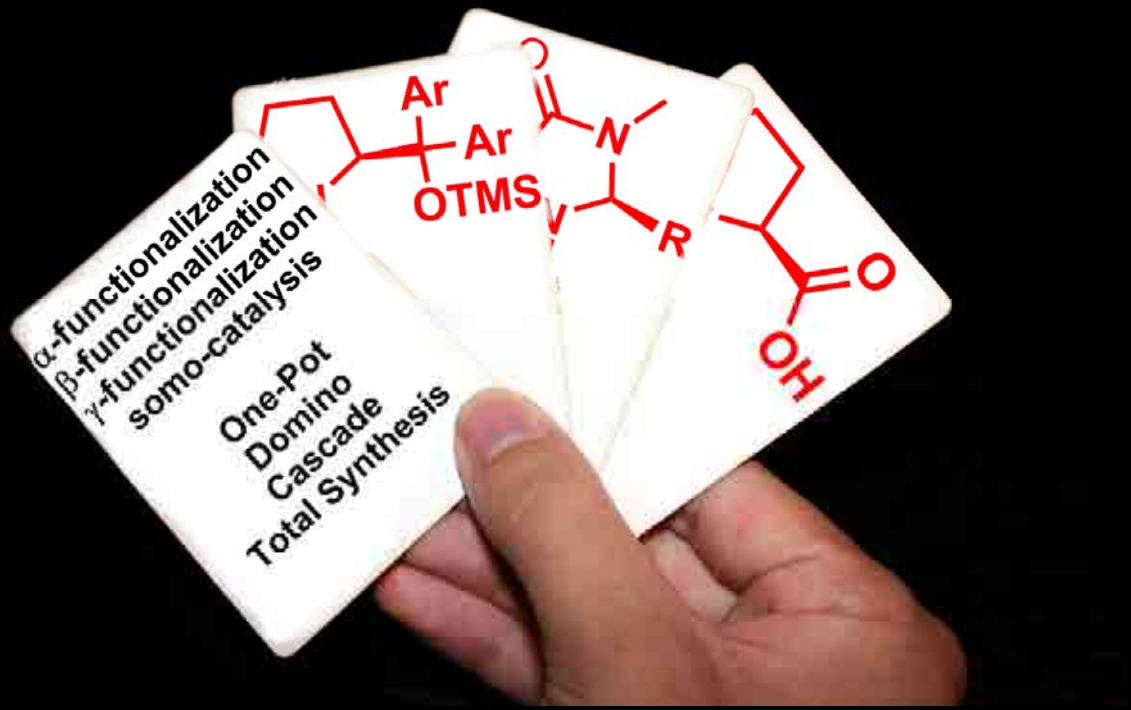
Organocatalysis – A New Tool for Industry

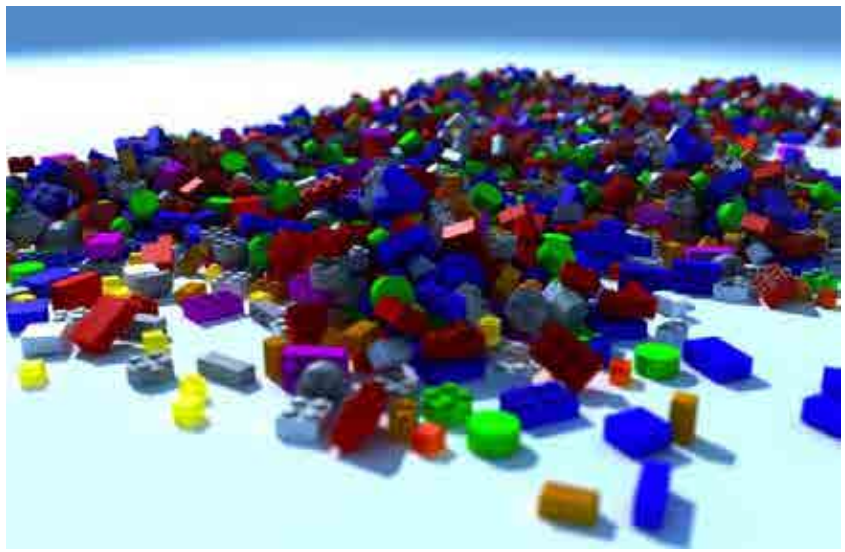


The Royal Society of Chemistry Symposium
Catalysts for Change

What is my mission

What is organocatalysis

To present an overview organocatalytic reactions



To show the synthesis of optically active building blocks and their application

To use simple and easy available starting compounds and catalysts

Organocatalysis

Advantages

a) Easy to prepare
b) Easy to handle – water, air
c) Easy to scale up
d) No metal contamination
e) Easy screening
f) "More flexible" than metal catalysis
g) More complex reactions and multiple stereocenter formation

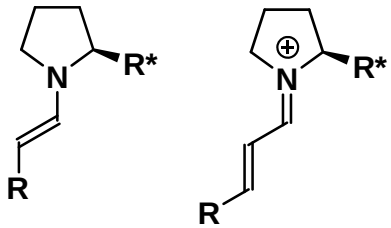
Disadvantages

a) High catalyst loadings
b) "Premature"

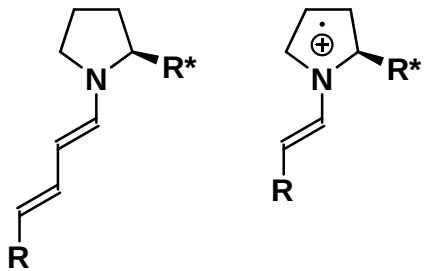
Organocatalysis - activation

Covalent catalysis

enamine iminium

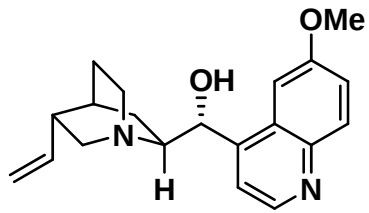


dienamine SOMO



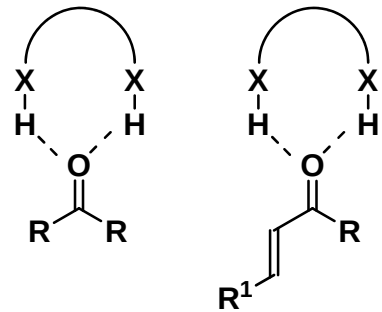
Non-covalent catalysis

cinchona alkaloids/PTC



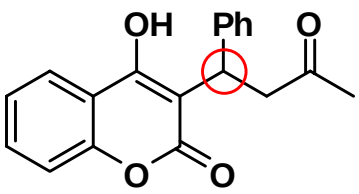
Quinine

proton activation



An "old" example – Warfarin – from lab to humans

100% atom economic, one-step synthesis of optically active anticoagulants



Warfarin
sold as racemate for 40 years

Activity: (*S*)-enantiomer is about 5 times higher than the activity of the (*R*)-enantiomer, and the enantiomers are metabolized by different metabolic pathways.

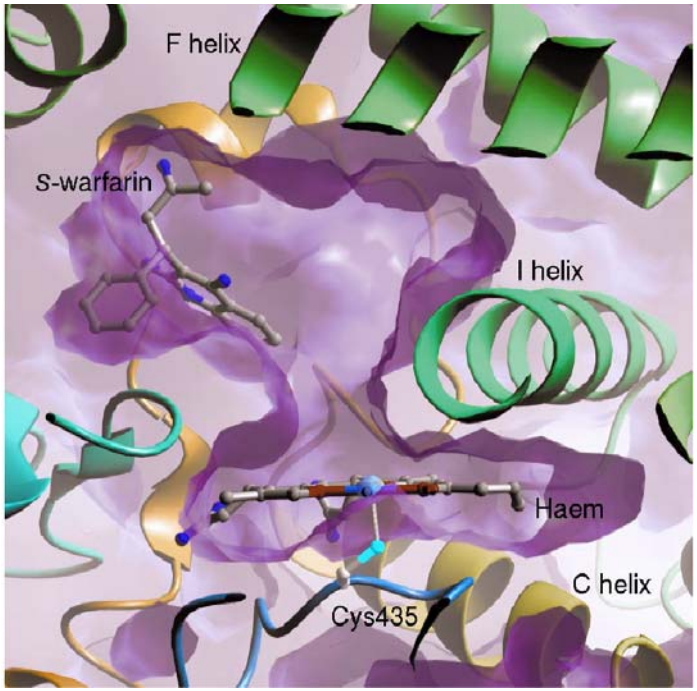
Different half-lives of the enantiomers: 21-43 and 37-89 h for (*S*)- and (*R*)-warfarin, respectively.

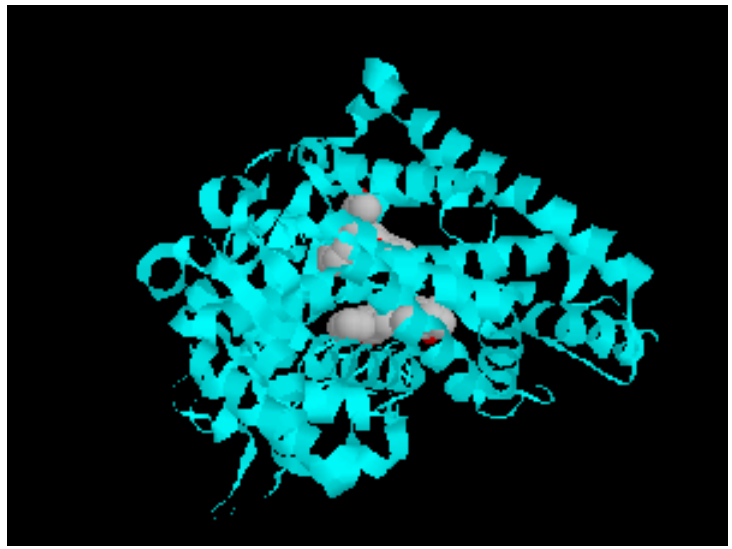
Problem: patients are responding very differently to racemic warfarin.

Treatment of patients with optically pure warfarin will reduce the dose problem.
Advantage: weak patients, unable to tolerate the stronger racemic or (*S*)-warfarin, could be treated with the milder (*R*)-warfarin.

The most important advantage of administrating optically pure warfarin is the possibility of eliminating drug-drug interactions, which represents another serious problem with racemic warfarin, as the cytochrome P-450 enzyme responsible for metabolising warfarin is also metabolizing other drugs

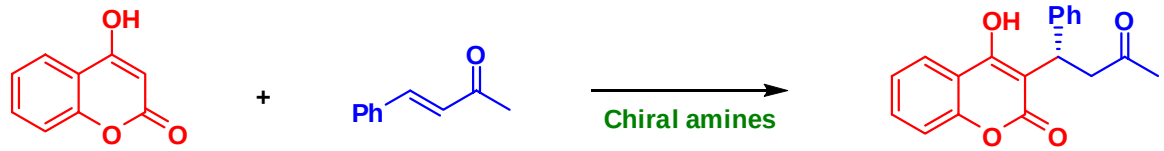
S-Warfarin metabolized by cytochrome P450

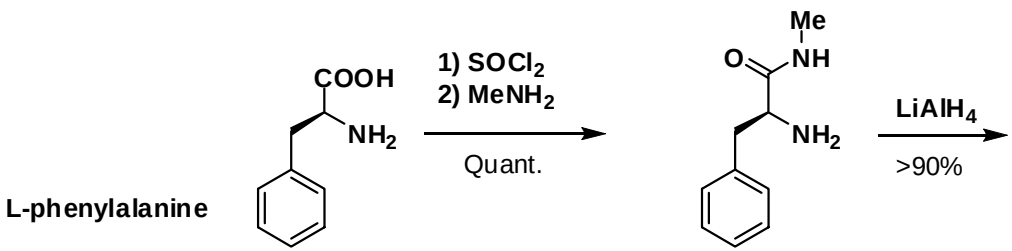


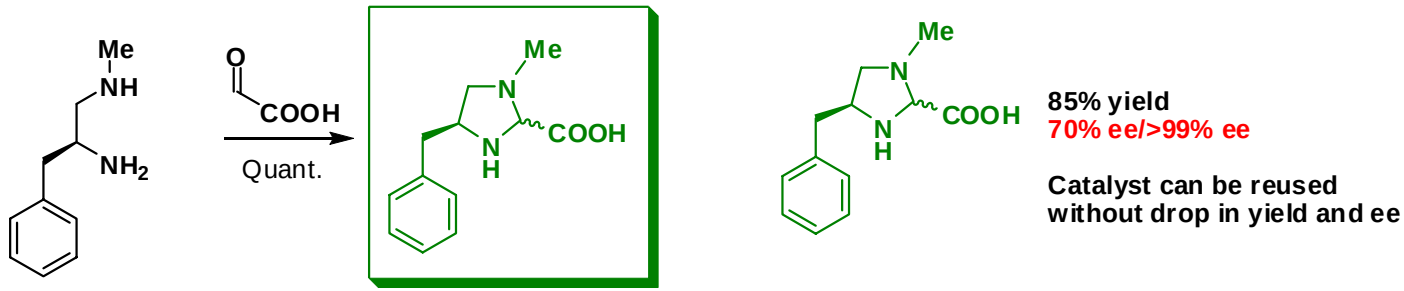


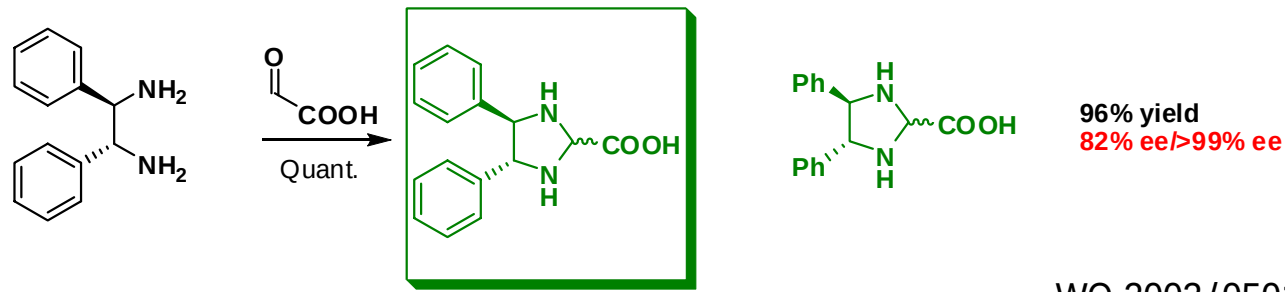
P. A Willams et al. *Nature*, **2003**, *424*, 464

Development of catalysts





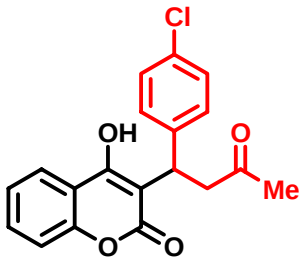




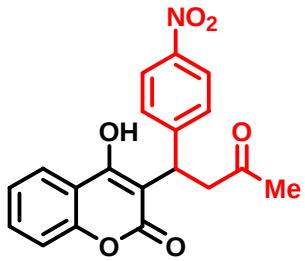
WO 2003/050105

Halland, Hansen, Jørgensen *Angew. Chem. Int. Ed.* **2003**, *42*, 4955

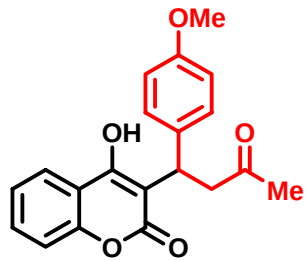
Variation of enones and coumarins



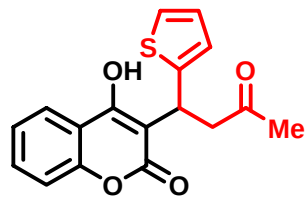
68% yield
87% ee



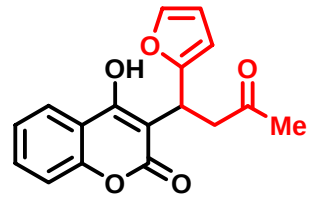
81% yield
83% ee



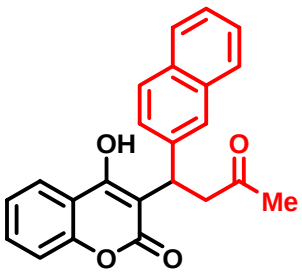
91% yield
82% ee



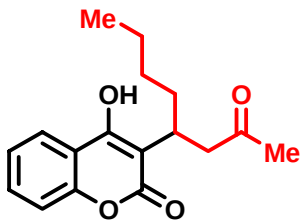
78% yield
79% ee



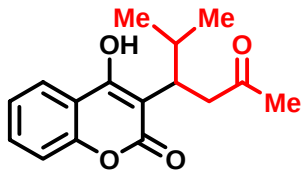
75% yield
76% ee



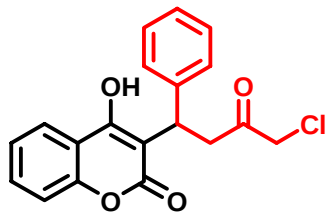
81% yield
83% ee



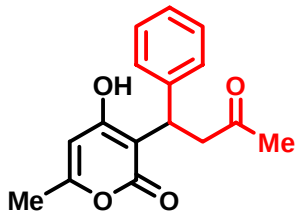
99% yield
84% ee



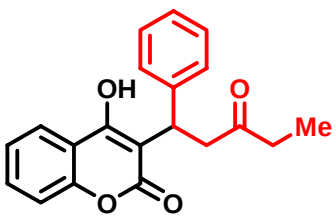
77% yield
83% ee



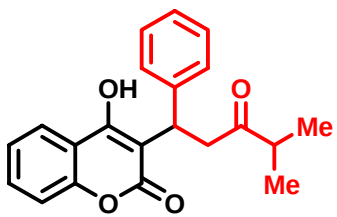
12% yield
84% ee



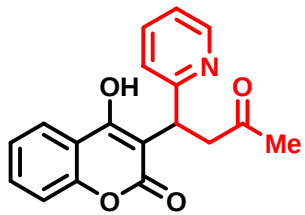
76% yield
85% ee



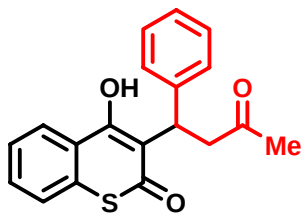
84% yield
82% ee



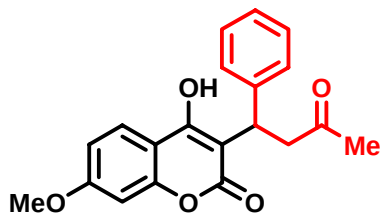
71% yield
85% ee



68% yield
87% ee



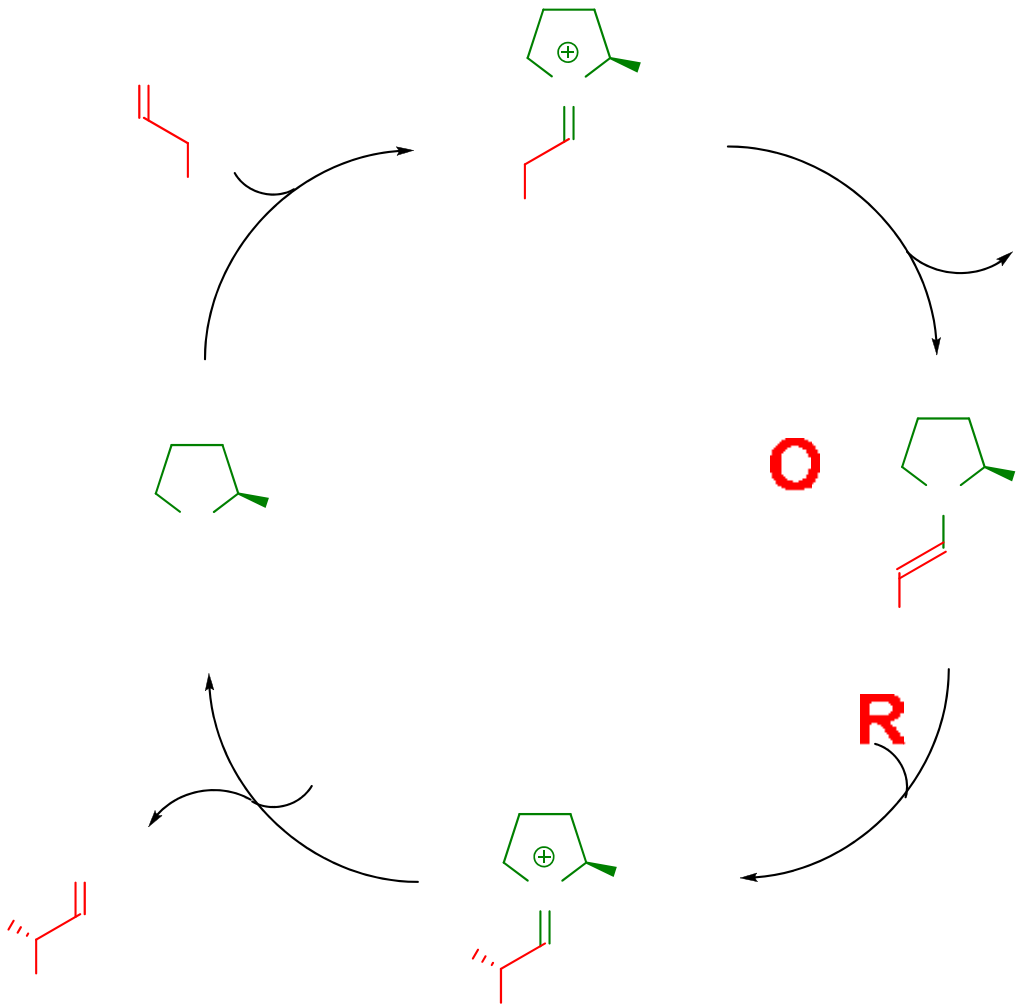
84% yield
78% ee



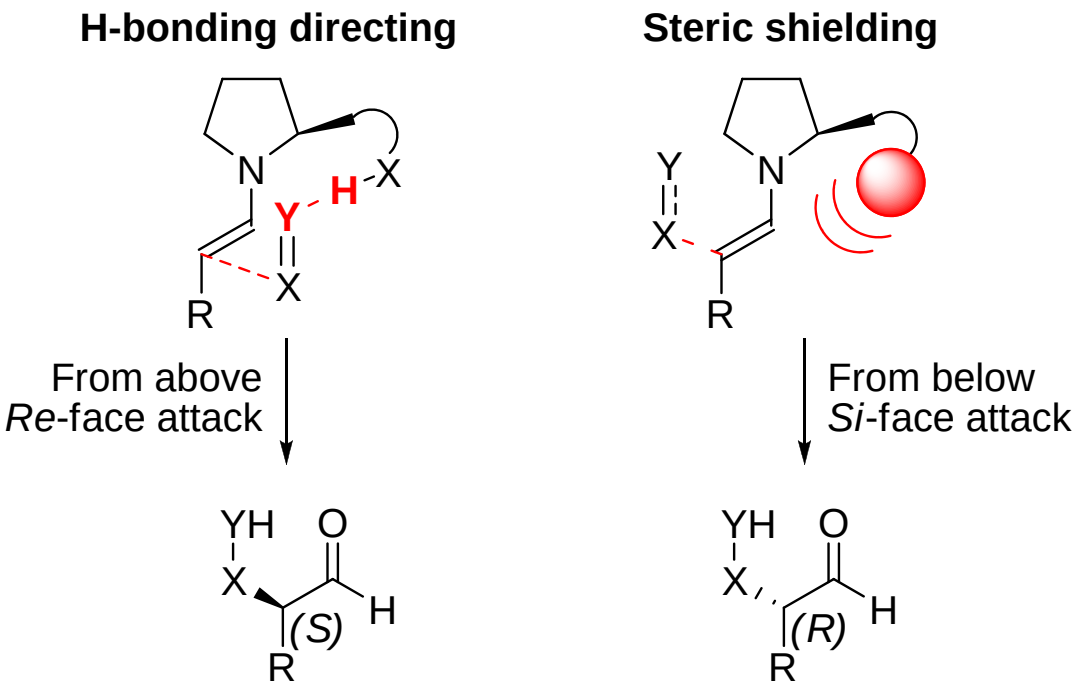
81% yield
85% ee

Aldehyde activation

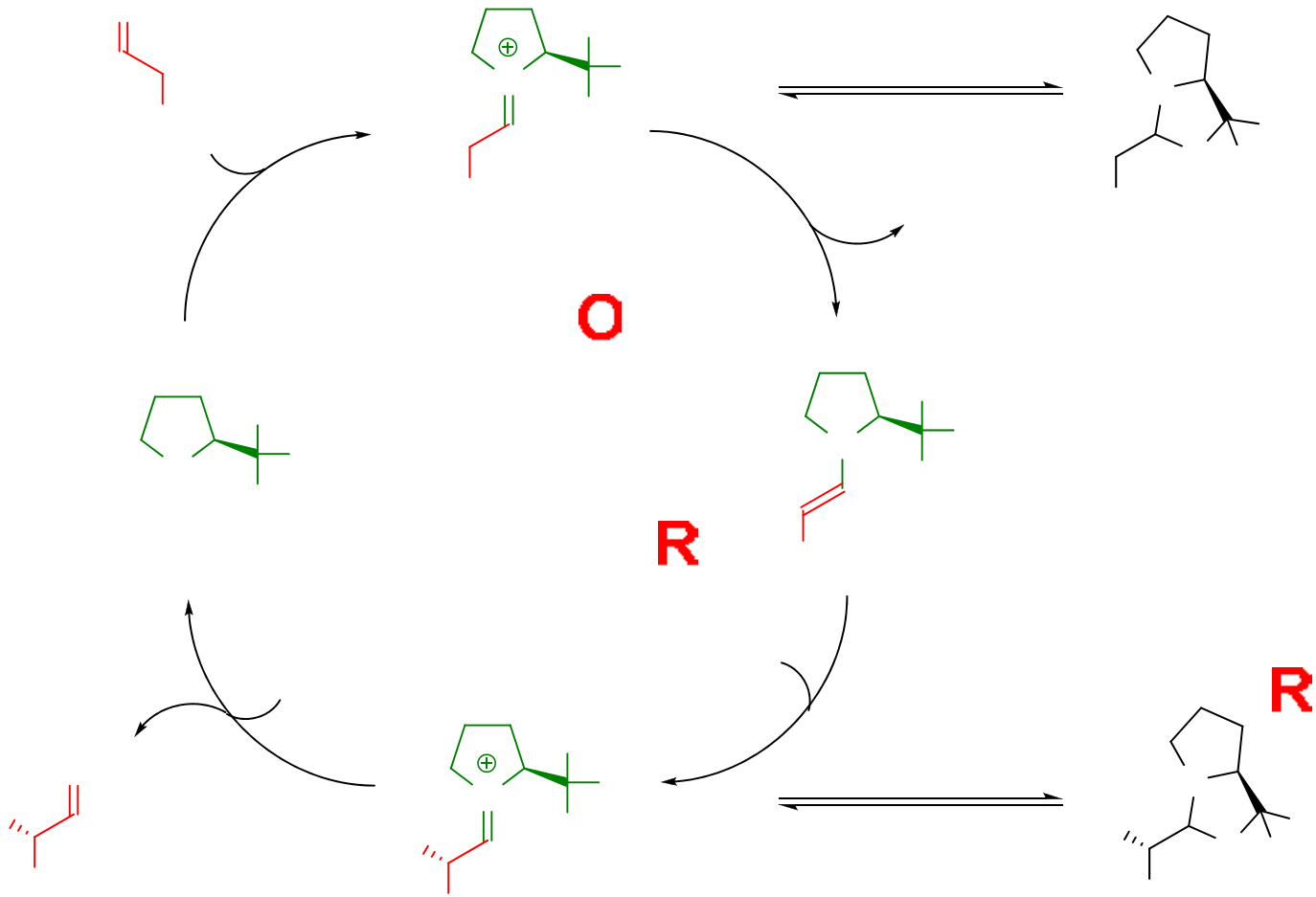
Aldehydes



H-Bonding directing vs. steric shielding

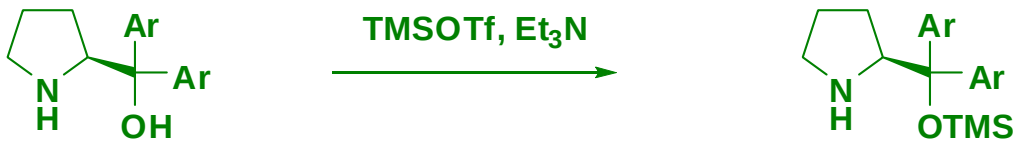


Catalyst design



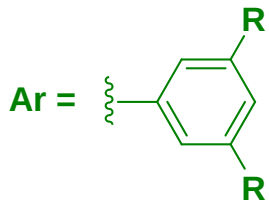
Marigo, Wabnitz, Fielenbach, Jørgensen *Angew. Chem. Int. Ed.* **2005**, *44*, 792
Franzén, Marigo, Fielenbach, Wabnitz, Kjærsgaard, Jørgensen *J. Am. Chem. Soc*. **2005**, *127*, 18296
Bertelsen, Jørgensen, *Chem. Soc. Rev*. **2009** Advanced article

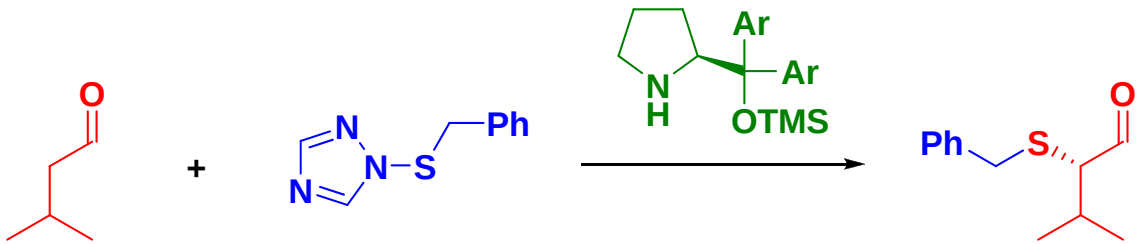
Catalyst synthesis and properties



>98% yield

1. **The TMS-group can be installed in one single quantitative step.**
2. **The catalyst is soluble in the most common organic solvents.**
3. **The reaction can be easily followed by ^{1}H NMR spectroscopy.**

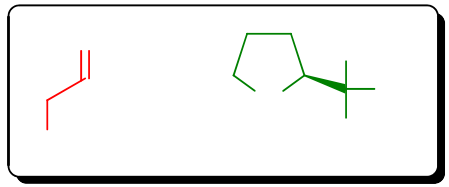


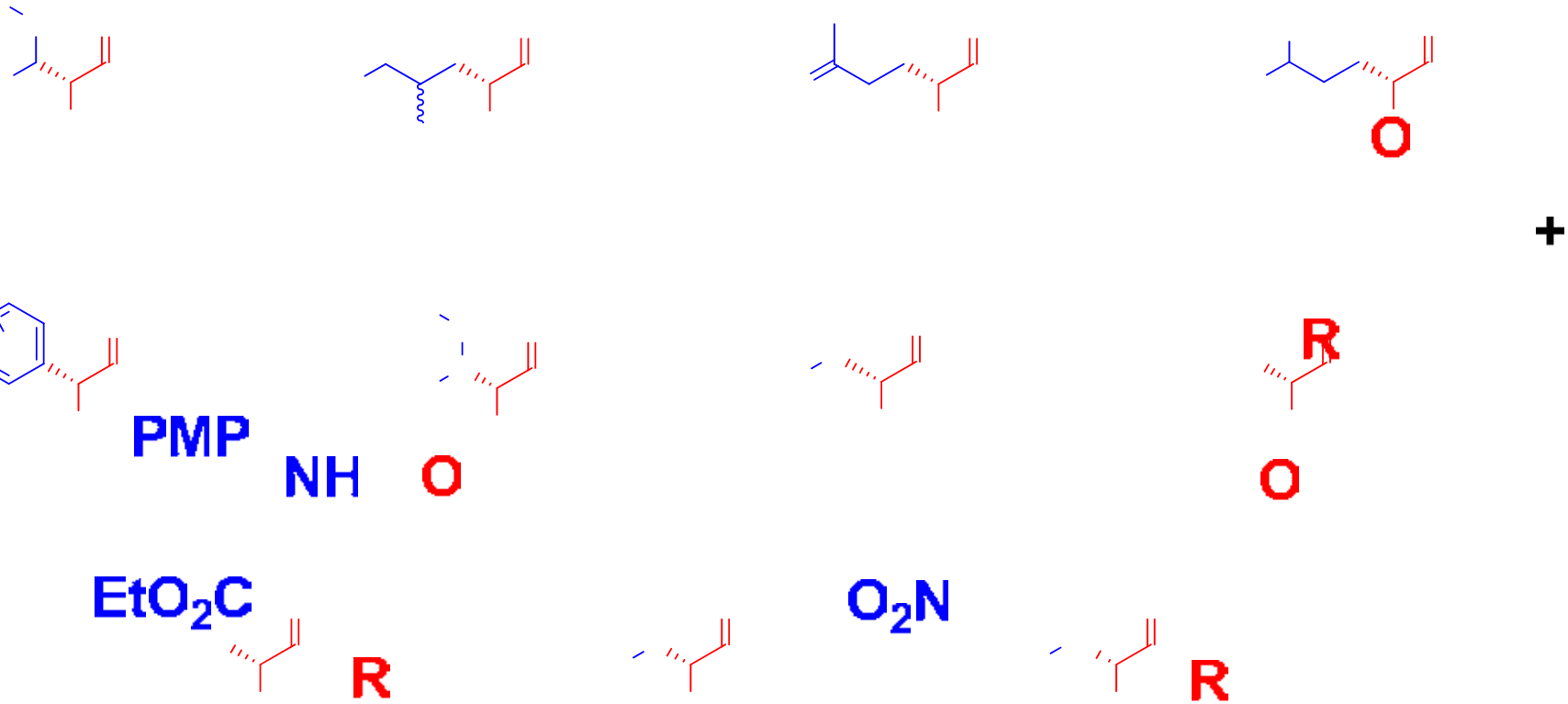


R	Taft E's Value	ee [%]
H	0	77
CH_3	- 1.24	90
CF_3	- 2.40	98

Franzén, Marigo, Fielenbach, Wabnitz, Kjærsgaard, Jørgensen *J. Am. Chem. Soc*. **2005**, *127*, 18296
Focus review: Mielgo, Palomo, *Chem Asian J*. **2008**, *3*, 922

α-Functionalization of aldehydes





98% ee

JACS 2005, *127*, 18286

85% ee

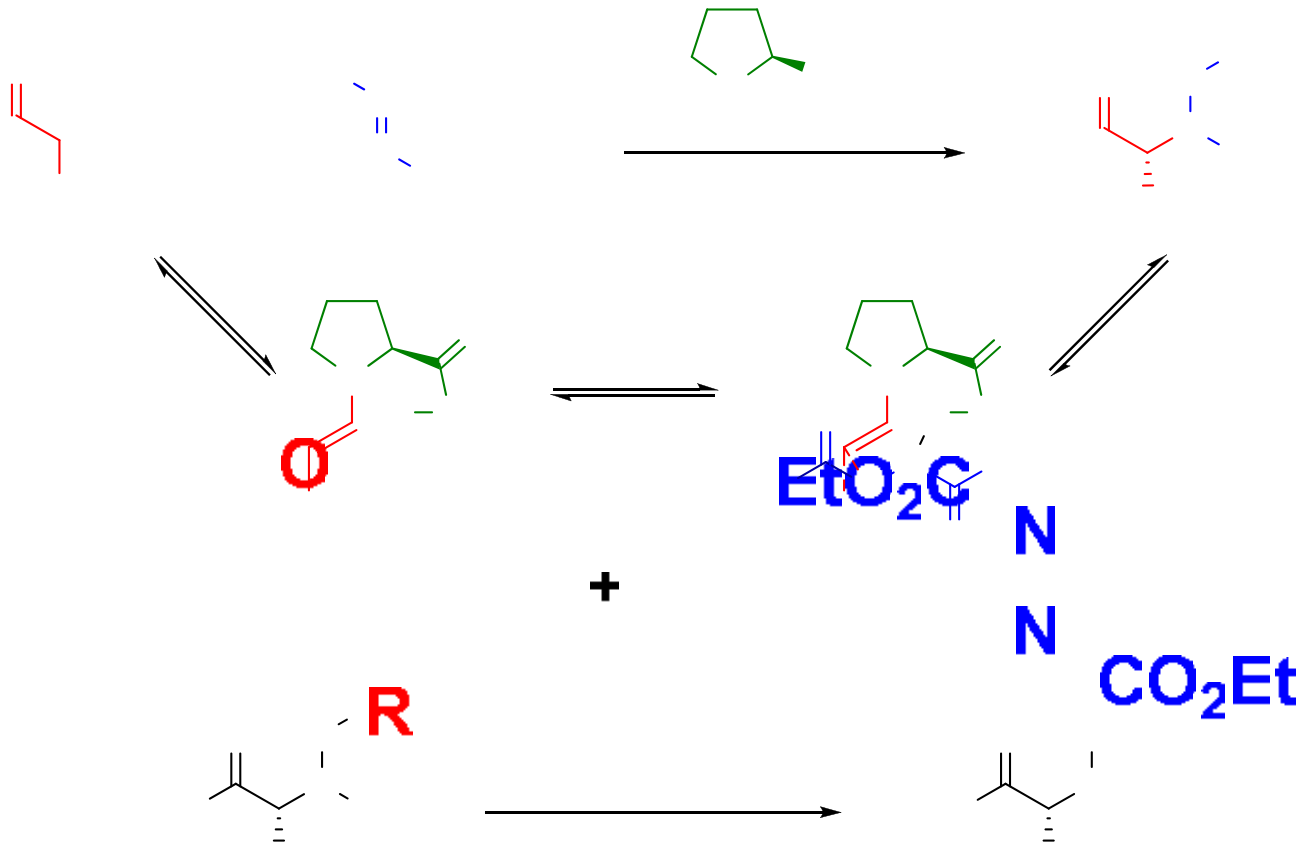
Hayashi: *ACIE* 2005, *44*, 4212

98% ee

Gellman: *JACS* 2008, *130*,5608

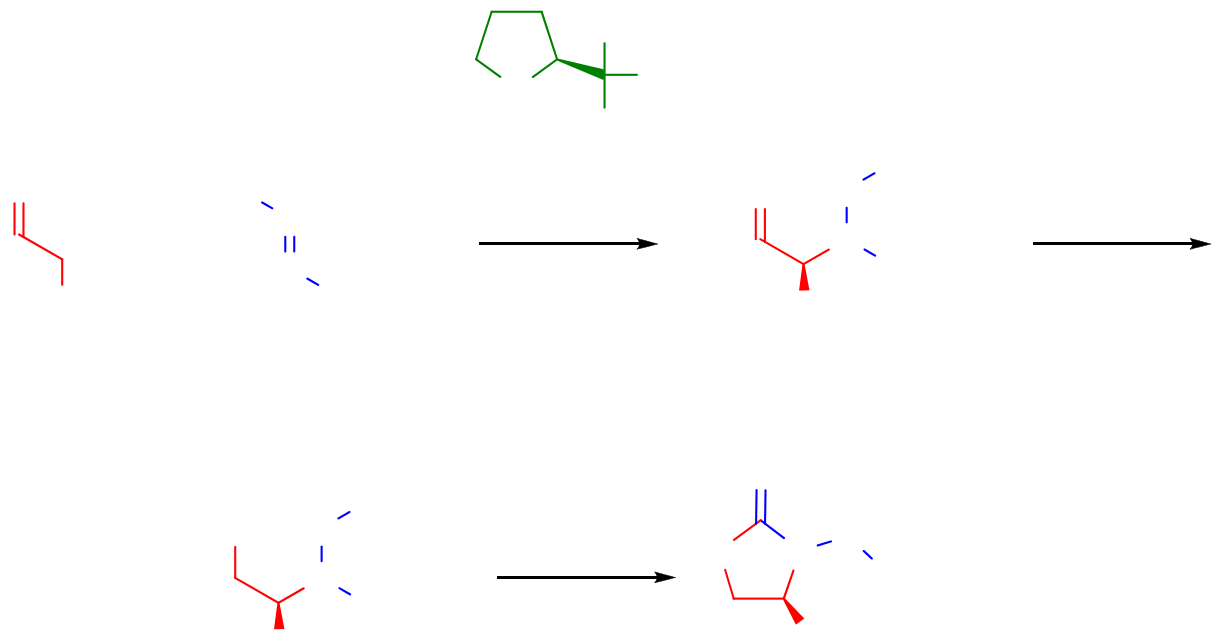
Feature article: Marigo, Jørgensen *Chem. Commun.* 2006, 2001
Bertelsen, Nielsen, Jørgensen *Angew. Chem. Int. Ed.* **2007**, *46*, 7356

α-Amination reactions



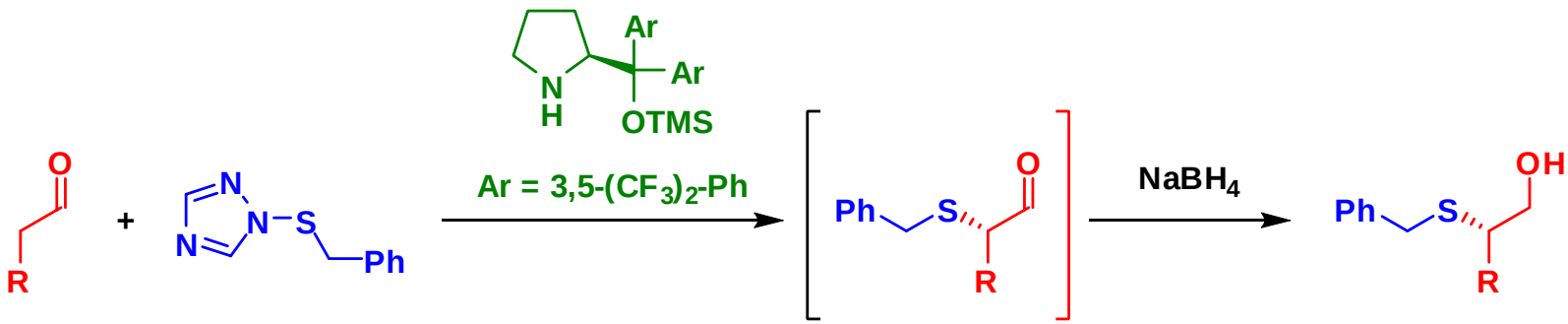
Bøgevig, Kumagurubaran, Juhl, Zhuang, Jørgensen *Angew. Chem. Int. Ed.* **2002**, *41*, 1790
List *J. Am. Chem. Soc.* **2002**, *124*, 5656
Ketones: Kumagurubaran, Juhl, Zhuang, Bøgevig, Jørgensen *J. Am. Chem. Soc.* **2002**, *124*, 6254

New catalyst and scope



Franzén, Marigo, Fielenbach, Wabnitz, Kjærsgaard, Jørgensen *J. Am. Chem. Soc*. **2005**, *127*, 18296

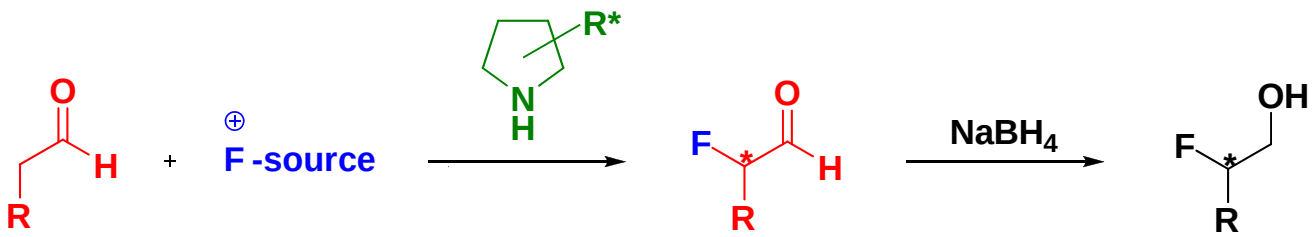
α-Sulfenylation reactions



R	Yield [%]	ee [%]
i-Pr	81	98
Me	60	95
Et	85	96
Bn	94	97
Allyl	64	96
t-Bu	83	95

Marigo, Wabnitz, Fielenbach, Jørgensen *Angew. Chem. Int. Ed.* **2005**, *44*, 792

α-Fluorination

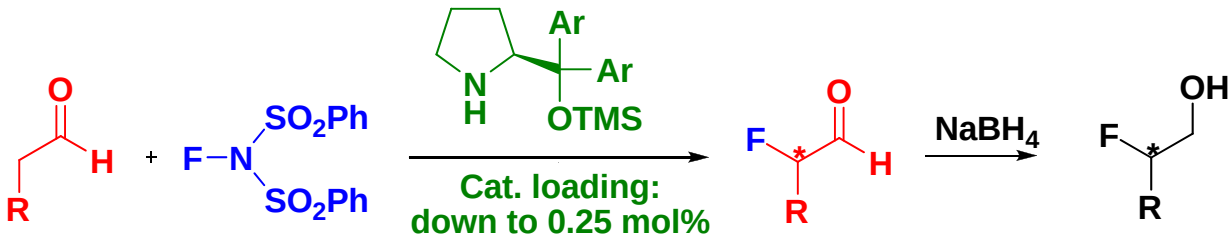


Direct use in pharmaceuticals, agro and material science

Problem-challenge:
α-Fluoro aldehydes are unstable and very volatile - racemization - the high electronegativity of F

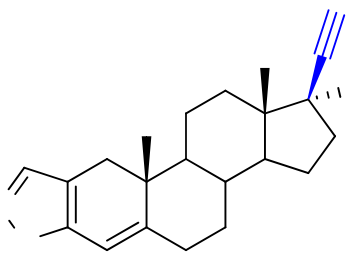
Enders, Hüttl *Synlett*, **2005**, 991
Marigo, Fielenbach, Braunton, Kjærsgaard, Jørgensen *Angew. Chem. Int. Ed.* **2005**, *44*, 3703
Steiner, Mase, Barbas *Angew. Chem. Int. Ed.* **2005**, *44*, 3706
Beeson, MacMillan *J. Am. Chem. Soc*. **2005**, *127*, 8826

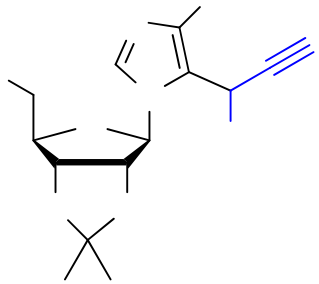
Scope of the reaction

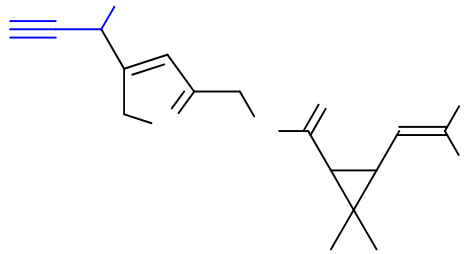


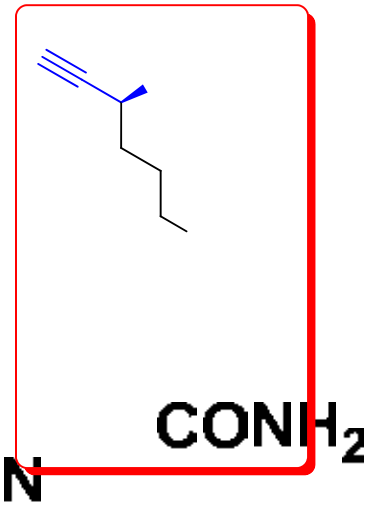
R	Yield	Ee
Pr	>95	96
Bu	>90	91
Hex	55	96
$Bn(CH_2)_3$	64	91
Bn	74	93
Cy	69	96
t-Bu	>90	97
1-Ad	75	96

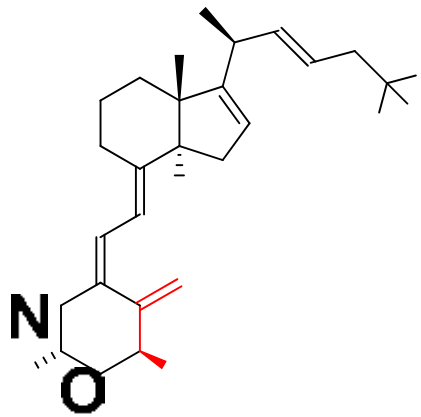
Propagylic and allylic fluorides

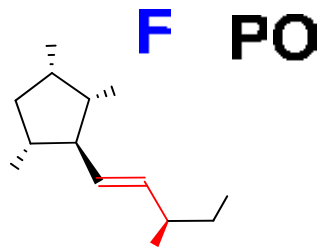


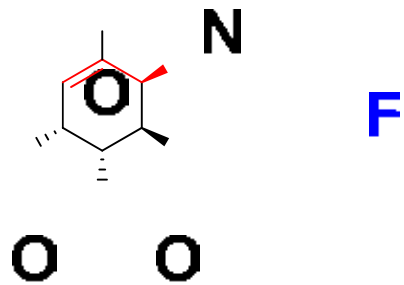






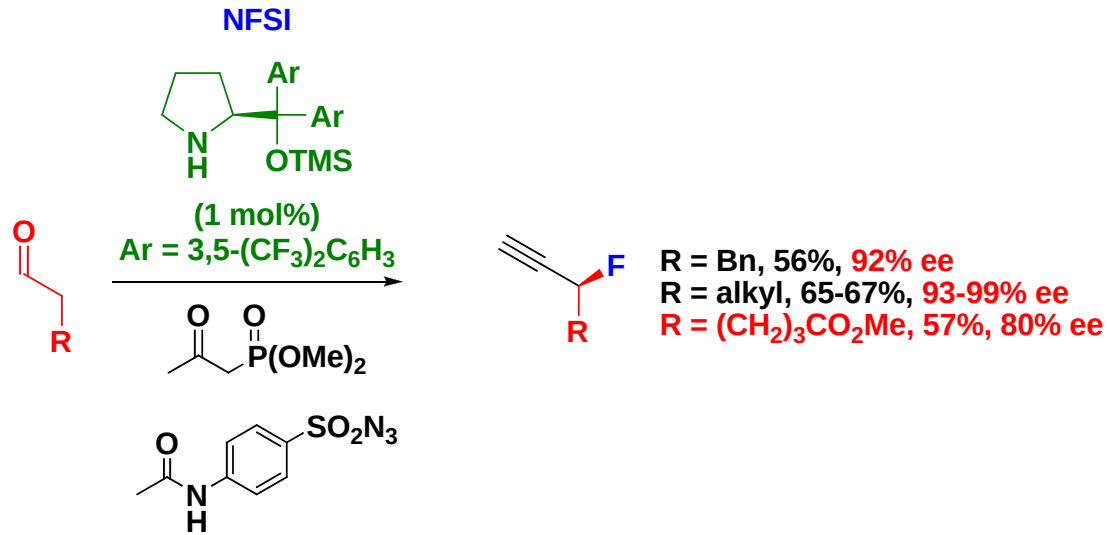


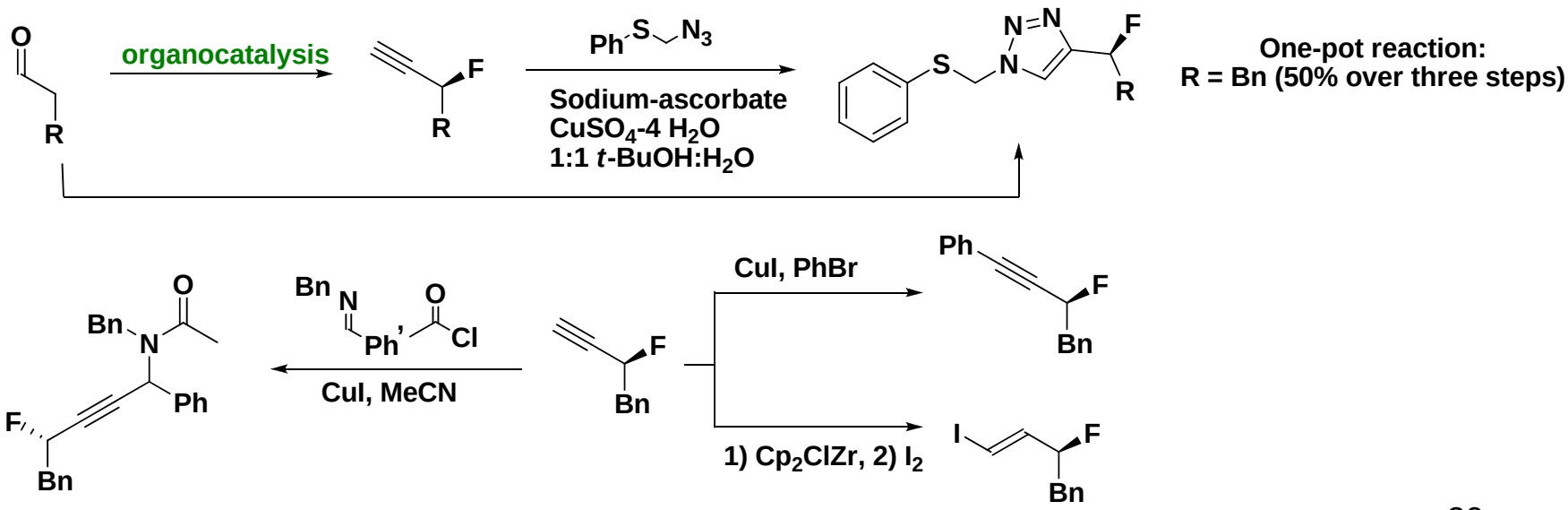




Fluorinated danzol analogue **Fluorinated**

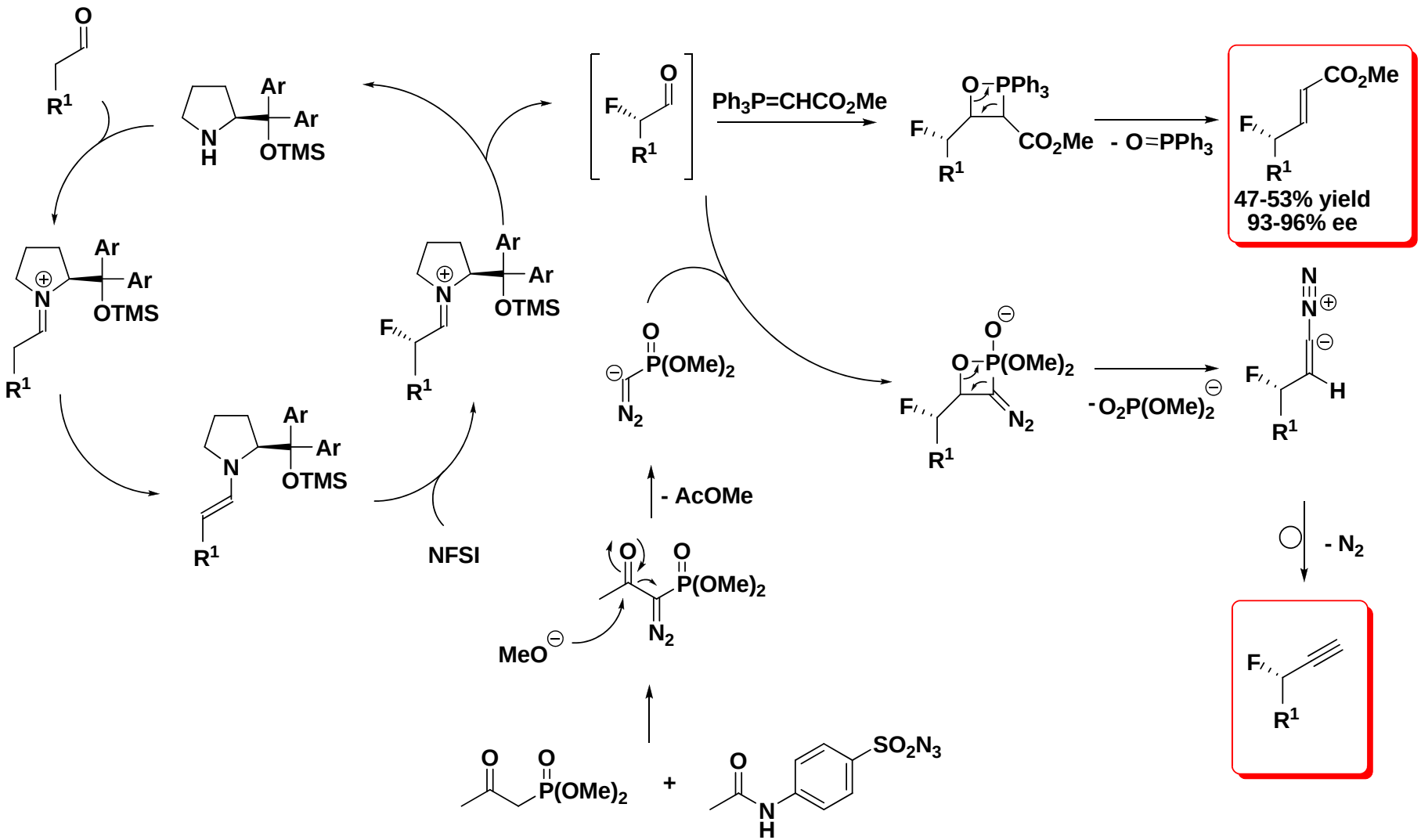
Propagylic fluorides



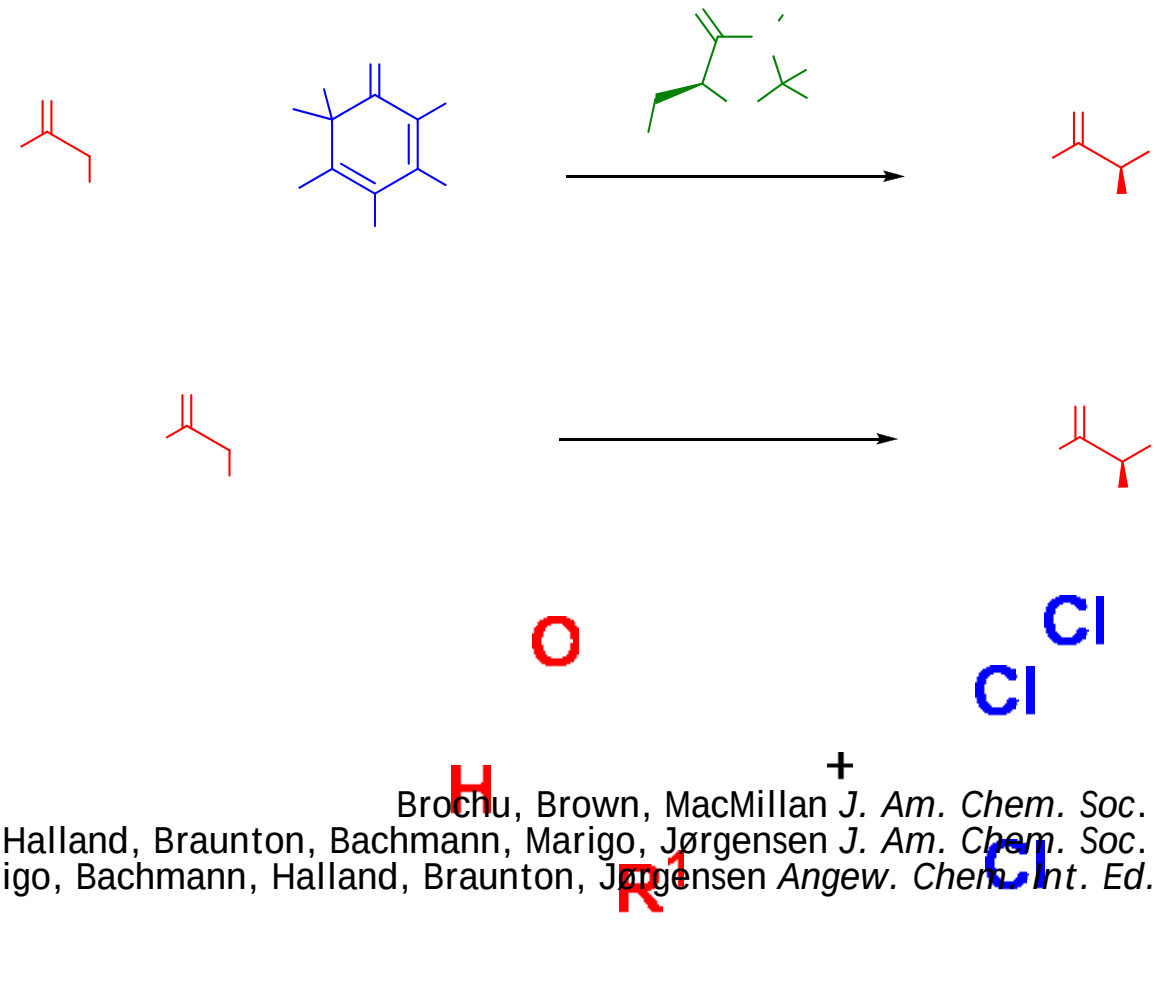


Jiang, Falcicchio, Jensen, Paixão, Bertelsen, Jørgensen *J. Am. Chem. Soc*. **2009**, *131*, 7153

Mechanism

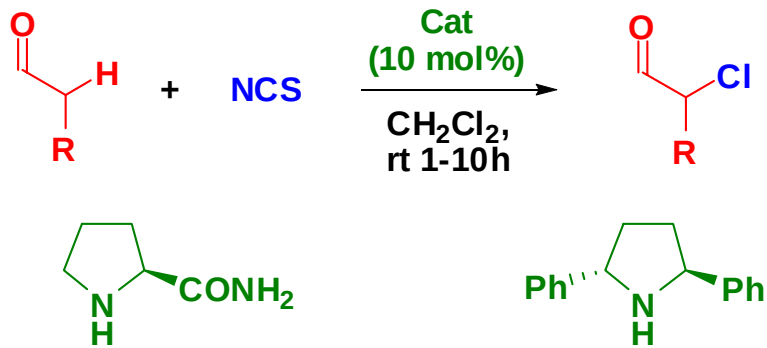


α-Chlorination of aldehydes



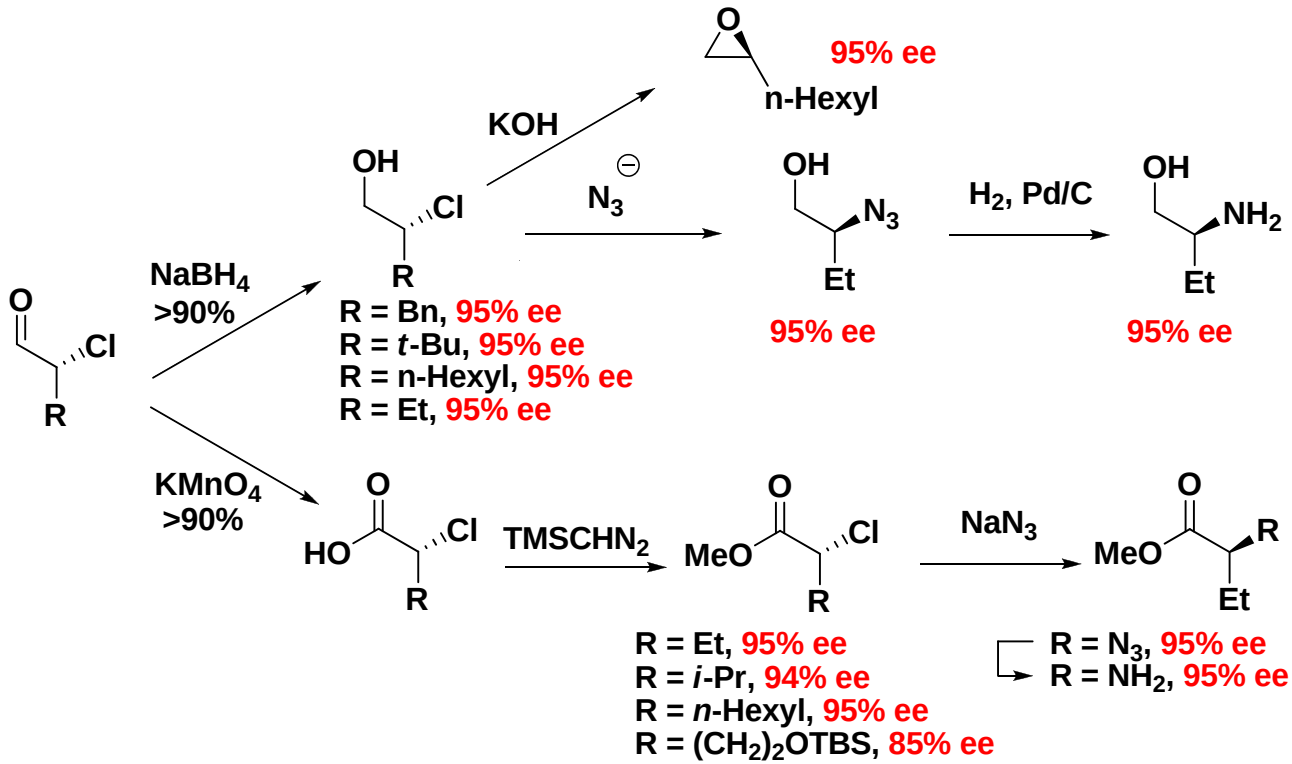
Brochu, Brown, MacMillan *J. Am. Chem. Soc*. **2004**, *126*, 4108
Halland, Braunton, Bachmann, Marigo, Jørgensen *J. Am. Chem. Soc*. **2004**, *126*, 4790
Ketones see: Marigo, Bachmann, Halland, Braunton, Jørgensen *Angew. Chem. Int. Ed.* **2004**, *43*, 5507

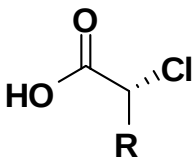
Variation in aldehydes



R	Yield	Ee	Yield	Ee
Me	99	75	-	-
Et	99	80	90	95
i-Pr	95	87	90	94
t-Bu	93	95	-	-
n-Hex	95	70	99	95
Allyl	90	74	90	95
CH_2Ph	75	78	82	95
$(CH_2)_2OTBS$	75	85	95	81

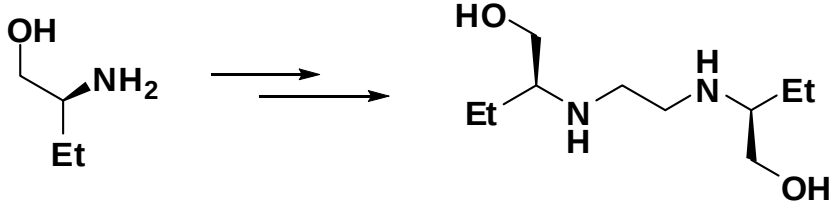
Synthetic manipulations





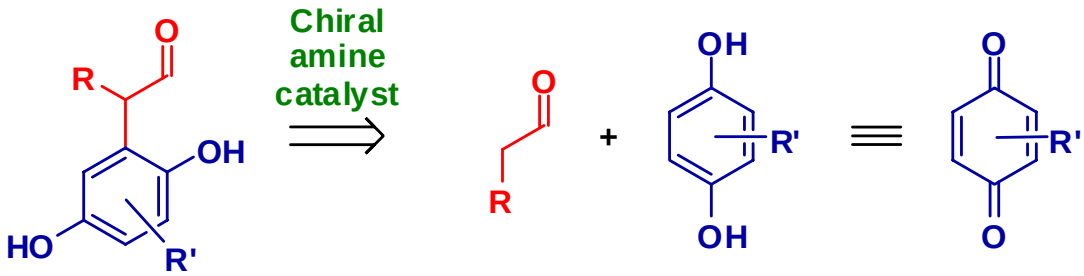
Prepared in multi-tons scale/year

One of the most important amino alcohols
ACIE 2004, *43*, 788

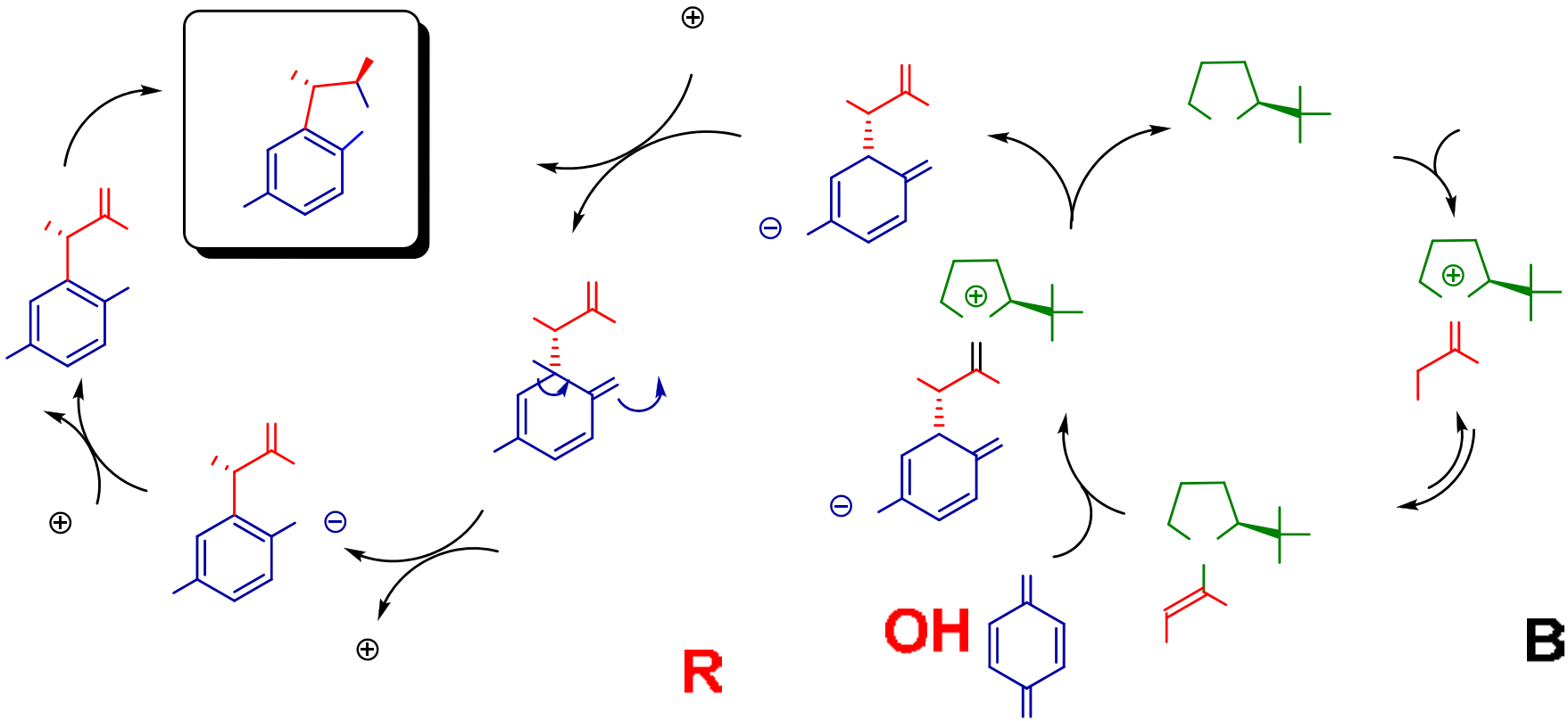


Tuberculostatic etambutol

α-Arylation

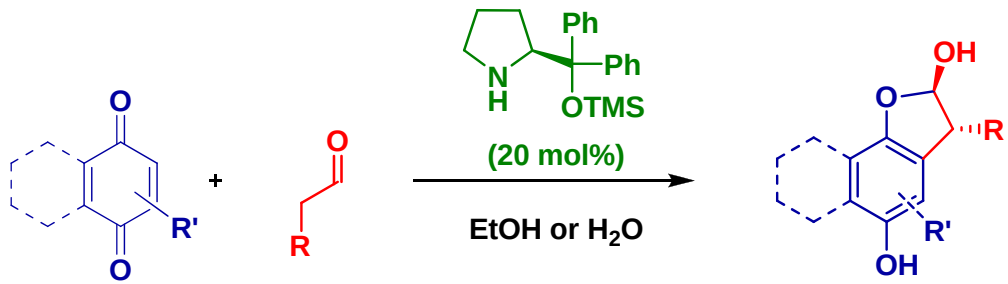


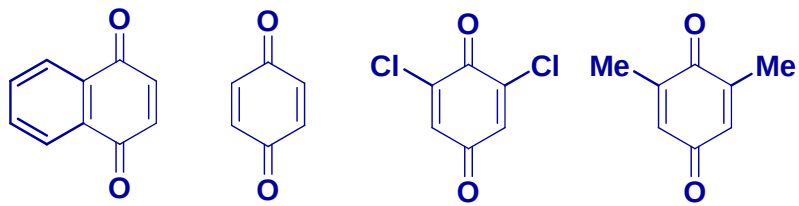
Mechanism – two catalytic cycles

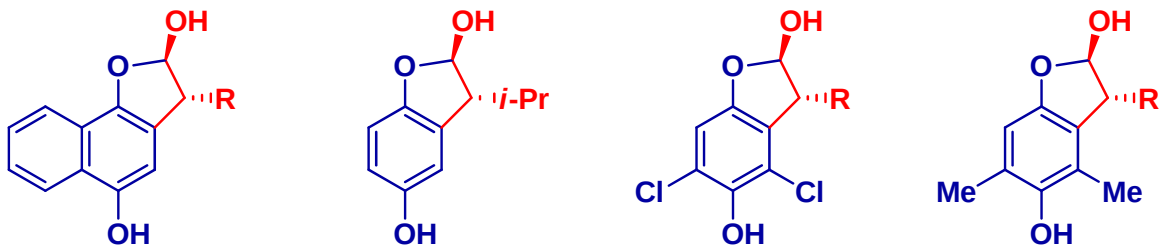


Aleman, Cabrera, Maerten, Overgaard, Jørgensen *Angew. Chem. Int. Ed.* **2007**, *46*, 5520

α-Arylation of aldehydes







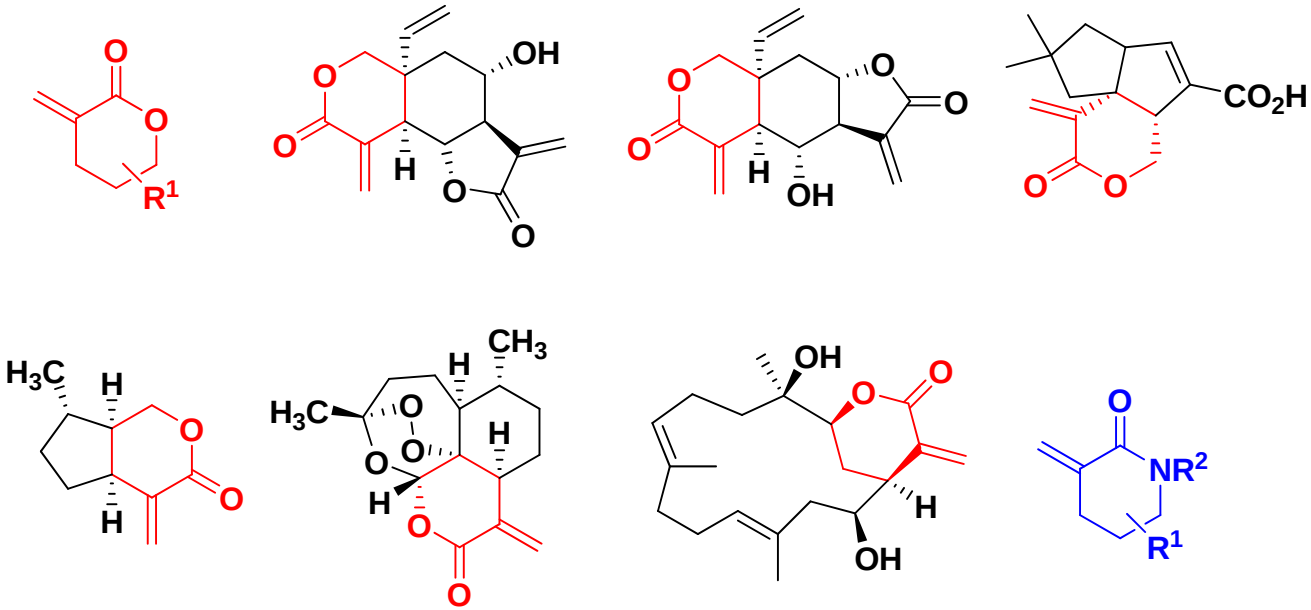
R = alkyl
86% - quant yield
96 - >99% ee

52% yield
99% ee

R = alkyl
65-95% yield
96 - >99% ee

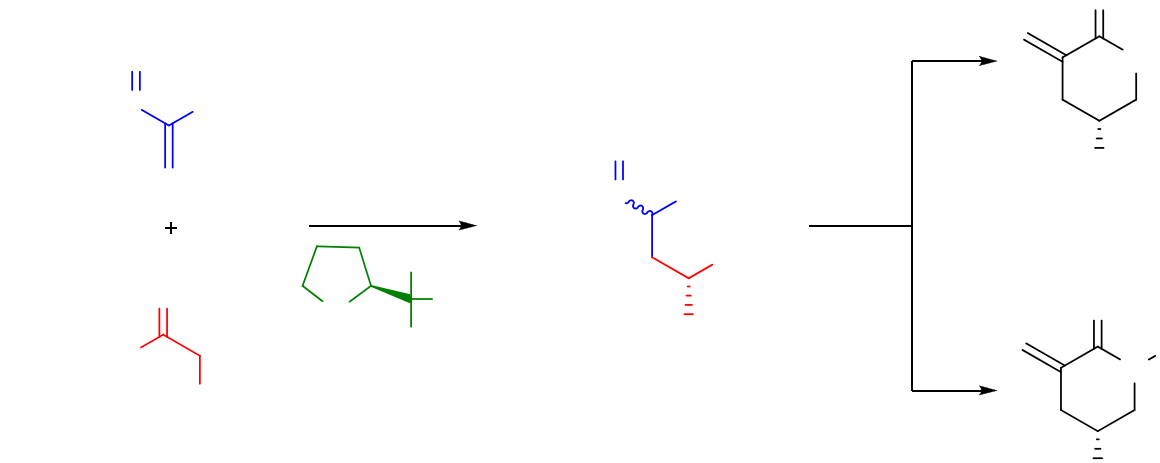
R = alkyl
72-85% yield
>98% ee

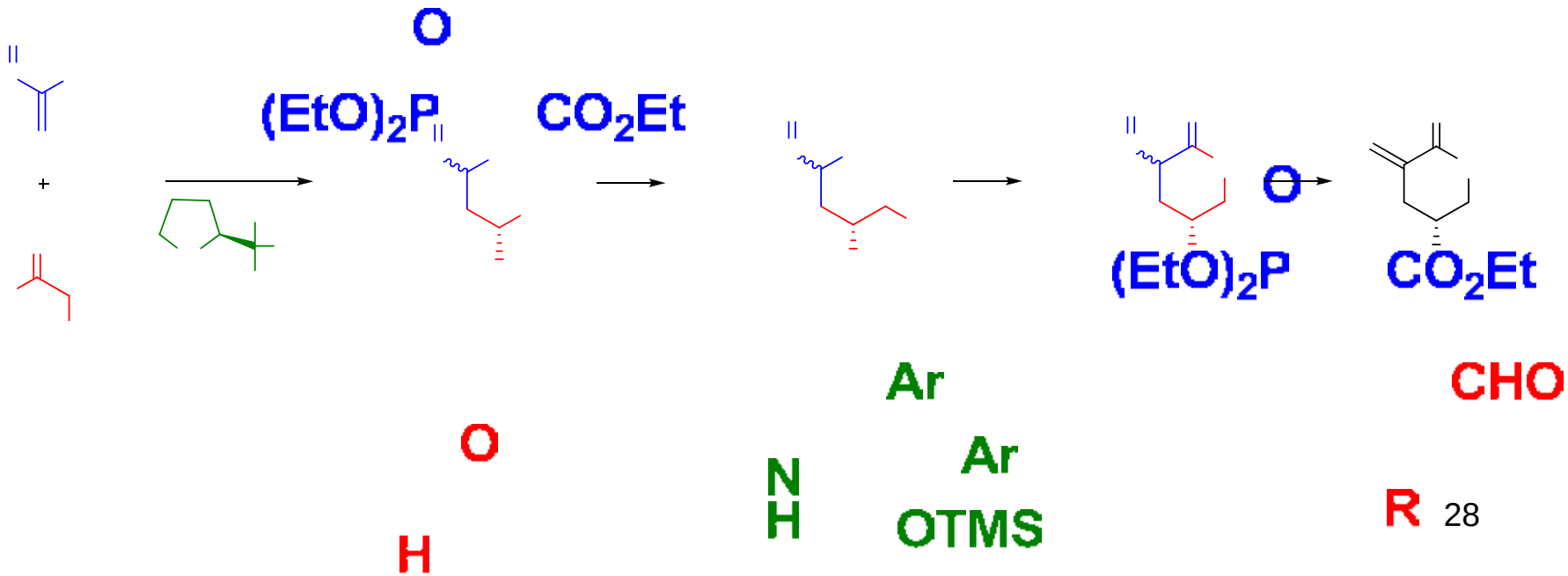
*Application - **α**-methylene-**δ**-lactones and **δ**-lactams*



Albrecht, Richter, Krawczyk, Jørgensen *J. Org. Chem*. **2008**, 73, 8337

α-Methylene-δ-lactones and δ-lactams



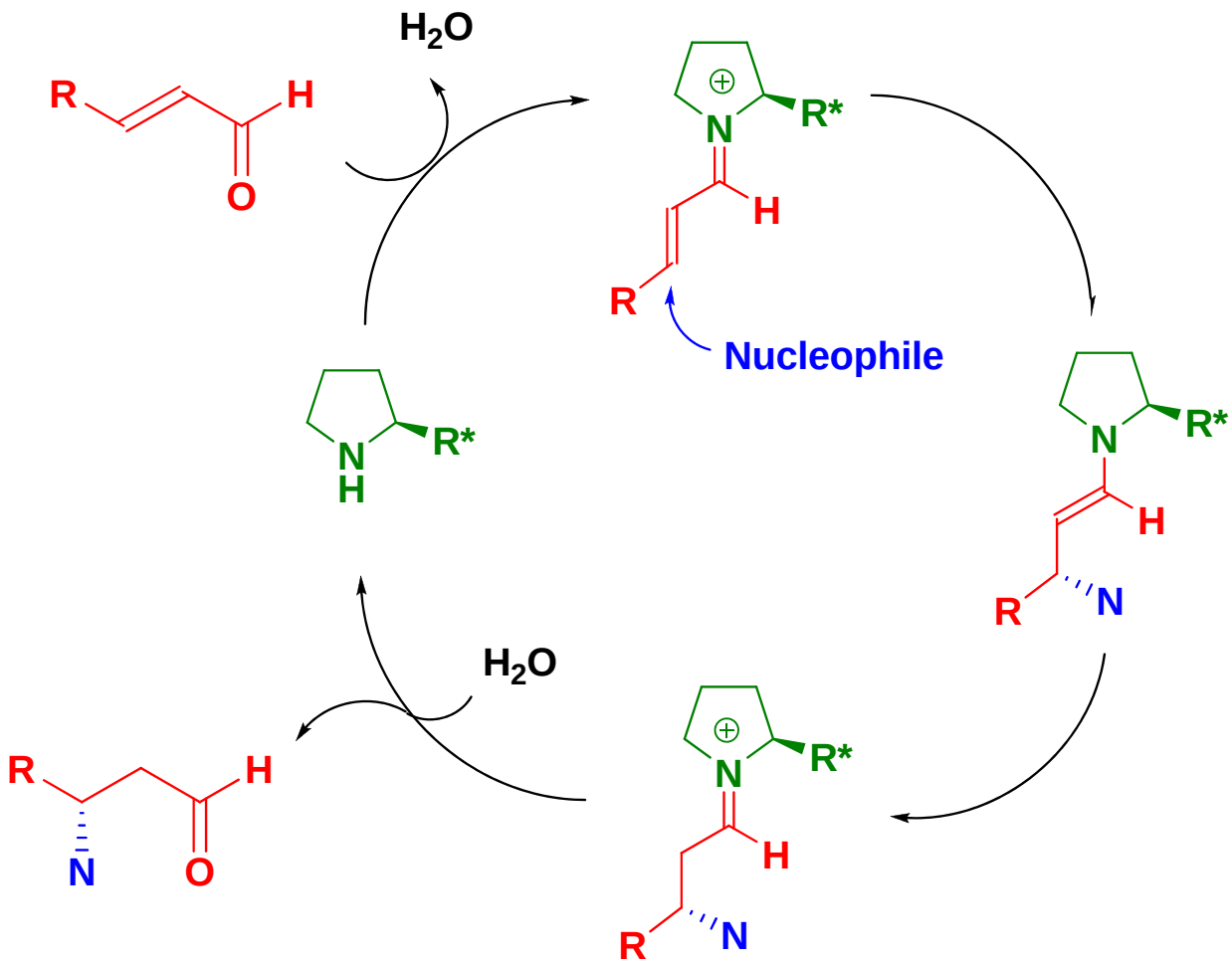


From α- to β-functionalization

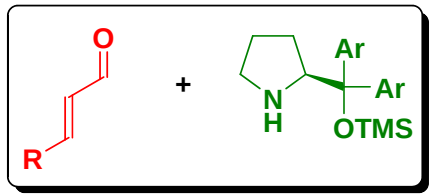
Jorge Cham – www.phdcomics.com

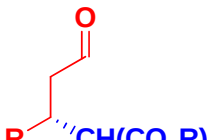
Aldehyde activation

α,β-Unsaturated aldehydes

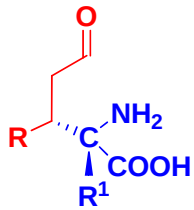


β-Functionalization of α,β-unsaturated aldehydes

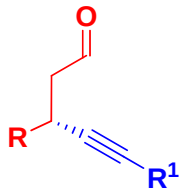




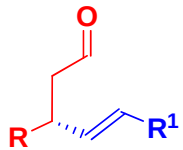
95% ee
ACIE 2006, *45*, 4305



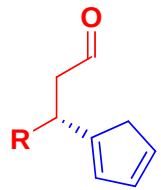
96% ee
JACS 2008, *130*, 12031



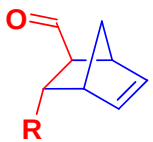
97% ee
JACS 2009, *131*, in press



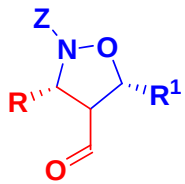
>20:1 (*E*):(*Z*); 97% ee
JACS 2009, *131*, in press



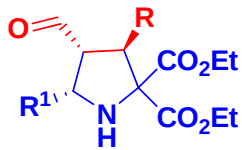
95% ee
Hayashi: *ACIE* 2006, *45*, 6853



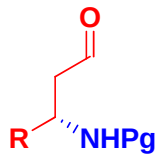
95% ee
Hayashi: *OrgLett* 2007, *9*, 2859



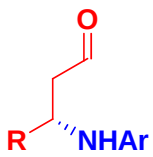
96% ee
Chow: *TetLett* 2007, *48,* 277
Cordova: *TetLett* 2007, *48,* 5701



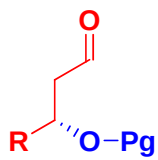
98% ee
Cordova: *TetLett* 2007, *48,* 6252



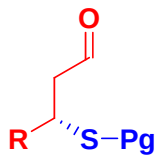
98% ee
ChemEurJ 2007, *13,* 9068
Cordova: *ChemCommun* 2007, 849



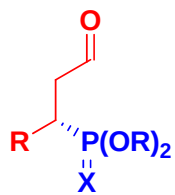
94% ee
ACIE 2007, *46*, 1983



97% ee
JACS 2007, *129,* 1536

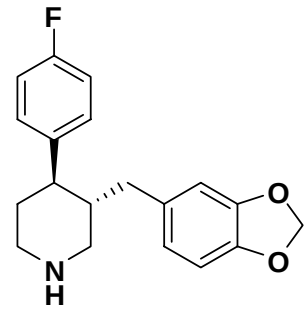


97% ee
JACS 2005, *127,* 15710

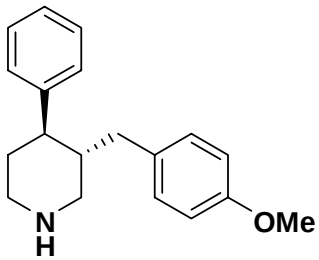


97% ee
Melchiorre: *ACIE* 2007, *46*, 4504
Cordova: *ACIE* 2007, *46*, 4507
JOC 2007, *72*, 8893

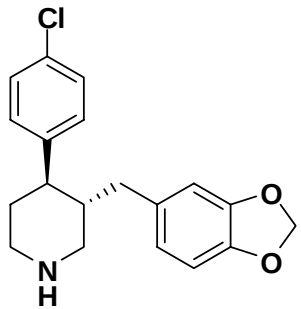
Application



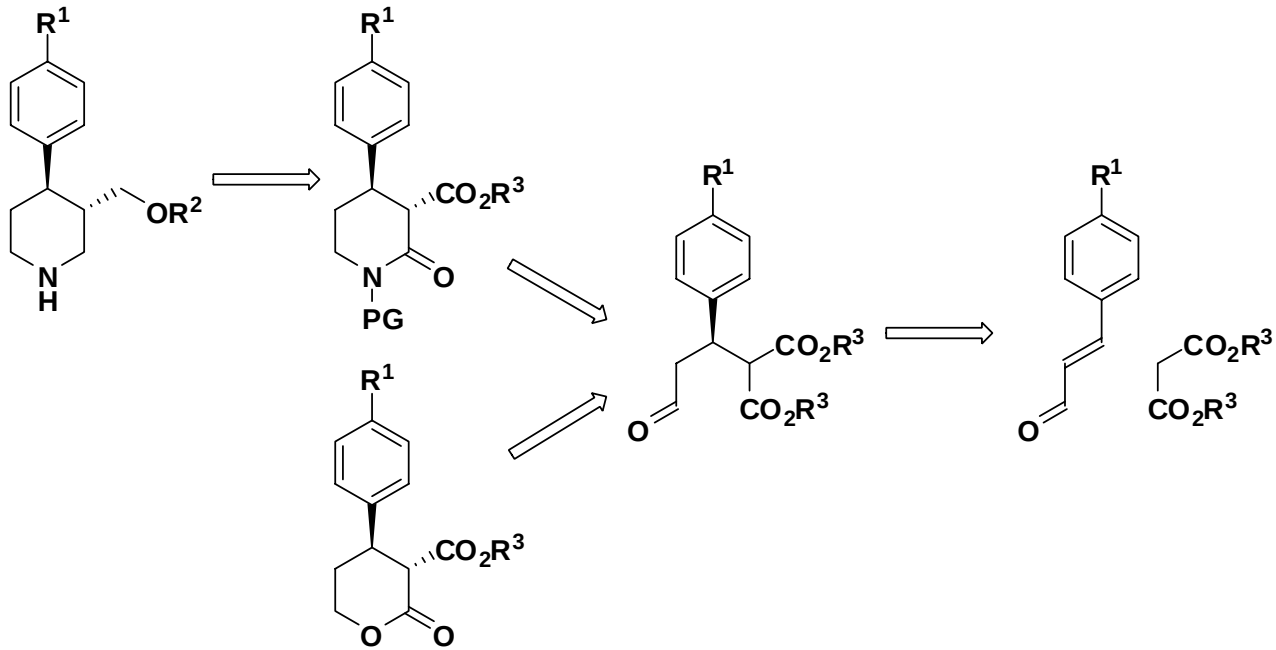
Paroxetine



Fermoexetine

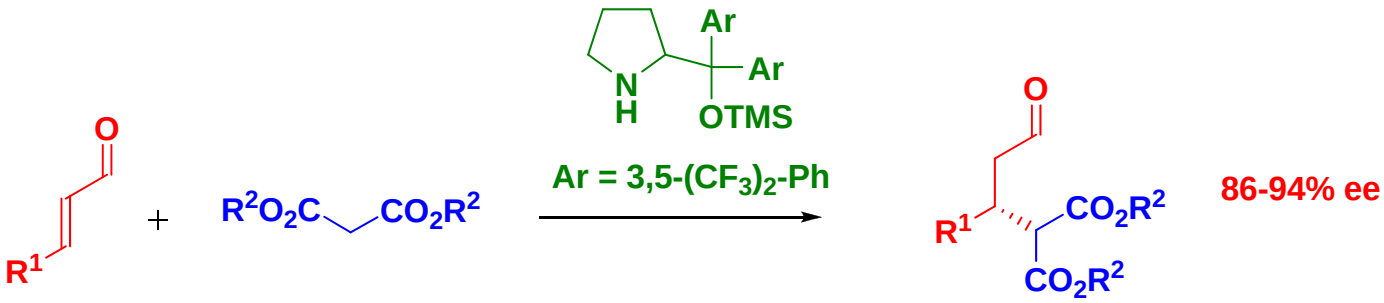


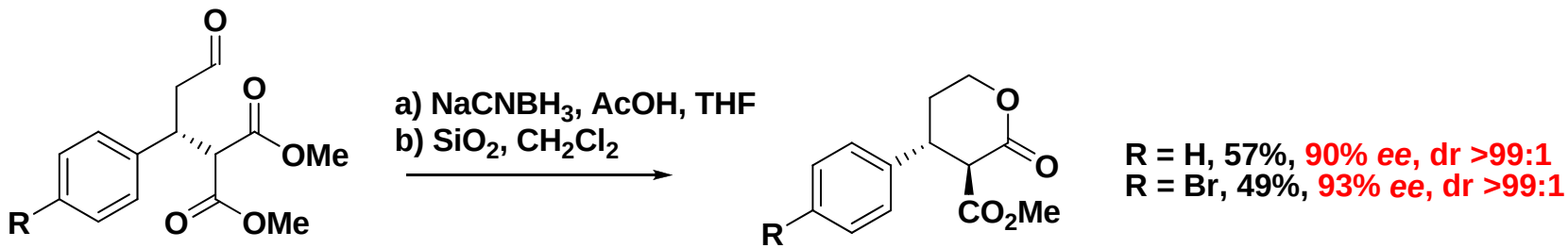
Rosche-1
Peptidomimetic inhibitor

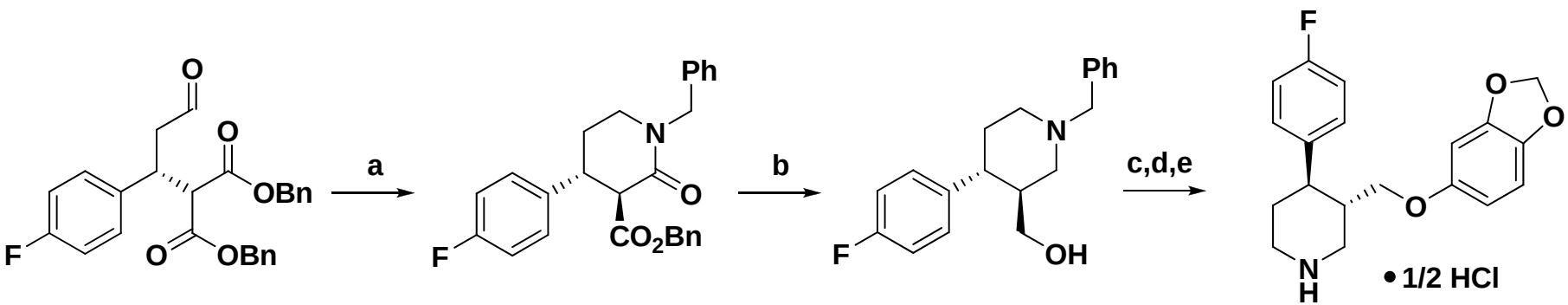


Brandau, Landa, Franzén, Marigo, Jørgensen *Angew. Chem. Int. Ed.* **2006**, *45*, 4305

Application

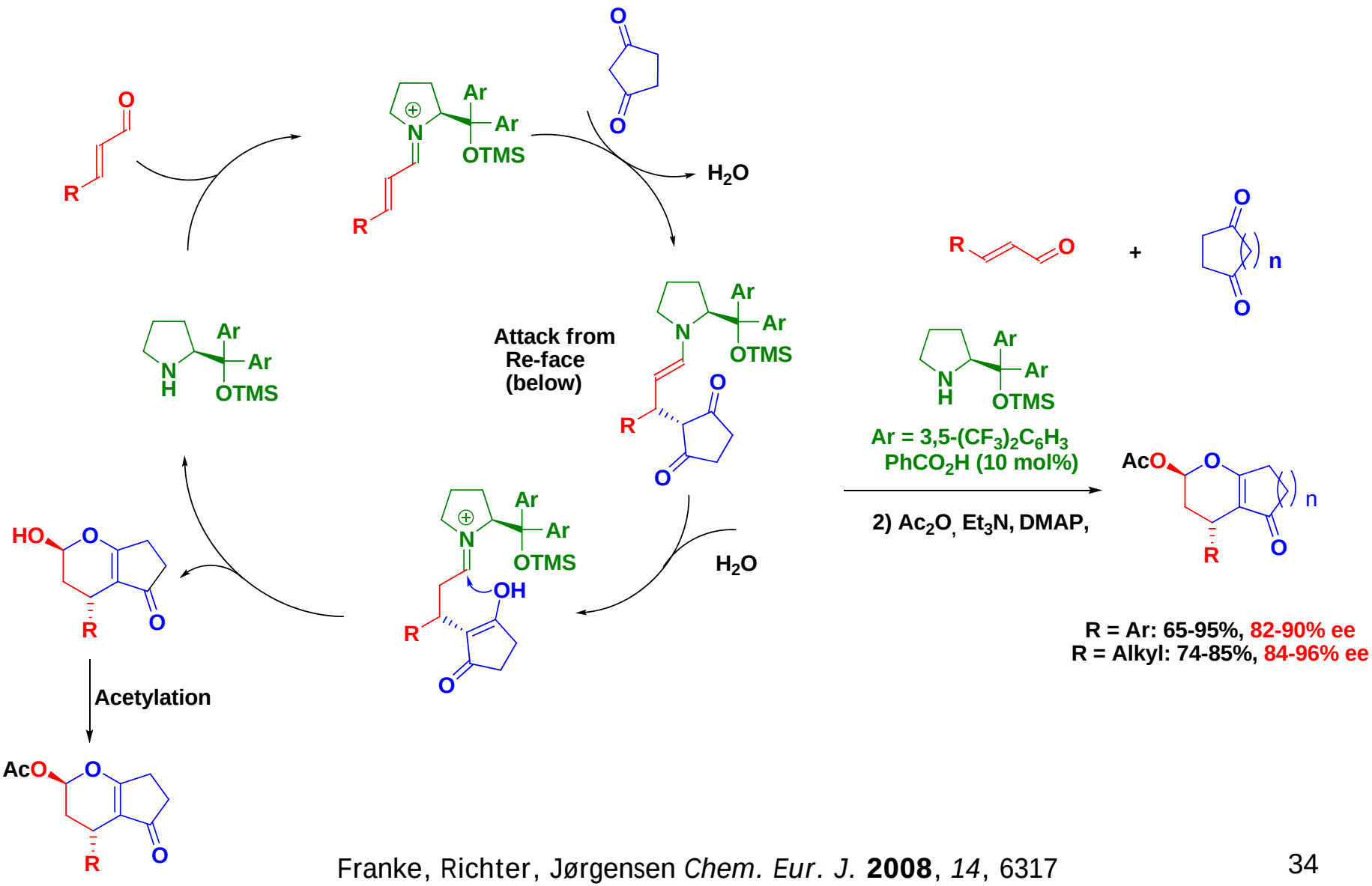






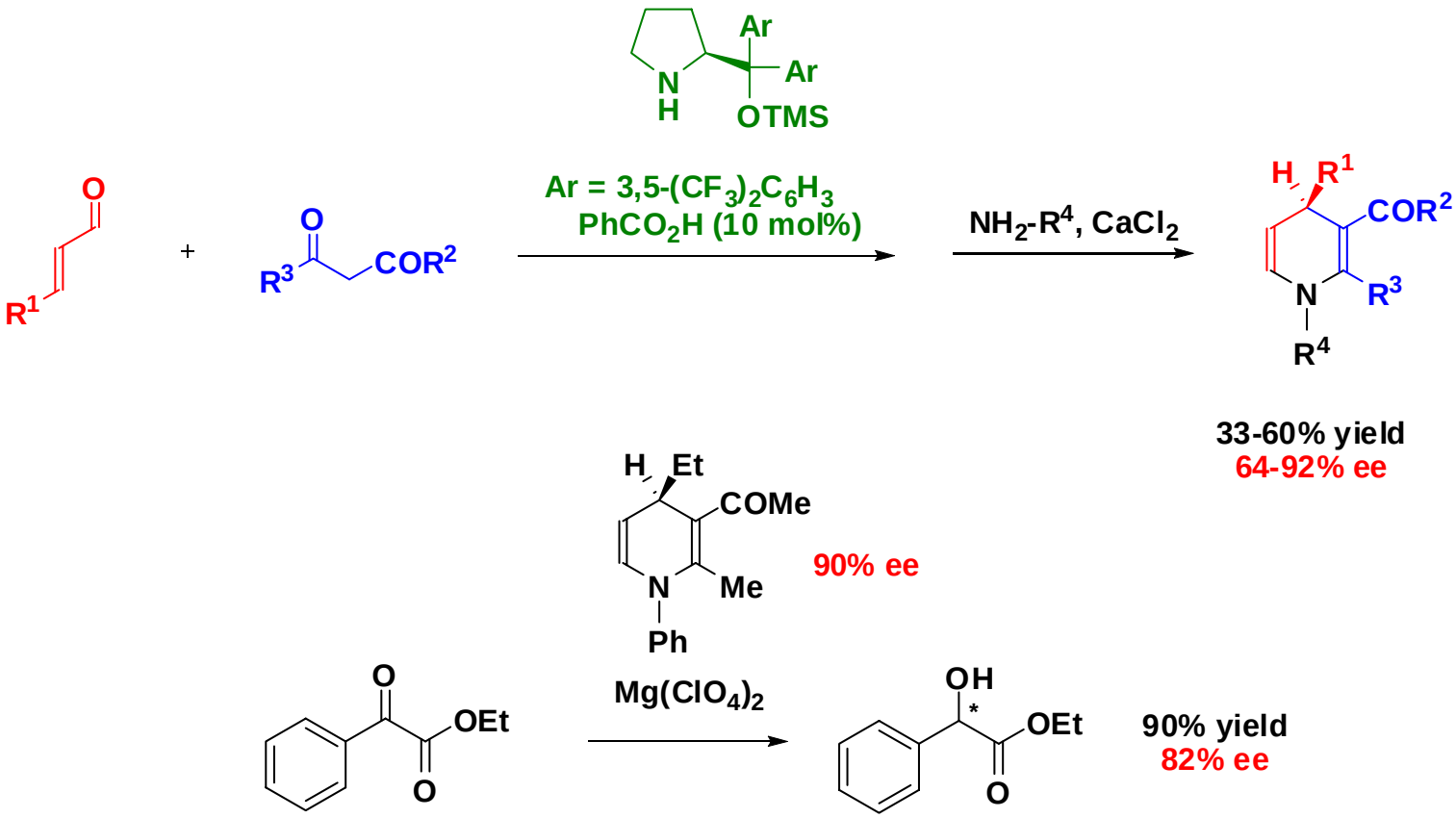
Synthesis of (-)-paroxetine: a) $PhCH_2NH_2$, $NaBH(OAc)_3$, dioxane, 70%; b) $LiAlH_4$, THF; c) MsCl, NEt_3, toluene; d) sesamol, NaH, DMF, 60 °C; e) i) H_2, 5% Pd/C; ii) HCl.

Optically active 3,4-dihydropyran derivatives



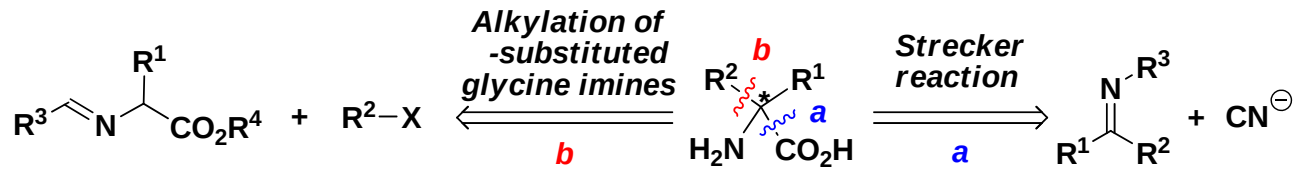
Franke, Richter, Jørgensen *Chem. Eur. J.* **2008**, *14*, 6317

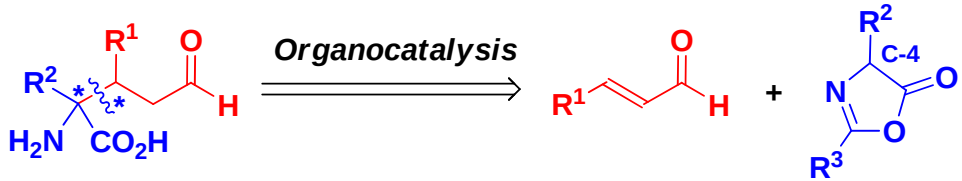
Optically active 1,4-dihydropyridines



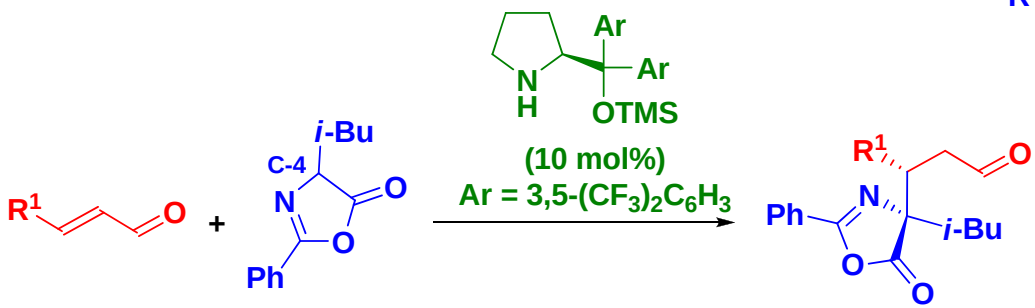
Franke, Johansen, Bertelsen, Jørgensen *Chem. Asian J.* **2008**, 3, 196

Application to amino acid synthesis

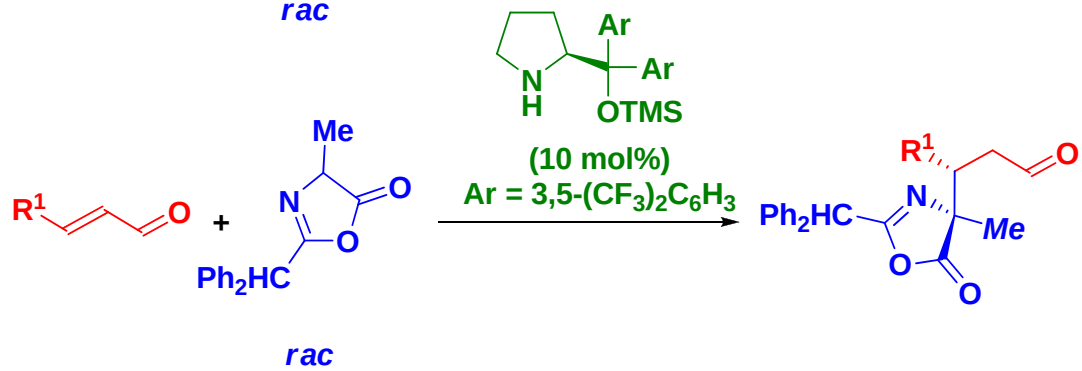




α



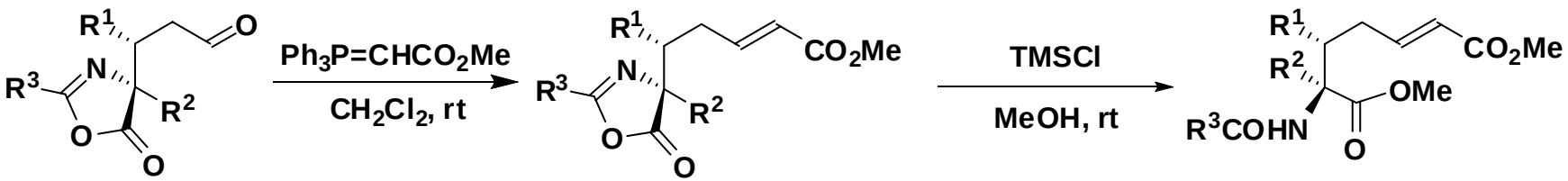
R^1: aryl: dr up to 20:1, 94%
R^1: alkyl: dr up to 7:1, 94%



R^1: aryl: dr up to 20:1, 96%
R^1: alkyl: dr up to >20:1, 94%

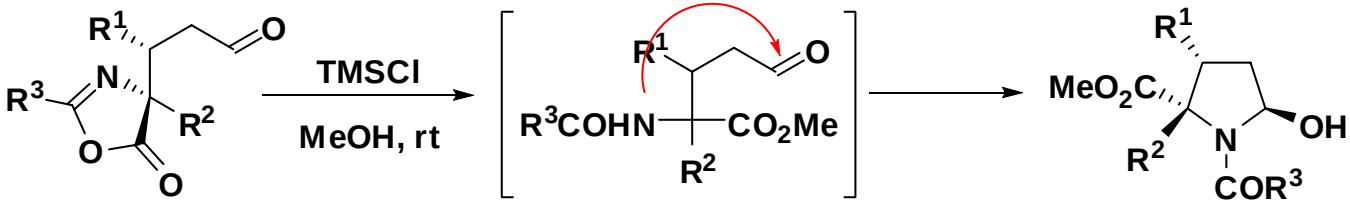
Cabrera, Reyes, Alemán, Mielli, Jørgensen *J. Am. Chem. Soc.* **2008**, *208*, 12031

Application to amino acid synthesis



60-92% yield

50-99% yield

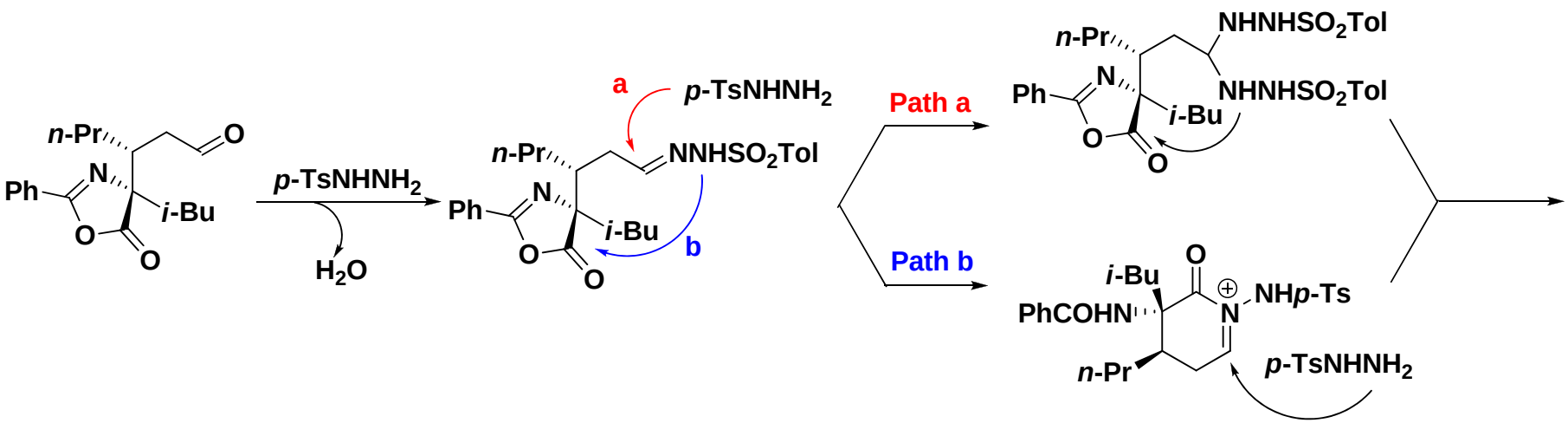


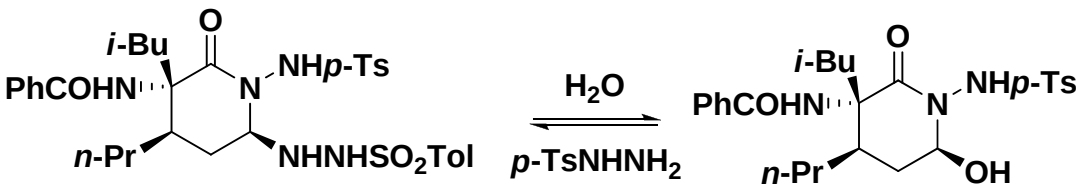
carbapenem antibiotics intermediate

R^1 = *n*-Pr, R^2 = *i*-Bu, R^3 = Ph (71% yield)

R^1 = Et, R^2 = *i*-Bu, R^3 = *o*-ClC_6H_4 (90% yield)

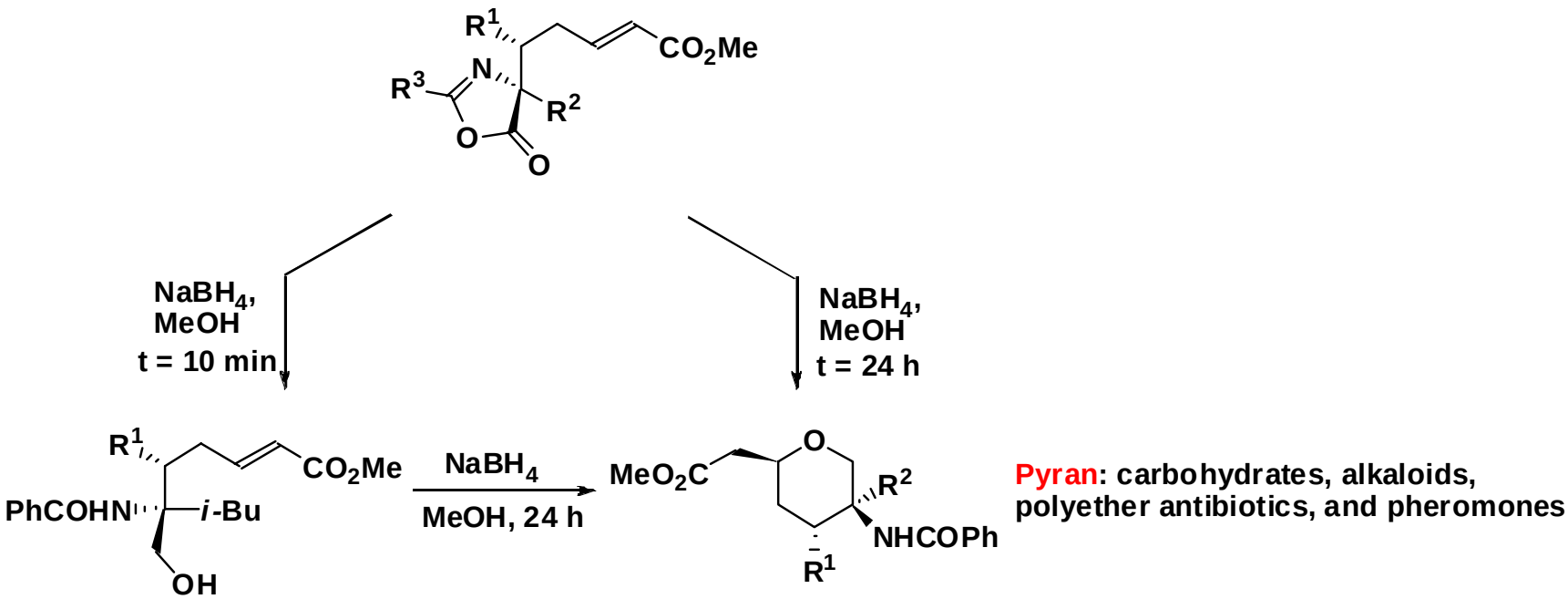
Application to amino acid synthesis





60 cyclic depsipeptides from cyanobacter

Application to amino acid synthesis

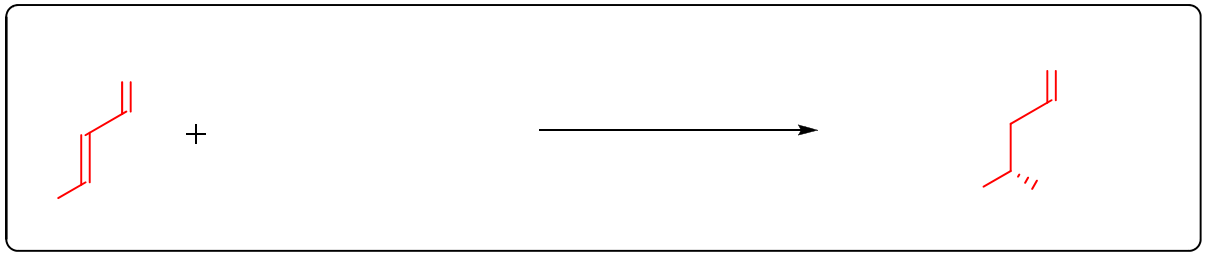


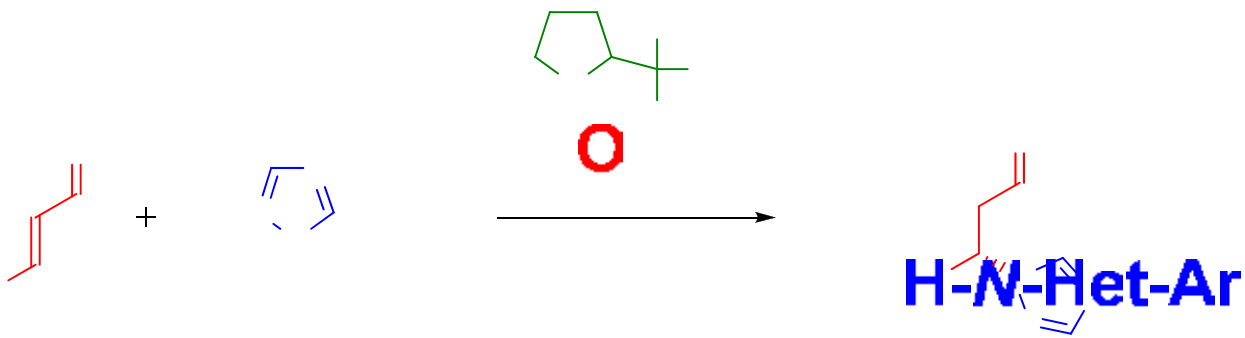
Pyran: carbohydrates, alkaloids, polyether antibiotics, and pheromones

R^1 = *n*-Pr (75% yield)
R^1 = (*Z*)-*n*-hex-3-enyl (65% yield)

R^1 = *n*-Pr, R^2 = *i*-Bu (80% yield)
R^1 = Et, R^2 = $MeSCH_2CH_2$ (40% yield)

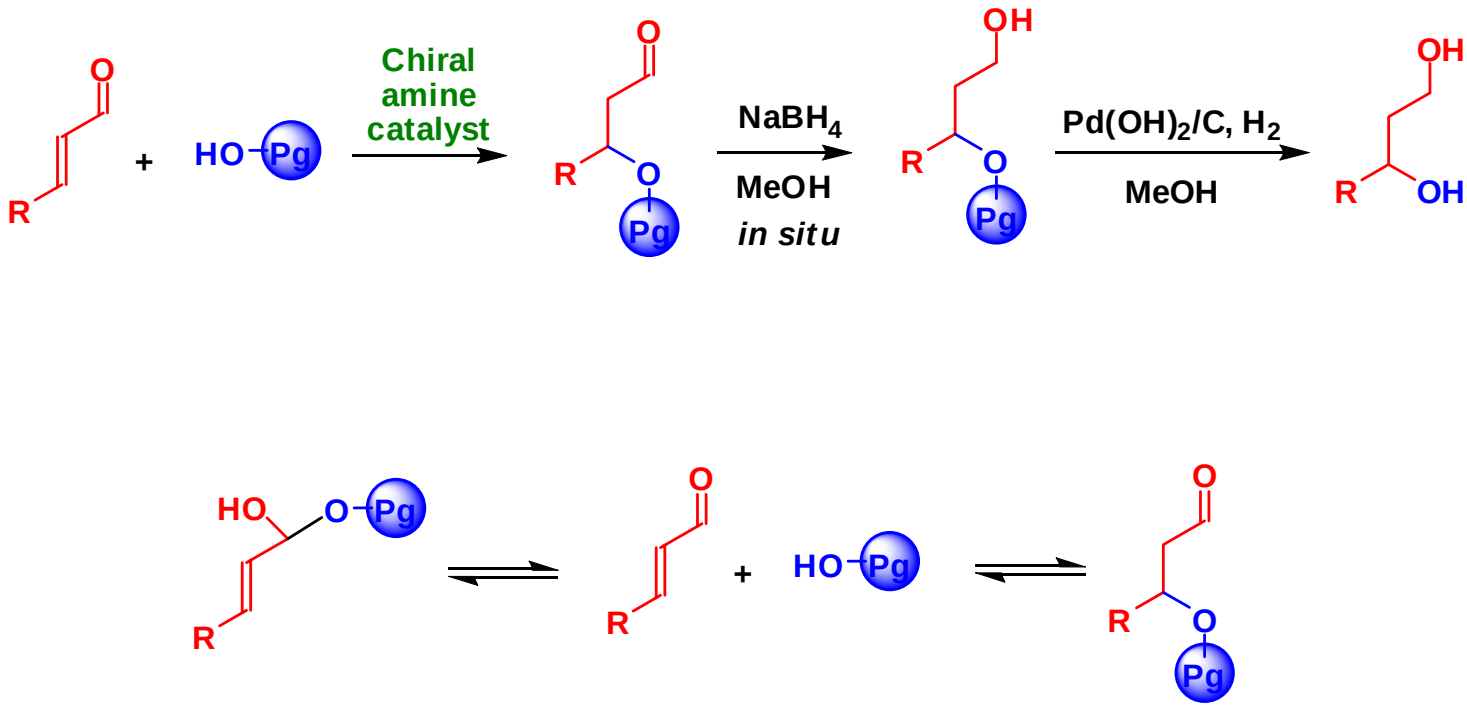
N-Heterocycle conjugate addition to α,β-unsaturated aldehydes





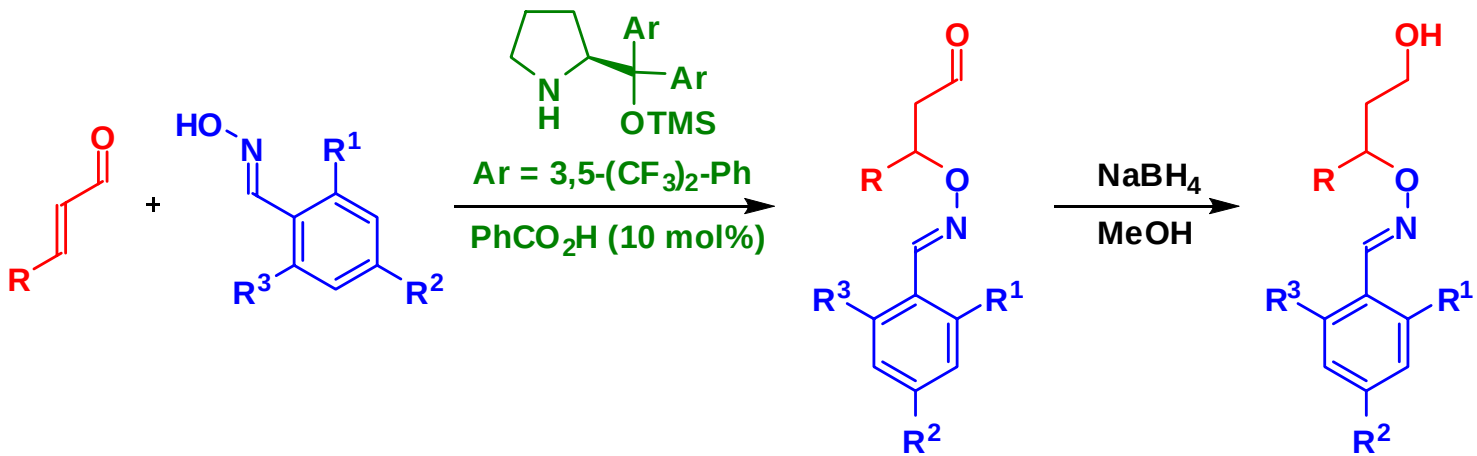
Dinér, Nielsen, Marigo, Jørgensen *Angew. Chem. Int. Ed.* **2007**, *46*, 1983

β-Hydroxylation of α,β-unsaturated aldehydes

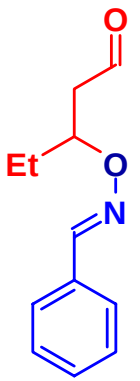


Bertelsen, Dinér, Johansen, Jørgensen *J. Am. Chem. Soc.* **2007**, *129*, 1536

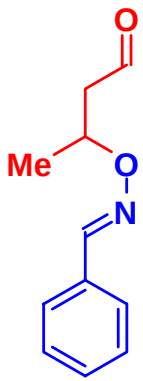
β-Hydroxylation of α,β-unsaturated aldehydes



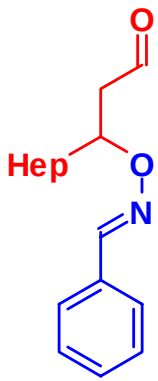
anitinflamatory agents
penicillin and cephalosporin analogues
sex phermone analogues



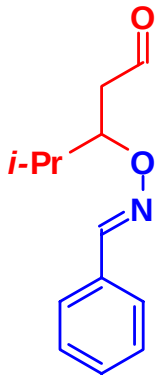
72% yield
95% ee



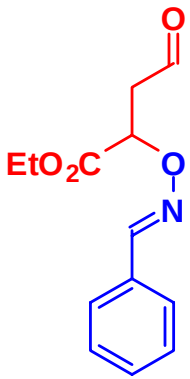
72% yield
95% ee



64% yield
95% ee

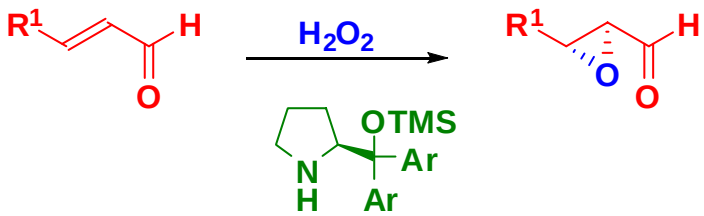


62% yield
97% ee

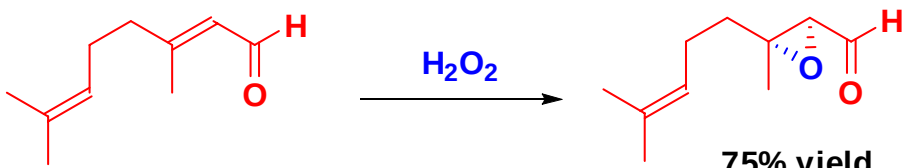


60% yield
88% ee

Asymmetric epoxidations



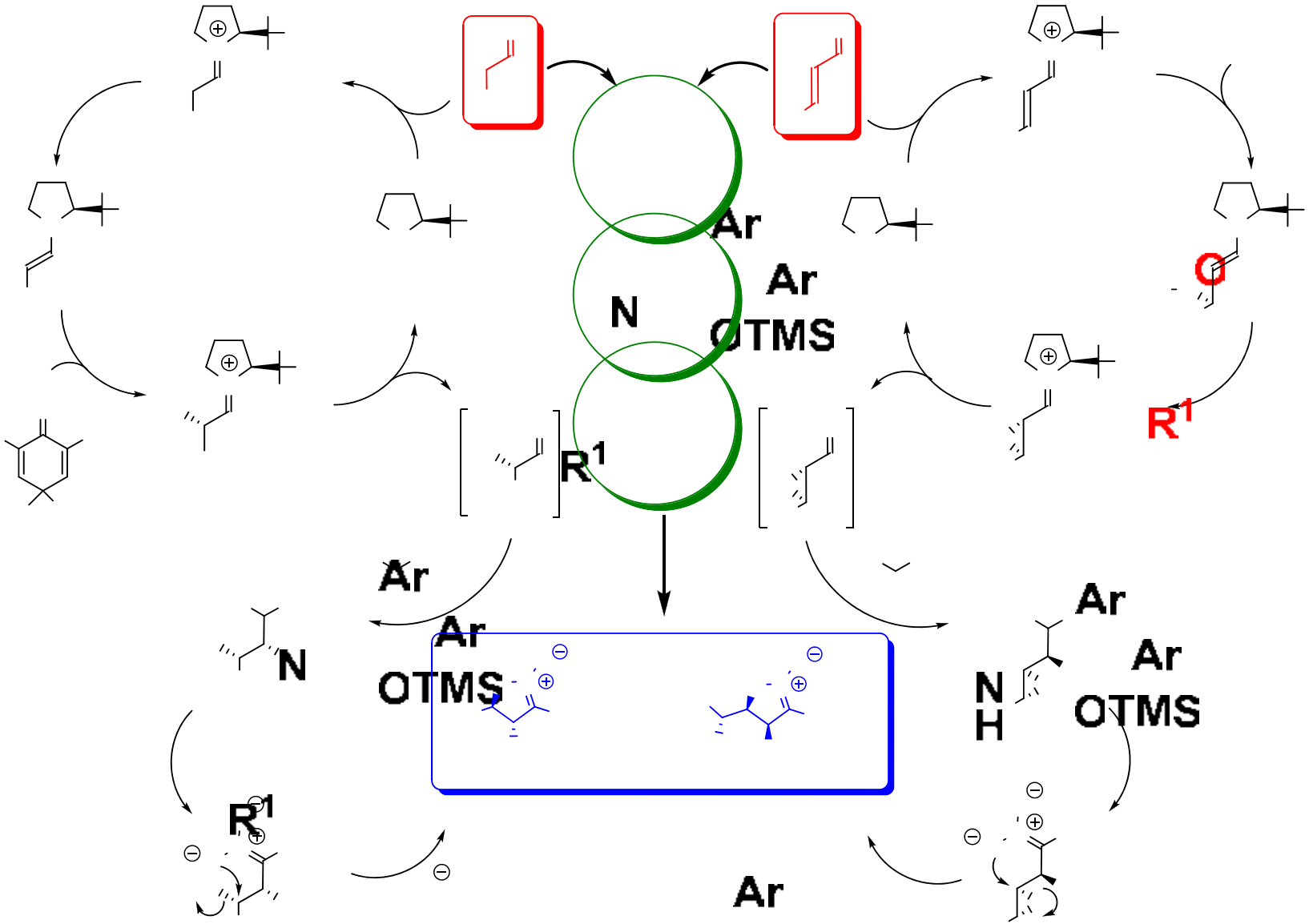
R^1	Yield	dr	ee
Ph	80	93:7	96
o-NO_2-Ph	90	91:9	97
o-Me-Ph	65	90:10	96
p-Cl-Ph	63	95:5	98
Et	90	97:3	96
i-Pr	75	98:2	96
CH_2OBn	85	94:4	94
CO_2Et	60	90:10	96



75% yield
85% ee

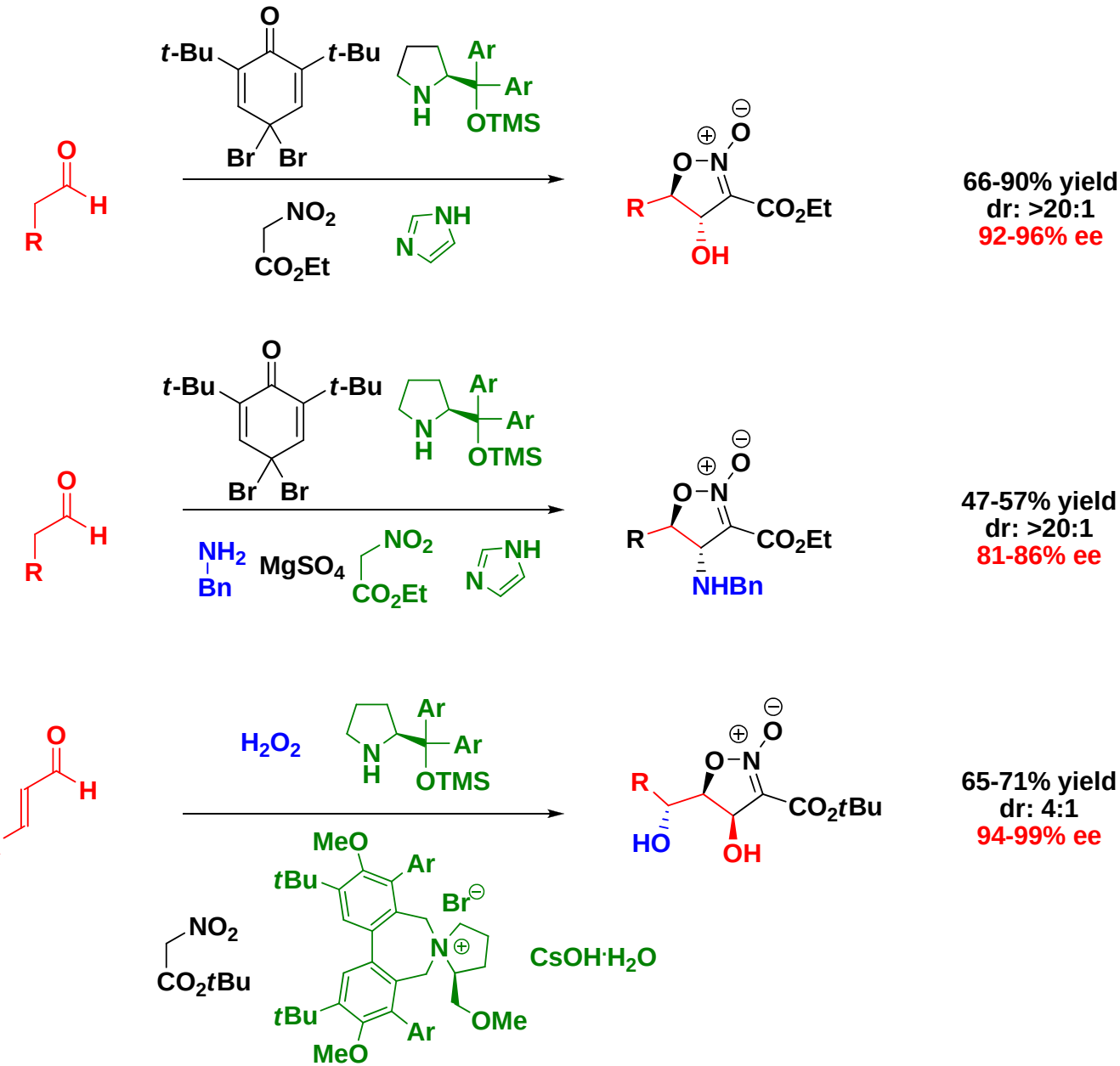
Marigo, Franzén, Poulsen, Zhuang, Jørgensen *J. Am. Chem. Soc*. **2005**, *127*, 6964

Organocatalytic leaving group strategy

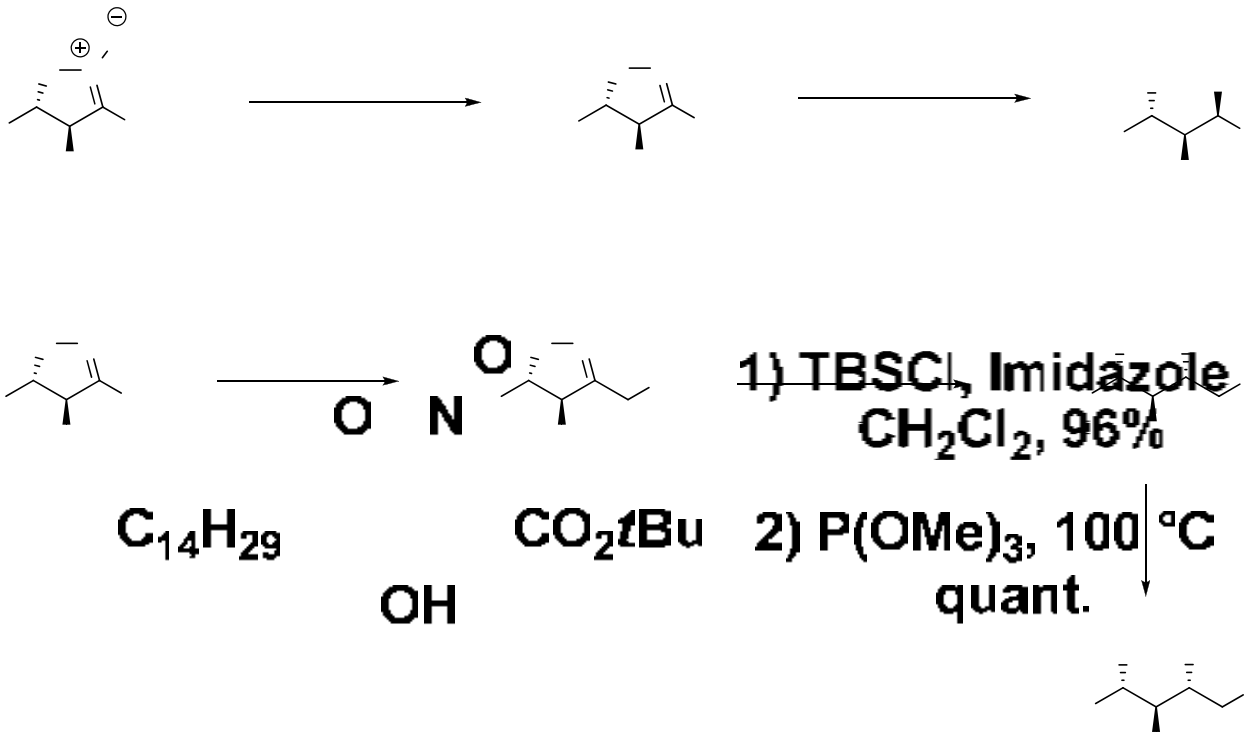


Jiang, Elsner, Jensen, Falcicchio, Marcos, Bertelsen Jørgensen *Angew. Chem. Int. Ed.* early view

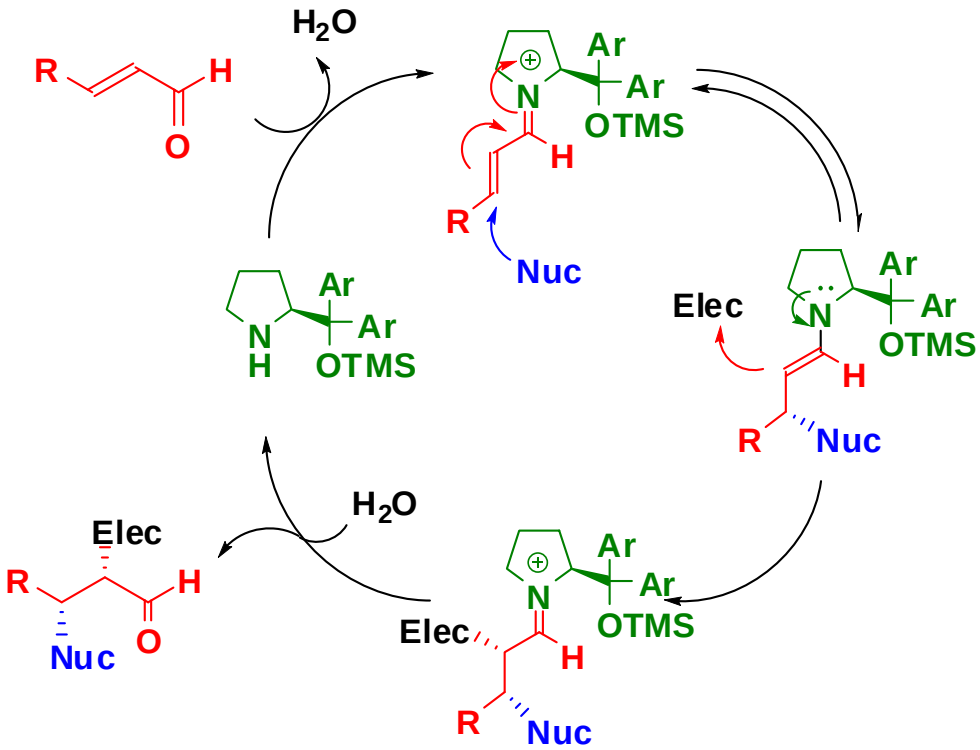
Scope


t-Bu
t-Bu
Br
Br
Ar
Ar
OTMS
N
H
O
H
R
NO2
CO2Et
NH
N
O
N
R
CO2Et
OH
66-90% yield
dr: >20:1
92-96% ee
NH2
Bn
MgSO4
NHBn
47-57% yield
dr: >20:1
81-86% ee
H2O2
HO
CO2tBu
65-71% yield
dr: 4:1
94-99% ee
MeO
tBu
OMe
CsOH·H2O

Potential

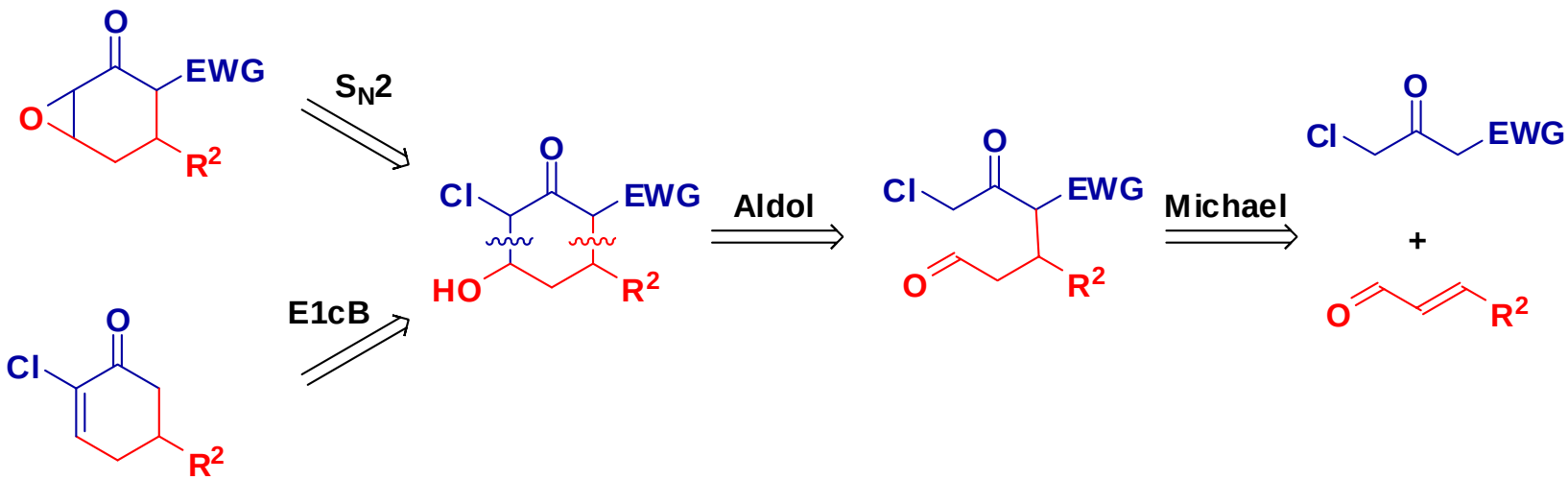

O N
CO2tBu
C14H29
OH
1) TBSCl, Imidazole
CH2Cl2, 96%
2) P(OMe)3, 100 °C
quant.
O N
C14H29
CO2
OTBS
O N
CO2Et
C14H29
OTBS
NaBH4, MeOH
rt, 91%
O N
C14H29
OH
OTBS
N

Organocatalyzed multicomponent reactions



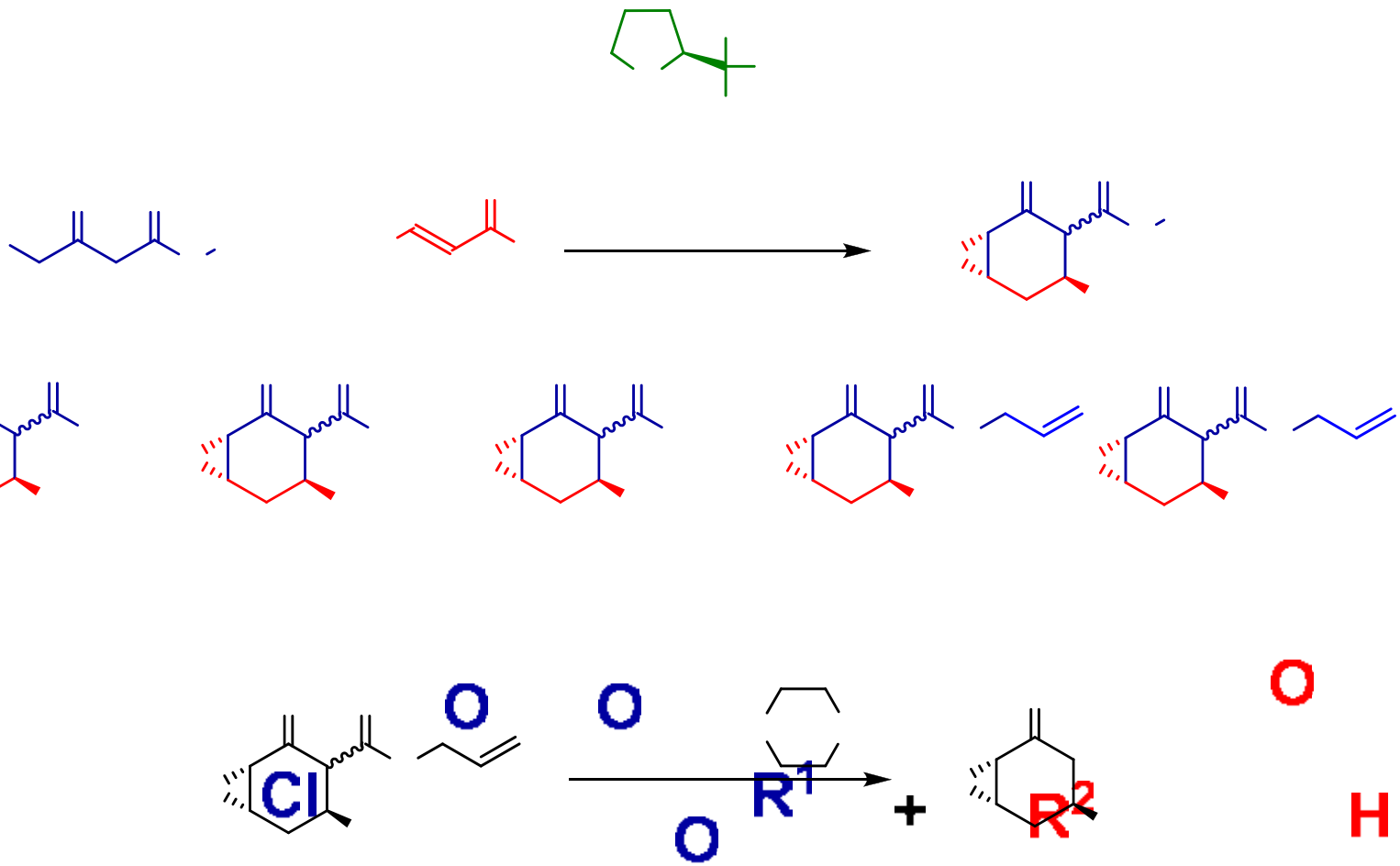
Yang, Hechavarria, List *J. Am. Chem. Soc*. **2005**, *127*, 15036
Huang, Walji, Larsen, MacMillan *J. Am. Chem. Soc*. **2005**, *127*, 15051
Marigo, Schulte, Franzén, Jørgensen *J. Am. Chem. Soc*. **2005**, *127*, 15710

Organocatalytic domino Michael-aldol reactions

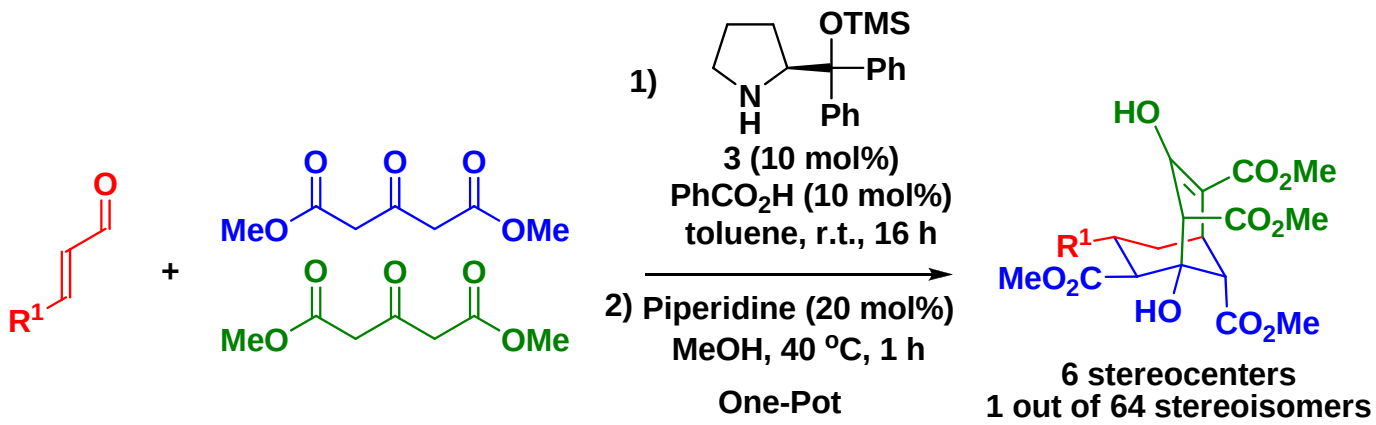


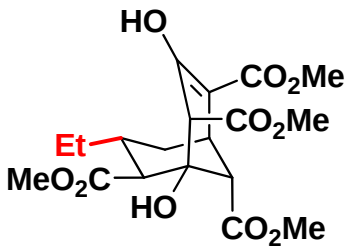
Marigo, Bertelsen, Landa, Jørgensen *J. Am. Chem. Soc*. **2006**, *128*, 5475

Scope

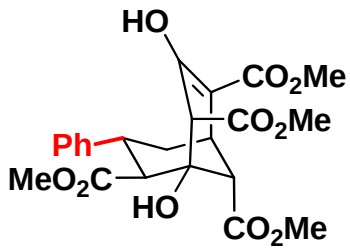


How to have six and 1 out of 64!

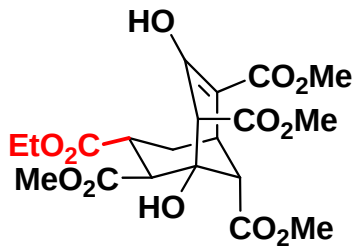




48% yield
dr >99:1
94% ee



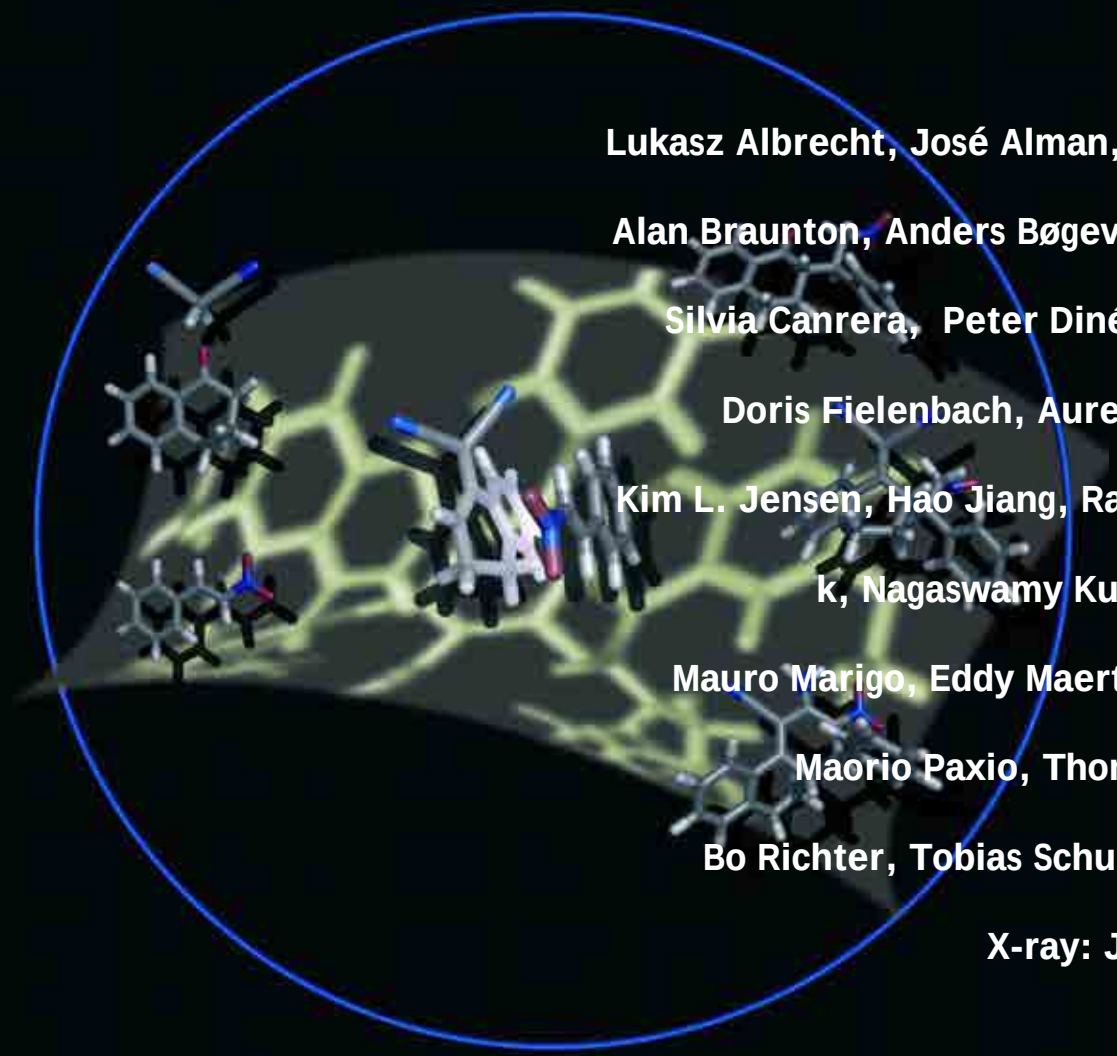
70% yield
dr >99:1
94% ee



38% yield
dr >99:1
89% ee

Bertelsen, Johansen, Jørgensen *Chem. Commun.* **2008**, *3016*

Acknowledgements



Lukasz Albrecht, José Alman, Stephan Bachmann, Søren Bertelsen

Alan Braunton, Anders Bøgevig, Patrick Boltze, Armando Carlone,

Silvia Canrera, Peter Dinér, Petteri Elsner, Johan Franzén,

Doris Fielenbach, Aurelia Falcicchio, Patrick Francke,

Kim L. Jensen, Hao Jiang, Rasmus L. Johansen, Anne Kjærsgaard,

k, Nagaswamy Kumargubaran, Aitor Landa,

Mauro Marigo, Eddy Maerten, Andrea Mielli, Martin Nielsen,

Maorio Paxio, Thomas Poulsen, Efraim Reyes,

Bo Richter, Tobias Schulte, Tobias Wabnitz, Wei Zhuang

X-ray: Jacob Overgaard

DANMARKS GRUNDFORSKNINGSFOND
DANISH NATIONAL RESEARCH FOUNDATION

Ochem GRADUATE SCHOOL

Carlsbergfondet