Chiral allenes :

Enantioselective synthesis of allenes and their use in cyclization reaction

StéRéO bibliographic seminar

Mylène ROUDIER

June, 16th, 2014

- Introduction
  - Generalities
  - History
- Chiral allenes synthesis
  - From achiral starting material
  - From chiral starting material
- Cyclization of allenes
  - Heterocycle formation
  - DFT calculations
  - Epimerization
- Conclusion

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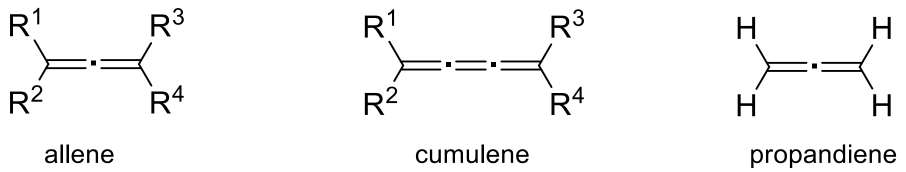
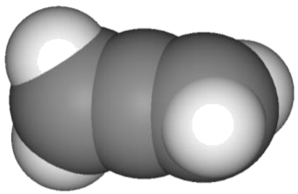
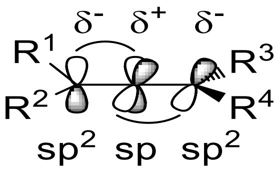
Generalities



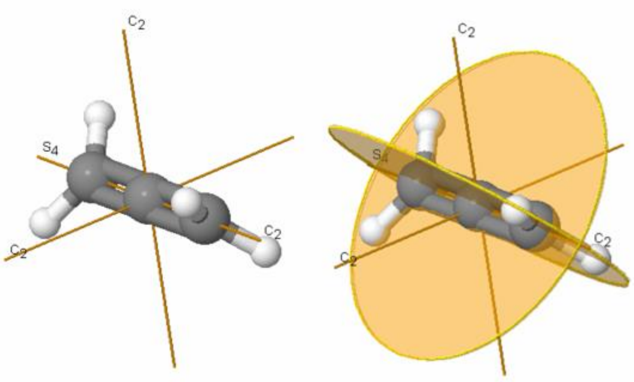
- Allenes classified as polyenes
- Propandiene : the simplest allene
- Compounds with an allene type structure but more than 3C are called cumullene
- More reactive than alkene
- The bond angle formed by the 3 C is 180° => linear geometry



- 2 σ bonds and 2 π bonds

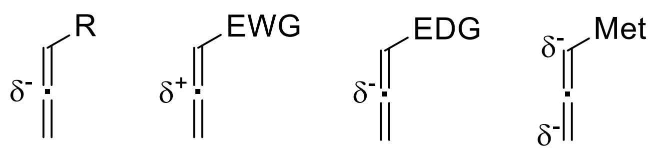


- 3 C_2 axes and 2 symmetric planes

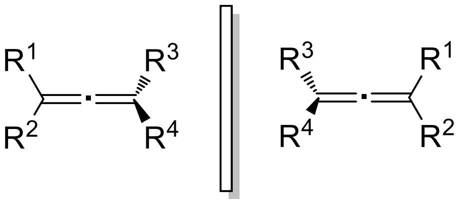


Generalities

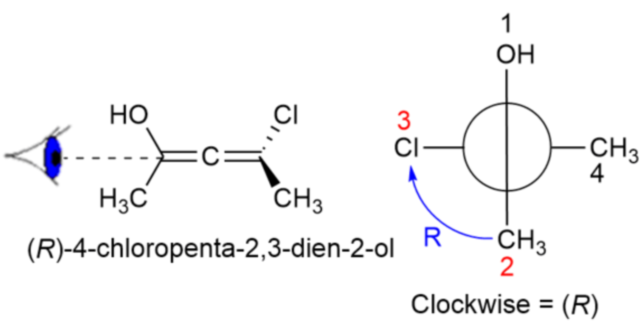
- Changing the substitutes can alter the reactivity => can react as both Nu⁻ and/or E⁺

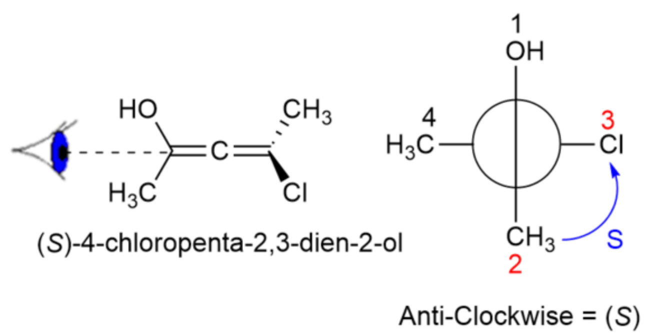


- Chiral if $R^1 \neq R^2$ and $R^3 \neq R^4$.
- Rotation barrier 46 $kcal.mol^{-1}$
- Could be separable under usual conditions



- Determination of the configuration





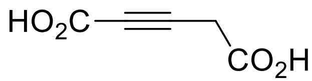
History

Possible existence of two enantiomeric forms

1875 : Van't Hoff

La chimie dans l'espace, **1875**, p.29

History



initial proposal (1887)

"glutinic acid"

Possible existence of two enantiomeric forms

First synthesis of an allene

1875 : Van't Hoff

La chimie dans l'espace, **1875**, p.29

1887 : Burton & Pechmann

Chem. Ber., **1887**, 145

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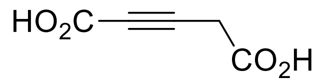
History



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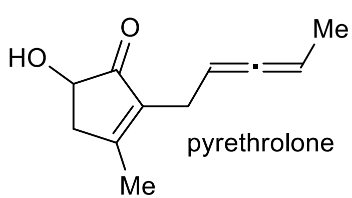
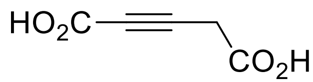


pyrethrolone

History



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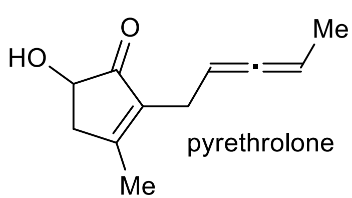

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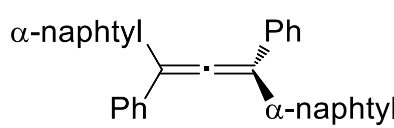
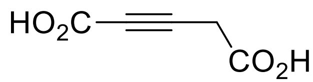


(S)-(+)
1,3-di(α-naphtyl)1,3-diphenylallene

History



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Possible existence of two enantiomeric forms	First synthesis of an allene	Isolation & caracterization of first natural allene	Experimental confirmation of Van't Hoff prediction	Resolution of the racemic allenic carboxylic acid

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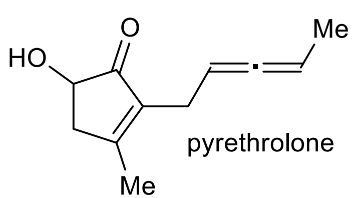

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Nature, **1935**, *135*, 994
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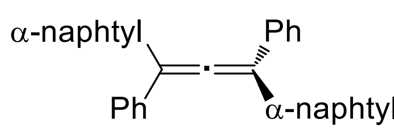

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1935 : Kohler, Walker & Tishler

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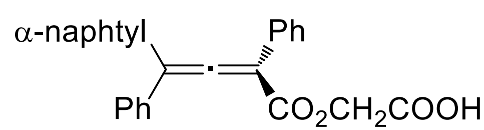

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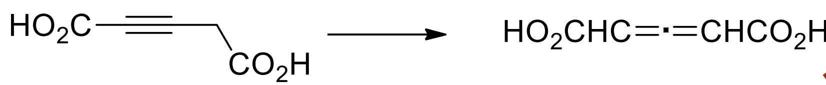

initial proposal (1887) "glutinic acid" revised structure (1954)

Event	Date	Authors	Reference
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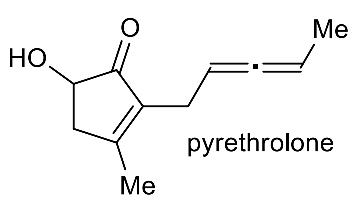
Resolution of the racemic allenic carboxylic acid	1935	Kohler, Walker & Tishler	*JACS*, **1935**, *57*, 1743
Confirmation of the glutinic acid structure	1954	Jones	*J. Chem. Soc.*, **1954**, 3208



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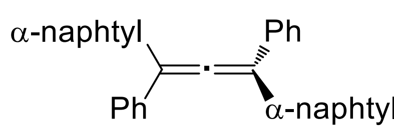

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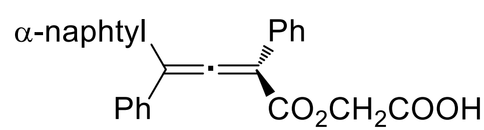

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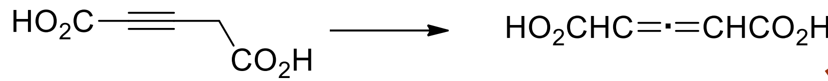

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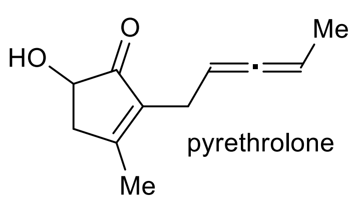
- **1989 : Elsevier** — First example of transition-metal-catalyzed asymmetric synthesis of axially chiral allene. *J. Organomet. Chem.*, **989**, *378*, 115



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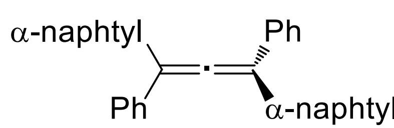

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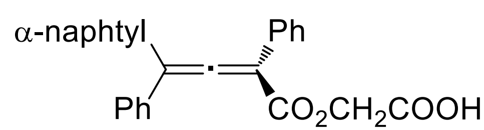

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- From achiral starting material
- From chiral starting material

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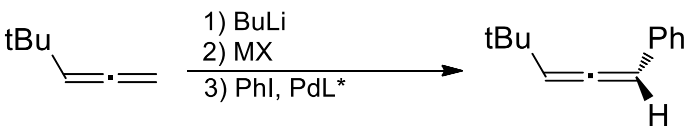
Synthesis of chiral allenes

- Starting from achiral compounds
  - *First example of transition-metal-catalyzed asymmetric synthesis of axially chiral allene*



MX = MgCl, ZnCl, CuCl
PdL* = Pd{(R,R)-diop}$_2$, PdCl$_2${(R,R)-diop}, PdIPh{(R,R)-diop}, PdCl$_2${nmdpp}$_2$

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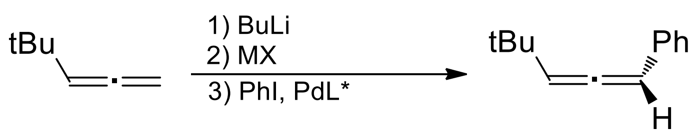

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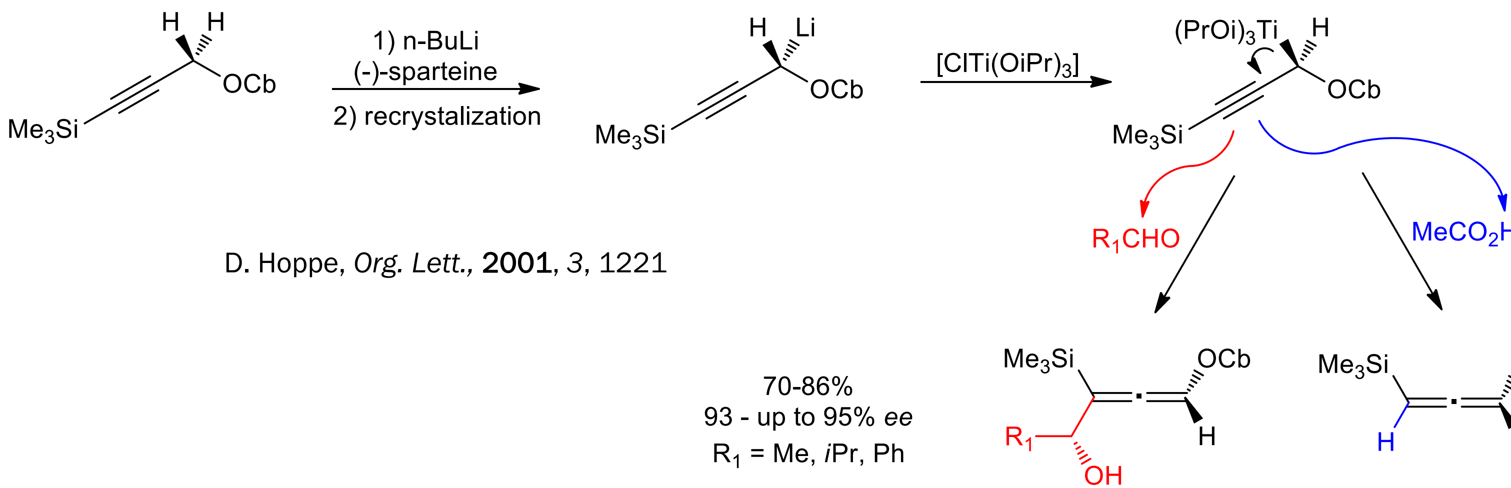
Elsevier, *J. Organomet. Chem.*, **1989**, *378*, 115

- *Deprotonation of prochiral secondary alkynyl carbamates*



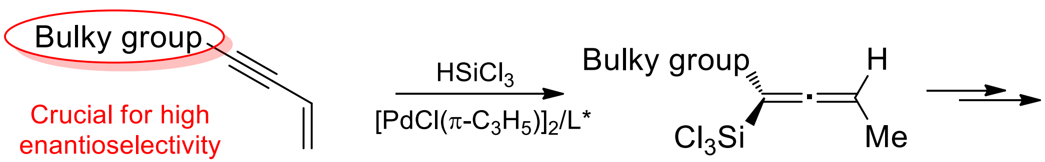
D. Hoppe, *Org. Lett.*, **2001**, *3*, 1221

70-86%
93 - up to 95% *ee*
R_1 = Me, *i*Pr, Ph

86%
88% *ee*

Synthesis of chiral allenes

- Starting from achiral compounds
  - *Sylilation of achiral enyne*



Asymmetric synthesis of homopropargylic alcohols

Bulky groups :
*t*Bu, 2,4,6-$Me_3C_6H_2$, $SiMe_2Bu$-*t*

37-94 % yield
27-90 % ee

L* = (S)-(R)-PPFOMe, (S)-(R)-bisPPFOMe

T. Hayashi, *JACS*, **2001**, *123*, 12915

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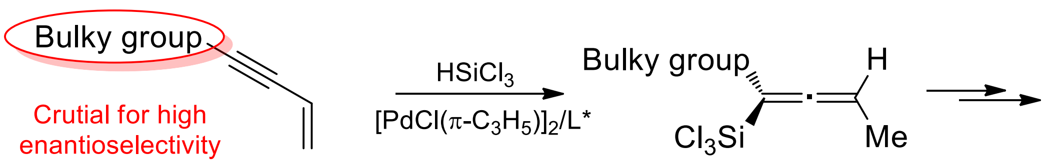

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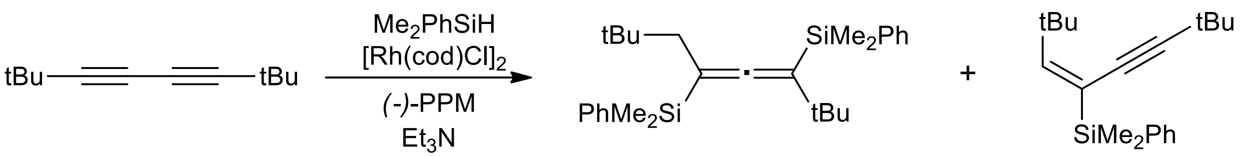
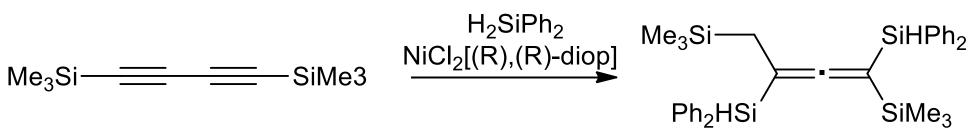
- *Double hydrosylilation of diynes*



27%, 22% *ee*
unknown configuration

56%

M. Michalik, *Tet. Lett.*, **1999**, *40*, 6567



11%, 11% ee
unknown configuration

C. Fischer, *J. Organomet. Chem.*, **2000**, *603*, 116

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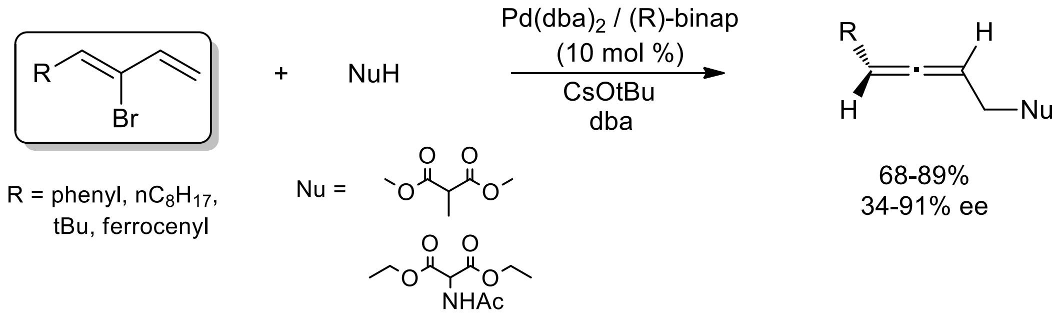
Synthesis of chiral allenes

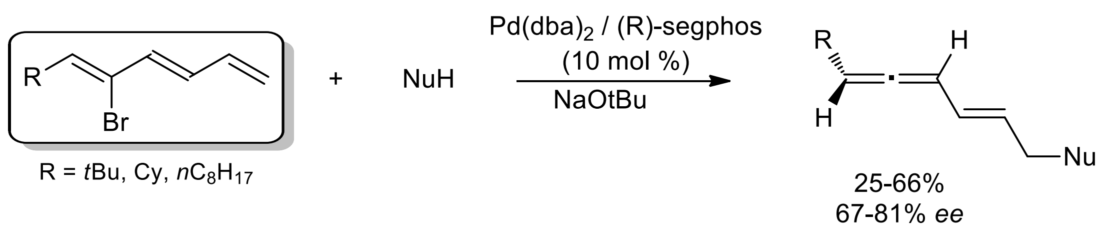
Starting from achiral compounds

- *Pd-catalyzed Sn$_2$' substitution of 2-bromo-1,3-dienes*



T. Hayashi, *Angew. Chem. Int. Ed.*, **2000**, 39, 1042

- *Pd-catalyzed Sn$_2$'' substitution of 2-bromo-1,3,5-trienes*



T. Takashashi, *Org. Lett.*, **2006**, *8*, 5409

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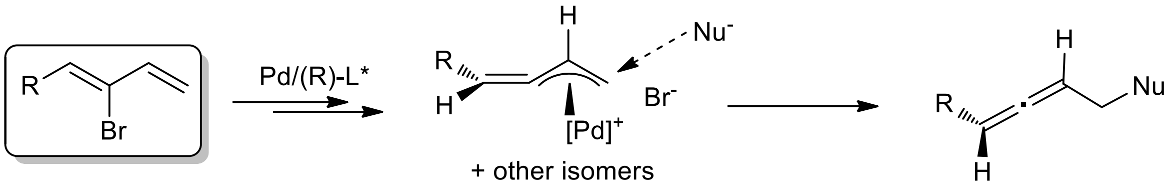

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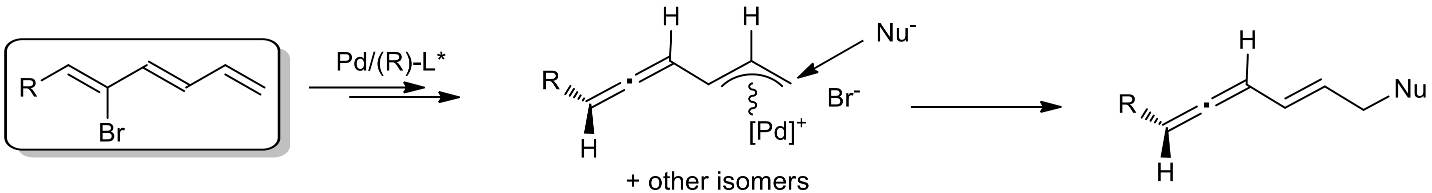
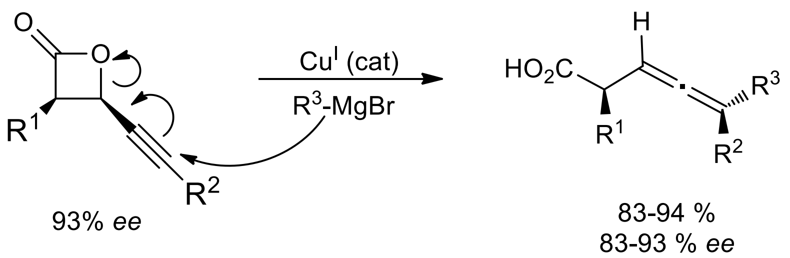


Synthesis of chiral allenes

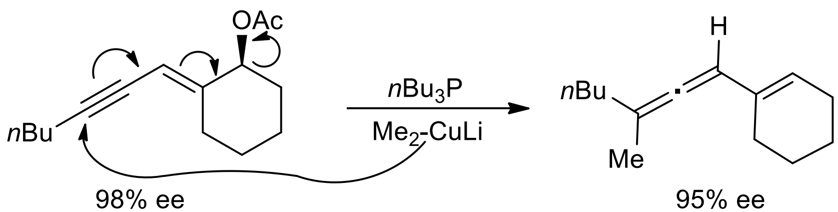
- Starting from chiral compounds
  - *Cu-catalyzed Sn_2' reaction with Grignard reagents*



R^1 = H, Me, Bn
R^2 = CH_2OBn, $SiMe_3$
R^3 = Me, *i*Pr, Ph

S.G. Nelson, *JACS.*, **2000**, *122*, 10470

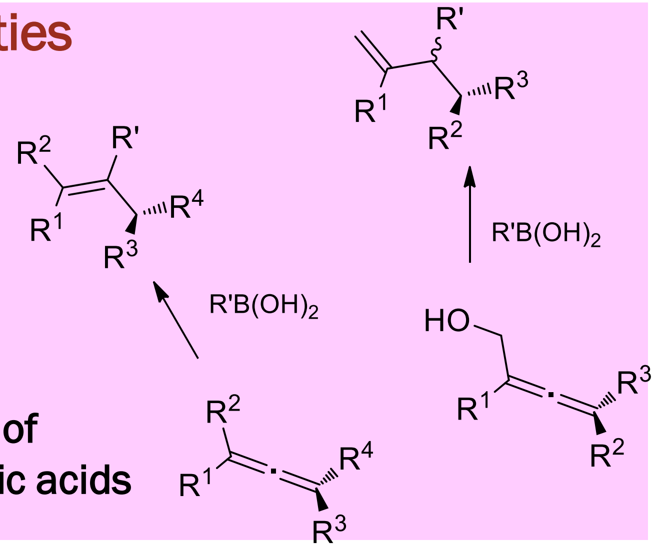
  - *1,5-Sn_2'' substitution of chiral enyne acetates with organocuprates*



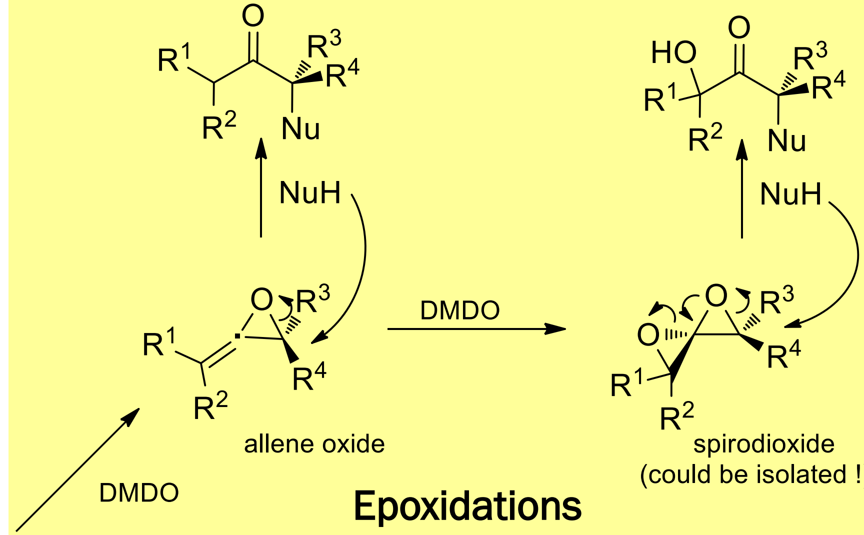
M. Purpuma, *Angew. Chem. Int. Ed.*, **2000**, *39*, 4355

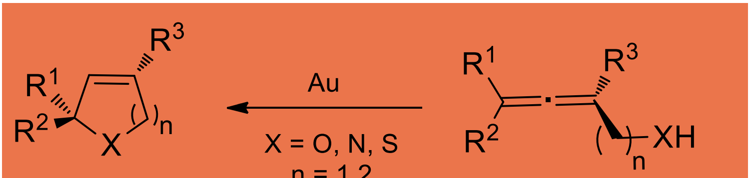
Reactivities

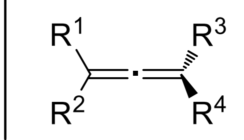
Additions of arylboronic acids



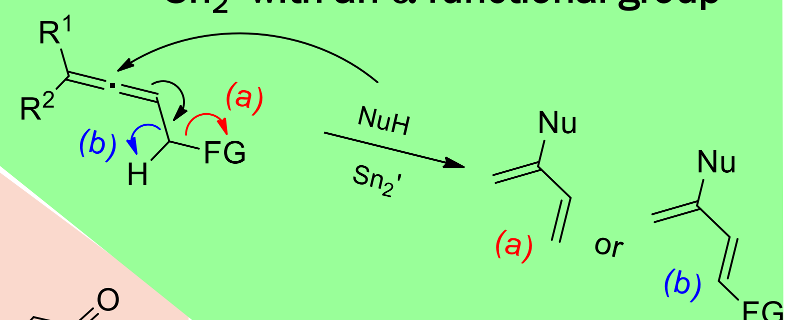
Epoxidations



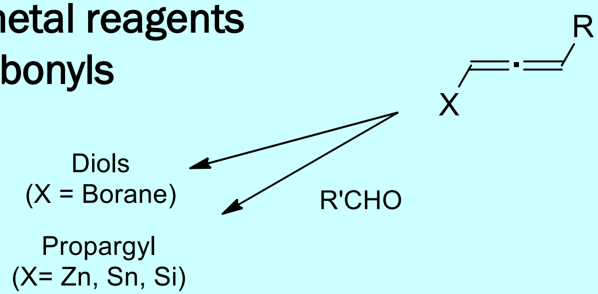


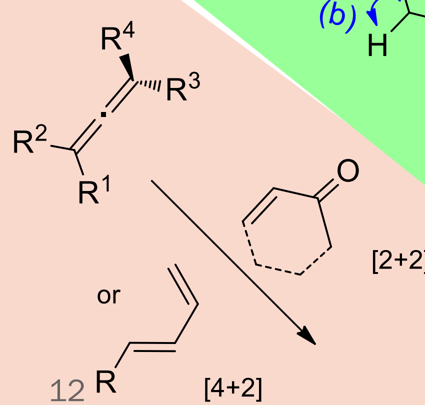


Sn_2' with an α-functional group



Allenylmetal reagents with carbonyls





Cycloadditions

ACIE, **2012**, *51*, 3074

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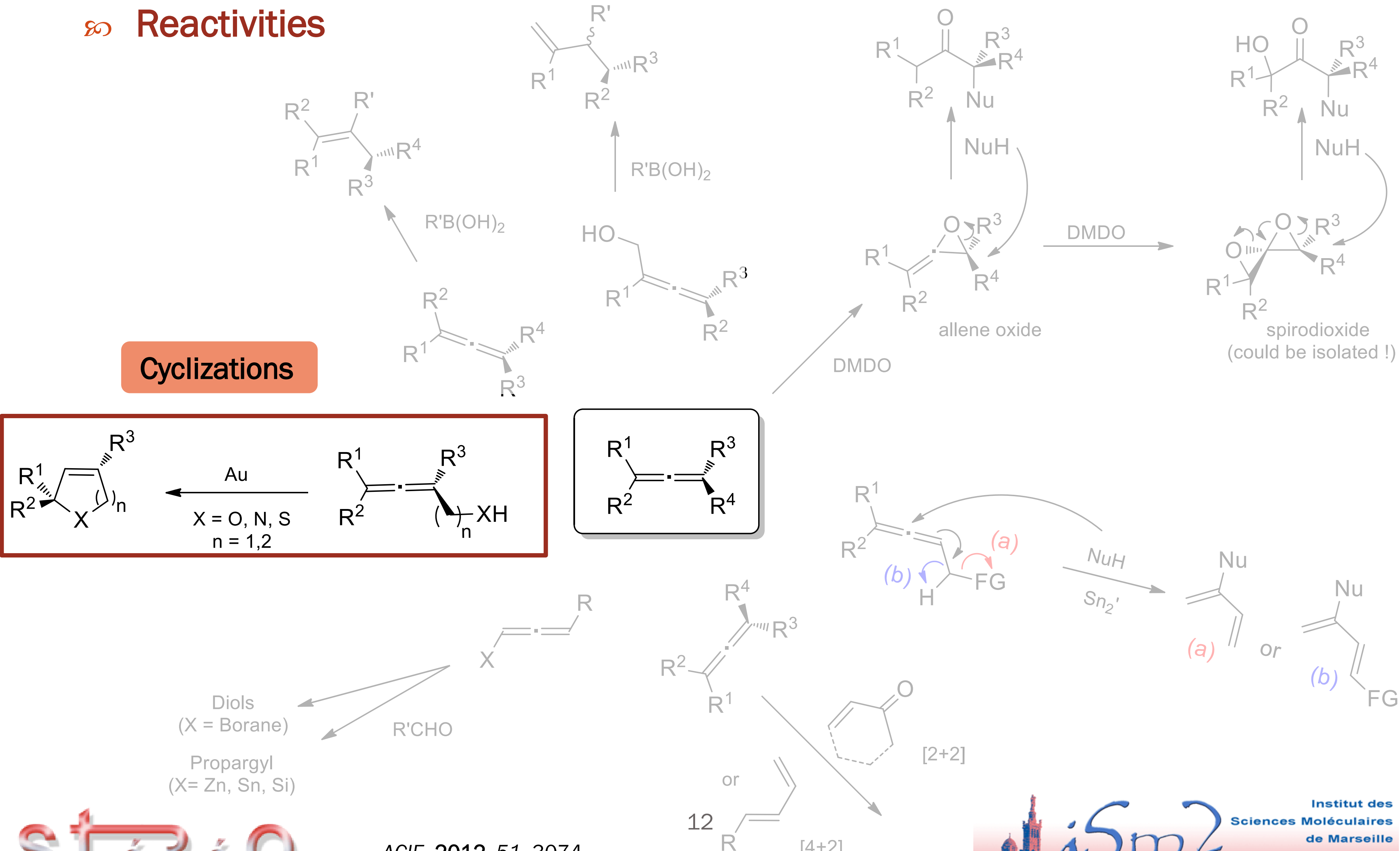
Reactivities

Cyclizations



ACIE, **2012**, *51*, 3074

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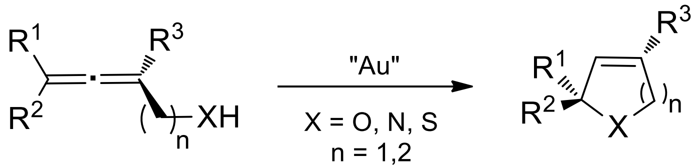
Gold chloride catalyzed cyclization

Why ?

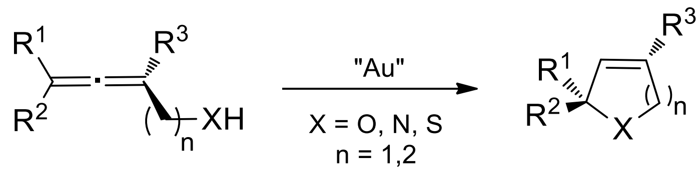
Gold chloride catalyzed cyclization

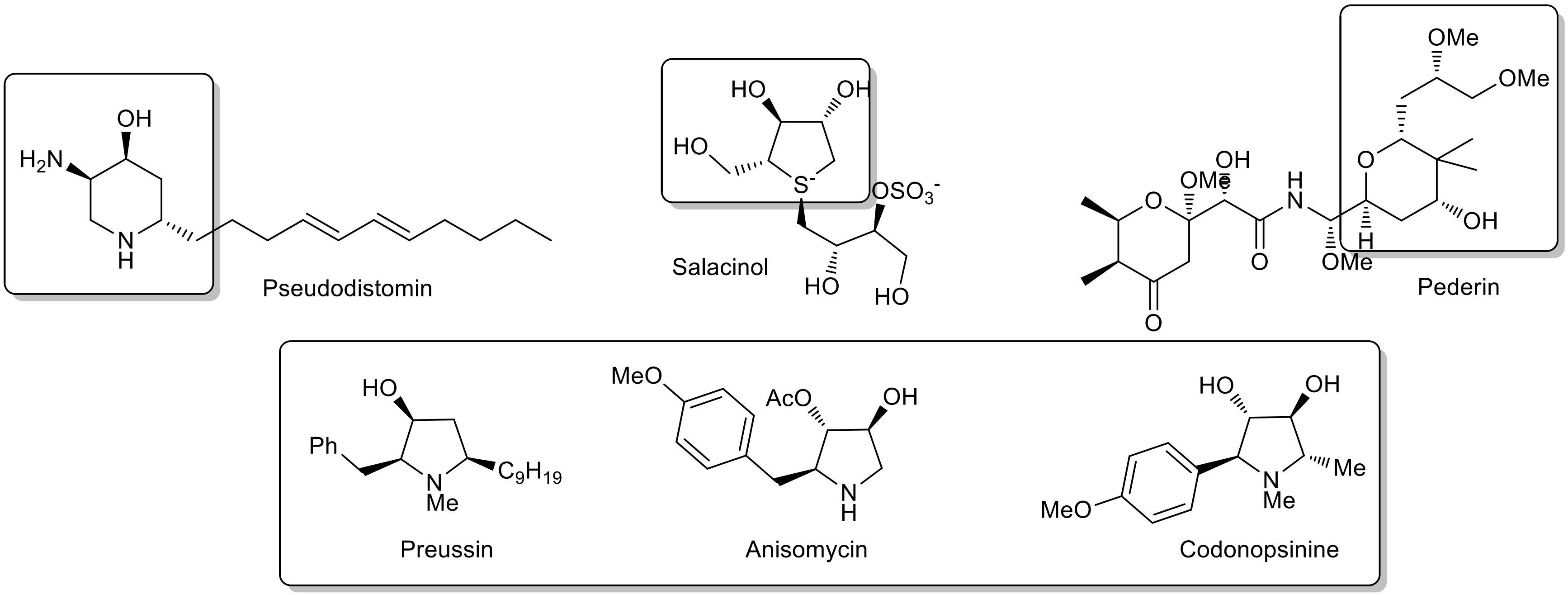
Why ?



Gold chloride catalyzed cyclization

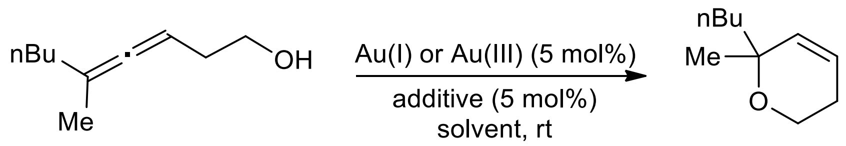
Why ?





Gold chloride catalyzed cyclization of β-hydroxyallenes

- Gockel B. and Krause N., *Org, Lett.*, **2006**, *8*, 4485

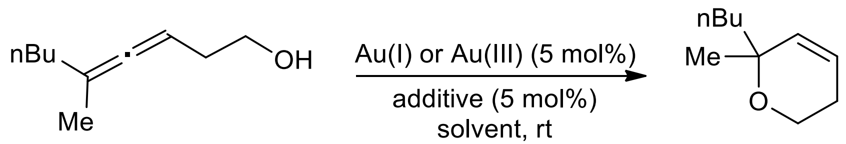


entry	Au salt	additive	solvent	time	yield (%)
1	$AuCl_3$[a]		toluene	6 d	58
2	$AuCl_3$[a]	3-hydroxy-propionitrile	toluene	1 d	62
3	AuCl		CH_2Cl_2	5 d	50
4	AuCl	$AgBF_4$	CH_2Cl_2	3 d	60
5	AuCl	$AgBF_4$	toluene	3 d	62

-> No trace of 5-*exo* isomer detected

Gold chloride catalyzed cyclization of β-hydroxyallenes

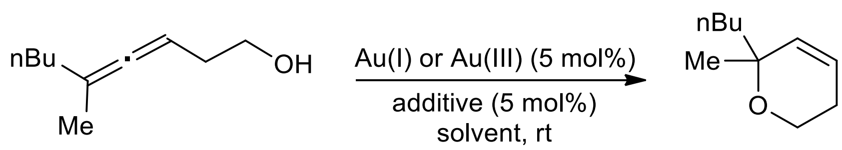
- Gockel B. and Krause N., *Org, Lett.*, **2006**, *8*, 4485



entry	Au salt	additive	solvent	time	yield (%)
1	$AuCl_3$[a]		toluene	6 d	58
2	$AuCl_3$[a]	3-hydroxy-propionitrile	toluene	1 d	62
3	AuCl		CH_2Cl_2	5 d	50
4	AuCl	$AgBF_4$	CH_2Cl_2	3 d	60
5	AuCl	$AgBF_4$	toluene	3 d	62
6	AuCl	pyridine	CH_2Cl_2	4.5 h	64
7	AuCl	2,2′-bipyridine	CH_2Cl_2	5 d	86
8		$AgBF_4$	toluene	5 d	–
9	$Au(OAc)_3$		toluene	14 d	–
10	Ph_3PAuCl		toluene	14 d	–

Gold chloride catalyzed cyclization of β-hydroxyallenes

- Gockel B. and Krause N., *Org, Lett.*, **2006**, *8*, 4485



entry	Au salt	additive	solvent	time	yield (%)
11	Ph_3PAuCl	$AgSbF_6$	toluene	25 min	54
12	Ph_3PAuCl	$AgBF_4$	toluene	1 h	60
13	Ph_3PAuCl	$AgBF_4$	CH_2Cl_2	1.5 h	60
14	Ph_3PAuCl	$AgBF_4$	THF	3 d	46
15	Ph_3PAuCl	$AgBF_4$	Et_2O	4 d	56
16	Ph_3PAuCl	$AgBF_4$	MeCN	27 d	62
17	Ph_3PAuCl	$AgBF_4$	toluene[b]	1.25 h	66
18	Ph_3PAuCl[c]	$AgBF_4$[c]	toluene	6.5 h	61

Works better in non-coordinating solvent

-> decrease lewis acidity of the gold catalyst

Gold chloride catalyzed cyclization of β-hydroxyallenes

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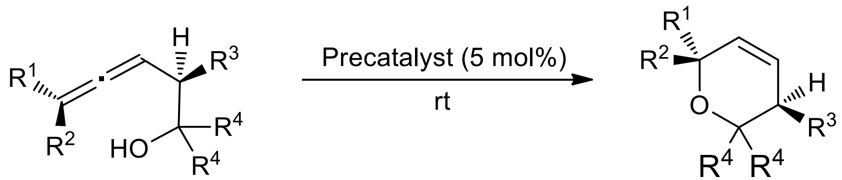
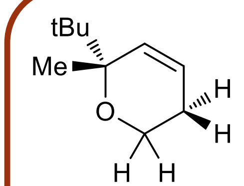
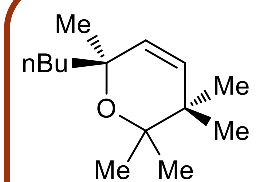


Cond. A : $Ph_3AuCl/AgBF_4$ in toluene
Cond. B : AuCl/pyridine in CH_2Cl_2

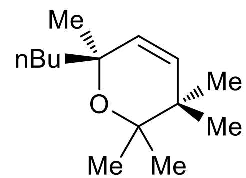
Extention of the scope to the sterically more hindered hydroxyallenes



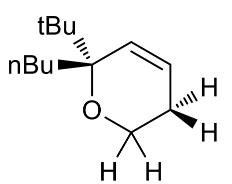
Cond. A : 22h, 42%



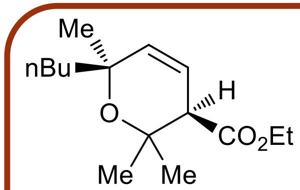
Cond. A : 24h, 32%



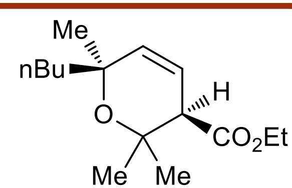
Cond. B : 6d, 46%



Cond. A : 10d, 36%
(67% conv of SM)



Cond. A : 24h, didn't work
(SM 70:30 *dr*)



Cond. B : 13d, 84%
(SM and product 70:30 *dr*)

Institut des Sciences Moléculaires de Marseille
UMR 7313

Gold chloride catalyzed cyclization of β-hydroxyallenes

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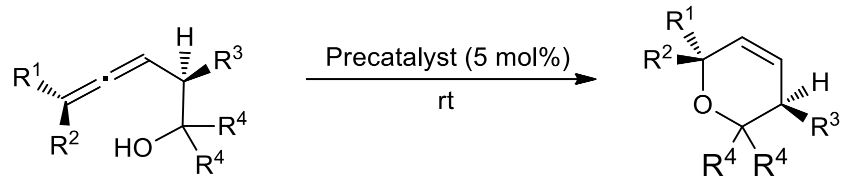
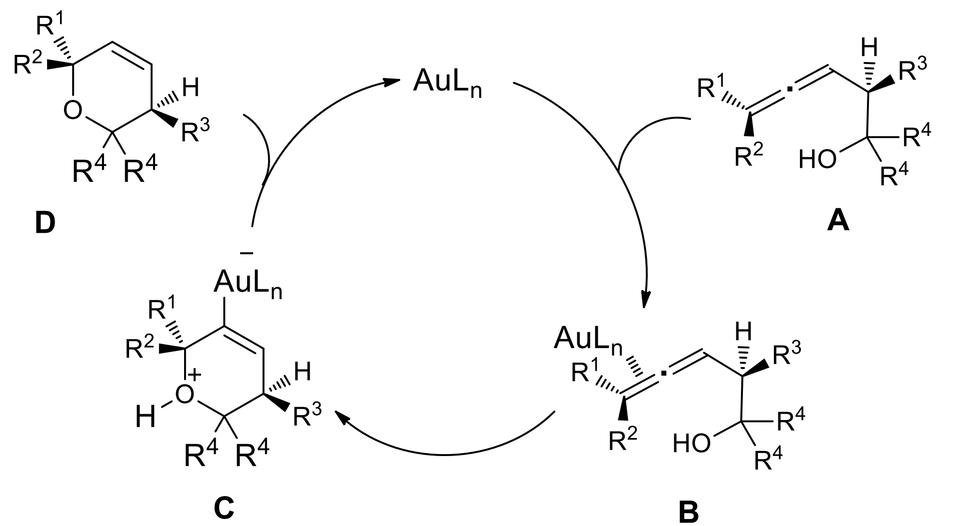
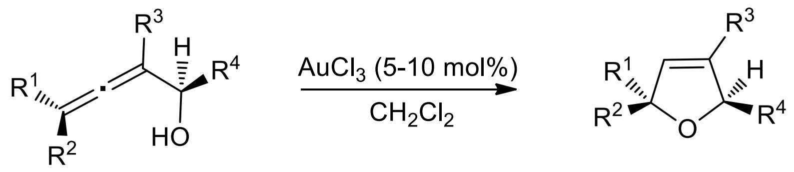


Proposed mechanism



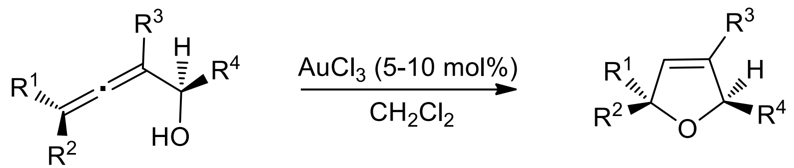
Gold(III) chloride catalyzed cyclization of α-hydroxyallenes

- Hoffmann-Röder A. and Krause N., *Org, Lett.*, **2001**, *3*, 2537



Gold(III) chloride catalyzed cyclization of α-hydroxyallenes

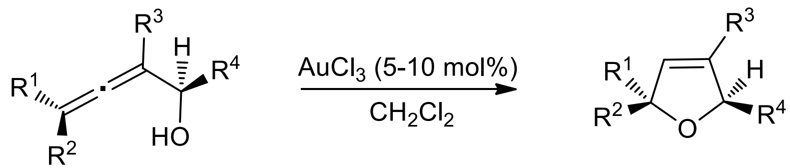
- Hoffmann-Röder A. and Krause N., *Org, Lett.*, **2001**, *3*, 2537



entry	hydroxyallene	R^1	R^2	R^3	R^4	electrophile	dihydrofuran (yield)
1	**1a**	*t*-Bu	Me	H	CO_2Et	Amberlyst 15	**2a** (quant)
2	**1a**	*t*-Bu	Me	H	CO_2Et	$AuCl_3$	**2a** (74%)

Gold(III) chloride catalyzed cyclization of α-hydroxyallenes

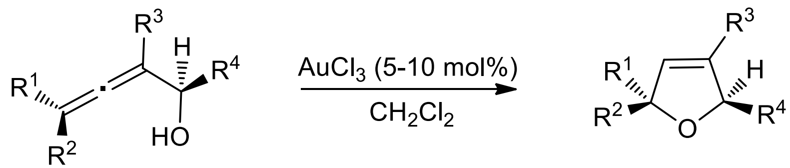
- Hoffmann-Röder A. and Krause N., *Org, Lett.*, **2001**, *3*, 2537



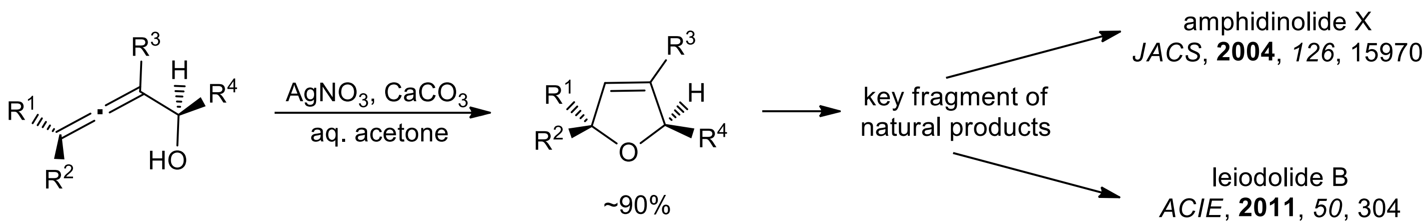
entry	hydroxyallene	R^1	R^2	R^3	R^4	electrophile	dihydrofuran (yield)
1	**1a**	*t*-Bu	Me	H	CO_2Et	Amberlyst 15	**2a** (quant)
2	**1a**	*t*-Bu	Me	H	CO_2Et	$AuCl_3$	**2a** (74%)
3	**1b**	*t*-Bu	Me	Me	CO_2Et	$AuCl_3$	**2b** (94%)
4	**1c**	*t*-Bu	*n*-Bu	H	CO_2Et	$AuCl_3$	**2c** (quant)
5	**1d**	*t*-Bu	H	Me	CO_2Me	$AuCl_3$	**2d** (78%)
6	**1e**	*t*-Bu	Me	H	CH_2OH	$AuCl_3$	**2e** (24%)
7	**1f**	*t*-Bu	H	Me	CH_2OTBS	$AuCl_3$	**2f** (95%)

Gold(III) chloride catalyzed cyclization of α-hydroxyallenes

- Hoffmann-Röder A. and Krause N., *Org, Lett.*, **2001**, *3*, 2537



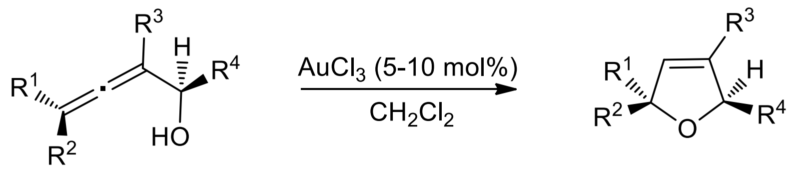
entry	hydroxyallene	R^1	R^2	R^3	R^4	electrophile	dihydrofuran (yield)
1	**1a**	*t*-Bu	Me	H	CO_2Et	Amberlyst 15	**2a** (quant)
2	**1a**	*t*-Bu	Me	H	CO_2Et	$AuCl_3$	**2a** (74%)
3	**1b**	*t*-Bu	Me	Me	CO_2Et	$AuCl_3$	**2b** (94%)
4	**1c**	*t*-Bu	*n*-Bu	H	CO_2Et	$AuCl_3$	**2c** (quant)
5	**1d**	*t*-Bu	H	Me	CO_2Me	$AuCl_3$	**2d** (78%)
6	**1e**	*t*-Bu	Me	H	CH_2OH	$AuCl_3$	**2e** (24%)
7	**1f**	*t*-Bu	H	Me	CH_2OTBS	$AuCl_3$	**2f** (95%)
8	**1f**	*t*-Bu	H	Me	CH_2OTBS	$AgNO_3$	**2f** (mixture)



Mixture of starting material and desired product after 24h

Gold(III) chloride catalyzed cyclization of α-hydroxyallenes

- Hoffmann-Röder A. and Krause N., *Org, Lett.*, **2001**, *3*, 2537



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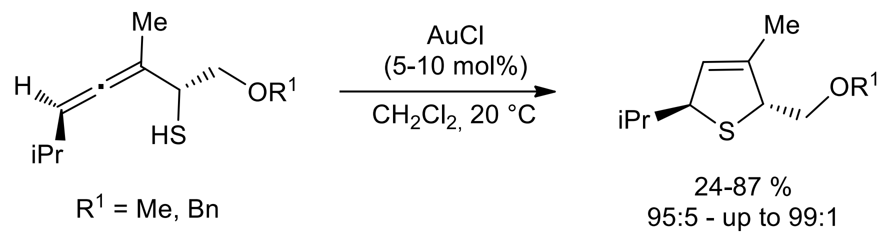
1	**1a**	*t*-Bu	Me	H	CO_2Et	Amberlyst 15	**2a** (quant)
2	**1a**	*t*-Bu	Me	H	CO_2Et	$AuCl_3$	**2a** (74%)
3	**1b**	*t*-Bu	Me	Me	CO_2Et	$AuCl_3$	**2b** (94%)
4	**1c**	*t*-Bu	*n*-Bu	H	CO_2Et	$AuCl_3$	**2c** (quant)
5	**1d**	*t*-Bu	H	Me	CO_2Me	$AuCl_3$	**2d** (78%)
6	**1e**	*t*-Bu	Me	H	CH_2OH	$AuCl_3$	**2e** (24%)
7	**1f**	*t*-Bu	H	Me	CH_2OTBS	$AuCl_3$	**2f** (95%)
8	**1f**	*t*-Bu	H	Me	CH_2OTBS	$AgNO_3$	**2f** (mixture)
9	**1g**	H	Me	Me	CH_2OTBS	$AuCl_3$	**2g** (77%)
10	**1h**	H	*n*-Hex	Me	CH_2OTBS	$AuCl_3$	**2h** (65%)
11	**1i**	*t*-Bu	Me	Me	CH_2OMe	$AuCl_3$	**2i** (90%)
12	**1j**	$H_2C{=}CH(CH_2)_2$	Me	Me	CH_2OMe	$AuCl_3$	**2j** (86%)

Cyclization of α-thioallenes to 2,5-dihydrothiophenes

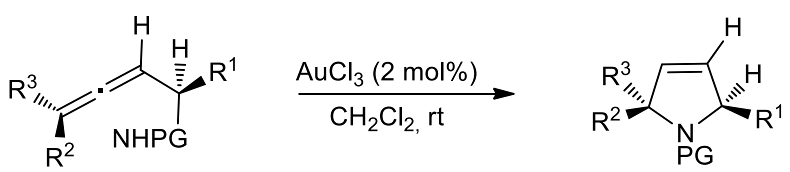
- Morita N. and Krause N., *Angew. Chem. Int. Ed.*, **2006**, *45*, 1897



-> First example of a gold-catalyzed carbon–sulfur bond formation

Gold catalyzed cyclization of α-Aminoallenes to 3-Pyrrolines

- Morita N. and Krause N., *Org, Lett.*, **2004**, *6*, 4121



Mechanistic studies of the gold catalyzed cyclization of α-Aminoallenes

- Zhu R-X., Zhang D-J., Guo J-X., Mu J-L., Duan C-G., Liu C-B., *J. Phys. Chem. A.*, **2010**, *14*, 4689

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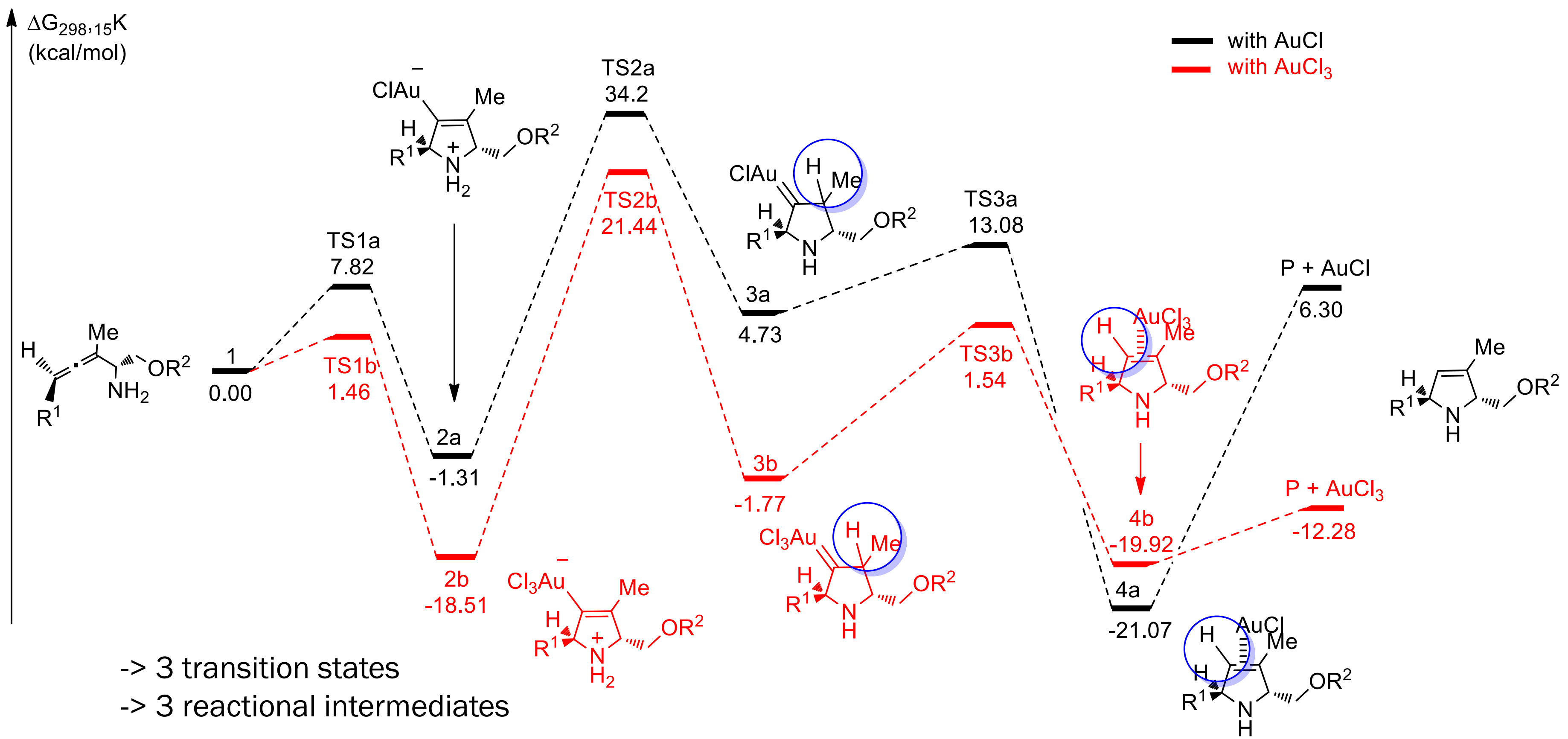

-> 3 transition states

-> 3 reactional intermediates

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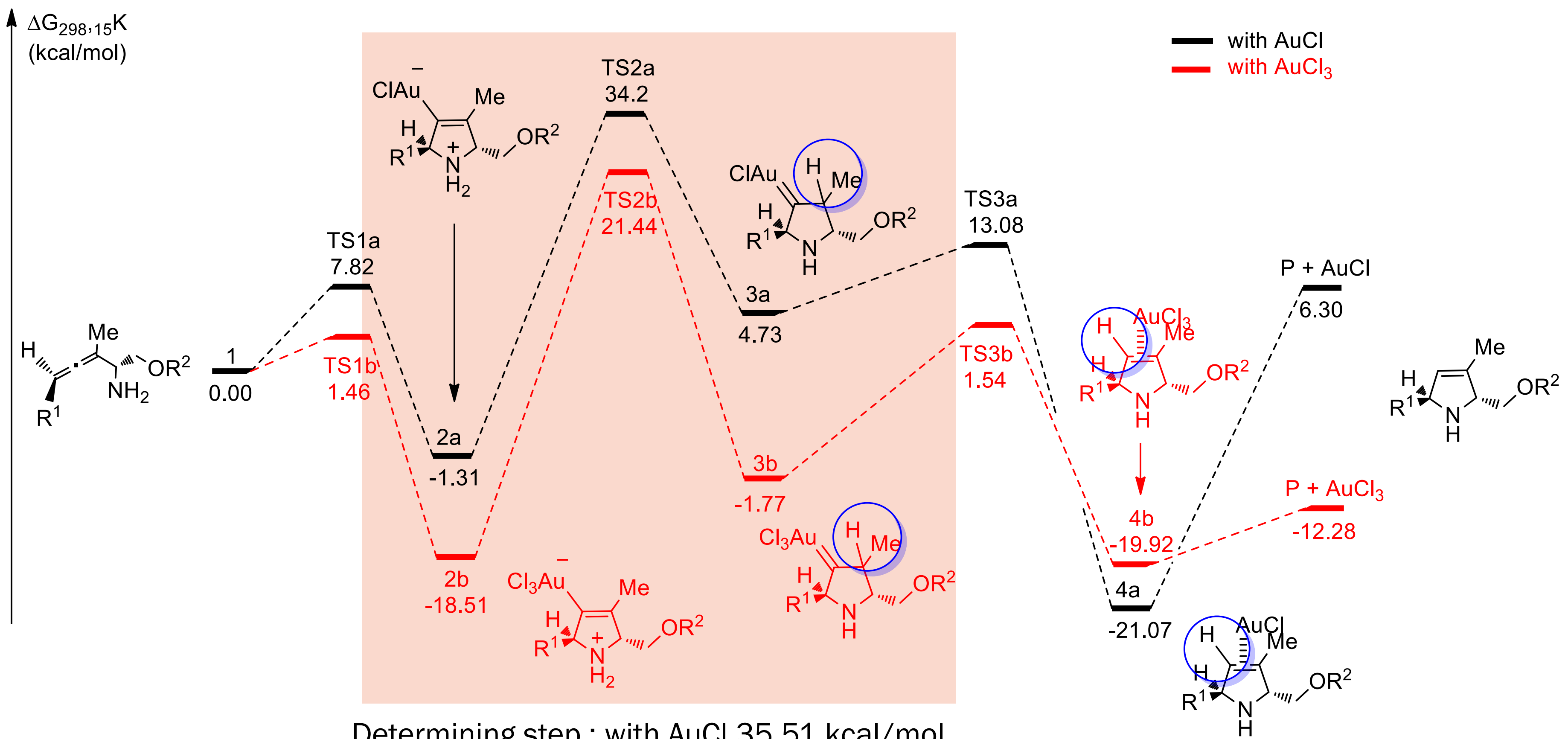

Determining step : with AuCl 35,51 kcal/mol

with $AuCl_3$ 39,95 kcal/mol

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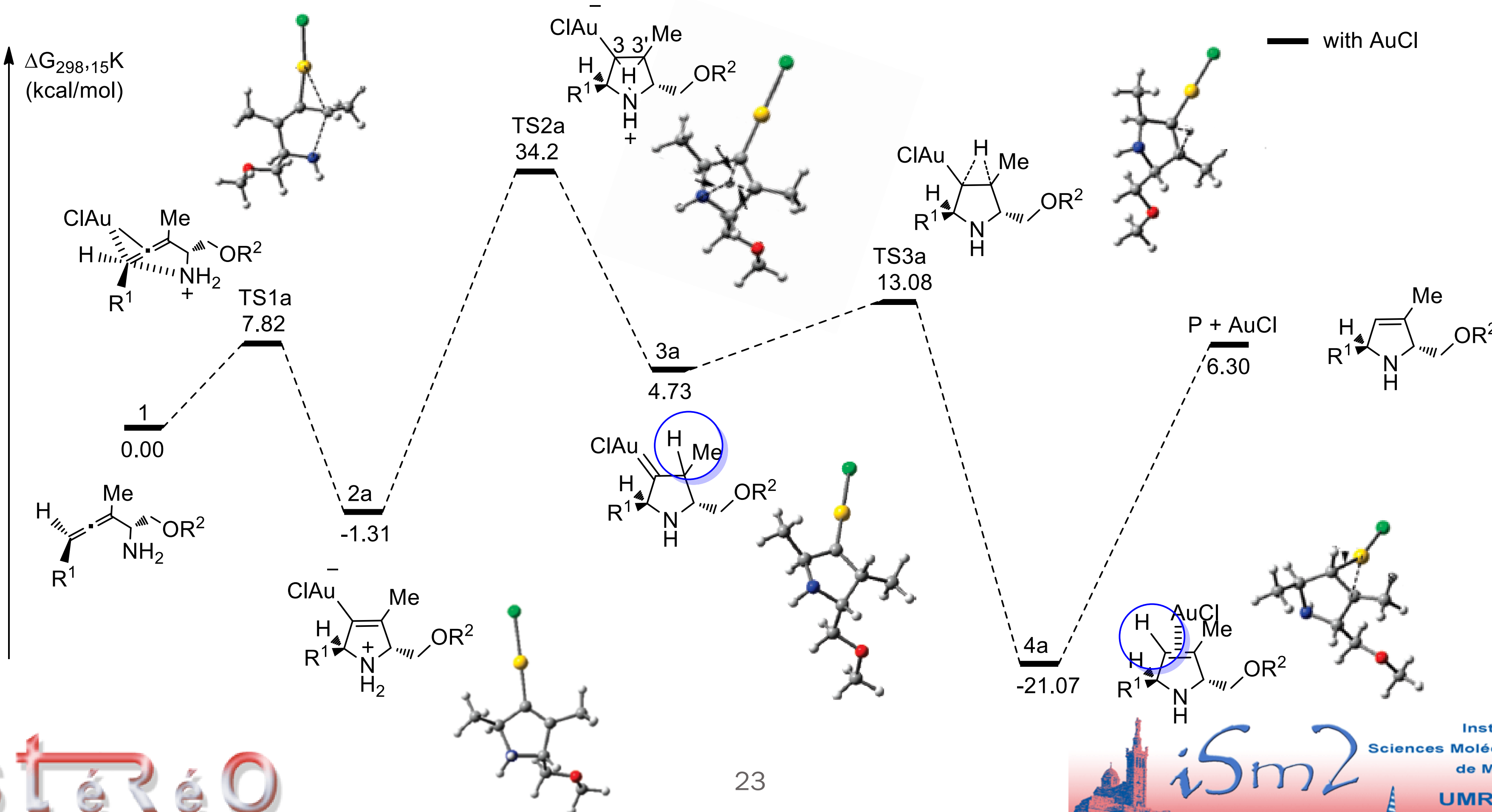

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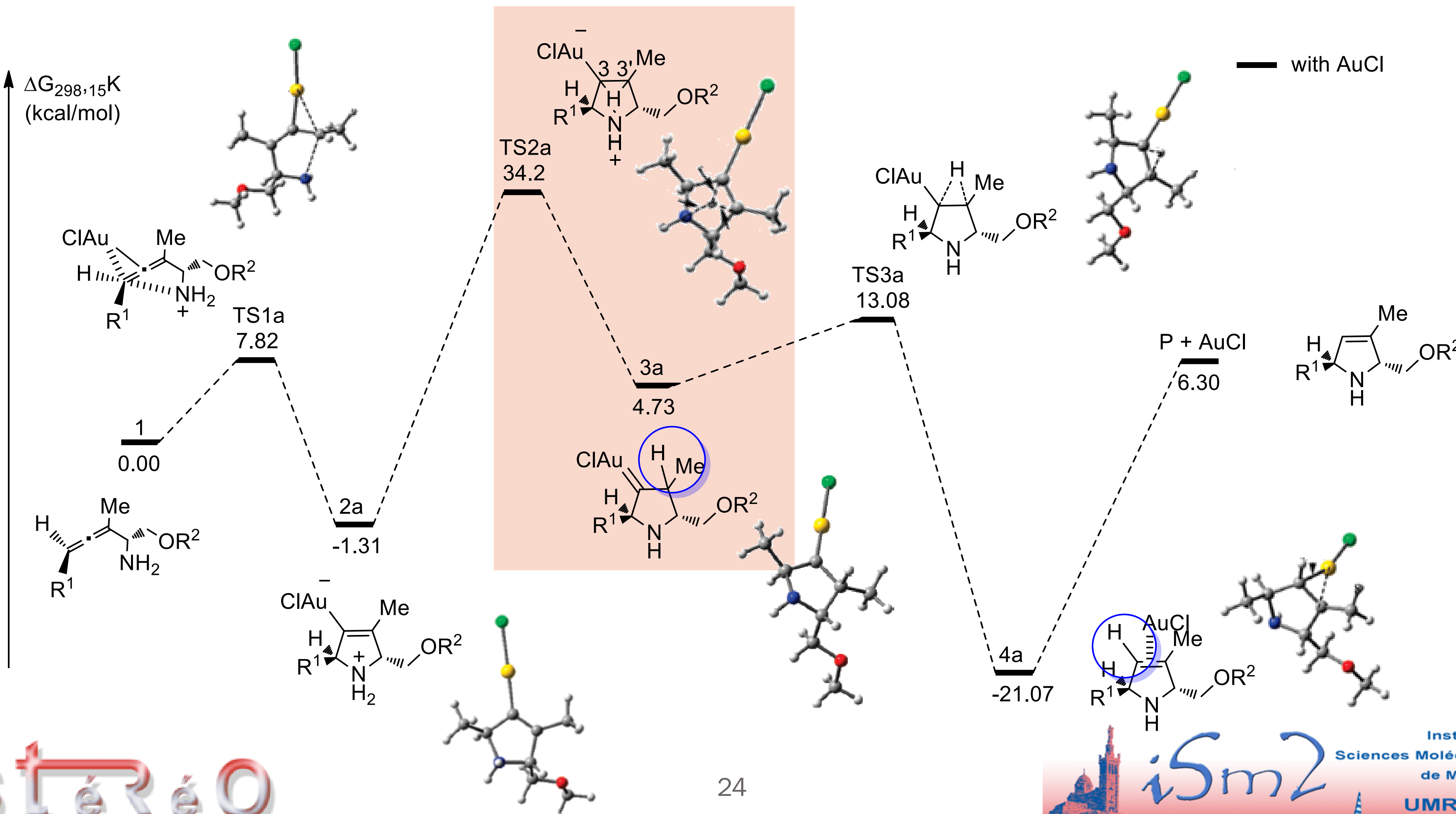

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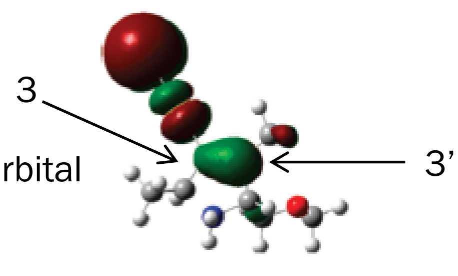
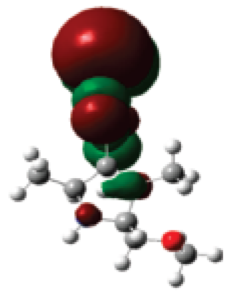
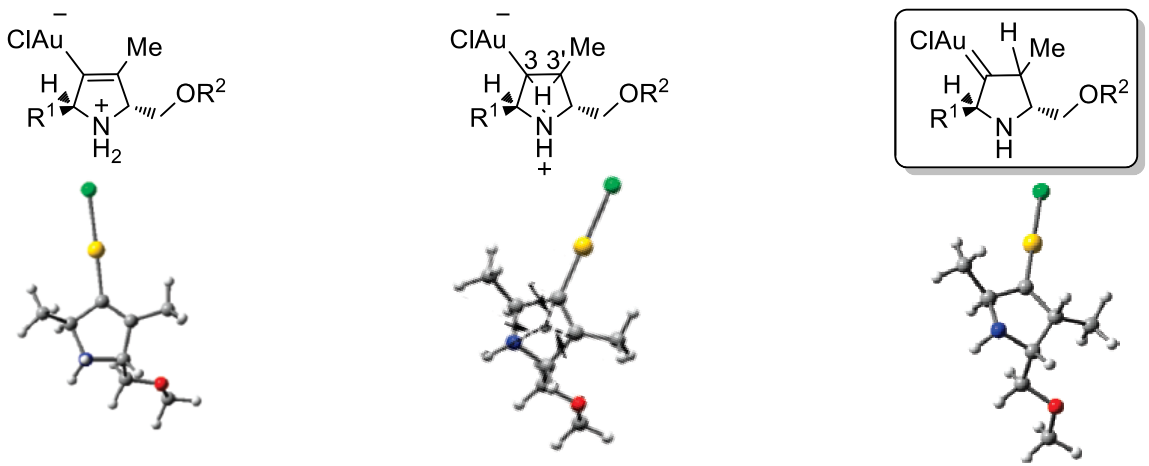
C(3)-C(3') Pz orbital





Overlap C(3') Pz – H s orbital



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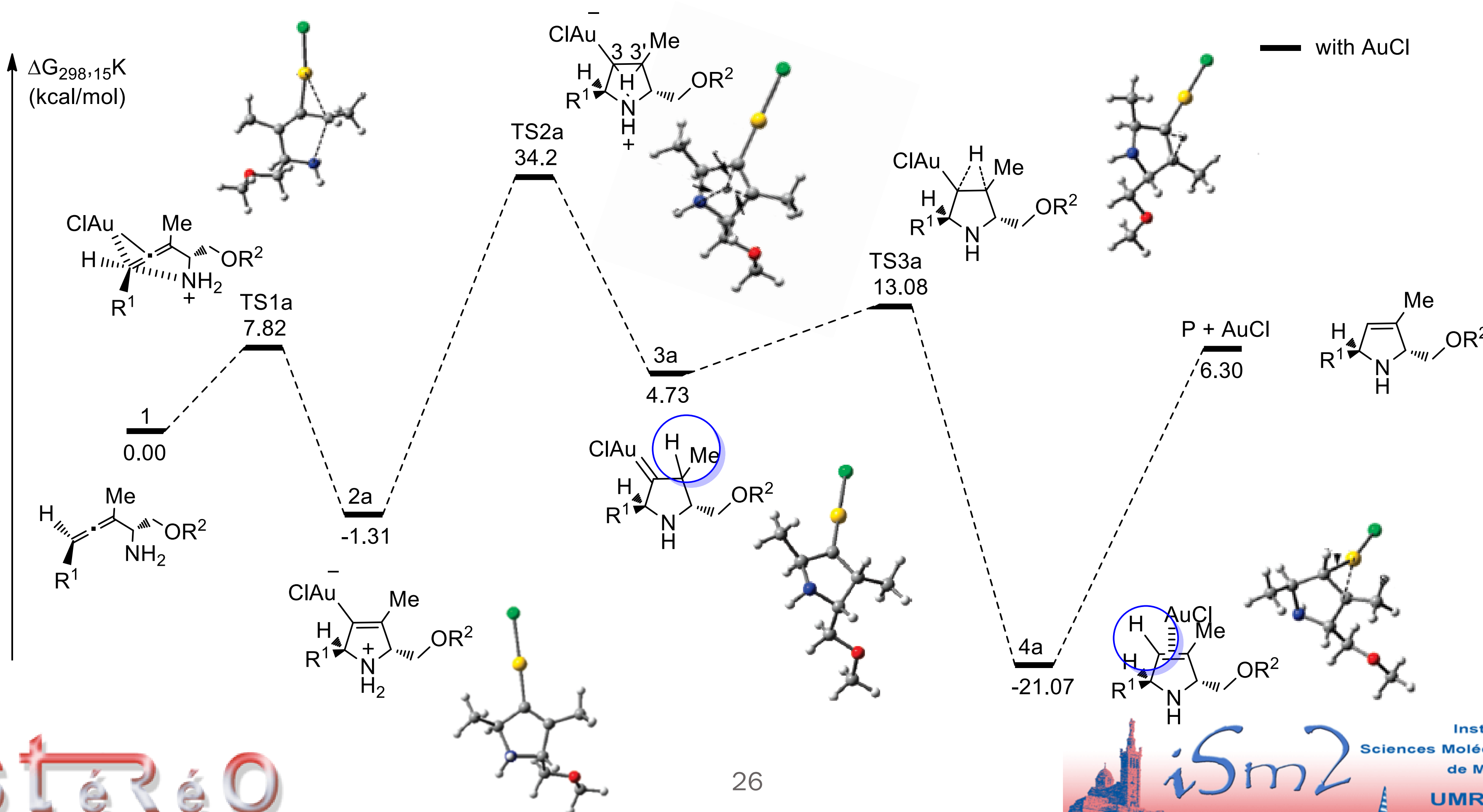

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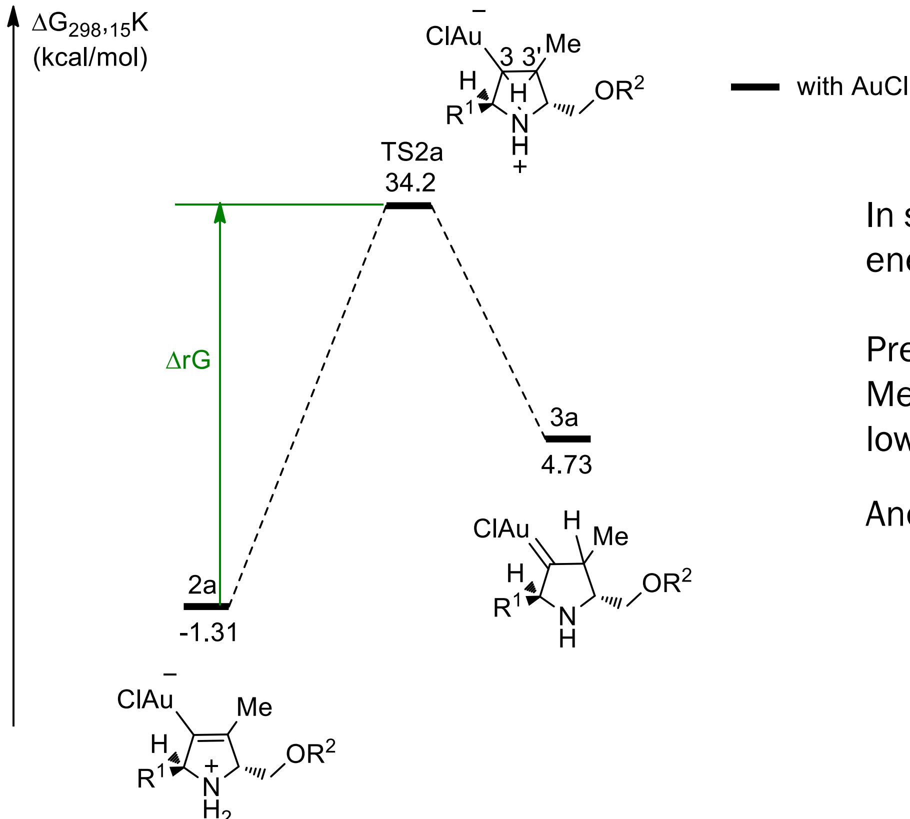

In solution and in gas phase the direct 1,3'H migration is energically unfavorable.

Previous calculations show a efficient parcipating role of MeOH, H_2O, in gold catalysis to facilitate the H migration by lowering their energy barrier[1,2]

Another α-aminoallene ?

[1] Xia L., Dudnik D. A. Gevorgyan V., Li Y., *JACS*, **2008**, *130*,6940
[2] Sordo T. L., Ardura D., *Eur JOC*, **2008**, 3004

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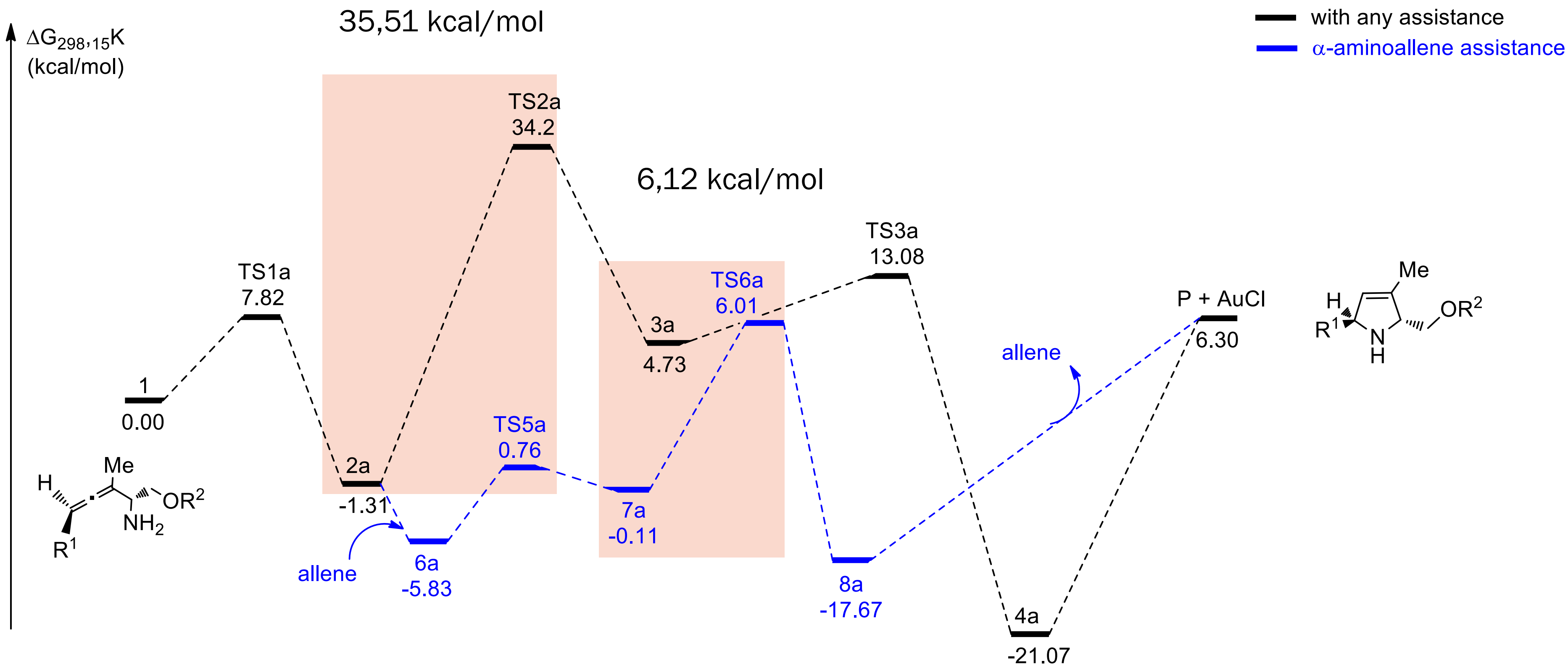

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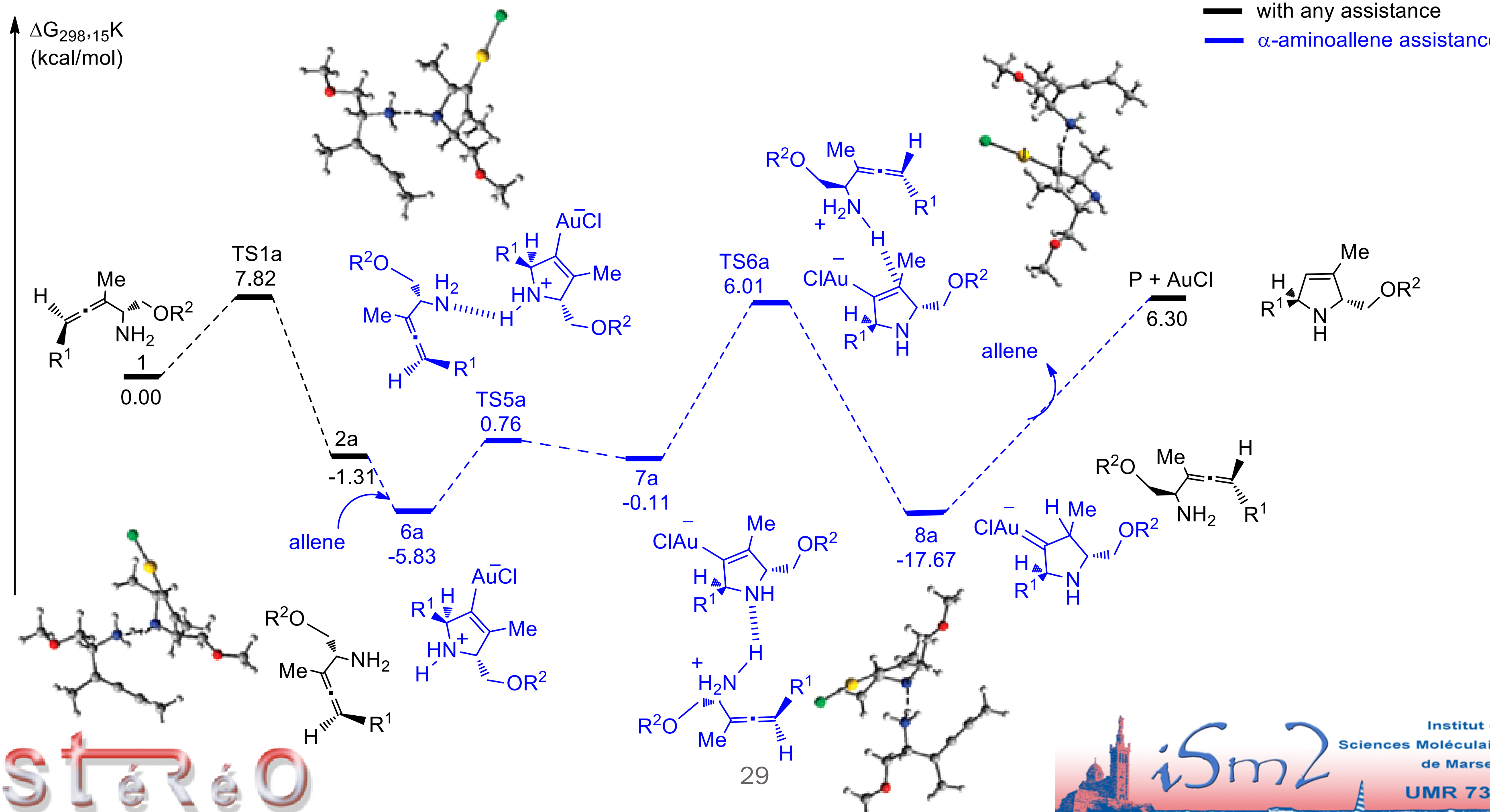

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Activation barrier (kcal/mol) for the 1,3'-H migration determining step

	With AuCl	With $AuCl_3$	With PPh_3AuCl	With $PPh_3AuCl/AgSbF_6$
In gas phase	35,51	39,95	58,60	35,54
In CH_2Cl_2	44,32	49,34	53,70	Not calculated
α-aminoallene assistance	6,12	31,75	Not calculated	/

The use of PPh_3AuCl for the cyclization is energetically unfavorable
The use of SbF_6- as a weak base could assist the H-shift process

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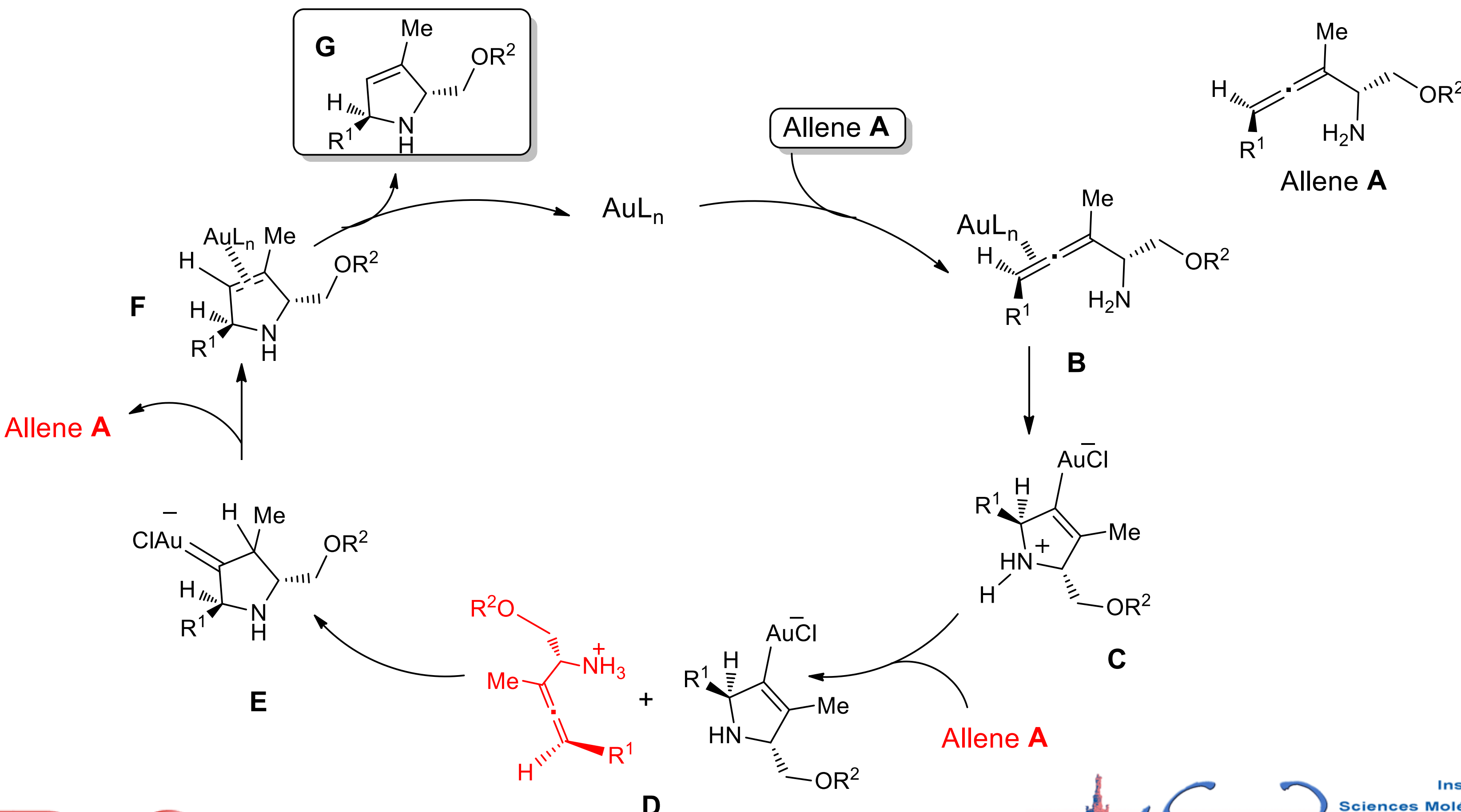
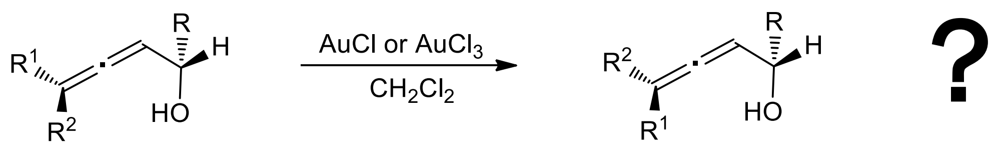


Epimerization of allenes & 2,5-dihydrofurans by gold(I) and gold(III) chloride

- Deutsch C., Gockel B., Hoffmann-Röder A. and Krause N., *Synlett*, **2007**, *11*, 1790



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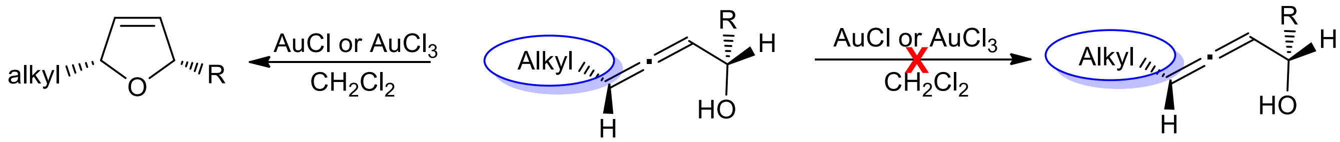
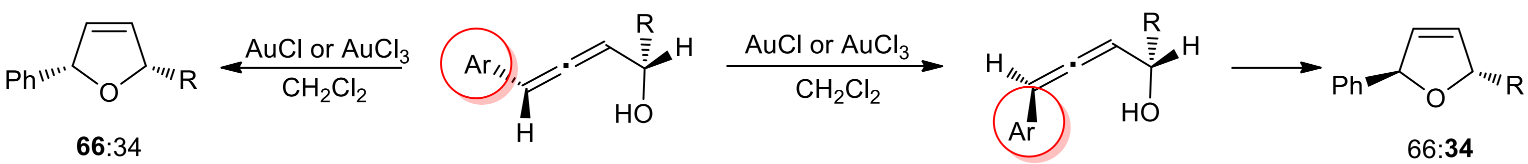


No epimerization



Epimerization

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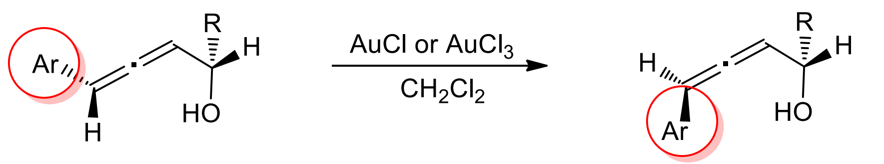
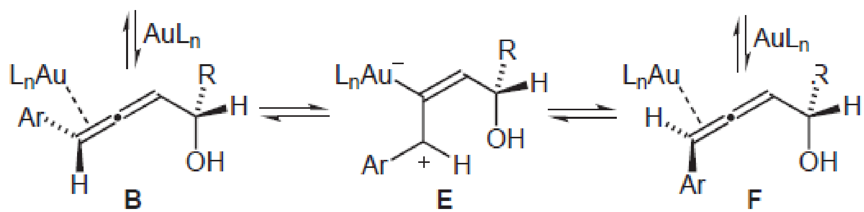
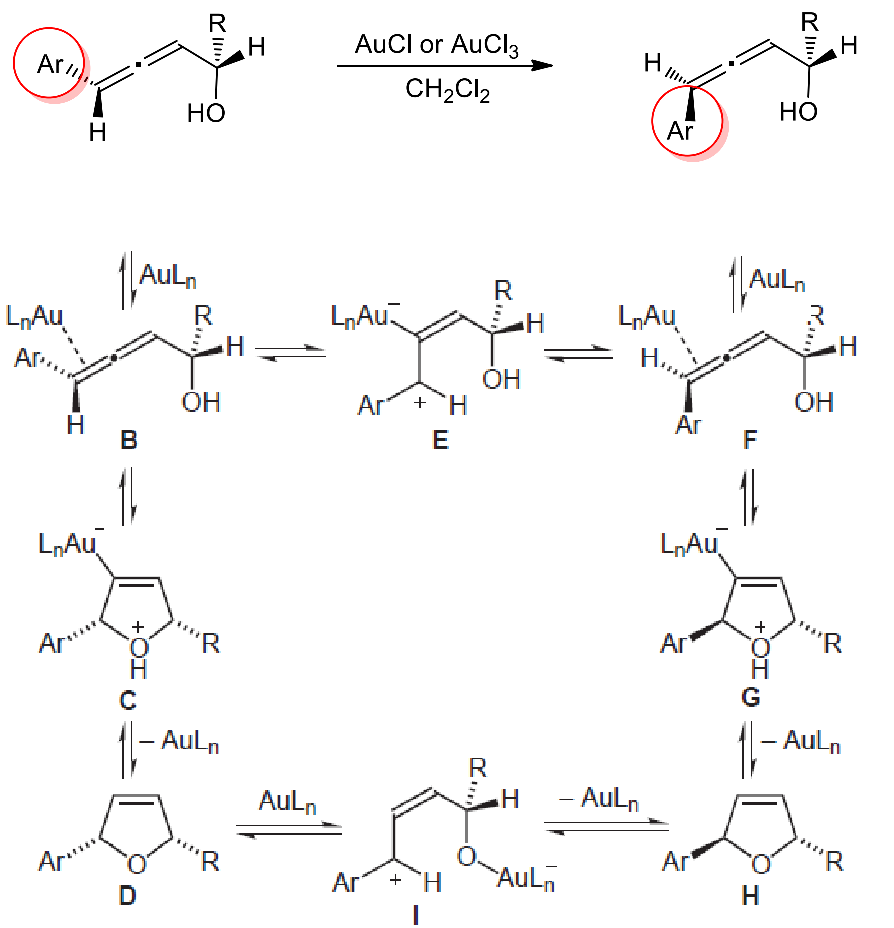




Epimerization of allenes & 2,5-dihydrofurans by gold(I) and gold(III) chloride

- Deutsch C., Gockel B., Hoffmann-Röder A. and Krause N., *Synlett*, **2007**, *11*, 1790

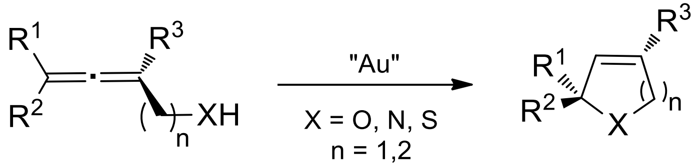


- Introduction
  - Generalities
  - History
- Chiral allenes synthesis
  - From achiral starting material
  - From chiral starting material
- Cyclization of allenes
  - Heterocycle formation
  - DFT calculations
  - Epimerization
- Conclusion

Conclusion

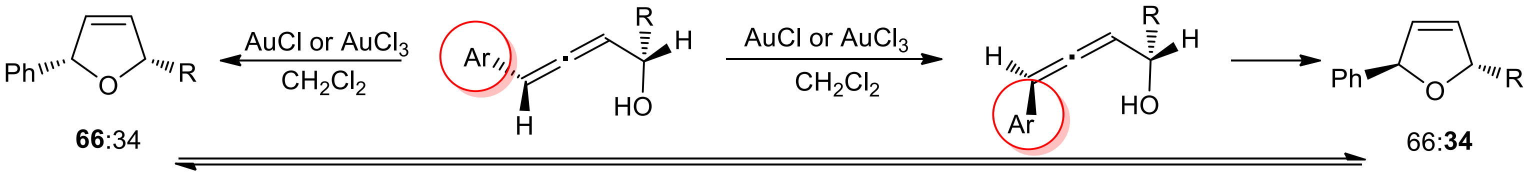
-> Rapid and easily access to chiral allenes starting from different achiral and chiral substrates.

-> Cyclization reaction catalyzed by gold is a good way to obtain heterocycles (pyrans, furans, thiophenes, pyrrolines) with a excellent chirality transfer under mild conditions.

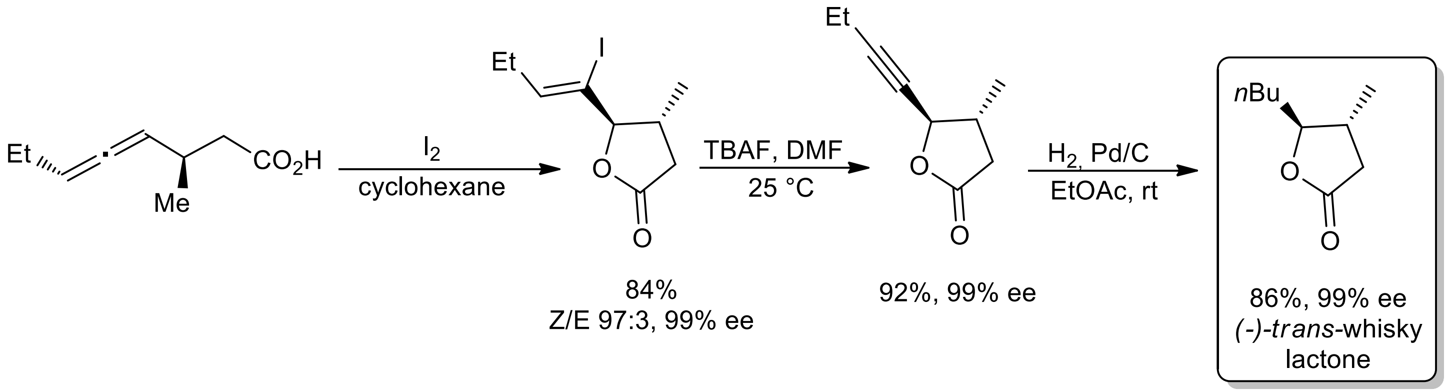


-> Thanks to the mechanistic studies we know that for this reaction, a participating allene is involved.

-> Limitation of the reaction : Due to the possible allene epimerization with gold(I) and/or gold(III) the reaction starting from an allene bearing a phenyl group leads to the desired product with a diminution of the dr.



- X. Jiang, C. Fu, S. Ma, *Eur. JOC.*, **2010**, 311
- X. Jiang, C. Fu, S. Ma, *Eur. JOC.*, **2010**, 687



Thank you for your attention