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Enantioselective Functionalization of Indoles and Pyrroles via an in Situ-Formed Spiro Intermediate

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Supporting Information

ABSTRACT: Herein we report a highly enantioselective synthesis of polycyclic indoles and pyrroles with up to 99% ee by an iridium catalyst system consisting of a commercially available iridium precursor and a readily accessible ligand. Investigation of the reaction mechanism led to the discovery of an unprecedented dearomatized spiro intermediate and its in situ migration phenomenon. The new reaction mode features switching of the substituent from the indole C-3 position to the C-2 position (from the C-2 position to the C-3 position in the case of pyrrole) without loss of the enantiomeric purity, providing a novel concept in designing the asymmetric construction of enantiopure polycyclic indoles and pyrroles.

Indoles and pyrroles are among the most widely distributed heterocyclic compounds in nature, and many enantiopure natural and synthetic derivatives thereof, including tryptophan, an essential amino acid, display interesting biological activities.[1] Representative examples, such as yohimbine, tadalafil (Cialis), and styloguanidine, all have polycyclic indole or pyrrole structures (Figure 1).[2,3] Consequently, the synthesis of enantiomerically pure polycyclic indoles and pyrroles is in great demand in both organic and medicinal chemistry.

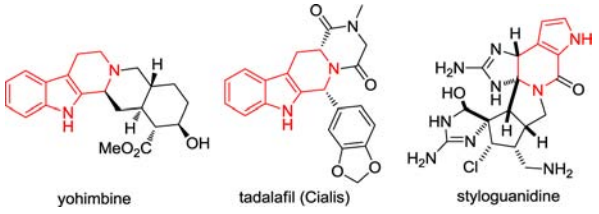
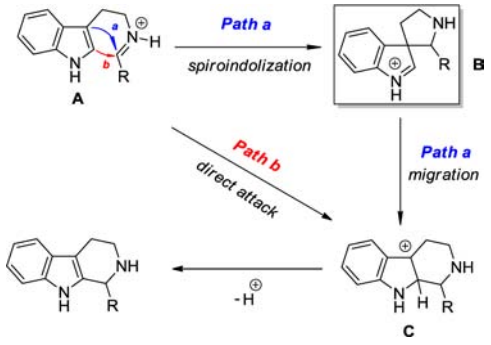


Figure 1. Selected naturally occurring compounds containing polycyclic indole or pyrrole units.

The Pictet–Spengler reaction has been recognized as one of the most direct and efficient methods for constructing tetrahydrocarboline frameworks.[4] The catalytic enantioselective Pictet–Spengler reaction has witnessed significant progress during the past decade.[5] In addition, asymmetric intramolecular alkylation of indoles and pyrroles provides another straightforward route to polycyclic indole and pyrrole structures.[6] In this regard, transition-metal-catalyzed allylic alkylation reactions have proved to be quite successful.[7,8] For the intramolecular alkylation of 3-indolyl substrates, in some cases spiroindolenine compounds were proposed as the intermediates, and the alkylation at the C-2 position was attributed to alkylation at the C-3 position followed by migration (Scheme 1, path a).[9]

Scheme 1. Two Alternative Reaction Pathways for the Pictet–Spengler Reaction



Evidence for the existence of the spiro intermediate was also documented in the literature.[10] However, whether the asymmetric Pictet–Spengler reactions of indole substrates proceed through dearomatized spiroindolenine intermediates (**B** in Scheme 1) remains a controversial topic.[11] In addition, in asymmetric intramolecular alkylation reactions of indoles, spiroindolenine formation has received little attention. The fact that the spiro intermediate was overlooked could cause misunderstanding of the reaction mechanism and even the incorrect assignment of the alkylation products.[12]

As part of our continuous efforts to study transition-metal-catalyzed allylic alkylation reactions, we found that both indoles and pyrroles undergo allylic dearomatization reactions in an intramolecular fashion, providing various heterocycles bearing a quaternary carbon center.[13,14] Interestingly, the isolated five-membered spiroindolenine products could further proceed with allyl group migration in a highly stereoselective manner under acid catalysis (Scheme 2, path a).[13d] The allyl group was speculated to have higher migratory aptitude than the methylene group. With this information in hand, we envisaged that by enhancing the migratory aptitude of the methylene portion, an alternative migration pathway might be observed, even in a tandem dearomatization/migration sequence (Scheme 2, path b). Herein we report an unprecedented

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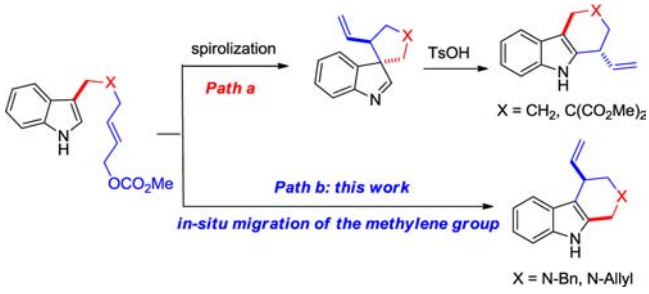
Scheme 2. Indole Dearomatization and Controllable Migration

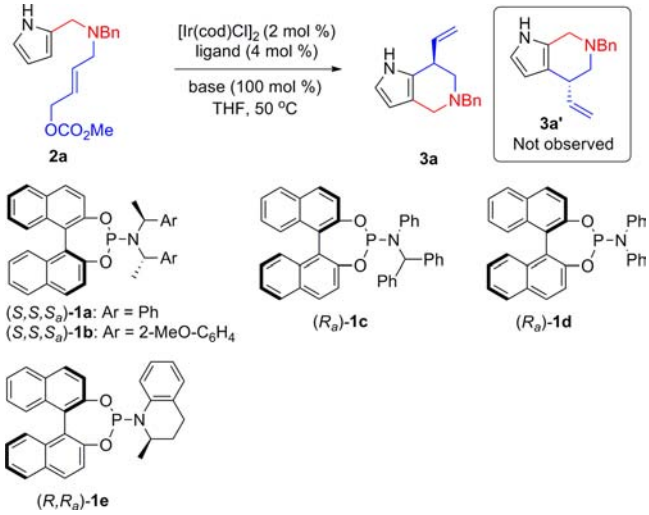


Friedel–Crafts-type allylic alkylation reaction in which alkylation of an indole at the C-3 position to afford a spiroindolenine is followed by migration of methanamine group to the indole C-2 position (in a pyrrole system, the methanamine migration is from C-2 to C-3). The process features well-preserved enantiomeric purity during the migration process and provides a general strategy for the construction of enantiopure polycyclic indoles and pyrroles.

Our studies began with a serendipitous discovery during our attempts at Ir-catalyzed intramolecular allylic Friedel–Crafts alkylation reactions of 2-pyrrolyl allylic carbonate **2a**.[15,16] In the presence of 2 mol % $[Ir(cod)Cl]_2$ (cod = 1,5-cyclooctadiene), 4 mol % ligand **1a**, and 1.0 equiv of Cs_2CO_3, the reaction of **2a** in tetrahydrofuran (THF) for 16 h did not lead to the directly alkylated product **3a′**. Instead, product **3a**, featuring the migration of the original substituent from the C-2 position to the C-3 position, was obtained in 72% conversion with 87% ee (Table 1, entry 1). Encouraged by these results, we carried out further optimization of the reaction conditions. Various bases such as K_3PO_4, K_2CO_3, Li_2CO_3 and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) were screened (entries 2–5), and K_3PO_4 was found to be the optimal base for the process. Catalysts generated from ligands **1b** and **1d** enabled the dearomatization/migration reaction of **2a** with good ee but in only moderate conversions (entries 6 and 8). Interestingly, ligands **1c** and **1e** developed by our group[17] formed efficient catalysts with $[Ir(cod)Cl]_2$ to provide product **3a** in good yields with excellent enantioselectivity (98 and 94% ee, respectively; entries 7 and 9). After the optimization study, the best conditions were obtained as the following: **2a** in THF (0.1 M) with 2 mol % $[Ir(cod)Cl]_2$, 4 mol % **1c**, and 1.0 equiv of K_3PO_4 at 50 °C. Under these reaction conditions, product **3a** was obtained in 80% yield with 98% ee (entry 7).

With the above optimized reaction conditions in hand, we explored various 2-pyrrolyl allylic carbonates to examine the generality of the process. The results are summarized in Table 2. Reactions of allylic carbonates containing different protecting groups (Bn, allyl) on the amine moiety in the tether both gave the corresponding products in good yields (57–80%) with excellent enantioselectivity (98% ee) (entries 1 and 2). Substrate **2c** bearing a phenyl group on the pyrrole core (R^2) reacted smoothly, affording the desired product **3c** in 91% yield with 99% ee (entry 3). Next, the electronic effect of substituents on the pyrrole core was probed. Substrates bearing either electron-donating [4-MeO, 3,4-$(MeO)_2$; entries 4 and 5] or electron-withdrawing groups (4-F, 4-Cl, 4-Br; entries 6–8) on the 5-phenyl moiety on the pyrrole core (R^2) all reacted to form the corresponding products in good to excellent yields (75–95%) and enantioselectivity (96–99% ee). Notably, the

Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	base	t (h)	conv. (%)[b]	ee (%)[c]
1	**1a**	Cs_2CO_3	16	72	87
2	**1a**	K_3PO_4	16	>95	89
3	**1a**	K_2CO_3	19	78	89
4	**1a**	Li_2CO_3	19	92	85
5	**1a**	DBU	16	60	85
6	**1b**	K_3PO_4	18	64	88
7	**1c**	K_3PO_4	34	>95 (80[d])	98
8	**1d**	K_3PO_4	18	36	87
9	**1e**	K_3PO_4	29	>95	94

[a]Reaction conditions: 2 mol % $[Ir(cod)Cl]_2$, 4 mol % ligand, 0.1 mmol of **2a**, and 0.1 mmol of base in THF (1.0 mL) at 50 °C. [b]Determined by ^1H NMR analysis of the crude reaction mixtures. [c]Determined by HPLC analysis. [d]Isolated yield.

reaction occurred smoothly for substrates **2i** and **2j** bearing alkyl groups on the pyrrole core (61–89% yields, 96–97% ee; entries 9 and 10). Interestingly, when 3-pyrrolyl allylic carbonate **2k** was utilized (entry 11), the reaction smoothly afforded product **3a** (the same product as obtained when **2a** was used as the substrate) in excellent yield (86%) and enantioselectivity (97% ee). The structure and stereochemistry of the products were confirmed unambiguously by X-ray crystallographic analysis of a crystal of enantiopure **3h**. The absolute configuration was determined to be *S*.

Next, we examined the generality of this asymmetric dearomatization/migration process with 3-indolyl allylic carbonates. After a systematic study of the reaction conditions, the optimized conditions were found to be the following: 2 mol % $[Ir(cod)Cl]_2$, 4 mol % **1c**, 0.2 mmol of **4a**, and 0.4 mmol of K_3PO_4 in refluxing THF (see the Supporting Information for details). Under these conditions, the substrate scope of the asymmetric allylic dearomatization/migration reaction was then investigated, and the results are summarized in Table 3. Reactions of 3-indolyl allylic carbonates with various protecting groups (Bn, allyl) on nitrogen atom in the tether both gave the corresponding products in good yields (63–80%) with high levels of enantiocontrol (88–96% ee) (entries 1 and 2). Meanwhile, substrates bearing either electron-withdrawing (5-F, 5-Cl, 5-Br, 6-Cl; entries 3–6) or electron-donating groups (5-Me, 5-MeO, 6-MeO; entries 7–9) on the indole core all afforded the corresponding products in good to excellent yields (72–93%) and enantioselectivity (94–96% ee). The structure

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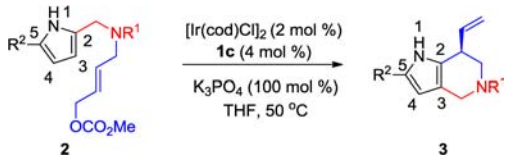
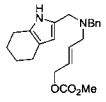
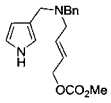
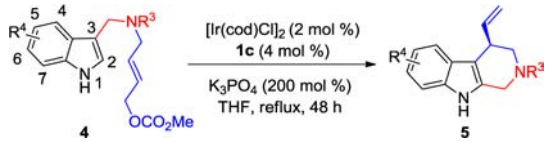
Table 2. Reaction Scope: 2-Pyrrolyl Substrates[a]



entry	2, R^1, R^2	t (h)	3, yield (%)[b]	ee (%)[c]
1	**2a**, Bn, H	34	**3a**, 80	98
2	**2b**, allyl, 4-Me-C_6H_4	58	**3b**, 57	98
3	**2c**, Bn, Ph	34	**3c**, 91	99
4[d]	**2d**, Bn, 4-MeO-C_6H_4	34	**3d**, 95	96
5	**2e**, Bn, 3,4-$(MeO)_2$-C_6H_3	34	**3e**, 89	98
6	**2f**, Bn, 4-F-C_6H_4	33	**3f**, 88	99
7	**2g**, Bn, 4-Cl-C_6H_4	33	**3g**, 88	99
8	**2h**, Bn, 4-Br-C_6H_4	48	**3h**, 75	98
9	**2i**, Bn, Et	33	**3i**, 89	97
10	 **2j**,	48	**3j**, 61	96
11	 **2k**,	33	**3a**, 86	97

[a]Reaction conditions: 2 mol % $[Ir(cod)Cl]_2$, 4 mol % **1c**, 0.2 mmol of **2**, and 0.2 mmol of K_3PO_4 in THF (2.0 mL) at 50 °C. [b]Isolated yields of **3**. [c]Determined by HPLC analysis. [d]3.5 mol % $[Ir(cod)Cl]_2$, 7 mol % **1c**, and 2 equiv of K_3PO_4 were used.

Table 3. Reaction Scope: 3-Indolyl Substrates[a]



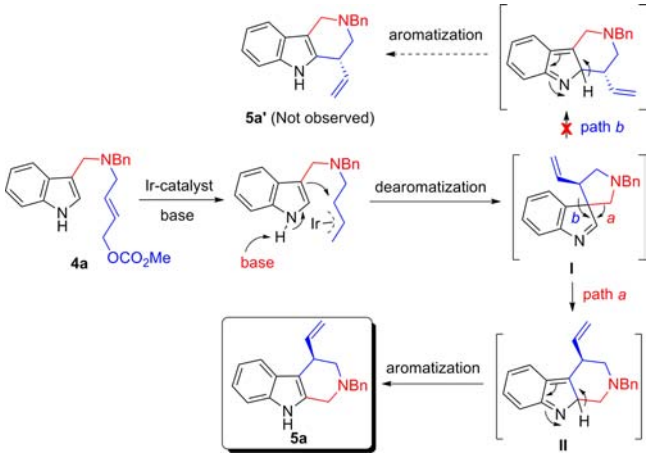
entry	4, R^3, R^4	5, yield (%)[b]	ee (%)[c]
1	**4a**, Bn, H	**5a**, 80	96
2	**4b**, allyl, H	**5b**, 63	88
3	**4c**, Bn, 5-F	**5c**, 88	96
4	**4d**, Bn, 5-Cl	**5d**, 80	94
5	**4e**, Bn, 5-Br	**5e**, 74	94
6	**4f**, Bn, 6-Cl	**5f**, 93	95
7	**4g**, Bn, 5-Me	**5g**, 75	96
8	**4h**, Bn, 5-MeO	**5h**, 80	94
9	**4i**, Bn, 6-MeO	**5i**, 72	95

[a]Reaction conditions: 2 mol % $[Ir(cod)Cl]_2$, 4 mol % **1c**, 0.2 mmol of **4**, and 0.4 mmol of K_3PO_4 in refluxing THF (2.0 mL). [b]Isolated yields of **5**. [c]Determined by HPLC analysis.

and stereochemistry of the products were determined by X-ray crystallographic analysis of a crystal of enantiopure **5e**. The absolute configuration was determined to be *R*.

On the basis of the obtained experimental results, we propose a plausible reaction pathway using indole-derived substrate **4a** as an example (Scheme 3). First, with the

Scheme 3. Plausible Reaction Pathway



preformed iridium(I) catalyst, oxidative addition of **4a** generates an Ir(III)−π-allyl complex. The Ir(III)−π-allyl moiety undergoes nucleophilic attack by the indole C-3 with the assistance of a base, leading to the formation of dearomatized spiroindolenine intermediate **I**, which is converted to intermediate **II** in situ; the latter yields the corresponding product **5a** after aromatization. The proposed intermediate **I** is highly reactive and difficult to isolate. By means of in situ IR spectroscopy, the formation of **I** could be observed (see the Supporting Information for details).

In summary, we have developed a highly efficient synthesis of enantioenriched polycyclic indoles and pyrroles (up to 99% ee) through an Ir-catalyzed intramolecular asymmetric allylic alkylation reaction. Studies of the reaction mechanism led to the discovery of an unprecedented dearomatized spiro intermediate and an in situ migration pathway. The switch of the substituent from the indole C-3 position to the C-2 position (or from C-2 to C-3 in the case of pyrroles) provides a novel concept for the asymmetric construction of enantiopure polycyclic indoles and pyrroles via asymmetric catalysis. Further mechanistic studies on the dearomatization/migration process, the design of new migration patterns, and applications of this methodology are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; spectral data; and single-crystal X-ray diffraction data for **3a**, **3h**, **5e**, and **5g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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