Evaluation of Asymmetric Hydrogenation Ligands in Asymmetric Hydroformylation Reactions. Highly Enantioselective Ligands Based on Bis-phosphacycles

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An evaluation of 47 phosphorus-based ligands has been conducted in rhodium-catalyzed asymmetric hydroformylation reactions, AHF, at high temperature. Most of the ligands exhibited poor enantio- and regioselectivity as well as low catalytic activity. Two ligands, (*R*)-Binapine and (*S*,*S*,*R*,*R*)-TangPhos, were found to give outstanding enantioselectivities in asymmetric hydroformylation of styrene, allyl cyanide, and vinyl acetate. (*R*)-Binapine gave 94% ee, 94% ee, and 87% ee, whereas (*S*,*S*,*R*,*R*)-TangPhos gave 90% ee, 93% ee, and 83% ee for hydroformylation products of styrene, allyl cyanide, and vinyl acetate, respectively. Enantioselectivity achieved for the allyl cyanide product with these ligands is the highest ever reported for this substrate. Excess of (*S*,*S*,*R*,*R*)-TangPhos leads to low enantioselectivities in the AHF of styrene and allyl cyanide due to in situ formation of the ionic complex [[((*S*,*S*,*R*,*R*)-TangPhos)$_2$]-Rh]$^+$[acac]$^-$. The noncoordinating acetylacetonate anion is responsible for this sharp decrease of enantioselectivity in hydroformylation products. X-ray crystal structures of [[((*S*,*S*,*R*,*R*)-TangPhos)$_2$]Rh]$^+$-[acac]$^-$ and [(*S*,*S*,*R*,*R*)-TangPhos]Rh(acac) have been determined and examined. The high success achieved with bis-phosphacycle ligands in asymmetric hydroformylation reactions suggests that this ligand class is unique and highly promising among previously investigated phosphorus-based systems and should be further explored in search of even better ligands for this important reaction.

Introduction

The asymmetric hydroformylation reaction (AHF) represents one of the most attractive chemoselective transformations for the preparation of chiral aldehydes from ubiquitous and generally accessible olefins.[1] The long-standing challenge in this area is the development of catalysts/ligands capable of producing very high product enantio- and regioselectivity and, at the same time, being applicable to a broad spectrum of olefins. In addition to inducing high % ee and regioselectivity, commercially viable catalysts/ligands are required to operate effectively at high temperatures (>60 °C) to maintain necessary reaction rates and at low catalyst loading to limit the high cost of rhodium and chiral ligands.

The first ligands investigated in rhodium-catalyzed AHF were chiral phosphines,[2,3] but relatively little success has been achieved in this area. Introduction of phosphite ligands in hydroformylation chemistry initiated investigation of this ligand class in AHF and led to the discovery of the ligands (*2R*,*4R*)-Chiraphite (**1**),[4] (*S*,*S*)-Kelliphite (**2**),[5] and (*R*,*S*)-Binaphos (**3**)[6] (Chart 1). Very recently, however, Landis' and our groups have reported, for the first time, the application of bis-phosphine ligands (diazaphospholane **4**) in highly enantioselective AHF.[7] In addition to giving very high enantioselectivities, diazaphospholane ligands were unexpectedly active in AHF, surpassing even the activity of bisphosphite ligands. Subsequently, we described the discovery of another bisphosphine, (*R*,*R*)-Ph-BPE (**6**),[8] as an excellent ligand in AHF. This was interesting, as this was the first time an outstanding asymmetric hydrogenation (AH) ligand[9] was also found to be an excellent AHF ligand. Zhang et al. recently described[10] a reversed scenario, where (*R*,*S*)-Binaphos (**3**), a highly effective AHF ligand, was suc-

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(1) Claver, C.; van Leeuwen, P. W. N. M. *Rhodium Catalyzed Hydroformylation*; Kluwer Academic Publishers: Dordrecht, 2000.

(2) Botteghi C.; Paganelli S.; Schionato A.; Marchetti M. *Chirality* **1991**, *3*, 355−369.

(3) Agbossou, F.; Carpentier, J.-F.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485−2506.

(4) (a) Babin, J. E.; Whiteker, G. T. WO 9303839, 1993. (b) Whiteker, G. T.; Briggs, J. R.; Babin, J. E.; Barner, B. A. *Chemical Industries*; Marcel Dekker: New York, 2003; Vol. 89, pp 359−367.

(5) (a) Cobley, C. J.; Gardner, K.; Klosin, J.; Praquin, C.; Hill, C.; Whiteker, G. T.; Zanotti-Gerosa, A.; Petersen, J. L.; Abboud, K. A. *J. Org. Chem.* **2004**, *69*, 4031−4040. (b) Cobley, C. J.; Klosin, J.; Qin, C.; Whiteker, G. T. *Org. Lett.* **2004**, *6*, 3277−3280.

(6) (a) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033−7034. (b) Sakai, N.; Nozaki, K.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1994**, 395−396. (c) Nanno, T.; Sakai, N.; Nozaki, K.; Takaya, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2583−2591. (d) Nozaki, K.; Nanno, T.; Takaya, H. *J. Organomet. Chem.* **1997**, *527*, 103−108. (e) Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1997**, *62*, 4285−4292. (f) Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Tetrahedron* **1997**, *53*, 7795−7804. (g) Horiuchi, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Organometallics* **1997**, *16*, 2981−2986. (h) Nozaki, K.; Li, W.; Horiuchi, T.; Takaya, H. *Tetrahedron Lett.* **1997**, *38*, 4611−4614. (i) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, *119*, 4413−4423.

(7) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5040−5042.

(8) Axtell, A. T.; Cobley, C. J.; Klosin, J.; Whiteker, G. T.; Zanotti-Gerosa, A.; Abboud K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5834−5838.

(9) Pilkington, C. J.; Zanotti-Gerosa, A. *Org. Lett.* **2003**, *5*, 1273−1275.

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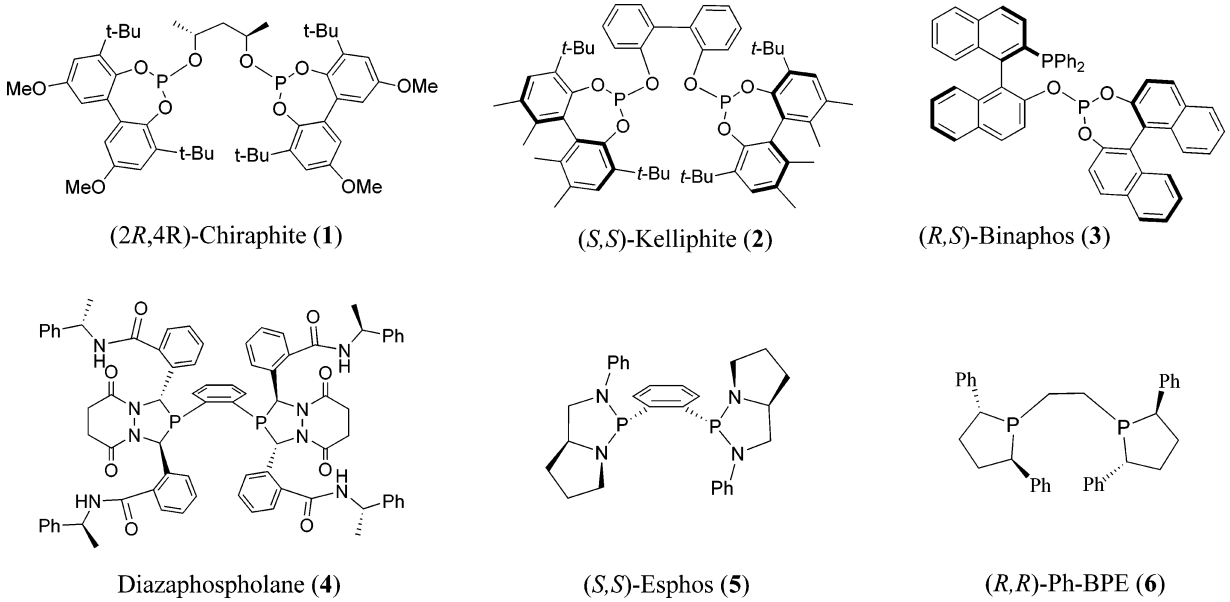
Chart 1. Asymmetric Ligands that Have Been Successfully Applied in AHF Reactions



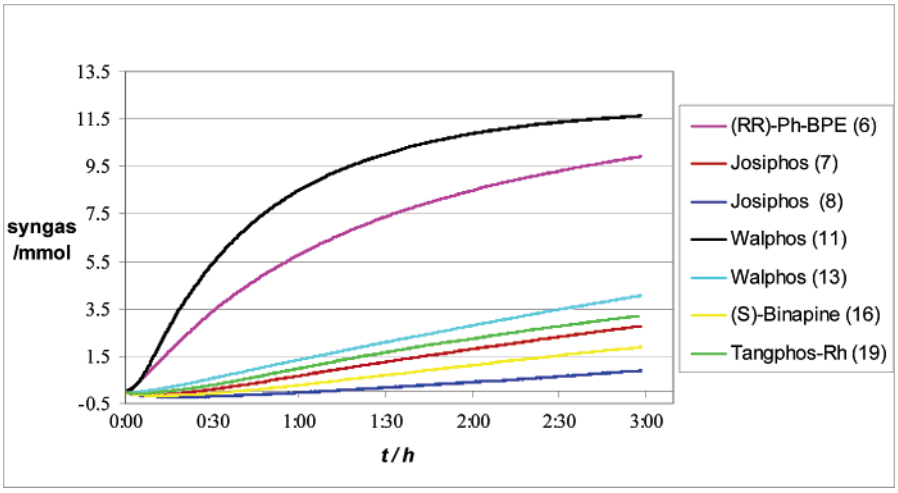


Figure 1. Syngas uptake curves (reactions performed with molar olefin:Rh = 3000 at 80 °C in toluene with 150 psi 1:1 CO:H_2 and L:Rh = 2).

cessfully applied in asymmetric hydrogenation of α-(*N*-acetamido)acrylates. Typically, ligands have been optimized for either asymmetric hydrogenation or asymmetric hydroformylation, so it is unusual to find examples where a single ligand is synthetically useful for both reactions.

The fact that ligands **3** and **6** performed very well in both asymmetric hydrogenation and asymmetric hydroformylation reactions raised the question of whether there are other asymmetric hydrogenation ligands that can be equally effective in AHF reactions. Since there are many asymmetric hydrogenation ligands commercially available, we decided to investigate them in our AHF screens. Herein, we report the evaluation of 47 commercially available ligands in AHF of styrene, allyl cyanide, and vinyl acetate. Through this study we identified several ligands that gave outstanding enantioselectivities in AHF reactions for all three substrates investigated. Most ligands screened, however, exhibited low catalytic activity compared to those obtained with phosphite ligands **1**−**3** and electron-poor bis-phosphine **4**.

(10) Yan, Y.; Chi, Y.; Zhang, X. *Tetrahedron*: *Asymmetry* **2004**, *15*, 2173-2175.

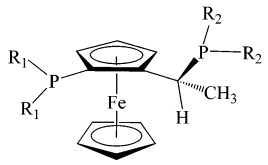
Results and Discussion

To identify ligands of commercial relevance for AHF, all screens were performed at 80 °C, 3000:1 substrate-to-rhodium ratio, and 150 psi CO/H_2 pressure. Since (*R,R*)-Ph-BPE (**6**) gives high hydroformylation activities and very reproducible enantioselectivities, it was used as standard in every Endeavor run (parallel screening reactor).[11] Active catalysts were prepared by combining $Rh(CO)_2(acac)$ with 2 equiv of each bidentate ligand in toluene followed by pressurizing the resulting solution with syngas (CO/H_2, 1:1 molar ratio). Styrene, allyl cyanide, and vinyl acetate were hydroformylated simultaneously under constant pressure with continuous monitoring of gas uptake. Olefin conversion, together with regio- and enantioselectivity of products, was determined using chiral gas chromatography as previously described.[5b] Syngas uptake curves for selected ligands are presented in Figure 1. The structures of the chiral phosphorus-based ligands utilized in this study are depicted in Chart 2.[12]

Among ferrocene-based ligands, the most active are the ones containing 3,5-bis(trifluoromethyl)phenyl substituents at the

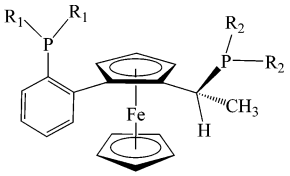
(11) See the Supporting Information for more details.

Chart 2. Subset of Asymmetric Ligands Screened in This Study



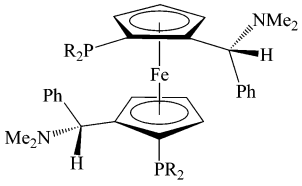
Josiphos

R1 = Ph, R2 = Cy (**7**)
R1 = Ph, R2 = *t*-Bu (**8**)
R1 = Ph, R2 = 3,5-di-CH_3-Ph (**9**)
R1 = 4-CF_3-Ph, R2 = *t*-Bu (**10**)



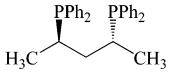
Walphos

R1 = Ph, R2 = 3,5-di-CF_3-Ph (**11**)
R1 = 3,5-di-CH_3-4-OMe-Ph, R2 = 3,5-di-CF_3-Ph (**12**)
R1 = Cy, R2 = 3,5-di-CF_3-Ph (**13**)

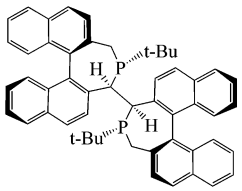


Mandyphos

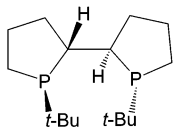
R = 3,5-di-CF_3-Ph (**14**)



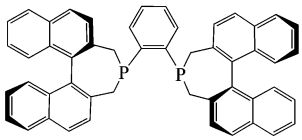
(*R*,*R*)-BDPP (**15**)



(*S*)-BINAPINE (**16**)



(*S*,*S*,*R*,*R*)-Tangphos (**17**)



(*R*)-BINAPHANE (**18**)

phosphorus atom. An analogous observation has been made in the case of previously investigated ferrocenylethyl diphosphine ligands.[13] Ligand **11**, **12**, and **14** led to almost quantitative conversion of all three olefins under our screening conditions. For this class of ligands, Josiphos ligands **7**, **8**, and **10** and Walphos **13** gave the highest enantioselectivity for all three substrates studied (between 40 and 80% ee) albeit with low regioselectivity. The syngas uptake curve for **11** (Figure 1) indicates that hydroformylation rate is approximately one order of magnitude higher than most of the diphosphines studied. Regioselectivity is of high importance in AHF as it co-determines, together with enantioselectivity, the ultimate reaction yields. Among all studied ligands, the highest regioselectivity for AHF of styrene and vinyl acetate was obtained for (*R*,*R*)-Ph-BPE (**6**) with branched-to-linear ratio of 45 and 507, respectively. For allyl cyanide hydroformylation, the highest regioselectivity was observed for (*R*,*R*)-BDPP (**15**) (b/l = 16, 70% ee) and Josiphos **9** (b/l = 14.1, 22% ee). These regioselectivities are higher than those obtained with the previous best ligand for this substrate, (*S*,*S*)-Kelliphite (b/l = 9.9, 68% ee),[8] at 80 °C.[14]

The most exciting results were obtained with (*S*)-Binapine (**16**) and (*S*,*S*,*R*,*R*)-TangPhos (**17**), two bis-phosphacycle ligands that were originally developed in Zhang's group for asymmetric hydrogenation of olefins[15,16] The highest enantioselectivities for all three substrates were obtained with (*S*)-Binapine[15] (**16**) (94% ee for styrene, 94% ee for allyl cyanide, and 87% ee for vinyl acetate) even though regioselectivities were relatively low. To our knowledge, the enantioselectivity achieved for AHF allyl cyanide with (*S*)-Binapine is the highest ever observed for this substrate. Initial experiments with (*S*,*S*,*R*,*R*)-TangPhos[16] (Rh:L = 2, entry 12) led to low enantioselectivity in styrene and allyl cyanide hydroformylation. Problems with reproducibility in experiments with (*S*,*S*,*R*,*R*)-TangPhos led us to investigate this catalytic system in more detail. When reaction was performed with only 20% excess of ligand (Rh:L = 1.2, entry 13) and lower olefin concentration (0.5 vs usual 1 mL), styrene and allyl cyanide enantioselectivities increased dramatically. These unexpected results seemed to suggest that excess free phosphine was responsible for reducing the enantioselectivities of styrene and allyl cyanide hydroformylation products. To test this hypothesis, a series of reactions has been conducted where the Rh:L ratio was carefully varied. To have a better control over the Rh:TangPhos ratio, a discrete complex, [(*S*,*S*,*R*,*R*)-TangPhos]Rh(acac) (**19**), was prepared by mixing (*S*,*S*,*R*,*R*)-TangPhos and Rh(COD)(acac) in toluene solution. The X-ray crystal structure of this complex has been determined (vide infra).

Screening of complex **19** revealed an even higher enantioselectivity in the case of styrene (90% ee) and allyl cyanide (93% ee) (Table 2, entry 1). To demonstrate the effect of phosphine on the enantioselectivity of styrene and allyl cyanide products, 20% excess (0.2 equiv) of (*S*,*S*,*R*,*R*)-TangPhos was introduced relative to **19** (Table 2, entry 2). Hydroformylation screening revealed significantly reduced enantioselectivity in the case of styrene and allyl cyanide hydroformylation products, whereas regioselectivity was unaffected. To investigate if excess TangPhos is responsible for the reduction of enantiopurity in the AHF products, isolated (*R*)-3-methyl-4-oxo-butyronitrile[17] (the hydroformylation product of allyl cyanide, 83% ee) was heated at 80 °C for 3 h with TangPhos (substrate:TangPhos = 1250:1) under either syngas or nitrogen atmosphere. In each case no decrease in enantiopurity of the (*R*)-3-methyl-4-oxo-butyronitrile was seen. When analogous experiments were conducted with a $Rh(CO)_2$(acac)/TangPhos mixture (substrate:Rh = 2000:1, Rh:TangPhos = 1:1.6), a sharp decrease (to 5% ee) in enantiopurity was observed. $Rh(CO)_2$(acac) by itself (substrate:Rh = 2000:1) also leads to the reduction of (*R*)-3-methyl-4-oxo-butyronitrile enantiopurity but to a lesser extent (65% ee). These experiments strongly suggest that a new TangPhos-Rh species is formed with excess ligand and that this species is responsible for reducing the products' enantiopurity during AHF reactions with TangPhos. To test this possibility, complex **19** was mixed with 1 equiv of (*S*,*S*,*R*,*R*)-TangPhos in THF-d_8 at room temperature. After 28 h at room temperature, a very clean formation of a new species was observed (25% conversion of **19**) at δ 101.37 ppm (d, $^1J_{P-Rh}$ = 131.2 Hz).[18] When the analogous reaction was performed at 80 °C in deuterated benzene/THF solvent

(12) Many of the ligands investigated in this study exhibited either low activity or low enantioselectivity in AHF. Structures of these ligands together with tabulated results can be found in the Supporting Information.

(13) Rampf, F. A.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *601*, 138−141.

(14) Due to its fast hydroformylation rates, (*S*,*S*)-Kelliphite can effectively hydroformylate allyl cyanide at 35 °C with even higher regioselectivity (b/l = 20) and enantioselectivity (80% ee).[5a]

(15) Tang, W.; Wang, W.; Chi, Y.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 3509−3511.

(16) (a) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612−1614. (b) Tang, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4159−4161. (c) Tang, W.; Liu, D.; Zhang, X. *Org. Lett.* **2003**, *5*, 205−207.

(17) The sample also contains 20% of 5-oxo-pentanenitrile (hydroformylation linear isomer).

(18) For $^{31}P\{^1H\}$ spectra of this reaction see the Supporting Information.

Table 1. Percentage Conversion (conv), Branched:Linear Ratio (b:l), and Enantioselectivity (% ee) for Hydroformylation of Styrene, Allyl Cyanide, and Vinyl Acetate (olefin:Rh = 3000)

Entry	L	Styrene			Allyl cyanide			Vinyl acetate		
		conv.	b:l	% ee	conv.	b:l	% ee	conv.	b:l	% ee
1	(*R*,*R*)-Ph-BPE (**6**)	74	44.6	94(*R*)	99	7.1	89 (*R*)	65	506.8	82(*S*)
2	Josiphos (**7**)	14	11.9	39(*R*)	59	6.9	59(*R*)	25	68.4	64(*S*)
3	Josiphos (**8**)	5	5.4	43(*R*)	24	8.9	60 (*R*)	18	23.5	73(*S*)
4	Josiphos (**9**)	45	20.1	38(*S*)	92	14.1	22(*S*)	27	205.2	17(*S*)
5	Josiphos (**10**)	9	4.8	40(*R*)	28	7.2	64(*R*)	22	15.2	79(*S*)
6	Walphos (**11**)	98	2.4	44(*S*)	99	0.9	6(*S*)	93	6.1	57(*R*)
7	Walphos (**12**)	95	2.5	27(*S*)	97	1.0	2(*R*)	86	5.7	48(*R*)
8	Walphos (**13**)	26	2.7	2(*S*)	47	3.5	53(*R*)	42	73.1	73(*R*)
9	Mandyphos (**14**)	99	3.5	17(*S*)	99	2.1	1(*R*)	96	15.2	21(*R*)
10	(*R*,*R*)-BDPP (**15**)	22	12.4	48 (*S*)	82	16.1	70 (*S*)	22	16.4	31 (*S*)
11	(*S*)-Binapine (**16**)	12	9.5	94 (*S*)	49	6.7	94 (*S*)	21	32.4	87 (*R*)
12	(*S*,*S*,*R*,*R*)-TangPhos (**17**)	10	14.9	13 (*S*)	49	7.5	6 (*S*)	26	138	81 (*R*)
13	(*S*,*S*,*R*,*R*)-TangPhos (**17**)[b]	15	13.7	65 (*S*)	61	7.4	84 (*S*)	29	59.3	80 (*R*)
14	(*R*)-Binaphane (**18**)	17	8.2	34 (*R*)	62	5.2	50 (*R*)	21	34	24 (*S*)

[a] All reactions performed at 80 °C in toluene with 150 psi 1:1 CO:H_2 with L:Rh = 2, total substrate:Rh = 3000, 1 mL of substrates, and 3 h reaction time. [b] L:Rh = 1.2, total substrate:Rh = 3000, 0.5 mL of substrates. Ligands in blue gave between 50 and 70% ee, whereas those in red gave enantioselectivities higher than 70%.

Table 2. Percentage Conversion (conv), Branched:Linear Ratio (b:l), and Enantioselectivity (% ee) for Hydroformylation of Styrene, Allyl Cyanide, and Vinyl Acetate (olefin:catalyst = 3000)

			styrene			allyl cyanide			vinyl acetate		
entry	catalyst	additive (%)	conv	b:l	% ee	conv	b:l	% ee	conv	b:l	% ee
1	**19**	none	12	14.8	90	61	7.5	93	17	30	83
2	**19**	(*S*,*S*,*R*,*R*)TangPhos (20)	11	15.2	49	55	7.3	27	17	145	80
3	**19**	$Rh(CO)_2(acac)$ (20)	31	2.8	33	82	4.1	50	27	92	19

[a] All reactions performed at 80 °C in toluene with 150 psi, 1:1 CO:H_2, total substrate:Rh = 3000, and 3 h reaction time.

mixture (v/v 2:1),[19] this new species is formed but at a faster rate (15%, 57%, and 83% conversion of **19** after 1, 6, and 21 h, respectively) by consuming equal amounts of **19** and (*S*,*S*,*R*,*R*)-TangPhos, as shown by $^{31}P\{^1H\}$ NMR spectroscopy.[18] When 2 equiv of (*S*,*S*,*R*,*R*)-TangPhos are reacted with 1 equiv of $Rh(CO)_2(acac)$ in toluene, rapid formation of this new species is observed, which separates within seconds from the solution as a red oil. This new product was isolated from this reaction as a red solid in 88% yield. After complete analysis (NMR, HRMS, elemental analysis, and X-ray analysis) this new product was identified as the ionic complex $[[((S,S,R,R)\text{-TangPhos})_2]\text{-Rh}]^+[acac]^-$, where acac (acetylacetonate) serves as a nonco-ordinating anion. Interestingly, formation of $[[((S,S,R,R)\text{-TangPhos})_2]Rh]^+[acac]^-$ from $Rh(CO)_2(acac)$ and 2 equiv of TangPhos is much faster (complete reaction within 30 min)[18] than in the case of reaction of **19** with TangPhos (days). This implies different reaction pathway for both reactions. When $[[((S,S,R,R)\text{-TangPhos})_2]Rh]^+[acac]^-$ is heated for 1 h with (*R*)-3-methyl-4-oxo-butyronitrile (83% ee) in toluene (substrate:Rh = 3400:1), a complete racemization of the chiral aldehyde was observed. To distinguish whether the cationic or anionic portion of the salt is responsible for the negative effect on the products' enantioselectivity, the salt $[N(n\text{-Bu})_4]^+[acac]^-$ was synthesized and tested. Heating $[N(n\text{-Bu})_4]^+[acac]^-$ for 1 h with (*R*)-3-methyl-4-oxo-butyronitrile (83% ee) in toluene (substrate:Rh = 3400:1) led to complete racemization of the chiral aldehyde. These results clearly indicate that the free acetylacetonate anion in $[[((S,S,R,R)\text{-TangPhos})_2]Rh]^+[acac]^-$ or $[N(n\text{-Bu})_4]^+[acac]^-$ is a strong enough base to induce racemization of the aldehydes formed during the AHF reactions. Since some of the $[[((S,S,R,R)\text{-TangPhos})_2]Rh]^+[acac]^-$ is even generated from equimolar amounts of $Rh(CO)_2(acac)$ and TangPhos, it is now apparent why optimal enantioselectivities cannot be achieved from standard catalyst preparation protocol in the hydroformylation of styrene and allyl cyanide. The molecular structure of $[[((S,S,R,R)\text{-TangPhos})_2]Rh]^+[acac]^-$ is presented in Figure 2. Due to the presence of four *t*-Bu groups in close proximity, there is substantial distortion from ideal square planar geometry around the rhodium atom. The dihedral angle between planes defined by atoms P1−Rh−P2 and P3−Rh−P4 is 36.9°. The acetylacetonate anion is separated from the rhodium complex with the closest distance between them being 2.44 Å (distance between O1 and hydrogen atoms of *t*-Bu groups). There are only a few reports describing the preparation of cationic phosphine/phosphite rhodium complexes with acetylacetonate or hexafluoroacetylacetonate (hfacac) as the anion.[20]

(19) If the reaction in conducted in pure C_6D_6, then the product separates from the solution as a red oil.

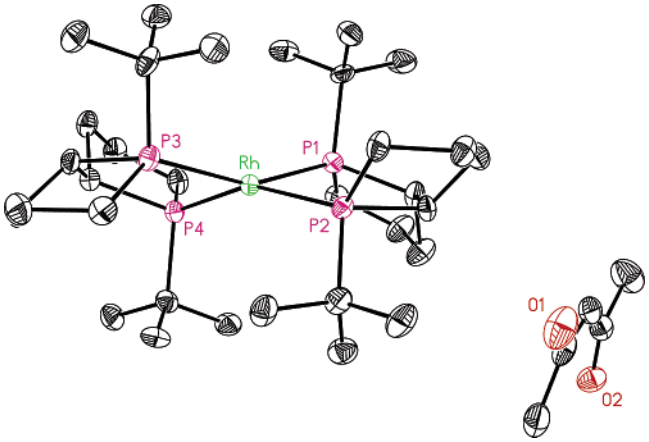


Figure 2. Molecular structure for $[[(S,S,R,R)\text{-TangPhos})_2]\text{-Rh}]^+[\text{acac}]^-$ with 40% probability thermal ellipsoids.

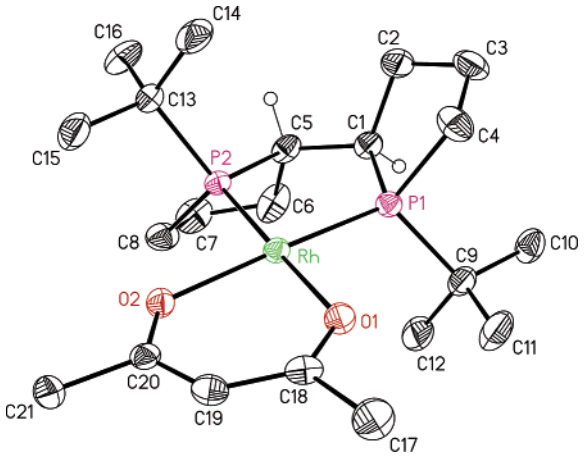


Figure 3. Molecular structure for [(*S*,*S*,*R*,*R*)-TangPhos]Rh(acac) with 40% probability thermal ellipsoids.

It is not clear, at this time, how common this phenomenon (reduction of % ee with excess ligand/formation of $[RhP_4]^+[acac]^-$ species) is during AHF. This behavior might be limited to relatively small and electron-rich phosphine ligands since (*R*,*R*)-Ph-BPE (**6**)[21,22] and phosphite ligands do not lead to lower % ee of AHF products when excess ligand is used. These results should, however, serve as a caution when screening new ligands in AHF, as low reaction enantioselectivity might not necessary reflect the ligands' true potential. In a separate experiment, 20% excess of rhodium precursor $Rh(CO)_2(acac)$ was added relative to **19** to the hydroformylation solution (Table 2, entry 3). Enantioselectivity substantially decreased for all the substrates, as did regioselectivity in the case of stryene and allyl cyanide products. This decrease in selectivity is due to the contribution of $Rh(CO)_2(acac)$, which gives racemic and low-regioselectivity hydroformylation products. An increase in regioselectivity of vinyl acetate products in the last two runs (Table 2, entries 2, 3) is most likely due to an increase of retro-Michael reaction, which leads to selective decomposition of the linear isomer. Catalytic activities obtained with **17**/**19** are low, which is expected for this class of ligands. AHF of styrene has been recently disclosed with **19** (76% ee, b/l = 15.7 at 70 °C, 600 psi, L/Rh = 1.2),[23] giving lower than optimal enantioselectivities. This is presumably due to the adverse effect of excess of free phosphine as discussed above. Interestingly, excess (*R*)-Binaphine (**16**) does not affect enantioselectivity of any of the three hydroformylation products. It is worth pointing out that the third bis-phosphacycle included in this study, (*R*)-Binaphane (**18**), gave relatively low enantioselectivities for all three substrates.

Other ligands that have been recently discovered for highly enantioselective hydroformylation of olefins include (*S*,*S*)-Esphos (**5**),[24] diazaphospholane (**4**),[7] and alkyl- and aryl-substituted BPE and DuPhos ligands.[8,23,25] Now two additional members from the bis-phosphacycle family, (*S*,*S*,*R*,*R*)-TangPhos (**17**) and (*S*)-Binapine (**16**), have been identified as highly enantioselective ligands in AHF. The common features of these ligands include the presence of a phosphacycle (which provides structural rigidity) and a two-carbon bridging group between the phosphorus atoms. The bridging group is an important element in setting an appropriate bite angle at the metal center. At this moment, however, it is not evident if the linking group between phosphorus atoms in the above-mentioned bis-phosphacycle ligands is of optimal length, and further research is needed to answer this question. Inspection of X-ray structures of [(*S*,*S*,*R*,*R*)-TangPhos]Rh(acac) (Figure 3) and [(*R*,*R*)-Ph-BPE]-Rh(acac)[8] reveals that the bite angle in both complexes is virtually identical with values of 85.88° and 84.85/85.46°,[26] respectively. There are, however, structural differences between **19** and [(*R*,*R*)-Ph-BPE]Rh(acac) with respect to the chiral pocket of the catalyst. In [(*S*,*S*,*R*,*R*)-TangPhos]Rh(acac), the *t*-Bu substituents are not protruding toward the Rh atom to the same extent as the phenyl groups are in the case of [(*R*,*R*)-Ph-BPE]-Rh(acac). On the other hand, the *t*-Bu groups are somewhat closer to the rhodium center in **19** than are the phenyls in [(*R*,*R*)-Ph-BPE]Rh(acac).

Unlike in the case of asymmetric hydrogenation, where structurally diverse families of ligands were found to give highly enantioselective catalysts,[27] there has not been analogous success in the AHF area. The lack of such success has hindered rapid development of better ligands in AHF. Even though the bis-phosphacycle motif does not guarantee success in AHF, very high enantioselectivities obtained with several structurally diverse bis-phosphacycle ligands (e.g., (*R*,*R*)-Ph-BPE, (*S*,*S*,*R*,*R*)-TangPhos, and (*S*)-Binapine) suggest that this ligand family is unique and very promising for future developments of novel ligands for AHF. It is evident that catalyst activity of bis-phosphacycle ligands is not correlated to structural features of the ligands but rather to the ligands' electronic character. Catalytic activity increases as phosphorus atoms become less electron rich, as exemplified by the relative activities **4** > **6** > **16** ~ **17**. Future ligand design in Rh-catalyzed AHF area should thus focus on the synthesis of novel bis-phosphacycle ligands

(20) (a) Rosales, M.; Gonzalez, A.; Gonzalez, B.; Moratinos, C.; Perez, H.; Urdaneta, J.; Sanchez-Delgado, R. A. *J. Organomet. Chem.* **2005**, *690*, 3095−3098. (b) Koroteev, A. M.; Teleshov, A. T.; Koroteev, M. P.; Nifant'ev, E. E. *Russ. J. Gen. Chem.* **2004**, *74*, 1313−1316. (c) Fornika, R.; Six, C.; Gorls, H.; Kessler, M.; Kruger, C.; Leitner, W. *Can. J. Chem.* **2001**, *79*, 642−648.

(21) No reduction in the products' enantioselectivity has been observed even with four-fold excess of (*R*,*R*)-Ph-BPE relative to $Rh(CO)_2(acac)$.

(22) When $Rh(CO)_2(acac)$ is reacted with 2 equiv of (*R*,*R*)-Ph-BPE (**6**), clean formation of [(*R*,*R*)-Ph-BPE]Rh(acac) is observed (free ligand also observed) and no further reaction occurs upon heating at 80 °C for 16 h.

(23) Huang, J.; Bunel, E.; Allgeier, A.; Tedrow, J.; Storz, T.; Preston, J.; Correll, T.; Manley, D.; Soukup, T.; Jensen, R.; Syed, R.; Moniz, G.; Larsen, R.; Martinelli, M.; Reider P. J. *Tetrahedron Lett.* **2005**, *46* 7831−7834.

(24) Breeden, S.; Cole-Hamilton, D. J.; Foster, D. F.; Schwarz, G. J.; Wills, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4106−4108.

(25) For a recent review on phospholane ligands see: Clark, T. P.; Landis, C. R. *Tetrahedron: Asymmetry* **2004**, *15*, 2123−2137.

(26) Values for two independent molecules found in the crystal lattice of [(*R*,*R*)-Ph-BPE]Rh(acac).

(27) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029−3069.

with electron-withdrawing substituents placed in close proximity to phosphorus atoms.

In summary, asymmetric hydroformylation of styrene, allyl cyanide, and vinyl acetate has been carried out using 47 commercially available phosphorus-based ligands. Except for a few ligands bearing electron-withdrawing substituents at the phosphorus atom, catalytic activities for this class of ligands were found to be quite low. Among all ligands studied, the best enantioselectivities in AHF of styrene, allyl cyanide, and vinyl acetate were achieved with the phospholane-type ligands (*S*)-Binapine and (*S*,*S*,*R*,*R*)-TangPhos. None of the ligands studied achieved higher regioselectivity in AHF of styrene and vinyl acetate than previously reported[8] (*R*,*R*)-Ph-BPE. In the case of allyl cyanide, the highest regioselectivity was achieved with the (*R*,*R*)-BDPP ligand. (*S*)-Binapine and (*S*,*S*,*R*,*R*)-TangPhos have joined the group of other highly enantioselective bis-phosphacycle ligands and further solidified the idea that the bis-phosphacycle ligand class is exceptional in the area of asymmetric hydroformylation of olefins.

Experimental Section

General Considerations. All syntheses and manipulations of air-sensitive materials were carried out in nitrogen atmosphere glove box. Solvents were first saturated with nitrogen and then dried by passage through activated alumina and Q-5 catalyst prior to use. Deuterated NMR solvents were dried over sodium/potassium alloy and filtered prior to use. NMR spectra were recorded on a Varian INOVA 300 and Mercury 300 (FT 300 MHz, ^{1}H; 75 MHz, ^{13}C; 121 MHz, ^{31}P) spectrometer. ^{1}H NMR data are reported as follows: chemical sift (multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, and m = multiplet), integration and assignment). Chemical shifts for ^{1}H NMR data are reported in ppm downfield from internal tetramethylsilane (TMS, δ scale) using residual protons in the deuterated solvents (C_6D_6, 7.15 ppm: CD_2Cl_2, 5.32 ppm, C_6H_5Cl, 6.97, 7.00, 7.13 ppm) as references. ^{13}C ^{31}P data were determined with ^{1}H decoupling and the chemical shifts are reported in ppm vs tetramethylsilane (C_6D_6, 128 ppm, CD_2Cl_2, 53.8 ppm, C_6H_5Cl, 125.77, 128.00, 129.06, 133.88 ppm) and 85% H_3PO^4 standard (external, 0 ppm), respectively. Mass spectra (both positive and negative electrospray) were recorded on a Waters/Micromass QTOF-II mass spectrometer (s/n UC-175), operated at 9000 resolution (FWHM). Elemental analyses were performed by University of Michigan analytical services.

Materials. Styrene and vinyl acetate were purchased from Aldrich, and allyl cyanide was obtained from Fluka. Styrene was purified by passing through activated alumina. Allyl cyanide and vinyl acetate were distilled and then degassed via nitrogen purge before use. All diphosphine ligands were purchased from either Strem or Aldrich.

Asymmetric Hydroformylation Procedure. Hydroformylation solutions were prepared by addition of ligand and $Rh(CO)_2(acac)$ stock solutions to toluene followed by addition of olefin solution. The total amount of liquids in each reactor cell was 4.5 mL. Ligand solutions (0.03 M) and $Rh(CO)_2(acac)$ (0.05 M) were prepared in the drybox by dissolving an appropriate amount of compound in toluene at room temperature. The styrene/allyl cyanide/vinyl acetate/dodecane solution was prepared by mixing 11.712 g of styrene, 7.544 g of allyl cyanide, 9.681 g of vinyl acetate, and 5.747 g of dodecane (1:1:1:0.3 molar ratio). Hydroformylation reactions were conducted in an Argonaut Endeavor reactor system housed in an inert atmosphere glovebox. The reactor system consists of eight parallel, mechanically stirred pressure reactors with individual temperature and pressure controls. Upon charging the catalyst solutions, the reactors were pressurized with 150 psi of syngas (CO: H_2 1:1) and then heated to 80 °C while stirring at 800 rpm. The runs were stopped after 3 h by cooling the reactor to 40−50 °C and subsequent venting the system and purging with nitrogen. Upon opening the reactor, a sample of each reaction mixture was taken out and diluted with 1.7 mL of toluene, and this solution was analyzed by gas chromatography. For analysis of styrene and vinyl acetate products Supelco's Beta Dex 225 column (30 m) was used. Temperature program: 100 °C for 5 min, then 4 °C/min to160 °C; retention times: 2.40 min for vinyl acetate, 6.76 (*S*) and 8.56 (*R*) min for the enantiomers of the acetic acid 1-methyl-2-oxo-ethyl ester (branched regioisomer), 11.50 min for acetic acid 3-oxo-propyl ester (linear regioisomer), 12.11 (*S*) and 12.34 (*R*) min for the enantiomers of 2-phenylpropionaldehyde (branched regioisomer), and 16.08 min for 3-phenylpropionaldehyde (linear regioisomer). For allyl cyanide product analysis an Astec Chiraldex A-TA column (30 m, 0.25 mm) was used. Temperature program:[28] from 60 °C to 100 °C at 2 °C/min, then from 100 to 120 °C at 20 °C/min, then from 120 to 160 °C at 25 °C/min. Retention times: 7.63 min for allyl cyanide, 22.98 (*S*) and 23.29 (*R*) min for the enantiomers of the 3-methyl-4-oxo-butyronitrile (branched regioisomer), and 28.48 min for the 5-oxo-pentanenitrile (linear regioisomer).

Preparation of [(*S*,*S*,*R*,*R*)-TangPhos]Rh(acac) (19). To a vial containing 126.8 mg (0.44 mmol) of (*S*,*S*,*R*,*R*)-TangPhos and 137.3 mg (0.44 mmol) of Rh(acac)(COD) was added 5 mL of toluene. After stirring overnight, solvent was removed under reduced pressure. To the residue was added 5 mL of hexane, and the mixture was heated until all solid dissolved. The solution was filtered and then put into a freezer overnight (−40 °C). The solvent was decanted, and large yellow X-ray-quality crystals were dried under reduced pressure to give 131 mg of product. Yield: 60.6%. ^{1}H NMR (C_6D_6, 300 MHz): δ 5.38 (s, 1H), 2.16 (dt, $^2J_{H-H}$ = 14.2 Hz, $^3J_{H-H}$ = 6.0 Hz, 2H), 1.90 (s, 6H), 1.83 (m, 2H), 1.5−1.7 (m, 6H), 1.44 (m, 4H), 1.29 (d, $^3J_{H-P}$ = 14.2 Hz, 18 H). ^{13}C{^{1}H} NMR (C_6D_6, 75 MHz): δ 184.19 (acac-*C*-O), 99.53 (d, J_{C-P} = 2.0 Hz, acac-*C*H), 45.46 (td, J_{C-P} = 9.4 Hz, *C*H), 36.26 (t, J_{C-P} = 4.8 Hz, *C*H_2), 32.00 (t, J_{C-P} = 9.4 Hz), 28.24 (s, C*H*$_3$), 27.92 (s, acac-C*H*$_3$), 26.71 (t, J_{C-P} = 8.7 Hz), 26.51 (*C*H_2). HSQC (C_6D_6): δ 99.53/5.38, 45.46/1.62, 36.26/(1.58, 1.44), 28.24/1.29, 27.92/1.90, 26.71/(2.16, 1.83), 26.51/(1.62, 1.44). ^{31}P NMR (C_6D_6, 121 MHz): δ 115.94 (d, $^1J_{P-Rh}$ = 191.5 Hz). ESMS $(M + H)^+$: calcd for $C_{21}H_{40}O_2P_2Rh$ 489.1553, found 489.1571. Anal. Calcd for $C_{21}H_{40}O_2P_2Rh$: C, 51.64; H, 8.05. Found: C, 51.88; H, 8.05.

Preparation of [((*S*,*S*,*R*,*R*)-TangPhos)$_2$Rh]$^+$[acac]$^-$. To a vial containing 121 mg (0.42 mmol) of (*S*,*S*,*R*,*R*)-TangPhos and 54.5 mg (0.42 mmol) of $Rh(CO)_2(acac)$ was added 2 mL of toluene. Within seconds a red oil separated from the solution and then solidified. The reaction mixture was stirred overnight. The solution was decanted, and the remaining red solid was washed with toluene (1 mL) and hexane (2 × 1 mL) and then dried under reduced pressure to give 144 mg of product (yield 88%). X-ray-quality crystals were grown from THF/hexane at room temperature. ^{1}H NMR (C_6D_5Cl, 300 MHz): δ 5.63 (s, 1H), 2.06−3.21 (br, 6H), 1.92−2.17 (m, 8H), 1.64−1.90 (m, 12H), 1.54 (m, 4H), 1.37 (m, 4H), 0.95 (vt, $^3J_{H-P}$ = 6.6 Hz, 36H). ^{13}C{^{1}H} NMR (C_6D_5Cl, 75 MHz) δ 99.60 (acac-*C*H), 46.27 (pd, J_{C-P} = 12.1 Hz, J_{C-P} = 1.8 Hz, *C*H), 35.73 (p, J_{C-P} = 2.6 Hz, *C*H_2), 34.72 (m, quat.), 29.07 (s, *C*H_3), 27.49 (s, *C*H_2), 27.37 (m, *C*H_2). Acac resonances not observed. ^{31}P NMR (C_6D_5Cl, 121 MHz): δ 101.37 (d, $^1J_{P-Rh}$ = 131.2 Hz). ESMS $(M)^+$: calcd for $C_{32}H_{64}P_2Rh$ 675.301, found 675.294. $(2M^+acac^-)^+$: calcd for $C_{64}H_{128}P_8Rh_2$ 1449.647, found 1449.639. Anal. Calcd for $C_{37}H_{71}O_2P_4Rh$: C, 57.36; H, 9.24. Found: C, 57.72; H, 9.36.

Preparation of [N(*n*-Bu)$_4$]$^+$[acac]$^-$. To 30 mL of a 1 M tetra-*n*-butylammonium hydroxide solution in methanol (30 mmol) was added 4.20 g (42 mmol) of acetylacetone followed by 10 mL of methanol. After stirring for 2.5 h, volatiles were removed under

(28) These conditions are somewhat different from the ones we used and reported previously. After column regeneration we found that the old temperature program was insufficient to resolve product enantiomers.

reduced pressure. The residue was suspended in 40 mL of THF. A white crystalline solid was collected by filtration, washed with THF (2 × 15 mL), and then dried under reduced pressure to give 8.2 g of product (yield 80.2%). Crystallization: Part of the product (2.5 g) was dissolved in 20 mL of methylene chloride followed by the addition of 30 mL of THF. Within seconds large colorless crystals start forming. After half an hour at room temperature the crystals were filtered, washed with THF (2 × 15 mL), and then dried under reduced pressure to give 2.1 g of product, mp = 153 °C. ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 4.69 (s, 1H), 3.18 (m, 8H), 2.06 (br, 3H), 1.68 (br, 3H), 1.56 (m, 8H), 1.34 (sex, 8H, ^3J = 7.5 Hz), 0.93 (t, ^3J = 7.5 Hz, 12H). ^{13}C{^{1}H} NMR (CD_2Cl_2, 75 MHz): δ 99.40 (acac-*C*H), 58.72, 28.73 (br), 24.03, 19.84, 13.55. Anal. Calcd for $C_{21}H_{43}NO_2$: C, 73.84; H, 12.69; N, 4.10. Found: C, 74.10; H, 12.80; N, 4.02.

Preparation of Enantioenriched (*R*)-3-Methyl-4-oxo-butyronitrile (83% ee). Allyl cyanide (5 cells × 4 mL) was hydroformylated (neat) in an Endeavor reactor at 60 °C for 24 h using $Rh(CO)_2$(acac)/**4** catalyst (allyl cyanide:Rh = 20 000), **4**:Rh = 1.4). Reaction products from all cells were combined and subjected to vacuum distillation (0.15 Torr). Three fractions have been collected: fraction #1, 3.5 mL (83% ee, b/l = 8.2) at 49−52 °C, fraction #2, 3.5 mL (83% ee, b/l = 7.4) at 52−55 °C, fraction #3, 12 mL (83% ee, b/l = 4.1) at 55−57 °C. The second and third fractions was used in our study.

Effect of Catalyst Components on Enantiopurity of (*R*)-3-Methyl-4-oxo-butyronitrile. To a vial containing 0.8 g of (*S*)-3-methyl-4-oxo-butyronitrile (83% ee) was added 3.5 mL of toluene followed by addition of catalyst component (82 μL of a 0.05 M solution of $Rh(CO)_2$(acac) in toluene or 219 μL of a 0.03 M solution of (*S*,*S*,*R*,*R*)-TangPhos in toluene or a mixture of $Rh(CO)_2$(acac)/(*S*,*S*,*R*,*R*)-TangPhos in 1:1.6 ratio) or 82 μL of a 0.03 M solution of [[((*S*,*S*,*R*,*R*)-TangPhos)$_2$]Rh]$^+$[acac]$^-$ in THF or 82 μL of a 0.03 M solution of [N(*n*-Bu)$_4$]$^+$[acac]$^-$ in CD_2Cl_2. Solutions were then heated for 1 or 3 h at 80 °C under syngas or nitrogen atmosphere. Reaction products were characterized using chiral GC. Reactions performed with syngas have been performed using an Endeavor reactor, whereas those under nitrogen have been conducted in closed vials in the hood.

X-ray Analysis of [(*S*,*S*,*R*,*R*)-TangPhos]Rh(acac) (19) and [[((*S*,*S*,*R*,*R*)-TangPhos)$_2$]Rh]$^+$[acac]$^-$. [(*S*,*S*,*R*,*R*)-TangPhos]Rh(acac) (**19**): $C_{21}H_{39}O_2P_2Rh$, M_r = 488.37, trigonal, $P3_121$, a = 11.0103(4) Å, b = 11.0103(4) Å, c = 33.178(3) Å, V = 3483.2(3) Å^3, Z = 6, D_{calc} = 1.397 g cm^{-3}, Mo Kα (λ = 0.71073 Å), T = 173 K. [[((*S*,*S*,*R*,*R*)-TangPhos)$_2$]Rh]$^+$[acac]$^-$: $C_{37}H_{71}O_2P_5Rh$, M_r = 744.73, orthorhombic, $P2_12_12_1$, a = 12.960(1) Å, b = 14.822-(1) Å, c = 20.997(2) Å, V = 4033.3(5) Å^3, Z = 6, D_{calc} = 1.276 g cm^{-3}, Mo Kα (λ = 0.71073 Å), T = 173 K. Data for both structures were collected at 173 K on a Bruker SMART PLATFORM equipped with a CCD area detector and a graphite monochromator utilizing Mo Kα radiation (λ = 0.71073 Å). Cell parameters were refined using the entire data set for each structure. A hemisphere of data (1381 frames) was collected using the ω-scan method (0.3° frame width). The first 50 frames were remeasured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1%). Absorption corrections were applied by integration based on indexed measured faces.

The structures were solved by the direct methods in SHELXTL6.1[29] and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. In the final cycle of refinement of **19**, 5023 observed reflections with $I > 2\sigma(I)$ were used to refine 243 parameters, and the resulting R_1, wR_2, and S (goodness of fit) were 2.7%, 5.61%, and 1.063, respectively. The Flack x parameter refined to a value of 0.00(2), confirming that the absolute configuration is correctly shown as the present enantiomer. For [[((*S*,*S*,*R*,*R*)-TangPhos)$_2$]Rh]$^+$-[acac]$^-$, 6624 observed reflections with $I > 2\sigma(I)$ were used to refine 397 parameters, and the resulting R_1, wR_2, and S (goodness of fit) were 5.67%, 12.41%, and 1.00, respectively. The Flack x parameter refined to a value of −0.04(4), confirming that the absolute configuration is correctly shown as the present enantiomer. Refinement was done using F^2.

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Supporting Information Available: Structures of chiral ligands, asymmetric hydroformylation results, NMR spectra of [[((*S*,*S*,*R*,*R*)-TangPhos)$_2$]Rh]$^+$[acac]$^-$ and [(*S*,*S*,*R*,*R*)-TangPhos]Rh(acac) (**19**), X-ray data table, and comprehensive bond lengths and angles tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) Sheldrick, G. M. *SHELXTL6.1*; Bruker AXS: Madison, WI, 2000.