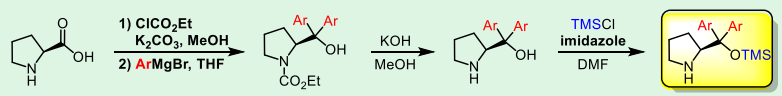
Hayashi Laboratory

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

Development of new reactions

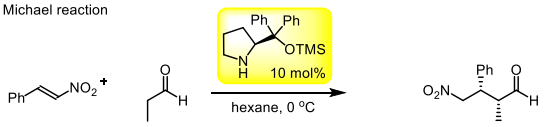
Asymmetric reaction using amino acid or their derivatives as a catalyst,
environmental conscious asymmetric reaction using water as a solvent, and research about origin of chirality

Reaction using diarylprolinol silyl ether derivatives as catalyst



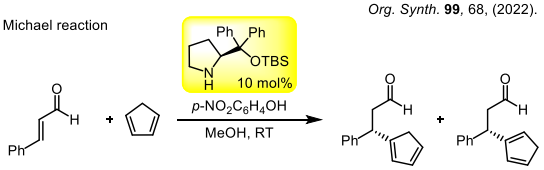
This catalyst is synthesized in short steps from proline.
Substituents on aryl and silyl moiety are easily modified.
Excellent enantioselectivity is obtained

Michael reaction



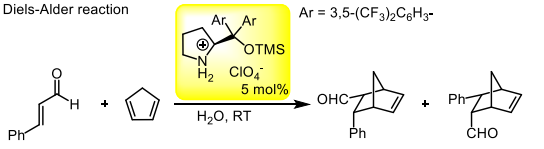
85%, 99% *ee*
Angew. Chem., Int. Ed., **44**, 4212 (2005).
Org. Synth. **99**, 68, (2022).

Michael reaction



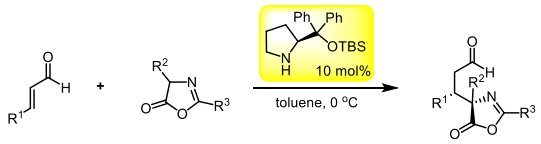
84%, 92% *ee*
Angew. Chem., Int. Ed., **45**, 6853 (2006).

Diels-Alder reaction



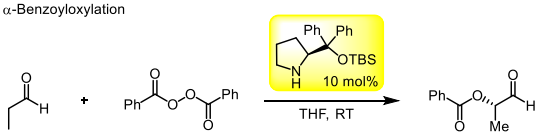
***exo* : *endo* = 80 : 20, 97% *ee* (*exo*)**
Org. Lett, **9**, 2859 (2007).
Angew. Chem., Int. Ed., **47**, 6634 (2008).

Michael reaction



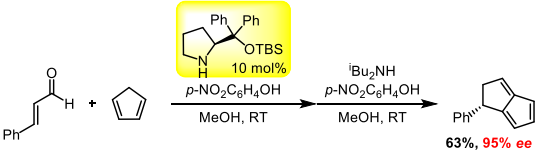
up to 99% *ee*
up to >90% *de*
Chem. Asian. J., **4**, 246 (2009).

α-Benzoyloxylation



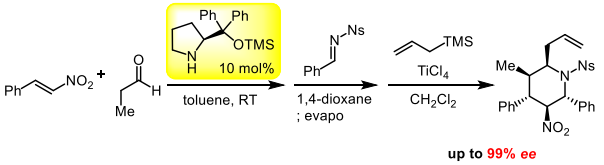
78%, 92% *ee*
Chem. Commun,, 3083 (2009).

Michael / cyclization reaction



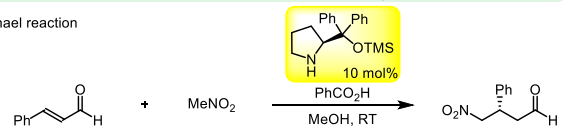
63%, 95% *ee*
Tetrahedron, **66**, 4894 (2010).

Michael / aza Henry / aminal formation / additional reaction



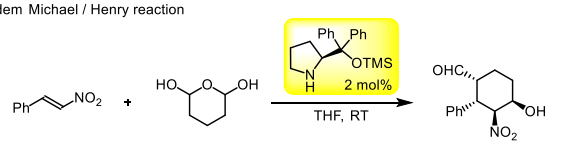
up to 99% *ee*
Single diastereomer
Org.Lett., **12**, 4588 (2010).

Michael reaction



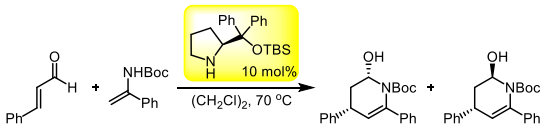
90%, 95% *ee*
Org. Lett., **9**, 5307 (2007).

Tandem Michael / Henry reaction



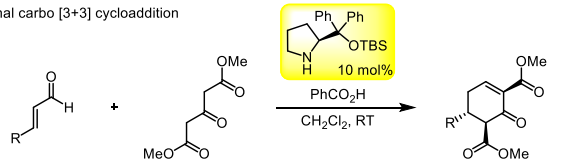
66%, 99% *ee*
Angew. Chem., Int. Ed., **46**, 4922 (2007).

Formal aza [3+3] cycloaddition



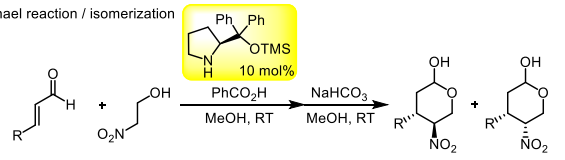
90%, 94% *ee*, α : β = 34 : 66
Angew. Chem., Int. Ed., **47**, 4012 (2008).

Formal carbo [3+3] cycloaddition



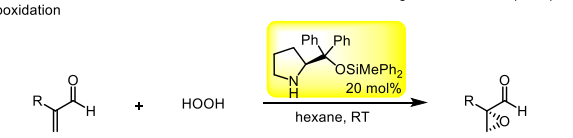
up to 99% *ee*
Org. Lett., **11**, 45 (2009).

Michael reaction / isomerization



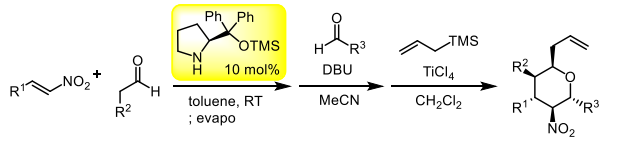
a **b**
up to 99% *ee*, a : b = 9 : 1
Org. Lett., **11**, 4056 (2009).

epoxidation



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

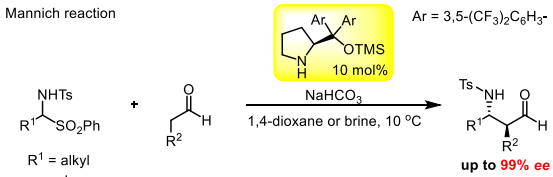
Michael / Henry / acetal formation / additional reaction



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

Reaction using diarylprolinol silyl ether derivatives as catalyst

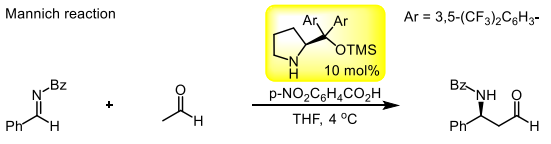
Mannich reaction



up to 99% *ee*

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

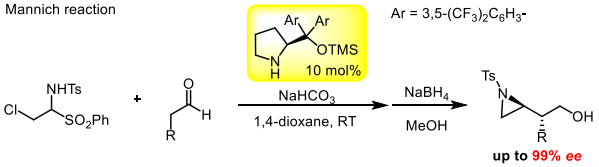
Mannich reaction



87%, 98% *ee*

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

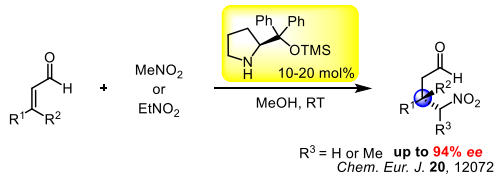
Mannich reaction



up to 99% *ee*

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

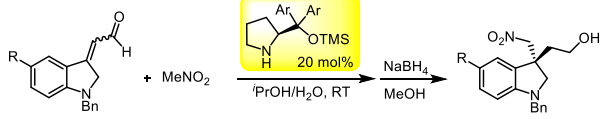
Michael reaction



R3 = H or Me up to 94% *ee*

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

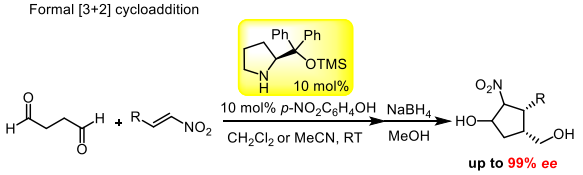
Michael reaction



up to 94% *ee*

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

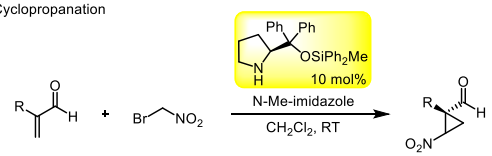
Formal [3+2] cycloaddition



up to 99% *ee*

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

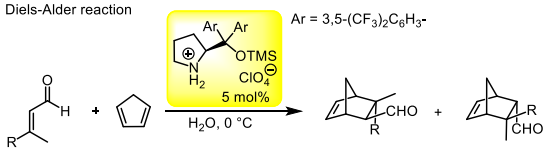
Cyclopropanation



up to 99% *ee*

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

Diels-Alder reaction

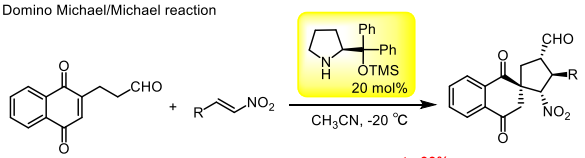


up to *exo* : *endo* = 88 : 12

up to 99% *ee*

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

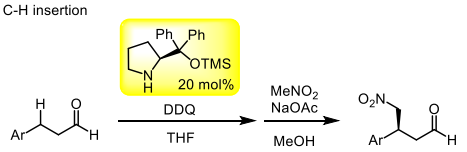
Domino Michael/Michael reaction



up to 99% *ee*

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

Formal C-H insertion

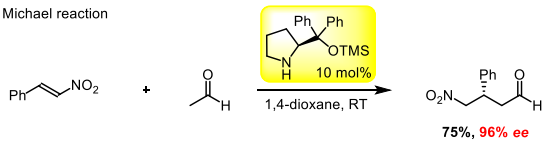


up to 95% *ee*

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

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

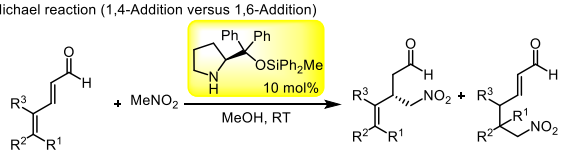
Michael reaction



75%, 96% *ee*

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

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



100 : 0

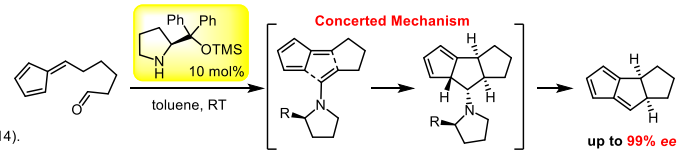
up to 95% *ee*

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

<Review>

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

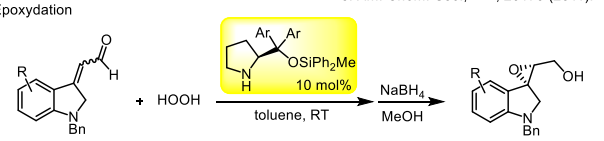
[6+2] cycloaddition reaction



up to 99% *ee*

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

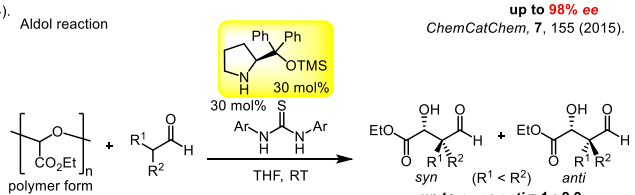
Epoxydation



up to 98% *ee*

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

Aldol reaction

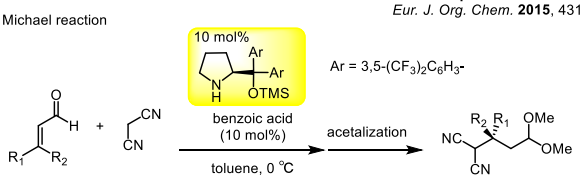


up to *syn* : *anti* = 1 : 2.9

up to 91% *ee*

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

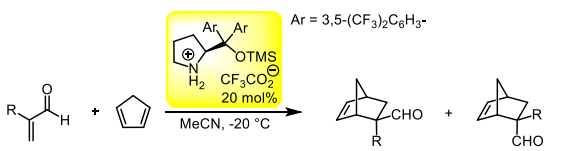
Michael reaction



up to 99% *ee*

Synlett **2022**, *33*, 1831.

Diels-Alder reaction

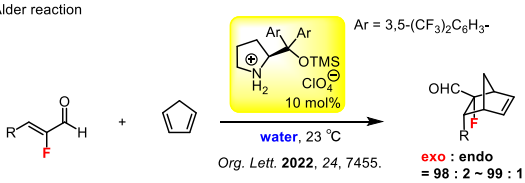


up to *exo* : *endo* = 99 : 1

up to 91% *ee*

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

Diels-Alder reaction



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

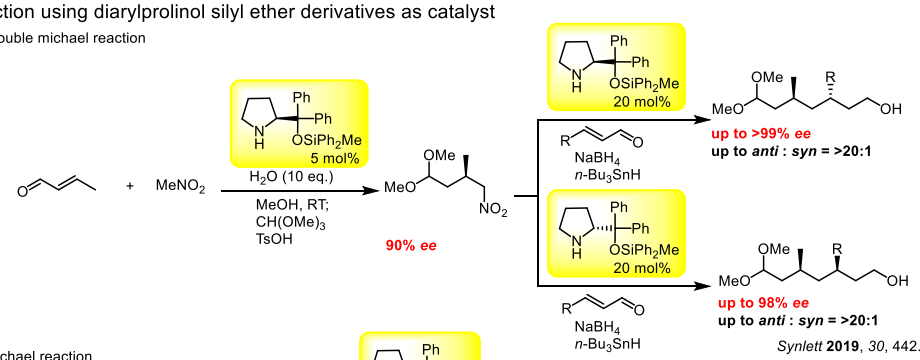
exo : endo

= 98 : 2 ~ 99 : 1;

up to 98% *ee*

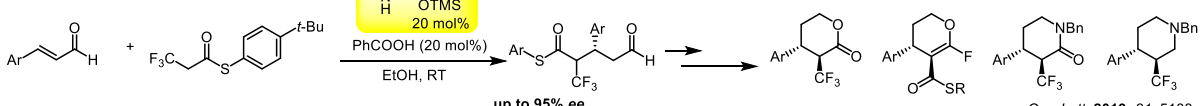
Reaction using diarylprolinol silyl ether derivatives as catalyst

Double michael reaction



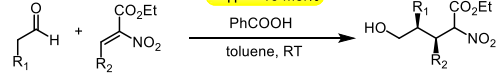
Synlett **2019**, *30*, 442.

Michael reaction



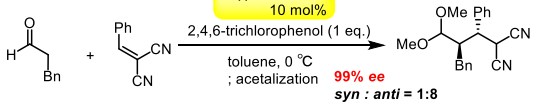
Org. Lett. **2019**, *21*, 5183.

Michael reaction



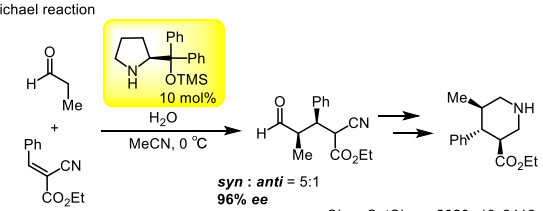
Chem. Lett., **2018**, *47*, 833.

Michael reaction



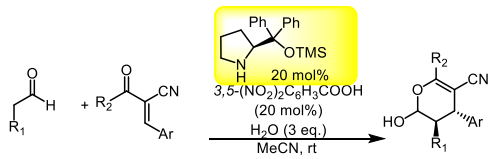
Eur. J. Org. Chem. **2018**, 6843.

Michael reaction



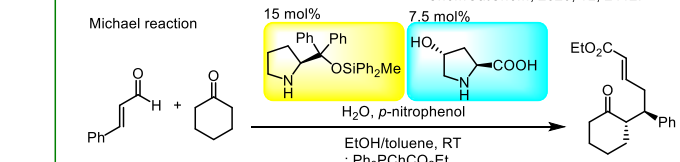
ChemCatChem, **2020**, *12*, 2412.

Domino Michael/ enolization / acetalization reactions



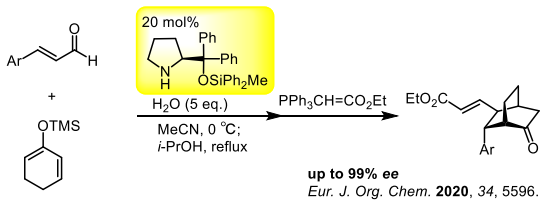
Synlett, **2024**, *35*, DOI: 10.1055/a-2324-8899.

Michael reaction



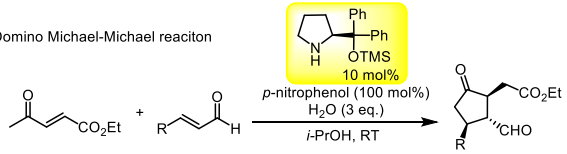
Angew. Chem. Int. Ed. **2018**, *57*, 1958.

Mukaiyama Michael-Michael reaction



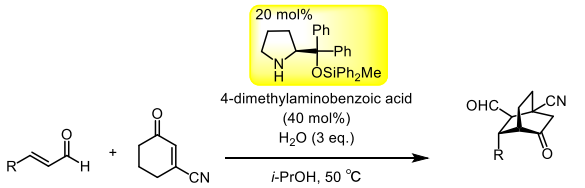
Eur. J. Org. Chem. **2020**, *34*, 5596.

Domino Michael-Michael reaciton



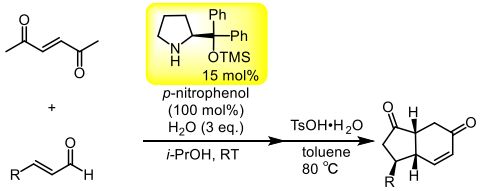
Chem. Sci. **2020**, *11*, 1205.

Domino Michael-Michael reaction



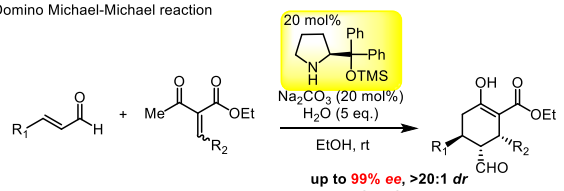
Asian. J. Org. Chem. **2021**, *10*, 3261.

Domino Michael-Michael-aldol reaciton



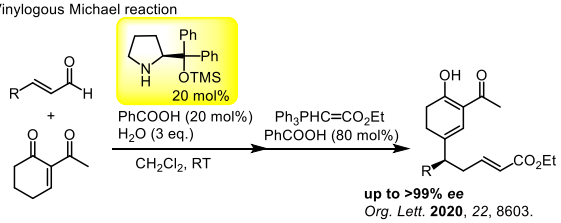
Chem. Lett. **2020**, *49*, 867.

Domino Michael-Michael reaction



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

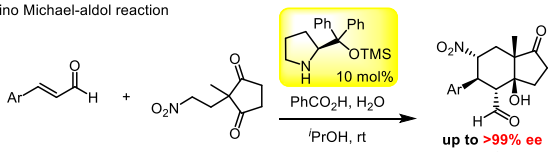
Vinylogous Michael reaction



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

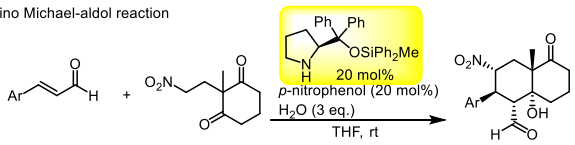
Reaction using diarylprolinol silyl ether derivatives as catalyst

Domino Michael-aldol reaction



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

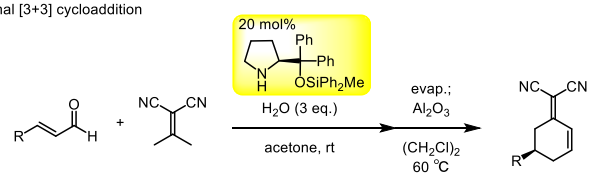
Domino Michael-aldol reaction



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

Reaction using diarylprolinol silyl ether derivatives as catalyst

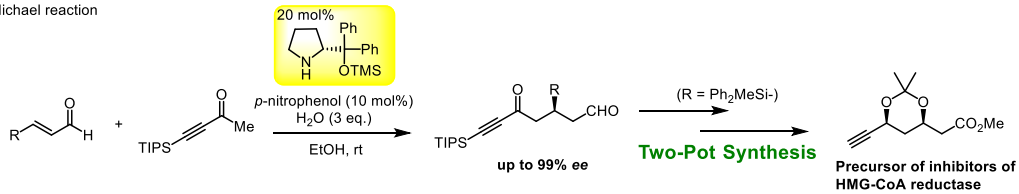
Formal [3+3] cycloaddition



up to 99% *ee*

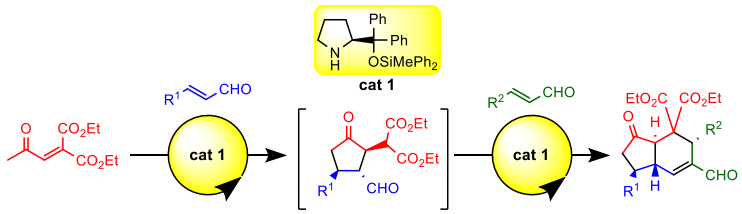
Eur. J. Org. Chem. **2022**, e202200603.

Michael reaction



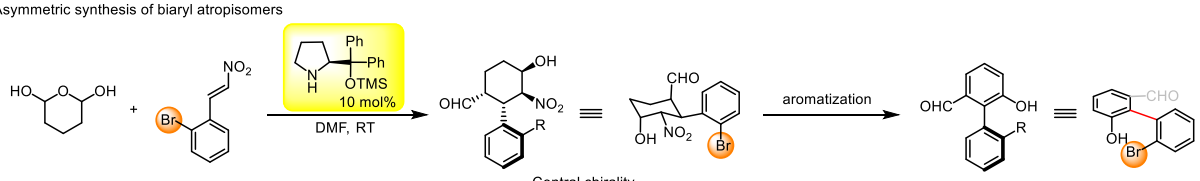
ACS Org. Inorg. Au **2022**, *2*, 245.

one-pot/two domino/three component coupling reactions



Chem. Sci., **2024**, *15*, 5627.

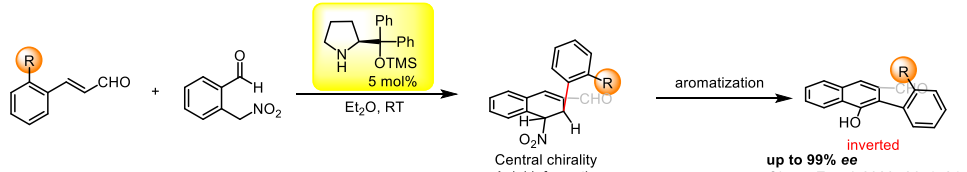
Asymmetric synthesis of biaryl atropisomers



96% *ee*

Chem. Eur. J. **2019**, *25*, 10319.

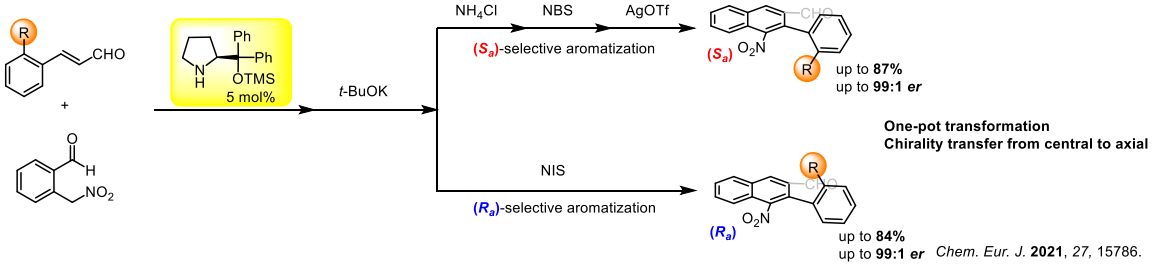
Asymmetric synthesis of biaryl atropisomers — inversion of axialchirarity



up to 99% *ee*

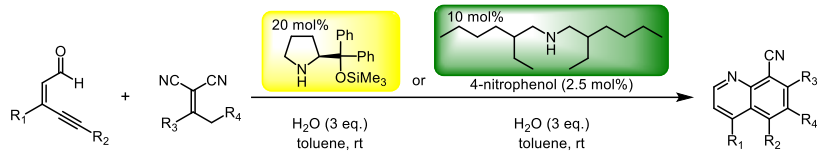
Chem. Eur. J. **2020**, *26*, 4524.

Enantiodivergent one-pot synthesis of axially chiral biaryls



Chem. Eur. J. **2021**, *27*, 15786.

Quinoline synthesis

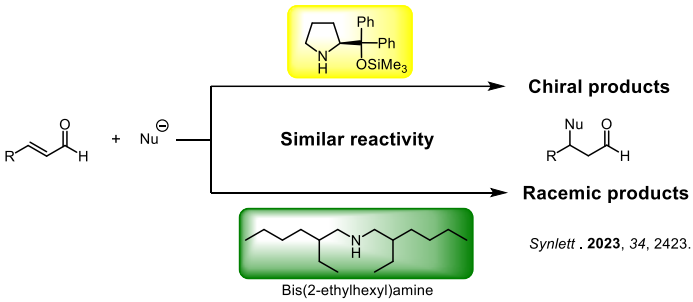


Bis(2-ethylhexyl)amine

up to 96% yield

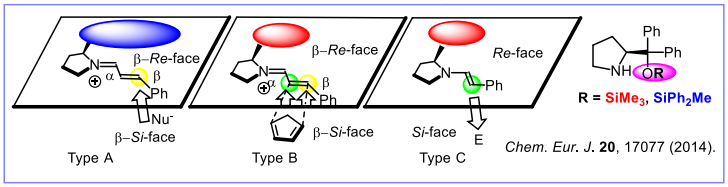
Chem. Eur. J. **2023**, *29*, e202301093.

Racemic Reactions of α,β-Unsaturated Aldehydes by using Bis(2-ethylhexyl)amine



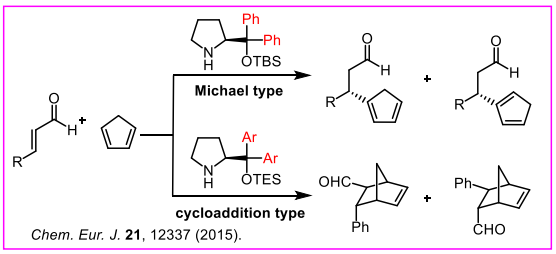
Synlett **. 2023**, *34*, 2423.

The effect of silyl substituents of diphenylprolinol silyl ether



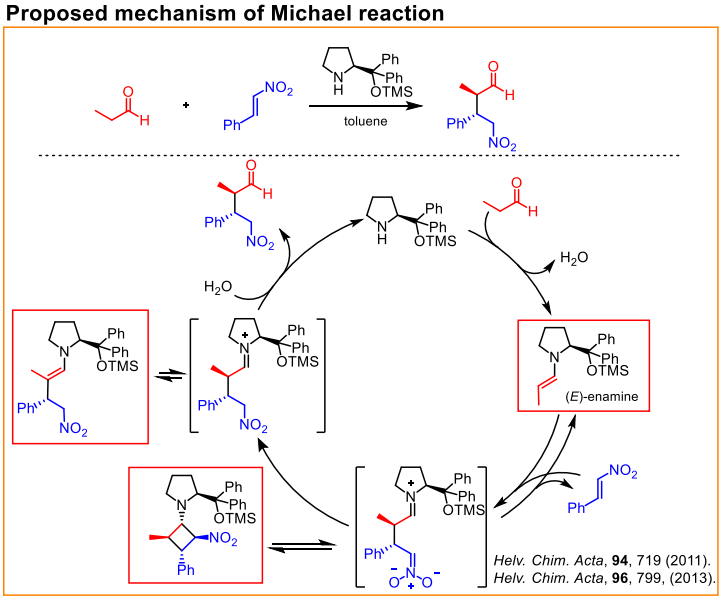
Chem. Eur. J. **20**, 17077 (2014).

The different reactivity of diphenylprolinol silyl ether and diarylprolinol silyl ether



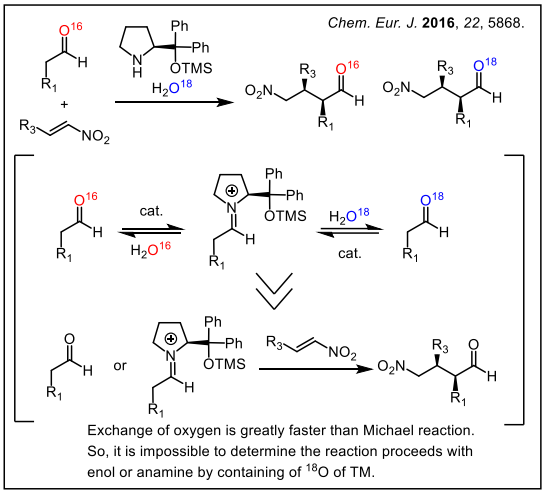
Chem. Eur. J. **21**, 12337 (2015).

Proposed mechanism of Michael reaction

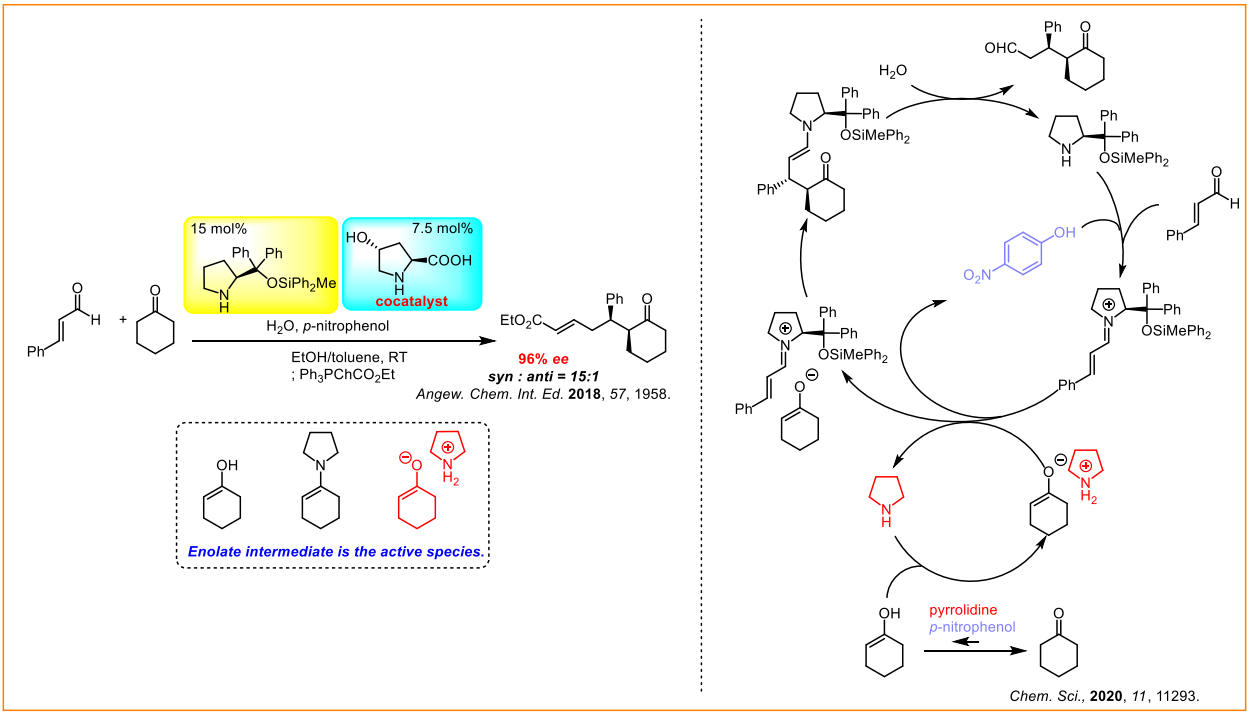


Helv. Chim. Acta, **94**, 719 (2011).
Helv. Chim. Acta, **96**, 799, (2013).

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

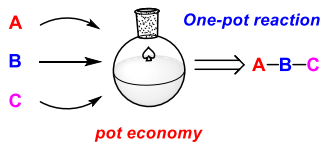


Angew. Chem. Int. Ed. **2018**, *57*, 1958.

Chem. Sci., **2020**, *11*, 11293.

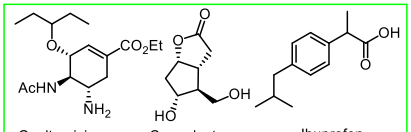
Review

Pot ecomomy



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

Time ecomomy



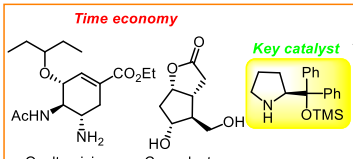
Oseltamivir: >37 h ⇩ 60 min

Corey lactone: >48 h ⇩ 152 min

Ibuprofen: 16 h batch ⇩ 3 min flow

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

Pot and Time economy



Oseltamivir: 1 pot, 60 min

Corey lactone: 1 pot, 152 min

Pot economy

ABT-341 (1 pot)

Baclofen (1 pot)

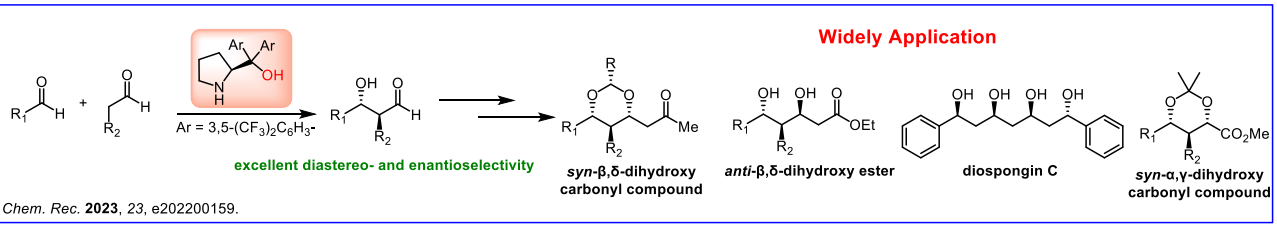
Estradiol methyl ether (5 pots)

PGE_1 methyl ester (3 pots)

Clinprost (7 pots)

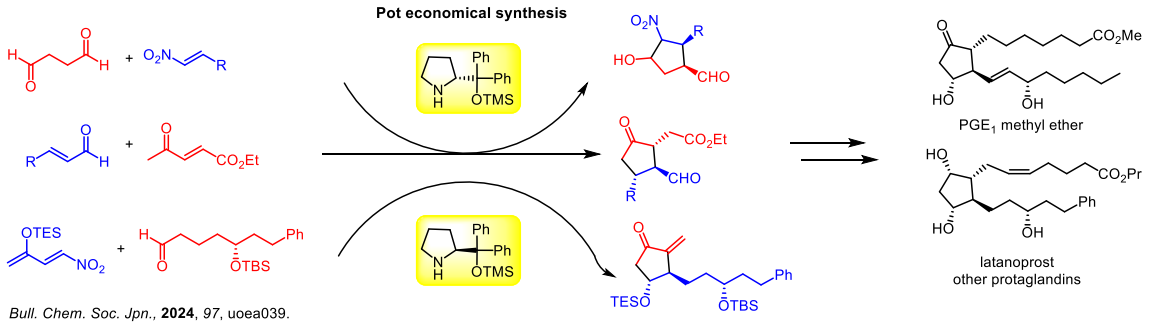
Acc. Chem. Res. **2021**, *54*, 1385.

Asymmetric Cross-aldol Reactions

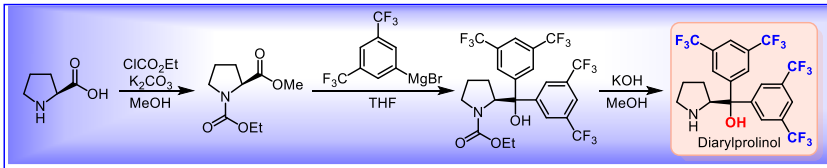


Chem. Rec. **2023**, *23*, e202200159.

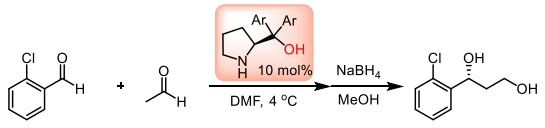
Pot economical total synthesis of protaglandins



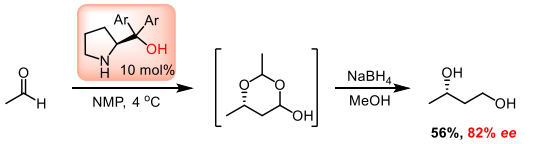
Bull. Chem. Soc. Jpn., **2024**, *97*, uoea039.



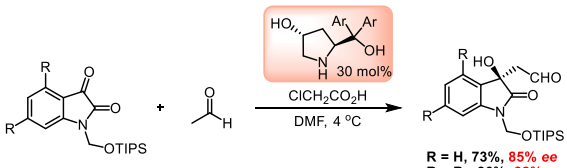
This catalyst is synthesized in short steps from proline.
This is effective organocatalyst of direct, enantioselective aldol reaction.
Excellent enantioselectivity is obtained.



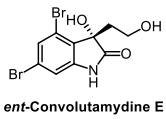
82%, 98% *ee*
Angew. Chem., Int. Ed., **47**, 2082 (2008).



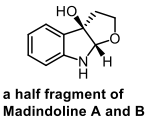
56%, 82% *ee*
Org. Lett., **10**, 5581 (2008).



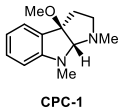
R = H, 73%, 85% *ee*
R = Br, 86%, 82% *ee*



***ent*-Convolutamydine E**

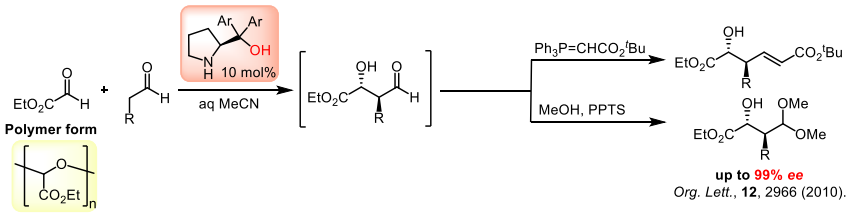


a half fragment of Madindoline A and B



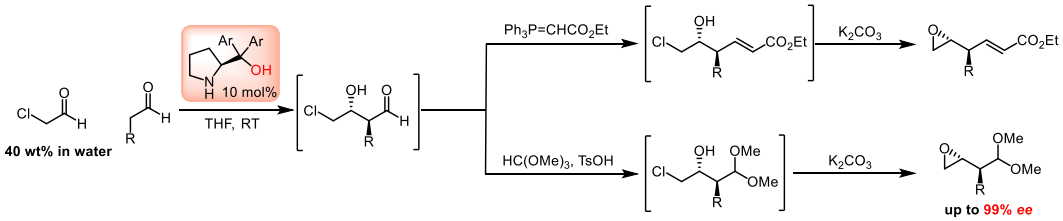
CPC-1

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

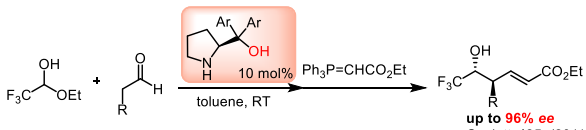


Polymer form

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

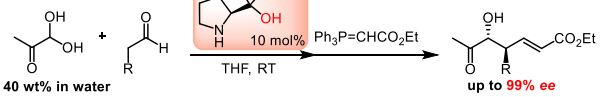


up to 99% *ee*
Angew. Chem., Int. Ed., **50**, 2804 (2011).

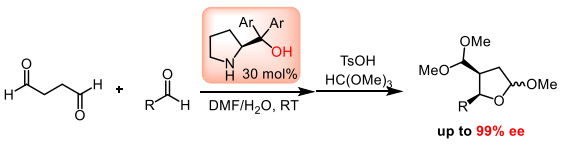


In 10% EtOH

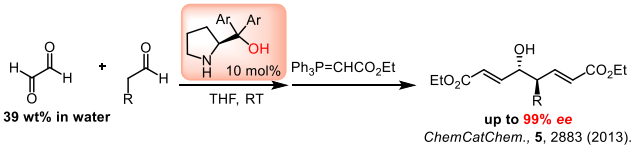
up to 96% *ee*
Synlett, **485**, (2011).



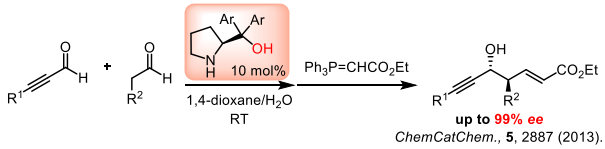
up to 99% *ee*
Chem. Commun., **48**, 4570 (2012).



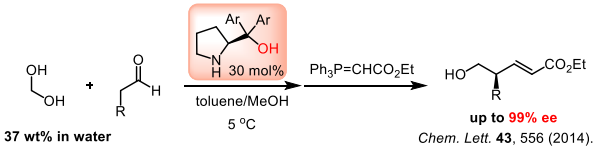
up to 99% *ee*
Chem. Lett. **42**, 1294 (2013).



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

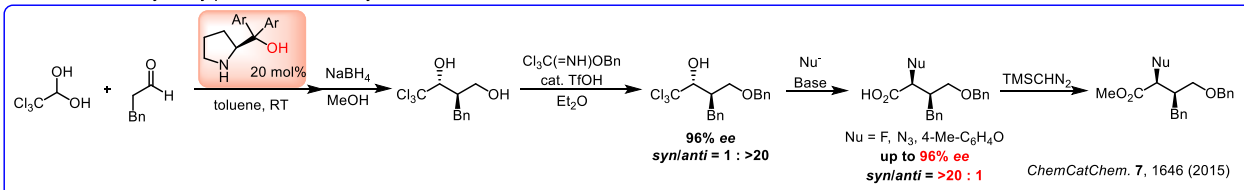


up to 99% *ee*
ChemCatChem., **5**, 2887 (2013).



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

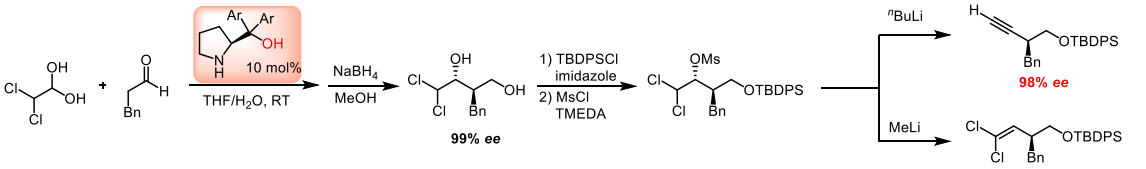
Aldol reaction by diarylprolinol as a catalyst



96% *ee*
syn/*anti* = 1 : >20

Nu = F, N_3, 4-Me-C_6H_4O
up to 96% *ee*
syn/*anti* = >20 : 1

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

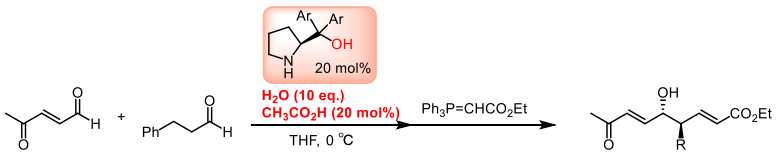


99% *ee*

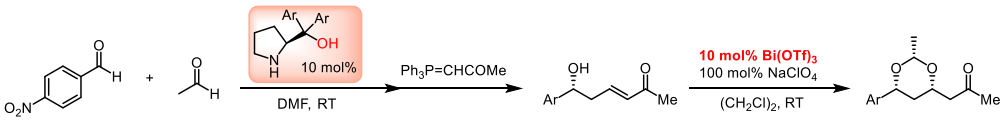
98% *ee*

98% *ee*

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

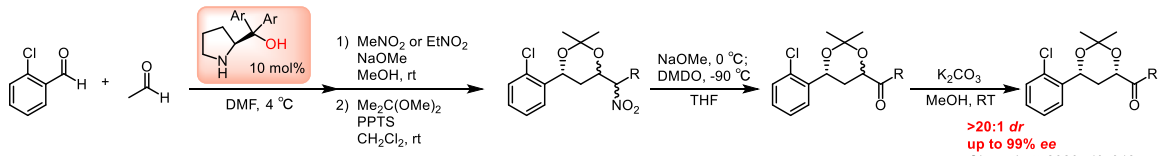


97% *ee*
anti : *syn* = 9:1
Chem. Asian J. **2019**, *14*, 4146.

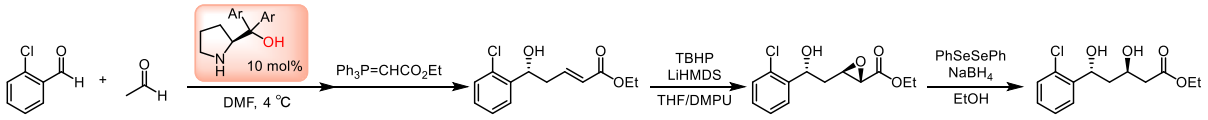


96% *ee*

d.r. >20:1
Chem. Eur. J. **2018**, *24*, 4909.



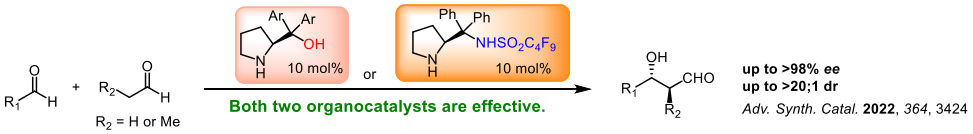
>20:1 *dr*
up to 99% *ee*
Chem. Lett. **2020**, *49*, 940.
2 pots synthesis of *syn*-1,3-diol



>98% *ee*

>20:1 *dr*

Org. Lett., **2021**, *23*, 5896.
3 pots synthesis of *anti*-1,3-diol

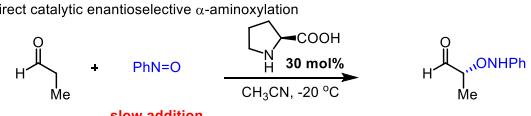


Both two organocatalysts are effective.

up to >98% *ee*
up to >20;1 dr
Adv. Synth. Catal. **2022**, *364*, 3424

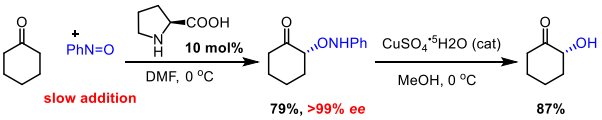
Reaction catalyzed by proline

Direct catalytic enantioselective α-aminoxylation



slow addition

quant, 98% *ee*
Tetrahedron Lett., **44**, 8293 (2003).



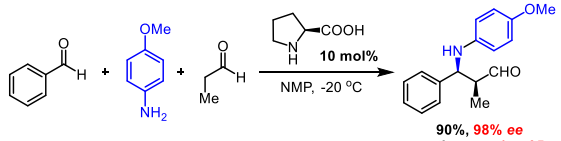
slow addition

79%, >99% *ee*

87%

Angew. Chem., Int. Ed., **43**, 1112 (2004).
J. Org. Chem., **69**, 5966 (2004).

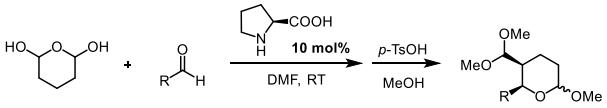
Three-Component Cross-Mannich reaction of aldehydes



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

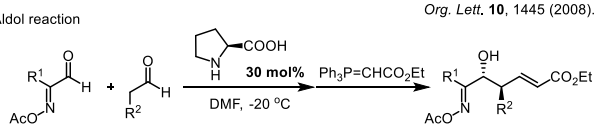
Angew. Chem., Int. Ed., **42**, 3677 (2003).
Adv. Synth. Catal., **347**, 1604 (2005).
Nature Protocols, **2**, 113 (2007).

Aldol / acetalization reaction



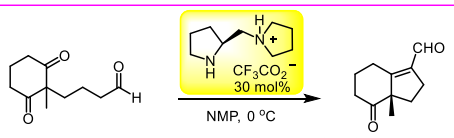
up to 99% *ee*
Org. Lett. **10**, 1445 (2008).

Aldol reaction



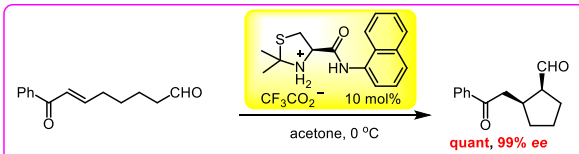
up to *anti* : *syn* = >20 : 1
up to 99% *ee*
Adv. Synth. Catal. **356**, 3106 (2014).

Reaction by proline-derived catalyst



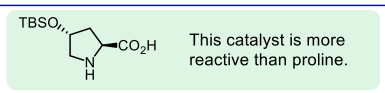
J. Org. Chem., **72**, 6493 (2007).

Reaction by cystein-derived catalyst

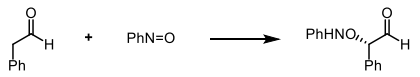


quant, 99% *ee*
***cis* : *trans* = 8.3 : 1**
J. Am. Chem. Soc., **127**, 16028 (2005).

Reaction by siloxyproline catalyst

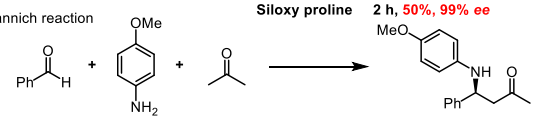


α-aminoxylation



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

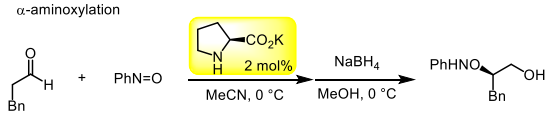
Mannich reaction



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

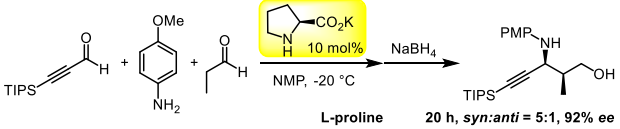
Reaction by prolinate salt catalyst

α-aminoxylation



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

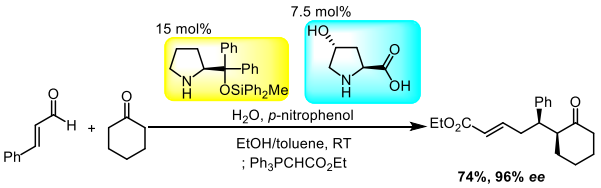
Mannich reaction



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

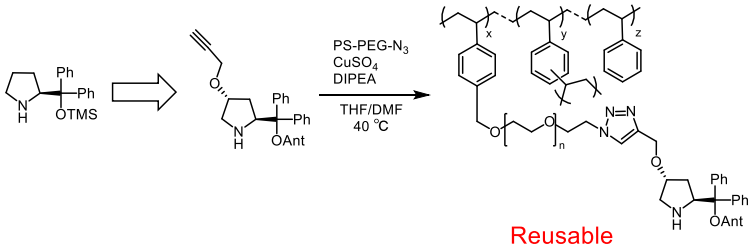
Michael reaction



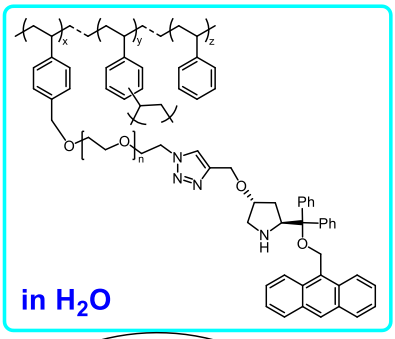
74%, 96% *ee*
***syn* : *anti* = 15 : 1**
Angew. Chem. Int. Ed. **57**, 1958 (2018).

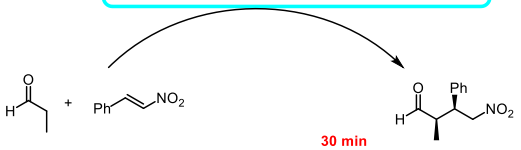
Polymer supported Diphenylprolinol catalysts

high reactive PS-PEG type catalyst



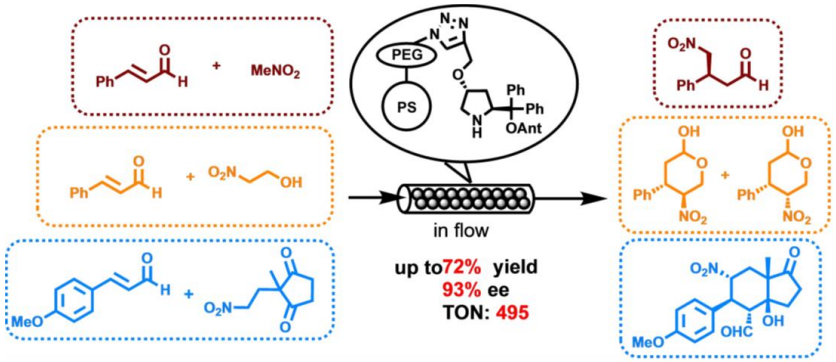
Reusable
Immobilized on PS-PEG resin





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

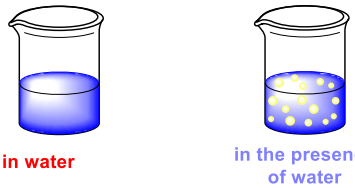
Flow reaction



Chem Asian J. **2022**, *17*, e202200314.

Organic solvent free reaction

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

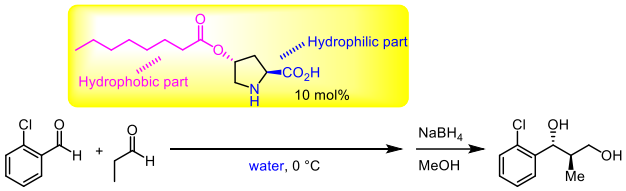


"in water" : The participating reactions are dossplved homogeneously in water.

"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.

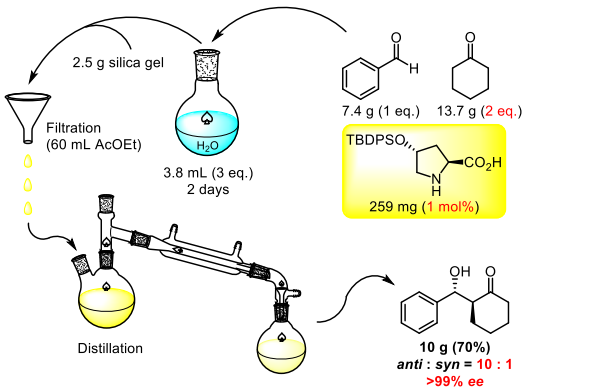
Angew. Chem. Int. Ed. **45**, 8103 (2006).

·Intermolecular aldol reaction between aldehydes in the presence of water



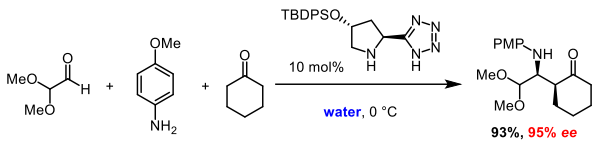
Angew. Chem. Int. Ed. **45**, 5527 (2006).

·Organic solvent free asymmetrric aldol reaction between ketone and aldehyde



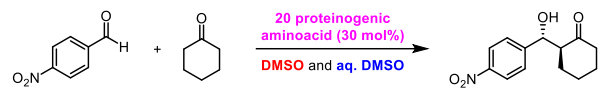
Angew. Chem. Int. Ed. **45**, 958 (2006).
Chem. Eur. J. **13**, 10246 (2007).

·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



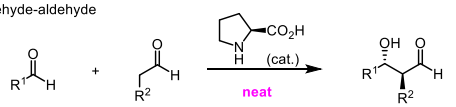
positive water effect

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

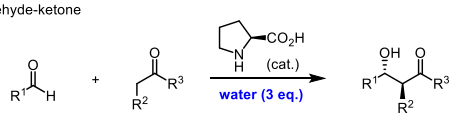
Synlett 1565 (2006).

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

aldehyde-aldehyde

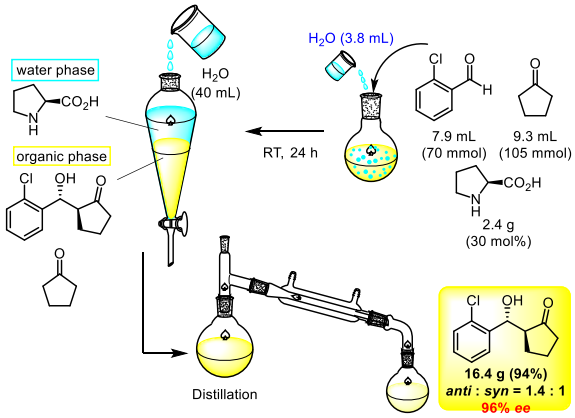


aldehyde-ketone

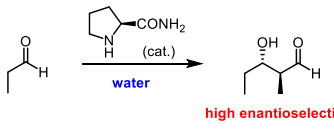


Chem. Commun. 957 (2007).

Organic solvent-free aldol reaction

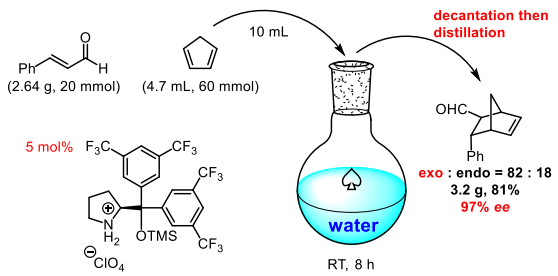


·Self aldol reaction of propanal in water - reaction in water with proline-amide catalyst



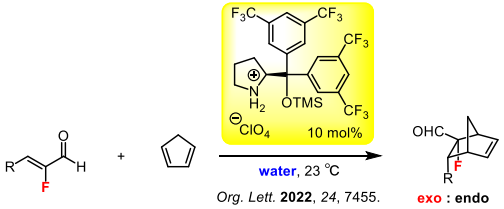
Chem. Commun. 2524 (2007).

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



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

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



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

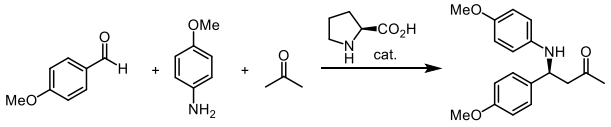
Application of High Pressure Induced by Water-Freezing to the direct catalytic asymmetric reaction

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***

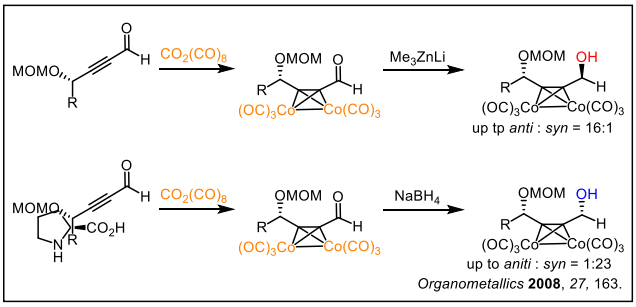
J. Am. Chem. Soc., **125**, 11208 (2003).

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

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

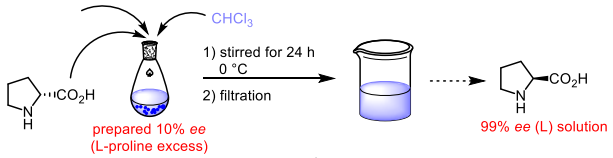
·Baylis-Hillman reaction
Tetrahedron Lett., **43**, 8683 (2004).

1,4-asymmetric induction using Cobalt alkyne complex



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

Research about of chirality

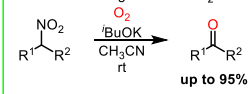


Amplification of *ee* from initial low *ee* ⇒ The key to find out origin of chirality

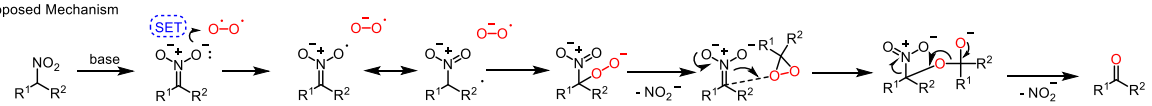
Angew. Chem., Int. Ed. **45**, 4593 (2006).

Metal-free oxidative transformations using O_2

Nef reaction using molecular O_2

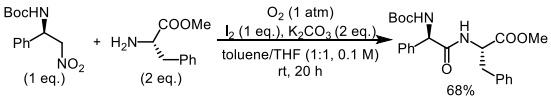


Proposed Mechanism



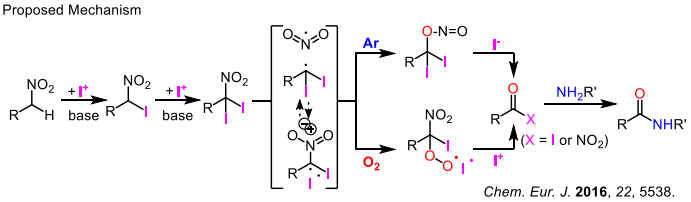
Chem. Eur. J. **2014**, *20*, 15753.

Oxidative amidation of primary nitroalkane and amine



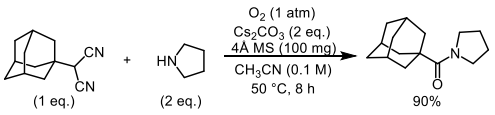
Angew. Chem. Int. Ed. **2015**, *54*, 12986.

Proposed Mechanism



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

Sterically demanding oxidative amidation of α-substituted malononitriles with amines

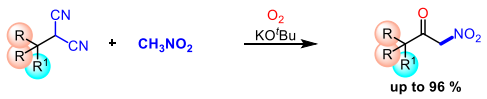


Angew. Chem. Int. Ed. **2016**, *55*, 9060.

Sterically demanding ester formation of α-substituted malononitriles with alcohol

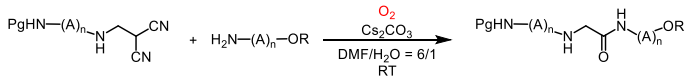
Eur. J. Org. Chem. **2019**, 675.

Sterically demanding ester formation of α-substituted malononitriles with alcohol



Eur. J. Org. Chem. **2024**, *27*, e202300964.

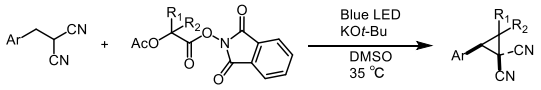
Application to peptipe synthesis

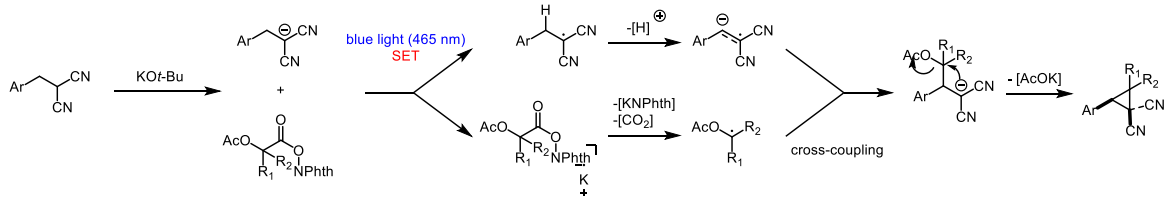


Broad scope
Tripeptide : **Boc-Phe-Gly-Phe-OMe (18 examples)**
Tetrapeptide : **Boc-Phe-Gly-Leu-Phe-O*t*-Bu (5 examples)**
Unprotected amino acid : **Boc-Phe-Gly-Phe-OH (4 examples)**

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

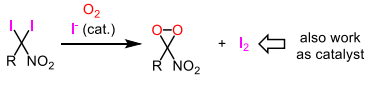
Direct cyclopropanation by light mediated single electron transfer

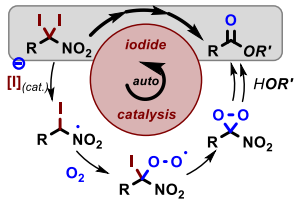




Chem. Eur. J. **2021**, *27*, 5901.

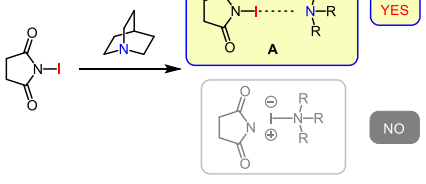
Autoinductive oxidation of α,α-diiodonitroalkanes

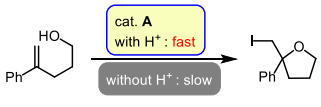




Chem. Commun., **2018**, *54*, 6360.

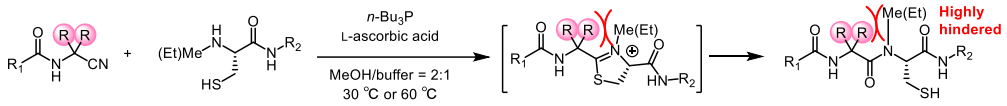
Halogen bonding of N-Halosuccinimides with amines





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



1) Coupling reagent free
2) Aqueous/green solvent
3) Good to excellent yield

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