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Asymmetric Hydrogenation of α-Alkyl-Substituted β-Keto Esters and Amides through Dynamic Kinetic Resolution

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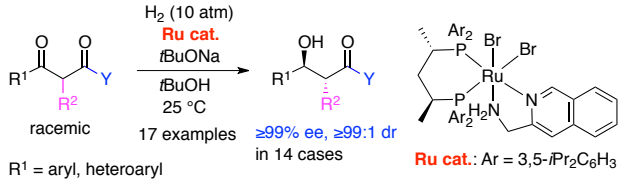
Supporting Information Placeholder



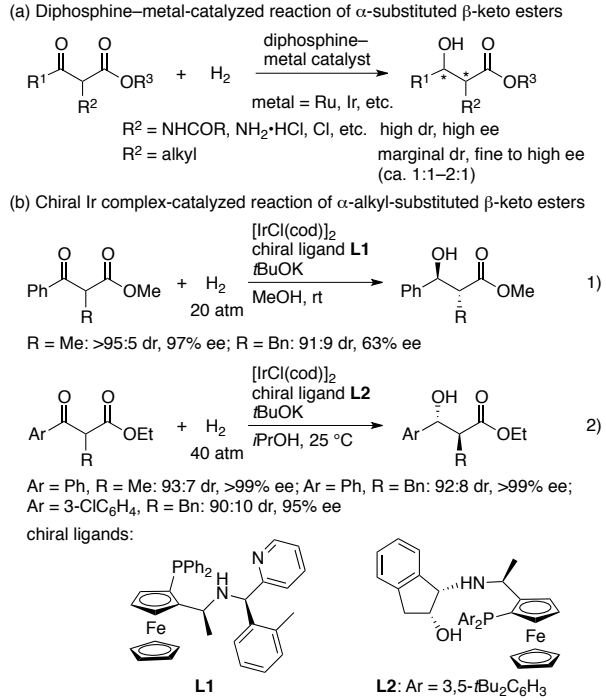
ABSTRACT: Asymmetric hydrogenation of α-alkyl-substituted β-keto esters and amides with the DIPSkewphos/3-AMIQ–Ru(II) catalyst system through dynamic kinetic resolution was examined. A series of β-keto esters and amides with a simple or functionalized α-alkyl group was applicable to this reaction, affording the α-substituted β-hydroxy esters and amides in ≥99% ee (*anti*:*syn* = ≥99:1) in many cases. The 5-gram-scale reaction was readily achieved. The mode of enantio- and diastereoselection in the transition state model was proposed.

Asymmetric hydrogenation of α-substituted β-keto esters through dynamic kinetic resolution (DKR) is an efficient and straightforward method to produce the enantio- and diastereo-controlled α-substituted β-hydroxy esters.[1] Under appropriate conditions, epimerization at the α-stereogenic center of the β-keto ester occurs rapidly. When enantioselective reduction of the β-keto-carbonyl group proceeds with recognition of the stereochemistry of the α position, the α-substituted β-hydroxy ester with precisely regulated two precisely regulated contiguous stereo-centers is obtained quantitatively from the racemic keto ester in theory.[2]

In 1989 Noyori and co-workers first reported the reaction catalyzed by BINAP–Ru(II) complexes.[3] Since this finding, various β-keto esters with a heteroatom-based α-substituent, such as NHCOR (R = Me, Ph, OBn), phthalimide, NH_2•HCl, Cl, and $CH_2NHCOPh$, have been converted to the corresponding α-substituted β-hydroxy esters in high enantio- and diastereoselectivity by using chiral diphosphine–metal (Ru, Ir, Ni, etc.) catalysts (Scheme 1a).[4] Some cyclic β-keto esters and α-acyl lactones were also successfully applied to this reaction.[4a,b,5] However, acyclic α-alkyl-substituted β-keto esters were difficult substrates to apply for the reaction with chiral diphosphine–metal catalysts, affording the alcoholic products as approximately 1:1–2:1 diastereomeric mixtures, probably due to the slow rate of stereoinversion and/or insufficient stereorecognition by the chiral catalysts at the α positions of the β-keto esters.[3,5] We then considered that the chiral catalyst with an appropriate asymmetric environment for the stereorecognition at the alkyl-substituted α position would be required to overcome this problem, and the catalyst should work under a basic condition that promotes stereoinversion of the α stereocenter of the β-keto ester.

We have developed asymmetric hydrogenation of unfunctionalized ketones catalyzed by BINAP/1,2-diamine–Ru(II) complexes in the presence of an alkaline base.[6] RuH_2(binap)(1,2-diamine) formed *in situ* efficiently promotes the reaction via an outer-sphere "metal–ligand cooperated transition state (TS)" with the H_2RuNXY (X,Y = H or alkaline metal) species. This type of chiral catalyst with a base is effective for the asymmetric hydrogenation of α-substituted simple ketones through DKR. However, the reaction of β-keto esters did not proceed well with these catalysts, probably because of

Scheme 1. Previous Works on Asymmetric Hydrogenation of α-Substituted β-Keto Esters through DKR

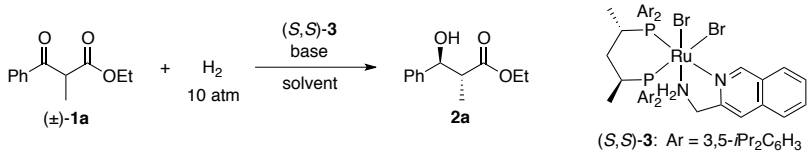


the strongly binding substrate inhibition. Recently, chiral ferrocene-based tridentate ligand–Ir(I) complexes were reported to catalyze the reaction of α-alkyl-substituted β-keto esters with an addition of *t*BuOK (Scheme 1b).[7,8] The **L1**–Ir system (Hu, 2016) hydrogenated methyl 2-methyl-3-oxo-3-phenylpropanoate to the *anti*-hydroxy ester (*anti*:*syn* = >95:5) in 97% ee (eq 1).[7] But the stereoselectivity was significantly decreased in the reaction of α-Bn-β-keto ester (91:9 dr, 63% ee). The **L2**–Ir system (Wen, Yin, Zhang, 2018) achieved excellent ee of >99% (eq 2).[8] But the diastereoselectivity had room for improvement: α-Me (93:7 dr), α-Bn (92:8 dr). Modification of the β-aryl ring tended to decrease the stereoselectivity—e.g., α-Bn-β-3-ClC_6H_4 (90:10 dr, 95% ee).

We recently devised $RuBr_2$(dipskewphos)(3-amiq) (**3**, see the scheme in Table 1), which catalyzes asymmetric hydrogenation of β- to ε-keto esters to afford the hydroxy esters and the 1,4- and 1,5-diols in high ee values in the presence of a base.[9,10] The isoquinolinyl moiety results in unique catalytic properties. We herein describe asymmetric hydrogenation of α-alkyl-substituted β-keto esters with the DIPSkewphos/3-AMIQ–Ru(II) catalyst system. A series of aromatic *anti*-α-alkyl-substituted β-hydroxy esters was obtained in excellent enantio- and diastereoselectivity. The asymmetric hydrogenation through DKR was also applicable to the α-alkyl-substituted β-keto amides.[11]

We selected racemic ethyl 2-methyl-3-oxo-3-phenylpropanoate ((±)-**1a**) as a typical substrate to optimize the reaction conditions (Table 1). We first employed the reaction conditions for hydrogenation of an unsubstituted β-keto ester, ethyl 3-oxo-3-phenylpropanoate, which were found in our previous work.[9a] The keto ester (±)-**1a** was hydrogenated with $RuBr_2$[(*S*,*S*)-dipskewphos](3-amiq) ((*S*,*S*)-**3**) and *t*BuOK (**1a**:**3**:base = 500:1:20) in ethanol under 10 atm of H_2 at 40 °C in 24 h to afford the *anti*-hydroxy ester **2a** (*anti*:*syn* = 96:4) in 97% ee quantitatively (entry 1). When *t*BuONa was used instead of *t*BuOK, almost enantiomerically pure **2a** was obtained (entry 2). As the result of solvent screening (entries 3–8), (2*R*,3*S*)-**2a** was solely obtained (*anti*:*syn* = >99:1, >99% ee) among four possible stereoisomers in *t*BuOH at 25 °C (entry 5). Excellent stereoselectivity was also obtained in *i*PrOH, but **2a** was accompanied by a transesterification product (entry 4). The reaction rate was significantly slowed in *t*AmOH and aprotic THF and toluene (entries 6–8). The reaction with a substrate-to-catalyst molar ratio (S/C) of 1000 was

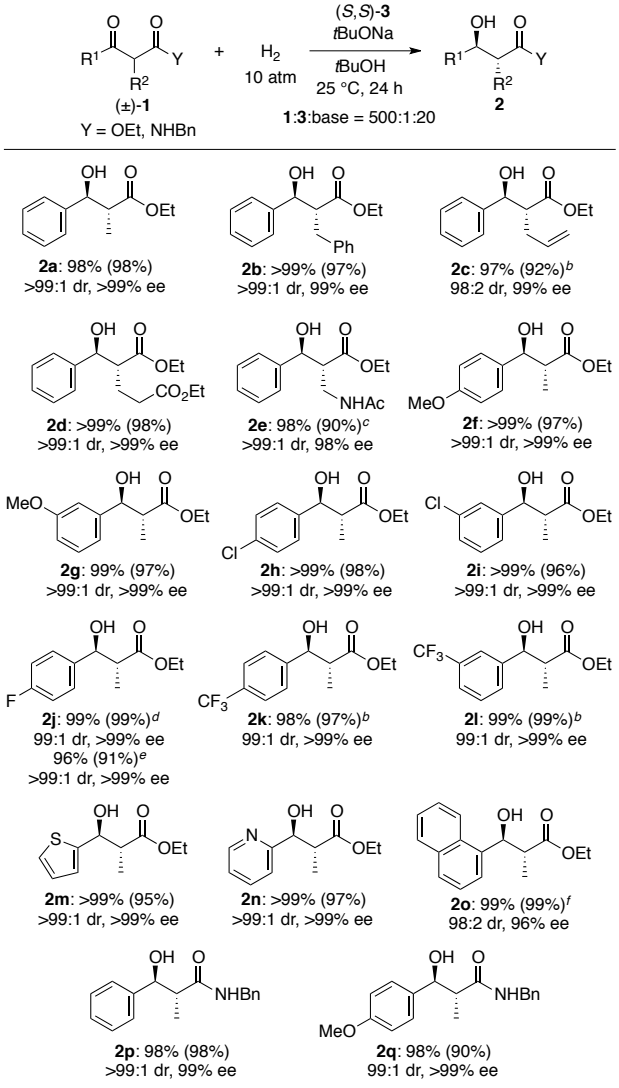
Table 1. Asymmetric Hydrogenation of α-Methyl β-Keto Ester (±)-1a through DKR[a]



entry	S/C[b]	Base	solvent	temp, °C	% convn.[c]	% yield[c,d]	*anti*:*syn*[c,e]	% ee[f]
1	500	*t*BuOK	EtOH	40	>99	97 (92)	96:4	97
2	500	*t*BuONa	EtOH	40	>99	97 (96)	94:6	>99
3	500	*t*BuONa	EtOH	25	>99	98 (94)	96:4	>99
4	500	*t*BuONa	*i*PrOH	25	>99	(79)[g]	>99:1	>99
5	500	*t*BuONa	*t*BuOH	25	>99	98 (98)	>99:1	>99
6	500	*t*BuONa	*t*AmOH	25	24	24 (21)	>99:1	>99
7	500	*t*BuONa	THF	25	5	5	nd[h]	nd[h]
8	500	*t*BuONa	toluene	25	31	28 (28)	>99:1	>99
9	1000	*t*BuONa	*t*BuOH	25	>99	>99 (96)	>99:1	>99
10	2000[i]	*t*BuONa	*t*BuOH	25	81	81 (80)	>99:1	>99

[a] Unless otherwise stated, the hydrogenation of keto ester (±)-**1a** was conducted under 10 atm of H_2 in solvent containing a Ru complex (*S*,*S*)-**3** and a base for 24 h. The **3**/base molar ratio was 1:20. [b] Substrate **1a**/catalyst **3** molar ratio. [c] Determined by ^{1}H NMR and HPLC analysis. [d] The isolated yield of **2a** is indicated in parentheses. [e] Molar ratio of *anti*-**2a** and *syn*-**2a**. [f] Data for the major diastereomer determined by chiral HPLC analysis. [g] Formation of *i*Pr ester was observed. [h] Not determined. [i] The reaction time was 40 h.

Scheme 2. Asymmetric Hydrogenation of α-Alkyl-Substituted β-Keto Esters and Amides (±)-1[a]



[a] Unless otherwise stated, reactions were conducted under 10 atm of H_2 at 25 °C for 24 h using keto ester or amide (±)-**1** in *t*BuOH containing a Ru complex (*S*,*S*)-**3** and *t*BuONa. The **1**/**3**/base molar ratio was 500:1:20. The yield of **2** and molar ratio of *anti*-**2** and *syn*-**2** (dr) were determined by ^{1}H NMR analysis. The isolated yield of **2** is indicated in parentheses. The ee of **2** was determined by chiral HPLC analysis. [b] The reaction time was 48 h. [c] The reaction with **1**:**3**:base = 200:1:20 for 72 h. [d] **1**:**3**:base = 500:1:40. [e] The reaction was conducted under 4 atm H_2 for 72 h. [f] The reaction with **1**:**3**:base = 200:1:20 for 38 h.

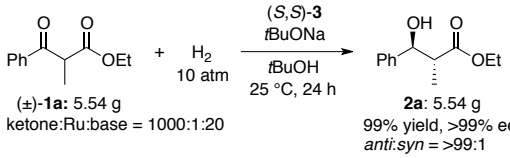
completed in 24 h with maintenance of the stereoselectivity (entry 9). When the reaction was conducted with an S/C of 2000 for 40 h, **2a** was obtained in 81% yield (entry 10).

We next examined the substrate scope of this reaction with an S/C of 500 under 10 atm of H_2 at 25 °C for 24 h as shown in entry 5 of Table 1 (Scheme 2). The DIPSkewphos/3-AMIQ–Ru(II) catalyst system was widely applicable to the α-alkyl-substituents. The keto esters with an α-Me or α-Bn group, **1a** and **1b**, were quantitatively converted to the (2*R*,3*S*)-hydroxy esters, **2a** and **2b**, in ≥99% ee with an *anti*/*syn* ratio of >99:1. By the previous hydrogenation methods, an α-Bn product **2b** having both high enantio- and diastereoselectivity was hardly available (see Scheme 1b). The (2*R*,3*S*)-α-allyl-β-hydroxy ester **2c** was obtained leaving the terminal olefin intact. The 2-benzoyl-1,5-diester **1d**, a functionalized β-keto ester, was also hydrogenated with almost perfect stereoselectivity. The reduction of α-acetamidomethyl-substituted compound **1e** was relatively slow even with an S/C of 200, affording *anti*-**2e** in 98% ee. The catalyst system well tolerated the introduction of substituents on the benzoyl phenyl rings. The α-methyl-β-keto esters with both an electron-donating MeO group and electron-withdrawing Cl, F, and CF_3 groups at the *para* and *meta* positions were completely converted to the *anti*-hydroxy esters, **2f**–**2l**, in almost enantio- and diastereomerically pure forms. The F-substituted ketone **1j** was hydrogenated even under 4 atm of H_2. The thienyl keto ester **1m**, a five-membered heteroaromatic ketone, was quantitatively converted to the desired product **2m** in stereochemically pure form. Hydrogenation of 2'-pyridyl ketones is often retarded due to strong binding of the substrates to the catalysts. But the performance of the DIPSkewphos/3-AMIQ–Ru(II) catalyst was not inhibited at all in the reaction of the β-(2-pyridyl)-α-methyl-β-keto ester **1n** to afford **2n** as a single stereoisomer. The 1-naphthyl ketone **1o** reacted slowly, and **2o** was obtained with relatively low stereoselectivity.

Notably, the asymmetric hydrogenation was successfully applied to the amide analogues.[11] The benzylamides, **1p** and **1q**, were transformed to the *anti*-(2*R*,3*S*)-hydroxy amides, **2p** and **2q**, exclusively.

The 5-gram-scale hydrogenation of **1a** was readily carried out under the optimized conditions (S/C = 1000, 10 atm H_2, 25 °C, 24 h). The hydroxy ester **2a** was obtained in 99% isolated yield without influence on the stereoselectivity (*anti*:*syn* = >99:1, >99% ee) (Scheme 3).

Scheme 3. Five-gram-scale Hydrogenation of 1a



Based on our previous related studies, *cis*-RuH_2[(*S*,*S*)-dipskewphos](3-amiq) is proposed as the active species derived from (*S*,*S*)-**3** and *t*BuONa in the reaction system.[6,9] The primary amine protons of 3-AMIQ are probably replaced with sodium cations. As shown in Figure 1 (side view), a ruthenium hydride, H_A, which locates *trans* to the phosphine group (PAr_2), acts as the nucleophile. The keto-carbonyl group of the keto ester **1a** is reduced through the six-membered cyclic TS, in which the $H_A^{\delta-}$–$Ru^{\delta+}$–$N^{\delta-}$–$X_{ax}^{\delta+}$ (X = H or Na) quadrupole of the catalyst effectively activates the carbonyl dipole ($C^{\delta+}$=$O^{\delta-}$) of **1a**.[12] The plate-shaped phenyl group of **1a** exclusively fits over the flat isoquinoline moiety of the catalyst, but does not match the side having a wall-like *P*-3,5-diisopropylphenyl (DIP) group (top view), achieving almost perfect enantioselectivity. Therefore, the sp^3-α-carbon of **1a** locates at the side of the *P*-DIP group, and the configuration of the α-stereogenic center is also controlled by the chiral environment of the catalyst. The bulky and rigid ester moiety of **1a** is directed to the far side from the *P*-DIP wall, and the medium-sized methyl (or flexible alkyl) moiety locates close to the *P*-DIP group. The smallest hydrogen is nearly positioned on

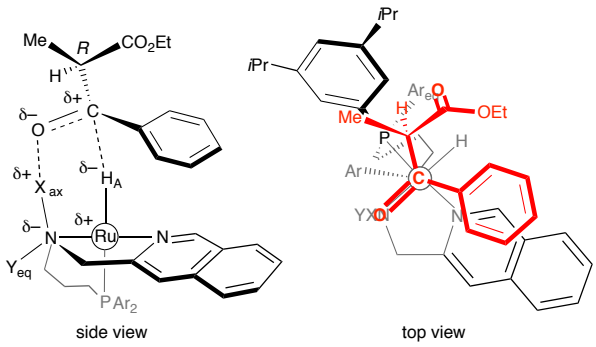


Figure 1. Plausible TS-Models in the Hydrogenation of (±)-1a through DKR. X, Y = H or Na. Ar = 3,5-*i*Pr$_2$C$_6$H$_3$.

the catalyst surface. Consequently, the keto ester **1a** is hydrogenated by the (*S*,*S*)-catalyst only when the α-position reversibly has the *R*-configuration, affording the *anti*-(2*R*,3*S*)-hydroxy ester **2a** predominantly.

In summary, we have reported herein asymmetric hydrogenation of α-alkyl-substituted β-keto esters and amides through dynamic kinetic resolution (DKR) with our original (*S*,*S*)-DIPSkewphos/3-AMIQ–Ru(II) catalyst system. The reaction was conducted with an S/C of 200 to 2000 under 10 atm of H_2 at 25 °C to afford exclusively the optically active *anti*-α-alkyl-substituted β-hydroxy esters and amides among four possible stereoisomers. The addition of *t*BuONa promoted formation of the active RuH_2 species and stereo-mutation at the α-position of the ketonic substrate. The β-phenyl-β-keto esters with a simple (Me, Bn, and allyl) and a functionalized ($(CH_2)_2CO_2Et$, CH_2NHAc) alkyl group at the α position were converted to the (2*R*,3*S*)-hydroxy esters in >99% ee (*anti*:*syn* = >99:1) in the best cases. The reaction allowed us to introduce both electron-donating (MeO) and electron-withdrawing (Cl, F, CF_3) substituents on the benzoyl phenyl groups. The β-heteroaryl (2-thienyl, 2-pyridyl) keto esters were hydrogenated with almost perfect enantio- and diastereoselectivity. The β-keto *N*-benzylamide analogues were also transformed to the β-hydroxy amides with excellent stereoselectivity. The 5-gram-scale reaction of the β-phenyl keto ester was readily performed with maintenance of the excellent stereoselectivity. The mode of enantio- and diasterselection in the transition state catalyzed by the (*S*,*S*)-DIPSkewphos/3-AMIQ–Ru(II) species was also proposed.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Full experimental procedures and analytical data (^{1}H, ^{13}C and ^{19} F NMR spectral data; HPLC data; optical rotation data; HRMS data) (PDF).

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Notes

The authors declare no competing financial interest.

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