Inversion of product selectivity in an enzyme-inspired metallosupramolecular tweezer catalyzed epoxidation reaction†

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Received (in Cambridge, UK) 5th May 2009, Accepted 25th June 2009
First published as an Advance Article on the web 16th July 2009
DOI: 10.1039/b908852k

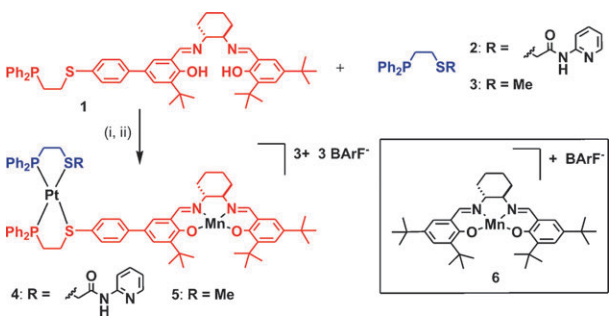
This study describes a heteroligated, hemilabile Pt^{II}–P,S tweezer coordination complex that combines a chiral Jacobsen–Katsuki Mn^{III}-salen epoxidation catalyst with an amidopyridine receptor, which leads to an inversion of the major epoxide product compared to catalysts without a recognition group.

Recognition and catalysis allow enzymes to select a specific substrate molecule from a large pool of potential reactants with identical functional groups and convert it to a specific product. For example, prostaglandin synthases[1] bind specifically to arachidonic acid, followed by the selective oxidation of the C13 position in a step towards the desired prostaglandin. Mimicking such substrate selectivity with synthetic catalysts is among the goals motivating the field of biomimetic chemistry.[2] Supramolecular recognition, organic linkers and rigid tweezer groups are strategically combined to preorganize a structure capable of aligning a substrate with respect to a catalytic site, thereby affecting product distribution.[3] While this strategy has led to numerous examples of reactions with unique or otherwise unattainable specificity, the synthetic effort to synthesize supramolecular catalysts based on organic frameworks is cumbersome. Recently, convergent, high-yielding methodologies have been developed to create coordination complexes capable of aligning functional groups or creating catalytically active pockets.[4] While such strategies have been used to create libraries of complexes with heteroligated ligand coordination modes around catalytically active metal centers, the alignment of receptor and catalyst units in a tweezer fashion *via* a metal coordination site has thus far not been reported.

By employing the weak-link approach (WLA)[5] and the halide-induced ligand rearrangement (HILR)[6] reaction, two different functional units can be oriented in a rigid, tweezer-like fashion. Herein, we describe the rational design and preparation of a novel, heteroligated, hemilabile Pt^{II}-phosphine coordination complex **4** (Scheme 1) that combines a catalytic metal center reminiscent of a Jacobsen–Katsuki chiral Mn^{III}-salen epoxidation catalyst[7] with an amidopyridine receptor.[8] The idea is that in the presence of a pool of olefin containing substrates, a carboxylic acid terminated olefin will form a supramolecular complex with the catalyst, thereby selecting and orienting the acid-functionalized olefin with respect to the catalytic metal center. Indeed, Monte Carlo conformation search simulations for a hydrogen bonded supramolecular complex between **4** and the substrate molecule 4-vinylbenzoic acid **7** were performed in the gas phase with the MM2 force field implemented in Macromodel,[9] showing that the global minimum structure (Fig. 1) exhibits a Mn^{III}–olefin distance of 3.9 Å, which is appropriate for catalysis while maintaining the hydrogen bonding interaction.[2,3] Additionally, a stabilizing π–π interaction between aryl groups on the substrate and the catalyst that enhances binding was found.[10]

Complexes **4** and **5** (analogue without receptor group) were synthesized under ambient conditions by a convergent route in high yield from salen ligand **1**, amidopyridine receptor ligand **2** (or ligand **3** without receptor group), NaBArF, a Pt^{II} metal precursor, a Mn^{III} precursor and 2,6-lutidinium-BArF (Scheme 1). ^{1}H NMR spectroscopic measurements for **4** and **5** exhibit large upfield and downfield resonances that are assigned to backbone protons on the Mn^{III}-salen unit, consistent with ^{1}H NMR spectroscopic studies of analogous (*R*,*R*)-[(salen)-Mn^{III}-Cl][11] and (*R*,*R*)-[(salen)-Mn^{III}-BArF] **6** complexes. As a result of the paramagnetic nature of these complexes, their $^{31}P\{^1H\}$ NMR spectra exhibit broad resonances, assigned to the κ^2-P,S-Pt^{II} chelating phosphine ligands.[6] High-resolution MS, ^{19}F NMR, IR, UV/Vis spectroscopy, and elemental analysis are fully consistent with the assigned structures (see ESI† for details).

The ability of the amidopyridine group in **4** to form a hydrogen bonded, supramolecular complex with **7**



Scheme 1 (i): [Pt(benzonitrile)$_2$Cl$_2$] (1 equiv.), NaBArF (2.1 equiv.), CH_2Cl_2, filtration, (ii): Mn(acac)$_3$ (2 equiv.), 2,6-lutidinium-BArF (7 equiv.), MeOH, 24 °C. Yield: **4**: 88%; **5**: 89%. BArF: B[3,5-(CF$_3$)$_2$(C$_6$H$_3$)]$_4$; acac: acetylacetonate. Inset: analogous (*R*,*R*)-[(salen)-Mn^{III}-BArF] **6** complex. MeOH may be partially coordinated to Mn^{III} sites in apical position.[7]

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization, ITC data, and computational details. See DOI: 10.1039/b908852k

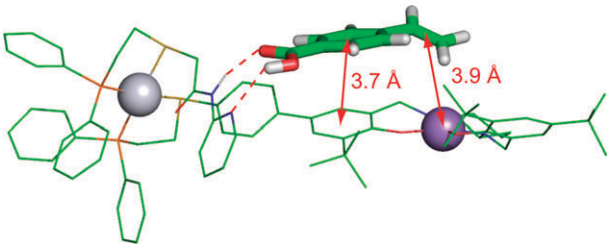
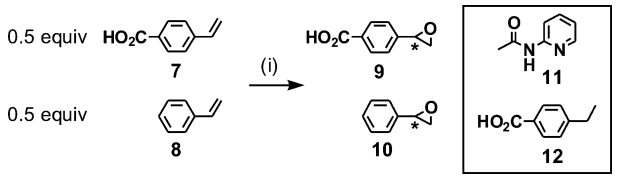


Fig. 1 Global minimum structure obtained from conformation search simulations of a hydrogen bonded supramolecular complex between catalyst **4** and 4-vinylbenzoic acid **7**.



Scheme 2 Catalytic competition experiment. (i) Catalyst (5 mol%), PhIO (1 equiv.), *n*-hexadecane (standard), CH_2Cl_2, 0 °C, N_2, 2 h. Total olefin concentration: 0.9 mM. Inset: additives to catalytic experiments.

(Scheme 2) was confirmed by isothermal titration calorimetry (ITC). The carboxylic acid **7** was added to a solution of catalyst **4** to form a complex predominantly held together *via* hydrogen bonding between the carboxylic acid and the amidopyridine group (K_a (CH_2Cl_2, 25 °C) = 3090 ± 360 M^{-1}). Consistent with this observation, 2-acetamidopyridine **11** and **7** form a complex with a similar binding constant (K_a (CH_2Cl_2, 25 °C) = 1440 ± 110 M^{-1}). Importantly, the combination of complex **5** and **7** in CH_2Cl_2 does not result in measurable binding *via* ITC. Addition of styrene **8** to a solution of 2-acetomidopyridine **11** in CH_2Cl_2 also does not result in measurable binding. These data all support the hypothesis that a hydrogen bonded complex forms between **4** and **7** in CH_2Cl_2 as a consequence of interactions between the carboxylic acid on **7** and the amidopyridine group on **4**.

The influence of noncovalent interactions between **4** and **7** on the epoxide product distribution and enantioselectivity from a two olefin pool of reactants was determined in a series of catalytic epoxidation reactions. Equimolar amounts of olefins **7** and **8** were oxidized to the corresponding chiral epoxides **9** and **10**, respectively, in the presence of catalysts **4–6** (Scheme 2, Table 1).[7] Reactions were carried out at 0 °C in CH_2Cl_2, and high dilution (0.9 mM total olefin concentration) was used to favor intramolecular reaction pathways. A limiting quantity of iodosobenzene oxidant kept substrate concentrations close to equimolar levels until the reaction was quenched with PPh_3 after 2 h at a total conversion (**9** + **10**) of 10 ± 2%, in accordance with previous studies.[3] 4-Ethylbenzoic acid **12** was added in entries 2–4 as a competitive inhibitor. 2-Acetamidopyridine **11** was added in entries 5 and 7 to equalize amidopyridine functionalities compared to entry 1.

Table 1 Product distribution and enantiomeric excess (ee) of chiral epoxides following catalytic epoxidation reactions. Catalytic reactions were carried out in duplicate or triplicate. Conversion and the absolute ee of **10** were determined *via* chiral gas chromatography (GC) after carboxylic acid methylation. Standard deviations for conversion: ≤0.7%; ee of **10**: ≤2%; approximate accuracy for ee of **9**: ± 5% (determined using a chiral ^{1}H NMR shift reagent after purification). Equiv., conversion and mol% are given with respect to total olefin concentration

Entry	Catalyst	Additive	Conversion (%) **9** (relative ee)	Conversion (%) **10** (absolute ee)
1	**4**	None	*6.9* (−26%)	3.4 (−13%)
2	**4**	**12** (0.5 equiv.)	*6.2* (−28%)	3.6 (−12%)
3	**4**	**12** (2.5 equiv.)	*4.2* (−28%)	3.9 (−19%)
4	**4**	**12** (5 equiv.)	3.5 (−24%)	*4.2* (−21%)
5	**5**	**11** (5 mol%)	2.9 (+5%)	*6.7* (−12%)
6	**6**	None	3.8 (+34%)	*7.3* (+5%)
7	**6**	**11** (5 mol%)	3.5 (+31%)	*6.3* (+6%)

Significantly, analysis of the product mixtures in entries 1 and 5 shows a 4.7 fold preference for epoxide product **9**, whose precursor **7** can form a supramolecular complex with **4**, resulting in an inversion of the major epoxide product depending on whether complex **4** or **5** is used for catalysis. Competitive binding by 4-ethylbenzoic acid **12** to the receptor (entries 2–4) gradually leads to diminished selectivity, suggesting that the preferred formation of epoxide **9** in entry 1 is indeed a consequence of the interaction between the amidopyridine group in **4** and the carboxylic acid group in substrate **7** and is not because of a general increase of steric bulk in the catalyst from the amidopyridine receptor. In entries 6 and 7, (*R*,*R*)-[(salen)-Mn^{III}-BArF] **6** shows similar epoxide distributions and turnover as complex **5**, confirming the preference for styrene oxide formation by this catalytic moiety. Significant variations in enantioselectivity are observed for both epoxide **9** and **10** in the different catalytic runs, which are attributed to a combination of hydrogen bonding and other interactions that affect epoxide enantioselectivity.[7]

In conclusion, the assembly of a receptor and a catalyst in a tweezer fashion *via* a highly convergent metal coordination linker is reported for the first time, resulting in a supramolecular complex with a specific substrate that leads to its preferential epoxidation compared to a substrate that does not bind to the receptor. Use of triple-decker structures[6] and a larger pool of hemilabile P,S receptor, cofactor and catalyst ligands should lead to improved catalytic selectivities.

We acknowledge the NSF, ARO, AFOSR, and DDRE for financial support of this research and IMSERC (Northwestern U.) for analytical services. C.A.M. is grateful for a NIH Director's Pioneer Award. A.B.B. is grateful for a NIH Postdoctoral fellowship (1F32CA136148-01). P.A.U. thanks Dr Christopher Oliveri, Dr Hyojong Yoo and Dr Sebastian Peter for helpful discussions.f

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