US
School of Life Sciences

Current Methods for the Stereocontrolled Assembly of (Chiral) Heterocycles

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Department of Chemistry,
University of Sussex

UCL, 1st April 2011
SCI, 26th Novembre 2012

Introduction

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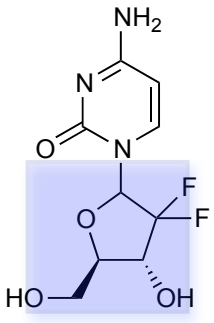
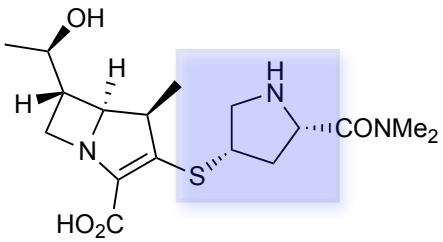
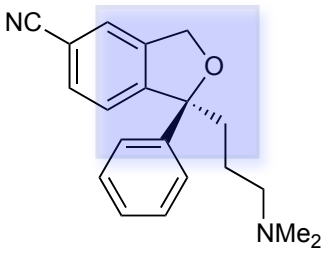
Economic Considerations



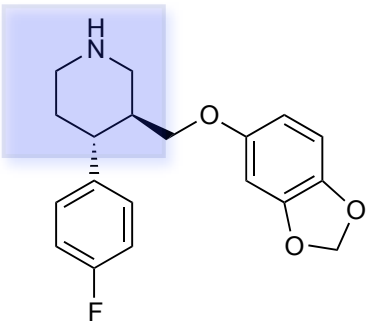
Gemzar (Gemcitabine)
Lilly
$1292 Million
Antimetabolites



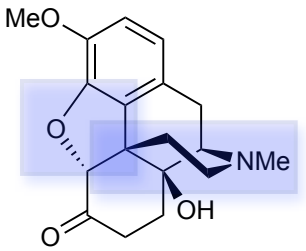
Merrem (Meropenem)
AZ
$772 Million
Antiobiotic



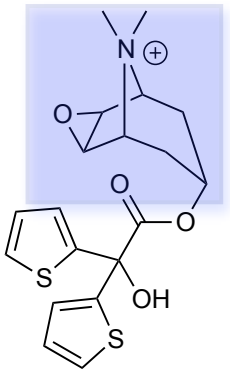
Lexapro (Escitalopram)
Forest Lab.
$2655 Million
Antidepress. & Mood Stab.



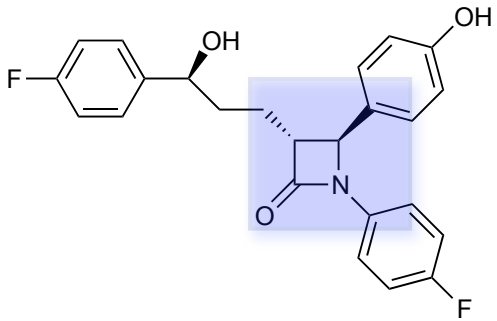
Seroxat (Paroxetine)
GSK
$788 Million
Antidepress. & Mood Stab.



Oxycontin (Oxycodone)
MundiPharma
$3410 Million
Narcotic Analgesics



Spiriva (Tiotropium)
Boehringer Ingelheim
$3499 Million
Anticholinergic + B2-Stim.



Zetia (Ezetimibe)
Merck
$2397 Million
Cholest. & Trigly. Regulator

Source: Top 200 Pharmaceutical Products by Worldwide Sales in 2009, Njardarson Group, Cornell University.

N,O,S,P Structures and Methods

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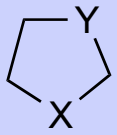
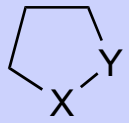
Structural Classification

5-Membered Rings

X = N, O, P, S

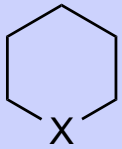


X = N, O, S
Y = N, O, S



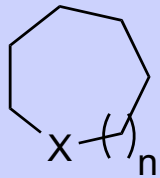
X = N, O, S
Y = N, O, S

6-Membered Rings



X = N, O, P, S

Larger Rings



X = N, O, P, S

Colour Key

Synthetic Example | Catalyst | Suggested mechanism

Structures and Methods

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Current Approaches

Metal-Catalysed Approaches

Organocatalysis

Substrate Control

(Enzymatic Methods)

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Transition Metal Catalysed Approaches

Cycloisomerisations

Transition Metal Catalysed Approaches

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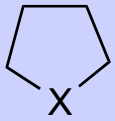
Au(I) and Mn(VII) Mediated Cycloisomerisations

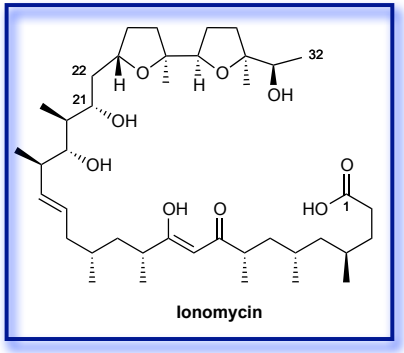
5-Membered Rings



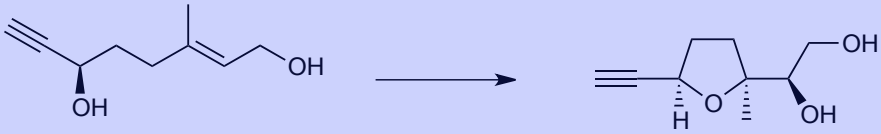
X = N, O, P, S

Chirality:
Substrate control

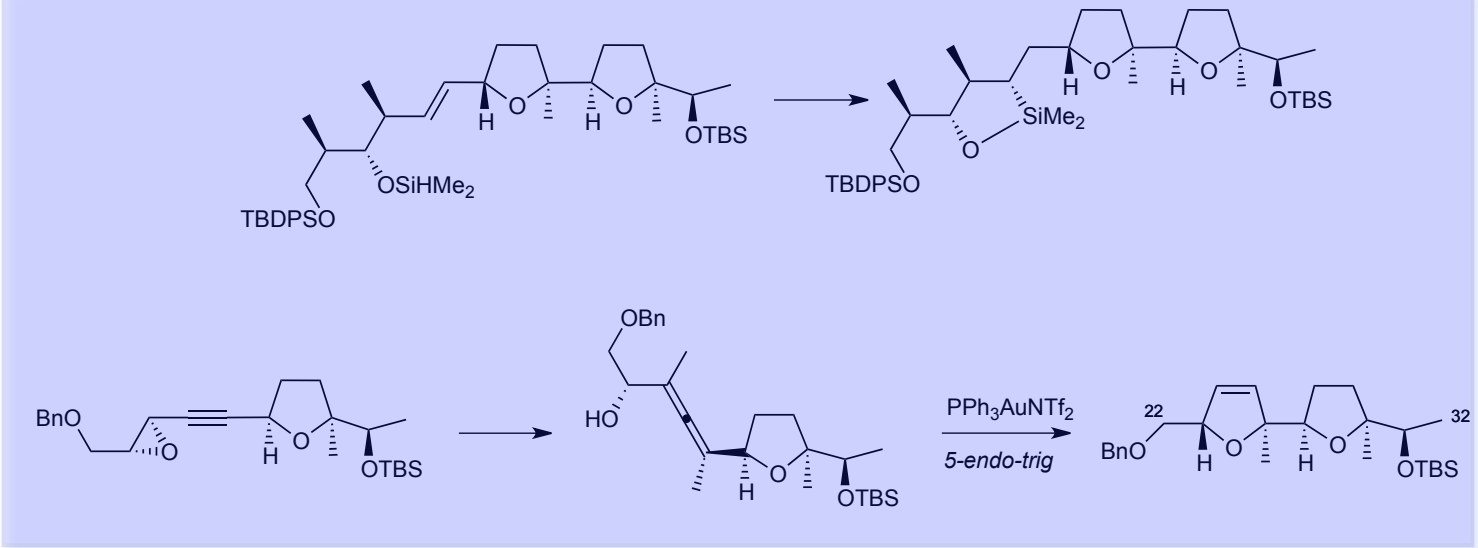
Chirality:
Catalyst control



Sharpless Epoxidation (Ti(IV))



Metal-Catalysed Additions



Z. Gao, Y. Li, E. M. E. Viseux, P. J. Kocienski, *et al.*, *Angew Chem Int Edit*, 2009, **48**, 5022–5025.

Transition Metal Catalysed Approaches

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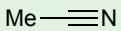
Some Current Chiral Gold Complexes

L - Au - X

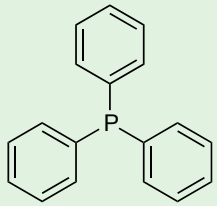
L:

- usually based on P, S, N, carbenes

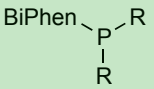
Usón, 1977

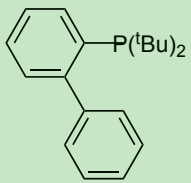


Puddephatt, 1987

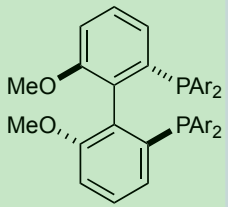


Nichols, 1969





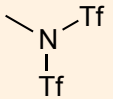
Widenhoefer, 2006



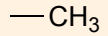
Widenhoefer, 2009

X:

- typically based on halogens, C, N
- can require a co-catalyst (AgX)



Gagosz



$AgOTf$, $AgBF_4$, $AgSbF_6$

Transition Metal Catalysed Approaches

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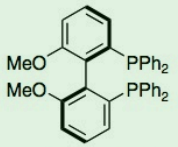
Some Current Chiral Gold Complexes

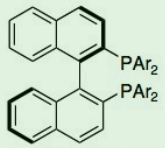
L - Au - X

X

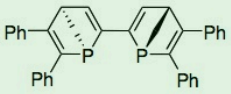
L



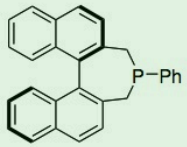
(*R*)-MeOBIPHEP



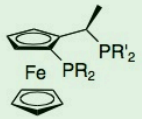
Ar = *p*-Me-C_6H_4, (*R*)-TolBINAP



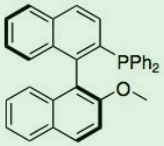
(+)-BIPNOR



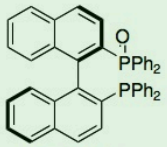
(*R*)-Ph-BINEPINE



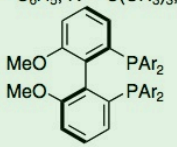
R = C_6H_5, R' = C_6H_{11}, (*R*,*S*)-Josiphos
R = C_6H_5, R' = $C(CH_3)_3$, (*R*,*S*)-PPF-P^tBu_2



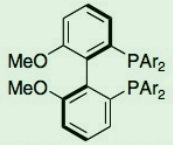
(*S*)-MeO-MOP



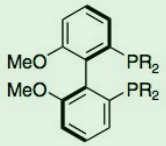
(*R*)-BINAPO



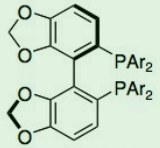
Ar = 4-Me_2N-C_6H_4
(*S*)-(4-NMe_2)-MeOBIPHEP
Ar = 4-Me-C_6H_4
(*S*)-*p*-Tol-MeOBIPHEP



Ar = phenyl, (*R*)-MeOBIPHEP
Ar = furyl, (*R*)-(2-furyl)-MeOBIPHEP
Ar = 3,5-*t*-Bu-4-MeO-C_6H_2, (*R*)-(3,5-*t*-Bu-4-MeO)-MeOBIPHEP
Ar = 3,5-Me-C_6H_3, (*R*)-(3,5-Me)-MeOBIPHEP
Ar = 3,5-*i*Pr-C_6H_3, (*R*)-(3,5-*i*-Pr)-MeOBIPHEP



R = Cy, (*R*)-Cy-MeOBIPHEP
R = *i*Pr, (*R*)-*i*-Pr-MeOBIPHEP



Ar = 3,5-*t*-Bu-4-MeO-C_6H_2,
(*R*)-(3,5-*t*-Bu-4-MeO)-SEGPHOS

C.-M. Chao, E. Genin, P. Y. Toullec, J.-P. Genêt, and V. Michelet, *J Organomet Chem*, 2009, **694**, 538–545.

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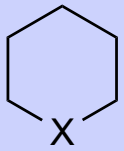
Gold(I) Mediated Cycloisomerisations

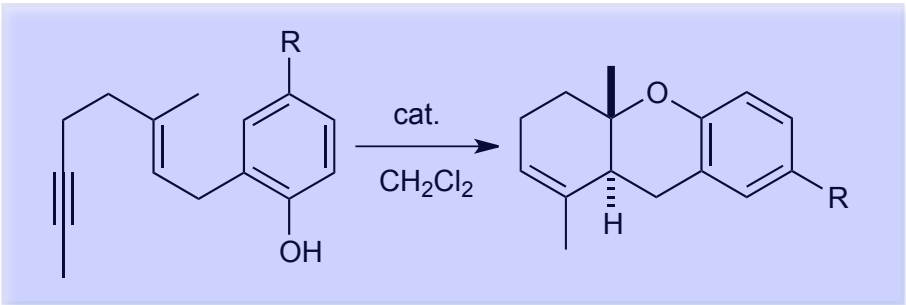
6-Membered Rings



X = N, O, P, S

Chirality:
Catalyst control

- PPh_3AuNTf_2 promotes highly efficient intramolecular phenoxycyclisation reactions on 1,5-enynes under mild conditions.
- The original tricyclic and functionalised heterocycles were isolated in good to excellent yields.
- The 6-*endo* cyclisation process is predominant and operates via a biomimetic cascade cation-olefin process.



P. Y. Toullec, T. Blarre, and V. Michelet, *Org Lett*, 2009, **11**, 2888–2891.

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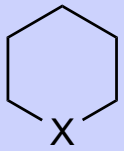
Gold(I) Mediated Cycloisomerisations

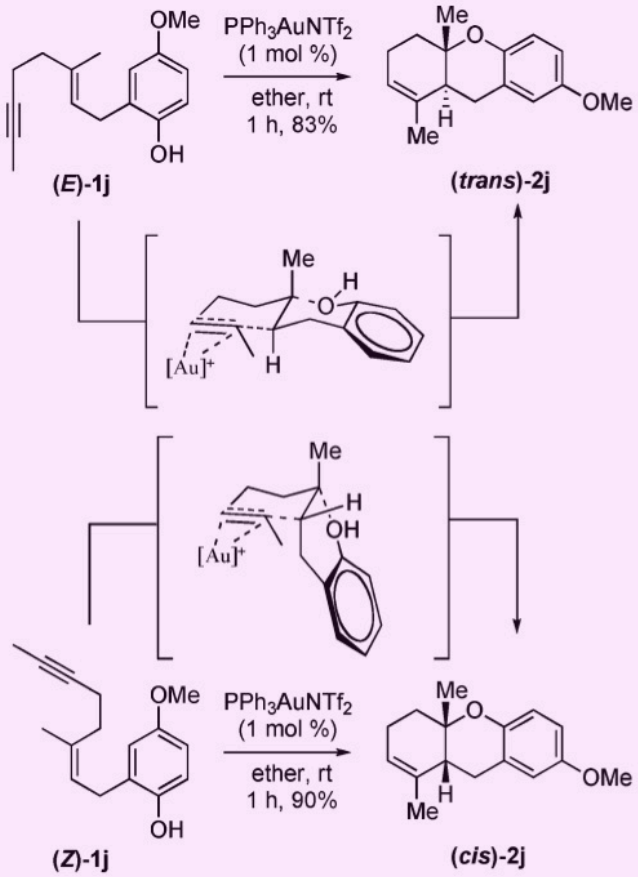
6-Membered Rings



X = N, O, P, S

Diastereoselectivity:
Substrate control

Suggested mechanism



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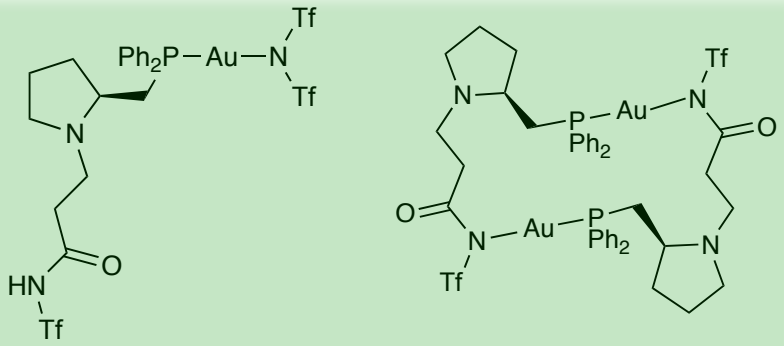
Gold(I) Mediated Cycloisomerisations

6-Membered Rings

X = N, O, P, S

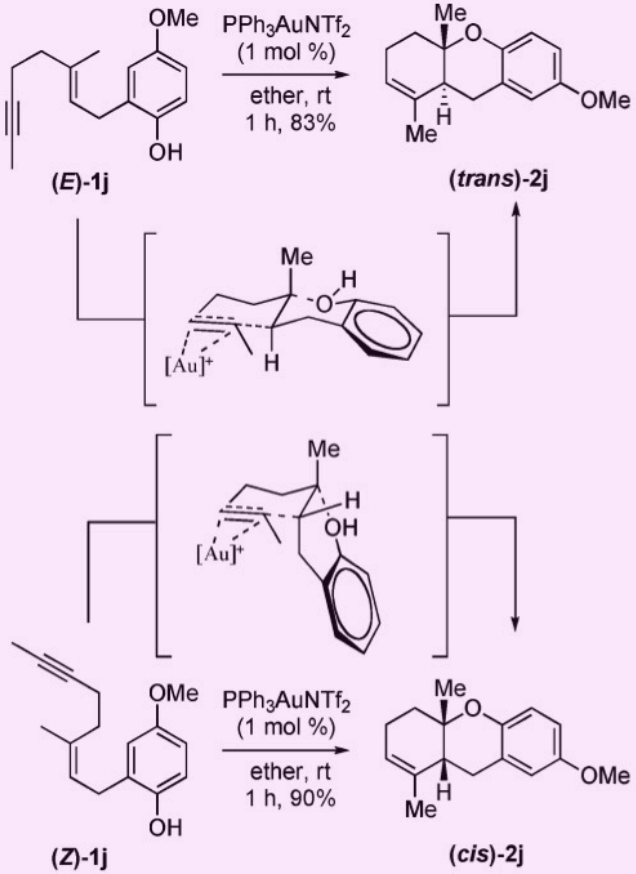
Diastereoselectivity:
Substrate control

Chirality:
Catalyst control



M. Bobin, E. M. E. Viseux, *Manuscript in preparation* **2012**.

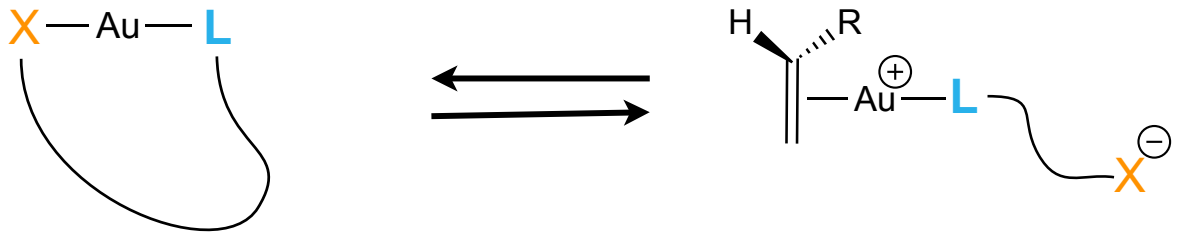
Suggested mechanism

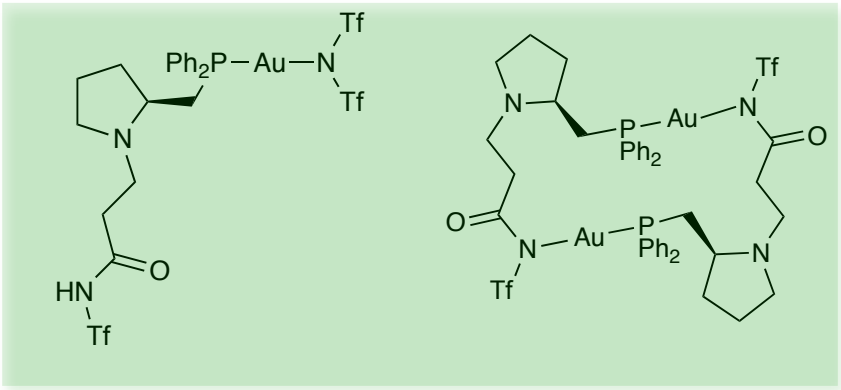


P. Y. Toullec, T. Blarre, and V. Michelet, *Org Lett*, 2009, **11**, 2888–2891.

Bidentate Ligands: Food for Thoughts

- influence the dissociation of X- as an initial step in the reaction.





M. Bobin, E. M. E. Viseux, *Manuscript in preparation* **2012**.

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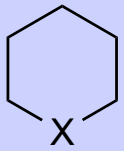
Access to Fused Pyrans / Chromene

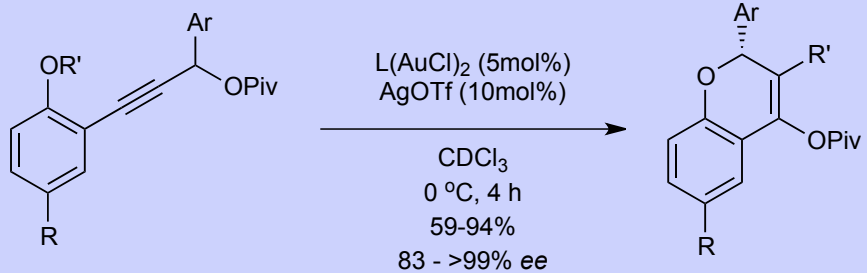
6-Membered Rings

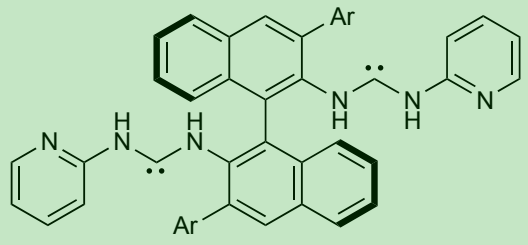


X = N, O, P, S

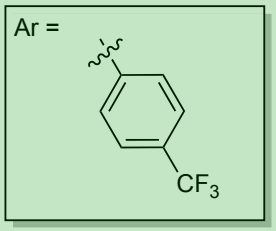
Chirality:
Catalyst control

- Highly enantioselective transformation catalyzed by chiral gold(I) complexes.
- 2-substituted chromenyl pivalates from racemic phenol-substituted propargyl pivalates.





L



Y.-M. Wang, C. N. Kuzniewski, V. Rauniyar, C. Hoong, and F. D. Toste, *J Am Chem Soc*, 2011, **133**, 12972–12975.

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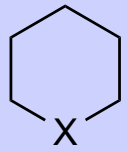
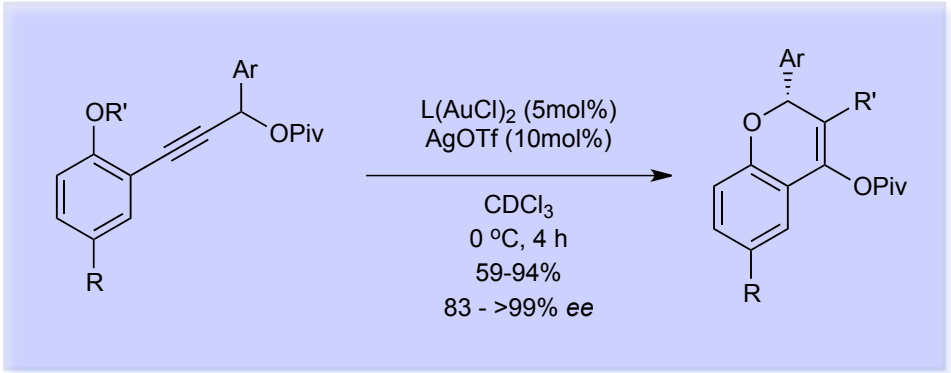
Access to Fused Pyrans / Chromene

6-Membered Rings



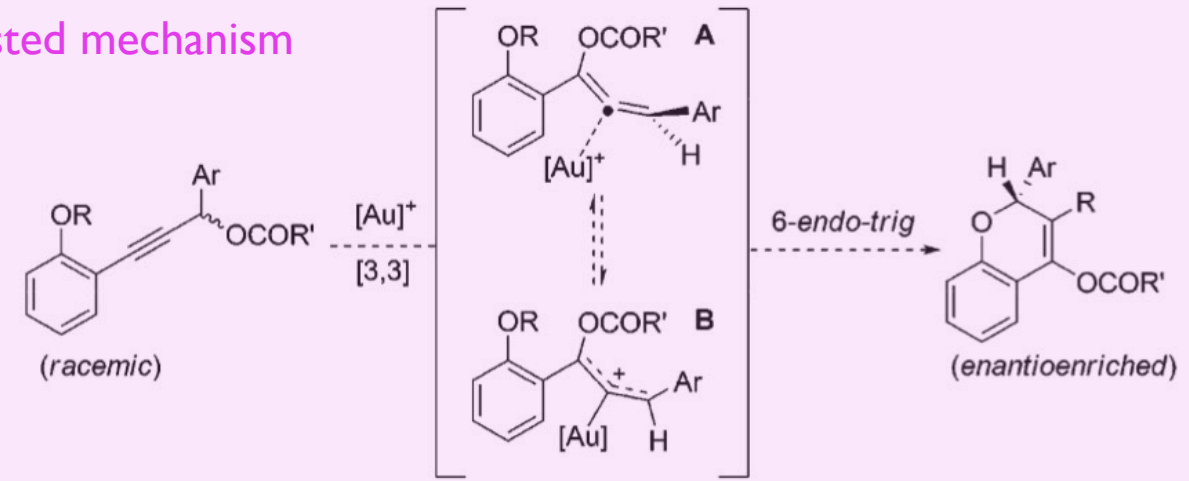
X = N, O, P, S

Chirality:
Catalyst control



- Rearrangement in the presence of cationic gold to give allene intermediates,
- Followed by cyclisation through a dynamic kinetic asymmetric transformation.

Suggested mechanism



Y.-M. Wang, C. N. Kuzniewski, V. Rauniyar, C. Hoong, and F. D. Toste, *J Am Chem Soc*, 2011, **133**, 12972–12975.

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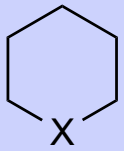
Access to Fused Pyrans / Chromene

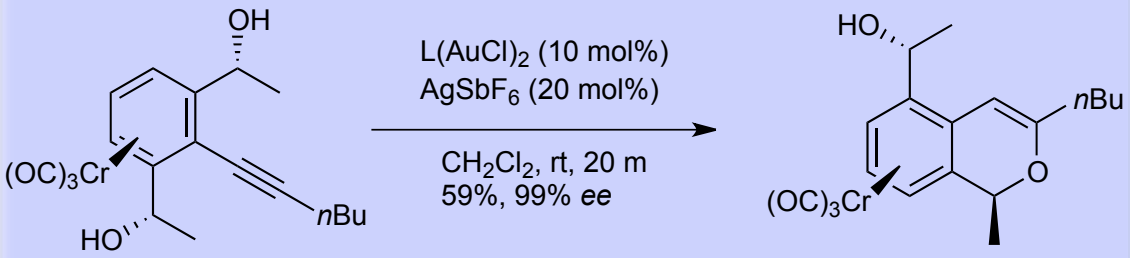
6-Membered Rings

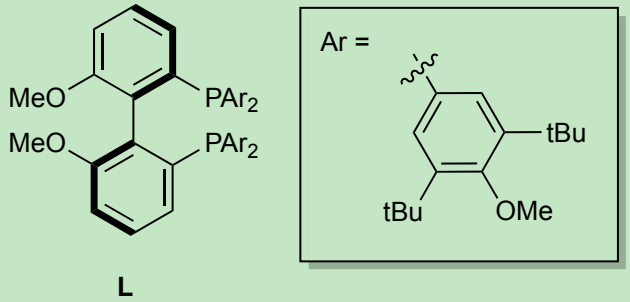


X = N, O, P, S

Chirality:
Catalyst control

- Gold(I)-catalysed asymmetric cyclisation of dihydroxymethylalkynylbenzene chromium complexes to give planar chiral isochromene chromium complexes.
- High enantioselectivity. Ees largely affected by a combination of axially chiral diphosphine$(AuCl)_2$ precatalysts and silver salts.
- A system of segphos$(AuCl)_2$ with $AgBF_4$ resulted in the formation of the corresponding antipode.





M. Murai, J. Uenishi, and M. Uemura, *Org Lett*, 2010, **12**, 4788–4791.

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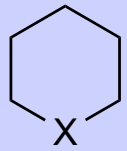
Access to Fused Oxazine

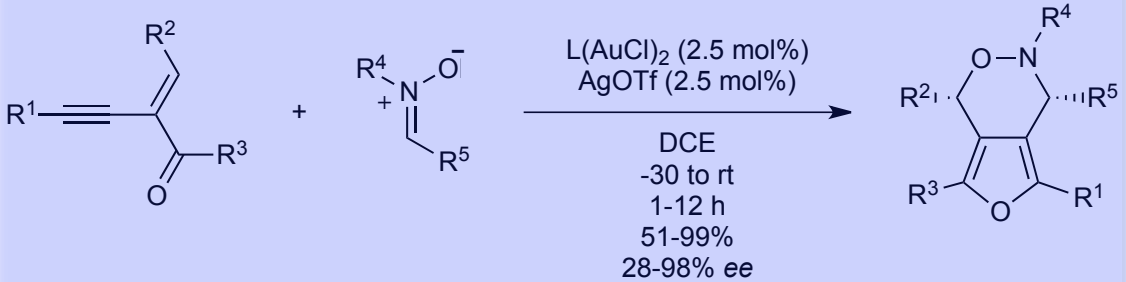
6-Membered Rings

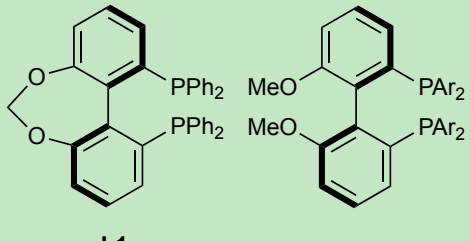


X = N, O, P, S

Chirality:
Catalyst control

- Gold(I)-catalysed diastereo- and enantioselective intermolecular tandem cyclisation/[3+3]-cycloaddition reaction of enynones with nitrones.
- First report using C_n-tunephos/$(AuCl)_2$ as a chiral catalyst in asymmetric gold-catalysed reactions.





F. Liu, D. Qian, L. Li, X. Zhao, and J. Zhang, *Angew Chem Int Edit*, 2010, **49**, 6669–6672.

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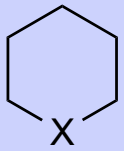
6-Membered Rings



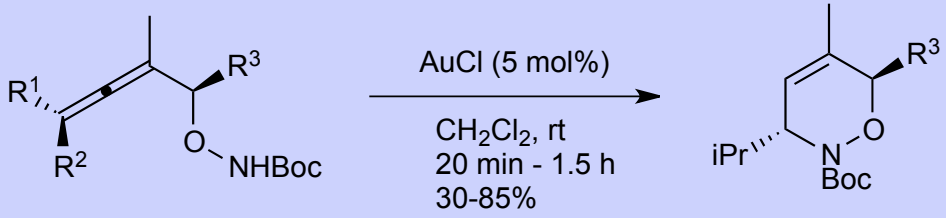
X = N, O, P, S

Chirality:
Substrate control

Gold(I) Mediated Cycloisomerisations

- Use of a *tert*-butoxy carbamate (as opposed to the unprotected hydroxylamine ether) leads to a regio- and stereoselective formation of the Boc-protected dihydrooxazine.

- $AuCl_3$ gave only incomplete conversion, and cationic gold complexes induces decomposition of the substrate.



C. Winter and N. Krause, *Angew Chem Int Edit*, 2009, **48**, 6339–6342.

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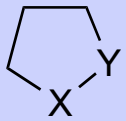
Gold(I) Mediated Cycloisomerisations

5-Membered Rings

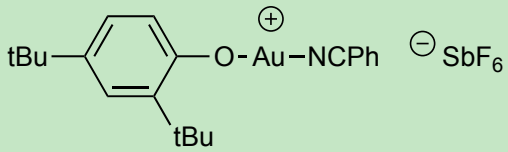
X = N, O, P, S

5-Membered Rings



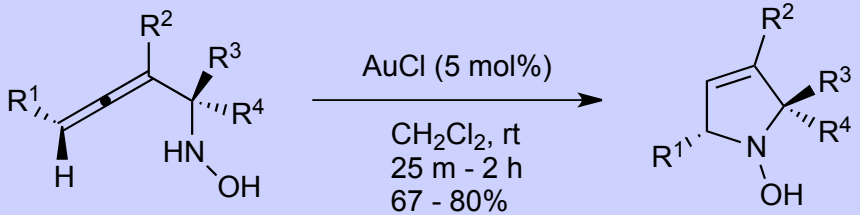
X = N, O, S
Y = N, O, S

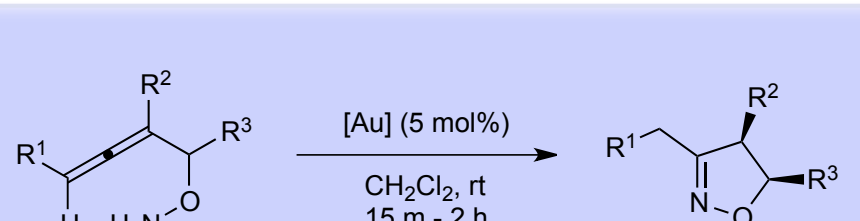
Chirality:
Substrate control



• Gold-catalysed *endo* cycloisomerisation of alpha-hydroxyallenes is usually faster than that of the corresponding aminoallenes (possibly due to the deactivation of the gold catalyst by the Lewis basic amine).

• *Endo* cyclisation of alpha-functionalised allenes to five-membered heterocycles is normally faster than the formation of dihydropyrans or dihydropyridines from ß-functionalised allenes.





C. Winter and N. Krause, *Angew Chem Int Edit*, 2009, **48**, 6339–6342.

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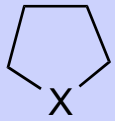
Gold(I) Mediated Cycloisomerisations

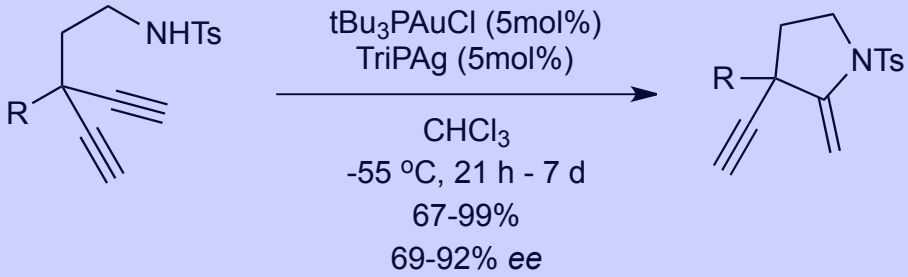
5-Membered Rings

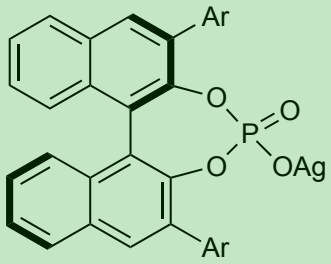


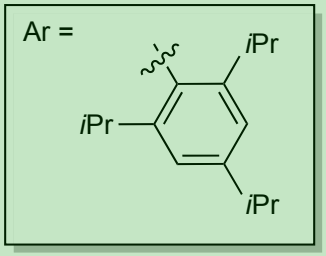
X = N, O, P, S

Chirality:
Catalyst control

- Enantioselective cycloisomerisation of diynamides.
- First example of a highly stereoselective desymmetrization of terminal alkynes by gold catalysts with chiral counteranions.







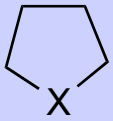
A. K. Mourad, J. Leutzow, and C. Czekelius, *Angew Chem Int Edit*, 2012, **51**, 11149–11152.

N Transition Metal Catalysed Approaches

University of Sussex

Gold(I) Mediated Cycloisomerisations

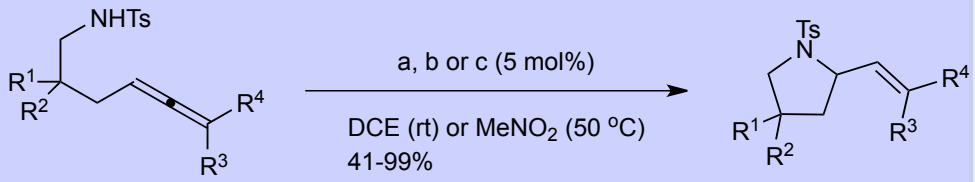
5-Membered Rings



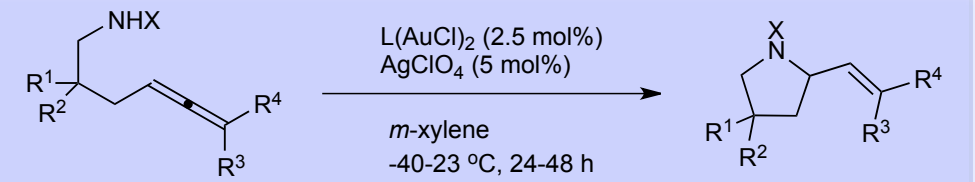
X = N, O, P, S

Chirality:
Catalyst control

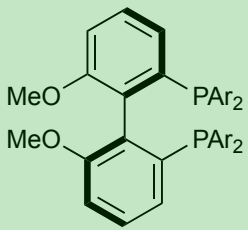
- Enantioselective hydroamination of N-allenyl carbamates.
- Carbamate and carboxamide nucleophiles.
- Tolerates disubstitution at the terminal allenyl carbon atom.
- Sensitive to substitution on the alkyl chain that tethers the carbamate group to the allenyl moiety.



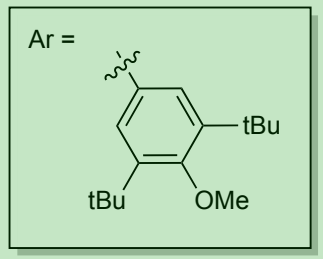
a) (*R*)-xylyl-BINAP(AuOPNB)$_2$
b) (*R*)-SEGPHOS(AuOPNB)$_2$
c) (*R*)-ClMeOBiPHEP(AuOPNB)$_2$



X = Fmoc, Troc, Cbz, CO_2Me, COMe
R^1, R^2 = Ph, H, cyclohexyl
R^3, R^4 = Alkyl, H, cyclohexyl



L



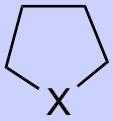
Z. Zhang, C. F. Bender, and R. A. Widenhoefer, *Org Lett*, 2007, **9**, 2887–2889.

N Transition Metal Catalysed Approaches

University of Sussex

Gold(I) Mediated Cycloisomerisations

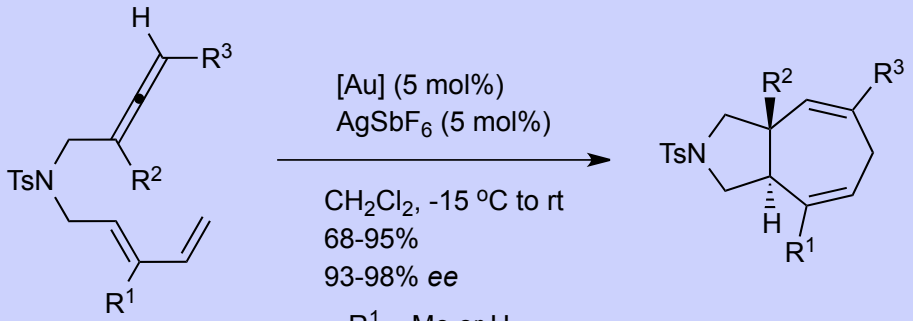
5-Membered Rings



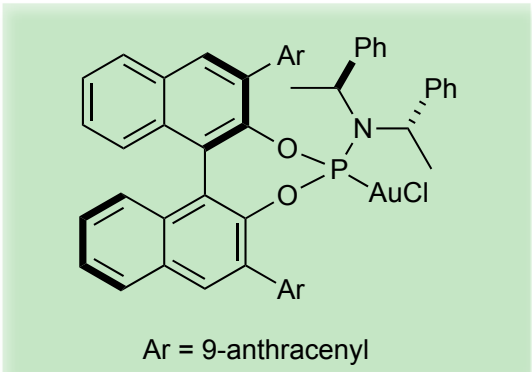
X = N, O, P, S

Chirality:
Catalyst control

- First examples of a catalytic and highly enantioselective intramolecular (4C +3C) cycloaddition reaction.
- Access to bicyclo[5.3.0]decadiene and bicyclo[5.4.0]undecadiene skeletons with good yields, complete diastereocontrol and excellent enantioselectivities.
- Electron-donating ortho-methoxy substituent on the aryl group of the allene gives higher yields.
- In contrast, electron-withdrawing substituents on the aromatic ring, such as a para-trifluoromethyl group, are not tolerated, thus leading to complete recovery of the starting material.



R^1 = Me or H
R^2 = Me or H
R^3 = aryl or alkyl



Ar = 9-anthracenyl

1. I. Alonso, B. Trillo, F. Lopez, S. Montserrat, G. Ujaque, L. Castedo, A. Lledos, and J. L. Mascarenas, *J Am Chem Soc*, 2009, **131**, 13020–13030.
2. I. Alonso, H. Faustino, F. Lopez, and J. L. Mascarenas, *Angew Chem Int Edit*, 2011, **50**, 11496–11500.

University of Sussex

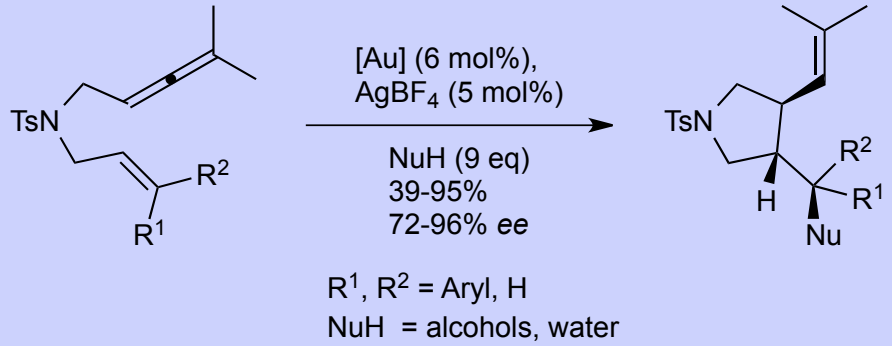
Gold(I) Mediated Cycloisomerisations

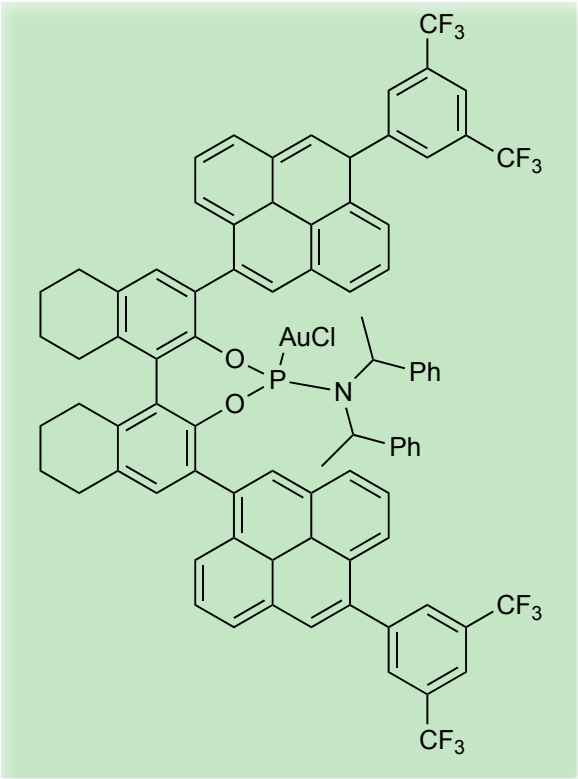
5-Membered Rings

X = N, O, P, S

Chirality:
Catalyst control

- Use of phosphoramidite ligands in enantioselective Au(I) catalysis was explored for the cycloadditions of allenenes.
- Access to 3,4-disubstituted pyrrolidines and γ-lactams.
- Formation of an intermediary carbocationic intermediate that is trapped by an exogenous nucleophile.
- Highly diastereoselective formation of three contiguous stereogenic centers.





A. Z. González, D. Benitez, E. Tkatchouk, W. A. Goddard III, and F. D. Toste, *J Am Chem Soc*, 2011, **133**, 5500–5507.

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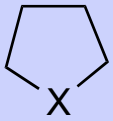
Gold(I) Mediated Cycloisomerisations

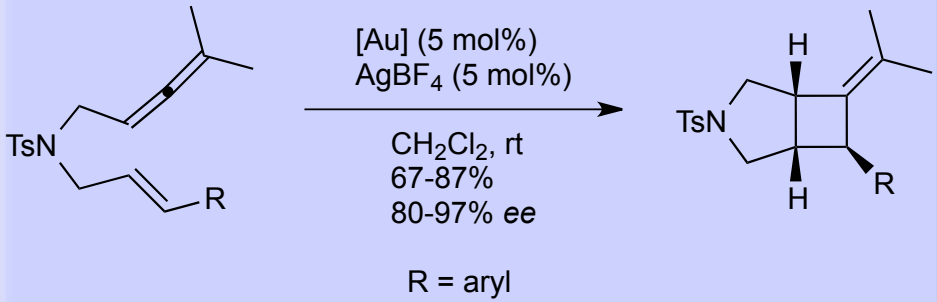
5-Membered Rings

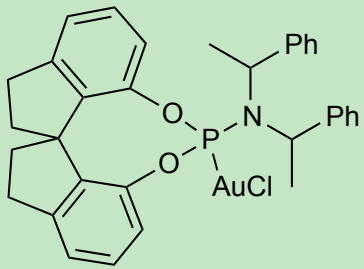


X = N, O, P, S

Chirality:
Catalyst control

- [2+2]-Cycloadditions of allenenes.
- Electron-withdrawing and -donating substituents as well as distinct substitution patterns on the arene moiety are well tolerated.





A. Z. González, D. Benitez, E. Tkatchouk, W. A. Goddard III, and F. D. Toste, *J Am Chem Soc*, 2011, **133**, 5500–5507.

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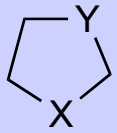
5-Membered Rings

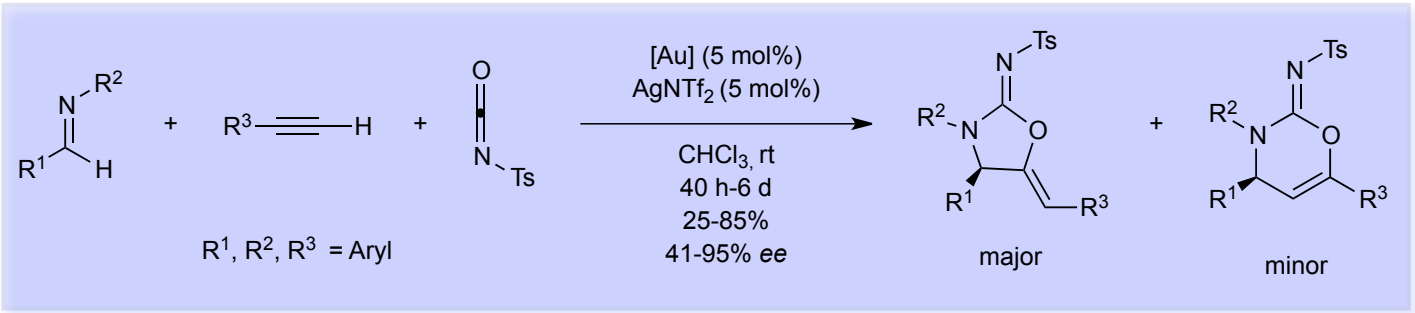


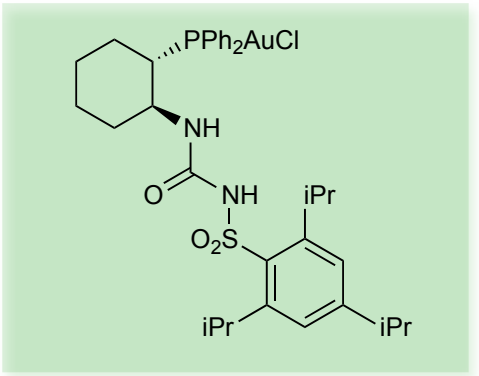
X = N, O, S
Y = N, O, S

Chirality:
Catalyst control

Gold(I) Mediated Cycloisomerisations

- Traditional biaryl bisphosphine ligands: not competent in the cyclisation step.
- Toste resorted to *trans*-1-diaryl-phosphino-2-aminocycloalkanes.
- Cyclic five-membered carbamimidates obtained in moderate to high regio- and enantioselectivities.





M. J. Campbell and F. D. Toste, *Chem. Sci.*, 2011, **2**, 1369.

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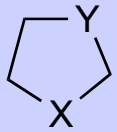
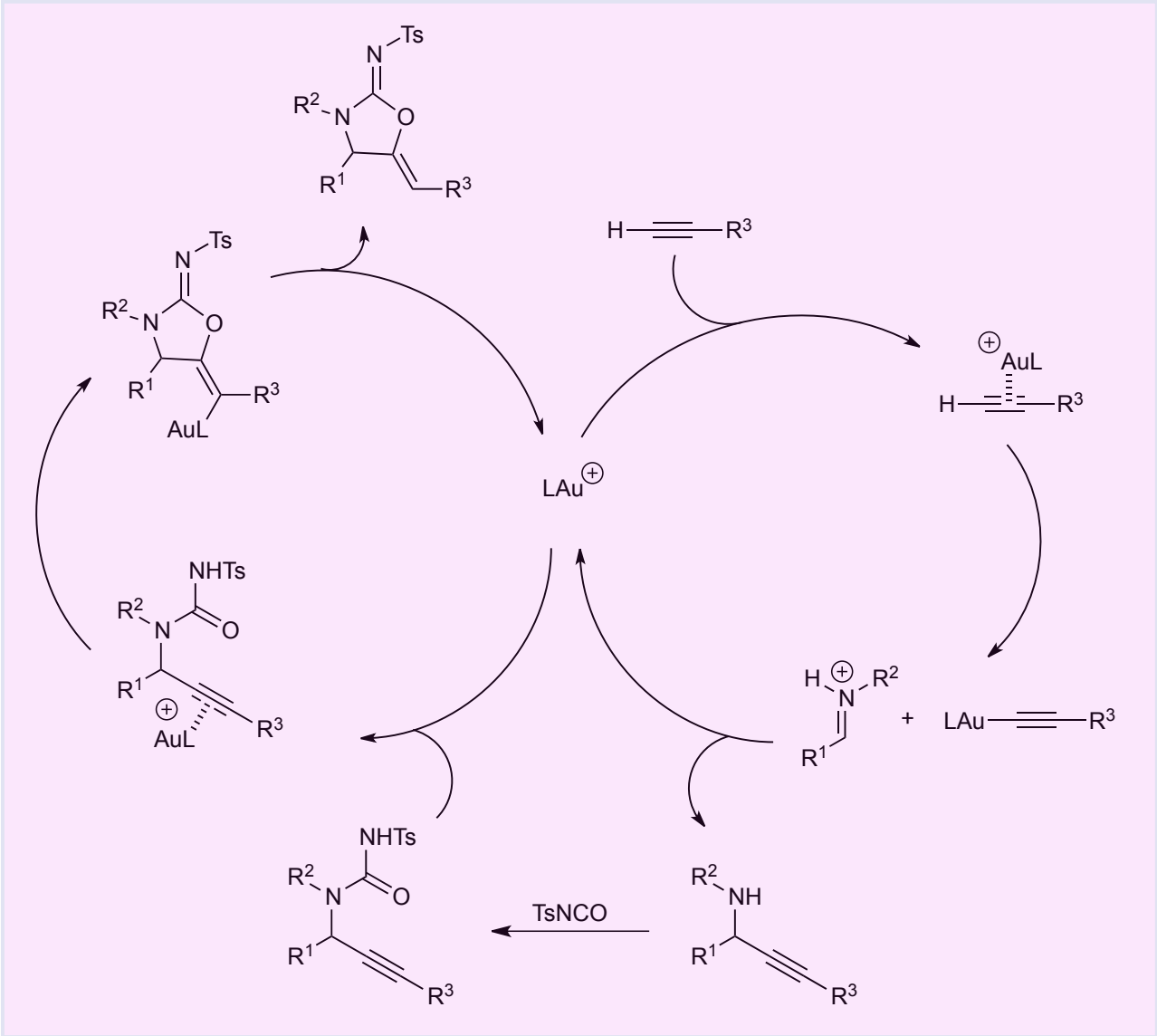
5-Membered Rings



X = N, O, S
Y = N, O, S

Chirality:
Catalyst control

Gold(I) Mediated Cycloisomerisations



M. J. Campbell and F. D. Toste, *Chem. Sci.*, 2011, **2**, 1369.

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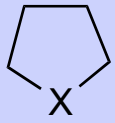
Gold(I) Mediated Cycloisomerisations

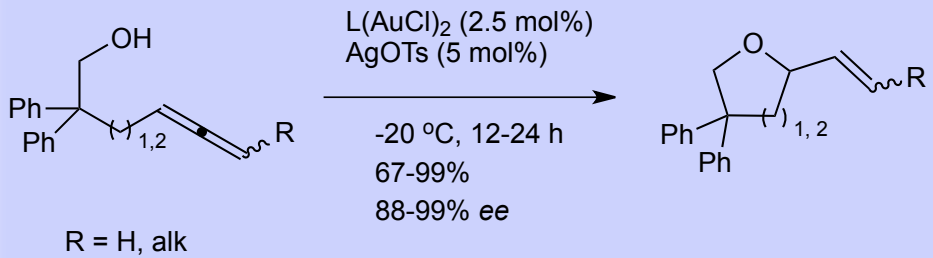
5-Membered Rings



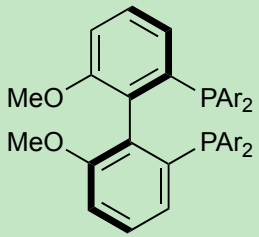
X = N, O, P, S

Chirality:
Catalyst control

- Enantioselective cycloisomerisation of racemic allenols.
- Use of a digold complex inspired by Echavarren.
- Non-polar solvents provides higher enantioselectivities than polar solvents.



R = H, alk



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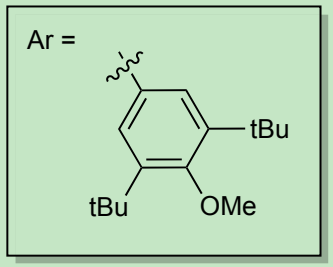

Z. Zhang and R. A. Widenhoefer, *Angew. Chem. Int. Ed. Engl.*, 2007, **46**, 283–285.

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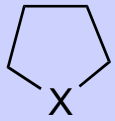
Gold(I) Mediated Cycloisomerisations

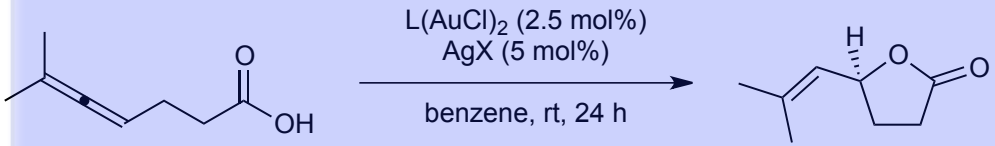
5-Membered Rings



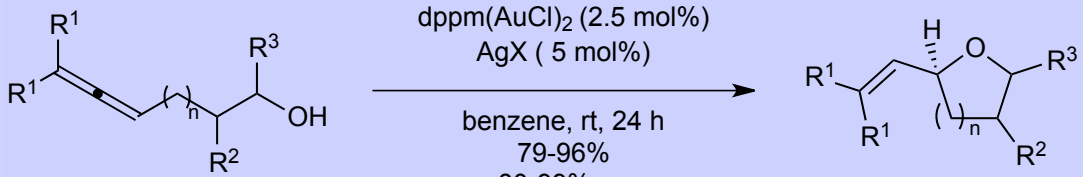
X = N, O, P, S

Chirality:
Catalyst control

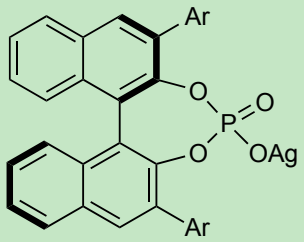
- Cationic gold(I) complexes generated products in 90 to 99% enantiomeric excess with the use of chiral binaphthol–derived phosphate anions.
- Chiral counterion can be combined additively with chiral ligands to enable an asymmetric transformation that cannot be achieved by either method alone.
- Very dependent on solvent (polar solvents yield lower ee).

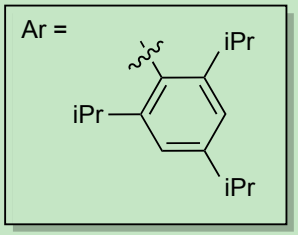


L = (*R*)-BINAP, X = (*R*), 91%, 3% *ee*
L = (*S*)-BINAP, X = (*R*), 88%, 82% *ee*



R^1= -$(CH_2)_4$-, Me, Et
R^2 = H or Me
R^3 = Ph, Me or H





G. L. Hamilton, E. J. Kang, M. Mba, and F. D. Toste, *Science*, 2007, **317**, 496–499.

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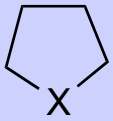
5-Membered Rings

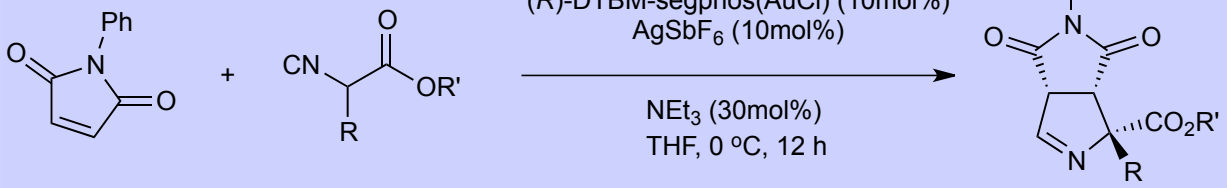


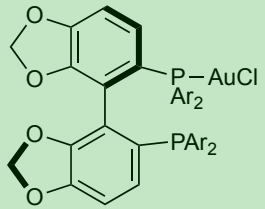
X = N, O, P, S

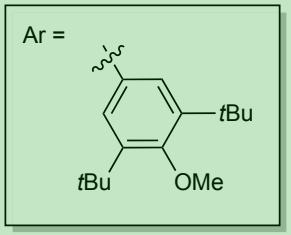
Chirality:
Catalyst control

Gold(I) Mediated Cycloisomerisations

- Formal [3 + 2] cycloaddition of isocyanoacetates with phenylmaleimide.
- Cationic Au(I)/DTBM-segphos complex.
- Excellent diastereoselectivity and high levels of enantioselectivity (up to 97% ee).
- Access to highly substituted pyrrolidines bearing a quaternary stereocentre.







S. Padilla, J. Adrio, and J. C. Carretero, *J Org Chem*, 2012, **77**, 4161–4166.

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Transition Metal Catalysed Approaches

Asymmetric Metathesis: Mo and Ru

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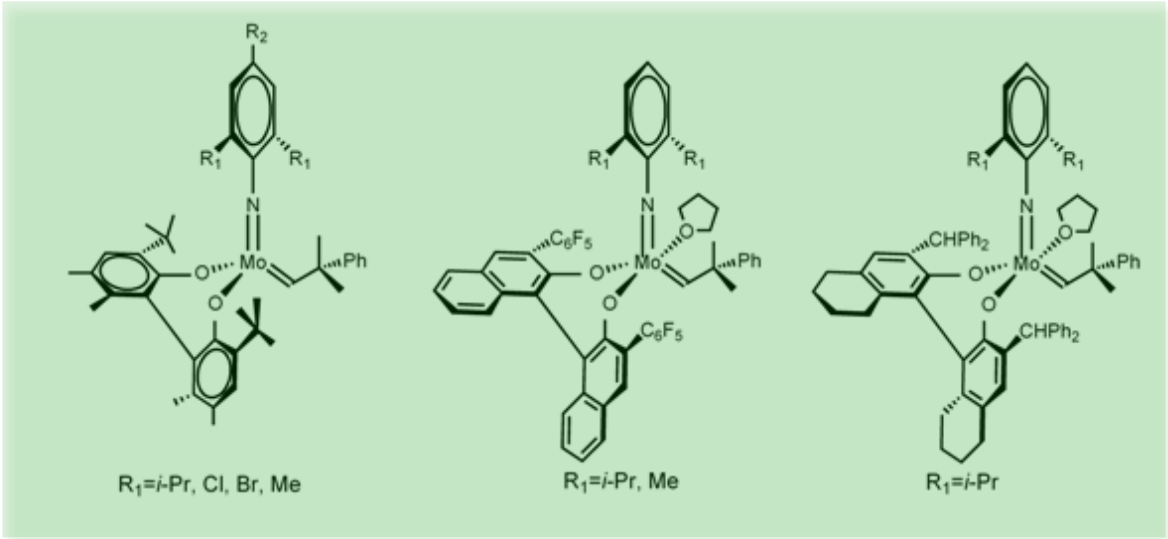
Asymmetric Metathesis: Mo and Ru

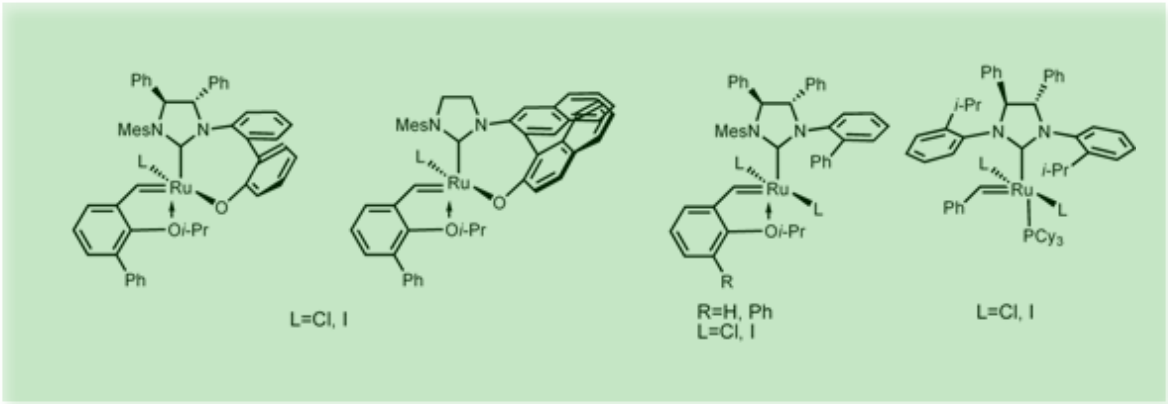
Chirality:
Catalyst control

- First asymmetric Mo-based metathesis by Grubbs.
(JACS, 1996, 2499)

- Mo-based usually best for RCM.
(OL, 2007, 2871)

Problems: lack extensive tolerance of functional groups and require rigorous exclusion of air and moisture.





Source: http://allthingsmetathesis.com/

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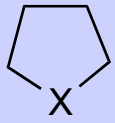
5-Membered Rings

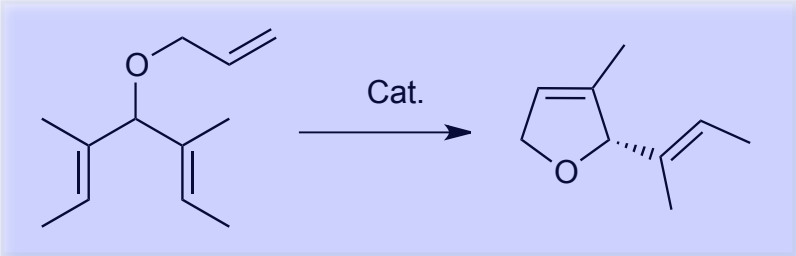


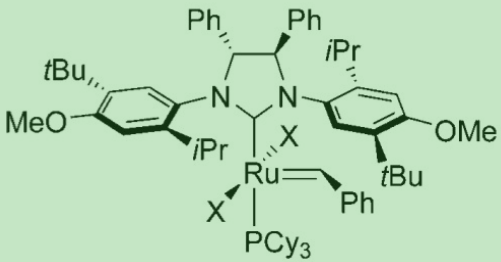
X = N, O, P, S

Chirality:
Catalyst control

ARCM: Ru

- Olefin metathesis: widespread application in small- molecule synthesis.
- Three transformations: ring-opening metathesis (ROM), ring-closing metathesis (RCM), and cross-metathesis (CM).
- Ex: Desymmetrisation reactions.





J. M. Berlin, S. D. Goldberg, and R. H. Grubbs, *Angew. Chem.*, 2006, **118**, 7753–7757.

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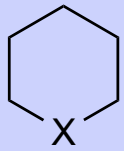
ARCM: Mo and Ru

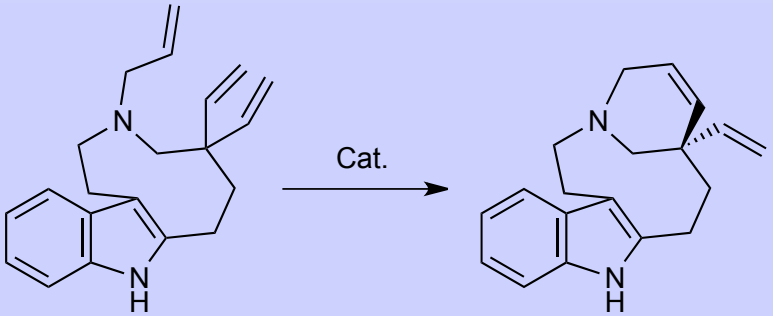
6-Membered Rings

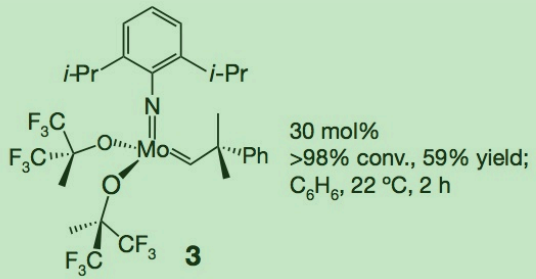


X = N, O, P, S

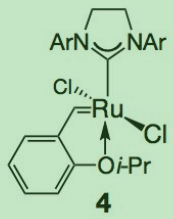
Chirality:
Catalyst control

- Mo-based complexes: presence of non-labile alkoxide ligands during the metathesis catalytic cycle.
- Fruitful collaboration between Richard Schrock (MIT) and Amir Hoveyda (Boston College).
- A recent example: high selectivity observed in the synthesis of the alkaloid quebrachamine.
- Desymmetrisation triene: challenge for even racemic RCM catalysts (hindered olefins, basic amine, strained transition state to ring closure).





30 mol%
>98% conv., 59% yield;
C_6H_6, 22 °C, 2 h



4a Ar = 2,4,6-$Me_3C_6H_2$ (Mes):
5 mol%
75% conv., 61% yield;
CH_2Cl_2, 22 °C, 6 h

4b Ar = 2-MeC_6H_4:
5 mol%
48% conv., 38% yield;
CH_2Cl_2, 22 °C, 6 h

1. S. J. Malcolmson, S. J. Meek, E. S. Sattely, R. R. Schrock, and A. H. Hoveyda, *Nature*, 2008, **456**, 933–937.
2. E. S. Sattely, S. J. Meek, S. J. Malcolmson, R. R. Schrock, and A. H. Hoveyda, *J Am Chem Soc*, 2009, **131**, 943–953.
3. A. H. Hoveyda, S. J. Malcolmson, S. J. Meek, and A. R. Zhugralin, *Angew Chem Int Edit*, 2009, **49**, 34–44.

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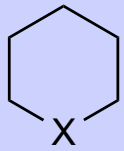
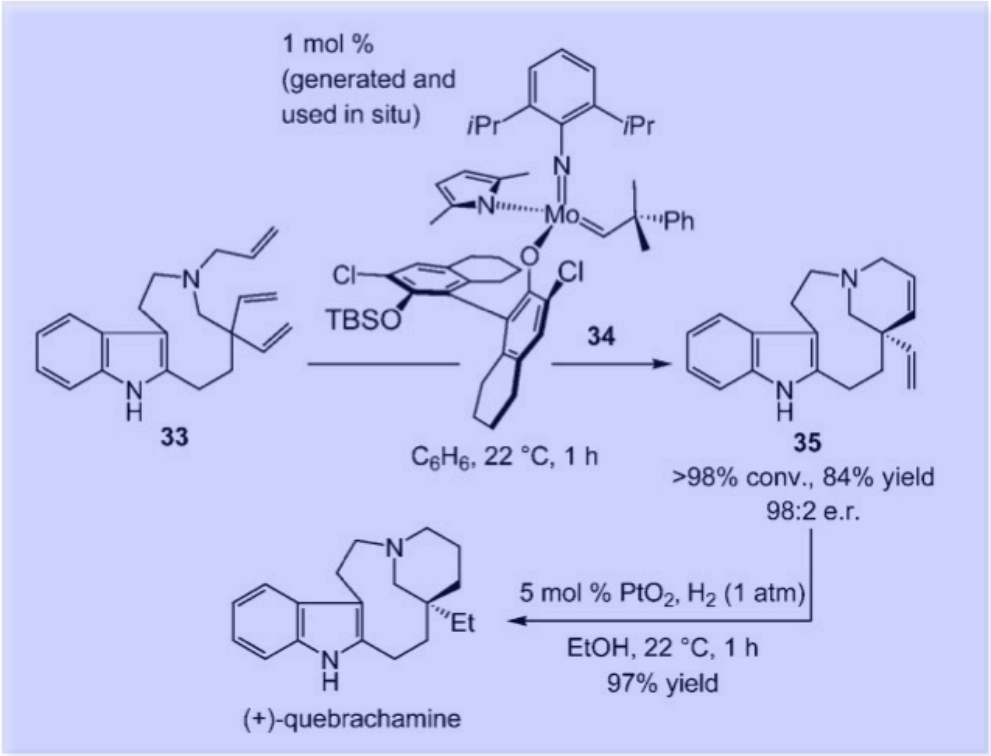
ARCM: Mo

6-Membered Rings



X = N, O, P, S

Chirality:
Catalyst control

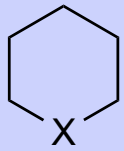


A. H. Hoveyda, S. J. Malcolmson, S. J. Meek, and A. R. Zhugralin, *Angew Chem Int Edit*, 2009, **49**, 34–44.

Transition Metal Catalysed Approaches

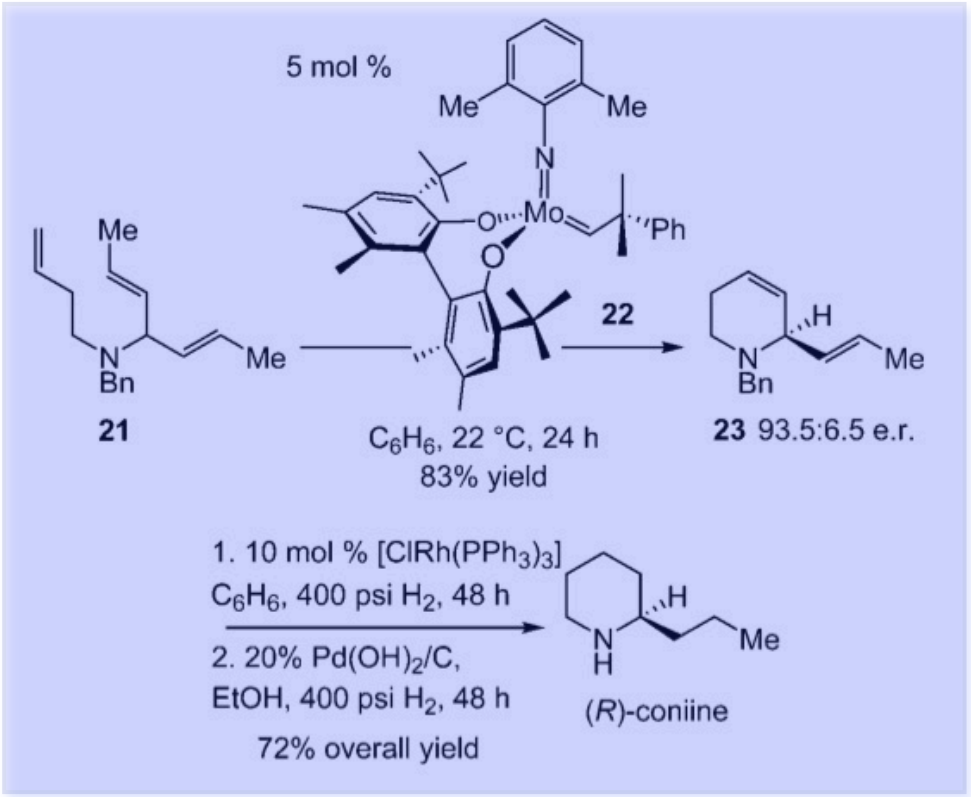
ARCM: Mo

6-Membered Rings



X = N, O, P, S

Chirality:
Catalyst control



A. H. Hoveyda, S. J. Malcolmson, S. J. Meek, and A. R. Zhugralin, *Angew Chem Int Edit*, 2009, **49**, 34–44.

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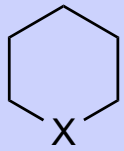
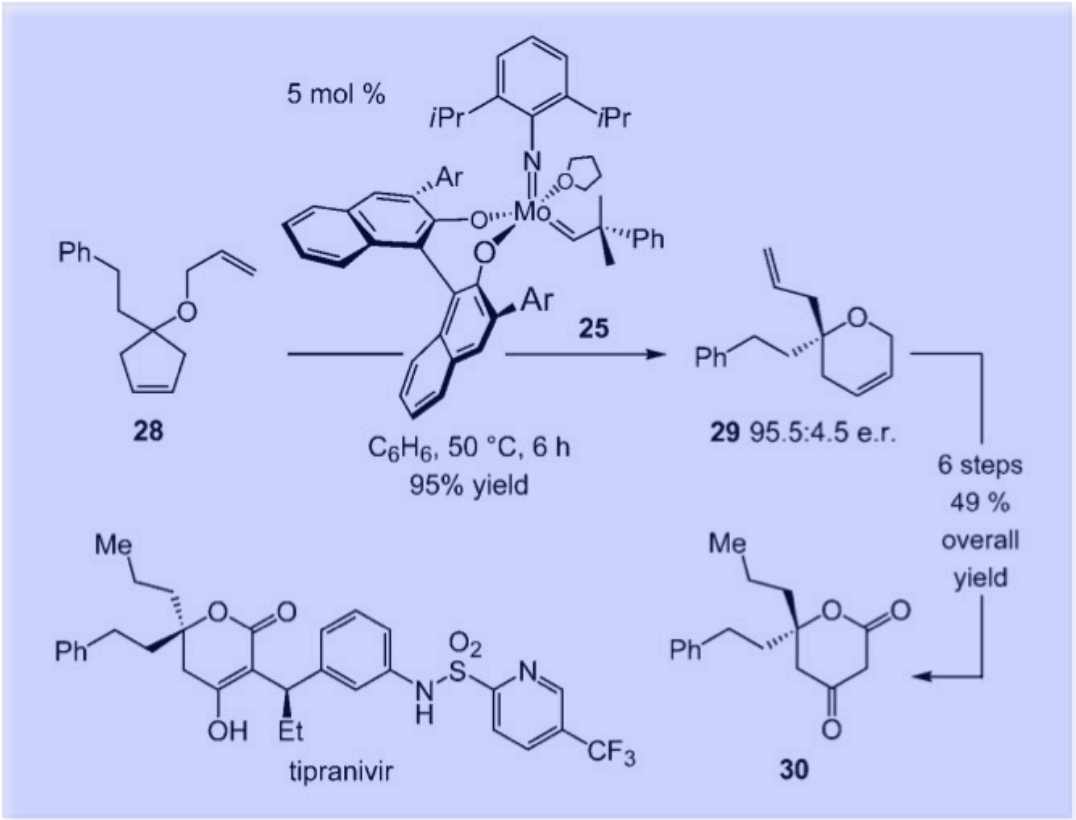
ARCM: Mo

6-Membered Rings



X = N, O, P, S

Chirality:
Catalyst control



A. H. Hoveyda, S. J. Malcolmson, S. J. Meek, and A. R. Zhugralin, *Angew Chem Int Edit*, 2009, **49**, 34–44.

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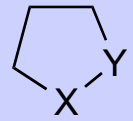
AROCM: Ru

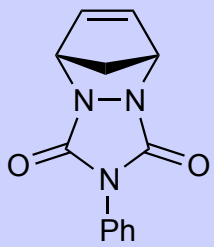
5-Membered Rings



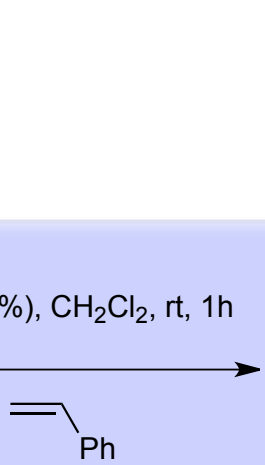
X = N, O, S
Y = N, O, S

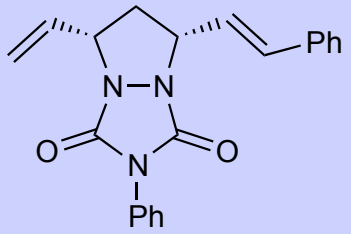
Chirality:
Catalyst control

- Heteroatoms into a norbornene skeleton slightly reduced the ee value to 68 %.

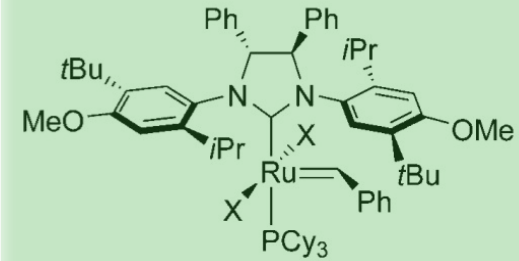


Cat. (1 mol%), CH_2Cl_2, rt, 1h





Yield: 99%
ee: 68%



J. M. Berlin, S. D. Goldberg, and R. H. Grubbs, *Angew. Chem.*, 2006, **118**, 7753–7757.

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Transition Metal Catalysed Approaches

Asymmetric Hydrogenation: Ir

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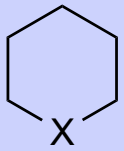
6-Membered Rings

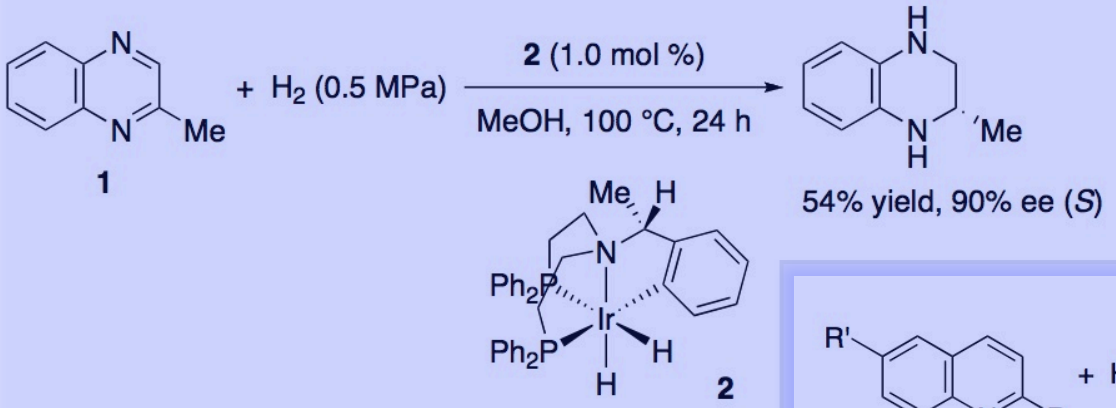


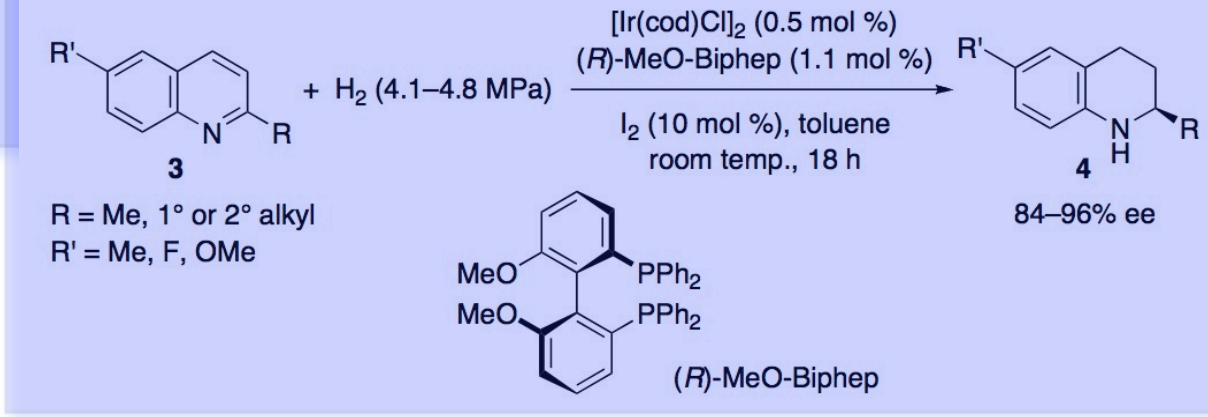
X = N, O, P, S

Chirality:
Catalyst control

Asymmetric Hydrogenation: Ir

- Enantioselective hydrogenation of heteroaromatics.
- Traditionally been conducted by using a heterogeneous catalyst.
- Examples:
  - Bianchini: 90% ee for the catalytic hydrogenation of quinoxaline.
  - Zhou: high enantioselectivity for the hydrogenation of 2-alkylquinolines





Review: R. Kuwano, *Heterocycles*, 2008, **76**, 909.

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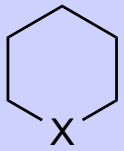
Asymmetric Hydrogenation: Ir

6-Membered Rings

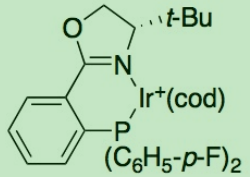


X = N, O, P, S

Chirality:
Catalyst control

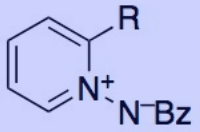
- Examples:

Ir *cat.* =



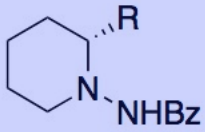
$[3,5\text{-}(CF_3)_2C_6H_3]_4B^-$

Charette (2005)



+ H_2 (2.8 MPa)

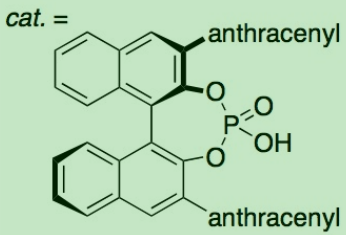
Ir *cat.* (2 mol %)
I_2 (2 mol %)
toluene
room temp., 6 h



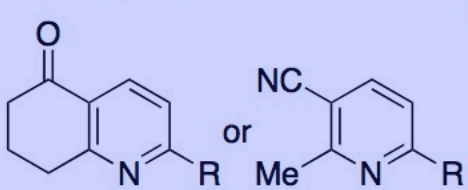
R = Me, Et, Pr, $(CH_2)_3OBn$

83–90% ee

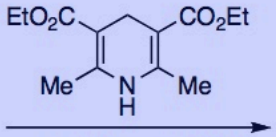
cat. =



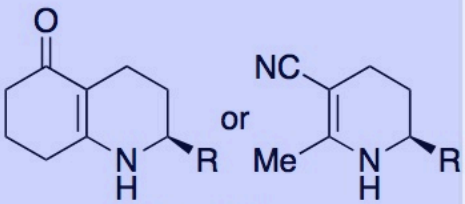
Rueping (2007)



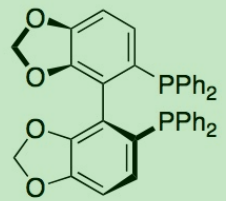
R = 1° alkyl



cat. (5 mol %)
benzene, 50 °C

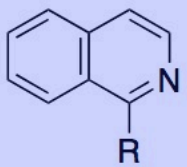


84–92% ee



(*S*)-SEGPHOS

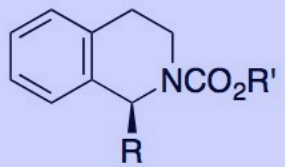
Zhou (2006)



+ $ClCO_2R'$

$LiCO_3$
THF
room temp.

$[IrCl(cod)]_2$ (0.5 mol %)
(*S*)-SEGPHOS (1.1 mol %)
H_2 (4.1 MPa), THF
room temp., 12–15 h



R = Me, Et, Bu, Ph

R' = Me, Bn

60–83% ee

Review: R. Kuwano, *Heterocycles*, 2008, **76**, 909.

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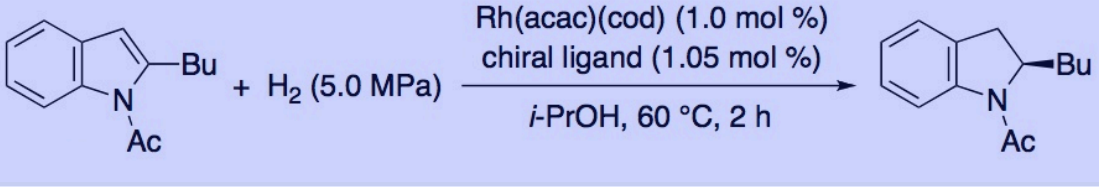
5-Membered Rings

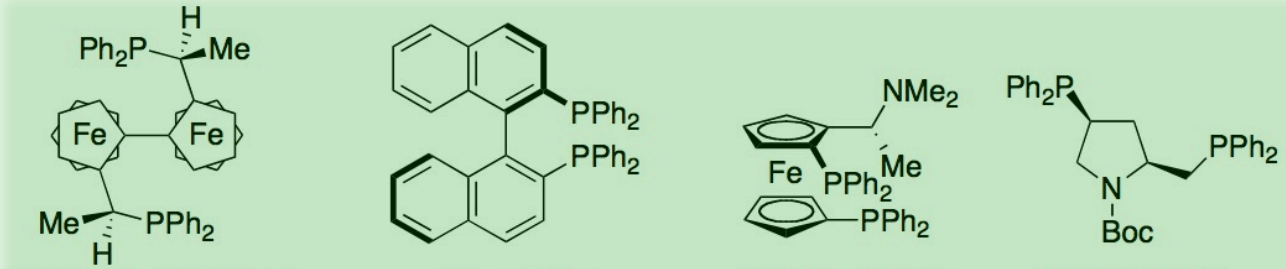
X = N, O, P, S

Chirality:
Catalyst control

Asymmetric Hydrogenation: Rh

- Examples:



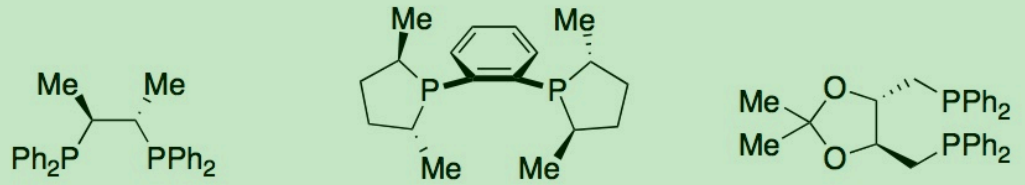


(*S*,*S*)-(*R*,*R*)-PhTRAP
77% yield, 85% ee (*R*)

(*R*)-BINAP
100% yield, 1% ee (*S*)

(*R*)-(*S*)-BPPFA
100% yield, 0% ee

(2*S*,4*S*)-BPPM
100%, 0% ee



(2*S*,3*S*)-CHIRAPHOS
100% yield, 1% ee (*S*)

(*R*,*R*)-Me-DuPHOS
100% yield, 0% ee

(2*S*,3*S*)-DIOP
100% yield, 0% ee

Review: R. Kuwano, *Heterocycles*, 2008, **76**, 909.

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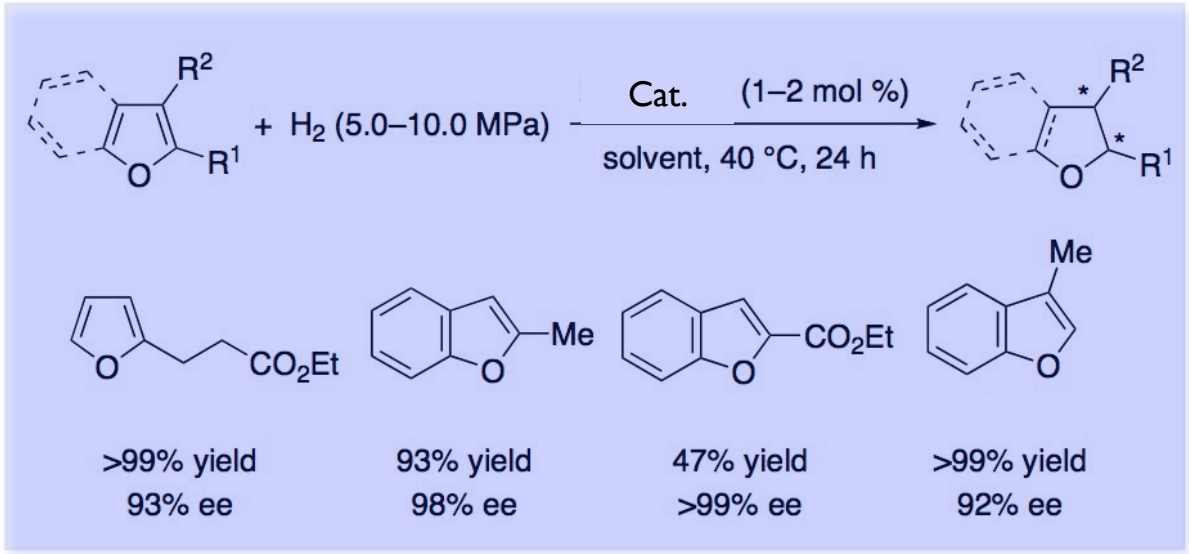
5-Membered Rings

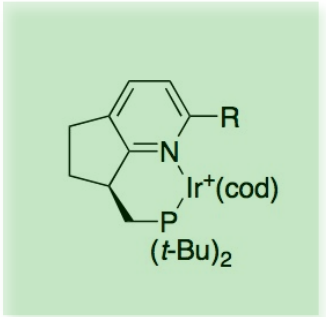
X = N, O, P, S

Chirality:
Catalyst control

Asymmetric Hydrogenation: Ir

- Pfaltz: high enantioselectivity for the hydrogenation of furans.
- Chiral pyridine-phosphinite ligands.
- Best catalyst: bulky electron-rich $(t\text{-Bu})_2P$ group.
- Choice of the substituents at the phosphorus atom strongly affects the catalytic activity as well as the enantioselectivity.
- Replacement of the tert-butyl by cyclohexyl group caused lower conversion and ee value.
- Use of diphenylphosphinite ligands resulted in no hydrogenation.





Review: R. Kuwano, *Heterocycles*, 2008, **76**, 909.

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Transition Metal Catalysed Approaches

Cycloaddition Reactions

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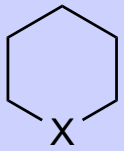
6-Membered Rings

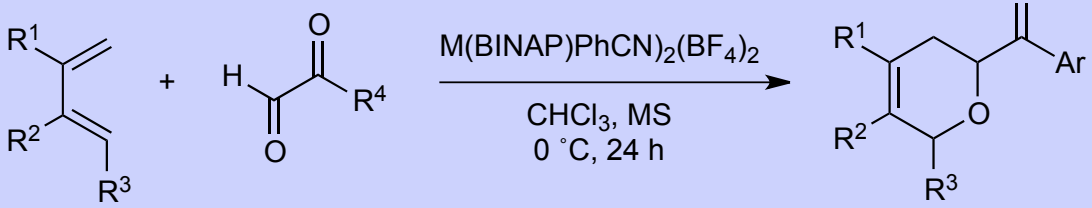


X = N, O, P, S

Chirality:
Catalyst control

Asymmetric Hetero Diels-Alder Reaction: Pd(II), Pt(II)

- Hetero Diels-Alder reaction of nonactivated conjugated dienes with arylglyoxals and glyoxylate esters.
- Cationic chiral BINAP-palladium or -platinum complexes.
- 3 Å molecular sieves to improve enantioselectivity.



R^i = H, Me R^4 = Ar, OAlk

Yield 20-80%
ee 1-99%

S. Oi, E. Terada, K. Ohuchi, T. Kato, Y. Tachibana, and Y. Inoue, *J Org Chem*, 1999, **64**, 8660–8667.

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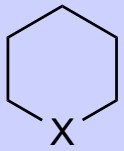
Asymmetric Hetero Diels-Alder Reaction: Cu(II)

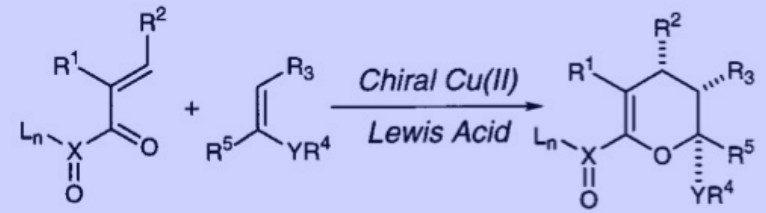
6-Membered Rings



X = N, O, P, S

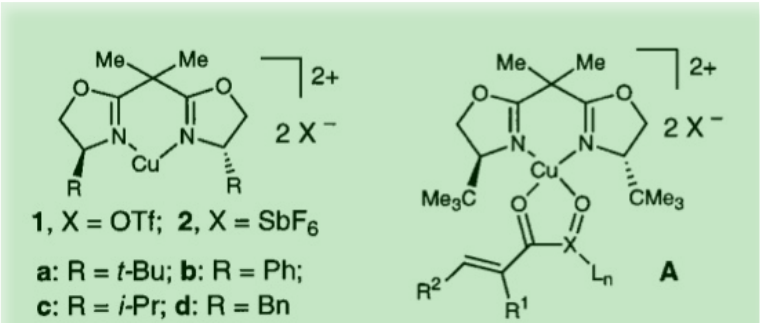
Chirality:
Catalyst control

- C2-symmetric bis(oxazoline)-Cu(II) complexes.
- Inverse electron demand hetero Diels-Alder reaction with electron-rich olefins (heterodienophile).
- High diastereo- and enantioselectivity.
- Acyl phosphonates and unsaturated keto esters and amides used as effective heterodienes.
- Enol ethers and sulfides used as heterodienophiles.
- Flexible subsitution pattern: terminal alkyl, aryl, alkoxy, and thioether.
- 0.2 mol % catalyst.
- Selectivities exceeding 90% even at room temperature.
- Solid air-stable catalyst, convenient reaction temperatures.



x = P, C Ri = Alk, COAlk Y = O, S

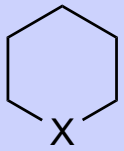
yields: 30-99%
ee: 39-99%
endo/exo: 32:1 to 99:1



D. A. Evans, J. S. Johnson, and E. J. Olhava, *J Am Chem Soc*, 2000, **122**, 1635–1649.

Asymmetric Hetero Diels-Alder Reaction

6-Membered Rings



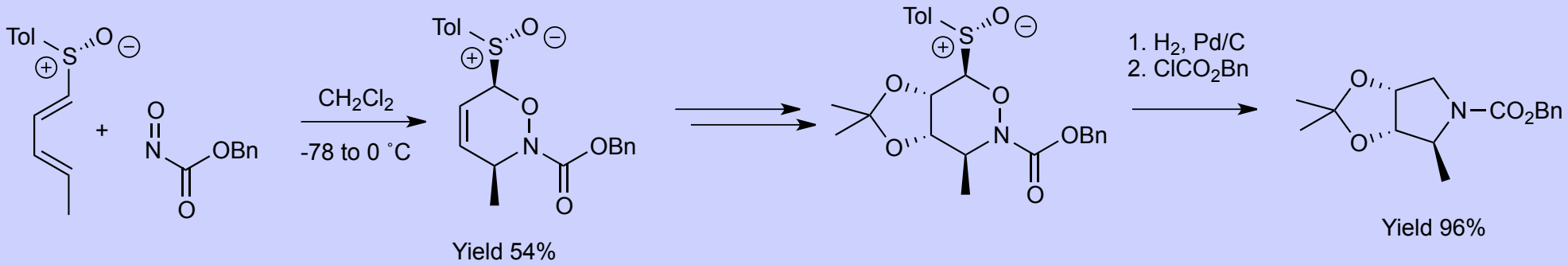
X = N, O, P, S

5-Membered Rings

X = N, O, P, S

Chirality:
Substrate control

- Hetero Diels–Alder cycloaddition of chiral 1-p-tolylsulfinyl-1,3-pentadiene with benzyl nitrosoformate.
- Mild conditions, complete regioselectivity and π-facial diastereoselectivity.
- Optically pure 1-sulfinyl-1,3-butadienes: efficient chiral dienes in asymmetric Diels-Alder reactions.
- Highly stereocontrolled rearrangement.
- Their use in asymmetric synthesis is strongly limited by their low reactivity even with good dienophiles.



C. Arribas, M. C. Carreño, J. L. García-Ruano, J. F. Rodríguez, M. Santos, and M. Ascensión Sanz-Tejedor, *Org Lett*, 2000, **2**, 3165–3168.

5-Membered Rings

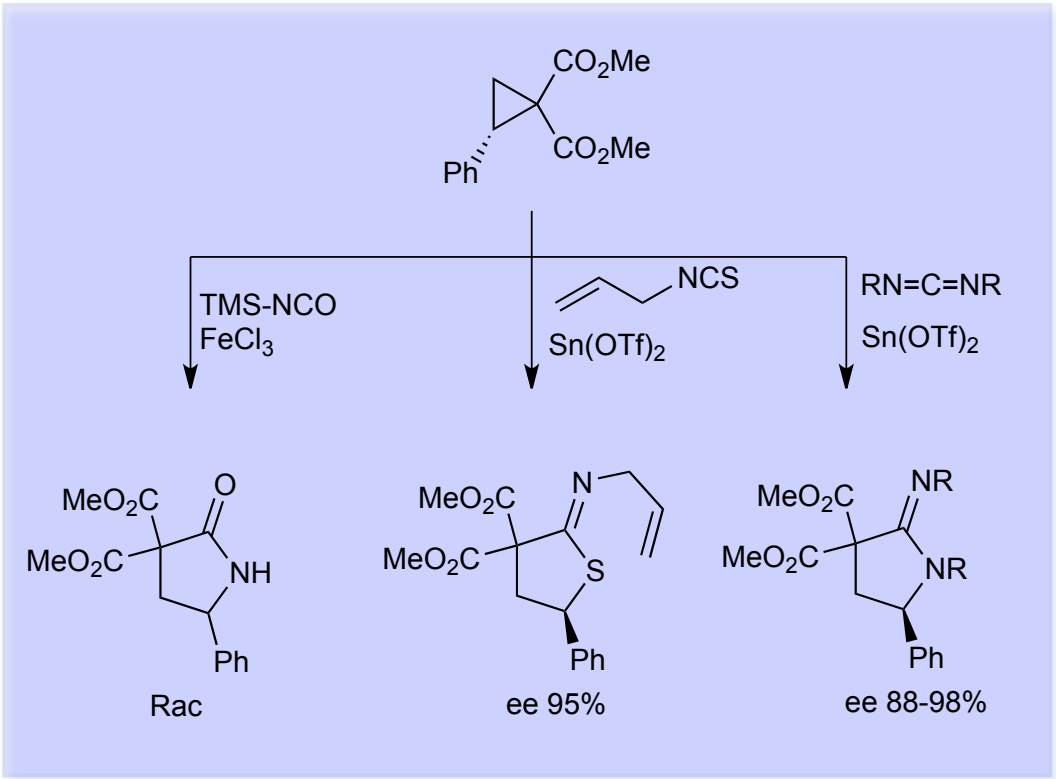
X = N, O, P, S

Chirality:
Substrate control

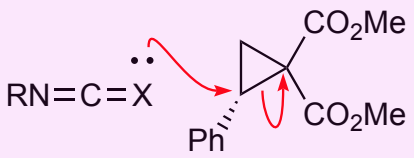
[3+2]-Cycloadditions

- Isocyanates, isothiocyanates, and carbodiimides are effective substrates in cycloadditions with cyclopropanes for the synthesis of five-membered heterocycles.

- High yields and well-defined chemoselectivity.



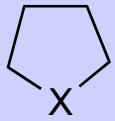
Via



A. F. G. Goldberg, N. R. O'Connor, R. A. Craig II, and B. M. Stoltz, *Org Lett*, 2012, **14**, 5314–5317.

Organo-SOMO Cycloadditions

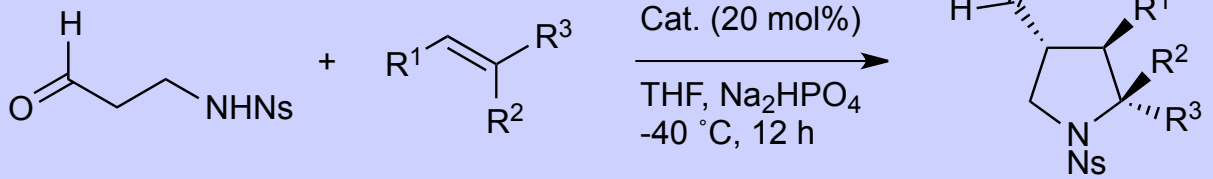
5-Membered Rings



X = N, O, P, S

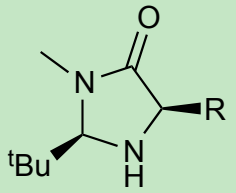
Chirality:
Catalyst control

- SOMO-activated enantioselective [3 + 2] coupling of aldehydes and conjugated olefins.
- Olefins include styrenes and dienes.
- High chemical efficiency and enantiocontrol.



R^i = H, alk, ar

yields:
55-85%

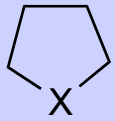


R = Me, Bn

$Fe(phen)_3(SbF_6)_3$

N. T. Jui, J. A. O. Garber, F. G. Finelli, and D. W. C. MacMillan, *J Am Chem Soc*, 2012, **134**, 11400–11403.

5-Membered Rings

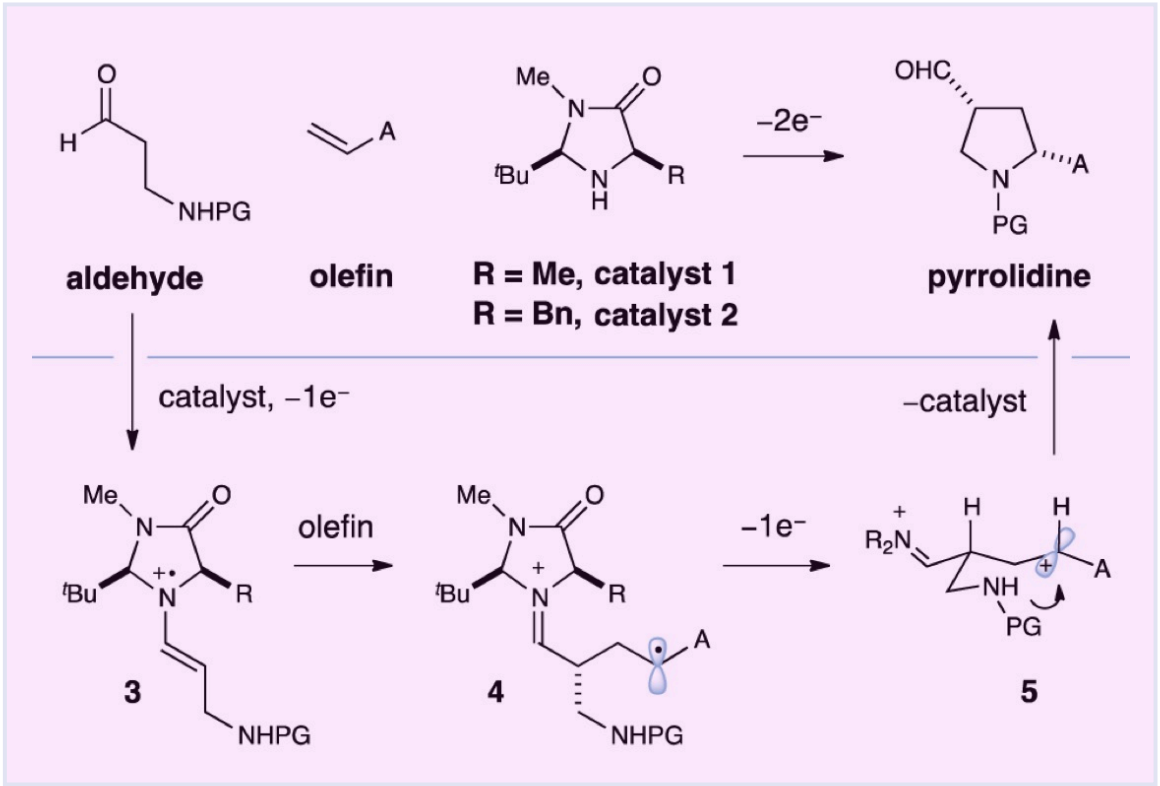


X = N, O, P, S

Chirality:
Catalyst control

Organo-SOMO Cycloadditions

- Radical-polar crossover mechanism:
  - olefin addition to a transient enamine radical cation
  - oxidation of the resulting radical to a cationic intermediate
  - nucleophilic addition of a tethered amine group.

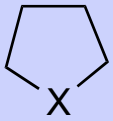


N. T. Jui, J. A. O. Garber, F. G. Finelli, and D. W. C. MacMillan, *J Am Chem Soc*, 2012, **134**, 11400–11403.

Diastereocontrol in Tandem Cyclisations

Cycloadditions

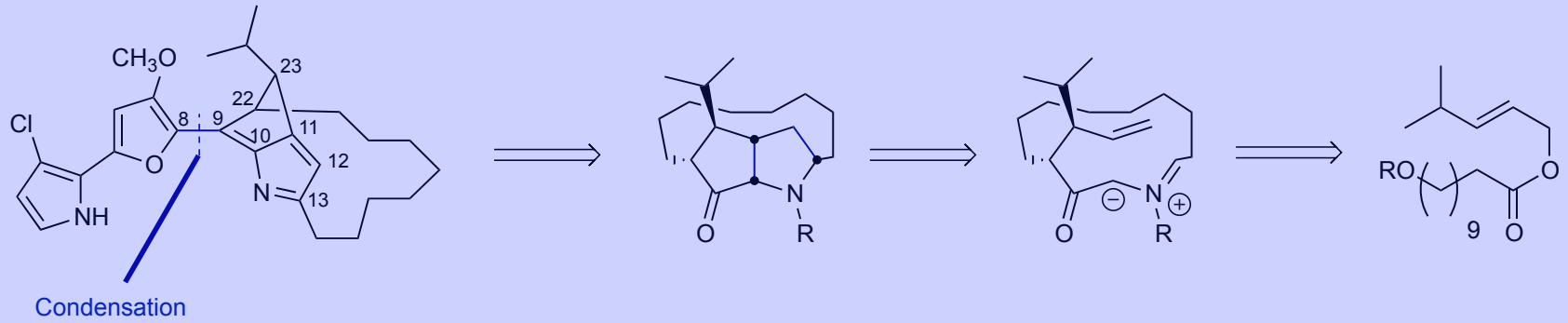
5-Membered Rings



X = N, O, P, S

Stereoselectivity: Substrate control

- Substrate control - Other centres introduced by an Ireland-Claisen rearrangement.
- Tandem reaction: aza-Wittig / dipolar cycloaddition.



E. Viseux, P. Parsons, J. Pavey, C. Carter, and I. Pinto, *Synlett*, 2003, 1856–1858.

N Diastereocontrol in Tandem Cyclisations

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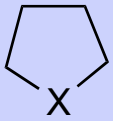
Cycloadditions

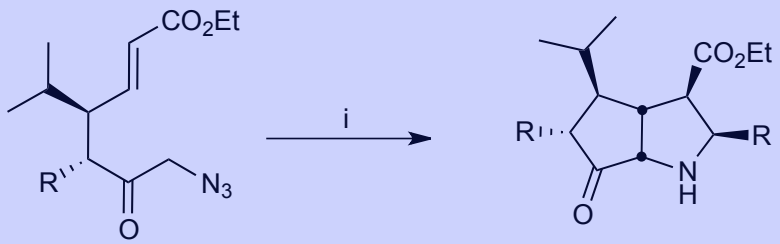
5-Membered Rings



X = N, O, P, S

Stereoselectivity:
Substrate control

- Use of Mg(II) salt to promote dipolar cycloaddition of azomethyne ylides (as opposed to Ag(I)).
- Diastereocontrol over 3 to 4 centres.



Reagents. (i) PPh_3, $MgSO_4$, RCHO, CH_3CN.

E. Viseux, P. Parsons, J. Pavey, C. Carter, and I. Pinto, *Synlett*, 2003, 1856–1858.

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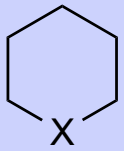
Organocatalysis

Access to Fused Piperidines

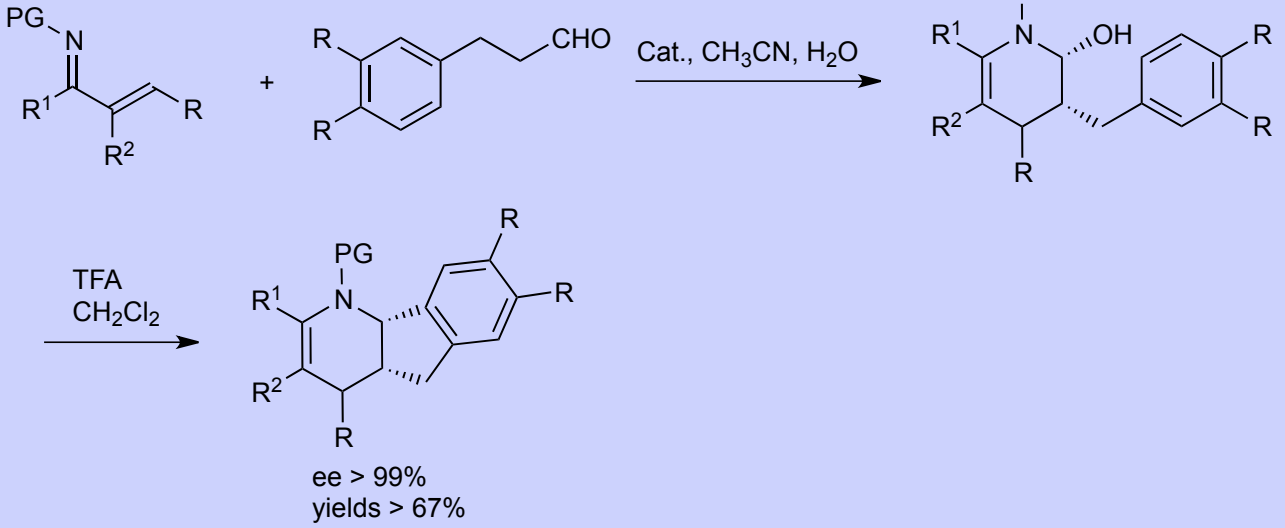
6-Membered Rings

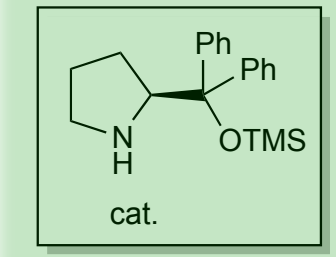


X = N, O, P, S

Chirality:
Catalyst control

- aza-Diels Alder and Friedel Crafts reaction.
- Precursors *N*-sulfonyl-1-aza-1,3-butadienes and aliphatic aldehydes tethered to an arene motif.
- Access to fused chiral piperidine frameworks.
- Access to complex chiral tetrahydroquinoxalines.

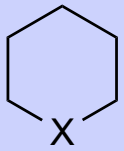




S.-L. Zhou, J.-L. Li, L. Dong, and Y.-C. Chen, *Org Lett*, 2011, **13**, 5874–5877.

Access to Fused Piperidines

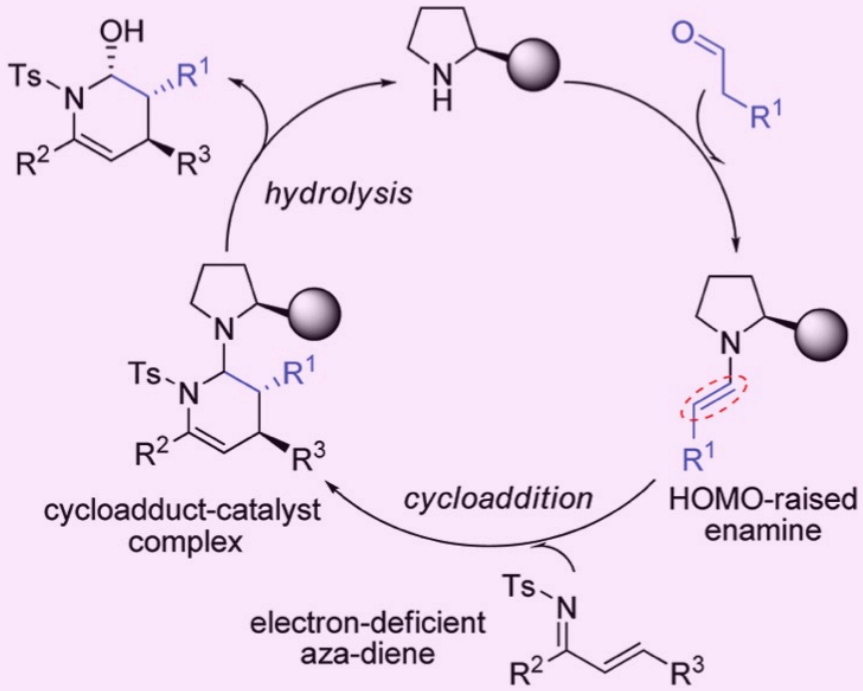
6-Membered Rings



X = N, O, P, S

Chirality:
Catalyst control

Suggested mechanism

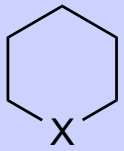


J.-L. Li, T.-Y. Liu, and Y.-C. Chen, *Accounts Chem Res*, 2012, **45**, 1491–1500.

University of Sussex

Access to Poly-Substituted Pyranoses

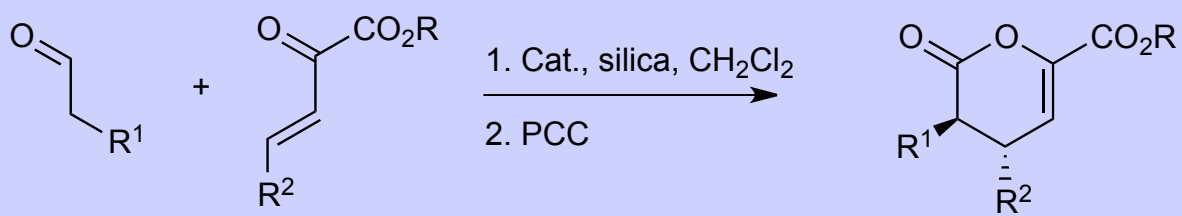
6-Membered Rings



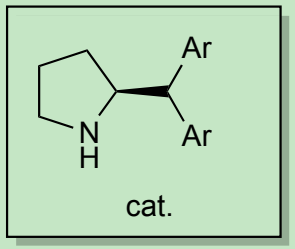
X = N, O, P, S

Chirality:
Catalyst control

- Asymmetric Diels Alder reactions based on the HOMO-raising effects of chiral amines.
- Enamine intermediates formed *in situ* between an amine catalyst and enolizable aliphatic aldehydes: electron-rich dienophiles in inverse-electron-demand Diels Alder reactions.
- Heterocycles with high optical purity.
- Reactions generally occur with high chemo-, regio-, and stereoselectivity.



ee 80-94%
yields 62-93%



Ar = 3,5-$(CH_3)_2C_6H_3$

Wolfgang Notz, A. Fujie Tanaka, and I. Carlos F Barbas, *Accounts Chem Res*, 2004.

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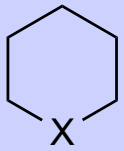
Access to Poly-Substituted Pyranoses

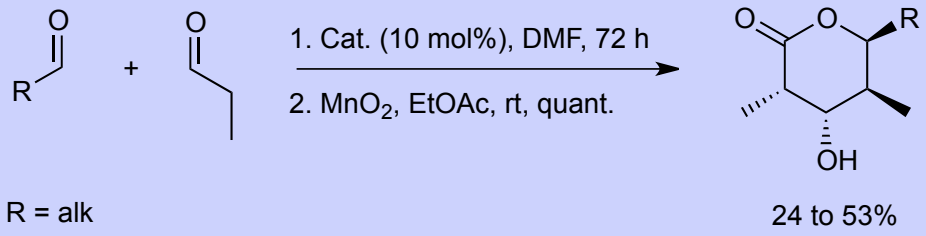
6-Membered Rings



X = N, O, P, S

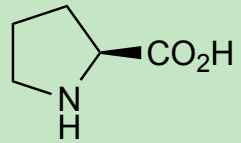
Chirality:
Catalyst control

- Asymmetric formation of carbohydrates from aldehydes.
- Triketides obtained from slow addition of propionaldehyde to an aldehyde.
- Isolated lactols readily converted to the corresponding δ-lactones (Mn(IV)).
- Comparable to the DERA (deoxyribose 5-phosphate aldolase)-catalysed reaction of propionaldehyde (only 13% yield after 2 weeks).



R = alk

24 to 53%



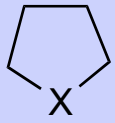
Wolfgang Notz, A. Fujie Tanaka, and I. Carlos F Barbas, *Accounts Chem Res*, 2004.

University of Sussex

Chiral Pool

University of Sussex

5-Membered Rings

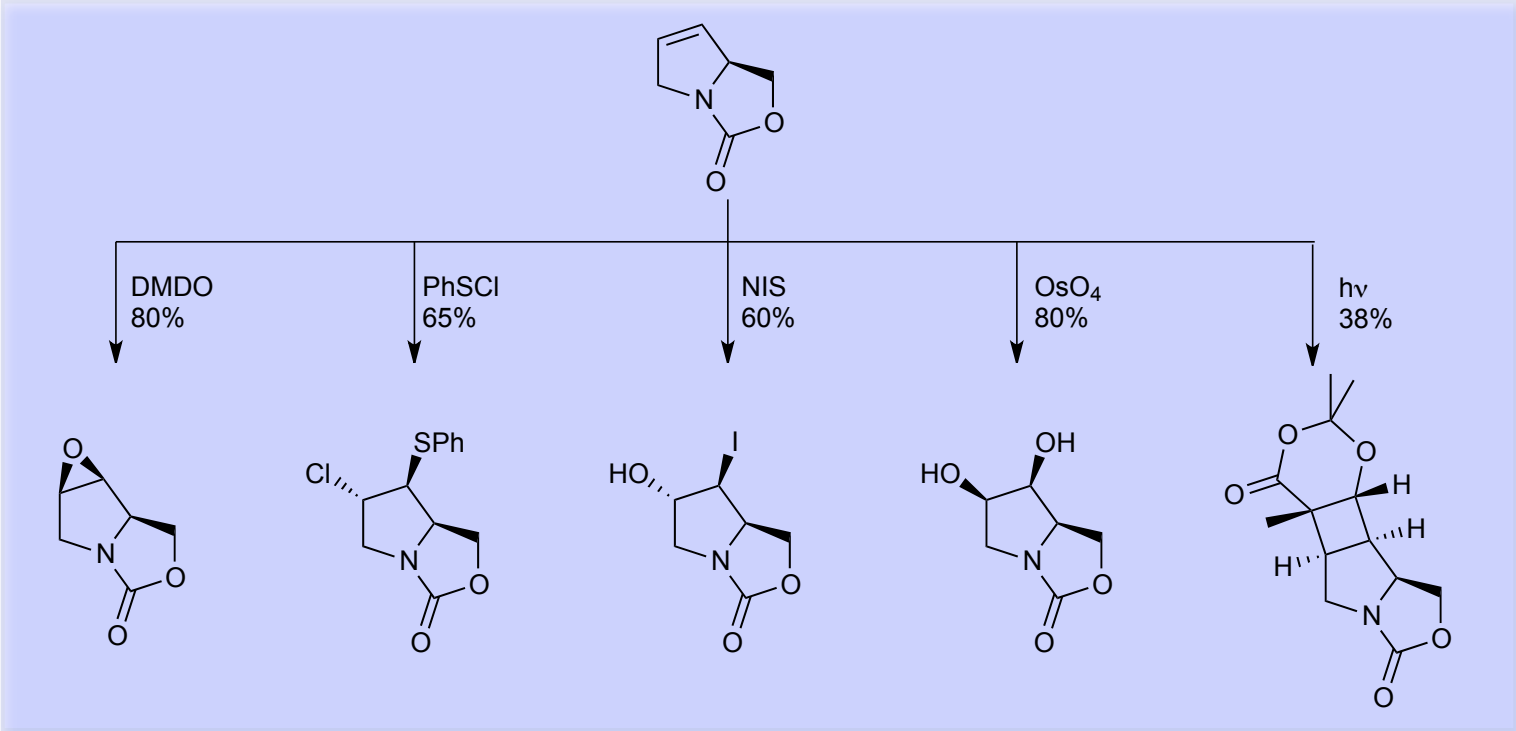


X = N, O, P, S

Chirality:
Chiral Pool

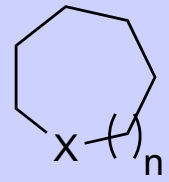
Unexpected Observations in Bicyclic Heterocycles

- Apparent reversal of selectivity in electrophilic additions.
- MM: unsymmetrical HOMO with a higher electronic density on the *endo* face.
- Cieplak's hyperconjugative electron release from an axial hydrogen atom ruled out.
- H_{alkyl} bonding gives partially selectivity in analogous bicyclic lactones.



A. J. Murray, P. J. Parsons, E. S. Greenwood, and E. M. E. Viseux, *Synlett*, 2004, 1589.

Larger Rings



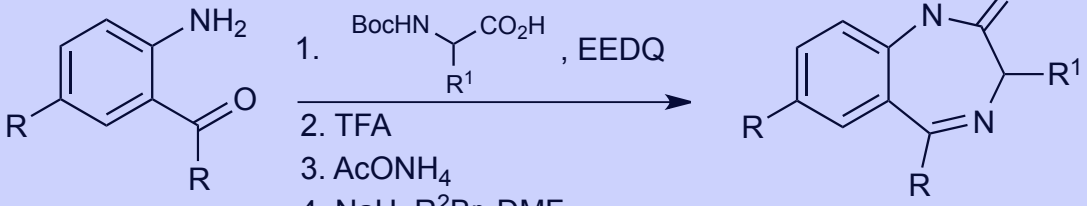
X = N, O, P, S

Chirality:
Chiral Pool

Access to Chiral Benzodiazepinones

- Human African Trypanosomiasis (HAT or sleeping sickness) is caused by two subspecies of the parasite *T. brucei*.

- Substitution at the C3 position is important for biological activity (eightfold decrease in activity compared with its enantiomer).



1. I. M. McDonald, C. Austin, I. M. Buck, D. J. Dunstone, E. Griffin, E. A. Harper, R. A. D. Hull, S. B. Kalindjian, I. D. Linney, C. M. R. Low, M. J. Pether, J. Spencer, P. T. Wright, T. Adatia, and A. Bashall, *J. Med. Chem.*, 2006, **49**, 2253–2261.
2. J. Spencer, R. P. Rathnam, and B. Z. Chowdhry, *Future Med Chem*, 2010, **2**, 1441–1449.
3. J. Spencer, R. P. Rathnam, A. L. Harvey, C. J. Clements, R. L. Clark, M. P. Barrett, P. E. Wong, L. Male, S. J. Coles, and S. P. Mackay, *Bioorganic & Medicinal Chemistry*, 2011, **19**, 1802–1815.

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Conclusion

Conclusion

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5-Membered Rings

X = N, O, P, S

5-Membered Rings

X = N, O, S
Y = N, O, S

5-Membered Rings

X = N, O, S
Y = N, O, S

6-Membered Rings

X = N, O, P, S

Larger Rings

X = N, O, P, S

Chirality: Substrate

Chirality: Catalyst

- The requirement for finer enantio- and diastereocontrolled tools parallels the call for an increasingly broader range of targets from developing areas in chemistry (Medicinal Chemistry and Drug Design).

- The importance of catalysts based on chiral transition metal complexes in the chemistry of heterocycles has certainly advanced rapidly to satisfy those requirements, including the refinement of ligand designs and the development of transformation- and substrate-specific complexes.

- Notably, the chemistry of gold catalysis has developped into a diverse, powerful and versatile tool for the assembly of small chiral heterocycles.

- The use of the chiral pool and enzymatic methods are also key synthetic tools in this field, especially with the advances of engineering technics adaptable to process chemistry (flow chemistry, MW, etc.). Though enzymatic approaches are not covered herein, they are paramount for the access to a variety of precursors used notably in substrate control transformations.

Contributor: Chris Gallop