

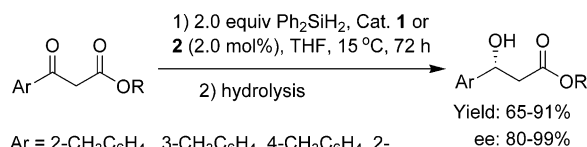
## The Use of Chiral BINAM NHC-Rh(III) Complexes in Enantioselective Hydrosilylation of 3-Oxo-3-arylpropionic Acid Methyl or Ethyl Esters

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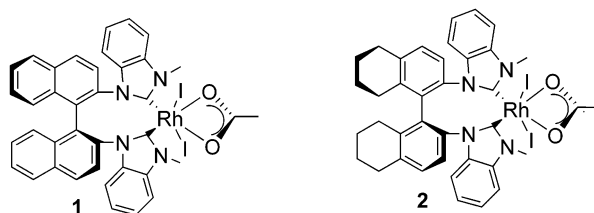
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Received November 29, 2006



Ar = 2-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 3-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 2-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 2-ClC<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>

R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>



Axially chiral BINAM N-heterocyclic carbene (NHC)-Rh(III) complexes were applied in the enantioselective hydrosilylation of 3-oxo-3-arylpropionic acid methyl or ethyl esters. The reduction products 3-hydroxy-3-arylpropionic acid methyl or ethyl esters could be obtained in good yields with good to excellent enantioselectivities under mild conditions.

Enantiopure  $\beta$ -hydroxy esters are important building blocks for the synthesis of biologically active compounds and natural products.<sup>1</sup> Thus far, medicinal importance has spurred the research of convenient and highly selective methods for the synthesis of optically active  $\beta$ -hydroxy esters or their derivatives. Metal-catalyzed asymmetric hydrogenation of  $\beta$ -ketoesters is one of the most practical and efficient methods to obtain such

compounds.<sup>2</sup> In addition, enzymatic reductions of  $\beta$ -ketoesters as well as aldol reactions can also efficiently provide optically active  $\beta$ -hydroxy esters.<sup>3,4</sup> Apart from those methods, biocatalytic deracemization<sup>5</sup> and optical resolution of racemic  $\beta$ -hydroxy esters<sup>6</sup> also have been frequently employed. Herein we report a new method to prepare optically active 3-hydroxy-3-arylpropionic acid methyl or ethyl esters by enantioselective hydrosilylation of 3-oxo-3-arylpropionic acid methyl or ethyl esters using NHC-Rh complexes derived from optically active 1,1'-binaphthalenyl-2,2'-diamine (BINAM) and H<sub>8</sub>-BINAM for the first time.

N-Heterocyclic carbenes (NHC), a flexible ligand, developed rapidly in the latest decade due to their stability to air and moisture and their strong  $\sigma$ -donor but poor  $\pi$ -acceptor abilities.<sup>7</sup> Great effort has been made to conduct chiral NHC-metal complex-catalyzed reactions in an enantioselective way, and this century has already witnessed remarkable achievements.<sup>8</sup> NHC-Rh complexes have been known as effective catalysts for enantioselective hydrosilylation of ketones to provide optically active secondary alcohols in moderate to good enantiomeric excesses under mild conditions.<sup>9</sup> Previously, we also reported the preparation of an axially chiral NHC-Rh(III) complex **1** derived from optically active 1,1'-binaphthalenyl-2,2'-diamine (BINAM) and demonstrated its high chiral induction ability in

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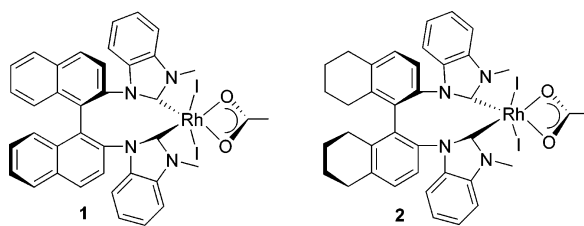
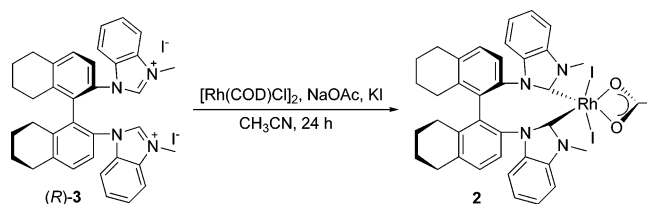


FIGURE 1. Axially chiral NHC-Rh(III) complex **1** and **2**.

SCHEME 1. Synthesis of Axially Chiral NHC-Rh(III) Complex **2**



the hydrosilylation of ketones.<sup>10</sup> However, to the best of our knowledge, there has been no report on the enantioselective hydrosilylation of  $\beta$ -ketoesters with NHC-Rh(III) complexes. Therefore, we attempted to utilize axially chiral NHC-Rh(III) complexes **1** and **2** in the enantioselective hydrosilylation of 3-oxo-3-arylpropionic acid methyl or ethyl esters to further examine their catalytic abilities (Figure 1).

**Results and Discussion.** The synthesis of novel NHC-Rh(III) complex **2** was accomplished by use of the corresponding dibenzimidazolium salt (*R*)-**3** derived from optically active H<sub>8</sub>-BINAM as the starting material and in a similar sequence for the preparation of axially chiral NHC-Rh complex **1**.<sup>11</sup> The structure of compound **2** was determined unambiguously by an X-ray diffraction. The ORTEP drawing of **2** is shown in Figure 2.<sup>12</sup>

Initial studies of the influence of reaction conditions were carried out with 3-oxo-3-phenylpropionic acid ethyl ester **4a** as a substrate and chiral NHC-Rh(III) complex **1** (2.0 mol %) as a catalyst at room temperature (15 °C) in a variety of solvents. We found that tetrahydrofuran (THF) is the best solvent among dichloromethane, toluene, acetonitrile, and hexane to give the corresponding (*S*)-3-hydroxy-3-phenylpropionic acid ethyl ester **5a** in 81% yield and 95% ee within 72 h at room temperature (15 °C) (Table 1, entries 1–5). Elevating the reaction temperature to 45 °C, the ee value of **5a** slightly decreased in THF (Table 1, entry 6). By using complex **1** (1.0 mol %) as a catalyst

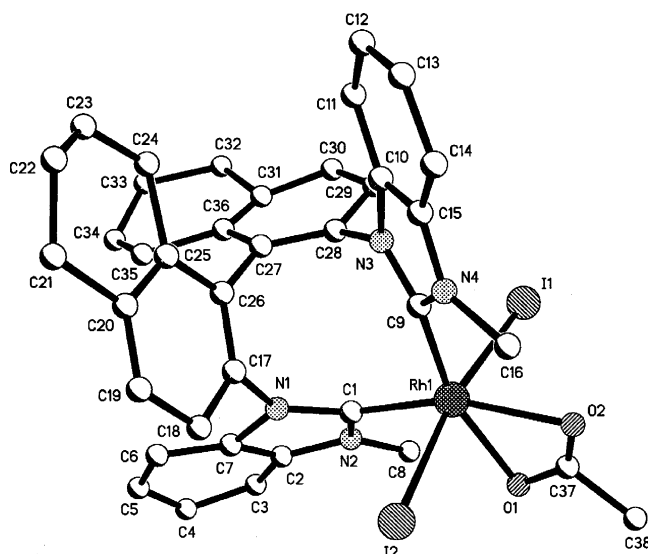
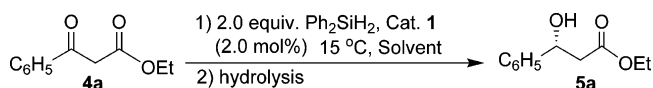


FIGURE 2. ORTEP drawing of chiral NHC-Rh(III) Complex **2**.

TABLE 1. Axially Chiral NHC-Rh(III) Complex **1** Catalyzed Enantioselective Hydrosilylation of **4a**



entry	solvent	time (h)	yield (%) <sup>a</sup>	ee (%) <sup>b</sup>	config. <sup>c</sup>
1 <sup>d</sup>	THF	72	81	95	<i>S</i>
2	CH <sub>2</sub> Cl <sub>2</sub>	72	30	45	<i>S</i>
3	toluene	72	50	79	<i>S</i>
4	CH <sub>3</sub> CN	72	75	73	<i>S</i>
5	hexane	72	20	50	<i>S</i>
6 <sup>e</sup>	THF	60	80	90	<i>S</i>

<sup>a</sup> Isolated yields. <sup>b</sup> Ee values were determined by HPLC on a Chiralcel OD-H column. <sup>c</sup> Absolute stereochemistry was determined by comparison of the sign of optical rotation to the literature value. <sup>d</sup> Using Cat. **1** (1.0 mol %) in this reaction, **5a** was obtained in 48% yield and 95% ee under otherwise identical conditions. <sup>e</sup> The reaction temperature is 45 °C.

in this reaction, **5a** was obtained in 48% yield and 95% ee under otherwise identical conditions (Table 1, entry 1).

Under these optimized reaction conditions, we subsequently investigated the substrate scopes of the enantioselective hydrosilylation of 3-oxo-3-arylpropionic acid methyl or ethyl esters **4** using NHC-Rh(III) complexes **1** and **2**. The results are summarized in Table 2. As can be seen from Table 2, various 3-oxo-3-arylpropionic acid methyl or ethyl esters **4** can be smoothly reduced to give the corresponding 3-hydroxy-3-arylpropionic acid methyl or ethyl esters **5** in good to high yields with >80% ee in most cases under mild conditions in spite of **4** with electron-rich, electron-neutral, and electron-poor substituents on the benzene ring. In addition, the position of substituent on the benzene ring did not significantly affect the ee of **5** under the catalysis of complex **1** or **2**. Chiral NHC-Rh(III) complexes **1** and **2** gave the corresponding 3-hydroxy-3-arylpropionic acid methyl or ethyl esters **5** in similar enantioselectivities and chemical yields under identical conditions.

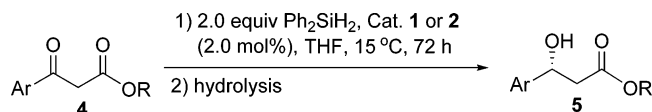
In conclusion, we have developed a fairly effective axially chiral NHC-Rh(III) complex system for the enantioselective hydrosilylation of various 3-oxo-3-arylpropionic acid methyl or ethyl esters **4** for the first time. This work adds to the growing

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(11) See the Supporting Information for the details on the preparation of chiral NHC-Rh(III) complexes **1** and **2**.

(12) The crystal data of NHC-Rh(III) complex **2** have been deposited in CCDC, number 287294. Empirical formula: C<sub>38</sub>H<sub>37</sub>I<sub>2</sub>N<sub>4</sub>O<sub>2</sub>Rh. Formula weight: 938.43. Crystal color, habit: colorless, prismatic. Crystal system: monoclinic. Lattice type: primitive. Lattice parameters: *a* = 9.843(2) Å, *b* = 19.500(4) Å, *c* = 19.388(4) Å,  $\alpha$  = 90°,  $\beta$  = 96.280(5)°,  $\gamma$  = 90°, *V* = 3698.8(15) Å<sup>3</sup>. Space group: *P*2(1). *Z* = 4. *D*<sub>calc</sub> = 1.685 g/cm<sup>3</sup>. *F*<sub>000</sub> = 1840. Diffractometer: Rigaku AFC7R. Residuals, *R*, *R*<sub>w</sub>: 0.1014, 0.2643.

**TABLE 2.** Chiral Rh Complex Catalyzed Enantioselective Hydrosilylation of 3-Oxo-3-arylpropionic Methyl or Ethyl Esters

entry	Rh catalyst	4 (Ar/R)	yield (%) <sup>a</sup>	ee (%)	config. <sup>b</sup>
1	1	4a (C <sub>6</sub> H <sub>5</sub> /Et)	5a, 81	95 <sup>c</sup>	S
2	2	4a	5a, 78	80 <sup>c</sup>	S
3	1	4b (4-MeC <sub>6</sub> H <sub>4</sub> /Et)	5b, 90	95 <sup>d</sup>	S
4	2	4b	5b, 83	99 <sup>d</sup>	S
5	1	4c (2-MeC <sub>6</sub> H <sub>4</sub> /Et)	5c, 88	92 <sup>e</sup>	S
6	2	4c	5c, 80	92 <sup>e</sup>	S
7	1	4d (3-MeC <sub>6</sub> H <sub>4</sub> /Et)	5d, 91	98 <sup>c</sup>	S
8	2	4d	5d, 88	99 <sup>c</sup>	S
9	1	4e (2-MeOC <sub>6</sub> H <sub>4</sub> /Et)	5e, 72	96 <sup>d</sup>	S
10	2	4e	5e, 65	90 <sup>d</sup>	S
11	1	4f (4-BrC <sub>6</sub> H <sub>4</sub> /Et)	5f, 89	95 <sup>e</sup>	S
12	2	4f	5f, 86	96 <sup>e</sup>	S
13	1	4g (4-ClC <sub>6</sub> H <sub>4</sub> /Et)	5g, 87	97 <sup>e</sup>	S
14	2	4g	5g, 80	97 <sup>e</sup>	S
15	1	4h (2-ClC <sub>6</sub> H <sub>4</sub> /Et)	5h, 75	81 <sup>d</sup>	S
16	2	4h	5h, 70	84 <sup>d</sup>	S
17	1	4i (4-ClC <sub>6</sub> H <sub>4</sub> /Me)	5i, 82	95 <sup>e</sup>	S
18	2	4i	5i, 81	92 <sup>e</sup>	S

<sup>a</sup> Isolated yields. <sup>b</sup> Absolute stereochemistry was determined by comparison of the sign of specific rotation with those of literature values. <sup>c</sup> Ee values were determined by HPLC on a Chiralcel OD-H column. <sup>d</sup> Ee values were determined by HPLC on Chiralpak AS-H column. <sup>e</sup> Ee values were determined by HPLC on Chiralpak AD-H column.

body of synthetic studies on the preparation of optically active 3-hydroxy-3-arylpropionic acid methyl or ethyl esters and also shows new application of the chiral NHC-metal complexes developed from this group, using BINAM or H<sub>8</sub>-BINAM as a chiral skeleton. Efforts to elucidate the mechanistic details of this catalytic system and to explore new types of NHC-metal complexes are underway.

## Experimental Section

**Synthesis of NHC-Rh(III) Complex 2.** A mixture of (*R*)-3 (156 mg, 0.20 mmol), [RhCl(COD)]<sub>2</sub> (48 mg, 0.10 mmol), NaOAc (132 mg, 0.80 mmol), and KI (66 mg, 0.40 mmol) was stirred in

CH<sub>3</sub>CN (12 mL) under reflux for 24 h. After cooling, volatiles were removed under reduced pressure and the residue was purified by a flash column chromatography (eluent: hexane/ethyl acetate = 1/1) to give NHC-Rh(III) complex 2 as an orange solid. Yield: 51 mg (27%). [α]<sub>D</sub><sup>20</sup> 72 (c 0.25, CHCl<sub>3</sub>); IR (CH<sub>2</sub>Cl<sub>2</sub>) ν 3727, 3630, 2933, 2858, 1721, 1465, 1335, 1090, 743 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, TMS) δ 1.35–1.57 (m, 8H, CH<sub>2</sub>), 1.93–2.05 (m, 4H, CH), 2.00 (s, 3H, CH<sub>3</sub>), 2.50–2.64 (m, 4H, CH), 4.36 (s, 6H, CH<sub>3</sub>), 6.73 (d, *J* = 8.1 Hz, 2H, ArH), 7.04–7.11 (m, 2H, ArH), 7.21 (t, *J* = 7.2 Hz, 2H, ArH), 7.30 (t, *J* = 8.1 Hz, 2H, ArH), 7.97 (d, *J* = 8.1 Hz, 2H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 22.0, 22.2, 24.96, 24.98, 27.1, 29.1, 38.0, 109.8, 111.5, 122.6, 123.2, 127.7, 129.9, 133.1, 134.7, 134.66, 134.69, 135.7, 136.3, 139.0; MS (EI) *m/z* (%) 879 (M<sup>+</sup> – OAc), 811 (M<sup>+</sup> – I). Anal. Calcd for C<sub>38</sub>H<sub>37</sub>I<sub>2</sub>N<sub>4</sub>O<sub>2</sub>: Rh: C 48.63, H 3.97, N 5.97. Found: C 48.02, H 4.18, N 5.82%.

**General Procedure for Rh-Catalyzed Enantioselective Hydrosilylation Reaction.** Under an Ar atmosphere, 3-oxo-3-arylpropionic acid methyl or ethyl esters (0.5 mmol) and Ph<sub>2</sub>SiH<sub>2</sub> (138 mg, 0.75 mmol) were added to a solution of NHC-Rh(III) complex (0.01 mmol) in anhydrous THF (2 mL). The reaction mixture was stirred at 15 °C for 72 h. The reaction was quenched by addition of H<sub>2</sub>O (1 mL) and 0.5 N HCl (0.5 mL). The resulting aqueous solution was stirred for 2–5 h at room temperature, extracted with Et<sub>2</sub>O (2 × 10 mL), and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by a flash column chromatography (eluent: pentane/Et<sub>2</sub>O = 10/1~4/1) to give the corresponding 3-hydroxy-3-arylpropionic acid methyl or ethyl esters. The enantiomeric excess of 3-hydroxy-3-arylpropionic acid methyl or ethyl esters was determined by chiral HPLC.

**Acknowledgment.** Financial support from Shanghai Municipal Committee of Science and Technology (04JC14083 and 06XD14005), the National Natural Science Foundation of China (203900502, 20472096, and 20672127), and the Cheung Kong Scholar Program is greatly appreciated.

**Supporting Information Available:** Experimental details and characterization data, chiral HPLC, and X-ray crystallographic files in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO062453D