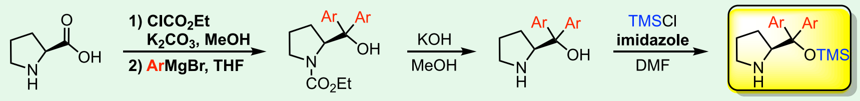
Development of new reactions

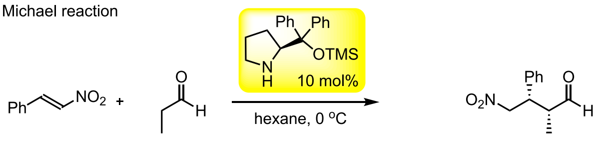
Asymmetric reaction using amino acid or their derivatives as a catalyst,
environmental conscious asymmetric reaction using water as a solvent, and research about origin of chirality

Reaction using diarylprolinol silyl ether derivatives as catalyst



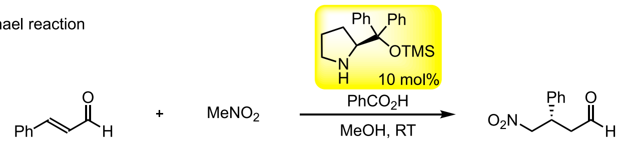
This catalyst is synthesized in short steps from proline.
Substituents on aryl and silyl moiety are easily modified.
Excellent enantioselectivity is obtained

Michael reaction



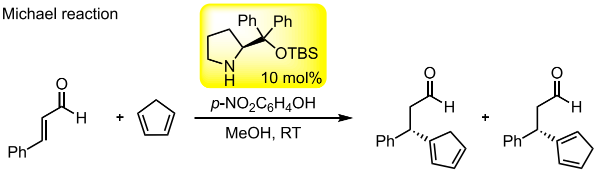
85%, 99% *ee*
Angew. Chem., Int. Ed., **44**, 4212 (2005).

Michael reaction



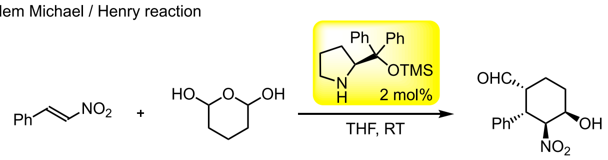
90%, 95% *ee*
Org. Lett., **9**, 5307 (2007).

Michael reaction



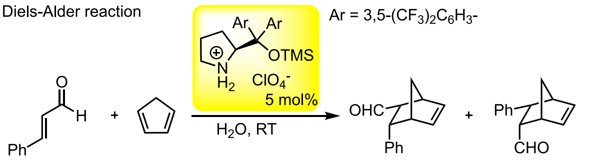
84%, 92% *ee*
Angew. Chem., Int. Ed., **45**, 6853 (2006).

Tandem Michael / Henry reaction



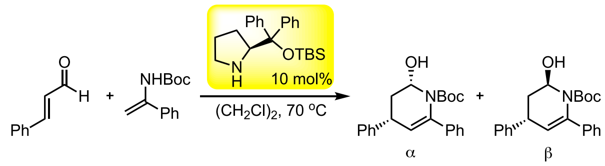
66%, 99% *ee*
Angew. Chem., Int. Ed., **46**, 4922 (2007).

Diels-Alder reaction



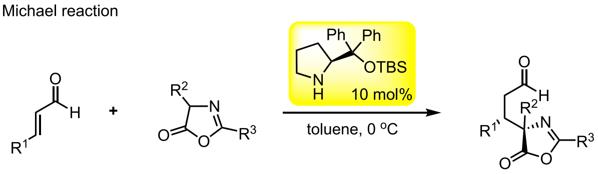
***exo* : *endo* = 80 : 20, 97% *ee* (*exo*)**
Org. Lett, **9**, 2859 (2007).
Angew. Chem., Int. Ed., **47**, 6634 (2008).

Formal aza [3+3] cycloaddition



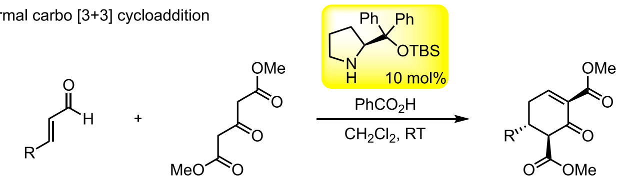
90%, 94% *ee*, α : β = 34 : 66
Angew. Chem., Int. Ed., **47**, 4012 (2008).

Michael reaction



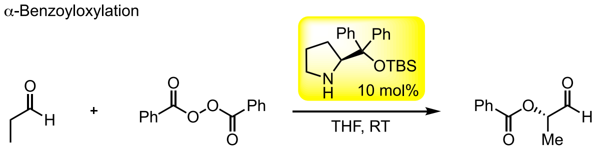
up to 99% *ee*
up to >90% *de*
Chem. Asian. J., **4**, 246 (2009).

Formal carbo [3+3] cycloaddition



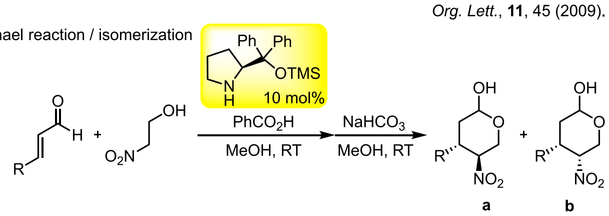
up to 99% *ee*
Org. Lett., **11**, 45 (2009).

α-Benzoyloxylation



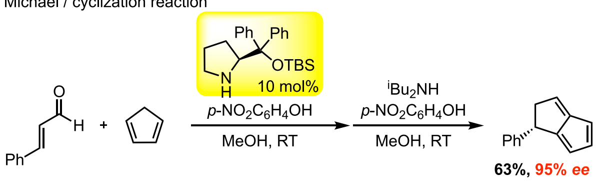
78%, 92% *ee*
Chem. Commun,, 3083 (2009).

Michael reaction / isomerization



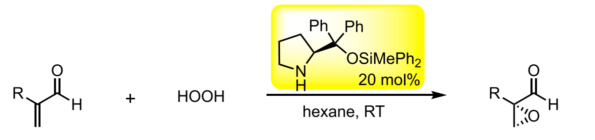
up to 99% *ee*, a : b = 9 : 1
Org. Lett., **11**, 4056 (2009).

Michael / cyclization reaction



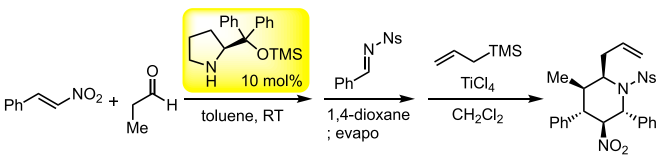
63%, 95% *ee*
Tetrahedron, **66**, 4894 (2010).

epoxidation



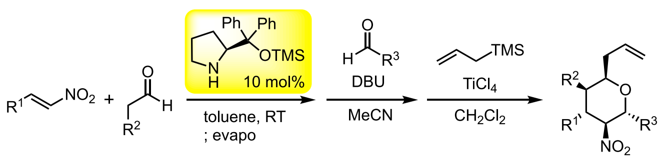
up to 95% *ee*
Org. Lett., **12**, 5434 (2010).

Michael / aza Henry / aminal formation / additional reaction



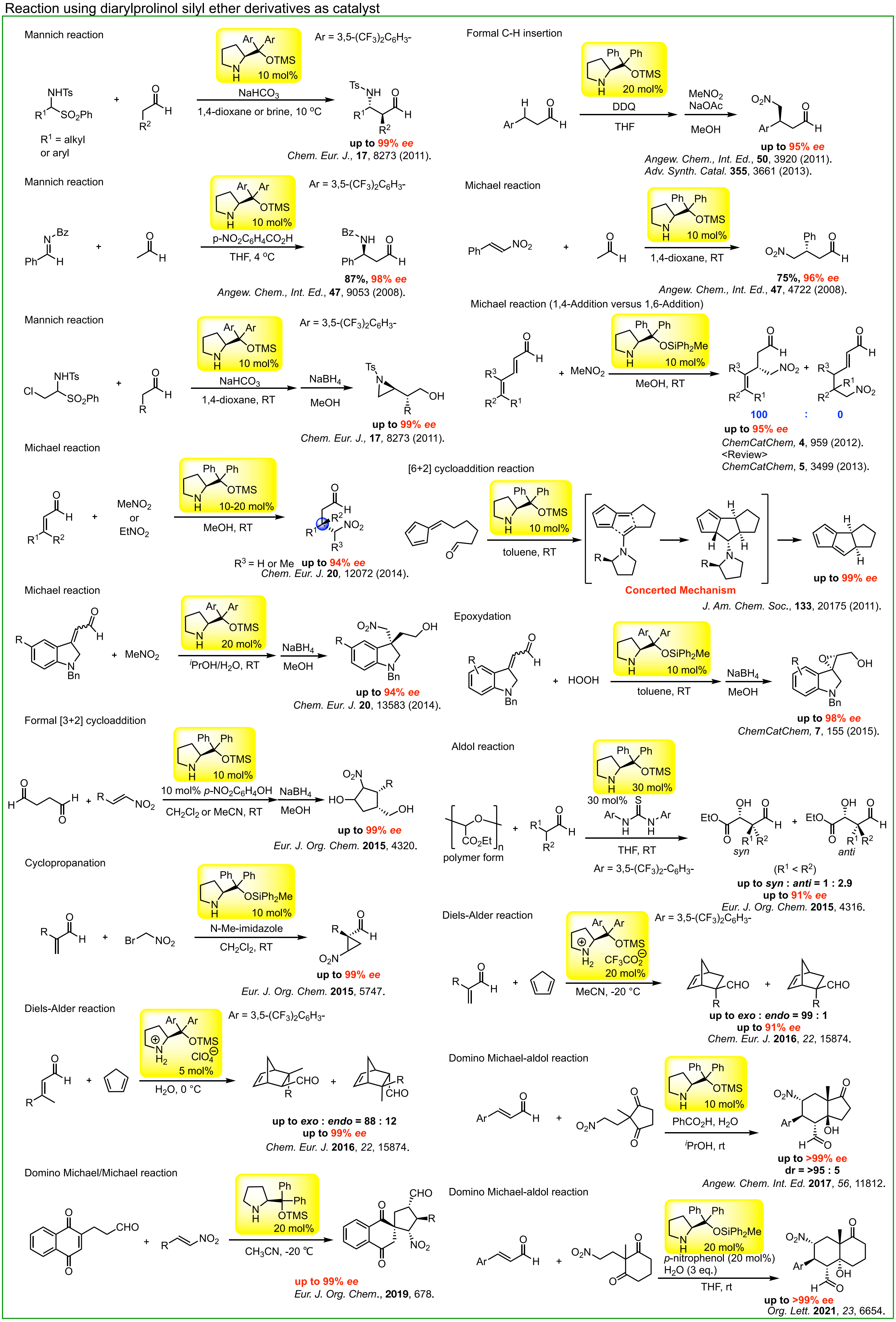
up to 99% *ee*
Single diastereomer
Org.Lett., **12**, 4588 (2010).

Michael / Henry / acetal formation / additional reaction

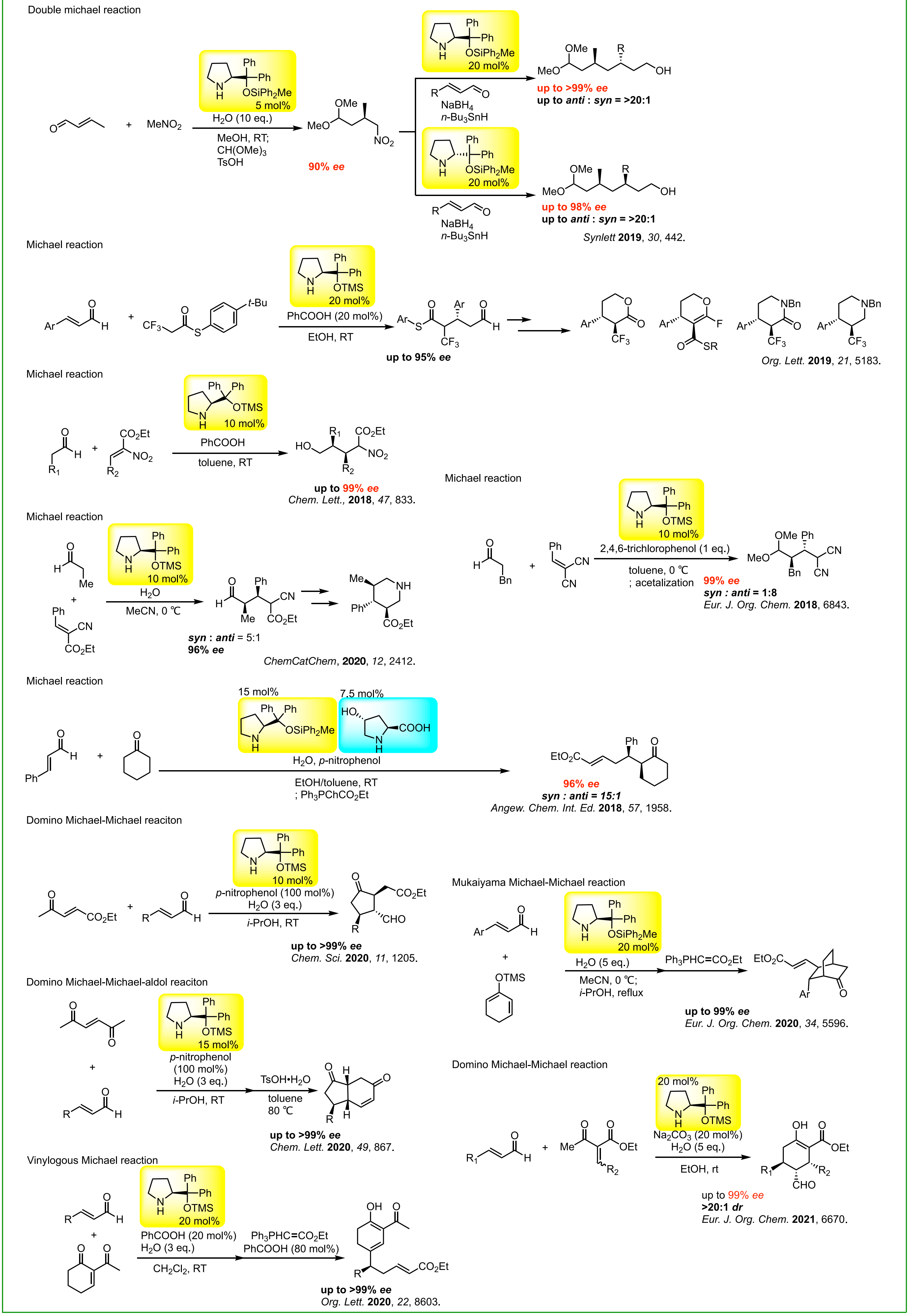


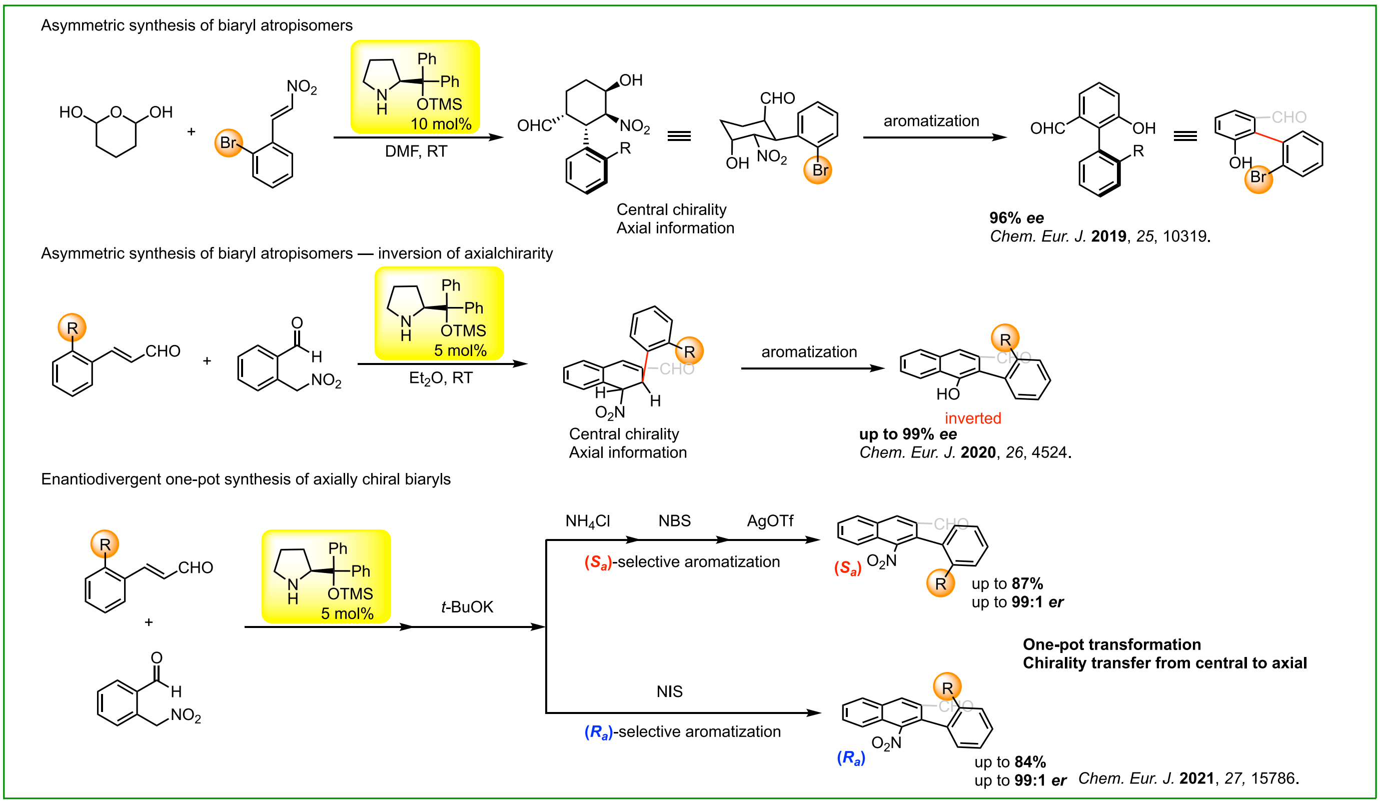
up to 99% *ee*
Single diastereomer
Angew. Chem., Int. Ed., **50**, 3774 (2011).

Reaction using diarylprolinol silyl ether derivatives as catalyst

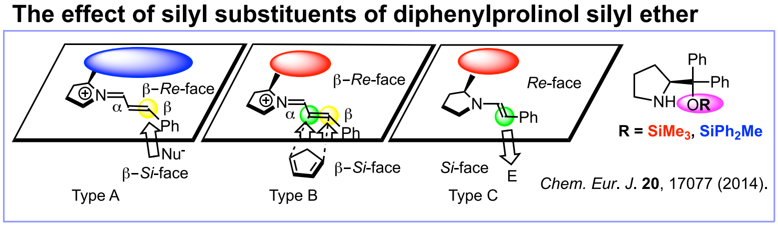


Reaction using diarylprolinol silyl ether derivatives as catalyst

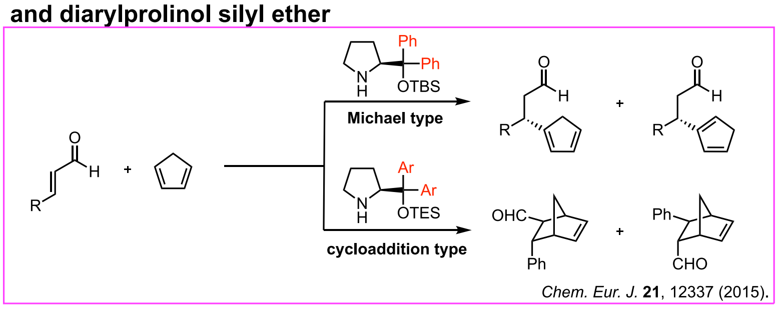




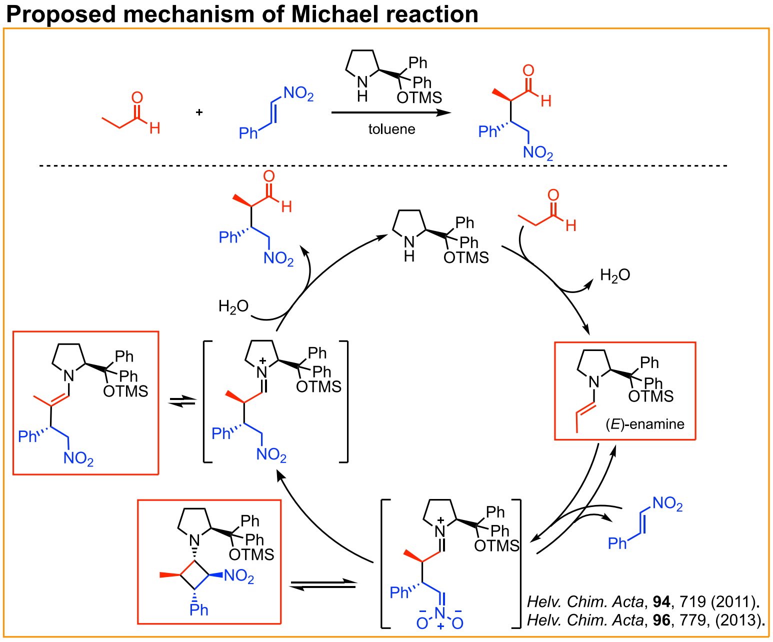
The effect of silyl substituents of diphenylprolinol silyl ether



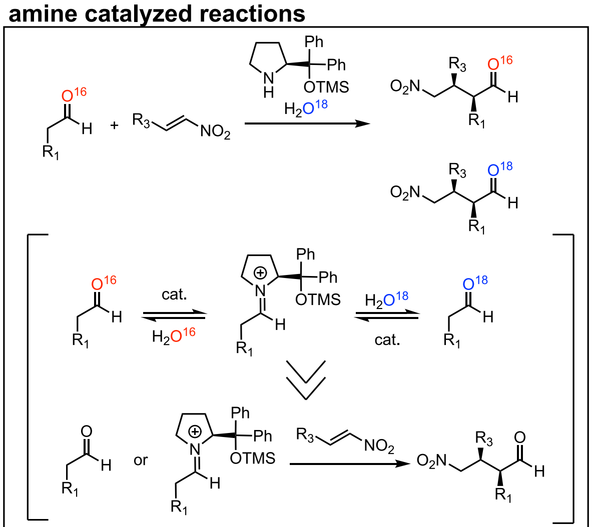
The different reactivity of diphenylprolinol silyl ether and diarylprolinol silyl ether



Proposed mechanism of Michael reaction



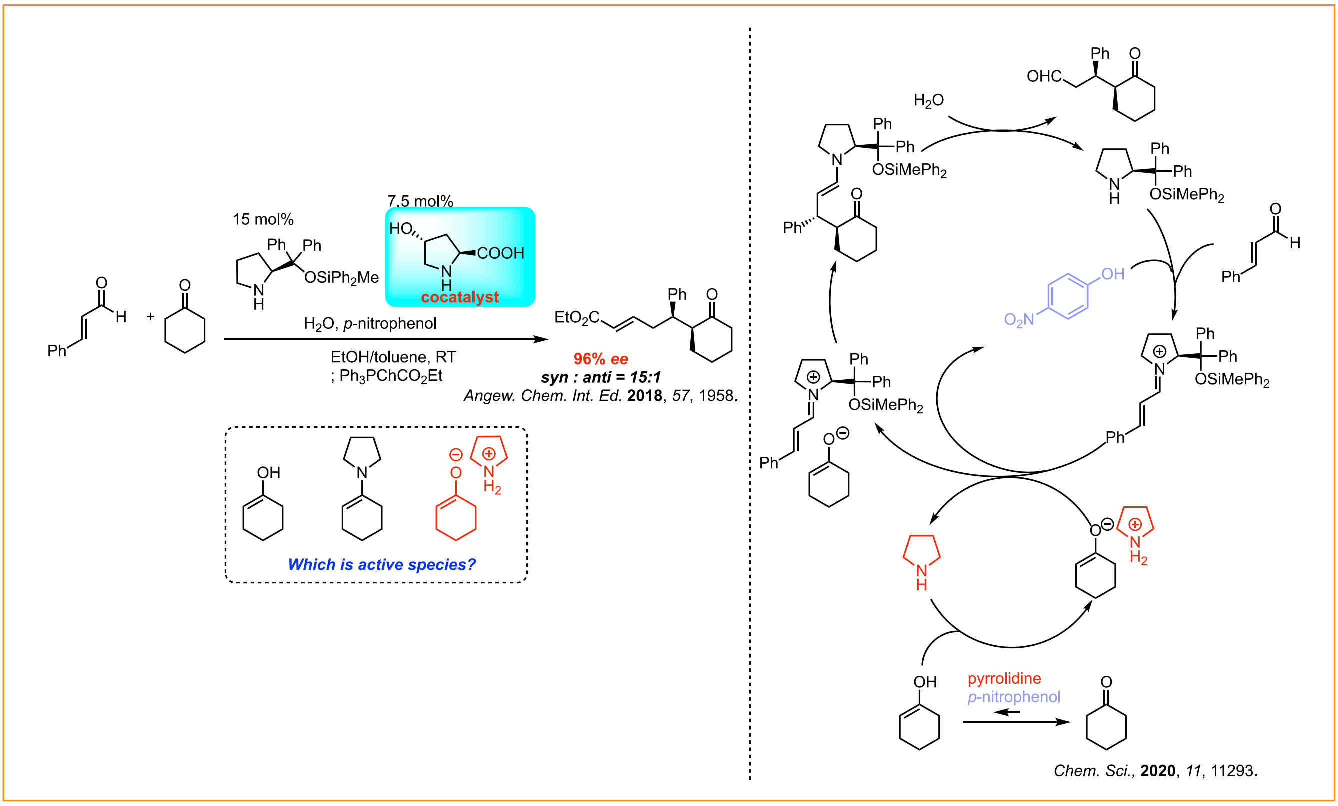
The $^{16}O/^{18}O$ exchanges existance in secondary amine catalyzed reactions



exchenge of oxygen is greatly faster than Michael reaction. So, it is impossible to determine the reaction proceeds with enol or enamine by containing of 18O of TM.

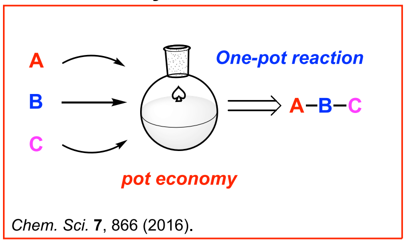
Chem. Eur. J. **2016**, *22*, 5868.

Proposed mechanism of α, β-unsaturated aldehyde and ketones via hydrid system of two secondary amine catalysts

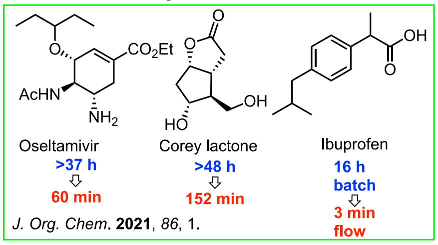


Review

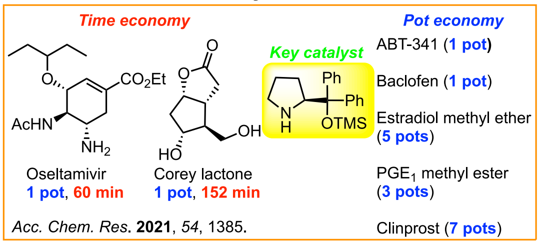
Pot ecomomy



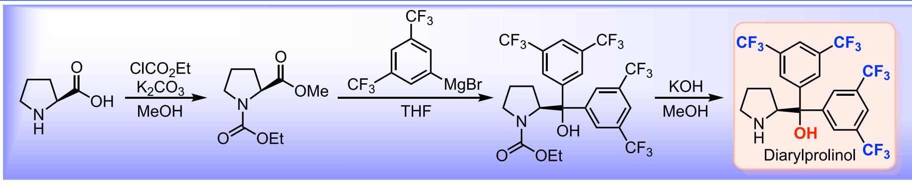
Time ecomomy



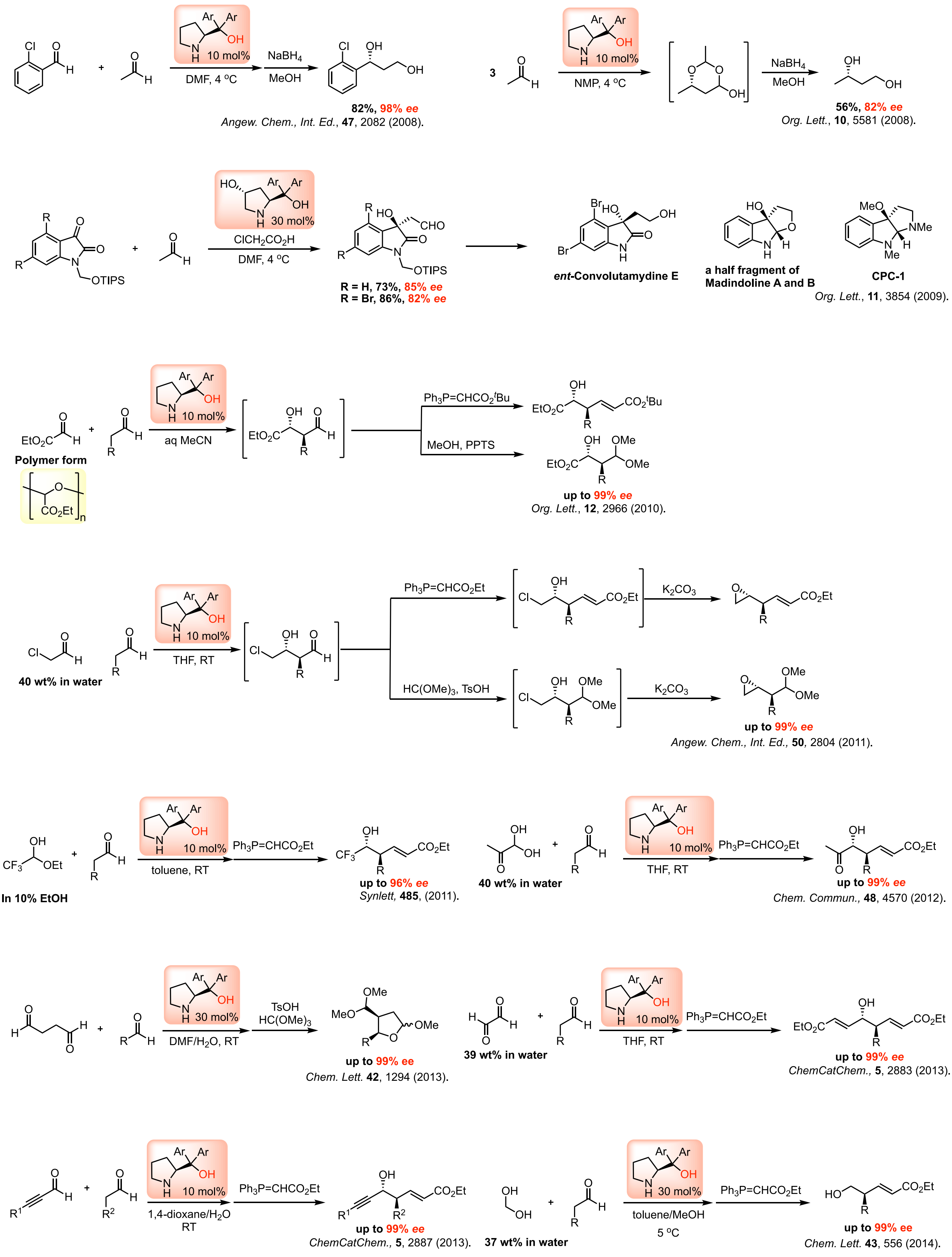
Pot and Time economy



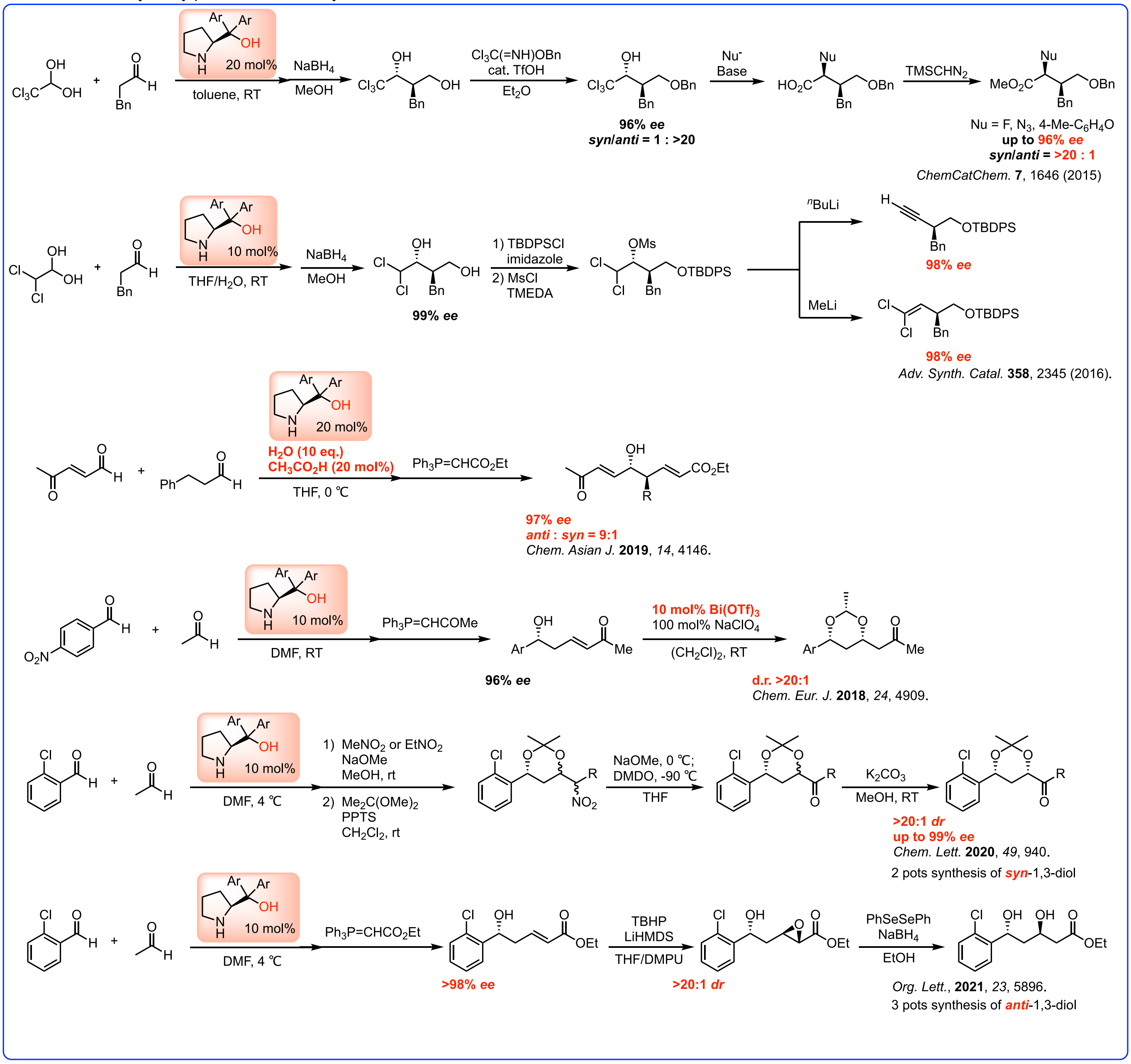
Aldol reaction by diarylprolinol as a catalyst



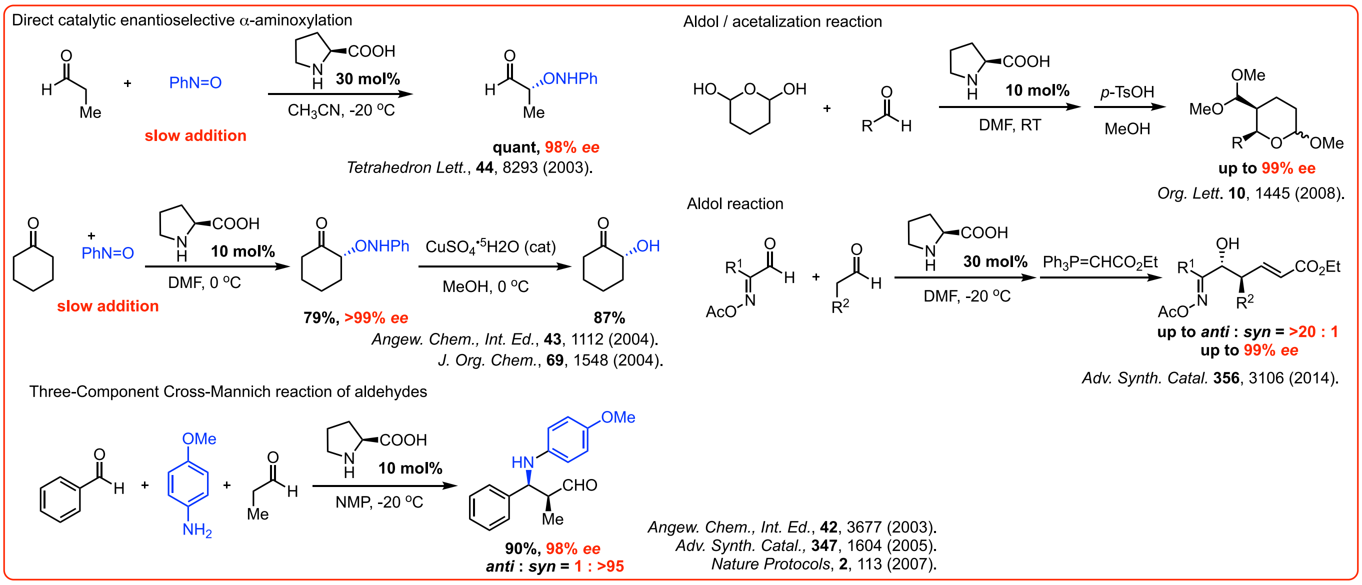
This catalyst is synthesized in short steps from proline.
This is effective organocatalyst of direct, enantioselective aldol reaction.
Excellent enantioselectivity is obtained.



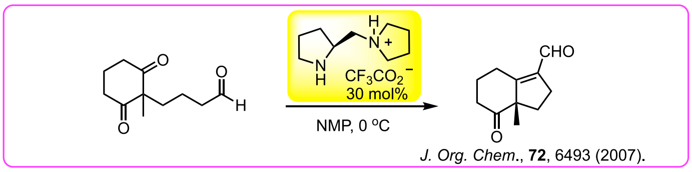
Aldol reaction by diarylprolinol as a catalyst



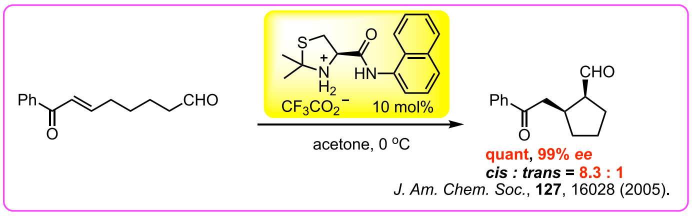
Reaction catalyzed by proline



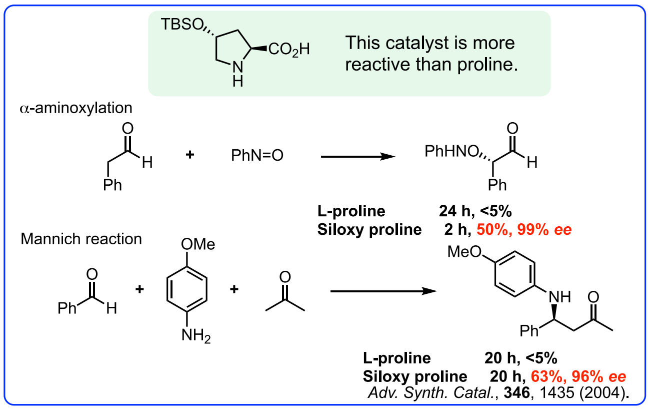
Reaction by proline-derived catalyst



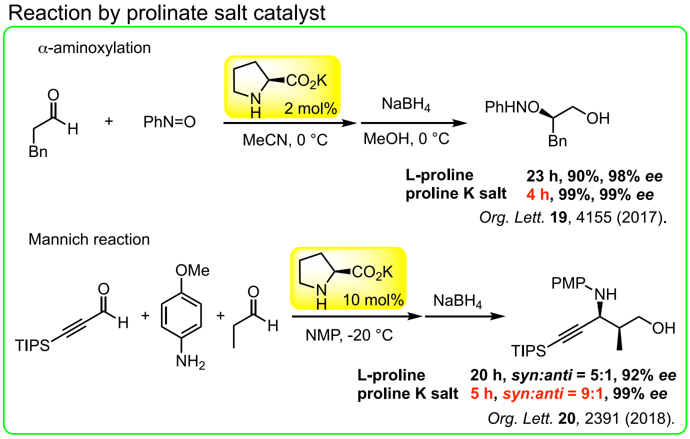
Reaction by cystein-derived catalyst



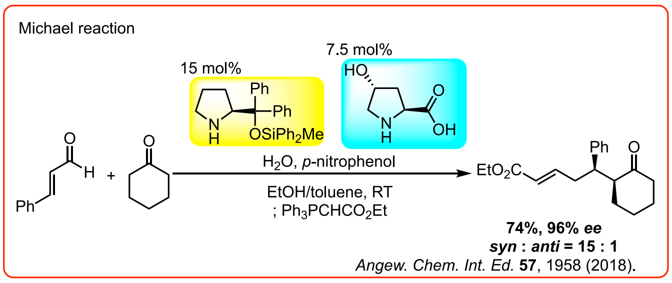
Reaction by siloxyproline catalyst



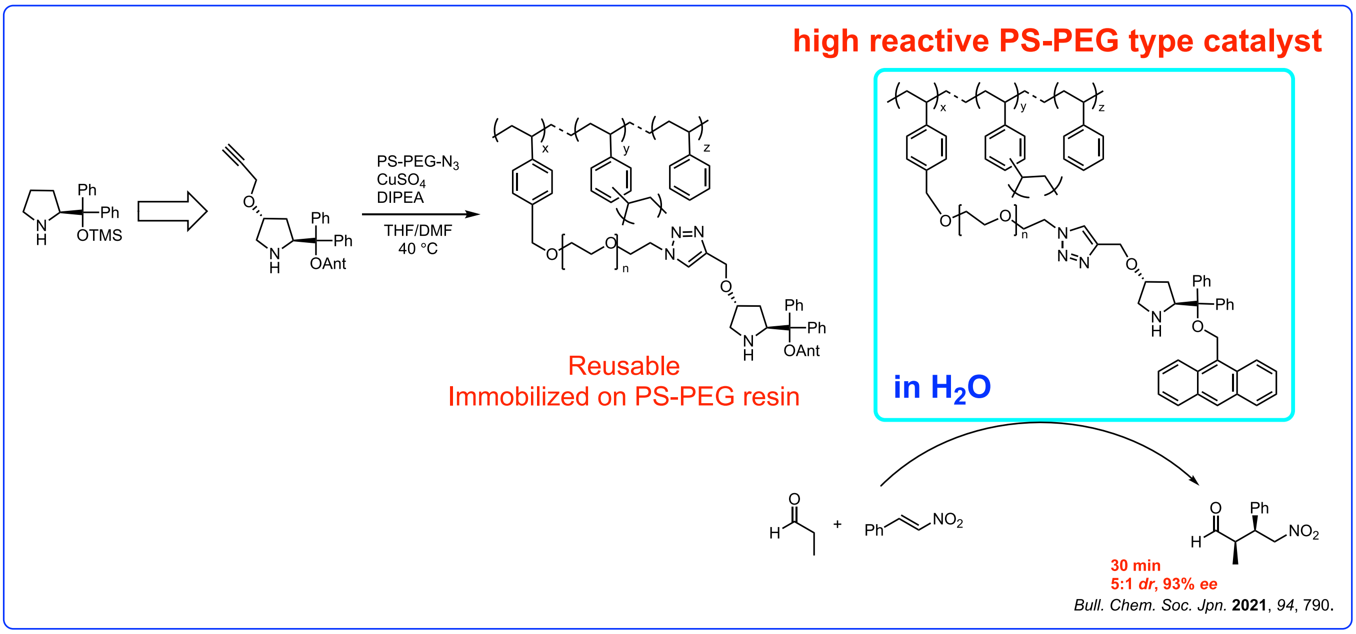
Reaction by prolinate salt catalyst



Reaction using two catalysts system

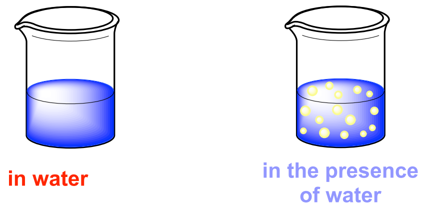


Polymer supported Diphenylprolinol catalysts



Organic solvent free reaction

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

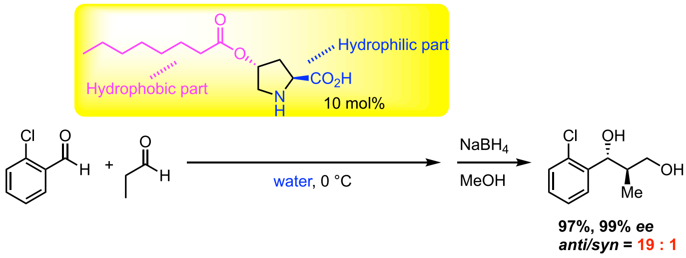


"in water" : The participating reactions are dossplved homogeneously in water.

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

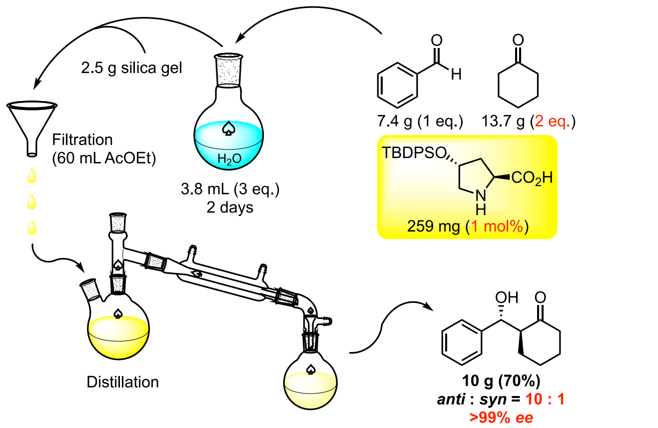
Angew. Chem. Int. Ed. **45**, 8103 (2006).

•Intermolecular aldol reaction between aldehydes in the presence of water



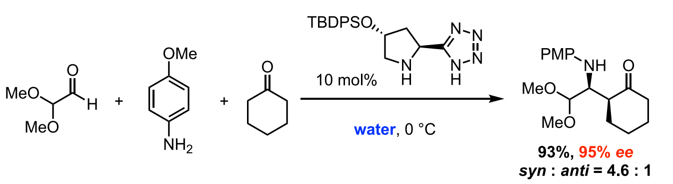
Angew. Chem. Int. Ed. **45**, 5527 (2006).

•Organic solvent free asymmetrric aldol reaction between ketone and aldehyde



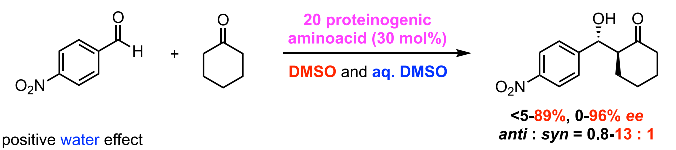
Angew. Chem. Int. Ed. **45**, 958 (2006).
Chem. Eur. J. **13**, 10246 (2007).

•Organic solvent free asymmetrric Mannich reaction with proline catalyst



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

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



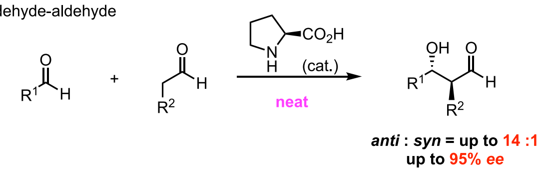
positive water effect

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

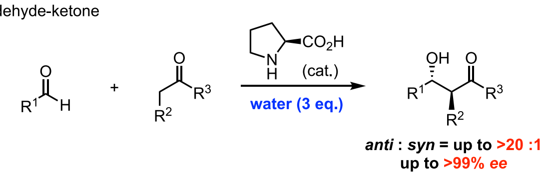
Synlett 1565 (2006).

•Organic solvent free Dry and Wet condition asymetric aldol reaction with proline catalyst

aldehyde-aldehyde

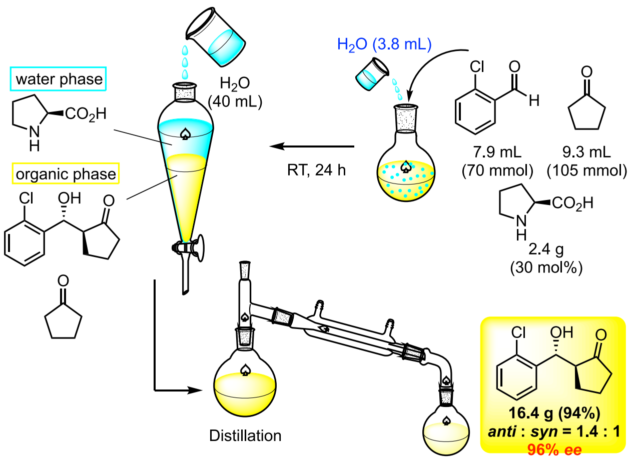


aldehyde-ketone

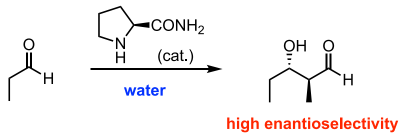


Chem. Commun. 957 (2007).

Organic solvent-free aldol reaction

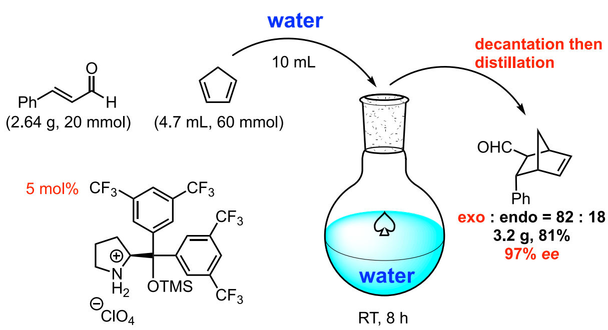


•Self aldol reaction of propanal in water - reaction in water with proline-amide catalyst



Chem. Commun. 2524 (2007).

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



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

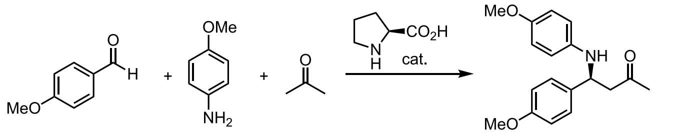
Application of High Pressure Induced by Water-Freezing to the direct catalytic asymmetric reaction

The novel method of high pressure by water-freezing:

The high pressre (cat. 200 MaPa) is easilly is essily achieved

simply by freesing water (-20 °C) in a sealed autoclave.

·Mannich reaction



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

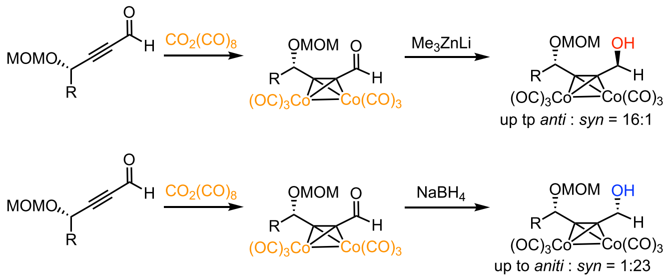
J. Am. Chem. Soc., **125**, 11208 (2003).

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

·Michael reaction
Chem. Lett., 296 (2002).

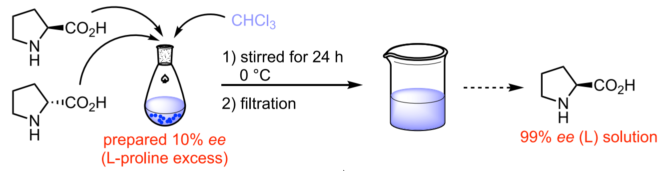
·Baylis-Hillman reaction
Tetrahedron Lett., **43**, 8683 (2004).

1,4-asymmetric induction using Cobalt alkyne complex



Organometallics **2008**, *27*, 163.

Research about of chirality

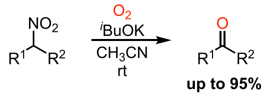


Amplification of *ee* from initial low *ee* ⇨ The key to find out origin of chirality

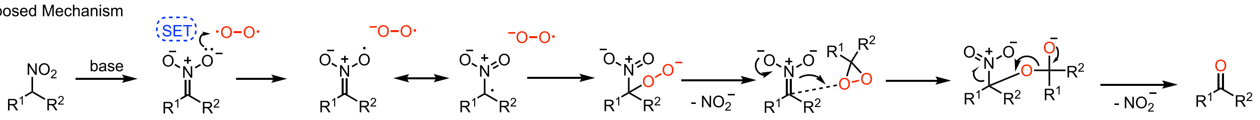
Angew. Chem., Int. Ed. **45**, 4593 (2006).

Metal-free oxidative transformations using O_2

Nef reaction using molecular O_2

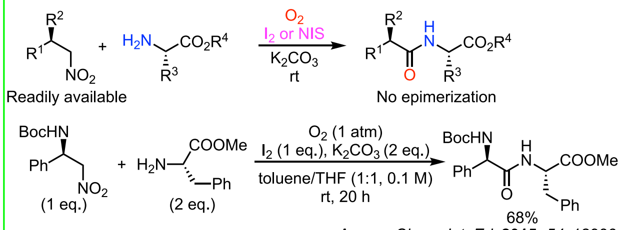


Proposed Mechanism



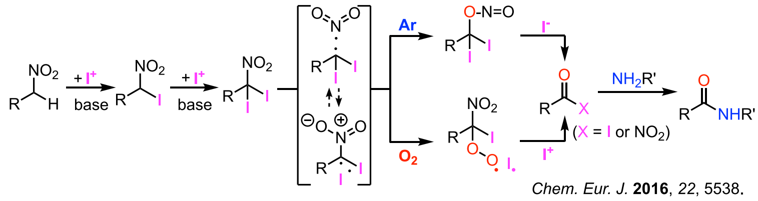
Chem. Eur. J. **2014**, *20*, 15753.

Oxidative amidation of primary nitroalkane and amine



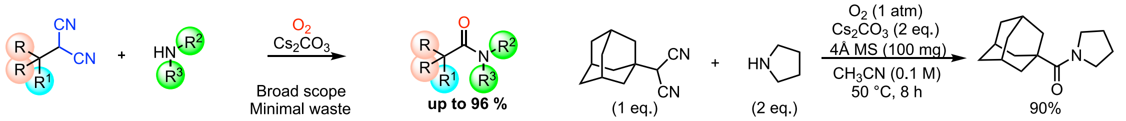
Angew. Chem. Int. Ed. **2015**, *54*, 12986.

Proposed Mechanism



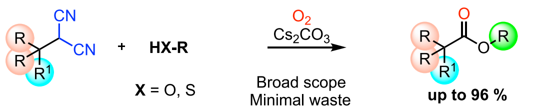
Chem. Eur. J. **2016**, *22*, 5538.

Sterically demanding oxidative amidation of α-substituted malononitriles with amines



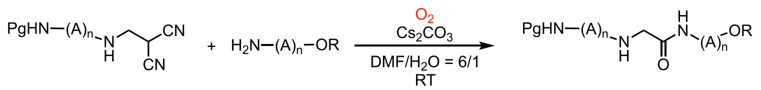
Angew. Chem. Int. Ed. **2016**, *55*, 9060.

Sterically demanding ester formation of α-substituted malononitriles with alcohol



Eur. J. Org. Chem. **2019**, 675.

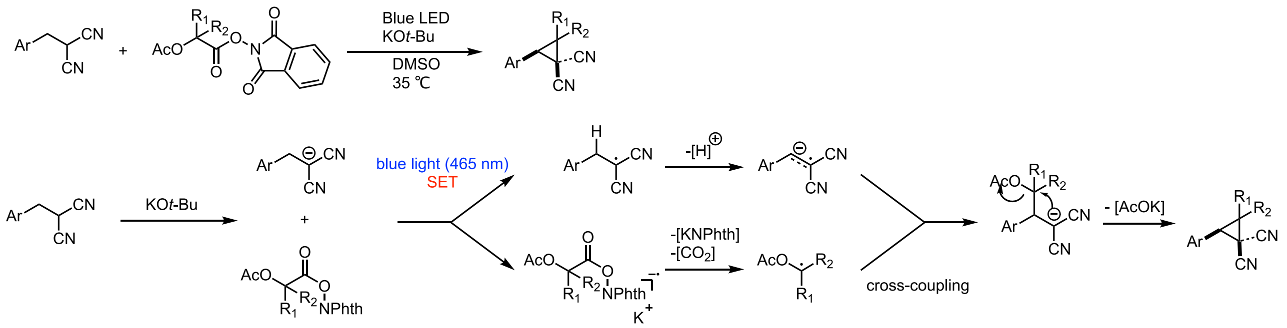
Application to peptipe synthesis



Broad scope
Tripeptide : **Boc-Phe-Gly-Phe-OMe (18 examples)**
Tetrapeptide : **Boc-Phe-Gly-Leu-Phe-O*t*-Bu (5 examples)**
Unprotected amino acid : **Boc-Phe-Gly-Phe-OH (4 examples)**

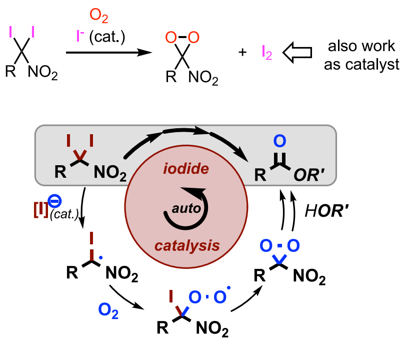
Chem. Commun., **2021**, *57*, 4283.

Direct cyclopropanation by light mediated single electron transfer



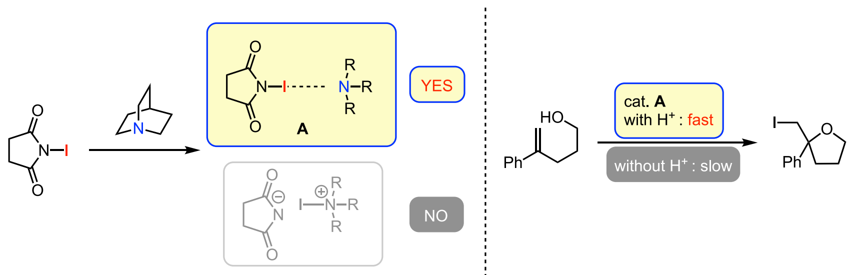
Chem. Eur. J. **2021**, *27*, 5901.

Autoinductive oxidation of α,α-diiodonitroalkanes



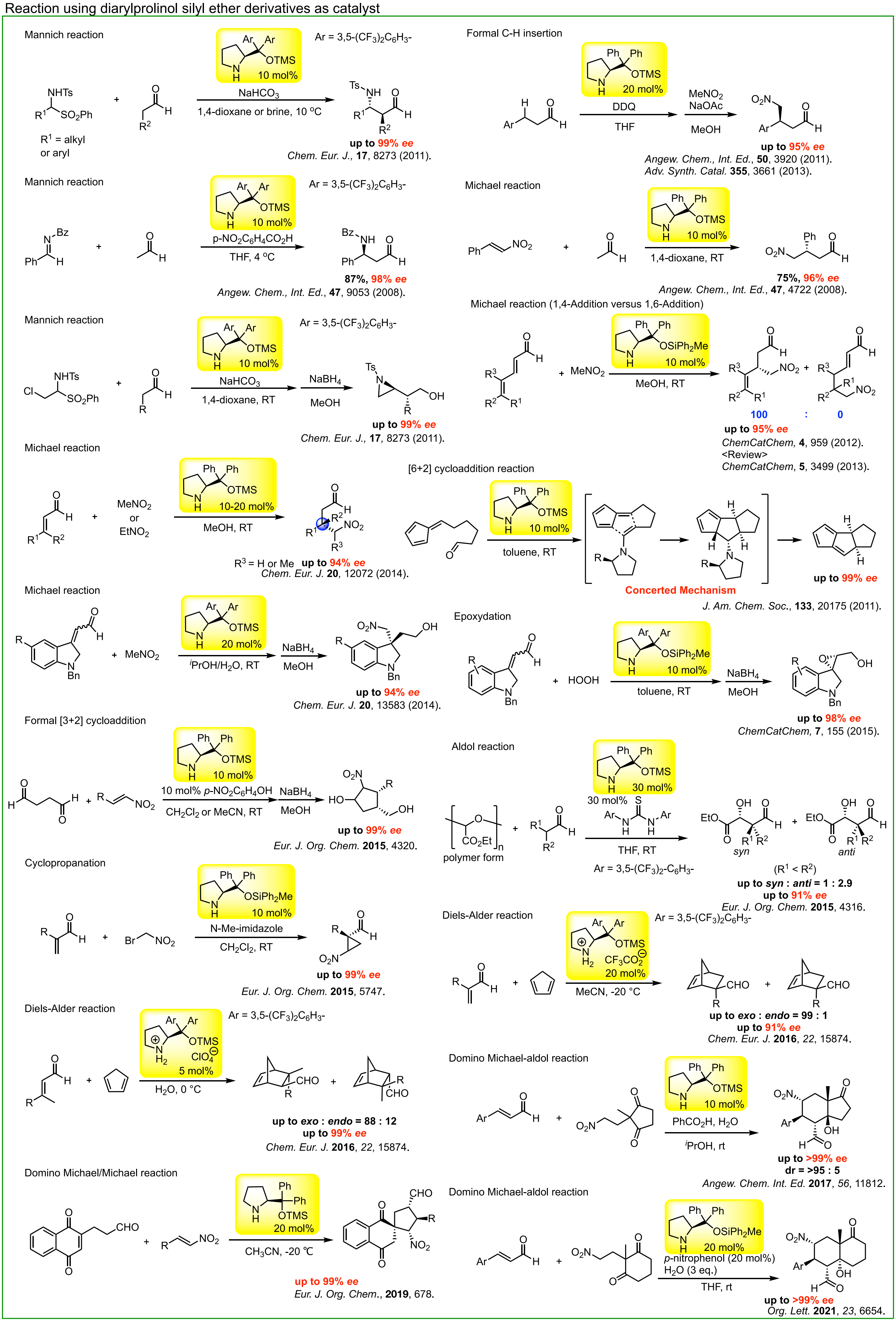
Chem. Commun., **2018**, *54*, 6360.

Halogen bonding of N-Halosuccinimides with amines

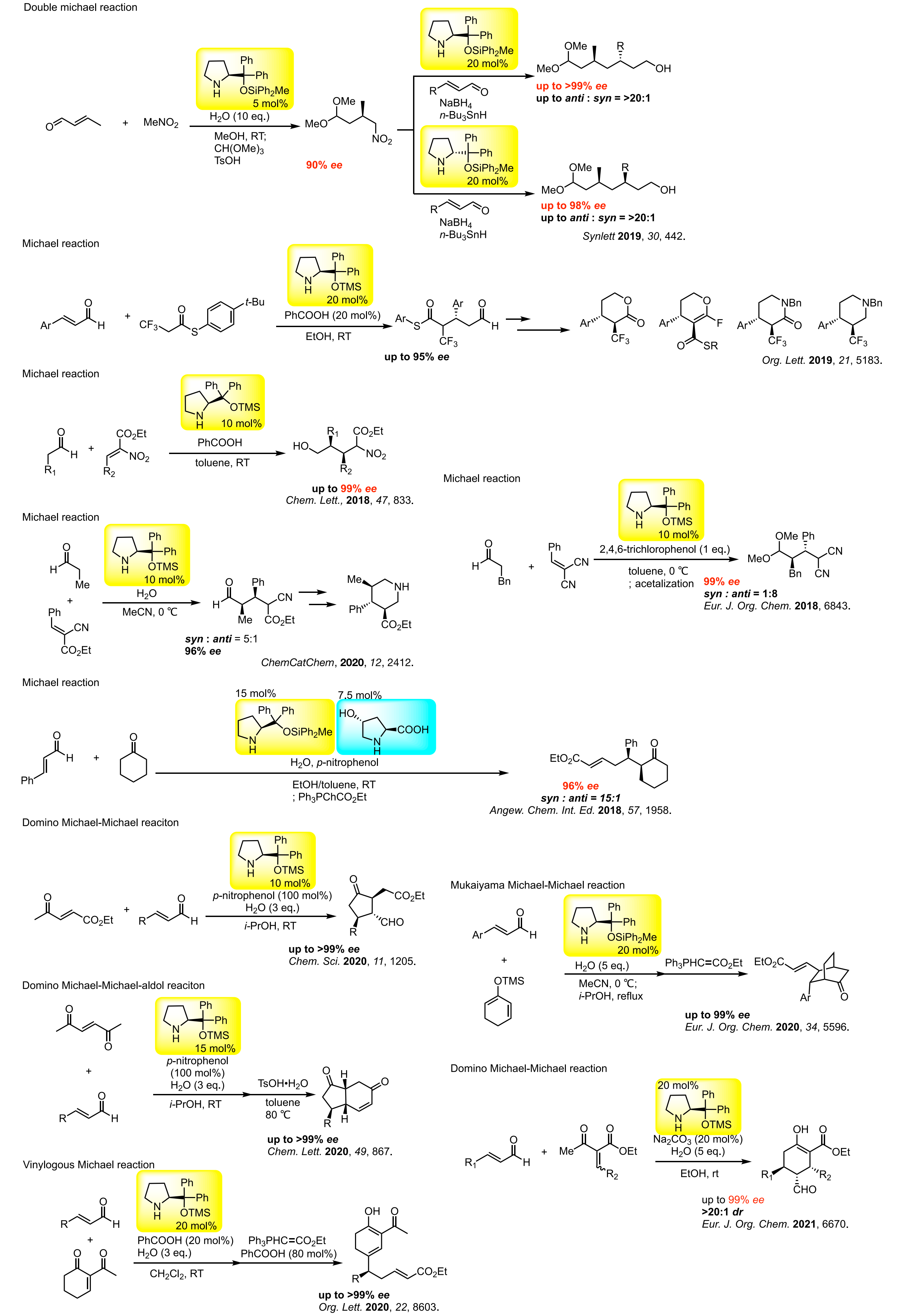


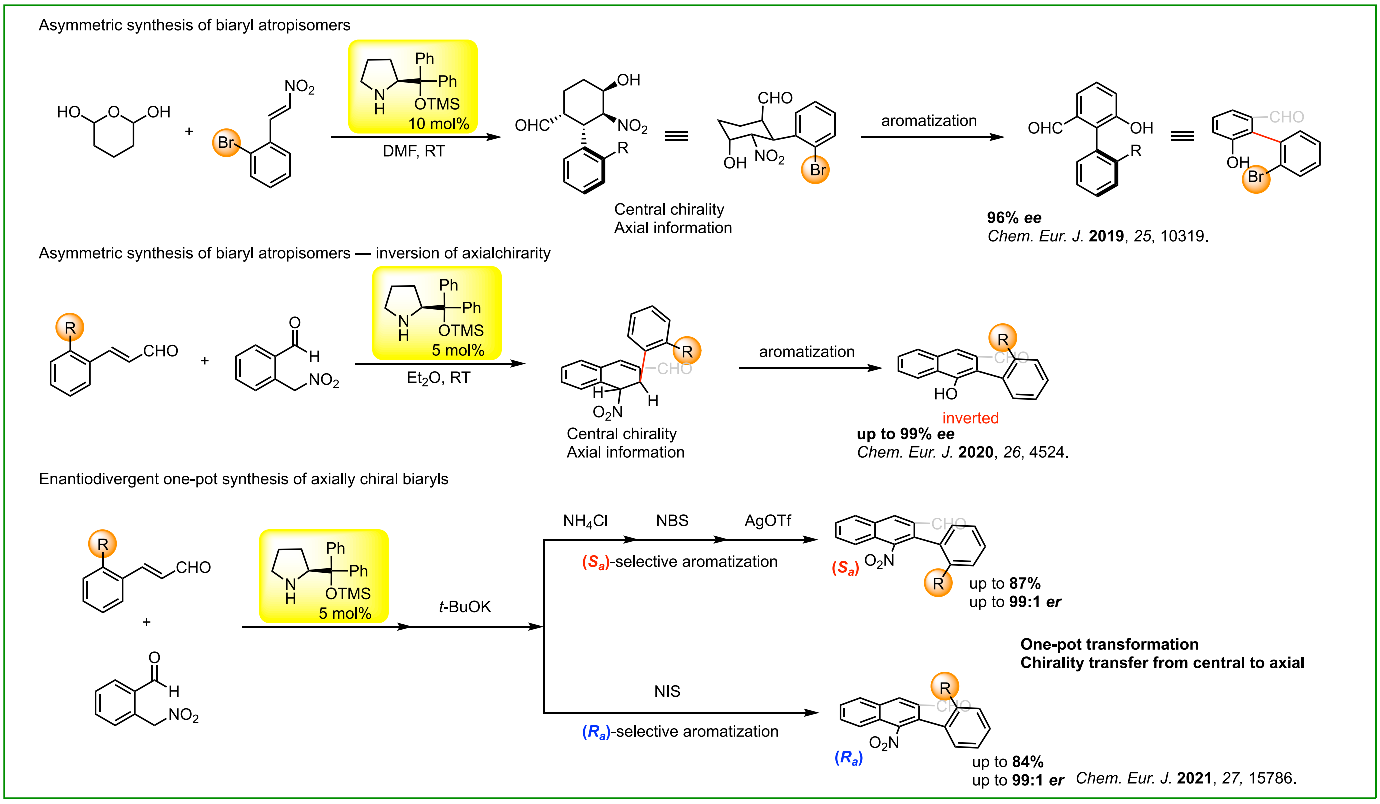
Helv. Chim. Acta., **2021**, *104*, e2100080

Reaction using diarylprolinol silyl ether derivatives as catalyst

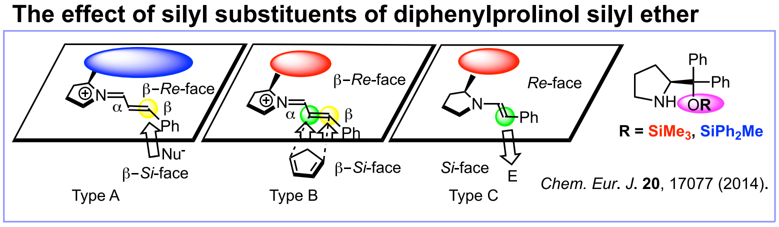


Reaction using diarylprolinol silyl ether derivatives as catalyst

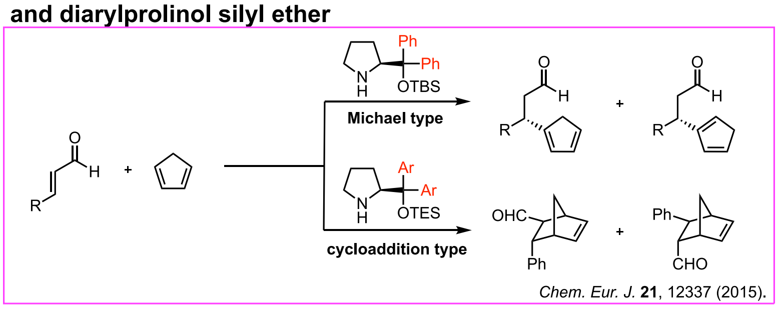




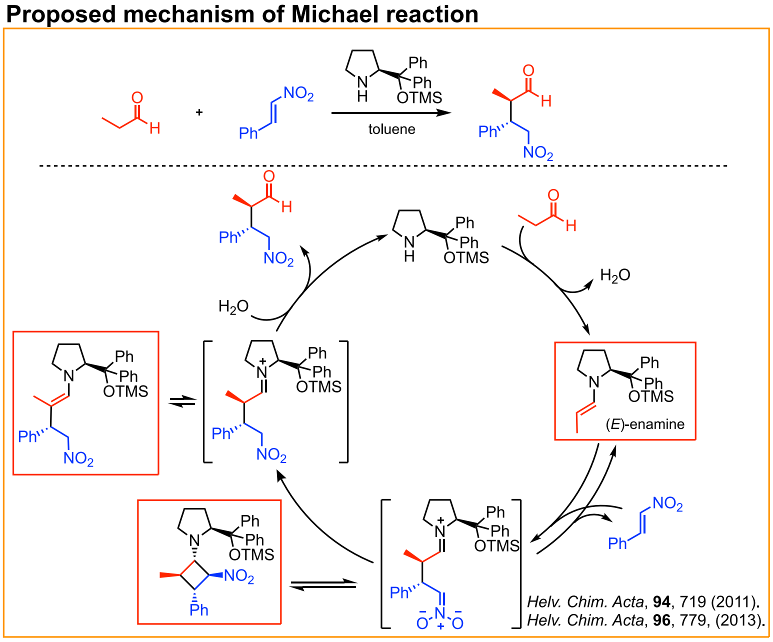
The effect of silyl substituents of diphenylprolinol silyl ether



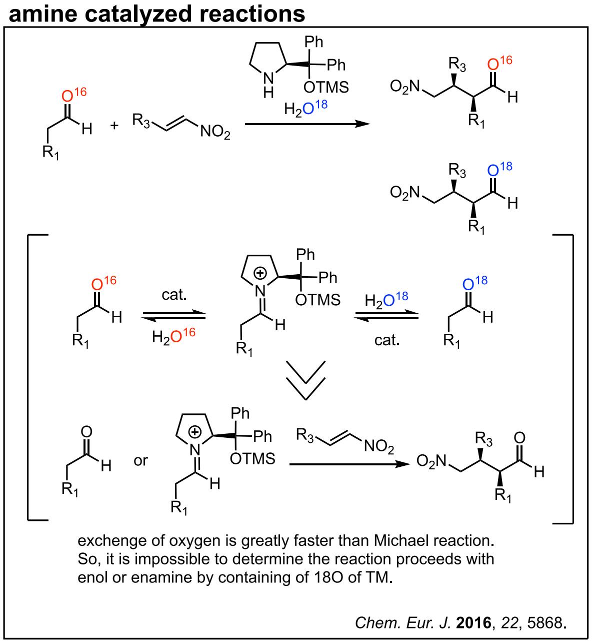
The different reactivity of diphenylprolinol silyl ether and diarylprolinol silyl ether



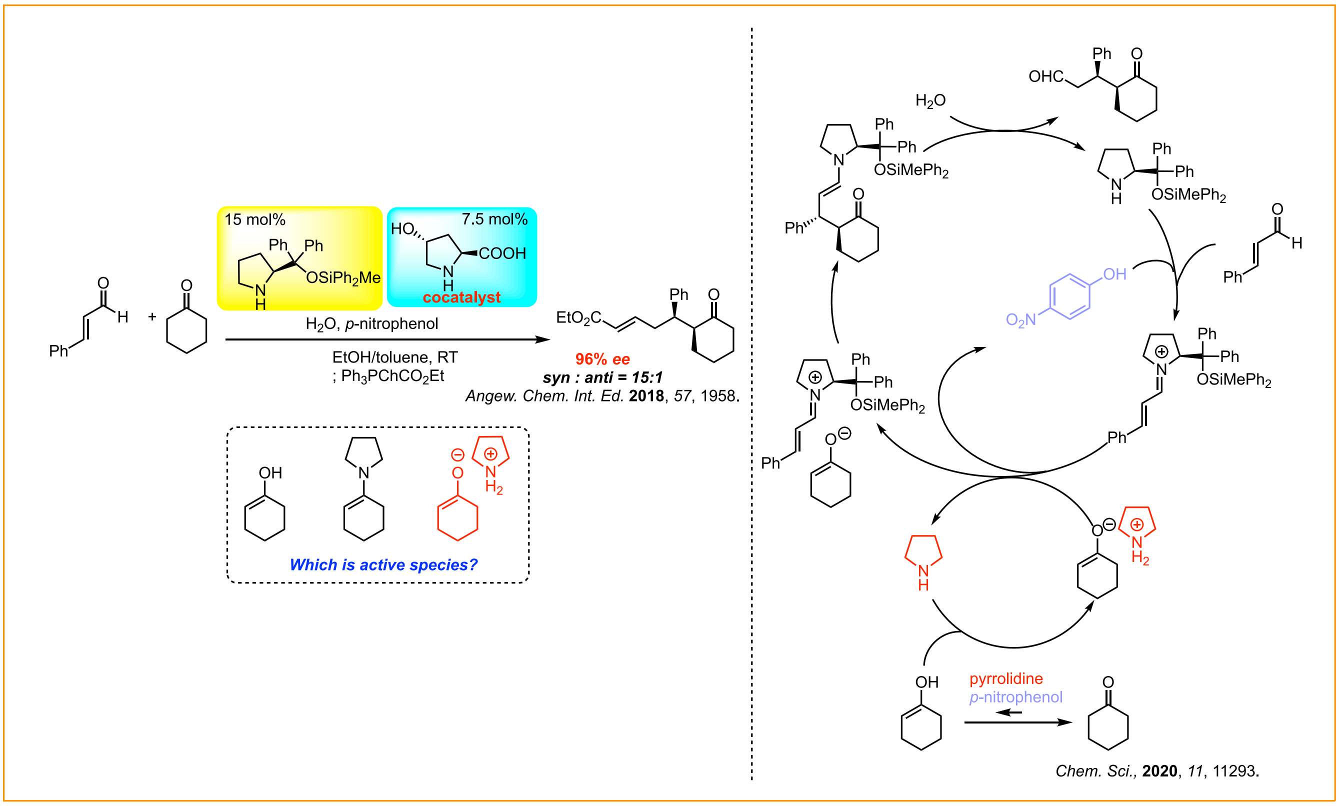
Proposed mechanism of Michael reaction



The $^{16}O/^{18}O$ exchanges existance in secondary amine catalyzed reactions

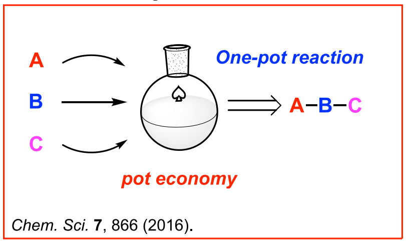


Proposed mechanism of α, β-unsaturated aldehyde and ketones via hydrid system of two secondary amine catalysts

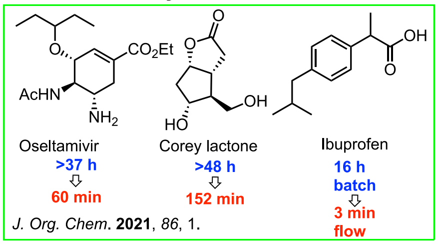


Review

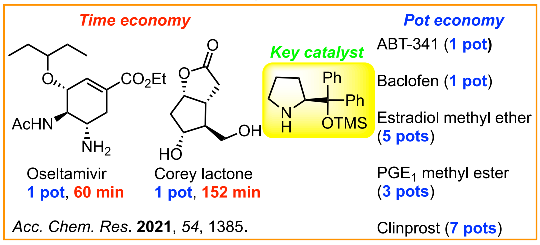
Pot ecomomy



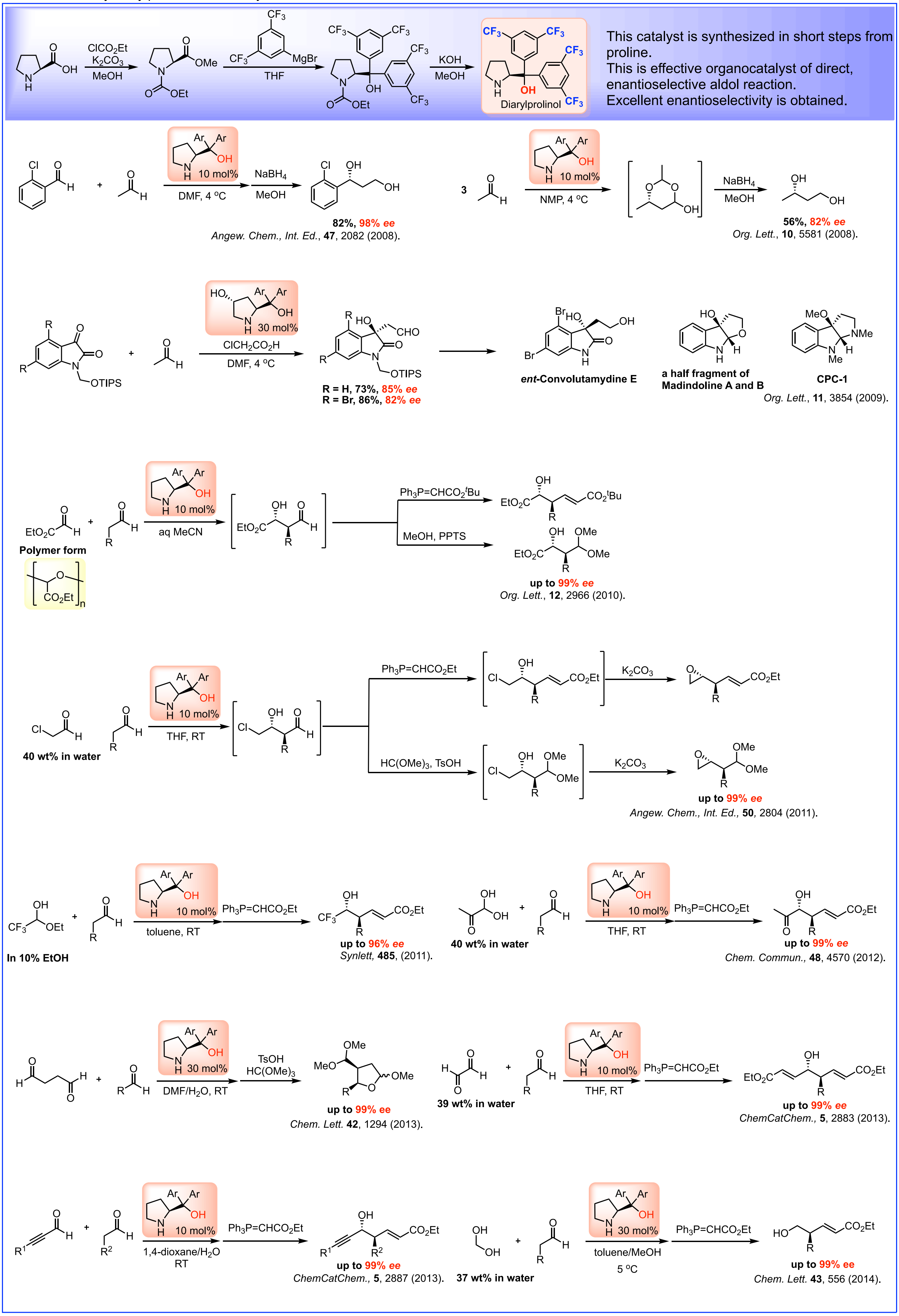
Time ecomomy



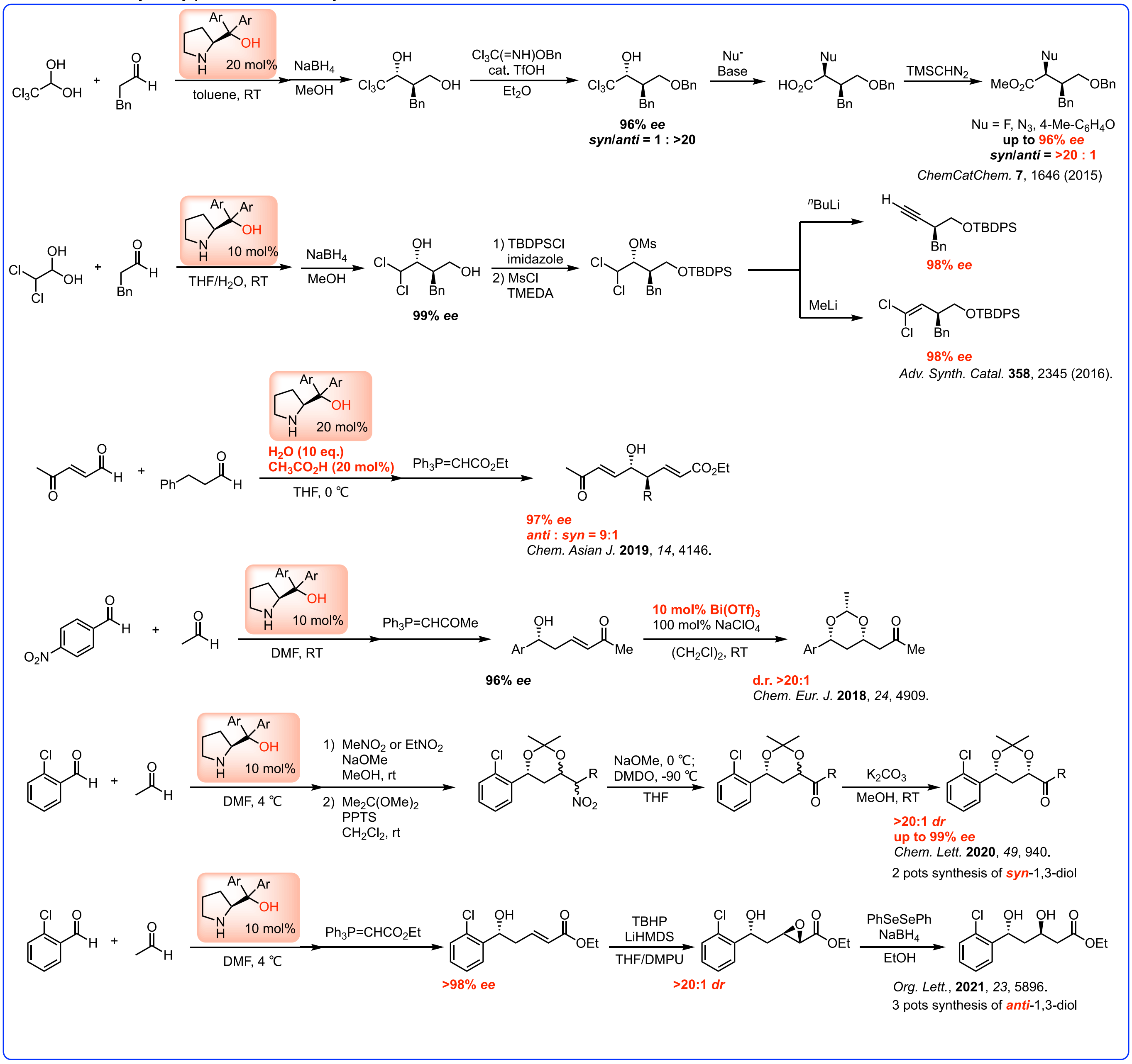
Pot and Time economy



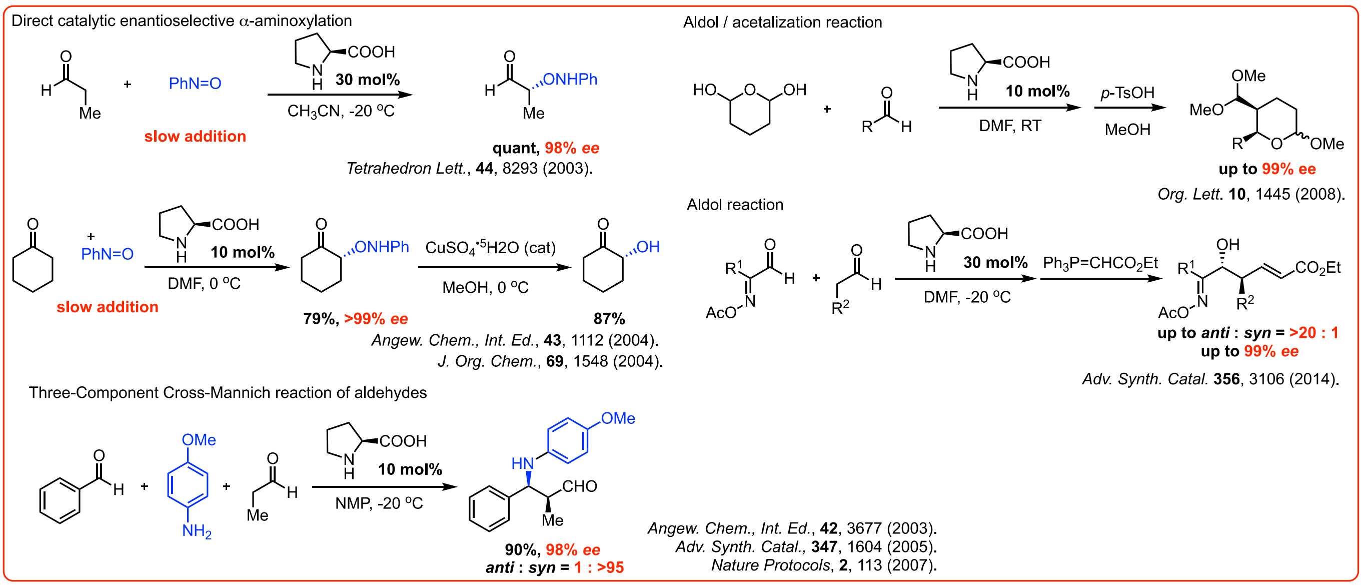
Aldol reaction by diarylprolinol as a catalyst



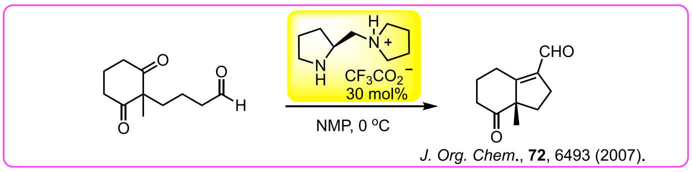
Aldol reaction by diarylprolinol as a catalyst



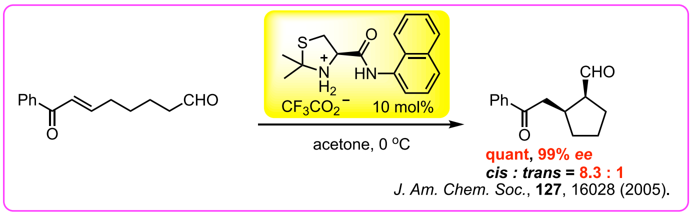
Reaction catalyzed by proline



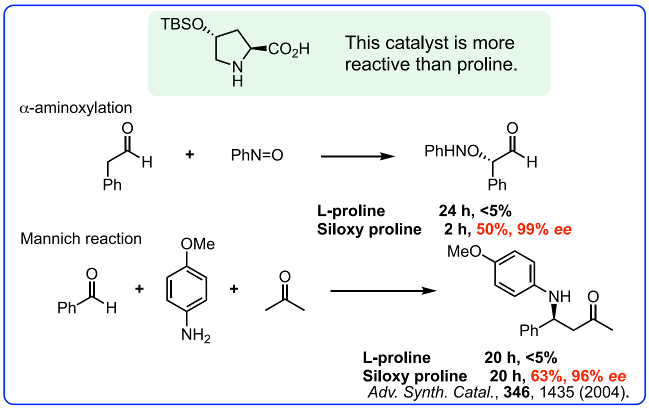
Reaction by proline-derived catalyst



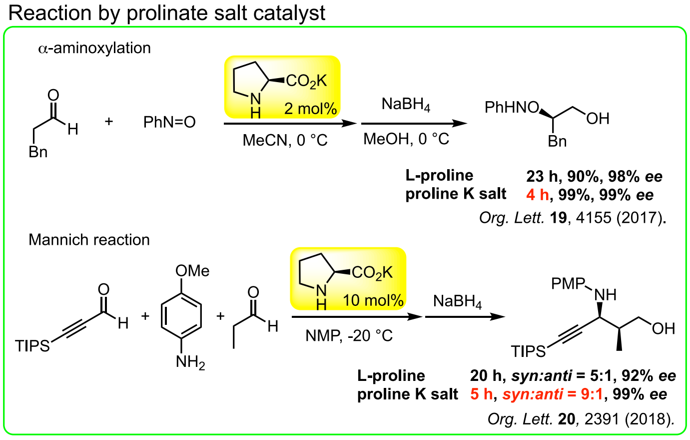
Reaction by cystein-derived catalyst



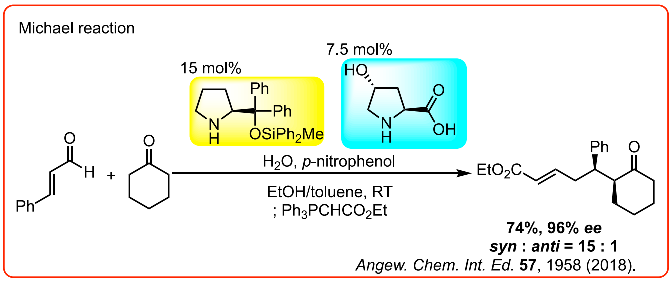
Reaction by siloxyproline catalyst



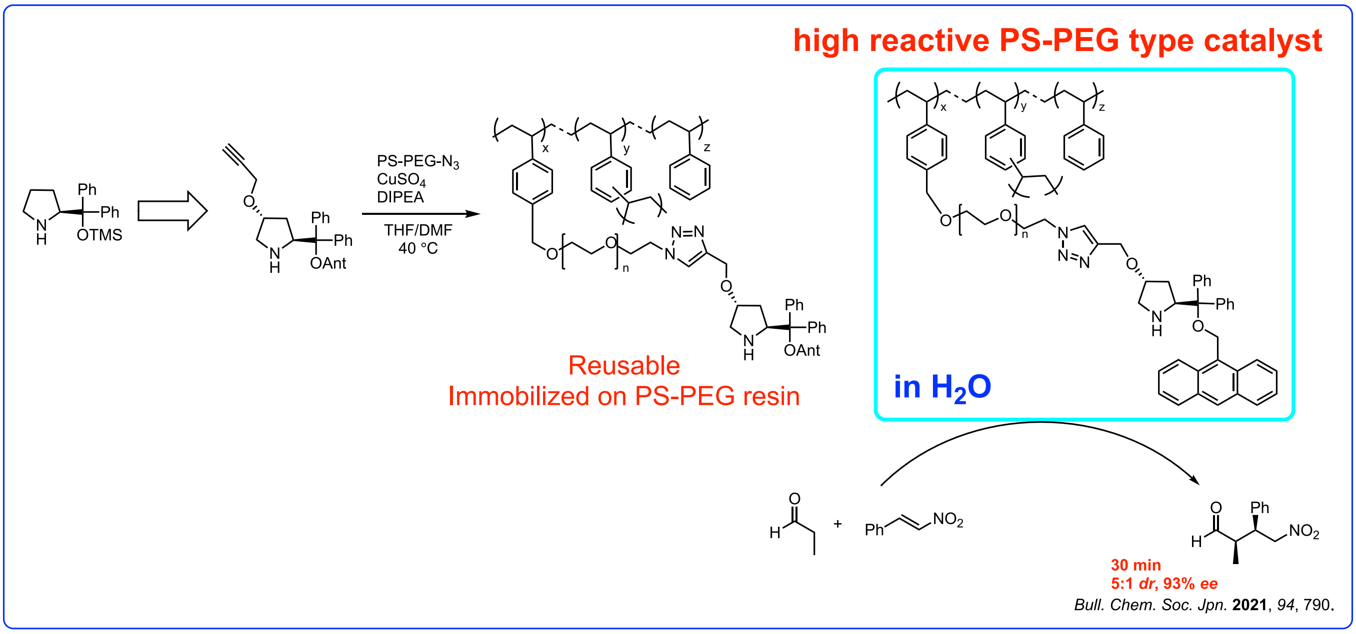
Reaction by prolinate salt catalyst



Reaction using two catalysts system



Polymer supported Diphenylprolinol catalysts



Organic solvent free reaction

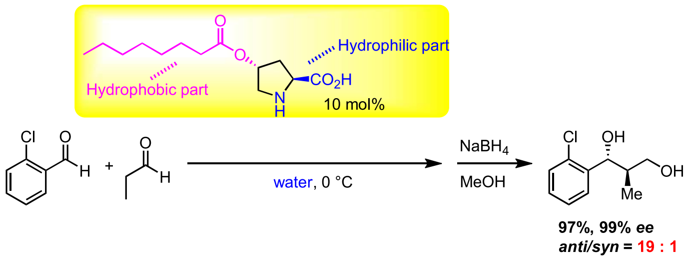
·"in the water" or "in the presence of water" ?

"in water" : The participating reactions are dossplved homogeneously in water.

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

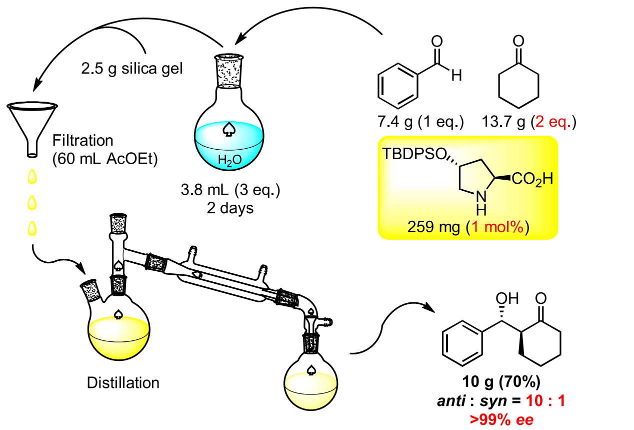
Angew. Chem. Int. Ed. **45**, 8103 (2006).

·Intermolecular aldol reaction between aldehydes in the presence of water



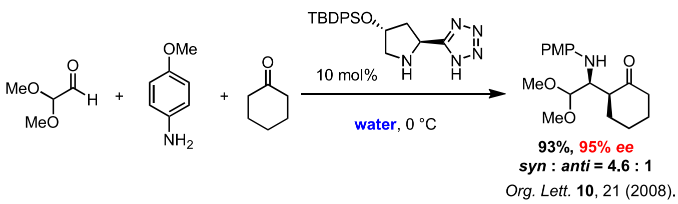
Angew. Chem. Int. Ed. **45**, 5527 (2006).

·Organic solvent free asymmetrric aldol reaction between ketone and aldehyde



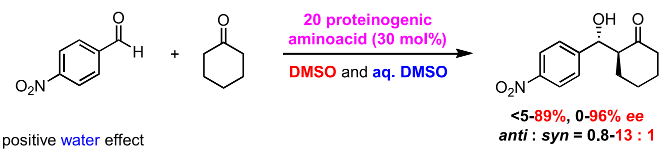
Angew. Chem. Int. Ed. **45**, 958 (2006).
Chem. Eur. J. **13**, 10246 (2007).

·Organic solvent free asymmetrric Mannich reaction with proline catalyst



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

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



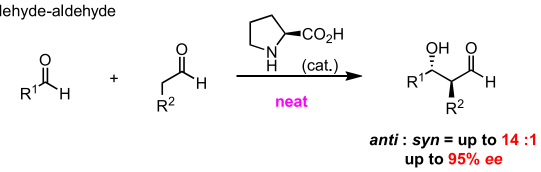
positive water effect

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

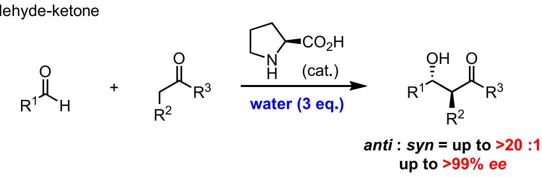
Synlett 1565 (2006).

·Organic solvent free Dry and Wet condition asymetric aldol reaction with proline catalyst

aldehyde-aldehyde

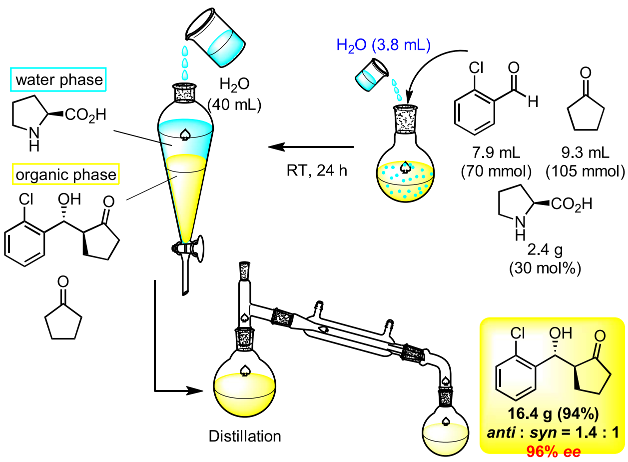


aldehyde-ketone

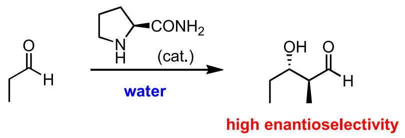


Chem. Commun. 957 (2007).

Organic solvent-free aldol reaction

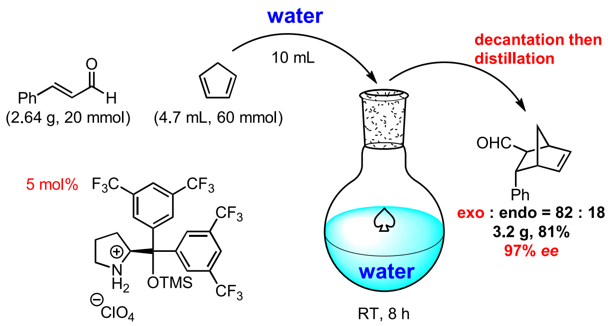


·Self aldol reaction of propanal in water - reaction in water with proline-amide catalyst



Chem. Commun. 2524 (2007).

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



Angew. Chem. Int. Ed. **47**, 6634 (2008).

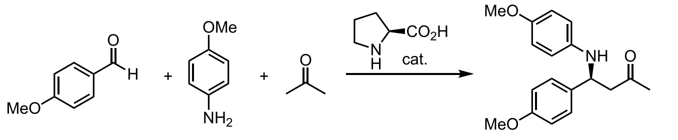
Application of High Pressure Induced by Water-Freezing to the direct catalytic asymmetric reaction

The novel method of high pressure by water-freezing:

The high pressre (cat. 200 MaPa) is easilly is essily achieved

simply by freesing water (-20 °C) in a sealed autoclave.

·Mannich reaction



1 atm, RT **0%, -% ee**

200 atm, -20 °C **99%, 96% ee**

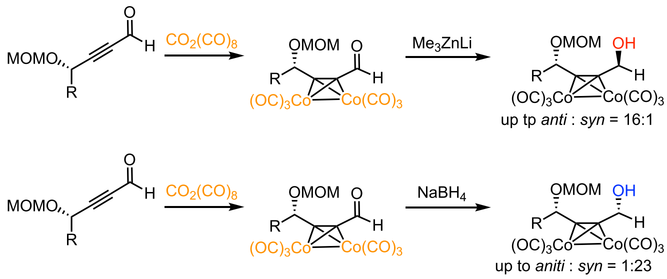
J. Am. Chem. Soc., **125**, 11208 (2003).

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

·Michael reaction
Chem. Lett., 296 (2002).

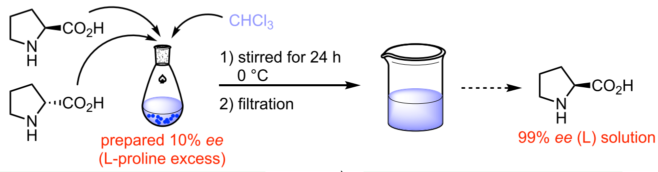
·Baylis-Hillman reaction
Tetrahedron Lett., **43**, 8683 (2004).

1,4-asymmetric induction using Cobalt alkyne complex



Organometallics **2008**, *27*, 163.

Research about chirality

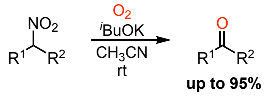


Amplification of *ee* from initial low *ee* ⇨ The key to find out origin of chirality

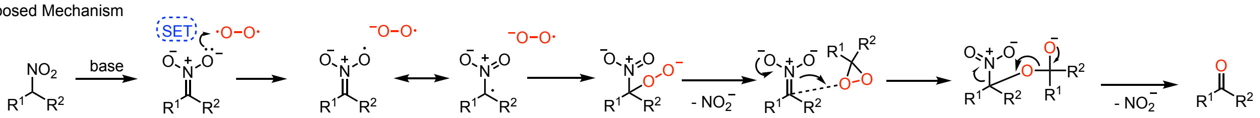
Angew. Chem., Int. Ed. **45**, 4593 (2006).

Metal-free oxidative transformations using O_2

Nef reaction using molecular O_2

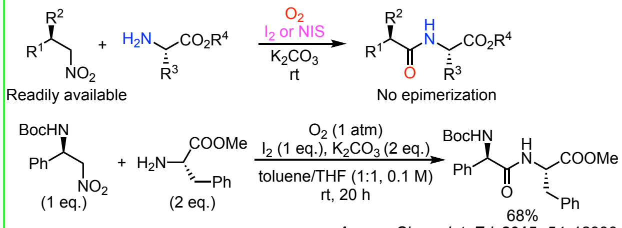


Proposed Mechanism



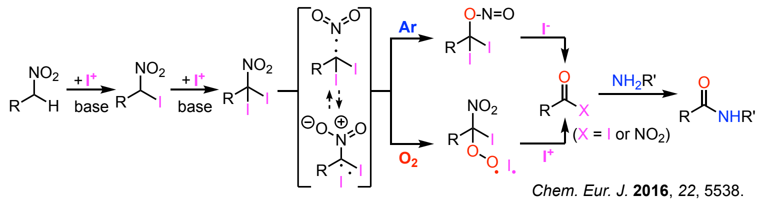
Chem. Eur. J. **2014**, *20*, 15753.

Oxidative amidation of primary nitroalkane and amine



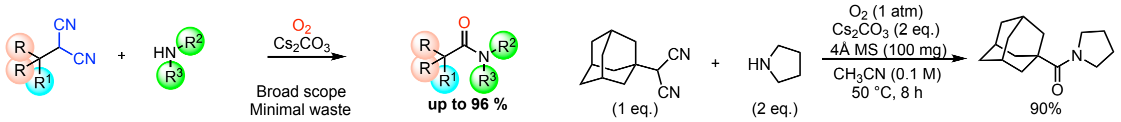
Angew. Chem. Int. Ed. **2015**, *54*, 12986.

Proposed Mechanism



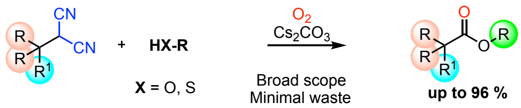
Chem. Eur. J. **2016**, *22*, 5538.

Sterically demanding oxidative amidation of α-substituted malononitriles with amines



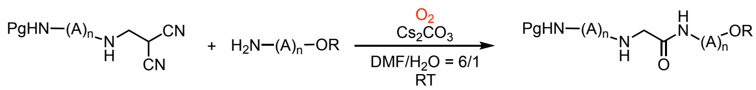
Angew. Chem. Int. Ed. **2016**, *55*, 9060.

Sterically demanding ester formation of α-substituted malononitriles with alcohol



Eur. J. Org. Chem. **2019**, 675.

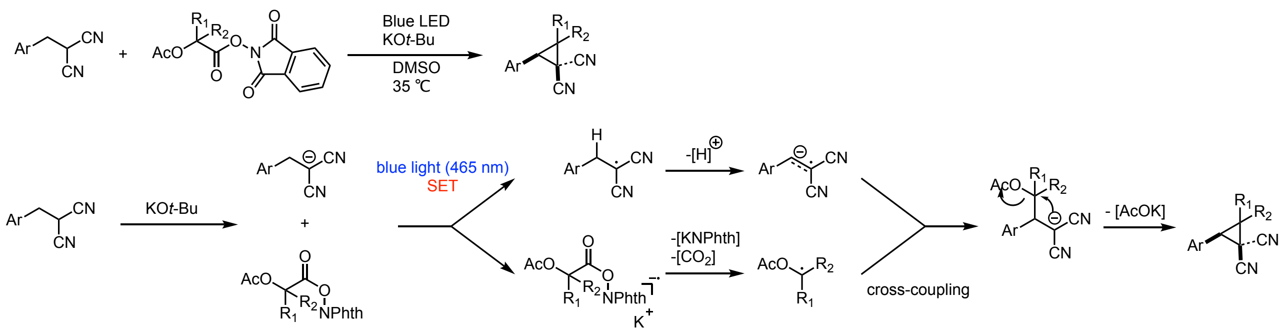
Application to peptipe synthesis



Broad scope
Tripeptide : **Boc-Phe-Gly-Phe-OMe (18 examples)**
Tetrapeptide : **Boc-Phe-Gly-Leu-Phe-O*t*-Bu (5 examples)**
Unprotected amino acid : **Boc-Phe-Gly-Phe-OH (4 examples)**

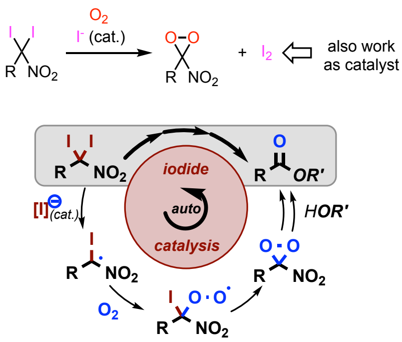
Chem. Commun., **2021**, *57*, 4283.

Direct cyclopropanation by light mediated single electron transfer



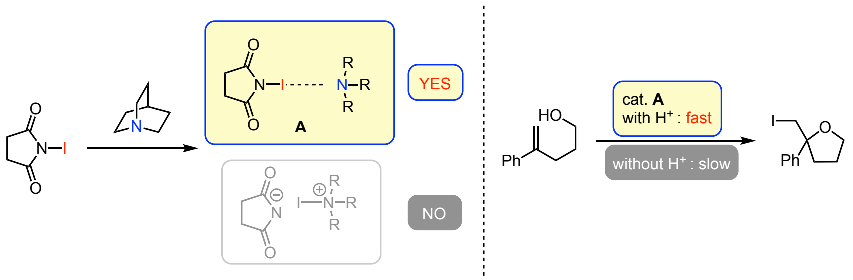
Chem. Eur. J. **2021**, *27*, 5901.

Autoinductive oxidation of α,α-diiodonitroalkanes



Chem. Commun., **2018**, *54*, 6360.

Halogen bonding of N-Halosuccinimides with amines



Helv. Chim. Acta., **2021**, *104*, e2100080