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Ruthenium(II) Complexes of Monodonor Ligands: Efficient Reagents for Asymmetric Ketone Hydrogenation

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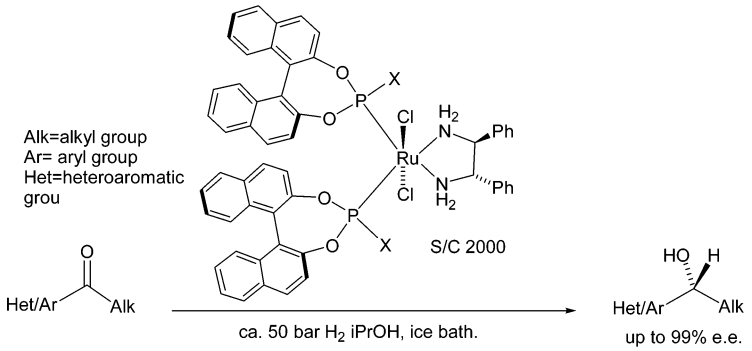

A series of BINOL-derived ligands have been prepared and incorporated into ruthenium(II) complexes containing a diamine ligand. The complexes have proven to be excellent catalysts for the asymmetric hydrogenation of ketones, giving reduction products with enantiomeric excesses of up to 99%.

Introduction

Asymmetric catalysis of the hydrogenation of ketones is a process for which a relatively large number of organometallic catalysts exist, the majority of which are based on ruthenium or rhodium.[1] The earliest catalysts, generally consisting of a metal/diphosphine combination **1**, are very active and exhibit high enantioselectivities.[2] However, their applications are usually limited to substrates containing a nearby coordinating group. This is required in order to facilitate the interaction of the ketone with metal center of the catalyst through a chelate effect

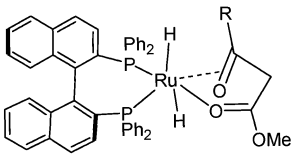

FIGURE 1. Cooperative effect of ester and ketone during asymmetric hydrogenation of β-keto esters using catalyst **1**.

(Figure 1).[3] Using diphosphine/Ru(II) catalysts, it is possible to reduce ketones containing nearby acid, ester, or hydroxy groups, among others.[1,4] The asymmetric hydrogenation of isolated ketones, i.e., lacking a suitable proximal coordinating group, has proved to be rather more difficult.[5] Recently, Noyori et al. discovered that the introduction of a diamine, for example, *SS*-1,2-diphenylethane-1,2-diamine (DPEN), into a Ru(II)/diphosphine complex produced a catalyst, e.g., **2**, that was capable of

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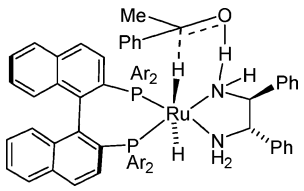
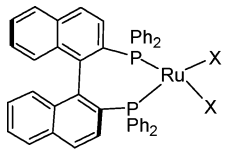
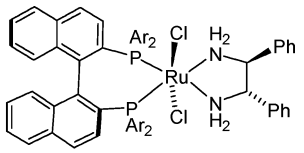


FIGURE 2. Asymmetric hydrogenation of ketones through an "outer-sphere" mechanism using catalyst **2**.

catalyzing the asymmetric reduction of ketones lacking nearby coordinating groups.[6] This new class of catalysts



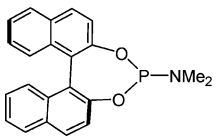
1 (X=Cl, OAc)



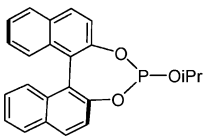
2 (Ar=pTol)

appear to work by engaging the ketone in an outer-sphere interaction, i.e., where there is no direct contact between ketone and metal (Figure 2). This class of catalyst has now been extensively studied by by a number of research groups.[6,7] As well as delivering outstanding enantioselectivities, these catalysts are active at extremely low catalyst loadings, the highest S/C reported being 2.4 million:1. Since these initial reports, a large number of related catalysts have been developed for ketone reduction,[8] and the mechanism has been studied in detail.[9] In virtually all of the studies that have been reported, diphosphine ligands have been employed in the catalyst.

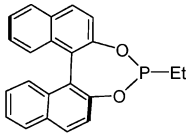
In unrelated studies on asymmetric catalysis, a number of research groups have reported that certain monodentate chiral ligands are as effective as the more established bidentate ones.[10−13] The use of monodentate phosphines in asymmetric catalysis is not new; indeed several monophosphine ligands were reported to give acceptable, but not outstanding, enantiomeric inductions for C=C reduction in substrates such as α-acylamino acrylates.[2e] The contemporary ligands differ from these early phosphines by being derived from a chiral diol, most commonly BINOL. (Nomenclature: P(III) ligands containing three P−O bonds, phosphites; containing two P−O and one P−N bond, phosphoramidite; containing two P−O bonds and a P−C bond, phosphonite.) Examples include MONOPHOS, **3**,[10] which has been used to great effect in alkene hydrogenation, as has the phosphite **4**[11] and the phosphonite **5**.[12] Closely related ligands derived from BINOL have also been used in the catalysis of a range of other reactions, including allylic substitution and conjugate additions to enones.[14]



3 MONOPHOS



4 Phosphite



5 Phosphonite

The new BINOL-derived monodonor phosphorus ligands are important because they are exceptionally easy to prepare (typically a condensation process with a bis-

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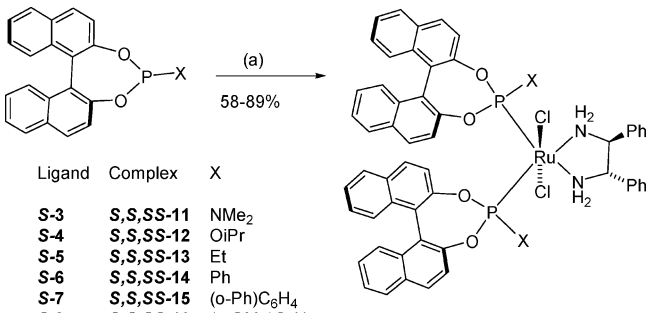
SCHEME 1. Preparation of Catalysts[a]



[a] Reagents and conditions: (a) 0.25 equiv of $[RuCl_2(C_6H_6)]_2$, DMF, 100 °C, 15 min, then 0.5 equiv of (*S*,*S*)-DPEN, 3 h, rt.

(dimethylamino)phosphine is used) from inexpensive chiral diols and do not require the complex routes that often characterize diphosphine synthesis.[14] As such, they represent economical and viable alternatives to established reagents for a large range of synthetic applications.

As a part of our own program of research into asymmetric catalysis of ketone reduction, we reasoned that monodonor ligands of the type derived from BINOL above may exhibit the same catalytic advantages to ketone hydrogenation when used in place of chiral diphosphine ligands. This paper describes the extended results from these investigations, which have been communicated in part in a preliminary publication.[15]

Results and Discussion.

Preliminary Results and Extended Substrate Studies. To determine what structural requirements were necessary for a successful ligand, we prepared a series of ligands **3**−**10** (initially all of the *S* configuration), which were selected on the basis of diversity. Although *S*-BINOL was the common diol from which all were derived, the ligands contained a mixture of P−C, P−N, and P−O bond-containing groups. Some of the ligands were known to be active in other applications;[10−12] however ligands **7**, **9**, and **10** were novel compounds. The introduction of the ligands into the ruthenium(II)·diamine catalysts **11**−**18** was achieved following the procedure used for the BINAP complexes on which they were based (Scheme 1). This involved a reaction with $[RuCl_2(benzene)]_2$ followed by the diamine.[6] When this work was undertaken, we were not aware of the relative geometry that the ligands might adopt in the complex, i.e., whether they would be *cis* or *trans* or indeed whether complexes of the required stoichiometry would be formed. In the case of bidentate ligands, such as BINAP, the situation is less complex, although even in these catalysts complexes of differing geometry can be formed.[7,9] However, there is precedent, for example, in the early work of Noyori, who reported that the complex $[(PPh_3)_2RuCl_2$-(DPEN)] is effective at asymmetric ketone hydrogenation.[6c] In tests upon the asymmetric hydrogenation of acetophenone, several of the catalysts proved to be active (Scheme 2, Table 1). However, the best results were obtained using

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SCHEME 2. Asymmetric Reduction of Acetophenone[a]

[a] Reagents and conditions: (a) catalyst (*S*,*S*,*SS*)-**11**−(*S*,*S*,*SS*)-**18**, ^{i}PrOH, 20−22 °C, [ketone] 0.30, 10 bar H_2, 20 h; see Table 1.

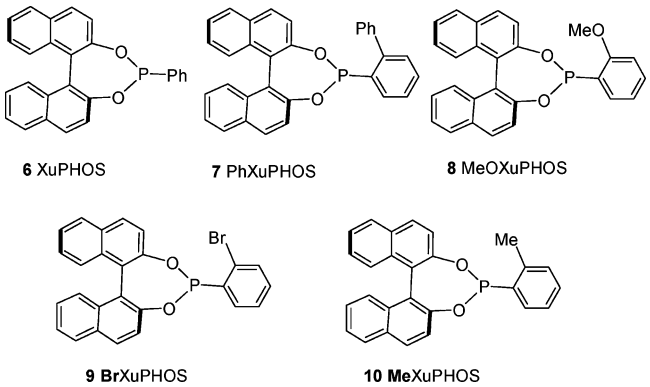
TABLE 1. Summary of Asymmetric Reductions of Acetophenone Using Ru(II) Catalysts (*S*,*S*,*SS*)-11−(*S*,*S*,*SS*)-18[a]

entry	catalyst	S/C	*P* (bar)	conv[b] (%)	ee[c] (%)
1[d]	**11**	1 000	10	100	54 (*R*)
2	**12**	1 000	10	11	43 (*R*)
3	**13**	1 000	10	2	17 (*R*)
4	**14**	1 000	10	7	37 (*R*)
5	**15**	1 000	10	5	35 (*R*)
6[e]	**16**	1 000	10	100	88 (*R*)
7[h]	**17**	1 000	10	99	84 (*R*)
8[f]	**17**	2 000	50	100	90 (*R*)
9[g]	**17**	10 000	50	80	90 (*R*)
10[f,i]	**17**	2 000	50	95	93 (*R*)
11	**18**	1 000	10	0	

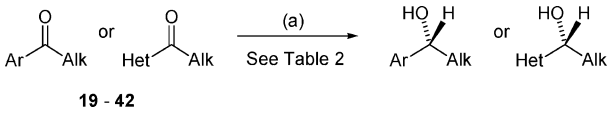
[a] 10 equiv base wrt catalyst. [b] Determined by GC or ^{1}H NMR. [c] The ee's were determined by chiral GC or HPLC. The absolute configuration was determined by comparison of the sign of optical rotation or retention time with literature data. [d] Reaction time 96 h. [e] Reaction time 40 h. [f] Reaction time <4 h. [g] Reaction time 26 h. [h] Reaction time 15 h. [i] Reaction conducted at 0 °C.

the complex **17** of the novel *o*-bromo-substituted **9** ("BrXuPHOS"), while good results were also obtained using complex **16**, derived from the known *o*-methoxy analogue ligand **8** ("MeOXuPHOS"). Using **17**, acetophenone was reduced in 90% ee within 4 h at a catalyst loading of 0.05 mol % under 50 bar of hydrogen at room temperature. The catalyst loading could even be reduced to 0.01 mol % without loss of enantiocontrol. The ee of the product could be increased slightly (to 93%) by reducing the temperature of the reaction to 0 °C. Surprisingly, complex **14** from the unsubstituted ligand **6** gave poor results, as did analogues containing large ortho substituents such as phenyl (comples **15**). This suggested strongly that a modestly sized ortho substituent was exerting an important directing effect upon the reaction. The poor result obtained with complex **18** hints at the possible involvement of lone pairs, i.e., of the bromine in **9** and the methoxy in **8**, in controlling the asymmetric induction in the reaction.

In sharp contrast to the ortho-substituted aromatic ligands, complexes **12** and **13** derived from phosphite **4**



SCHEME 3. Asymmetric Reduction of Acetophenone[a]



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[a] Reagents and conditions: (a) catalyst (*S,S,SS*)-**17**, ^{i}PrOH, 0 °C (ice bath), H_2; see Table 2.

TABLE 2. Asymmetric Hydrogenation of Ketones Catalyzed by Ruthenium(II) Complex (*S,S,SS*)-17[a]

entry	aryl/het	alkyl	ketone	*T* (h)	*P* (bar)	conv[b] (%)	ee[c] (%)
1	C_6H_5	CH_3	**19**	4	50	95	93 (*R*)
2	*o*-FC_6H_4	CH_3	**20**	8	50	68	54 (*R*)
3	*p*-ClC_6H_4	CH_3	**21**	8	50	99	86 (*R*)
4	*m*-ClC_6H_4	CH_3	**22**	8	50	96	88 (*R*)
5	*o*-ClC_6H_4	CH_3	**23**	8	60	97	95 (*R*)
6	*o*-BrC_6H_4	CH_3	**24**	8	50	93	99 (*R*)
7	*p*-IC_6H_4	CH_3	**25**	8	50	100	89 (*R*)
8	*o*-IC_6H_4	CH_3	**26**	8	60	98	99 (*R*)
9	*o*-$CH_3C_6H_4$	CH_3	**27**	8	60	99	95 (*R*)
10[e]	*m*-$CF_3C_6H_4$	CH_3	**28**	6.5	50	100	83 (*R*)
11[e]	*o,m*-$F_2C_6H_3$	CH_3	**29**	8	80	97	62 (*R*)
12[e]	*o,m*-$Cl_2C_6H_3$	CH_3	**30**	10	80	100	95 (*R*)
13	1′-naphthyl	CH_3	**31**	8	50	92	99 (*R*)
14e	C_6H_5	C_2H_5	**32**	7	70	97	90 (*R*)
15[d]	C_6H	$CH(CH_3)_2$	**33**	10	65	99	75 (*R*)
16	C_6H	CH_2OPh	**34**	8	70	100	76 (*S*)
17[f]	2-thienyl	CH_3	**35**	8	50	100	52 (*R*)
18[g]	3-thienyl	CH_3	**36**	8	50	100	91 (*R*)
19[l]	2,5(Cl_2)thienyl	CH_3	**37**	8	80	100	92 (*R*)
20[l]	2,5(Me_2)thienyl	CH_3	**38**	8	80	95	97 (*R*)
21[h]	3-pyridyl	CH_3	**39**	20	50	99	70 (*R*)
22[i]	4-pyridyl	CH_3	**40**	8	55	100	93 (*R*)
23[j]	cyclohexyl	CH_3	**41**	10	70	99	68 (*S*)
24[k]	1-adamantyl	CH_3	**42**	24	50	100	61 (*S*)

[a] Reactions were conducted in 2-propanol, 0.5 mol % *t*-BuOK, S/C = 2000, (the hydrogenation autoclave placed in the ice bath) under hydrogen pressure with a 0.15 M solution of ketone. [b] Determined by GC or ^{1}H NMR. [c] The ee's were determined by chiral GC or HPLC, and the absolute configuration was determined by comparison of the sign of the optical rotation and the retention time with literature data. [d] S/C = 500, [ketone] = 0.10 M, base ratio = 2 mol %. [e] S/C = 1000, base ratio = 1 mol %. [f] S/C = 500, [ketone] = 0.15 M, base ratio = 2 mol %. [g] S/C = 500, [ketone] = 0.075 M, base ratio = 2 mol %. [h] Room temperature. [i] S/C = 200, base ratio = 5%. [j] S/C = 1000, [ketone] = 0.075 M, base ratio = 1 mol %. [k] S/C = 300, [ketone] = 0.065 M, base ratio = 3.3 mol %, room temperature. [l] S/C = 300.

and the phosphonite **5**, respectively, proved to be rather poor in this application, despite being excellent ligands in a number of other applications.[11,12] Complex **11**, formed from phosphoramidite ligand **3** ("MONOPHOS"), was highly active but gave a reduction product of only 54% ee. In contrast, MONOPHOS is an outstanding ligand in Rh(I)-catalyzed asymmetric C=C bond reduction.[10]

Given the highly promising results obtained in preliminary studies,[15] we extended our investigations to further substrates (Scheme 3, Table 2). In all cases we chose to focus on the use of complex **17**, derived from BrXuPHOS **9**, as this had given the best preliminary results. Reactions were carried out in an ice bath, typically under 50−70 bar of hydrogen. Our initial investigations had given results that suggested that methyl ketone substrates containing an ortho-substituted aromatic ring were the best for asymmetric reduction. For example, *p*-bromoacetophenone was reduced in 80% ee, whereas *o*-bromoacetophenone gave an alcohol in 91% ee at room temperature (S/C 2000, 10 bar, 100% conversion). The ee of the latter could be increased to 99% by conducting the reaction at 0 °C. In another example, the reduction of 2′-acetonaphthone was achieved in only 85% ee, compared to 94% ee for the 1′-acetonaphthone under identical conditions (and 99% ee at 0 °C). In view of these observations we examined the structural requirements further through the use of an extended range of ketones (Table 2). The reactions were typically carried out at ice bath temperature in 2-propanol at an S/C of 2000.

The results confirmed that, with the exception of fluorine, substrates containing an ortho substituent gave the best results. For example, *o*-chloroacetophenone **23** gave a product of 95% ee, whereas the electronically similar *m*-chloroacetophenone **22** was reduced in only 88% ee and *p*-chloroacetophenone **21** in 86% ee. A similar trend was apparent for *o*-iodoacetophenone **26** (99% ee) and *p*-iodoacetophenone **25** (89% ee). *o*-Bromoacetophenone **24** was reduced in 99% ee under these conditions, whereas the *o*-methylacetophenone **27** was converted to the alcohol in 95% ee. A significant exception was found in the reduction of *o*-fluoroacetophenone **20** (54% ee, and only 68% conversion). These results indicate that the effect is primarily steric in nature; however, it seems that strong electron-withdrawing groups will reduce the level of stereocontrol. A similar pattern is observed for the hydrogenation of ortho/meta-disubstituted acetophenones **29** and **30**, which were reduced in enantioselectivities similar to those of the mono-ortho-substituted substrates. These results suggest that the principle directing effects are those exerted in each case by the substituent closest to the ketone, whether steric or electronic.

Increasing the size of the alkyl substituent in aryl/alkyl ketones results in a loss of enantioselectivity (Table 2, entries 14 and 15). Although only a small drop is observed upon going from acetophenone to propiophenone, a larger decrease is seen when an isopropyl group opposes the phenyl in the ketone substrate. It is likely that the methyl group of methyl ketones occupies a sterically constrained region of the catalyst during the asymmetric reduction. An ee of only 76% was obtained in the reduction of α-phenoxyacetophenone **34**, which again may reflect a size-increase issue. However, electronic factors may well be playing a part in determining the enantioselectivity of the reduction of this particular substrate. The change in product configuration for this reduction reflects a change in priority rules rather than an absolute change to the face selectivity of reduction relative to the aryl group, which is preserved throughout the substrates examined.

The combination of BrXuPHOS with ruthenium/DPEN in **17** also proved effective for the reduction of heterocyclic ketones (Table 2, entries 17−22). The 3-thienyl and 4-pyridyl substrates **36** and **40** were reduced quantatively and in over 90% ee; however, the related 2-thienyl and 3-pyridyl ketones **35** and **39** gave products of modest ee. The advantage of an ortho substituent in the substrate, as demonstrated for acetophenone derivatives, appears to be extended to heterocyclic substrates. The reduction of 2,5-dichlorothienyl and 2,5-dimethylthienyl ketones **37** and **38** was achieved in 92% and 97% ee, respectively. In all cases the products were of *R* configuration. These results underline the fact that substrates can be designed

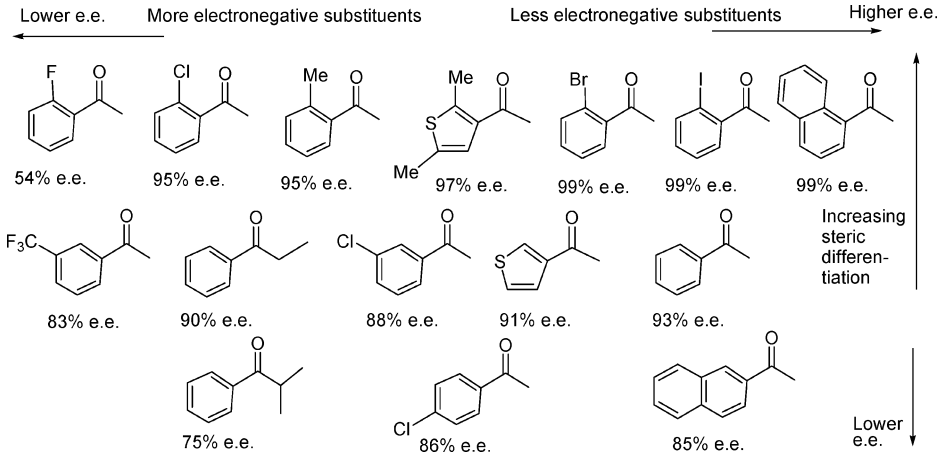


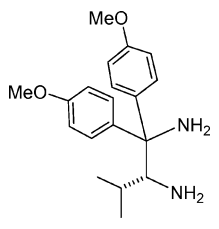
FIGURE 3. Relationship of structure to ee of hydrogenation using catalyst **17**.

to give high enantioselectivities by incorporation of an appropriate ortho or 2-substituent relative to the ketone.

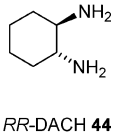
A graphical representation of the pattern of enantioselectivities with respect to ketone structure highlights the observed trend (Figure 3). Methyl ketones with a large ortho-substituted aryl ring give the highest enantioselecitivities, which approach perfect selectivity, while the ee's drop away with the removal of steric differentiation or with the introduction of electron-withdrawing groups.

Two ketones bearing alkyl groups at either side of the ketone were investigated. Cyclohexyl/methyl ketone **41** was cleanly reduced in 68% ee to give a product of *S* configuration, which is opposite to what would be predicted on the basis of the preceding studies and on steric grounds alone. The 1-adamanyl ketone **42** was reduced in only 61% ee despite the large difference in steric bulk between the substituents. The results suggest that steric effects alone are not influencing the reaction, but rather that the situation is more complex.

Further Catalyst Structures. At an early stage in the project we had considered the issue of matched/mismatched enantioselectivity between the ligand and the diamine in the catalyst. Our preliminary studies indicated that the (*S*,*S*,*SS*) configuration was the matched one, while the (*S*,*S*,*RR*) was the mismatched on the basis that the latter gave only 33% ee (*S*) for acetophenone reduction under conditions where the "all-*S*" catalyst gave 90% ee (*R*). This result also indicated that the major directing effect was coming from the diamine. To probe this issue further, an extended series of catalysts were prepared, containing alternative diamines. Table 3 summarizes the results that were obtained using complexes of BrXuPHOS with *RR*-DPEN, *R*-di-1,1-(*p*-anisyl)-2-isopropyl-ethane-1,2-diamine (*R*-DIAPEN) **43**, and *RR*-1,2-diaminocyclohexyl (*RR*-DACH) **44** for the reduction of



R-DIAPEN **43**



RR-DACH **44**

TABLE 3. Asymmetric Hydrogenation of Ketones Catalyzed by Ruthenium(II) Complex Derived from *R*- or *S*-BrXuPHOS 17 and *SS*-DPEN, *R*-DIAPEN 43, and *RR*-DACH 44[a]

catalysts		substrates	
BrXuPHOS **9**	diamines	acetophenone ee[b] (%)	CyCOMe **41** ee[b] (%)
S,S	*SS*-DPEN	93.0[c] (*R*)	68.0 (*S*)
R,R	*SS*-DPEN	35.0 (*R*)	36.4 (*R*)
S,S	*R*-DAIPEN **43**	1.2 (*S*)	5.0 (*S*)
R,R	*R*-DAIPEN **43**	25.0 (*S*)	N/A
S,S	*RR*-DACH **44**	11.6 (*R*)	41.0 (*S*)
R,R	*RR*-DACH **44**	88.2 (*S*)	8.3 (*R*)

[a] Reactions were conducted under hydrogen in 2-propanol. [b] The ee's were determined by chiral GC or HPLC. The absolute configuration was determined by comparison of the sign of optical rotation or retention time with literature data. [c] In an ice bath.

acetophenone and a representative dialkyl ketone (CyCOMe, **41**). All six combinations of potentially matched and mismatched phosphorus ligand (BrXuPHOS **17**) and diamine were prepared by standard methods described above and characterized before being tested (Table 3).

In the reduction of acetophenone, we first reconfirmed our initial observation regarding the DPEN complex. The fact that the same major enantiomer is formed reconfirms that the diamine has the dominant stereodirecting effect. This pattern was also exhibited using the DAIPEN complexes, although the asymmetric inductions were low. In the case of the DACH complexes, however, the phosphorus ligand appears to have the major directing effect. The matched complex gave a respectable ee of 88.2%; however, the mismatched complex gave a product of very low ee (11.6%). The latter result suggests that the phosphorus ligand and the diamine have reasonably equally strong directing influences on the reaction. From this study, it appears that DACH **44** is a viable alternative diamine for use in this class of ruthenium catalyst.

In the case of CyCOMe **41**, another complex picture emerged. The highest ee was obtained using the "all-*S*" BrXuPHOS/DPEN combination. This was reduced and reversed upon replacement of the phosphorus ligand with that of the opposite configuration, underlining its dominance in the enantiodirection of the process. Products were formed in low conversions when R-DIAPEN **43** was used, and the enantioselectivities were low in the case of RR-DACH **44**.

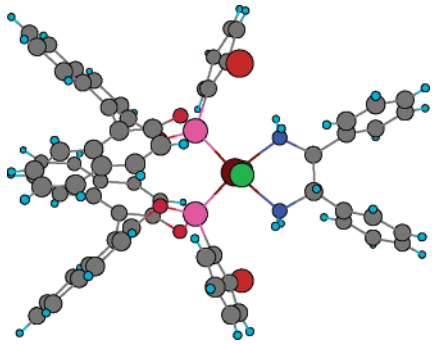
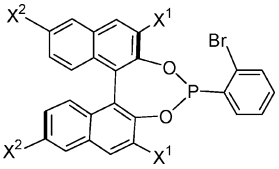


FIGURE 4. Plan view of X-ray crystallographic structure of *S*,*S*,*SS*-**17**.

Some brief investigations were also carried out into the modification of the BINOL part of the ligand. Ligands **45**−**47**, all of *R*-configuration, were all prepared through standard methods by condensation of the known prerequisite diols[16] with *o*-bromophenyl-bis(dimethylamino)-phosphine. In the cases of **45** and **46**, however, no ruthenium complex could be prepared. In the first step, coupling the ligand to the ruthenium(II), a promising ^{31}P NMR shift to 220 ppm was observed. However, no further upfield shift (typically 15−20 ppm) occurred upon addition of DPEN and overnight stirring at 40 °C. This may be a reflection of the increased steric hindrance associated with the substituents in close proximity to the phosphorus atom of the ligand. A complex of **47** was prepared successfully and gave an acetophenone reduction product of 49.1% ee (*S*), but in only 10% conversion (*R*,*R*,*RR*-complex, S/C 1000, [ketone] = 0.15 M, 10 bar, 20 h). Although the remote dibromo substitution clearly does not prevent catalyst formation, the halides appear to have a negative effect on the performance of the catalysts, presumably due to a distant electronic effect.



45 X^1= Br, X^2 =H
46 X^1= Me, X^2 =H
47 X^1= H, X^2 =Br

Model for the Asymmetric Control. The X-ray crystallographic structure of *S*,*S*,*SS*-**17** was obtained (Figure 4).[15] This revealed an octahedral structure with two cis-orientated phosphorus ligands in the same plane as the chelating diamine. Chloride ions sit above and below the plane described by the neutral ligands. The two phosphorus ligands are packed extremely closely together; the space-filling view from behind the ligands (Figure 5) reveals a structure in which the naphthyl rings are orientated in an interspersed manner with very little scope for rotation or movement. There may also be

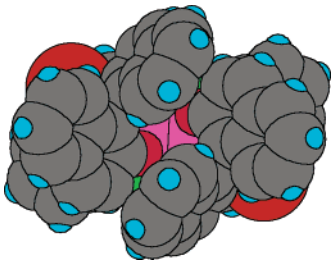


FIGURE 5. Reverse, space-filling, view of *S*,*S*,*SS*-**17**, illustrating close packing of the naphthyl rings of the BINOL ligands.

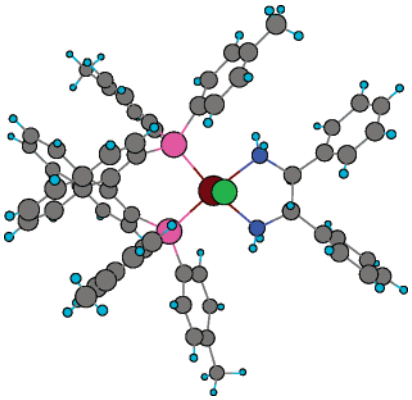


FIGURE 6. Plan view of X-ray crystallographic structure of *S*,*SS*-**2**.[6c]

TABLE 4. Comparison of Key Bond Lengths (Å) and Angles (deg) between *S*,*SS*-2 and *S*,*S*,*SS*-17

	S,SS-**2**	S,S,SS-**17**
Cl−Ru−Cl angle	162.968	166.820
P−Ru−P angle	92.228	92.764
N−Ru−N angle	77.72	78.815
Ru−Cl bonds	2.421/2.420	2.393/2.400
Ru−P bonds	2.282/2.273	2.217/2.200
Ru−N bonds	2.196/2.183	2.260/2.160

π-stacking, stabilizing interactions between these rings. This packing of the ligands results in the orientation of the *o*-bromophenyl rings into the region close to the ruthenium reaction center. The tightly packed structure of the complex leaves little extra room for further ligand substitution, which may account for the failure of attempts to form complexes of the ligands **45** and **46**.

The X-ray structure allows some comparisons to be made with the TolBINAP complex **2** (Figure 6; note that the reported crystallographic structure of *R*,*RR*-**2**[6c] has been inverted for comparison with our *SS*-diamine-derived structure), which served as the inspiration for our catalyst design. The use of *S*,*SS*-**2** results in asymmetric hydrogenation of acetophenone to give a product of *R* configuration, again providing a useful point of agreement with the result from our catalyst. A comparison of key bond lengths and angles reveals a remarkably close agreement between very different structures (Table 4). In fact the positions of the key atoms surrounding the ruthenium atom are almost superimposable. Notably, the five-membered ring created by the diamine in **17** with the ruthenium is puckered in a manner very similar to the Noyori catalyst **2**. A side view of each complex illustrates their similarity in this respect (Figure 7), as

(16) (a) Wipf, P.; Jung, J.-K. *J. Org. Chem.* **2000**, *65*, 6319. (b) Tomson, F.; Bailey, J. A.; Gennis, R. B.; Unkefer, C. J.; Li, Z.; Silks, L. A.; Martinez, R. A.; Donohoe, R. J.; Dyer, R. B.; Woodruff, W. H. *Biochemistry* **2002**, *41*, 14384. (c) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc*. **2003**, *125*, 5139. (d) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett*. **2004**, *6*, 2701. (e) Tian, Y.; Yang, Q. C.; Mak, T. C. W.; Chan, K. S. *Tetrahedron* **2002**, *58*, 3951.

(17) Fletcher, D. A.; McMeeking,; R. F. Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746.

(18) Allen, F. H. *Acta Crystallogr*. **2002**, *B58*, 380.

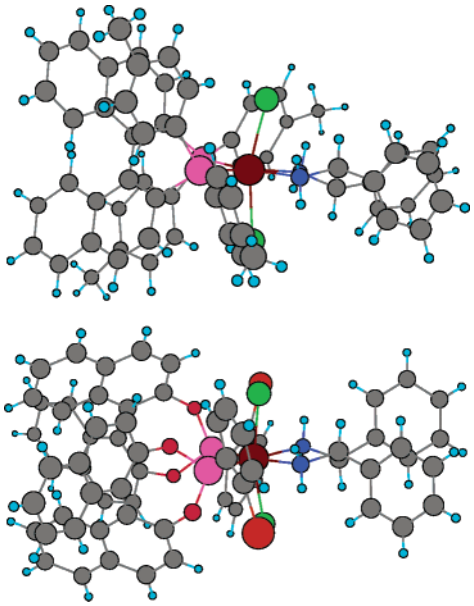


FIGURE 7. Side views of X-ray crystallographic structure of *S*,*SS*-**2** (upper)[6c] and *S*,*S*,*SS*-**17** (lower), comparing the puckered δ conformation of the ring formed by coordination of the diamine to ruthenium.

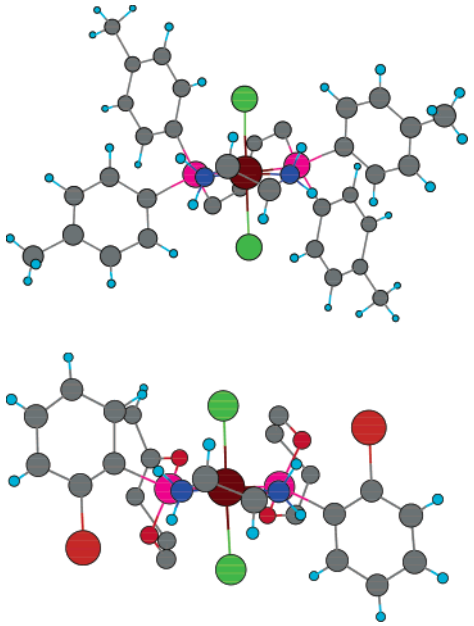


FIGURE 8. "Front" views of X-ray crystallographic structure of *S*,*SS*-**2** (upper)[6c] and *S*,*S*,*SS*-**17** (lower), comparing the puckered δ conformation of the ring formed by coordination of the diamine to ruthenium. The ligands have been depleted of substituents for clarity.

does a comparative "front" view of the (simplified) diamine to the ruthenium (Figure 8). Although the situation of the complex when it enters the catalytic cycle is prone to many fluxional changes, it is likely, on the basis of literature precedent, that the active catalyst will have hydrogen atoms substituted in the positions currently occupied by the chlorine atoms in structure **17**.[6,7,9]

Assuming that the puckering is preserved through the catalytic cycle, then there shall be an axially oriented NH bond on either side of the postulated dihydride complex.

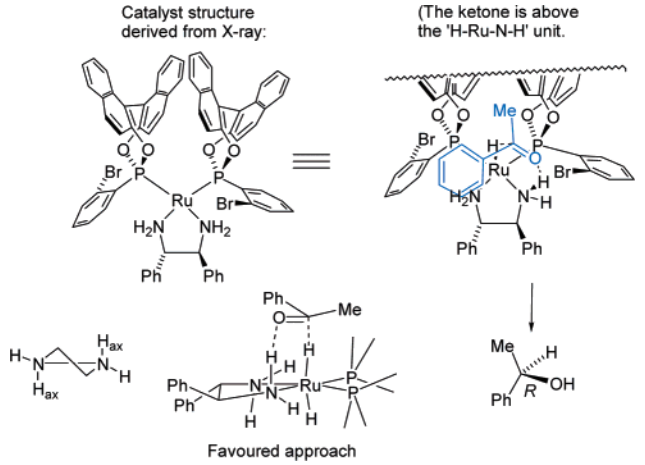


FIGURE 9. Schematic plan view of *S*,*S*,*SS*-**17** and favored "outer-sphere" approach of substrate to minimize steric interactions; *R*-configuration product is predicted.

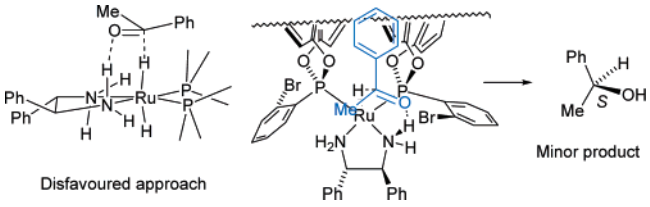


FIGURE 10. Schematic plan view of *S*,*S*,*SS*-**17** and disfavored approach of substrate due to excessive steric interactions of substrate with phosphorus ligands.

Literature precedent suggests that the oxygen atom of the incoming ketone substrate is likely to interact with one of these axially located hydrogen atoms, whereas the carbon of the ketone will align with the hydride on the ruthenium.[6,7,9] Through this "outer-sphere" mechanism, hydrogen can be effectively transferred to the ketone through a six-center transition state (Figure 9) in a highly stereocontrolled manner. The two phosphorus ligands present a significant steric obstacle within the complex, and our expectation is that only the smallest group in the ketone shall be able to occupy the region of space close to them. There may also be a stabilizing interaction between the aryl ring of the substrate and some component of the diamine ligand. This approach would give a product of a configuration that matches what is observed. The alternative approach (Figure 10) would be disfavored by the unfavorable steric clash between the phenyl of the ketone with the ligand. This model is analogous to that accepted for *S*,*SS*-**2**.[6,7,9] Increasing the level of substitution on the aromatic ring of the ligand would be expected, on the basis of this model, to give improved selectivity, while increasing the size of the group opposite the arene (i.e., from Me to Et to ^{i}Pr) would be predicted to have the opposite effect. This pattern is observed in the results of the hydrogenation and lends support to the model. The reasons for the low selectivity with the *o*-fluoro and trifluoromethyl groups and the reversed selectivity with alkyl/alkyl substrates are less clear, and their elucidation remains the objective of ongoing studies.

Although the diamine in *S*,*S*,*SS*-**17** is the dominant ligand in terms of asymmetric control, the phosphorus ligands also exert a significant directing effect that must

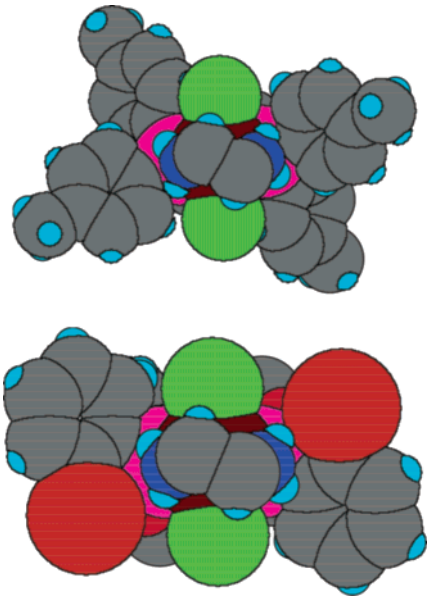


FIGURE 11. "Front" space-filling views of X-ray crystallographic structure of *S*,*SS*-**2** (upper)[6c] and *S*,*S*,*SS*-**17** (lower), comparing the positions of the pTol ring (upper) and the Br atoms (lower). The ligands have been depleted of substituents for clarity.

be matched for maximum selectivity. It is our speculation that the positions of the bromine atoms provide an important secondary controlling effect to operate. The space-filling view of the complex (with parts of the ligands removed for clarity) with the ruthenium in front of the phosphorus ligands (Figure 11) highlights the bulky nature of the bromine atoms. A contrast with the same view of *S*,*S*,*SS*-**2** (also shown in Figure 10) reveals that the bromines occupy a position identical to that occupied by the two pTol rings (from the pTolBINAP) that are projected into the region closest to the catalytic center at the ruthenium(II) atom. Although the specific role of the pTol (in **2**) and the Br atoms (in **17**) is not yet fully understood, the presence of both of these large groups in such close proximity to the Ru(II) center suggests that they have an opportunity to "moderate" the structure of the transition state. This may be achieved through some form of steric restriction of the space around the reaction center or possibly through a more complex electronic influence. An interaction of the bromine lone pairs in the transition state can also not be ruled out. Ongoing studies are currently underway to address these questions.

Conclusions

In conclusion, we have discovered that Ru(II) complexes of monodentate phosphorus ligands derived from BINOL and a C_2-symmetric diamine ligand represent excellent catalysts for the asymmetric hydrogenation of ketones. This catalytic system represents a viable and practical alternative to the well-established analogous complexes that contain a bindentate diphosphine ligand. Our systems have the advantage that the ligands may be prepared in one step from inexpensive BINOL, which is abundantly available in either enantiomeric form. Alcohols are formed in enantiomeric excesses of up to 99%, at S/C levels of typically more than 2000. The enantiocontrol appears to depend on steric differentiation between the groups on either side of the ketone. A mechanistic rationale for the absolute control of the reduction has been forwarded, in which a close analogy to the BINAP/Ru/DPEN catalyst system is highlighted.

Experimental Section

General experimental details, the synthesis of compounds **2**−**10** and complexes **11**−**18**, a procedure for asymmetric hydrogenation of ketones using these complexes, and the X-ray crystal structure data for *S*,*S*,*SS*-**17** have been reported in a previous publication.[15]

(*R*,*R*,*R*)-BrXuPHOS-Ru-DAIPEN. $[RuCl_2(C_6H_6)]_2$ (79.5 mg, 0.159 mmol) and (*R*)-BrXuPHOS (300 mg, 0.637 mmol, 4 equiv) were placed in a 50-mL round-bottom flask. After the air in the flask was replaced with argon 3 times, anhydrous DMF (3.5 mL) was added, and the mixture was degassed and stirred under argon at 100 °C for 15 min to form a reddish brown solution. After the solution was cooled to the room temperature, (*R*)-DAIPEN (100 mg, 0.318 mmol, 2 equiv) was added, and the mixture was degassed again and stirred for 3 h to form a clear orange solution. During the reaction, a yellow solid precipitated out. After the reaction finished, DCM (30−60 mL) was added into the reaction mixture several times, each time subjected to high vacuum and back to argon, to remove the remaining DMF azeotropically. The resulting dark brown solid was dried under the high vacuum to give the final dark orange product (*R*,*R*,*R*)-BrXuPHOS-Ru-DAIPEN (0.237 g, 52.2%): mp 205−207 °C (dec); $[\alpha]^{20}_D = +425.5$ (*c* 0.10, CH_2Cl_2); IR υ_{max} solid (cm^{-1}) 3055, 2928, 1671, 1508, 1225, 953, 826; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (1H, d, J = 8.8 Hz), 8.31 (1H, d, J = 9.1 Hz), 7.97−7.92 (4H, m), 7.68 (2H, t, J = 8.0 Hz), 7.42−6.90 (20H, m), 6.80−6.63 (6H, m), 6.48−6.25 (6H, m), 5.12−5.09 (1H, m), 4.37−4.33 (1H, m), 3.79 (3H, s), 3.76 (3H, s), 3.52−3.47 (1H, m), 3.18−3.15 (1H, m), 2.74−2.71 (1H, m), 1.84−1.81 (1H, m), 0.39 (3H, d, J = 6.7 Hz), 0.08 (3H, d, J = 6.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 203.0 (d, J = 71.1 Hz), 202.3 (d, J = 71.1 Hz); LSIMS *m*/*z* (FAB^+) 1393 ($[M]^+$, 100%), 1079 (40%); HRMS calc for $C_{71}H_{58}Br_2Cl_2N_2O_6P_2Ru$ 1393.087, due to the difficulties of inspecting such a high molecular weight and very complex combination of isotopes of Cl, Br, and Ru atoms, molecular weights found overlapped around 1393 are 1393.083 (20%), 1393.085 (100%), 1393.088 (53%), and 1393.089 (43%).

(*S*,*S*,*R*)-BrXuPHOS-Ru-DAIPEN. $[RuCl_2(C_6H_6)]_2$ (79.5 mg, 0.159 mmol) and (*S*)-BrXuPHOS (300 mg, 0.637 mmol, 4 equiv) were placed in a 50-mL round-bottom flask. After the air in the flask was replaced with argon 3 times, anhydrous DMF (3.5 mL) was added, and the mixture was degassed and stirred under argon at 100 °C for 15 min to form a reddish brown solution. After the solution was cooled to the room temperature, (*R*)-DAIPEN (100 mg, 0.318 mmol, 2 equiv) was added, and the mixture was degassed again and stirred for 3 h to form a clear orange solution. During the reaction, yellow solid precipitated out. After the reaction finished, DCM (30−60 mL) was added into the reaction mixture several times, each time subjected to high vacuum and back to argon, to remove the remaining DMF azeotropically. The resulting dark brown solid was dried under the high vacuum to give the final dark orange product (*R*,*R*,*R*)-BrXuPHOS-Ru-DAIPEN (0.227 g, 50.0%): mp 202−204 °C (dec); $[\alpha]^{25}_D = -330.4$ (*c* 0.12, CH_2Cl_2); IR υ_{max} solid (cm^{-1}) 3327, 2954, 1671, 1509, 1225, 953; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (1H, d, J = 8.8 Hz), 8.00 (1H, d, J = 9.1 Hz), 7.77−7.72 (4H, m), 7.68 (2H, t, J = 7.9 Hz), 7.42−6.90 (20H, m), 6.80−6.63 (6H, m), 6.48−6.25 (6H, m), 5.12−5.09 (1H, m), 4.37−4.33 (1H, m), 3.76 (3H, s), 3.75 (3H, s), 3.52−3.47 (1H, m), 3.18−3.15 (1H, m), 2.74−2.71 (1H, m), 1.84−1.81 (1H, m), 0.98 (3H, d, J = 6.7 Hz), − 0.11 (3H, d, J = 6.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 203.2 (d, J = 73.4 Hz), 202.6 (d, J = 73.4 Hz); LSIMS *m*/*z* (FAB^+) 1393 ($[M]^+$, 100%), 1079 (40%); HRMS calcd for $C_{71}H_{58}Br_2Cl_2N_2O_6P_2Ru$ 1393.087, due

to the difficulties of inspecting such a high molecular weight and very complex combination of isotops of Cl, Br, and Ru atoms, molecular wights found overlapped around 1393 are 1393.083 (20%), 1393.085 (100%), 1393.088 (53%) and 1393.089 (43%).

(*R*,*R*,*RR*)-BrXuPHOS-Ru-DACH. $[RuCl_2(C_6H_6)]_2$ (91 mg, 0.182 mmol) and (*R*)-BrXuPHOS (343 mg, 0.728 mmol, 4 equiv) were placed in a 50-mL round-bottom flask. After the air in the flask was replaced with argon 3 times, anhydrous DMF (3.5 mL) was added, and the mixture was degassed and stirred under argon at 100 °C for 15 min to form a reddish brown solution. After the solution was cooled to the room temperature, (*R*,*R*)-DACH (41.5 mg, 0.364 mmol, 2 equiv) was added, and the mixture was degassed again and stirred for 3 h to form a clear orange solution. During the reaction, a yellow solid precipitated out. After the reaction finished, DCM (30−60 mL) was added into the reaction mixture several times, each time subjected to high vacuum and back to argon, to remove the remaining DMF azeotropically. The resulting dark brown solid was dried under the high vacuum to give the final dark brown product (*R*,*R*,*RR*)-BrXuPHOS-Ru-DACH (0.420 g, 94%): mp 116−118 °C (dec); $[\alpha]^{26}_D = +340.5$ (*c* 0.042, CH_2Cl_2); IR υ_{max} solid (cm^{-1}) 2925, 1659, 1385, 1229, 955, 832; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (2H, d, J = 8.8 Hz), 8.10 (2H, d, J = 8.8 Hz), 7.96−7.92 (2H, m), 7.86−7.83 (2H, m), 7.47 (2H, d, J = 8.2), 7.39 (4H, d, J = 7.3 Hz), 7.18−7.08 (4H, m), 7.06−7.00 (4H, m), 6.90−6.81 (4H, m), 6.55 (2H, t, J = 7.3 Hz), 6.39 (2H, d, J = 8.2 Hz), 6.25 (2H, d, J = 8.8 Hz), 4.09−4.07 (2H, m), 2.71−2.69 (2H, m), 1.95 (4H, m), 1.60 (2H, m), 1.08 (4H, m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 203.6; LSIMS *m/z* (FAB^+) 1193 ($[M - Cl]^+$, 100%); HRMS calcd for $C_{58}H_{46}N_2O_4P_2ClBr_2Ru^{100}$ 1189.0030 $[M - Cl]^+$, found 1189.0031.

(*S*,*S*,*RR*)-BrXuPHOS-Ru-DACH. $[RuCl_2(C_6H_6)]_2$ (89 mg, 0.177 mmol) and (*R*)-BrXuPHOS (334 mg, 0.709 mmol, 4 equiv) were placed in a 50-mL round-bottom flask. After the air in the flask was replaced with argon 3 times, anhydrous DMF (5 mL) was added, and the mixture was degassed and stirred under argon at 100 °C for 15 min to form a reddish brown solution. After the solution was cooled to the room temperature, (*R*,*R*)-DACH (40.5 mg, 0.354 mmol, 2 equiv) was added, and the mixture was degassed again and stirred for 3 h to form a clear orange solution. During the reaction, a yellow solid precipitated out. After the reaction finished, DCM (30−60 mL) was added into the reaction mixture several times, each time subjected to high vacuum and back to argon, to remove the remaining DCM azeotropically. The resulting dark brown solid was dried under the high vacuum to give the final yellow product (*R*,*R*,*RR*)-BrXuPHOS-Ru-DACH (0.285 g, 66%): mp 116−118 °C (dec); $[\alpha]^{26}_D = -428.4$ (*c* 0.044, CH_2Cl_2); IR υ_{max} solid (cm^{-1}) 2920, 1670, 1228, 954, 830, 807; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (2H, d, J = 8.8 Hz), 8.10 (2H, d, J = 8.8 Hz), 7.96−7.92 (2H, m), 7.86−7.83 (2H, m), 7.47 (2H, d, J = 8.2), 7.39 (4H, d, J = 7.3 Hz), 7.18−7.08 (4H, m), 7.06−7.00 (4H, m), 6.90−6.81 (4H, m), 6.55 (2H, t, J = 7.3 Hz), 6.39 (2H, d, J = 8.2 Hz), 6.25 (2H, d, J = 8.8 Hz), 4.09−4.07 (2H, m), 2.71−2.69 (2H, m), 1.95 (4H, m), 1.60 (2H, m), 1.08 (4H, m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 203.6; LSIMS *m/z* (FAB^+) 1193 ($[M - Cl]^+$, 100%); HRMS calcd for $C_{58}H_{46}N_2O_4P_2ClBr_2Ru^{100}$ 1189.0030 $[M - Cl]^+$, found 1189.0031.

(*R*,*R*,*SS*)-BrXuPHOS-Ru-DPEN. $[RuCl_2(C_6H_6)]_2$ (100 mg, 0.200 mmol) and (*R*)-Br XuPHOS (377 mg, 0.800 mmol, 4 equiv) were placed in a 50-mL Schlenk flask. After the air in the flask was replaced with argon, anhydrous DMF (10 mL) was added, and the mixture was degassed and stirred under argon at 100 °C for 10 min to form a reddish brown solution. After the solution was cooled to 25 °C, (*S*,*S*)-DPEN (85 mg, 0.400 mmol) was added, and the mixture was degassed again and stirred for 3 h. After the reaction finished, the supernatant was removed, and DCM was added several times into the reaction mixture, each time subjected to high vacuum and back to argon. The resulting dark yellow solid was dried under the high vacuum to give the final product (*R*,*R*,*SS*)-BrXuPHOS-Ru-DPEN (257 mg, 49%) with the melting point 235−237 °C (dec). IR υ_{max} solid (cm^{-1}) 2360, 2341, 1224, 1193, 953, 832; $[\alpha]^{21}_D = +162.5$ (*c* 0.044, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.43−8.41 (2H, m), 8.15−8.14 (2H, m), 7.92−7.86 (4H, m), 7.51−7.26 (6H, m), 7.12−7.10 (10H, m), 6.98−6.84 (12H, m), 6.55−6.30 (6H, m), 4.55−4.53 (2H, m), 4.23−4.20 (2H, m), 2.88−2.83 (2H, m); ^{31}P NMR (121 MHz, $CDCl_3$) δ 203.9; LSIMS *m/z* (FAB) 1291 ($[M - Cl]^+$, 100%), 1247 (65%), 1196 (50%), 1079 (35%); HRMS calcd for $C_{66}H_{48}Br^{79}Br^{81}Cl^{35}{}_2N_2O_4P_2Ru^{102}$ 1291.0168 ($[M - Cl]^+$), found 1291.0167.

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Supporting Information Available: General experimental details, details of synthesis and characterization of ligands **45**−**47**, data for all reduction products, and ^1H and ^{13}C NMR of all new compounds lacking elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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