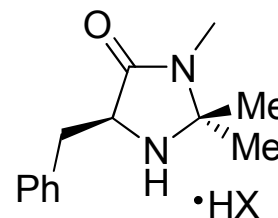
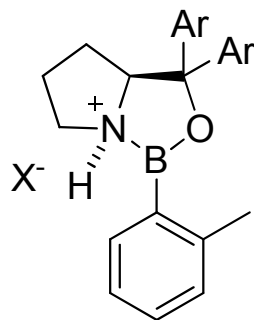


Protonated Chiral Organocatalysts: A Literature Review

David Daniels – 22/5/09



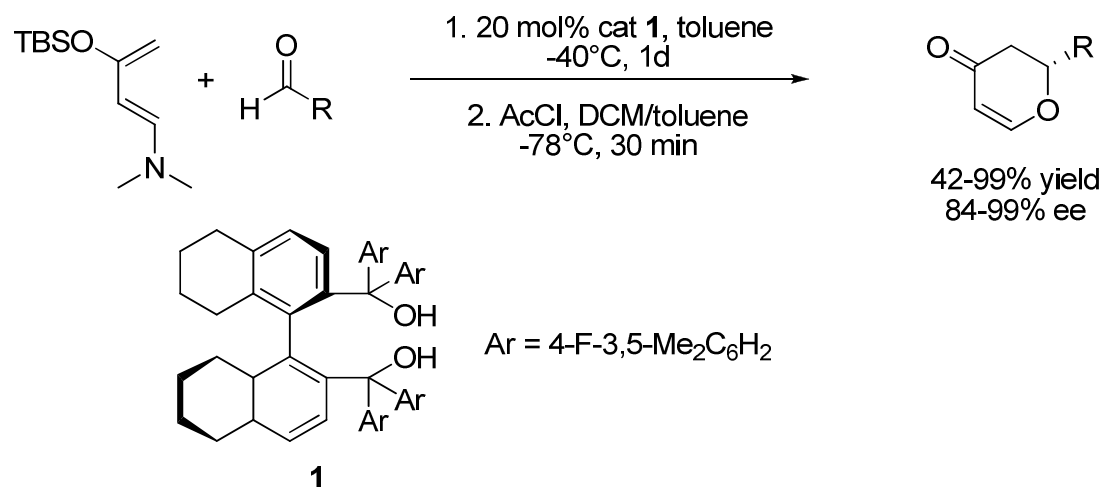


Introduction

- Asymmetric Catalysis is one of the main research fields in chemistry.
- Classical methods utilise chiral transition-metal complexes.
- These are often expensive, difficult to prepare and handle, and have high molecular weights resulting in unfavourable substrate to catalyst mass ratios.
- Metal-free chiral catalysts are being increasingly investigated as solutions to these disadvantages.

Introduction

- In many cases the effectiveness of these catalysts relies on the formation of strictly orientated hydrogen bonds. The substrate(s) are then activated by non-covalent interactions, allowing highly enantioselective transformations using low molecular weight metal-free catalysts.
- An elegant example of this is the catalysis of a hetero-Diels-Alder reaction by Rawal and co-workers:

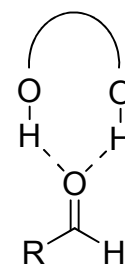
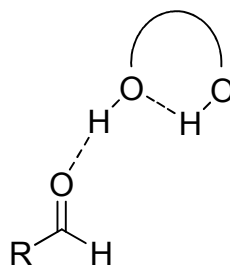
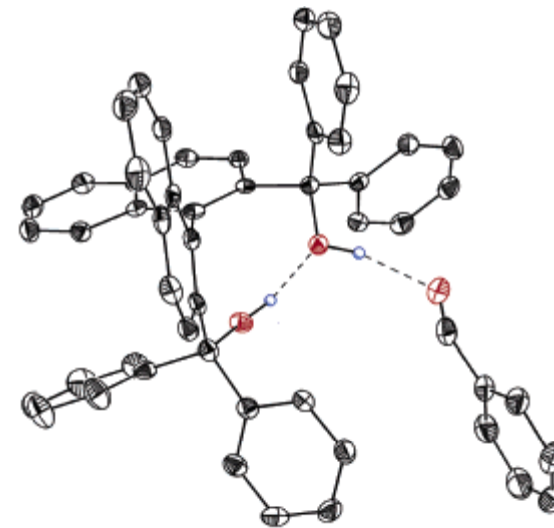
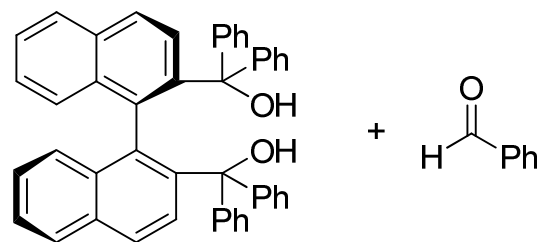


C. Bolm *et al.*, *Angew. Chem. Int. Ed.*, **2005**, *44*, 1758.

T. Steiner, *Angew. Chem. Int. Ed.*, **2002**, *41*, 48.

A. K. Unni *et al.*, *J. Am. Chem. Soc.*, **2005**, *127*, 1336.

Introduction



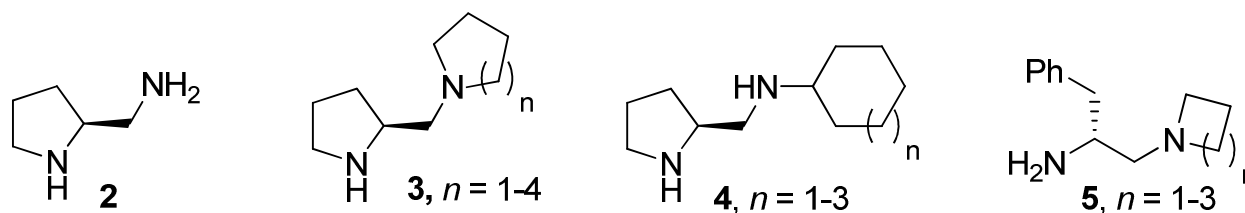
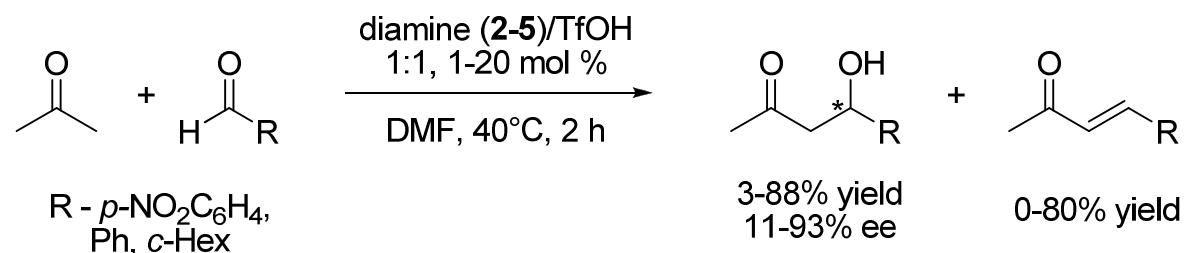
Introduction

- Conceptually different to these neutral organocatalysts is the use of a chiral Brønsted base, which on its own is catalytically inactive and requires an acid to give the active catalyst.

The Brønsted base and the acid do not act independently, but their combination leads to a cationic species that is a potent catalyst. Chiral examples have led to remarkable enantioselectivities.

Asymmetric Direct Aldol

- In 2001, Yamamoto and co-workers described the use of acid-diamine catalysts for the direct asymmetric aldol reaction between acetone and aromatic or aliphatic aldehydes.

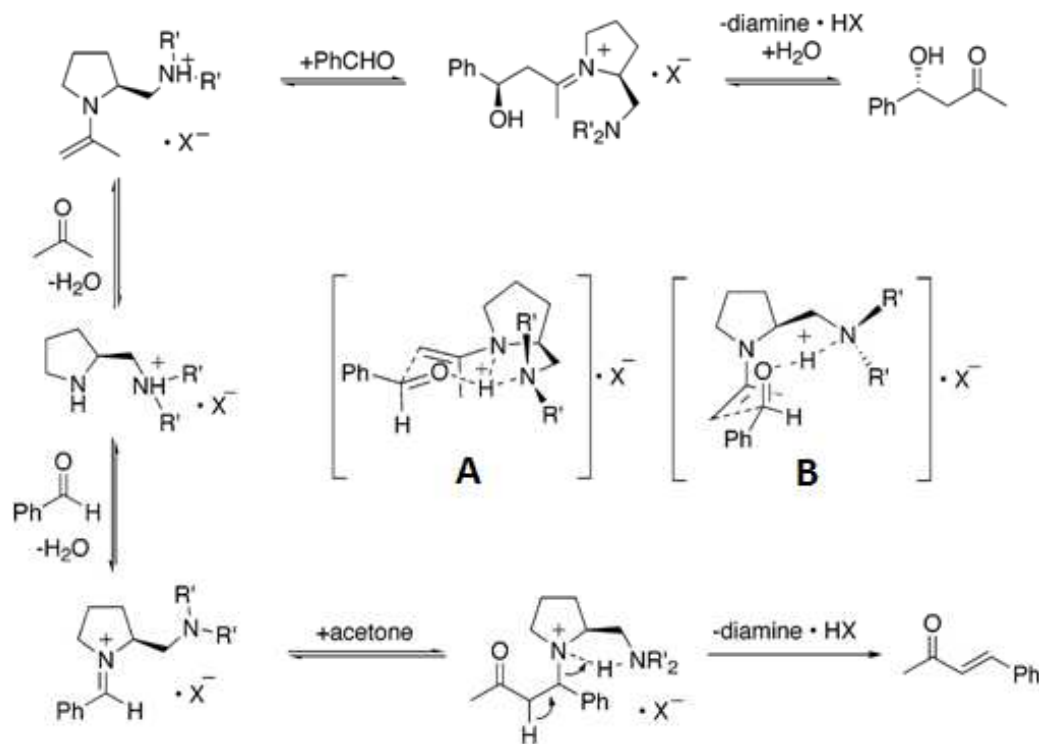
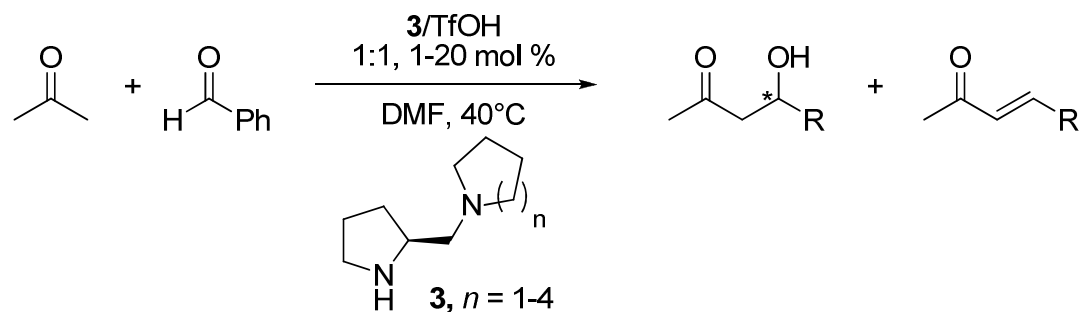


S. Saito *et al.*, *Synlett*, **2001**, 1245.

M. Nakadai *et al.*, *Tetrahedron*, **2002**, 58, 8167.

S. Saito *et al.*, *Acc. Chem. Res.*, **2004**, 37, 570.

Asymmetric Direct Aldol

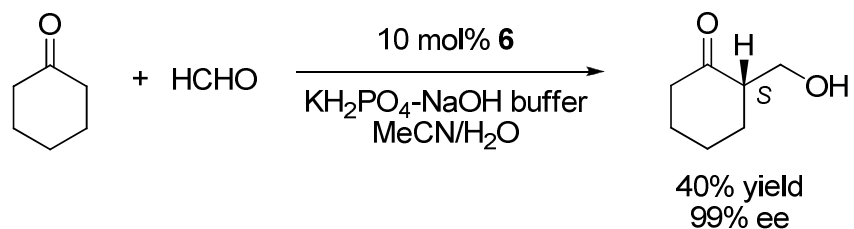
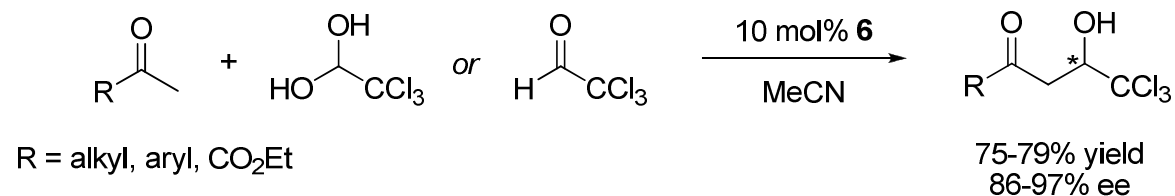
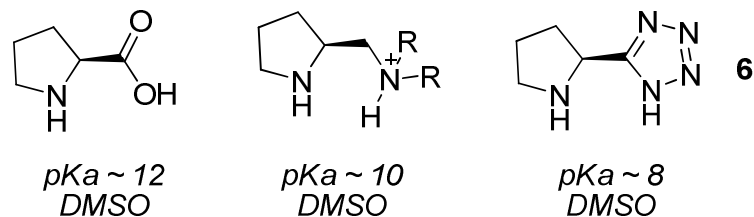


S. Saito *et al.*, *Acc. Chem. Res.*, **2004**, *37*, 570.

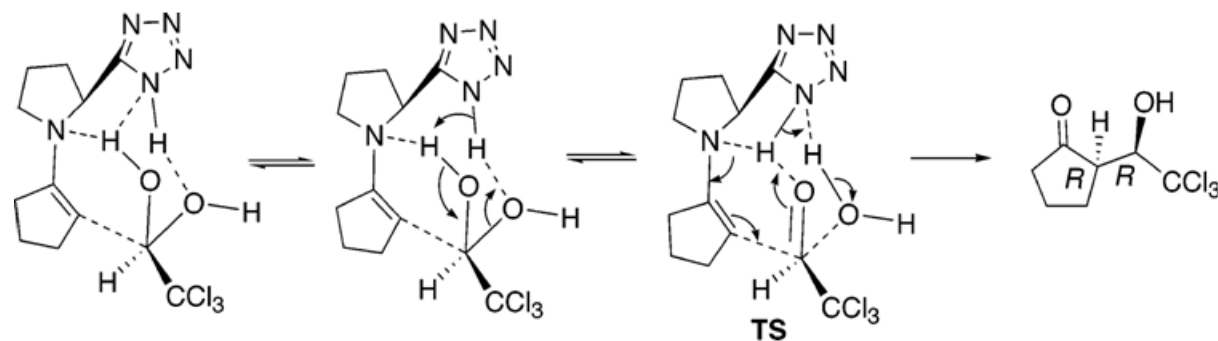
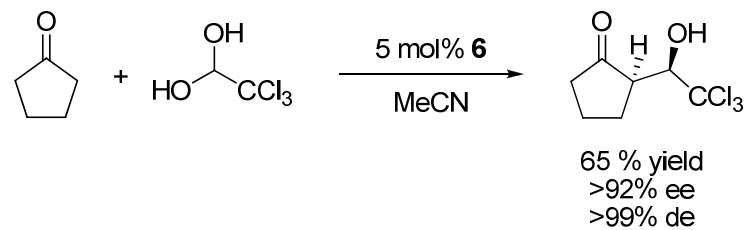
S. Baymanyar *et al.*, *J. Am. Chem. Soc.*, **2001**, *123*, 11273.

Asymmetric Direct Aldol

- Second Generation Catalysts:

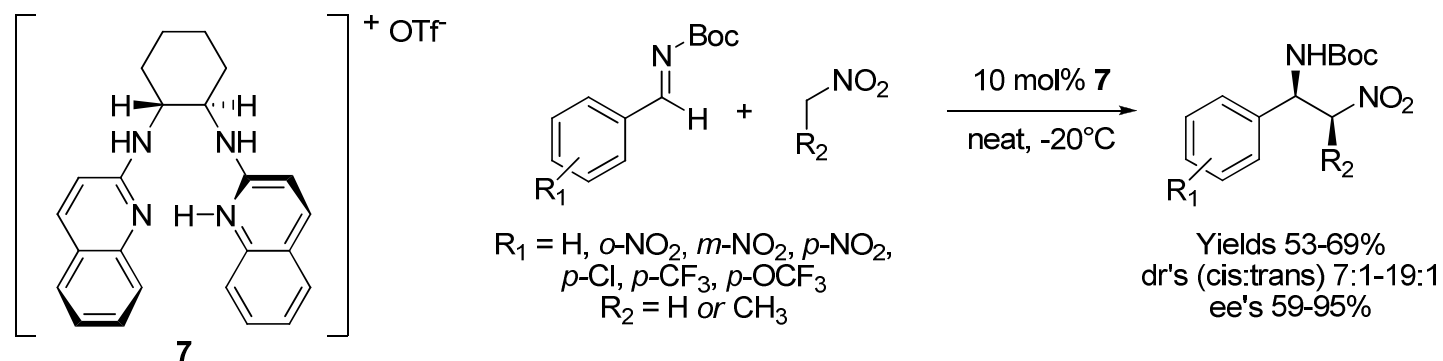


Asymmetric Direct Aldol



Asymmetric Aza-Henry Reaction

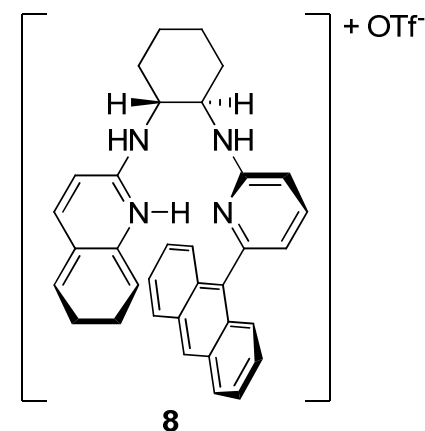
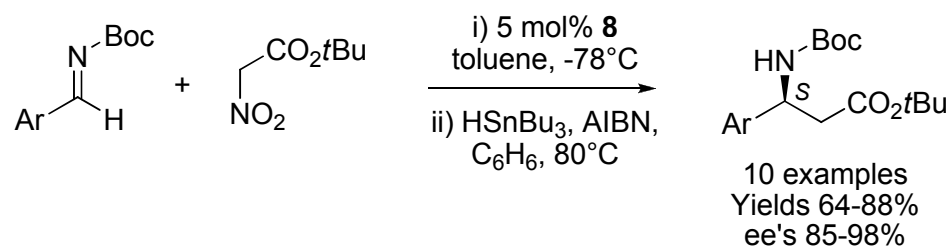
- In 2004 Johnston and co-workers described the use of a catalyst comprising of an axially chiral diamine and triflic acid to catalyse the aza-Henry reaction between imines and nitroalkanes.



- Without the addition of triflic acid, the results were consistent with the uncatalysed version of the reaction.

Asymmetric Aza-Henry Reaction

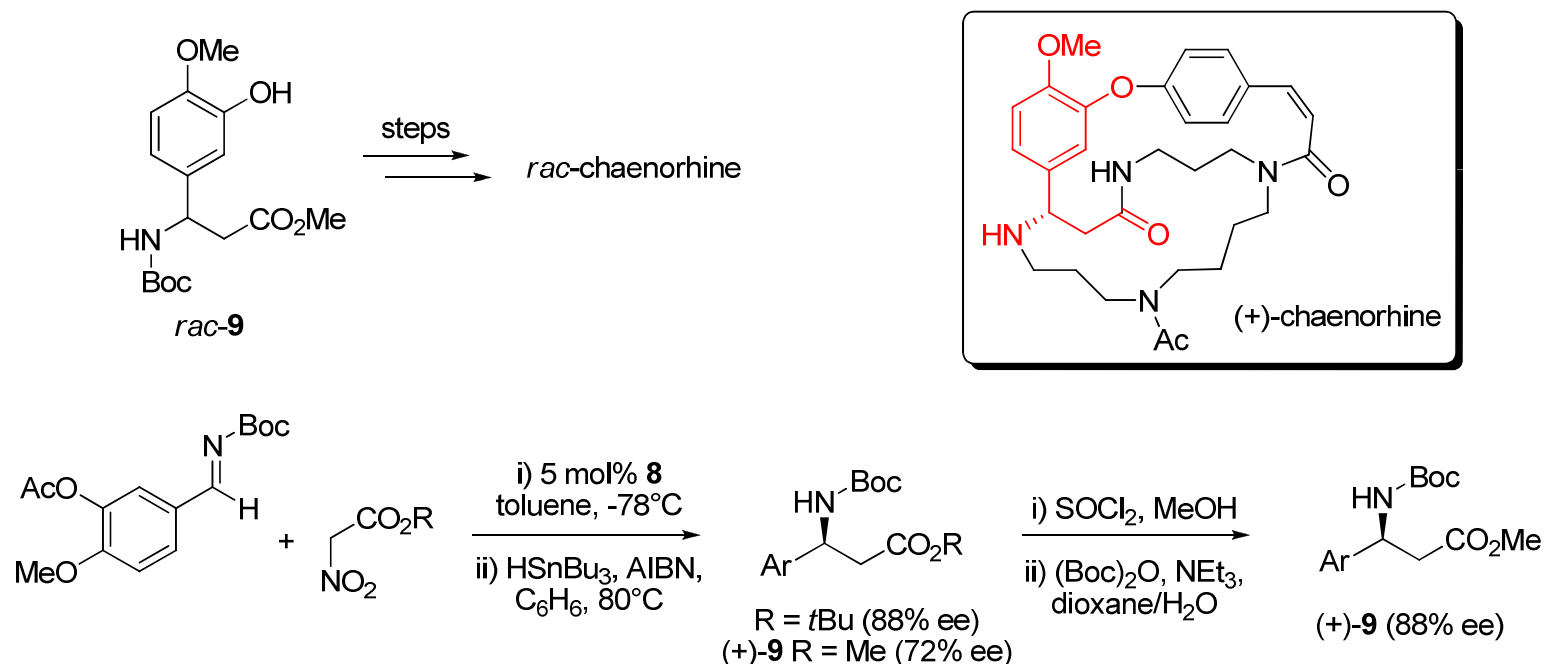
- This asymmetric catalysis was applied to the synthesis of enriched β -amino acids.



Asymmetric Aza-Henry Reaction

- The authors demonstrated the synthesis of an enriched form of the β -amino acid intermediate used by Wasserman in the racemic synthesis of Chaenorhine.

Wasserman:

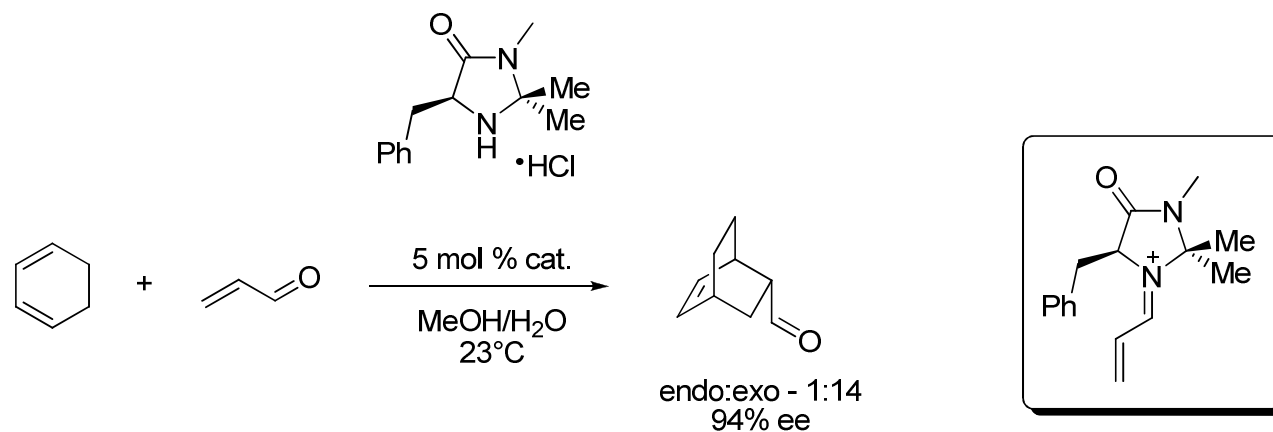


H. H. Wasserman *et al.*, *J. Am. Chem. Soc.*, **1983**, *105*, 1697.

B. Shen and J. N. Johnston, *Org. Lett.*, **2008**, *10*, 4397.

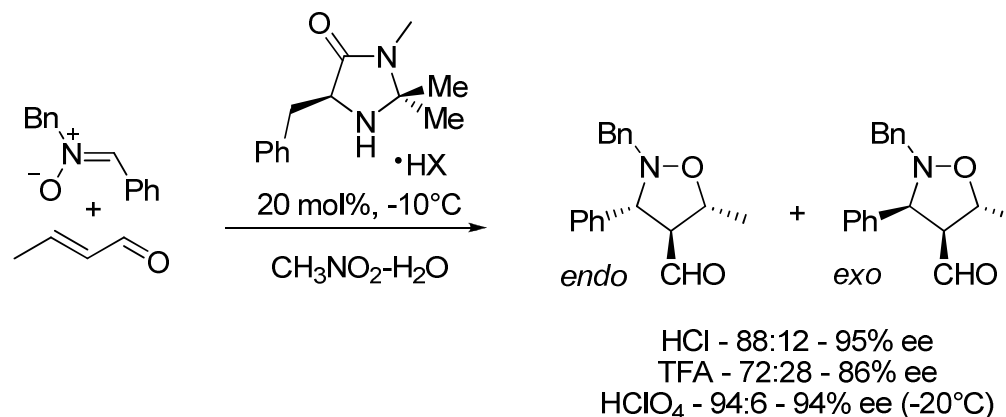
Imidazolidinones - Versatility

- The work of MacMillan and co-workers has shown that these catalysts can be versatile. The catalysis of, among others, cycloadditions, Mukaiyama-Michael reactions and α -chlorinations have all been demonstrated by MacMillan.
- Diels-Alder Cycloadditions, so called 'LUMO-lowering catalysis':



Imidazolidinones - Versatility

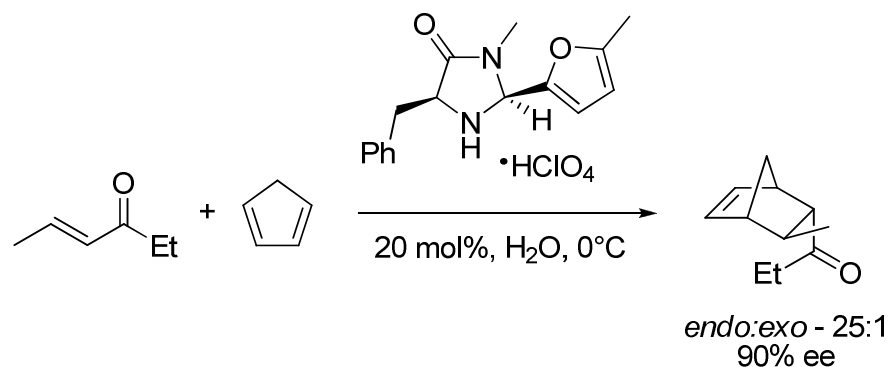
- This Catalyst was also successfully applied to 1,3-Dipolar cycloadditions:



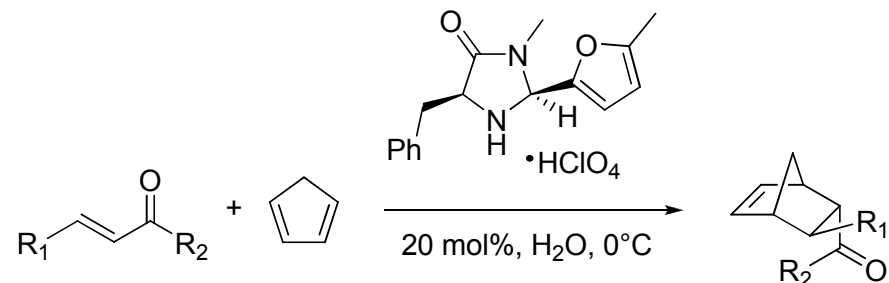
- This catalyst gave >90% ee with a wide range of α,β -unsaturated aldehydes and substituted nitrones.

Imidazolidinones - Versatility

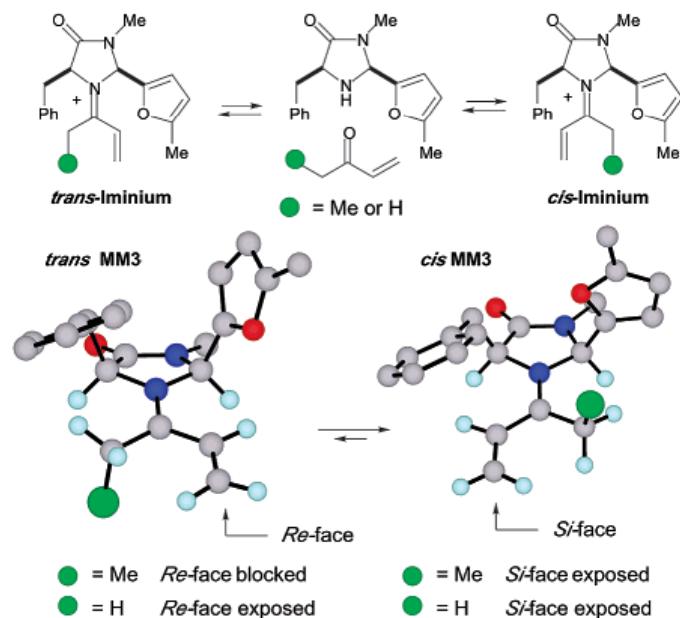
- The original *gem*-dimethyl catalyst was found to be ineffective in inducing chirality when applied to α,β -unsaturated ketones.
- Further development of the catalyst led to the 5-Me-furyl derived imidazolidinone, which exhibited high potency.



Imidazolidinones - Versatility



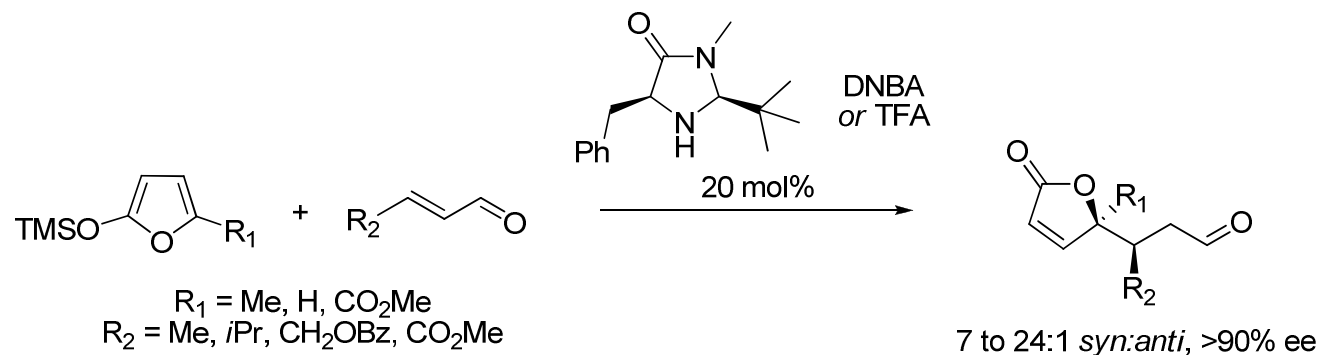
$R_1, R_2 = \text{Me}, 14:1, 61\% \text{ ee}$
 $R_1 = \text{Me}, R_2 = \text{Et}, 25:1, 90\% \text{ ee}$



A. B. Northrup and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2002**, *124*, 2458.

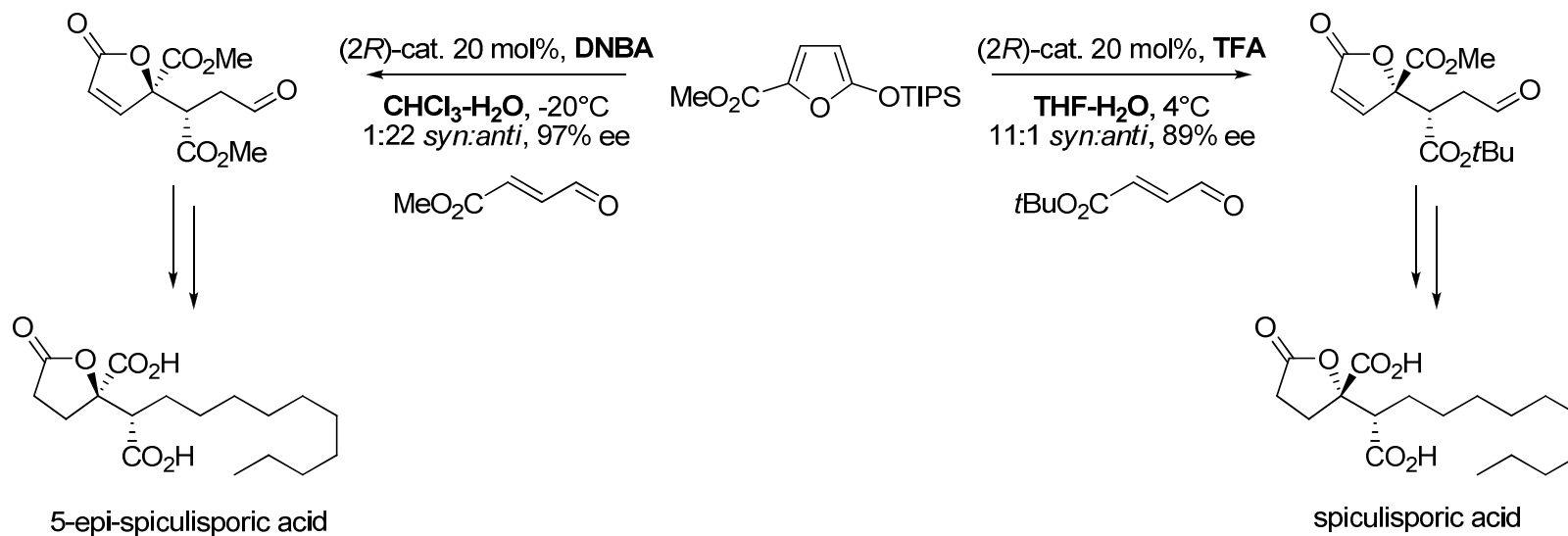
Imidazolidinones - Versatility

- These catalysts have also been applied to Mukaiyama-Michael reactions, specifically the addition of silyloxy furans to α,β -unsaturated aldehydes.
- Slight modification of the original catalyst led to excellent selectivity.



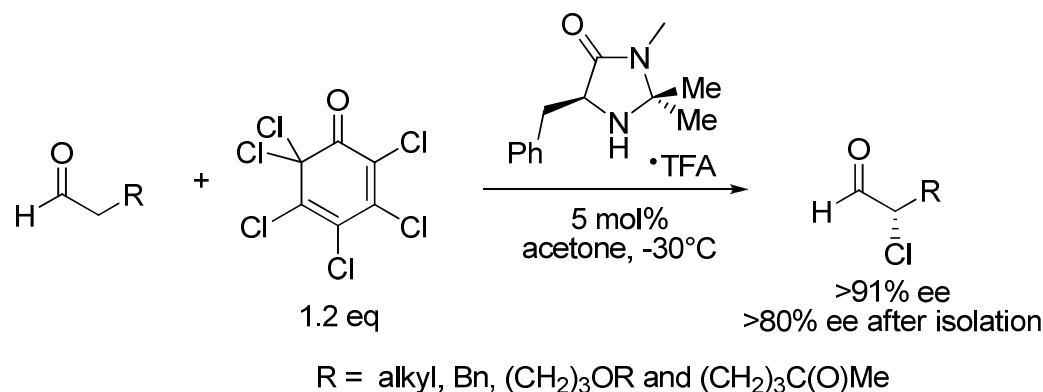
Imidazolidinones - Versatility

- Modification of solvent and cocatalyst leads to *syn* and *anti* selectivity:



Imidazolidinones - Versatility

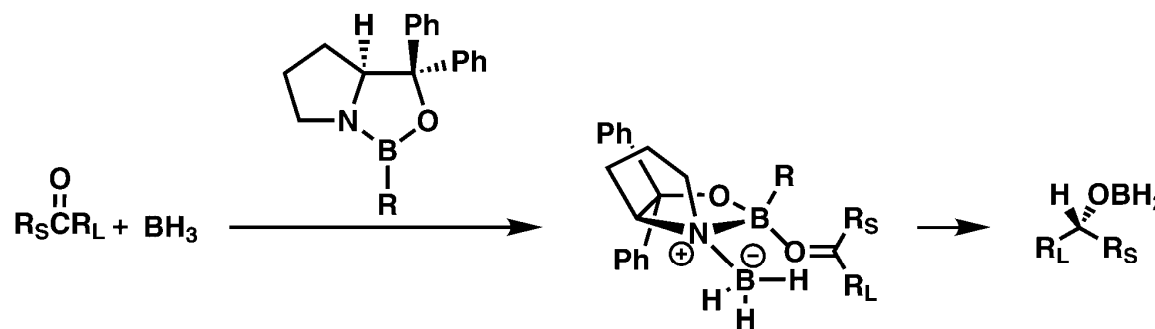
- Another excellent application of these catalysts was made to the α -chlorination of aldehydes.



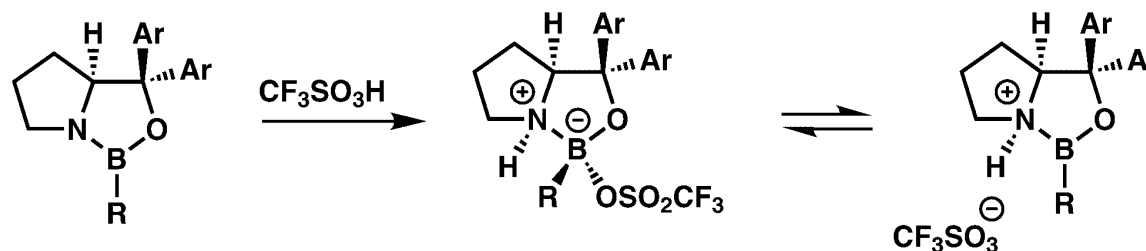
- Crude ee's were in general excellent, but on purification some enantiomeric excess was lost; especially in the case where R = Bn (ee = 92% to 80%).

Oxazaborolidines

- Oxazaborolidines, the Corey-Bakshi-Shibata (CBS) catalysts, have for some time been employed in the enantioselective reduction of ketones:

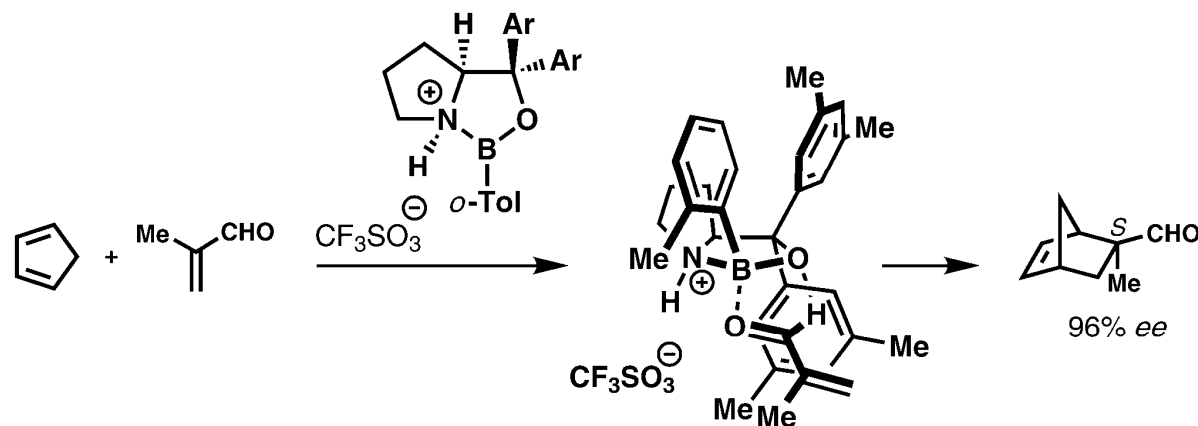


- Protonation of these species leads to potent cationic lewis acids:



Oxazaborolidines

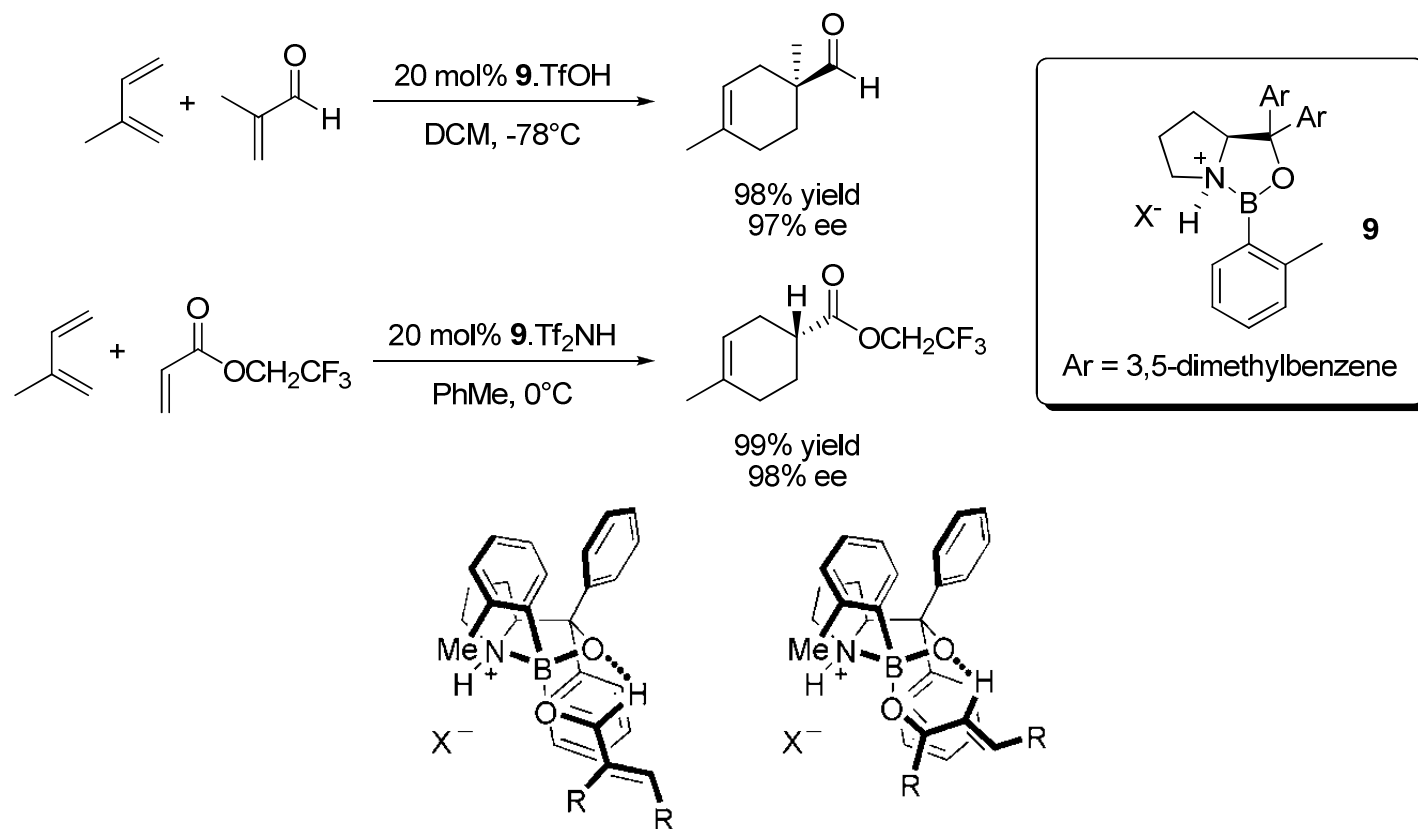
- These chiral cationic Lewis acids were found to be excellent catalysts for enantioselective the Diels-Alder reaction.



- α,β -unsaturated carbonyl compounds are activated by these protonated oxaborolidines, undergoing reactions with relatively unreactive dienes such as butadiene at low temperatures with high enantioselectivities.

Oxazaborolidines

- Opposite facial selectivities are observed in reactions with α,β -unsaturated aldehydes compared to α,β -unsaturated esters and enones.

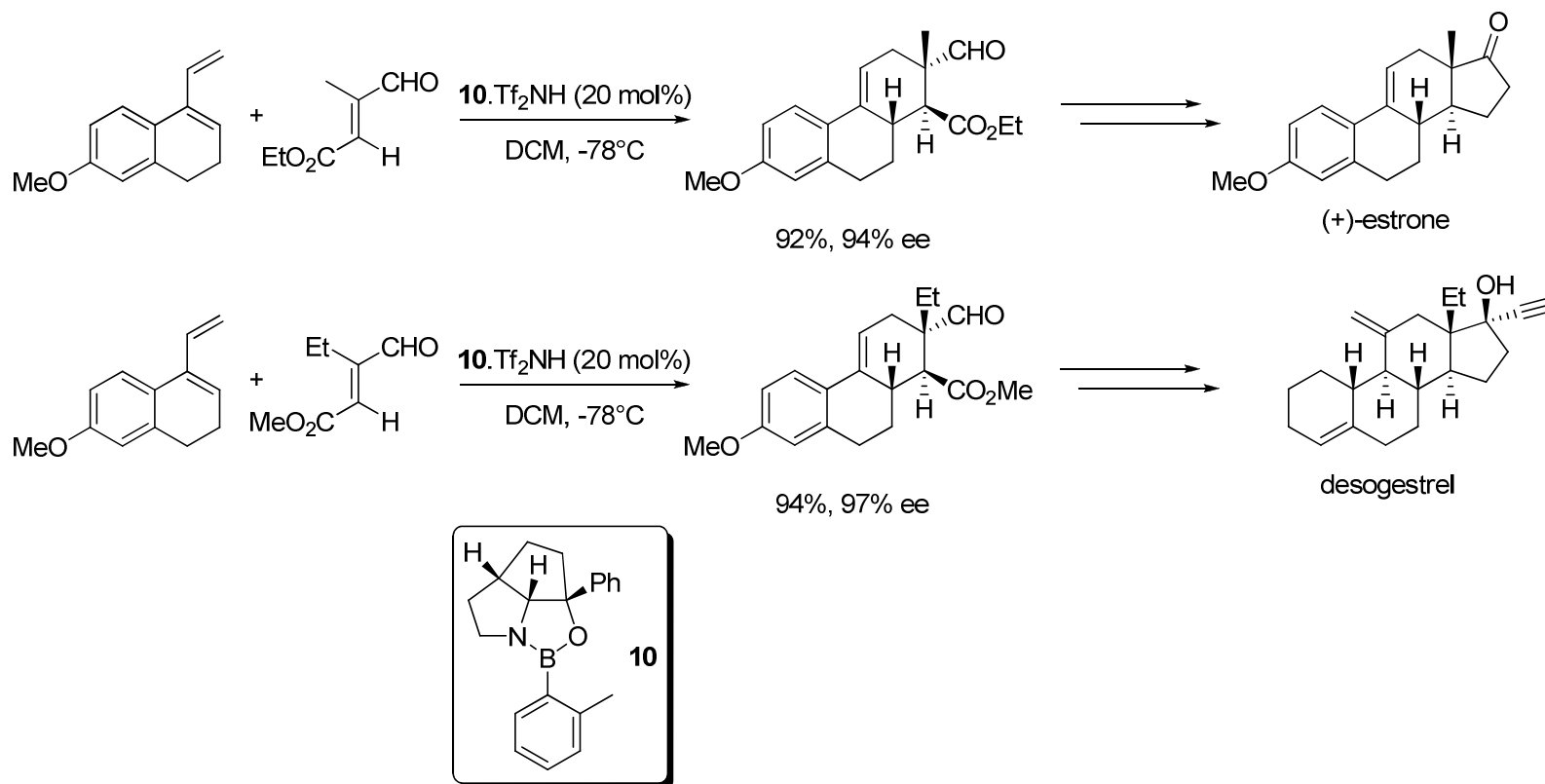


E. J. Corey *et al.*, *J. Am. Chem. Soc.*, **2002**, *124*, 3808.

D. H. Ruy and E. J. Corey, *J. Am. Chem. Soc.*, **2003**, *125*, 6388.

Oxazaborolidines

- These catalysts have been used in the key steps of numerous natural products, for example the synthesis of the steroids (+)-estrone and desogestrel.



Q-Y. Hu *et al.*, *J. Am. Chem. Soc.*, **2004**, 126, 5984.

Conclusions

- The combination of inactive, neutral molecules with strong Brønsted acids has led to the development of highly enantioselective catalytic reactions.
 - The methods described use diverse modes of action, from enamine and imine catalysis to formal hydrogen bonding catalysis.
 - The explosion of interest in the area of organocatalysis since 2000 will undoubtedly lead to the development of even more wide-ranging and efficient catalysts.
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