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Benzimidazoles as Ligands in the Ruthenium-Catalyzed Enantioselective Bifunctional Hydrogenation of Ketones

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A series of $Cl_2Ru(diphosphane)L_2$ (II) complexes in which L = *N*1-alkylated benzimidazoles, bonding to the metal through nitrogen, have been synthesized and characterized. In the case of 1-methylbenzimidazole, the resulting complexes exist as statistical mixtures of all possible conformational isomers. When the size of the substituent on the benzimidazole was increased to complexes could be prepared that exist as a single diastereomer. All complexes possessing benzimidazole ligands bound to the ruthenium center are active for the mild and chemoselective hydrogenation of ketones in the presence of alkenes. Catalysts that exist as a single diastereomer, prepared with enantiomerically pure diphosphanes, catalyze the hydrogenation of prochiral ketones with moderate levels of enantioselectivity that are significantly improved relative to catalysts existing in several conformations.

Introduction

The hydrogenation of carbonyl compounds is an important reaction on both laboratory[1] and industrial[2] scales. Considering the complexity and functional group density of common synthetic targets, efficient and chemoselective methods to affect this transformation are necessary.[3] Furthermore, the development of enantioselective methods to affect this transformation is highly desirable.[4]

The greatest breakthrough in this field has come from the Noyori laboratories,[5] where it was discovered that the addition of a protic diamine to ruthenium diphosphane species results in catalysts displaying extraordinary chemoselectivity for carbonyl groups over olefins under relatively mild hydrogenation conditions.[6,7] Furthermore, proper matching of a chiral diamine, for example (*R*,*R*)-diphenylethylenediamine (dpen), with the correct enantiomer of a chiral ruthenium diphosphane (e.g., $Cl_2Ru((R)$-Binap); Binap=2,2′-bis(diphenylphosphino)-1,1′-binapthyl) produces an exceptionally enantioselective precatalyst, with high turnover numbers and frequencies[8−12] (Scheme 1). Noyori's research group,[13] among others,[14−17] has investigated the mechanism of this reaction, with the aim of explaining its remarkable reactivity and selectivity.

It is clear from numerous studies that the presence of a diamine ligand bearing at least one N−H bond is critical for high activity and chemoselectivity;[6,18] however, the precise explanation of this effect has been the subject of recent debate. The most commonly accepted mechanism has the reaction occurring through a six-membered, concerted transition state, in which the metal is coordinatively saturated, preventing coordination of substrates directly to the metal and instead promoting their interaction with the coordinating ligands.[13,15,19] The protic amine is believed to act as a Brønsted acid, activating the carbonyl compound to reduction by the metal hydride, which adds to the carbonyl carbon concurrently with the proton of the diamine ligand, simultaneously generating a Ru−N double bond. This rationale also

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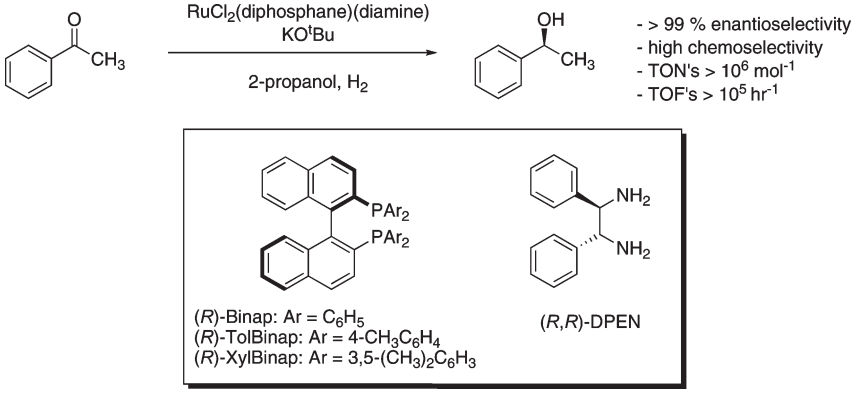
Scheme 1. Representative Hydrogenation of a Simple Aromatic Ketone under Noyori Conditions



explains the chemoselectivity of this system, since the less basic, electronically symmetrical π system of the alkene interacts poorly with the weakly acidic bound amine. The orthogonal electrostatics of the diamine and hydride ligands and the unique reactivity they impart to the system lead to the use of the phrase "bifunctional catalysis" to describe this process.[5,20,21]

Stoichiometric studies by Bergens on this system have shown that while the protic diamine may act as a binding point for the nucleophilic oxygen atom, activating the π-bond toward attack of the hydride, its addition to the carbonyl does not necessarily occur concurrently with reformation of the Ru−N double bond.[22−24] As evidence for this alternative mechanism, they were able to isolate a ruthenium alkoxide resulting from a 1,2-addition of the carbonyl. This suggests that, after reduction of the bound carbonyl compound, the amine ligand is deprotonated by the alkoxide base present in solution, generating a lone pair on nitrogen that ejects the alkoxide and forms the ruthenium−amide complex proposed by Noyori to be the catalyst resting state.

Interested by these observations, we endeavored to discover whether alternative Lewis acidic functional groups might be capable of promoting the hydrogenation of carbonyl compounds. Bergens has previously demonstrated that Ru bisphosphane catalysts modified by pyridyl substituents instead of protic diamines are capable of affecting the hydrogenation of ketones with enantioselectivities up to 49% ee.[25] It is well-known from the preparation of *N*-heterocyclic carbene chemistry that the C2 position of *N*, *N*′-disubstituted imidazolium[26a] and benzimidazolium[26b] salts are sufficiently acidic to be deprotonated by relatively mild alkoxide bases (Figure 1). Furthermore, in studies of

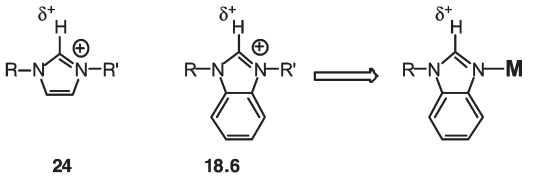


Figure 1. Relative acidities of imidazolium and benzimidazolium cations in DMSO and representative polarization of the C2−H bond by coordination of benzimidazole to a metal.

ionic liquids, α values of Kamlet−Taft parameters for imidazoliums have been determined and these solvents are about as protic as *tert*-butyl alcohol (0.627[27] versus 0.68,[28] respectively). A recent example in the literature has also shown that imidazolium-based ionic liquids are capable of acting as protic catalysts in the BOC protection of phenols.[29]

In analogy with benzimidazolium cations, coordination of the basic nitrogen of 1-substituted benzimidazoles results in polarization of the C2−H bond in a manner similar to alkylation at this position (Figure 1). Coordinative saturation of the metal is important (vide supra); therefore, in order to generate a chemoselective hydrogenation catalyst, addition of 2 equivalents of the benzimidazole to a Ru(diphosphane) precursor would be required. Herein we report the synthesis of a number of ruthenium−diphosphane precatalysts disubstituted with benzimidazole ligands and their application in the chemoselective hydrogenation of aromatic ketones under relatively mild conditions.

Results and Discussion

In order to generate the desired benzimidazole-substituted Ru complex, Cl_2Ru(*rac*-Binap) was reacted overnight with 2 equivalents of methylbenzimidazole (BIMe) to give Cl_2Ru(*rac*-Binap)$(BIMe)_2$ (**1**) in 46% yield after recrystallization. ^{31}P NMR of a pure sample of the orange solid in C_6D_6 showed signals attributable to a mixture of three different diastereomeric conformers: two singlets (one sharp and one broad) and a pair of doublets. The two conformers represented in the ^{31}P NMR by singlets, stem from two C_2-symmetric systems in which the phosphorus atoms of the Binap ligand are magnetically equivalent. The other conformer, which

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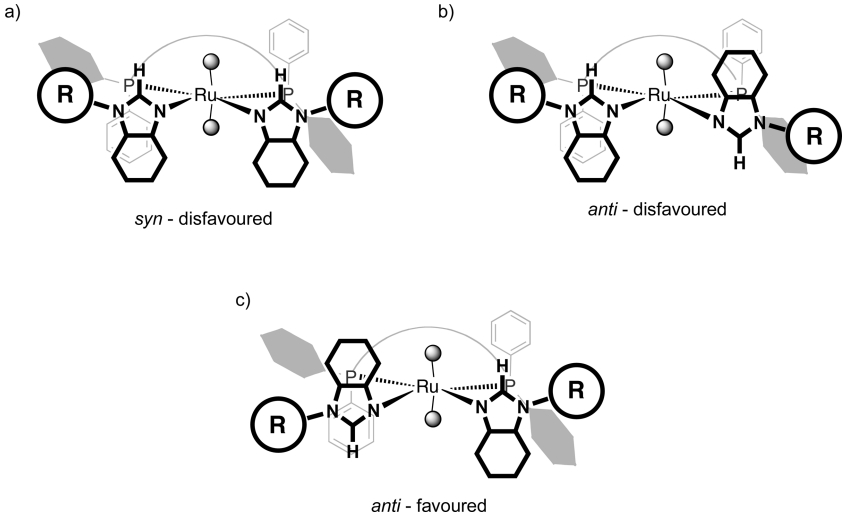
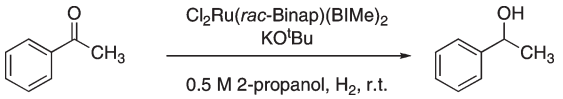


Figure 2. Possible conformations of the benzimidazole ligands bound to Cl_2Ru(diphosphane).

Table 1. Catalytic Results in the Hydrogenation of Acetophenone with Cl_2Ru((*rac*)-Binap)$(BIMe)_2$ (1)



entry	amt of Ru (mol %)	amt of KO^{t}Bu (mol %)	time (h)	amt of H_2 (atm)	yield (%)[a]
1	1	10	3	10	>98
2	0.1	1	3	5	50
3	0.1	1	3	1	14
4	0.1	1	16	0	9

[a] Yields determined by ^{1}H NMR with an internal standard (1,4-dimethoxybenzene).

gives a pair of doublets in the ^{31}P NMR, indicates that the two phosphorus atoms of the Binap ligand are inequivalent in this conformer. NMR evidence also indicates that two benzimidazoles are bound to a single ruthenium center, resulting in coordinatively saturated and octahedral complexes. Interestingly, addition of 1 equivalent of methylbenzimidazole per mole of ruthenium results only in the formation of complex **1** and Cl_2Ru(*rac*-Binap); no other species could be detected by ^{31}P NMR, illustrating the strong preference in this system for coordinative saturation.

Once bound to Ru, the benzimidazole ligands can exist in two possible conformations, syn and anti, relative to each other with the *N*1 methyl substituents on the same or opposite sides of the plane defined by P−Ru−P, respectively. In addition to this, the presence of the C_2-symmetric Binap ligand further differentiates these planes into two inequivalent quadrants, allowing for two possible anti conformations, both of which have overall C_2 symmetry (Figure 2b,c). On the basis of the ^{31}P NMR spectra, **1** appears to exist as a mixture of all three of these conformations. Analysis of a related compound by X-ray crystallography confirms this hypothesis (vide infra).

In order to test the catalytic activity of this benzimidazole-containing Ru complex, acetophenone was exposed to catalyst **1** in basic 2-propanol at room temperature. The reduction of acetophenone was complete in 3 h under mild conditions (100:10:1 substrate/KO^{t}Bu/Ru, 0.5 M in 2-propanol, 293 K, 10 atm of H_2). This is in stark contrast to Cl_2Ru(Binap) itself, which is essentially unreactive under identical conditions, without the addition of a diamine or benzimidazole. To further test the ability of **1** as a hydrogenation catalyst, its loading was decreased to 0.1% and the pressure of hydrogen gas in the reactions reduced. The turnover frequency was greatly reduced upon lowering the pressure of hydrogen from 5 to 1 atm (Table 1, entries 2 and 3), and very little conversion was observed when the reaction was performed under an atmosphere of argon (<10% after 16 h). The dependence of the reaction rate on hydrogen pressure suggests that the primary mechanism of ketone reduction is hydrogenation and not transfer hydrogenation as might be expected from use of a solvent such as 2-propanol. In the latter case, hydrogen gas would not be required, and the metal hydride would be regenerated by oxidation of the solvent to acetone.

On the basis of our initial hypothesis, after formation of a ruthenium hydride, coordination of the carbonyl oxygen to the C2−H of one of the benzimidazoles may occur, orienting and activating the carbonyl toward insertion, forming a ruthenium alkoxide. Unlike Noyori's catalysts, however, deprotonation of the assisting ligand (in our case the benzimidazole, in Noyori's the diamine) likely does not occur, and the protic solvent likely facilitates release of the product molecule. It is also possible that an alternative mechanism for hydrogenation is responsible for the observed reactivity, since there have been some reports of hydrogenations with non-*N*-protic complexes.[25]

Although complex **1** obviously displayed the desired catalytic activity, the presence of multiple conformations did not bode well for eventual enantiodiscrimination. In fact, C_2-symmetric metal−BINAP complexes are known to react

with high enantioselectivity in a variety of processes, since the number of possible diastereomeric transition states is reduced by a factor of 2. In the case of Binap-derived and related ligands, the remaining binding sites on the metal are differentiated into pairs of sterically hindered and open quadrants by the edge-on and face-on phenyl groups of the chelating diphosphane.[30] Thus, we hypothesized that if a large substituent were employed on the benzimidazole, steric interactions between this group and the phenyl substituents of BINAP might enforce only one binding mode of the benzimidazole, resulting in a compound with overall C_2 symmetry (Figure 2c). If steric congestion in the quadrant is not great enough, the two substituents can face the same way (Figure 2, syn conformation a) or even adopt an anti conformation with the substituents of both benzimidazoles in unfavorable quadrants (Figure 2b). As mentioned above, this is believed to be the case for 1-methylbenzimidazole-substituted compound **1**, whose ^{31}P NMR spectrum is consistent with a near-equal mixture of all possible conformations. On the basis of this hypothesis, we prepared complexes with larger substituents at this position.

Thus, $Cl_2Ru((R)$-TolBinap) (TolBinap = 2,2′-bis(di-4-tolylphosphino)-1,1′-binaphthyl) was reacted with a number of different benzimidazoles substituted at N1 with alkyl groups of increasing size (BIR, where R = Me, Et, Ph, Bz, CPh_3) and the resulting solids were analyzed by ^{31}P NMR in C_6D_6. Compound **2a** (R = Me) yielded a ^{31}P NMR spectrum nearly identical with that of its racemic counterpart **1**, again consisting of a mixture of diastereomers (vide supra). Increasing the size of the substituent at N1 on the benzimidazole had little effect on the distribution of the mixture of diastereomers for compounds BIEt, BIPh, and BIBz as observed by ^{31}P NMR; however, **2b** (R = CPh_3) exhibits only a single resonance in the ^{31}P NMR with no evidence of any other diastereomer. This indicates that the very large R substituent at N1 has induced only the favorable C_2-symmetric conformation in which the R substituents on the two cis benzimidazoles are oriented anti to one another. The ^1H NMR spectra are also consistent with the existence of a single species in solution. A similar synthesis was performed with $Cl_2Ru((R)$-XylBinap) (XylBinap=2,2′-bis(3,5-xylylphosphino)-1,1′-binaphthyl) to prepare $Cl_2Ru((R)$-Xylbinap)$(BIMe)_2$ (**3a**) and $Cl_2Ru((R)$-XylBinap)$(BICPh_3)_2$ (**3b**) in 23 and 28% yields, respectively, after recrystallization. Apart from the additional methyl signals attributable to the xylyl groups, the spectra were analogous to those of the TolBinap-based complexes. The ^{31}P NMR spectra of Cl_2Ru(XylBinap) after reaction with 2 equiv of BIMe (**3a**) and $BICPh_3$ (**3b**) are shown in Figure 3.

X-ray-quality crystals of **3a** were obtained by slow diffusion of hexanes into a dichloromethane solution of **3a**, which further confirmed our hypothesis of its molecular structure. The solid-state structure is a distorted octahedron about Ru, with the two benzimidazoles positioned cis to one another and the chlorines trans. Consistent with our interpretation of the NMR spectra of this and related compounds, the crystal is a statistical mixture of three conformational diastereomers, one syn and two anti. The two anti conformations are nonidentical C_2-symmetric structures. The benzimidazoles are canted slightly and appear nearly parallel to the axial xylyl rings of the XylBinap ligand, possibly as a result of π stacking between the two aromatic groups. Two of the possible conformers are displayed in Figure 4, and the crystallographic data are presented in Table 2.

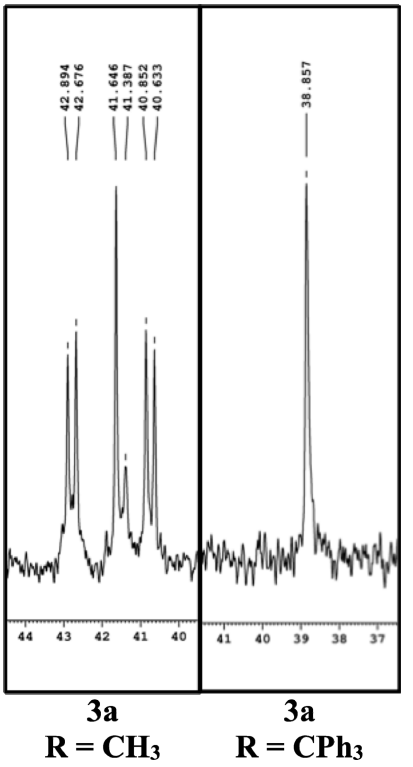


Figure 3. Relevant areas of the $^{31}P\{^1H\}$ spectra of compounds **3a** and **3b**.

The catalytic activity of these new complexes, synthesized from chiral enantiomerically pure diphosphane ligands, was then tested in the hydrogenation of acetophenone under our standard conditions (1000:10:1 ketone/KO^{t}Bu/Ru, 0.5 M in 2-propanol, 5 bar of H_2, 293 K) (Table 3). The methylbenzimidazole-modified catalyst (**2a**) gave the *S* enantiomer of the product alcohol in 27% ee (Table 3, entry 1). Increasing the size of the group on the benzimidazole from methyl to ethyl and eventually phenyl and benzyl resulted in only modest increases in the observed enantioselectivity. As expected, however, a large increase in enantioselectivity was observed for the catalyst substituted with 2 equivalents of *N*-(triphenylmethyl)benzimidazole, which gave *sec*-phenethanol in 67% ee. Thus, it appears that the presence of only one diastereomeric form in solution does lead to a more enantioselective catalyst. By decreasing the temperature of the reaction to 273 K and increasing the pressure of hydrogen gas pressure to 20 bar, a slight increase to 71% ee was achieved (Table 3, entry 6). The use of the slightly bulkier (*R*)-XylBinap as the chiral diphosphane gave marginal increases in enantioselectivity relative to the TolBinap catalysts.

Interestingly, the hydrogenation of acetophenone with **2b** does proceed under a nitrogen atmosphere (i.e., in the absence of hydrogen gas), however, at a significantly diminished rate. If the reaction is carried out under 5 atm H_2, it reaches completion in 6 h; however, under a nitrogen atmosphere, only 7% yield is achieved after 6 h and only 60% after 72 h. The presence of base in the catalytic reaction is also essential; in its absence no conversion is observed.

Using catalyst **2b**, we then examined the effect of solvent on the reaction (Table 4). Neither CH_2Cl_2 nor THF gave any

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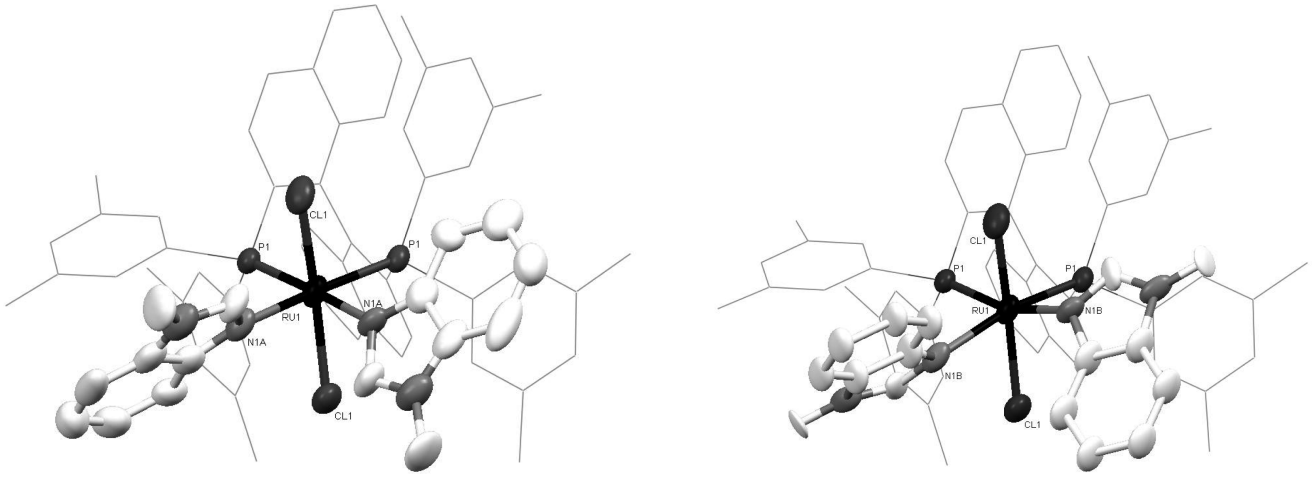

Figure 4. Crystallographically determined structure of **3a** with selected atoms displayed as ellipsoids at the 50% confidence level. Hydrogen atoms have been omitted for clarity. Two of the three different diastereomeric conformations present in the unit cell are shown. Selected interatomic distances (Å) and angles (deg): Ru(1)−N(1A), 2.187(6); Ru(1)−N(1B), 2.20(2); Ru(1)−P(1), 2.3042(11); Ru(1)−Cl(1), 2.4206(12); N(1A)−Ru(1)−N(1A)#1, 81.9(3); N(1B)−Ru(1)−N(1B)#1, 104.3(10); N(1B)−Ru(1)−N(1A)#1, 91.5(5); N(1A)#1−Ru(1)−P(1), 94.28(14); N(1B)#1−Ru(1)−P(1), 84.8(5); N(1A)−Ru(1)−P(1)#1, 94.28(14); P(1)−Ru(1)−P(1)#1, 89.52(5); Cl(1)−Ru(1)−Cl(1)#1, 166.76(6).

Table 2. Crystallographic Information for Compound 3a

formula	$C_{68}H_{64}Cl_2N_4P_2Ru{\bullet}C_4H_8O$
fw	1243.25
T (K)	180(2)
color/habit	orange/prism shaped
cryst dimens (mm^3)	$0.25 \times 0.16 \times 0.08$
cryst syst	orthorhombic
space group	$C222(1)$
a (Å)	12.5121(16)
b (Å)	22.639(3)
c (Å)	21.746(3)
β (deg)	90
V ($Å^3$)	6162.6(13)
Z	4
D_{calcd} (Mg/m^3)	1.34
μ (mm^{-1})	0.441
$F(000)$	2592
θ range (deg)	1.80 - 25.99
index ranges (h,k,l)	$\pm 15, \pm 27, \pm 26$
no. of rflns collected	30803
no. of indep rflns/R_{int}	6045/0.0783
no. of data/restraints/params	6045/12/436
R1/wR2 ($I > 2\sigma(I)$)[a]	0.0446/0.0898
R1/wR2 (all data)[a]	0.0671/0.1000
GOF (on F^2)[a]	1.022
largest diff peak/hole (e $Å^{-3}$)	0.653/−0.692

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$; $wR2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$; $GOF = \{\sum[w(F_o^2 - F_c^2)^2]/(n-p)\}^{1/2}$.

reaction, but aromatic solvents such as benzene and toluene were effective, giving comparable enantioselectivities. Interestingly, the use of *tert*-butyl alcohol as the solvent gave a much less reactive system than 2-propanol under the same conditions (entries 6 and 7, Table 4, the reaction was performed at 303 K instead of 293 K; mp(*tert*-butyl alcohol) 298 K). Given the slow rate of background transfer hydrogenation operative in this system, this is quite surprising but could be attributable to the larger size of size of *tert*-butyl alcohol making approach into the coordination sphere of the metal to protonate and release a possible ruthenium−alkoxide intermediate more difficult.

Having chosen 2-propanol as our optimal solvent and encouraged by the moderate enantioselectivities achieved with this catalyst system, we next examined the effect of different chiral diphosphanes on the catalyst precursor. In the recent literature, a number of atropisomeric chiral diphosphanes have been reported which have shown exceptional results when employed as ligands in asymmetric hydrogenations.[31−35] We chose a number of these diphosphanes (Chart 1), and, using a similar procedure for **2b**, prepared the analogous ruthenium precatalysts (**4**−**8**) in moderate to good yields after recrystallization from THF/hexanes solutions (Scheme 2). While all of these new ruthenium species were able to efficiently hydrogenate acetophenone under our standard conditions, giving quantitative conversion in less than 6 h, none of them gave better enantioselectivity than the BINAP-based catalysts **2b** and **3b** (Table 5). Interestingly, catalyst **8**, prepared using (*R*)-XylPhanePhos, gives a nearly racemic product mixture, with a slight excess of the opposite enantiomer (Table 5, entry 7); this is consistent with previous reports in which (*R*)-PhanePhos matches with (*S,S*)-dpen (the opposite match to (*R*)-Binap) to give the *R* enantiomer.[35]

With 2-propanol as the solvent, and **3b** as our best catalyst, the hydrogenation of a number of other aromatic ketones was examined (Table 6). Under these conditions, benzophenone was readily reduced (Table 6, entry 1), negating the possibility of the catalyst hydrogenating an enolate intermediate. While aryl methyl ketones with mildly electron withdrawing groups *p*-bromo and *p*-fluoro or electron-donating *p*-methoxy groups were all hydrogenated at faster rates than was acetophenone, *p*-nitroacetophenone (Table 6, entry 2) was completely unreactive under our standard conditions. Of the compounds that were reactive, the highest

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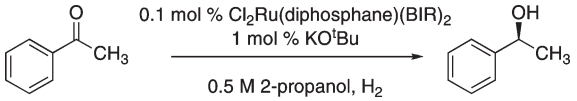
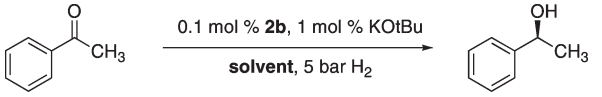
Table 3. Hydrogenation of Acetophenone with Cl_2Ru(diphosphane) Precatalysts Bis-Substituted with Different Benzimidazoles[a]



entry	catalyst	amt of H_2 (atm)	temp (K)	TOF (h^{-1})[b]	ee (%)[c]
1	Ru((*R*)-TolBinap)Cl_2	5	293	NR[d]	ND[e]
2	**2a**	5	293	320	27
3	**2b**	5	293	162	67
4	**3a**	5	293	293	34
5	**3b**	5	293	210	72
6	**2a**	20	273	67	71

[a] Reaction conditions: 1000:10:1 ketone/KO^{t}Bu/Ru, 0.5 M in 2-propanol, H_2 gas. [b] Turnover frequencies determined at low conversion (t_R = 1.5 h) by ^{1}H NMR. [c] % ee was determined using supercritical fluid chromatography. [d] No reaction was observed after 1.5 h. [e] % ee not determined.

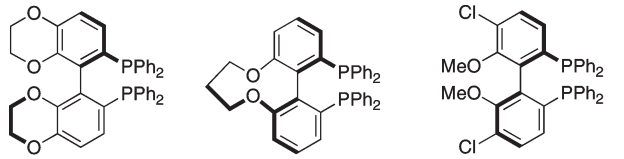
Table 4. Optimization of the Solvent in Hydrogenation of Acetophenone by Catalyst 2b[a]

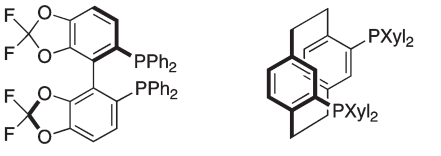


entry	solvent	TOF (h^{-1})[b]	ee (%)
1	2-propanol	162	67
2	THF	NR[c]	ND
3	CH_2Cl_2	NR[c]	ND
4	benzene	40	70[d]
5	toluene	80	58
6[e]	*tert*-butyl alcohol	88	31
7[e]	2-propanol	282	30

[a] Reaction conditions: 1000:10:1 ketone/KO^{t}Bu/Ru, [substrate] = 0.5 M, 5 bar of H_2, 293 K. [b] Turnover frequencies determined at low conversion (t_R = 1.5 h) by ^{1}H NMR. [c] % ee was determined using supercritical fluid chromatography. [d] Catalyst **3b** used instead of **2b**. [e] T = 303 K.

Chart 1. Chiral Atropisomeric Diphosphane Ligands Used in This Study[31−35]

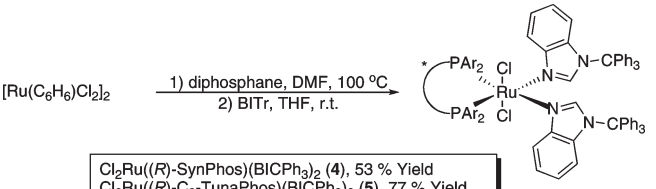




enantioselectivity was observed for the methylene dioxy substrate shown in entry 6, at 70% ee; all others gave enantioselectivities in the 50% range.

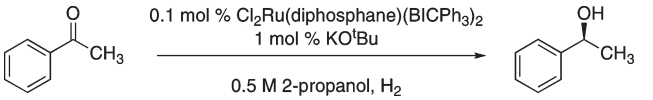
Finally, we examined the chemoselectivity of catalyst **3b** under our optimized conditions for the hydrogenation of acetophenone versus the isoelectronic alkene α-methylstyrene (Scheme 3). At complete conversion of the ketone to its corresponding alcohol, only a 6% yield of the corresponding styrene was detected by GC, indicating a greater than 15:1 selectivity for the carbonyl functionality under these

Scheme 2. Synthesis of 1-(Triphenylmethyl)benzimidazole-Modified Ruthenium−Diphosphane Precatalysts



Cl_2Ru((*R*)-SynPhos)($BICPh_3$)$_2$ (**4**), 53 % Yield
Cl_2Ru((*R*)-C_3-TunaPhos)($BICPh_3$)$_2$ (**5**), 77 % Yield
Cl_2Ru((*R*)-Cl-OMe-BIPHEP)($BICPh_3$)$_2$ (**6**), 58 % Yield
Cl_2Ru((*R*)-FluorPhos)($BICPh_3$)$_2$ (**7**), 79 % Yield
Cl_2Ru((*R*)-XylPhanePhos)($BICPh_3$)$_2$ (**8**), 22 % Yield

Table 5. Turnover Frequencies and Enantioselectivities of 1-(Triphenylmethyl)benzimidazole-Modified Ruthenium−Diphosphane Precatalysts[a]



entry	diphosphane	TOF (h^{-1})[b]	ee (%)[c]
1	(*R*)-TolBinap (**2b**)	162	67
2	(*R*)-XylBinap (**3b**)	210	72
3	(*R*)-SynPhos (**4**)	302	57
4	(*R*)-C_3-TunaPhos (**5**)	337	59
5	(*R*)-Cl-OMe-BIPHEP (**6**)	261	4
6	(*R*)-FluorPhos (**7**)	388	65
7	(*R*)-PhanePhos (**8**)	306	−8

[a] Reaction conditions: 1000:10:1 ketone/KO^{t}Bu/Ru, 0.5 M in 2-propanol, 5 atm of H_2, 293 K. [b] Turnover frequencies determined at low conversion (t_R = 1.5 h) by ^{1}H NMR. [c] % ee was determined by using supercritical fluid chromatography.

conditions. While not nearly as selective as Noyori's diamine-modified catalyst, the observed preference for carbonyl hydrogenation is consistent with the catalyst acting similarly to those prepared with NH diamines. The decrease in selectivity relative to the Noyori catalyst may be related directly to the decreased rate of turnover of our catalyst relative to Noyori's, making the alkene hydrogenation more competitive. Alternatively, dissociation of one of the monodentate benzimidazole ligands to give an open coordination site capable of binding the alkene may also occur.

Conclusions

A number of ruthenium-diphosphane bis-benzimidazole complexes have been prepared and characterized. Through crystallographic and NMR analysis, it has been demonstrated

Scheme 3. Intermolecular Competition Experiment between Acetophenone and α-Methylstyrene

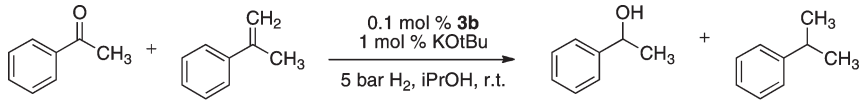
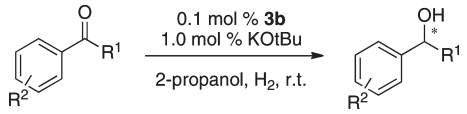


Table 6. Hydrogenation of Various Aromatic Ketones with $Cl_2Ru(XylBinap)_2(BICPh_3)_2$[a]



entry	R^1	R^2	TOF (h^{-1})[b]	ee (%)[c]
1	Ph	H	375	N/A
2	CH_3	*p*-NO_2	NR	ND
3	CH_3	*p*-F	332	52
4	CH_3	*p*-Br	286	55
5	CH_3	*p*-OCH_3	351	56
6[d]	CH_3	*m,p*-OCH_2O	126	70

[a] Reaction conditions: 1000:10:1 ketone/KO^tBu/Ru, 0.5 M in 2-propanol, 5 atm of H_2, 293 K. [b] Turnover frequencies determined at low conversion (t_R = 1.5 h) by ^1H NMR. [c] % ee was determined using by supercritical fluid chromatography. [d] Solvent 4:1 2-propanol/toluene.

that the relative conformations of the benzimidazoles within the complexes are dependent on the N1 substituent present on the benzimidazole; small substituents such as methyl give mixtures of all possible conformations, while the very large triphenylmethyl results in a single C_2-symmetric conformation. Benzimidazole modification of chiral ruthenium diphosphanes resulted in complexes capable of hydrogenating carbonyls under mild conditions both enantioselectively and chemoselectively. While these studies are far from providing conclusive evidence for one mechanism in preference to the other, they do demonstrate that Ru complexes ligated by species other than monoprotic diamines are capable of catalyzing the chemo- and enantioselective hydrogenation of ketones.

Experimental Section

General Considerations. $[Ru(C_6H_6)Cl_2]_2$, chiral diphosphanes, methylbenzimidazole, ketone substrates, and potassium *tert*-butoxide were purchased from commercial sources and used as received. Isopropyl alcohol was dried and purified by distillation from magnesium activated with iodine. Benzene, d_6-benzene, and *tert*-butyl alcohol were dried over CaH_2 and purified by distillation. All other solvents (THF, CH_2Cl_2, hexanes, toluene) were purified using an MBraun SPS solvent system. All solvents were purged of oxygen using a minimum of three freeze−pump−thaw cycles before being brought into the glovebox. ^1H and $^{13}C\{^1H\}$ NMR spectra were performed using Bruker Avance 400 and 500 MHz spectrometers. Elemental analysis was performed by Canadian Microanalytical Systems Ltd. X-ray data collection was performed on a Bruker SMART CCD 1000 X-ray diffractometer. Analytical supercritical fluid chromatography (SFC) was performed on a Berger SFC HPLC using the specified Chiracel Berger Silica column and specified conditions of coeluent, flow rate, and pressure in order to determine enantiomeric purity.

1-(Triphenylmethyl)benzimidazole. In a 100 mL flame-dried round-bottom flask was added benzimidazole (1.00 g, 8.46 mmol) and 20 mL of THF. Once dissolved, the mixture was cooled in an ice bath and sodium hydride (264 mg, 11.0 mmol) added in a single portion. After the mixture was stirred for 30 min at 0 °C, trityl chloride (3.06 g, 11.0 mmol) and a catalytic amount of tetrabutylammonium iodide were added, the flask was fitted with a condenser, and the reaction mixture was refluxed for 24 h. The reaction mixture was then cooled to room temperature, quenched by the addition of water, and extracted three times with 100 mL of $CHCl_3$. The combined organic fractions were dried over $MgSO_4$, the solvent was evaporated, and the residue was purified by column chromatography (2:1 hexanes/EtOAc) to give 2.53 g of a yellow solid (82% yield). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.82 (s, 1H, NC*H*N); 7.70 (d, 1H, J = 8.1 Hz, Ar-C*H*); 7.26−7.05 (m, 16H, Ar-C*H*); 6.81 (t, 1H, J = 8.1 Hz); 6.39 (d, 1H, J = 8.1 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.6, 144.2, 141.4, 134.8, 130.0, 128.2, 128.0, 122.3, 122.0, 120.3, 115.4, 75.4. HRMS (EI-TOF): calcd for $[M]^+$ ($C_{26}H_{20}N_2$) m/z 360.1626, found 360.1620.

Synthesis of Catalysts (Cl_2Ru(diphosphane)(κ-*N3*-(1-R)-benzimidazole)$_2$. General Procedure. In a nitrogen atmosphere glovebox, $[Ru(C_6H_6)Cl_2]_2$ (0.050 mmol) and a chiral diphosphane (0.100 mmol) were added to a 50 mL Schlenk flask with a magnetic stirrer and the solids were dissolved in 5 mL of DMF. The reaction flask was then put on the Schlenk line and the solution degassed three times via freeze−pump−thaw cycles before being heated to 100 °C. After cooling to 35 °C, the volatiles were removed in vacuo overnight to give a brown, solid residue. The reaction flask was then brought back into the glovebox, the residue was dissolved in 10 mL of THF, benzimidazole was added (0.220 mmol), and the reaction mixture was stirred for 16 h. The reaction mixture was then concentrated to about 1 mL on the glovebox vacuum pump and the concentrated mixture filtered through a plug of Celite. This was then reduced to a minimal amount of THF, layered with hexanes, and recrystallized at −20 °C and the solid collected by filtration.

Cl_2Ru(*rac*-Binap)(κ*N3*-1-methylbenzimidazole)$_2$ (1). Orange solid, 46% yield. Anal. Found (calcd) for $C_{60}H_{48}Cl_2N_4P_2Ru\cdot H_2O$: C, 67.11 (66.91); H, 5.09 (4.68); N, 5.14 (5.20). ^{31}P NMR (C_6D_6, 161 MHz): δ 43.74 (d, J = 28 Hz), 43.03, 42.21 (br), 41.78 (d, J = 28 Hz). ^1H NMR (C_6D_6, 400 MHz): δ 9.45 (m, 2H, NC*H*N, three conformers); 8.83−8.17 (m, 12H, Ar-*CH*); 7.72−7.54 (m, 2H, Ar-CH_{Binap}, three conformers); 7.45−7.31 (m, 2H, Ar-CH_{BI}, three conformers); 7.01−6.39 (m, 24H, Ar-C*H*); 2.34, 2.30, 2.25 (6H, NCH_3, three conformers) ppm.

Cl_2Ru((*R*)-TolBinap)(κ*N3*-1-methylbenzimidazole)$_2$ (2a). Orange solid, 56% yield. Anal. Found (calcd) for $C_{64}H_{56}Cl_2N_4P_2Ru$: C, 68.60 (68.94); H, 5.20 (5.06); N, 5.03 (5.02). ^{31}P NMR (C_6D_6, 161 MHz): δ 41.40 (d, J = 35 Hz), 40.81, 40.20, 39.45 (d, J = 35 Hz). ^1H NMR (C_6D_6, 400 MHz): δ 9.48−9.27 (m, 2H, NC*H*N, three conformers); 8.87−8.10 (m, 12H, Ar-C*H*); 7.74−7.62 (m, 2H, Ar-CH_{Binap}, three conformers); 7.45−7.34 (m, 2H, Ar-CH_{BI}, three conformers); 7.08−6.30 (m, 20H, Ar-C*H*); 2.37, 2.32, 2.31 (6H, NCH_3, three conformers); 1.77, 1.74, 1.71 (12 H, $PC_6H_4CH_3$, three conformers).

Cl_2Ru((*R*)-TolBinap)(κ*N3*-1-(triphenylmethyl)benzimidazole)$_2$ (2b). Yellow solid, 74% yield. Anal. Found (calcd) for $C_{100}H_{80}Cl_2N_4P_2Ru$: C, 76.96 (76.42); H, 5.13 (5.56); N, 3.56 (3.62). ^{31}P NMR (C_6D_6, 161 MHz): δ 40.43 ppm. ^1H NMR (C_6D_6, 400 MHz): δ 9.03 (s, 2H, NC*H*N), 8.37 (m, 4H, Ar-CH_{P-Ar}), 8.15 (m, 2H, Ar-CH_{Binap}), 8.09 (d, 2H, J = 8.0 Hz, Ar-CH_{BI}), 8.01 (m, 4H, Ar-CH_{P-Ar}), 7.38 (d, 2H, J = 8.7 Hz, Ar-CH_{Binap}), 7.30 (d, 2H, J = 8.0 Hz, Ar-CH_{BI}), 7.01−6.87 (m, 30H, Ar-CH_{Tr}), 6.67 (d, 4H, J = 8.0 Hz, Ar-CH_{P-Ar}), 6.61 (t, 2H, J = 8.0, Ar-CH_{BI}), 6.48 (m, 6H, Ar-C*H*), 6.15 (d, 2H, J = 8.7 Hz), 1.93 (s, 6H, $C_6H_4CH_3$), 1.83 (s, 6H, $PC_6H_4CH_3$) ppm.

Cl_2Ru((*R*)-XylBinap)(κ*N3*-1-methylbenzimidazole)$_2$ (3a). Orange solid, 23% yield. ^{31}P NMR (C_6D_6, 161 MHz): δ 42.79 ppm (d, J = 36 Hz), 41.69, 41.43, 40.79 (d, J = 36 Hz). ^1H NMR (C_6D_6, 400 MHz): δ 9.34 (m, 2H, NC*H*N, three conformers); 8.90−8.69 (m, 2H, Ar-CH_{Binap}, three conformers); 8.45−7.98 (m, 6H, Ar-C*H*); 7.70−7.58 (m, 2H, Ar-CH_{Binap}, three conformers); 77.41−7.31 (m, 2H, Ar-CH_{BI}, three conformers); 7.06−6.20 (m, 16H, Ar-C*H*); 6.20, 5.96, 5.91 (4H, Ar-CH_{PAr}, three conformers); 2.32, 2.26, 2.21 (NCH_3, three conformers); 1.86, 1.72 (m, $PC_6H_3(CH_3)_2$, three conformers).

Cl_2Ru((*R*)-XylBinap)(κ*N3*-1-(triphenylmethyl)benzimidazole)$_2$ (3b). Yellow solid, 28% yield. Anal. Found (calcd) for $C_{104}H_{88}Cl_2N_4P_2Ru\cdot 2H_2O$: C, 75.45 (75.08); H, 5.59 (5.57); 3.47 (3.37). ^{31}P NMR (C_6D_6, 161 MHz): δ 38.86 ppm. ^1H NMR (C_6D_6, 400 MHz): δ 8.93 (s, 2H, NC*H*N), 8.36 (d, 2H, J = 8.4 Hz, Ar-CH_{BI}), 8.31 (m, 2H, Ar-CH_{Binap}), 7.86 (br, 4H, Ar-CH_{P-Ar}), 7.37 (d, 2H, J = 8.5 Hz, Ar-CH_{Binap}), 7.31 (d, 2H, J = 8.0 Hz, Ar-CH_{Binap}), 7.03−6.87 (m, 30H, Ar-CH_{Tr}), 6.78-6.57 (m, 14H, Ar-C*H*), 6.41 (m, 4H, Ar-CH_{BI}), 5.92 (s, 2H, Ar-CH_{P-Ar}), 1.90 (s, 12H, $PC_6H_3(CH_3)_2$), 1.79 (s, 12H, $PC_6H_3(CH_3)_2$).

Cl_2Ru((*R*)-SynPhos)(κ*N3*-1-(triphenylmethyl)benzimidazole)$_2$ (4). Yellow solid, 53% yield. Anal. Found (calcd) for $C_{92}H_{72}Cl_2N_4O_4P_2Ru\cdot H_2O$: C, 71.05 (71.31); H, 4.89 (4.81); N, 3.32 (3.62). ^{31}P NMR (C_6D_6, 161 MHz): δ 38.25 ppm. ^1H NMR (C_6D_6, 400 MHz): δ 9.09 (s, 2H, NC*H*N); 8.41 (m, 6H, Ar-C$H_{Binap,\ PAr}$); 8.21 (m, 4H, Ar-CH_{PAr}); 7.27 (m, 2H, Ar-CH_{biaryl}); 7.08−6.88 (m, 28H, Ar-C*H*); 6.73 (t, 4H, J = 7.3 Hz, Ar-CH_{PAr}); 6.64 (t, 2H, J = 7.7 Hz, ArCH_{BI}); 6.52 (d, 2H, J = 8.4 Hz, Ar-CH_{biaryl}); 6.46 (t, 2H, J = 7.7 Hz, Ar-CH_{BI}); 6.37 (d, 2H, J = 8.4 Hz, Ar-CH_{BI}); 3.48 (m, 8H, OCH_2) ppm.

Cl_2Ru((*R*)-C3-TunaPhos)(κ*N3*-1-(triphenylmethyl)benzimidazole)$_2$ (5). Brown solid, 77% yield. Anal. Found (calcd) for $C_{91}H_{72}Cl_2N_4O_2P_2Ru$: C, 73.52 (73.48); H, 4.88 (4.88); N, 3.77 (3.78). ^{31}P NMR (C_6D_6, 161 MHz): δ 42.48 ppm. ^1H NMR (C_6D_6, 400 MHz): δ 9.02 (s, 2H, NC*H*N); 8.44 (d, 2H, J = 8.5 Hz, ArCH_{BI}); 8.25−8.07 (m, 8H, Ar-C*H*); 7.23 (m, 2H, Ar-CH_{biaryl}); 7.10−6.43 (m, 40H, aromatic H); 6.38 (d, 2H, J = 8.5 Hz, Ar-CH_{BI}); 3.80−3.57 (m, 4H, OCH_2); 1.31 (m, 2H, $(OCH_2)_2CH_2$) ppm.

Cl_2Ru((*R*)-Cl-OMe-BIPHEP)(κ*N3*-1-(triphenylmethyl)benzimidazole)$_2$ (6). Yellow solid, 58% yield. Anal. Found (calcd) for $C_{90}H_{70}Cl_4N_4O_2P_2Ru\cdot H_2O$: C, 68.92 (69.19); H, 4.83 (4.64); N, 3.49 (3.59). ^{31}P NMR (C_6D_6, 161 MHz): δ 40.43 ppm. ^1H NMR (C_6D_6, 400 MHz): δ 9.00 (s, 2H, NC*H*N); 8.37 (d, 2H, J = 8.3 Hz, Ar-CH_{BI}); 8.14 (m, 8H); 7.28 (m, 2H, Ar-CH_{biaryl}); 7.01−6.72 (m, 44H); 6.67 (t, 2H, J = 7.3 Hz, Ar-CH_{BI}); 6.47 (t, 2H, J = 8.3 Hz, Ar-CH_{BI}); 6.42 (d, 2H, J = 8.1 Hz, Ar-CH_{BI}); 3.47 (s, 6H, OCH_3) ppm.

Cl_2Ru((*R*)-FluorPhos)(κ*N3*-1-(triphenylmethyl)benzimidazole)$_2$ (7). Yellow solid, 79% yield. Anal. Found (calcd) for $C_{90}H_{64}Cl_2F_4N_4O_4P_2Ru\cdot 2H_2O$: C, 67.42 (67.08); H, 4.14 (4.25); N, 3.48 (3.48). ^{31}P NMR (C_6D_6, 161 MHz): δ 41.96 ppm. ^1H NMR (C_6D_6, 400 MHz): δ 9.06 (s, 2H, NC*H*N); 8.31 (d, 2H, J = 8.5 Hz, Ar-CH_{BI}); 8.11 (m, 8H, Ar-CH_{P-Ar}); 7.09−6.65 (m, 46H, Ar-C*H*); 6.47 (t, 2H, J = 8.1 Hz, Ar-CH_{BI}); 6.40 (d, 2H, J = 8.1 ppm, Ar-CH_{BI}); 6.05 (d, 2H, J = 8.5 Hz, Ar-CH_{biaryl}) ppm.

Cl_2Ru((*R*)-XylPhanePhos)(κ*N3*-1-(triphenylmethyl)benzimidazole)$_2$ (8). Anal. Found (calcd) for $C_{100}H_{90}Cl_2N_4P_2Ru\cdot H_2O$: C, 75.46 (75.08); H, 6.21 (5.80); N, 3.64 (3.54). ^{31}P NMR (C_6D_6, 161 MHz): δ 33.69 ppm. ^1H NMR (C_6D_6, 400 MHz): δ 10.02 (m, 2H, Ar-CH_{Phane}); 9.68 (s, 2H, NC*H*N); 9.48 (d, 2H, J = 8.5 Hz, Ar-CH_{BI}); 9.23 (m, 2H, Ar-CH_{Phane}); 8.17 (m, 2H, Ar-CH_{Phane}); 7.24 (m, 12H, Ar-CH_{Tr}); 7.06−6.49 (m, 32H, Ar-C*H*); 6.41 (d, 2H, J = 8.5 Hz, ArCH_{Phane}); 6.19 (d, 2H, J = 8.5 Hz, ArCH_{biaryl}); 3.18 (m, 2H); 2.76 (m, 2H); 2.34 (m, 2H); 1.98, 1.94, 1.83 (s, 24H, $PC_6H_3(CH_3)_2$); 1.75 (m, 2H) ppm.

Representative Hydrogenation Procedure. In the glovebox, the glass liner of a steel autoclave was charged with acetophenone (5.0 mmol), potassium *tert*-butoxide (5.6 mg, 0.05 mmol), Cl_2Ru((*R*)-TolBinap)(κ*N3*-1-(triphenylmethyl)benzimidazole)$_2$ (**2b**; 7.9 mg, 0.005 mmol), and 1,4-dimethoxybenzene (69.1 mg, 0.5 mmol, internal standard). The solid mixture was then dissolved in 10 mL of 2-propanol and placed in the autoclave, which already contained 1 mL of solvent to prevent unwanted movement of the liner. The autoclave was removed from the glovebox, and the gauge block assembly was attached and pressurized with 5 atm of hydrogen gas. The reaction mixture was then stirred at room temperature for 6 h, after which time the pressure was released, and the crude reaction mixture was passed through a plug of silica to remove the ruthenium catalyst. The crude mixture was then analyzed by chiral supercritical fluid chromatography to determine the enantiopurity and analyzed by ^1H NMR in $CDCl_3$ to determine the yield.

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Supporting Information Available: A CIF file giving crystallographic data for **3a** and text giving the experimental procedure for acquisition of X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.