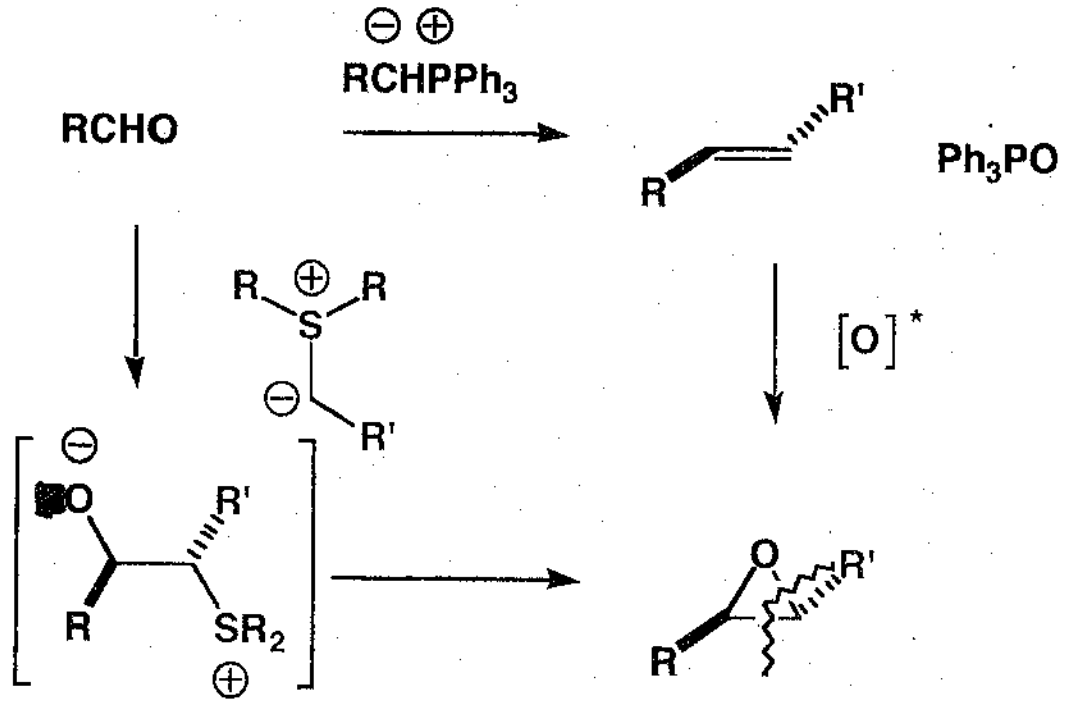
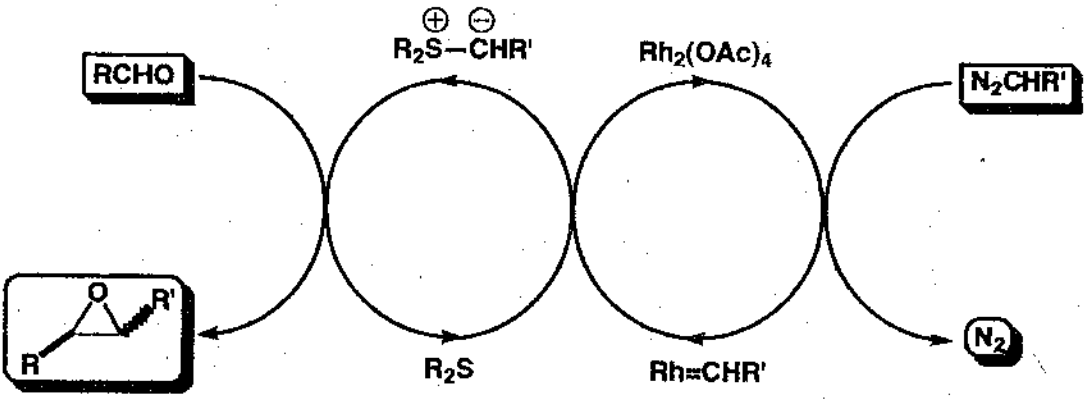
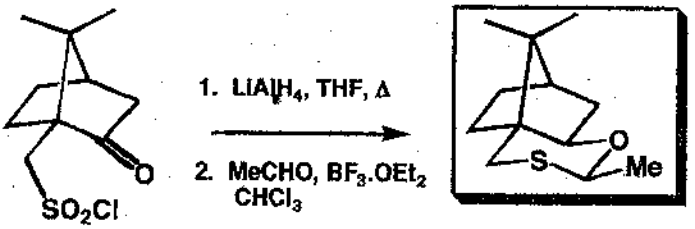
Epoxide Synthesis Using Sulfur Ylides



A.W. Johnson, JACS, 1961, 417; E.J. Corey, JACS, 1962, 3782.

Summary of Catalytic Cycle for Epoxidation

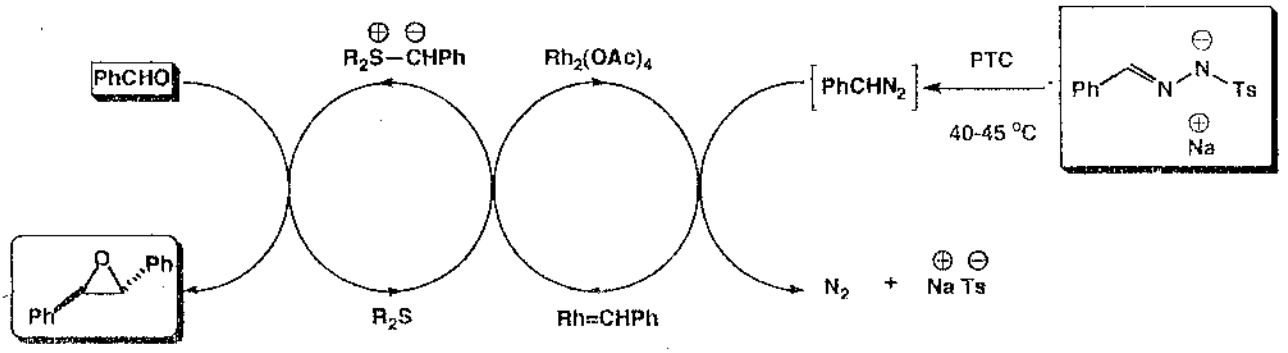


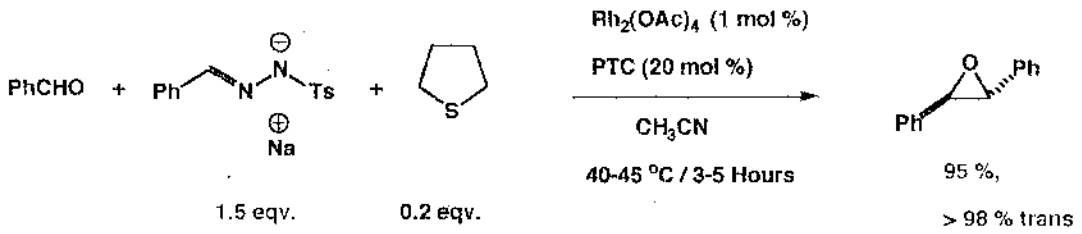


90-94% ee, high de, 35-74% yield.

V.K. Aggarwal, Comprehensive Asymmetric Catalysis, Springer, 1999, Vol II, 679-697; V. K. Aggarwal, *Synlett*, 1998, 329-336; A.-H. Li, L.-X. Dai, V. K. Aggarwal, *Chem. Rev.* 1997, 2341-2372. *J. Am. Chem. Soc.* 1996, 7004-5; *J. Am. Chem. Soc.* 1998, 8328-8339;

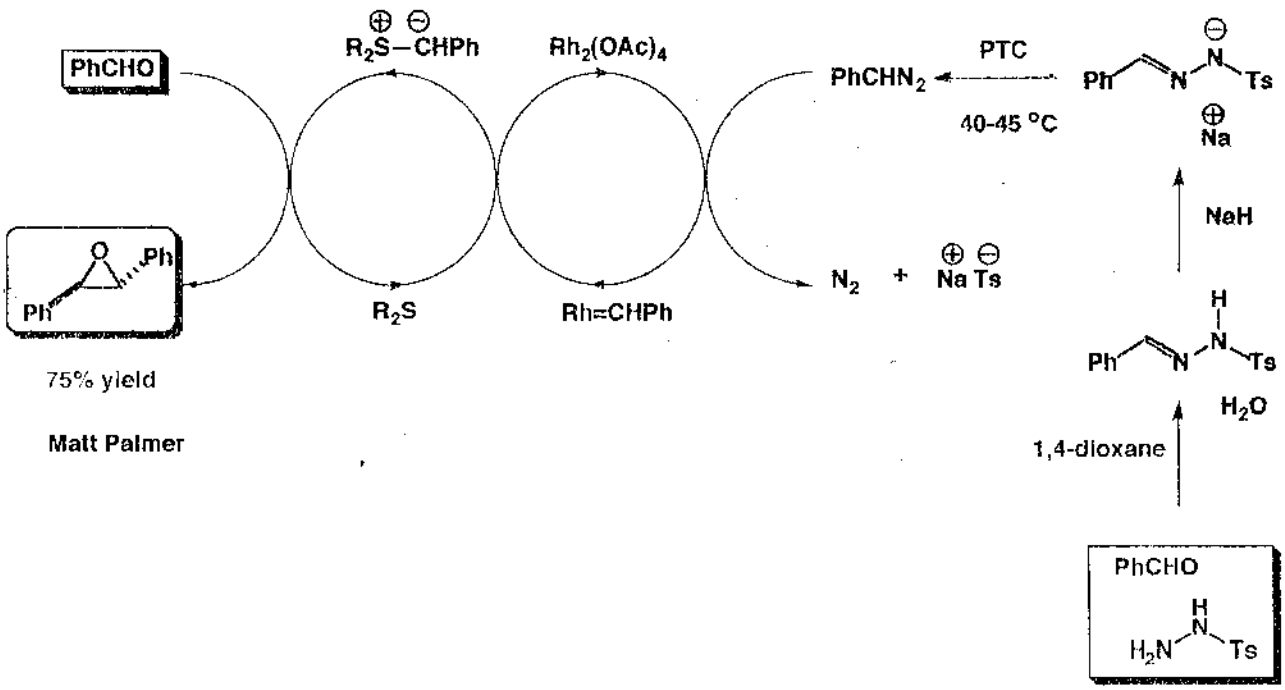
Can Diazocompound be Formed *In Situ* ? YES





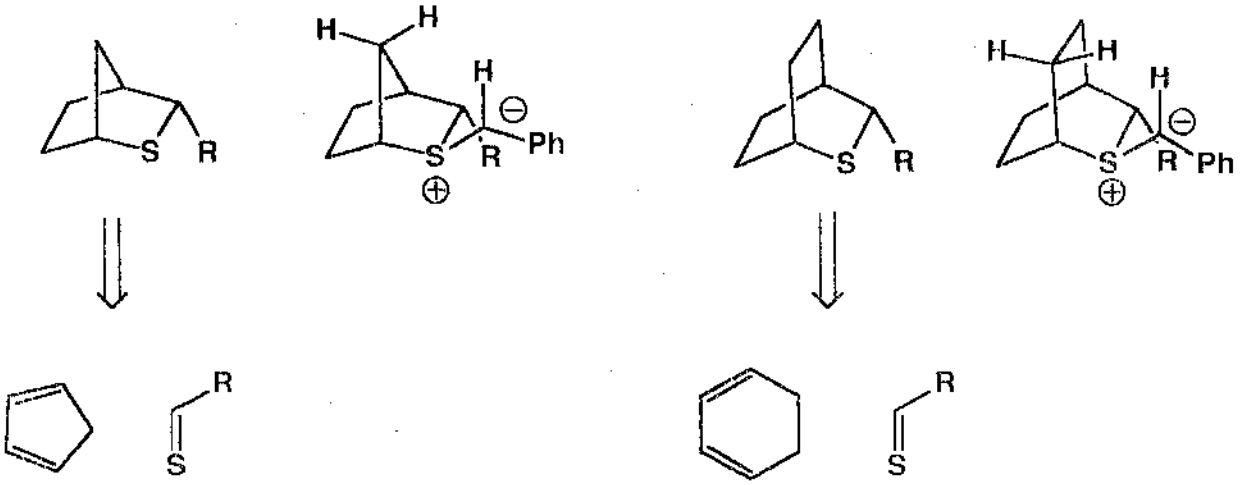
John Studley Angew.Chem. Int. Ed. 2001, 1430-3.

Can the hydrazone be formed *In Situ* ? YES

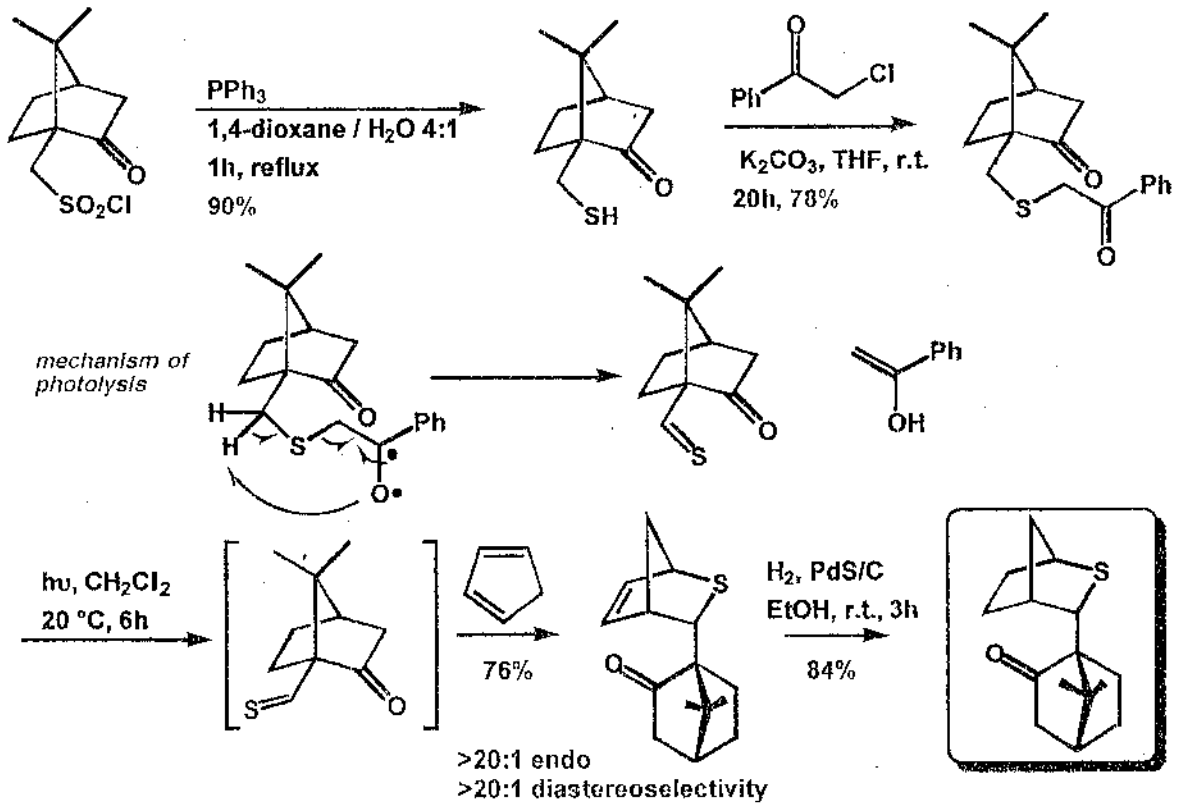


75% yield

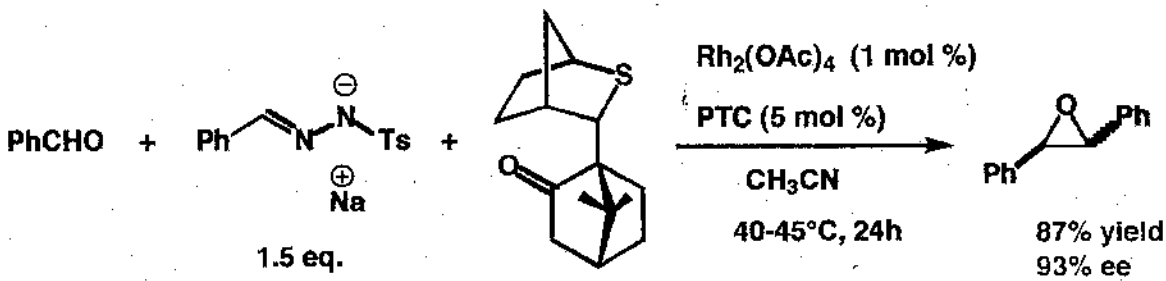
Matt Palmer



Bridged Bicyclic Sulfides: Synthesis



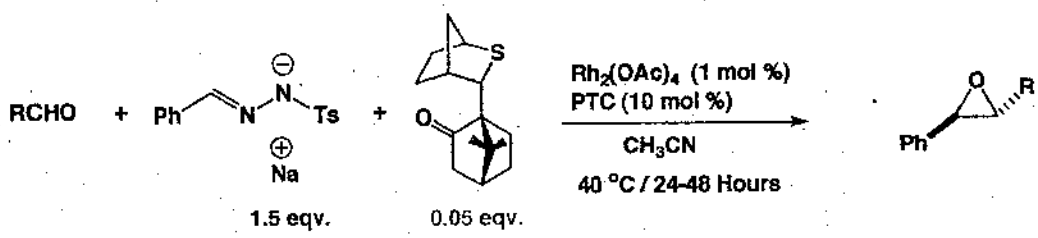
Bicyclic Sulfides: Results in Epoxidation

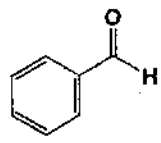


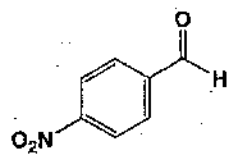
	0.1 eq.	85% yield, 94% ee, >98:2 (t:c)
2.0 eq.	0.05 eq.	82% yield, 94% ee, >98:2 (t:c)

Marina Porcelloni, Emma Alonso Angew.Chem. Int. Ed. 2001, 1430-3.

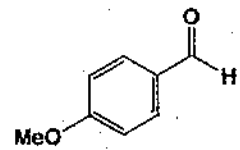
In Situ Generation of Diazo Compound: Application to Aromatic and Aliphatic Aldehydes



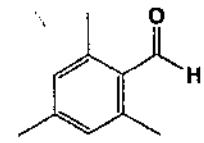

80 % yield
100:0 (*trans:cis*)
94% ee

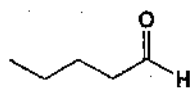


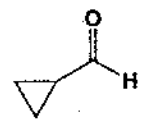
84 % yield
100:0 (*trans:cis*)
90% ee

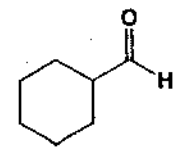


68 % yield
100:0 (*trans:cis*)
92% ee


55 % yield
100:0 (*trans:cis*)
94% ee

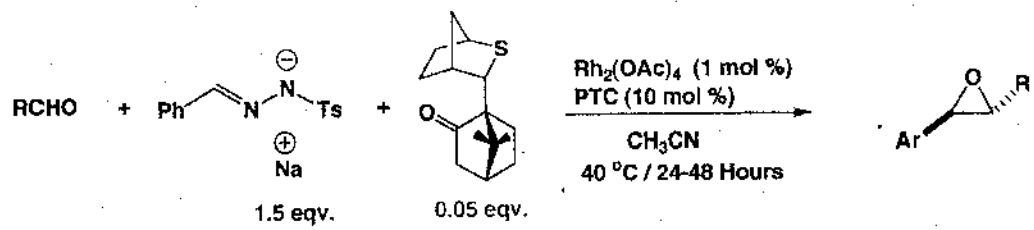

51 % yield
78:22 (*trans:cis*)
77% ee

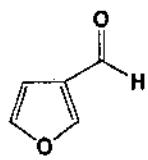

50 % yield
98:2 (*trans:cis*)
94% ee


58 % yield
88:12 (*trans:cis*)
90% ee

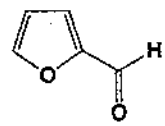
Marina Porcelloni
Mamta Patel
Jeff Richardson
Emma Alonso

In Situ Generation of Diazo Compound: Application to Heteroaromatic and Unsaturated Aldehydes

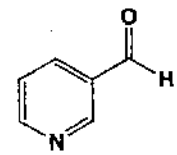




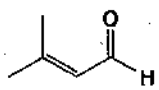
77 % yield
98:2 (*trans:cis*)
92% ee



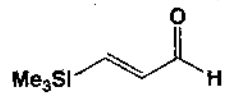
60 % yield
98:2 (*trans:cis*)
91% ee



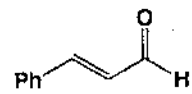
0% yield



21 % yield
98:2 (*trans:cis*)
87% ee



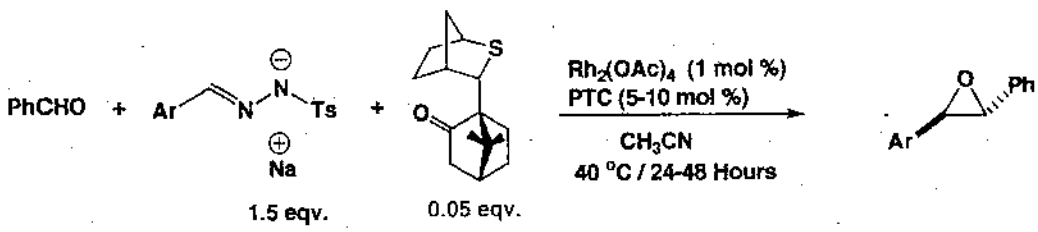
35 % yield
98:2 (*trans:cis*)
88% ee

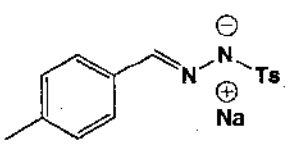


70 % yield
98:2 (*trans:cis*)
87% ee

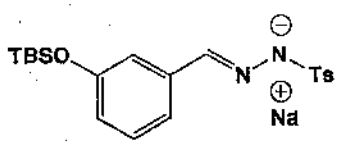
Marina Porcelloni
Jeff Richardson
Emma Alonso

Use of Aromatic and Heteroaromatic Sulfonylhydrazones

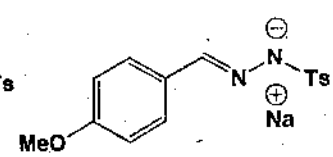




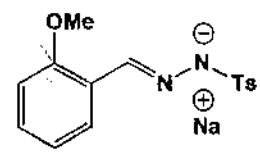
74 % yield
95:5 (*trans:cis*)
93% ee



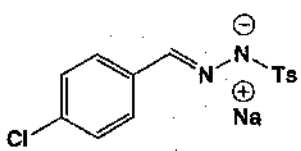
67 % yield
100:0 (*trans:cis*)
92% ee



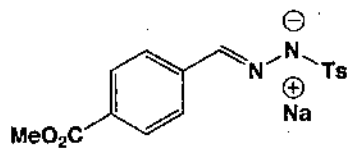
95 % yield
80:20 (*trans:cis*)
91% ee



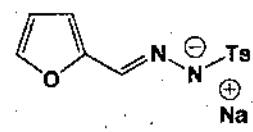
70 % yield
100:0 (*trans:cis*)
93% ee



81 % yield
98:2 (*trans:cis*)
93% ee



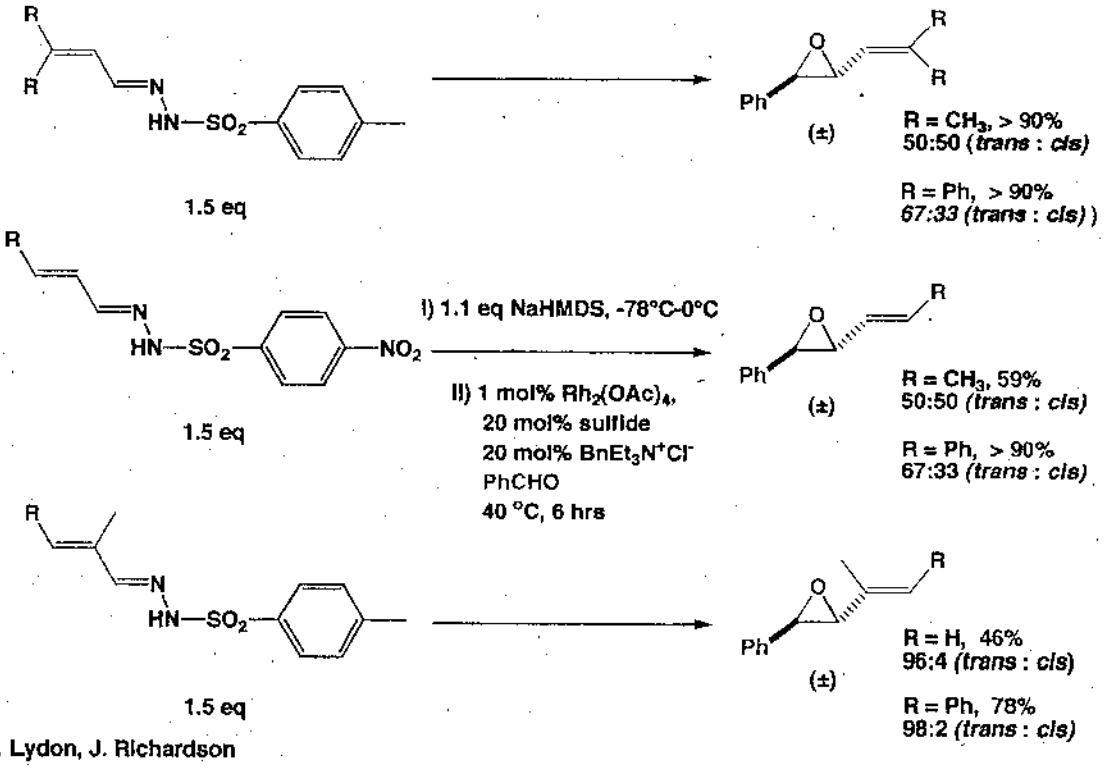
80 % yield
100:0 (*trans:cis*)
73% ee



58 % yield
95:5 (*trans:cis*)
83% ee

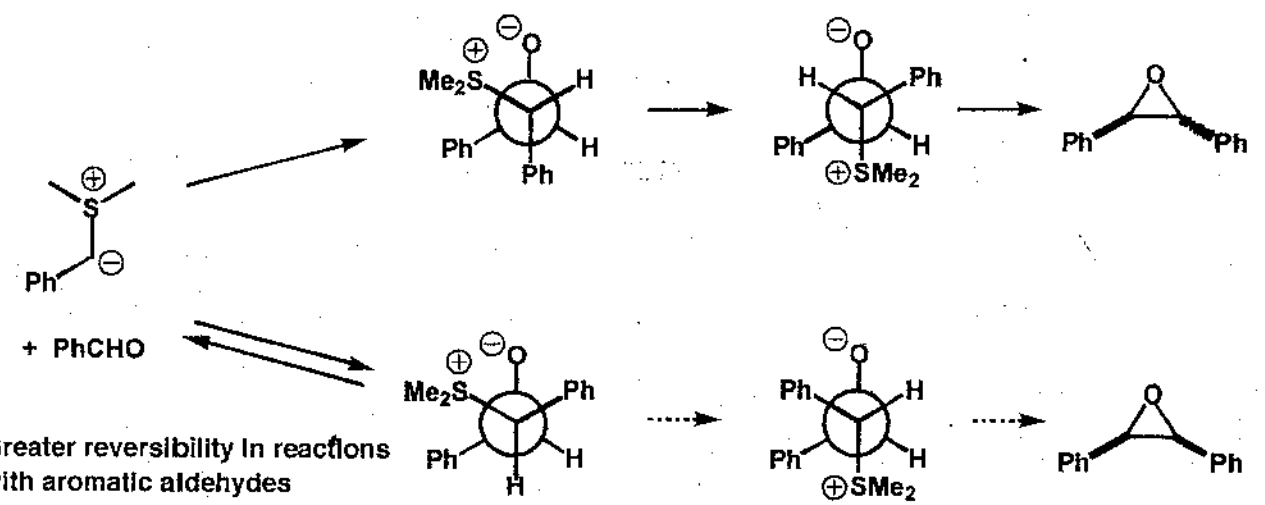
Mamta Patel
Jeff Richardson
Emma Alonso

Use of Unsaturated Sulfonylhydrazones



K. Lydon, J. Richardson

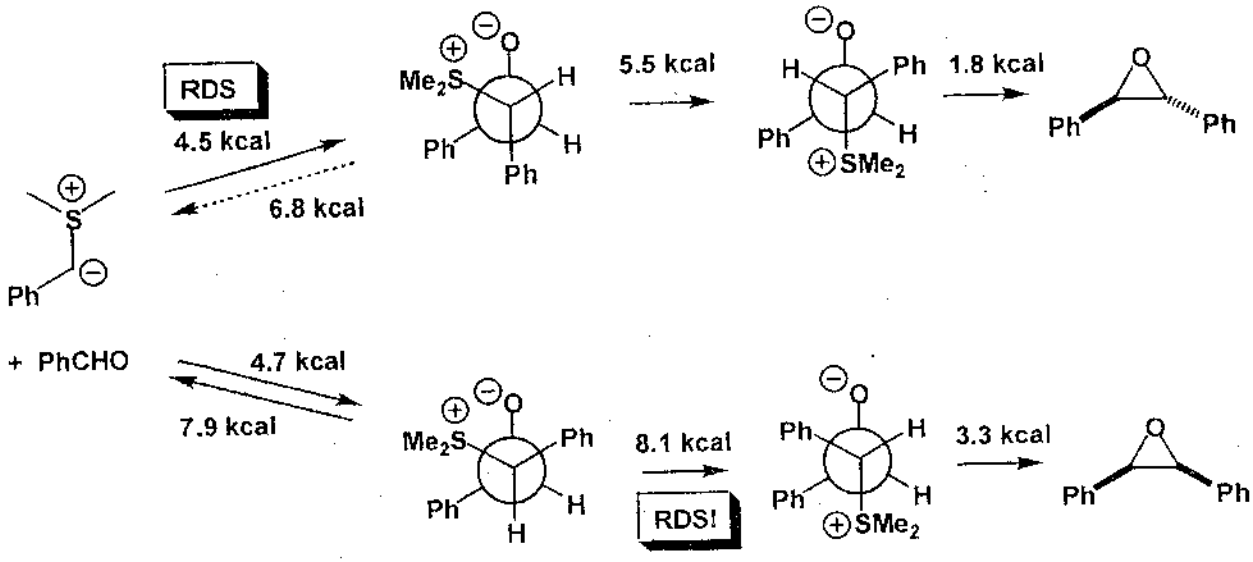
Diastereocontrol in Epoxidation



Greater reversibility in reactions with aromatic aldehydes compared to aliphatic aldehydes; greater trans selectivity

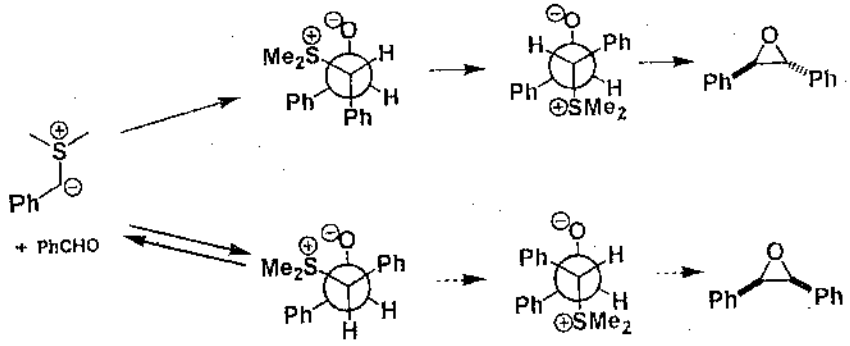
S. Calamai, J. Chem. Soc. Perkin 1, 1997, 593.

B3LYP/6-311+G**(MeCN) Calculations of Reaction Pathway



Jeff Richardson JACS, 2002, 5747- 5756.

Diastereocontrol in Epoxidation



Increasing conjugation of aldehyde
⇒ Increased reversibility
⇒ Increased trans selectivity

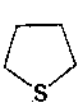
Increasing steric hindrance of ylide
⇒ Increased reversibility
⇒ Increased trans selectivity

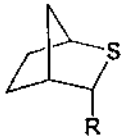
Reducing stability of ylide
⇒ Reduced reversibility
⇒ Reduced trans selectivity

Diastereocontrol results from both steric and electronic control

PhCHO $C_6H_{11}CHO$

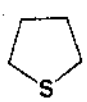
	PhCHO	$C_6H_{11}CHO$
	98:2	65:35





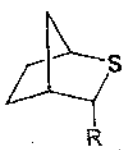
65:35 88:12

PhCHO

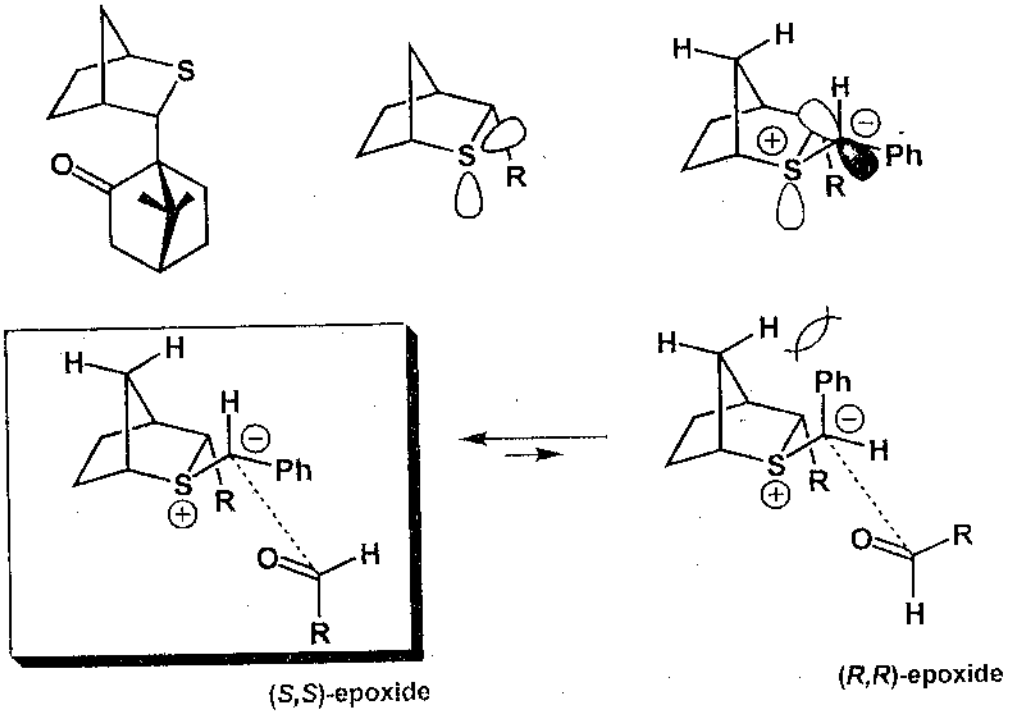


	$PhCHN_2$	p-$MeOC_6H_4CHN_2$
	98:2	71:29

PhCHO

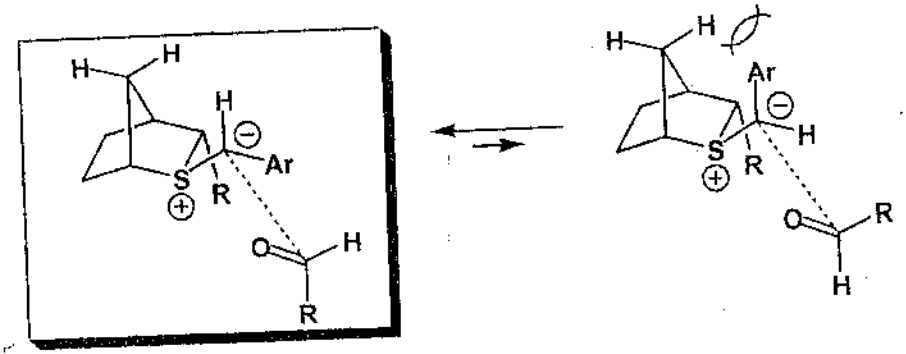


	o-$MeOC_6H_4CHN_2$	p-$MeOC_6H_4CHN_2$
	100:0	80:20



All aldehydes give 91 ± 4% ee
Controlled by ylide conformation

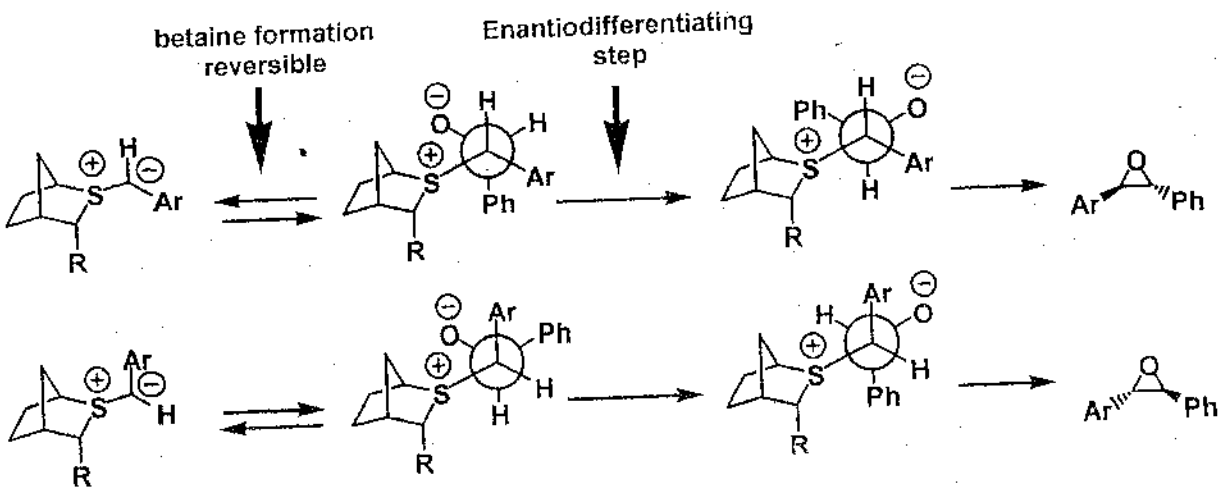
Origin of Enantiocontrol with More Stable Ylides



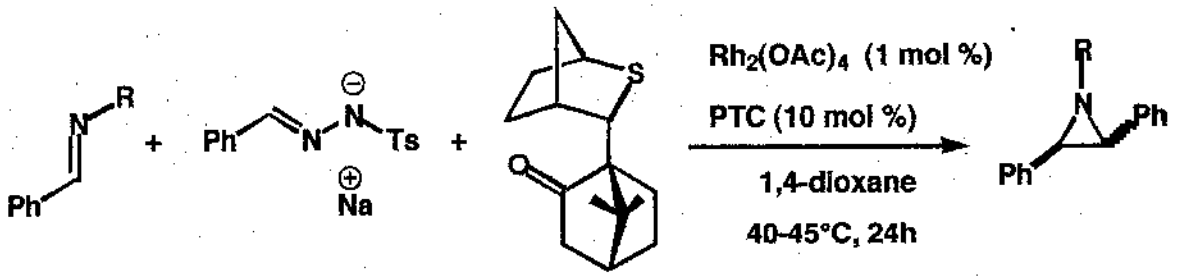
For more stabilised ylides, betaine formation is partially reversible.

Results in reduced ee's.

E.g. Ar = p-CNC_6H_4 , 64% ee



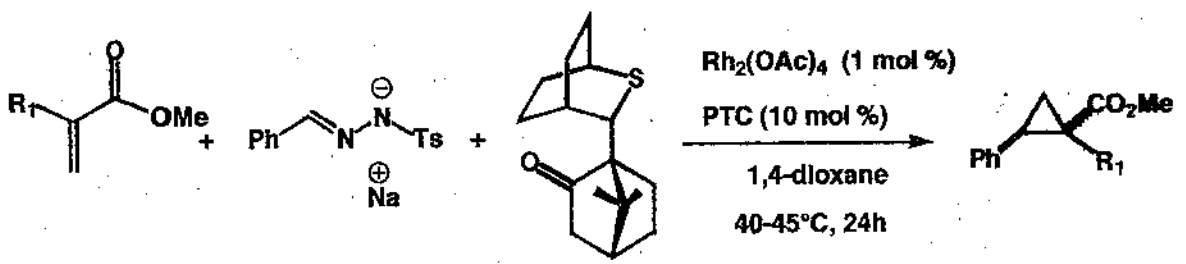
Bicyclic Sulfides: Results in Aziridination



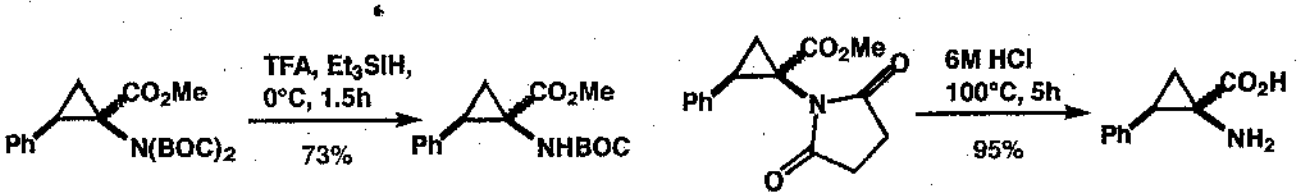
R	1.5 eq.	0.2 eq.	Yield	t:c	ee
SES			75	70:30	94
Ts			68	70:30	98
$CO_2CMe_2CCl_3$			71	86:14	90
BOC			33	89:11	92

Marina Porcelloni, Emma Alonso Angew.Chem. Int. Ed. 2001, 1433-6.

Synthesis of Cyclopropane Amino Acids



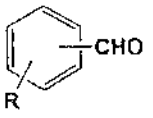
R_1	1.5 eq.	0.2 eq.	Yield	t:c	ee
H			10	7.3:1	-
$N(BOC)_2$			98	1:6	92 (c)
$N\text{-}(COCH_2CH_2CO)$			55	1:7	91 (c)

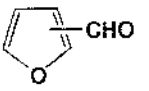


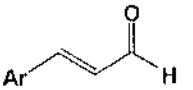
Fang Gangyu Angew.Chem. Int. Ed. 2001, 1433-6.

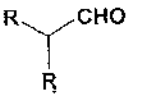
Scope and Limitations in Catalytic Asymmetric Epoxidation

Good electrophiles
(high yield/ high ee)

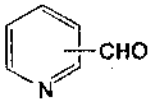


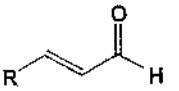


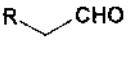




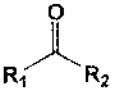
Poor electrophiles
(low yield/ low selectivity)



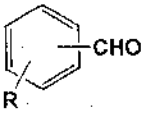


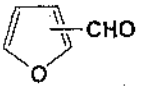


lower de
and ee

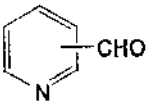


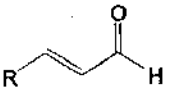
Good Carbene Precursors



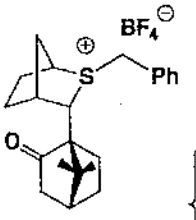


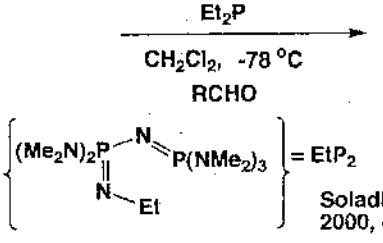
Poor Carbene Precursors



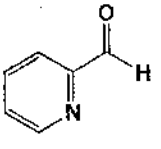


Problem Substrates: Use of Stoichiometric Sulfide

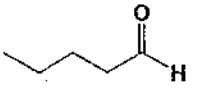




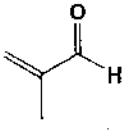
Soladié-Cavallo, Tet. Lett.
2000, 41, 7309



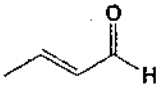
88 % yield
98:2 (*trans:cis*)
*99% ee



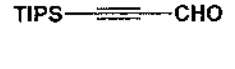
64% yield
92:8 (*trans:cis*)
97% ee



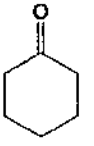
52% yield
98:2 (*trans:cis*)
99% ee



90% yield
98:2 (*trans:cis*)
95% ee



57% yield
65:35 (*trans:cis*)
99% ee



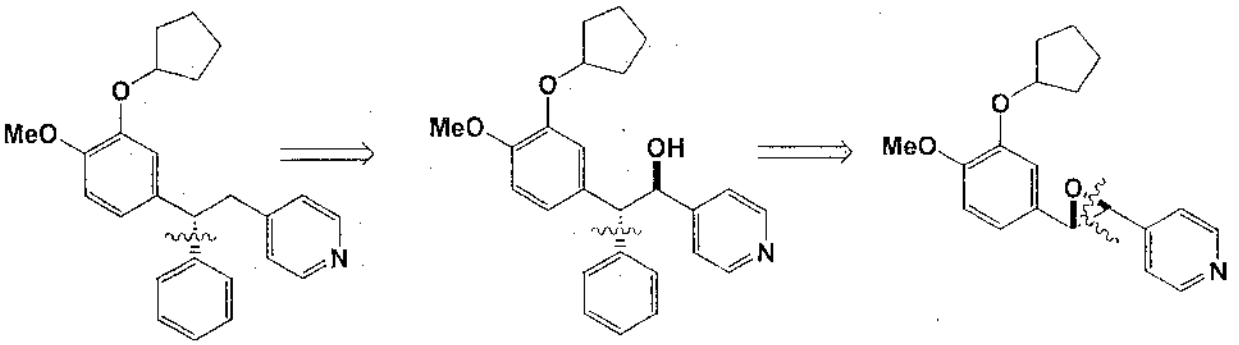
37 % yield

94% ee

David Williams

Retrosynthesis of CDP-840

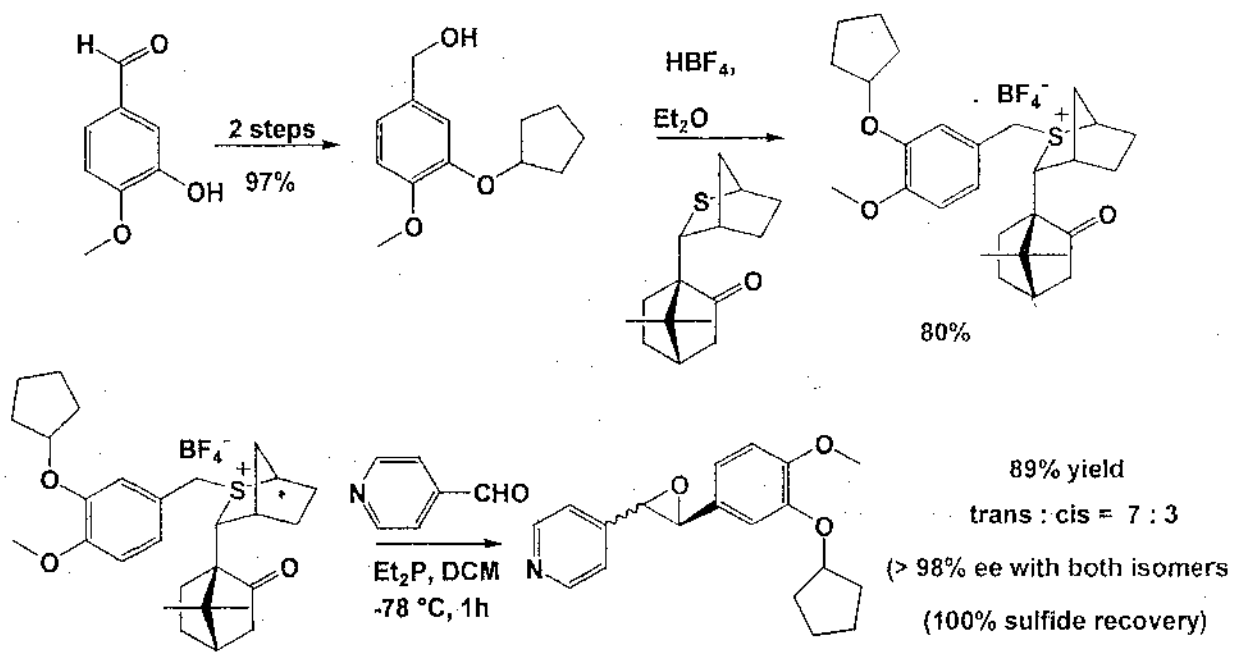
- Selective PDE IV inhibitor, potential anti-asthma agent.
- Discovered by Celltech, 1997 (patent), licensed to Merck.



CDP-840

Hee Yoon Lee, KAIST

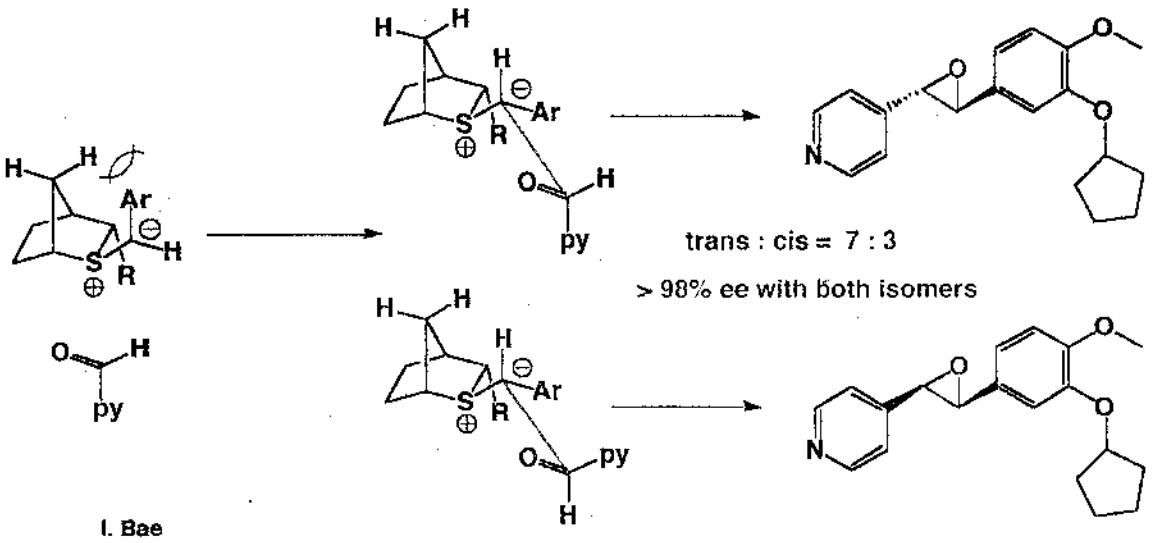
Synthesis of CDP-840



80% from alcohol

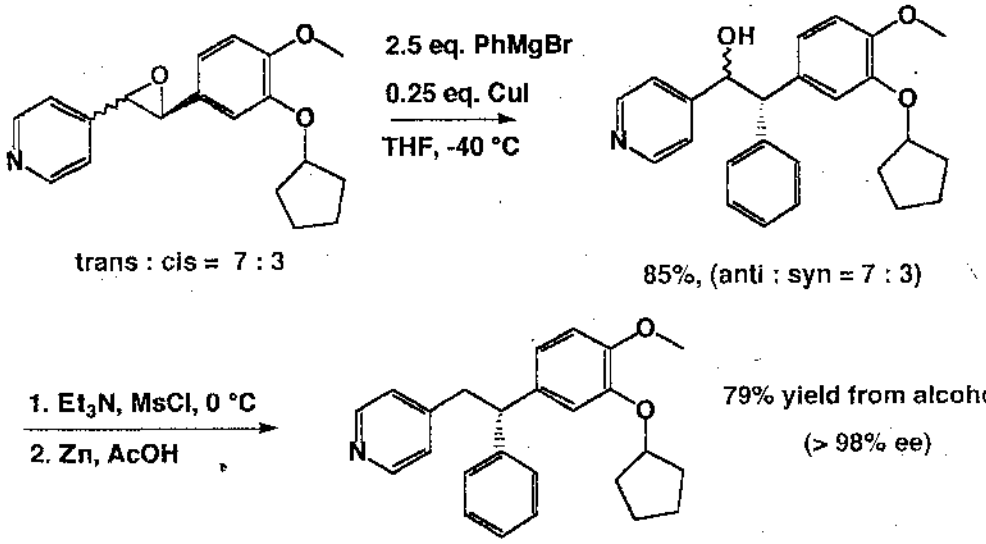
I. Bae

Rationale for Enantiocontrol



I. Bae

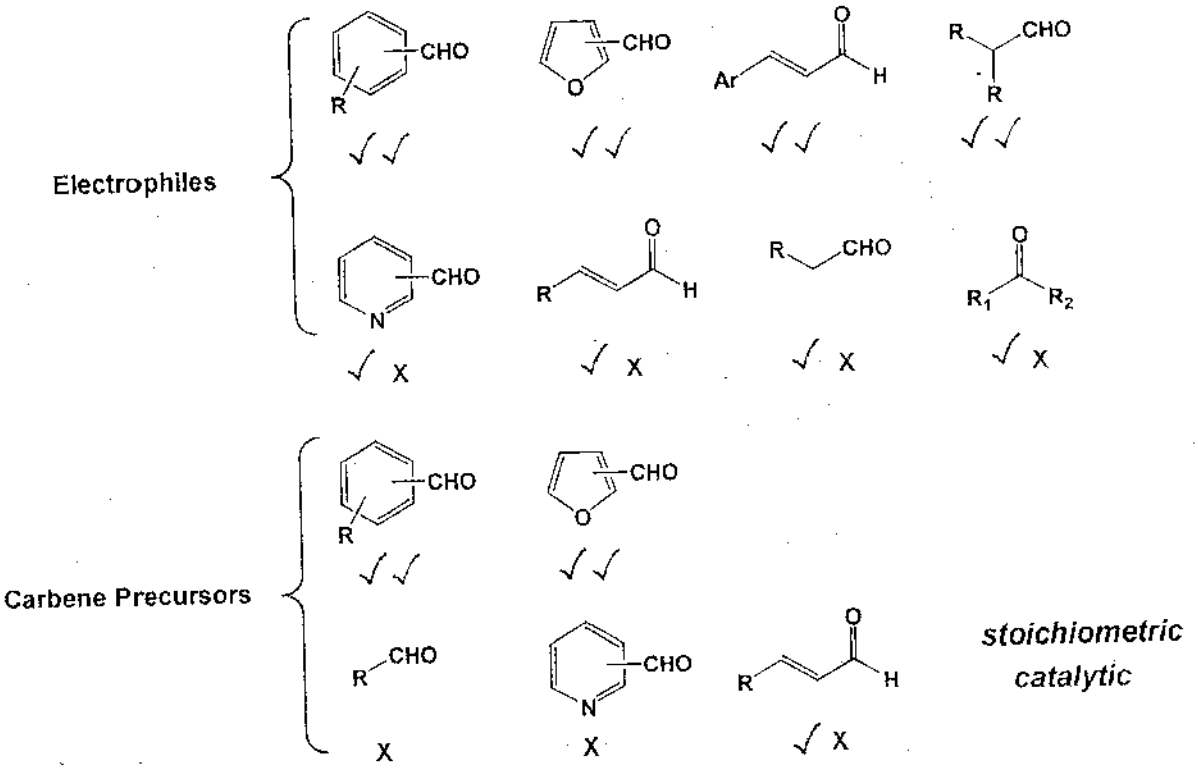
Synthesis of CDP-840



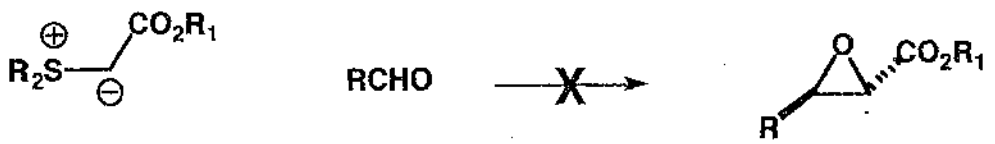
- Overall Yield: 47% from commercially available aldehyde
- Enantiomerically pure
- 7 steps
- Sulfide reisolated
- Competitive with published literature routes

I. Bae

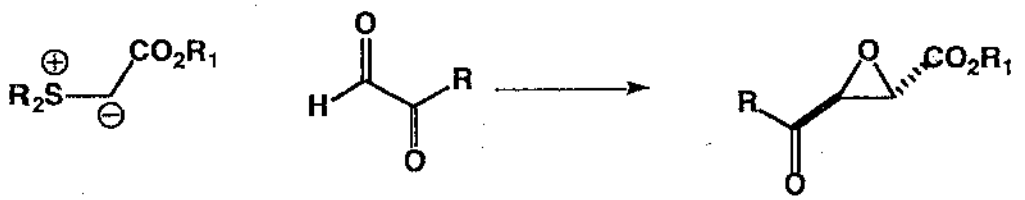
Scope and Limitations in Asymmetric Epoxidation



Alternative Diazo Compounds: Reactivity of Ylides



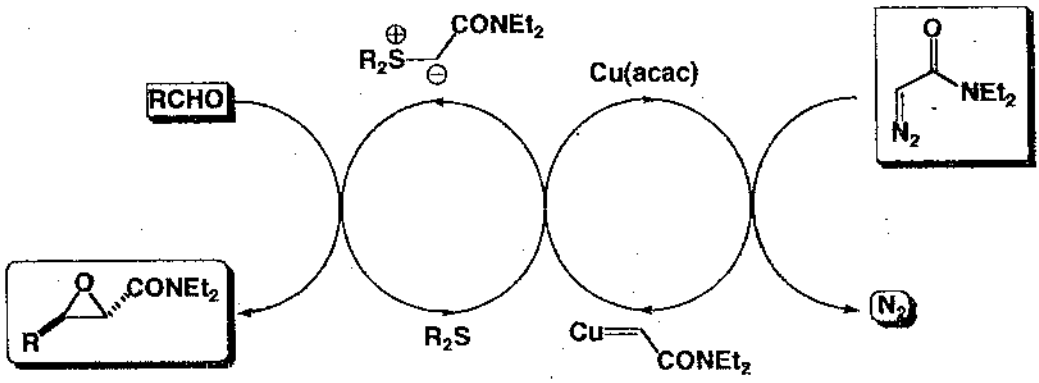
K. Ratts, A. Yoa, JOC, 1966, 1689.
A.W. Johnson, JOC, 1969, 1240.

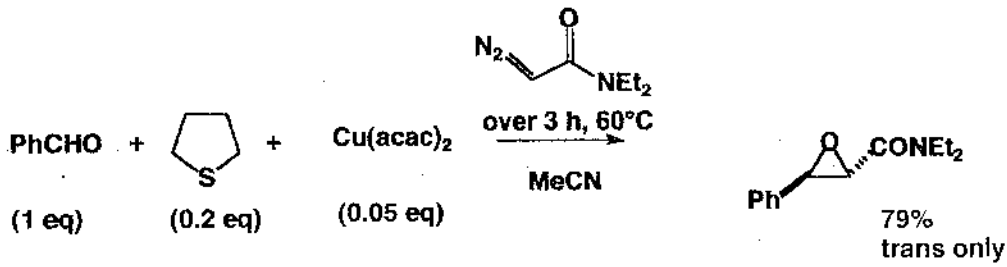


G.B. Payne, JOC, 1968, 3517.

K. Ratts, A. Yoa, JOC, 1966, 1689.
M.V. Fernandez, Tet. 1990, 7911

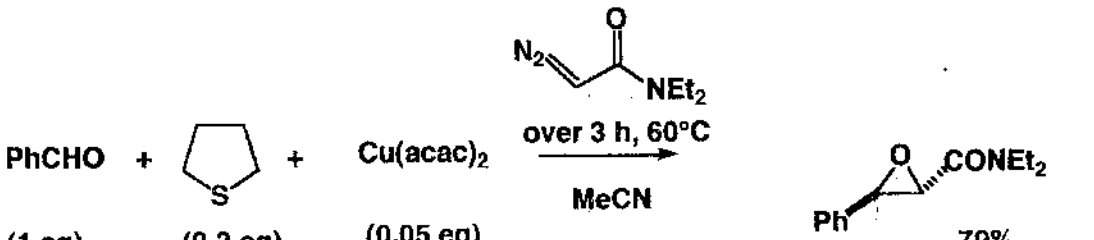
The Catalytic Cycle: Use of Diazoacetamides

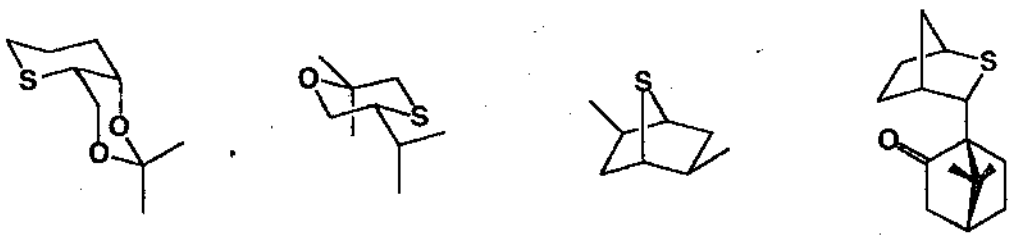




Paul Blackburn Tet. Lett., 1998, *39*, 8517-8520

The Catalytic Cycle: Use of Diazoacetamides





44% yield
10% ee

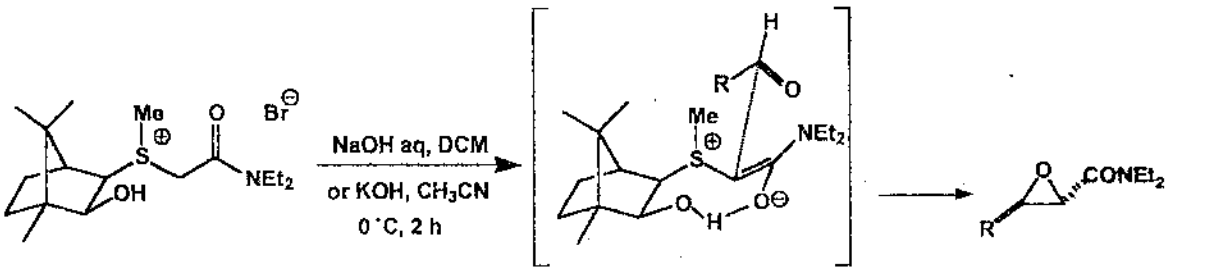
60% yield
8% ee

8% yield
10% ee

65% yield
14% ee

Paul Blackburn Tet. Lett., 1998, *39*, 8517-8520

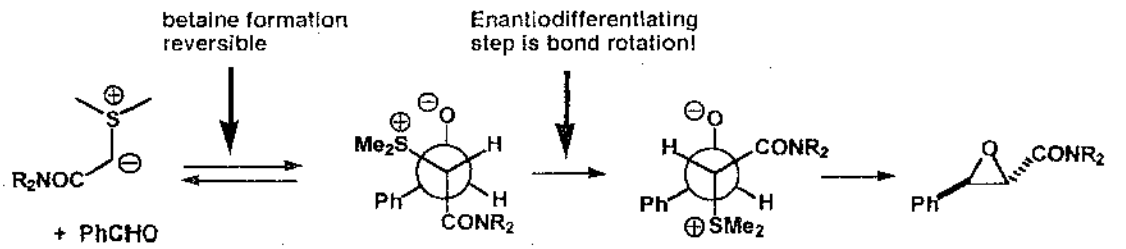
Asymmetric Synthesis of Epoxyamides using Sulfur Ylides



R = Ar, Yield 80-94%, ee 57-70%

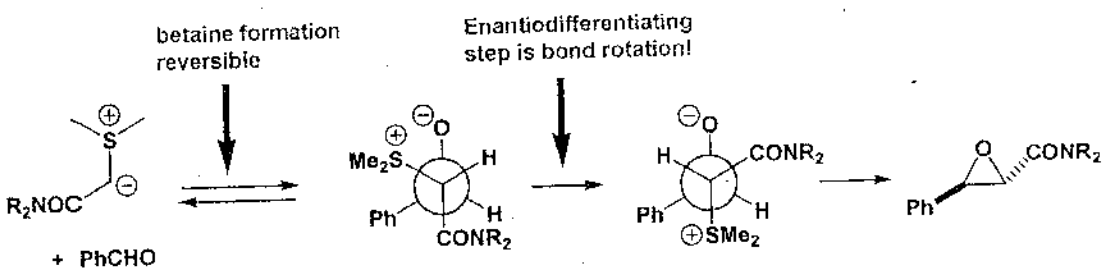
R = Alk, Yield 70-80%, ee 1-11%

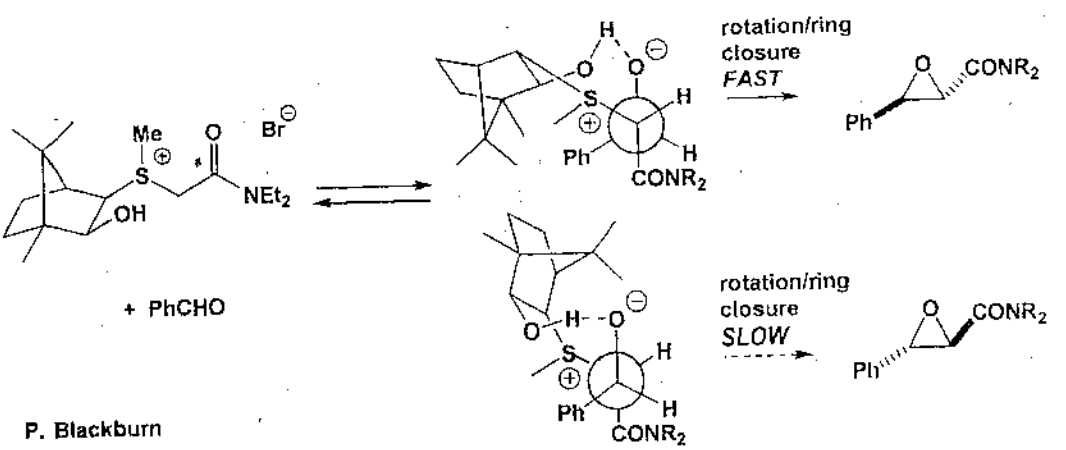
L. X. Dai, *J. Chem. Soc. Perkin Trans. I*, 1999, 77-80



P. Blackburn

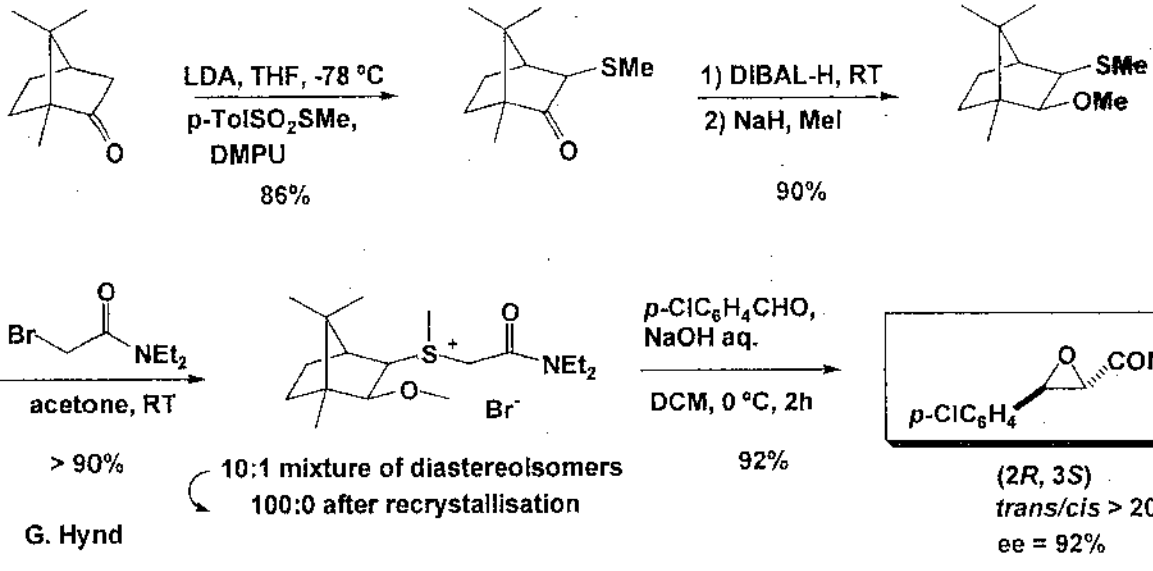
Mechanism of Epoxidation: Reversible Formation of Betaine



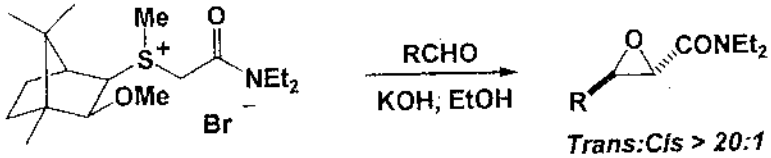


P. Blackburn

Synthesis of the Auxiliary and Initial Results
Mechanism-based Discovery



Synthesis of Epoxyamides : Optimised Conditions
Mechanism-based Discovery

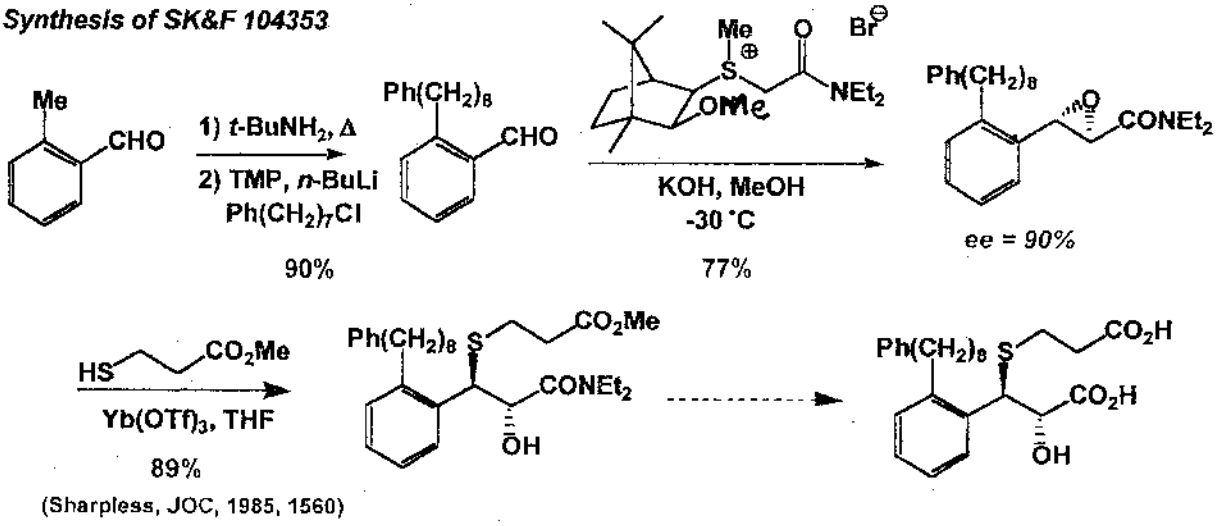


R	T (°C)	Yield (%)	Ee (%)
p-MeOC6H4	- 50	90	97
Ph	- 50	93	97
p-ClC6H4	- 50	87	99
p-MeC6H4	- 50	88	98
p-FC6H4	- 50	85	96
p-CF3C6H4	- 50	89	96
p-NO2C6H4	- 50	85	92
3-Pyridyl	- 50	87	95
o-Ph-(CH2)8-	- 30	77	90
Dodecyl	- 20	84	63
t-Butyl	- 20	84	93

G. Hynd, W. Picoul, J. Am. Chem. Soc., 2002, 9964-5

Applications

Synthesis of SK&F 104353



W. Picoul

Applications

Synthesis of SK&F 104353