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A New Approch for Catalyst Optimization: Host/Guest Complexes of Chiral Bisphosphine Bearing Imidazolidinone and Their Application in Rh-Catalyzed Asymmetric Hydrogenation†

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As a new strategy for the optimization of a chiral catalyst, the catalytic activity of the host-guest complexes of chiral bisphosphine bearing imidazolidinone was investigated in Rh-catalyzed asymmetric hydrogenation of enamide. Marginal enhancement in enantioselectivity was observed and the nature of interaction between host-guest was experimentally elucidated.

Key Words: Chiral catalyst, Catalyst optimization, Host/guest

Introduction

Metal catalyzed asymmetric catalysis is one of the important synthetic methods for the preparation of optically active compounds, for which more than thousands of chiral catalysts themselves have been designed during last 20 years mostly on the basis of the intuition of the chemists.[1] Recently, a new strategy to the development of chiral catalysts has been emerged. The use of a chiral ligand in combination with an achiral- or a meso ligand is employed to generate new chiral catalysts, in which one of the possible diastereomeric metal complexes is formed preferentially *via* coordination of the exogenous chiral source to the metal.[2] An advantage of this approach is easiness of catalyst optimization using readily available achiral or meso ligands, thus minimizing an arduous task for the synthesis of enantiopure ligands.

In this paper, we present a new way for fine-tuning chiral catalysts using hydrogen-bonded host-guest concept. In nature, the non-covalent intermolecular interactions such as π-π interaction and hydrogen-bonding played an important role to alter molecular conformation and consequently regulate dynamic functions such as molecular recognition and catalytic activity in biological system. Inspired by theses natural system, Roelfes and co-workers utilized the non-covalent interactions between DNA and organic-metal complex to generate the DNA-based chiral catalysts, in which the chiral information of the DNA could be transferred to the reaction site of the achiral metal complex through the non-covalent interactions between DNA and achiral metal complex.[3] In present work, we envisioned that the strong intermolecular hydrogen-bonding interactions between achiral host and chiral ligand could influence on the conformation of metal-complex of the guest chiral ligand. In this manner, the ligand conformation in reaction site could easily be tuned by the non-covalent intermolecular interactions between achiral host and chiral metal-complex, where the catalytic activity of a chiral ligand-metal complex could be optimized by varying achiral host.

To demonstrate the H/G-based catalyst optimization concept, we chose the chiral bisphosphine ligand bearing imidazolidin-2-one (abbreviated as H-BDPMI)[4] as a chiral guest which is one of the well-known moieties as hydrogen-bonding donor/receptor.[5] The five different achiral hosts **1-5** were easily synthesized from commercially available amines and isophthaloyl dichloride, which were frequently used as a hydrogen-bonding donors/receptors.[6] The Rh-catalyzed asymmetric hydrogenation of an enamide was carried out as a model catalytic reaction. The Rh-complex was prepared *in situ* by mixing equivalent amount of H-BDPMI and $[Rh(COD)_2]BF_4$ in CH_2Cl_2 for 1 h at room temperature under argon atmosphere. To the

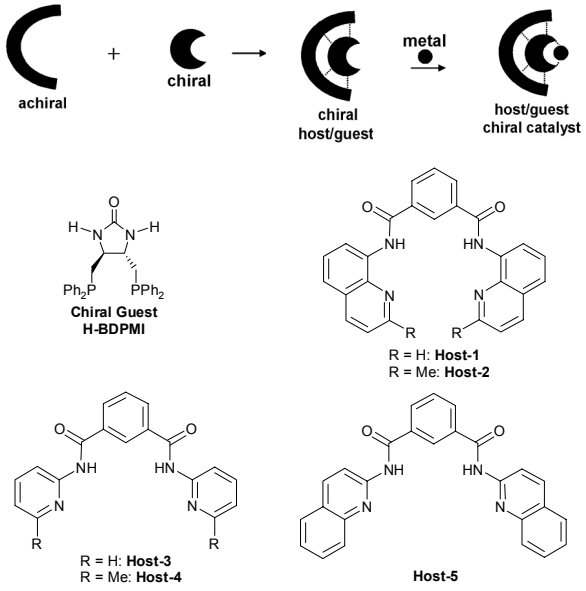
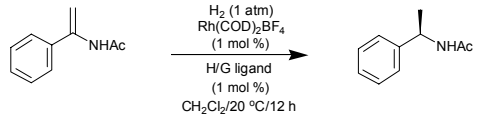


Figure 1. Schematic presentation of H/G-based chiral catalyst, and the structures of chiral bisphosphine guest and achiral hosts.

†This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.

mixture was added host, and the mixture was stirred for 2 h. The hydrogenation was conducted for 12 h at 1 atm of hydrogen pressure. As shown in Table 1, the enantioselectivities obtained with all of the H/G-based chiral catalysts **H-1**~**5/G** (entries 2~6) were higher (+1.7 ~ +6.1%ee) than that obtained with H-BDPMI catalyst (83.8%ee, entry 1). The same results were obtained with the catalyst prepared different way, *i.e.* H/G complex was prepared first by mixing with H-BDPMI and host, then $Rh(COD)_2BF_4$ was added to form a Rh-complex. However, it was found that the catalyst, which was prepared by mixing the host and $Rh(COD)_2BF_4$ first followed by the addition of chiral bisphosphine, did not showed any catalytic activity. These results suggest that the observed catalytic activity come from the Rh-complex of the chiral bisphosphine ligand, and moreover, the host or guest ligand chelated with Rh-metal did not exchanged each other. We next varied the ratio of host/guest to see whether the catalysis is derived from the depicted 1:1 complex of achiral host and chiral guest or not. Therefore, at higher host:H-BDPMI-Rh complex ratios, the amounts of unbound H-BDPMI-Rh complex in solution will be negligible and the ee obtained should be derived from 1:1 complex of achiral host and chiral guest. However, the ee values were not significantly increased as increasing the host concentration, which suggested that the host-guest binding is saturated. In addition, when the hydrogenations were carried out in a protic solvent, MeOH, in which host-guest complexation is prohibited by competitive H-bond by solvent, the Rh-complex of **H-5/G** and Rh-H-BDPMI complex exhibited the same enantioselectivity (73.6%ee) (compare entries 7 and 8), but with lowered conversion with **H-5/G** compare to H-BDPMI Combining all the observation into account, it is reasonable to conclude that the formation of host-guest complex increased the enantioselectivity +1.7 ~ +6.1% ee (entries 2-6, Table 1).

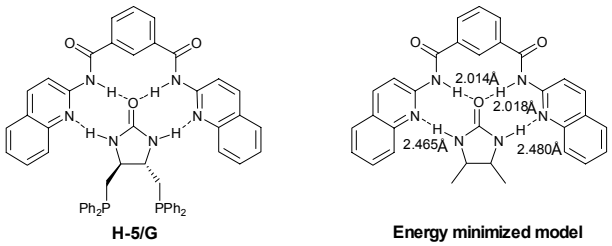
Table 1. Rh-Catalyzed asymmetric hydrogenation of N-acetyl-phenylethenamine using H/G-complex ligands prepared from **H-BDPMI** and host **1-5**[a]



entry	ligand	Conv. (%)[b]	%ee[c]	Δ%ee
1	**H-BDPMI**	100	83.8	-
2	**H-1/G**	100	85.8	+2.3
3	**H-2/G**	100	86.2 (87.2, 87.4, 87.2)[d]	+2.7 ~ +3.6
4	**H-3/G**	15	89.6	+6.1
5[d]	**H-4/G**	100	85.2	+1.7
6	**H-5/G**	100	86.0 (86.6, 86.8, 86.6)[d]	+2.5 ~ +3.0
7[e]	**H-BDPMI**	100	73.6	-
8[e]	**H-5/G**	14	73.6	-

[a]The catalyst was made *in situ* by mixing $Rh(COD)_2BF_4$ (0.062 mmol) with H-BDPMI (0.062 mmol) followed by addition of equimolar amount of host (0.062 mmol) in CH_2Cl_2 (2 mL). After addition of substrate (0.62 mmol, 0.31 M), the mixture was subjected into 1 atm of hydrogen atmosphere for 12 h. [b]Determined by ^1H NMR. [c]Determined by chiral GC using CP-Chirasil Dex CB column at 120 °C (isothermal). [d] %ees obtained with the catalysts prepared from ratio of host/guest is 2, 3, and 4. [e]Reactions carried out in MeOH solvent.

Even though the precise nature of the interaction between achiral host and chiral guest is not clear yet, the hydrogen-bonding would be dominated. To evaluate the interaction of the chiral guest to host forming **H/G** complexes, ^1H NMR titration was conducted by adding incremental amounts of the H-BDPMI to a 0.005 M solution of host **5** in CD_2Cl_2 at 23 °C.[7] A remarkable downfield shift ($\Delta\delta$ = 2.04 ppm) was observed for the N-H signal (δ = 9.004 ppm) of host **5**. Moreover, the aromatic C-H (δ = 8.629 ppm) also slightly shifted to downfield ($\Delta\delta$ = 0.28 ppm). The NMR titration data were analyzed



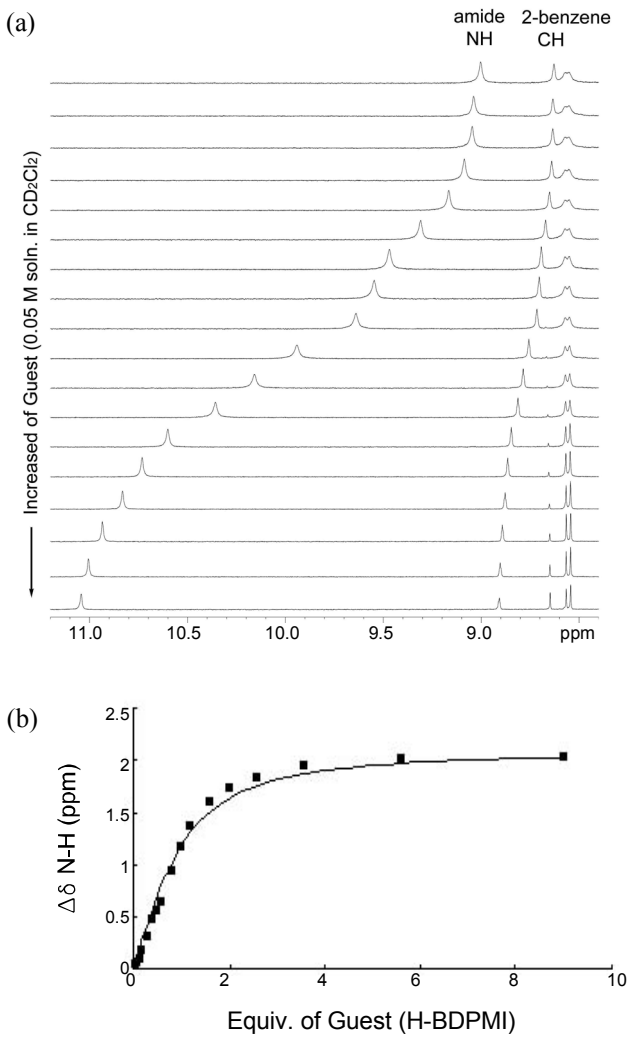


Figure 2. Structures of **H-5/G** and energy minimized model H/G complex, and (a) ^1H NMR titration spectra of the **H-5** (NH, CH_{ph}, $CH_{quinoline}$ resonances are shown) with H-BDPMI guest (0.0 ~ 10.0 equivalent). (b) Plot of the observed downfield chemical shifts of the d_{N-H} resonances of **H-5** as a function of added H-BDPMI.

using a linear least squares fitting procedure similar to that described by Wilcox and Cowart,[8] and the calculated association constant was K_a = 550. Formation of present host-guest complex *via* hydrogen bonding was further evidenced by energy minimized conformation of 4,5-dimethylimidazolidin-2-one as a guest. The amide hydrogen atoms were hydrogen-bonded with the carbonyl oxygen of the guest (H---O: 2.014 Å and 2.018 Å) and quinoline nitrogen atoms were hydrogen- bonded with amide hydrogen of the guest (N---H: 2.465 Å and 2.480 Å). Based on these results, it could be concluded that there is multiple hydrogen bonding interaction between imidazolidinone moiety of chiral bisphosphine guest and host to form chiral **H/G** complexes.

In summary, we presented a host/guest-based asymmetric catalysis. Although the effects are not so dramatic, it was found that the intermolecular hydrogen-bonding interactions between achiral host and chiral guest affected positively on the enantioselectivity. However, the exact role of the host in the transmission of asymmetry remains to be elucidated. This work set up a stage for further catalyst optimization with structurally diverse achiral host available from combinatorial preparation, and for conceptual design on chiral host and achiral guest, in which the chiral information of the host could be transferred to the reactive site of the metal complex of the achiral guest ligand.

Experimental

Achiral hosts **1**~**5** were synthesized by reaction of isophthaloyl dichloride with the corresponding amines, 8-aminoquinoline (**H-1**), 2-methyl-8-aminoquinoline (**H-2**) which prepared by hydrogenation of 8-nitroqunaldine, 2-aminopyridine (**H-3**), 2-amino-6-picoline (**H-4**), and 2-aminoquinoline (**H-5**).

An example synthetic procedure for achiral host. A solution of isophthaloyl dichloride (1.0 g, 4.93 mmol) in anhydrous benzene (50 mL) was added dropwise to a suspension of 8-aminoquinoline (1.5 g, 10.04 mmol) and triethylamine (1.4 mL, 10.0 mmol) in anhydrous benzene (20 mL). The mixture was stirred at 75 °C for 12 h under nitrogen atmosphere. After benzene was removed from the mixture by evaporation, the residue was dissolved in chloroform and washed with water. The chloroform solution was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

***N,N'*-Bis[(8-quinolyl)carbamoyl]isophthalamide (Host-1).** Re-crystallization from benzene. Yield: 92%; White solid (mp 194 ~ 195 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 4.24 & 4.20 Hz, 2H, 7-quinoline protons), 7.57-7.65 (m, 4H, 5,6-quinoline protons), 7.75 (t, *J* = 7.73 Hz, 1H, benzene proton), 8.20 (dd, *J* = 1.60 & 1.60 Hz, 2H, 3-quinoline protons), 8.30 (dd, *J* = 1.80 & 1.80 Hz, 2H, 4-quinoline protons), 8.79 (d, *J* = 1.56 Hz, 1H, benzene proton), 8.87 (dd, *J* = 1.64 & 1.60 Hz, 2H, benzene protons), 8.97 (dd, *J* = 1.52 & 1.52 Hz, 2H, 2-quinoline protons), 10.87 (s, 2H, amide NH protons); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 116.75, 121.78, 122.01, 126.10, 127.41, 128.00, 129.41, 130.55, 134.39, 135.90, 136.40, 138.78, 148.44, 164.65. Anal. Calcd. for $C_{26}H_{18}N_4O_2$: C, 74.63; H, 4.34; N, 13.39. Found: C, 74.62; H, 4.29; N, 13.49; HRMS (ES): *m*/*z* calcd. for $C_{26}H_{18}N_4O_2$: $[M + H]^+$ = 419.1509, found = 419.1507.

***N,N'*-Bis[(2-methyl-8-quinolyl)carbamoyl]isophthalamide (Host-2).** Re-crystallization from benzene. Yield: 78.5%; Yellowish solid (mp 245~246 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (s, 6H, $2CH_3$), 7.35 (d, *J* = 8.36 Hz, 2H, 7- quinoline protons), 7.51-7.57 (m, 4H, 5,6-quinoline protons), 7.76 (t, *J* = 7.72 Hz, 1H, benzene proton), 8.07 (d, *J* = 8.36 Hz, 2H, 3-quinoline protons), 8.29 (dd, *J* = 1.80 & 1.80 Hz, 2H, 4-quinoline protons), 8.82 (t, *J* = 1.64 Hz, 1H, benzene proton), 8.91 (dd, *J* = 2.32 & 2.32 Hz, 2H, benzene protons), 10.95 (s, 2H, amide NH protons); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.41, 116.69, 121.73, 122.55, 126.10, 122.16, 126.36, 129.39, 130.35, 133.76, 136.06, 136.48, 138.15, 157.47, 164.46; Anal. Calcd. for $C_{28}H_{22}N_4O_2$: C, 75.32; H, 4.97; N, 12.55. Found: C, 75.37; H, 4.77; N, 12.37; HRMS (ES): *m*/*z* calcd. for $C_{28}H_{22}N_4O_2$: $[M + H]^+$ = 447.1822, found = 447.1824.

1,3-Bis[{(pyridine-2-yl)amino}carbonyl]benzene (Host-3). Re-crystallization from ethanol. Yield: 64%; White solid (mp 177 ~ 178 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (q, *J* = 7.18 Hz, 2H, 5-pyridine protons), 7.65 (t, *J* = 7.75 Hz, 1H, benzene proton), 7.76-7.80 (m, 2H, 4-pyridine protons), 8.15 (dd, *J* = 1.60 & 1.56 Hz, 2H, benzene protons), 8.28 (d, *J* = 4.10 Hz, 2H, 6-pyridine protons), 8.39 (d, *J* = 8.34 Hz, 2H, 3-pyridine protons), 8.56 (s, 1H, benzene proton), 8.95 (s, 2H, amide NH protons); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 114.30, 120.19, 126.04, 129.51, 130.88, 134.94, 138.57, 147.91, 151.34, 164.60**;** Anal. Calcd. for $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43; N, 17.60. Found: C, 65.07; H, 4.50; N, 18.41; HRMS (ES): *m*/*z* calcd. for $C_{18}H_{14}N_4O_2$: $[M + H]^+$ = 319.1196, found = 319.1196

1,3-Bis[{(6-methyl-pyridine-2-yl)amino}carbonyl]benzene (Host-4). Crystallization from ethyl acetate and *n*-hexane. Yield: 76%; White solid (mp 143 ~ 144 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 6H, $2CH_3$), 6.95 (d, *J* = 7.46 Hz, 2H, 5-pyridine protons), 7.63 (t, *J* = 7.78 Hz, 1H, benzene proton), 7.66 (t, *J* = 7.87 Hz, 2H, 4-pyridine protons), 8.13 (dd, *J* = 1.80 & 1.80 Hz, 2H, benzene protons), 8.18 (d, *J* = 8.24 Hz, 2H, 3-pyridine protons), 8.51 (t, *J* = 1.64 Hz, 1H, benzene proton), 8.70 (s, 2H, amide NH protons); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.98, 110.99, 119.69, 125.84, 129.44, 130.76, 135.03, 138.79, 150.54, 157.03, 164.44; Anal. Calcd. for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17. Found: C, 69.34; H, 5.47; N, 16.25: HRMS (ES): *m*/*z* calcd. for $C_{20}H_{18}N_4O_2$: $[M + H]^+$ = 347.1509, found = 347.1503.

***N,N'*-Bis[(2-quinolyl)carbamoyl]isophthalamide (Host-5).** Re-crystallization from benzene. Yield: 65%; White solid (mp 215 ~ 216 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.51 (m, 2H, 3-quinoline protons), 7.70 (dd, *J* = 1.08 & 1.01 Hz, 2H, 6-quinoline protons), 7.70 (t, *J* = 1.46 Hz, 1H, benzene proton), 7.83 (dd, *J* = 0.82 & 0.84 Hz, 2H, 7-quinoline protons), 7.86 (d, *J* = 8.53 Hz, 2H, 8-quinoline protons), 8.22 (dd, *J* = 1.41 & 1.40 Hz, 2H, 5-quinoline protons), 8.26 (d, *J* = 8.99 Hz, 2H, benzene protons), 8.57 (bs, 2H, 4-quinoline protons), 8.64 (s, 1H, benzene proton), 8.95 (s, 2H, amide NH protons); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 114.38, 125.44, 126.27, 126.52, 127.39, 127.64, 129.58, 130.19, 131.08, 135.06, 138.85; Anal. Calcd. for $C_{26}H_{18}N_4O_2$: C, 74.63; H, 4.34; N, 13.39. Found: C, 74.73; H, 4.18; N, 13.17; HRMS (ES): *m*/*z* calcd. for $C_{26}H_{18}N_4O_2$: $[M + H]^+$ = 419.1509, found = 419.1508.

General procedure for the asymmetric hydrogenation of *N*-acetyl-1-phenylethenamide. In an argon-filled glovebox, a reaction flask was charged with $[Rh(cod)_2]BF_4$ (6.2×10^{-3} mmol) and H-BDPMI (6.2×10^{-3} mmol) in 2.0 mL of solvent, and the mixture was stirred for 1 h at room temperature. Then, the host (6.2×10^{-3} mmol) was added to the reaction mixture and stirred for additional 2 h at the same temperature. *N*-Acetyl-1-phenylethenamide (100 mg, 0.62 mmol) was added to the reaction mixture, and then hydrogenation performed under 1 atm of H_2 pressure for 12 h. The reaction mixture was passed through a short silica gel column to remove the catalyst. After evaporation of the solvent, the crude reaction mixture was subjected into the ^{1}H NMR and capillary GC to determine the conversion and enantiomeric excess, respectively.

Determination of enantiomeric excess. Chiral Capillary GC column: CP-Chiralsil-Dex-CB column (dimension 30 m × 0.32 mm (i.d.)); Carrier gas: N_2 (1.8 mL/min); 120 °C, isothermal; retention time: (*S*)-isomer = 29.37 min, (*R*)-isomer = 33.06 min.

Ka calculation. Energy-minimized structure was obtained from MacroModel 7.1 program on a Silicon Graphics Indigo IMPACT workstation.[9] The structure was generated with MM2* force field *via* 3000 separated search steps in Monte Carlo conformational search. A least square fitting program was used to calculate Ka according to an adaptation of the method of Wilcox and Cowart.[8] The expression involved was:

$$\delta_{obs} = (\delta_{inf} - \delta_0)\Big[\{(1+[G]/[H]+1/K_a[H])/2\} - \sqrt{[(1+[G]/[H]+1/(Ka[H])^2/4\ [G]/[H])}\Big] + \delta_0$$

Where

[H] = conc. of host

[G] = conc. of guest

$\delta_{obs} = \delta_{N\text{-}H}$ of pure host

$\delta_{inf} = \delta_{N\text{-}H}$ of complex (calaulated)

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