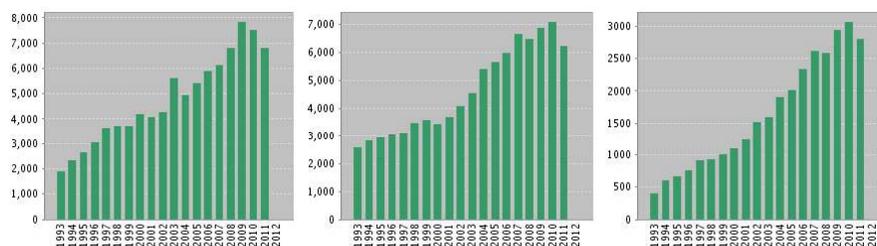


Making the strain: recent developments in the synthesis of small rings

Dr Christopher Bray



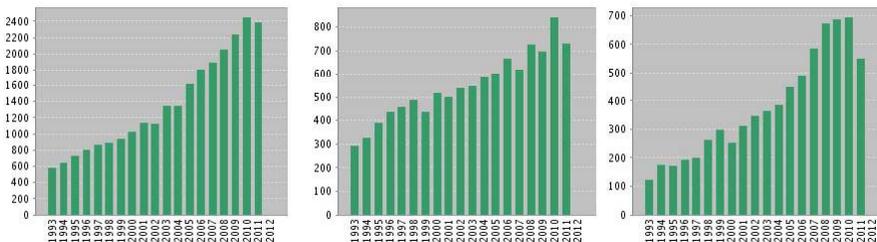
Number of citations per year to small rings



Cyclopropanes

Epoxide

Aziridines



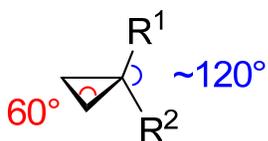
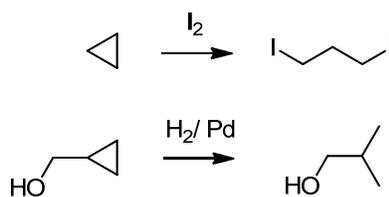
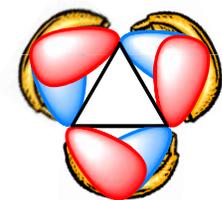
Cyclobutanes

Oxetane

Azetidine

Cyclopropanes

Some reminders about cyclopropanes

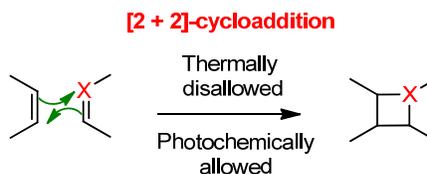


Often used as bioisosteres of alkenes. Informally referred to as "fat alkenes".

Compare to cyclobutanes



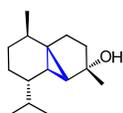
Puckered ring reduces torsional strain at the expense of ring strain.



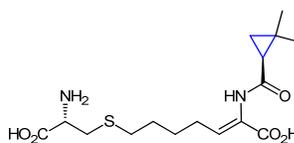
(N.B. 4-*exo-tet* Baldwin favoured)

Cycloalkane	ΔH kcal/mole	ΔH per CH ₂ Unit
Cyclopropane	468.7	156.2
Cyclobutane	614.3	153.6
Cyclopentane	741.5	148.3
Cyclohexane	882.1	147.0

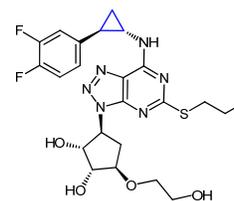
Why make cyclopropanes?



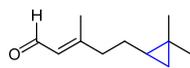
Cubebol
Sesquiterpene used in the food industry



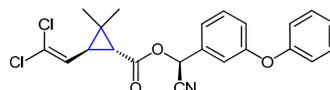
Cilastatin (Primaxin), Merck
Sales (2006) \$705 m



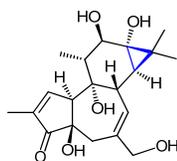
AZD 6140 (Ticagrelor), AstraZeneca
Platelet aggregation inhibitor



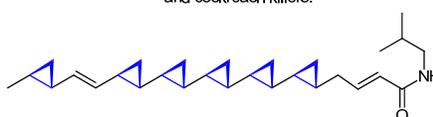
Acitral
Lemon smell just like citral but stable in acid



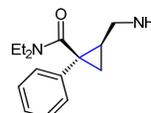
Cypermethrin found in many household ant and cockroach killers.



Phorbol a potent tumour promoter

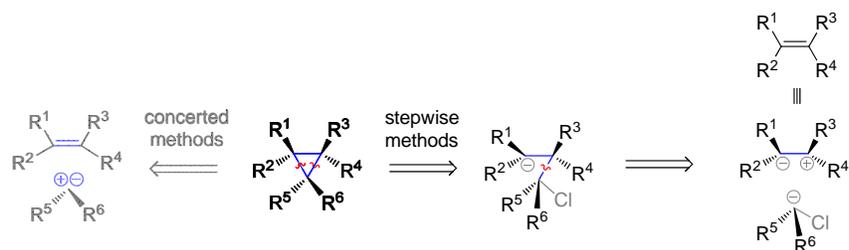


U106305
A polycyclopropane containing cholesteryl ester transferase inhibitor



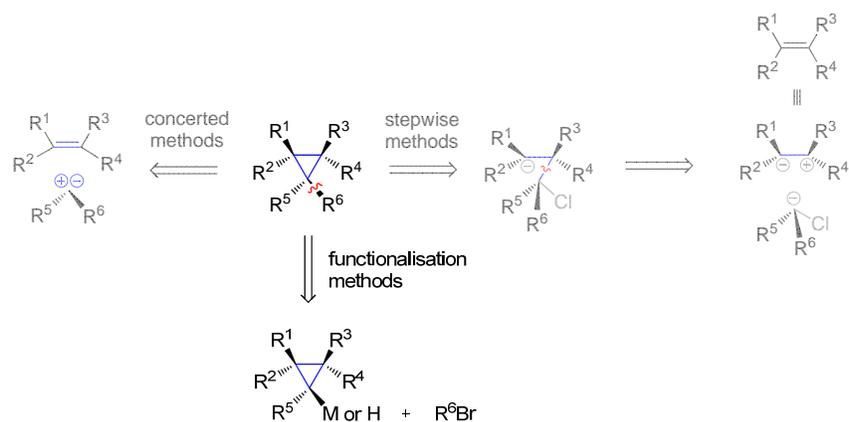
Milnacipran (Ixel), Pierre Fabre
Approval for fibromyalgia, Jan 2009

Strategies for making cyclopropanes

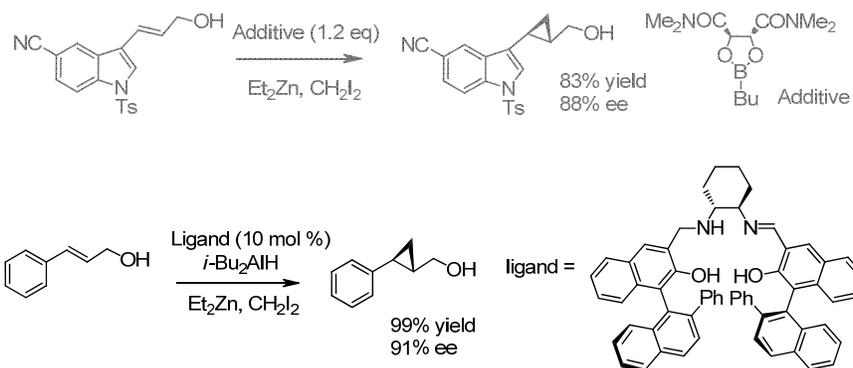


Last major review, see: Charette et al. *Chem. Rev.* **2003**, *103*, 977.

Strategies for making cyclopropanes

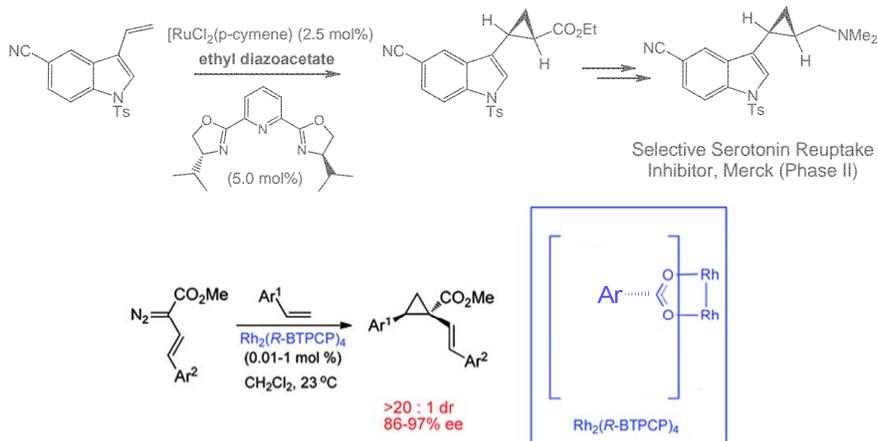


Concerted Methods: Simmons-Smith Cyclopropanation



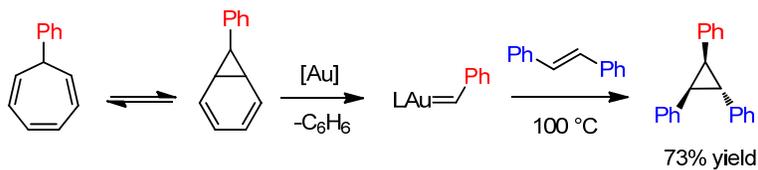
Org. Process Res. Dev., **2008**, *12*, 178.
 Katsuki *et al.* *Angew. Chem. Int. Ed.* **2008**, *47*, 2450.

Concerted Methods: Diazo decomposition/olefin insertion



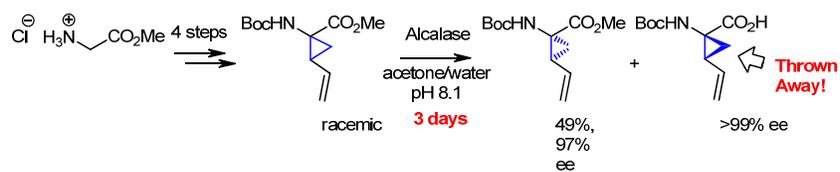
Org. Process Res. Dev., **2008**, *12*, 168.
 Davies *et al.* *J. Am. Chem. Soc.*, **2011**, *133*, 19198.

Concerted Methods: Carbene Equivalents

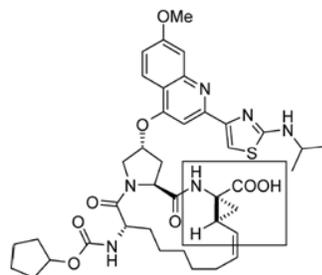


Toste *et al.* *J. Am. Chem. Soc.* **2005**, *127*, 18002.
Echavarren *et al.* *J. Am. Chem. Soc.*, **2011**, *133*, 11952.

Resolution Methods



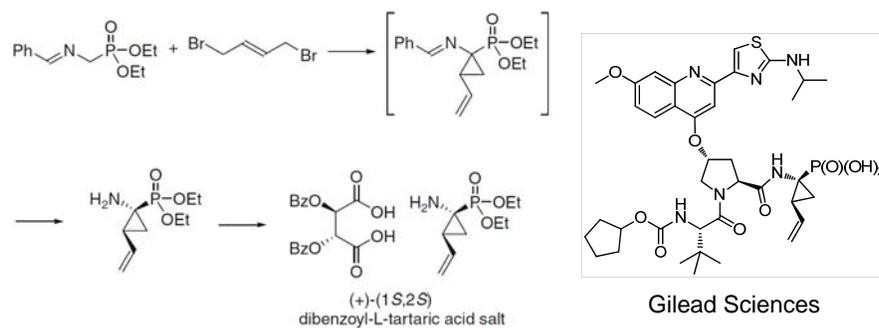
5.7 kg (300 litre) scale



Boehringer Ingelheim
BILN 2061
(HCV NS3 Protease Inhibitor)

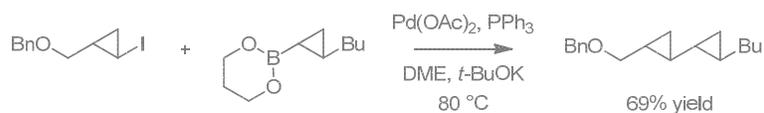
J. Org. Chem. **2005**, *70*, 5869.

Resolution Methods

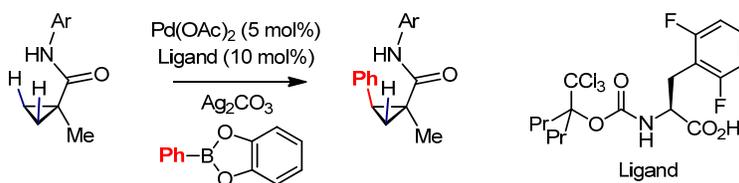


Tetrahedron Lett. **2009**, 3833.

Functionalisation Methods

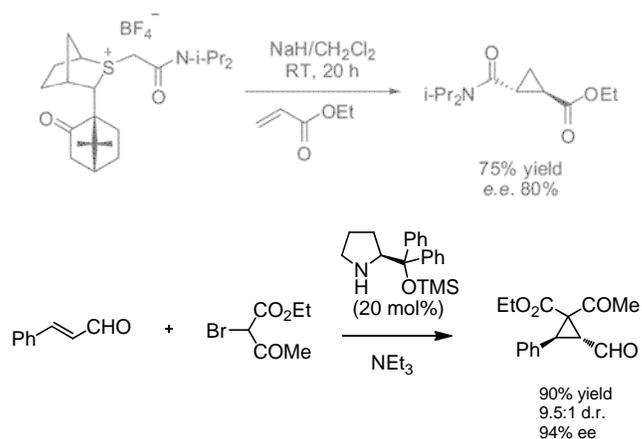


β -hydride elimination is precluded in cyclopropanes.
Suzuki and Stille cross-couplings are possible.



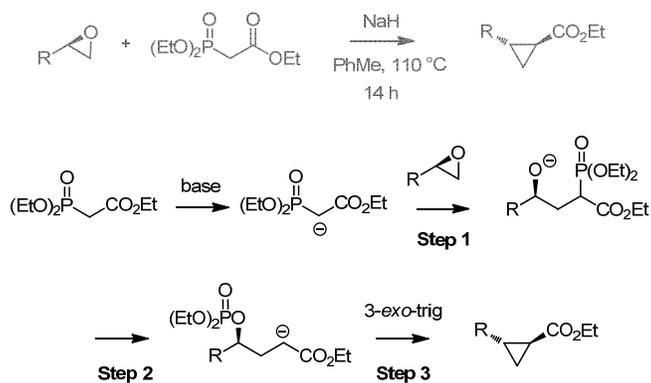
Charette *et al.* *J. Org. Chem.* **1996**, *61*, 8718.
Yu *et al.* *J. Am. Chem. Soc.* **2011**, ASAP.

Connective Methods: Ylide addition to alkenes



Aggarwal *et al.* *J. Am. Chem. Soc.* **2010**, 132, 7626.
Rios *et al.* *Eur. J. Org. Chem.* **2009**, 3075

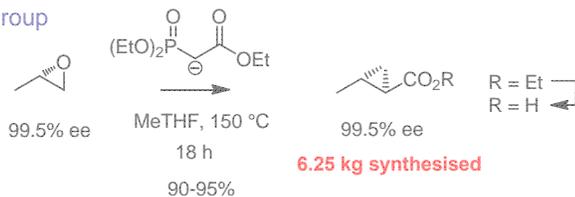
Connective Methods: Wadsworth-Emmons Cyclopropanation



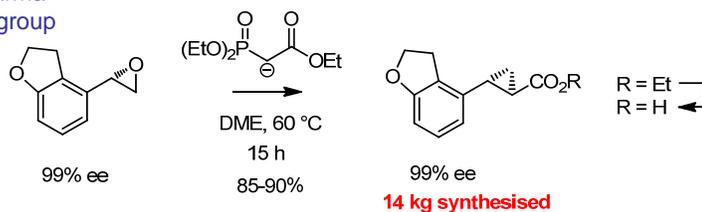
Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, 83, 1733.

Connective Methods: Wadsworth-Emmons Cyclopropanation

Merck process group

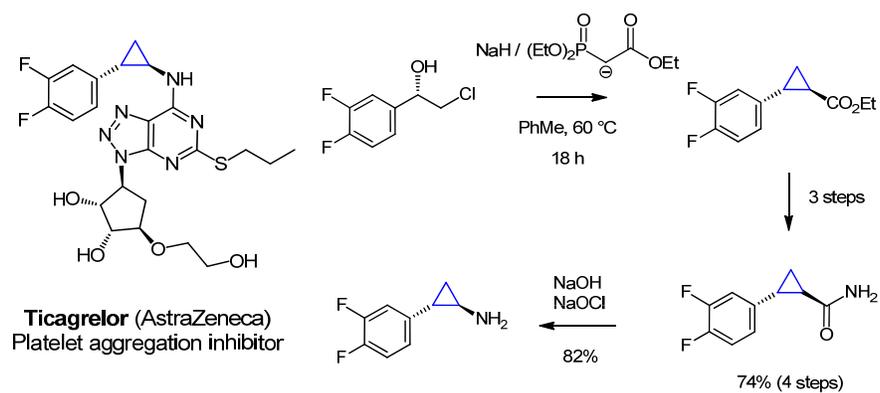


UCB Pharma process group



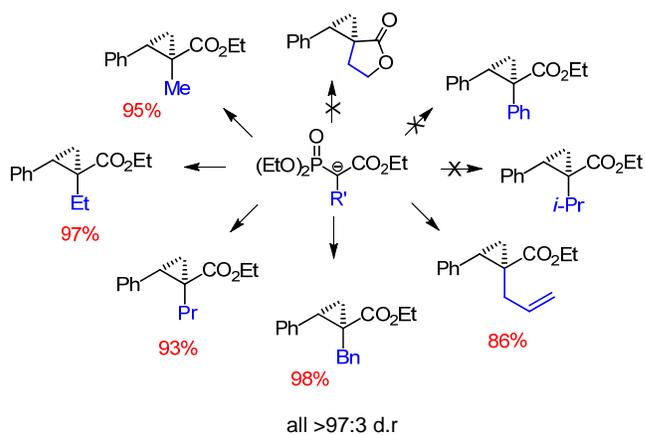
Singh et al. *Org. Proc. Res. Dev.* **2002**, 6, 618.
Merschaert et al. *Org. Proc. Res. Dev.* **2007**, 11, 689.

Use in Ticagrelor synthesis



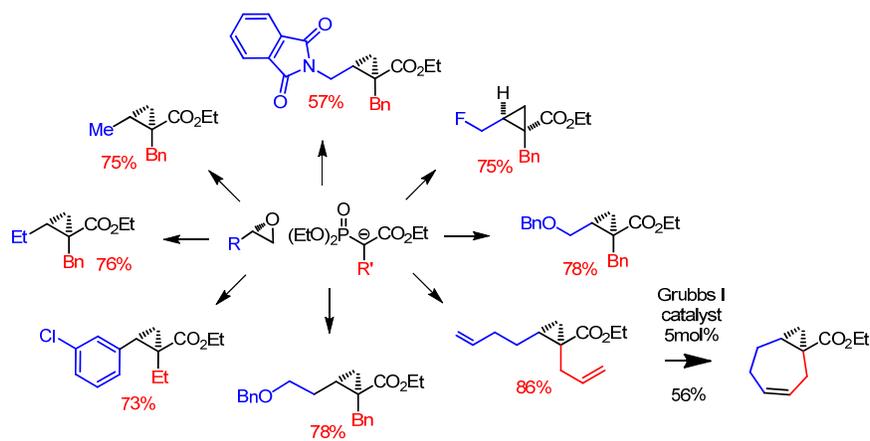
WO/2008/018822

Extension to the Synthesis of Quaternary Stereocentres



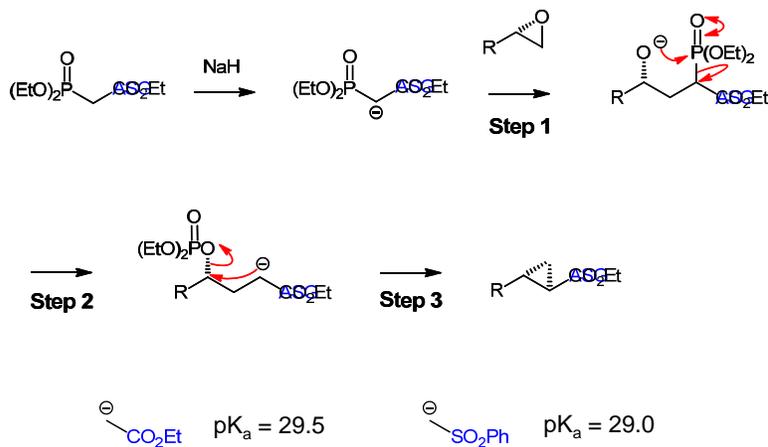
Bray, C. D.; Minicone, F. *Chem. Commun.* 2010, 46, 5867-5869.

Epoxide Scope

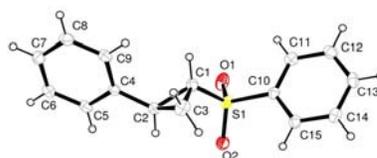
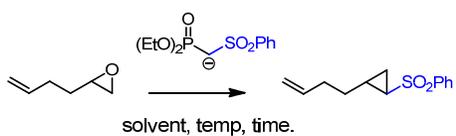


Bray, C. D.; Minicone, F. *Chem. Commun.* 2010, 46, 5867-5869.

A Question of pK_a ...
so consult Bordwell tables



Extension to Sulfones

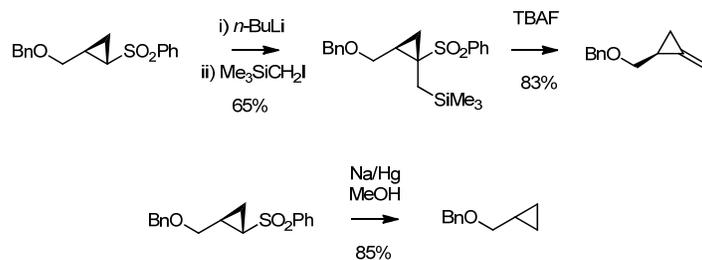


Entry	Solvent	Temp/°C	Time/h	Yield
1	PhMe	110	16	74
2	DME	86	16	70
3	dioxane	100	16	67
4	DMF	120	16	65
5	THF	67	20	56
6	DME	86	16	61
7	DME	120	16	80
8	DME	140	8	83

Entry	Epoxide	Product	Yield
1			86
2			85
3			82
4			74
5			60

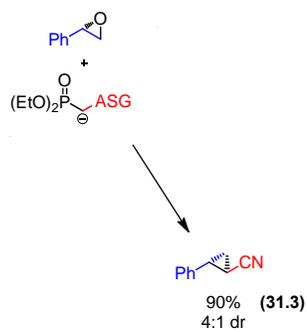
Bray, C. D.; De Faveri, G. *J. Org. Chem.* **2010**, *75*, 4652.

Some Uses of Cyclopropyl Sulfones

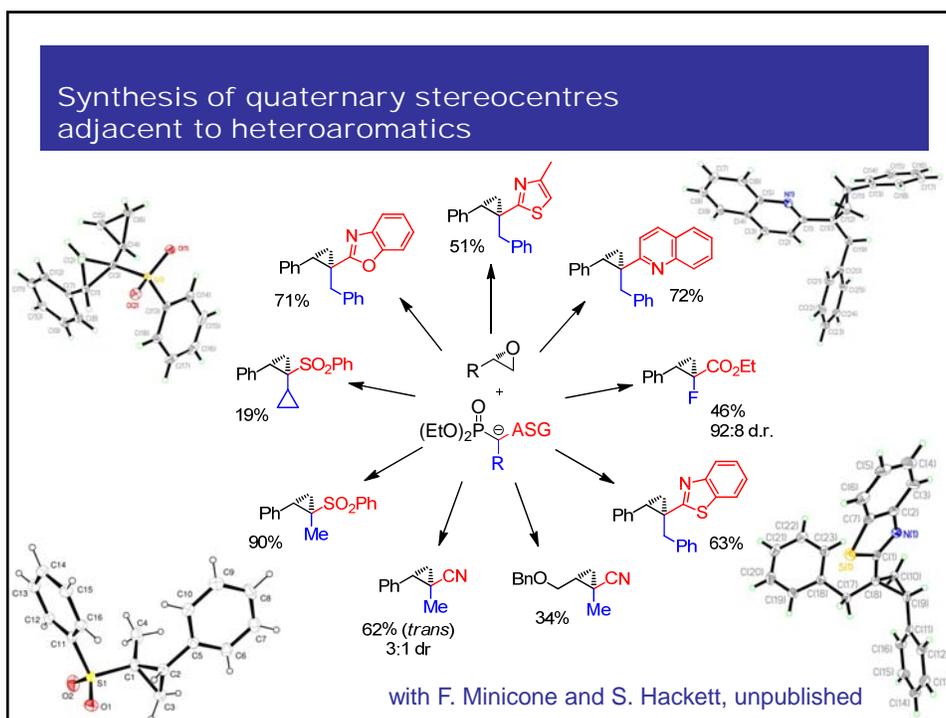


Bray, C. D.; De Faveri, G. *J. Org. Chem.* **2010**, *75*, 4652.

Other Anion Stabilising Groups

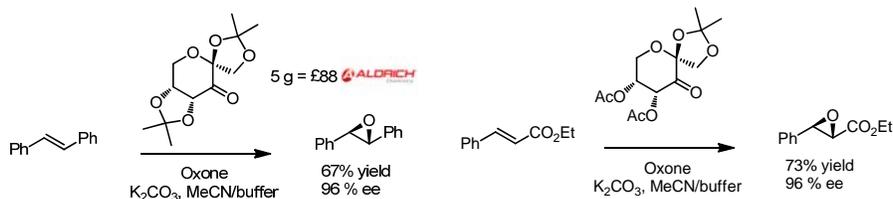


with F. Minicone, unpublished



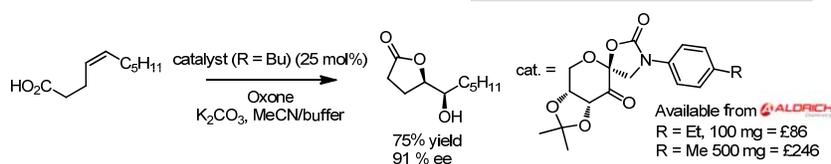
Epoxides

Shi epoxidation



Original Shi ketone was good for *trans*-di and tri-substituted olefins, and styrenes.

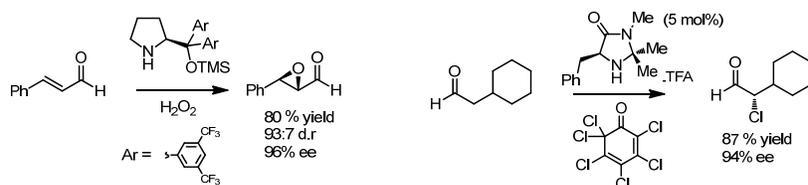
2nd generation catalyst was also good for α,β -unsaturated carbonyls



Newer oxazolidinone catalysts also work for *cis*-disubstituted olefins & chromenes

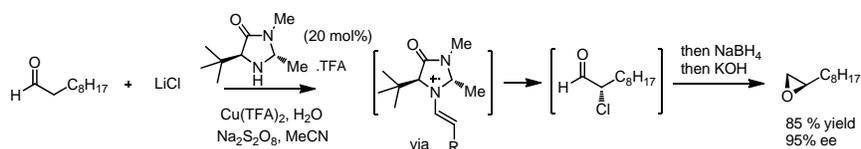
For a review, see: Wong, O.A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958.
Burke, C.P.; Shi, Y. *Org. Lett.* **2009**, *11*, 5150.

Organocatalytic Routes to Epoxides



Jørgensen et al. *J. Am. Chem. Soc.* **2005**, *127*, 6964.
See also: MacMillan & Lee, *Tetrahedron*, **2006**, 11413.

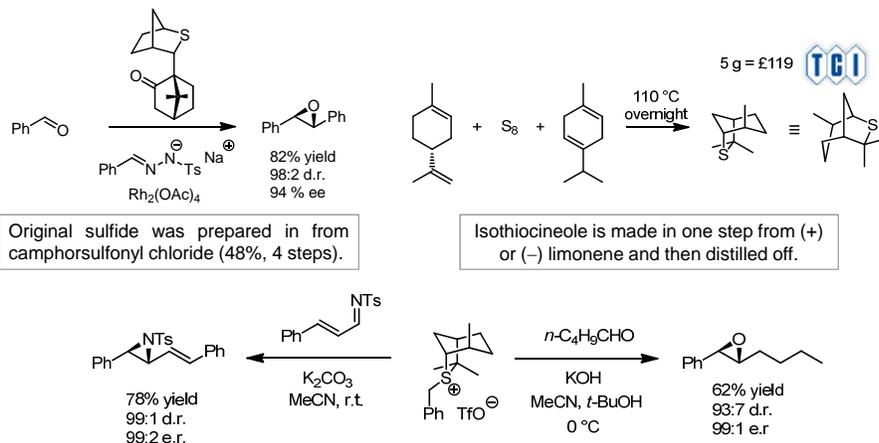
Macmillan et al. *J. Am. Chem. Soc.* **2004**, *126*, 4108.
See also; Jørgensen, *J. Am. Chem. Soc.* **2004**, *127*, 4790.



MacMillan et al. *Angew. Chem. Int. Ed.*, **2009**, *48*, 5121.

For a review on iminium ion catalysis, see: Pihko et al. *Chem. Rev.* **2007**, *107*, 5416.

Asymmetric Methylene Addition to Aldehydes



For a review, see: V. K. Aggarwal *et al. Chem. Rev.*, **2007**, *107*, 5841-5883
V. K. Aggarwal *et al. J. Am. Chem. Soc.*, **2010**, *132*, 1828-1830.

Acknowledgements

The Chemists

Current	Past
Fabrizio Minicone	Giorgio de Faveri
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Nicky Willis	James Green
Harry Shirley	Gajan Santhakumar
Geoffrey Smith	

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Majid Motevalli

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Royal Society	Univ. London Central
Queen Mary	Research Fund

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contact: c.bray@qmul.ac.uk



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