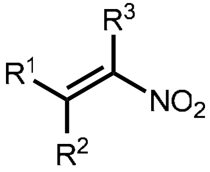
Enantioselective Reactions of Conjugated Nitroalkenes



Lead references:

Conjugated Nitroalkenes: Versatile Intermediates in Organic Synthesis
Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751.

Nitroalkenes: Conjugated Nitro Compounds
Perekalin, V. V.; Lipina, E. S.; Berestovitskaya, V. M.; Efremov, D. A.
Wiley: New York, **1994**.

Asymmetric Michael Additions to Nitroalkenes
Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877

Bo Shen

10/22/09

Preparation of Nitroalkenes
Nitration of Alkenes

$$R^1CH{=}CHR^2 \xrightarrow{HNO_3} R^1CH{=}C(NO_2)R^2 + R^1(NO_2)C{=}CHR^2 + R^1(HO)CH{=}CH(NO_2)R^2$$

R^1=H or Alkyl

R^2=Alkyl, ester, or fattay ester chain

poor selectivity, low yield

Shin, C.; Masaki, M.; Ohta, M. *Bull. Chem. Soc. Jpn.*, **1970**, *43*, 3219

Shin, C.; Yonezawa, Y.; Narukawa, H.; Nanjo, K.; Yashimura, J. *Bull. Chem. Soc. Jpn.*, **1972**, *45*, 3595

Other nitration reagents: $C(NO_2)_4$, $N_2O_4{=}2\ {\bullet}NO_2$

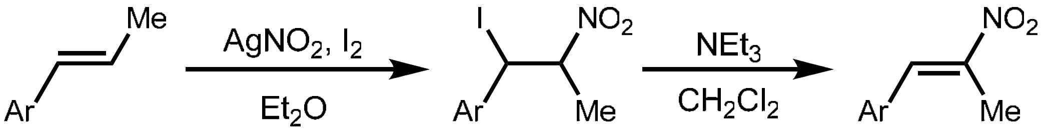
$$RCH{=}CH_2 \xrightarrow[\text{or } N_2O_4 + X_2]{NO_2X} RCHXCH_2NO_2 \xrightarrow[-HX]{\text{base}} RCH{=}CHNO_2$$

X= Cl or I

Schechter, H. *Rec. Chem. Progr.*, **1964**, *25*, 56

Szarek, W. A.; Lance, D. G.; Beach, R. L. *J. Chem. Soc., Chem. Commun.*, **1968**, 356

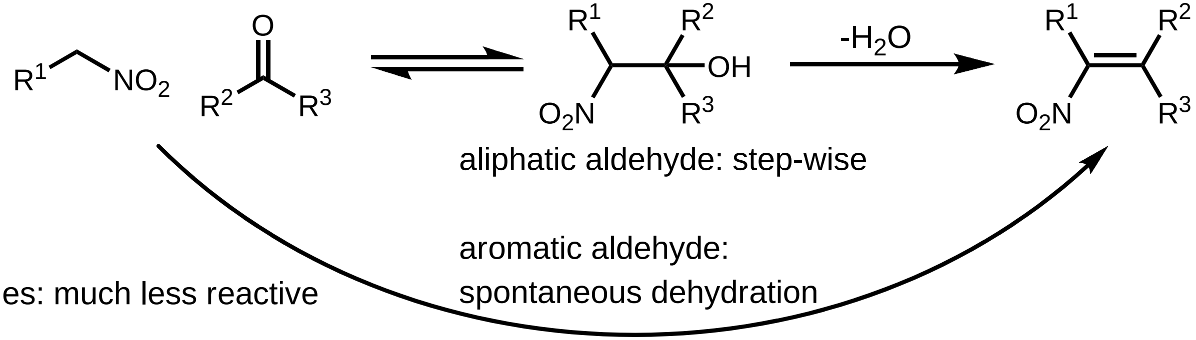
Hassner, A.; Kropp, J. E.; Kent, G. J. *J. Org. Chem.* **1969**, *34*, 2628



(53-82% yield)

Sy, W.-W.; By, A. W. *Tetrahedron Lett.*, **1985**, *26*, 1193

Preparation of Nitroalkenes:
Henry Reaction



aliphatic aldehyde: step-wise

aromatic aldehyde:
spontaneous dehydration

ketones: much less reactive

Most widely used conditions: MOH or MOR in ROH

NH_4OAc: an efficient catalyst in the synthesis of arylnitroalkenes, shortens the time and depresses polymerization

Other condensing reagents: carbonates, NR_3, ion-exchange resins

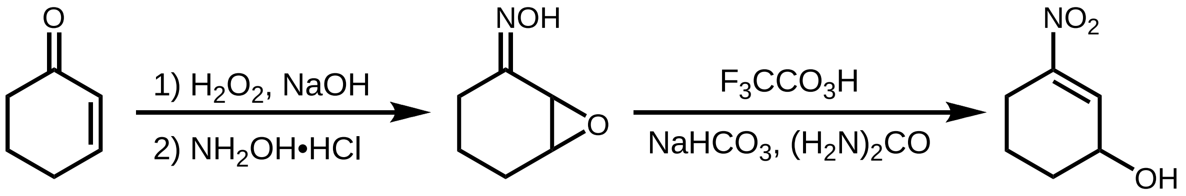
Difficulty: reversibility. Solution: Silylnitronate w/ cat. F^-

Often acylation (Ac, Bz, Ms) followed by elimination is preferred to dehydration of nitroalcohols
acylation/elimination in situ: $(MeCO)_2O$/DMAP, $(CF_3CO)_2O/NEt_3$, DCC/CuCl

Alternertive way:

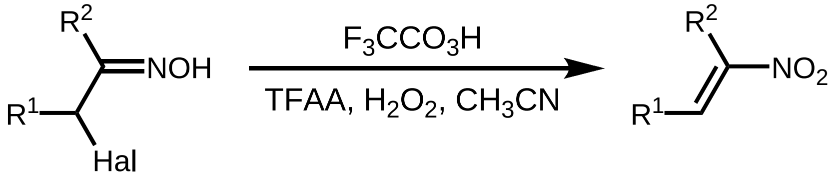
$$RCH{=}NR' + R''CH_2NO_2 \xrightarrow{HOAc} RCH{=}CR''NO_2$$

Preparation of Nitroalkenes: Other Methods

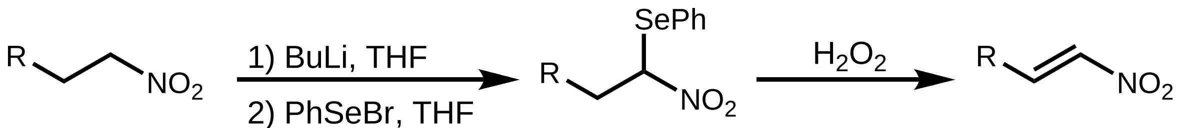


75% yield

Takamoto, T.; Ikeda, Y.; Tachimori, Y.; Seta, A.; Sudoh, R. *J. Chem. Soc. Chem. Commun.*, **1978**, 350



Sakakibara, T.; Ikeda, Y.; Sudoh, R. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 635

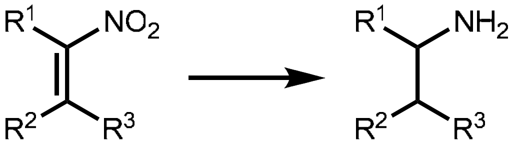


55-83% yield

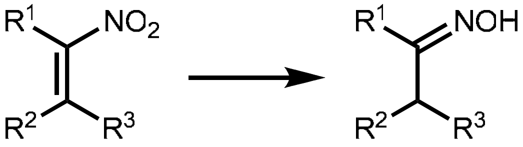
Sakakibara, T.; Takai, I.; Ohara, E.; Sudoh, R. *J. Chem. Soc. Chem. Commun.*, **1981**, 261

Reduction of Nitroalkenes

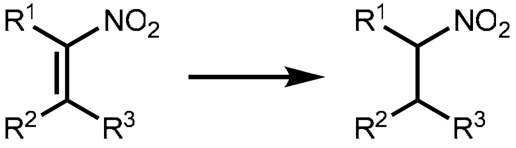
Reduction to alkyl amines: $LiAlH_4$, Pd/Ni+H_2

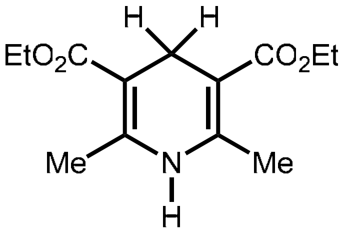


Reduction to oximes: Zn+HOAc, Fe+HCl/HOAc, $SnCl_2 \cdot 2H_2O$, $CrCl_2$



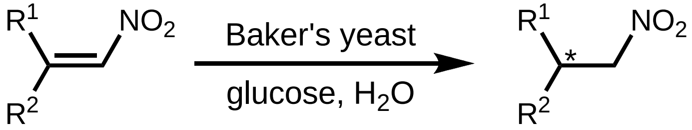
Reduction to nitroalkanes: $NaBH_4$, HEH/SiO_2, Bakers' yeast
$Zn(BH_4)_2$: depending on substrates, sometimes to oximes





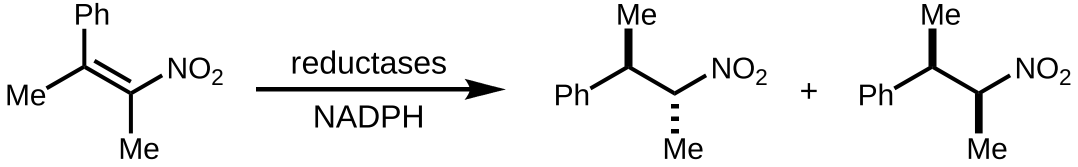
HEH
Hantzsch ester

Reduction with Bakers' Yeast



R^1=aryl, R^2=alkyl, >90 %ee

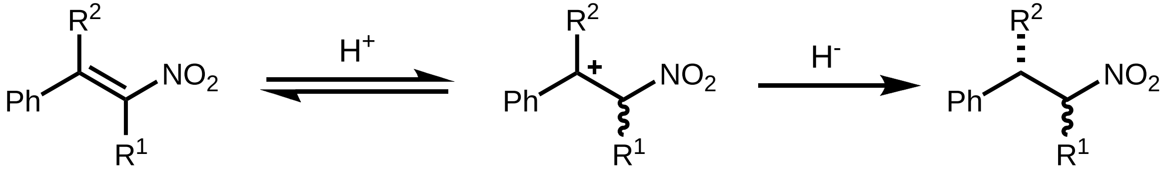
Ohta, H.; Ozaki, K.; Tsuchihashi, G. *Chem. Lett.* **1987**, 191
Ohta, H.; Kobayashi, N.; Ozaki, K. *J. Org. Chem.* **1989**, *54*, 1802



high ee, low dr

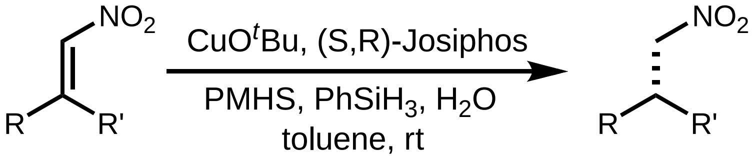
Kawai, Y.; Inaba, Y.; Hayashi, M.; Tokitoh, N. *Tetrahedron Lett.* **2001**, *42*, 3367

Mechanism study:



McAnda, A. F.; Roberts, K. D.; Smallridge, A. J.; Ten, A.; Trewhella, M. A.
J. Chem. Soc., Perkin Trans. 1, **1998** 501

Enantioselective 1,4-Reduction

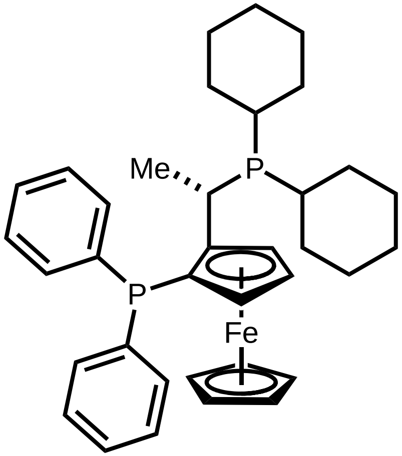


CuO^tBu, (S,R)-Josiphos

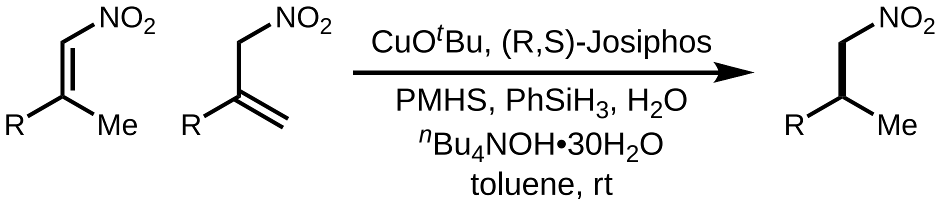
PMHS, $PhSiH_3$, H_2O
toluene, rt

PMHS=Poly(methylhydrosiloxane)

Czekelius, C.; Carreira, E. M.
Angew. Chem. Int. Ed. **2003**, *42*, 4793



(S,R)-Josiphos



CuO^tBu, (R,S)-Josiphos

PMHS, $PhSiH_3$, H_2O
$^nBu_4NOH \bullet 30H_2O$
toluene, rt

Czekelius, C.; Carreira, E. M. *Org. Proc. Res. Dev.* **2007**, *11*, 633

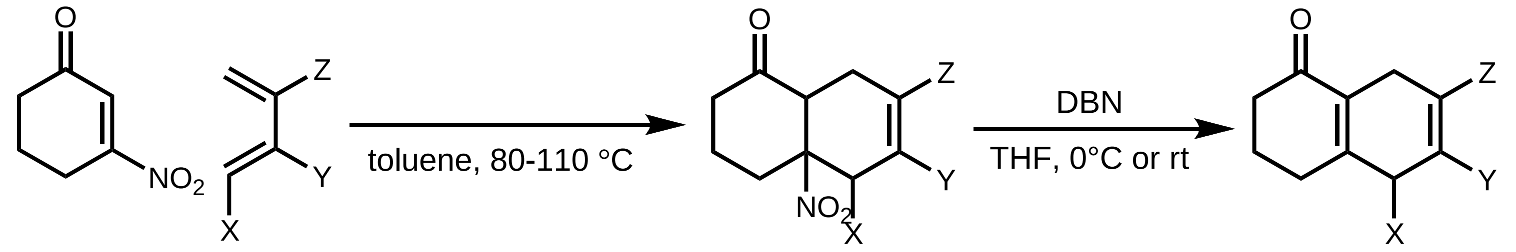
Diels-Alder Reaction

Nitroalkenes as a typical dienophile:

Reacts with both strongly nucleophilic and weakly nucleophilic dienes

Often requires low temperature

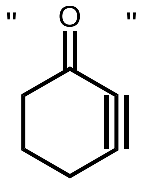
Very effective at controlling the regiochemistry, overwhelming other e-withdrawing groups on β-position



formal alkynone synthetic equivalent with reversed polarization

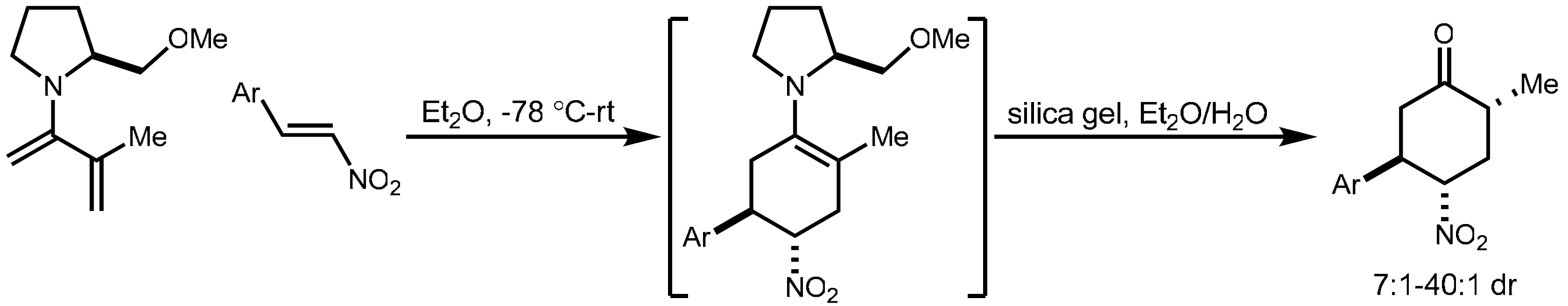
51-99% yield

Corey, E. J.; Estreicher, H. *Tetrahedron Lett.* **1981**, *22*, 603



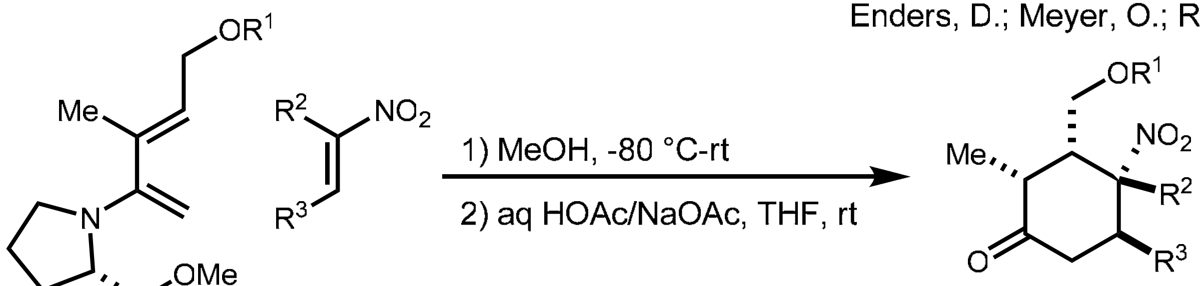
Diastereoselective Diels-Alder Reaction

Some diastereoselective Diels-Alder reaction of nitroalkenes, but no enantioselective version



7:1-40:1 dr
>95 %ee
26-60% yield

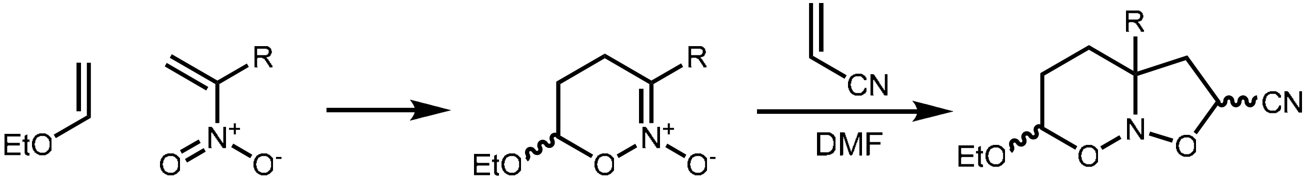
Enders, D.; Meyer, O.; Raabe, G. *Synthesis* **1992**, 1242



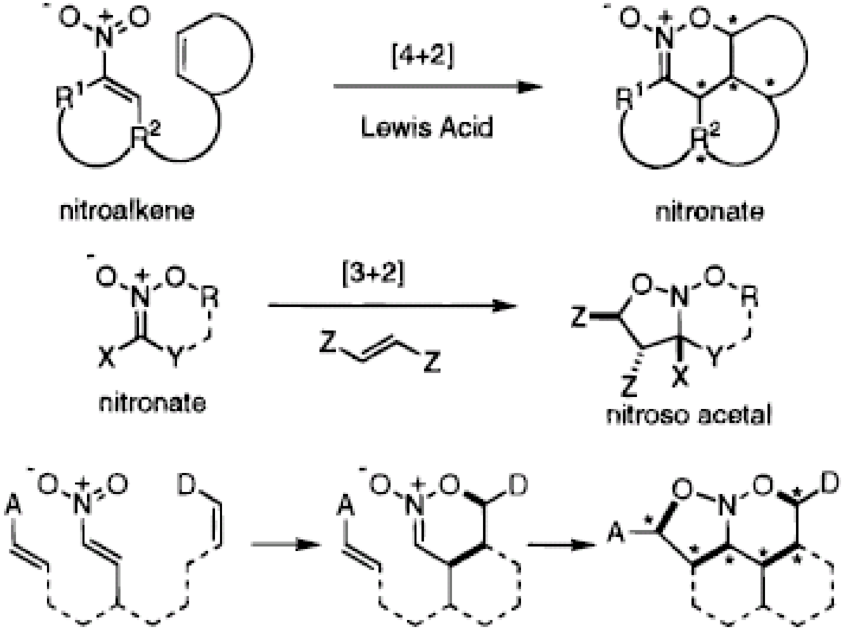
mostly >90 %ee
32-88% yield

Barluenga, J.; Aznar, F.; Ribas, C.; Valdes, C. *J. Org. Chem.* **1997**, *62*, 6746

Nitroalkenes as Heterodienes



Barco, A.; Benetti, S.; Pollini, G. P.; Spalluto, G.;
Zanirato, V. *Tetrahedron Lett.* **1991**, *32*, 2517



Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137

Michael Addition

O-, S- Nu: ROM/ROH, MOOR, H_2S, RSH

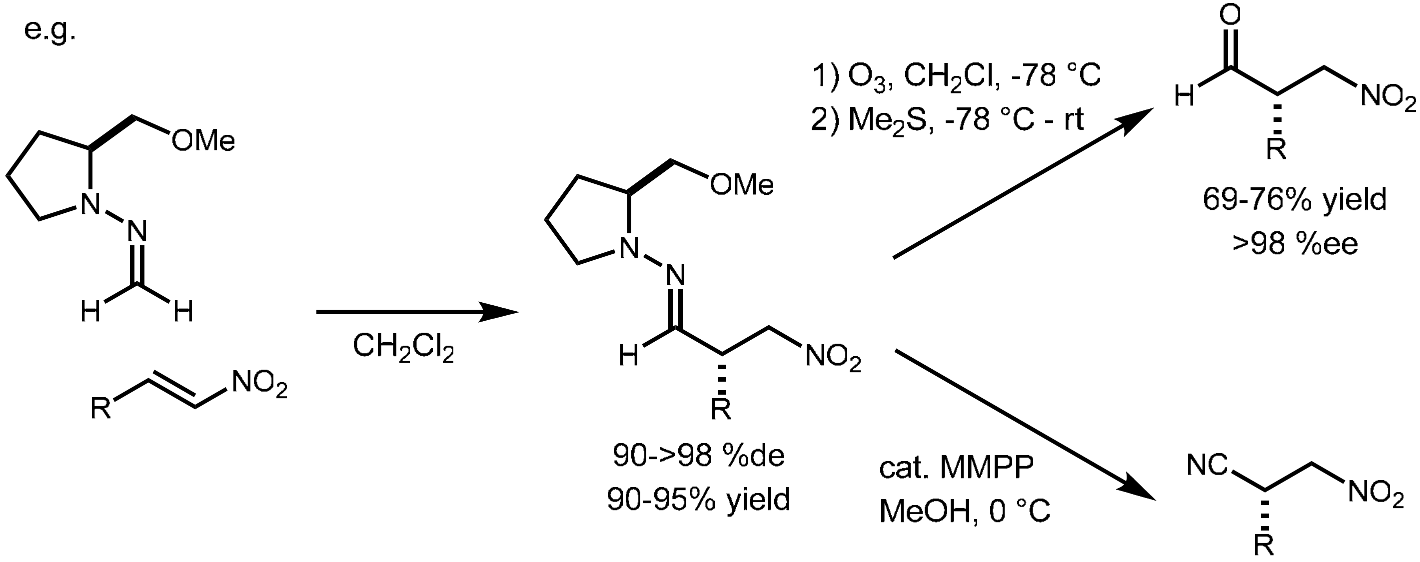
N- Nu: amines, amides

C- Nu: enolates, silyl enolates, enamines, RLi, R_2Zn

P- Nu: R_2PH, $R_2P(O)H$, $(RO)_2POH$
$P(OR)_3$ - complicated results

Substrate-controlled diastereoselective Michael reactions were well-documented

e.g.



90->98 %de
90-95% yield

69-76% yield
>98 %ee

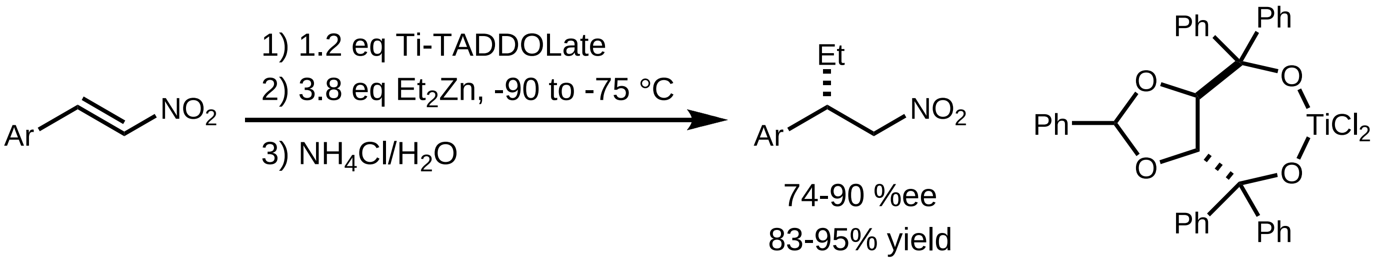
MMPP=magnesium monoperoxyphthalate

93-95% yield
90->99 %ee

R. Fernandez, C. Gasch, J.-M. Lassaletta, J.-M. Llera, *Tetrahedron Lett*. **1994**, *35*, 471

D. Enders, R. Syrig, G. Raabe, R. Fernandez, C. Gasch, J.-M. Lassaletta, J.-M. Llera, *Synthesis* **1996**, 48

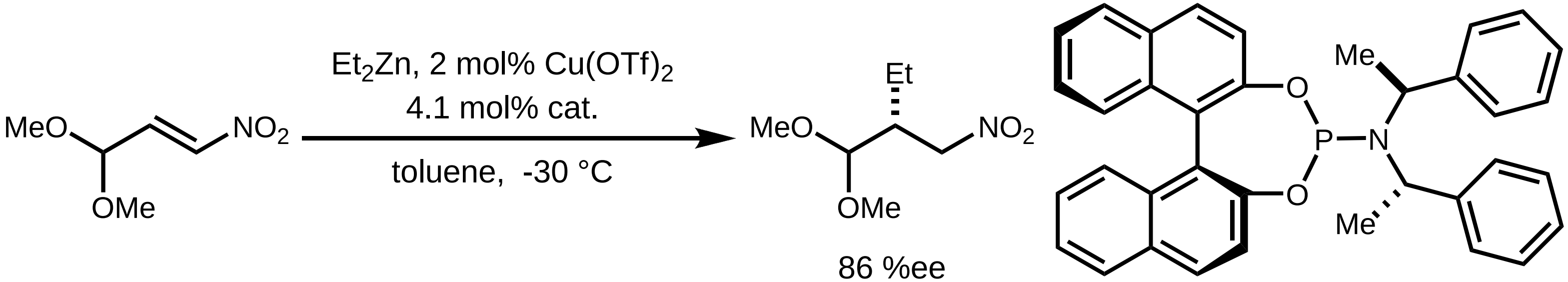
Et_2Zn Addition



1) 1.2 eq Ti-TADDOLate
2) 3.8 eq Et_2Zn, -90 to -75 °C
3) NH_4Cl/H_2O

74-90 %ee
83-95% yield

Schäfer, H; Seebach, D. *Tetrahedron* **1995**, *51*, 2305

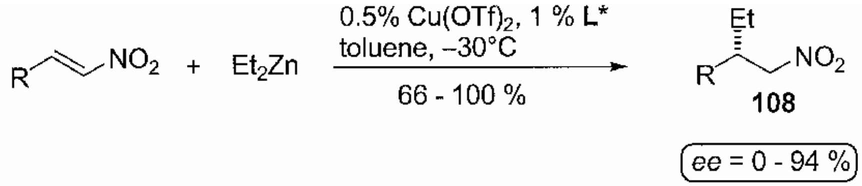


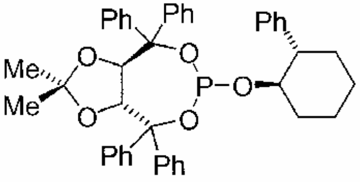
Et_2Zn, 2 mol% $Cu(OTf)_2$
4.1 mol% cat.
toluene, -30 °C

86 %ee
100% conversion

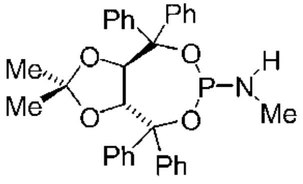
Sewald, N.; Wendisch, V. *Tetrahedron: Asymmetry* **1998**, *9*, 1341
Ligand first reported by Feringa, B. L.; Pineschi, M.; Arnold, L. A.;
Imbos, R.; de Vries, A. H. M. *Angew. Chem. Int. Ed.* **1997**, *36*, 2620

Et_2Zn Addition

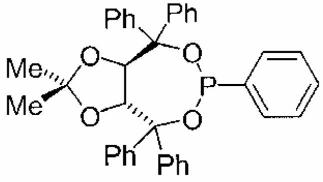




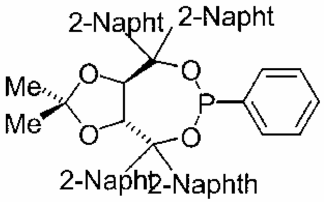
L1(64% *ee*)



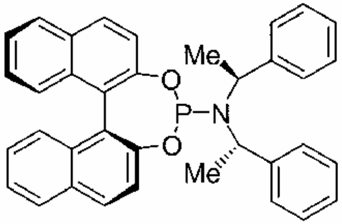
L2 (28% *ee*)



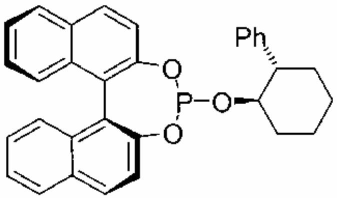
L3(81% *ee*)



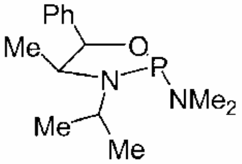
L4(50% *ee*)



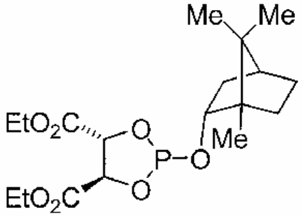
L5(94% *ee*)



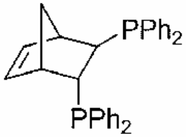
L6(35% *ee*)



L7(7% *ee*)



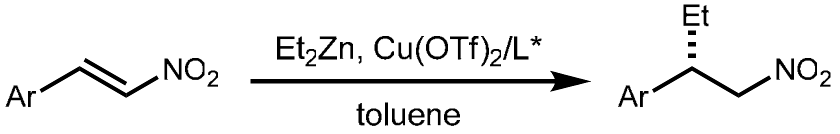
L8 (33% *ee*)

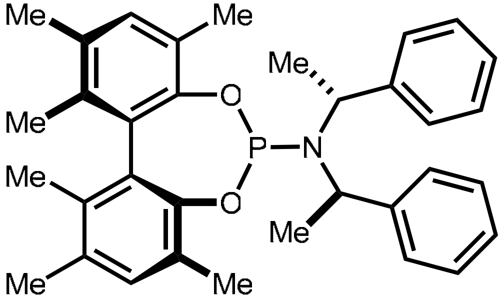


L9(2% *ee*)

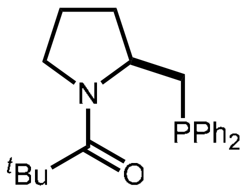
Alexakis, A.; Benhaim, C. *Org. Lett.* **2000**, *2*, 2579

R_2Zn Addition





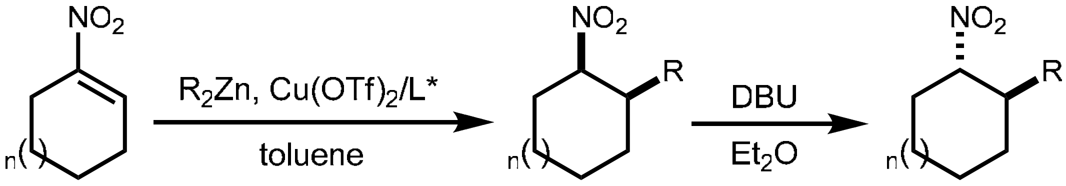
mostly >90 %ee



50-60 %ee

Choi, H.; Hua, Z.; Ojima, I. *Org. Lett.*, **2004**, *6*, 2689

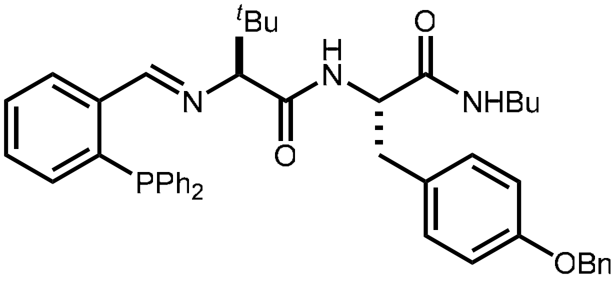
Valleix, F.; Nagai, K.; Soeta, T.; Kuriyama, M.; Yamada, K.; Tomioka, K. *Tetrahedron* **2005**, *61*, 7420



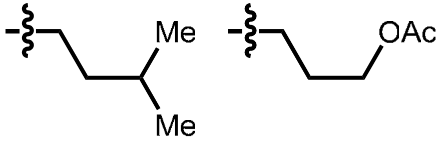
n=1

93-96 %ee

93-96 %ee



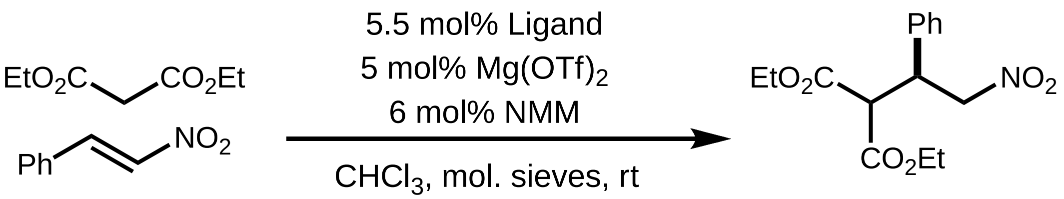
R= Me, Et,



also n=0, 2, 7

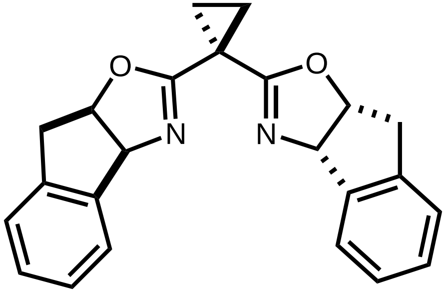
Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.*, **2002**, *124*, 8192

Michael Addition by Metal Catalysis

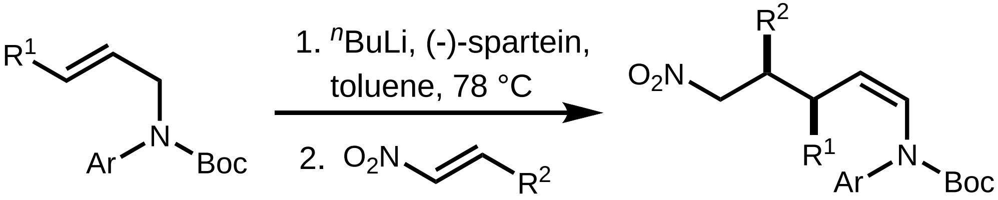


5.5 mol% Ligand
5 mol% $Mg(OTf)_2$
6 mol% NMM
$CHCl_3$, mol. sieves, rt

95 %ee
92% yield

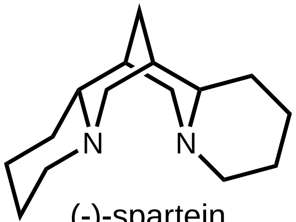


Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittemberg, S. J.; Morton, H. E.
J. Am. Chem. Soc. **1999**, *121*, 10215.



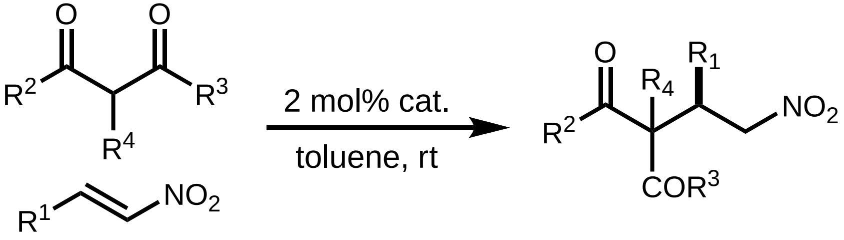
1. ^{n}BuLi, (-)-spartein, toluene, 78 °C
2. O_2N–CH=CH–R^2

86-96 %de
>80 %ee

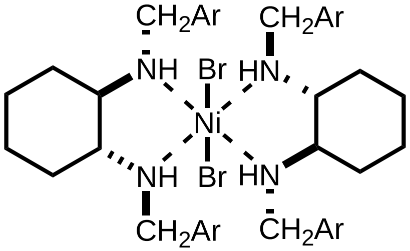


(-)-spartein

Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 1004.



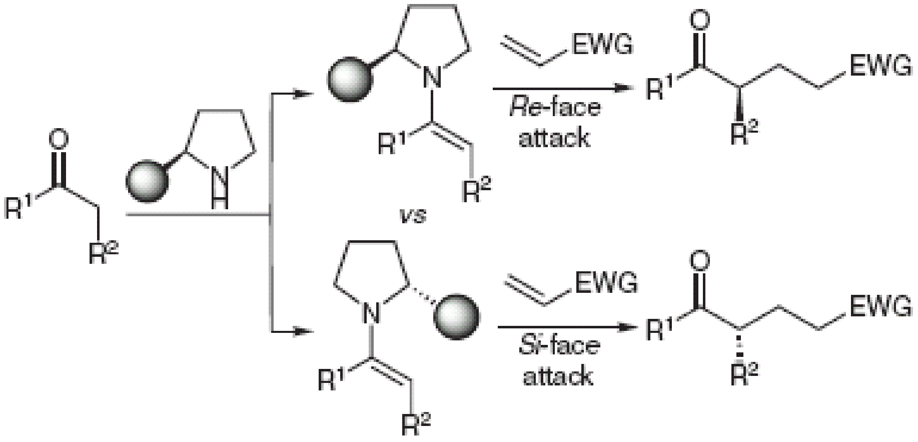
2 mol% cat.
toluene, rt

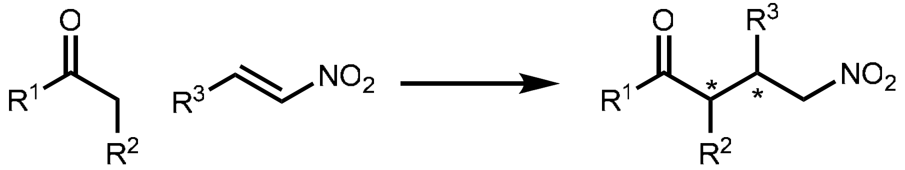


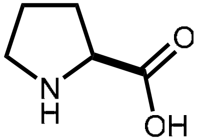
Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583.

Michael Addition by Organocatalysis

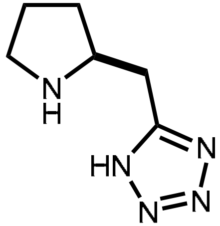
Chiral amines as catalysts via enamine intermediates



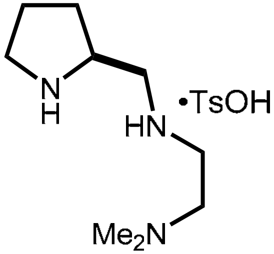




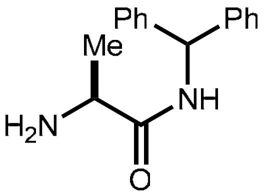
>10:1 dr
7-23 %ee
List
Org. Lett. **2001**, *3*, 2423



>19:1 dr
~90 %ee
Ley
Synlett **2005**, 611



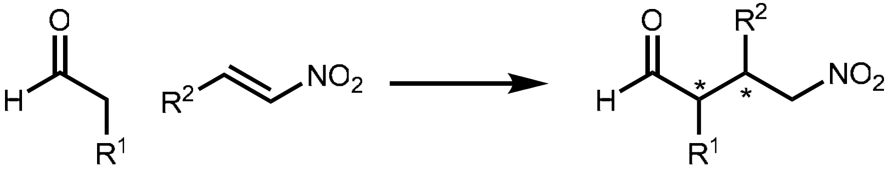
mostly >19:1 dr
~90 %ee
Pansare
JACS **2006**, *128*, 9624

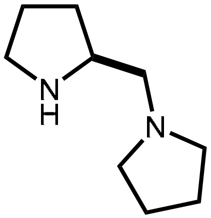


mostly >19:1 dr
mostly >90 %ee
Cordova
Chem. Commun. **2006**, 460

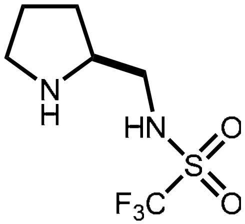
Michael Addition by Organocatalysis

Chiral amines as catalysts via enamine intermediates

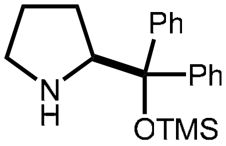




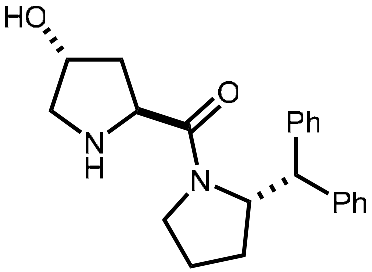
moderate dr
59-91 %ee
Barbas
Org. Lett. **2004**, *6*, 2527
good for α,α-dialkyl aldehyde



>20:1 dr
89-99 %ee
Wang
ACIEE **2005**, *44*, 1369
good for α,α-dialkyl aldehyde



5:1-19:1 dr
99 %ee
Hayashi
ACIEE **2005**, *44*, 4212
Hayashi
ACIEE **2008**, *47*, 4722
Acetaldehyde addition(R_1=H)

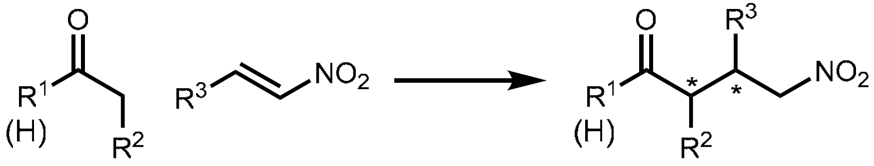


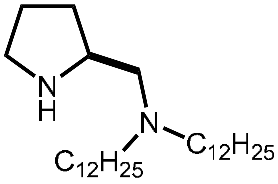
9:1-99:1 dr
mostly >91 %ee
Palomo
ACIEE **2006**, *45*, 5984
low catalyst loading
more efficient

Michael Addition by Organocatalysis

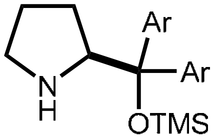
Chiral amines as catalysts via enamine intermediates

"environmentally benign" catalysts



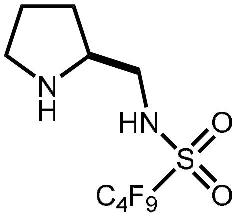


Barbas
JACS **2006**, *128*, 4966
reaction in brine

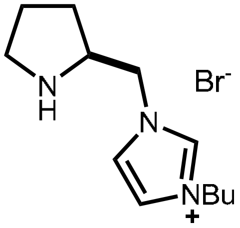


Ar=4-(C_8F_{17})C_6H_4

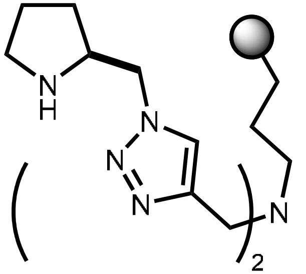
Wang
Tetrahedron Lett.
2006, *47*, 5131
fluorous tag allows the
cat. to recycle and reuse



Wang
Org. Lett. **2006**, *8*, 3077
reaction in water and cat.
recycled and reused



Cheng
ACIEE **2006**, *45*, 3093
ionic liquid
reaction under neat condition

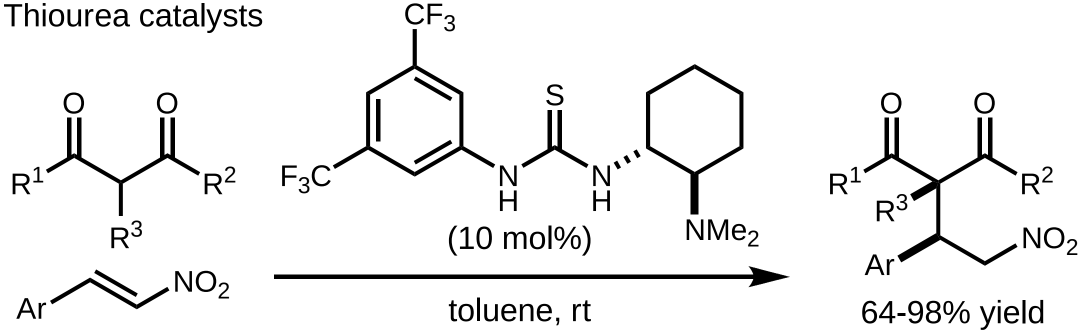


Ma
Tetrahedron: Asymmetry
2008, 19, 1352
insoluble, recyclable

Fluorous Reverse Phase Silica Gel
Curran, D. P. *Synlett* **2001**, 1488

Michael Addition by Organocatalysis

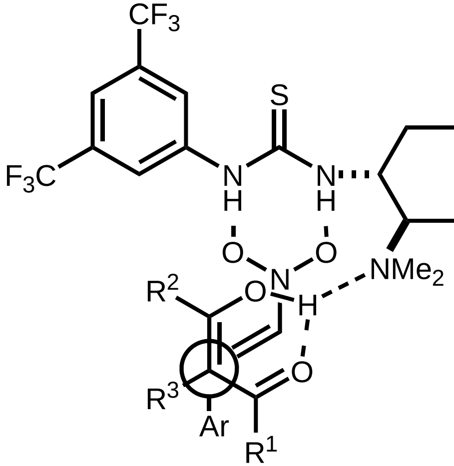
Thiourea catalysts



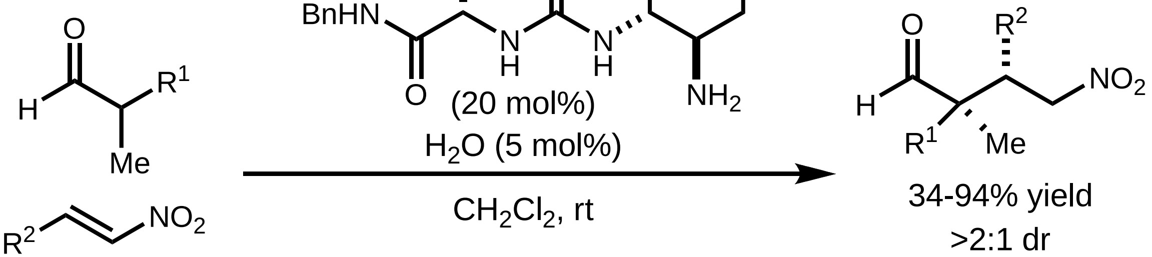
(10 mol%)

toluene, rt

64-98% yield
79-95 %ee



Okino, T.; Hoashi, Y.; Takemoto, Y.
J. Am. Chem. Soc. **2003**, *125*, 12672.
Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.;
Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.



(20 mol%)
H_2O (5 mol%)

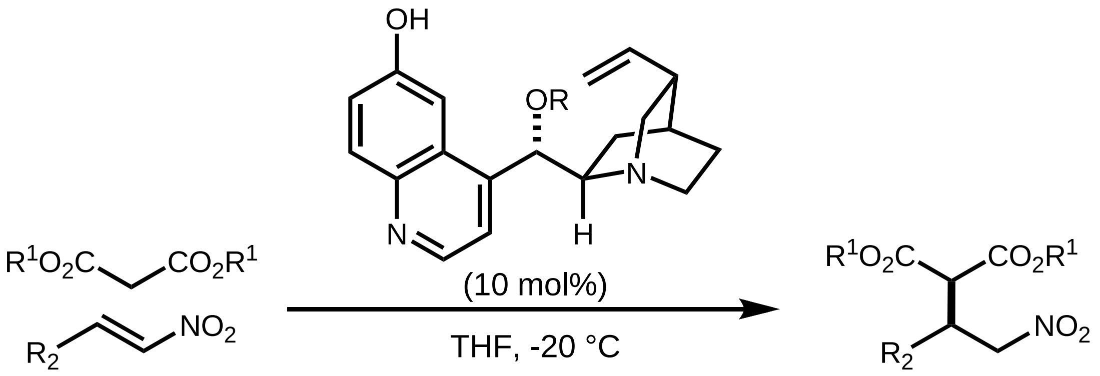
CH_2Cl_2, rt

34-94% yield
>2:1 dr
92-99 %ee

Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *26*, 6366.
Some other similar thiourea catalysts for ketone addition to nitroalkenes from other groups

Michael Addition by Organocatalysis

Cinchona alkaloids catalysts



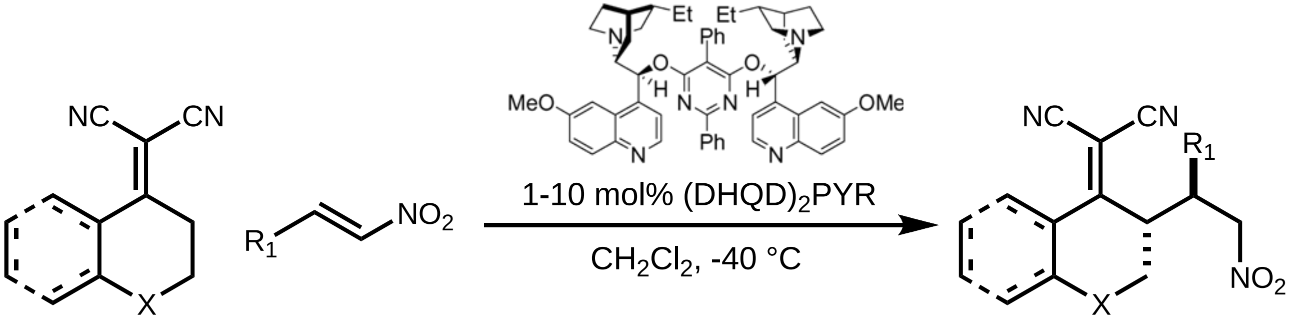
(10 mol%)

THF, -20 °C

80-99% yield

91-96 %ee

Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906.



1-10 mol% $(DHQD)_2$PYR

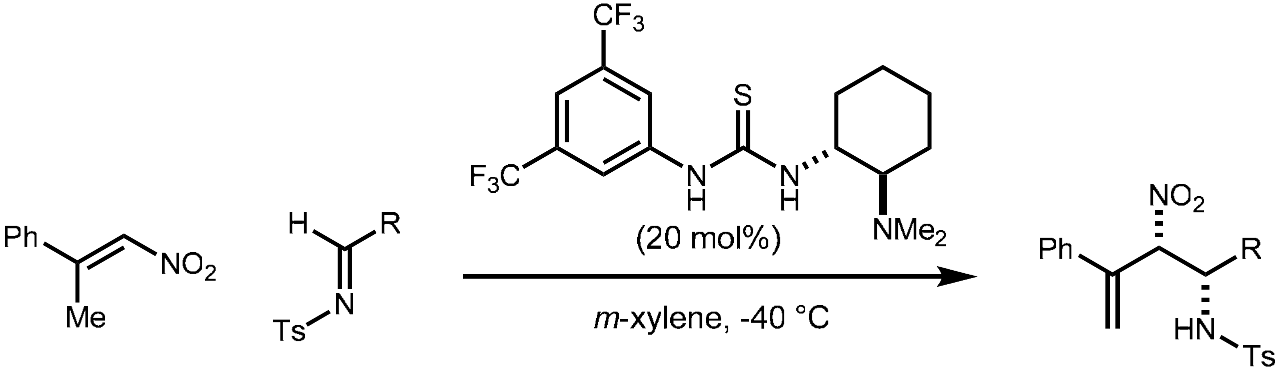
CH_2Cl_2, -40 °C

Vinyl Malononitriles

Xue, D.; Chen, Y.-C.; Wang, Q.-W.; Cun, L.-F.; Zhu, J.; Deng, J.-G. *Org. Lett.* **2005**, *7*, 5293.

Poulsen, T. B.; Bell, M.; Jorgensen, K. A.; *Org. Biomol. Chem.* **2006**, *4*, 63.

Aza-MBH Reaction by Organocatalysis

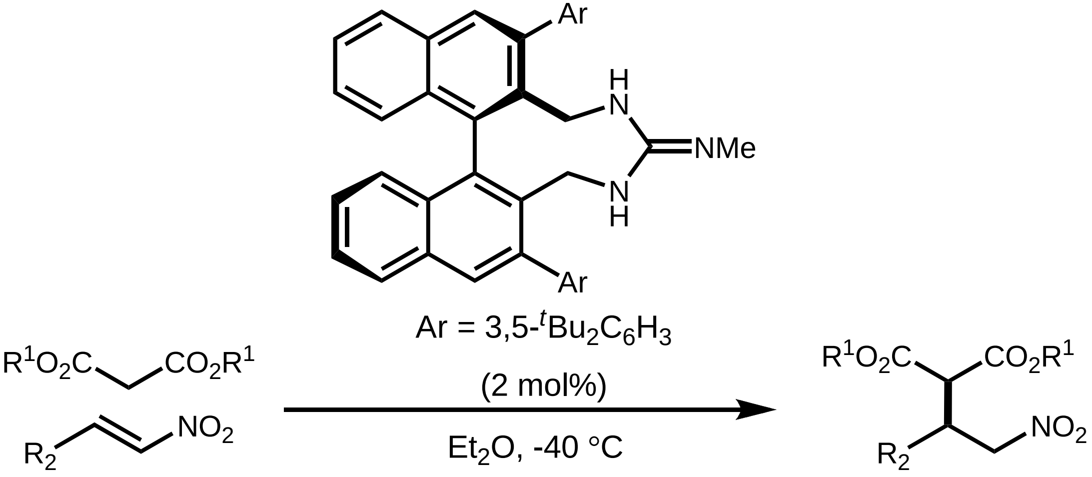


82-95% yield
72-91% ee
2:1-99:1 dr

Wang, X.; Chen, Y.-F.; Niu, L.-F.; Xu, P. F. *Org. Lett.* **2009**, *11*, 15

Michael Addition by Organocatalysis

Chiral guanidine catalyst



Ar = 3,5-^{t}Bu$_2$C$_6$H$_3$

(2 mol%)

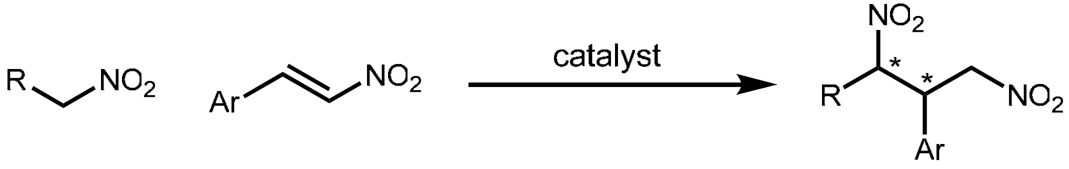
Et$_2$O, -40 °C

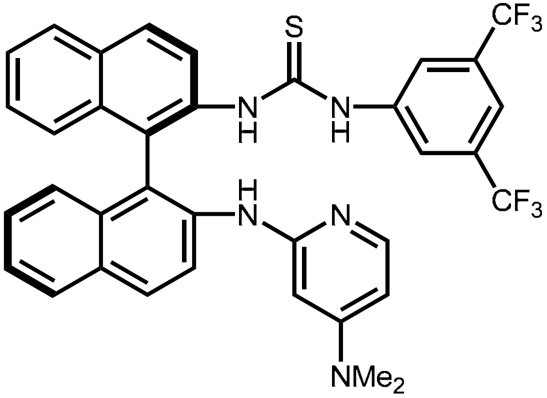
79-99% yield

87-98 %ee

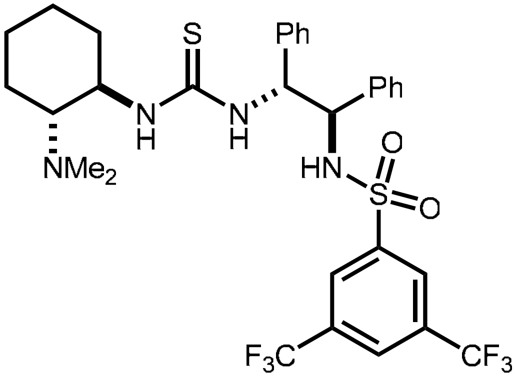
Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454.

Nitroalkane Michael Addition by Organocatalysis



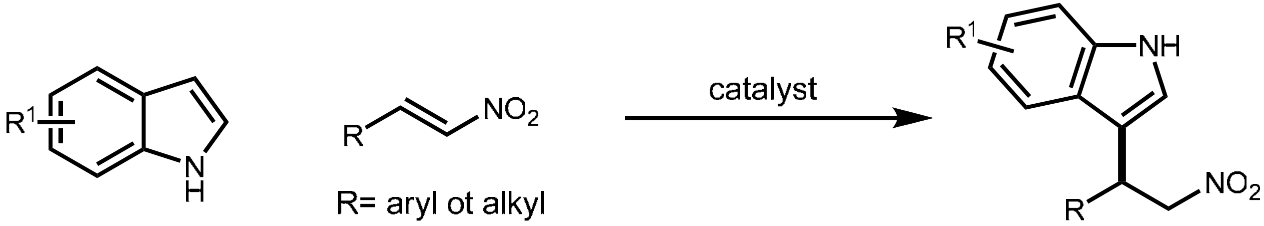


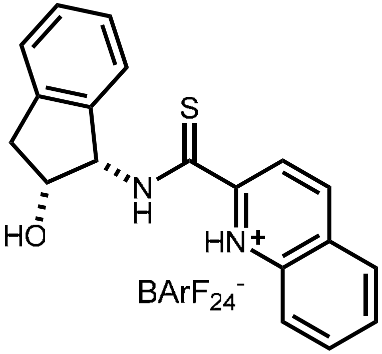
Wulff
J. Am. Chem. Soc. **2008**, *130*, 13524
Low catalyst loading (2 mol%)



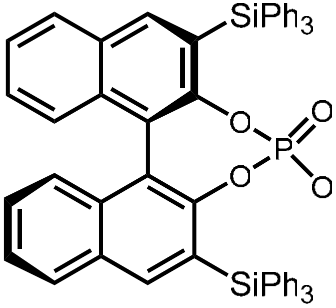
Wang
Org. Lett. **2009**, *11*, 1265
also works for aliphatic
nitroalkene, but low dr

Indole Michael Addition by Organocatalysis



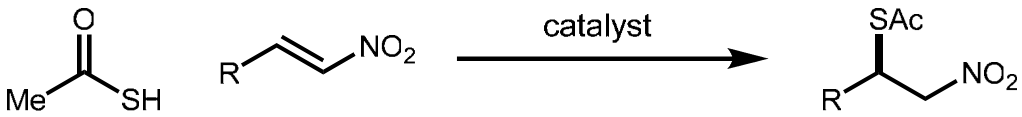


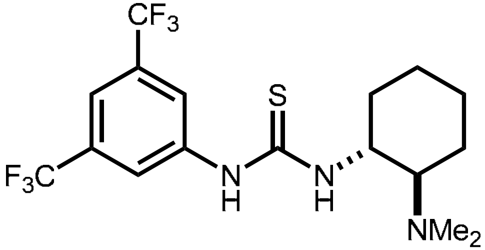
90-97% ee
Ganesh, M.; Seidel, D.
J. Am. Chem. Soc. **2008**, *130*, 16464



88-94% ee
Itoh, J.; Fuchibe, K.; Akiyama, T.
Angew. Chem. Int. Ed. **2008**, *47*, 4016

Sulfur-Michael Addition by Organocatalysis



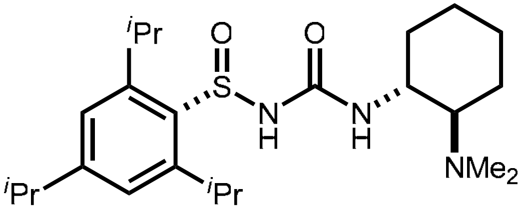


91-98% yield

20-70 %ee

Li, H.; Wang, J.; Zu, L.-S.; Wang, W.

Tetrahedron Lett. **2006**, *47*, 2585

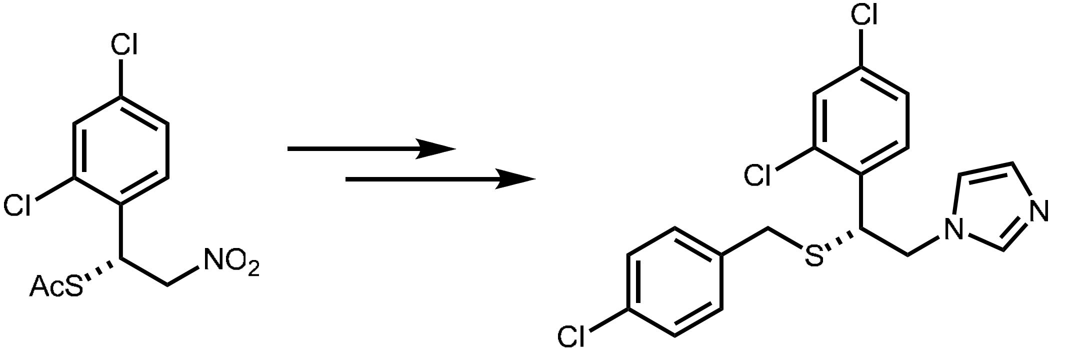


63-95% yield

78-96 %ee

Kimmel, K.L.; Robak, M. T.; Ellman, J. A.

J. Am. Chem. Soc. **2009**, *131*, 8754



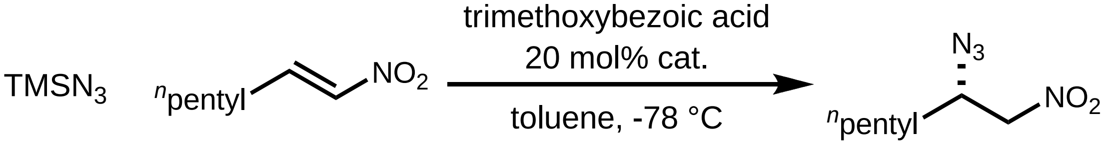
96% ee

96% ee

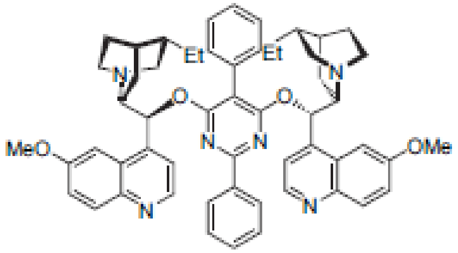
(*R*)-sulconazole

a clinically used azole antifungal drug

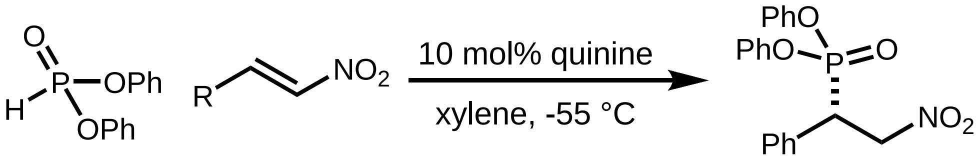
N and *P* Michael Addition by Organocatalysis



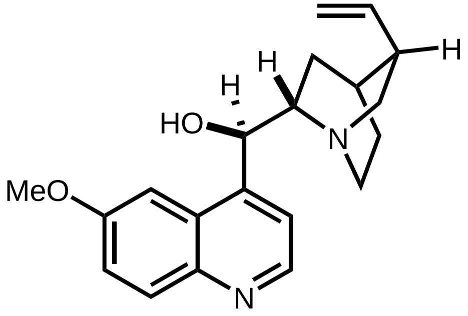
85% yield
62 %ee



Nielsen, M.; Zhuang W.; Jørgensen, K. A.
Tetrahedron **2007**, *63*, 5849



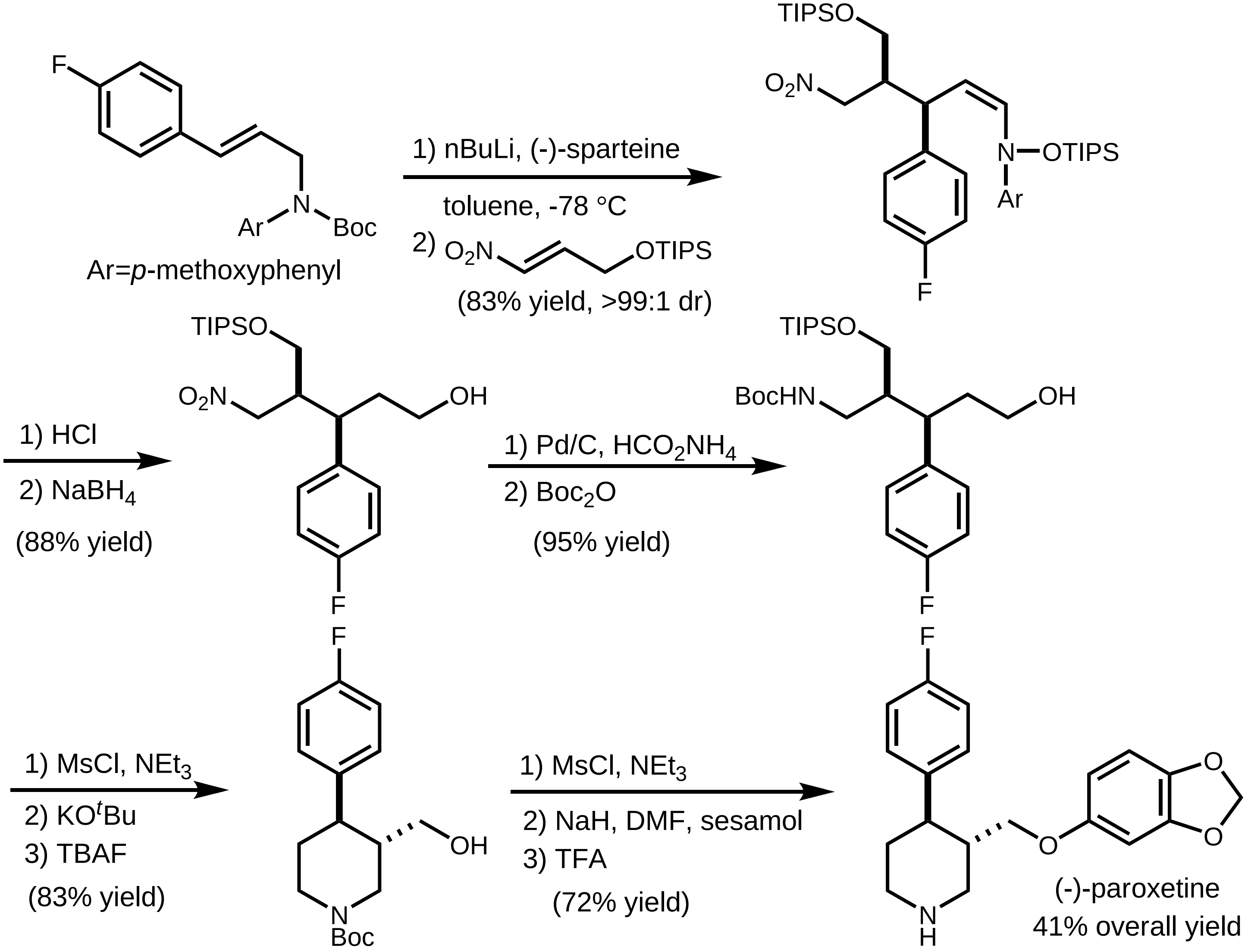
60-85% yield
45-88 %ee



quinine

Wang, J.; Heikkinen, L. D.; Li, H.; Zu, L.; Jiang, W.; Xie, H. Wang. W.
Adv. Synth. Catal. **2007**, *349*, 1052

Application in Total Synthesis



Ar=*p*-methoxyphenyl

1) nBuLi, (-)-sparteine

toluene, -78 °C

2) O_2N / OTIPS

(83% yield, >99:1 dr)

1) HCl

2) $NaBH_4$

(88% yield)

1) Pd/C, HCO_2NH_4

2) Boc_2O

(95% yield)

1) MsCl, NEt_3

2) KO^tBu

3) TBAF

(83% yield)

1) MsCl, NEt_3

2) NaH, DMF, sesamol

3) TFA

(72% yield)

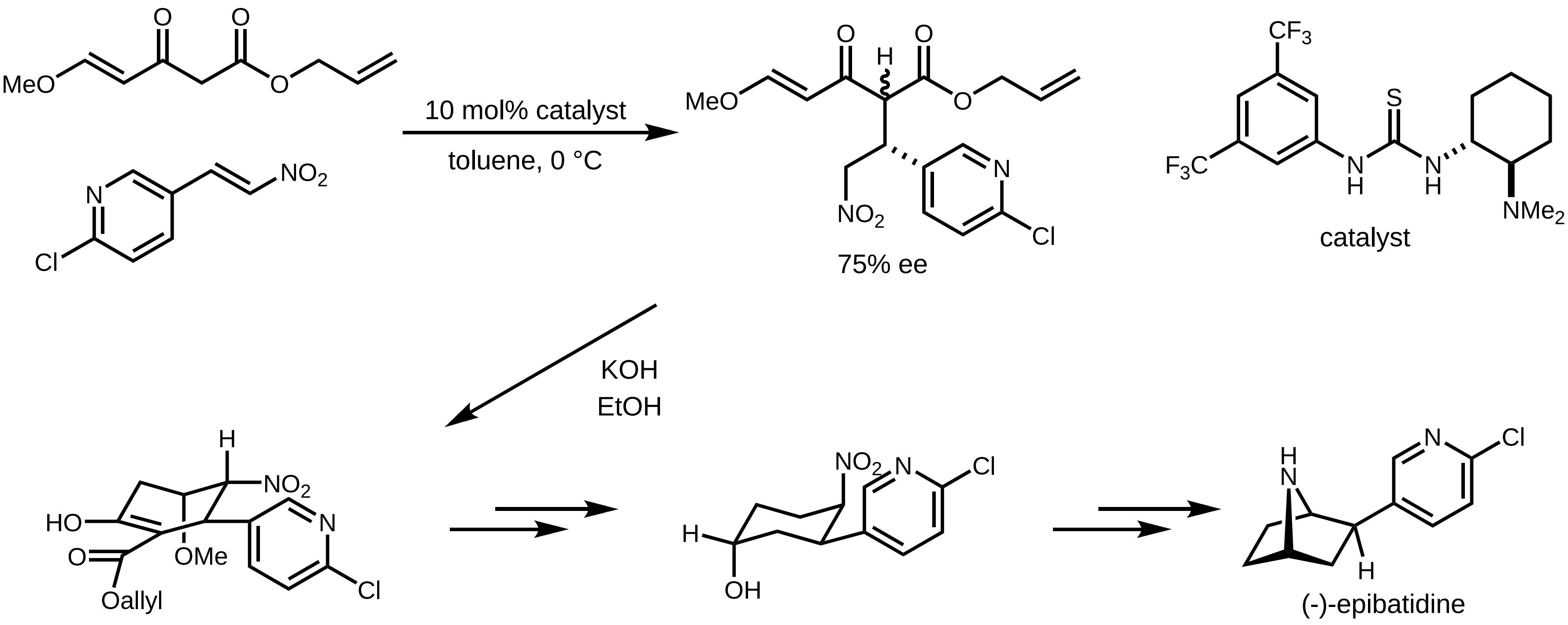
(-)-paroxetine

41% overall yield

>94 %ee

Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 1004.

Application in Total Synthesis



Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y.
Tetrahedron **2006**, *62*, 365