Special Seminar about Mark Lautens' Chemistry

Personal:
Place and Date of Birth: Hamilton, Ontario, Canada, July 9, 1959.

Education:
B.Sc. 1981 University of Guelph (Canada) with P.M. Henry
Ph.D. 1985 University of Wisconsin Madison (USA) with B.M. Trost
PostDoc 1985-1987 Harvard University (USA) with D.A. Evans

Academic positions:
1992-1995 Associate Professor, University of Toronto, Canada
1995-1998 Professor, University of Toronto
1998-present AstraZeneca Professor of Organic Synthesis, University of Toronto
2003-present NSERC/Merck Frosst Industrial Research Chair, NSERC/Merck Frosst

(Comme un arbre au fil du temps)

Current group size: 4 M.Sc., 10 Ph.D., 7 PostDocs
Number of previous group members: 15 M.Sc., 23 Ph.D., 49 Postdocs

Publications: around 215 (January 2008) (42 JACS, 40 Org.Lett., 35 JOC, 21 Tetrahedron Lett., 9 Angew. Chem., 6 Tetrahedron, 4 Chem. Rev., 3 patents, 2 books…)

Editorial Board: Synthesis, Synfacts, Organic Syntheses (2004-2012), Science of Synthesis (Vol. 1)

Special Seminar about Mark Lautens' Chemistry

Areas Of Research Interest/Expertise :

- new synthetic methods
- metal catalyzed cycloadditions
- asymmetric catalysis with focus on nickel, rhodium and palladium catalysts
- cyclopropane synthesis and reactions
- hydrometallation reactions
- reactions of organosilicon and organotin compounds
- fragmentation reactions
- natural product synthesis

Awards:

- A.C. Cope Scholar (ACS)
- Alfred Bader Award (CSC)
- R.U. Lemieux Award (CSC)
- Solvias ligand Contest Winner (Solvias AG)
- Novartis Chemistry Lecturer
- Rutherford Memorial medal (RSC)

… and many other awards

Visiting Professor in:

- Paris (1993) - Tokyo (1994) - Marburg (1996) - Barcelona (1996) - Geneva (1996)
- MPI Mulheim (1997) -Tokyo (2004) - Santiago de Compostela (2006) - Marseille (2008)

Some Current Topics of Research

1- Indoles Synthesis :	**Agnès and Sridhran**
2- Modified Catellani's Reaction:	**Marc and Christophe**
3- Rhodium Chemistry:	**Raphaël, Romain and Sébastien**
4- Cyclopropanes Chemistry:	**Thomas and Corinne**
5- Oxa- and Azabicycles Ring Opening:	**Marie-Alice, Mathieu and Aurélie**

Synthesis of Indole and related compounds

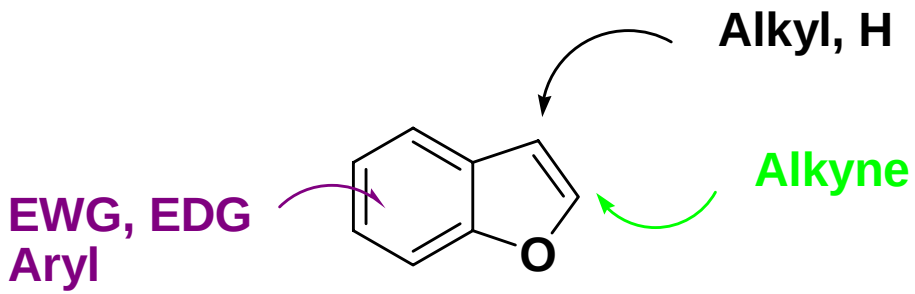
1- Scope of Mark Lautens' work on indoles family compounds:

⇢ **Indoles, azaindoles and thienopyrroles are all very useful subunits found in biologically relevant structure:**

Tubulin-inhibitory properties

Antimitotic activity

Protein kinase inhibitor…



Mahboobi, S.; Pongratz, H.; Hufsky, H. *J. Med. Chem.* **2001**, *44*, 4535.
Wentzler, S.; El Ahmad, Y.; Filoche, R.; FR 2868422, 2005
Fang, Y. Q.; Yuen, J.; Lautens, M. *J. Org. Chem*. **2007**, *72*, 5152-5160

Synthesis of Indole and related compounds

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⇢ **Indoles, azaindoles and thienopyrroles are all very useful subunits found in biologically relevant structure:**

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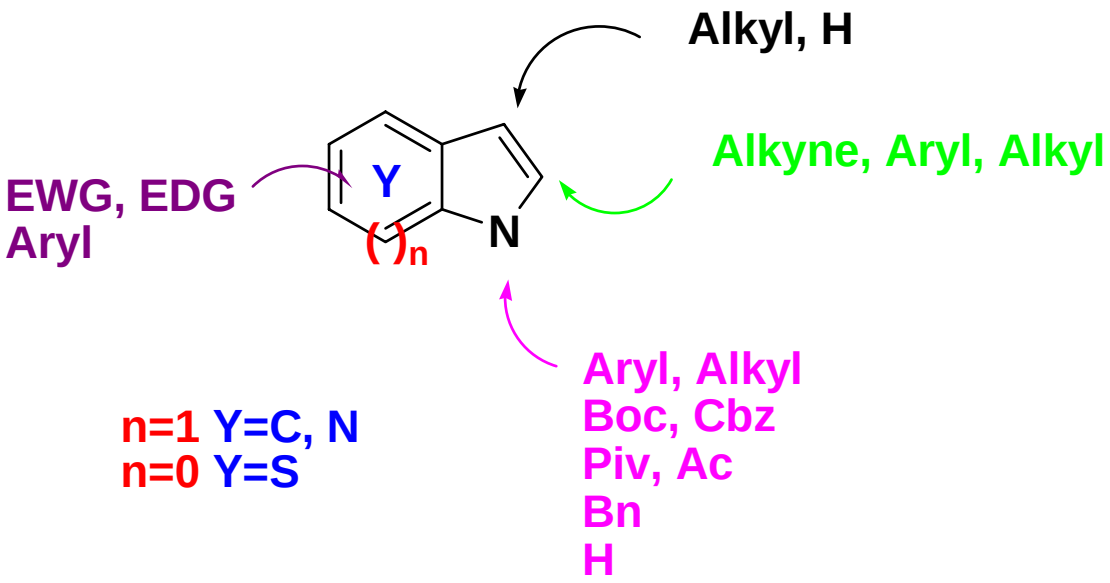
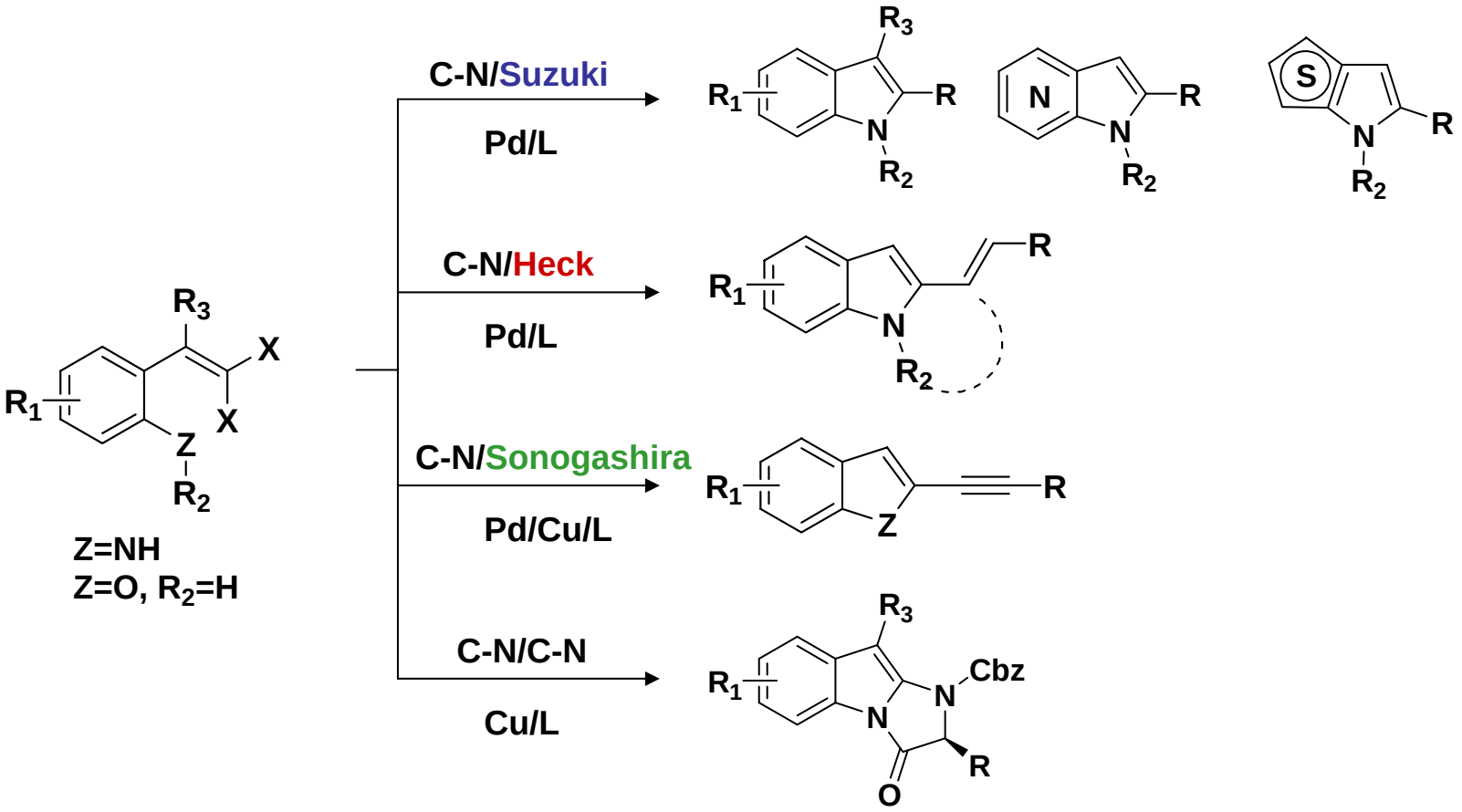


Mahboobi, S.; Pongratz, H.; Hufsky, H. *J. Med. Chem.* **2001**, *44*, 4535.
Wentzler, S.; El Ahmad, Y.; Filoche, R.; FR 2868422, 2005
Fang, Y. Q.; Yuen, J.; Lautens, M. *J. Org. Chem*. **2007**, *72*, 5152-5160

Methodology General scheme

1- Tandem Cross-coupling of gem-Dihalovinylanilines or gem-Dihalovinylphenols:

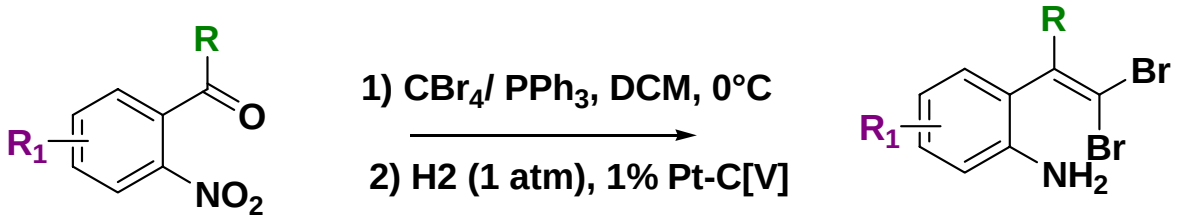


Lautens, M.; Fang, Y. Q. *J. Org. Chem.* **2008**, *73*, 538-549.

Starting material synthesis

1- gem-Dihalovinylanilines :

➙**From aldehydes or activated ketones: Corey-Fuchs procedure**

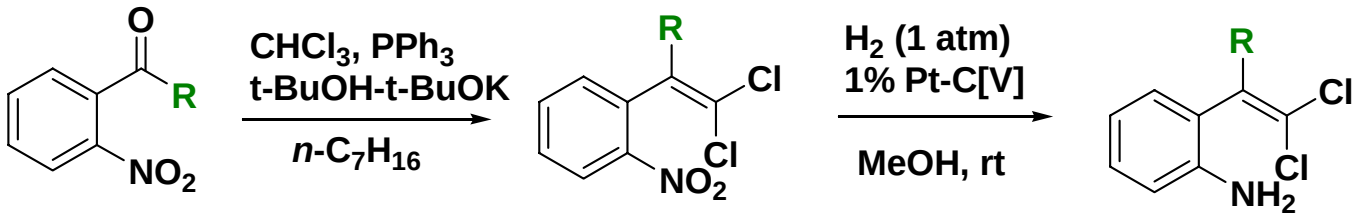


R= H
CF_3
Ph

R_1= H, Me, F, OMe, OBn, CF_3, CO_2Me

yield: 40-88%

➙**From non-activated ketones:**



R=H
CH_3

Yield: 79%
94%

Yield: 94%
93%

➙***Access to 3 substituted indoles***

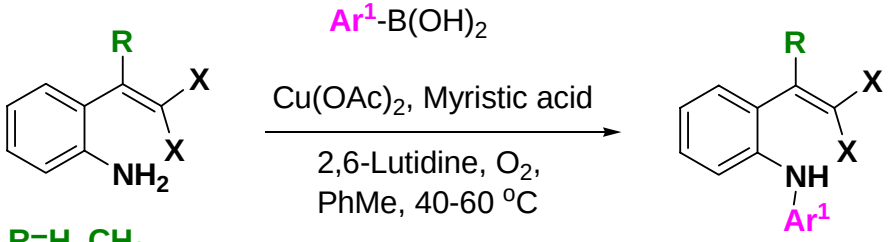
Lautens, M.; Fang, Y. Q. *J. Org. Chem.* **2008**, *73*, 538-549.

Pd-catalyzed tandem intramolecular amination and intermolecular Suzuki coupling

⇢Access to 2-3 disubstituted and 1-2-3 trisubstituted indoles

1- gem-Dihalovinylanilines N-alkylation via S_NAr or S_N2 reactions.

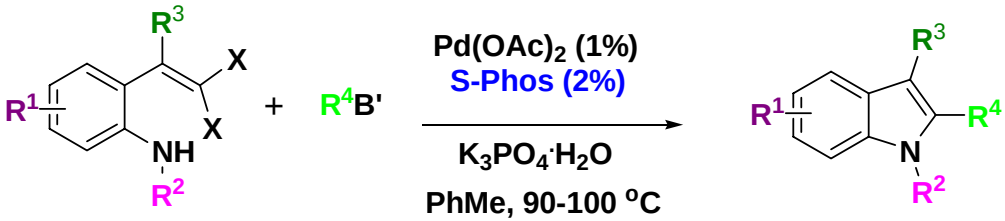
2- gem-Dihalovinylanilines N-arylation:



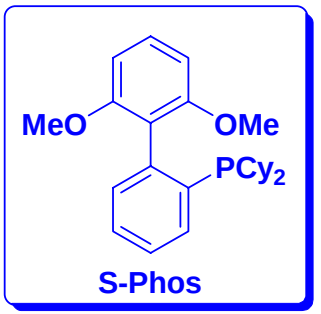
R=H, CH_3
X= Br, Cl

Yield: 56-98%

3- Tandem cross coupling reaction: Buchwald-Hartwig amination and Suzuki coupling



Yield: 57-96%



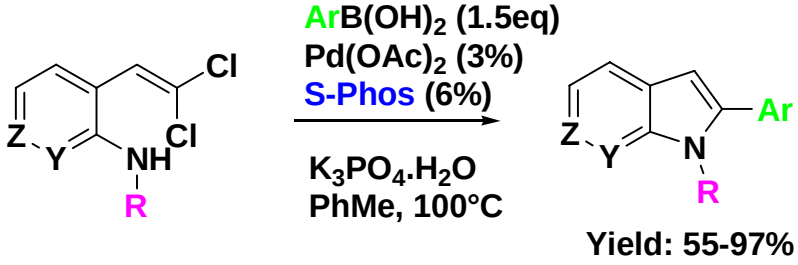
X = Br, Cl

R^1 = H, Me, OMe, OBn, F, CF_3, CO_2Me
R^2 = H, Bn, Ar, Alk
R^3 = H, Me, CF_3
R^4 = Ar, Et, ^{n}Hex, $(CH_2)_4OBn$

Lautens, M.; Fang, Y. Q. *J. Org. Chem.* **2008**, *73*, 538-549.
Fang, Y.-Q.; Lautens, M, *Org. Lett.* **2005**, *7*, 3549-3552.

Pd-catalyzed tandem intramolecular amination and intermolecular Suzuki coupling

1- Synthesis of 6 and 7-Azaindoles :

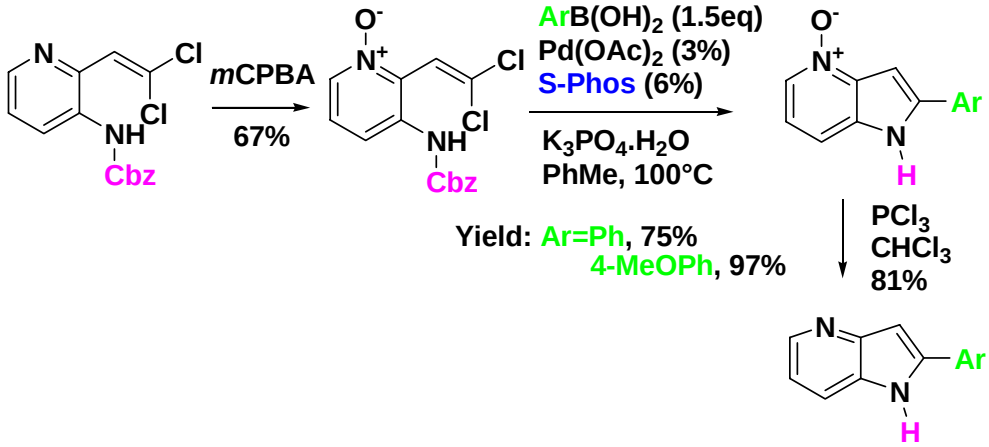


Yield: 55-97%

Z=N, Y=C — R=Boc; Ar=Ph, o-tolyl, 4-CF_3Ph, 4-MeOPh, Naph

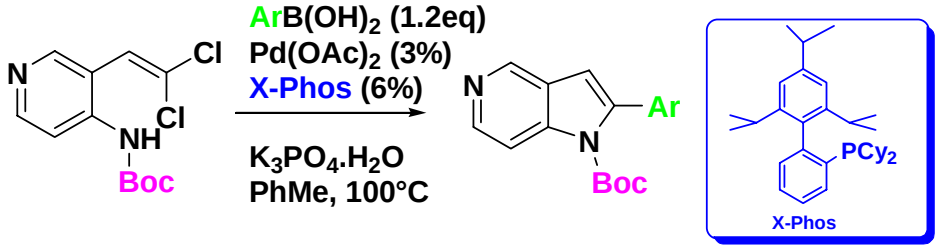
Z=C, Y=N — R=Me, Bn, Boc; Ar=Ph, 4-MeOPh, 4-CF_3Ph

3- Synthesis of 4-Azaindoles :



Yield: Ar=Ph, 75%
4-MeOPh, 97%

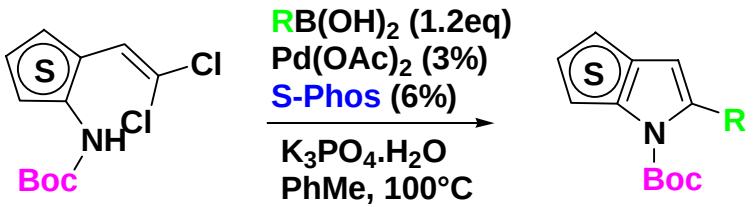
2- Synthesis of 5-Azaindoles :



Ar=Ph, 4-FPh, 4-MeOPh, o-tolyl

Yield: 75-88%

4- Synthesis of Thienopyrroles :



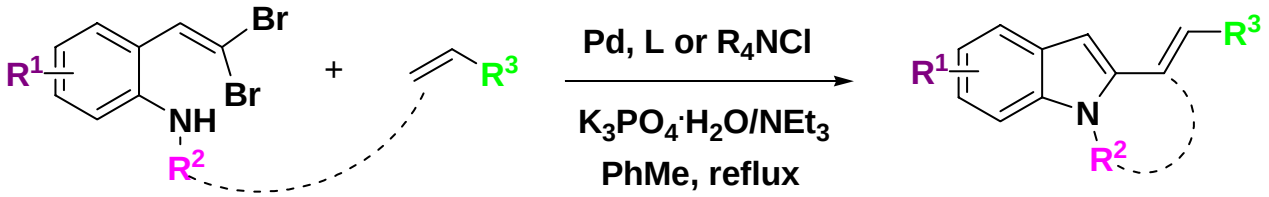
R=Ph, 4-FPh, 4-CF_3Ph, $(CH)_2$Ph

Yield: 66-81%

Fang, Y. Q.; Yuen, J.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 5152-5160.

Synthesis of 2-Vinylic Indoles and Derivatives: Pd-Catalyzed Tandem Intramolecular Amination and Intermolecular Heck Coupling

1- Tandem cross coupling reaction: Buchwald-Hartwig amination and Heck coupling

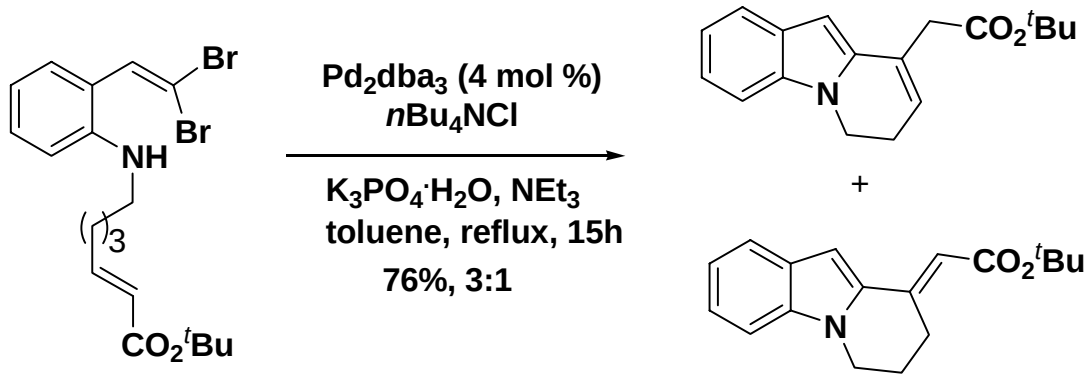


Yield: 39-79%

(26 examples)

R^1 = H, OMe, OBn, F, CO_2Me
R^2 = H, Bn, Ar, ^{i}Pr, Bu
R^3 = $CO_2{}^t$Bu, Ph, Ph-*p*Cl, Ph-*p*OMe, CN, SO_2Ph

2- Intramolecular pathway: access to fused indoles



Fayol, A.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 4203-4206.

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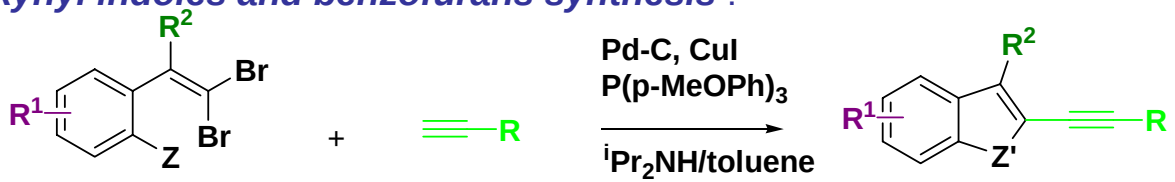
Pd/C and CuI catalyzed tandem Ullmann/Sonogashira couplings

⇢Access to 2-alkynyl indoles and benzofurans

1- *2-alkynyl indoles and benzofurans synthesis* :



Z=NH_2 R^1=F, OMe, OBn, CO_2Me, Ph, R^2=H

Z=NH-Alkyl, NH-Aryl R^1=H, R^2=H

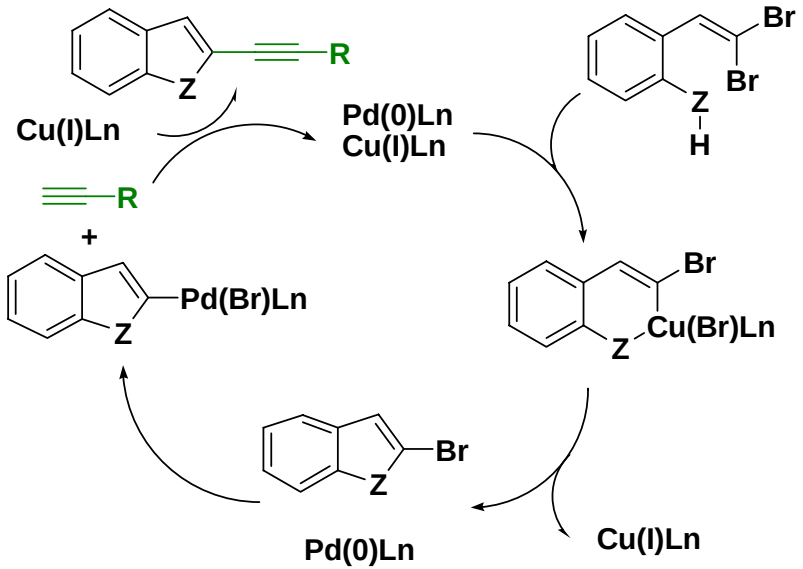
Z=O R^1=OMe, CO_2Me, Ph, R^2=H, Me

Yield:

Z'=NH, N-Alkyl, N-Aryl: 51-85%
Z'=O: 47-98%

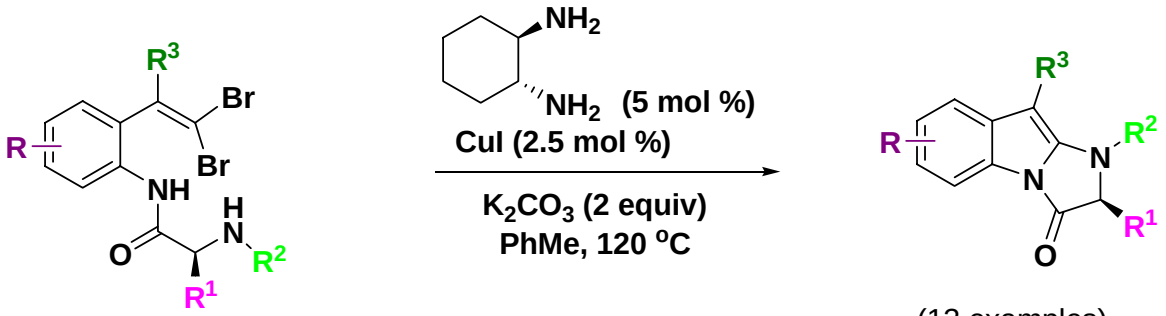
R=C_6H_{13}, TMS, $CH_2OTBDPS$, $(CH_2)_2OH$, $(CH_2)_3CN$, Ph, py

2- *Mechanism*:



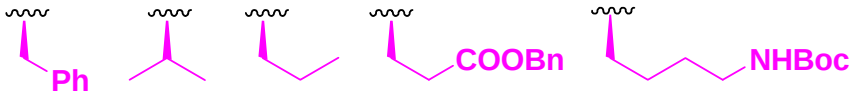
Nagamochi, M.; Fang, Y. Q.; Lautens, M. *Org. Lett.* **2007**, *9*, 2955-2958.

CuI-Catalyzed Tandem Intramolecular Amidation Using gem-Dibromovinyl Systems

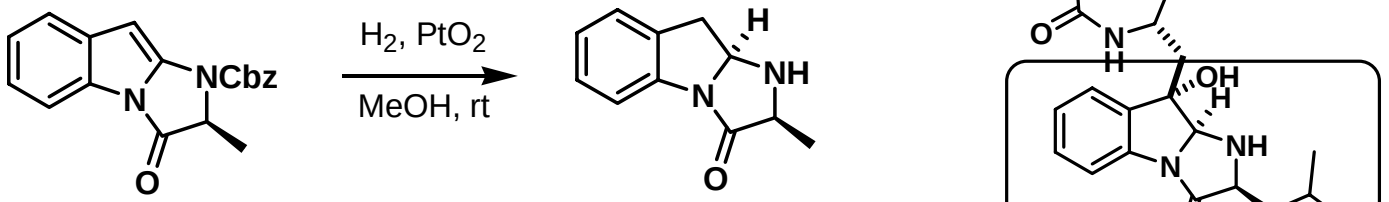


(13 examples)

R = H, Me, OBn, OMe, F, CF_3

R^1 = H, Me, 

R^2 = Boc, Cbz

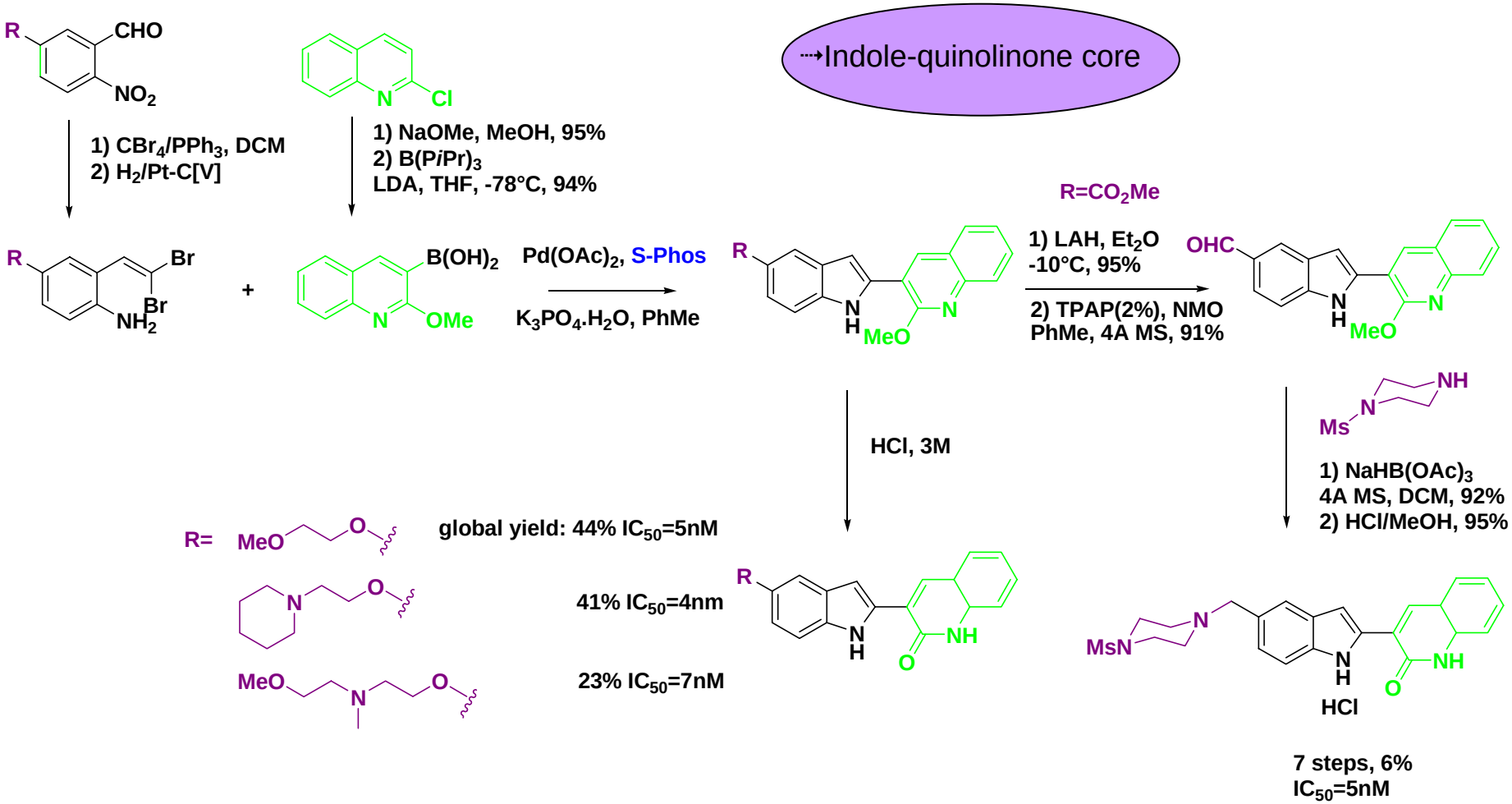


Asperlicin

Yuen, J.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 653-656.

Few synthetic applications

1- KDR Kinase Inhibitors disclosed by Merck :



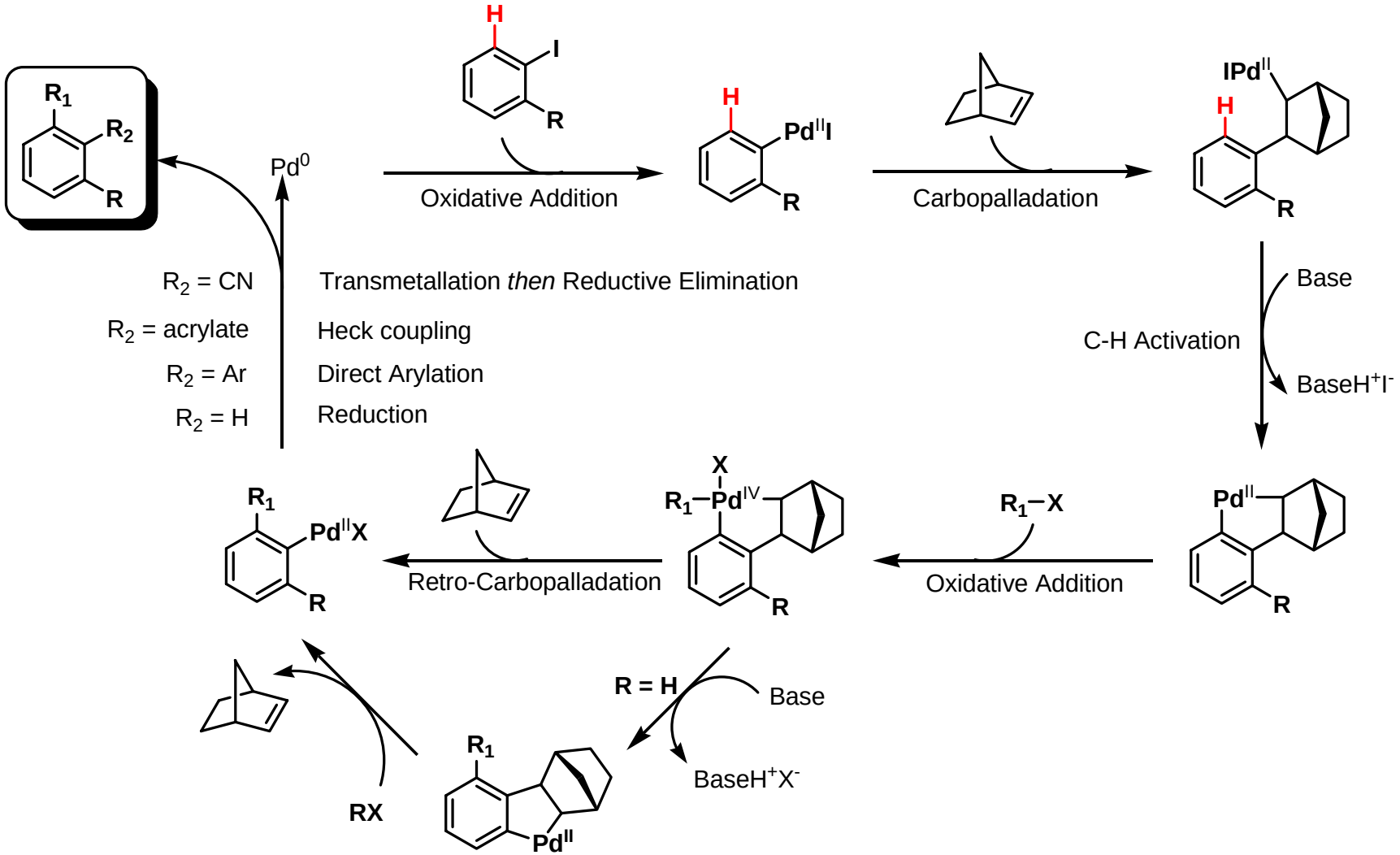
Fang, Y. Q; Karish, R.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 1341-1346.

Some Current Topics of Research

1- Indoles Synthesis :	**Agnès and Sridhran**
2- Modified Catellani's Reaction:	**Marc and Christophe**
3- Rhodium Chemistry:	**Raphaël, Romain and Sébastien**
4- Cyclopropanes Chemistry:	**Thomas and Corinne**
5- Oxa- and Azabicycles Ring Opening:	**Marie-Alice, Mathieu and Aurélie**

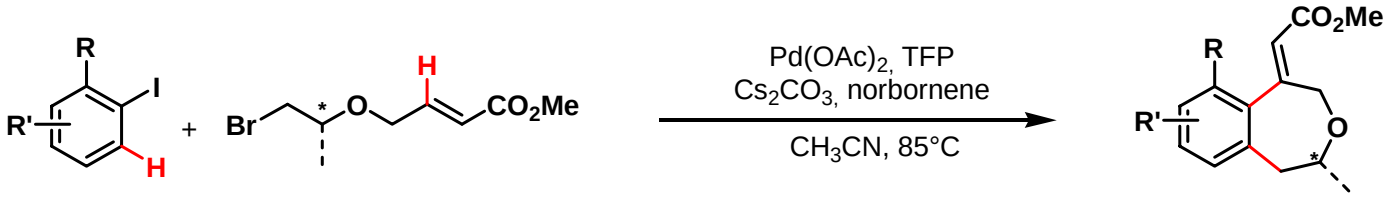
Modified Catellani's reaction

General Mechanism



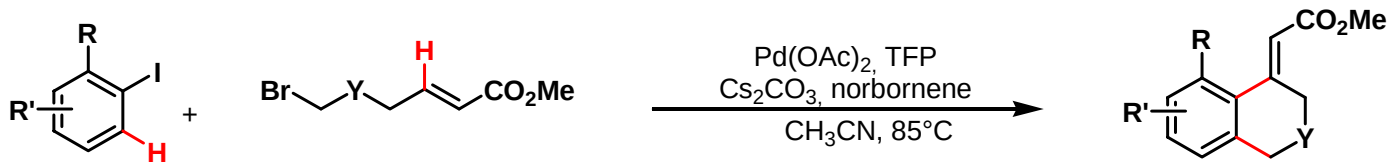
Modified Catellani's reaction

Palladium-Catalyzed Sequential Alkylation-Alkenylation Reactions[1]



23-85%

Palladium-Catalyzed Sequential Alkylation-Alkenylation Reactions[2]



Y = CHMe,CHOBn,CHPh

44-83%

Y = CHOMOM-CH_2
CHOMOM-CHMe

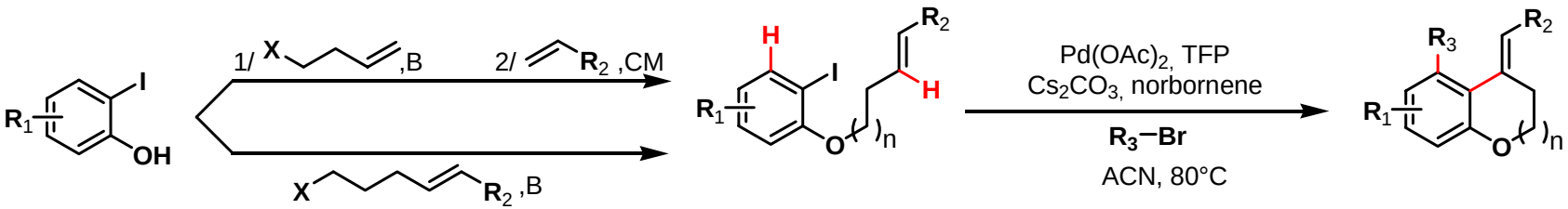
33-61%

---

[1] Lautens, M.; Paquin, J.-F.; Piguel, S. *J. Org. Chem.* **2002**, 67, 3972-3974
[2] Alberico, D.; Paquin, J.-F.; Lautens, M. *Tetrahedron* **2005**, 61, 6283-6297

Modified Catellani's reaction

Synthesis of Substituted Benzoxacycles via a Domino Ortho-Alkylation/Heck Coupling Sequence[1]

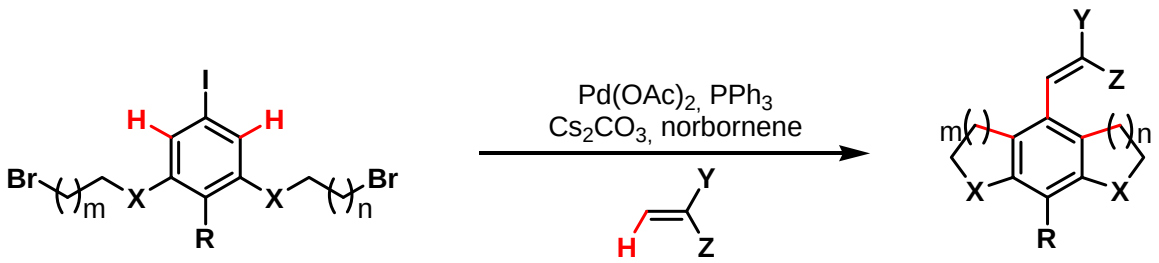


n = 1,2

R_2 = EWG

50 - 96%

Synthesis of Tricyclic Heterocycles via a Tandem Aryl Alkylation/Heck Coupling Sequence[2]



X = O, S, NTs, $-CH_2O^-$, $-OCH_2SiMe_2$
R = H, OMe
m, n = 1, 2, 3

Y or Z = EWG

37-85%

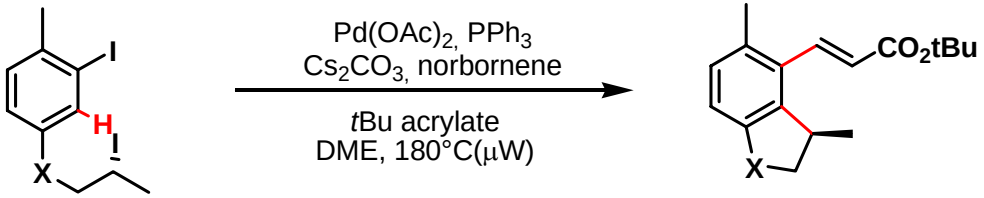
---

[1] Martins, A.; Marquardt, U.; Kasravi, N.; Alberico, D.; Lautens, M. *J. Org. Chem.* **2006**, *71*, 4937-4942

[2] Alberico, D.; Rudolph, A.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 775-781

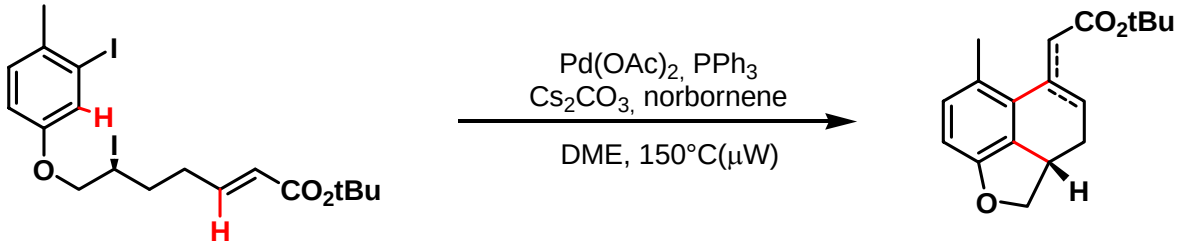
Modified Catellani's reaction

Stereochemical and Mechanistic Investigations of a Pd-Catalyzed Annulation of Secondary Alkyl Iodides



n=1 X = O (96%ee)
n=1 X= NTs (80%ee)

42% (92%ee)
55% (63%ee)



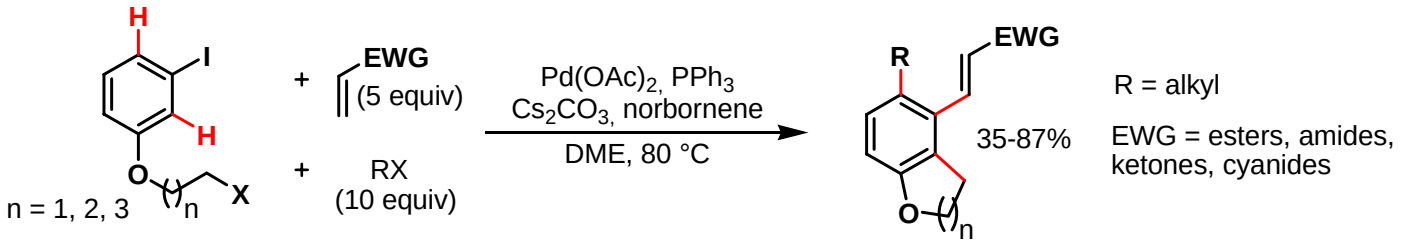
(82%ee)

78% (80%ee)

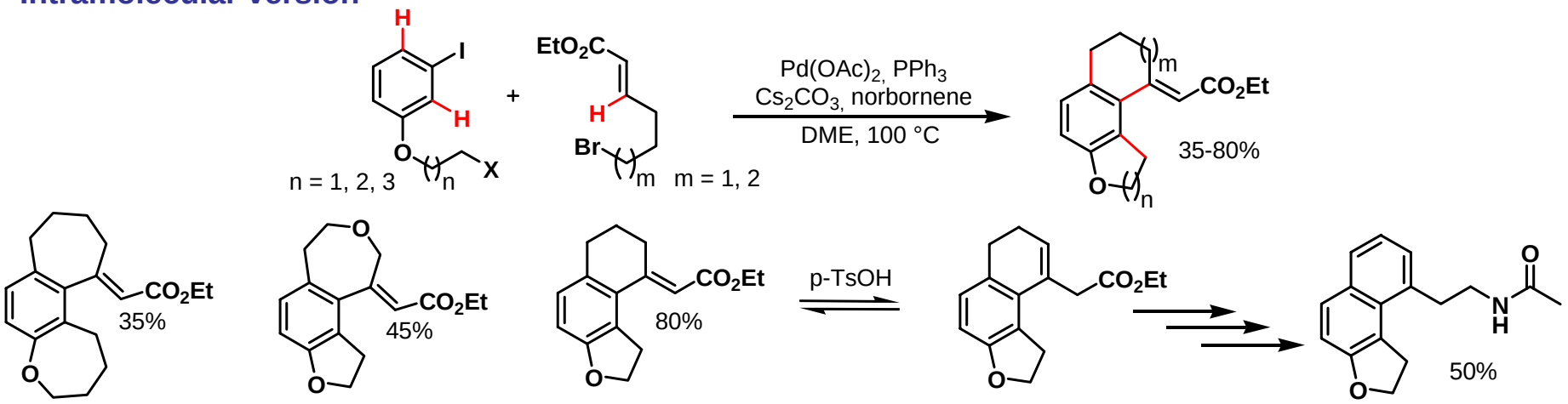
Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1485-1488.

Modified Catellani's reaction

Sequential alkylation-alkenylation reactions : Pd-catalyzed synthesis of oxacycles[1]



Intramolecular version[2]



affinity and selectivity for binding to melatonin receptors : treatment of cancer, psychiatric disorder...

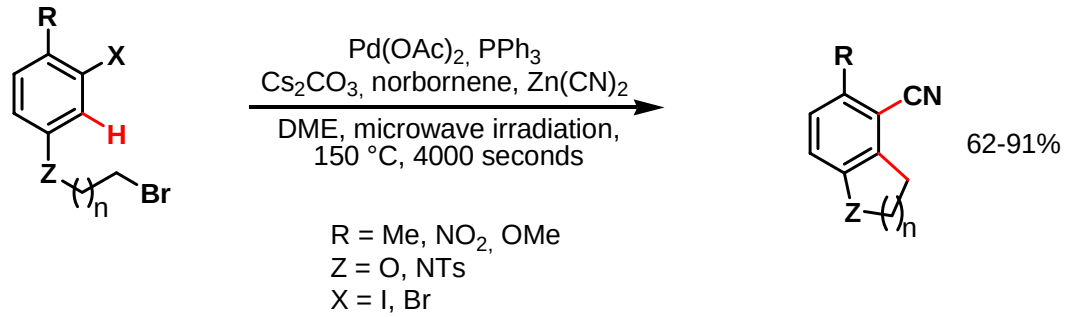
---

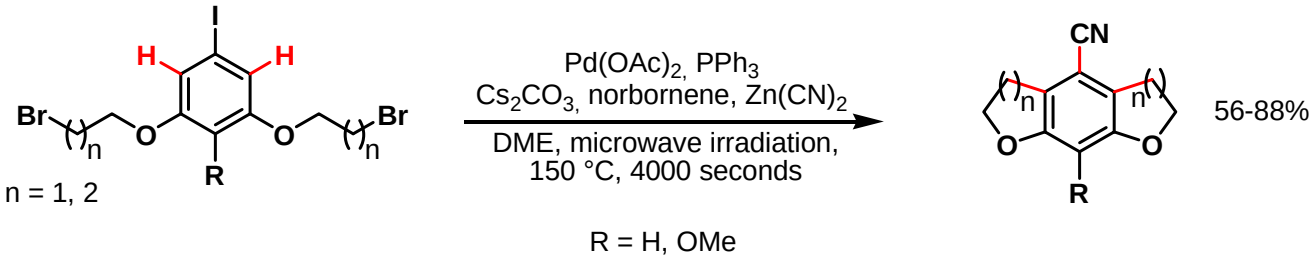
[1] Lautens, M.; Pache, S. *Org. Lett.* **2003**, *5*, 4827-4830.

[2] Lautens, M.; Jafarpour, M. *Org. Lett.* **2006**, *8*, 3601-3604.

Modified Catellani's reaction

Sequential Alkylation-Cyanation Reactions : Pd-catalyzed Synthesis of Benzonitriles

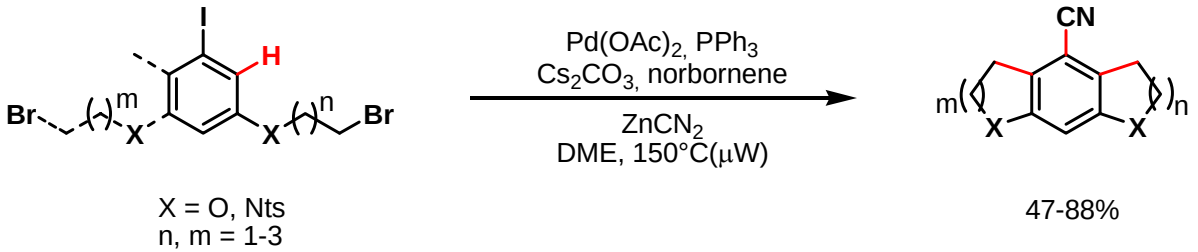




Mariampillai, B.; Alberico, D.; Bidau, V.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 14436-14437.

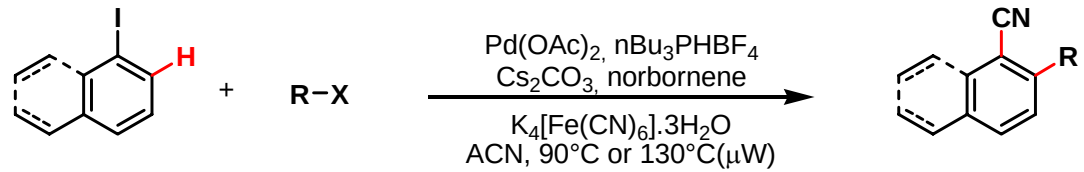
Modified Catellani's reaction

A Convergent Synthesis of Polysubstituted Aromatic Nitriles via Pd-Catalyzed C-H Functionnalization[1]



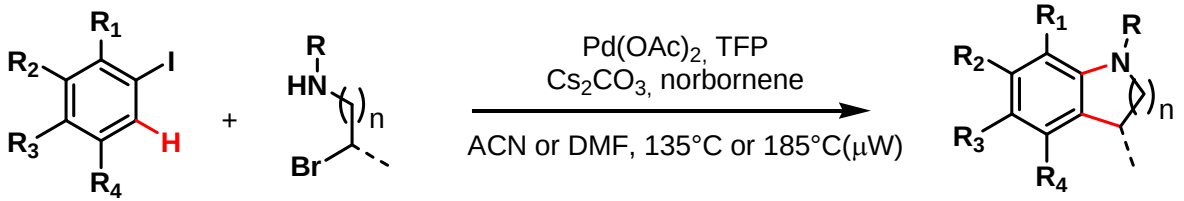
X = O, Nts
n, m = 1-3

47-88%



34-91%

Synthesis of Benzannulated N-Heterocycles by a Pd-Catalyzed C-C/C-N Coupling of Bromoalkylamines[2]



n = 1, 2

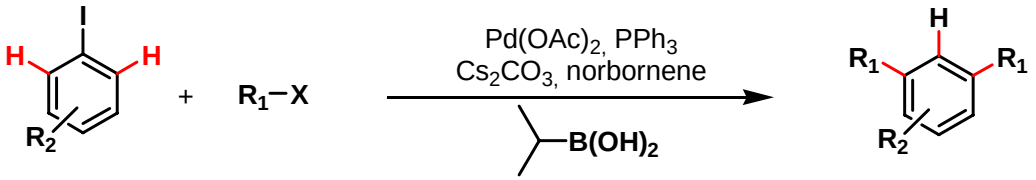
24-80%

---

[1] Mariampillai, B.; Alliot, J.; Li, M.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 15372-15379.
[2] Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, *9*, 5255-5258.

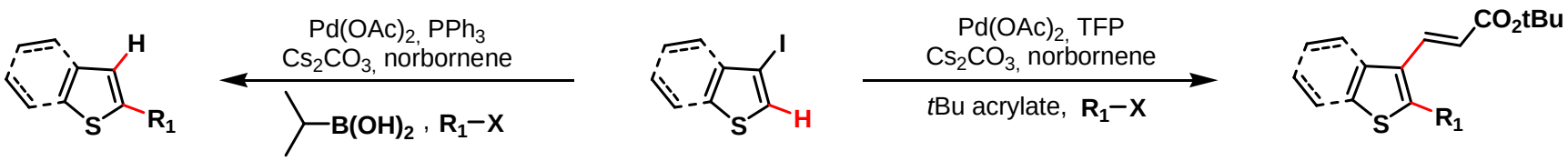
Modified Catellani's reaction

Palladium-Catalyzed Alkylation-Hydride Reaction Sequence : Synthesis of Meta-Substituted Arenes[1]



36-89%

Selectively Substituted Thiophenes and Indoles by a Tandem Pd-Catalyzed Multicomponent Reaction[2]



24-54%

52-96%

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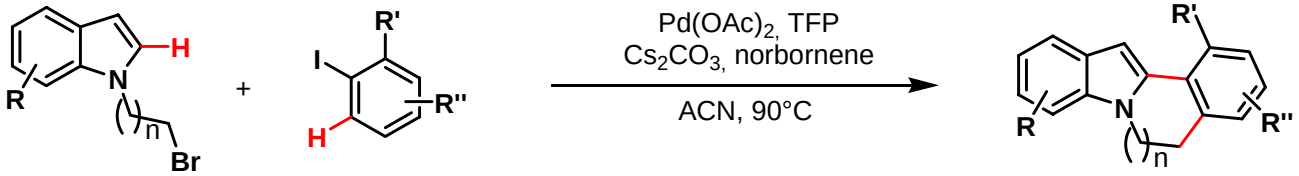
[1] Wilhelm, T.; Lautens, M. *Org. Lett.* **2005**, *7*, 4053-4056.
[2] Mitsudo, K.; Thandansote, P.; Wilhelm, T.; Mariampillai, B.; Lautens, M. *Org. Lett.* **2006**, *8*, 3939-3942.

Modified Catellani's reaction

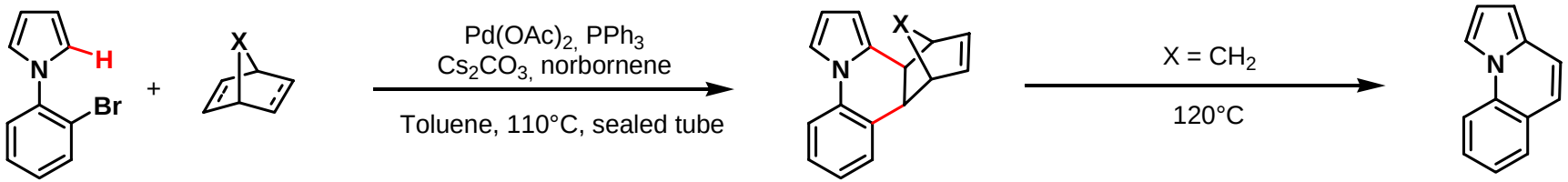
A Route to Annulated Indoles via a Pd-Catalyzed Tandem Alkylation/Direct Arylation Reaction[1]



n = 1, 2

38-93%

Palladium-Catalyzed Annulation of Aryl Heterocycles with Strained Alkenes[2]



X = CH_2, O

79-100%

70-100%

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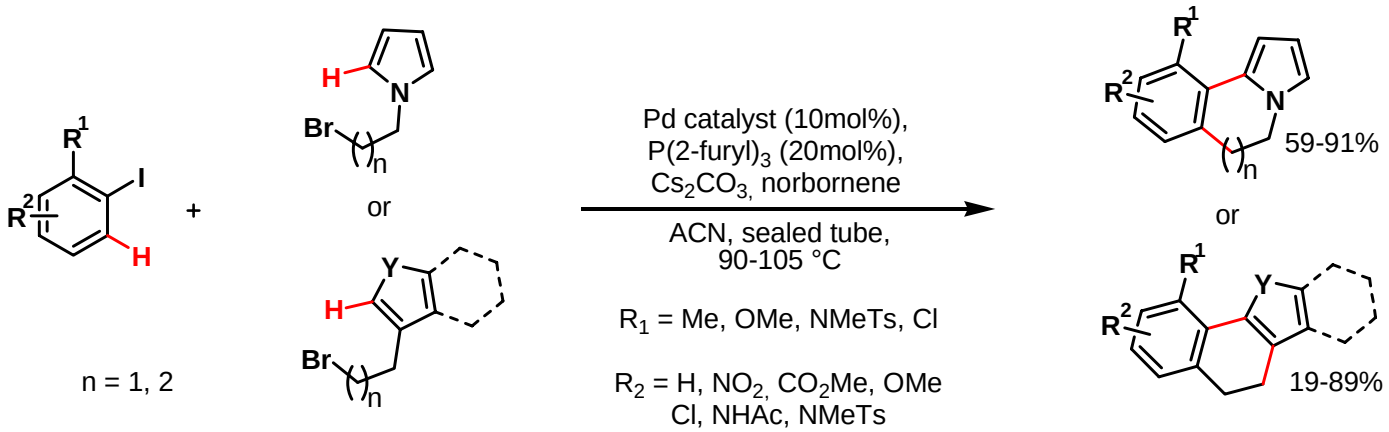
[1] Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148-13149.

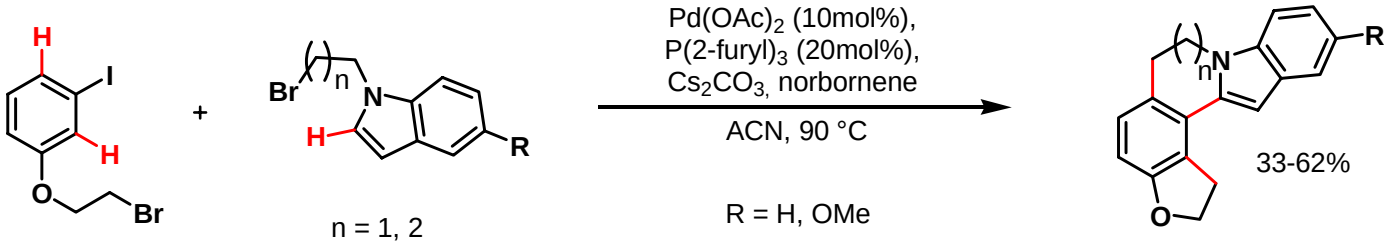
[2] Hulcoop, D. G.; Lautens, M. *Org. Lett.* **2007**, *9*, 1761-1764.

Modified Catellani's reaction

Sequential Alkylation-Arylation Reactions : Pd-catalyzed Synthesis of Annulated Heterocycles[1]



Sequential Alkylation-Arylation Reactions : Pd-catalyzed Synthesis of Annulated Indoles[2]



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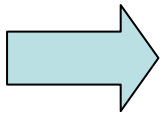
[1] a) Blaszykowski, C.; Aktoudianakis, E.; Bressy, C.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 2043-2045.
b) Lautens, M.; Martins, A.; Alberico, D. *Org. Lett.* **2006**, *8*, 4827-4829.
[2] Lautens, M.; Jafarpour, M. *Org. Lett.* **2006**, *8*, 3601-3604.

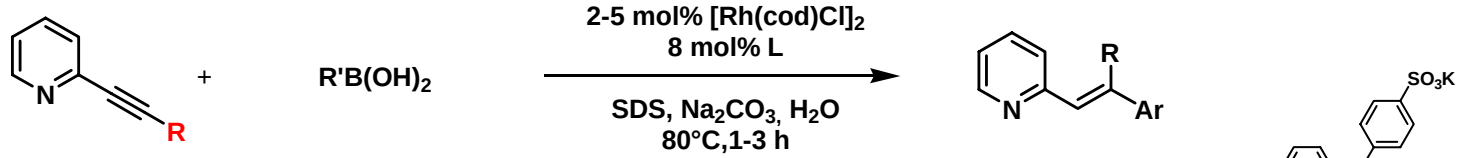
Some Current Topics of Research



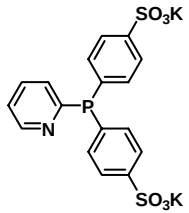
1- Indoles Synthesis :	**Agnès and Sridhran**
2- Modified Catellani's Reaction:	**Marc and Christophe**
3- Rhodium Chemistry:	**Raphaël, Romain and Sébastien**
4- Cyclopropanes Chemistry:	**Thomas and Corinne**
5- Oxa- and Azabicycles Ring Opening:	**Marie-Alice, Mathieu and Aurélie**

Rhodium Chemistry

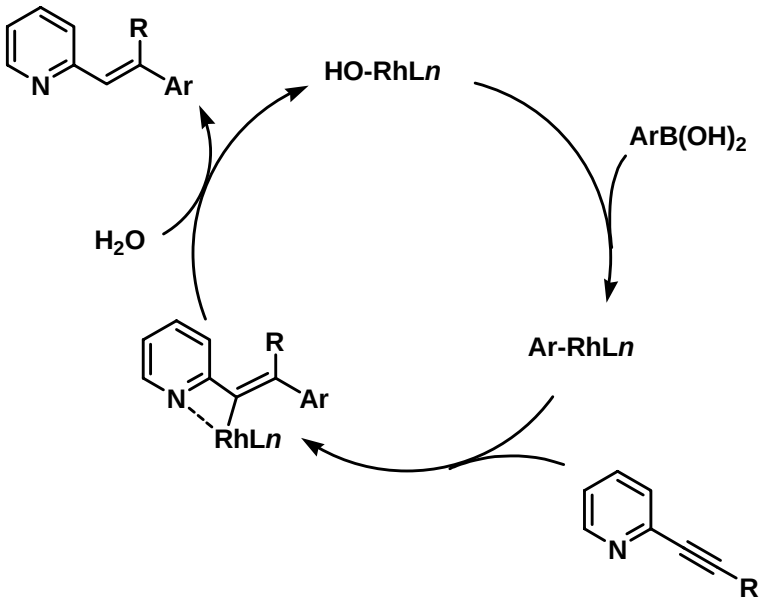
1. Rhodium-Catalysed addition of arylboronic acids to alkynyl aza-heteroaromatic compounds in water

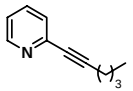
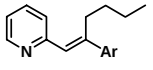
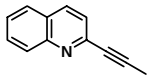
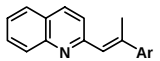
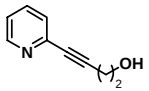
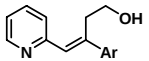
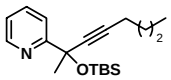
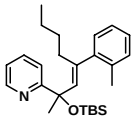


R = alkyl, aromatic R' = Ph, 2Me-Ph, 2,6 Dimethyl



Ligand pyridyl phosphine

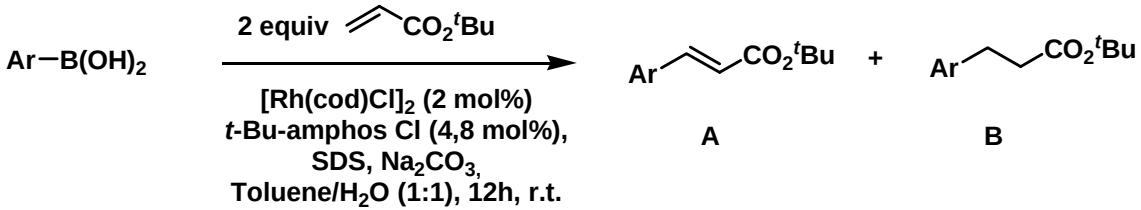


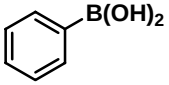
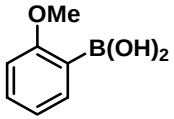
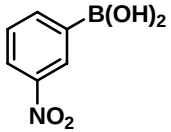
Entry	Substrat	Product	Yield (%)
1			81
4			63
5			60
8			90

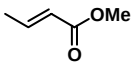
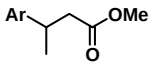
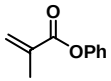
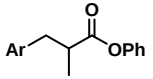
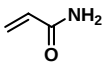
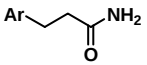
Lautens, M.; Yoshida. M. *J. Org. Chem.* **2003**, *68*, 762-769.

Rhodium Chemistry

2. Rhodium-Catalysed Heck-type of boronic acids with activited alcenes in aqueous emulsion



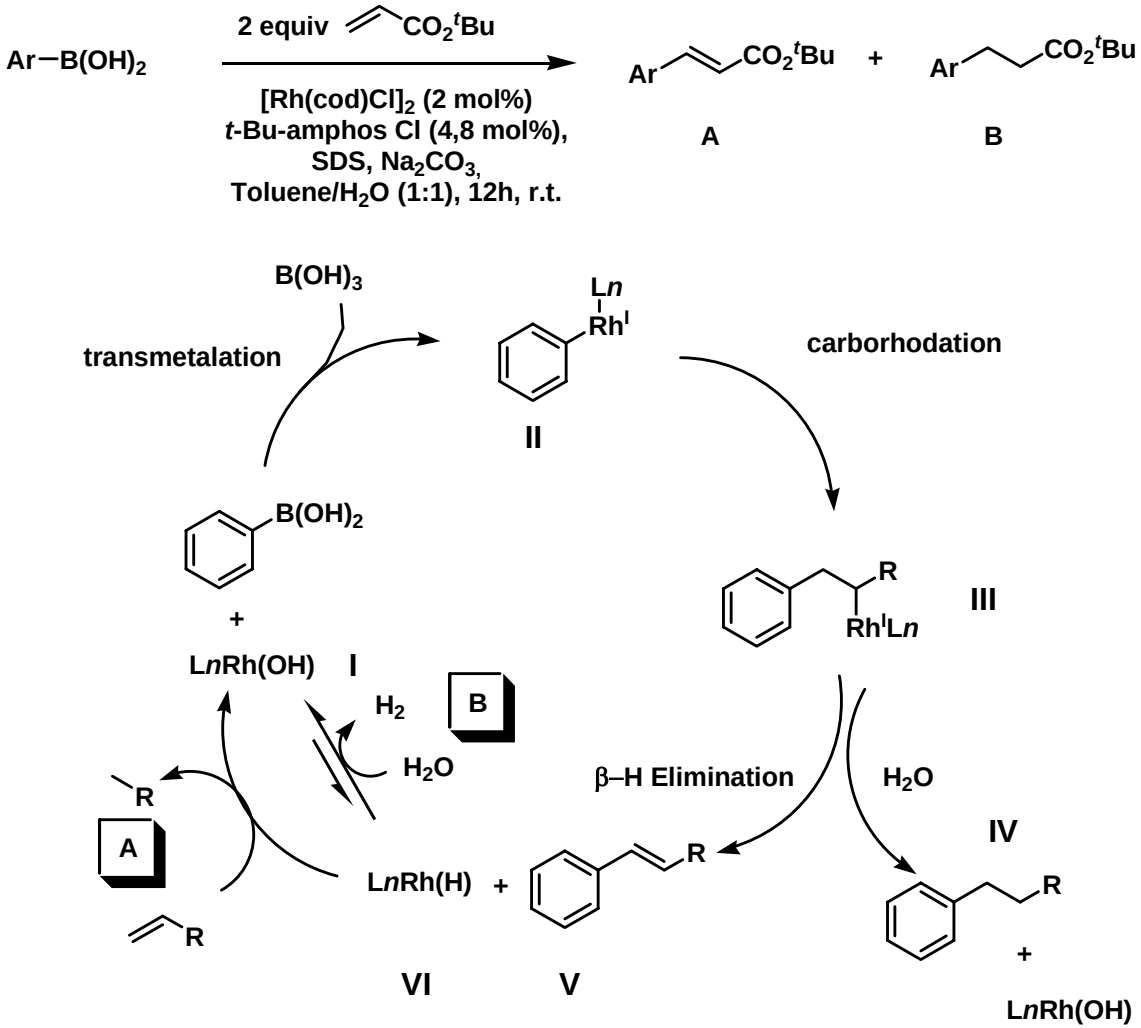
Entry	Acid	Yield	Product (A/B)
1		>99%	(80:20)
2		99%	(96:4)
3		>99%	(87:13)

Entry	Alkene	Product	Yield (%)
4			73
5			94
6			29

Lautens, M.; Mancuso, J.; Grover, H. *Synthesis* **2004**, 2006-2014.

Rhodium Chemistry

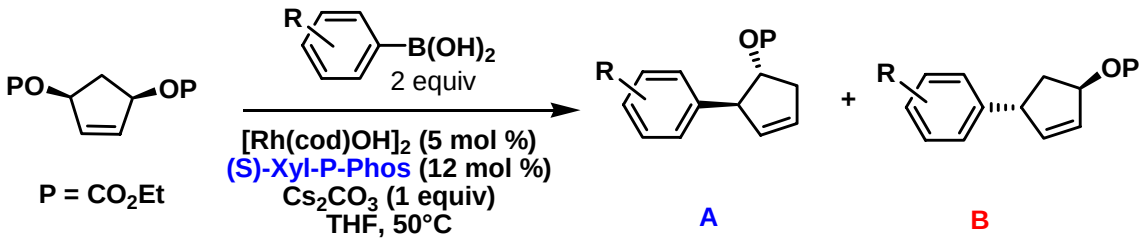
2. Rhodium-Catalysed Heck-type of boronic acids with activited alcenes in aqueous emulsion



Lautens, M.; Mancuso, J.; Grover, H. *Synthesis* **2004**, 2006-2014.

Rhodium Chemistry

3. Rhodium-Catalysed asymmetric allylic substitution with boronic acid nucleophiles

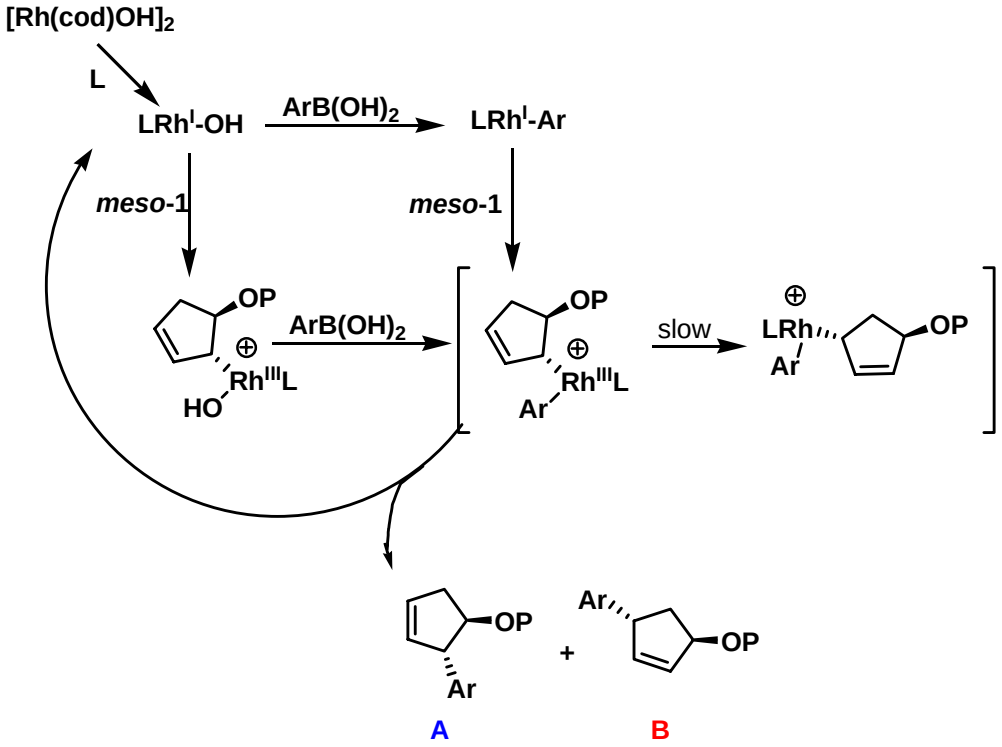


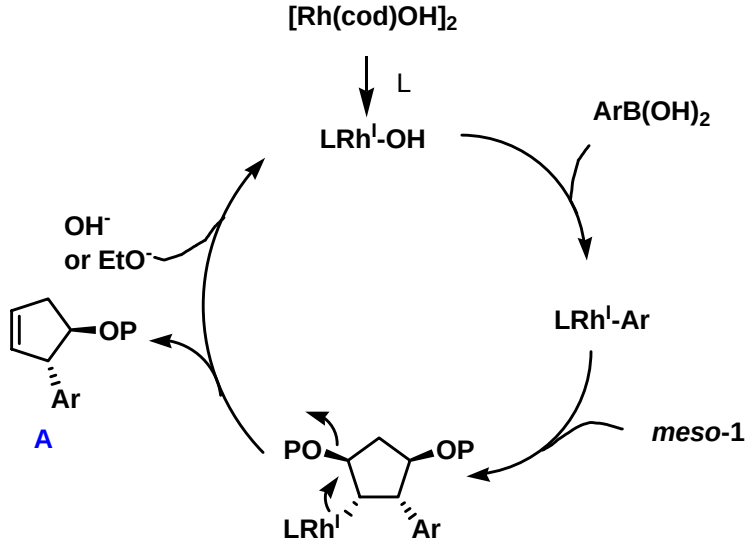
Entry	R	Yields (%)	A/B	ee (%)
1	H	87	18:1	92
2	4-CO_2Me	95	>20:1	90
3	4-Cl	53	13:1	90
4	4-Me	70	20:1	84
5	4-OMe	49	>20:1	89
6	3-Cl	87	10:1	90
7	3-Me	78	20:1	92
8	3-OMe	63	>20:1	92

Lautens, M.; Menard, F.; Chapman, T. M.; Dockendorff, C. *Org. Lett* **2006**, *8*, 4569-4572.

Rhodium Chemistry

Two proposed mechanisms :

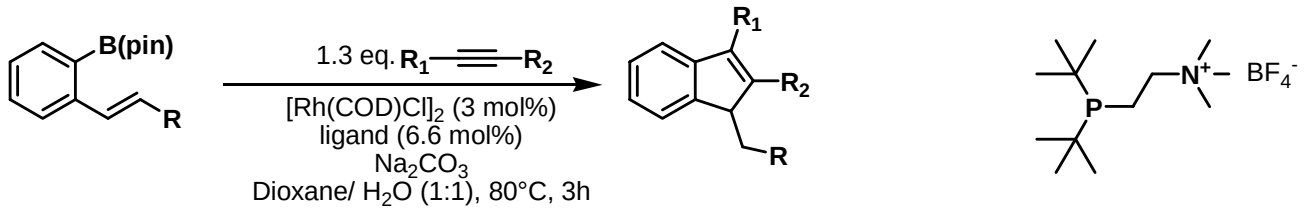




Lautens, M.; Menard, F.; Chapman, T. M.; Dockendorff, C. *Org. Lett* **2006**, *8*, 4569-4572.

Rhodium Chemistry

4. Rhodium-catalyzed tandem cyclisation: formation of indene

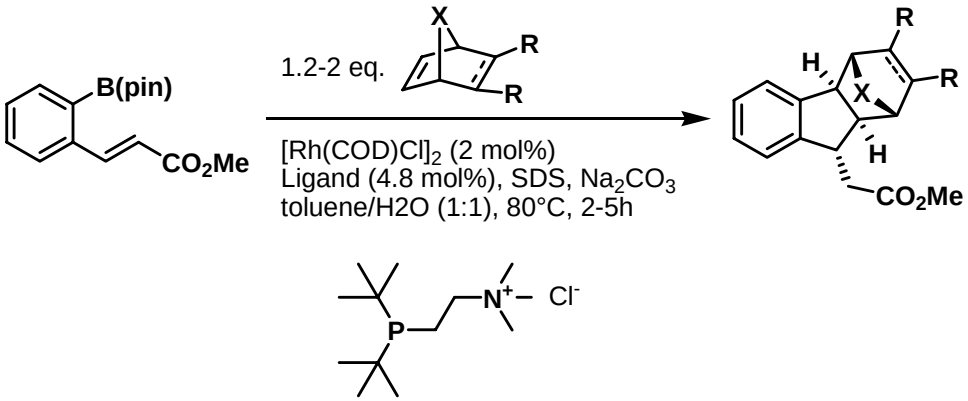


R1	R2	Yield	Regioisomers ratio
aryl	alkyl	77- 99%.	>20:1
aryl	EWG	30%	>20:1
EWG	EWG	70-80%	>20:1
alcoxy	EWG	36-95%	5:1 to 9:1

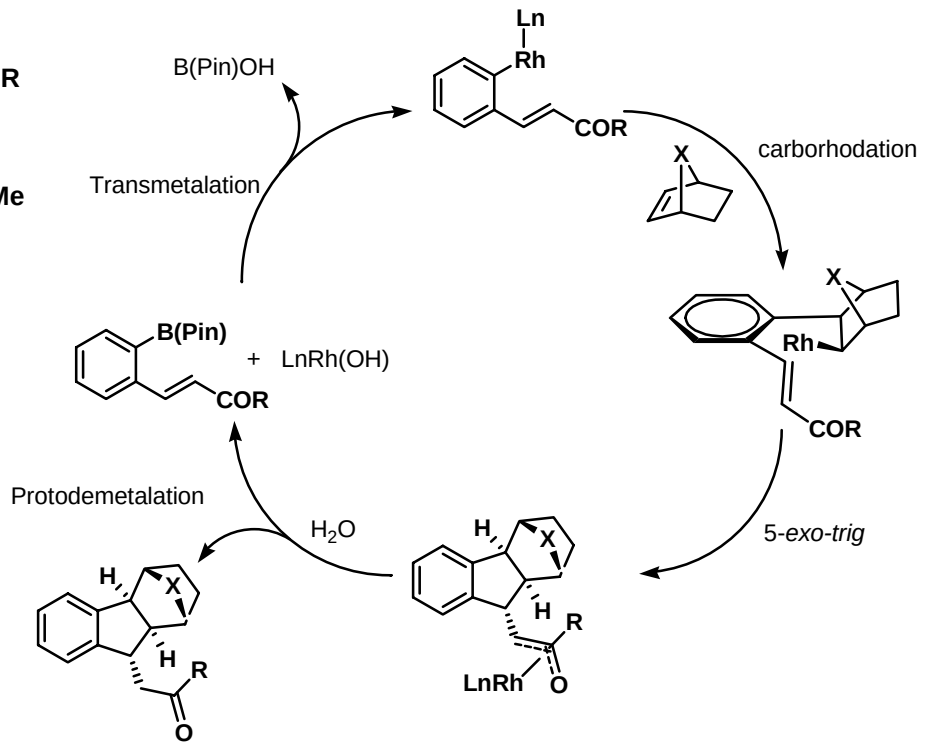
Lautens, M.; Marquardt T. *J. Org. Chem.* **2004**, *69*, 4607-4614.

Rhodium Chemistry

5. Addition of bifunctionnal organoboron reagents to strained alkenes



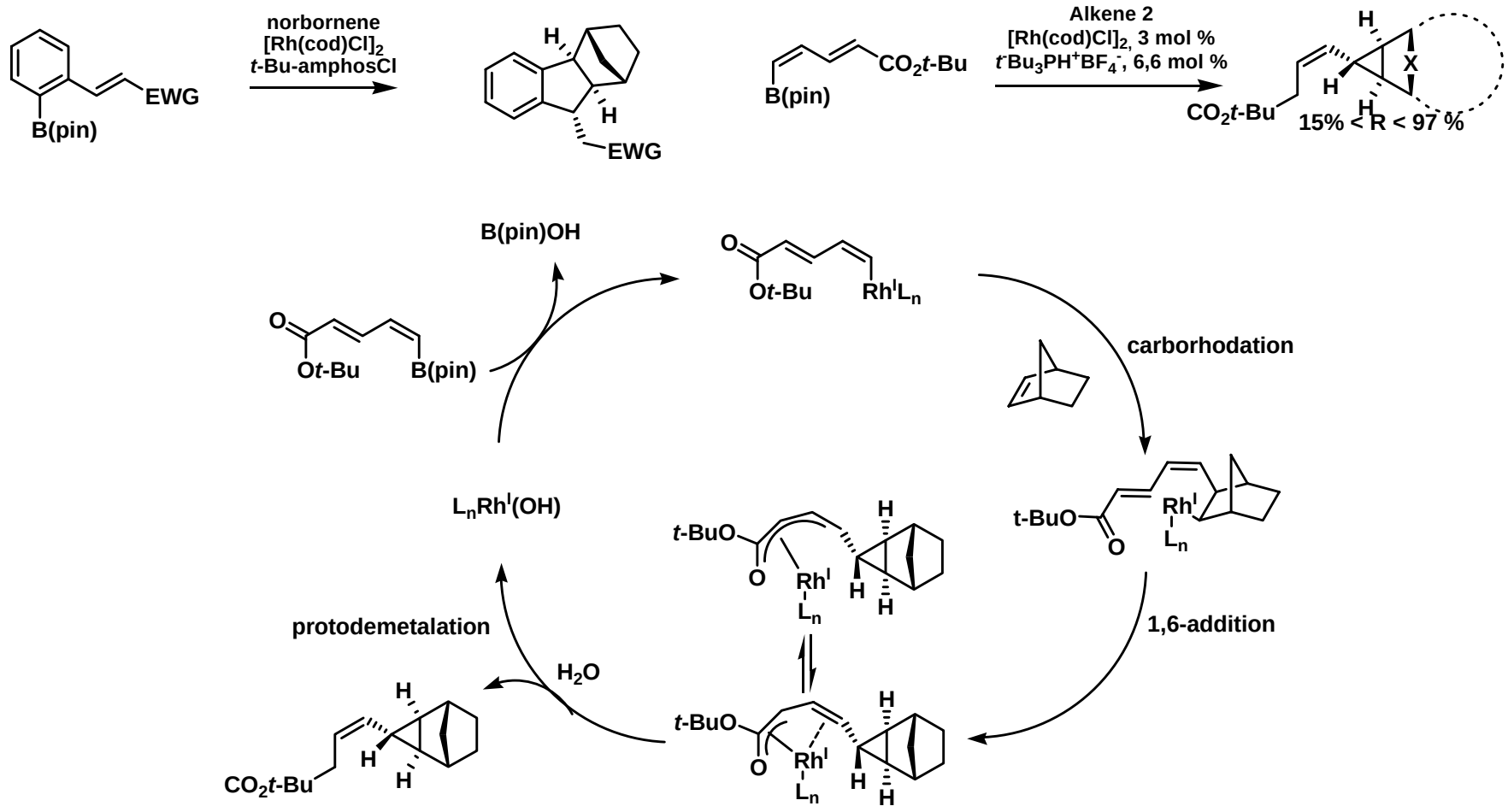
X	R	Yield
C	H, Alkyl, aryl, ester	62-99%
O	Alkyl, aryl, alkoxy	60%-97%
N	Alkyl, aryl, ester	76-99%



Lautens, M.; Mancuso J. *J. Org. Chem.* **2004**, *69*, 3478-3487.

Rhodium Chemistry

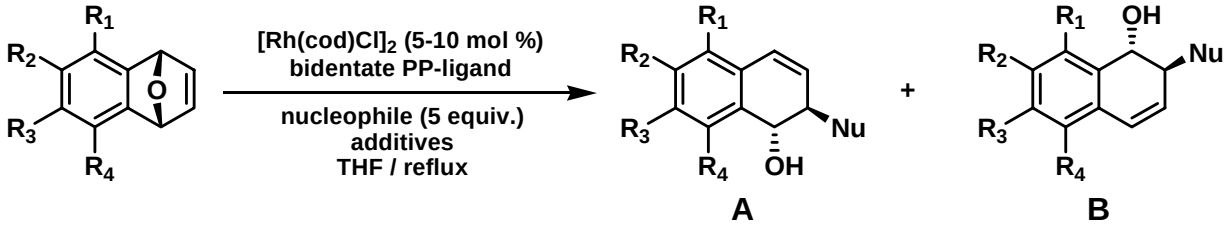
6. Rhodium-Catalyzed tandem vinylcyclopropanation of strained alkenes



Tseng, N. W.; Mancuso, J.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 5338-8339.

Rhodium Chemistry

7. Remote electronic effects in the rhodium-catalyzed nucleophilic ring opening of oxabenzonorbonadienes



Entry	Nu	Yield (ratio A:B)
1	N-methylaniline	84% (11:1)
2	Dibenzylamine	77% (11:1)
3	Phenol	74% (>25:1)
4	Dimethylmalonate	55% (>25:1)
5	4-hydroxyacetophenone	50% (18:1)

Regioselectivity using different nucleophiles (R_1, R_3 = OMe; R_2, R_4 = H)

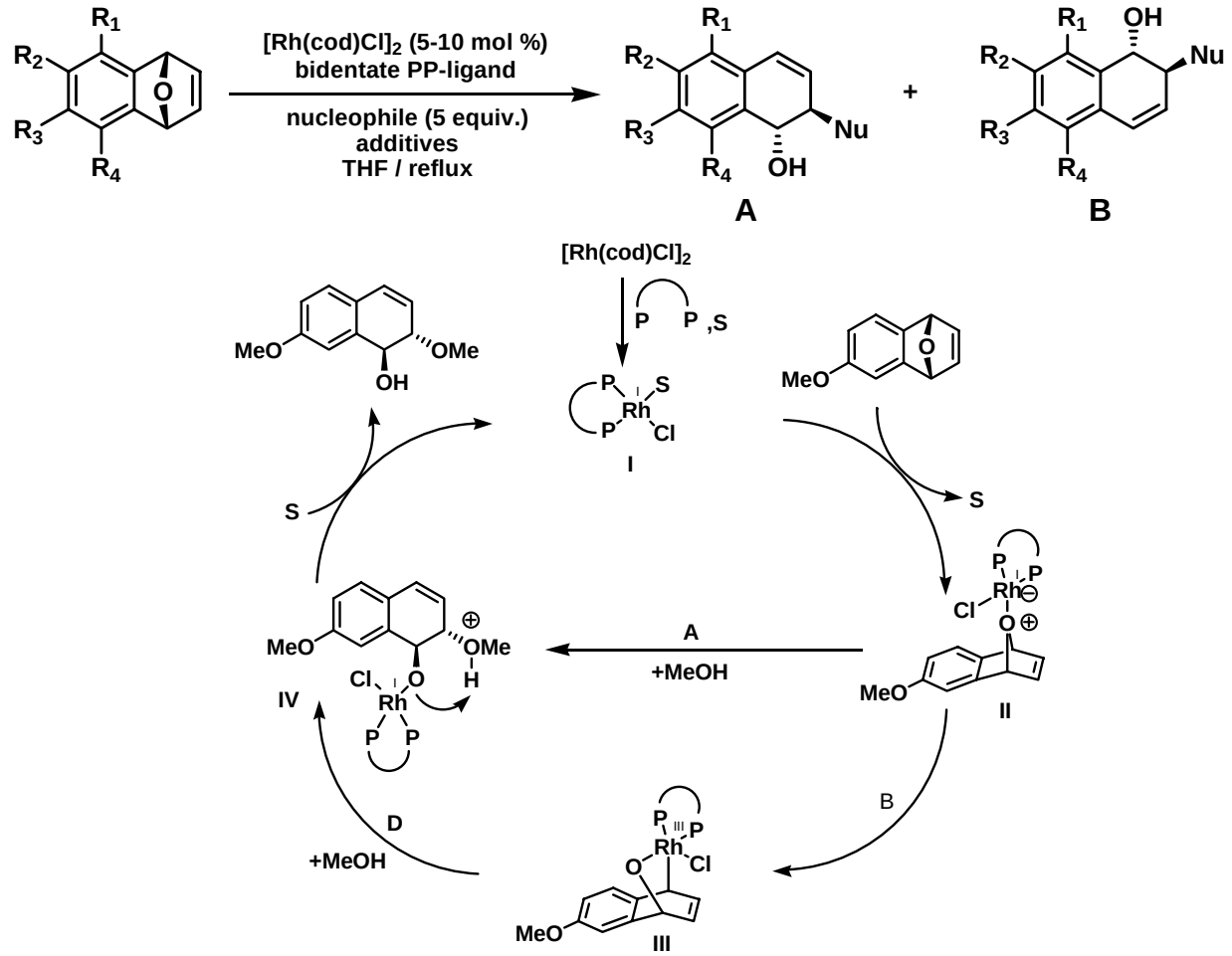
Entry	R_1	R_2	R_3	R_4	Yield (ratio A:B)
1	H	Ac	H	H	83% (1.05:1)
2	H	H	CF_3	H	84% (1.05:1)
3	OMe	H	H	H	81% (3.5:1)
4	OMe	H	Cl	H	82% (3.9:1)
5	H	H	OMe	H	89% (12:1)
6	OMe	H	OMe	H	80% (>25:1)
7	H	H	$N(CH_3)Ph$	H	58% (>25:1)

Regioselectivity using methanol as a nucleophile

Lautens, M.; Schmid, G. A. *J. Org. Chem.* **2002**, *67*, 8043-8053.

Rhodium Chemistry

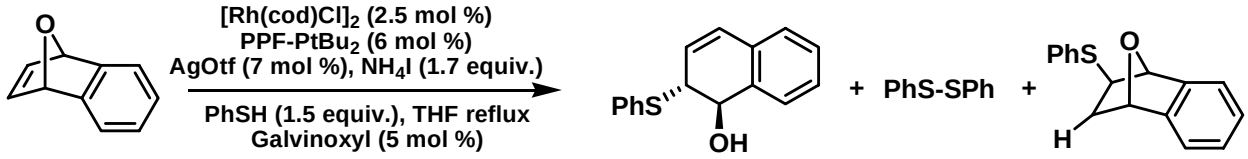
7. Remote electronic effects in the rhodium-catalyzed nucleophilic ring opening of oxabenzonorbonadienes

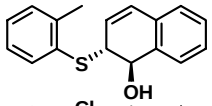
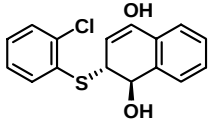
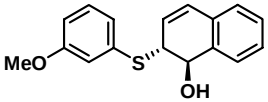
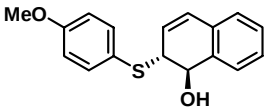
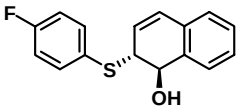
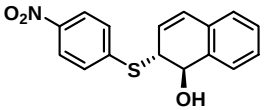


Lautens, M.; Schmid, G. A. *J. Org. Chem.* **2002**, *67*, 8043-8053.

Rhodium Chemistry

8. Rhodium-Catalyzed asymetric ring opening of oxabicyclic alkenes with sulfur nucleophiles

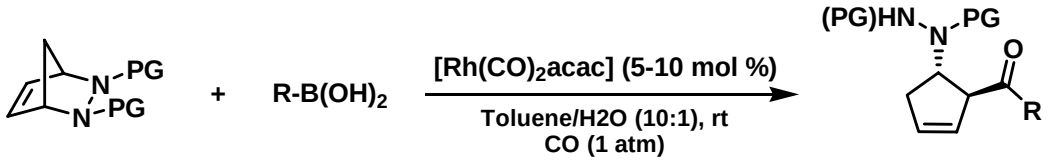


Entry	Product	Yield (%)	%ee
1		92	93
2		91	91
3		75	94
4		81	92
5		90	90
6		88	96

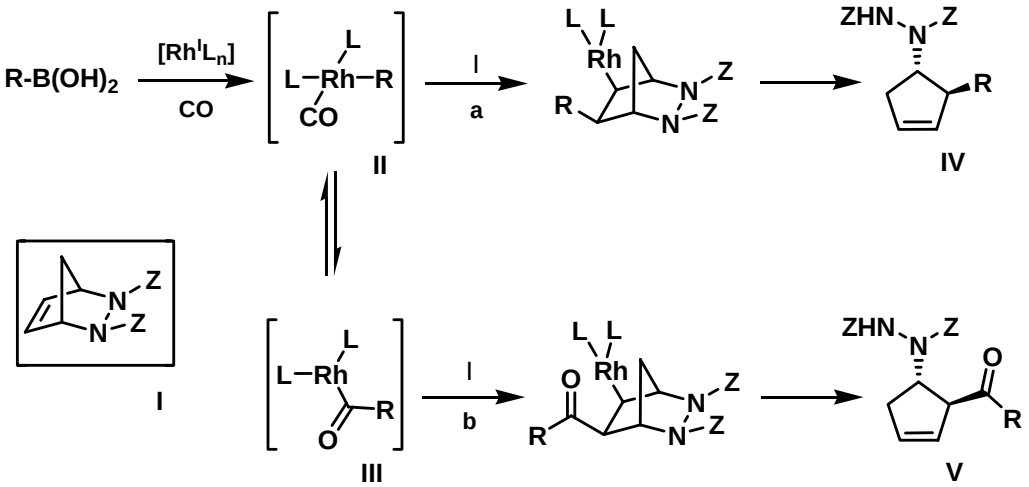
Leong, P.; Lautens, M. *J. Org. Chem.* **2004**, *69*, 2194-2196.

Rhodium Chemistry

9. Rhodium-Catalyzed carbonylative ring opening of diazabicycles with acyl anion



Proposed ring opening with acyl rhodium species

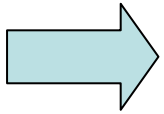


Optimisation of the ring opening with benzoyl anion

Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	$[Rh(CO)_2acac]$	CH_2Cl_2	72	74
2	$[Rh(CO)_2acac]$	Toluene	20	70
3	$[Rh(CO)_2acac]$	Tol./H2O	20	95
4	$[Rh(CO)_2Cl]_2$	Tol./H2O	20	92
5	$[Rh(cod)Cl]_2$	Tol./H2O	20	95
6	$[Rh(cod)OH]_2$	Tol./H2O	20	91
7	$[Rh(cod)_2]Otf$	Tol./H2O	20	4

Menard, F.; Weise, C. F.; Lautens, M. *Org. Lett.* **2007**, *9*, 5365-5367.

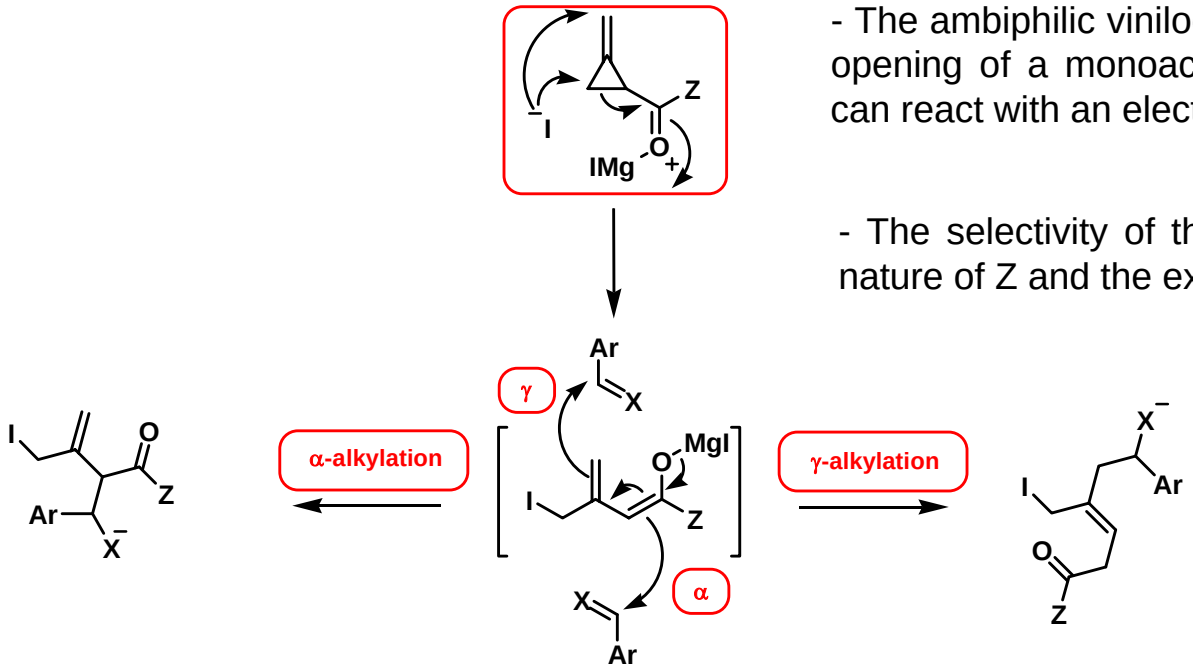
Some Current Topics of Research



1- Indoles Synthesis :	**Agnès and Sridhran**
2- Modified Catellani's Reaction:	**Marc and Christophe**
3- Rhodium Chemistry:	**Raphaël, Romain and Sébastien**
4- Cyclopropanes Chemistry:	**Thomas and Corinne**
5- Oxa- and Azabicycles Ring Opening:	**Marie-Alice, Mathieu and Aurélie**

Methylenecyclopropanes (MCP)

1- Reactivity of Methylenecyclopropane :



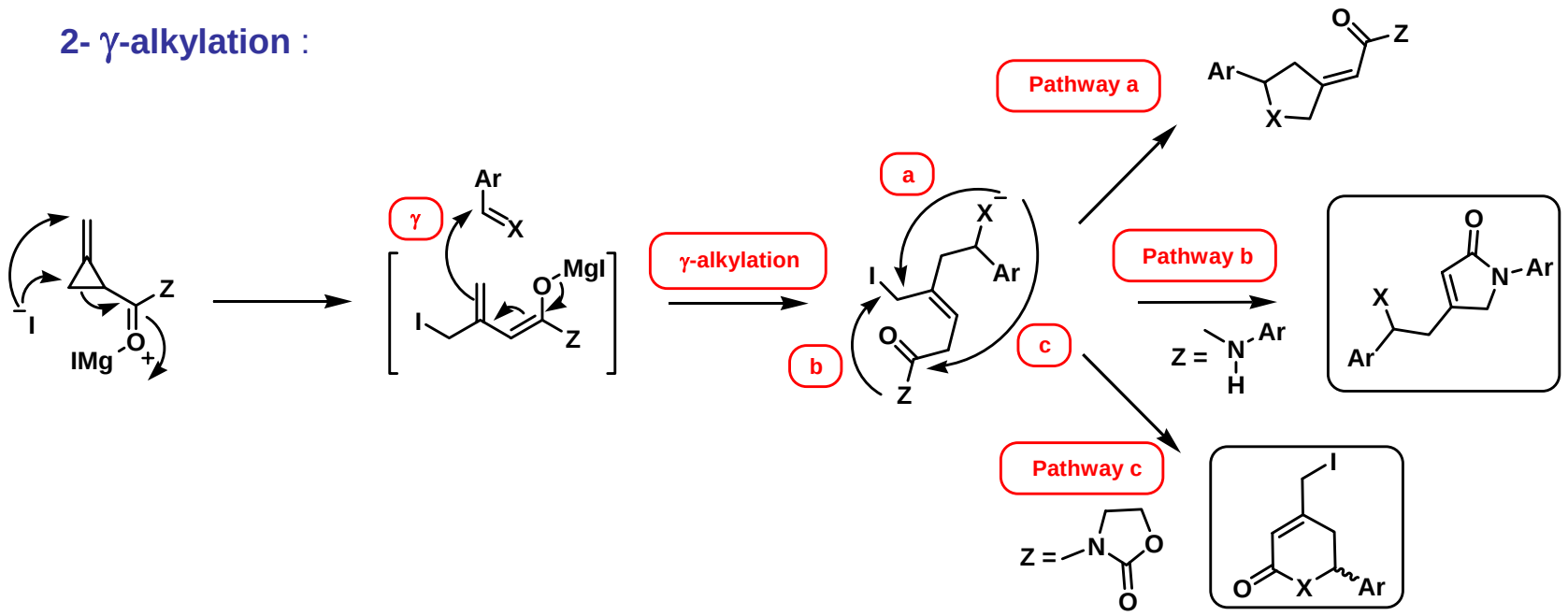
- The ambiphilic vinilogous enolate is generated by the opening of a monoactivated MCP, using MgI_2, which can react with an electrophilic compound.

- The selectivity of the alkylation is controlled by the nature of Z and the experimental conditions.

Lautens, M.; Wooseok, H. *J. Am. Chem. Soc.* **2002**, *124*, 6312-6316.

Methylenecyclopropanes (MCP)

2- γ-alkylation :



The two only products obtained by a γ-alkylation are **b** and **c**:

- For the **pathway b**, the Aryl group (on the amide) acidified the N-H bond that participates in the cyclization.

- For the **pathway c**, the facility of the cyclization can be attributed to the presence of a good leaving group.

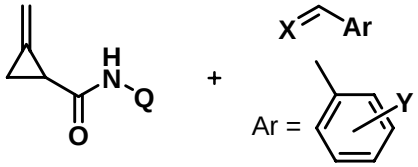
Lautens, M.; Wooseok, H. Liu, J. *J. Am. Chem. Soc.* **2003**, *125*, 4028-4029.

Lautens, M.; Wooseok, H. *J. Am. Chem. Soc.* **2002**, *124*, 6312-6316.

Methylenecyclopropanes (MCP)

2- γ-alkylation (examples) :

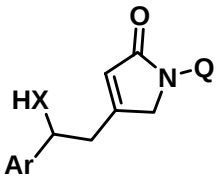
Pathway b



MgI_2 (1.1 eq)

THF (0,1 M)
reflux

0.5-2 h



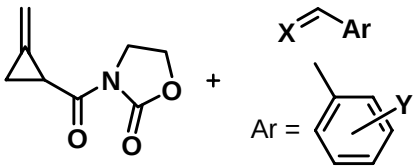
Yields = 45-95 %

Q = Py, Ph, Pyrimidine, isoxazole

Y = Br, Me, CF_3, H, OMe

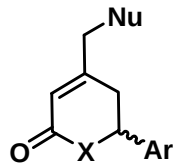
X = N-Ts, O

Pathway c



1. MgI_2 (1.1 eq)
   THF (0.05 M)
   0°C-Ta
2. work-up
3. Nu (5 eq)
   Acetone
   Ta

1-3 h



Yields = 65-88 %

Y = Br, NO_2, Cl, Me, CF_3, H, OMe

X = N-Ts, O

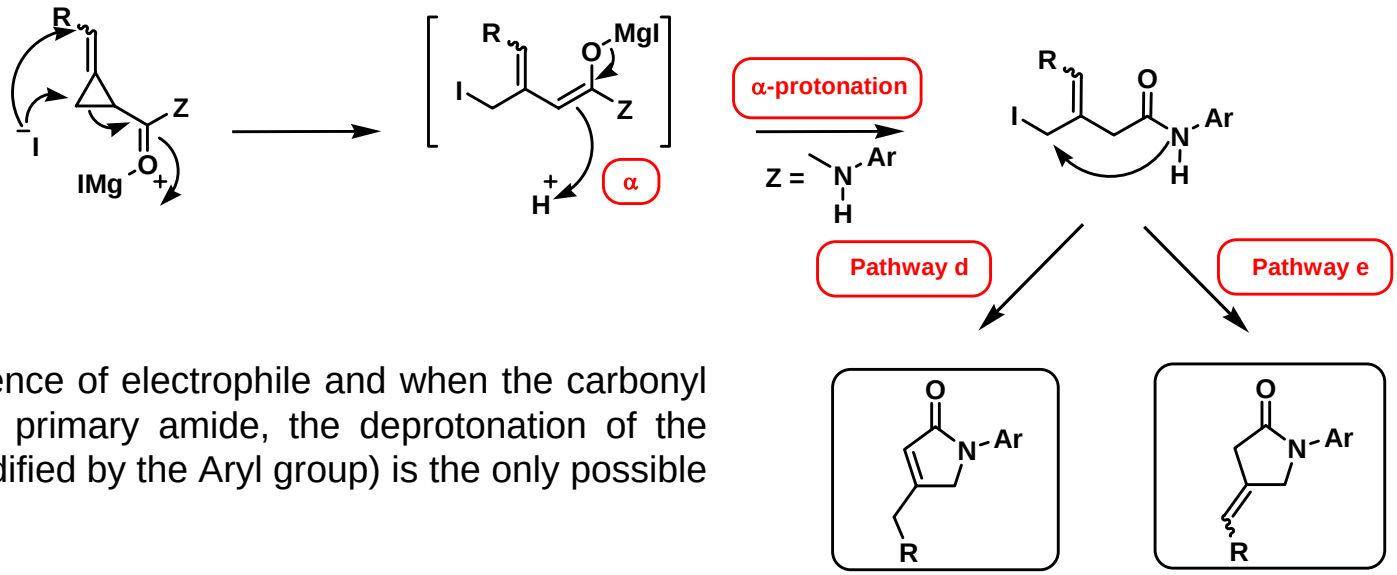
Nu = N_3, Ts, OAc, SPh

Lautens, M.; Wooseok, H. *J. Am. Chem. Soc.* **2002**, *124*, 6312-6316.

Lautens, M.; Wooseok, H. Liu, J. *J. Am. Chem. Soc.* **2003**, *125*, 4028-4029.

Methylenecyclopropanes (MCP)

3- α-protonation :



In the absence of electrophile and when the carbonyl group is a primary amide, the deprotonation of the amide (acidified by the Aryl group) is the only possible reaction.

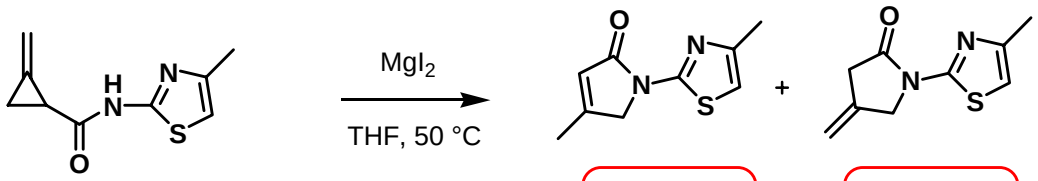
The nature of the Aryl group, the experimental conditions and the nature of R, control the ratio of the endo or exocyclic double bond product.

Scott, M.; Schwarz, C.; Lautens, M. *Org. Lett.* **2006**, *8*, 5521-5524.

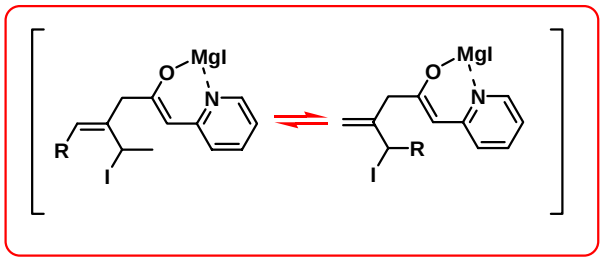
Lautens, M.; Wooseok, H. Liu, J. *J. Am. Chem. Soc.* **2003**, *125*, 4028-4029.

Methylenecyclopropanes (MCP)

3- γ-protonation (examples) :

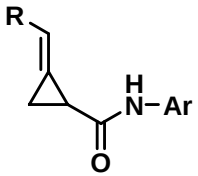


MgI_2	Concentration	Yields	Ratio d/e
1.0 eq	0.1 M	75 %	6.3:1
0.2 eq	0.05 M	91 %	<1:10
0.2 eq	0.005	98 %	<1:20



The presence of *o*-Nitrogen atom of the Aryl group appeared to play a crucial role in the ring expansion process.

Pathway e



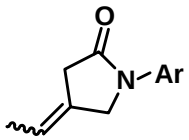
Ar = o-Py, o-Pyrimidine, o-derivatives Py

R = H, Me, Bn, Cy, Dimethyl

MgI_2 (0.2 eq)

THF (0.004 M)
50°C

12-60 h



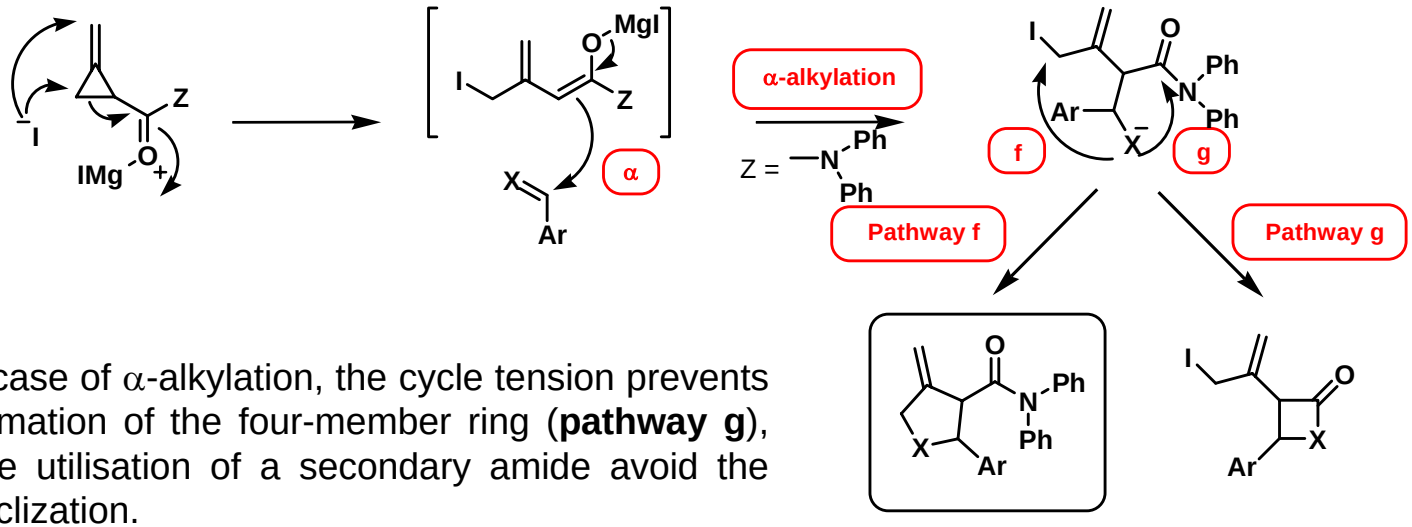
Yields = 45-99 %
d/e = <1:20

Scott, M.; Schwarz, C.; Lautens, M. *Org. Lett.* **2006**, *8*, 5521-5524.

Lautens, M.; Wooseok, H. Liu, J. *J. Am. Chem. Soc.* **2003**, *125*, 4028-4029.

Methylenecyclopropanes (MCP)

4- α-alkylation :



In the case of α-alkylation, the cycle tension prevents the formation of the four-member ring (**pathway g**), and the utilisation of a secondary amide avoid the aza-cyclization.

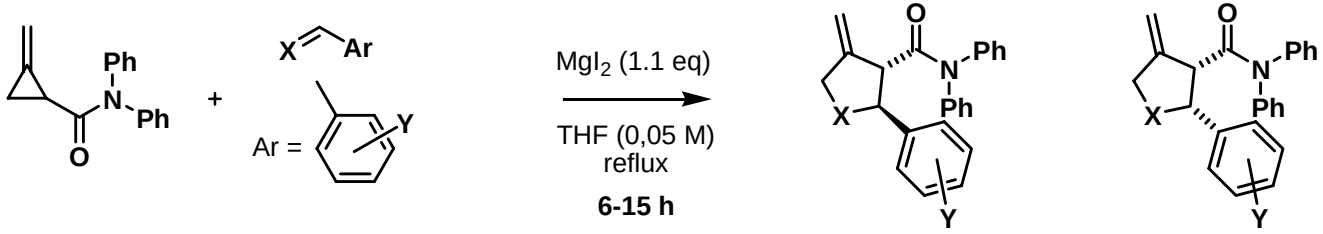
The intermediate can only lead to the five-member ring product, by the substitution of the iodide atom by the X atom (**pathway f**).

Lautens, M.; Wooseok, H. *J. Am. Chem. Soc.* **2002**, *124*, 6312-6316.

Methylenecyclopropanes (MCP)

4- α-alkylation (examples) :

Pathway f



Y = NO_2, Br, Me, CF_3, H, OMe

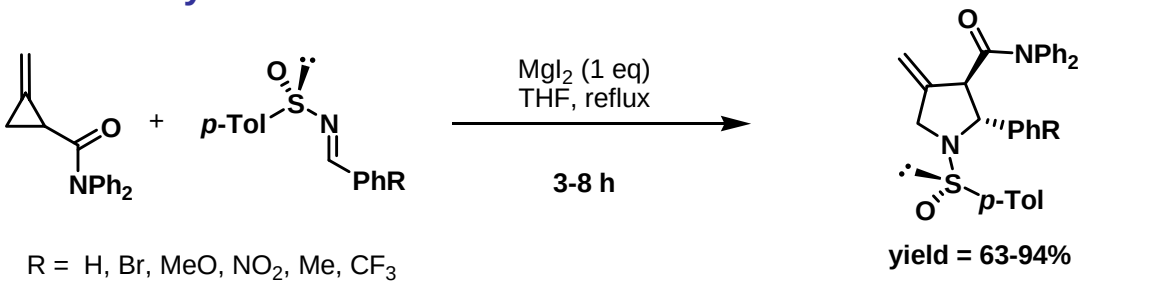
X = N-Ts, N-Bs

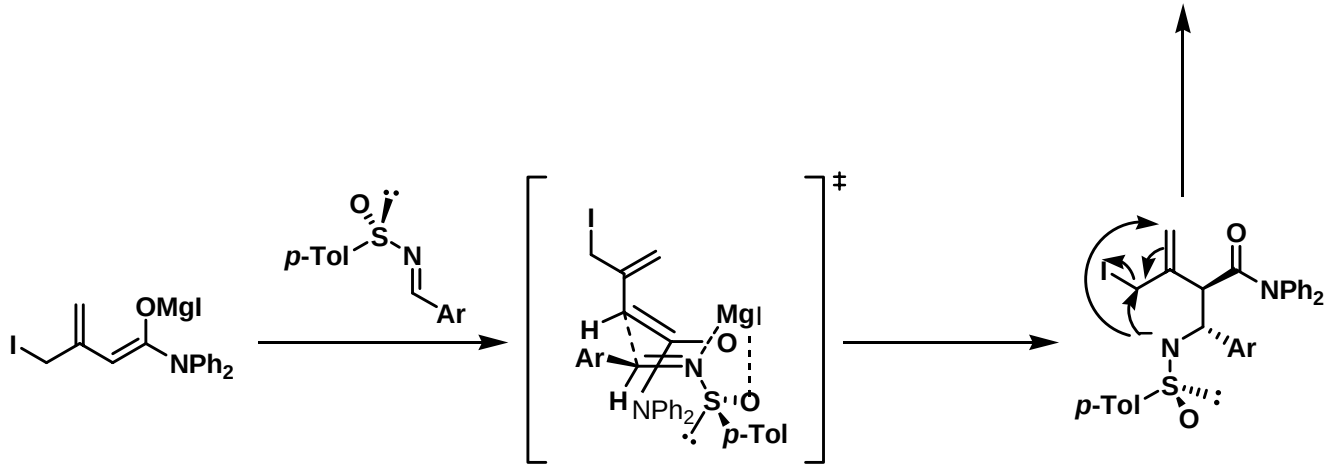
Yields = 65-85 %
dr = 1.6:1->20:1

Lautens, M.; Wooseok, H. *J. Am. Chem. Soc.* **2002**, *124*, 6312-6316.

Methylenecyclopropanes (MCP)

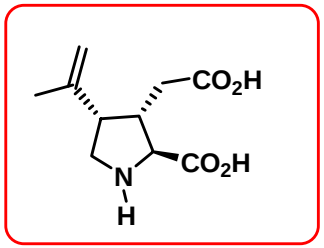
5- Diastereoselective α-alkylation



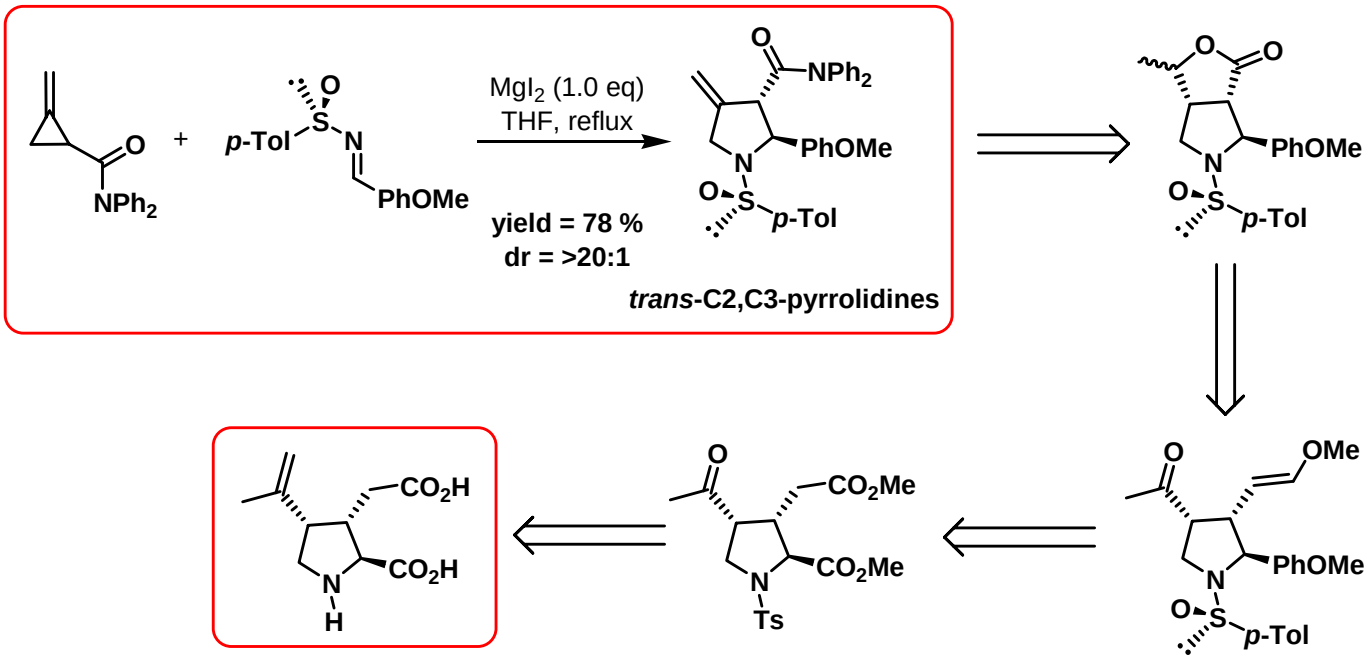


Scott, M. E.; Han, W.; Lautens, M. *Org. Lett.* **2004**, *6*, 3309-3312.

Methylenecyclopropanes (MCP)



6- Total synthesis of (-)-(α)-Kainic Acid : kainoid amino acids : neuroexcitant compounds used in the study of Huntington's chorea and Alzheimer's disease
analogues of glutamic acid
trans-C2,C3/*cis*-C3,C4 pyrrolidine core

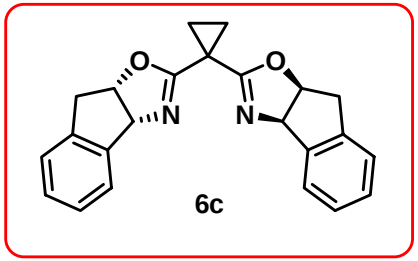


Diastereoselective synthesis of (-)-(α)-kanaic acid in 13 steps with an overall yield of 15 %

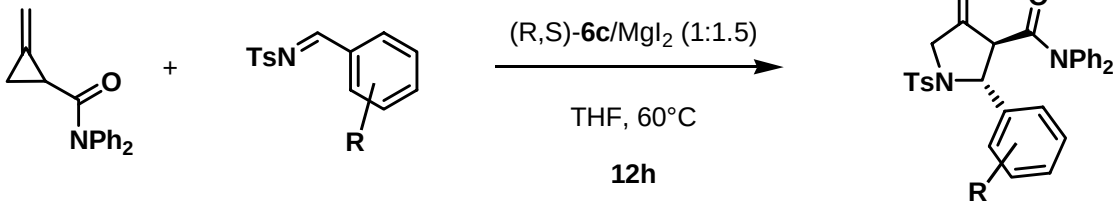
Scott, M. E.; Lautens, M.; *Org. Lett.* **2005**, *7*, 3045-3047.

Methylenecyclopropanes (MCP)

7- Enantioselective α-alkylation



6c



R = CF_3, Br, 2,4-dichloro, 2,4-dimethyl, OMe, 3,4-O-CH_2-O, 4-OAc, Ph, 2-pyridine

yield = 52-92 %

ee = 47-86 %

Strategy based on the use of chiral magnesium complex

The availability of either enantiomer of the ligand enable the synthesis of the either enantiomer of the target molecule

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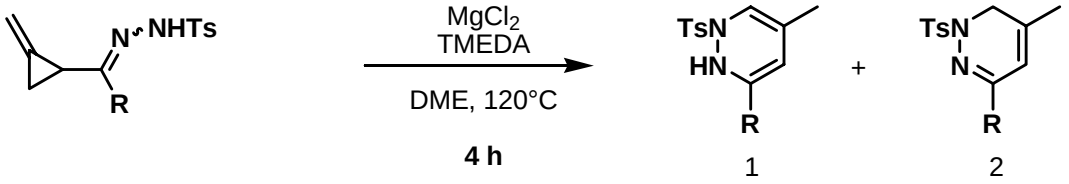
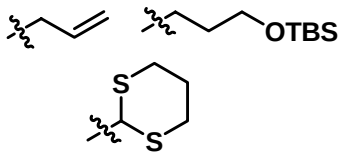
Taillier, C.; Lautens, M. *Org. Lett.* **2007**, *9*, 591-593.

Methylenecyclopropanes (MCP)

8- Synthesis of cyclic diazadienes



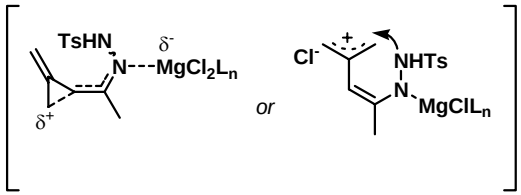
R = Me, Et, Bn, Bu,Ph, 2-Furyl,



yield = 68-93 %

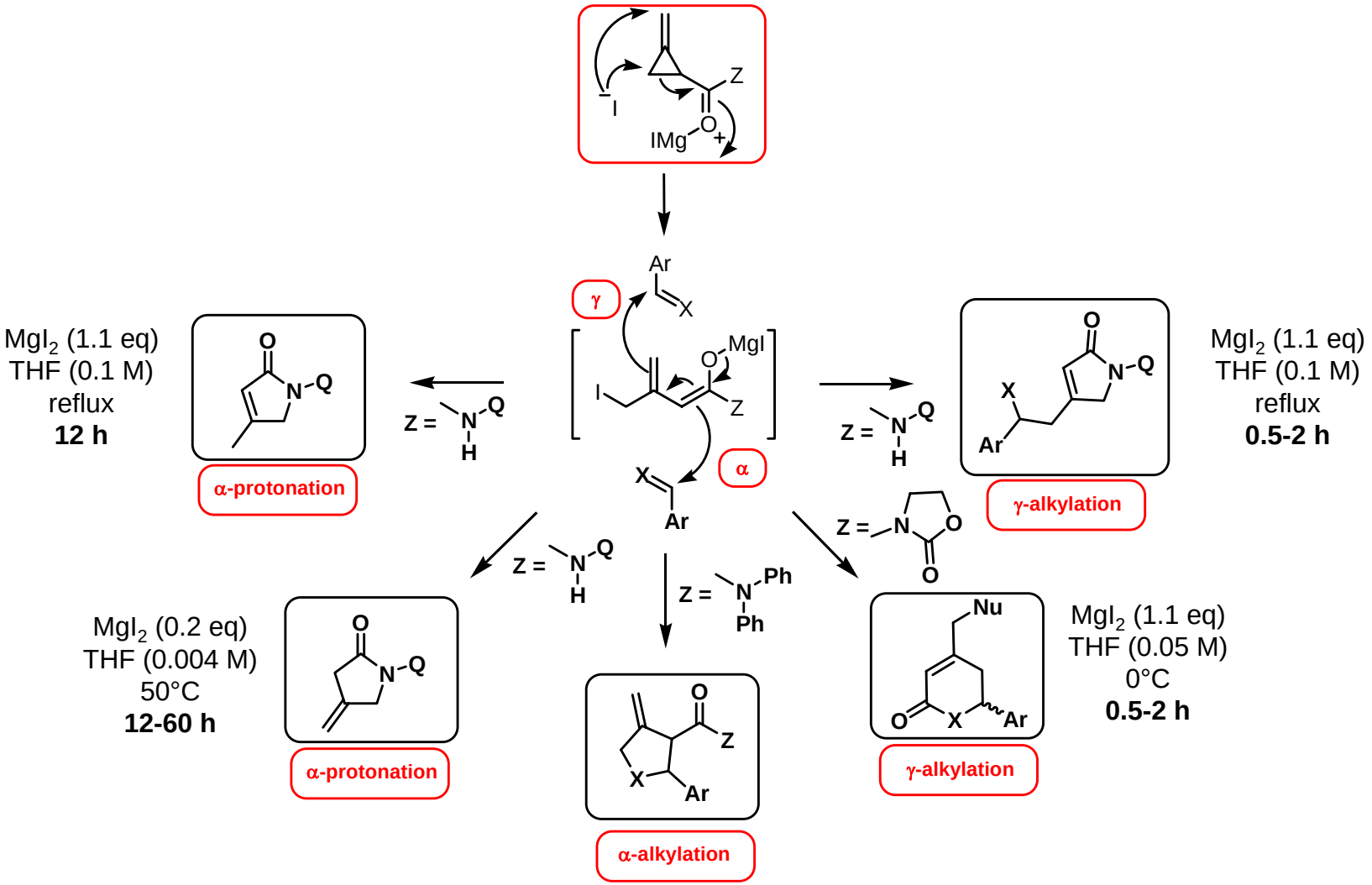
1:2
5:1->20:1

Proposed reaction intermediates :



Scott, M. E.; Bethuel Y.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 1482-1483.

Methylenecyclopropanes (MCP)

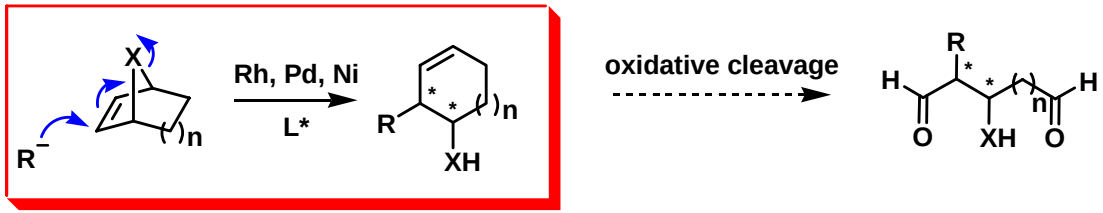


Some Current Topics of Research

1- Indoles Synthesis :	**Agnès and Sridhran**
2- Modified Catellani's Reaction:	**Marc and Christophe**
3- Rhodium Chemistry:	**Raphaël, Romain and Sébastien**
4- Cyclopropanes Chemistry:	**Thomas and Corinne**
5- Oxa- and Azabicycles Ring Opening:	**Marie-Alice, Mathieu and Aurélie**

Oxa- and Azabicycles Ring Opening

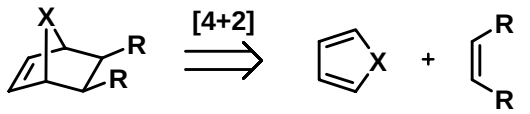
1- General Scheme of the Reaction :



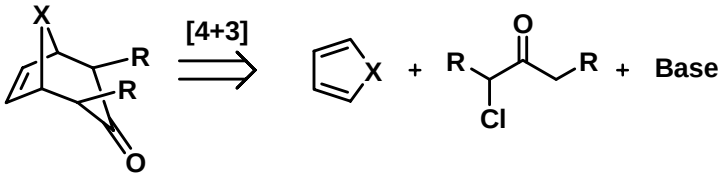
X=O, NR' n=1, 2 R=hydride, alkyl, aryl, heteroatom

2- Synthesis of Oxa and Aza Bicyclic Alkenes

[2.2.1] oxa or aza bicyclic alkenes



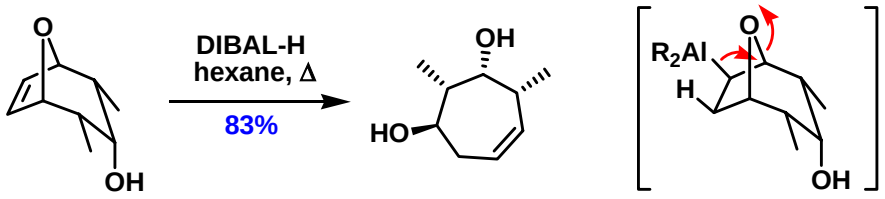
[3.2.1] oxa or aza bicyclic alkenes



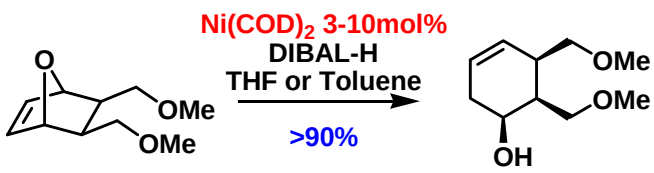
[4+3]: Lubineau, A.; Bouchain, G. M. *Tetrahedron Lett.* **1997**, *38*, 8031-8032.

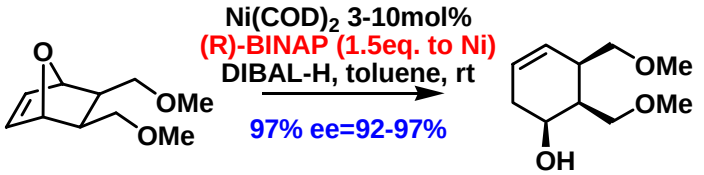
Oxa- and Azabicycles Ring Opening
(1) Ni-Catalyzed Reactions

1.1- Ring Opening with a Hydride Nucleophile :



1.2- Asymmetric Reductive Ring-Opening





⇨ better yields

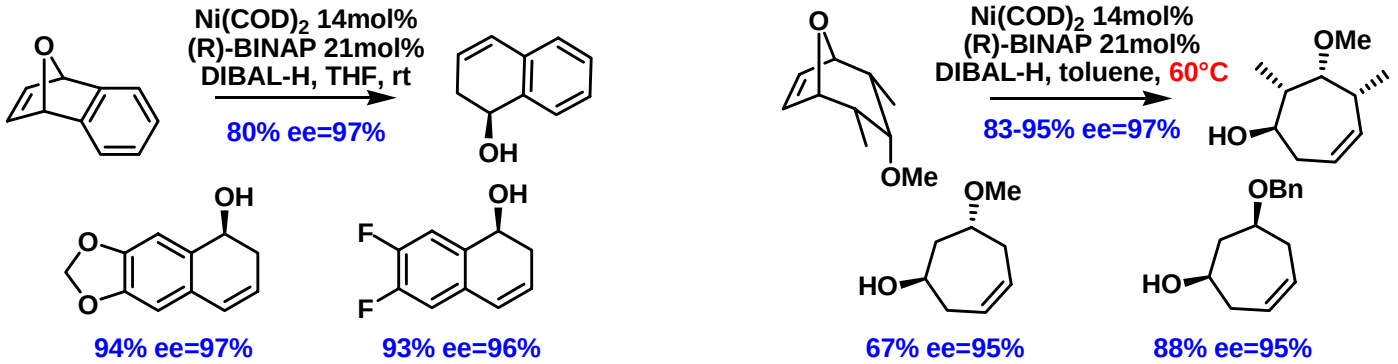
⇨ asymmetric version ?

For good enantioselectivity, DIBAL-H must be added slowly

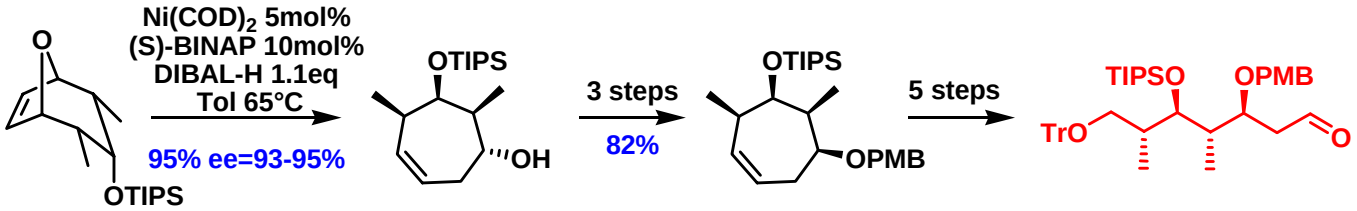
Lautens, M.; Ma, S.; Chiu, P. *J. Am. Chem. Soc.* **1997**, *119*, 6478-6487.
Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48-58.

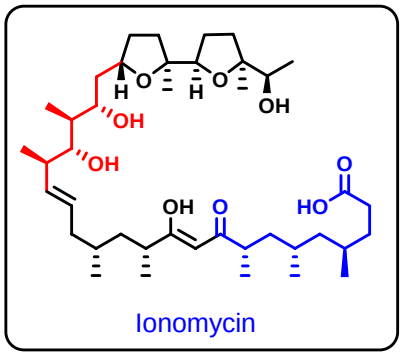
Oxa- and Azabicycles Ring Opening
(1) Ni-Catalyzed Reactions

1.3- Scope :



1.4- Application

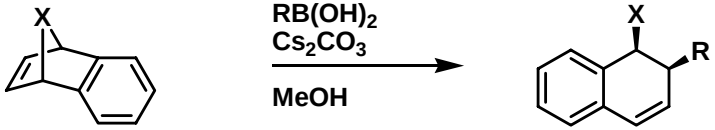




Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48-58.
Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879-1882.

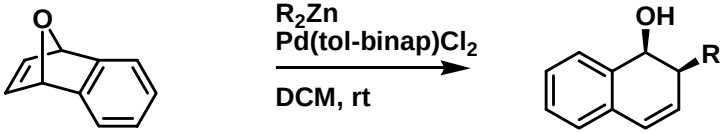
Oxa- and Azabicycles Ring Opening
(2) Pd-Catalyzed Alkylative Ring Opening

2.1- Addition of boronic acid



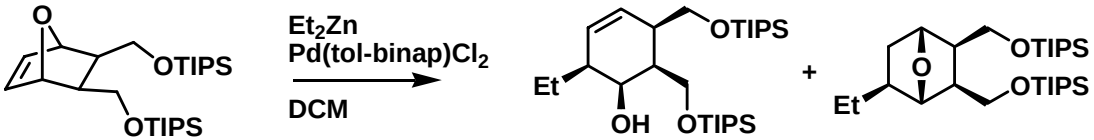
Entry	X	Catalyst	$RB(OH)_2$	Yield (%)
1	O	$Pd(DPPP)Cl_2$	2-OMePh	74
2	O	$[Pd(tol\text{-}binap)OH]_2^{2+}OTf^-_2$	3-furyl	82
3	NHBoc	$Pd(DPPP)Cl_2$	2-OMePh	93
4	NHBoc	$Pd(DPPP)Cl_2$	3-furyl	94

2.2- Addition of dialkylzinc



R= Bu, i-Pr, Bn

35-84%, 82-96%ee



Ring Opening product I

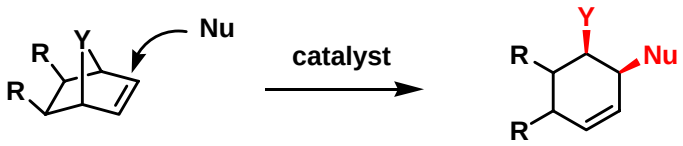
Transmetallation product II

Entry	Conditions	Ratio I:II
1	rt	1.5:1
2	reflux	3:1
3	reflux, $Zn(OTf)_2$	3.5:1

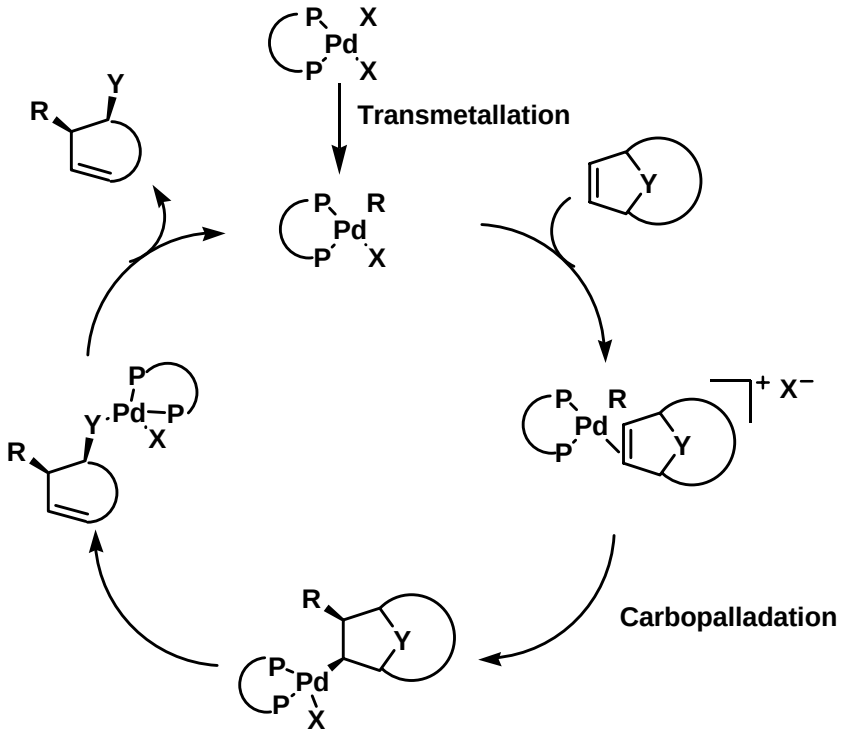
Lautens, M.; Dockendorff, C. *Org. Lett.* **2003**, *5*, 3695-3698.
Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437-1447.

Oxa- and Azabicycles Ring Opening
(2) Pd-Catalyzed Mechanism

2.3- General scheme



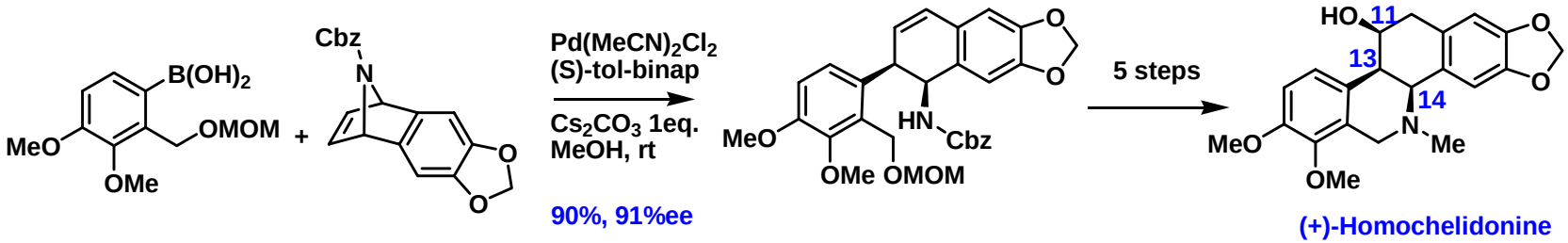
2.4- Catalytic cycle



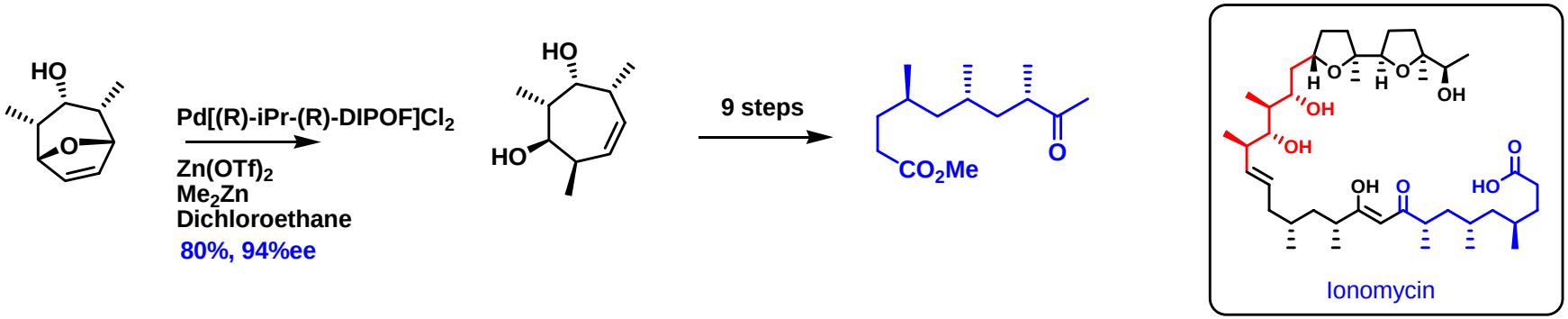
Lautens, M.; Dockendorff, C. *Org. Lett.* **2003**, *5*, 3695-3698.

Oxa- and Azabicycles Ring Opening
(2) Pd-Catalyzed Applications

2.5- Enantioselective total synthesis of (+)-Homochelidonine



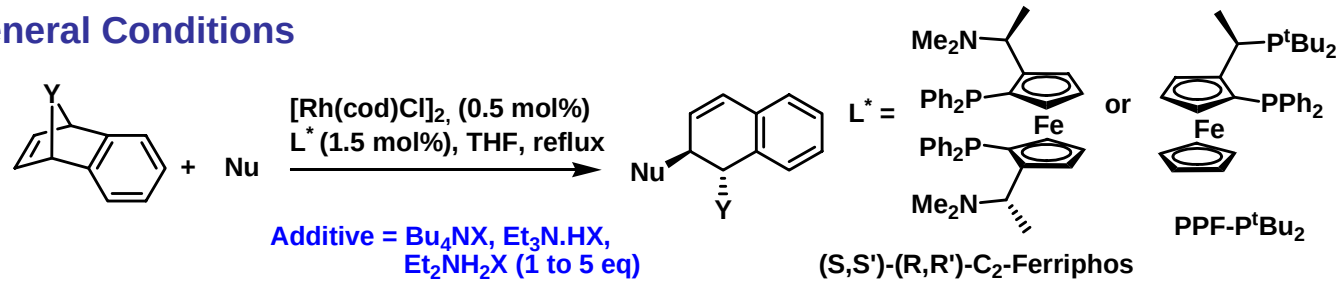
2.6- Total synthesis of Ionomycin



McManus, H. A.; Fleming, M. J.; Lautens, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 433-436.
Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879-1882.

Oxa- and Azabicycles Ring Opening
(3) Rh-Catalyzed Reactions

3.1- General Conditions



Additive = Bu_4NX, $Et_3N.HX$, Et_2NH_2X (1 to 5 eq)

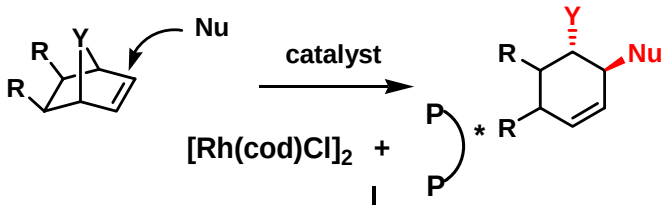
(S,S')-(R,R')-C_2-Ferriphos

Nucleophile	Outcome Without Additive	Outcome With Additive
Alcools and Phenols	>90% Yield >90% ee	>90% Yield >90% ee
Aliphatic Amines	No reaction	>90% Yield >90% ee
Aromatic Amines	>90% Yield 30-74% ee	>90% Yield >90% ee
Carboxylates	>80% Yield 30-60% ee	>70% yield >90%ee
Malonates	<50% yield 50%ee	>70% yield >90%ee

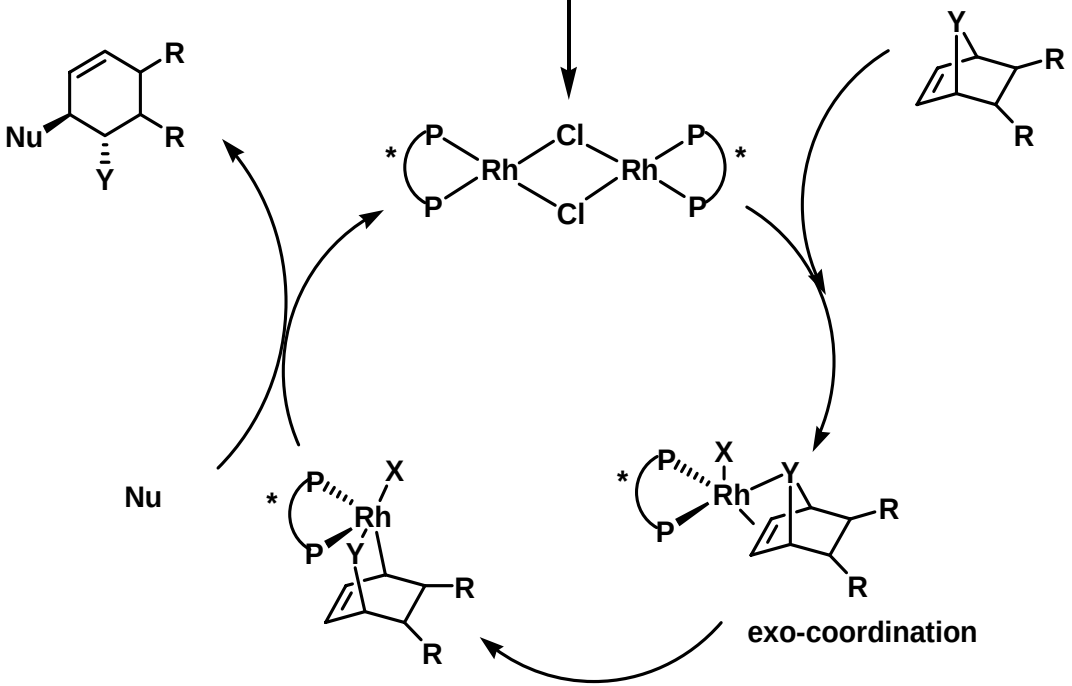
Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 14884-14892.
Cho, Y.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837-6846.
Cho, Y. H.; Fayol, A.; Lautens, M. *Tetrahedron: Asymmetry* **2006**, *17*, 416-427.

Oxa- and Azabicycles Ring Opening
(3) Rh-Catalyzed Mechanism

3.2- General scheme



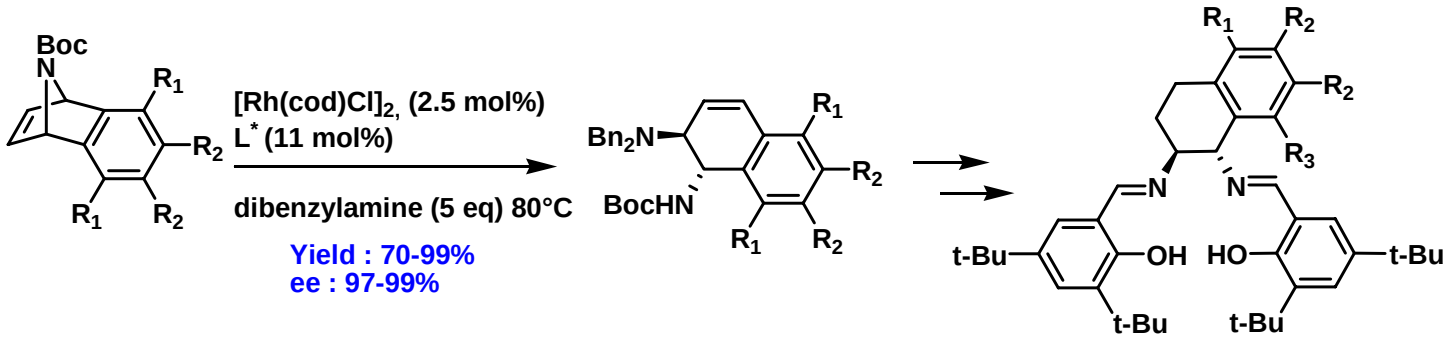
3.3- Catalytic cycle



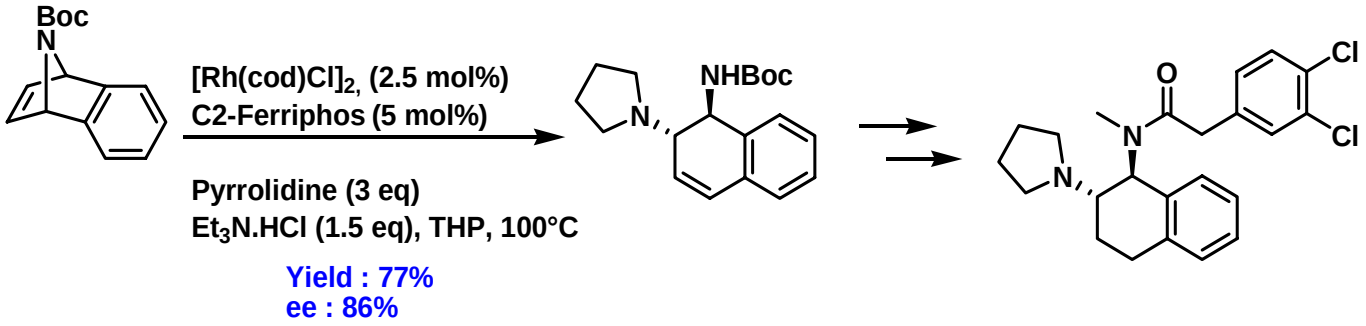
Cho, Y.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837-6846.

Oxa- and Azabicycles Ring Opening
Rh-Catalyzed Applications (3)

3.4- Synthesis of Jacobsen-type salen ligands

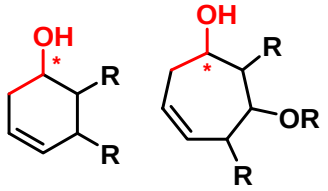


3.5- Enantioselective synthesis of Diaminotetralins (Analgesic compounds)



Cho, Y. H.; Fayol, A.; Lautens, M. *Tetrahedron: Asymmetry* **2006**, *17*, 416-427.
Lautens, M.; Fagnou, K.; Zunic, V. *Org. Lett.* **2002**, *4*, 3465-3468.

Oxa- and Azabicycles Ring Opening

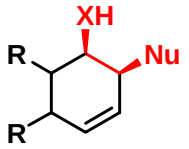


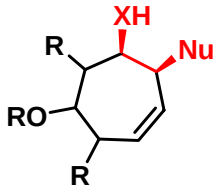
[Ni] /L* cat.

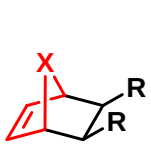
DIBAL-H

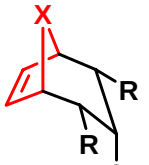
[Pd] / L* cat.

$RB(OH)_2$
R_2Zn

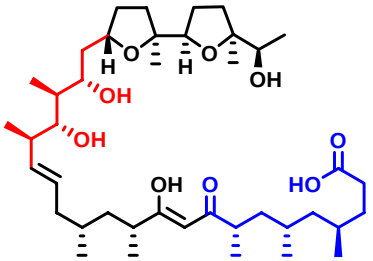




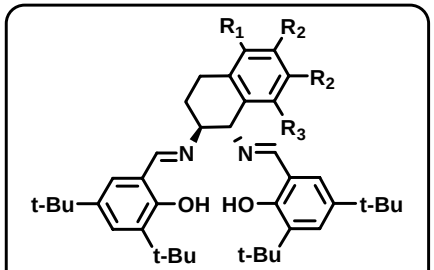




X=O, NR'



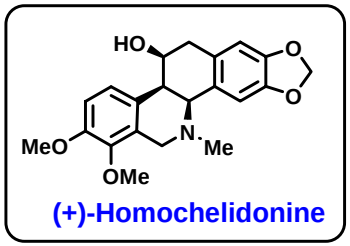
Ionomycin



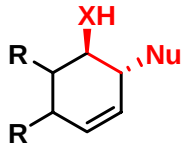
Jacobsen-type salen ligands

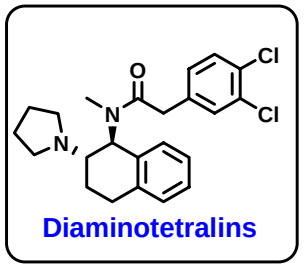
[Rh] /L* cat.

Heteroatom nucleophiles



(+)-Homochelidonine





Diaminotetralins