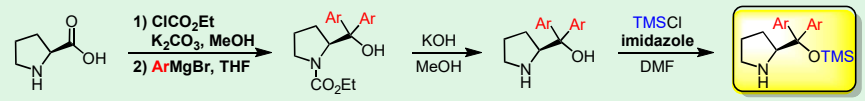
Hayashi Laboratory

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

Development of new reactions

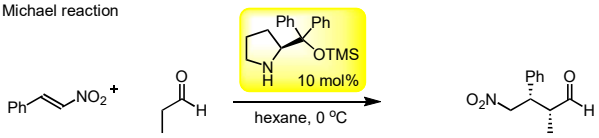
Asymmetric reaction using amino acid or their derivatives as a catalyst,
environmental conscious asymmetric reaction using water as a solvent, and research about origin of chirality

Reaction using diarylprolinol silyl ether derivatives as catalyst



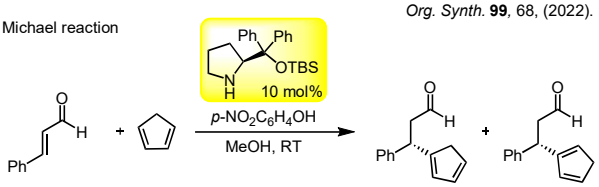
This catalyst is synthesized in short steps from proline.
Substituents on aryl and silyl moiety are easily modified.
Excellent enantioselectivity is obtained

Michael reaction



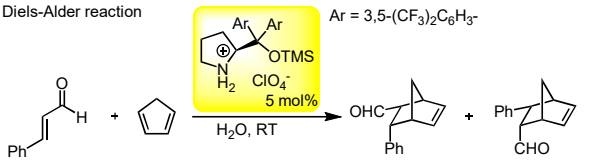
85%, 99% *ee*
Angew. Chem., Int. Ed., **44**, 4212 (2005).
Org. Synth. **99**, 68, (2022).

Michael reaction



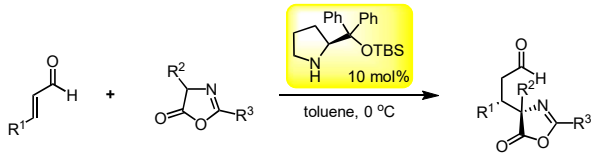
84%, 92% *ee*
Angew. Chem., Int. Ed., **45**, 6853 (2006).

Diels-Alder reaction



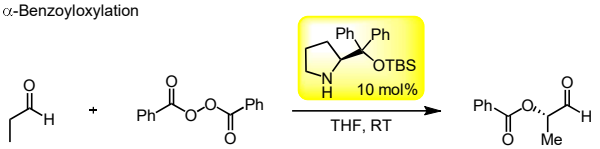
***exo* : *endo* = 80 : 20, 97% *ee* (*exo*)**
Org. Lett, **9**, 2859 (2007).
Angew. Chem., Int. Ed., **47**, 6634 (2008).

Michael reaction



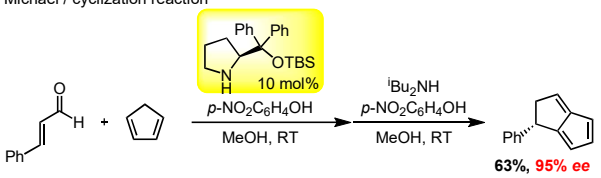
up to 99% *ee*
up to >90% *de*
Chem. Asian. J., **4**, 246 (2009).

α-Benzoyloxylation



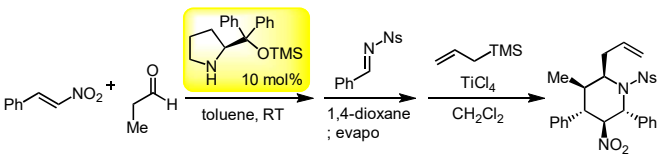
78%, 92% *ee*
Chem. Commun,, 3083 (2009).

Michael / cyclization reaction



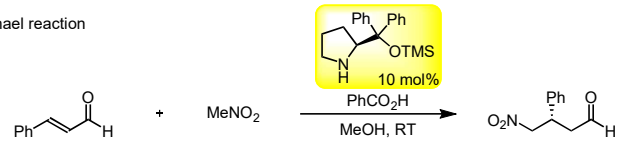
63%, 95% *ee*
Tetrahedron, **66**, 4894 (2010).

Michael / aza Henry / aminal formation / additional reaction



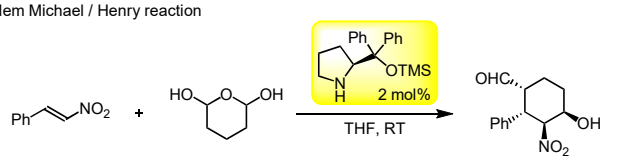
up to 99% *ee*
Single diastereomer
Org.Lett., **12**, 4588 (2010).

Michael reaction



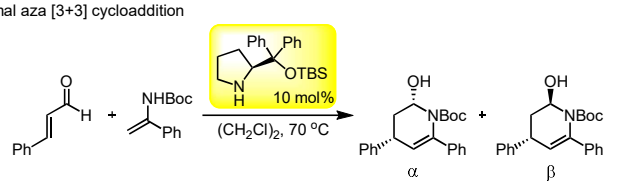
90%, 95% *ee*
Org. Lett., **9**, 5307 (2007).

Tandem Michael / Henry reaction



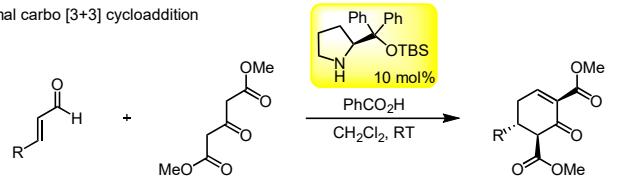
66%, 99% *ee*
Angew. Chem., Int. Ed., **46**, 4922 (2007).

Formal aza [3+3] cycloaddition



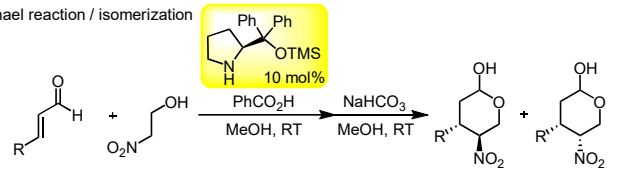
90%, 94% *ee*, α : β = 34 : 66
Angew. Chem., Int. Ed., **47**, 4012 (2008).

Formal carbo [3+3] cycloaddition



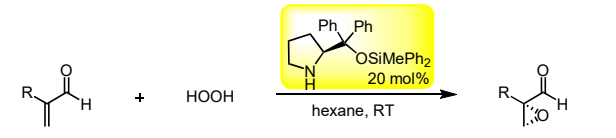
up to 99% *ee*
Org. Lett., **11**, 45 (2009).

Michael reaction / isomerization



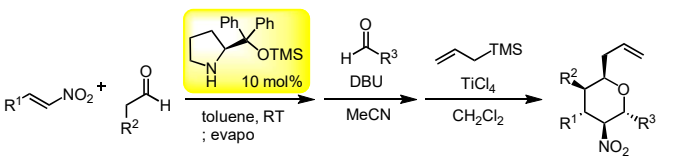
a **b**
up to 99% *ee*, a : b = 9 : 1
Org. Lett., **11**, 4056 (2009).

epoxidation



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

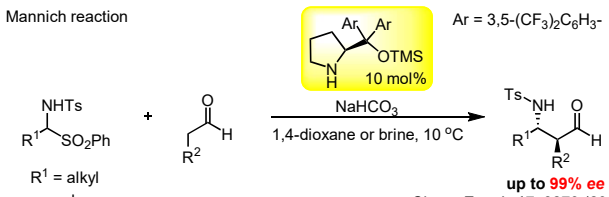
Michael / Henry / acetal formation / additional reaction



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

Reaction using diarylprolinol silyl ether derivatives as catalyst

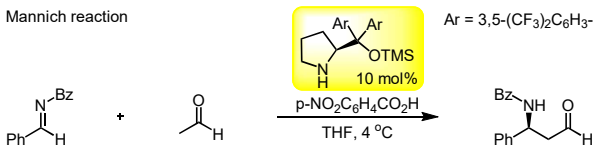
Mannich reaction



up to 99% *ee*

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

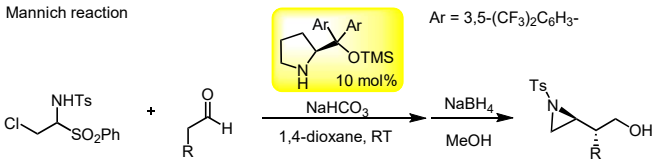
Mannich reaction



87%, 98% *ee*

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

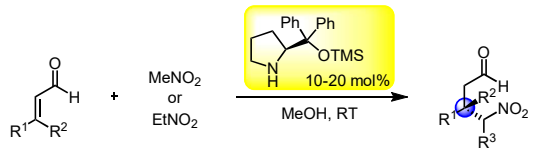
Mannich reaction



up to 99% *ee*

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

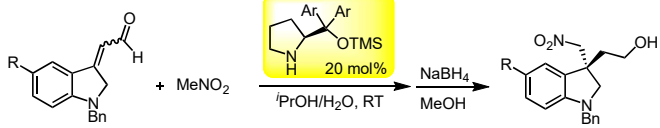
Michael reaction



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

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

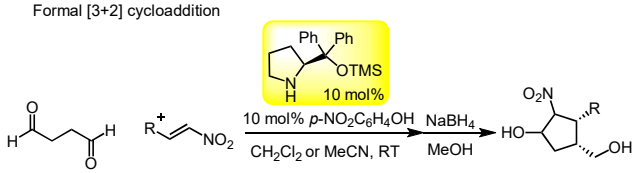
Michael reaction



up to 94% *ee*

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

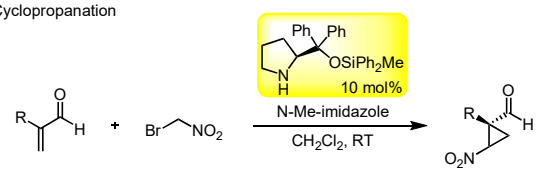
Formal [3+2] cycloaddition



up to 99% *ee*

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

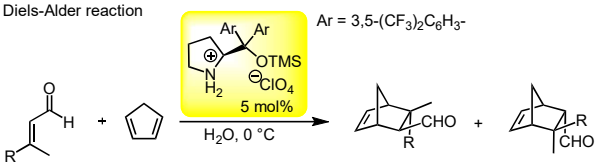
Cyclopropanation



up to 99% *ee*

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

Diels-Alder reaction

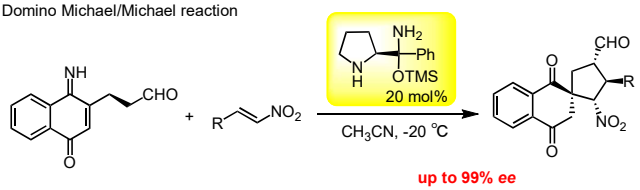


up to *exo* : *endo* = 88 : 12

up to 99% *ee*

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

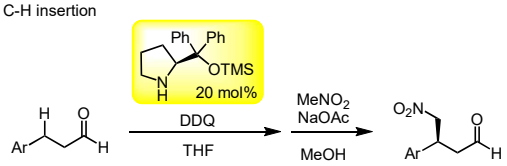
Domino Michael/Michael reaction



up to 99% *ee*

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

Formal C-H insertion

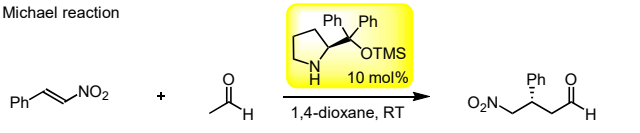


up to 95% *ee*

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

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

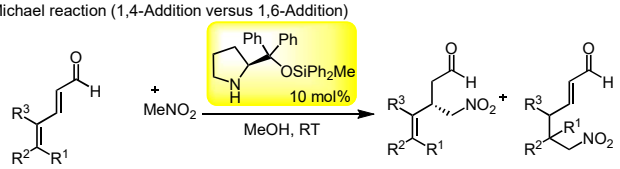
Michael reaction



75%, 96% *ee*

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

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



100 : 0

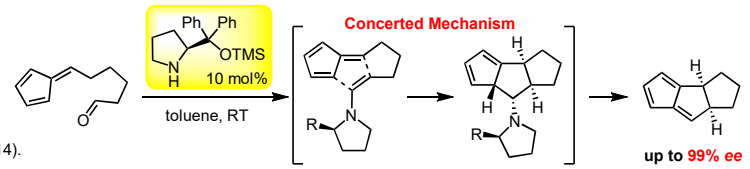
up to 95% *ee*

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

<Review>

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

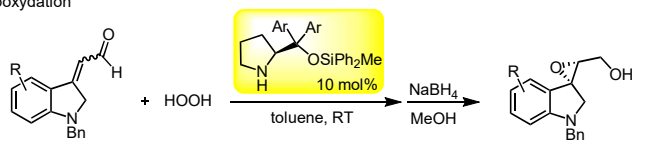
[6+2] cycloaddition reaction



up to 99% *ee*

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

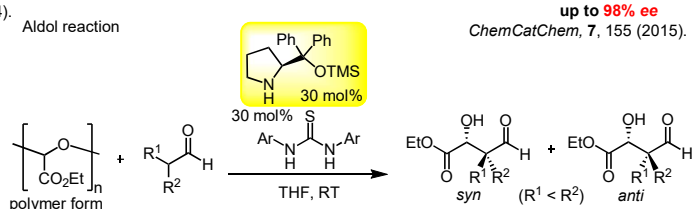
Epoxydation



up to 98% *ee*

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

Aldol reaction

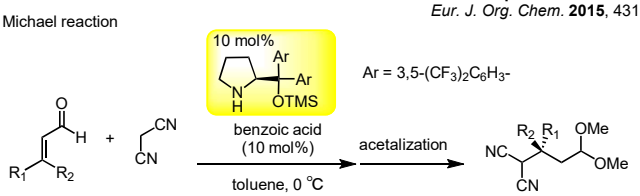


up to *syn* : *anti* = 1 : 2.9

up to 91% *ee*

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

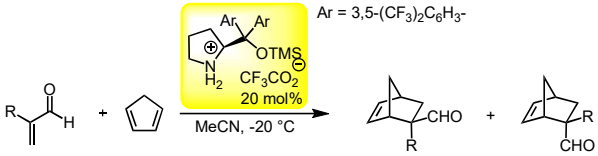
Michael reaction



up to 99% *ee*

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

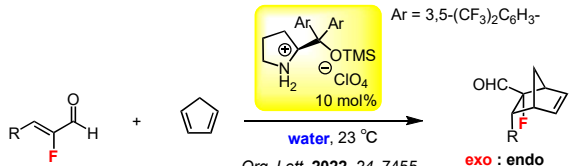
Diels-Alder reaction



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

up to 91% *ee*

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



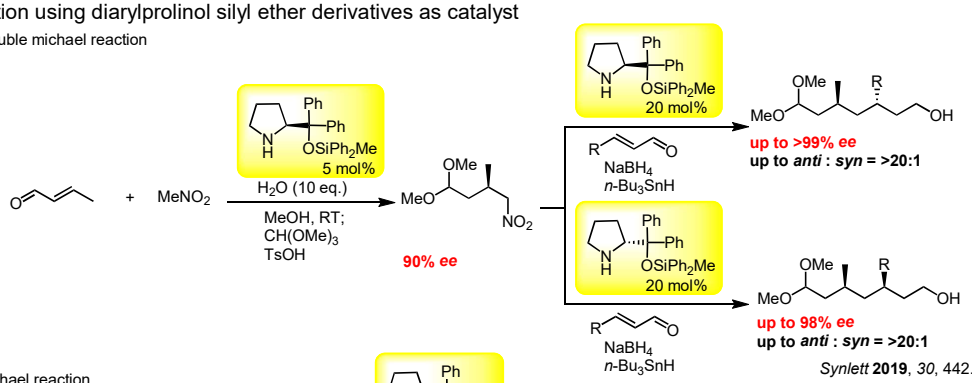
Org. Lett. **2022**, *24*, 7455.

exo : endo = 98 : 2 ~ 99 : 1;

up to 98% *ee*

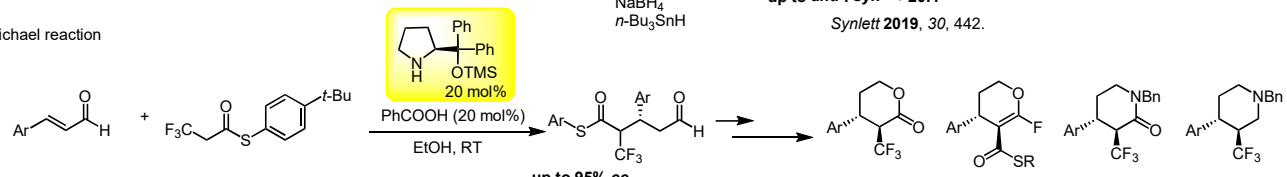
Reaction using diarylprolinol silyl ether derivatives as catalyst

Double michael reaction



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

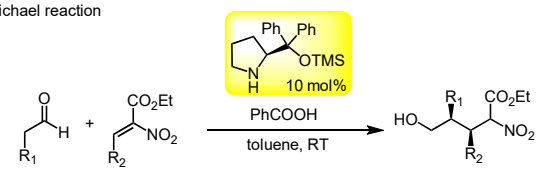
Michael reaction



up to 95% *ee*

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

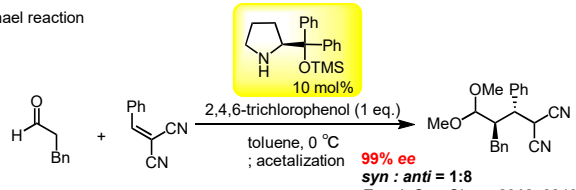
Michael reaction



up to 99% *ee*

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

Michael reaction

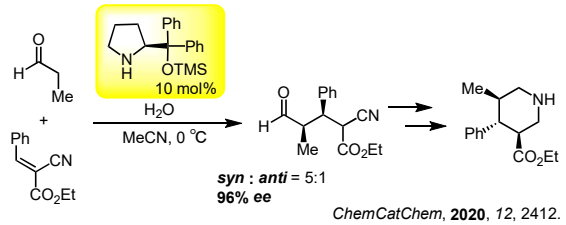


99% *ee*

***syn : anti* = 1:8**

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

Michael reaction

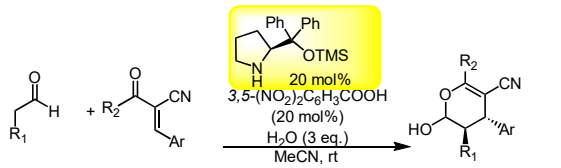


syn* : *anti = 5:1

96% *ee*

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

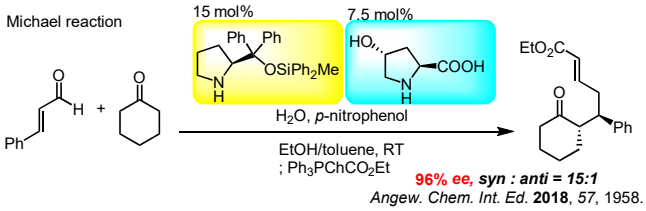
Domino Michael/ enolization / acetalization reactions



up to trans : cis = 9 : 1
(C3/C4)
up to >99% ee

Synlett, **2024**, *35*, 2391

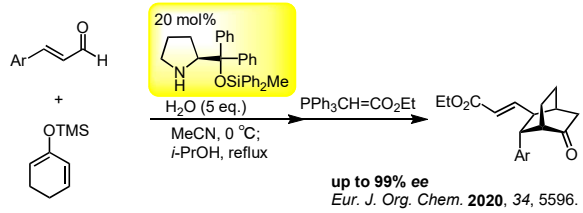
Michael reaction



96% *ee*, *syn : anti* = 15:1

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

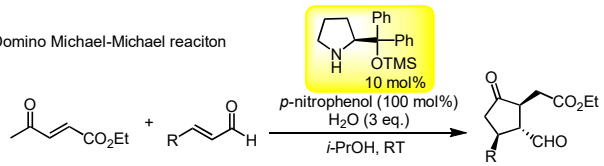
Mukaiyama Michael-Michael reaction



up to 99% *ee*

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

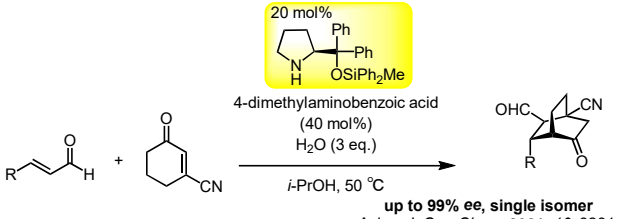
Domino Michael-Michael reaciton



up to >99% *ee*

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

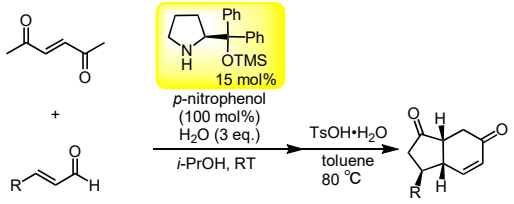
Domino Michael-Michael reaction



up to 99% *ee*, single isomer

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

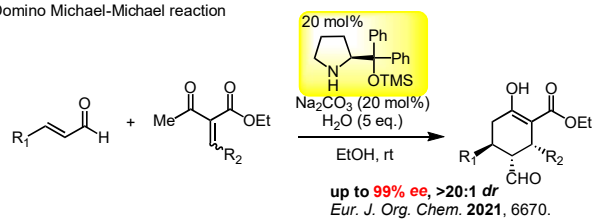
Domino Michael-Michael-aldol reaciton



up to >99% *ee*

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

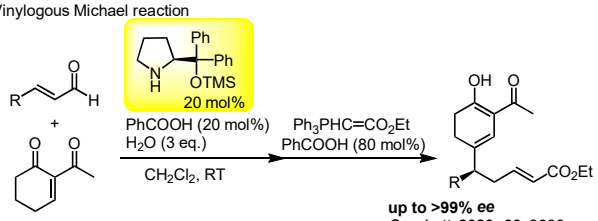
Domino Michael-Michael reaction



up to 99% *ee*, >20:1 *dr*

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

Vinylogous Michael reaction

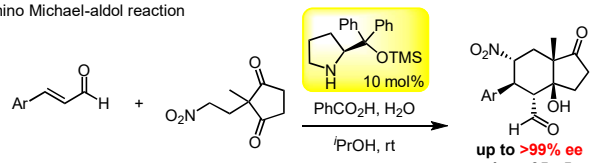


up to >99% *ee*

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

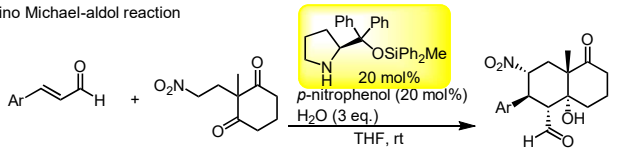
Reaction using diarylprolinol silyl ether derivatives as catalyst

Domino Michael-aldol reaction



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

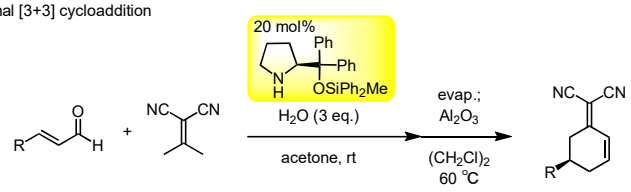
Domino Michael-aldol reaction



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

Reaction using diarylprolinol silyl ether derivatives as catalyst

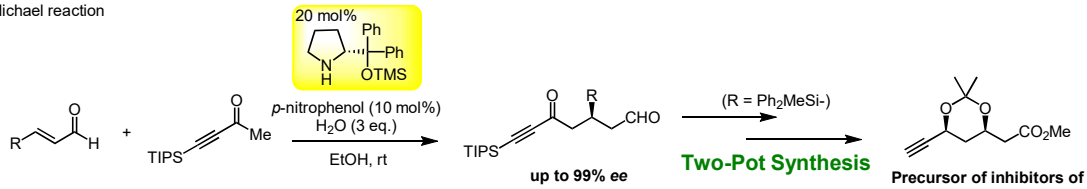
Formal [3+3] cycloaddition



up to 99% *ee*

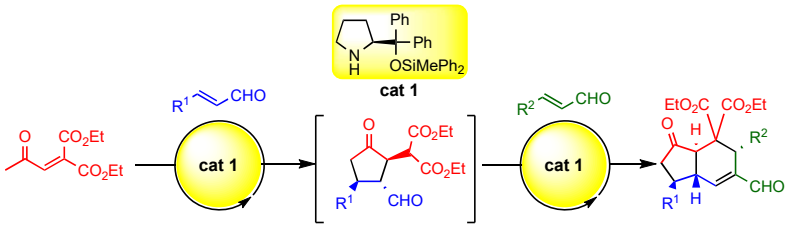
Eur. J. Org. Chem. **2022**, e202200603.

Michael reaction



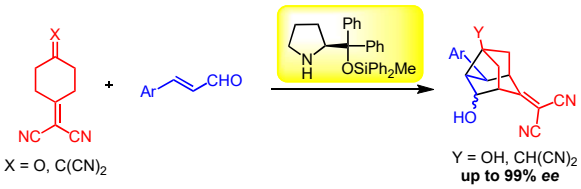
ACS Org. Inorg. Au **2022**, *2*, 245.

one-pot/two domino/three component coupling reactions



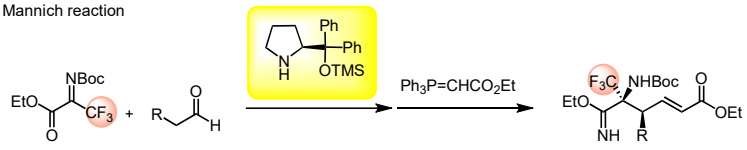
Chem. Sci., **2024**, *15*, 5627.

Domino Michael/Epimerization/Michael (or Aldol)/1,2-Addition Reactions



Angew. Chem. Int. Ed. **2025**, e202500378

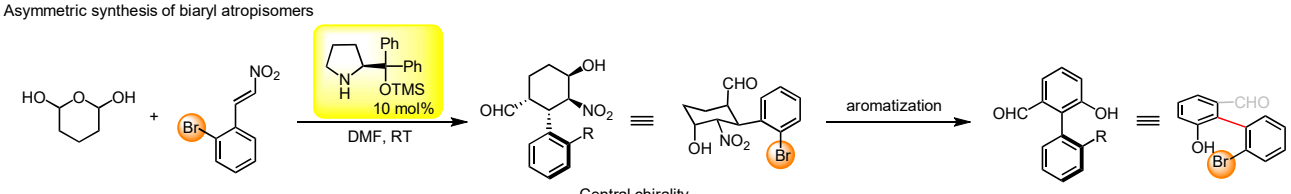
Mannich reaction



up to 92% *ee*

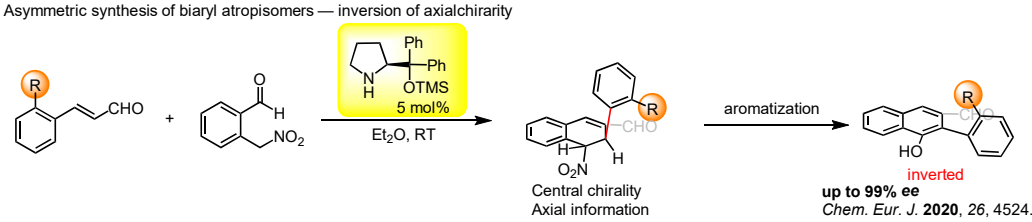
Asian J. Org. Chem. **2025,** e202500035

Asymmetric synthesis of biaryl atropisomers



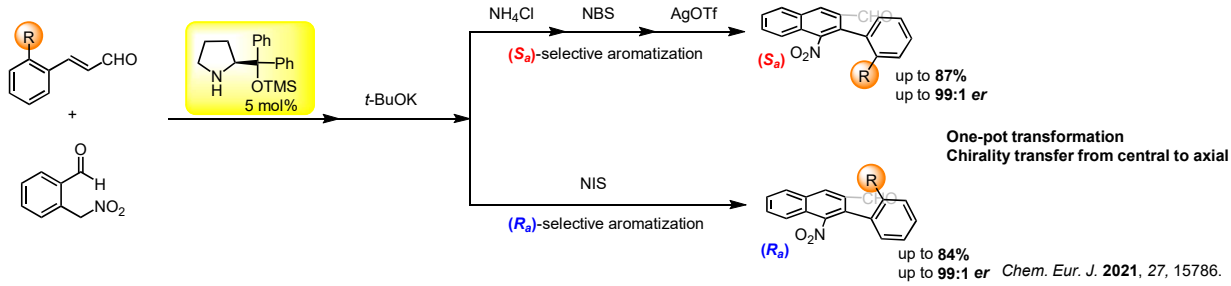
96% *ee*
Chem. Eur. J. **2019**, *25*, 10319.

Asymmetric synthesis of biaryl atropisomers — inversion of axialchirarity



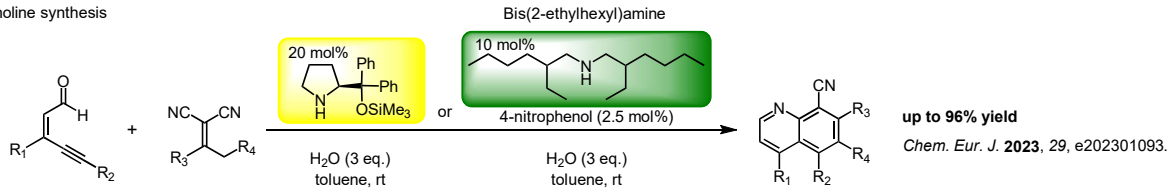
up to 99% *ee*
Chem. Eur. J. **2020**, *26*, 4524.

Enantiodivergent one-pot synthesis of axially chiral biaryls



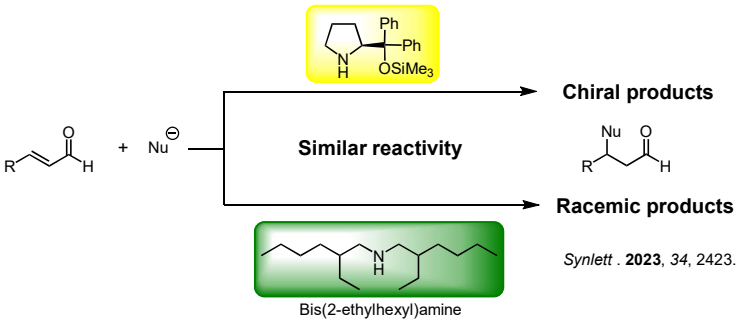
Chem. Eur. J. **2021**, *27*, 15786.

Quinoline synthesis



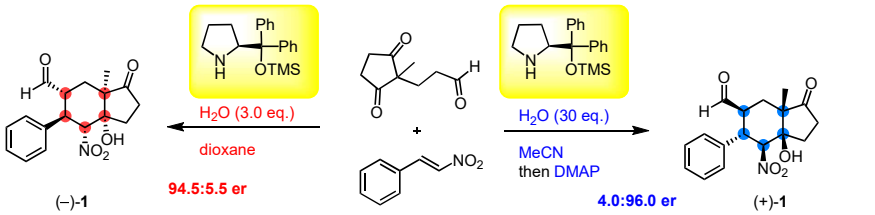
up to 96% yield
Chem. Eur. J. **2023**, *29*, e202301093.

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



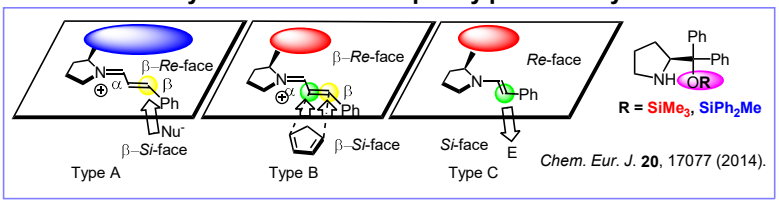
Synlett . **2023**, *34*, 2423.

Switch of Five Contiguous Chiral Centers in the Synthesis (Enantio divergent synthesis)



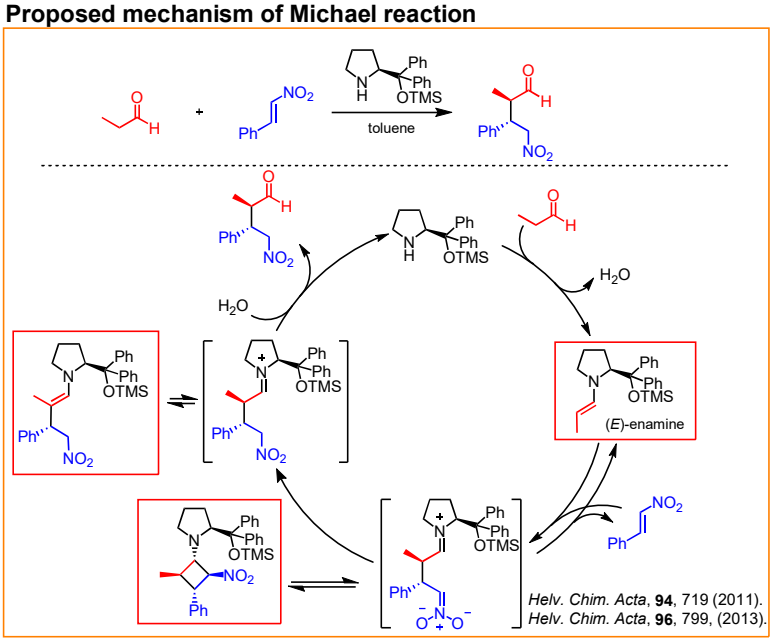
Chem. Eur. J., **2024,** e202403580

The effect of silyl substituents of diphenylprolinol silyl ether



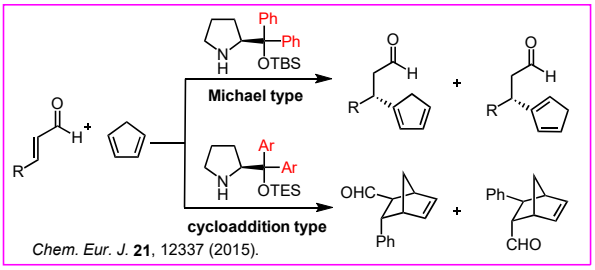
Chem. Eur. J. **20**, 17077 (2014).

Proposed mechanism of Michael reaction



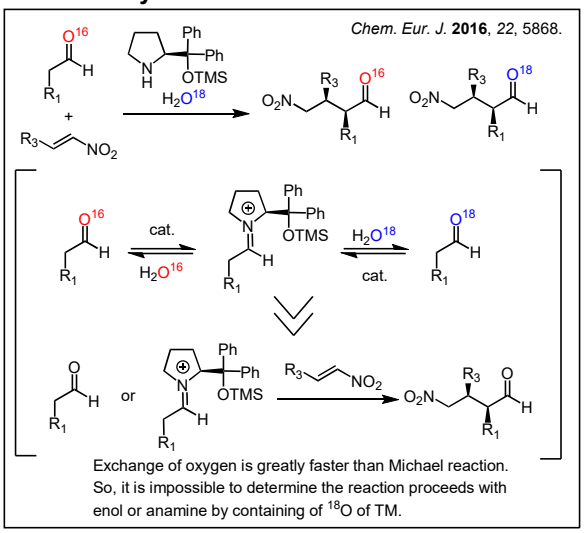
Helv. Chim. Acta, **94**, 719 (2011).
Helv. Chim. Acta, **96**, 799, (2013).

The different reactivity of diphenylprolinol silyl ether and diarylprolinol silyl ether

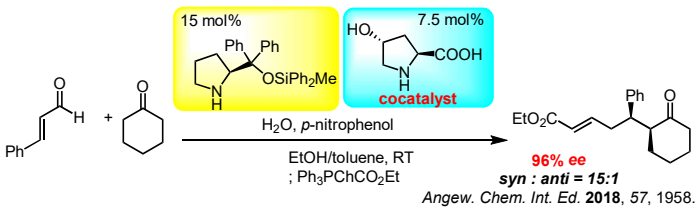


Chem. Eur. J. **21**, 12337 (2015).

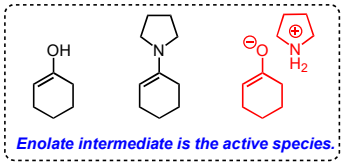
The $^{16}O/^{18}O$ exchanges existance in secondary amine catalyzed reactions

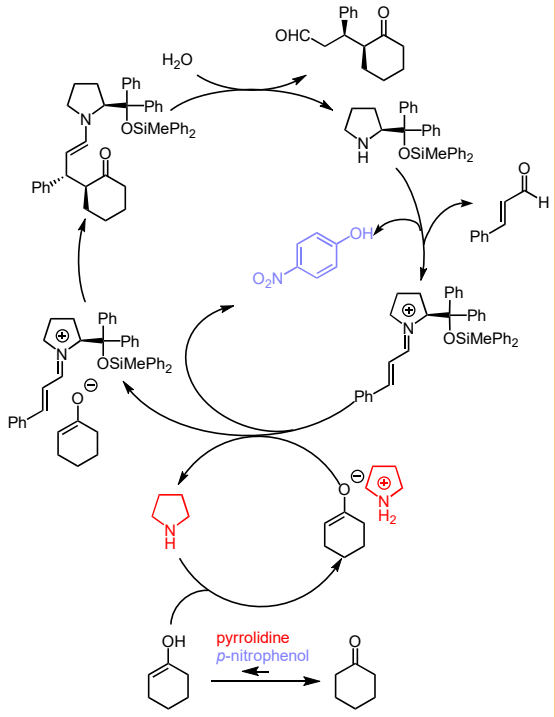


Proposed mechanism of α, β-unsaturated aldehyde and ketones via hydrid system of two secondary amine catalysts



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

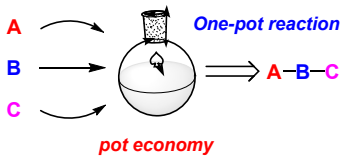




Chem. Sci., **2020**, *11*, 11293.

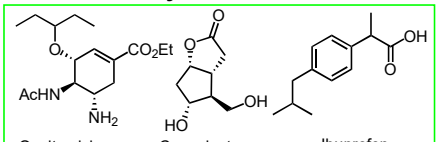
Review

Pot ecomomy



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

Time ecomomy



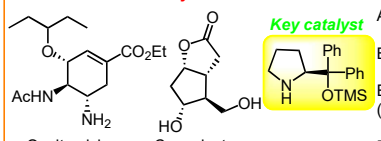
Oseltamivir: >37 h ⇩ 60 min

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)

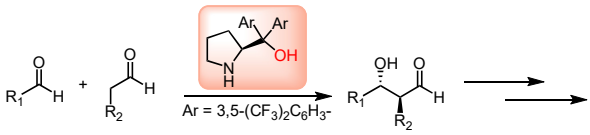
Estradiol methyl ether (5 pots)

PGE_1 methyl ester (3 pots)

Clinprost (7 pots)

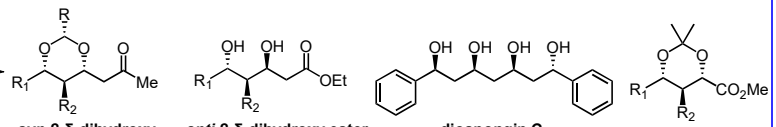
Acc. Chem. Res. **2021**, *54*, 1385.

Asymmetric Cross-aldol Reactions



excellent diastereo- and enantioselectivity

Widely Application



***syn*-β,δ-dihydroxy carbonyl compound**

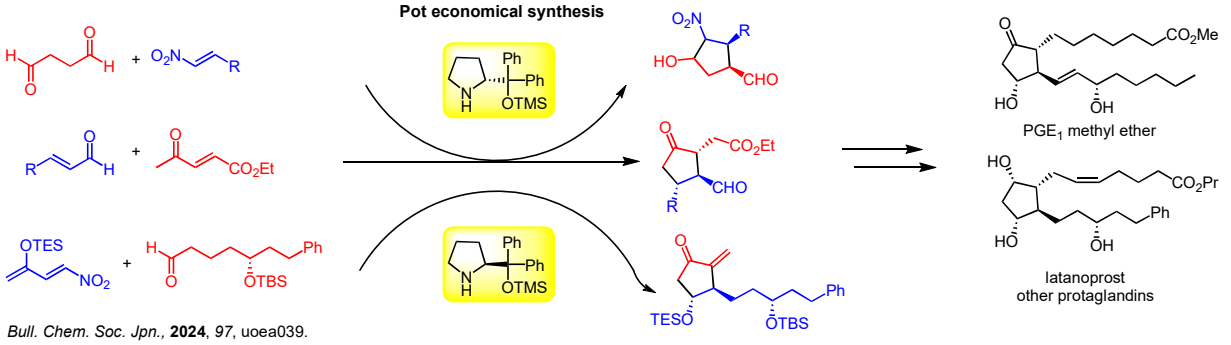
***anti*-β,δ-dihydroxy ester**

diospongin C

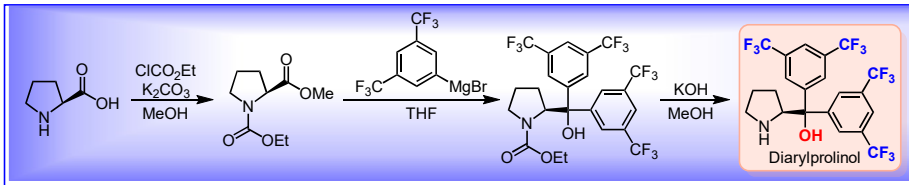
***syn*-α,γ-dihydroxy carbonyl compound**

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

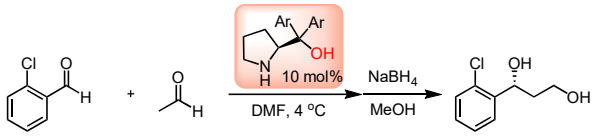
Pot economical total synthesis of protaglandins



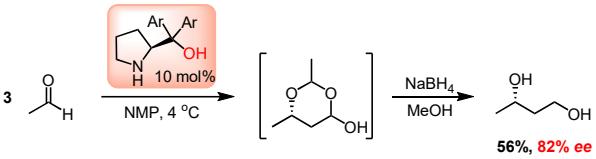
Bull. Chem. Soc. Jpn., **2024**, *97*, uoea039.



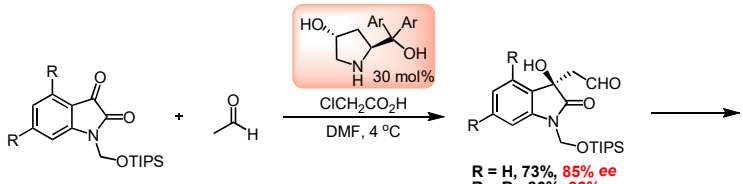
This catalyst is synthesized in short steps from proline.
This is effective organocatalyst of direct, enantioselective aldol reaction.
Excellent enantioselectivity is obtained.



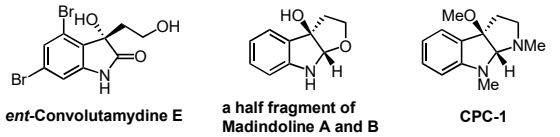
82%, 98% *ee*
Angew. Chem., Int. Ed., **47**, 2082 (2008).



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

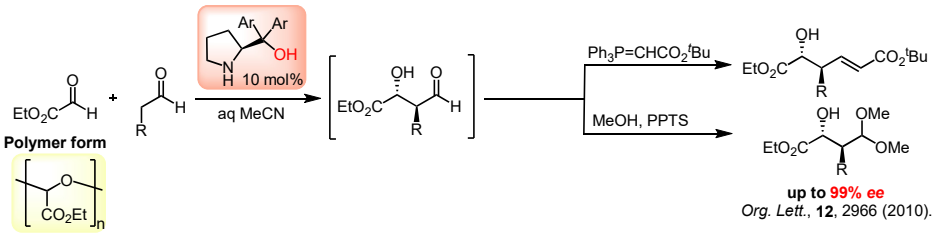


R = H, 73%, 85% *ee*
R = Br, 86%, 82% *ee*



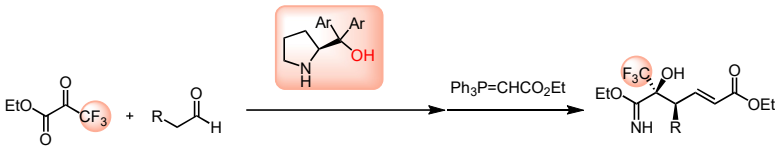
***ent*-Convolutamydine E** | **a half fragment of Madindoline A and B** | **CPC-1**

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

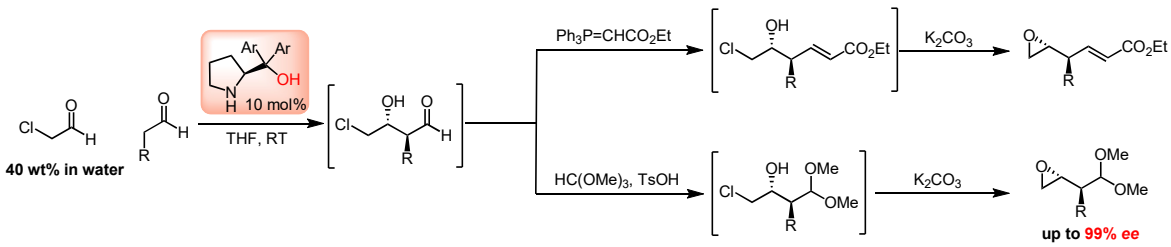


Polymer form

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

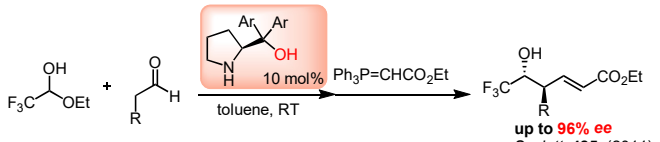


up to 96% *ee*
Asian J. Org. Chem. **2025**, e202500035



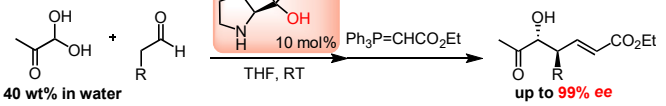
40 wt% in water

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



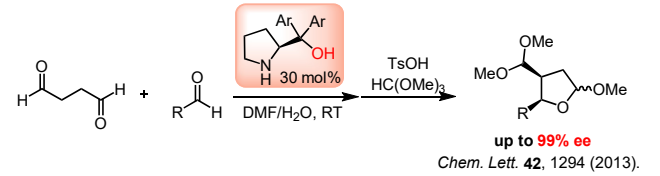
In 10% EtOH

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

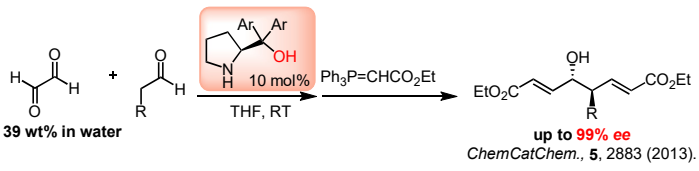


40 wt% in water

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

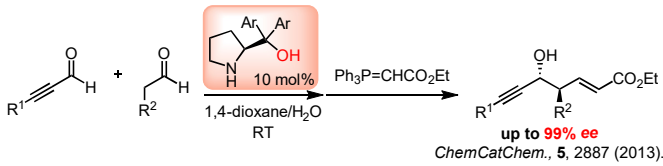


up to 99% *ee*
Chem. Lett. **42**, 1294 (2013).

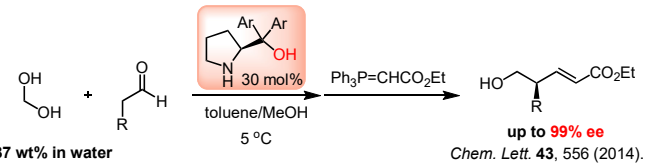


39 wt% in water

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



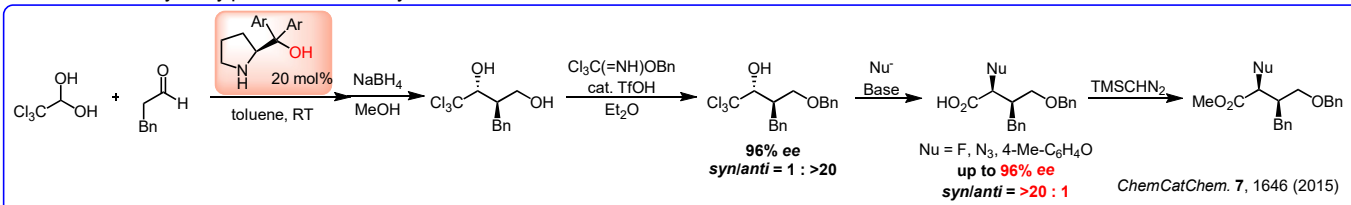
up to 99% *ee*
ChemCatChem., **5**, 2887 (2013).



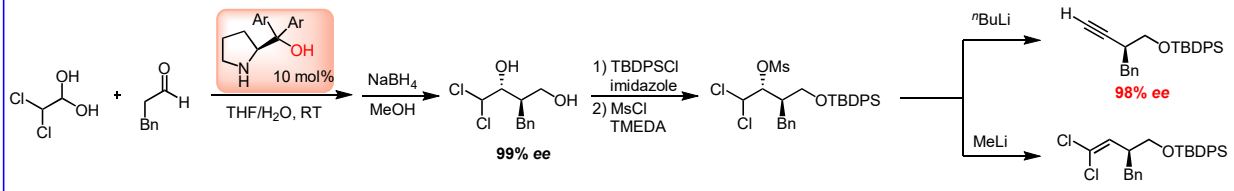
37 wt% in water

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

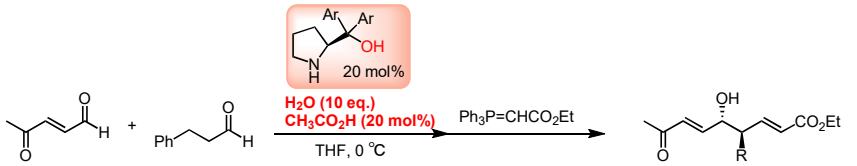
Aldol reaction by diarylprolinol as a catalyst



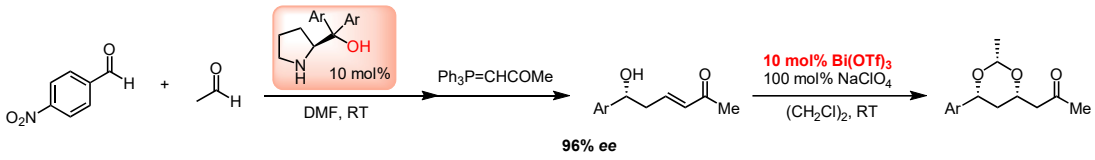
ChemCatChem. **7**, 1646 (2015)



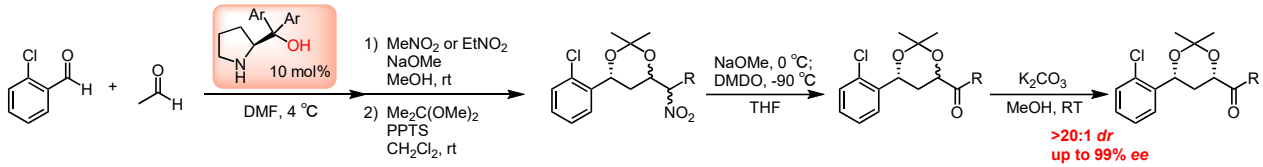
Adv. Synth. Catal. **358**, 2345 (2016).



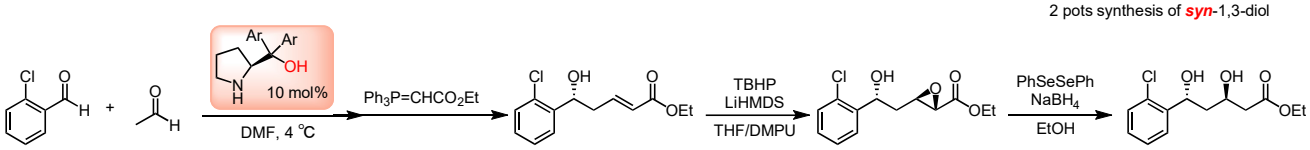
97% *ee*
***anti* : *syn* = 9:1**
Chem. Asian J. **2019**, *14*, 4146.



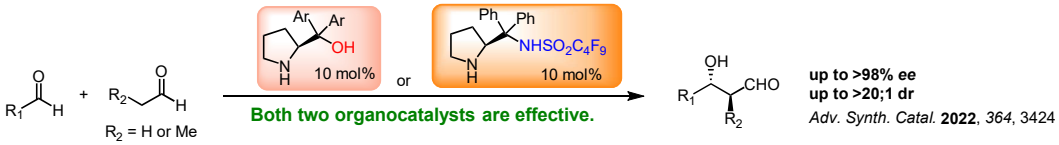
d.r. >20:1
Chem. Eur. J. **2018**, *24*, 4909.



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



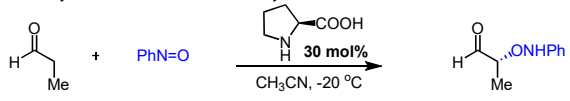
Org. Lett., **2021**, *23*, 5896.
3 pots synthesis of ***anti***-1,3-diol



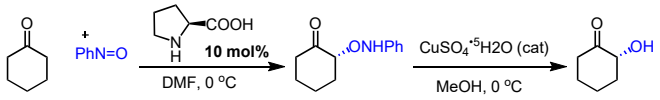
up to >98% *ee*
up to >20;1 dr
Adv. Synth. Catal. **2022**, *364*, 3424

Reaction catalyzed by proline

Direct catalytic enantioselective α-aminoxylation

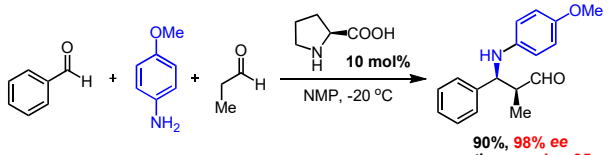


quant, 98% *ee*
Tetrahedron Lett., **44**, 8293 (2003).



79%, >99% *ee* **87%**
Angew. Chem., Int. Ed., **43**, 1112 (2004).
J. Org. Chem., **69**, 5966 (2004).

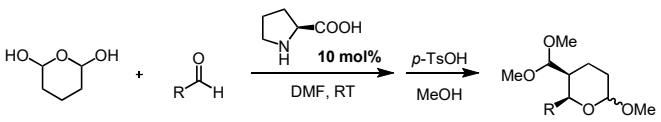
Three-Component Cross-Mannich reaction of aldehydes



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

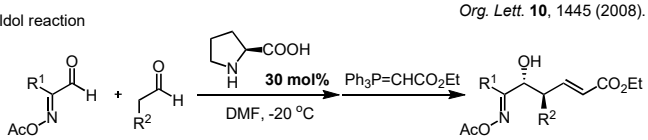
Angew. Chem., Int. Ed., **42**, 3677 (2003).
Adv. Synth. Catal., **347**, 1604 (2005).
Nature Protocols, **2**, 113 (2007).

Aldol / acetalization reaction



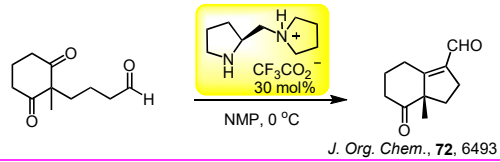
up to 99% *ee*
Org. Lett. **10**, 1445 (2008).

Aldol reaction



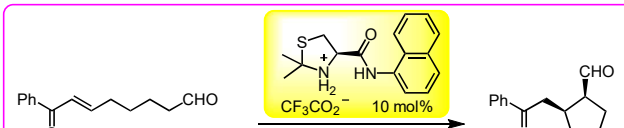
up to *anti* : *syn* = >20 : 1
up to 99% *ee*
Adv. Synth. Catal. **356**, 3106 (2014).

Reaction by proline-derived catalyst



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

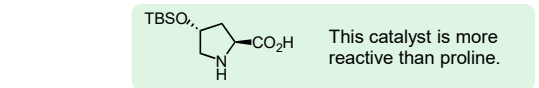
Reaction by cystein-derived catalyst



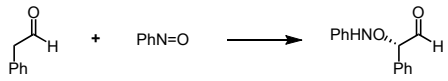
quant, 99% *ee*
***cis : trans* = 8.3 : 1**

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

Reaction by siloxyproline catalyst

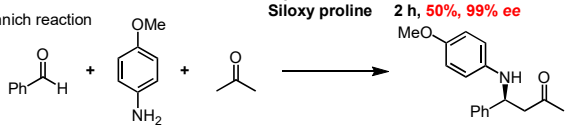


α-aminoxylation



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

Mannich reaction

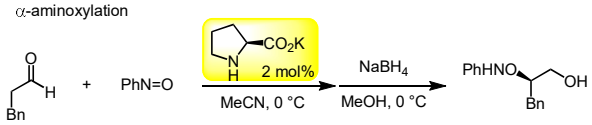


L-proline **20 h, <5%**
Siloxy proline **20 h, 63%, 96% *ee***

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

Reaction by prolinate salt catalyst

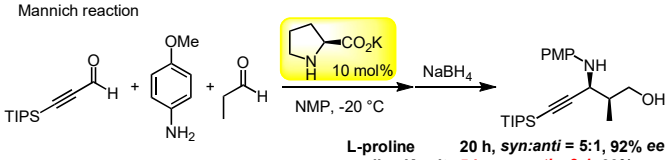
α-aminoxylation



L-proline **23 h, 90%, 98% *ee***
proline K salt **4 h, 99%, 99% *ee***

Org. Lett. **19**, 4155 (2017).

Mannich reaction

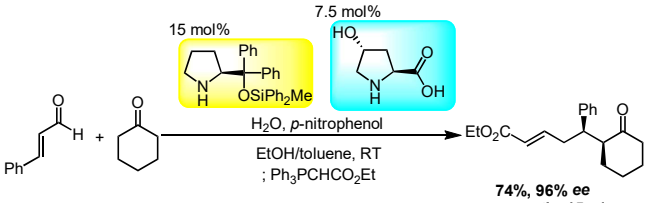


L-proline **20 h, *syn:anti* = 5:1, 92% *ee***
proline K salt **5 h, *syn:anti* = 9:1, 99% *ee***

Org. Lett. **20**, 2391 (2018).

Reaction using two catalysts system

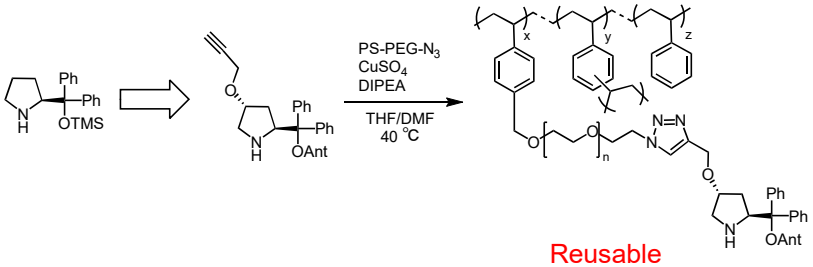
Michael reaction



74%, 96% *ee*
***syn* : *anti* = 15 : 1**

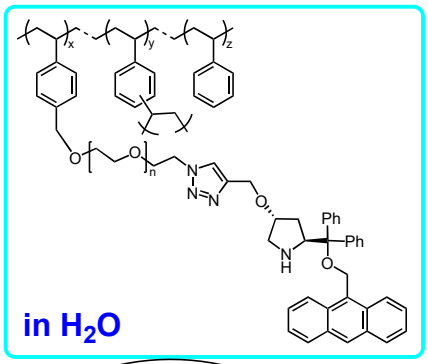
Angew. Chem. Int. Ed. **57**, 1958 (2018).

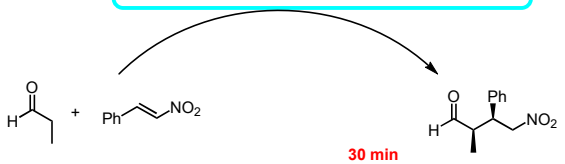
Polymer supported Diphenylprolinol catalysts



Reusable
Immobilized on PS-PEG resin

high reactive PS-PEG type catalyst

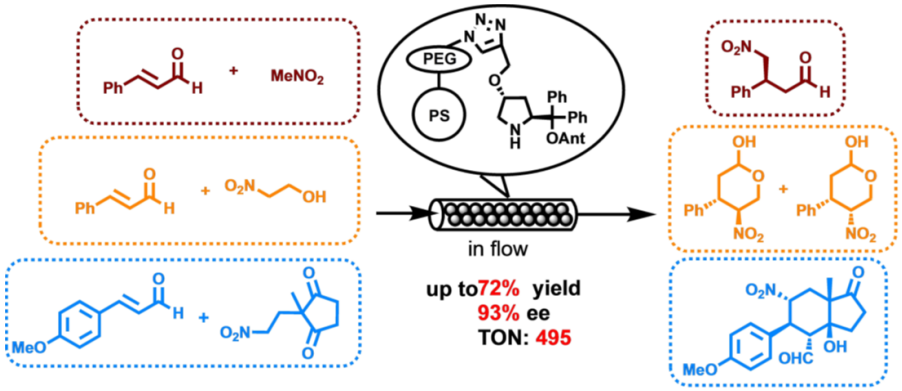




30 min
5:1 *dr*, 93% *ee*

Bull. Chem. Soc. Jpn. **2021**, *94*, 790.

Flow reaction



up to72% yield
93% ee
TON: 495

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

Organic solvent free reaction

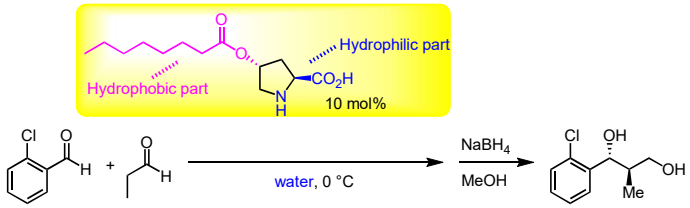
·"in the water" or "in the presence of water" ?

"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).

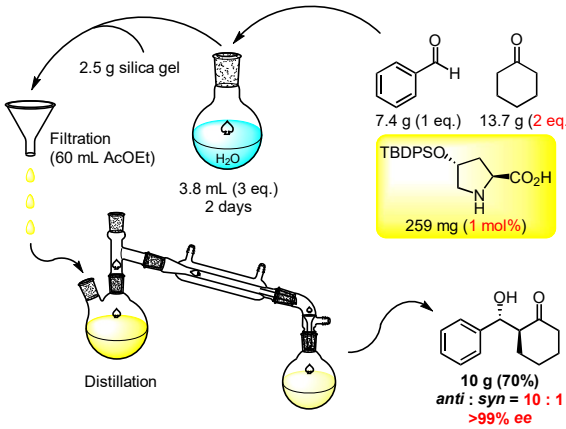
·Intermolecular aldol reaction between aldehydes in the presence of water



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

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

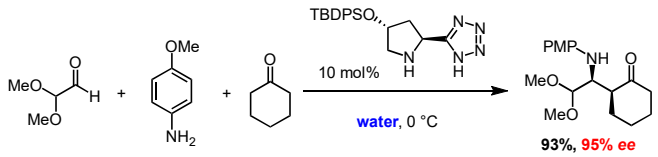
·Organic solvent free asymmetrric aldol reaction between ketone and aldehyde



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

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

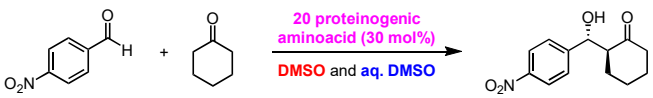
·Organic solvent free asymmetrric Mannich reaction with proline catalyst



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**

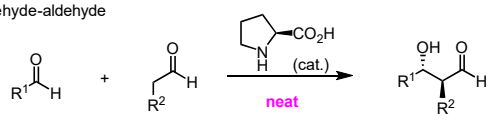
positive water effect

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

Synlett 1565 (2006).

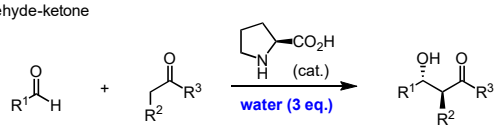
·Organic solvent free Dry and Wet condition asymetric aldol reaction with proline catalyst

aldehyde-aldehyde



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

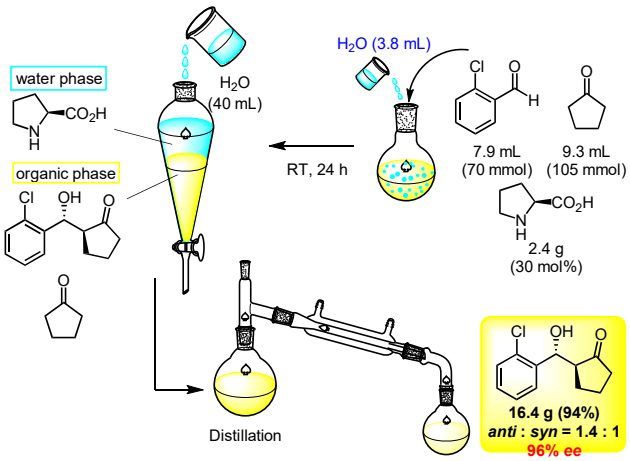
aldehyde-ketone



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

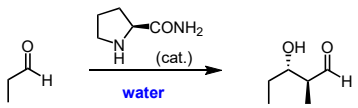
Chem. Commun. 957 (2007).

Organic solvent-free aldol reaction



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

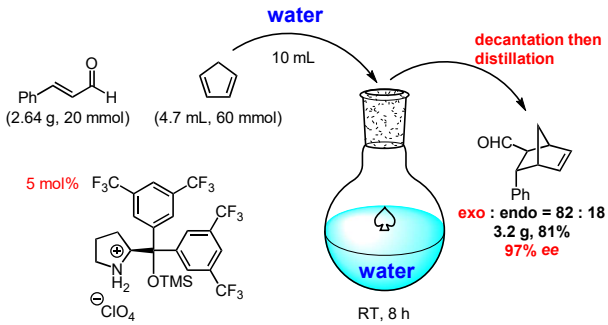
·Self aldol reaction of propanal in water - reaction in water with proline-amide catalyst



high enantioselectivity

Chem. Commun. 2524 (2007).

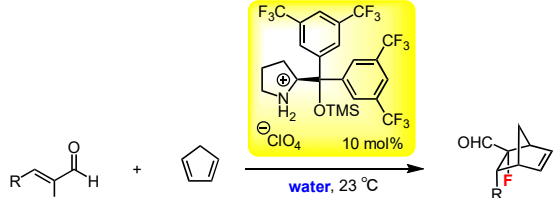
·Organic solvent free asymmetric Diels-Alder reaction with proline derived catalyst



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

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

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



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

exo : endo
= 98 : 2 ~ 99 : 1;
up to 98% *ee*

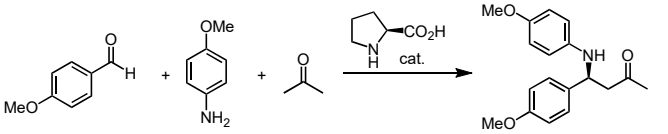
Application of High Pressure Induced by Water-Freezing to the direct catalytic asymmetric reaction

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***

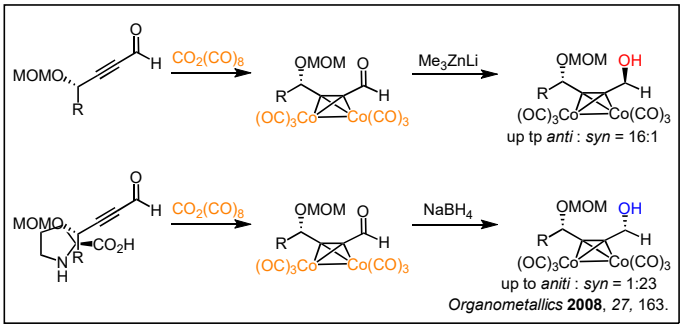
J. Am. Chem. Soc., **125**, 11208 (2003).

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

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

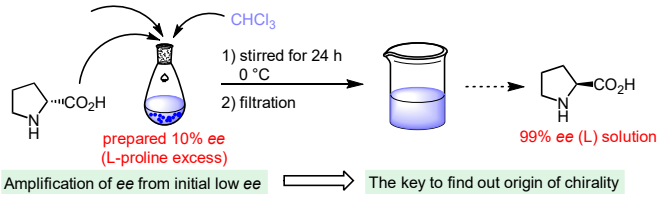
·Baylis-Hillman reaction
Tetrahedron Lett., **43**, 8683 (2004).

1,4-asymmetric induction using Cobalt alkyne complex



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

Research about of chirality

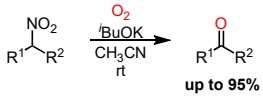


Amplification of *ee* from initial low *ee* ⇨ The key to find out origin of chirality

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

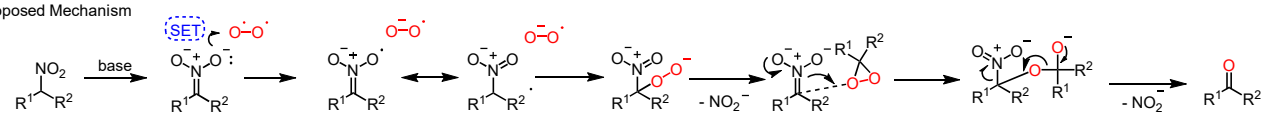
Metal-free oxidative transformations using O_2

Nef reaction using molecular O_2



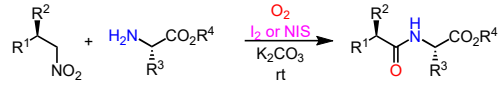
up to 95%

Proposed Mechanism

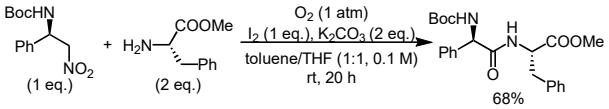


Chem. Eur. J. **2014**, *20*, 15753.

Oxidative amidation of primary nitroalkane and amine

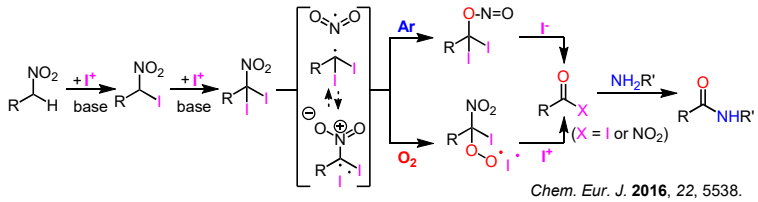


Readily available — No epimerization



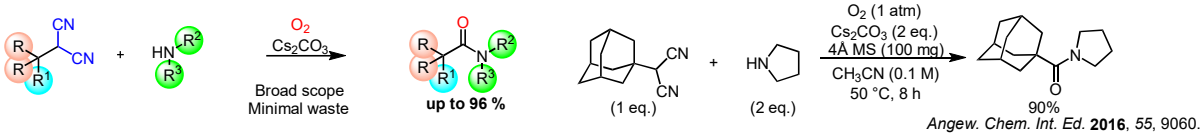
Angew. Chem. Int. Ed. **2015**, *54*, 12986.

Proposed Mechanism



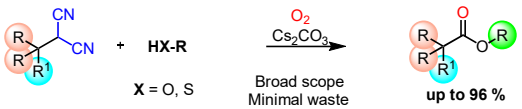
Chem. Eur. J. **2016**, *22*, 5538.

Sterically demanding oxidative amidation of α-substituted malononitriles with amines



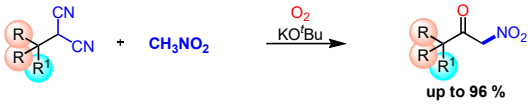
Angew. Chem. Int. Ed. **2016**, *55*, 9060.

Sterically demanding ester formation of α-substituted malononitriles with alcohol



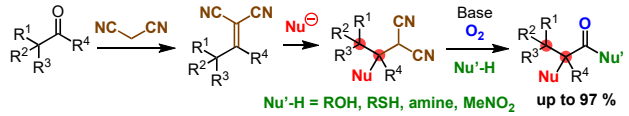
Eur. J. Org. Chem. **2019**, 675.

Sterically demanding ester formation of α-substituted malononitriles with alcohol



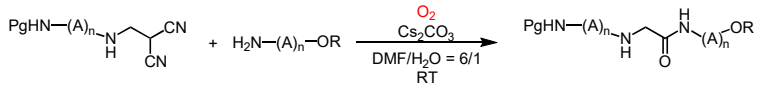
Eur. J. Org. Chem. **2024**, *27*, e202300964.

Synthesis of Consecutive All-Carbon Quaternary Centers via Three Step Reactions



Org. Lett. **2024**, *26*, 10840.

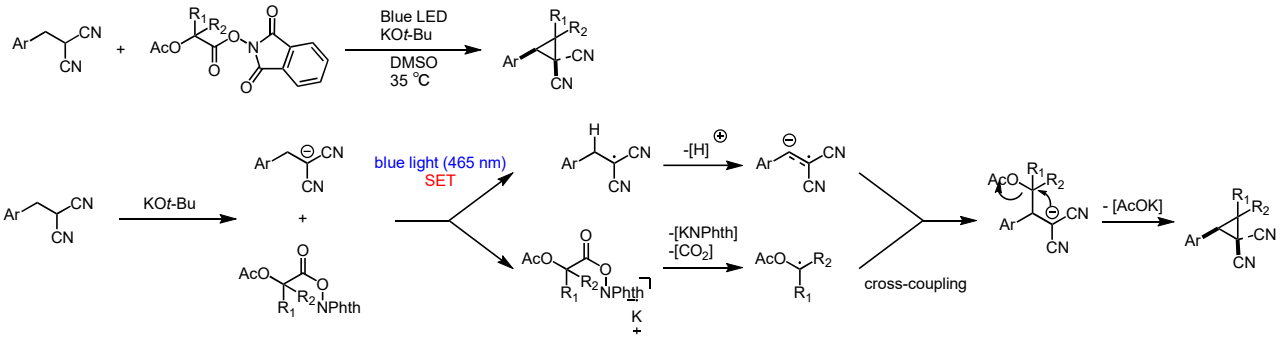
Application to peptipe synthesis



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)**

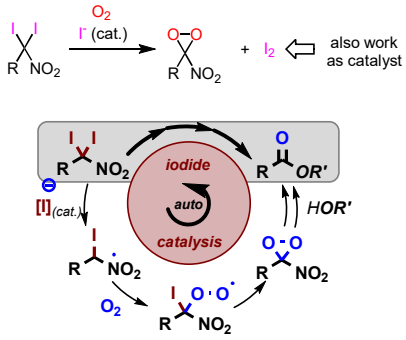
Metal-free oxidative transformations using O_2

Direct cyclopropanation by light mediated single electron transfer



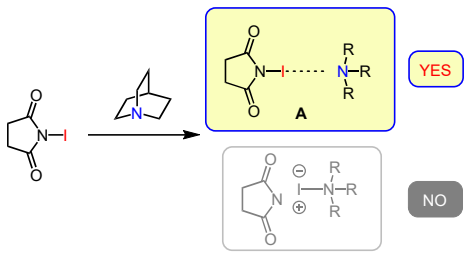
Chem. Eur. J. **2021**, *27*, 5901.

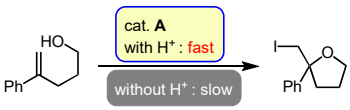
Autoinductive oxidation of α,α-diiodonitroalkanes



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

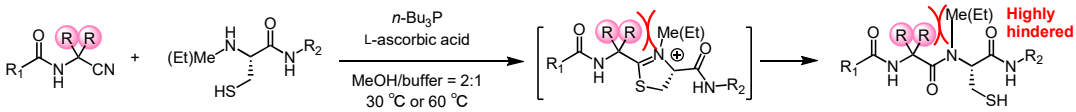
Halogen bonding of N-Halosuccinimides with amines





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