

# Asymmetric Organocatalysis

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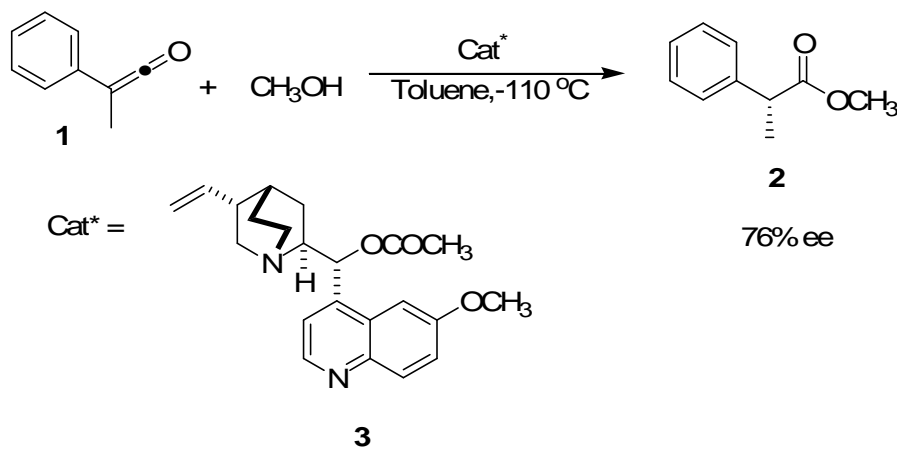
Literature Seminar

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## Introduction:

Organocatalysis is the process of acceleration of chemical reaction with a substoichiometric amount of an organic compound which does not contain a metal atom.<sup>1</sup>

In the early 1960`s Pracejus reported asymmetric induction in the addition of achiral alcohol to ketene **1** catalyzed by alkaloid **3** (**Scheme 1**).<sup>2</sup> Role of the catalyst is to transfer chirality information through a well defined transition state to achiral or prochiral substrate.<sup>3</sup>



### Scheme1: Asymmetric addition of alcohols to ketenes catalysed by chiral amines

Apart from organocatalysts, organometallic catalysts and enzymes are used as catalysts for the asymmetric induction in prochiral or achiral substrates to get chiral compounds.

Organocatalysts are complimentary to organometallic catalysts or enzymes but not competent.<sup>4</sup> The advantages of organometallic catalysts stems from the metal part. Since metals can act as either Lewis acids or Lewis bases, One can tune the reactivity of the organometallic catalyst by varying the ligands surrounding the metal atom. The disadvantages of these catalysts are (i) high price, (ii) toxicity, (iii) pollution, (iv) waste

treatment and (v) product contamination. Enzyme catalyzed reactions are reversible and forms enzyme substrate complexes, and they are known have higher turn over numbers. Organocatalyzed reactions mechanistically resemble, the enzyme catalyzed reactions with respect to formation of reversible complexes with substrates. They also emulate the role of a metal as a Lewis acid or Lewis base. The acidity basicity arises from type of heteroatom present in the organocatalyst.<sup>5</sup>

An ideal organocatalyst should possess (i) easy availability; (ii) accessibility of both the enantiomers with comparable price, (iii) low molecular weight, (iv) easy separation from the product, (v) easy recovery after work-up, without racemization.<sup>5</sup>

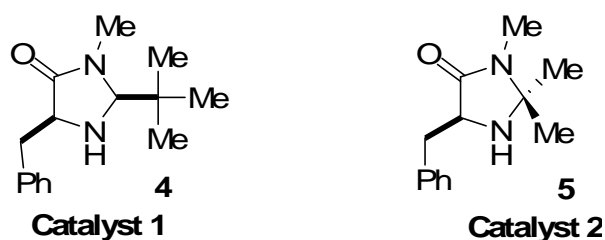
Organocatalyst can perform reactions under aerobic atmosphere with wet solvents. The catalysts are inexpensive and some of them are by-products from the other organic reactions. They are stable at ambient conditions. They can be easily separated from the products without racemization. They can be anchored to a solid support and be reused without losing catalytic activity.

Organocatalysts can be broadly classified as Lewis acids, Lewis bases, Bronsted acids, and Bronsted bases.<sup>6</sup> Lewis base catalyst initiates the catalytic cycle by nucleophilic attack on the substrate. The resulting complex undergoes reaction and releases product and the catalyst for the further turn over. Lewis acid catalysts also activates substrate in a similar manner. Bronsted base and acid catalysis is initiated by the partial protonation or deprotonation, respectively. The following report illustrates the case studies of organocatalysts exploring Lewis basicity or Lewis acidity in catalyzing organic reactions.

### Lewis base catalysis:

Lewis basic, organocatalysts are dominated by the organic molecules containing heteroatoms like N, C, S, O, and P. They operate through diverse mechanisms and convert substrates into either electrophiles or nucleophiles.<sup>6</sup> Typical reactive intermediates of these catalysts are iminium ions, enamines, acylammonium ion catalysis. The following examples will explain the reactions involving iminium and enamine intermediate catalysts.

Macmillan et al., designed imidazolidinone organocatalysts and these catalysts, catalyze the reactions through iminium ion intermediates (**Figure 1**).<sup>7</sup>

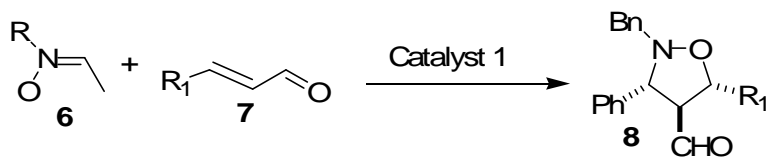


**Figure 1: MacMillan's Imidazolidinone Catalysts**

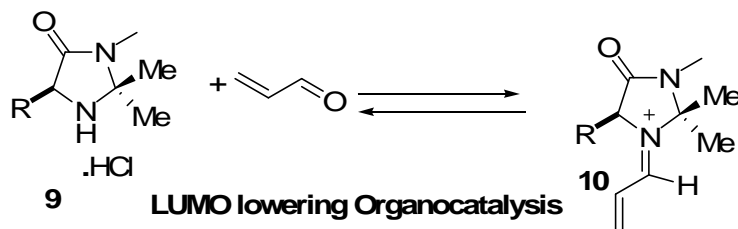
Some illustrations for the imidazolidinone catalyzed reactions are

#### (i) 1,3-Dipolar cycloadditions:

$\alpha$ ,  $\beta$ -unsaturated aldehydes **7** are poor substrates for metal catalyzed 1,3-dipolar cycloadditions, because of the preferential coordination of the Lewis acids to nitron oxides **6**, in presence of the monodentate carbonyls. This problem can be overcome by using the organocatalysts. Compound **7** in presence of imidazolidinone catalyst **2** forms the iminium ions reversibly, thereby lowering the energy of LUMO, resulting in [3+2] cycloaddition with the nitrones (**Scheme 2**).<sup>8</sup>

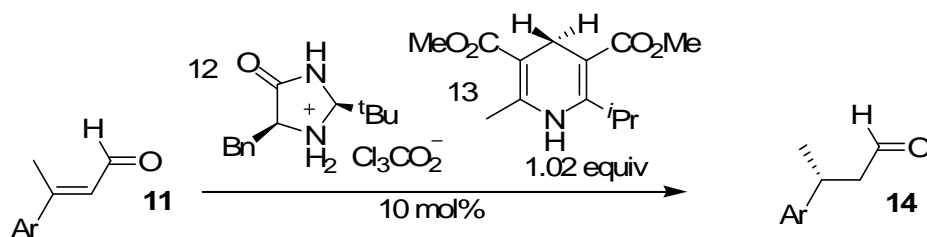


**Scheme 2: [3+2] Nitron-alkene Cycloaddition**



**(ii) Asymmetric hydride transfer:**

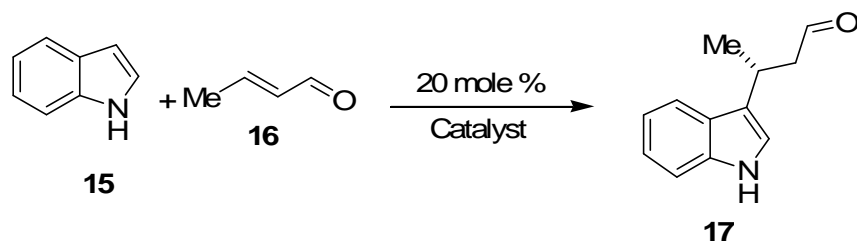
$\alpha,\beta$ -unsaturated aldehydes **11** can be selectively reduced at 1,4-positions using imidazolidinone catalyst, involving iminium ion intermediate. Hantzsch ester serves as the hydride source (**Scheme 3**).<sup>9</sup>



**Scheme 3: Asymmetric Hydride Transfer**

**(iii) Alkylation of Indole Ring:**

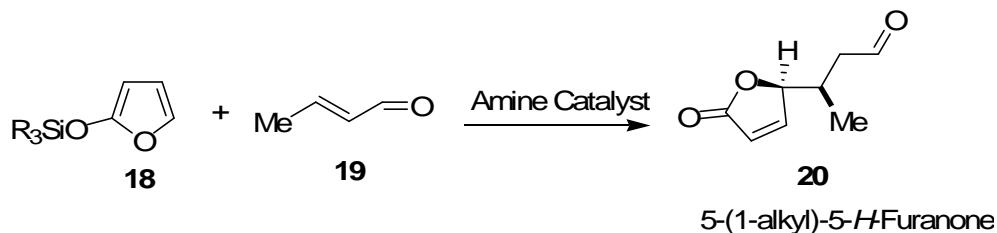
Another example of imidazolidinone catalyst alkylating indole ring systems and inducing asymmetry is outlined in **Scheme 4**.<sup>10</sup> In this case  $\alpha,\beta$ -unsaturated aldehydes are acting as source of electrophile.



**Scheme 4: Alkylation of Indole Ring**

*(iv) Mukaiyama–Michael addition:*

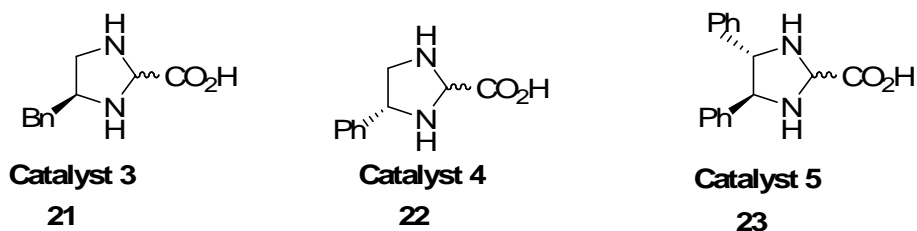
An example demonstrating the utility of imidazolidinone catalyst for 1,4-addition in contrast to organometallic catalyst for 1,2-addition is shown in Scheme 5. Silyloxy furans (**18**) on coupling with aldehyde catalysed by the chiral Lewis acid undergoes 1,2-addition predominantly (Mukaiyama-aldol). Where as chiral amine catalysed coupling of  $\alpha,\beta$ -unsaturated aldehydes undergoes 1,4-addition yielding the  $\gamma$ -Butenolide derivatives (**20**).<sup>11</sup>



**Scheme 5: Mukaiyama-Michael Reaction**

*(v) Enantioselective Asymmetric Michael Reaction: Warfarin synthesis.*

Warfarin (**26**), a widely used anti-coagulant that can be prepared upon the Michael addition of 1,3-dicarbonyl compound with  $\alpha,\beta$ -unsaturated ketones.<sup>12</sup> This is another example for the iminium ion catalyzed reactions (**Scheme 7**).



**Figure 2: Imidazole Catalyst**



**Scheme 7: Enantioselective Asymmetric Michael Reaction: Warfarin**

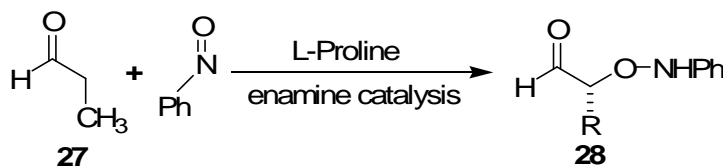
### Enamine Catalysis:

Enamine catalysis is another class of the organocatalysed Lewis base catalysis reactions

#### (i) *α*-Oxidation of Aldehydes.

Aldehydes can be oxidized at the *α*-position enantioselectively in presence of L-proline.

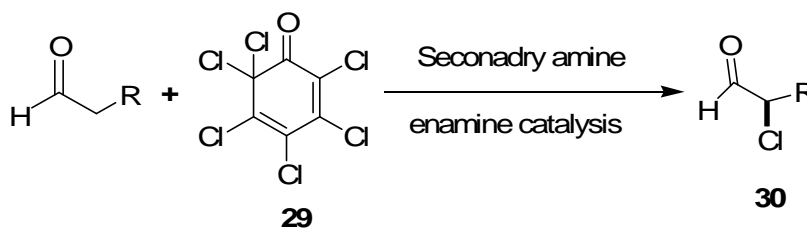
Nitrosobenze acts as the source of oxygen (**Scheme 8**).<sup>13</sup>



**Scheme 8: *α*-Oxidation of Aldehydes**

**(ii)  $\alpha$ -Chlorination**

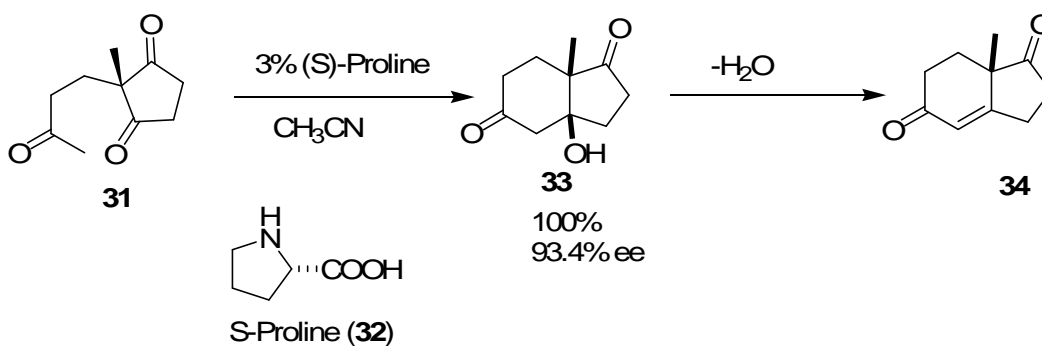
Aldehydes can be enantioselectively chlorinated at the  $\alpha$ -position by using L-proline catalyst. The role of Lectka quinone here is to serve as the source of chlorine (**Scheme 9**).<sup>14</sup>



**Scheme 9:  $\alpha$ -Chlorination**

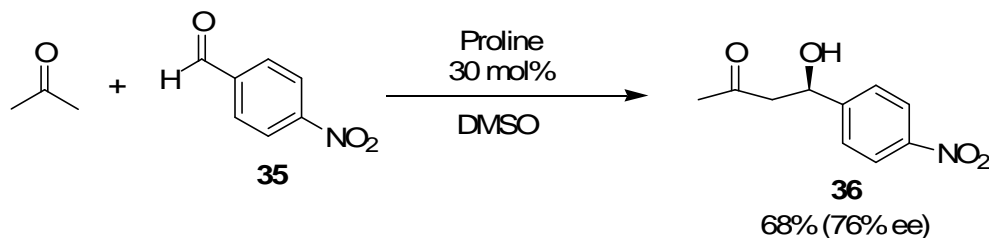
**(iii) Aldol condensation**

Hajos et al., in 1970's first reported the (S)-proline catalysed intramolecular aldol reaction.<sup>15</sup> A *meso*-triketone **31** in the presence of (S)-proline (**32**) yields (+)-bicyclic ketol (**33**). The 5/6 fused bicyclic system is useful intermediate for steroid synthesis.



**Scheme 10: Enantioselective Intramolecular Aldol Reaction**

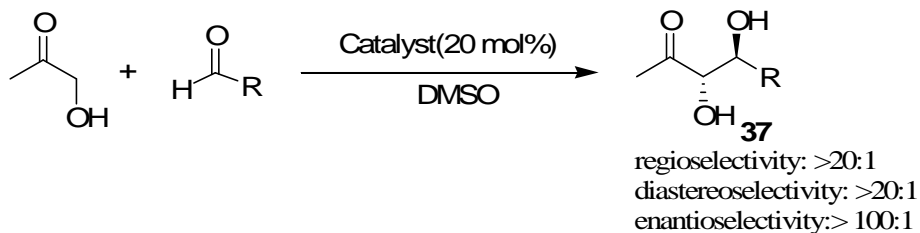
Benjamin List et al.,<sup>16</sup> in 2000 reported the intermolecular aldol condensation between two unmodified carbonyl compounds using the same catalyst. In this case the ketones serve as the aldol donor and aldehyde as the aldol acceptor (Scheme 11).



**Scheme 11: Intermolecular Aldol Reaction between two Unmodified Carbonyl Compounds**

*(iv) Catalytic asymmetric synthesis of 1, 2-antidiols:*

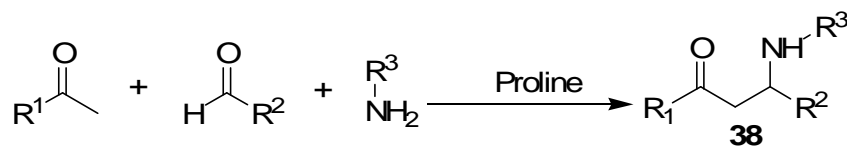
Hydroxy acetones on reaction with aldehydes in presence of L-proline yield 1,2-antidiols. This is a highly regio- and enantioselective aldol reaction (**Scheme 12**).<sup>17,18</sup>



**Scheme 12: Synthesis of 1,2-Antidiols**

*(v) Direct Asymmetric Mannich Reaction:*

An aldehyde, ketone and a primary amine in presence of a proline predominantly gives the mannich products. Aldol condensation products are the major byproducts.<sup>19</sup>



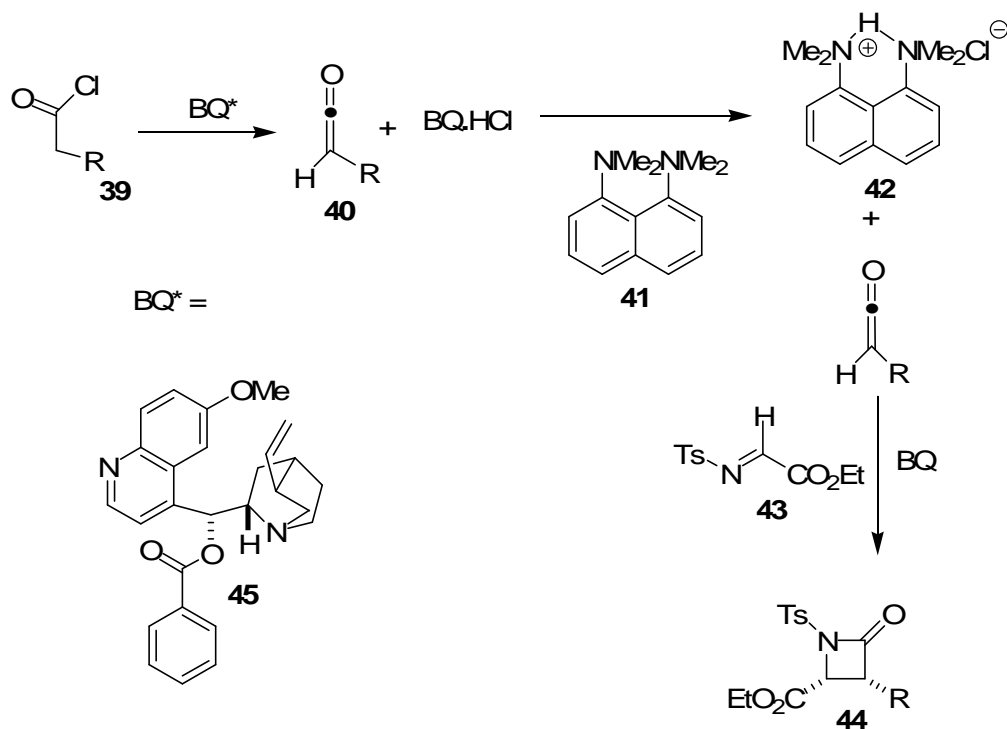
**Scheme 13: Mannich Reaction**

### Lewis acid Organocatalysis:

Organocatalysts activates carbonyl compounds as Lewis acids. One popular example is the phase transfer catalysis.

### Asymmetric synthesis of $\beta$ - Lactams:

$\beta$ -Lactams are in demand as antibacterial agents.



**Scheme 14: Catalytic Shuttle-Based Optically Active  $\beta$ -Lactams**

Acetyl chlorides in presence of Benzoyl Quinone generates ketene, undergoes addition with imine generated forms the  $\beta$ -Lactams.<sup>20</sup> Compound **41** acts as a proton sponge and scavenges generated HCl. The role of the catalyst is to act as a Shuttle base (**Scheme 14**).

### **Conclusion:**

An increasing number of asymmetric organic reactions can be accelerated by a catalytic amount of a chiral organic molecule. This novel type of catalysts have emerged as a major concept in organic chemistry in the last few years and is currently experiencing its golden age. Although substrate dependence remains an important issue in many of the reactions discussed, more and more transformations meet the standards of established asymmetric reactions. Despite the considerable progress that has been made in the elucidation of transition states, we are only beginning to understand the basic factors that control the reactivity and selectivity in these reactions, and the rational design of catalyst remains in most cases a dream. The number of organocatalytic (non-asymmetric) reactions is steadily increasing, which provides a solid basis for the development of novel enantioselective reactions. Although creativity and persistence will certainly remain the major factors in the success of this research, the increasing use of automation and computational techniques may facilitate both the discovery of novel catalytic structures and the screening of reactions for the next generations.

The enantioselective organocatalysis in which the reaction is mediated by a catalytic amount of chiral organic molecule is an emerging powerful tool in organic synthesis. Despite the fact that the field is in infancy, it offers new perspectives for academic, industrial, economic and ecological benefit.

## References:

1. Pracejus, E.; Matje, H. *J. Prakt. Chem. Fur Reihe* **1964**, *24*, 195.
2. Mangion, I. K.; Nothrup, A.B.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6722.
3. Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726.
4. Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.
5. Groger, H.; Wilken, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 529.
6. Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719.
7. Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.
8. Jen, W. S.; Weiner, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.
9. Yang, J. W.; Fonseca, M. T. H.; Vignola, N.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 108.
10. Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172.
11. Holland, N.; Hansen, T.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4995.
12. Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192.
13. Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808.
14. Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108.
15. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.
16. List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395.

17. Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.
18. Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III *J. Am. Chem. Soc.* **2001**, *123*, 5260.
19. List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.
20. Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, III, W. J.; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831.