Synthesis of a Novel Chiral Binaphthyl Phospholane and Its Application in the Highly Enantioselective Hydrogenation of Enamides
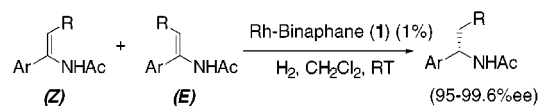
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ABSTRACT

A new chiral phosphine, (*R,R*)-1,2-bis{(*R*)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]phosphepino}benzene {abbreviated as (*R,R*)-binaphane] was prepared on the basis of a practical route from a readily accessible enantiomerically pure binaphthanol. This ligand possesses both binaphthyl chirality and pholsphane functionality. Excellent enantioselectivities (95–99.6% ee) have been observed in hydrogenation of an isomeric mixture of (*E*)- and (*Z*)-β-substituted-α-arylenamides by using a Rh–binaphane catalyst. These enantioselectivities are the highest reported to date for this transformation.

Discovery of new chiral ligands is a major driving force in developing highly enantioselective transition metal-catalyzed reactions. New structural motifs play important roles in determining enantioselectivities and reactivities for a given transformation. For example, biaryl atropisomeric ligands have been explored as effective scaffolds for many asymmetric transformations.[1] One of the most frequently used chiral chelating phosphines is BINAP.[2] "DuPhos" describes another family of excellent chiral phosphines,[3] which have a rigid 1,2-bis(phosphino)benzene backbone and electron-donating phospholane groups. Prompted by these studies, we choose to make a new chiral chelating phosphine that possesses both binaphthyl chirality and a phospholane functionality. The resulting chiral ligand with a rigid 1,2-bis(phosphino)benzene backbone, (*R,R*)-1,2-bis{(*R*)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]phosphepino}benzene, is abbreviated as (*R,R*)-binaphane (**1**) (Figure 1). Herein we report the synthesis of this novel chiral phosphine and its application in Rh-catalyzed highly enantioselective hydrogenation of enamides.

Recently, Gladiali et al.[4] and Stelzer et al.[5] made several monodentate chiral phospholanes as well as the corresponding racemic chelating derivatives bearing the 1,1′-binaphthyl framework. However, only limited applications in asymmetric catalysis were reported.[4a] Reetz et al.[6] prepared chelating chiral phosphites using readily accessible binaphthanols as starting materials and demonstrated that they are excellent ligands for Rh-catalyzed asymmetric hydrogenation

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of dehydroamino acids. Although the synthesis of binaphane (**1**) is a more demanding task compared with preparation of the chiral phosphite ligands reported by Reetz et al., the arguably greater electron-donating ability of the phospholane moiety compared with a phosphite makes it an attractive ligand for many applications.[3,7] A calculated structure of a Rh complex with **1** (CAChe MM2 program) is shown in Figure 1. Two naphthyl groups protrude into two opposite
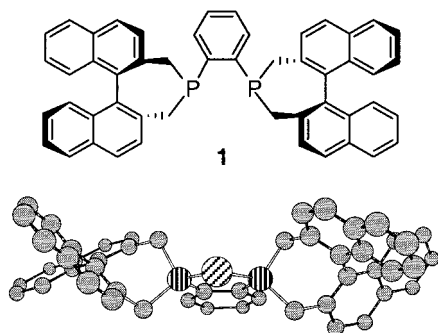
Figure 1. (*R,R*)-Binaphane (**1**) and its Rh complex.

quadrants, and another two naphthyl groups stay back to leave open the other two quadrants. This steric environment may be conducive to achieving highly enantioselective transformations.

To make the desired chiral chelating phospholane **1**, we have developed a practical synthesis route based upon readily accessible starting materials (Scheme 1). Enanatiomerically

Scheme 1[a]
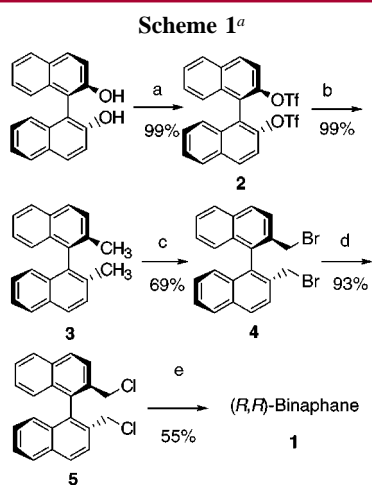
[a] Tf$_2$O, Py, CH$_2$Cl$_2$. [b] MeMgBr, NiCl$_2$(dppp), Et$_2$O. [c] NBS, benzoyl peroxide, CCl$_4$. [d] LiCl, DMF. [e] 1,2-Bisphosphinobenzene, NaH, THF.

pure binaphthol can be easily obtained using a classic resolution procedure.[8] (*R*)-2,2′-Bistriflate-1,1′-binaphthyl (**2**) was made from (*R*)-binaphthol with excess triflic anhydride and pyridine in CH$_2$Cl$_2$. Kumada-type coupling of bistriflate

2 with methylmagnesium bromide gave (*R*)-2,2′-dimethyl-1,1′-binaphthyl (**3**) in high yield. (*R*)-2,2′-Dibromomethyl-1,1′-binaphthyl (**4**) was prepared by bromination of **3** with NBS. A simple anion exchange of (*R*)-2,2′-dibromomethyl-1,1′-binaphthyl (**4**) with LiCl afforded (*R*)-2,2′-dichloromethyl-1,1′-binaphthyl (**5**) in high yield. *A key element in our synthesis of chelating phospholane **1** is utilization of a less reactive (R)-2,2′-dichloromethyl-1,1′-binaphthyl (**5**) to suppress the intermolecular reaction with phosphine anions that attends use of a more reactive (R)-2,2′-dibromomethyl-1,1′-binaphthyl (**4**).* While we failed to prepare the desired phosphine **1** using (*R*)-2,2′-dibromomethyl-1,1′-binaphthyl (**4**) as a starting material, refluxing (*R*)-2,2′-dichloromethyl-1,1′-binaphthyl (**5**) with 1,2-bis(phosphino)benzene and NaH in THF, followed by recrystallization from ether, gave (*R,R*)-binaphane **1** in 55% yield. This efficient synthesis allows us to make binaphane **1** on a large scale. Using this procedure, we have also made the corresponding monodentate chiral binaphthyl phospholane from phenylphosphine in >90% yield.

Many chiral phosphine ligands have been designed to achieve high enantioselectivity and reactivity for the asymmetric hydrogenation of unsaturated substrates such as ketones, olefins, and imines.[9] Electron-deficient olefins (e.g., dehydroamino acids) are easily reduced with high enantioselectivities using the current suite of catalysts. However, only a few chiral ligands are effective for the highly enantioselective hydrogenation of electron-rich olefins such as simple enamides.[10] In particular, hydrogenation of an isomeric mixture of (*Z*)- and (*E*)-enamides with high enantioselectivity remains a significant challenge.

To test the synthetic utility of (*R,R*)-binaphane (**1**), we have explored the asymmetric hydrogenation of enamides using a Rh−(*R,R*)-binaphane (**1**) complex as the catalyst. Initially, several experiments were performed to screen optimal conditions for hydrogenation of *N*-acetylphenylethenamine **6a**. Rh(COD)$_2$PF$_6$ was found to be a more effective catalyst precursor compared with a neutral Rh species [Rh(COD)-Cl]$_2$.[10d,f] An increase in H$_2$ pressure resulted in a decrease of enantioselectivity upon hydrogenation of **6a**. For example, 85% ee was obtained under 300 psi of H$_2$ while 90% ee was achieved under 20 psi of H$_2$. Variation of solvents caused dramatic changes in both enantioselectivity and reactivity. While hydrogenation of *N*-acetylphenylethenamine was complete in CH$_2$Cl$_2$ with 90% ee, both the reactivity and

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the enantioselectivity were lower in methanol (14% ee and 86% conversion). The reaction did not proceed in toluene.

Next, a variety of enamides were prepared according to literature procedures[10a−f] and employed as substrates for this asymmetric hydrogenation reaction (Table 1). These experi-

Table 1. Highly Enantioselective Hydrogenation of Enamides Catalyzed by a Rh−(R,R)-Binaphane Complex[a]

entry	substrate[c]	Ar, R	ee %[d]
1	**6a**	C_6H_5, H	90.0
2	**6b**	3-Me-C_6H_4, H	89.0
3	**6c**	4-CF_3-C_6H_4, H	82.0
4	**6d**	4-Ph-C_6H_4, H	75.7
5	**6e**	4-Cy-C_6H_4, H	90.0
6	**6f**	2-Np, H	89.5
7	**6g**	C_6H_5, CH_3	99.1
8	**6h**	4-MeO-C_6H_4, CH_3	99.6
9	**6i**	4-CF_3-C_6H_4, CH_3	97.0
10	**6j**	C_6H_5, CH_2CH_3	97.0
11	**6k**	C_6H_5, CH_2Ph	95.0
12	**6l**	C_6H_5, $CH(CH_3)_2$	97.6
13	**6m**	2-Np, CH_3	98.3

[a] The reaction was carried out at room temperature under an initial hydrogen pressure of 20 psi for 24 h. The catalyst was made in situ by stirring a solution of Rh(COD)$_2$PF$_6$ and (R,R)-binaphane (**1**) in CH$_2$Cl$_2$. [Substrate (0.04 M)]:[Rh]:(R,R)-binaphane (**1**) =100:1:1.5. The reaction proceeded in quantitative yield. [b] The configuration of the product was determined by comparison of optical rotation with reported data. [c] Enamides **6** were made according to the literature methods. [d] Enantiomeric excesses were determined by chiral GC with a Supelco chiral select 1000 column or by chiral HPLC with a Regis (S,S)-Whelk-01 column.[10f]

ments were performed under the optimal conditions for hydrogenation of N-acetylphenylethenamine (**6a**). The electronic character of attached aryl groups in α-arylenamides had only a small effect on the enantioselectivity. Introducing an electron-withdrawing group into the α-arylenamides resulted in lower enantioselectivity (entry 3, 82% ee) while

substrates with an electron-donating group showed higher enantioselectivity (entry 2, 89% ee; entry 5, 90% ee). Although very good enantioselectivities have been obtained for hydrogenation of α-arylenamides without substitituents in the β-position, the highlight of the Rh−binaphane (**1**) catalyst is its ability to reduce β-substituted-α-arylenamides with excellent enantioselectivities. Several β-substituted-α-arylenamides, as a mixture of (E)/(Z) isomers, were reduced with high enantioselectivities (entries 7−13, 95−99.6% ee). A small electronic effect was observed. For example, hydrogenation of **6h** bearing an electron-donating 4-methoxy substituent in the aryl group proceeded with the higher enantioselectivity (entry 8, 99.6% ee) compared with the result obtained with **6i** with an electron-withdrawing 4-CF$_3$ substituent (entry 9, 97% ee). Although there are several chiral phosphine systems such as DuPhos, BPE, and BICP that are effective for hydrogenation of an isomeric mixture of (E)- and (Z)-enamides,[10d−f] *the enantioselectivities achieved with the Rh−(R,R)-binaphane (**1**) catalyst are the highest reported to date*. Since the product **7** can be easily converted to the corresponding arylalkylamine through hydrolysis under acidic conditions, hydrogenation with the Rh−binaphane (**1**) complex provides a practical method for preparing a variety of chiral arylalkylamines.

In conclusion, a new axially chiral ligand (R,R)-binaphane (**1**) has been developed. This ligand afforded excellent enantioselectivities when utilized in Rh-catalyzed asymmetric hydrogenation of trisubstituted electron-rich enamides. The detailed mechanism is under investigation, and other applications of this new ligand for asymmetric catalysis will be disclosed in due course.

Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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