Ligands for Practical Rhodium-Catalyzed Asymmetric Hydroformylation

JERZY KLOSIN*,† AND CLARK R. LANDIS*,‡

Corporate R&D, The Dow Chemical Company, 1776 Building, Midland, Michigan 48674, and Department of Chemistry, University of Wisconsin—Madison, 1101 University Avenue, Madison, Wisconsin 53706

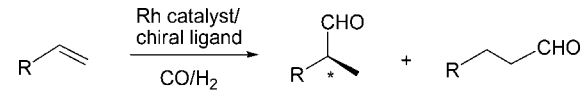
Received April 27, 2007

ABSTRACT

A series of bis-phosphite and bis-phosphine ligands for asymmetric hydroformylation reactions has been evaluated. Bis-phosphite ligands lead, in general, to high regioselectivities across a range of substrates while good enantioselectivities are limited to only a few examples. We found that bis-phospholane-type ligands, such as bis-diazaphospholanes and bis-phospholanes, can lead to very high regio- and enantioselectivities for several different substrates.

1. Introduction

There is a growing need to efficiently produce chemicals in their enantiopure form as more and more pharmaceutical drugs are required to be marketed as a single enantiomer.[1] This need has led to greater interest in asymmetric catalysis and development of new chiral ligands for metal-catalyzed reactions. Asymmetric hydroformylation (AHF) is among very promising but underdeveloped catalytic reactions.[2] Asymmetric hydroformylation is a catalytical, atom-economic, one-carbon homologation reaction that produces chiral aldehydes from inexpensive feedstock (olefins, syngas) in a single step under essentially neutral reaction conditions (eq 1). Since the aldehyde group is one of the most versatile functional groups, a variety of useful chiral chemicals such as amines, imines, alcohols, and acids can be easily prepared from chiral aldehydes. Even though AHF offers great promise to the fine chemical industry, this reaction has not yet been utilized on a commercial scale due to several technical challenges. Among the most significant are (a) low reaction rates at low temperature where good selectivities are usually observed, (b) difficulty in controlling regio- and enantioselectivities concurrently, and (c) limited substrate scope for any single ligand.



(1)

Reaction rates in Rh-catalyzed hydroformylation are commonly slower than those of asymmetric hydrogenation reactions[3] when conducted near ambient temperature. Commercially practicable rates of several thousand turnovers per hour can be achieved in AHF at temperatures higher than 60 °C. However, at higher temperatures, lower regio- and enantioselectivities are usually observed. Thus, to be commercially viable for less reactive substrates, ligands may be required to operate at higher temperature without compromising selectivity. Unlike in asymmetric hydrogenation where a single product is produced upon double bond reduction, the additional challenge in AHF is control of reaction regioselectivity. The ability of a ligand to give high regioselectivities in AHF (high branched (b) to linear (l) ratio) is a very important attribute since any amount of achiral linear isomer can be regarded as an impurity that requires separation from the desired chiral product. For example, a reaction mixture with b/l of 9 represents a 90% pure product (10% linear isomer impurity), whereas b/l of 99 represents a 99% pure product. Although regioselectivity can be controlled to some extent by reaction conditions (temperature and syngas pressure), it is mainly controlled by the nature of the chelating ligand.

Considerable research effort has been devoted to identifying effective chiral ligands for AHF; however, success has been limited to only a few examples. The initial success in rhodium-catalyzed hydroformylation came from Union Carbide with the discovery of the bis-phosphite ligand (2*R*,4*R*)-chiraphite (**1**).[4] This ligand was designed to develop an AHF route to anti-inflammatory 2-aryl-propionic acid drugs, such as (*S*)-naproxen. Good enantioselectivities can be obtained with (2*R*,4*R*)-chiraphite in AHF of styrene but only when the reaction is performed at around room temperature. (2*R*,4*R*)-chiraphite analogs with different length of the diolate bridge and different bridge substitution, reported by van Leeuwen et al.,[5] led to significantly lower regio- and enantioselectivities. Somewhat improved enantioselectivity was observed with (2*R*,4*R*)-chiraphite analog **2**, where (*R*,*R*)-pentane-2,4-diol was substituted with a sugar-derived bridge.[6] It is worth pointing out that the bridge in **2** represents a three-carbon linker between oxygen atoms similar to that found in (2*R*,4*R*)-chiraphite. A breakthrough in AHF came from Takaya's laboratory with the synthesis of (*R*,*S*)-binaphos (**3**)[7] and its analogs. These ligands were found to lead to high enantioselectivities for a variety of olefins;[2c] however, regioselectivities are typically quite low. Wills et

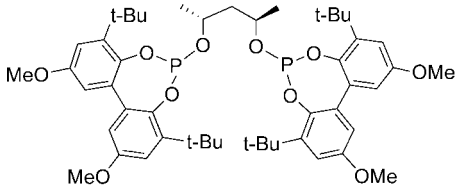
Jerzy Klosin received his M.S. degree from Adam Mickiewicz University, Poznan, Poland, in 1991, where he worked in the laboratory of Prof. Bogdan Marciniec. After earning a Ph.D. from the University of Florida in 1995 under the guidance of Prof. William M. Jones, he accepted a position in Corporate R&D of The Dow Chemical Company where he is currently a research leader. His research interests include asymmetric catalysis and olefin polymerization chemistry.

Clark Landis' research interests focus on catalysis, reaction mechanisms, ligand design, instrumentation development, and bonding theory. After completing his undergraduate work at the University of Illinois—Urbana and Sheffield University, he received his Ph.D. from the University of Chicago under the guidance of Prof. Jack Halpern in 1983. After three years of work in the Corporate Research Laboratory at the Monsanto Company, Prof. Landis began his academic career at the University of Colorado—Boulder. In 1990, he moved to the University of Wisconsin—Madison where he is a Professor of Chemistry.

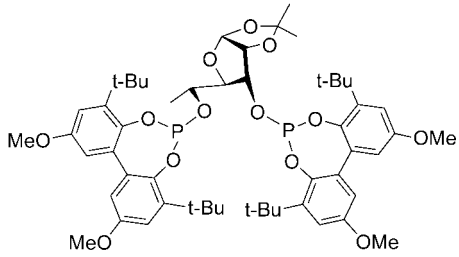
* E-mail addresses: jklosin@dow.com; landis@chem.wisc.edu.
† The Dow Chemical Company.
‡ University of Wisconsin—Madison.

10.1021/ar7001039 CCC: $37.00
Published on Web 11/13/2007

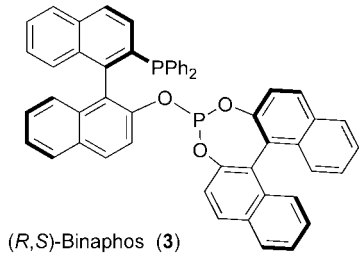
al.[8] reported the first phospholane-type ligand (**4**) that was found to be effective for AHF of vinyl acetate but, interestingly, quite unselective toward hydroformylation of styrene. These advances, although impressive, have not led to the application of the asymmetric hydroformylation reaction on a commercial scale. A new generation of ligands is needed to realize its commercial potential. New AHF ligands must have the ability to produce optically active aldehydes at high reaction rates (turnover rates of several thousand per hour) and operate at high temperature where necessary, while maintaining very high product regio- and enantioselectivity. Our research goal has been to find such ligands.



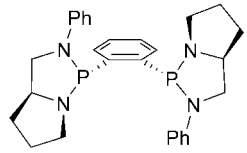
(2*R*,4*R*)-Chiraphite (**1**)



(1*R*,2*R*,3*R*,4*R*,5*S*) (**2**)



(*R*,*S*)-Binaphos (**3**)

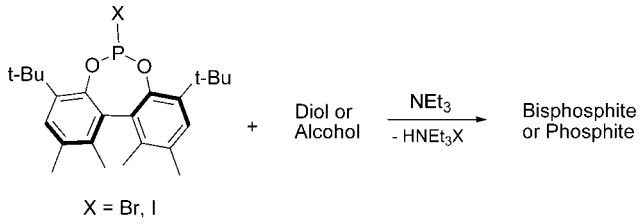


(*S*,*S*)-Esphos (**4**)

2. Ligand Evaluation

At the outset of our research we decided to develop a screening method that would allow us to evaluate rapidly and reliably many new ligands in AHF. For this purpose, we utilized an Argonaut Endeavor reactor system consisting of eight parallel stirred autoclaves. To increase the ligand screening throughput further, we developed one-pot screening of multiple olefinic substrates.[9] In this screening, three substrates (styrene, allyl cyanide, and vinyl acetate) are combined together in a 1:1:1 molar ratio and are simultaneously hydroformylated under the same reaction conditions. Our choice of styrene, allyl cyanide, and vinyl acetate was dictated by the recent interest in applying these substrates in the synthesis of fine chemicals via AHF. Additionally, these three substrates represent different types of terminal olefins with their unique reactivity and selectivity in hydroformylation reactions. Our hope was that screening against all three of these substrates in a single run would allow us to identify ligands applicable to a broad range of olefins. An additional benefit of multisubstrate screening is that relative reaction rates of different substrates can be ascertained in a single experiment. A series of control experiments using a few different ligands and toluene as a solvent showed that the products' regio- and enantioselectivities as well as relative reaction rates were very similar regardless of whether the reactions were conducted on the pooled substrates or on individual components. To rapidly quantify the products of these reactions (ten possible components per individual reactor—three substrates, three branched products, three linear products, and dodecane as internal standard), we utilized two different GCs equipped with two different chiral columns. The first GC column (Supelco Beta Dex 225), based on β-cyclodextrin, allowed complete separation of both enantiomers of branched aldehyde and the achiral linear aldehyde derived from both styrene and vinyl acetate, thus allowing for direct measurements of regio- and enantioselectivity. The second GC column (Astec Chiraldex A-TA), based on α-cyclodextrin, yielded good separation of all products derived from allyl cyanide hydroformylation. We found that this column was also capable of resolving all vinyl acetate products although we did not use this column for this purpose. It was our practice to prepare two sets of GC vials and perform GC analyses on both instruments at the same time. It is important to prepare samples for GC analysis immediately after the reaction is complete because products' enantioselectivities (especially those derived from styrene and allyl cyanide hydroformylation) decrease noticeably when the reaction mixture is left standing even for 24 h at ambient temperature. In the absence of syngas, rhodium species present in the solution can serve as racemization catalysts for aldehyde products.[10] We also found that frequent replacement of GC liners is necessary because accumulated rhodium particles can lead to a decrease in enantiopurity of hydroformylation products. During every Endeavor run, one out of eight pressure vessels was devoted to a high selectivity ligand for which enantio- and regioselectivity were well known. This type of control experiment was essential to monitor the quality of the asymmetric hydroformylation screen and allowed us to detect problems due to equipment contamination (e.g., GC liners) or any changes to the screen, such as introduction of new batches of gases, solvents, or reagents. Since commercially viable ligands in rhodium-catalyzed AHF may be required to operate at higher temperature to maintain acceptable reaction rates, our new ligands were evaluated at temperatures >70 °C.

Scheme 1. General Method for Synthesis of Phosphite Ligands



3. Phosphite Ligands

Since chiraphite-type ligands contain epimerizable biaryl fragments linked by an optically active diolate moiety, access to a structurally diverse set of such ligands is limited. To eliminate the requirement of optically active bridging diols, we set out to prepare a new family of bisphosphite ligands that contain a conformationally rigid, optically active fragment bridged by achiral diols.[11] The advantage of this ligand design is that a large library of ligands can be easily assembled from readily available achiral diols. Commercially available (*S*)-3,3′-di-*tert*-butyl-5,5′,6,6′-tetramethyl-biphenyl-2,2′-diol (biphen-H_2) was selected as a chiral auxiliary. The general synthesis of phosphites derived from biphen-H_2 is presented in Scheme 1. We found that preparation of phosphites (especially sterically hindered ones) can be best accomplished with the use of phosphorobromidites or phosphoroiodidites instead of more traditional phosphorochloridite reagents. Phosphoroiodidite derivatives can be conveniently prepared quantitatively by reaction of the corresponding phosphorochloridites with excess TMS-I at room temperature.

Of all the new bisphosphite ligands prepared (subset is shown in Figure 1, ligands **5**–**8** and **12**), the 2,2′-biphenol-bridged ligand, (*S,S*)-kelliphite (**8**), was found to exhibit the highest regio- and enantioselectivity for the asymmetric hydroformylation of both allyl cyanide[11] and vinyl acetate[9] (Table 1). This situation resembles that of the (2*R*,4*R*)-chiraphite ligand family where only a very limited subset of ligands leads to good enantioselectivity in AHF. For AHF of neat allyl cyanide, (*S,S*)-kelliphite gave 79% ee and a b/l ratio of 17–18 at 35 °C and low catalyst

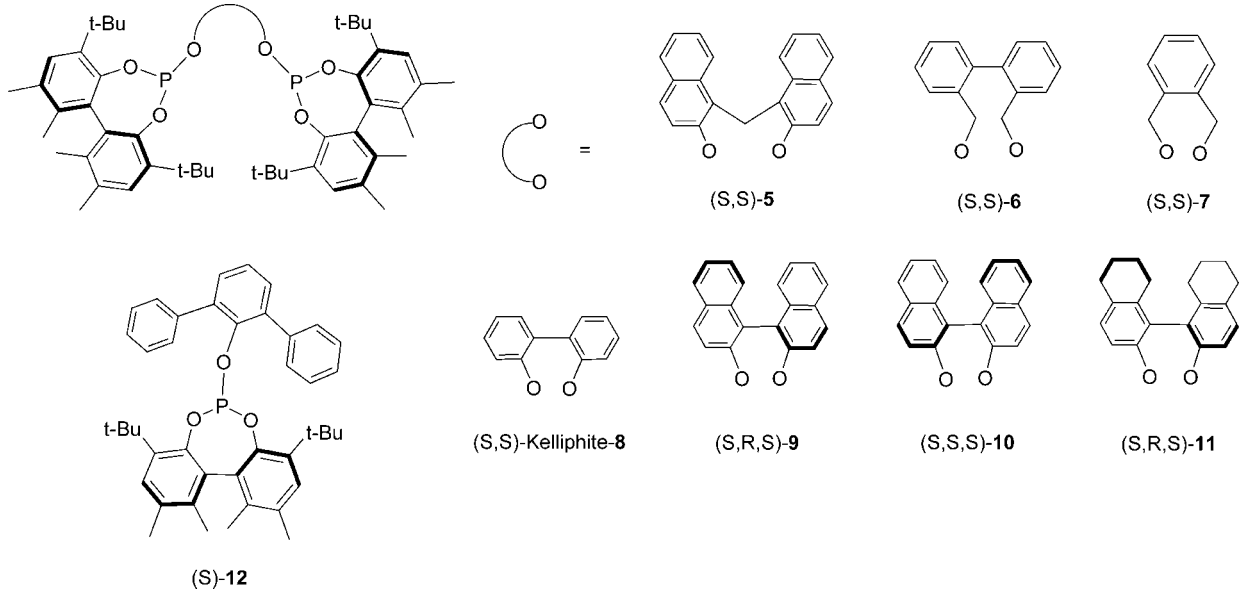


FIGURE 1. Phosphite ligands with (*S,S*)-biphen chiral moiety.

Table 1. Asymmetric Hydroformylation of Styrene, Allyl Cyanide, and Vinyl Acetate with Phosphite Ligands Shown in Figure *1*

			styrene			allyl cyanide			vinyl acetate		
entry	L	*T* (°C)	conv[c]	b/l[d]	% ee	conv[c]	b/l[d]	% ee	conv[c]	b/l[d]	% ee
1[a]	(2*R*,4*R*)-chiraphite (**1**)	35	54	47	76 (*R*)	67	6.7	13 (*R*)	22	109	58 (*R*)
		70	98	13	56 (*R*)	100	6.1	15 (*R*)	95	100	47 (*R*)
2[a]	(*R,S*)-binaphos (**3**)	70	100	5.3	85 (*R*)	100	2.2	69 (*R*)	94	6.5	62 (*S*)
3[a]	(*S,S*)-**5**	70	100	12	7 (*S*)	100	10.5	18 (*S*)	99	16.4	30 (*R*)
4[a]	(*S,S*)-**6**	70	99	7.6	7 (*R*)	100	5.3	1 (*R*)	81	11.3	12 (*R*)
5[a]	(*S,S*)-**7**	70	100	12.6	21 (*S*)	100	7.1	5.7 (*R*)	99	180	7 (*R*)
6[a]	(*S,S*)-kelliphite (**8**)	35	40	68	18 (*S*)	95	16	75 (*S*)	19	125	88 (*R*)
		70	100	17	1 (*R*)	100	11	70 (*S*)	99	56	77 (*R*)
7[b]	(*S,S*)-kelliphite (**8**)	70	95	16.9	1 (*R*)	100	10.6	70 (*S*)	88	63.5	77 (*R*)
8[b]	(*S,R,S*)-**9**	70	90	10.9	24 (*R*)	100	8.5	59 (*S*)	85	48.1	74 (*R*)
9[b]	(*S,S,S*)-**10**	70	84	1.7	5 (*R*)	100	2.5	12 (*R*)	81	47.3	3 (*S*)
10[b]	(*S,R,S*)-**11**	70	84	12.9	13 (*R*)	100	7.0	58 (*S*)	71	37.5	60 (*R*)
11[a]	(*S*)-**12**	70	63	1.1	13 (*S*)	100	3.4	4 (*R*)	84	166	2 (*S*)

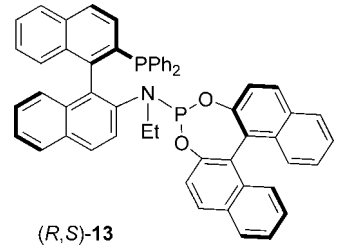
[a] Reaction conditions: 150 psi of 1:1 H_2/CO; ligand/Rh = 1.2:1 for bidentate and 2.2:1 for monodentate phosphites; molar ratio of olefin/Rh = 300:1 (acetone as solvent) at 35 °C and 500:1 at 70 °C. [b] Reaction conditions: 150 psi of 1:1 H_2/CO; ligand/Rh = 1.2:1; molar ratio of olefin/Rh =1000:1; solvent = toluene. [c] Percentage conversion of olefins after 3 h. [d] b/l = branched to linear ratio.

loading (substrate to Rh ratio of 10 000:1). Under the same reaction conditions (*R*,*S*)-binaphos gave similar enantioselectivity for allyl cyanide (75–77% ee) but much lower regioselectivity (b/l of 2.8). Interestingly, we found that enantioselectivities achieved with (*R*,*S*)-binaphos exhibit strong solvent dependence and were 25% higher when the reaction was conducted neat or in acetone instead of toluene. This effect appears to correlate with the polarity of the reaction medium, although it is not well understood. Analogous enantioselectivity enhancement was not observed in the case of (*S*,*S*)-kelliphite.

To probe the factors that influence regio- and enantioselectivity of (*S*,*S*)-kelliphite in AHF, a series of (*S*,*S*)-kelliphite analogs was prepared where the bridging biaryl group was systematically altered to vary its dihedral angle (ligands **9**, **10**, and **11**) (Figure 1).[12] Single-crystal X-ray analyses of five different rhodium complexes confirmed that changes of substituents in the 6 and 6′ positions of the bridging biaryl groups influence their dihedral angles. The values of those dihedral angles fall in the range between 60° and 80° with the smallest for biphenyl and the largest for the octahydrobinaphthyl bridge. DFT calculations performed on a five-coordinate model complex $LRh(CO)_2H$ (L = biaryl bridged bis-phosphite) suggest that decreasing the dihedral angle of the biaryl bridging group leads to smaller P–Rh–P bite angles. An AHF study showed a correlation between regio- and enantioselectivity for AHF of allyl cyanide and vinyl acetate and the dihedral angle found in metal complexes derived from ligands **8**, **9**, and **11**. Ligands with smaller dihedral angles between biaryl bridging fragments (smaller P–Rh–P bite angle) lead to higher selectivities. The correlation between bite angle and selectivities in linear selective (achiral) hydroformylation was previously documented.[13]

The molecular structure of the (*S*,*S*)-kelliphite ligand and its rhodium complex shows that the bridging biphenyl adopts the *R* configuration.[11] It was of interest to us to determine whether the *R* configuration of the biphenyl bridge is also maintained during hydroformylation reactions. To probe this question, kelliphite analogs **7** and **9**, containing configurationally stable *R*- and *S*-binaphthol fragments, respectively, have been synthesized and examined.[12] The selectivities of AHF reactions (Table 1, entries 7–9) obtained with (*S*,*S*)-kelliphite were much closer to those obtained with **9** than **10**, strongly suggesting that the biphenyl moiety in (*S*,*S*)-kelliphite does indeed maintain the *R* configuration during catalysis. Monodentate phosphite ligands based on (*S*)-biphen (e.g., **12**) lead to very poor enantioselectivities, highlighting the necessity of a multidentate ligand structure for optimum selectivity control.

Within the group of bisphosphites examined, kelliphite and chiraphite provide a complementary pair of easily synthesized ligands. Kelliphite is highly effective for AHF of allyl cyanide and vinyl acetate, whereas chiraphite remains a good choice for screening against vinyl arene substrates. Of all ligands in our initial study, only (*R*,*S*)-binaphos exhibited enantioselectivities higher than 60% for all three substrates, albeit with poor regioselectivities (b/l below 10 for all three substrates). (*R*,*S*)-Binaphos yields high enantioselectivities for a wide range of olefins including α-olefins, vinylarylenes, butadienes, and cyclic ethers.[2c] Recently, Zhang et al. reported the preparation of phosphite-phosphoramidite (**13**), a ligand structurally related to (*R*,*S*)-binaphos (**3**), where an oxygen atom was replaced by an NEt fragment.[14] Ligand **13** showed improvement in enantioselectivity over (*R*,*S*)-binaphos for AHF of vinyl arenes and vinyl acetate. Very high enantioselectivity (98%) was achieved for styrene hydroformylation at 60 °C. Unfortunately, similarly to (*R*,*S*)-binaphos, ligand **13** gave poor regioselectivities for both styrene (b/l = 7.3) and vinyl acetate (b/l = 13.3) hydroformylation products.



(*R*,*S*)-**13**

4. Diazaphospholane Ligands

Recently, we reported a new, versatile synthesis of a novel class of phosphines that are based on the diazaphospholane framework.[15,16] The synthesis of diazaphospholanes, which involves simple condensation of primary phosphines and azines, is tolerant of many functional groups thus allowing access to diverse arrays of diazaphospholane ligands. In most cases, the synthesis is highly *rac* selective giving pure *rac* phosphines after a single crystallization. The ability to incorporate various fragments into the diazaphospholane ligand framework gives access to ligands with broadly tunable steric and electronic features. The IR carbonyl stretching measurements of Rh carbonyl complexes containing diazaphospholane ligands indicate that this phosphine class is significantly more electron-deficient than trialkyl phosphines.[17] Since electron deficient phosphines are required for achieving high reaction rates in Rh-catalyzed hydroformylation reactions,[2a] chiral diazaphospholanes were a natural choice for exploration in AHF. Optically active bis-diazaphospholanes are prepared in three steps starting from commercially available materials (Scheme 2). The first step involves preparation of azine **15**, which is then reacted with a mixture of diphosphinobenzene and diacid chloride in THF to yield tetra-acid **16** as a single diastereoisomer in about 35% yield. Tetra-acid **16** is subsequently derivatized with enantiopure amines to yield a mixture of diastereoisomers, which is then separated into individual components. Using this general synthetic protocol, we prepared a small library of bis-diazaphospholanes (Figure 2) and evaluated them in AHF (Table 2).[18]

We were pleased to discover that bis-3,4-diazaphospholanes **17**–**20** exhibit even faster hydroformylation rates than (*R*,*S*)-binaphos, (*S*,*S*)-kelliphite and (2*R*,4*R*)-chiraphite ligands. At 80 °C and a substrate to Rh ratio of 5000:1,

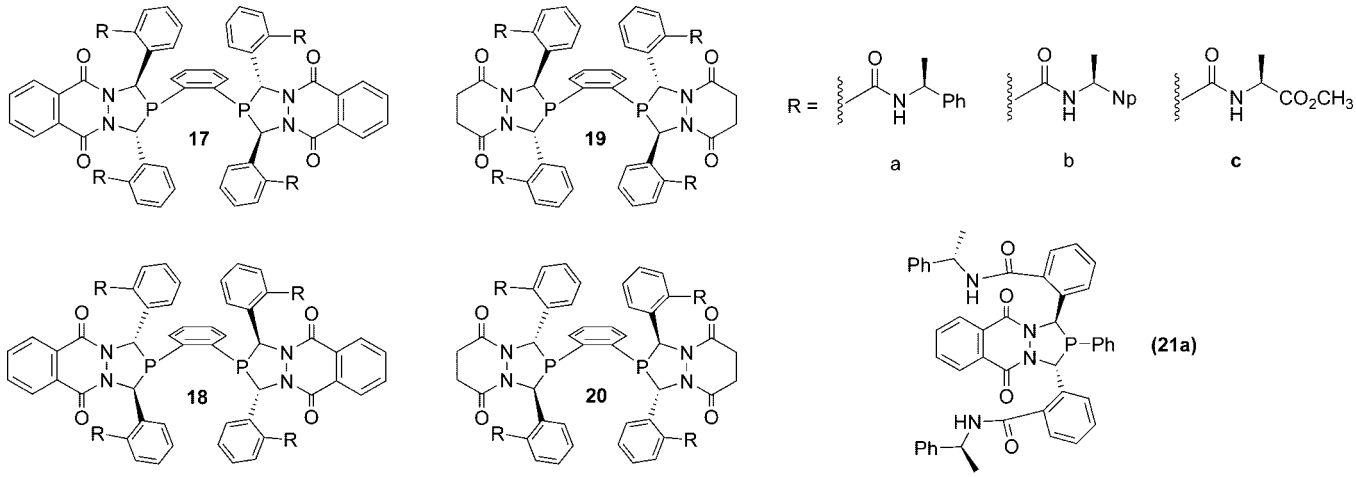


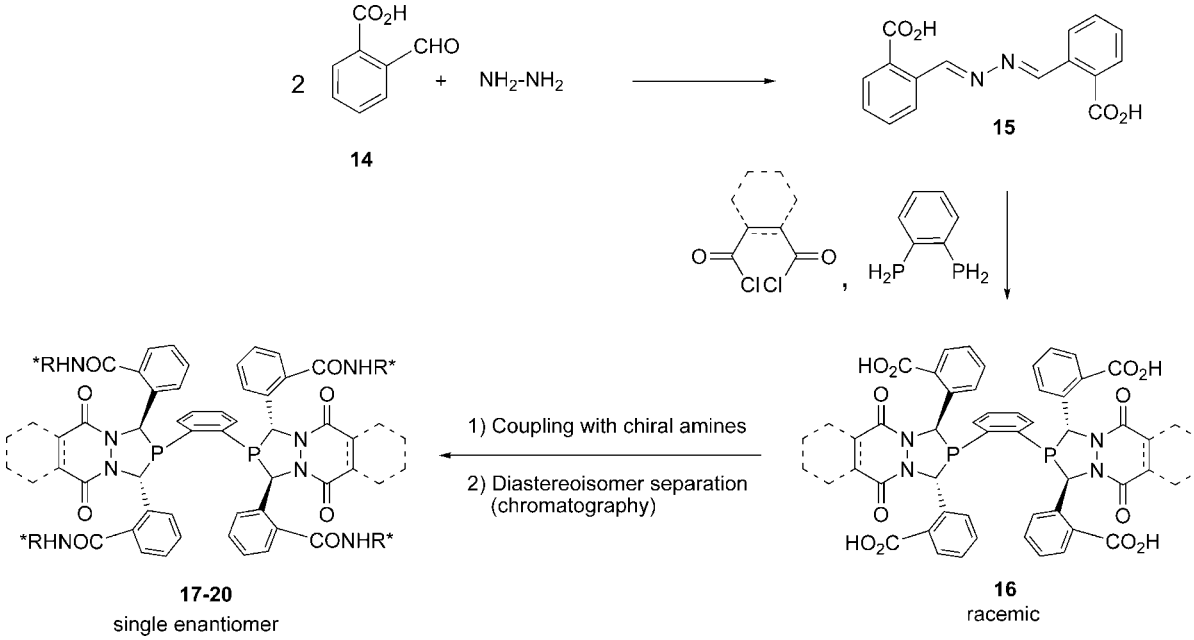
FIGURE 2. Structures of diazaphospholane ligands studied in asymmetric hydroformylation reactions.

Table 2. Asymmetric Hydroformylation of Styrene, Allyl Cyanide, and Vinyl Acetate with Diazaphospholane Ligands Shown in Figure *2*[a]

		styrene			allyl cyanide			vinyl acetate		
entry	L	conv	b/l	% ee	conv	b/l	% ee	conv	b/l	% ee
1	**17a**	93	8.4	76 (*S*)	100	5.3	64 (*S*)	94	24	85 (*R*)
2	**18a**	100	8.1	75 (*R*)	100	4.1	75 (*R*)	100	22	92 (*S*)
3	**19c**	100	5.7	65 (*S*)	100	4.0	69 (*S*)	100	36	86 (*R*)
4	**20c**	100	5.3	73 (*R*)	100	3.5	82 (*R*)	100	41	96 (*S*)
5	**19a**	100	6.3	73 (*S*)	100	4.1	77 (*S*)	100	31	91 (*R*)
6	**20a**	100	6.6	82 (*R*)	100	4.1	87 (*R*)	100	37	96 (*S*)
7[b]	**20a**	42	30	89 (*R*)	73	4.8	87 (*R*)	31	40	95 (*S*)
8[c]	**20a**	85	13	82 (*R*)	100	4.0	86 (*R*)	86	37	96 (*S*)
9	**21a**	28	1.1	12 (*R*)	93	1.3	10 (*R*)	31	39	23 (*S*)
10	(2*R*,4*R*)-chiraphite (**1**)	90	9.0	49 (*R*)	100	5.5	13 (*R*)	75	190	50 (*R*)
11	(*R*,*S*)-binaphos (**3**)	96	4.5	82 (*R*)	98	2.1	72 (*R*)	72	8.2	48 (*S*)
12	(*S*,*S*)-kelliphite (**8**)	78	8.9	2 (*R*)	100	9.3	66 (*S*)	78	61	73 (*R*)

[a] All reactions performed at 80 °C in toluene with 150 psig of 1:1 CO/H_2 with L/Rh = 1.2 (2.1 for monophosphine **21a**), total molar substrate/Rh = 5000, and 3 h reaction time. [b] 60 °C; 500 psi; total substrate/Rh = 30 000. [c] 80 °C; 500 psi; total molar substrate/Rh = 30 000.

Scheme 2. General Synthesis of Bis-diazaphospholane Ligands



the bis-3,4-diazaphospholanes **17**–**20** led to quantitative conversion of all three substrates after 3h. Syngas uptake curves shown in Figure 3 clearly illustrate high reaction rate capabilities of diazaphospholane ligands in hydro-

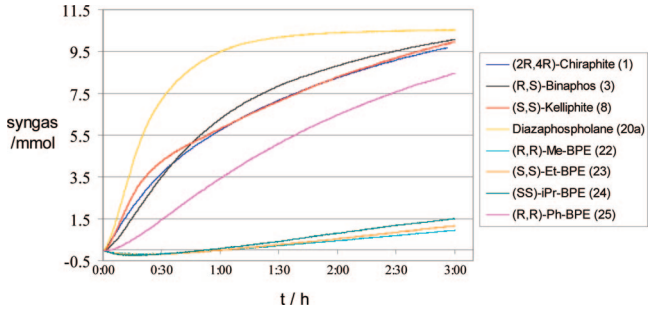


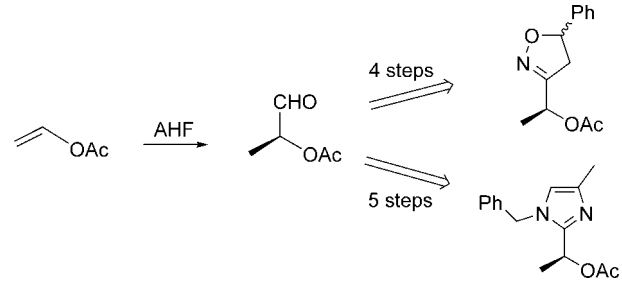
FIGURE 3. Syngas uptake curves for AHF of styrene, allyl cyanide and vinyl acetate (substrate/catalyst = 5000 at 80 °C in toluene with 150 psi of 1:1 CO/H_2 and L/Rh = 1.2).

formylation reactions. AHF with **20a** at a substrate to catalyst ratio of 30 000:1, 80 °C, and 500 psi syngas pressure led to 85%, 100%, and 86% conversion in 3 h for styrene, allyl cyanide, and vinyl acetate, respectively, giving an average turnover frequency of 9000 h^{-1} (Table 2, entry 8). Bis-diazaphospholanes are the most active ligands, not only among bis-phosphines, but among all phosphorus-based ligands that we examined in our AHF screens. Enantioselectivity values were dependent on the particular ligand structure investigated. At 60 °C and 500 psi of syngas pressure, **20a** led to 89% ee and b/l = 30 for styrene, 87% ee and b/l = 4.8 for allyl cyanide, and 95% ee and b/l = 40 for vinyl acetate (Table 2, entry 7). Regioselectivities are sensitive to reaction conditions and can be increased (especially for styrene) at higher syngas pressure and lower temperature.

Monodentate 3,4-diazaphospholane **21a**, on the other hand, exhibited lower activity and significantly lower regio- and enantioselectivities. These data clearly demonstrate that the bidentate nature of the bis-diazaphospholane ligands is a critical feature for achieving very high selectivities and activities in AHF, at least for terminal olefins. The results obtained with **19a** (diastereoisomer of **20a** having the opposite chirality at the 2 and 5 positions of the phospholane rings and the same chirality of the amine fragment) led to formation of the opposite enantiomers in the products indicating that the chirality of the phospholane ring rather than the amine chirality prevails in determining product stereochemistry. Product enantioselectivities obtained for diastereomeric pairs **17/18** and **19/20** were found to be within 10% ee, indicating a modest match/mismatch effect.

AHF of neat vinyl acetate with **20a** was also successfully conducted at 80 °C with a substrate to catalyst ratio of 100 000:1 leading to 97% conversion within 5 h (95% ee, b/l = 28.7), which translates into an average TOF of 19 400 h^{-1}.[19] Scale-up of this reaction was carried out on a 135 g scale using both **19a** and **20a** in a 300 mL Parr reactor. The enantiomers of 2-acetoxypropanaldehyde (product of AHF of vinyl acetate), which were recovered by distillation, showed very high selectivities ((*R*)-product, 93.8% ee and b/l = 102 for **19a** and (*S*)-product, 96.8% ee, and b/l = 139 for **20a**). Enhanced regioselectivities of recovered products are due to the lower boiling points of branched isomers. Both enantiomers of 2-acetoxypropanaldehyde were used as

Scheme 3. Synthesis of Optically Active Isoxazoline and Imidazole Derivatives



starting materials in the synthesis of optically active isoxazoline and imidazole derivatives, which proceeded without racemization of the chiral center (Scheme 3).[19]

5. Phospholane Ligands

High activity and selectivity achieved with bis-diazaphospholane ligands prompted the evaluation of other bis-phospholane ligands in AHF. We were particularly interested in screening 1,2-bis(2,5-dialkylphospholano)benzene (duphos), 1,2-bis(2,5-dialkylphospholano)ethane (BPE)[20] (**22–24**), (*R,R*)-1,2-bis(2,5-diphenylphospholano)ethane ((*R,R*)-Ph-BPE)[21] (**25**), and (*S,S,R,R*)-tangphos[22] because all these ligands possess key structural features (phospholane rings bridged by a two carbon linker) found in bis-diazaphospholanes (Figure 4). The olefin conversion data obtained with phospholane ligands pictured in Table 3 are in close agreement with syngas uptake curves (Figure 3) and demonstrate that (*R,R*)-Ph-BPE (**25**) exhibits the fastest hydroformylation rates of all phospholanes studied.[23] At 80 °C and 150 psi syngas pressure, (*R,R*)-Ph-BPE (**25**) exhibits an average turnover frequency of 1139 h^{-1}, which is about 5 times more than values observed with (*S,S*)-*i*-Pr-BPE (**24**). The most likely reason for the en-

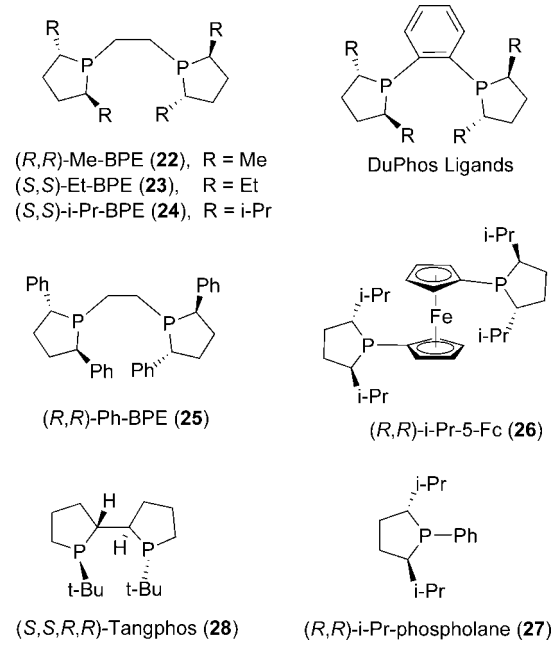


FIGURE 4. Structures of some of the phospholane ligands studied in AHF.

Table 3. Asymmetric Hydroformylation of Styrene, Allyl Cyanide, and Vinyl Acetate with Phospholane Ligands Shown in Figure 4[a]

		styrene			allyl cyanide			vinyl acetate		
entry	L	conv	b/l	% ee	conv	b/l	% ee	conv	b/l	% ee
1	(*R*,*R*)-Me-BPE (**22**)	8	14	43 (*S*)	36	5.8	37 (*S*)	23	97	59 (*R*)
2	(*S*,*S*)-Et-BPE (**23**)	10	11.3	55 (*R*)	40	6.2	49 (*R*)	23	152	66 (*S*)
3	(*S*,*S*)-*i*-Pr-BPE (**24**)	11	9.5	82 (*S*)	48	6.7	83 (*S*)	28	142	70 (*R*)
4	(*R*,*R*)-Ph-BPE (**25**)	57	45.0	94 (*R*)	96	7.1	90 (*R*)	52	340	82 (*S*)
5	(*R*,*R*)-*i*-Pr-5-Fc (**26**)	9	3.2	15 (*R*)	28	3.9	49 (*R*)	22	94	29 (*R*)
6	(*R*,*R*)-*i*-Pr-phospholane (**27**)	11	4.4	11 (*R*)	30	3.5	7 (*R*)	17	21	8 (*S*)
7[b]	(*S*,*S*,*R*,*R*)-tangphos (**28**)	10	14.9	13 (*S*)	49	7.5	6 (*S*)	26	138	81 (*R*)
8[b]	[(*S*,*S*,*R*,*R*)-tangphos]Rh(acac)	12	14.8	90 (*S*)	61	7.5	93 (*S*)	17	30	83 (*R*)

[a] Reactions performed at 80 °C in toluene with 150 psig of 1:1 CO/H_2 with L/Rh = 1.2 (2.1 for **27**), total molar substrate/Rh = 5000, catalyst concentration 0.037 mol %, 3 h reaction time. [b] Total molar substrate/Rh = 3000, ligand/Rh = 2 (entry 7).

Table 4. Asymmetric Hydroformylation of Styrene, Allyl Cyanide, and Vinyl Acetate with Molar Substrate to Catalyst Ratio of 30 000:1[a]

		styrene			allyl cyanide			vinyl acetate		
entry	L	conv	b/l	% ee	conv	b/l	% ee	conv	b/l	% ee
1	(2*R*,4*R*)-chiraphite (**1**)	32	10.8	51 (*R*)	74	5.8	13 (*R*)	34	204	50 (*R*)
2	(*R*,*S*)-binaphos (**3**)	35	4.6	81 (*R*)	58	2.1	68 (*R*)	23	7.1	58 (*S*)
3	(*S*,*S*)-kelliphite (**8**)	32	9.2	3 (*S*)	99	10.1	66 (*S*)	32	100	75 (*R*)
4	diazaphospholane (**20a**)	73	5.7	80 (*R*)	100	3.9	80 (*R*)	92	47	95 (*S*)
5	(*R*,*R*)-Ph-BPE (**25**)	33	45.0	92 (*R*)	67	7.6	90 (*R*)	34	263	82 (*S*)

[a] Reactions performed at 80 °C in toluene with 150 psi of 1:1 $CO:H_2$ with L:Rh = 1.2, total molar substrate:Rh = 30,000, 4.43 mL of styrene: allyl cyanide: vinyl acetate: dodecane (1:1:1:0.3 molar ratio), 3 hour reaction time.

hanced activity of (*R*,*R*)-Ph-BPE (**25**) over other phospholane ligands is the presence of the electron-withdrawing phenyl rings, which reduce the electron density at the phosphorous atoms. The IR data ν_{CO} obtained for a series of molybdenum carbonyl complexes containing BPE ligands (**22–25**) confirmed that (*R*,*R*)-Ph-BPE is the least basic phosphine among the BPE ligands.[23] At very low catalyst loadings (molar ratio of substrate to Rh of 30 000:1), the rate of hydroformylation with (*R*,*R*)-Ph-BPE (**25**) (an average turnover frequency of 4467 h^{-1}) was virtually identical to those of (2*R*,4*R*)-chiraphite (**1**) and (*R*,*S*)-binaphos (**3**) and only slower than (*S*,*S*)-kelliphite (**8**) and bis-diazaphospholane (**20a**) (Table 4).

Enantioselectivity data show that BPE and duphos ligands having larger substituents in the 2,5-positions of phospholane rings (*i*-Pr or Ph vs. Me or Et) lead to noticeably higher enantioselectivities. As in the case of bis-diazaphospholanes, bis-phospholane ligands appear to be equally effective toward all three olefins (styrene, allyl cyanide, and vinyl acetate), suggesting potential broad applicability of this ligand class across a wide range of substrates. Under the standard screening conditions, (*R*,*R*)-Ph-BPE (**25**) combines high enantioselectivity and regioselectivity for styrene hydroformylation giving 94% ee and an unprecedented branched to linear isomer ratio of 45. The ligand (*R*,*R*)-Ph-BPE (**25**) also is very effective in AHF of allyl cyanide (90% ee, b/l = 7.1) and vinyl acetate (82% ee, b/l = 340). The very high regioselectivity achieved in vinyl acetate hydroformylation (b/l = 340) is quite surprising because it is significantly higher than that observed with any other ligand. As in the case of monodentate phosphite and diazaphospholane ligands, the monodentate phospholane (*R*,*R*)-*i*-Pr-phospholane (**27**) was unremarkable in its performance toward all three olefins. Ferrocene-based ligand (**26**) bearing 2,5-di-*i*-Pr-phospholane moieties is significantly worse than *i*-Pr-BPE (**24**) in terms of both regio- and enantioselectivity, suggesting that a ferrocene backbone imparts a too large of a bite angle for optimal ligand performance.

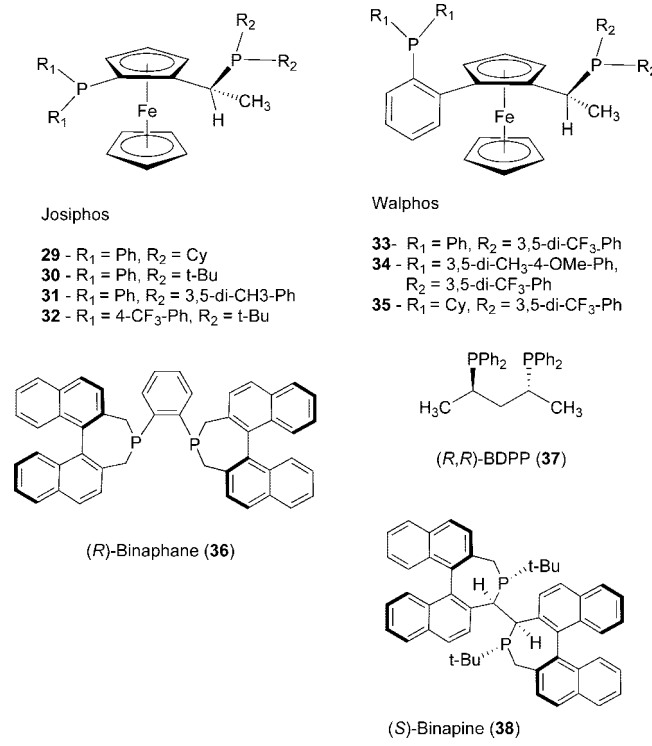


FIGURE 5. Structures of the bis-phosphine ligands studied in AHF.

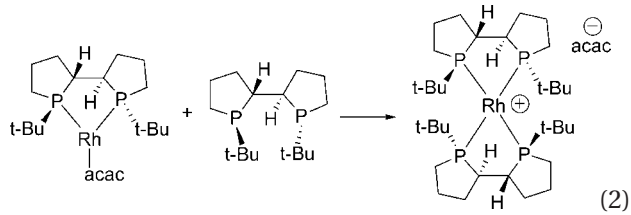
Our initial screening experiments with (*S*,*S*,*R*,*R*)-tangphos (**28**) were frustrated by a lack of reproducibility.[10] After a series of control experiments, we discovered that the enantioselectivity of styrene and allyl cyanide hydroformylation products varies substantially as a function of

Table 5. Asymmetric Hydroformylation of Styrene, Allyl Cyanide, and Vinyl Acetate with Bis-phosphine Ligands Shown in Figure 5[a]

		styrene			allyl cyanide			vinyl acetate		
entry	L	conv	b/l	% ee	conv	b/l	% ee	conv	b/l	% ee
1	josiphos (**29**)	14	11.9	39 (*R*)	59	6.9	59 (*R*)	25	68.4	64 (*S*)
2	josiphos (**30**)	5	5.4	43 (*R*)	24	8.9	60 (*R*)	18	23.5	73 (*S*)
3	josiphos (**31**)	45	20.1	38 (*S*)	92	14.1	22 (*S*)	27	205.2	17 (*S*)
4	josiphos (**32**)	9	4.8	40 (*R*)	28	7.2	64 (*R*)	22	15.2	79 (*S*)
5	walphos (**33**)	98	2.4	44 (*S*)	99	0.9	6 (*S*)	93	6.1	57 (*R*)
6	walphos (**34**)	95	2.5	27 (*S*)	97	1.0	2 (*R*)	86	5.7	48 (*R*)
7	walphos (**35**)	26	2.7	2 (*S*)	47	3.5	53 (*R*)	42	73.1	73 (*R*)
8	(*R*)-binaphane (**36**)	17	8.2	34 (*R*)	62	5.2	50 (*R*)	21	34	24 (*S*)
9	(*R,R*)-BDPP (**37**)	22	12.4	48 (*S*)	82	16.1	70 (*S*)	22	16.4	31 (*S*)
10	(*S*)-binapine (**38**)	12	9.5	94 (*S*)	49	6.7	94 (*S*)	21	32.4	87 (*R*)

[a] Reactions performed at 80°C in toluene, 150 psi of 1:1 CO:H_2, L:Rh = 2, total substrate:Rh = 3000, 1 mL of substrates, 3 hr. reaction time.

(*S,S,R,R*)-tangphos/Rh ratio. The highest enantioselectivities were obtained with ratios close to 1 and they rapidly decreased at ratios higher than 1.2 (excess of ligand). This unusual behavior was eventually traced to the *in situ* formation of the ionic complex [((*S,S,R,R*)-tangphos)$_2$Rh]$^+$[acac]$^-$ when excess of ligand was used (eq 2). The acetylacetonate anion present in this complex was found to be responsible for this sharp decrease of enantioselectivity in hydroformylation products.



(2)

It is not clear whether enantioselectivity reduction (formation of [RhP_4][acac] species) with excess of ligand is a common occurrence during AHF. We believe that this behavior is limited to relatively small and electron-rich phosphine ligands since (*R,R*)-Ph-BPE (**6**) and phosphite ligands do not show this unusual behavior.[10] These results should, however, serve as a caution when screening new ligands in AHF because low reaction enantioselectivity might not necessarily reflect the ligands' true capabilities. One approach to eliminate this uncertainty would be to premake rhodium complex LRh(acac), a procedure frequently used in asymmetric hydrogenation studies. We wonder whether AHF results obtained with Me- and Et-BPE ligands (**22**, **23**) (small and electron-rich phosphines) were adversely affected by the excess of ligands we used in our screens. Optimum enantioselectivities of 90%, 93%, and 83% were obtained with premade complex [(*S,S,R,R*)-tangphos)]Rh(acac) for hydroformylation of styrene, allyl cyanide, and vinyl acetate, respectively. As expected based on electronic characteristics of (*S,S,R,R*)-tangphos (**28**), the AHF reaction rates are low even at 80 °C. (*S,S,R,R*)-tangphos was recently used with high success in AHF of bicyclic olefins.[24]

6. Other Bis-phosphine Ligands

Since several of the ligands traditionally used in asymmetric hydrogenation also happened to be very selective in AHF, we carried out AHF screening of a variety of commercially available asymmetric hydrogenation ligands.[10] Structures of selected ligands together with relevant AHF results are shown in Figure 5 and Table 5, respectively. (*R,R*)-BDPP (**37**) exhibited the highest regioselectivity for AHF of allyl cyanide at 80 °C (b/l = 16, 70% ee) but only mediocre regioselectivities in the case of styrene (b/l = 12.4) and vinyl acetate (b/l = 16.4) hydroformylation. Josiphos (**29**–**32**) and walphos (**33**–**35**) ligands lead to enantioselectivities up to 73% ee for vinyl acetate, but in general these ligands are much less selective than bis-phosphacycle ligands. In this set of ligands, the most interesting was (*S*)-binapine (**38**)[25] because it gave 94% ee (b/l = 9.5), 94% ee (b/l = 6.7), and 87% ee (b/l =32.4) for hydroformylation products of styrene, allyl cyanide, and vinyl acetate, respectively.[10] Enantioselectivities obtained with (*S,S,R,R*)-tangphos (**28**) and (*S*)-binapine (**38**) for AHF of allyl cyanide are the highest ever reported for this substrate. Interestingly, (*R*)-binaphane (**36**), structurally related to (*S*)-binapine (**38**), exhibited relatively poor selectivities across all three olefins.

Ligand structures such as (*S,S,R,R*)-tangphos (**28**) and (*S*)-binaphine (**38**) are very promising, but their electronic nature (electron-rich) prohibits them from achieving high reaction rates. One approach to address this deficiency would be to synthesize novel bis-phosphacycles with electron-withdrawing substituents placed in close proximity to phosphorous atoms.

7. Conclusions

Bis-phosphites are one of the best classes of ligands for controlling regioselectivities in AHF across a number of substrates; however, high enantioselectivity has only been observed for a limited number of ligands. Enantioselectivities obtained with bis-phosphites are usually quite temperature dependent with lower values being observed at higher temperatures. This may indicate that bis-phosphite ligands are configurationally less stable at elevated temperatures, presumably due to the large size of the linking group between phosphorus atoms. On the other hand, bis-phosphacycle ligands such as bis-diazaphospholanes, bis-phospholanes, and (*S*)-binaphine con-

tain a two carbon bridge, which, when coupled with rigidity of a phosphacycle ring, leads to outstanding enantioselectivity control in AHF. Our data suggest that the bis-phosphacycle ligand family is unique and most promising for future advances in asymmetric hydroformylation. The remarkable ability of bis-diazaphospholane (**20a**) and (*R*,*R*)-Ph-BPE (**25**) to yield high enantioselectivities at higher temperature with high reaction rates renders these ligands candidates for commercial application in AHF. The ease with which the diazaphospholane ligand structure can be diversified and extended, along with the intrinsically high activities, should facilitate the discovery of new ligands for broader classes of substrates. Our current research focuses on the determination of factors that control selectivity of bis-diazaphospholane and bis-phospholane ligands in AHF in the hope to further improve the performance of these ligands.

We are most grateful to our co-workers, especially to Gregory Whiteker, Tom Clark, Alex Axtel, Christopher Cobley, Cynthia Rand, P. J. Thomas, Susan Freed, Rob Froese and Guy Casy, for their numerous contributions to this research. Additionally, we thank Dowpharma for funding of this research.

References

(1) Rouhi, A. M. Chiral chemistry. *Chem. Eng. News.* **2004**, (June 14), 51.

(2) For recent reviews on asymmetric hydroformylation, see: (a) Agbossou, F.; Carpentier, J.-F.; Mortreux, A. Asymmetric Hydroformylation. *Chem. Rev.* **1995**, *95*, 2485–2506. (b) Claver, C.; van Leeuwen, P. W. N. M. Asymmetric Hydroformylation. In *Rhodium Catalyzed Hydroformylation*; Claver, C., van Leeuwen, P. W. N. M., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2000. (c) Diéguez, M.; Pàmies, O.; Claver, C. Recent advances in Rh-catalyzed asymmetric hydroformylation using phosphite ligands. *Tetrahedron: Asymmetry* **2004**, *15*, 2113–2122. (d) Claver, C.; Dieguez, M.; Pamies, O.; Castillon, S. Asymmetric hydroformylation. *Top. Organomet. Chem.* **2006**, *18*, 35–64.

(3) Tang, W.; Zhang, X. New chiral phosphorus ligands for enantioselective hydrogenation. *Chem. Rev.* **2003**, *103*, 3029–3069.

(4) (a) Babin, J. E.; Whiteker, G. T. Asymmetric Synthesis, World Patent, WO 9303839, 1993. (b) Whiteker, G. T.; Briggs, J. R.; Babin, J. E.; Barne, B. A. Asymmetric Catalysis Using Bisphosphite Ligands. In *Chemical Industries*; Marcel Dekker, Inc.: New York, 2003; Vol. 89, pp 359–367.

(5) (a) Buisman, G. J. H.; Vos, E. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. Hydridorhodium diphosphite catalysts in the asymmetric hydroformylation of styrene. *J. Chem. Soc., Dalton Trans.* **1995**, 409–417. (b) Buisman, G. J. H.; van der Veen, L. A.; Klootwijk, A.; de Lange, W. G. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vogt, D. Chiral cooperativity in diastereomeric diphosphite ligands: effects on the rhodium-catalyzed enantioselective hydroformylation of styrene. *Organometallics* **1997**, *16*, 2929–2939.

(6) Dieguez, M.; Pamies, O.; Ruiz, A.; Castillon, S.; Claver, C. Chiral diphosphites derived from d-glucose: new ligands for the asymmetric catalytic hydroformylation of vinyl arenes. *Chem.—Eur. J.* **2001**, *7*, 3086–3094.

(7) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. Highly enantioselective hydroformylation of olefins catalyzed by rhodium(I) complexes of new chiral phosphine–phosphite ligands. *J. Am. Chem. Soc.* **1997**, *119*, 4413–4423.

(8) Breeden, S.; Cole-Hamilton, D. J.; Foster, D. F.; Schwarz, G. J.; Wills, M. Rhodium-mediated asymmetric hydroformylation with a novel bis(diazaphospholidine) ligand. *Angew. Chem., Int. Ed.* **2000**, *39*, 4106–4108.

(9) Cobley, C. J.; Klosin, J.; Qin, C.; Whiteker, G. T.; Parallel ligand screening on olefin mixtures in asymmetric hydroformylation reactions. *Org. Lett.* **2004**, *6*, 3277–3280; *Org. Lett.* **2005**, *7*, 1197.

(10) Axtell, A. T.; Klosin, J.; Abboud, K. A. Evaluation of asymmetric hydrogenation ligands in asymmetric hydroformylation reactions. Highly enantioselective ligands based on bis-phosphacycles. *Organometallics* **2006**, *25*, 5003–5009.

(11) Cobley, C. J.; Gardner, K.; Klosin, J.; Praquin, C.; Hill, C.; Whiteker, G. T.; Zanotti-Gerosa, A.; Petersen, J. L.; Abboud, K. A. Synthesis and application of a new bisphosphite ligand collection for asymmetric hydroformylation of allyl cyanide. *J. Org. Chem.* **2004**, *69*, 4031–4040.

(12) Cobley, C. J.; Froese, R. D. J.; Klosin, J.; Qin, C.; Whiteker, G. T. The effect of dihedral angle of biaryl-bridged bisphosphite ligands on enantioselectivity and regioselectivity of asymmetric hydroformylation. *Organometallics* **2007**, *26*, 2986–2999.

(13) For effects of catalyst bite angle on selectivity in hydroformylation reactions, see: Casey, C. P.; Whiteker, G. T.; Melville, M. G.; Petrovich, L. M.; Gavney, J. A., Jr.; Powell, D. R. Diphosphines with natural bite angles near 120° increase selectivity for n-aldehyde formation in rhodium-catalyzed hydroformylation. *J. Am. Chem. Soc* **1992**, *114*, 5535–5543. (b) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. Wide bite angle diphosphines: xantphos ligands in transition metal complexes and catalysis. *Acc. Chem. Res.* **2001**, *34*, 895–904.

(14) Yan, Y.; Zhang, X. A hybrid phosphorus ligand for highly enantioselective asymmetric hydroformylation. *J. Am. Chem. Soc.* **2006**, *128*, 7198–7202.

(15) Landis, C. R.; Jin, W.; Owen, J. S.; Clark, T. C. Rapid access to diverse arrays of chiral 3,4-diazaphospholanes. *Angew. Chem., Int. Ed.* **2001**, *40*, 3432–3434.

(16) Clark, T. C.; Landis, C. R. Recent developments in chiral phospholane chemistry. *Tetrahedron: Asymmetry* **2004**, *15*, 2123–2137.

(17) Landis, C. R.; Nelson, R. C.; Jin, W.; Bowman, A. C. Synthesis, characterization, and transition-metal complexes of 3,4-diazaphospholanes. *Organometallics* **2006**, *25*, 1377–1391.

(18) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. Highly active, regioselective, and enantioselective hydroformylation with Rh catalysts ligated by bis-3,4-diazaphospholanes. *J. Am. Chem. Soc.* **2005**, *127*, 5040–5042.

(19) Thomas, P. J.; Axtell, A. T.; Klosin, J.; Peng, W.; Rand, C. R.; Clark, T. P.; Landis, C. R.; Abboud, K. A. Asymmetric hydroformylation of vinyl acetate: application in the synthesis of optically active isoxazolines and imidazoles. *Org. Lett.* **2007**, *9*, 2665–2668.

(20) (a) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. Preparation and use of C2-symmetric bis(phospholanes): Production of α-amino acid derivatives via highly enantioselective hydrogenation reactions. *J. Am. Chem. Soc.* **1993**, *115*, 10125–10138. (b) Burk, M. J. Modular phospholane ligands in asymmetric catalysis. *Acc. Chem. Res.* **2000**, *33*, 363–372.

(21) Pilkington, C. J.; Zanotti-Gerosa, A. Expanding the family of phospholane-based ligands: 1,2-Bis(2,5-diphenylphospholano)ethane. *Org. Lett.* **2003**, *5*, 1273–1275.

(22) Tang, W.; Zhang, X. A. Chiral 1,2-bisphospholane ligand with a novel structural motif: Applications in highly enantioselective Rh-catalyzed hydrogenations. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612–1614.

(23) Axtell, A. T.; Cobley, C. J.; Klosin, J.; Whiteker, G. T.; Zanotti-Gerosa, A.; Abboud, K. A. Highly regio- and enantioselective asymmetric hydroformylation of olefins mediated by 2,5-disubstituted phospholane ligands. *Angew. Chem., Int. Ed.* **2005**, *44*, 5834–5838.

(24) 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. A highly enantioselective catalyst for asymmetric hydroformylation of [2.2.1]-bicyclic olefins. *Tetrahedron Lett.* **2005**, *46*, 7831–7834.

(25) Tang, W.; Wang, W.; Chi, Y.; Zhang, X. A. Bisphosphepine ligand with stereogenic phosphorus centers for the practical synthesis of β-aryl-β-amino acids by asymmetric hydrogenation. *Angew. Chem., Int. Ed.* **2003**, *42*, 3509–3511.

AR7001039