Enantiomeric Synthesis

Remarkable 4,4′-Substituent Effects on Binap: Highly Enantioselective Ru Catalysts for Asymmetric Hydrogenation of β-Aryl Ketoesters and Their Immobilization in Room-Temperature Ionic Liquids**

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Catalytic asymmetric hydrogenation has been established as one of the most efficient strategies for the synthesis of optically active molecules.[1] The reactivity and enantioselectivity of a transition-metal-based asymmetric catalyst are highly sensitive to the conformational, steric, and electronic properties of the chiral ligand. Numerous chiral ligands, including 1,1′-binaphthalene-2,2′-diylbis(diphenylphosphane) (binap),[2] 1,2-bis(phosphanyl)benzene (duphos),[3] 1-[2-(diphenylphosphanyl)ferrocenyl]ethyldicyclohexylphosphane (josiphos),[4] 1-(*S*)-diphenylphosphanyl-2-(*O*-diphenylphosphanylphenylmethyl)ferrocene (taniaphos),[5] *P*,*P*′-1,2-phenylenebis(*endo*-2,5-dialkyl-7-phosphabicyclo[2.2.1]hepzanes (pennphos),[6] 1,1′-di-*tert*-butyl-2,2′-diphospholane (tangphos),[7] and (3,5-dioxa-4-phosphacyclohepta[2,1-a;3,4-a′]-dinaphthalene-4-yl)dimethylamine (monophos),[8] have been synthesized over the past 30 years to effect a variety of catalytic asymmetric hydrogenation processes. However, many prochiral olefins, ketones, and imines still cannot be reduced in high enantiomeric excesses and with high turnover numbers with the currently available hydrogenation methods. As an example, Noyori et al. reported a highly enantioselective hydrogenation of β-alkyl β-ketoesters by using the Ru–binap system; however, much more inferior *ee* values were obtained for analogous β-aryl ketoester substrates.[9] Herein, we report the design of a family of highly tunable and enantioselective Ru catalysts for the asymmetric hydrogenation of a wide range of β-aryl ketoesters by taking advantage of the remarkable effects of 4,4′-substituents on binap. These highly enantioselective Ru catalysts have also been effectively immobilized in room temperature ionic liquids (RTILs).

Enantiomerically pure β-aryl β-hydroxy acids, which are obtainable from the asymmetric hydrogenation of β-aryl ketoesters, are important precursors to β-amino acids, β-hydroxy-α-amino acids and their derivatives, which are building blocks for novel peptides and peptidomimetic-drugs.[10] β-Hydroxy esters are also precursors to a number of important drugs including tomoxetine, a norpinephrine reuptake-inhibiting antidepressant; fluoxetine, a serotonin-reuptake-inhibiting antidepressant; and pinostrobin, a candidate for treatment of estrogen-related tumors.[11] In spite of the extensive search for chiral ligands for effective asymmetric hydrogenation of β-aryl ketoesters, none of the many chiral diphosphanes examined have shown ee values useful for practical applications[12] and the best system based on chiral bisphosphanite binapo gave high *ee* values only for selected substrates.[13]

A family of 4,4′-substituted binap derivatives were readily synthesized starting from **1a**[14] by two different approaches (Scheme 1). In the first, compounds **2**–**6** were synthesized from **1a** by halogen metathesis, Suzuki coupling, or a Pd-catalyzed phosphonation reaction followed by $Ti(OiPr)_4$-mediated reduction with triethoxysilane or reduction with phenylsilane.[15] In the second approach, **1a** was reduced to 4,4′-dibromo-binap (**1**) by $Ti(OiPr)_4$-mediated reduction with triethoxysilane. Compounds **7**–**11** were then obtained in good yields by lithiation of **1** with *n*-butyllithium followed by treatment with various electrophiles. Monosubstituted binap derivatives **8b** and **11b** were obtained as minor by-products from the reactions leading to **8** and **11**. All the new compounds were characterized by optical rotation studies; ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectroscopic analysis; and mass spectrometric analysis.

Ruthenium precatalysts were prepared by mixing 4,4′-binap ligands and $[\{RuCl_2(benzene)\}_2]$ in hot DMF and were used for catalysis without further purification. As shown in Table 1, ethyl benzoylacetate was hydrogenated in 85.0 % *ee*. Complete conversion was obtained using a Ru–binap catalyst in methanol under a hydrogen pressure of 1400 psi at room temperature for 20 hours.[9] Although all these Ru–4,4′-binap catalysts showed similar reactivities, their enantioselectivities varied drastically. Electron-withdrawing groups seem to decrease the *ee* values obtained, as exemplified by the trend of **2**(Cl) < **1**(Br) < binap ≦ **9**(I). The placing of phenyl groups on the 4,4′-positions also has deleterious effects on the enantiomeric excess. Remarkably, enantioselectivity was drastically enhanced when bulky groups were placed in the 4,4′-positions of BINAP. The combination of the steric demands and electron-donating abilities of the 4,4′-substituents gave the best enantioselectivities, for example, *ee* values of 99.5, 99.3, and 99.2 % were obtained for the hydrogenation of ethyl benzoylacetate with Ru catalysts based on chiral ligands **7** (R = R′ = TMS; TMS = trimethylsilane), **10** (R = R′ = diphenylmethanol), and **11** (R = R′ = 1-cyclopentanol), respectively. Compound **8**, which contains electron-donating bulky triisopropylsilyl groups, was obtained in a lower enantiomeric excess probably because of the low solubility of the Ru-catalyst in methanol. Interestingly, the C_1-symmetric ligands **8b** and **11b**, which look like binap on one side and **8** or **11** on the other side, exhibited *ee* values that were between those of binap and **8** or **11**. It is evident from Table 1 that the Ru catalyst based on 4,4′-TMS-binap (**7**) give the highest enantiomeric excess, and was thus chosen to further

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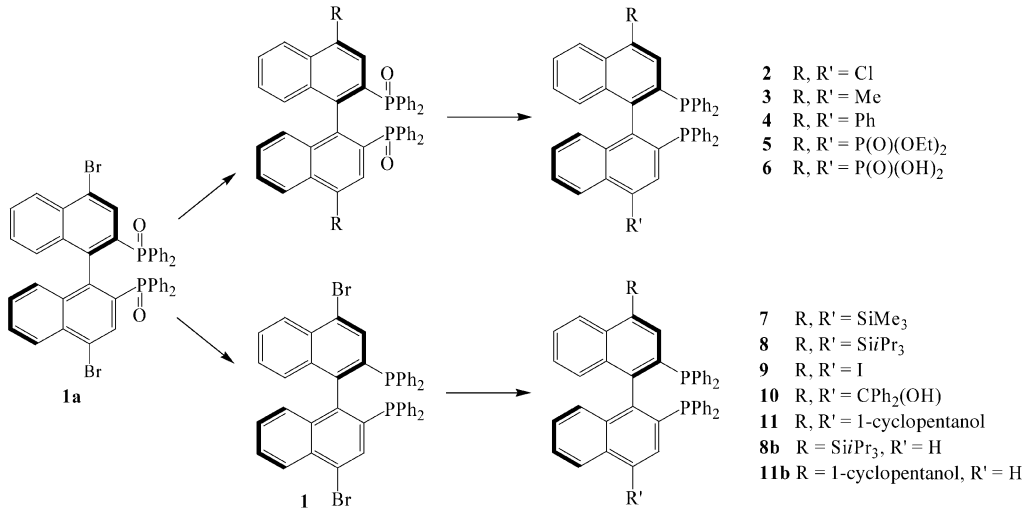
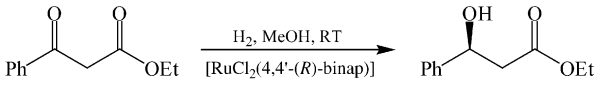


Scheme 1. Synthesis of 4,4′-substituted binap derivatives from **1a**.

Table 1: Asymmetric hydrogenation of ethyl benzoylacetate with 4,4′-substituted binap derivatives as the ligand.



Entry	Ligand	4,4′-Substituent groups	*ee* [%][c]
1	binap	none	85.0
2	**1**	R = R′ = Br	80.8
3	**2**	R = R′ = Cl	77.0
4	**3**	R = R′ = Me	85.0
5	**4**	R = R′ = Ph	71.8
6	**5**	R = R′ = P(O)(OEt)$_2$	98.8
7	**6**	R = R′ = P(O)(OH)$_2$	97.2
8	**7**	R = R′ = SiMe$_3$	99.5
9	**8**	R = R′ = Si*i*Pr$_3$	98.6
10	**9**	R = R′ = I	86.5
11	**10**	R = R′ = CPh$_2$(OH)	99.3
12	**11**	R = R′ = 1-cyclopentanol	99.2
13	**8b**	R = Si*i*Pr$_3$, R′ = H	95.1
14	**11b**	R = 1-cyclopentanol, R′ = H	94.2

[a] All reactions were carried out under 1400 psi of hydrogen gas in methanol at room temperature for 20 hours with 1 mol% catalyst loading. [b] All the reactions were judged to have >98% conversions based on the integrations of NMR signals for the starting material and product. [c] The *ee* values (%) were determined by gas chromatography (GC) on a Superco γ-Dex 225 column.

study the scope of the substrate. Polar 4,4′-P(O)(OH)$_2$-binap (**6**) was also examined so that its performance in RTILs could be evaluated.

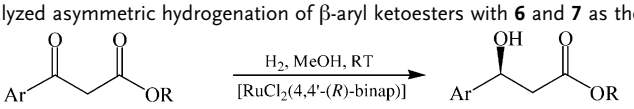
A variety of β-aryl ketoesters were successfully hydrogenated with complete conversions and very high *ee* values of 97.8–99.6% by using 1 mol% Ru-catalyst derived from ligand **7** (Table 2). A slight decrease in enantiomeric excess was observed when an electron-withdrawing bulky substituent was placed in the *ortho* position of the aryl group. Such a level of enantioselectivity is the highest observed for the hydrogenation of β-aryl ketoesters. Low conversion (<10%) and *ee* values (<60%) were observed when the hydrogenation of ethyl benzoylacetate was carried out with 0.1% catalyst loading. Interestingly, however, a much higher conversion (90%) and *ee* value (97.6%) were obtained when the same reaction was carried out in the presence of 0.1 mol% Ru–**7** catalyst and 0.2 mol% $AgSbF_6$ or AgOTf (OTf = trifluoromethanesulfonate), presumably because of a counterion effect that facilitates the binding of ketoester substrates. The tunable nature of this family of chiral diphosphanes should allow them to be applied to other asymmetric catalytic processes.

Remarkable enhancement of the *ee* values by the 4,4′-substituents on binap can be rationalized by molecular modeling studies (Figure 1). Unlike the analogous β-alkyl ketoesters, the aryl group on the β-aryl ketoesters can form weak π–π stacking interactions with one of the phenyl groups on binap in the disfavored transition state, which will slightly stabilize the disfavored transition state and lead to a deterioration in the enantiomeric excess. In contrast, bulky substituents at the 4,4′-positions will have significant repulsive interactions with the aryl group, cause destabilization of the disfavored transition state, and thus enhance the enantioselectivity drastically.

We have also attempted to immobilize Ru-catalysts based on 4,4′-substituted-binap derivatives in RTILs. RTILs have recently received much attention as alternative reaction media because they are nonvolatile, thermally and oxidatively stable, and weakly coordinating.[16] In particular, RTILs represent viable alternative solvents for the synthesis of high-value chiral organic compounds by catalytic processes. RTILs have indeed been used as alternative solvents for the asymmetric hydrogenation of a variety of prochiral substrates.[17] Ideally, the organic products could be separated by extraction with nonpolar solvents and the ionic liquid phase containing the active catalyst could be reused.

As shown in Table 2, Ru–**6** and Ru–**7** catalysts are highly active for catalytic asymmetric hydrogenation of a wide range of β-aryl ketoesters in the homogeneous 1-butyl-3-methyl-

Table 2: Ru-catalyzed asymmetric hydrogenation of β-aryl ketoesters with **6** and **7** as the ligand.



Ar	R	**7** MeOH	**7** RTIL/MeOH	**6** MeOH	**6** RTIL/MeOH
Ph	Et	99.5[c]	98.9	97.2	99.3
4′-MeO-Ph	Et	99.5[d]	94.4	94.0	95.9
4′-F-Ph	Me	99.3[e]	98.1	97.1	98.9
4′-Cl-Ph	Me	99.1[e]	97.8	97.6	98.3
2′-Cl-Ph	Me	99.6[f]	98.9	97.2	99.8
4′-CF_3-Ph	Me	99.0[e]	98.4	97.2	98.9
3′-CF_3-Ph	Me	98.4[f]	98.9	98.4	98.8
2′-CF_3-Ph	Me	97.8[e]	96.7	97.3	97.5

[a] All reactions were carried out under 1400 psi of hydrogen gas in methanol at room temperature for 20 hours with 1 mol% catalyst loading. [b] All the reactions were judged to have >98% conversions based on the integrations of NMR signals for the material and product. [c] The *ee* value (%) was determined by GC using a Superco γ-Dex 225 column. [d] The *ee* value (%) was determined by supercritical fluid chromatography using a Chiralpak AS column. [e] The *ee* values (%) were determined by GC using a Superco β-Dex 120 column. [f] The *ee* values (%) were determined by high-performance liquid chromatography using a Chiralpak AD column.

imidazolium tetrafluoroborate ($BMImBF_4$)/methanol system. A slight deterioration in *ee* values (1%) was observed for the Ru–**7** catalysts in the RTIL, while an increase (up to 2.6%) was seen for the Ru–**6** catalysts in the RTIL (Table 2). This result is consistent with our earlier observation that the polar nature of asymmetric catalysts can lead to enhanced performances in RTILs.[17d] Both Ru catalysts were recycled and reused four times, with *ee* values (conversions) of 97.3 (>98), 93.9 (94), 85.7 (81), and 95.1% (62%) for Ru–**6** and 97.5 (>98), 86.9 (91), 82.7 (77), and 75.7% (44%) for Ru–**7**. Direct current plasma (DCP) spectroscopic analysis showed that no appreciable leaching of Ru occurred during the extraction of the organic products. We estimated from DCP experiments that less than 0.02 and 0.04% of the Ru catalysts leached into the organic layer for the Ru–**6** and Ru–**7** systems, respectively. Thus we believe that the deterioration in the conversion rates and *ee* values for the reused catalysts is probably because of the instability of the active Ru–hydride species.

In summary, we have synthesized a family of tunable 4,4′-substituted binap derivatives and applied them to a highly enantioselective hydrogenation of β-aryl ketoesters in both methanol and a RTIL by taking advantage of the 4,4′-substituent effects. The easy tunability of this family of chiral diphosphanes should allow other synthetically useful asymmetric catalysts to be developed.

Experimental Section

Detailed synthetic procedures and spectroscopic data for 4,4′-substituted binap derivatives can be found in the Supporting Information. Typical procedure for the synthesis of the Ru precatalyst: A mixture of $[\{RuCl_2(benzene)\}_2]$ (23 mg, 0.046 mmol) and 4,4′-Br-BINAP (**1**) (78 mg, 0.1 mmol) in anhydrous DMF (2 mL) was heated at 100°C under argon for 30 min and then cooled to 25°C. The solvent was removed under vacuum to give a dark red solid, which was used for asymmetric hydrogenation without purification.

Typical procedure for the asymmetric hydrogenation of β-aryl ketoesters: Ethyl benzoylacetate (47 μL, 0.25 mmol) and anhydrous methanol (1 mL) were added to the Ru precatalyst (3.0 mg, 2.5 μmol) previously loaded into a teflon-capped vial in a dry box under argon. The vial was quickly transferred into a stainless-steel autoclave and sealed. After purging the autoclave with hydrogen gas six times, the final pressure of the hydrogen gas was adjusted to 1400 psi. After 20 h, the hydrogen gas pressure was released and water (10 mL) was added. The hydrogenated product was extracted with diethyl ether and passed through a small column of silica gel. The conversions were

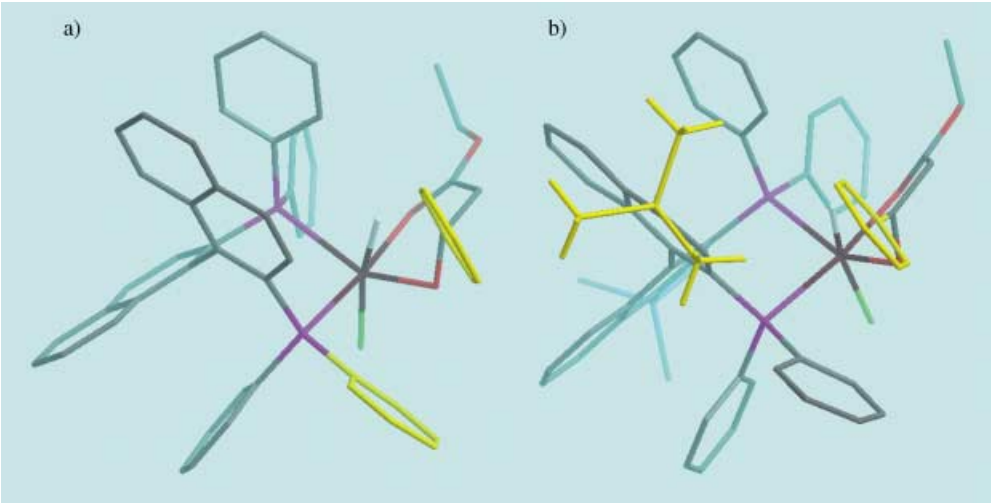


Figure 1. PC Spartan-generated models for the disfavored transition state of a) [Ru((*R*)-binap)(H)(Cl)(ethyl benzoylacetate)] and b) [Ru(4,4′-TMS-(*R*)-binap)(H)(Cl)(ethyl benzoylacetate)]. The groups shown in yellow have dominant interactions.

assessed based on the integration of the peaks of the products and starting materials in the ^{1}H NMR spectra, while the *ee* values were determined by gas chromatography, high-performance chromatography, or supercritical fluid chromatography.

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