CH₂ Linkage Effects on the Reactivity of Bis(aminophosphine)–Ruthenium Complexes for Selective Hydrogenation of Esters into Alcohols

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A novel ruthenium complex binding to two subtly different aminophosphine ligands, (o-PPh₂C₆H₄CH₂NH₂)(o-PPh₂C₆H₄NH₂)RuCl₂, was successfully isolated. This bis(aminophosphine)–ruthenium complex shows efficient activity in both dimethyl oxalate (DMO) and methyl benzoate (MB) hydrogenation. On the contrast, similar complexes (o-PPh₂C₆H₄NH₂)₂RuCl₂ and (o-PPh₂C₆H₄CH₂NH₂)₂RuCl₂ can only effectively catalyze the hydrogenation of DMO and MB, respectively. Our experimental studies in combination of theoretical calculations reveal that the remarkable substrate selectivity in the hydrogenation of esters arises from the nonbonding interactions operated by the CH₂ linkage of the ligand.

The function and importance of nonbonding interactions have been recognized in enzymatic catalysis¹,², chiral organometallic catalysis³–⁵, chiral organocatalysis⁶–⁹, and small molecular conversions¹⁰,¹¹, and they can influence the reaction efficiency and stereoselectivity¹²–¹⁵. These weak interactions are becoming an essential component that can even govern the reaction mechanism and may facilitate the design of new catalysts¹⁶–¹⁸. Normally, these weak interactions keep step with the change of the steric and electronic environments. However, efficient modulation of nonbonding interactions during catalysis is still of great challenge for chemists¹⁹.

Metal–NH catalysis, a representative system in organometallic catalysis of small molecules¹⁹–²³, has been increasingly used to improve the hydrogenation of esters into alcohols in the last decade²⁴–³⁵. Two main mechanisms, namely, Noyori-Ikariya-type out-sphere pathway²⁴–²⁶ and classical inner-sphere pathway²⁸,²⁹, have been proposed. However, the existing mechanism can not well explain some cases of hydrogenation²⁸,²⁹,³⁶,³⁷. For instance, the ruthenium complexes [{PPh₃}(o-PPh₂C₆H₄NH₂)RuCl₂] (1) and (o-PPh₂C₆H₄NH₂)₂RuCl₂ (2) containing the rigid ligand o-PPh₂C₆H₄NH₂ can efficiently catalyze the hydrogenation of several aliphatic and cyclic esters to corresponding alcoholic compounds, but they show poor activities in the conversion of aromatic esters³⁸. For example, they can be applied in DMO hydrogenation into methyl glycolate (MG, Fig. 1a), but are not suitable for MB hydrogenation into benzyl alcohol (BA, Fig. 1b). Unpredictably, the complex (o-PPh₂C₆H₄CH₂NH₂)₂RuCl₂ (3), which exhibits a structure similar to that of 2, effectively converts aromatic esters but show only moderate activities in the hydrogenation of oxalate esters. The distinct difference between the activities of complexes 3 and 2 containing ligands with and without CH₂ linkage is interesting.

Herein, the new ruthenium complex (o-PPh₂C₆H₄CH₂NH₂)(o-PPh₂C₆H₄NH₂)RuCl₂ (4) contains two different aminophosphine ligands (N,P-ligands) similar to those in 2 and 3; the complex exhibits satisfactory

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performance both in the hydrogenation of oxalate and aromatic esters. The significant effect of the CH2 linkage of the o-PPh2C6H4CH2NH2 ligand (also named as soft ligand), which is demonstrated ascribable to the nonbonding interactions between the ruthenium catalyst and substrates, was confirmed by comprehensive experimental and theoretical methods.

Results and Discussion

The reaction of 1 with two equivalents of o-PPh2C6H4CH2NH2 successfully produced 4 with 86% yield (Fig. 2). Complex 4 was characterized by spectroscopic methods (1H, 13C{1H}, and 31P{1H} NMR and IR) and X-ray single crystal diffraction. The 31P{1H} NMR spectrum indicates the incorporation of the two inequivalent N,P-ligands at the ruthenium center of complex 4, which exhibits two doublets with significant P-P coupling \( J(P,P) = 30.3 \text{ Hz} \). The X-ray diffraction pattern of complex 4 reveals that the ruthenium atom adopts a distorted octahedral geometry (Fig. 3), where the two N,P-ligands bind to the ruthenium center in cis-arrangement and form an equatorial RuN2P2 coordination plane. The two Cl atoms are located trans to each other at the axial position. Apparently, the introduction of the CH2 linkage reduces the steric hindrance but increases the electronic density around the NH2 group.

As shown in Fig. 4, the four complexes that contain two inequivalent N,P-ligands at the ruthenium center, (o-PPh2C6H4CH2NH2)(o-PPh2C6H4NMe2)RuCl2 (5), (o-PPh2C6H4CH2NH2)(o-PPh2C6H4NMe2)(o-PPh2C6H4NH2)RuCl2 (6),
(PPh₂CH₂CH₂NH₂)(o-PPh₂C₆H₄NH₂)RuCl₂ (9), and [PPh₂(CH₂)₃NH₂](o-PPh₂C₆H₄NH₂)RuCl₂ (10) were also successfully synthesized and spectroscopically characterized. The X-ray single crystal structures of complexes 5 and 6 are shown in Fig. S2 and S3, respectively, which feature similar skeletal structures with that of complex 4, but one of the NH₂ groups in o-PPh₂C₆H₄NH₂ and o-PPh₂C₆H₄CH₂NH₂ is replaced with the NMe₂ group. Complexes 9 and 10 also contain rigid ligand o-PPh₂C₆H₄NH₂ like 4, while the soft ligand o-PPh₂C₆H₄CH₂NH₂ is changed to PPh₂CH₂CH₂NH₂ and PPh₂(CH₂)₃NH₂, respectively.

Complex 4 was used to catalyze the hydrogenation of DMO and MB at 100 °C and 50 bar H₂ for 4 h. As shown in Fig. 5, complex 4 exhibited satisfactory activities in the conversions, and the corresponding alcohols were obtained in excellent yields [93% MG and 6% ethylene glycol (EG) for DMO, 93% BA for MB]. In the absence of complex 4 or NaOMe, no hydrogenation product was obtained (Table S1). Similar to our previous report³⁸, complex 2 promoted DMO hydrogenation into MG but was inactive in MB transformation into BA; the yields of MG and BA were 97% and 1%, respectively. The hydrogenation rate of MB increased as a result of introducing the
CH₂ linkage into one of the o-PPh₂C₆H₄NH₂ ligands. Under the same conditions, the corresponding yields of MG and BA for complex 3 were 49% and 93%, respectively.

Encouraged by the success of complex 4 in DMO and MB hydrogenation, we further investigated hydrogenation of various substrates shown in Fig. 6, under different reaction conditions (Table 1). As listed in entries 1–6, 7–11 and 12–17, respectively, lactones (E1–E6), aromatic esters (E7–E11), and aliphatic esters (E12–E17) all were converted smoothly and the corresponding alcohols were obtained in moderate to good yields (49–100%).

**Table 1.** Hydrogenation of substrates shown in Fig. 6 with 4. Reaction conditions: 7.57 mmol substrate, the molar ratio of NaOMe to ruthenium was 20, 10 mL THF, 50 bar H₂, 100 °C. Unless otherwise noted, conversion of substrate and yield of alcohol were analyzed by gas chromatograph (GC). 24% fatty-fatty esters present. 14% fatty-fatty esters present. Carboxamide conversion and alcohol yield were analyzed by ¹H NMR spectroscopy. 120 °C, NaOEt was used.

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Actually, complex 4 also exhibited good activity in ester hydrogenation under lower H2 pressure (Table S2). Under the conditions at 100 °C and 50 bar H2 for 10 h, complex 4 showed good activity in the hydrogenation of carboxamides A1–A4, and desired alcohols were obtained in yields between 64–100% (entries 18–21). Surprisingly, after increasing the reaction temperature from 100 °C to 120 °C, complex 4 could also catalyze the hydrogenation of ethylene carbonate (C1) and dimethyl carbonate (C2), and the methanol yield attained 91% and 44% (entries 22 and 23), respectively. Thus, the combination of the rigid \( \text{o-PPh}_2\text{C}_6\text{H}_4\text{NH}_2 \) and soft \( \text{o-PPh}_2\text{C}_6\text{H}_4\text{CH}_2\text{NH}_2 \) ligands in complex 4 significantly promotes the reaction efficiency.

According to the slight difference of these two ligands, we also determined the manipulation of the CH2 linkage in the catalytic performance, where we performed extensive density functional theory (DFT) calculations and molecular dynamics (MD) simulations on the proposed catalysts \( 2H^* \) and \( 3H^* \), and their corresponding \( 2H^*s \) and \( 3H^*s \) models (Fig. S6). The results are displayed in Table 2, Figs 7 and 8. Details are provided in Fig. S6–20 (SI, section IV).

The entire catalytic hydrogenation of esters into alcohols can be assumed to proceed through two stages: hydrogenation of esters into aldehydes (stage I) and subsequent hydrogenation into alcohols (stage II).\(^{31, 39–41} \) Our calculations (Figs S11 and S12) and previous studies\(^{36, 42, 43} \) propose that stage II is more favorable than stage I both kinetically and thermodynamically. Accordingly, stage II might be insignificant for evaluation of ester

| Entry | Reaction system | Gas Phase | Solution |
|-------|----------------|-----------|----------|
|       |                | TS1 | TS1\(^*\) | TS2 | TS2\(^*\) | TS3 | TS3\(^*\) |
| 1     | 2H-DMO         | 10.7 | 8.2      | 6.7 | 8.2     | 8.9 | 6.4      | 7.6 |
| 2     | 3H-DMO         | 12.4 | 10.7     | 2.9 | —       | —   | 8.2      | 9.4 |
| 3     | 2H-MB          | 19.3 | 15.9     | 2.3 | 2.8     | 0.2 | 13.7     | 14.7|
| 4     | 3H-MB          | 21.6 | 17.3     | 6.0 | 9.1     | 7.9 | 16.8     | 15.0|

Table 2. Predicted relative Gibbs free energies for hydrogen transfers involved in the hydrogenation of esters. Unit in kcal/mol. "\(^*\)" refers to \( 2H^* \) and \( 3H^* \), which is the simplified model of \( 2H \) and \( 3H \).

Figure 7. (a) The flexible scanning for the NH proton transfer (N–H \( \rightarrow \) O–CH) in DMO hydrogenation. (b) The flexible scanning for the NH proton transfer (N–H \( \rightarrow \) O–CH) in MB hydrogenation. (c) Calculated partial pair correlation function \( g(r) \) for the distance between the ruthenium hydride and carbonyl carbon of MB in 3–5 ns. (d) Percentage of effective attack to MB in \( 2H^* \) and \( 3H^* \).
hydrogenation here, and this is also supported by the experimental fact that complexes 2 and 3 exhibit identical performances in benzaldehyde hydrogenation (Table S3).

The optimized structures of transition states and intermediates for 2H catalyzing hydrogenation of MB into benzaldehyde and methanol are collected in Fig. S8, and the corresponding relative free-energy profiles are shown in Fig. S9. Here, two possible reactive configurations with the outward or inward carbonyl (refer to 2H-TS1MB and 2H-TS1MB’ in Fig. S8) for MB have been considered, and the results show that the initial hydride transfer to the outward carbonyl is more favorable, which experiences a relatively low free energy barrier. The low-energy reaction channel follows a multi-step mechanism (Fig. S7)31, 40, where the initial hydride transfer from ruthenium to the carbonyl carbon of the ester experiences a relatively high energy barrier and it might be the rate-determining step. Further calculations reveal that the hydrogenation of DMO by the ruthenium catalysts follows a similar mechanism of the hydrogenation of MB. The optimized structures of the transition states (TS1) are depicted in Fig. S10.

Table 2 lists the predicted thermodynamic quantities of the hydrogen transfer in DMO and MB hydrogenation. The relatively low free energy barriers less than 17 kcal/mol in solution suggest that the initial hydride transfer in DMO and MB hydrogenation can occur at room temperature. This is consistent with the experimental fact that 2 and 3 can catalyze the hydrogenation of DMO and MB at room temperature, respectively. As is shown in Table 2 (entries 1 and 2) and Fig. 7a, the DFT-predicted free energy barriers indicate that complex 2 is more active toward DMO hydrogenation than complex 3 as observed experimentally (refer to Fig. 5). On the contrast, experimentally, complex 3 is much more active than complex 2 for MB hydrogenation (Fig. 5), while DFT calculations suggest that both catalysts exhibit comparable activities (Table 2 and Fig. 7b).

As mentioned above, the hydrogenation reaction is initiated by the hydride transfer from ruthenium to the carbonyl carbon of ester and this step is influenced by the carbonyl position (Fig. S7–9). Considering the inconsistency of the experimental observations and DFT calculations, we performed extensive MD simulations to investigate the steric and attractive nonbonding interaction effect on these bimolecular reactions. As shown in Fig. S17, the simulations reveal that the reaction system of 3H-MB possesses more effective reaction conformers than 2H-MB; the former has remarkably higher conformer contributions in the reactive region of 2.5–3.5 Å between the ruthenium hydride and the carbonyl carbon of MB from MD simulations in 3–5 ns. In addition, the snapshots of the reactive systems reveal the optimal attack configuration for the initial hydride transfer, where the Ru–H group is approximately perpendicular to the carbonyl group of MB (Fig. S17). These configurations can survive in a larger reactive region for the reaction system of 3H-MB compared with that of 2H-MB. Further
geometry optimizations of the near attack reactive configurations by DFT + D show that the Ru–H–C angles of conformers ii and iii in the reaction system of 3H-MB (Fig. 8) is larger than the sole conformer i in the 2H-MB reaction system (Fig. S18). This finding indicates that the attractive nonbonding interactions (N–H–O, N–H–C and N–H–H, Fig. 8) and the less steric hindrance operated by the CH linkage dominate the accessibility of the reactive conformer. Therefore, the activity difference between complexes 2 and 3 toward MB hydrogenation exclusively originates from the accessibility of the near attack reactive conformer and their relative stabilities.

Interestingly, complex 4, bearing two kinds of N,P-ligands with or without the CH linkage appearing in complexes 3 and 2, generally exhibits superior performance in the hydrogenation of DMO and MB. Previous studies reported that the NH proton for the metal-NH catalysis is crucial and indispensable in hydrogenation\(^\text{44, 45}\). Accordingly, we synthesized two complexes, namely, \((o\text{-PPh}_2\text{C}_6\text{H}_4\text{CH}_2\text{NH})_2\text{RuCl}_2\) (5) and \((o\text{-PPh}_2\text{C}_6\text{H}_4\text{NHMe})_2\text{RuCl}_2\) (6), to elucidate the critical roles of the two inequivalent \(\text{NH}_2\) groups in hydrogenation (Fig. 4).

Activity tests show that no conversion was observed using complex 5 in DMO hydrogenation; however, the activity of complex 5 in MB hydrogenation had a BA yield of 88%, which is comparable with that of complex 4 (Fig. 5). Interestingly, complex 6 exhibited opposite performance in DMO and MB hydrogenation to that of complex 5, and the corresponding yields were 79% and 1%, respectively. The shutdown of the activity in DMO or MB hydrogenation after \(\text{NMe}_2\) group substitution shows that the \(\text{NH}_2\) groups of complex 4 are indispensable in hydrogenation; nevertheless, these groups are inclined to participate in the hydrogenation of DMO and MB, respectively, similar to those in complex 2 or 3. These results are consistent with the computational results, indicating that the function of the CH linkage in complex 4 is similar to that in complex 3. The CH linkage facilitates the modulation of attractive nonbonding and steric interactions between the catalyst and the ester MB. Hence, the co-coordination of the rigid \(o\text{-PPh}_2\text{C}_6\text{H}_4\text{NH}_2\) and soft \(o\text{-PPh}_2\text{C}_6\text{H}_4\text{CH}_2\text{NH}_2\) ligands in complex 4 positively influences DMO and MB hydrogenation.

Furthermore, the catalytic performances of complexes 9 and 10 in ester hydrogenation were examined under the same conditions as in Fig. 5. The results in Fig. S5 indicated that both 9 and 10 could exhibit exceptional performances in DMO hydrogenation (86% yield of MG and 13% yield of EG by 9, 100% yield of MG by 10) and MB hydrogenation (100% yield of BA by 9, 56% yield of BA by 10). Previous results showed that the catalytic performances of complexes \((\text{Ph}_2\text{P}(\text{CH}_2)_2\text{NH})_2\text{RuCl}_2\) (7) and \((\text{Ph}_2\text{P}(\text{CH}_2)_2\text{NH})_2\text{RuCl}_2\) (8) with flexible N,P-ligand were similar to complex 3, which was effective for the reduction of aromatic esters but low active for the reduction of oxalate esters\(^\text{43}\). Thus, combination of the rigid \(o\text{-PPh}_2\text{C}_6\text{H}_4\text{NH}_2\) and soft \(o\text{-PPh}_2\text{C}_6\text{H}_4\text{CH}_2\text{NH}_2\) or \(\text{PPh}_2\text{CH}_2\text{CH}_2\text{NH}_2\) in complexes 9 and 10 significantly promotes the reaction efficiency. Further optimization of the structure of the ligands is under process.

In summary, we have demonstrated the first result of modulating nonbonding interactions for the selective hydrogenation of esters into alcohols. The newly-developed ruthenium complex 4 containing one CH linkage in the structure exhibits satisfactory performance in the hydrogenation of DMO and MB, whereas complexes 2 and 3 with two CH linkage ligands show high catalytic activity only toward DMO or MB hydrogenation, respectively. The computational analyses and the corresponding comparative studies show that the CH linkage modulates the attractive nonbonding and steric interactions between the reactants, which dominate the accessibility of reactive configurations with the favorable orientation for the initial hydride transfer. These findings not only demonstrate the remarkably effects of nonbonding interactions on the selective hydrogenation of esters but also provide a new perspective on the mechanistic understanding of catalysis with uncommon reactivity and selectivity. The exceptional performance of complex 4 as well as of complexes 9 and 10 in catalytic hydrogenation may encourage further efforts to develop efficient catalyst systems through ligand combination.

**Methods**

**Materials and general methods.** All manipulations were carried out under a dry Ar or N\(_2\) atmosphere by using Schlenk line and glovebox techniques. The organic solvents toluene, \(n\)-hexane, tetrahydrofuran (THF) and \(\text{CHCl}_3\) were distilled from CaH\(_2\) and kept in the glovebox for use. The substrates employed in the catalytic reactions were purchased from Aldrich, \&Re, or Alfa-Aesar Chemical Co. and used after purification according to the standard method. Complexes \((\text{Ph}_2\text{P}(\text{CH}_2)_2\text{NH})_2\text{RuCl}_2\) (PPh\(_2\)EM, \((\text{Ph}_2\text{P}(\text{CH}_2)_2\text{CH}_2\text{NH})_2\text{RuCl}_2\) (7)\(^\text{46}\), and \((\text{Ph}_2\text{P}(\text{CH}_2)_2\text{NH})_2\text{RuCl}_2\) (8)\(^\text{48}\) were prepared according to the procedure reported in literatures. The NMR (\(^1\text{H}, ^{13}\text{C}(\text{H}), ^{31}\text{P}(\text{H})) spectra were measured on a Bruker AVIII-500 spectrometer and the IR spectra were recorded on a Nicolet FT-IR 330 spectrometer. Elemental analysis was performed on a Thermo Quest Italia SPA EA 1110 instrument. X-ray crystal structure information is available at the Cambridge Crystallographic Data Centre (CCDC) under deposition numbers CCDC-1521753 (4), CCDC-1521754 (5), and CCDC-1521755 (6). See Supplementary Information for detailed experimental procedures, and crystallographic, spectroscopic and computational analyses.

**Catalytic reaction.** The hydrogenation reactions were performed in a 100 mL Teflon-lined Parr stainless-steel autoclave. Generally, ruthenium complex, THF solvent, substrate, NaOMe, and diethyl ether were dried by refluxing with sodium/potassium benzophenone under N\(_2\) prior to use. CHCl\(_3\) and n-hexane, tetrahydrofuran (THF) and \(\text{CHCl}_3\) were distilled from CaH\(_2\) and kept in the glovebox for use. The substrates employed in the catalytic reactions were purchased from Aldrich, \&Re, or Alfa-Aesar Chemical Co. and used after purification according to the standard method. Complexes \((\text{Ph}_2\text{P}(\text{CH}_2)_2\text{NH})_2\text{RuCl}_2\) (PPh\(_2\)EM, \((\text{Ph}_2\text{P}(\text{CH}_2)_2\text{CH}_2\text{NH})_2\text{RuCl}_2\) (7)\(^\text{46}\), and \((\text{Ph}_2\text{P}(\text{CH}_2)_2\text{NH})_2\text{RuCl}_2\) (8)\(^\text{48}\) were prepared according to the procedure reported in literatures. The NMR (\(^1\text{H}, ^{13}\text{C}(\text{H}), ^{31}\text{P}(\text{H})) spectra were measured on a Bruker AVIII-500 spectrometer and the IR spectra were recorded on a Nicolet FT-IR 330 spectrometer. Elemental analysis was performed on a Thermo Quest Italia SPA EA 1110 instrument. X-ray crystal structure information is available at the Cambridge Crystallographic Data Centre (CCDC) under deposition numbers CCDC-1521753 (4), CCDC-1521754 (5), and CCDC-1521755 (6). See Supplementary Information for detailed experimental procedures, and crystallographic, spectroscopic and computational analyses.
Theoretical computation. All of the DFT calculations were carried out with the Gaussian 09 program. The molecular geometries of reactants, transition states, and intermediates were fully optimized by the B3LYP functional. Here the LanL2DZ basis set augmented with polarization functions (Ru(5d) = 1.235 and P(3d) = 0.340) was chosen to describe ruthenium and phosphorus atoms, and the basis set of 6-31 + G(d,p) was used for all other atoms. The solvent effect on the hydrogen transfer was evaluated by the SMD model with the experimentally used THF, and the total energies were calibrated by M06/6-311++G(d,p)//B3LYP/6-31 + G(d,p) single-point calculations. For comparison, all the initial reactive conformers were re-optimized at the B3LYP-D3/6-31 G(d,p) level of theory. The counterpoise correction scheme of Boys and Bernardi was applied to correct the basis-set superposition error. At the same time, a correction of −2.6 kcal/mol (temperature = 298.15 K) was applied to measure the free energy change based on the theory of free volume.

MD simulations were performed using the Focite module encoded in the Material Studio software with the universal force field (UFF). A 3.59 × 3.59 × 3.59 Å3 cubic box with the periodic boundary conditions in all directions was constructed by the Amorphous Cell module. In terms of the reaction conditions in experiment, the cubic box contains one catalyst and two hundred substrates with a density of 1.0 g/cm3. The annealing approach with 20-annealing cycle was adopted for the minimization of reaction system (temperature: 300–800 K, total time: 20 ps, Nose thermostat, NVE ensemble). Afterwards, MD simulations were carried out under the NPT ensemble at a constant temperature of 300 K using a Nose-Hoover thermostat. The equations of motion were integrated with the velocity Verlet algorithm for a total simulation time of 5 ns with a time step of 1 fs, and the cut-off value is 18.0 Å selected for the electrostatic and van der Waal summation method.

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Author Contributions

Y.Y. conceived the project. X.F. carried out synthesis, characterization and testing; H.Z. solved all X-ray structures. M.S. and Z.C. conducted theoretical calculations. I.Z., B.L., L.Y. and X.W. analysed and interpreted the experimental data. X.F. and Y.Y. wrote the main manuscript text. All authors discussed and reviewed this paper.

Additional Information

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