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COMMUNICATION

Direct Asymmetric Hydrogenation of α -Keto Acids by Using the Highly Efficient Chiral Spiro Iridium CatalystsPu-Cha Yan,^a Jian-Hua Xie,^{b,c} Xiang-Dong Zhang,^a Kang Chen,^a Yuan-Qiang Li,^a Qi-Lin Zhou,^{*b,c} and Da-Qing Che^{*,a,c}⁵ Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

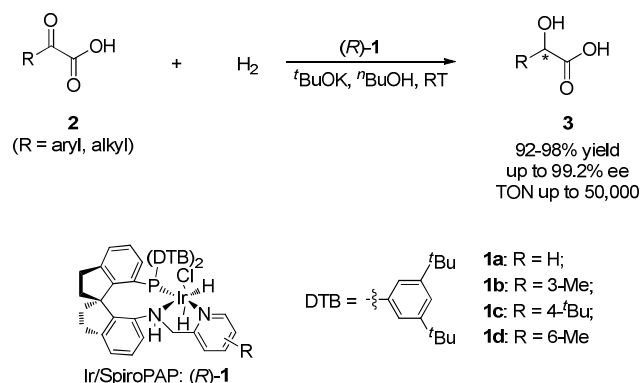
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A new efficient and highly enantioselective direct asymmetric hydrogenation of α -keto acids employing the Ir/SpiroPAP catalyst under mild reaction conditions has been developed.¹⁰ This method might be feasible for the preparation of a series of chiral α -hydroxy acids in large scale.

Optically active α -hydroxy acids and their derivatives are of considerable significance as chiral building blocks in numerous pharmaceuticals and chemical industries,¹ and also are utilized as resolving agents.² Therefore various methodologies have been developed for preparing optical pure α -hydroxy acids, including the enantioselective reduction of prochiral α -keto esters,³ kinetic resolution of racemic α -hydroxy esters,⁴ enzymatic or biomimetic methods,⁵ Cannizzaro reactions,⁶ Friedel-Crafts reactions,⁷ synthesis of cyanohydrins as precursors,⁸ and hydrogen mediated reductive C-C bond formation reactions.⁹ The transition metal catalyzed asymmetric hydrogenation proved to be an efficient and economically feasible method for preparing these important chiral compounds.¹⁰ Although a few papers are devoted to the development of straight forward procedures involving the direct conversion of α -keto acids to chiral α -hydroxy acids, the direct asymmetric hydrogenation of α -keto acids has rarely attracted attention.¹¹ To the best of our knowledge, only one example was reported so far employing Ru-Sunphos catalyst for the conversion of (*E*)-2-oxo-4-arylbut-3-enoic acids and 2-oxo-4-arylbutanoic acids directly into optically active 2-hydroxy-4-arylbutanoic acids in up to 89.5% ee and 92.6% ee respectively.¹² Therefore, the development of effective, high enantioselective, and direct approaches to α -hydroxy acids is still of significance.

³⁵ Be different from α -keto ester, the α -keto acid has a carboxyl group which might competitively coordinate to the center metal and then cause deactivation of the catalyst, thus resulting in low enantioselectivity and reactivity. On the other hand, the hydrogenation product (α -hydroxy acid) usually serves as a ligand, restricting its liberation from the catalyst.¹² The chiral iridium catalysts containing SpiroPAP ligands (Ir/SpiroPAP) developed by Xie and Zhou in 2011, have shown excellent enantioselectivity and reactivity in the hydrogenation of simple ketones and β -aryl β -ketoesters,¹³ however, the hydrogenation of α -phenyl α -keto ester gave almost racemic product. Recently, we successfully applied these catalysts for the hydrogenation of *m*-hydroxyacetophenone in the presence of more than one equiv base obtaining high enantioselectivity (up to 97% ee) and an high

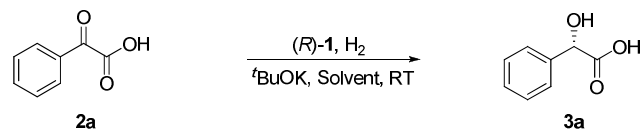
TON (as high as 100,000).¹⁴ On the basis of this work, we speculate that the same strategy seems to be working in the direct hydrogenation of α -keto acids. Herein we report that the Ir/SpiroPAP (**1**) catalyzed direct asymmetric hydrogenation of α -keto acids (**2**) to provide the chiral α -hydroxy acids (**3**) with excellent enantioselectivity (up to 99.2% ee) and high TON (as high as 50,000) under mild reaction conditions (Scheme 1).

Scheme 1. Asymmetric hydrogenation of α -keto acids with Ir/SpiroPAP catalysts.

As revealed in Table 1, we employed benzoylformic acid (**2a**) as the model substrate to optimize the reaction conditions. The effects of base quantity, solvents and ligands on reactivity and enantioselectivity were screened. Hydrogenation of **2a** was initially carried out under similar conditions previously optimized for the reaction of β -aryl β -keto esters ((*R*)-**1b**, S/C = 1000, 0.05 equiv base, 15 atm H₂, 25–30 °C).^[13b] However, only trace product was obtained within 24 h (Table 1, entry 1). The same result was observed even when 0.5 equiv *t*BuOK was added (Table 1, entry 2). Dramatically improved reactivity was obtained when 1.0 equiv *t*BuOK was used, the hydrogenation reaction could be completed smoothly within 10 h, giving (*S*)-**3a** in 87% ee (Table 1, entry 3). We speculated that the catalyst might be activated with a relatively weak base such as carboxylic acid potassium salt. The reaction rate could be accelerated by adding 1.06 equiv *t*BuOK, and the full conversion was obtained within 2 h (Table 1, entry 4). Solvent screening showed that *n*-butanol gave the best enantioselectivity (Table 1, entries 5–8). By comparison of various chiral SpiroPAP ligands, it was found that the introduction of an alkyl group at the 6- position of the

pyridine ring of the ligand reduced the enantioselectivity (compare entry 12 with entry 9), however, the presence of an alkyl group at either the 3- or 4- position of the pyridine ring could increase the enantioselectivity (compare entries 8 and 10 with entry 9). Increasing the substrate concentration from 0.4 M to 1.0 M resulted in slightly lower enantioselectivity (Table 1, entry 11). Based on the above results, the optimized reaction conditions were therefore set as follows: 0.1 mol% of (*R*)-**1c** as the catalyst, 1.06 equiv ^tBuOK as base, ⁿBuOH as the solvent with a substrate concentration of 0.4 M at room temperature.¹⁵

Table 1: Asymmetric hydrogenation of benzoylformic acid (**2a**). Optimizing reaction conditions.^a



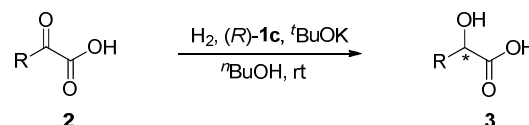
Entry	(<i>R</i>)- 1	B/S ^b	Solvent	Time (h)	Conv. ^c (%)	Ee ^d (%)
1	1b	0.05	EtOH	24	trace	n.d. ^e
2	1b	0.5	EtOH	24	trace	n.d. ^e
3	1b	1.0	EtOH	10	100	87 (<i>S</i>)
4	1b	1.06	EtOH	2	100	87 (<i>S</i>)
5	1b	1.06	MeOH	21	92	78 (<i>S</i>)
6	1b	1.06	^t PrOH	20	100	87 (<i>S</i>)
7	1b	1.06	ⁿ PrOH	2	100	88 (<i>S</i>)
8	1b	1.06	ⁿ BuOH	2	100	89 (<i>S</i>)
9	1a	1.06	ⁿ BuOH	3	100	85 (<i>S</i>)
10	1c	1.06	ⁿ BuOH	1.5	100	93 (<i>S</i>)
11 ^f	1c	1.06	ⁿ BuOH	1.5	100	91 (<i>S</i>)
12	1d	1.06	ⁿ BuOH	2	100	83 (<i>S</i>)

^a Reaction conditions unless otherwise noted: 2.0 mmol scale, [substrate] = 0.4 M, (*R*)-**1** (0.1 mol%), Solvent (5.0 mL), 15 atm H₂, room temperature (25–30 °C). ^b Base to substrate ratio. ^c Determined by ¹H NMR spectroscopy. ^d Determined by HPLC analysis on a chiral OD-H column of the corresponding methyl ester. The absolute configuration of **3a** is *S* by comparing the specific rotation with reported data. ^e n.d. = not determined. ^f [substrate] = 1.0 M, Solvent (2.0 mL).

Under the optimal reaction conditions, we examined the scope of substrate (Table 2). A series of α -keto acids (**2a–p**) were hydrogenated to afford the corresponding chiral α -hydroxy acids (**3a–p**) in high yield (92–98%) and moderate to excellent enantioselectivity (56–99.2% ee). The results summarized in Table 2 indicate that the influence of electronic properties is not obvious, substrates with electron-donating substituents only gave a little better enantioselectivity than those with electron-withdrawing substituents. Apparently, steric hindrance played a crucial role in the asymmetric hydrogenation of these substrates. For the α -aryl- α -keto acids, *ortho*-substituted benzoylformic acid usually reacted rapidly and gave higher ee values (Table 2, entries

2–4 vs entries 5–11). For more sterically hindered *o*-methylbenzoylformic acid (**2c**), the hydrogenation was extremely fast and high enantioselective. Full conversion was completed within 1 hour to give the (*S*)-2-hydroxy-2-(*o*-tolyl)acetic acid (**3c**) in 98% ee (Table 2, entry 3). This was further supported by the fact that the highest enantioselectivity (99.2% ee) was obtained when 2-(naphthalen-1-yl)-2-oxoacetic acid (**2l**) was employed as the substrate (Table 2, entry 12). It is worth noting that only sporadic papers have been reported on the asymmetric hydrogenation of *ortho*-substituted benzoylformic esters and the enantioselectivities were usually not very high.^{3k, 3n, 16}

Table 2: Asymmetric hydrogenation of α -keto acids **2** with (*R*)-**1c**.^a



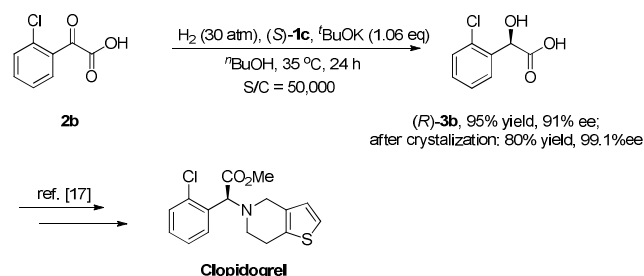
Entry	R	3	Time (h)	Yield ^b (%)	Ee ^c (%)
1	C ₆ H ₅	3a	1.5	96	93 (<i>S</i>)
2	2-Cl-C ₆ H ₄	3b	1	93	91 (<i>S</i>)
3	2-Me-C ₆ H ₄	3c	1	98	98 (<i>S</i>)
4	2-OMe-C ₆ H ₄	3d	3	97	92 (<i>S</i>)
5	3-Cl-C ₆ H ₄	3e	5	94	91 (<i>S</i>)
6	3-Me-C ₆ H ₄	3f	3	95	92 (<i>S</i>)
7	3-OMe-C ₆ H ₄	3g	4	97	94 (<i>S</i>)
8	4-F-C ₆ H ₄	3h	5	94	90 (<i>S</i>)
9	4-Cl-C ₆ H ₄	3i	4	97	88 (<i>S</i>)
10	4-Me-C ₆ H ₄	3j	4	97	90 (<i>S</i>)
11	4-OMe-C ₆ H ₄	3k	8	96	90 (<i>S</i>)
12	1-Naphthyl	3l	1	98	99.2 (<i>S</i>)
13	2-Naphthyl	3m	12	98	91 (<i>S</i>) 95 (<i>S</i>) ^d
14	Ph(CH ₂) ₂	3n	1	96	56 (<i>S</i>) ^e
15	Cyclohexyl	3o	2	95	82 (<i>S</i>) ^f
16 ^g	^t Bu	3p	21	92	77 (<i>R</i>) ^f 85 (<i>R</i>) ^{d,f}

^a Reaction conditions unless otherwise noted: 2.0 mmol scale, [substrate] = 0.4 M, (*R*)-**1c** (0.1 mol%, S/C = 1000), ⁿBuOH (5.0 mL), 15 atm H₂, room temperature (25–30 °C). ^b Isolated yield. ^c Determined by HPLC analysis on a chiral OD-H or AD-H column of the corresponding methyl ester. The absolute configuration was determined by comparing the specific rotation with reported data. ^d (*R*)-**1b** was used as catalyst. ^e Determined by HPLC analysis on a chiral OD-H column of the corresponding ethyl ester. ^f Determined by HPLC analysis on a chiral OD-H column of the corresponding benzyl ester. ^g 0.2 mol% catalyst was used (S/C = 500).

The hydrogenation of 2-(naphthalen-2-yl)-2-oxoacetic acid (**2m**)

provided direct access to **3m** in 91% ee. When (*R*)-**1b** was used as catalyst, **3m** was obtained in 95% ee (Table 2, entry 13). Longer reaction time was needed presumably due to the poor solubility of the corresponding carboxylic acid potassium salt. Aliphatic α -hydroxy acids were also obtained in high yield, albeit with only moderate to good enantioselectivities (56–85% ee, Table 2, entry 14–16). For more sterically hindered 3,3-dimethyl-2-oxobutanoic acid (**2p**), the hydrogenation was extremely sluggish even when 0.2 mol% catalyst was used (Table 2, entry 16). Interestingly, the absolute configuration of **3p** was opposite to that of other products.

The fast reaction rate of *o*-chlorobenzoylformic acid (**2b**) prompted us to develop a practical preparation of optical pure *o*-chloromandelic acid which is a key intermediate for a platelet aggregation inhibitor named Clopidogrel¹⁷ with high TON. When the substrate/catalyst ratio was increased to 50,000 (Scheme 2), the hydrogenation of **2b** completed at room temperature under an initial hydrogen pressure of 30 atm within 24 h without loss of enantioselectivity. The ee value of **3b** could be upgraded to >99% by crystallization from toluene in 80% yield. This is a promising procedure for a large-scale or even industrial setting.



Scheme 2. Asymmetric hydrogenation of *o*-chlorobenzoylformic acid with high TON.

Conclusions

In summary, we have developed a new efficient and highly enantioselective direct asymmetric hydrogenation of α -keto acids into optically active α -hydroxy acids employing the Ir/SpiroPAP catalyst. The achieved catalyst performance (ee, TON) indicated that this method might be feasible for the preparation of a series of chiral α -hydroxy acids especially *ortho*-substituted α -hydroxy phenylacetic acids in large scale. Further investigations are focused on the application of this methodology to the synthesis of chiral pharmaceuticals.

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Notes and references

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