Frontiers in Chemical Synthesis II
Heterocyclic Chemistry

Seminar Program
May 23-24, BCH 3118

	Speaker	Title
May 23, 2012		
Session I: Gold and Carbenes (Chairman: Victoria Vita)		
14h00-15h15	Valentin Manzanares	*Au-NHC Complexes: Applications in Synthetic and Medicinal Chemistry*
15h15-16h30	Yifan Li	*Non-Classical Heterocyclic Carbenes: Recent Applications in Small Molecule Activation and Organic Synthesis*
16h30-17h45	Van Manh Pham	*Furan and Pyran Synthesis from Functionalized Allenes by Gold Catalysis*
May 24, 2012		
Session II: N-Containing Heterocycles and Natural Products (Chairman: Valentin Manzanares)		
13h00-14h15	Victoria Vita	*Radical Methods for the Synthesis of N-Heterocycles*
14h15-15h30	Christopher Kourra	*Direct C-H Functionalization of Five-membered N-Containing Heterocycles*
15h30-16h45	Christophe Heinz	*Vindoline: Synthetic Approaches towards a Highly Complex Polycyclic Alkaloid.*

Gold-*N*-Heterocyclic Carbene complexes

Versatile tools for catalysis and medicinal chemistry

Frontiers in Organic Chemistry II Lectures
V. Manzanares (LCOM) – May 23rd 2012

Synthesis-wise and user-wise, what are the advantages of Au-NHCs over Au-phosphines complexes? What are the possibilities for "greener chemistry" arising from the use of these ligands?
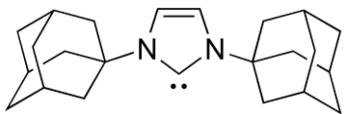
Which properties of Au-NHC complexes were critical to induce apoptosis in cells? Which pathways are supposed to be active in tumor repression?
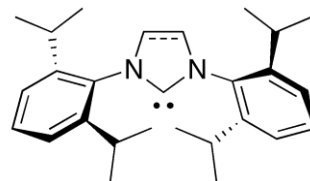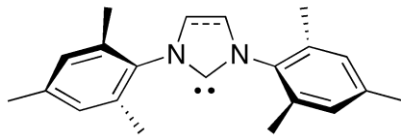
Initially supposed to be inert, gold has been increasingly used for catalysis over the last decade.
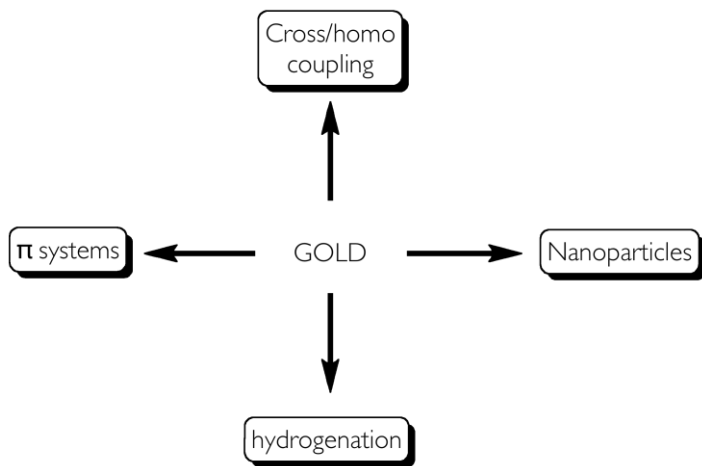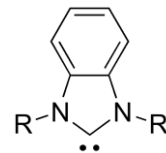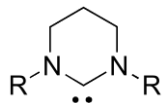
IAd: 1st air-stable NHC
(Arduengo 1991)

Workhorses of metal-NHC catalysis: **(S)IMes** and **(S)IPr**
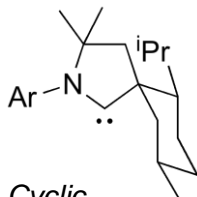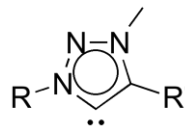
Benzimidazole-based NHCs

IMIDAZOLE-BASED NHCs ARE THE MOST USED LIGANDS FOR
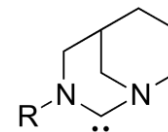GOLD CATALYSIS & MEDICINIAL CHEMISTRY

*Diamino
carbenes
(Bertrand
2004)*

*Cyclic
(Alkyl)(Amino)
Carbene
(Bertrand
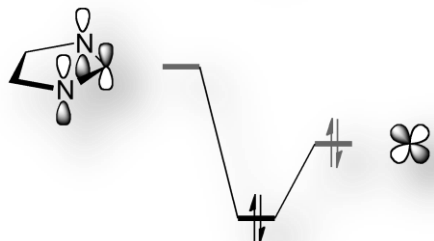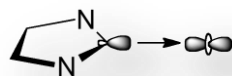2005)*

*Click-assembled
triazolium NHC
(Crowley 2010)*

*Push-pull NHC sporting
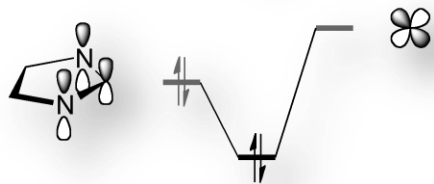enhanced electrophilicity
(Bertrand 2012)*

a) σ(NHC) ➝ d_z(metal): σ-donation

b) d_xy(metal) ➝ π(NHC): π-backdonation*

b) π(NHC) ➝ d_xz(metal): π-donation

- NHCs act as strong σ donors and weak π acceptor;
- In the case of group 11 metals (Cu, Ag, Au), the π interaction (π and π*) contributes significantly more (15 to 30% of the overall orbital interaction);
  - π* back-donation especially strong with gold complexes;
- Additional π-donation from the nitrogen atoms help stabilize the carbene;

- Because of this, NHCs show an increased σ-donation and decreased π*-backdonation compared to phosphine ligands.

Coord. Chem. Rev. **2009**, *687*; *Chem. Soc. Rev.* **2011**, *5151*;

NHCs are often viewed as advantageous alternatives to phosphines:

- Side substituents can play a significant role in metal reactivity and catalysis;
- Diversity of structures and synthetic approaches;
    - Unsymmetrical side functionalization of NHC is rather easy;
    - Heterocyclic backbone can also bear additional functionality to alter the electronic properties of the ligand
- Increased robustness of the ligand and catalyst;

NHC are more than phosphine mimics!

Chem. Commun. **2010**, 841; *Coord. Chem. Rev.* **2009**, 687; *Acc. Chem. Res.* **2011**, 91
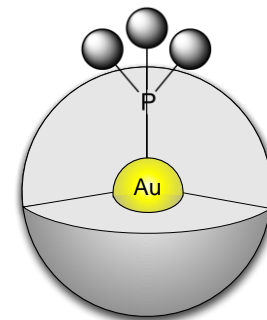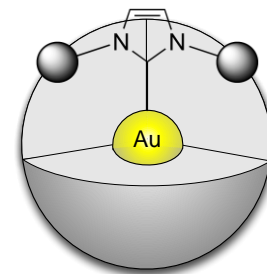
Synthetic approaches to Au-NHC complexes
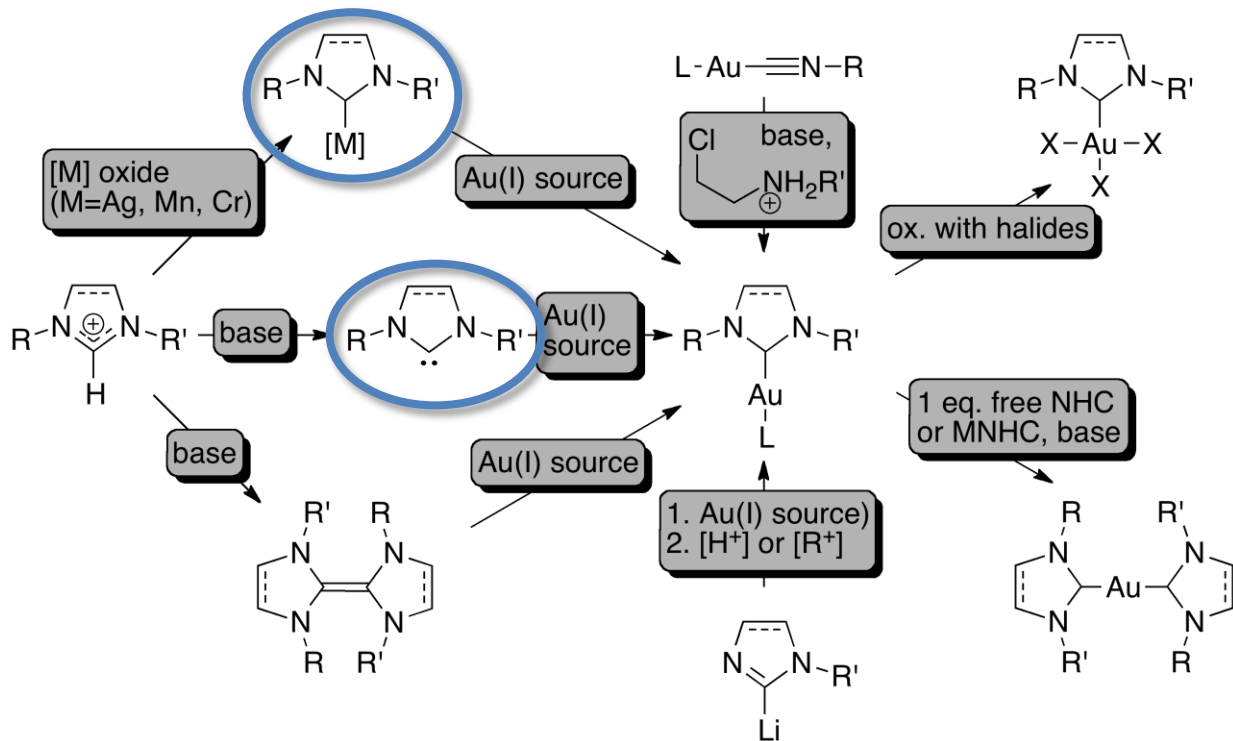
Cationic complexes in the form $[Au(L)_2]^+$ are often paired with a weakly coordinating anion (e.g. PF_6^-);
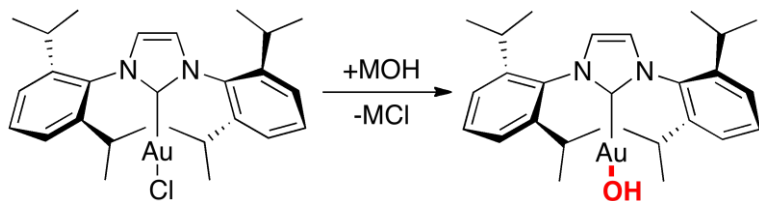
For coordination of gold to free NHCs of electron-rich olefins, the metallic center is often coordinated with a labile ligand such as SMe_2 or tht.

Chem. Rev. **2009**, *3561; Angew. Chem. Int. Ed.* **2010**, *6940;*

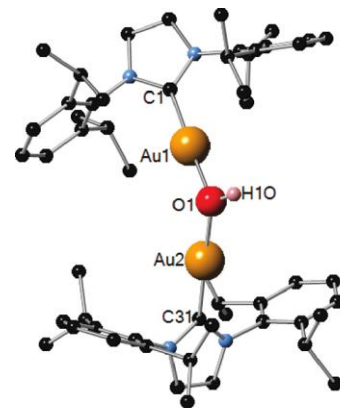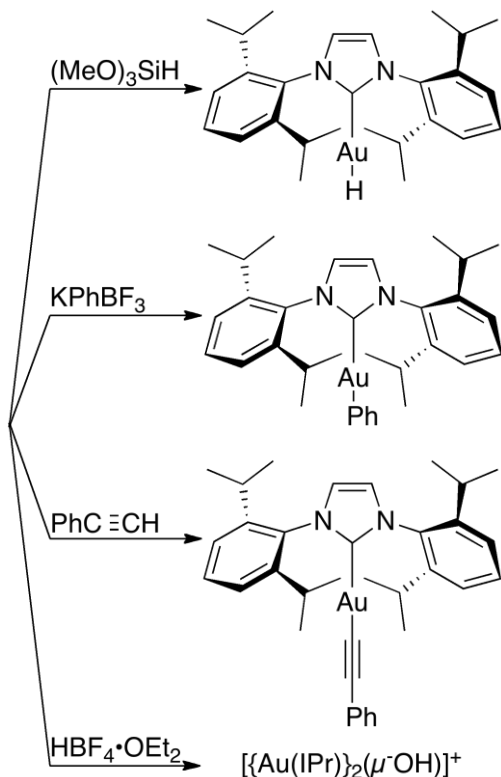# [Au(NHC)(OH)]: a versatile synthon for catalysis

Methodology is robust and can be conducted in *air* and *technical solvents*.

The Au-O bond is *covalent* in character.
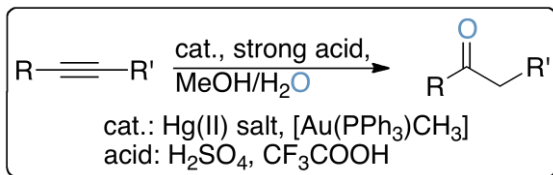

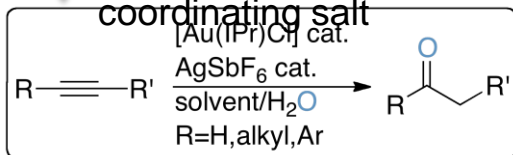[Au(IPr)(OH)] can be viewed as a strong Brønsted base.
This eliminates the need for external bases and expensives silver salts to obtain the active catalyst [Au(IPr)]⁺.

(MeO)₃SiH

KPhBF₃

PhC≡CH

HBF₄·OEt₂ → [{Au(IPr)}₂(μ⁻OH)]⁺

Au-NHC-catalyzed alkyne and nitrile hydration

Replacement of toxic cat., strong acid with mild cat, non-coordinating salt

The use of [Au(IPr)Cl] catalyst allows the easy conversion of terminal and internal alkynes with low catalyst loadings and good tolerance for adjacent moieties.

The range of the reaction can be extended to nitrile substrates with acid-activated [Au(IPr)(OH)] and [{Au(IPr)}$_2$(μ-OH)]$^+$. Moreover, the use of these catalysts removes the need for Ag salts.

J. Am. Chem. Soc. **2009**, *448*; *Chem Eur. J.* **2010**, *13729*; *J. Organometallic Chem.* **2011**, *7*; *Chem. Eur. J.* **2011**, *1238*
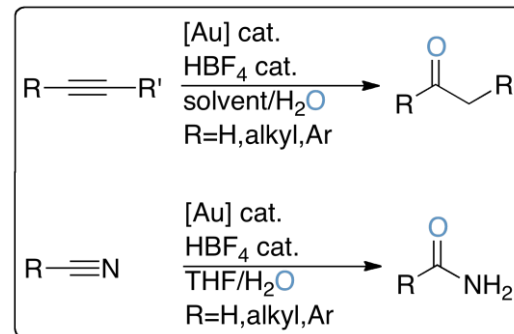
Au-NHC-catalyzed Meyer-Schuster rearrangement
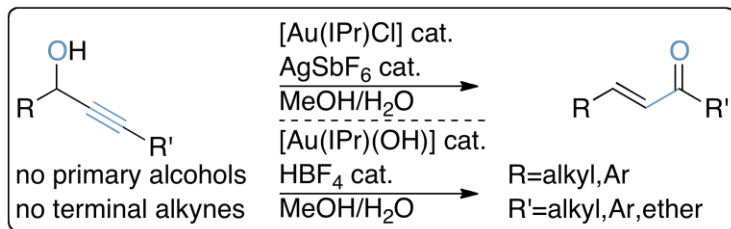
Au-NHC catalyst presents equivalent or better activity compared to other catalytic systems.

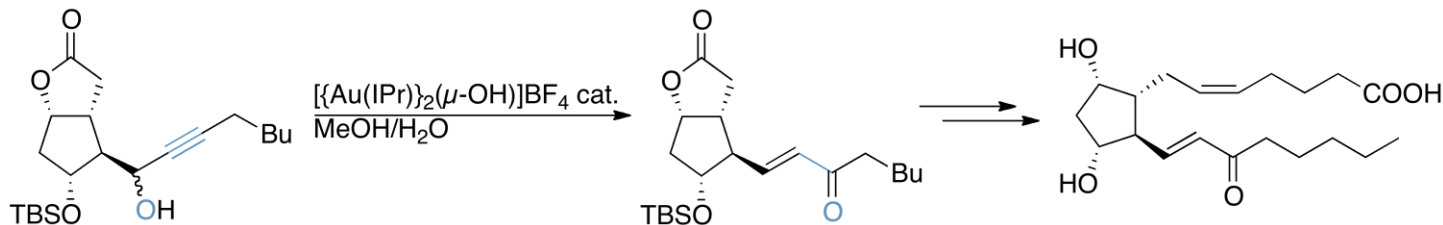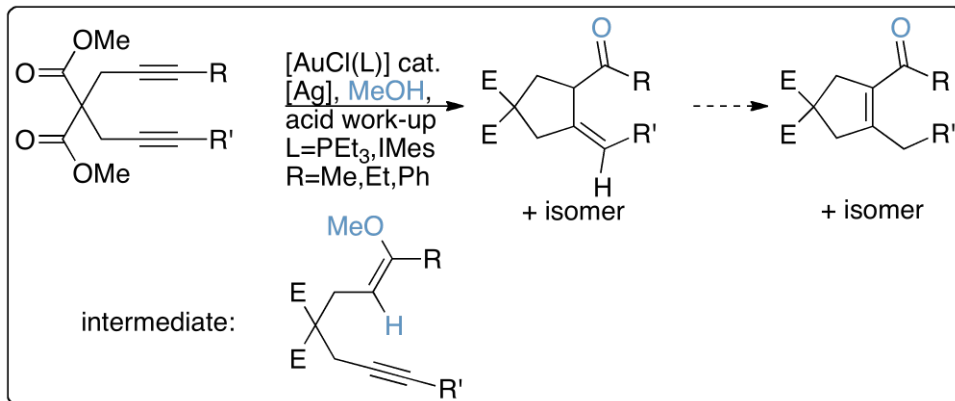Replacement of the chloride complex by acid-activated [Au(IPr)(OH)] and [{Au(IPr)}$_2$(μ-OH)]$^+$ removed the need for an Ag salt.

A direct application of the Meyer-Schuster rearrangement lies in the synthesis of prostaglandins.
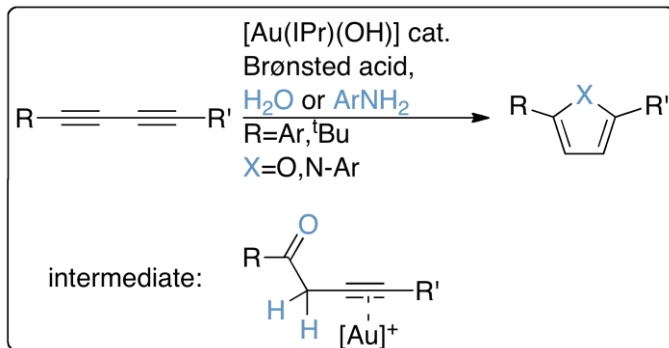
Formation of cyclic products from 1,6- and 1,3-diynes was efficiently catalyzed by Au-NHC catalysts;

- In both cases, activation of the catalyst was required (Cl scavenger, Brønsted acid);
- Choice of the counteranion was also critical;

Both reaction based on a cascade starting with alkyne hydration.

Org. Lett. **2009**, *2449; Catal. Sci. Technol.* **2011**, *58*

Stable aurated intermediates were produced from common alkynes using the [Au(IPr)]+ cation;

- The presence of a base was necessary to slow down the deauration process;
- The alkyl-functionalized alkyne afforded only the deaurated product.
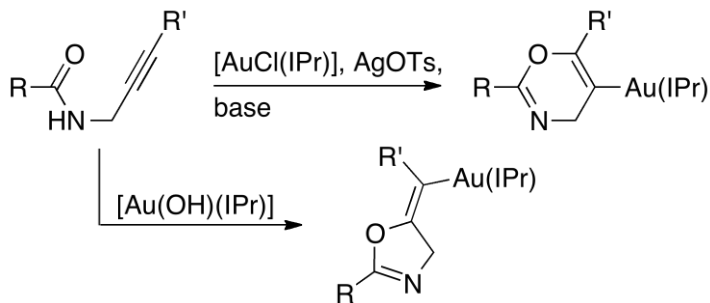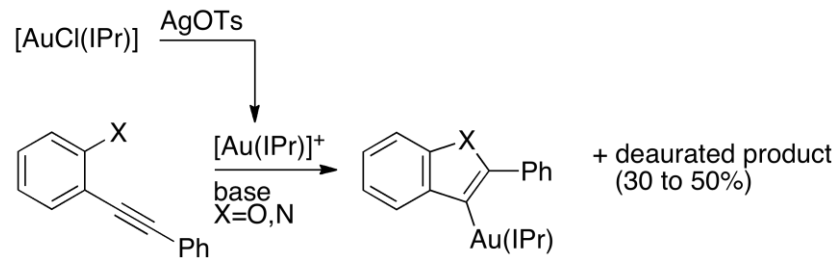
N-propargylamides exhibit similar reactivity, affording aurated oxazine when treated with [Au(IPr)]+.
The selectivity changes considerably when switching from [Au(IPr)]+ to [Au(OH)(IPr)];

- The switch in selectivity is mainly due to the superior basicity of [Au(OH)(IPr)];
- Electron-rich alkynes also favour the formation of the oxazolines.

Angew. Chem. Int. Ed. **2009**, 8247; *Adv. Synth. Catal.* **2010**, 971; *Angew. Chem. Int. Ed.* **2010**, 5232; *Organometallics* **2011**, 6328
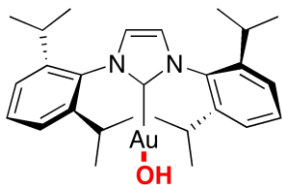
Good precursor for C-H activation:
- Included powerful Brønsted base;
- Only product of activation is H_2O;
- Atom economy.

Note that C-H activation occurs on the most acidic sites of the different substrates; this is consistent with the basic properties of [Au(OH)(IPr)].

Aurated aromatics can be obtained through decarboxylation.

Dalton Trans. **2010**, 10382; *Acc. Chem. Res.* **2011**, ASAP; *J. Am. Chem. Soc.* **2010**, 8858; *Chem. Comm.* **2011**, 3021, *Chem. Comm.* **2011**, 5455
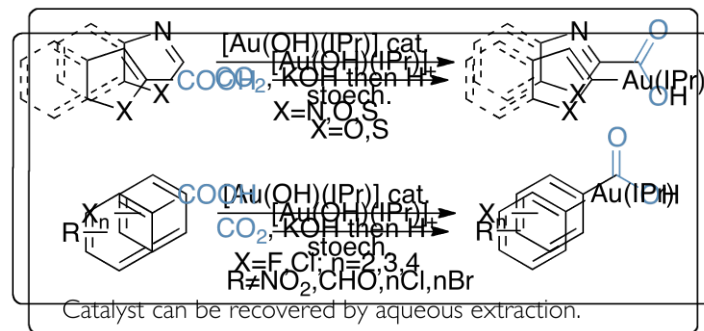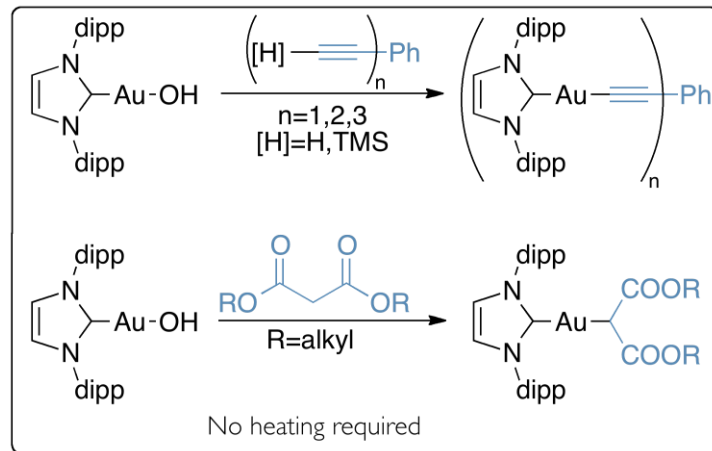
Backbone switches:
- Ferrocene;
- Benzoquinone;
- Enolate;
- Photochromic process.
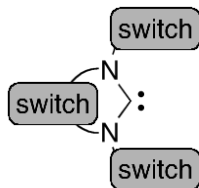
Substituents switches:
- Ferrocene.

Thiophene-bearing AuNHCs undergo reversible photocyclization.

However, no catalytic applications yet.

J. Am. Chem. Soc. **2009**, *912; Angew. Chem. Int. Ed.* **2010**, *6940; Organometallics* **2012**, *3373*

Pathway allows the synthesis
of unsymmetrical NHCs.

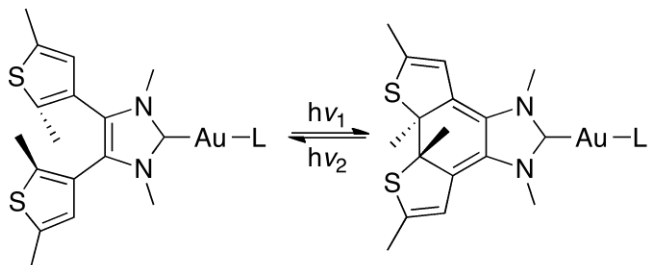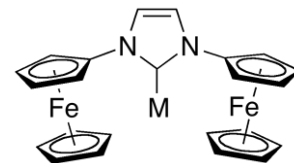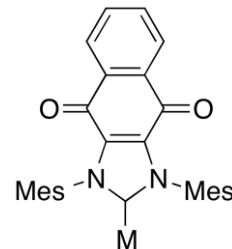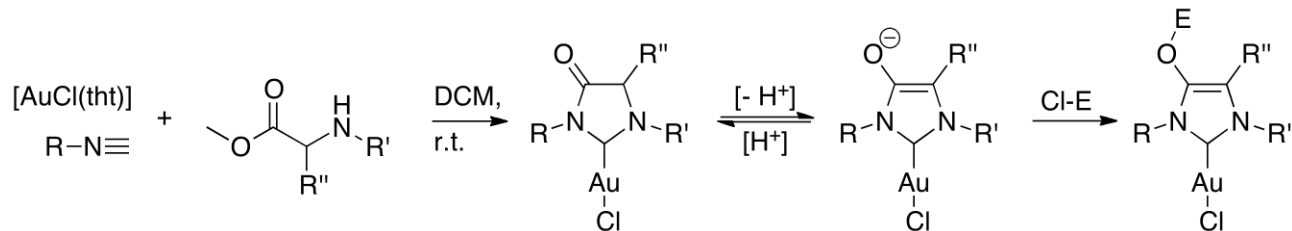Can be trapped under
enolate form with
electrophile (e.g.
benz-aldehyde,
trialkylsilanes).

The ketone moiety decreases the π-donation from the
nitrogen to the carbene, making the amido carbene
more electron-poor. Switching to the enolate provides
an electron-rich system.

This switchable system showed a high activity in the
conversion of terminal and internal alkynes.

TOF [AuCl(NHOC)]: 350h^{-1}
TOF [AuCl(IPr)]: 130h^{-1}
Similar TON

Adv. Synth. Catal. **2011**, *1407*; *Organometallics* **2012**, *3373*
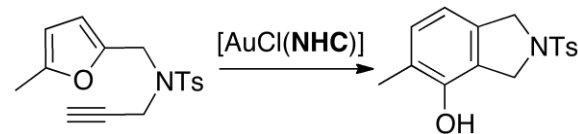
Green(er) chemistry: immobilized and water-solubleAu-NHCs

- Au-NHC covalently bound to and dispersed on support material (silica, zeolithe);
- High efficiency in alkene hydration, cross-coupling and homo-coupling;
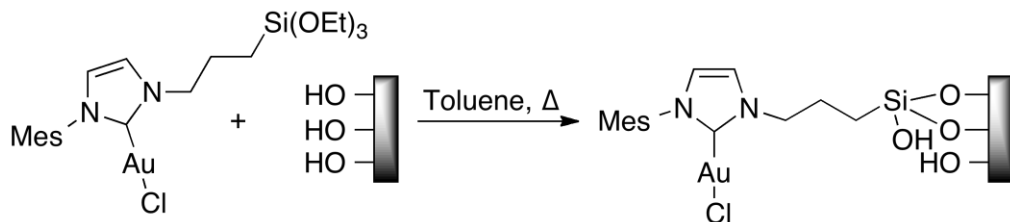- 5 cycles with recycled catalyst showed no loss of efficiency.

- Water-soluble alkyl- and arylsulfonated Au-NHC complexes were used for alkyne hydration;
- Catalyst showed high activity even without acid cocatalyst in monophasic conditions;
- Biphasic conditions also possible;
- In both cases, activity was comparable to phosphine catalysts under similar conditions.

Adv. Synth. Catal. **2006**, *1899*; *Synlett* **2007**, *1771*; *ACS Catal.* **2012**, *399*; *Organometallics* **2010**, *2484*
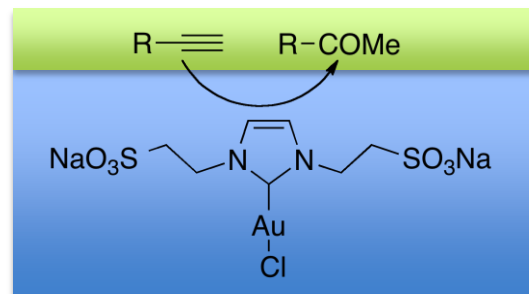
Au(I) drugs such as auranofin inhibate thioredoxin reductase (TrxR) by binding to the Gly-Cys-Sec-Gly motive in the active site; other related enzymes such as glutathione reductase (missing the Sec residue) are also inhibited, but with lesser affinity.
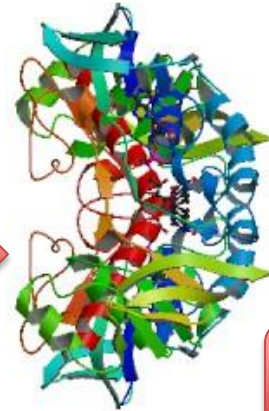
$(Et)_3P \ Au-Cl$

AcO, AcO — O — S-Au-P(Et)$_3$ (OAc, OAc)
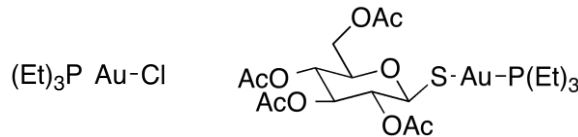
INHIBITION OF TrxR

Reduction of ox. stress

Mitochondrial regulation

Anti-mitochondrial effects, apoptosis

TrxR posesses S- and Se-containing residues (Cys, Sec), with which gold has a high affinity.

- TrxR identified in malaria parasite and human cells;
- TrxR overexpressed in numerous tumor cell lines.

Some antimitochondrial effects caused by gold drugs:

- Decrease of the mitochondrial membrane potentiel;
- Swelling of the mitochondriae (MMP);
- Apoptosis can be caused by the decrease of the ATP pool in mitochondriae.

Auranofin analogues and complexes of biocompatible molecules
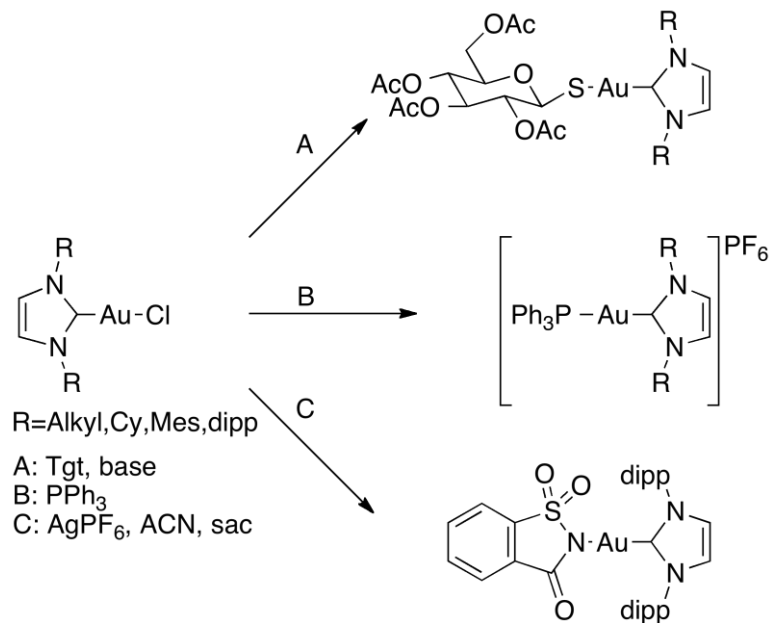
NHC ligands are especially interesting befause it is easy to synthesize series of compounds with slightly varying properties.

Coordinating the gold complex in order to create auranofin analogues is also interesting since it allows to observe the impact of the biomolecules on the activity and the processing of the drug inside the cell.

- Tgt and phosphine complexes showed cytotoxicity under 3 µM for various cell lines, displaying activity superior to *cis*-platin;
- Neutral complexes (saccharine shown) were much less active.

J. Organometallic. Chem. **2005**, *5625; Organometallics* **2006**, *5824; Chem. Eur. J.* **2011**, *6620*

Anti-tumor complexes of biomolecules and peptides

Biomolecules and peptides can be used to help deliver and/or activate the drug.

Coordination of peptides to the metal center induces a loss of activity but would make the complex more selective towards tumorous cells with increased amimo-acid transport activity.

- The Cys-Leu and Cys complexes nevertheless displayed activitiey comparable to *cis*-platin.
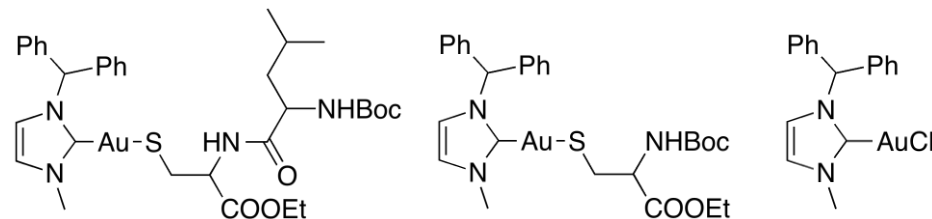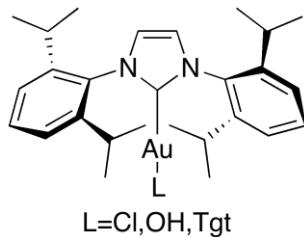

Activity of the complex towards tumorous cells

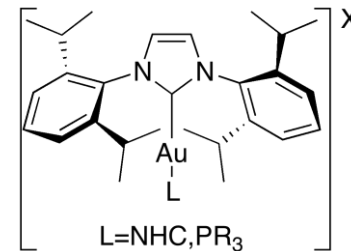|	IC_{50} in µM (HeLa cells, resazurin dye)
[Au(NHC)Cl]	5.8±1.9
[Au(NHC)(Cys)]	8.3±1.4
[Au(NHC)(Cys-Leu)]	29.4±1.8
cis-platin	7.3±0.4

Cationic anticancerous complexes

Cationic compounds were tested for cytotoxicity in carcinoma cells; the neutral complexes [Au(IPr)OH], [Au(IPr)Cl] and the auranofin analogue [Au(IPr)Tgt] were also subject to this study.

These cationic complexes present higher activities than their neutral counterparts, resulting from the processing of the latters into the cell.

L=Cl,OH,Tgt

	IC$_{50}$ in µM (LNCaP cells)
[Au(IPr)Cl]	1.90
[Au(IPr)OH]	1.40
[Au(IPr)Tgt]	1.25
[Au(IPr)(BMIM)]BF4	0.63
[Au(IPr)$_2$]BF4	0.37
[Au(IPr)(PPh3)]BF4	0.73
cis-platin	18

L=NHC,PR$_3$

Cationic lipophilic [Au(NHC)2]X complexes induced mitochondrial swelling (MMP) at µM concentration;

Variation in lipophilicity yielded a family of bioactive compounds, including tumor-selective linear gold complexes.

Assessment of the kinetics of the substitution of a di-NHC complex by Cys or Sec pointed towards a two-step mechanism, with the substitution by Sec being 20 times faster than by Cys.

*Dalton Trans.* **2006**, *3708; J. Am. Chem. Soc.* **2008**, *12570*
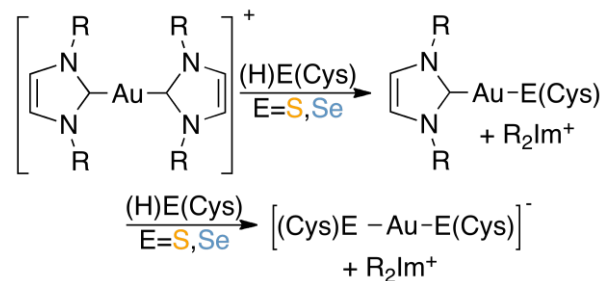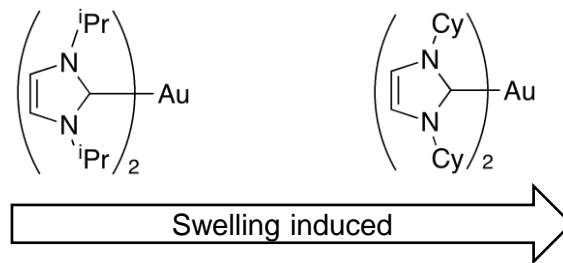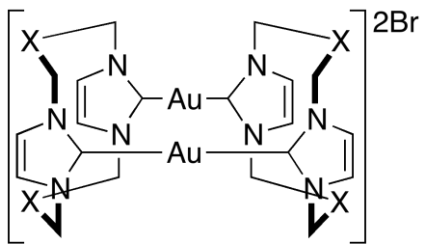
X=CH$_2$,2CH$_3$,1,2-phenyl,
1,3-phenyl,1,3-pyridine,

Dinuclear Au(I) complexes of bridged bidentate NHC show both antimitochondrial and luminescent behaviour.

These compounds can be specially tailored to tune the luminescence to the desired absorption and emission wavelength. Distance between the two gold centers can also be tuned to induce aurophilic interaction and shift the luminescence profile.

Au---Au interactions often gives rise to visible luminescence, due to the strong relativistic electronic effects (**aurophilicity**). Typically, these aurophilic bonds are 3 Å long and comparable in strength to hydrogen bonds.
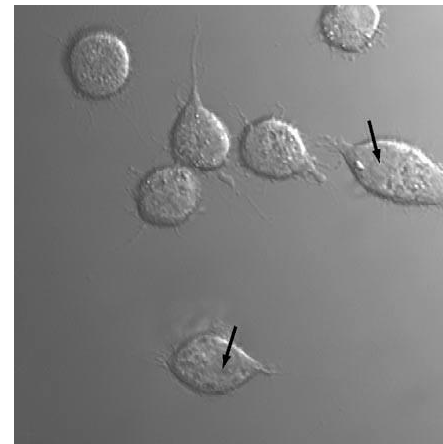

Luminescence image (λ$_{ex}$ 351 nm). White arrows indicate position of nuclei.
(Cis-complex with X=CH$_2$,1,2-phenyl)

J. Inorg. Biochem. **2004**, *1642; Angew. Chem. Int. Ed.* **2006**, *5966; Gold Bull.* **2000**, *3*
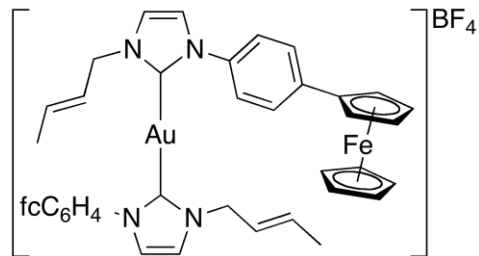
A bis-carbene complex carrying ferrocene moieties was synthesized and tested on tumorous cell lines.

Ferrocene (fc) is an electrophoric and cytotoxic function, which results in high activity and selectivity towards HeLa and leukemia cell lines.
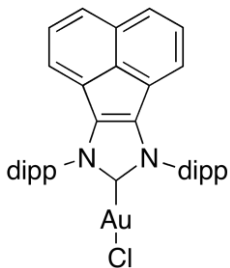

The BIAN ligands present extensive redox behaviour which could be used to control the metal release from drugs.

The Cl complex showed activity towards both Gram-positive and –negative bacterias; the acetate complex was selective towards Gram-positive bacterias.

Imidazoline- and benzimidazole-based complexes showed antimicrobial activity in the same ranges that the standard antibiotic ampicillin.

The nature of the N-substituent is of paramount importance on the antimicrobial activity
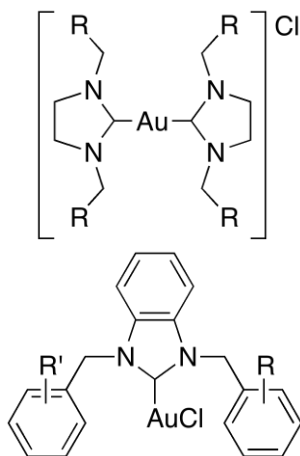
	MIC in µg/mL, *S. Aureus*	MIC in µg/mL, *E. Coli*
R=3,4,5-(OCH$_3$)$_3$	3.12	1600
R=2,4,6-(CH$_3$)$_3$	1600	3.12
R=3,4,5-(OCH$_3$)$_3$, R'=4-^{t}Bu	12.5	200
ampicilin	<3.12	<3.12

Appl. Organometal. Chem. **2004**, 318; *Molecules* **2010**, 2203

N-Heterocyclic Carbenes advantageously replace phosphines ligands in gold coordination chemistry;

- The synthesis of similar ligands with various substituents at the same time is made possible due to the modular synthesis of the ligands; very diverse function can then be incorporated into the ligand.

- Au-NHC catalysts often allow the use of harsher condition, but they also remove the need for some environment-damaging co-catalysts or activating agents;

- The catalysts were tolerant to various substrate moieties

- The production of aurated intermediates opens the way to further functionalization;

- The bioactivity of many Au-NHC complexes can be linked to the lipophilicity of their N-substituents; precise tuning of these can lead to increased selectivity and activity;

- The ancillary gold ligand also moderates the cytotoxicity of the complexes; the rate of processing of the compound in the cell is often dependant of this ancillary ligand.

The most proeminent class of Au-NHC complexes is based on imidazole ligands, due to the easy synthesis of the ligand. However, new classes of NHCs have been developed over the last few years (e.g. triazoles, tetrazoles, pyrazoles, etc.).

Moreover, a fine tuning of the electronic factors, as well as sterics, should be investigated;

- Novel Au-NHC complexes of these ligands will be (or are) tested in comparable reactions;
- New ways to stabilize the active specie need to be found to expand the range of compatible reactions;

- NHCs based on biomolecules (e.g. xanthine alkaloids) should display new and interesting activities;
- The investigation of new, selective ancillary ligands should be pursued.

Synthesis-wise and user-wise, what are the advantages of Au-NHCs over Au-phosphines complexes? What are the possibilities for "greener chemistry" arising from the use of these ligands?

Which properties of Au-NHC complexes were critical to induce apoptosis in cells? Which pathways are supposed to be active in tumor repression?

Non-classical Heterocycle Carbene: Recent Applications In Small Molecule Activation And Organometallic Chemistry

LI Yifan

Frontiers in chemical synthesis II
Heterocycle chemistry
23 th May 2012

Content

Questions to public
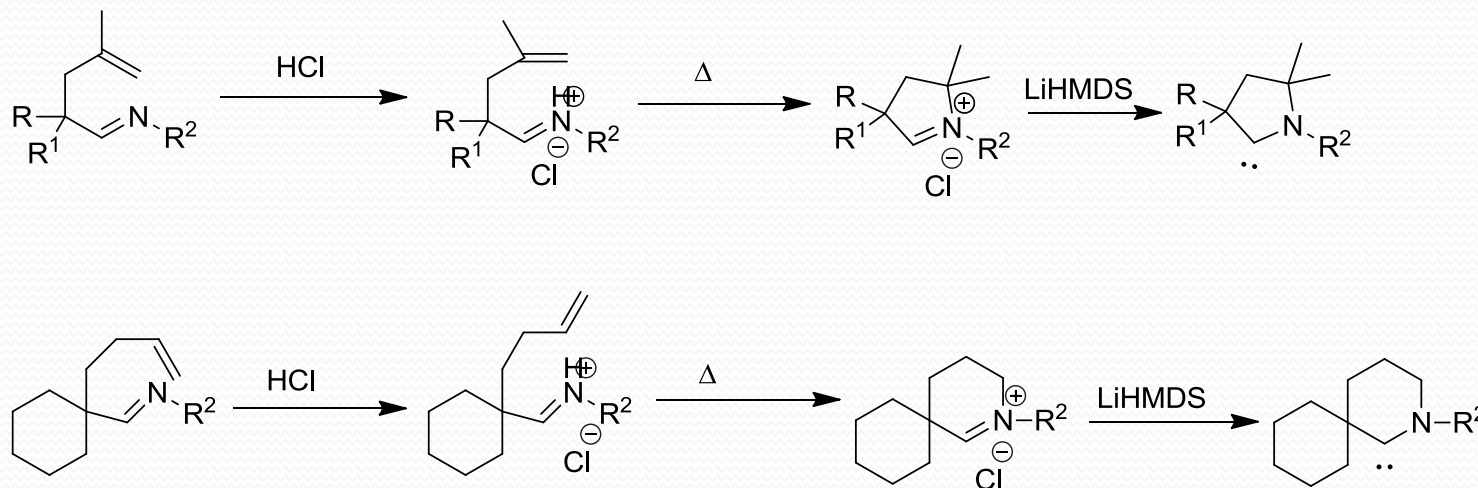
1. From the aspect of orbital energy, the difference of NHC and CAAC in ability of chelating with organometallic catalyst, and the difference could be for the reactivities of the catalyst?

2. What are the differences between the heterolytic cleavage of H_2 for metal center and CAAC?

3. Why is the activation of P_4 important in organic chemistry?

4. What is the different mechanism in H-X (X= Si, B, P) between metal and CAAC during the primary interaction?

What is cyclic alkyl amino carbene (CAAC)?

Classical N-heterocyclic carbene
cyclic alkyl amino carbene
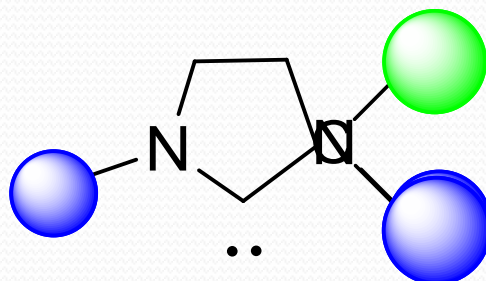
Angew. Chem. Int. Ed. **2005**. *44*. 5705

The difference between NHC and CAAC
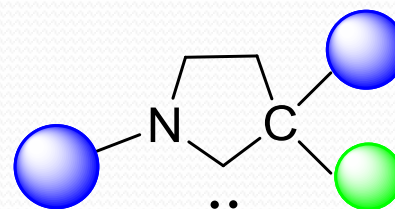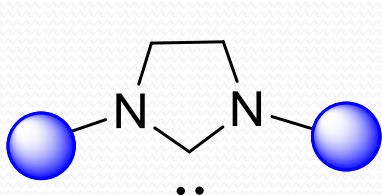
LUMO

more electrophilic
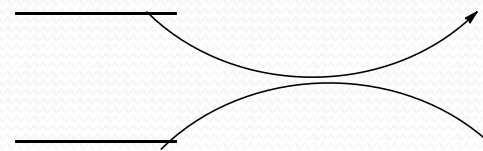
more nucleophilic

HOMO

Question1. From the aspect of orbital energy, the difference of NHC and CAAC in ability of chelating with organometallic catalyst, and the difference could be for the reactivities of the catalyst?

Organometallic, **2001**, *30*, 5304

The genenral procedure to synthesize CAAC

CO fixation with CAAC

Ketene is an unstable intermediate which is tough to be isolated

Ar: 2,6-*i*PrC6H3

blue crystal
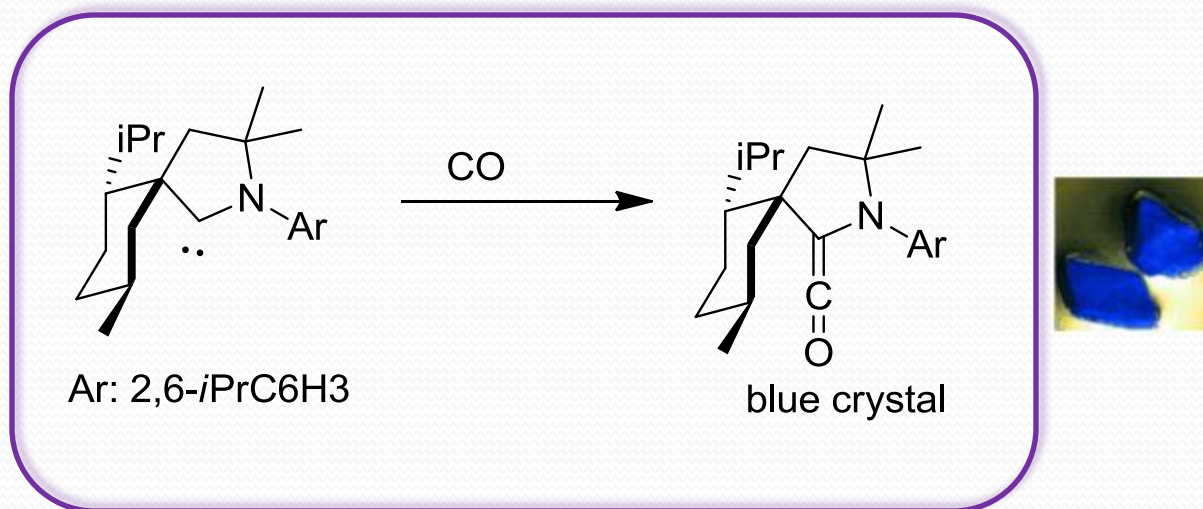
Angew. Chem. Int. Ed. **2006**. *45*. 3488

CO fixation with CAAC

Which NHC can't do

R= adamentyl, H
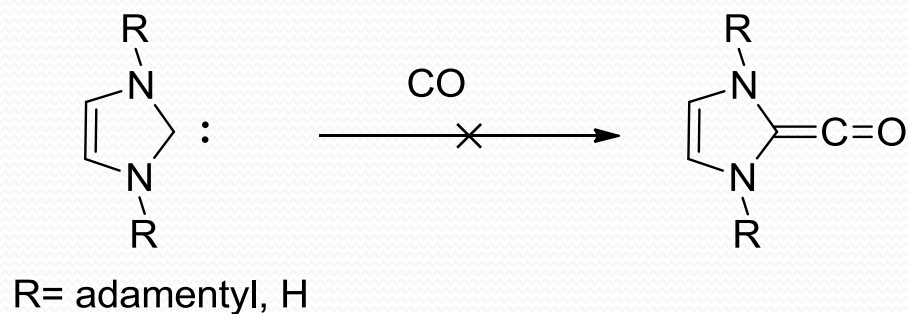
With computational study, there is only a non-bond interaction complexe could exit

8
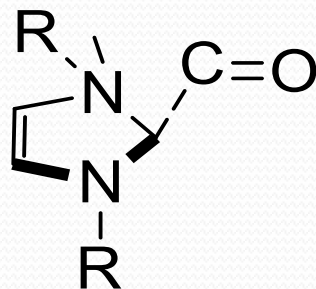
Activation of H_2

Which transition metals always do
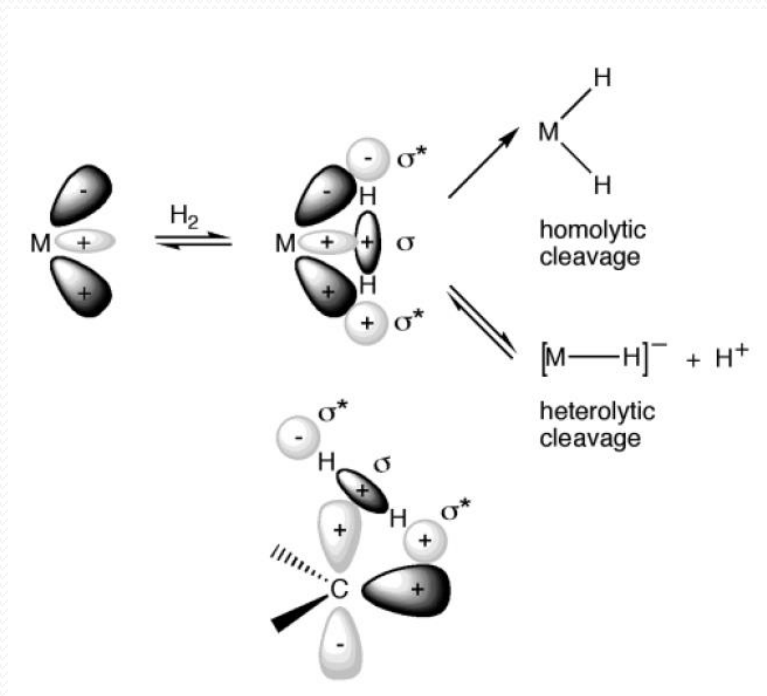
Science, **2007**, *316*, 439-441

Activation of H_2

Singlet carbene resembles transition metal center
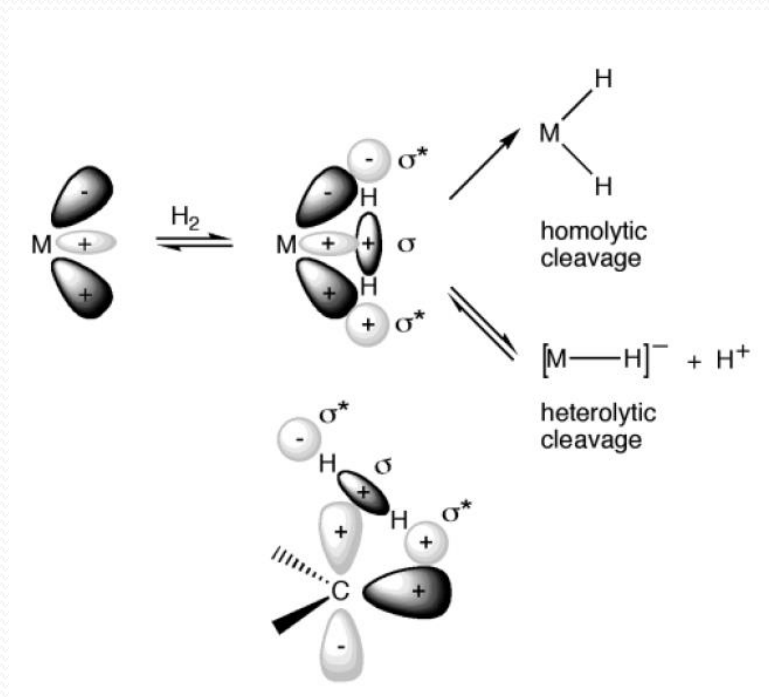
Science, **2007**, *316*, 439-441
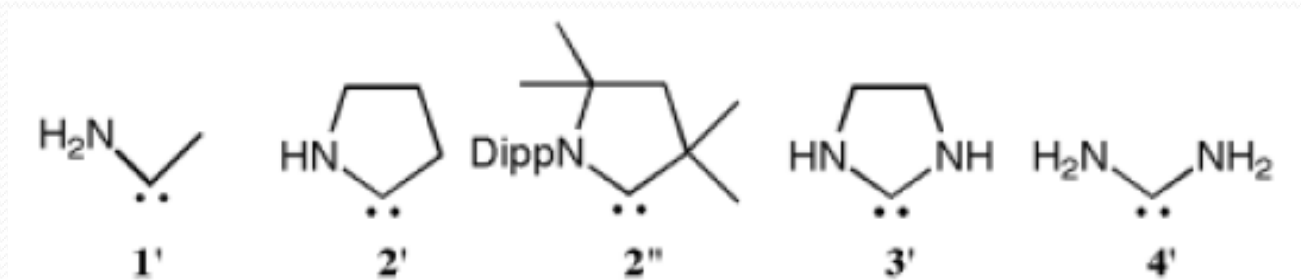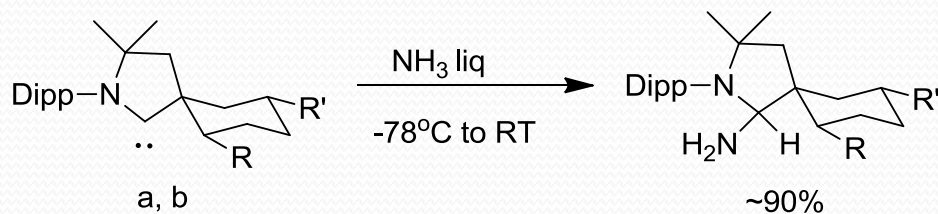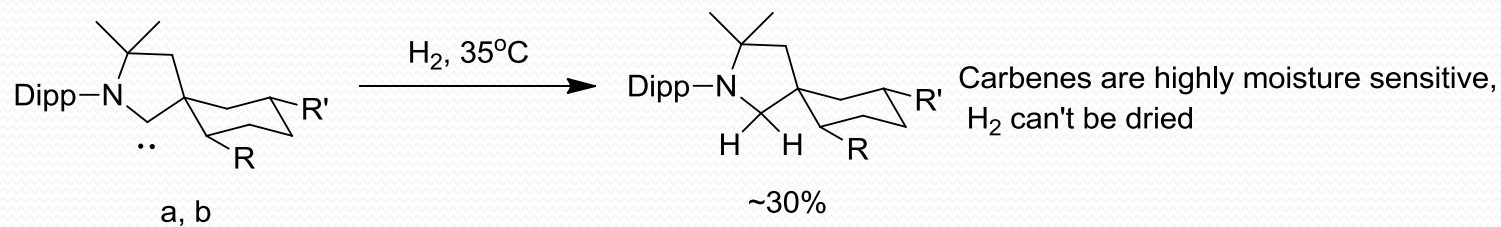
Activation of H$_2$

Table 1. Calculated energy of the HOMO (E_{HOMO}) and singlet-triplet energy gap [$-(E_S - E_T)$] for the model carbenes shown in Fig. 4, as well as energy changes (ΔE) and activation energies ($\Delta E^{\ddagger}$) for their reactions with H$_2$ and NH$_3$ calculated at the B3LYP/6-311 g** level of theory.

	1'	2'	2"	3'	4'
E_{HOMO} (eV)	−5.0	−5.0	−4.9	−5.2	−5.1
$-(E_S - E_T)$ (kj/mol)	139.2	193.5	188.9	285.1	214.0
$\Delta E(H_2)$ (kj/mol)	−211.8	−189.4	−180.0	−106.3	−121.0
$\Delta E(H_2)^{\ddagger}$ (kj/mol)	93.0	99.1	108.3	150.0	147.8
$\Delta E(NH_3)$ (kj/mol)	−161.9	−139.3		−70.8	−73.4
$\Delta E(NH_3)^{\ddagger}$ (kj/mol)	87.4	94.5		141.3	137.5

Question2. What are the differences between the heterolytic cleavage of H$_2$ for metal center and CAAC?

Science, **2007**, *316*, 439-441

Activation of NH_3

Which transition metals barely can do, because of Werner type complexe

Table 1. Calculated energy of the HOMO (E_{HOMO}) and singlet-triplet energy gap [$-(E_S - E_T)$] for the model carbenes shown in Fig. 4, as well as energy changes (ΔE) and activation energies ($\Delta E^{\ddagger}$) for their reactions with H_2 and NH_3 calculated at the B3LYP/6-311 g** level of theory.

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$\Delta E(NH_3)^{\ddagger}$ (kj/mol)	87.4	94.5		141.3	137.5

Science, **2007**, *316*, 439-441

Activation of H_2 and NH_3

H$_2$, 35°C

Dipp−N

a, b

Dipp−N

H   H   R

~30%

Carbenes are highly moisture sensitive, H$_2$ can't be dried

NH$_3$ liq

-78°C to RT

Dipp−N

a, b

Dipp−N

H$_2$N   H   R

~90%

Dipp: 2,6-i-Pr$_2$C$_6$H$_3$; a: R = R' = H; b: R = Me, R' = i-Pr

NHC can do neither
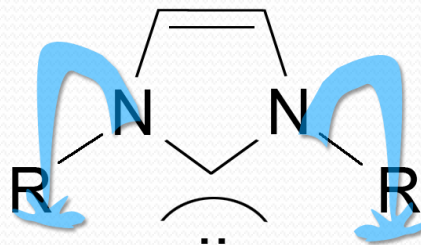
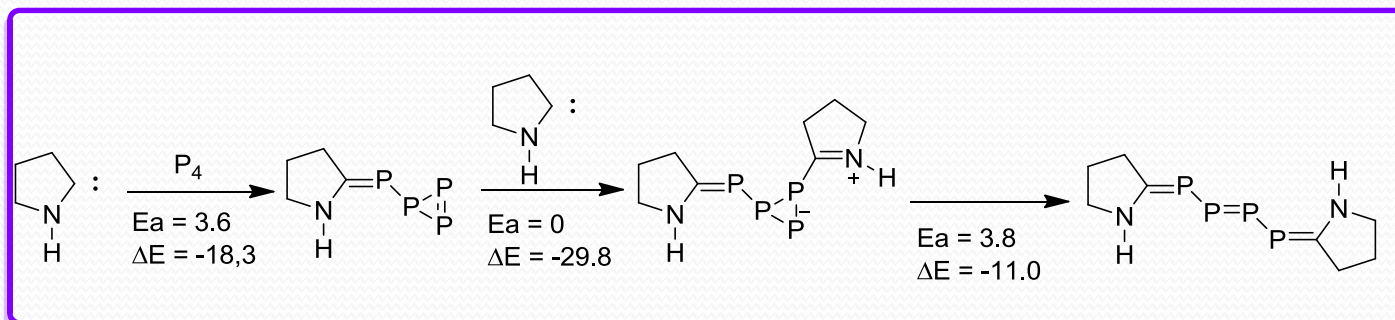*Science*, **2007**, *316*, 439-441. *Chem. EUR. J*, **1996**, *2*, 772

Activation of P_4

which some Transition Metals can do and NHC can do a different way

Ar= 2,6-diisopropylphene

0.5P_4

Major isomere

65% in all isomeres

minor isomere

Angew. Chem. Int. Ed. **2007**. *46*. 7052

Activation of P$_4$

35% from CAAC + P$_4$
95% diasteoselectivity
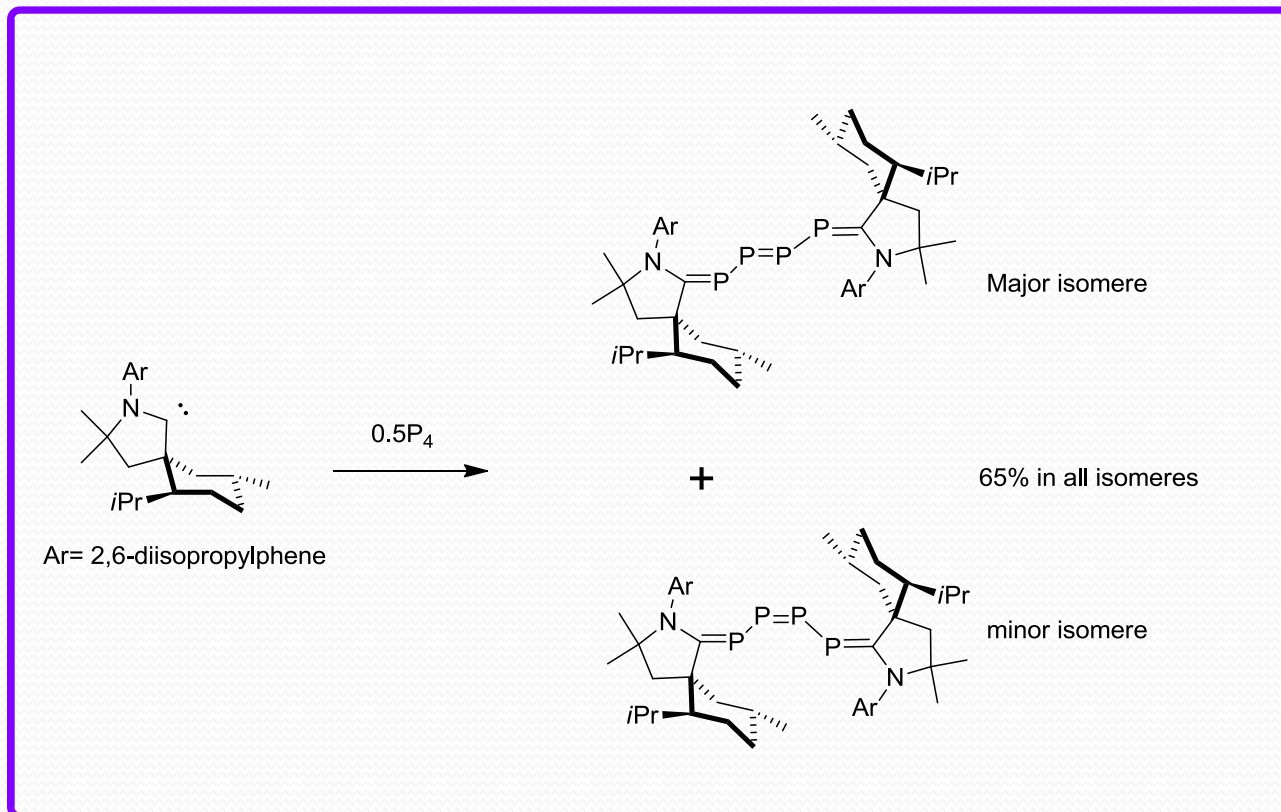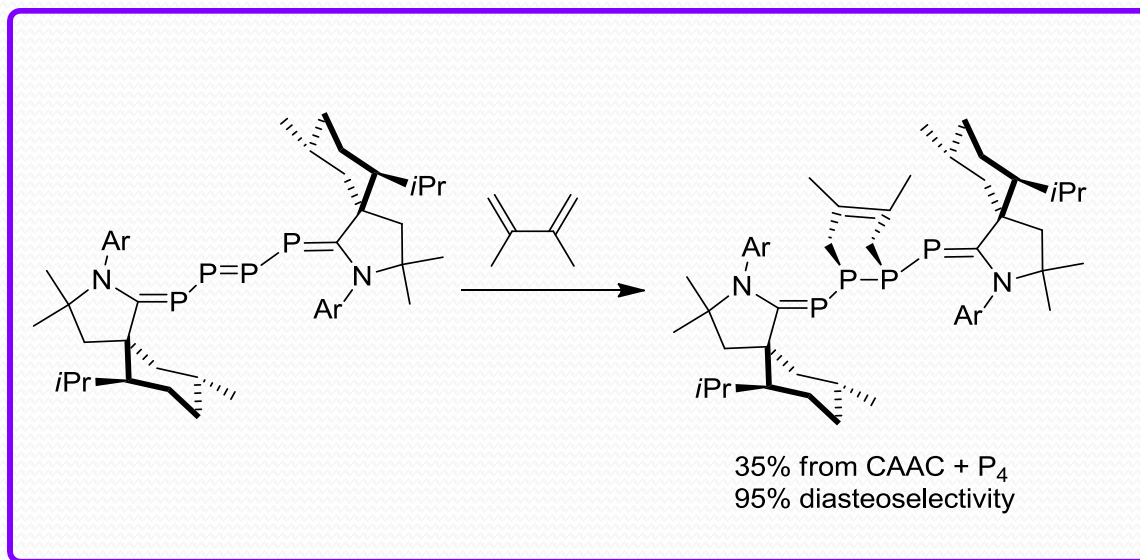
Caculation at the B3LYP/6-311g(d,p)level

Angew. Chem. Int. Ed. **2007**. *46*. 7052

Activation of P_4

The capture of intermediate

Ar= 2,6-diisopropylphene

52% in all, one diastereomer
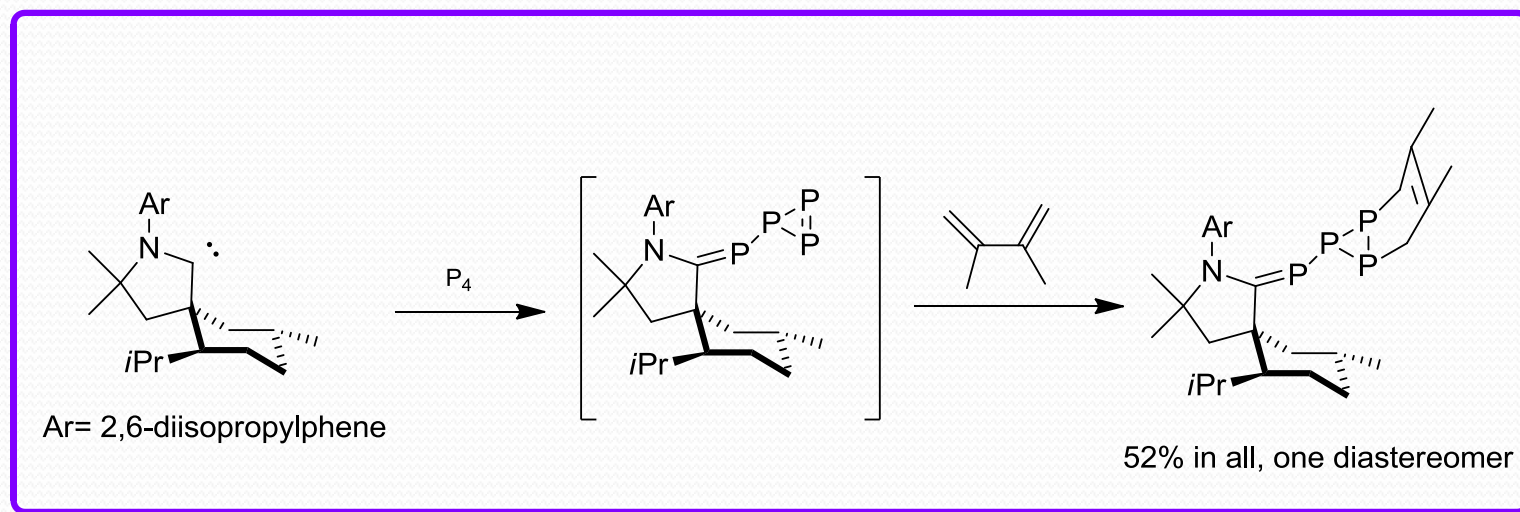
Question 3. Why is the activation of P_4 important in organic chemistry?

Angew. Chem. Int. Ed. **2007**. *46*. 7052

Activation of P_4

P_4 can be further activated into P_2 specie

Ar= 2,6-diisopropylphene

12% as a minor product
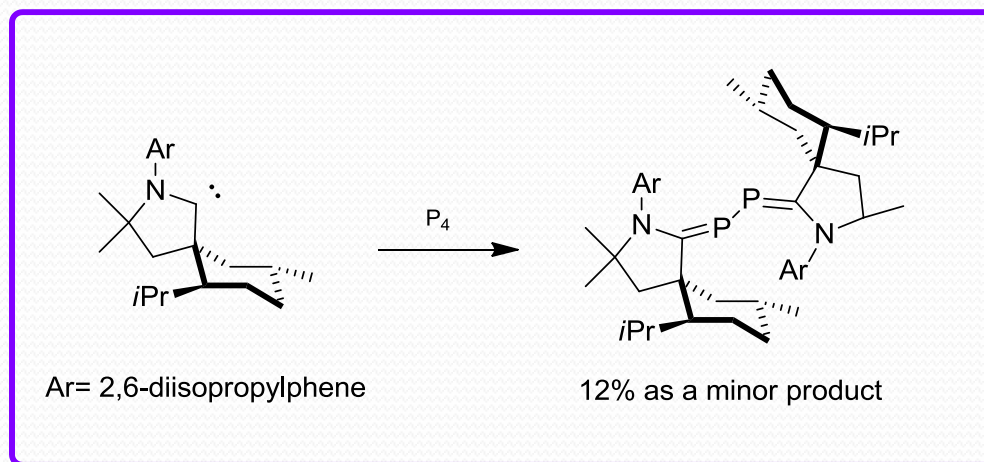
P_1 specie can be obtained by another carbene

Stabilisation of PN (phosphorus mononitride)

Which NHC and CAAC have to do the work together

PN specie is detected in the wind of the oxygen rich super giant star

ARE YOU READY?

THINGS START TO GET CRAZY!!

68% in two steps

85%

Dipp = 2,6-diisopropylphene
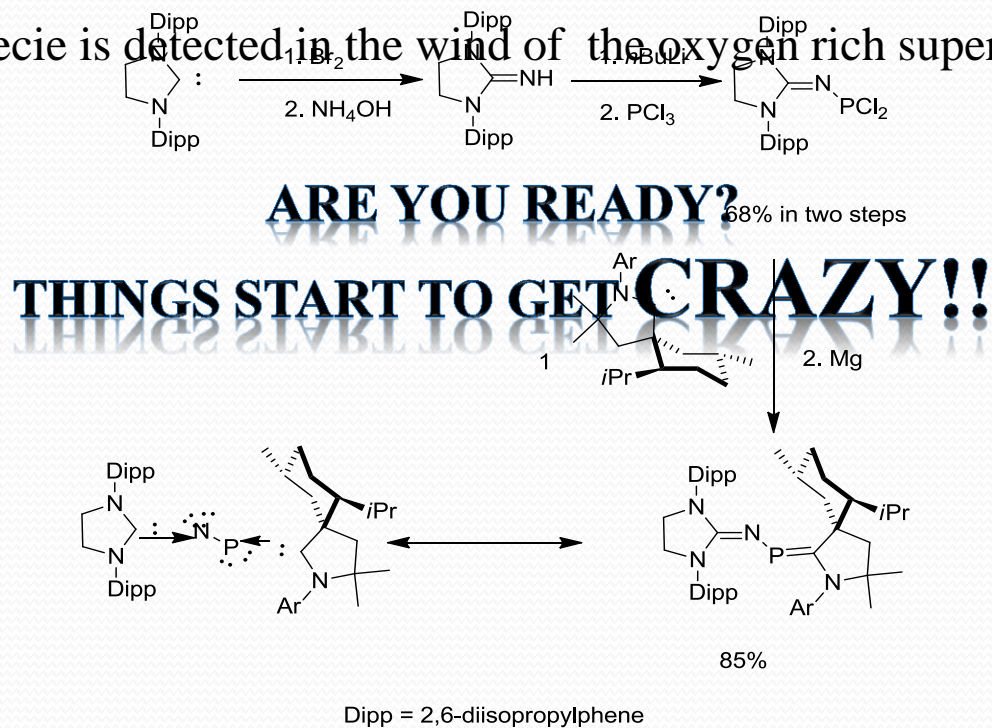
Activation of Si-H bond

Which NHC and CAAC can do in different way from metals

H_3SiPh

14h RT

2a 91% dr= 2:1
2b 83%

$HSi(OEt)_3$

48h, RT

3a 64% dr=3:1
3b 73%

1a, 1b
enantiopure starting material

H_2SiPh_2

16h, 80°C

4a no reaction
4b 65%

Dipp: 2,6-i-Pr$_2$C$_6$H$_3$; a: R = Me, R' = i-Pr; b: R = R' = H

Angew. Chem. Int. Ed, **2010**, *49*, 9444
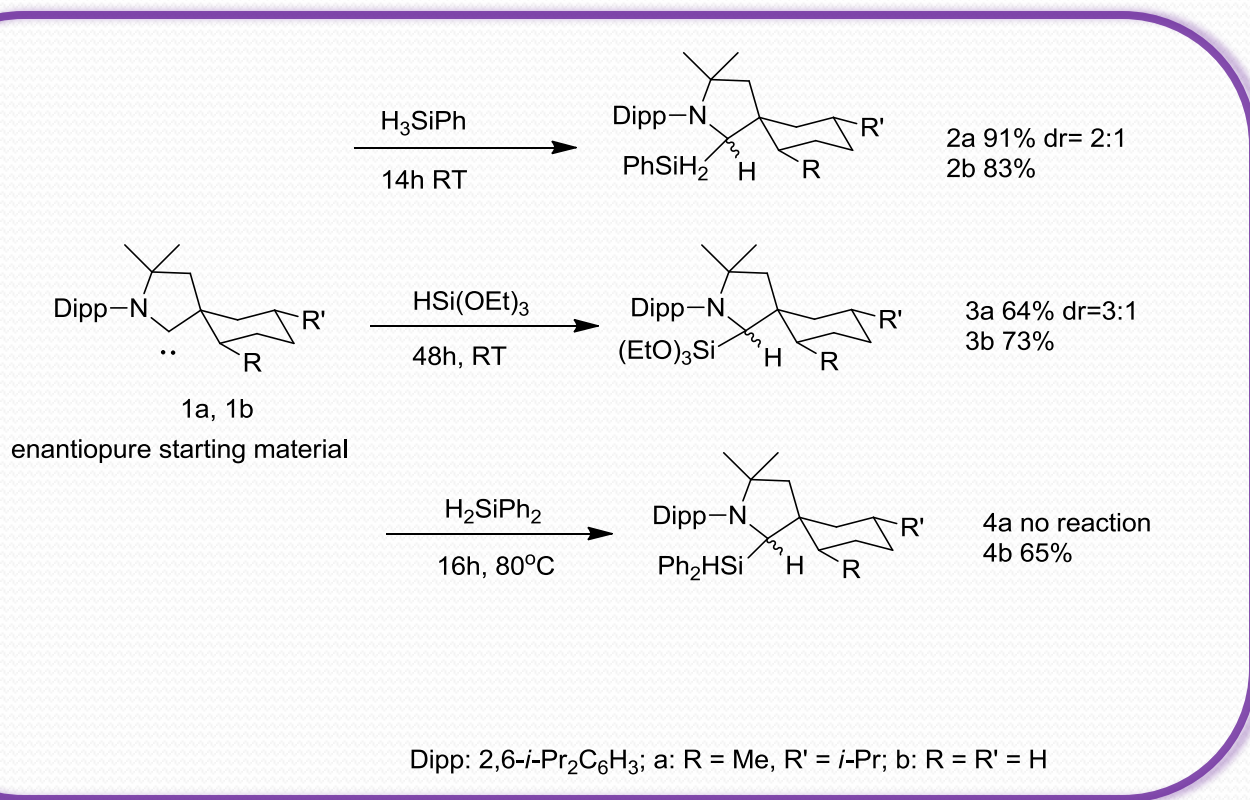
Activation of B-H bond

Which NHC can't do and metals can do in a different way

BH$_3$

2h RT

Lewis acid-base product

Dipp−N

1a, 1b
enantiopure starting material

H−B

2h, RT

5a 79% dr= 1:1
5b 85%

Dipp: 2,6-i-Pr$_2$C$_6$H$_3$; a: R = Me, R' = i-Pr; b: R = R' = H

Angew. Chem. Int. Ed, **2010**, *49*, 9444
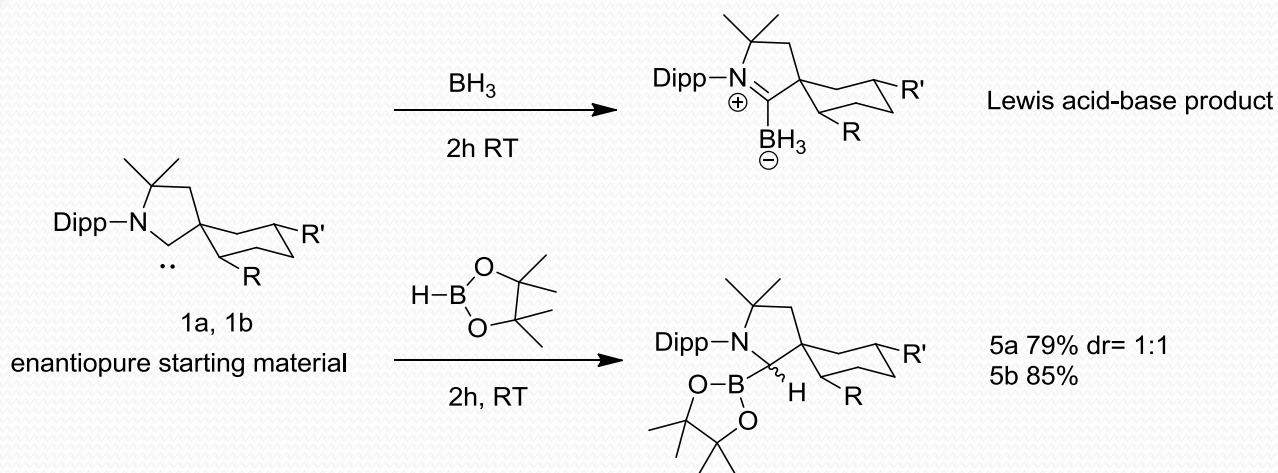
Activation of P-H bond

Which NHC and CAAC can do in a different from metal

This reaction is done with that phosphane reacts with 1a, 1b together to give 10a, 10b mixture of 1.0: 1.4: 1.3: 1.8
10a 93% dr= 3:1
10b 96%

10a, 10b no reaction
10c 73%

Dipp: 2,6-*i*-Pr$_2$C$_6$H$_3$; a: R = Me, R' = *i*-Pr; b: R = R' = H

Angew. Chem. Int. Ed, **2010**, *49*, 9444
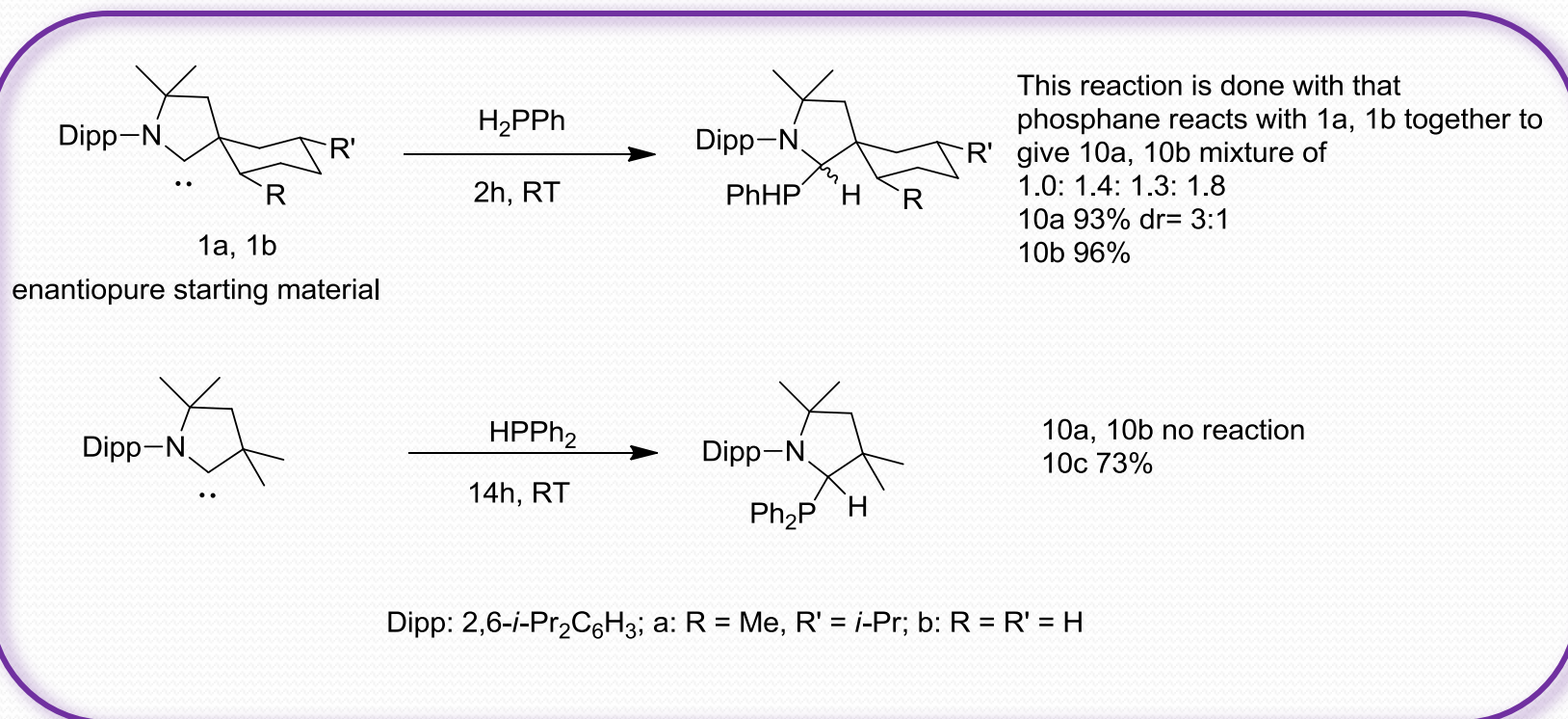
Activation of E-H bond (E = Si, B, P)

Plausible mechanism
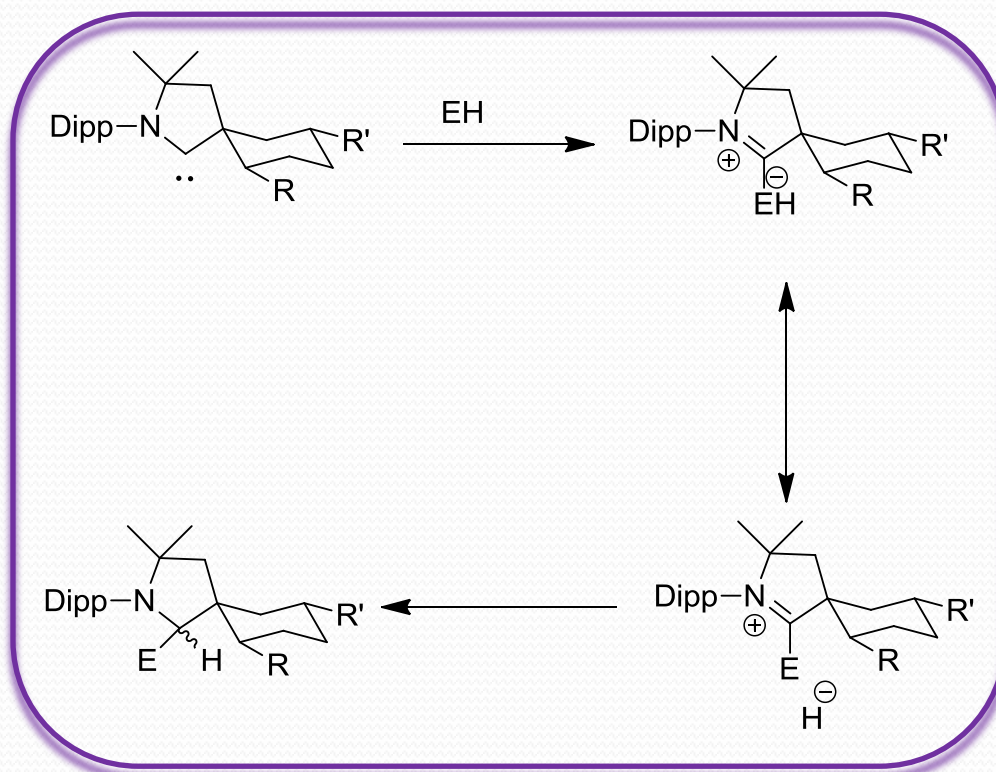
Question 4. What is the different mechanism in H-X (X= Si, B, P) between metal and CAAC during the primary interaction?

Angew. Chem. Int. Ed, **2010**, *49*, 9444

Stabilisation of BH specie

Which NHC can also do
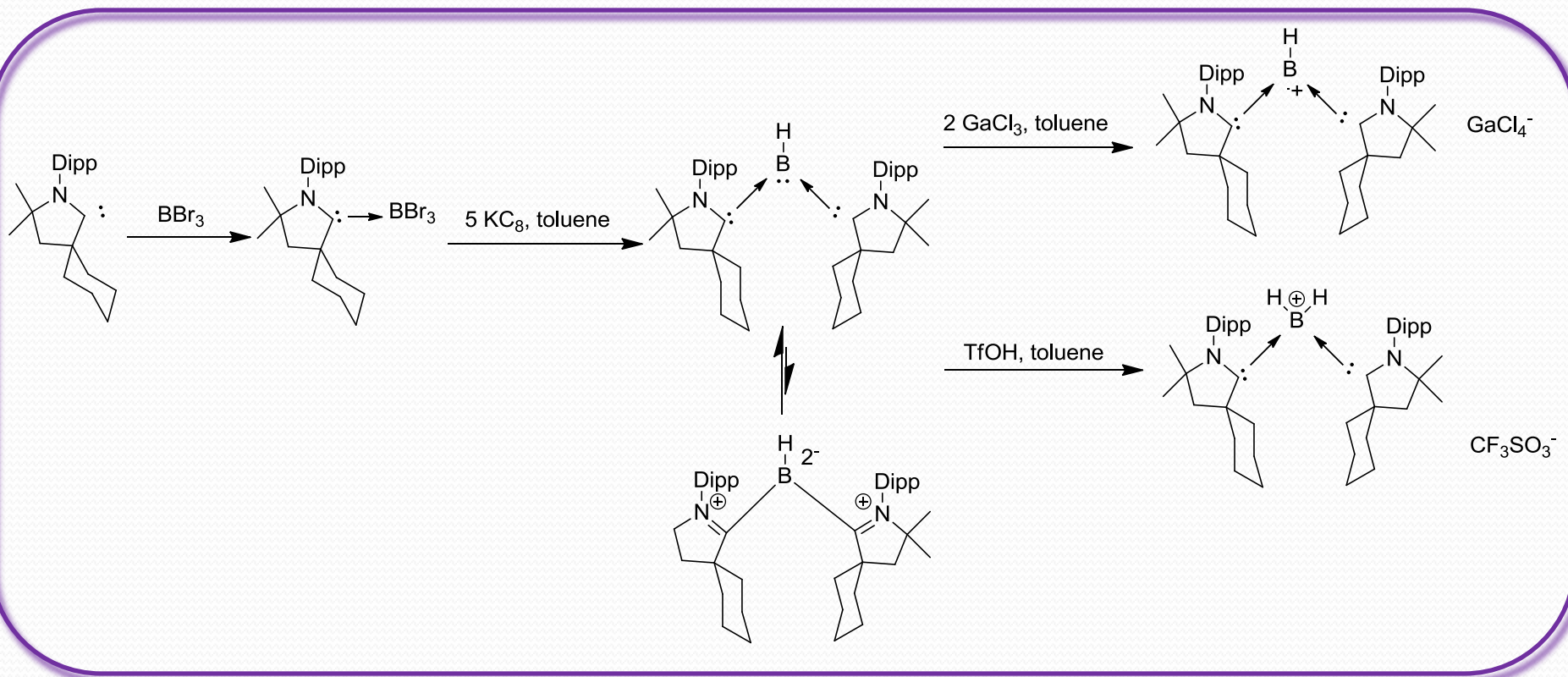
CAAC Ru catalyst

The synthesis of CAAC Ru catalyst
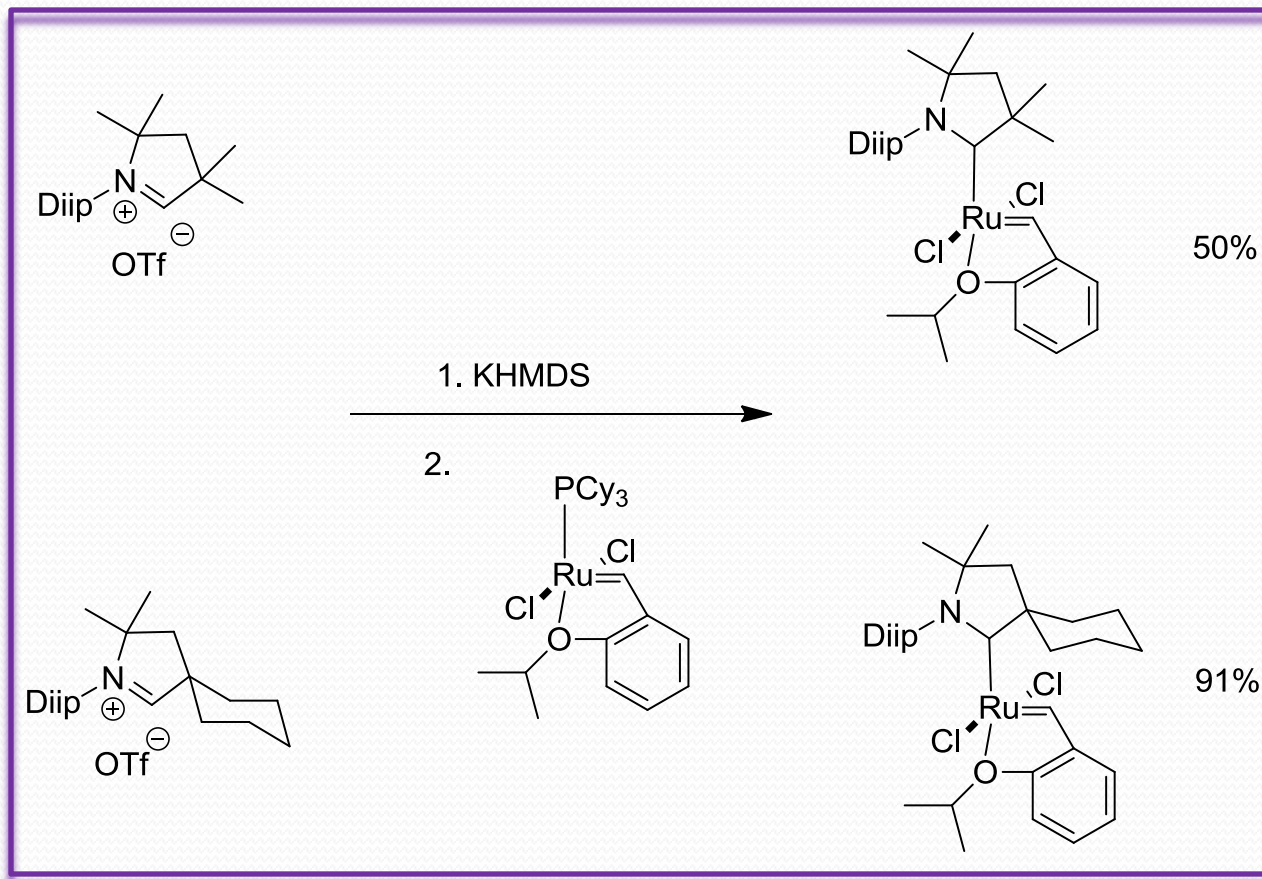
Angew. Chem. Int. Ed, **2007**, *46*, 7262

CAAC Ru catalyst

The different activity compared classical NHC Ru catalyst
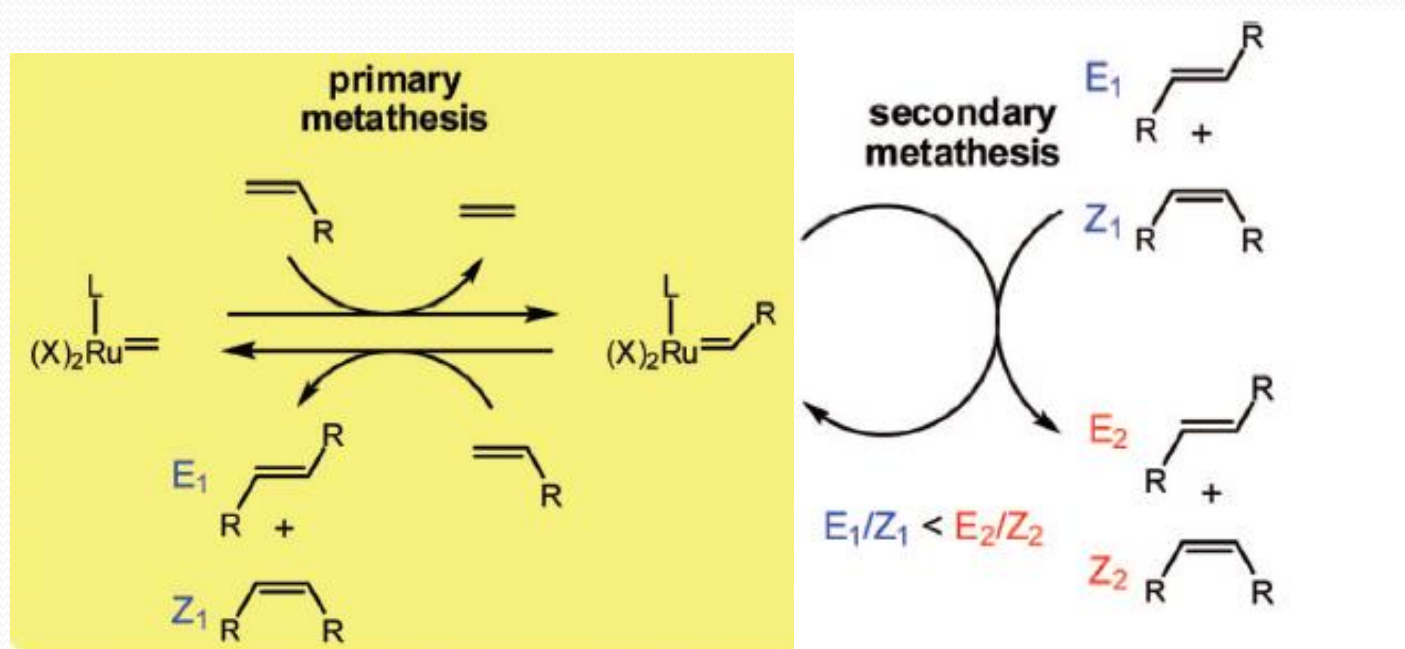
Due to the competition reaction, E olefin is major isomere

Organometallic, **2008**, *27*, 563
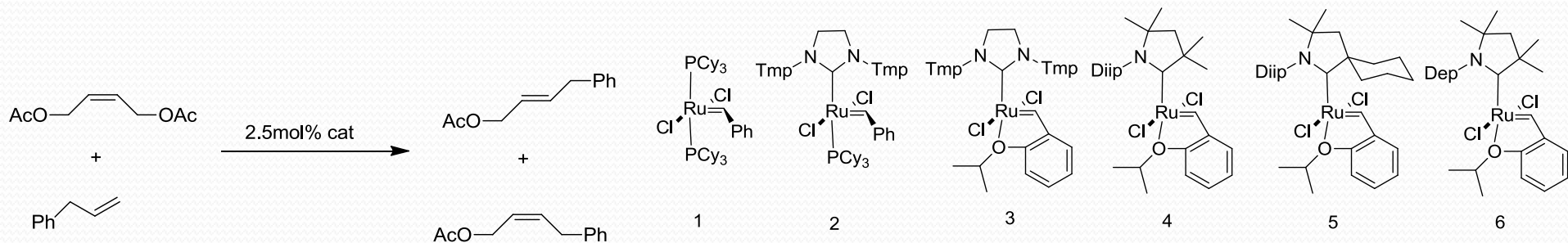
CAAC Ru catalyst

Tmp: 2,4,6-methylC$_6$H$_3$; Diip: 2,6-iPr$_2$C$_6$H$_3$; Dep: 2,6-ethylC$_6$H$_3$

E/Z

Conversion to Product E+Z
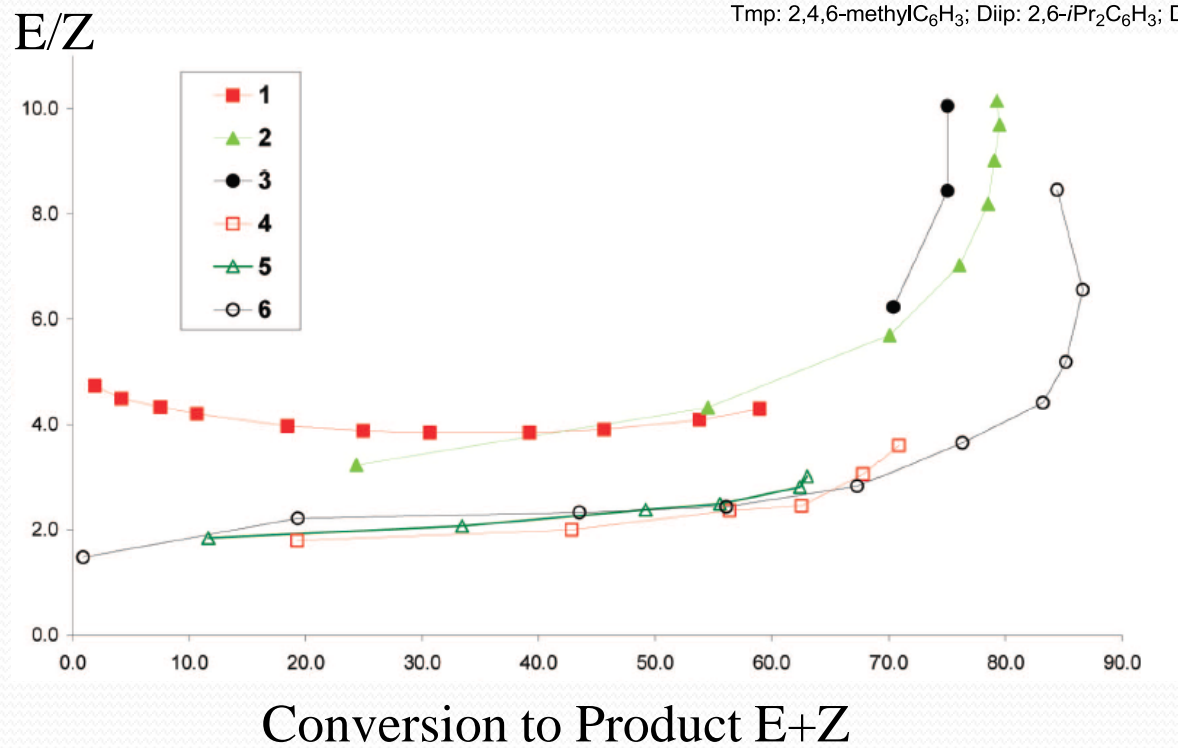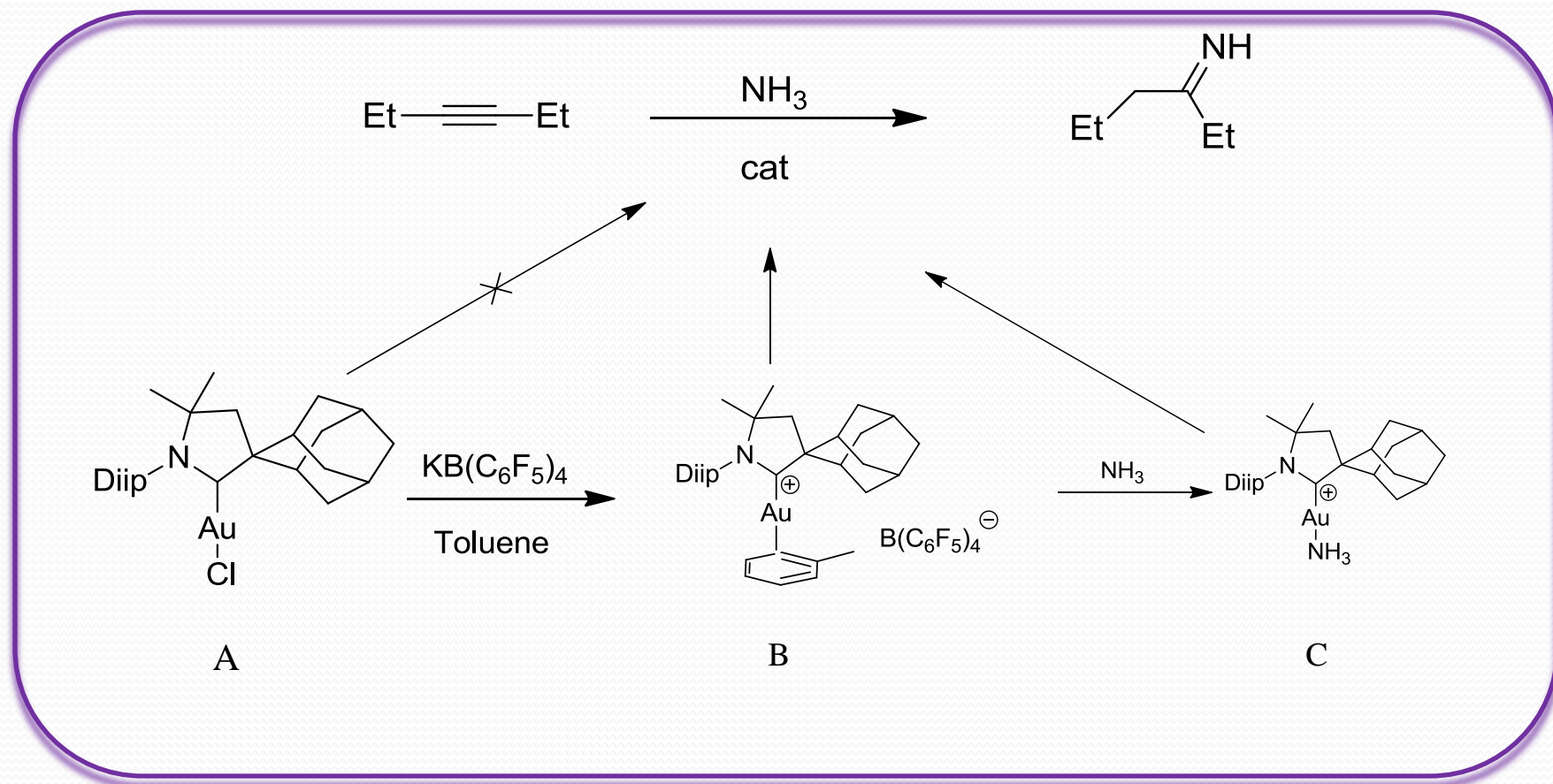
CAAC Au catalyst

CAAC Au catalyst
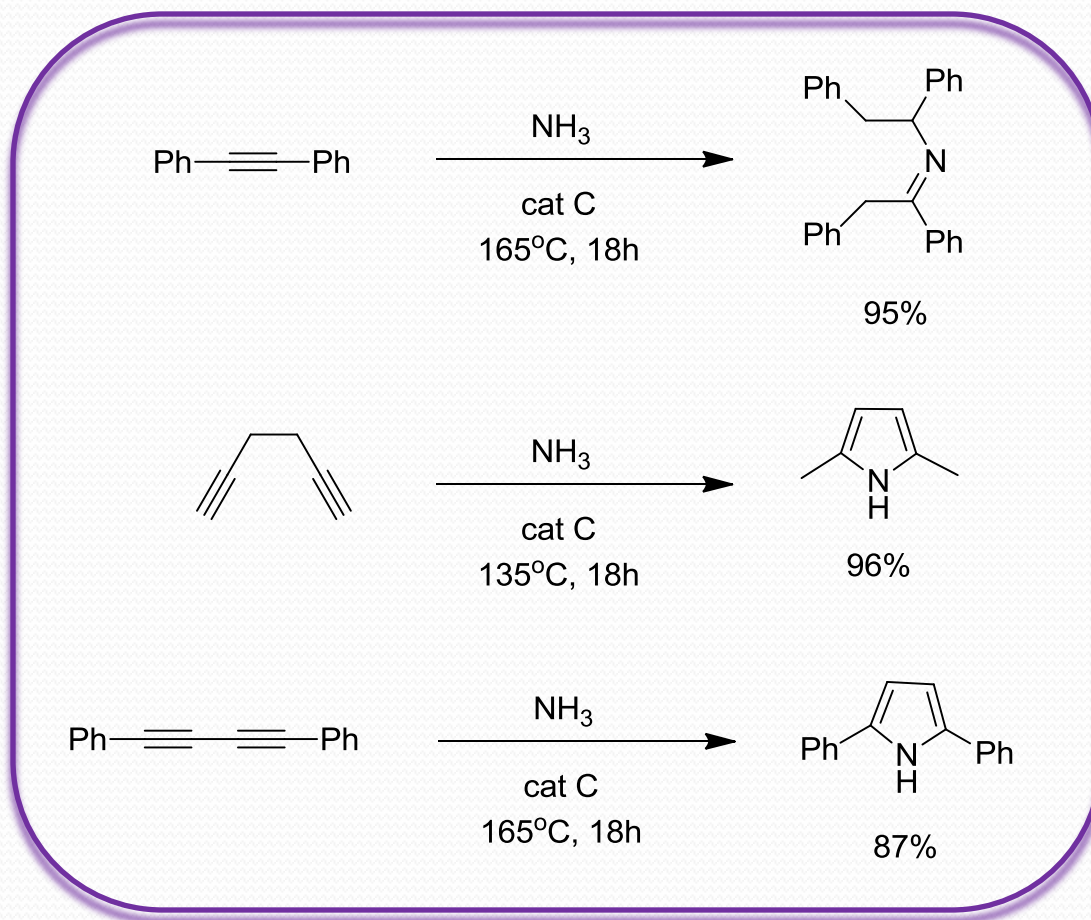
Conclusion

- Cyclic alkyl amino carbene (CAAC) and its different electro property

- CAAC in small molecule activation and the different reactivaties compared to transition metals and NHC

- CAAC as ligant in organometallic catalyst (Ru and Au) and its different reactivities

THANK YOUR FOR YOUR KIND ATTENTION

Mr & Mrs Carbene
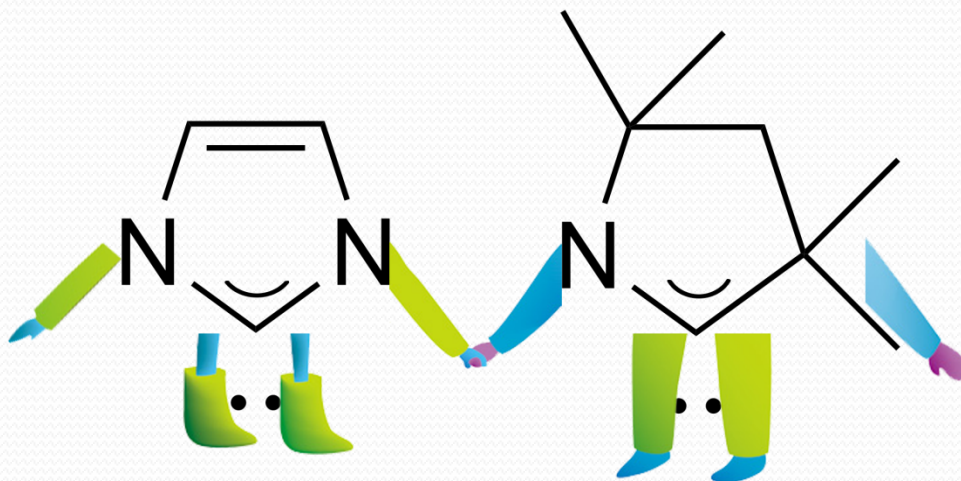
Furan and Pyran Derivatives Synthesis from Functionalized Allenes by Gold Catalysis

Van-Manh PHAM

23 Mai 2012

Plan

- **Au-catalysis**
- **Allenes chemistry**

- **Pioneering works : Allenones**
- **Halogeno-allenones**
- **Allenic esters or allenoates**
- **α-Hydroxy allenes or allenols**
- **Applications synthetic**
- **Tandem reactions**
- **Exo-attack selective / enantioselective**
- **Au-cat. Recycle**

- **Conclusion and development**

Gold catalysis

- **Less expensive than Rh, Pt**
- **Characteristics of Homogenous Gold Catalysis**
  - Soft transition metal: ideally suitable to activate selectively C-C triple bonds and double bonds in presence of many others functional groups
  - Allows for the formation of C-C, C-O, C-N, C-S bonds
  - Au(I) and Au(III) are stable oxidation states
  - Non-toxic
  - Faster than other transition metals for the same reaction
  - Low tendency for β-hydride elimination
  - Fast proto-demetallation
  - Easy to reduce, difficult to oxidize
  - Cross-coupling chemistry difficult with Au

Gold catalysis

Some typical Au catalysis

■ **Ph$_3$PAuCl, and converted to cationic Au by Ag salts**

Ph$_3$P–Au
Cl
Cl
Au–PPh$_3$
$\xrightarrow{\text{AgX}}$
PPh$_3$Au$^+$X$^-$ + AgCl

X = SbF$_6$, BF$_4$, OTf

■ **AuCl$_3$ and NaAuCl$_4$**

■ **Advantage of Au cat. compare to Ag, Pd**
- Shorter reaction time
- Milder condition
- Low cat. loading

Allenes chemistry

Highly valuable synthetic :undergo a variety of transformations[1]

- Ionic Additions to Allenes
- Cycloadditions of Allenes
- Cyclizations of Allenes
- Transitions-Metal-Catalyzed Cross-Couplings of Allenes
- …
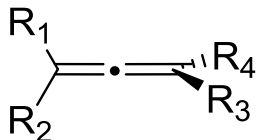
Axial chirality: transformation with chirality transfer

1) Krause et al., *Modern Allene chemistry*

First Au-catalyzed addition of a heteroatom nucleophile has been accomplished by using AuCl$_3$[2]
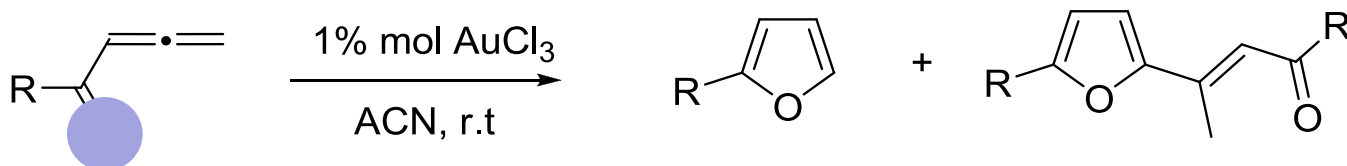
R = 4-MeOC$_6$H$_4$CH$_2$ 66 : 34 (91%)

     4-NO$_2$C$_6$H$_4$ 96 : 4   (92%)

     Me   50 : 50 (94%)

- **AgNO$_3$ (5% mol) for 1 week**
- **PdCl$_2$(ACN)$_2$ (1% mol) for 1h**
- **AuCl$_3$ (1% mol) for 1 min at rt**
- **Au cat. can be decreased to 0.1%**

2) Hashmi et al., *Angew. Chem., Int. Ed.* **2000,** *39,* 2285

Mechanism
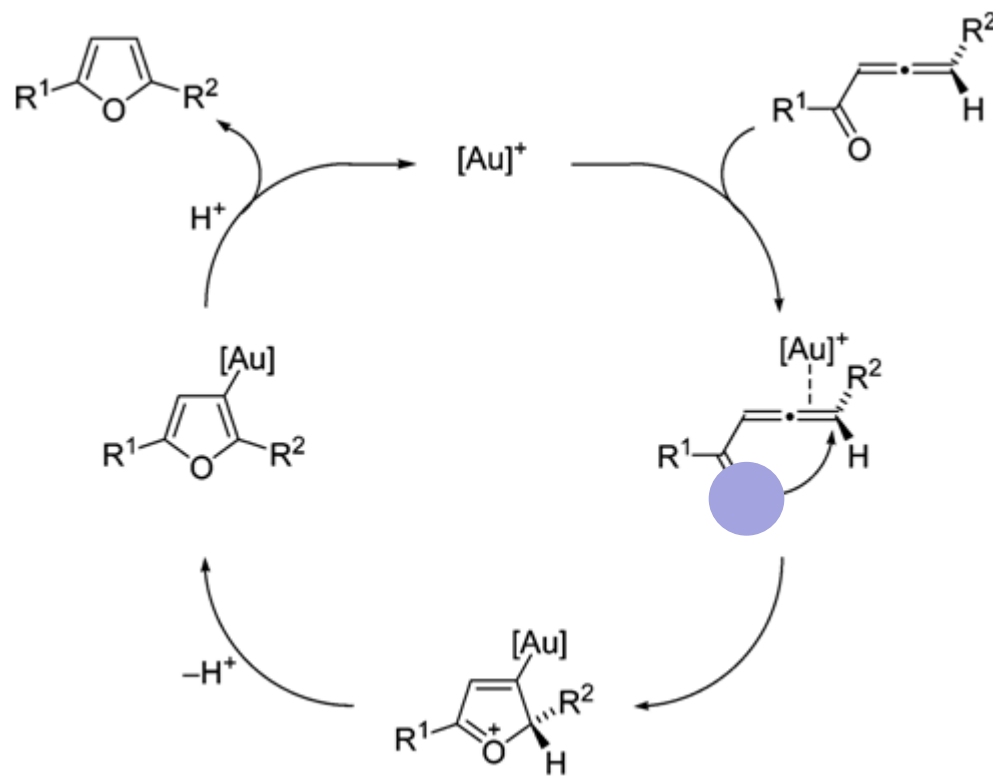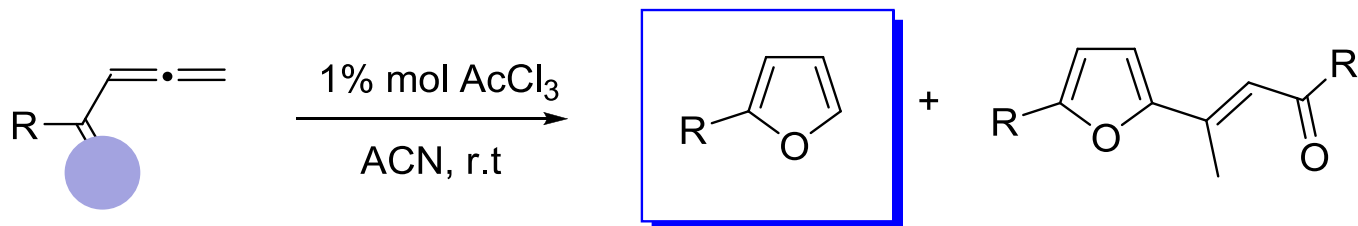
Formation of side product
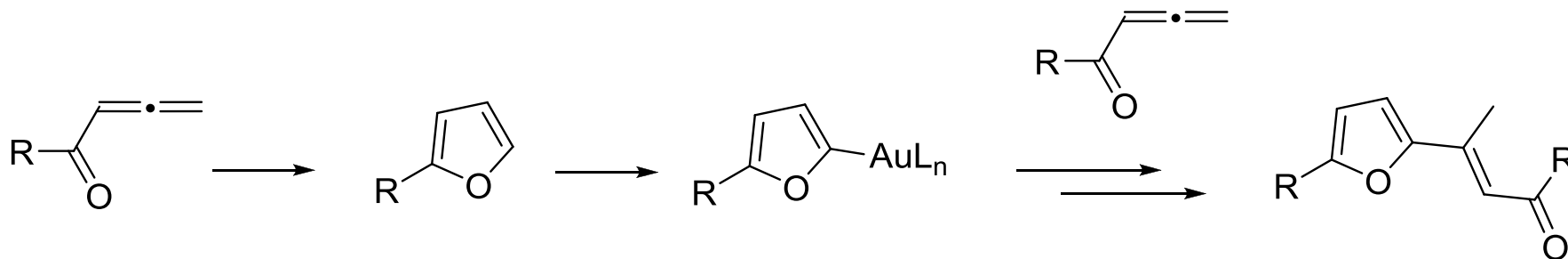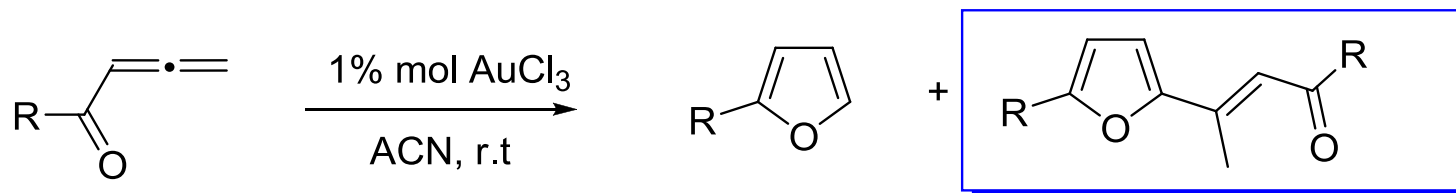
Pioneering works : Allenones

To avoid side product, cationic Au(III)-porphyrin complex was used[3]

1 mol% [Au(TPP)Cl]
10 mol% TFA

acetone, 60C

Au(TPP)Cl
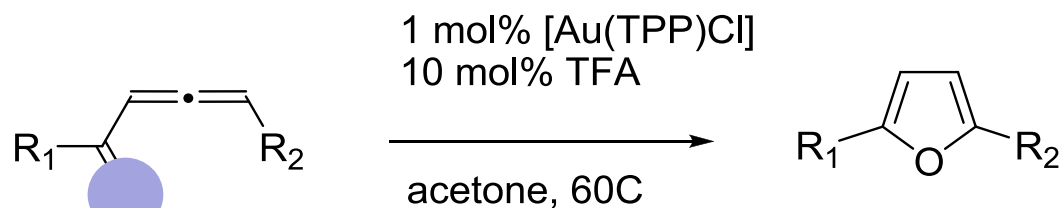
R₁	R₂	Yield
Ph	H	88
4-NO₂C₆H₄	H	91
Me	H	89
Me	n-C₅H₁₁	97
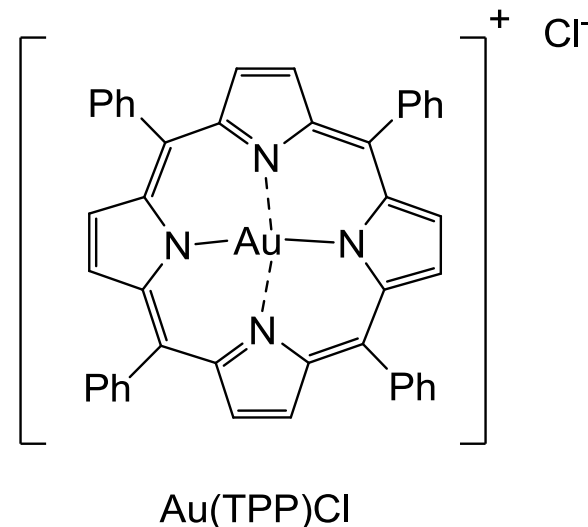
- **TFA and high temp. : acid labile substrates**
- **Room temp. : 20 % conv.**
- **No TFA: no reaction: demetallation process**

3) Che et al., *Org. Lett.* **2006**, *8*, 325

Structure of product is highly dependant on Au cat[4]
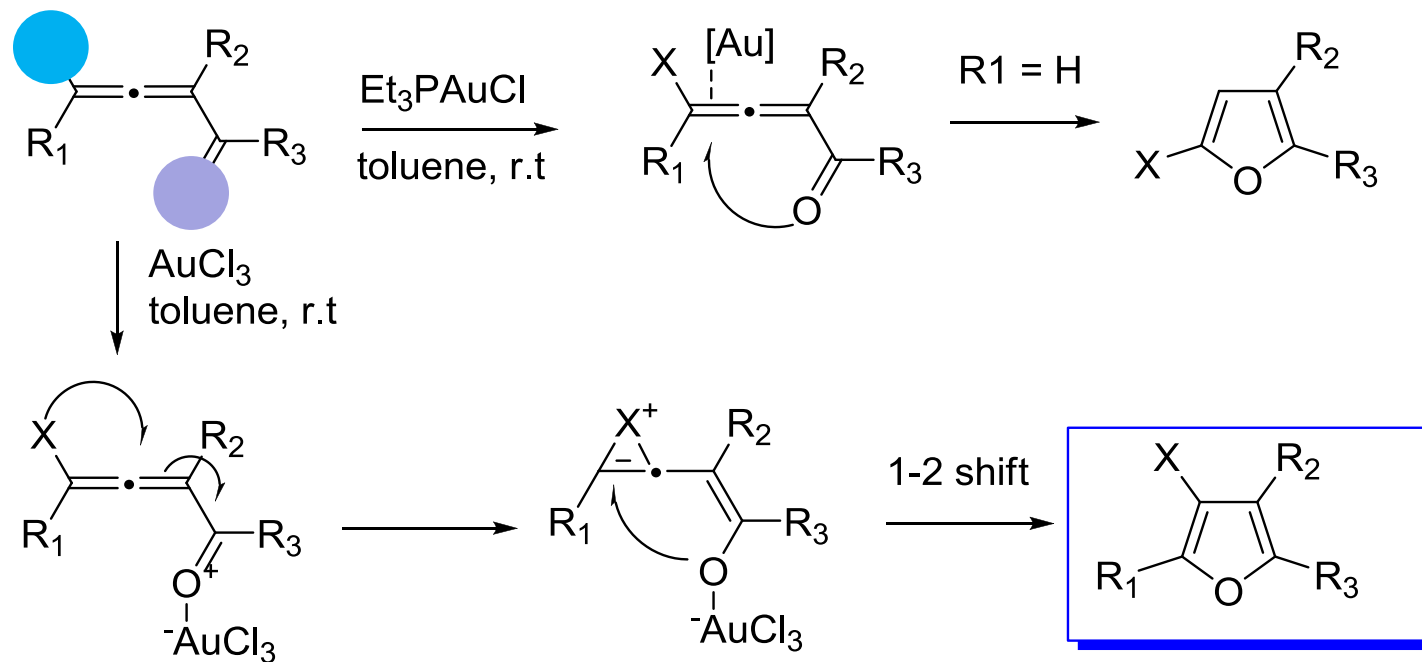
R1	R2	R3	X	time	yield
C_7H_{15}	Me	H	Br	1 hr	73%
H	H	C_8H_{17}	I	5 min	97%
$(CH_2)_2OTBS$	Ph	Ph	Cl	3 days	48%

4) Gevorgyan et al., *J. Am. Chem. Soc.* **2005**, *127*, 10500

Aryl-Aryl migration

1-5 shift of Ph group with good to excellent yield[5]

5) Gevorgyan et al*., Angew. Chem., Int. Ed*. **2007**, *46*, 5195

Allenic esters or allenoates[6]

AuCl₃ (5 mol%)

DCM, 80C
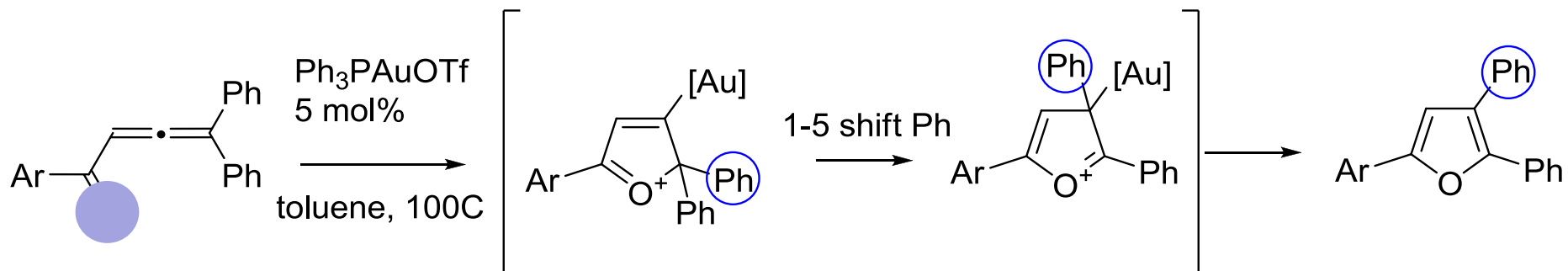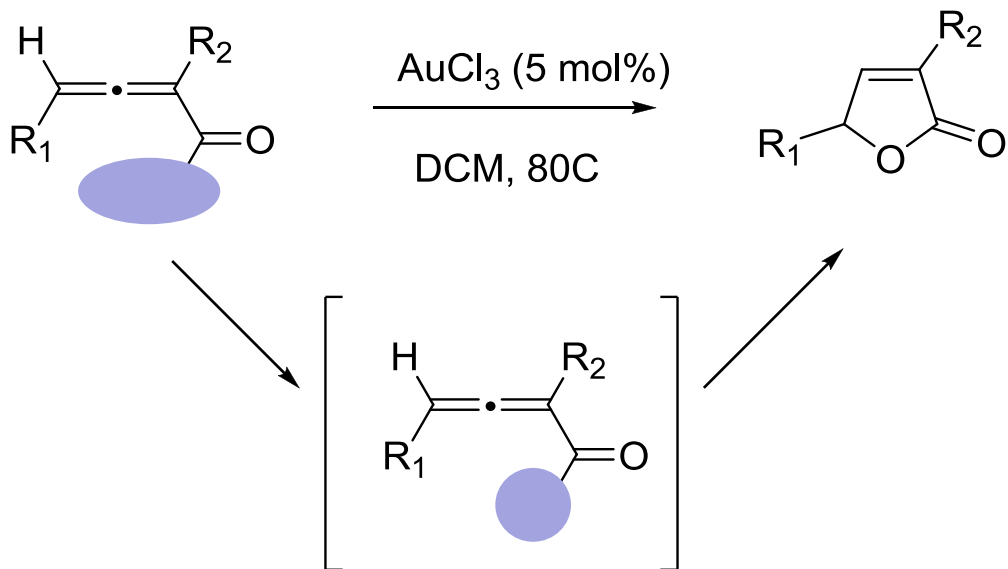
R1	R2	Yield
Bn	H	88
Bn	Me	77
Bn	Bn	96
n-C₉H₁₉	H	65

AuCl₃ (5% mol)
AgSbF₆ (15% mol)

AcOH, 70C, 4-6 hrs

E = CO₂Me
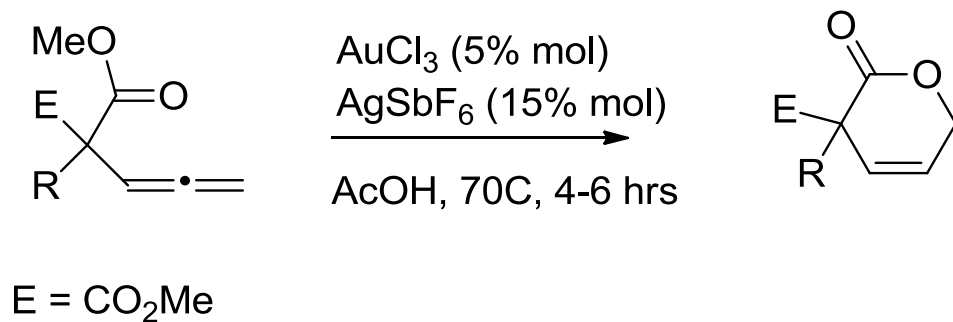
R	yield
	79%
	98%
	89%

6a) Backvall et al., *Org. Lett.* **2007**, *9,* 2235

6b) Hammond et al., *J. Am.Chem. Soc.* **2008**, *130*, 17642

α-Hydroxy allenes or allenols

Allenone: product achiral

Allenols: chiral heterocycles product from chiral allenols: complete chirality transfer[7]
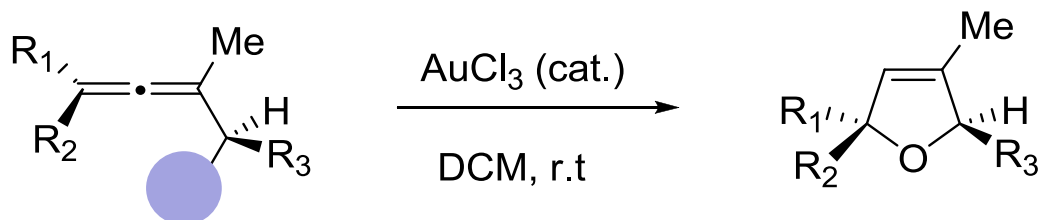
R1	R2	R3	Yield
t-Bu	Me	CO_2Et	94
t-Bu	H	CH_2OTBS	95
H	Me	CH_2OTBS	77
$CH_2=CHCH_2$	Me	CH_2OMe	86

Functionalities tolerated : carbonyl, free alcohol, acide sensitive protecting group

7) Krause et al*., Org. Lett. **2001**, 3, 2537; Synthesis **2002**, 1759; Angew. Chem., Int. Ed*. **2008**, 47, 2178

Mechanism
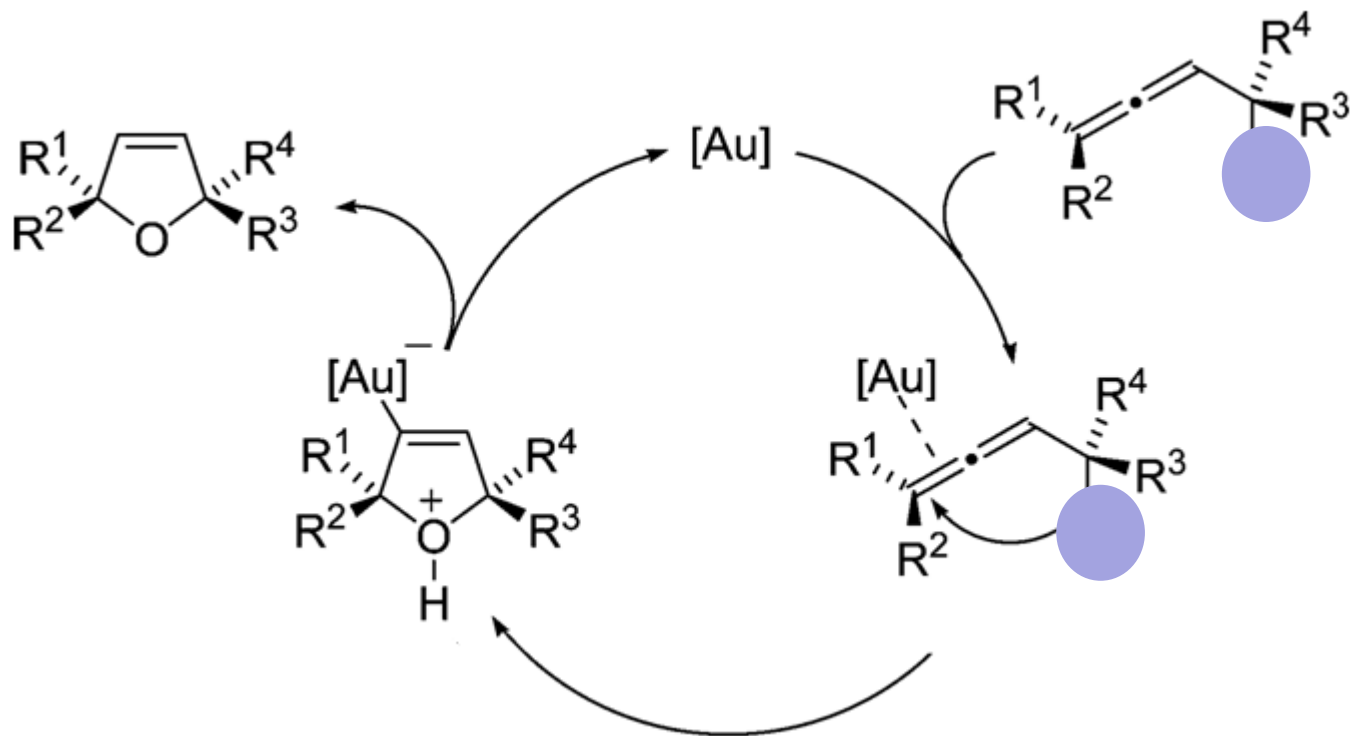
α-Hydroxy allenes or allenols

Chirality transfer depends on Lewis acidity of Au[8]

- **Use of bipyridine**

dr : 97:3

no additive: d.r : 66:34
bipiridine: d.r : 97:3
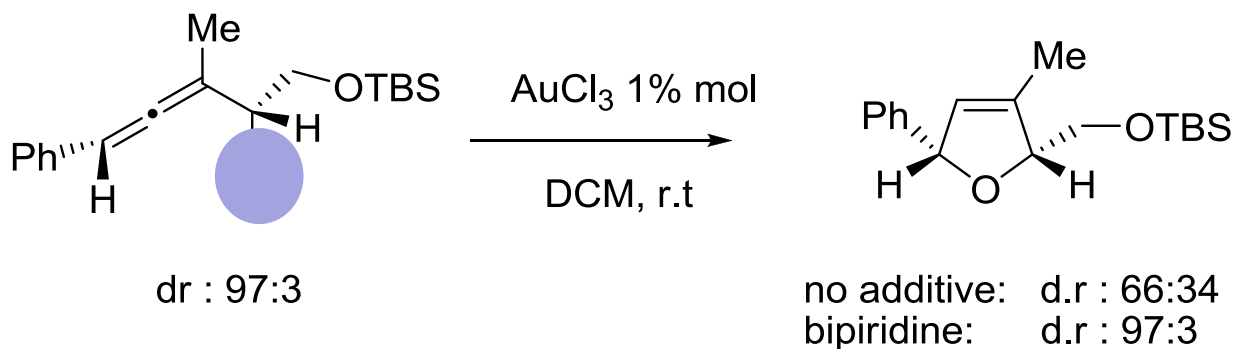
- **Weakly coordinating solvent THF**
  - AuCl$_3$/THF : efficient catalyst

- **0C instead of r.t**

8) Krause et al*., Synlett **2007**, 1790

Synthesis of antibiotic amino acid furanomycin analogue[9]

9) Krause et al*., Synthesis* **2007***,* 3741

Synthesis of β-carboline alkaloids[10]

>98% de/ee

AuCl₃ (0.05 mol%)
THF, r.t.

97%, 96% de, >98% ee

1. MeI
2. NaOH

(-)-Isocyclocapitelline
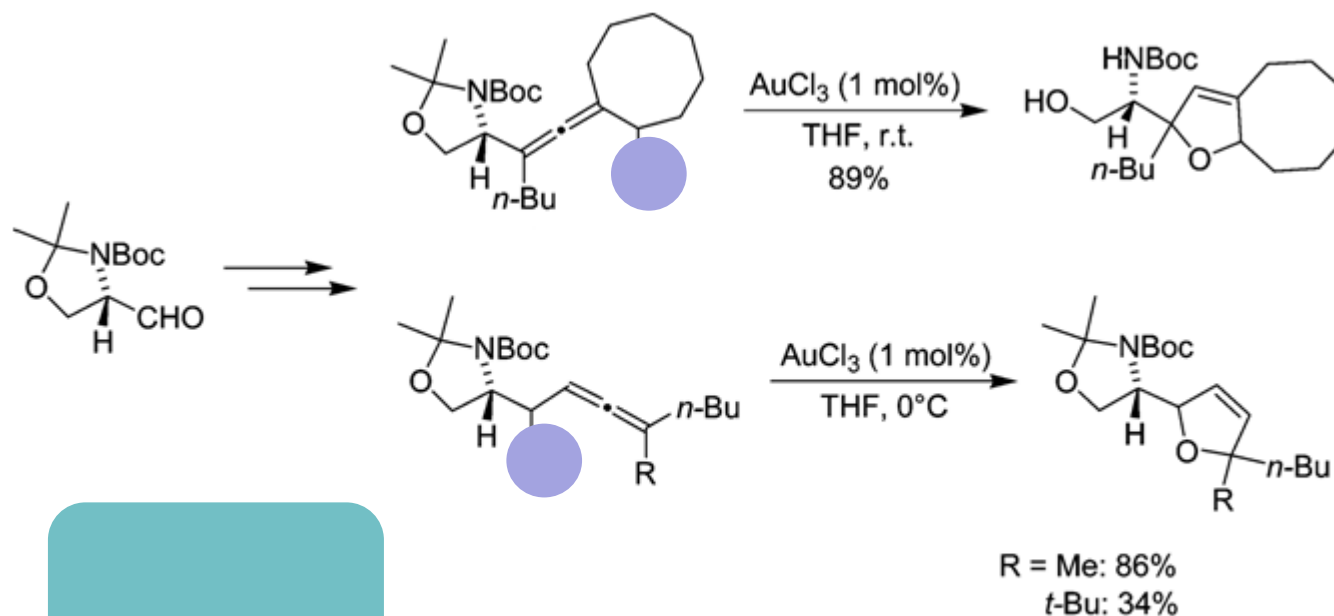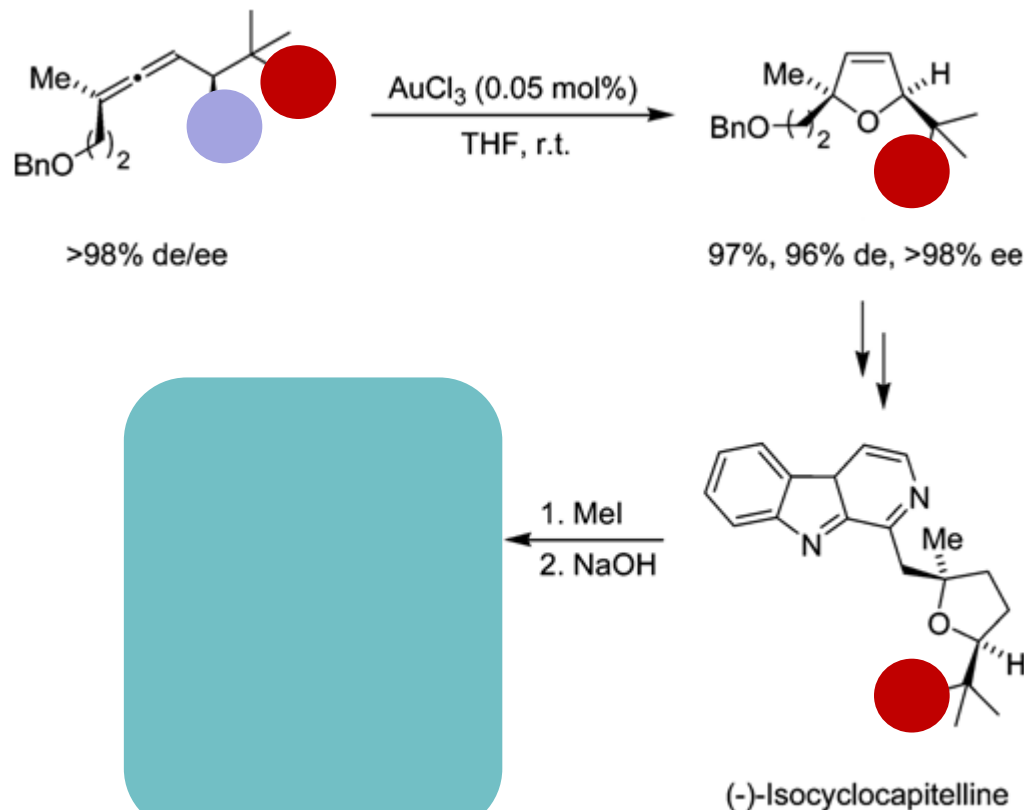
■ **Stereoselective and chemeoselective**

10) Krause et al*., Org. Biomol. Chem.* **2007**, *5,* 1519; *Tetrahedron* **2009**, *65,* 1902

Synthesis of Ionomycin-calcium complex[11]

Ionomycin-Ca Complex
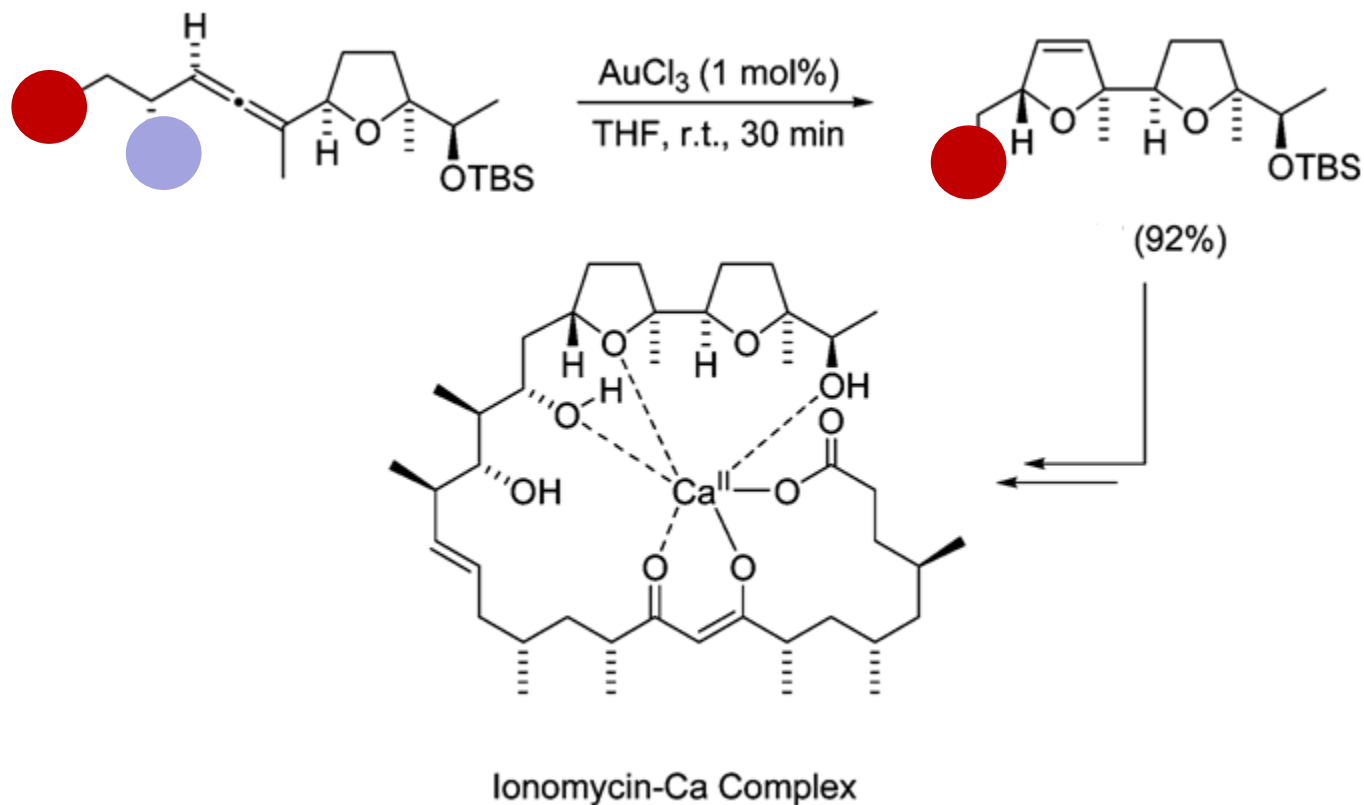
■ **Stereoselective and chemeoselective**

11) Kocienski et al., *Angew. Chem., Int. Ed.* **2009**, *48*, 5022

β-hydroxyallene : pyran formation[12]
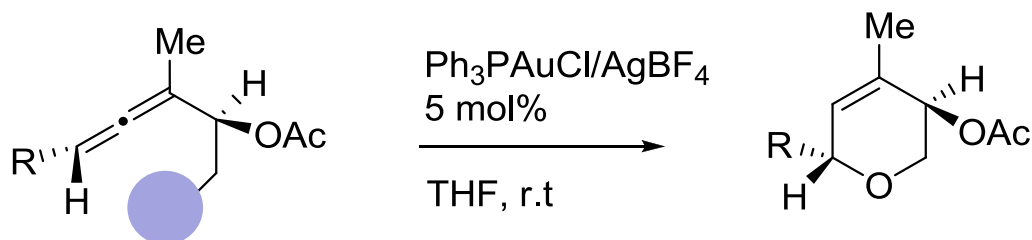
R	Time	Yield
t-Bu	30 min	50
n-Bu	20 min	84
Ph	60 min	65

App: synthesis of Bejarol[12]

(85%)

(R,R,R)-Bejarol
>98% de/ee
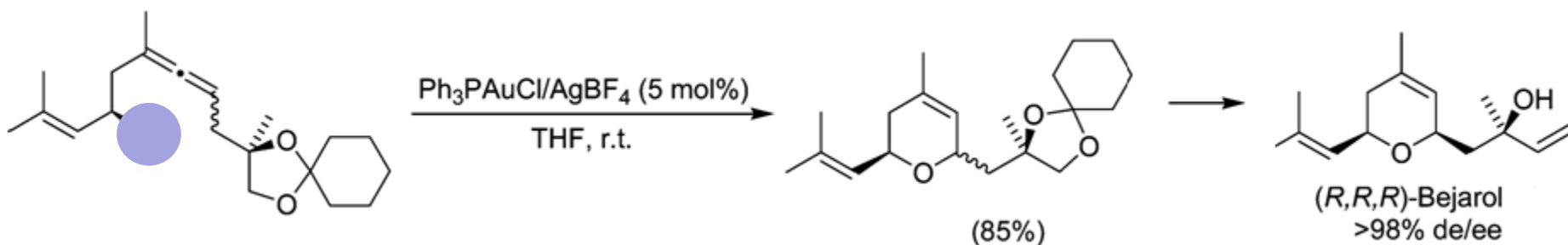
12a) Krause et al., *Org. Lett.* **2006**, *8,* 4485

12b) Krause et al., *Org. Biomol. Chem.* **2008**, *6,* 3573

Lipase / Au-cyclisation[13]
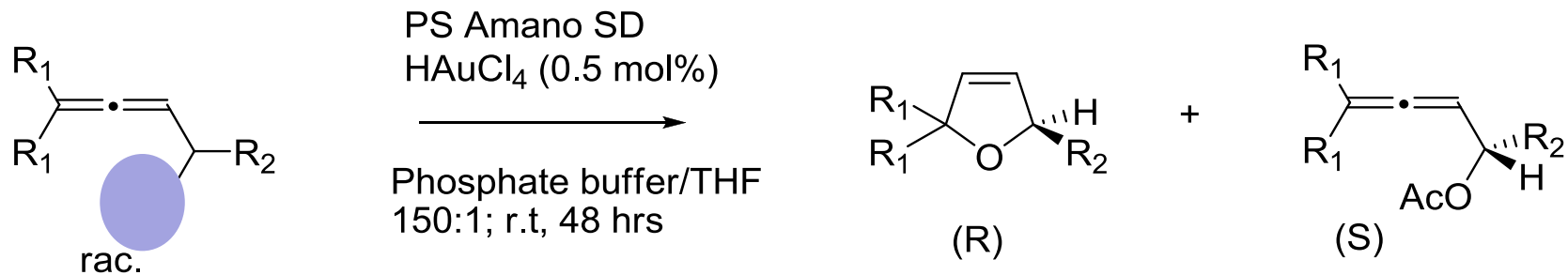
R1	R2	R		S	
		Yield	ee	Yield	ee
-(CH$_2$)$_5$-	Me	28	86	31	93
-(CH$_2$)$_5$-	n-Pr	45	95	40	95
-(CH$_2$)$_4$-	n-Pr	38	88	33	95
Me	C$_8$H$_{17}$	50	98	36	95

13) Krause et al., *Adv. Synth. Catal.* **2009**, *351*, 2305

Au-cyclisation / Pd coupling[14]

14) Blum et al., *J. Am. Chem. Soc.* **2009**, *131*, 18022
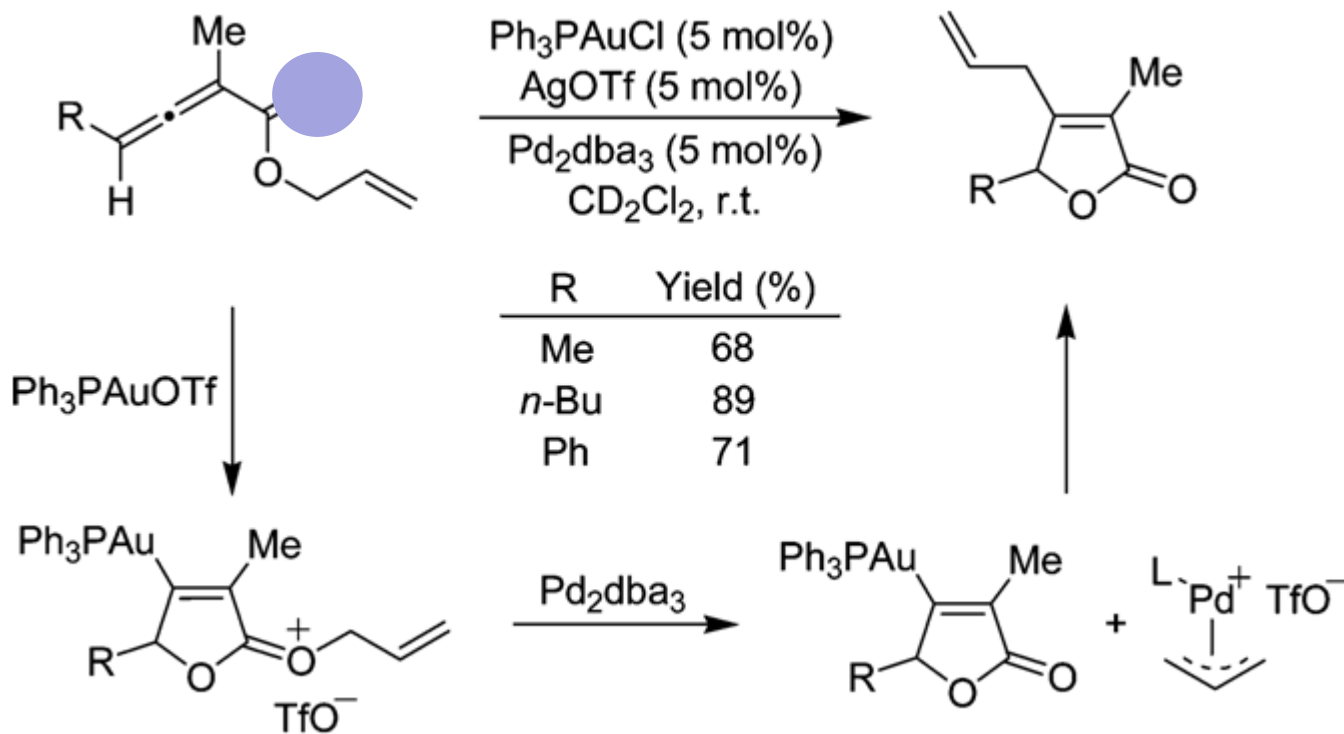
Au-cyclisation / Oxidative C-C coupling[15]
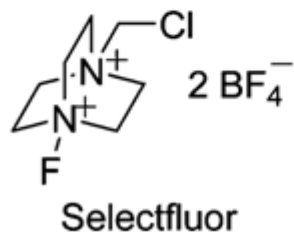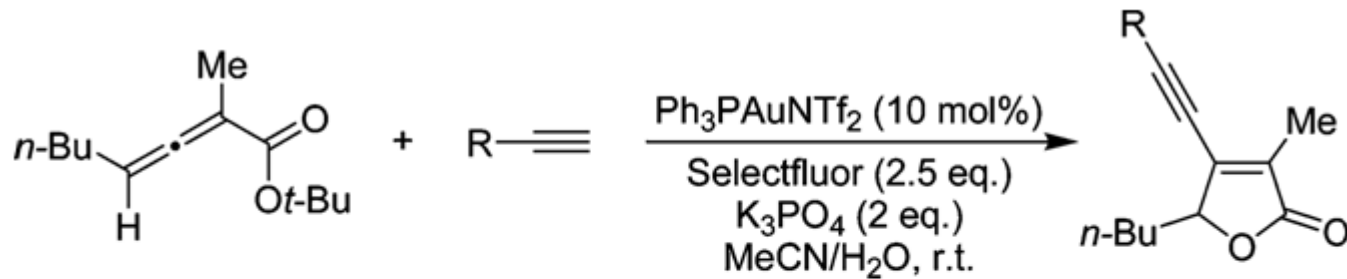
15) Gouverneur et al., *Chem.-Eur. J.* **2010**, *16*, 4739; *Org. Lett.* **2010**, *12*, 4904

Au-cyclisation / Oxidative C-C coupling
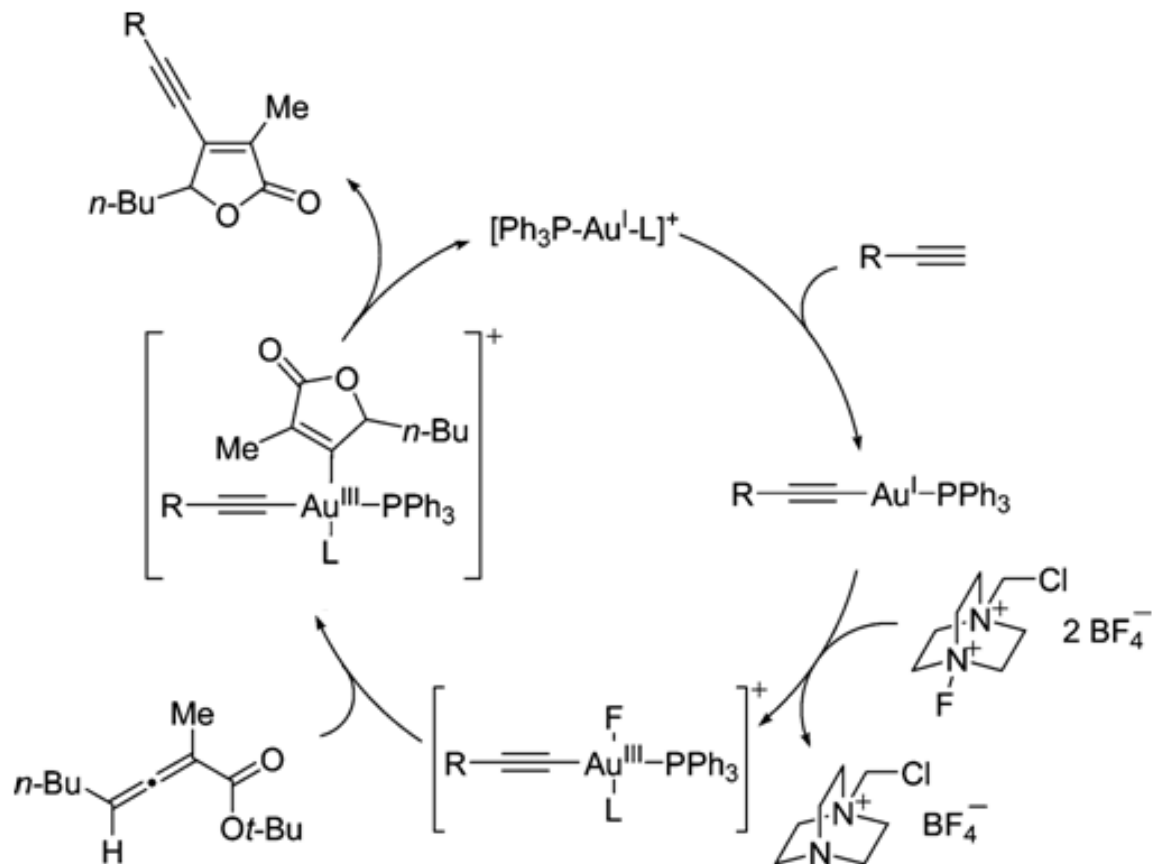
Allenic epoxide with exo-attack[16]

(PhO)$_3$PAuCl (5 mol%)
AgOTf (5 mol%)

DCM, r.t
55%

16) Gagne et al., *Org. Lett.* **2009**, *11*, 3490
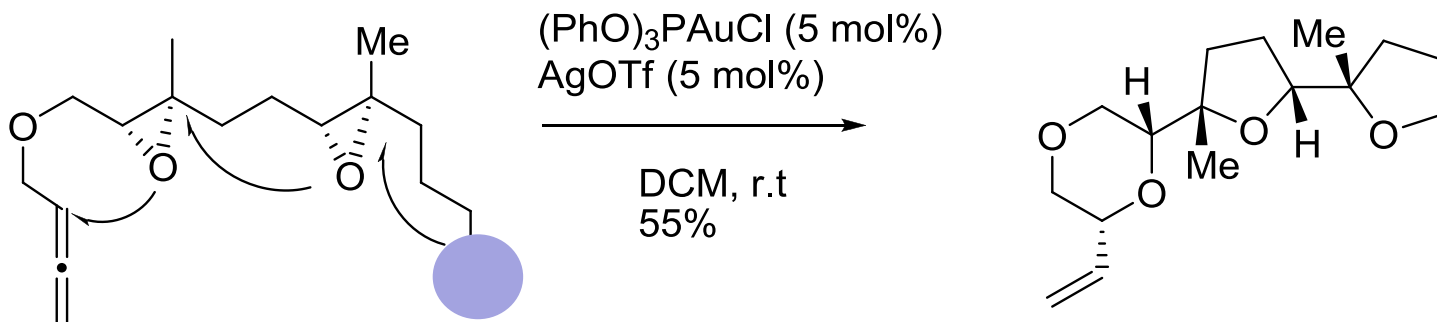
Exo-attack selective allenol[17]

[(t-Bu)2(o-biphenyl)P]AuCl
5 mol%
AgOTs (5 mol%)

toluene, r.t
>90%

R1 = Ph; H
R2 = H; Me
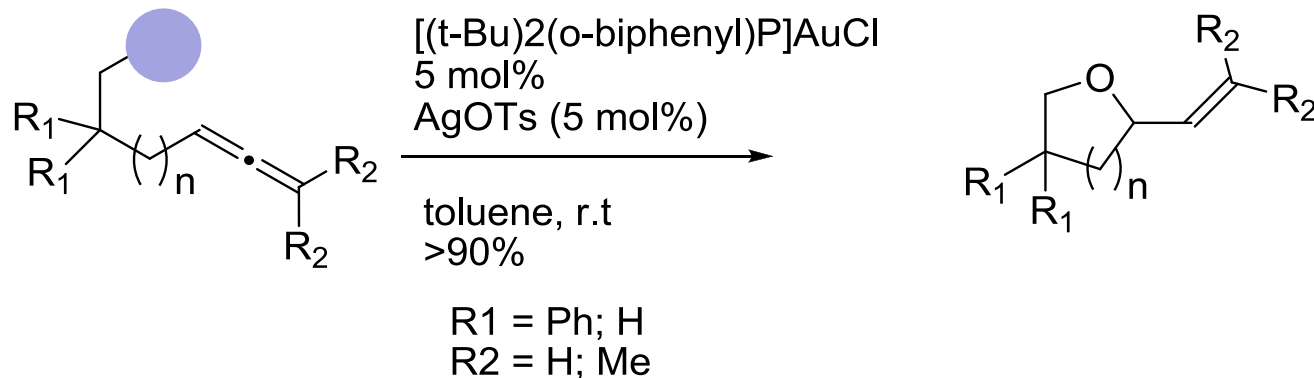
- **Regio-selectivity up on counterion**
  - AgOTs: exo
  - AgOTf: endo

17) Widenhoefer et al., *J. Am. Chem. Soc.* **2006**, *128*, 9066

Chiral ligand to control selectivity[18]
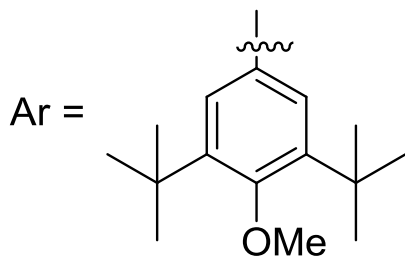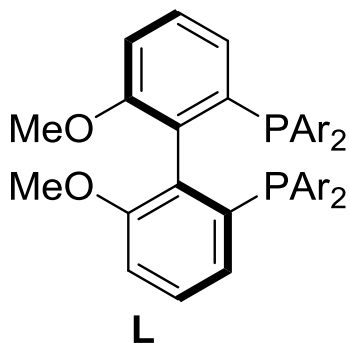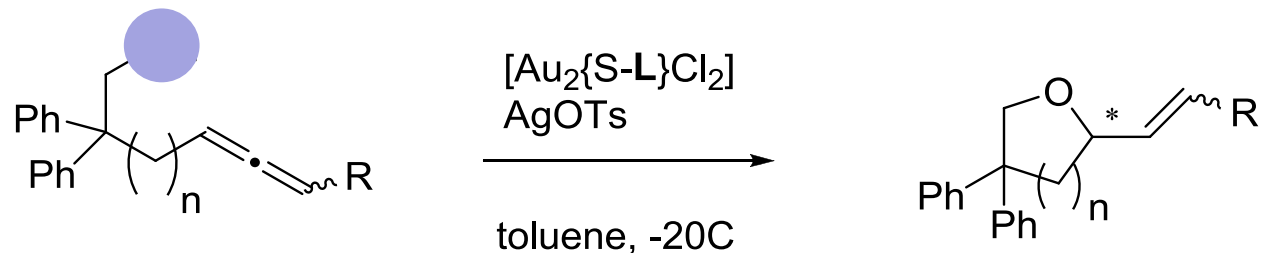
n	R	Yield	E/Z	ee
1	H	67	-	93
1	Me	96	1 : 1	97/99
1	C_5H_{11}	94	1 : 1	95/95
2	H	96	-	88
2	C_5H_{11}	92	1,5 : 1	67/93

18) Widenhoefer et al., *Angew. Chem., Int. Ed.* **2007**, *46*, 283; *Chem.-Eur. J.* **2008**, *14*, 5382

Chiral counterion[19].
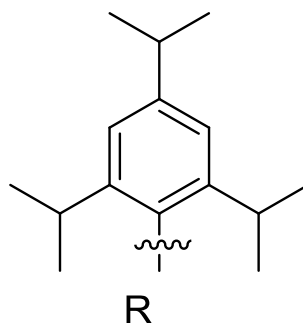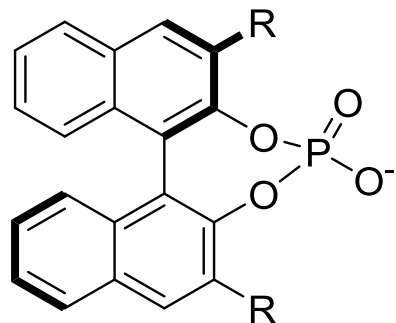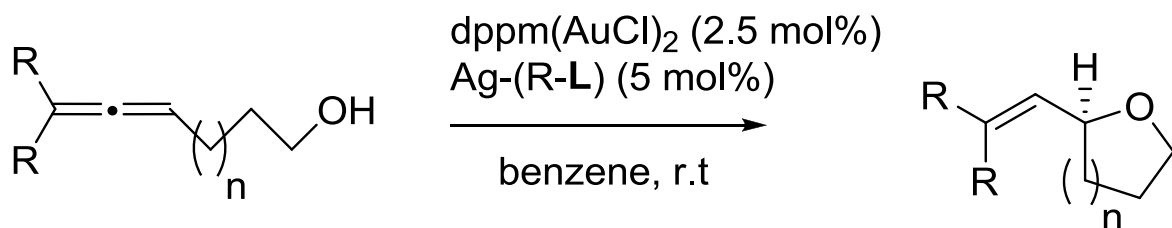
n	R	Yield	ee
1	-(CH$_2$)$_4$-	90	97
1	Me	91	95
2	Me	81	90
2	H	96	80

19) Mikami et al., *Adv. Synth. Catal.* **2010**, *352*, 3131

Use of cationic Au-porphyrin complexe

Cat. loading can be decreased to 0.1% and be recovered and reused 9 consecutive runs with no appreciable loss of reactivity or yield.

Au(TPP)Cl
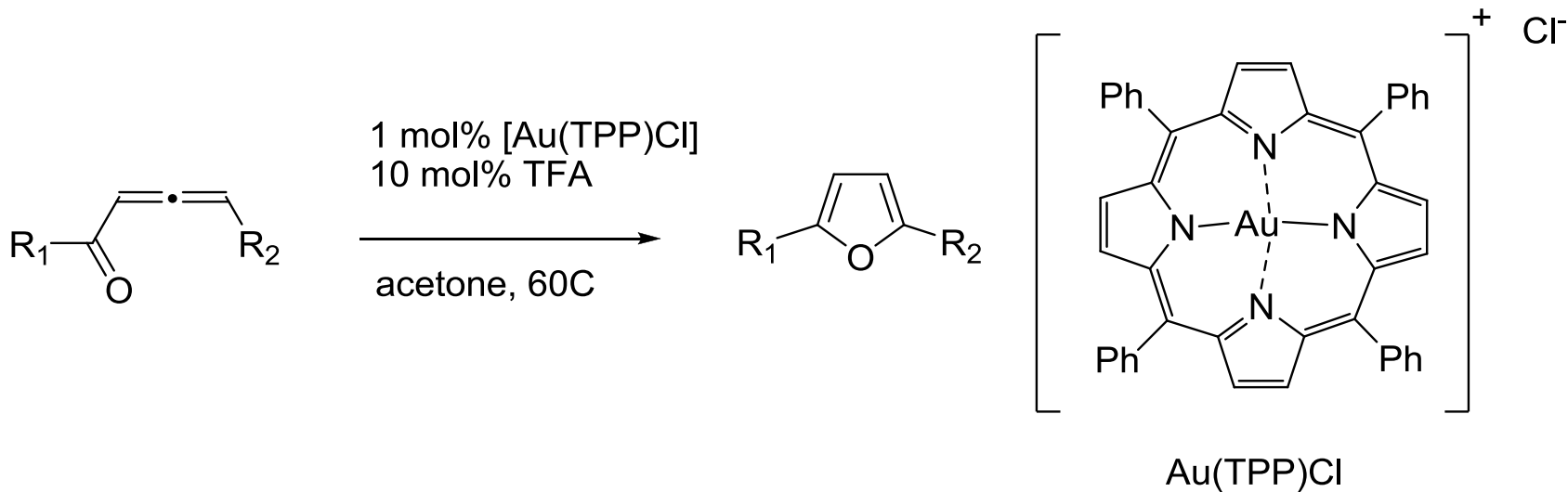
Au-cat. recycle

In ionic liquid[20] : over 5 runs, only 0.03% of original cat loading is lost due to extraction of the product.

- **Highly attractive method with potentially recyclable several thousands times**
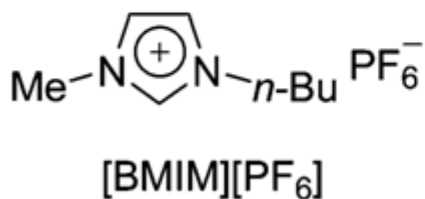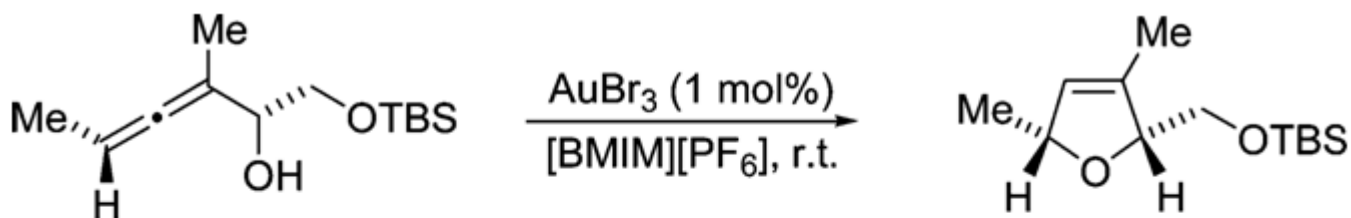
Run	Time	Yield (%)
1	10 min	84
2	3 h	74
3	3 h	81
4	3 h	84
5	3 h	84

20) Krause et al., *Adv. Synth. Catal.* **2008**, *350*, 1106

Au-cat. recycle

Micellar system[21]

Cat. is recycled with only 0.29% lost over 4 runs
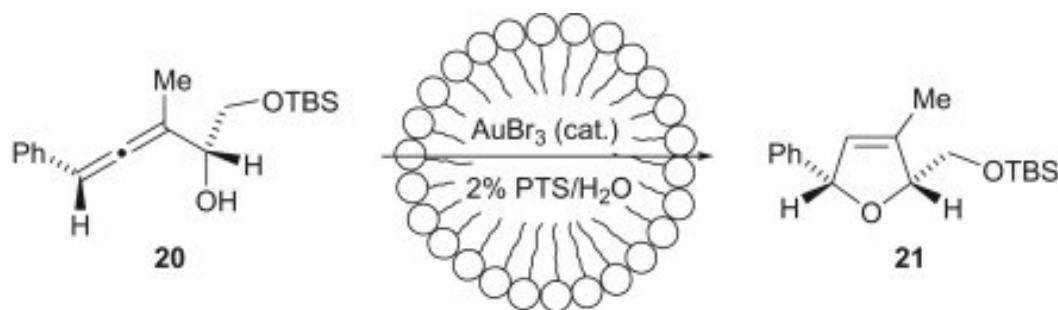
AuBr$_3$ (mol%)	NaCl	Time (min)	Yield (%)
5	0 M	45	80
5	1 M	30	88
5	2 M	20	86
5	3 M	10	88
2	3 M	20	88
1	3 M	30	84

21) Krause et al., *Angew. Chem. Int. Ed.* **2011**, *50,* 7820
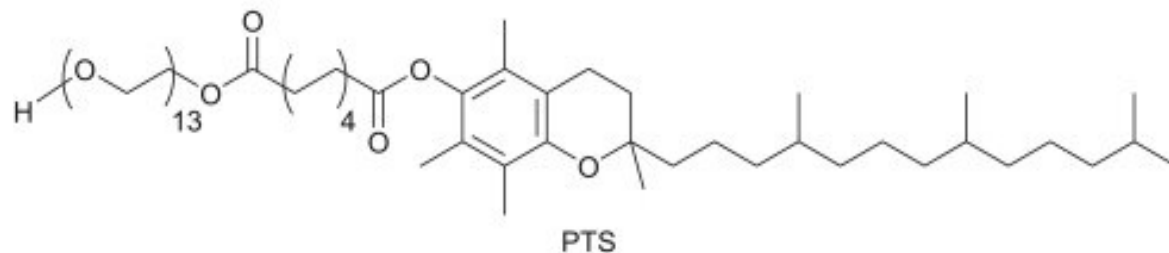
Conclusion and future developpement

Highly stereoselective gold catalyzed transformations

Au-cat recovery

Improve: stability, reactivity, selectivity and recyclability of Au-cat

- Environmentally friendly solvents, purifications, rt…

Thank you for your attention

Introduction :
  - basic principle and reactivity of radicals

Nitrogen based radicals:
  - reactivity and secies

Examples of N-cycles formation via radical intermediates

Examples of radical cascade in total synthesis

A chemical species with an unpaired electron:
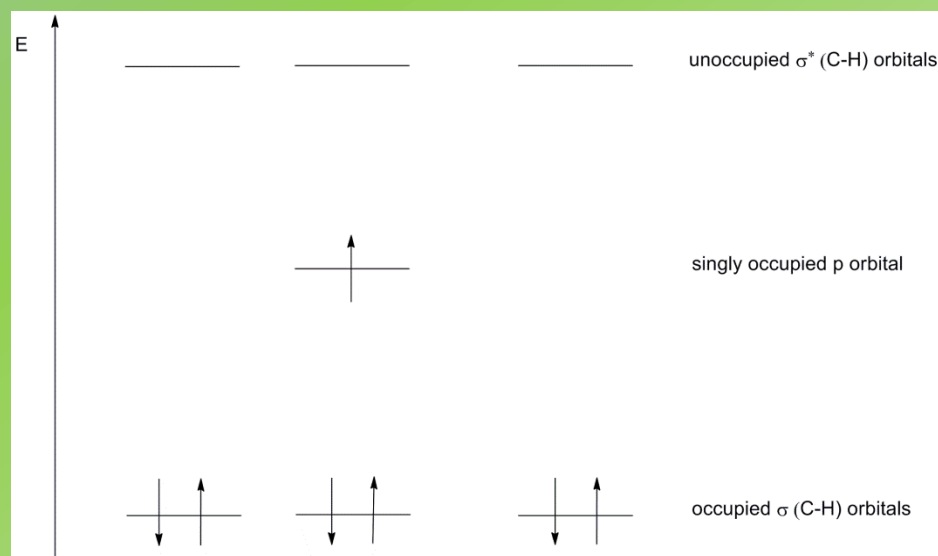
Single occupied molecular orbital (SOMO)

Organic free radicals: *short life time*
- Dimerize or disproportionate
- React with O_2
- Abstract H

$$2\ R_3\overset{\cdot}{C} \longrightarrow R_3C{-}CR_3$$

$$2\ R_2HC{-}\overset{\cdot}{C}HR_2 \longrightarrow R_2HC{-}CHR_2 \ + \ R_2C{=}CR_2$$

$$R_3\overset{\cdot}{C}\ +\ O_2 \longrightarrow R_3CO{-}\overset{\cdot}{O}$$

$$R_3\overset{\cdot}{C}\ +\ HX \longrightarrow R_3CH\ +\ \overset{\cdot}{Y}$$
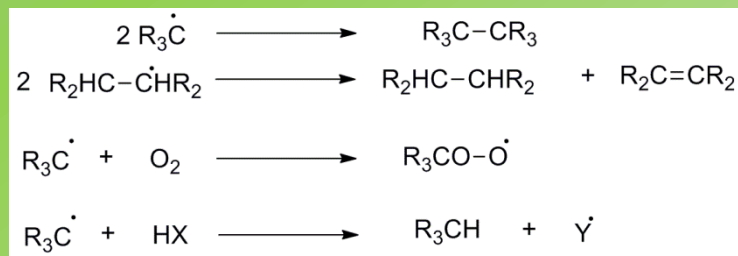
Persistent free radicals: *indefinite life time*
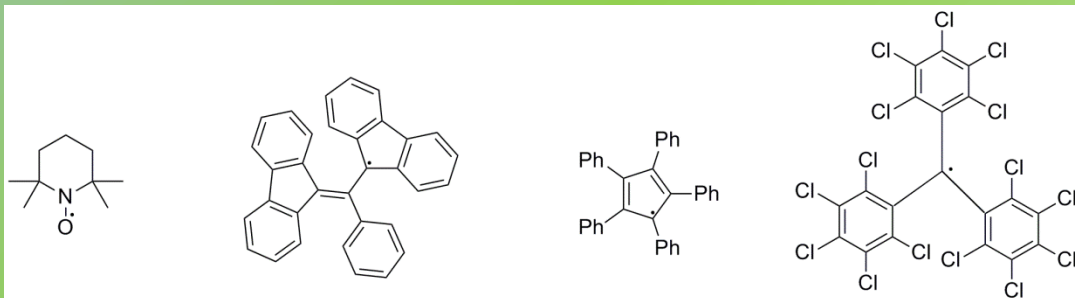
Extensive delocalization of the unpaired electron and steric hinderence

Functional group free radicals:

Used in biochemical studies as probes

4

Radical stability: based on dissociation energies
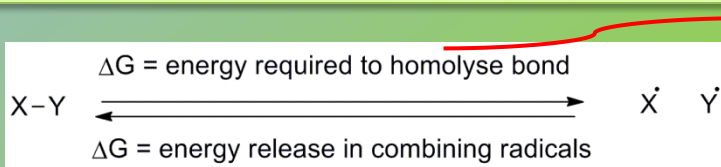
Greater value means stronger bond

ΔG = energy required to homolyse bond

X−Y $\rightleftarrows$ Ẋ Ẏ

ΔG = energy release in combining radicals

Greater value means more unstable radicals
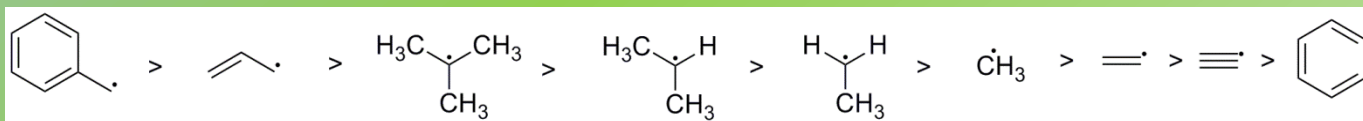
372 kj mol^{-1}　　　　　　　　　　　　　　　　　464 kj mol^{-1}

More stable　　　　　　　　　　　　　　　　　Less stable

Hyperconjugation effect stabilize the radical

Radicals adjacent to functional groups
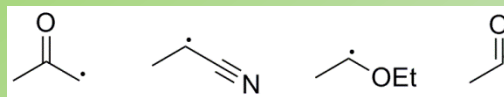
Weaken the C-H bonds – more stables than tertiary alkyl radicals

Both EWG and EDG stabilize the radical

Methods to generate radicals

Thermolysis

Covalent bonds cleave at 800°C

<150° weak bonds: azo compounds, peroxides, nitrite esters, ect - <30/40 kcal/mol dissociation energies
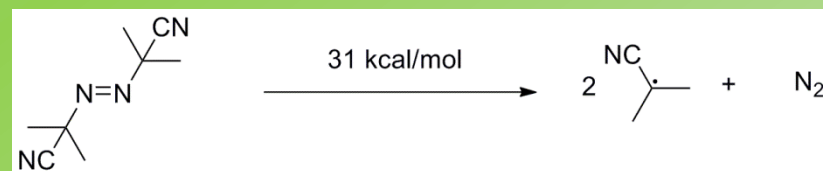
Photolysis: homolytic fission
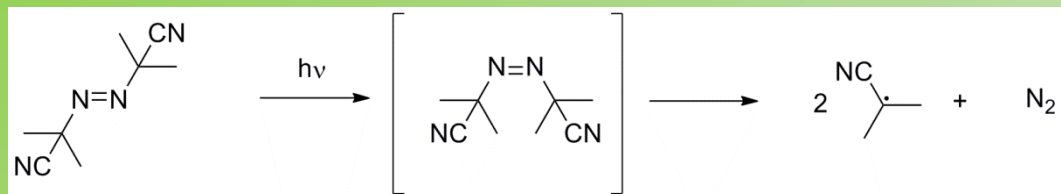
Radiation: X-rays or γ-rays

Redox system: oxidation or reduction by intermolecular electron transfer
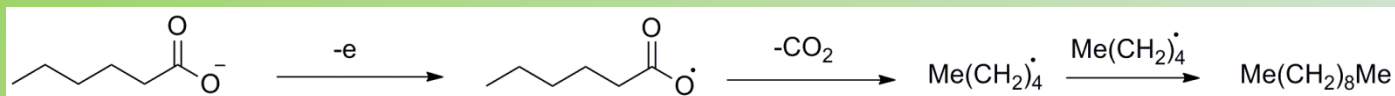
Common radical initiatiors

- **Azo compounds**
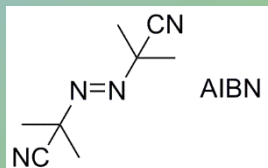
High decomposition and stability
Safer than many peroxides

- **Peroxides**: *low temperatures - low activation energies*
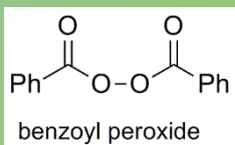
Phenyl radicals
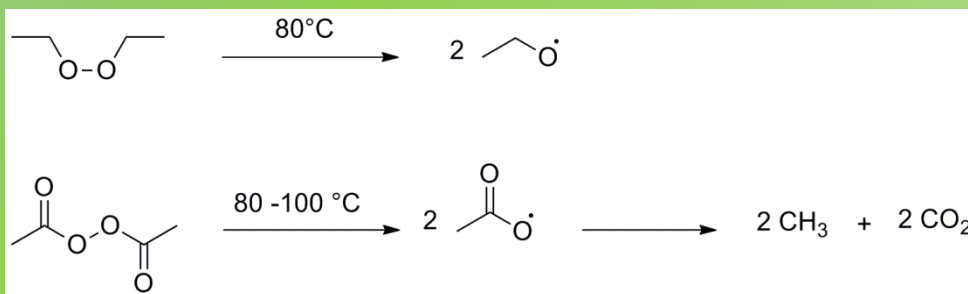
Thermal decomposition

Metal oxidation

Unpaired electron $\longrightarrow$ Paramagnetic properties $\longrightarrow$ Electron paramagnetic resonance (ESR) spectroscopy

Methyl radical ESR spectrum
a_H coupling constant gives info on the radical geometry

Works like ^{1}H NMR: energy gap between the 2 possible states is bigger

Weaker magnet fields

Info:
Existence of these species
Structure

Transition of an electron between the energy levels associated with two possible orientations of electron spin in a magnetic field
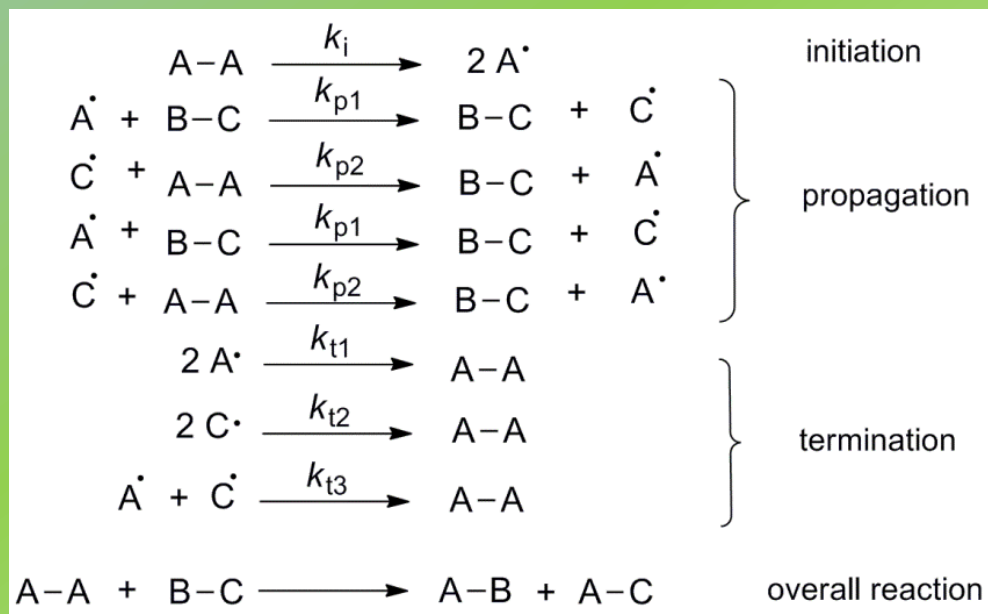
Initiation step : form reactive specie – radical
Propagation phase: sequence of repeated reaction – determines the radical chain length
Termination steps : destroy reactive intermedietes that alimentates the propagation phase

Radical vs ionic reactions:

Radicals are uncharged – neutral

- Not solvated → More reactive, less sensitive to sterics

- reaction operate under mild, neutral conditions

- No basicity → Sensitive functionalities no need to be protected

Radicals are not subject to rearrangements:
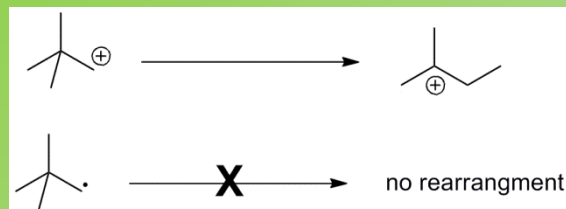
β-elimination are much slower:
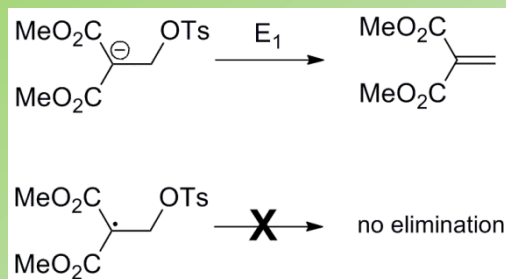
Nitrogen centered radicals

- Unpaired electron sits on a nitrogen atom → Aminyl radical

Reactivity:

$$\underset{R'}{\overset{R}{N}} \cdot \; < \; \underset{R'}{\overset{R}{CH}} \cdot \; < \; \underset{R'O}{\overset{R}{O}} \cdot$$
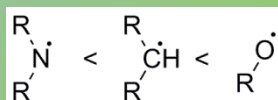
Bond dissociation energies : N-H weaker bonds
X-C electronic repulsion is big

Dialkylaminyl radical Aminium radical Metal-complexed radical Amidyl radical Cyanamidyl radical

Nucleophilic radical

Electrophilic radicals
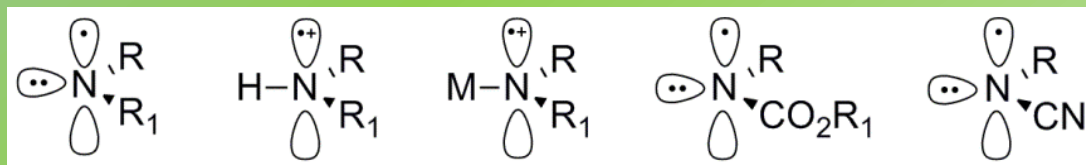
Nature of substituents & **reaction conditions**:
Type of intermediate
Efficiency
Selectivity

Types of Nitrogen Radicals

Neutral aminyl radicals
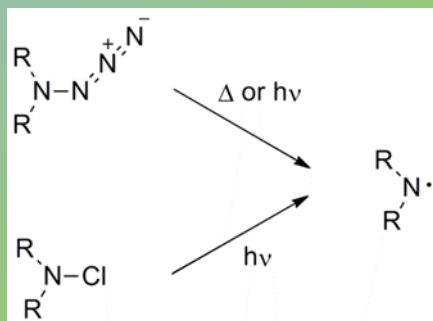
Dimerize to hydrazine and disproportionate to
Schiff bases and amines
With olefins abstract H$^+$

General mechanism

Application:

Suarez E. *J. Chem. Soc. Perkin Trans I*, **1987**, 937; Stella L., *Angew. Chem. Int. Ed.*, 22 (**1983**) 337
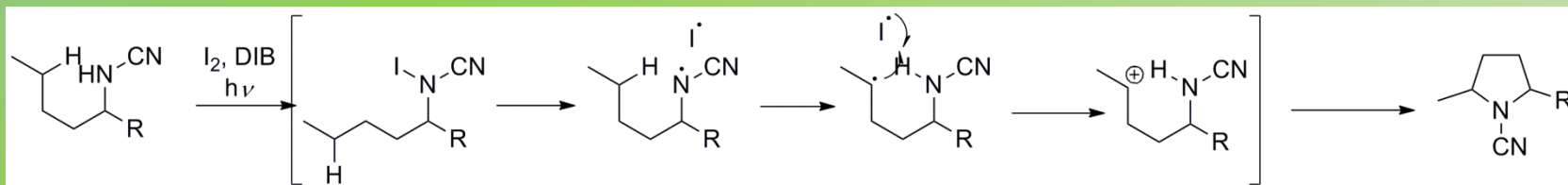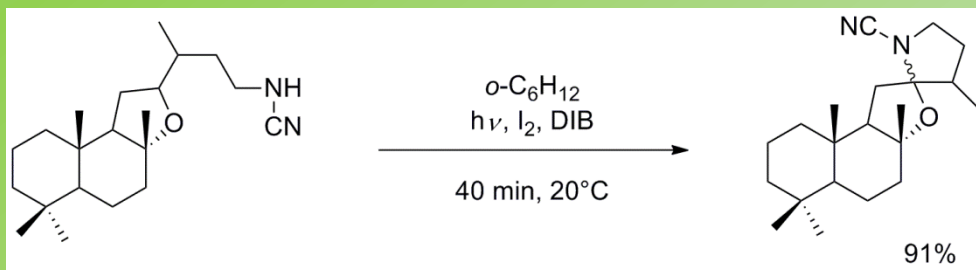
Types of Nitrogen Radicals

- Aminyl radicals complexed to metal ions
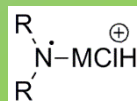
More electrophilic
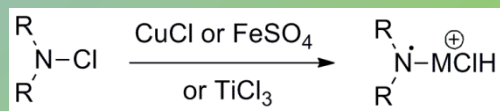
Efficiently reacts with: dienes, alkenes and acetylenes

Generated in neutral conditions
Complexation *via* lone pair
Don't abstract H intermolecularly, don't dimerize or disproportionate

Cu(II) and Fe(III)

Mechanism for heterocyclization
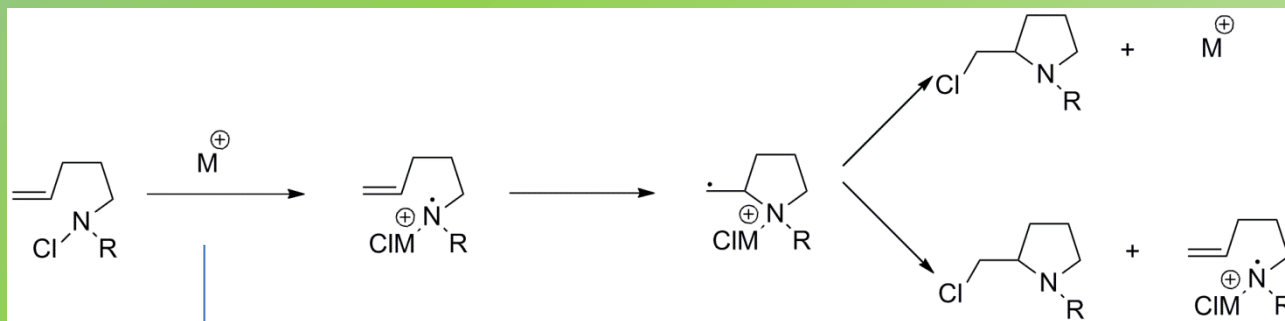
Ligand transfer
Electron transfer

Reducing metal

Stella L., *Angew. Chem. Int. Ed.*, 22 (**1983**) 337
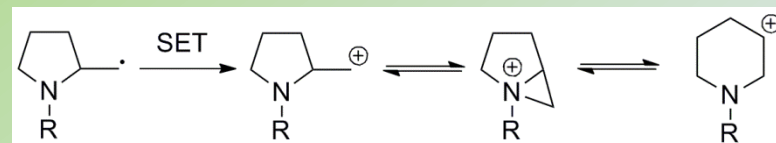
- Protonated aminyl radicals
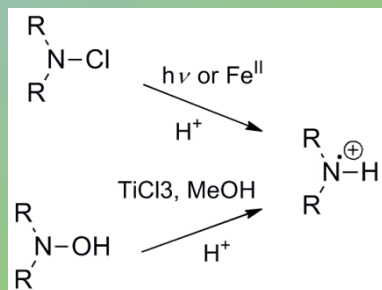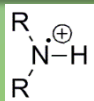
No dimerization or disproportionatin
Prefers to add to unsaturated systems than to abstract H
Abstract H intramolecularly

Mechanism:

Cyclization kinetically controlled

Ring expansion

Ratio depends on nucleophile

Heating conditions

Stella L., *Angew. Chem. Int. Ed.*, 22 (**1983**) 337
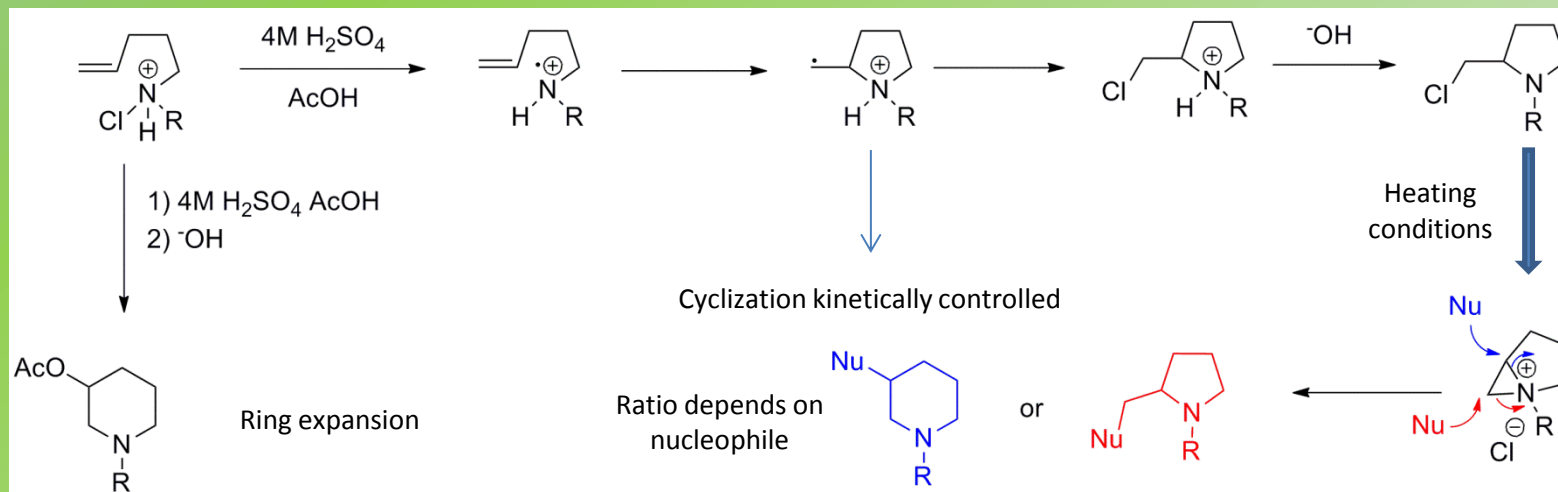
1881 - Hofmann
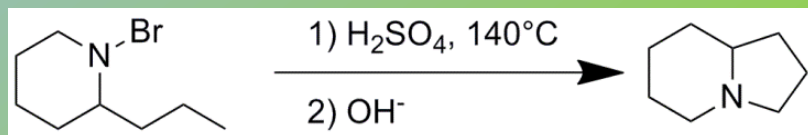
70 years after – **1950** Wawzonek and Thelen   ⟶   Mechanism insights

Stella L., *Angew. Chem. Int. Ed.*, 22 (**1983**) 337

15
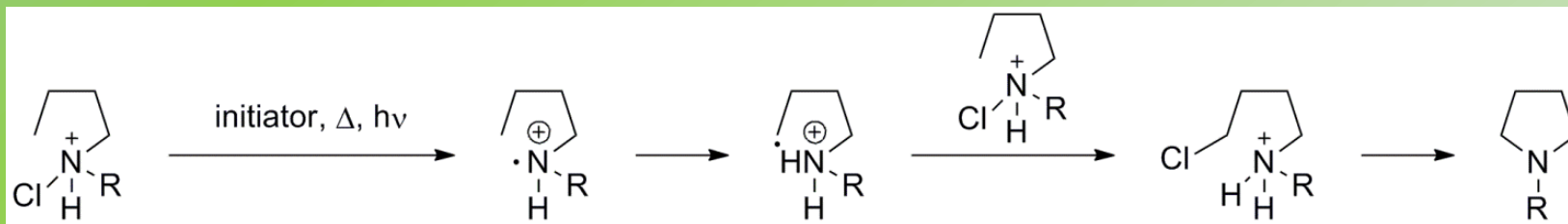
Today : Hofmann-Löffler-Freytag
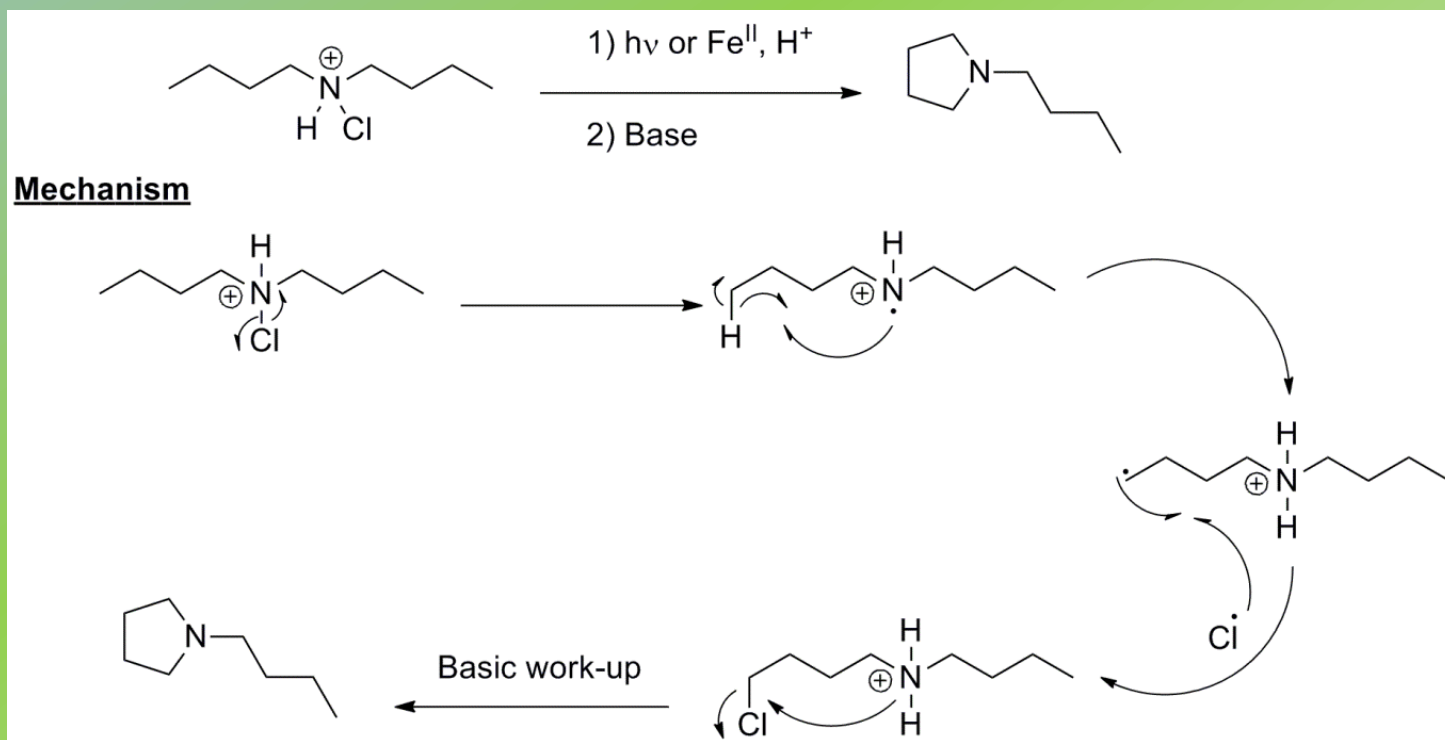
Main side reaction with protonated aminyl radicals
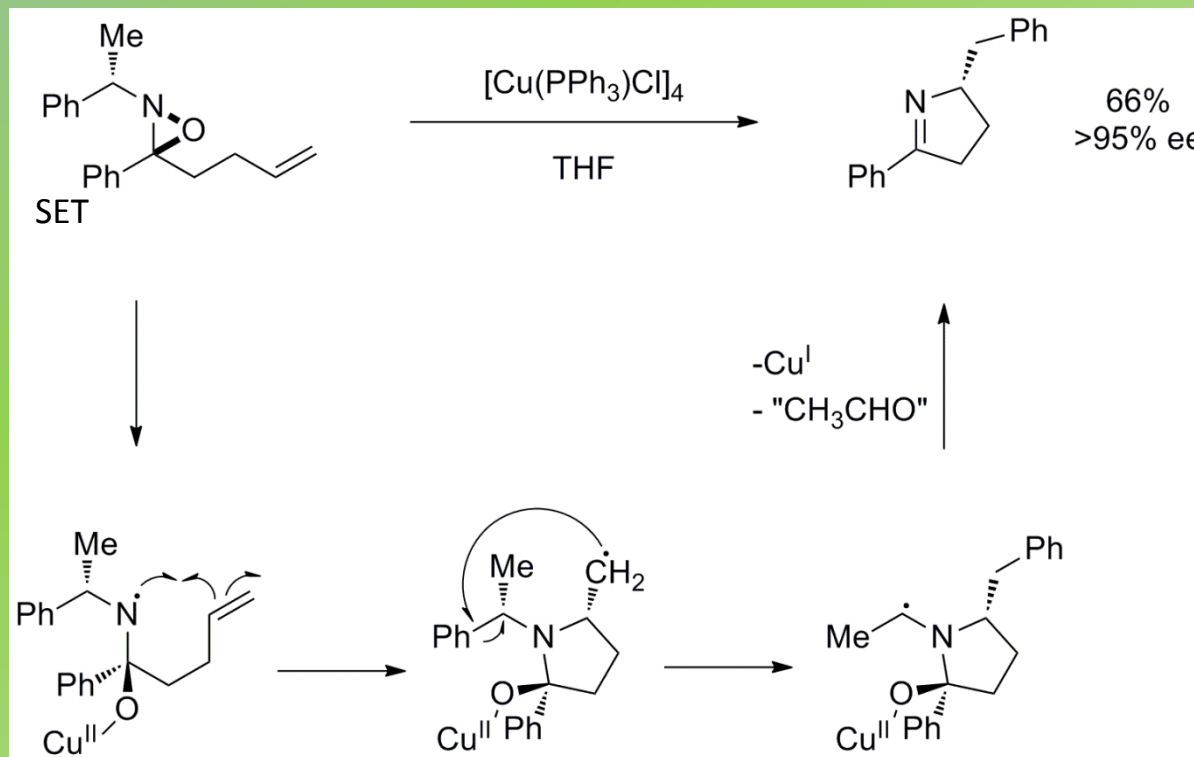
Pyrroline

Ipso attack on Ph
1,4-aryl migration

Aubé J., *J. Am. Chem. Soc.* **1992**, 114, 5466

17

Tandem cyclization on nitrile group through **IMINYL RADICAL**

Bowman W.R.*, Tetrahedr. Lett.* 41 (**2000**) 8989

18
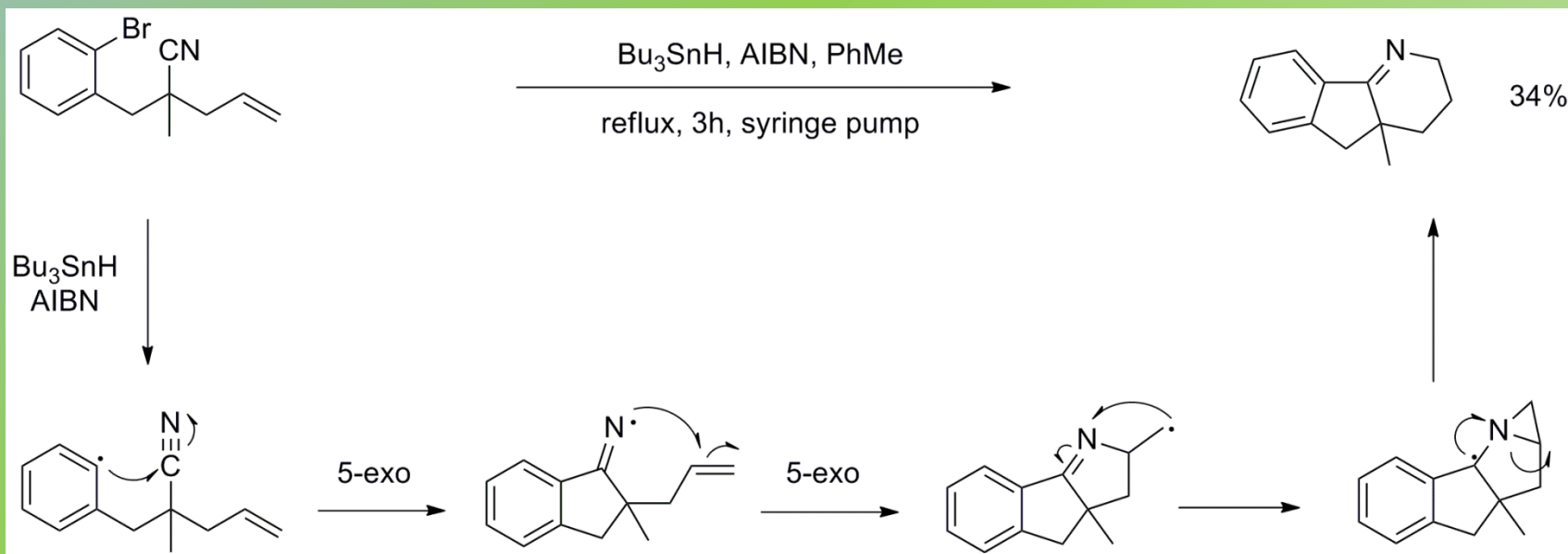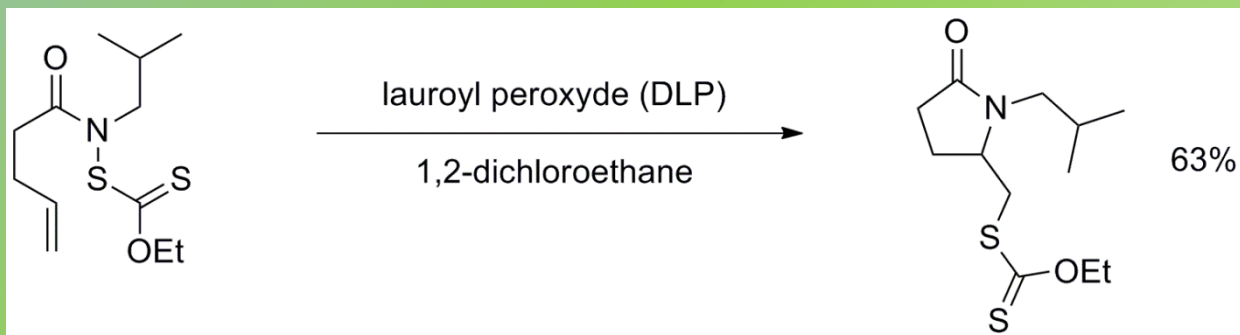
Pyrrolidinone

Pyrrolidinone – useful for alkaloids synthesis
Tin free methodology – purification and toxicity concerns
5-exo cyclization

γ-lycorane

Zard S.Z., *Org. Lett.* Vol. 4, N°16, **2002**, 2707; *Tetrahedron Lett.* 40 (**1999**) 2125
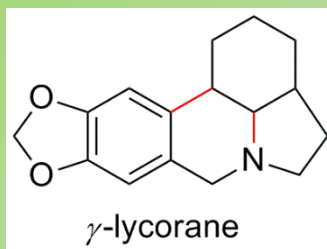
Mechanism monocyclic pyrrolidinones
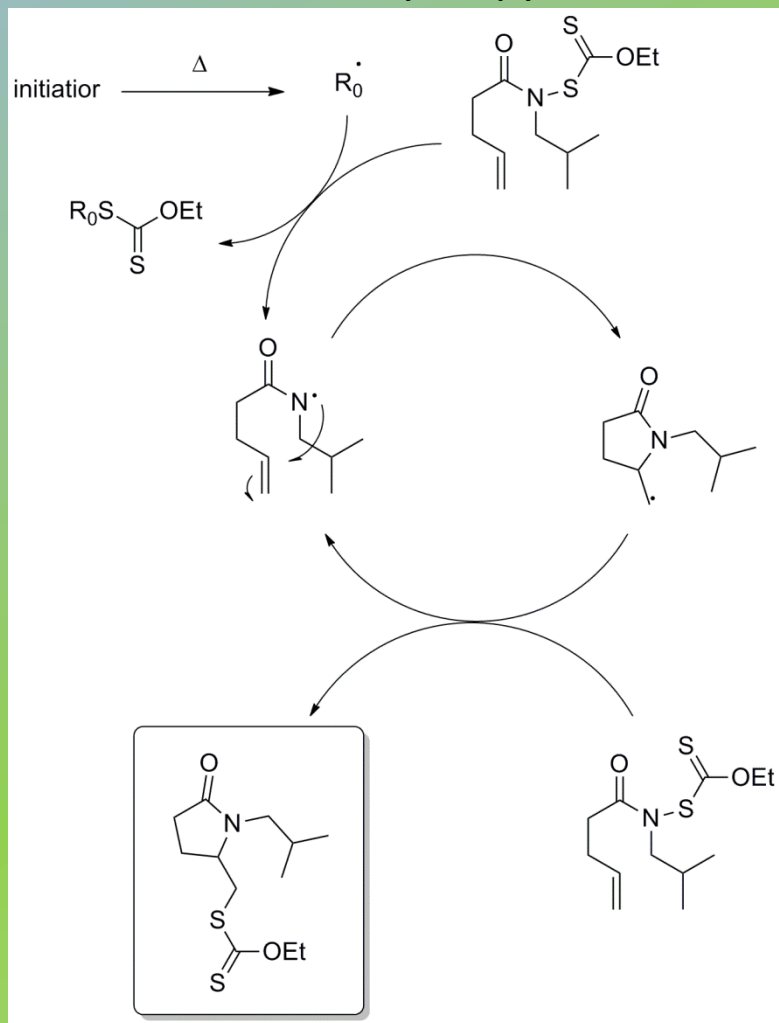
Mechanism bicyclic pyrrolidinones
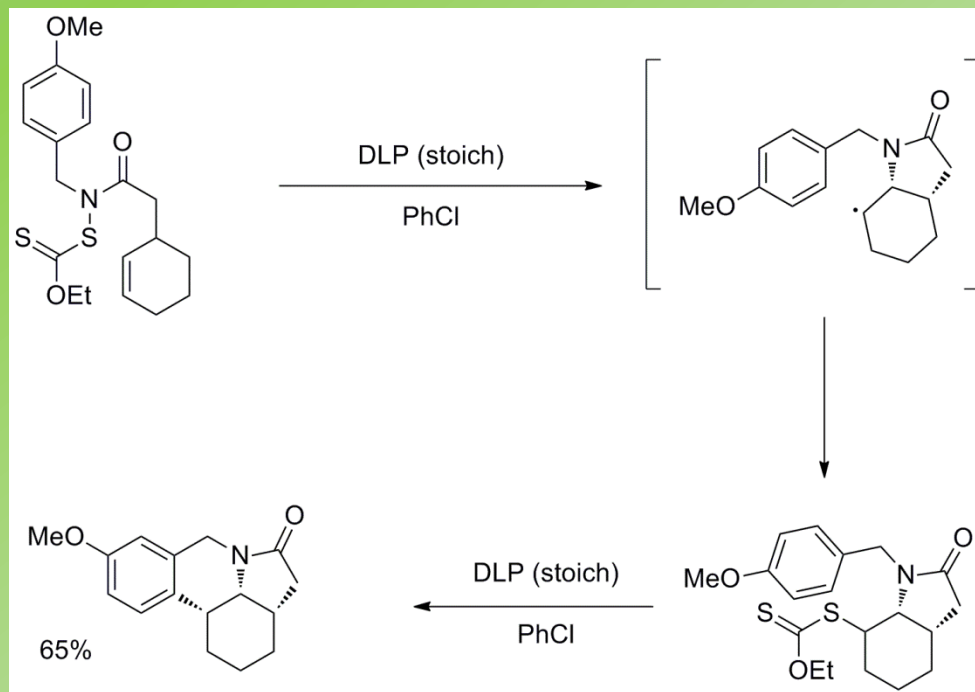
N-acylynamides for total synthesis of **Luotonin A**

- human DNA topoisomeraseI poison - alkaloid

Luotonin A   Iminyl radical
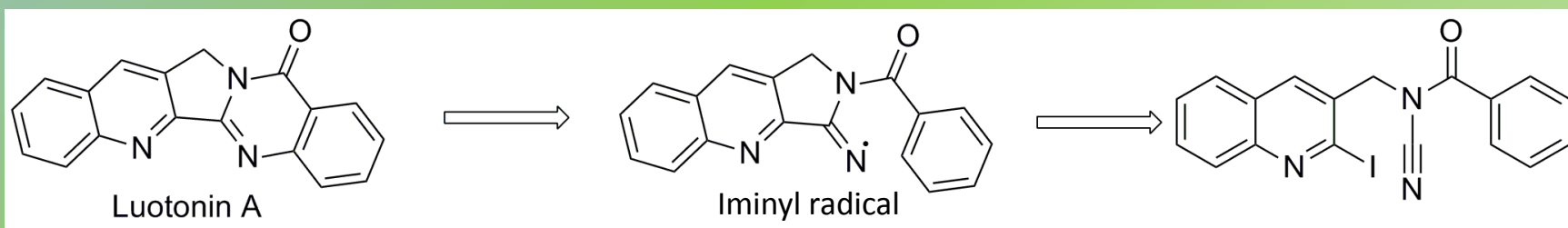
I· form I-H – molecule degradation

5eq. pyridine

PhH, air, hν

54%

rearomatization

Mechanism

Malacria M., *Chem. Eur. J.* **2008**, 14, 1238

22
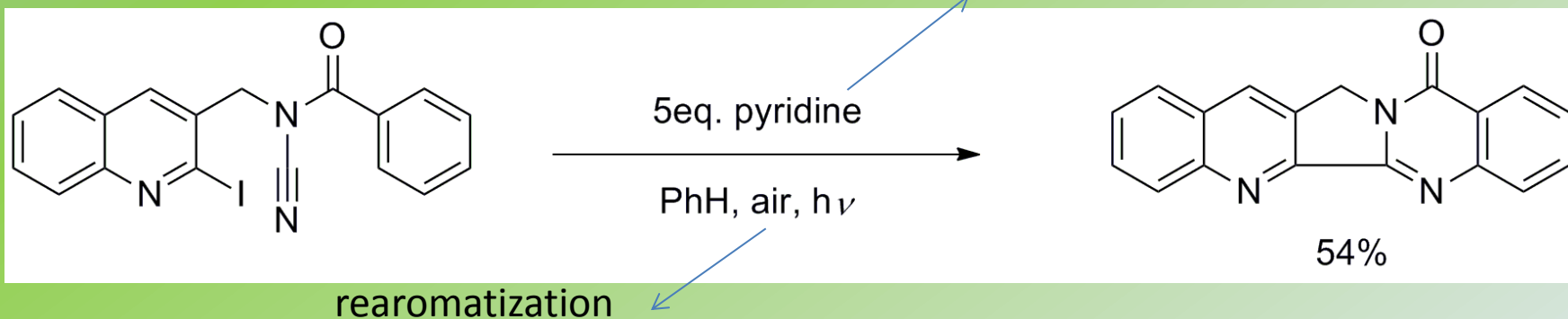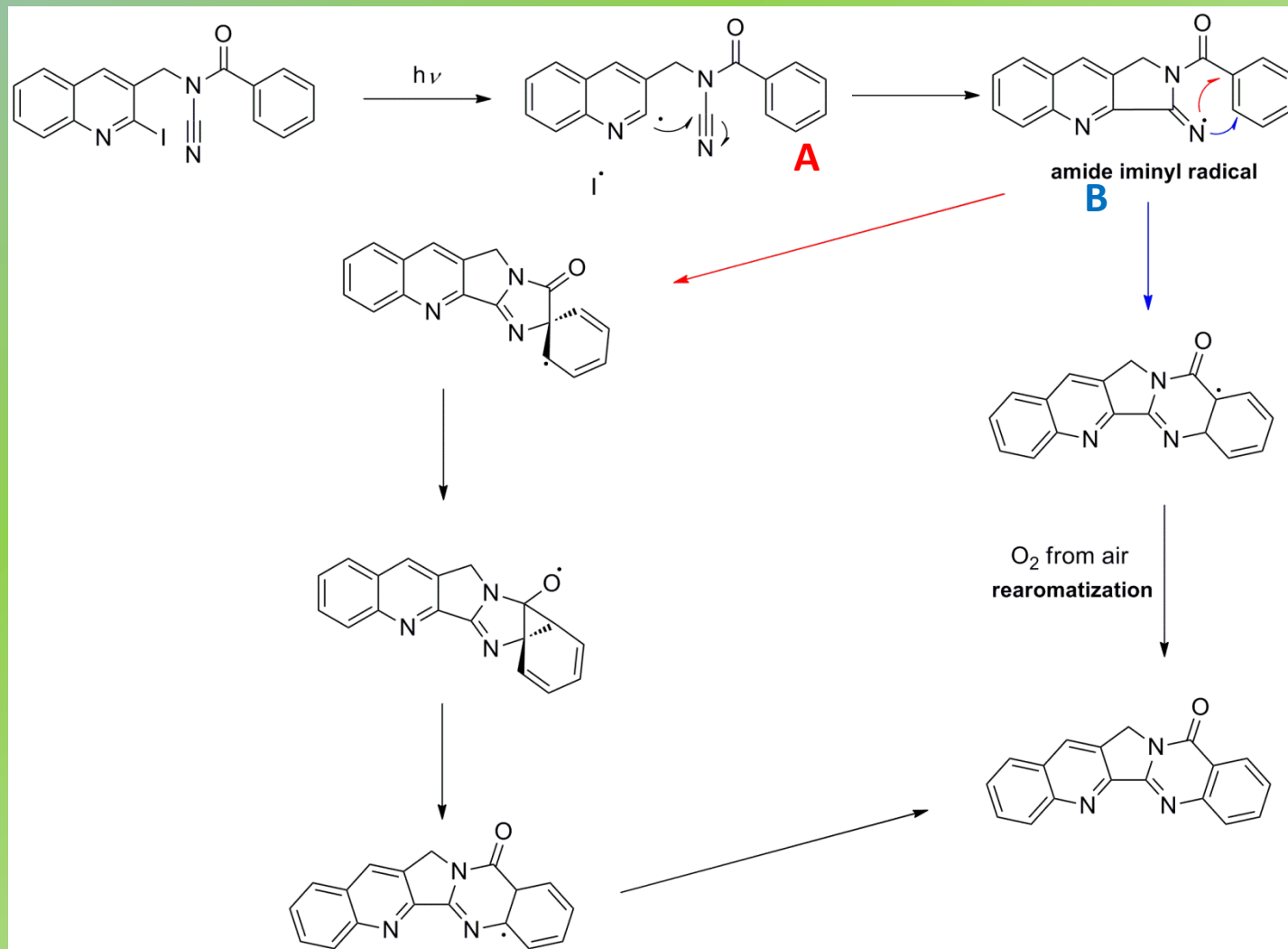
(±)-13-Deoxyserratine – alkaloid

Retrosynthetic Strategy
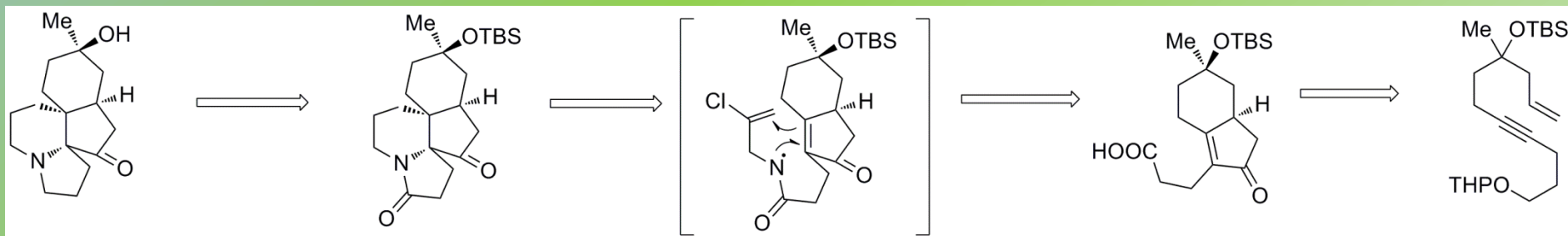
- Amidyl radical cyclization forms 2 quanternary centers in one step
- Two key step to control 4 stereogenic centers
- 10 steps total synthesis

Zard S.Z., *Angew. Chem. Int. Ed*. **2002**, 41, 1783

Mechanism
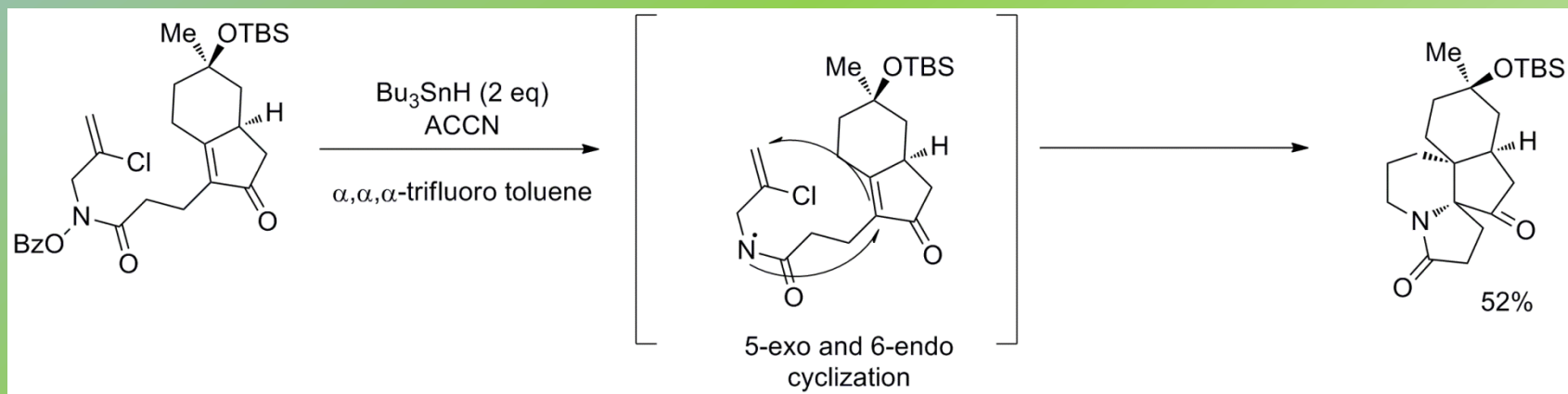
- Chlorine needed to go 6-endo
- 2eq of initiator to remove Cl
- 2 consecutive quaternary centers created in one step

Zard S.Z., *Angew. Chem. Int. Ed*. **2002**, 41, 1783

24

Radicals chemistry – powerful tool to achieve selective transformations in very efficient ways

Nitrogen based radicals are useful intermediate, stable and manageble species that allows many type of cyclizations – sometimes without wasteful initiators (Sn)

Application in total synthesis demonstrate that radical chemistry can be selective just as much as 'normal-polar reactivity', accomplishing stereoselective transformations on complex molecules

CH-708: Heterocyclic and Heteroaromatic Course

Direct C-H Activation of
Five-Membered Nitrogen-Containing Heterocycles

Contents for C-H Functionalisation Presentation

-Introduction to C-H activation and its importance

-Direct C-H (hetero)arylation of 5-membered N-containing heterocycles

-ASIDE: One example of Direct C-H functionalisation of thiophenes

- Direct alkynylation of 5-membered N-containing heterocycles

-Summary and Outlook

C-H Bond Functionalisation Exercises

1) What are the advantages of direct C-H activation and/or oxidative direct C-H activation over classical approaches to the synthesis of biarenes?

2) Can you think of one possible method of synthesising 1-bromo-alkynes?

*Ref.= "Copper as a Powerful Catalyst in the Direct Alkynylation of Azoles" ACIE, **2009**, 48, pg 9553-9556; S. Piguel et al.*

$$Br-\!\!\!\equiv\!\!\!-R$$

The Importance of C-H Activation
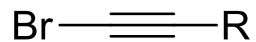
What is C-H Activation?
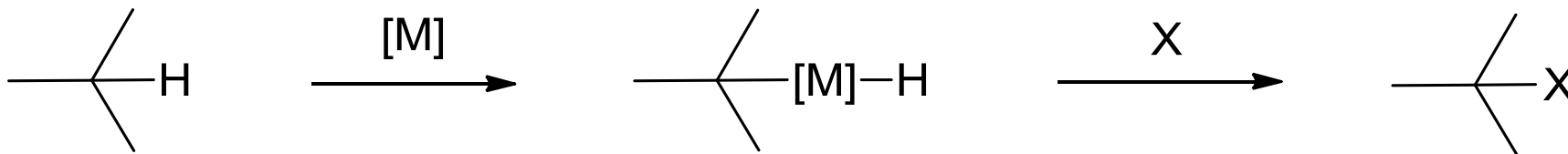
C-H activation:

-Enables reactivity that otherwise could not be achieved

-Offers new disconnection strategies to rival traditional methods that often require prior manipulation of functional groups.

-Thus C-H activation allows for the simplification of synthetic approaches

"C-H Bond Functionalization in Complex Organic Synthesis" *Science,* **2006**, *312,* pg 67- 72; K. Godula; D. Sames

The Advantage over Traditional Approaches

C-H activation offers a shorter, more efficient synthetic pathway to the desired product.

This possesses both environmental and economic advantages, namely reducing the drain on

resources and minimizing the generation of waste.

TRADITIONAL APPROACHES:
ALDOL CONDENSATION
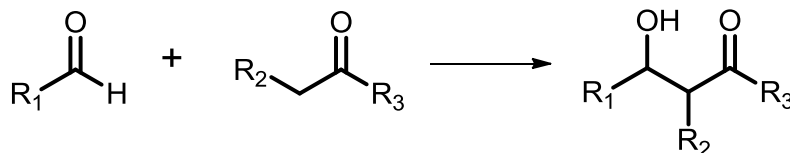
TRANSITION METAL-CATALYSED:
OLEFIN CROSS METATHESIS
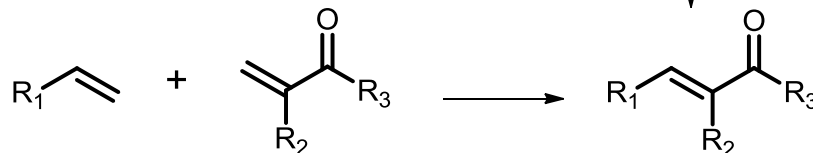
FUNCTIONAL GROUP
TRANSFORMATION

C-H BOND FUNCTIONALIZATION
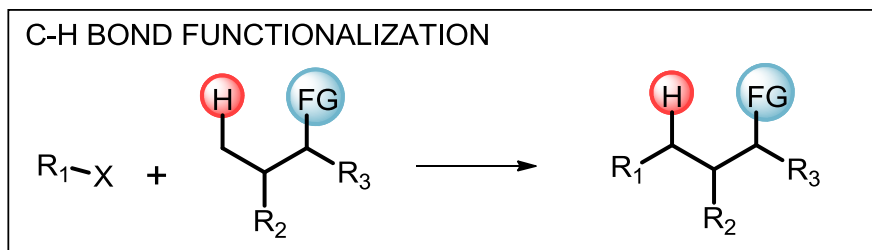
Why Five-Membered Nitrogen Containing Heterocycles?

Out of the top 200 brand-name selling drugs in the US retail market[*], **25** of them incorporate five membered nitrogen containing heterocycles in their structure.

<u>N.B.</u> This is not including **fused** five-membered nitrogen containing heterocycles e.g. indoles.
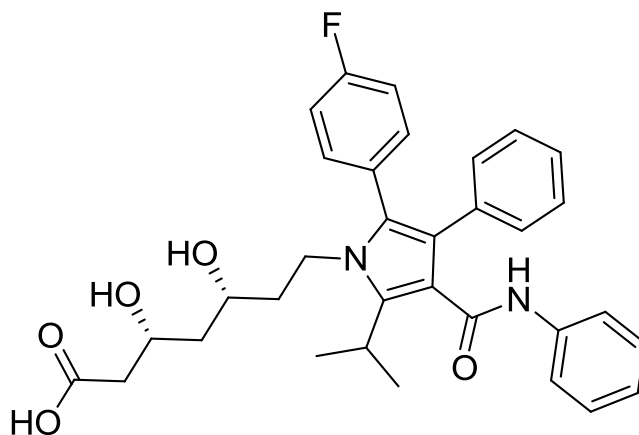
2nd Top-selling drug in the US retail market in 2010
Lipitor (Atorvastatin); Pfizer; US $5.3 Billion

Many of these '25' consist of highly-substituted five membered nitrogen containing heterocycles, where 4 or 5 ring positions are substituted.

Structural Core Diversification

C-H functionalization provides the opportunity to systematically and selectively target specific C-H bonds in complex substrates, enabling direct access to a variety of chemical analogues originating from a common structural core.
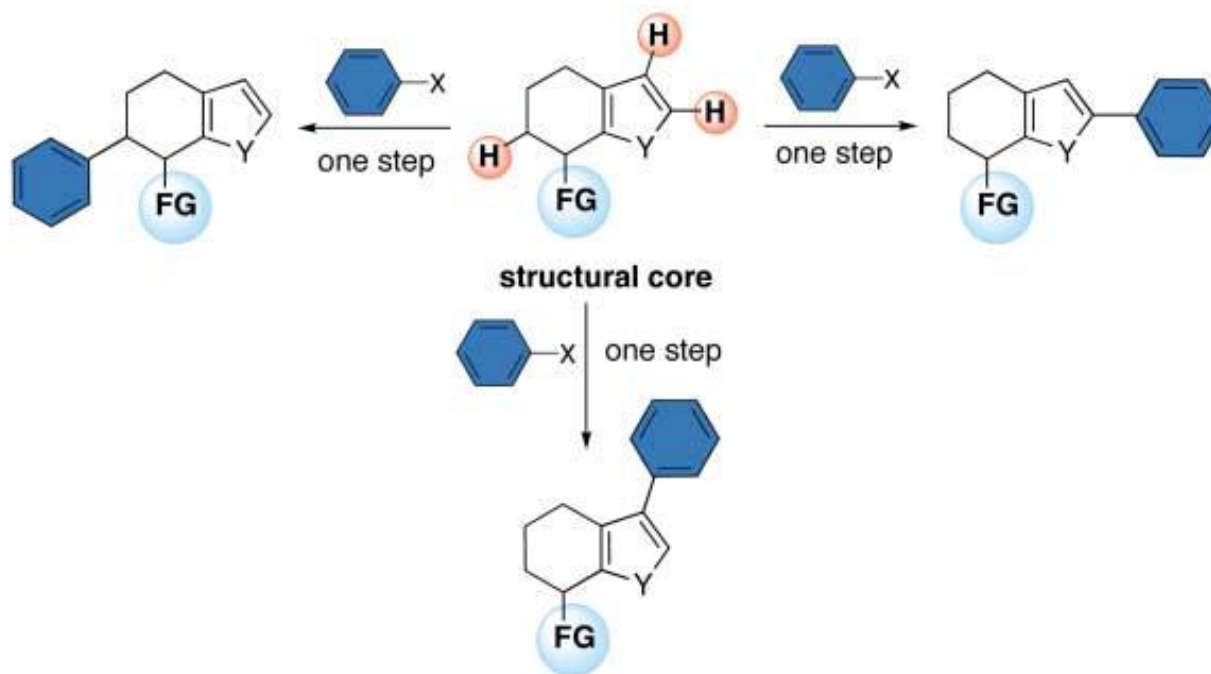
Structural core diversification by C-H functionalization is a sharp contrast to traditional approaches whereby structural derivatives often require multistep and distinctive sequences.

"C-H Bond Functionalization in Complex Organic Synthesis" *Science,* **2006**, *312*, pg 67- 72; K. Godula; D. Sames

C-H Bond Activation: Strategies for C-C Bond Formation 1

-(Hetero)aryl – (hetero)aryl bonds are an important substructure within many natural products, pharmaceuticals, fragrances, dyes, materials and agrochemicals.

<u>Classical Transition Metal-Catalysed Cross Coupling</u>

Ar—H —Step(s)→ Ar—X^1

Precursor

Activated component
X^2 = B(OR)$_2$, SnR$_3$, SiR$_3$ ....

Ar—Ar

Desired biaryl product

Ar—H —Step(s)→ Ar—X^2

Precursor

Activated component
X^2 = Br, Cl, I, OTf ....
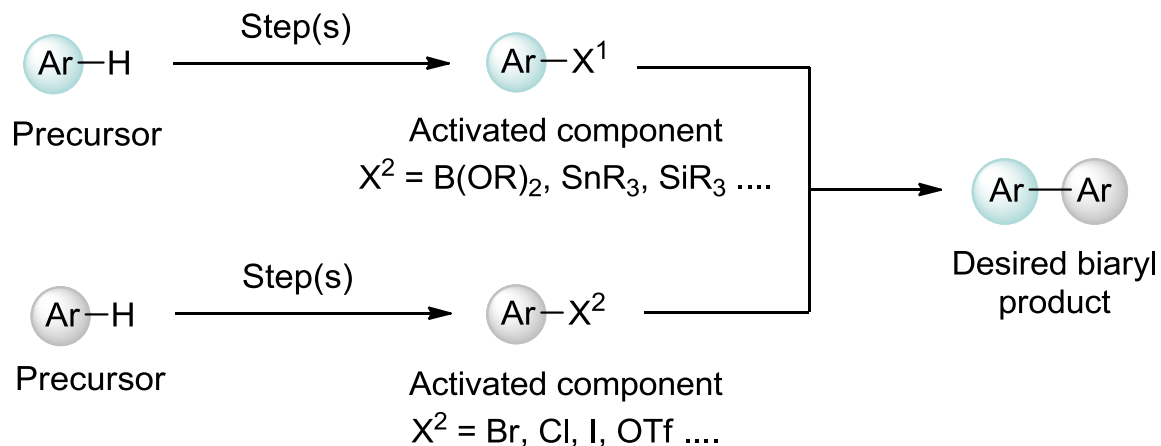
-Through conventional methods, these bonds are forged by TM catalysed cross-coupling of a (hetero)aryl halide with a (hetero)aryl organometallic reagent, e.g. Stille, Suzuki, Hiyama, Sonogashira, Kumada, Negishi, etc....

-However, these classical techniques for synthesising biaryls require prefunctionalised arenes for the selective linkage of two arenes through a C-C bonds.

-Pre-activation of the (hetero)arenes fragments with metal-containing functionalities and halides may involve several synthetic steps. Can avoid prefunctionalisation in at least one of the two coupling partners.

Ar—H + H—Ar

pre-activation (both sides)

pre-activation (one side)

Ar—X^1 + X^2—Ar

[O]

Ar—X + H—Ar

path *III*

path *I*

path *II*

Ar—Ar
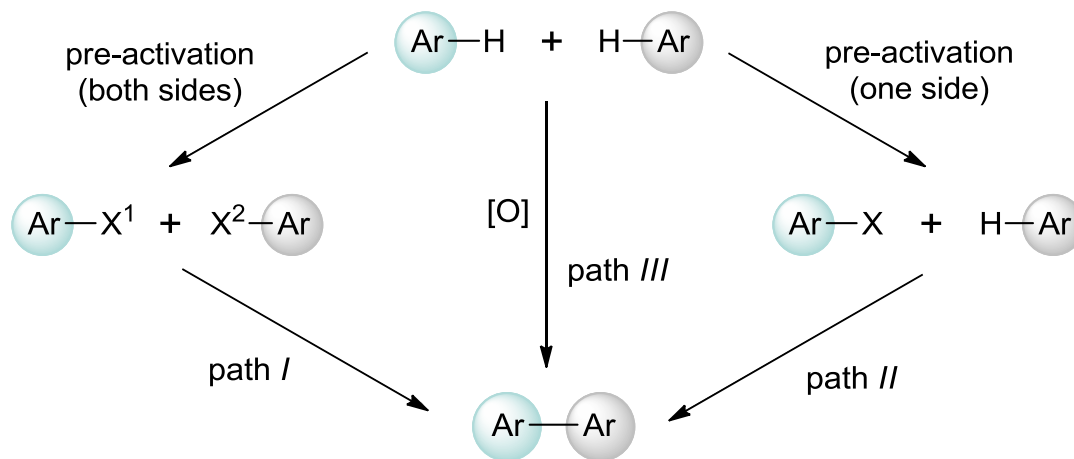
-The most ideal transformation would occur by transition metal catalysed direct oxidative intermolecular C-H/C-H cross coupling of (hetero)arenes via a double C-H bond activation process.

NO PREFUNCTIONALISATION OF THE HETERO(ARENE) SUBSTRATE(S) REQUIRED!

Diagrammatic representation: *Org. Lett.* , **2011**, *13,* pg 1474-1477; S. Kim; J. Yoon; S. Chang

Palladium Catalysed Oxidative Arene Cross Coupling

-A greener and more efficient alternative to Suzuki or Stille couplings is the direct catalytic cross coupling of two arenes and/or heteroarenes without the need of activating groups.

Ar—H + Ar—H ⟶ Ar—Ar   Hetero-coupled (hetero)arene

-Selective C2-arylation of unactivated pyrroles and benzene was achieved by Fagnou and co-workers by employing catalytic Pd(OPiv)$_2$ and excess AgOAc as an oxidant.

-However, small amounts (< 10%) of pyrrole dimerization was observed.
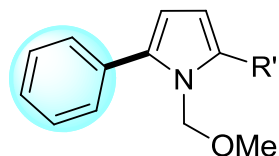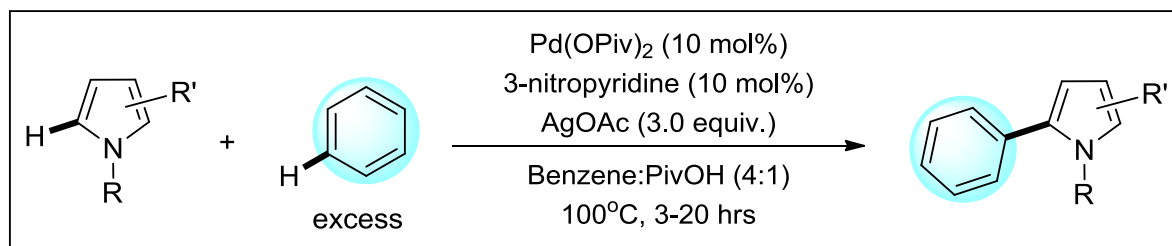
R' = -COCH$_3$ 64%
R' = -CO$_2$CH$_3$ 66%
R' = -CN   67%
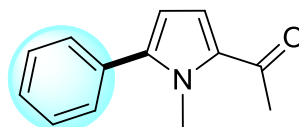
68%
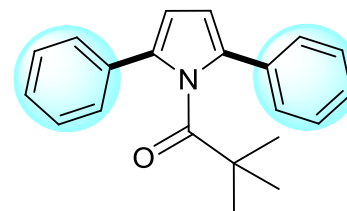
53%

"Elements of Regiocontrol in Palladium-Catalyzed Oxidative Arene Cross-Coupling" *JACS,* **2007**, *129,* pg 12072-12073; D. Stuart; E. Villemure; K. Fagnou

Palladium Catalysed Arylation of 4-Chloropyrazoles

-Selective C5 arylation of N-methylpyrazoles with electron-rich and electron-poor aryl bromides under palladium catalysis.
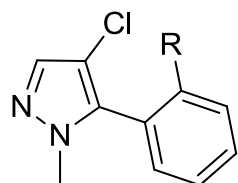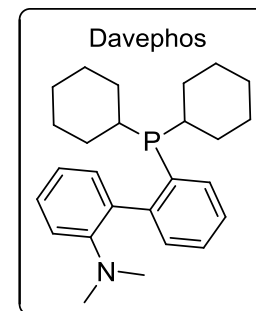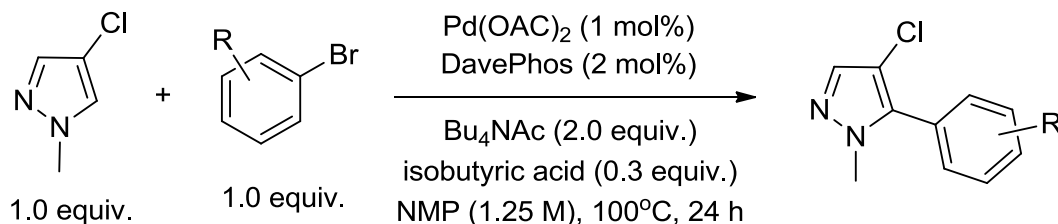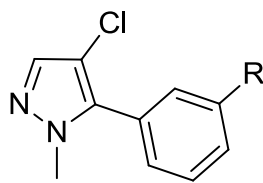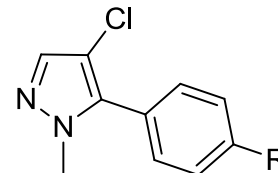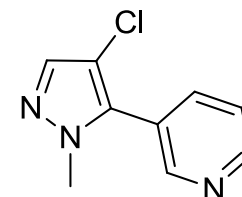
-Variety of functional groups (Cl, F, CN, NO$_2$, Me, MeO) were tolerated.

-Reaction proceeded efficiently with *meta-* and *para*-substituted derivatives.

-However, ortho substitution showed very poor reactivity or no reaction due to steric hindrance.

"Regioselective Palladium-Catalyzed Arylation of 4-Chloropyrazoles" *Org. Lett.,* **2010**, *12*, pg 4924-4927; J. M. Minguez

Intramolecular Direct C-H Arylation of 5-iodotriazoles

-Compounds consisting of fused triazoles are becoming increasingly common in pharmaceutical targets and biologically substances.
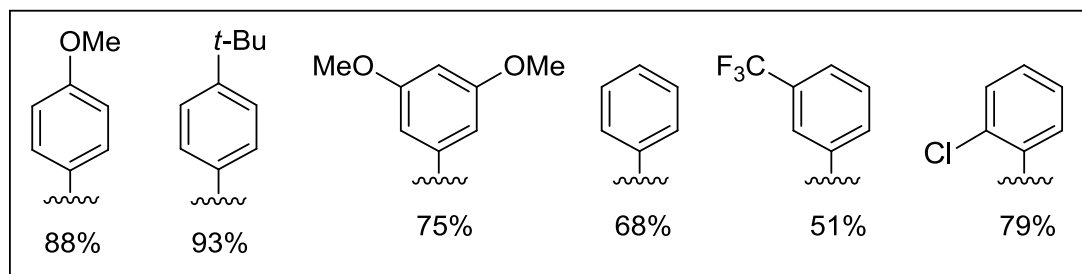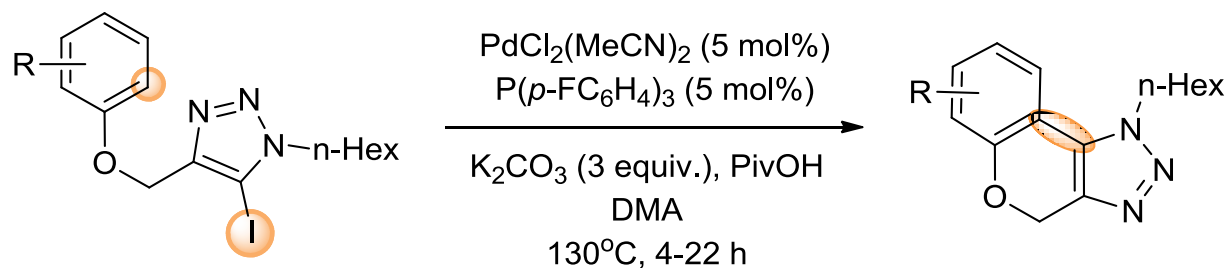
-Electron-rich and electron-poor aromatic substituents were all amenable to the reaction protocol giving moderate to excellent yields.

-Substitution at the ortho, meta and para positions of the aryl group were all tolerated.

-However, the triazole must be preactivated to contain an iodo substituent at the 5-position.

"Synthesis of 1,2,3-triazole-fused heterocycles via Pd-catalyzed cyclization of 5-iodotriazoles" *Chem. Comm.,* **2012**, *48,* pg 55-57; M. Lautens et al.

-C-H arylation onto the PMB triazole protecting group lead to the 'unexpected product'.

-Following this result, substrates capable of only cyclising onto the N-tether were investigated.

Isoindoline building block
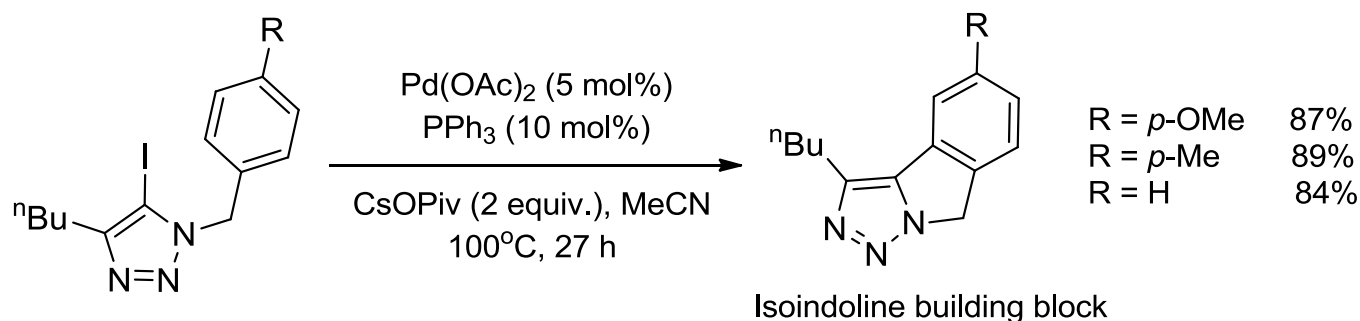
Would it possible to perform direct C-H arylation of triazoles without any prior functionalisation of either of the cross-coupling partners?

Intramolecular Direct C-H Arylation of Unactivated Triazoles

-Highly efficient palladium-catalysed intramolecular dehydrogenative direct arylation of triazoles, **without** the need for prefunctionalised arylating reagents.
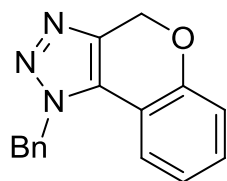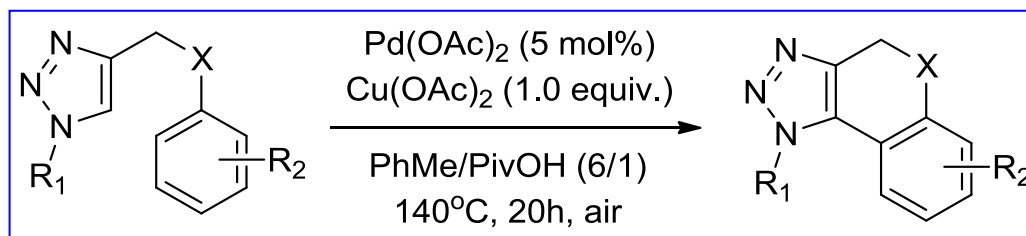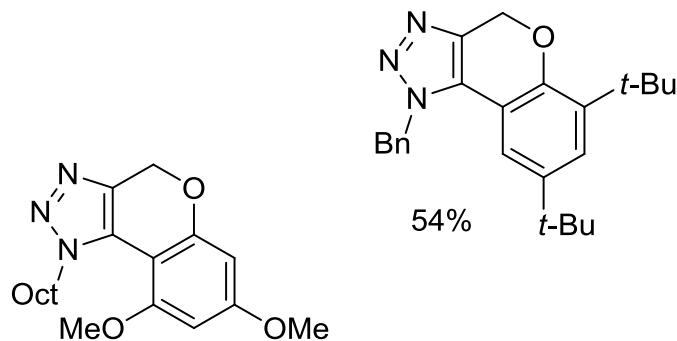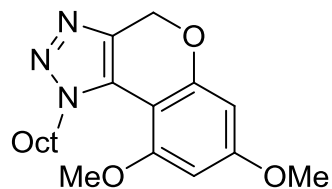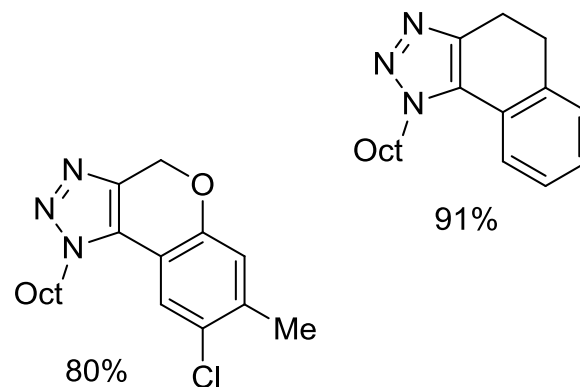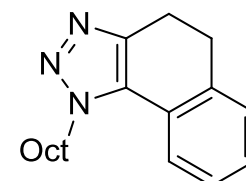
-This method allows for the regioselective preparation of highly decorated triazoles.

-Reactions performed under an ambient atmosphere of **air** (although not mandatory.)

Sequential Catalytic Direct C-H Arylations Involving Unactivated Triazoles

-Sequential synthesis of heteroannulated phenanthrenes proceeding by **two** distinct direct C-H bond functionalisations.

Representative Example:
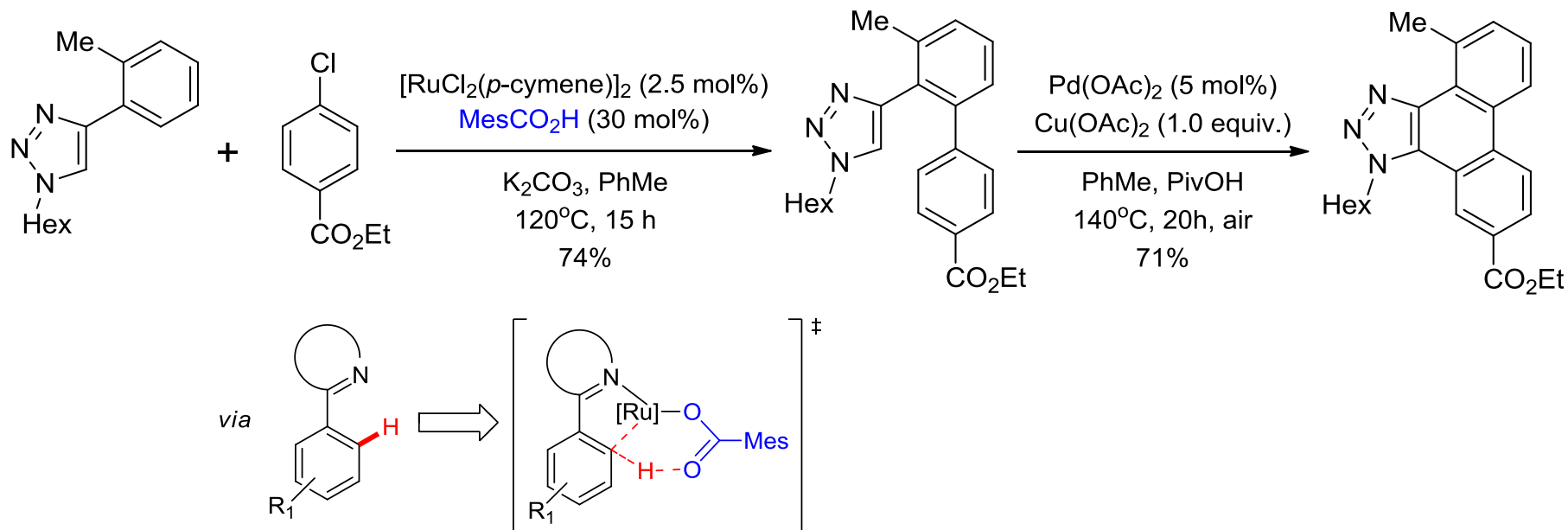
(1) "Palladium-Catalyzed Dehydrogenative Direct Arylations of 1,2,3-Triazoles"
   Org. Lett., **2010**, *12,* pg 2056-2059; L. Ackermann et al.
(2) "Assisted Ruthernium-Catalyzed C-H Bond Activation: Carboxylic Acids as Co-catalysts for Generally Applicable Direct Arylations in Apolar Solvents" *Org. Lett.,* **2008**, *10,* pg 2299-2302; L. Ackermann et al.

Pd catalysed Oxidative
C-H/C-H Cross Coupling of Pyrroles with Heteroarenes

-(Hetero)arylated pyrroles and indoles represent an important structural core for a range of uses within different chemical industries.

-The most efficient pathway would occur by transition metal catalysed direct oxidative intermolecular C-H/C-H cross coupling of pyrroles with heteroarenes via a double C-H bond activation process. This avoids the need for prefunctionalization of both substrates prior to the coupling reaction.

-However, literature precedence of TM catalysed direct oxidative C-C couplings between **two heteroarenes** is limited.

The Problems

① Documented to undergo homo-coupling of heteroarenes

② Pyrroles (and other π-electron rich heteroarenes) are susceptible to oxidative decomposition under the oxidative reaction conditions

③ Presence of heteroarenes can result in low reactivity and selectivity due to the binding of the heteroatom in both the substrate and product to the metal complex

④ Inadequate stability of pyrroles and other heteroarenes for participating in the coupling process

⑤ Regioselective control of C2 vs C3 C-H bond activation

"Palladium-Catalyzed Oxidative C-H/C-H Cross-Coupling of Indoles and Pyrroles with Heteroarenes"
Angew. Chem. Int. Ed. **2011**. *50*. pg 5365-5369; J. Lan et al.; J. You et al.

The Goal

-In 2007, K. Fagnou made a significant breakthrough with Pd(II) oxidative cross-coupling of unactivated heteroaryls with simple unactivated arene.

(*Science,* **2007**, *316,* pg 1172-1175; K. Fagnou et al.;_ *JACS,* **2007**, *129,* pg 12072-12073; K. Fagnou et al.)

-But the same process, oxidative double C-H activation, to form unsymmetrical **bi**heteroaryl molecules remains a daunting prospect
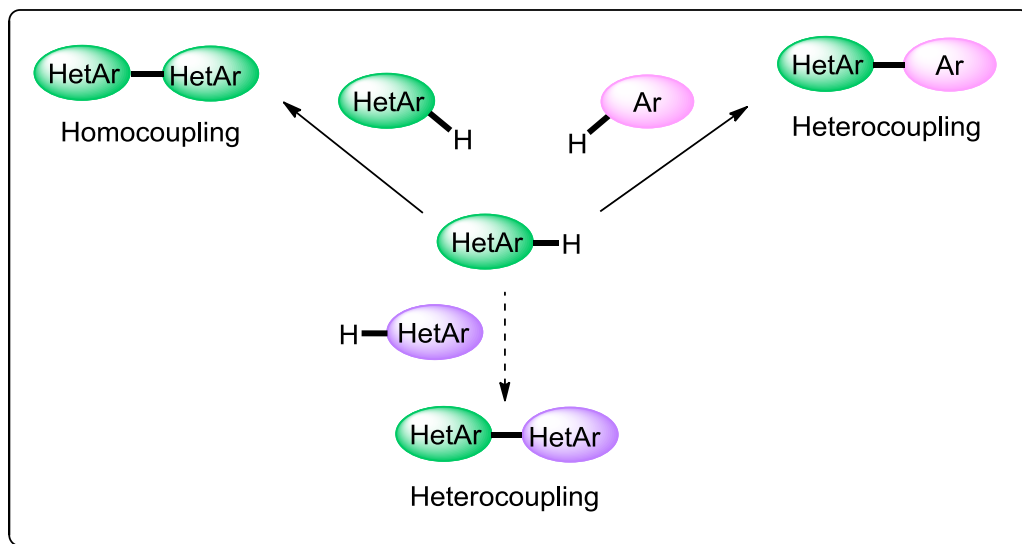
-Furthermore, there is a need to suppress the homocoupling of the heteroaryl species.

Diagrammatic representation: *JACS ,* **2010**, *132,* pg 1822-1824; J. Lan et al, J. You et al.

The Solution

Pd(dppf)Cl$_2$ (2.5 mol%), X-Phos (5.0 mol%)
CuCl (20 mol%), Cu(OAc)$_2$.H$_2$O (3.0 equiv.)

Pyridine (1.0 equiv.), 1,4-dioxane/DMSO
105°C, 30h
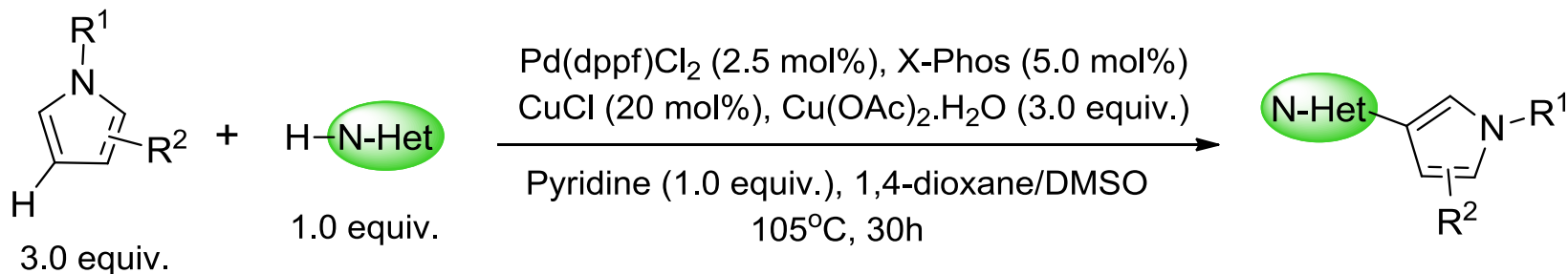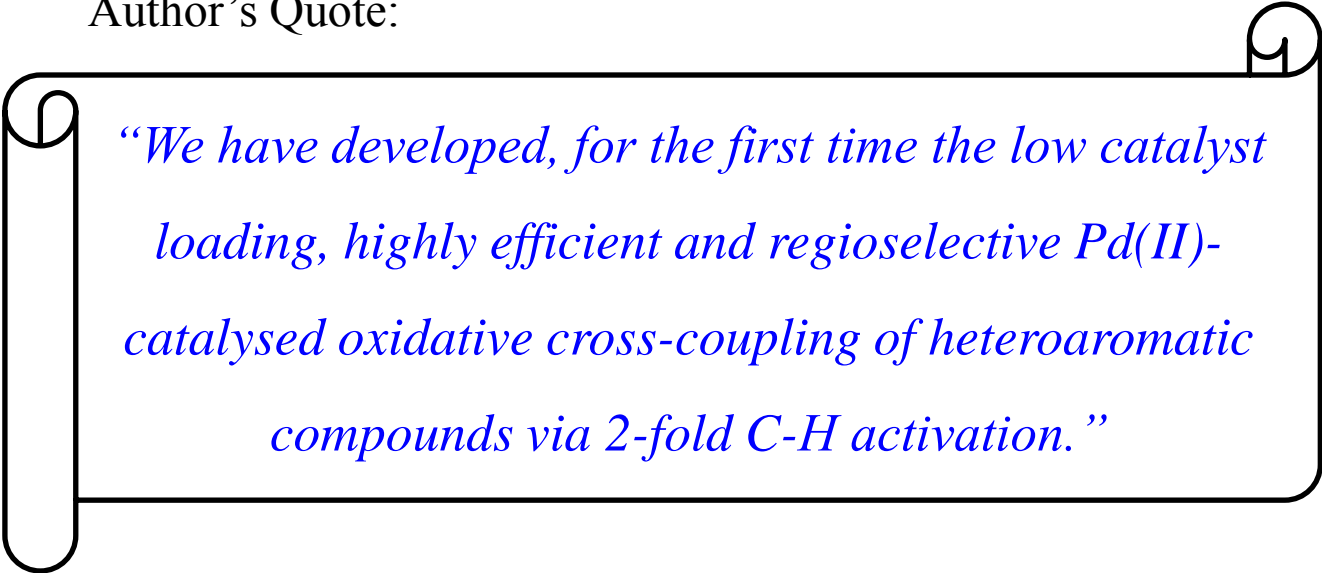
-The Pd/Cu bimetallic co-catalytic system suppressed pyrrole dimerisation (homocoupling).

-J. Lan, J. You and co-workers discovered the addition of X-Phos greatly prevented the decomposition of the N-heteroarene and pyrrole substrates and improved the yield.

-Highly regioselective C3 heteroarylation of the pyrrole substrate was achieved.

-Catalytic amounts of CuCl improved the reaction efficiency and C3 regioselectivity.

Pd(dppf)Cl$_2$ Catalyst

R = Me   80%
R = Bn   83%

53%
N.B. (130°C)

66%
N.B. CuBr (20 mol%), pyr (2.0 equiv.)

X-Phos Ligand

X = S   51%
X = O   60%
N.B. 5 mol% [Pd]

59%

70%
N.B. (140°C)
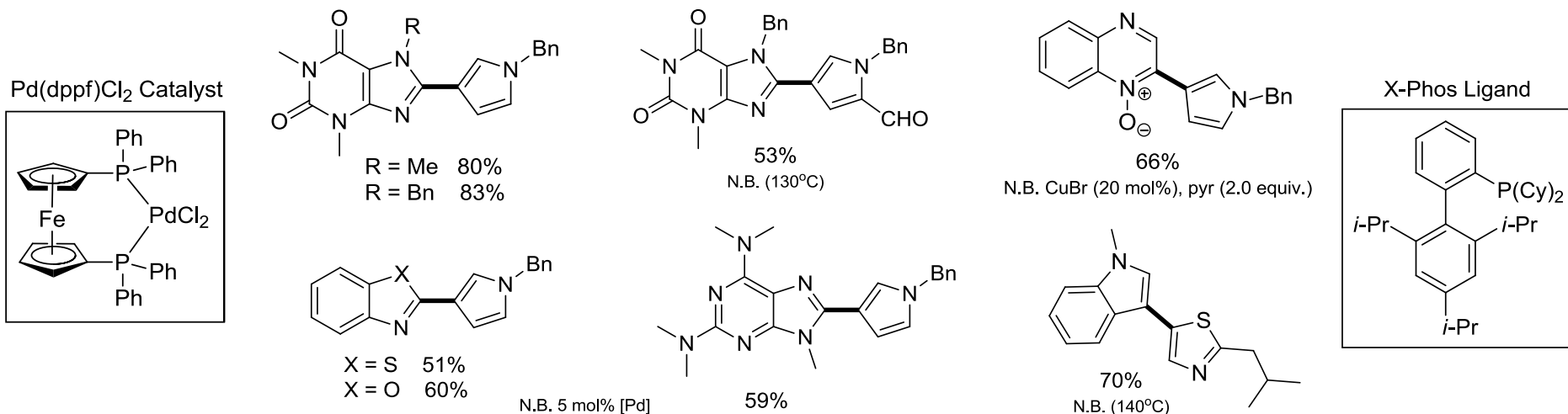
-This catalytic system allows the C-H/C-H heterocoupling of both electron-rich N-containing heteroarenes (e.g. xanthines, azoles as well as electron-poor pyridine N-oxides with a diverse array pyrroles (and furans, thiophenes and indoles)[*]

Author's Quote:

"We have developed, for the first time the low catalyst loading, highly efficient and regioselective Pd(II)-catalysed oxidative cross-coupling of heteroaromatic compounds via 2-fold C-H activation."

-Significant impact for the future synthesis of unsymmetrical biheteroaryl molecules

* (1) "Palladium-Catalyzed Oxidative C-H/C-H Cross-Coupling of Indoles and Pyrroles with Heteroarenes" *Angew. Chem. Int. Ed.,* **2011**, *50,* pg 5365-5369; J. Lan et al, J. You et al.
(2) "Palladium(II)-Catalyzed Oxidative C-H/C-H Cross-Coupling of Heteroarenes" *JACS ,* **2010**, *132,* pg 1822-1824; J. Lan et al, J. You et al.

<u>Aside:</u> C-H Activation of Thiophenes

-An example of unique reactivity being displayed by C-H bond activation is the selective *ß*-functionalization of thiophenes.

-The reaction protocol can be applied successfully to 2,3- disubstituted, 2-substituted and 3-substituted thiophenes as well as thiophene-containing fused aromatic systems.

Selective functionalization of the otherwise less reactive ß-position

PdCl$_2$ (5-10 mol%)
P{OCH(CF$_3$)$_2$}$_3$ (10-20 mol%)

Ag$_2$CO$_3$ (1 equiv.)
m-xylene
130°C, 12 h

1.5 equiv.　　　1.0 equiv.

R = H, alkyl, aryl, alkoxy, acyl, halogen

23 examples
Yields: 40-81%

Regioselectivity
(ß:a) 99:1 - 83:17

Br$_2$　　Zn, AcOH　　ArB(OH)$_2$
Pd cat.
Base
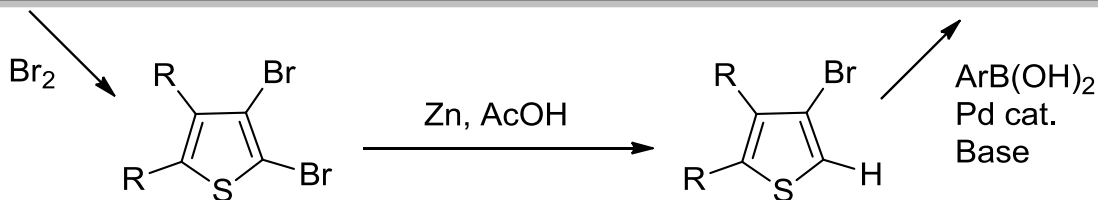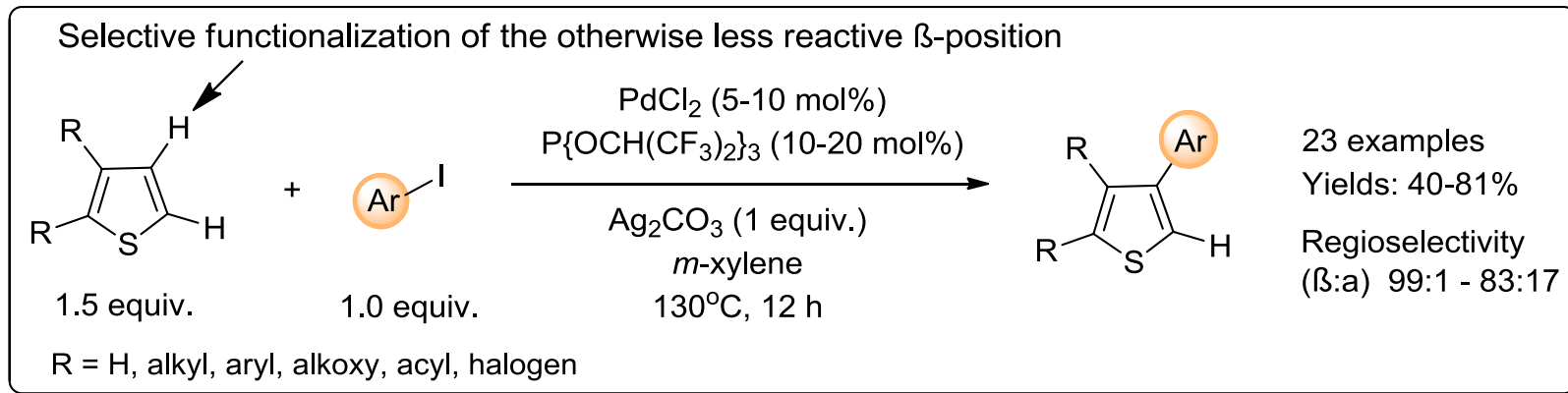
-The reaction was highly specific for the extremely electron withdrawing P{OCH(CF$_3$)$_2$}$_3$ ligand.

-Iodoarene coupling partner: both electron donating aryl substituents (Me, OMe) and electron withdrawing aryl substituents (CF_3, CO_2Et, NO_2, Br, Cl) were tolerated, as well as steric hindrance at the ortho position of the arene.

-Furthermore C-Cl and C-Br bonds present in the reactant are left intact in the products.

reaction site under C-H activation with Pd/P{OCH(CF_3)$_2$}$_3$ catalyst

typical reaction site

R = Ph, Cl   R = OPh, Cl   R = Ac
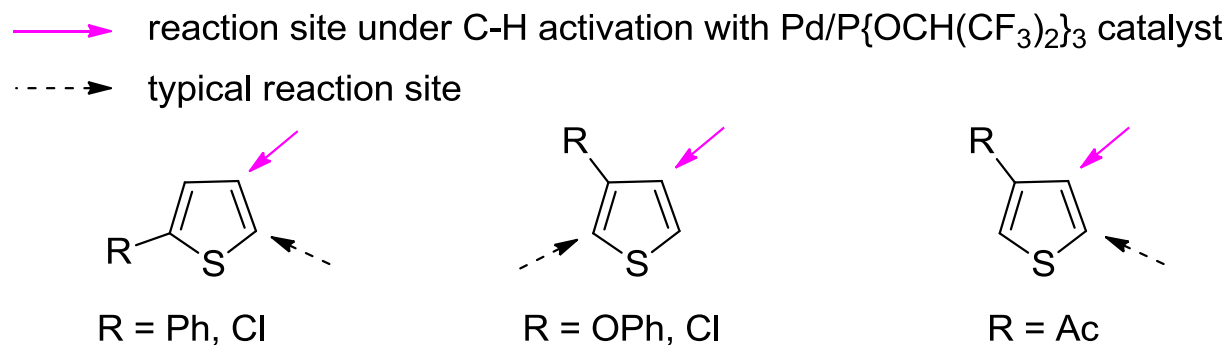
-TM-catalysed arylation of thiophene C-H bonds generally proceeds at the α-positions (C2/C5).

-The observed C4 (β) selective functionalization of the thiophenes overrides the inherent influence of the directing effects of the substituent and has been attributed to catalyst control.

Can this catalyst-ligand-silver salt combination be applied to pyrroles or furans to give selective β-arylation in these five membered heteroaromatics?

-Novel intermolecular decarboxylative C-H cross coupling between two unactivated azoles, proceeding with moderate to good yields.
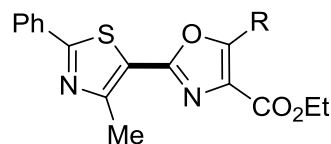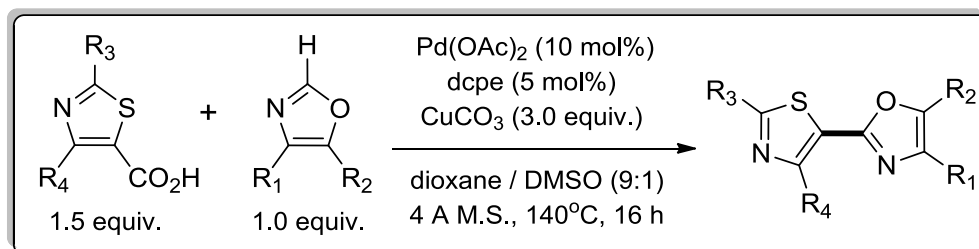
R = Me   80%
  = ^{i}Pr   51%
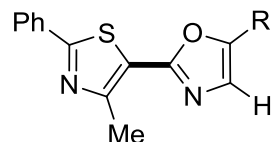
R = CO$_2$Et   45%
  = Ph   62%
  = o-ClC$_6$H$_4$ 48%
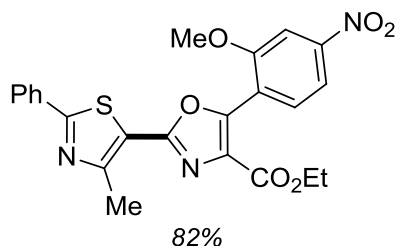
82%
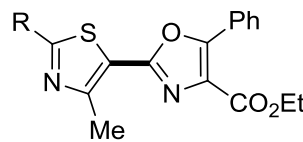
R = Me   52%
  = p-CF$_3$C$_6$H$_4$ 77%
  = p-ClC$_6$H$_4$ 56%
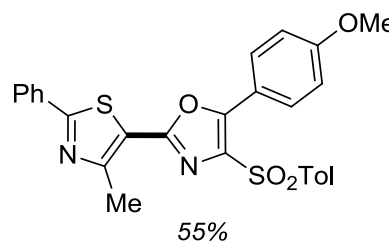
55%
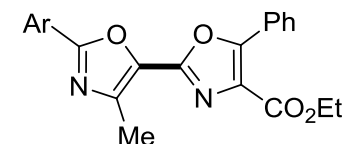
Ar = Ph   79%
  = p-OMeC$_6$H$_4$ 56%
  = p-MeC$_6$H$_4$ 56%
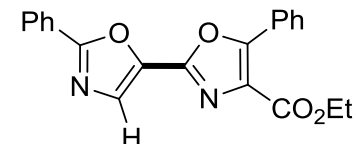
61%

-A variety of alkyl and aryl substituents were tolerated at the C2 for both the oxazole and thiazole components.

-Also functional groups including: esters, sulfones, nitro and chloro groups were all tolerated.

Decarboxylative C-H Cross Coupling of Azoles: 2

-This reaction protocol possesses some regiocontrol issues: Oxazoles containing two C-H bonds at the C2 and C5 position resulted in a mixture of products due to the difficulty in discriminating between the two positions because of the electron-rich nature of the 5-position.

-The presence of the ester functionality in the coupled product provides a useful handle to repeat the decarboxylative cross-coupling in a second C-C bond-forming reaction.

Formed by facile
hydrolysis of the
ester precursor

Pd(OAc)$_2$ (10 mol%)
dcpe (5 mol%)
CuCO$_3$ (3.0 equiv.)

dioxane / DMSO (9:1)
4 A M.S., 140°C, 16 h
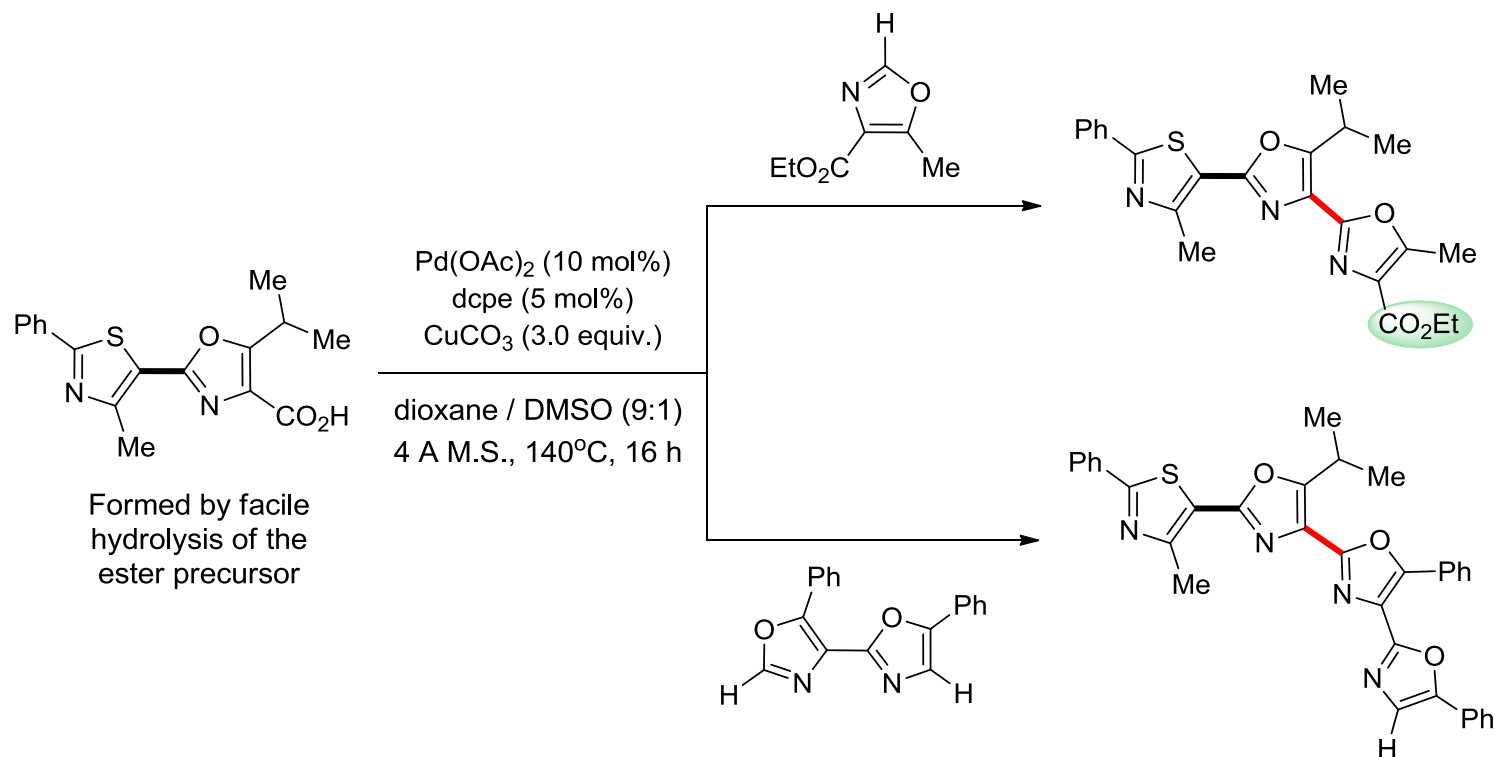
-An intertwined copper-catalysed decarboxylation cycle and a Pd-catalysed C-H arylation cycle
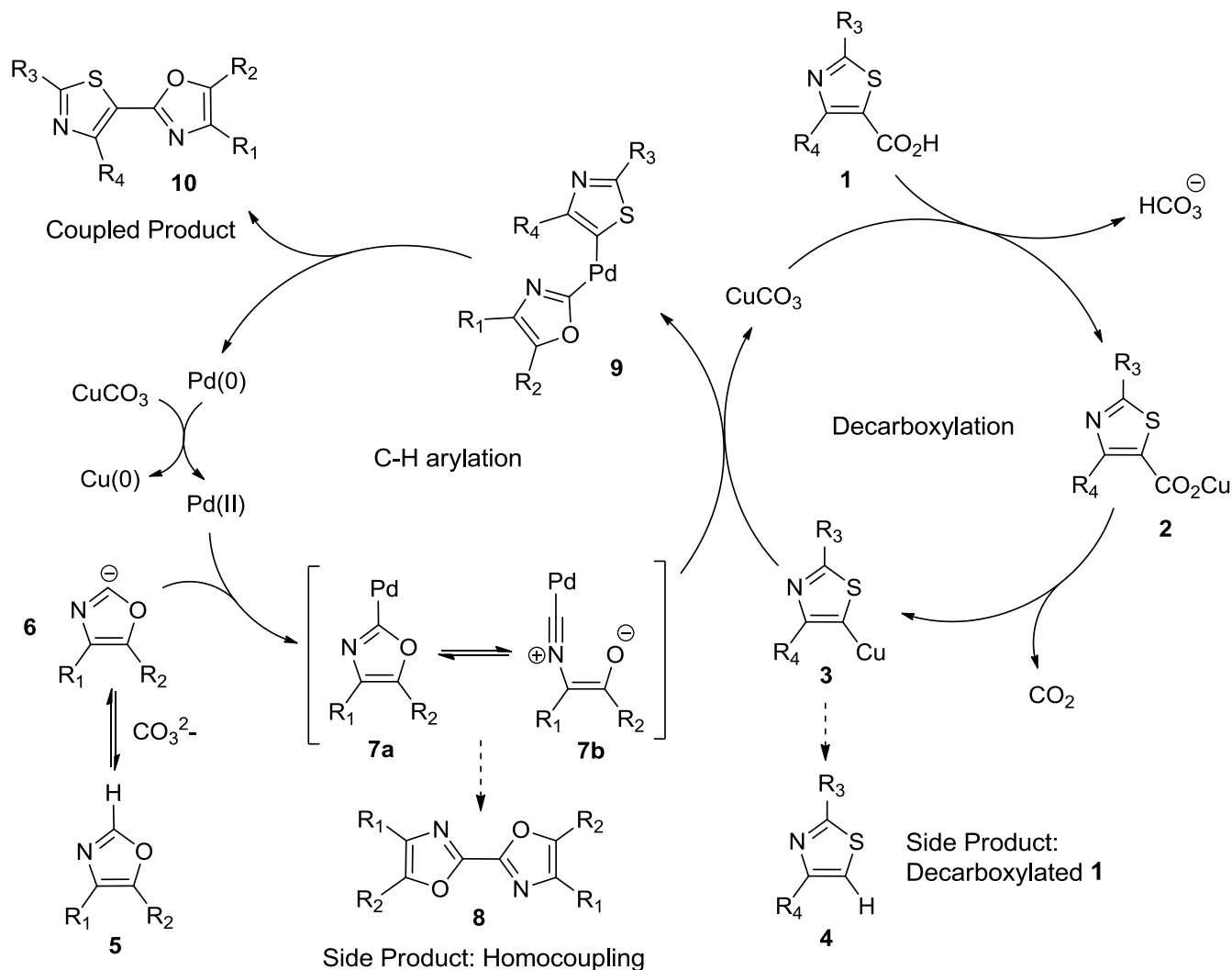
-Decarboxylation confirmed by the use of stoichiometric $CuCO_3$ in absence of palladium

C-H Cross Coupling of Benzazoles with Azoles: 1

-Two heteroarenes ideally connected via an atom-economic two-fold C-H bond activation.

-Highly regioselective palladium(II)-catalysed direct C2 heteroarylation of benzazoles with O-, N-, and S-containing azoles, which can be carried out under an ambient air atmosphere.

1.0 equiv.   1.5 equiv.

X = S, NR^3 Y = O, S, NR^4

Conditions A or B

Cu(OAc)$_2$ (2.0 equiv.)
DMF, air, 120°C

Conditions **A**: Pd(OAc)$_2$ (5 mol%)
KF/AgNO$_3$ (3 + 1.5 equiv.), 24h
Conditions **B**: Pd(OAc)$_2$ (10 mol%)
AgF (2.0 equiv.), 48 h

Conditions **A**

X = NMe   91%
= O   86%
= S   65%

R = H   67%
= Me   92%

87%

Ar = p-BrC$_6$H$_4$ 71%

71%
N.B. Under O$_2$ atmosphere

95%

86%

Conditions **B**

R = H   91%
= Me   88%
= Ph   84%
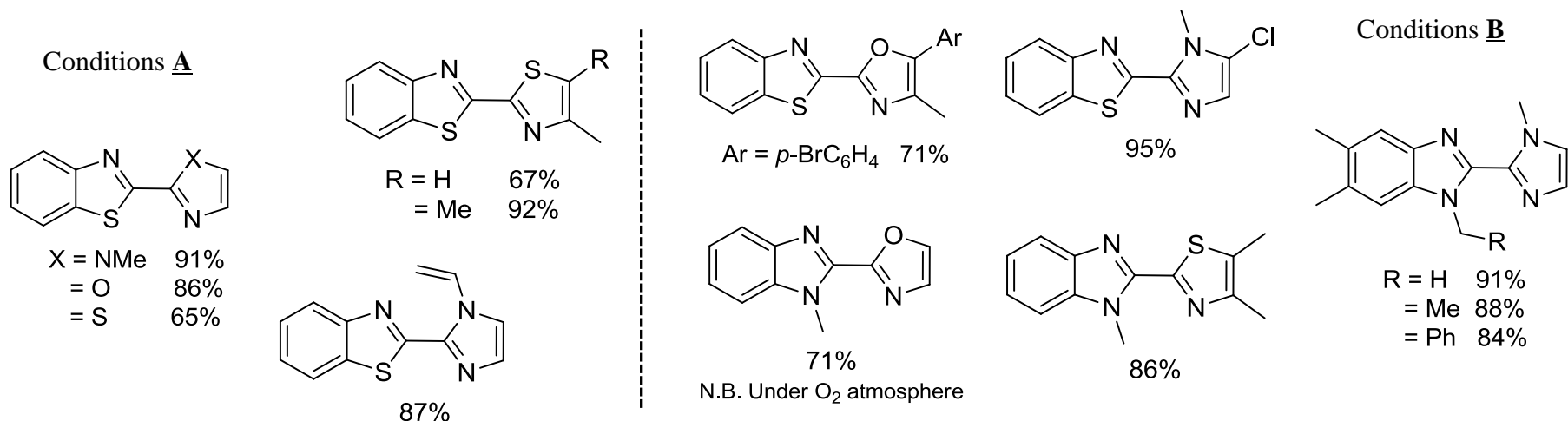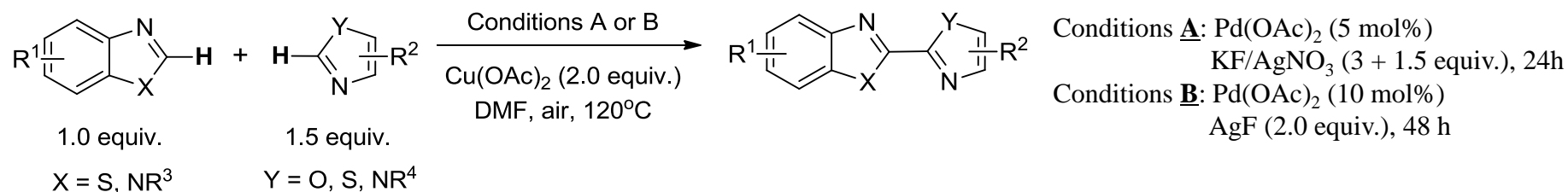
-Two equivalently efficient additive combinations Cu(OAc)$_2$.H$_2$O with either KF/AgNO$_3$ or AgF

C-H Cross Coupling of Benzazoles with Azoles: 2

-Pivotally the presence of Ag$^+$ ions successfully suppressed the formation of the homocoupled products and favoured the cross-coupled product.
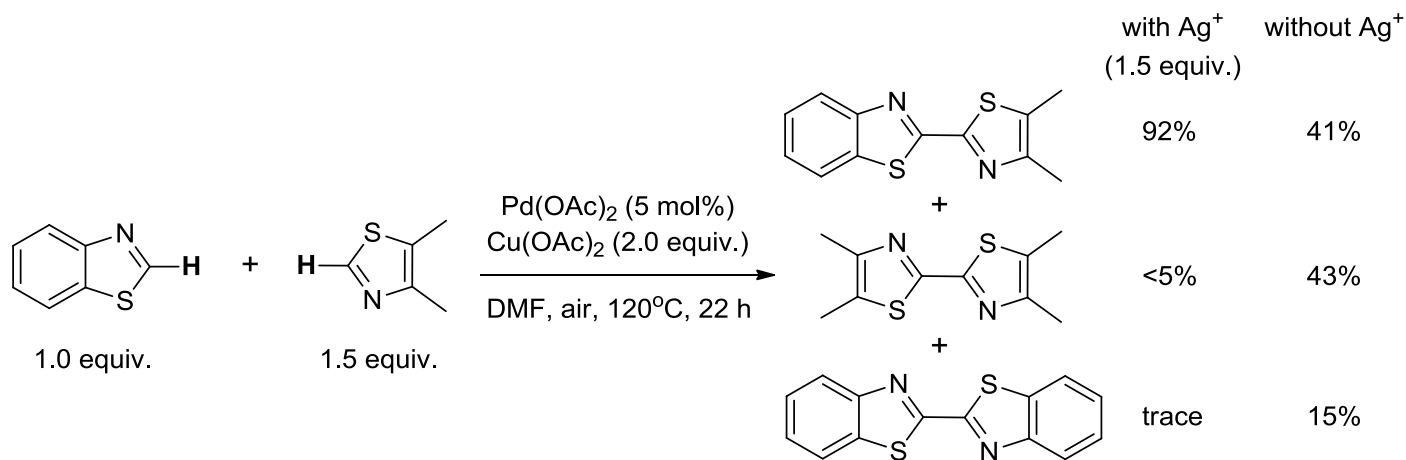
-Synthesis of mixed biheteroaryls obtained through the selective C-H bond cleavage in both substrates without the requirement of prefunctionalised azoles, designed ligands or a huge excess of one azole over the other.

"Palladium-Catalyzed Dehydrogenative Cross-Couplings of Benzazoles with Azoles"
Angew. Chem. Int. Ed., **2011**, *50*, pg 2178-2182; A. Ofial et al.

Iron Mediated Direct Suzuki-Miyaura Reaction

-Suzuki-Miyaura Reaction: the coupling between an aryl halide and an organic boronic acid.

-**First** example of an Iron-mediated **direct** Suzuki-Miyaura reaction for the regioselective 2-arylation of pyrroles.
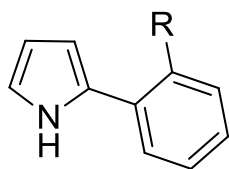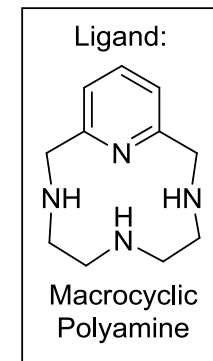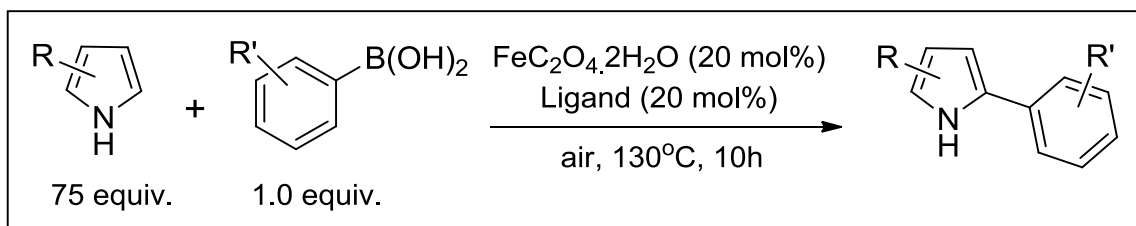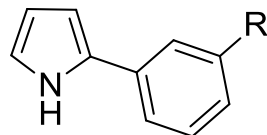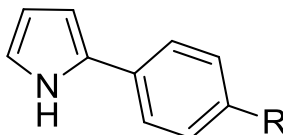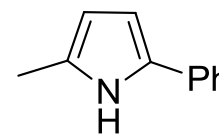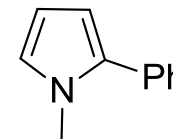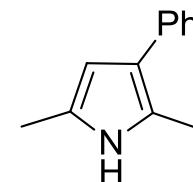
-Boronic acids are non-toxic, stable and compatible with most functional groups.

-Iron is abundant, cheap, environmental benign.

"Iron-Mediated Direct Suzuki-Miyaura Reaction: A New Method for the *ortho*-Arylation of Pyrrole and Pyridine"
Org. Lett., **2010**, *12*, pg 2694-2697; C.-W. Hu et al.; X.-Q. Yu et al.

Palladium Catalysed Oxidative Direct Suzuki-Miyaura Reaction

-Palladium catalysed, C4-selective, oxidative C-H arylation of (thiophenes) and thiazoles with arylboronic acids.
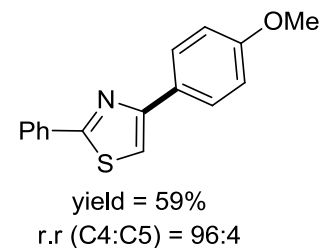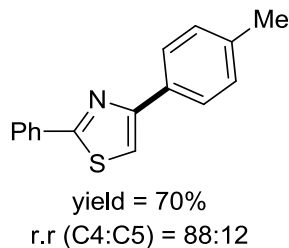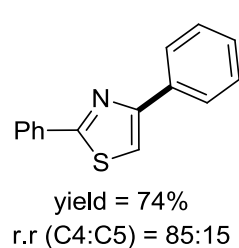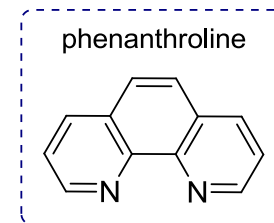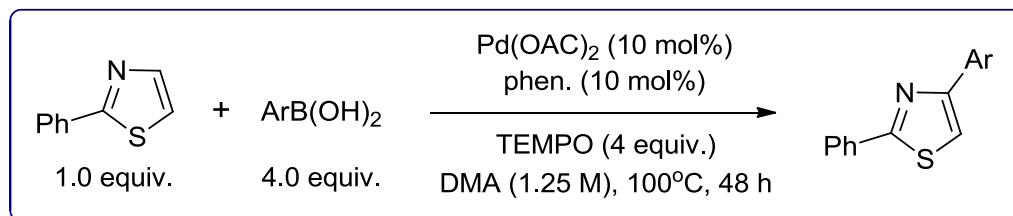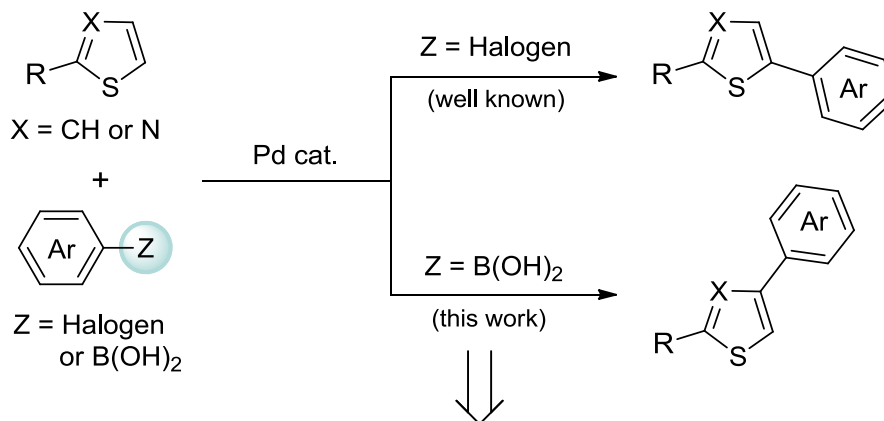
"Oxidative Biaryl Coupling of Thiophenes and Thiazoles with Arylboronic Acids through Palladium Catalysis:
Otherwise Difficult C4-Selective C-H Arylation Enabled by Boronic Acids"
Angew. Chem. Int. Ed., **2011**, *50*, pg 2387-2391; K. Itami et al.

-So far, much of the focus has been on the C-H bond functionalisation of five-membered N-containing heteroarenes with **another** (hetero)arene.

-Could we achieve C-H functionalisation with other reagents?

WHAT ABOUT DIRECT ALKYNYLATION OF HETEROARENES?

Direct Alkynylation of Azoles with Alkynyl Bromides: 1

-Highly regioselective copper catalysed C2 alkynylation of azoles with alkynyl bromides
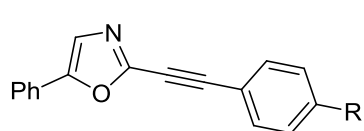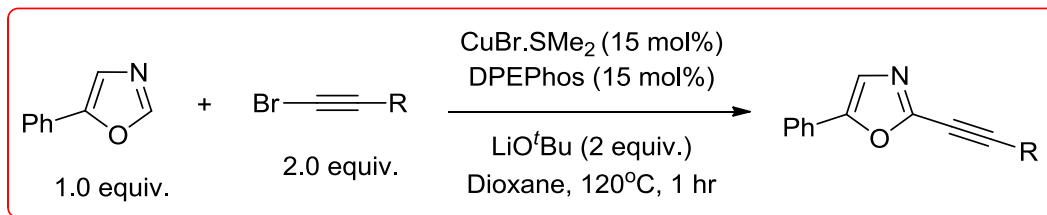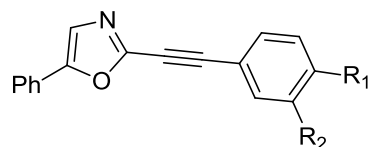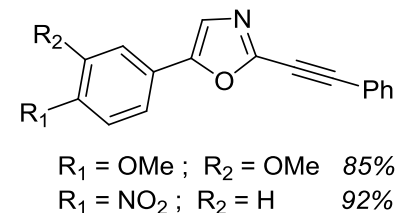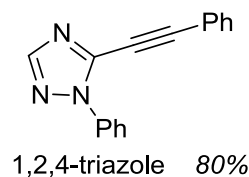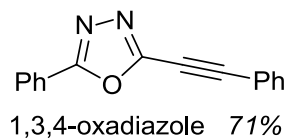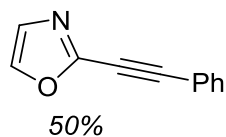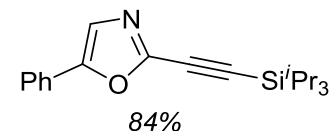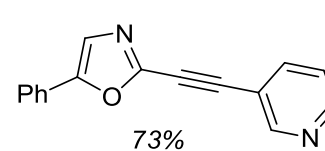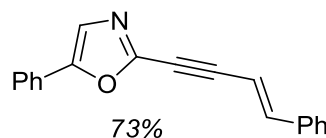
-Electron rich and electron deficient variants of both substrates react efficiently.

-Substitution tolerated at each of the *ortho*, *meta*, and *para* positions.

-However, synthesis of the corresponding 1-bromo-alkynes is required prior to reaction.

"Copper as a Powerful Catalyst in the Direct Alkynylation of Azoles"
Angew. Chem. Int. Ed., **2009**, *48*, pg 9553-9556; S. Piguel et al.

-At a similar time, a nickel catalysed variant of the direct alkynylation of azoles with alkynyl bromides was developed by Muira et al.
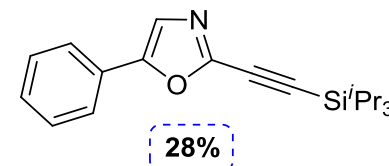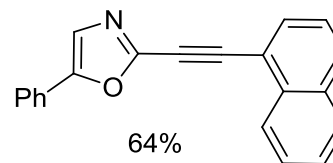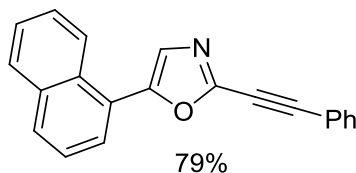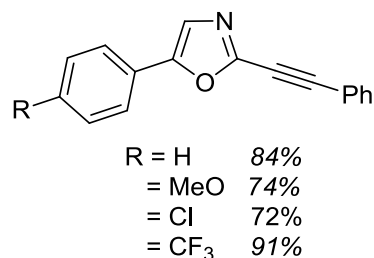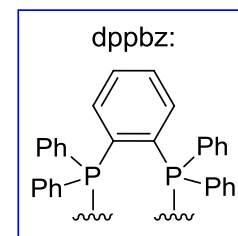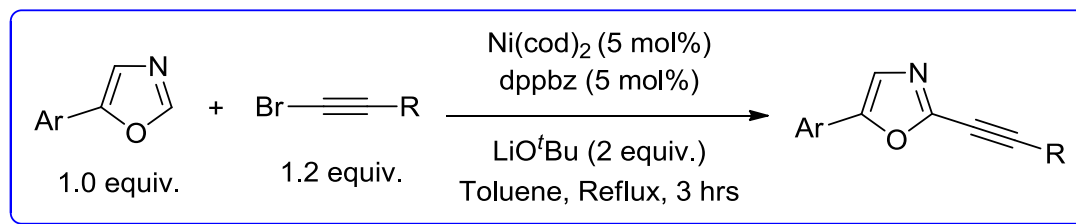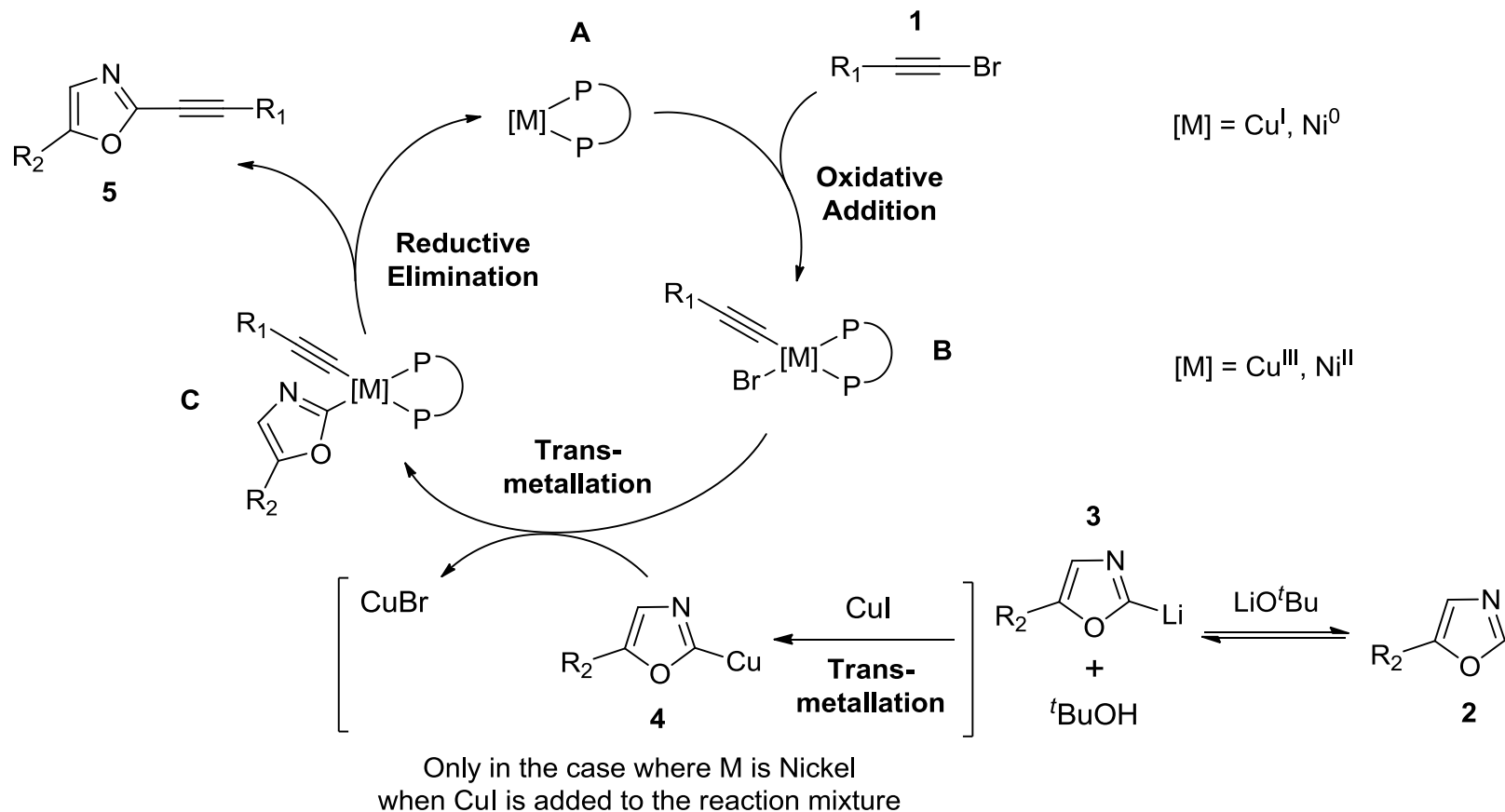

-Array of oxazoles were tolerated as was the steric bulk of the naphthalene moiety.
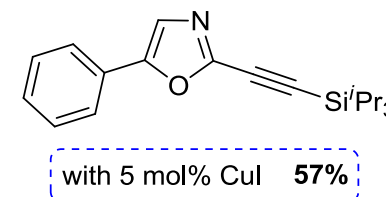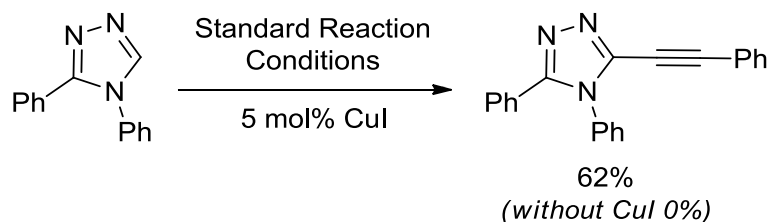
-Addition of 5 mol% CuI enhances the reactivity dramatically (see next slide for mechanism)

"Nickel-Catalyzed Direct Alkynylation of Azoles with Alkynyl Bromides" *Org. Lett.*, **2009**, *11*, pg 4156-4159; M. Miura et al.

# Proposed Mechanism of Direct C-H Alkynylation of Heteroarenes

-Organocopper reagent **4** undergoes transmetallation with **B** more readily than the corresponding organolithium, **3**.

-"**Reverse Sonogashira**": organocopper species derives from the heterocycle and not the alkyne : the alkyne (and not the heterocycle) is involved in the oxidative addition step.

Gold Catalysed Alkynylation of Pyrroles

-The **first** example of gold-catalysed C-H alkynylation of pyrroles.

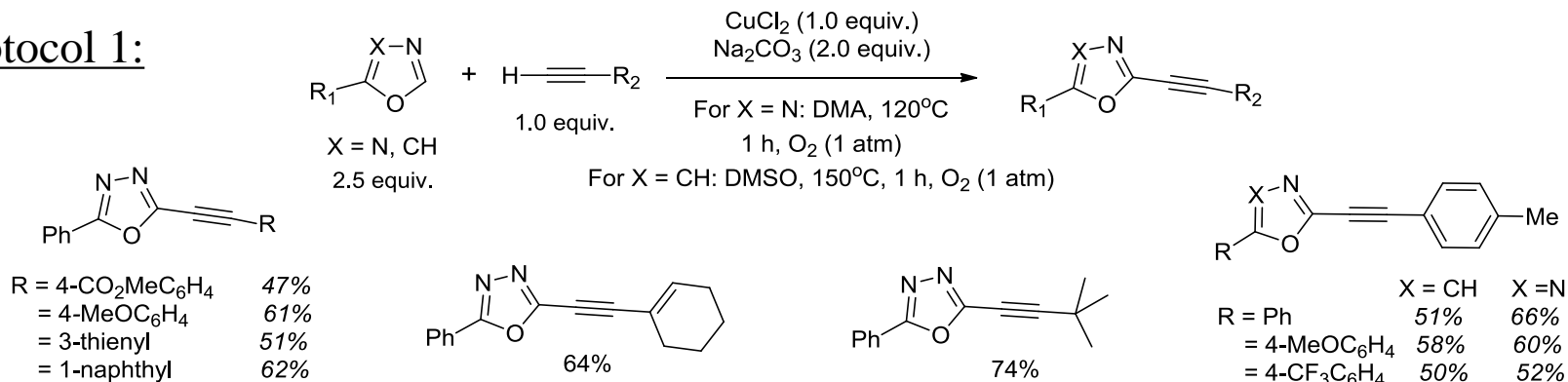-Reaction proceeds under mild conditions (23°C, air) and no need for anhydrous solvents.
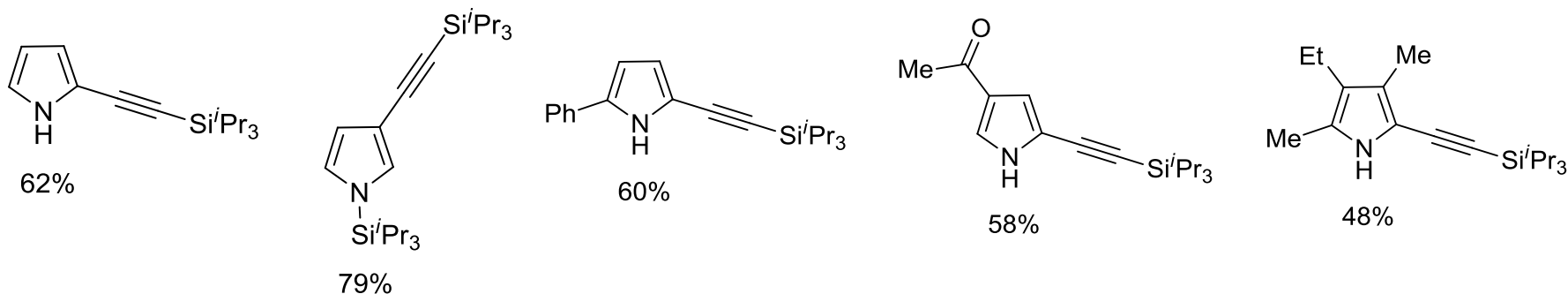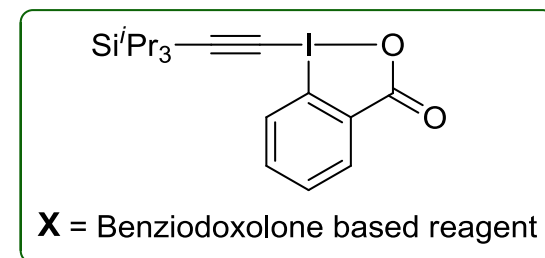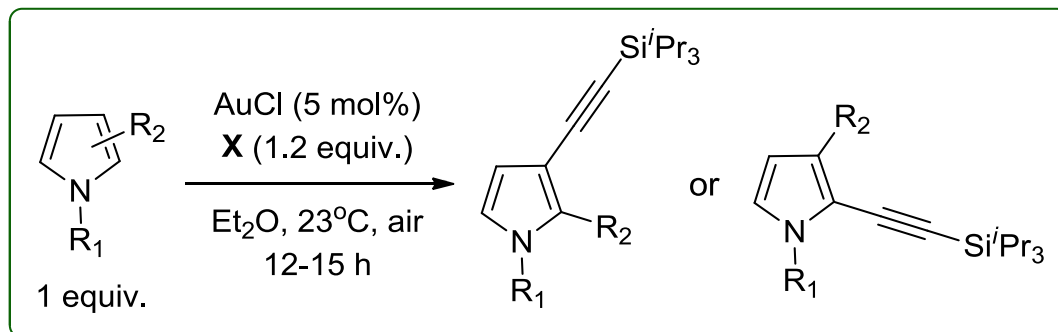
-**X** can be prepared by a straightforward two step synthesis, on a large scale, if required.

-Control of regioselectivity was possible by manipulation of the PG on the pyrrole nitrogen.

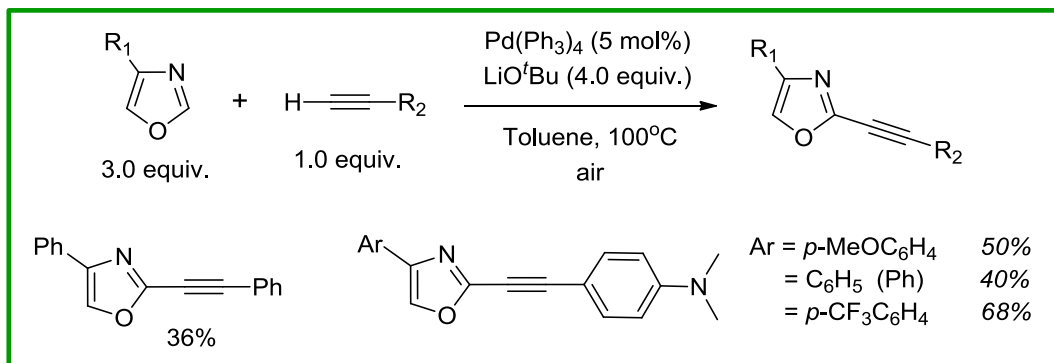-Deprotection of the silyl PG with TBAF provides for access to the free acetylene substituent.

"Direct Alkynylation of Indole and Pyrrole Heterocycles" *Angew. Chem. Int. Ed.*, **2009**, *48*, pg 9346-9349; J. Waser et al.

Direct Alkynylation of Azoles with Unactivated Terminal Alkynes

-Direct cross-coupling between an sp^2 and the sp C-H bond of a terminal alkyne.

Protocol 1:

CuCl$_2$ (1.0 equiv.)
Na$_2$CO$_3$ (2.0 equiv.)

For X = N: DMA, 120°C
1 h, O$_2$ (1 atm)
For X = CH: DMSO, 150°C, 1 h, O$_2$ (1 atm)

X = N, CH
2.5 equiv.

1.0 equiv.

R = 4-CO$_2$MeC$_6$H$_4$ 47%
= 4-MeOC$_6$H$_4$ 61%
= 3-thienyl   51%
= 1-naphthyl   62%

64%

74%

	X = CH	X = N
R = Ph	51%	66%
= 4-MeOC$_6$H$_4$	58%	60%
= 4-CF$_3$C$_6$H$_4$	50%	52%

Protocol 2:

Pd(Ph$_3$)$_4$ (5 mol%)
LiO^{t}Bu (4.0 equiv.)

Toluene, 100°C
air

3.0 equiv.

1.0 equiv.

36%

Ar = p-MeOC$_6$H$_4$ 50%
= C$_6$H$_5$ (Ph)   40%
= p-CF$_3$C$_6$H$_4$ 68%

-Both protocols suffer from only moderate isolated yields (max. of 74% in both cases).

(1) "Copper Mediated Direct Cross-Coupling of 1,3,4-Oxadiazoles and Oxazoles with Terminal Alkynes"
    Chemistry – A European Journal, **2010**, *16,* pg 1772-1775; M. Miura et al.
(2) "Palladium-Catalyzed Oxidative Alkynylation of Heterocycles with Terminal Alknyes under Air Conditions "
    Org. Lett. , **2011**, *13,* pg 1474-1477; S. Kim; J. Yoon; S. Chang

One Final Example:
Cascade Sequence Involving Oxidative Direct C-H/N-H Coupling

-A copper catalysed oxidative direct C-H/N-H coupling–annulation sequence between

azoles and o-alkynylanilines.
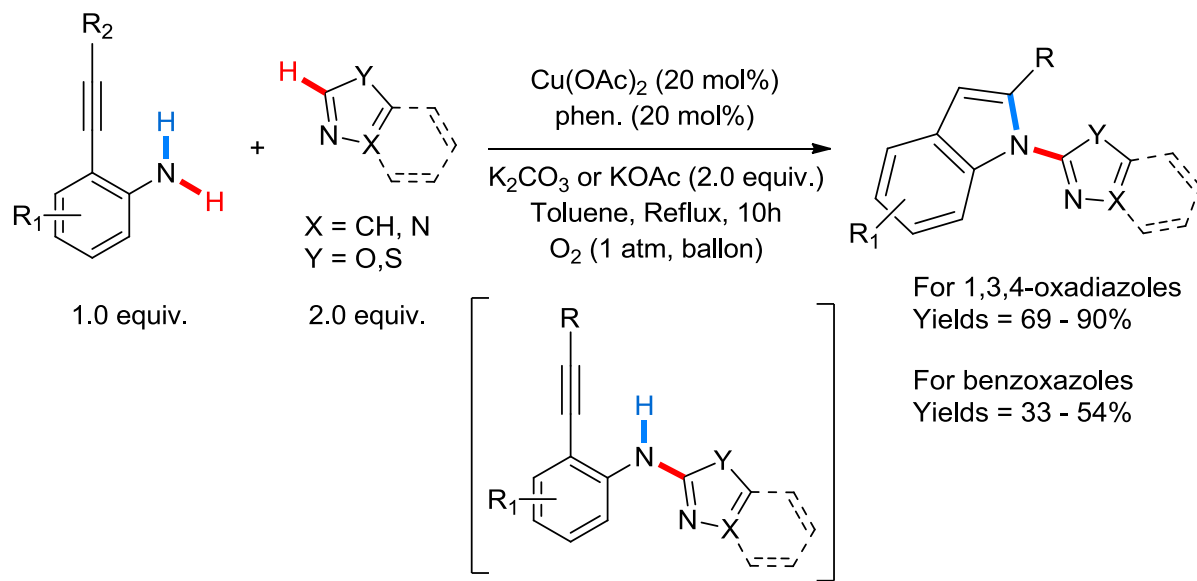
-This **domino reaction** proceeds efficiently with molecular oxygen as the sole oxidant and

provides a new dehydrogenative approach to N-azolylindoles.

-Wide range of substituents tolerated at the alkynyl position and on the aniline aromatic ring.

"Synthesis of N-Azolylindoles by Copper-Catalyzed C-H/N-H Coupling–Annulation Sequence of *o*-Alkynylanilines" *Org. Lett.*, **2012**, *14*, pg 664-667; M. Miura et al.

Summary and Outlook

-The field of C-H activation has become a very topic within the past five years, with many significant achievements and advancements being made by research groups throughout the World.

-Today, a mixture of recent work on the C-H functionalisation of five-membered (non-fused) N-containing rings has been presented.

-Both by means of direct C-H functionalisation with the use of a pre-activated substrate or the oxidative direct C-H functionalisation whereby neither substrate requires prior activation and two C-H bond functionalisations occur simultaneously.

-Vast amount of work on direct arylation and alkenylation but much less so on alkynylations.

-Two nice examples of direct C-H functionalisation within a sequence presented, the later being a one pot domino reaction using the same catalyst.

- Vindoline -

Synthetic approaches towards a

highly complex polycyclic alkaloid
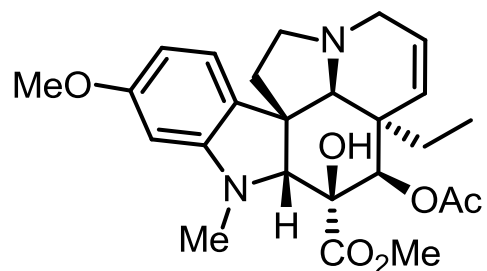
(−)-vindoline

Frontiers in Chemical Synthesis I: *Heterocyclic Chemistry*

(Prof. Jérôme Waser, Prof. Xile Hu)

Lausanne, May 24, 2012

Question 1: Why is the total synthesis of (−)-vindoline of great interest?

Question 2: Why did Büchi et al. use a tosylated 6-hydroxyindol derivative instead of a 6-methoxyindol for their key step? Can you think of a certain side reaction in the cyclization step?

- Introduction

- Synthethic approaches

  ➡ Büchi (1975)

  ➡ Langlois (1985)

  ➡ Rapoport (1987)

  ➡ Kuehne (1987)

  ➡ Boger (2010)

- Summary

- Indole alkaloid

- most highly oxygenated member of the *aspidosperma* alkaloid family
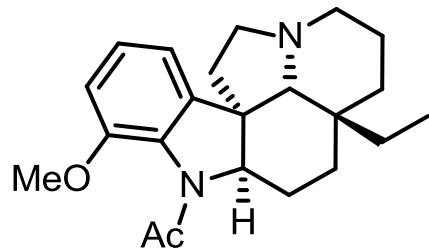
(−)-Aspidospermine
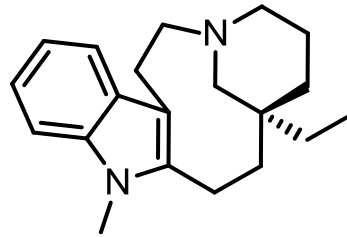
(+)-*N*-Methylquebrachamine
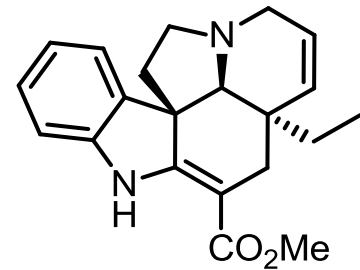
(−)-Tabersonine
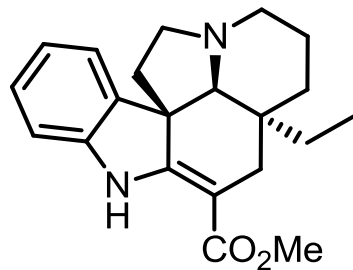
(−)-Vincadifformine
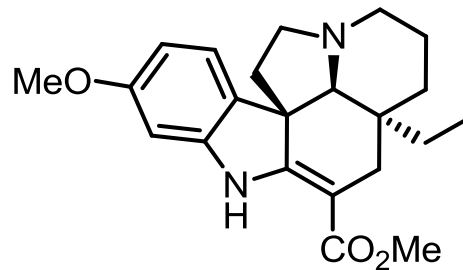
(−)-Ervinceine
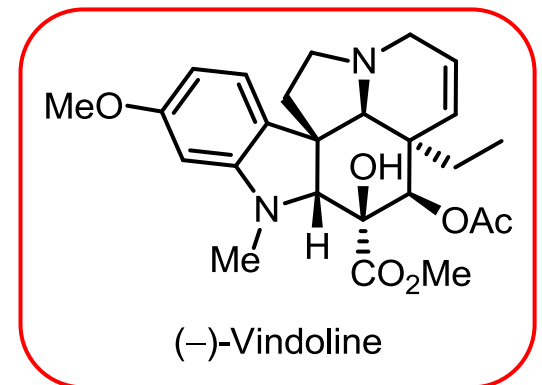
(−)-Vindoline

- isolated from *Catharanthus roseus* G. Don.

- (−)-vindoline lacks physiological activity

  ➡ biosynthetic and synthetic precursor of vinblastine

Catharanthus roseus

(−)-Vindoline

S. Yokoshima, T. Ueda, S. Kobayashi, A. Sato, T. Kuboyama, H. Tokuyama, T. Fokuyama,
J. Am. Chem. Soc. **2002**, *124*, 2137-2139.
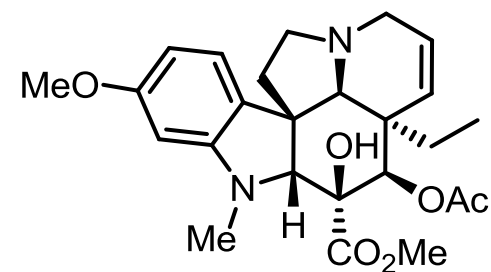
chemical features of (−)vindoline

- pentacyclic alkaloid structure (**A**,**B**,**C**, **D** and **E** ring)

- 6 stereogenic centers

  ➡ 2 quarternary, 4 heteroatom substituted
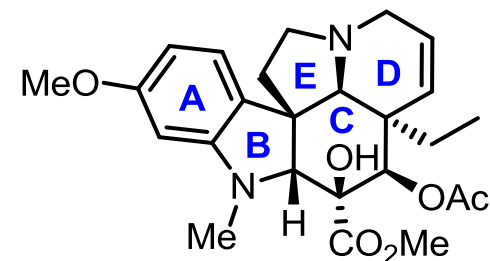
(−)-Vindoline

Büchi's approach (1975)

J. Am. Chem. Soc. **1975**, *97*, 6880-6881.

M. Ando, T. Ohnuma, G. Büchi, *J. Am. Chem. Soc.* **1975**, *97*, 6880-6881.

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M. Ando, T. Ohnuma, G. Büchi, *J. Am. Chem. Soc.* **1975**, *97*, 6880-6881.

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1. H_2O_2, KOtBu
2. Red-Al$^®$, AlCl$_3$

3. Ac$_2$O, NaOAc
(43% over 3 steps)
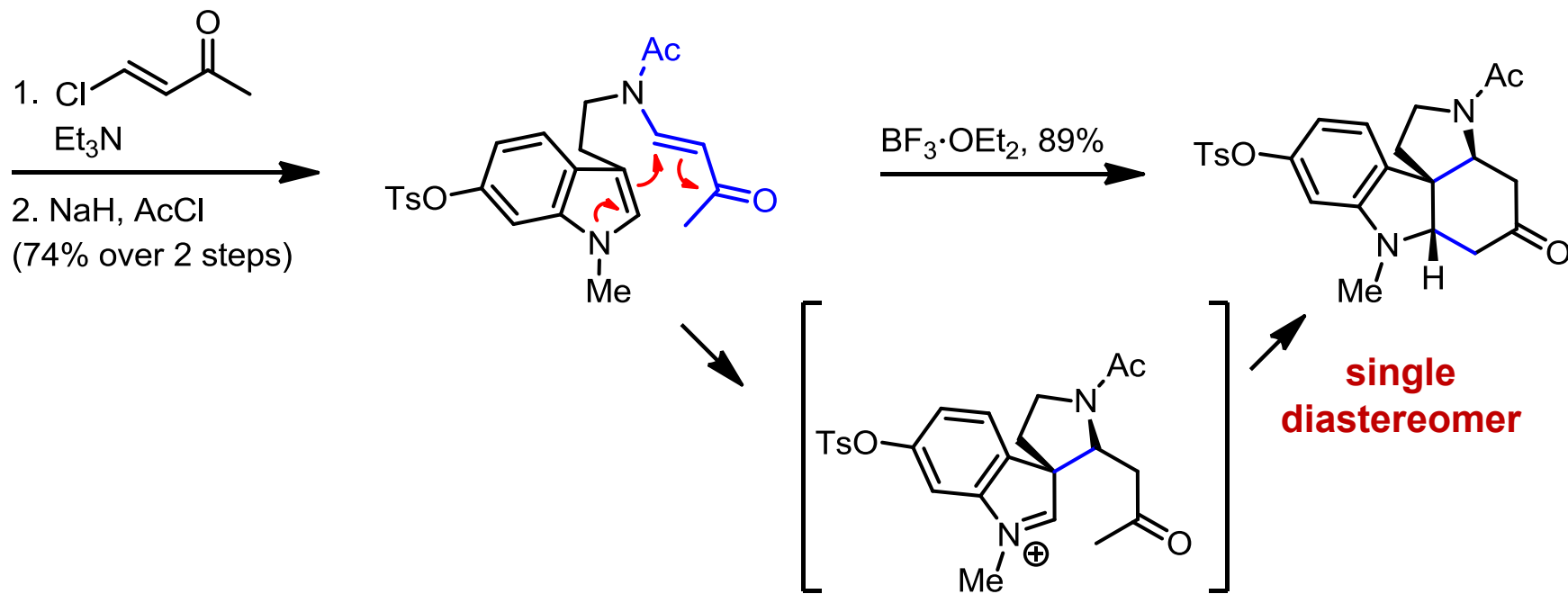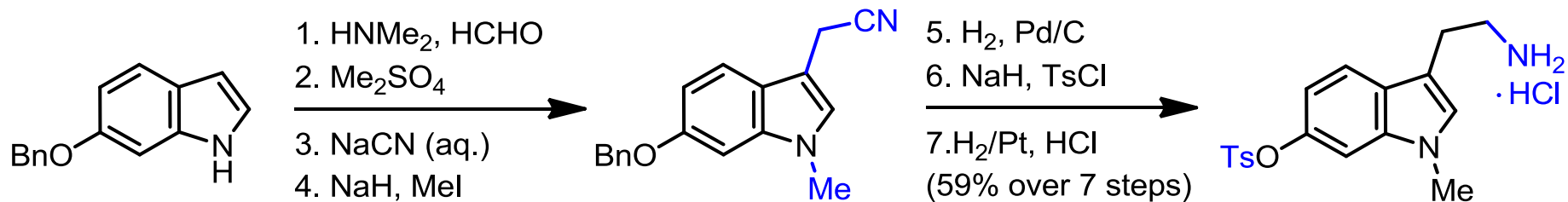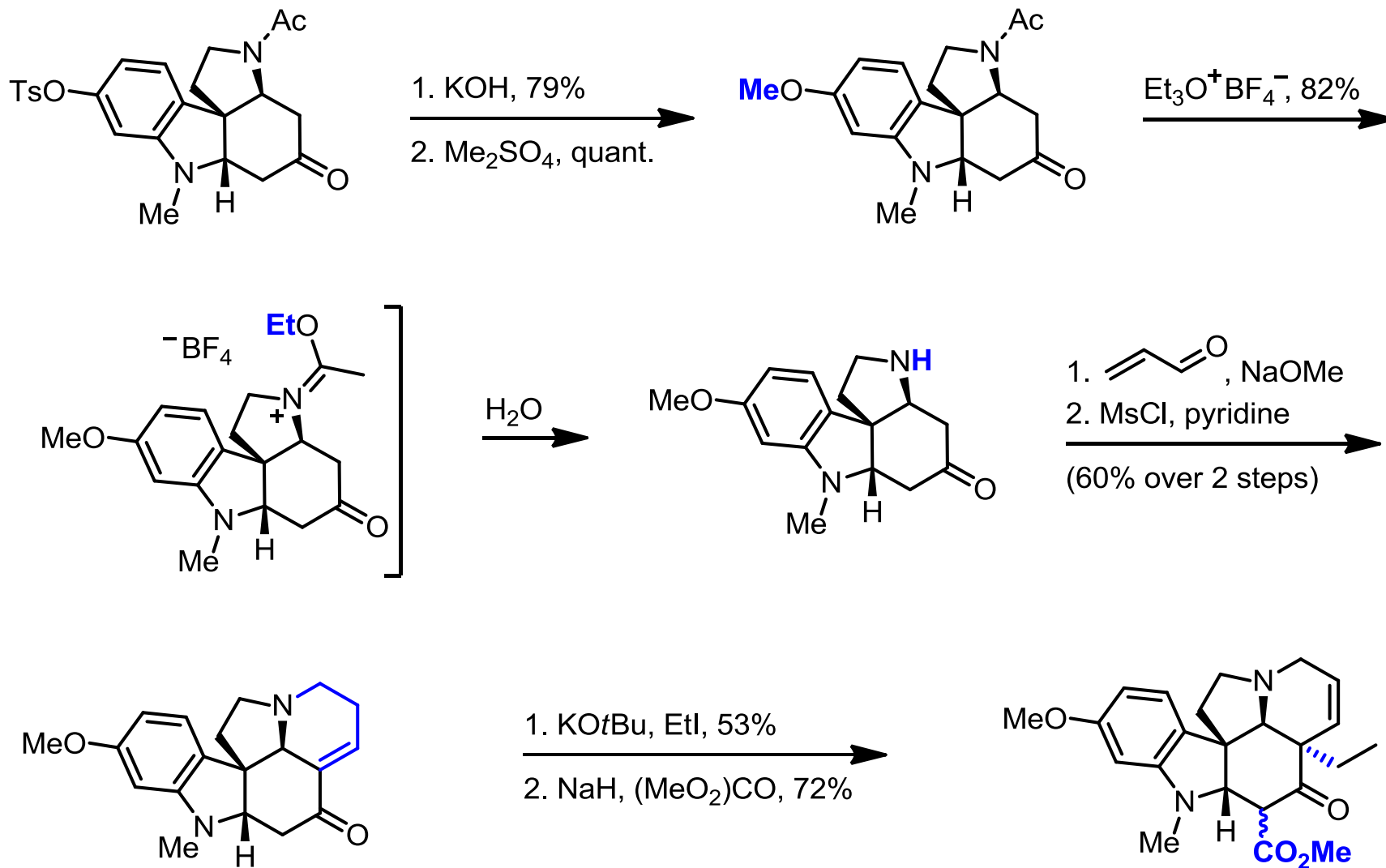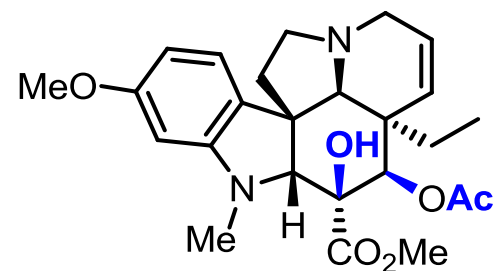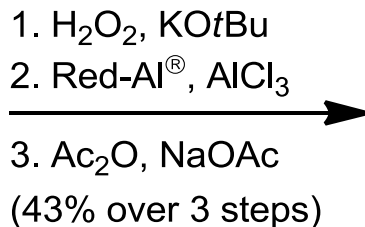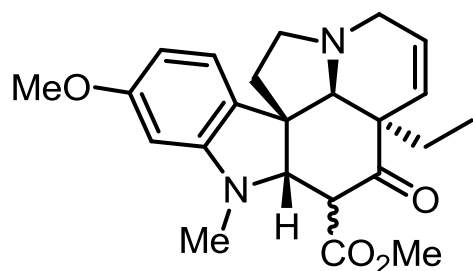
(±)-vindoline

single epimer

Büchi's approach (1975)

- 20 steps from commercial 6-benzyloxyindole to (±)-vindoline

- ≈ 2.5% overall yield

- **key step**: diastereoselective intramolecular cycloaddition
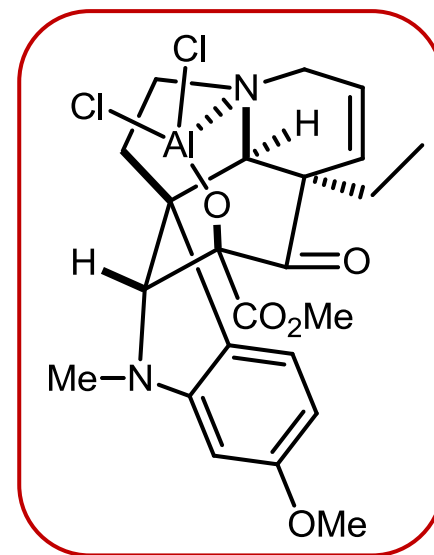
Langlois' approach (1985)

J. Org. Chem. **1985**, *50*, 961-967.

R. Zo Andriamialisoa, N. Langlois, Y. Langlois, *J. Org. Chem.* **1985**, *50*, 961-967.

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R. Zo Andriamialisoa, N. Langlois, Y. Langlois, *J. Org. Chem.* **1985**, *50*, 961-967.

1. NaBH$_3$CN
2. Raney-Ni

(89% over 2 steps)
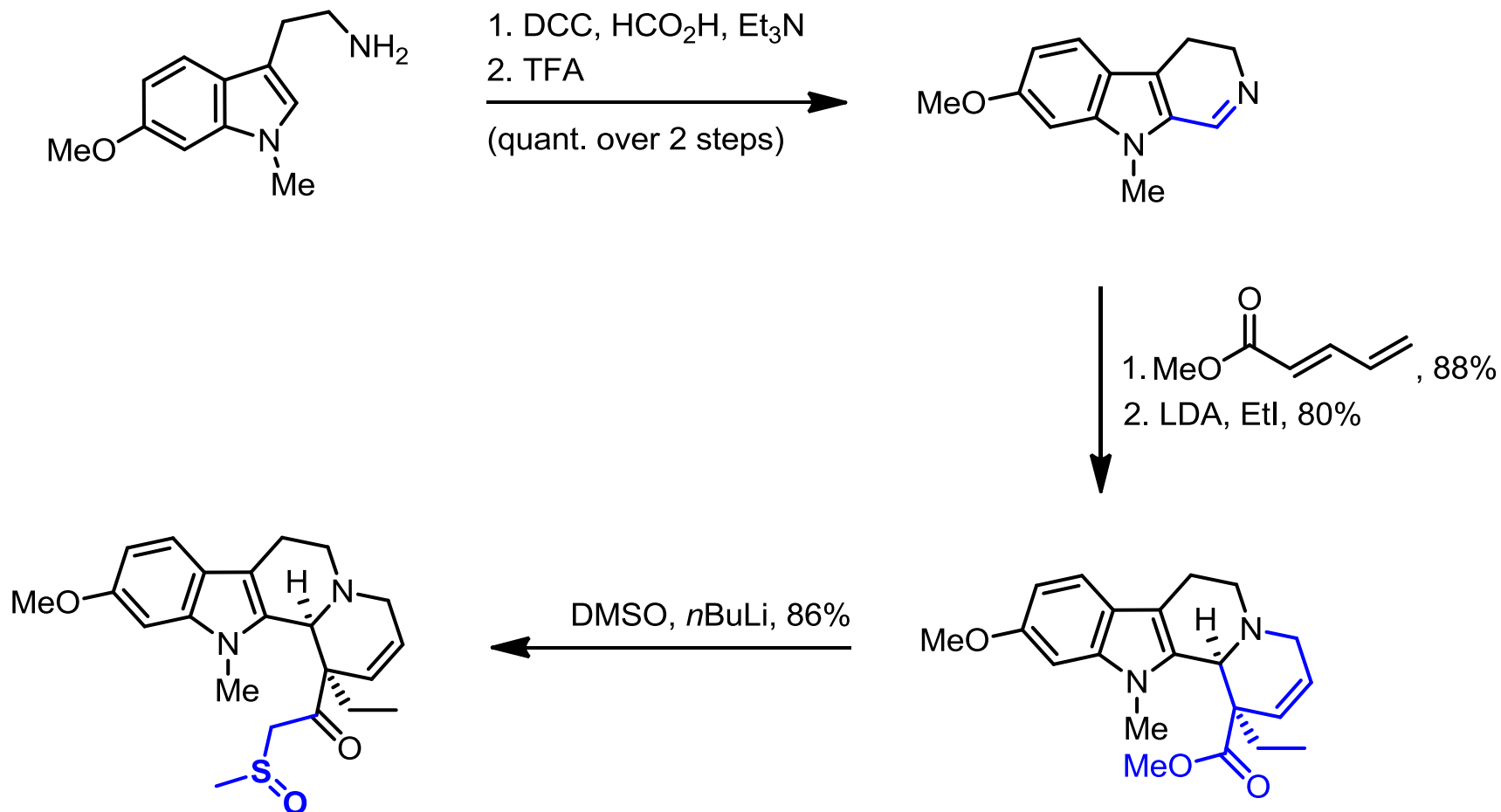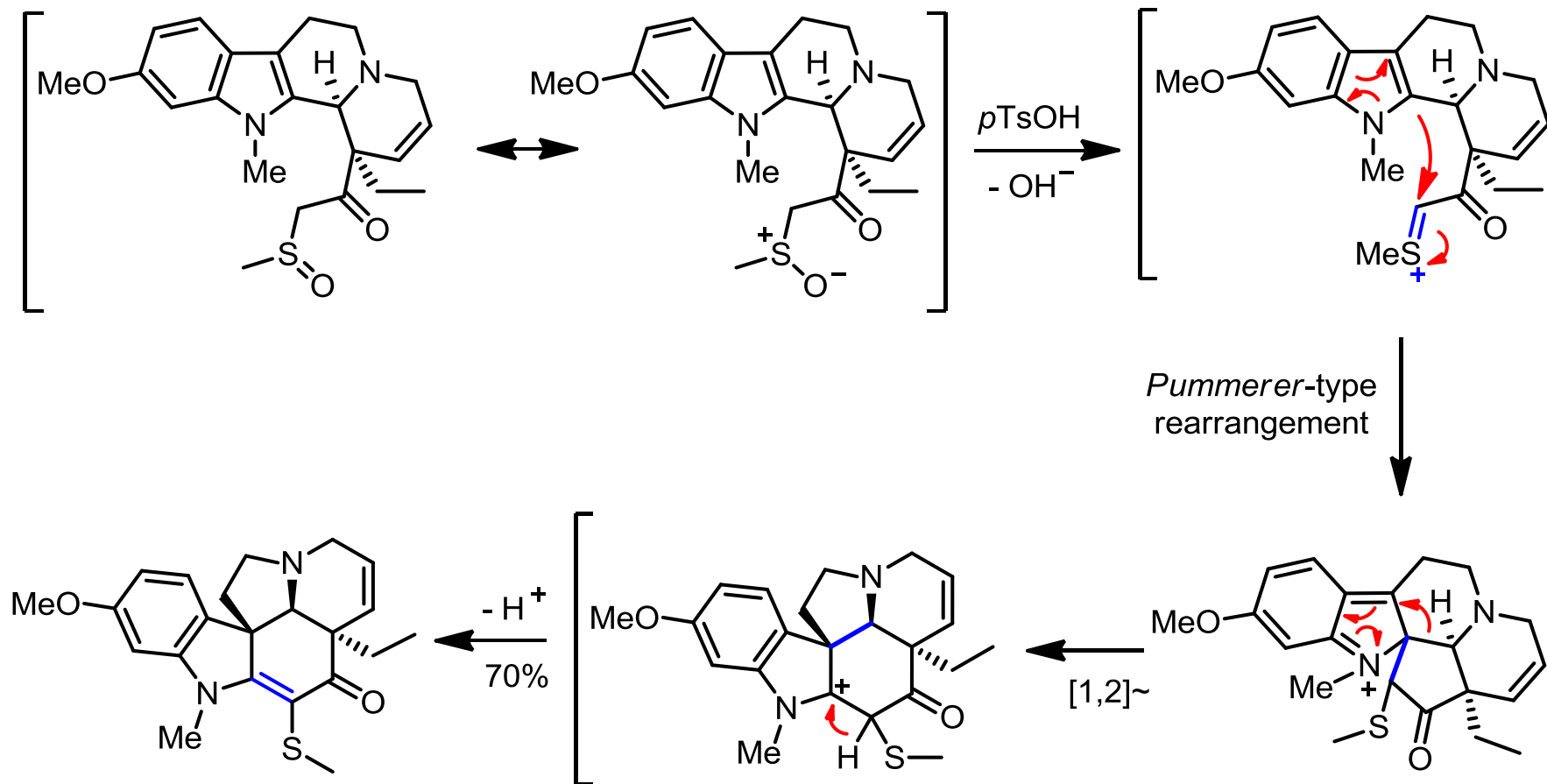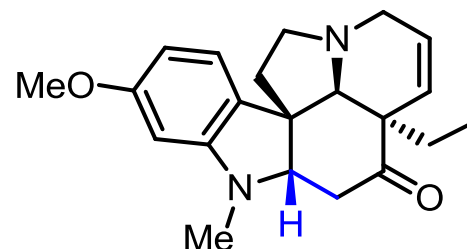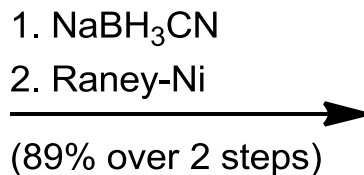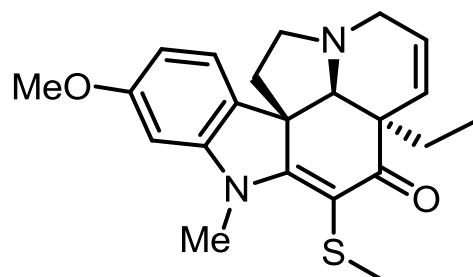
similar to
Büchi`s synthesis
(37% over 5 steps)
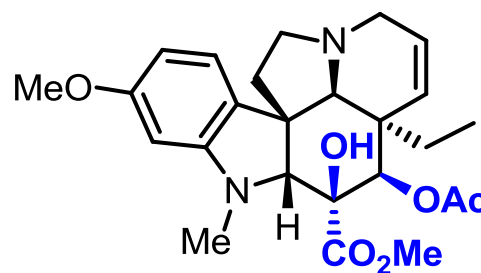
Langlois' approach (1985)

- 16 steps from commercial *N*-methyl-
  6-methoxytryptamin to (±)-vindoline

- ≈ 10% overall yield

- **key step**: *Pummerer*-type rearrangement
  to *aspidosperma* skeleton

(±)-vindoline

Rapoport's approach (1987)

J. Am. Chem. Soc. **1987**, *109*, 1603-1604.

1. NaH, Ac₂O
2. LDA

3. NaOMe
(40% over 3 steps)

*t*BuOCl

10 steps

*t*BuOCl,
then DBU
75%

DBU

Wagner-Meerwein
rearrangement

p-cresol   L-aspartic acid
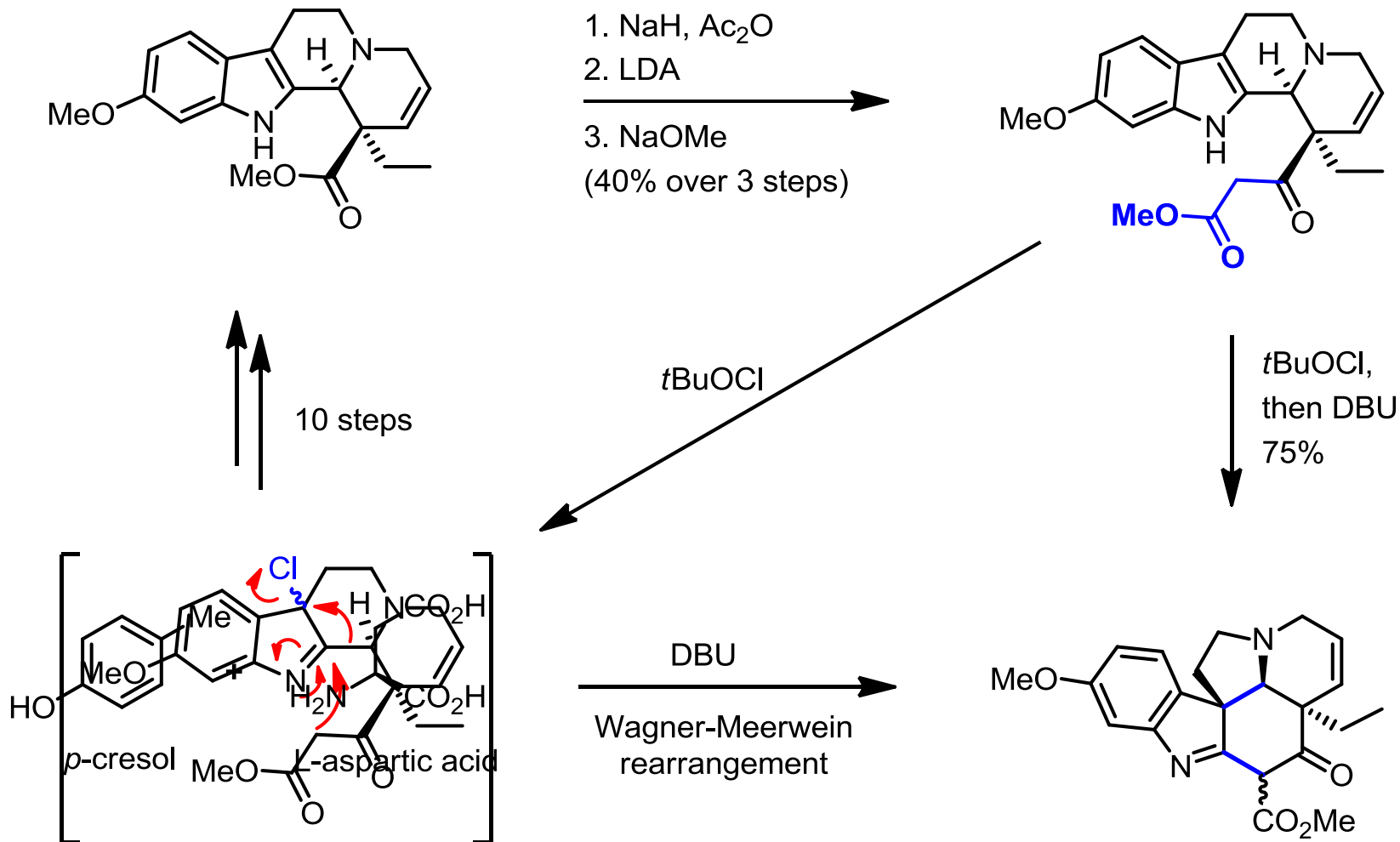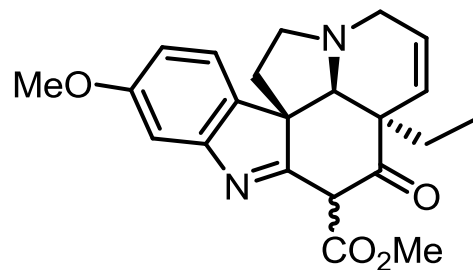
1. NaBH$_3$CN

2. HCHO, NaBH$_3$CN
(85% over 2 steps)

similar to
Büchi`s synthesis
(3 steps)
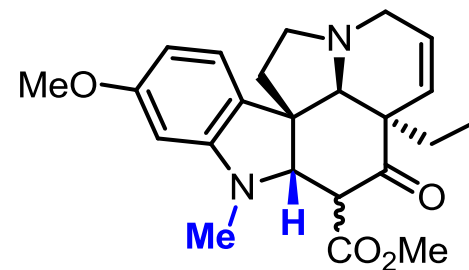
Rapoport's approach (1987)

- 19 steps from *p*-cresol and L-aspartic acid to (−)-vindoline
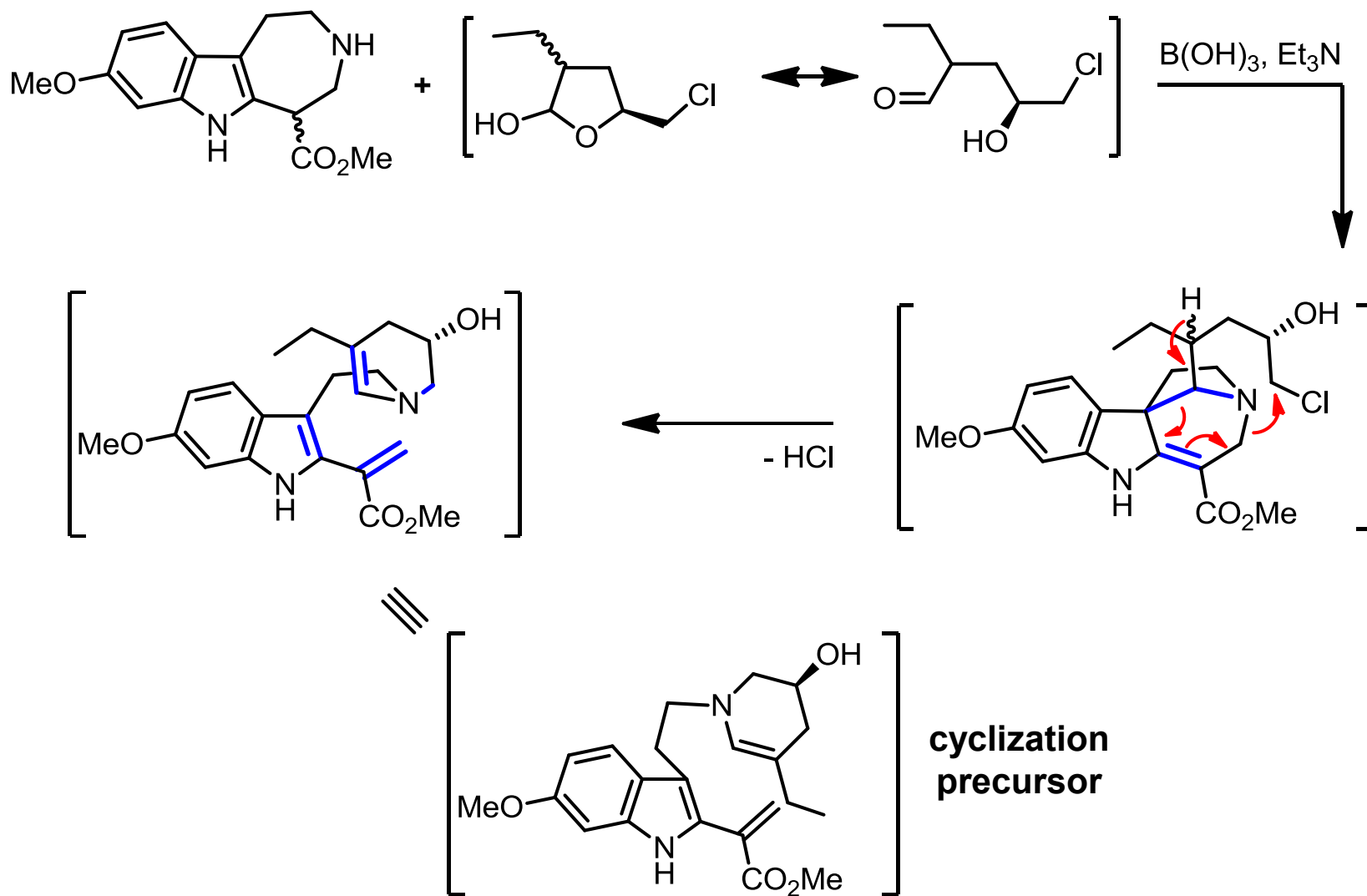
- approx. 1% overall yield

- **key step**: Wagner-Meerwein rearrangement

(−)-vindoline

P. L. Feldmann, H. Rapoport, *J. Am. Chem. Soc.* **1987**, *109*, 1603-1604.

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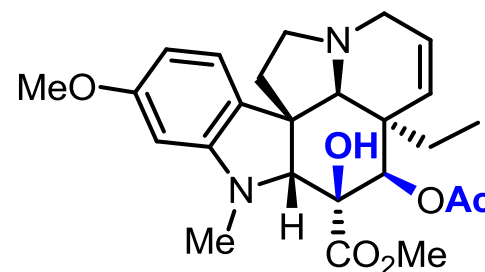
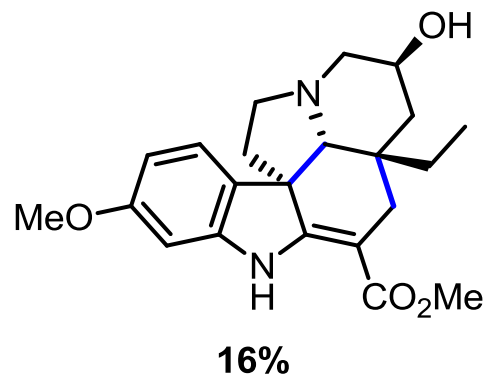# Kuehne's approach (1987)
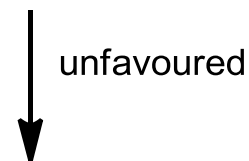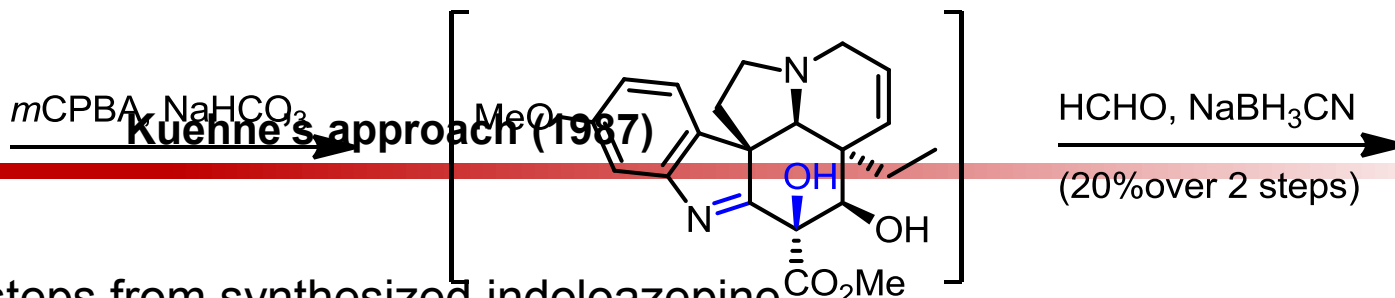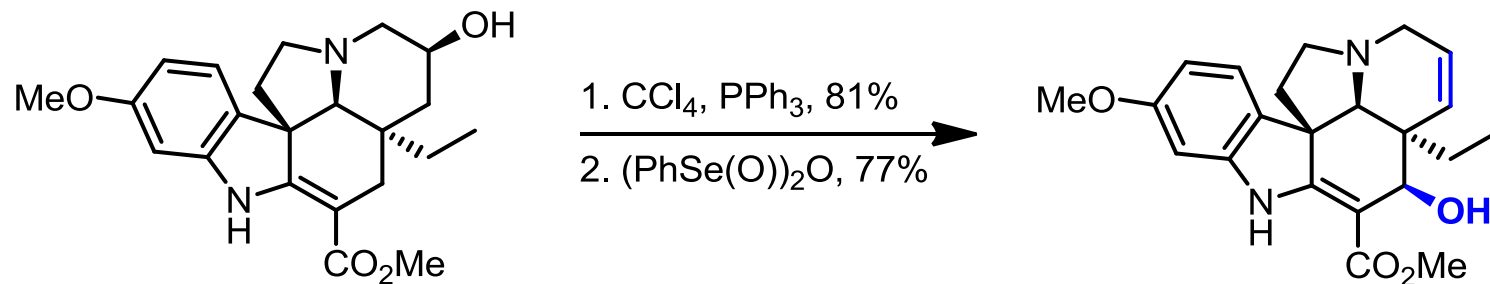
J. Org. Chem. **1987**, *52*, 347-353.

equatorial OH

favoured

inverse electron
demand DA

unfavoured

axial OH

52%

16%

W. G. Bornmann, D. E. Podhorez, T. Mulamba, M. E. Kuehne, *J. Org. Chem.* **1987**, *52*, 347-353.

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1. CCl$_4$, PPh$_3$, 81%

2. (PhSe(O))$_2$O, 77%

*m*CPBA, NaHCO$_3$
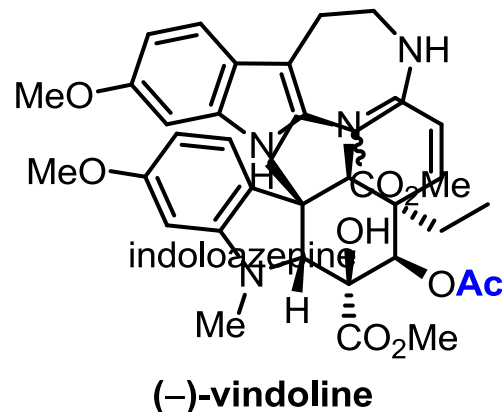
HCHO, NaBH$_3$CN

(20% over 2 steps)

Ac$_2$O, pyridine, 55%
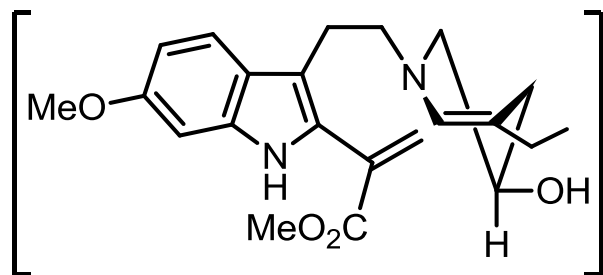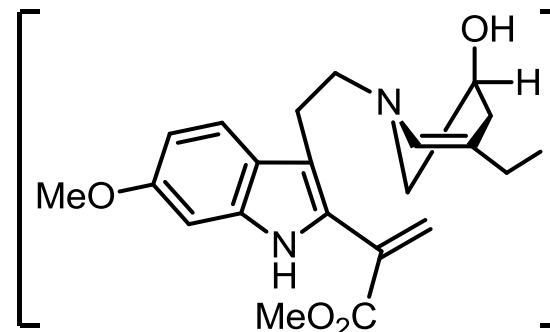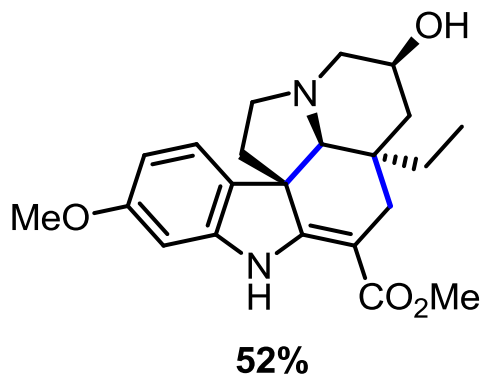
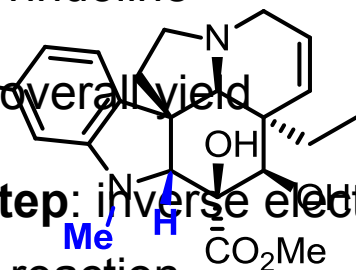- 6 steps from synthesized indoloazepine to (−)-vindoline
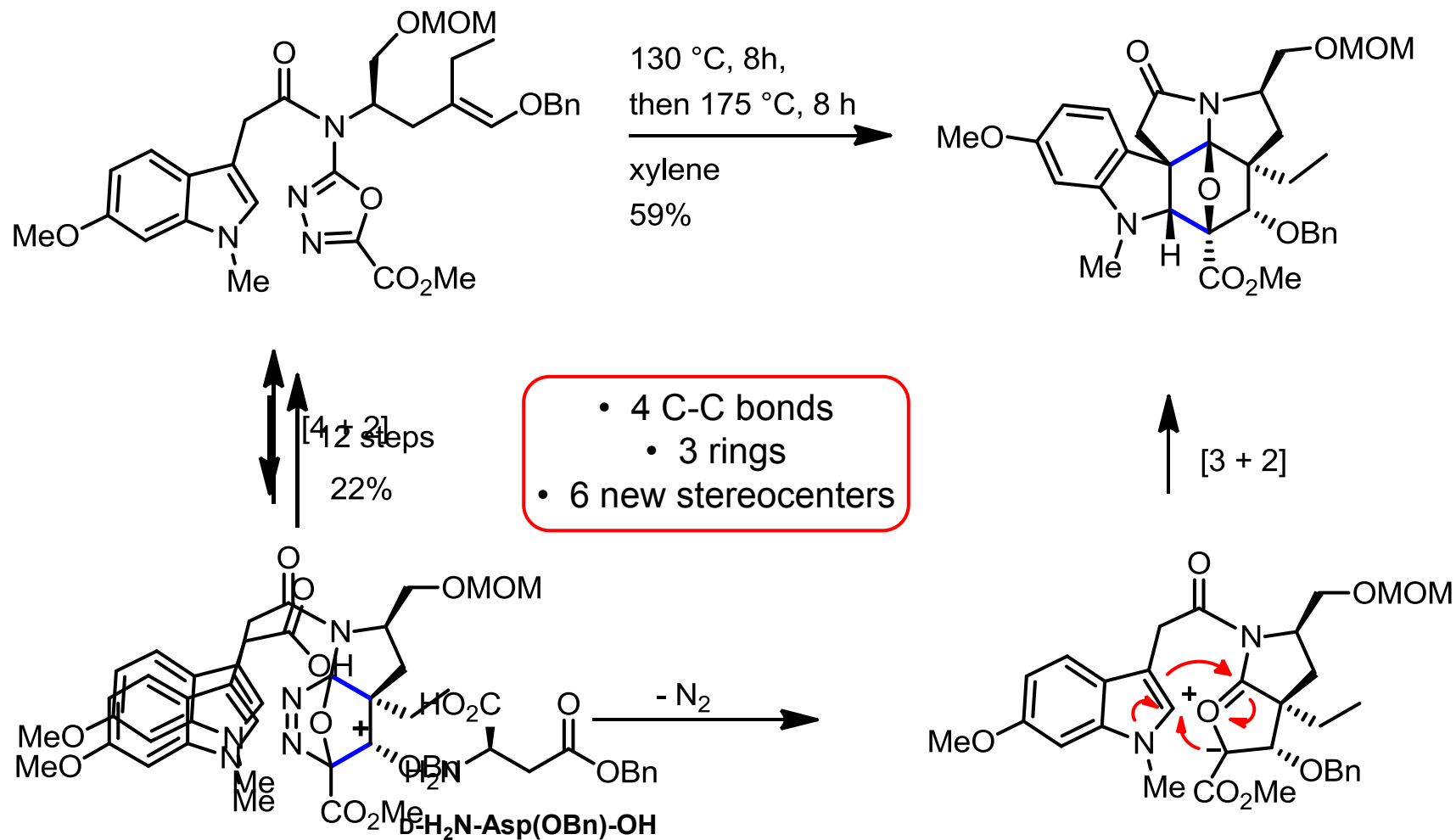
- ≈4% overall yield

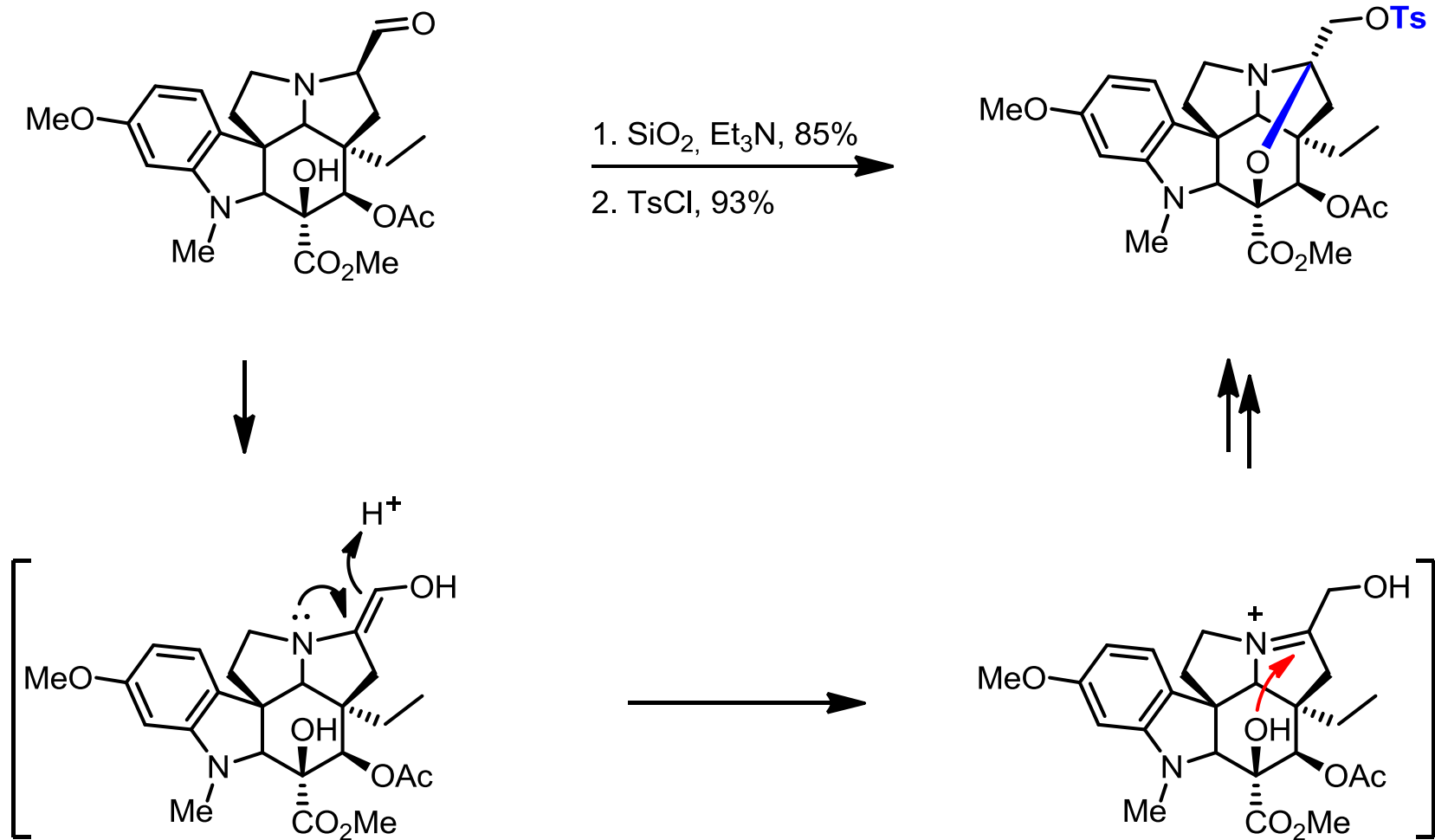- **key step**: inverse electron demand Diels-Alder reaction

indoloazepine

(−)-vindoline

Boger's approach (2010)

J. Am. Chem. Soc. **2010**, *132*, 3685-3687.

- 4 C-C bonds
- 3 rings
- 6 new stereocenters

130 °C, 8h, then 175 °C, 8 h

xylene

59%

[4 + 2]

12 steps

22%

[3 + 2]

- N₂

D-H₂N-Asp(OBn)-OH

D. Kato, Y. Sasaki, D. L. Boger, *J. Am. Chem. Soc.* **2010**, *132*, 3685-3687.

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1. NaBH₃CN, 94%
2. H₂, Pd(OH)₂, 91%

3. DMP, 76%
4. LiAlH(OtBu)₃, 87%
5. Ac₂O, 95%

1. MeOTf
2. NaBH₄
(96% over 2 steps)

1. HCl, 89%

2. SO₃-Py

D. Kato, Y. Sasaki, D. L. Boger, *J. Am. Chem. Soc.* **2010**, *132*, 3685-3687.

24

D. Kato, Y. Sasaki, D. L. Boger, *J. Am. Chem. Soc.* **2010**, *132*, 3685-3687.

25
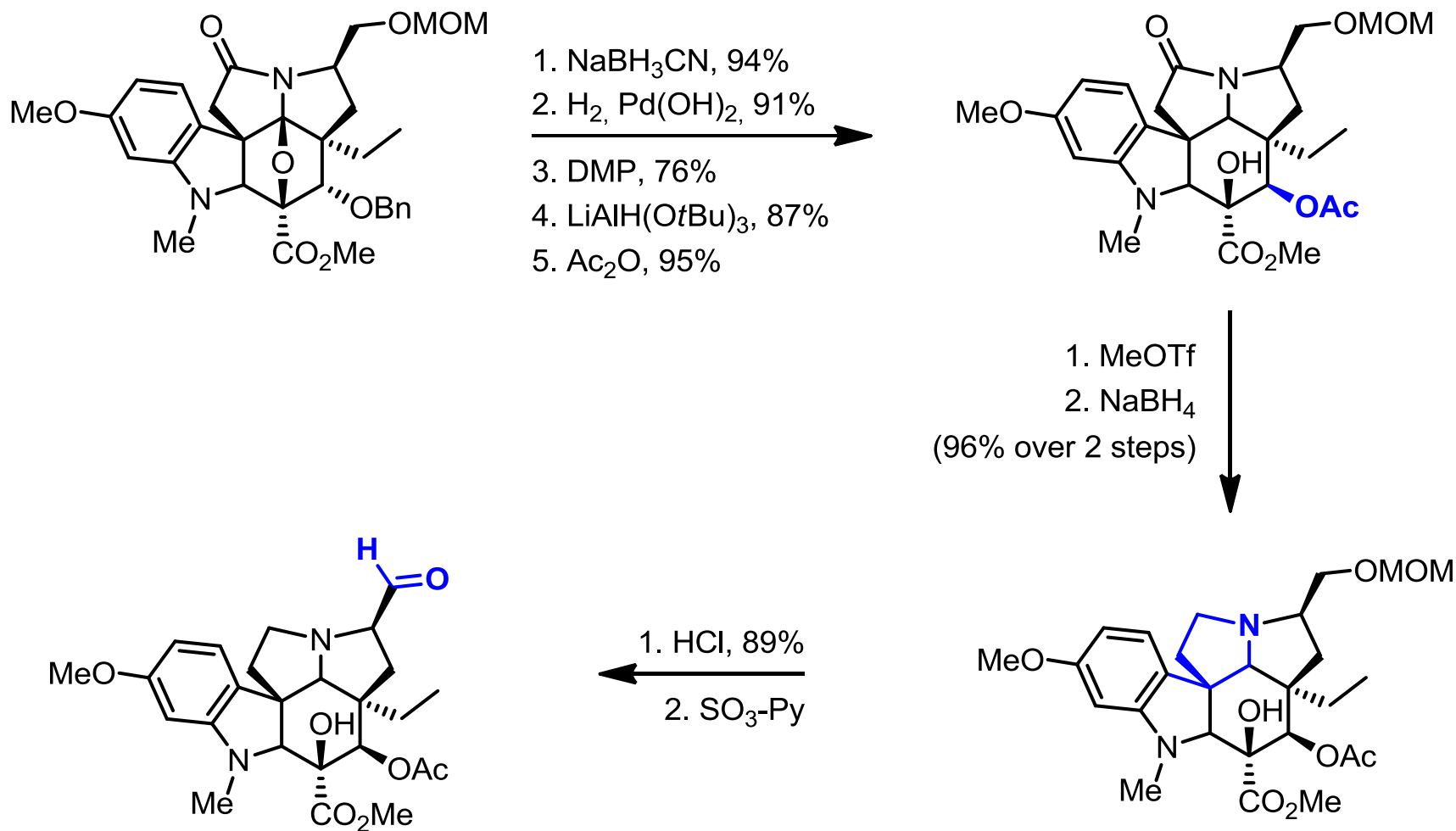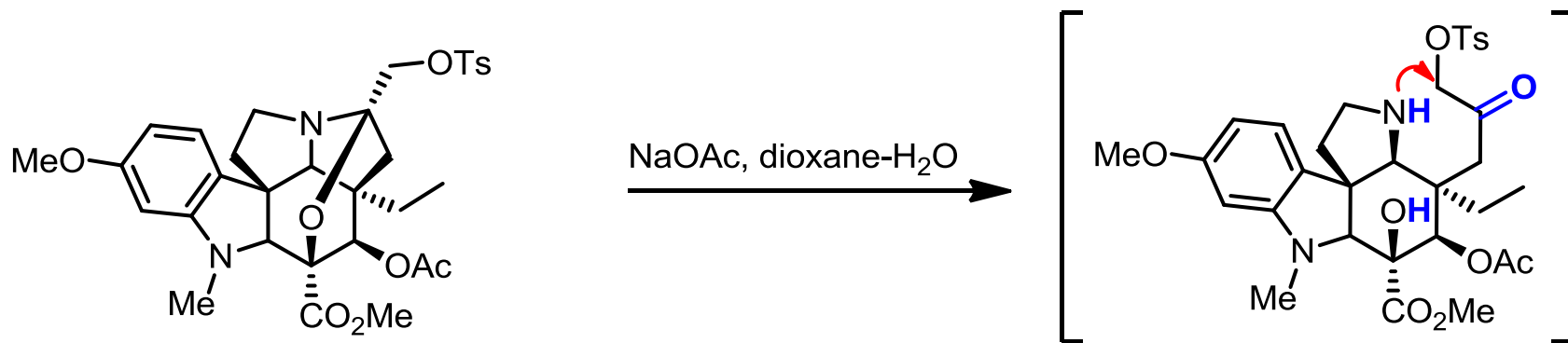
Bogers' approach (2010)

- 27 steps from commercial D-H$_2$N-Asp(OBn)-OH to (−)-vindoline
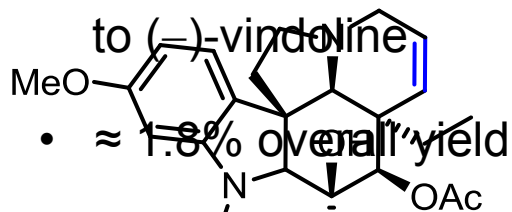
- ≈ 1.8% overall yield

- **key step**: tandem [4+2/]/[3+2] cycloaddition cascade

- (±)-vindoline can be optained in only 11 steps via:

D. Kato, Y. Sasaki, D. L. Boger, *J. Am. Chem. Soc.* **2010**, *132*, 3685-3687.
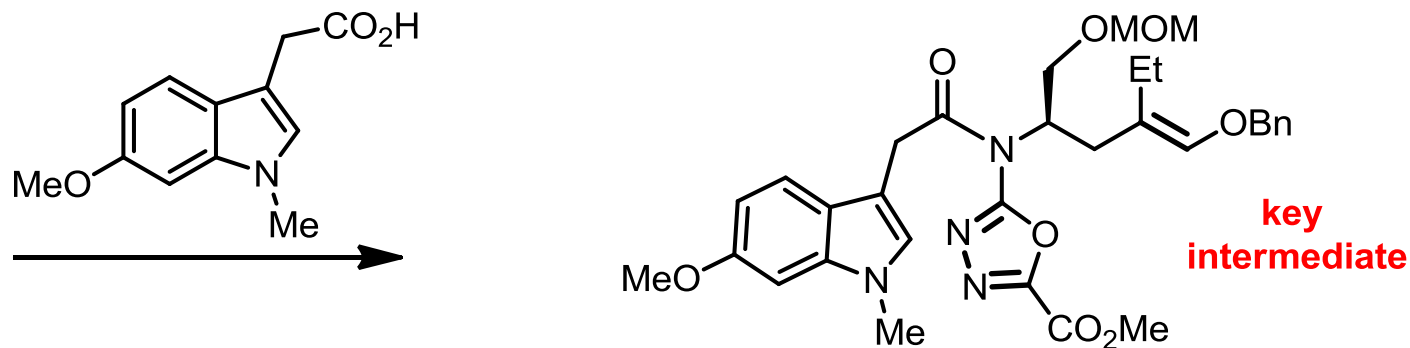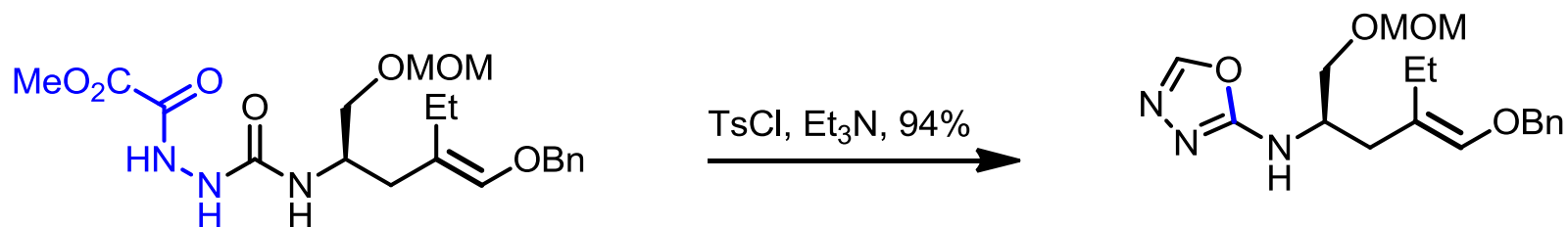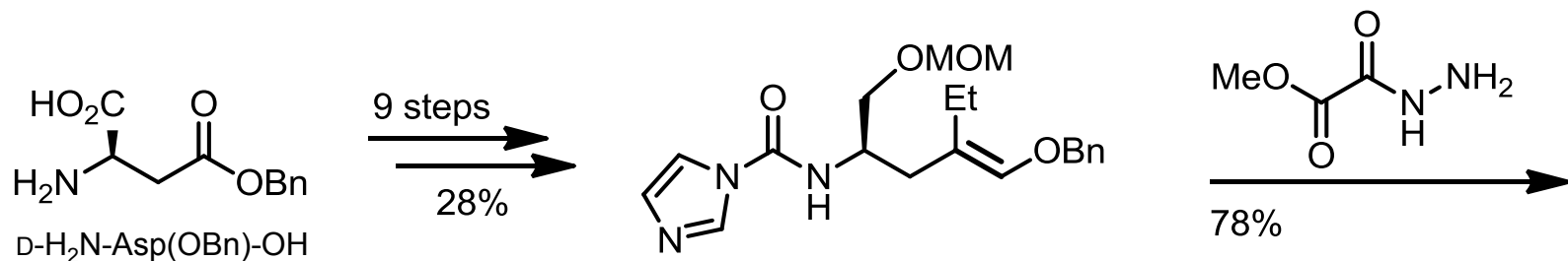
26
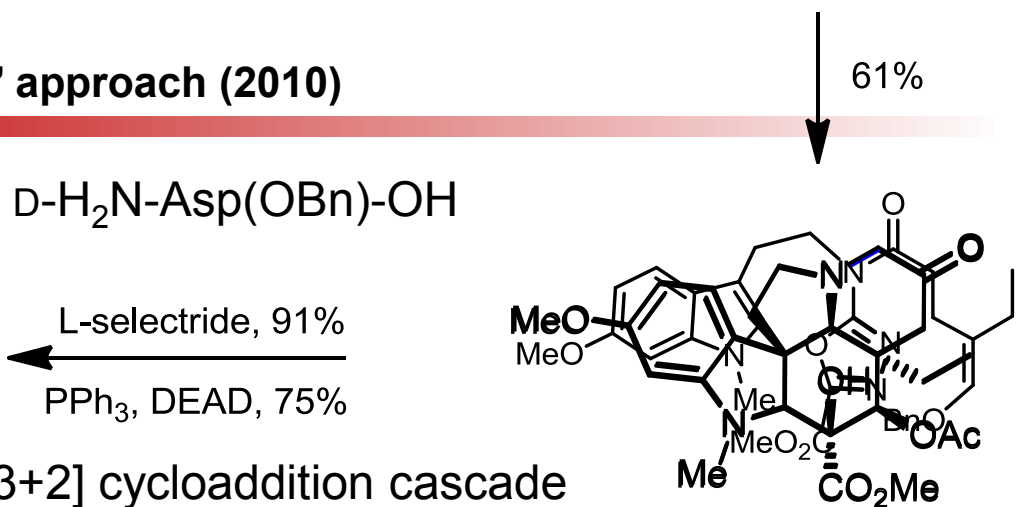
vindoline

- indole alkaloid of the *aspidosperma* family

- lacks physiological activity

- 17 syntheses published (racemic, formal and enantioselective)

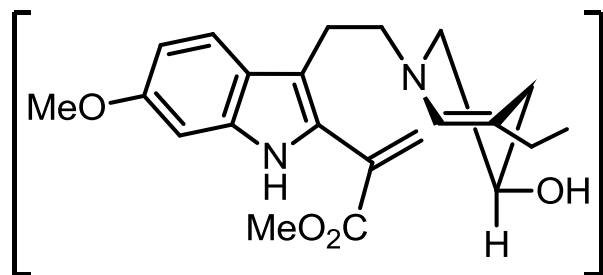- in this talk: 5 syntheses with different skeleton forming approaches
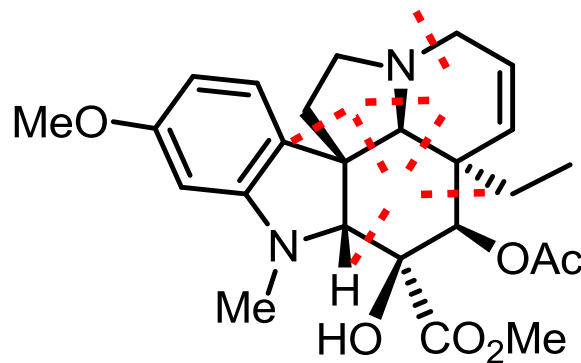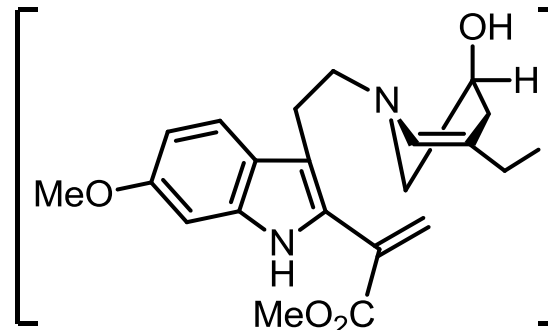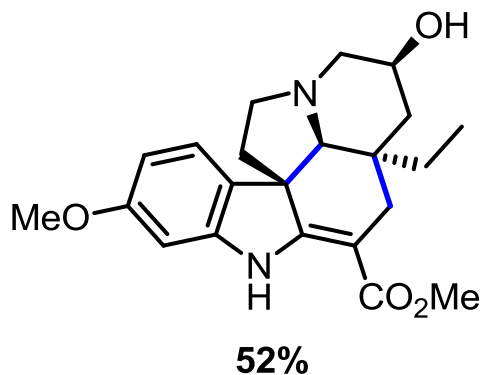

(−)-vindoline

Thank you for your kind attention!

Feel free to ask questions and make suggestions….

D. Kato, Y. Sasaki, D. L. Boger, *J. Am. Chem. Soc.* **2010**, *132*, 3685-3687.

29

equatorial OH

axial OH

favoured

inverse electron demand DA

unfavoured

52%

16%

W. G. Bornmann, D. E. Podhorez, T. Mulamba, M. E. Kuehne, *J. Org. Chem.* **1987**, *52*, 347-353.

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cyclization precursor

W. G. Bornmann, D. E. Podhorez, T. Mulamba, M. E. Kuehne, *J. Org. Chem.* **1987**, *52*, 347-353.
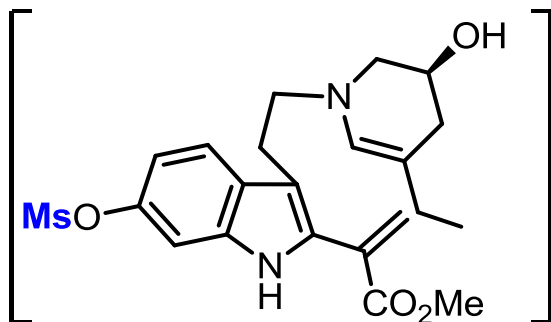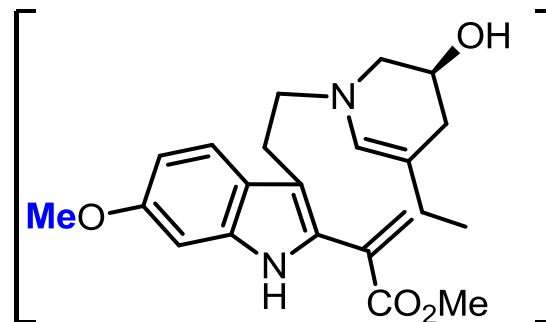
31
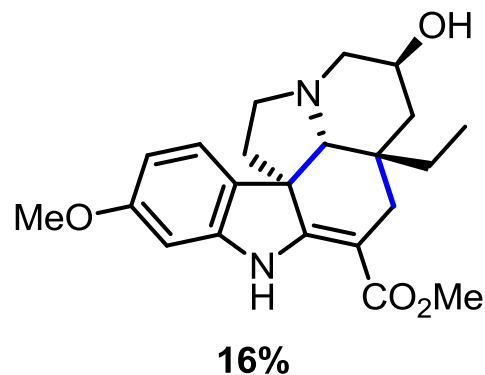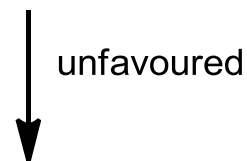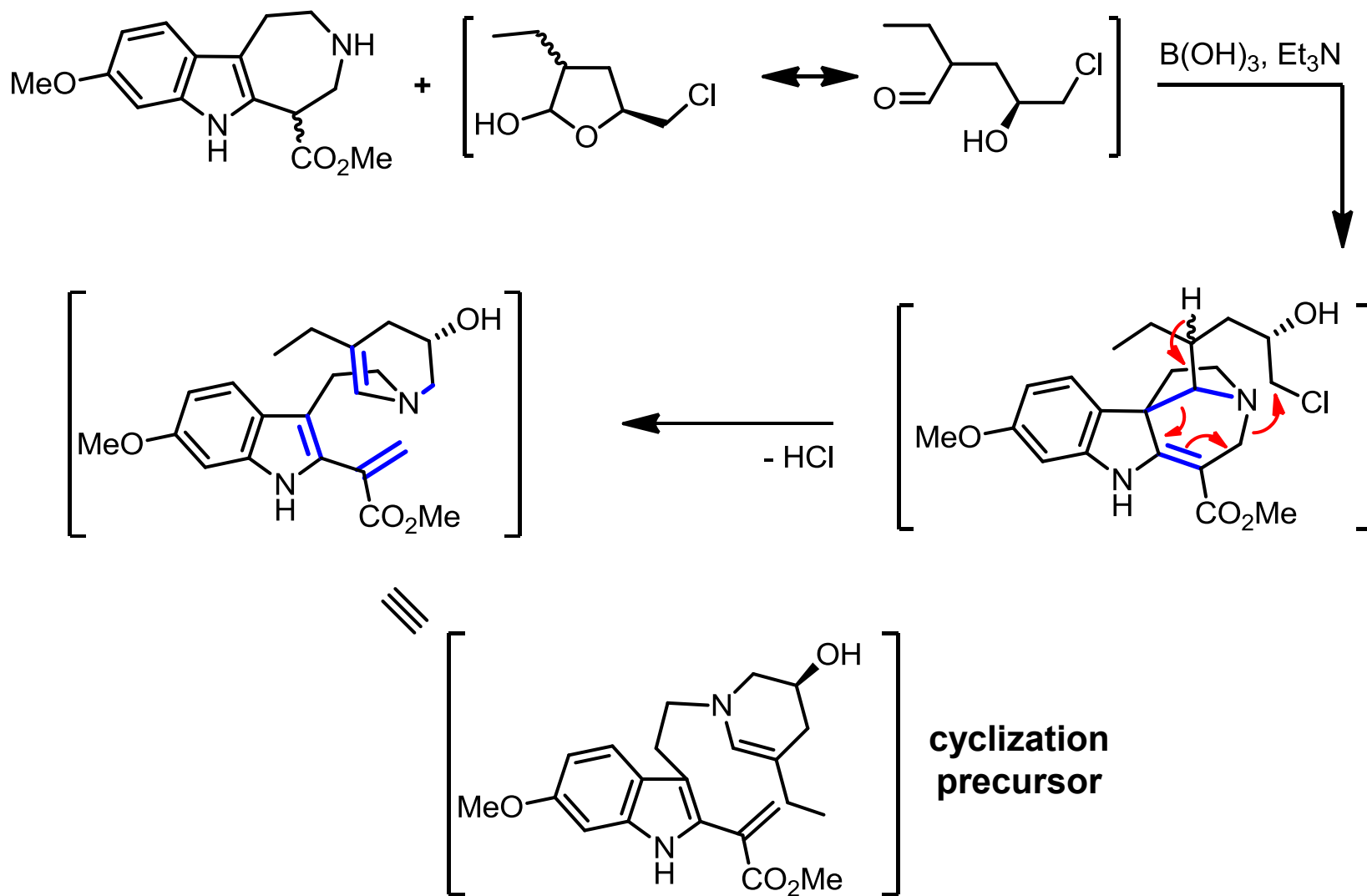
Fukuyama's approach (2002)
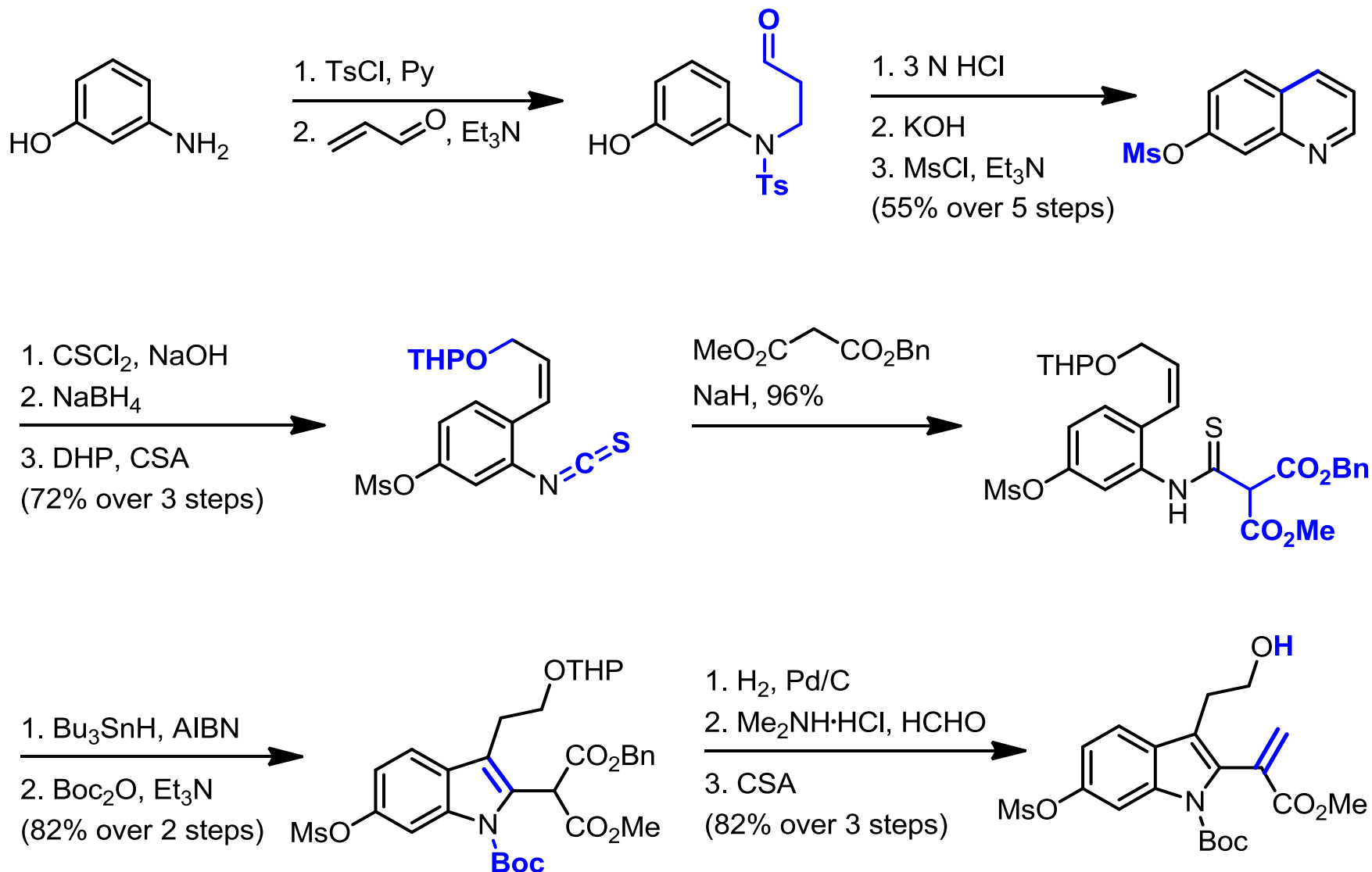
J. Am. Chem. Soc. **2002**, *124*, 2137-2139.

- Fukuyama's approach resembles the strategy of Kuehne

  ➡ almost similar key intermediates for the inverse electron demand DA

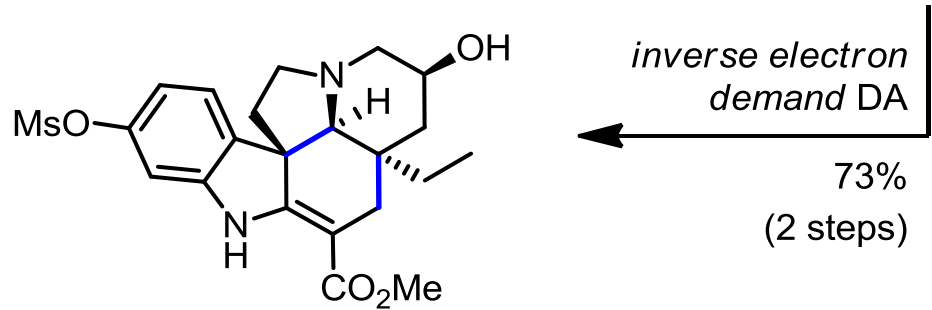**Fukuyama**   **Kuehne**

S. Kobayashi, T. Ueda, T. Fukuyama, *Synlett.* **2000**, *124*, 883-886; S. Yokoshima, T. Ueda, S. Kobayashi, A. Sato, T. Kuboyama, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* **2002**, *124*, 2137-2139.

S. Kobayashi, T. Ueda, T. Fukuyama, *Synlett.* **2000**, *124*, 883-886; S. Yokoshima, T. Ueda, S. Kobayashi, A. Sato, T. Kuboyama, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* **2002**, *124*, 2137-2139.

S. Kobayashi, T. Ueda, T. Fukuyama, *Synlett.* **2000**, *124*, 883-886; S. Yokoshima, T. Ueda, S. Kobayashi, A. Sato, T. Kuboyama, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* **2002**, *124*, 2137-2139.

(−)-vindoline
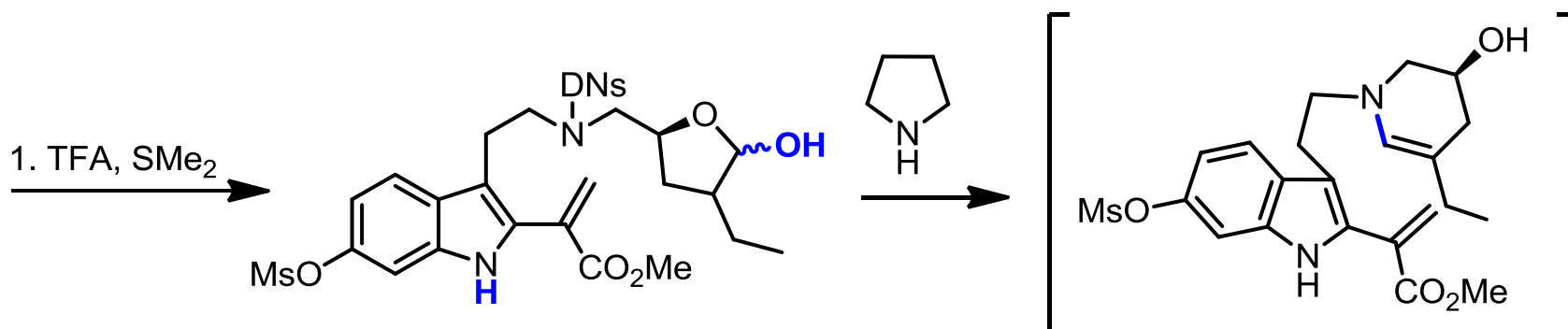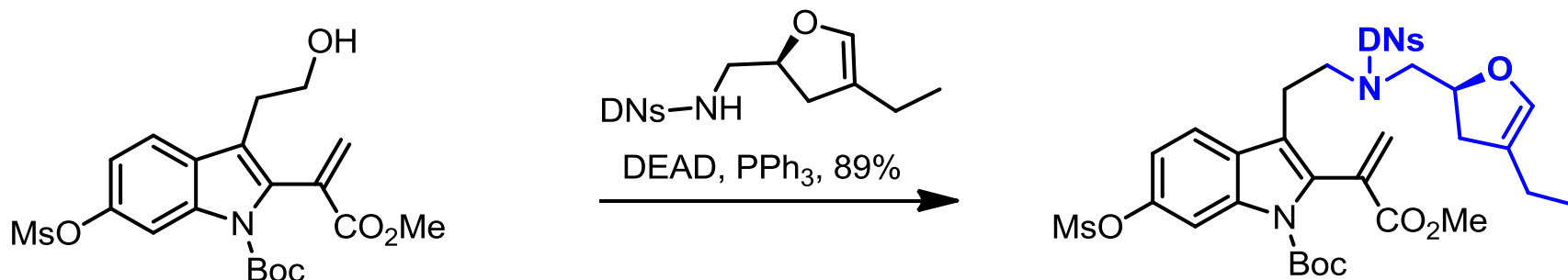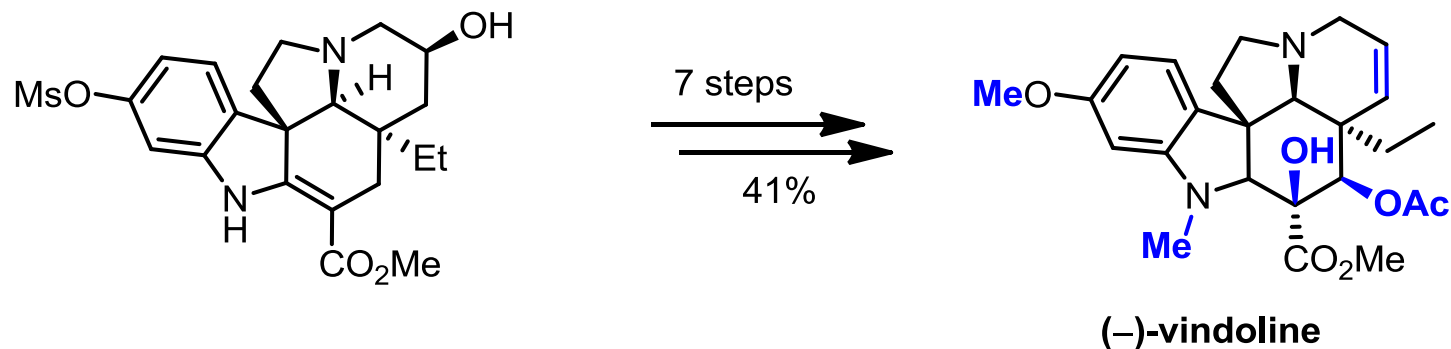
Fukuyama's approach (2002)

- 24 steps from commercial 3-hydroxyaniline to (−)-vindoline

- 6.8% overall yield

- **key step**: inverse electron demand *DA*

key intermediate

S. Kobayashi, T. Ueda, T. Fukuyama, *Synlett.* **2000**, *124*, 883-886; S. Yokoshima, T. Ueda, S. Kobayashi, A. Sato, T. Kuboyama, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* **2002**, *124*, 2137-2139.