Asymmetric Catalysis

International Edition: DOI: 10.1002/anie.201507193
German Edition: DOI: 10.1002/ange.201507193

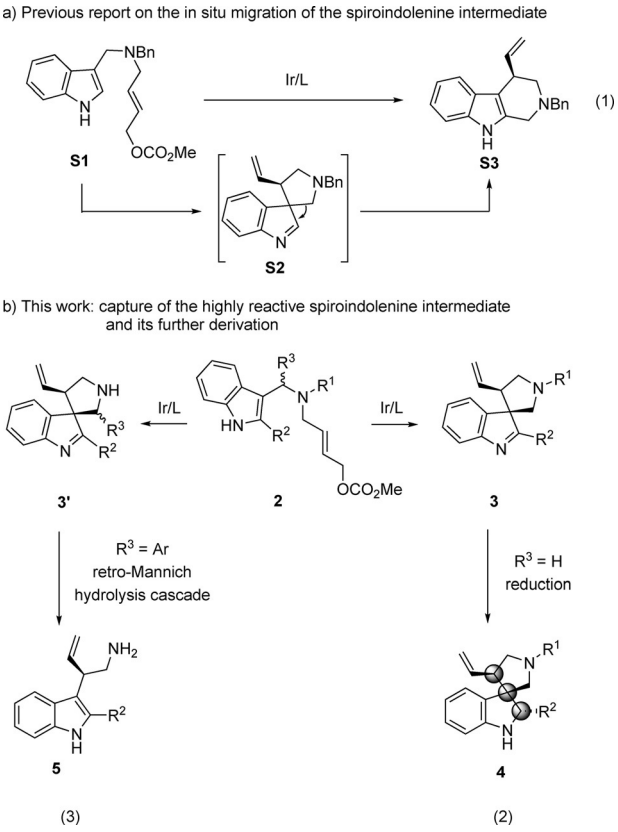
Enantioselective Construction of Spiroindolines with Three Contiguous Stereogenic Centers and Chiral Tryptamine Derivatives via Reactive Spiroindolenine Intermediates

*Chun-Xiang Zhuo, Yong Zhou, Qiang Cheng, Lin Huang, and Shu-Li You**

Abstract: *The highly efficient synthesis of the enantioenriched spiroindolines by iridium-catalyzed asymmetric allylic dearomatization and reduction is presented. Spiroindolines containing three contiguous stereogenic centers were obtained with excellent diastereo- and enantioselectivity. In addition, a chiral tryptamine derivative could be easily accessed in good yield with excellent ee value through an unprecedented dearomatization/retro-Mannich/hydrolysis cascade reaction of an indole derivative.*

Chiral spiroindolenine and spiroindoline moieties are often found as structural cores for biologically active natural products and pharmaceutical agents.[1,2] In this regard, great effort has been devoted to the development of enantioselective construction of these skeletons.[3] Among the methods, the syntheses of spiroindolenine and spiroindoline derivatives by catalytic asymmetric dearomatization (CADA) reactions of indoles feature high efficiency, step economy, and ready availability of starting materials.[4,5] However, the diastereo- and enantioselective control usually suffers when the vicinal tertiary and all-carbon quaternary stereocenters are generated in the dearomatization process.[6] Therefore, developing an efficient strategy for the highly diastereo- and enantioselective formation of spiroindolenine and spiroindoline motifs, having multiple contiguous stereogenic centers, is highly desirable.

In our ongoing efforts to investigate the transition-metal-catalyzed asymmetric allylic dearomatization reactions, we found that substituted indoles could undergo the asymmetric allylic dearomatization reaction in an intramolecular fashion, thus affording various spiroindolenines bearing vicinal tertiary and quaternary carbon stereocenters.[4,7] Interestingly, when the NBn-tethered indole substrate **S1** was used, the novel tetrahydro-β-carboline derivative **S3**, featuring the migration of the original substituent from the C3 to C2 position of indole was obtained in excellent yield and *ee* [Eq. (1), Scheme 1].[8] Preliminary mechanistic studies demonstrated the spiroindolenine **S2** was formed first and then underwent a rapid methanamine group migration. However, the spiroindolenine intermediate was highly reactive and could not be isolated. Therefore, we envisaged that installing a substituent group on the 2-position of the indole ring may prevent the migration, and thus enable the isolation of the spiroindolenines **3** [Eq. (2), Scheme 1]. Herein, we report the highly diastereo- and enantioselective syntheses of spiroindolines (**4**) by iridium-catalyzed asymmetric allylic dearomatization and reduction reactions. Furthermore, the chiral tryptamine derivative **5** was easily accessed in good yield and with excellent *ee* value by retro-Mannich/hydrolysis cascade reaction of the spiroindolenine intermediate **3'** when an aromatic substituent was introduced in the benzylic position of the indole substrate **2** [Eq. (3), Scheme 1].



Scheme 1. Derivation of the reactive spiroindolenine intermediates: syntheses of the spiroindolines with three contiguous stereogenic centers, and chiral tryptamine derivatives.

Our study was initiated by an exploration of the reaction of the indole **2a** with an iridium catalytic system comprising

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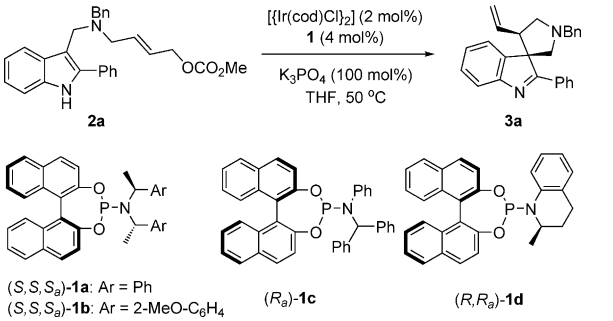
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201507193.

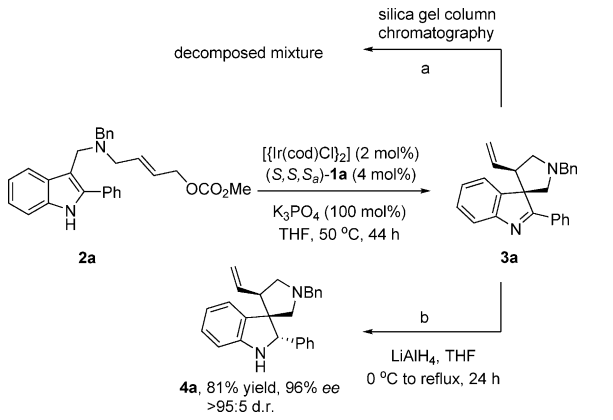
Table 1: Ligand effect.[a]



Entry	1	*t* [h]	Conv. [%][b]	d.r.[b]	*ee* [%][c]
1	**1a**	41	>95	>95:5	96
2	**1b**	35	>95	>95:5	96
3	**1c**	35	79	91:9	91
4	**1d**	35	>95	>95:5	96

[a] Reaction conditions: 2 mol% of $[\{Ir(cod)Cl\}_2]$, 4 mol% of **1**, 0.2 mmol of **2a** and K_3PO_4 in THF (2.0 mL). [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis. cod = 1,5-cyclooctadiene, THF = tetrahydrofuran.

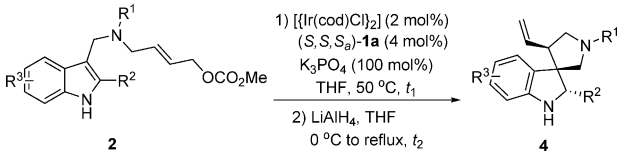
$[\{Ir(cod)Cl\}_2]$ and the Feringa ligand **1a** (Table 1).[9,10] In the presence of 2 mol% of $[\{Ir(cod)Cl\}_2]$, 4 mol% of **1a**, and 1.0 equivalents of K_3PO_4, the reaction of **2a** in THF for 41 hours gave the spiroindolenine **3a** in greater than 95% conversion, greater than 95:5 d.r., and 96% *ee* (entry 1). The effect of different chiral ligands was examined. The Alexakis ligand **1b**, combined with $[\{Ir(cod)Cl\}_2]$, was also quite efficient for the reaction (entry 2). The catalyst derived from the BHPphos **1c**[11] catalyzed the reaction of **2a** with moderate conversion, and d.r. and *ee* values (entry 3). In addition, the iridium catalyst derived from the THQphos **1d**[11] was quite effective in promoting the allylic dearomatization process (entry 4). However, during the purification of the spiroindolenine product **3a** from the crude reaction mixture by silica gel column chromatography, decomposition was observed (Scheme 2a). To our delight, **3a** could be reduced in situ to form the stable spiroindoline **4a**. By using $LiAlH_4$ as the reductant, **4a**, containing three contiguous stereogenic centers, was easily accessed in 81% yield, 96% *ee*, and with excellent diastereoselectivity (Scheme 2b).



Scheme 2. Derivation of the spiroindolenine product.

By employing the newly developed asymmetric allylic dearomatization/reduction reactions, various 3-indolyl allylic carbonates (**2**) were explored to examine the generality of the process (Table 2). Reactions of allylic carbonates having various protecting groups (Bn, PMB, allyl), on the N in the tether, all afforded the corresponding spiroindoline products

Table 2: The reaction substrate scope.[a]



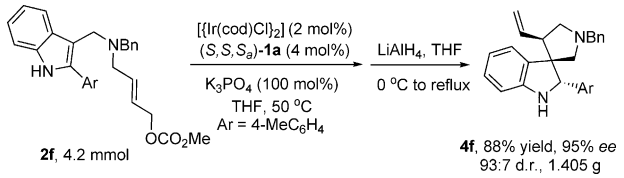
Entry	**2**: R^1, R^2, R^3	t_1, t_2 [h]	d.r.[b]	Yield [%][c]	*ee* [%][d]
1	**2a**: Bn, Ph, H	44, 24	>95:5	**4a**, 81	96
2	**2b**: PMB, Ph, H	41, 19	>95:5	**4b**, 81	94
3	**2c**: allyl, Ph, H	41, 19	>95:5	**4c**, 73	94
4	**2d**: Bn, 4-FC_6H_4, H	42, 23	94:6	**4d**, 62	95
5	**2e**: Bn, 4-Cl-C_6H_4, H	40, 19	91:9	**4e**, 62	94
6	**2f**: Bn, 4-MeC_6H_4, H	37, 18	94:6	**4f**, 83	95
7	**2g**: Bn, 4-MeOC_6H_4, H	42, 14	94:6	**4g**, 71	93
8	**2h**: Bn, Ph, 5-F	42, 14	93:7	**4h**, 79	89
9	**2i**: Bn, Ph, 5-Cl	37, 18	>95:5	**4i**, 83	90
10	**2j**, Bn, Ph, 6-F	27, 18	95:5	**4j**, 66	96
11	**2k**, Bn, Ph, 6-Cl	27, 18	93:7	**4k**, 75	95
12	**2l**, Bn, Ph, 5-Me	36, 21	>95:5	**4l**, 80	94

[a] Reaction conditions: (for step 1) 2 mol% of $[\{Ir(cod)Cl\}_2]$, 4 mol% of (S,S,S_a)-**1a**, 0.2 mmol of **2** and K_3PO_4 in THF (2.0 mL) at 50°C; (for step 2) 300 mol% of $LiAlH_4$ in refluxed THF (2.0 mL). [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Yield of the isolated product. [d] Determined by HPLC analysis.

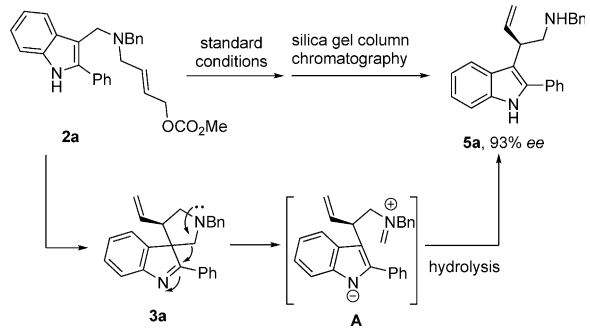
in good yields with excellent d.r. and *ee* values (**4a–c**; entries 1–3). Next, the electronic effect of the aromatic substituents on the 2-position of the indole ring was explored. Substrates bearing either an electron-withdrawing (4-F, 4-Cl) (entries 4 and 5) or electron-donating (4-Me, 4-MeO) (entries 6 and 7) group on the 2-aryl moiety of the indole core all reacted to form the corresponding products in good yields with excellent d.r. and *ee* values (**4d–g**; entries 4–7). Meanwhile, when substrates bearing either an electron-withdrawing (5-F, 5-Cl, 6-F, 6-Cl; entries 8–11) or electron-donating (5-Me; entry 12) group on the indole core were tested, the corresponding spiroindoline products **4** were obtained in good to excellent yields, and d.r. and *ee* values (**4h–l**; entries 8–12). The structure and stereochemistry of the products were determined by an X-ray crystallographic analysis of a crystal of the enantiopure **4a**. The absolute configuration of **4a** was determined as (2*S*, 3*S*, 4′*R*).[12]

To test the practicality of the newly developed methodology, a gram-scale synthesis of chiral spiroindoline was carried out. The intramolecular allylic dearomatization reaction of **2f** on a 4.2 mmol scale and subsequent reduction gave the desired product **4f** in 88% yield, 93:7 d.r., and 95% *ee* (Scheme 3).

During the separation of the spiroindolenine product **3a**, the chiral tryptamine derivative **5a** was obtained in 93% *ee*, albeit with low yield (8% yield; Scheme 4). Next, we sought

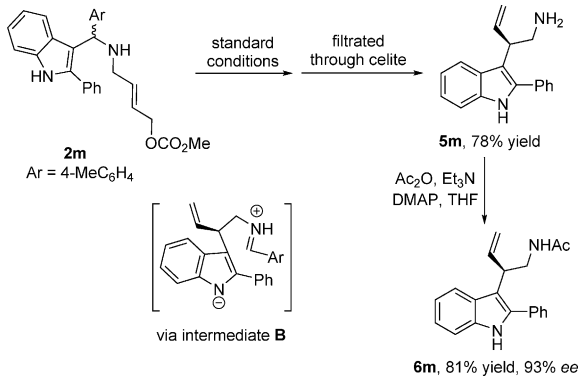


Scheme 3. A gram-scale synthesis of the spiroindoline **4 f**.



Scheme 4. Rationale for the formation of the chiral tryptamine derivative.

to understand why the tryptamine derivative was generated in this process. A possible reaction pathway is proposed for the formation of **5a**. Firstly, **3a** was formed by the iridium-catalyzed asymmetric allylic dearomatization. Then the intermediate **A** was generated by a retro-Mannich reaction, and was further hydrolyzed to form **5a**. However, **5a** was obtained in low yield, and might be due to the rapid decomposition of the unstable iminium cation of **A**. To solve this problem, we installed an aromatic group at the benzylic position of the indole core, as it was proposed to stabilize the iminium cation of the intermediate **B** (Scheme 5). To our great delight, the substrate **2m** reacted smoothly under the standard reaction conditions to afford the corresponding spiroindolenine, which was readily transformed into the chiral tryptamine derivative **5m** in good yield. The protection of the primary amine moiety with Ac_2O also occurred smoothly, thus providing the acetyl-protected chiral tryptamine derivative **6m** in excellent yield and *ee* (Scheme 5).



Scheme 5. Synthesis of a chiral tryptamine derivative by rational design.

In summary, we have developed an efficient strategy for the synthesis of spiroindolines by the iridium-catalyzed asymmetric allylic dearomatization and reduction reactions. The spiroindoline products containing three contiguous stereogenic centers were obtained in good yields, as well as excellent diastereo- and enantioselectivity. In addition, the chiral tryptamine derivative could be easily obtained by an unprecedented dearomatization/retro-Mannich/hydrolysis cascade reaction of an indole derivative. This new reaction mode provides an efficient method for the synthesis of chiral tryptamine derivatives. Furthermore, the observation and derivation of the spiroindolenines also provide experimental evidence for the existence of the spirointermediate during the dearomatization/in situ migration of indoles[8] [Eq. (1), Scheme 1]. Further investigation of the reaction mechanism and application of the spiroindoline products are currently underway in our laboratory.

Acknowledgements

We thank the National Basic Research Program of China (973 Program 2015CB856600) and National Natural Science Foundation of China (21332009, 21421091) for generous financial support.

Keywords: asymmetric catalysis · dearomatization · heterocycles · iridium · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 14146–14149
Angew. Chem. **2015**, *127*, 14352–14355

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[12] CCDC 1409200 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Received: August 2, 2015
Published online: September 25, 2015

