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Enantiomer Recognition of Amides by Dirhodium(II) Tetrakis[methyl 2-oxopyrrolidine-5(*S*)-carboxylate]

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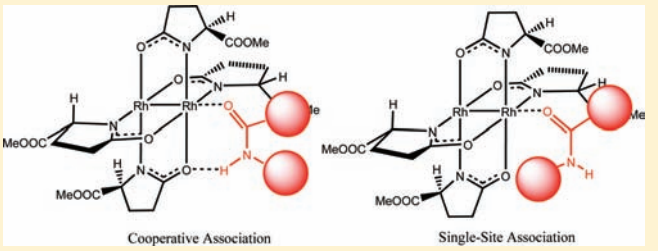
Supporting Information

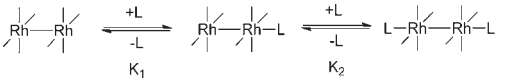
ABSTRACT: Association constants of the chiral dirhodium(II) carboxamidate $Rh_2(5S\text{-MEPY})_4$ with Lewis bases including acetonitrile and amides have been determined by UV−vis titration experiments. With chiral lactams and acyclic acetamides in their *R*- and *S*-configurations equilibrium constants with chiral dirhodium carboxamidates are measures of chiral differentiation, and equilibrium constant ratios as high as three have been determined. From equilibrium associations with acetamide, *N*-methylacetamide, and *N*,*N*-dimethylacetamide, as well as equilibrium constants for lactams and acyclic amides, higher values occur when both the amide carbonyl oxygen and N−H are bound to $Rh_2(5S\text{-MEPY})_4$. This cooperative bonding mode is confirmed by NMR measurements that show a distinctive shift of a N−H absorption, as well as perturbation of the ligands on dirhodium compound, and they suggest N−H association with a ligated oxygen of $Rh_2(5S\text{-MEPY})_4$. Measurements were made on the dirhodium(II) compound from which protective axial ligands have been removed to enhance their reliability.



INTRODUCTION

The chemistry of dirhodium(II) carboxylates and carboxamidates is intimately linked to the events that take place at the axial coordination sites of these μ-bridged paddlewheel complexes.[1−3] With one exception,[4] descriptions of catalytic reactions portray the equatorial-ligated scaffold of dirhodium(II) compounds as rigid and not prone to exchange under ordinary conditions,[5−8] whereas the axial sites of the dirhodium(II) compound coordinate with Lewis bases[1−3] and *N*-heterocyclic carbenes[9] in a dynamic fashion. This association is the basis for understanding the suitability of dirhodium carboxylates and carboxamidates as Lewis acid catalysts,[10] as well as in catalysis for metal carbene reactions;[11−14] axial coordination is responsible for the biological activity of dirhodium(II) complexes.[15] Dirhodium carboxylates have also been used to cross-link proteins via axial coordination.[16]

Equilibrium association with dirhodium(II) compounds has long been a topic of interest.[1] Quantitative determination of equilibrium constants by Drago and co-workers with dirhodium(II) carboxylates established that, consistent with expected back-bonding from rhodium(II) to the axial ligand, association with the first base (acetonitrile or pyridine) occurs with an equilibrium constant that is 10^2 times greater than association with the second base, eq 1.[17] These studies have been extended to equilibrium determinations of association with weak bases that have included alkenes,[18,19] aldehydes,[10a] and even alkynes,[20] in which cases only K_1 was determined. Effort was taken in these studies to remove the axial ligand(s) prior to addition of the Lewis base so that the axial coordination site of the dirhodium species was either associated with a basic site of another dirhodium compound[21] or with a weakly binding solvent. In contrast, others have determined equilibrium constants with dirhodium complexes in which the axial coordination sites are occupied by water;[22,23] in these cases the measured quantities are those for displacement of water, eq 2, and the values do not necessarily reflect the Lewis acidity of the dirhodium complex nor are they easily reproducible.



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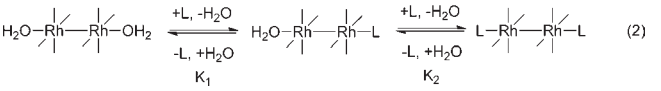

(2)

We have developed dirhodium(II) carboxamidates having chiral amide ligands and used them as catalysts for highly stereoselective transformations.[5,10,11] To evaluate the Lewis acidity of the axial coordination sites of these compounds, the equilibrium constants for their association with acetonitrile were determined.[24,25] Their values were more than an order of magnitude lower than those obtained with dirhodium(II) carboxylates, which confirmed their lower Lewis acidity compared to dirhodium(II) carboxylates. Chiral dirhodium(II) carboxamidates were subsequently evaluated for their ability to differentiate between enantiomers of racemic diazo compounds by means of product formation,[26] but they have not been evaluated for their

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ability to discriminate between enantiomeric Lewis bases under thermodynamic equilibrium.

Amides have been selected for evaluation because of their potential for cooperative association between rhodium atom and the amide carbonyl group together with hydrogen bond formation between the amide N−H and a ligand oxygen. This structural framework has been reported by Bear for dirhodium(II) pyrrolidinate and valerolactamate with their corresponding lactams in the solid state,[27] but the solution equilibria of such compounds have not been reported. Use of chiral dirhodium carboxamidates also provides an opportunity to explore differential selectivity for association with chiral carboxamides.

EXPERIMENTAL SECTION

Materials. Glassware was dried overnight in an oven at 140 °C. Dichloromethane (HPLC grade) and deuterochloroform ($CDCl_3$) used in the NMR titration experiment were refluxed under nitrogen atmosphere in the presence of CaH_2 and distilled prior to use. All other solvents (HPLC grade) were used as received. Pyrrolidinone, valerolactam, and caprolactam were purchased from Acros and used directly. L-/D-Alanine, L-/D-phenylalanine, and L-/D-leucine were purchased from Alfa Aesar and used without further purification. The synthesis of amide derivatives of α-amino acids followed the literature procedure, and similar results were obtained.[28] Rh_2(5*S*-MEPY)$_4$(CH_3CN)$_2$,[29] Rh_2(4*S*-MEOX)$_4$(CH_3CN)$_2$,[25] Rh_2(4*S*-MPPIM)$_4$(CH_3CN)$_2$,[30] (*S*)-/(*R*)-methyl 5-oxopyrrolidine-2-carboxylate (MEPYH),[29] and (*S*)-/(*R*)-methyl 2-oxooxazolidine-4-carboxylate (MEOXH)[25] were synthesized according to reported methods. The removal of axial acetonitriles on dirhodium compounds was performed by heating the dirhodium compounds at 110 °C under high vacuum (0.05−0.10 Torr) for 4 h. The complete removal of axial ligands was verified by ^{1}H NMR analysis with evidence for the absence of the methyl absorption of acetonitrile. The dirhodium compound that was free of axial ligand (sensitive to oxygen) was stored in a glovebox under argon.

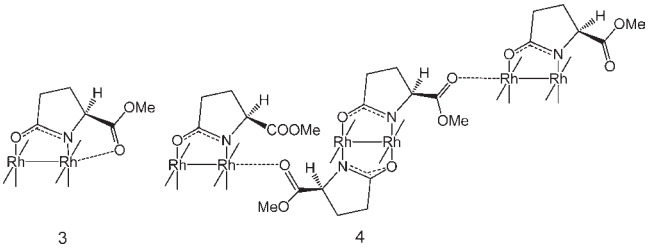
Instrumentation. Absorption measurements were performed on a Carey 50 Bio UV−vis spectrometer. A glass cell (1 cm path length) from Starna Cells, Inc., with screw top was used. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 400 MHz spectrometer. Chemical shifts were reported in ppm with the solvent signals as reference, and coupling constants (*J*) were given in Hertz. Optical rotation data were obtained on a Jasco DIP-1000 digital polarimeter.

Method. *General Procedure for UV−Vis Titrations.* Rh_2(5*S*-MEPY)$_4$ (15.0 mg, 0.0193 mmol) with no axial acetonitrile was weighed into a 10.00 mL volumetric flask inside a glovebox under argon. Dichloromethane (DCM) was added into the volumetric flask to the 10.00 mL mark to prepare the stock solution (1.93×10^{-3} M) of Rh_2(5*S*-MEPY)$_4$ in the glovebox. A DCM solution of ligand (1.98×10^{-1} M) was prepared in a similar way. A 3.00 mL portion of the Rh_2(5*S*-MEPY)$_4$ solution was transferred to the cell using a 3.00 mL pipet. The cell was sealed inside the glovebox with the screw top containing a septum. Prior to addition of ligand solution the UV−vis (400 nm-800 nm) spectrum of Rh_2(5*S*-MEPY)$_4$ was recorded. A 5.0 μL of ligand solution was added to the cell using a 10.0 μL syringe. The cell was inverted twice to ensure thorough mixing before the UV−vis spectrum was recorded at 20 °C. Fifteen additional aliquots (5.0 μL each) were sequentially added to the cell over 30 min, and the total change in volume was less than 3%. Upon addition of the concentrated ligand solution, the color of the mixture gradually turned from bright green to deep red. The UV−vis spectrum was recorded after the addition of each aliquot. Association constants were calculated by the method previously developed.[31]

Typical Procedure for NMR Measurement. Rh_2(5*S*-MEPY)$_4$ (15.0 mg, 0.0193 mmol) was weighed and then transferred into a 5 mm NMR tube, and 1.00 mL of deuterochloroform was added to the NMR tube inside the glovebox. The ligand solution was prepared in a similar way as in the UV−vis titration experiment except that deuterochloroform instead of dichloromethane was used. Both the NMR tube and the volumetric flask containing the ligand solution were sealed with appropriate septa. The ^{1}H NMR spectrum of Rh_2(5*S*-MEPY)$_4$ was recorded, and 5−50 μL of concentrated ligand solution (1.98×10^{-1} M) was added via syringe. The temperature of the measurements was 20 °C. After each addition the contents of the NMR tube were mixed, and the NMR spectrum of the mixture was recorded. The series of spectra was plotted in a single graph for analysis.

RESULTS AND DISCUSSION

The determination of equilibrium constants followed the procedures used by Drago[17] for dirhodium(II) carboxylates and previously reported by us for association of chiral dirhodium(II) carboxamidates with acetonitrile[24,25] and with aldehydes.[10a] In the course of our continuing studies of dirhodium carboxamidates as Lewis acids,[10,32,33] we were concerned with discrepancies that we were beginning to discover in equilibrium constant values. We recognized that although storage of these dirhodium compounds with acetonitrile ligands prevented their oxidation by atmospheric oxygen, the presence of axial ligands such as water or acetonitrile on dirhodium compounds distorted the values of spectroscopically determined equilibrium constants.[3,33] Furthermore, we recognized that complete removal of axial ligands produced an electrophilic rhodium center that could associate with another dirhodium compound to form dimers and/or oligomers.[1,10a] As a consequence, we decided to remove the axial acetonitrile ligands, producing Lewis acidic dirhodium carboxamidates whose resting state may be the uncoordinated compound, one internally coordinated with a ligand attachment (e.g., a carbonyl group of the MEPY ligand, **3**) or dimers/oligomers (**4**). As acetonitrile could be potentially removed by subjecting the solid dirhodium carboxamidate to high vacuum, and the absence of acetonitrile could be easily assessed by proton NMR spectroscopy through the absence of its methyl singlet, we evaluated this procedure with several chiral dirhodium(II) carboxamidate complexes. However, only with Rh_2(5*S*-MEPY)$_4$ could all of the acetonitrile be removed under high vacuum at 110 °C for 4 h. Removal of acetonitrile from Rh_2(4*S*-MEOX)$_4$ and Rh_2(4*S*-MPPIM)$_4$ was incomplete under the same conditions as used for Rh_2(5*S*-MEPY)$_4$, and this stronger association of acetonitrile prevented us from obtaining comparable data with these dirhodium(II) compounds.



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Our first goal was to establish the equilibrium constant for association of Rh_2(5*S*-MEPY)$_4$ with acetonitrile. Following the planned procedure, we used Rh_2(5*S*-MEPY)$_4$ from which acetonitrile had been completely removed, obtained the spectrum of this compound from 400 to 800 nm as a function of acetonitrile

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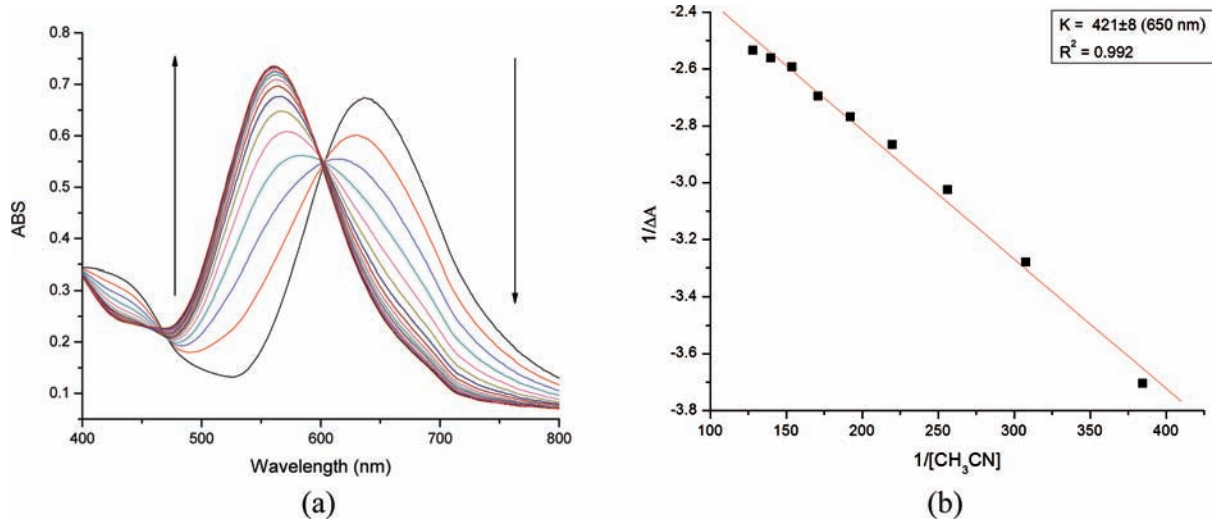

Figure 1. (a) Visible spectral changes accompanying sequential additions of 0.325 equiv of acetonitrile solution to $Rh_2(5S\text{-MEPY})_4$ (2.00×10^{-3} M) in DCM at room temperature. The concentration of acetonitrile increases by 6.5×10^{-4} M upon each addition of acetonitrile solution. (b) Linear regression analysis of data obtained at 650 nm with a plot of $1/\Delta A$ versus $1/[CH_3CN]$.

concentration (Figure 1), and determined the absorbance data at three different wavelengths (650, 660, and 670 nm). From this data we plotted $1/\Delta A$ versus $1/[CH_3CN]$ from which equilibrium constants were determined (correlation coefficient $R^2 >$ 0.99). Multiple experiments were performed, and recorded equilibrium constants were within ±5% from calculations at different wavelengths. In each experiment the observed sharp isosbestic point in the range of 580−610 nm guided our understanding that we were measuring the association of $Rh_2(5S\text{-MEPY})_4$ with only one acetonitrile ligand. The equilibrium constant determined in DCM by this process is 427 ± 9 M^{-1}, which is significantly greater than the previously reported value of 65 ± 6 M^{-1} (in 1,2-dichloroethane, DCE).[24] The cause of the discrepancy in values appeared to have originated from insufficient removal of axial acetonitrile ligand in the former determination of equilibrium constant. In that procedure, acetonitrile was removed in a vacuum oven at 60 °C and 25 Torr pressure, and the color change in the complex was used to validate axial ligand removal. In the present study acetonitrile in $Rh_2(5S\text{-MEPY})_4\text{-}(CH_3CN)_2$ was removed at 110 °C under 0.05−0.10 Torr pressure, and complete ligand removal was validated by ^{1}H NMR analysis with no sign of decomposition of $Rh_2(5S\text{-MEPY})_4$. To confirm this explanation, the equilibrium constant for association with acetonitrile was determined in DCE on $Rh_2(5S\text{-MEPY})_4$ from which acetonitrile had been completely removed, and that value was 122 ± 10 M^{-1}: nearly twice that previously reported. The λ_{max} for $Rh_2(5S\text{-MEPY})_4$ was 636 nm, and that for $Rh_2(5S\text{-MEPY})_4(CH_3CN)$ was 560 nm, which is same as previously reported.

Having established the procedure for determination of equilibrium constants with $Rh_2(5S\text{-MEPY})_4$, we measured equilibrium constants for coordination with simple amides. If binding of amides to dirhodium(II) carboxamidates occurs through a cooperative association between rhodium and the amide carbonyl together with hydrogen bonding between the amide N−H and a ligand oxygen of rhodium(II) carboxamidates, the equilibrium constants from association with acetamide, *N*-methylacetamide, and *N*,*N*-dimethylacetamide should reflect this cooperative binding mode. Indeed, these measurements show the expected decrease in equilibrium constants with decreasing numbers of N−H bonds (Table 1). Moreover, ^{1}H NMR spectrometric analysis also provides evidence for hydrogen bond formation between acetamide and $Rh_2(5S\text{-MEPY})_4$. When the first portion of acetamide (0.3 equiv) was added to the $Rh_2(5S\text{-MEPY})_4$ solution, the chemical shifts of the two protons of the NH_2 group were 8.32 and 5.67 ppm, respectively, and the acetamide CH_3 group had a chemical shift of 2.23 ppm. With further addition of acetamide (6.0 equiv), the chemical shifts of the two amide N−H hydrogens moved upfield to 6.09 and 5.59 ppm, respectively, and the chemical shift of the CH_3 group shifted upfield to 2.08 ppm. These observations are consistent with coordination of the carbonyl oxygen of acetamide with the vacant axial position of $Rh_2(5S\text{-MEPY})_4$, which explains the moderate change in chemical shifts of the acetamide CH_3 group (<0.2 ppm) and of one proton of the NH_2 group (<0.2 ppm). At the same time, the second proton of the acetamide NH_2 group bonds to one of the ligated oxygens of $Rh_2(5S\text{-MEPY})_4$, which is in accordance with the large change in chemical shift (>2.0 ppm) upon increasing acetamide concentration (Figure 2).[34] The two hydrogens of NH_2 group constitute two separate proton absorptions with distinctive chemical shifts, which informs us that the C−N single bond rotation of acetamide is restricted in the complex.[35] Furthermore, the degree of association should also be qualitatively visualized in the breadth of their absorbance (ΔA) versus wavelength plots, and this is what is observed (Figure 3).[36]

Table 1. Association Constants of $Rh_2(5S\text{-MEPY})_4$ with Acetamide, *N*-Methylacetamide, and *N*,*N*-Dimethylacetamide

ligand	$\lambda_{max\text{-}complex}$ (nm)	association constant K_1[a]
acetamide	600	400 ± 18
N-methylacetamide	608	67 ± 7
N,*N*-dimethylacetamide	616	19 ± 6

[a] Experiments were conducted three times at room temperature. Values reported are the average values. Concentrations of both $Rh_2(5S\text{-MEPY})_4$ and ligands were optimized to maximize the change in ABS with no drift of isosbestic point.

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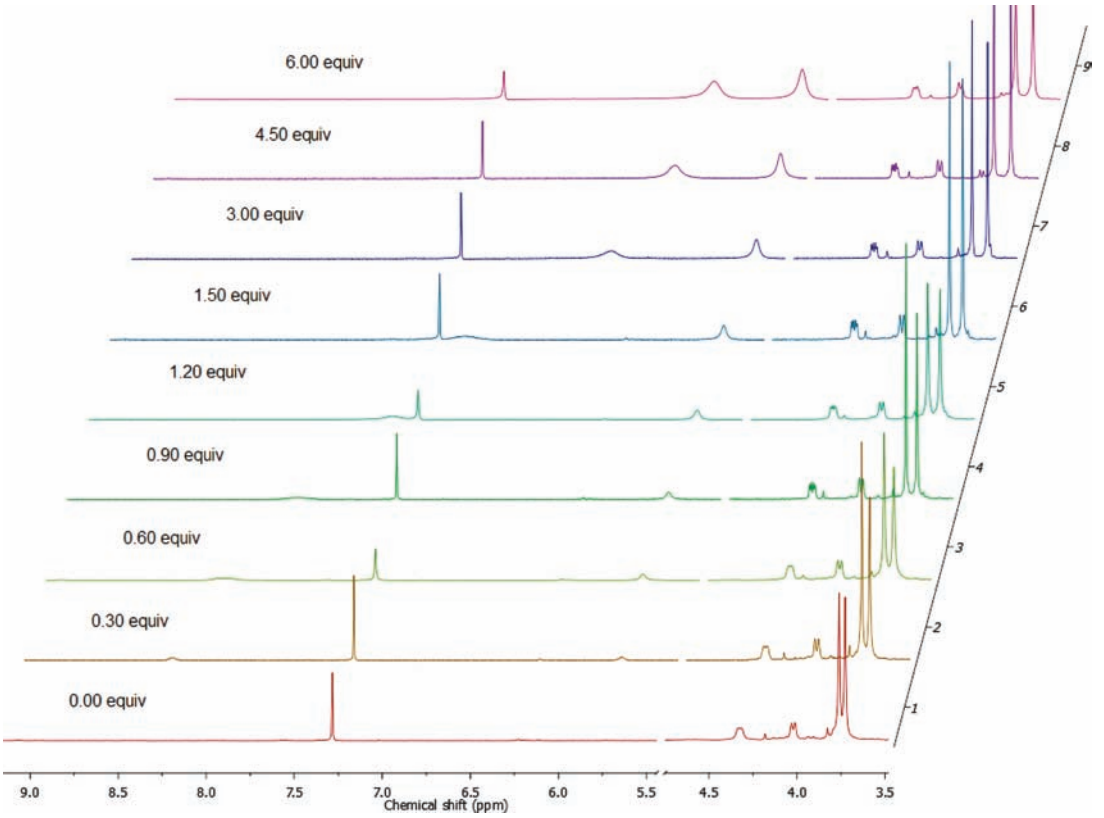

Figure 2. NMR titration of $Rh_2(5S\text{-MEPY})_4$ with acetamide. The numbers of equivalents are those of acetamide relative to $Rh_2(5S\text{-MEPY})_4$.

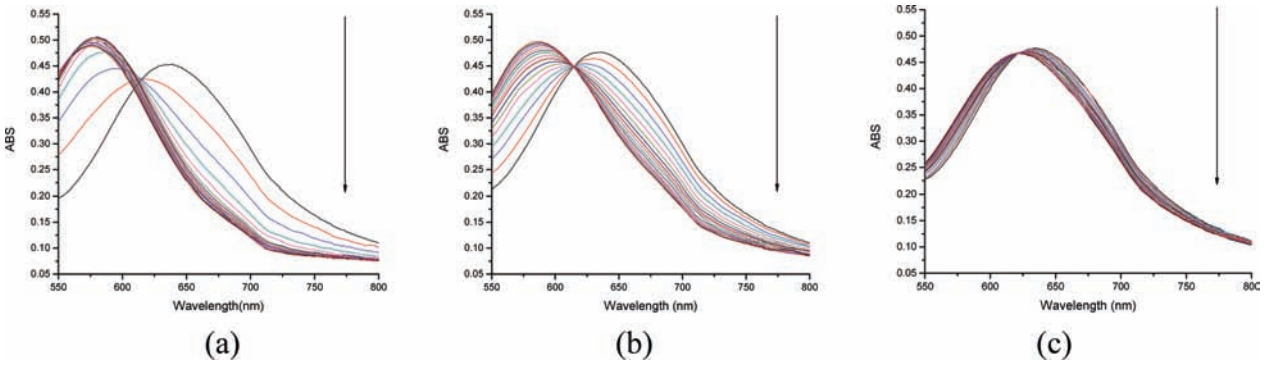

Figure 3. Spectral changes with sequential additions of 0.222 equiv of (a) acetamide, (b) *N*-methylacetamide, and (c) *N*,*N*-dimethylacetamide. Concentration of $Rh_2(5S\text{-MEPY})_4$ is 1.5×10^{-3} M, and concentrations of acetamide, *N*-methylacetamide, *N*,*N*-dimethylacetamide all increase by 3.33×10^{-4} M with each addition of corresponding amide solution.

The decrease in intensity of the absorption at 650 nm of $Rh_2(5S\text{-MEPY})_4$ under the same ligand concentrations of acetamide, *N*-methylacetamide and *N*,*N*-dimethylacetamide, reveals that acetamide has the highest binding affinity with $Rh_2(5S\text{-MEPY})_4$ and that *N*,*N*-dimethylacetamide has the lowest. Together with the association constants of the three amides (Table 1), the conclusion that that can be drawn from this data is that hydrogen bonding is a major determinant in complex formation between amides and $Rh_2(5S\text{-MEPY})_4$ (Figure 4). Consistent with this picture of amide bonding to $Rh_2(5S\text{-MEPY})_4$, the measured equilibrium constants with cyclic lactams, in which their carbonyl oxygen and N−H are positioned for cooperative association to one face of $Rh_2(5S\text{-MEPY})_4$, were 366 ± 17 for pyrrolidinone, 400 ± 15 for valerolactam, and 380 ± 6 for caprolactam. That *N*-methylacetamide provided an equilibrium constant between those of acetamide and *N*,*N*-dimethylacetamide may be a reflection of the percentage of the *E*-isomer that is positioned for the same cooperative association (3%).[37]

Although the current experiments focus on those coordination events under thermodynamic equilibrium with dirhodium carboxamidates, the conclusion that hydrogen bonding to a ligated oxygen is an important determinant of association in dirhodium(II) carboxamidates can be extended to dirhodium carboxylates and suggests how dirhodium(II) compounds may influence stereocontrol in catalytic reactions. For example, a computational study investigating dirhodium tetrakisformate catalyzed cyclopropenation

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reaction between methyl styryldiazoacetate and propyne as a model process suggests that there is hydrogen bonding between the terminal alkyne hydrogen and a ligated oxygen of rhodium in the transition state, although without experimental evidence.[38]

In addition to the influence of $Rh_2(5S\text{-MEPY})_4$ on amide coordination, the ^1H NMR experiment with acetamide (Figure 2) also shows that the associated acetamide perturbs the ligand methyl ester attachments of $Rh_2(5S\text{-MEPY})_4$. With increasing concentrations of acetamide in the solution, the two resonances for the methyl esters have different responses to ligated acetamide. The chemical shift of one methyl resonance remains nearly constant. However, the chemical shift of the other methyl resonance shifts upfield by 0.1 ppm. This differential response to acetamide is consistent with the expected interaction of a distal and proximal group as suggested by the fixed conformation that is depicted in Figure 4.

The complexes between the two enantiomers of a chiral amide and $Rh_2(5S\text{-MEPY})_4$ are diastereoisomers. To determine if $Rh_2(5S\text{-MEPY})_4$ can differentiate amide enantiomers we used lactams whose positioning of carbonyl and N−H groups would maximize their interactions. In separate experiments the equilibrium constants for association of $Rh_2(5S\text{-MEPY})_4$ with both MEPYH and MEOXH in their *R*- and *S*-configurations were determined, and these results are reported in Table 2. Comparing the association constants of $Rh_2(5S\text{-MEPY})_4$ with *S*-MEPYH and *S*-MEOXH as well as with *R*-MEPYH and *R*-MEOXH, there is clear evidence that MEPYH has a higher binding affinity than MEOXH irrespective of their configurations. Furthermore, the *S*-configurated ligands have higher association constants than the *R*-configurated ligands. Compared to the values for equilibrium constants of acetamides in Table 1, those for MEPYH and MEOXH ligands fall between those for acetamide and *N*-methylacetamide, suggesting that factors other than the unperturbed amide−$Rh_2(5S\text{-MEPY})_4$ association represented in Figure 4, namely electronic or steric influences, are operative.

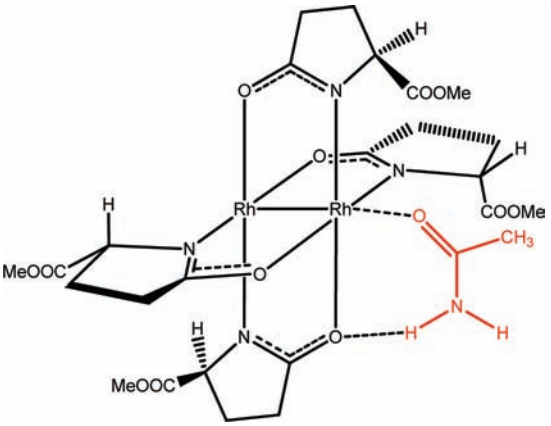
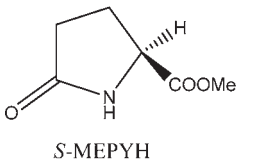


Figure 4. Proposed coordination of acetamide with $Rh_2(5S\text{-MEPY})_4$.

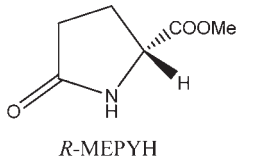
The values of K_S/K_R (the ratios of K_1 for the two enantiomers of the same amide) show the complexity that can be encountered in interpreting the outcome. The difference between the MEPYH and MEOXH ligands is small: they differ only by the placement of an oxygen atom or a methylene group adjacent to the carbonyl group. Nevertheless, the outcome is larger than expected: the K_S/K_R for MEPYH is only 1.1 but with MEOXH the ratio is 2.5.

An NMR titration experiment offers additional insight into the coordination of MEPYH and MEOXH with $Rh_2(5S\text{-MEPY})_4$. MEOXH was selected for this experiment because this ligand can be better differentiated than MEPYH from $Rh_2(5S\text{-MEPY})_4$. Addition of aliquots of *S*- and *R*-MEOXH to $Rh_2(5S\text{-MEPY})_4$ under identical conditions provide the data that are shown in Figure 5. Proton signals from both MEOXH and $Rh_2(5S\text{-MEPY})_4$ show significant changes upon sequential additions of ligand MEOXH. The most pronounced change in the chemical shifts for $Rh_2(5S\text{-MEPY})_4$ comes from one of the methyl resonances that moved upfield by 0.08 ppm with the addition of either *R*- or *S*-MEOXH. At the same time, the chemical shift of the other methyl resonance did not change to any significant

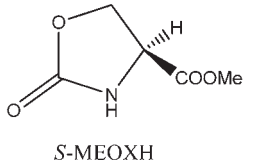
Table 2. Association Constants of $Rh_2(5S\text{-MEPY})_4$ with Chiral Lactams



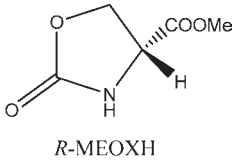
S-MEPYH



R-MEPYH



S-MEOXH



R-MEOXH

ligand	association constant, K_1[a]	K_S/K_R[b]
(*S*)-methyl 5-oxopyrrolidine-2-carboxylate (*S*-MEPYH)	174 ± 9	1.1
(*R*)-methyl 5-oxopyrrolidine-2-carboxylate (*R*-MEPYH)	152 ± 7	
(*S*)-methyl 2-oxooxazolidine-4-carboxylate (*S*-MEOXH)	103 ± 7	2.5
(*R*)-methyl 2-oxooxazolidine-4-carboxylate (*R*-MEOXH)	41 ± 5	

[a] Each entry was repeated for three times at room temperature, and values reported are average values. [b] K_S/K_R stands for the ratio of K_1 of *S*-enantiomer to *R*-enantiomer.

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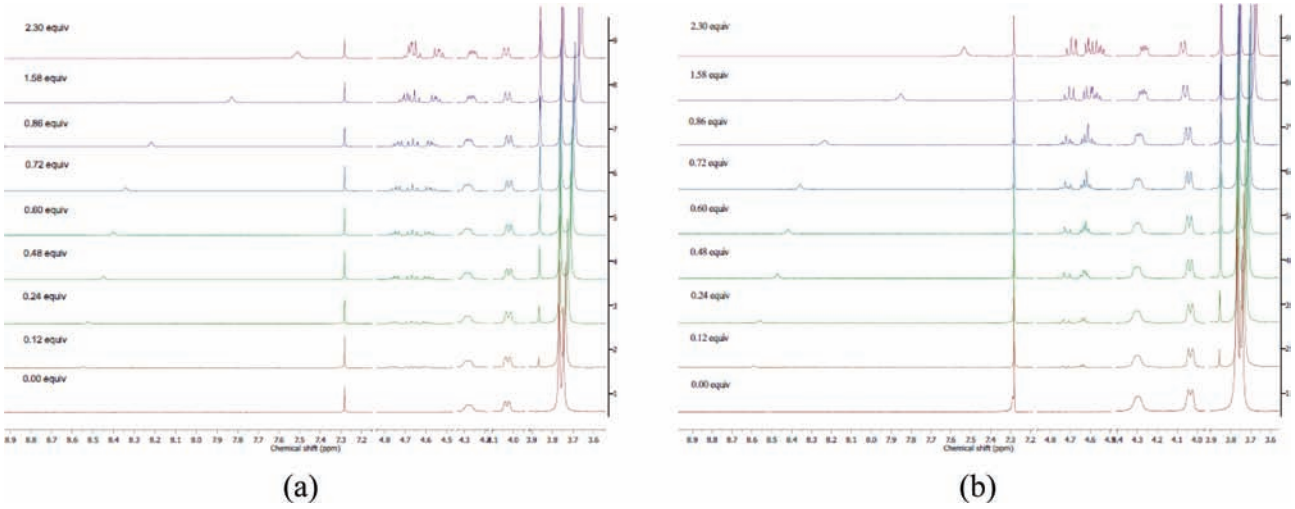

Figure 5. NMR titration of $Rh_2(5S\text{-MEPY})_4$ with (a) *S*-MEOXH and (b) *R*-MEOXH. The number of equivalents of MEOXH relative to $Rh_2(5S\text{-MEPY})_4$ are denoted in the NMR spectra.

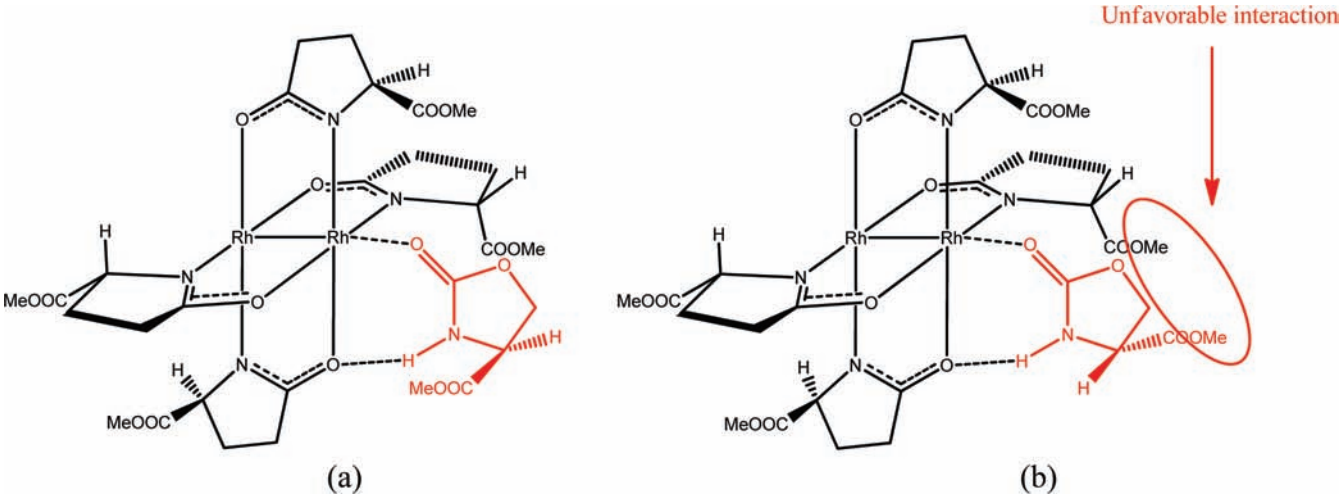

Figure 6. Modes of coordination of (a) *S*-MEOXH and (b) *R*-MEOXH with $Rh_2(5S\text{-MEPY})_4$. The coordination shown in part b projects the carboxylate group of *R*-MEOXH in close proximity to a methyl ester group of $Rh_2(5S\text{-MEPY})_4$.

degree. Complexation with MEOXH has a greater influence on one methyl ester group than on the other, and this is consistent with a fixed association of MEOXH with $Rh_2(5S\text{-MEPY})_4$. This observation is further confirmed by the relatively large change (~1.0 ppm) in chemical shift of NH group upon coordination, which indicates hydrogen bonding between the NH group and a rhodium-ligated oxygen. Both *S*- and *R*-MEOXH show similar results upon coordination. Thus, the two enantiomers of MEOXH share a similar coordination pattern with $Rh_2(5S\text{-MEPY})_4$, and chiral discrimination is very likely to derive in part from the unfavorable interaction of *R*-MEOXH with one of the methyl esters of $Rh_2(5S\text{-MEPY})_4$ (see part b in Figure 6). However, another cause may be interactions at the face of the dirhodium compound by the ring oxygen of the ligand.

Since $Rh_2(5S\text{-MEPY})_4$ can distinguish between two enantiomers of chiral lactams, is it possible for $Rh_2(5S\text{-MEPY})_4$ to differentiate between the two enantiomers of acyclic chiral amides? Three pairs of acyclic chiral acetamides (**5*S***, **5*R***, **6*S***, **6*R***, **7*S***, **7*R***) prepared from α-amino acids were subjected to UV−vis titration experiments. The principal conformation of these amides is *s-trans* in which the carbonyl oxygen and N−H bond are trans (or *E*),[39] rather than the *cis* (or *Z*) arrangement of lactams such as MEPYH and MEOXH. Consequently, we anticipated that the primary mode of association would be through the carbonyl oxygen to rhodium and that hydrogen bonding would not be a determinant in complex formation for these α-amino acid derivatives. As expected, comparing the equilibrium constants for the three pairs of acyclic amides (Table 3) with those for MEPYH and MEOXH (Table 2), cyclic amides have higher binding affinity toward dirhodium compounds than do acyclic amides. The absence of hydrogen bonding for acyclic amides significantly reduces their overall binding affinity with $Rh_2(5S\text{-MEPY})_4$. In addition, proton NMR titration experiments of $Rh_2(5S\text{-MEPY})_4$ with *N*-acetyl-L-phenylalanine methyl ester show that the change in chemical shift for its NH group upon addition to $Rh_2(5S\text{-MEPY})_4$ falls within a comparable range to those of all other protons on the same molecule (~0.08 ppm) which is consistent with association

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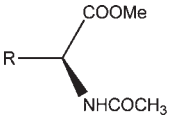
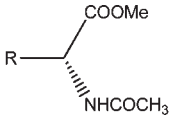
Table 3. Association Constants of $Rh_2(5S\text{-MEPY})_4$ with Amino Acid Derivatives



R = Me, 5*S*
R = *i*-Bu, 6*S*
R = Bn, 7*S*



R = Me, 5*R*
R = *i*-Bu, 6*R*
R = Bn, 7*R*

ligand	association constant K_1[a]	K_R/K_S[b]
N-acetyl-L-alanine methyl ester (**5*S***)	23 ± 9	~1.0
N-acetyl-D-alanine methyl ester (**5*R***)	20 ± 4	
N-acetyl-L-leucine methyl ester (**6*S***)	22 ± 5	3.3
N-acetyl-D-leucine methyl ester (**6*R***)	71 ± 7	
N-acetyl-L-phenylalanine methyl ester (**7*S***)	17 ± 3	3.3
N-acetyl-D-phenylalanine methyl ester (**7*R***)	54 ± 9	

[a] Each entry was repeated three times at room temperature, and values reported are average values. [b] K_R/K_S represents the ratio of K_1 of *R*-enantiomer to *S*-enantiomer.

of the amide carbonyl oxygen at the axial coordination site of $Rh_2(5S\text{-MEPY})_4$ without hydrogen bonding. This association can be explained as due to the preferred *trans* (*E*)-conformation of these amides that places the amide carbonyl oxygen and the N−H on opposite sides of the C−N bond, unlike the *cis* (*Z*)-arrangement of MEPYH and MEOXH. The methyl ester attachments of $Rh_2(5S\text{-MEPY})_4$ also exhibit similar behavior to that shown in Figure 5 indicating differential interaction of the acyclic chiral amide with a distal and proximal methyl ester resonances.

The primary differences among the three pairs of amino acid derivatives are the side chains. The K_R/K_S ratios correlate well with the sizes of the side chains. With the *N*-acetyl alanine methyl ester enantiomers, the side chain is only a methyl group; within the uncertainty level of our measurements there is no difference in association constants for its two enantiomers. When the side chains increase in size from methyl to isopropyl and phenyl, the ratios of K_R/K_S have the same value: 3.3.

CONCLUSION

Because chiral dirhodium carboxamidates have a rigid chiral environment around their rhodium atoms, they can differentiate both cyclic and acyclic chiral amide enantiomers through cooperative association. The binding constants of lactams and amino acid derivatives with $Rh_2(5S\text{-MEPY})_4$ have been determined by a UV−vis titration method. Cyclic lactams with their *syn* N—H and C═O orientation have higher association constants with dirhodium carboxamidates than do acyclic amides having the *anti* N—H and C═O orientation. The higher equilibrium constants are a direct result of hydrogen bonding between $Rh_2(5S\text{-MEPY})_4$ and the NH group of cyclic amides. Selective perturbation of one methyl ester attachment of $Rh_2(5S\text{-MEPY})_4$ that is evident in the NMR spectra of the association complex is due to the positioning of the amide relative to the MEPY ligand's carboxylate attachments and is seen with both cyclic and acyclic amides. The chiral dirhodium carboxamidate $Rh_2(5S\text{-MEPY})_4$ is capable of differentiating chiral amides, and relatively high K_S/K_R values have been found with both cyclic and acyclic amides.

ASSOCIATED CONTENT

Supporting Information. NMR titration data of $Rh_2(5S\text{-MEPY})_4$ with *N*-acetyl L-phenylalanine methyl ester and additional UV−vis titration data. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) Chifotides, H. T.; Dunbar, K. R. In *Multiple Bonds Between Metal Atoms*, 3rd ed.; Cotton, F. A., Murillo, C. A., Walton, R. A., Eds.; Springer: New York, 2005; Chapter 12.
(2) Evans, P. A. *Modern Rhodium-Catalyzed Organic Reactions*; Wiley-VCH: New York, 2005.
(3) Doyle, M. P.; Ren, T. In *Progress in Inorganic Chemistry*; Karlin, K. D., Ed.; Wiley-Interscience: New York, 2001; Vol. 49, p 113.
(4) Lou, Y.; Remarchuk, T. P.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 14223.
(5) (a) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704.(b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley-Interscience: New York, 1998.
(6) (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (b) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.
(7) Müller, P. *Acc. Chem. Res.* **2004**, *37*, 243.
(8) Wee, A. G. H. *Curr. Org. Synth.* **2006**, *3*, 499.
(9) (a) Trindade, A. F.; Góis, P. M. P.; Veiros, L. F.; André, V.; Duarte, M. T.; Alfonso, C. A. M.; Caddick, S.; Cloke, F. G. N. *J. Org. Chem.* **2008**, *73*, 4076. (b) Snyder, J. P.; Padwa, A.; Stengal, T.; Arduengo, A. J., III; Jockisch, A.; Kim, H.-L. *J. Am. Chem. Soc.* **2001**, *123*, 11318.
(10) (a) Doyle, M. P.; Valenzuela, M.; Huang, P. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5391. (b) Doyle, M. P.; Phillips, I. M.; Hu, W. H. *J. Am. Chem. Soc.* **2001**, *123*, 5366.
(11) (a) Doyle, M. P. *J. Org. Chem.* **2006**, *71*, 9253.(b) Doyle, M. P.; Timmons, D. In *Multiple Bonds Between Metal Atoms*, 3rd ed.; Cotton, F. A., Murillo, C. A., Walton, R. A., Eds.; Springer: New York, 2005; Chapter 13. (c) Doyle, M. P. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 5.5.
(12) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.
(13) Padwa, A. *J. Org. Chem.* **2009**, *74*, 6421.
(14) Merlic, C. A.; Zechman, A. L. *Synthesis* **2003**, 1137.
(15) (a) Aguirre, J. D.; Lutterman, D. A.; Angeles-Boza, A. M.; Dunbar, K. R.; Turro, C. *Inorg. Chem.* **2007**, *46*, 7494. (b) Chifotides, H. T.; Dunbar, K. R. *Acc. Chem. Res.* **2005**, *38*, 146. (c) Chifotides, H. T.; Fu, P. K.-L.; Dunbar, K. R.; Turro, C. *Inorg. Chem.* **2004**, *43*, 1175.
(16) (a) Chen, J.; Kostic, N. M. *Inorg. Chem.* **1988**, *27*, 2682. (b) Trynda, L.; Pruchnik, F. *J. Inorg. Biochem.* **1995**, *58*, 69.
(17) (a) Drago, R. S.; Long, J. R.; Cosmano, R. *Inorg. Chem.* **1981**, *20*, 2920. (b) Drago, R. S. *Inorg. Chem.* **1982**, *21*, 1697. (c) Drago, R. S.; Long, J. R.; Cosmano, R. *Inorg. Chem.* **1982**, *21*, 2196.
(18) (a) Doyle, M. P.; Colesman, M. R.; Chinn, M. C. *Inorg. Chem.* **1984**, *23*, 3684. (b) Doyle, M. P.; Mahapatro, S. N.; Caughey, A. C.; Chinn, M. S.; Colsman, M. R.; Harn, N. K.; Redwine, A. E. *Inorg. Chem.* **1987**, *26*, 3070.

(19) Schurig, V. *Inorg. Chem.* **1986**, *25*, 945.
(20) Doyle, M. P.; High, K. G.; Nesloney, C. L.; Clayton, T. W., Jr.; Lin, J. *Organometallics* **1991**, *10*, 1225.
(21) (a) Dikarev, E. V.; Shpanchenko, R. V.; Andreini, K. W.; Block, E.; Jin, J.; Petrukhina, M. A. *Inorg. Chem.* **2004**, *43*, 5558. (b) Cotton, F. A.; Dikarev, E. V.; Feng, X. *Inorg. Chim. Acta* **1995**, *237*, 19.
(22) (a) Das, K.; Simmons, E. L.; Bear, J. L. *Inorg. Chem.* **1977**, *16*, 1268. (b) Rainen, L.; Howard, R. A.; Kimball, A. P.; Bear, J. L. *Inorg. Chem.* **1976**, *14*, 2752.
(23) Hirva, P.; Esteban, J.; Lloret, J.; Lahuerta, P.; Pérez-Prieto, J. *Inorg. Chem.* **2007**, *46*, 2619.
(24) Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.* **1993**, *115*, 9968.
(25) Doyle, M. P.; Dyatkin, A. B.; Protopopova, M. N.; Yang, C. I.; Miertschin, C. S.; Winchester, W. R.; Simonsen, S. H.; Lynch, V.; Ghosh, R. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 163.
(26) Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A.; Martin, S. F.; Spaller, M. R.; Liras, S. *J. Am. Chem. Soc.* **1995**, *117*, 11021.
(27) Bear, J. L.; Lifsey, R. S.; Chau, L. K.; Ahsan, M. Q.; Korp, J. D.; Chavan, M.; Kadish, K. M. *J. Chem. Soc., Dalton Trans.* **1989**, 93.
(28) (a) Applewhite, T. H.; White, H.; Niemann, C. *J. Am. Chem. Soc.* **1958**, *80*, 1465. (b) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.
(29) Doyle, M. P.; Winchester, W. R.; Protopopova, M. N.; Kazala, A. P.; Westrum, L. J. *Org. Synth.* **1996**, *73*, 13.
(30) Doyle, M. P.; Colyer, J. T. *Tetrahedron: Asymmetry* **2003**, *14*, 3601.
(31) Brown, K. L. *Inorg. Chim. Acta* **1979**, *37*, L513.
(32) Wang, Y.; Wolf, J.; Zavalij, P.; Doyle, M. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1439.
(33) Wang, X.; Li, Z.; Doyle, M. P. *Chem. Commun.* **2009**, 5612.
(34) Jeffrey, G. A. *An Introduction to Hydrogen-Bonding*; Oxford University Press, Inc: New York, 1997.
(35) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2006.
(36) Note that Figure 3a exhibits the expected single isosbestic point only through the first few additions, then the point of intersection drifts to lower wavelengths. This could be due to the association of a second acetamide to the unoccupied axial position of the dirhodium(II) core or to association of a second acetamide to the coordinated acetamide.
(37) Eliel, E. E.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Carbon Compounds*; Wiley: New York, 1994; pp 620−621.
(38) Briones, J. F.; Hansen, J.; Hardcastle, K. I.; Autschbach, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 17211.
(39) Plassa, M.; Griehlb, C.; Kolbe, A. *J. Mol. Struct.* **2001**, *570*, 203.