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Enantioselective α-Fluorination and Chlorination of β-Ketoesters by Cobalt Catalyst

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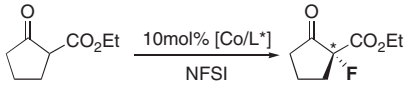
We demonstrated the cobalt-catalyzed asymmetric α-fluorination and α-chlorination of β-ketoesters. Both reactions were achieved using a catalytic amount of $Co(acac)_2$ with (*R*,*R*)-Jacobsen's salen ligand; α-fluorinated or α-chlorinated products were thus obtained with a good enentioselectivity.

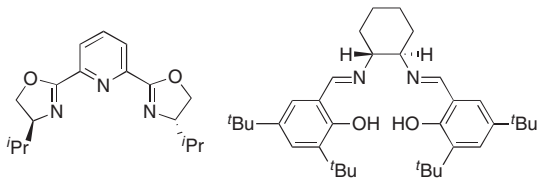
Chiral fluorinated organic compounds are well recognized as important materials in the field of biological and medicinal chemistry.[1] Recently, the transition metal catalyzed highly enantioselective α-fluorination of β-ketoesters has been achieved by several groups.[2] For example, Togni reported the [$TiCl_2$(TADDOLato)]-catalyzed reaction with Selectfluor, and they also discovered a ruthenium catalyst system.[3] Sodeoka demonstrated a Pd/BINAP-catalyzed system with *N*-fluorobenzenesulfonimide (NFSI).[4] Cahard also described that Cu/Box is an effective catalyst for the α-fluorination of β-ketoesters.[5] Furthermore, Shibata and Toru attained a high enantioselectivity with a Ni/dbfox catalyst.[6] More recently, a Ni or Mg/*N*,*N*,*N*-tridentate ligand system was reported by Shibatomi and Iwasa,[7] and chiral rare earth perfluorinated organophosphate catalysts were developed by Inanaga.[8] 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 α,β-unsaturated carbonyl compounds.[9] 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 α-fluorination of β-ketoesters.

We examined the reaction of ethyl 2-oxocyclopentanecarboxylate (**1a**) with NFSI using cobalt catalysts.[10] Based on the results of our previous chiral cobalt catalyzed asymmetric reaction,[9] we tested the α-fluorination reaction of β-ketoesters by $Co(ClO_4)_2 \cdot 6H_2O$ with (*S*,*S*)-*ip*-pybox. However, the reaction produced an α-fluorinated product with a poor result; i.e., a 55% yield and 25% enatiomeric excess (Table 1, Entry 1). Reinvestigation of the effective combination of a cobalt salt and chiral ligand revealed that $Co(acac)_2$ with the (*R*,*R*)-Jacobsen's salen ligand (**L2**) exhibited a higher enatiomeric 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 °C (84% isolated yield with 89% ee). According to the reported results of the metal-catalyzed α-fluorination of cyclic β-ketoesters by other groups, it seems that moderately bulky groups, such as *tert*-butyl, at the ester functionality are necessary to attain high 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,[3c,8] 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 α-fluorination of the ethyl ester **1a** (89% ee, Entry 7).

Table 1. Cobalt catalysts for the α-fluorination of ethyl 2-oxocyclopentanecarboxylate (**1a**)[a]



1a **2a**



L1: (*S*,*S*)-*ip*-pybox **L2**: (*R*,*R*)-Jacobsen's salen ligand

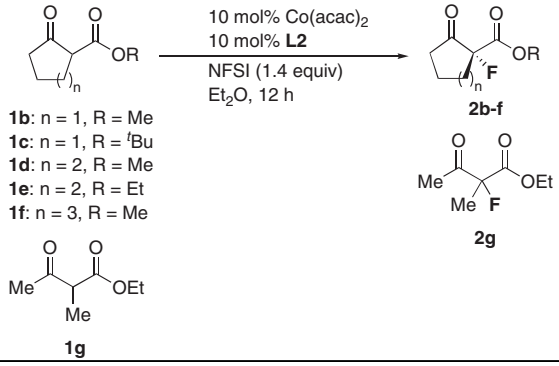
Entry	[Co]	L	Solv./ Temp (°C)	Yield /%[b]	ee/%[c]
1	$Co(ClO_4)_2 \cdot 6H_2O$	**L1**	THF/rt	55	25
2	$Co(ClO_4)_2 \cdot 6H_2O$	**L2**	THF/rt	50	8
3	$Co(acac)_2$	**L1**	THF/rt	86	34
4	$Co(acac)_2$	**L2**	THF/rt	60	60
5	$Co(acac)_2$	**L2**	Et_2O/rt	41	73
6	$Co(acac)_2$	**L2**	Et_2O/0	68	85
7	$Co(acac)_2$	**L2**	Et_2O/−20	84	89

[a]Reaction conditions: **1a** (0.32 mmol), [Co] (0.032 mmol), **L1** or **L2** (0.032 mmol), NFSI (0.45 mmol), solvent (1.0 mL). [b]Isolated yield. [c]Enantiomeric excess values were determined by GC analysis using Chiraldex G-TA.

We used the $Co(acac)_2$/**L2** catalyst for the α-fluorination of other β-ketoesters. These results are summarized in Table 2. The ketoester **1b** (methyl ester) produced the desired α-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 β-ketoesters containing six- or seven-membered rings (**1d**–**1f**) (Entries 3–5). We further examined the reaction of acyclic β-ketoester **1g**, but both yield and enantioselectivity were moderate (Entry 6).[11]

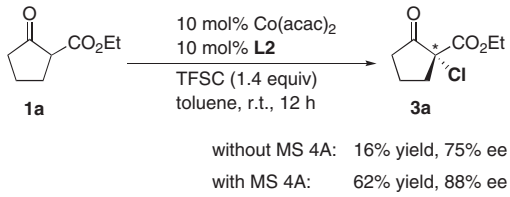
Furthermore, the $Co(acac)_2$/**L2** catalyst worked as a good system for the the enantioselective α-chlorination of **1a** with CF_3SO_2Cl (TFSC) (Scheme 1).[6,12] The reaction was carried out

Table 2. Cobalt-catalyzed α-fluorination of β-ketoesters (**1b**–**1g**)[a]



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

[a]Reaction conditions: β-ketoester (0.32 mmol), $Co(acac)_2$ (0.032 mmol), **L2** (0.032 mmol), NFSI (0.45 mmol), diethyl ether (1.0 mL). [b]Isolated yield. [c]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 α-fluorination and α-chlorination of β-ketoesters. Both of these desired reactions were catalyzed by a chiral cobalt catalyst, which was prepared from $Co(acac)_2$ with (*R,R*)-Jacobsen's salen ligand, and the α-fluorinated or α-chlorinated products were obtained with good enantioselectivities.

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10 Typical procedure: A solution of $Co(acac)_2$ (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 β-ketoester **1a** (50 mg, 0.32 mmol), then stirred for 12 h. Saturated NH_4Cl was added for quenching, and the water layer was extracted with diethyl ether (1.0 mL × 3). The combined organic layers were washed with brine and dried over $MgSO_4$. 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^{-1}, inj. temperature 160 °C, det. temperature 100 °C: $t(R) = 26.0$ min, $t(S) = 30.5$ min). $[\alpha]_D^{25}$ 85.8 (*c* 0.56, $CHCl_3$) (89% ee) {lit.[3c] $[\alpha]_D^{25}$ 169.0 (*c* 1.53, $CHCl_3$) (99.7% ee)}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 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). ^{13}C NMR (125 MHz, $CDCl_3$): δ 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). ^{19}F NMR (470 MHz, $CDCl_3$, internal standard: C_6F_6): δ −2.39 (t, $J = 18.8$ Hz).

11 We also examined the fluorination reactions of 2-methoxycarbonyl-1-indanone and 2-ethoxycarbonyl-1-indanone by $Co(acac)_2$/**L2** catalyst, but the enantioselectivities were 55% ee (98% yield) and 50% ee (94% yield), respectively.

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