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Parallel Ligand Screening on Olefin Mixtures in Asymmetric Hydroformylation Reactions

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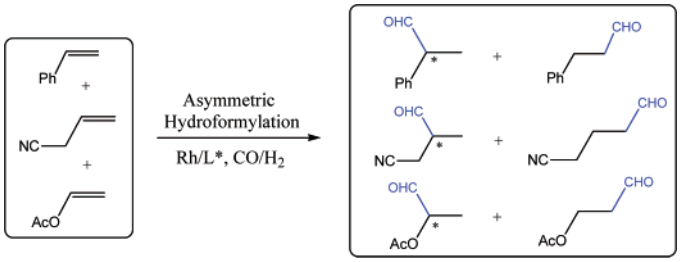
ABSTRACT



Herein we describe a new protocol for catalyst evaluation in asymmetric hydroformylation reactions where multisubstrate screening is performed in an array of parallel reactors. This method was successfully demonstrated using a mixture of styrene, allyl cyanide, and vinyl acetate. Using this screening methodology, a set of phosphite ligands was evaluated and led to the discovery of a bisphosphite ligand that gave 88% ee and unprecedented >100:1 branched:linear regioselectivity in asymmetric hydroformylation of vinyl acetate.

Asymmetric hydroformylation is a catalytic, atom-economic, one-carbon homologation that produces chiral aldehydes.[1] The historical challenge of asymmetric hydroformylation has been to maximize both enantioselectivity and regioselectivity through ligand design. Unfortunately, no single ligand has been identified that leads to high selectivity with a wide range of olefin substrates. As with many asymmetric catalytic reactions, ligands required for a specific hydroformylation substrate need to be optimized empirically. We recently described a simple ligand design to access a wide range of structurally diverse bisphosphite ligands for use in rhodium-catalyzed asymmetric hydroformylation.[2] By use of optically active biphenols as chiral auxiliaries, a wide variety of chelating ligands can be prepared using achiral bridging diols. This ligand design allows for the variation of ligand bite angle, a structural feature that has been previously implicated in hydroformylation regiocontrol.[1,3] To rapidly evaluate this class of easily synthesized bisphosphite ligands, we utilized parallel pressure reactors. To increase the ligand screening throughput even further, we decided to explore the possibility of a one-pot screening of multiple olefinic substrates. This methodology was recently introduced by Kagan for screening of a single catalyst in the asymmetric reduction of ketones.[4] Herein, we demonstrate simultaneous screening of pooled substrates in the asymmetric hydroformylation of olefins using parallel reactors that allows screening throughput to be dramatically increased.

The phosphite ligands investigated in this study are depicted in Figure 2. The synthesis and use of these

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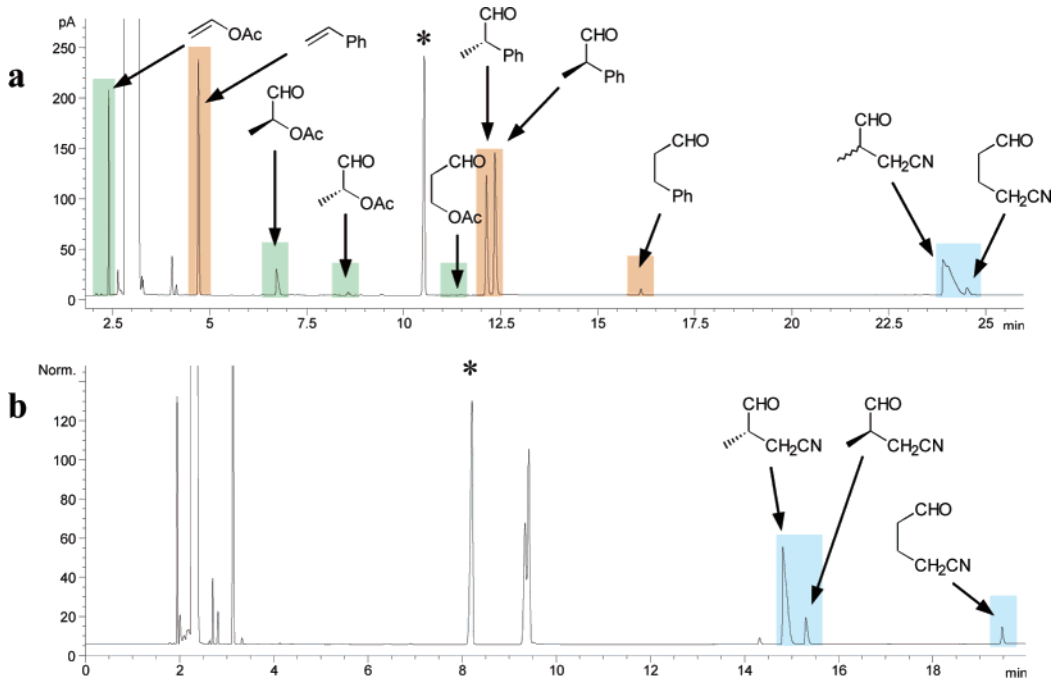

Figure 1. Gas chromatograms of aldehyde product mixture produced with Rh−Kelliphite catalyst. Enantioselectivity and regioselectivity measurements of styrene and vinyl acetate hydroformylation products were obtained using a Supelco Beta Dex 225 column (chromatogram a). Allyl cyanide hydroformylation products were analyzed using an Astec Chiraldex A-TA column (chromatogram b). Peaks marked with an asterisk are due to dodecane (internal standard).

phosphites in asymmetric hydroformylation of allyl cyanide has been recently described.[2] All screening experiments were performed in an Argonaut Endeavor reactor system consisting of eight parallel stirred autoclaves. Ligands were tested against an olefin mixture composed of styrene, vinyl acetate, and allyl cyanide in 1:1:1 molar ratio. These olefins were chosen because of their significance in the potential synthesis of fine chemicals via asymmetric hydroformylation. For example, styrene was studied because of its relevance in the synthesis of antiinflammatory 2-aryl-propionic acid drugs, such as (*S*)-Naproxen. Additionally, these three substrates represent different types of terminal olefins with their unique reactivity and selectivity in hydroformylation reactions. Screening against all three substrates in a single run should thus allow for identification of ligands applicable to a broad range of olefins.

Simultaneous screening of pooled substrates can be successfully applied only if appropriate analytical techniques are developed and the presence of other components in the reaction mixture does not influence reactivity and selectivity of any individual reaction. Chiral GC methods were developed to rapidly analyze the aldehyde mixtures resulting from hydroformylation of the mixture of three olefins (Figure 1). Use of a β-cyclodextrin GC column allowed complete separation of both enantiomers of branched aldehyde and the achiral linear aldehyde derived from both styene and vinyl acetate, thus allowing for measurements of enantioselectivity and regioselectivity. As a result of incomplete separation of the linear aldehyde regioisomer and chiral branched aldehydes derived from allyl cyanide in this first analysis, a parallel chiral GC analysis using an α-cyclodextrin column was developed. Dodecane was used as internal standard in all experiments. These methods also allowed quantitative analysis of unreacted olefin as well as the products from olefin hydrogenation.

To ensure that the presence of additional olefins did not influence catalyst performance, a series of control experiments was performed[5] at 35 and 70 °C using Chiraphite, which was previously developed for hydroformylation of vinylarenes[6] (Table 1). Reactions were studied with separate

Table 1. Asymmetric Hydroformylation of Styrene (St), Allyl Cyanide (AC), and Vinyl Acetate (VA) with Chiraphite at 70 °C in Toluene; Control Experiment[5]

		separate olefins			
		St	AC	VA	combined olefins
% conv	St	68(3)[a]			97.9(9)
	AC		100		100
	VA			95.6(9)	96(1)
% ee	St	54.8(3)			57.7(5)
	AC		14.2(2)		14.6(1)
	VA			52.2(1)	52.3(1)
b/l	St	12.9(1)			14.3(3)
	AC		6.2		6.18(5)
	VA			74(3)	95(3)

[a] Numbers in parentheses are confidence intervals at a 95% confidence level obtained from four independent runs.

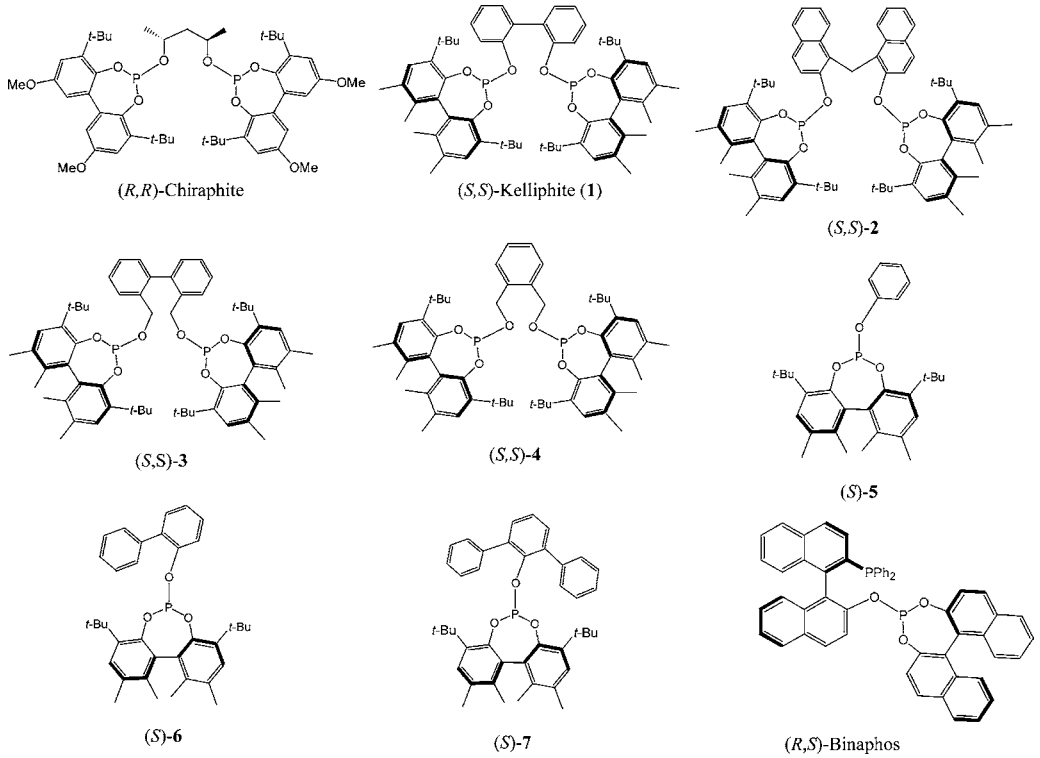

Figure 2. Ligands used in this study.

olefins as well as their mixture in toluene and acetone as solvents.[7] All reactions were found to proceed at a faster rate in acetone. Acetone was found to be the optimal solvent for reactions at 35 °C, since at 70 °C enantioselectivities of products derived from styrene and allyl cyanide were reduced by about 20% when using the mixture of olefins as compared to experiments with separate olefins. In toluene, regardless of temperature, enantioselectivities were found to be independent[8] of whether hydroformylation reactions were performed using a single olefin or the mixture of three olefins; therefore toluene was selected as solvent for runs at 70 °C. In addition, conversions were typically unchanged; however, styrene hydroformylation using Chiraphite was slightly accelerated for the mixed olefins reaction. Analogous control experiments performed with ligand **1** further validated this method.[5]

Following the demonstration of the simultaneous hydroformylation of pooled olefins, we next applied this procedure to parallel asymmetric hydroformylation screening of the phosphite ligands shown in Figure 2. (*R*,*S*)-Binaphos,[9] which is perhaps the most widely used ligand in asymmetric hydroformylation, was included in the screens (cell 8) for comparison.[10] Data for this parallel, multisubstrate screening are given in Table 2. Through use of this screening methodology, the catalytic performance of eight different ligands with three different substrates was obtained under identical reaction conditions (24 reactions all together). Inspection of the data in Table 2 revealed a range of regioselectivities and enantioselectivities for the three olefins studied. In particular, ligand **1**, which we refer to as Kelliphite, exhibited very high enantioselectivity (88% ee at 35 °C) for hydroformylation of vinyl acetate. There are very few ligands capable of inducing such high enantioselectivity in rhodium-catalyzed hydroformylation of vinyl acetate as Binaphos,[9] Esphos[11] and ABDPP.[12] What distinguishes Kelliphite from these other highly enantioselective ligands, however, is its ability to induce unprecedented high regioselectivity. This is very significant as the chemical yield of chiral product in asymmetric hydroformylation depends both on enantioselectivity and regioselectivity of the reaction. None of the ligands previously reported[9,11,12] for asymmetric hydroformylation of vinyl acetate gave such high regioselectivities. For example, the regioselectivity observed with Kelliphite is considerably higher than that obtained with

(5) See Supporting Information for details.

(6) (a) Babin, J. E.; Whiteker, G. T. Union Carbide U.S. Patent 5,360,938, 1994. (b) Buisman, G. J. H.; Vos, E. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1995**, 409.

(7) The concentration of each olefin was held constant: 1.4 mM [styrene], 1.4 mM [vinyl acetate], 1.4 mM [allyl cyanide]. For reactions of individual olefins, the same olefin concentration was used.

(8) Regioselectivities varied slightly presumably as a result of polarity differences between individual and combined olefins solutions.

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(10) Data for Chiraphite were obtained from a separate set of comparative experiments.

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(12) Lu, S.; Li, X.; Wang, A. *Catal. Today* **2000**, *63*, 531. ABDPP = 1,6-anhydro-2,6-bis(diphenylphosphino)pyranose.

Table 2. Asymmetric Hydroformylation of Styrene (St), Allyl Cyanide (AC), and Vinyl Acetate (VA) with Chiraphite, **1**−**7**, and Binaphos[a]

entry	ligand	T (°C)	conversion[b] (%) (St, AC, VA)	regioselectivity[c] (b/l) (St, AC, VA)	enantioselectivity (% ee, configuration) (St, AC, VA)
1	Chiraphite	35	53.5, 67.2, 21.9	46.8, 6.7, 109.2	76.4 (*S*), 12.6 (*R*), 58.0 (*S*)
		70	98.1, 100, 94.8	13.3, 6.1, 100.2	55.9 (*S*), 15.3 (*R*), 47.2 (*S*)
2	**1**	35	39.6, 95.1, 19.4	68.3, 15.9, **124.7**	17.7 (*R*), 75.2 (*S*), **87.7** (*S*)
		70	99.6, 100, 98.7	17.2, 10.8, **55.7**	0.7 (*S*), 69.8 (*S*), **77.2** (*S*)
3	**2**	35	81.9, 99.6, 18.9	29.6, 12.2, 21.5	9.0 (*S*), 5.3 (*S*), 30.0 (*S*)
		70	99.9, 100, 98.7	12.0, 10.5, 16.4	7.2 (*R*), 18.4 (*S*), 29.5 (*S*)
4	**3**	35	31.3, 57.9, 2.5	26.8, 5.4, 160.0	37.4 (*S*), 12.9 (*R*), 3.5 (*S*)
		70	99.4, 100, 80.9	7.6, 5.3, 11.3	6.6 (*S*), 0.8 (*R*), 11.7 (*S*)
5	**4**	35	92.6, 99.6, 15.5	35.1, 6.5, 107.0	18.8 (*R*), 2.1 (*R*), 5.9 (*S*)
		70	100, 100, 98.6	12.6, 7.1, 180.0	20.8 (*R*), 5.7 (*S*), 6.8 (*S*)
6	**5**	35	43.3, 61.1, 2.8	16.1, 5.3, 12.3	37.6 (*S*), 43.1 (*R*), 2.8 (*R*)
		70	100, 100, 100	2.3, 4.2, 35.8	7.7 (*R*), 34.8 (*R*), 4.6 (*R*)
7	**6**	35	59.4, 86.7, 11.1	16.6, 5.0, 13.9	27.6 (*S*), 37.4 (*R*), 8.3 (*R*)
		70	100, 100, 99.9	2.4, 4.0, 28.4	10.4 (*R*), 30.3 (*R*), 7.5 (*R*)
8	**7**	35	15.2, 23.4, 6.2	16.2, 5.0, 20.7	3.7 (*R*), 13.2 (*R*), 4.6 (*R*)
		70	63.2, 99.9, 83.7	1.1, 3.4, 166.3	12.7 (*R*), 3.9 (*R*), 2.2 (*R*)
9	Binaphos	35	33.0, 49.3, 9.9	9.7, 2.7, **7.0**	85.6 (*R*), 80.4 (*S*), **70.0** (*S*)
		70	99.8, 99.9, 94.2	5.3, 2.2, **6.5**	84.8 (*R*), 69.3 (*S*), **62.1** (S)

[a] Pressure = 150 psi (1:1 H_2/CO), ligand:Rh = 1.2:1 for bidentate and 2.2:1 for monodentate phosphites, solvent = acetone (35 °C runs) and toluene (70 °C) (3.66 mL), olefins:Rh = 300:1 at 35 °C and 500:1 at 70 °C. [b] Percentage conversion of olefins after 3 h. [c] b/l = branched-to-linear ratio. Each data point is an average obtained from two independent runs.

Binaphos (b/l = 125 vs 7.0 at 35 °C; Table 2, entries 2 and 9). Enantioselectivities obtained with Binaphos for styrene and vinyl acetate (Table 2, entry 9) in this study are somewhat lower than reported[9] values. This is most likely due to different reaction conditions used.

A larger scale reaction in neat vinyl acetate with the Rh−Kelliphite catalyst system[13] proceeded with satisfactory rates (minimum average TOF of 200 h^{-1}) and high enantio- and regioselectivity (82% ee, b/l = 86).

Ligand **1** was also recently found to lead to quite high enantio- and regioselectivity in the asymmetric hydroformylation of allyl cyanide.[2] Surprisingly, Kelliphite also led to very high regioselectivity (b/l = 68.3 at 35 °C) for styrene hydroformylation; however, the reaction occurred with only marginal enantioselectivity.

In addition to increased throughput, an additional benefit of multisubstrate screening in parallel reactors is that relative reaction rates of different substrates can be measured in one experiment.[14] The data in Table 2 indicate that allyl cyanide is the most reactive olefin for all hydroformylation catalysts in this study. Vinyl acetate is a less reactive substrate and exhibits lower conversions under these conditions.

We have further increased the throughput of our multisubstrate screens by utilizing larger arrays of parallel reactors. Use of the Symyx Parallel Pressure Reactor[15] (PPR-48) allowed 48 different catalysts to be screened simultaneously with styrene, vinyl acetate, and allyl cyanide (144 discrete reactions). Using this methodology, we have screened a library of 78 catalysts based on phosphites, phosphines, and phosphoroamidites. Kelliphite remained the most selective ligand uncovered by this screen for both allyl cyanide and vinyl acetate hydroformylation.

In summary, we have demonstrated for the first time that multisubstrate screening in combination with parallel techniques leads to higher reactor throughput. Using this methodology we have discovered a ligand that gives high enantio- and regioselectivity for the asymmetric hydroformylation of vinyl acetate. This method should be applicable to other homogeneous catalyzed reactions.

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Supporting Information Available: Experimental procedures and hydroformylation data for control experiments using Chiraphite and Kelliphite. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Reaction conditions: VA:Rh = 2000, neat VA (4 mL), temp = 60 °C, time = 10 h, 100% conversion.

(14) Conversions obtained from experiments with separate olefins (see Supporting Information) are very similar to those obtained for the mixture of olefins.

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