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Exploiting the Synergy between Coordination Chemistry and Molecular Imprinting in the Quest for New Catalysts

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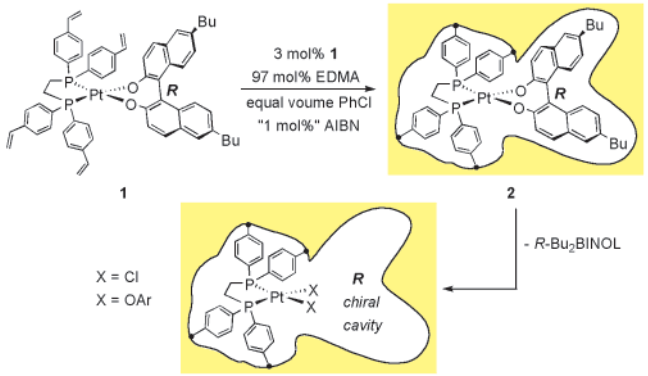
ABSTRACT
The synthesis of transition metal active sites by the molecular imprinting of polymerizable metal complexes into highly cross-linked organic polymers is described. The emphasis of this Account is on the synergy between the long-term goals associated with new catalyst development and the more short-term goal of addressing fundamental questions in coordination chemistry, particularly emphasizing stereochemistry and structure. An argument is presented that the latter is necessary for ultimately achieving the more difficult but more important goal of designer catalysts that achieve reaction selectivities and reactivities not obtainable with traditional homo- or heterogeneous catalysts.

Introduction

The quest for the perfect catalyst has long provided the justification for many a fundamental research program, and ours is no exception. We seek catalysts that have high reactivities, longevities, and selectivities, are easy to separate from the products of the reaction, and are tolerant of water, the atmosphere, and contaminants in the feedstock. Oh yes, we'd also like them to be inexpensive and never pollute. We still have not found this catalyst, though we keep trying.

Although these goals are elusive, we have embarked on a path that we hope will lead us closer to this ideal, though forward progress requires a significant investment in the development of new techniques and strategies, along with fundamental coordination chemistry studies. This Account highlights our progress in developing new synthetic catalysts that operate in an enzyme-inspired active site, while also underpinning these advances with the fundamental inorganic coordination chemistry that (1) supported our efforts to synthesize these active sites and (2) provided the stereochemical foundations necessary to understand and interpret the data.

Scheme 1



Our work in this area has been spurred by the generic idea that since enzymes use their active site to control and carry out chemical reactions, transition metal catalysts that existed in their own active site (tailored to their needs of course) would lead to unique chemical reactivities not available in normally solvated environments. Our approach of immobilizing catalysts into a cross-linked polymer to control their outer-sphere environment provides the basis for our expectation that desirable properties will emerge. Moreover, the physical properties of the cross-linked polymers could also provide properties related to phase separation of catalysts and reactants that would help round out the perfect catalyst.

The technique that we have adapted for creating synthetic active sites is made possible by molecular imprinting. In our application of this procedure, we have synthesized polymerizable metal complexes that contain a combination of polymerizable and nonpolymerizable ligands.[1] This experiment transfers the three-dimensional structure of the metallomonomer into the surrounding matrix by copolymerization into rigid polymers. Subsequent removal of the nonpolymerizable ligand vacates a cavity that is shaped (or functionalized or both) with the structure (or functionality or both) of the removable ligand (the imprint). As Scheme 1 diagrams, this approach has the potential to tailor the chemical environment of the transition metal catalyst and thus give rise to wholly new chemical reactivities.

At the onset of this work, a significant body of literature existed on the utilization of molecular imprinted polymers (MIPs) for analytical applications,[2] but many fewer reports focused on utilizing imprinting techniques to catalyze organic reactions, though this has changed significantly in the past 5 years or more.[3] Because information regarding how associated cavities would affect transition metal reactivity was lacking, we began our efforts by determining how a chiral cavity affected the reactivity of a square-planar transition metal site. The results of these experiments also stimulated a series of studies examining how chiral ligands communicated across the square plane,

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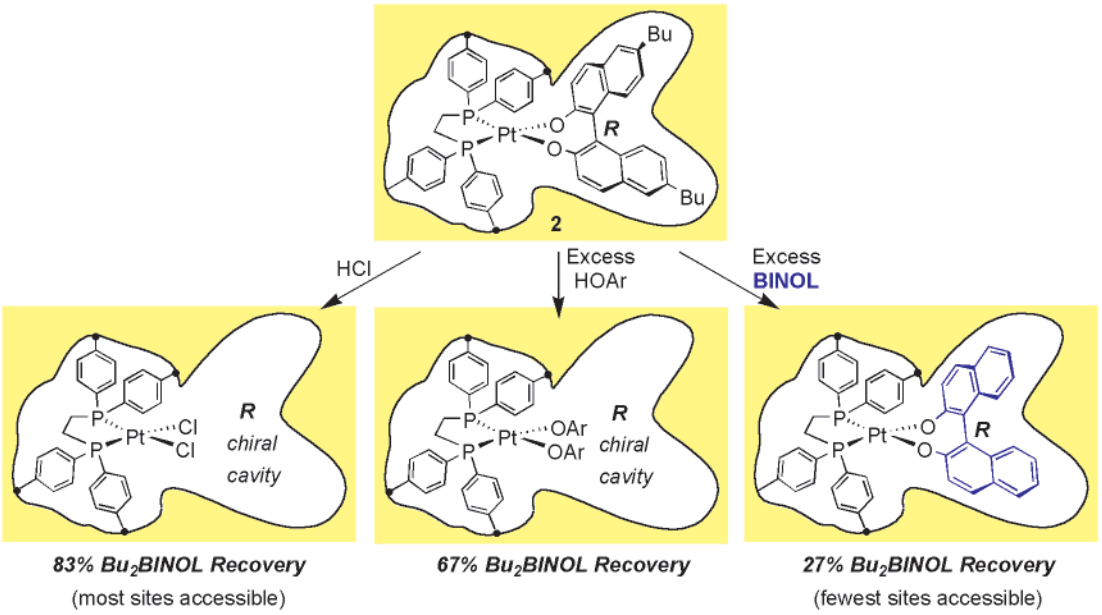
Scheme 2



which in turn provided information relevant to the interpretation of the results of the imprinting experiments. This initial study also stimulated new ideas for creating more tailorable active sites that utilize stereochemical communication across the square plane, imprinting into the metallomonomer itself, or secondary interactions within the active sites.

The interrelation of imprinting and coordination chemistry has been key to making progress on the bigger challenge, not only for securing stereochemical details but also for ensuring that each intended reaction is clean and predictable since the characterization of metal complexes in the polymer is difficult. Several examples of this synergy will be discussed in the following sections.

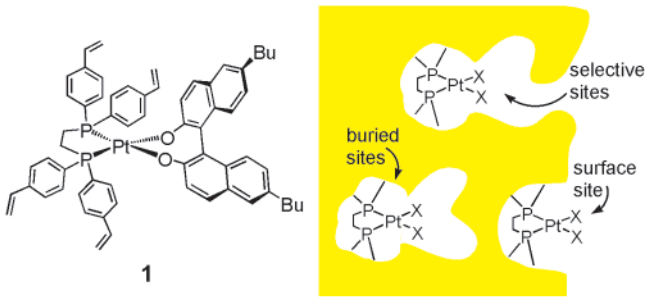
A. Demonstrating and Interpreting a Chiral Cavity Effect

To first investigate how an associated chiral cavity would affect the reactivity of a transition metal, we designed an experiment wherein a cavity would be created by the postpolymerization removal of a chiral, nonpolymerizable ligand. Metallomonomer **1** consists of a polymerizable, achiral diphosphine (1,2-bis-di-4-vinylphenylphosphinoethane, vinyl dppe) and a nonpolymerizable, chiral imprinting ligand ((*R*)-Bu_2BINOL, 1,1′-binaphthyl-2,2′-diol)) coordinated to a square-planar Pt(II) center.[4] Copolymerization of **1** with a cross-linking agent (ethylene dimethacrylate, EDMA) and an equal volume of a porogenic solvent incorporates the template into a highly cross-linked but porous polymer (Scheme 1). The highly porous nature of the polymer (surface area $\approx$ 200−600 m^2/g)[5] allows reagent access to the internal sites and enables the chemical removal of the imprinting ligand, which reveals a chiral cavity associated with the platinum metal center.[6]

The enantiopure (*R*)-Bu_2BINOL imprinting ligand could be removed in a variety of ways (Scheme 2). Treating the imprinted polymer with HCl liberated the Bu_2BINOL and presumably generated a P_2PtCl_2 species in the polymer. This method excised 83% of the imprinted Bu_2BINOL; however, bleaching of the polymer suggested that complete protonation of the BINOL occurred.[7] A second method to remove the imprinting ligand was by treatment with excess of an acidic phenol, α,α,α-trifluoro-*m*-cresol. This method excised 67% of the imprinting ligand and generated a $P_2Pt(OAr)_2$ species in the polymer. A final method was the direct exchange of one BINOL for another. In this case, the large size of the reactants leads to only 27% of the sites being accessed. These data pointed to a distribution of sites, smaller reagents (HCl) being able to access more sites than bulkier ones (BINOL).

The reactions in Scheme 2, along with a fourth (the reverse of phenol for BINOL exchange), were then utilized to probe the distribution of active sites. Polymer **2** was first treated with a large excess of α,α,α-trifluoro-*m*-cresol to generate a reactive $P_2Pt(OAr)_2$ site. Since $P_2Pt(OAr)_2$ readily exchanges its OAr ligands for BINOL, treating with excess *rac*-BINOL exchanges it into most of the reactive sites. To label those sites that were presumably most open, we then reacted the polymer with *rac*-Br_2BINOL, taking advantage of the fact that only a small number of sites were capable of BINOL/BINOL exchange. HCl cleavage then enabled quantitation of both the rebound BINOL and Br_2BINOL. The enantiomeric excess (ee, %) for the rebound BINOL was much higher than that of the rebound Br_2BINOL; in other words, those sites able to undergo a BINOL/BINOL exchange were much less selective than those sites that were too small to accommodate these two large ligands (associative ligand substitution) but were able to accommodate OAr/BINOL exchange. The conclusion is that the MIP was composed of a distribution of sites with BINOL rebinding selectivities ranging from 2:1 to nearly 97:3 in favor of the imprinted enantiomer, which summed to an 85:15 enantiomer selectivity. Obtaining the

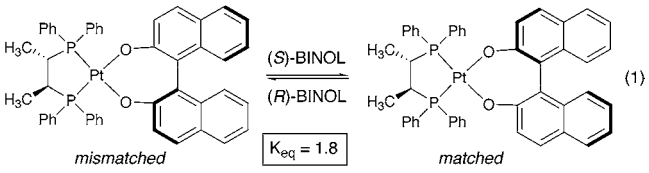
Scheme 3



highest rebinding selectivities (97:3), however, required that many of the less selective sites be poisoned (the Br_2-BINOL uptake sites), taking advantage of the fact that these less selective sites were also more reactive. The conclusion was that these MIPs were composed of a complex distribution of sites that ranged from completely encapsulated and inaccessible to entirely solvent-exposed (no chiral cavity) (Scheme 3).

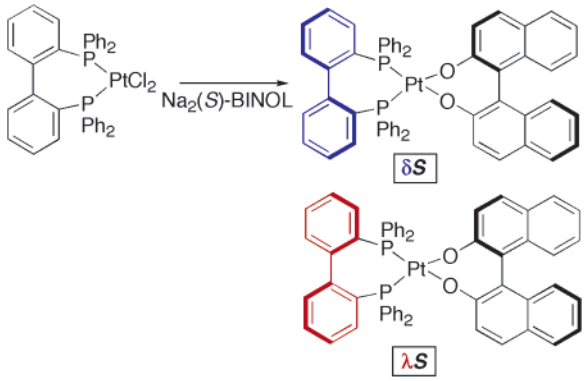
Our interpretation of these data revolved around simple-minded notions of how an *R*-Bu_2BINOL shaped cavity would affect the selectivity of a Pt metal center. A different explanation of the results that we considered less likely but required attention was the possibility that the cross-linked rigid polymer matrix was freezing the normally conformationally flexible dppe ligand into chiral conformations and that these chiral conformations were somehow responsible for the BINOL rebinding enantioselectivities. We did not consider this possibility completely unreasonable since the solid-state structure of (dppe)Pt(*R*-BINOL) showed that *R*-BINOL induced the λ-skew conformation in the diphosphine.[8] It was thus conceivable that this λ-skew was being locked into the polymer matrix, resulting in a chiral dppe inner sphere contribution to the selectivity at the metal center.

To test this hypothesis, we conducted a series of solution experiments with a chiral dppe analogue, (*S*,*S*)-chiraphos, to determine what effect a bona fide chiral diphosphine would have on BINOL enantioselectivity.[8] Both matched (from a crystallographic analysis) and mismatched complexes of (*S*,*S*)-chiraphosPtBINOL were synthesized. BINOL exchange reactions (eq 1) showed that



the matched diastereomer was more thermodynamically favored, and the bias was slight ($K_{eq} = 1.8$, 0.4 kcal mol^{-1}). Thus if the achiral dppe were locked exclusively into the λ-skew conformation during polymerization,[9] this inner sphere component could only account for 28% ee, lower than what was observed in the rebinding experiments. These solution coordination chemistry studies on the stereochemical communication of ligands across the Pt(II) square plane[10] allowed us to confidently ascribe the observed BINOL rebinding results to the effect of chiral cavities in the outer sphere of these metal complexes. Thus, the imprinted metal sites were capable of differentiating two enantiomeric ligands in a fashion that was not possible under normal solution solvation environments.

Scheme 4



B. Maximizing the Inner Sphere Contribution: An Aborted Imprinting Experiment

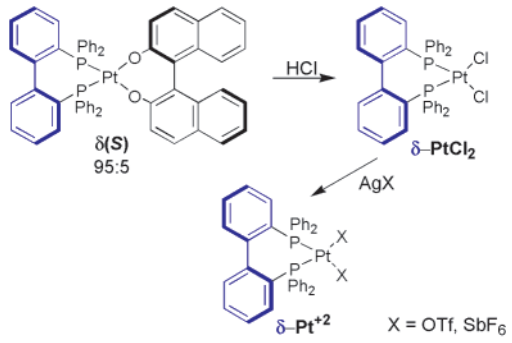
One hypothesis that we had for improving the selectivity of reactions in MIPs was to increase the inner sphere contribution. Initially our goal was to combine a chiral diphosphine (inner sphere contribution) and a chiral imprinting ligand (outer sphere contribution) in the same template molecule. Upon copolymerization and removal of the imprinting ligand, an active metal site with a chiral diphosphine and associated chiral cavity should result, which could provide catalysts with superior selectivities.

To initially test the notion of two chiral ligands in the same Pt(II) complex, we investigated the solution coordination chemistry of a (biphep)Pt(BINOL) (biphep = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl) complex.[11] Although biphep is not resolvable due to rapid rotation about the biaryl C−C bond, when coordinated to a substitution inert metal such as Pt(II), it can be dynamically resolved. As Scheme 4 illustrates, reaction of enantiopure BINOL with (biphep)$PtCl_2$ resulted in a 1:1 ratio of diastereomers, the result of biphep adopting either the λ- or δ-skew conformation. The biphep ligand can be dynamically resolved on-metal by heating to provide the thermodynamically preferred diastereomer ($\delta(S)$) (95:5); the minor diastereomer ($\lambda(S)$) was separated by fractional precipitation.

Treatment of the diastereomers with HCl provided enantiopure (biphep)$PtCl_2$ complexes, which could be activated with AgOTf or $AgSbF_6$ to provide highly enantioselective Lewis acid catalysts the stereochemistry of which came exclusively from a classically nonresolvable ligand (Scheme 5).[12] These results confirmed that an otherwise nonresolvable diphosphine ligand could be used in asymmetric catalysis[13,14] and initiated a new line of research.[11]

Although our original intention was to lock the biphep stereochemistry into a rigidified polymer with a dia-

Scheme 5



stereopure metallomonomer and high enantioselectivities were demonstrated with these complexes (effective inner sphere control), the physical properties of the complexes were such that they did not lend themselves to imprinting experiments,[15] particularly since characterization of metal complexes in the polymer is difficult. Nevertheless, the stimulation for designing these experiments came directly from considerations of inner sphere contributions to catalysis in active sites.

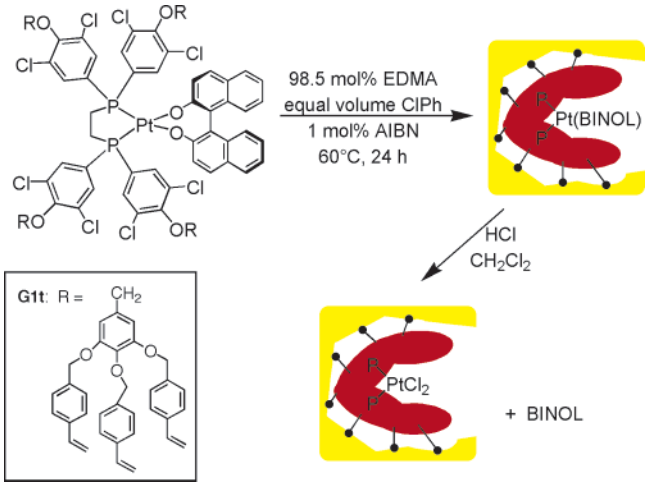
C. Synthesis of More Well-Defined Active Sites by Imprinting into Oneself

As described in section A, copolymerization of **1** into a highly cross-linked porous polymer led, after Bu_2BINOL removal, to P_2Pt- sites capable of enantiomer recognition in BINOL rebinding. However, the metal sites were displayed in a complex distribution of environments ranging from completely encapsulated by polymer to entirely solvent-exposed, Scheme 3. The goal of catalysis requires eliminating site heterogeneity and surface sites, since unselective reactive sites (surface sites) would disproportionately contribute to selectivity and erode the selectivity of the catalyst.

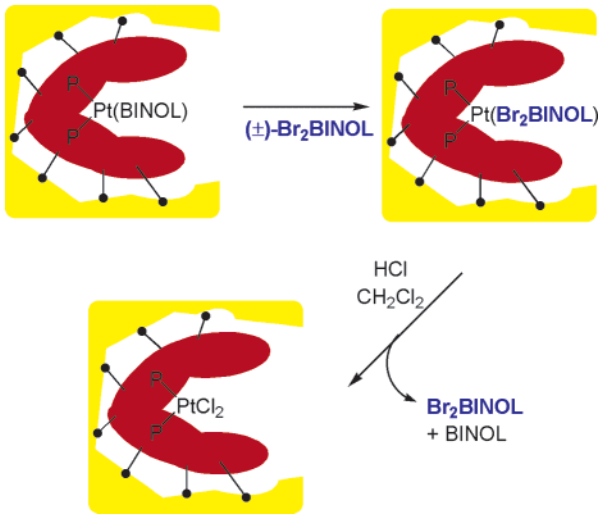
Copolymerization is a complex process that starts with a 1:1 ratio of monomers to a porogenic solvent and ends with a biphasic monolith.[5a] Given the complexity of this process, we thought it unlikely that tweaking the polymerization conditions would create significantly more defined and controllable active sites. We considered, however, that to a first approximation it was the interface between the bulk polymer and the cavity that was essential to the structure of the active site. Consequently, tailorable active sites with enhanced structural and compositional homogeneity would be possible if each metallomonomer were provided with its own interface to bulk polymer. Our first choice was a metallomonomer with relatively short, polymerizable dendritic arms that would provide such an interface. Since each site would now contain the same amount of dendritic foliage, each should be chemically and compositionally similar, at least when compared to the traditional MIP protocol for generating active sites. In this scenario, the imprinting media would be rigidified dendrimer instead of cross-linked bulk polymer,[16] hence the term imprinting into oneself.

To test this strategy, a metallomonomer with polymerizable dendrons was synthesized and the fidelity of the

Scheme 6



Scheme 7



imprint examined. Active site accessibility was first measured by protonative removal of BINOL with HCl. Not surprisingly, fewer sites were amenable to BINOL removal for **G1t** (67%) compared to a nondendritic control system similar to **2** (87%) (Scheme 6). Bleaching of both polymers upon treatment with HCl suggested that complete protonation occurred[17] but that egress of the BINOL from the polymer is more hindered in the dendrimer system. This hindered egress could be caused by a dendritic arm physically blocking the BINOL from escaping the active site or by changes in the solvent channels.

The molecular recognition properties of the P_2PtBINOL imprinted sites were assayed with a BINOL/Br_2BINOL exchange reaction (Scheme 7), which enabled site accessibility, selectivity, and heterogeneity to be quantified. Data analysis showed that dendritic metallomonomers provided active sites capable of enantiomer recognition in BINOL rebinding reactions; however, fewer of the sites were able to accommodate the associative ligand exchange compared to the nondendritic system. In addition, the overall selectivity dropped from a best case of 85:15 *S*/*R* to 75:25. An active site distribution analysis indicated that *fewer low selectivity sites were formed* but that this

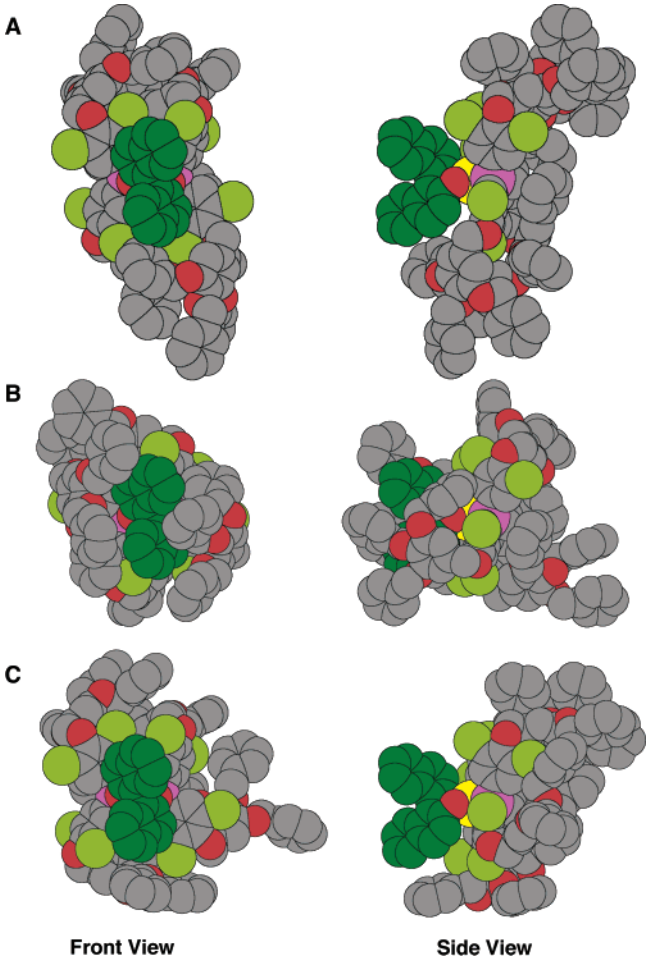
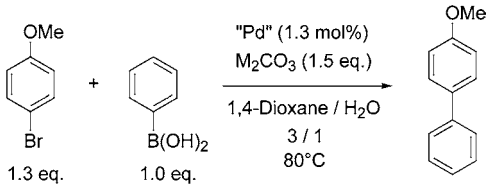


FIGURE 1. Space filling representations (H-atoms removed for simplification) of the three representative local minima from the Spartan MMFF94 Monte Carlo conformer analysis of the nonstyryl version of **G1t-Cl$_2$**. Structure **A** is the lowest energy structure, while structures **B** and **C** are randomly chosen local minima of nearly equal relative energy (see text). Light green denotes Cl; dark green denotes BINOL carbons; red denotes O; pink denotes P; yellow denotes Pt.

was also accompanied by *fewer of the superselective sites* (97:3). Thus, although the averaged selectivity diminished, the dendrimer system successfully created a more narrowed distribution of sites.

A critical evaluation of the loss of superselective sites ultimately led to an analysis of the mobility of the flexible benzyl ether linkages. These types of dendrimers are known to adopt compact or extended structures depending on the solvent,[18] polymerization of a combination of which would lead to a natural, undesirable structural heterogeneity. To model the conformational flexibility of **G1t**, a Monte Carlo simulation was carried out on the dendritic portion. Figure 1 contains three of the lowest 10 kcal mol^{-1} structures (of ~60 local minima), chosen to represent the diversity of the possible structures. These structures range from the most compact, where the BINOL ligand is completely encapsulated, to structures with the dendrites pointing in seemingly random directions. This variability in dendrimer arm conformation most likely accounts for the diminished selectivities in BINOL rebinding.

Table 1. Suzuki Reaction Catalyzed by MIP−Pd or CE−MIP−Pd



entry	M_2CO_3	% conv[a,b]	% conv$_{CE}$[a,c]	gain[d]
1	K_2CO_3	26	66	2.5
2	Rb_2CO_3	48	77	1.6
3	Cs_2CO_3	49	70	1.4
4	Na_2CO_3	57	71	1.2
5	Li_2CO_3	42	44	1.1

[a] Determined by GC after 6 h. [b] MIP−Pd catalyst. [c] CE−MIP−Pd catalyst. [d] conversion by CE−MIP−Pd/conversion by MIP−Pd.

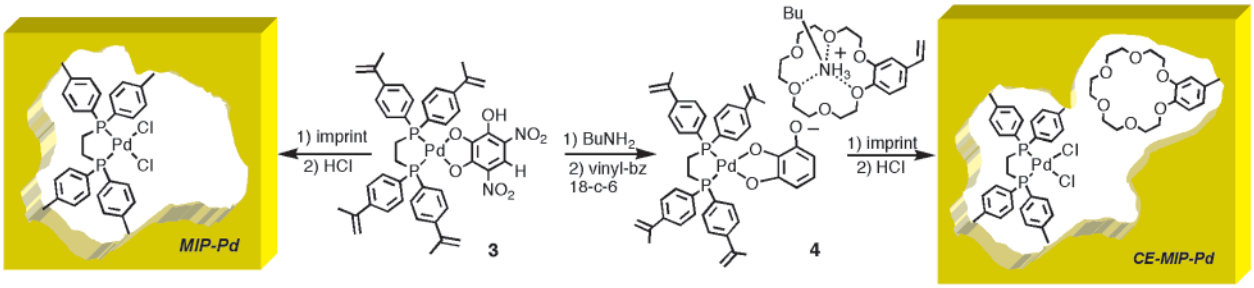
These modeling studies have stimulated the design and synthesis of new metallomonomers that put a premium on minimizing the number of conformational degrees of freedom that the dendrites can populate. Metallodendrimers with repeat units that adopt more extended conformations (e.g., esters and amides)[19] should enhance site-to-site homogeneity while also reducing the number of buried/encapsulated sites.

D. Cavity Functionalization as a Strategy for Improving Homogeneity and Selectivity

In another approach to improving site selectivity and homogeneity, we sought to functionalize the second coordination sphere of a palladium catalyst with a crown ether. It had previously been noted that reversible noncovalent binding between difunctional analytes and difunctionalized MIP sites led to a situation where *the most reactive sites were also the most selective*.[20] This scenario is, of course, far more desirable than having the most reactive sites also be the least selective, which occurs in unfunctionalized sites such as those described in section A. To test whether this situation could be engineered in a catalytic experiment, we examined the combination of palladium catalysis and crown ethers since they are known to provide synergistic effects in asymmetric catalysis.[21]

The palladium complex **4** was designed to generate an ion pair that would assemble a polymerizable crown ether and catalyst precursor.[22] This prepolymerization complex was obtained by treating **3** with a primary amine and a crown ether. Both were copolymerized with EDMA and the resultant polymers treated with HCl to remove the template pyrogallol ligand (Scheme 8). The Suzuki reaction[23] was used to test the effect of the crown ether in this system. As seen in Table 1, the crown ether modified catalyst was more active than the catalyst lacking the crown; more important, however, is the response to the alkali metal carbonate. Viewed as a ratio of rates, it was clear that the trend exactly follows the relative binding affinities of the metal to 18-c-6 ($K^+ > Rb^+ > Cs^+ > Na^+ > Li^+$),[24] that is, the best cation for 18-c-6 provides the largest rate gain. While we do not yet know the mechanistic source of the rate acceleration (which step(s) in the

Scheme 8[a]



[a] Reagents and Conditions: imprint, (i) **3** or **4**, EDMA, ClPh (Pd/EDMA/ClPh = 1:99:100), AIBN (1%), 60 °C, 24 h and (ii) CH_2Cl_2 Soxhlet extraction, 16 h; HCl, (i) HCl in dioxane (4 N), CH_2Cl_2 and (ii) Soxhlet extraction, 16 h.

catalytic cycle), the beneficial effect of binding the counterion of the nucleophile on the rate is evident. We hope to eventually utilize similar noncovalent binding processes to provide the preequilibrium event that turns on the *more reactive/more selective* scenario.

Although this rate enhancement was most likely due to a counterion/crown ether binding event, the intimate structure and stereochemical relationship between the catalyst and crown ether in the active site was not obvious. At the heart of this ambiguity were questions about the exact structure of the metallomonomer as ^{1}H NMR spectra of **4** are broad, indicative of dynamic behavior. Numerous processes could account for this fluxionality, not the least of which are association/dissociation processes involving the ammonium/crown and cation/anion. Since the later noncovalent interactions are also relatively nondirectional, the degree of uncertainty in the structure of the imprinted site is high. Nevertheless, a significant and broadly interpretable effect is observed suggesting that even larger synergistic effects could reward further refinements in the structure and homogeneity of the active site.

This analysis of the structure of **4** has initiated the development of new catalyst crown ether assemblies that utilize more directional and controllable interfaces between the polymerizable catalyst and crown fragments. Highly directional noncovalent bonds, which replace the ion pair assembly of crown and catalyst, should provide new solutions to the problem of active site homogeneity and functionality in catalysis.

Summary

A clear synergy exists between fundamental coordination chemistry and the technically demanding problem of active site engineering in synthetic polymers. Characterization limitations in the described polymers can be partially supported and compensated for by knowledge of the structure and reactivity (especially regarding stereochemistry) of the imbedded metal complexes and catalysts. Moreover, the questions that arise from considering these same complexes in imprinted environments stimulate new complexes for study. Conversely, the examination of mechanisms of chirality transfer in homogeneous compounds can stimulate new approaches to the synthesis of supported active metal catalysts. We have benefited from both.

We gratefully acknowledge our co-workers, whose names appear in the references, along with the Petroleum Research Fund, the NSF (Grants CHE-0075717 and CHE-0315203 most recently) and the NIGMS (Grant GM-60578) for financial support. M.R.G. is a Camille Dreyfus Teacher Scholar.

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