Synthetic Methods

DOI: 10.1002/ange.201105780

Chiral Iridium Catalysts Bearing Spiro Pyridine-Aminophosphine Ligands Enable Highly Efficient Asymmetric Hydrogenation of β-Aryl β-Ketoesters**

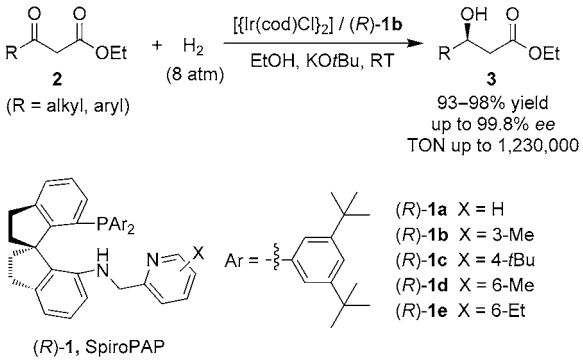
Jian-Hua Xie, Xiao-Yan Liu, Xiao-Hui Yang, Jian-Bo Xie, Li-Xin Wang, and Qi-Lin Zhou**

Dedicated to Professor Christian Bruneau on the occasion of his 60th birthday

Optically active β-hydroxy acids and their derivatives are versatile chiral building blocks for many useful molecules, including pharmaceuticals and natural products.[1] Catalytic asymmetric hydrogenation of β-ketoesters is an efficient and economically feasible method for preparing these important chiral compounds. Pioneered by Noyori and co-workers,[2] the chiral ruthenium diphosphine complexes [RuX_2-(diphosphine)] (X = Cl or Br) and their analogues have become by far the most popular catalysts for this transformation.[3] Many of them show excellent enantioselectivity [> 99% enantiomeric excess (*ee*)] and extraordinarily high activity (turnover number (TON) of up to 100000) for the hydrogenation of β-alkyl β-ketoesters.[4] However, only a few of these complexes exhibit high enantioselectivity for the hydrogenation of β-aryl β-ketoesters. Zhang et al. reported that the ruthenium catalysts bearing the ligands xylyl-*o*-binapo[5] (3,3′-bis(3,5-dimethylphenyl)-2,2′-bis(diphenylphosphinoxy)-1,1′-binaphthyl) and C_3*-TunePhos[6] give up to 99% *ee* for the hydrogenation of β-aryl β-ketoesters. Using ruthenium complexes of 4,4′-substituted binap ligands (binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), Lin et al.[7] obtained up to 99.8% *ee* for the hydrogenation of a range of β-aryl β-ketoesters. The highest TON (10000) was achieved by Saito and co-workers[8] in the asymmetric hydrogenation of methyl 3-oxo-3-phenylpropanoate. Note that chiral rhodium or iridium complexes, which efficiently catalyze olefin and imine hydrogenation, are seldom used for the asymmetric hydrogenation of β-ketoesters.[9] Furthermore, chiral [$RuCl_2$(diphosphine)(diamine)] complexes, which catalyze the hydrogenation of simple ketones extremely efficiently, are also inert for the hydrogenation of β-ketoesters.[10] The major reason for the inertness may be that the strong base, such as KO*t*Bu, that is required for activation of the [$RuCl_2$(diphosphine)(diamine)] catalysts enolizes the β-ketoester substrates instead of activating the catalysts.

Recently, we developed chiral iridium catalysts containing a chiral SpiroPAP ligand, and these catalysts show excellent enantioselectivity (up to 99.9% *ee*) and an extremely high TON (as high as 4550000) for the hydrogenation of simple ketones.[11] These Ir/SpiroPAP catalysts are likely to have a "metal–ligand bifunctional catalysis" mechanism, similar to the [$RuCl_2$(diphosphine)(diamine)] catalysts.[12] The aromatic N−H of the Ir/SpiroPAP catalysts is more acidic than the aliphatic N−H of [$RuCl_2$(diphosphine)(diamine)] catalysts (the proton resonances of the NH or NH_2 group of the catalysts are as follows: Ir[IrH_2((*R*)-**1a**)Cl]: $\delta = 5.3$ ppm ($CDCl_3$), [$RuCl_2$((*R*)-Tol-binap)((*R*,*R*)-dpen)] (dpen = 1,2-diphenylethylenediamine): $\delta = 3.3$ and 3.5 ppm (C_6D_6)[13]), thus indicating that the Ir/SpiroPAP catalysts may be more easily activated with a relatively weak base such as the enolate salt of a β-ketoester. To confirm this possibility, we tested Ir/SpiroPAP catalysts for the hydrogenation of β-ketoesters and found that the catalysts were extremely efficient for hydrogenation of β-aryl β-ketoesters. Herein, we report that the Ir/SpiroPAP-catalyzed asymmetric hydrogenation of β-aryl β-ketoesters **2** provide the chiral β-hydroxy esters **3** with excellent enantioselectivity (up to 99.8% *ee*) and extremely high TONs (as high as 1230000) under mild reaction conditions (8 atm H_2 at room temperature; Scheme 1).

The reaction conditions were optimized for the hydrogenation of ethyl 3-oxo-3-phenylpropanoate (**2a**). When the reaction was carried out at room temperature under 8 atm of



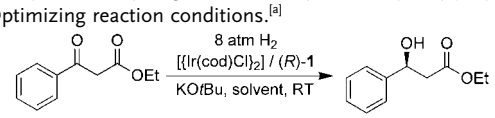
Scheme 1. Asymmetric hydrogenation of β-ketoesters with Ir/SpiroPAP catalysts. cod = 1,5-cyclooctadiene.

[*] Prof. J.-H. Xie, X.-Y. Liu, X.-H. Yang, J.-B. Xie, Prof. L.-X. Wang, Prof. Q.-L. Zhou
State Key Laboratory and Institute of Elemento-Organic Chemistry
Nankai University
Tianjin 300071 (China)
E-mail: jhxie@nankai.edu.cn
qlzhou@nankai.edu.cn

[**] We thank the National Natural Science Foundation of China, the National Basic Research Program of China (2010CB833300), and the "111" project (B06005) of the Ministry of Education of China for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201105780.

Table 1: Asymmetric hydrogenation of ethyl 3-oxo-3-phenylpropanoate (**2a**). Optimizing reaction conditions.[a]



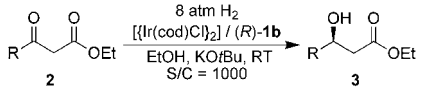
2a **3a**

Entry	Ligand	Solvent	*t* [h]	Conv. [%][b]	Yield [%][c]	*ee* [%][d]
1	(*R*)-**1b**	EtOH	1.0	100	98	98
2[e]	(*R*)-**1b**	MeOH	0.7	100	95	86
3[e]	(*R*)-**1b**	*n*PrOH	2.5	100	95	73
4[e]	(*R*)-**1b**	*i*PrOH	15	100	94	85
5	(*R*)-**1b**	toluene	15	43	40	99.2
6[f]	(*R*)-**1b**	EtOH	3.0	100	95	98
7[g]	(*R*)-**1b**	EtOH	0.7	100	98	98
8	(*R*)-**1a**	EtOH	2.0	100	97	93
9	(*R*)-**1c**	EtOH	2.5	100	97	96
10	(*R*)-**1d**	EtOH	1.5	100	96	89
11	(*R*)-**1e**	EtOH	1.5	100	96	76
12[h]	(*R*)-**1b**	EtOH	19	>99	98	98
13[i]	(*R*)-**1b**	EtOH	96	82	78	98

[a] Reaction conditions: 1.5 mmol scale, [substrate] = 2.1 M, [{Ir(cod)Cl}$_2$] (0.05 mol%), ligand (0.11 mol%), [KO*t*Bu] = 0.02 M, solvent (2.0 mL), room temperature (25–30°C). [b] Determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product. [d] Determined by HPLC analysis using a chiral stationary phase. The absolute configuration of the product is *S*. [e] The hydrogenation product contains a certain amount of intere-esterification product. [f] At 15°C. [g] At 50°C. [h] S/C = 100,000, 50 atm H_2 (initial). [i] S/C = 1500000, at 50°C, 100 atm H_2 (initial).

hydrogen with Ir/(*R*)-**1b** generated in situ from 0.05 mol% [{Ir(cod)Cl}$_2$] and 0.11 mol% (*R*)-**1b**, the hydrogenation product (*S*)-ethyl 3-hydroxy-3-phenylpropanoate (**3a**) was obtained in 98% yield and 98% *ee* (Table 1, entry 1), along with a small amount of (*E*)-ethyl 3-phenylacrylate (<2%), which was generated by elimination of the β-hydroxy group of **3a** under the basic conditions. Solvent experiments showed that the reaction was faster in a less bulky alcohol solvent and that EtOH gave the best enantioselectivity (entries 1–4). Enantioselectivity as high as 99.2% *ee* was obtained in toluene, but, the conversion was quite low (entry 5). The reaction temperature had little effect on the enantioselectivity, but reducing the temperature lowered the reaction rate (compare entry 1 with entries 6 and 7). Comparison of various chiral SpiroPAP ligands indicated that the introduction of an alkyl group at the 6-position of the pyridine ring of the ligand reduced the enantioselectivity (compare entry 8 with entries 10 and 11); however, the presence of an alkyl group at either the 3- or 4-position of the pyridine ring increased the enantioselectivity (compare entry 8 with entries 1 and 9). When the catalyst loading was lowered from 0.1 to 0.001 mol% (S/C = 100000), Ir/(*R*)-**1b** worked well and yielded the hydrogenation product (*S*)-**3a** in 98% yield and 98% *ee* within 19 hours at an initial hydrogen pressure of 50 atm (entry 12). When the catalyst loading was additionally lowered to 0.000067 mol% (S/C = 1500000), the reaction had to be carried out at 50°C and at an initial hydrogen pressure of 100 atm; (*S*)-**3a** was obtained in 78% yield with a conversion of 82% (TON = 1230000) and the same level of enantioselectivity (entry 13).

Table 2: Asymmetric hydrogenation of β-ketoesters **2** with Ir/(*R*)-**1b**.[a]



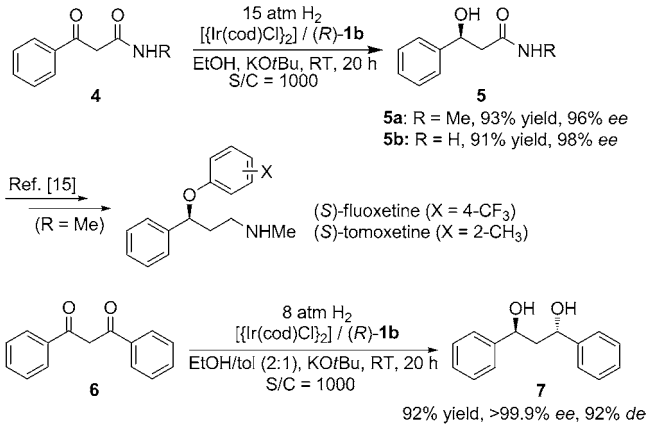
2 **3**

Entry	R	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	C_6H_5	**3a**	1.0	98	98
2	4-MeC_6H_4	**3b**	0.4	97	99.3
3	4-$MeOC_6H_4$	**3c**	0.7	95	99.3
4	4-ClC_6H_4	**3d**	1.0	94	96
5	4-BrC_6H_4	**3e**	0.8	96	99
6	3-MeC_6H_4	**3f**	0.7	95	99.2
7	3-$MeOC_6H_4$	**3g**	1.7	93	96
8	3-BrC_6H_4	**3h**	1.7	95	95
9	2-MeC_6H_4	**3i**	1.0	94	99.8
10	2-$MeOC_6H_4$	**3j**	0.8	94	99.5
11	2-ClC_6H_4	**3k**	4.0	97	99.3
12	*i*Pr	**3l**	20	90	88

[a] Reaction conditions were the same as those used for the reaction in entry 1 of Table 1. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase (see the Supporting Information); the absolute configuration of the product is *S*.

Under the optimal reaction conditions, various β-aryl β-ketoesters (**2a–k**) were hydrogenated over Ir/(*R*)-**1b** at S/C = 1000 to afford the corresponding chiral β-hydroxy esters **3a–k** in high yield (93–98%) and excellent enantioselectivity (95–99.8% *ee*). The results listed in Table 2 indicate that the electronic properties of the group on the phenyl ring of the β-aryl β-ketoester had little effect on the enantioselectivity; however, *ortho*-chloro substitution resulted in a longer reaction time (entry 11). The catalyst Ir/(*R*)-**1b** was less efficient for the hydrogenation of β-alkyl β-ketoesters such as β-isopropyl β-ketoester (**2l**; entry 12).

Catalytic asymmetric hydrogenation of β-keto amides is an efficient approach to the synthesis of optically pure chiral β-hydroxy amides,[14] which are useful building blocks for the synthesis of biologically active compounds. For example, the optically pure chiral β-hydroxy amide **5a** (R = Me) has been used in the enantioselective synthesis of the antidepressants fluoxetine and tomoxetine[15] (Scheme 2). We were delighted to find that Ir/(*R*)-**1b** efficiently catalyzed the asymmetric



Scheme 2. Asymmetric hydrogenation of the β-keto amides **4** and 1,3-diketone **6**.

hydrogenation of β-keto amides. For example, the β-phenyl β-ketoamides **4** were hydrogenated to give the chiral β-hydroxy amides **5a** and **5b** in high yield (93 and 91%, respectively) with excellent enantioselectivity (96 and 98% *ee*, respectively). Moreover, Ir/(*R*)-**1b** also efficiently catalyzed the hydrogenation of 1,3-diketone **6** to afford the 1,3-dialkanol **7** in 92% yield with greater than 99.9% *ee* and a diastereomeric excess of 92%.

In conclusion, we have developed a highly efficient asymmetric hydrogenation of β-aryl β-ketoesters catalyzed by Ir/SpiroPAP complexes. The reaction provides a readily accessible method for the synthesis of β-hydroxy esters in excellent enantioselectivity (up to 99.8% *ee*) and extremely high TONs (up to 1230000), which represents the highest level of efficiency in the asymmetric hydrogenation of β-ketoesters.

Experimental Section

General procedure for asymmetric hydrogenation of β-ketoesters at S/C = 1000: The catalyst precursor [{Ir(cod)Cl}$_2$] (0.5 mg, 0.75 μmol), ligand (*R*)-**1b** (1.2 mg, 1.6 μmol), and anhydrous EtOH (1 mL) were added to a 20 mL hydrogenation vessel under a nitrogen atmosphere. The mixture was stirred for 1.0 h at 25–30°C to give a clear yellow solution. The vessel was then placed in an autoclave and purged with hydrogen by pressurizing to 1 atm and releasing the pressure. This procedure was repeated three times and the solution was stirred for 1.0 h under 1 atm of H_2. After releasing the pressure, the β-ketoester (1.5 mmol) and a solution of *t*BuOK in EtOH (0.13 mmol mL^{-1}, 0.3 mL, 0.04 mmol) were added through the injection port. The autoclave was then pressurized to 8 atm of H_2 and the reaction mixture was stirred at room temperature (25–30°C) until no obvious hydrogen pressure drop was observed. After releasing the hydrogen pressure, the reaction mixture was concentrated in vacuum and chromatographed on silica gel column using ethyl acetate/petroleum ether (v/v = 1:10) to afford the corresponding hydrogenation product. The enantioselectivity of the product was determined by either GC or HPLC analysis using a chiral stationary phase.

Received: August 16, 2011
Published online: November 16, 2011

Keywords: enantioselectivity · hydrogenation · iridium · ligand effects · synthetic methods

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