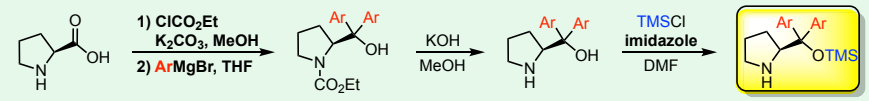
Hayashi Lab. Homepage http://www.ykbsc.chem.tohoku.ac.jp/

Development of new reactions

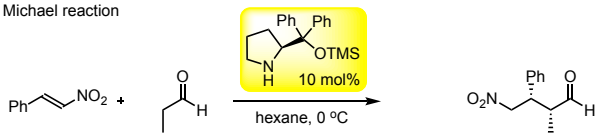
Asymmetric reaction using amino acid or their derivatives as a catalyst,
environmental conscious asymmetric reaction using water as a solvent, and research about origin of chirality

Reaction using diarylprolinol silyl ether derivatives as catalyst



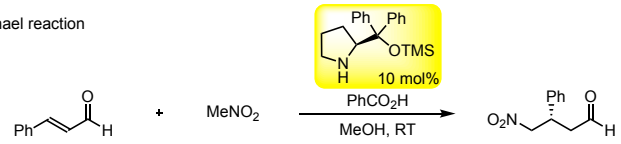
This catalyst is synthesized in short steps from proline.
Substituents on aryl and silyl moiety are easily modified.
Excellent enantioselectivity is obtained

Michael reaction



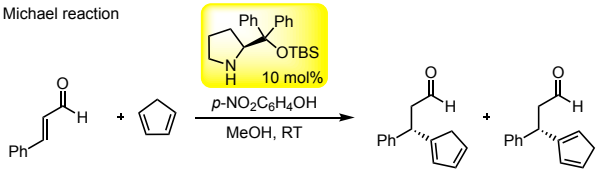
85%, 99% *ee*
Angew. Chem., Int. Ed., **44**, 4212 (2005).

Michael reaction



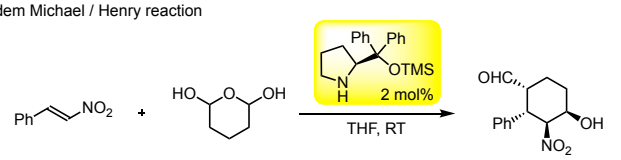
90%, 95% *ee*
Org. Lett., **9**, 5307 (2007).

Michael reaction



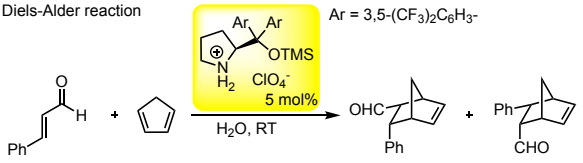
84%, 92% *ee*
Angew. Chem., Int. Ed., **45**, 6853 (2006).

Tandem Michael / Henry reaction



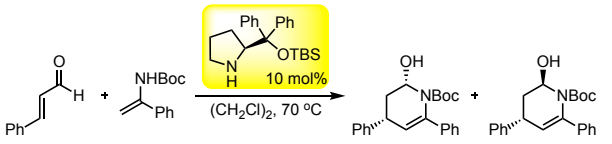
66%, 99% *ee*
Angew. Chem., Int. Ed., **46**, 4922 (2007).

Diels-Alder reaction



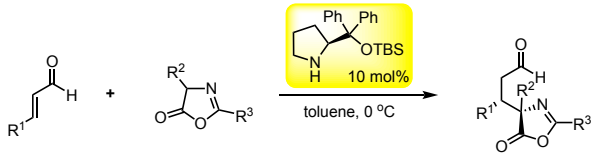
***exo* : *endo* = 80 : 20, 97% *ee* (*exo*)**
Org. Lett, **9**, 2859 (2007).
Angew. Chem., Int. Ed., **47**, 6634 (2008).

Formal aza [3+3] cycloaddition



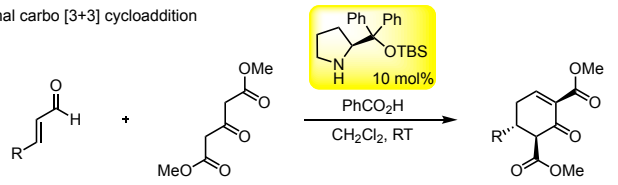
90%, 94% *ee*, α : β = 34 : 66
Angew. Chem., Int. Ed., **47**, 4012 (2008).

Michael reaction



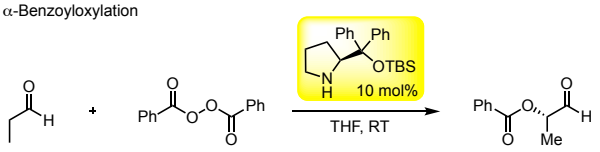
up to 99% *ee*
up to >90% *de*
Chem. Asian. J., **4**, 246 (2009).

Formal carbo [3+3] cycloaddition



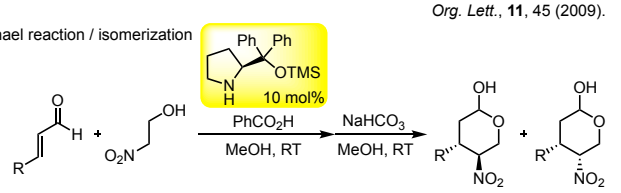
up to 99% *ee*
Org. Lett., **11**, 45 (2009).

α-Benzoyloxylation



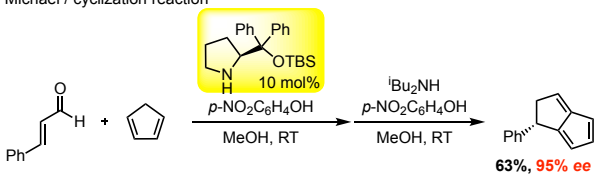
78%, 92% *ee*
Chem. Commun,, 3083 (2009).

Michael reaction / isomerization



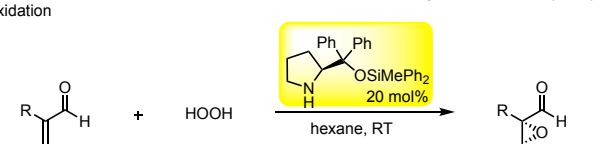
a **b**
up to 99% *ee*, a : b = 9 : 1
Org. Lett., **11**, 4056 (2009).

Michael / cyclization reaction



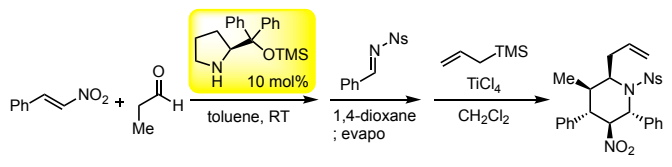
63%, 95% *ee*
Tetrahedron, **66**, 4894 (2010).

epoxidation



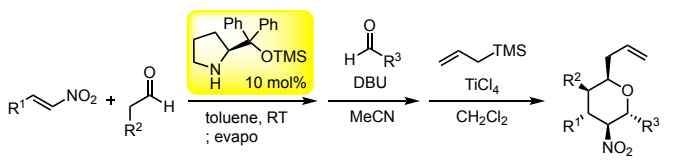
up to 95% *ee*
Org. Lett., **12**, 5434 (2010).

Michael / aza Henry / aminal formation / additional reaction



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

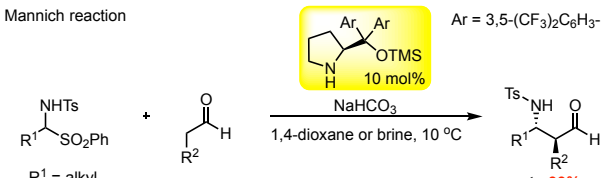
Michael / Henry / acetal formation / additional reaction



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

Reaction using diarylprolinol silyl ether derivatives as catalyst

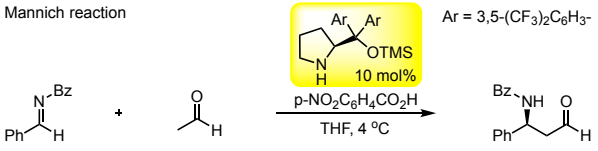
Mannich reaction



up to 99% *ee*

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

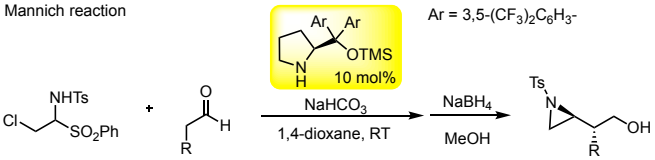
Mannich reaction



87%, 98% *ee*

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

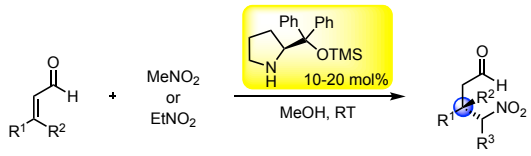
Mannich reaction



up to 99% *ee*

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

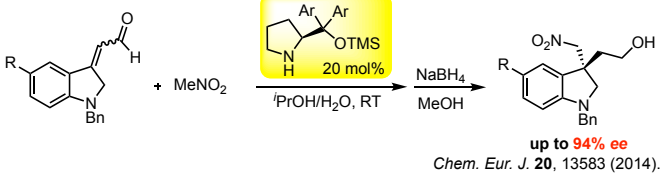
Michael reaction



up to 94% *ee*

Chem. Eur. J. **20**, 12072 (2014).

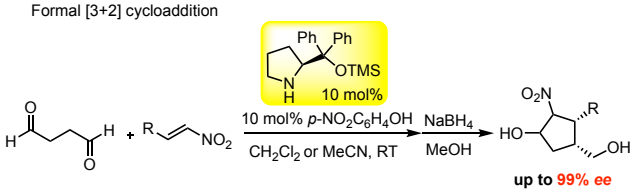
Michael reaction



up to 94% *ee*

Chem. Eur. J. **20**, 13583 (2014).

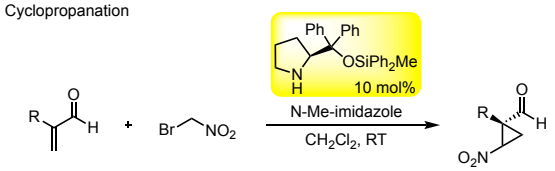
Formal [3+2] cycloaddition



up to 99% *ee*

Eur. J. Org. Chem. **2015**, 4320.

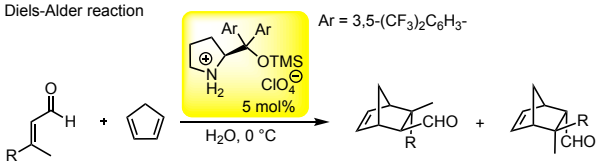
Cyclopropanation



up to 99% *ee*

Eur. J. Org. Chem. **2015**, 5747.

Diels-Alder reaction

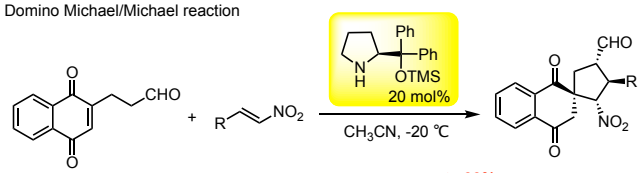


up to *exo* : *endo* = 88 : 12

up to 99% *ee*

Chem. Eur. J. **2016**, *22*, 15874.

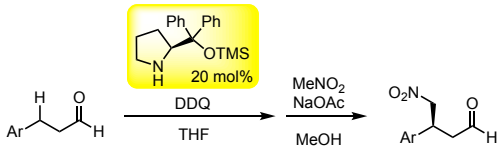
Domino Michael/Michael reaction



up to 99% *ee*

Eur. J. Org. Chem., **2019**, 678.

Formal C-H insertion

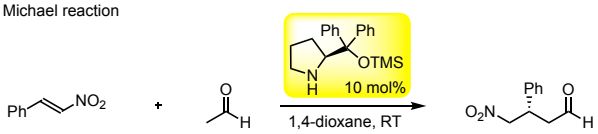


up to 95% *ee*

Angew. Chem., Int. Ed., **50**, 3920 (2011).

Adv. Synth. Catal. **355**, 3661 (2013).

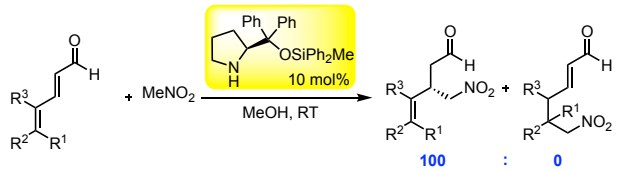
Michael reaction



75%, 96% *ee*

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

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



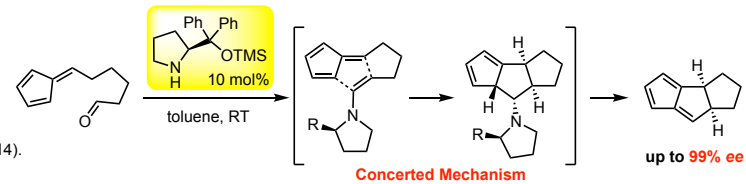
up to 95% *ee*

ChemCatChem, **4**, 959 (2012).

<Review>

ChemCatChem, **5**, 3499 (2013).

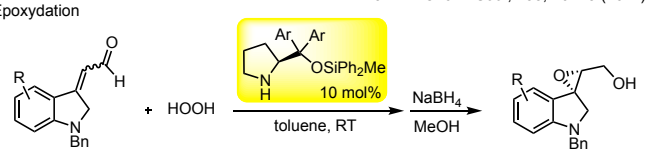
[6+2] cycloaddition reaction



up to 99% *ee*

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

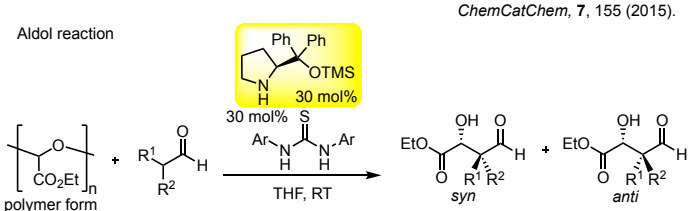
Epoxydation



up to 98% *ee*

ChemCatChem, **7**, 155 (2015).

Aldol reaction



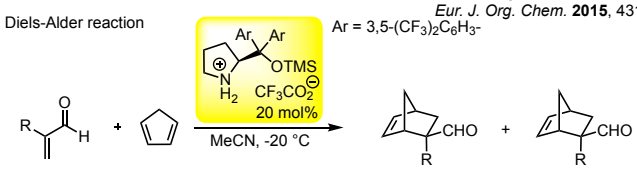
(R1 < R2)

up to *syn* : *anti* = 1 : 2.9

up to 91% *ee*

Eur. J. Org. Chem. **2015**, 4316.

Diels-Alder reaction

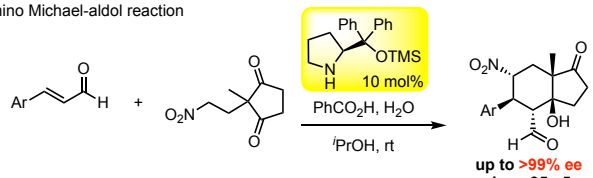


up to *exo* : *endo* = 99 : 1

up to 91% *ee*

Chem. Eur. J. **2016**, *22*, 15874.

Domino Michael-aldol reaction

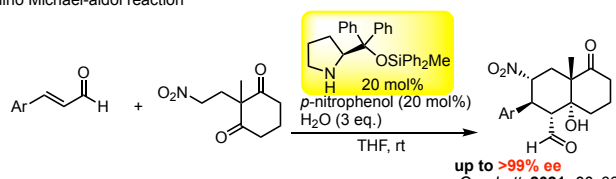


up to >99% *ee*

dr = >95 : 5

Angew. Chem. Int. Ed. **2017**, *56*, 11812.

Domino Michael-aldol reaction

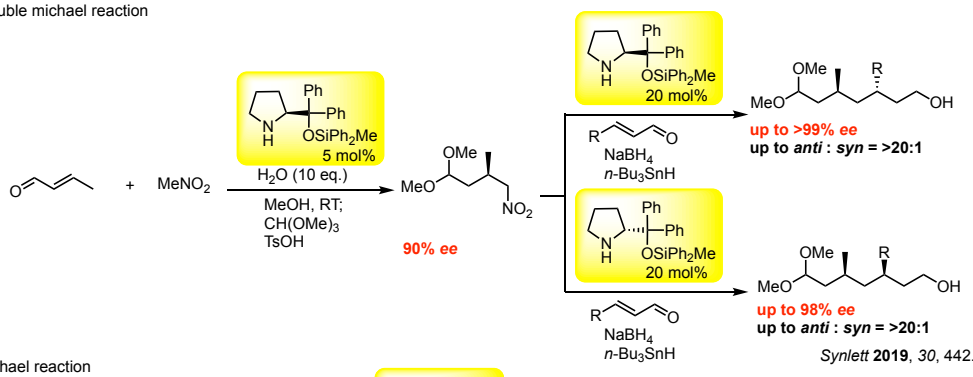


up to >99% *ee*

Org. Lett. **2021**, *23*, 6654.

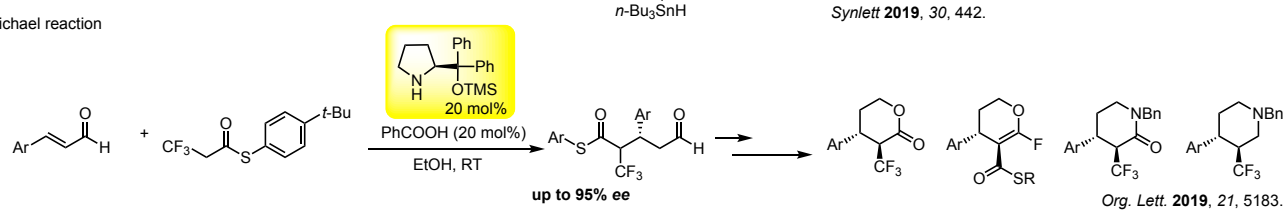
Reaction using diarylprolinol silyl ether derivatives as catalyst

Double michael reaction



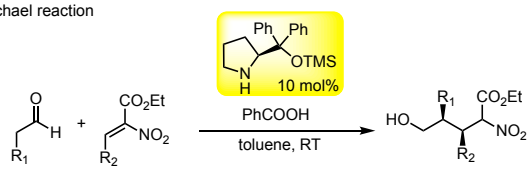
Synlett **2019**, *30*, 442.

Michael reaction



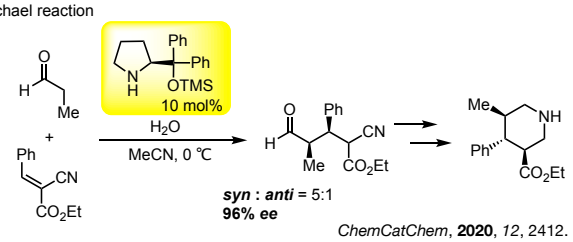
Org. Lett. **2019**, *21*, 5183.

Michael reaction



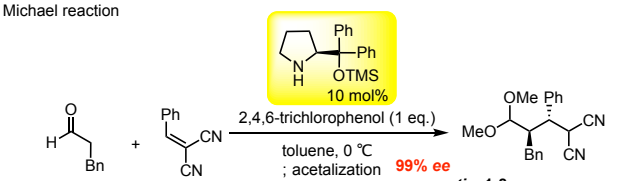
Chem. Lett., **2018**, *47*, 833.

Michael reaction



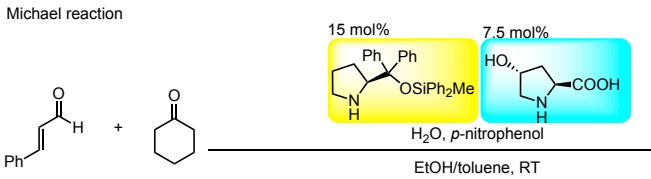
ChemCatChem, **2020**, *12*, 2412.

Michael reaction



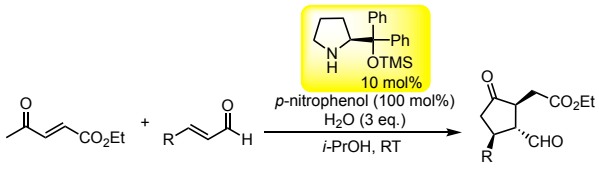
Eur. J. Org. Chem. **2018**, 6843.

Michael reaction



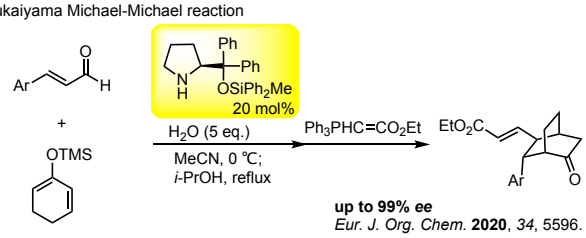
Angew. Chem. Int. Ed. **2018**, *57*, 1958.

Domino Michael-Michael reaciton



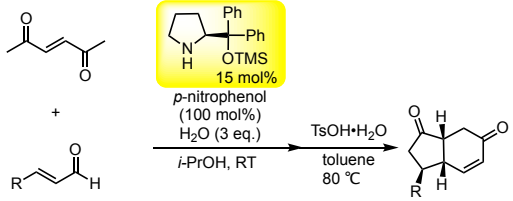
Chem. Sci. **2020**, *11*, 1205.

Mukaiyama Michael-Michael reaction



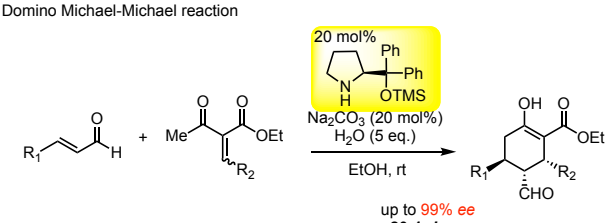
Eur. J. Org. Chem. **2020**, *34*, 5596.

Domino Michael-Michael-aldol reaciton



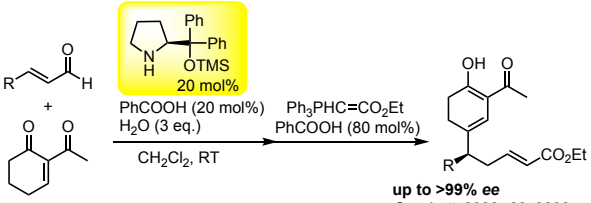
Chem. Lett. **2020**, *49*, 867.

Domino Michael-Michael reaction



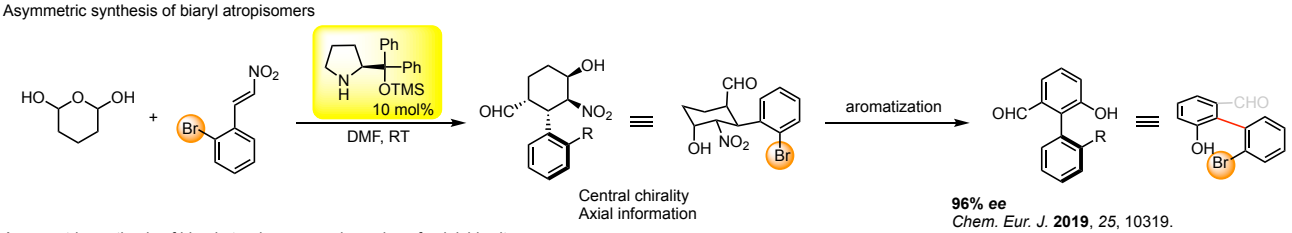
Eur. J. Org. Chem. **2021**, 6670.

Vinylogous Michael reaction



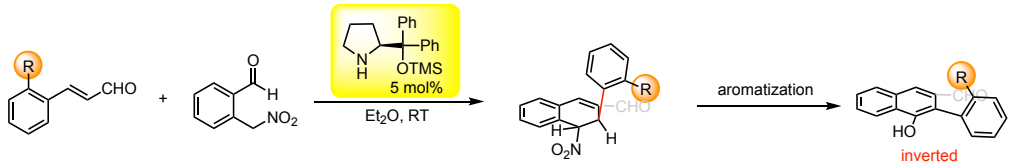
Org. Lett. **2020**, *22*, 8603.

Asymmetric synthesis of biaryl atropisomers



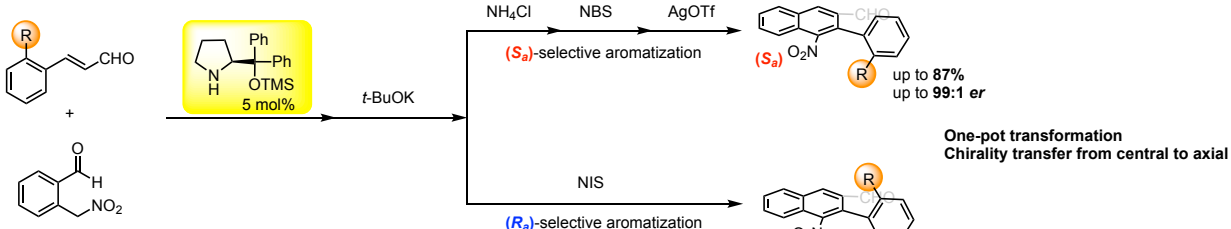
96% *ee*
Chem. Eur. J. **2019**, *25*, 10319.

Asymmetric synthesis of biaryl atropisomers — inversion of axialchirarity



up to 99% *ee*
Chem. Eur. J. **2020**, *26*, 4524.

Enantiodivergent one-pot synthesis of axially chiral biaryls

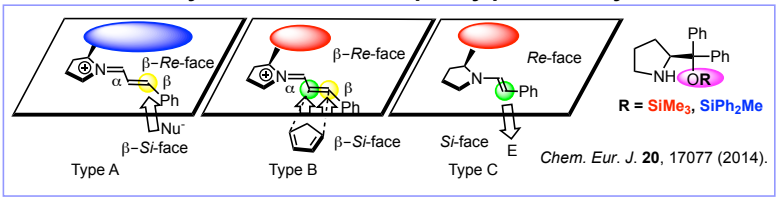


up to **87%**
up to **99:1 *er***

One-pot transformation
Chirality transfer from central to axial

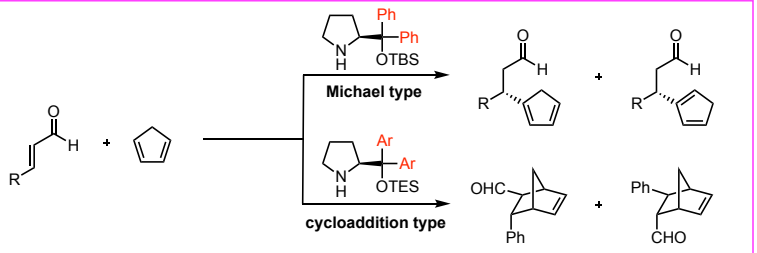
up to **84%**
up to **99:1 *er*** *Chem. Eur. J.* **2021**, *27*, 15786.

The effect of silyl substituents of diphenylprolinol silyl ether



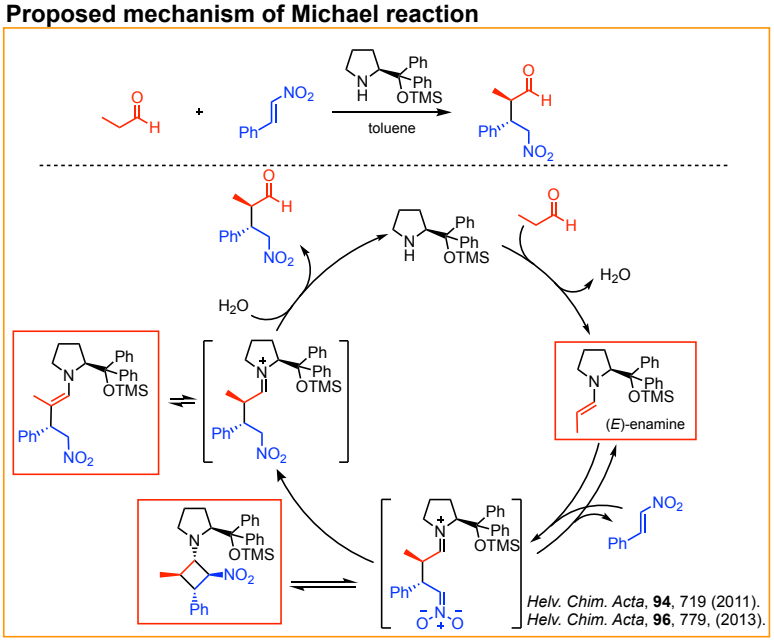
Chem. Eur. J. **20**, 17077 (2014).

The different reactivity of diphenylprolinol silyl ether and diarylprolinol silyl ether



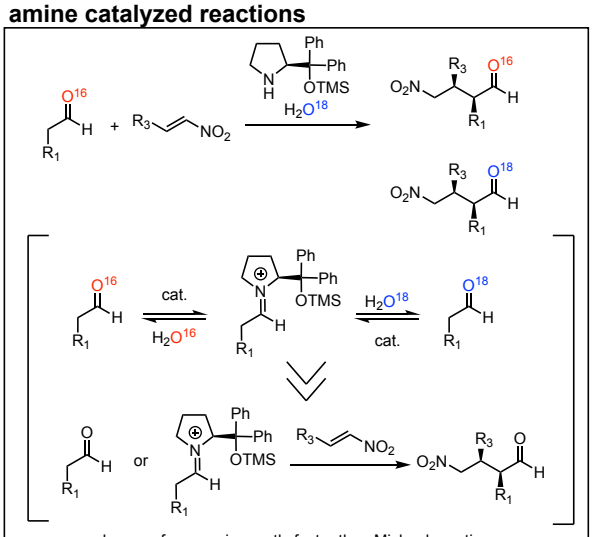
Chem. Eur. J. **21**, 12337 (2015).

Proposed mechanism of Michael reaction



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

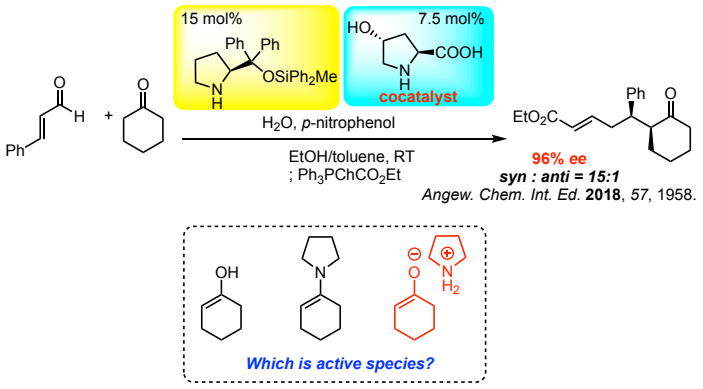
The $^{16}O/^{18}O$ exchanges existance in secondary amine catalyzed reactions

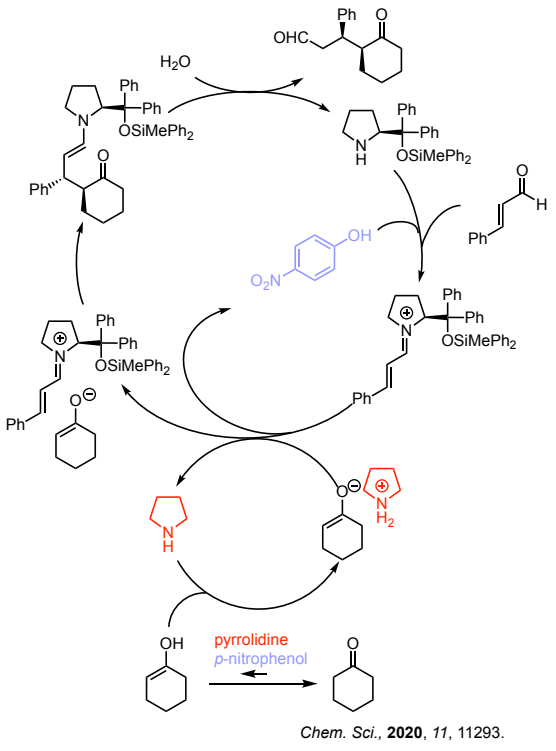


exchenge of oxygen is greatly faster than Michael reaction.
So, it is impossible to determine the reaction proceeds with enol or enamine by containing of 18O of TM.

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

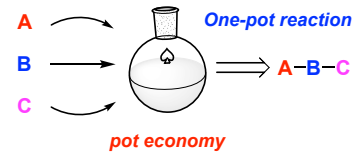
Proposed mechanism of α, β-unsaturated aldehyde and ketones via hydrid system of two secondary amine catalysts





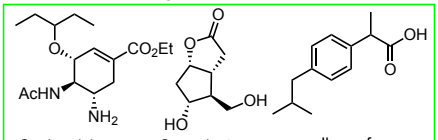
Review

Pot ecomomy



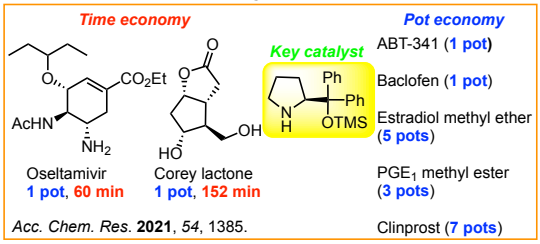
Chem. Sci. **7**, 866 (2016).

Time ecomomy



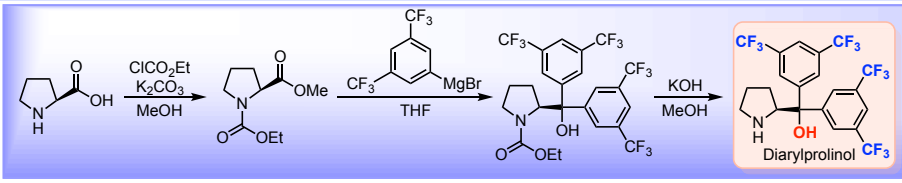
J. Org. Chem. **2021**, *86*, 1.

Pot and Time economy

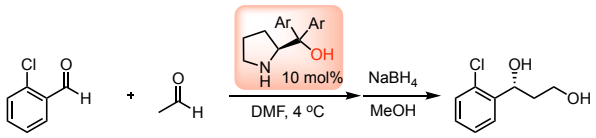


Acc. Chem. Res. **2021**, *54*, 1385.

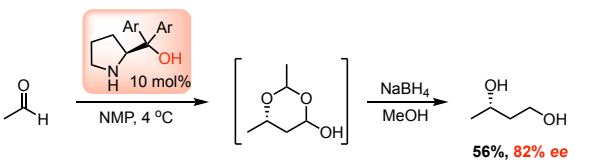
Aldol reaction by diarylprolinol as a catalyst



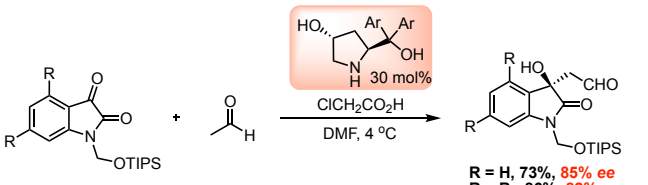
This catalyst is synthesized in short steps from proline.
This is effective organocatalyst of direct, enantioselective aldol reaction.
Excellent enantioselectivity is obtained.



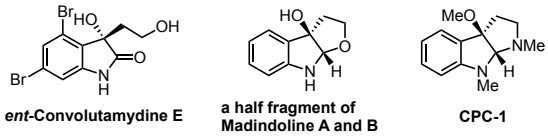
82%, 98% *ee*
Angew. Chem., Int. Ed., **47**, 2082 (2008).



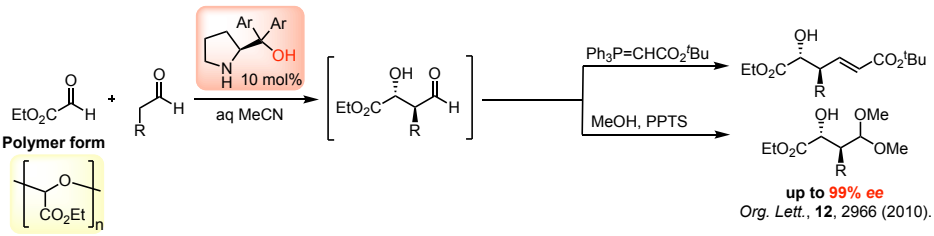
56%, 82% *ee*
Org. Lett., **10**, 5581 (2008).



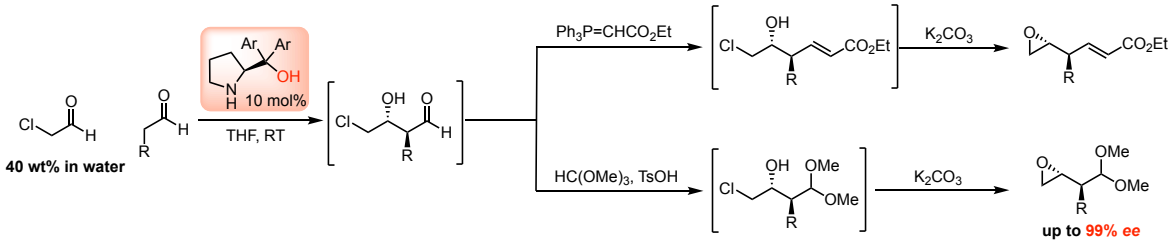
R = H, 73%, 85% *ee*
R = Br, 86%, 82% *ee*



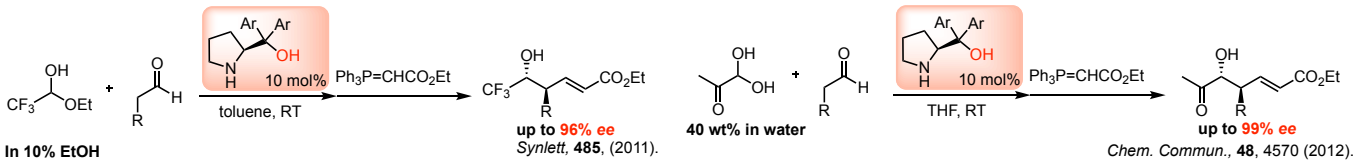
Org. Lett., **11**, 3854 (2009).



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

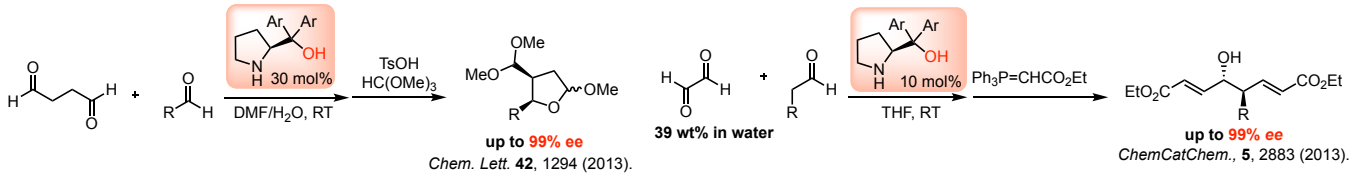


up to 99% *ee*
Angew. Chem., Int. Ed., **50**, 2804 (2011).



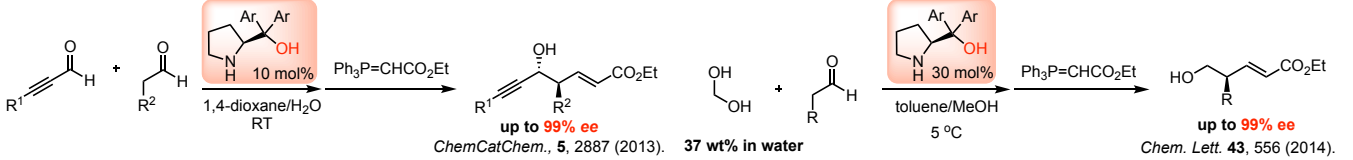
up to 96% *ee*
Synlett, **485**, (2011).

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



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

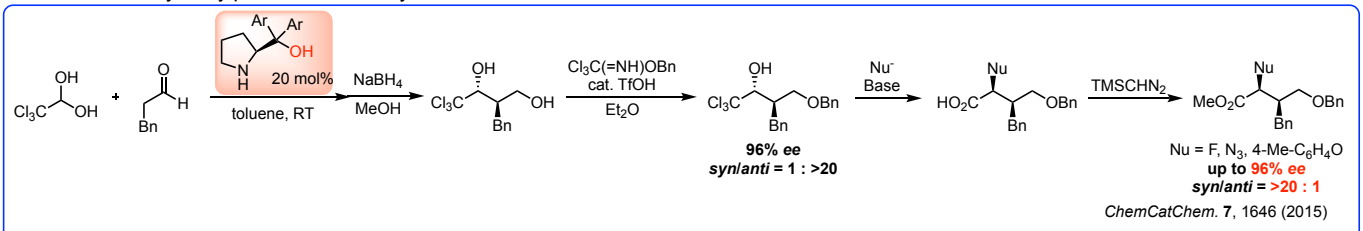
up to 99% *ee*
ChemCatChem., **5**, 2883 (2013).



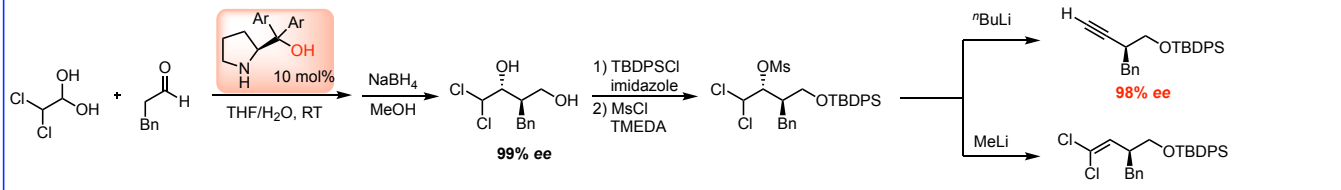
up to 99% *ee*
ChemCatChem., **5**, 2887 (2013).

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

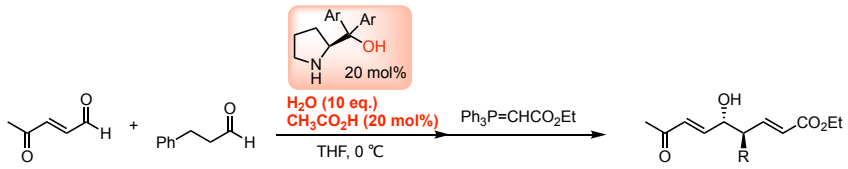
Aldol reaction by diarylprolinol as a catalyst



ChemCatChem. **7**, 1646 (2015)

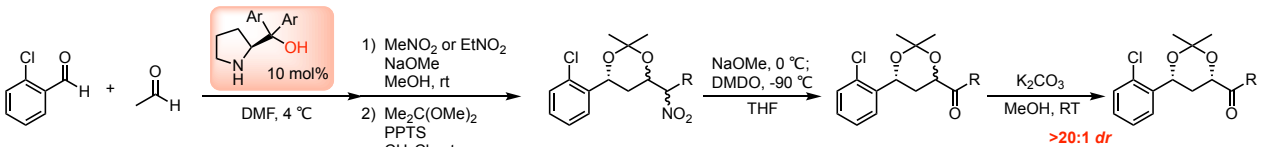


Adv. Synth. Catal. **358**, 2345 (2016).



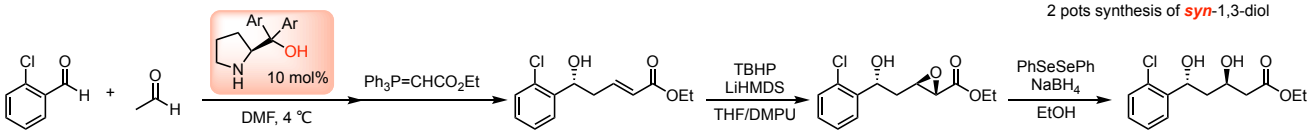
Chem. Asian J. **2019**, *14*, 4146.

Chem. Eur. J. **2018**, *24*, 4909.



Chem. Lett. **2020**, *49*, 940.

2 pots synthesis of ***syn***-1,3-diol

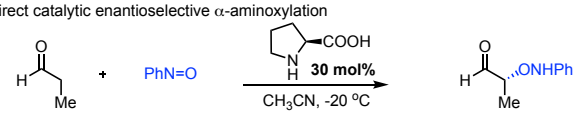


Org. Lett., **2021**, *23*, 5896.

3 pots synthesis of ***anti***-1,3-diol

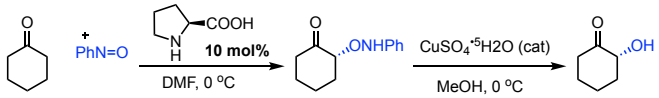
Reaction catalyzed by proline

Direct catalytic enantioselective α-aminoxylation



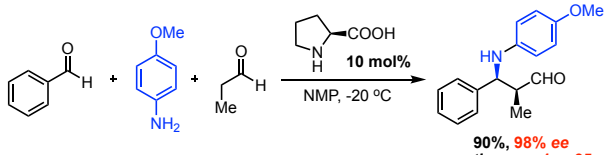
quant, 98% ee

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



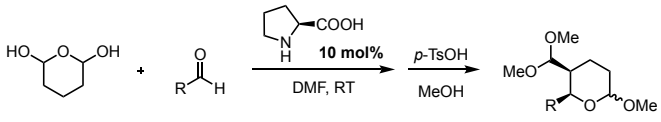
Angew. Chem., Int. Ed., **43**, 1112 (2004).
J. Org. Chem., **69**, 1548 (2004).

Three-Component Cross-Mannich reaction of aldehydes



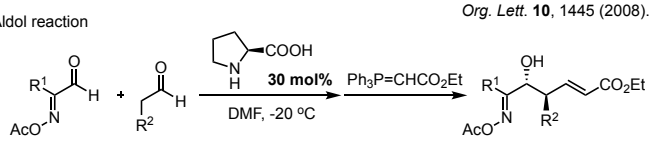
Angew. Chem., Int. Ed., **42**, 3677 (2003).
Adv. Synth. Catal., **347**, 1604 (2005).
Nature Protocols, **2**, 113 (2007).

Aldol / acetalization reaction



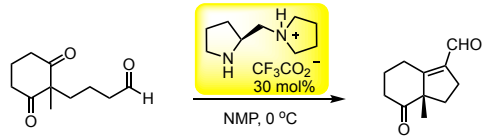
Org. Lett. **10**, 1445 (2008).

Aldol reaction



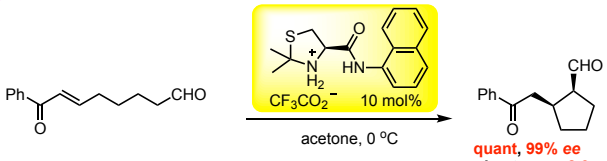
Adv. Synth. Catal. **356**, 3106 (2014).

Reaction by proline-derived catalyst



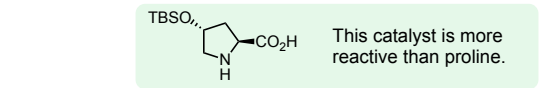
J. Org. Chem., **72**, 6493 (2007).

Reaction by cystein-derived catalyst

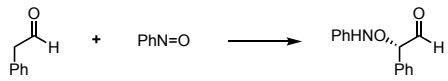


quant, 99% *ee*
***cis* : *trans* = 8.3 : 1**
J. Am. Chem. Soc., **127**, 16028 (2005).

Reaction by siloxyproline catalyst

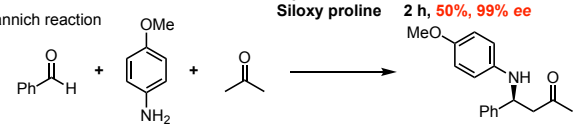


α-aminoxylation



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

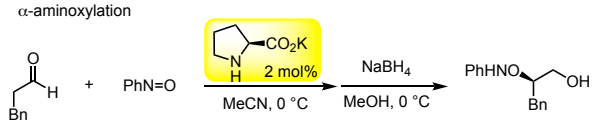
Mannich reaction



L-proline **20 h, <5%**
Siloxy proline **20 h, 63%, 96% *ee***
Adv. Synth. Catal., **346**, 1435 (2004).

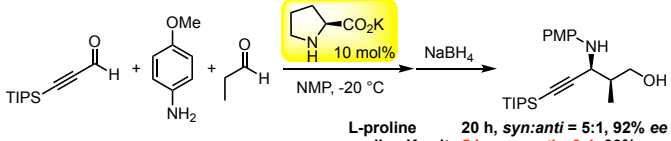
Reaction by prolinate salt catalyst

α-aminoxylation



L-proline **23 h, 90%, 98% *ee***
proline K salt **4 h, 99%, 99% *ee***
Org. Lett. **19**, 4155 (2017).

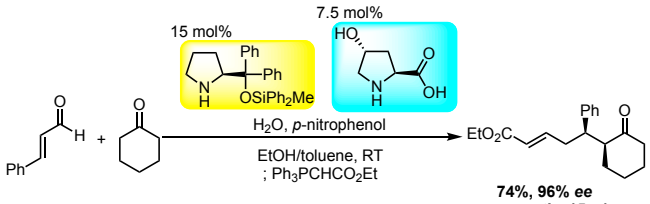
Mannich reaction



L-proline **20 h, *syn:anti* = 5:1, 92% *ee***
proline K salt **5 h, *syn:anti* = 9:1, 99% *ee***
Org. Lett. **20**, 2391 (2018).

Reaction using two catalysts system

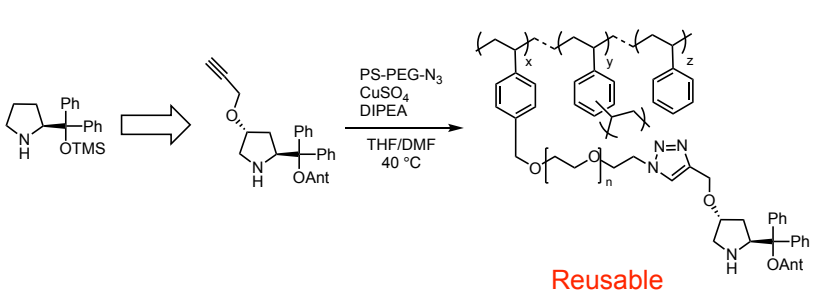
Michael reaction



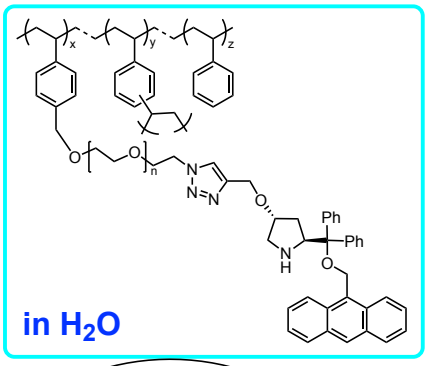
74%, 96% *ee*
***syn* : *anti* = 15 : 1**
Angew. Chem. Int. Ed. **57**, 1958 (2018).

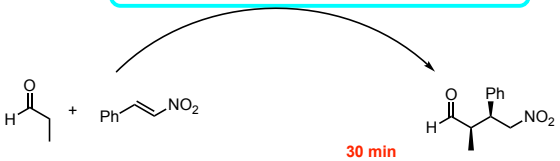
Polymer supported Diphenylprolinol catalysts

high reactive PS-PEG type catalyst



Reusable
Immobilized on PS-PEG resin

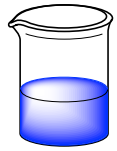




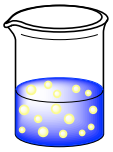
30 min
5:1 *dr*, 93% *ee*
Bull. Chem. Soc. Jpn. **2021**, *94*, 790.

Organic solvent free reaction

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



in water



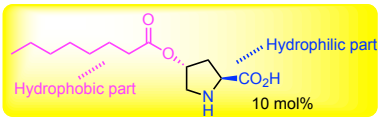
in the presence of water

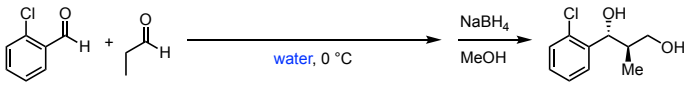
"in water" : The participating reactions are dossplved homogeneously in water.

"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

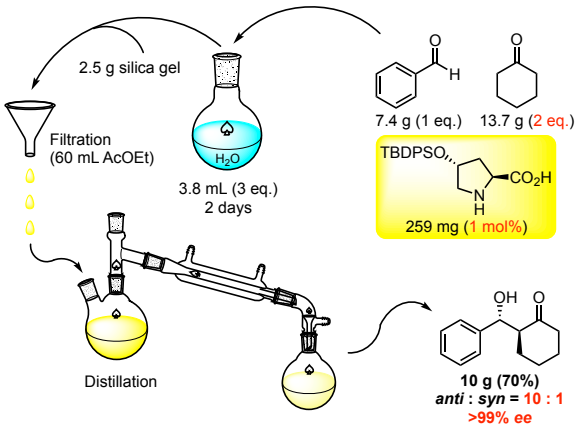




97%, 99% *ee*
***anti*/*syn* = 19 : 1**

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

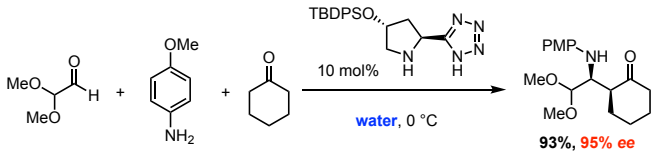
·Organic solvent free asymmetrric aldol reaction between ketone and aldehyde



10 g (70%)
***anti* : *syn* = 10 : 1**
>99% *ee*

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

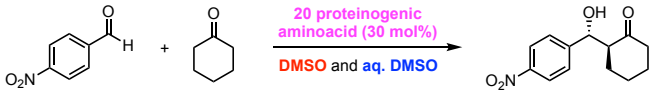
·Organic solvent free asymmetrric Mannich reaction with proline catalyst



93%, 95% *ee*
***syn* : *anti* = 4.6 : 1**

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

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



<5-89%, 0-96% *ee*
***anti* : *syn* = 0.8-13 : 1**

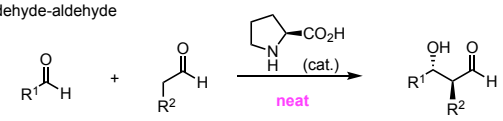
positive water effect

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

Synlett 1565 (2006).

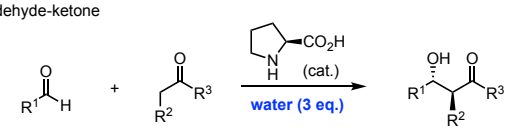
·Organic solvent free Dry and Wet condition asymetric aldol reaction with proline catalyst

aldehyde-aldehyde



***anti* : *syn* = up to 14 :1**
up to 95% *ee*

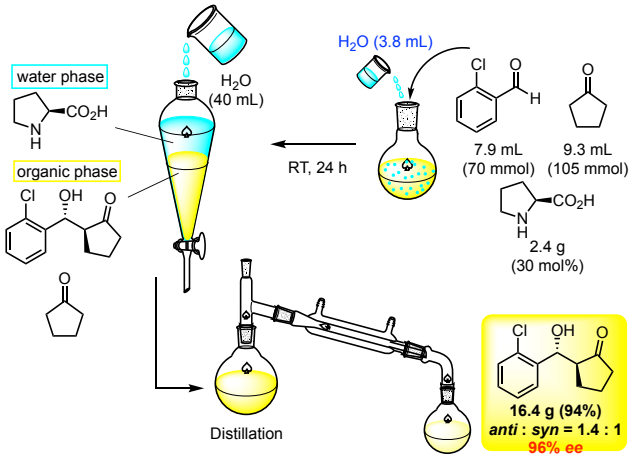
aldehyde-ketone



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

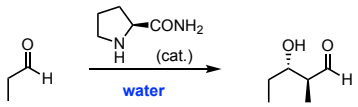
Chem. Commun. 957 (2007).

Organic solvent-free aldol reaction



16.4 g (94%)
***anti* : *syn* = 1.4 : 1**
96% *ee*

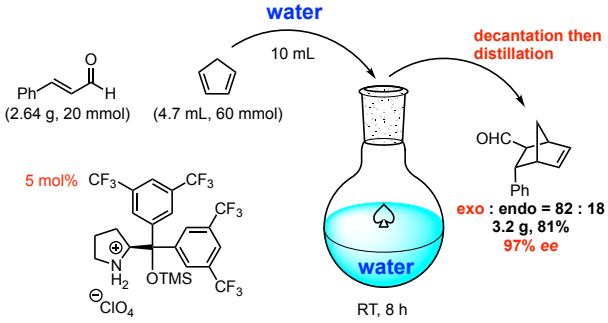
·Self aldol reaction of propanal in water - reaction in water with proline-amide catalyst



high enantioselectivity

Chem. Commun. 2524 (2007).

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



exo : endo = 82 : 18
3.2 g, 81%
97% *ee*

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

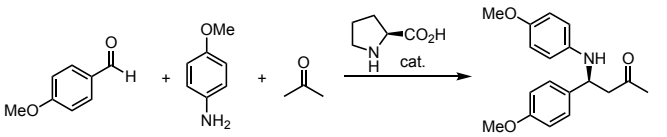
Application of High Pressure Induced by Water-Freezing to the direct catalytic asymmetric reaction

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***

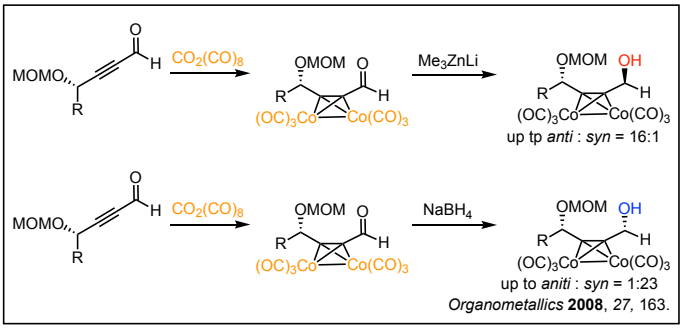
J. Am. Chem. Soc., **125**, 11208 (2003).

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

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

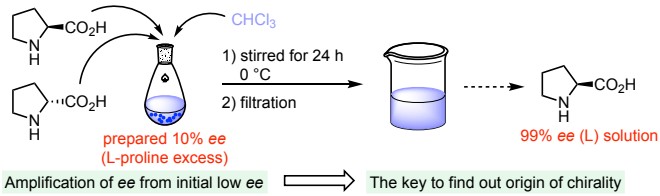
·Baylis-Hillman reaction
Tetrahedron Lett., **43**, 8683 (2004).

1,4-asymmetric induction using Cobalt alkyne complex



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

Research about of chirality

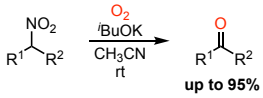


Amplification of *ee* from initial low *ee* ⇒ The key to find out origin of chirality

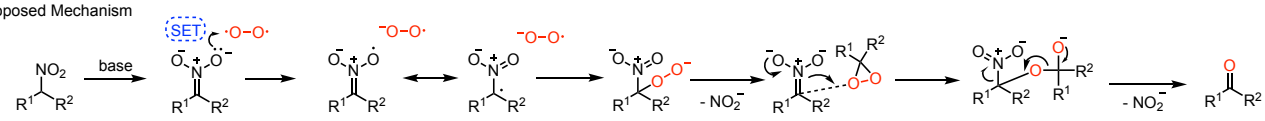
Angew. Chem., Int. Ed. **45**, 4593 (2006).

Metal-free oxidative transformations using O_2

Nef reaction using molecular O_2

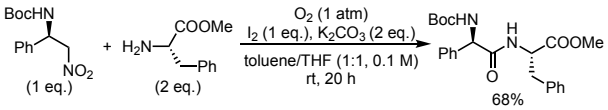


Proposed Mechanism



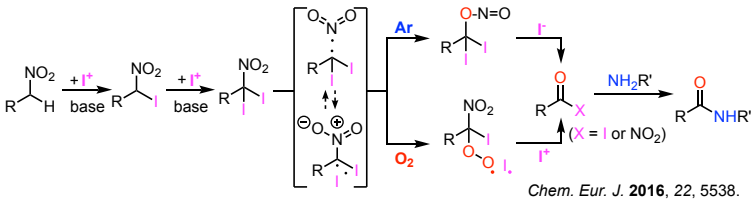
Chem. Eur. J. **2014**, *20*, 15753.

Oxidative amidation of primary nitroalkane and amine



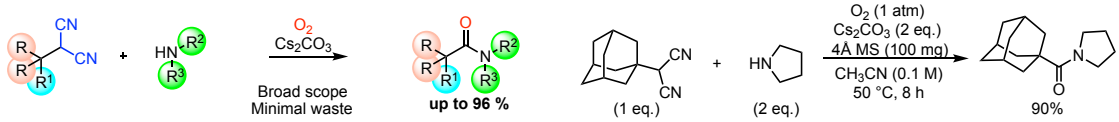
Angew. Chem. Int. Ed. **2015**, *54*, 12986.

Proposed Mechanism



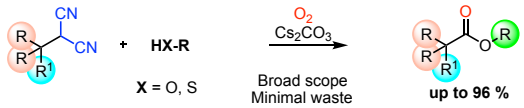
Chem. Eur. J. **2016**, *22*, 5538.

Sterically demanding oxidative amidation of α-substituted malononitriles with amines



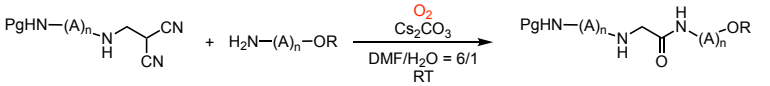
Angew. Chem. Int. Ed. **2016**, *55*, 9060.

Sterically demanding ester formation of α-substituted malononitriles with alcohol



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

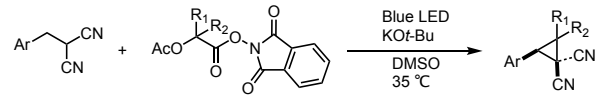
Application to peptipe synthesis

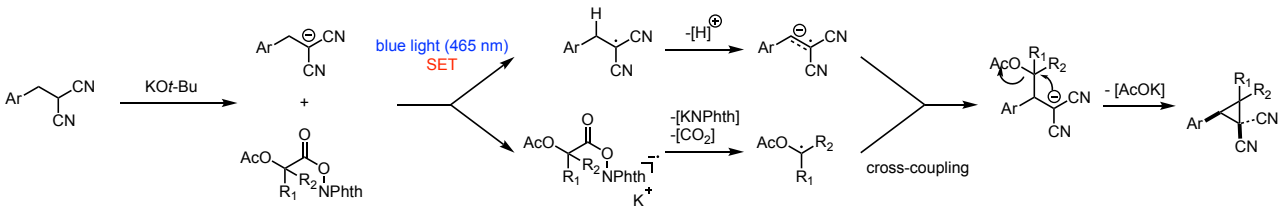


Broad scope
Tripeptide : **Boc-Phe-Gly-Phe-OMe (18 examples)**
Tetrapeptide : **Boc-Phe-Gly-Leu-Phe-Ot-Bu (5 examples)**
Unprotected amino acid : **Boc-Phe-Gly-Phe-OH (4 examples)**

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

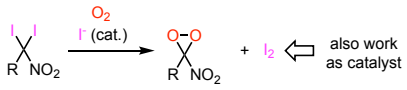
Direct cyclopropanation by light mediated single electron transfer

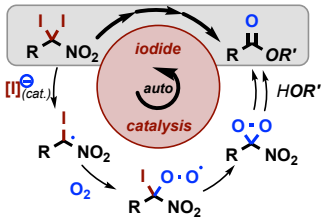




Chem. Eur. J. **2021**, *27*, 5901.

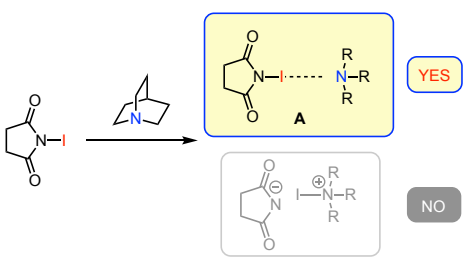
Autoinductive oxidation of α,α-diiodonitroalkanes

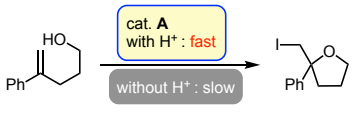




Chem. Commun., **2018**, *54*, 6360.

Halogen bonding of N-Halosuccinimides with amines





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