JOC The Journal of Organic Chemistry

Featured Article

Libraries of Bisdiazaphospholanes and Optimization of Rhodium-catalyzed Enantioselective Hydroformylation

Tyler T. Adint, Gene W Wong, and Clark Read Landis

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo400525w • Publication Date (Web): 12 Apr 2013

Just Accepted

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Libraries of Bisdiazaphospholanes and Optimization of Rhodium-catalyzed Enantioselective Hydroformylation

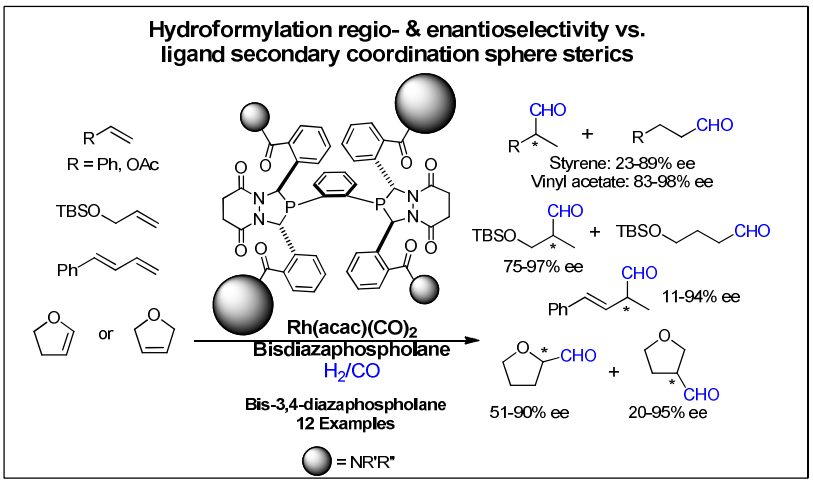
Tyler T. Adint, Gene W. Wong, Clark R. Landis*

Department of Chemistry, University of Wisconsin—Madison, 1101 University Avenue, Madison WI 53706

landis@chem.wisc.edu

KEYWORDS: Ligand design, hydroformylation, asymmetric catalysis, rhodium.

ABSTRACT: Twelve chiral bis-3,4-diazaphospholane ligands and six alkene substrates (styrene, vinyl acetate, allyloxy-*t*-butyldimethylsilane, (*E*)-1-phenyl-1,3-butadiene, 2,3-dihydrofuran, and 2,5-dihydrofuran) probe the influence of steric bulk on the activity and selectivity of asymmetric hydroformylation (AHF) catalysts,. Reaction of an enantiopure bisdiazaphospholane tetraacyl fluoride with primary or secondary amines yields a small library of tetracarboxamides. For all six substrates manipulation of reaction conditions and bisdiazaphospholane ligands enables state-of-the-art performance (90% or higher ee, good regioselectivity, and high turnover rates). For the non-dihydrofuran substrates the previously reported ligand, (*S*,*S*)-2, is generally most effective. However, optimal regio- and enantioselective hydroformylation of 2,3-dihydrofuran (up to 3.8:1 α-isomer:β-isomer ratio and 90% ee for the α-isomer) and 2,5-dihydrofuran (up to <1:30 α-isomer:β-isomer ratio and 95% ee for the β-isomer) arises from bisdiazaphospholanes containing tertiary carboxamides. Hydroformylation of either 2,3- or 2,5-dihydrofuran yields some of the β-formyl product. However , the absolute sense of stereochemistry is inverted. A stereoelectronic map rationalizes the opposing enantiopreferences.



Introduction

An outstanding challenge in asymmetric hydroformylation (AHF) is the development of robust catalysts that give high regio- and enantioselectivity, high turnover numbers, and fast rates for a variety of alkenes. Our group and many others previously have demonstrated effective enantioselective hydroformylation of various alkenes at mild conditions and with low catalyst loadings.[1,2] Although many phosphorus-containing ligands have been reported for rhodium-catalyzed AHF, just a few structure types combine high regio- and enantioselectivity along with high activity. Applications of AHF that are particularly appealing (and challenging) include di- and tri-substituted alkene substrates. Because increased substitution of alkenes commonly leads to substantially decreased rates, it makes sense to focus further development of ligands on frameworks that give high rates and turnover numbers.

Bisdiazaphospholane ligands enable exceptionally high activity and selectivity for rhodium-catalyzed AHF under mild reaction conditions. AHF with bisdiazaphospholanes makes efficient use of expensive rhodium catalysts without the requirement of high pressure steel reactors (most reactions can be performed in glass pressure bottles).[1e] Herein, we report the synthesis of a small library of bis-3,4-diazaphospholanes and its application to AHF of six different substrates. Three ligand subsets were synthesized to compare bisdiazaphospholane steric bulk and hydroformylation selectivity: type **I**, secondary carboxamides with slight steric modifications from previously reported (*S*,*S*)-**2** ligand; type **II**, secondary carboxamides with achiral R-groups of varying steric bulk; and type **III**, tertiary carboxamides. AHF of benchmark substrates styrene, vinyl acetate, allyloxy-*t*-butyldimethylsilane and (*E*)-1-phenyl-1,3-butadiene provide baseline comparisons for this ligand library to previously reported ligands. The dihydrofurans, 2,3- and 2,5-dihydrofuran, represent a challenging class of disubstituted alkenes for which there are few high performing catalysts. Previously we have reported that the related dihydropyrroles, N-Boc-2,3- and N-Boc-2,5-dihydropyrrole, are hydroformylated with state-of-the-art selectivity in the presence of (*S*,*S*)-**2** ligand and common rhodium catalyst precursors.[1c]

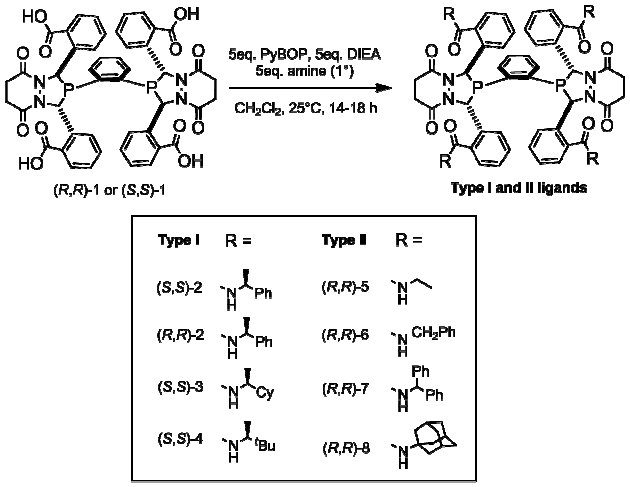
Results and Discussion

We previously have reported the synthesis of C_2-symmetric tetraacid bis-3,4-diazaphospholane ligand [(*rac*)-**1**] from 1,2-bisphosphinobenzene, 2-carboxybenzaldehyde azine, and succinyl chloride.[1a] Resolution of the bisdiazaphospholane enantiomers was accomplished by coupling of the carboxylic acid groups with enantiopure methylbenzylamine to yield diastereomeric tetracarboxamide bisdiazaphospholane ligands followed by chromatography. We find outstanding regio- and enantioselective hydroformylation using the *(S,S)* phospholane ring stereochemistry and (*S*)-methylbenzylamine [(*S*,*S*)-**2**] or its diastereomer [(*R*,*R*)-**2**].[2, 3] Based on the crystal structures

of (*S*,*S*)-**2** and (*rac*)-**1** [see Supporting Information], we hypothesize that steric interaction between the benzamide substituents and the substrate can be significantly modulated by the bulk of the benzamide. Such steric interactions could significantly affect rate and selectivity in AHF. To facilitate construction of a library, (*rac)*-**1** was resolved by chiral SFC.

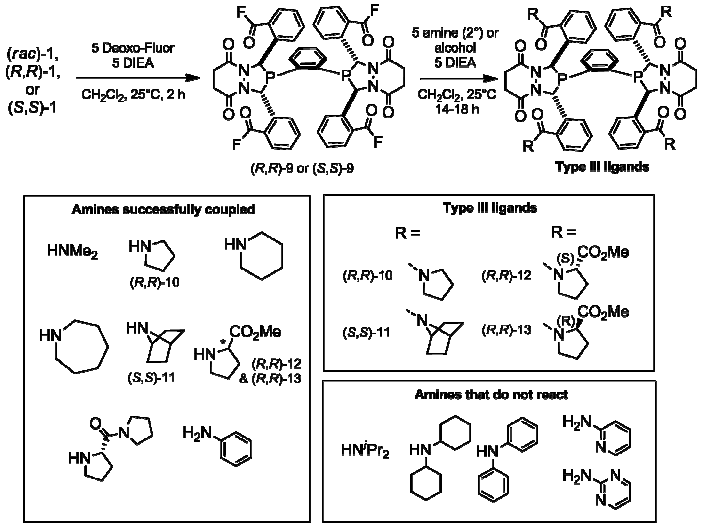
Synthesis of a bisdiazaphospholane library. Coupling of the tetraacid bisdiazaphospholane **1** with various amines yields tetracarboxamides. Most primary amines underwent quantitative coupling in the presence of PyBOP/DIEA to form secondary carboxamide bisdiazaphospholane ligands (Scheme 1; Type I and II ligands).

Scheme 1. PyBOP coupling of enantioenriched tetraacid bisdiazaphospholane 1 with various primary amines



Quantitative transformation of **1** to tertiary carboxamide bisdiazaphospholane ligands could not be effected with common coupling reagents such as PyBOP or DCC. However, successful coupling is achieved by first transforming **1** into the tetraacyl fluoride bisdiazaphospholane **9** with Deoxo-Fluor™.[4] Acyl fluorides have been used for coupling of sterically hindered peptide sequences in typically higher yields than other methods.[5] Tetraacyl fluoride precursor **9** can be isolated quantitatively or generated in situ. Scheme 2 summarizes the range of successful couplings that can be achieved with the **9**; dimethylamine, cyclic amines, or aniline undergo coupling to their respective carboxamide substituted ligands. Sterically encumbering secondary amines (diisopropylamine and dicyclohexylamine) and less nucleophilic primary amines (2-aminopyridine and 2-aminopyrimidine) are unreactive and result in the re-isolation of **9**. Acyl fluorides enable rapid access to a library of bisdiazaphospholanes that can be used

Scheme 2. Deoxo-Fluor™ coupling of enantioenriched tetraacid bisdiazaphospholane 1 with various amines

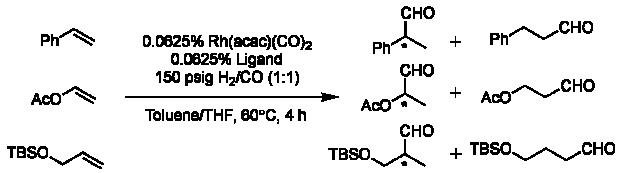


without chromatographic purification. The tetraacyl fluoride **9** exhibits low reactivity with water (enabling aqueous work-up procedures) and alcohols.[6] From preliminary experiments, higher alcohol concentration and forcing conditions are required to produce analogous tetraester bisdiazaphospholanes (*AHF results of tetraester ligands is enclosed in the supporting information*).

AHF of styrene, vinyl acetate, and allyloxy-*tert*-butyldimethylsilane. Similar to previously reported studies, one-pot AHF of styrene, vinyl acetate, and allyloxy-*t*-butyldimethylsilane was used to screen the effects of ligand structure on activity and selectivity.[1a,7] Styrene, vinyl acetate, and allyloxy-*t*-butyldimethylsilane underwent effective hydroformylation in glass pressure bottles at 150 psig H_2/CO (1:1) and 60˚C for all three classes of bis-3,4-diazaphospholane ligands (Table 1).

AHF using tetraacid (*R*,*R*)-1 as the ligand (entry 1) requires atypical conditions (MeOH/Et_3N) for ligand solubilization and yielded modest enantioselectivity (presumably due to base-induced racemization during the course of the reaction). Type **I** ligands include previously reported (*S*,*S*)-**2** and its less selective diastereomer (*R*,*R*)-**2** (entries 2 and 3, respectively). Compared to the standard ligand (*S*,*S*)-**2**, the ligand (*S*,*S*)-**3** (for which cyclohexyl replaces phenyl) results

Table 1. Results of one-pot AHF screening of a library of bisdiazaphospholane ligands



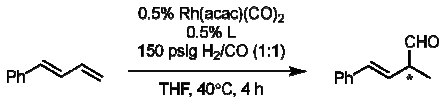
Entry	Type	Ligand	Styrene		Vinyl acetate		Allyloxy-*t*-butyldimethylsilane	
			b:l ratio[a]	% ee[b]	b:l ratio[a]	% ee[b]	b:l ratio[a]	% ee[b]
1[c]		(*R*,*R*)-1	10.9:1	53	15:1	83	1.6:1	75
2	I	(*S*,*S*)-2	18.3:1	87	53:1	98	2.0:1	96
3		(*R*,*R*)-2	9.2:1	75	29:1	84	1.7:1	80
4		(*S*,*S*)-3	7.5:1	63	53:1	97	1.9:1	91
5		(*S*,*S*)-4	6.2:1	88	55:1	95	1.5:1	90
6	II	(*R*,*R*)-5	9.0:1	87	34:1	95	1.8:1	94
7		(*R*,*R*)-6	8.0:1	89	33:1	97	1.8:1	97
8		(*R*,*R*)-7	6.7:1	82	36:1	90	1.6:1	97
9		(*R*,*R*)-8	3.2:1	68	40:1	94	1.9:1	95
10	III	(*R*,*R*)-10	4.7:1	26	44:1	85	1.2:1	92
11		(*S*,*S*)-11	12.9:1	83	27:1	92	1.3:1	90
12		(*R*,*R*)-12	6.8:1	23	20:1	90	1.2:1	90
13		(*R*,*R*)-13	8.0:1	84	25:1	90	1.1:1	>95

Conditions: 4 h, 60°C, 150 psig H_2/CO (1:1), 4.3 M total substrate (equal concentrations of each), 1600:1 total substrate:Rh; complete conversion of alkene is observed in each case expect entry 6: 69%,76%, and 97% conversion of styrene, vinyl acetate, and allyloxy-*t*-butyldimethylsilane respectively. [a] Determined by ^{1}H NMR spectroscopy. [b] Determined by chiral GC analysis. [c] 1mL MeOH as solvent with 1eq. Et_3N to (*R*,*R*)-1 to solubilize ligand.

in decreased regio- (18.3:1 vs. 7.5:1) and enantioselectivity (87% ee vs. 63% ee) in hydroformylation of styrene, but little affect on vinyl acetate and allyl silyl ether hydroformylation (entries 2 and 4). In contrast, (*S*,*S*)-**4** (entry 5), which bears *t*-butyl in place of phenyl, gives decreased regioselectivity but retains high enantioselectivity. Type **II** ligands, which contain secondary carboxamides with increasing R-group steric bulk (ethyl, benzyl, benzhydryl, and 1-adamantyl), decrease styrene regio- and enantioselectivity in AHF while leaving selectivities for vinyl acetate and allyl silyl ether relatively unaffected (entries 6—9). Type **III** tertiary carboxamide ligands exhibit uniformly lower regioselectivities than *(S,S)*-**2** for all three terminal alkenes. Whereas styrene enantioselectivity varied from 23-86% ee amongst the four type **III** ligands, the enantioselectivities for the allyl silyl ether and vinyl acetate were generally similar to (*S*,*S*)-**2**. Overall, (*S*,*S*)-**2** exhibits optimal regio- and enantioselectivity in the hydroformylation of styrene, vinyl acetate, and allyl silyl ether.

AHF of (*E*)-1-phenyl-1,3-butadiene. We previously reported enantioselective hydroformylation of 1,3-dienes using bisdiazaphospholanes (*S*,*S*)-**2**, (*R*,*R*)-**2**, and (*R*,*R*)-**5** leading to β,γ-unsaturated aldehydes that are useful intermediates in the synthesis of complex molecules.[1b] With the bisdiazaphospholane library reported here, AHF of (*E*)-1-phenyl-1,3-butadiene produces just one regioisomer, consistent with our previous studies, but with widely ranging enantioselectivity (11-94% ee). Ligands (*S*,*S*)-**2** and (*S*,*S*)-**3** give the highest enantioselectivity for AHF of (*E*)-1-phenyl-1,3-butadiene (entries 1 and 2; 94% and 93% ee, respectively). In contrast, (*S*,*S*)-**3** gives poor enantioselectivity (64% ee) for styrene. Using type **II** and **III** ligands with increasingly bulky carboxamides results in decreased enantioselectivity: 51-83% ee for type **II** ligands [83% ee for (*R*,*R*)-**5**] and 11-33% ee for type **III** ligands.

Table 2. AHF of (E)-1-phenyl-1,3-butadiene with library of bisdiazaphospholanes



Entry	Type	Ligand	% conv.[a]	% ee[b]
1	I	(*S*,*S*)-2	97	94
2		(*S*,*S*)-3	95	93
3		(*S*,*S*)-4	92	44
4	II	(*R*,*R*)-5	95	83
5		(*R*,*R*)-6	92	78
6		(*R*,*R*)-7	60	79
7		(*R*,*R*)-8	90	51
8	III	(*R*,*R*)-10	95	16
9		(*S*,*S*)-11	95	11
10		(*R*,*R*)-12	95	33
11		(*R*,*R*)-13	97	30

Following conditions: 4 h, 40°C, 150 psig H_2/CO (1:1), 0.55 M 1-phenyl-1,3-butadiene, 200:1 substrate:catalyst. [a] Determined by ^{1}H NMR spectroscopy. [b] Determined by

AHF of dihydrofurans. Hydroformylation of dihydrofurans leads to enantioenriched carbaldehyde intermediates useful for organic synthesis.[7] A few groups have reported that AHF of dihydrofurans proceeds with modest overall performance when one takes both rate and selectivity into account.[9]

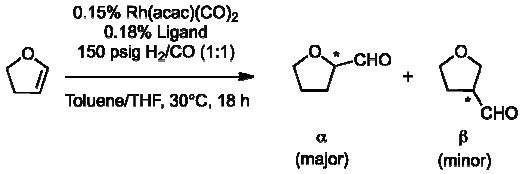
The AHF of 2,3-dihydrofuran with bisdiazaphospholanes is modestly regioselective, yielding both α- and β-carbaldehyde regioisomer products. Initial screening (Table 3) of 2,3-dihydrofuran hydroformylation with a subset of

the library at 30°C for 18 hours resulted in modest conversions (<50%), 1.7:1—3.9:1 α:β regioselectivity, and enantioselectivities as high as 89% for both regioisomers. For the initial screening conditions type **III** ligands exhibited the highest enantioselectivity (77—90% ee) and conversion.

Increasing the reaction temperature for AHF of 2,3-dihydrofuran yields substantially improved conversion with little change in selectivity (Table 4). At 60°C the α- and β-aldehyde regioisomers are produced with high enantioselectivity (ca. 90% ee) and conversions exceeding 90% (600 turnovers) in 4 hours. Under these conditions the α-regioisomer predominates by an approximately 3:1 ratio. The highest previously reported enantioselectivity for AHF of 2,3-dihydrofuran to the α-aldehyde was 62% ee with only 8% conversion (16 turnovers) after 22 hours.[9a]

Hydroformylation of 2,5-dihydrofuran isomer with all ligands at 40°C for 4 hours proceeds smoothly to the expected β-regioisomer, with minor formation of the α-carbaldehyde and 2,3-dihydrofuran byproducts (Table 5). Compared to 2,3-dihydrofuran, AHF of 2,5-dihydrofuran is faster and more enantioselective. The advantage of the bulky type III ligands is particularly clear; these ligands give much higher conversions (94%, 630 turnovers, 4 hours) and enantioselectivities as high as 95 %ee. For comparison, similar conversions with slightly lower selectivities require 10-fold longer reaction times with phosphine-phosphite ligands.[9a]

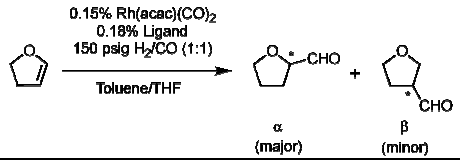
Table 3. Initial screening results for AHF of 2,3-dihydrofuran using bisdiazaphospholane ligands



Entry	Type	Ligand	α:β ratio[a]	% conv.[a]	% ee α[b]	% ee β[b]
1	I	(*S*,*S*)-2	2.8:1	11	69 (*S*)	86 (*S*)
2		(*R*,*R*)-2	1.7:1	37	85 (*R*)	85 (*R*)
3	II	(*R*,*R*)-8	1.7:1	7	75 (*R*)	70 (*R*)
4	III	(*R*,*R*)-10	3.8:1	45	90 (*R*)	89 (*R*)
5		(*S*,*S*)-11	3.6:1	16	77 (*S*)	87 (*S*)
6		(*R*,*R*)-12	3.9:1	41	87 (*R*)	87 (*R*)
7		(*R*,*R*)-13	3.7:1	15	77 (*R*)	78 (*R*)

Conditions: 2.6 M 2,3-dihydrofuran, 670:1 substrate:catalyst. [a] Determined by ^{1}H NMR spectroscopy. [b] Determined by chiral GC analysis.

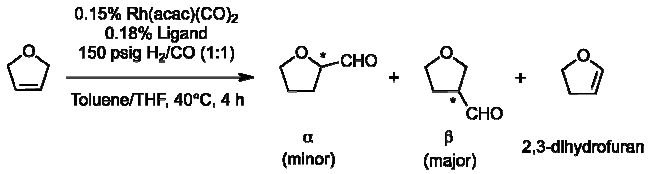
Table 4. Optimization of selected ligands for the AHF of 2,3-dihydrofuran



Entry	Type	Ligand	Temp.	α:β ratio[a]	% conv. [a]	% ee α[b]	% ee β[b]
1	I	(*S*,*S*)-2	40°C	2.8:1	25	89 (*S*)	82 (*S*)
2	II	(*R*,*R*)-6	40°C	1.5:1	23	83 (*R*)	84 (*R*)
3	III	(*R*,*R*)-10	40°C	3.4:1	30	88 (*R*)	86 (*R*)
4		(*S*,*S*)-11	40°C	3.2:1	16	88 (*S*)	80 (*S*)
5		(*R*,*R*)-12	40°C	3.5:1	27	90 (*R*)	85 (*R*)
6	I	(*S*,*S*)-2	60°C	3.1:1	94	80 (*S*)	85 (*S*)
7	III	(*R*,*R*)-10	60°C	3.3:1	92	87 (*R*)	90 (*R*)
8		(*R*,*R*)-12	60°C	3.5:1	83	88 (*R*)	88 (*R*)

Conditions: 4 h, 150 psig H_2/CO (1:1), 2.6 M 2,3-dihydrofuran, 670:1 substrate:catalyst. [a] Determined by ^{1}H NMR spectroscopy. [b] Determined by chiral GC analysis.

Table 5. AHF of 2,5-dihydrofuran using bisdiazaphospholane ligands



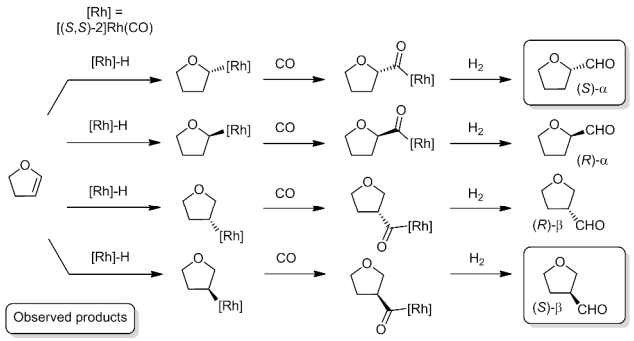
Entry	Type	Ligand	α:β ratio[a]	% conv. [a]	% 2,3-dihydrofuran[a]	% ee α[b]	% ee β[b]
1	I	(*S*,*S*)-2	1:15	80	18	74 (*S*)	86 (*R*)
2		(*R*,*R*)-2	1:14	61	34	57 (*R*)	82 (*S*)
3	II	(*R*,*R*)-8	<1:30	28	4	51 (*R*)	82 (*S*)
4	III	(*R*,*R*)-10	<1:30	94	4	81 (*R*)	95 (*S*)
5		(*S*,*S*)-11	1:28	97	3	86 (*S*)	20 (*R*)
6		(*R*,*R*)-12	<1:30	92	5	81 (*R*)	95 (*S*)
7		(*R*,*R*)-13	1:17	52	21	88 (*R*)	56 (*S*)

Conditions: 40°C, 4 h, 150 psig H_2/CO (1:1), 2.6 M 2,5-dihydrofuran, 670:1 substrate:catalyst. [a] Determined by ^{1}H NMR spectroscopy. [b] Determined by chiral GC analysis.

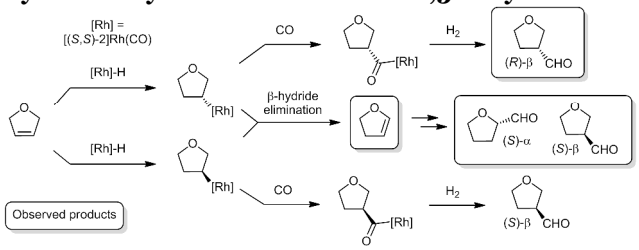
Both 2,3-dihydrofuran and 2,5-dihydrofuran yield some amount of the α- and β-carbaldehydes. Although the α-regioisomers produced from 2,3- and 2,5-dihydrofuran have the same absolute sense of stereoinduction, the β-regioisomer produced from 2,3-dihydrofuran (a minor product) has opposite chirality from AHF of 2,5-dihydrofuran. Similar behavior was first reported by Nozaki et al. for these substrates with BINAPHOS ligand.[9e] Insertion of 2,5-dihydrofuran into the Rh-H bond leads to four possible products (Scheme 3): (*R*)-α, (*S*)-α, (*R*)-β, and (*S*)-β isomers. With ligand (*R*,*R*)-**10**, the main products are (*R*)-α and (*R*)-β. In contrast, direct hydroformylation of 2,5-dihydrofuran should result in just two aldehydes (Scheme 4): (*R*)-β or (*S*)-β. However, α-products may arise via isomerization of the 2,5-dihydrofuran to the thermodynamically preferred 2,3-dihydrofuran followed by AHF. For ligand (*R*,*R*)-**10**, the α-

product has primarily the (R) configuration but the β-product is primarily (S)! These results indicate that (1) hydroformylation occurs on opposite enantiofaces of the two dihydrofuran isomers and (2) the β-carbaldehyde product observed in the hydroformylation of 2,5-dihydrofuran arises from both direct hydroformylation and isomerization/hydroformylation but with opposite stereochemical preferences. The counteracting selectivity preferences of direct and isomerization/hydroformylation pathways indicate that the direct pathway must have higher intrinsic enantioselection than the observed enantioselectivity.

Scheme 3. Observed products in the hydroformylation of 2,3-dihydrofuran



Scheme 4. Observed products in the hydroformylation of 2,5-dihydrofuran



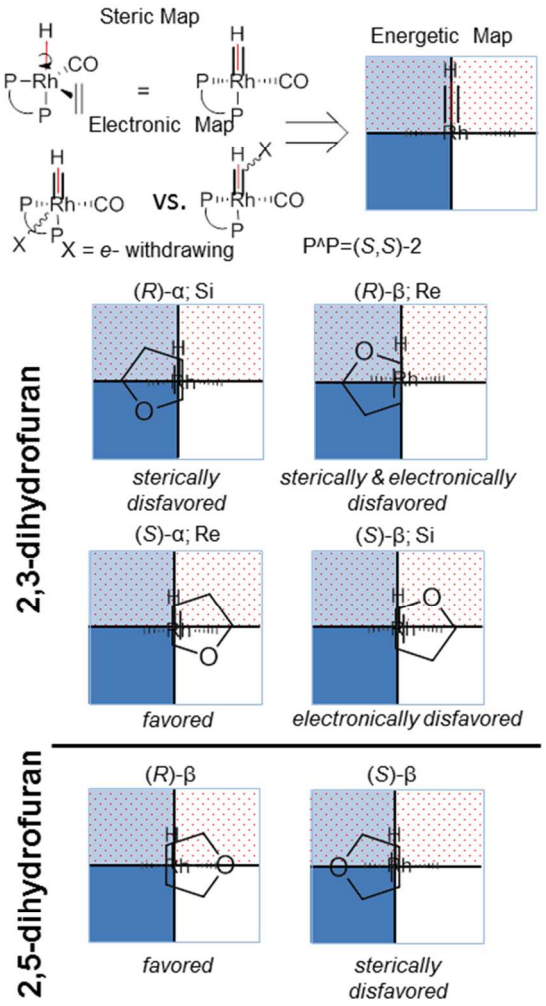


Figure 1. Empirical energetic map to rationalize regio- and enantioselectivity of 2,3-dihydrofuran and 2,5-dihydrofuran hydroformylation using Rh-bisdiazaphospholane catalysts. Blue boxes indicate varying levels of steric bulk (dark blue = large repulsion, light blue = small repulsion), red dots indicate electronically unfavorable orientations of inductively electron withdrawing substituents. Boxes labeled as product carbaldehydes. Absolute stereochemistry based on (*S,S*)-bisdiazaphospholanes.

Previously we have developed an energetic quadrant map that graphically summarizes hypothetical steric and electronic contributions to the transition state energies for alkene insertion in the Rh-H bond (Figure 1).[1a, 10] We presume equatorial-axial coordination of all bisdiazaphospholane ligands in trigonal bipyramidal rhodium-alkene intermediates. The perspective shown places the axial Rh-H and Rh-P bonds in the plane of the paper, the coordinated alkene lies in front of that plane and the remaining Rh-P and Rh-CO vectors behind. Regions colored in blue indicate varying levels of steric bulk and red dots indicate less favorable orientations of

inductively electron withdrawing alkene substituents. Application of this map to 2,3-dihydrofuran suggests a preference for *Re*-face coordination with the ether oxygen lying in the bottom right quadrant. This model predicts formation of the (*S*)-α stereoisomer [based on (*S*,*S*)-bisdiazaphospholane ligands] as is observed. For the hydroformylation of 2,5-dihydrofuran, the energetic map correctly predicts formation of the (*R*)-β product. Furthermore, the stereoelectronic map of Figure 1 reveals that *E*-1,2-disubstituted alkenes should hydroformylate more slowly than the *Z*-stereoisomers because one of the substitutents of the *E*-isomer necessarily lies in a sterically crowded quadrant. The map also predicts lower enantioselectivity for the *E*-isomer, as seen for β-methylstyrene and 1-acetamido-1-propene.[1c, d] Remarkably, the energetic quadrant map developed for terminal alkenes robustly rationalizes the absolute configuration of dihydrofuran AHF products, the selection of different enantiofaces for 2,3- and 2,5-dihydrofurans, and rates and selectivities for *E*- vs. *Z*-1,2-disubstituted alkenes.

Conclusions

This work addresses the challenge of AHF of dihydrofurans with useful selectivities and activities by exploiting the synthetic extensibility of bisdiazaphospholane ligands. The creation of small ligand libraries is made possible by formation of enantiopure tetraacyl fluoride **9** which can be rapidly transformed to a variety of bulky secondary and tertiary tetracarboxamides. Application of this library to rhodium-catalyzed AHF of styrene, vinyl acetate, alloxy-*t*-butyldimethylsilane, and 1-phenyl-1,3-butadiene appears to follow the "principle of initial optimization" [11] in which one of the earliest ligands, (*S*,*S*)-**2**, uncovered in the discovery process exhibits the best overall selectivity trends. For the substrate styrene, highly varied enantio- and regioselectivity results with different library members, in keeping with previous observations[10] of a delicate balance among competing pathways for aryl alkene hydroformylation. For the substrate 1-phenyl-1,3-butadiene an inverse correlation of steric bulk with enantioselectivity (increasing steric bulk leads to decreasing enantioselectivity) is observed. The value of a library approach is seen in the hydroformylation of 2,3- and 2,5-dihydrofurans. The tertiary carboxamide, type **III** ligands (*R*,*R*)-**10** and (*R*,*R*)-**12** give unprecedented combination of high activity with high regio- and enantioselectivity for the AHF of 2,3- and 2,5-dihydrofuran. Stereoelectronic maps predict the qualitative activity and selectivity trends for a wide variety of mono- and disubstituted alkenes. These results provide encouragement as applications of catalytic AHF move to bulky di- and tri-substituted alkenes and other challenging substrates.

Experimental

Materials and Methods

All phosphines were prepared under N_2 using standard Schlenk line techniques. Work up and flash column chromatography were performed open to air. Ligands (*rac)*-**1**, (*S*,*S*)-**2**, (*R*,*R*)-**2** were prepared according to literature

procedure[1a] and (*rac)*-**1** was resolved by chiral supercritical fluid chromatography. Unless mentioned below all chemicals were purchased and used without further purification. $Rh(acac)(CO)_2$ was recrystallized from toluene/hexanes (green needles) prior to use. THF and toluene were distilled over Na/benzophenone under a nitrogen atmosphere was further deoxygenated by at least three freeze-thaw cycles prior to use. Dichloromethane was distilled under nitrogen over P_2O_5. The percent conversion and regioisomer ratios were determined by ^1H NMR analysis of the crude reaction mixture. Gas chromatography (GC) was performed using a β-DEX 225 column (30m x 0.25mm ID). Super Critical Fluid Chromatography (SFC) was performed using a Chiracel OJ-H column. Silica gel, 230-400 mesh (40-63μm) was used for column chromatography. Vinyl acetate, styrene, TBSO allyl ether, phenyl-1,3-butadiene, 2,5-dihydrofuran, and 2,3-dihydrofuran were all sparged w/ N_2 before use. Phenyl-1,3-(*E*)-butadiene[1b] and 7-azanoraborane[12] was synthesized according to literature procedure. (*R*) and (*S*)-Methylprolinate were synthesized from (*R*) and (*S*)-proline respectively, and recrystallized. Synthesis of bisdiazaphospholanes using PyBOP often contains low amounts of the tris(pyrollidinophosphine) oxide byproduct (^{31}P δ: 16 (s)), even after column chromatography, which has not been observed or is expected to affect AHF. Proton (^1H) and carbon (^{13}C) NMR spectra were referenced to TMS (0.00 ppm) and CDCl3 (77.0 ppm) respectively. The fluorine (^{19}F) spectra were referenced to TMS in the ^1H spectra, using the Unified Scale. Phosphorus (^{31}P) chemical shifts were referenced to an external 85% phosphoric acid (H_3PO_4) sample. ^1H NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q). First-order splitting patterns were assigned on the basis of the multiplet. Splitting patterns that could not be interpreted are designated as multiplet (m) or broad (br). Mass spectra were collected using an instrument with electrospray ionization and a TOF analyzer. Ligands **7** and **8** were prepared from a sample of tetraacid bisdiazaphospholane (**1**) that was partially oxidized at one phosphine, <5% by ^{31}P NMR (δ: 42.7 (d, J = 238 Hz), 0.3 (d, J = 238 Hz)).

Caution: Syngas (1:1 H_2:CO) is flammable! Carbon monoxide is toxic! All hydroformylation reactions should be carried out in a well ventilated fume hood.

General Method A An oven-dried 50mL Schlenk flask was loaded with 0.2g (0.22mmol) enantiopure tetraacid bisdiazaphospholane (*R,R)*-1 and 5 eq. of PyBOP and pumped/purged three times with N_2. The solid was suspended in 20-30mL of dichloromethane and stirred at room temperature. DIEA (5eq.) was added to the stirred suspension (0.2mL, 1.15mmol) at which point the solution becomes homogenous. Primary amine (5 eq.) was added by syringe or cannula and the solution was stirred overnight. The reaction mixture was washed with sat. $NaHCO_3$ solution, 1M HCl, and brine. The organic layer was dried with Na_2SO_4 followed by removal of volatiles on a rotary evaporator to give crude material which is purified by flash column chromatography.

General Method B An oven-dried 50mL Schlenk flask was loaded with 0.2g (0.22mmol) enantiopure tetraacyl fluoride bisdiazaphospholane (*R,R)*-**9** and pumped/purged three times with N_2. The solid was dissolved in 20-30mL of

dichloromethane and stirred at room temperature. DIEA (5 eq) was added to the stirred solution (0.2mL, 1.15mmol). Secondary amine (5 eq.) was added by syringe to the stirred solution (solid amines dissolved in DCM) and stirred overnight. The reaction mixture was washed with sat. $NaHCO_3$ solution, 1M HCl, and brine. The organic layer was dried with Na_2SO_4 followed by rotary evaporation to give the corresponding tetraamide bisdiazaphospholane.

2,2',2'',2'''-(1,2-phenylenebis((1*S*,3*S*)-tetrahydro-5,8-dioxo-1*H*-(1,2,4)diazaphospholo(1,2-*a*)pyridazine-2,1,3(3*H*)-triyl))tetrakis(N-((1*S*)-1-(1-cyclohexyl)ethylbenzamide)) (*S*,*S*)-3. Following general method A using 0.2g (0.22mmol) enantiopure tetraacid bisdiazaphospholane (*S,S*-1) and 5 eq. of (*S*)-cyclohexylethylamine (0.17mL, 1.1mmol). (*S,S*)-**3** was isolated from silica gel chromatography using 2:1 ethyl acetate and dichloromethane (R_f = 0.43). Isolated 0.21g, 69% yield, quantitatively pure by ^{31}P NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.72 ppm (d, J = 6.6 Hz), 0.81 – 0.93 (m), 1.03 – 1.22 (m), 1.46 – 1.82 (m), 2.41 – 2.71 (m), 3.53 – 3.60 (m), 3.99 – 4.09 (m), 6.14 – 6.16 (m), 6.64 – 6.69 (m), 6.90 – 6.94 (m), 7.03 – 7.11 (m), 7.23 – 7.26 (m, overlap with $CHCl_3$ residual solvent peak), 7.33 – 7.40 (m), 7.45 – 7.50 (m), 7.54 – 7.56 (m), 7.62 – 7.68 (m), 7.75 – 7.78 (m), 8.06 – 8.08 (m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.3, 17.8, 26.4, 26.6, 26.7, 29.0, 29.2, 29.5, 29.8, 304, 42.6, 42.9, 50.5, 51.3, 55.6, 57.6, 125.3, 125.9, 126.4, 127.1, 127.9, 128.3, 128.7, 128.8, 129.9, 130.5, 130.6, 131.5, 133.6, 134.3, 137.1, 138.6, 165.7, 167.3 , 168.3, 168.6. $^{31}P\{^{1}H\}$ NMR (120 MHz, $CDCl_3$) δ: 5.6 (broad s). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{78}H_{96}N_8NaO_8P_2$, 1357.6719; found, 1357.6763 (Δ = 3.2 ppm).

2,2',2'',2'''-(1,2-phenylenebis((1*S*,3*S*)-tetrahydro-5,8-dioxo-1*H*-(1,2,4)diazaphospholo(1,2-*a*)pyridazine-2,1,3(3*H*)-triyl))tetrakis(N-((1*S*)-1-(1,2,2-trimethyl)propylbenzamide)) (*S*,*S*)-4. Following general method A using 0.2g (0.22mmol) enantiopure tetraacid bisdiazaphospholane (*S,S*-1) and 5 eq. of (*S*)-3,3-dimethyl-2-butylamine(0.15mL, 1.1mmol). (*S,S*)-**4** was isolated from silica gel chromatography using 4:1 ethyl acetate and dichloromethane solvent mixture. Isolated 0.14g, 51% yield, quantitatively pure by ^{31}P NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.81 ppm (d, J = 6.6 Hz), 0.90 (s), 1.00 (s), 1.20 (d, J = 6.9), 2.38 – 2.69 (m), 3.49 – 3.54 (m), 4.12 – 4.17 (m), 6.20 (d, J = 8.1 Hz), 6.35 (br s), 6.66 – 6.80 (m), 6.98 (br d, J = 9.0 Hz), 7.16 (br s), 7.30 – 7.40 (m), 7.45 – 7.52 (m), 7.66 – 7.69 (m), 7.76 – 7.79 (m), 7.90 (br d, J = 9.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.8, 16.1, 26.7, 26.9, 29.2, 29.4, 34.3, 34.6, 54.1, 54.7, 55.3, 57.2, 117.5, 125.0, 126.4, 127.6, 128.5, 128.9, 129.1, 130.8, 132.9, 134.1, 135.9, 137.7, 165.7, 166.7, 168.7, 169.4. $^{31}P\{^{1}H\}$ NMR (120 MHz, $CDCl_3$) δ: 10.4 (broad s). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{70}H_{88}N_8NaO_8P_2$, 1253.6093; found, 1253.6074 (Δ = 1.5 ppm).

2,2',2'',2'''-(1,2-phenylenebis((1*R*,3*R*)-tetrahydro-5,8-dioxo-1*H*-(1,2,4)diazaphospholo(1,2-*a*)pyridazine-2,1,3(3*H*)-triyl))tetrakis(N-ethylbenzamide) (*R*,*R*)-5. Following general method A using 0.25g (0.28mmol) enantiopure tetraacid bisdiazaphospholane (*R,R*-1) and 5 eq. of ethylamine 2M in THF(0.7mL, 1.4mmol).

(*R*,*R*)-**5** can be recrystallized from 8:1 hexane:ethyl acetate solution obtaining a white solid. Isolated 0.09g, 30% yield, 95% pure by ^{31}P NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.04 (t, J = 7.3 Hz), 1.24 (t, J = 7.3 Hz), 2.40 – 2.85 (m, 8 H), 3.12 – 3.30 (m, 3H), 3.45 – 3.75 (m, 5H), 6.17 (d, J = 7.5 Hz, 2H), 6.33 (s, 2H), 6.67 (m, 2H), 6.85 – 7.00 (m, 4 H) 7.05 – 7.30 (m, overlap with $CHCl_3$ residual solvent peak), 7.40 – 7.68 (m, 9H), 8.61 (broad t, J = 5.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.8, 15.0, 29.1, 29.4, 34.6, 35.0, 55.1, 57.5, 125.6, 127.1, 127.6, 128.3, 128.7, 129.1, 129.7, 130.2, 130.6, 130.7, 134.0, 134.4, 134.6, 137.3, 138.6, 165.7, 167.3, 168.1, 169.0. ^{31}P{^{1}H} NMR (120 MHz, $CDCl_3$) δ: 9.2 (s). HRMS-ESI (m/z): $[M + NH_4]^+$ calcd for $C_{54}H_{60}N_9O_8P_2$, 1024.4035; found, 1024.4059 (Δ = 2.3 ppm).

2,2',2'',2'''-(1,2-phenylenebis((1*R*,3*R*)-tetrahydro-5,8-dioxo-1*H*-(1,2,4)diazaphospholo(1,2-*a*)pyridazine-2,1,3(3*H*)-triyl))tetrakis(N-benzylbenzamide) (*R*,*R*)-6. Following general method A using 0.3g (0.33mmol) enantiopure tetraacid bisdiazaphospholane (*R*,*R*-1) and 5 eq. of benzylamine (0.18mL, 1.7mmol). (*R*,*R*)-**6** was purified by flash column chromatography using ethyl acetate as eluent (Rf = 0.05). Isolated 95mg, 32% yield, 95% pure by ^{31}P NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.30 – 2.63 (m, 8 H), 3.64 (dd, J = 15.6, 5.1 Hz, 2H), 4.26 (dd, J = 15.1, 6.4 Hz, 2H), 4.29 – 4.71 (m, 4H), 6.16 (d, J = 7.8 Hz, 2H), 6.22 (s, 2H), 6.61 – 6.67 (m, 2H), 6.78 – 6.86 (m, 4H), 7.03 – 7.12 (m, 9 H), 7.18 – 7.40 (m, overlap with $CHCl_3$ residual solvent peak), 7.49 – 7.52 (m, 2H), 7.60 – 7.80 (m, 2H), 8.68 (broad s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.0, 29.4, 43.3, 44.4, 55.7, 57.7, 125.6, 127.1, 127.6, 128.3, 128.8, 129.1, 129.7, 130.2, 130.6, 130.7, 134.0, 134.4, 134.6, 137.4, 138.6, 165.5, 167.3, 168.6, 169.6. ^{31}P{^{1}H} NMR (120 MHz, $CDCl_3$)δ: 7.3 (s). HRMS-ESI (m/z): $[M + NH_4]^+$ calcd for $C_{74}H_{68}N_9O_8P_2$, 1272.4661; found, 1272.4634 (Δ = 2.1 ppm).

2,2',2'',2'''-(1,2-phenylenebis((1*R*,3*R*)-tetrahydro-5,8-dioxo-1*H*-(1,2,4)diazaphospholo(1,2-*a*)pyridazine-2,1,3(3*H*)-triyl))tetrakis(N-benzhydrylbenzamide) (*R*,*R*)-7. Following general method A using 0.20g (0.22mmol) enantiopure tetraacid bisdiazaphospholane (*R*,*R*-1) and 5 eq. of benzhydrylamine (0.19mL, 1.1mmol). Ligand (*R*,*R*)-**7** was isolated by way of flash column chromatography using 2:1 ethyl acetate and dichloromethane (R_f = 0.30) solvent mixture. Isolated 215mg, 64% yield, 79% pure by ^{31}P NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.30 – 2.63 (m, 8 H), 4.29 – 4.71 (m, 4H), 6.16 (d, J = 7.8 Hz, 2H), 6.22 (s, 2H), 6.61 – 6.67 (m, 2H), 6.78 – 6.86 (m, 4H), 7.03 – 7.12 (m, 9 H), 7.18 – 7.40 (m, overlap with $CHCl_3$ residual solvent peak), 7.49 – 7.52 (m, 2H), 7.60 – 7.80 (m, 2H), 8.68 (broad s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.9, 29.1, 57.7, 57.9, 125.3, 125.9, 127.6, 127.9, 128.3, 128.7, 129.1, 129.3, 129.9, 130.3, 130.8, 133.4, 134.0, 134.3, 136.3, 137.4, 166.1, 167.0, 168.4, 168.6. ^{31}P{^{1}H} NMR (120 MHz, $CDCl_3$) δ: 9.8 (broad s). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{98}H_{80}N_8NaO_8P_2$, 1581.5467; found, 1581.5500 (Δ = 2.1 ppm).

2,2',2'',2'''-(1,2-phenylenebis((1*R*,3*R*)-tetrahydro-5,8-dioxo-1*H*-(1,2,4)diazaphospholo(1,2-*a*)pyridazine-2,1,3(3*H*)-triyl))tetrakis(N-(1-adamantyl)benzamide) (*R*,*R*)-8. Following general method A

using 0.20g (0.22mmol) enantiopure tetraacid bisdiazaphospholane (*R,R*-1) and 5 eq. 1-adamantylamine (0.17g, 1.1mmol) dissolved in dichloromethane solution and cannula transferred to the (*R,R*-1**)**, PyBOP, and DIEA mixture. After 4 hours stirring, a white solid precipitated out of solution; this material was separated from the supernatant. The filtrate was washed with sat. $NaHCO_3$ solution, 1M HCl, and brine. The organic layer was dried with Na_2SO_4 followed by rotary evaporation to give crude material which is purified by flash column chromatography. The solvent from the filtrate was removed and (*R,R*)-**8** was purified by way of silica gel chromatography utilizing ethyl acetate (R_f = 0.05) as an eluent, resulting in a white solid. Isolated 130mg, 41% yield, 85% pure by ^{31}P NMR. ^{1}H NMR (500 MHz, CD_2Cl_2) δ: 1.54 (apparent Abs, J_{AB} = 61.6 Hz, J = 11.8 Hz, 14 H), 1.74 (m, 13H), 1.89 (m, 16H), 2.14 (m, 17H) 2.25 – 2.55 (m, 8H), 6.23 (broad s, 2H), 6.45 – 6.70 (m), 6.78 (broad s), 6.92 (m), 7.18 – 7.40 (m), 7.40 – 7.50 (m), 7.60 – 7.85 (m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.3, 21.1, 29.4, 29.6, 36.3, 36.6, 41.4, 41.9, 53.1, 53.4, 60.5, 111.4, 117.3, 125.0, 126.2, 126.4, 127.4, 127.7, 128.7, 130.8, 132.2, 136.5, 137.9, 166.1, 166.9, 168.5, 171.3. $^{31}P\{^{1}H\}$ NMR (120 MHz, $CDCl_3$) δ: 10.9 (broad s). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{86}H_{96}N_8NaO_8P_2$, 1453.6719; found, 1453.6727 (Δ < 1 ppm).

2,2',2'',2'''-(1,2-phenylenebis((1*R*,3*R*)-tetrahydro-5,8-dioxo-1*H*-(1,2,4)diazaphospholo(1,2-*a*)pyridazine-2,1,3(3*H*)-triyl))tetrakiscarbonyl fluoride (*R,R*)-9. An oven-dried 50mL Schlenk flask was loaded with 0.2g (0.22mmol) enantiopure tetraacid bisdiazaphospholane (*R,R*-**1)** and pumped/purged three times with N_2. Solid was suspended in 20-30mL of dichloromethane and stirred at 24°C. Addition of 5 eq. of DIEA (0.2mL, 1.15mmol) resulted in a homogenous yellow solution. Addition of 5 eq. of Deoxo-Fluor™(0.21mL, 1.15mmol) immediately resulted in an orange homogenous solution. The reaction was stirred for 2 hours then washed with sat. $NaHCO_3$ solution, 1M HCl, and brine. The organic layer was dried with Na_2SO_4 followed by rotary evaporation. Isolated yellow/orange powder, 0.2g, quantitative yield. ^{1}H NMR: (300.1 MHz, $CDCl_3$) δ 8.07 (dd, J = 7.9, 1.1 Hz, 2H), 7.70 (td, J = 8.4, 1.2 Hz, 2H), 7.51 (t, J = 7.9 Hz, 2H), 7.36 (dd, J = 7.9, 1.5 Hz, 2H), 7.28 (m, 2H), 7.20 (m, overlap with residual $CHCl_3$), 7.13 (d, J = 7.8 Hz, 2H), 7.08 (td, J = 7.7, 1.5 Hz, 2H), 7.00 (dd, J = 7.8, 0.9 Hz, 2H), 6.94 (t, J = 8.2 Hz, 2H), 6.83 (s, 2H), 6.54 (d, J = 8.1 Hz, 2H), 2.75-2.27 (AA'BB', 8H). ^{13}C NMR: (75.4 MHz, $CDCl_3$) δ 166.3, 164.0, 139.9, 135.0, 133.0, 131.6, 131.5, 130.2, 127.9, 126.7, 125.7, 125.2, 57.1, 53.9, 28.5, 19.8. $^{19}F\{^{1}H\}$ NMR: (282 MHz, $CDCl_3$) δ 30.12 (s), 28.12 (s). $^{31}P\{^{1}H\}$ NMR: (120 MHz, $CDCl_3$) δ 3.936 (s). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{46}H_{32}F_4N_4NaO_8P_2$, 929.1524; found, 929.1519 (Δ < 1 ppm).

2,2',2'',2'''-(1,2-phenylenebis((1*R*,3*R*)-tetrahydro-5,8-dioxo-1*H*-(1,2,4)diazaphospholo(1,2-*a*)pyridazine-2,1,3(3*H*)-triyl))tetrakis(N-pyrrolidinyl-benzamide) (*R,R*)-9. Following general method B using 0.13g (0.14mmol) enantiopure tetraacyl fluoride bisdiazaphospholane (*R,R*-**9**) 5 eq. of pyrrolidine (0.06mL, 0.7mmol) Isolated 0.14g, 88% yield, quantitatively pure by ^{31}P NMR. ^{1}H NMR: (299.9 MHz, $CDCl_3$) δ 7.70 (t, J = 5.7 Hz), 7.64 (dd, J = 7.7, 1.2 Hz), 7.52 (m), 7.34 (m), 7.24 (m), 6.99 (m), 6.81 (m), 6.59 (d, J = 6.8 Hz), 6.48 (m), 6.15 (s),

5.88 (t, J = 10.1 Hz), 3.7-3.1 (m), 2.7-2.4 (m), 1.9-1.7 (m), 1.51 (d, J = 6.7 Hz), 1.42 (d, J = 6.8 Hz); ^{13}C NMR: (75.4 MHz, $CDCl_3$) δ 169.0, 167.9, 167.2, 165.9, 137.1, 134.6, 133.5, 133.1, 129.3, 128.8, 128.1, 127.4, 127.2, 126.4, 126.0, 125.7, 58.9, 58.4, 53.5, 49.6, 48.6, 46.1, 45.9, 45.5, 29.9, 29.6, 26.1, 24.7, 24.6, 24.4; ^{31}P {^{1}H} NMR: (120 MHz, $CDCl_3$) δ 9.2. HRMS-ESI (m/z): $[M+NH_4]^+$ calcd for $C_{62}H_{68}N_9O_8P_2$ 1128.4661; found, 1128.4612 (Δ = 4.3 ppm).

2,2',2'',2'''-(1,2-phenylenebis((1*S*,3*S*)-tetrahydro-5,8-dioxo-1*H*-(1,2,4)diazaphospholo(1,2-*a*)pyridazine-2,1,3(3*H*)-triyl))tetrakis(N-(7-azabicyclo[2.2.1]heptane) benzamide) (*S*,*S*)-11. Following general method B using 0.10g (0.11mmol) enantiopure tetraacyl fluoride bisdiazaphospholane (*S,S*-**9**) and 5eq. 7-azanorbornane•HCl (7.5mg, 0.55mmol) dissolved in DCM and mixed with Et_3N (8μL, 0.55mmol). Isolated 0.11g, 80% yield, quantitatively pure by ^{31}P NMR. ^{1}H NMR: (299.9 MHz, $CDCl_3$) δ 7.83 (d, J = 8.1 Hz, 2H), 7.54 (m, 2H), 7.380 (m, 4H), 7.11 (m, 2H), 6.93 (t, J = 6.91 Hz, 4H), 6.85 (m, 4H), 6.74 (m, 4H), 6.12 (bs, 2H), 5.98 (t, J = 10.2 Hz, 2H), 4.71 (bs, 2H), 4.06 (bs, 4H), 3.67 (bs, 2H), 2.78 (m, 4H), 2.57 (m, 4H), 2.43 (m, 2H), 1.80 (m, 12H), 1.36 (m, 16H); ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 167.2, 166.7, 165.5, 135.3, 132.7, 129.4, 129.0, 128.8, 128.5, 127.7, 127.5, 126.9, 126.6, 125.7, 58.7, 58.3, 58.2, 53.6, 53.4, 53.1, 30.5, 30.3, 30.3, 30.2, 30.1, 29.9, 29.6, 29.3, 29.1, 28.8, 28.4, 14.1; ^{31}P {^{1}H} NMR: (120 MHz, $CDCl_3$) δ 12.4 (s).HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{70}H_{72}N_8NaO_8P_2$, 1237.4841; found, 1237.4899 (Δ = 4.7 ppm).

2,2',2'',2'''-(1,2-phenylenebis((1*R*,3*R*)-tetrahydro-5,8-dioxo-1*H*-(1,2,4)diazaphospholo(1,2-*a*)pyridazine-2,1,3(3*H*)-triyl))tetrakis((S)-N-2-(methoxycarbonyl)pyrrolidinyl-benzamide) (*R*,*R*)-12. Following general method B using 0.10g (0.11mmol) enantiopure tetraacyl fluoride bisdiazaphospholane (*R,R*-**9**) and 5 eq. of (*S*)-methylprolinate (90mg, 0.7mmol) in 10mL DCM. Silica gel column chromatography can be performed using 5% MeOH in DCM but was found to be unnecessary. Isolated 0.15g, quantitative yield, quantitatively pure by ^{31}P NMR. ^{1}H NMR: (299.9 MHz, $CDCl_3$) δ 7.55 (t, J = 6.3 Hz), 7.49 (d, J = 7.0 Hz), 7.45 (t, J = 3.1 Hz), 7.42 (br), 7.40 (d, J = 2.6 Hz), 7.36 (br), 7.25 (m), 7.2-6.8 (br), 6.82 (d, J = 8.4 Hz), 6.77 (d, J = 7.9 Hz), 6.71 (t, J = 7.3 Hz), 6.51 (m), 6.26 (s), 6.22 (d, J = 7.9 Hz), 5.91 (t, J = 9.6 Hz), 4.77 (m), 4.53 (m), 4.19 (t, J = 7.3 Hz), 3.79 (s), 3.70 (s), 3.54 (m), 2.6-2.2 (br); ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 173.2, 172.9, 168.9, 168.3, 167.2, 165.8, 139.4, 136.2, 135.1, 134.8, 133.0, 131.4, 130.1, 129.8, 128.2, 127.7, 127.5, 126.9, 126.7, 58.5, 58.2, 53.5, 52.2, 52.1, 52.0, 51.8, 50.4, 49.4, 29.9, 29.8, 29.7, 29.6, 25.2, 25.1; ^{31}P {^{1}H} NMR: (120 MHz, $CDCl_3$) δ 7.479 (s).HRMS-ESI (m/z): $[M+NH_4]^+$ calcd for $C_{70}H_{76}N_9O_{16}P_2$, 1360.4880; found, 1360.4912 (Δ = 2.4 ppm).

2,2',2'',2'''-(1,2-phenylenebis((1*R*,3*R*)-tetrahydro-5,8-dioxo-1*H*-(1,2,4)diazaphospholo(1,2-*a*)pyridazine-2,1,3(3*H*)-triyl))tetrakis((R)-N-2-(methoxycarbonyl)pyrrolidinyl-benzamide) (*R*,*R*)-13. Following general method B using 0.10g (0.11mmol) enantiopure tetraacyl fluoride bisdiazaphospholane (*R,R*-**9**) and 5 eq. of (*R*)-methylprolinate (90mg, 0.7mmol) in 10mL DCM. Silica gel column chromatography can be performed using 5% MeOH in DCM but was found to be unnecessary. Isolated 0.15g, quantitative yield, quantitatively pure by ^{31}P NMR.

^{1}H NMR: (400.2 MHz, $CDCl_3$) δ 8.45 (d, J = 9.0 Hz), 8.27 (d, J = 7.9 Hz), 8.12 (m), 8.07 (d, J = 9.0 Hz), 7.98 (m), 7.90 (d, J = 7.89 Hz), 7.78 (d, J = 9.0 Hz), 7.71 (t, J = 7.9 Hz), 7.64 (m), 7.57-7.49 (m), 7.46 (m), 7.39-7.26 (m), 7.13-6.93 (m), 6.83 (s), 6.75-6.68 (m), 6.54 (d, J = 6.8 Hz) 4.77 (m), 4.53 (m), 4.19 (t, J = 7.3 Hz), 3.79 (s), 3.70 (s), 3.54 (m), 2.6-2.2 (br); ^{31}P {^{1}H} NMR: (120 MHz, $CDCl_3$) δ 2.93 (s).HRMS-ESI (m/z): $[M+NH_4]^+$ calcd for $C_{70}H_{76}N_9O_{16}P_2$, 1360.4880; found, 1360.4843 (Δ = 2.7 ppm). Material synthesized on small scale, not enough material for ^{13}C NMR.

2,2',2",2"'-(1,2-phenylenebis((1*R*,3*R*)-tetrahydro-5,8-dioxo-1*H*-(1,2,4)diazaphospholo(1,2-*a*)pyridazine-2,1,3(3*H*)-triyl))tetrakis(methylbenzoate) (*R*,*R*)-MeO-BDP. Following general method B using 0.07g (0.08mmol) enantiopure tetraacyl fluoride bisdiazaphospholane (*R,R*-**9**) and 50 eq. methanol. Isolated .06g, 78% yield, 72% pure by ^{31}P NMR. ^{1}H NMR: (400.2 MHz, $CDCl_3$) δ 8.37 (J = 10.3 Hz), 8.12 (J = 7.4 Hz), 8.08 (J = 8.8 Hz), 8.00 (J = 7.4 Hz), 7.89 (m), 7.52 (t, J = 8.8 Hz), 7.41-6.7 (m), 6.38 (d, J = 7.6 Hz), 6.20 (d, J = 8.7 Hz), 5.92 (s), 3.91 (s), 3.33 (s), 2.71-2.15 (m);^{31}P {^{1}H} NMR: (120 MHz, $CDCl_3$) δ 2.81 (s).HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{50}H_{45}N_4O_{12}P_2$, 955.2504; found, 955.2543 (Δ = 4 ppm). Material synthesized on small scale, not enough material for ^{13}C NMR.

2,2',2",2"'-(1,2-phenylenebis((1*R*,3*R*)-tetrahydro-5,8-dioxo-1*H*-(1,2,4)diazaphospholo(1,2-*a*)pyridazine-2,1,3(3*H*)-triyl))tetrakis(phenylbenzoate) (*R*,*R*)-PhO-BDP. Following general method B using 0.07g (0.08mmol) enantiopure tetraacyl fluoride bisdiazaphospholane (*R,R*-**9**) and 5 eq. phenol. Isolated .07g, 73% yield, 90% pure by ^{31}P NMR. ^{1}H NMR: (400.2 MHz, $CDCl_3$) δ 7.98 (d, J = 7.97 Hz), 7.66 (t, J = 8.2 Hz), 7.37 (m), 7.31 (s), 7.29 (s), 7.22 (m), 7.12 (m), 7.01 (m), 6.89 (m), 6.52 (t, J = 6.49 Hz), 6.27 (d, J = 7.9 Hz), 2.66-2.17 (m); ^{13}C NMR: (100.6 MHz, $CDCl_3$) δ 167.3, 164.2, 163.7, 163.7, 149.9, 149.4, 138.3, 137.7, 137.6, 132.7, 131.1, 130.9, 130.5, 129.8, 128.6, 128.3, 128.2, 128.1, 127.2, 126.5, 126.0, 125.0, 124.3, 124.2, 121.0, 120.8, 58.5, 58.3, 53.4, 53.0, 52.5, 28.7, 28.4, 28.2, 17.4, 17.4, 16.2, 11.0; ^{31}P {^{1}H} NMR: (120 MHz, $CDCl_3$) δ -1.74 (s).HRMS-ESI (m/z): $[M+NH_4]^+$ calcd for $C_{70}H_{56}N_5O_{12}P_2$, 1220.3396; found, 1220.3397 (Δ < 1 ppm).

General asymmetric hydroformylation procedure

An oven dried 15mL Ace glass pressure bottle with magnetic stir bar is charged with a $Rh(acac)(CO)_2$ toluene solution, bisdiazaphospholane THF solution, and neat substrate using 1000μL and 200μL Eppendoft® pipettes in a dinitrogen filled glove box. Pressure bottle is attached to pressure reactor and removed from the glove box, placed in a fume hood, purged three times with 150psi of synthesis gas to remove dinitrogen and filled to the appropriate synthesis gas pressure. The pressure bottle is placed in an oil bath and stirred at a high speed to ensure gas mixing. Upon completion of the reaction, the reaction tube is removed from the oil bath, allowed to cool to room temperature, and vented inside the fume hood. An aliquot of the reaction mixture is dissolved in d^8-toluene for ^{1}H NMR for percent

conversion and determining regioselectivity. Enantiomeric excess of the branched hydroformylation product is determined by chiral GC/SFC.

Hydroformylation Product Analysis. Vinyl acetate. (GC) Supelco's Beta Dex 225, 100°C for 5 min, then 4°C/min to 160°C, $t_R(S)$ = 6.7 and $t_R(R)$ = 8.5 min.[7a] **Styrene** (GC) Supelco's Beta Dex 225, 100°C hold 5 min, then 160°C (4°C /min), $t_{R(S)}$ = 9.0 min, $t_{R(R)}$ = 9.2 min, , β isomer t_R = 12.4 min.[1d] **Allyloxy-*t*-butyldimethylsilane** (GC) Supelco's Beta Dex 225, 65 °C, isothermal); $t_R(R)$ = 60.8 min, $t_R(S)$ = 62.4.[1c] **1-Phenylbutadiene** Crude aldehyde products reduced using $NaBH_4$ followed by SFC analysis: Chiracel OJ-H column, (50°C oven temp, 3% MeOH, pressure = 100 bar, 3ml/min flow rate); $t_R(R)$ = 6.8 min, $t_R(S)$ = 7.5 min.[1b] **2,3-Dihydrofuran/2,5-dihydrofuran** (GC) Supelco BETA–DEX 225, initial temperature 50 °C, hold for 0.10 min.; ramp 1, 15 °C/min. to 150 °C, hold 0.2 min.; ramp 2, 100 °C/min. to 215 °C. α-Carbaldehyde t_R (*R*)= 4.8 min., t_R (*S*)= 5.0 min. β-Carbaldehyde; t_R (*S*) = 5.3 min., t_R (*R*) = 5.6 min. Absolute configuration for the β-carbaldehyde has been previously reported.[9a]

Determination of absolute configuration of tetrahydrofuran-2-carboxaldehyde

Reduction of (*S*)-(-)-tetrahydrofuran-2-carboxylic acid (TCI 97% pure) with $LiAlH_4$ to tetrahydrofurfuryl alcohol was compared with the reduction of the crude hydroformylation product of 2,3-dihydrofuran with $NaBH_4$. Resolution of the resulting alcohols using GC, Supelco's BETA–DEX 225, method: initial temperature 50 °C, hold for 5 min.; ramp 1, 5 °C/min. to 70 °C, hold 55 min.; ramp 2, 20 °C/min. to 180 °C. Tetrahydrofurfuryl alcohol; t_R (*R*)= 55.9 min., t_R (*S*)= 57.2 min.

ASSOCIATED CONTENT

Supporting Information. Representative GC trace for 2,3-dihydrofuran, NMR/MS spectra for ligands **3-12**, preliminary results of tetraester bisdiazaphospholane AHF, and X-ray structure of (*rac*)-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

landis@chem.wisc.edu

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank The Dow Chemical Company for their generous donation of $Rh(acac)(CO)_2$, Merck & Co. (Dr. Neil Strotman) for resolution of ligand **1**, Prof. Tehshik Yoon and co-workers (UW-Madison) for access to chiral SFC instrumentation, and Dr. Ilia Guzei (UW-Madison) for the X-ray structure of (rac)-1. The National Science Foundation (CHE-0715491, CHE-1152989, and a graduate fellowship to G.W.W.) supported this work. We also acknowledge the NSF (CHE-9208463 and CHE-0342998) for funding the NMR facilities.

REFERENCES

(1)(a) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc.* **2005**, 127, 5040-5042. (b) Watkins, A. L.; Landis, C. R. *Org. Lett.* **2011**, 13, 164-167.(c) McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, 132, 14027-14029. (d) Watkins, A. L.; Hashiguchi, B. G.; Landis, C. R. *Org. Lett.* **2008,** 10, 4553-4556 (e) Wong, G. W.; Adint, T. T.; Landis, C. R. *Org. Synth.* **2012**, *89*, 243-254.

(2)(a) Leeuwen, P. W. N. M. v.; Kamer, P. C. J.; Claver, C.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2011**, *111*, 2077-2118. (b)Breit, B.; Seiche, W. *Synthesis* **2001**, 1, 1. (c) Zhang, X.; Cao, B.; Yu, S.; Zhang, X. *Angewandte Chemie International Edition* **2010**, 49, 4047-4050. (d) Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007**, 40, 1251-1259. (e) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, 119, 4413-4423. (f) Zhang, X.; Cao, B.; Yan, Y.; Yu, S.; Ji, B.; Zhang, X. *Chem. Eur. J.* **2010**, 16, 871-877. (g) Worthy, A. D.; Joe, C. L.; Lightburn, T. E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 14757-14759.

(3) Previously sold by Sigma-Aldrich as Bis[(*S*,*S*,*S*)-DiazaPhos-SPE], currently discontinued.

(4)White, J. M.; Tunoori, A. R.; Turunen, B. J.; Georg, G. I. *J. Org. Chem.* **2004**, 69, 2573-2576.

(5) Wenschuh, H.; Beyermann, M.; Winter, R.; Bienert, M.; Ionescu, D.; Carpino, L. A. *Tetrahedron Lett.* **1996,** *37,* 5483-5486.

(6) Example of a tetraacyl fluoride purified by aqueous extraction. Sasine, J. S.; Brewster, R. E.; Caran, K. L.; Bentley, A. M.; Shuker, S. B.. *Org. Lett.* **2006**, 8, 2913-2915.

(7)(a) Cobley, C. J.; Klosin, J.; Qin, C.; Whiteker, G. T. *Org. Lett.* **2004**, 6, 3277-3280. (b) Axtell, A. T.; Cobley, C. J.; Klosin, J.; Whiteker, G. T.; Zanotti-Gerosa, A.; Abboud, K. A. *Angewandte Chemie International Edition* **2005**, *44*, 5834-5838. (c) Axtell, A. T.; Klosin, J.; Whiteker, G. T.; Cobley, C. J.; Fox, M. E.; Jackson, M.; Abboud, K. A. *Organometallics* **2009**, *28*, 2993-2999.

(8)(a) Carley, S.; Brimble, M. A. *Org. Lett.* **2009**, 11, 563. (b) Stepan, A. F.; Karki, K.; McDonald, W. S.; Dorff, P. H.; Dutra, J. K.; DiRico, K. J.; Won, A.; Subramanyam, C.; Efremov, I. V.; O'Donnell, C. J.; Nolan, C. E.; Becker, S. L.; Pustilnik, L. R.; Sneed, B.; Sun, H.; Lu, Y.; Robshaw, A. E.; Riddell, D.; O'Sullivan, T. J.; Sibley, E.; Capetta, S.; Atchison, K.; Hallgren, A. J.; Miller, E.; Wood, A.; Obach, R. S. *J. Med. Chem.* **2011**, 54, 7772-7783.

(9)(a) Chikkali, S. H.; Bellini, R.; de Bruin, B.; van, d. V.; Reek, J. N. H. *J. Am. Chem. Soc.* **2012**, 134, 6607-6616. (b) Dieguez, M.; Pamies, O.; Claver, C. *Chem. Commun.* **2005**, 9, 1221. (c) Mazuela, J.; Coll, M.; Pamies, O.; Dieguez, M. *J. Org. Chem.* **2009**, 74, 5440-5445. (d) Río, I. d.; van Leeuwen, P. W.; Claver, C. *Can. J. Chem.* **2001**, 79, 560. (e) Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1997**, 62, 4285-4292. (f) Chikkali, S. H.; Bellini, R.; Berthon-Gelloz, G.; van der Vlugt, J. I.; de Bruin, B.; Reek, J. N. H. *Chem. Commun.* **2010**, *46*, 1244.

(10) Watkins, A. L.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, 132, 10306-10317.

(11) Peters, J. C.; Mehn, M. P. in *Activation of Small Molecules: Organometallic and Bioinorganic Perspectives*, Tolman, W. C., ed.; Chapter 3, page 82, Wiley-VCH (**2006**).

(12) Cheng, J.; Trudell, M. L. *Org. Lett.* 2001, *3*, 1371.