Universität Konstanz

Angewandte Chemie International Edition Methodologies 2010 - 2016

Maximilian Häfner

Konstanz, 12.07.2017

ANCIE 2010 - 2016

Cyclobutanes and -butenes

Heptacycles

Cross-Couplings

Ring contractions or expansions

Various methods

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Angewandte International Edition Chemie
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97014 pages published
More than 1000 methods…

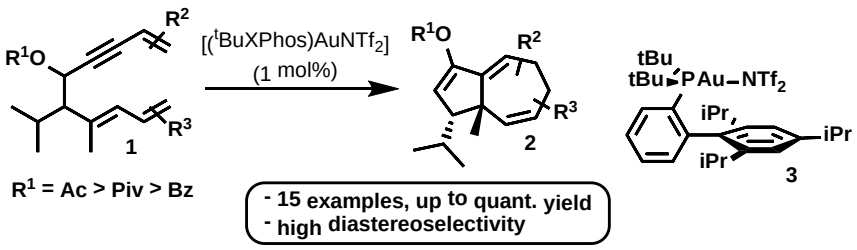
Azomethin-Ylides

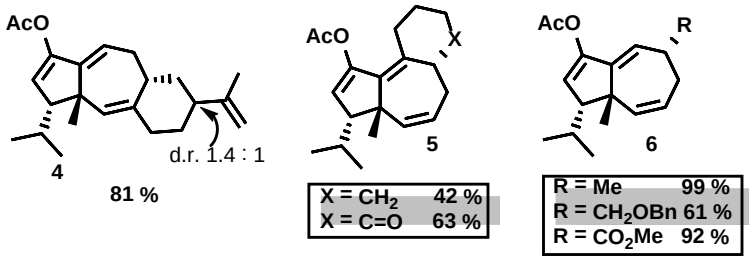
Allylic manipulations

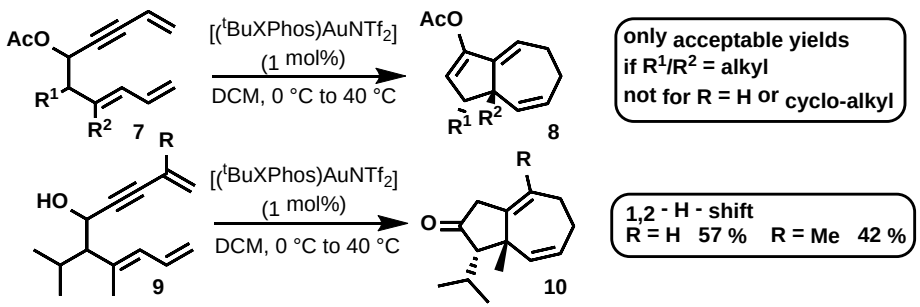
Photo-chemistry

CH - oxidation

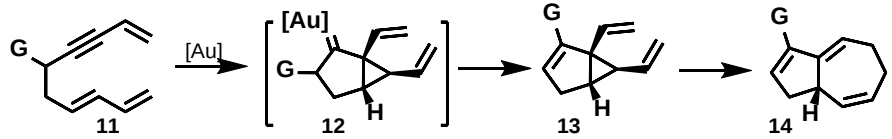
Synthesis of heptacycles – Gold-catalysis

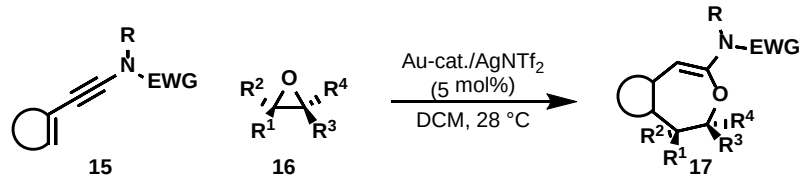


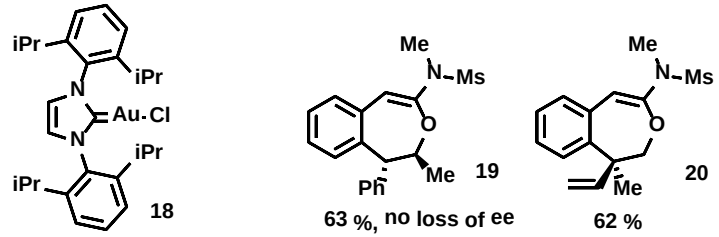




Gagosz and Cao, *Angew. Chem. Int. Ed*. **2013**, 9014 – 9018.

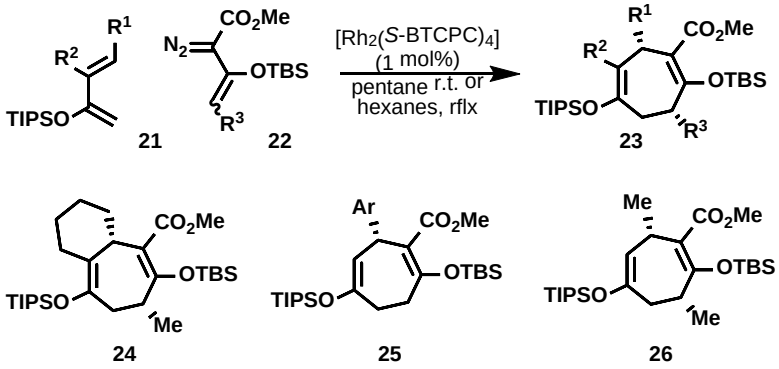


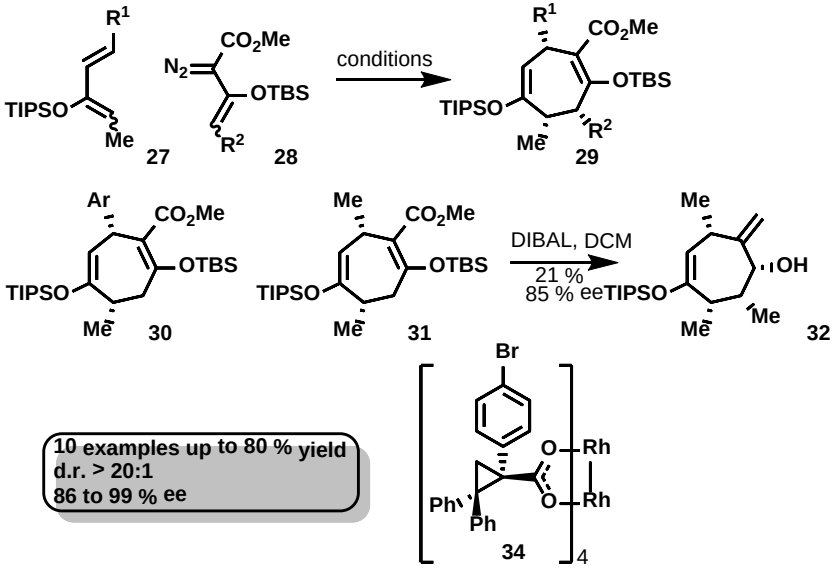




Liu *et al., Angew. Chem. Int. Ed*. **2012**, 8722 – 8726.

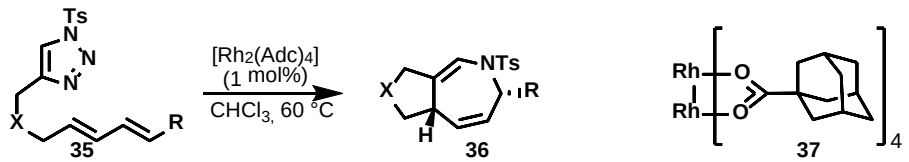
Synthesis of heptacycles – *via* Diazo-intermediates





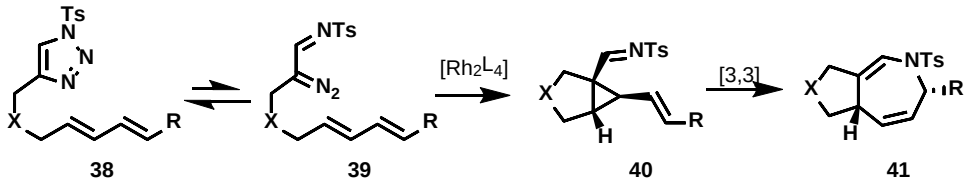
10 examples up to 80 % yield
d.r. > 20:1
86 to 99 % ee

Davies *et al., Angew. Chem. Int. Ed.* **2014**, 13083 - 13087.



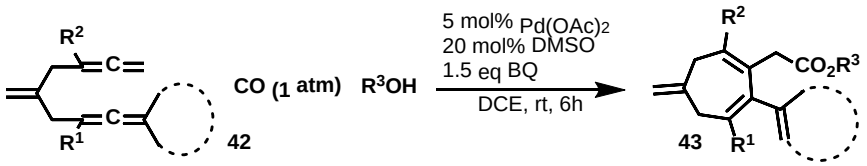
- 9 examples, up to 92 %yield
- diastereoselective reaction
- gram scale

X = O, NTs, $(MeO_2C)_2C$, H_2C
R = Me, Ph, *p*-NO_2-Ph, *p*-MeO-Ph



Sarpong *et al., Angew. Chem. Int. Ed.* **2014**, 9904 – 9908.

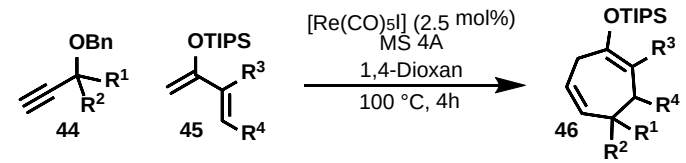
Synthesis of heptacycles – other methodologies



24 examples, up to 92 %yield

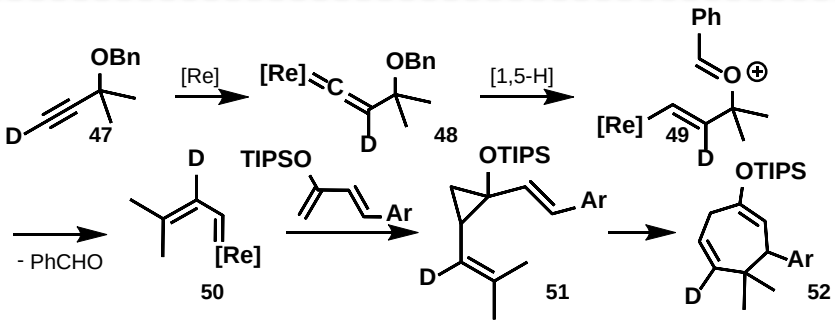
R^1/R^2 = Alkyl
R^3 = Alkyl, Aryl, Alkynyl, Allyl

Bäckvall *et al., Angew. Chem. Int. Ed.* **2016**, 14406 – 14408.

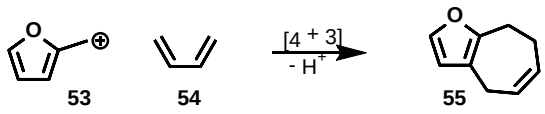


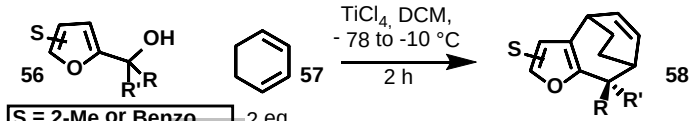
22 examples, up to 93 % yield
average yield ~80 %

R^1/R^2 = Me, Alkyl, Cycloalkyl
R^3/R^4 = Alkyl, Aryl, HetAryl



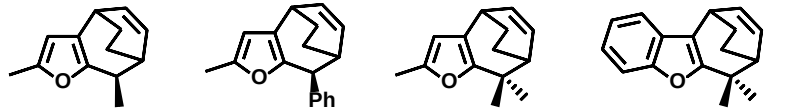
Iwasawa and Sogo, *Angew. Chem. Int. Ed.* **2016**, 10057 – 10060.

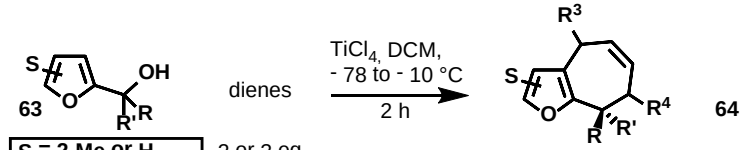




S = 2-Me or Benzo
R/R' = Me, Et, Ph, Me_2

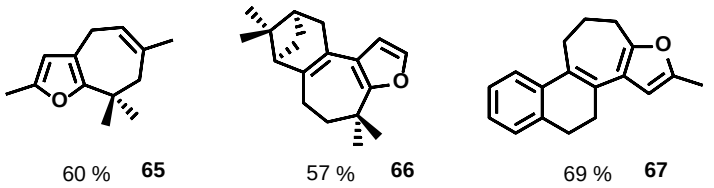
6 examples, > 70% yield





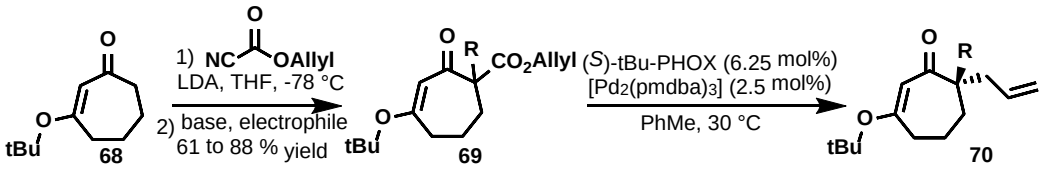
S = 2-Me or H
R/R' = H_2, Me_2, Me

7 examples, 25 to 85% yield

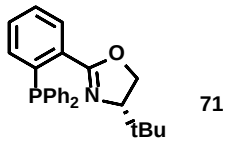


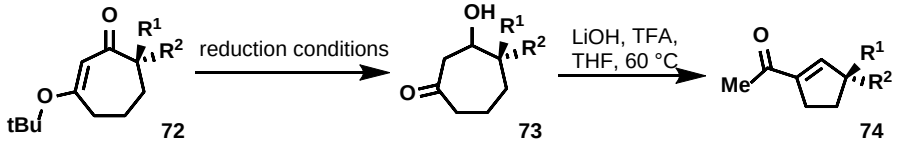
Winne *et al., Angew. Chem. Int. Ed.* **2011**, 11990 – 11993.

Ring contraction – Synthesis of γ-quat. Acyclcyclopentenes



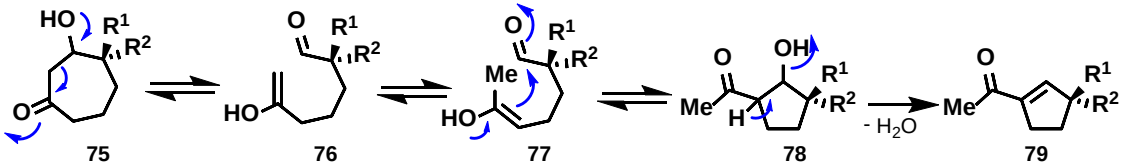
R = alkyl, allyl, propargyl, benzyl
yields 89 to 99 %
ee 80 to 92 %

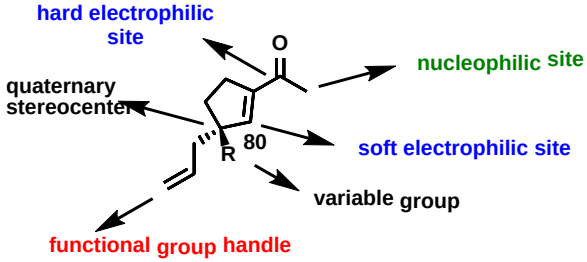




reduction conditions
- LAH, Et_2O, 0 °C then 10% HCl
- DIBAL, PhMe, -78 °C then oxalic acid, MeOH
- $CeCl_3$* $7H_2O$, $NaBH_4$, MeOH, 0 °C, then 10% HCl

R^1 = alkyl, allyl, propargyl, benzyl, HetBenzyl
R^2 = allyl, crotyl, cyclohexenyl
overall yields 02s 80 to 95 %

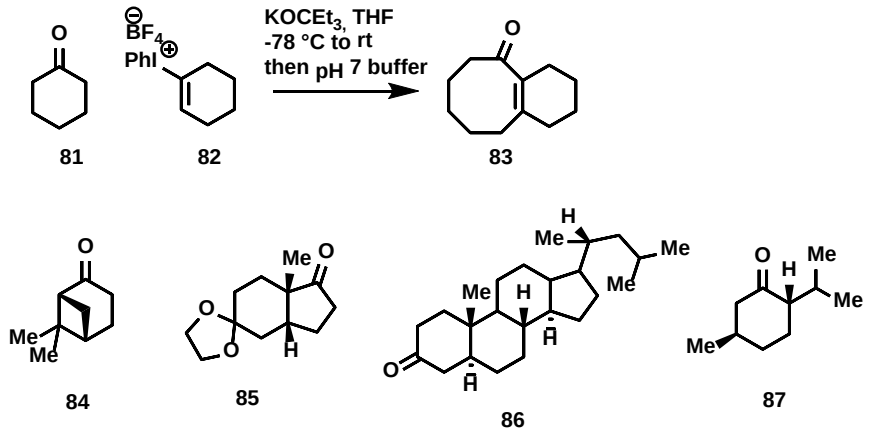


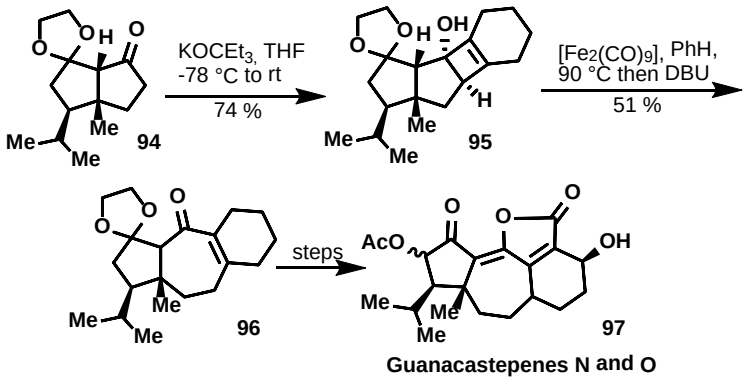


many possible further manipulations

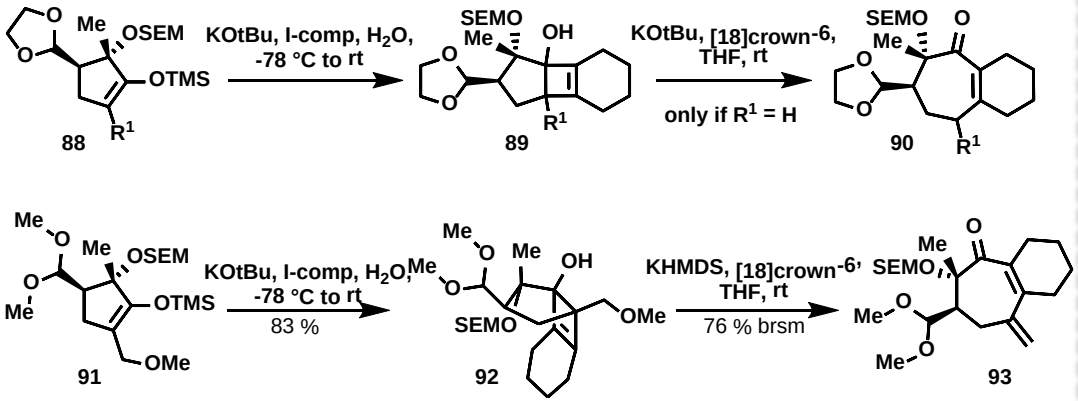
Stoltz *et al., Angew. Chem. Int. Ed.* **2011**, 2756 – 2760.

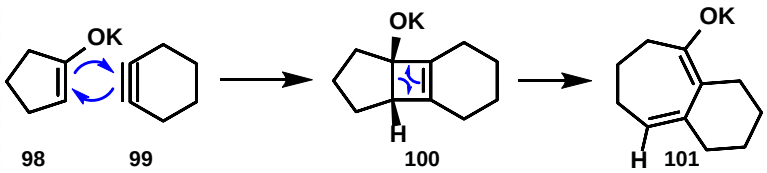
Ring expansion – Cyclohexyne Cycloinsertion





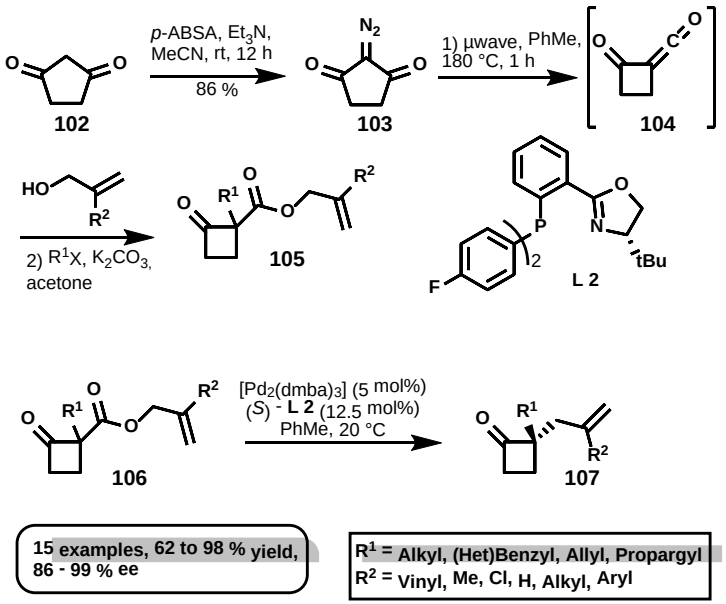
Carreira and Gampe., *Angew. Chem. Int. Ed.*, **2011**, 2962 – 2965.

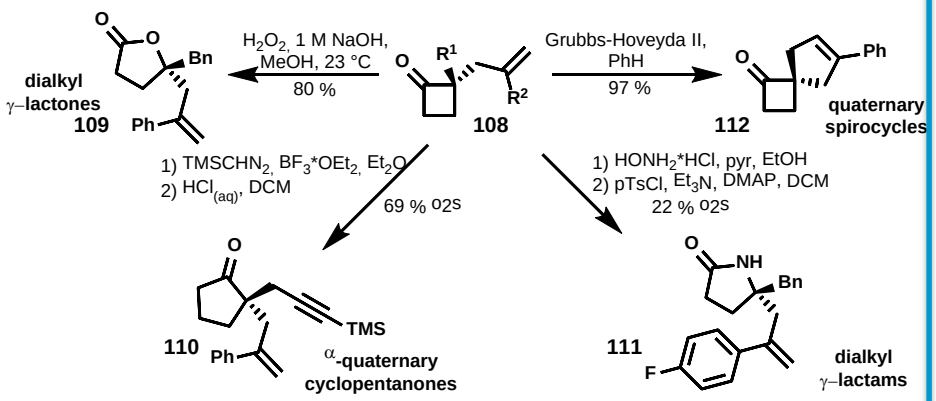




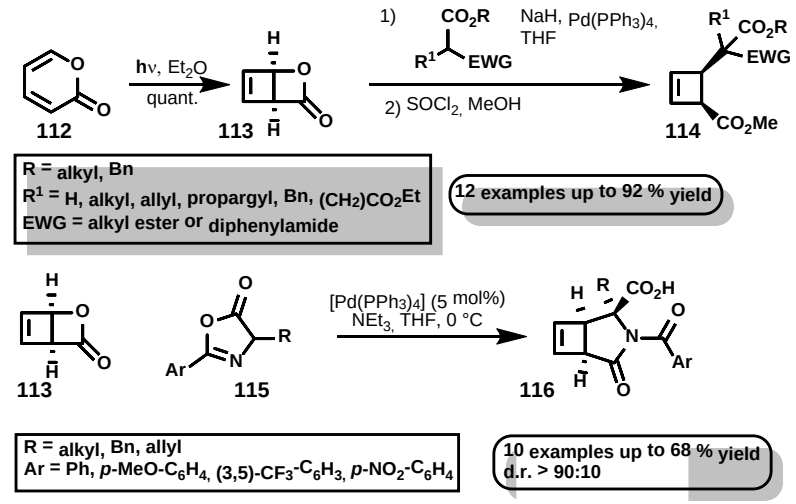
Carreira *et al., Angew. Chem. Int. Ed.*, **2010**, 4092 – 2095.

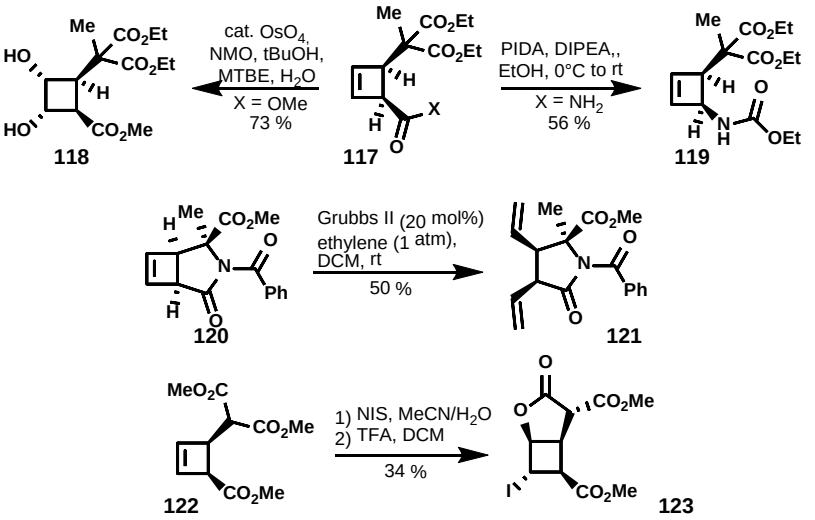
4-membered Rings – (asymm.) allylic alkylation





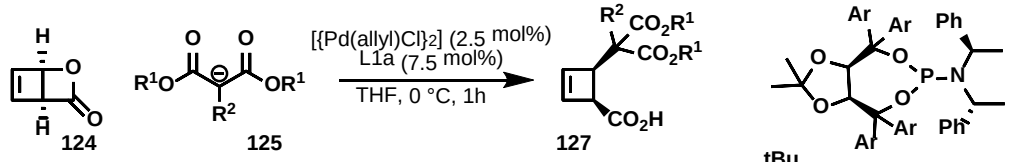
Stoltz *et al., Angew. Chem. Int. Ed.* **2013**, 6718 – 6721.





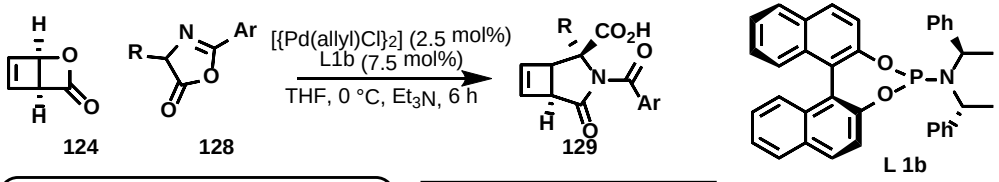
Maulide *et al., Angew. Chem. Int. Ed.* **2010**, 5672 – 5676.

4-membered Rings – asymm. allylic alkylation



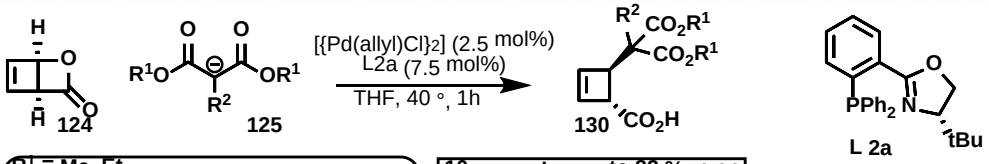
R^1 = Me, Et
R^2 = Alkyl, Allyl, Propargyl, $(CH_2)_3OBn$, $(CH_2)_3Cl$, $(CH_2)_2CN$

9 examples up to 85 % yield
d.r. > 95:5
ee 90 to 96 %



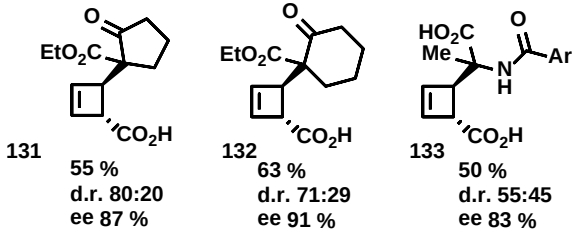
Ar = *p*-NO_2-C_6H_4
R = alkyl, allyl, benzyl, benzyl, *p*-BrBn
$(CH)_2Bn$

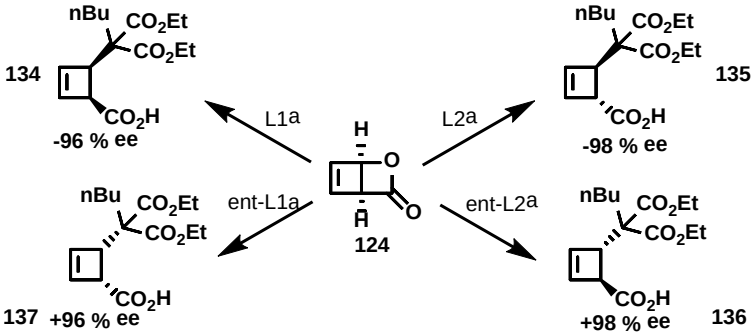
7 examples up to 76 % yield
d.r. > 91:9
ee 94 to 98 %



R^1 = Me, Et
R^2 = alkyl, allyl, $(CH)_2CO_2Et$, $(CH_2)_3OBn$, Bn, *p*-NO_2-Bn

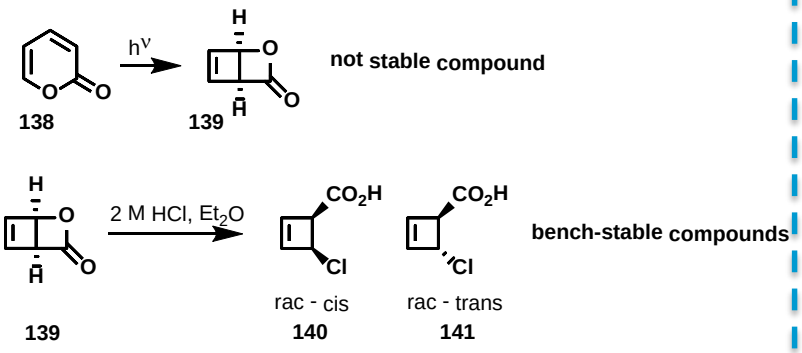
10 examples up to 82 % yield
d.r. > 95:5
ee 92 to 99 %

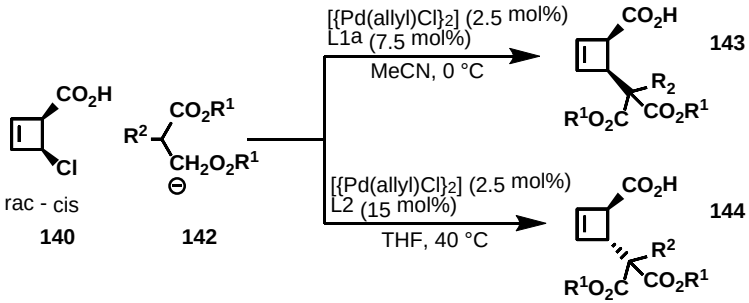


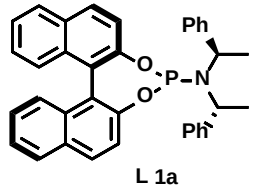


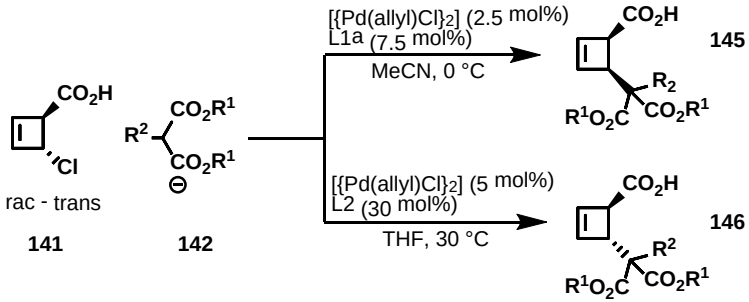
Maulide *et al., Angew. Chem. Int. Ed.* **2011**, 12631 – 12653.

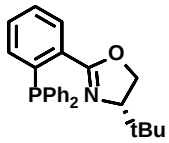
4-membered Rings – asymm. allylic alkylation









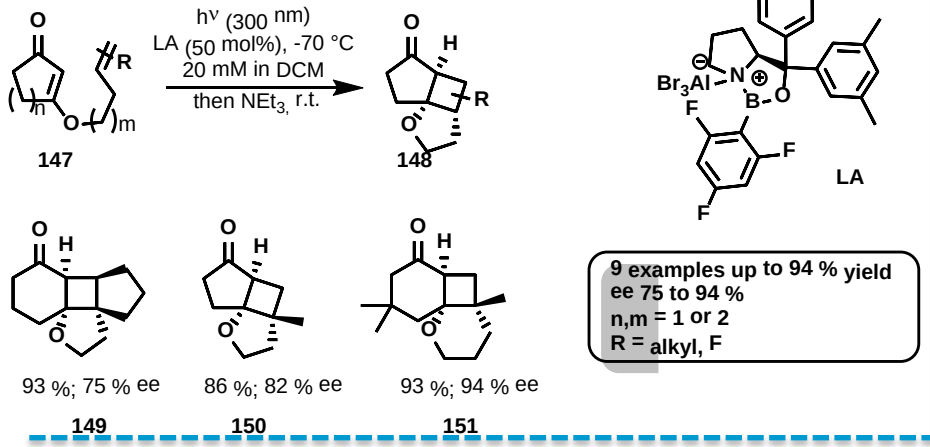


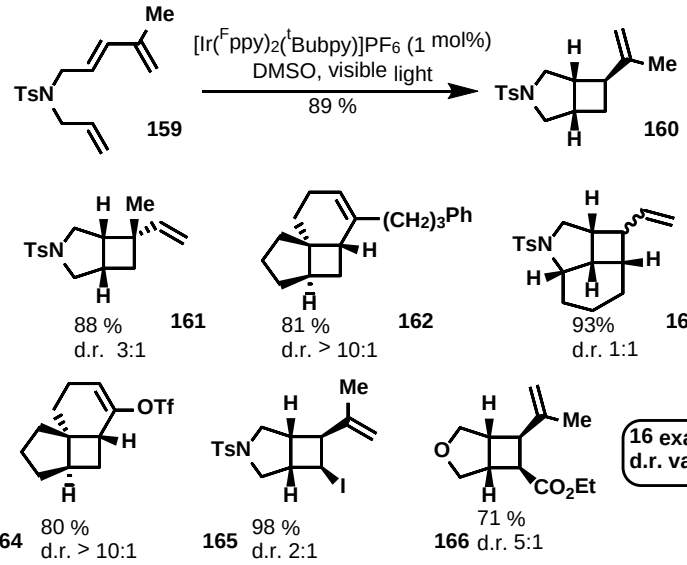
15 examples up to 76 % yield
d.r. > 95:5
ee 81 to 96 %

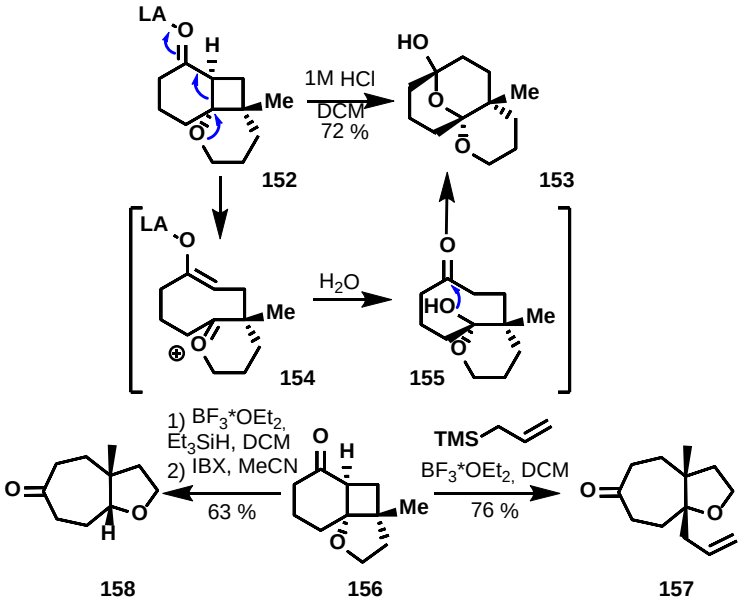
enantiomeric approach:
8 examples up to 95 % yield
d.r. > 90:10
ee 65 to 96 %

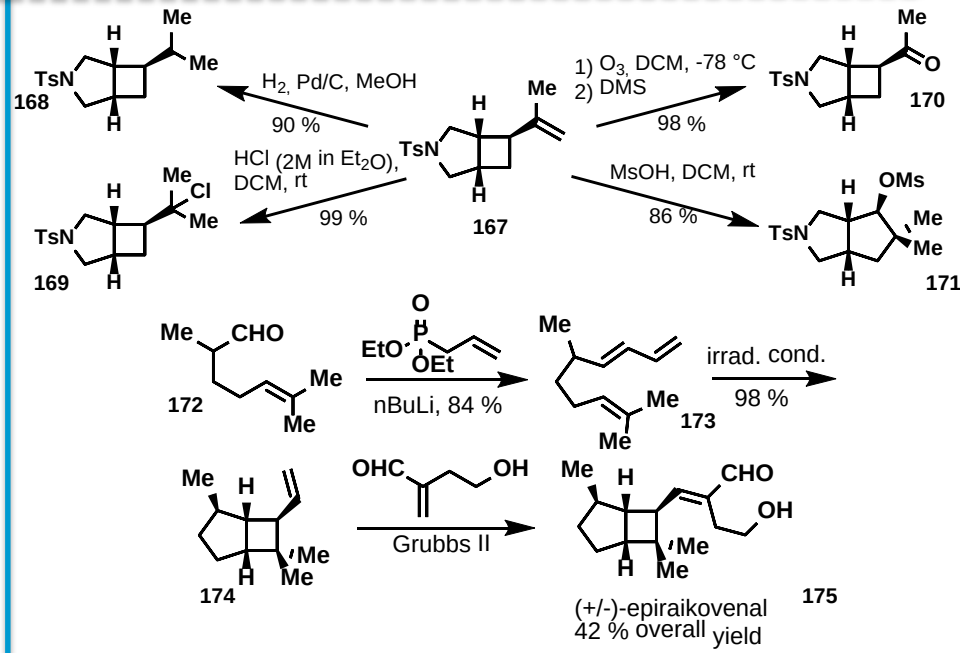
Maulide *et al., Angew. Chem. Int. Ed.* **2012**, 7314 – 7317.

Photochemical methods





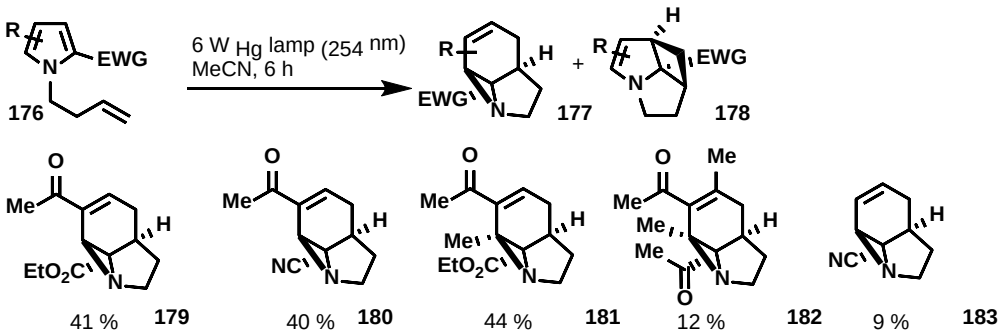




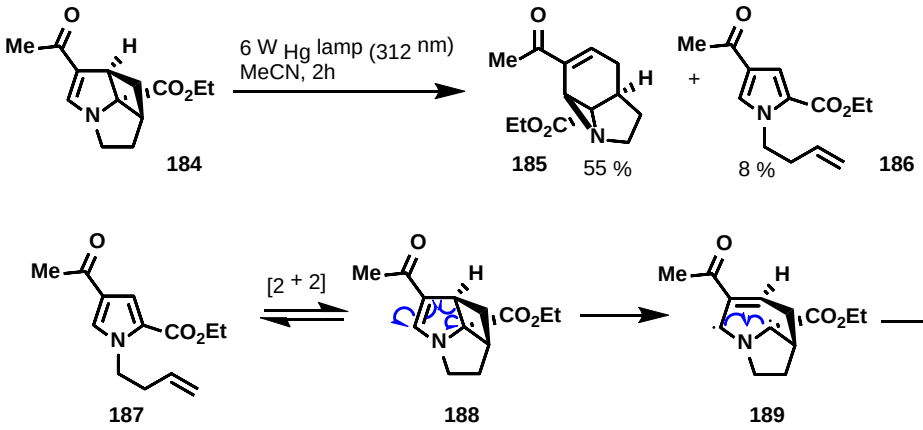
Bach and Brimioulle, *Angew. Chem. Int. Ed.* **2014**, 12921 – 12924.

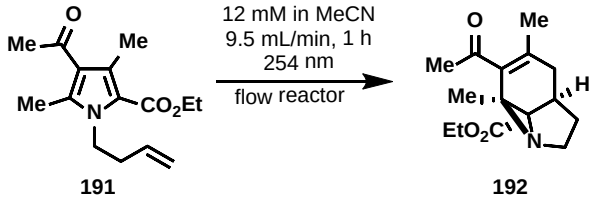
Yoon et al., *Angew. Chem. Int. Ed.* **2014**, 8991 – 8994.

Photochemical methods



14 examples up to 44 % yield of aziridine and up to 29 % cyclobutane formation clean reaction

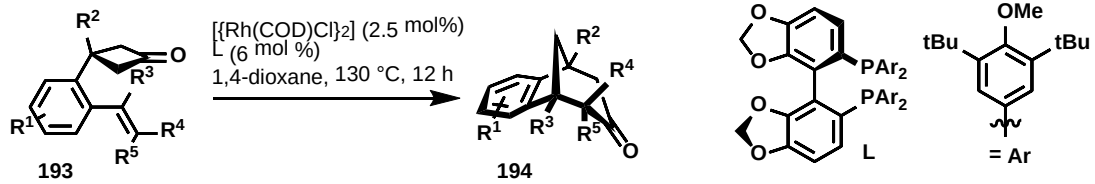




0.91 g, 51 %
Productivity 21.8 g/d

Milburn et al., *Angew. Chem. Int. Ed.* **2013**, 1499 – 1502.

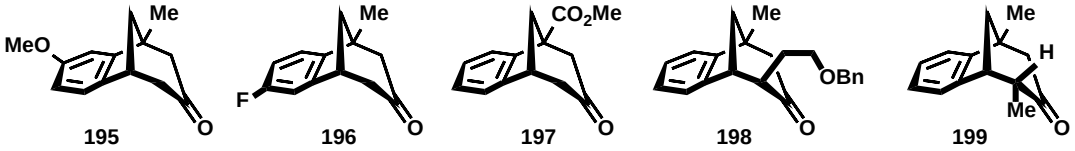
C-C-bond activation – synthesis of tropane systems



193 194

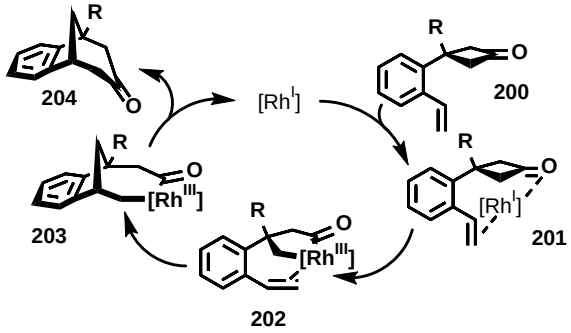
15 examples up to 96 % yield
ee 95 up to >99 %

Tolerant to (protected) functional groups
esters, prot. alcohols, nitriles

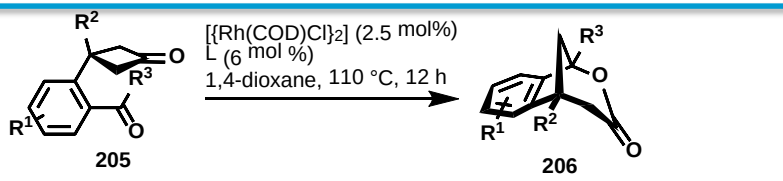


195 196 197 198 199

Cramer *et al., Angew. Chem. Int. Ed*, **2014**, 3001 – 3005.

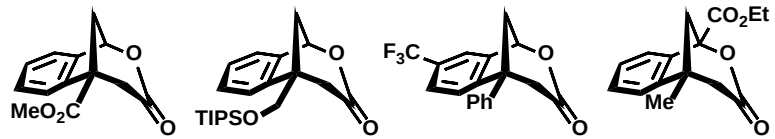


204 200 203 201 202



205 206

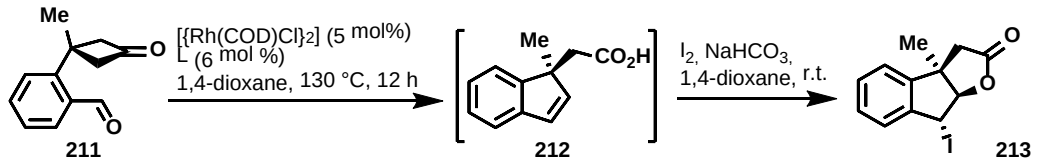
13 examples up to 89 % yield
ee 95 up to >99 %



207 208 209 210

Cramer *et al., Angew. Chem. Int. Ed*, **2014**, 9640 – 9644.

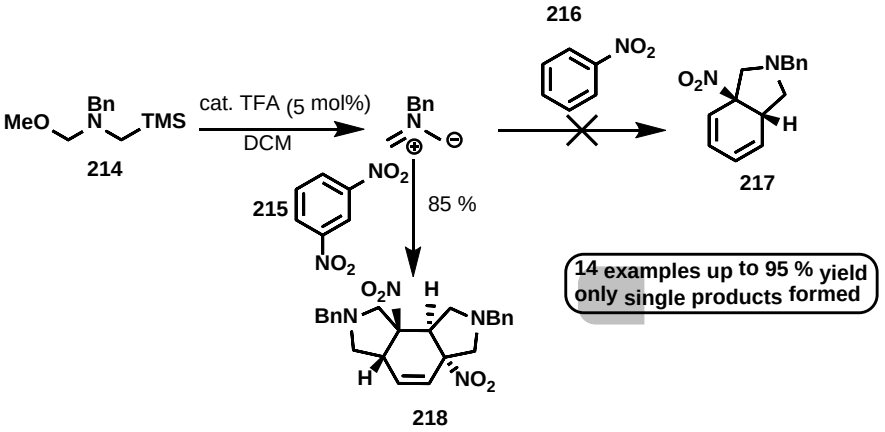
with higher temperatures:

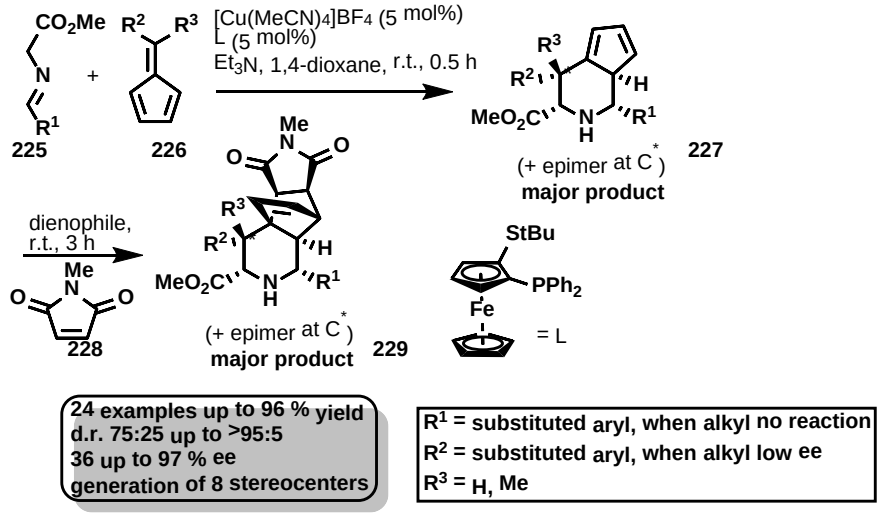


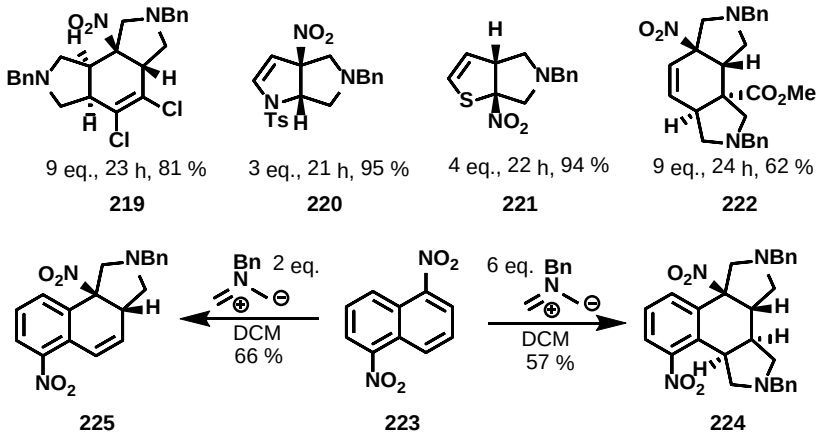
211 212 213

81 % o2s, ee > 99 %

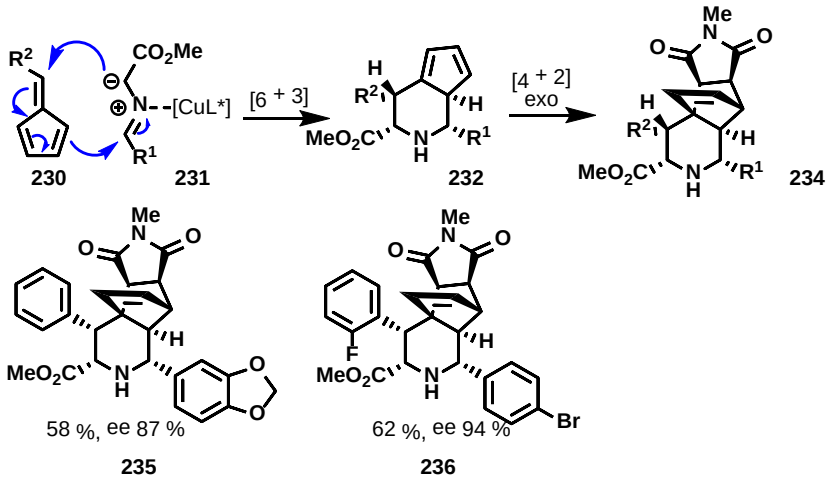
Azomethin Ylides – Dearomatization and [6 +3]-Cycloaddition





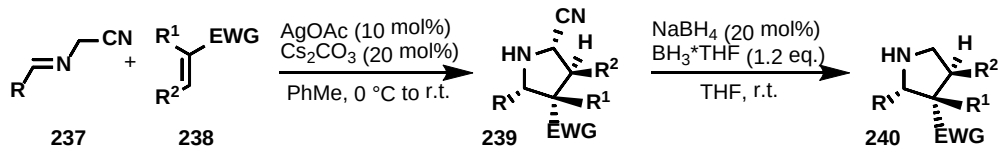


Piettre *et al., Angew. Chem. Int. Ed.* **2011**, 472 – 476.



Waldmann *et al., Angew. Chem. Int. Ed.* **2012**, 9512 – 9516.

Azomethin Ylides – Cyano Group as a traceless activator

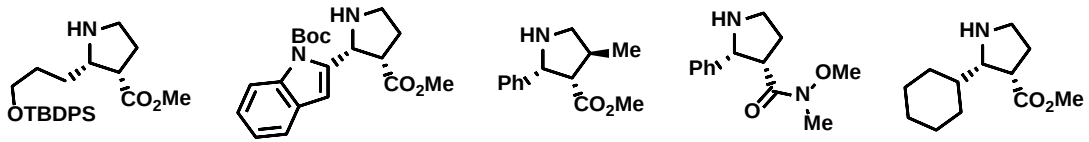


237 238 239 240

25 examples up to 96 % yield [3 + 2] and in gram scale
and up to 94 % yield in decyanation and in gram scale

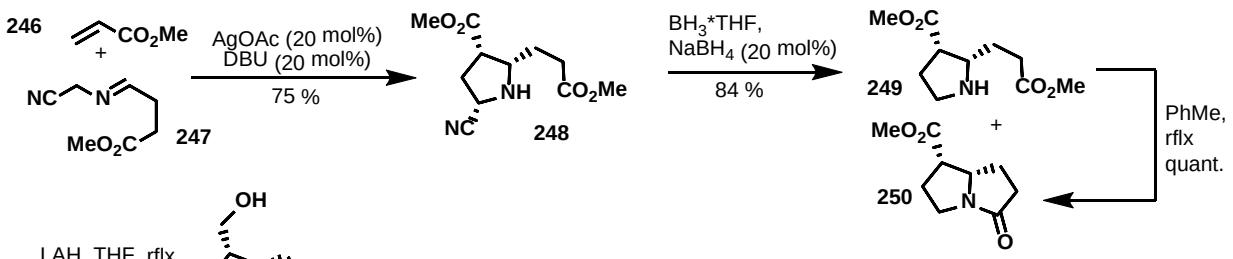
endo/exo 10:1 up to >20:1

R = substituted aryls, heteroaryls, alkyl
R^1 = H, Me
R^2 = H, Me
EWG = CO_2Me, CO_2tBu, CONMeOMe, SO_2Ph



56 % o2s 70 % o2s 52 % o2s 76 % o2s 80 % o2s

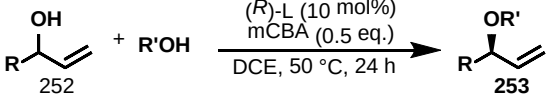
241 242 243 244 245

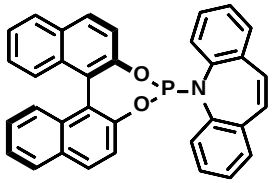


246 247 248 249 250 251

Zhang *et al., Angew. Chem. Int. Ed.* **2015**, 6306 – 6310.

Allylic transformations



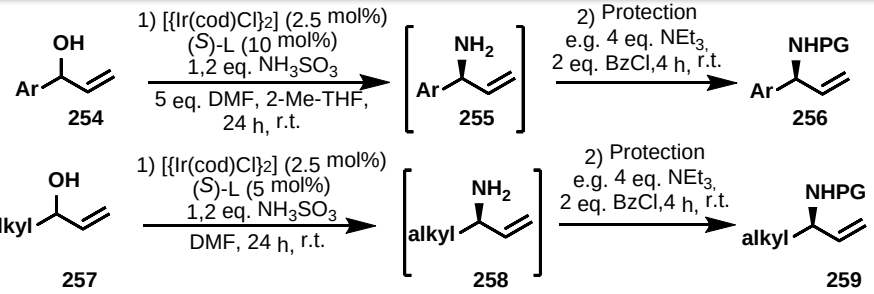


(*R*)-L

16 examples up to quant. yield
63 to 99 % ee

R = (substituted) aryl, heteroaryl, (substituted) alkyl
R' = Me, Et, iPr, PMB, Bn

Carreira and Roggen, *Angew. Chem. Int. Ed.* **2011**, 5568 – 5571.



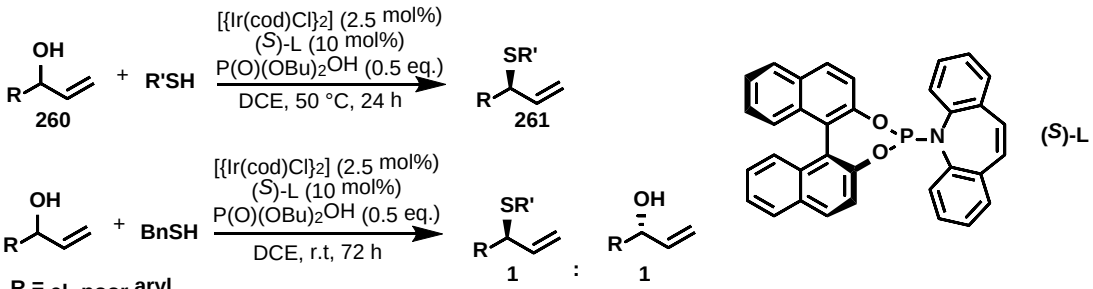
Ar:
20 examples up to 85 % yield
80 to 99 % ee

Ar = (substituted) aryl, heteroaryl
PG = Bz, Ts, Fmoc, NH_3Cl

alkyl:
7 examples up to 87 % yield
68 to 99 % ee

alkyl = (substituted) (cyclo)alkyl
PG = Bz, Ts, Fmoc, NH_3Cl

Carreira *et al.*, *Angew. Chem. Int. Ed.* **2012**, 3470 – 3473.

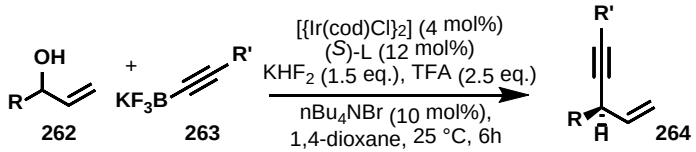


(*S*)-L

12 examples up to 92 % yield
86 to 97 % ee

R = el.-rich (substituted) aryl, heteroaryl
R' = Bn, Ph, PMB, Cy, *p*-HO-C_6H_4

Carreira *et al.*, *Angew. Chem. Int. Ed.* **2012**, 8652 – 8655.

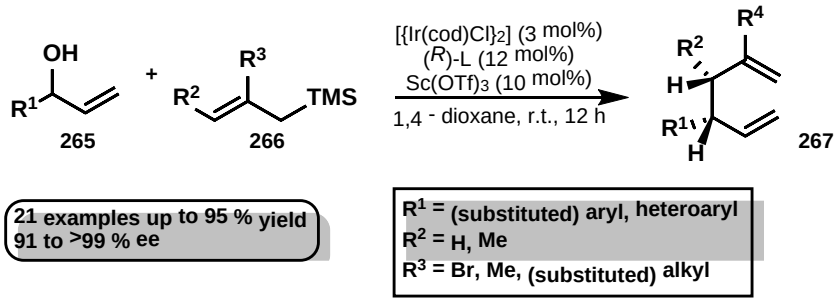


26 examples up to 99 % yield
95 to >99 % ee

R = (substituted) aryl, heteroaryl
R' = aryl, heteroaryl, (cyclo)alkenyl/alkyl

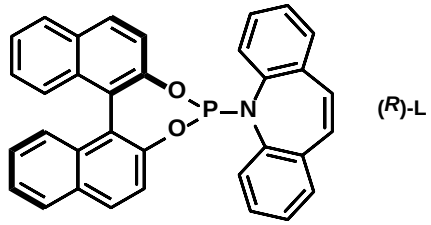
Carreira *et al.*, *Angew. Chem. Int. Ed.* **2013**, 7532 – 7535.

Allylic transformations



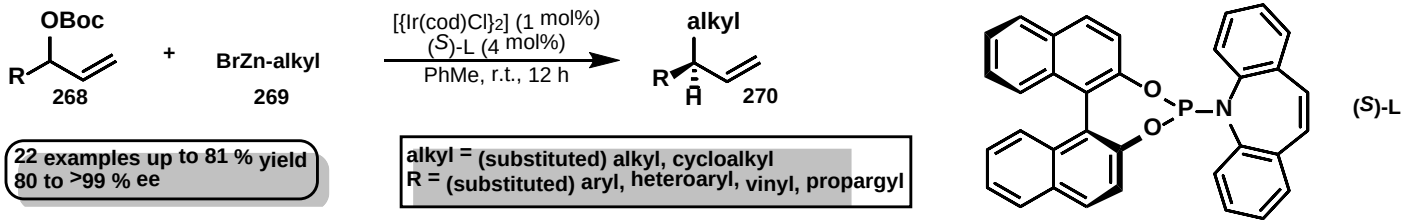
21 examples up to 95 % yield
91 to >99 % ee

R^1 = (substituted) aryl, heteroaryl
R^2 = H, Me
R^3 = Br, Me, (substituted) alkyl



(*R*)-L

Carreira *et al.*, *Angew. Chem. Int. Ed.* **2014**, 10759 – 10762.



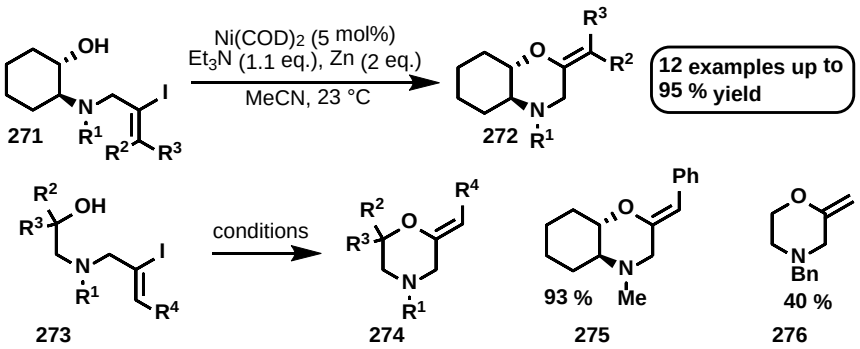
22 examples up to 81 % yield
80 to >99 % ee

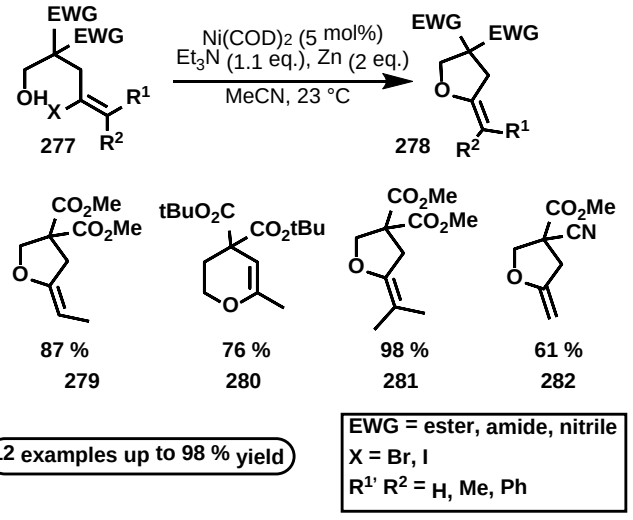
alkyl = (substituted) alkyl, cycloalkyl
R = (substituted) aryl, heteroaryl, vinyl, propargyl

(*S*)-L

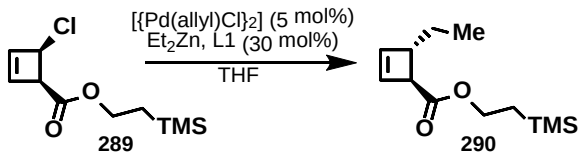
Carreira *et al.*, *Angew. Chem. Int. Ed.* **2015**, 7644 – 7647.

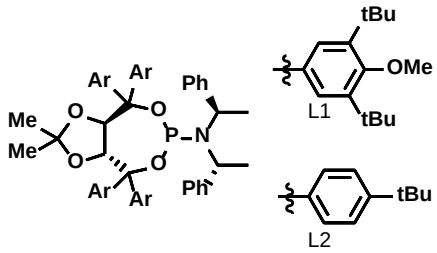
Cross Coupling reactions

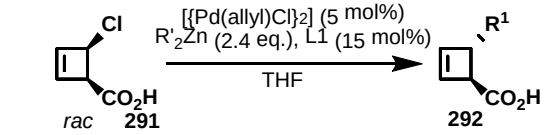


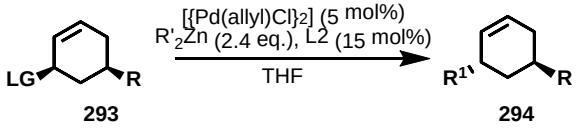


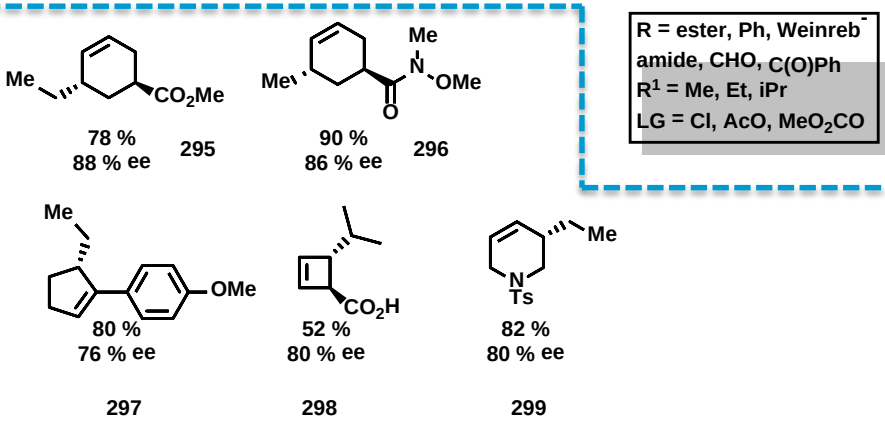
Stoltz *et al., Angew. Chem. Int. Ed.* **2016**, 7437 – 7440.





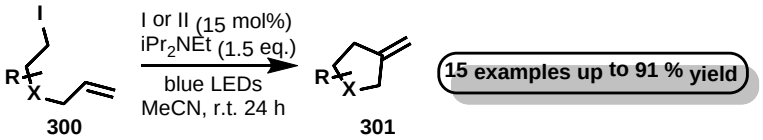


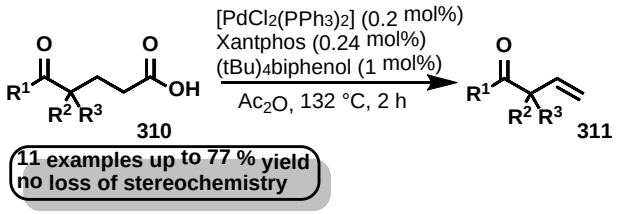


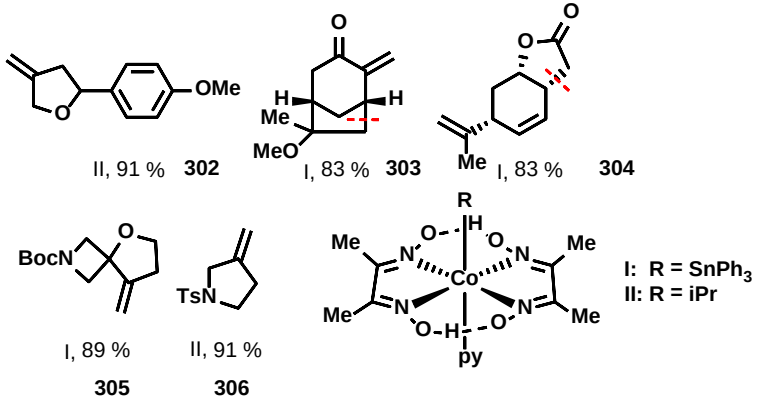


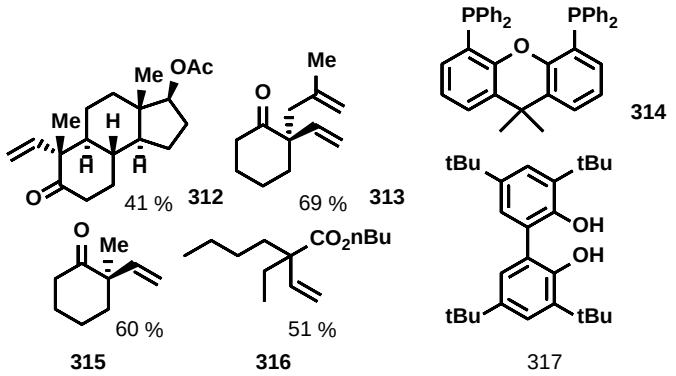
Maulide *et al., Angew. Chem. Int. Ed.* **2014**, 7068 – 7073.

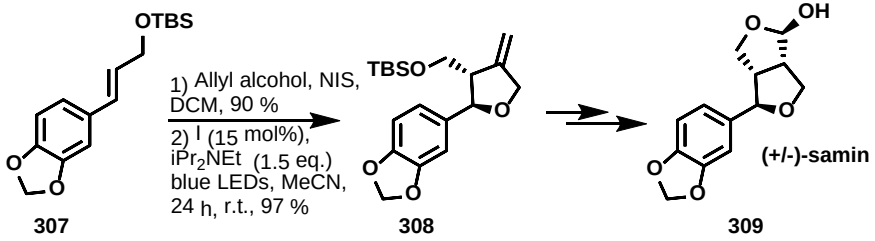
Cross Coupling reactions

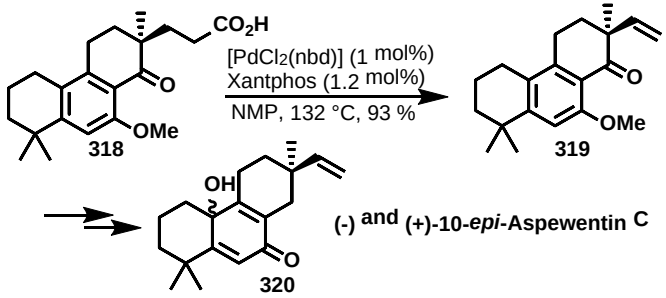








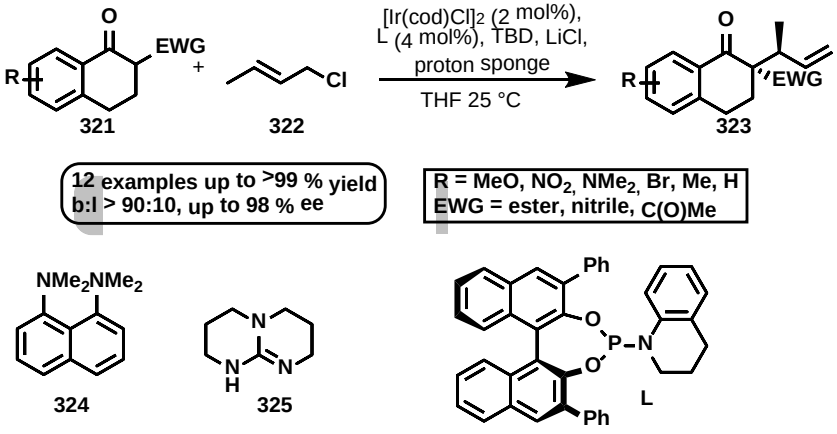


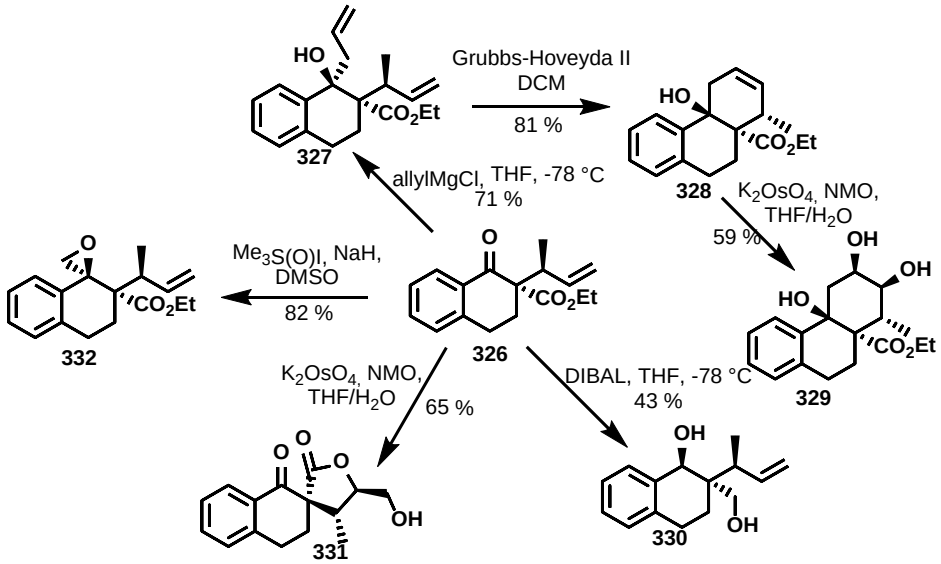


Carreira *et al., Angew. Chem. Int. Ed.* **2011**, 11125 – 11128.

Grubbs, Stoltz *et al., Angew. Chem. Int. Ed.* **2015**, 11800 – 11803.

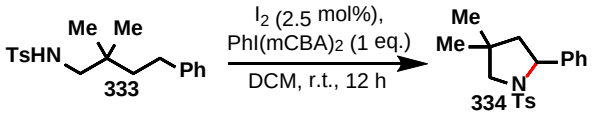
Cross Coupling reactions

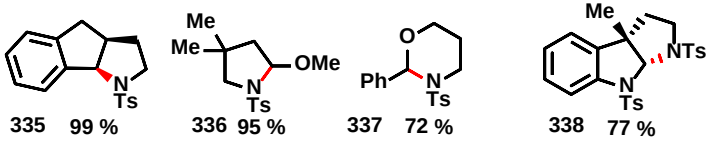


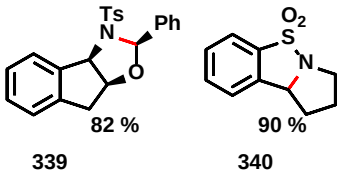


Stoltz *et al., Angew. Chem. Int. Ed.* **2016**, 16092 – 16095.

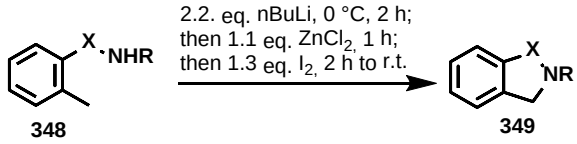
C-H – Oxidation

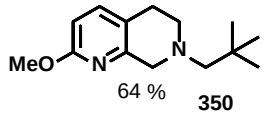






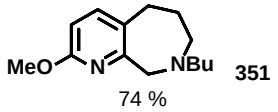
31 examples up to 99 % yield
selectivity >95 %



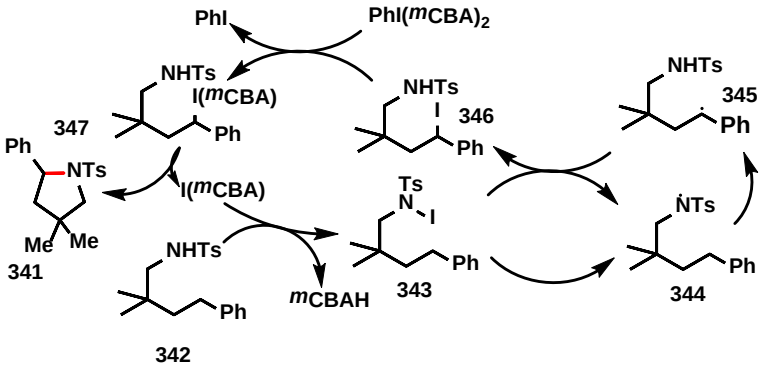


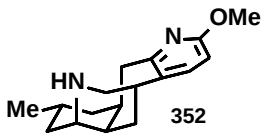
18 examples up to 75 % yield
5-, 6- and 7-membered rings

X = CH_2, C=O
R = (cyclo) alkyl, aryl, amide



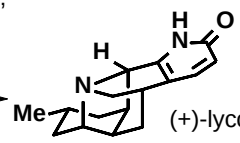
Sarpong *et al., Angew. Chem. Int. Ed.* **2013**, 2194 – 2197.





1) 2 eq. nBuLi;
then 1 eq. I_2
THF, -78 °C
90 %

2) NaSEt
76 %

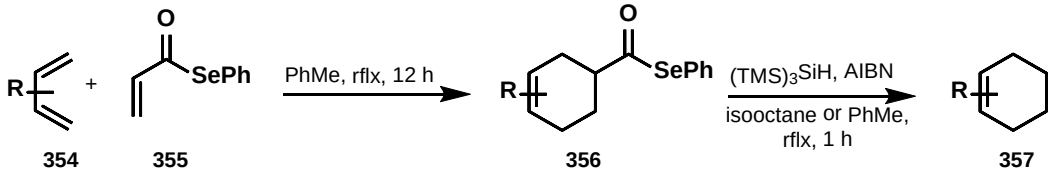


(+)-lyconadin A 353

Muniz and Martínez, *Angew. Chem. Int. Ed.* **2015**, 8287 – 8291.

Sarpong *et al., J. Am. Chem. Soc.* **2009**, 11187 – 11194.

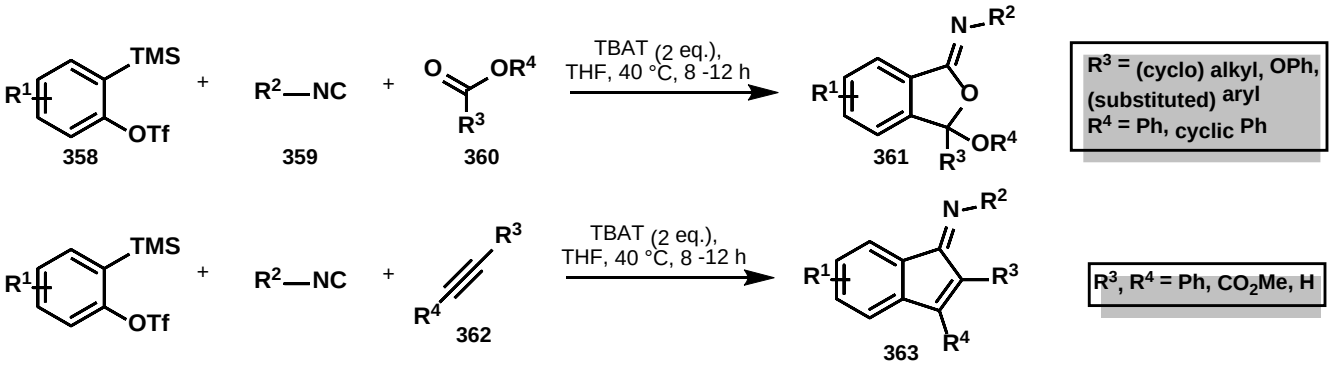
Various Methods



12 examples up to to 97 % yield (Diels-Alder) and up to 99 % yield (reduction)

Phenylselenoacrylate as ethylene equivalent

Jung *et al., Angew. Chem. Int. Ed*. **2013**, 2060 – 2062.

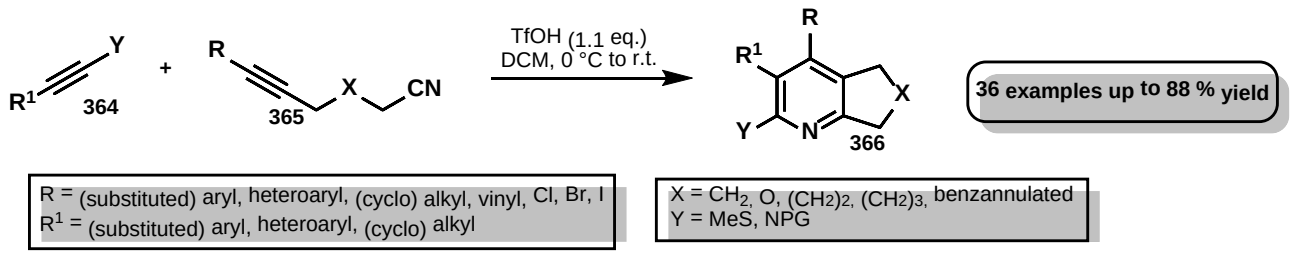


32 examples up to 96 % yield

R1 = (substituted) aryl
R2 = alkyl, (substituted) aryl

Three component aryne reactions

Stoltz *et al., Angew. Chem. Int. Ed*. **2011**, 4488 – 4491.



36 examples up to 88 % yield

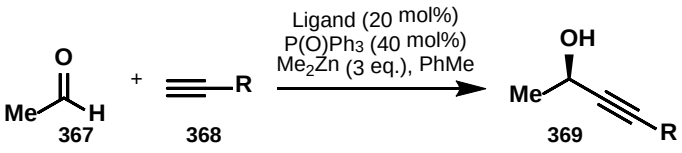
R = (substituted) aryl, heteroaryl, (cyclo) alkyl, vinyl, Cl, Br, I
R1 = (substituted) aryl, heteroaryl, (cyclo) alkyl

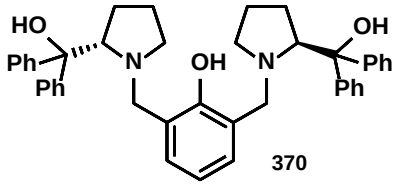
X = CH2, O, (CH2)2, (CH2)3, benzannulated
Y = MeS, NPG

Metal-free formal [2+2+2]-Cycloaddition

Maulide *et al., Angew. Chem. Int. Ed*. **2016**, 12864 – 12867.

Various Methods



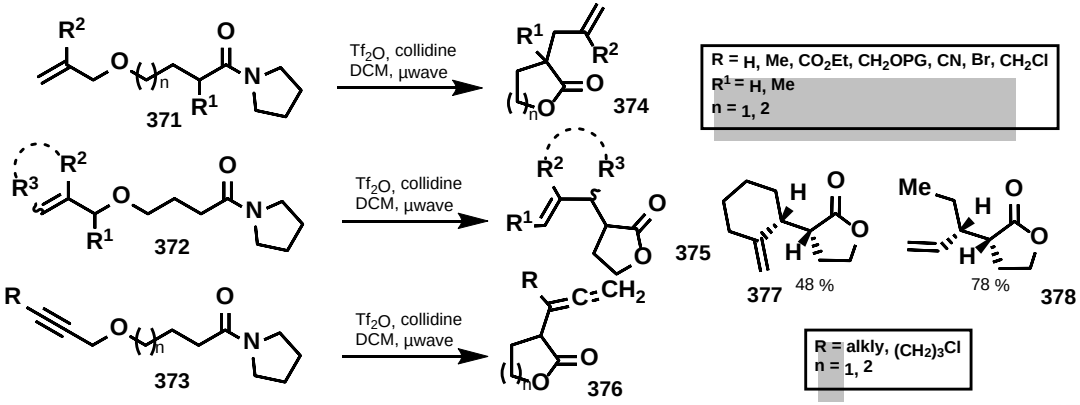


Asymm. alkynylation of acetaldehyde

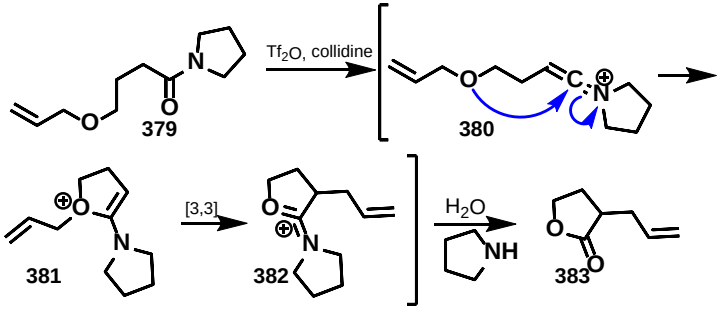
11 examples up to 98 % yield

R = aryl, alkenyl, silyl, alkyl, CO_2Me, highly functionalized residues

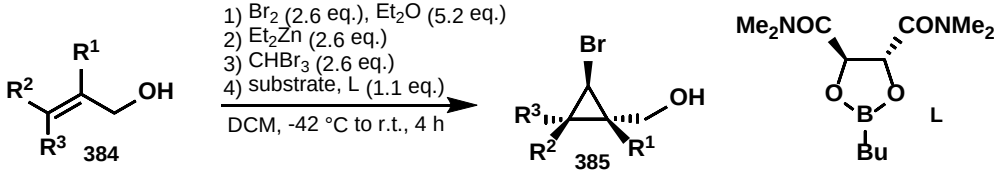
Trost and Quintard, *Angew. Chem. Int. Ed*. **2012**, 6704 – 6708.



20 examples up to 90 % yield



Maulide *et al., Angew. Chem. Int. Ed*. **2010**, 1583 – 1586.



Enantioselective Bromocyclopropanation

15 examples up to 92 % yield
d.r. > 20:1
94 up to 98 % ee

R^1 = H, Me
R^2 = (substituted) aryl, (cyclo) alkyl
R^3 = H, alkyl, (if alkyl low yield)

Charette *et al., Angew. Chem. Int. Ed*. **2015**, 14108 – 14112.