Moleculary Imprinted Polymers as Reagents and Catalysts in Organic Chemistry

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MacMillan Group Meeting
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Good Reviews

Alexander, C. *Tetrahedron*, **2003**, *59*, 2025.

Whitcombe, M.J. *Synlett*, **2000**, (6), 911.

Mosbach, K. *Curr. Op. in Chem. Bio.*, **1999**, *3*, 759.

Motherwell, W.B. *Tetrahedron*, **2001**, *57*, 4663.

What are Molecularly Imprinted Polymers (MIPs)?

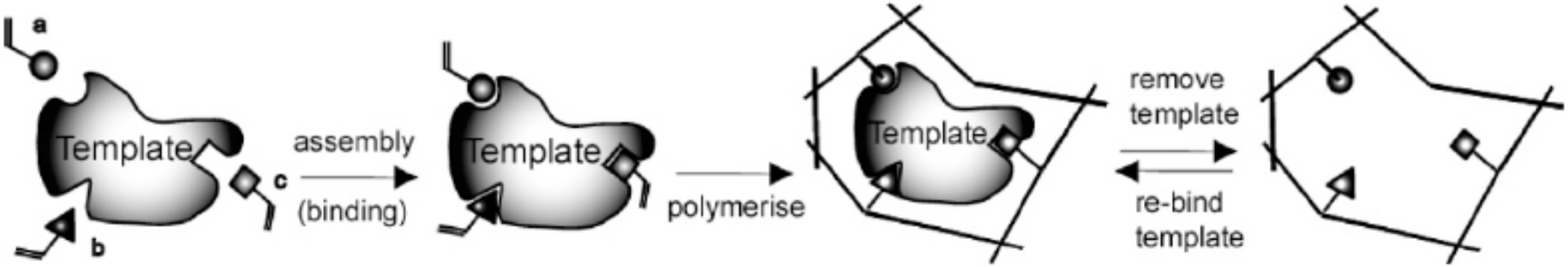
- MIPs are polymers that contain highly selective recognition sites as a result of polymerization around a template molecule bound covalently or non-covalently to functional monomers

- MIP synthesis is a three step process:

  1. Assembly of the template with funtional monomer units via covalent bonding, hydrogen bonding, hydrophobic, π-π or ionic interactions

  2. Polymerization around the template/monomer complex, incroporating the monomers into the polymer backbone to create a recognition pocket

  3. Removal of the template by washing with organic solvent or acid/base hydrolysis



- To date a wide range of templates have been used including organic compounds, sugars, peptides, nucleotides, proteins, crystals and even cells

What are MIPs Used For?

■ Industrial Use

Purification: selectively removing reaction products or by-products

■ Organic Chemistry

Stoichiometric Reagents: scavengers, passive supports, supported reagents, protecting groups

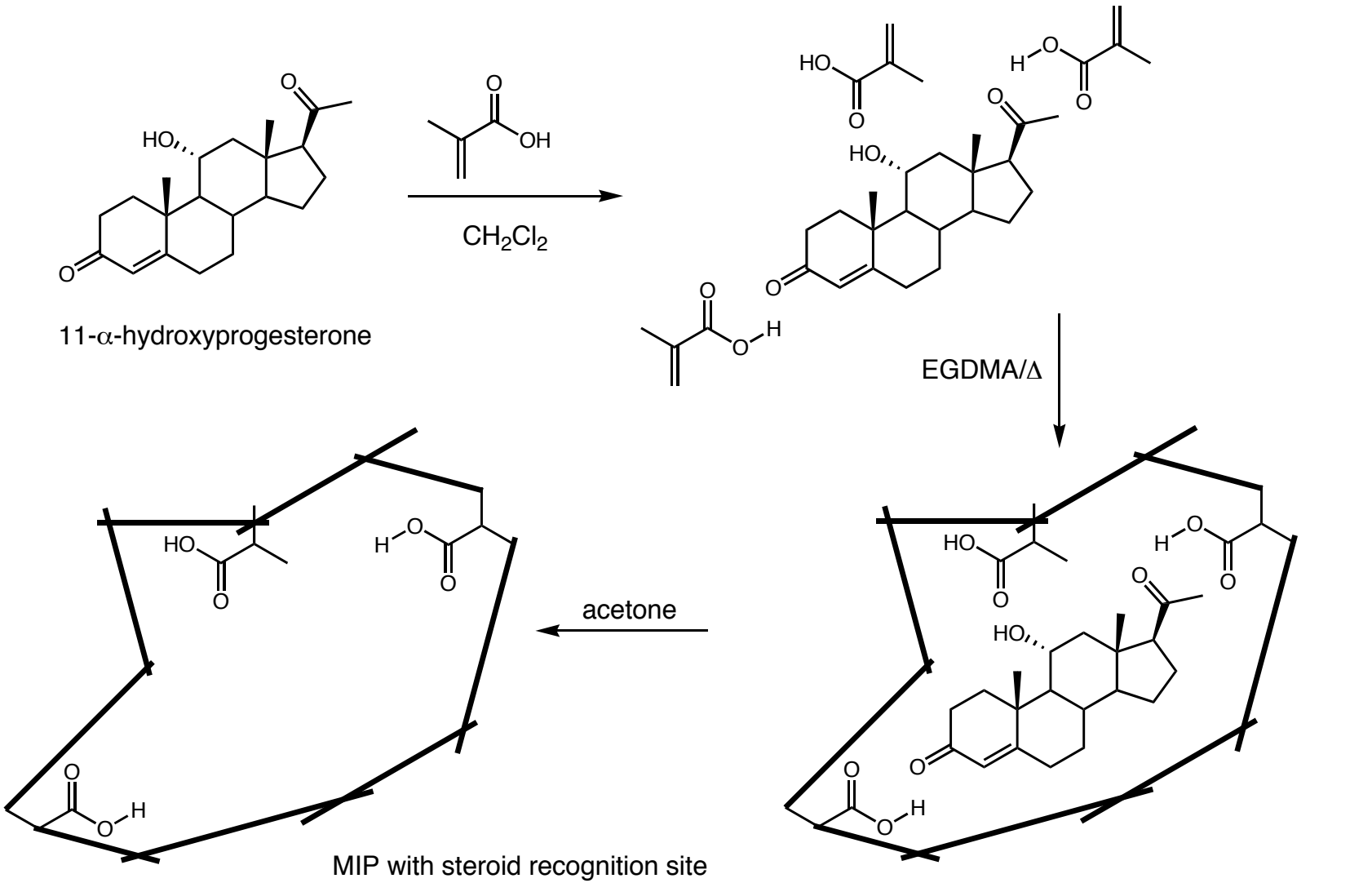
- In this aspect they are similar to other polymer supported reagents in that they are valued for their ease of use, however, they offer the advantage of being able to differentiate between enantiomers and regioisomers

Catalysts: C-C bond formation, elimination reactions, mimics of natural enzymes, transition metal mediated reactions

- In this function, MIPs are most often compared to catalytic antibodies and have been shown to catalyze a wide variety of reactions, in some cases exerting control over regio- and stereoselectivity

MIPs as Selective Adsorbents

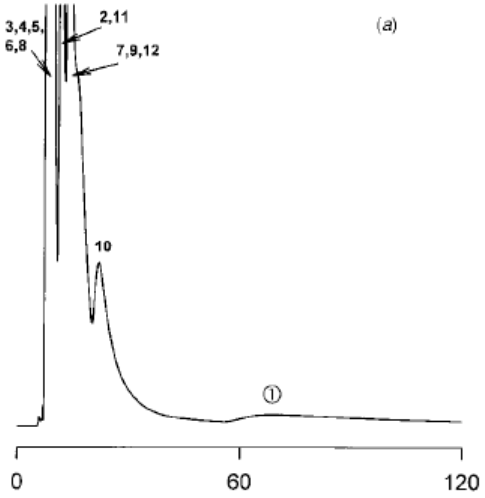
■ Mosbach *et. al.* developed a method of screening combinatorial steroid libraries using an MIP imprinted with the steroid 11-α-hydroxyprogesterone.



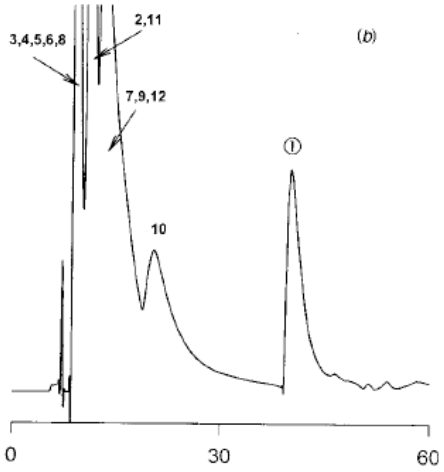
Mosbach, K., Ramstrom, O. *Anal. Comm.,* **1998**, *35*, 9

MIPs as Selective Adsorbents:

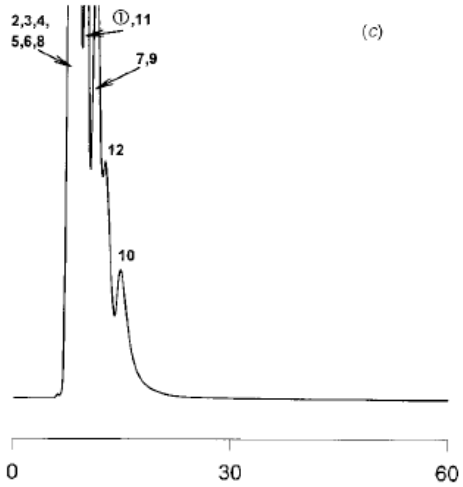
■ The bulk MIP was then packed into HPLC columns and tested for its ability to selectively remove the imprint from a mixture of 12 steroids with various substitution patterns



0.1% AcOH/DCM



0.1%-5% AcOH/DCM



0.1% AcOH/DCM

■ Conclusions:

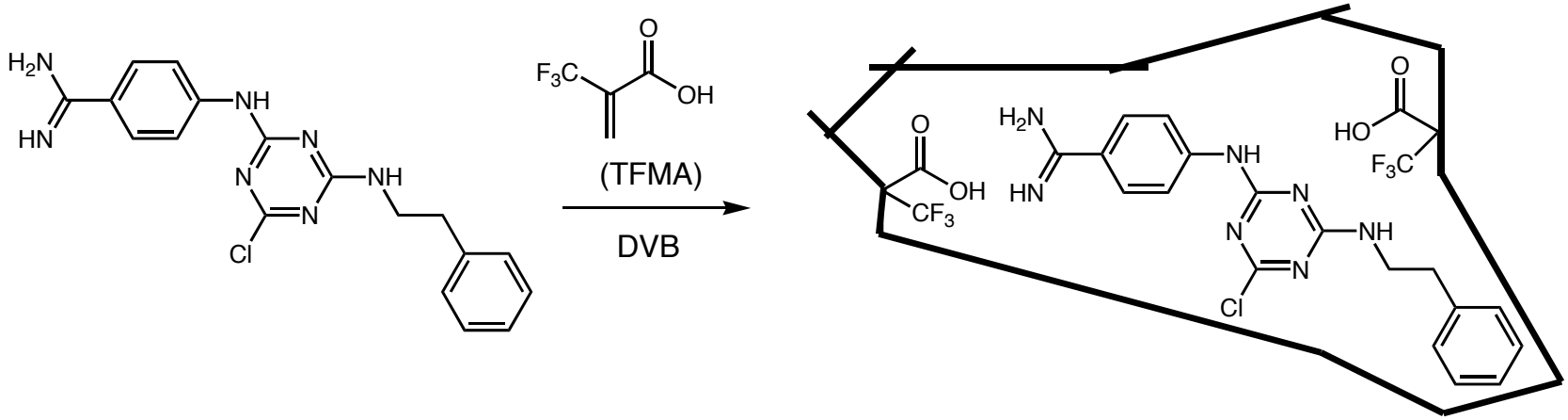
- MIP showed high selectivity for the template molecule
- Stereochemical information is retained – 11-β-hydroxyprogesterone not selected for

■ Mosbach proposes that MIPs can be used as artificial receptors for screening combinatorial libraries

Mosbach, K., Ramstrom, O. *Anal. Comm.,* **1998**, *35*, 9

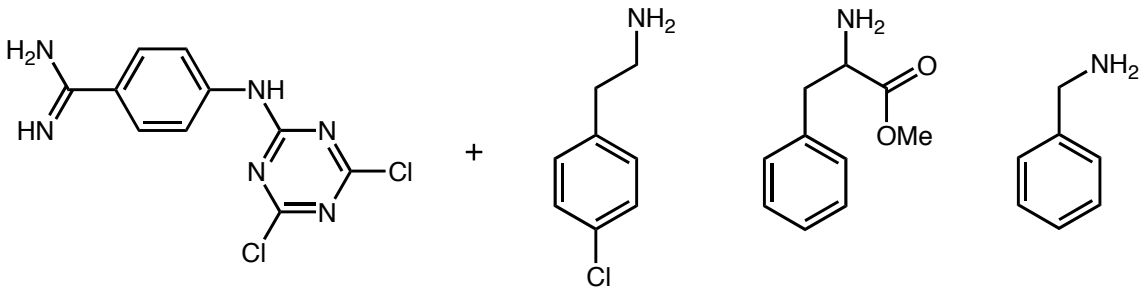
The Anti-Iodiotypic Approach: Imprinting to Find New Drug Candidates

■ Mosbach used an MIP imprinted with a kallikrein inhibitor to screen new compounds for activity



■ Control experiments using template fragments showed that multiple interactions are necessary for better binding

■ Imprinted sites used to direct synthesis of new compounds by incubating MIP with **1** and adding amine coupling partners **2**-**4**



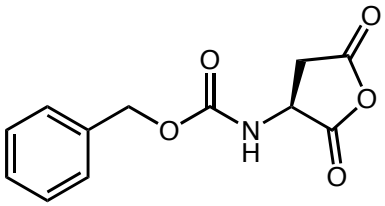
1 **2** **3** **4**

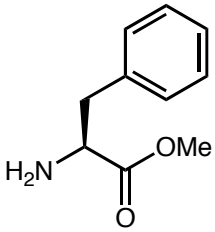
The coupling product with **4** was shown to inhibit kallikrein with a K_i (5.2 μM) similar to the template coumpound (K_i = 4.5 μM)

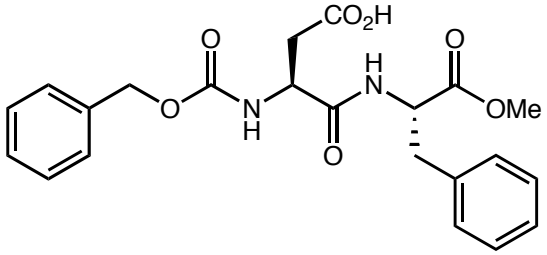
Mosbach K. *JACS.*, **2001**, *123,* 12420

MIPs as Adsorbents: Stereoselective Byproduct Removal

■ Mosbach takes advantage of the high substrate specificity exhibited by MIPs to selectively remove the undesired product enantiomer in the synthesis of *N*-(benzyloxy-carbonyl)aspartylphenylalanine methyl ester (ZAPM) from L-aspartic anhydrideand L-phenylalanine methyl ester

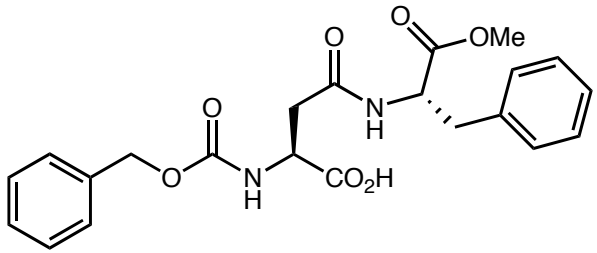






α-L, L-ZAPM

+



β-L, L-ZAPM

MIP imprinted against β-L, L-ZAPM increased product purity from 59% to 96%when used for solid phase extraction

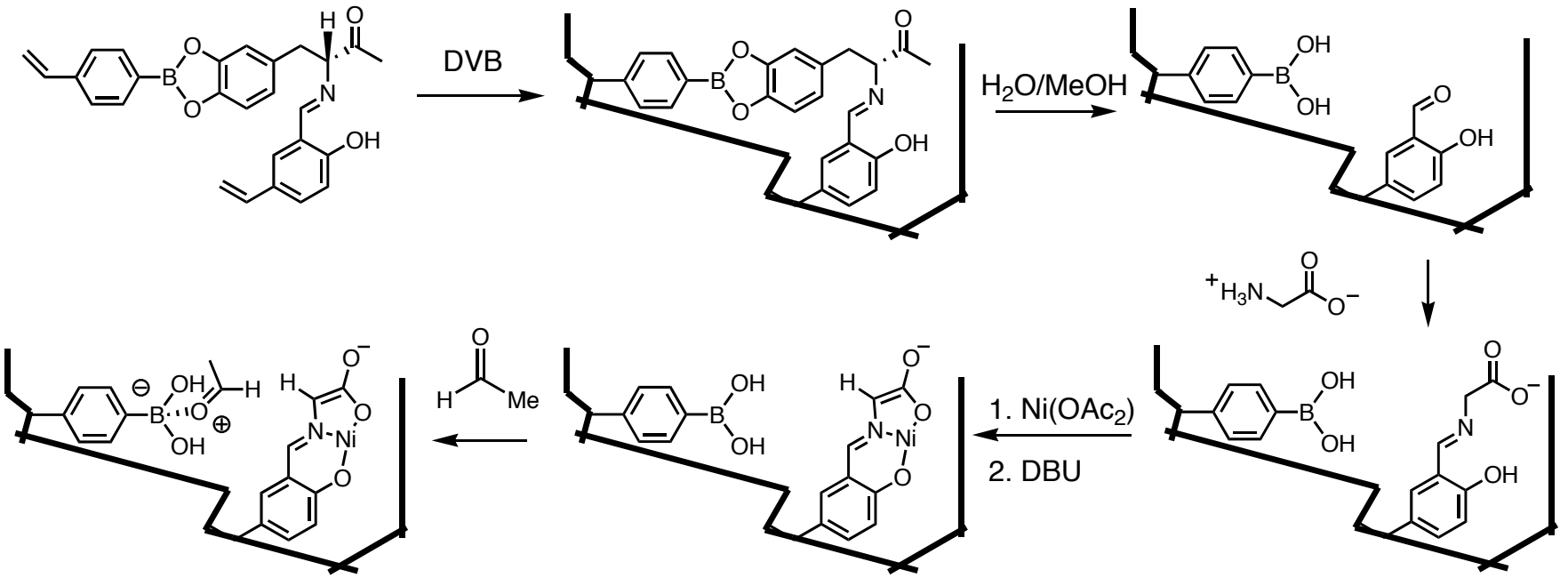
■ Interesting observations:

- Imprinting with two functional monomers (4-vinylpyridine and methacrylic acid) afforded MIPs with higher affinities that those imprinted using only one functional monomer.
- Imprinted polymer beads were just as effective as bulk polymer in selective removal of β-L, L-ZAPM

Mosbach, K., Ramstrom, O. *Anal. Chem.,* **1998**, *70*, 2789

MIPs as Chiral Microreactors

- First reported independently by Shea (cyclopropanation) and Neckers (photodimerization) in 1980
- Wulff used this concept to synthesize α-amino acids from glycine using Schiff base chemistry



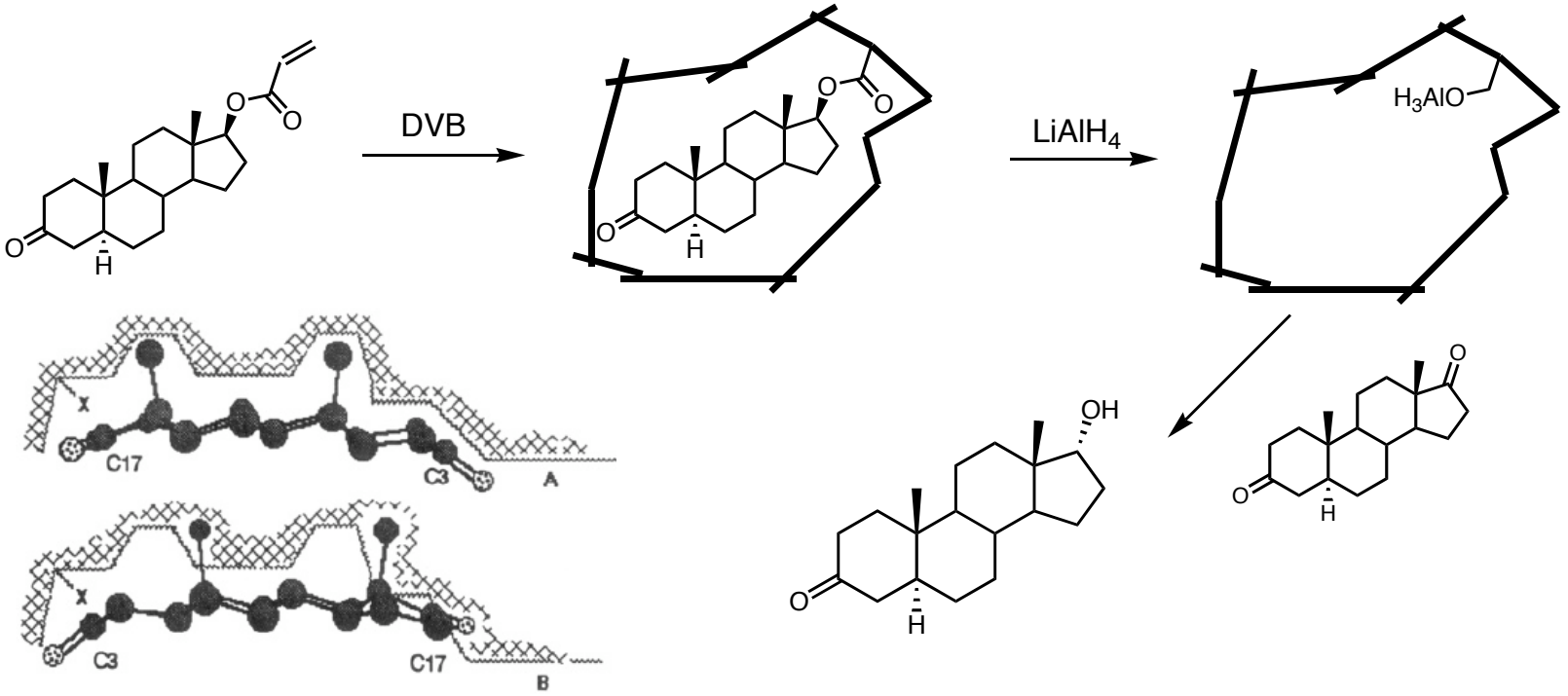
36% ee

electrophile approach at the Si face of the enolate is controlled by the chiral environment of the recognition pocket

Wulff, G. *Macromol. Chem. Phys.*, **1998**, *190*, 1717&1719

Reactive MIPs: Stereoselective Supported Reagents

■ Bystroem showed that MIPs can regioselectively reduce steroids and also exhibit a measure of enantiocontrol



■ Results

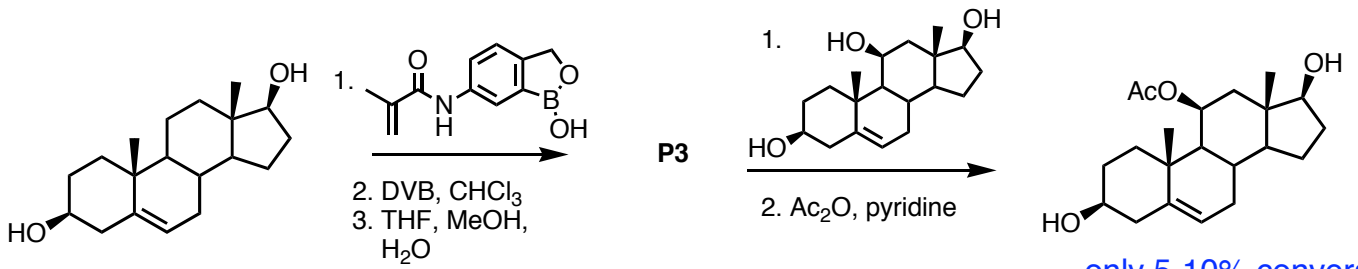
- Complete preference for reduction at C17, this preference is reversed when imprinted with ester at C3
- Obtain a 70:30 mix (β, α) with templated polymer vs. 96:4 for the control polymer

■ Swelling is very important, better template removal and higher conversion is observed in polymers with high swellability (200%) than those with low swellability (120%). However, low swelling polymers exert a stronger stereochemical influence

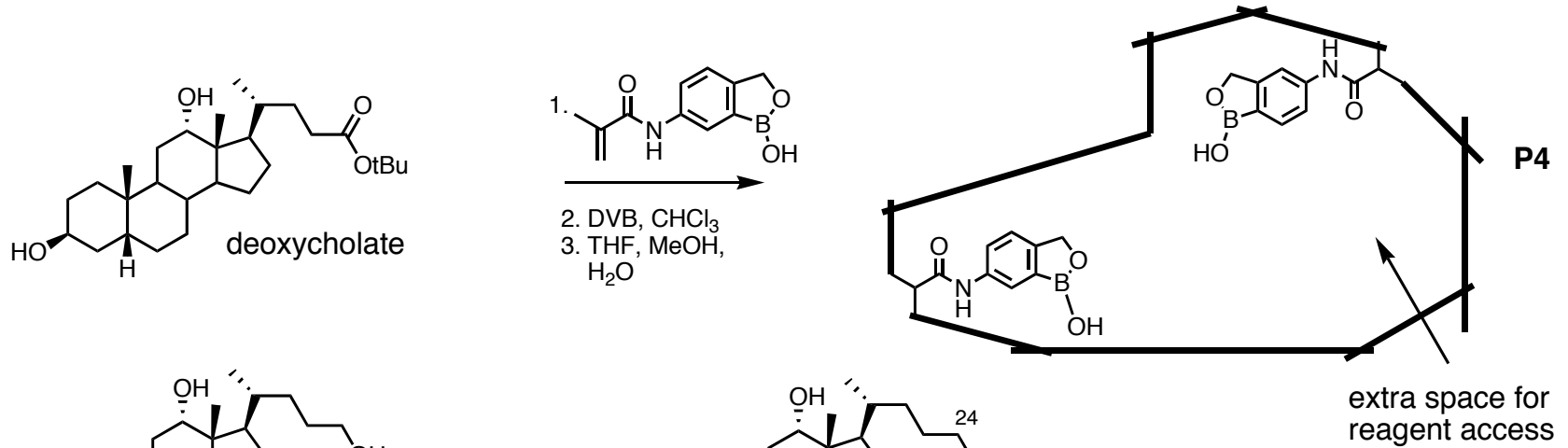
Bystroem, S. *JACS.,* **1993**, *115,* 2081

MIPs as Protecting Groups for Polyfunctional Substrates

■ Whitcombe *et. al.* designed MIPs that serve as protecting groups for regioselective steroid acylation. Careful control experiments showed that the template was covalently rebound within the polymer. However reactivy was poor and attributed to the inablility of the reagents to access the steroid in the recognition site



■ Imprinting with a template designed to create a larger recognition pocket resulted in greater reactivity



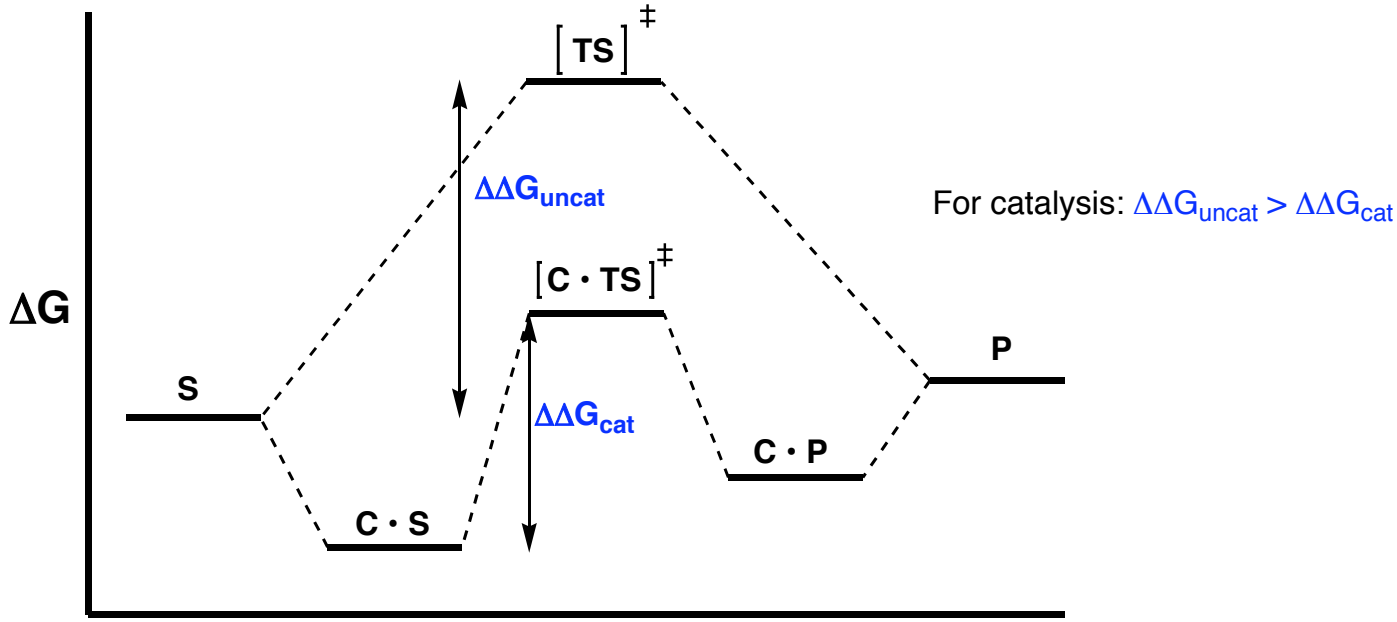
Whitcombe, M.. *JACS.*, **1999**, *121,* 6640

Catalytic Applications of MIPs

■ MIPs are well-suited for catalytic applications

- The recognition site is geometrically well-defined and can exert stereoselectivity
- They exhibit a high degree of substrate specificity

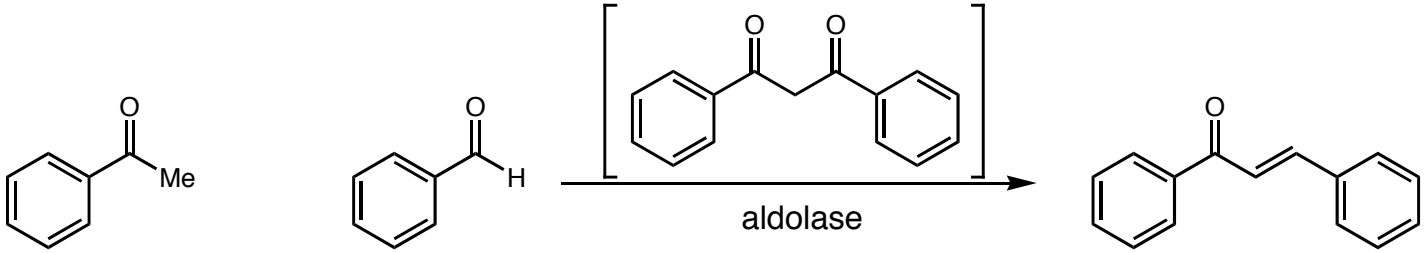
■ In order for catalysis to occur, an MIP needs to stabilize the transition state of the reaction more than the starting materials or the product. Therefore, to create an MIP catalyst a transition state analog (TSA) is used as the imprinting template.

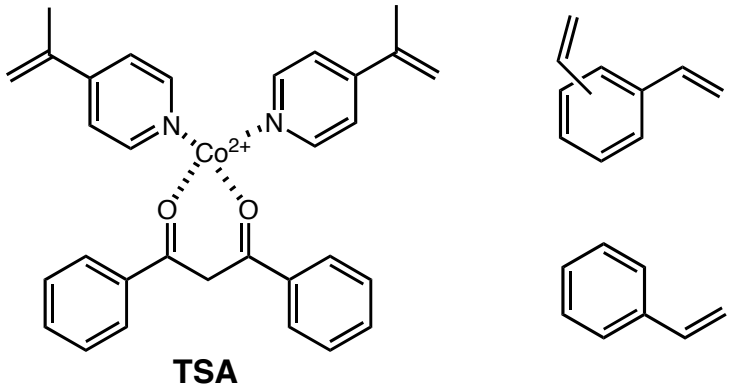


■ Ironically, the characteristics that make MIPs useful as catalysts, the rigidity of the recognition pocket and tight substrate binding can also lead to problems such as low reactivity and product inhibition

Carbon-Carbon Bond Forming Catalysis

■ Matsui and Mosbach designed an MIP with class II aldolase activity by imprinting with a dibenzoylmethane(DBM) cobalt(II) complex





TSA

Aspects of TSA design

Turnover – dicarbonyl vs α,β-unsaturated ketone

Reactivity – 4-vinylpyridine also acts as base

Stabilization – π –π interactions with polymer backbone

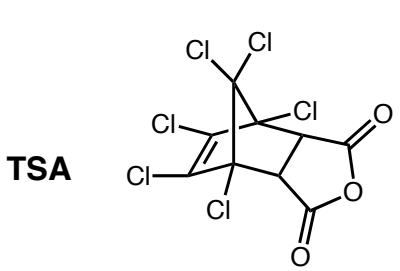
■ Three polymers were imprinted, the first with the DBM-Co^{2+} complex, the second with DBM and and the third with Co^{2+} DBM had the greatest affinity for the DBM-Co^{2+} MIP while acetophenone, benzaldehyde and chalcone had very low affinities

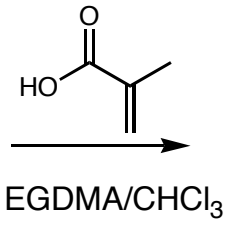
■ Reaction rate was eight times faster in the DBM-Co^{2+} MIP as compared to solution phase. Addition of DBM inhibited the reaction which the authors interpret as proof that the reaction is taking place within a recognition pocket, not just on the polymer surface

Matsui, J., Mosbach K. *JACS.,* **1996**, *61*, 5414

Carbon-Carbon Bond Forming Catalysis

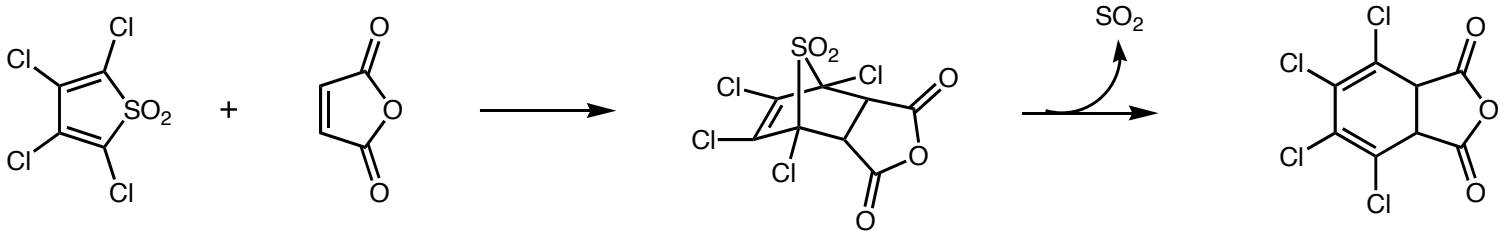
■ Mosbach employed the same technique to make an efficient Diels-Alder MIP catalyst





P1

	yield (mM)
P1:	15
control:	6
solution:	5



■ Kinetic studies demonstrated a 270-fold rate enhancement over the reaction in solution

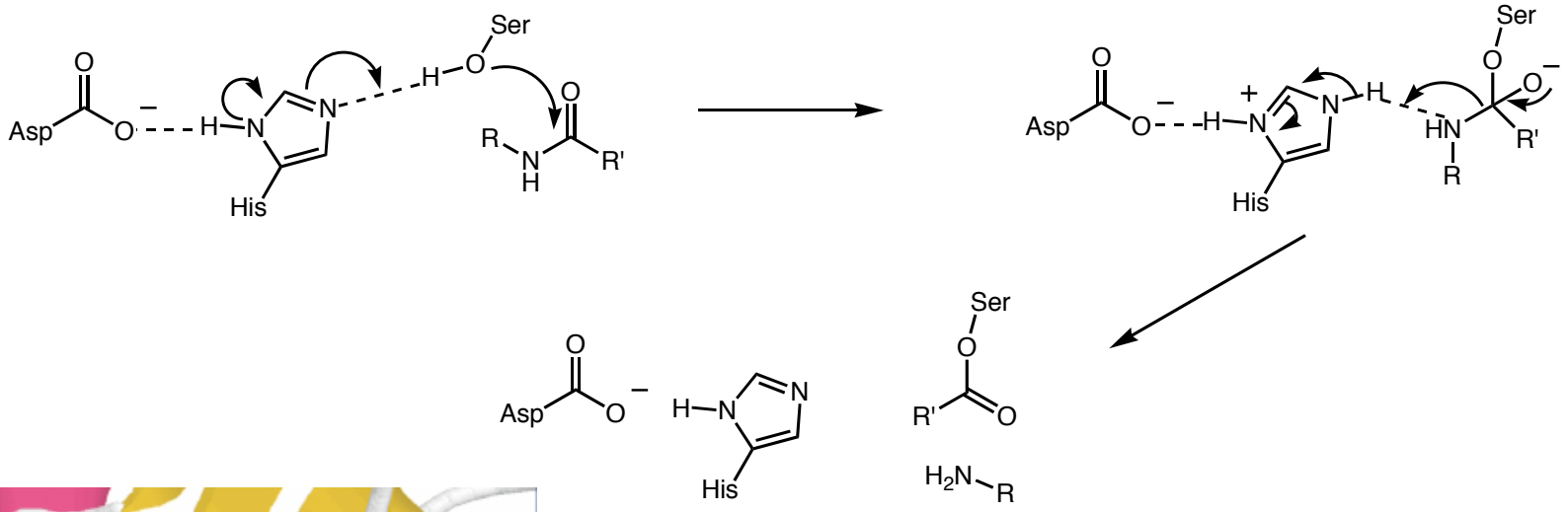
■ Addition of chlorendic anhydride (TSA) resulted in 41% inhibition of the MIP catalyzed reaction, indicating that the reaction occurs within the polymer cavities

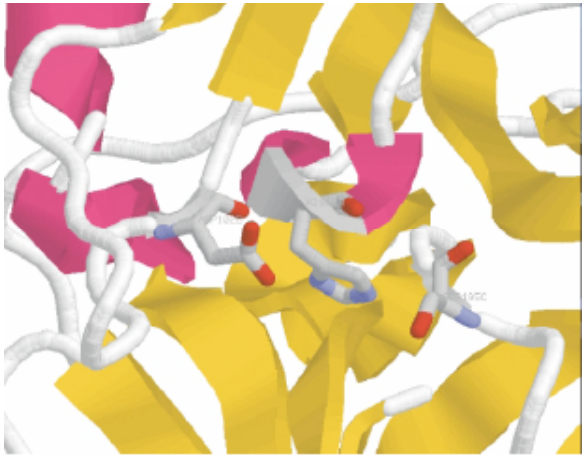
Mosbach K. *Makromol. Rapid. Comm.*, **1997**, *18*, 609

Ester Hydrolysis: A Common Target for Enzyme Mimics

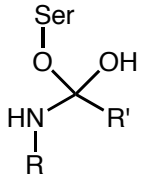
■ The ester hydrolysis activity of proteases, such as trypsin, chymotrypsin and subtilisin, are attractive targets because their mode of action using the "catalytic triad" of serine, histidine and aspartate residues is well understood.

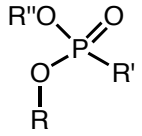
The catalytic triad: a proton shuttle





■ Mimic the tetrahedral intermediate with a phosphonate ester

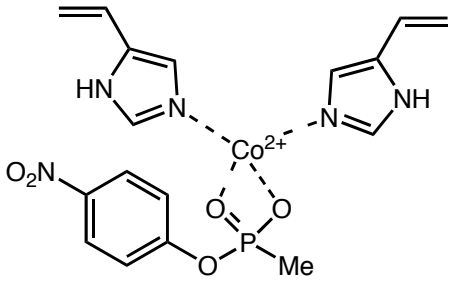




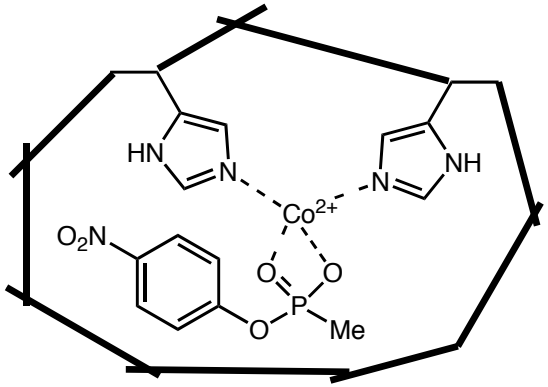
Drawing on the Catalytic Triad for TSA Design

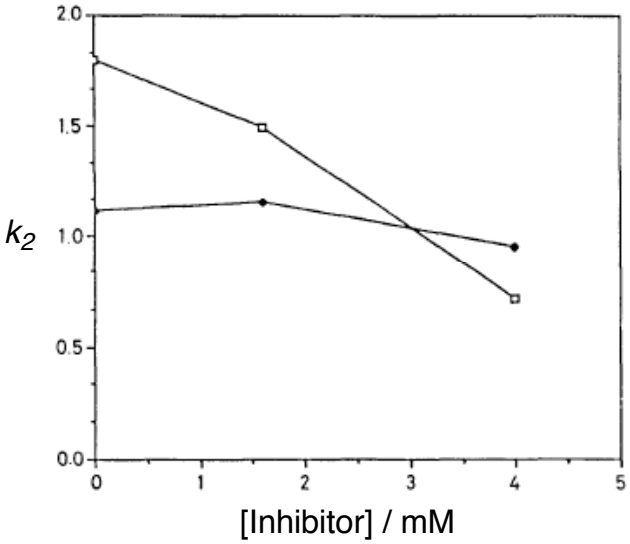
- First attempt by Mosbach using a substrate analog proved to be unsuccessful, saw only a 2-fold rate enhancement as compared to control polymers

- Imprinting with a TSA resulted in a more active polymer



1,4-dibromobutane

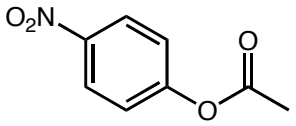


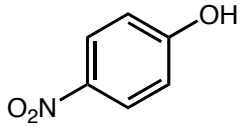


◆ - control polymer

◘ - MIP

1. MeOH/phosphonate buffer

2. 



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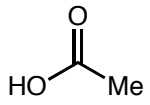
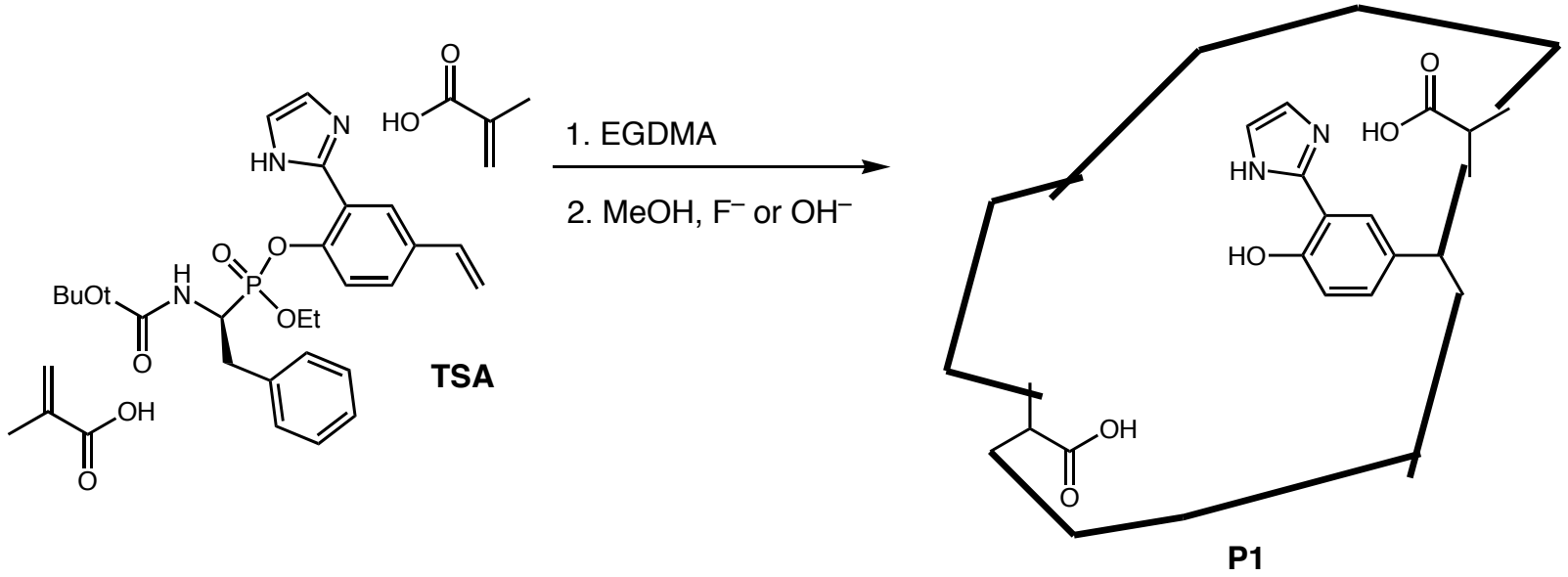


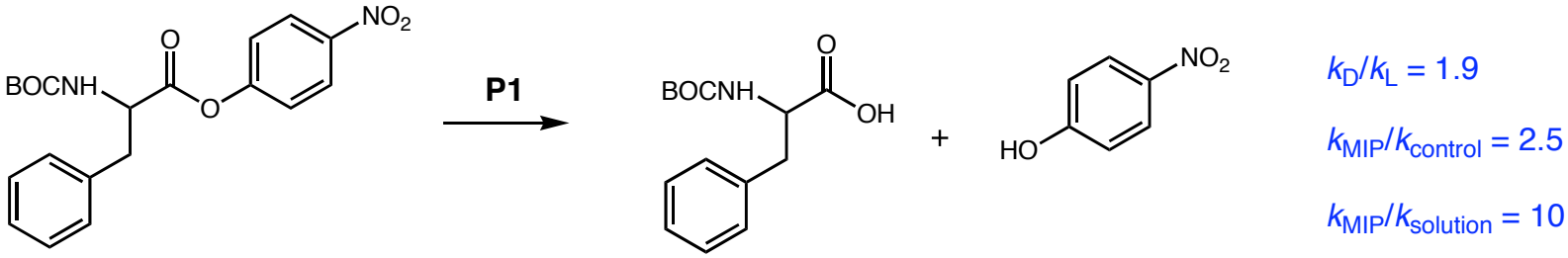
- The TSA successfully inhibited the MIP catalyzed reaction but did not affect reaction with a control polymer

Mosbach, K., Robinson, D. *J. Chem. Soc. Chem Comm.* **1989**, 969

Drawing on the Catalytic Triad for TSA Design

■ Shea and Sellergren went further by mimicking all three catalytic triad residues and were able to catalyze the hydrolysis in a stereoselective manner by imprinting with D-phosphonate ester TSA

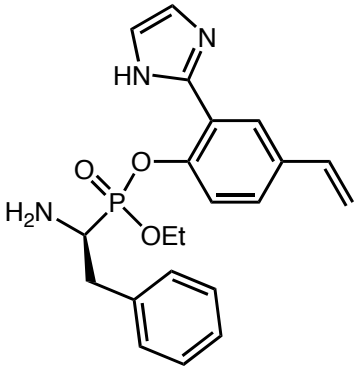




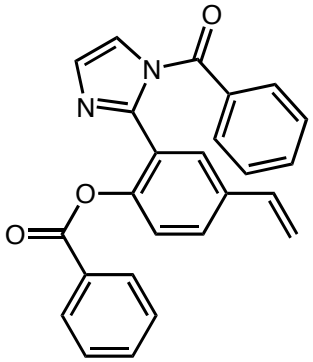
Sellergren, B., Shea, K. *Tet.* Asym., **1994**, 1403
Sellergren, B., Shea, K. *JOC.,* **2000**, 4009

Probing the Source of Reactivity

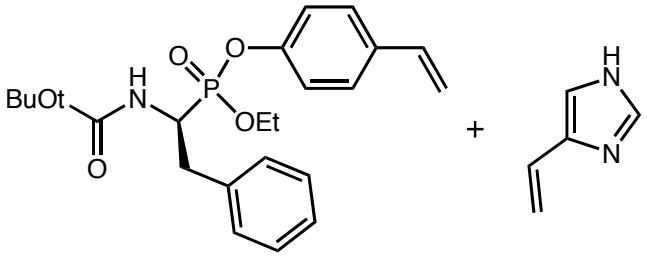
■ Extensive control experiments using polymers inprinted with a variety of templates examine the importance of the different characteristics of the TSA.



steric demands



achiral non-TSA

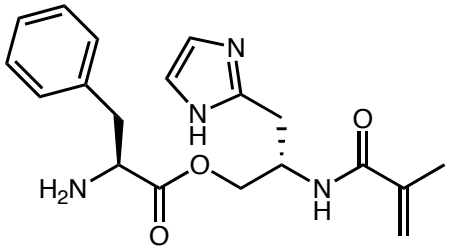


defined imidazole geometry

■ Also examined the effect of pH, hydrolysis conditions and degree of polymer swelling

■ Conclusions

- H-bonding involving the carboxylic acid groups primarily drives stereoselective binding
- The imidazole group is responsible for catalytic action
- Higher reactivity is seen with a TSA vs a substrate analog



substrate analog

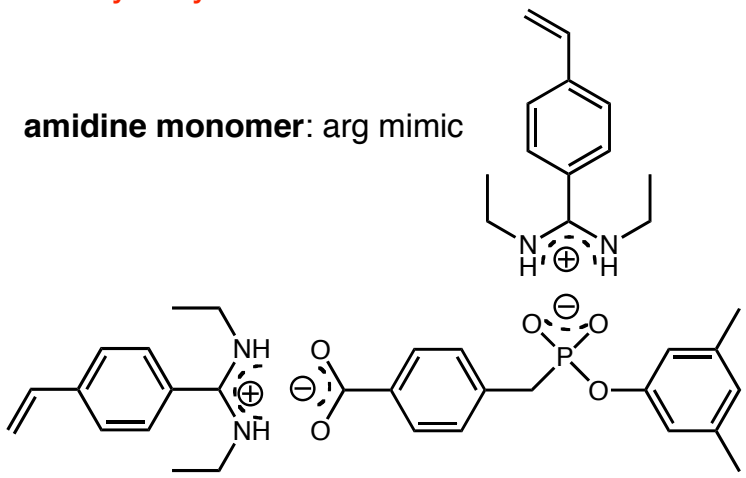
Sellergren, B., Shea, K. *Tet.* Asym., **1994**, 1403

Sellergren, B., Shea, K. *JOC.,* **2000**, 4009

Designing a Functional Monomer to Increase Reactivity

■ Wulff used a technique dubbed stoichiometric non-covalent imprinting to produce the most active ester hydrolysis MIP to date

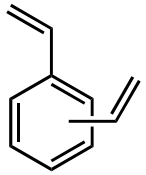
amidine monomer: arg mimic



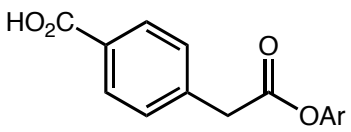
Association constant of the amidine monomer for carboxyl groups is > 10^6 M^{-1}

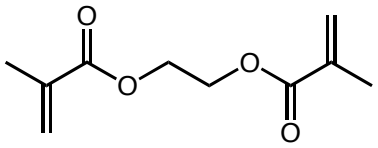
$k_{solution}$	$k_{solution/amidine}$	k_{MIP}	$k_{polymer/amidine}$
1.0	2.4	102.2	20.5

■ Polymers cross-linked with DVB were more active than those with EGDMA, attributed to hydrophobic interactions with the substrate



DVB





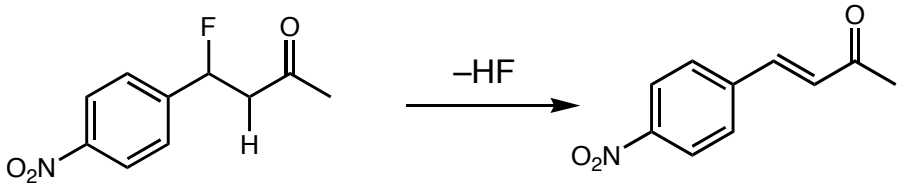
EGDMA

■ Observed product inhibition with ester substrates, demonstrated similarly enhanced hydrolysis rates for carbonates and carbamates without exhibiting product inhibition

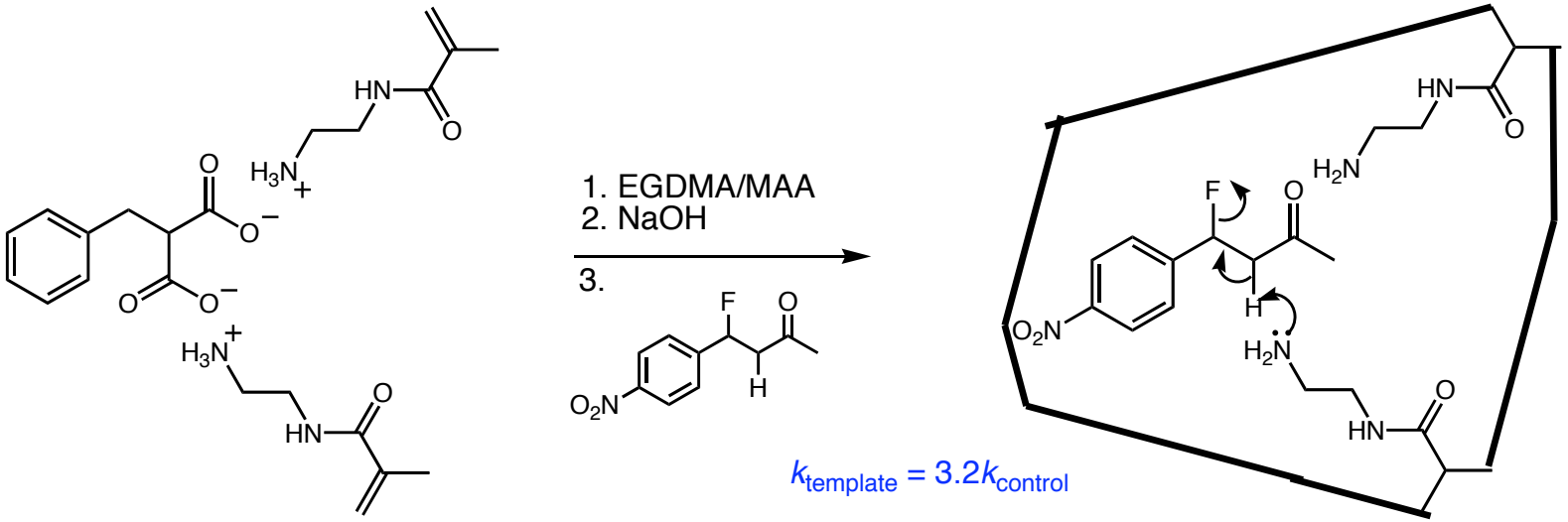
Wulff, G. *ACIEE*., **1997**, 1962

Elimination Reactions

■ The elimination of 4-fluoro-4(*p*-nitrophenyl)butan-2-one is the model reaction Shea chose to study



■ Functional monomer orients the substrate and acts as a base



■ Rate of MIP reaction was lower in polar solvents, implying that hydrogen bonding is playing an important role. This effect is opposite of what would be expected for an E2 mechanism

Shea, K.; Beach, J. *JACS*, **1994**, 379

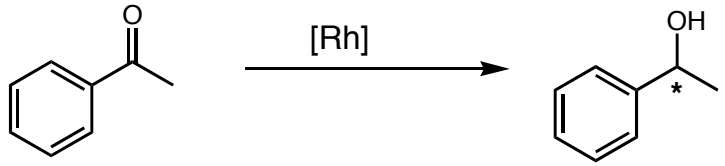
MIPs inTransition Metal Mediated Catalysis

■ Can control inner and outer sphere geometry around the reactive metal species

- As MIPs are highly crosslinked, their rigidity can enforce binding orientation about the metal and directionality of substrate approach

■ MIPs offer the added benefit of ease of use and purification

■ Lemaire reported some of the first work in 1995, the enantioselective hydride reduction of acetophenone using a Rh complex

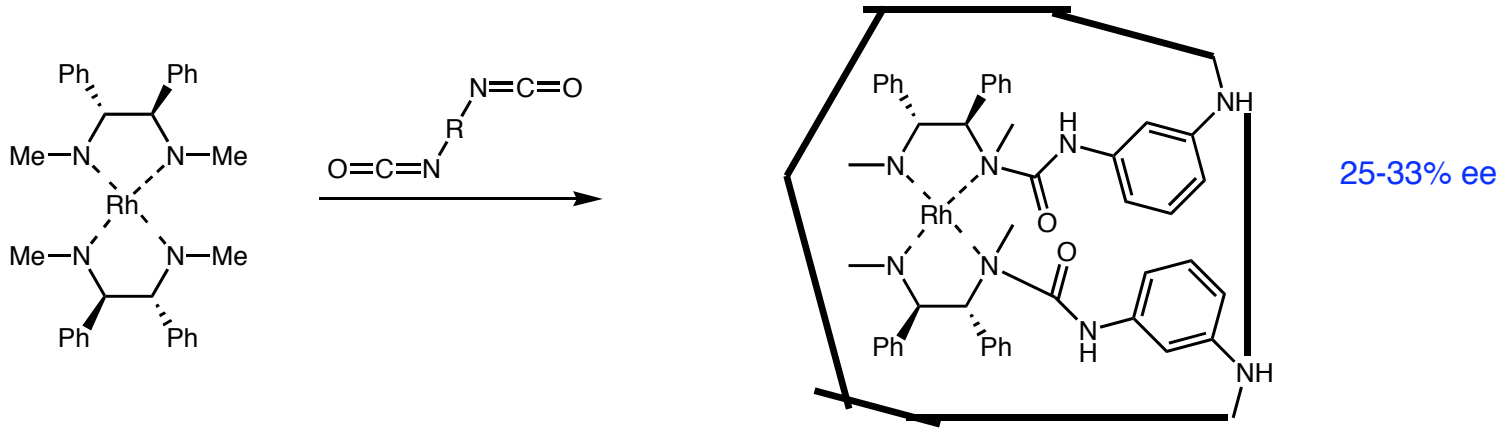


■ The reaction occurred with very low ee, leading him to investigate different types of imprinting templates.

Lemaire, M. *Tet. Lett.,* **1995**, *36*, 8779

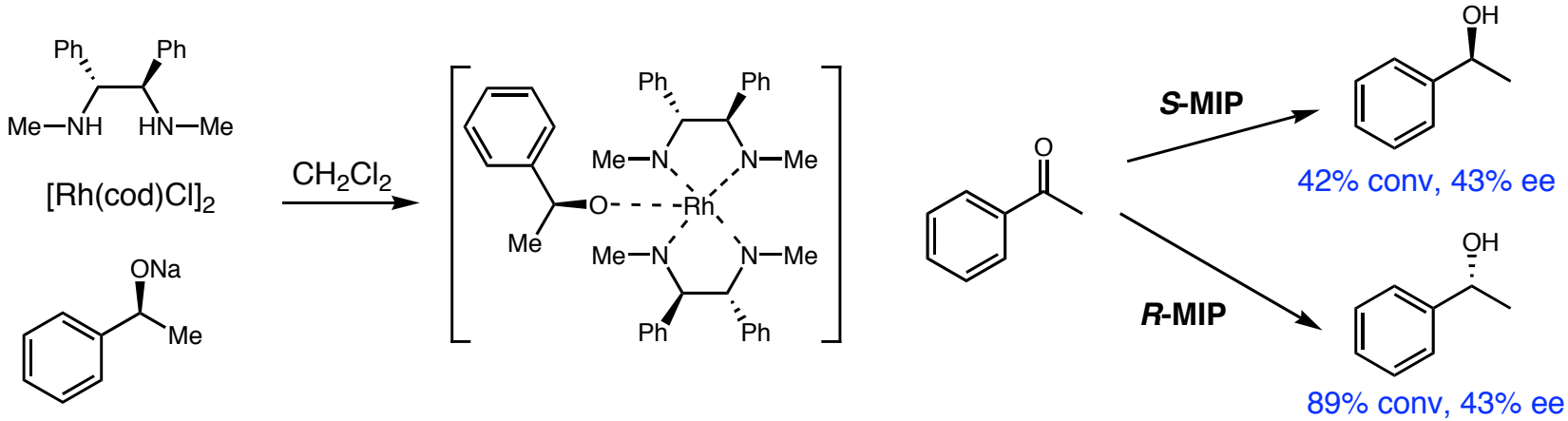
The Importance of Using the Right Template

■ First generation MIP used a chiral Rh complex as the template but gave low ee's when compared to the homogenous catalyst (55% ee)



25-33% ee

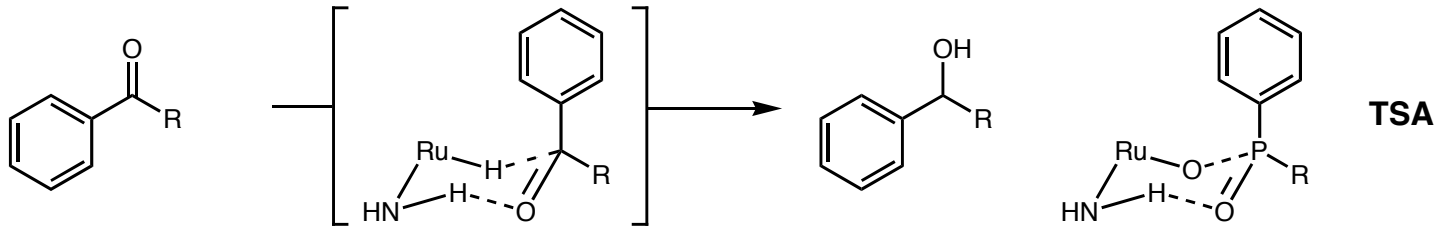
■ Imprinting the chiral Rh complex along with a substrate template resulted in polymers that gave higher ee's



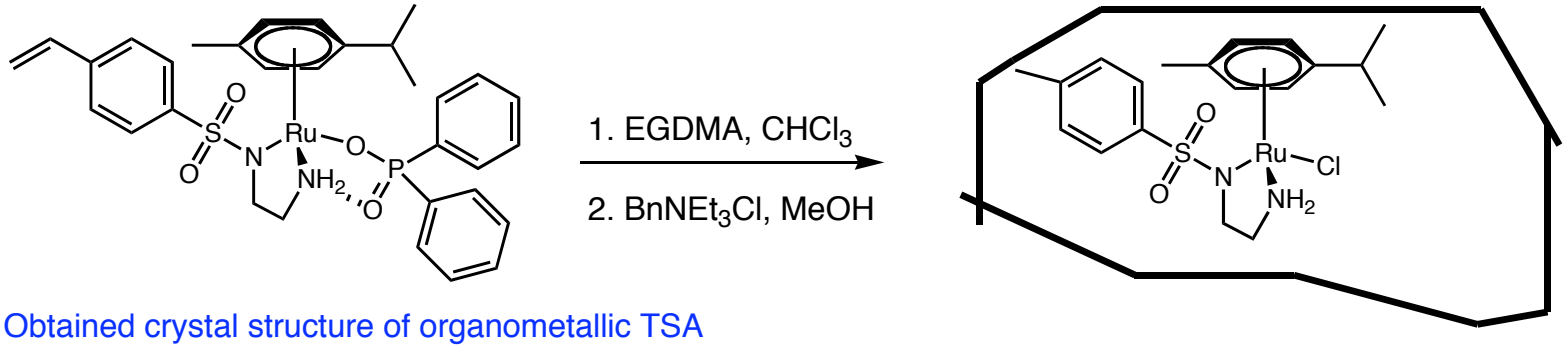
Lemaire, M. *Tet. Lett.*, **1995**, *36*, 8779

Multiple Attachments Result in Greater Reactivity

■ Severin and Polborn use a phosphonate ester TSA to design an MIP for the transfer hydrogenation of aromatic ketones

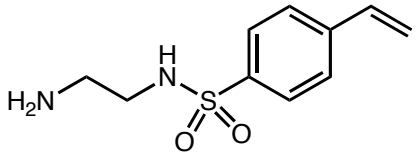


■ Building upon the idea of a functional monomer in non-metal catalysis, they produce active MIPs by using a modified metal ligand that is incorporated into the polymer backbone

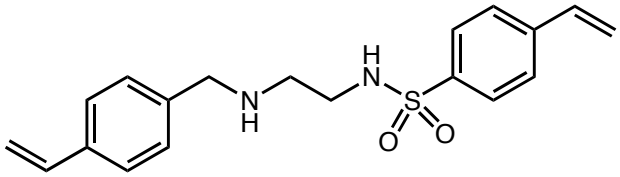


Obtained crystal structure of organometallic TSA

■ Using a diamine ligand with two styrenyl substituents lead to even greater activity



5% conv after 25min



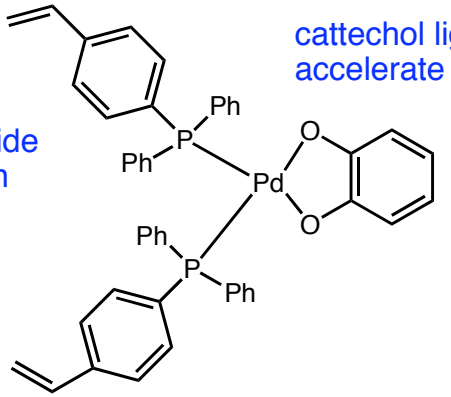
20% conv after 25min

Severin, K.; Polborn, K. *Chem. Comm.,* **1999**, 2481; *Chem. Eur. J.*, **2000**, *6*, 4604

Pd Cross-Coupling Catalysts

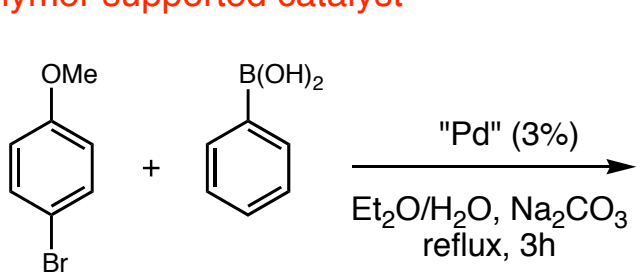
■ By controlling the geometry around Pd, Cammidge is able to produce MIP catalysts that are more active than the equivalent solid supported catalysts

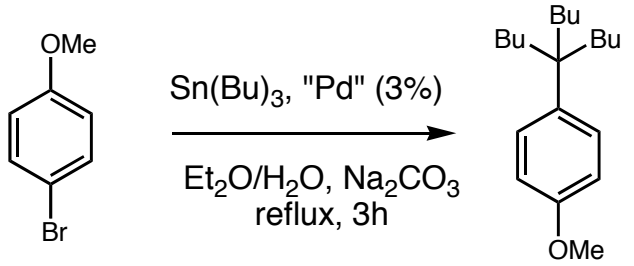
polymerizable PPh_3 ligands provide structual rigidity in the recognition site



cattechol ligand enforces cis square planar geometry to accelerate the rate limiting reductive elimination step

■ MIP catalyzed Suzuki and Stille couplings occur with higher yields than with a non imprinted polymer supported catalyst



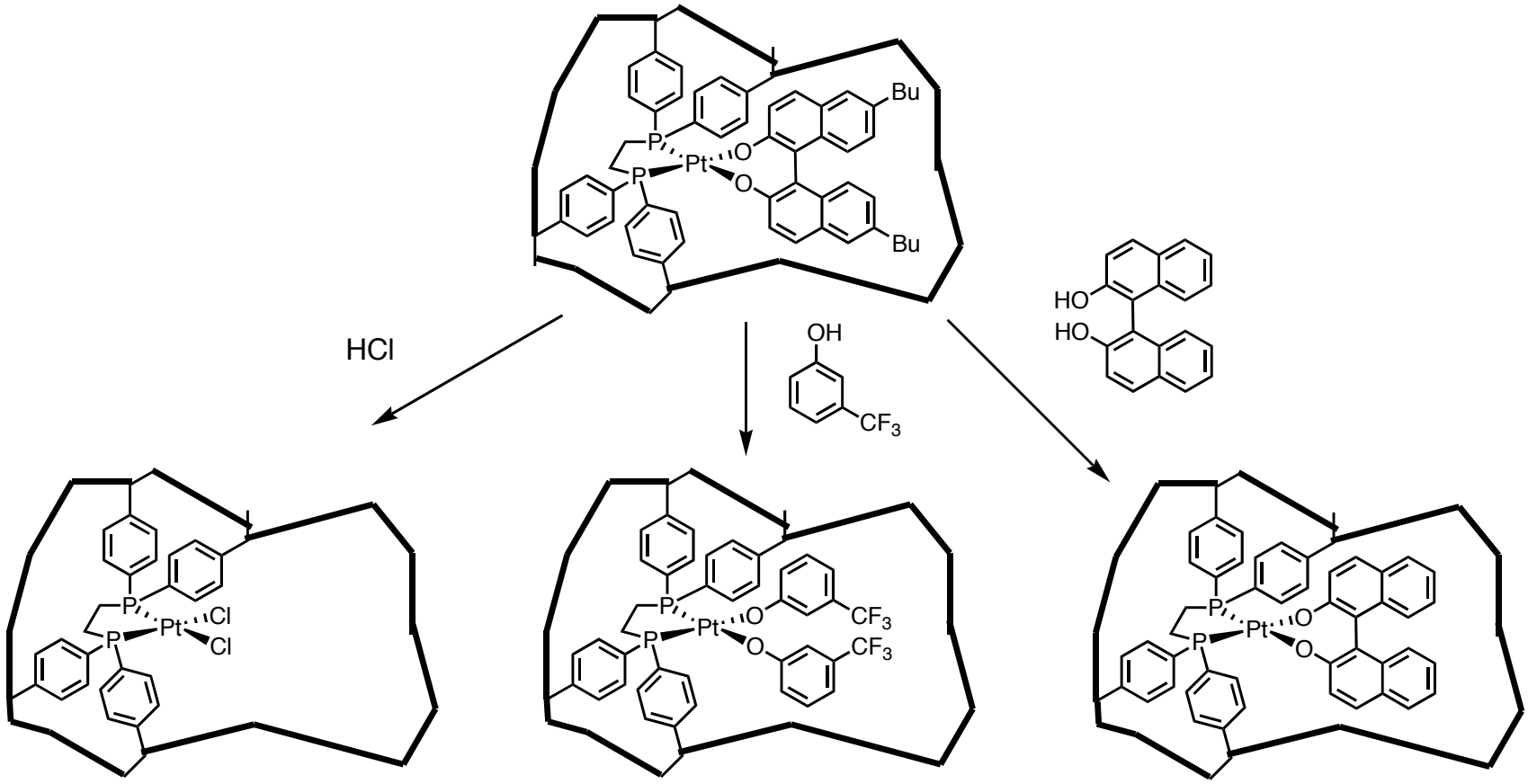


	yield	**yield**
MIP:	81%	65-95%
polymer:	56%	trace
solution:	55%	65-95%

Cammidge, A.; Bellingham, R. *Chem. Comm.,* **2001**, 2588

Not All Recognition Sites Are Created Equal

■ Gagne wants to take advantage of MIPs' ability to control a catalyst's outer coordination sphere but initial results lead him to conduct a thorough investigation of site variation within the polymer

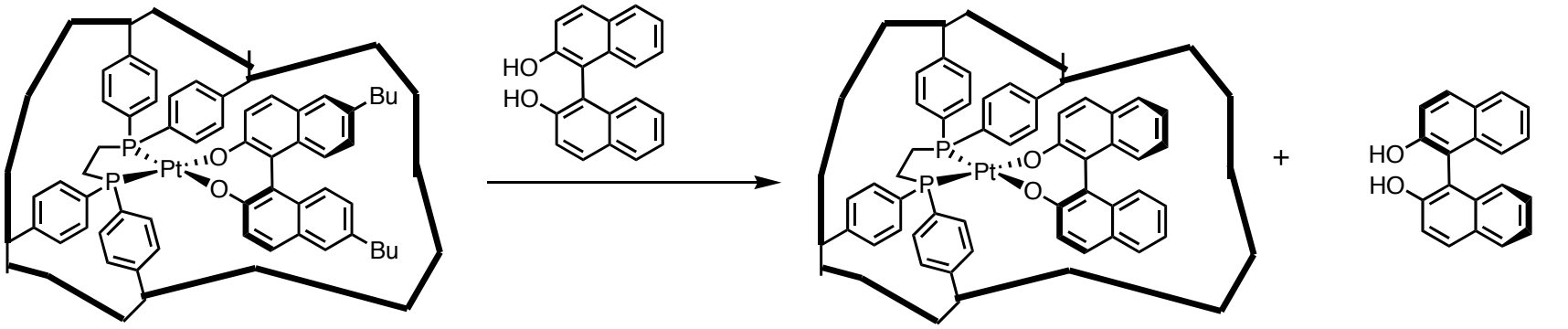


■ "The amount of imprinting ligand released by treatment of an MIP with a given reagent is inversely related to the steric bulk of that reagent, implying that a distribution of Pt sites with varying accessibilities exists within the polymer."

Gagne, M.; Brunkan, N. *JACS,* **2000**, *122*, 6217

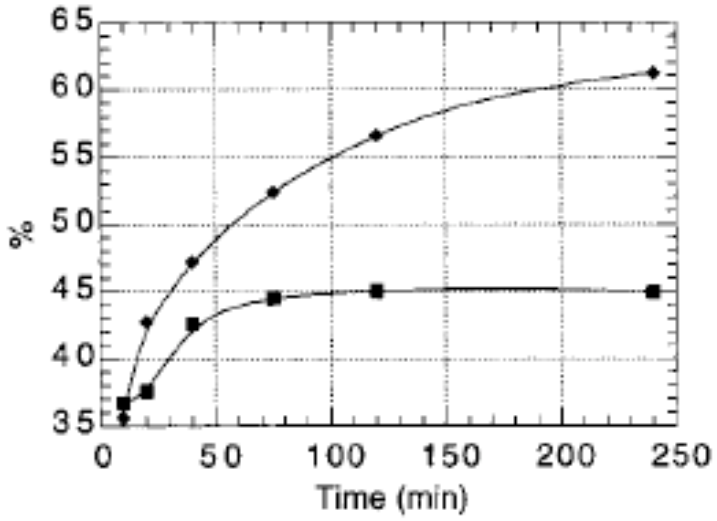
Not All Recognition Sites Are Created Equal

■ MIPs imprinted with (*R*)-Bu_2BINOL preferentially rebound (*R*)-BINOL when exposed to racemic BINOL.



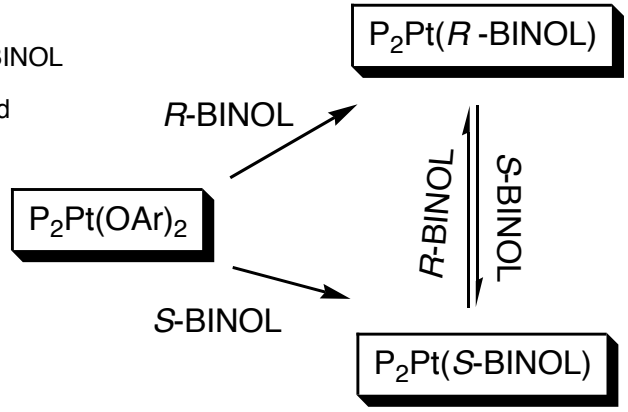
(*R*)-MIP **Bound (*R*)-BINOL** **Unbound (*S*)-BINOL**

■ Selectivity increases over time, eventually stabilizing at 65-70% ee after 8 hours, leading the authors to conclude there is a kinetically controlled initial binding event and thermodynamic ligand exchange within the polymer.



◆ - % ee rebound BINOL

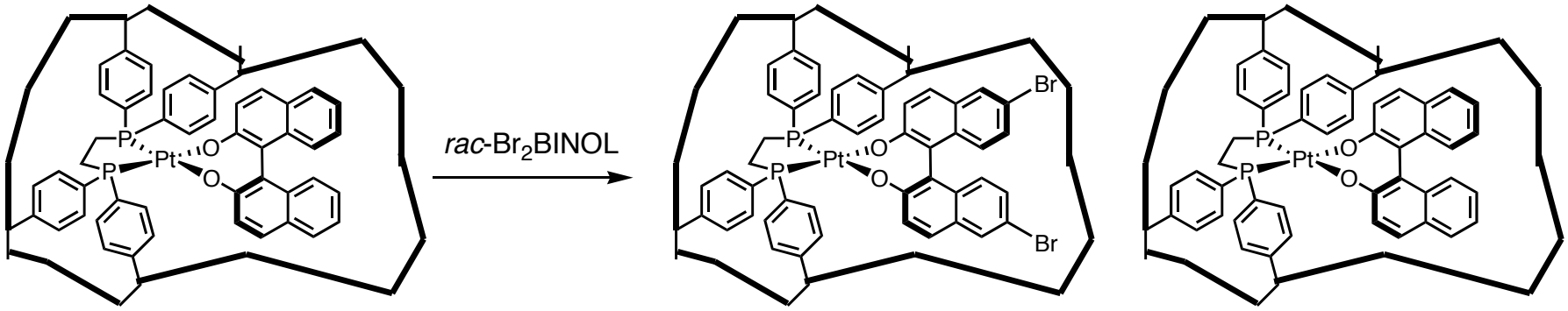
■ - % Pt sites bound



Gagne, M.; Brunkan, N. *JACS,* **2000**, *122*, 6217

Not All Recognition Sites Are Created Equal

■ In order to determine the kinetic selectivity of the most tightly imprinted and least accessible sites, (*R*)-Bu_2BINOL imprinted polymer is allowed to react with *rac*-BINOL, then exposed to *rac*-Br_2BINOL at higher temp.



Bound (*R*)-BINOL

Bound (*R*)-Br_2BINOL in unselective sites

Bound (*R*)-BINOL in selective sites

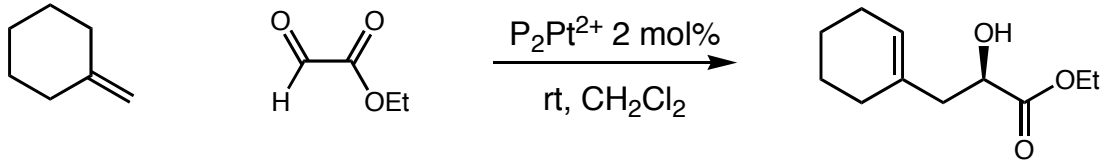
Br_2BINOL rebinding temp (^oC)	% Pt sites bound by Br_2BINOL	Br_2BINOL % ee	% Pt sites bound by BINOL	BINOL % ee	% Pt sites rebound (total)
60	41	46	20	**89**	61
80	46	58	13	**94**	59
100	50	61	8	**94**	58

■ The least accessible sites in the MIP are significantly more selective than easily accesible sites. But as any reaction is more likely to occur in an easily accessible site, how can MIPs be made more selective?

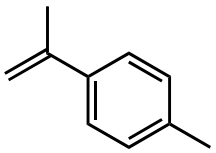
Gagne, M.; Brunkan, N. *JACS,* **2000**, *122*, 6217

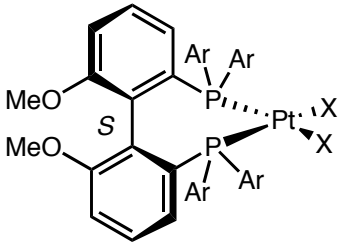
Can Chiral Poisoning Lead to Better Selectivity?

■ Gagne examined the effect of chiral poisioning with BINAM in the glyoxylate ene reaction



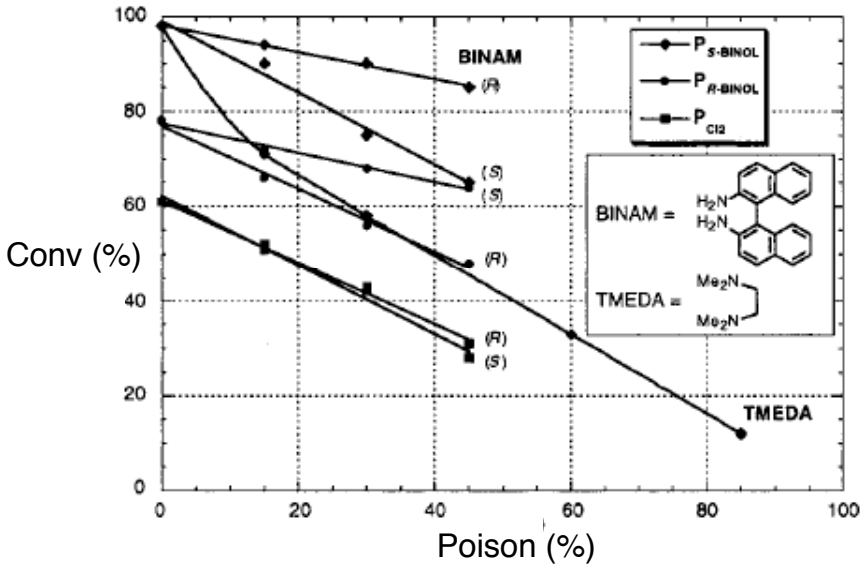
Ar =





X = Cl, *R*-BINOL, *S*-BINOL

	% ee	% conv	time
solution:	75	98	30 min
$P_{S\text{-BINOL}}$:	72	98	3 hr
$P_{R\text{-BINOL}}$:	25	61	3 hr



■ Even though the chiral BINAMs effectively poisoned the corresponding MIP catalysts, no enhancement in ee was observed.

■ Hypothesized that the BINOL imprinted cavity is too large to have an effect on the transition state of the ene reaction, the chirality of the product comes entirely from the chiral environment created by the phosphine ligands

Gagne, M. *Organometallics* **2002**, *21*, 7

Conclusions

- MIPs have a wide range of uses in organic chemistry as both stoichiometric reagents and catalysts

- Careful design of imprinting templates results in polymers that can differentiate between regio- and stereoisomers, making them useful as scavengers, supported reagents and protecting groups.

- A wide range of covalent and noncovalent interactions can be used in designing an imprinting template. In general, using a combination of different types of interactions results in more active and selective MIPs

- MIPs offer a new way to approach enantioselective catalysis and offer new ways to control the aspects that determine the stereochemical outcome of a reaction by allowing a chemist to fix reactive components in three dimensional space.

- More investigation into the homogeneity of recognition sites and thorough characterization of the various factors that affect the reaction in the site is needed before MIPs become a truly useful synthetic aid in organic chemistry