Practical Syntheses of β-Amino Alcohols via Asymmetric Catalytic Hydrogenation

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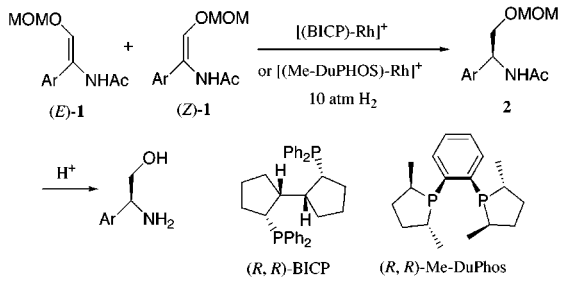
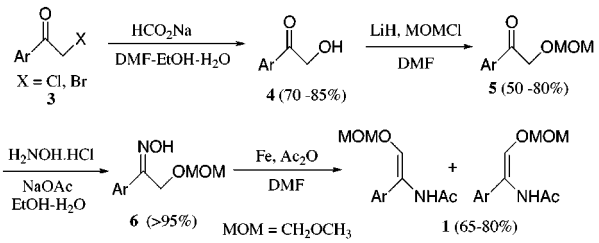
Enantiomerically pure β-amino alcohols have been extensively used as building blocks for the syntheses of pharmaceuticals[1] and insecticidal agents,[2] as chiral ligands in asymmetric catalysis,[3] or as auxiliaries[4] and resolving agents[5] in asymmetric synthesis. Furthermore, they can be converted to chiral oxazoline ligands, which show tremendous utility in various asymmetric catalytic processes.[6] The broad application of amino alcohol derivatives has generated considerable interest in developing efficient synthetic routes to these compounds.[7] Such amino alcohols generally are obtained by reduction of the corresponding α-amino acids or esters.[8] However, not all of the precursor α-amino acids are readily available, and sometimes low yields are observed in this reduction. To overcome these deficiencies, several alternative asymmetric synthetic methods have been developed.[9] In principle, asymmetric catalytic hydrogenation of protected β-hydroxy enamides is a practical way to generate such amino alcohols. Although high enantioselectivities and reactivities have been reported for the asymmetric hydrogenation of dehydroamino acids,[10] there have been no reports describing the synthesis of β-amino alcohols via asymmetric catalytic hydrogenation of enamides as illustrated in Scheme 1. *Herein, we describe the first highly enantioselective, practical synthesis of β-amino alcohols using BICP-Rh and Me-DuPhos-Rh complexes as the catalysts [BICP, 2,2′-bis-(diphenylphosphino)-1,1′-dicyclopentane; DuPhos, 1,2-bis-(2,5-dialkylphospholane)benzene]. The key elements of this method involve: (a) facile synthesis of α-hydroxy ketones, (b) new enamide formation procedure from oximes using Fe/Ac$_2$O in DMF as reagents, and (c) high enantioselectivity in the hydrogenation step.*

Scheme 1



Scheme 2



The basic strategy for the synthesis of chiral β-amino alcohols involves asymmetric hydrogenation of α-arylenamides with a MOM-protected β-hydroxy group.[11] Rh-catalyzed asymmetric hydrogenation must tolerate the *E* and *Z* isomers of these enamides since preparation and isolation of the isomerically pure *E* and *Z* isomers are difficult. Another practical issue in this approach is the formation of the β-hydroxy-substituted enamide substrates. We have prepared these MOM-protected β-hydroxy-substituted enamides in gram quantities from readily available 2-haloacetophenone derivatives **3** as outlined in Scheme 2.[11] The first step involves synthesis of 2-hydroxyacetophenone derivatives **4** through nucleophilic attack on corresponding 2-haloacetophenone by sodium formate. An in situ hydrolysis reaction then follows. Nucleophiles other than formate such as acetate or hydroxide are not desirable for the synthesis of 2-hydroxyacetophenone derivatives. Protection of the hydroxy group with methoxymethyl chloride (MOMCl) went smoothly, giving MOM-protected keto alcohol **5** in good yield. The key step in the synthesis of enamide **1** is the conversion of the corresponding oxime **6** of the MOM-protected keto alcohol by Fe/Ac$_2$O in DMF. The reported

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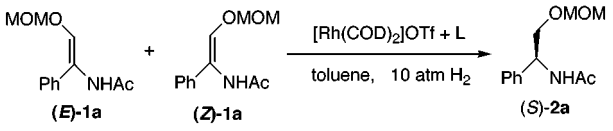
Table 1. Ligand Effect on Rh-Catalyzed Asymmetric Hydrogenation of an Enamide[15]



entry	ligand	% ee
1	(+)-DIOP	88
2	(*R*)-BINAP	15
3	(*R*,*R*)-BICP	94
4	(*R*,*R*)-Me-DuPhos	97

method by Kagan[12a,b] for the synthesis of enamides from nitriles and Grignard reagents not only generates many impurities but also cannot be used for making the hetereoatom-substituted enamide **1**. Conversion of oximes to enamides using Barton's procedure (Ac_2O/Py) require high temperature.[12e] In a related study, Zard applied Fe/Ac_2O for reduction of vinyl nitrites and formation of acetyl enamides.[12f] Recently, Casalnuovo[12c] and Burk[12d] independently discovered synthetic protocols for conversion of oximes to enamides with Fe/Ac_2O. The presence of DMF in Casalnuovo's procedure is crucial for lowering the reaction temperature, and the reduction reaction of oxime **6** proceeded cleanly in the presence of Fe/Ac_2O to give hetereoatom-substituted enamide **1**.

Hydrogenation of **1** catalyzed by Rh complexes with different chiral bisphosphines produces β-amino alcohol derivatives (Table 1). The reaction was typically carried out at room temperature in toluene with 1 mol % Rh under an initial H_2 pressure of 10 atm for 24−36 h. Our experimental results show that cationic Rh complexes bearing a variety of chiral bisphosphines are active catalysts in this transformation, but the enantioselectivities are ligand dependent. For examples, by using α-phenylenamide **1a** (Ar = C_6H_5) as a model substrate, the hydrogenation catalyzed by rhodium complexes with three different chiral bisphosphines bearing diphenylphosphino groups all went in quantitative yield but with quite different enantioselectivities: 88% ee with DIOP (entry 1, Table 1), 15% ee with BINAP (entry 2, Table 1), and 94% ee with BICP (entry 3, Table 1). The (*R*,*R*)-BICP ligand, (2*R*,2′*R*)-bis(diphenylphosphino)-(1*R*,1′*R*)-dicyclopentane ((*R*,*R*)-BICP, Scheme 1) is a conformationally rigid chiral 1,4-bisphosphine that was recently reported by our group as an efficient ligand for the rhodium-catalyzed asymmetric hydrogenation of dehydroamino acids.[13] The high enantioselectivities in the asymmetric hydrogenation of these isomeric *Z* and *E* mixtures of the MOM-protected β-hydroxy-substituted enamides **1** demonstrates a broader utility for our new ligand system. Prior to our study, the only asymmetric catalysts reported to efficiently hydrogenate mixtures of (*E*)- and (*Z*)-α-arylenamides are the Me-DuPhos-Rh and Me-BPE-Rh catalysts developed by Burk et al.[14] Indeed, high enantioselectivity (97% ee, entry 4) has been obtained in the hydrogenation of α-arylenamide **1a** using a Me-DuPhos-Rh complex as a catalyst.

Table 2. Asymmetric Catalytic Synthesis of β-Amino Alcohol Derivatives via Rh-Catalyzed Hydrogenation[15]

entry	Ar (**1**)	ligand	% ee
1	C_6H_5 (**1a**)	(*R*,*R*)-BICP	94
2	*p*-CH_3-C_6H_4 (**1b**)	(*R*,*R*)-BICP	94
3	*p*-MeO-C_6H_4 (**1c**)	(*R*,*R*)-BICP	90
4	*p*-C_6H_5-C_6H_4 (**1d**)	(*R*,*R*)-BICP	99
5	*p*-Cl-C_6H_4 (**1e**)	(*R*,*R*)-BICP	97
6	*p*-F-C_6H_4 (**1f**)	(*R*,*R*)-BICP	97
7	2,4-$F_2C_6H_3$ (**1g**)	(*R*,*R*)-BICP	98
8	2-naphthyl (**1h**)	(*R*,*R*)-BICP	95
9	C_6H_5 (**1a**)	(*R*,*R*)-Me-DuPhos	97
10	*p*-CH_3-C_6H_4 (**1b**)	(*R*,*R*)-Me-DuPhos	96
11	*p*-MeO-C_6H_4 (**1c**)	(*R*,*R*)-Me-DuPhos	95
12	*p*-C_6H_5-C_6H_4 (**1d**)	(*R*,*R*)-Me-DuPhos	97
13	*p*-Cl-C_6H_4 (**1e**)	(*R*,*R*)-Me-DuPhos	98
14	*p*-F-C_6H_4 (**1f**)	(*R*,*R*)-Me-DuPhos	98
15	2,4-$F_2C_6H_3$ (**1g**)	(*R*,*R*)-Me-DuPhos	95
16	2-naphthyl (**1h**)	(*R*,*R*)-Me-DuPhos	98

Under the standard set of conditions,[15] we have performed asymmetric hydrogenations of various α-arylenamides **1** with a MOM-protected β-hydroxy group (Table 2) catalyzed by Rh-BICP and Rh-Me-DuPhos complexes. A variety of *N*-acetyl- and *O*-MOM-protected arylglycinols were obtained in quantitative yield with high enantiomeric excesses (Table 2). Overall, the BICP-Rh catalyst gives comparable results with the Me-DuPhos-Rh catalyst. However, the Me-DuPhos-Rh catalyst displays slightly broader substrate generality than the BICP-Rh catalyst. For example, while 90% ee was obtained with the BICP-Rh catalyst for the *p*-methoxylphenyl enamide **1c** (entry 3), 95% ee was obtained in the Me-DuPhos-Rh system under identical conditions (entry 11). Enamides with either electron-withdrawing groups on the aryl ring or sterically demanding groups display enhanced enantioselectivity with the BICP-Rh catalytic system (entries 4−7 vs entries 1−3). The trend is less compelling with the Me-DuPhos-Rh catalyst. To test if the MOM group is necessary for high enantioselectivity in this reaction, we replaced the MOM protective group in enamide **1a** with a methyl group (**1i**). Under the same reaction conditions, the enamide (**1i**) with a β-methoxyl group was hydrogenated in high yield with 98% ee using the BICP-Rh catalyst. This result suggests that a variety of substrates with substituents on the β-position may be hydrogenated with high enantioselectivities using the BICP-Rh catalyst. The hydrogenation products **2** can be easily converted to α-arylglycinols by deprotection of *O*-MOM and *N*-acetyl groups under acidic conditions. For example, hydrogenation product **2a** was hydrolyzed to (*S*)-phenylglycinol in 81% yield in acidic MeOH solution, thus permitting the absolute configuration of hydrogenation product **2a** to be assigned as *S*. The N-protected α-arylglycinols can be oxidized to obtain useful α-arylglycines according to a recent study by Sharpless et al.[9e]

In conclusion, we have reported efficient syntheses of enantiomerically enriched β-amino alcohols using a practical asymmetric hydrogenation method. Cationic BICP-Rh and Me-DuPhos-Rh complexes are excellent catalysts for this transformation.

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Supporting Information Available: Spectroscopic data and experimental details (41 pages).

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