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Rhodium-catalyzed asymmetric hydrogenation of tetrasubstituted β-acetoxy-α-enamido esters and efficient synthesis of droxidopa†

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A rhodium-catalyzed asymmetric hydrogenation of challenging tetrasubstituted β-acetoxy-α-enamido esters was developed, giving chiral β-acetoxy-α-amido esters in high yields with excellent enantioselectivities (up to >99% ee). The products could be easily transformed to β-hydroxy-α-amino acid derivatives which are valuable chiral building blocks and a novel route for the synthesis of droxidopa was also developed.

Enantiomerically pure β-hydroxy-α-amino acids are not only important constituents of biologically active peptides and related compounds,[1] but also useful chiral precursors in organic synthesis,[2] for instance, (3*S*,4*S*)-DHGA,[3a] droxidopa,[3b] chiral thiamphenicol building blocks,[3c] drug candidates,[3d] florfenicol[3e] and Eliglustat[3f] (Fig. 1). The synthesis of chiral β-hydroxy-α-amino acid derivatives has attracted considerable interest and many approaches have been developed. Representative synthetic methods include the Sharpless kinetic resolution epoxidation process,[4a] dynamic kinetic resolution through transition metal-catalyzed asymmetric hydrogenation,[4b–d,m–u] diastereoselective nucleophilic addition,[4e] Rh-catalyzed asymmetric hydrogenation,[2b] Aldol reactions,[4fg] Pd(II)-catalyzed aza-Claisen rearrangement,[4h] and other transformations.[4i–l] Although the asymmetric hydrogenation of tetrasubstituted enamides is one of the most practical methods for making these important compounds, successful results have rarely been reported in the literature.[5,6] For the hydrogenation of tetrasubstituted β-aryl-β-acetoxy-α-enamino esters (Scheme 1), only one report with poor asymmetric hydrogenation results (12% yield, 73% ee) has been reported.[2b] Therefore, searching for a highly effective catalytic system with high enantioselectivity and a broad substrate scope is still challenging and interesting.

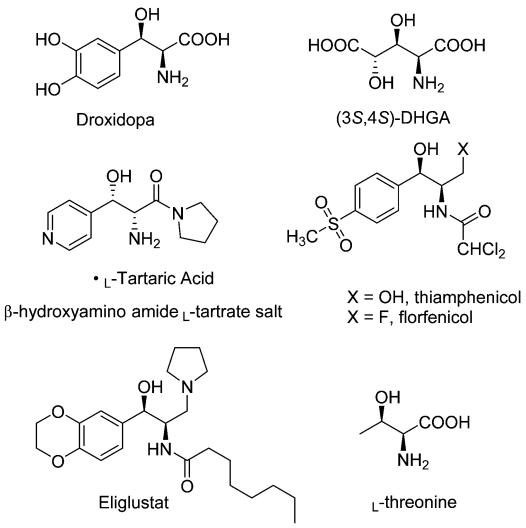
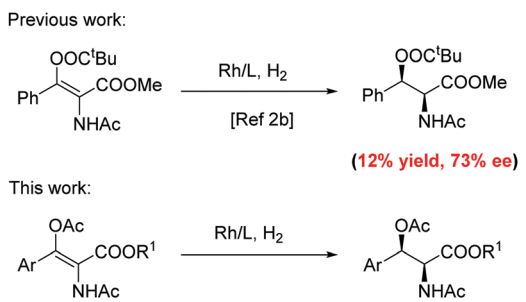


Fig. 1 Structures of biologically active compounds containing a β-hydroxyl-α-amino acid moiety.



Scheme 1 Enantioselective routes to chiral α-amino acid derivatives.

In the past few decades, transition metal catalyzed asymmetric hydrogenation of enamides has been developed as a powerful and environmentally friendly methodology to afford enantiomerically pure amino acids and amines.[7] Nevertheless the asymmetric hydrogenation of tetrasubstituted enamides remains a challenge. Herein, we report an efficient and general

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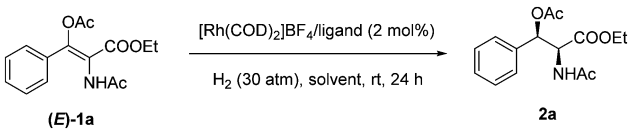
Table 1 Reaction condition optimization of Rh-catalyzed asymmetric hydrogenation of (*E*)-ethyl-2-acetamido-3-acetoxy-3-phenyl acrylate **(*E*)-1a**[a]



(*E*)-1a 2a

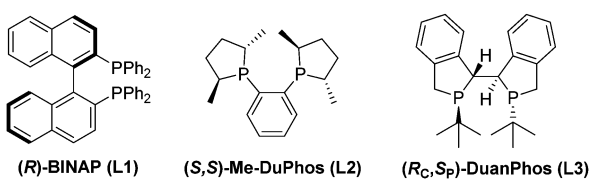
Entry	Ligand	Solvent	Conversion[b] (%)	ee[c] (%)
1	**L1**	CH_2Cl_2	84	−10
2	**L2**	CH_2Cl_2	73	−99
3	***L3***	***CH_2Cl_2***	***>99***	***>99***
4	**L3**	THF	NR	—
5	**L3**	EtOAc	NR	—
6	**L3**	MeOH	40	>99
7[d]	**L3**	CH_2Cl_2	95	>99
8[e]	***L3***	***CH_2Cl_2***	***>99***	***>99***

[a] Unless otherwise mentioned, all reactions were carried out with a [Rh]/(R_C,S_P)-DuanPhos/substrate ratio of 1 : 1.1 : 50 in 0.5 mL of solvent, at room temperature under hydrogen (30 atm) for 24 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis using a chiral stationary phase. COD = 1,5-cyclooctadiene. [d] The hydrogenation was performed under 10 atm of H_2 pressure. [e] The hydrogenation was performed under 50 atm of H_2 pressure.

method for the asymmetric hydrogenation of tetrasubstituted β-acetoxy-α-enamido esters (>99% ee, 500 TON) and its application to an efficient synthesis of droxidopa.

Initially, the asymmetric hydrogenation of (*E*)-ethyl-2-acetamido-3-acetoxy-3-phenyl acrylate **(*E*)-1a** was investigated by using [Rh(COD)$_2$]BF$_4$/(*R*)-BINAP as the catalyst. We found **(*E*)-1a** was converted under 30 atm of H_2 pressure in CH_2Cl_2 at room temperature for 24 h, generating the desired product in good yield but with very low enantioselectivity (Table 1, entry 1). Subsequently, several chiral ligands (Fig. 2) were screened. Both (*S*,*S*)-Me-DuPhos and (R_C,S_P)-DuanPhos showed 99% ee, but the yield with (R_C,S_P)-DuanPhos was higher than that with (*S*,*S*)-Me-DuPhos (Table 1, entries 2 and 3). To optimize the reaction conditions, we investigated the solvent effect. No reaction occurred in ethyl acetate (EtOAc) and tetrahydrofuran (THF) (Table 1, entries 4 and 5). High enantioselectivity and poor conversion were observed in methanol (MeOH) (Table 1, entry 6). The effect of H_2 pressure on 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 maintained the same high conversion and ee (Table 1, entries 7 and 8). Therefore, the optimized reaction conditions are [Rh(COD)$_2$]BF$_4$/(R_C,S_P)-DuanPhos as a catalyst under 30 atm of H_2 pressure in CH_2Cl_2 at room temperature for 24 h.

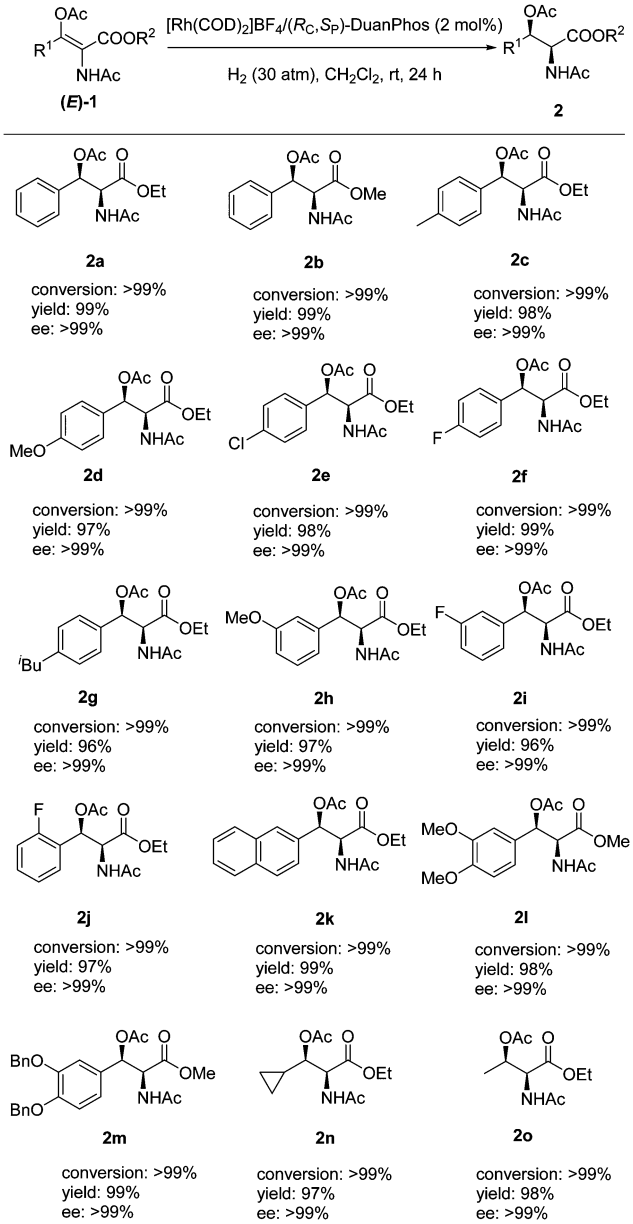
Under the optimized reaction conditions, a series of β-acetoxy-α-enamido esters were examined to evaluate the substrate scope and generality of this catalytic reaction. As shown in Table 2, compounds **(*E*)-1** with different ester groups were found to be good substrates to give desired β-acetoxy-α-amido esters in excellent yields with outstanding stereocontrol (**2a** and **2b**). A wide range of β-aryl-β-acetoxy-α-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 (**2c**–**2j**). When the phenyl group was replaced with the more sterically hindered 2-naphthyl substituent, the reaction proceeded quite smoothly and gave the



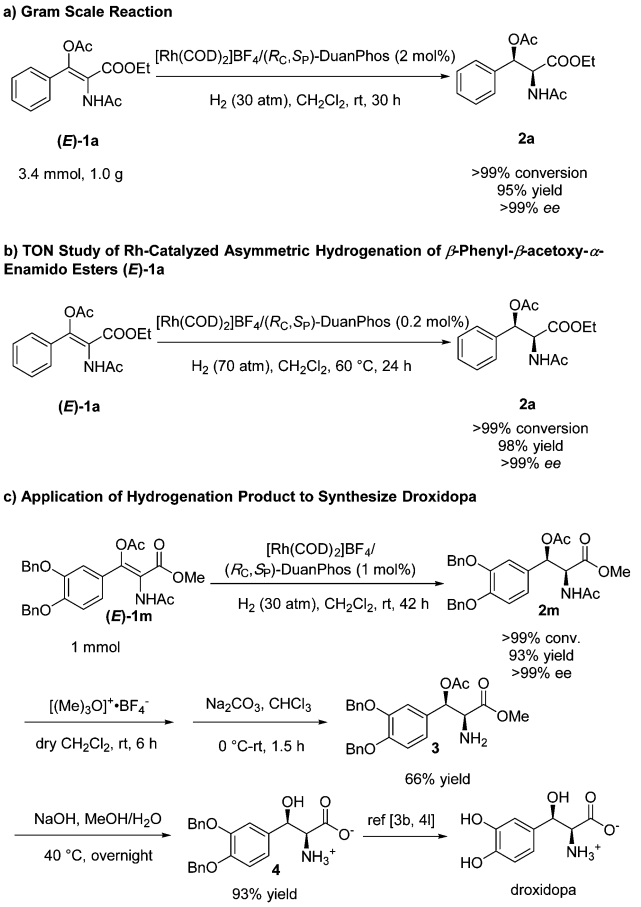
(*R*)-BINAP (L1) (*S*,*S*)-Me-DuPhos (L2) (R_C,S_P)-DuanPhos (L3)

Fig. 2 Structures of the phosphine ligands for hydrogenation of **(*E*)-1a**.

Table 2 Rh-catalyzed asymmetric hydrogenation of β-acetoxy-α-enamido esters **(*E*)-1**[a]



[a] Unless otherwise mentioned, all reactions were carried out with a [Rh(COD)$_2$]BF$_4$/(R_C,S_P)-DuanPhos/substrate ratio of 1 : 1.1 : 50 in CH_2Cl_2 at room temperature under hydrogen (30 atm) for 24 h. The conversion was determined by ^{1}H NMR analysis; the yield was the isolated product; and the ee value was determined by GC or HPLC analysis.



Scheme 2 Synthetic application.

product in 99% yield with high enantioselectivity (>99% ee) (**2k**). Inspiringly, 3,4-disubstituted phenyl group derivatives were also obtained with high ee and high conversions (**2l** and **2m**). Additionally, the hydrogenation of the β-alkyl-substituted derivatives showed similar enantioselectivities with high yields (**2n** and **2o**). Comparing the optical rotation of **2m** with the literature reports,[4l] the absolute configuration of **2** is determined to be (2*S*,3*R*).

To demonstrate the synthetic utility of the current methodology, the asymmetric hydrogenation of ***E*-(1a)** was performed on a gram scale, and the desired product (**2a**) was obtained in 95% yield and >99% ee (Scheme 2a). When the catalyst loading was further reduced to 0.2 mol% (S/C = 500), the catalytic system could also achieve >99% ee and >99% conversion (Scheme 2b). In addition, an efficient synthetic route to droxidopa, a prodrug to neurotransmitter norepinephrine, was also developed (Scheme 2c). The substrate **(*E*)-1m** was easily hydrogenated to give **2m** (>99% conversion, 93% yield, >99% ee) using $[Rh(COD)_2]BF_4$/(R_C,S_P)-DuanPhos (S/C = 100). Subsequently, the asymmetric hydrogenation product **2m** was treated with trimethyloxonium tetrafluoroborate in dry CH_2Cl_2,[8] followed by hydrolysis with a Na_2CO_3 aqueous solution to furnish **3**. By treating a methanol solution of **3** with a NaOH aqueous solution, **4** was obtained with high yield. Then, droxidopa could be easily synthesized by the deprotection of O–Bn according to reported literature.[3b,4l]

In summary, a $[Rh(COD)_2]BF_4$/(R_C,S_P)-DuanPhos complex catalyzed asymmetric hydrogenation of tetrasubstituted β-acetoxy-α-enamido esters has been achieved, giving chiral β-hydroxy-α-amino acid derivatives in high yields with excellent enantioselectivities (up to >99% ee). In addition, a concise synthetic route to droxidopa was also developed. This method features a broad substrate scope, mild reaction conditions, and potential application to the construction of bioactive important molecules containing a β-hydroxy-α-amino acid unit, which will attract great interest from organic communities. Further investigations on the asymmetric hydrogenation of challenging substrates are in progress in our lab.

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