Hayashi Laboratory

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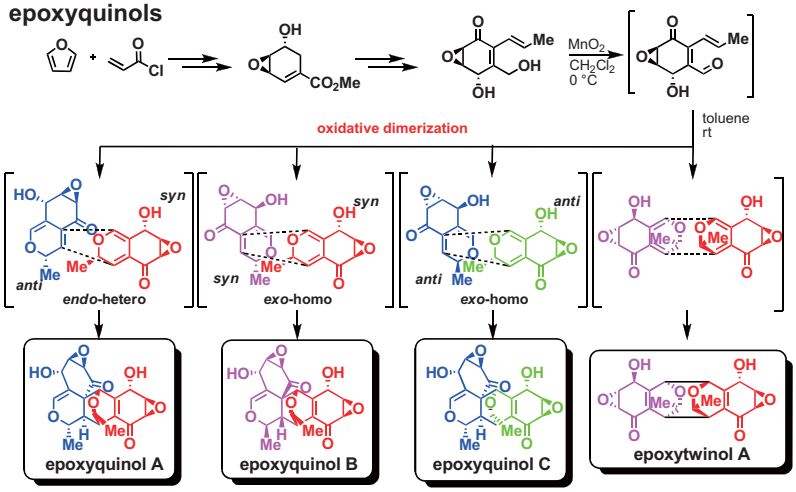
Hayashi Lab. Homepage http://www.ykbsc.chem.tohoku.ac.jp/

Total Synthesis of Bioactive Compounds

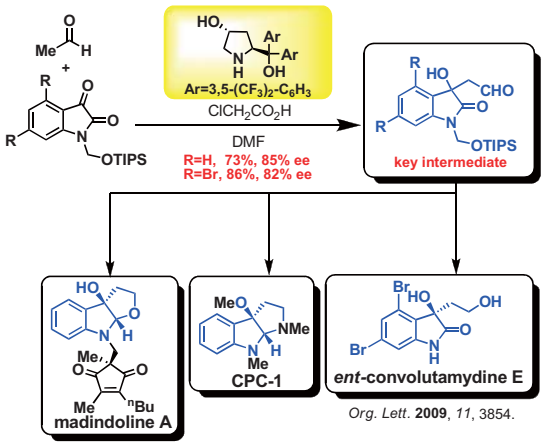
epoxyquinols



angiogenesis inhibitor

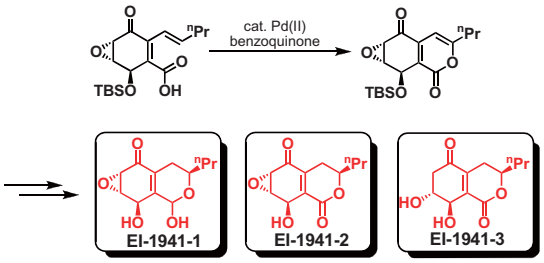
Angew. Chem., Int. Ed., **41**, 3192 (2002); *Tetrahedron Lett.*, **43**, 9155 (2002); *Tetrahedron Lett.*, **44**, 7205 (2003);*J. Org. Chem.*, **69**, 1548 (2004); *J. Org. Chem.*, **70**, 79 (2005) ; *Org. Lett.*, **8**, 1041 (2006). Review; *Eur. J. Org. Chem.*, **23**, 3783 (2007).

CPC-1, *ent*-convolutamydine E, and half segment of madindoline A



Org. Lett. **2009**, *11*, 3854.

EI-1941-1, EI-1941-2, EI-1941-3

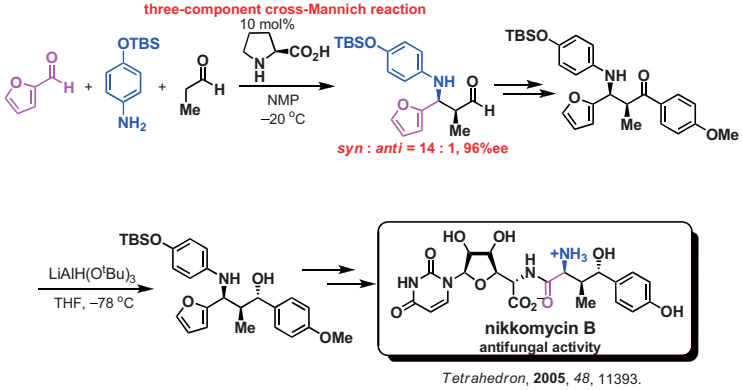


ICE (interleukin 1-β converting enzyme) inhibitor

Org. Lett. **2004**, *6*, 4535.
J. Org. Chem. **2005**, *70*, 9905.

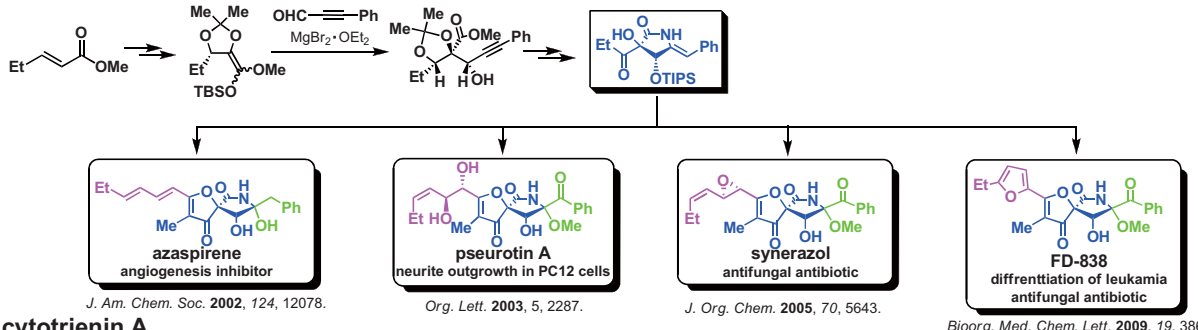
formal total synthesis of nikkomycin B

three-component cross-Mannich reaction



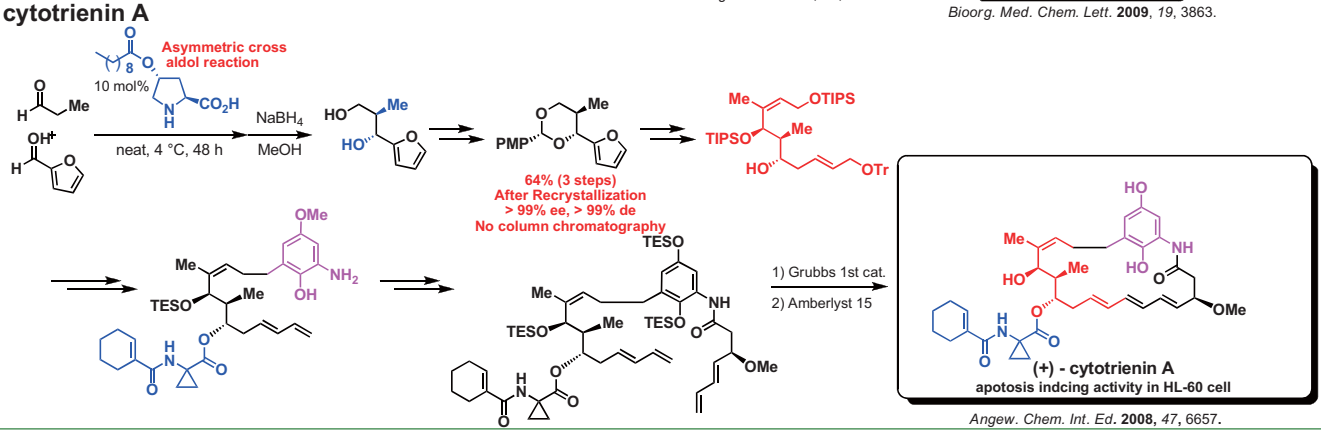
Tetrahedron, **2005**, *48*, 11393.

azaspirene, pseurotin A, synerazol, FD-838



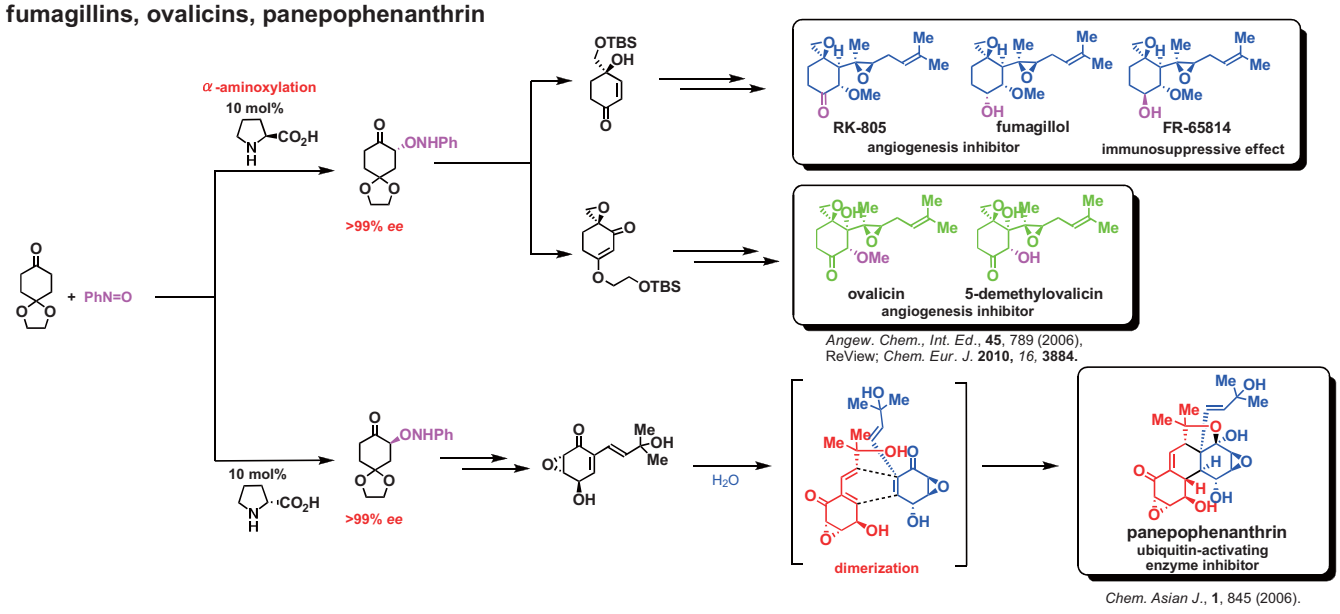
J. Am. Chem. Soc. **2002**, *124*, 12078.
Org. Lett. **2003**, 5, 2287.
J. Org. Chem. **2005**, *70*, 5643.
Bioorg. Med. Chem. Lett. **2009**, *19*, 3863.

(+) - cytotrienin A



Angew. Chem. Int. Ed. **2008**, *47*, 6657.

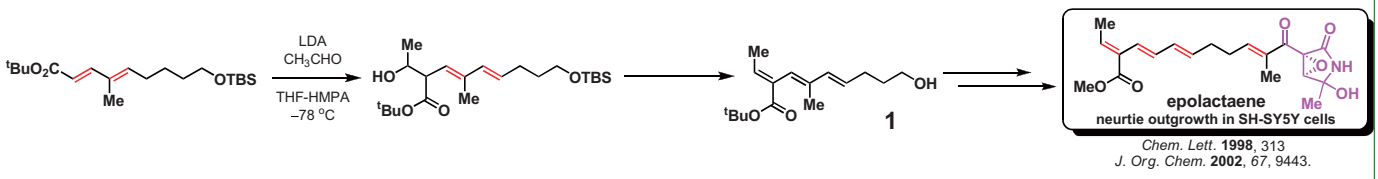
fumagillins, ovalicins, panepophenanthrin



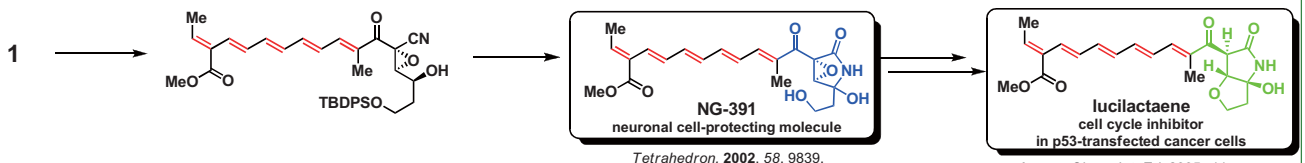
Angew. Chem., Int. Ed., **45**, 789 (2006), ReView; *Chem. Eur. J.* **2010**, *16*, **3884.**

Chem. Asian J., **1**, 845 (2006).

epolactaene, NG-391, lucilactaene



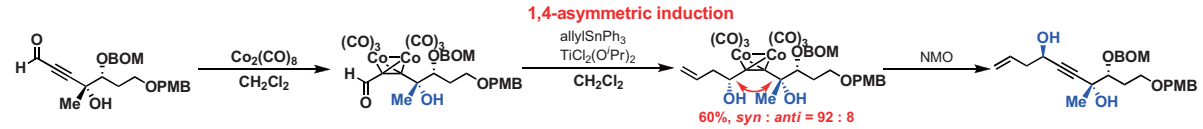
Chem. Lett. **1998**, 313
J. Org. Chem. **2002**, *67*, 9443.

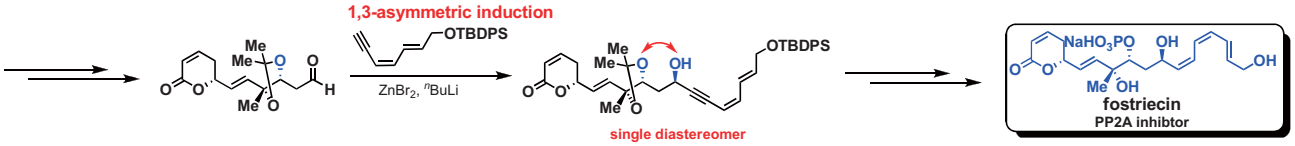


Tetrahedron, **2002**, *58*, 9839.

Angew. Chem. Int. Ed. **2005**, *44*, 3110.

formal total synthesis of fostriecin

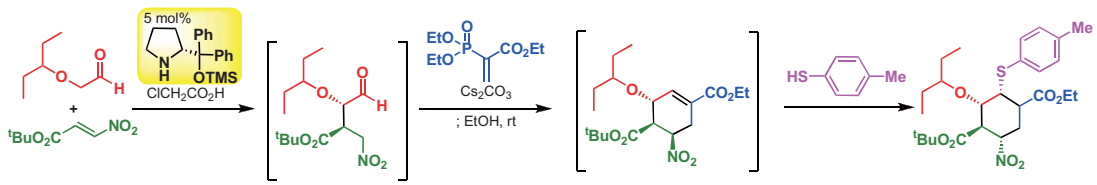


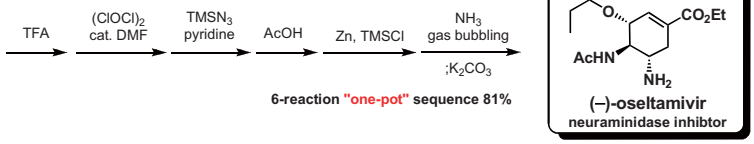


Org. Lett. **2008**, *10*, 1405.
Chem. Eur. J. **2010**, *16*, 10150.

(–)- oseltamivir (Tamiflu®)

1 st and 2nd generation



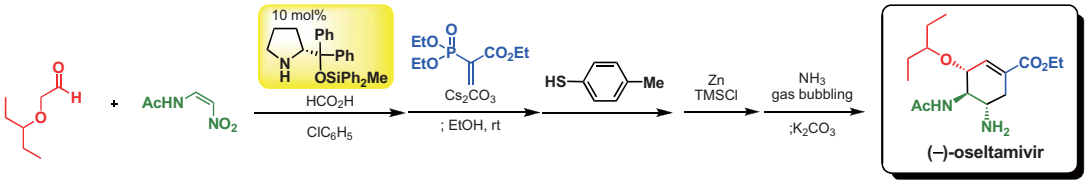


Total yield : 60%

Angew. Chem. Int. Ed. **2009**, *48*, 1304.
Chem. Eur. J. **2010**, *16*, 12616.
Eur. J. Org. Chem. **2011**, 6020.

(–)- oseltamivir (Tamiflu®)

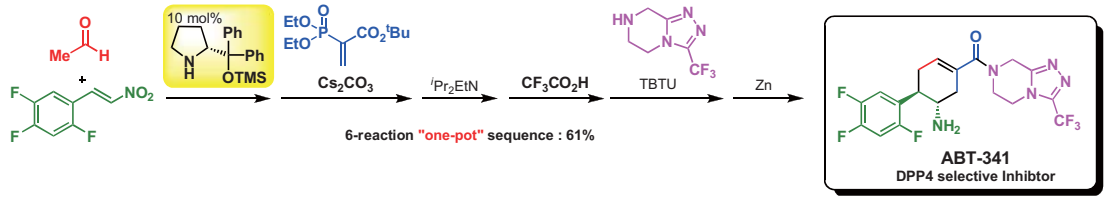
3rd generation



"one-pot" operation : 34%

Chem. Eur. J. **2013**, *19*, 17789.

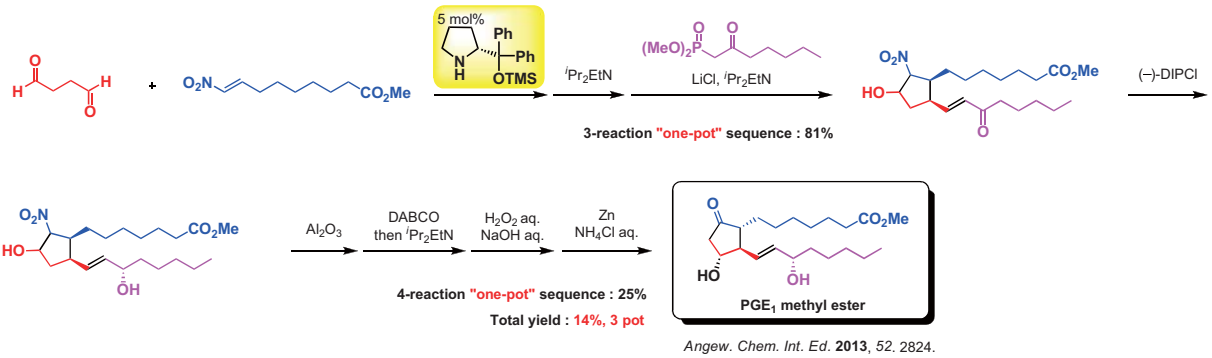
ABT-341



6-reaction "one-pot" sequence : 61%

Angew. Chem. Int. Ed. **2011**, *50*, 2824.

Prostaglandin E_1 methyl ester



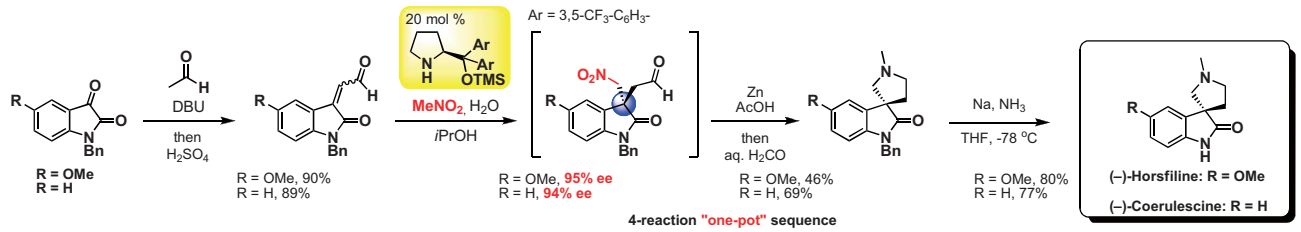
3-reaction "one-pot" sequence : 81%

4-reaction "one-pot" sequence : 25%

Total yield : 14%, 3 pot

Angew. Chem. Int. Ed. **2013**, *52*, 2824.

(–)-Horsfiline and (–)-Coerulescine



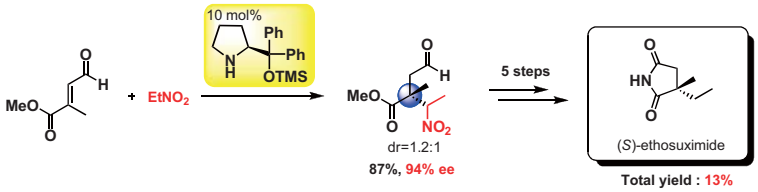
4-reaction "one-pot" sequence

Three "one-pot" operations

Total yield
(–)-Horsfiline : 33%
(–)-Coerulescine : 46%

Chem. Eur. J. accepted for publication

(*S*)-ethosuximide



87%, 94% ee

Total yield : 13%

Chem. Eur. J. accepted for publication

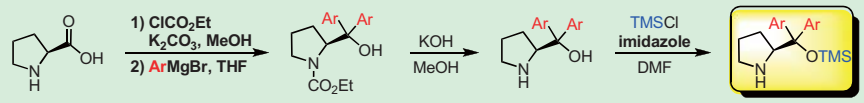
Hayashi Laboratory

Hayashi Lab. Homepage http://www.ykbsc.chem.tohoku.ac.jp/

Development of new reactions

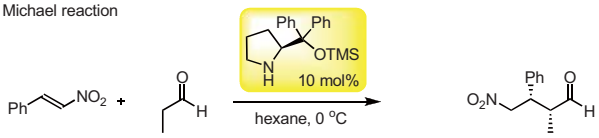
Asymmetric reaction using amino acid or their derivatives as a catalyst,
environmental conscious asymmetric reaction using water as a solvent, and research about origin of chirality

Reaction using diarylprolinol silyl ether derivatives as catalyst



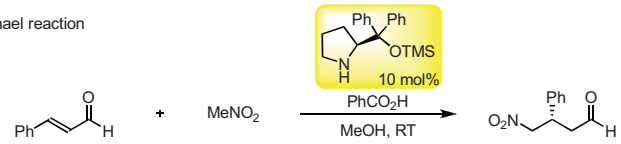
This catalyst is synthesized in short steps from proline.
Substituents on aryl and silyl moiety are easily modified.
Excellent enantioselectivity is obtained

Michael reaction



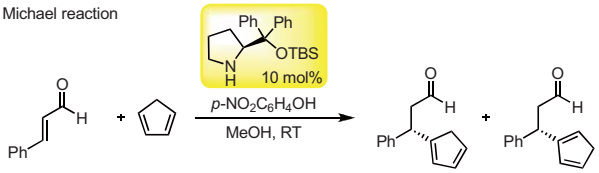
85%, 99% *ee*
Angew. Chem., Int. Ed., **44**, 4212 (2005).

Michael reaction



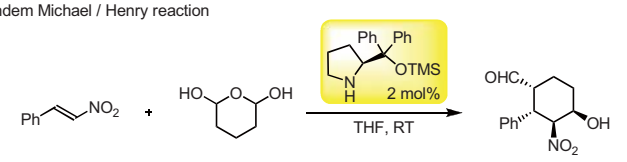
90%, 95% *ee*
Org. Lett., **9**, 5307 (2007).

Michael reaction



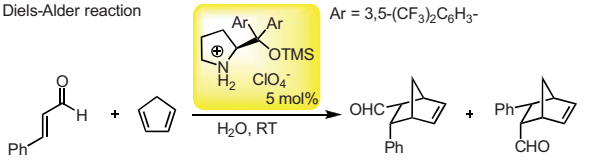
84%, 92% *ee*
Angew. Chem., Int. Ed., **45**, 6853 (2006).

Tandem Michael / Henry reaction



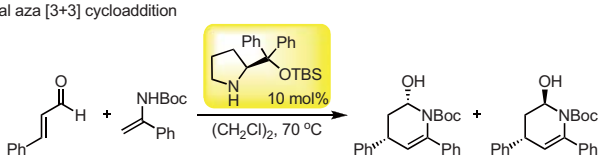
66%, 99% *ee*
Angew. Chem., Int. Ed., **46**, 4922 (2007).

Diels-Alder reaction



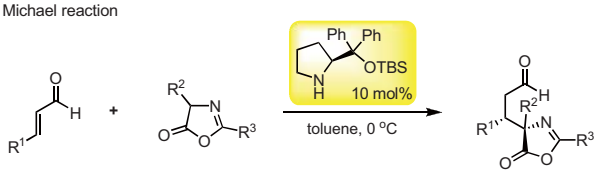
***exo* : *endo* = 80 : 20, 97% *ee* (*exo*)**
Org. Lett, **9**, 2859 (2007).
Angew. Chem., Int. Ed., **47**, 6634 (2008).

Formal aza [3+3] cycloaddition



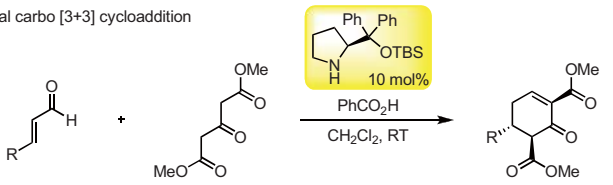
α β
90%, 94% *ee*, α : β = 34 : 66
Angew. Chem., Int. Ed., **47**, 4012 (2008).

Michael reaction



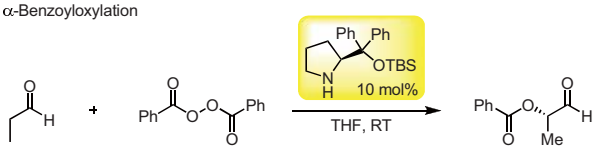
up to 99% *ee*
up to >90% *de*
Chem. Asian. J., **4**, 246 (2009).

Formal carbo [3+3] cycloaddition



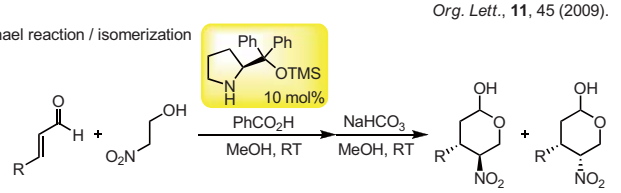
up to 99% *ee*
Org. Lett., **11**, 45 (2009).

α-Benzoyloxylation



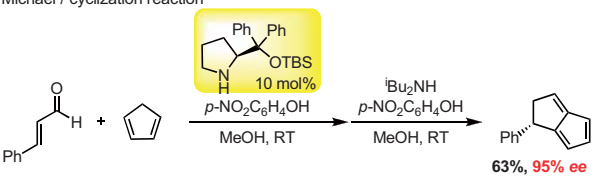
78%, 92% *ee*
Chem. Commun,, 3083 (2009).

Michael reaction / isomerization



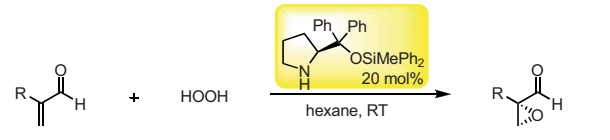
a b
up to 99% *ee*, a : b = 9 : 1
Org. Lett., **11**, 4056 (2009).

Michael / cyclization reaction



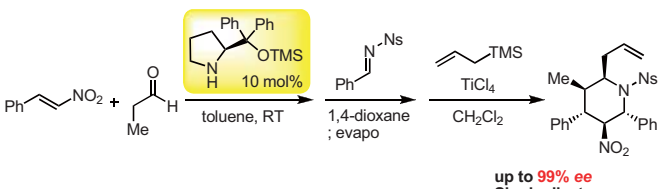
63%, 95% *ee*
Tetrahedron, **66**, 4894 (2010).

epoxidation



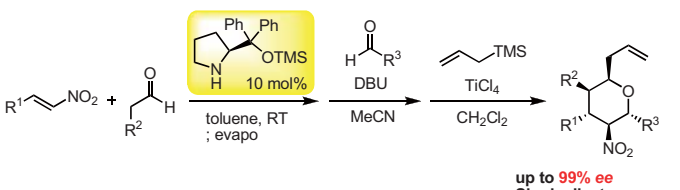
up to 95% *ee*
Org. Lett., **12**, 5434 (2010).

Michael / aza Henry / aminal formation / additional reaction



up to 99% *ee*
Single diastereomer
Org.Lett., **12**, 4588 (2010).

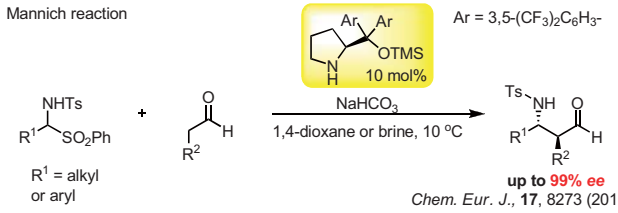
Michael / Henry / acetal formation / additional reaction



up to 99% *ee*
Single diastereomer
Angew. Chem., Int. Ed., **50**, 3774 (2011).

Reaction using diarylprolinol silyl ether derivatives as catalyst

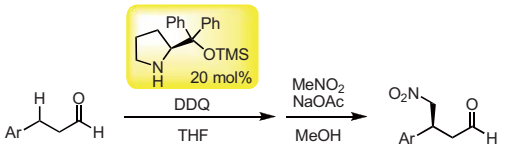
Mannich reaction



up to 99% *ee*

Chem. Eur. J., **17**, 8273 (2011).

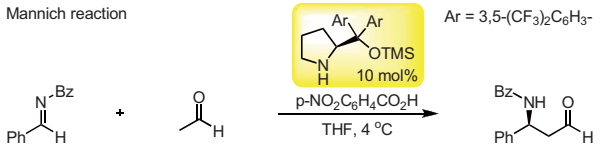
Formal C-H insertion



up to 95% *ee*

Angew. Chem., Int. Ed., **50**, 3920 (2011).
Adv. Synth. Catal. **355**, 3661 (2013).

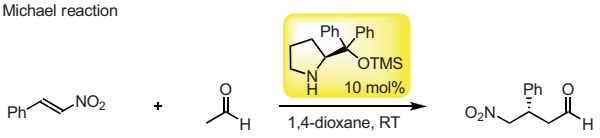
Mannich reaction



87%, 98% *ee*

Angew. Chem., Int. Ed., **47**, 9053 (2008).

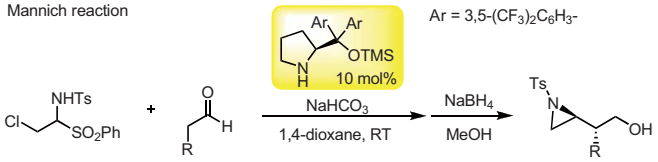
Michael reaction



75%, 96% *ee*

Angew. Chem., Int. Ed., **47**, 4722 (2008).

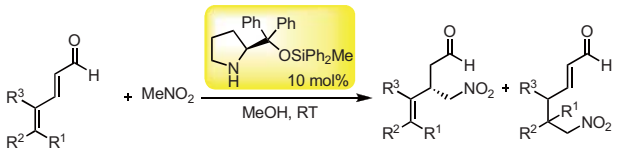
Mannich reaction



up to 99% *ee*

Chem. Eur. J., **17**, 8273 (2011).

Michael reaction (1,4-Addition versus 1,6-Addition)

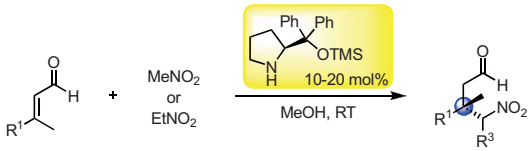


100 : 0

up to 95% *ee*

ChemCatChem, **4**, 959 (2012).
<Review>
ChemCatChem, **5**, 3499 (2013).

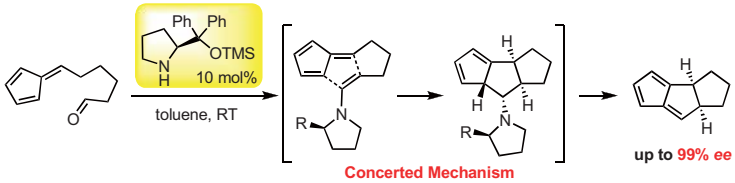
Michael reaction



up to 94% *ee*

Chem. Eur. J. accepted for publication

[6+2] cycloaddition reaction

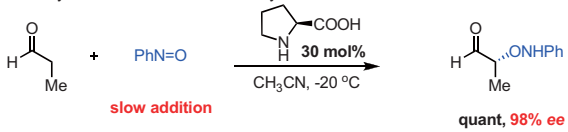


up to 99% *ee*

J. Am. Chem. Soc., **133**, 20175 (2011).

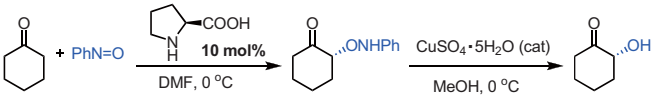
Reaction catalyzed by proline

Direct catalytic enantioselective α-aminoxylation



quant, 98% *ee*

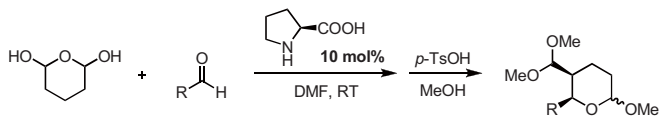
Tetrahedron Lett., **44**, 8293 (2003).



79%, >99% *ee* 87%

Angew. Chem., Int. Ed., **43**, 1112 (2004).
J. Org. Chem., **69**, 1548 (2004).

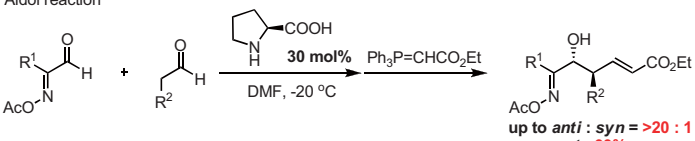
Aldol / acetalization reaction



up to 99% *ee*

Org. Lett. **10**, 1445 (2008).

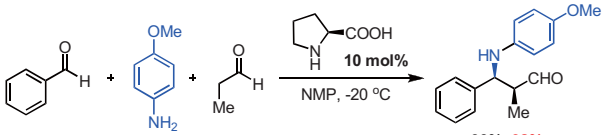
Aldol reaction



up to *anti* : *syn* = >20 : 1
up to 99% *ee*

Adv. Synth. Catal. accepted for publication

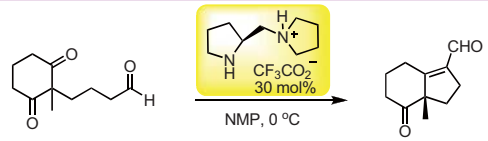
Three-Component Cross-Mannich reaction of aldehydes



90%, 98% *ee*
anti : *syn* = 1 : >95

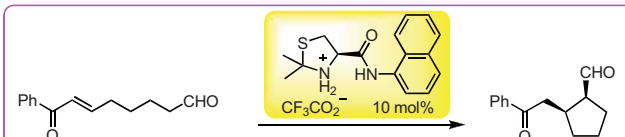
Angew. Chem., Int. Ed., **42**, 3677 (2003).
Adv. Synth. Catal., **347**, 1604 (2005).
Nature Protocols, **2**, 113 (2007).

Reaction by proline-derived catalyst



J. Org. Chem., **72**, 6493 (2007).

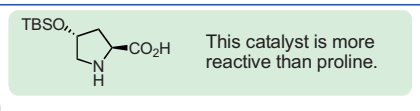
Reaction by cystein-derived catalyst



quant, 99% *ee*
cis : *trans* = 8.3 : 1

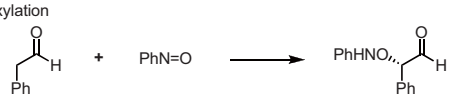
J. Am. Chem. Soc., **127**, 16028 (2005).

Reaction by siloxyproline catalyst



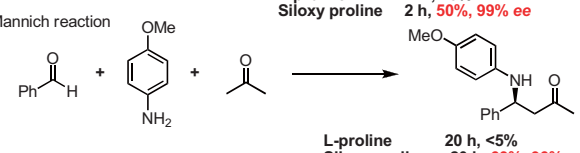
This catalyst is more reactive than proline.

- α-aminoxylation



L-proline 24 h, <5%
Siloxy proline 2 h, 50%, 99% *ee*

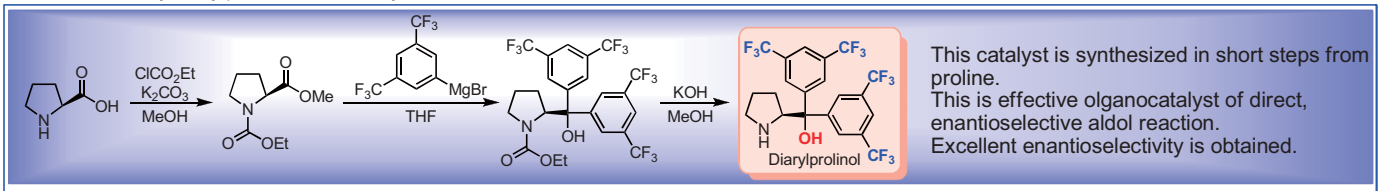
- Mannich reaction

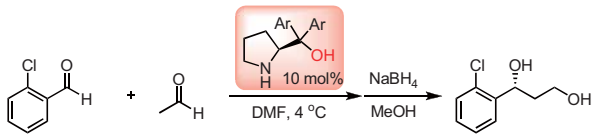


L-proline 20 h, <5%
Siloxy proline 20 h, 63%, 96% *ee*

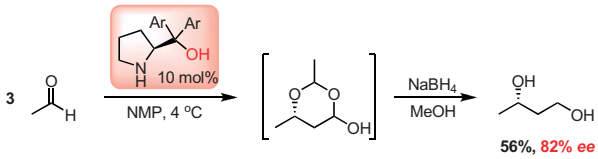
Adv. Synth. Catal., **346**, 1435 (2004).

Aldol reaction by diarylprolinol as a catalyst

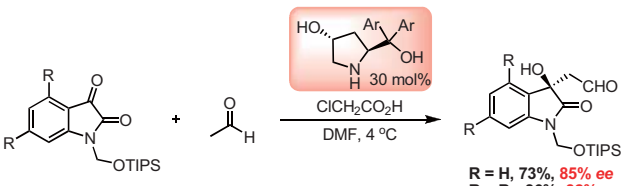




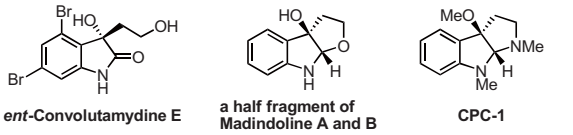
82%, 98% *ee*
Angew. Chem., Int. Ed., **47**, 2082 (2008).



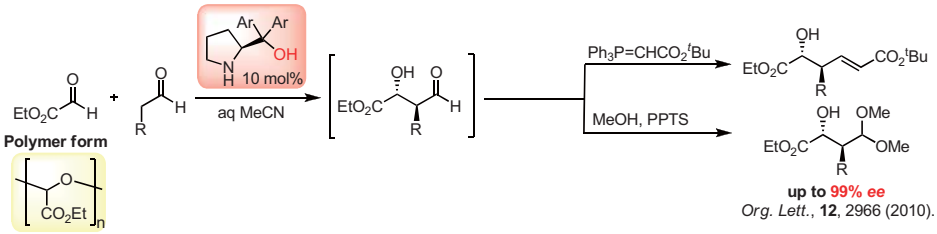
56%, 82% *ee*
Org. Lett., **10**, 5581 (2008).



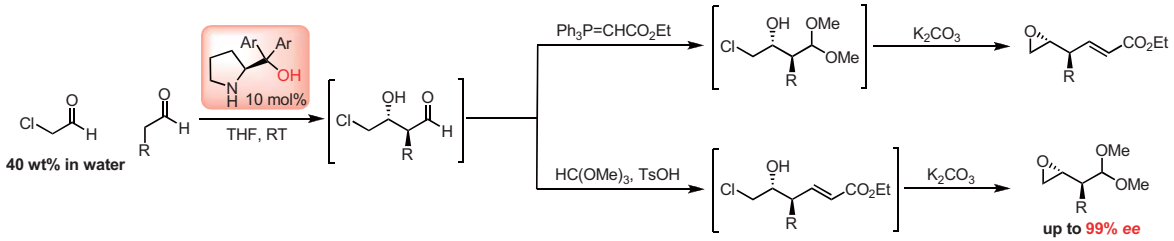
R = H, 73%, 85% *ee*
R = Br, 86%, 82% *ee*



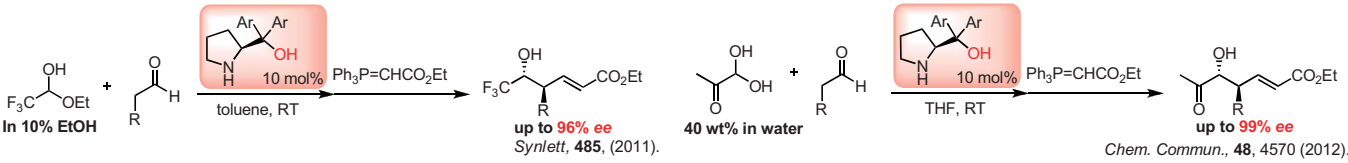
Org. Lett., **11**, 3854 (2009).



up to 99% *ee*
Org. Lett., **12**, 2966 (2010).

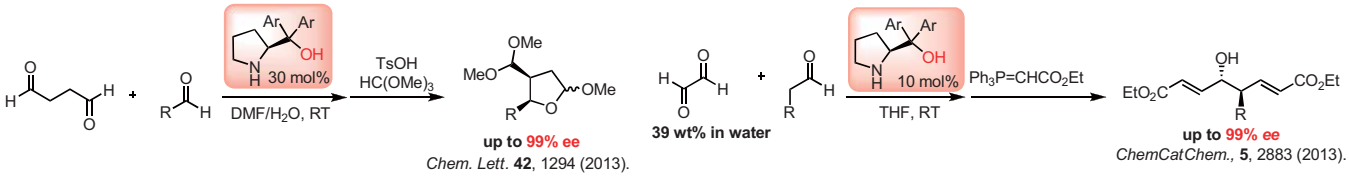


up to 99% *ee*
Angew. Chem., Int. Ed., **50**, 2804 (2011).



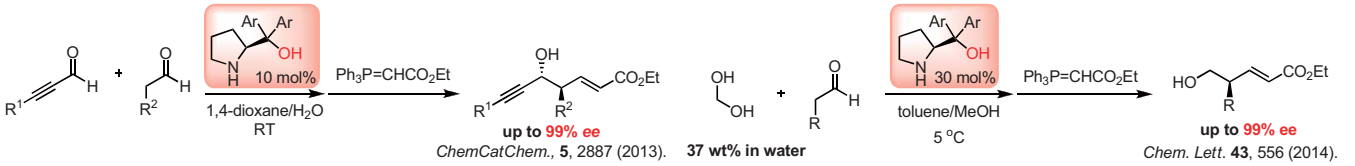
up to 96% *ee*
Synlett, **485**, (2011).

up to 99% *ee*
Chem. Commun., **48**, 4570 (2012).



up to 99% *ee*
Chem. Lett. **42**, 1294 (2013).

up to 99% *ee*
ChemCatChem., **5**, 2883 (2013).

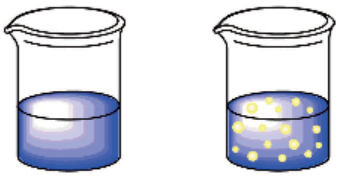


up to 99% *ee*
ChemCatChem., **5**, 2887 (2013).

up to 99% *ee*
Chem. Lett. **43**, 556 (2014).

Organic solvent free reaction

・"in the water" or "in the presence of water" ?

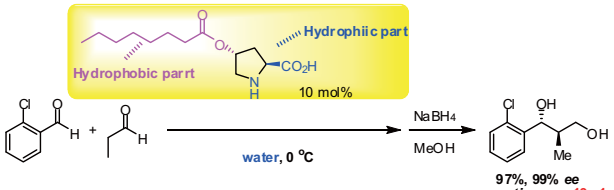


"in water" : The participating reactants are dissolved homogeneously in water.

"in the presence of water" : The reaction proceeds in a concentrated organic phase with water present as a second phase that influences the reaction in the former.

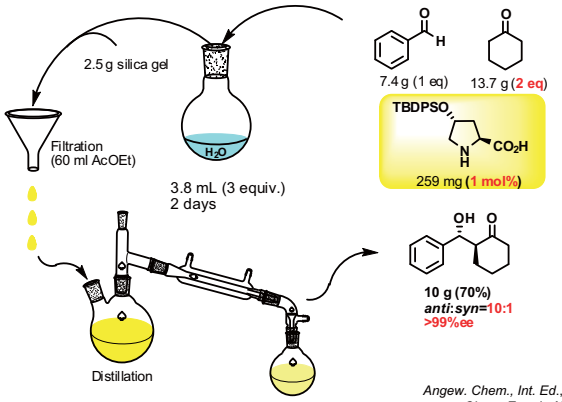
Angew. Chem., Int. Ed., **47**, 634 (2008).

・Intermolecular aldol reaction between aldehydes in the presence of water



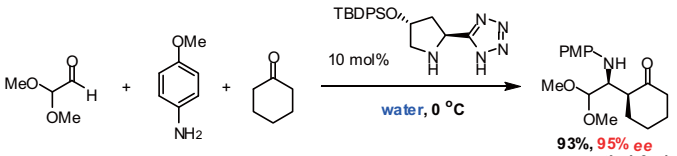
Angew. Chem., Int. Ed., **45**, 5527 (2006).

・Organic solvent free asymmetric aldol reaction between ketone and aldehyde



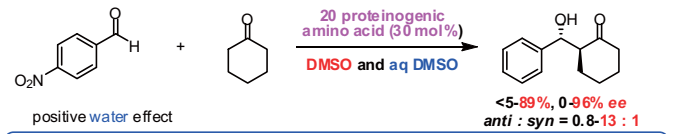
Angew. Chem., Int. Ed., **45**, 958 (2006).
Chem. Eur. J., **13**, 10246 (2007).

・Organic solvent free asymmetric Mannich reaction with proline catalyst



Org. Lett., **10**, 21 (2008).

・Effect of water on aldol reaction with 20 proteinogenic amino acid

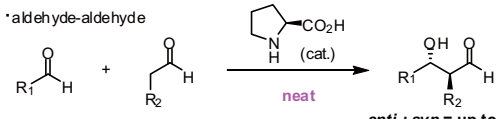


Gly, Ala, Val, Leu, Ile, Phe, Trp, Pro, Ser, Thr, Tyr, Cys, Met, His, Lys, Arg, Asp, Asn, Glu, Gln

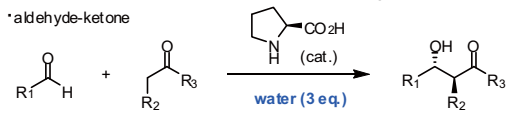
Synlett., 1565 (2006).

・Organic solvent free Dry and Wet condition asymmetric aldol reaction with proline catalyst

・aldehyde-aldehyde

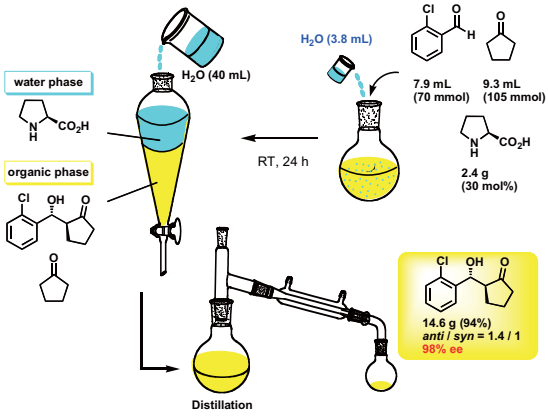


・aldehyde-ketone

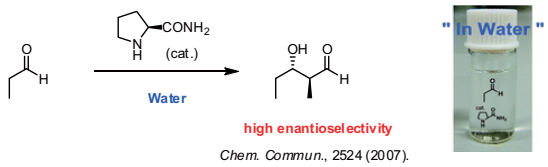


Chem. Commun., 957 (2007).

Organic solvent-free aldol reaction

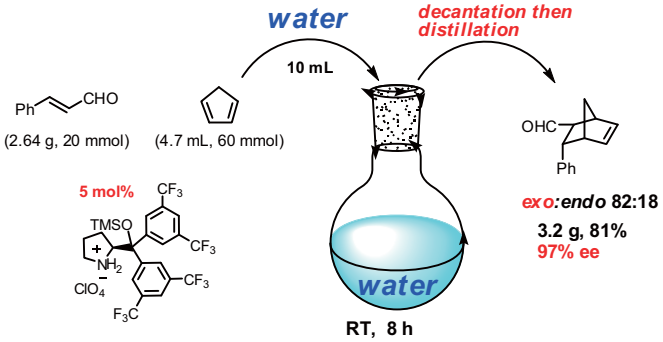


・Self aldol reaction of propanal in water – reaction in water with proline-amide catalyst



Chem. Commun., 2524 (2007).

・Organic solvent free asymmetric Diels-Alder reaction with proline derived catalyst

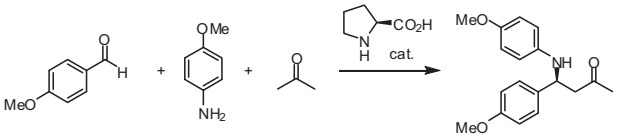


Angew. Chem., Int. Ed., **47**, 634 (2008).

Application of High Pressure Induced by Water-Freezing to the direct catalytic asymmetric reaction

The novel method of high pressure by water-freezing:
The high pressure (cat. 200 MaPa) is easilly is essily achieved simply by freesing water (-20 ℃) in a sealed autoclave.

・Mannich reaction



1 atm, RT **0%, -% *ee***
200 atm, -20°C **99%, 96% *ee***

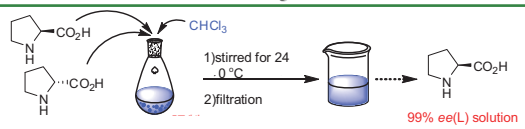
J. Am. Chem. Soc., **125**, 11208 (2003).

・Aldol reaction
Tetrahedron Lett., **45**, 4353 (2004).

・Michael reaction
Chem. Lett., **2002**, 296.

・Baylis-Hillman reaction
Tetrahedron Lett., **43**, 8683 (2004).

Research about of chirality



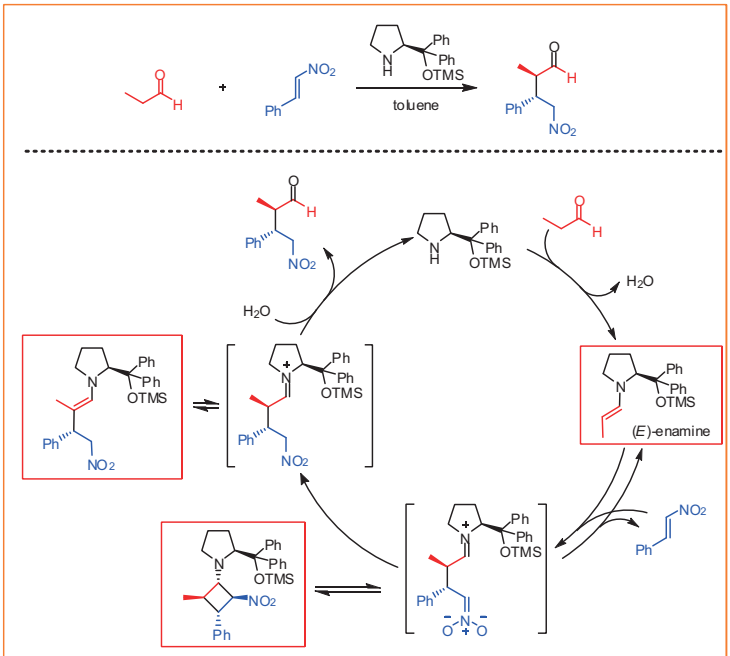
prepared 10% *ee*
(L-Proline excess)

99% *ee*(L) solution

Amplification of *ee* from initial low *ee* → The key to find out origin of chirality

Angew. Chem., Int. Ed., **45**, 4593 (2006).

Proposed Mechanism of Michael Reaction



Helv. Chim. Acta, **94**, 719 (2011).
Helv. Chim. Acta, **96**, 779, (2013).