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Rh-Catalyzed Asymmetric Hydrogenation of β-Branched Enol Esters for the Synthesis of β-Chiral Primary Alcohols

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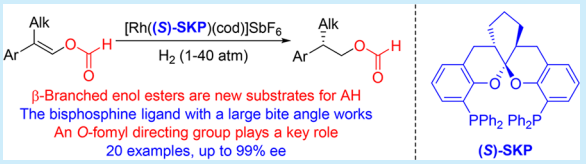
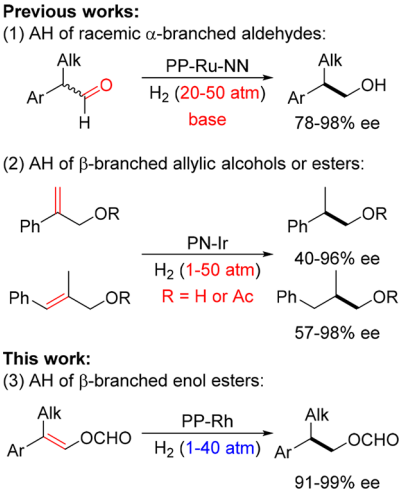
Supporting Information

ABSTRACT: An asymmetric hydrogenation of β-branched enol esters has been developed for the first time, providing a new route for the synthesis of β-chiral primary alcohols. Using a (*S*)-SKP-Rh complex bearing a large bite angle and enol ester substrates possessing an *O*-fomyl directing group, the desired products were obtained in quantitative yields and with excellent enantioselectivities.



Chiral alcohols are versatile intermediates for the synthesis of various important pharmaceuticals and bioactive compounds, either directly or in the form of esters and ethers. Therefore, numerous methodologies have been developed for the asymmetric catalytic synthesis of chiral alcohols. However, most of these reports concern the construction of chiral secondary and tertiary alcohols, while the preparation of chiral primary alcohols has been less studied. Enzyme-catalyzed (dynamic) acylative kinetic resolution of racemic β-branched primary alcohols[1] and dynamic reductive kinetic resolution of racemic α-branched aldehydes[2] are the most attractive methodologies for the synthesis of such compounds with satisfactory enantioselectivities. Two indirect methods, asymmetric hydroboration/oxidation of 1,1-disubstituted alkenes[3] and asymmetric carboalumination/or carboboration/oxidation of 1-substituted alkenes,[4] have also been developed. However, several problems associated with these processes, such as low efficiency, high catalyst loading, complex reaction system, or large amounts of byproduct, render them impractical. Since its discovery, asymmetric hydrogenation (AH) has been considered to be a practical process because of its high efficiency, environmental friendliness, and low economic cost.[5] According to retrosynthetic analyses, one can conclude that there are three routes of asymmetric hydrogenations for the synthesis of β-chiral primary alcohols (Scheme 1). One route involves the asymmetric hydrogenation of racemic α-branched aldehydes via dynamic kinetic resolution which has been developed independently by Zhou's and List's groups.[6] Using a catalytic system of bisphosphine-Ru-diamine, high enantioselectivities were obtained for substrates bearing bulky α-alkyl substituents. However, high hydrogen pressure (20−50 atm) and a strong base (usually *t*-BuOK) are required to complete the reaction. A second route involves the asymmetric hydrogenation of β-branched allylic alcohols or esters which has been primarily studied by Andersson, Diéguez and co-workers using a PN−Ir catalytic system.[7] However, only two types of substrates were used in order to obtain the β-chiral propanols and their acetate derivatives with 40−98% ee. Considering the limitations of the aforementioned routes, herein we propose a third route for the

Scheme 1. Three Asymmetric Hydrogenations for the Synthesis of β-Chiral Primary Alcohols



synthesis of β-chiral primary alcohols via the asymmetric hydrogenation of β-branched enol esters. To the best of our knowledge, the asymmetric hydrogenation of enol esters bearing an α-branched substituent has been widely studied,[8] but no report has been published concerning the asymmetric hydrogenation of enol esters bearing only a β-branched substituent (Figure 1), probably due to the difficulties in preparing pure substrates with only a *Z*- or *E*-configuration and developing active catalytic systems with good stereocontrol.

The initial hydrogenation reactions were conducted on the model substrate (*E*)-2-phenylprop-1-en-1-yl acetate (**1a-Me**) which was synthesized by acetylation of 2-phenylpropanal. In order to utilize the directing effect of the acetyl group, rhodium complexes with the ability to chelate to enol esters were chosen. Several bisphosphine ligands bearing C_{2-4} backbones were

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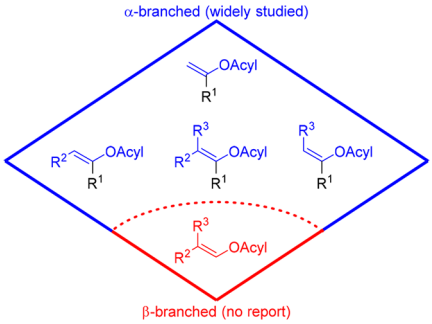
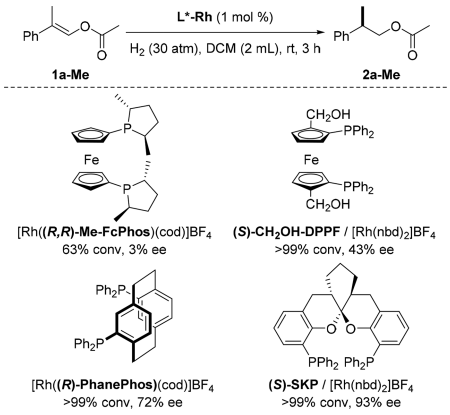


Figure 1. Enol esters for asymmetric hydrogenation.

evaluated. Irrespective of whether or not its chirality is central, axial, planar, or even P-stereogenic, almost all the commonly used chiral bisphosphine ligands gave the desired product with poor conversions (all <10%) and low enantioselectivities ([Rh((*R*,*R*)-NorPhos)(cod)]BF_4: 9% ee; (*R*)-BINAP/[Rh-(nbd)$_2$]BF_4: 29% ee; (*R*,S_p)-JosiPhos/[Rh(nbd)$_2$]BF_4: 12% ee; (*R*,*R*)-Me-DuPhos/[Rh(nbd)$_2$]BF_4: 45% ee; [Rh((*R*,*R*)-BenzP*)(cod)]SbF_6: 30% ee) (the reaction conditions were the same as those described in Scheme 2). To our surprise, a

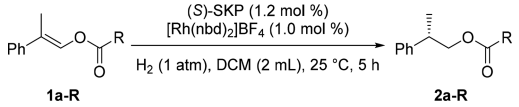
Scheme 2. Screen of Ligands



DuPhos analogue bearing a ferrocene backbone ((*R*,*R*)-Me-FcPhos) showed a dramatically improved activity. However, the enantioselectivity was still not acceptable (Scheme 2). This result suggested that ligands bearing a large bite angle appear to be more active in this reaction. A similar trend was also observed in our previous work concerning the asymmetric hydrogenation of *β*-branched allylic alcohols.[9] Thus, three chiral bisphosphine ligands, (*R*)-PhanePhos,[10] (*S*)-CH_2OH-DPPF,[11] and (*S*)-SKP[12] possessing a large bite angle, were tested. To our delight, all of these ligands gave the desired product with complete conversion and improved enantioselectivities. In particular, (*S*)-SKP, which was developed by Ding et al.,[12] was found to be the most promising (Scheme 2). Attempts at hydrogenation of an (*E*/*Z*)-mixture (45/55) under 30 atm of hydrogen pressure only gave a racemic product (−6% ee), indicating that the (*E*)- and (*Z*)-isomers generate the desired product with opposite enantioselectivity. Further optimization of the reaction conditions, such as solvent, temperature, and hydrogen pressure, did not provide any obvious improvement for this reaction (see Table S1 in Supporting Information). It is noteworthy that this reaction can go to completion under 1 atm of hydrogen pressure within a few hours.

In order to investigate the effect of the acyl group on the reaction, we synthesized other substrates and subjected them to hydrogenation (Table 1). The enantioselectivities gradually

Table 1. Effect of Acyl Groups



entry[a]	R	conv/%[b]	ee/%[c]
1	Me	>99	93
2	Et	>99	90
3	*i*Pr	>99	85
4	*t*Bu	>99	76
5	H	<10	nd
6[d]	H	>99	97
7[d,e]	H	>99	97
8[d,f]	H	trace	nd
9[d,f,g]	H	73	−92

[a]Conditions: **1a-R** (0.2 mmol), (*S*)-SKP (1.2 mol %), [Rh(nbd)$_2$]BF_4 (1.0 mol %), H_2 (1 atm), DCM (2 mL), 25 °C, 5 h, unless otherwise noted. [b]The conversions were calculated from ^{1}H NMR spectra. [c]The ee's were determined by HPLC using chiral columns. [d][Rh(cod)$_2$]-SbF_6 was used instead of [Rh(nbd)$_2$]BF_4. [e]1 h. [f](*Z*)-isomer was used instead of (*E*)-isomer. [g]5 atm.

decreased when the size of the acyl group increased (entries 1−4). These results inspired us to explore a new directing group—the *O*-formyl group. To avoid the difficult separation for the *Z*- and *E*-isomers, a selective synthetic route for the preparation of the *E*-isomer has been developed.[13] Methyl (*E*)-3-phenylbut-2-enoates were selectively synthesized via Horner−Wadsworth−Emmons reaction using commercially available acetophenones and subsequently transformed to *β*,*β*′-disubstituted-(*E*)-vinyl formates via sequential DIBAL-H reduction, MnO_2 oxidation, and Baeyer−Villiger oxidation (see Supporting Information for details). However, the hydrogenation using the same rhodium salt with a BF_4 anion showed poor activity for this substrate (entry 5). Therefore, a more active rhodium salt bearing a SbF_6 counterion was utilized and gave the desired product in quantitative conversion and 97% ee under the same reaction conditions or even in a short reaction time of 1 h (entries 6 and 7). The hydrogenation of the (*Z*)-isomer (R = H) was also conducted under 1 atm of hydrogen pressure, but almost no product was detected (entry 8). When increasing the hydrogen pressure to 5 atm, the hydrogenated product was obtained with 73% conversion and with an opposite enantioselectivity of 92% ee (entry 9).

With the optimized reaction conditions in hand, we investigated the substrate scope of the hydrogenation reaction catalyzed by the isolated rhodium complex [Rh((*S*)-SKP)-(cod)]SbF_6 (Scheme 3). All substrates bearing different phenyl moieties gave their corresponding products **2a−l** in satisfactory yields and excellent enantioselectivities (91−99%), regardless of the presence of electron-withdrawing or -donating substituents. The 1- and 2-naphthyl group-substituted substrates showed the best results giving their corresponding products **2m** and **2n** with 99% and 97% ee's, respectively. Furthermore, substrates bearing an alkyl unit at the *β*-position furnished their related products **2o−r** with excellent results, irrespective of the steric size of the substituted group.

To gain insight into the reaction mechanism, a deuterium-labeling experiment was conducted. The use of D_2 instead of H_2

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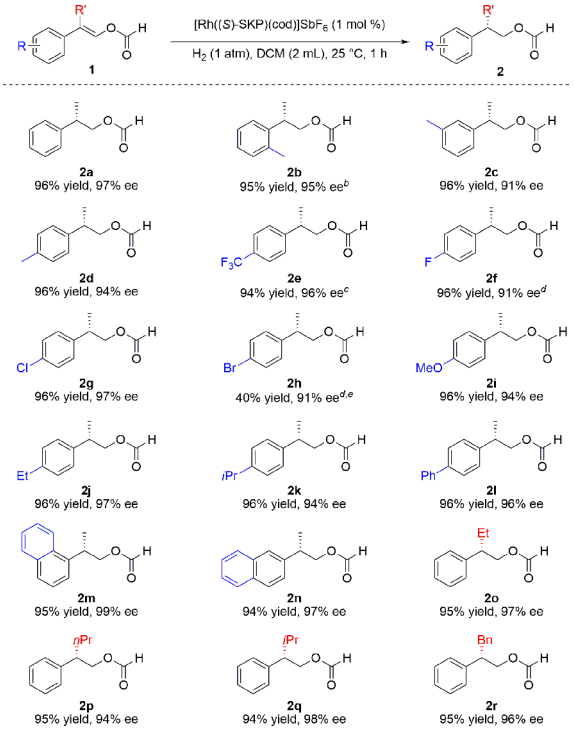
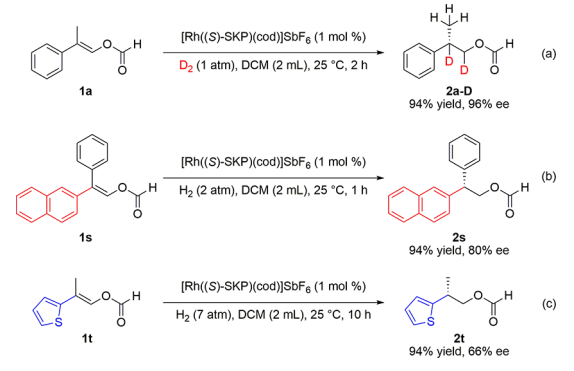
Scheme 3. Substrate Scope[a]



[a]Conditions: **1** (0.2 mmol), [Rh((*S*)-SKP)(cod)]SbF_6 (1 mol %)], DCM (2 mL), H_2 (1 atm), 25 °C, 1 h, unless otherwise noted. Isolated yields. The ee's were determined by HPLC using chiral columns. [b]6 h. [c]30 atm, 24 h. [d]Determined after hydrolysis. [e]40 atm, 24 h.

resulted in deuterium addition to the alkene with no double-bond-shift occurring (Scheme 4a). This result, combined with

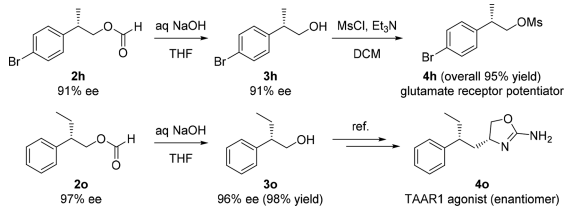
Scheme 4. Mechanism Study



the above-mentioned hydrogenation performance of **2a** and **2o**–**r** that no decrease in ee value was observed following an increase in the size of the alkyl chain, and that the (*E*)- and (*Z*)-isomers generate products with the opposite enantioselectivity, reveals that the stereoselectivity is predominantly controlled by the chelating direction of the enol ester to the bisphosphine–rhodium–dihydride complex, and not because of the diffenence between the two β-substituents. These results are consistent with the reported mechanism concerning the asymmetric hydrogenation of enamides.[14] Additional experiments that were also conducted may support this evidence to some extent. A substrate with two similar β-aromatic groups (**1s**) was hydrogenated to give the desired product **2s** with complete conversion and good enantioselectivity (Scheme 4b). Additionally, we examined the hydrogenation of substrate **1t** bearing a heteroaromatic 2-thienyl group (regarded as a coordinating substituent) and obtained the hydrogenated product **2t** with reduced activity and enantioselectivity (Scheme 4c).

To demonstrate the practicality of this methodology, the hydrogenated products were transformed to useful bioactive molecules (Scheme 5). For instance, compound **2h** was

Scheme 5. Applications of Hydrogenated Products



hydrolyzed to the corresponding alcohol **3h** and then reacted with mesyl chloride to give a glutamate receptor potentiator **4h**.[15] The product **2o** underwent hydrolysis in aqueous NaOH to give (*S*)-2-phenyl-1-butanol (**3o**), which can be transformed to an enantiomer of an orally active TAAR1 agonist **4o**.[16]

In conclusion, based on a new strategy that allows access to substrates as a single *E*-isomer, and the development of an efficient system to control the enantioselectivity by using the bisphosphine ligand bearing a large bite angle and substrates possessing an *O*-fomyl directing group, β-branched enol esters have been hydrogenated for the first time to give β-chiral primary alcohols quantitatively and with excellent enantioselectivities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03469.

Synthetic details for substrates, procedures for hydrogenation reactions, spectra of NMR and HPLC data (PDF)

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Notes

The authors declare no competing financial interest.

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