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Iridium-Catalyzed Enantioselective and Diastereoselective Hydrogenation of Racemic β'-Keto-β-Amino Esters via Dynamic Kinetic Resolution

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Abstract: An iridium/*f*-diaphos catalytic system for the enantioselective hydrogenation of α-substituted β-ketoesters via dynamic kinetic resolution is reported. The desired anti β'-hydroxy-β-amino esters were obtained in moderate to good yields (60–95%) with 72–99% *ee*s and 91:9 to 99:1 *dr*s. This protocol tolerates various functional groups and could be easily conducted on gram scale with lower catalyst loading (TON up to 9100).

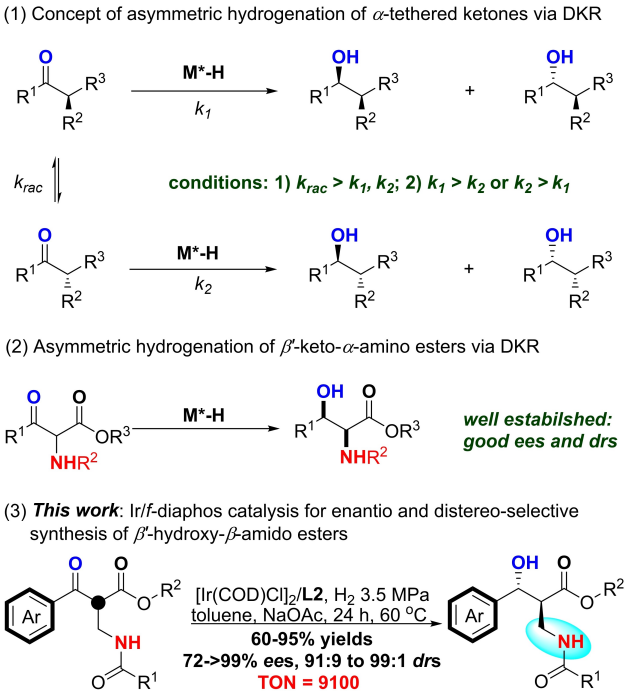
Keywords: asymmetrical hydrogenation; dynamic kinetic resolution; iridium; *f*-diashos; β'-keto-β-amino esters

The conversion of racemic compounds into enantiomerically enriched products via the dynamic kinetic resolution (DKR) represents one of the most powerful approaches to asymmetric synthesis.[1] Particularly, pioneered by Noyori[2] and Genêt,[3] this strategy has been widely used in the transition metal catalyzed asymmetrical hydrogenation (AH) of configurationally labile substrates containing carbon-oxygen double bonds, thus offering versatile chiral alcohols with two or more stereogenic centers (Scheme 1-1).[4,5] Chiral β-hydroxy amino acids and derivatives represent a class of versatile structural motifs or building blocks in the construction of pharmacological compounds, natural products, and biologically active molecules.[6] Although numerous mythologies have been developed for the access these important scaffolds,[7–10] asymmetric hydrogenation of racemic β-keto amino esters via DKR is considered as the most atom-economical and straightforward way.

Since the pioneering work reported in 2004 by Hamada[11] and Ratovelomanana-Vidal,[12] numerous metal-ligand catalytic systems have been developed for the asymmetric hydrogenation of β-keto-α-amino esters with a DKR process, achieving the highly enatioselective and diastereoselective construction of diverse β-hydroxy-α-amino acids (up to >99% *ee* and 99:1 *dr*) (Scheme 1-2).[13] However, the DKR-AH of racemic β'-keto-β-amino esters was far less studied.

The limited examples were reported by Zhang[14] and Rimoldi[15] who independently realized the enantio- and diastereoselective synthesis of β'-hydroxy-β-amino esters using ruthenium-diphosphine ligand catalysis, albeit with narrow scope and low turnover numbers. Nevertheless, the development of metal-ligand catalysis with high efficiency, good compatibility and excellent enantio- and stereo-selectivities for chiral β'-hydroxy-β-amino esters have still remained elusive, but highly desirable.

Very recently, our group[16] has developed a series of tridentate ferrocene-based diamine-phosphine sulfonamide ligands (*f*-diaphos), which showed excellent enantioselectivities in the iridium-catalyzed asymmetric hydrogenation of various ketones, including aryl alkyl ketones, diaryl ketones and 2-pyridyl aryl ketones, providing very useful chiral alcohols with up to >99% *ee* and 100 000 TON. Encouraged by these works, we envisioned that the Ir/*f*-diaphos catalytic system may work well with the hydrogenation of β'-keto-β-amino esters. Herein, we wish to report a highly diastereo- and enantio-selective Ir-*f*-diaphos catalyzed DKR-AH of racemic β'-keto-β-amino esters, which led

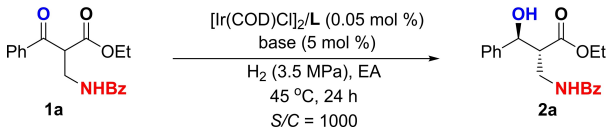


Scheme 1. Dynamic kinetic resolution (DKR) in the transition-metal (TM)-catalyzed hydrogenation of α-tethered ketones.

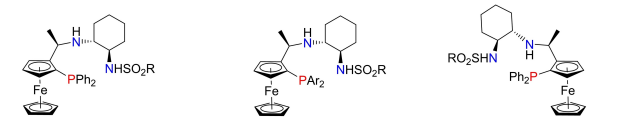
to a variety of optically active anti-*β'*-hydroxyesters (Scheme 1-3).

We initially selected **1a** as a model substrate to evaluate various chiral Ir/*f*-diaphos catalysts generated in situ by mixing $[Ir(COD)Cl]_2$ with *f*-diaphos ligands **L1**–**L5**. Delightfully, **L1** exhibited inspiring results with ethyl acetate (EA) as the solvent and Na_2CO_3 as a base to produce **2a** in 90% conversion with 80% *ee* and 90:10 *dr* (Table 1, entry 1).[17] With an increase in steric hindrance on the benzene ring of the sulfonyl group from **L1** to **L2** by switching 4-methyl to 2,4,6-trimethyl, the enantiomeric selectivity of the reaction increased to 92% *ee* with a slight loss of diastereoselectivity (Table 1, entry 2). Unexpectedly, **L3** gave a low yield, presumably owing to its oversized steric hindrance (Table 1, entry 3). Notably, **L4** and **L5**, enantiomers of **L1** and **L2**, also showed moderate performances in the reduction of **1a** with opposite configuration of the product (Table 1, entries 4 and 5). Next, a set of bases were examined, and the results revealed that strong gave lower *ee* and *dr* than weak bases. NaOAc turned out to be optimal, delivering the desired **2a** in 92% *ee* with 96:4 *dr* (Table 1, entries 6–10). Moreover, several solvents were screened, and toluene performed results to afford **2a** in 99% *ee* with excellent diastereoselectivity, albeit in relatively lower conversion (Table 1, entries 11–13). It was noteworthy that elevating the reaction temperature from 45 °C to 60 °C gave full conversions of **1a** without any loss of *ee* or *dr* (Table 1, entry 14).

Table 1. Optimization of Reaction Conditions.[a]



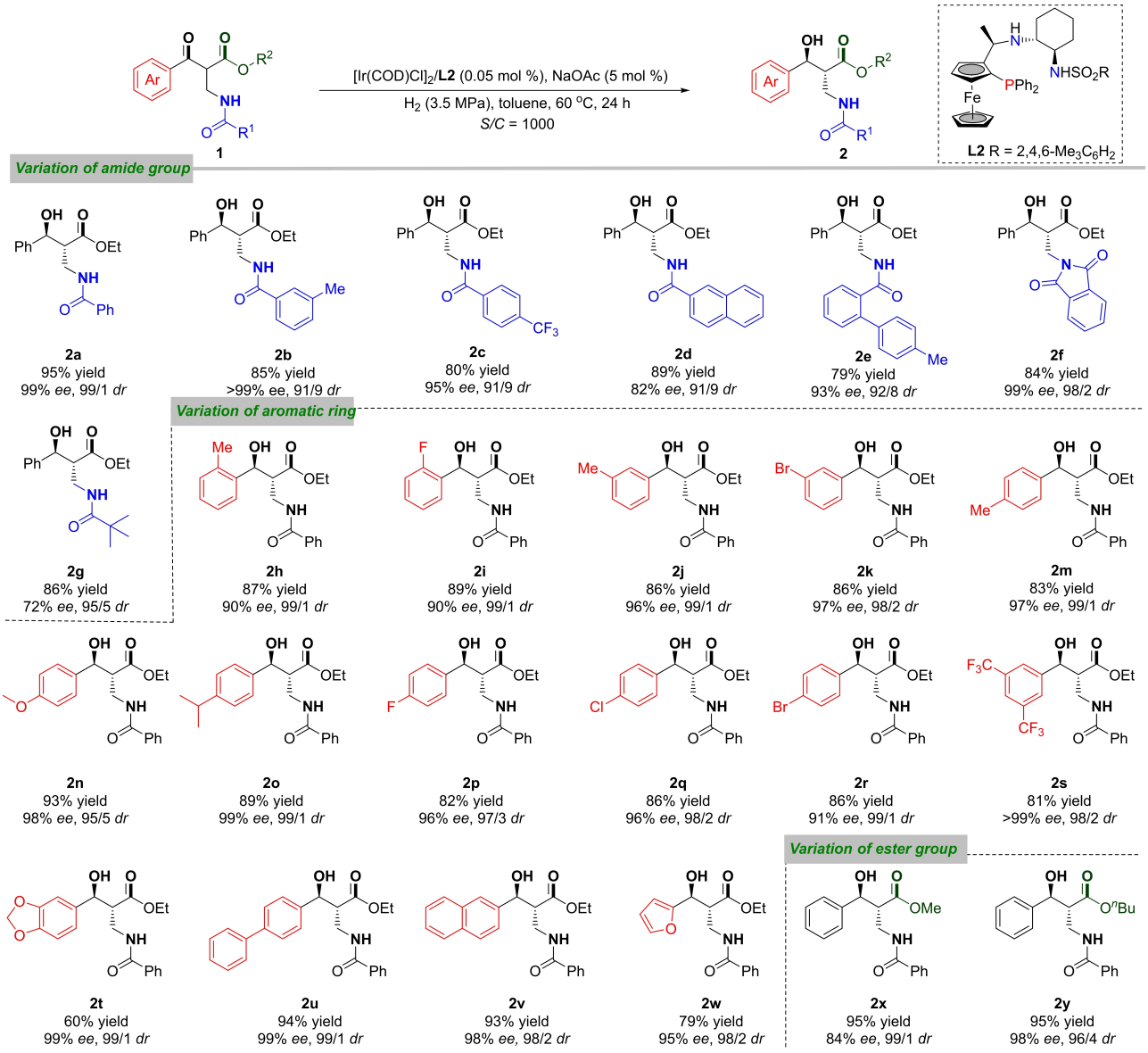
Entry	Ligand	Base	Conv. (%)[b]	ee (%)[c]	dr[c]
1	**L1**	Na_2CO_3	90	80	90/10
2	**L2**	Na_2CO_3	99	92	88/12
3	**L3**	Na_2CO_3	73	58	89/11
4	**L4**	Na_2CO_3	91	−73	6/94
5	**L5**	Na_2CO_3	94	−70	5/95
6	**L2**	tBuOLi	46	10	69/31
7	**L2**	NaOH	95	57	75/25
8	**L2**	$NaHCO_3$	92	90	92/8
9	**L2**	K_2CO_3	93	85	87/13
10	**L2**	NaOAc	94	92	96/4
11[d]	**L2**	NaOAc	99	78	88/12
12[e]	**L2**	NaOAc	57	90	89/11
13[f]	**L2**	NaOAc	95	99	99/1
14[f,g]	**L2**	**NaOAc**	**99 (95)**[h]	**99**	**99/1**



[a] *Reactions conditions:* 0.5 mmol, scale, 0.2 M substrate, 0.05 mol% $[Ir(COD)Cl_2]_2$, 0.105 mol% ligand **L**, 5 mol% base, 2.5 mL of EA, 45 °C, 24 h.
[b] Determined by GC analysis.
[c] The *ee* and *dr* values were determined by HPLC on a chiral stationary phase.
[d] DCM was used instead of EA.
[e] THF was used instead of EA.
[f] Toluene was used instead of EA.
[g] At 60 °C.
[h] Isolated yield.

With the optimized conditions in hand, we then turned our focus to the scope and functional group compatibility of the reaction (Table 2). Initially, the scope of amide groups was examined. Meta-methyl substituted amide performed well to give **2b** in up to >99% *ee* with 91:9 *dr*, while substrates with electro-withdrawing amide group delivered the targeted **2c** in a slightly lower *ee* and *dr* compared with those with electron-donating amide scaffolds (**2a** and **2b**). Moderate outcomes were obtained when using naphthalimide (**1d**) as substrate, owing to its large steric hindrance. Benzidine (**1e**) was hydrogenated well to offer **2e** in good results. Notably, phthalamide was suitable substrate which was reduced efficiently to afford **2f** in 84% yield with 99% *ee* and 98:2 *dr*. Moreover, this DKR-AH reaction also tolerated substrate with alkyl amide, leading to the corresponding

Table 2. Investigation of substrate scope.[a]

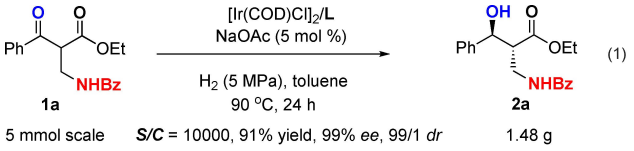


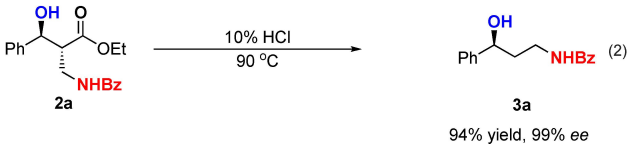
[a] *Reaction condition*: 0.5 mmol scale, 0.2 M substrate **1**, 0.05 mol% $[Ir(COD)]_2$, 0.105 mol% ligand **L2**, 5 mol% base, 2.5 mL of toluene, temperature 60 °C, 24 h, H_2 3.5 MPa. Isolated yields. The *ee* and *dr* values were determined by HPLC on a chiral stationary phase.

product **2g** in moderate *ee* but with extremely high *dr*s. Next, the focus has been paid on the examination of aromatic rings. Substitution factors on the benzene rings adjacent to the carbonyl group had a little effect on the enantioselectivities, where *ortho* substituted *β'*-hydroxy-*β*-amino esters expressed a lower *ee* than *meta* or *para* substituted amino esters (**2h** vs **2j** and **2m**; **2i** vs **2p**). Benzene rings with strong donating groups (-OMe and -*i*-Pr) yielded the targeted products (**2n** and **2o**) in higher *ees*. Halogens were also compatible in this reaction to generate the targeted chiral alcohols (**2k**, **2p**–**2r**) in excellent enantioselectivities and diastereoselectivities, providing a further chance for late-stage diversifications. Di-trifluoromethyl benzene (**1s**) performed well to deliver the desired product **2s** in >99% *ee* and 99/1 *dr*, albeit in moderated isolated yield. It was noteworthy that the benzene ring could be effectively replaced by other aromatic substituents like benzo[*d*][1,3]dioxol-5-yl (**1t**), biphenyl (**1u**) and naphthyl (**1v**) to forge the corresponding alcohols in extraordinary outcomes. Finally, the ester group in *β'*-hydroxy-*β*-amino esters was examined. Moderate *ee* with 99/1 *dr* was obtained when using small methyl ester substrate (**1w**), while

tert-butyl ester (**1 y**) reacted smoothly to provide **2 y** in 98% *ee* and 96/4 *dr*.

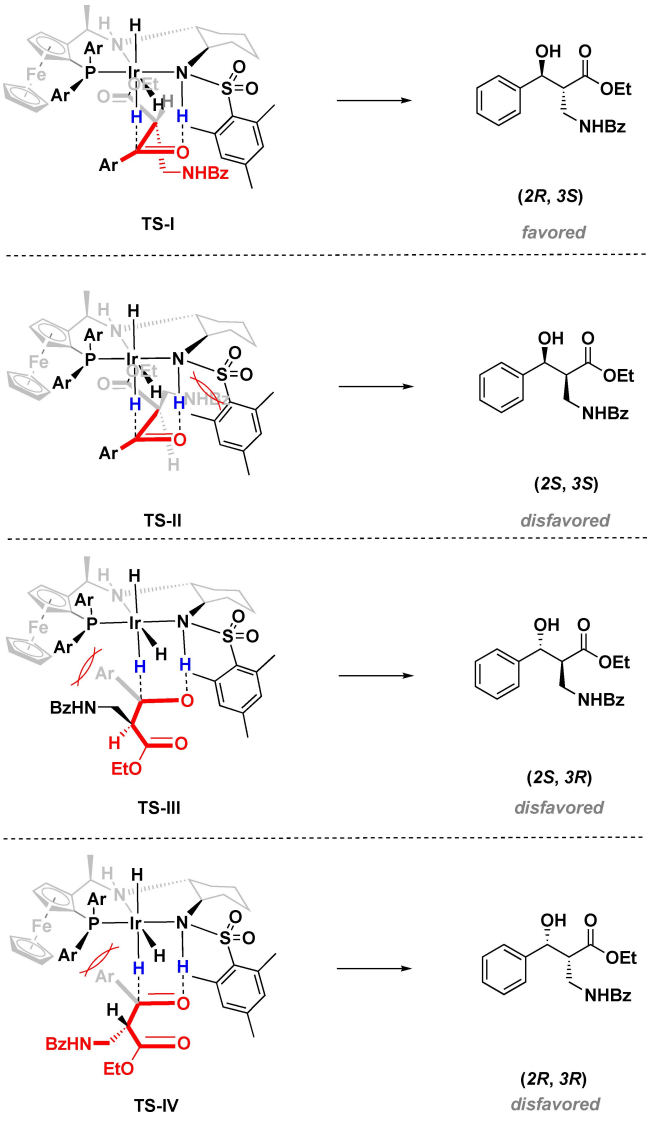
In order to demonstrate the synthetic utility of the current methodology, a gram-scale experiment (eq. 1) was performed using **1 a** as substrate with 0.01% Ir-*f*-diaphos catalysis (*S/C* = 10000). An amount of 1.48 g of product **2 a** was obtained from 5 mmol of **1 a** (91% yield, 99% *ee* and 99/1 *dr*) (eq. 1). In addition, phenylpropanoate **2 a** could be easily transformed into chiral *γ*-amino alcohol **3 a** by deesterification (eq. 2).[18]





To further explain the reason for excellent performance of this catalysis, models for the interactions between catalyst and substrate were established. Based on our previous work[16c] and previous literature,[19] hydrogen bonding interaction plays an important role in the enantioselective induction (Scheme 2). We hypothesize that the more acidic hydrogen in the sulfamide group of the ligand links the substrate with catalyst, therefore reducing the Gibbs energy and benefitting the formation of a stable catalyst substrate complex. Scheme 2 shows four models of transition states in the stereocontrol step, generating four possible isomers. **TS-I** has the lowest free energy than others, owing to its smallest steric hindrance, thus yielding the desired (*2S*, *3R*)-**2 a**. This modelling rationale helps to explain the high stereoselectivities in this transformation. Detailed mechanistic studies on this issue are currently underway.

In conclusion, we have identified an Ir/*f*-diaphos catalysis for stereoselective asymmetric hydrogenation of *β'*-keto-*β*-amino esters. A dynamic kinetic resolution has been achieved with remarkably high enantioselectivities and diastereoselectivities (up to >99% *ee* and >99:1 *dr*), thus leading to a plenty of versatile chiral anti *β'*-hydroxy-*β*-amino esters. This protocol tolerated various functional groups and could be easily conducted on gram-scale with up to 9 100 TON. Transformations allowed the production of versatile chiral γ-amino alcohol. The proposed transition states gave a reasonable explanation for these outstanding results.



Scheme 2. Proposed transition states.

Experimental Section

General Procedure for the Asymmetric Hydrogenation of *β'*-Keto-*β*-Amino Esters 1

Under argon atmosphere, $[Ir(COD)Cl]_2$ (1.68 mg, 0.0025 mmol), **L2** (3.63 mg, 0.00525 mmol), and anhydrous ^{i}PrOH (1.0 mL) were added to an oven-dried vial (5.0 mL) and then stirred at 30 °C for 1.5 h to give a clear yellow solution. An aliquot of the catalyst solution (0.1 mL) was transferred into a 5.0 mL hydrogenation vessel, and then ketones **1** (0.5 mmol), NaOAc in toluene (2.05 mg, 0.025 mmol), and anhydrous toluene (2.5 mL) were added. The vessel was placed in an autoclave, which was then charged with 35 atm of H_2 and stirred at 60 °C for 24 h. After the hydrogen pressure was slowly released, the solvent was removed, and the mixture was purified by passing through a short column of silica gel to afford the corresponding alcohol **2**. The ee values of all compounds were determined by HPLC with a chiral column.

Procedures and analytical data for all compounds are given in the Supporting Information.

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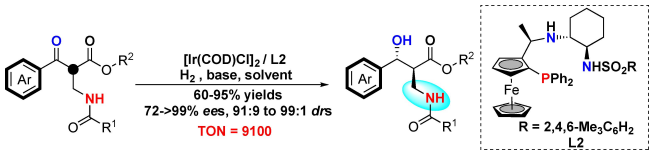
COMMUNICATIONS

Iridium-Catalyzed Enantioselective and Diastereoselective Hydrogenation of Racemic *β'*-Keto-*β*-Amino Esters via Dynamic Kinetic Resolution



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