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$CeCl_3 \cdot 7H_2O$: An Effective Additive in Ru-Catalyzed Enantioselective Hydrogenation of Aromatic α-Ketoesters

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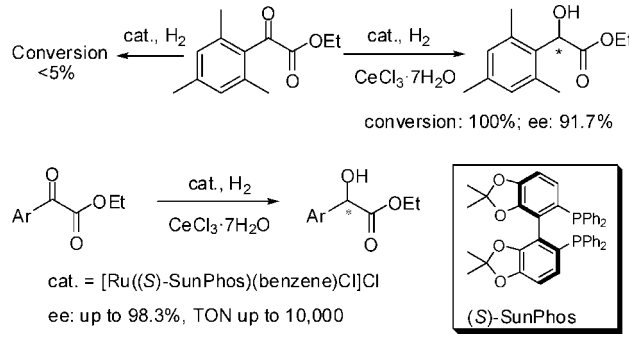

In the presence of catalytic amounts of $CeCl_3 \cdot 7H_2O$, [RuCl(benzene)(*S*)-SunPhos]Cl is a highly effective catalyst for the asymmetric hydrogenation of aromatic α-ketoesters. A variety of ethyl α-hydroxy-α-arylacetates have been prepared in up to 98.3% ee with a TON up to 10 000. Challenging aromatic α-ketoesters with ortho substituents are also hydrogenated with high enantioselectivities. The addition of $CeCl_3 \cdot 7H_2O$ not only improves the enantioselectivity but also enhances the stability of the catalyst. The ratio of $CeCl_3 \cdot 7H_2O$ to [RuCl(benzene)(*S*)-SunPhos]Cl plays an important role in the hydrogenation reaction with a large substrate/catalyst ratio.

Introduction

Asymmetric hydrogenation is the most broadly utilized catalytic enantioselective method and accounts for over half of the chiral compounds manufactured other than resolution.[1] It is well-known that asymmetric catalytic systems are often very sensitive to small variations in substrates, catalysts, and reaction conditions. Frequently, small amounts of achiral or chiral additives have been attributed to remarkable changes in conversion rate, yield, enantioselectivity, and even reaction pathway.[2]

Enantiomerically pure α-hydroxy acids and their derivatives are very important structure motifs in numerous biologically interesting compounds and have also been extensively utilized in a number of stereoselective processes.[3] Among the many methods (reductions by chiral boranes,[4] diastereoselective reductions involving chiral auxiliaries,[5] homogeneous asymmetric catalytic hydrogenations and hydrogen transfer reactions,[6] heterogeneous catalytic enantioselective hydrogenations,[7] enzymatic or biomimetic methods,[8] kinetic resolution of racemic

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α-hydroxy ester,[9] hydrogen mediated C−C bond formation,[10] and synthesis of chiral cyanohydrins as precursors via metal catalysts and organocatalysts[11]) available for the preparation of these compounds, transition metal catalyzed enantioselective hydrogenation proved most efficient. However,asymmetric hydrogenation of α-ketoesters has received much less attention than the hydrogenation of dehydroamino acid derivatives and *β*-ketoesters, and there are only a few ligands that afford high enantioselectivities for this substrate class.[6m−o] Therefore, the search for effective, high enantioselective, and universal approaches to α-hydroxy acids or esters is still of significance.

We have reported that aromatic α-ketoesters were hydrogenated efficiently with high enantioselectivities by employing Lewis acid additives and our chiral diphosphines.[12] We extended these studies to a variety of aromatic α-ketoesters, and here we report the effect of different substituents of aryls on the catalyst performances and the function of the additives.

Results and Discussion

In our previous letter, with the use of methyl benzoylformate as the model substrate, the effect of ligands, solvents, and the additives on reactivity and enantioselectivity was screened.[12] In general, both Brønsted acids and Lewis acids could be used as additives to improve enantioselectivities in the asymmetric hydrogenations, but when Lewis acids were used as additives in the hydrogenation of our model substrate with [RuCl(benzene)(*S*)-SunPhos]Cl (**4**) as the catalyst, dramatically improved enantioselectivities (90−96% ee vs 85−89% ee) were obtained. A variety of lanthanide ($LnCl_3 \cdot XH_2O$) salts proved effective, and for reasons of simplicity, $CeCl_3 \cdot 7H_2O$ was chosen as the preferred additive.

Based on the initial success of asymmetric hydrogenation of α-ketoesters with **4** and $CeCl_3 \cdot 7H_2O$ as the additive, we employed ethyl benzoylformate as the model substrate to study the effect of Ru catalyst precursors. Toward this end, [RuCl(benzene)(*S*)-SunPhos]Cl (**4**),[6c] $RuCl_2$[(*S*)-SunPhos](DMF)$_m$ (**5**),[13] and $[NH_2Me_2]^+$[{RuCl [(*S*)-SunPhos]}$_2$(μ-Cl_3)] (**6**)[14] were tested across a range of reaction temperatures and concentrations for enantioselectivity, and the results are summarized in Table 1. In the presence of $CeCl_3 \cdot 7H_2O$, all Ru precursors led to complete conversion with comparable enantioselectivities, and the results are superior to those obtained without addition of $CeCl_3 \cdot 7H_2O$ (Table 1, entries 2, 4, 6 vs entries 1, 3, 5). Increasing the reaction temperature improved the reaction rate; however, a slight decrease in ee was observed. Lowering the substrate concentration from 0.5 to 0.1 M increased the ee value from 96.3% to 97.5% (Table 1, entry 2 vs entry 8). Some other atropisomer ligands (**L1**, **L2**, **L4**, **L5**) were also tested for the asymmetric hydrogenation of ethyl benzoylformate. Although the enantioselectivities were greatly dependent on ligands, the addition of $CeCl_3 \cdot 7H_2O$ was proved efficient in improving the enantioselectivities (Table 1, entries 9, 11, 13, 15 vs entries 10, 12, 14, 16). Because both ruthenium complex **5** and **6** were prepared from complex **4**, for simplicity and convenience the optimized reaction conditions were therefore set as the following: 1 mol % of [RuCl(benzene)(*S*)-SunPhos]Cl (**4**) as the catalyst, 5 mol % of $CeCl_3 \cdot 7H_2O$ as the additive, ethanol as the solvent with the substrate concentration of 0.5 M, and 50 bar of H_2 at 50 °C.

The results for asymmetric hydrogenation of aromatic α-ketoesters **1a**−**1t** (Figure 1)[15] under the optimized conditions are summarized in Table 2. Column A illustrates the results of hydrogenation without additive. As a matter of fact, without $CeCl_3 \cdot 7H_2O$ the enantioselectivities showed a striking dependence on the nature of the substrates. The *para*- (column A, entries 1−6) and *meta*- (column A, entry 10) monosubstituted and *para* and *meta*-polysubstituted phenylglyoxylate (column

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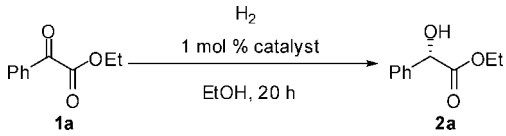
TABLE 1. Optimization of Reaction Conditions for Asymmetric Hydrogenation of Ethyl Benzoylformate[a]



entry	catalyst/additive[b]	ee (%)[c]
1	**4**/none	85.4
2	**4**/$CeCl_3 \cdot 7H_2O$	96.3
3	**5**/none	86.1
4	**5**/$CeCl_3 \cdot 7H_2O$	96.2
5	**6**/none	89.1
6	**6**/$CeCl_3 \cdot 7H_2O$	95.7
7[d]	**4**/$CeCl_3 \cdot 7H_2O$	96.0
8[e]	**4**/$CeCl_3 \cdot 7H_2O$	97.5
9[f]	**7**/none	81.0
10	**7**/$CeCl_3 \cdot 7H_2O$	88.2
11[f]	**8**/none	84.6
12	**8**/$CeCl_3 \cdot 7H_2O$	96.3
13[f]	**9**/none	71.0
14	**9**/$CeCl_3 \cdot 7H_2O$	92.8
15[f]	**10**/none	85.2
16	**10**/$CeCl_3 \cdot 7H_2O$	95.6

[a] All reactions were carried out with a substrate (1 mmol) concentration of 0.5 M in EtOH at 50 °C and 50 bar of H_2. Conversion: 100%. [b] The molar ratio of catalyst/additive was 1:5. [c] ee values were determined by HPLC on a Chiracel OD-H column. The configuration was determined to be *S* by comparing the specific rotation with reported data. [d] The reaction was carried out at 70 °C. [e] The reaction was carried out with a substrate concentration of 0.1 M. [f] **7**: [RuCl(benzene)**L1**]Cl. **8**: [RuCl(benzene)**L2**]Cl. **9**: [RuCl(benzene)**L4**]Cl. **10**: [RuCl(benzene)**L5**]Cl.

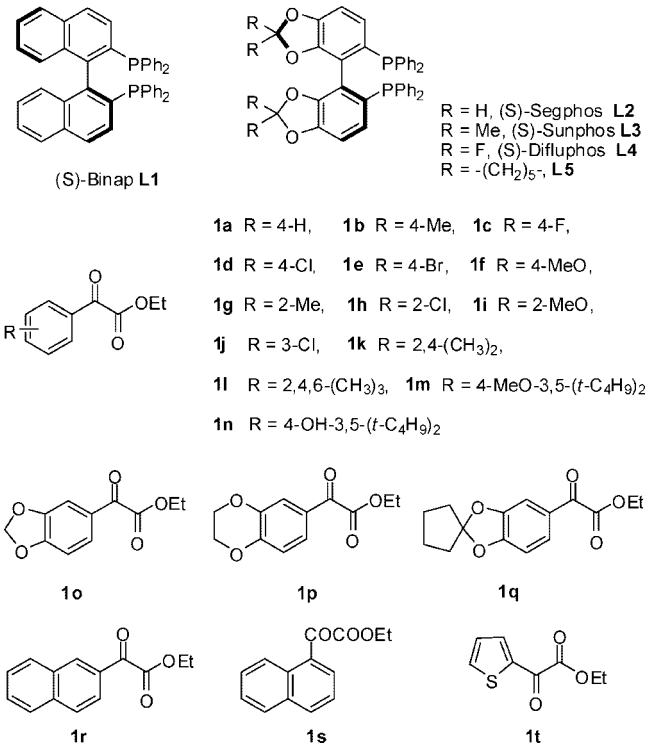
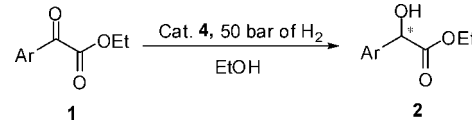


FIGURE 1. Structure of ligands **L1**−**L5** and aromatic α-ketoesters **1a**−**1t**.

A, entries 13−18) led to moderate to good ee values (ee: 74.3−91.0%). Substrates with electron-donating substituents usually gave higher ee values (column A, entries 2, 6, 13−18 vs entries 3, 4, 5, 10). However, all *ortho*-substituted phenylglyoxylates gave poor ee values (column A, entries 7−9, 11−12, and 19; ee: 16.0−40.4%). Apparently, steric hindrance played a crucial role in the asymmetric hydrogenation of these substrates. For sterically more hindered ethyl 2,4,6-trimethylphenylglyoxylate (**1l**), the hydrogenation was extremely sluggish (column A, entry 12, conversion <5%). Ethyl 2-thienylglyoxylate (**1t**), with a sulfur atom proximately situated for possible coordination to ruthenium, was hydrogenated with a moderate ee (column A, entry 20).

TABLE 2. Asymmetric Hydrogenation of $ArCOCO_2Et$ by 4/$CeCl_3 \cdot 7H_2O$[a]



		ee (%)[b]	
entry	substrate	A[c]	B
1	**1a**	85.3	96.3
2	**1b**	87.2	96.1
3	**1c**	75.1	96.4
4	**1d**	74.8	96.1
5	**1e**	80.3	96.1
6	**1f**	89.3	89.3
7	**1g**	39.1	89.2
8	**1h**	29.1	78.2
9	**1i**	−16.0	95.4
10	**1j**	74.3	95.4
11	**1k**	40.2	88.1
12	**1l**	N/D[d]	91.7
13	**1m**	81.6	93.0
14	**1n**	83.3	94.3
15	**1o**	79.3	93.1
16	**1p**	80.5	93.6
17	**1q**	84.5	93.5
18	**1r**	91.0	98.3
19	**1s**	40.4	90.0
20	**1t**	60.9	86.9

[a] All reactions were carried out in EtOH with a substrate (1 mmol) concentration of 0.5 M in EtOH at 50 °C and 50 bar of H_2 for 20 h. Substrate/[Ru(benzene)Cl_2]$_2$/(*S*)-Sunphos/additive: 100:0.5:1.1:5. Conversion was 100% except where indicated. [b] ee values were determined by HPLC. A, no additive; B, $CeCl_3 \cdot 7H_2O$ as additive. [c] Reactions were carried out at 70 °C. The data of entries 1−8 were cited from ref 12. [d] Conversion was <5%. ee value not determined.

Column B illustrates the results of hydrogenation with $CeCl_3 \cdot 7H_2O$ as the additive. In sharp contrast to the results in column A, a dramatic increase in reaction efficiency and enantioselectivity was achieved, and substrate dependency was significantly attenuated.

For *para*- (column B, entries 1−5) and *meta*- (column B, entry 7) monosubstituted phenylglyoxylate, excellent enantioselectivities (ee: 95.4−96.4%) have been achieved with the exception of ethyl *p*-methoxyphenylglyoxylate (**1f**) (column B, entry 6, ee: 89.3%). Interestingly, *para* and *meta*-dialkoxy-substituted phenylglyoxylates (column B, entries 15−17, ee: 93.1−93.6%) gave higher ee values than that of ethyl *p*-methoxyphenylglyoxylate (**1f**). With $CeCl_3 \cdot 7H_2O$ as the additive, it seemed that stereo rather than electronic factors controlled the enantioselectivity: the bigger aryl planar tends to induce higher enantioselectivities for the aromatic α-ketoesters without ortho substituents. This was further supported by the fact that when ethyl 2-(naphthalen-2-yl)-2-oxoacetate (**1r**) was employed as the substrate the highest enantioselectivity (column B, entry 18, ee: 98.3%) was obtained.

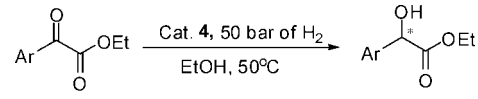
Only sporadic reports up to now have been disclosed on the asymmetric hydrogenation of aromatic α-ketoesters possessing

a substituent at the ortho position of the aromatic ring.[8k] Genêt and co-workers have reported the Ru-catalyzed asymmetric hydrogenation of methyl *o*-chlorophenylglyoxylate with ee values up to 50%.[16] Zhang and co-workers have reported that methyl *o*-fluorophenylglyoxylate was hydrogenated with 84.6% ee,[6p] and Rh-catalyzed hydrogenation of *ortho* and *para*-disubstituted phenylglyoxylates led to 51−81% ee.[6f] With $CeCl_3 \cdot 7H_2O$ as the additive, all of the tested *ortho*-substituted phenylglyoxylates were hydrogenated with much higher ee values (column B, entries 7−9, 11−12, and 19; ee: 78.2−95.4%) than those without $CeCl_3 \cdot 7H_2O$ (ee: <41%). Remarkably, addition of $CeCl_3 \cdot 7H_2O$ (entry 9) even reverse the product configuration (ee 95.4% vs ee −16.0%) for ethyl *o*-methoxylphenylglyoxylate (**1i**). Ethyl 2,4,6-trimethylphenylglyoxylate (**1l**), which was inactive in the absence of $CeCl_3 \cdot 7H_2O$, was also smoothly hydrogenated with high enantioselectivity (column B, entry 11, ee: 91.7%). Obviously, the addition of $CeCl_3 \cdot 7H_2O$ eliminated, or at least weakened, the negative effect of the steric hindrance on the reactivity and enantioselectivity. The addition of $CeCl_3 \cdot 7H_2O$ also suppressed the competing coordination of the adjacent heteroatom; for example, hydrogenation of ethyl 2-hydroxy-2-(thiophen-2-yl) acetate (**2t**) afforded good ee (column B, entry 20, ee: 86.9%).

As a mild and water-tolerant Lewis acid, cerium(III) chloride is widely used in carbonyl chemistry.[17] In the course of our exploration of these hydrogenation reactions, we found that the cerium chloride hydrate not only improved the reaction activity and enantioselectivity but also stabilized the catalyst [RuCl(benzene)(*S*)-SunPhos]Cl.[12] Unfortunately, attempts to isolate and identify the catalytic intermediates have not been successful. From the mechanistic point of view,[2d] Lewis acids (LA) and transition metals (TM) may cooperate in the following ways: (a) the Lewis acid activates organic substrates, for example, by forming adducts with carbonyl groups (C═O → LA) mainly through σ-coordination, to generate more reactive electrophiles toward attack by transition metal hydride; (b) the Lewis acid activates transition metals or transition metals−organic substrate intermediates, for example, by abstracting halides from the transition metals to generate more reactive species, TM^{n+}; (c) the Lewis acid affects the stereo- or chemoenvironment of the reactive intermediates via coordination to transition metals−organic substrate species. The Lewis acids may play either one of these or multiple roles in a single reaction process.

To investigate the function of $CeCl_3 \cdot 7H_2O$ in the ruthenium-catalyzed asymmetric hydrogenation, we have run a series of experiments. First, we recorded the ^{31}P NMR spectrum of the ethanol solution of [RuCl (benzene)(*S*)-SunPhos]Cl (ethanol as solvent and 75% H_3PO_4 as internal standard). It showed a set of doublets at 32.7 and 39.7 ppm with $J_{P-P} = 64.8$ Hz, but the ^{31}P NMR spectrum became complicated after the ethanol solution was heated under nitrogen for 16 h at 60 °C. In contrast, when the ethanol solution of [RuCl (benzene)(*S*)-SunPhos]Cl was added to 5 equiv of $CeCl_3 \cdot 7H_2O$, the chemical shifts of the phosphorus atoms moved downfield by 0.4 ppm with a J_{P-P} unchanged (a set of doublets at 33.1 and 40.1 ppm with $J_{P-P} = 64.8$ Hz). The solution remained unchanged by NMR upon being heated under nitrogen for 16 h at 60 °C. It was reported that the [RuCl(benzene)(*S*)-BINAP]Cl would form the inactive halide-bridged trinuclear Ru complex in methanol when heated at 60 °C for 12 h.[18a] These ^{31}P NMR data do not support the coordination of Ce with the diphosphine directly or its abstraction of halides from the [RuCl (benzene)(*S*)-SunPhos]Cl, though it might be coordinated with ruthenium through a halide bridge.[18] This coordination may have resulted in a relatively electron-poor Ru(II) complex which was more stable to the oxygen, and it may have also prevented the formation of a trinuclear Ru complex.

TABLE 3. Effects of Additives under Controlled Conditions[a]



1 **2**

entry	substrate	ee (%)[b] A	ee (%)[b] B
1	**1a**	94.4	96.1
2	**1d**	93.5	94.3
3	**1i**	93.6	90.3
4	**1o**	93.9	90.1
5	**1h**	24.3	25.6
6	**1i**	1.3	31.2
7	**1l**	N/D[c]	78.7[d]

[a] All reactions were carried out in EtOH with a substrate (1 mmol) concentration of 0.5 M in EtOH at 50 °C and 50 bar of H_2 for 20 h. Substrate/[Ru(benzene)Cl_2]$_2$/(*S*)-SunPhos/additive: 100:0.5:1.1:5. Conversion was 100% except where indicated. [b] ee values were determined by HPLC on a Chiracel OD-H column. A, 1 N HCl as additive; B, both 1 N HCl and $CeCl_3 \cdot 7H_2O$ as the additive. [c] Conversion was <5%. ee value not determined. [d] Conversion was 64% determined by ^1H NMR.

It was reported that high enantioselectivities (up to 94% ee) were obtained when methyl *p*-chlorophenylglyoxylate was hydrogenated with a Ru catalyst generated in situ from [RuI_2(*p*-cymene)]$_2$ and MeObiphep, and the addition of catalytic amounts of 1 N HCl was essential both for good activity and for enantioselectivity.[6n] Brønsted acids have been proved to play a very important role in the asymmetric hydrogenation of functionalized ketones.[19] It is well established that Brønsted acids facilitate intramolecular hydride transfer through the protonation of the keto oxygen.[1d]

To confirm whether $CeCl_3 \cdot 7H_2O$ hydrolyzed to produce hydrogen chloride, we carried out some parallel experiments (1 N HCl as the additive or both 1 N HCl and $CeCl_3 \cdot 7H_2O$ as the additive), and the results were shown in Table 3.

For ethyl arylglyoxylate without ortho substituents, the addition of catalytic amounts of 1 N HCl also improved the enantioselectivities (Table 3, entries 1−4, column A, ee: 93.5−94.4%), which was comparable to the result of using MeObiphep as the ligand.[6n] Employing both $CeCl_3 \cdot 7H_2O$ and 1 N HCl as the additives did not increase or reduce the

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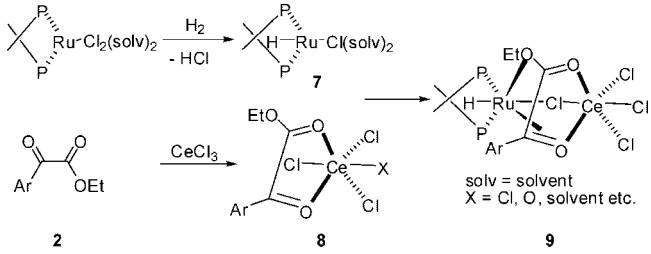


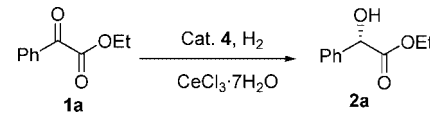
FIGURE 2. Proposed intermediates of the catalytic cycle.

enantioselectivities (Table 3, entries 1−4). Surprisingly, with the phenylglyoxylates possessing the ortho substituents at the aromatic ring, the results became complicated. In the presence of catalytic amounts of 1 N HCl, hydrogenation of ethyl 2-chlorophenylglyoxylate (**1h**) and ethyl 2-methoxyphenylglyoxylate (**1i**) gave much lower ee values (Table 3, column A, entries 5−6, ee: 24.3% and 1.3%) than those without any additive or with $CeCl_3 \cdot 7H_2O$ as the additive. Ethyl 2,4,6-trimethylphenylglyoxylate (**1l**) could not be hydrogenated with 1 N HCl as additive (Table 3, column A, entry 4, conversion <5%). In the presence of both 1 N HCl and $CeCl_3 \cdot 7H_2O$ (Table 3, entries 5−7, column B), lower enantioselectivities and activities were obtained than those of with only $CeCl_3 \cdot 7H_2O$ as the additive. Therefore, cerium(III) chloride would not undergo hydrolysis or ethanolysis to produce hydrogen chloride under the Ru-catalyzed asymmetric hydrogenation conditions. In catalytic hydrogenation of aromatic α-ketoesters, cerium(III) chloride activates aromatic α-ketoesters by forming adducts with carbonyl groups (C═O → LA) mainly through σ-coordination.[2d] The reaction proceeded through a different transition state when using $CeCl_3 \cdot 7H_2O$ or 1 N HCl as the additive, though both of them could improve the enantioselectivity.

It was reported that the α-dicarbonyl compound coordinates to the copper cation in a bidentate fashion with the two carbonyl oxygen atoms, activating carbonyl functionality toward nucleophiles. This activation is realized by lowering the energy of the $\pi_{C=O*}$ orbital (LUMO) compared with the unactivated substrate.[6q,20] On the basis of these results, we assume that two glyoxylate carbonyl oxygen atoms chelate to the Ce(III) ion to form the coordination complex **8** (Figure 2). In the catalytic cycle,[1d] Ru(II) monohydride **7** formed by the heterolysis of a hydrogen molecule by the ruthenium dichloride interacts reversibly with the complex to form intermediate **9** for hydride transfer. The formation of a five-membered ring through competitive coordination of the ketoester to the Ce(III) ion alters the coordination geometry of Ru(II) to carbonyl from the σ to the π style, at the same time, it increases the electrophilicity of the carbonyl carbon, and facilitates intramolecular hydride transfer. In addition, the halide-bridge linker between Ce(III) and Ru(II) makes the transition state more rigid, and it also serves as a good linker between the catalyst and substrate. Therefore, the aromatic α-ketoesters (**1**), even the challenging aromatic α-ketoesters with ortho substituents, are hydrogenated efficiently with high enantioselectivities.

For larger scale preparation of single enantiomer of mandelic acid, we applied the [RuCl(*S*)-SunPhos(benzene)]Cl/$CeCl_3 \cdot 7H_2O$ catalyst with increased substrate/catalyst ratio and the substrate concentration. As shown in table 4, when the substrate/catalyst ratio increased to 5,000 with a substrate concentration of 1.5 M (Table 4, entry 1), the hydrogenation of **1a** achieved complete conversion at 85 °C for 15 h, while the enantioselectivity decreased to 91.8% ee. On the basis of proposed transition state, we believe that increasing the additive/substrate ratio would be feasible for the formation of Ce(III) coordinated five-membered ring complex, and thus reduce the probability of direct coordination of Ru(II) with ketoester without involvement of Ce(III) and improve the enantioselectivity. As we expected, the enantioselectivity elevated gradually when increasing the additive/substrate ratio from 0.1 mol % to 0.8 mol % (Table 3, entries 2−4, ee: 92.3% to 94.3%). The experiment of s/c up to 10,000 is realized to give ethyl mandelate with 93.6% ee at 100 °C for 20 h (Table 4, entry 5). The reduced product could be hydrolyzed to mandelic acid and easily upgraded to >99% ee by a simple recrystallization from $ClCH_2CH_2Cl$.[12] Despite the fact that this hydrogenation was not fully optimized, the achieved catalyst performance (ee, TON, TOF) indicated that this hydrogenation might be feasible for the production of chiral building blocks for the synthesis of a wide variety of natural products and biologically active molecules[21] both from a technical and an economical point of view.[22]

TABLE 4. Preparative and Scale-up Experiments[a]



entry	S/C/additive[b]	ee (%)[c]
1	5000/1/5	91.8
2	5000/1/10	92.3
3	5000/1/20	93.2
4	5000/1/40	94.3
5	10000/1/200	93.6[d]

[a] The reactions were carried out in EtOH with a substrate (12.5 mmol) concentration of 1.5 M at 85 °C and 50 bar of H_2 for 15 h except where indicated. Conversion was 100%. [b] Molar ratio of substrate/catalyst/additive. [c] ee values were determined by HPLC on a Chiracel OD-H column. [d] The reactions were carried out in EtOH with a substrate (0.20 mol) concentration of 1.5 M at 100 °C and 50 bar of H_2 for 20 h. Conversion was 100%.

Conclusions

In summary, $CeCl_3 \cdot 7H_2O$ was found to be an effective additive for the asymmetric hydrogenation of a variety of aromatic α-ketoesters. To our knowledge, using $CeCl_3 \cdot 7H_2O$ as the additive, the enantioselectivities obtained are among the best ones reported in the literature for the hydrogenation of aromatic α-ketoesters, especially for substrates possessing a substituent at the ortho position of the aromatic ring. The synthesis of chiral ethyl 2-hydroxy-2-mesitylacetate (**2l**) was achieved for the first time through asymmetric hydrogenation. Our ongoing experiments are focused on the function of the Lewis acids on asymmetric hydrogenation and investigation of the reaction mechanism.

Experimental Section

Typical Procedure for the Asymmetric Hydrogenation of Aromatic α-Ketoesters. To a 20 mL Schlenk tube were added

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$[Ru(benzene)Cl_2]_2$ (10 mg, 0.02 mmol) and (*S*)-SunPhos (30 mg, 0.045 mmol). The tube was vacuumed and purged with nitrogen three times before addition of freshly distilled and degassed EtOH/CH_2Cl_2 (3 mL/3 mL). The resulting mixture was heated at 50 °C for 1 h and then cooled to room temperature. The solvent was removed under vacuum to give the catalyst. The catalyst was dissolved in degassed ethanol (8 mL) containing $CeCl_3 \cdot 7H_2O$ (75 mg, 0.20 mmol), and then the solution was put into 4 vials equally. To these vials α-ketoesters (1 mmol) were introduced, and then the vials were taken into an autoclave. The autoclave was purged three times with H_2, and the pressure of H_2 was set to 50 bar. The autoclave was stirred under specified reaction conditions. After being cooled to ambient temperature and release of the hydrogen, the autoclave was opened and the solvent was evaporated. The enantiomeric excess was determined by HPLC after passing the samples through a short pad of silica gel with petroleum ether and ethyl acetate.

2a. ^{1}H NMR (400 MHz, $CDCl_3$): 1.23 (t, J = 7.6 Hz, 3H), 3.48 (d, J = 5.2 Hz, 1H), 4.13∼4.31 (m, 2H), 5.26 (d, J = 5.2 Hz, 1H), 7.32∼8.44 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.8, 62.0, 72.8, 126.4, 128.2, 128.4, 138.3, 173.5. HPLC (Chiralcel OD-H column, hexane/^{i}PrOH 90/10, 0.5 mL min^{-1}, 254 nm): t_R (major) = 12.7 min, t_R (minor) = 22.8 min.

2i. ^{1}H NMR (400 MHz, $CDCl_3$): 1.20 (t, J = 7.2 Hz, 3H), 3.58 (dd, J = 1.2, 7.2 Hz, 1H), 3.83 (s, 3H), 4.15∼4.27 (m, 2H), 5.26 (d, J = 7.6 Hz, 1H), 6.89∼6.98 (m, 2H), 7.26∼7.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.7, 55.2, 61.3, 69.7, 110.8, 120.5, 127.0, 129.0, 129.5, 156.8, 173.4. HPLC (Chiralcel OD-H column, hexane/^{i}PrOH 90/10, 0.5 mL min^{-1}, 254 nm): t_R (major) = 15.7 min, t_R (minor) = 18.7 min.

2l. ^{1}H NMR (400 MHz, $CDCl_3$): 1.22 (t, J = 7.2 Hz, 3H), 2.26 (s, 3H), 2.33 (s, 6H), 3.24 (d, J = 3.2 Hz, 1H), 4.15∼4.32 (m, 2H), 5.52 (d, J = 3.2 Hz, 1H), 6.84 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.9, 19.8, 20.7, 61.9, 68.9, 129.6, 131.4, 137.0, 137.6, 174.7. HPLC (Chiralcel OD-H column, hexane/^{i}PrOH 90/10, 0.5 mL min^{-1}, 254 nm): t_R (major) = 11.9 min, t_R (minor) = 13.6 min.

2r. ^{1}H NMR (400 MHz, $CDCl_3$): 1.21 (t, J = 7.2 Hz, 3H), 3.65 (d, J = 5.6 Hz, 1H), 4.12∼4.31 (m, 2H), 5.32 (d, J = 5.6 Hz, 1H), 7.24∼7.90 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.7, 61.9, 72.9, 124.0, 125.7, 126.0, 127.4, 127.9, 128.1, 132.95, 133.02, 135.7, 173.4. HPLC (Chiralcel OD-H column, hexane/^{i}PrOH 90/10, 0.5 mL min^{-1}, 254 nm): t_R (major) = 18.1 min, t_R (minor) = 21.4 min.

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Supporting Information Available: NMR and/or HPLC data of compounds **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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