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4,4′-Disubstituted BINAPs for Highly Enantioselective Ru-Catalyzed Asymmetric Hydrogenation of Ketones

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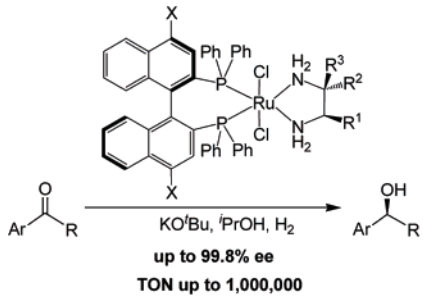
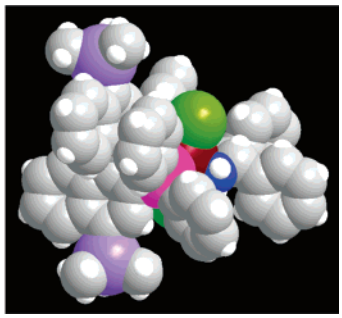
ABSTRACT





A family of tunable precatalysts Ru(4,4′-BINAP)(chiral diamine)Cl_2 was synthesized and used for highly enantioselective hydrogenation of aromatic ketones. This result differs from previous chiral diphosphines that rely on the bis(xylyl)phosphino groups to control enantioselectivity. An X-ray structural study reveals that the bulky substituents on the 4,4′-positions of BINAP can effectively create a suitable chiral pocket in the transition state and thus provide a new mechanism for the enantiocontrol in such a remarkable asymmetric catalytic process.

Asymmetric hydrogenation of prochiral olefins, ketones, and imines is one of the most powerful methods for the industrial production of optically active compounds.[1] Among these methodologies, hydrogenation of simple ketones catalyzed by the chiral Ru(diphosphine)(diamine)Cl_2 system discovered by Noyori et al. shows the most remarkable enantioselectivity and activity characteristics.[2] Subsequent mechanistic studies by Noyori et al. and Morris et al. also established a very unusual catalytic pathway for this remarkable system in which the key step involves simultaneous transfer of a hydride on the Ru center and a proton of the RNH_2 ligand to the carbonyl group via a six-membered pericyclic transition state to afford chiral secondary alcohols.[3] Since the original disclosure in 1995, many chiral diphosphines have been used to give highly enantioselective Ru(diphosphine)-(diamine)H_2 catalysts for the hydrogenation of simple ketones.[4] Although the enantio-differentiation event has not been explicitly established, empirical evidence points to the need of 3,5-dimethylphenyl (xylyl) moieties in all the chiral

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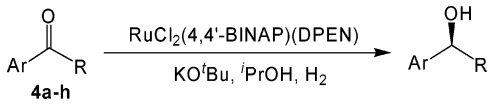
Table 1. Enantiomeric Excesses (%) for Asymmetric Hydrogenation of Ketones with Ru[(*R*)-4,4′-BINAP)][(*R*)-DPEN]Cl_2[a,b]



	Ar, R	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k
4a	Ph, Me	83.0	85.7	89.9	88.8	88.1	88.9	91.5	91.5	94.1	96.0	97.1
4b	Ph, Et	85.4	86.2	90.5	87.1	88.8	91.1	95.2	91.4	95.7	96.8	94.2
4c	1-naphthyl, Me	96.9	97.9	98.0	97.7	97.8	97.9	98.5	98.5	98.3	99.0	99.0
4d	4-*t*Bu-Ph, Me	94.0	91.4	90.9	94.8	95.2	97.7	95.4	96.4	96.2	99.0	99.1
4e	2-Naphthyl, Me	75.2	85.4	86.5	88.8	86.4	91.1	86.2	93.1	93.9	96.7	97.9
4f	4-Me-Ph, Me	83.1	79.0	77.5	85.2	86.7	87.7	83.8	83.3	93.2	95.4	97.4
4g	4-MeO-Ph, Me	80.7	77.9	86.5	86.0	85.7	86.1	70.0	90.8	91.1	95.8	95.4
4h	4-Cl-Ph, Me	60.0	66.9	60.9	71.1	71.6	77.3	88.4	89.3	89.6	90.5	95.8

[a] All of the reactions were carried out at room temperature with 0.1 mol % catalyst and 1 mol % KO*t*Bu additive under 700 psi hydrogen pressure in 20 h, and the ee values were determined by GC on a Supelco β-Dex 120 column. The absolute configurations of the products are identical to those obtained by the Ru[(*R*)-BINAP][(*R*,*R*)-DPEN)]Cl_2 (**2a**) catalyst. All conversions were >99% as judged by the integrations of GC peaks. [b] See Figure 1 for the structures of precatalysts **2a**−**2k**. Precatalysts **2a**, **2d**, **2f**, **2j**, and **2k** were purified by column chromatography before use, whereas the other precatalysts were generated in situ (without purifications).

diphosphines in order to achieve high enantiomeric excesses (ee's). The analogous phenyl- or tolyl-based diphosphines give much lower ee's. We wish to report here the execution of enantiocontrol via a drastically different pathway by installing bulky substituents on the 4,4′-positions of 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) to provide the first diphenylphosphino-based Ru(diphosphine)(diamine)H_2 catalysts for highly enantioselective hydrogenation of aromatic ketones. X-ray structure of the Ru[(*R*)-4,4′-$(TMS)_2$-BINAP][(*R*,*R*)-DPEN]Cl_2 precatalyst (where DPEN is 1,2-diphenylethylenediamine) indicates that the trimethylsilyl substituents on the 4,4′-positions of BINAP can effectively create a suitable chiral pocket in the transition state to lead to excellent enantiocontrol in the asymmetric hydrogenation of a wide range of ketones.

4,4′-Disubstituted BINAPs (**1b**, **1c**, and **1e**−**1k**) were synthesized starting from known 4,4′-dibromo-2,2′-bis(diphenylphosphinyl)-1,1′-binaphthyl according to our recently published procedures.[5] The chiral precatalysts Ru[(*R*)-4,4′-BINAP][(*R*,*R*)-DPEN]Cl_2, **2a**−**2k**, were synthesized by reacting 4,4′-BINAP and [Ru(benzene)Cl_2]$_2$ (0.92 equiv) in DMF at 100 °C for 30 min, followed by treatment with 1 equiv of (*R*,*R*)-DPEN at 80 °C for 2 h (Figure 1). The resulting orange-red solids after the removal of organic volatiles were used for asymmetric hydrogenation. The precatalysts **3i**, **3j**, and **3k** were similarly prepared with (*R*)-1,1-dianisyl-2-isopropyl-1,2-ethylenediamine (DAIPEN) in place of (*R*,*R*)-DPEN. All of these Ru precatalysts are stable in air and can be purified by silica gel chromatography[6] except for the precatalysts prepared from ligand **1k**, which do not elute in silica gel columns.[7]

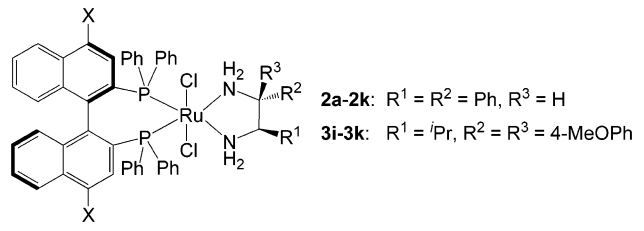


Figure 1. Structures of the Ru(4,4′-BINAP)(diamine)Cl_2 precatalysts.

Asymmetric hydrogenation reactions of aromatic ketones were carried out with 0.1 mol % of precatalysts **2a**−**2k** in the presence of KO*t*Bu in 2-propanol. Complete conversions were observed for all of the precatalysts **2a**−**2k**, but ee values vary significantly among **2a**−**2k** (Table 1). For the hydrogenation of acetophenone (**4a**) to generate 1-phenylethanol, a moderate ee of 83.0% was obtained with **2a**, as previously reported by Noyori et al.[2] The small substituents in the 4,4′-positions of BINAP in **2b**−**2e** only slightly affect the ee, while the bulky 4,4′-substituents in **2i**−**2k** drastically enhance the ee for the hydrogenation of aromatic ketones. Acetophenone was, for example, completely reduced to 1-phenylethanol in 97.1% ee with **2k**, an ee value far superior to earlier Ru(diphosphine)(diamine)Cl_2 systems with diphenylphosphino moieties (with the only exception of Phanephos).[4c] This ee value is also comparable to those of the best catalysts made from xylyl-based phosphines including Xyl-BINAP [2,2′-bis(di-3,5-xylylphosphino)-1,1′-binaphthyl],[2] Xyl-Phanephos {4,12-bis(di-3,5-xylylphosphino)-[2,2]paracyclophane},[4c] Xyl-P-Phos [2,2′,6,6′-tetramethoxy-

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(6) Since these precatalysts were synthesized on relatively small scales, we found it more convenient to purify them by column chromatography than recrystallization.

(7) Purified precatalysts showed slightly higher ee's (typically 1−2% higher) than the crude precatalysts prepared in situ.

4,4′-bis(di-3,5-xylylphosphino)-3,3′-bipyridine],[4d,e] and Xyl-SDP [7,7′-bis(di-3,5-xylylphosphino)-1,1′-spirobiindane].[4f]

Dark yellow crystals of (*R*)-(*R*,*R*)-**2j**·toluene were obtained by recrystallization from a toluene/hexane mixture.[8] An X-ray structure analysis revealed that the Ru center adopts an octahedral coordination environment with the P atoms of ligand **1j** and the N atoms of DPEN in the same plane and the two chlorine atoms *trans* to each other (Figure 2). The bond distances and angles around the Ru center are within the normal range expected for a six-coordinate Ru(II) complex.

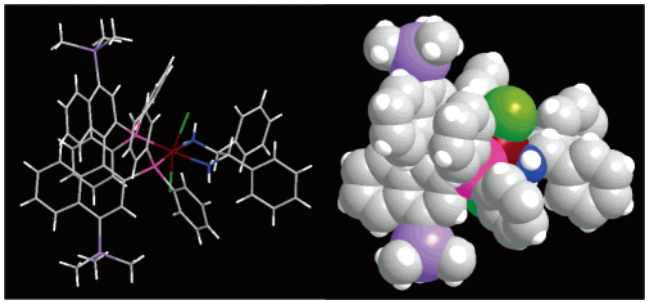
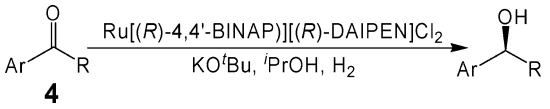


Figure 2. Stick presentation (left) and space-filling model (right) of single-crystal X-ray structure of (*R*)-(*R*,*R*)-**2j**. Red, Ru; green, Cl; blue, N; pink, P; purple, Si; light gray, C; white, H. Key bond distances and angles are Ru−N1, 2.170(4) Å; Ru−N2, 2.173(4) Å; Ru−P1, 2.278(2) Å; Ru−P2, 2.290(2) Å; Ru−Cl1 2.418(2) Å; Ru−Cl2, 2.433(2) Å; N1−Ru−N2, 79.2(2)°; N1−Ru−P1, 94.7(2)°; N2−Ru−P1, 173.8(2)°; N1−Ru−P2, 173.3(2)°; N2−Ru−P2, 94.2(2)°; P1−Ru−P2, 91.88(4)°.

In the key enantiocontrol step of the proposed catalytic cycle for the hydrogenation of aromatic ketones, the C═O group is hydrogen-bonded to the Ru-H and NH_2 moieties, and the relative orientation of the alkyl and aryl groups determines the stereochemistry of the products.[3] It is evident from the space-filling model in Figure 2 that the TMS groups on the 4,4′-positions of BINAP block one side of the complex and will have significant repulsive interactions with the aryl group of the ketone in the disfavored transition state (also see the models in Supporting Information for a comparison between the two diastereomeric transition states). Such a steric differentiation will result in a higher energy difference of the two diastereomeric transition states and lead to higher ee's. The substituents on the 4,4′-positions of BINAP achieve a similar effect as the methyl groups of xylyl-based phosphines in the creation of a suitable chiral pocket in the transition state.

In contrast to the xylyl-based phosphines, the 4,4′-substituents in the present system are readily tunable and thus allow the design of a wide variety of catalysts to accommodate different ketone substrates. We have carried out the hydrogenation of a variety of aromatic ketones with high activity and ee's using **2a**−**2k** (Table 1). It is also evident from Table 1 that precatalysts **2i**, **2j**, and **2k** gave the highest ee's for the hydrogenation of aromatic ketones. We have thus examined the performances of precatalysts **3i**, **3j**, and **3k** by combining **1i**, **1j**, and **1k** with a more stericically demanding chiral diamine, DAIPEN. As shown in Table 2, a range of aromatic ketones can be readily

Table 2. Selected Enantiomeric Excesses (%) for the Asymmetric Hydrogenation of Aromatic Ketones[a]



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	Ar, R	3i	3j	3k
4a	Ph, Me	97.3	98.5	98.5
4b	Ph, Et	98.3	99.4	98.5
4c	1-naphthyl, Me	99.5	99.8	99.5
4d	4-^{t}Bu-Ph, Me	99.3	99.6	99.2
4e	2-naphthyl, Me	98.7	98.8	99.2
4f	4-Me-Ph, Me	98.3	98.4	98.6
4 g	4-MeO-Ph, Me	99.0	98.3	98.6
4h	4-Cl-Ph, Me	97.1	96.1	98.2

[a] All of the reactions were carried out at room temperature with 0.1 mol % purified precatalysts of **3i** and **3j** and in situ generated **3k** and 1 mol % KO^{t}Bu under 700 psi hydrogen pressure in 20 h. All conversions were >99% as judged by the integrations of GC peaks.

hydrogenated with complete conversions and ee's in the range of 98.2−99.8% with precatalysts **3i**, **3j**, and **3k**. The fact that the highest ee's scatter among **3i**, **3j**, and **3k** indicates the need for a tunable catalyst platform for practical asymmetric hydrogenation of different substrates.

Our data also suggest that the precatalysts with electron-donating substituents on the 4,4′-positions of BINAP afford higher activity than those with electron-withdrawing groups. The precatalyst **3j** thus combines three favorable features, 4,4′-bulky substituents (TMS), electron-donating groups (TMS), and steric demanding diamine (DAIPEN), and is highly active and enantioselective for the hydrogenation of aromatic ketones. For example, **3j**-catalyzed hydrogenation of acetophenone (**4a**) with a substrate/catalyst (S/C) ratio of 1,000,000 completed in 50 h at room temperature with 98.6% ee (a TON of >1,000,000), whereas **3j**-catalyzed hydrogenation of a bulkier ketone, 1-acetonaphthone (**4c**) with a S/C ratio of 100,000 completed in 20 h at room temperature with an ee value as high as 99.8% (a TON of >100,000).[9] A TON of greater than 100,000 was also obtained for the hydrogenation of 1-acetonaphthone by **2j** with a S/C ratio of 100,000. In comparison, less electron-rich precatalyst **2k** catalyzed the hydrogenation of 1-acetonaphthone with a TON of 13,000 under similar conditions.

(8) Crystal data for (*R*)-(*R*,*R*)-**2j**·toluene: orthorhombic, space group $P2_12_12_1$, with a = 11.856(1), b = 24.087(1), c = 24.626(1) Å; V = 7032.6(3) Å^3, Z = 4, D_{calc} = 1.17 g/cm^3. $R1$ = 0.062, $wR2$ = 0.176, and GOF = 1.12. Flack parameter = −0.01(3).

(9) Lipshutz et al. has disclosed powerful methodologies for the synthesis of chiral alcohols via asymmetric hydrosilylation. See: Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779−8789.

In summary, we have applied a family of tunable 4,4′-substituted BINAPs in the asymmetric hydrogenation of aromatic ketones. By taking advantage of bulky 4,4′-substituents on the BINAP moiety, excellent ee's were obtained without resorting to the bis(xylyl)phosphino groups. The present work thus shed new light on the enantiocontrol mechanism of this remarkable asymmetric catalytic process. Ongoing work is targeted at designing even more efficient catalysts by combining favorable features of both 4,4′-substituents and xylyl moieties in the chiral diphosphines.

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Supporting Information Available: Detailed experimental procedures and additional data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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