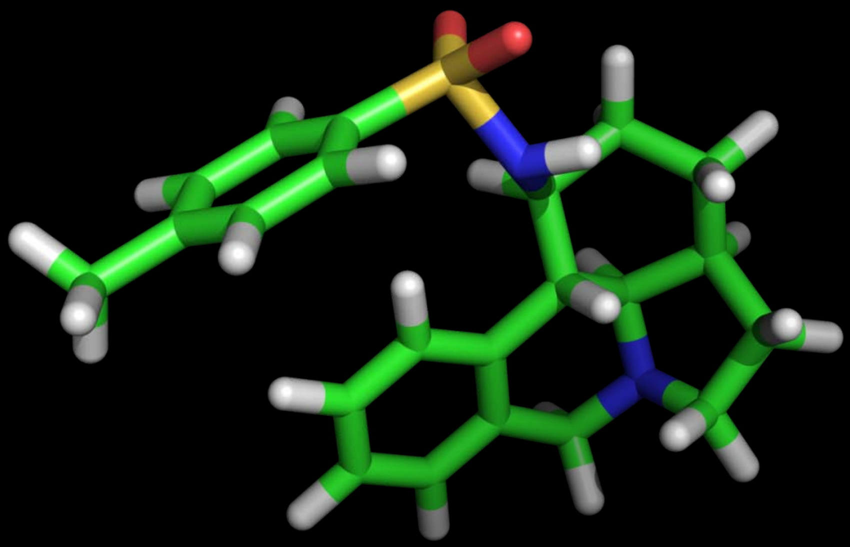

19th Annual Review Meeting: Advances in Asymmetric Synthesis

Recent Advances In Hydrogen Bonding Catalysis

Dr Andre Cobb,
University of Reading.
a.j.a.cobb@reading.ac.uk

Overview

- A brief introduction to hydrogen bond (H-bond) catalysis.
- Chiral phosphoric acids and related systems
- Thioureas (Monofunctional and Bifunctional)
- Amino alcohols
- Enamine catalysis
- Conclusions
- Acknowledgements

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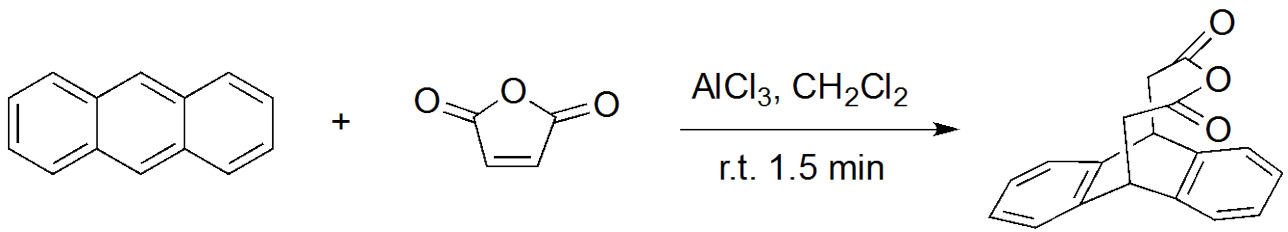
Lewis Acid vs Brønsted Acid Catalysis

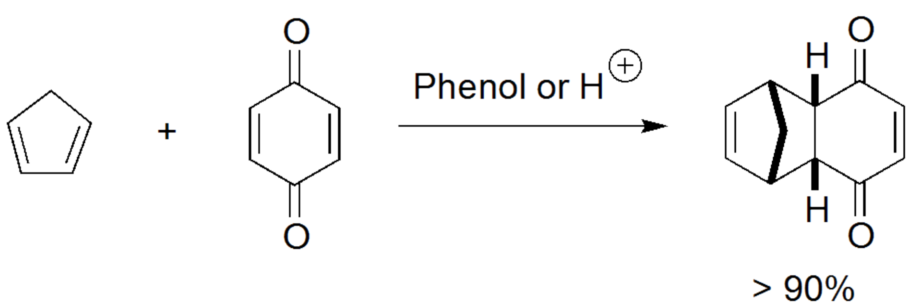
Yates and Eaton (1960)



without $AlCl_3$, ca. 95% conversion after 200 d

Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436

Wassermann (1942)



$H^{\oplus}$ = AcOH, $ClCH_2CO_2H$, $BrCH_2CO_2H$, Cl_3CCO_2H

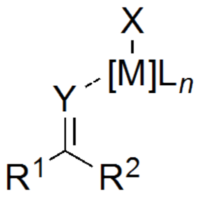
Wassermann, A. *J. Chem. Soc.* **1942**, 618.

Lewis Acid vs Brønsted Acid Catalysis

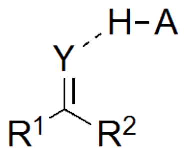
"Why did the report of Yates and Eaton, and not that of Wassermann, capture the imagination of the vast majority of early practitioners of asymmetric catalysis, leading to the current situation where chiral Lewis acid catalysis, rather than chiral Brønsted acid catalysis, is the dominant strategy for promotion of enantioselective additions to electrophiles?"

Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.

Lewis Acid vs Brønsted Acid Catalysis



Lewis Acid Catalysts



Hydrogen Bond Catalysts

Pros

- Highly tunable structures
- Low catalyst loadings
- Strong Lewis acid/Lewis base interactions

- Moderately tuneable (structure of A/pKa)
- Exists as the active catalyst
- Water, moisture stable/tolerant
- Potentially recoverable/reuseable

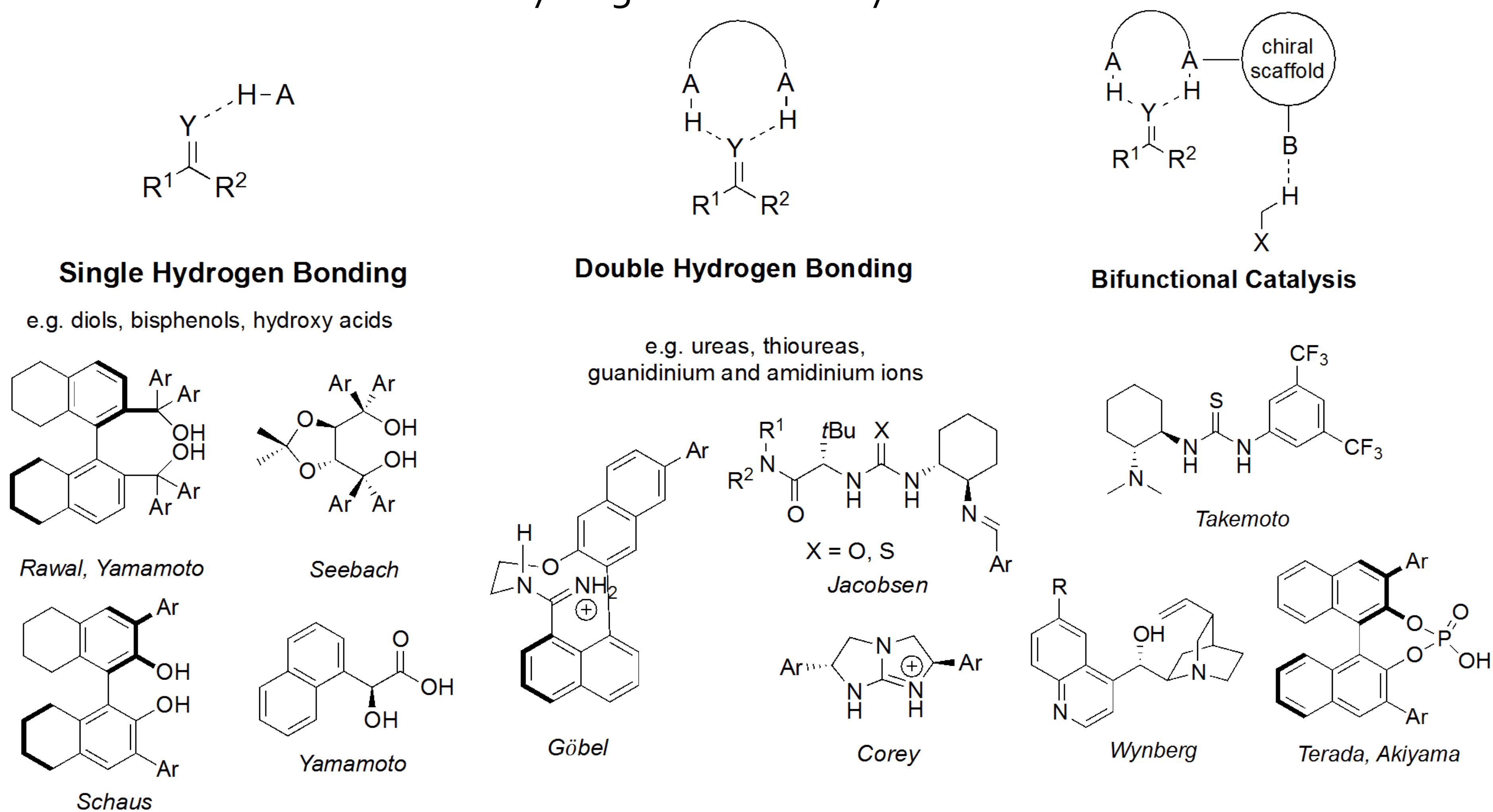
Cons

- Often require preparation *in situ*
- Often water/moisture sensitive

- Higher catalyst loadings

Hydrogen Bond Catalysis

- Three distinct modes of hydrogen bond catalysis will be discussed.



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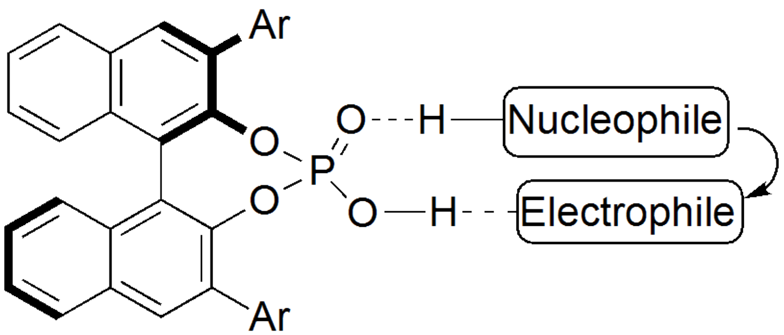
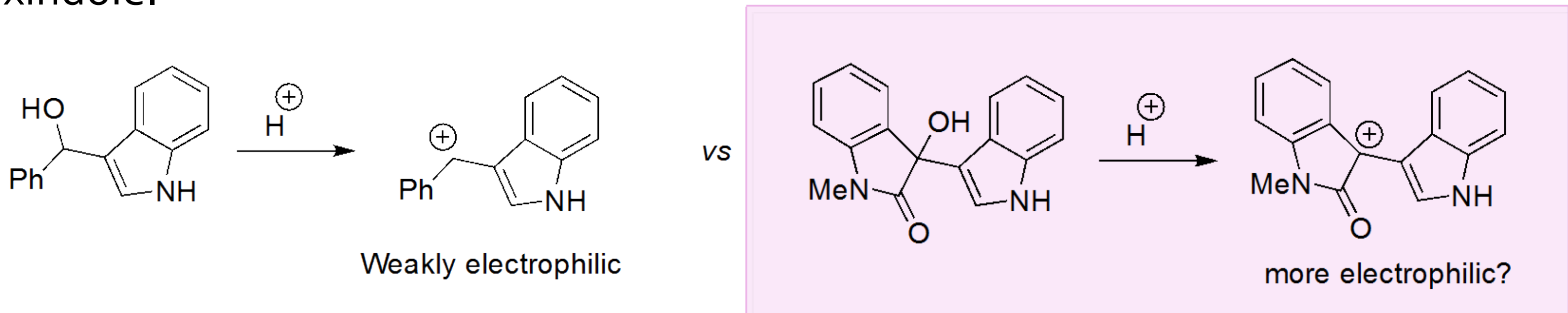
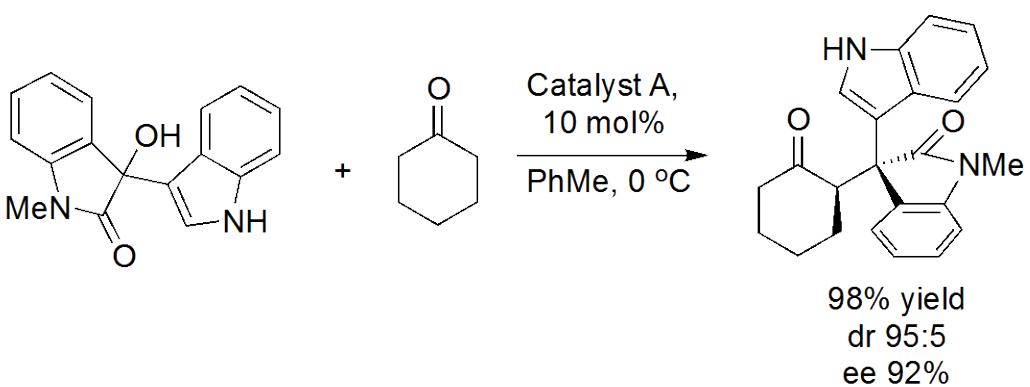
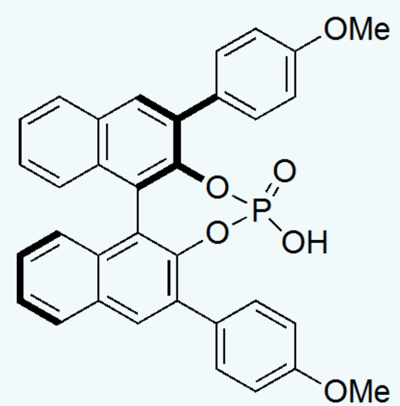


Recent Work Using Chiral Phosphoric Acids – Peng and Guo's α-Alkylation of Ketones

Uses an isatin-derived 3-hydroxy-3-indolyoxindole to improve the electrophilicity of the oxindole.



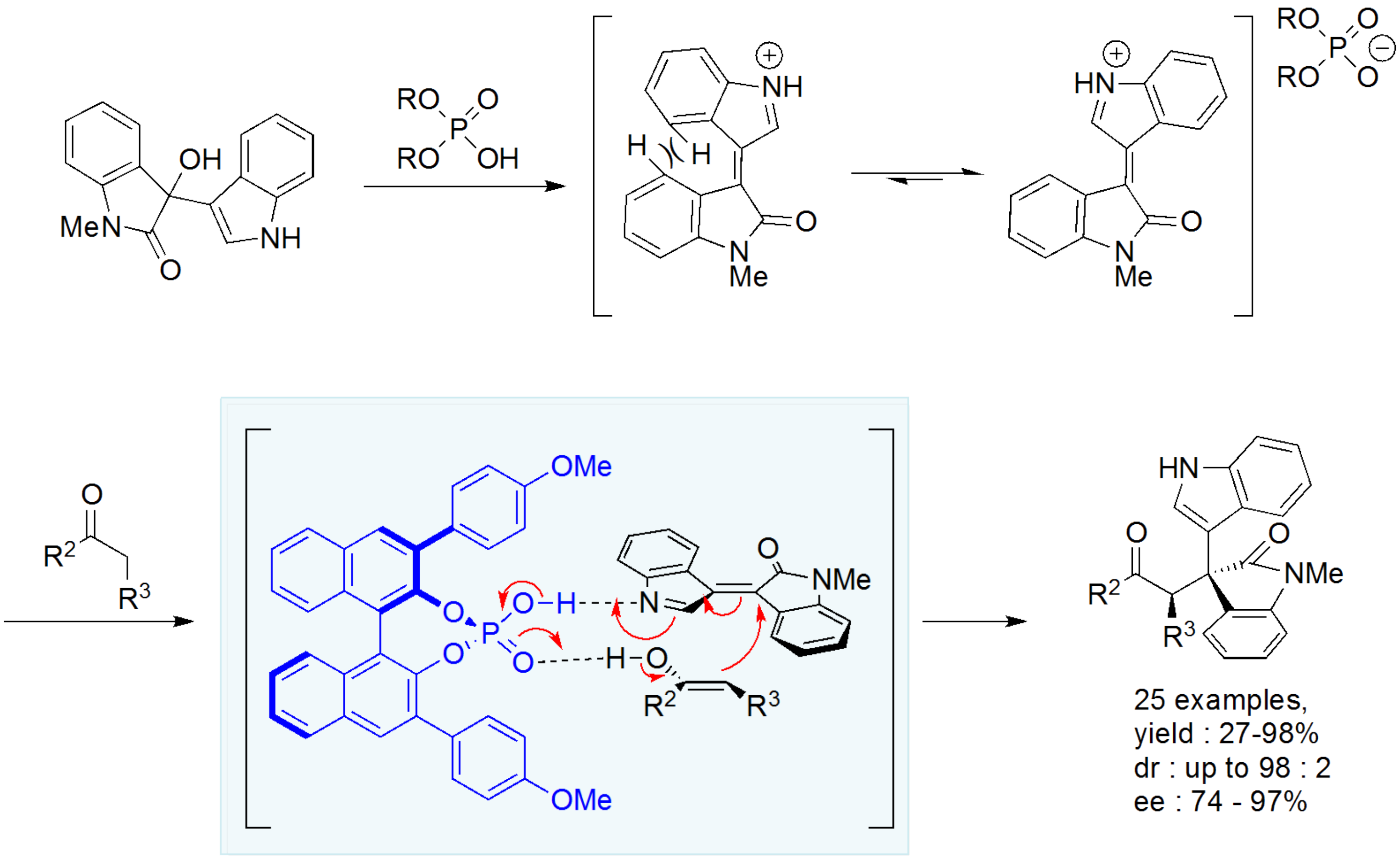




Catalyst **B**

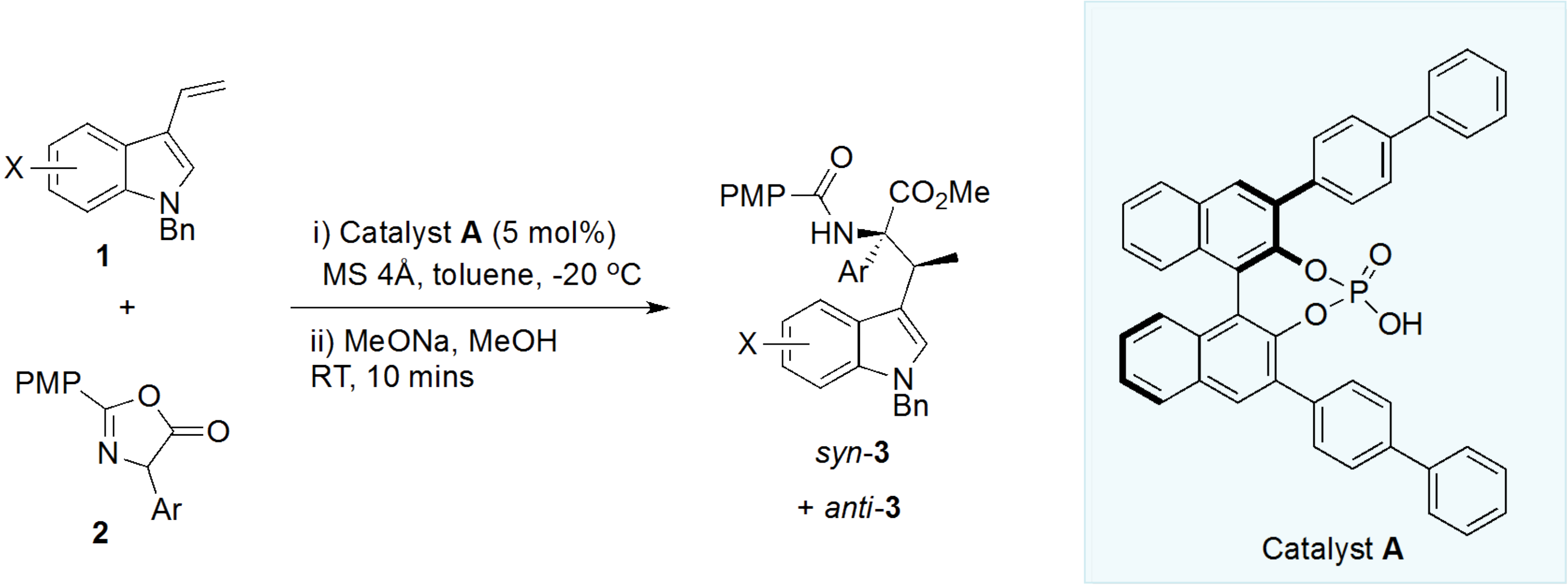
Song, L.; Guo, Q.-X.; Li, X.-C.; Tian, J.; Peng, Y. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 1899.

Recent Work Using Chiral Phosphoric Acids – Peng and Guo's α-Alkylation of Ketones



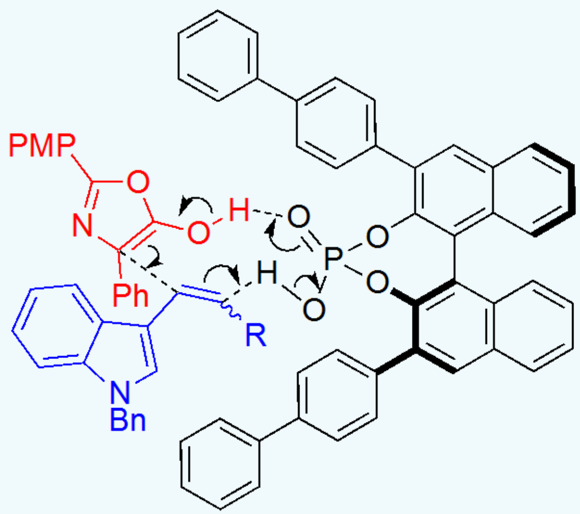
Song, L.; Guo, Q.-X.; Li, X.-C.; Tian, J.; Peng, Y. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 1899.

Recent Work Using Chiral Phosphoric Acids – Terada's Synthesis of Tryptophan Derivatives



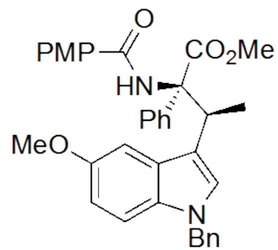
Terada, M.; Moriya, K.; Kanomata, K.; Sorimachi, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 12586.

Recent Work Using Chiral Phosphoric Acids – Terada's Synthesis of Tryptophan Derivatives

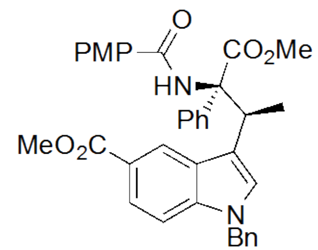


Proposed Ene Reaction Co-ordination by Chiral Phosphoric Acid Catalyst

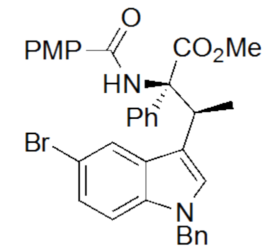
	syn	anti
R=(*E*)-Me ⟹ 69% yield,	86 (74% ee) :	14 (22% ee)
R=(*Z*)-Me ⟹ 35% yield,	59 (19% ee) :	41 (25% ee)



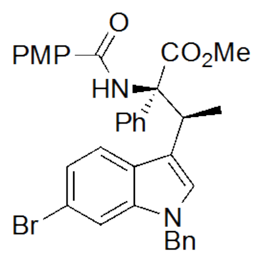
76% yield,
96 : 4 (syn : anti),
91% ee



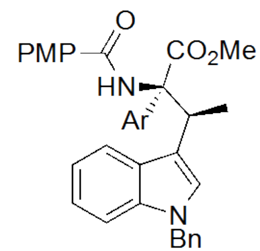
73% yield,
98 : 2 (syn : anti),
94% ee



63% yield,
98 : 2 (syn : anti),
95% ee

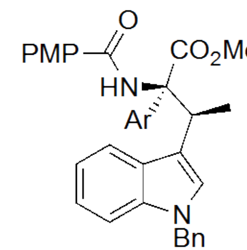


41% yield,
96 : 4 (syn : anti),
75% ee



Ar = 3-$MeOC_6H_4$-

82% yield,
93 : 7 (syn : anti),
89% ee



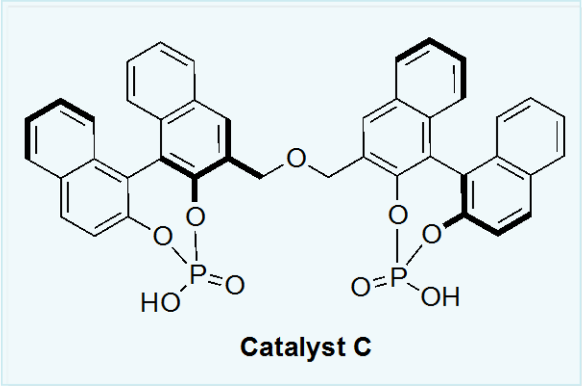
Ar = 4-$MeOC_6H_4$-

87% yield,
98 : 2 (syn : anti),
90% ee

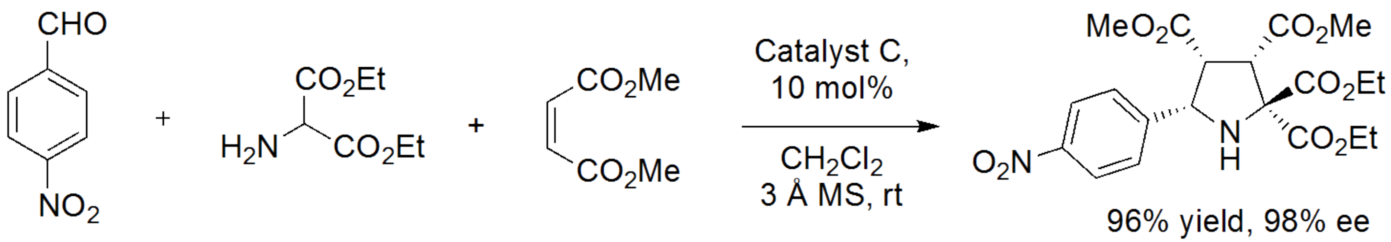
Terada, M.; Moriya, K.; Kanomata, K.; Sorimachi, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 12586.

Recent Work Using Chiral Phosphoric Acids – Gong's Bisphosphoric Acids for 1,3-Dipolar Cycloadditions

- Uses a bisphosphoric acid.



- Synthesis of proline derivatives.



He, L.; Chen, X.-H.; Wang, D.-N.; Luo, S.-W.; Zhang, W.-Q.; Yu, J.; Ren, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2011**, *133*, 13504.

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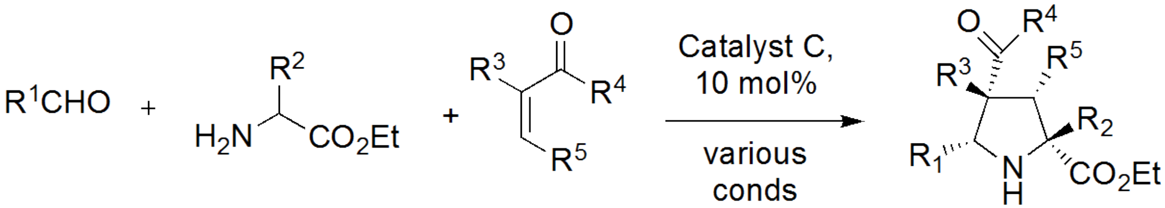
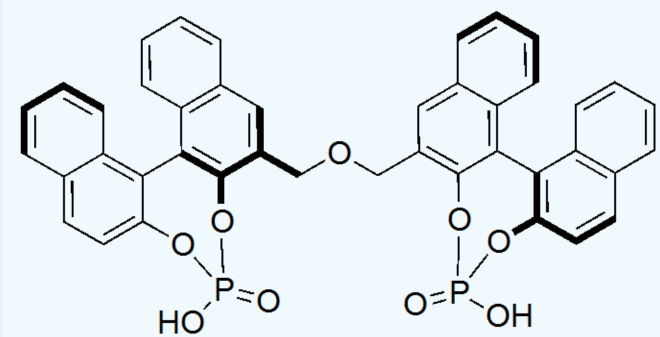
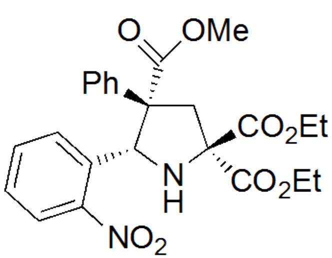


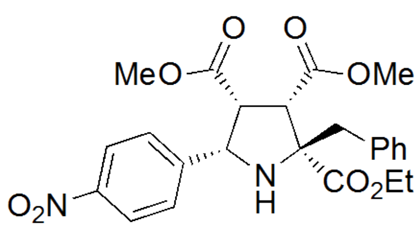
Yield : 43 - 98%
ee : 74 - 98%



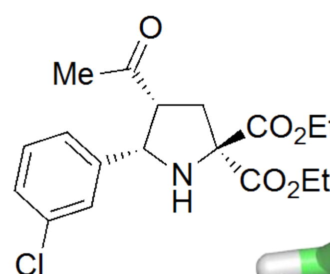
Catalyst C



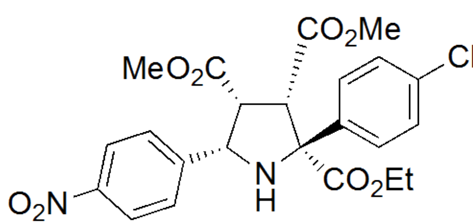
85% yield, 98%ee



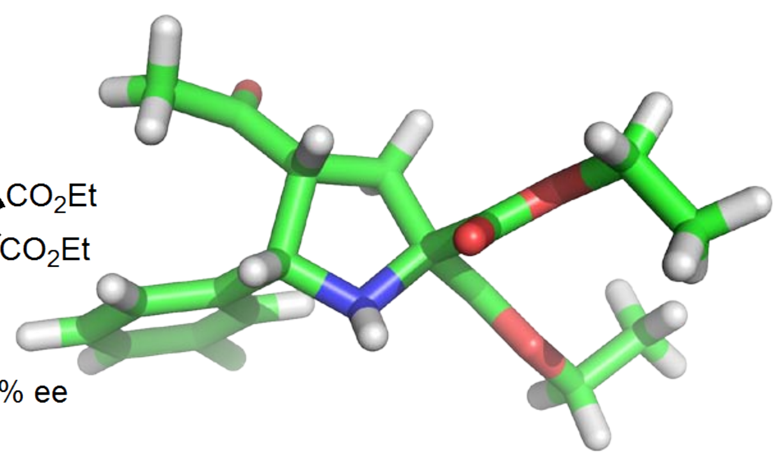
88% yield, 98% ee



43% yield, 96% ee

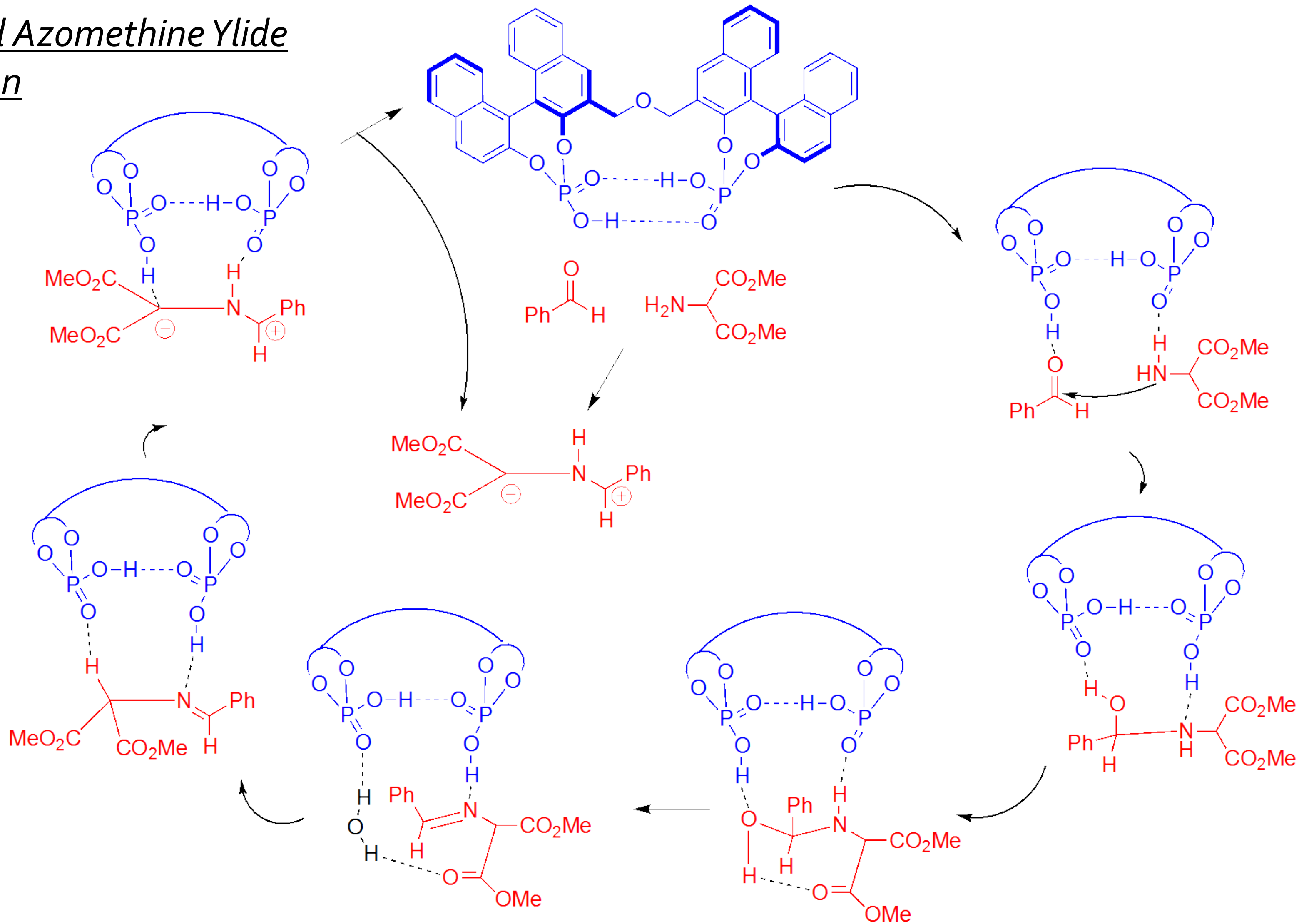


96% yield, 97% ee



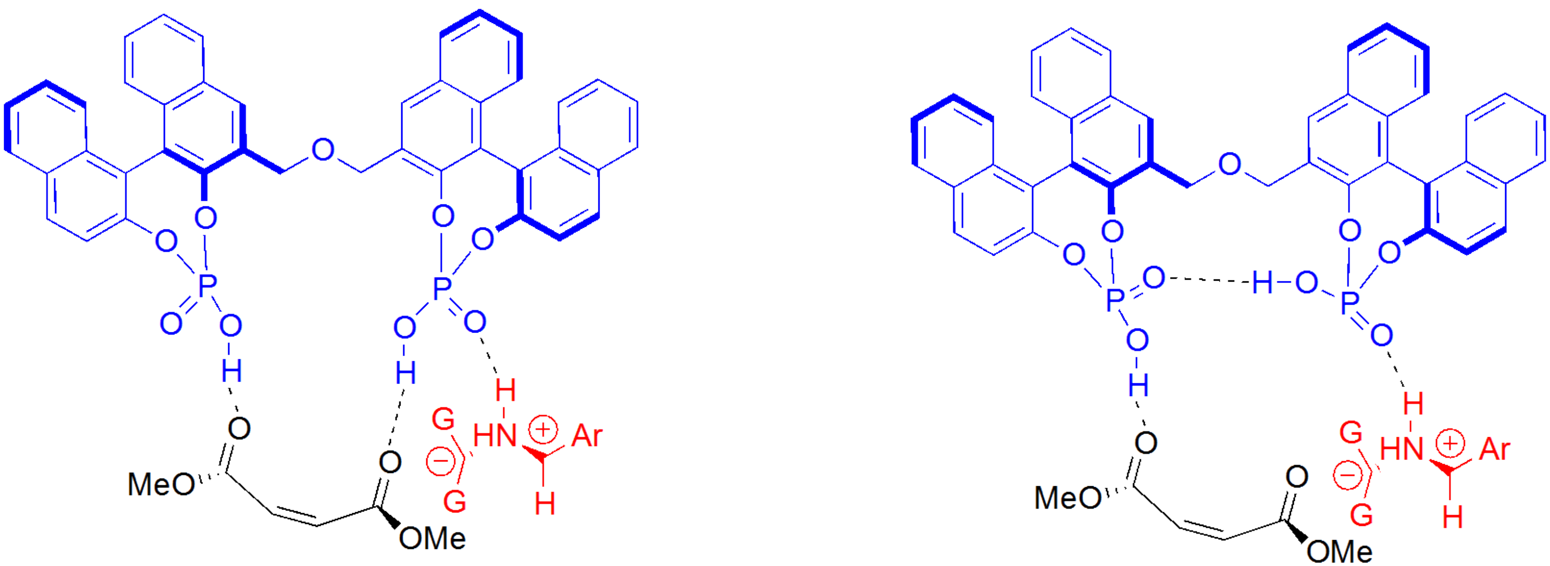
Recent Work Using Chiral Phosphoric Acids – Gong's Bisphosphoric Acids for 1,3-Dipolar Cycloadditions

Proposed Azomethine Ylide Formation



Recent Work Using Chiral Phosphoric Acids – Gong's Bisphosphoric Acids for 1,3-Dipolar Cycloadditions

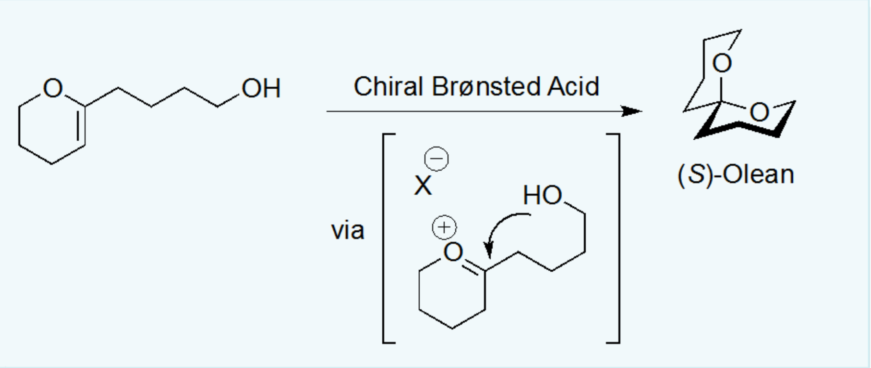
Proposed Models for 1,3-Dipolar Cycloaddition

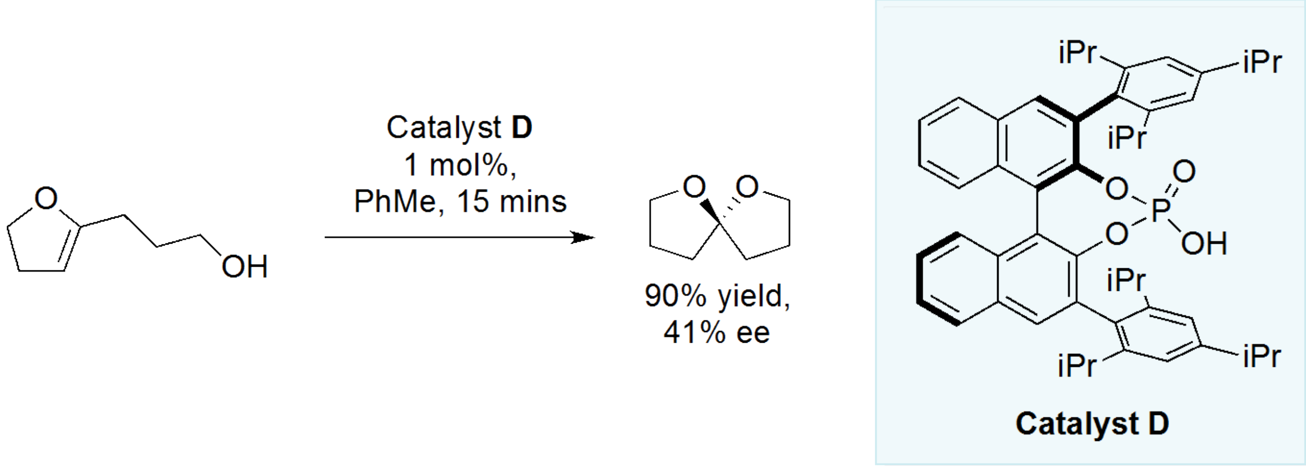


He, L.; Chen, X.-H.; Wang, D.-N.; Luo, S.-W.; Zhang, W.-Q.; Yu, J.; Ren, L.' Gong, L.-Z. *J. Am. Chem. Soc.* **2011**, *133*, 13504.

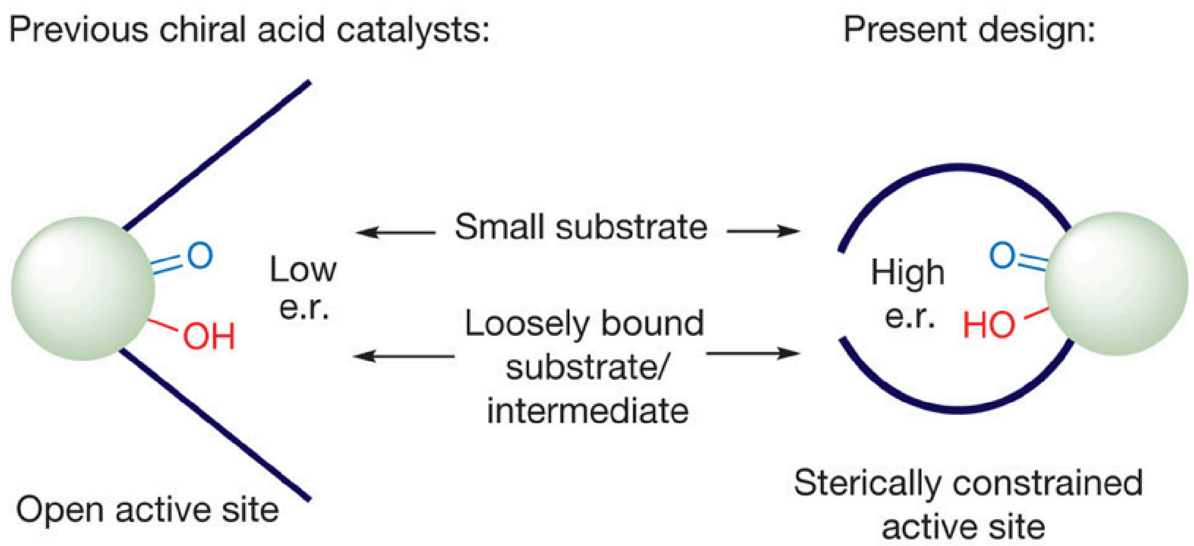
Recent Work Using Chiral Phosphoric Acids – List's Spiroacetalization

- Concept

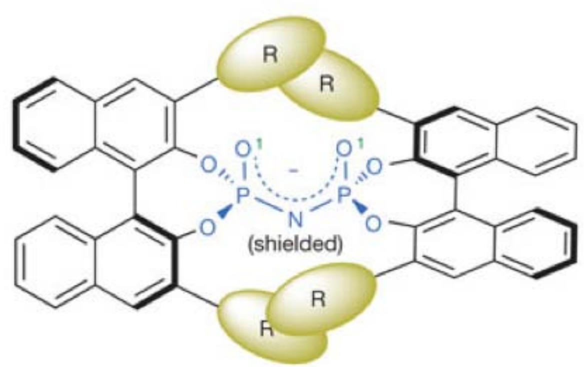




List's Spiroacetalization - New C_2-Symmetric 'Confined' Brønsted Acids



Proposed that the compact chiral environment will lead to greater enantioselectivity



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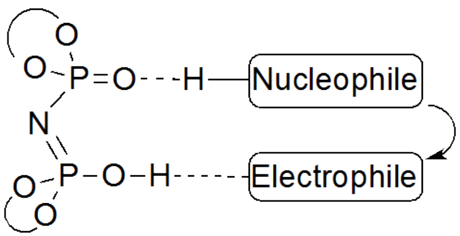
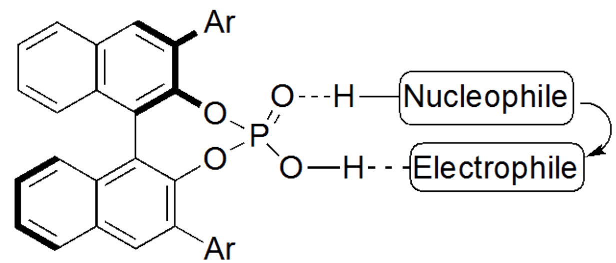
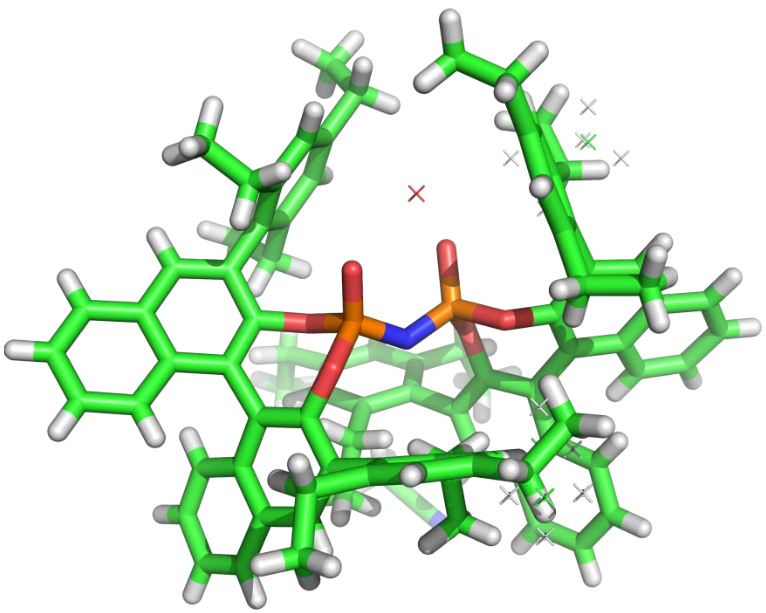
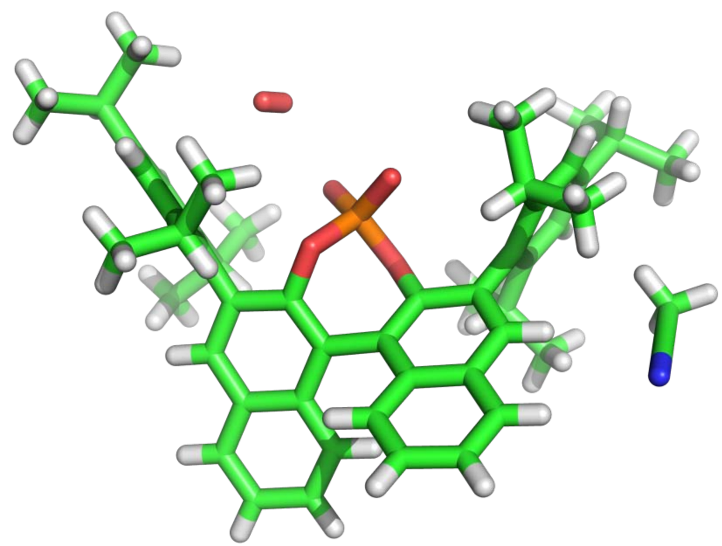


vs







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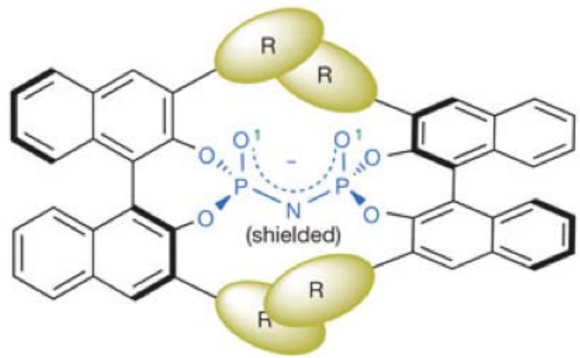
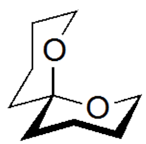
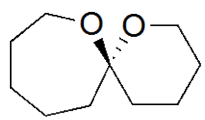
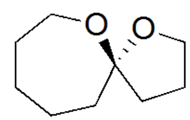




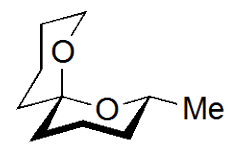
Yield 77%
ee 96%



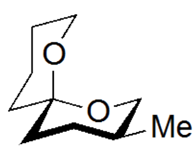
Yield 78%
ee 92%



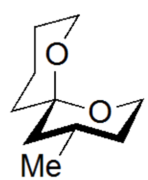
Yield 88%
ee 97%



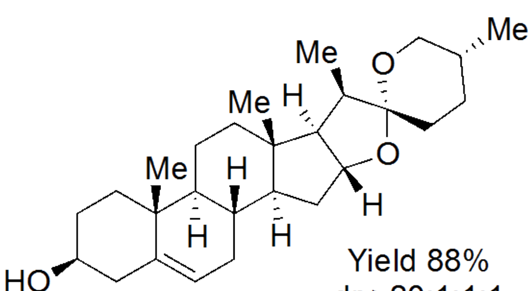
Yield 89%
dr 65:1



Yield 70%
dr 50:1



Yield 86%
dr 100:1



Yield 88%
dr >20:1:1:1

Čorić, I.; List, B. *Nature* **2012**, *583*, 315.

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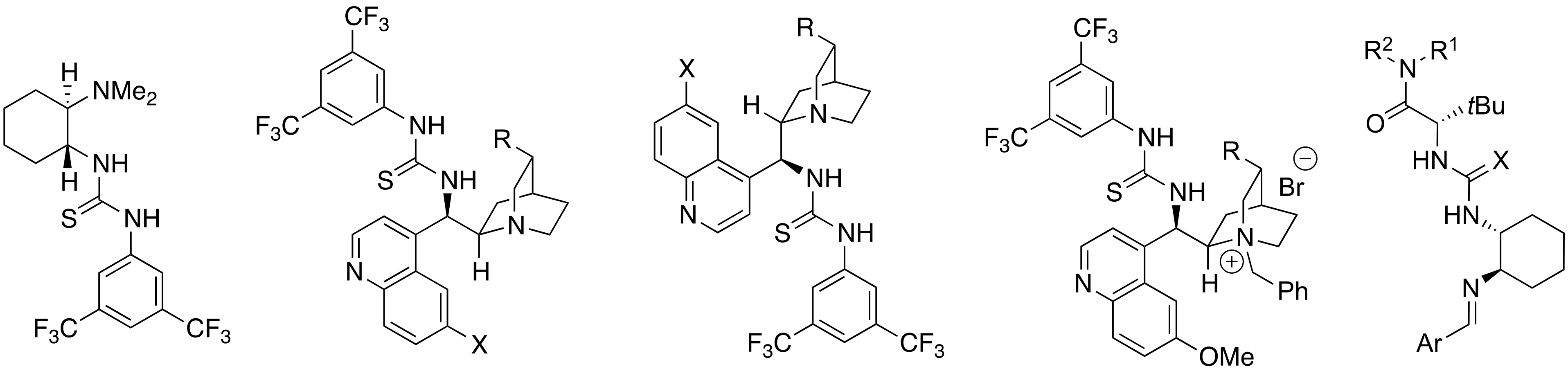
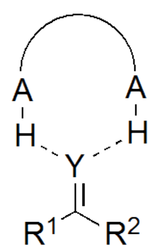
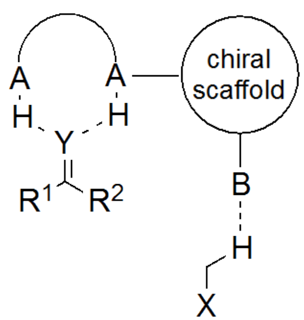
(Thio)ureas and Related Systems



R = CH=CH$_2$, CH$_2$CH$_3$; X = H, OMe



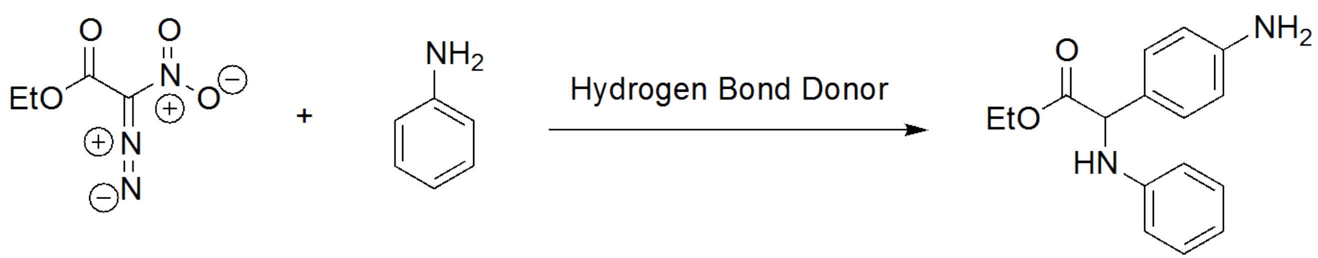
Double Hydrogen Bonding

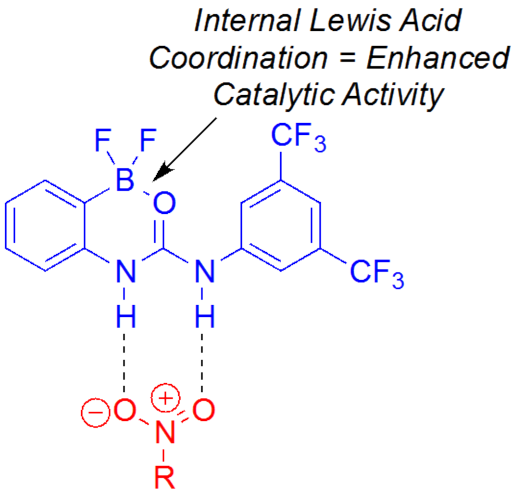


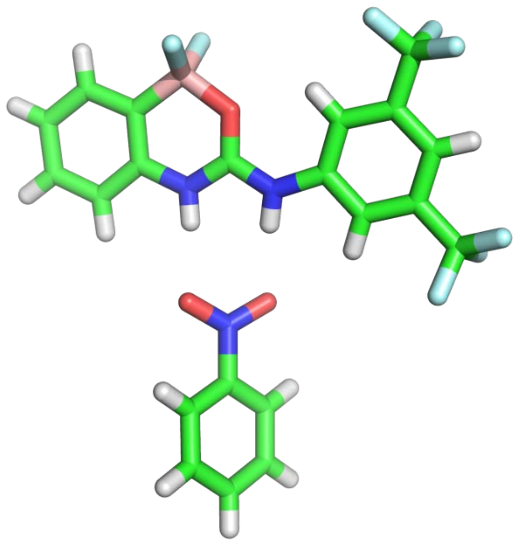
Bifunctional Catalysis

Mattson's N-H Insertion Reaction

- Not asymmetric, but still very impressive.

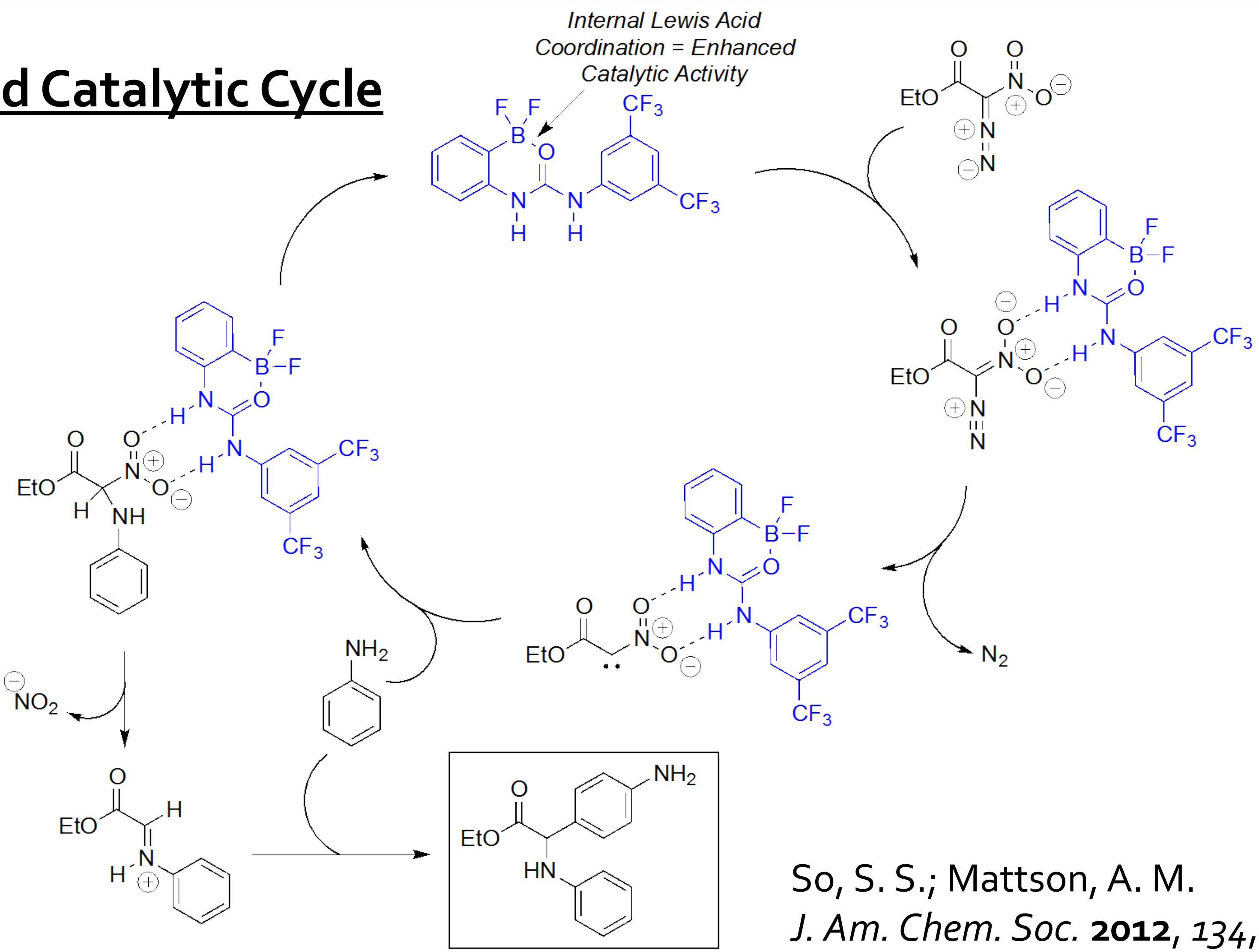






Mattson's N-H Insertion Reaction

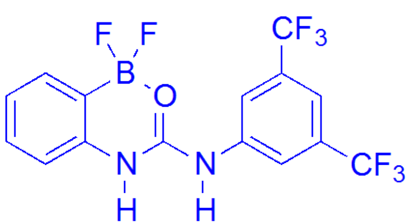
Proposed Catalytic Cycle

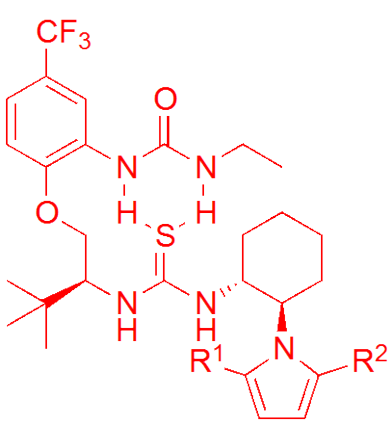


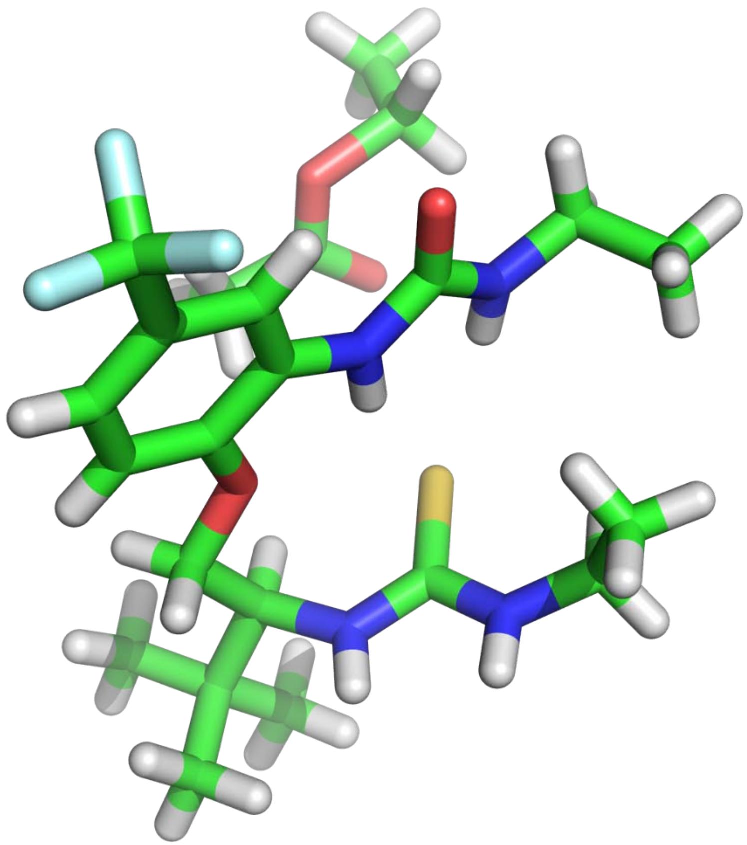
So, S. S.; Mattson, A. M.
J. Am. Chem. Soc. **2012**, *134*, 8798

Smith's Co-operative (Thio)urea Catalysts

- Just seen how to improve catalyst activity

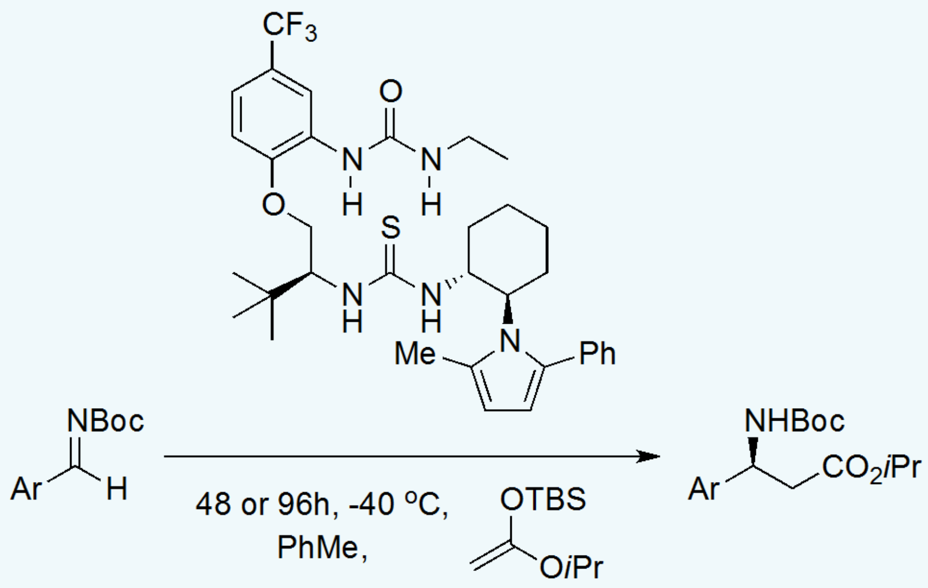






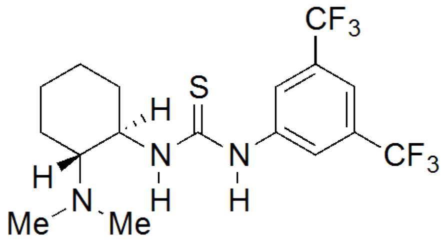
- Preorganised hydrogen-bonded turn structure minimizes entropic cost of TS binding.
- Noncovalent interactions within the catalyst structure are strengthened upon TS binding.
- Higher reaction rates, lower catalyst loading and high enantioselectivity.

Smith's Co-operative (Thio)urea Catalysts – Mukaiyama-Mannich



Ar	0.1 mol% cat yield%	ee%	1 mol% cat yield%	ee%	5 mol% cat yield%	ee%
Ph	75	99	96	>99	97	>99
4-MeC_6H_4	63	81	79	95	97	97
1-Napth	81	93	86	96	84	98
3-$NO_2C_6H_4$	75	93	74	99	73	>99

Bifunctional Thiourea Catalysis in Nitrogroup Reactivity



Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2003**, *5*, 625.

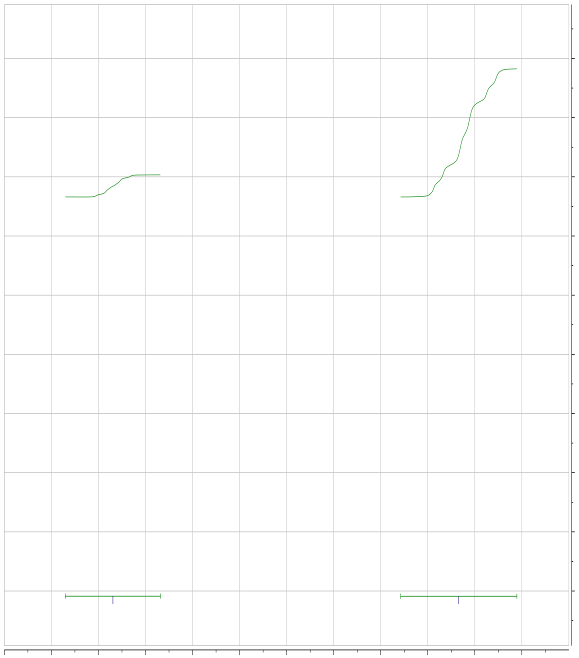
Our Synthesis of Cyclic Amino Acids

Solvent Screen

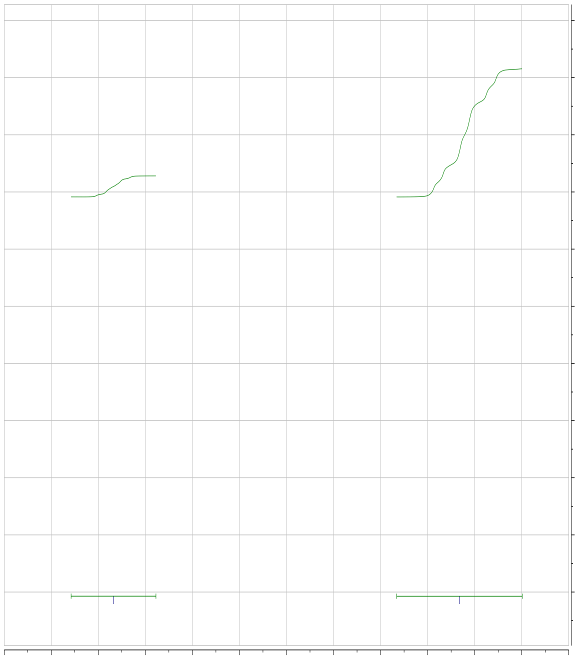
Entry	Solvent	Yield	d.r.	e.e. (%)
1	THF	67	>19:1	95
2	C_6H_6	71	2:1	96
3	CH_2Cl_2	83	>19:1	95
4	H_2O	51	9:1	95
5	MeCN	87	>19:1	95
6	None	80	5:1	96

A note on diastereoselectivity

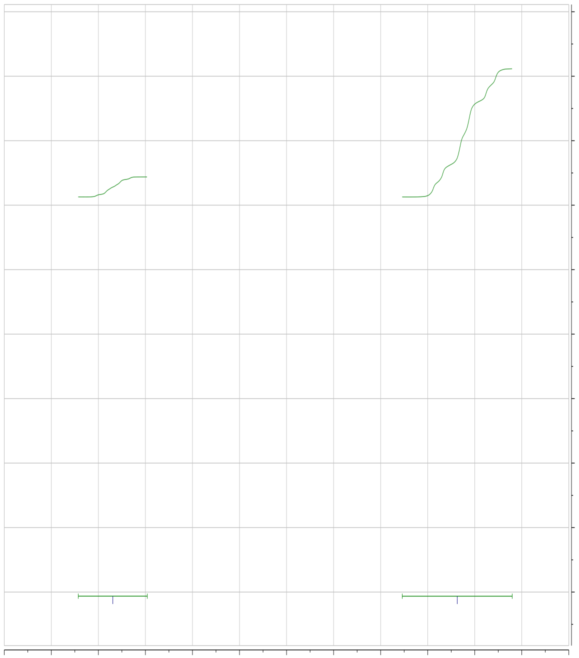
- Reaction time is important



1 day, 1:5.8

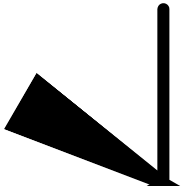


3 day2, 1:6.1



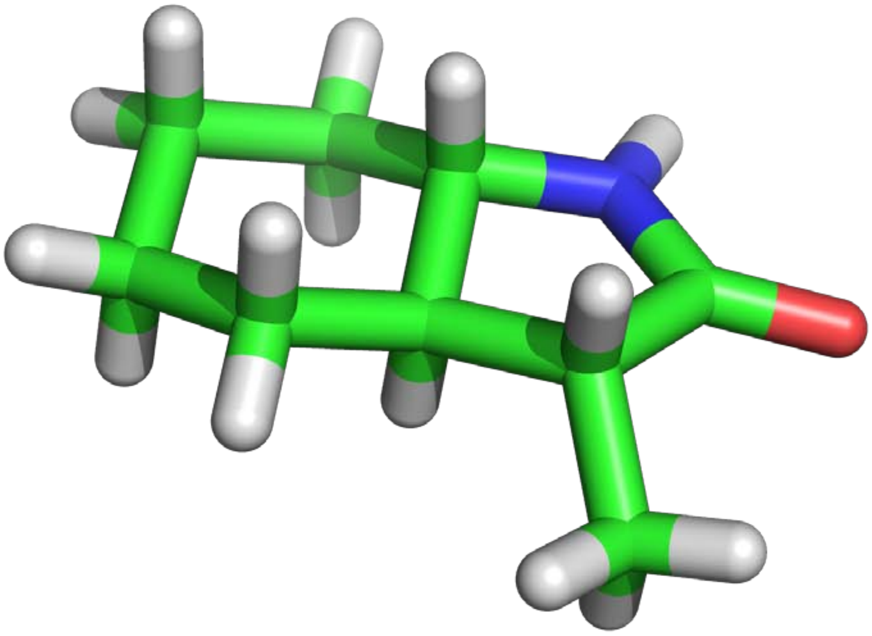
6 days, 1:6.4

Substrate Scope



Determining sterochemistry of three stereocentred substrates

Determining stereochemistry of compounds with three stereocentres

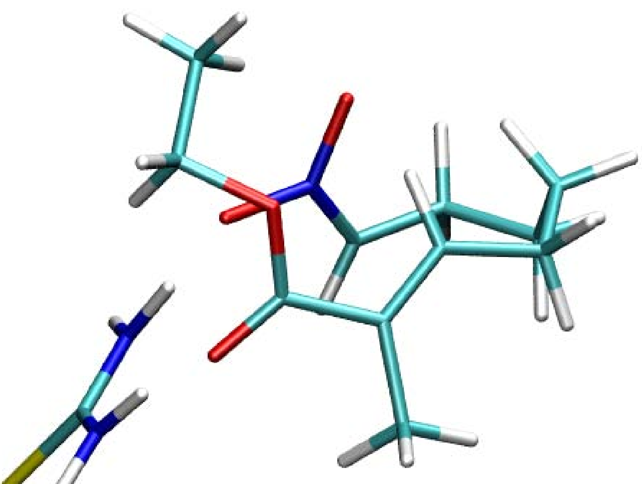


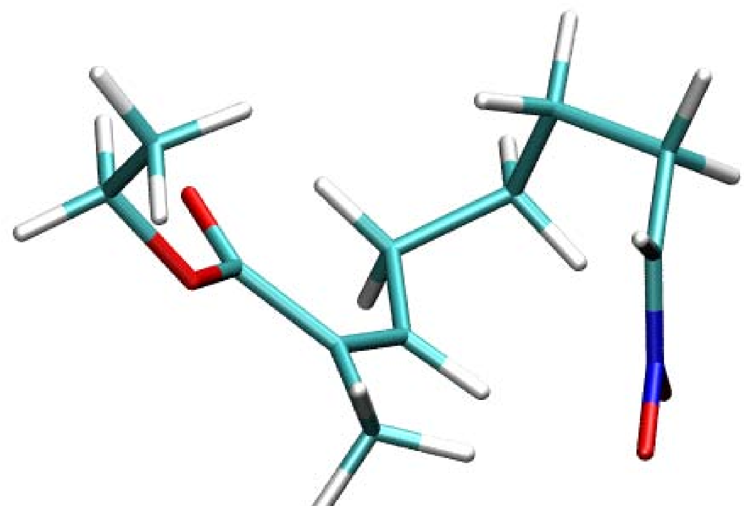
But…..

- Z-esters do not work as well

- What is going on?

Proposed mode of action



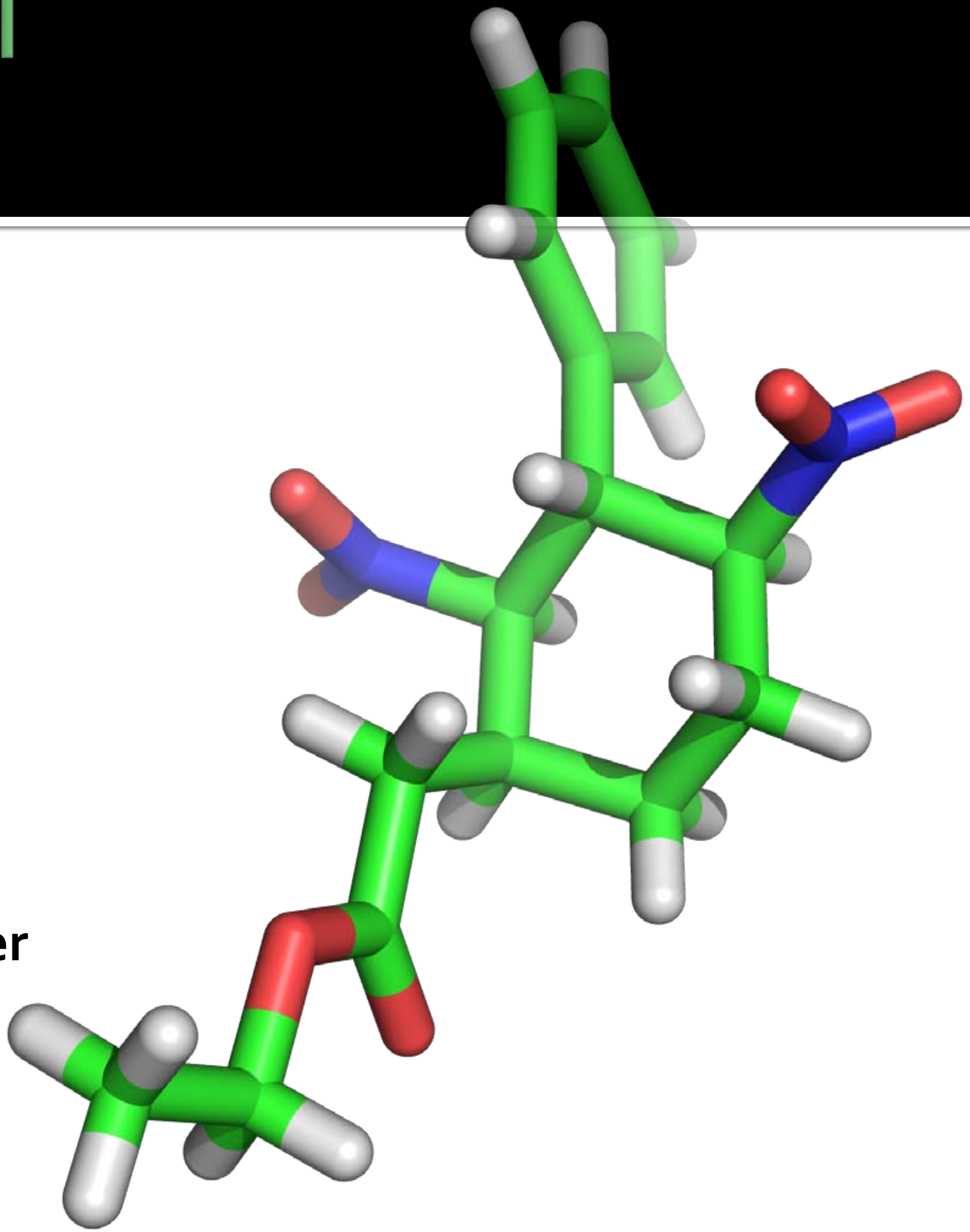


Nodes, W. J.; Nutt, D. R.; Chippindale, A. M.; Cobb, A. J. A. *J. Am. Chem. Soc.* **2009**, *131*, 16016

More Complex Systems : Domino Reactivity

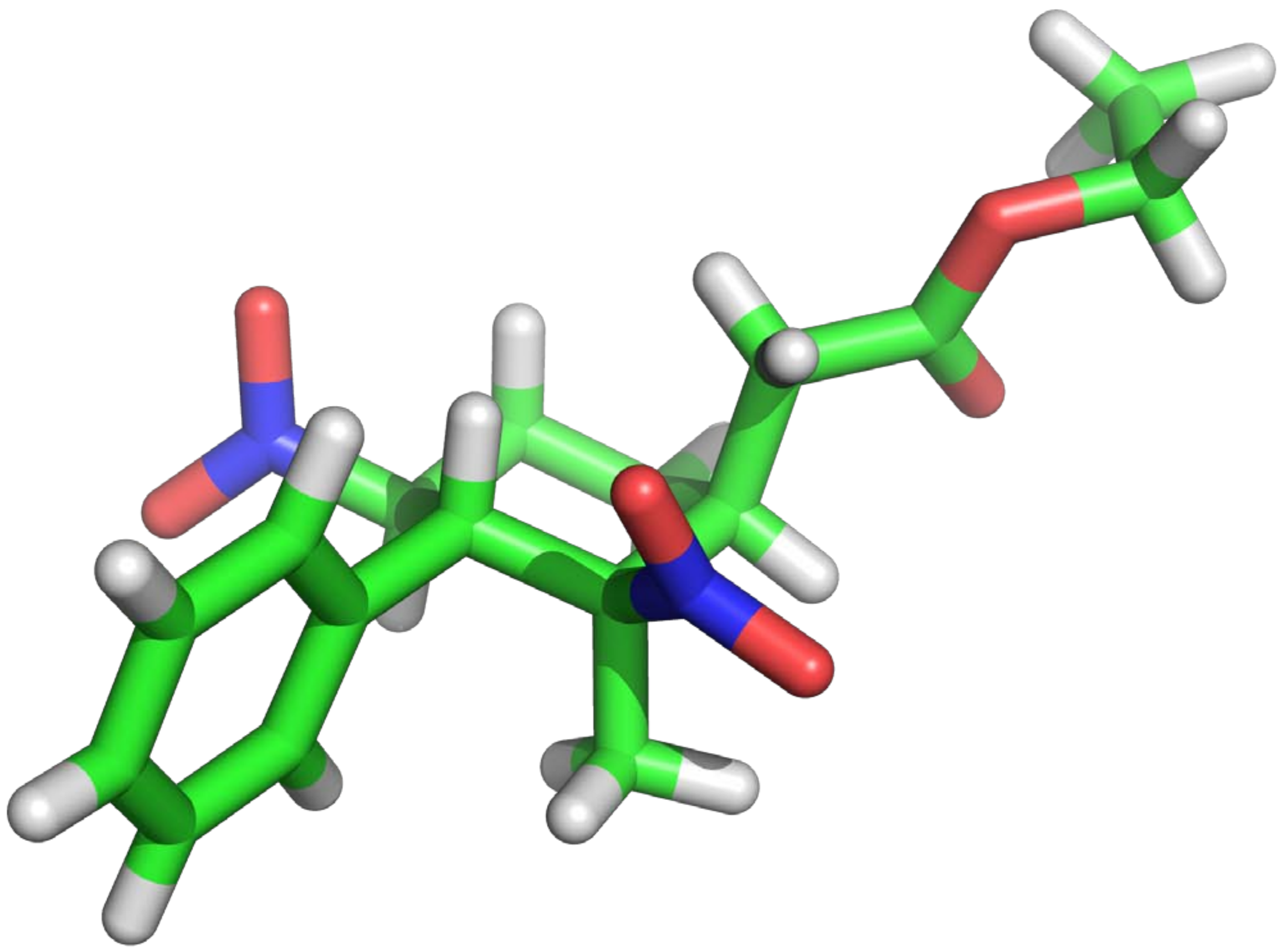
Catalyst Screen

Absolute Crystal Structure

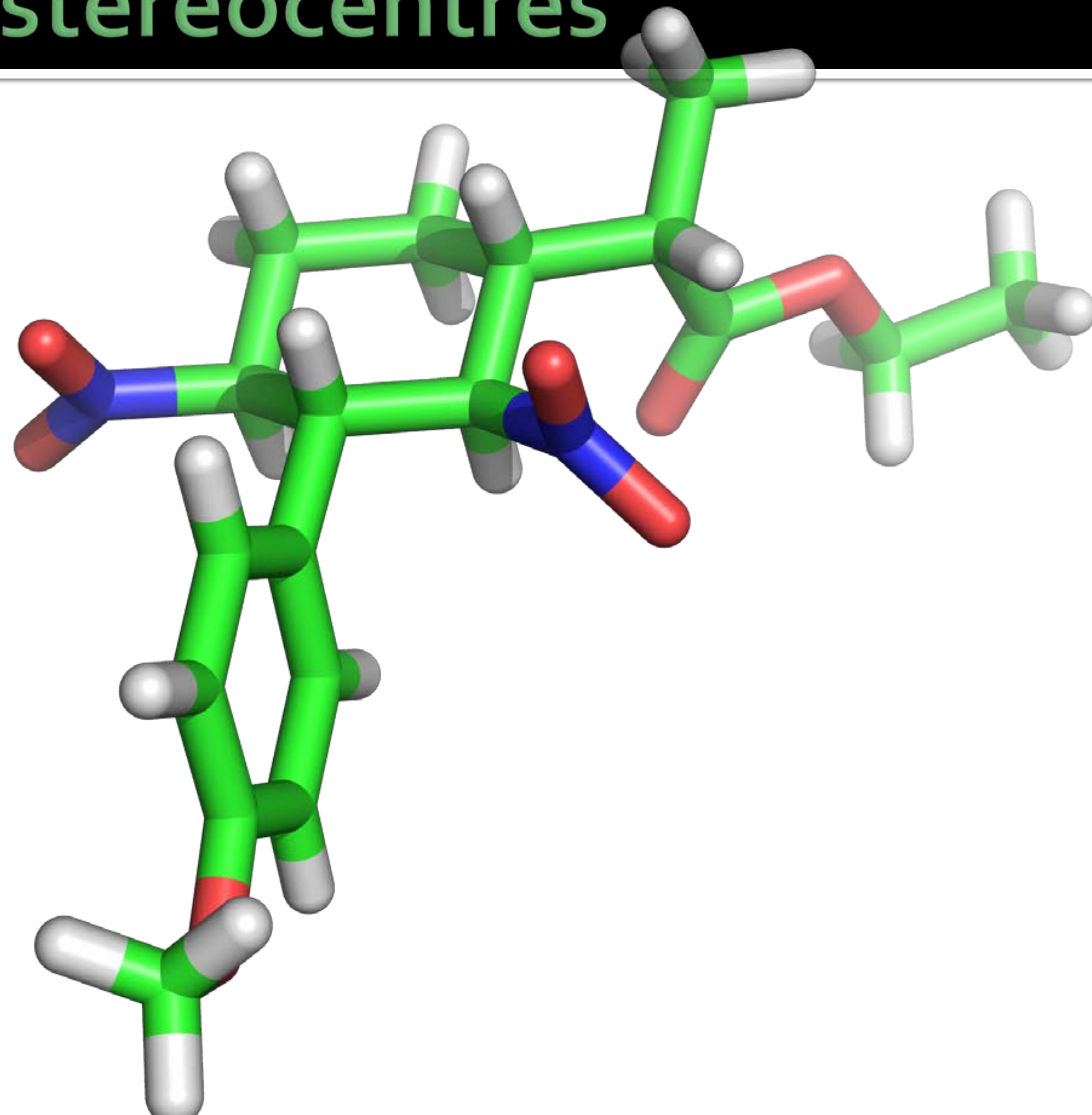


Major diastereoisomer

Substrate Scope for the Domino Reaction



Substrates with five contiguous stereocentres

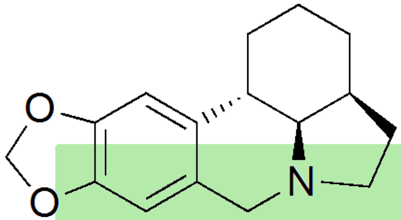


OMe

OMe

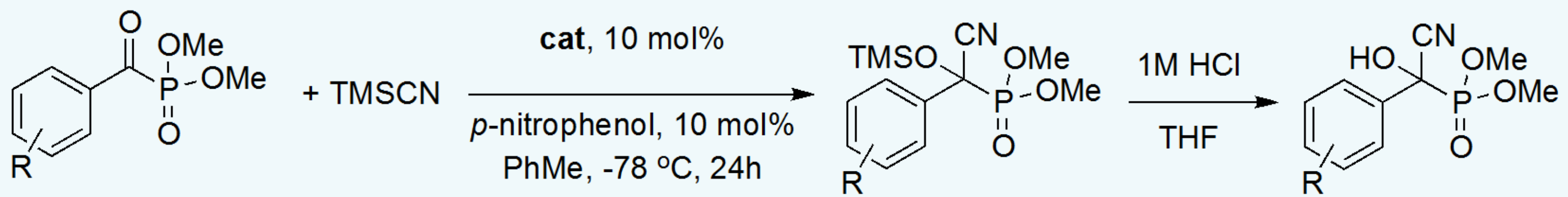
Synthesis of an α-lycorane-like compound

Rajkumar, S.; Shankland, K.; Brown, G. D.; Cobb, A. J. A. *Chem. Sci.* **2012**, *3*, 584..

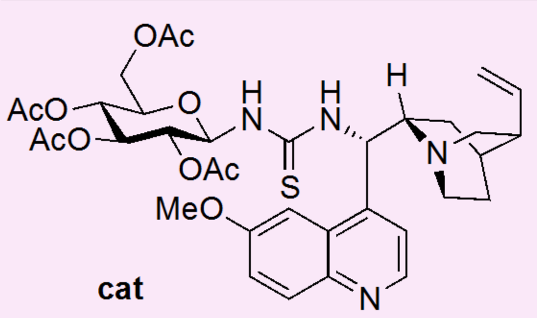


α-lycorane

Miao's α-Hydroxyphosphonate Synthesis

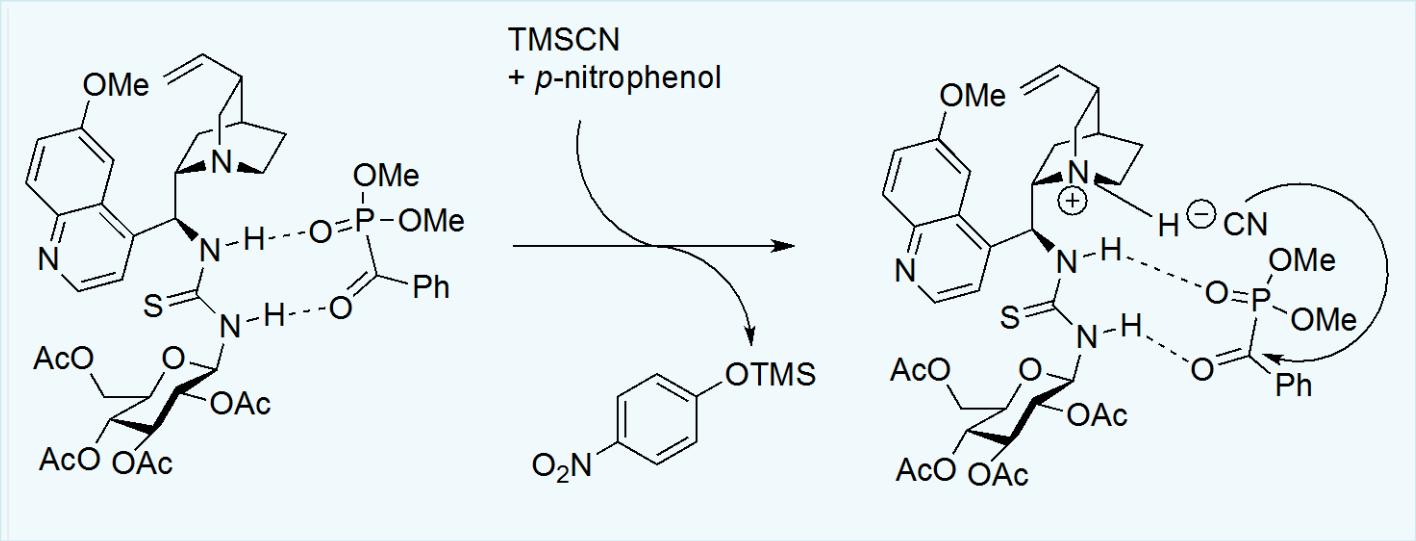


R	*t* (h)	Yield, %	ee, %
H	48	85	99
p-Cl	48	82	86
p-Me	36	89	94
p-Br	48	89	93
p-F	36	88	93
p-MeO	36	80	89
m-Me	48	89	92



Miao's α-Hydroxyphosphonate Synthesis

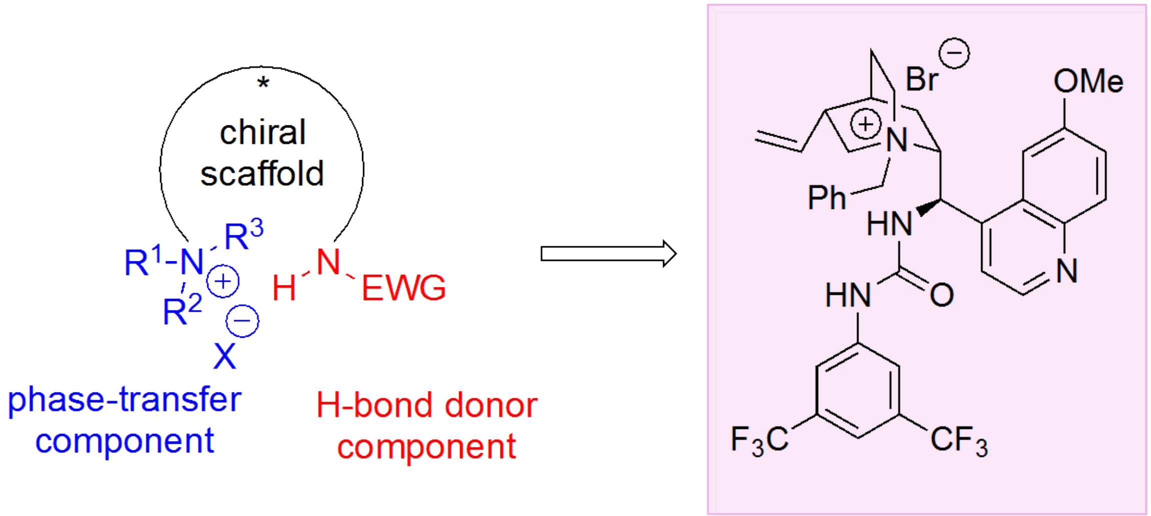
Proposed Reaction Mechanism



Kong, S.; Fan, W.; Wu, G.; Miao, Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 8864

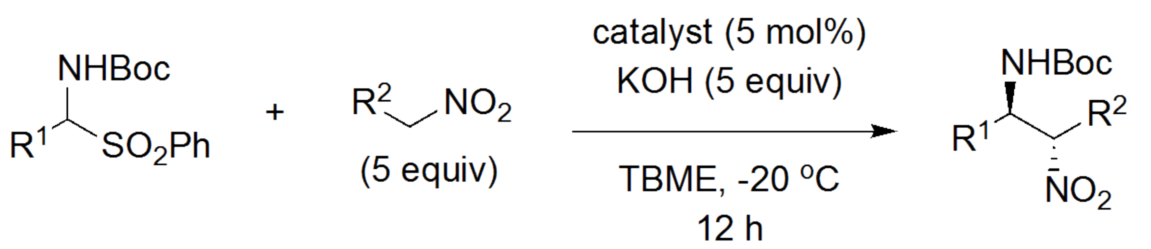
Dixon's Bifunctional Phase Transfer Catalysts

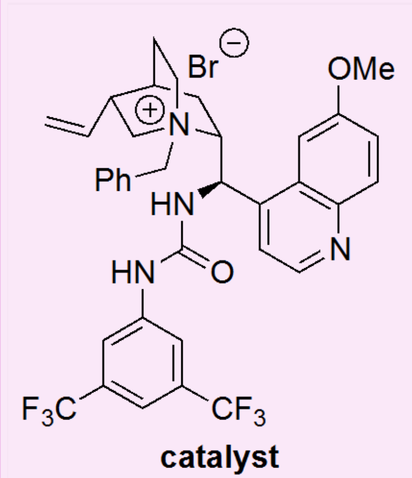
- Combines both H-bond Catalysis and Phase Transfer Catalysis



Combines pro-nucleophile activiation (under strong base promotion) with substrate control, preorganisation and activation.

Dixon's Bifunctional Phase Transfer Catalysts





R^1	R^2	Yield (%)	d.r. *anti:syn*	e.e.(%)
4-MeC_6H_4	H	64	-	91
3-pyridyl	H	73	-	92
Ph	Me	83	24:1	94
Ph	$CH_2CH=CH_2$	64	6:1	95
cyclohexyl	Me	75	9:1	95

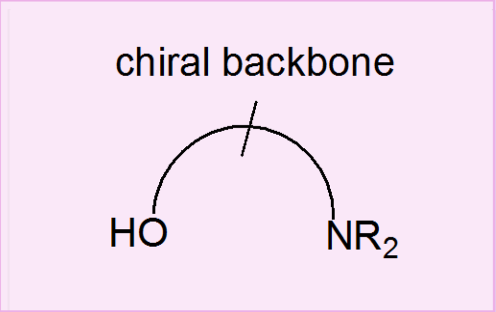
Johnson, K. M.; Rattley, M. S.; Sladojevich, F.; Barber, D. M.; Nuñez, M. G.; Goldys, A. M.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 2492.

Overview

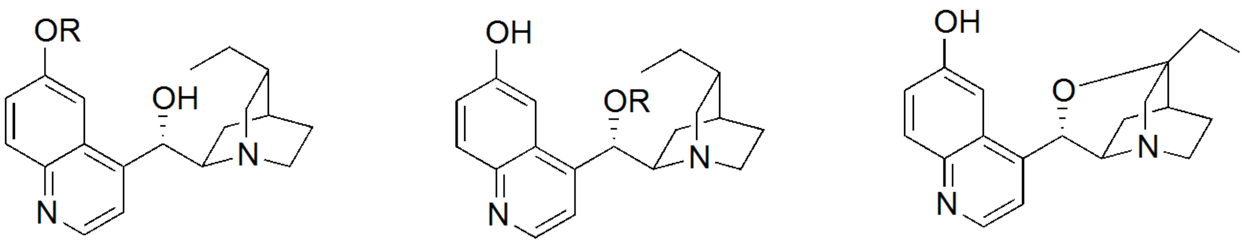
- A brief introduction to hydrogen bond (H-bond) catalysis.
- Chiral phosphoric acids and related systems
- Thioureas (Monofunctional and Bifunctional)
- Amino alcohols
- Enamine catalysis
- Conclusions
- Acknowledgements

Aminoalcohols in H-bonding Catalysis

- Bifunctional aminoalcohol systems

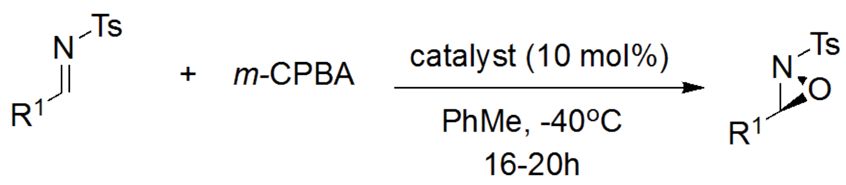


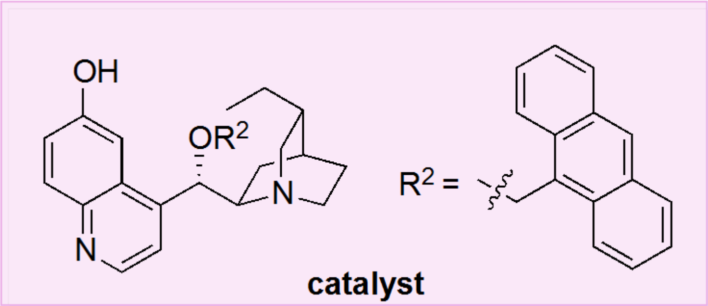
Typical catalysts



Jørgensen's Synthesis of Oxaziridines

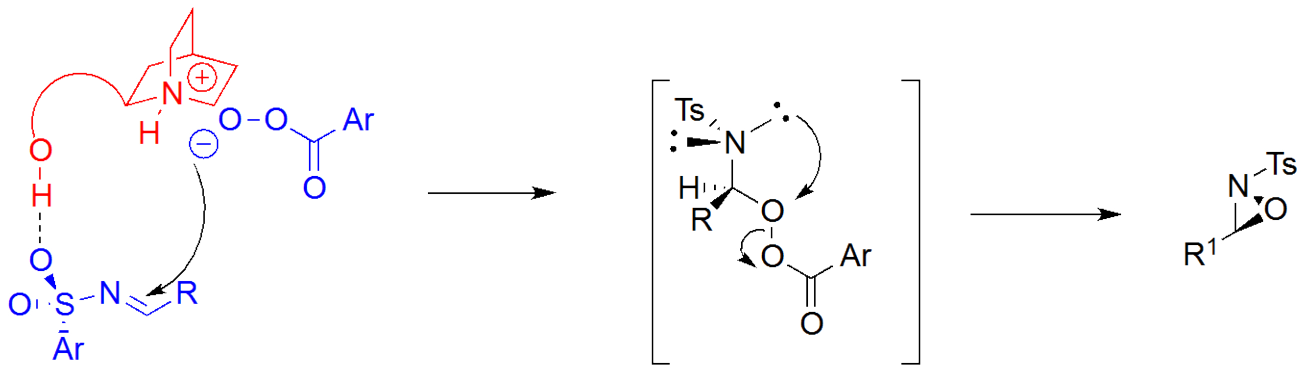
- First catalytic enantioselective synthesis of oxaziridines.

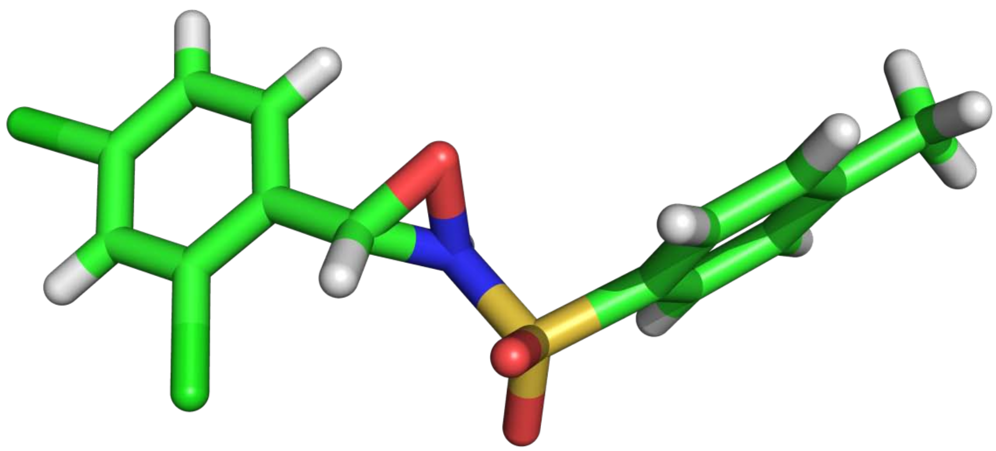




R^1	Yield (%)	e.e.(%)
Ph	89	92
o-F-C_6H_4	96	94
p-Me-C_6H_4	56	87
p-Cl-C_6H_4	83	89
cyclohexyl	89	94
2-Napthyl	60	86

Jørgensen's Synthesis of Oxaziridines

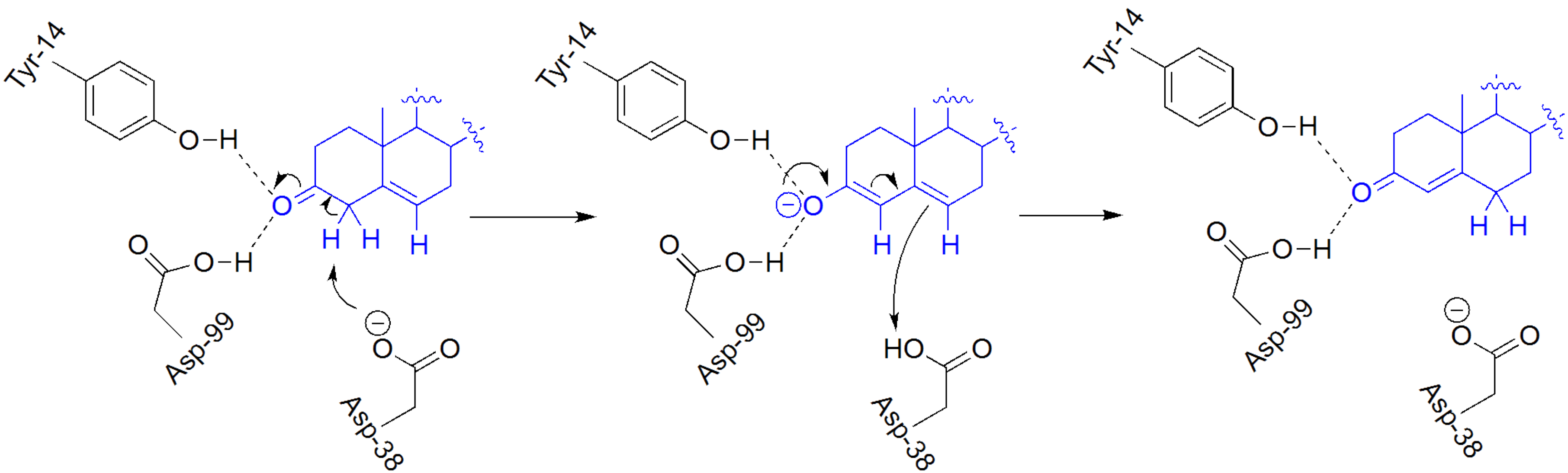




Lykke, L.; Rodríguez-Escrich, C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 14932

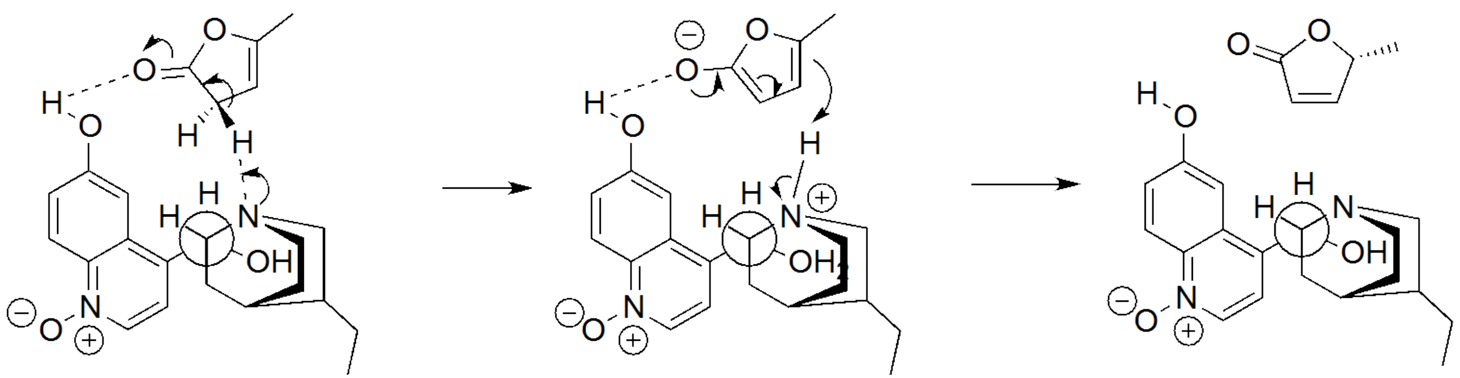
Deng's Olefin Isomerisation

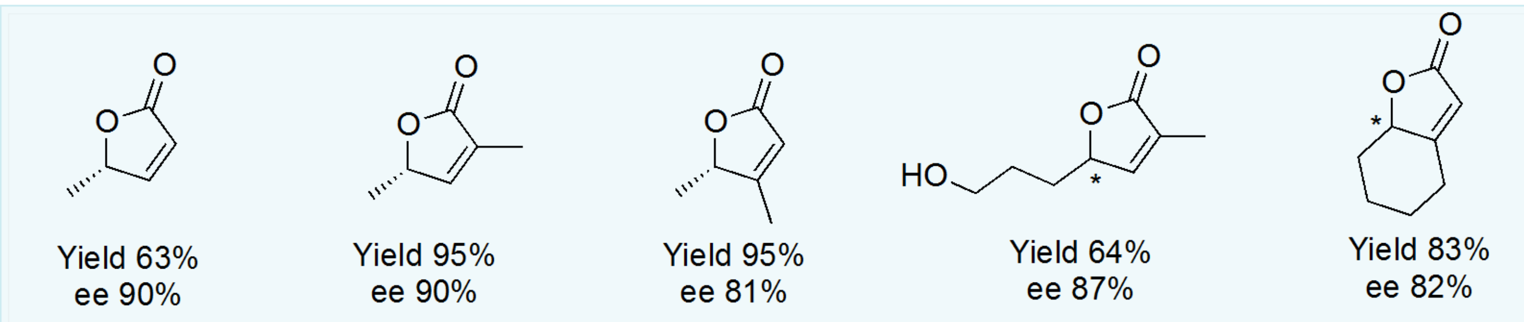
- Inspired by isomerisation of steroidal ketones catalysed by Δ5-3-ketosteroid isomerase (KSI).



Deng's Olefin Isomerisation

Proposed Isomerisation of Butenolides by Cinchona Alkaloids





Wu, Y.; Singh, R. P.; Deng, L. *J. Am. Chem. Soc.* **2011**, *133*, 12458.

Overview

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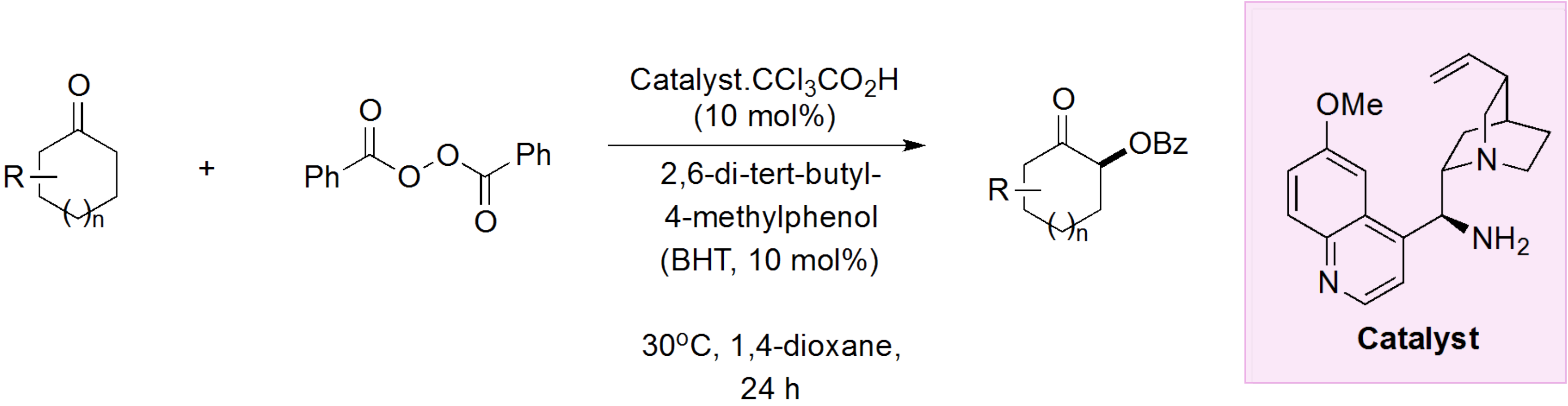
- Enamine catalysis
- Conclusions
- Acknowledgements

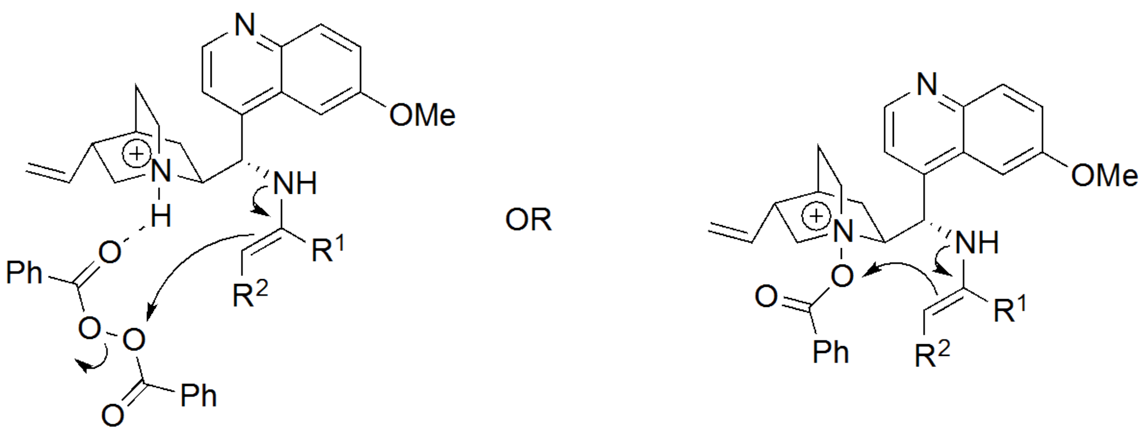
Primary and Secondary Amines in Asymmetric Organocatalysis

- Very extensive within the literature.
- An Interesting recent example is List's asymmetric α-benzoyloxylation

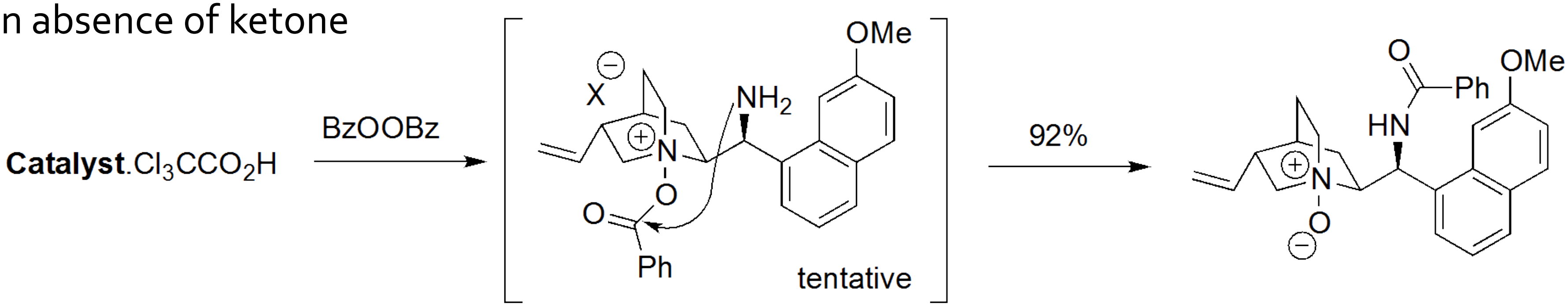


List's Asymmetric α-Benzoyloxylation

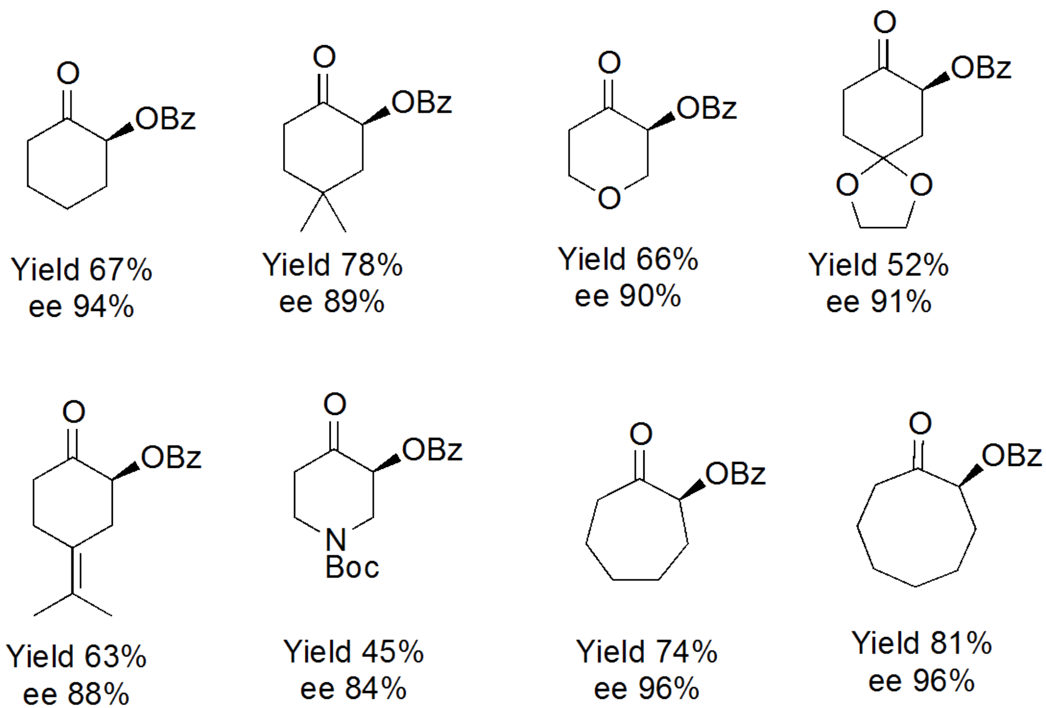
- Proposed transition state



In absence of ketone



List's Asymmetric α-Benzoyloxylation



Lifchits, O.; Demoulin, N.; List, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 9680.

In Conclusion

- Seen a wide variety of H-Bond catalysts, as well as reactions that they can enhance.
- Refinement of the catalyst structure has a huge effect on success.
- Much work is still to be done in order to rival metal based catalysis (particularly on catalyst loading).

Acknowledgements

- Will Nodes
- Sundaram Rajkumar
- Dr Kenneth Shankland
- Dr Ann Chippindale
- Dr David Nutt
- Dr Geoff Brown

- EPSRC
- Felix Foundation