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Enantioselective and Diastereoselective Ir-Catalyzed Hydrogenation of α-Substituted β-Ketoesters via Dynamic Kinetic Resolution

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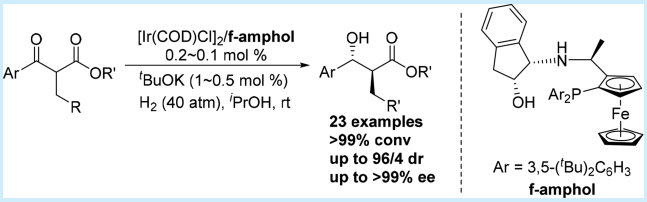
Supporting Information

ABSTRACT: An iridium/f-amphol catalytic system for the enantioselective hydrogenation of α-substituted β-ketoesters via dynamic kinetic resolution is reported. The desired *anti* products were obtained in high yields (up to 98%) with good diastereoselectivity (up to 96:4 diastereomeric ratio (dr)) and excellent enantioselectivity (up to >99% enantiomeric excess (ee)). A catalytic model is proposed to explain the stereoselectivity.



Compared to kinetic resolution, which achieves no more than 50% transformation of the substrates, dynamic kinetic resolution (DKR) could theoretically realize 100% conversion of the substrates to the products. In this chemical process, each enantiomer of a configurationally labile racemic substrate has a different reaction rate in a chiral environment. If the racemization step is fast enough prior to the transformation, both enantioselectivity and diastereoselectivity would be achieved.

Transition-metal (TM)-catalyzed hydrogenation of α-substituted β-ketoesters is an example with DKR. If controlled hydrogenation is performed, two contiguous stereocenters are constructed in a single reaction (see Figure 1a). This reaction has drawn great interest[1] since Noyori[2] and Genêt,[3] who independently used ruthenium/bisphoshine complexes to perform the hydrogenation of the keto group, giving chiral β-hydroxy esters. Many efforts have been made to improve this reaction. Various ligands were designed to fit this reaction.[4] In the meanwhile, TMs other than ruthenium,[5] such as iridium[6] and nickel,[7] were also surveyed in this reaction. In addition, transfer hydrogenation[8] and biocatalytic reduction[9] were also developed. Note that a cobalt-catalyzed borohydride reduction could also be applied in this reaction with high efficiency and stereoselectivity.[10] Although enantiomeric control has been achieved, diastereoselectivity is still historically problematic. The most applied strategy is substrate control (see Figure 1b), via either a covalent bond or an intramolecular hydrogen bond. Therefore, the reaction scope is limited to cyclic substrates or substrates with hydrogen bond donors. A simple alkyl group at the α-position remains challenging until Hu[11] reported an iridium-catalyzed hydrogenation via DKR, giving *anti* products. In this case, a relatively narrow substrate scope and modest enantiomeric excess (ee) values for some substrates were reported. However, the synthesis of chiral β-hydroxyesters is still in demand.

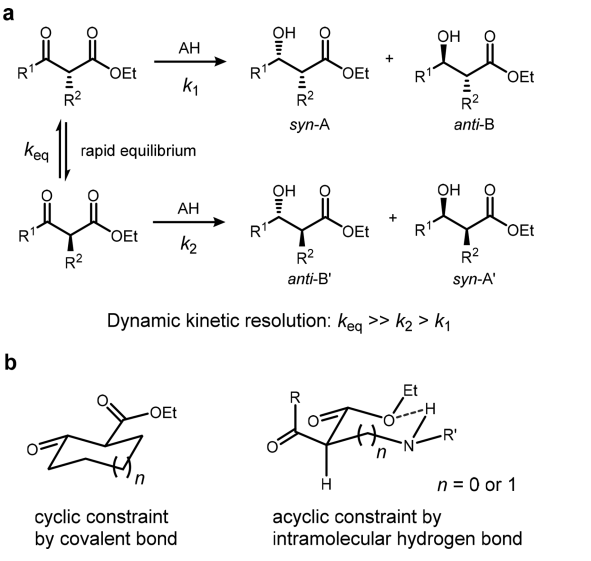


Figure 1. Dynamic kinetic resolution (DKR) in the transition-metal (TM)-catalyzed hydrogenation of β-ketoesters: (a) general reaction pathway and (b) substrate control for high diastereoselectivity.

Our group has developed a series of ferrocene-based tridentate ligands[12] to facilitate iridium-catalyzed enantioselective hydrogenation of ketones. A bifunctional model (Figure 2, top) was proposed: with a secondary interaction between a polar functional group in the ligand and carbonyl group in the substrate, a hydride could be stereoselectively delivered from the TM to the unsaturated bond. We envisioned that iridium with those ligands could catalyze stereoselective reduction of α-substituted β-ketoesters. If the racemization step is fast enough, a dynamic kinetic resolution would be achieved.

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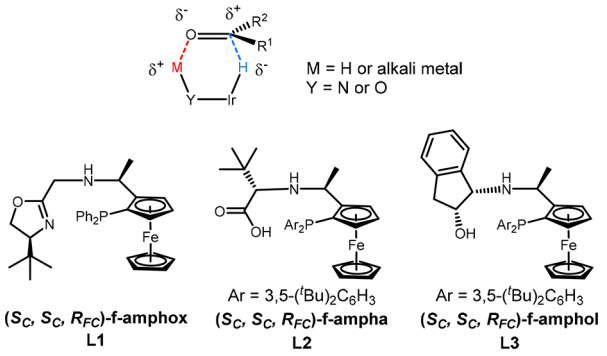
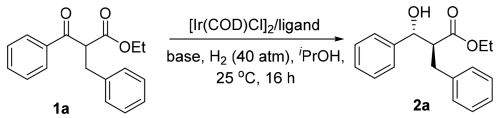


Figure 2. Ferrocene-based tridentate ligands for highly efficient Ir-catalyzed enantioselective hydrogenation of ketones.

Our investigation was initiated with ethyl 2-benzyl-3-oxo-3-phenylpropanoate (**1a**) as the model substrate and $[Ir(COD)Cl]_2$ as the metal precursor. Ligands were first tested in isopropanol with sodium *tert*-butoxide as the base (Table 1, entries 1−3). To our surprise, these ligands, which are efficient for the AH of simple ketones, behaved differently under these conditions. Iridium complexes with **f-amphox** and **f-ampha** did not show any reactivity, with a substrate-to-catalyst molar ratio (S/C) of 1000/1. In a sharp contrast, Ir/**f-amphol** gave the reduction product with excellent enantioselectivity, albeit with moderate diastereoselectivity (99% ee, 83/17 dr). In order to increase the diastereoselectivity, screening of bases and solvents was undertaken. In isopropanol, inorganic bases with alkali-metal cations worked well in conversion and enantioselectivity, but the dr values were not satisfactory (see entries 4−8 in Table 1). With potassium *tert*-butoxide as the base, a series of solvents were screened. Tetrahydrofuran (THF) gave no product while other aprotic solvents did not bring benefit to the dr value (see entries 11−15 in Table 1). Methanol gave high dr values but moderate enantiomeric excess (ee) (entry 9 in Table 1). Gratifyingly, ethanol provided both high diastereoselectivity (92/8 dr) and high enantioselectivity (>99% ee) (entry 10 in Table 1). The reaction proceeded completely by extending the reaction time (entry 16 in Table 1). Lowering the reaction temperature slightly increased the dr value but slowed down the reaction (entry 17 in Table 1). Increasing the catalyst loading enabled a full conversion in a shorter time (entry 18 in Table 1). This Ir/**f-amphol** catalyst was demonstrated to be highly efficient: 97% conversion and >99% ee was achieved at S/C = 5000 (entry 19 in Table 1).

To examine the substrate scope, a series of α-substituted β-ketoesters are prepared and hydrogenated afterward. The results were summarized in Scheme 1. Methyl esters (**2b**, 90/10 dr, >99% ee) and tertiary butyl esters (**2c**, 91/9 dr, 95% ee) showed similar reactivities and stereoselectivities to the model ethyl ester substrate (**2a**, 92/8 dr, >99% ee). Various α-substitution groups did not bring significant influence to this reaction. Substrates with various substituents on the α-benzyl group (**2d**−**2l**) were hydrogenated smoothly under the optimal condition with both high enantioselectivities (all ≥99% ee) and diastereoselectivities; those containing *ortho*-substitiuents, regardless of electron-donating or electron-withdrawing groups, on α-benzyl group, gave product in diminished dr values (**2f**, 84/46 dr; **2j**, 88/12 dr; **2k**, 83/17 dr); those with an *para*-electron-withdrawing group on α-benzyl group provided the

Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	base	solvent	conversion (%)[b]	diastereomeric ratio, dr[c]	enantiomeric excess, ee (%)[c]
1	**L1**	^{t}BuONa	^{i}PrOH	0	N.A.	N.A.
2	**L2**	^{t}BuONa	^{i}PrOH	0	N.A.	N.A.
3	**L3**	^{t}BuONa	^{i}PrOH	98	83/17	99
4	**L3**	^{t}BuOK	^{i}PrOH	>99	86/14	99
5	**L3**	^{t}BuOLi	^{i}PrOH	96	75/25	98
6	**L3**	Cs_2CO_3	^{i}PrOH	>99	86/14	99
7	**L3**	K_2CO_3	^{i}PrOH	70	80/20	99
8	**L3**	NaOH	^{i}PrOH	>99	83/17	99
9	**L3**	^{t}BuOK	MeOH	70	93/7	69
10	**L3**	^{t}BuOK	EtOH	81	92/8	>99
11	**L3**	^{t}BuOK	toluene	70	80/20	98
12	**L3**	^{t}BuOK	DCM	40	80/20	97
13	**L3**	^{t}BuOK	THF	0	N.A.	N.A.
14	**L3**	^{t}BuOK	EtOAc	50	89/11	98
15	**L3**	^{t}BuOK	*n*-hexane	66	80/20	99
16[d]	**L3**	^{t}BuOK	EtOH	>99	92/8	>99
17[e]	**L3**	^{t}BuOK	EtOH	77	93/7	>99
18[f]	**L3**	^{t}BuOK	EtOH	>99	92/8	>99
19[g]	**L3**	^{t}BuOK	EtOH	97	92/8	>99

[a]Reaction conditions: 0.10 mmol **1a**, **1a**/$[Ir(COD)Cl]_2$/ligand = 2000/1.0/2.0, 0.001 mmol ^{t}BuONa, 1.0 mL solvent. [b]Determined via ^{1}H NMR analysis. [c]Determined by HPLC on a chiral stationary phase, the absolute configuration of **2a** was determined by comparing the HPLC and optical rotation data with those reported in the literature.[13] [d]After 24 h. [e]Conditions: −5 °C, 24 h. [f]**1a**/$[Ir(COD)Cl]_2$/ligand = 1000/1.0/2.0, 7 h. [g]**1a**/$[Ir(COD)Cl_2]$/ligand = 10 000/1.0/2.0, 96 h.

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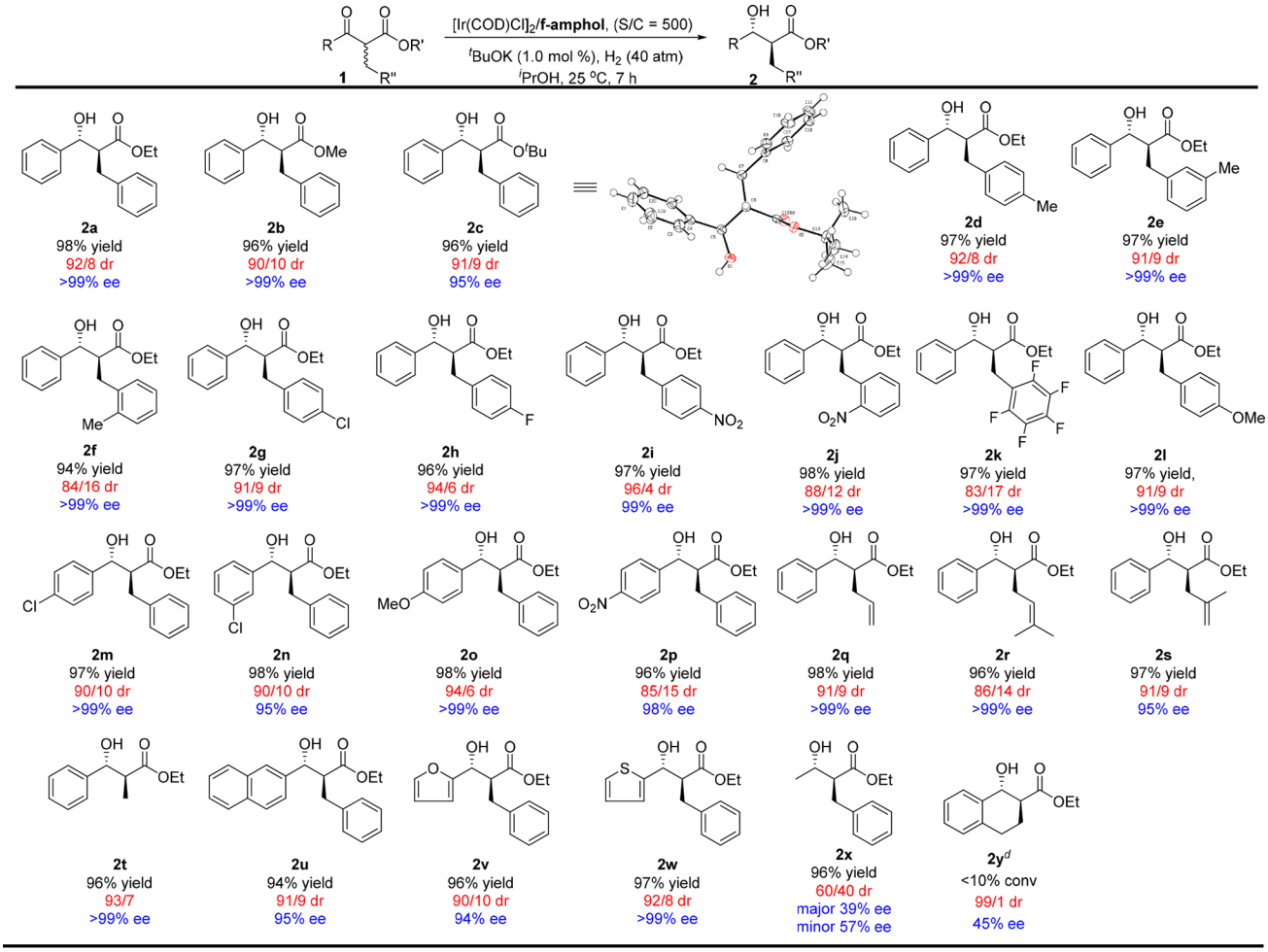
Scheme 1. Substrate Scope for Iridium-Catalyzed Stereoselective Hydrogenation of α-Substituted β-Ketoesters[a,b,c]

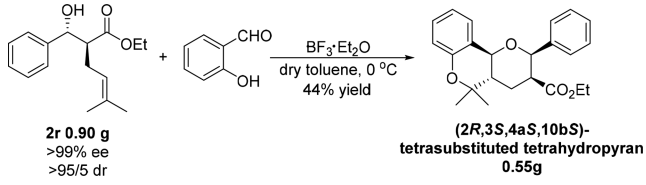


[a]Reaction conditions: 0.10 mmol **1**, **1**/[Ir(COD)Cl]$_2$/ligand = 1000/1.0/2.0, 0.001 mmol ^{t}BuOK, 1.0 mL solvent. [b]Isolated yields. [c]The ee and dr values were determined by HPLC on a chiral stationary phase. [d]Reaction time of 24 h.

hydrogenated products with higher dr values (**2h**, 94/6 dr and **2i**, 96/4 dr). Substrates bearing various substituents adjacent to the keto group also work well (**2m**−**2p**). It is interesting that substrates with electron-withdrawing group on benzoyl gave product in decreased dr values (**2p**, 85/15 dr, 98% ee), while substrate with electron-donating groups gave product in elevated dr values (**2o**, 96/4 dr, > 99% ee). Allylic groups (**2q**−**2s**) and methyl group (**2t**) at the α-position were also tested, giving the corresponding β-hydroxy esters with excellent yields and stereoselectivities. Heteroaromatic groups, which usually cause incompatibility in the TM-catalyzed homogeneous hydrogenation reactions, did not inhibit this reaction (**2v**, 90/10 dr, 94% ee and **2w**, 92/8 dr, >99% ee). However, aliphatic groups gave a high conversion but seriously decreased enantioselectivity and diastereoselectivity (**2x**, 60/40 dr, 39% ee). The system also does not apply to the hydrogenation of cyclic β-ketoesters (**2y**, <10% conversion and 45% ee).

Chiral β-hydroxyesters are important synthons that play a fundamental role as intermediates in total synthesis. In order to showcase the utility of this method, we selected one substrate (**2r**) to demonstrate the easy transformation of β-hydroxyesters. In the presence of Lewis acid boron trifluoride, the purified **2r** condensed with salicylaldehyde, giving a complex chiral tetrahydropyran structure with four stereogenic centers was obtained[14] (see Scheme 2). The broad substrate scope, high stereoselectivities, and easy transformation of the products

Scheme 2. Elaboration on the Product Transformation



together demonstrate that this method to prepare chiral β-hydroxyesters is practical in synthetic chemistry.

In order to explain the high stereoselectivities, models of catalyst−substrate interaction were established. Based on our computational studies in the case of the Ir/**f-amphox**-catalyzed AH of α-ketoamides,[15] electrostatic interaction plays an important role in the enantioselective induction (see Figure 3, top). We hypothesize that the metal cation links the substrate with catalyst, lowering the Gibbs energy and benefitting the formation of a stable catalyst−substrate complex. Four models of transition states in the stereocontrol step are shown in Figure 3, yielding four possible isomers. However, because of steric hindrance, only one catalyst−substrate complex has lower free

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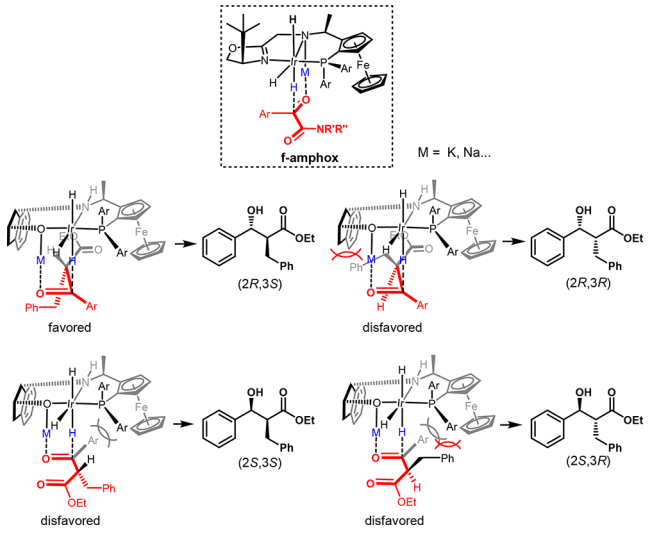

Figure 3. Proposed models to elucidate enantiomeric induction in Ir/f-amphol catalyzed hydrogenation of **1a** via DKR.

energy. This modeling rationale helps to explain the high stereoselectivities in this chemical transformation. Another interesting question is this: why does *only* **f-amphol** show reactivity in the reaction condition with 0.1 mol % catalyst loading? We failed to give any plausible explanations at this stage, and mechanistic studies on this issue are currently underway.

In summary, we have identified a highly efficient Ir/**f-amphol** complex for stereoselective hydrogenation of β-ketoesters. A dynamic kinetic resolution has been achieved with remarkably high enantioselectivities and diastereoselectivities. Various α-substituted β-ketoesters were hydrogenated to afford chiral *anti* β-hydroxyesters. A model is proposed to explain the origin of stereoselectivities based on our previous mechanistic studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00433.

Complete experimental details and characterization data (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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