

Enantioselective  $\alpha$ -Fluorination and Chlorination of  $\beta$ -Ketoesters by Cobalt Catalyst

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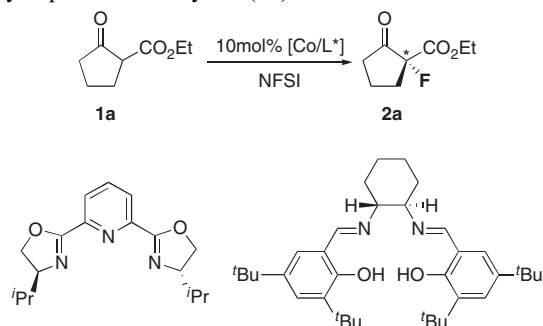
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We demonstrated the cobalt-catalyzed asymmetric  $\alpha$ -fluorination and  $\alpha$ -chlorination of  $\beta$ -ketoesters. Both reactions were achieved using a catalytic amount of  $\text{Co}(\text{acac})_2$  with (*R,R*)-Jacobsen's salen ligand;  $\alpha$ -fluorinated or  $\alpha$ -chlorinated products were thus obtained with a good enantioselectivity.

Chiral fluorinated organic compounds are well recognized as important materials in the field of biological and medicinal chemistry.<sup>1</sup> Recently, the transition metal catalyzed highly enantioselective  $\alpha$ -fluorination of  $\beta$ -ketoesters has been achieved by several groups.<sup>2</sup> For example, Togni reported the  $[\text{TiCl}_2(\text{TADDOLato})]$ -catalyzed reaction with Selectfluor, and they also discovered a ruthenium catalyst system.<sup>3</sup> Sodeoka demonstrated a Pd/BINAP-catalyzed system with *N*-fluorobenzenesulfonimide (NFSI).<sup>4</sup> Cahard also described that Cu/Box is an effective catalyst for the  $\alpha$ -fluorination of  $\beta$ -ketoesters.<sup>5</sup> Furthermore, Shibata and Toru attained a high enantioselectivity with a Ni/dbfox catalyst.<sup>6</sup> More recently, a Ni or Mg/*N,N,N*-tridentate ligand system was reported by Shibatomi and Iwasa,<sup>7</sup> and chiral rare earth perfluorinated organophosphate catalysts were developed by Inanaga.<sup>8</sup> Despite these pioneering studies of enantioselective fluorination, the development of a new catalyst system is still required in this area. Recently, we have been interested in the development of the cobalt-catalyzed asymmetric reaction, and realized the cobalt/pybox-catalyzed asymmetric conjugate addition of thiols to  $\alpha,\beta$ -unsaturated carbonyl compounds.<sup>9</sup> During the course of the cobalt-catalyzed asymmetric reactions, we found that the cobalt/Jacobsen's salen ligand system exhibited a high enantioselectivity for the  $\alpha$ -fluorination of  $\beta$ -ketoesters.

We examined the reaction of ethyl 2-oxocyclopentanecarboxylate (**1a**) with NFSI using cobalt catalysts.<sup>10</sup> Based on the results of our previous chiral cobalt catalyzed asymmetric reaction,<sup>9</sup> we tested the  $\alpha$ -fluorination reaction of  $\beta$ -ketoesters by  $\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  with (*S,S*)-*ip*-pybox. However, the reaction produced an  $\alpha$ -fluorinated product with a poor result; i.e., a 55% yield and 25% enantiomeric excess (Table 1, Entry 1). Reinvestigation of the effective combination of a cobalt salt and chiral ligand revealed that  $\text{Co}(\text{acac})_2$  with the (*R,R*)-Jacobsen's salen ligand (**L2**) exhibited a higher enantiomeric excess (60% ee) with almost the same yield (60%) (Entry 4). The enantioselectivity was improved when diethyl ether was used as the solvent, but the yield had decreased to 41% (Entry 5). Fortunately, both the chemical yield and enantioselectivity of the desired products significantly increased at lower reaction temperature (Entries 6 and 7), and the best result was obtained at  $-20^\circ\text{C}$  (84% isolated yield with 89% ee). According to the reported results of the metal-catalyzed  $\alpha$ -fluorination of cyclic  $\beta$ -ketoesters by other groups, it seems that moderately bulky groups, such as *tert*-butyl, at the ester functionality are necessary to attain high

**Table 1.** Cobalt catalysts for the  $\alpha$ -fluorination of ethyl 2-oxocyclopentanecarboxylate (**1a**)<sup>a</sup>



Entry	[Co]	L1: ( <i>S,S</i> )- <i>ip</i> -pybox		L2: ( <i>R,R</i> )-Jacobsen's salen ligand	
		L	Solv./Temp ( $^\circ\text{C}$ )	Yield /% <sup>b</sup>	ee/% <sup>c</sup>
1	$\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	<b>L1</b>	THF/rt	55	25
2	$\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	<b>L2</b>	THF/rt	50	8
3	$\text{Co}(\text{acac})_2$	<b>L1</b>	THF/rt	86	34
4	$\text{Co}(\text{acac})_2$	<b>L2</b>	THF/rt	60	60
5	$\text{Co}(\text{acac})_2$	<b>L2</b>	$\text{Et}_2\text{O}$ /rt	41	73
6	$\text{Co}(\text{acac})_2$	<b>L2</b>	$\text{Et}_2\text{O}$ /0	68	85
7	$\text{Co}(\text{acac})_2$	<b>L2</b>	$\text{Et}_2\text{O}$ / $-20$	84	89

<sup>a</sup>Reaction conditions: **1a** (0.32 mmol), [Co] (0.032 mmol), **L1** or **L2** (0.032 mmol), NFSI (0.45 mmol), solvent (1.0 mL).

<sup>b</sup>Isolated yield. <sup>c</sup>Enantiomeric excess values were determined by GC analysis using Chiraldex G-TA.

enantioselectivity. Actually, most of the reports mainly examined the *tert*-butyl esters, and there are only two examples of the reaction of the ethyl ester,<sup>3c,8</sup> which is commercially available. To the best of our knowledge, the highest enantioselectivity reported for the reaction of **1a** was 76% ee, and it was attained using a scandium catalyst. It should be emphasized that our cobalt catalyst is superior to the scandium catalyst for the  $\alpha$ -fluorination of the ethyl ester **1a** (89% ee, Entry 7).

We used the  $\text{Co}(\text{acac})_2/\text{L2}$  catalyst for the  $\alpha$ -fluorination of other  $\beta$ -ketoesters. These results are summarized in Table 2. The ketoester **1b** (methyl ester) produced the desired  $\alpha$ -fluorinated product with 90% ee (Entry 1). The reaction of **1c** (*tert*-butyl ester) also exhibited a good enantioselectivity (86% ee). On the other hand, reduced enantioselectivities were obtained for the reaction of other cyclic  $\beta$ -ketoesters containing six- or seven-membered rings (**1d–1f**) (Entries 3–5). We further examined the reaction of acyclic  $\beta$ -ketoester **1g**, but both yield and enantioselectivity were moderate (Entry 6).<sup>11</sup>

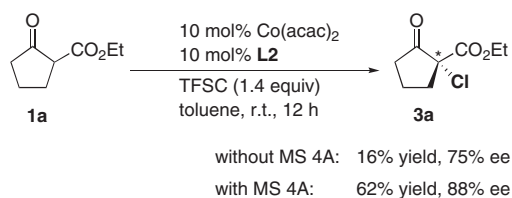
Furthermore, the  $\text{Co}(\text{acac})_2/\text{L2}$  catalyst worked as a good system for the enantioselective  $\alpha$ -chlorination of **1a** with  $\text{CF}_3\text{SO}_2\text{Cl}$  (TFSC) (Scheme 1).<sup>6,12</sup> The reaction was carried out

**Table 2.** Cobalt-catalyzed  $\alpha$ -fluorination of  $\beta$ -ketoesters (**1b–1g**)<sup>a</sup>

**1b:** n = 1, R = Me  
**1c:** n = 1, R = <sup>t</sup>Bu  
**1d:** n = 2, R = Me  
**1e:** n = 2, R = Et  
**1f:** n = 3, R = Me

Entry	<b>1</b>	Temp/°C	Yield/% <sup>b</sup>	ee/% <sup>c</sup>
1	<b>1b</b>	−20	74	90
2	<b>1c</b>	−20	65	86
3	<b>1d</b>	0	65	79
4	<b>1e</b>	0	65	75
5	<b>1f</b>	0	75	79
6	<b>1g</b>	rt	64	71

<sup>a</sup>Reaction conditions:  $\beta$ -ketoester (0.32 mmol), Co(acac)<sub>2</sub> (0.032 mmol), **L2** (0.032 mmol), NFSI (0.45 mmol), diethyl ether (1.0 mL). <sup>b</sup>Isolated yield. <sup>c</sup>Enantiomeric excess values were determined by GC analysis with a Chiraldex G-TA for **1b** and **1d–1g**, or chiral HPLC using Daicel CHIRALPAK AD-H for **1c**.

**Scheme 1.**

in toluene at room temperature, and the desired chlorinated product was obtained with a 75% ee, but the yield was insufficient (16%). Fortunately, both the yield and enantioselectivity increased to 62% and 88% ee by the addition of molecular sieves 4A.

In conclusion, we demonstrated the cobalt-catalyzed asymmetric  $\alpha$ -fluorination and  $\alpha$ -chlorination of  $\beta$ -ketoesters. Both of these desired reactions were catalyzed by a chiral cobalt catalyst, which was prepared from Co(acac)<sub>2</sub> with (*R,R*)-Jacobsen's salen ligand, and the  $\alpha$ -fluorinated or  $\alpha$ -chlorinated products were obtained with good enantioselectivities.

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- Typical procedure: A solution of Co(acac)<sub>2</sub> (8.2 mg, 0.032 mmol), (*R,R*)-Jacobsen's salen ligand (17.5 mg, 0.032 mmol) and NFSI (141 mg, 0.45 mmol) in anhydrous diethyl ether (1.0 mL) was stirred at −20 °C for 10 min. To this solution was added a  $\beta$ -ketoester **1a** (50 mg, 0.32 mmol), then stirred for 12 h. Saturated NH<sub>4</sub>Cl was added for quenching, and the water layer was extracted with diethyl ether (1.0 mL  $\times$  3). The combined organic layers were washed with brine and dried over MgSO<sub>4</sub>. Removal of the solvent, followed by flash column chromatography (hexane/ethyl acetate = 2/1), afforded the desired product **2a** as a colorless oil (47 mg, 84%). The enantiomeric purity was determined to be 89% ee by GC analysis with a Chiraldex G-TA (initial temperature 60 °C, final temperature 165 °C, rate 3 °C min<sup>−1</sup>, inj. temperature 160 °C, det. temperature 100 °C: *t*(*R*) = 26.0 min, *t*(*S*) = 30.5 min). [ $\alpha$ ]<sub>D</sub><sup>25</sup> 85.8 (*c* 0.56, CHCl<sub>3</sub>) (89% ee) {lit.<sup>3c</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> 169.0 (*c* 1.53, CHCl<sub>3</sub>) (99.7% ee)}. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.32 (t, *J* = 7.2 Hz, 3H), 2.01–2.19 (m, 2H), 2.28–2.39 (m, 1H), 2.48–2.60 (m, 3H), 4.30 (q, *J* = 7.2 Hz, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  14.00, 18.02 (d, *J* = 2.9 Hz), 33.88 (d, *J* = 21.1 Hz), 35.68, 62.33, 94.61 (d, *J* = 199.6 Hz), 167.44 (d, *J* = 26.8 Hz), 207.52 (d, *J* = 16.2 Hz). <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>, internal standard: C<sub>6</sub>F<sub>6</sub>):  $\delta$  −2.39 (t, *J* = 18.8 Hz).
- We also examined the fluorination reactions of 2-methoxycarbonyl-1-indanone and 2-ethoxycarbonyl-1-indanone by Co(acac)<sub>2</sub>/**L2** catalyst, but the enantioselectivities were 55% ee (98% yield) and 50% ee (94% yield), respectively.
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