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Rhodium-Catalyzed Enantioselective Hydrogenation of Tetrasubstituted α-Acetoxy β-Enamido Esters: A New Approach to Chiral α-Hydroxyl-β-amino Acid Derivatives

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Supporting Information

ABSTRACT: Asymmetric hydrogenation of tetrasubtituted α-acetoxy β-enamido esters with rhodium catalysts based on chiral diphosphine ligands provides an efficient and concise route to the synthesis of chiral α-hydroxyl-β-amino acid derivatives in excellent enantioselectivities. The products are valuable chiral building blocks in many biologically active compounds and have important applications in organic synthesis.

Chiral α-hydroxy-β-amino acid moieties are versatile chiral building blocks occurring in a variety of biologically active natural products, for instance, the side chains of taxol[1] and its analogues, (±)-*epi*-cytoxazone,[2] bestatin,[3] KNI-227 and KNI-272,[4] KRI-1314,[5] dideoxy-kanamycin A,[6] amastatin,[7] and microginin[8] (Figure 1). Thus, the synthesis of chiral α-hydroxyl-β-amino acid derivatives has attracted considerable interest and many approaches have been developed. Representative synthetic methods include the following: ring opening of chiral epoxides,[9] Sharpless aminohydroxylation,[10] hetero-Diels–Alder reactions,[11] asymmetric hydrosilylation,[12] asymmetric Mannich reactions,[13] asymmetric tandem-multicomponent reactions,[14] and other transformations.[15] However, asymmetric hydrogenation of α-acetoxy β-enamido esters, the most straightforward access to construct chiral α-hydroxyl-β-amino acid derivatives, has not been reported.

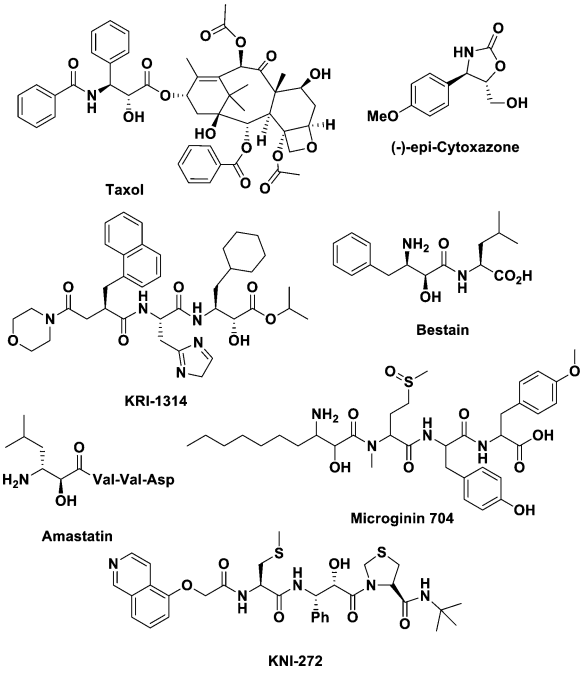
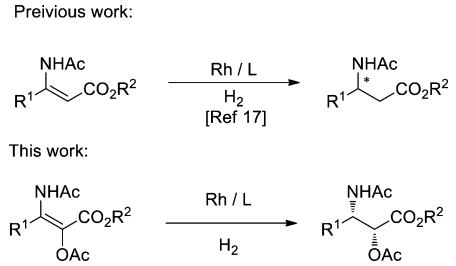


Figure 1. Structures of biologically active compounds containing an α-hydroxyl-β-amino acid moiety.

In the past decades, transition metal catalyzed asymmetric hydrogenation of enamides has been certified as a powerful and environmentally friendly methodology to obtain chiral amine derivatives.[16] However, most of the substrate scope was confined to di- and trisubstituted enamides, especially for β-acylamido acrylates (Scheme 1).[17] While employing asymmetric hydrogenation to make β-amino acids is an important strategy and major advances have been made, reports on asymmetric hydrogenation of tetrasubstituted acyclic β-enamides to make α-substituted β-amino acids are rare. In the literature, only a few special tetrasubstituted enamides have been succefully hydrogenated.[18] Finding the optimal catalyst for asymmetric hydrogenation of tetrasubstituted enamides to make α-hydroxyl-β-amino acid derivatives is a very challenging test in asymmetric hydrogenation. Herein, we presented results on asymmetric hydrogenation of tetrasubstituted enamides for the concise synthesis of chiral α-hydroxyl-β-amino acid derivatives.

Scheme 1. Enantioselective Routes to Chiral β-Amino Acid Derivatives



Initially, asymmetric hydrogenation of (*E*)-ethyl 3-acetamido-2-acetoxy-3-phenyl acrylate (***E*)-1a**[19] was investigated by using [Rh(NBD)(*Sc*,*Rp*)-DuanPhos]BF_4 as the catalyst. To our delight, we found (***E*)-1a** was completely converted under 30 atm of H_2 pressure in CH_2Cl_2 at room temperature for 24 h,

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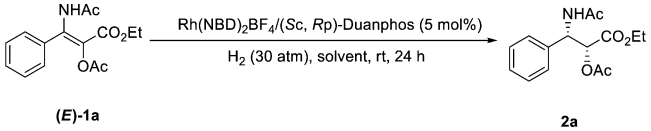
generating the desired product in good yield with excellent enantioselectivity (Table 1, entry 1). Subsequently, we

Table 1. Solvent Screening for Rh-Catalyzed Asymmetric Hydrogenation of (*E*)-Ethyl 3-acetamido-2-acetoxy-3-phenylacrylate (*E*)-1a[a]



(*E*)-1a 2a

entry	metal	solvent	conversion (%)[b]	ee (%)[c]
1	**$Rh(NBD)_2BF_4$**	**CH_2Cl_2**	**>99**	**97**
2	$Rh(NBD)_2BF_4$	EtOAc	52	98
3	$Rh(NBD)_2BF_4$	IPA	46	97
4	$Rh(NBD)_2BF_4$	TFE	>99	89
5	$Rh(NBD)_2BF_4$	THF	60	89
6	$Rh(NBD)_2BF_4$	dioxane	52	94
7	$Rh(NBD)_2BF_4$	MeOH	34	90
8	$Rh(NBD)_2BF_4$	EtOH	27	93
9	$Rh(NBD)_2BF_4$	toluene	9	30
10	$Rh(COD)_2BF_4$	CH_2Cl_2	>99	95

[a]Unless otherwise mentioned, all reactions were carried out with a [Rh]/(*Sc*, *Rp*)-DuanPhos/substrate ratio of 1:1.1:20 in 1 mL of solvent, at room temperature under hydrogen (30 atm) for 24 h. [b]Determined by ^1H NMR spectroscopy. [c]Determined by HPLC analysis using a chiral stationary phase. NBD = 2,5-norbornadiene, COD = 1,5-cyclooctadiene, TFE = trifluoroethanol, IPA = isopropanol.

investigated the solvent effect and found that different solvents have great influence on the conversions and ee values. EtOAc and isopropanol (IPA) gave high enantioselectivities but poor conversions (Table 1, entries 2−3). Except for trifluoroethanol (TFE) which showed high activity (Table 1, entry 3), both ethereal solvents and alcoholic solvents gave lower conversions, albeit with promising enantioselectivities (89−94% ee, entries 5−8). Metal precursor $[Rh(COD)_2]BF_4$ was also investigated. Compared with $[Rh(NBD)_2]BF_4$, similar ee values and full conversion were achieved when using $[Rh(COD)_2]BF_4$ as a metal precursor.

In order to further optimize the reaction conditions, a series of chiral ligands (Figure 2) were screened carefully. As shown in Table 2, chiral ferrocenyl ligand JosiPhos and electron-donating P-chiral diphosphine ligand TangPhos exhibited the same high reactivity with DuanPhos in this reaction and afforded the expected product in quantitative yield but only with moderate enantioselectivities (Table 2, entries 1 and 3). Other chiral ligands, such as (*S, S*)-Me-DuPhos, (*S*)-Binapine, (*R*)-QuinoxP, (*R*)-BINAP, and (*S*)-C_3-TunePhos, showed poor reactivity with decreased stereocontrol (Table 2, entries 2 and 4−7). Only the electron-donating P-chiral diphosphine ligand (*Sc,Rp*)-DuanPhos developed in our group gave excellent enantioselectivity and high activity in the hydrogenation of α-acetoxy β-enamido ester (*E*)-**1a** (Table 2, entry 8). The effect of H_2 pressure for this reaction was also evaluated. Under a lower hydrogen pressure of 10 atm, the enantioselectivity was maintained but with a slightly lower conversion, while an increase in the hydrogen pressure to 50 atm resulted in the ee value reducing to 92% (Table 2, entries 9−10).

Under the optimized reaction conditions, a series of α-acetoxy β-enamido esters were examined to evaluate the substrate scope and generality of this catalytic reaction. As

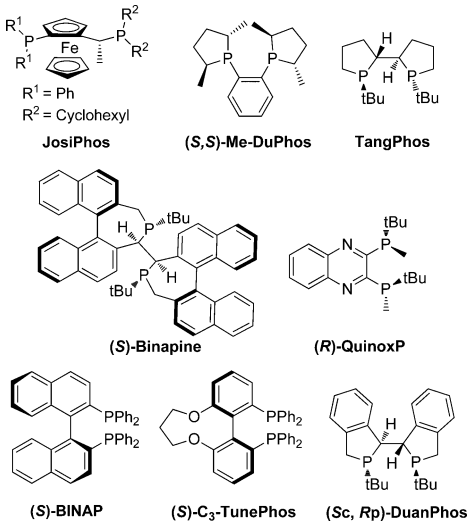
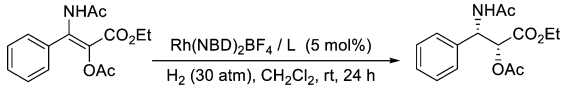


Figure 2. Structures of the phosphine ligands for hydrogenation of (*E*)-ethyl 3-acetamido-2-acetoxy-3-phenyl acrylate (*E*)-**1a**.

Table 2. Ligands and H_2 Pressure Screening for Rh-Catalyzed Asymmetric Hydrogenation of (*E*)-Ethyl 3-Acetamido-2-acetoxy-3-phenylacrylate (*E*)-1a[a]



(*E*)-1a 2a

entry	ligand	conversion (%)[b]	ee (%)[c]
1	JosiPhos	>99	28
2	(*S,S*)-Me-DuPhos	17	13
3	TangPhos	>99	69
4	(*S*)-Binapine	61	7
5	(*R*)-QuinoxP	<5	3
6	(*S*)-BINAP	64	5
7	(*S*)-C_3-TunePhos	31	28
8	**(*Sc,Rp*)-DuanPhos**	**>99**	**97**
9[d]	(*Sc,Rp*)-DuanPhos	92	97
10[e]	(*Sc,Rp*)-DuanPhos	>99	92

[a]Unless otherwise mentioned, all reactions were carried out with a $[Rh(NBD)_2]BF_4$/L/substrate ratio of 1:1.1:20 in CH_2Cl_2 at room temperature under hydrogen (30 atm) for 24 h. [b]Determined by ^1H NMR spectroscopy. [c]Determined by HPLC analysis using a chiral stationary phase. [d]The hydrogenation was under 10 atm of H_2 pressure. [e]The hydrogenation was under 50 atm of H_2 pressure.

shown in Table 3, (*E*)-**1** compounds with different ester groups were found to be good substrates to give desired α-acetoxy β-amido esters in excellent yields with outstanding stereocontrol (Table 3, entries 1−2). A wide range of β-aryl-α-acetoxy β-enamido esters with electron-rich or -poor aryl groups were examined. High yields and excellent enantioselectivities were observed in most cases, regardless of the substitution position (Table 3, entries 3−11). When the phenyl group was replaced by the more sterically hindered 2-naphthyl substituent, the reaction proceeded quite smoothly and gave the product in 96% yield with up to 95% ee (Table 3, entry 12). However, the β-alkyl-substituted derivatives showed a somewhat lower ee value albeit with good yields (Table 3, entries 13−14).

To demonstrate the synthetic utility of the current methodology, the taxol C13 side chain was synthesized as shown in Scheme 2. The asymmetric hydrogenation product **2a**

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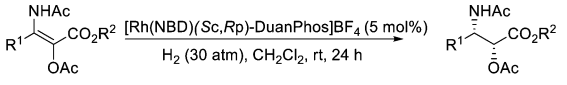
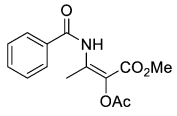
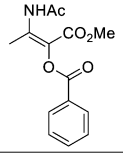
Table 3. Rh-Catalyzed Asymmetric Hydrogenation of α-Acetoxy β-Enamido Esters (*E*)-1[a]

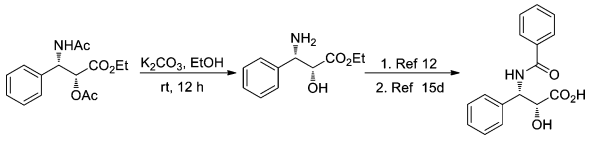


(*E*)-1 2

Entry	Substrates	Product	Conversion(%)[b]	ee(%)[c]
1	**(*E*)-1a**: R^1= Ph, R^2=Et	**2a**	>99(98)	97
2	**(*E*)-1b**: R^1= Ph, R^2=Me	**2b**	>99(94)	96
3	**(*E*)-1c**: R^1= 4-Cl-Ph, R^2=Me	**2c**	>99(97)	97
4	**(*E*)-1d**: R^1= 4-F-Ph, R^2=Me	**2d**	>99(97)	96
5	**(*E*)-1e**: R^1= 4-Br-Ph, R^2=Me	**2e**	>99(97)	97
6	**(*E*)-1f**: R^1= 4-Me-Ph, R^2=Me	**2f**	>99(94)	95
7	**(*E*)-1g**: R^1= 4-OMe-Ph, R^2=Me	**2g**	>99(94)	96
8	**(*E*)-1h**: R^1= 4-Cy-Ph, R^2=Me	**2h**	>99(96)	94
9	**(*E*)-1i**: R^1= 3-Cl-Ph, R^2=Me	**2i**	>99(96)	97
10	**(*E*)-1j**: R^1= 3-Me-Ph, R^2=Me	**2j**	>99(95)	94
11	**(*E*)-1k**: R^1= 3-MeO-Ph, R^2=Me	**2k**	>99(95)	95
12	**(*E*)-1l**: R^1= 2-Napthyl, R^2=Me	**2l**	>99(96)	95
13	**(*E*)-1m**: 	**2m**	>99(94)	77
14	**(*E*)-1n**: 	**2n**	>99(95)	86

[a]Unless otherwise mentioned, all reactions were carried out with a [Rh(NBD)(*Sc*,*Rp*)-DuanPhos]BF_4/substrate ratio of 1:20 in CH_2Cl_2 at room temperature under hydrogen (30 atm) for 24 h. [b]Determined by ^{1}H NMR spectroscopy, data in parentheses are the yields of isolated product based on consumed starting material. [c]Determined by HPLC analysis using a chiral stationary phase.

Scheme 2. Synthesis of the Taxol C13 Side Chain



2a 3 (89 % yield, 94 % ee) 4

was treated with K_2CO_3 in EtOH and afforded **3** in 89% yield and 94% ee. Then, the C13 side chain of taxol **4** could be easily synthesized by N-Bz protection and ester hydrolysis according to reported literature.[12,15d] Upon comparison of the optical rotation of **3** with the literature,[20] the absolute configuration of **3** was determined as (2*R*,3*S*).

In conclusion, we have reported the first asymmetric hydrogenation of tetrasubstituted α-acetoxy β-enamido esters to synthesize α-hydroxyl-β-amino acid derivatives. [Rh(NBD)(*Sc*,*Rp*)-DuanPhos]BF_4 was found to be an efficient catalyst for the hydrogenation of tetrasubstituted enamides with excellent enantioselectivities and full conversions. More importantly, this methodology provides a concise route to the synthesis of biologically important molecules containing an α-hydroxyl-β-amino acid unit. Further investigation into using other sterically demanding and stereochemically challenging substrates for catalytic asymmetric hydrogenation are in progress in our lab.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and complete characterizations of the substrates and hydrogenation products (NMR spectra, HPLC chromatograms of racemic and enantioenriched compounds and HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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