Disparate Roles of Chiral Ligands and Molecularly Imprinted Cavities in Asymmetric Catalysis and Chiral Poisoning

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Received October 29, 2001

Summary: The activation of molecularly imprinted metal complexes generates Lewis acid catalysts for the ene reaction, each of which contains a chiral diphosphine ligand and a chiral BINOL-shaped cavity. Poisoning experiments with (R)- and (S)-BINAM indicate that while the chiral cavity can differentiate the chiral poisons, it is the chiral diphosphine ligand which controls the enantioselectivity of the ene product.

Many outstanding ligands have been developed for asymmetric catalysis, and with a few exceptions, they modify the immediate coordination environment (inner sphere) of the metal to influence the reactivity and selectivity of the catalyst. Enzymes, and in particular, metalloenzymes, additionally utilize the outer sphere to more completely and effectively define the metal's coordination environment, thus creating *active sites* that cannot exist in solution.

To mimic the active site concept more wholly, we and others have examined how molecular imprinting, which provides shaped and functionalized polymer cavities by a templated polymerization process,[1] can be used to generate transition-metal catalysts in an environment where both their inner and outer spheres are controllable and functional (i.e. an active site).[2] To date, results in this area indicate that (1) catalysts immobilized within the macroporous resin of a molecularly imprinted polymer (MIP) are highly accessible and reactive and benefit from many features of heterogeneous catalysts[3] and (2) the active sites, when properly constructed, lead to chemoselectivities,[3c,d,4] enantioselectivities,[5] and reaction modes[6] that are *inaccessible in solution*.

One disadvantage of MIPs, however, is that some "surface sites" result: sites that do not contain a cavity and are completely solvent-exposed. These sites tend to be unselective but more reactive, since no polymer is present to control access to the catalyst, and thus lose the uniqueness of the "site" phenomena.[5] Reactive site poisoning, a ubiquitous technique in heterogeneous catalysis, should be viable for deactivating these less desirable sites, though its use in MIP catalysis is unknown.[7] This paper reports catalysis experiments demonstrating the viability of active site poisoning for probing site catalytic activity and selectivity and the notion that *chiral* poisons uniquely probe the stereochemistry of the cavity.

The strategy in Scheme 1 summarizes our approach to obtaining MIPs that contain, at their core, a (*S*-MeOBiphep)$PtCl_2$ precatalyst polymerized at the termini of the P−Ar substituents. A family of these precatalysts is obtained where the members differ by the shape and structure of an associated cavity, which is generated by the imprinting process. Appropriately chosen metallomonomers enable BINOL-shaped[5] cavities (both matched and mismatched) and nonchiral cavities to be associated with the chiral P_2PtCl_2 precatalyst.[8] When BINOL-containing metallomonomers are utilized, the desired dichloride precatalysts are obtained by removing the BINOL ligand with HCl (94% BINOL recovery) prior to activation for catalysis.[9] Each of the three polymers thus contains a polymerized P_2PtCl_2, distinguished only by the shape of the associated cavity (Cl_2, *R*-BINOL, and *S*-BINOL; $\mathbf{P_{Cl2}}$, $\mathbf{P_{\textit{R}-BINOL}}$, and $\mathbf{P_{\textit{S}-BINOL}}$, respectively). Comparing these polymeric precatalysts provides an experimentally tractable method of assessing the importance of an associated cavity on the activity and selectivity of a molecularly imprinted catalyst.

In solution, (*S*-MeOBiphep)$PtCl_2$ can be activated with $AgSbF_6$ to generate a dicationic complex that catalyzes (2 mol %, room temperature) the glyoxylate−

(1) Sellergren, B., Ed. *Molecularly Imprinted Polymers: Man-Made Mimics of Antibodies and Their Applications in Analytical Chemistry*; Elsevier: Amsterdam, 2001.

(2) Severin, K. *Curr. Opin. Chem. Biol.* **2000**, *4*, 710−714. Santora, B. P.; Gagné, M. R. *Chem. Innov.* **2000**, 23−29. Davis, M. E.; Katz, A.; Ahmad, W. R. *Chem. Mater.* **1996**, *8*, 1820−1839.

(3) (a) Vinson, S. L.; Gagné, M. R. *Chem. Commun.* **2001**, 1130−1131. (b) Taylor, R. A.; Santora, B. P.; Gagné, M. R. *Org. Lett.* **2000**, *2*, 1781−1783. (c) Polborn, K.; Severin, K. *Chem. Eur. J.* **2000**, *6*, 4604−4611. (d) Polborn, K.; Severin, K. *Eur. J. Inorg. Chem.* **2000**, 1687−1692. (e) Nozaki, K.; Itoi, Y.; Shibahara, F.; Shirakawa, E.; Ohta, T.; Takaya, H.; Hiyama, T. *J. Am. Chem. Soc.* **1998**, *120*, 4051−4052. (f) Santora, B. P.; White, P. S.; Gagné, M. R. *Organometallics* **1999**, *18*, 2557−2560. (g) Matsui, J.; Nichols, I. A.; Karube, I.; Mosbach, K. *J. Org. Chem.* **1996**, *61*, 5414−5417.

(4) Matsui, J.; Higashi, M.; Takeuchi, T. *J. Am. Chem. Soc.* **2000**, *122*, 5218−5219, Hart, B. R.; Shea, K. J. *J. Am. Chem. Soc.* **2001**, *123*, 2072−2073.

(5) Brunkan, N. M.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 6217−6225.

(6) For evidence of site isolation in imprinted metal complexes, see: Sharma, A. C.; Borovik, A. S. *J. Am. Chem. Soc.* **2000**, *122*, 8946−8955. Krebs, J. F.; Borovik, A. S. *J. Am. Chem. Soc.* **1995**, *117*, 10593−10594.

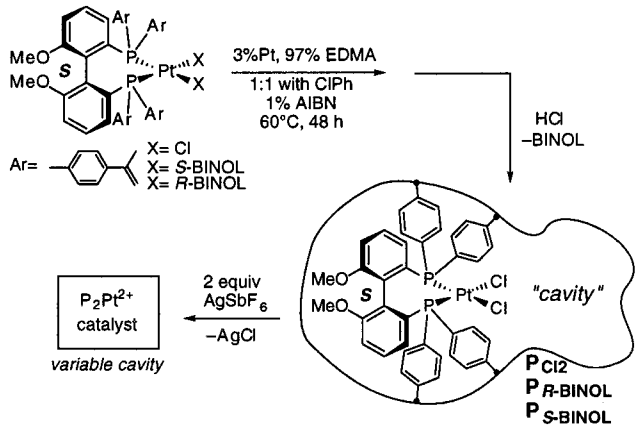
(7) Poisoning has been used to modify MIPs for chromatography and binding; see: Kirsch, N.; Alexander, C.; Lübke, M.; Whitcombe, M. J.; Vulfson, E. N. *Polymer* **2000**, *41*, 5583−5590. McNiven, S.; Yokobayashi, Y.; Cheong, S. H.; Karube, I. *Chem. Lett.* **1997**, 1297−1298 and footnote 5.

(8) The MIPs typically contain ∼125 μmol of Pt/g of dry polymer and have surface areas of ∼400 m^2/g;[12] see also: Santora, B. P.; Gagné, M. R.; Moloy, K. G.; Radu, N. S. *Macromolecules* **2001**, *34*, 658−661.

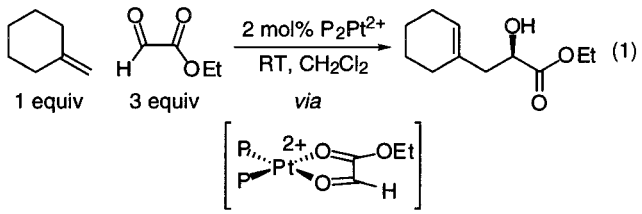
(9) Although $\mathbf{P_{Cl2}}$ does not contain a BINOL ligand, it was similarly treated with HCl, though this was found not to affect reactivity or selectivity.

10.1021/om010944c CCC: $22.00
Publication on Web 12/07/2001

Scheme 1



ene reaction (75% ee, eq 1).[10] Treating the P_2PtCl_2 in



$\mathbf{P_{S-BINOL}}$ with $AgSbF_6$ in CH_2Cl_2 generated the putative dicationic catalyst for the ene reaction.[11] Unfortunately, this polymeric catalyst (2 mol %) generated numerous elimination byproducts and an ene product of reduced enantiopurity. Suspecting that $HSbF_6$ was being generated from $AgSbF_6$ and traces of HCl remaining from the BINOL removal procedure (Scheme 1), a macroporous scavenger polymer was synthesized from *N*,*N*-dimethyl-4-vinylbenzylamine ($\mathbf{P_{Amine}}$).[12] Adding this polymer to the reaction prior to substrates effectively removed the trace of acid and provided a highly reproducible and elimination-free route to the ene product with 72% ee, only slightly lower than that obtained in solution. As is typically observed with MIP catalysts, the $\mathbf{P_{S-BINOL}}$ activity is lower than in solution, and in this case ~98% conversion requires 3 h; comparable conversion requires 30 min in solution.

Significant differences were observed between the three polymeric catalysts, which should a priori only differ by the structure of their associated cavities. In comparison to $\mathbf{P_{S-BINOL}}$, catalysis with $\mathbf{P_{R-BINOL}}$ was slower (78% conv, 3 h) and provided the product in only 25% ee, while the catalyst with no chiral cavity, $\mathbf{P_{Cl2}}$, was slower still (61% conversion, 3 h), though the enantioselectivity was only slightly lower (67% ee). Apparently, the absence of a large BINOL ligand in the latter metallomonomer during polymer formation generates a more hindered active site.[13]

With the goal of improving the enantioselectivity of the ene reaction by deactivating the most open (presumably less selective) sites, we investigated the effect of poisoning additives. First tested were (*R*)- and (*S*)-1,1′-binaphthyl-2,2′-diamine (BINAM), chelating ligands with shapes similar to the imprinting BINOL ligands and, by extension, to their respective cavities.

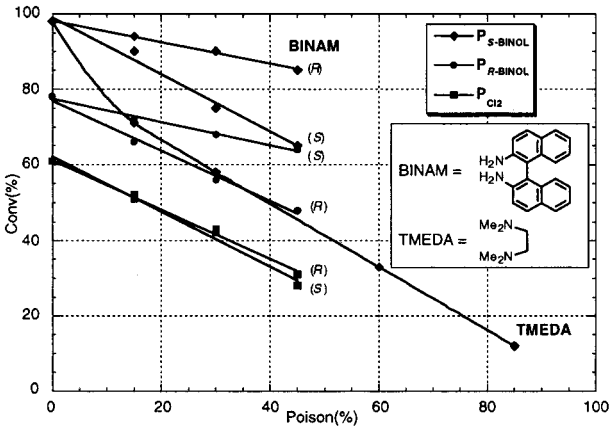


Figure 1. Effect of poisoning (percent vs catalyst), on MIP polymer activity for eq 1 (3 h reaction time). The labels indicate the type and absolute configuration of the poison. Irrespective of the amount of poison, product ee's for $\mathbf{P_{S-BINOL}}$, $\mathbf{P_{R-BINOL}}$, and $\mathbf{P_{Cl2}}$ are 72, 25, and 67%, respectively.

To benchmark our polymer experiments, we first examined the effect of BINAM poisons on the reactivity of (*S*-MeOBiphep)$PtCl_2$ in solution. The dication was generated as before, but 1 equiv (to catalyst) of the ligand was added prior to substrates. After 30 min, the *S*-BINAM and *R*-BINAM reactions had reached conversions of 81 and 41%, respectively (cf. 100% in the absence of BINAM),[14] with no change in enantioselectivity (75% ee). The stereochemical aspects of these results were surprising, since the *S*,*S* combination is thermodynamically more stable (matched), and so *S*-BINAM was expected to bind more strongly and poison the reaction more efficiently.[15]

When the MIP catalyst derived from the matched phosphine/BINOL metallomonomer (*S*,*S*) is poisoned by *S*- and *R*-BINAM, a turnover in poisoning efficiency is observed (Figure 1). Unlike the solution example, when the (*S*-MeOBiphep)Pt^{2+} catalyst has an *S*-BINOL shaped cavity, *it is selectively poisoned by the like-shaped S-BINAM* (Figure 1), presumably because *S*-BINAM binds more strongly and thus inhibits catalysis more efficiently. Similarly, the catalyst with the associated *R*-BINOL-shaped cavity ($\mathbf{P_{R-BINOL}}$) is more effectively poisoned by *R*-BINAM. These results clearly indicate that the chiral phosphine is subordinate and that it is the cavity's shape that controls the energetics and stereochemistry of BINAM binding/poisoning. Consistent with this notion is the lack of a bias for the poisoning of $\mathbf{P_{Cl2}}$ (Figure 1), again showing that the chiral phosphine has little effect on poisoning; the chiral cavity (or lack thereof) dictates the chiral poisoning.

Although the above poisoning results suggest a significant chiral cavity effect, the product enantioselec-

(10) (*S*)-MeOBiphep gives the *R* ene product: (a) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059−4062. (b) Koh, J. H.; Larsen, A. O.; Gagné, M. R. *Org. Lett.* **2001**, *3*, 1233−1236.

(11) Control experiments indicate that finely divided AgCl is not a catalyst; see the Supporting Information for details.

(12) See the Supporting Information for details.

(13) Severin has similarly observed an imprinting effect on the rate of a reaction and reasoned that a rate acceleration occurs because every site is sure to contain a suitably sized pocket.[3c,d]

(14) BINAM is a reversible poison, one that competes with, but does not exclude, substrate coordination.

(15) Like (*S*-MeOBiphep)Pt(BINOL) complexes, (*S*-MeOBiphep)Pt^{2+} binds to (*S*)-BINAM (>98:2) in preference to (*R*)-BINAM in competition experiments; see the Supporting Information for details. This unusual poisoning preference will be the subject of a future investigation.

tivities are insensitive to the amount of BINAM poison that is added, in direct contrast to our hypothesis that poisoning the most accessible (surface) sites would reveal more selective sites. Two interpretations are reasonable for the data: (1) BINOL-shaped cavities, though able to distinguish BINAM enantiomers, are too large to efficiently perturb the energetics of the competing ene transition states and (2) rather than poisoning surface sites, BINAM coordinates to sites with the best shaped cavities,[16] leaving the exposed surface sites catalytically active.

To distinguish between these two possibilities, poisoning experiments with TMEDA on $\mathbf{P}_{S\text{–BINOL}}$ were carried out. TMEDA has the advantage of being an achiral, irreversible poison (1.0 equiv suppresses solution catalysis). As measured by changes in conversion (3 h), incremental amounts of TMEDA slow the catalyst, generating a reactivity profile that points to nearly every site being catalytically competent and, with the exception of the first 15% of sites (which provides ~30% of the total activity), nearly equally so (Figure 1). However, even the least reactive sites, those most likely to have a well-structured BINOL cavity, are ineffective at perturbing normal reaction selectivities (72% ee for 85% poisoning). Scenario 1 is thus the more reasonable interpretation of the data and suggests two obvious options for future studies: smaller cavities and larger reactions.

Taken together, the data indicate that the cavity (chiral or not) and chiral diphosphine independently control the stereochemistry of poisoning by chiral BINAM ligands and the selectivity of the ene catalysis, respectively. The associated chiral cavity does not affect the stereochemistry of the C−C bond-forming process (unfortunately), and the chiral diphosphine does not influence the sense of chiral poisoning.

The drop in ee observed with $\mathbf{P}_{R\text{–BINOL}}$ was significant (25% ee) and unexpected. Consistent with the data discussed above, we suggest that, rather than being a cavity effect, the diminished selectivity is actually a result of a structurally distorted active site (an inner-sphere effect). The X-ray structure of two models for the mismatched (*S*-MeOBiphep)Pt(*R*-BINOL) metallomonomer (BINAP and Biphep[17]) each show the same distortion in the diphosphine portion. As shown in Figure 2, steric clashes between the *R*-BINAP and *S*-BINOL ligands result in a significant distortion away from the typical C_2-symmetric arrangement of axial and equatorial P−Ph groups of a chiral diphosphine ligand.[17] Rigidifying this non-C_2-symmetric fragment into the polymer by anchoring (polymerizing) the para positions of the P−Ph units must generate a chiral ligand/metal

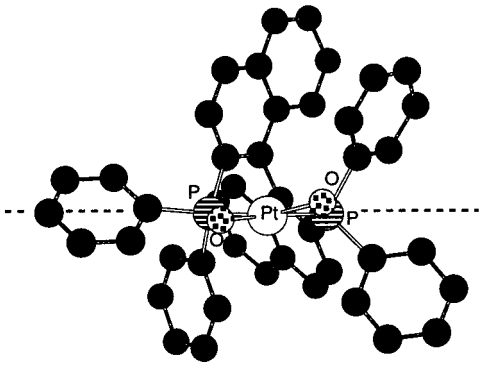


Figure 2. Chem3D picture of the distorted, non-C_2-symmetric P−Ph arrangement in (*R*-BINAP)Pt(*S*-BINOL); the dotted line delineates the P−Pt−P square plane (BINOL removed for clarity).[12]

combination that is much less able to create the asymmetric environment necessary for efficient chirality transfer; the dichloride and matched cases adopt more idealized C_2-symmetric structures and ee's closer to that expected for pure inner-sphere control.

In summary, we have demonstrated that the molecular imprinting of transition-metal complexes can provide catalysts with features that are unavailable to solution catalysts. Our data show that (1) BINOL-shaped cavities influence the stereochemistry of catalyst poisoning by like-shaped ligands, though they do not influence ene selectivities, (2) reaction enantioselectivity is exclusively controlled by diphosphine stereochemistry and structural information in the metallomonomer can be transmitted to the forming active site, (3) immobilized precatalysts can be chemically manipulated and activated for asymmetric catalysis, and (4) most of the sites are equally reactive and selective for the ene reaction.

Acknowledgment. We thank the NSF (Grant No. CHE-0075717), the NIH (Grant No. GM60578), the Petroleum Research Fund, and Union Carbide for support of this research. M.R.G. is a Camille-Dreyfus Teacher-Scholar (2000−2004). Additional thanks are due to Dr. Nicole M. Brunkan for synthesis of (*R*-BINAP)Pt(*S*-BINOL) and Dr. Rudolph Schmid (Hoffmann-La Roche, Basel, Switzerland) for helpful discussions on MeOBiphep synthesis.

Supporting Information Available: Text giving synthetic procedures and tables of metrical parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) In kinetic terms, ligand substitution is slower for a well-matched cavity and ligand, and so the BINAM poison accumulates in the well-defined sites. In this manner, the most well-matched sites for the poison are selectively retarded for catalysis, and surface sites dominate product output.

(17) For a discussion, see: Tudor, M. D.; Becker, J. J.; White, P. S.; Gagné, M. R. *Organometallics* **2000**, *19*, 4376−4384.