Asymmetric Dearomatization

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Iridium-Catalyzed Intramolecular Asymmetric Allylic Dearomatization of Phenols**

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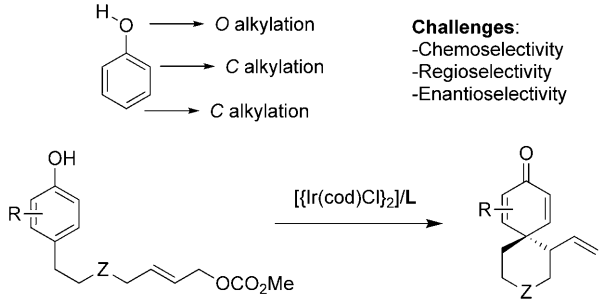
Dearomatization reactions provide the most direct synthesis of ring systems starting from readily available aromatic compounds.[1] The combination of a dearomatization reaction with asymmetric synthesis would lead to the enantioselective construction of carbocyclic and heterocyclic derivatives.[2] Despite progress in this area, the reported methods have so far focused on a stepwise protocol, which involves the dearomatization process and a subsequent asymmetric reaction.[3] The direct asymmetric dearomatization reaction where the dearomatization and asymmetric catalysis occur in one step is highly desirable but very challenging.[4]

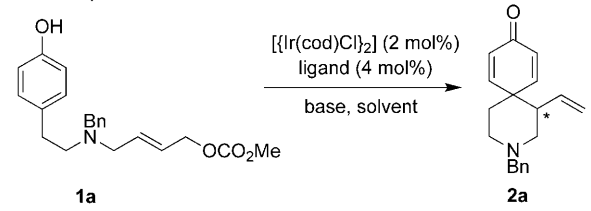
As part of our recent studies on iridium-catalyzed allylic substitution reactions,[5–7] we found that iridium-catalyzed intramolecular asymmetric allylic alkylation of indole provided enantioenriched spiroindolenine compounds.[8]

Phenols are cheap and abundant chemicals widely used in organic synthesis. Transition-metal-catalyzed allylic alkylation reactions of phenols generally proceeds as O allylation[9] with limited examples of C allylation.[9c,10] Despite the challenges of chemo-, regio-, and enantio-selectivity, we recently envisaged that phenols might function as carbon nucleophiles in the iridium-catalyzed intramolecular allylic dearomatization reactions (Scheme 1). This protocol would provide a direct access to enantiopure spirocyclohexadienones, which serve as a popular structural core in numerous biologically interesting natural products and pharmaceuticals.

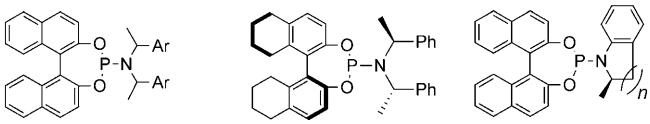


Scheme 1. Iridium-catalyzed asymmetric allylic dearomatization of phenols. cod = cycloocta-l,5-diene.

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



1a **2a**



L1 (*S, S, Sa*), Ar = Ph
L2 (*S, S, Sa*), Ar = 2-MeOC$_6$H$_4$
L3 (*S, S, Sa*), Ar = 2-naphthyl
L4 (*R, R, Sa*), Ar = Ph

L5 (*S, S, Sa*)

L6 (*R, Ra*) *n* = 2
L7 (*R, Sa*) *n* = 2
L8 (*R, Ra*) *n* = 1
L9 (*R, Sa*) *n* = 1

Entry	Ligand	Solvent	Base	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**L1**	THF	Cs_2CO_3	50	65	92
2	**L1**	CH_2Cl_2	Cs_2CO_3	reflux	80	44
3	**L1**	1,4-dioxane	Cs_2CO_3	50	65	92
4	**L1**	DME	Cs_2CO_3	50	59	90
5	**L1**	Et_2O	Cs_2CO_3	reflux	52	66
6	**L1**	THF	Li_2CO_3	50	70	93
7	**L1**	THF	KOAc	50	65	93
8	**L1**	THF	DMAP	50	63	93
9	**L1**	THF	DABCO	50	45	92
10	**L1**	THF	DIEA	50	50	93
11	**L1**	THF	DBU	50	63	92
12	**L1**	THF	Et_3N	50	64	94
13	**L1**	THF	KHMDS	50	52	93
14	**L2**	THF	Li_2CO_3	50	68	96
15	**L3**	THF	Li_2CO_3	50	60	92
16	**L4**	THF	Li_2CO_3	50	55	90
17	**L5**	THF	Li_2CO_3	50	trace	–
18	**L6**	THF	Li_2CO_3	50	75	57
19	**L7**	THF	Li_2CO_3	50	50	59[d]
20	**L8**	THF	Li_2CO_3	50	48	69
21	**L9**	THF	Li_2CO_3	50	trace	–

[a] Reaction conditions: 0.2 mmol of **1a**, 0.4 mmol of base in solvent (2.0 mL), 24 h. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] Product with opposite configuration was obtained. Bn = benzyl, DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIEA = *N*,*N*-diisopropylethylamine, DMAP = 4-dimethylaminopyridine, DME = 1,2-dimethoxyethane, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, THF = tetrahydrofuran.

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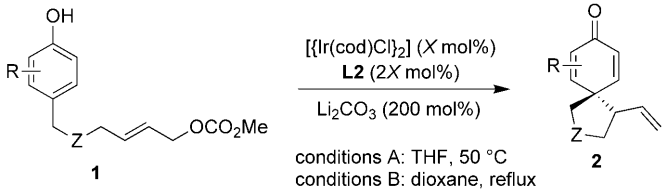
Herein, we report the first iridium-catalyzed asymmetric allylic dearomatization reaction of phenols, leading to the substituted spirocyclohexadienones with up to 97% *ee*.[11] The reaction features readily available starting materials and synthetically challenging products.

We began our studies by testing substrate **1a** with the iridium-catalytic system derived from [{Ir(cod)Cl}$_2$] and phosphoramidite ligand **L1** (Table 1). Pleasingly, in the presence of 2 mol% of [{Ir(cod)Cl}$_2$], 4 mol% of **L1**, and 2 equivalents of Cs_2CO_3, the reaction of **1a** in THF at 50°C for 24 hours gave **2a** in 65% yield with 92% *ee* (Table 1, entry 1). After screening solvents such as CH_2Cl_2, 1,4-dioxane, DME, and Et_2O, we found that THF and 1,4-dioxane were the optimal solvents in terms of yield and *ee* (Table 1, entries 2–5). Next, various bases were examined, as summarized in Table 1, entries 6–13. A variety of bases such as Li_2CO_3, KOAc, DMAP, DABCO, DIEA, DBU, Et_3N, and KHMDS showed that using Li_2CO_3 gave the best yield (Table 1, entry 6). Notably, dearomatization product **2a** was obtained with excellent *ee* for all the bases tested. Further screening of the phosphoramidite ligands (Table 1, entries 14–21) led to the identification of 2-MeO-substituted ligand **L2** as the best, and afforded **2a** in 68% yield and 96% *ee* (Table 1, entry 14). The reaction with ligand **L6**, the best one in iridium-catalyzed intramolecular asymmetric allylic alkylation of indoles, gave the best yield but only moderate enantioselectivity (57% *ee*; Table 1, entry 18).

With the appropriate iridium-catalyst in hand, which was formed in situ from [{Ir(cod)Cl}$_2$] and **L2**, various 4-hydroxyphenyl-tethered allylic carbonates were tested to examine the generality of the reaction. The results are summarized in Table 2. Reaction of allylic carbonate derivatives bearing Bn and *p*-$BrC_6H_4CH_2$ groups on the linking nitrogen atom both gave the spiro-

Table 2: The reaction substrate scope.



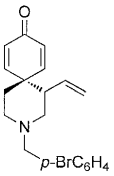
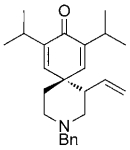
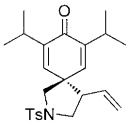
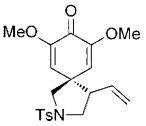
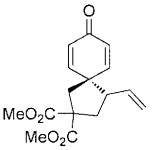
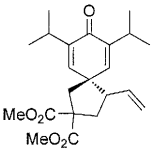
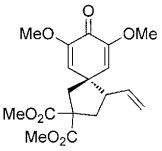
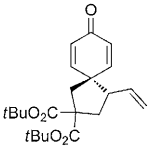
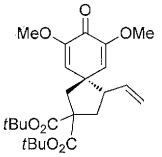
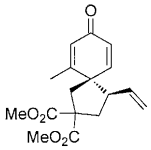
Entry	Substr.	*X* [mol%]	Conds.	Prod.	Yield [%][a]	*ee* [%][b]
1	**1a**	2	A	**2a**	68	96
2	**1b**	2	A		60	91
3	**1c**	4	A		65	89
4	**1d**	4	A		92	95
5	**1e**	4	A		65	88
6	**1f**	4	B		95 (92)[c]	97 (95)[c]
7	**1g**	4	B		85	94
8	**1h**	4	B		86	91
9	**1i**	4	B		75	86
10	**1j**	4	B		85	85

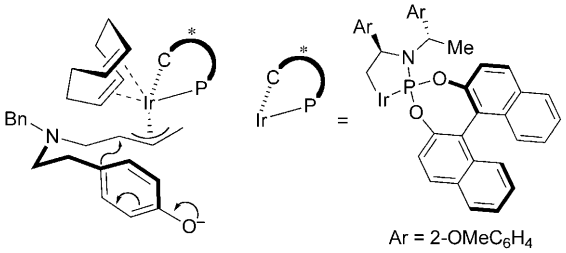
Table 2: (Continued)

Entry	Substr.	*X* [mol%]	Conds.	Prod.	Yield [%][a]	*ee* [%][b]
11	**1k**	4	B		95	93[d]

[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase. [c] The results in the parentheses were obtained for a 1 mmol reaction scale. [d] d.r. 11:1, for the minor diastereoisomer, 80% *ee*. Ts = 4-toluenesulfonyl.

cyclohexadienone products, thus forming the six-member spiro ring in good yields with excellent *ee* (60–68% yields, 91–96% *ee*; Table 2, entries 1 and 2). Formation of the six-membered ring also proceeded smoothly starting from the 2,6-diisopropylphenol-derived substrate **1c** (65% yield, 89% *ee*; Table 2, entry 3). The NTs linked five-member-ring formation was also achieved in good to excellent yields and *ee* values for substrates **1d–e** (65–92% yields, 88–95% *ee*; Table 2, entries 4 and 5). The reaction proceeded smoothly for the carbocyclic ring formation. Good to excellent yields and excellent *ee* values were obtained for the allylic dearomatization reaction of **1f–j**, varying substituents on 2,6-positions of the phenol and ester groups in the substrates (75–95% yields, 85–97% *ee*; Table 2, entries 6–10). Notably, when substrate **1k** was used, two stereogenic centers were generated. Fortunately, the asymmetric allylic dearomatization of **1k** led to the product in 95% yield and 11:1 d.r. (93% *ee* and 80% *ee*, respectively; Table 2, entry 11,).

The absolute configuration of the dearomatization products was assigned by comparison with literature report.[11,12] The stereocontrol of the allylic dearomatization reaction is also in accord with the general rule for the iridium-catalytic system (Scheme 2).[5b–d]



Scheme 2. Plausible working model.

In summary, we have developed the first iridium-catalyzed intramolecular asymmetric allylic dearomatization reaction of phenols. The reaction provides facile access to enantioenriched, substituted spirocyclohexadienone derivatives with up to 97% *ee*. Further extension of the reaction scope and investigation of applications for the spirocyclohexadienone products are currently underway.

Experimental Section

General procedure for the iridium-catalyzed enantioselective allylic alkylation: A flame-dried Schlenk tube was cooled to RT and filled with argon. {[Ir(cod)Cl]$_2$}, phosphoramidite ligand **L2**, THF, and propylamine were then added to this flask. The reaction mixture was heated at 50°C for 30 min and then the volatile solvents were removed in vacuo to give a pale yellow solid. After that, allylic carbonate **1** (0.20 mmol, dissolved in THF or 1,4-dioxane) and lithium carbonate (29.6 mg, 0.40 mmol) were added. The reaction mixture was stirred for 24 h at 50°C. Then, the crude reaction mixture was filtrated through celite and washed with EtOAc. The solvent was then removed under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (eluents: petroleum ether/ethyl acetate 6:1 to 2:1) to afford the desired product **2**.

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[11] During the preparation of this manuscript, Hamada and co-workers reported a palladium-catalyzed *ipso*-Friedel–Crafts allylic alkylation of phenols. In their report, six-membered-ring product was not accessible and iridium catalysis was not effective. For details, see: T. Nemoto, Y. Ishige, M. Yoshida, Y. Kohno, M. Kanematsu, Y. Hamada, *Org. Lett.* **2010**, *12*, 5020.

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