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# Very Low Pressure Rh-Catalyzed Hydroformylation of Styrene with (*S,S,S*-Bisdiazaphos): Regioselectivity Inversion and Mechanistic Insights

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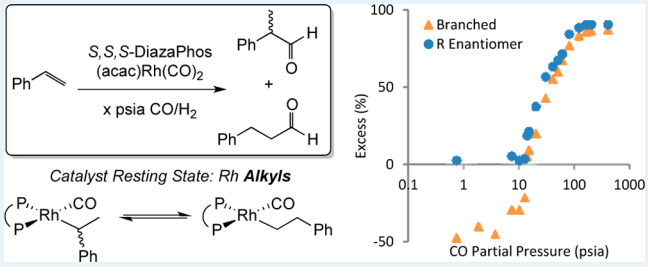
Supporting Information

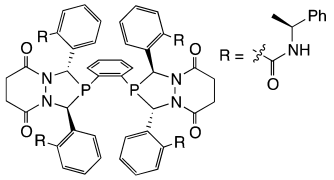
**ABSTRACT:** Rates and selectivities of styrene hydroformylation as catalyzed by the rhodium coordination complex of (*S,S,S*)-bis-diazaphos (BDP) under extremely low pressures of syngas ($CO/H_2$) are reported. At pressures <10 psia, the catalyst system is selective for the linear regioisomer, 3-phenyl-1-propanal, whereas at high pressure, it is highly selective for branched (*R*)-2-phenylpropanal. Lowered pressures severely degrade the enantioselectivity of the branched product. Qualitative kinetic data reveal large changes in the form of the apparent rate law, suggesting significant changes in catalyst speciation prior to selectivity-determining transformations. Most strikingly, under low-pressure conditions, the qualitative kinetic data imply that the catalyst accumulates as either 4-coordinate (bisphosphine)Rh(CO)(alkyl) (**4**) or 5-coordinate (bisphosphine)Rh(CO)(alkyl)(styrene) (**5**) complexes, neither of which have been previously observed as hydroformylation resting states under catalytic conditions. Although styrene is electronically biased to yield branched product, simple changes in the pressure of CO change the rate law and regio- and enantioselectivity while maintaining useful catalytic rates. These observations suggest that a broad range of selectivity regimes can be accessed with a single catalyst, instead of a catalyst library, simply by varying across different magnitudes of CO pressure.




**KEYWORDS:** *catalysis, enantioselectivity, regioselectivity, kinetics, mechanism, asymmetric hydroformylation*

Alkene hydroformylation, the atom-economic addition of syngas ($CO/H_2$) across a C=C double bond, is one of the largest homogeneous metal-catalyzed reactions in industry.[1] Hydroformylation of 1-alkenes results in mixtures of linear *n*-aldehydes and branched isoaldehyde products. Commodity applications of hydroformylation commonly are optimized for linear products, whereas branched-selective hydroformylation is the natural focus of fine chemical and pharmaceutical applications, especially the production of chiral aldehydes.[2] Regardless of the ultimate application, precise control of regio- and stereoselectivity is critical because unwanted isomers lower the process efficiency and are difficult to separate from the desired products. Unsurprisingly, modern development of hydroformylation catalysts centers on the design of new ligands that enable greater selectivity control.[3,4] Sometimes overlooked is the strong influence that reaction conditions (pressure, temperature, etc.) can exert on catalytic selectivity and activity.[5] In this paper, we demonstrate that low gas pressure can reverse the "intrinsic" selectivities of styrene hydroformylation using rhodium complexes of bis-diazaphos ligands (hereafter denoted as Rh(BDP)) and that the reaction kinetics imply dramatic shifts in catalyst speciation.

Recent work from our group has focused on developing a robust kinetic model of asymmetric hydroformylation of styrene using chiral Rh(BDP) catalysts.[6] Under typical high-pressure conditions ($P_{H_2} + P_{CO}$ = 20−200 psia), the regio- and enantioselectivity of styrene hydroformylation is strongly dependent on CO partial pressures. Under these conditions, all kinetic and spectroscopic data are consistent with the majority of catalyst pooling in the form of the hydridodicarbonyl complex, $Rh(BDP)H(CO)_2$. Furthermore, the kinetic data point to high selectivity for alkene insertion to give the *R*-branched alkyl; however, this selectivity is degraded at low pressures by competition of CO insertion into *R*-branched alkyls and *reversible* $\beta$-H elimination (Scheme 1).




Given the strong influence of CO partial pressure on reversibility along the *R*-branched pathway in Rh(BDP)

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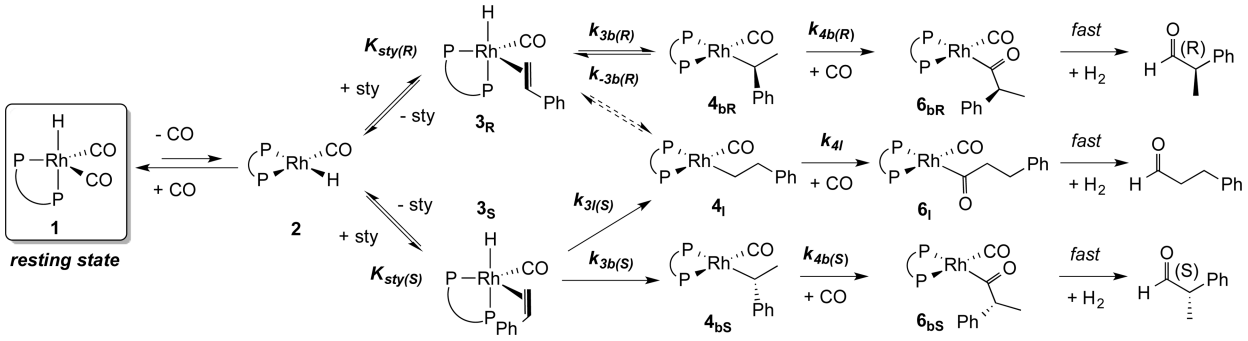
**Scheme 1. Mechanism of Rh(BDP)-Catalyzed Styrene Hydroformylation at Higher Pressures**[a]




[a]See ref 6. Product formation along linear and *S*-branched pathways is inhibited by CO, whereas competitive reversible hydride insertion along the *R*-branched (kinetic product) pathway imparts a net rate that is zero-order in CO.

catalysts, we sought to test the reversibility of hydride and CO insertions along the *linear* and *S*-branched pathways under very low pressures. Will the branched/linear (b/l) product ratio decrease monotonically to pure linear product as the pressure is decreased, or will it reach a plateau? Will the enantioselectivity invert, favoring the *S*-branched aldehyde, or simply become nonenantioselective at very low pressures? In the limit of very low pressure, what controls selectivity?

Under *extremely low* pressures of CO, preliminary calculations suggested that the regio- and enantioselectivity of Rh(BDP) catalysts could invert, yielding predominantly linear aldehyde.[7] Furthermore, under stoichiometric (no $H_2$) conditions, we have directly observed by NMR methods Rh alkyl and acyl complexes that are commonly presumed intermediates along the hydroformylation cycle.[8] Such reactions have shown that the five-coordinate *linear* Rh acyl (BDP)Rh-$(CO)_2$(acyl) is the thermodynamic product of the reaction of (BDP)Rh$(CO)_2$H with styrene, despite the catalyst system being highly branched-selective under normal catalytic reaction conditions. Given these predictions, observations, and a desire to develop a comprehensive kinetic model for the hydroformylation reaction, we initiated a study of the *catalytic* hydroformylation of styrene under extremely low $CO/H_2$ pressures and herein report new indirect observations of Rh alkyl and styrene adducts under catalytic reaction conditions.

## HYDROFORMYLATION AT VERY LOW PRESSURES YIELDS INVERSION OF THE BRANCHED/LINEAR RATIO

The regio- and enantioselectivity of styrene hydroformylation was measured across a broad $CO/H_2$ pressure range, from 0.15 to 160 psia. Experiments at 15 psia and below were carried out by diluting $CO/H_2$ with $N_2$ and bubbling the resultant gas mixture through the reaction solution at ambient pressure at a rate of 100 mL/min (Figure 1). Experiments above ambient pressure were carried out in a pressure bottle connected to an electronic pressure transducer to ensure accurate pressure measurements. In all experiments, the catalyst precursor, Rh(acac)$(CO)_2$, and BDP ligand were exposed to 150 psig syn gas at 80 °C for 60 min to generate the activated species Rh(BDP)H$(CO)_2$. The pressure was then adjusted to the desired conditions for 5 min, and the reaction was initiated by injection of styrene. Although conversions were low, a minimum of 10 catalyst turnovers was achieved to ensure steady-state catalyst distributions. Typical experimental conditions are given in Figure 2. Reactions were performed in the

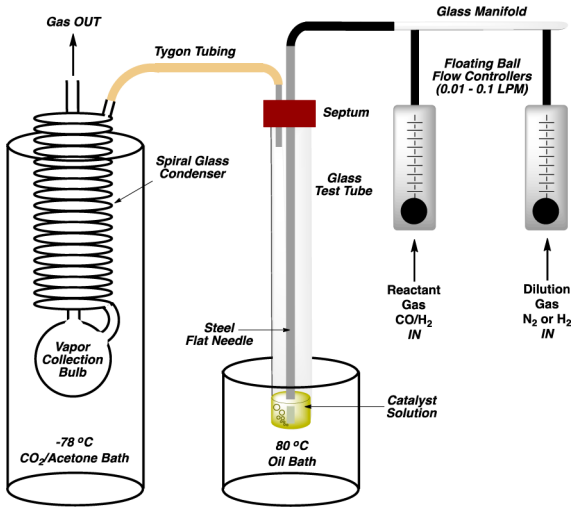



**Figure 1.** Schematic drawing of low-pressure experimental apparatus. Figure not drawn to scale.

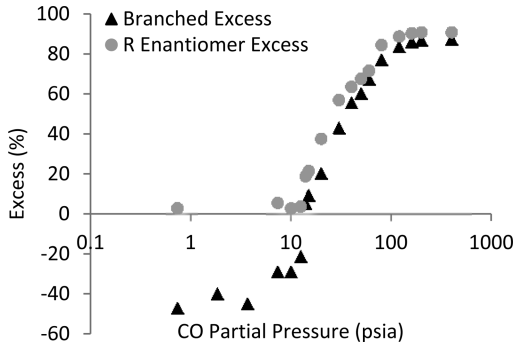



**Figure 2.** Regio- and enantiomeric excess for styrene hydroformylation as a function of syn gas pressure at 80 °C ($[styrene]_0$ = 2.2M, $[RhH(BDP)(CO)_2]$ = 5 × $10^{-4}$ M, $P_{H_2} = P_{CO}$).

initial rate regime with <5% conversion of styrene. Because of the nature of the low-pressure experimental setup, in which some solvent loss due to high gas flow rates is inevitable, the kinetic information obtained is semiquantitative; however, the trends presented below reveal surprising changes to the kinetic and mechanistic manifold of Rh(BDP)-catalyzed styrene hydroformylation.

Figure 2 illustrates the regio- and enantiomeric excess for styrene hydroformylation across the measured pressure range.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At extremely low pressures, the regioselectivity inverts, favoring the linear isomer and reaching an asymptotic ratio of approximately 3:1 linear/branched, while the enantioselectivity erodes to a plateau value of approximately 0% ee.

## KINETIC ANALYSIS AT LOW PRESSURES REVEALS UNEXPECTED RATE LAWS

Initial catalytic rates under low pressure conditions appear to be first-order in $P_{CO}$ and independent of $P_{H_2}$ for all products (two branched enantiomers and the linear isomer) (Figures 3,

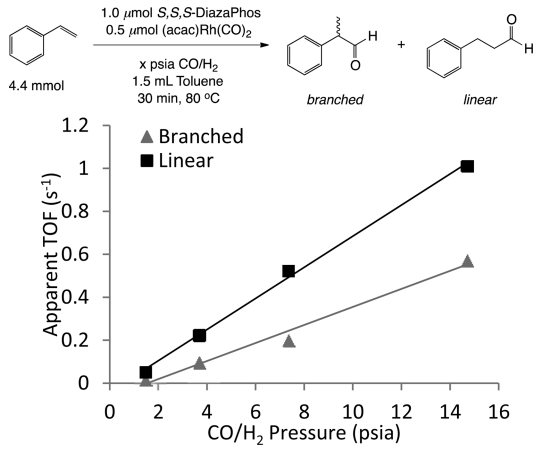


**Figure 3.** Apparent initial rates of branched and linear aldehyde production as a function of $P_{CO/H_2}$.

Supporting Information (SI) Figure SI4).[9] For comparison, over the 20−200 psia range, the production of linear and *S*-branched products are inhibited by CO, and the rate of *R*-branched product formation is approximately independent of CO.[6] Thus, for the linear aldehyde products, the apparent rate law shifts from −1 order in CO concentration to +1 upon lowering the pressure to ∼1 psia. Notably, the catalyst activity is synthetically useful (e.g., ∼1 turnover/s at 14 psia CO), even at very low pressures.

Initial rate studies in the low-pressure regime (1.5 psia $H_2$/CO) reveal that the rate is first-order in [Rh] (SI Figure SI5), but more complex for styrene. At this pressure, styrene has an apparent inhibitory effect on the rate over the styrene concentration range of 1 to 5 M but at [styrene] < 1 M, and the inhibitory effect dissipates to become roughly independent of the concentration of styrene (Figure 4). In contrast, previous measurements in the high-pressure regime[6] showed the rate to be rigorously first-order in the concentration of styrene. These results indicate dramatic changes in catalyst speciation as the pressure is lowered to subatmospheric levels.

Surprisingly, variable temperature studies in the low pressure regime indicate that the rate of reaction decreases as the temperature is increased (SI Figure SI6). Eyring plots are not linear, precluding extraction of enthalpies and entropies of activation. Commonly, increasing rates with decreasing temperature indicate an apparent negative $\Delta H^{\ddagger}$.

Table 1 summarizes the critical attributes of Rh(BDP)-catalyzed hydroformylation of styrene under low- and high-pressure conditions.

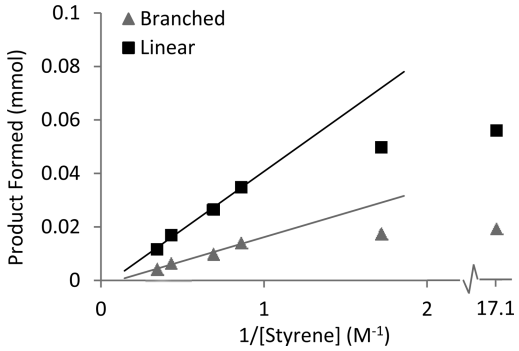


**Figure 4.** Apparent rate of branched and linear aldehyde production as a function of 1/[styrene]. Reaction conditions: 1 μmol BDP, 0.5 μmol (acac)Rh(CO)$_2$, 1.5 psia CO/$H_2$ @ 100 mL/min, 1.5 mL toluene, 80 °C, 30 min.

**Table 1. Comparison of Styrene Hydroformylation at 1.5 psia CO/$H_2$ and 150 psia CO/$H_2$ under Conditions in Figure 1**

| | 1.5 psia CO/$H_2$ | 150 psia CO/$H_2$[a] |
|---|---|---|
| resting state | (PP)Rh(CO)alkyl | (PP)Rh(CO)$_2$H |
| regioselectivity | linear | branched |
| ee | 2% ee *R* | 90% ee *R* |
| order, $P_{CO}$ | 1[b] | −1[c] or 0[d] |
| order, $P_{H_2}$ | 0 | 0 |
| order, [styrene] | −1 | 1 |
| temp effect | $T$ ↑ rate ↓ | $T$ ↑ rate ↑ |
| TOF ($s^{-1}$) | >0.1 | ∼1 |

[a]Data adapted from ref 6. [b]Order for all aldehyde isomers. [c]Order for linear and *S*-branched aldehyde pathways. [d]Order for *R*-branched pathway.

## LOW-PRESSURE KINETIC AND SELECTIVITY DATA POINT TO RH-ALKYL RESTING STATES

The qualitative rate data observed in the low-pressure regime require modification of the kinetic model developed for high pressure studies (Scheme 2). First, because the reaction appears to be first-order in [CO], it is unlikely that (BDP)RhH(CO)$_2$ (**1**) is the catalyst resting state because entry into the catalytic cycle requires loss of CO to form (BDP)RhH(CO) (**2**). Rather, the data implicate pooling of the catalyst at a point prior to rate-determining CO association/insertion to form (BDP)Rh(CO)(acyl) (**6**) species. Such a scenario would lead to an Rh-alkyl resting state and a rate that is first-order in [CO].

The observation that the rate is inhibited by the styrene concentration at concentrations >1 M suggests the existence of a resting state with a formulation of (BDP)Rh(alkyl)(CO)(styrene) (**5**). At lower styrene concentration, where there is no inhibition, the implied resting state comprises the 4-coordinate (BDP)Rh(alkyl)(CO) isomers (**4**). Thus, under low-pressure conditions, the regio- and enantioselectivity plateau as a Curtin−Hammett kinetic limit is reached. In this Curtin−Hammett limit, the rate is determined by the equilibrium concentration of the three intermediary Rh-alkyls isomers, **4**, and their rates of CO association/insertion. The drop in enantioselectivity with decreasing pressure indicates that the transition state energies for CO insertion into diasteromeric alkyls are nearly identical at the low-pressure plateau. The inversion of the regioselectivity suggests that under conditions of rapid alkyl equilibration among alkyl regioisomers, the


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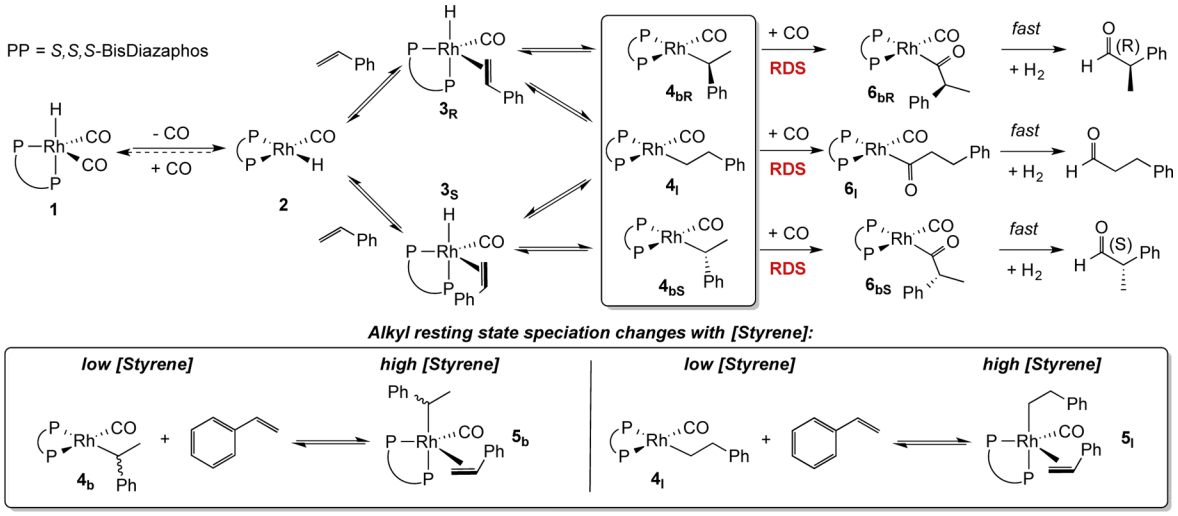
**Scheme 2. Plausible Kinetic Scheme for Rh(BDP)-Catalyzed Styrene Hydroformylation under Low Pressure Conditions**[a]




[a]Rh alkyls are in equilibrium prior to rate-determining CO insertion, and product distributions are determined by Curtin−Hammett kinetics.

barrier to formation of the linear aldehyde is lower.[10] This could reflect that the linear alkyl is thermodynamically preferred, is faster to associate and insert CO, or some combination of the two.[11] To the best of our knowledge, these data provide the most compelling support for the existence of an alkyl resting state, followed by rate-determining CO insertion for Rh-catalyzed hydroformylation.[12]

It is not so common that the substrate for a catalytic reaction inhibits its own transformation. However, because it is well-established that CO strongly coordinates to 4-coordinate (BDP)Rh(CO)(R) (R = alkyl, acyl, hydride) species,[13] it is reasonable to assume that a similar $\sigma$-donor/$\pi$-acceptor ligand such as styrene could competitively coordinate, especially under these low-pressure conditions when the CO concentration in solution is orders of magnitude lower than that of styrene. Although adducts such as **5** have not been invoked in typical hydroformylation cycles, complexes similar to **5** containing tethered anionic alkyl olefins are well characterized.[14]

To understand competitive binding between CO and styrene, computations were performed with the M06 method and a triple-$\zeta$ quality basis set (see the Supporting Information for details). As expected, the standard free energy of binding CO to the hydride (BDP)Rh(CO)(H) (**2**) is significantly more favorable than styrene association; however, the standard free energy difference between CO and styrene binding to the 4-coordinate alkyl (BDP)Rh(CO)(alkyl) (**4**) is smaller: the CO adduct is favored by only 1.4 kcal/mol over the styrene adduct. However, because of the large difference in concentrations of CO and styrene at nonstandard conditions (i.e., [CO] < 0.001 M at <1 psi and [styrene] > 1.0 M),[15] the equilibrium favors styrene's binding. From a free energy perspective, neither binding is particularly strong (CO, $\Delta G^\circ$ = −3.8 kcal/mol; styrene, $\Delta G^\circ$ = −2.4 kcal/mol), indicating that at low enough CO pressures/styrene concentrations, it is likely that both will remain dissociated and the coordinately unsaturated (BDP)-Rh(CO)(alkyl) (**4**) will be favored.[8] Figure 5 depicts the optimized structure of linear (BDP)Rh(styryl)(CO)(styrene), which is the anticipated resting state at high styrene concentration and low CO pressure. The inhibitory effect of styrene and first-order dependence of CO on the reaction rate at low pressure suggests that the rate-limiting process involves a sequence starting with styrene dissociation, followed by association of CO, and concluding with insertion of CO to form the acyl.

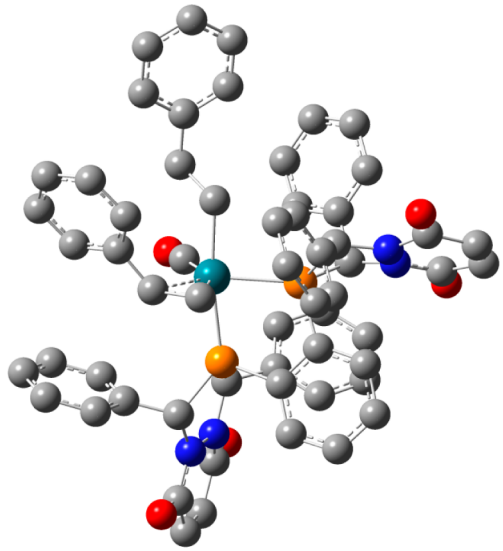


**Figure 5.** The M06 optimized geometry of the lowest energy (BDP)Rh(alkyl)(CO)(styrene) structure ($\mathbf{5_l}$).

## SUMMARY

Hydroformylation of styrene with Rh(BDP) catalysts exhibits dramatically different rate laws in low-pressure and high-pressure regimes (Table 1). At high pressure, the catalytic kinetics are dominated by (a) the requirement of CO loss from the (BDP)RhH(CO)$_2$ (**1**) resting state and (b) competitive CO association/insertion and $\beta$-hydride elimination for the fast-formed *R*-branched alkyl. Conversely, at low pressure, the observed kinetics appear to indicate pooling as, and rapid equilibration among, Rh alkyl species (**4** or **5**) prior to rate-determining CO association/insertion. Upon reaching the Curtin−Hammett limit, the rate law becomes apparently first-order in CO for all products, and dramatic changes in regioselectivity result. Similarly, the kinetic dependence of the rate on the concentration of styrene changes dramatically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between pressure regimes. At high pressure the reaction rate is rigorously first-order in styrene concentration, but at low pressure the reaction is inhibited by styrene. These data are consistent with pooling of catalysts as an equilibrium mixture of **4** and **5**.

Decreased b/l selectivity for styrene hydroformylation with lowered syn gas pressure is not uncommon.[10] This study uniquely extends the "low pressure" regime to very low pressures (<1 psia) and examines changes in rate laws associated with pressure changes. The significance of the dramatic changes in catalyst rate laws as a function of CO pressure is twofold. First, from a practical standpoint, it is significant that simply lowering of CO pressure leads to large changes in regio- and enantioselectivity while retaining good catalyst activity. This result emphasizes that exploration of "reaction condition space" can be as, or even more, important as focusing on "ligand space" in catalyst optimization. Second, from a fundamental mechanistic perspective, studies under nontraditional, low pressures of syngas corroborate the general mechanistic steps of catalytic hydroformylation while drawing attention to the delicate balance of competing processes that must occur for rapid, multistep catalytic reactions. Fast catalysis requires that the intrinsic rates and barriers of all steps of the catalytic cycle must not be very different. Low-pressure conditions result in accumulation of catalytic intermediates and off-cycle species that are rarely observed; for example, the 4-coordinate Rh alkyl species ($\mathbf{4}_b$ and $\mathbf{4}_l$) and the 5-coordinate Rh alkyl olefin species ($\mathbf{5}_b$ and $\mathbf{5}_l$). Thus, it should be possible, by careful choice of reaction conditions, to directly observe these intermediates by NMR and other information-rich techniques.

## ■ ASSOCIATED CONTENT

### Supporting Information

Full experimental details and additional kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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