Asymmetric Catalysis

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Achieving Enantioselectivity with Chiral Cyclopentadienylrhodium Complexes**

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A significant number of interesting otherwise hard-to-accomplish transformations can be catalyzed by half-sandwich complexes of transition metals, especially by complexes of late transition metals with a single cyclopentadienyl (Cp) or pentamethylcyclopentadienyl (Cp*) ligand. While it is deceptively easy to conceive of and prepare chiral half-sandwich complexes, there are only few examples of late-transition-metal complexes that have been used successfully as enantioselective catalysts. Recently, two different strategies have been employed to introduce chirality to rhodium Cp complexes, and their application as enantioselective catalysts for the formation of dihydroisoquinolones from benzamides and olefins has been demonstrated.[1–3]

In many half-sandwich complexes the aromatic ligand, particularly the formally mono-anionic Cp ligand, binds strongly enough to the metal atom to be reasonably inert even under harsh thermal or photochemical reaction conditions. This is easily rationalized by thinking of the arene or Cp ligand as a tridentate ligand occupying three *fac*-oriented sites in an octahedral coordination sphere. This leaves three coordination sites for labile ligands, such as solvent molecules, which can easily dissociate and make room for the binding and reaction of substrate molecules. It is indeed this combination of the inert supporting Cp ligand and the readily available open coordination sites, which make these piano stool complexes highly reactive catalysts for a number of challenging and useful transformations. Examples include cobalt-catalyzed cyclotrimerizations,[4] a host of rhodium-catalyzed C–H activation reactions,[5] and the oxidative addition of alkanes to coordinatively unsaturated iridium complexes.[6]

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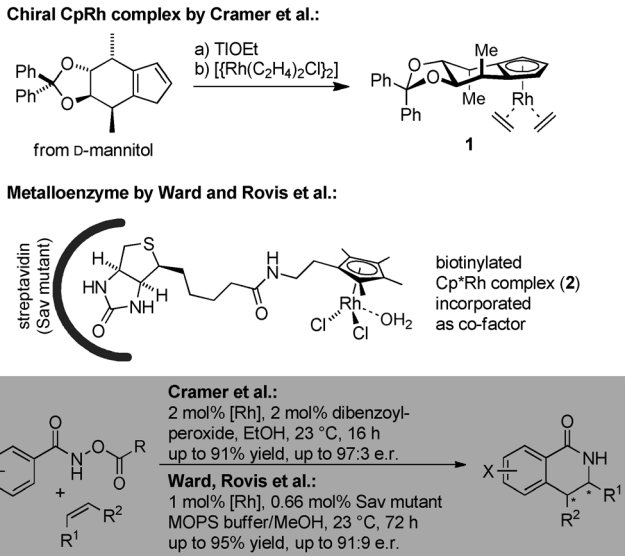
Numerous functionalized and chiral derivatives of Cp and related indenyl ligands and their corresponding metal complexes have been prepared,[7] but to date, only comparably few synthetically useful and stereoselective applications for late-transition-metal half-sandwich complexes have been reported. This is in stark contrast to the successful application of chiral sandwich complexes or half-sandwich complexes with additional bidentate chiral ligands. Chiral-at-metal half-sandwich complexes have been studied, but relatively few applications have been reported and racemization and epimerization are serious issues.[8] Why is it inherently difficult to create a chiral environment around a half-sandwich complex that translates into high enantioselectivity during a catalyzed reaction? The root of this problem can be traced back to the negligible barrier for the rotation of the Cp ligand. Hence, in the case of a chiral Cp ligand, an intermediate with a coordinated substrate can access numerous different conformations of similar energy, unless the Cp ligand locks the bound substrate in a specific orientation. The tethering of additional donor groups to the Cp ring can prevent the rotation; however, the number of open coordination sites available for substrate coordination and reaction is concomitantly reduced.[9] The problem of free rotation is aggravated in chiral Cp ligands with stereocenters that are either too far away from the metal center or too flexible to induce stereoselectivity. A further difficulty which arises from the use of unsymmetrical Cp derivatives is the formation of diastereomeric complexes because of the lack of facial selectivity.[10]

Ye and Cramer addressed the major challenges of chiral Cp derivatives by insightful design and optimization, and were rewarded with a highly enantioselective rhodium catalyst (Rh^{I}-precatalyst **1**; Scheme 1).[1] The chirality of the ligand was derived from D-mannitol in an eight-step synthesis, which allowed for structural variation. Because of its C_2 symmetry, the 1,2-substituted chiral cyclopentadiene circumvents the otherwise inevitable formation of diastereomeric complexes with potentially different selectivity. The cyclic *trans*-acetal imparts rigidity to the ligand and forces the methyl substituents of the annulated six-membered ring into an axial orientation. These details are crucial for keeping the chiral information in proximity to the metal center (Figure 1). Therefore, in the cyclometalated intermediate of the catalytic reaction the bound substrate is not only prevented from free



Scheme 1. Asymmetric catalysis with chiral CpRh complexes. MOPS = 3-(*N*-morpholino)propanesulfonic acid.

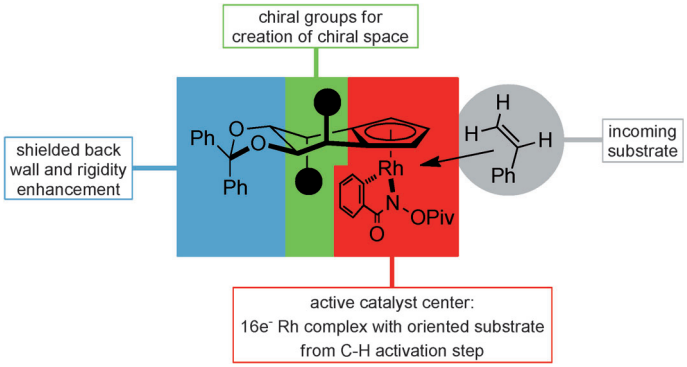


Figure 1. Chiral CpRh complexes as catalysts by Cramer et al.

rotation but also locked in one preferred orientation. The alkene substrate can bind to the complex only from one side in the enantiodiscriminating step of the reaction. The success of this approach seems to be hinged on the very delicately balance extent of steric hinderance and rigidity.[11] Larger, smaller or more flexible substituents lacking the acetal lead to lower yields or selectivities.

The groups led by Ward and Rovis developed an artificial metalloenzyme to catalyze the enantioselective synthesis of dihydroisoquinolinones.[2] In contrast to the approach described above, the chiral environment of the half-sandwich Rh^{III} complex is created by the surrounding protein rather than by the Cp ligand. Ward et al. have previously demonstrated the incorporation of catalytically active metal complexes as nonnatural co-factors into protein scaffolds in enantioselective hydrogenations with Rh–diphosphine complexes, allylic alkylations with Pd–phosphine complexes, and asymmetric transfer hydrogenations with Ru–arene–diamine complexes.[12] The underlying principle of the co-factor design is the attachement of a biotin label to the metal complex (**2**, Scheme 1), which is consequently bound by streptavidin (Sav) to finally assemble the complete artificial metalloenzyme.[13]

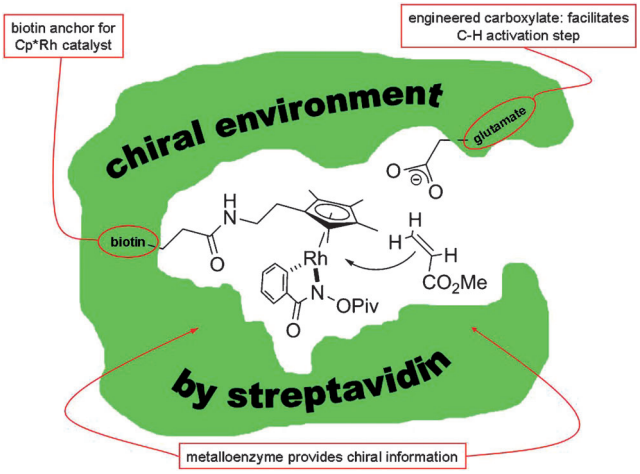


Figure 2. A chiral Cp*Rh complex serves as a catalytic center and mutant streptavidin as a chiral environment in work by Ward and Rovis et al.

The optimization of the protein relies on genetic engineering and in the present case, on site-directed mutagenesis. A carboxylate residue was introduced at a position close to the metal center, which was found essential to the efficient C–H activation by means of the concerted cyclometalation–deprotonation mechanism (Figure 2). Thus, this artificial benzannulase performed as a true artificial enzyme in the C–H activation/insertion reaction as it not only gave high yields and enantioselectivities, but also exhibited a significant rate enhancement over that of the free metal complex.

Both discussed approaches provide chirality to Cp ligands in conceptually different fashions and they mark milestones in the design and use of chiral Cp ligands in asymmetric catalysis. The methodologies have the potential for transforming many reactions known to be catalyzed by half-sandwich complexes into their enantioselective counterparts. Although the presented reactions do not involve enantiodiscrimination in the C–H activating step, quite possibly enantioselective C–H activation might be among the next examples employing this ligand concept in the future.

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