Toward the Molecular Imprinting of Titanium Lewis Acids: Demonstration of Diels−Alder Catalysis

Brian P. Santora, Andrew O. Larsen, and Michel R. Gagné*

Department of Chemistry CB#3290, The University of North Carolina, Chapel Hill, North Carolina 27599-3290

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Summary: This communication reports the free radical incorporation of a titanium(IV) complex containing polymerizable aryloxide ligands into a rigid and porous polystyrene/divinylbenzene-based matrix. This yields a yellow-orange insoluble polymer that can be converted into a dark red polymer with $SiCl_4$; the latter polymer is a good catalyst for the Diels−Alder reaction.

Asymmetric catalysis as an area of intense research interest has produced numerous examples of highly selective and useful reactions.[1] The control of reaction selectivities, however, is still unpredictable and could benefit from fundamentally new approaches. Homogeneous catalysts typically rely on inner-sphere control (via ancillary ligands) to influence the reactivity/selectivity of the metal center. In contrast, enzymes control selectivity (broadly speaking) through outer-sphere coordination events; suggesting that *the selectivity of a transition-metal catalyst could be enhanced by better defining its outer sphere*. This is normally difficult, since in solution the outer sphere is the dynamic and ill-defined solvent shell.

It is our long-term goal to control a catalyst's outer sphere (i.e. the coordination sphere that extends beyond the immediate effect of its ligands) using molecular imprinting, a technique wherein a template molecule is covalently incorporated into a highly cross-linked yet porous polymer matrix.[2] Selective removal of a non-cross-linked portion of the template will *create spatially well-defined, kinetically stable cavities that are associated with a cross-linked catalyst* (Figure 1).

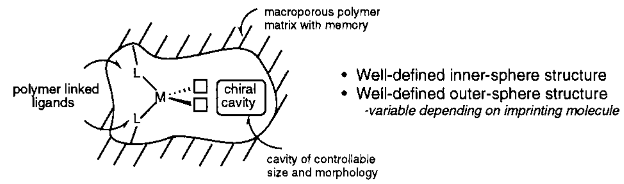
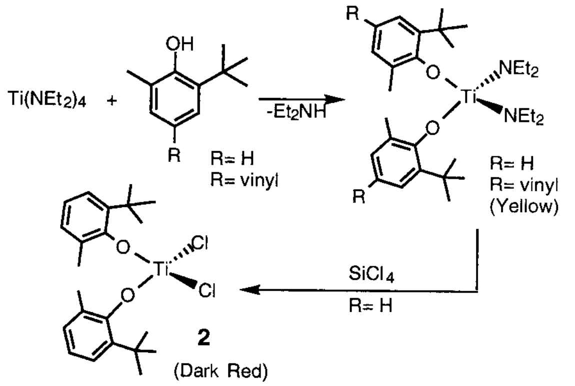


Figure 1. Combined inner-/outer-sphere approach to catalyst design.

Scheme 1



Molecular imprinting studies aimed at installing active metal complexes into well-defined outer-sphere environments are rare.[3,4] Rather, the emphasis has been on creating polymer active sites that utilize enzyme-like motifs (general acids and bases) to accelerate reactions.[5] Our approach separates the phenomena of reactivity and selectivity by providing the reactivity in the form of a metal catalyst and using the imprinted environment to control the selectivity. As a first step to achieving our long-term goal, we demonstrate herein the feasibility of cross-linking a metallo monomer into a rigid, porous polymer matrix that is amenable to the strategy outlined in Figure 1. Furthermore, we document that this polymer can be chemically activated for catalysis and that Diels−Alder reaction rates are competitive with rates observed in solution using homogeneous catalysts.

The desired metallo monomer was synthesized from the phenol and $Ti(NEt_2)_4$ (**1b**, Scheme 1)[6] and was designed to resemble the monomers for efficient polymer incorporation. Thermolysis of monomer/cross-linking solutions[7] at 80 °C for 12 h and 120 °C for 12 h generates the amorphous and insoluble yellow-orange polymer **P1**

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[1] (a) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; pp 23−24.

[2] For reviews see: (a) Wulff, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1812−1832. (b) Steinke, J.; Sherrington, D. C.; Dunkin, I. R. *Adv. Polym. Sci.* **1995**, *123*, 81−125. (c) Shea, K. J. *Trends Polym. Sci.* **1994**, *2*, 166−173. (d) Mosbach, K. *Trends Biochem. Sci.* **1994**, 9−14. (e) Wulff, G. In *Polymeric Reagents and Catalysis*; Ford, W. T., Ed.; ACS Symposium Series 308; American Chemical Society: Washington, DC, 1986; pp 186−230.

[3] (a) Mutsui, J.; Nicholls, I. A.; Karube, I.; Mosbach, K. *J. Org. Chem.* **1996**, *61*, 5414−5417. (b) De, B. B.; Lohray, B. B.; Sivaram, S.; Dhal, P. K. *Tetrahedron: Asymmetry* **1995**, *6*, 2105−2108. (c) De, B. B.; Lohray, B. B.; Sivaram, S.; Dhal, P. K. *Macromolecules* **1994**, *27*, 1291−1296.

[4] For examples of molecularly imprinted metal complexes see: (a) Krebs, J. F.; Borovik, A. S. *Chem. Commun.* **1998**, 553−554. (b) Krebs, J. F.; Borovik, A. S. *J. Am. Chem. Soc.* **1995**, *117*, 10593−10594. (c) Mallik, S.; Plunkett, S. D.; Dhal, P.; Johnson, R. D.; Pack, D.; Shnek, D.; Arnold, F. H. *New J. Chem.* **1994**, *18*, 299−304 and references therein. (d) Fujii, Y.; Matsutani, K.; Kikuchi, K. *J. Chem. Soc., Chem. Commun.* **1985**, 415−417. (e) Minutolo, F.; Pini, D.; Salvadori, P. *Tetrahedron. Lett.* **1996**, *37*, 3375−3378.

[5] (a) Wulff, G.; Gross, T.; Schönfeld, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1962−1964. (b) Beach, J. V.; Shea, K. J. *J. Am. Chem. Soc.* **1994**, *116*, 379−380. (c) Robinson, D. K.; Mosbach, K. *J. Chem. Soc., Chem. Commun.* **1989**, 969−970.

[6] Duff, A. W.; Kamarudin, R. A.; Lappert, M. F.; Norton, R. J. *J. Chem. Soc., Dalton Trans.* **1986**, 489−498.

[7] Composition: 75% divinylbenzene, 18.5% styrene, 6.25% **1b**, AIBN, 1:1 volume ratio of porogen (toluene) to monomers.

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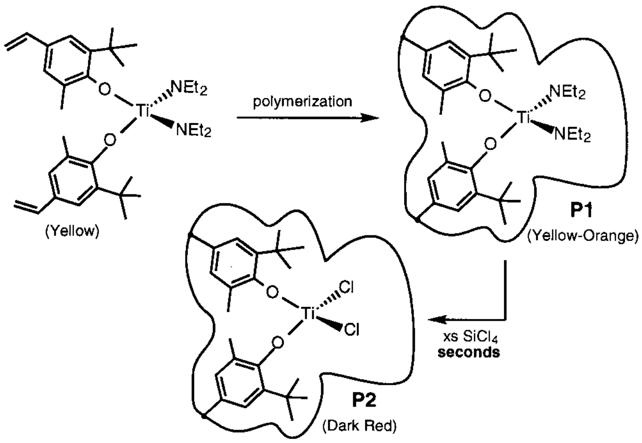
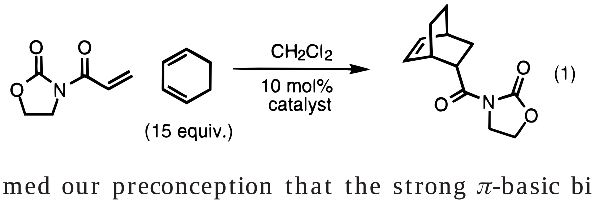
Scheme 2



(Scheme 2).[8] Rinsing with toluene does not leach out the color, indicating good matrix attachment.[9] Quenching **P1** with HCl/Et$_2$O followed by washing in a Soxhlet extractor with ether removes unbound vinylphenol. Quantification (by GC) of the released ligand indicates that ~95% of the template molecules are two-point bound, confirming the qualitative polymer washing observations.

The bis(amido) species **1a** was conveniently converted to the bright red dichloride **2** with excess SiCl$_4$ in toluene (Scheme 1, quantitative by ^{1}H NMR). Similar treatment of a toluene suspension of yellow-orange **P1** with SiCl$_4$ (20 equiv) results in a rapid color change to the dark red characteristic of the dichloride (**P2**). Even with large lumps (~1 cm^3), the color changes throughout the polymer, demonstrating the good mobility of reactants within the matrix of these porous materials. Subsequent washing and removal of the SiCl$_4$ and SiCl$_3$-NR$_2$ *in vacuo* generates polymer-immobilized Ti(IV) Lewis acid catalysts.

To test such fundamental properties as substrate/product diffusion in and out of the polymer in the context of catalysis, the Diels–Alder reaction in eq 1 was studied.[10,11] Control experiments with **1a** confirmed our preconception that the strong π-basic bis(amido) ligand set would result in a poor catalyst[12] (<5% conversion; 10 mol %; 48 h; room temperature; same as background), while **2** would be a better Lewis acid and accelerate the reaction (100% conversion; 3 h; 10 mol %; room temperature). The dichloride **2** yields the product with a high diastereoselectivity (98:2 *endo*:*exo*),[13] however, it precipitates upon diene addition and the reaction proceeds heterogeneously.



(1)

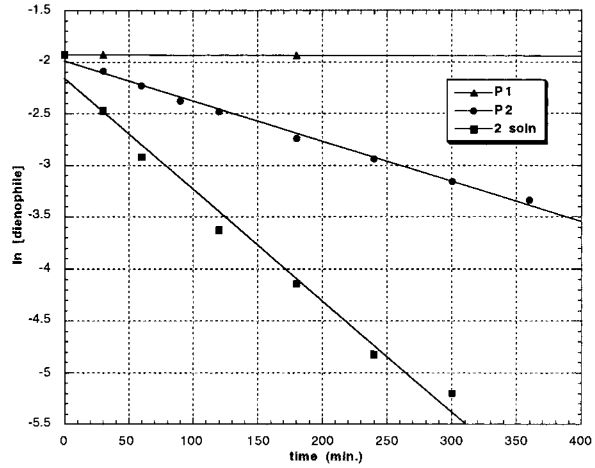


Figure 2. Plots of ln[dienophile] vs time (pseudo first order in diene) in solution and for **P1** and **P2**.

Catalysis of eq 1 using **P1** and **P2** under reaction conditions similar to those of solution experiments yielded the data highlighted in Figure 2.[14] The bis(amido) polymer **P1** was similar to **1a** and showed negligible activity (<5%, 48 h).[15] However, conversion of the polymer to the more Lewis acidic dichloride-based active site (**P2**) generates a competent polymer-based catalyst. In fact, *the rate of reaction catalyzed by 10 mol % **P2** is only 3–5 times slower than an analogous experiment using **2** in solution*.[16,17] Highlighting the diffusional mobility in the porous polymer are control experiments demonstrating that reaction rates are relatively insensitive to particle size; lumps (~0.5 cm^3) gave only slightly depressed rates (~1.5×) compared to crushed samples. Moreover, catalysis was determined to occur solely in the matrix (rather than leached catalyst), since removal of the polymer after ~40% conversion halted product formation.

In summary, these experiments demonstrate a proof-of-principle that suitably derivatized titanium aryloxide complexes can be incorporated into rigid organic polymer matrixes amenable to molecular imprinting[2] and that these complexes can be activated for catalysis and are kinetically competent when compared to solution analogues. Future studies will explore the effect of the associated cavity's size and shape on catalyst reactivity and selectivity.

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(8) Vapor phase osmometry experiments have confirmed the monomeric nature of **1a**, ensuring that no aggregate structures get imprinted.

(9) Repeating these experiments using the non-cross-linkable **1a** allows the template molecule to be recovered intact, in good yield, by washing the polymer with toluene.

(10) Hexadiene gives a negligible background rate and is considered an unreactive diene; see: Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miler, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798–800.

(11) For a molecular imprinted polymer that catalyzes the Diels–Alder reaction, see: Liu, X.; Mosbach, K. *Macromol. Rapid Commun.* **1997**, *18*, 609–615.

(12) Hillhouse, G. L.; Bulls, A. R.; Santarsiero, B. D.; Bercaw, J. E. *Organometallics* **1988**, *7*, 1309–1312.

(13) For recent references on asymmetric Ti-catalyzed Diels–Alder reactions, see: (a) Gothelf, K. V.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 111–115 and references therein. (b) Haase, C.; Sarko, C. R.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 1777–1787 and references therein. (c) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kühnle, F. N. M. *J. Org. Chem.* **1995**, *60*, 1788–1799.

(14) We assume, on the basis of the stoichiometry of materials, a catalyst loading of 140 μmol/g of polymer in **P1** and further assume a 100% conversion to the dichloride for **P2**. Inaccessible sites will reduce the effective concentration of catalyst (~5–10% based on literature precedence; see ref 2).

(15) The small decrease in dienophile observed in Figure 2 is a result of a slow substrate decomposition process not observed with the dichloride.

(16) Under the pseudo-first-order conditions employed, neither **2** nor **P2** behaves ideally, as some curvature in the plots is observed, suggestive of competitive inhibition byproduct. The precipitation of **2** upon diene addition complicates the direct comparison of these systems.

(17) SiCl$_4$ does not catalyze the Diels–Alder reaction.

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Supporting Information Available: Text giving synthesis and characterization details for the vinyl-substituted phenol ligand, complexes **1a**,**b**, **2**, and polymers **P1** and **P2** and catalysis experimental conditions and kinetic analysis (7 pages). Ordering information is given on any current masthead page.

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