Asymmetric Catalysis

Reversibly Addressing an Allosteric Catalyst In Situ: Catalytic Molecular Tweezers**

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In biology, allosteric regulation is the control of enzyme activity by the fast, reversible binding of molecules or ions to structural sites that are remote from, but control conformational changes that occur at, the active site.[1] If one considers that reversibility in a biological sense implies in situ control over activity, then there are no known abiotic systems that are truly allosteric catalysts. Recently, the first efforts towards the development of artificial allosteric catalysts have been described.[2,3] Thus far, there have been two distinct approaches to realizing systems that mimic biological allosteric regulation of catalysis. One approach consists of organic

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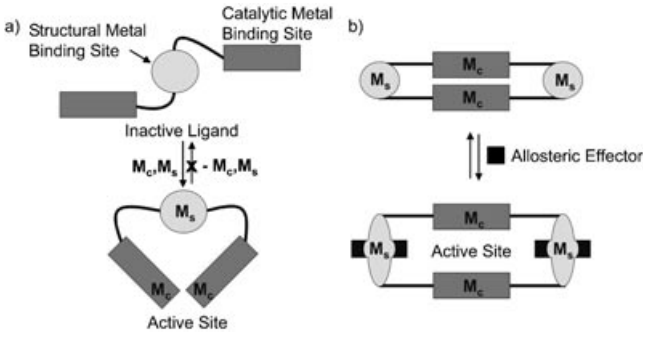
frameworks in which structural metal ions induce conformational changes that affect the ability of catalytic metals, within the same complex, to function.[2] Essentially, structural metal coordination prepares a suitable ligand for the catalytically active metal centers.[4] However, in a biological context, this strategy is more reminiscent of the way various enzymes, notably Zn-finger proteins,[1] use structural metals to define their tertiary structure in a static fashion rather than behaving dynamically and reversibly (Scheme 1 a).



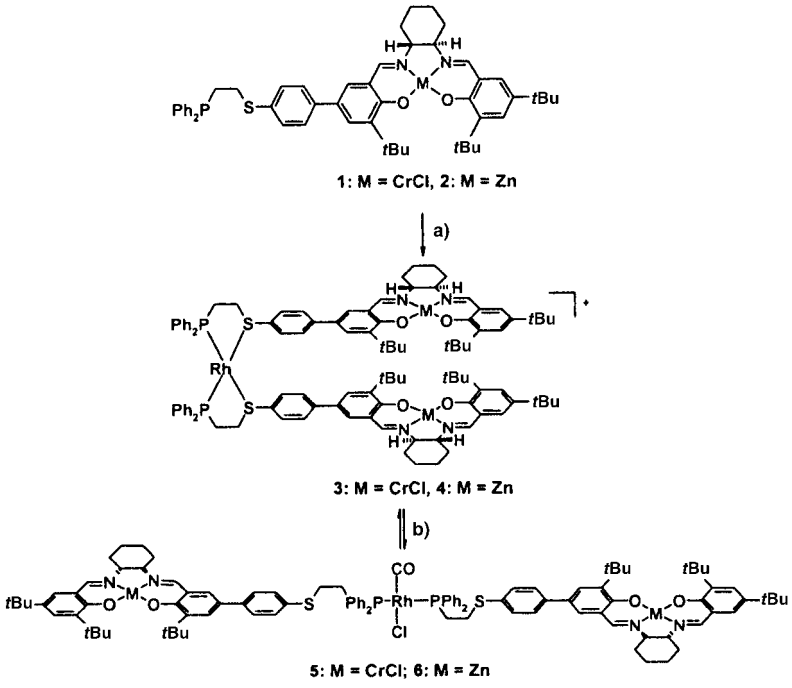
Scheme 1. M_s = Structural transition-metal center. M_c = Catalytic transition-metal center. M_s and M_c may be the same or different depending on the system. a) The metal-ion directed arrangement of an active site. b) The allosteric effector mediated shape change of a catalytic heterobimetallic macrocycle.

The second approach is based upon heterobimetallic supramolecular complexes in which one metal center acts as a structure control site and the other acts as a catalytic site (Scheme 1 b).[3] These large macrocyclic complexes are assembled in high yield by the weak-link approach.[5] This strategy provides a close mimic of a biological allosteric catalyst in the sense that it contains structural and catalytic sites that are independently addressable. The structural metal centers hold the catalyst in different conformations depending on the presence or absence of the allosteric effectors. However, these effectors prove difficult to remove from this system, making the reversibility slow and difficult to achieve.

Herein, we describe the synthesis and characterization of a new allosteric catalyst based upon a novel class of tweezer complex with catalytic rates and selectivities that can be increased and decreased reversibly in situ by selectively opening and closing the catalytic cleft through reactions that occur at the allosteric hinge. By using supramolecular coordination chemistry as a synthetic tool, we are beginning to understand how to construct addressable, conformationally flexible entities capable of catalyzing reactions with allosteric enzyme-like control.

We present the synthesis and catalytic activity of tweezer complexes that contain a Rh^I hinge and two Cr^{III}–salen catalytic arms (Scheme 2). The Rh^I–thioether bonds can be broken by reaction with CO and Cl^-, while leaving the Rh^I–phosphine bonds intact. The result of the selective breaking of these bonds is a significant topological change coupled with a change in the selectivity and rate of the reaction occurring at the Cr^{III} metal center. Essentially, the catalysis is controlled using changes in coordination chemistry at a structural site distal to a catalytic site. This is a rare example of a tweezer complex capable of undergoing an actual modulation of the distance between the arms of the complex in situ by the introduction and removal of small molecules and ions capable of addressing the hinge.[6] In this manner we have a unique, biologically inspired, reversible switch for catalyst activity and selectivity.

The asymmetric ring opening of cyclohexene oxide by $TMSN_3$ (TMSN = azidotrimethylsilane) was used to demonstrate the utility of this approach to catalytic control. This reaction was selected because of its demonstrated bimetallic mechanism that requires two metal–salen monomeric catalysts to activate both the epoxide and the nucleophile.[7] We hypothesized that the incorporation of a bimetallic catalyst into a tweezer complex that can be opened and closed would provide control over catalyst activity and selectivity by virtue of the ability to address the relative orientation of the two catalytic sites involved in the bimetallic reaction. We were encouraged to move towards a tweezer-type catalyst because of our earlier experience with the related, macrocyclic salen-based system.[3] Notably, the tweezer complex (Scheme 2)



Scheme 2. Synthesis of the allosteric tweezer complexes. Counterions are BF_4^-. All cyclohexyl salen backbones have (*R*,*R*) stereochemistry. Reagents and solvents; a) $[Rh(NBD)_2]BF_4$, CH_2Cl_2; b) PPNCl/CO (PPNCl = bis(triphenylphosphoranylidene)ammonium chloride); **3** and **4** may be synthesized from **5** and **6**, respectively, by the removal of CO in vacuo or by purging with N_2.

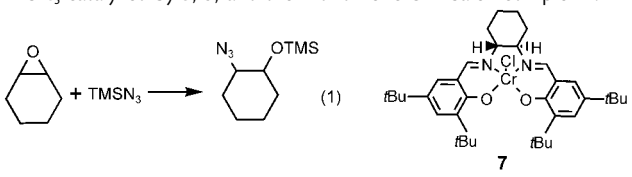
offers an increase in the solubility in comparison with the macrocycle, thus allowing the epoxide ring-opening reactions to be performed over greater ranges of catalyst concentration in THF. In addition, upon Rh^I–thioether bond breakage the catalyst changes from the compact tweezers-shaped molecule into a flexible, linear molecule. This dramatic change in shape was expected to generate a larger allosteric effect than the related macrocyclic analogue.

The novel enantiomerically pure hemilabile ligands **1** and **2** were synthesized in eight steps (see Supporting Information) and incorporate a binding site for a Rh^I metal center (Scheme 2). Compounds **3** and **4** were synthesized in almost quantitative yield by treating **1** and **2** respectively with $[Rh(NBD)_2]BF_4$ in CH_2Cl_2 (NBD is norbornadiene). Compound **3** has been characterized by elemental analysis, ^{31}P NMR spectroscopy (compounds **3** and **5** are paramagnetic, due to the incorporation of Cr^{III} metal centers, which results in broad NMR signals), and electrospray mass spectrometry, and all data are consistent with its proposed structure. In addition, **4** has been fully characterized in solution. Compounds **3** and **4** can be converted to **5** and **6**, respectively, by treating with 1 equivalent of PPNCl and CO (1 atm) in benzonitrile, CH_2Cl_2, or THF at room temperature. Compounds **5** and **6** exhibit diagnostic ν_{CO} bands at 1976 cm^{-1} and 1978 cm^{-1}, respectively.[5c] The $^{31}P\{^1H\}$ NMR spectra of **5** and **6** also support the proposed structures with each exhibiting a single resonance at 25 ppm ($J_{P\text{-}Rh} = 123$ Hz) diagnostic of square-planar *trans*-phosphine, Cl/CO complexes of Rh^I.[5c,8] Significantly, the tweezer complexes **5** and **6** undergo reversible conversion to **3** and **4** upon vacuum removal of the solvent or by purging N_2 through the solution. The conversion can be monitored easily by $^{31}P\{^1H\}$ NMR and infrared spectroscopies.

The differences in catalytic reactivity between the open, closed, and monomeric forms of the catalyst were evaluated using the asymmetric ring opening of cyclohexene oxide by $TMSN_3$ to yield 1-azido-2-(trimethylsiloxy)cyclohexane [Eq. (1); Table 1]. The incorporation of two catalysts into the tweezer complex results in competing intramolecular and intermolecular mechanisms. This is further complicated by the observation that linked, dimeric Cr^{III}–salen catalysts display increased intermolecular reaction rates, with respect to their monomeric analogues, in which highly reactive multimetallic assemblies have been implicated.[7b,c] Theoretically, if only one molecule of either **3** or **5** were present in solution the catalytic reaction would be entirely intramolecular and as the catalyst concentration is increased the reaction would become more intermolecular. If this theory is true, we expect that the catalytic activity of **3** and **5** will be affected differently by dilution and we can optimize the allosteric effect by varying the concentration of the catalyst. We were able to demonstrate this effect by monitoring the enantiomeric excess of product formed by **3** and **5** at various catalyst concentrations (Table 1) and plotting the resulting data as a function of catalyst concentration (Figure 1).

The difference in the selectivity of the open and closed tweezer complexes is enhanced at low concentrations (Figure 1). As the concentration of **3** and **5** increases, the difference between the selectivity of the two catalysts

Table 1: Selectivity data for the ring opening of cyclohexene oxide by $TMSN_3$ catalyzed by **3**, **5**, and the monomeric Cr^{III}–salen complex **7**.[a]



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Entry	Catalyst	[Catalyst] M 1×10^{-3}	% *ee* of product[b]
1	**3**	7.2	80
2	**5**	7.2	74
3	**7**	7.2	26
4	**3**	4.7	80
5	**5**	4.7	73
6	**3**	3.6	79
7	**5**	3.6	68
8	**7**	3.6	12
9	**3**	2.5	77
10	**5**	2.5	60
11	**3**	1.8	72
12	**5**	1.8	54
13	**3**	0.72	65
14	**5**	0.72	44
15	**3**	0.36	63
16	**5**	0.36	32
17	**3**	0.14	49
18	**5**	0.14	21

[a] All reactions were performed at room temperature in THF. [b] % *ee* of 1-azido-2-(trimethylsiloxy)cyclohexane was determined by chiral GC.

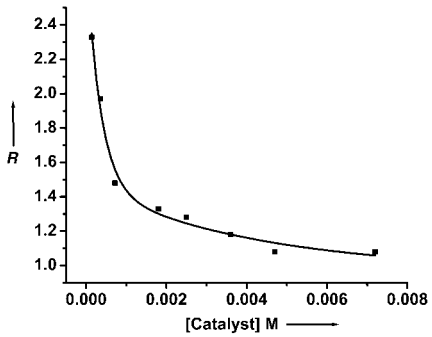

Figure 1. The allosteric effect expressed in terms of selectivity. *R* is the allosteric selectivity ratio = (% *ee* of the product formed by using **3**):(% *ee* of the product formed by using **5**).

decreases until they both reach a maximum of approximately 80% *ee* (Table 1). A similar trend is seen for the monomeric version of the catalyst (**7**) in which the selectivity of the catalyst increases with concentration (Table 1, entries 3 and 8). We hypothesize that the predefined cavity of complex **3** is able to maintain a selective environment for catalysis over a broad range of concentrations. Complex **5** is comparatively more adversely affected by solvent and reagent molecules that contribute to a reduction in the selectivity of the catalyst. The allosteric effect is enhanced as we move to lower concentrations of catalyst and the system becomes more dependent on the intramolecular reaction (Figure 1).

Open and closed tweezer complexes, **3** and **5**, are more selective and active than the monomeric version of the

catalyst, which suggests that cooperativity is present for both of the dimers. However, for **5** that cooperativity is reduced, thus rendering the catalyst less selective. The selectivity depends greatly on the nature of the alignment of the two catalytic centers in each tweezer complex. By monitoring the catalysis over a range of concentrations, we were able to map out and optimize the allosteric effect with respect to selectivity.

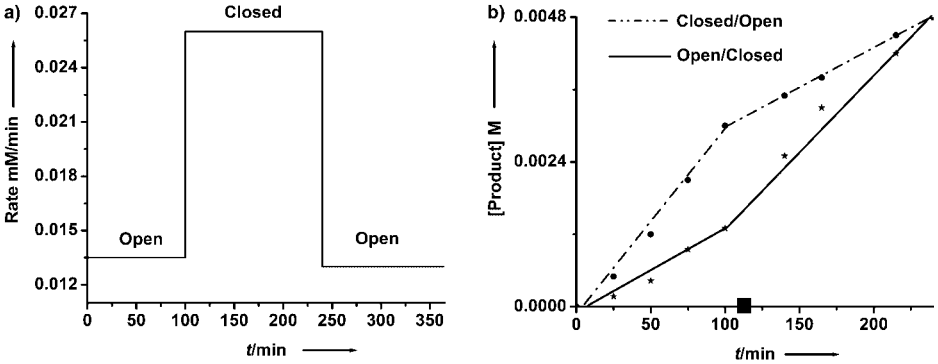

Figure 2. In situ reversibility of the catalysis. a) The catalyst being taken through an open/closed/open cycle. b) The switch point (■) indicates CO saturation or CO desaturation (N_2 purge) points at which the catalyst is opened (complex **5** from complex **3**) or closed (complex **3** from complex **5**) respectively. Reaction conditions: Cyclohexene oxide (6.1 mmol), $TMSN_3$ (2.3 mmol), 3.6 mM catalyst in benzonitrile at room temperature (see Supporting Information for details).

As mentioned earlier, a key requirement of a system that seeks to mimic biological-like allosteric control over catalysis, is its reversibility. The ease by which the allosteric initiator molecules and ions can be introduced and removed from the system dictates the plausibility of this approach to catalytic control. Hence, the use of a gas as an allosteric protagonist is ideal if one wishes to develop a system that can easily be addressed during the course of the reaction. Both members of the CO/Cl^- pair are required to break the Rh^I–thioether bonds, as confirmed by $^{31}P\{^1H\}$ NMR and FTIR spectroscopies. A catalytic reaction occurring in a solution containing Cl^- ions and lacking CO will have only one of the necessary allosteric elements and vice versa. Subsequently, the ability to reversibly convert from **3** to **5** in situ by CO saturation and CO desaturation of a solution containing Cl^- ions allows us to conveniently cycle the catalyst through two modes. With the introduction and removal of CO (1 atm) as our switch, we were able to demonstrate this allosteric effect with respect to the rate of formation of 1-azido-2-(trimethylsiloxy)cyclohexane (Figure 2). A catalyst concentration of 3.6 mM in benzonitrile was chosen owing to the relatively large difference in rates observed between **3** and **5** under these conditions (Supporting Information).[9]

By introducing and removing CO from the system, we can alternatively slow and speed up the reaction in situ. Figure 2 shows the process occurring for two cycles that mirror each other. One begins with an open catalyst that is subsequently closed by purging with N_2 at 110 minutes and then reopened at approximately 240 minutes by purging with CO. A second experiment shows that one may begin with a closed catalyst and cycle in the opposite direction and achieve comparable results.

To the best of our knowledge, this data represents the only nonbiological example of an allosteric catalyst that provides control over catalytic activity and selectivity and can be addressed in a reversible fashion, in situ. In view of the growing number of reactions that are catalyzed in a bimetallic fashion,[7,10] this could become a reliable and general approach to catalyst preparation and modulation.

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