Asymmetric Catalysis

DOI: 10.1002/anie.201303011

Catalytic Asymmetric Hydrogenation of δ-Ketoesters: Highly Efficient Approach to Chiral 1,5-Diols**

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The development of environmentally benign methods for the production of fine chemicals has attracted increasing attention in recent years. The reduction of esters to the corresponding alcohols is widely used for many purposes, including pharmaceutical production. This reductive transformation is generally accomplished with a stoichiometric amount of a highly reactive metal hydride (e.g. $LiAlH_4$),[1] and the reaction generates large amounts of inorganic waste and requires tedious and time-consuming work-up procedures. Therefore, considerable effort has been devoted to the development of an efficient catalytic process for the reduction of an ester with H_2, an atom-efficient and environmentally benign reducing reagent, and remarkable progress has been made.[2]

The asymmetric hydrogenation of ketoesters to chiral hydroxyesters is a well-established and useful procedure developed by Noyori by using ruthenium catalysts containing chiral diphosphine ligands.[3] However, the catalytic hydrogenation of esters with H_2 under mild reaction conditions is a long-lasting challenge. In 1981, Grey et al. reported that the ruthenium complexes with phosphine ligands catalyze the hydrogenation of simple esters such as methyl and ethyl acetates.[4] Since then, several ruthenium complexes have been developed to catalyze ester hydrogenation, including the ruthenium complexes **1**–**6** (Figure 1). Milstein et al. introduced the pincer-type ruthenium complex **1**, which catalyzes the hydrogenation of both aromatic and aliphatic esters under 5.3 atmospheres of H_2 at 115–140 °C with 1 mol% catalyst.[2d] Saudan et al. reported that the complexes **2** and **3** are more efficient catalysts for the hydrogenation of esters. Turnover numbers (TONs) up to 9900 were achieved under 10–50 atmospheres of H_2 at 60–100 °C.[2e] The ruthenium catalysts **4**–**6** developed by Gusev et al. showed high TONs for hydrogenation of both aromatic and aliphatic esters:[2j–l] 18000 for methyl benzoate with **5** under 50 atmospheres of H_2 at 100 °C[2k] and 58400 for ethyl acetate with **6** under 50 atmospheres of H_2 at 40 °C.[2l] The osmium complex also exhibited good activity for the hydrogenation of esters.[2k]

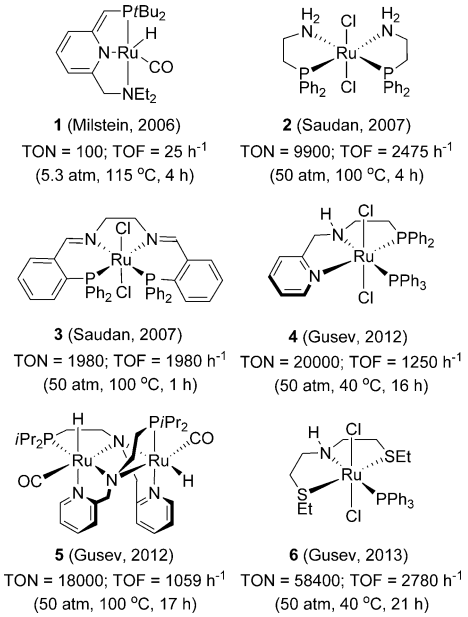
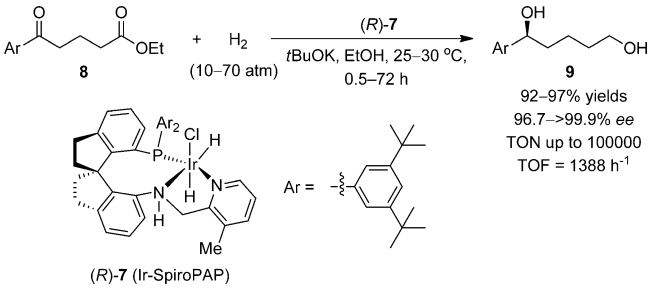


Figure 1. Examples of efficient ruthenium catalysts for ester hydrogenation.

However, the efficiencies of the reported catalysts for the hydrogenation of esters are still far from what is required for practical use.

Recently, we developed the iridium catalyst (*R*)-**7** containing a chiral spiropyridine aminophosphine SpiroPAP ligand, which has an extraordinary activity and enantioselectivity for the hydrogenation of ketones.[5] When we employed the catalyst (*R*)-**7** for the hydrogenation of the ketoesters **8**, we were delighted to find that both the keto and ester groups are hydrogenated (Scheme 1). Herein we report the highly efficient hydrogenation of the δ-aryl-δ-ketoesters **8** catalyzed



Scheme 1. Catalytic hydrogenation of the δ-aryl δ-ketoesters **8** with (*R*)-**7**.

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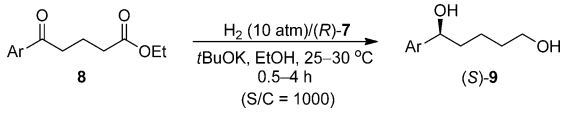
[**] We thank the National Natural Science Foundation of China, the National Basic Research Program of China (2010CB833300), and the "111" project of the Ministry of Education of China (Grant No. B06005) for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201303011.

by (*R*)-**7**, thus affording the chiral 1-arylpentane-1,5-diols **9**[6] with unprecedented activity (TONs up to 100000) and excellent enantioselectivity (up to 99.9% *ee*). To the best of our knowledge, this is the first example of highly efficient iridium-catalyzed hydrogenation of esters.

We started with the hydrogenation of ethyl 5-oxo-5-phenylpentanoate (**8a**) with (*R*)-**7**, which was generated in situ from [{Ir(cod)Cl}$_2$] and (*R*)-SpiroPAP.[5a] The hydrogenation was carried out for 1 hour under 10 atmospheres of H_2 at room temperature in EtOH at a substrate/catalyst ratio (S/C) of 1000. The chiral diol (*S*)-**9a** was produced in 96% yield with 99.9% *ee* (Table 1, entry 1). Remarkably, when the

Table 1: Hydrogenation of the ketoesters **8** to chiral the diols **9** with (*R*)-**7**.[a]



Entry	Ar	9	*t* [h]	Yield [%][b]	*ee* [%][c]
1	C_6H_5	**9a**	1.0	96	>99.9 (*S*)
2[d]	C_6H_5	**9a**	72	96	>99.9 (*S*)
3	4-MeC_6H_4	**9b**	1.0	95	>99.9
4	4-MeOC_6H_4	**9c**	1.0	95	99.5
5	4-ClC_6H_4	**9d**	0.5	94	99.3
6	4-FC_6H_4	**9e**	1.0	95	>99.9
7	3-MeOC_6H_4	**9f**	1.5	97	96.7
8	3-MeC_6H_4	**9g**	1.5	94	>99.9
9	2-MeC_6H_4	**9h**	1.5	94	>99.9
10	2-MeOC_6H_4	**9i**	1.5	97	>99.9
11[e]	2-pyridinyl	**9j**	1.5	92	>99.9
12[e]	2-furyl	**9k**	3.0	94	>99.9

[a] Reaction conditions: 1.0 mmol scale, [substrate] = 0.5 M, 0.1 mol% of (*R*)-**7**, [KO*t*Bu] = 0.02 M, ethanol (2.0 mL), room temperature (25–30°C). All reactions have 100% conversion as determined by ^{1}H NMR spectroscopy. [b] Yield of isolated product. [c] Determined by HPLC using a chiral column. [d] 0.001 mol% of (*R*)-**7** (S/C = 100000), 70 atm of H_2 (initial). [e] 0.2 mol% of (*R*)-**7** (S/C = 500).

catalyst loading was decreased to 0.001 mol% (S/C = 100000), the hydrogenation of **8a** was also performed smoothly in 72 hours under an initial H_2 pressure of 70 atmospheres at room temperature to give (*S*)-**9a** in 96% yield with 99.9% *ee* (entry 2). This result indicates that the catalyst (*R*)-**7** was exceptionally efficient for ester hydrogenation, and the observed TON of 100000 is the highest TON reported to date for the ester reduction.

By using the catalyst (*R*)-**7**, we investigated the reactions of various δ-aryl δ-ketoesters (**8**; Table 1). The substituent on the phenyl ring of **8** has little effect on the enantioselectivity of the reaction. Most of the products were obtained with *ee* values of greater than 99% *ee*. Only the substrate with a 3-MeO substituent (**8f**) gave slightly lower enantioselectivity (entry 7). δ-Heteroaryl δ-ketoesters such as **8j** (Ar = 2-pyridinyl) and **8k** (Ar = 2-furyl) were also suitable substrates for the reaction, thus providing the corresponding diols (*S*)-**9j** and (*S*)-**9k** in high yields with greater than 99.9% *ee* at S/C = 500 (entries 11 and 12). However, no hydrogenation was observed for the esters without a keto group, such as ethyl 5-phenylpentanoate, under the same reaction conditions, thus indicating that the keto group in **8** is necessary for the hydrogenation of esters.

To probe the pathway of the ester reduction, we monitored the reaction by GC. As shown in Figure 2 the δ-ketoester **8a** was hydrogenated to the hydoxy ester (*S*)-**10a** as a major product in 5 minutes. The compound (*S*)-**10a** was further hydrogenated to the diol (*S*)-**9a** through the intermediate (*S*)-**11a** (Scheme 2),[7] which explained why the keto

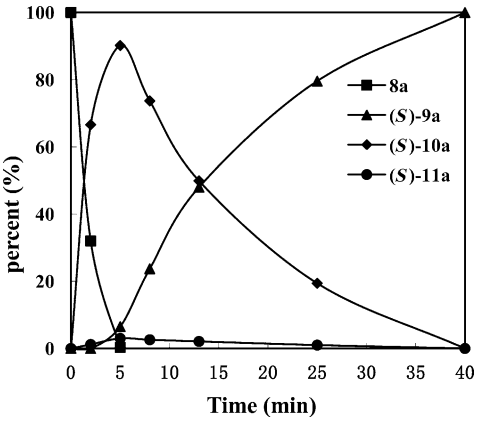
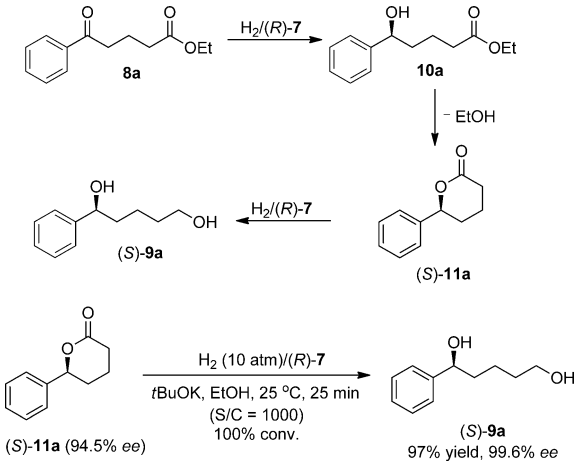


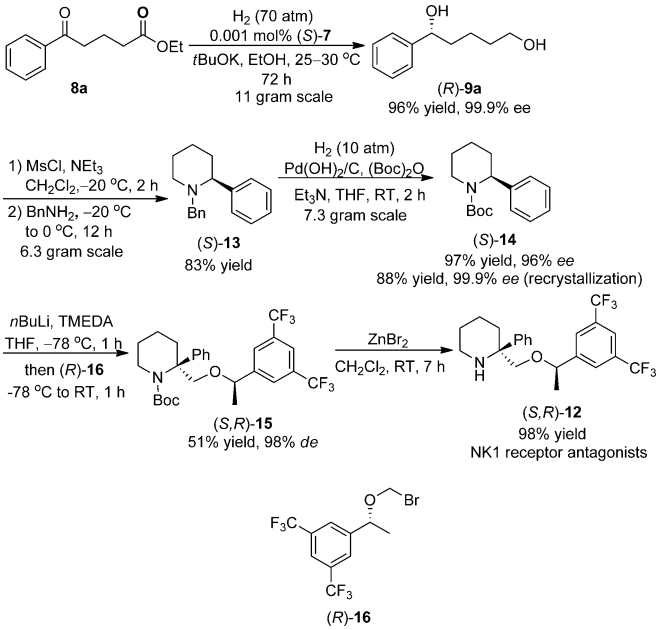
Figure 2. The plots of hydrogenation of **8a** with (*R*)-**7**.



Scheme 2. Hydrogenation of the δ-phenyl δ-ketoester **8a** and δ-lactone (*S*)-**11a**.

group in **8** is indispensable for the ester reduction. This explanation was confirmed by the experiment with the pre-prepared δ-lactone (*S*)-**11a**, which was hydrogenated by (*R*)-**7** to (*S*)-**9a** in 25 minutes (Scheme 2). We also investigated the hydrogenation of γ-ketoester, ethyl 4-phenylbutanoate, under the same reaction conditions. The reaction was rather sluggish, thus producing the chiral diol (61% yield, 98.7% *ee*), keto-reduced product (21% yield, 96.3% *ee*), and γ-lactone (12% yield, 96.6% *ee*; see the Supporting Information).

To demonstrate the applications of this highly efficient method for ester reduction, we synthesized the chiral 2,2-



Scheme 3. Enantioselective synthesis of the optically active 2,2-disubstituted piperidine (*S*,*R*)-**12**. Ms = methanesulfonyl.

disubstituted piperidine (*S*,*R*)-**12**, a lead compound in the search for orally active NK_1 receptor antagonists (Scheme 3).[8] The chiral N-protected 2-phenylpiperidine (*S*)-**13** or (*S*)-**14** is a key intermediate for the preparation of **12**.[9] With (*S*)-**7** as a catalyst at S/C = 100000, we obtained (*R*)-**9a** in gram-scale quantities in 96% yield with 99.9% *ee* by asymmetric hydrogenation of **8a**. The (*R*)-**9a** was activated with methanesulfonyl chloride (MsCl) in the presence of triethylamine (Et_3N) in dichloromethane (CH_2Cl_2) at −20 °C, and treated with benzyl amine[10] to produce the N-benzyl-protected piperidine (*S*)-**13** in 83% yield. The piperidine (*S*)-**13** was hydrogenated over $Pd(OH)_2$/C under 10 atmospheres of H_2 in the presence of di-*tert*-butyldicarbonate [$(Boc)_2O$] and Et_3N to afford the N-Boc-protected piperidine (*S*)-**14** in 97% yield with 96% *ee* (88% yield, 99.9% *ee* after recrystallization). The piperidine (*S*)-**14** was treated with *n*BuLi and tetramethylethylenediamine (TMEDA) in THF at −78 °C for 1 hour, and the resulting anion was captured with (*R*)-**16**[11] to give (*S*,*R*)-**15** in 51% yield with 98% *de* by means of a literature procedure.[12] Finally, reaction of (*S*,*R*)-**15** with $ZnBr_2$ in CH_2Cl_2 at room temperature for 7 hours yielded the desired product (*S*,*R*)-**12** in 98% yield. It is worth mentioning that (*R*)-1-(3,5-bis(trifluoromethyl)phenyl)ethanol, the starting material for the chiral intermediate (*R*)-**16**, was also prepared on a large-scale by asymmetric hydrogenation of 1-(3,5-bis(trifluoromethyl)phenyl)ethanone catalyzed by (*S*)-**7**[4a] (see the Supporting Information).

In conclusion, we developed a highly efficient iridium-catalyzed asymmetric hydrogenation of δ-aryl δ-ketoesters. With catalyst Ir-SpiroPAP [(*R*)-**7**], we prepared a series of chiral 1,5-diols in high yields and excellent enantioselectivities. The key feature of this methodology is that the ester group of the substrates can be hydrogenated effectively under mild reaction conditions.

Experimental Section

General procedure for asymmetric hydrogenation of δ-aryl δ-ketoester (S/C = 1000): The ketoester substrate **8** (1.0 mmol), a solution of iridium catalyst (*R*)-**7** in EtOH (0.002 mmol mL^{-1}, 0.5 mL, 0.001 mmol), a solution of *t*BuOK in EtOH (0.08 mmol mL^{-1}, 0.5 mL, 0.04 mmol), and 1.0 mL of anhydrous EtOH were added to a 20 mL hydrogenation vessel in an autoclave. The autoclave was purged with hydrogen by pressurizing to 5 atm and releasing the pressure. This procedure was repeated three times and then pressurized to 10 atm of H_2. The reaction mixture was stirred at room temperature (25–30 °C) until no obvious hydrogen pressure drop was observed. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (1:2) as the eluent to afford the chiral diol **9** and the enantioselectivity was determined by HPLC using a chiral column.

Received: April 11, 2013
Published online: June 14, 2013

Keywords: asymmetric catalysis · catalyst design · hydrogenation · iridium · synthetic methods

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