# A Kinetic Study on Rh/Binap-Catalyzed 1,4-Addition of Phenylboronic Acid to Enones: Negative Nonlinear Effect Caused by Predominant Homochiral Dimer Contribution

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The 1,4-addition of organometallic reagents to $\alpha,\beta$-unsaturated compounds is a widely used process for carbon−carbon bond formation.[1] Chiral catalytic system for the 1,4-addition of aryl and alkenylboronic acids has been developed by use of a Rh/binap catalyst.[2,3] Although its catalytic cycle has been proposed on the basis of NMR studies of the intermediates,[4] its kinetic understanding has not been afforded due to the difficulty of analysis of the multistep catalytic reaction.[5] Recently, Blackmond developed the methodology of reaction progress kinetic analysis utilizing reaction calorimetry and provided a powerful tool for kinetic analysis on complicated catalytic reactions including transition-metal-catalyzed reactions.[6] Here we report a detailed kinetic study of Rh/binap-catalyzed 1,4-addition of phenylboronic acid to $\alpha,\beta$-unsaturated ketones. An inactive dimeric hydroxorhodium complex is found to be a dominant species in the catalytic cycle, which was confirmed by quantitative investigation of the nonlinear effect.

**Scheme 1**
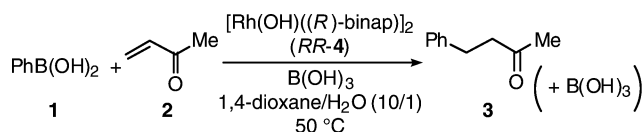
The reactions between phenylboronic acid (PhB(OH)$_2$, **1**)[7] and an excess amount of methyl vinyl ketone (MVK, **2**)[8] in aqueous 1,4-dioxane in the presence of [Rh(OH)((*R*)-binap)]$_2$ (*RR*-**4**) as a catalyst and boric acid (H$_3$BO$_3$)[9] (Scheme 1) were continuously monitored in a reaction calorimeter (Omnical SuperCRC), and the kinetic behavior was analyzed by using the method of ["excess"] relationship and graphical rate equation developed by Blackmond.[10,11] Constant catalyst concentration and steady-state behavior were confirmed by the results of kinetic profiles for two reactions at the same ["excess"] overlaid with one another when plotted as rate versus the concentration of PhB(OH)$_2$ [**1**] (Figure 1, a and b). The plot of rate versus [**1**] is a straight line suggestive of first-order kinetics, and zero-order kinetics in the concentration of MVK [**2**] is confirmed by the reaction employing different ["excess"] (a, c, and d). It is significant that the reaction rate does not show proportional increase by the addition of catalyst. Rate divided by the square root of rhodium concentration (rate/[Rh]$_{total}^{0.5}$) is plotted versus PhB(OH)$_2$ concentration [**1**] to show that the reaction is half-order in rhodium concentration throughout the entire course of the reaction (Figure 1, inset, a and e).

Our previous NMR studies have revealed[4] that the catalytic cycle involves transmetalation of phenyl group from boron to hydroxo-rhodium, addition of the resulting phenylrhodium bond to an enone

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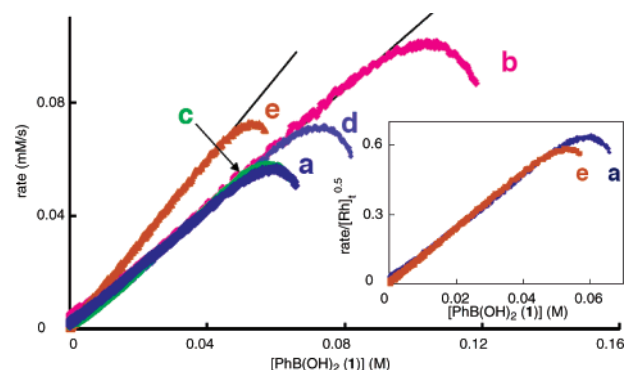
**Figure 1.** Rate vs [**1**] and rate/[Rh]$_t^{0.5}$ vs [**1**] (inset) for the reactions of **1** with **2** in 1,4-dioxane (3.0 mL) and H$_2$O (0.3 mL) in the presence of [B(OH)$_3$]$_0$ = 260 mM at 50 °C. The progress of the reaction runs from right to left in these figures. The data during the first 3 min were omitted for the clarify. The solid lines represent the kinetic model given in eq 2. Reaction conditions: (a) [**1**]$_0$ = 71.7 mM, [**2**]$_0$ = 194 mM, [*RR*-**4**] = 8.00 mM Rh; (b) [**1**]$_0$ = 128 mM, [**2**]$_0$ = 248 mM, [*RR*-**4**] = 8.00 mM Rh; (c) [**1**]$_0$ = 69.7 mM, [**2**]$_0$ = 124 mM, [*RR*-**4**] = 8.00 mM Rh; (d) [**1**]$_0$ = 88.7 mM, [**2**]$_0$ = 197 mM, [*RR*-**4**] = 8.00 mM Rh; (e) [**1**]$_0$ = 66.0 mM, [**2**]$_0$ = 184 mM, [*RR*-**4**] = 16.0 mM Rh.

**Scheme 2.** Reaction Network of Rh/Binap-Catalyzed 1,4-Addition of Phenylboronic Acid (**1**) to Methyl Vinyl Ketone (**2**)
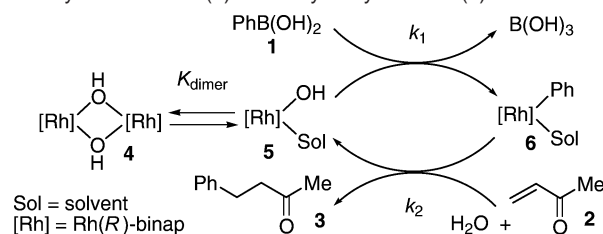
forming oxo-$\pi$-allylrhodium, and its hydrolysis giving the 1,4-addition product and hydroxorhodium species. Due to the half-order kinetics in [Rh]$_{total}$, this catalytic cycle was modified to involve an equilibrium between the monomeric species **5** and the dimeric hydroxorhodium **4**, which is characterized by the dimerization constant $K_{dimer}$ (Scheme 2).[12] The dissociation of the catalytically inactive dimer **4** forms the active monomeric rhodium **5**, which has a reactive vacant site coordinated weakly with a solvent molecule. As a kinetic model, we assumed the transmetalation step characterized by the rate constant $k_1$. The subsequent two steps, insertion of MVK **2** and hydrolysis forming product **3**, were combined and characterized by the rate constant $k_2$.[13] Using the steady-state treatment for the rhodium species **4**, **5**, and **6**, we wrote a reaction rate expression (eq 1). The large value for $K_{dimer}$, which is demonstrated by the half-order kinetics in [Rh]$_{total}$, simplifies eq 1 to eq 2, which is in good agreement with the reaction orders in substrates and catalyst described above. Excellent fits between experimental rate data and calculated rate were found when the

constant for eq 2 has the value of $k_1/(2K_{dimer})^{0.5} = 12$ $M^{-0.5}$ $s^{-1}$ ($R^2 = 0.98$).[14]

$$\nu = \frac{2k_1k_2[\text{PhB(OH)}_2(\mathbf{1})][\text{MVK}(\mathbf{2})][\text{Rh}]_{\text{total}}}{A + \{A^2 + 8K_{\text{dimer}}(k_2[\text{MVK}(\mathbf{2})])^2[\text{Rh}]_{\text{total}}\}^{0.5}}$$

$$A = k_1[\text{PhB(OH)}_2(\mathbf{1})] + k_2[\text{MVK}(\mathbf{2})] \quad (1)$$

$$\nu = \frac{k_1}{(2K_{\text{dimer}})^{0.5}}[\text{PhB(OH)}_2(\mathbf{1})][\text{Rh}]_{\text{total}}^{0.5} \quad (2)$$

The existence of the dominant dimeric species prompted us to carry out a quantitative nonlinear effect (NLE) analysis, because NLE is generally attributed to the formation of diastereomeric species or higher-order agglomerates.[15] ^{31}P NMR of the racemic binap−hydroxorhodium complex (10 mM in 1,4-dioxane/$H_2O$ (10/1) at 29 °C) showed only one doublet at $\delta$ 54.9 Hz ($J_{P-Rh} = 185$ Hz), which is the same as that of enantiopure binap−hydroxorhodium complex, indicating that the homochiral dimer is overwhelmingly more stable than the heterochiral dimer. Kitamura and Noyori described mathematical treatment of NLE in their reports on asymmetric alkylation of aldehydes with dialkylzinc reagents.[16] A negative NLE in ee_prod and an amplified reaction rate are expected in our reaction system characterized by the preferential formation of homochiral dimer.[15,16] Considering that the formation of heterochiral dimer $RS$-$\mathbf{9}$ is negligible, calculation to obtain the concentrations of monomers [$R$-$\mathbf{5}$] and [$S$-$\mathbf{5}$] is very simple, readily available from the dimerization constant $K_{dimer}$ obtained for the homochiral dimer. The equations for ee_prod and the reaction rate ($\nu_{ee}$) are defined by the concentrations of active monomeric rhodium complexes [$R$-$\mathbf{5}$] and [$S$-$\mathbf{5}$], where ee$_{100\%ee}$ (>99% ee) and $\nu_{100\%ee}$ are the enantioselectivity and the rate of the reaction by the enantiopure catalyst, respectively.[17]

$$\text{ee}_{\text{prod}} = \text{ee}_{100\%ee}\frac{[R\text{-}\mathbf{5}] - [S\text{-}\mathbf{5}]}{[R\text{-}\mathbf{5}] + [S\text{-}\mathbf{5}]}, \quad \frac{\nu_{ee}}{\nu_{100\%ee}} = \frac{[R\text{-}\mathbf{5}] + [S\text{-}\mathbf{5}]}{[R\text{-}\mathbf{5}]_{100\%ee}} \quad (3)$$

**Scheme 3.** Nonlinear Effect and Equilibrium Scheme
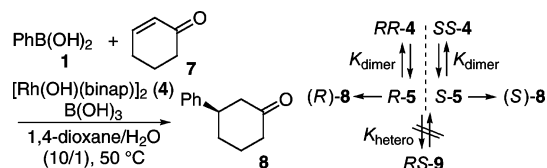
A negative NLE was actually observed in Rh/binap-catalyzed asymmetric addition of PhB(OH)$_2$ (**1**) to 2-cyclohexenone (**7**), giving phenylation product **8**[2–4] ([$R$] > [$S$], Scheme 3, and squares in Figure 2). The dimerization constant was estimated to be $K_{dimer} = 8 \times 10^2$ $M^{-1}$ by fitting the deviation from the linear relationship as well as the increase in the reaction rate to eq 3 (solid lines, Figure 2). By substituting this $K_{dimer}$ value for the slope of eq 2 ($k_1/(2K_{dimer})^{0.5} = 12$ $M^{-0.5}$ $s^{-1}$), the rate constant for transmetalation $k_1$ is readily extracted to be $k_1 = 0.5$ $M^{-1}$ $s^{-1}$. Thus, we finally obtained kinetic constants for both $k_1$ and $K_{dimer}$. Unfortunately, it is statistically difficult to extract the constant $k_2$ under our experimental conditions.

In conclusion, our detailed kinetic study and quantitative simulation of nonlinear effect determined the rate constant for rate-determining transmetalation and the dimerization constant, revealing that the reaction mechanism involves the equilibrium between the catalytically inactive dimeric hydroxorhodium complex [Rh(OH)((R)-binap)]$_2$ ($RR$-$\mathbf{4}$) and the active monomeric species $R$-$\mathbf{4}$ and that
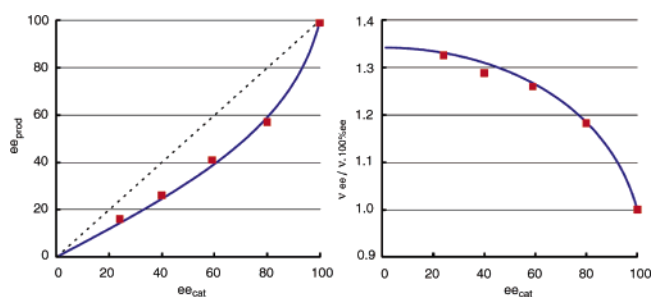
**Figure 2.** ee_prod vs ee_cat (left) and $\nu_{ee}/\nu_{100\%ee}$ vs ee_cat (right). Simulation (solid lines) and observation (squares) of the nonlinear effect in the reaction of **1** to **7**.

the inactive dimer species $RR$-$\mathbf{4}$ is the resting state. These results are consistent with our previous reaction mechanism proposed by the NMR studies of key intermediates.[4]

**Supporting Information Available:** Experimental procedures and detailed kinetic study data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) An expert review: Blackmond, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4302.
(7) In the experiments, phenylboroxine ((PhBO)$_3$) was used as a precursor of phenylboronic acid (**1**), because the boroxine is easier to be purified. Arylboroxine and water is in a fast equilibrium with arylboronic acid, and hence the reaction starting from phenylboronic acid and that starting from arylboroxine in water should result in the same outcome. Tokunaga, Y.; Ueno, H.; Shimomura, Y.; Seo, T. *Heterocycles* **2002**, *57*, 787.
(8) In the reaction of reactive MVK, hydrolysis of **1** giving benzene as a side reaction is negligible. ^{1}H NMR analysis of the reaction mixture showed <3% formation of benzene.
(9) An excess of boric acid was added to minimize the change of its concentration throughout the reaction.
(10) The methodology of reaction progress kinetic analysis is described in ref 6 and in the following literature: (a) Rosner, T.; Le Bars, J.; Pfaltz, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 1848. (b) Singh, U. K.; Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14104. (c) Mathew, S. P.; Gunathilagan, S.; Roberts, S. M.; Blackmond, D. G. *Org. Lett.* **2005**, *7*, 4847.
(11) The parameter ["excess"] is defined as the difference in the initial concentrations of two substrates, [reagent]$_0$ − [substrate]$_0$ to manipulate the large number of data pairs. The two reactions carried out at the same ["excess"] reveal unsteady-state influence on kinetic behavior, and the reactions at the different ["excess"] give sufficient data required for the determination of kinetic constants within a kinetic model.
(12) The half-order kinetics in [catalyst] was reported in ref 10a.
(13) We observed that the hydrolysis is much faster than the insertion (ref 4).
(14) Kinetic modeling of the data to fit the proposed rate expression in eq 2 was carried out using the Excel least-squares program.
(15) For the first example, see: (a) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353. For reviews, see: (b) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922. (c) Blackmond, D. G. *Acc. Chem. Res.* **2000**, *33*, 402.
(16) (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028. (b) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800.
(17) This type of mathematical treatment has been reported in refs 15c and 16b.

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