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Highly Enantioselective Synthesis of Tetrahydrocarbolines *via* Iridium-Catalyzed Intramolecular Friedel–Crafts Type Allylic Alkylation Reactions

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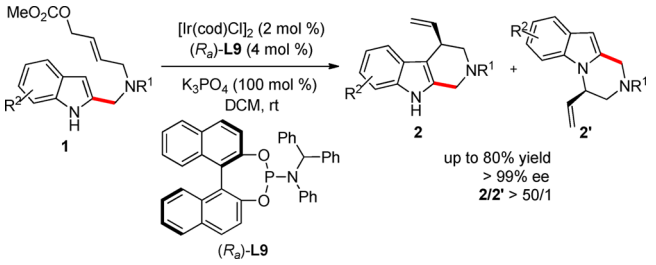
ABSTRACT



A highly enantioselective synthesis of substituted tetrahydrocarbolines *via* Ir-catalyzed Friedel–Crafts type intramolecular asymmetric allylic alkylation of 2-indolyl allyl carbonates has been developed. This strategy features excellent chemoselectivity and enantioselectivity, mild reaction conditions, and an easily accessed chiral ligand.

The substituted indole nucleus is a common component of a vast number of biologically active natural products and pharmaceuticals.[1] Particularly, the tetrahydrocarboline scaffold is among the privileged heterocycles. Therefore, the functionalization of indole and synthesis of tetrahydrocarboline derivatives have been an intense subject in chemical research, and various methods are now available.[2,3] To be noted, the asymmetric Friedel–Crafts reactions including the Pictet–Spengler reactions have been the most successful approach for the synthesis of tetrahydrocarboline derivatives.[4] On the other hand, despite the fact that a transition-metal-catalyzed asymmetric allylic substitution reaction has been widely studied,[5,6] only a few examples of Friedel–Crafts type asymmetric allylic alkylation reactions have been reported to date.[7]

Recently, we reported an efficient synthesis of tetrahydrocarbolines by an iridium-catalyzed asymmetric allylic dearomatization/migration sequence of 3-indolyl

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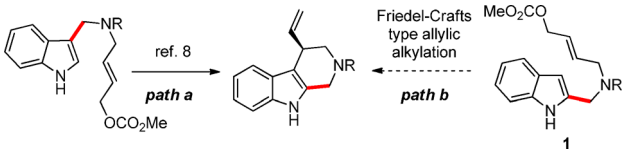
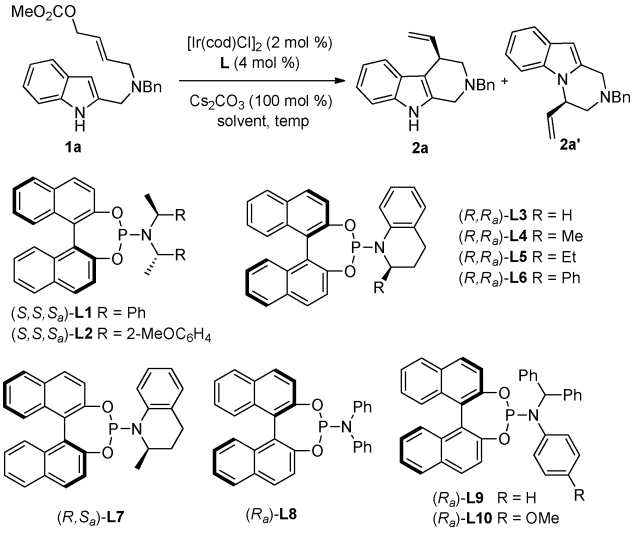
allyl carbonates (Scheme 1, path a).[8] The reaction proceeded *via* a dearomatized spiro-indolenine intermediate, featuring the switch of the substituent from the C3 to the C2 position of the indole. Given the high reactivity of the C3 position of indole, we envisaged, by utilizing the 2-indoyl allyl carbonate **1** as the substrate, the chiral tetrahydrocarboline framework could also be easily accessed *via* the iridium-catalyzed intramolecular Friedel–Crafts type allylic alkylation reaction (Scheme 1, path b). The two approaches utilized different starting materials but led to identical products. Herein, we describe such a highly enantioselective synthesis of substituted tetrahydrocarbolines *via* Ir-catalyzed Friedel–Crafts type intramolecular asymmetric allylic alkylation of 2-indolyl allyl carbonates.

Scheme 1. Different Approaches for the Synthesis of Chiral Tetrahydrocarboline Frameworks



To begin the study, indoyl allyl carbonate **1a** was taken as the model substrate for optimizing the reaction conditions. First, different bases were tested in the reaction with an iridium-catalytic system derived from $[Ir(cod)Cl]_2$ and phosphoramidite ligand **L1** (Table 1).[9,10] To our great delight, with either Cs_2CO_3 or K_3PO_4 as the base, the reaction proceeded with excellent chemoselectivity in favor of the alkylation product, delivering the tetrahydrocarboline **2a** in excellent yields and enantioselectivity (82–86% yields, 85% ee, entries 1–2, Table 1). Notably, the reaction also occurred smoothly in 74% yield and 85% ee in the absence of an additional base (entry 3, Table 1).

Table 1. Optimization of Reaction Conditions[a]



entry	L	solvent	temp (°C)	*t* (h)	conv (%)[b]	**2a**/**2a'**[b]	yield (%)[c]	ee (%)[d]
1	**L1**	THF	50	3	>95	50/1	82	85
2[e]	**L1**	THF	50	3	>95	20/1	86	85
3[f]	**L1**	THF	50	5	85	>50/1	74	85
4	**L2**	THF	50	2	>95	3.5/1	58	–
5	**L3**	THF	50	21	57	50/1	–	–
6	**L4**	THF	50	2	>95	>50/1	81	90
7	**L5**	THF	50	2	>95	>50/1	79	84
8	**L6**	THF	50	2	>95	>50/1	90	81
9	**L7**	THF	50	2	>95	>50/1	64	−83
10	**L8**	THF	50	2	>95	>50/1	85	80
11	**L9**	THF	50	2	>95	>50/1	80	92
12	**L10**	THF	50	2	>95	>50/1	88	85
13	**L9**	THF	rt	2.5	>95	>50/1	81	96
14[e]	**L9**	THF	rt	2.5	>95	>50/1	84	96
15[e]	**L9**	toluene	rt	2.5	>95	>50/1	76	98
16[e]	**L9**	Et_2O	rt	2	>95	>50/1	74	99
17[e]	**L9**	CH_2Cl_2	rt	2	>95	>50/1	80	>99

[a] Reaction conditions: 2 mol % of $[Ir(cod)Cl]_2$, 4 mol % of **L**, 0.2 mmol of **1a**, and 100 mol % of Cs_2CO_3 in solvent (2 mL), unless noted otherwise. [b] Determined by ^1H NMR of the crude reaction mixture. [c] Isolated yield of **2a**. [d] Determined by HPLC analysis. [e] 100 mol % of K_3PO_4 was used. [f] No base was used in the reaction.

With Cs_2CO_3 as the base, different ligands were then examined. The results are summarized in Table 1. All ligands led to the complete conversion affording the desired product **2a**, except for **L3** with only 57% conversion (entries 4–12, Table 1). The reaction with ligand **L9** gave the best enantioselectivity (entry 11, Table 1).[11] Interestingly, when

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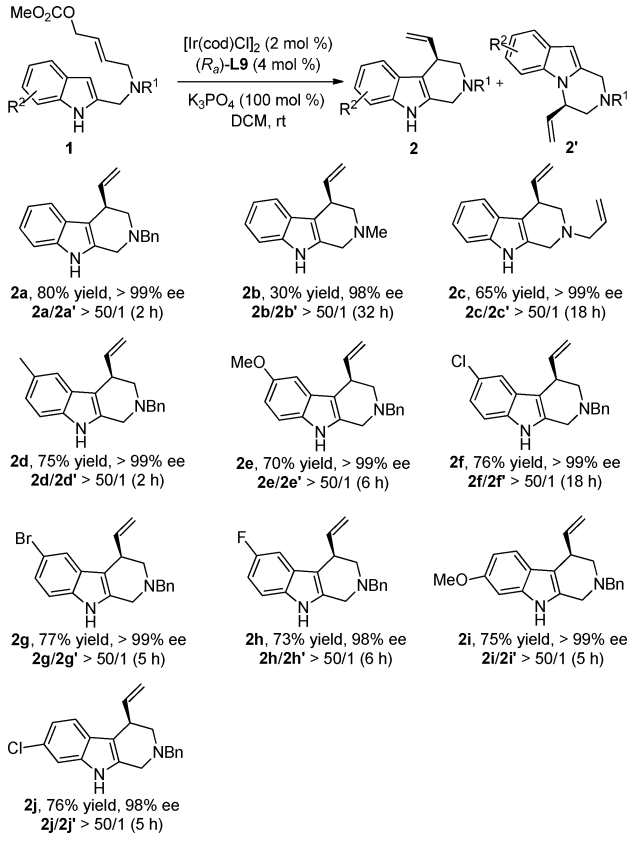
Scheme 2. Reaction Substrate Scope[a]



[a] Reaction conditions: 2 mol % of $[Ir(cod)Cl]_2$, 4 mol % of (R_a)-**L9**, 0.2 mmol of **1**, and 100 mol % of K_3PO_4 in DCM (2 mL) at rt. **2**/**2′** ratios were determined by ^1H NMR analysis of the crude reaction mixture. Ee value of **2** was determined by HPLC analysis.

the reaction was run at room temperature, the enantioselectivity of the product was increased to 96% ee (entry 13, Table 1). With K_3PO_4 as the base, the yield can be further improved to 84% with 96% ee (entry 14, Table 1). In addition, several additional solvents (toluene, Et_2O, and CH_2Cl_2) were tested, and all led to the formation of the desired product **2a** in excellent enantioselectivity (98−> 99% ee, entries 15−17, Table 1). After the optimization study, the optimized conditions were obtained as follows: **1a** in DCM (0.1 M), 2 mol % of $[Ir(cod)Cl]_2$, 4 mol % of **L9**, 1.0 equiv of K_3PO_4 at rt. Under these reaction conditions, product **2a** was obtained in 80% yield and > 99% ee (entry 17, Table 1).

Under the optimized reaction conditions, the substrate scope of the reaction was explored. The results are summarized in Scheme 2. As to substituents on the nitrogen linkage, Bn, Me, and allyl groups could be well tolerated delivering alkylated products (**2a**−**2c**) in excellent enantioselectivity (98−> 99% ee). The reactions of 5-substituted indole substrates generated the products (**2d**−**2h**) in good yields (70−77%) and excellent enantioselectivity (98−> 99% ee). Substrates bearing either an electron-donating group (MeO) or an electron-withdrawing group (Cl) at the 6-position of indole could be employed in the reaction, and the products were obtained in good yields with excellent enantioselectivity (**2i**−**2j**, 75−76% yields, 98−> 99% ee). To further confirm the absolute configuration of the product, an X-ray crystallographic analysis of a derivative of the enantiopure compound **2j** disclosed the absolute configuration as (*R*) (see the Supporting Information for details), which is consistent with the previous study.[8]

In summary, we have developed an efficient iridium-catalyzed Friedel−Crafts type intramolecular asymmetric allylic alkylation reaction of 2-indolyl allyl carbonates, affording tetrahydrocarboline derivatives in moderate to good yields as well as excellent chemoselectivity and enantioselectivity. The products obtained in this study from 2-indolyl allyl carbonates are identical with those from the 3-indolyl allyl carbonates with higher enantioselectivity. The reaction features mild reaction conditions, excellent chemo- and enantioselectivity, and the utilization of an easily accessed ligand.

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Supporting Information Available. Experimental procedures and analysis data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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