Supramolecular Ligands

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METAMORPhos: Adaptive Supramolecular Ligands and Their Mechanistic Consequences for Asymmetric Hydrogenation**

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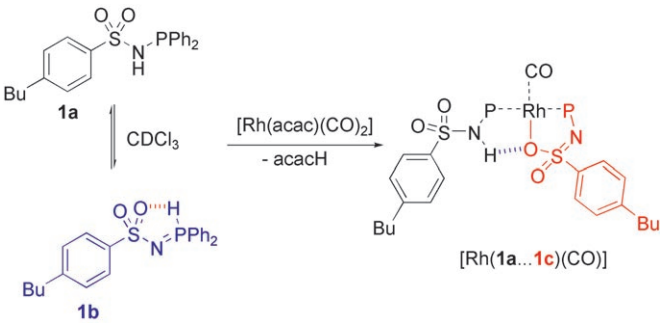
Bidentate ligands are an important class of ligands for transition metal catalysis[1] even though their synthesis is usually more tedious and time-consuming than that of their monodentate counterparts. Supramolecular ligands[2] have recently been introduced as a new class of ligands that form by the self-assembly of ligand building blocks through specific interactions. For example, it has been demonstrated that hydrogen bonds,[3] ionic interactions,[4] and metal–ligand interactions[5] can all be involved in the assembly process. Interestingly, the number of supramolecular bidentate ligands grows exponentially with the number of available building blocks, which clearly shows the power of the supramolecular approach, therefore this approach is generally associated with combinatorial routes to rapid catalyst discovery. The dynamic character inherent to the class of supramolecular ligands could also introduce new reactivity, and as such we are currently exploring the character of this new class of ligands. Herein we report the synthesis of METAMORPhos (from the Greek: *meta* "change" + *morphe* "shape"), a supramolecular ligand building block which dynamically adapts to various tautomeric forms, even when coordinated to a metal center. This adaptive behavior gives rise to a unique mechanism in the asymmetric hydrogenation reaction.

METAMORPhos ligand **1** was prepared by a simple condensation reaction between *para-n*-butylphenylsulfonamide and Ph_2PCl[6] and was initially designed as a novel ligand with a hydrogen bond motif (donor/acceptor type) close to the phosphorus ligand. Upon characterization we found that the compound exists as two different tautomers in $CDCl_3$ that are in slow exchange on the NMR time-scale (Scheme 1).[7] The peaks of these tautomers (**1a** and **1b**) in the ^{31}P NMR spectrum were assigned on the basis of their specific P-H couplings of 7 and 490 Hz, respectively. No coalescence was observed in the temperature window of 323 to 223 K,



Scheme 1. Tautomeric equilibrium of METAMORPhos ligand **1** and its coordination behavior with $[Rh(acac)(CO)_2]$ (phenyl groups have been omitted in the complex for clarity).

although the **1a**/**1b** ratio changed dramatically from 4.43 at 323 K to 0.85 at 223 K. This interesting exchange behavior between the tautomeric forms of ligand **1** stimulated us to explore the coordination properties of the ligand and their effects on catalytic reactions.

The unusual coordination behavior of ligand **1** became evident when two equivalents of **1** were added to a $CDCl_3$ solution of $[Rh(acac)(CO)_2]$. Thus, in contrast to the usually formed *cis*-bis-phosphorus Rh(acac) complex, the AB pattern observed in the ^{31}P NMR spectrum indicated the formation of a complex with two *different* ligands, and the large P-P coupling constant ($^2J_{P1,P2} = 335$ Hz) pointed to a *trans* geometry (Figure 1). The ^1H and ^{13}C NMR spectra show the

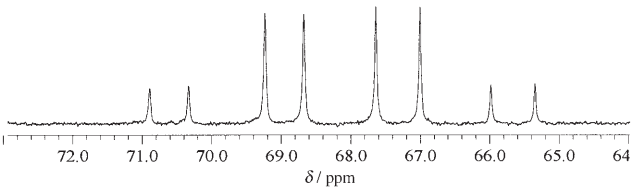


Figure 1. ^{31}P NMR spectrum of [Rh(**1a**···**1c**)(CO)] (202.3 MHz, 12.68 mM in $CDCl_3$, 223 K).

stoichiometric formation of acacH, thus demonstrating that complex formation proceeds by a proton transfer from tautomer **1b** to the acac anion to yield tautomer **1c** and acacH (Scheme 1).[6] The complex was characterized by FAB mass spectrometry (*m*/*z* 925.31) and solution IR ($\nu(CO) = 1986\ cm^{-1}$) and NMR spectroscopy. A hydrogen-bonding interaction, presumably between the NH moiety of coordinated **1a** and the S–O group of **1c**, was evident from solution IR spectroscopy—the NH vibration is shifted from 3341 (free ligand) to 3281 cm^{-1} (coordinated ligand). Dilution studies

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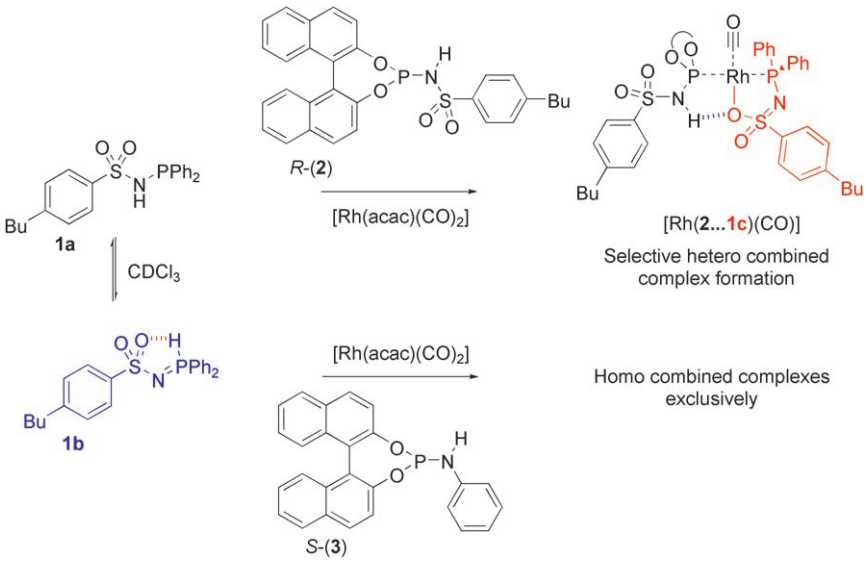
revealed that the signal of the hydrogen-bonded NH proton in the ^{1}H NMR spectrum is concentration independent in the [Rh(**1a**···**1c**)(CO)] complex, in line with the presence of an intramolecular hydrogen bond between **1a** and **1c** (Scheme 1 and Figure 2).[6] The calculated structure (by density functional theory) shows that if the anionic ligand **1c** coordinates to the metal in a P,O-chelate fashion, the oxygen atom is in an ideal position for hydrogen-bond formation with the NH group of the ligand coordinated *trans* to the phosphorus (Figure 2).

We anticipated that the dual character of the ligand—hydrogen-bond acceptor in the anionic form and hydrogen-bond donor in the neutral state—should also provide new routes for the



Scheme 2. Formation of [Rh(**2**···**1c**)(CO)] and a control experiment with ligand **3**.

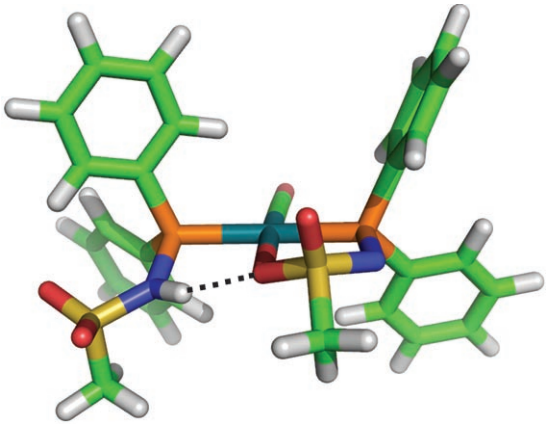


Figure 2. DFT calculated structure of [Rh(**1a**···**1c**)(CO)]. C green, H white, O red, S yellow, N purple, P orange, Rh turquoise.

selective formation of hetero-bisligated metal complexes by mixing two slightly different METAMORPhos-type ligands. We therefore prepared chiral ligand **2** which, in contrast to **1**, gives only one signal in the ^{31}P NMR spectrum. Ligand **2** apparently exists in only one dominant tautomeric form, presumably because of the different basicity of the phosphorus atom. Interestingly, a $CDCl_3$ solution of ligands **1** and **2** and [Rh(acac)$(CO)_2$] yields selectively the hetero self-assembled complex [Rh(**2**···**1c**)(CO)] which, as is clear from the coupling constants in the ^{31}P NMR spectrum, again has the phosphorus ligands in the *trans* position (Scheme 2 and Figure 3). In contrast, a $CDCl_3$ solution of ligand **1**, chiral ligand **3**,[8] and [Rh(acac)$(CO)_2$] yields only the homo Rh complexes, thereby indicating the importance of subtle changes in the acidity of the NH group for the formation of such supramolecular structures (Scheme 2).

We were interested in determining whether the typical METAMORPhos coordination would also result in new catalytic properties for its rhodium complexes. As expected,

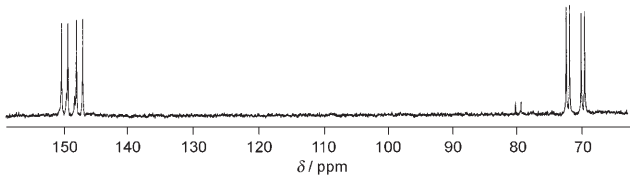
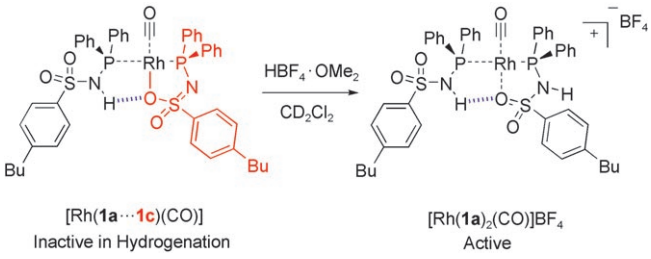


Figure 3. ^{31}P NMR spectrum of [Rh(**2**···**1c**)(CO)] (202.3 MHz, 298 K, 36.5 mM in $CDCl_3$; $J_{P1,P2}$ = 470.8 Hz).

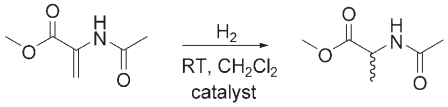
the neutral Rh^I complexes [Rh(**1a**···**1c**)(CO)] and [Rh(**2**···**1c**)(CO)] were found to be inactive in the Rh-catalyzed asymmetric hydrogenation of methyl 2-acetamidoacrylate (MAA). Interestingly, however, these neutral complexes can be converted into their cationic analogs by simple protonation of the ligand with HBF_4·OMe_2,[6] which leads to active complexes for the hydrogenation reaction (Scheme 3).[6] For the remaining catalysis experiments, however, the active metal complexes were generated in situ from the commonly used precursor [Rh(nbd)$_2$][BF_4] (nbd = norbornadiene). This is obviously a more convenient method than activation of the neutral complexes with HBF_4·OMe_2. Furthermore, because it is difficult to precisely dose HBF_4·OMe_2 on a catalytic scale, the activation route is also less reproducible. The various Rh complexes based on homo- and hetero-METAMORPhos



Scheme 3. Protonation of the neutral catalytically inactive complex [Rh(**1a**···**1c**)(CO)] with HBF_4·OMe_2 gives the catalytically active cationic [Rh(**1a**)$_2$(CO)BF_4].

systems were applied in the Rh-catalyzed asymmetric hydrogenation of MAA and the results compared to those obtained with complexes based on ligand **3** and PPh_3. All reactions went to completion after 8 h, even when only 0.1 mol% of catalyst was used (entries 8–14, Table 1). However, whereas

Table 1: Rh-catalyzed asymmetric hydrogenation of MAA.



MAA

Entry	L^{A}[a]	L^{B}[a]	Rh [mM]	MAA/Rh	*ee* [%]	*R*,*S*
1	**1**	**1**	1	10^2	–	–
2	**1**	**2**	1	10^2	90.6	*S*
3	**2**	**2**	1	10^2	95.8	*S*
4	PPh_3	PPh_3	1	10^2	–	–
5	PPh_3	**3**	1	10^2	13.3	*S*
6	**3**	**3**	1	10^2	62.1	*R*
7	**3**	**1**	1	10^2	41.7	*R*
8	**1**	**1**	0.1	10^3	–	–
9	**1**	**2**	0.1	10^3	91.7	*S*
10	**2**	**2**	0.1	10^3	99.0	*S*
11	PPh_3	PPh_3	0.1	10^3	–	–
12	PPh_3	**3**	0.1	10^3	3.6	*S*
13	**3**	**3**	0.1	10^3	65.0	*R*
14	**3**	**1**	0.1	10^3	46.0	*R*

[a] Ligands L^A and L^B were added in a 1:1 ratio; $(L^A+L^B)/[Rh(nbd)_2][BF_4]=2.4:1$; solvent: CH_2Cl_2. Reaction performed at 10 bar H_2 pressure at 298 K for 8 h. Full conversions were obtained in all cases.

complexes based on the new ligand **2** provided the product with the highest *ee* (99%; entry 10, Table 1), the hetero-METAMORPhos ligand structure **2**···**1c** was found to be twice as active (TOF: 1.2×10^3 mol mol^{-1} h^{-1}, Table 2) whilst still being selective (92% *ee*; entry 9, Table 1).

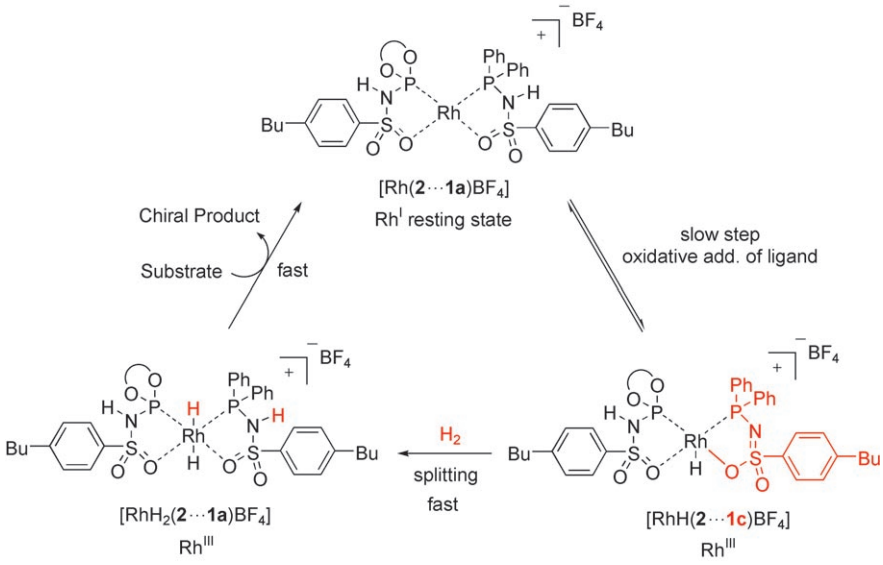
Whereas the high selectivities displayed by the METAMORPhos-based catalysts are interesting, they do not provide much information about the role of this new class of ligands in the metal complex. We therefore studied the kinetics of the Rh-catalyzed hydrogenation reaction using the various METAMORPhos ligands by systematically varying the hydrogen pressure, substrate concentration, and catalyst concentration and determined the reaction rate from the gas-uptake profiles. Much to our surprise, the catalysts based on ligands **1a**···**1c**, **2**···**1c**, and **2**···**2** all showed different behavior, as summarized in Table 2 (P = positive order, 0 = zero order). Strikingly, the most active rhodium complex (that based on ligand **2**···**1c**; TOF: 1.2×10^3 mol mol^{-1} h^{-1}) shows very unusual kinetic behavior as it is zero order in substrate concentration *and* in H_2 pressure which is, as far as

Table 2: Kinetics and TOFs for the Rh-catalyzed asymmetric hydrogenation of MAA obtained for various METAMORPhos ligands.

Entry	Cat. structure[a]	H_2	Substrate	Catalyst	TOF[b]
1	[Rh(**1a**···**1c**)]	P	0	P	652
2	[Rh(**2**···**1c**)]	0	0	P	1186
3	$[Rh(\mathbf{2})_2]$	P	P	P	574

[a] Complex based on self-assembled ligand **1**, ligand **2**, or a combination of both. [b] TOF [mol mol^{-1} h^{-1}] determined from H_2 gas-uptake profiles at 20% conversion. P: positive order; 0: zero order. Conditions: 10 bar of H_2 pressure, 0.1 mM of catalyst in CH_2Cl_2, with a MAA/Rh ratio of 10^3:1, $(L^A+L^B)/Rh=2.4:1$, at 298 K. Kinetics: H_2 pressure 4–16 bar, substrate concentration 50–200 mM, catalyst concentration 0.025–0.1 mM.

we know, unprecedented. Based on the coordination behavior and the kinetics we propose a new mechanism for asymmetric hydrogenation that is specific for METAMORPhos ligand systems of the type **2**···**1** (Scheme 4). The rate-determining step in this mechanism must be intramolecular as the reaction rate depends only on the catalyst concentration, therefore we suggest that this rate-determining step involves the intramolecular oxidative addition of the neutral ligand **1a** of the Rh(**2**···**1a**) cation to provide the cation HRh(**2**···**1c**). This highly reactive cationic Rh^{III} hydride species rapidly heterolytically splits a molecule of H_2, with the anionic ligand **1c** functioning as the base, to give the cationic Rh^{III} dihydride species $H_2Rh(\mathbf{2}\cdots\mathbf{1a})$.[9] Subsequent decoordination of the oxygen atoms of the ligands creates the required vacant sites for substrate coordination, and the cationic Rh^{I} resting state is re-formed after hydride migration and reductive elimination of the product.[10] Heterolytic splitting of molecular hydrogen could also take place after substrate coordination and the first migration reaction, but because these steps all occur after the rate-determining step we cannot distinguish between these different sequences. The kinetic behavior of the current complex, which can be explained by the intramolecular



Scheme 4. Proposed mechanism for the Rh-catalyzed asymmetric hydrogenation of MAA based on the hetero METAMORPhos ligand system **2**···**1**.

oxidative addition of METAMORPhos to the rhodium, is different from any other reported in the literature[10] and is clearly a consequence of the adaptability of METAMORPhos ligands.

In summary, we have introduced METAMORPhos as a new class of supramolecular ligands that are adaptive through tautomerism. This property gives rise to a new coordination behavior, and the dual character also enables the selective formation of hydrogen-bonded hetero bis-ligated metal complexes. The adaptive behavior of the ligand when coordinated to the metal center gives rise to rhodium complexes that show unique kinetics—zero order in H_2 and substrate—in the asymmetric Rh-catalyzed hydrogenation of MAA. Since the enantioselectivities obtained are high (above 90%), we are currently exploring whether this strategy is suited to creating large ligand libraries for fast catalyst discovery by a combinatorial approach.

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