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Ru-Catalyzed Asymmetric Hydrogenation of α-Ketoesters with $CeCl_3 \cdot 7H_2O$ as Additive

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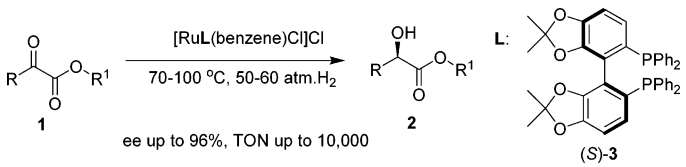
ABSTRACT



An efficient asymmetric hydrogenation of α-ketoesters is reported with use of a catalyst prepared from [Ru((*S*)-3)(benzene)Cl]Cl and $CeCl_3 \cdot 7H_2O$. α-Hydroxy esters are obtained in up to 96% ee. The addition of $CeCl_3 \cdot 7H_2O$ not only improves the enantioselectivity, but also enhances the stability of the catalyst. As a result, the hydrogenation of methyl benzoylformate affords the product with 92% ee with a substrate/catalyst ratio of 10 000. Hydrolysis of 2 provides the final compound with 83% yield at 99% ee after a single recrystallization from 1,2-dichloroethylene.

Optically active α-hydroxy acids and their derivatives are very important structural motifs in numerous biologically interesting compounds[1] and are often utilized as resolving agents.[2] Accordingly, considerable effort has been devoted to their preparation via asymmetric synthesis. Besides optical resolution of the racemates with resolving agents, reductive approaches have been developed extensively,[3] including (1) reductions by chiral boranes,[4] (2) diastereoselective reductions with the help of chiral auxiliaries,[5] (3) homogeneous hydrogenations and hydrogen transfer reactions,[6] (4) heterogeneous catalytic enantioselective hydrogenations, especially hydrogenation with Pt-cinchona modifiers,[3,7] and (5) enzymatic or biomimetic methods.[8] Recently, a few other catalytic approaches have been reported: namely, carbon−carbon bond formation reaction,[9] kinetic resolution/asymmetric

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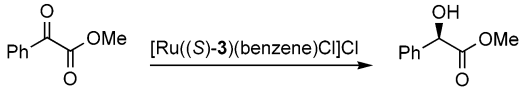
oxidation of α-hydroxy esters,[10] and dynamic kinetic resolution of dioxolanediones.[11] However, the catalytic reductive approaches to nonracemic α-hydroxy acids or esters are the most attractive due to their simplicity and efficiency. Despite all of these achievements, developing effective, easily reproducible, highly stereoselective and universal approaches to α-hydroxy acids or esters is still challenging.

In this Letter, we report a Ru-catalyzed homogeneous hydrogenation reaction of α-ketoesters with various Lewis acids as additives. Our model reactions were conducted with [Ru((*S*)-**3**)(benzene)Cl]Cl as the catalyst,[12] which is efficient in the hydrogenation of *β*-ketoesters,[12c] and which is easily prepared by heating $[Ru(benzene)Cl_2]_2$ and (*S*)-**3** (molar ratio 1:2.2) in a solution of EtOH and CH_2Cl_2 (1:1, v/v) at 50 °C. Hydrogenation reactions were carried out with a ketoester/Ru ratio of 100 at 0.5 M concentration. The reaction was completed within 20 h at 70 °C with a hydrogen pressure of 50 atm. Under these catalytic conditions, the hydrogenation of methyl benzoylformate (**1a**) afforded the product with good enantioselectivity (85% ee, Table 1, entry 1). (*S*)-**3** is superior to BINAP and comparable to SEGPhos (Table 1, entries 1−4).

It is reported that catalytic additives play a crucial role in improving the reactivity and enantioselectivity of many asymmetric reactions.[13] King et al.[14] reported that acid additives can promote the reaction rates in ruthenium-catalyzed hydrogenations of *β*-ketoesters. Utilizing Brønsted acids as additives, Takaya and co-workers [12b] also acquired elevated enantioselectivities (79% vs to 89% ee) in the asymmetric hydrogenation of α-ketoesters. Noyori and co-workers[15] found that Ru(II) catalysts in situ modified with acid facilitate the hydrogenation of simple ketones and 4-oxoesters. They also showed that no reaction takes place without acid additives. Although it is not quite clear what these additives do in terms of the reaction mechanism, they are often beneficial in the ruthenium-catalyzed hydrogenation of ketones. Therefore, Brønsted acids were tested and results were positive but still not excellent (87−89% ee, Table 1, entries 5 and 6).

Table 1. Asymmetric Hydrogenation of Methyl Benzoylformate with (Ru(L*)(benzene)Cl)Cl[a]



1a **2a**

entry	additive	ee (%)[b]
1		85
2[c]		85
3[d]		84
4[e]		79
5	HBF_4 aq	87
6	CSA	89
7	CuCl	90
8	$CuCl_2$	91
9	$MgCl_2 \cdot 6H_2O$	85
10	$AlCl_3$	87
11	$FeCl_3$	92
12	$CeCl_3 \cdot 7H_2O$	96
13	$LaCl_3 \cdot 7H_2O$	95
14	$NdCl_3 \cdot 6H_2O$	96
15	$SmCl_3 \cdot 6H_2O$	95
16	$YbCl_3 \cdot 6H_2O$	93
17[c]	$CeCl_3 \cdot 7H_2O$	96
18[f]	$CeCl_3 \cdot 7H_2O$/CSA	96

[a] All reactions were carried out in MeOH with a substrate concentration of 0.5 M at 70 °C under 50 atm of H_2 for 20 h. Substrate/$[Ru(benzene)Cl_2]_2$/(*S*)-**3**/additive: 100/0.5/1.1/5; conversion:100%. [b] Ee values were determined by HPLC on a Chiracel OD-H column. The configuration was determined to be *R* by comparing the specific rotation with reported data. [c] Ethyl benzoylformate (**1b**) was hydrogenated in EtOH under the same conditions. [d] **1b** was hydrogenated in EtOH under the same conditions with SEGPhos as ligand. [e] [Ru(binap)(benzene)Cl]Cl as the catalyst according to ref 12b. [f] **1b** was hydrogenated in EtOH under the same conditions. Both $CeCl_3 \cdot 7H_2O$ and CSA are 5 equiv relative to the catalyst.

Lewis acids are among the most useful reagents in reactions with ketones as substrates.[16] For example, $CeCl_3 \cdot 7H_2O$ was used in the selective reduction of the carbonyl group of α,*β*-unsaturated ketones with $NaBH_4$.[17] When Lewis acids were used as additives in the hydrogenation of our model substrate **1a** with ruthenium as the catalyst (Table 1, entries 7−16), dramatically improved enantioselectivities (90−96% ee) were obtained. The best results were achieved with $LnCl_3 \cdot XH_2O$ as additives and ee values of the reduced product were comparable (Table 1, entries 12−16). There was no detectable difference between the hydrogenations of methyl and ethyl benzoylformates (Table 1, entries 12 and 17). The reactions with both $CeCl_3 \cdot 7H_2O$ and CSA (1:1) (CSA: D-camphor-10-sulfonic acid) as additives provided the same ee value as those with only $CeCl_3 \cdot 7H_2O$ as the additive (96% ee, Table 1, entries 17 vs 18). For simplicity and better reproducibility, substrate/$[Ru(benzene)Cl_2]_2$/(*S*)-**3**/$CeCl_3 \cdot 7H_2O$ with a ratio of 100/0.5/1.1/5 was employed as the standard set of reaction conditions.

Under the optimized reaction conditions, a variety of substrates were tested in the asymmetric hydrogenations with

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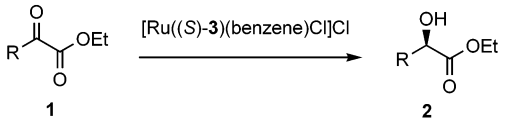
[Ru((*S*)-**3**)(benzene)Cl]Cl and the $CeCl_3 \cdot 7H_2O$ system (Table 2, column C). Hydrogenation of 4-halo or 4-methyl benzoylformic acid ethyl esters gave comparable ee values (94−95% ee, Table 2, entries 2 and 5−7, column C), while 4-methoxy (strong electron-donating substituent), 2-methyl (stereohindering substituent), and 2-chloro (coordinating substituent) benzoylformate were reduced with only 88% ee, 87% ee, and 76% ee, respectively (Table 2, entries 3, 4, and 8, column C).

Table 2. Asymmetric Hydrogenation of $RCOCO_2Et$ with Additives[a]



1 2

		ee[b]		
entry	Ar	A	B	C
1	Ph (**1b**)	85	89	96
2	4-Me-C_6H_4 (**1c**)	87	90	95
3	4-MeO-C_6H_4 (**1d**)	89	89	88
4	2-Me-C_6H_4 (**1e**)	29	30	87
5	4-F-C_6H_4 (**1f**)	75	88	95
6	4-Cl-C_6H_4 (**1g**)	75	87	94
7	4-Br-C_6H_4 (**1h**)	80	86	95
8	2- Cl-C_6H_4 (**1i**)	40	−9	76
9[c]	Me (**1j**)	83	92	84

[a] All reactions were carried out in EtOH with a substrate concentration of 0.5 M at 70 °C and 50 atm of H_2 for 20 h. Substrate/[Ru(benzene)Cl_2]$_2$/(S)-**3**/ additive: 100/0.5/1.1/5; conversion 100%. [b] Ee values were determined by HPLC on a Chiracel OD-H column. A, no additive; B, CSA as additive; C, $CeCl_3 \cdot 7H_2O$ as additive. [c] Ee values were determined by GC on a β-DEX-325 column.

In general, both Brønsted acids and Lewis acids can be used as additives to improve enantioselectivities in the asymmetric hydrogenation of α-ketoester, but $CeCl_3 \cdot 7H_2O$ was found to be the most effective additive examined (Table 2, columns B and C vs A). However, when ethyl pyruvate (**1j**, R = alkyl) was employed as substrate, $CeCl_3 \cdot 7H_2O$ showed no enantioselectivity improvement although CSA worked much better (Table 2, entry 9). When the benzoylformates possessed a substituent at the ortho position of the aromatic ring, the results became complicated. Hydrogenation of 2-methyl benzoylformate with CSA as additive gave similar ee values to those without any additive. On the other hand, much higher ee was obtained with $CeCl_3 \cdot 7H_2O$ as additive (Table 2, entry 4). Hydrogenation of 2-chloro benzoylformic ethyl ester gave the product with only 40% ee with no additive, and 76% ee with $CeCl_3 \cdot 7H_2O$; however, in the presence of CSA, a reversed low enantioselectivity was observed (Table 2, entry 8).

In the course of our exploration of these hydrogenation reactions, we also found that the cerium chloride hydrate had some effect on stabilizing the catalyst ([Ru((*S*)-**3**)-(benzene)Cl]Cl). The freshly prepared catalyst in MeOH was orange and gradually turned green upon contact with air, which indicated that the catalyst was decomposing (Figure 1). When this greenish solution is employed in the hydrogenation of α-ketoesters, the reaction was very sluggish and the enantioselectivity was poor. However, the catalyst in the MeOH solution with 5 equiv of $CeCl_3 \cdot 7H_2O$ (relative to Ru) remained orange after the solution was stirred in air for 10 days, and hydrogenation of **1a** with this solution under the standard reaction condition gave complete conversion of substrate and the product with 87% ee.

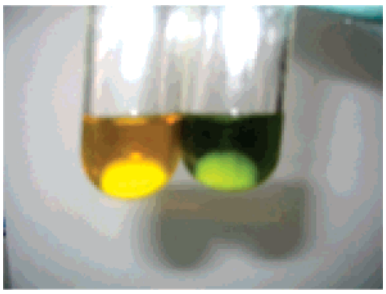


Figure 1. The color difference between the catalyst solutions with and without $CeCl_3 \cdot 7H_2O$ Left: Catalyst in methanol solution with 5 equiv of $CeCl_3 \cdot 7H_2O$ (relative to Ru) as additive. Right: Catalyst in methanol solution without any additive. Both of the solutions were stirred in air for 10 days.

The stabilizing effect of $CeCl_3 \cdot 7H_2O$ prompted us to develop a practical asymmetric hydrogenation reaction of benzoylformate with high TON. [Ru((*S*)-**3**)(benzene)Cl]Cl (37 mg, 0.04 mmol) and $CeCl_3 \cdot 7H_2O$ (75 mg, 0.2 mmol) were dissolved in 80 mL of MeOH in an autoclave in a glovebox, and combined with freshly distilled and degassed methyl benzoylformate (**1a**) (65.6 g, 400 mmol). The autoclave was purged three times with H_2, and the pressure of H_2 was set to 60 atm. The autoclave was placed to an oil bath at 100 °C for 10 h to achieve complete conversion. Routine workup gave 66.0 g of **2a** as a white solid (99.3% yield, 92% ee). The reduced product was hydrolyzed to mandelic acid and recrystallized from $ClCH_2CH_2Cl$ to afford material of >99% ee in 83% yield. This is a promising procedure for a large-scale or even industrial setting.

In conclusion, using Lewis acid additives, we have developed an efficient homogeneous asymmetric hydrogenation reaction of α-ketoesters; high enantioselectivities and TON were achieved. Further applications of this method to extend the scope of substrates and exploration of the mechanism are currently underway in our group.

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Supporting Information Available: Experimental details and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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