

Cyclopropanation

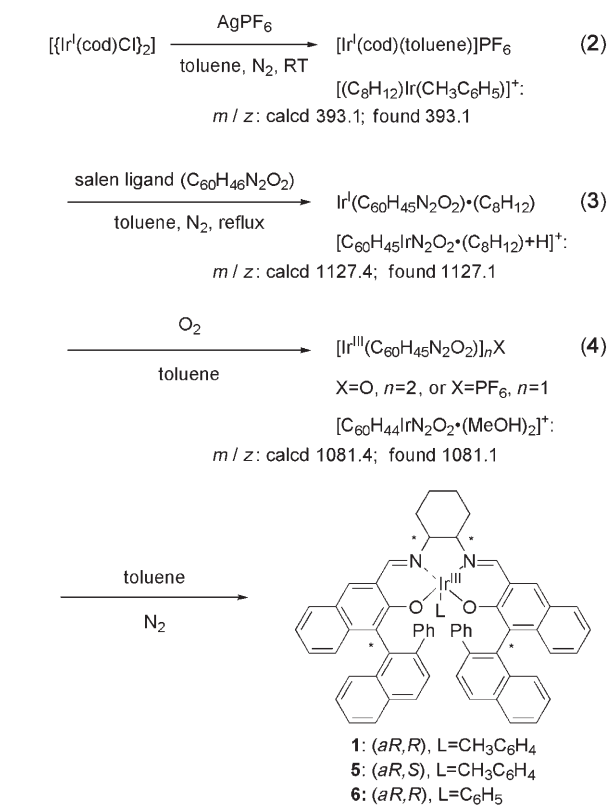
Construction of an Aryliridium–Salen Complex for Highly *cis*- and Enantioselective Cyclopropanations**

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Optically active cyclopropane moieties are frequently found in natural products and bioactive compounds, and the metal-catalyzed asymmetric cyclopropanation of olefins is a potent method for their synthesis.^[1] There are two stereochemical issues that need to be considered in asymmetric cyclopropanation, namely enantioselectivity and diastereoselectivity (*cis/trans* selectivity). Since the seminal report on metal-mediated asymmetric cyclopropanation by Nozaki et al.,^[2] significant effort has been devoted to the development of transition-metal-catalyzed enantioselective cyclopropanation reactions. However, most of these methods are *trans*-selective;^[3] *cis*-selective methods are very limited in number.^[4,5] Recently, we achieved the highly *cis*- and enantioselective cyclopropanation of simple olefins with ruthenium–salen or cobalt–salen complexes as the catalyst.^[6,7] Mezzetti et al. subsequently reported a Ru(PNNP) complex (PNNP = (1*S*,2*S*)-*N,N'*-bis[2-(diphenylphosphino)benzylidene]cyclohexane-1,2-diamine) that catalyzes cyclopropanation with a high *cis*- and good enantioselectivity,^[8] although the scope of these reactions is narrow.

Among complexes of the Group 9 metals, chiral cobalt and rhodium complexes have been shown to be useful as asymmetric carbene-transfer catalysts.^[9,10] To the best of our knowledge, however, there is no report of both an asymmetric carbene-transfer reaction using an iridium complex and the synthesis of a stable Ir–salen complex.^[11] Thus, we were intrigued by our synthesis of a new chiral Ir–salen complex and the subsequent discovery that such complexes bearing an aryl ligand at the apical position are stable and can be handled in air at room temperature. Herein, we describe the synthesis of a new class of Ir^{III}–salen complexes and their application as asymmetric cyclopropanation catalysts.

The Ir–salen complex **1** was synthesized by the sequence depicted in Scheme 1:^[12] 1) a mixture of [$\text{Ir}(\text{cod})\text{Cl}$]₂ (cod = 1,5-cyclooctadiene) and AgPF₆ in toluene was stirred for 30 min at room temperature and then filtered through celite. After concentration of the filtrate, the resultant solid, [$\text{Ir}^{\text{I}}(\text{cod})\text{Cl}$]₂, was washed sequentially with toluene and water, and dried; 2) treatment of complex **2** with the salen ligand in toluene at reflux under nitrogen for 10 h gave complex **3**; 3) filtration of the solution and concentration on a rotary evaporator in air led to the Ir^{III} complex **4**; 4) heating **4** in toluene under nitrogen gave the (*aR,R*)-Ir^{III}–salen complex **1**, which contains a tolyl group. High-resolution fast-atom bombardment (FAB) mass spectrometry suggested that the tolyl group is σ -coordinated to the iridium ion.^[13] This σ -coordination of the tolyl group is probably determined by an S_EAr mechanism in the final step as no involvement of a toluene component is observed until the Ir^I complex **3** is exposed to air.^[14] The diastereomeric (*aR,S*)-Ir^{III}–salen complex **5** was synthesized in the same manner. Complex **6** was also synthesized from **2** following the same procedure but with benzene as the solvent.



Scheme 1. Synthesis of Ir–salen complexes.

(cod)(toluene)]PF₆ (**2**), was washed sequentially with toluene and water, and dried; 2) treatment of complex **2** with the salen ligand in toluene at reflux under nitrogen for 10 h gave complex **3**; 3) filtration of the solution and concentration on a rotary evaporator in air led to the Ir^{III} complex **4**; 4) heating **4** in toluene under nitrogen gave the (*aR,R*)-Ir^{III}–salen complex **1**, which contains a tolyl group. High-resolution fast-atom bombardment (FAB) mass spectrometry suggested that the tolyl group is σ -coordinated to the iridium ion.^[13] This σ -coordination of the tolyl group is probably determined by an S_EAr mechanism in the final step as no involvement of a toluene component is observed until the Ir^I complex **3** is exposed to air.^[14] The diastereomeric (*aR,S*)-Ir^{III}–salen complex **5** was synthesized in the same manner. Complex **6** was also synthesized from **2** following the same procedure but with benzene as the solvent.

To explore the properties of Ir^{III}–salen complexes in asymmetric catalysis, we initially examined the cyclopropanation of styrene with *tert*-butyl α -diazoacetate as the carbene source and complexes **1**, **4**, and **5** as the catalysts (Table 1).^[15]

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Table 1: Asymmetric cyclopropanation of styrene and its derivatives with *tert*-butyl α -diazoacetate.^[a]

$\text{Ar-CH=CH}_2 \xrightarrow[\text{THF, N}_2]{\text{cat. (5 mol\%), N}_2\text{CHCO}_2\text{tBu (1 equiv)}} \text{Ar-CH(CH}_2\text{CO}_2\text{tBu)-CH}_2\text{CO}_2\text{tBu} + \text{Ar-CH(CH}_2\text{CO}_2\text{tBu)-CH}_2\text{CO}_2\text{tBu}$						
Entry	Ar	T [°C]	Yield [%] ^[b]	<i>cis/trans</i> ^[c]	<i>ee</i> _{<i>cis</i>} [%] ^[d]	<i>ee</i> _{<i>trans</i>} [%] ^[d]
1 ^[e]	Ph	RT	40	40:60	76 ^[f]	96 ^[f]
2	Ph	RT	87	55:45	84 ^[f]	96 ^[f]
3 ^[g]	Ph	RT	43	58:42	–37 ^[f]	70 ^[f]
4 ^[h]	Ph	RT	36	66:34	64 ^[f]	18 ^[f]
5	Ph	–20	87	87:13	93 ^[f]	96 ^[f]
6	Ph	–40	85	96:4	96 ^[f]	93 ^[f]
7	Ph	–78	> 99	> 99:1	99 ^[f]	92 ^[f]
8 ^[i]	Ph	–78	> 99	> 99:1	99 ^[f]	–
9 ^[j]	Ph	–78	> 99	> 99:1	98 ^[f]	–
10 ^[j]	<i>o</i> -MeOC ₆ H ₄	–78	90	97:3	99 ^[k]	–
11 ^[j]	<i>m</i> -MeOC ₆ H ₄	–78	88	> 99:1	97 ^[k]	–
12 ^[j]	<i>p</i> -MeOC ₆ H ₄	–50	> 99	> 99:1	97 ^[k]	–
13 ^[j,l]	<i>o</i> -ClC ₆ H ₄	–78	90	99:1	98 ^[k]	–
14 ^[j]	<i>m</i> -ClC ₆ H ₄	–78	91	> 99:1	98 ^[k]	–
15 ^[j]	<i>p</i> -ClC ₆ H ₄	–78	> 99	> 99:1	98 ^[k]	–
16 ^[i,m]	Ph	–78	90 ^[n]	> 99:1	99 ^[k]	–
17 ^[i,o]	Ph	–78	> 99	> 99:1	97 ^[f]	–

[a] Reactions were carried out in THF for 24 h on a 0.1-mmol scale with a 1/diazo ester/olefin molar ratio of 0.05:1:10, unless otherwise noted. [b] Yields are based on the amount of diazo acetate used. Total yields of the *cis* and *trans* cyclopropanes were determined by ¹H NMR spectroscopy (400 MHz) using 1-bromonaphthalene as an internal standard. [c] Determined by ¹H NMR spectroscopy (400 MHz). [d] Determined by HPLC analysis on a chiral column (Daicel Chiralcel OD-H). [e] 1 equiv of styrene was used. [f] The absolute configurations of the *cis* and *trans* isomers were determined to be 1*R*,2*S* and 1*R*,2*R*, respectively, by comparing their elution order in the HPLC analysis with that of authentic samples. [g] Complex **5** was used as the catalyst. [h] Complex **4** was used as the catalyst. [i] 1 mol % of **1** was used as the catalyst. [j] Complex **6** was used as the catalyst. [k] The absolute configuration was not determined. [l] The reaction was carried out for 48 h. [m] The reaction was carried out on a 1-mmol scale. [n] Yield of isolated product. [o] Ethyl α -diazoacetate was used instead of *tert*-butyl α -diazoacetate.

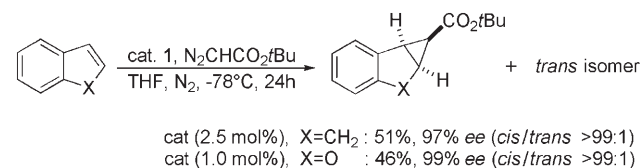
The reaction proceeded rapidly with good enantioselectivity at room temperature, although the diastereoselectivity was low and the yield of the desired product was unsatisfactory because of the competitive production of fumaric and maleic esters (Table 1, entry 1). We therefore decided to carry out the reaction in the presence of an excess of styrene to suppress this undesired diazo coupling (Table 1, entry 2). As expected, the formation of the diesters was suppressed and the yield of the desired products improved considerably. In addition, the diastereoselectivity shifted from *trans* to *cis* products and the enantiomeric excess of the *cis* isomer increased. The reaction with **5** gave a similar level of diastereoselectivity but its enantioselectivity was inferior to that with **1** (Table 1, entry 3). The reaction with **4** also gave only moderate enantioselectivity (Table 1, entry 4).

We next examined the reactions with **1** at lower temperatures and found that both the *cis* selectivity and the enantiomeric excess of the *cis* isomer improved as the reaction temperature decreased, while the enantiomeric excess of the *trans* isomer diminished slightly (Table 1,

entries 5–7): the reaction proceeded even at –78 °C and gave the *cis* isomer exclusively, in quantitative yield, with 99% *ee*. These results suggest that more than one active species might participate in this cyclopropanation and that the ratio of the species depends on the reaction conditions. The formation of the diesters was almost completely suppressed at –78 °C. The reaction with 1 mol % of **1** proceeded with the same stereoselectivity and yield (Table 1, entry 8), and the reaction with complex **6** also led to identical stereochemical outcome (Table 1, entry 9).

The cyclopropanation of substituted styrenes also proceeded with excellent stereoselectivity, irrespective of the nature and the position of the substituents (Table 1, entries 10–15). Although we carried out the reactions on a 0.1-mmol scale, they can just as easily be carried out on a 1-mmol scale (see Table 1, entry 16 and the Experimental Section). It is noteworthy that high enantio- and excellent diastereoselectivity were also achieved in the reaction of styrene with commercial ethyl α -diazoacetate (Table 1, entry 17).

The cyclopropanation of indene and benzofuran also proceeded with high enantio- and *cis* selectivity, albeit with only moderate yield (Scheme 2).^[16] To the best of our knowledge, this is the first selective approach to optically active cyclopropanes of this type.



Scheme 2. Asymmetric cyclopropanation of cyclic olefins.

A single crystal of the phenyliridium–salen complex **6** was obtained by crystallization from dichloromethane and methanol and examined by X-ray crystallography, which clearly demonstrated that the phenyl group is σ -coordinated to the iridium ion at the apical position.^[17] This analysis also disclosed that two complexes with different conformations are present in each unit cell. The salen ligand in each conformer adopts an umbrella-shaped or planar conformation and the conformation of the apical phenyl substituent in each conformer is also different (Figure 1).

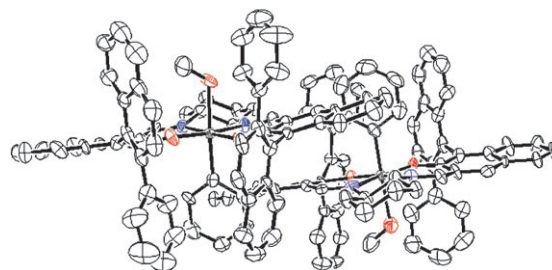


Figure 1. X-ray structure of **6**. Hydrogen atoms and solvent molecules are omitted for clarity. Ir small gray, C black, N blue, O red.

In conclusion, we have synthesized stable chiral Ir^{III}–salen complexes that contain a σ -coordinated aryl ligand. Preliminary results show that complex **1** is a unique and potent catalyst for asymmetric cyclopropanation. Application of these new Ir^{III}–salen complexes to other asymmetric reactions is now in progress.

Experimental Section

Cyclopropanation of styrene with **1**: *tert*-Butyl α -diazoacetate (0.14 mL, 1 mmol) and styrene (1.4 g, 10 mmol) were dissolved in anhydrous THF (2.4 mL) under N₂ and the solution was cooled to –78 °C and stirred for 10 min. Complex **1** (11 mg, 10 μ mol) was added and the mixture was stirred for one day at this temperature. The mixture was then allowed to warm to room temperature and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (neat hexane to hexane/*i*Pr₂O 10:1) to give the *cis* product (197 mg, 90 %) as a colorless oil.

The *trans* product could not be detected by ¹H NMR (400 MHz) spectroscopic analysis of the crude reaction mixture. The enantiomeric excess of the *cis* product was determined by HPLC analysis (Daicel Chiralcel OD-H; 99 % *ee*).

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- [13] **1** (red solid): Elementary analysis (%) calcd for C₆₀H₄₄IrN₂O₂·CH₃C₆H₄·2H₂O: C 70.32, H 4.84, N 2.45; found: C 70.11, H 4.85, N 2.54. HR FAB MS: *m/z* calcd. for C₆₀H₄₄IrN₂O₂·CH₃C₆H₄: 1108.3580; found: 1108.3577. FAB MS: *m/z* calcd. for C₆₀H₄₄IrN₂O₂·CH₃C₆H₄: 1108.37 (100%), 1109.37 (68.1 %), 1106.36 (50.9 %), 1107.37 (38.4 %); found: 1108.36 (100 %), 1109.36 (68.6 %), 1106.36 (50.8 %), 1107.36 (38.6 %).
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