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Sulfonamido−Phosphoramidite Ligands in Cooperative Dinuclear Hydrogenation Catalysis

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Natural enzymes often contain active sites constructed from multiple metal centers that are capable of cooperative substrate activation.[1] Reports of artificial dinuclear structures for homogeneous transition-metal catalysis are still scarce, despite interesting examples showing enhanced reactivity and selectivity compared with the analogous mononuclear species.[2] Indeed, all of the rhodium-based catalysts for asymmetric hydrogenation of alkenes used to date are mononuclear, and the potential for use of bimetallic analogues in this industrially important reaction is unexplored. We now present a new class of anionic P−N-bridging ligands based on the sulfonamido−phosphoramidite scaffold that form neutral boat-shaped Rh−P−N−Rh-bridged dinuclear species, which are active in the asymmetric hydrogenation of acetamidoalkene substrates via a proposed unprecedented cooperative binuclear mechanism.

Functionalized phosphoramidite ligands of the type **1H** (and **2H**) can be prepared by simple condensation of a sulfonamide onto a C_2-chiral (*R*)-binaphthol−PCl.[3,4] These ligands can be deprotonated by Et_3N to form the ion pairs $[NEt_3H][\mathbf{1}]$ and $[NEt_3H][\mathbf{2}]$.[4] In the presence of 1 equiv of $Rh(nbd)_2BF_4$, a common hydrogenation catalyst precursor, the symmetrical dinuclear Rh species $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})_2(nbd)_2$ (Scheme 1) was formed rather than the expected mononuclear species (with a chelating P,O-bidentate ligand).

The dark-purple solution of $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})_2(nbd)_2$ gave the expected typical AA′XX′ four-spin system in the ^{31}P NMR spectrum (Figure 1), in which $J_{XX'} \approx 0$ Hz was also confirmed by ^{103}Rh NMR experiments.[4,5] $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{2})_2(nbd)_2$ gave a similar ^{31}P NMR spectrum and was identified by fast-atom-bombardment mass spectrometry.[4] Alternatively, $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})_2(nbd)_2$ could also be formed by a simple acid−base reaction between **1H** and neutral Rh(acac)(nbd), leading to protonation of $acac^-$ by the acidic proton of **1H** and formation of the neutral dinuclear rhodium complex.[4] The reaction of $[NEt_3H][\mathbf{1}]$, $[NEt_3H][\mathbf{2}]$, and 2 equiv of $Rh(nbd)_2BF_4$ led to a statistical mixture (50:25:25) of $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})(\mu_2\text{-}N,P\text{-}\mathbf{2})(nbd)_2$, $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})_2(nbd)_2$, and $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{2})_2(nbd)_2$. The dinuclear species $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})(\mu_2\text{-}N,P\text{-}\mathbf{2})(nbd)_2$ bridged by two different ligands has a lower symmetry and accordingly no longer reveals a second-order pattern in the ^{31}P NMR spectrum ($^3J_{P1-P2} = 25$ Hz).[4]

The density functional theory (DFT)-optimized structure of $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})_2(nbd)_2$ reveals that the six-membered ring constructed of the two Rh atoms and the two bridging anionic $(\mu_2\text{-}N,P\text{-}\mathbf{1})^-$ ligands adopts a preferred "boat" conformation with each Rh atom in a square-planar coordination mode (Figure 1). The "chair" conformation is uphill from this by +5 kcal/mol. We also considered other conformations with bridging oxygen atoms of the sulfonamido fragment, but these were all substantially (>10 kcal/mol) higher in energy than the μ_2-*N*,*P*-bridged structures.[4]

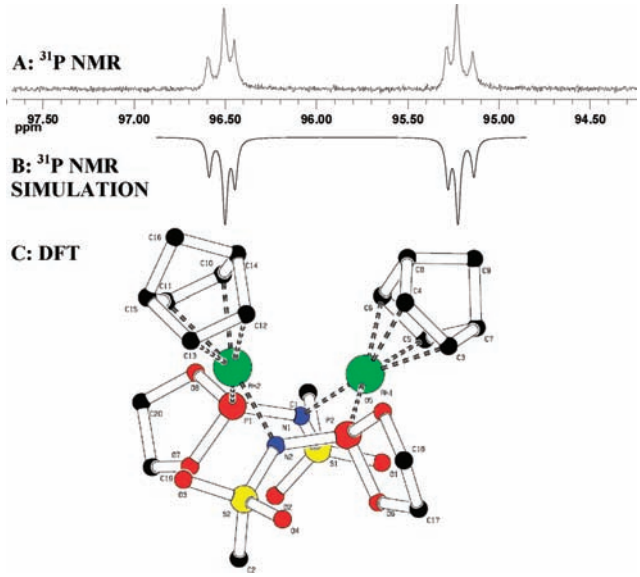
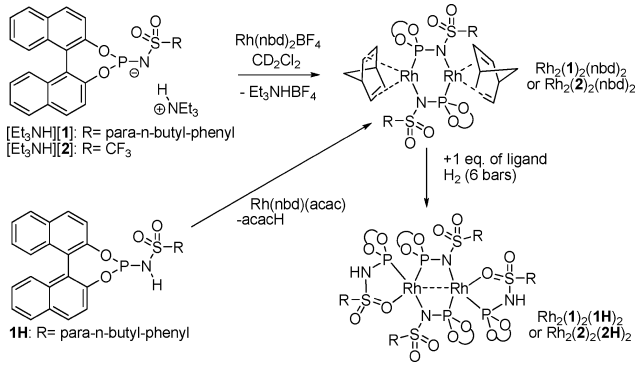


Figure 1. (A) ^{31}P NMR spectrum (202.3 MHz, 298 K in CD_2Cl_2, δ = +95.9 ppm) of $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})_2(nbd)_2$. (B) Corresponding simulated spectrum ($^1J_{P-Rh} = 260.7$ Hz; $^2J_{P-Rh'} = -2.6$ Hz; $^3J_{P-P'} = 28.7$ Hz; $^3J_{Rh-Rh'} \approx 0$ Hz). (C) DFT-optimized structure of a model compound in which the binaphthol backbone was simplified to $-OCH_2CH_2O-$.

Scheme 1. Coordination of Ligands **1H**, $[Et_3NH][\mathbf{1}]$, and $[Et_3NH][\mathbf{2}]$ to Rhodium To Give Dinuclear Complexes



Rhodium-based hydrogenation catalysts for asymmetric functionalization of alkenes are generally cationic.[6] We evaluated the neutral complexes $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})_2(nbd)_2$ and $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{2})_2(nbd)_2$ for hydrogenation activity toward a range of acetamidoalkenes (Table 1). The reactions were performed in the presence of an additional equivalent of the neutral ligand, thus producing the complexes $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})_2(\mathbf{1H})_2$ and $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{2})_2(\mathbf{2H})_2$, respectively (Scheme 1). Surprisingly, these neutral catalysts gave full

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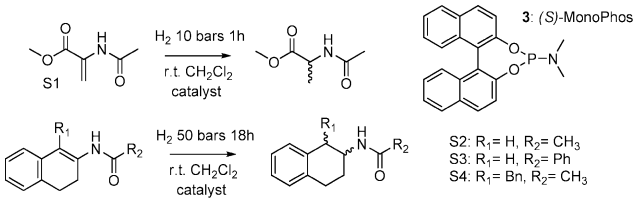
Table 1. Rh-Catalyzed Asymmetric Hydrogenation of Acetamidoalkenes



entry	complex[a]	substrate	Rh (mM)	subst/Rh	conv. (%)	ee (%)[b]
1	$Rh_2(\mathbf{1})_2(\mathbf{1H})_2$	S1	1	10^2	full	95.8
2	$Rh_2(\mathbf{2})_2(\mathbf{2H})_2$	S1	1	10^2	**full**	>99
3	$Rh_2(\mathbf{1})_2(\mathbf{1H})_2$	S1	0.1	10^3	full	99.0
4	$Rh(\mathbf{3})_2BF_4$	S2	1	10^2	68.5	1.0
5	$Rh_2(\mathbf{1})_2(\mathbf{1H})_2$	S2	1	10^2	3.5	9.3
6	$Rh_2(\mathbf{2})_2(\mathbf{2H})_2$	S2	1	10^2	**97.9**	**81.3**
7	$Rh_2(\mathbf{2})_2(\mathbf{2H})_2$	S3	1	10^2	30.4	**82.7**
8	$Rh_2(\mathbf{2})_2(\mathbf{2H})_2$	S4[c]	1	10^2	56.4	>**99**

[a] Ligand L/$Rh(nbd)_2BF_4$ = 2.2, solvent = CH_2Cl_2, reaction time 8 h, reaction of S1 finished after 1 h according to gas-uptake curves. [b] Absolute ee values. [c] Cis diastereoselectivity >99%.

conversion in the hydrogenation of methyl-2-acetamidoacrylate (MAA, S1) with very high enantioselectivities (>99% ee for the ligand combination **2**−**2H**; Table 1). The results were similar when the neutral dinuclear catalyst was prepared from $Rh(acac)(C_2H_4)_2$ and ligand **1H** (full conversion of MAA, 93% ee). Also, *N*-(3,4-dihydronaphthalen-2-yl)acetamide (DNA, S2), which is reputed to be a difficult substrate (highly conjugated, trisubstituted),[7] was converted in high yield and selectivity (98% conversion, 81% ee; Table 1). Interestingly, the neutral dinuclear catalyst $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{2})_2(\mathbf{2H})_2$ clearly outperformed $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})_2(\mathbf{1H})_2$, indicating that the ligands are tunable by substitution on the sulfonamide. Also, the neutral dinuclear catalyst performed much better than the traditional mononuclear cationic catalyst $Rh(\mathbf{3})_2BF_4$ (based on MonoPhos, a privileged ligand in the Rh-catalyzed asymmetric hydrogenation reaction;[8] Table 1, entry 4), as both the activity and selectivity were much higher (1 vs 81% ee, 68 vs 98% conversion; compare entries 4 and 6, Table 1).[4] Intriguingly, the very hindered tetrasubstituted substrate *N*-(1-benzyl-3,4-dihydronaphthalen-2-yl)acetamide (S4), a relevant structural motif because of the potential biological activity of the hydrogenated product,[9] was also selectively hydrogenated by $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{2})_2(\mathbf{2H})_2$ (>99% ee), although this process was slower (56% conversion after 18 h; Table 1, entry 8). The enantioselectivity provided by the dinuclear catalyst is by far the highest ever reported for this particular substrate; previously, a mononuclear ruthenium catalyst was shown to give 56% ee.[10] These interesting results stimulated us to study the mechanism in more detail.

A kinetic study through gas-uptake measurements with complex $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})_2(\mathbf{1H})_2$ revealed a turnover frequency (TOF) of 574 mol mol^{-1} h^{-1} (0.1 mM catalyst, 100 mM substrate, 10 bar H_2, 298 K, 20% conversion) and positive orders with respect to H_2 (0.5), substrate (0.9) and catalyst (1.0).[4] This gives the following kinetic rate equation: rate = k_{obs}[catalyst][substrate]$^{0.9}$[P_{H_2}]$^{0.5}$. The order of 1.0 with respect to the catalyst indicates that catalyst activation does not involve complex dissociation into mononuclear species (which would lead to a fractional order with respect to the catalyst).[4] Furthermore, a high-pressure NMR study revealed that the binuclear species $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})_2(\mathbf{1H})_2$ represents the resting-state species of the catalytic cycle. After exposure to 5 bar H_2, 2 molar equiv of $[NEt_3H][\mathbf{1}]$ and $Rh(nbd)_2BF_4$ provided $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})_2(\mathbf{1H})_2$, which was characterized by NMR and mass spectrometry.[4] This species also exists under catalytic conditions, i.e., under H_2 pressure in the presence of the substrate while the product is being formed.[4] Interestingly, in the absence of an additional equivalent of ligand, neutral $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})_2(nbd)_2$ disproportionates after exposure to H_2 to exclusively form the same $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})_2(\mathbf{1H})_2$ resting state (together with Rh black). Accordingly, under these conditions the kinetics shows that the activity is also reduced by a factor of 2 (TOF of 276 vs 574 mol mol^{-1} h^{-1}) but the ee remains the same. This indicates that the neutral dinuclear species $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})_2(\mathbf{1H})_2$ is the active species in both experiments.

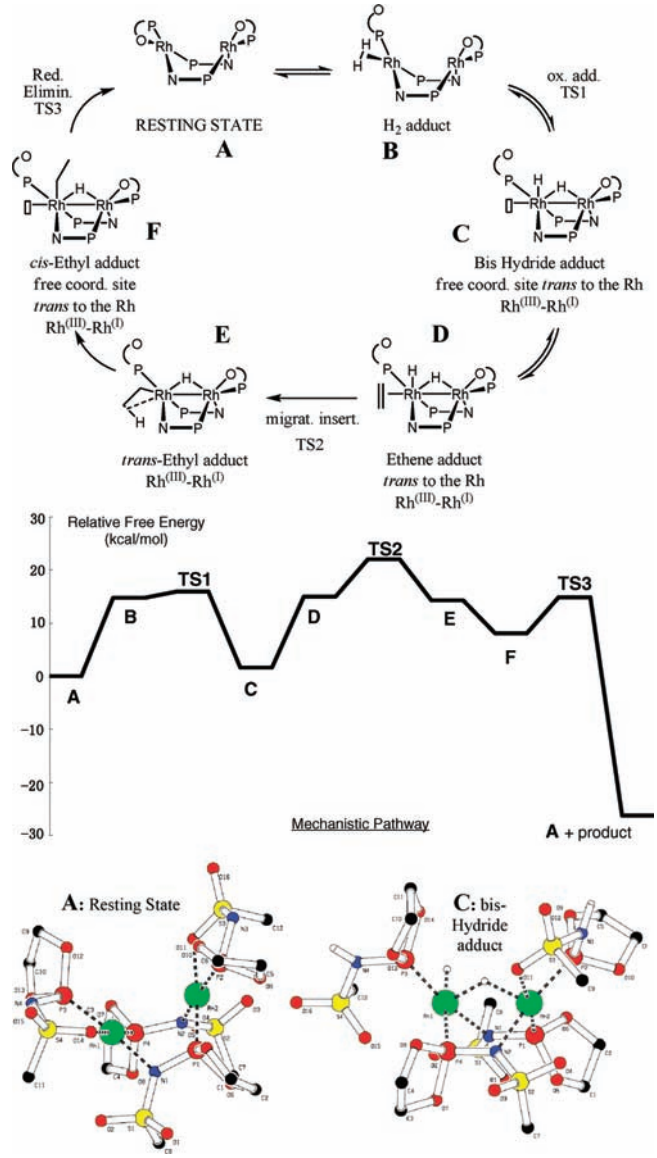


Figure 2. (top) DFT-calculated mechanistic pathway, (middle) relative free energies (kcal mol^{-1}), and (bottom) DFT-optimized structures of intermediates **A** and **C**.

To obtain detailed insight into the new dinuclear mechanism of the hydrogenation reaction, various pathways were calculated via DFT using a simplified model of $Rh_2(\mu_2\text{-}N,P\text{-}\mathbf{1})_2(\mathbf{1H})_2$ in which the binaphthol units of the ligand were replaced by smaller −OCH_2CH_2O− fragments; we used ethylene as a model for the substrate. As expected, the boat conformation proved to be the preferred geometry, with the chair being uphill by +11 kcal/mol (Figure 2).[4] The calculated Rh−Rh distance of 3.23 Å is rather short and should be regarded as a (weak) metal−metal bond.[11] This small distance suggests the possibility of cooperative substrate activation by the dinuclear complex **A**. In principle, the coordinated

sulfonamido functionalities could also allow heterolytic splitting over the metal and nitrogen,[12] but this leads to a species that is too high in energy. Cooperative (endocyclic) H_2 splitting over the two Rh atoms leads to the much lower energy bishydride species **C** having one terminal and one bridging hydride. Exocyclic ("normal") oxidative addition of H_2 to a single metal site is unlikely to be productive, as it leads to a higher-energy (+6 kcal mol^{-1}) bishydride species than species **C**. Furthermore, unlike **C**, this species is a coordinatively saturated P,P,N,O-coordinated Rh^{III} species with two terminal hydrides that has no affinity for the alkene substrate. Formation of **C** from H_2 adduct **B** proceeds via a low-barrier transition state **TS1** due to cooperative H−H bond activation over the two Rh atoms. Formation of the hydride bridge shortens the Rh−Rh distance from 3.23 Å in **A** to 3.16 Å in **C**. The bridging hydride is closer to the Rh atom containing the terminal hydride (1.65 vs 1.84 Å), suggesting that the species is best described as a Rh^{III}−Rh^{I} complex rather than a Rh^{II}−Rh^{II} species. Interestingly, the increased proximity of the Rh^{III} and Rh^{I} centers results in the elongation of the O−Rh bond of the hemilabile neutral sulfonamide fragment (from 2.24 to 2.94 Å), likely as a result of the strong trans influence[6] of the Rh^{I} atom acting as a (σ-donor) ligand to the Rh^{III} center. This leaves a vacant coordination site, which has only a weak affinity for σ-donating ligands but a decent affinity for π-accepting alkenes. Ethene binds to the vacant site of **C** to form **D**. Migratory insertion of the coordinated alkene fragment (**TS2**) produces the alkyl species **E**, with the alkyl fragment and the bridging hydride in mutual trans positions. **E** must rearrange to the lower-energy species **F** having the alkyl group in the position cis to the bridging hydride. Reductive elimination of the alkane product (**TS3**) has a sizable barrier because it involves the migration to the alkyl by a bridging hydride instead of a terminal hydride, as is normally encountered in mononuclear hydrogenation catalysts.[6] The energies associated with the mechanistic pathway depicted in Figure 2 are based on calculated free energies. The calculated free energy of **TS2** and that of the alkene adduct **D** are likely overestimated, as the gas-phase negative entropy is generally smaller in solution and DFT calculations tend to underestimate rhodium−alkene interactions.[13] These combined effects make it difficult to precisely predict the relative energies of **TS2** and **TS3**. According to the energy profile, every step prior to the reductive elimination is reversible, and **TS1** and **TS2** are similar and highest in energy, which is in line with the rate equation showing fractional orders with respect to hydrogen and substrate.[4] The DFT calculations show that the neutral dinuclear rhodium complexes allow a new cooperative mechanistic pathway for the hydrogenation of alkenes.

In conclusion, we have prepared a unique dinuclear rhodium catalyst bridged by two anionic sulfonamido−phosphoramidite ligands. The complex forms an unusual six-membered organometallic ring consisting of two Rh atoms and two μ_2-*N*,*P*- bridging units that adopts a preferred "boat" conformation in which the complex is preorganized for cooperative H_2 activation over the two Rh atoms. This type of dinuclear catalyst allows very selective hydrogenation of several acetamidoalkenes and is particularly selective for hindered tri- and tetrasubstituted alkenes (81 and >99% ee, respectively). For these reactions, the cooperative dinuclear catalysts outperform traditional cationic monometallic catalysts (Table 1, entries 4 and 6). The dinuclear substrate activation mode in combination with substrate orientation using H-bonding interactions in the second coordination sphere[14] resembles mechanistic features that are normally only encountered in natural metalloenzymes.[1]

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Supporting Information Available: Synthetic procedures, product characterization, computational details, and a zip file containing structure files (PDB) and a spreadsheet containing computational results (XLS). This material is available free of charge via the Internet at http://pubs.acs.org.

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