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Enantioselective Synthesis of Tetrahydroisoquinolines via Iridium-Catalyzed Intramolecular Friedel–Crafts-Type Allylic Alkylation of Phenols

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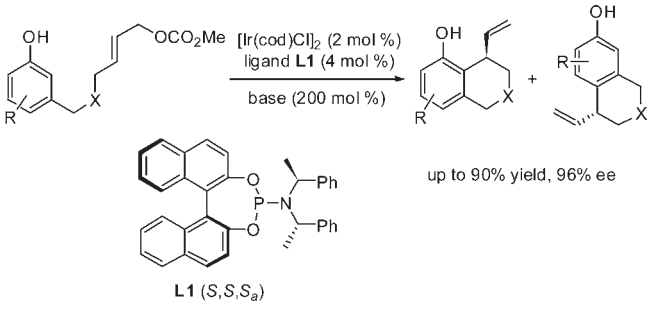
ABSTRACT



An efficient iridium-catalyzed intramolecular Friedel–Crafts-type allylic alkylation reaction of phenols was developed, affording tetrahydroisoquinolines with moderate to excellent yields, enantioselectivity, and good regioselectivity.

Phenols are cheap and abundant chemical feedstock widely used in chemical industry and academic laboratories.[1] They also serve as nucleophiles in transition-metal-catalyzed allylic substitution reactions.[2] Transition-metal-catalyzed allylic substitution reactions with phenols generally proceed as *O*-allylation.[3−6] There are only limited examples of *C*-allylation where phenols proceed as Friedel–Crafts-type alkylation reactions. To date, Pd-,[7] Mo-,[8] Ru-,[9] Rh-,[10] and Au-type[11] catalysts have been reported to catalyze the Friedel–Crafts-type allylic alkylation of phenols.[12]

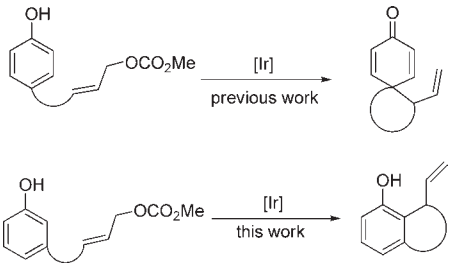


Figure 1. Intramolecular allylic dearomatization and Friedel–Crafts alkylation of phenols.

However, all these known procedures are limited with racemic synthesis,[13] even with poor regioselectivity on phenol rings in many cases. As part of our ongoing efforts toward iridium-catalyzed allylic substitution reactions,[14] we recently realized the Ir-catalyzed intramolecular asymmetric allylic dearomatization reaction of phenols by tethering allylic carbonate at the *para*-position (Figure 1).[15] In this paper, we report an iridium-catalyzed asymmetric

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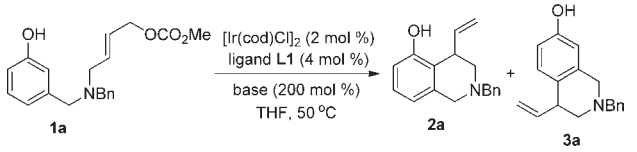
intramolecular Friedel–Crafts-type allylic alkylation reaction of phenols by tethering the allylic carbonate at the *meta*-position. This reaction provides a facile access to enantioenriched tetrahydroisoquinoline derivatives.

In our initial investigation, allyl carbonate tethered phenol **1a** was chosen as a model substrate. In the presence of 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of phosphoramidite ligand **L1**, and 200 mol % of Cs_2CO_3, reaction of **1a** in THF for 10 h gave Friedel–Crafts-type allylic alkylation product **2a** in 68% yield and 90% ee (entry 1, Table 1). Encouraged by this result, we screened readily available bases and solvents. The results are summarized in Table 1. Various solvents such as THF, CH_2Cl_2, toluene, CH_3CN, ether, DME, dioxane, and DCE were examined. All of the solvents could be tolerated in the reaction, and ether-type solvents such as THF, dioxane, ether, and DME gave the product with high enantioselectivity (entries 1, 3, 6, and 8, Table 1). With THF as the solvent, various bases including inorganic and organic ones could be tolerated to afford product **2a** with excellent enantioselectivity (90–93% ee), except for BSA (entry 15, Table 1). Notably, the reaction with DMAP as a base gave overall the best combination of isolated yield and selectivities (**2a**/**3a**: 4.7/1, yield of **2a**: 68%, ee of **2a**: 91%, entry 16, Table 1).

Table 1. Screening Different Bases and Solvents[a]



entry	base	solvent	time (h)	conv[b] (%)	**2a**/**3a**[b]	yield (%) (**2a**)[c]	ee[d] (%)
1	Cs_2CO_3	THF	10	100	4.8/1	68	90
2	Cs_2CO_3	DCM	5	100	1.8/1	47	25
3	Cs_2CO_3	dioxane	5	100	7.3/1	65	90
4	Cs_2CO_3	MeCN	5	100	1.0/1	40	62
5	Cs_2CO_3	DCE	5	100	1.5/1	50	30
6	Cs_2CO_3	Et_2O	6	100	9.0/1	67	84
7	Cs_2CO_3	toluene	6	100	9.2/1	62	58
8	Cs_2CO_3	DME	6	100	4.8/1	67	89
9	K_3PO_4	THF	10	100	3.5/1	47	91
10	Li_2CO_3	THF	20	58	2.5/1	34	92
11	KOAc	THF	10	100	3.5/1	55	92
12	K_2CO_3	THF	10	100	4.0/1	64	91
13	Et_3N	THF	10	80	5.0/1	51	91
14	DBU	THF	10	100	5.3/1	49	93
15	BSA	THF	10			NR	
16	DMAP	THF	10	100	4.7/1	68	91

[a] Reaction conditions: 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of **L1**, 0.2 mmol of **1a**, and 200 mol % base in solvent (2 mL). [b] Determined by ^1H NMR of the crude reaction mixture. [c] Isolated yield of **2a**. [d] Determined by HPLC analysis.

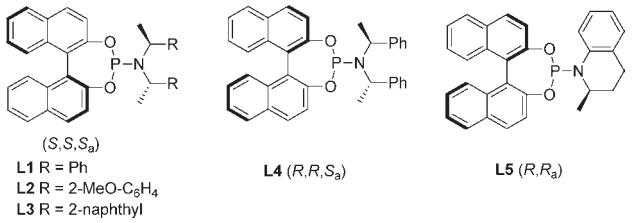


Figure 2. Ligands used in the present work.

Under the above conditions (entry 16, Table 1), several ligands were further evaluated (Figure 2). The results are summarized in Table 2. The results suggested that ligands **L1**–**L3** could be employed for the reaction, giving similar results (entries 1–3, Table 2). The catalyst derived from **L4**, a diastereoisomer of **L1**, could catalyze the reaction in a lower yield and enantioselectivity (36% yield, 88% ee, entry 4, Table 2). Ligand **L5** was tested but afforded only a trace amount of product (entry 5, Table 2). When the reaction was run at room temperature with ligand **L1**, the product was obtained with slightly higher enantioselectivity (92% ee, entry 6, Table 2).

Under the optimized reaction conditions [2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of **L1**, 200 mol % of DMAP,

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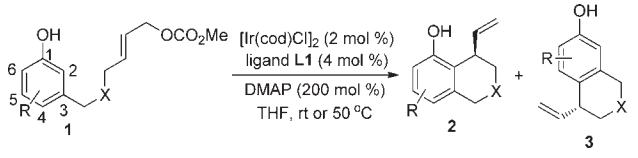
Table 2. Screening Different Ligands and Temperature[a]

entry	ligands	conv[b] (%)	**2a**/**3a**[b]	yield (%) (**2a**)[c]	ee[d] (%)
1	**L1**	100	4.7/1	68	91
2	**L2**	100	2.0/1	55	92
3	**L3**	100	4.6/1	73	89
4	**L4**	32	4.0/1	26	88
5	**L5**			trace	ND
6[e]	**L1**	100	4.8/1	68	92

[a] Reactions were conducted under the conditions of entry 16, Table 1. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Isolated yield of **2a**. [d] Determined by HPLC analysis. [e] Room temperature.

Table 3. Substrate Scope[a]



entry	**1**, R	yield[b] (%)	**2**/**3**[c]	ee[d] (%)
1	**1a**, X = NBn, R = H	84	4.8/1	92
2	**1b**, X = N-allyl, R = H	88	6.0/1	92
3	**1c**, X = NBn, R = 2-MeO	72	**3c**[g]	93
4	**1d**, X = NBn, R = 2-Cl	80	**3d**[g]	94
5	**1e**, X = NBn, R = 6-MeO	82	4.0/1	95
6[e]	**1f**, X = NBn, R = 6-NO_2	25	**2f**[h]	93
7[e]	**1g**, X = NBn, R = 4-Br	78	**2g**[g]	89
8[e]	**1h**, X = NBn, R = 2-Br, 6-MeO	50	**3h**[g]	96
9[e]	**1i**, X = NBn, R = 4-Br, 6-MeO	80	**2i**[g]	92
10	**1j**, X = NBn, R = 5-OH	90	**2j**[g]	86
11	**1k**, X = NBn, R = 5-OH, 6-MeO	86	**2k**[g]	88
12[f]	**1l**, X = C(COOMe)$_2$, R = H	87	4.0/1	91

[a] Reactions were conducted under the conditions of entry 6, Table 2. [b] Isolated yield of **2** and **3**. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] Determined by HPLC analysis. [e] 50 °C. [f] Using 200 mol % of Cs_2CO_3, and dioxane (2 mL), at 50 °C. [g] Isolated as a single isomer. [h] Ratio of **2**/**3** was not determined by ^{1}H NMR.

THF, rt], various substrates were tested to examine the scope of the reaction. The results are summarized in Table 3. Both benzyl and allyl groups on the linked nitrogen atom could be well tolerated to deliver alkylated products in excellent enantioselectivity (92% ee) (entries 1 and 2, Table 3). Substrates bearing either electron-withdrawing or electron-donating groups at the 2-, 4-, or 6-position of phenol were tested in the reaction. When a substituent was introduced at the 2-position of the phenol, the allylic alkylation reaction proceeded smoothly to afford a single regioisomer by reacting at the *para*-position of the phenols. In all cases, excellent enantioselectivity was obtained (2-MeO, 93% ee, entry 3; 2-Cl, 94% ee, entry 4; 2-Br, 6-MeO, 96% ee, entry 8). When a substituent was introduced at the 4 or 5 position of the phenol ring, a single isomer of **2** was obtained with good to excellent yields and ee values (4-Br,

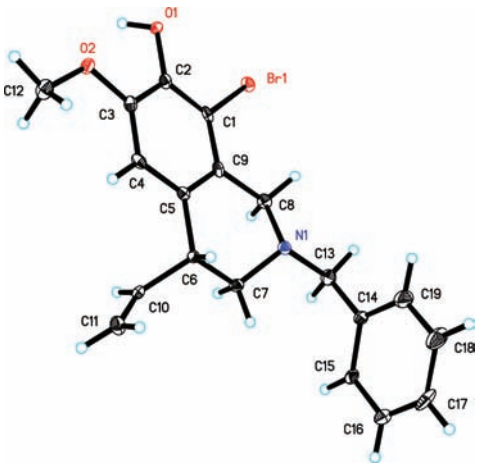


Figure 3. ORTEP representation of enantiopure (*R*)-**3h** (thermal ellipsoids are set at 30% probability).

78% yield, 89% ee, entry 7; 4-Br, 6-MeO, 80% yield, 92% ee, entry 9; 5-OH, 90% yield, 86% ee, entry 10; 5-OH, 6-MeO, 86% yield, 88% ee, entry 11). Notably, two hydroxyl groups were well tolerated. With a strong electron-withdrawing group (6-NO_2) on the phenol scaffold, the product was obtained with only 25% yield, but excellent enantioselectivity (93% ee) (entry 6, Table 3). The carbon-tethered phenol **1l** was also a suitable substrate, affording the product in 87% yield with 4.0/1 regioselectivity and 91% ee, under the conditions of 200 mol % Cs_2CO_3, and dioxane (2 mL), 50 °C (entry 12, Table 3).

To determine the absolute configuration of the product, an X-ray crystallographic analysis of enantiopure bromine-containing compound **3h** disclosed the configuration as *R* (Figure 3).

In summary, we have developed an efficient iridium-catalyzed intramolecular Friedel–Crafts-type allylic alkylation reaction of phenols, affording tetrahydroisoquinolines with moderate to excellent yields, enantioselectivity and regioselectivity.

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Note Added after ASAP Publication. Compound **2h** was changed to **3h** in the Figure 3 caption, the last line of the second to last paragraph of the main text on p 3, and the second to last line of the right column on p 3, the correct version reposted May 1, 2012.

Supporting Information Available. Detailed experimental procedures and spectroscopic data for all new compounds and X-ray crystal data of (*R*)-**3h**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.