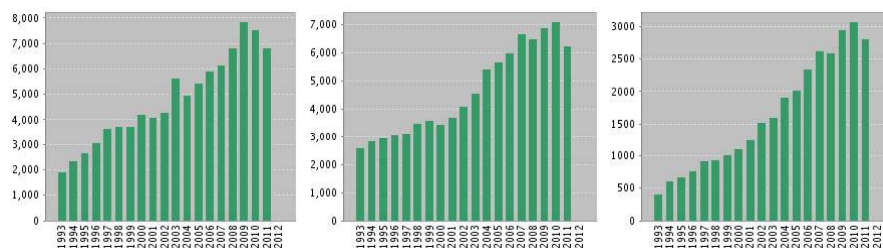


# Making the strain: recent developments in the synthesis of small rings

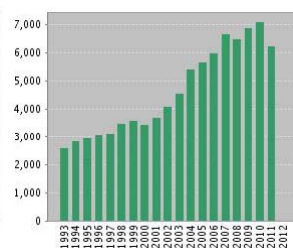
Dr Christopher Bray



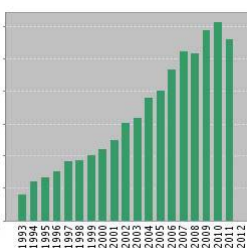
## Number of citations per year to small rings



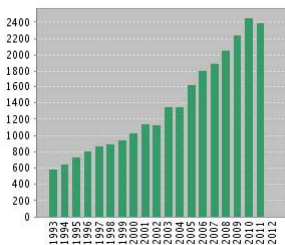
Cyclopropanes



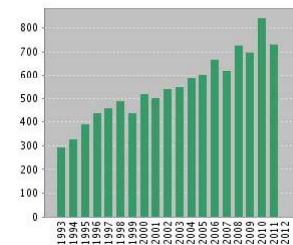
Epoxide



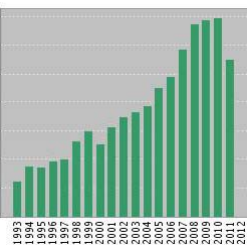
Aziridines



Cyclobutanes



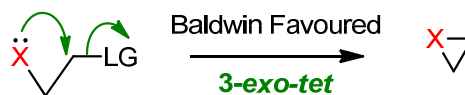
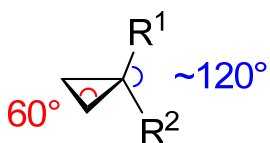
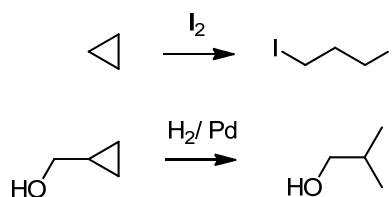
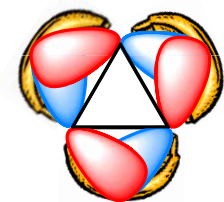
Oxetane



Azetidine

# Cyclopropanes

## Some reminders about cyclopropanes

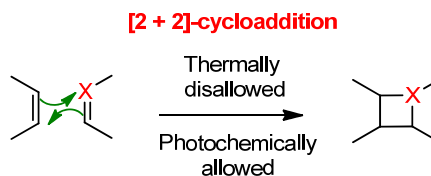


Often used as bioisosteres of alkenes. Informally referred to as "fat alkenes".

## Compare to cyclobutanes



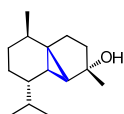
Puckered ring reduces torsional strain at the expense of ring strain.



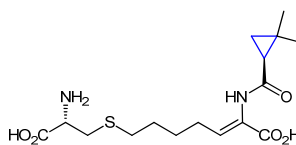
(N.B. 4-*exo-tet* Baldwin favoured)

Cycloalkane	$\Delta H$ kcal/mole	$\Delta H$ per CH <sub>2</sub> Unit
Cyclopropane	468.7	156.2
Cyclobutane	614.3	153.6
Cyclopentane	741.5	148.3
Cyclohexane	882.1	147.0

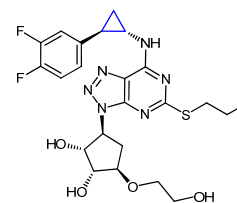
## Why make cyclopropanes?



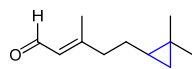
**Cubebol**  
Sesquiterpene used in the food industry



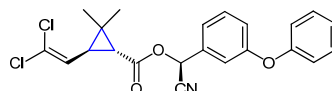
**Cilastatin** (Primaxin), Merck  
Sales (2006) \$705 m



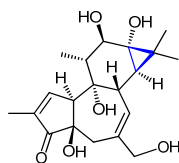
**AZD 6140** (Ticagrelor), AstraZeneca  
Platelet aggregation inhibitor



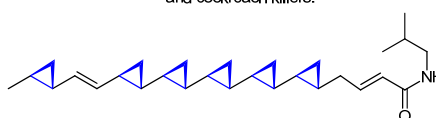
**Acitral**  
Lemon smell just like citral but stable in acid



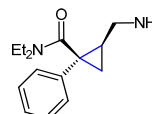
**Cypermethrin** found in many household ant and cockroach killers.



**Phorbol** a potent tumour promoter

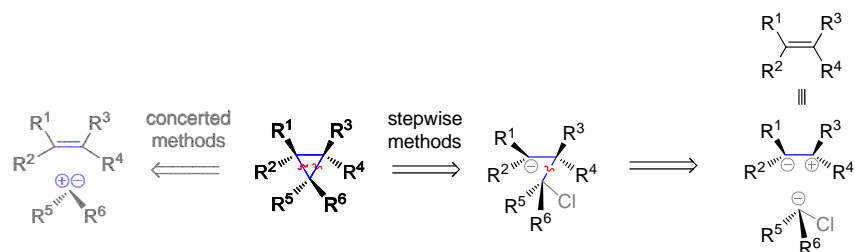


**U106305**  
A polycyclopropane containing cholesteryl ester transferase inhibitor



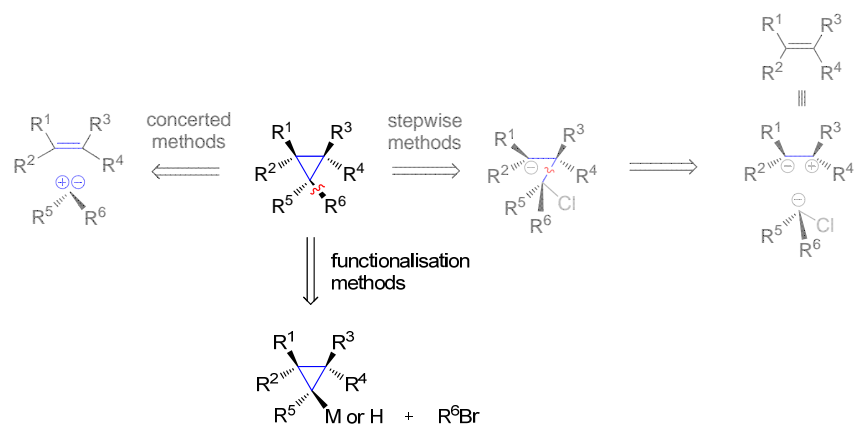
**Milnacipran** (Ixel), Pierre Fabre  
Approval for fibromyalgia, Jan 2009

## Strategies for making cyclopropanes

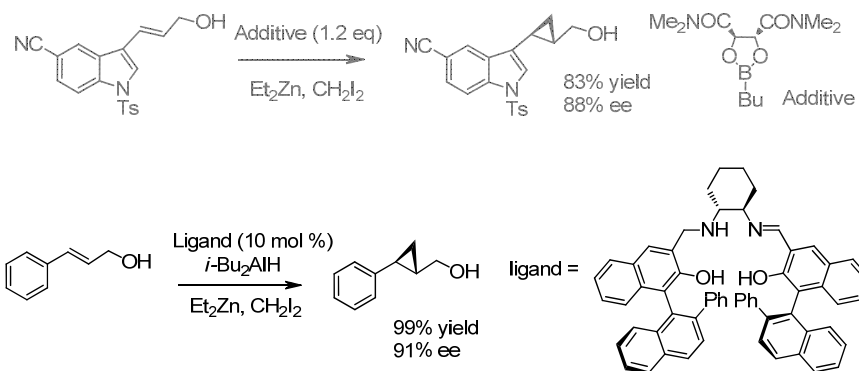


Last major review, see: Charette et al. *Chem. Rev.* **2003**, *103*, 977.

## Strategies for making cyclopropanes

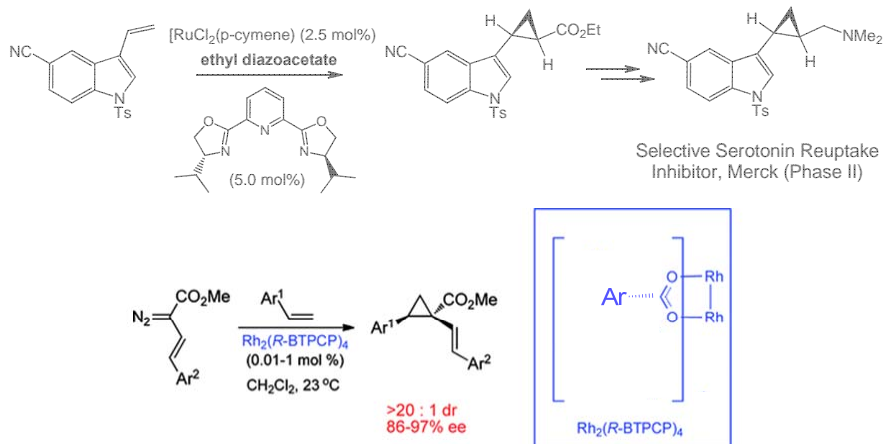


### Concerted Methods: Simmons-Smith Cyclopropanation



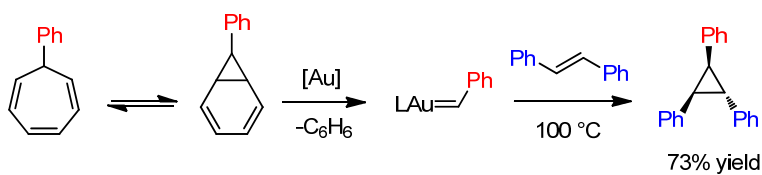
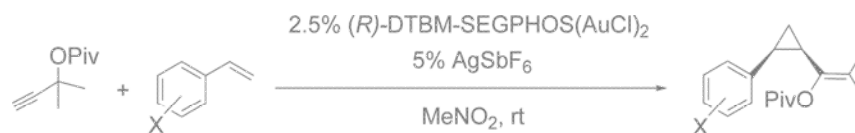
*Org. Process Res. Dev.*, **2008**, *12*, 178.  
Katsuki *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 2450.

### Concerted Methods: Diazo decomposition/olefin insertion



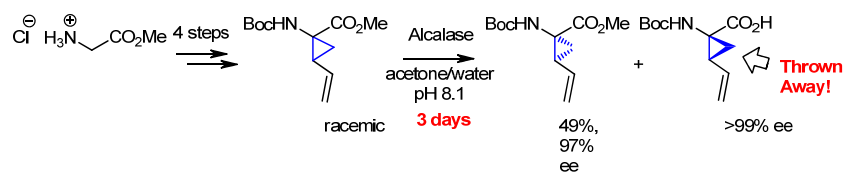
*Org. Process Res. Dev.*, **2008**, *12*, 168.  
Davies *et al. J. Am. Chem. Soc.*, **2011**, *133*, 19198.

## Concerted Methods: Carbene Equivalents

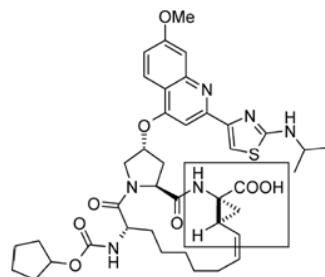


Toste *et al.* *J. Am. Chem. Soc.* **2005**, *127*, 18002.  
Echavarren *et al.* *J. Am. Chem. Soc.*, **2011**, *133*, 11952.

## Resolution Methods



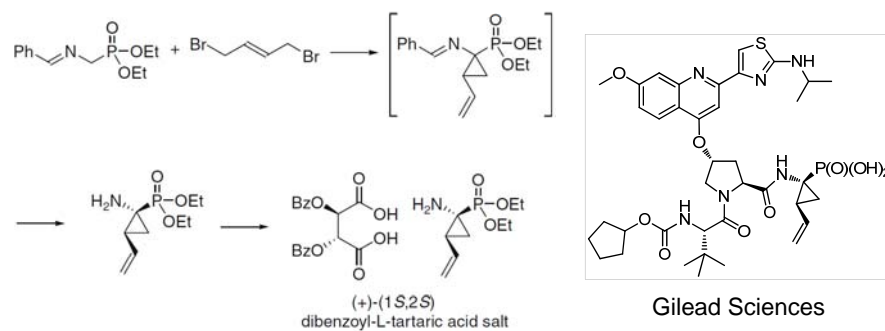
5.7 kg (300 litre) scale



Boehringer Ingelheim  
BILN 2061  
(HCV NS3 Protease Inhibitor)

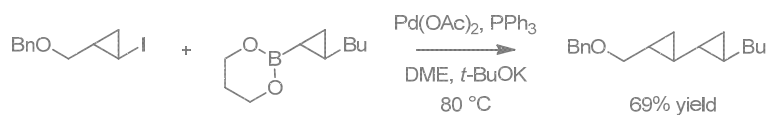
*J. Org. Chem.* **2005**, *70*, 5869.

## Resolution Methods

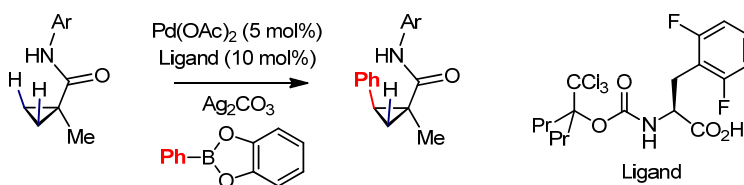


*Tetrahedron Lett.* **2009**, 3833.

## Functionalisation Methods

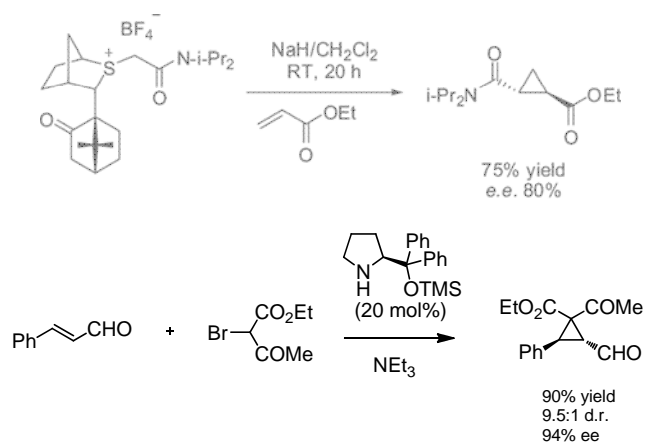


$\beta$ -hydride elimination is precluded in cyclopropanes.  
Suzuki and Stille cross-couplings are possible.



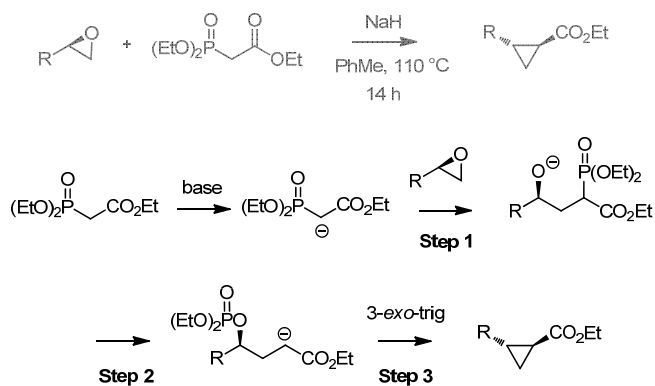
Charette *et al.* *J. Org. Chem.* **1996**, *61*, 8718.  
Yu *et al.* *J. Am. Chem. Soc.* **2011**, ASAP.

## 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

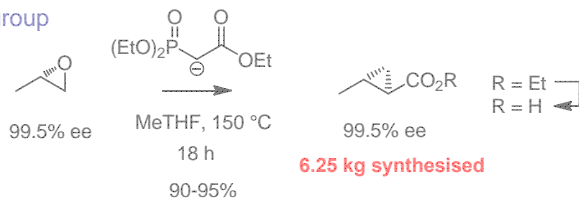


Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, 83, 1733.

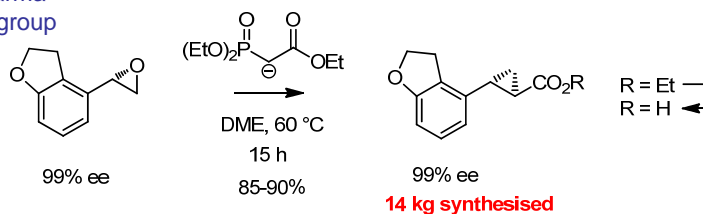


## Connective Methods: Wadsworth-Emmons Cyclopropanation

Merck process group

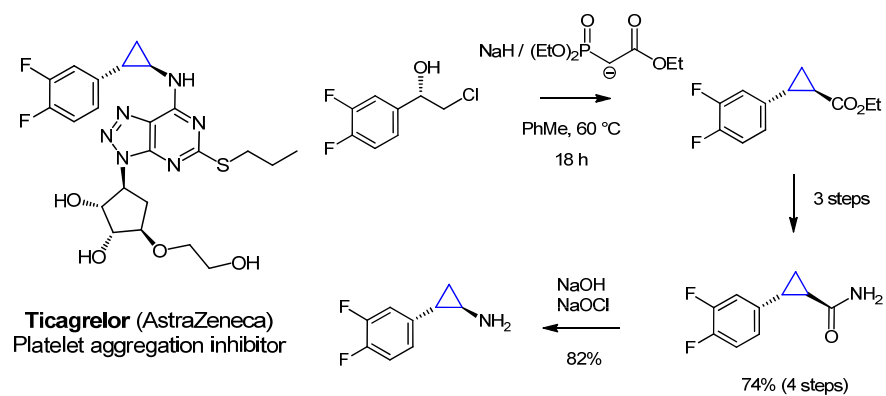


UCB Pharma process group



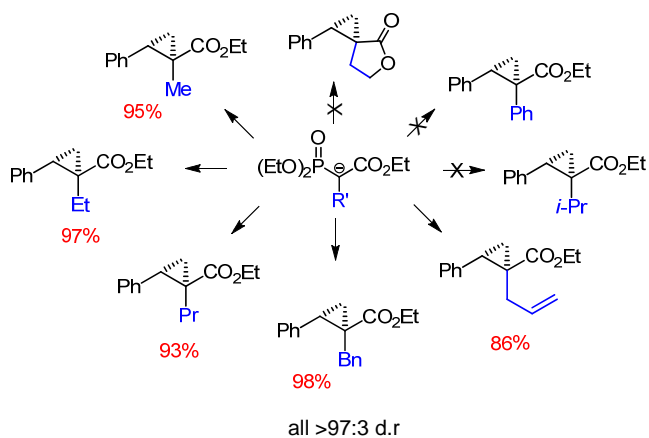
Singh et al. *Org. Proc. Res. Dev.* **2002**, 6, 618.  
Merschaert et al. *Org. Proc. Res. Dev.* **2007**, 11, 689.

## Use in Ticagrelor synthesis



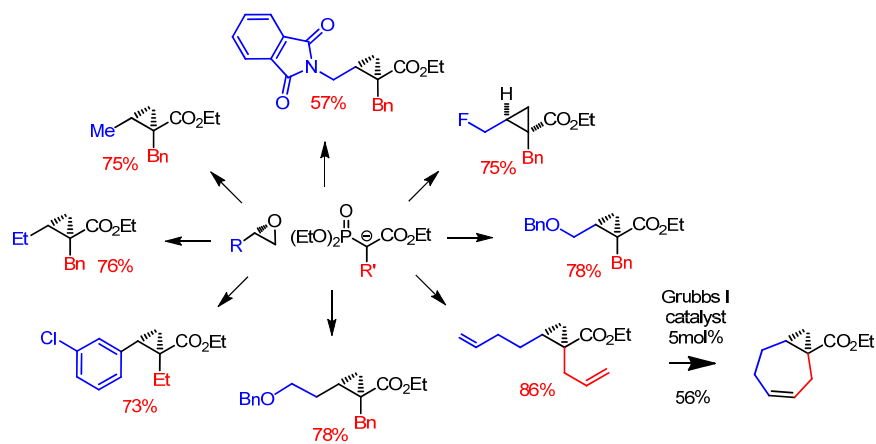
WO/2008/018822

## Extension to the Synthesis of Quaternary Stereocentres



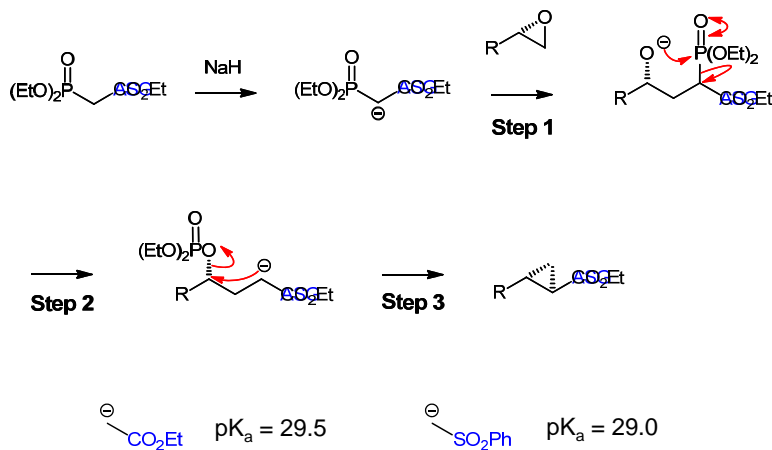
Bray, C. D.; Minicone, F. *Chem. Commun.* **2010**, *46*, 5867-5869.

## Epoxide Scope

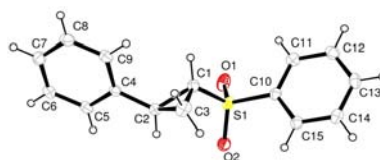
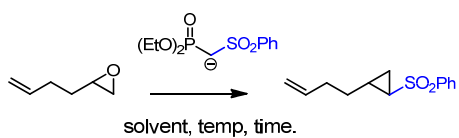


Bray, C. D.; Minicone, F. *Chem. Commun.* **2010**, *46*, 5867-5869.

A Question of  $pK_a$ ...  
so consult Bordwell tables



### Extension to Sulfones

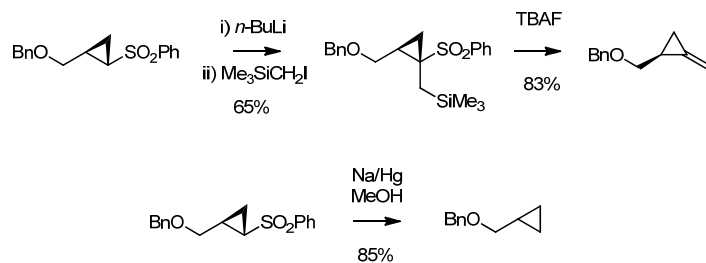


Entry	Solvent	Temp/°C	Time/h	Yield
1	PhMe	110	16	74
2	DME	86	16	70
3	dioxane	100	16	67
4	DMF	120	16	65
5	THF	67	20	56
6	DME	86	16	61
7	DME	120	16	80
8	DME	140	8	83

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

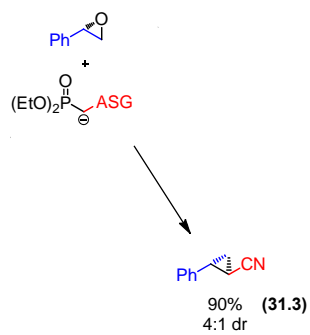
Bray, C. D.; De Faveri, G. *J. Org. Chem.* **2010**, *75*, 4652.

## Some Uses of Cyclopropyl Sulfones

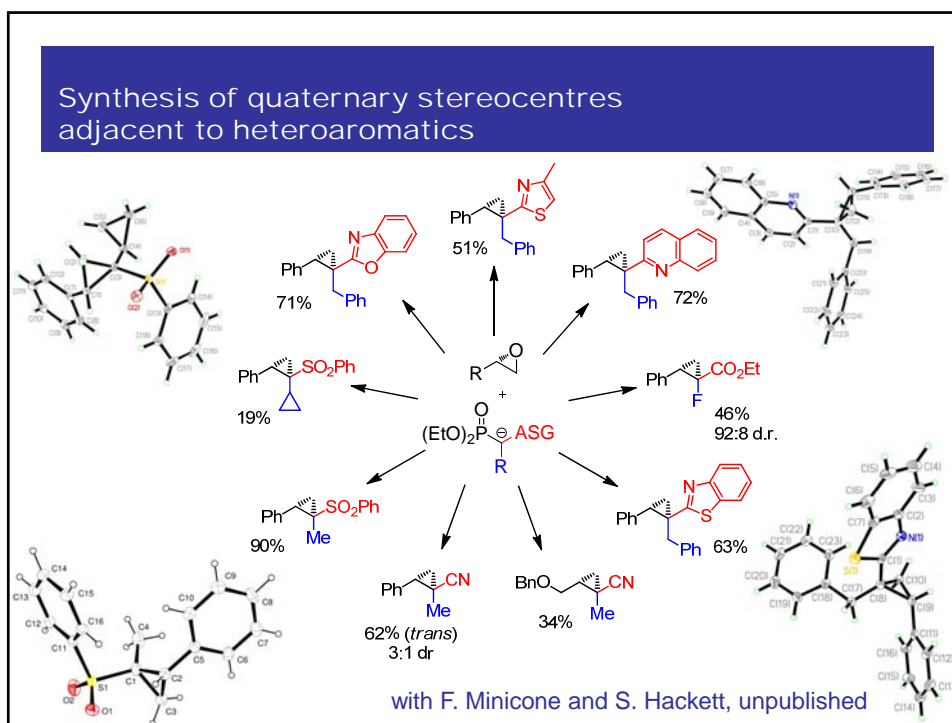


Bray, C. D.; De Faveri, G. *J. Org. Chem.* **2010**, *75*, 4652.

## Other Anion Stabilising Groups

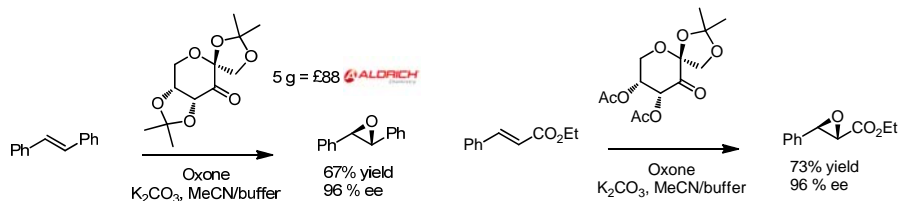


with F. Minicone, unpublished



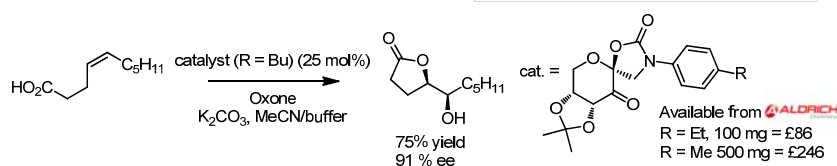
# Epoxides

## Shi epoxidation



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

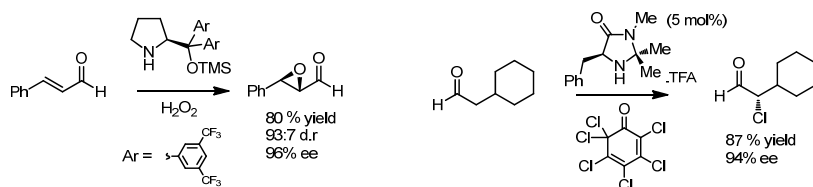
2<sup>nd</sup> generation catalyst was also good for  $\alpha,\beta$ -unsaturated carbonyls



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

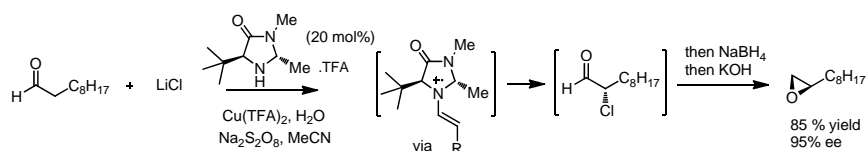
For a review, see: Wong, O.A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958.  
Burke, C.P.; Shi, Y. *Org. Lett.* **2009**, *11*, 5150.

## Organocatalytic Routes to Epoxides



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

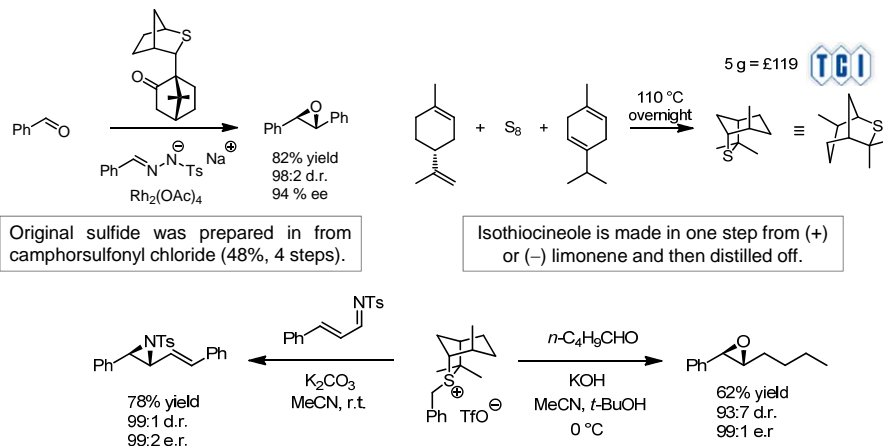
Macmillan et al. *J. Am. Chem. Soc.* **2004**, *126*, 4108.  
See also; Jørgensen, *J. Am. Chem. Soc.* **2004**, *127*, 4790.



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

<i>Current</i>	<i>Past</i>
Fabrizio Minicone	Giorgio de Faveri
Siobhan Hackett	Bhavin Patel
Nicky Willis	James Green
Harry Shirley	Gajan Santhakumar
Geoffrey Smith	

## X-Ray Crystallography

Majid Motevalli

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Royal Society	Univ. London Central
Queen Mary	Research Fund

CASE support much appreciated in this area  
contact: c.bray@qmul.ac.uk



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