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Highly Enantioselective Hydrogenation of *o*-Alkoxy Tetrasubstituted Enamides Catalyzed by a Rh/(*R*,*S*)-JosiPhos Catalyst

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Supporting Information

ABSTRACT: Rh/(*R*,*S*)-JosiPhos complex-catalyzed asymmetric hydrogenation of *o*-alkoxy tetrasubstituted enamides has been achieved, and it furnished a set of *β*-amino alcohol analogues in high yields and excellent enantiomeric excesses (>99% conversion, up to 99% ee).This method provides valuable chiral building blocks in chiral pharmaceuticals and useful motifs for catalysts.

Enantiopure *β*-amino alcohols are valuable building blocks for the synthesis of pharmaceuticals.[1] The incorporation of bulky *β*-amino alcohol motifs allows for the development of chiral ligands[2] and chiral auxiliaries,[3] glycine templates,[4] as well as organocatalysts[5] in asymmetric catalysis (Figure 1). Therefore,

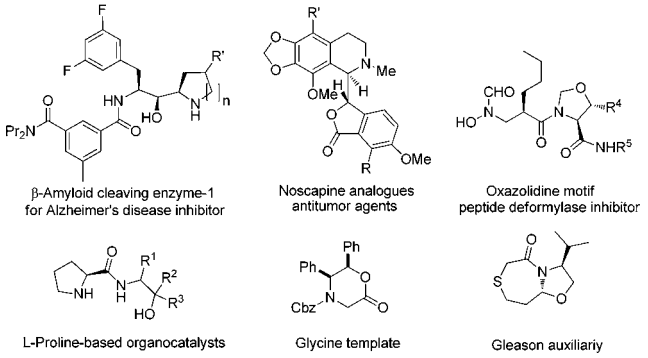
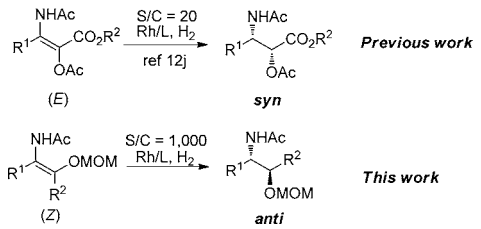


Figure 1. Selected applications of *β*-amino alcohol motif and their derivatives.

developing efficient synthetic routes for making chiral amino alcohols has attracted considerable interest. Over the past two decades, great efforts have been devoted to the synthesis of *β*-amino alcohol derivatives, and many methods have been developed. Typical approaches included Sharpless asymmetric aminohydroxylation,[6] ring-opening of chiral epoxides[7] and aziridines,[8] nucleophilic addition to protected imines,[9] aldol reaction of aldehydes,[10] and so on. However, these approaches suffer from some drawbacks such as limited substrate scope, low functional group tolerance, and poor atom economy. Alternatively, asymmetric hydrogenation of *o*-alkoxy enamides, one of the most straightforward routes to synthesize *β*-amino alcohols, could solve this problem.

In the past decades, great progress had been made in transition-metal-catalyzed asymmetric hydrogenation of enamides, and it has become a robust and readily accessible route to making chiral amines.[11,12] However, in most cases, these approaches are only suitable for less steric di- or trisubstituted enamides, and highly efficient hydrogenation of hindered tetrasubstituted enamides remains a challenge. Although our group recently achieved Rh/DuanPhos-catalyzed asymmetric hydrogenation of tetrasubstituted *α*-acetoxy-*β*-enamido esters and afforded *syn* *β*-amino alcohol motifs with excellent enantioselectivities, there are several challenges need to be solved, such as *E* substrate limitation and low turnover number (S/C = 20/1) (Scheme 1).[12j] Therefore, achieving asymmetric

Scheme 1. Hydrogenation Methods for Making Chiral *β*-Amino Alcohol Motifs



hydrogenation of *Z*-tetrasubstituted substrates with low catalyst loading is highly desired (Figure 2). Herein, we disclose a

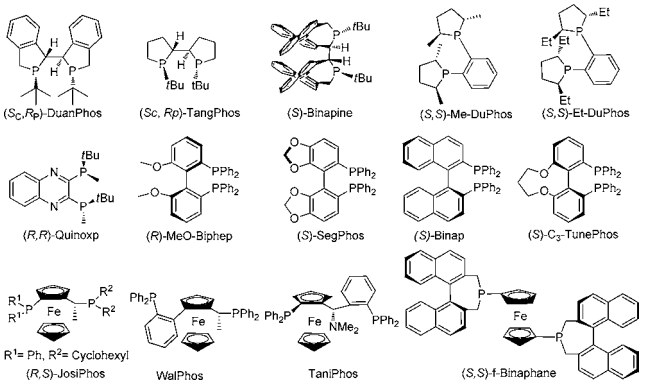


Figure 2. Structures of the phosphine ligands for hydrogenation of **5a**.

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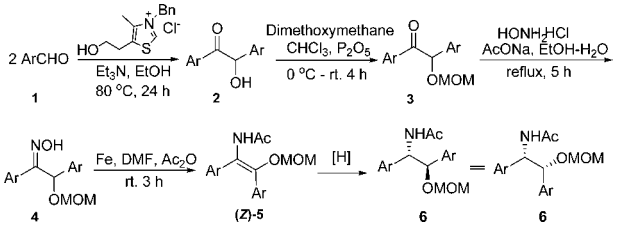
highly enantioselective hydrogenation of (*Z*)-*o*-alkoxy tetrasubstituted enamides catalyzed by the Rh/JosiPhos complexes for *anti* chiral *β*-amino alcohol synthesis.

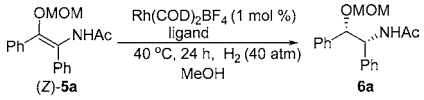
Our strategy for the synthesis of *β*-amino alcohol analogues **6** is described in Scheme 2. First, (*Z*)-*o*-alkoxy-tetrasubstituted

Scheme 2. Design and Synthesis of *β*-Amino Alcohol Analogues 6



enamide **5a**[13] was efficiently synthesized and chosen as a model substrate to optimize the reaction conditions. The Rh-(cod)$_2$BF$_4$/DuanPhos catalytic system, previously found to be effective in hydrogenation of (*E*)-tetrasubstituted enamides, exhibited very poor reactivity and enantioselectivity, but when electron-rich TangPhos was employed, the reaction worked very smoothly and afforded the desired product **6a** with excellent yield and 86% ee (Table 1, entries 1−2). (*S*)-Binapine

Table 1. Ligand Screening for Rh-Catalyzed Asymmetric Hydrogenation of 5a[a]



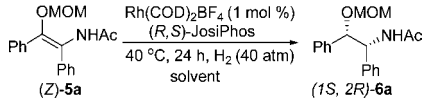
entry	ligand	conversion[b] (%)	ee[c] (%) (config[d])
1	(S_aR_p)-DuanPhos	5	5 (1*R*,2*S*)
2	(S_aR_p)-TangPhos	>99	86 (1*S*,2*R*)
3	(*S*)-binapine	>99	51 (1*S*,2*R*)
4	(*S*,*S*)-Me-DuPhos	67	61 (1*R*,2*S*)
5	(*S*,*S*)-Et-DuPhos	78	68 (1*R*,2*S*)
6	(*R*,*R*)-Quinoxp	0	-
7	(*R*)-MeO-Biphep	trace	-
8	(*S*)-SegPhos	4	4 (1*R*,2*S*)
9	(*S*)-Binap	trace	-
10	(*S*)-C$_3$-TunePhos	trace	-
11	(*R*,*S*)-JosiPhos	>99	91 (1*S*,2*R*)
12	(*S*)-WalPhos	>99	46 (1*R*,2*S*)
13	TaniPhos	>99	45 (1*R*,2*S*)
14	(*S*,*S*)-f-binaphane	>99	7 (1*R*,2*S*)

[a]Unless otherwise mentioned, all reactions were carried out with a Rh(COD)$_2$BF$_4$/ligand/**5a** (0.05 mmol) ratio of 1:1.1:100, at 40 °C, 40 atm hydrogen for 24 h. [b]The conversion of the isolated product based on consumed starting material. [c]Determined by HPLC analysis using a chiral stationary phase. [d]Assignment through comparison of sign of optical rotation and chiral HPLC elution order with configurationally defined sample.

and DuPhos exhibited good activities for this reaction but furnished **6a** only with moderate enantioselectivities (entries 3−5). (*R*,*R*)-Quinoxp and some chiral biaryl bisphosphorus ligands such as (*R*)-MeO-Biphep, (*S*)-SegPhos, (*S*)-Binap, and (*S*)-C$_3$-TunePhos are sluggish for this transformtaion (entries 6−10). When ferrocene-type chiral phosphorus ligands were employed, the reaction worked very well and gave the desired product with excellent yields. Remarkably, using (*R*,*S*)-JosiPhos as ligand, the reaction gave the best results and provided **6a** in 99% yield and 91% ee (entries 11−14).

In order to further optimize the reaction conditions, solvents and Rh(I) species were evaluated. As shown in Table 2, the

Table 2. Solvent and Rh(I) Species Screening for Rh-Catalyzed Asymmetric Hydrogenation[a]



entry	solvent	conversion[b] (%)	ee[c] (%)
1	1,2-dichloroethane	0	-
2	dichloromethane	52	52
3	toluene	35	35
4	THF	56	55
5	ethyl acetate	trace	-
6	dioxane	>99	85
7	methanol	>99	91
8	propan-2-ol	>99	86
9	trifluoroethanol	>99	94
10	Rh(NBD)$_2$BF$_4$	>99	92
11	Rh(COD)$_2$SO$_3$CF$_3$	>99	93

[a]Unless otherwise mentioned, all reactions were carried out with a Rh(COD)$_2$BF$_4$/ligand/**5a** (0.05 mmol) ratio of 1:1.1:100, at 40 °C, 40 atm hydrogen for 24 h. [b]The conversion of the isolated product based on consumed starting material. [c]Determined by HPLC analysis using a chiral stationary phase.

reaction showed dramatic solvent effects. Generally, aprotic solvents except dioxane had negative effects on this reaction, but the reaction exhibited excellent activities when protic solvents were employed, of which trifluoroethanol gave the best results and furnished the desired products in 99% yield and 94% enantioselectivity (Table 2, entries 1−9). In addition, Rh(I) species such as Rh(NBD)$_2$BF$_4$ and Rh(COD)$_2$SO$_3$CF$_3$ were also investigated and showed the same activities but slightly lower ee values (Table 2, entries 10 and 11). Under the optimized reaction conditions (Table 2, entry 9), a variety of *o*-alkoxy-tetrasubstituted enamides were examined (Table 3). To our delight, all aryl group substituted substrates examined here can work smoothly and afford the corresponding chiral *β*-amino alcohols in quantitative yield with excellent enantiomeric excesses. It was revealed that the position and the electronic property of the substituents on the phenyl rings have little effect on the conversion and enantioselectivities (entries 1−10). However, the profile of this system has not yet been completely established for cyclic enamides. The hydrogenation of cyclic enamides derived from *α*-indanone and *α*-tetralone gave excellent yields but with poor enantioselectivities (entries 11 and 12). The corresponding five-membered cyclic enamide gave moderate ee (56%). Significantly lower ee was observed for the enamide made from *α*-tetralone (3.7%).[14] Since there is a need to develop a catalyst to handle all substrates, we will next continue to develop a simple but powerful strategy for addressing this problem.

To demonstrate the potential utilities of the protocol for synthesis of *β*-amino alcohols, the reactions were carried out on gram scale, and the desired products **6a**, **6e**, and **6h** could be prepared in high yields and excellent enantioselectivities (94−97% ee). Moreover, when the catalyst loading was decreased to 0.1 mol %, there was no influence on the yield and enantioselectivity (Scheme 3).

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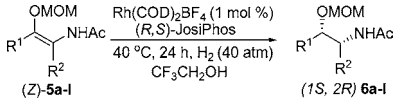
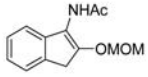
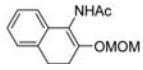
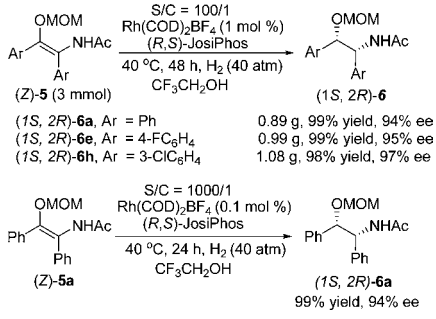
Table 3. Asymmetric Hydrogenation of Enamides Catalyzed by a Rh/(*R*,*S*)-Josiphos Complex[a]



entry	substrate	product	yield (%)[b]	ee (%)[c]
1	$R^1 = R^2 =$ Ph	(*1S,2R*)-**6a**	99	94
2	$R^1 = R^2 =$ 3-MeOC$_6$H$_4$	(*1S,2R*)-**6b**	98	91
3	$R^1 = R^2 =$ 4-MeOC$_6$H$_4$	(*1S,2R*)-**6c**	99	94
4	$R^1 = R^2 =$ 4-MeC$_6$H$_4$	(*1S,2R*)-**6d**	99	96
5	$R^1 = R^2 =$ 4-FC$_6$H$_4$	(*1S,2R*)-**6e**	97	95
6	$R^1 = R^2 =$ 4-ClC$_6$H$_4$	(*1S,2R*)-**6f**	99	98
7	$R^1 = R^2 =$ 4-BrC$_6$H$_4$	(*1S,2R*)-**6g**	99	96
8	$R^1 = R^2 =$ 3-ClC$_6$H$_4$	(*1S,2R*)-**6h**	98	97
9	$R^1 = R^2 =$ 3-BrC$_6$H$_4$	(*1S,2R*)-**6i**	99	99
10	$R^1 = R^2 =$ 2-Napthyl	(*1S,2R*)-**6j**	99	94
11		(*1S,2R*)-**6k**	98	56
12		(*1S,2R*)-**6l**	98	4

[a]Unless otherwise mentioned, all reactions were carried out with a Rh(COD)$_2$BF$_4$/(*R*,*S*)-JosiPhos/**5** (0.05 mmol) ratio of 1:1.1:100, at 40 °C, 40 atm hydrogen for 24 h. [b]The yield of the isolated product based on consumed starting material. [c]Determined by HPLC analysis using a chiral stationary phase.

Scheme 3. Gram-Scale Reaction and S/C Evaluation for (1*S*,2*R*)-6 Synthesis



In summary, we have developed a highly efficient route to synthesize *β*-amino alcohol derivatives in high yields and excellent enatioselectivities via asymmetric hydrogenation. Rh/(*R*,*S*)-JosiPhos complexes are excellent catalysts for this transformation. Further studies on expanding the substrate scope to tetrasubstituted cyclic enamides are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, characterization data, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra as well as HPLC results. 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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(13) The X-ray crystal data of (*Z*)-**5a** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1025711. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 (1223)336033 or E-mail: deposit@ccdc.cam.ac.uk].

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