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# Enantioselective Construction of Spiroindolenines by Ir-Catalyzed Allylic Alkylation Reactions

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***Abstract:*** With 2-methyl-1,2,3,4-tetrahydroquinoline-derived phosphoramidite ligand ($R$,$R_a$)-$\mathbf{L_6}$, Ir-catalyzed intramolecular C-3 allylic alkylation of indoles has been realized to afford highly enantioenriched spiroindolenine derivatives in 92−98% yields with up to >99/1 *dr* and 97% *ee*.

The spiroindolenine and spiroindoline units are privileged heterocyclic motifs that form the structural core for a large family of alkaloid natural products such as koumine, perophoramidine, and communesins.[1] Consequently, enormous efforts have been devoted to the development of efficient synthetic protocols for the construction of these skeletons.[2]

The synthesis of indolenines from indoles features a straightforward route and ready availability of starting materials but is faced with the difficulty of constructing a quaternary stereocenter *via* a dearomatization process.[3] In 2005, Tamaru and co-workers reported a C-3 selective Pd-catalyzed allylation of 1*H*-indoles promoted by triethylborane using allylic alcohols.[4] Soon after, Trost and Quancard described an enantioselective Pd-catalyzed C-3-alkylation of various 3-substituted indoles to construct a range of indolenine and indoline derivatives bearing quaternary stereocenters.[3b] Rawal and co-workers recently extended the reaction to 2,3-disubstituted indoles.[3c] Since Ir-catalysts have been successfully applied to the allylic alkylation of indoles at C-3 and N-1 by us and Hartwig,[5,6] we envisaged that the spiroindolenines might be accessed via Ir-catalyzed intramolecular allylic alkylation of indoles. As an inspiration, Bandini and co-workers reported a highly enantioselective Pd-catalyzed intramolecular allylic alkylation for the synthesis of tetrahydro-$\beta$-carbolines and tetrahydro-$\gamma$-carbolines (Scheme 1).[7] Recently, we found the spiroindolenine substructures could be formed through intramolecular allylic alkylation by extending the linker. Herein, we describe the first highly enantioselective synthesis of spiroindolenines via Ir-catalyzed asymmetric allylic alkylation reaction.

At the outset, we utilized a well-developed Ir-catalytic system including $[Ir(COD)Cl]_2$ and phosphoramidite $\mathbf{L_1}$ (Table 1) as catalyst.[8] In the presence of 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of $\mathbf{L_1}$, and 2 equiv of $Cs_2CO_3$, reaction of **1a** in THF for 1.5 h gave spiroindolenine **2a** in 70% yield, 76/24 *dr*, and 95% *ee* (entry 1, Table 1). Screening various bases, DABCO, $K_3PO_4$, DBU, $Et_3N$, DIEA, DBN, and BSA (entries 2−8, Table 1), confirmed that $Cs_2CO_3$ was optimal. Next, we examined several chiral ligands, as summarized in Table 1. Ligands $\mathbf{L_2}$, $\mathbf{L_3}$, and $\mathbf{L_5}$ could catalyze the reaction in excellent *ee*'s, but with only moderate *dr* ratios. To our delight, after screening two ligands developed in our group, $\mathbf{L_6}$ and $\mathbf{L_7}$,[5b] we found that catalyst derived from $\mathbf{L_6}$ gave satisfactory results in terms of yield, *dr*, and *ee* (entry 13, Table 1). Varying the solvent (DCM, toluene, dioxane, DME, and $Et_2O$) influenced the outcome considerably. Refluxed DCM gave the best result, affording **2a** in 95% yield, >99/1 *dr*, and 96% *ee* (entry 15, Table 1).

In the presence of 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of $\mathbf{L_6}$, and 2 equiv of $Cs_2CO_3$ under DCM reflux, various 3-indolyl allyl carbonates were tested to examine the generality of the reaction. The results are summarized in Table 2. Reaction of allylic carbonates with a varying protecting group on the linking N atom (Bn, *p*-Br-$C_6H_4CH_2$, Me, allyl) all gave the spiroindolenine products in good yields with

***Scheme 1.*** Pd- and Ir-Catalyzed Intramolecular Allylic Alkylation

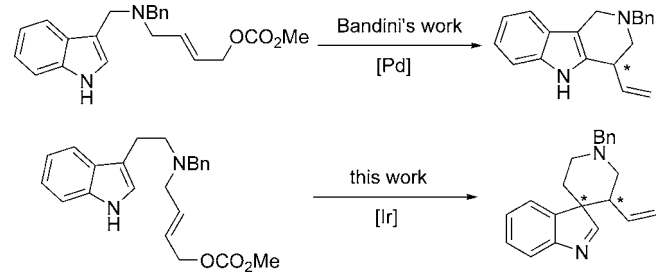
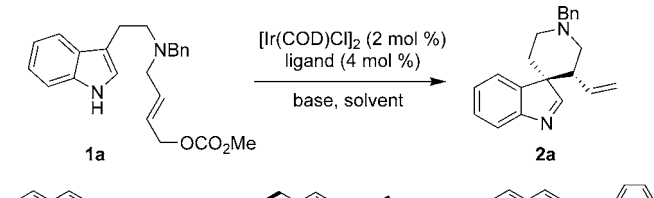
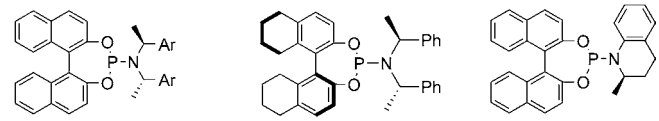



***Table 1.*** Optimization of the Reaction Conditions[a]




$\mathbf{L_1}$ ($S$, $S$, $S_a$), Ar = Ph
$\mathbf{L_2}$ ($S$, $S$, $S_a$), Ar = 2-MeO-$C_6H_4$
$\mathbf{L_3}$ ($S$, $S$, $S_a$), Ar = 2-naphthyl
$\mathbf{L_4}$ ($S$, $S$, $R_a$), Ar = Ph

$\mathbf{L_5}$ ($S$, $S$, $S_a$)

$\mathbf{L_6}$ ($R$, $R_a$)
$\mathbf{L_7}$ ($R$, $S_a$)

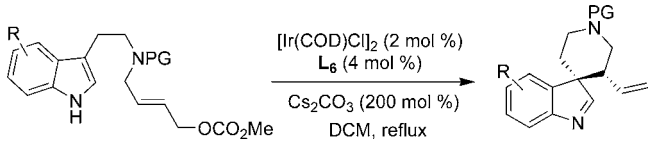
| entry | ligand | solvent | base | temp (°C) | $t$ (h) | yield (%)[b] | $dr$[c] | *ee* (%)[d] |
|---|---|---|---|---|---|---|---|---|
| 1 | $\mathbf{L_1}$ | THF | $Cs_2CO_3$ | 50 | 1.5 | 75 | 76/24 | 95 |
| 2 | $\mathbf{L_1}$ | THF | DABCO | 50 | 1.5 | 48 | 61/39 | 95 |
| 3 | $\mathbf{L_1}$ | THF | $K_3PO_4$ | 50 | 1.5 | 62 | 74/26 | 95 |
| 4 | $\mathbf{L_1}$ | THF | DBU | 50 | 1.5 | 68 | 68/32 | 95 |
| 5 | $\mathbf{L_1}$ | THF | $Et_3N$ | 50 | 1.5 | 63 | 77/23 | 95 |
| 6 | $\mathbf{L_1}$ | THF | DIEA | 50 | 1.5 | 67 | 66/34 | 95 |
| 7 | $\mathbf{L_1}$ | THF | DBN | 50 | 1.5 | 41 | 70/30 | 95 |
| 8 | $\mathbf{L_1}$ | THF | BSA | 50 | 1.5 | 56 | 75/25 | 95 |
| 9 | $\mathbf{L_2}$ | THF | $Cs_2CO_3$ | 50 | 1.5 | 74 | 84/16 | 96 |
| 10 | $\mathbf{L_3}$ | THF | $Cs_2CO_3$ | 50 | 1.5 | 72 | 81/19 | 93 |
| 11 | $\mathbf{L_4}$ | THF | $Cs_2CO_3$ | 50 | 24 | trace | | |
| 12 | $\mathbf{L_5}$ | THF | $Cs_2CO_3$ | 50 | 24 | 40 | >99/1 | 82 |
| 13 | $\mathbf{L_6}$ | THF | $Cs_2CO_3$ | 50 | 1.5 | 95 | 96/4 | 91 |
| 14 | $\mathbf{L_7}$ | THF | $Cs_2CO_3$ | 50 | 24 | 30 | 97/3 | 80[e] |
| 15 | $\mathbf{L_6}$ | DCM | $Cs_2CO_3$ | reflux | 1.5 | 95 | >99/1 | 96 |
| 16 | $\mathbf{L_6}$ | toluene | $Cs_2CO_3$ | 50 | 1.5 | 84 | >99/1 | 93 |
| 17 | $\mathbf{L_6}$ | dioxane | $Cs_2CO_3$ | 50 | 1.5 | 73 | 90/10 | 86 |
| 18 | $\mathbf{L_6}$ | DME | $Cs_2CO_3$ | 50 | 1.5 | 60 | 94/6 | 90 |
| 19 | $\mathbf{L_6}$ | $Et_2O$ | $Cs_2CO_3$ | reflux | 1.5 | 85 | >99/1 | 93 |

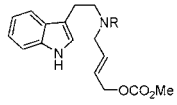
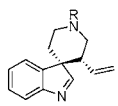
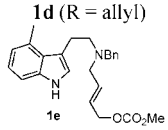
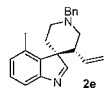
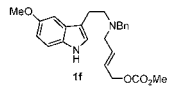
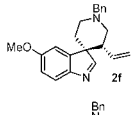
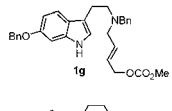
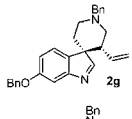
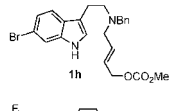
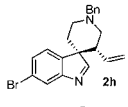
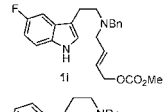
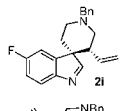
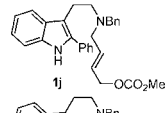
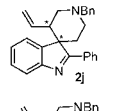
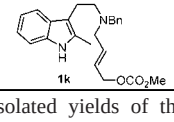
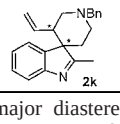
[a] Reaction conditions: 0.2 mmol of **1a**, 0.4 mmol of base in solvent (1.0 mL). [b] Isolated yield of the major diastereoisomer. [c] Determined by $^1$H NMR of the crude reaction mixture. [d] Determined by chiral HPLC analysis. [e] Product with opposite configuration was obtained.



**10.1021/ja105111n** 

***Table 2.*** Reaction Substrate Scope




| entry | substrate | product | yield (%)[a] | *dr*[b] | *ee* (%)[c] |
|---|---|---|---|---|---|
| 1 |  **1a** (R = Bn) |  **2a** | 95 | >99/1 | 96 |
| 2 | **1b** (R = *p*-Br-$C_6H_4CH_2$) | **2b** | 92 | 96/4 | 95 |
| 3 | **1c** (R = Me) | **2c** | 95 | >99/1 | 96 |
| 4 | **1d** (R = allyl) | **2d** | 93 | 96/4 | 96 |
| 5 |  **1e** |  **2e** | 97 | >99/1 | 93 |
| 6 |  **1f** |  **2f** | 98 | >99/1 | 94 |
| 7 |  **1g** |  **2g** | 93 | 96/4 | 94 |
| 8 |  **1h** |  **2h** | 95 | >99/1 | 93 |
| 9 |  **1i** |  **2i** | 93 | 97/3 | 88 |
| 10 |  **1j** |  **2j** | 68/ 20[d] | 75/25 | 93/91 |
| 11 |  **1k** |  **2k** | 50/ 40[d] | 58/42 | 97/97 |

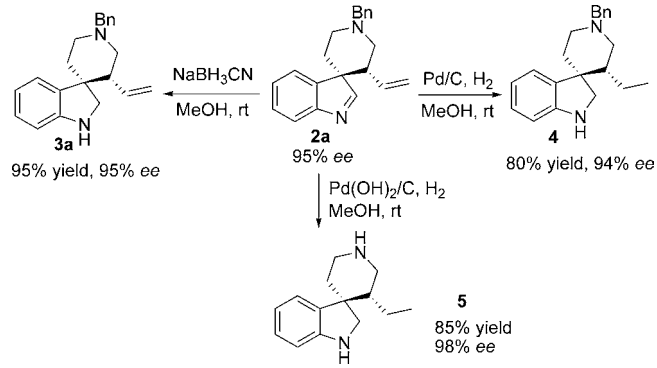
[a] Isolated yields of the major diastereoisomer. [b] Determined by $^1$H NMR of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] Isolated yields of the minor diastereoisomer.

excellent *dr* and *ee* (92−95% yields, 96/4→99/1 *dr*, 95−96% *ee*, entries 1−4, Table 2). Notably, the allyl protecting group in **1d** did not interfere with the alkylation process. The stereochemistry of the products was determined by X-ray structural determination of their enantiopure bromine-containing derivatives.[9] Substrates bearing either an electron-donating group (4-Me, 5-MeO, 6-BnO) (entries 5−7, Table 2) or electron-withdrawing group (6-Br, 5-F) (entries 8−9, Table 2) on the indole core all led to their corresponding products in excellent yields, *dr*, and *ee* (93−98% yields, 96/4→99/1 *dr*, 88−94% *ee*). The 2-substituted indolyl allyl carbonates were also tolerated and afforded the corresponding products in excellent yields and *ee* (88−90% yields, 91−97% *ee*, entries 10−11, Table 2), although in moderate *dr*.

To test the five-member ring spiroindolenine formation, Bandini's substrate, by shortening one carbon in **1a** (as shown in Scheme 1),[7] was tested in the current catalytic system. Interestingly, tetrahydro-$\gamma$-carboline product was obtained,[9] which suggests the formation of spiroindolenine is likely caused by the favorable six-member ring product by reacting at the C-3 position over the seven-member ring product at the C-2 position.

The multifunctionalized spiroindolenine products obtained here could undergo versatile transformation. As shown in Scheme 2,

***Scheme 2.*** Transformation of Product **2a**




treatment of **2a** with sodium cyanoborohydride afforded the spiroindoline **3**. The C═C and C═N could be reduced by Pd/C catalyzed hydrogenation to give spiroindoline **4**. Interestingly, for $Pd(OH)_2$/C catalyzed hydrogenation, the Bn group was also removed. In all cases, there was no notable loss of the optical purity.[10]

In summary, we have developed a highly enantioselective synthesis of spiroindolenine derivatives via Ir-catalyzed intramolecular C-3 allylic alkylation of indoles. The spiroindolenine derivatives were obtained in excellent yields with up to >99/1 *dr* and 97% *ee*. Further extension of the reaction scope and development of more efficient catalytic systems are currently underway in our laboratory.

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**Supporting Information Available:** Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) See the Supporting Information (SI).

(10) The *ee* of **4** and **5** were determined after their conversion to N-Ts derivatives (see the SI for details).

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