Communication

# Enantioselective Functionalization of Indoles and Pyrroles via An in-situ Formed Spiro-intermediate

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# Enantioselective Functionalization of Indoles and Pyrroles *via* An in-situ Formed Spiro-intermediate

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*Supporting Information Placeholder*

**ABSTRACT:** Herein we report a highly enantioselective synthesis of polycyclic indoles and pyrroles with up to 99% *ee* by an iridium-catalytic system comprised of commercially available iridium precursor and 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 the switch of the substituent from the C-3 position of indole to the C-2 position (C-2 position to C-3 position in the case of pyrrole) without loss of the enantiomeric purity, providing a novel concept in designing 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 are in great demand in both organic and medicinal chemistry.

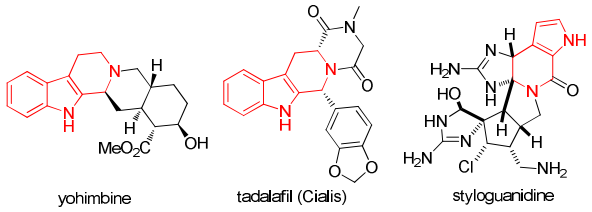
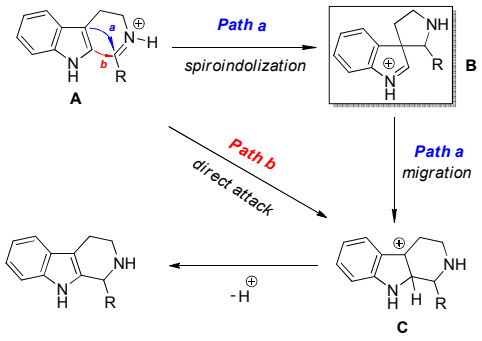



**Figure 1.** Selected naturally occurring compounds containing polycyclic indole or pyrrole units.

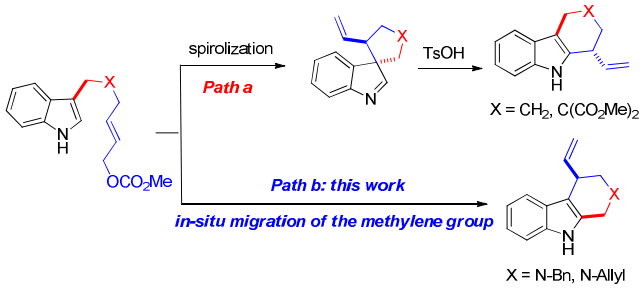
The Pictet-Spengler reaction has been recognized as one of the most direct and efficient methods for construction of tetrahydrocarboline frameworks[4]. Catalytic enantioselective Pictet-Spengler reaction witnessed significant progress during the past decade[5]. In addition, asymmetric intramolecular alkylation of indoles and pyrroles provide another straightforward access to polycyclic indole and pyrrole structures[6]. In this regard, transition-metal-catalyzed allylic alkylation reactions prove to be quite successful[7,8]. For the intramolecular alkylation of 3-indolyl substrates, in some cases, spiro-indolenine compounds were proposed as the intermediates and the alkylation at the C-2 position was attributed as a result of alkylation at the C-3 position followed by migration (Scheme 1, Path a)[9]. Evidences on the existence of the spiro-intermediate were also documented in the literature[10]. However, it remains a controversial topic whether asymmetric Pictet-Spengler reaction of indole substrates proceeds through dearomatized spiro-indolenine intermediates (**B**, Scheme 1)[11]. In addition, in the asymmetric intramolecular alkylation reactions of indoles, the spiro-indolenine formation received little attention. The fact that spiro-intermediate was overlooked could cause misunderstanding of the reaction mechanism and even the incorrect assignment of the alkylation products[12].




**Scheme 1.** Two alternative reaction pathways of Pictet-Spengler reaction.

As our continuous efforts to study transition-metal-catalyzed allylic alkylation reactions, we found that both indoles and pyrroles undergo allylic dearomatization reaction in an intramolecular fashion, providing various heterocycles bearing a quaternary carbon center[13,14]. Interestingly, the isolated five-membered spiro-indolenine products could further proceed 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 compared to the methylene group. With this information in hands, 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 Friedel-Crafts type allylic alkylation reaction in which the alkylation of indole at the C-3 position proceeds to afford spiro-indolenine followed by the migration of methanamine

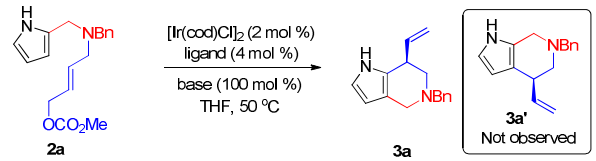
group to the C-2 position of indole (methanamine migration from C-2 position to C-3 position in pyrrole system). The process features the well-preserved enantiomeric purity during the migration process and provides a general strategy in construction of enantiopure polycyclic indoles and pyrroles.

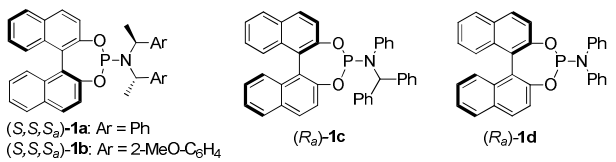


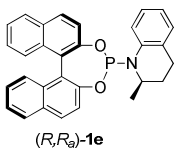

**Scheme 2.** Dearomatization of indole and controllable migration.

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

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



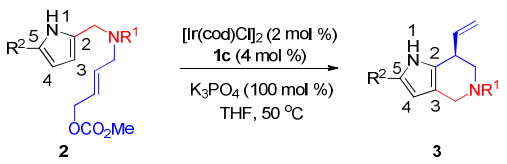



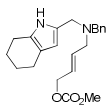
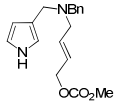




| entry | ligand | base | *t* (h) | conv. (%)[b,c] | *ee* (%)[d] |
|---|---|---|---|---|---|
| 1 | **1a** | $Cs_2CO_3$ | 16 | 72 | 87 |
| 2 | **1a** | $K_3PO_4$ | 16 | >95 | 89 |
| 3 | **1a** | $K_2CO_3$ | 19 | 78 | 89 |
| 4 | **1a** | $Li_2CO_3$ | 19 | 92 | 85 |
| 5 | **1a** | DBU | 16 | 60 | 85 |
|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

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

**Table 2**. The reaction substrate scope[a].

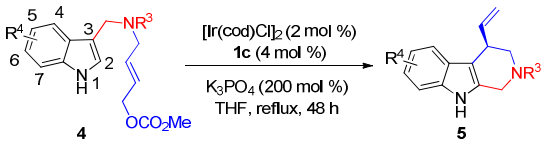



| entry | **2**, $R^1$, $R^2$ | time (h) | **3**, yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|
| 1 | **2a**, Bn, H | 34 | **3a**, 80 | 98 |
| 2 | **2b**, allyl, 4-Me-$C_6H_4$ | 58 | **3b**, 57 | 98 |
| 3 | **2c**, Bn, Ph | 34 | **3c**, 91 | 99 |
| 4[d] | **2d**, Bn, 4-MeO-$C_6H_4$ | 34 | **3d**, 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 % of $[Ir(cod)Cl]_2$, 4 mol % of **1c**, 0.2 mmol of **2**, 0.2 mmol of $K_3PO_4$ in THF (2.0 mL) at 50 °C. [b] Isolated yield of **3**. [c] Determined by HPLC analysis. [d] 3.5 mol % of $[Ir(cod)Cl]_2$, 7 mol % of **1c**, 2 equiv of $K_3PO_4$ were used.

With the above optimized reaction conditions in hand, various 2-pyrrolyl allylic carbonates were explored 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 and excellent *ee* (57-80% yields, 98% *ee*, entries 1-2, Table 2). Substrate bearing a phenyl group on the pyrrole core ($R^2$) reacted smoothly affording desired product **3c** in 91% yield and 99% *ee* (entry 3, Table 2). Next, the electron effect on the pyrrole core was probed. Substrates bearing either electron-donating [4-MeO, 3,4-$(MeO)_2$] (entries 4-5, Table 2) or electron-withdrawing groups (4-F, 4-Cl, 4-Br) (entries 6-8, Table 2) on the 5-phenyl moiety ($R^2$) on the pyrrole core all reacted to form their corresponding products in good to excellent yields and *ee* (75-95% yields, 97-99% *ee*). Notably, reaction occurred smoothly for substrates **2i** and **2j** in which alkyl goups are present at the pyrrole core (61-89% yields, 96-97% *ee,* entries 9-10, Table 2). Interestingly, when 3-pyrrolyl allylic carbonate **2k** was utilized, the reaction went smoothly affording product **3a** (the same product obtained when **2a** was used as a substrate) in excellent yield and *ee* (86% yield, 97% *ee*, entry 11, Table 2). The structure and stereochemistry of the products were confirmed unambiguously by an X-ray crystallographic analysis of a crystal of enantiopure **3h**. The absolute configuration was determined as (*S*).

**Table 3**. The reaction substrate scope[a].

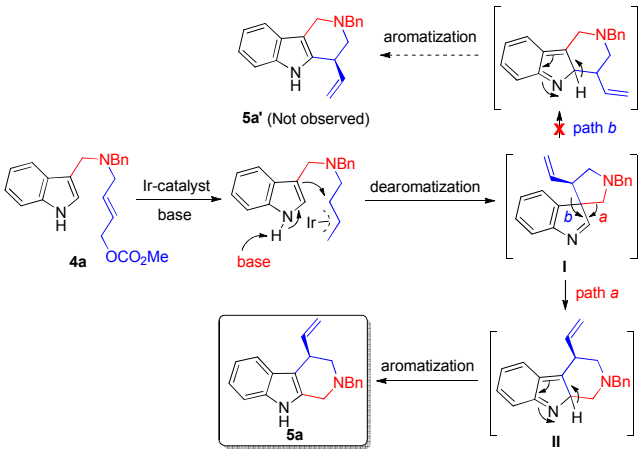



| entry | **4**, $R^3$, $R^4$ | **5**, yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|
| 1 | **4a**, Bn, H | **5a**, 80 | 96 |
| 2 | **4b**, allyl, H | **5b**, 63 | 88 |
| 3 | **4c**, Bn, 5-F | **5c**, 88 | 96 |
| 4 | **4d**, Bn, 5-Cl | **5d**, 80 | 94 |
| 5 | **4e**, Bn, 5-Br | **5e**, 74 | 94 |
| 6 | **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 % of $[Ir(cod)Cl]_2$, 4 mol % of **1c**, 0.2 mmol of **4**, 0.4 mmol of $K_3PO_4$ in THF (2.0 mL), refluxed. [b] Isolated yield of **5**. [c] Determined by HPLC analysis.

Next, we examined the generality of this asymmetric dearomatization/migration process with indole system. After a systematic study of the reaction conditions, the optimized conditions for the reaction are the following: 2 mol % of $[Ir(cod)Cl]_2$, 4 mol % of **1c**, 0.2 mmol of **4a**, 0.4 mmol of $K_3PO_4$ in refluxed THF (see the Supporting Information for details). Under these conditions, the substrate scope was then investigated for the asymmetric allylic dearomatization/migration reaction. The results are summarized in Table 3. Reactions of allylic carbonates varying protecting group (Bn, allyl) on nitrogen atom both gave the corresponding products in good yields with high levels of enantiocontrol (63-80% yields, 88-96% *ee*, entries 1-2, Table 3). Meanwhile, substrates bearing either electron-withdrawing group (5-F, 5-Cl, 5-Br, 6-Cl) (entries 3-6, Table 3) or electron-donating group (5-Me, 5-MeO, 6-MeO) (entries 7-9, Table 3) on the indole core all led to their corresponding products in good to excellent yields and *ee* (72-93% yields, 94-96% *ee*). The structure and stereochemistry of the products were determined by an X-ray crystallographic analysis of a crystal of enantiopure **5e**. The absolute configuration was determined as (*R*).

Based on the obtained experimental results, we proposed a plausible reaction pathway using indole-derived substrate **4a** as an example, as depicted in Scheme 3. Firstly, with the preformed iridium(I) catalyst, the oxidative addition of **4a** proceeds to generate Ir(III)-π-allyl complex. Ir(III)-π-allyl moiety receives the nucleophilic attack of the C-3 indole with the assistance of a base to lead to the formation of dearomatized spiro-indolenine intermediate **I**, which in-situ converted to intermediate **II**, and the latter yields the corresponding product **5a** after aromatization. The proposed intermediate **I** is highly reactive and difficult to isolate. By using the in-situ IR, the formation of the intermediate **I** could be observed (see the Supporting Information for details).




**Scheme 3.** Plausible reaction pathway

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 the in-situ migration pathway. The switch of the substituent from the C-3 position of indole to the C-2 position (C-2 position to C-3 position in the case of pyrrole) provides a novel concept in developing novel asymmetric construction of enantiopure polycyclic indoles and pyrroles in asymmetric catalysis. Further mechanistic studies on the dearomatization/migration process, design of new migration pattern and application of this methodology are currently underway in our laboratory.

## ASSOCIATED CONTENT

## Supporting Information

Experimental procedures and spectral data. Single crystal X-ray diffraction data for compounds **3a**, **3h**, **5e**, **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 interests.

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Graphic for TOC