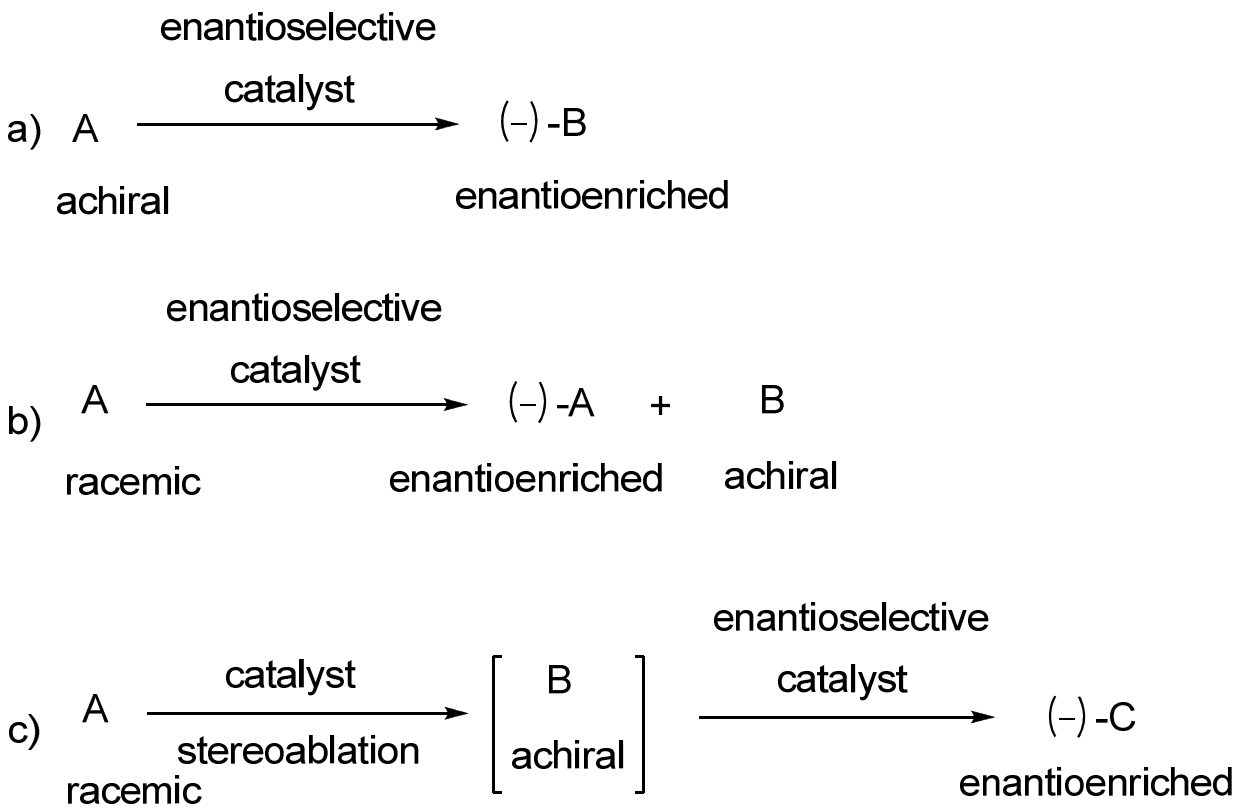
The total synthesis of (-)-cyanthiwigin F by means of double catalytic enantioselective alkylation

Hong Ren
07-19-08

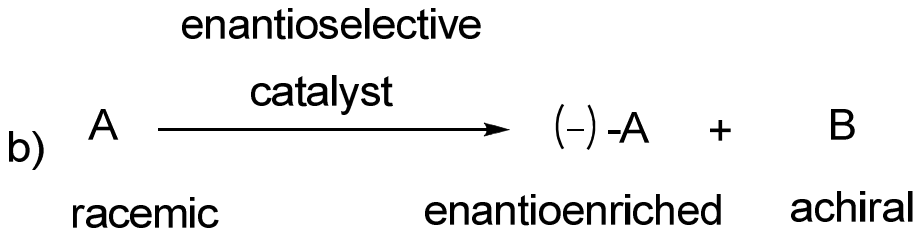
Enquist, J. A.; Stoltz, B. M. *Nature*, **2008**, *453*, 1228-1231

Strategies for enantioselective catalysis

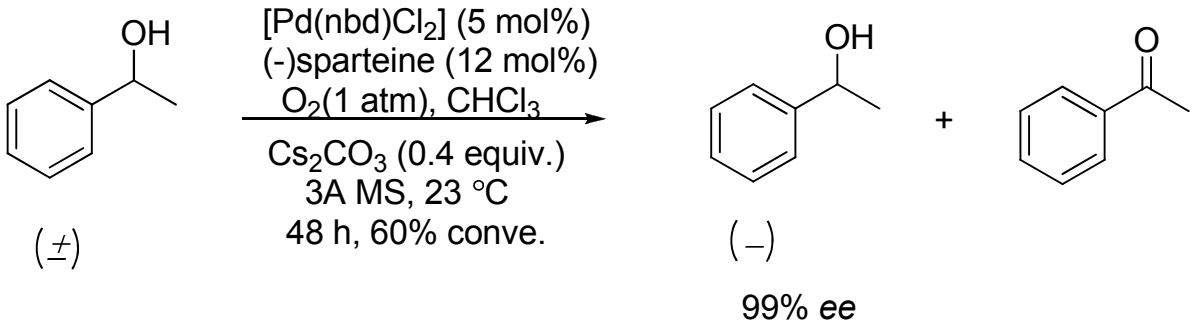


Mohr, J. T.; Ebner, D. C.; Harned, A. M.; Stoltz, B. M. *Org. Biomol. Chem*. **2007**, *5*, 3571-3576

Strategies for enantioselective catalysis



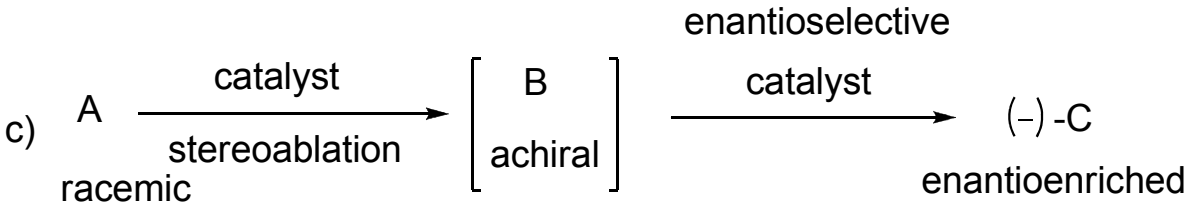
Example:



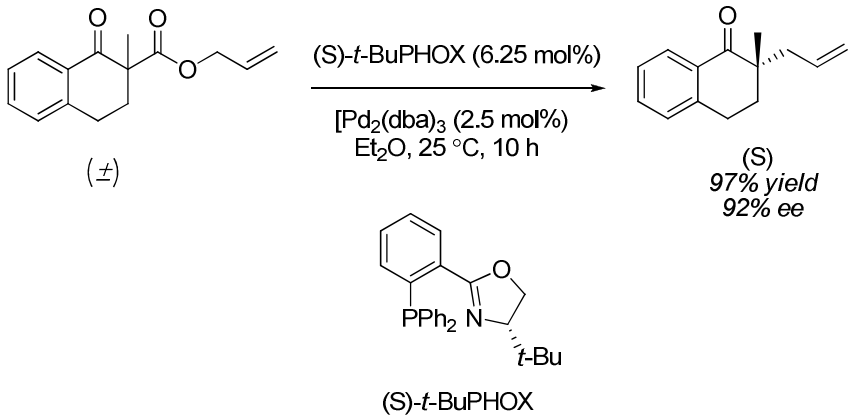
Oxidative kinetic resolution of secondary alcohol

Nielson, R. J.; Keith, J. M.; Stoltz, B. M. Goddard, W. A. *J. Am, Chem. Soc*. **2004**, *126*, 7967, 7974

Strategies for enantioselective catalysis



Example:



Stereoablative enantioconvergent allylation

Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924-6927

Stereoablation

- 2005

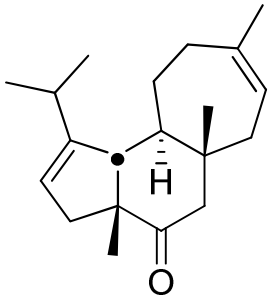
  “The conversion of a chiral molecule to an achiral molecule”

- 2007

  “Reactions where an existing stereocenter in a molecule is destroyed, but the intermediate molecule need not be wholly achiral”

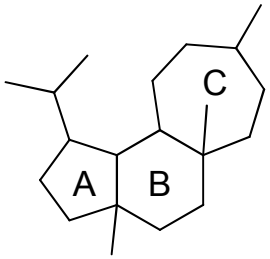
Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924-6927
Mohr, J. T.; Ebner, D. C.; Harned, A. M.; Stoltz, B. M. *Org. Biomol. Chem*. **2007**, *5*, 3571-3576

Now, It is the story of Cyanthiwigin F



Cyanthiwigin F

Cytotoxic activity against human primary tumor cells

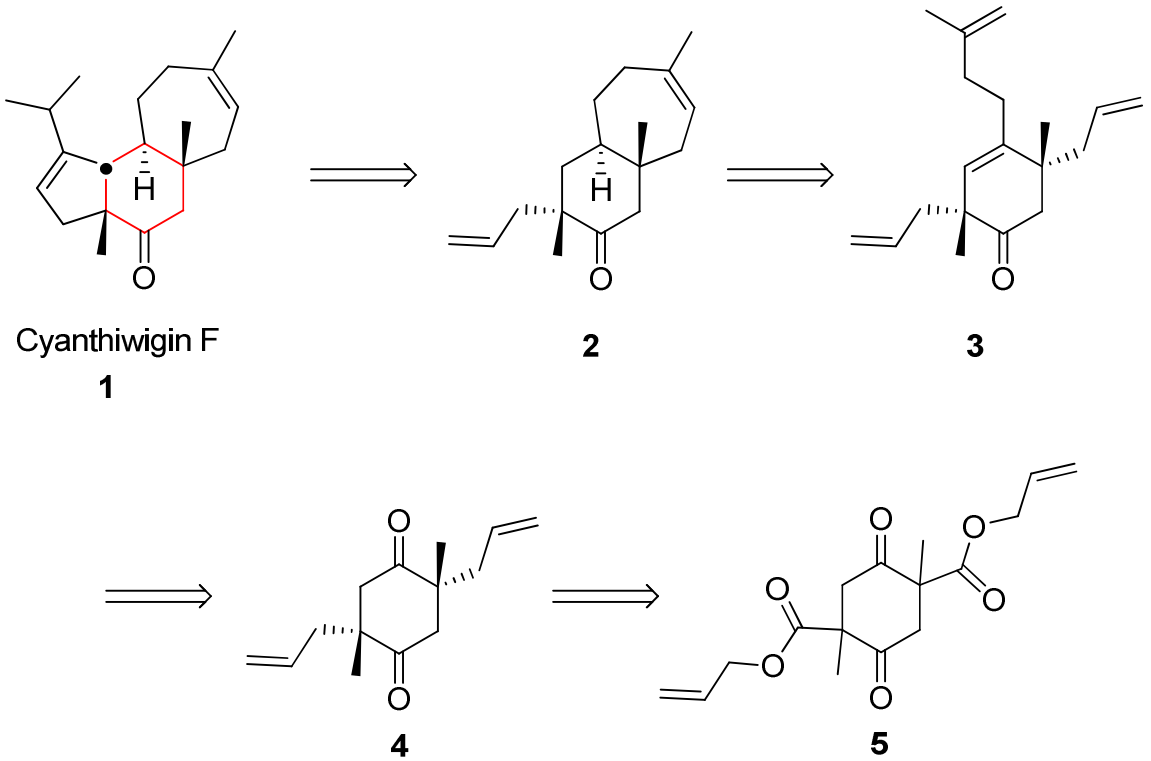


Antimicrobial activity
Antineoplastic action
Stimulation of nerve growth factor
K-opioid receptor agonism

But, only 2 of the 30 Cyanthiwigin molecules have been synthesized so far.

Enquist, J. A.; Stoltz, B. M. *Nature*, **2008**, *453*, 1228-1231

Retrosynthetic analysis



Cyanthiwigin F

1

2

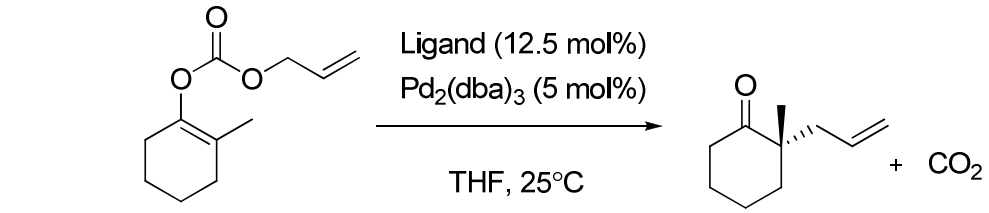
3

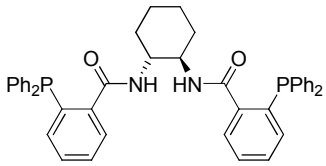
4

5

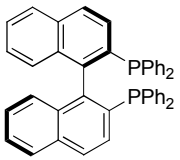
Enquist, J. A.; Stoltz, B. M. *Nature*, **2008**, *453*, 1228-1231

Stage 1--- Enantioselective Tsuji Allylation

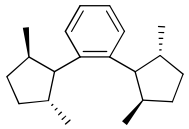




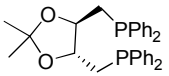
(*R, R*)-Trost ligand



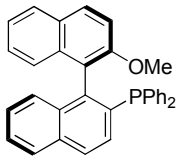
(*R*)-*BINAP*



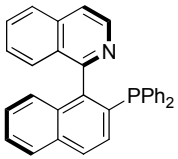
(*R, R*)-*Me-DUPHOS*



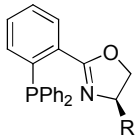
(*R, R*)-DIOP



(*R*)-*MOP*



(*R*)-*QUINAP*

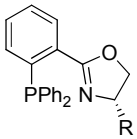


R= *Ph*

(*R*)-*Ph-PHOX*

R= *i-Pr*

(*R*)-*i-Pr-PHOX*



R= *Bn*

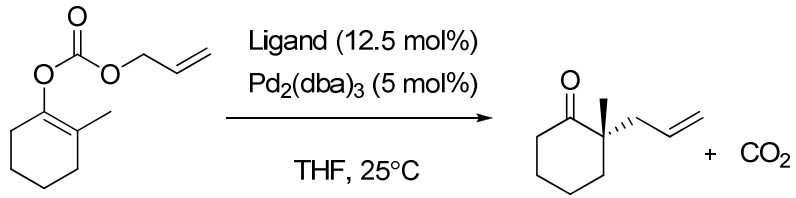
(*S*)-*Bn-PHOX*

R= *i-Pr*

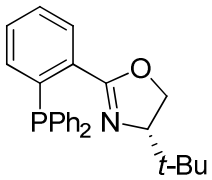
(*S*)-*t-Bu-PHOX*

Nielson, R. J.; Keith, J. M.; Stoltz, B. M. Goddard, W. A. *J. Am, Chem. Soc*. **2004**, *126*, 7967, 7974

Stage 1--- Enantioselective Tsuji Allylation

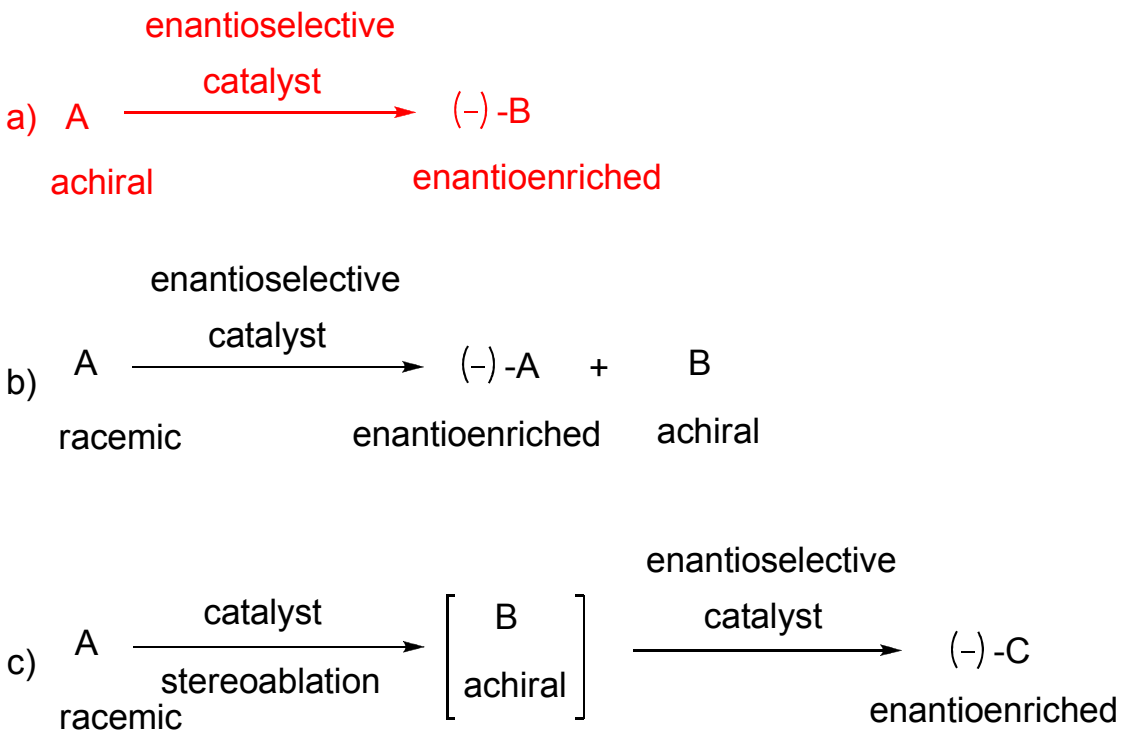


Ligand	Time (h)	% yield[a]	% ee
(*R, R*)-Trost ligand	5	92	64
(*R*) -*BINAP*	5	76	2
(*R, R*)-*Me-DUPHOS*	5	66	0
(*R, R*)-DIOP	2	59	2
(*R*) -*MOP*	3	47	13
(*R*) -*QUINAP*	2	97	61
(*R*) -*Ph-PHOX*	2	95	65
(*R*) -*i-Pr-PHOX*	5	94	63
(*S*) -*Bn-PHOX*	2	95	83
(*S*) -*t-Bu-PHOX*	2	95	88

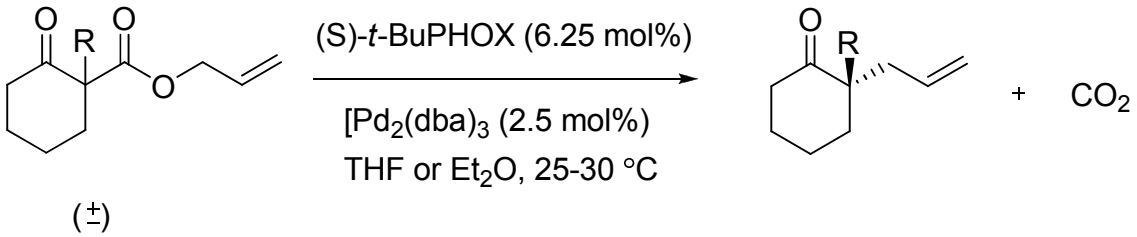


Nielson, R. J.; Keith, J. M.; Stoltz, B. M. Goddard, W. A. *J. Am, Chem. Soc*. **2004**, *126*, 7967, 7974

Strategies for enantioselective catalysis



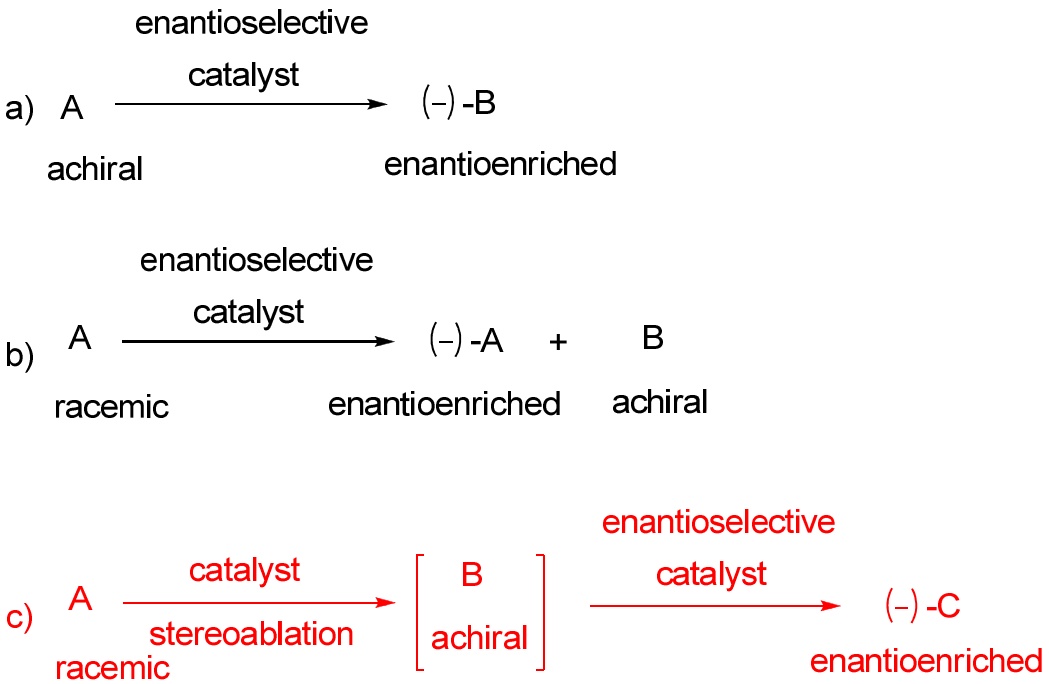
Stage 2--- catalytic stereoablative enantioconvergent allylation



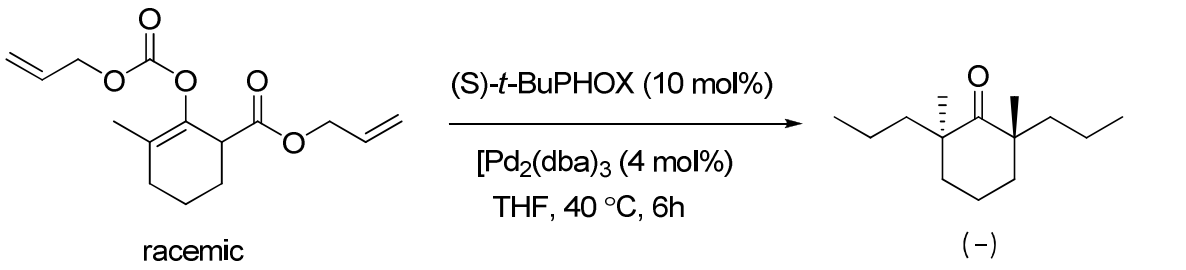
R	Solvent	T(°C)	t (h)	Yield (%)	ee (%)
CH_3	THF	25	7.5	85	88
CH_3	Et_2O	25	4.75	89	88
prenyl	Et_2O	30	6	97	91
CH_2CH_2CN	Et_2O	25	6.5	97	88
$CH_2CH_2CO_2Et$	Et_2O	25	6	96	90
$CH_2C_6H_5$	THF	25	0.5	99	85
$CH_2(4\text{-}CH_3OC_6H_4)$	THF	25	10	80	86
$CH_2(4\text{-}CF_3C_6H_4)$	THF	25	0.5	99	82
$CH_2OTBDPS$	THF	25	5	86	81
F	Et_2O	30	3.5	80	91

Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924-6927

Strategies for enantioselective catalysis

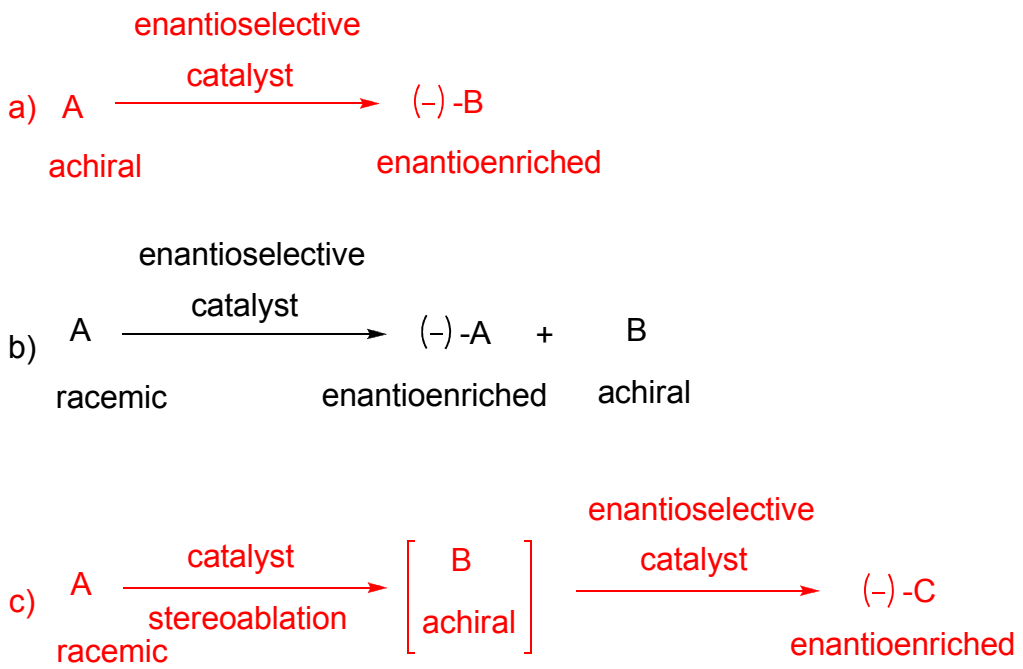


Stage 3---Double allylation cascade generating two all-carbon quaternary stereocenters

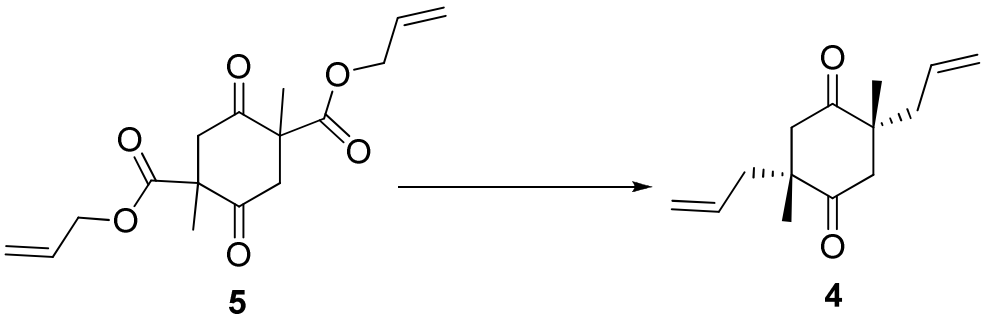


Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924-6927

Strategies for enantioselective catalysis



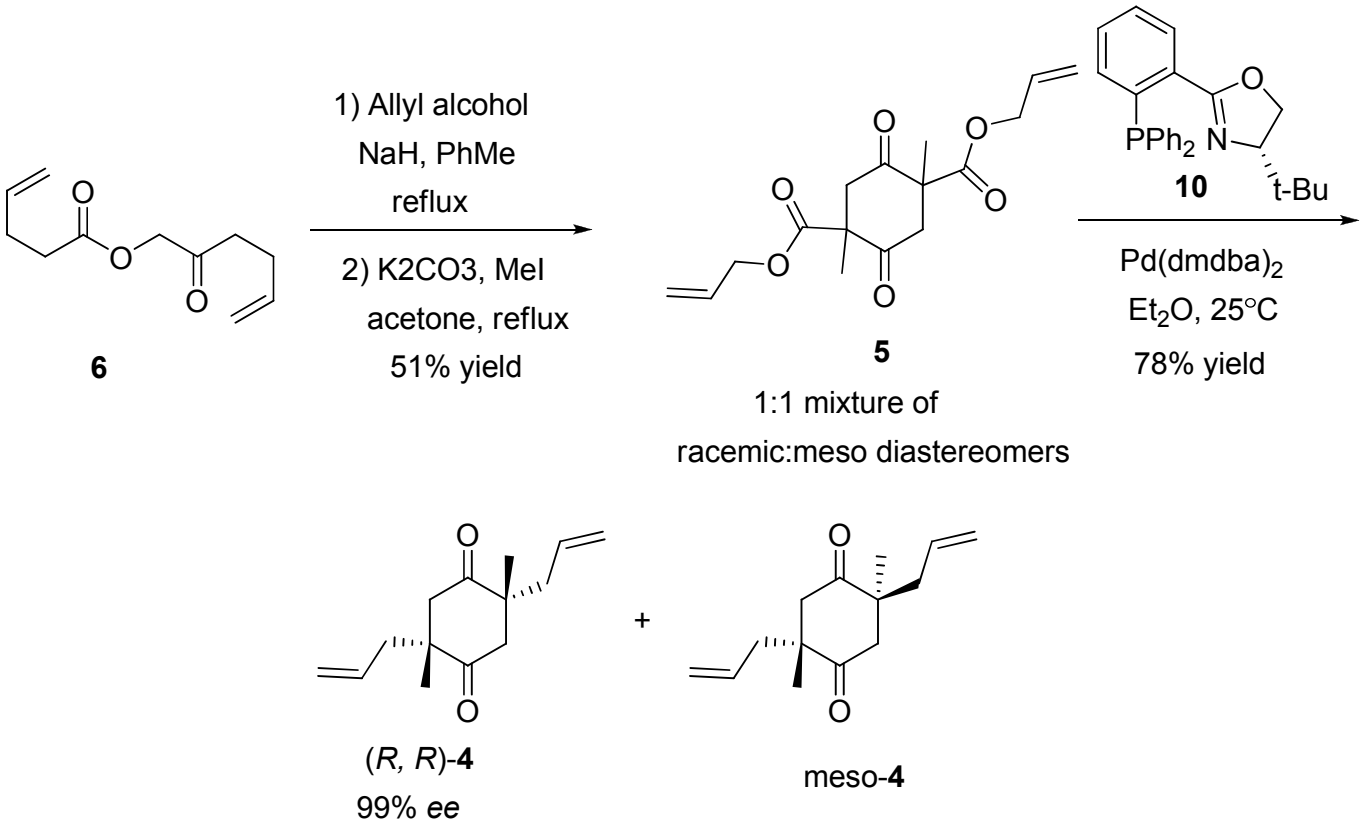
Stage 4---Cascade catalytic stereoablative enantioconvergent allylation



5 **4**

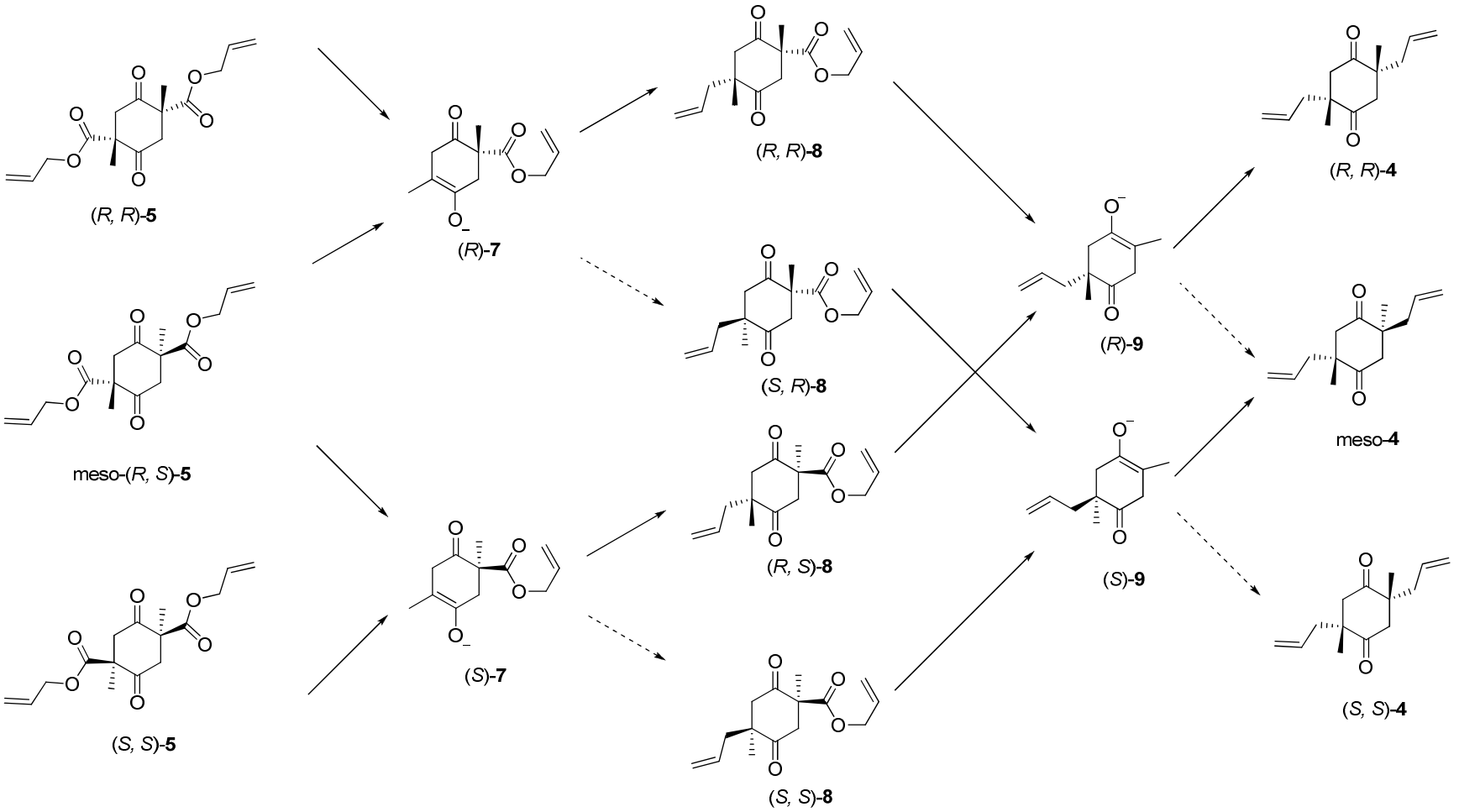
Enquist, J. A.; Stoltz, B. M. *Nature*, **2008**, *453*, 1228-1231

Forward Synthesis



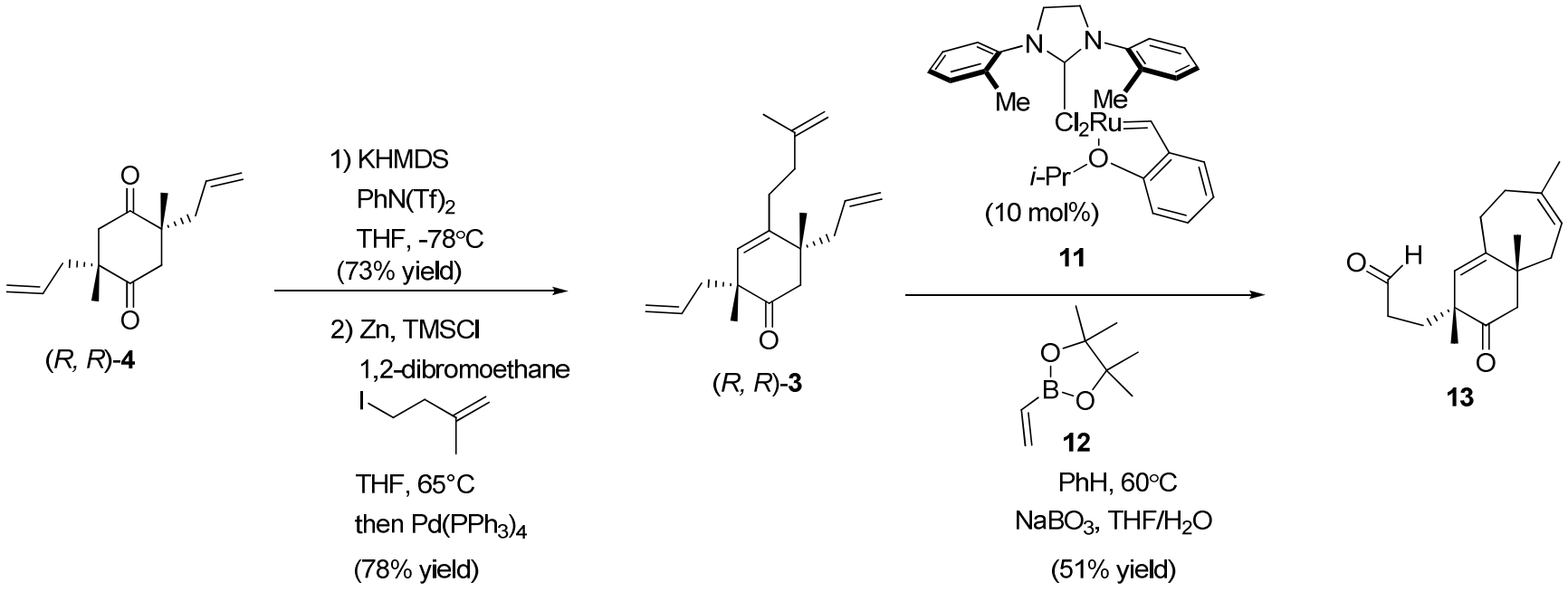
Enquist, J. A.; Stoltz, B. M. *Nature*, **2008**, *453*, 1228-1231

Stereochemical analysis



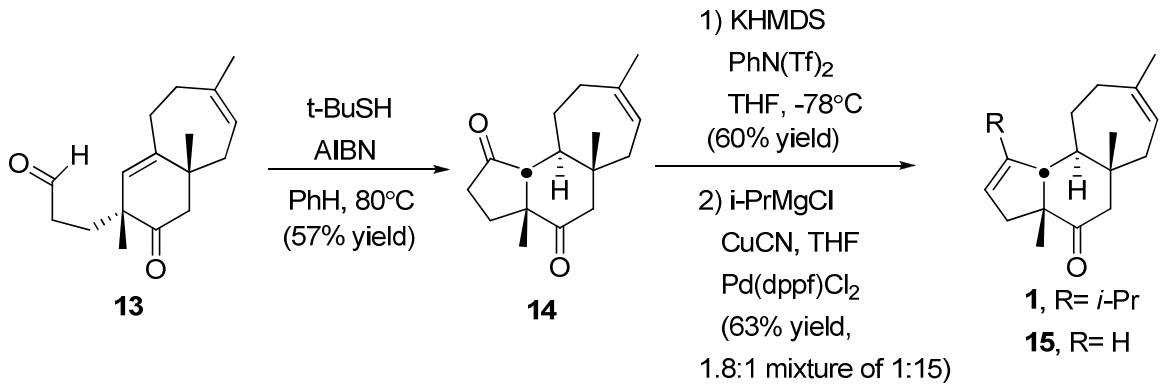
Enquist, J. A.; Stoltz, B. M. *Nature*, **2008**, *453*, 1228-1231

Forward Synthesis



Enquist, J. A.; Stoltz, B. M. *Nature*, **2008**, *453*, 1228-1231

Forward Synthesis



Enquist, J. A.; Stoltz, B. M. *Nature*, **2008**, *453*, 1228-1231

Credits

- Introduction of two chiral centers in one pot with excellent ee
- Tandem ring-closing metathesis and cross-metathesis
- No protections and deprotections involved