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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-β-carbolines and tetrahydro-γ-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

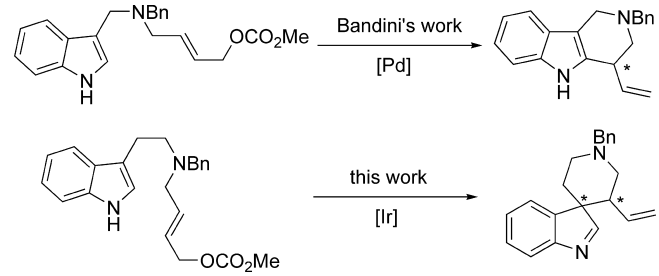
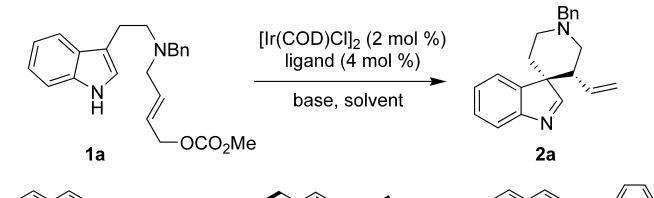
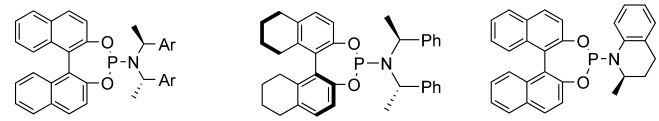


Table 1. Optimization of the Reaction Conditions[a]





$\mathbf{L_1}$ (*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.

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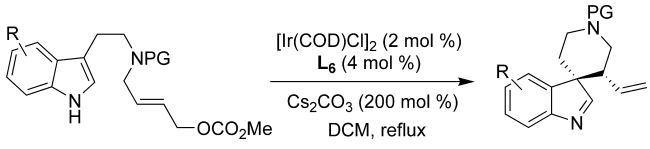
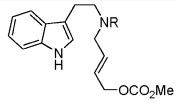
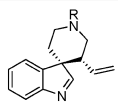
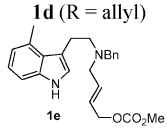
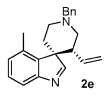
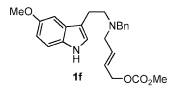
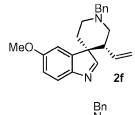
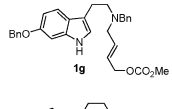
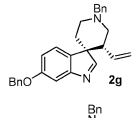
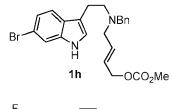
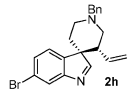
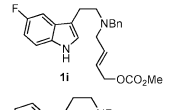
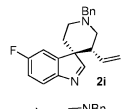
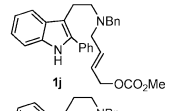
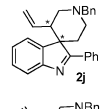
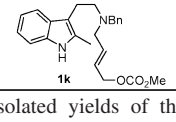
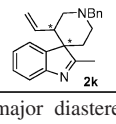
Table 2. Reaction Substrate Scope



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

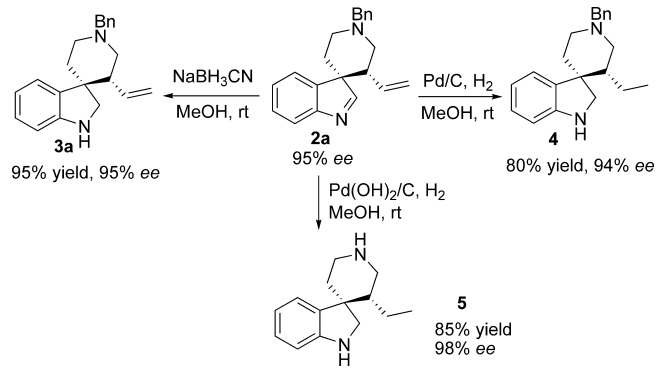
[a] Isolated yields of the major diastereoisomer. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] Isolated yields of the minor diastereoisomer.

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-γ-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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