J|A|C|S
COMMUNICATIONS

Published on Web 03/17/2005

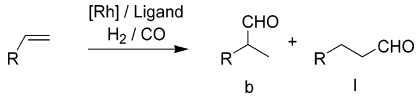
Highly Active, Regioselective, and Enantioselective Hydroformylation with Rh Catalysts Ligated by Bis-3,4-diazaphospholanes

Thomas P. Clark,[§] Clark R. Landis,*[,§] Susan L. Freed,[†] Jerzy Klosin,*[,†] and Khalil A. Abboud[‡]

Department of Chemistry, University of Wisconsin—Madison, 1101 University Avenue, Madison, Wisconsin 53706, Chemical Sciences, The Dow Chemical Company, 1776 Building, Midland, Michigan 48674, and Department of Chemistry, University of Florida, Gainesville, Florida 32611

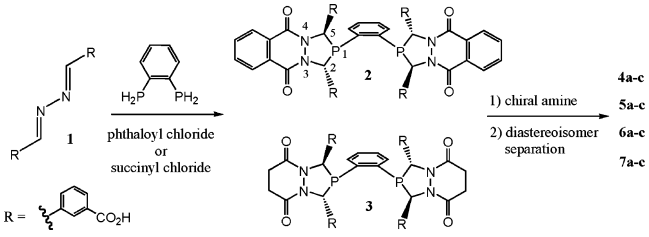
Received January 10, 2005; E-mail: landis@chem.wisc.edu; jklosin@dow.com

As with catalytic hydrogenation of alkenes by rhodium complexes, key attributes of rhodium-catalyzed alkene hydroformylation[1] (perfect atom economy, inexpensive reactants, demonstrated performance on industrial scales, readily modified phosphorus ligands) make pursuit of the enantioselective transformation irresistible. Whereas hydrogenation effects net loss of the C═C functional group, hydroformylation results in its transformation to a more versatile functional group, the aldehyde. Although new ligand developments over the last fifteen years have yielded significant progress, the general application of enantioselective hydroformylation lags well behind that of enantioselective hydrogenation. Several factors are responsible: (1) enantioselective hydroformylation is relatively slow, with turnover frequencies commonly in the range of tens to hundreds per hour for terminal alkenes and much slower rates for internal alkenes; (2) effective enantioselective hydroformylation of terminal alkenes requires control of regioselectivity that favors branched isomers; and (3) few of the effective ligands exhibit good activity and selectivity for a range of different substrates, even when one considers only 1-alkenes. We report new chiral bis-3,4-diazaphospholane ligands that constitute unusually active and selective ligands for rhodium-catalyzed hydroformylation of styrene, allyl cyanide, and vinyl acetate.

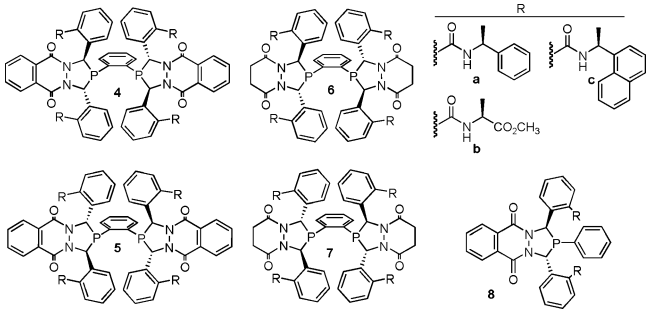


Recently, we reported the facile synthesis of a wide variety of chiral mono- and bis-3,4-diazaphospholanes[2] that are readily resolved, extended into small libraries, and applied to asymmetric allylic alkylation both in solution[3] and on bead.[4] This work demonstrated that mono-3,4-diazaphospholanes bearing carboxylic acid functionalized substituents in the 2 and 5 positions can be

Scheme 1



expanded to collections of new ligands using simple coupling chemistry. One-step synthesis of bis-3,4-diazaphospholanes **2** and **3** proceeds with ca. 30% yield upon reaction of the azine **1** with 1,2-diphosphinobenzene in the presence of either succinyl chloride or phthaloyl chloride (Scheme 1). Coupling the carboxylic acid groups of either **2** or **3** with resolved chiral amines followed by chromatographic separation of the resulting diastereomers yields enantiomerically pure bis-3,4-diazaphospholanes **4**, **5**, **6**, and **7**.



The crystallographic structure of **7a** is shown in Figure 1.

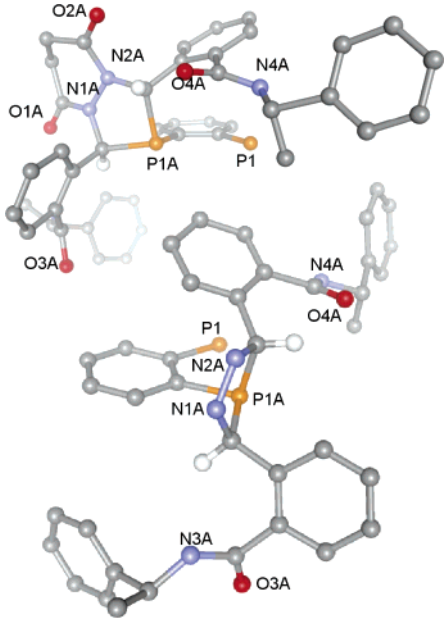
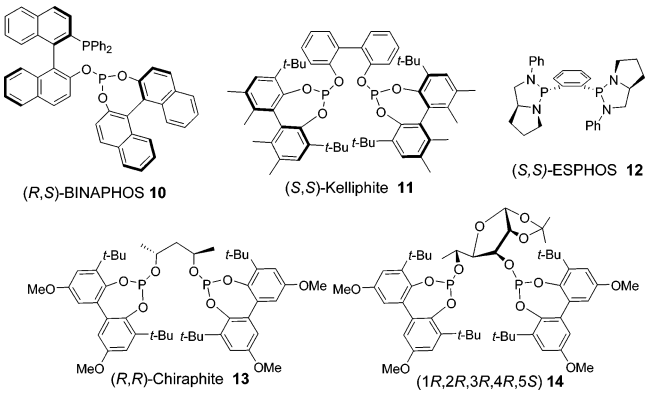


Figure 1. Two views of the crystallographic structure of **7a**. For clarity, only one of the nearly C_2-related diazaphospholane rings is shown. Hydrogens are shown for the phospholane 2 and 5 positions, only. The succinyl group was eliminated from the lower view for ease of viewing.

Prominent ligands for enantioselective hydroformylation include BINAPHOS (**10**),[5] Kelliphite (**11**),[6,7] ESPHOS (**12**),[8] Chiraphite (**13**),[9] and the sugar-derived phosphite (**14**).[10] Literature data for these ligands suggest that **10** is generally the most useful.

[§] The University of Wisconsin—Madison.
[†] The Dow Chemical Company.
[‡] University of Florida.

10.1021/ja050148o CCC: $30.25



Styrene, vinyl acetate, and allyl cyanide undergo hydroformylation with generally high enantioselectivities (94, 92, and 69%, respectively), modest branched:linear (b:l) ratios (7.3:1, 6.2:1, and 2.2:1, respectively), and modest turnover frequencies (ca. 200 h^{-1} for all substrates) under reaction conditions of 60−70 °C and ca. 10 atm of 1:1 CO:H_2.[5] Ligands **11**−**14**, in contrast, have more specialized utility. The ESPHOS ligand **12** is highly selective for vinyl acetate (ee = 90%, b:l = 16:1) but exhibits low enantioselectivity for styrene.[8] Of the three bisphosphite ligands shown above, **13**[9] and **14**[10] are effective for styrene in the temperature range of 20−35 °C, yielding enantioselectivities of 76.4 and 89%, respectively, with very high regioselectivity control (b:l = 47:1 and 49:1, respectively). Kelliphite (**11**) is particularly well suited for hydroformylation of allyl cyanide (ee = 75 %, b:l = 16:1) and vinyl acetate (ee = 87.7%, b:l = 56:1) at low temperatures. Enantioselective hydroformylation turnover frequencies commonly fall in the range of 10−600 turnovers h^{-1} over the temperature range of ca. 35−60 °C, with BINAPHOS generally leading to the lowest activity. For comparison, modern enantioselective hydrogenation catalysts have been reported, in favorable cases, with turnover frequencies of over 100 000 turnovers h^{-1} and nearly quantitative enantioselectivity with ketone, itaconate, and enamide substrates.[11]

Following a previously published screening protocol,[7] the performance of rhodium hydroformylation catalysts modified by ligands **4**−**8**, **10**, **11**, and **13** has been examined by simultaneous hydroformylation of allyl cyanide, styrene, and vinyl acetate (see Table 1). Under the screening conditions (150 psig, 80 °C, total substrate:catalyst loading of 5000:1, toluene solvent, L:Rh = 1.2, CO:H_2 = 1:1), bis-3,4-diazaphospholanes consistently exhibit state-of-the-art selectivities and activities for aldehyde production from all three substrates with no indication of hydrogenation or other side reactions. In contrast, the mono-3,4-diazaphospholane **8a** is slow and unselective, at least at the P:Rh ratios used in screening runs. We note that these conditions of low P:Rh ratios, modest pressure, and relatively high temperature lead to substantially poorer selectivity, but significantly higher activity, with BINAPHOS **10** than has been previously reported. Such observations serve to caution against indiscriminate comparisons of selectivities without noting details of the reaction conditions. Particularly effective ligands emerging from this screen are those bearing benzoamides of methyl benzylamine in the 2 and 5 positions of the phospholane ring. Comparison of aldehyde configurations obtained with the diastereomeric pairs **4**/**5** and **6**/**7** demonstrates that the stereochemistry of the phospholane ring, rather than the stereochemistry of the chiral amine, controls the absolute chirality of the product and reveals a small mismatching effect of ca. 10% ee.

The influence of reaction conditions on hydroformylation was explored with special focus on ligand **7a**. Interestingly, the influence

Table 1. Percent Conversion (conv), Branched:Linear Ratio (b:l), and Enantioselectivity (% ee) for Hydroformylation[a] of Styrene, Allyl Cyanide, and Vinyl Acetate with Chiral Phosphorus Ligands (L)

	Styrene			Allyl Cyanide			Vinyl Acetate		
L	conv	b:l	% ee	conv	b:l	% ee	conv	b:l	% ee
10	96	4.5	82(*R*)	98	2.1	72(*R*)	72	8.2	48(*S*)
11	78	8.9	2(*R*)	100	9.3	66(*S*)	78	61	73(*R*)
13	90	9.0	49(*R*)	100	5.5	13(*R*)	75	190	50(*R*)
8a	28	1.1	12(*R*)	93	1.3	10(*R*)	31	39	23(*S*)
4a	93	8.4	76(*S*)	100	5.3	64(*S*)	94	24	85(*R*)
5a	100	8.1	75(*R*)	100	4.1	75(*R*)	100	22	92(*S*)
4b	51	9.7	76(*S*)	97	5.7	61(*S*)	54	19	79(*R*)
5b	75	6.9	70(*R*)	100	5.0	61(*R*)	81	26	83(*S*)
4c	97	8.5	76(*S*)	100	5.5	67(*S*)	98	22	83(*R*)
5c	100	7.4	63(*R*)	100	3.7	75(*R*)	100	19	92(*S*)
6c	100	5.7	65(*S*)	100	4.0	69(*S*)	100	36	86(*R*)
7c	100	5.3	73(*R*)	100	3.5	82(*R*)	100	41	96(*S*)
6a	100	6.3	73(*S*)	100	4.1	77(*S*)	100	31	91(*R*)
7a	100	6.6	82(*R*)	100	4.1	87(*R*)	100	37	96(*S*)

[a] All reactions performed at 80 °C in toluene with 150 psig 1:1 CO:H_2 with L:Rh = 1.2 (2.1 for monophosphine **8a**), total substrate:Rh = 5000, and 3 h reaction time.

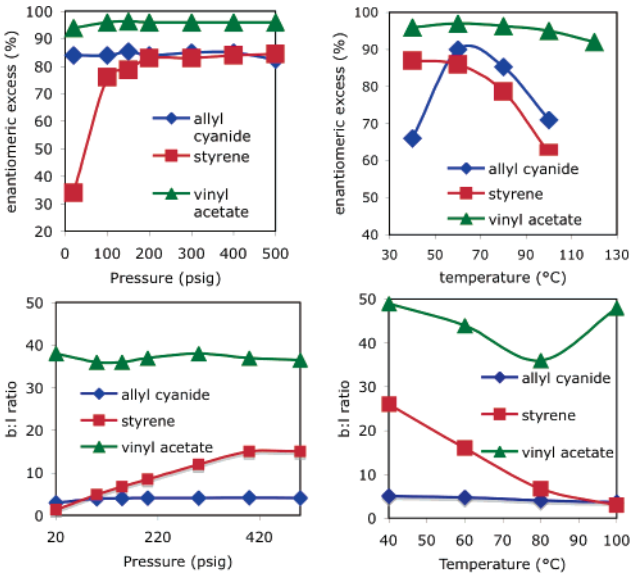


Figure 2. Graphs depicting the influence of 1:1 CO:H_2 pressure and temperature on the enantiomeric excess (% ee, top left and right) and regioselectivity (b:l ratio, bottom left and right) of hydroformylation of allyl cyanide, styrene, and vinyl acetate as catalyzed by **7a** and Rh(acac)$(CO)_2$. (L:Rh = 1.2, total substrate:Rh = 5000, toluene solvent, standard temperature of 80 °C, and standard pressure of 150 psig 1:1 CO:H_2).

of pressure and temperature on enantioselectivities (Figure 2) varies significantly with substrate. Whereas higher pressures and lower temperatures increase the percent of enantiomeric excess for styrene hydroformylation, temperature only affects allyl cyanide enantioselectivities, and the percent enantiomeric excess for vinyl acetate is largely insensitive to both temperature and pressure. Regioselectivities follow a similar pattern. For styrene hydroformylation at 60 °C, the branched-to-linear ratio increases from 16:1 to 30:1 upon increasing the syn gas pressure from 150 to 500 psig, respectively. Over the same pressure range at 60 °C, both allyl cyanide and vinyl acetate exhibit unperturbed regioselectivities (4.7:1 and 40:1, respectively). *Overall, 60°C and 500 psig syn gas enable outstanding regio- and enantioselectivities for all three substrates (styrene, 89% ee, b:l = 30:1; allyl cyanide, 87% ee, b:l = 4.8:1; vinyl acetate, 95% ee, b:l = 40:1) while achieving average*

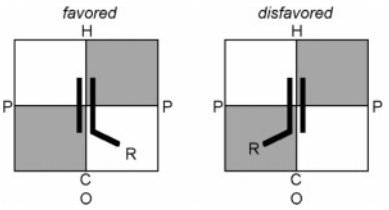
turnover frequencies greater than ca. 3000 h^{-1} over 90% consumption of the substrate.

Both the high cost of rhodium catalysts and the attractiveness of applying hydroformylation to more substituted alkenes emphasize the importance of hydroformylation activity. Our reaction screening conditions lead to higher catalyst activities than commonly are reported, particularly, with bis-3,4-diazaphospholane ligands. For example, in the presence of 1.2 equiv of **7a** at a total substrate:Rh loading of 30 000:1 under 500 psig of syn gas at 80 °C, conversions of styrene, allyl cyanide, and vinyl acetate are 85, 100, and 86% in just 3 h. Analysis of gas uptake curves under these conditions reveals average turnover frequencies of at least ca. 9000 h^{-1}, or 2.5 turnovers s^{-1}, over 90% conversion of substrate. Under otherwise identical conditions, hydroformylations with bis-3,4-diazaphospholane-modified catalysts proceed approximately twice as fast as bisphosphites **11** and **13** and the mixed phosphine−phosphite **10**.

Interestingly, hydroformylation rate laws with bis-3,4-diazaphospholanes are approximately first-order in alkene and independent of the synthesis gas pressure in the range of 100−500 psi. Preliminary data suggest that the rate law for hydroformylation is zero-order in both H_2 and CO concentrations over the 60−80 °C temperature range. Furthermore, the data indicate that styrene enantioselectivities and regioselectivities primarily respond to changes in CO pressure; lower CO partial pressure results in lower selectivity. Allyl cyanide selectivities also decrease with decreased CO pressure, but the effect is not so large. These rate laws are consistent with bimolecular reaction of the catalyst and substrate comprising or preceding the turnover-limiting step. Presumably, the influence of CO pressure on hydroformylation selectivity for styrene (both enantiomeric excess and b:l ratio), combined with the absence of any influence of gas pressures on the rate of styrene conversion, reflects the interruption of Rh−alkyl isomerizations occurring after the turnover-limiting step. More detailed examination of the reaction kinetics is underway.

Hydroformylation of vinyl acetate, allyl cyanide, or styrene in the absence of the other substrates yields selectivities and rates identical to those of the mixed substrates. Single substrate hydroformylations using ligand **7a** at 80 °C and 150 psig syn gas with 1.8×10^{-4} M Rh achieve 50% conversion of 10 000 equiv of substrate in 30 (allyl cyanide), 37 (vinyl acetate), and 60 min (styrene). These data demonstrate, at least for these substrates and catalysts, that the mixed substrate screening protocol does not introduce kinetic or selectivity artifacts. Without appropriate controls, one cannot assume that mixed substrate and single substrate results, particularly with respect to apparent rates, will be identical.

The absolute configurations of the branched hydroformylation products for styrene (R), allyl cyanide (R), and vinyl acetate (S) with ligand **7a** reveal that formal addition of formaldehyde across the C═C double bond occurs at the same enantioface for all substrates. A useful quadrant diagram, based on the assumption of a trigonal bipyramidal coordination environment with diequatorial phosphorus atoms, for rationalizing the product stereochemistry is shown. We emphasize that this model is purely mnemonic. Better characterization of catalyst coordination geometries through spectroscopic and computational model studies is underway.



In summary, bis-3,4-diazaphospholanes bearing benzoic acid in the 2 and 5 positions are readily accessible and extensible ligands for enantioselective hydroformylation with rhodium catalysts. Significantly, these ligands demonstrate effective control of regio- and enantioselectivity for three different classes of substrates while achieving very high catalyst activity. These properties suggest broad applicability to catalytic, enantioselective synthesis of aldehydes.

Acknowledgment. We thank Dowpharma for financial support of this research. We thank Mr. Ryan Nelson for numerous contributions.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. Crystallographic data for **7a**, including a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Claver, C.; van Leeuwen, P. W. N. M. In *Rhodium Catalyzed Hydroformylation*; Claver, C., van Leeuwen, P. W. N. M., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2000.
(2) Landis, C. R.; Jin, W.; Owen, J. S.; Clark, T. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 3432−3434.
(3) Clark, T. P.; Landis, C. R. *J. Am. Chem. Soc.* **2003**, *125*, 11792−11793.
(4) Landis, C. R.; Clark, T. P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5428−5432.
(5) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, *119*, 4413−4423.
(6) Cobley, C. J.; Gardner, K.; Klosin, J.; Praquin, C.; Hill, C.; Whiteker, G. T.; Zanotti-Gerosa, A.; Petersen, J. L.; Abboud, K. A. *J. Org. Chem.* **2004**, *69*, 4031−4040.
(7) Cobley, C. J.; Klosin, J.; Qin, C.; Whiteker, G. *Org. Lett.* **2004**, *6*, 3277−3280.
(8) Breeden, S.; Cole-Hamilton, D. J.; Foster, D. F.; Schwarz, G. J.; Wills, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4106−4108.
(9) (a) Babin J. E.; Whiteker, G. T. Patent WO 93/03830, 1992. (b) Whiteker, G. T.; Briggs, J. R.; Babin, J. E.; Barner, B. A. In *Catalysis of Organic Reactions*; Morrell, D. G., Ed.; Marcel Dekker: New York, 2003; p 359.
(10) Dieguez, M.; Pamies, O.; Ruiz, A.; Castillon, S.; Claver, C. *Chem.—Eur. J.* **2001**, *7*, 3086−3094.
(11) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029−3070.

JA050148O