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Ru-catalyzed hydrogenation of 3,5-diketo amides: simultaneous control of chemo- and enantioselectivity†

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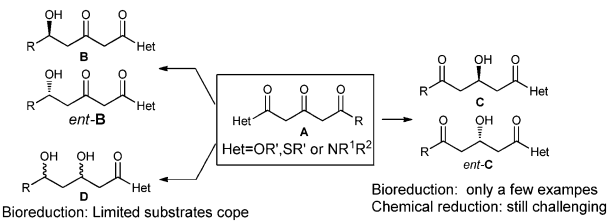
By modulating the chelating priorities of the different directing groups in 3,5-diketo amides with the assistance from coordinating solvent, highly chemo- and enantioselective hydrogenation of the C3-carbonyls was achieved in the presence of [RuCl(benzene)(*S*)-SunPhos]Cl in THF.

Enantiopure 3,5-dioxygenated acid derivatives are found in many important molecules or their synthetic intermediates,[1] such as Berkeleyamide A[2] (high inhibition activity against MMP-3 and caspase-1), Ixempra (anti-cancer drug),[3] and side chains of atorvastatin and rosuvastatin (HMG-CoA reductase inhibitors).[4] Accordingly, various approaches have been devised to synthesize these important substructures. For instance, asymmetric aldol-type reactions[5] were extensively used in acquiring the 3-oxo-5-hydroxy acid derivatives. Alternative protocols relied mainly upon Claisen condensation of acetates with chiral β-hydroxy esters[6] or α,β-epoxy carboxylic derivatives.[7]

Compared with the aforementioned methods, selective reduction of the 3,5-diketo acid derivatives (**A**) is most straightforward (Scheme 1). However, this transformation is plagued by the chemoselectivity concern from the similarity in the 3- and 5-carbonyl. Consequently, even many enzymatic methods failed to give ideal selectivity.[8]



Scheme 1 Selective reduction of 3,5-diketo acid derivatives.

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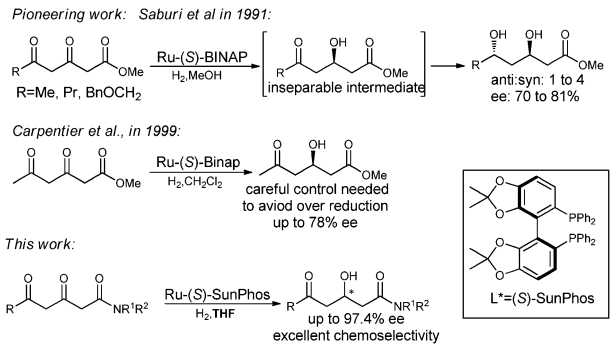
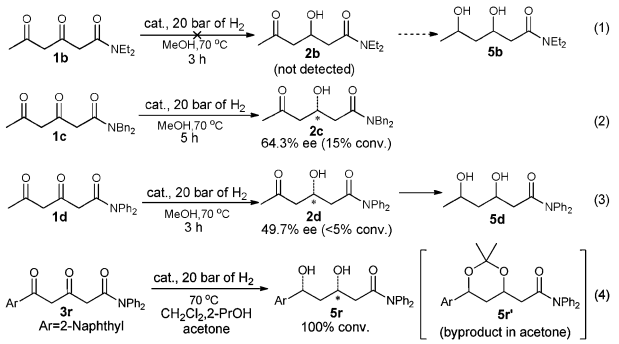
In contrast to the diverse paths to 3-oxo-5-hydroxy acid derivatives (**B** and *ent*-**B**), sporadic reduction methods lead to 3-hydroxy-5-oxo acid derivatives (**C** and *ent*-**C**).[9] Ru-catalyzed asymmetric hydrogenation of functionalized ketones has become a routine method for many advanced chiral alcohols.[10] It was also employed for the stereoselective reduction of 3,5-diketo acid esters (**A**). Saburi[11] and Carpentier[12] have independently reported the asymmetric hydrogenation of 3,5-diketo esters but they failed to obtain ideal chemo- and stereoselectivity. The next two decades witnessed some progress in this continuing subject,[12,13] but hitherto *it is still impossible to achieve simultaneously high chemo-, enantio- and diastereoselectivity*. Herein we present our recent work on highly selective hydrogenation of 3,5-diketo amides at the C3-carbonyls (Scheme 2).

Ru-catalyzed asymmetric hydrogenation of β-keto esters has been extensively investigated, but far fewer examples have been reported on the hydrogenation of β-keto amides.[14] Kramer and Brückner[14e,f] proved that β-keto amides were hydrogenated faster than β-keto esters in alcohol under specified conditions. Based on the rate comparison method, we realized the recognition of similar carbonyls within one molecule and fulfilled the efficient asymmetric hydrogenation of 3-oxoglutaric acid derived with ester and amide moieties at the two ends.[15] Considering that β-keto amides can be hydrogenated preferentially with faster reaction rate in alcohol than that in THF, we firstly tried the hydrogenation of 3,5-diketo amides in MeOH (Scheme 3).

Initially, 0.5 mmol of **1b** was hydrogenated with [Ru(benzene)-((*S*)-SunPhos)Cl]Cl (1 mmol%) in MeOH (20 bar of H_2, 70 °C)



Scheme 2 Asymmetric hydrogenation of 3,5-diketo acid derivatives.

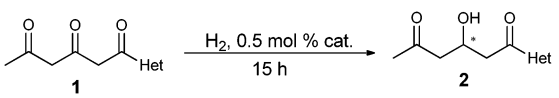


Scheme 3 Asymmetric hydrogenation of several 3,5-diketo acid amides in different solvents.

for 3 h (longer reaction time may lead to over-reduced product, **5b**) in the hope of obtaining **2b** as the main product [eqn (1)]. Unexpectedly, **1b** remained almost untouched and neither **2b** nor **5b** was detected. When the reaction time was prolonged to 15 h, **1b** was partially alcoholized to form methyl 3,5-dioxohexanoate. Further investigation showed that a trace amount of freed diethylamine poisoned the catalyst. When **1c** was hydrogenated under the same conditions for 5 h [eqn (2)], only 64.3% ee and 15% conversion were obtained. The conversion of **1d** under the same conditions for 3 h was less than 5% (by ^{1}H NMR) and the ee of **2d** was only 49.7%. Longer reaction time leads to the over-hydrogenation product **5d**. Anyway, it was considerably difficult to achieve selective hydrogenation and good enantioselectivities in MeOH (similar results were obtained in EtOH). Several other solvents were also tested and the chemoselectivity was not as good as in THF. For example, hydrogenation of **3r** in CH_2Cl_2 and 2-PrOH under the same conditions gave 3,5-dihydroxy product **5r**, while in acetone a mixture of **5r** and **5r′** [eqn (4)] was obtained.

Next, we performed these hydrogenation reactions in THF (Table 1). **1b**, which was inactive in MeOH, can be smoothly hydrogenated to **2b** with 97.2% ee in THF. Besides, the ee's of the hydrogenation products of **1c** and **1d** (Scheme 3) increased from 64.3 to 87.2% (entry 3, Table 1) and 49.7 to 93.5% (entry 4, Table 1), respectively. Generally, secondary amides gave somewhat higher enantioselectivity. The *tert*-butyl amide gave

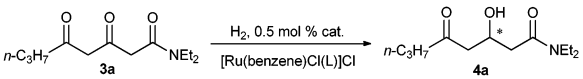
Table 1 Screening of the acid derivatives[a]



Entry	1	Het	Yield (%)	ee[b] (%)
1	**1a**	NMe_2	91	96.8
2	**1b**	NEt_2	**94**	**97.2**
3	**1c**	NBn_2	92	87.2
4	**1d**	NPh_2	90	93.5
5	**1e**	*N*-Morpholinyl	92	92.5
6	**1f**	NHBu-*t*	93	87.2[c]
7	**1g**	OBu-*t*	86	55.1[c]

[a] All reactions were carried out in THF (5 mL) with substrate (1 mmol) at 70 °C under 20 bar of H_2 for 15 h. S/C = 200. Conversion: 100%, isolated yield. [b] Determined by HPLC. [c] ee of its 4-nitrobenzoate.

Table 2 Optimization of the reaction conditions with **3a**[a]



L1=(*S*)-SunPhos, **L2**=(*S*)-BINAP, **L3**=(*S*)-SegPhos

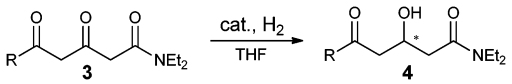
Entry	Ligand	T (°C)	H_2 (bar)	Time (h)	Yield (%)	ee (%)
1	**L1**	50	20	18	51[b]	95.0
2	**L1**	70	20	15	91	94.3
3	**L1**	70	40	12	89[c]	90.7
4	**L1**	80	20	8	87[c]	90.9
5	**L2**	70	20	15	92	88.2
6	**L3**	70	20	15	90	72.3

[a] All reactions were carried out in THF (5 mL) with substrate (1 mmol) S/C = 200. Isolated yield. Conversion was 100% unless otherwise noted. [b] 60% conversion based on recovered **3a**. [c] A small amount of over-hydrogenation product was detected.

the lowest ee (entry 6, Table 1). The ester substrate (**1g**) can also be selectively hydrogenated at the C3-carbonyl, but the ee of **2g** was only 55.1% (entry 7, Table 1). Therefore, we focused our attention on the amide substrates.

The reaction conditions were optimized with **3a** (Table 2). Lower temperature leads to somewhat higher ee but the reaction became much slower (entries 1, 2 and 4, Table 2). The higher hydrogen pressure had some negative influence on the enantioselectivity (entries 2 and 3, Table 2). Other ligands like (*S*)-BINAP and (*S*)-SegPhos were inferior to (*S*)-SunPhos in enantioselectivity: the ee's of **4a** were 88.2 and 72.3%

Table 3 Asymmetric hydrogenation of various 3,5-diketo amides[a]



Entry	Substrates	R	Yield[b] (%)	ee[c] (%)
1	**3a**	*n*-Pr	91	94.3
2[d]	**3b**	n-C_8H_{17}	92	93.5
3	**3c**	Cy	93	92.3
4	**3d**	*t*-Bu	92	87.8
5	**3e**	$Ph(CH_2)_2$–	95	94.2
6	**3f**	Isobutenyl	94[e]	91.5
7	**3g**	C_6H_5	95	95.6
8	**3h**	2-MeC_6H_4	94	93.7
9[d]	**3i**	2-$MeOC_6H_4$	93	80.7
10	**3j**	2-FC_6H_4	96	95.2
11	**3k**	3-ClC_6H_4	95	95.9
12	**3l**	3-MeC_6H_4	96	94.4
13	**3m**	4-ClC_6H_4	95	95.5
14[d]	**3n**	4-BrC_6H_4	90	95.5
15	**3o**	4-$MeOC_6H_4$	94	92.8
16	**3p**	4-$CF_3C_6H_4$	91	93.5
17	**3q**	1-Naphthyl	95	90.7[f]
18	**3r**	2-Naphthyl	94	91.8
19	**3s**	2-Furanyl	95	97.4
20	**3t**	2-Thienyl	96	96.4

[a] All reactions were carried out with 1 mmol of substrate in 5 mL of THF at 70 °C under 20 bar of H_2 for 15 h. S/C = 200. Conversion = 100%. [b] Isolated yields. [c] Determined by HPLC. [d] 8 h, longer reaction time leads to somewhat lower yields due to over-hydrogenation of the product at C5-carbonyls. For **3n**, a trace amount of debromination product was detected by HPLC/HRMS. [e] A trace amount of over-hydrogenation of the olefin product was detected by ^{1}HNMR. [f] ee of its 2-bromoacetate.

respectively (entries 5 and 6, Table 2). Finally, the optimum reaction conditions with (*S*)-SunPhos were set at 70 °C and 20 bar of H_2.

Under the optimized conditions, various diethyl amides were hydrogenated with very good ee's (Table 3). Longer alkyl chains decreased the ee to some extent (entry 2, Table 1 *vs.* entries 1 and 2, Table 3). Bulkier substituents like *tert*-butyl and cyclohexyl further impaired the enantioselectivity, the ee's of **4c** and **4d** were only 92.3% and 87.8% (entries 3 and 4, Table 3), respectively. Trisubstituted conjugated olefin (**3f**) was also tolerated under the hydrogenation conditions (entry 6, Table 3).[16] The halides on the phenyl rings had little effect on the enantioselectivity of the reaction. Intriguingly, the introduction of an *ortho*-methoxy (**3i**), which might participate in the coordination to some degree, decreased the ee from 95.6% to 80.7% (entry 7 *vs.* 9, Table 3). A similar adverse effect on enantioselectivity from *ortho*-methoxy was also observed in the Rh-catalyzed asymmetric hydrogenations of aryl-substituted enamides.[17]

Based on our earlier studies[15,18] we reckoned that the hydrogenation of C3-carbonyl was directed by the amide carbonyl, which could be validated by the absolute configuration of the hydrogenation product (*S*)-**4s** (see the X-ray crystallography data in the ESI†).

In summary, we have succeeded in the asymmetric hydrogenation of 3,5-diketo amides with simultaneous control of high chemo- and enantioselectivity, such precise recognition has not been accomplished by any other chemical methods. The excellent C3-selectivity rivalled and supplemented the delicacy of the biocatalysis and also meet the common criterion of high selectivity[19] and atom-economy[20] for efficient organic synthesis. The resultant products furnished valuable precursors for the stereoisomers of the 1,3-diol substructures. A more detailed scenario of the reaction pathway and the 3,5-double stereo control in this hydrogenation is underway.

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