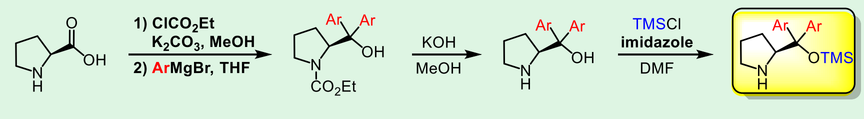
Development of new reactions

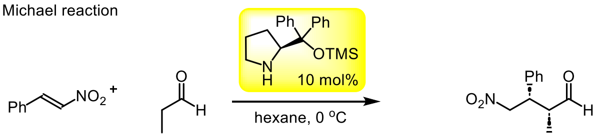
Asymmetric reaction using amino acid or their derivatives as a catalyst, environmental conscious asymmetric reaction using water as a solvent, and research about origin of chirality

Reaction using diarylprolinol silyl ether derivatives as catalyst



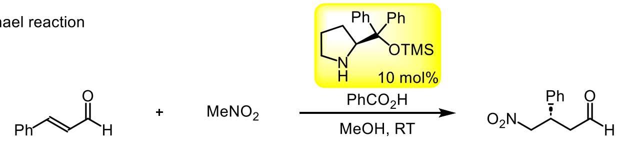
This catalyst is synthesized in short steps from proline.
Substituents on aryl and silyl moiety are easily modified.
Excellent enantioselectivity is obtained

Michael reaction



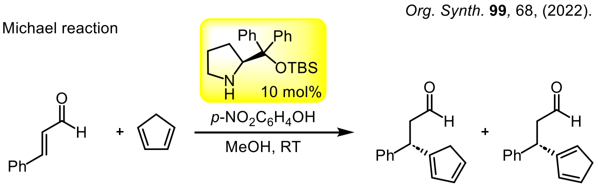
85%, 99% *ee*
Angew. Chem., Int. Ed., **44**, 4212 (2005).
Org. Synth. **99**, 68, (2022).

Michael reaction



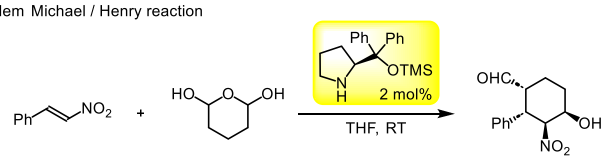
90%, 95% *ee*
Org. Lett., **9**, 5307 (2007).

Michael reaction



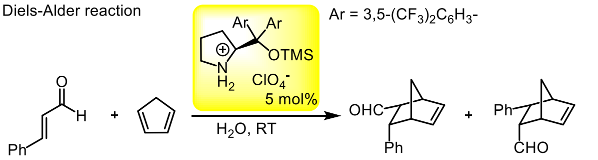
84%, 92% *ee*
Angew. Chem., Int. Ed., **45**, 6853 (2006).

Tandem Michael / Henry reaction



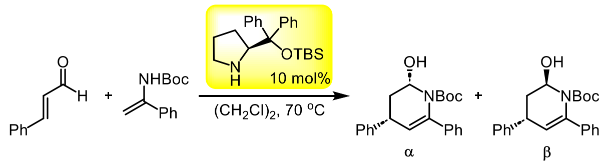
66%, 99% *ee*
Angew. Chem., Int. Ed., **46**, 4922 (2007).

Diels-Alder reaction



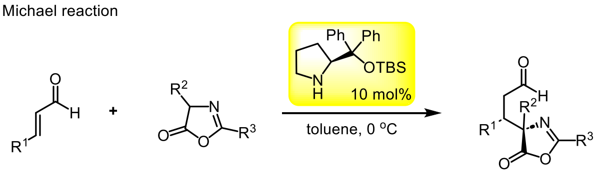
***exo* : *endo* = 80 : 20, 97% *ee* (*exo*)**
Org. Lett, **9**, 2859 (2007).
Angew. Chem., Int. Ed., **47**, 6634 (2008).

Formal aza [3+3] cycloaddition



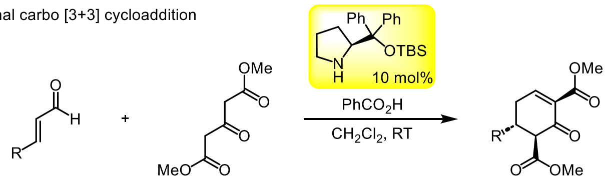
90%, 94% *ee*, α : β = 34 : 66
Angew. Chem., Int. Ed., **47**, 4012 (2008).

Michael reaction



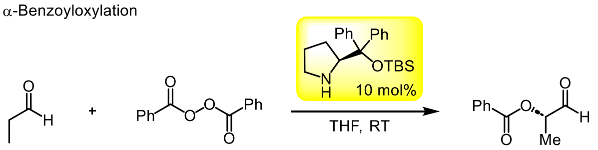
up to 99% *ee*
up to >90% *de*
Chem. Asian. J., **4**, 246 (2009).

Formal carbo [3+3] cycloaddition



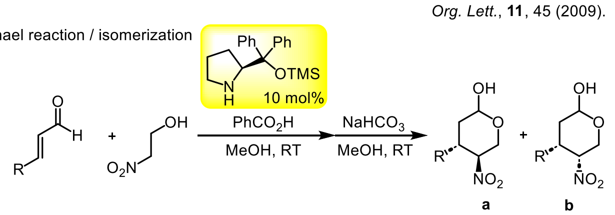
up to 99% *ee*
Org. Lett., **11**, 45 (2009).

α-Benzoyloxylation



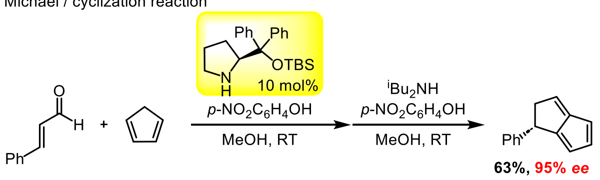
78%, 92% *ee*
Chem. Commun,, 3083 (2009).

Michael reaction / isomerization



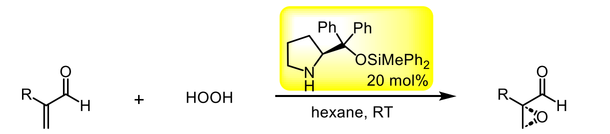
up to 99% *ee*, a : b = 9 : 1
Org. Lett., **11**, 4056 (2009).

Michael / cyclization reaction



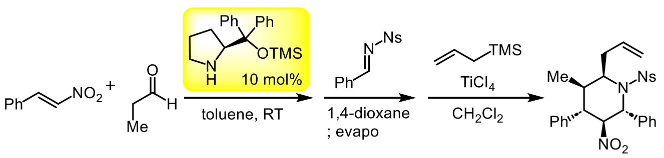
63%, 95% *ee*
Tetrahedron, **66**, 4894 (2010).

epoxidation



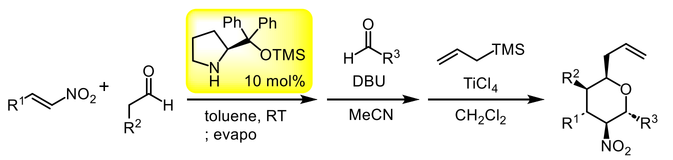
up to 95% *ee*
Org. Lett., **12**, 5434 (2010).

Michael / aza Henry / aminal formation / additional reaction



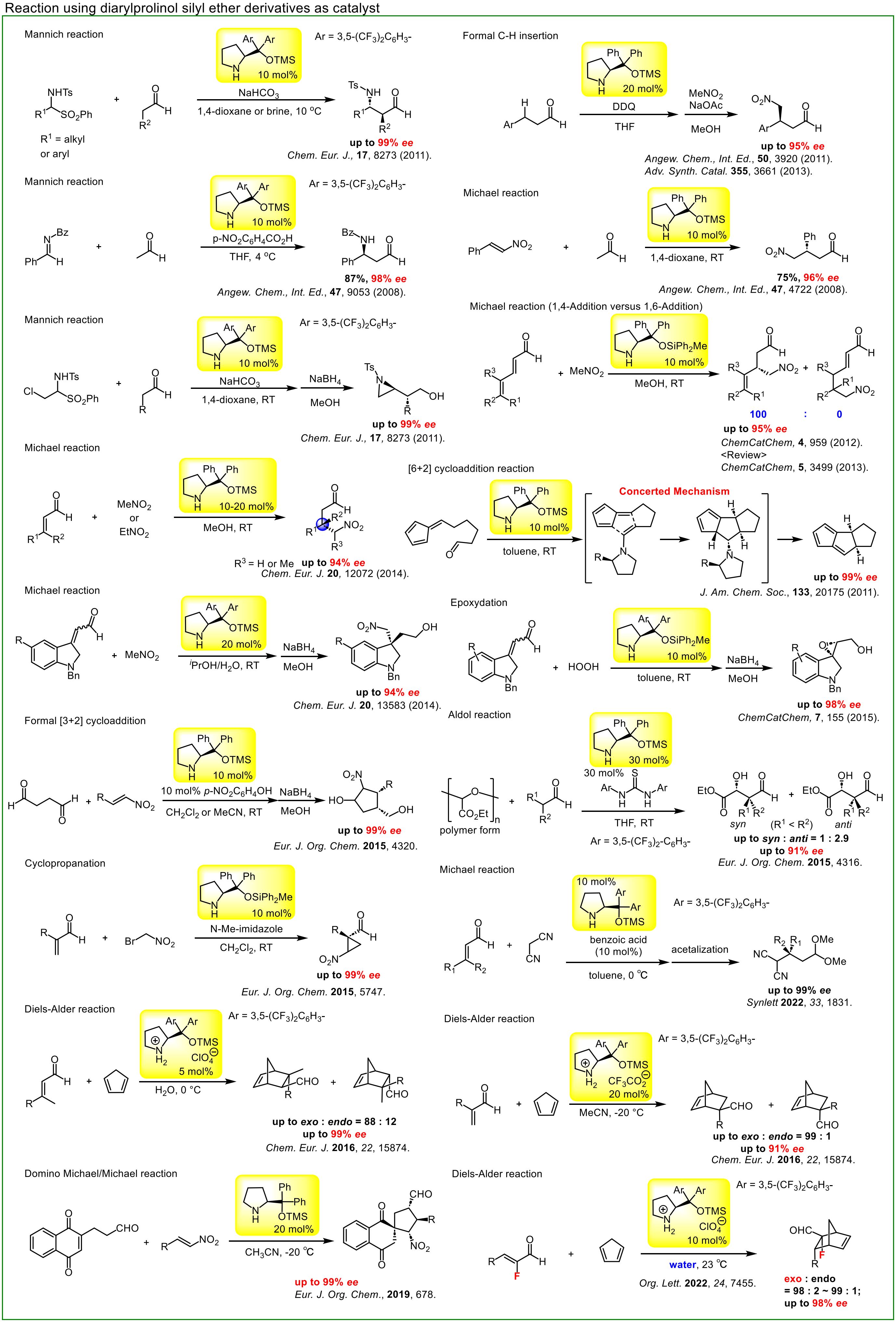
up to 99% *ee*
Single diastereomer
Org.Lett., **12**, 4588 (2010).

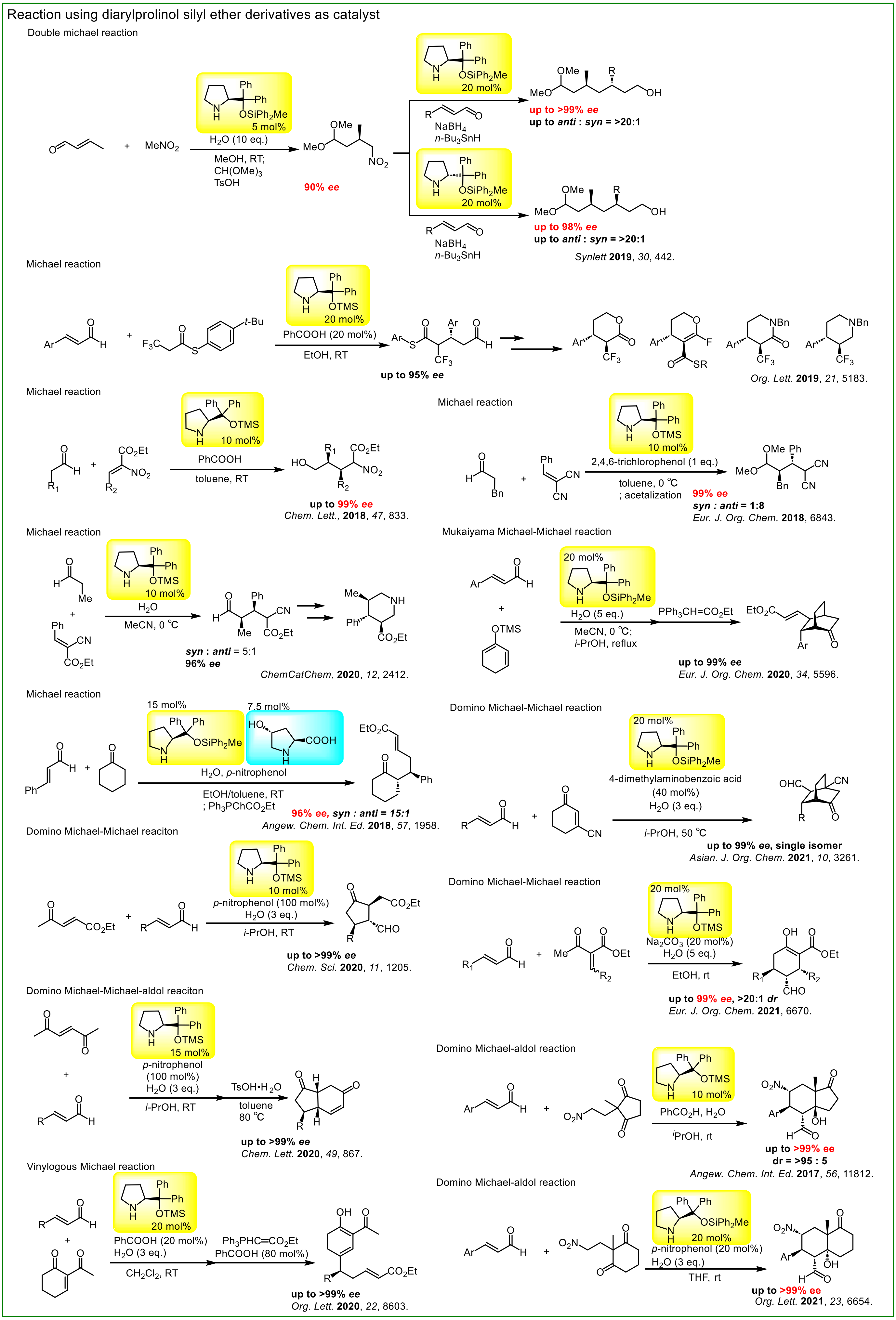
Michael / Henry / acetal formation / additional reaction



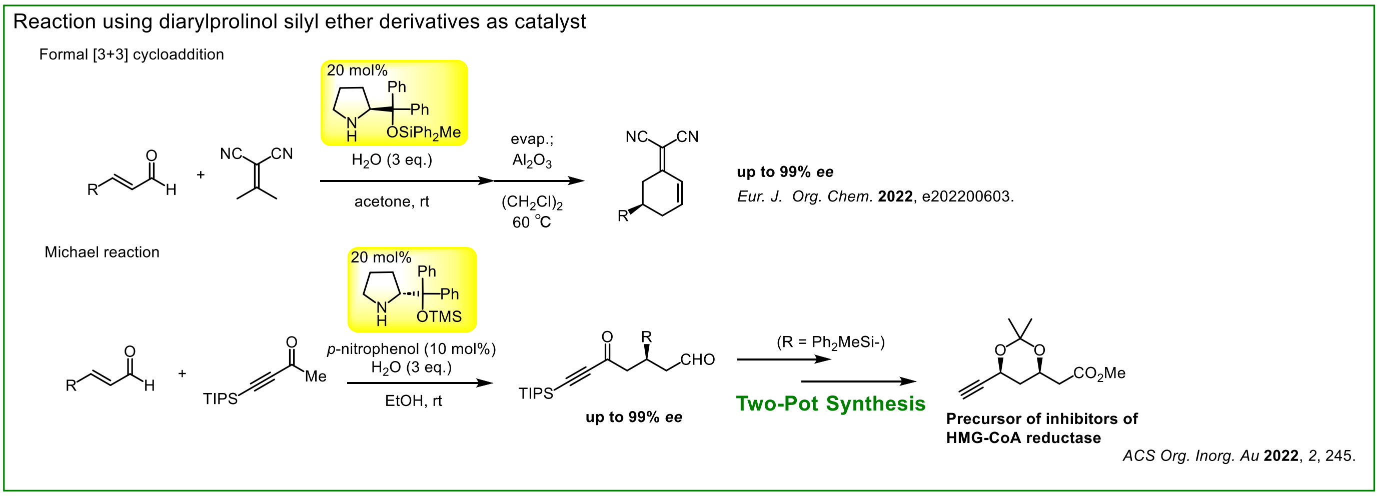
up to 99% *ee*
Single diastereomer
Angew. Chem., Int. Ed., **50**, 3774 (2011).

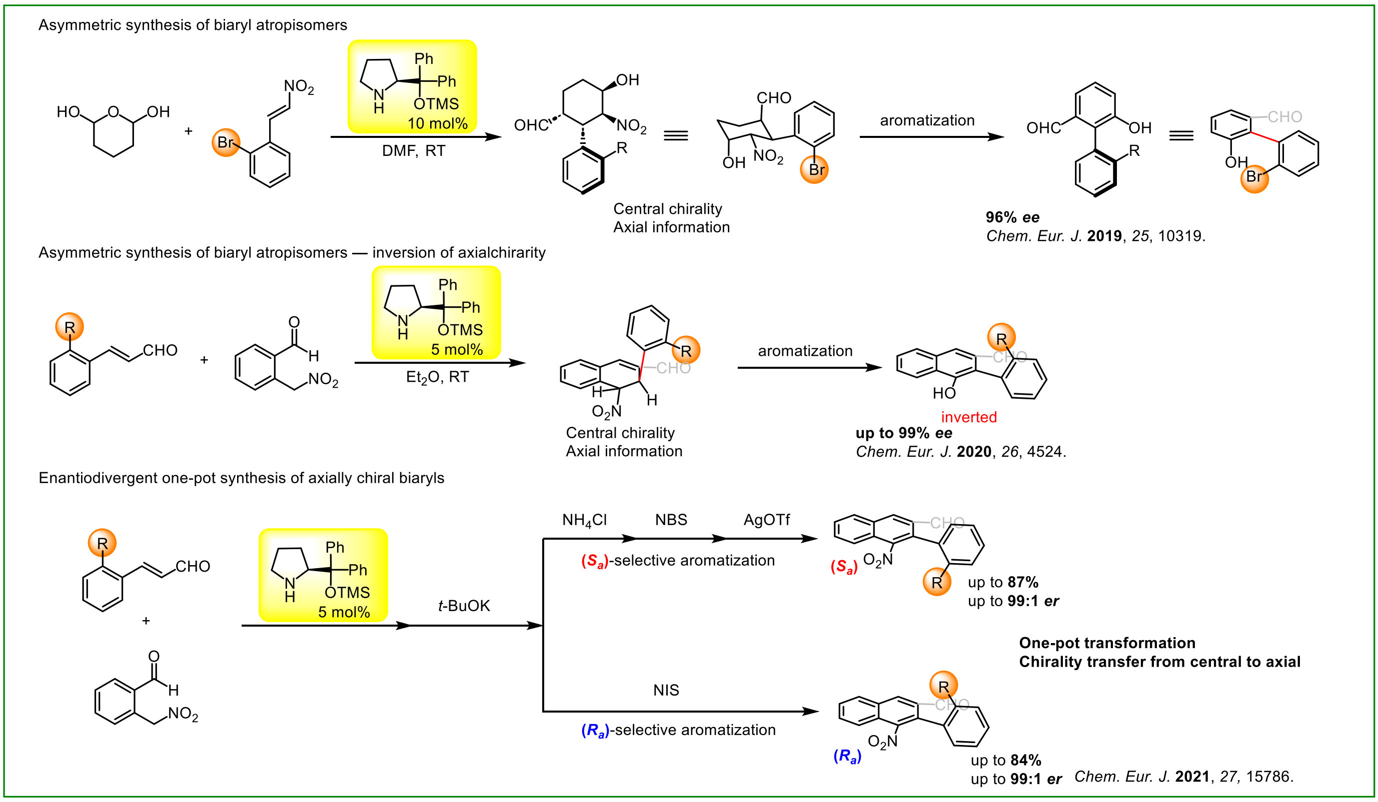
Reaction using diarylprolinol silyl ether derivatives as catalyst

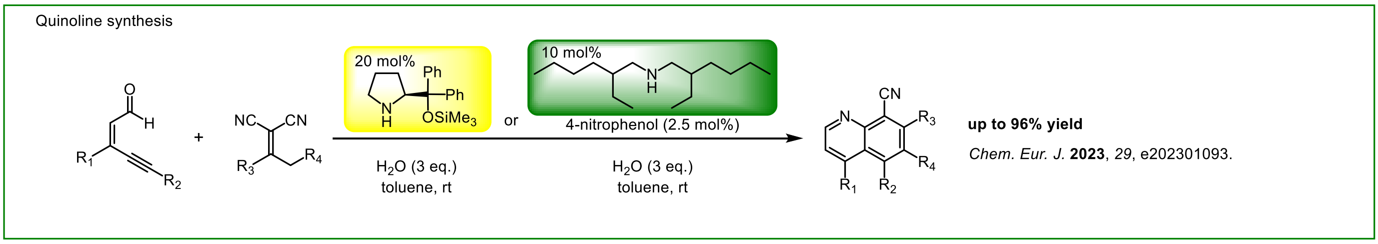




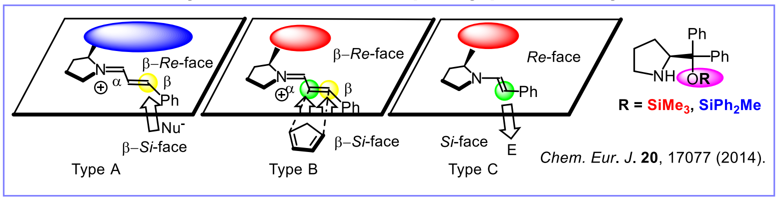
Reaction using diarylprolinol silyl ether derivatives as catalyst
Double michael reaction
MeNO2
Ph
Ph
OSiPh2Me
5 mol%
H2O (10 eq.)
MeOH, RT;
CH(OMe)3
TsOH
OMe
MeO
NO2
90% ee
20 mol%
NaBH4
n-Bu3SnH
MeO
OMe
R
OH
up to >99% ee
up to anti : syn = >20:1
up to 98% ee
up to anti : syn = >20:1
Synlett 2019, 30, 442.
Michael reaction
Ar
H
F3C
S
t-Bu
OTMS
20 mol%
PhCOOH (20 mol%)
EtOH, RT
CF3
up to 95% ee
F
SR
NBn
Org. Lett. 2019, 21, 5183.
Michael reaction
CO2Et
R1
R2
10 mol%
PhCOOH
toluene, RT
HO
up to 99% ee
Chem. Lett., 2018, 47, 833.
Michael reaction
Bn
CN
2,4,6-trichlorophenol (1 eq.)
toluene, 0 °C
; acetalization
99% ee
syn : anti = 1:8
Eur. J. Org. Chem. 2018, 6843.
Michael reaction
Me
H2O
MeCN, 0 °C
syn : anti = 5:1
96% ee
NH
ChemCatChem, 2020, 12, 2412.
Mukaiyama Michael-Michael reaction
OTMS
H2O (5 eq.)
MeCN, 0 °C;
i-PrOH, reflux
PPh3CH=CO2Et
EtO2C
up to 99% ee
Eur. J. Org. Chem. 2020, 34, 5596.
Michael reaction
15 mol%
7.5 mol%
COOH
H2O, p-nitrophenol
EtOH/toluene, RT
; Ph3PChCO2Et
96% ee, syn : anti = 15:1
Angew. Chem. Int. Ed. 2018, 57, 1958.
Domino Michael-Michael reaction
4-dimethylaminobenzoic acid
(40 mol%)
H2O (3 eq.)
i-PrOH, 50 °C
OHC
up to 99% ee, single isomer
Asian. J. Org. Chem. 2021, 10, 3261.
Domino Michael-Michael reaciton
p-nitrophenol (100 mol%)
H2O (3 eq.)
i-PrOH, RT
CHO
up to >99% ee
Chem. Sci. 2020, 11, 1205.
Domino Michael-Michael reaction
Na2CO3 (20 mol%)
H2O (5 eq.)
EtOH, rt
OEt
up to 99% ee, >20:1 dr
Eur. J. Org. Chem. 2021, 6670.
Domino Michael-Michael-aldol reaciton
15 mol%
p-nitrophenol
(100 mol%)
H2O (3 eq.)
i-PrOH, RT
TsOH•H2O
toluene
80 °C
up to >99% ee
Chem. Lett. 2020, 49, 867.
Domino Michael-aldol reaction
O2N
PhCO2H, H2O
iPrOH, rt
up to >99% ee
dr = >95 : 5
Angew. Chem. Int. Ed. 2017, 56, 11812.
Vinylogous Michael reaction
PhCOOH (20 mol%)
H2O (3 eq.)
CH2Cl2, RT
Ph3PHC=CO2Et
PhCOOH (80 mol%)
up to >99% ee
Org. Lett. 2020, 22, 8603.
Domino Michael-aldol reaction
p-nitrophenol (20 mol%)
H2O (3 eq.)
THF, rt
up to >99% ee
Org. Lett. 2021, 23, 6654.


Reaction using diarylprolinol silyl ether derivatives as catalyst
Formal [3+3] cycloaddition
20 mol%
Ph
Ph
OSiPh2Me
H2O (3 eq.)
acetone, rt
evap.;
Al2O3
(CH2Cl)2
60 °C
NC
CN
R
up to 99% ee
Eur. J. Org. Chem. 2022, e202200603.
Michael reaction
20 mol%
OTMS
p-nitrophenol (10 mol%)
H2O (3 eq.)
EtOH, rt
TIPS
Me
CHO
up to 99% ee
(R = Ph2MeSi-)
Two-Pot Synthesis
CO2Me
Precursor of inhibitors of
HMG-CoA reductase
ACS Org. Inorg. Au 2022, 2, 245.

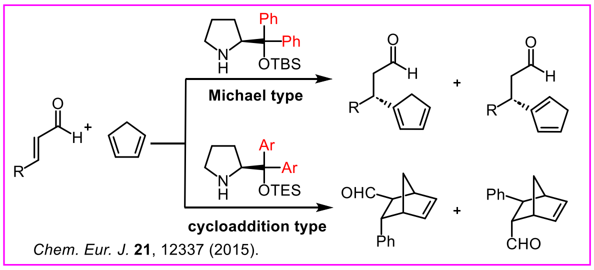

Asymmetric synthesis of biaryl atropisomers
HO
OH
Br
NO2
10 mol%
DMF, RT
OHC
CHO
Central chirality
Axial information
aromatization
96% ee
Chem. Eur. J. 2019, 25, 10319.
Asymmetric synthesis of biaryl atropisomers — inversion of axialchirarity
5 mol%
Et2O, RT
inverted
up to 99% ee
Chem. Eur. J. 2020, 26, 4524.
Enantiodivergent one-pot synthesis of axially chiral biaryls
t-BuOK
NH4Cl
NBS
AgOTf
(Sa)-selective aromatization
up to 87%
up to 99:1 er
One-pot transformation
Chirality transfer from central to axial
NIS
(Ra)-selective aromatization
up to 84%
up to 99:1 er
Chem. Eur. J. 2021, 27, 15786.


Quinoline synthesis
20 mol%
OSiMe3
or
10 mol%
4-nitrophenol (2.5 mol%)
H2O (3 eq.)
toluene, rt
up to 96% yield
Chem. Eur. J. 2023, 29, e202301093.

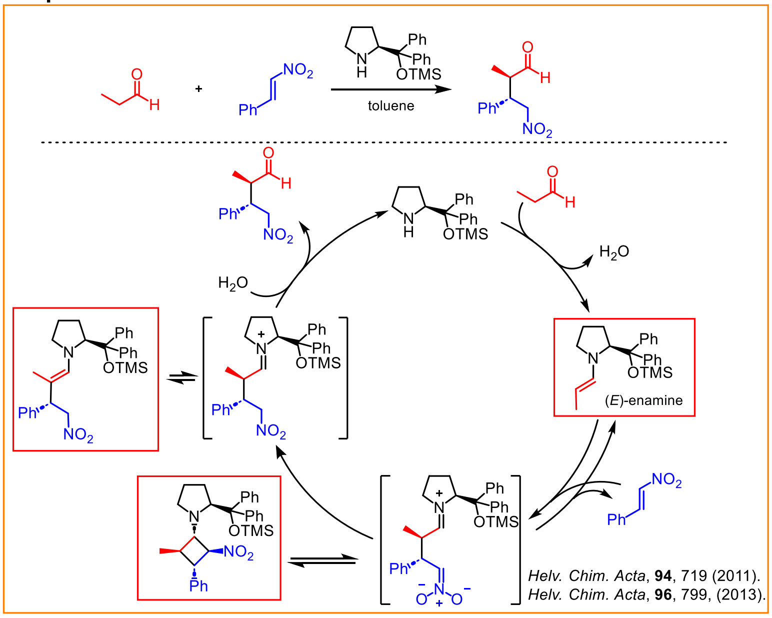
The effect of silyl substituents of diphenylprolinol silyl ether



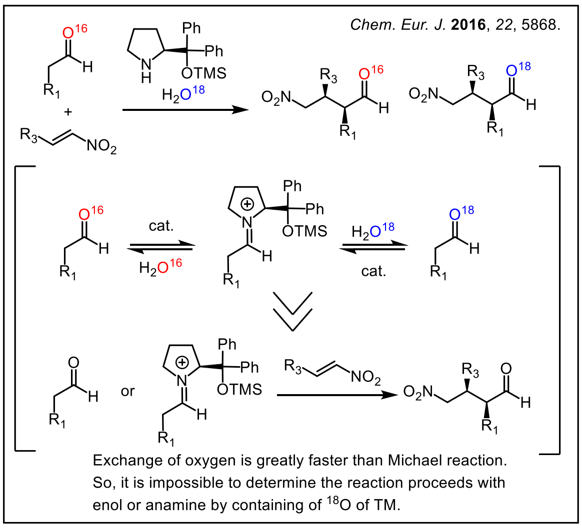
The different reactivity of diphenylprolinol silyl ether and diarylprolinol silyl ether



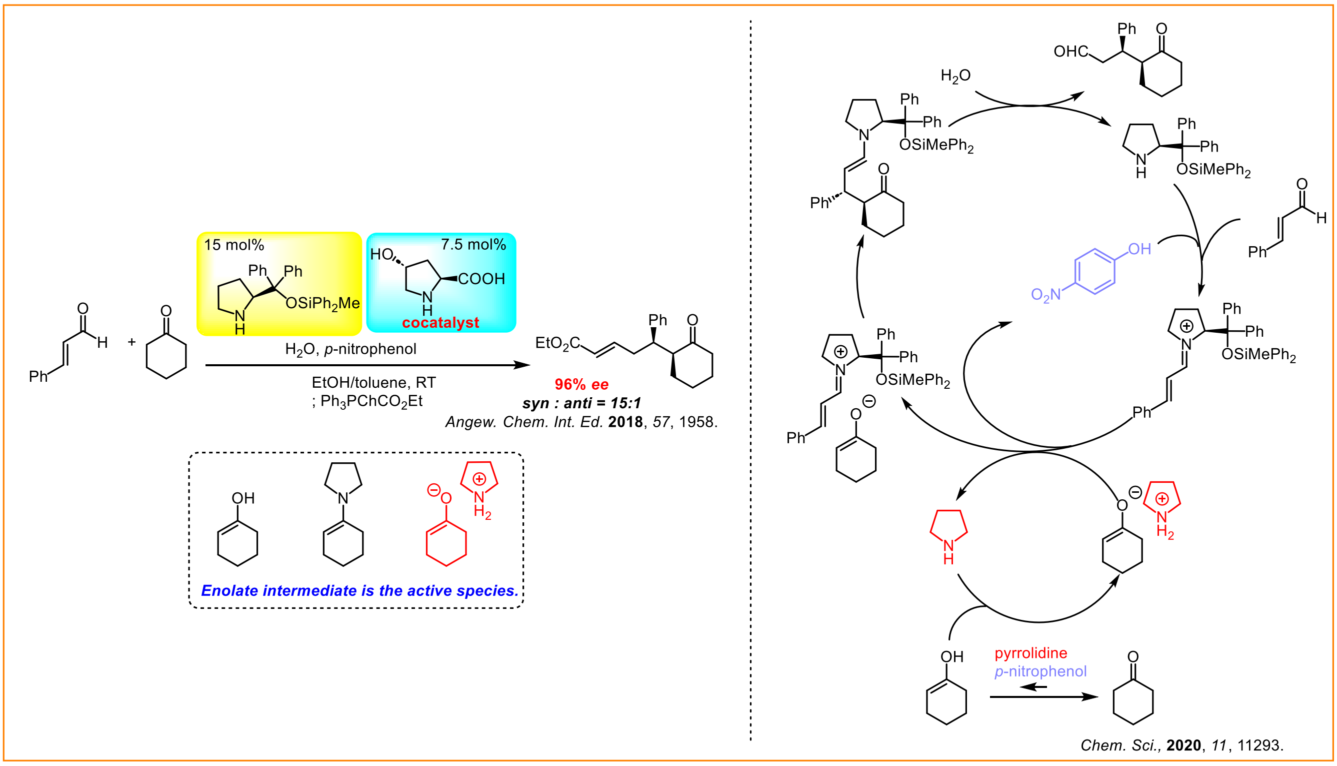
Proposed mechanism of Michael reaction



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

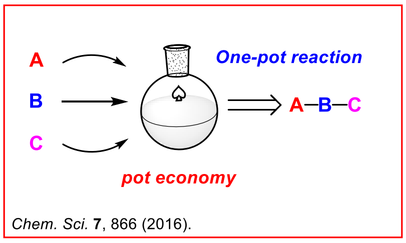


Proposed mechanism of α, β-unsaturated aldehyde and ketones via hydrid system of two secondary amine catalysts

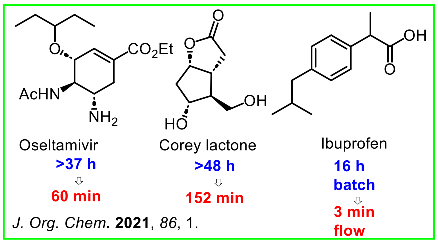


Review

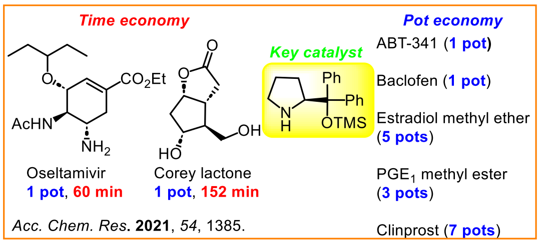
Pot ecomomy



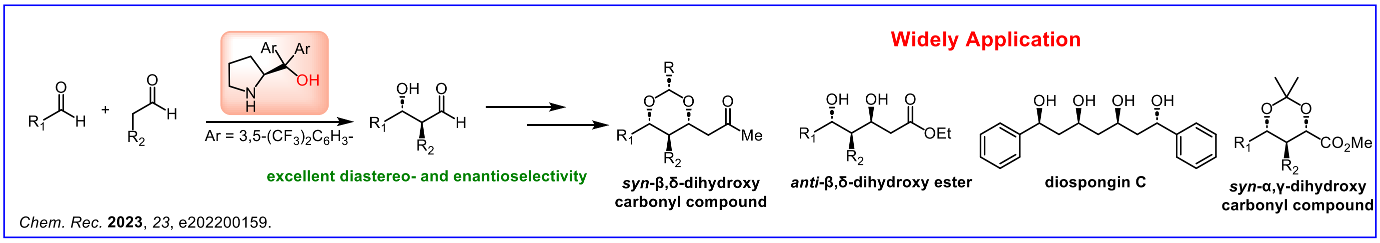
Time ecomomy



Pot and Time economy

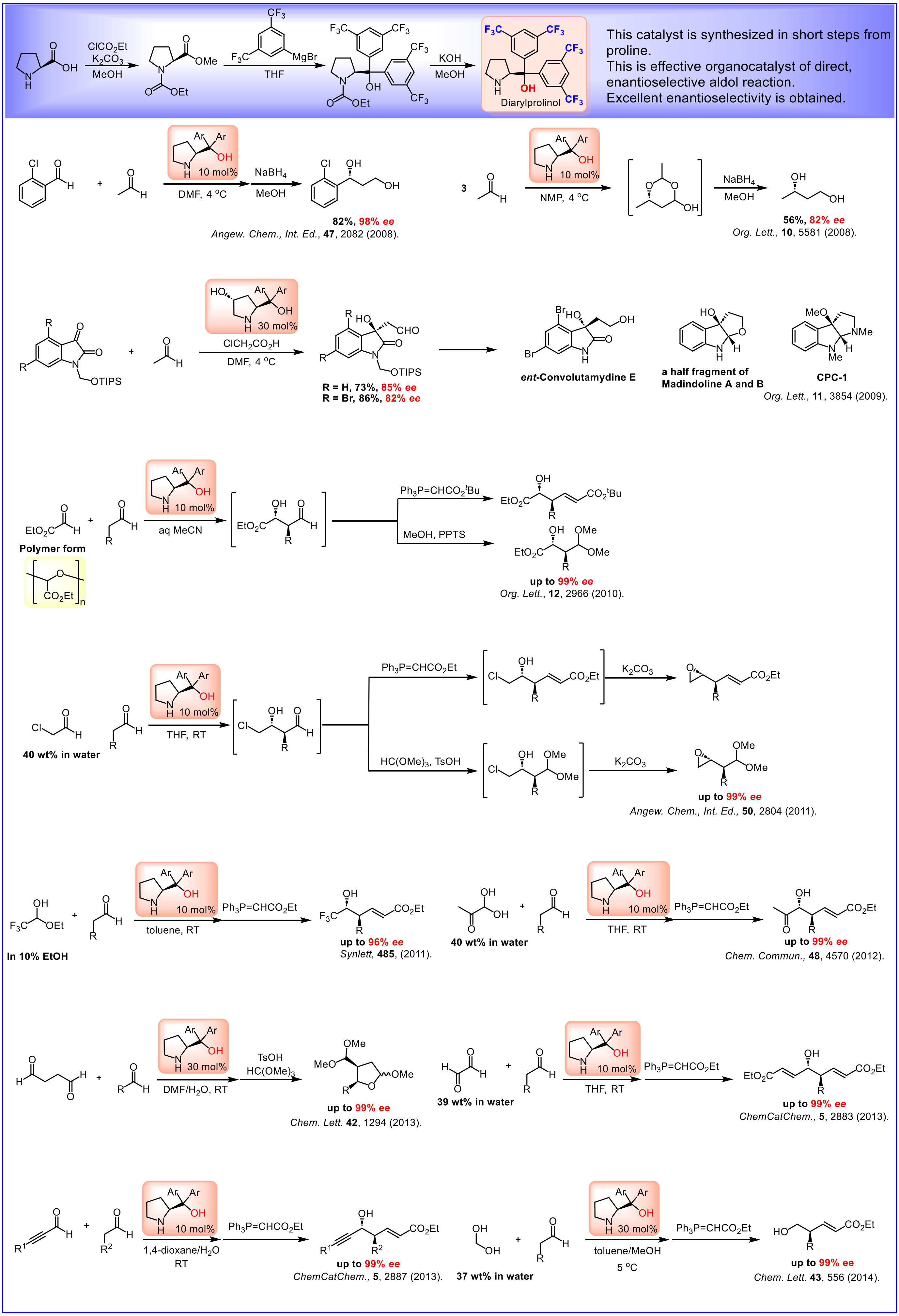


Asymmetric Cross-aldol Reactions

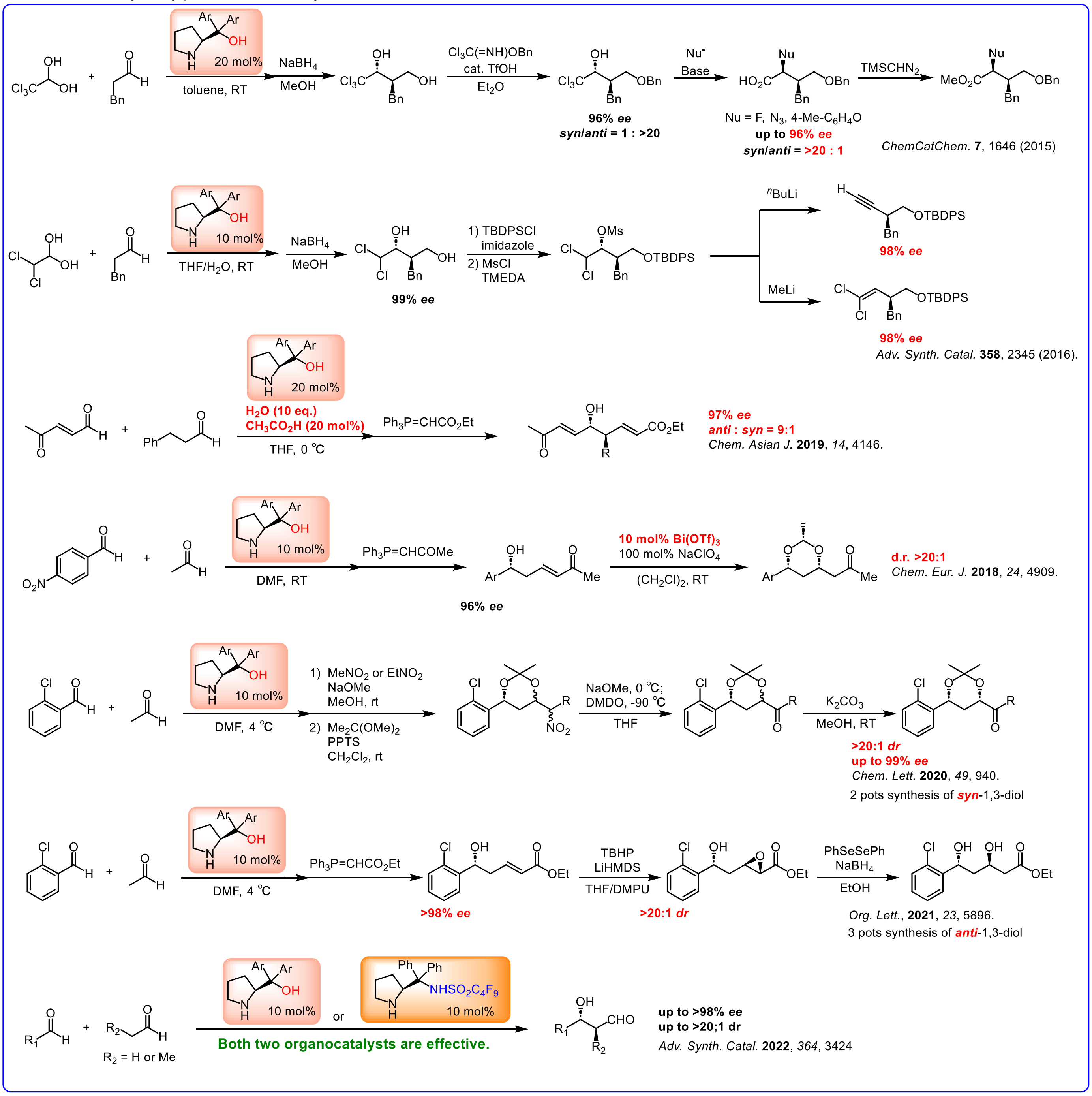


Aldol reaction by diarylprolinol as a catalyst

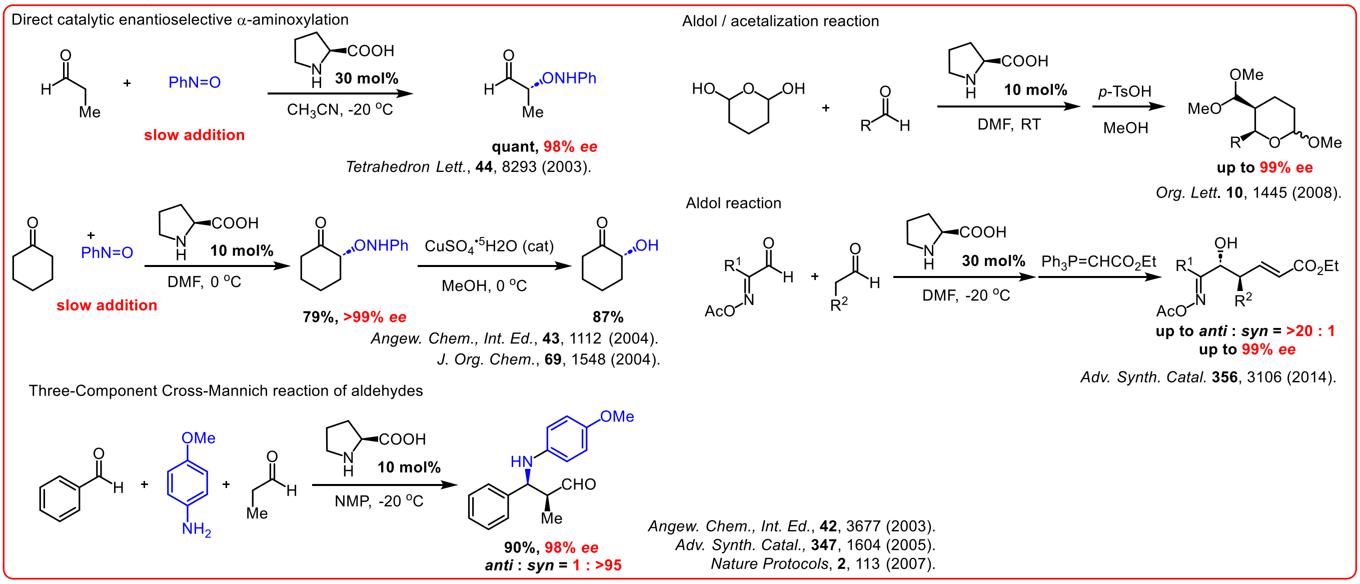
Review: *Chem. Rec.* **2023**, *23*, e202200159.



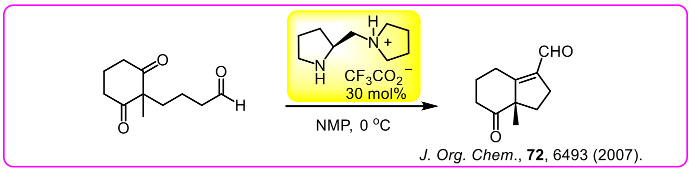
Aldol reaction by diarylprolinol as a catalyst



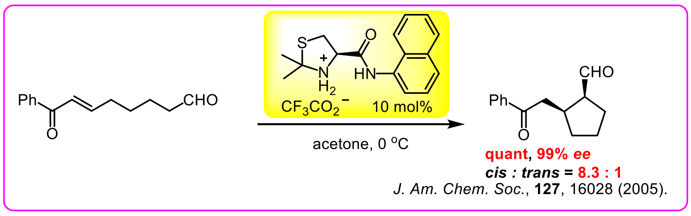
Reaction catalyzed by proline



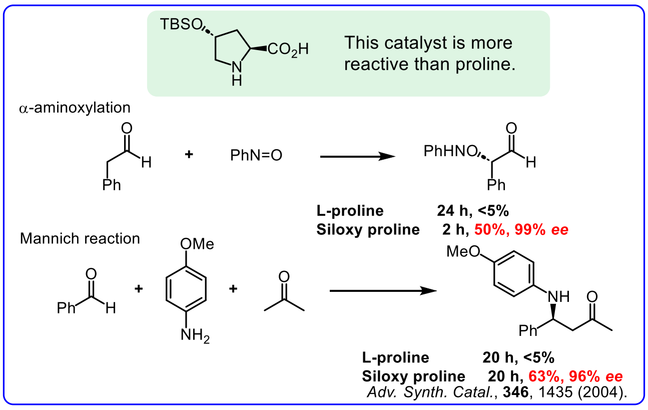
Reaction by proline-derived catalyst



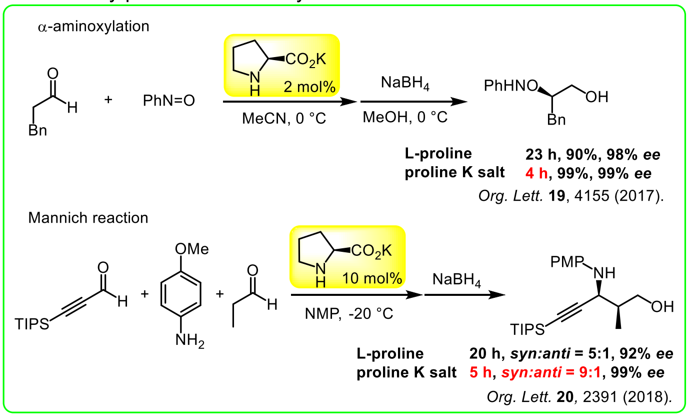
Reaction by cystein-derived catalyst



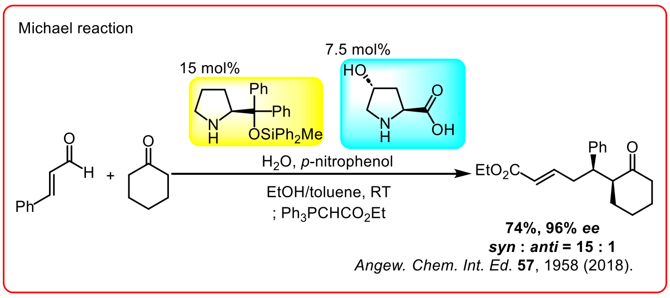
Reaction by siloxyproline catalyst



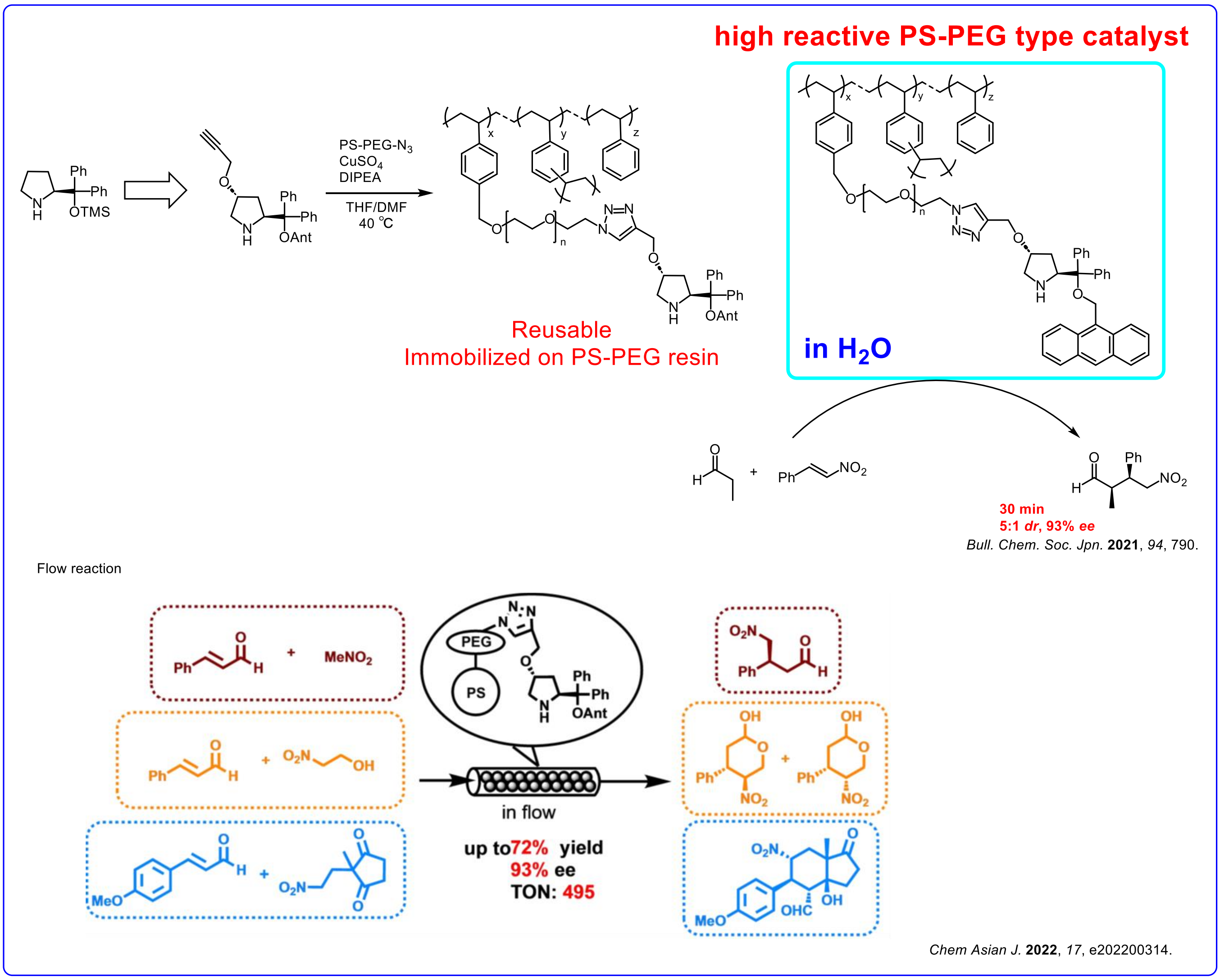
Reaction by prolinate salt catalyst



Reaction using two catalysts system

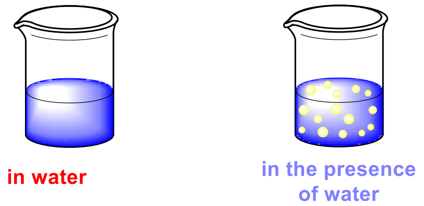


Polymer supported Diphenylprolinol catalysts



Organic solvent free reaction

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

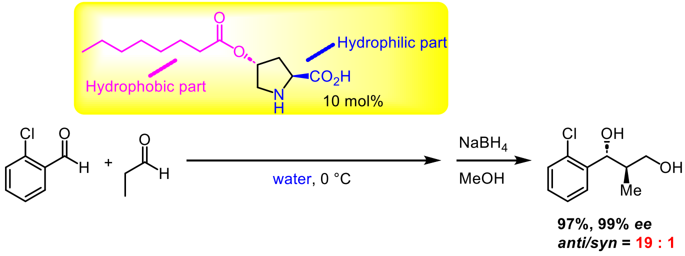


"in water" : The participating reactions are dossplved homogeneously in water.

"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.

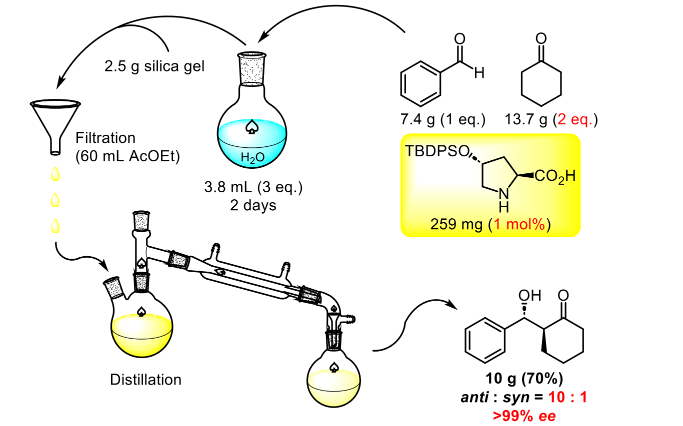
Angew. Chem. Int. Ed. **45**, 8103 (2006).

·Intermolecular aldol reaction between aldehydes in the presence of water



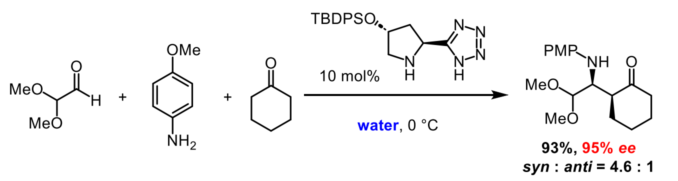
Angew. Chem. Int. Ed. **45**, 5527 (2006).

·Organic solvent free asymmetric aldol reaction between ketone and aldehyde



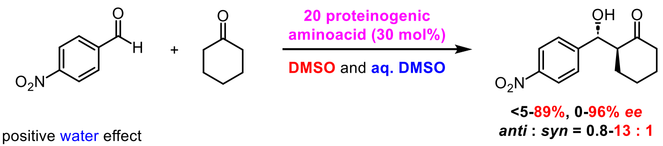
Angew. Chem. Int. Ed. **45**, 958 (2006).
Chem. Eur. J. **13**, 10246 (2007).

·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



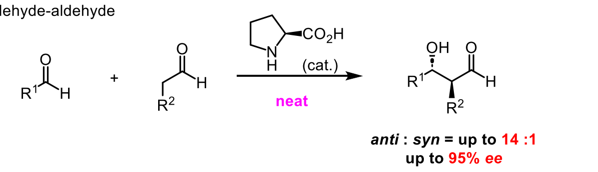
positive water effect

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

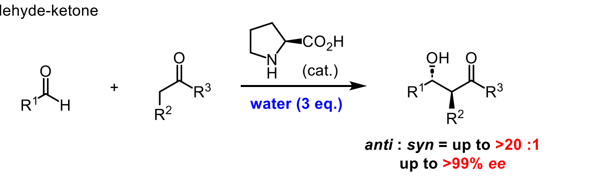
Synlett 1565 (2006).

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

aldehyde-aldehyde

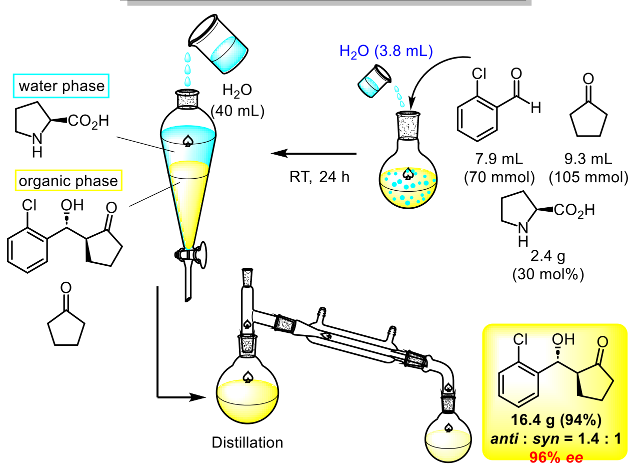


aldehyde-ketone

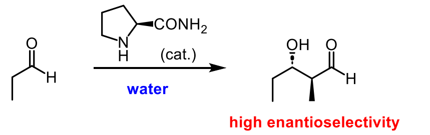


Chem. Commun. 957 (2007).

Organic solvent-free aldol reaction

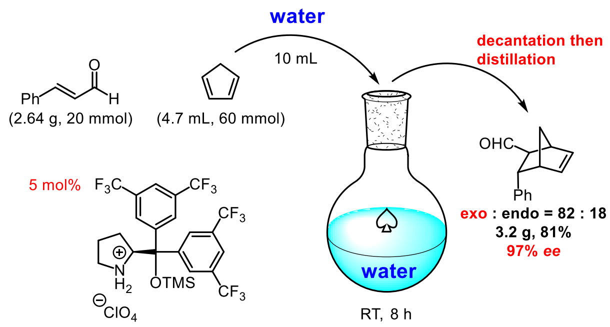


·Self aldol reaction of propanal in water - reaction in water with proline-amide catalyst



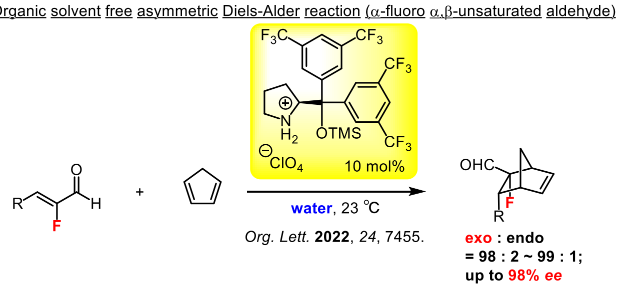
Chem. Commun. 2524 (2007).

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



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

·Organic solvent free asymmetric Diels-Alder reaction (α-fluoro α,β-unsaturated aldehyde)



Org. Lett. **2022**, *24*, 7455.

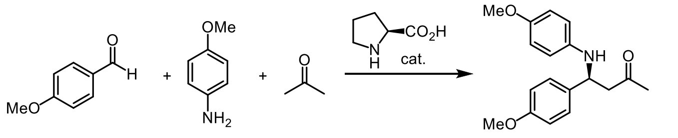
Application of High Pressure Induced by Water-Freezing to the direct catalytic asymmetric reaction

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***

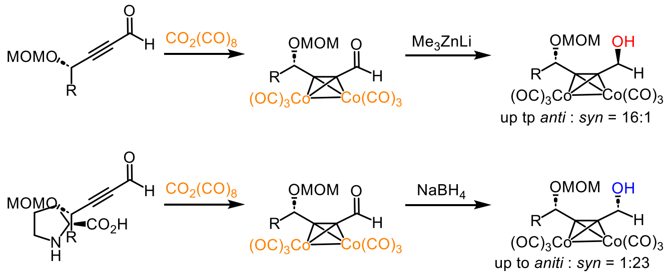
J. Am. Chem. Soc., **125**, 11208 (2003).

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

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

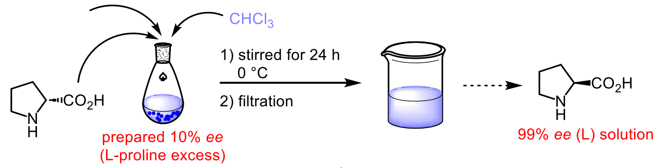
:Baylis-Hillman reaction
Tetrahedron Lett., **43**, 8683 (2004).

1,4-asymmetric induction using Cobalt alkyne complex



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

Research about of chirality

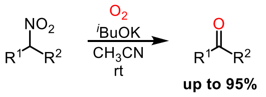


Amplification of *ee* from initial low *ee* ⇨ The key to find out origin of chirality

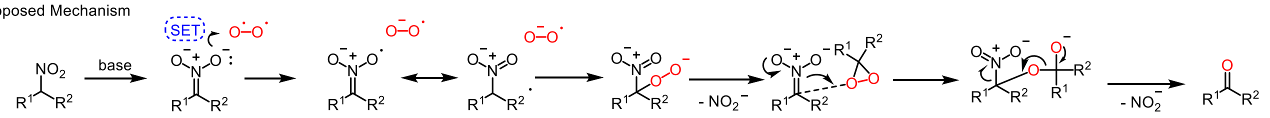
Angew. Chem., Int. Ed. **45**, 4593 (2006).

Metal-free oxidative transformations using O_2

Nef reaction using molecular O_2

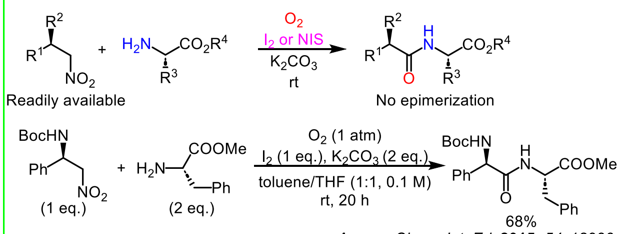


Proposed Mechanism



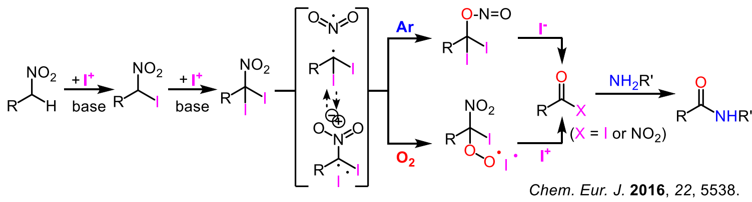
Chem. Eur. J. **2014**, *20*, 15753.

Oxidative amidation of primary nitroalkane and amine



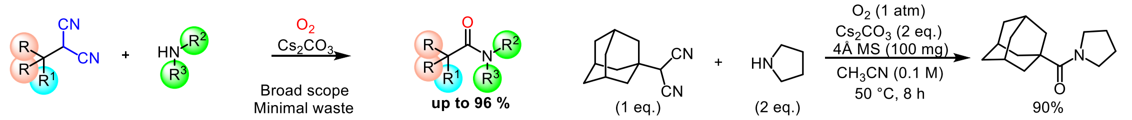
Angew. Chem. Int. Ed. **2015**, *54*, 12986.

Proposed Mechanism



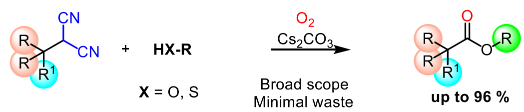
Chem. Eur. J. **2016**, *22*, 5538.

Sterically demanding oxidative amidation of α-substituted malononitriles with amines



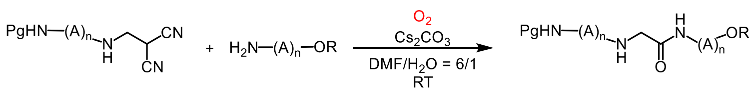
Angew. Chem. Int. Ed. **2016**, *55*, 9060.

Sterically demanding ester formation of α-substituted malononitriles with alcohol



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

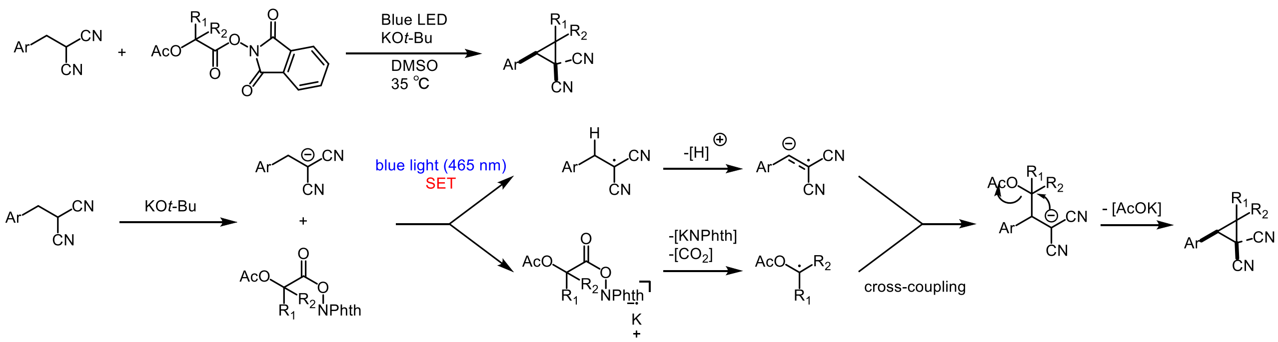
Application to peptipe synthesis



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)**

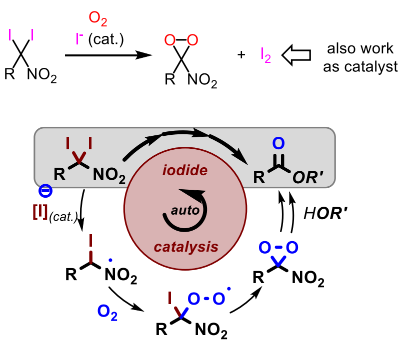
Chem. Commun., **2021**, *57*, 4283.

Direct cyclopropanation by light mediated single electron transfer



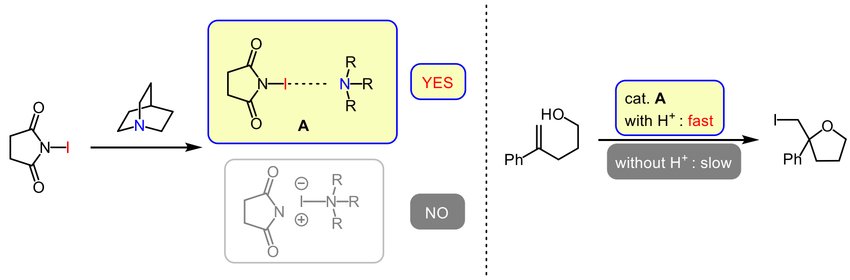
Chem. Eur. J. **2021**, *27*, 5901.

Autoinductive oxidation of α,α-diiodonitroalkanes



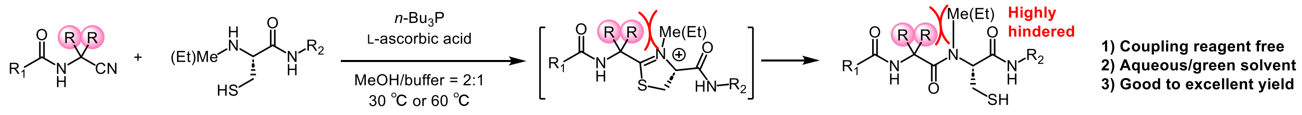
Chem. Commun., **2018**, *54*, 6360.

Halogen bonding of N-Halosuccinimides with amines



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

Highly Sterically Hindered Peptide Bond Formation between α,α-Disubstituted α-Amino Acids and N-Alkyl Cysteines Using α,α-Disubstituted α-Amidonitrile



J. Am. Chem. Soc. **2022**, *144*, 10145