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Ru-Catalyzed Asymmetric Hydrogenation of 3-Oxoglutaric Acid Derivatives via Solvent-Assisted Pinpoint Recognition of Carbonyls in Close Chemical Propinquity

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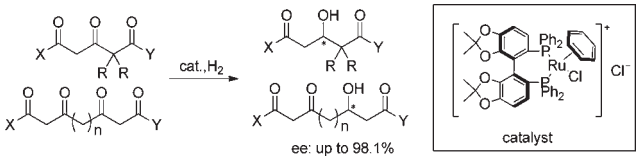
ABSTRACT



Upon comparison of hydrogenation rates of various β-ketocarboxylic acid derivatives, β-ketoamides were found to be hydrogenated slightly faster than β-ketoesters in EtOH in the presence of [RuCl(benzene)(*S*)-SunPhos]Cl at 70 °C with 20 bar of hydrogen. In THF these differences were so sharpened that β-ketoamides were hydrogenated even faster than in EtOH while the esters were extremely slow. Based on these findings, a series of 3-oxoglutaric acid derived with ester and amide moieties on the two ends were hydrogenated to 3-hydroxyl products with high enantioselectivities.

Asymmetric hydrogenation of carbonyls has become a routine method for building up chiral alcohol centers in organic synthesis.[1] Both mono- and nonfunctionalized ketones can be enantioselectively hydrogenated by the delicate catalytic systems developed by Noyori and co-workers.[2] Hitherto, polyfunctionalized ketones have been relatively intractable substrates. The primary difficulty lies in the emulative coordinations of multiple directing groups with the catalyst.[3] When two carbonyl directing groups C(O)X and C(O)Y are present in one molecule (Scheme 1), the configurations of the resultant alcohol are usually antipodal in cases when one overrides in the emulation.[3] High ee's are expected only if one of them dominated in the directing effect. More often than not, both directing groups would comparably participate in the chelating. The more polyfunctionalized a ketone is, the more versatile the hydrogenation product will be as a synthetic block. For example (Figure 1), *syn*-3,5-dihydroxyhept-6-enoic acid is a key substructure in side chains for statins.[4] Epothilone and its congeners contain a common C_1–C_6 block derived from an enantiopure 3-hydroxyl glutaric acid structure.[5]

Our group has been devoted to studying the asymmetric hydrogenation of various functionalized ketones and its applications in organic synthesis.[6] Herein we report our recent attempts to realize the pinpoint recognition of two

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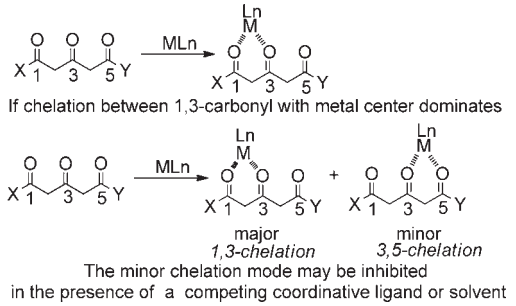
Scheme 1. Emulative Coordination Model of Carbonyls with X and Y



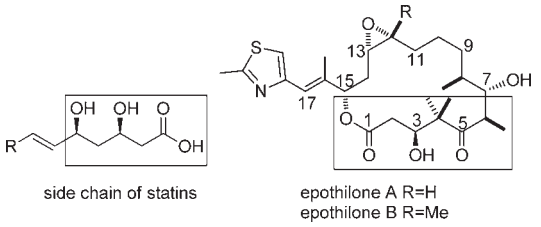


Figure 1. Polyfunctionalized chiral alcohol blocks in important pharmaceuticals and natural products.

carbonyls in close chemical propinquity by [RuCl(benzene)-(*S*)-SunPhos]Cl demonstrated in Scheme 1.

To this end, we intended to either select the proper X and Y, with such enormously different coordinating abilities that only the 1,3-chelation mode dominates, or introduce an assistant ligand or solvent whose coordination abilities are somewhere in between the 1,3- and 3,5-dicarbonyls as their presence may expel the weaker coordinating carbonyl away from the metal (Scheme 1) which would probably impair the minor chelation mode.

Brückner et al. concluded that β-ketocarboxylic acid derivatives with more electron-rich $C(O)NR_2$ moieties had a faster onset hydrogenation rate than those with C(=O)—OR by studying their rate differences in alcohols with $[RuCl_2(S)\text{-BINAP}]_2 \cdot NEt_3$ under relatively mild conditions (4 bar of H_2, ambient temperature).[7] They also mentioned that the conclusion was based on their specified conditions. We felt that the rate difference might be further modulated to achieve more subtle differentiation. Several competitive hydrogenation tests in ethanol by mixing as many as six substrates with an equivalent molar ratio were performed with [RuCl(benzene)(*rac*)-SunPhos]Cl under our conditions: 0.5% mol of catalyst, 20 bar of H_2 at 70 °C (Scheme 2). Conversion analysis with more components in the mixture failed due to the following: (1) **1b**–**k** underwent ethanolysis on GC to various extents; (2) **1h** and **2g**–**k** were ungasifiable and unable to produce signals for GC. To obtain a qualitative rate order, TLC and NMR methods were employed.

By mixing **1a**–**c** (0.5 mmol of each, 1% mmol of catalyst) in EtOH, small residual **1a** and **1b** were detected by TLC after 3 h, while **1c** was not. This indicated that *tert*-butyl acetoacetate undergoes hydrogenation faster than its ethyl and isopropyl counterparts. The rate difference between **1a** and **1d** were too subtle for TLC comparison, as they both remained untouched after 1 h and almost consumed after 4 h. Other triad mixing tests revealed that the difference between the esters and amides was not very evident but the latter were slightly faster. For example, when **1a** and **1j** were mixed under the standard conditions for 3 h, the NMR conversions were 18% and 75% respectively. By comparing the integration value of the residual $CH_3(C{=}O)$— group in NMR of the reaction mixtures, we noted that β-keto primary amides **1j** and **1k** were slightly slower than β-keto secondary amides **1h** and **1g**, respectively.

Scheme 2. Competitive Hydrogenation Test of Various β-Keto Acid Derivatives

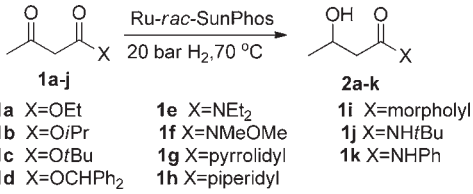
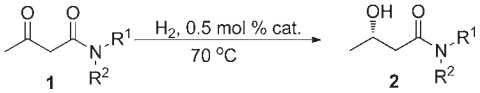


Table 1. Asymmetric Hydrogenation of **1** with [RuCl(benzene)-(*S*)-SunPhos]Cl[a]



entry	**1**	R^1	R^2	ee (%) in EtOH	ee (%) in THF
1	**1f**	OMe	Me	N/A[b]	97.2[c]
2	**1i**	-($CH_2CH_2OCH_2CH_2$) -		N/A[b]	99.3
3	**1k**	Ph	H	98.9	99.4

[a] All reactions were carried out with a substrate (1 mmol) concentration of 0.2 M in EtOH or THF (5 mL) at 70 °C with 20 bar of H_2 for 8 h. Substrate/catalyst = 200. Conversions were 100% and ee's were determined by HPLC. The absolute configurations were determined by the specific rotations (see Supporting Information). [b] No product was separated. [c] 15 h for full conversion.

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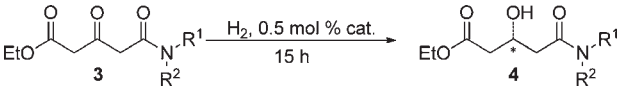
Unexpectedly, when **1f** and **1i** were involved in the mixing tests, the substrates became rather inert to the catalyst and hardly any product was detected. Finally we found that **1f** and **1i** were partially ethanolyzed to give **1a** and the freed amines poisoned the catalyst. To solve this problem, we performed the hydrogenation of **1f** and **1i** in nonalcohol solvent. To our delight, **2f** and **2i** were obtained quantitatively in THF. It is known that solvents played important roles in the asymmetric hydrogenation of methyl acetoacetate[8] while THF is an infrequently used solvent[9] for the ruthenium catalyzed hydrogenation of keto esters due to its competitive coordination to metal with substrates. Such oddities of THF prompted us to compare the hydrogenation rates of **1a**−**k** in it. Under the same conditions, we found more conspicuous differences in THF: *all esters **1a**−**d** reacted extremely slowly (almost no conversion after 7 h which was long enough for full conversion in EtOH) while amides reacted very fast*. An apparent order of reaction rate was observed: **1e**, **1g**, **1h**, **1i** > **1j** > **1k** > **1f** ≫ **1a**−**d**.

Having such a qualitative order in hand, we wondered if β-keto amides can be hydrogenated with good ee's in THF as in EtOH.[10] Asymmetric reaction versions of **1f**, **1i**, and **1k** with chiral (*S*)-SunPhos were tested. The exhilarating results in Table 1 indicated a more direct route to useful chiral blocks **2f**[11] and **2i**[12] for natural products. The β-keto(*N*-phenyl)amide **2k** also gave a very high ee (98.9% in EtOH and 99.4% in THF).

Based on the above observations, we assembled a series of 3-oxoglutaric acid derivatives with ethyl ester on one end and amides moieties on the other. As expected, excellent enantioselectivities were obtained for **4a**−**d** in THF, and the ee's range from 95.2% to 96.7% (entries 1−4, Table 2). The *N*,*N*-diphenylamide **3e** also gave an ee as high as 98.1% (entry 5, Table 2). As it can be inferred from the rate order in which the Weinreb amide moiety slowed down the hydrogenation rate that the ee of **4f** would be lower than **4a**−**d**, this was validated by the outcome of an 87.3% ee of **4f** (entry 6, Table 2).

The ee's of **4g** and **4i**, 94.4% (entry 7, Table 2) and 86.7% (entry 9, Table 2) respectively, were also consistent with the rate order in THF. The benzylamide **3h** (entry 8, Table 2) gave a little higher ee than **3i** (entry 9, Table 2). Preferably, amide moieties were the dominant directing groups when the hydrogenations were performed in THF. The effect of the substituents on the *N*-phenyl rings provided further evidence: the electron-donating groups such as methyl on **3j** (entry 10, Table 2) and methoxyl on **3k** (entry 11, Table 2) improved the ee by 6.9 and 1.5% respectively; the electron-withdrawing group like trifluoromethyl in **3l** (entry 12, Table 2) drastically impaired the ee from 86.7% to 49.3%.

Table 2. Asymmetric Hydrogenation of **3** with [RuCl(benzene)(*S*)-SunPhos]Cl[a]



entry	**3**	R^1	R^2	ee (%) in THF	ee (%) in EtOH
1	**3a**	Et	Et	96.5	93.4
2	**3b**	-$(CH_2)_4$-		96.7	81.7
3	**3c**	-$(CH_2)_5$-		95.2	86.5
4	**3d**	-$CH_2CH_2OCH_2CH_2$-		96.4	**N/A**[b]
5	**3e**	Ph	Ph	98.1(*R*)[c]	53.3(*R*)[c]
6	**3f**	Me	OMe	87.3	**N/A**[b]
7	**3g**	*t*Bu	H	94.4[d]	91.4[d]
8	**3h**	Bn	H	87.1	79.3
9	**3i**	Ph	H	86.7	88.4
10	**3j**	2,6-DiMe-Ph	H	93.6	70.1
11	**3k**	*p*-MeO-Ph	H	88.2	90.2
12	**3l**	*p*-CF_3-Ph	H	49.3	88.6

[a] All reactions were carried out in THF or in EtOH with a substrate (1 mmol) concentration of 0.2 M at 70 °C with 20 bar of H_2 for 15 h. Substrate/catalyst = 200. Conversions were 100% except where indicated. Ee's were determined on HPLC. [b] No product was obtained due to alcoholysis of the substrate. [c] The absolute configuration was determined by X-ray crystallography (see Supporting Information). [d] Ee of its 4-nitrobenzoate.

For comparison, the reactions in EtOH were also performed. For most substrates, higher ee's were obtained in THF than in EtOH, with an increase of ee ranging from 3.0 (entry 7, Table 2) to 44.8% (entry 5, Table 2). For **3i**, **3k**, and **3l**, an inversed trend was found.The absolute configuration of **4e** was determined to be *R* by X-ray crystallography, which also proved domination of the amide carbonyl as the directing group.

These hydrogenation products may provide important intermediates for statins.[13] For extension, several geminal substituents were introduced onto the methylenes in hoping that they may influence the competing coordinations between the two pairs of the β-dicarbonyl system to the catalyst center.

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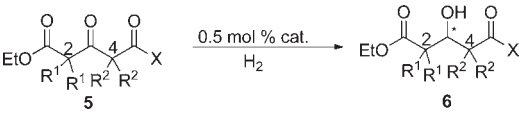
Table 3. Asymmetric Hydrogenation of Substituted 3-Oxoglutaric Acid Derivatives[a]



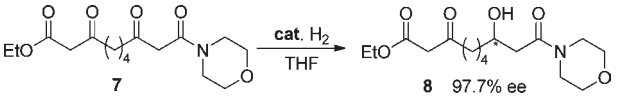
entry	5	R^1, R^2	X	ee (%) in THF	ee (%) in EtOH
1	**5a**	Me, H	NEt_2	90.3[b]	44.7
2	**5b**	Me, H	NMeOMe	92.4[c]	81.6[d]
3	**5c**	H, Me	NMeOMe	NR	98.1[e]
4	**5d**	H, -$(CH_2)_4$-	NMeOMe	NR	91.7

[a] All reactions were carried out in EtOH or THF with a substrate (1 mmol) concentration of 0.2 M at 70 °C with 20 bar of H_2 for 15 h. Substrate/catalyst = 200. Conversions were 100% except where indicated. [b] 100% conversion for 26 h. [c] 36% conversion for 20 h. [d] Less than 10% conversion due to alcoholysis. [e] 75 °C, 30 bar of H_2. NR = no reaction even under harsher conditions and prolonged reaction times.

For **5a** and **5b**, better enantioselectivities were observed in THF than in EtOH, with the ee's increased from 44.7% to 90.3% (entry 1, Table 3) and from 81.6% to 92.4% (entry 2, Table 3), respectively. However, the reactions in THF became sluggish for the 2,2-disubstituted substrates. Weinreb amides **5c** and **5d** remained untouched in THF under even harsher conditions (90 °C, 30 bar of H_2, 16 h) while they underwent smooth hydrogenation in EtOH to produce **6c** and **6d** with very good ee's: 98.1% (entry 3, Table 3) and 91.7% (entry 4, Table 3), respectively. As Weinreb amide facilitates diversified transformations in organic synthesis,[14] enantiomerically pure **6c** may provide an important intermediate for a C_1–C_6 chiral block in Epothilones and congeners.[15]

The distinct behavior in hydrogenation of β-keto acid esters and amides in THF enlightened us to envisage that two independent β-keto acid derivative systems within one molecule might be recognized by the catalyst. When ethyl 10-morpholino-3,8,10-trioxodecanoate (**7**) was subjected to the same conditions (20 bar of H_2, 70 °C, 15 h), only the β-carbonyl to the amide was saturated with 97.7% ee (Scheme 3, confirmed by $^1H-^{13}C$ HMBC experiment; see Supporting Information). This excellent regio- and enantioselectivity is the first example of asymmetric monohydrogenation of bis(β-ketocarboxylic acid) derivatives.[7,16]

Scheme 3. Higly Selective Monohydrogenation of Bis(β-ketocarboxylic Acid) Derivatives within One Molecule



In summary, we have discovered that in THF β-keto amides showed fast hydrogenation rates while esters were almost inert. A series of 3-oxoglutaric acid derivatives were hydrogenated to the 3-hydroxyl products with excellent ee's. Such serendipity with THF also made it possible to distinguish β-keto amides from β-keto esters within one molecule, which had previously remained difficult in asymmetric hydrogenation. Moreover, our findings may furnish new concepts for more challenging recognitions in various highly functionalized carbonyl substrates.

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Supporting Information Available. The experiment details of substrates synthesis, NMR and/or HPLC data of **1**–**8**, crystallographic data of (*R*)-**4e** (cif). This material is available free of charge via the Internet at http://pubs.acs.org.

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