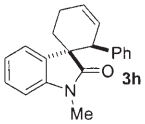
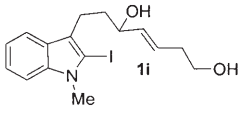
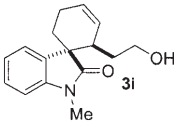
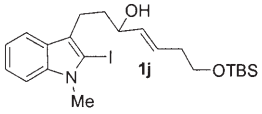
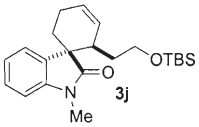
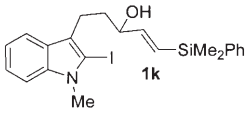
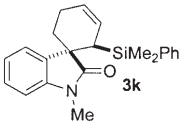
In the case of bromoindole **4**, although the reactivity in the IUC is apparently lower than that of iodide **1b**, the reaction proceeded to afford oxindole **3b** in 55% yield (Table 2, entry 2). Notably, sterically hindered substrates such as **1e** and **1g** gave the desired **3e** and **3g**, respectively, in good yields (Table 2, entries 5, 7). The slow reaction of **1g** could be accelerated without any side reactions by increasing the temperature. The fact that diol **1i** gave **3i** exclusively in 93% yield indicates that the allylic hydroxy group reacts selectively and that the IUC is tolerant of unprotected hydroxy groups (Table 2, entry 9). The low yield observed for **1k**, which bears a silyl group, is due to the formation of the desilylated products **3a** and its double-bond isomer (Table 2, entry 11).

The synthetic utility of N-methylated oxindoles is rather limited owing to the difficulty in the deprotection of the *N*-



Scheme 3. Preparation of oxindole **6a**. Reagents and conditions: a) TMSCl, NaI, CH_3CN, 0 °C; then Et_3N, MeOH, 55 °C, 81%. MOM = methoxymethyl.

Table 2: Synthesis of spirocyclic oxindoles.[a]

Entry	Substrate	Product[b]	Conditions	Yield [%][c]	*de* [%][d]
1	 **1b**	 **3b**	100 °C, 30 min 150 °C, 1 h	89	> 95
2	 **4**	**3b**	100 °C, 24 h	55[e]	> 95
3	 **1c**	Complex mixture	100 °C, 1.5 h 150 °C, 6 h	–	–
4	 **1d**	 **3d**	100 °C, 4 h 150 °C, 1 h	80	–
5	 **1e**	 **3e**	130 °C, 21 h 150 °C, 1 h	84	–
6	 **1f**	 **3f**	100 °C, 1 h 150 °C, 1 h	92	> 95
7	 **1g**	 **3g**	100 °C, 22 h 120 °C, 11 h	89 90	> 95 > 95
8	 **1h**	 **3h**	100 °C, 1 h	84	> 95
9	 **1i**	 **3i**	100 °C, 30 min 150 °C, 1 h	93	> 95
10	 **1j**	 **3j**	100 °C, 1 h 150 °C, 40 min	66[f]	> 95
11	 **1k**	 **3k**	100 °C, 5 h 150 °C, 2 h	20[g]	> 95

[a] Reaction conditions: substrate (0.5 mmol), CuCl (10 mol%), 2-aminopyridine (10 mol%), DME (10 mL), NaOMe/MeOH (25 wt%; 2.0 equiv), Ar, sealed tube. Reaction time and temperature were not optimized for each substrate. [b] For the determination of relative configuration, see the Supporting Information. [c] Yield of isolated product. [d] Determined by ^{1}H NMR spectroscopic analysis. [e] **4** was recovered (31%). [f] **3i** was isolated in 25% yield (> 95% *de*). [g] **3a** and its regioisomer were isolated in 47% yield (**3a**/isomer 2:1). TBS = *tert*-butyldimethylsilyl.

methyl group. Thus, we extended this method to the synthesis of free (NH) oxindoles. The unprotected iodoindole **5a** is not a suitable starting material for conversion into **6a**, as **5a** readily decomposes. Thus, several N-protected iodoindole substrates were prepared and exposed to similar conditions. *N*-TBS indole **5b** afforded the desired **6a** in 57% yield (Scheme 3). In this reaction, all of **5b** was converted into **5a** upon heating to 100 °C, as monitored by HPLC analysis. However, the subsequent IUC of **5a** was rather slow, and the reaction temperature had to be elevated to 150 °C to allow complete consumption of **5a**. In contrast, the methoxymethyl (MOM) group was found to be a suitable protecting group for the present transformation. The IUC of **5c** and Claisen rearrangement of the resultant pyranoindole proceeded smoothly to give **6c** in 92% yield as a single isomer. The MOM group was readily cleaved (81% yield) by the Fukuyama procedure.[17]

In summary, we have developed a convenient and efficient method for the preparation of spirocyclic oxindoles with vicinal stereogenic centers from the corresponding 2-haloindoles by a one-pot IUC and Claisen rearrangement. The IUC is a simple and low-cost method for the preparation of the rearrangement precursors, alkenyl pyranoindoles. The Claisen rearrangement of the pyranoindoles proceeds smoothly to give the desired oxindoles in good yields with high diastereoselectivities. The Claisen rearrangement is stereospecific in most cases; hence this method is also applicable to the enantioselective synthesis of spirocyclic oxindoles. Further applications of this reaction to chiral nonracemic substrates and the synthesis of natural products are underway.

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