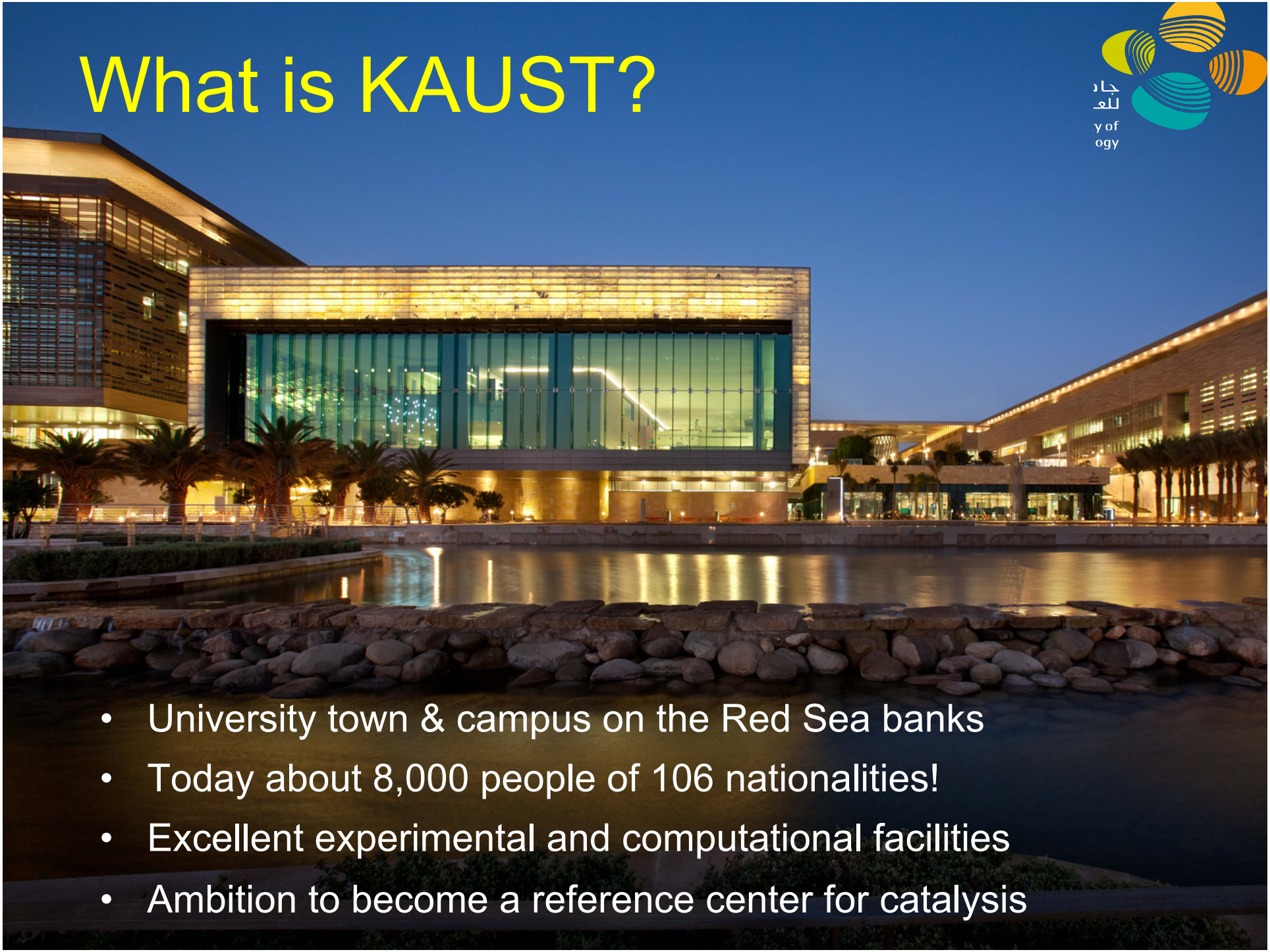
Understanding and Controlling Gold Catalysis the Hard Way

Luigi Cavallo

KAUST Catalysis Center
King Abdullah University of Science and Technology

What is KAUST?



- University town & campus on the Red Sea banks
- Today about 8,000 people of 106 nationalities!
- Excellent experimental and computational facilities
- Ambition to become a reference center for catalysis

Today presentation

- **First half (around 45-50 mins)**
  - My personal view of gold catalysis
  - You ask me questions (5 mins)
- **Second half (until 10.30)**
  - Being a computational chemist for a day
  - I ask you questions (30 mins)

My personal view of gold catalysis

- Introduction
- The Call for Help
- The Golden Carousel
- After the Puzzle
- Conclusions

Why computational catalytic chemistry ?

- Catalysis
- Computational chemistry

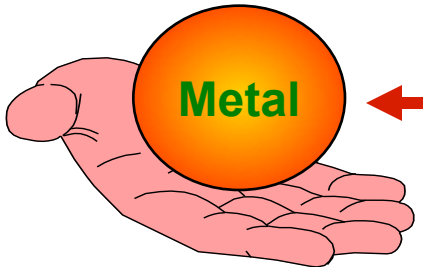
Catalysis contributes to ~30% of global gross national product

One of the main goals of chemists is “catalyst design”

Reagents → **Catalysis** → **Products**

Catalysis in:

- Oil refining
- Energy & H_2 production
- Agrochemicals
- Pharma industry
- Life sciences



Active metal

Homogeneous, heterogeneous or biological “ligand”

The Catalyst

Bad Catalyst

Reagents → **Product 1**, **Product 2**, **Product 3**

Good Catalyst

Reagents → **THE Product**

Keywords of an excellent catalyst

- Selectivity
- Efficiency
- Stability
- Activity
- Environmentally friendly
- Energetically moderate

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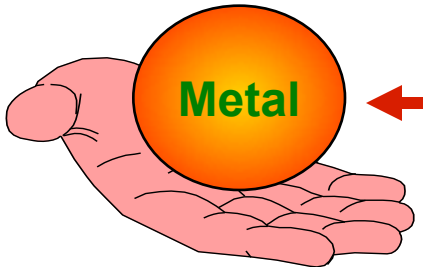

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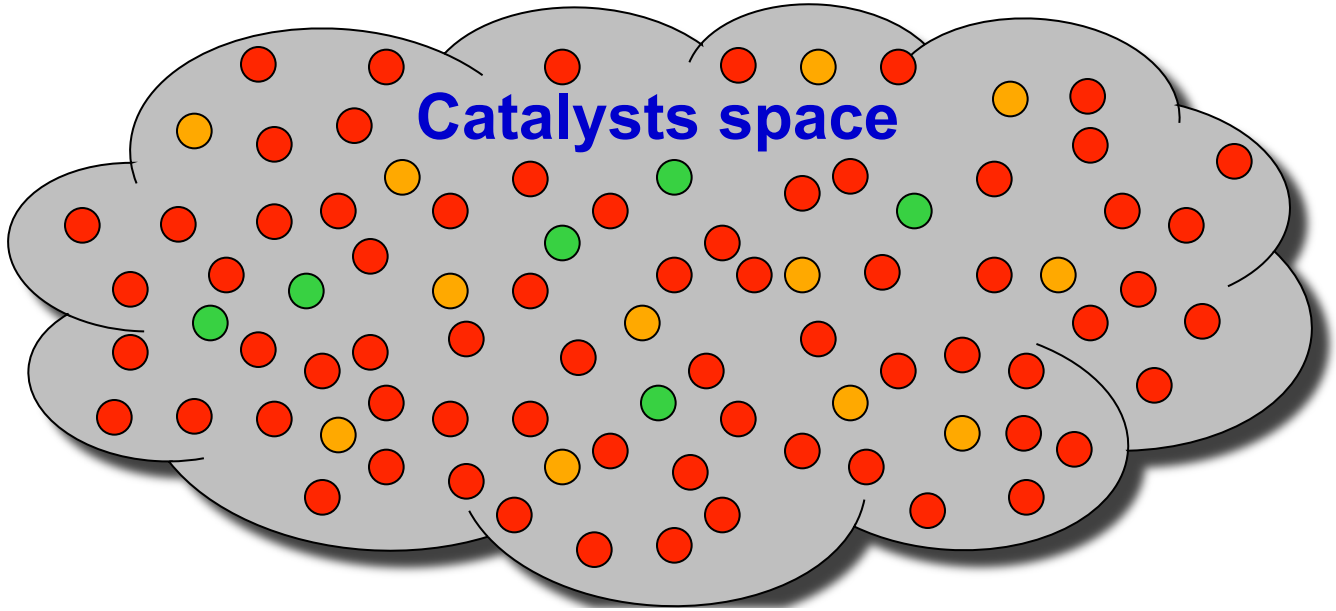

- Bad catalyst
- So so catalyst
- Good catalyst

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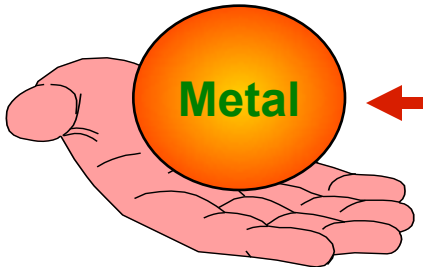

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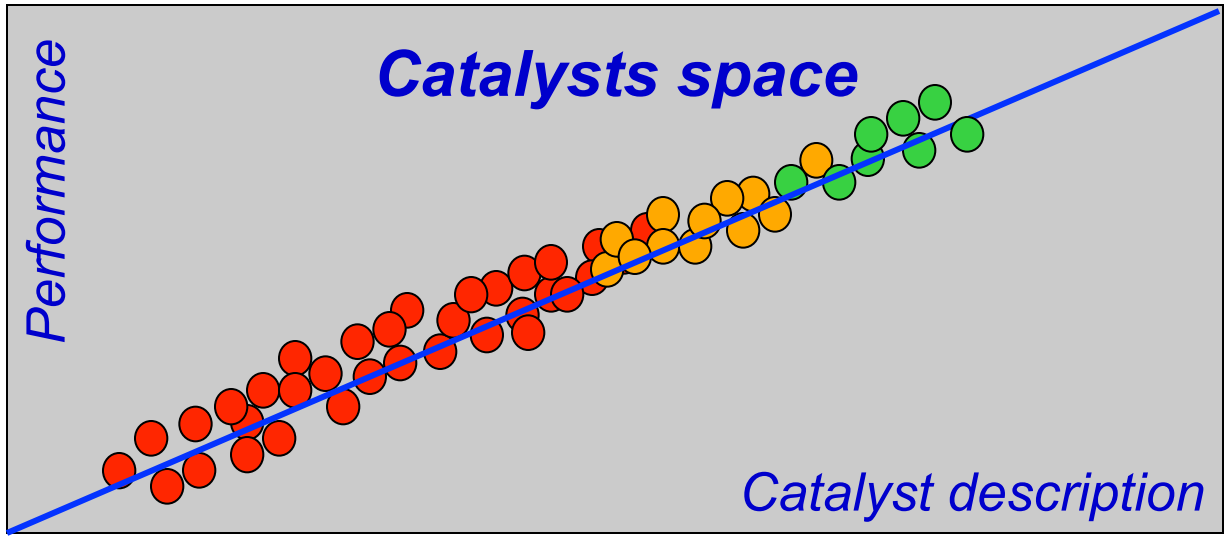

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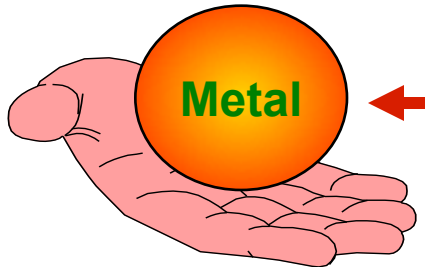


The Catalyst

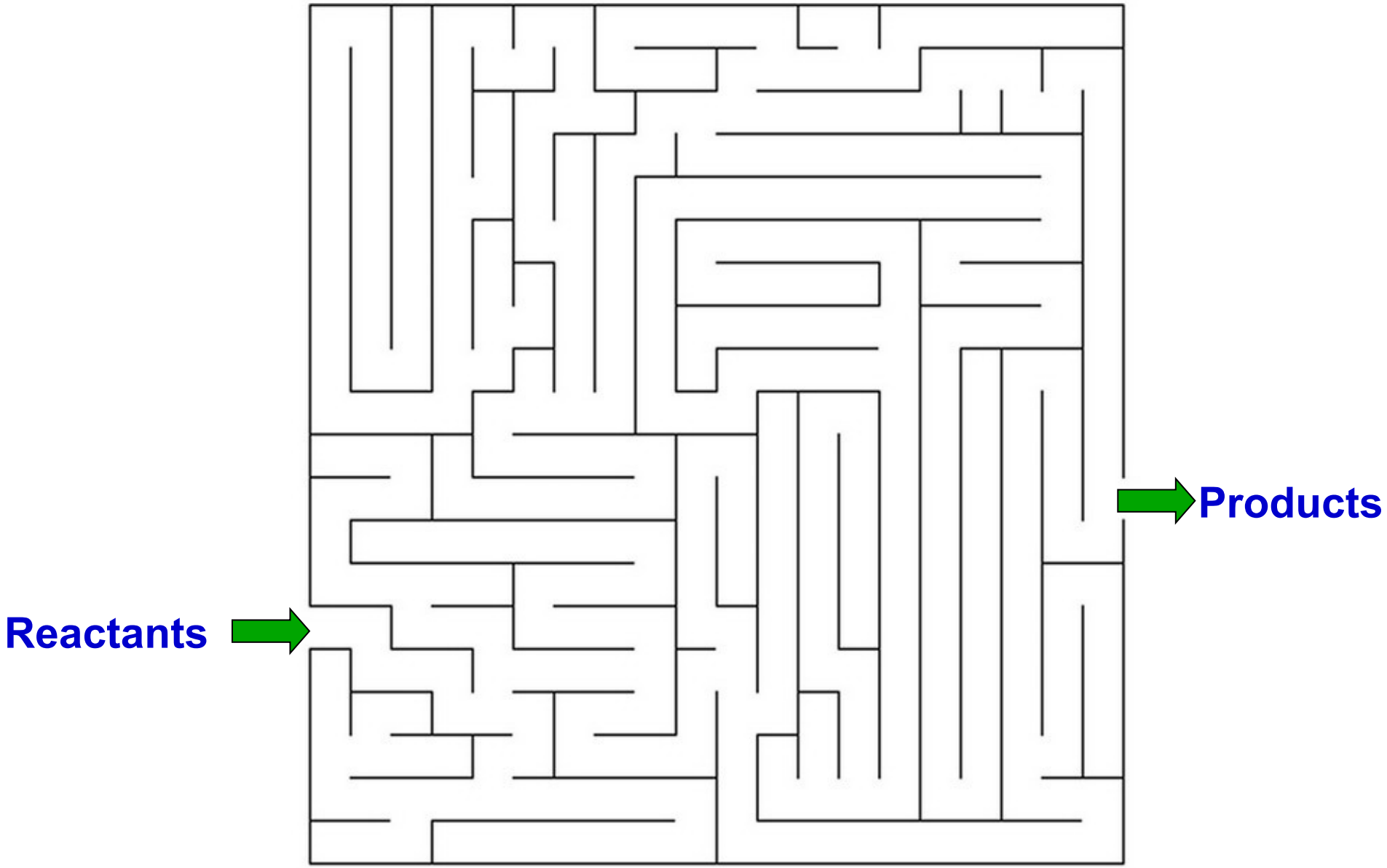
Active metal

Homogeneous, heterogeneous or biological “ligand”

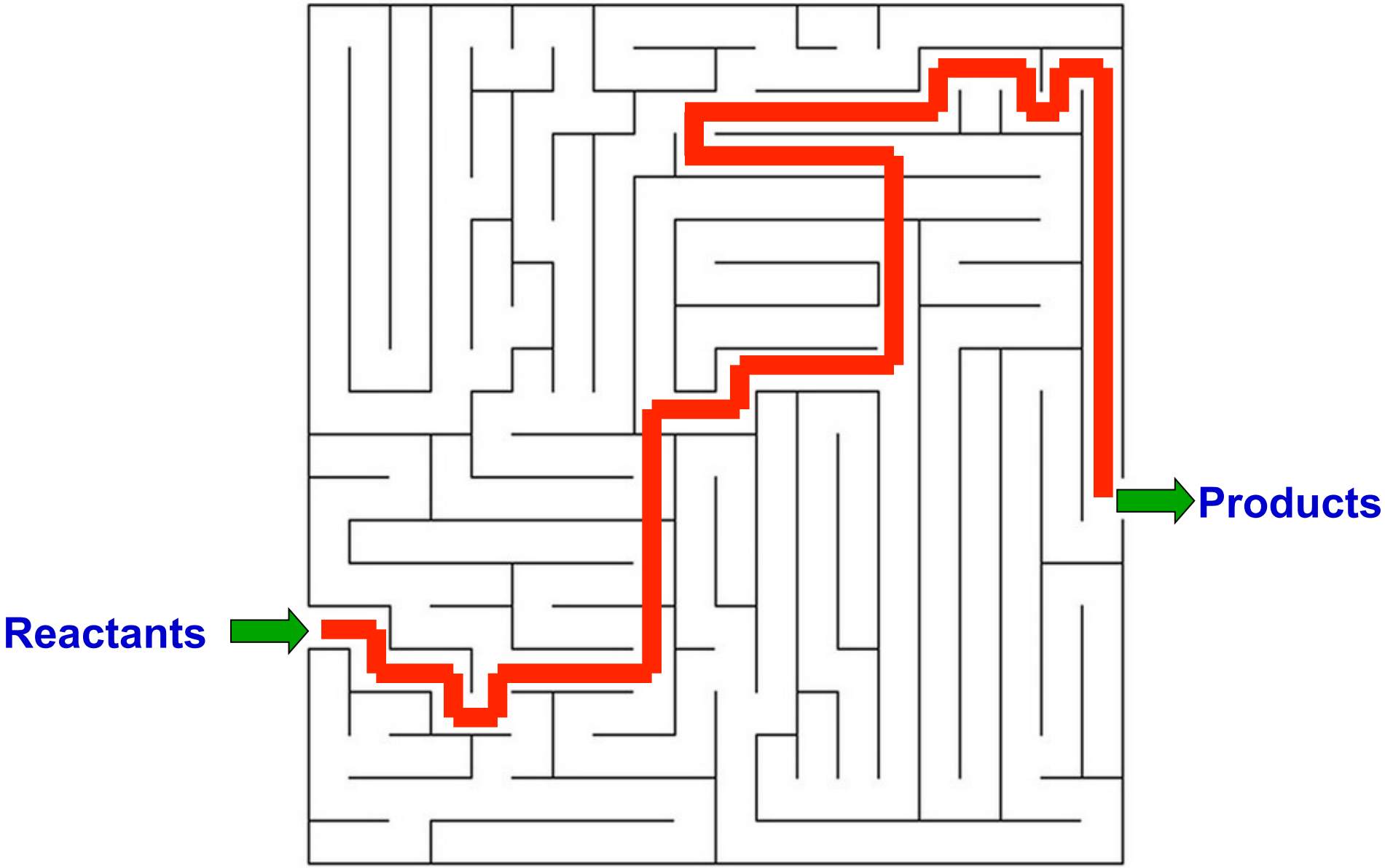
Excellent catalysts are like golden nuggets.
Very few of them, hidden among a huge amount of bad catayst.

Chemists are like gold miners.
A tedious search among mud and sand to find the nugget.
A few excellent chemists have a talent to search in the right place.

Experimentally difficult to know the reaction pathway



Computational chemistry can help to solve the maze



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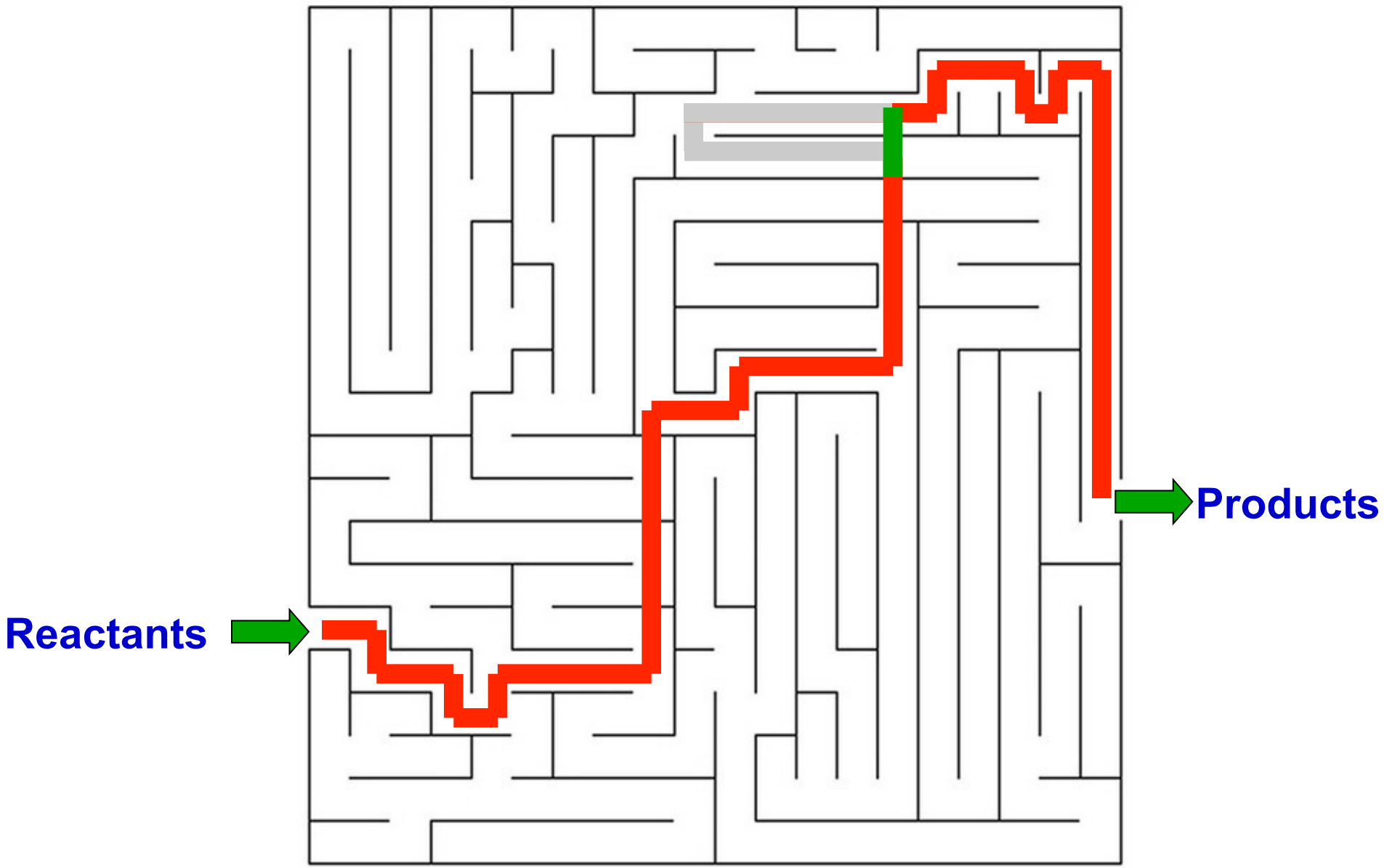

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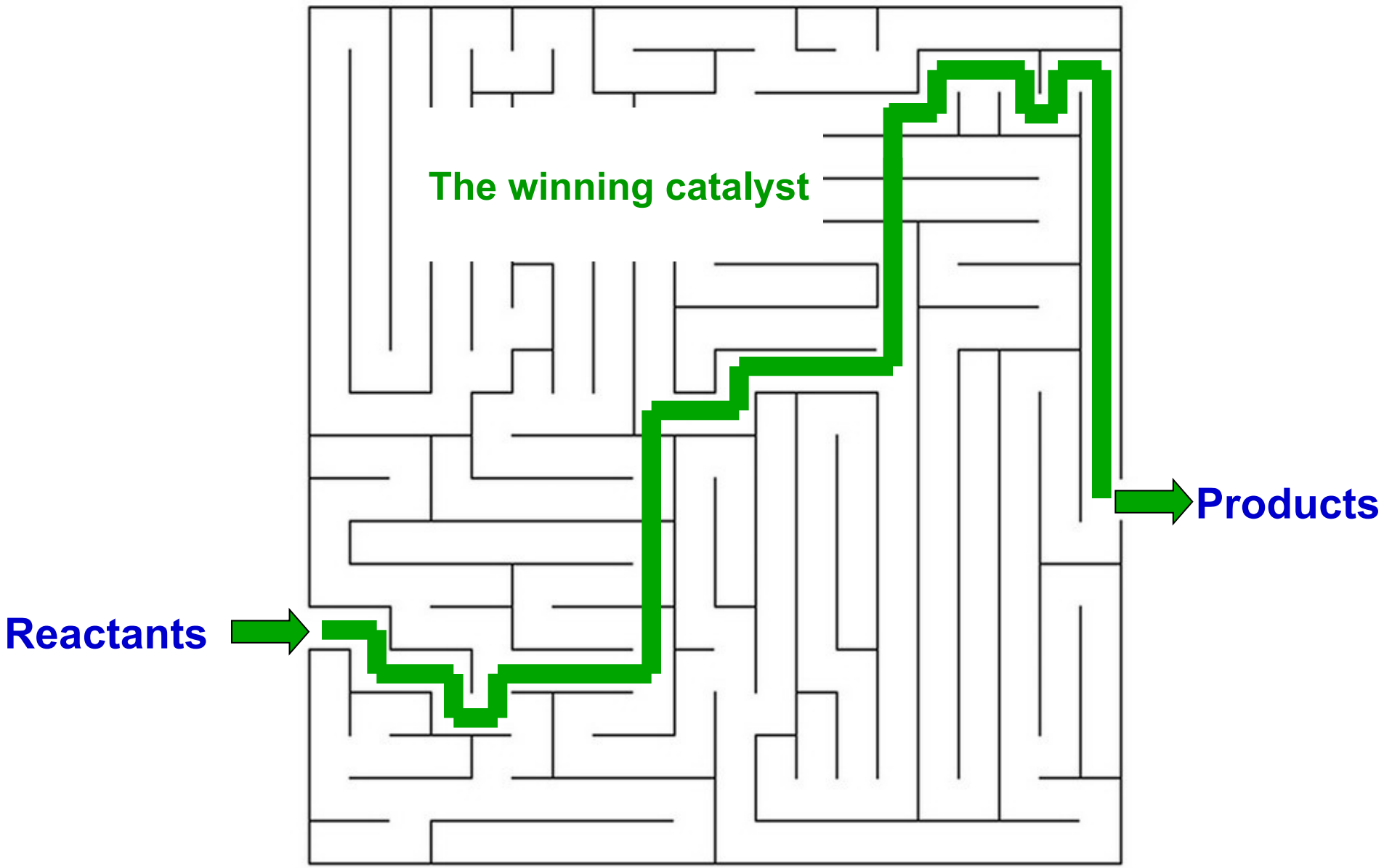

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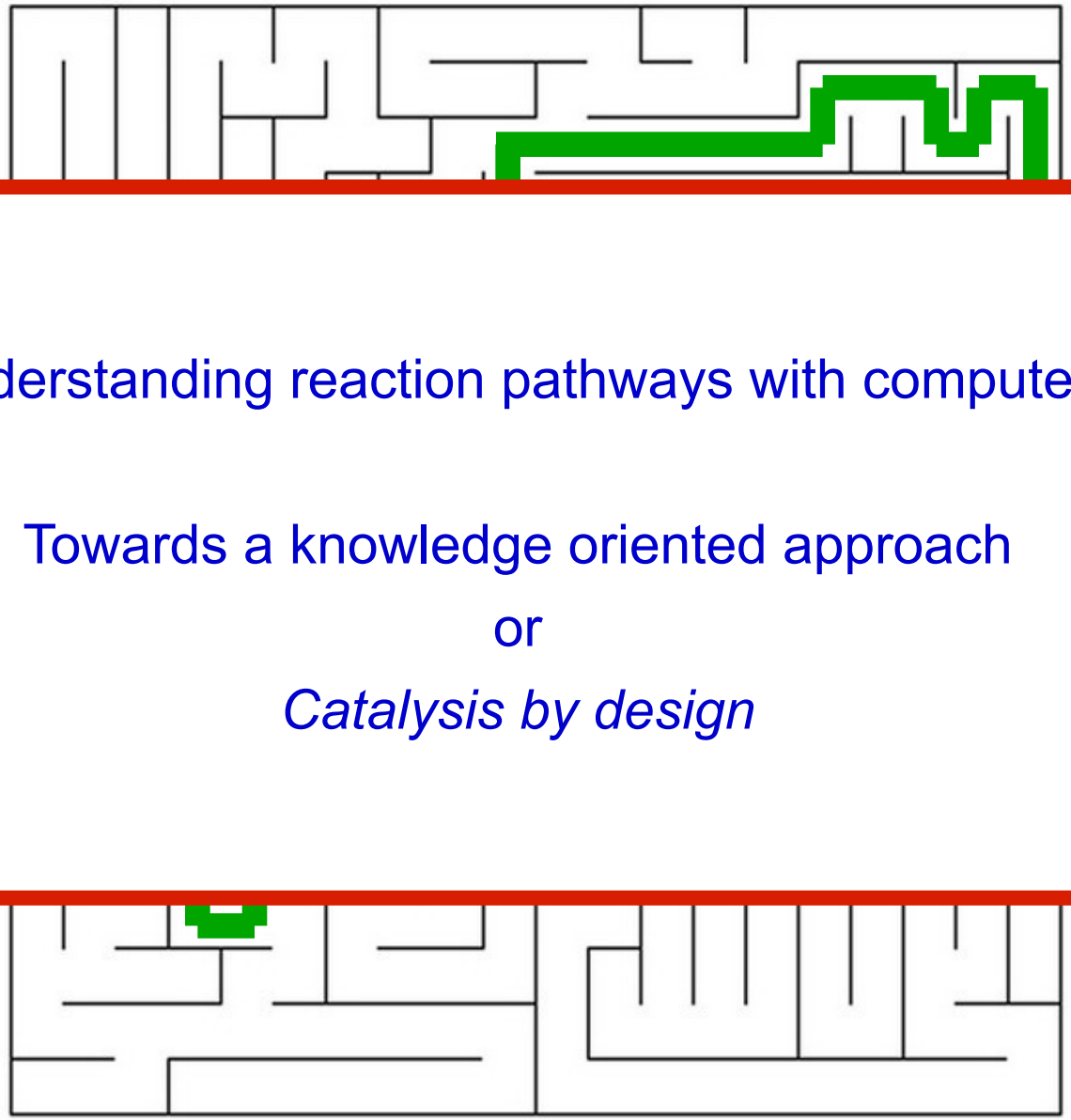


Understanding reaction pathways with computers

Towards a knowledge oriented approach

or

Catalysis by design

Now let’s move to Gold in catalysis

The Explosion of Gold Catalysis

Tunable Gold Catalysts for Selective Hydrocarbon Oxidation under Mild Conditions
Hutchings, G. J. et al., A. S. *Nature* **2005**, *437*, 1132

Gold Rush
Haruta M. *Nature* **2005**, *437*, 1098

Raising the Gold Standard
Hashmi, A. S. *Nature* **2007**, *449*, 292

Catalytic Gold Rush
Nolan, S. P. *Nature* **2007**, *445*, 496

Golden Opportunities in Stereoselective Catalysis
Bongers, N.; Krause, N. *ANIE* **2008**, *47*, 2178

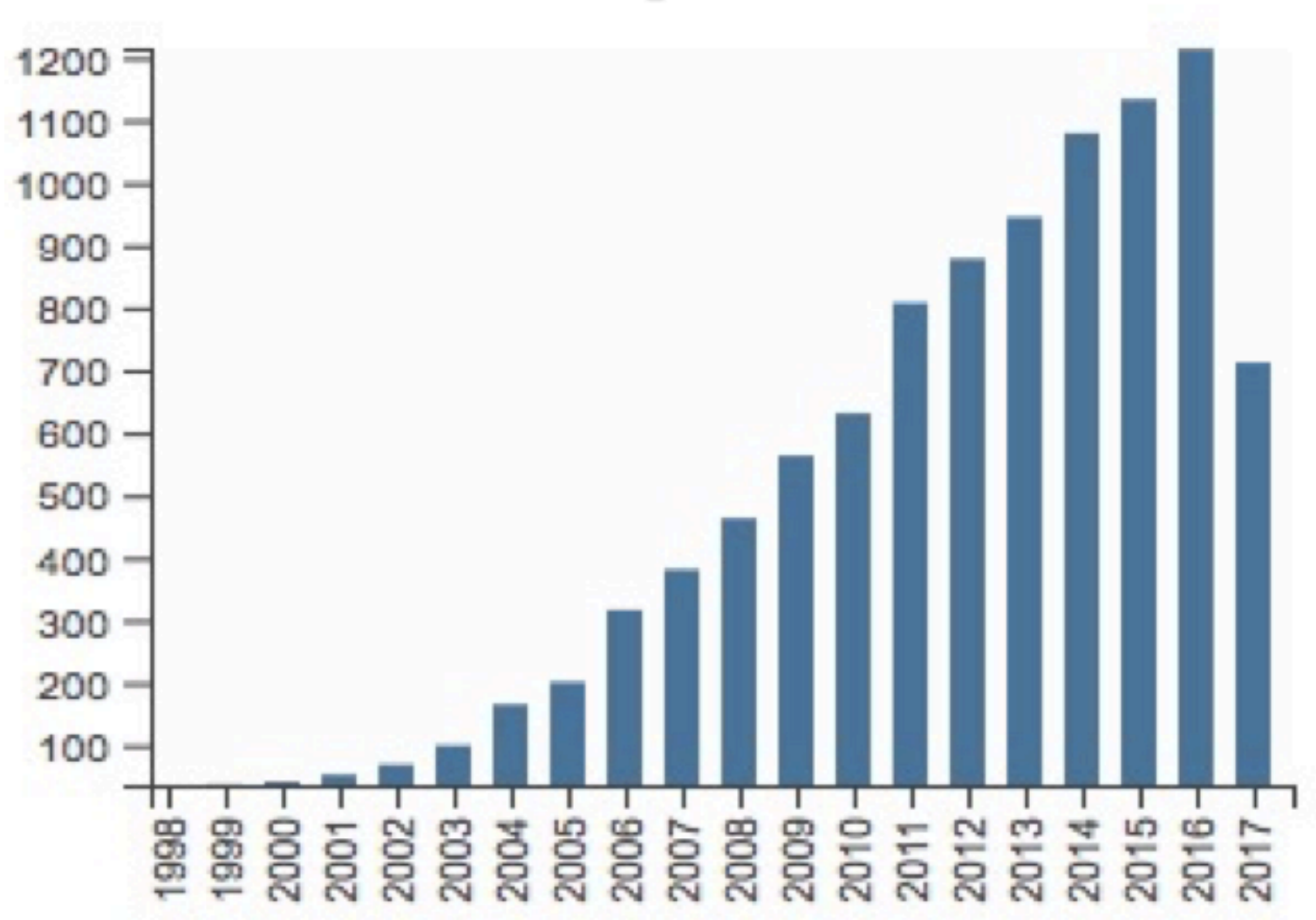
One full issue of Chem. Rev. on “Coinage Metals in Organic Synthesis”
Chem. Rev. **2008**, *108*, 2793-3442

One full issue of Acc. Chem. Res. on “Gold Catalysis”
Acc. Chem. Res. **2014**, *47*, 729-978.

The Gold Rush

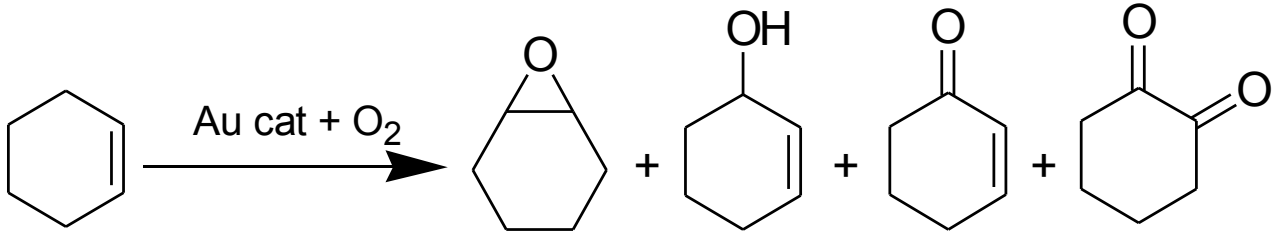
The chemical gold rush started at the beginning of the ’90s

Yearly number of papers dealing with “Gold Catalysis”

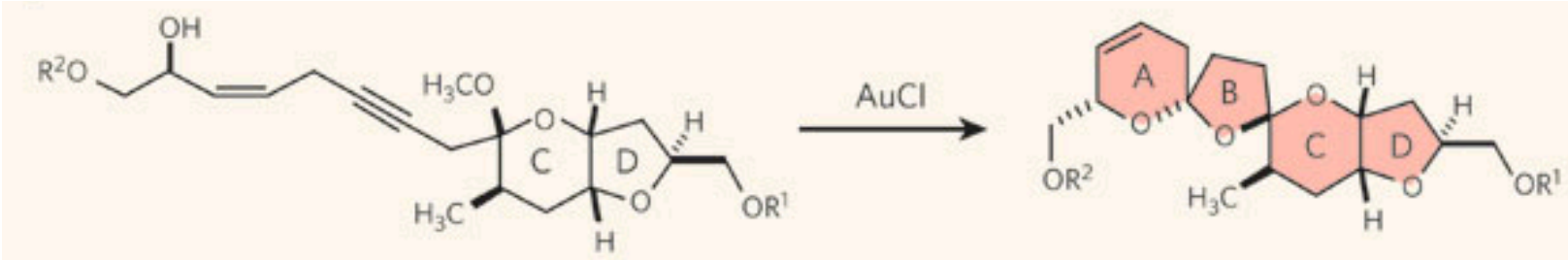


Golden Examples of Gold-Mediated Reactions

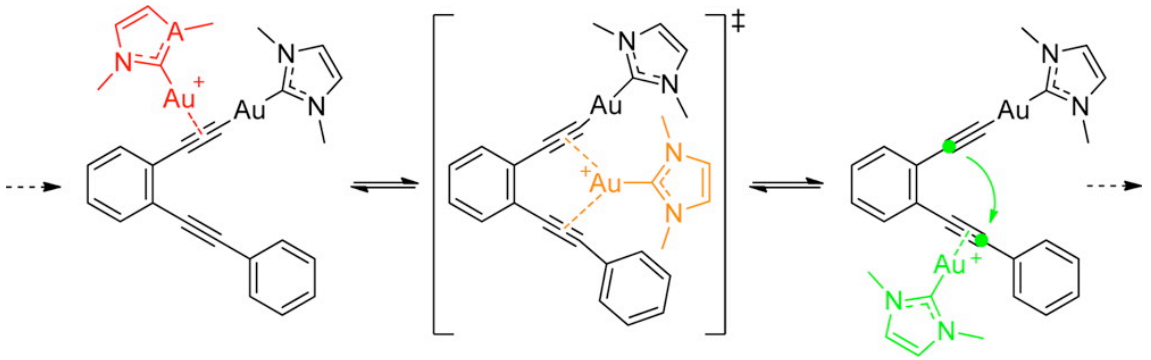
1) Hydrocarbon oxidation under mild conditions
Hutchings, G. J. et al., A. S. *Nature* **2005**, *437*, 1132



2) Synthesis of the A-D rings of Azaspiracids
Li, Y.; Zhou, F.; Forsyth, C. J. *ANIE* **2007**, *46*, 279



3) Dual gold catalysis
Hashmi S. *Acc. Chem. Res.* **2014**, *47*, 864.



Outline

- Introduction
- The Call for Help
- The Golden Carousel
- After the Puzzle
- Conclusions

The Beginning of the Project

29 August 2005, the Kathrina Hurricane hits New Orleans, and Steve Nolan escapes with the whole group to Canada, hosted at the University of Ottawa by Deryn Fogg.

31 October 2005, his group is back at work, and he writes this email

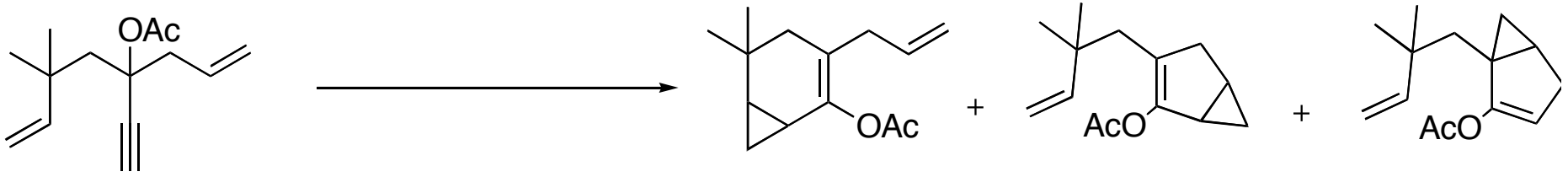
From: Steve P. Nolan
Sent: Mon 10/31/2005 4:24 PM
To: Luigi Cavallo
Subject: ElDorado

Hi GG,
we are getting strange results on a Au assisted cycloisomerization, see the attachment.
Do you think you can help to explain results ?
Looking forward to hearing from you.

Cheers,
Steve

The Attachment

We tested some (NHC)AuCl in the cycloisomerization of dienyne **1**. The benefits of using gold instead of platinum is that the reaction can be done at rt (vs 80°C) in short reaction time and with a lower catalyst loading. Interestingly, we have observed the formation of the unprecedented product **4**.



1 **2** **3** **4**

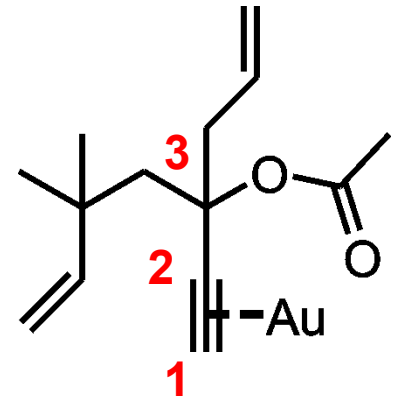
(IPr)AuCl/$AgBF_4$	30%	12%	42%
$PtCl_2$	85%	5-10%	--

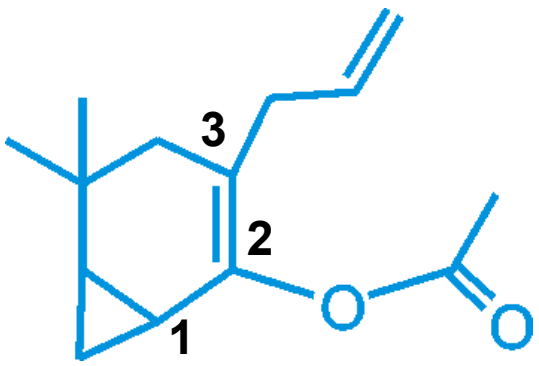
Obviously, these results raise a lot of questions, notably on a plausible mechanism for the formation of **4**. Traditionally, after a 1,2-migration of the acetate on the C=C, the formation of a metallocarbene that performs a cyclopropanation with the olefin is proposed. Products **2** and **3** can be explained with that mechanism but not **4**.

Any idea ?

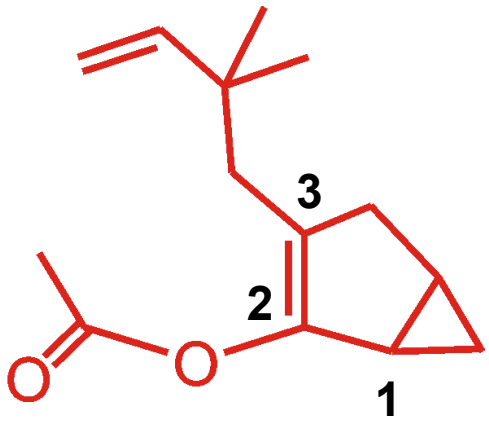
Nicolas
(Nicolas Marion, PhD student in Nolan's group)

The Products

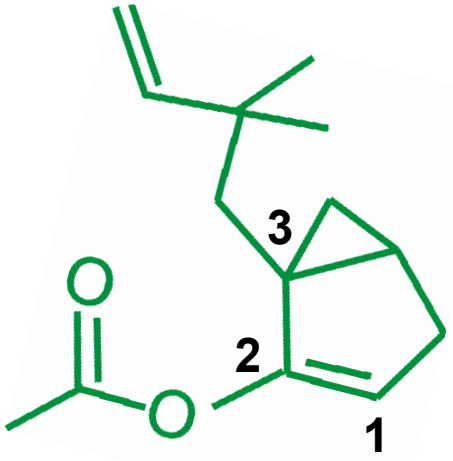




P2



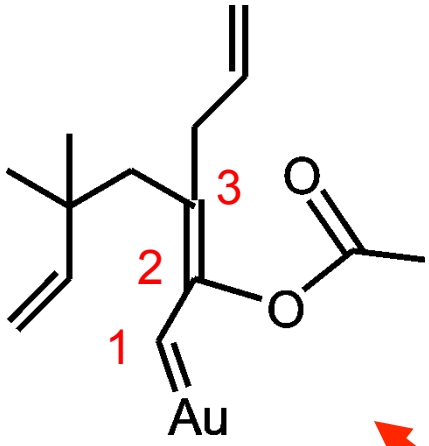
P3



P4

All products present the Ac group migrated to position 2 of the reactant

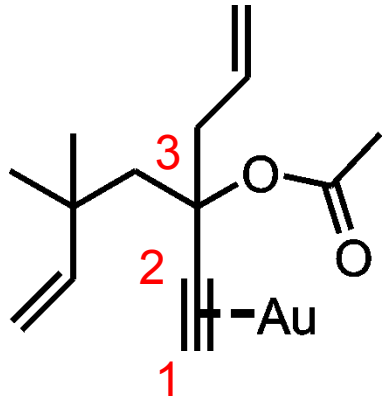
The Basic Steps of the Traditional Mechanisms



1,2-shift

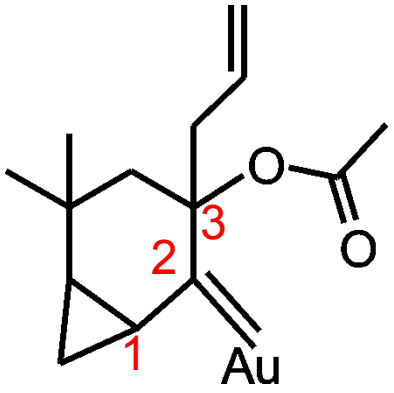
Nu attack of the C=O to the coordinated alkyne

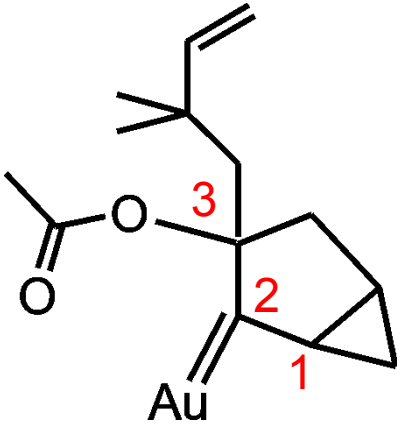
Standard products **P2** and **P3** can be explained with the following steps.
The only question is: Which occurs first ?



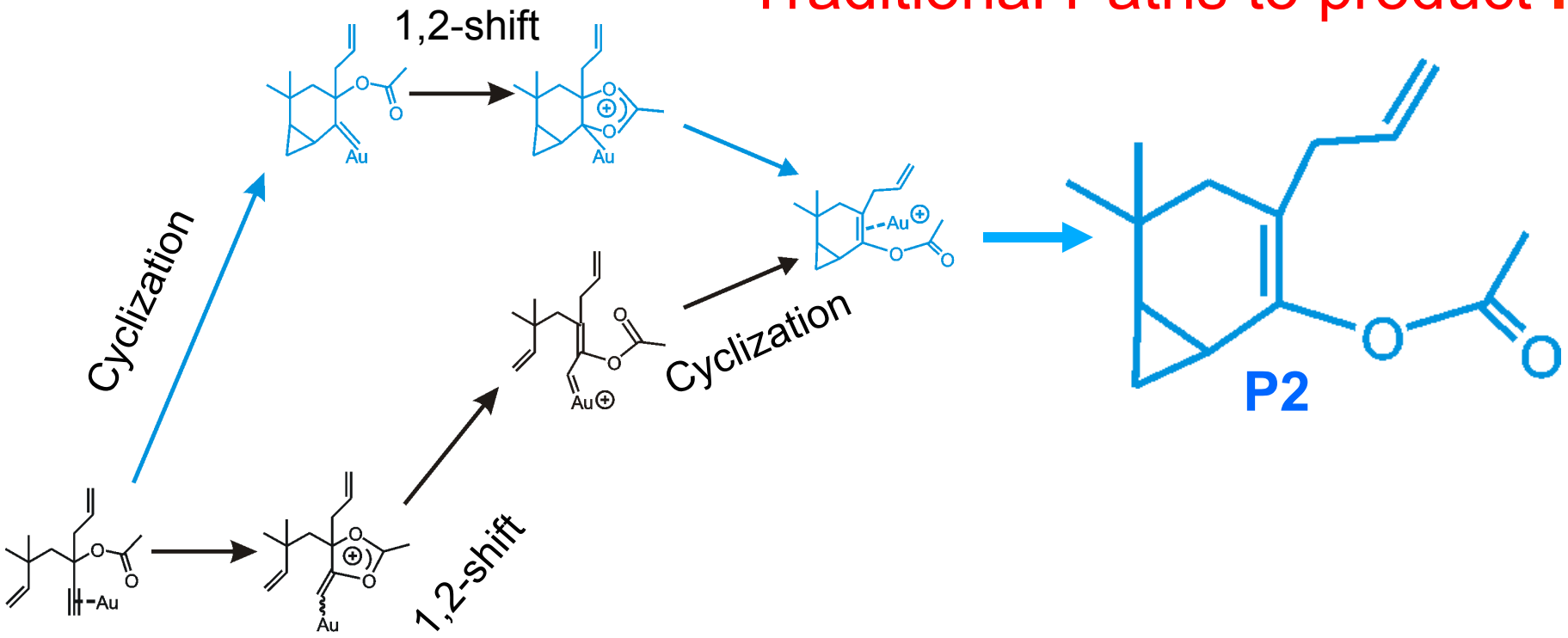
Cyclization

Nu attack of an uncoordinated alkene to the coordinated alkyne





Traditional Paths to product **P2**



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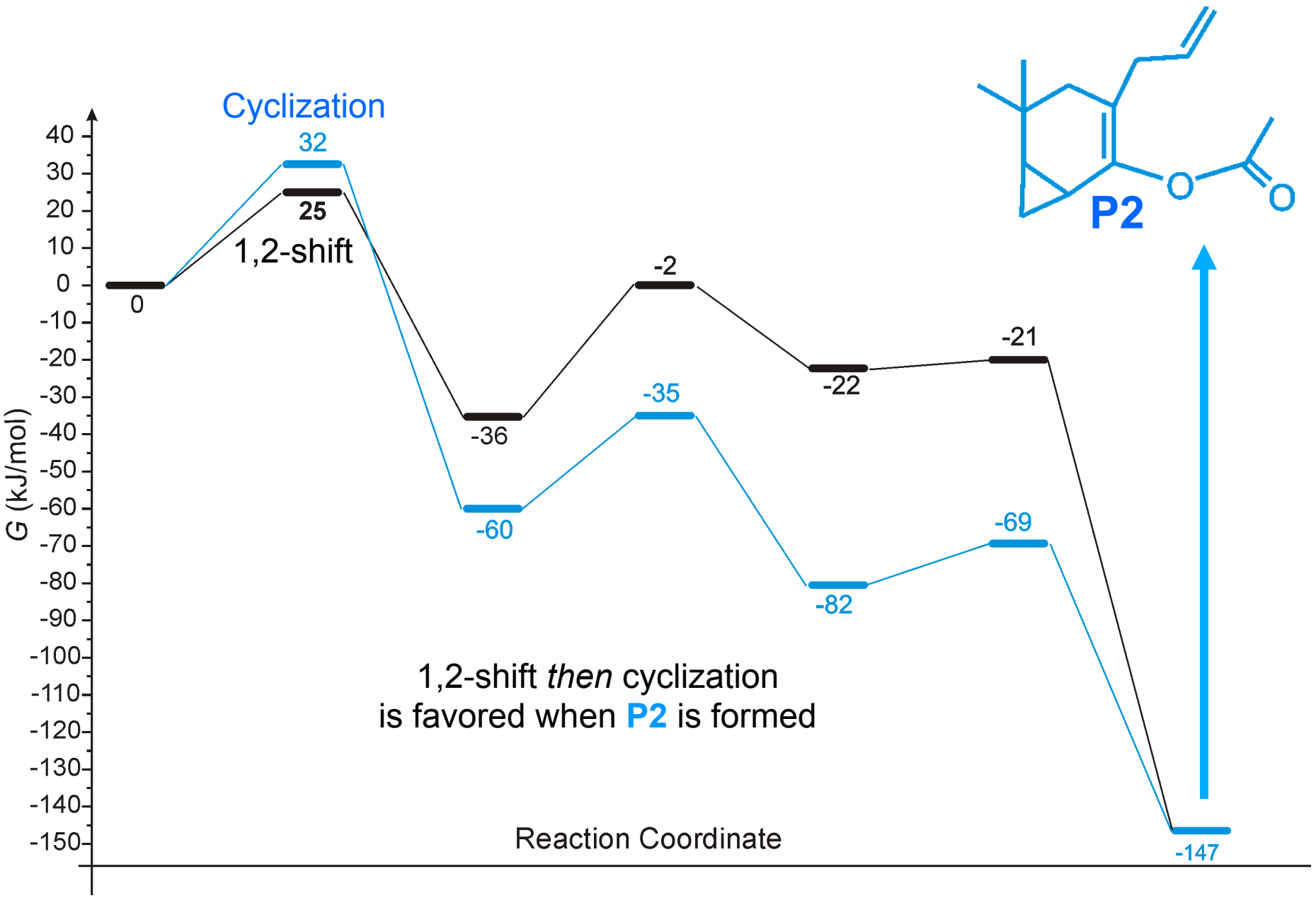
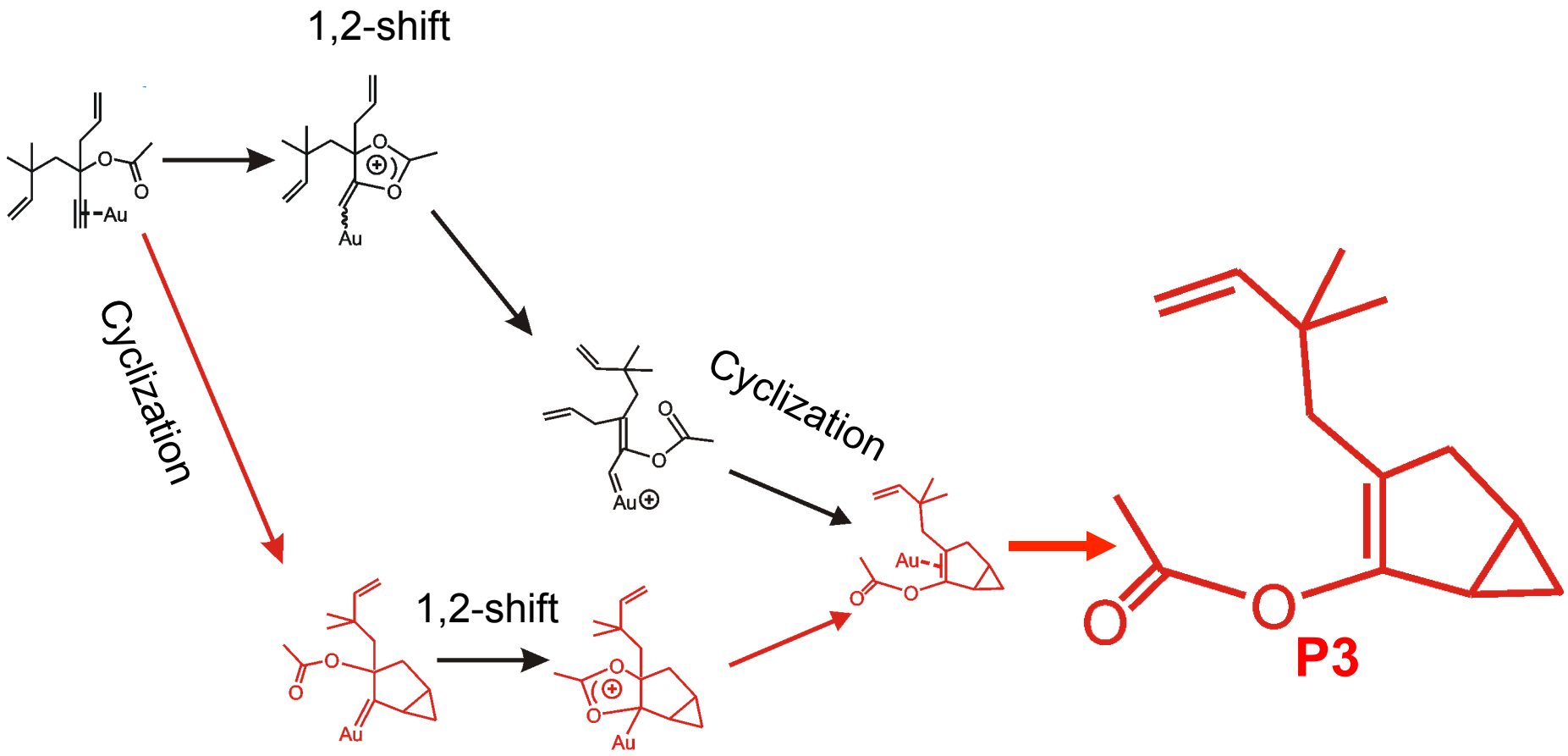
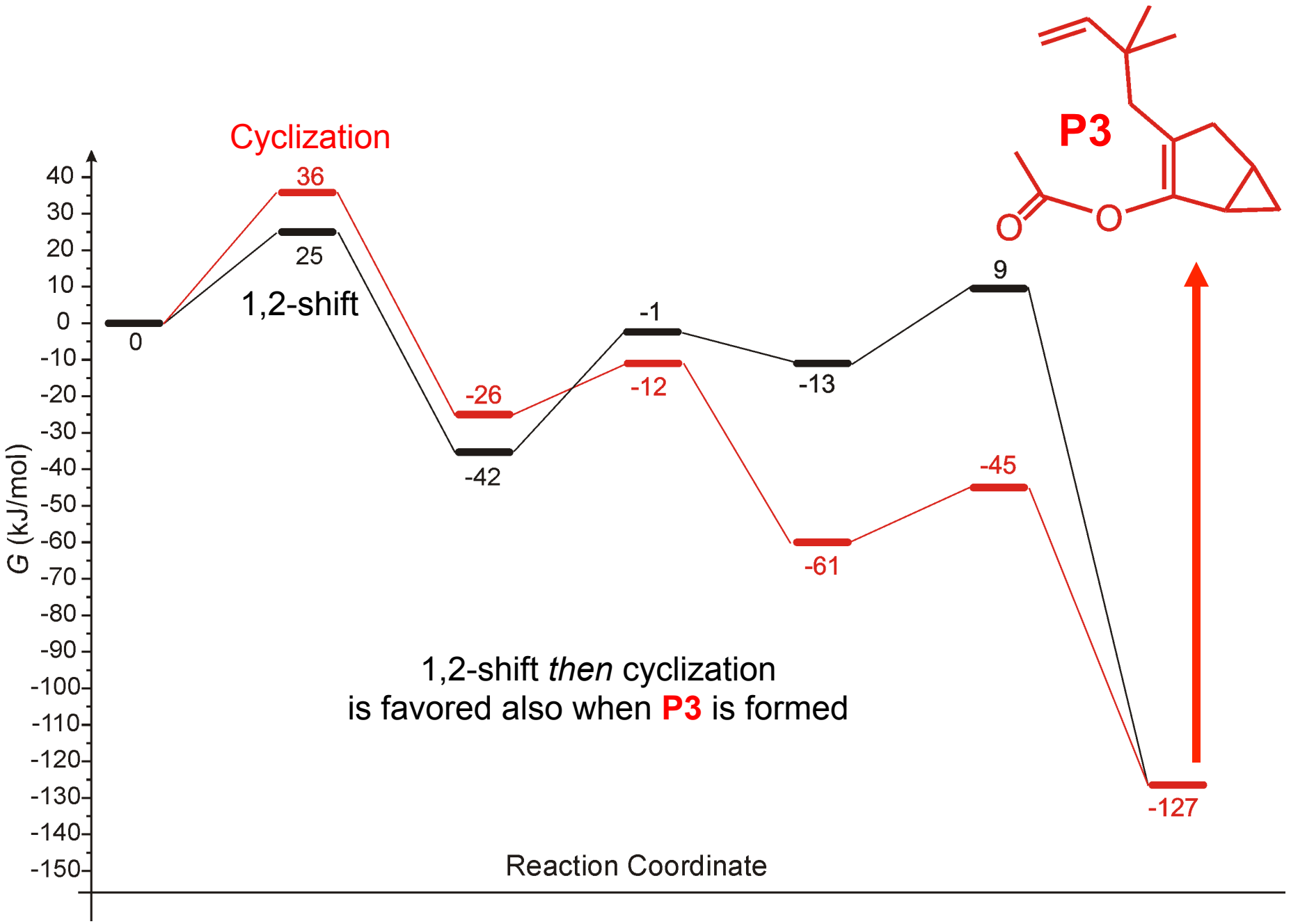


Traditional Paths to product **P3**

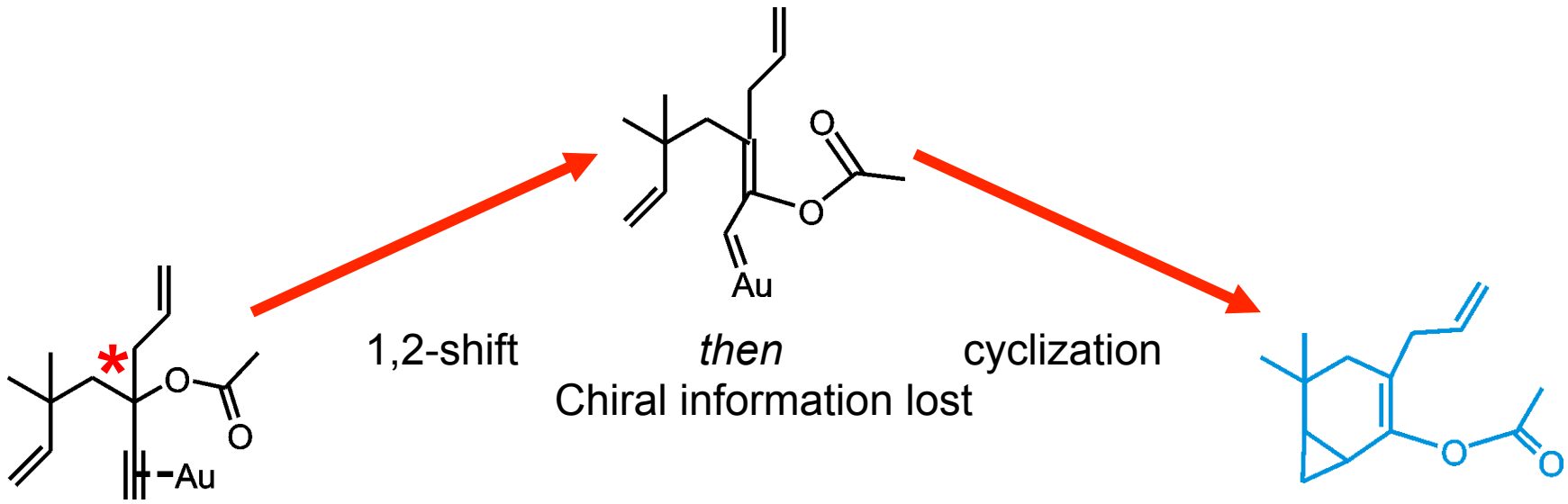


Traditional Paths to product **P3**



First cross check between theory and experiments

Which step occurs first can be determined by
cycloisomerization of enantioenriched substrates



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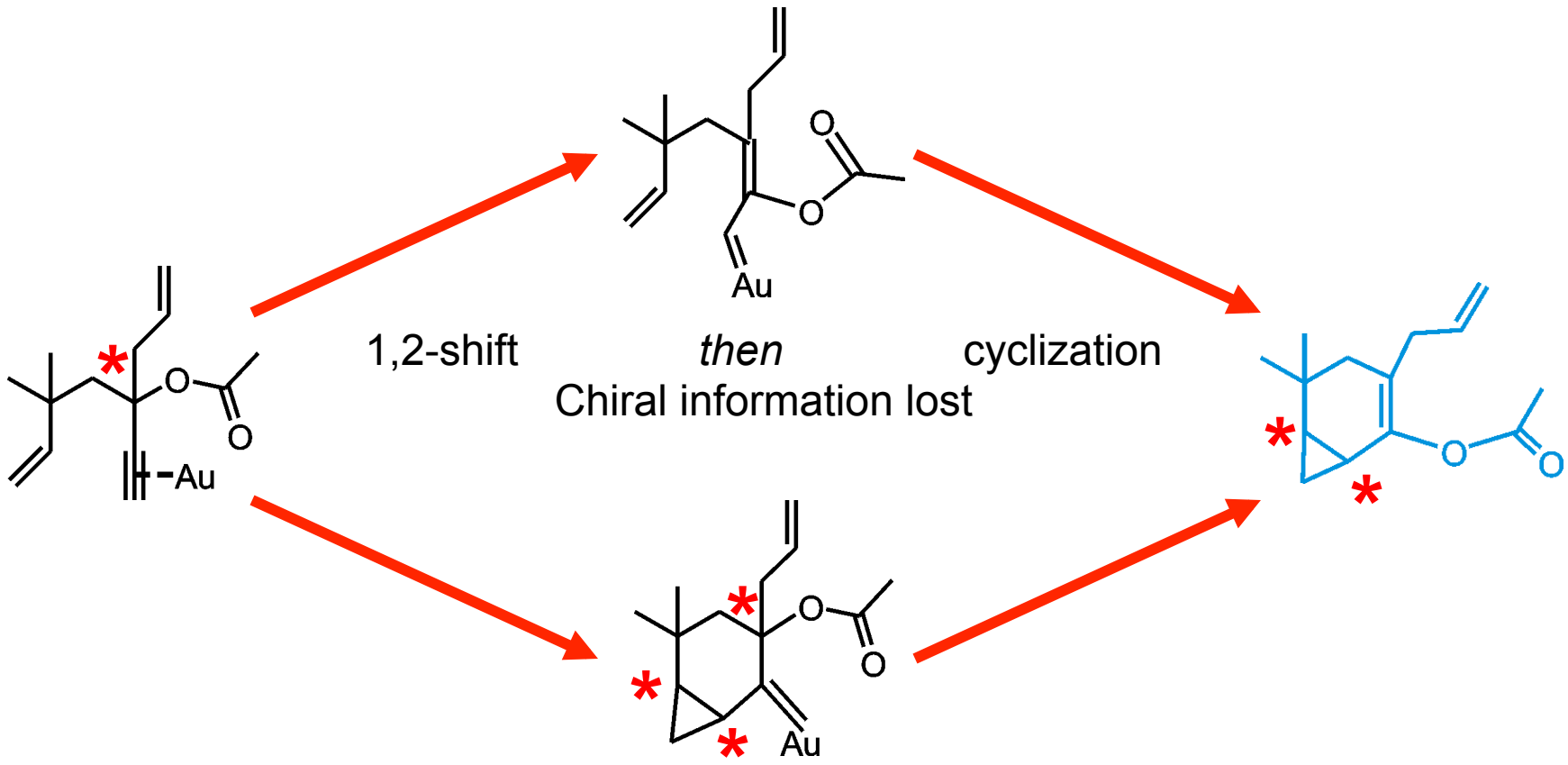

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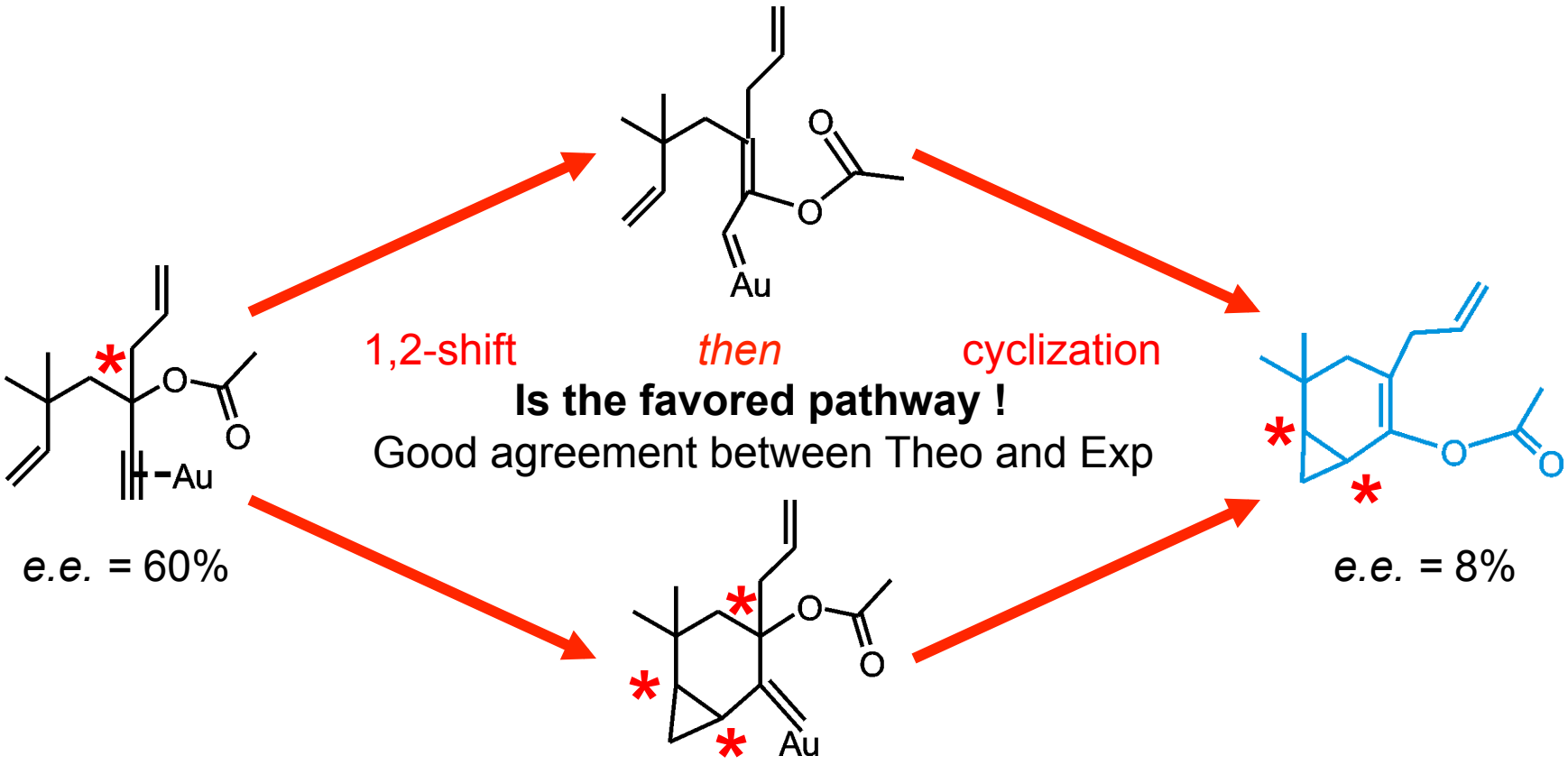


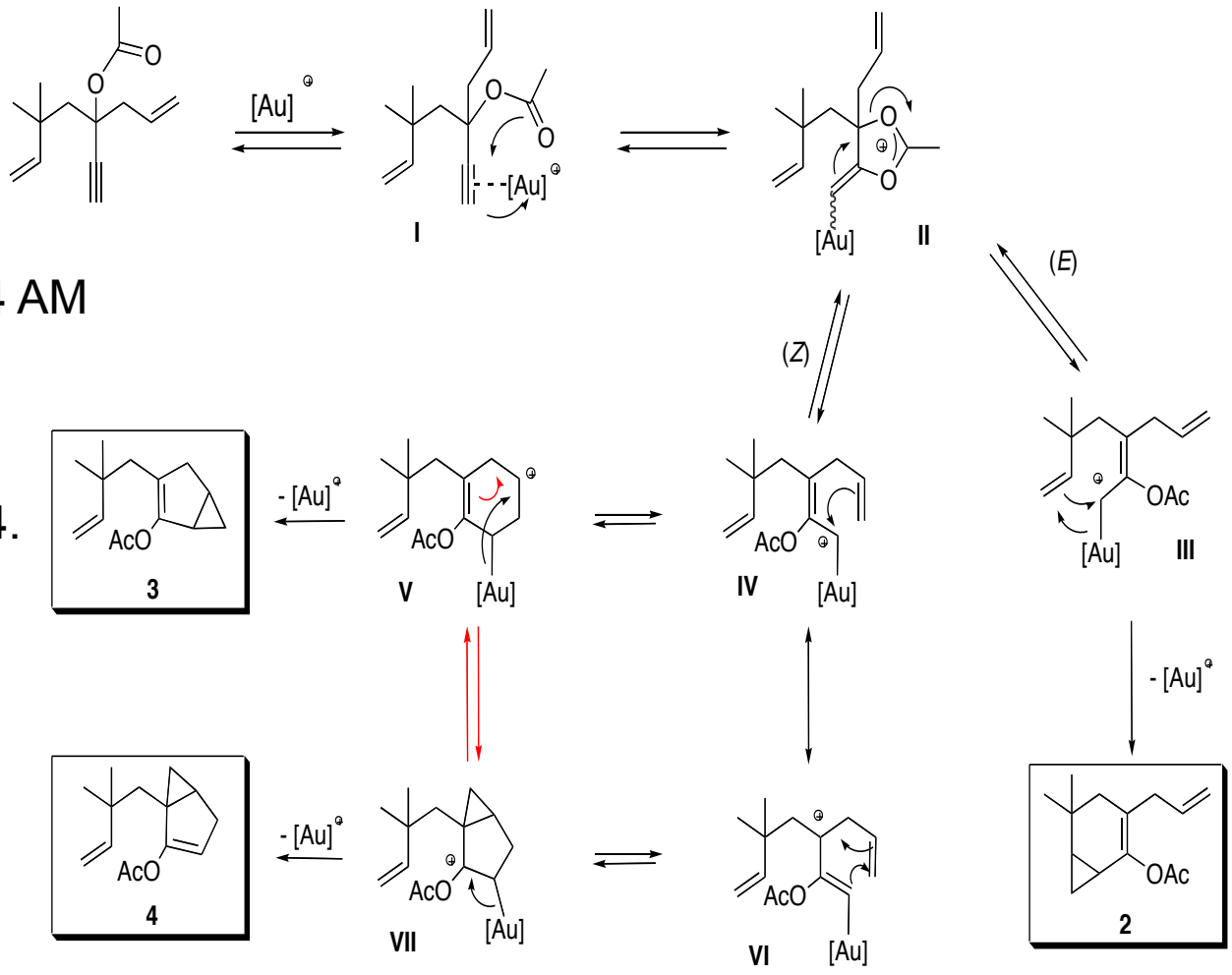
Spring 2006: the Search of the Path to **P4** Begun

By spring 2006 we fully characterized pathways to products **P2** and **P3**.
We optimistically started to search for possible pathways to product **P4**….

The first trial…

From: Steven P. Nolan
Sent: Wed 02/18/2006 11:14 AM
To: Luigi Cavallo
Subject: RE: Re: ElDorado

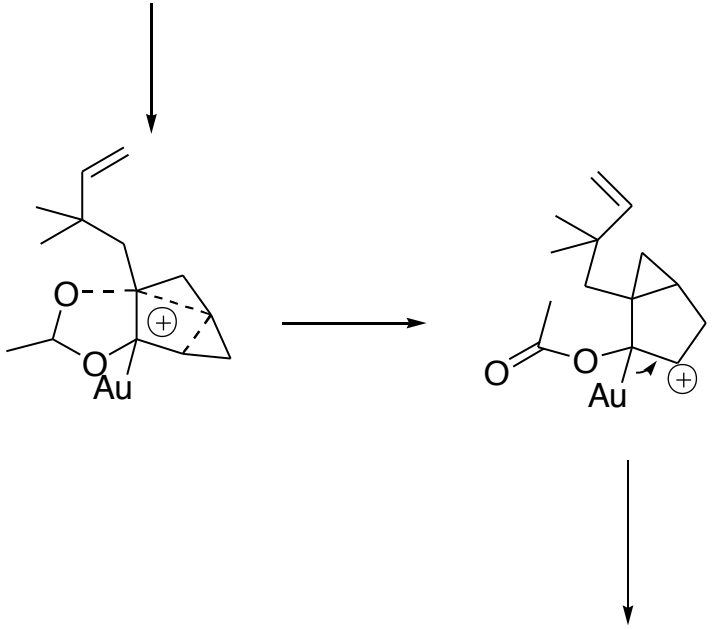
This is the possible path to 4.
Bye,
steve



P4

Beginning of 2007: Keep Searching…

A great number of paths (some of them clearly unrealistic) were tested.
None was the solution...

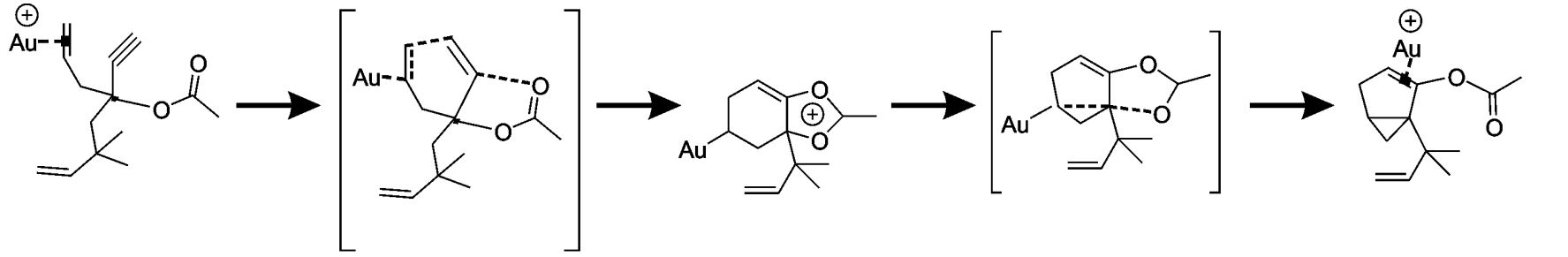


From: Nicolas Marion
Sent: Tue 02/24/2007 04:56 PM
To: Luigi Cavallo
Subject: The last chance ?

Hi GG,
here is the last hypothesis for the Au-mecha. I don't remember if you tried that one, it consists of a sequence cyclopropanation/OAc migration and then rearrangement of the cationic intermediate. cheers,
nicolas

Spring 2007: the Blue Days…

In spring 2007 the best we had is the very high energy pathway that starts with a C=C bond coordinated. Almost giving up…



m (*E* = 2 kJ/mol) → **[m-n]** (*E* =62 kJ/mol) → **n** (*E* = -43 kJ/mol) → **[n-5Au]** (*E* = -47 kJ/mol) → **5Au** (*E* = -112 kJ/mol)

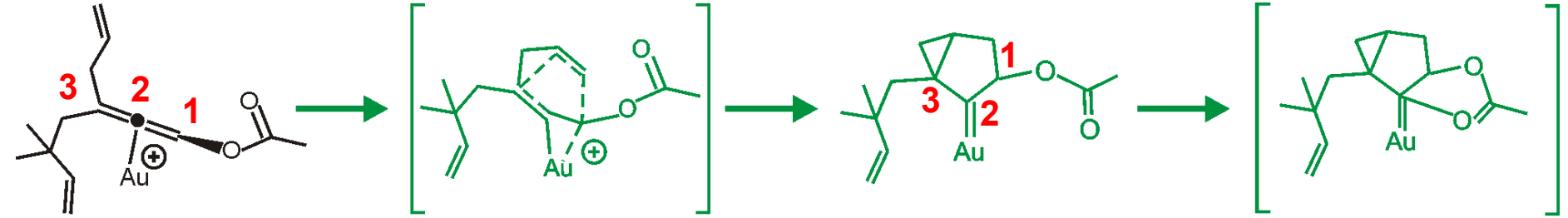
From: Steven P. Nolan
Sent: Fri 03/27/2007 11:22 AM
To: Luigi Cavallo
Subject: RE: Re: RE: Re: RE: Re: RE: Re: RE: Re: RE: Re: Re: Re: RE: ElDorado

hola gg,
we are about to put together a full paper on gold…
cheers,
steve

Marion, de Frémont, Lemière, Stevens, Fensterbank, Malacria, Nolan
Chem. Comm. **2006**, 2048

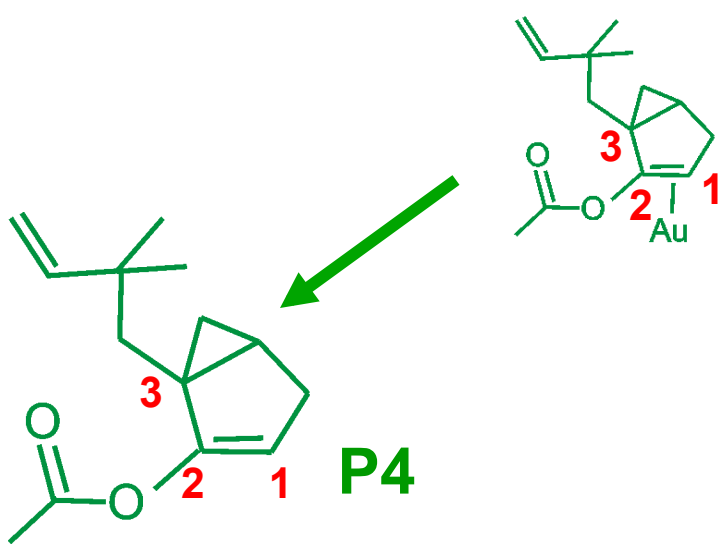
One day…

… we found that an allene complex could be connected to the strange product **P4**.



Allene complex
Ac migrated to 1!

Cyclization step with Ac in 1



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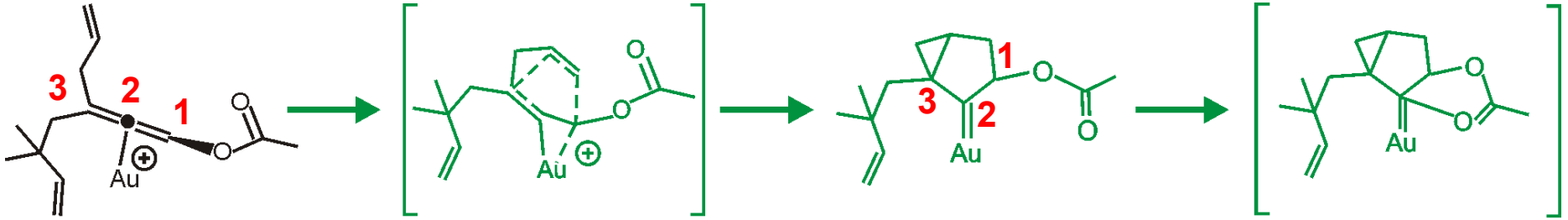

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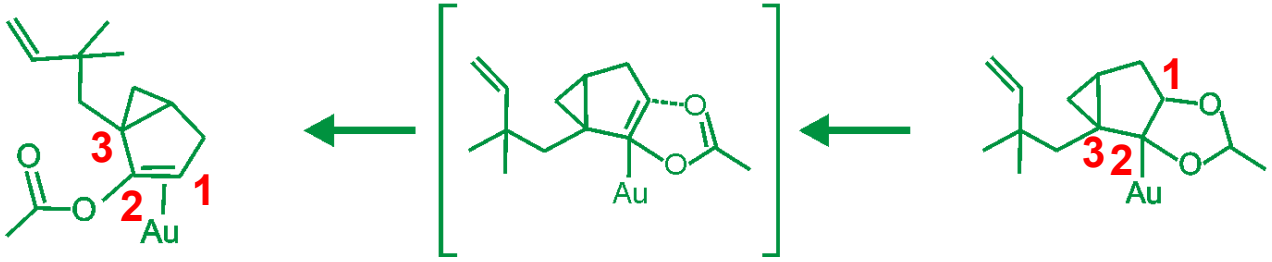
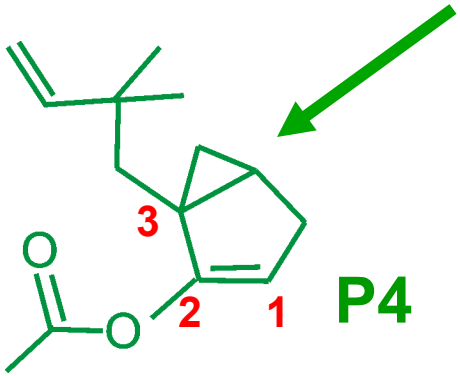


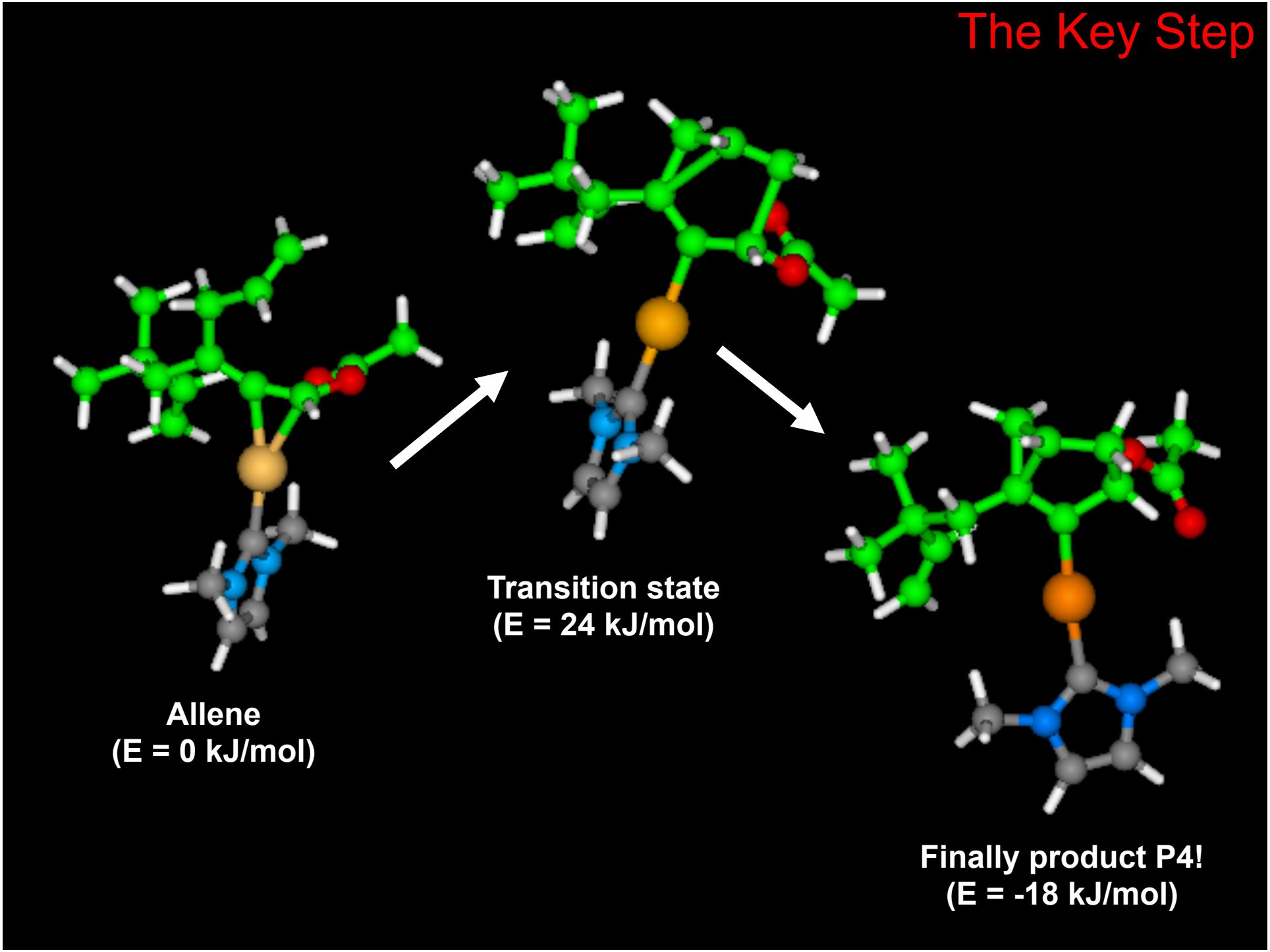
Retro-migration of Ac to 2 !!!
(Almost no reports in literature)



P4

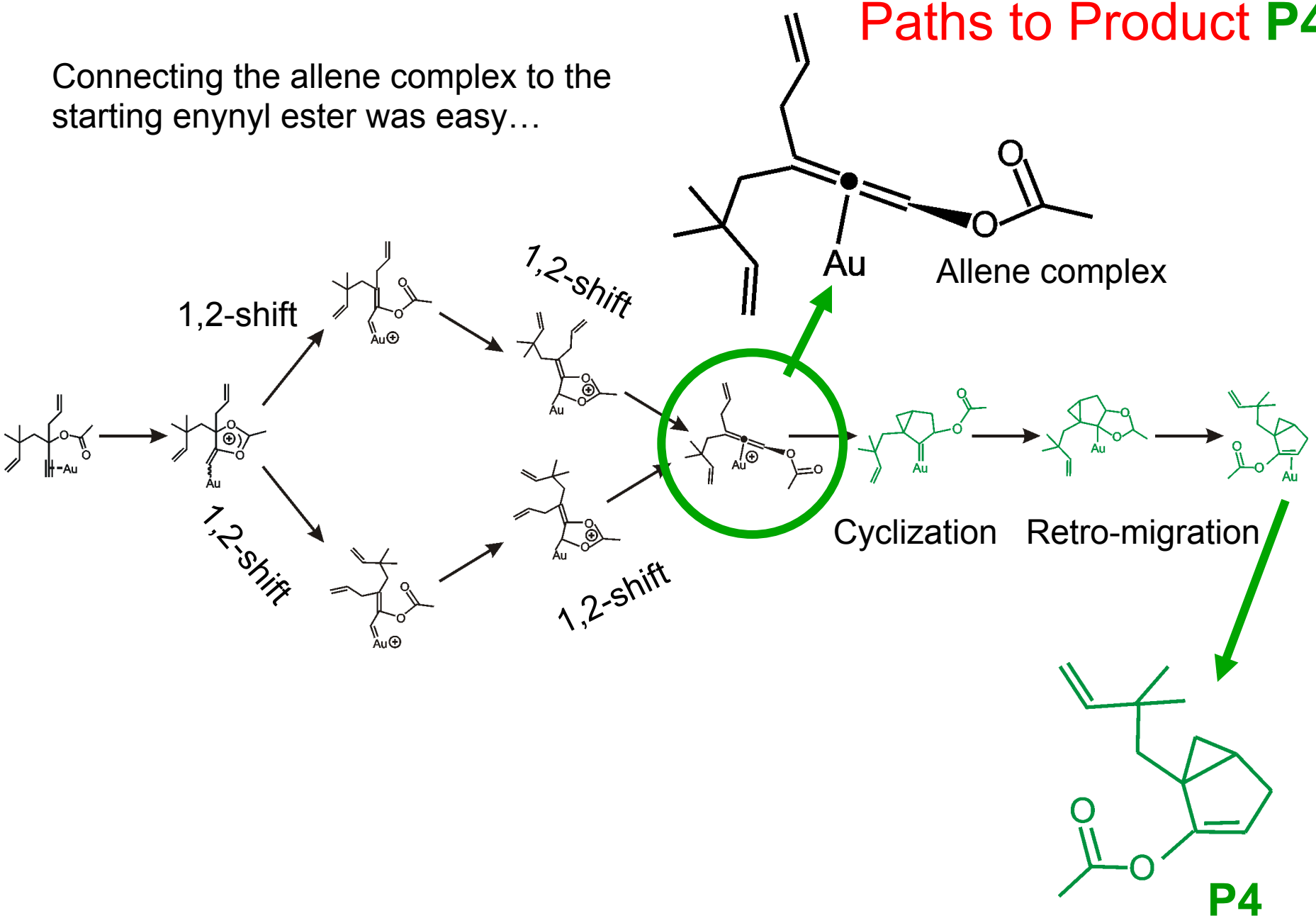
Allene formation, which requires a 1,3-shift, masked by the retro-migration…

The Key Step


Allene
(E = 0 kJ/mol)
Transition state
(E = 24 kJ/mol)
Finally product P4!
(E = -18 kJ/mol)

Paths to Product **P4**

Connecting the allene complex to the starting enynyl ester was easy…



Paths to Product **P4**

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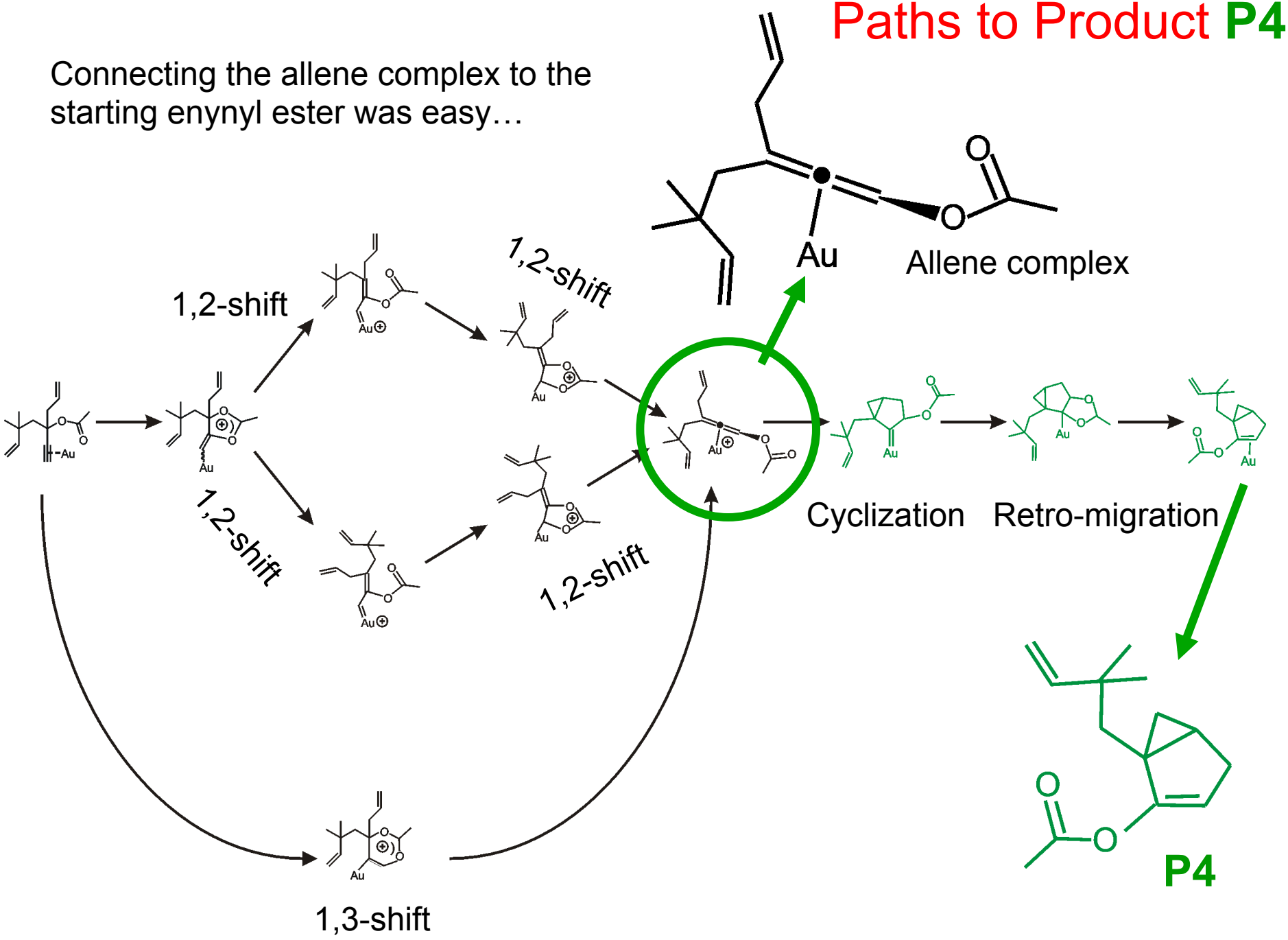
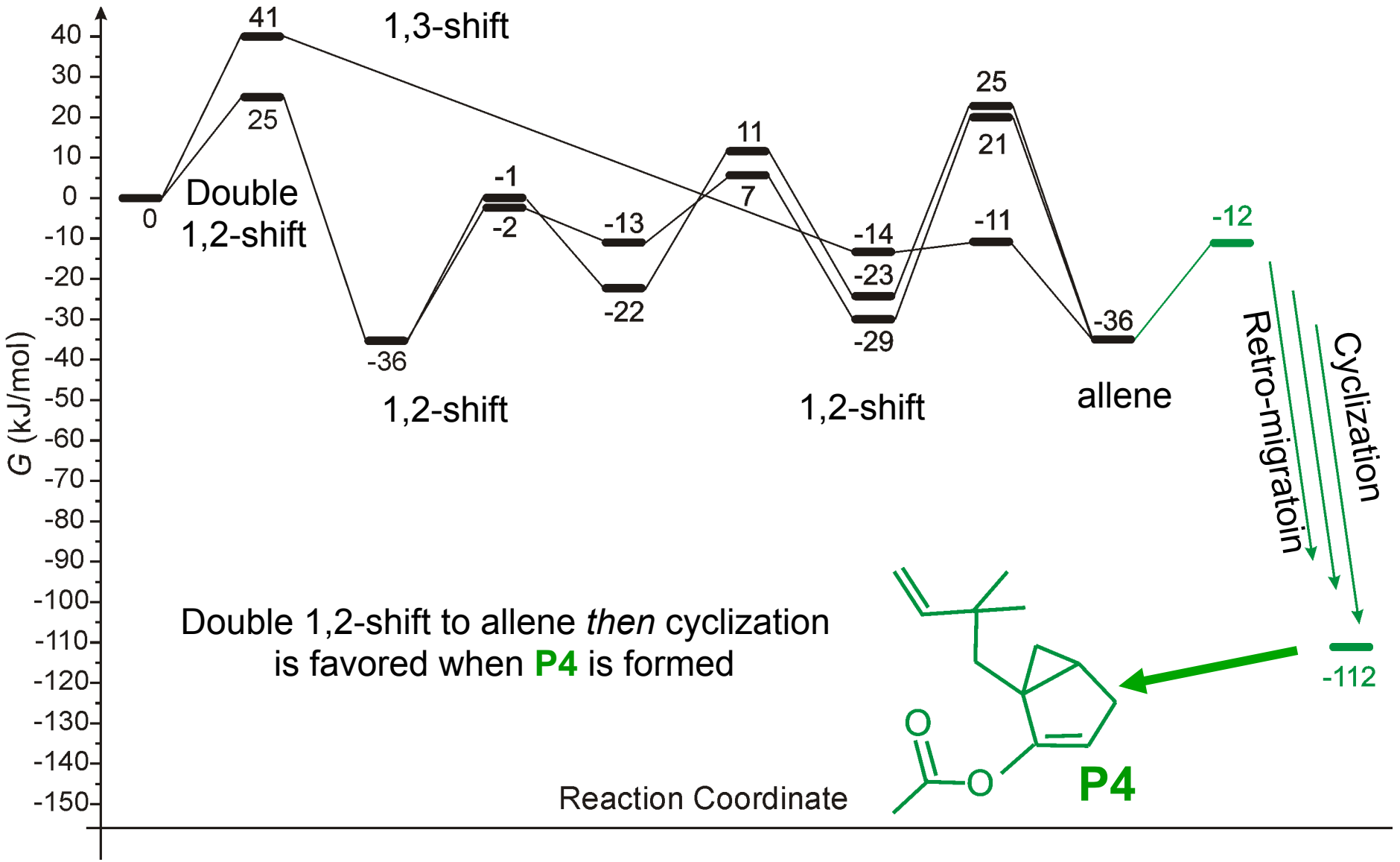


Paths to Product **P4**



Validating the New Path

From: Luigi Cavallo
Sent: Fri 06/01/2007 07:41
To: Steve Nolan
Cc: Nicolas Marion
Subject: Last chance for the naugthy gold…

Hola Spain,

maybe (maybe) we found a solution (see the attachment)!
Waiting for your comments…

Andrea is cleaning/checking that we have all the pieces, and that they actually fit together.

Ciao,
gg

(Andrea Correa, post-doc in my group)

Validating the New Path

From: Nicolas Marion
Sent: Fri 06/01/2007 10:28
To: Luigi Cavallo,snolan@iciq.es,acorrea@unisa.it
Subject: Re: Last chance for the naugthy gold…

Hi Luigi, hi all,

I'm really excited by your new proposal...

I'll try to start from the preformed allene and activate it with Au+.
Unfortunately I won't be in the lab before monday but as soon as I come back, I will try experimentally.

I'll let you know asap.

cheers,
nicolas

Validating the New Path

From: Nicolas Marion
Sent: Mon 06/04/2007 23:43
To: Luigi Cavallo,snolan@iciq.es,acorrea@unisa.it
Subject: Re: Re: Last chance for the naugthy gold…

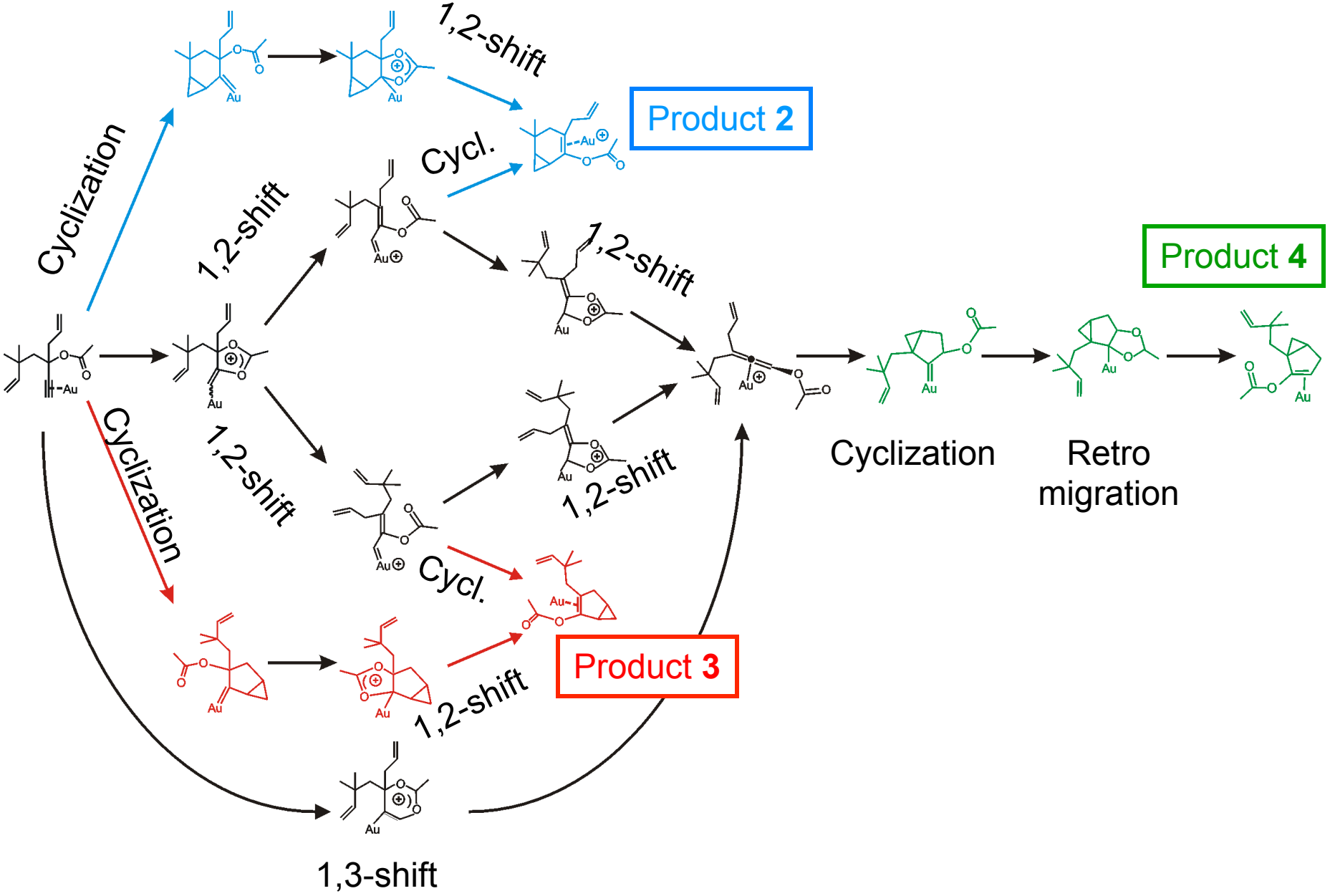
I have excellent news... I made the allene today and put it under Au-conditions and guess what... **P4** as the major cyclised product along with a little bit (around 15%) of **P3**. And as a bonus, the reaction seems quantitative with no formation of **P2**.

It was just a test reaction, so chemical yields will come later but I think that what you proposed is well backed up now, so enjoy.

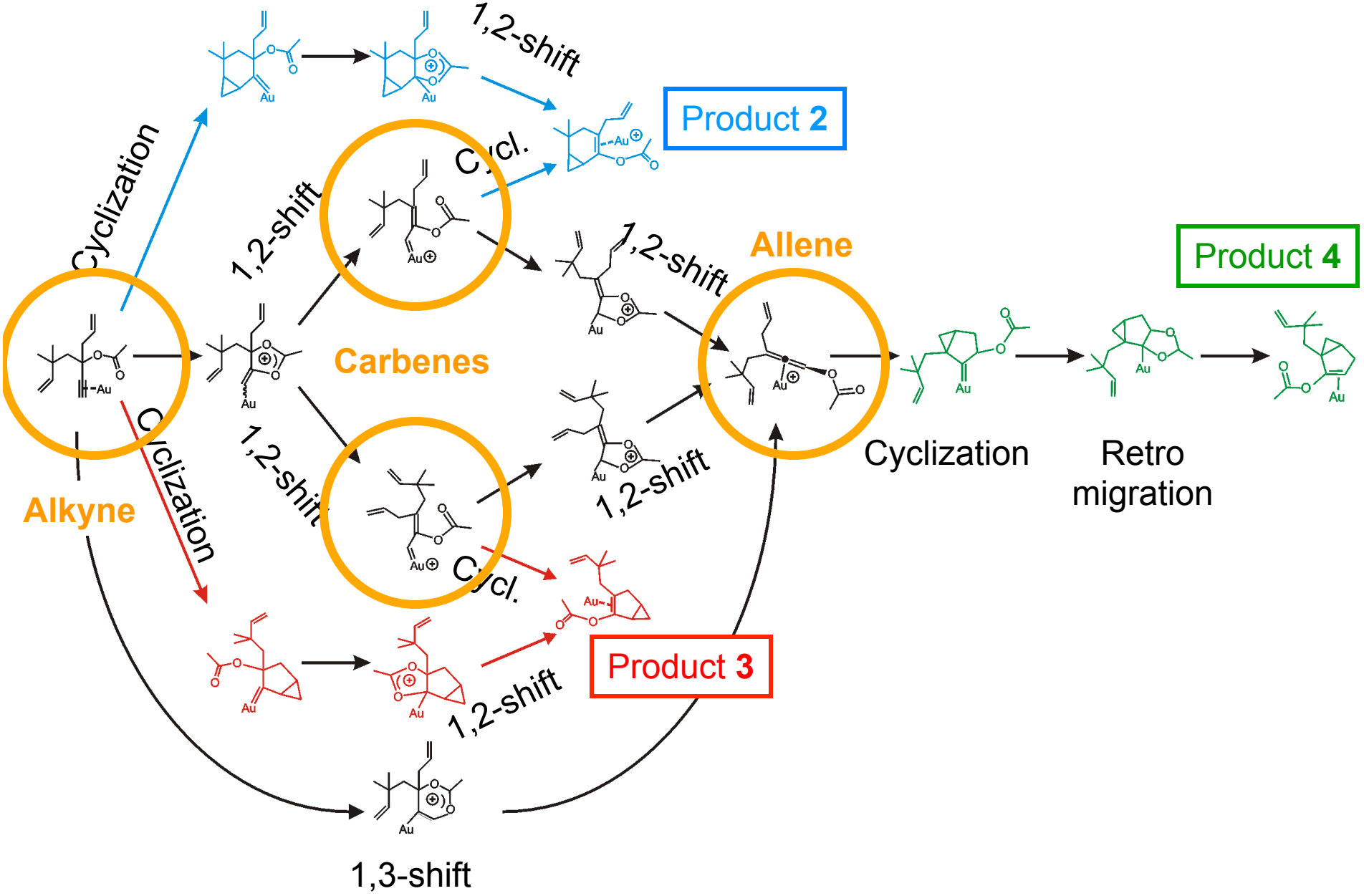
Cheers,
A very happy Nicolas.

June 2007, the game was (finally) over…

All Paths Together



All Paths Together

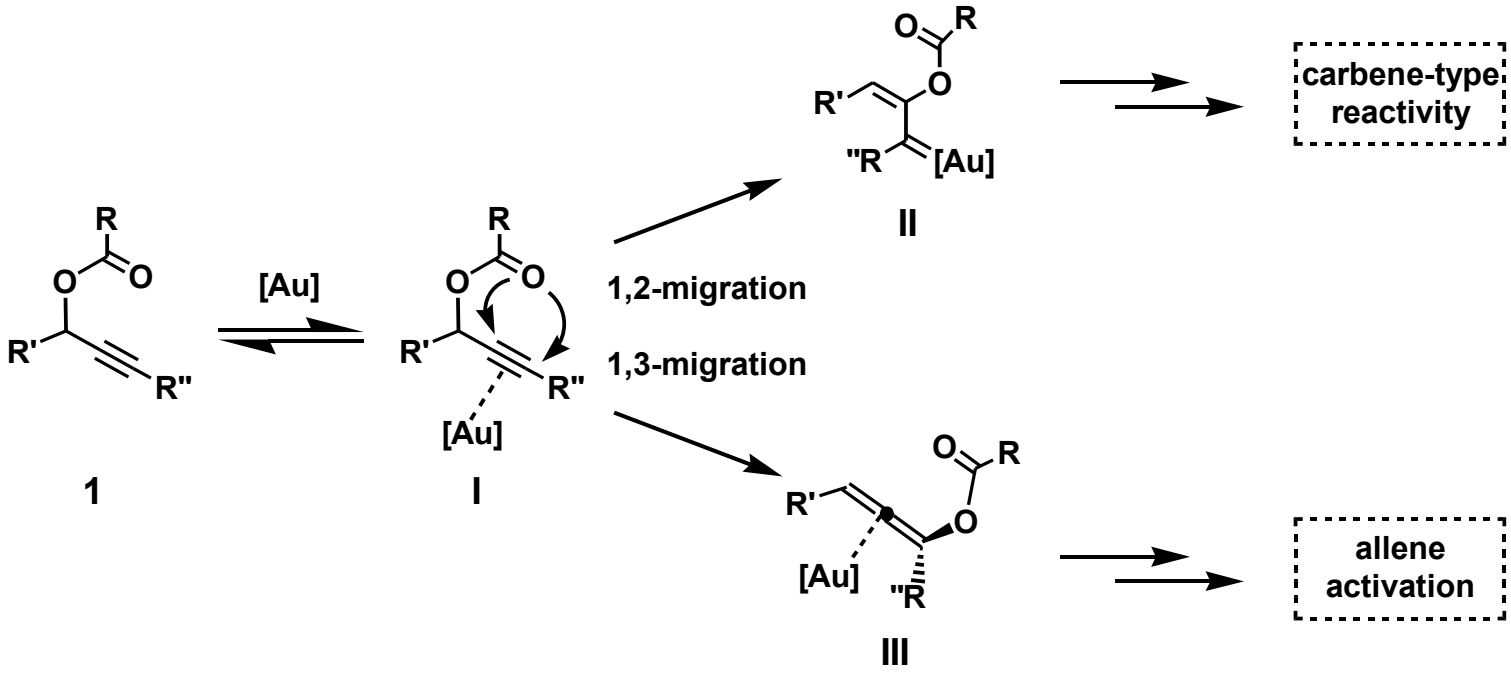


Outline

- Introduction
- The Call for Help
- The Golden Carousel
- After the Puzzle
- Conclusions

Current Knowledge at theTime

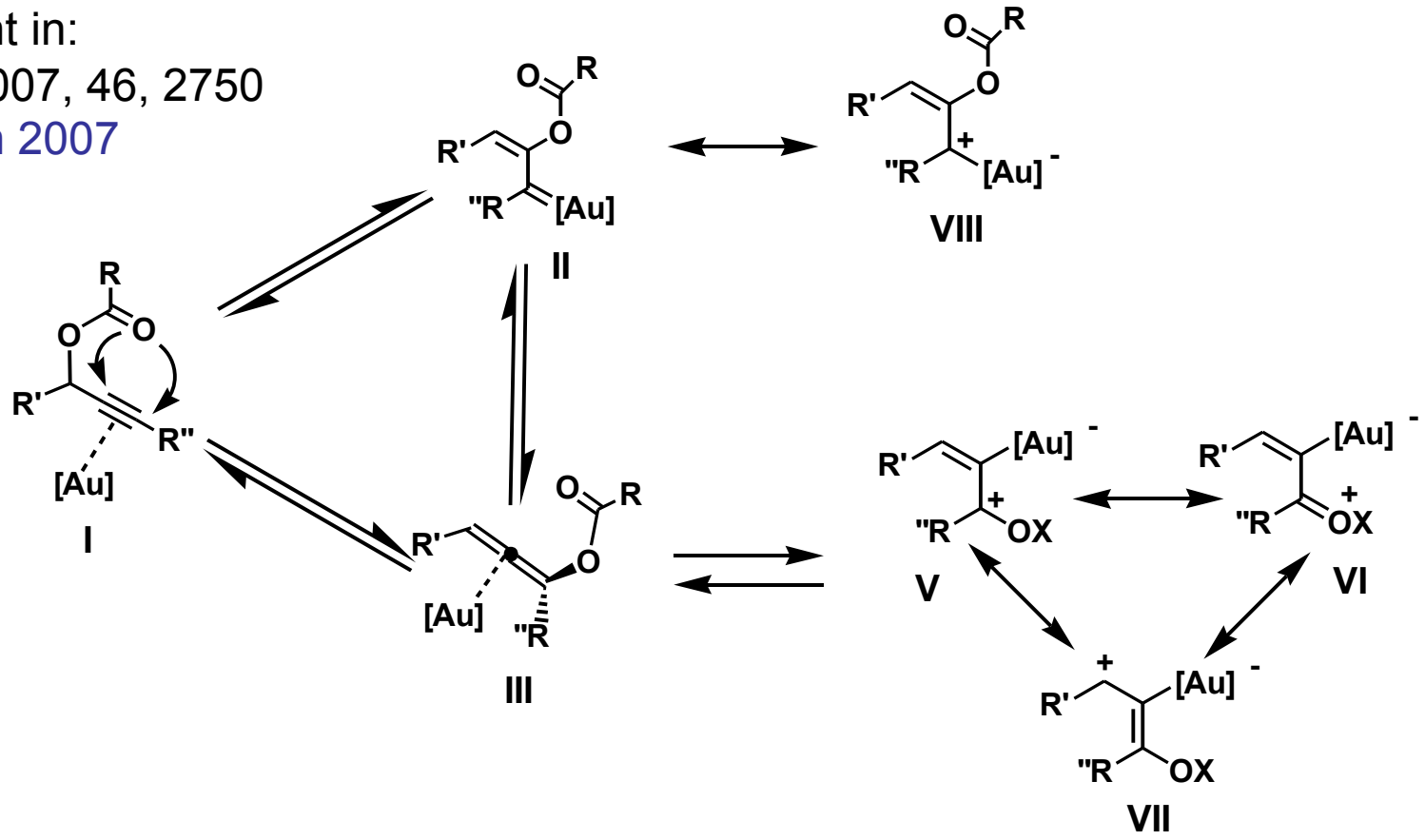
Marion & Nolan
Highlight in:
ANIE 2007, 46, 2750
9 march 2007



However, it was unclear if the carbene and the allene are just intermediates along different branches or there is some connection between them

What Was Hypothesized…

Marion & Nolan
Highlight in:
ANIE 2007, 46, 2750
9 march 2007



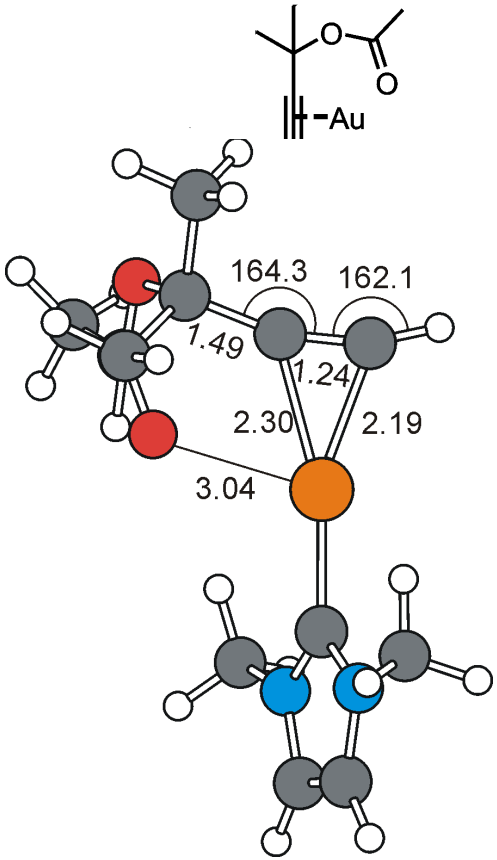
Scheme 4. Plausible intermediates in equilibrium upon coordination of oxionic Au onto a propargylic ester.

"…it is most likely that the intermediates in Scheme 4 are all in equilibrium and react further as a function of the tethered groups."

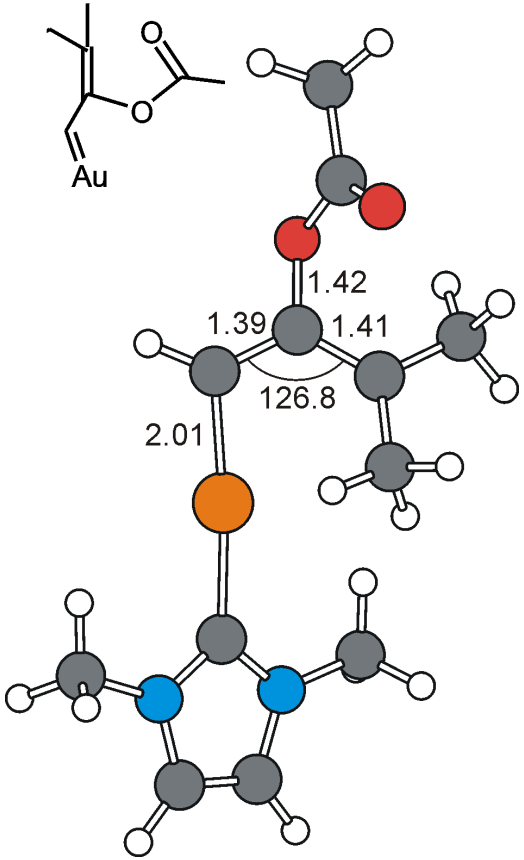
"…furthermore, numerous mechanistic questions, including the nature of the 1,3-acyl shift (1,3- or double 1,2-shift) are still subjects of debate."

Simplifying the Key Intermediates

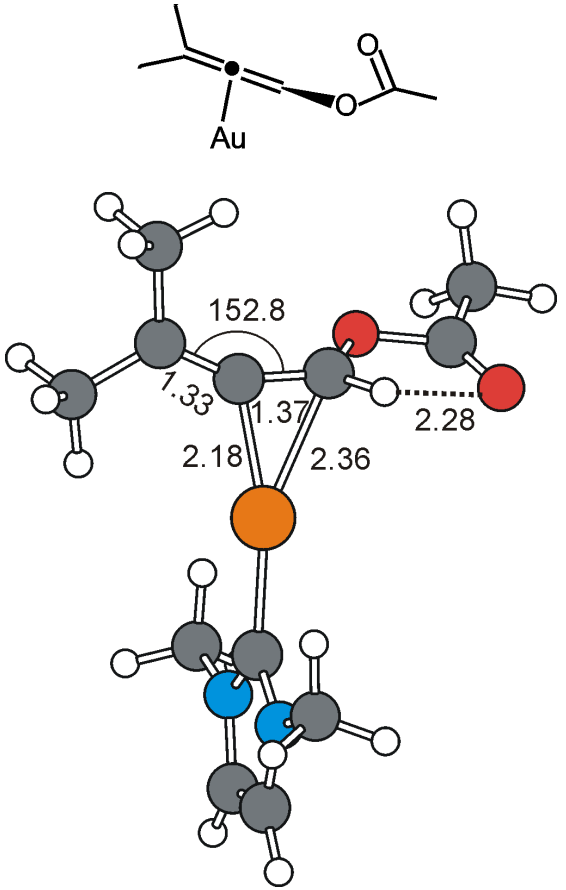
Coordinated Alkyne



Au-carbene



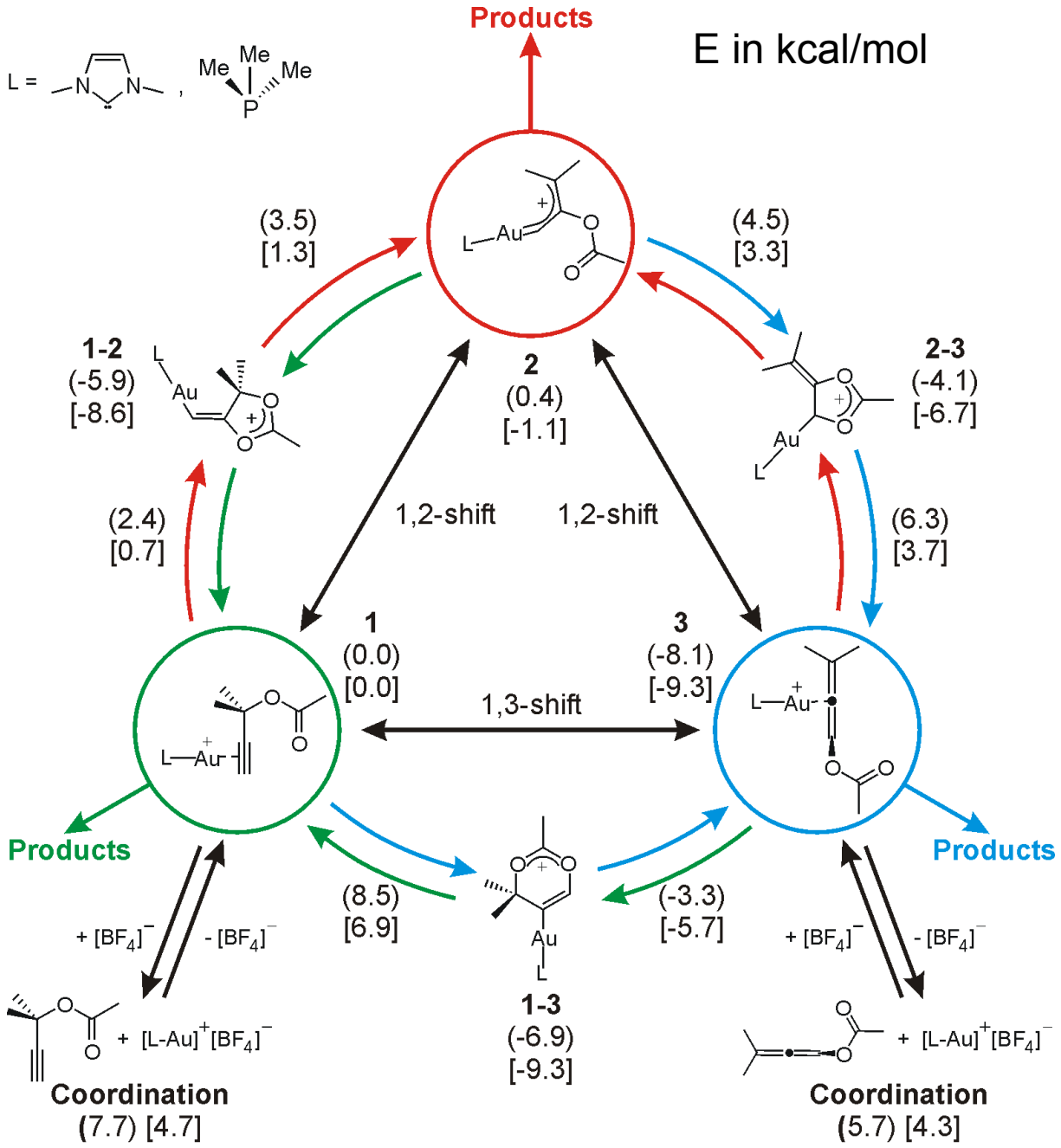
Allene



New Questions We Decided To Tackle!

1) Are they in equilibrium ?
2) How do they interconvert into each other ?
3) How to explain the products distribution from starting conditions ?

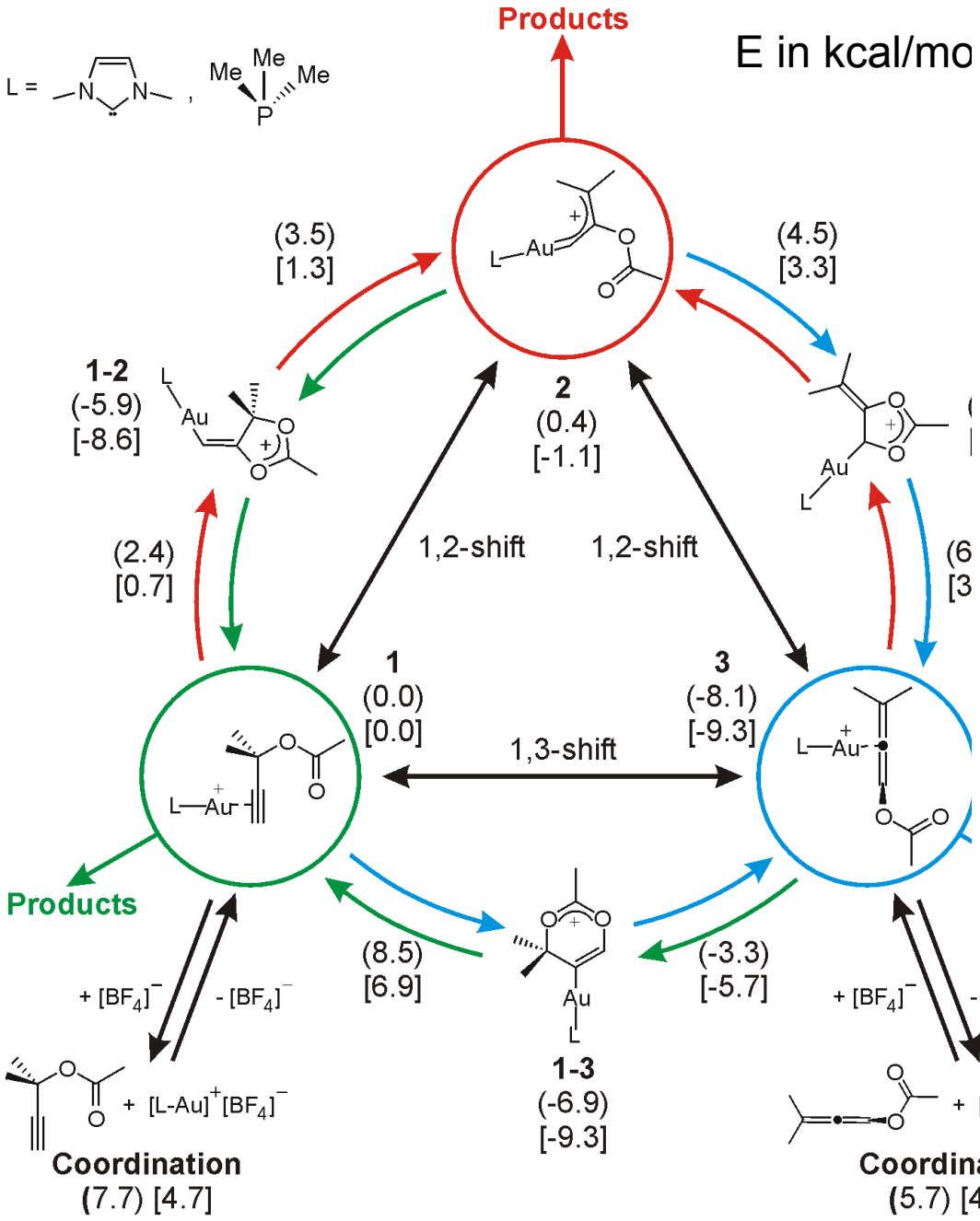
The Cationic Gold-Propargylic Ester Cycle



A Golden Carousel

Correa, Marion, Fensterbank, Malacria, Nolan, Cavallo
ANIE **2008**, *47*, 718
(Hot paper)
Submitted 16/08/07

The Cationic Gold-Propargylic Ester Cycle



Nolan, Cavallo
ANIE **2008**, *47*, 718
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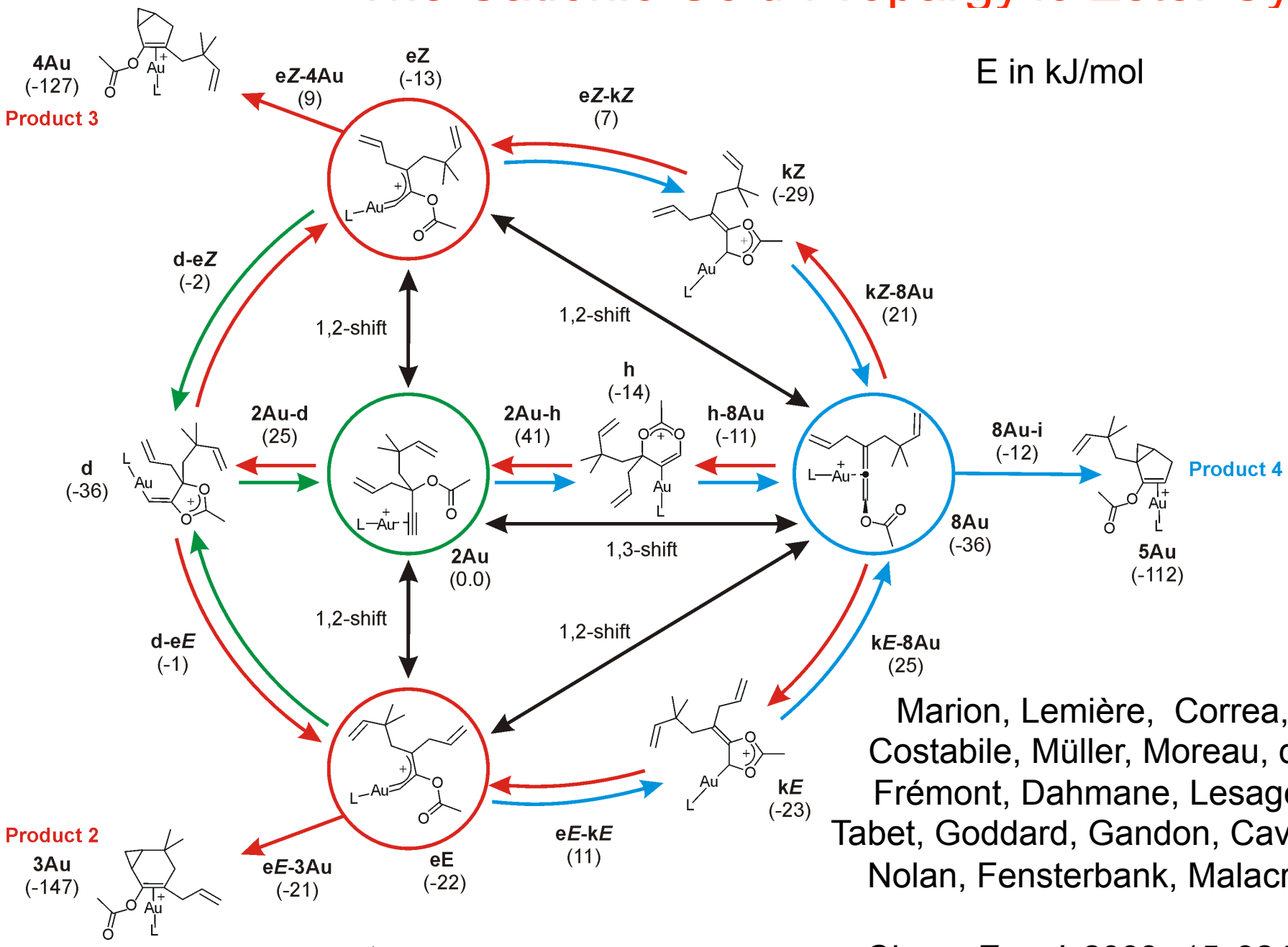
The Cationic Gold-Propargylic Ester Cycle



Marion, Lemière, Correa, Costabile, Müller, Moreau, de Frémont, Dahmane, Lesage, Tabet, Goddard, Gandon, Cavallo, Nolan, Fensterbank, Malacria

Chem. Eur. J. **2009**, *15*, 3243.

Outline

- Introduction
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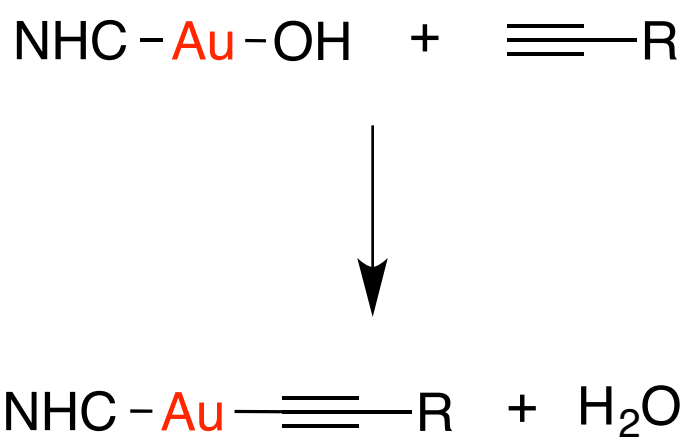
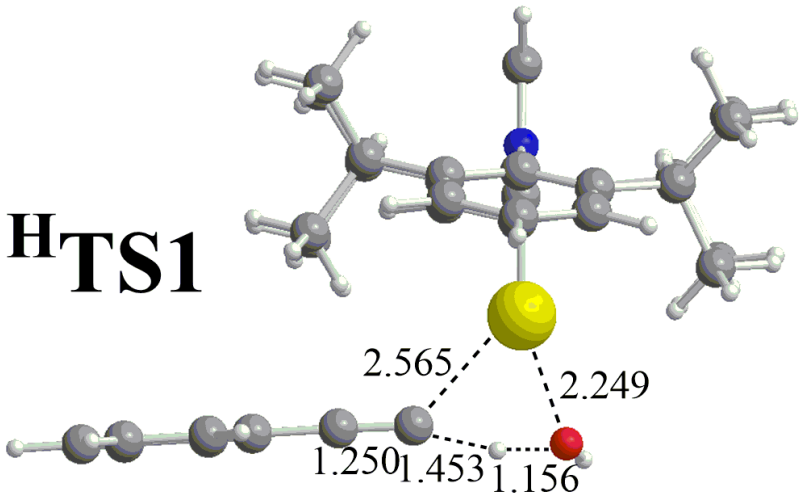
How to best use these 3 years experience ?

2010 : Au promoted C-H activation

A versatile gold synthon for acetylene C-H bond activation



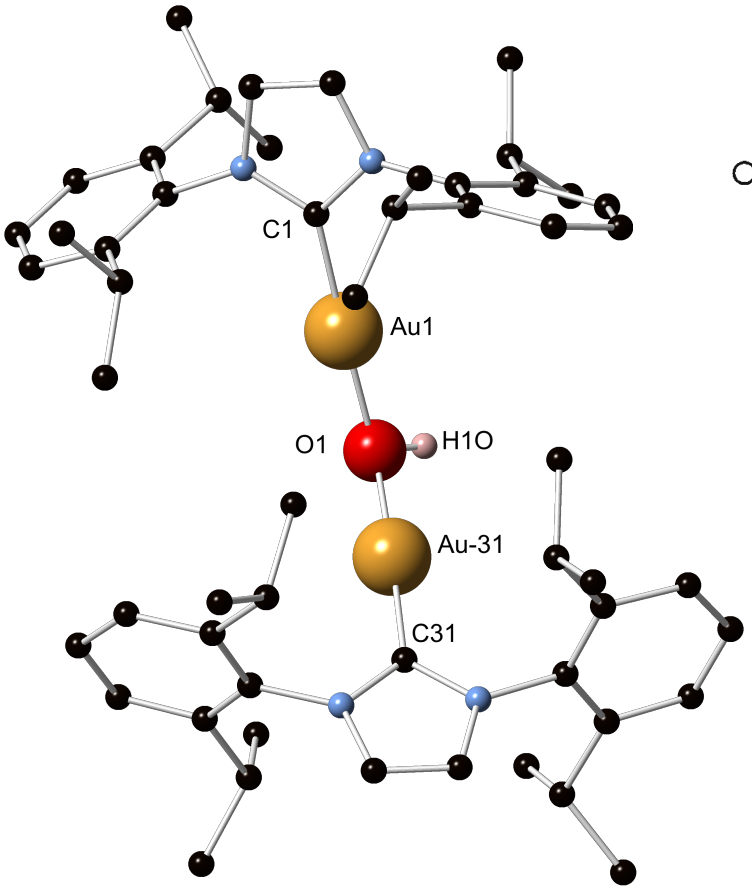


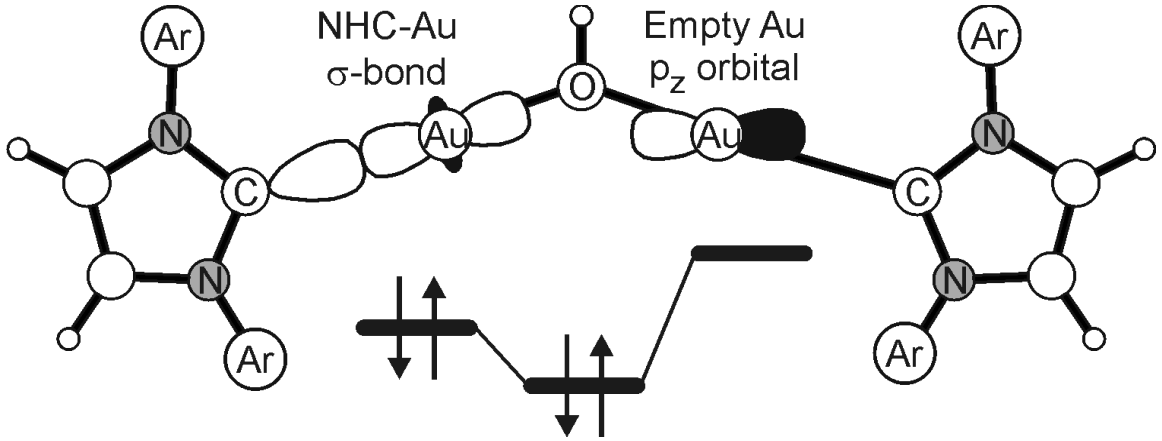
19.1

Calculations indicated a concerted TS for C-H activation

Fortman, Poater, Levell, Gaillard, Slawin, Samuel, Cavallo and Nolan
Dalton Trans. **2010**, *39*, 10382.

2011 : 1-Characterization of Au-dimers





A bond order of 0.14 between the Au centers indicated they interact.

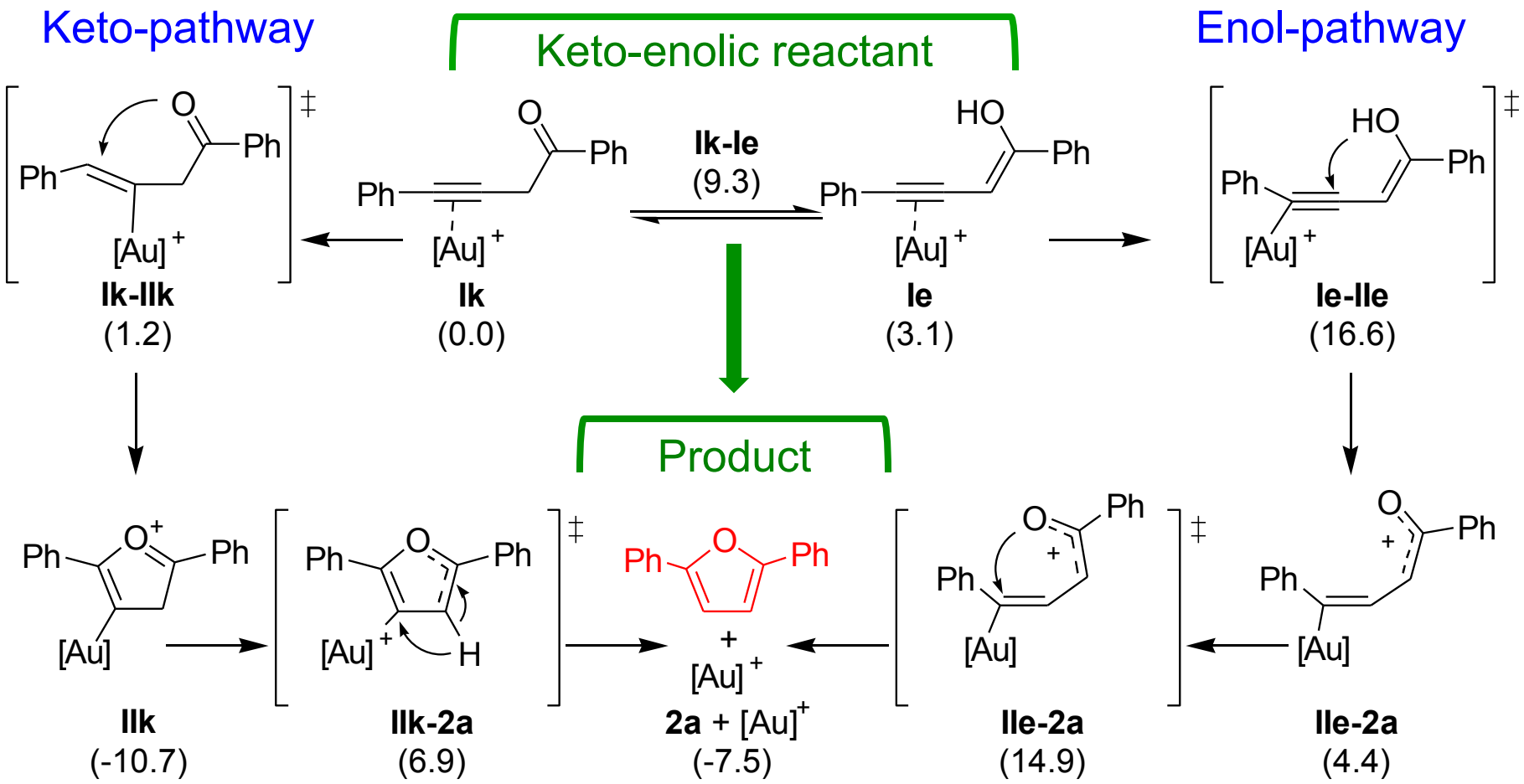
Donation is from each [Au(IPr)] σ-bond into an empty MO on the other Au center.

Calculations gave insight on the bonding mode

[{Au(IPr)}(2)(mu-OH)]X Complexes: Synthetic, Structural and Catalytic Studies

Ramon, Gaillard, Poater, Cavallo, Slawin, Nolan *Chem. Eur. J.* **2011**, *17*, 1238.

2011 : 2-Synthesis of Furanes and Pyrroles

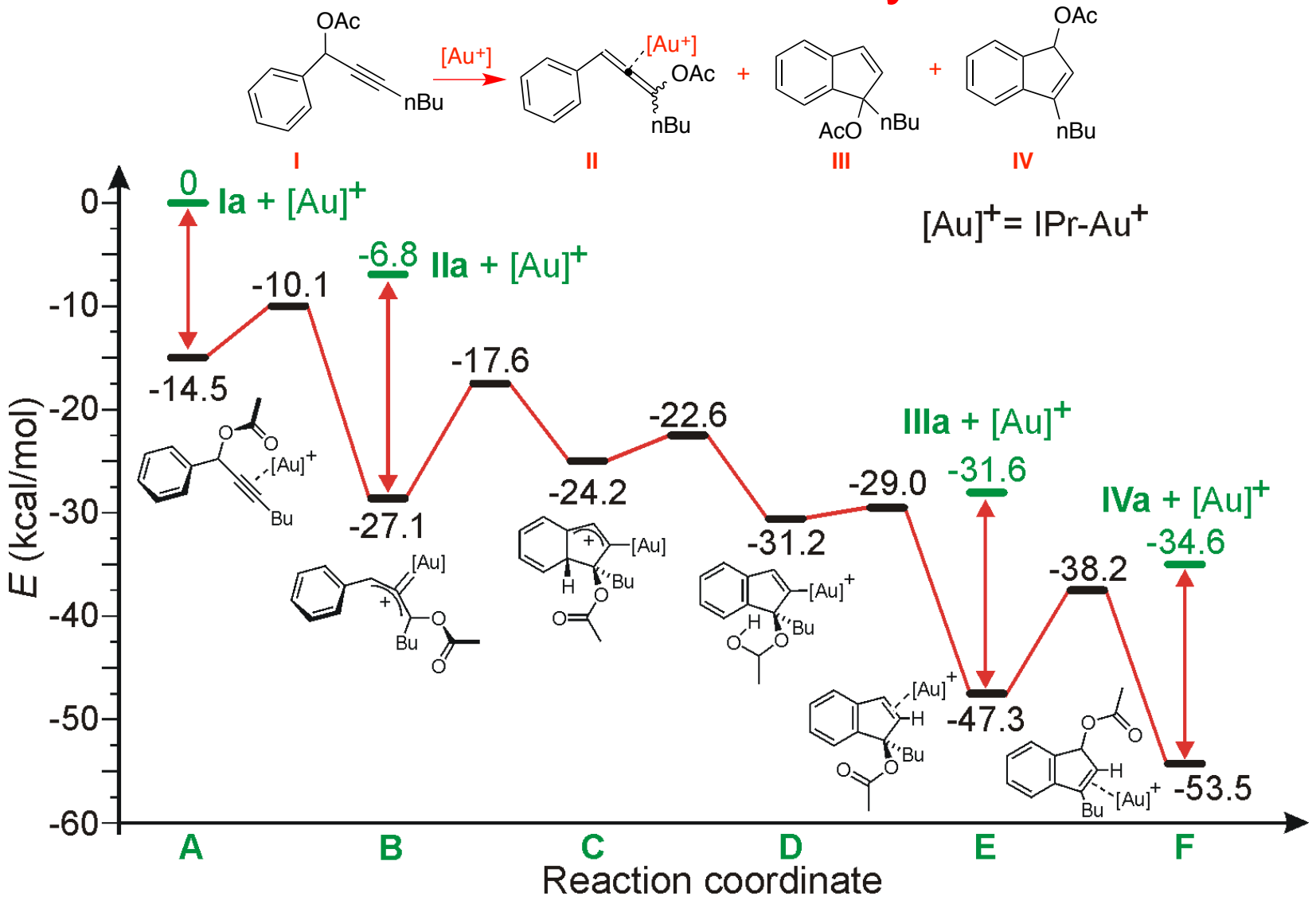


Calculations indicated that the keto pathway is favored

Gold(I)-catalyzed synthesis of furans and pyrroles via alkyne hydration

Nun, Dupuy, Gaillard, Poater, Cavallo and Nolan *Catal. Sci. Tech.* **2011**, *1*, 58.

2011 : 3-Synthesis of Indenes

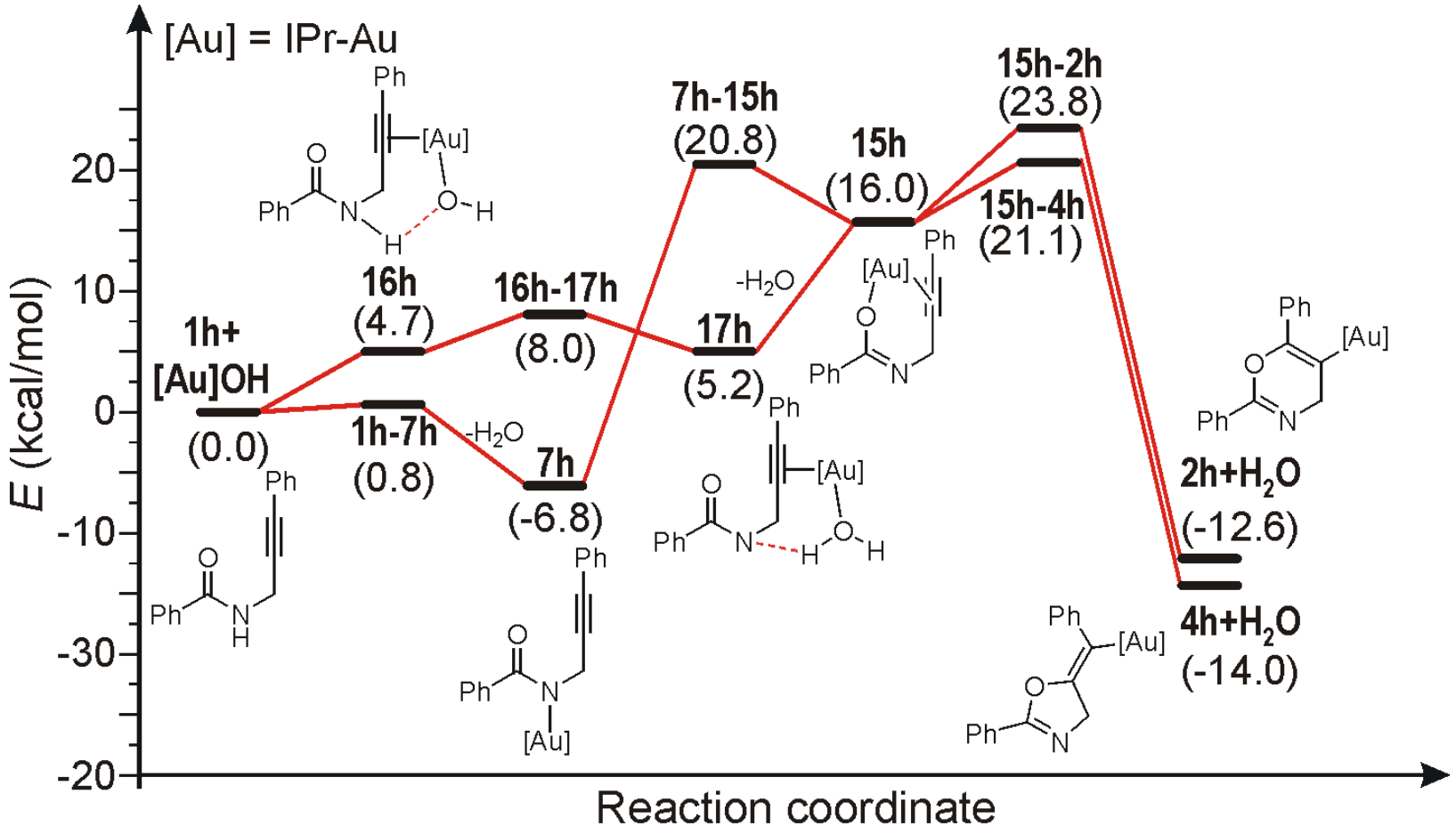


Insight on the Gold(I)-catalyzed synthesis of substituted indenes via [3,3] Rearrangement-Hydroarylation-[1,3] O-Acyl shift sequence.

Nun, Gaillard, Poater, Cavallo and Nolan *Org. Biomol. Chem.* **2011**, *9*, 101.

2012 : Formation of another 5-membered ring

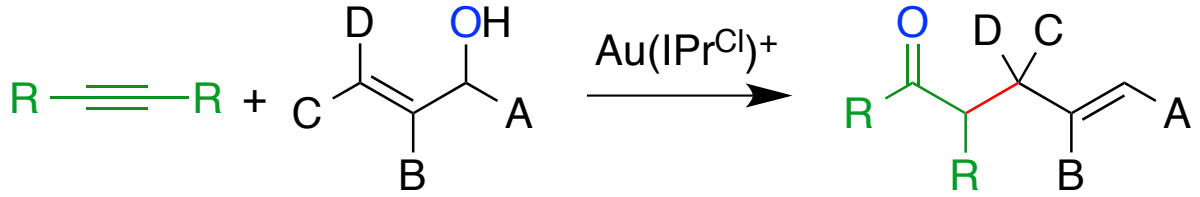
Calculations explained the switch to 5-exo cyclization with NHC-Au-OH versus the known 6-endo cyclization with NHC-Au-Cl

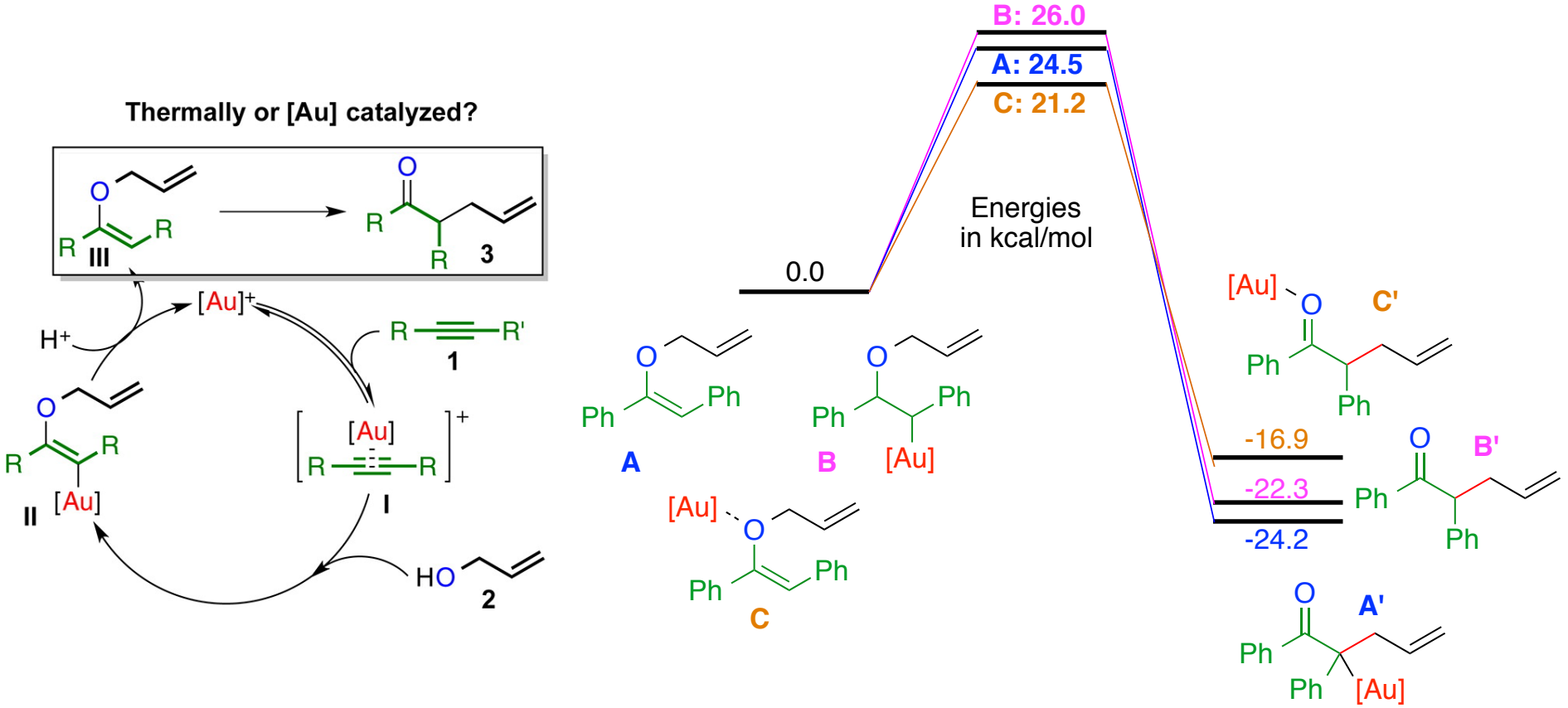


Selectivity Switch in the Synthesis of Vinylgold(I)-Intermediates

Hashmi, Schuster, Gaillard, Cavallo, Poater and Nolan *OM* ***2012****, 30, 6328*

2014 : Synthesis of homoallylic ketones

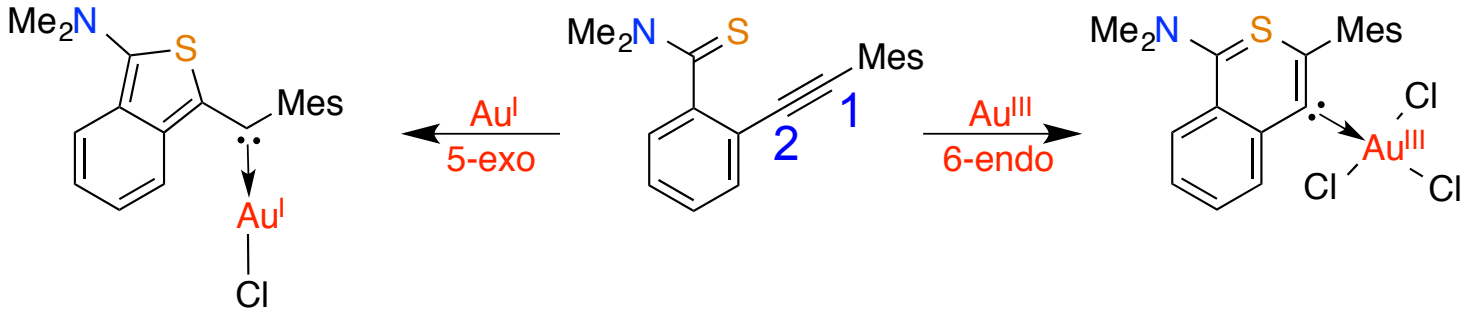




Calculations indicated the Claisen step as assisted by Au-O interaction

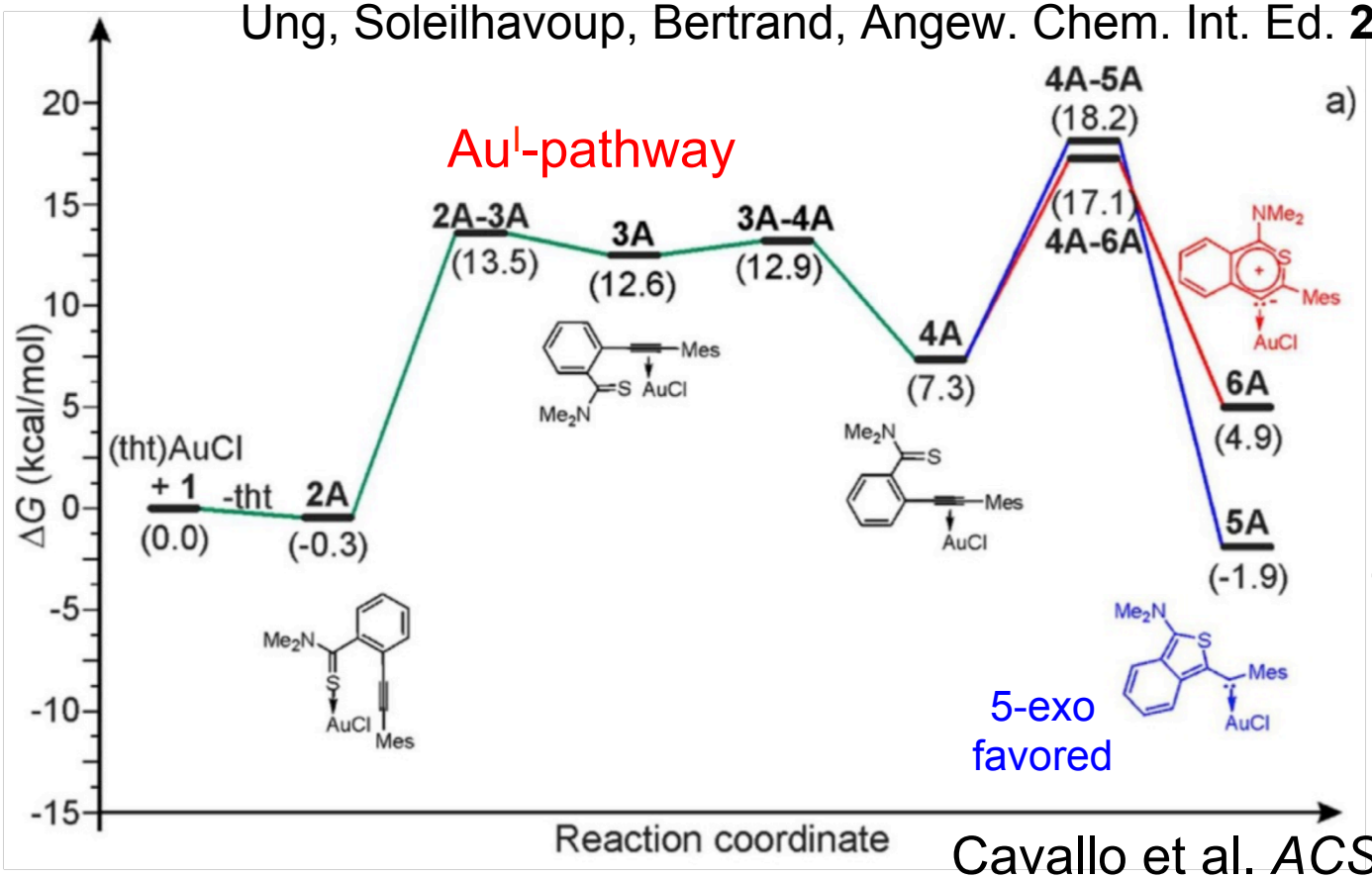
Gomez-Suarez, Gasperini, Vummaleti, Poater, Cavallo and Nolan
ACS Catal ***2014****, 4, 2701*

2014 : 5-*exo* *vs* 6-*endo-dig* cyclization-Au^{I} *vs* Au^{III}



The selectivity dictated by the oxidation state of the gold promoter

Ung, Soleilhavoup, Bertrand, Angew. Chem. Int. Ed. **2013**, 52, 758

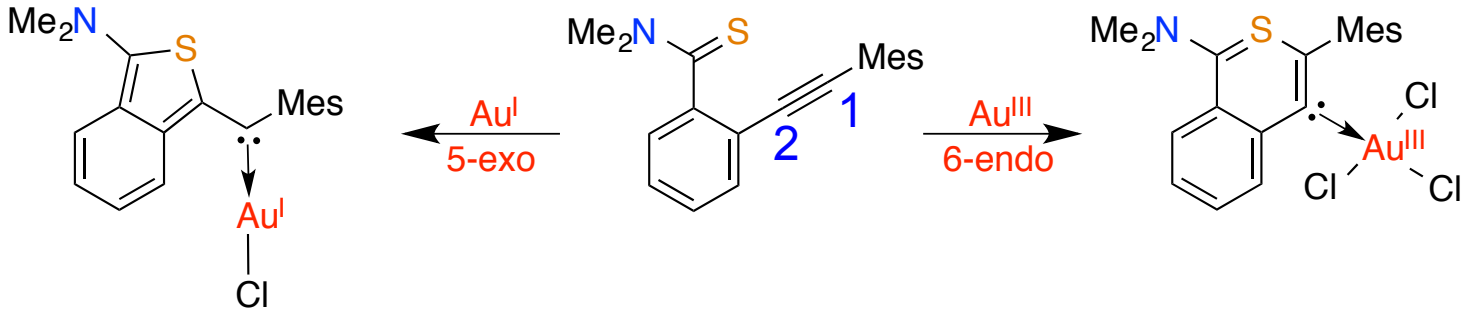


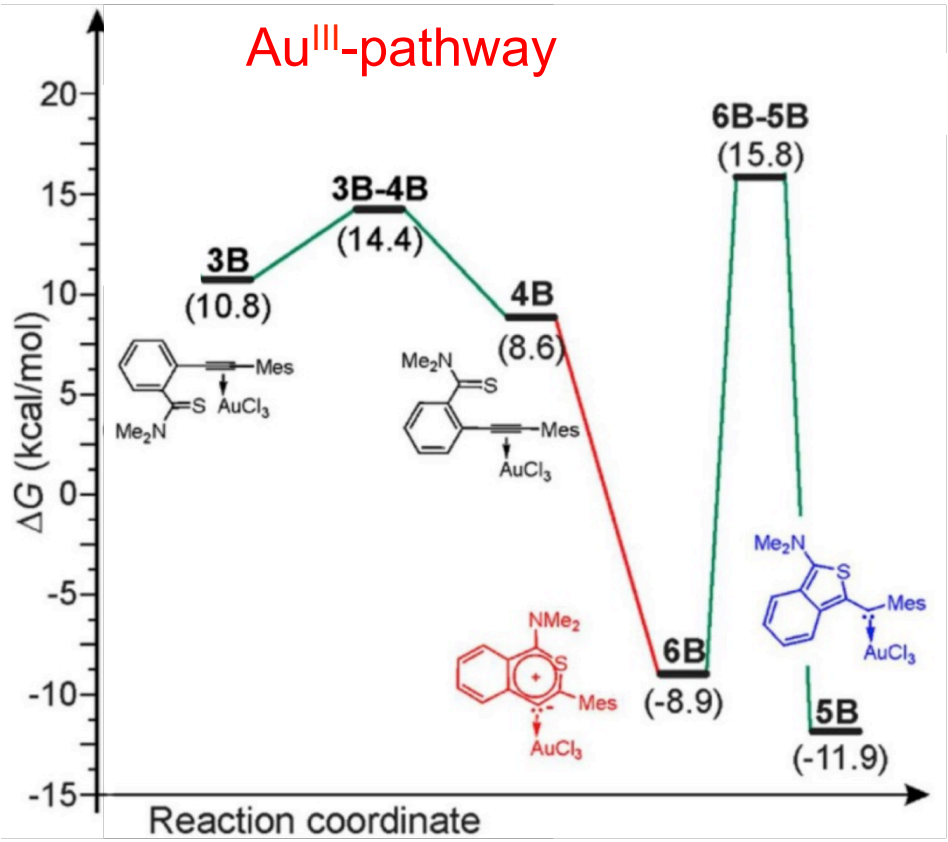
Cyclization under thermodynamic control

Easy to understand

Cavallo et al. *ACS Catal* ***2014***, *4, 1287*

2014 : 5-*exo* *vs* 6-*endo-dig* cyclization-Au^{I} *vs* Au^{III}





No way to find a TS connecting 4B to either 5B or 6B

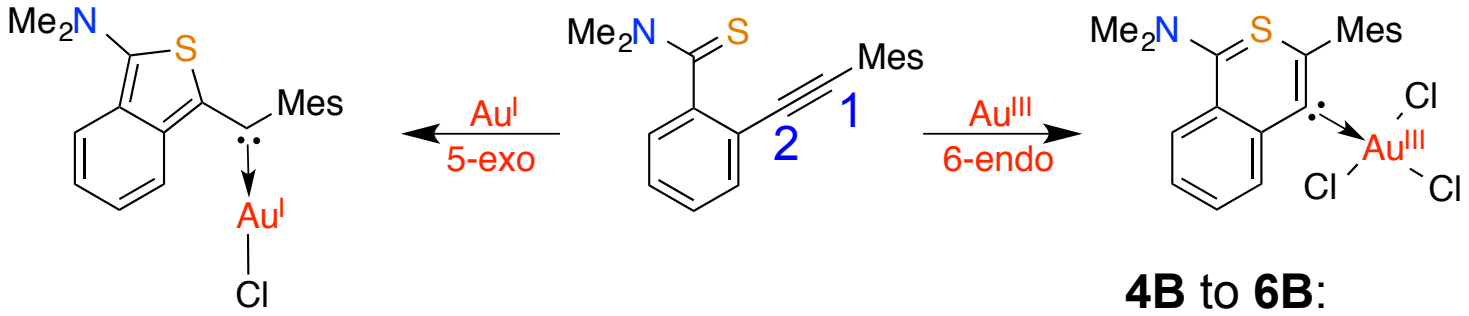
We found a TS between 5B and 6B

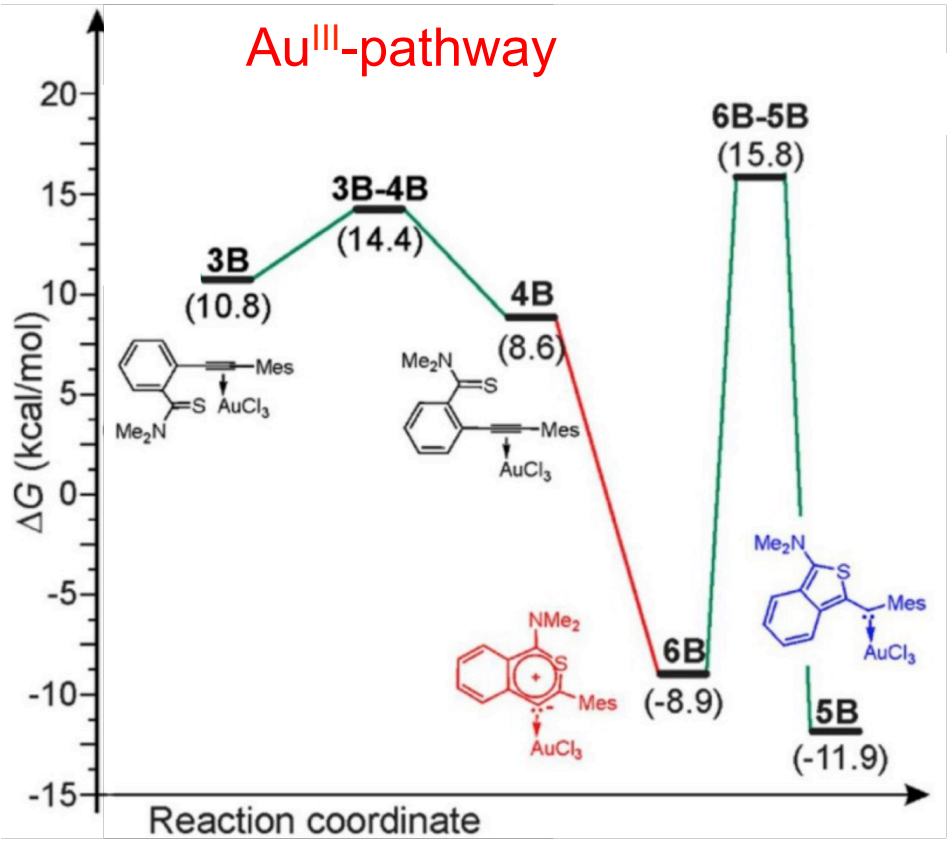
MD trajectories started from TS 3B-4B collapse into 3B (stable) or 4B (after a while they collapse into 6B).

MD trajectories started from TS 5B-6B collapse into 5B (stable) or 4B (after a while they collapse into 6B).

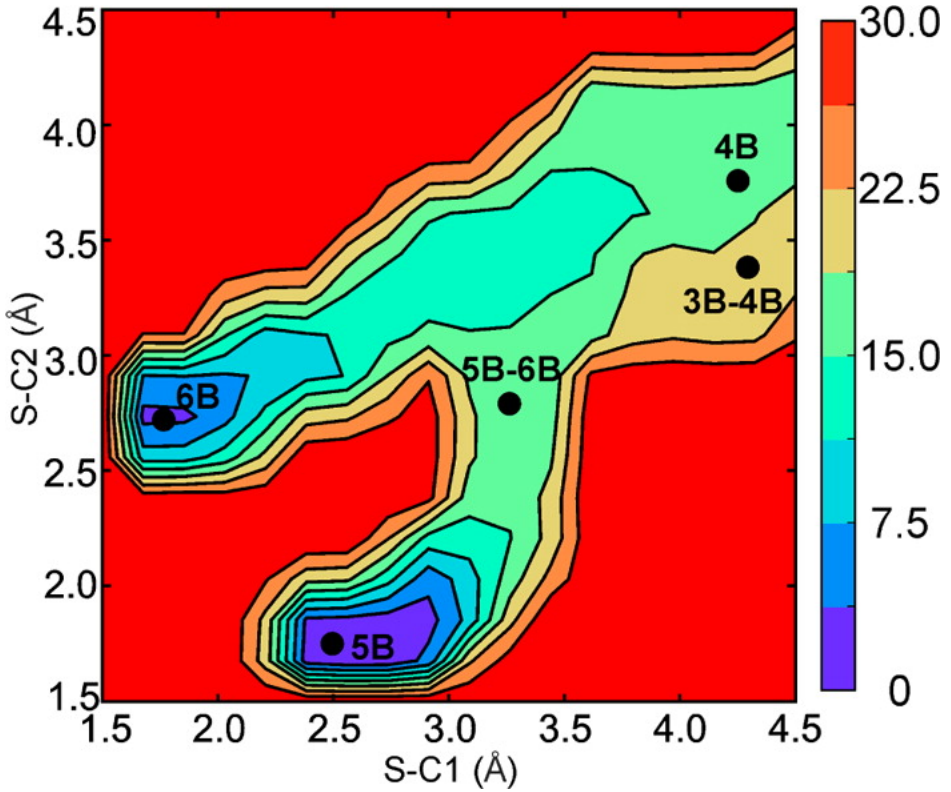
Cavallo et al. *ACS Catal* ***2014***, *4, 1287*

2014 : 5-*exo* *vs* 6-*endo-dig* cyclization-Au^{I} *vs* Au^{III}



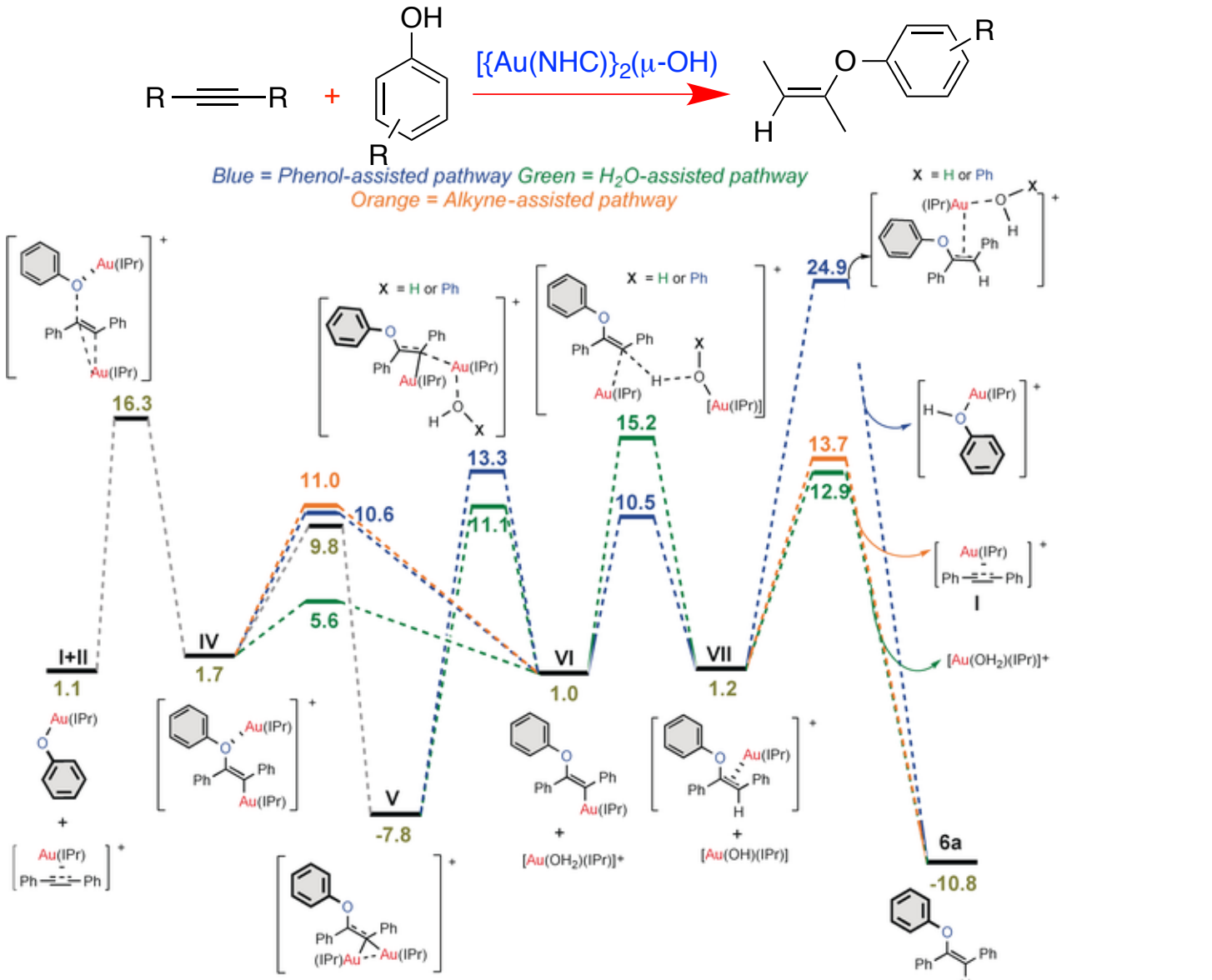


4B to **6B**:
2 intermdiates no TS.



a) Carpenter PCCP 2011, 13, 20906. b) Nevado JACS 2010, 132, 4720. c) Goddard III, Toste, JACS 2010, 132, 13064. e) Houk JACS 2012, 134, 1078. f) Tantillo Nature Chem. 2014, 6, 104.

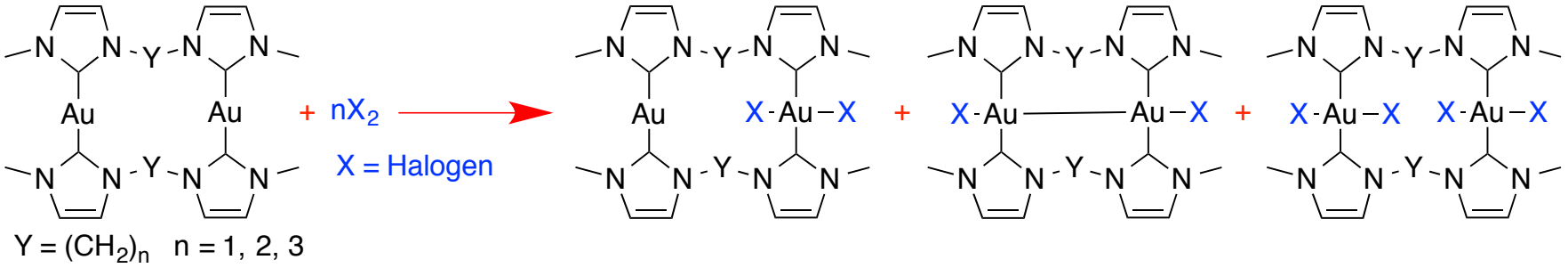
2016 : Di Au^{I}–Hydroxide Hydrophenoxylation of Alkynes

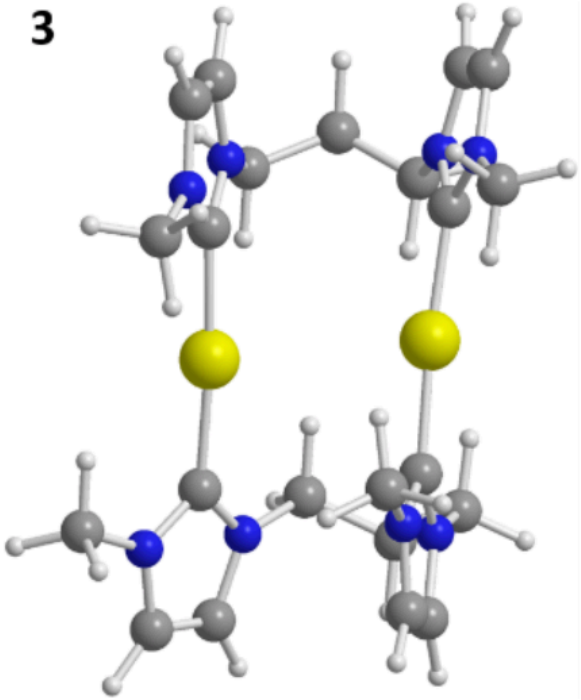


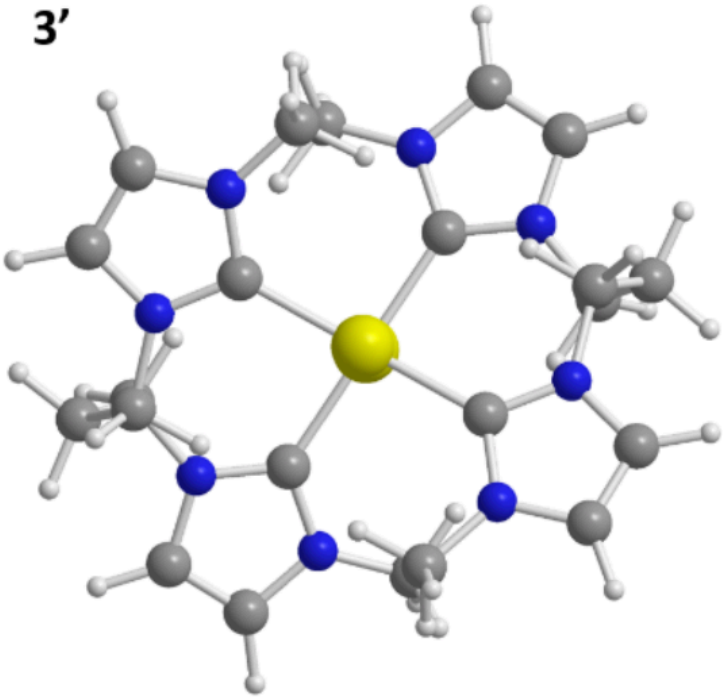
Di-gold mechanism possible, PhOH or H_2O can assist the reaction

Cavallo, Nolan et al. Chem. Eur. J. 2016, 22, 1125−1132.

2016 : Halogen Addition to bis-Au^{I} (NHC) Complexes







π-π stacked rings

Staggered rings

Rationalizing the product distribution based on linker length

Cavallo, Biffis, Tubaro et al. Chem. Eur. J. 2016, 22, 1125−1132.

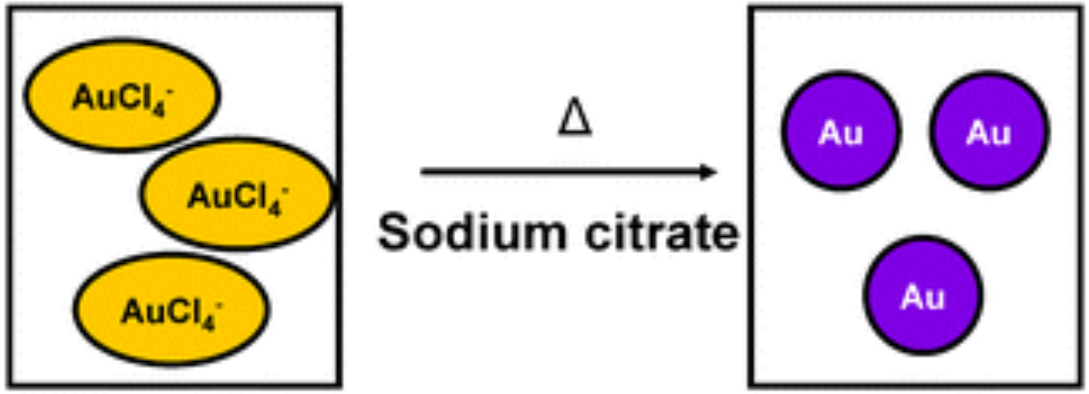
A few facts about gold NP

Applications

- Gold NP have applications in almost any branch of current science
- About 30,000 entries in physics, 70,000 in chemistry (Web of Science)

Synthesis

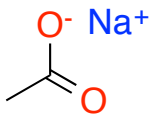
- The most popular protocol is the Turkevich method



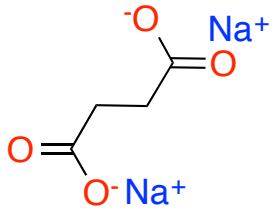
- Surprisingly, clear and detailed characterization of the Au-citrate at the surface of the AuNP not achieved yet. Most updated work:

Park J. W. et al. *J. Am. Chem. Soc.* **2014**, 136, 1907.

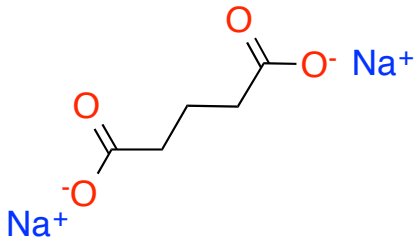
2017 : Citrate-Au interaction in Au nanoparticles



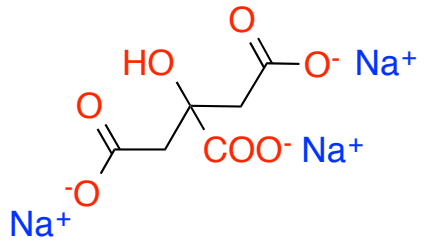
Acetate



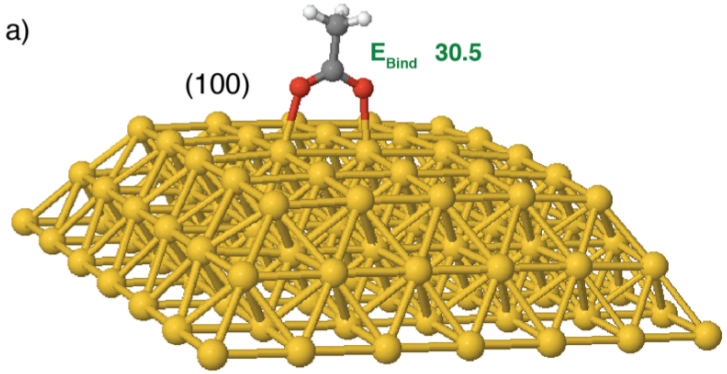
Succinate

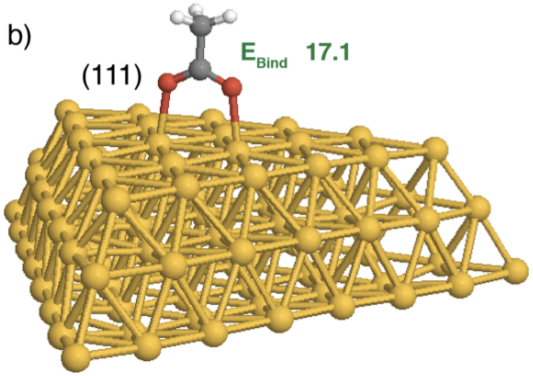


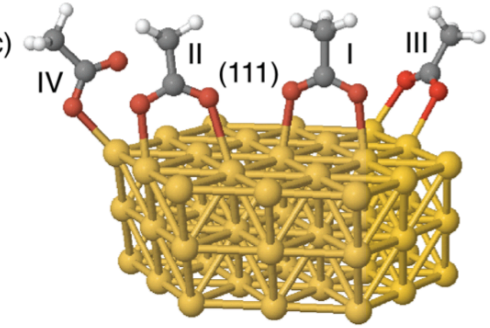
Glutarate

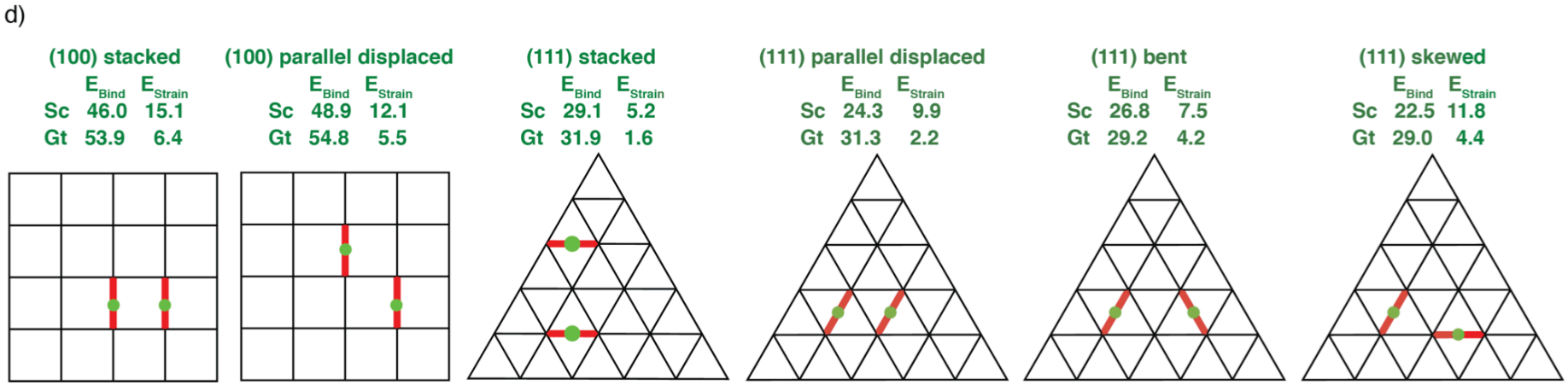


Citrate







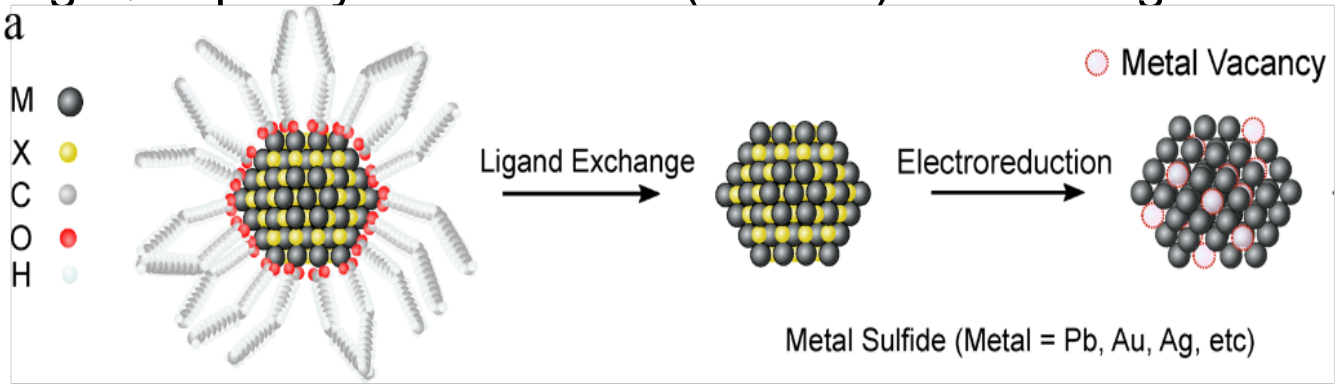


DFT indicates that bicarboxylates can assume a variety of binding modes

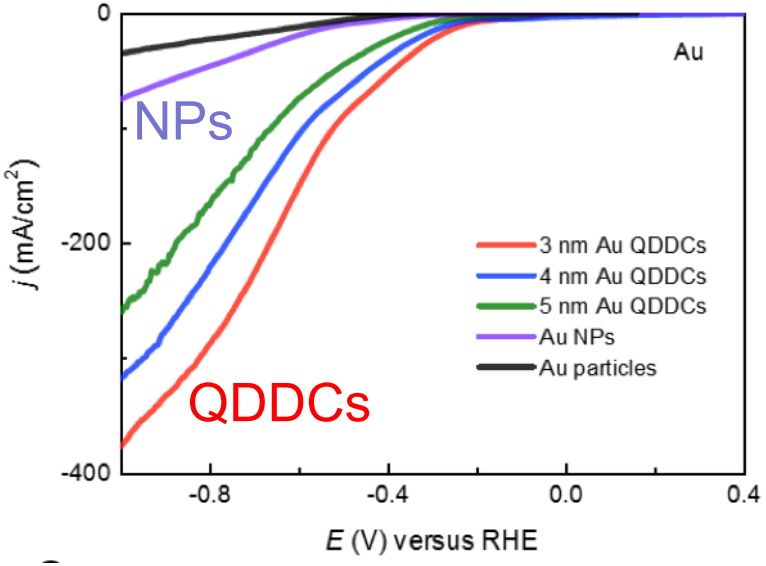
Cavallo, Basset, Emsley et al. Nat. Chem. 2017, 9, 890.

2017 : Quantum Dot Derived Catalysts

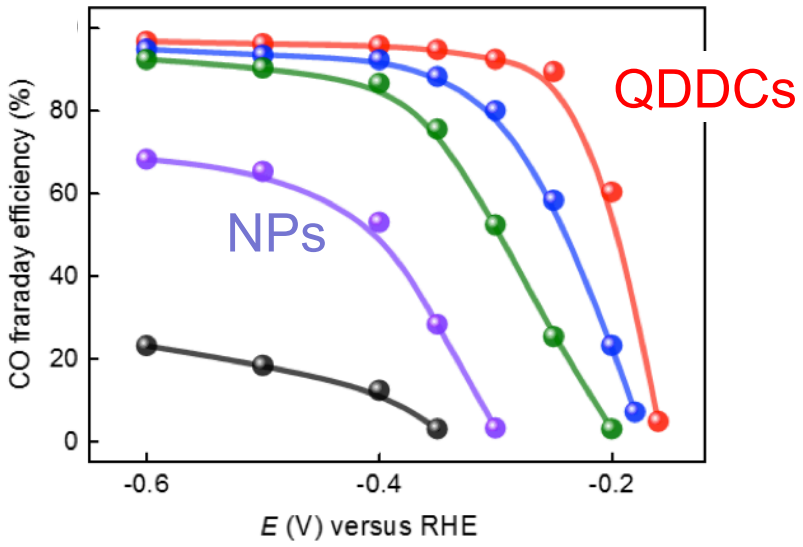
In heterogeneous catalysis it is accepted that very active sites can be defects.
Synthesizing QDs plenty of vacancies (defects) and testing them in catalysis



Performance of Au QDDCs in CO_2 electrochemical reduction



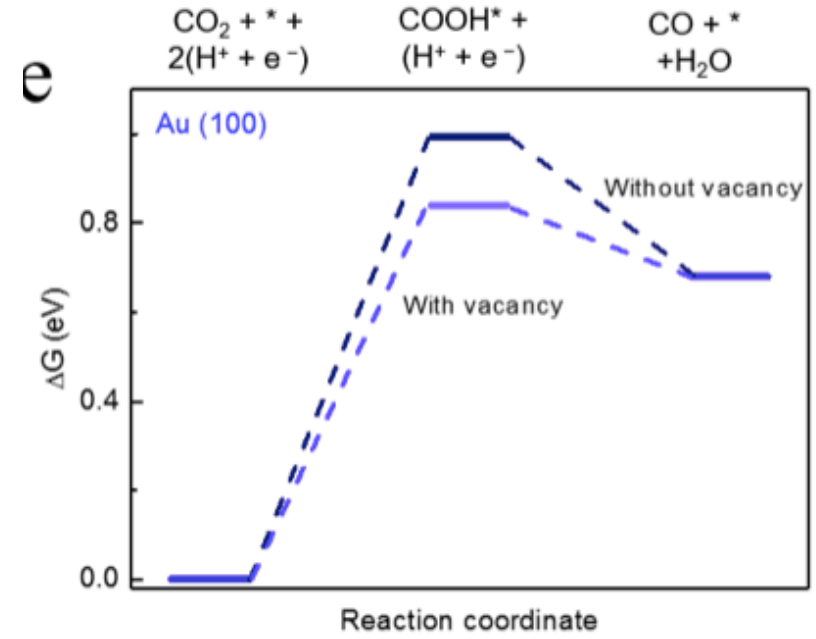
Lower on set potentials
for QDDCs compared to NPs

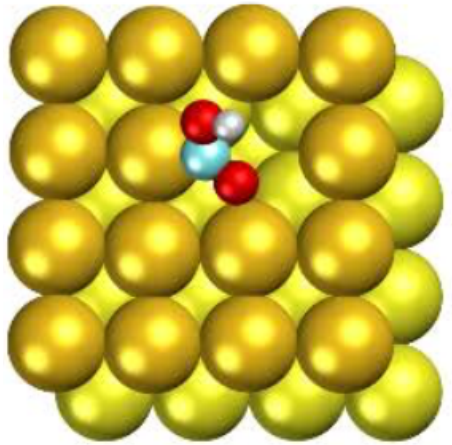


Higher Faradic efficiency
for QDDCs compared to NPs

Cavallo, Sargent et al. Submitted

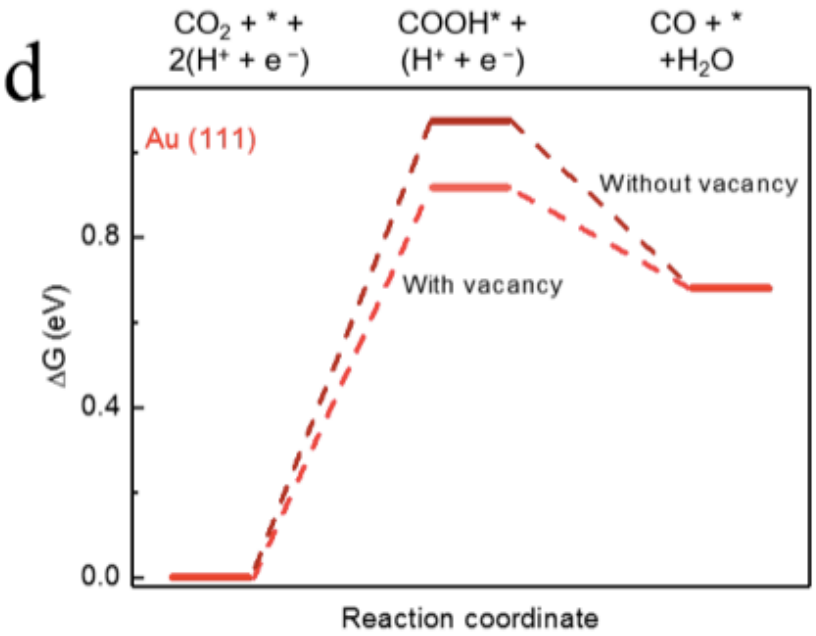
2017 : Quantum Dot Derived Catalysts

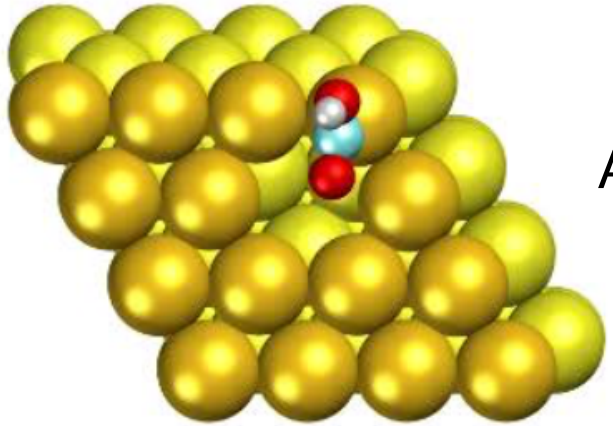




Au (100)

A defect stabilizes COOH adsorption





Au (111)

Cavallo, Sargent et al. Submitted

Outline

- Introduction
- The Call for Help
- The Golden Carousel
- After the Puzzle
- Conclusions

Conclusions

Entering a new field can be sometimes difficult.

Hitting the ground hurts…

Conclusions

But if you keep practicing….

…one day you will master it, finally !

Acknowledgments

Hard work

Albert Poater Laura Falivene Abdesslem Jedidi

Stimulating collaboration/discussions

Steve Nolan (Ghent University)
Andrea Biffis (University of Padova)
Lyndon Emsley (EPFL)
Jean Marie Basset (KAUST)
Ted Sargent (U Toronto)

Support

The KAUST, SABIC

People here

For your kind attention

Questions ?

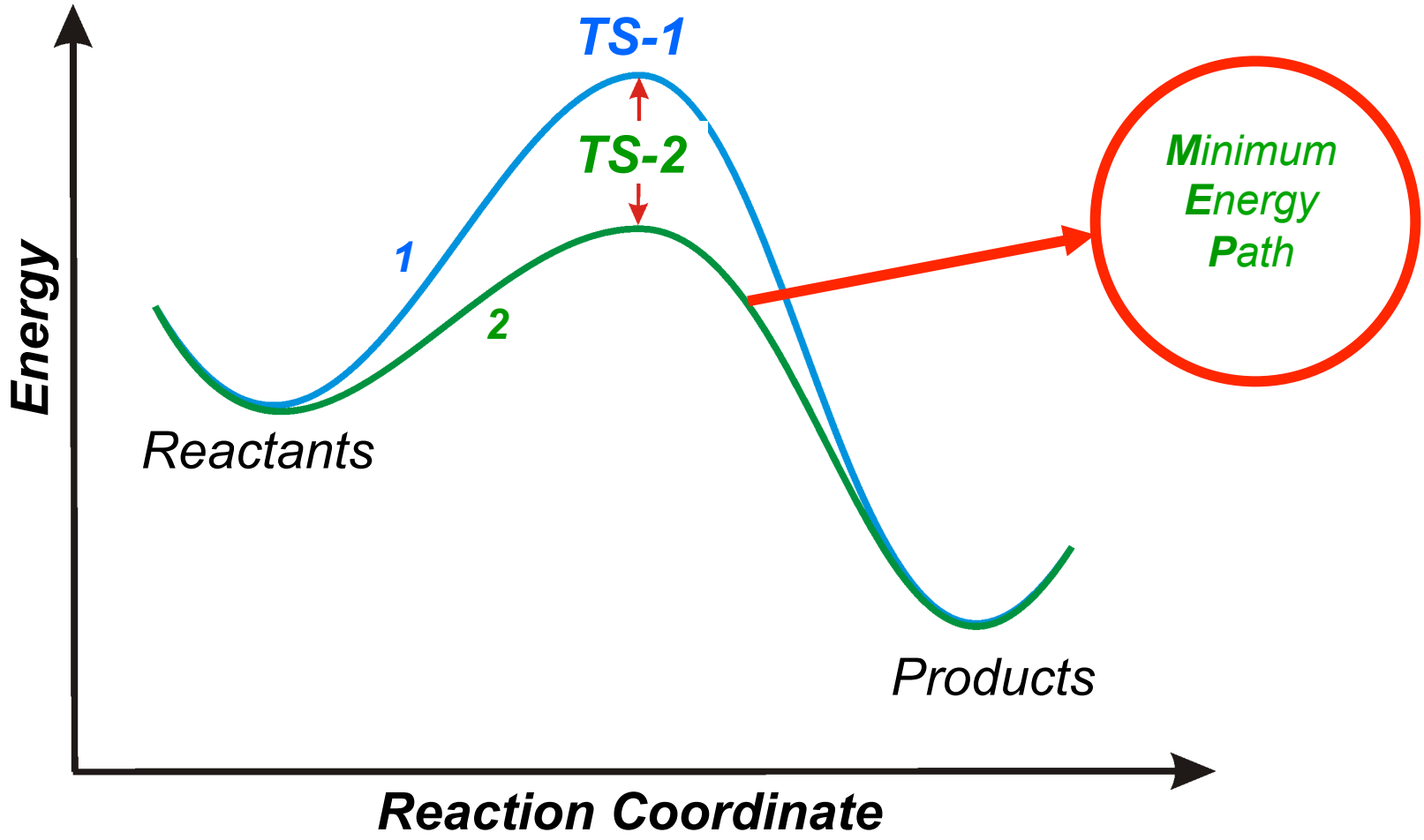
Being a computational chemist for a day

- Introduction
- Quiz 1 : Geometries
- Quiz 2 : Energies
- Quiz 3 : Predicting selectivity
- Quiz 4 : Understanding selectivity
- Conclusions

How do we study a reaction ?

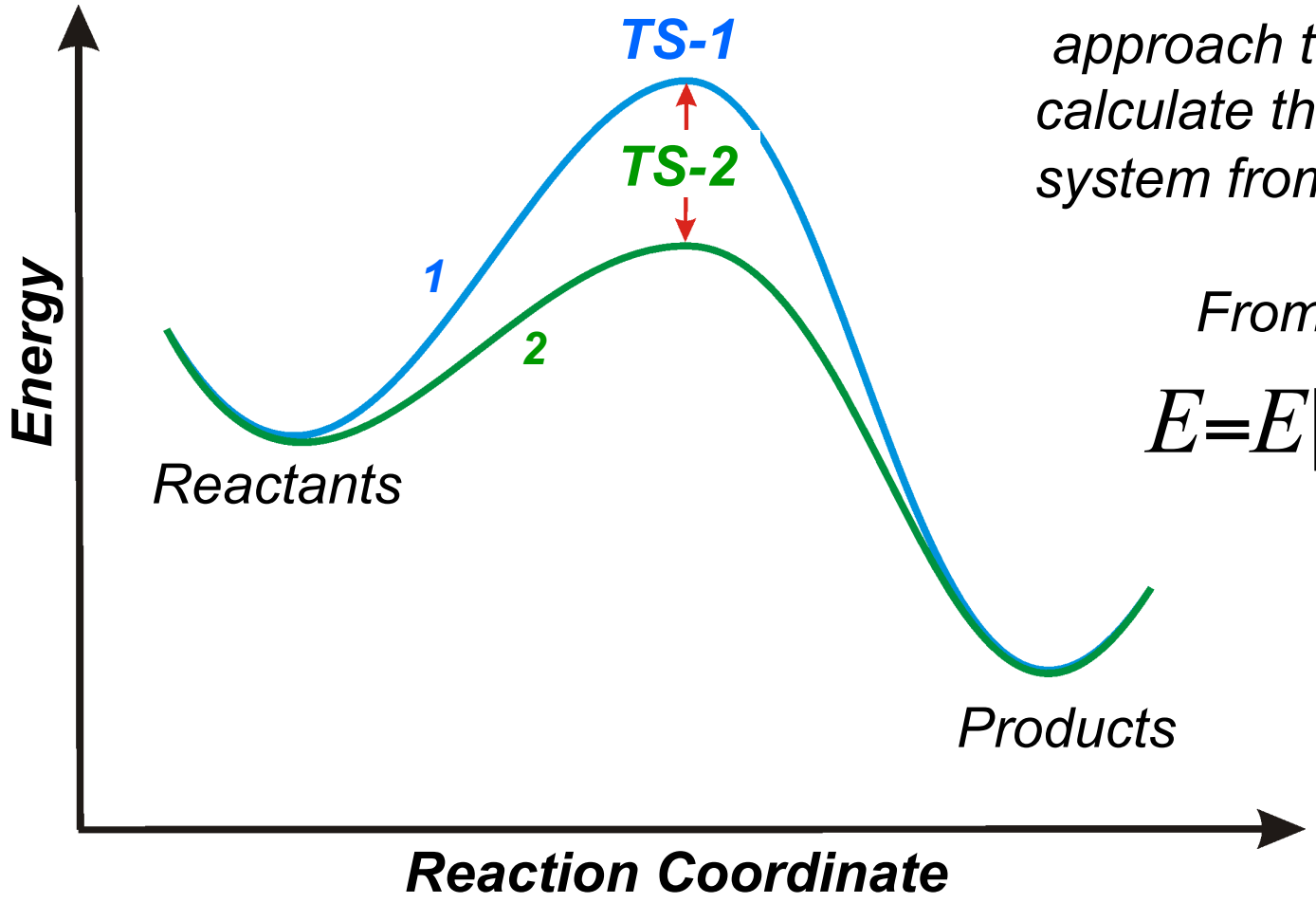
In the simplest description, a chemical reaction takes place along the lowest path connecting the reactants and the products passing for the lowest TS

*The reaction surface can be determined by **static** or **dynamics** approaches*



How do we study a reaction ?

All intermediates and transition states involved in the chemical process are calculated separately.

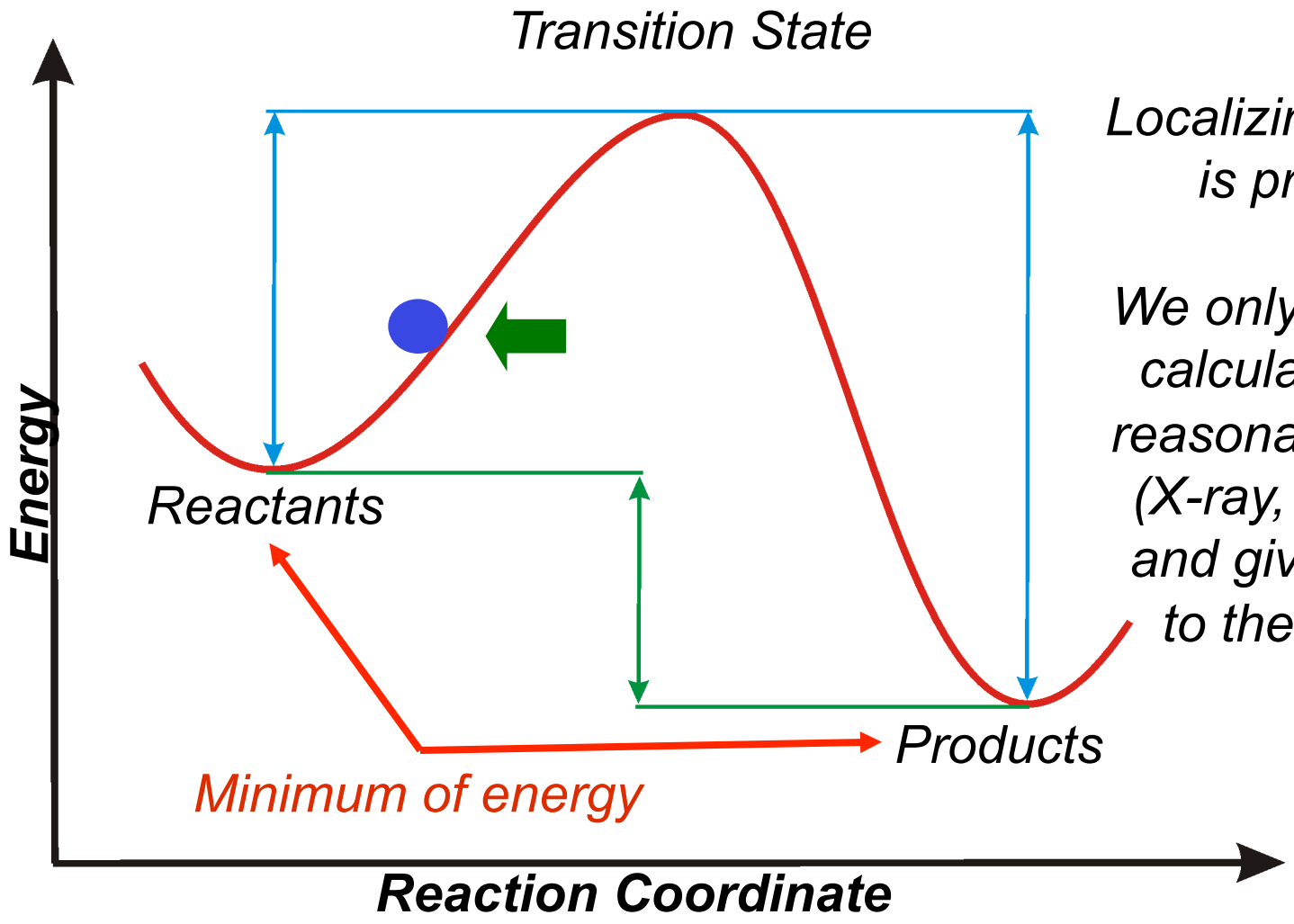


We need a theoretical approach that allows to calculate the energy of a system from coordinates

From DFT :

$$E=E[\rho(r_i)]$$

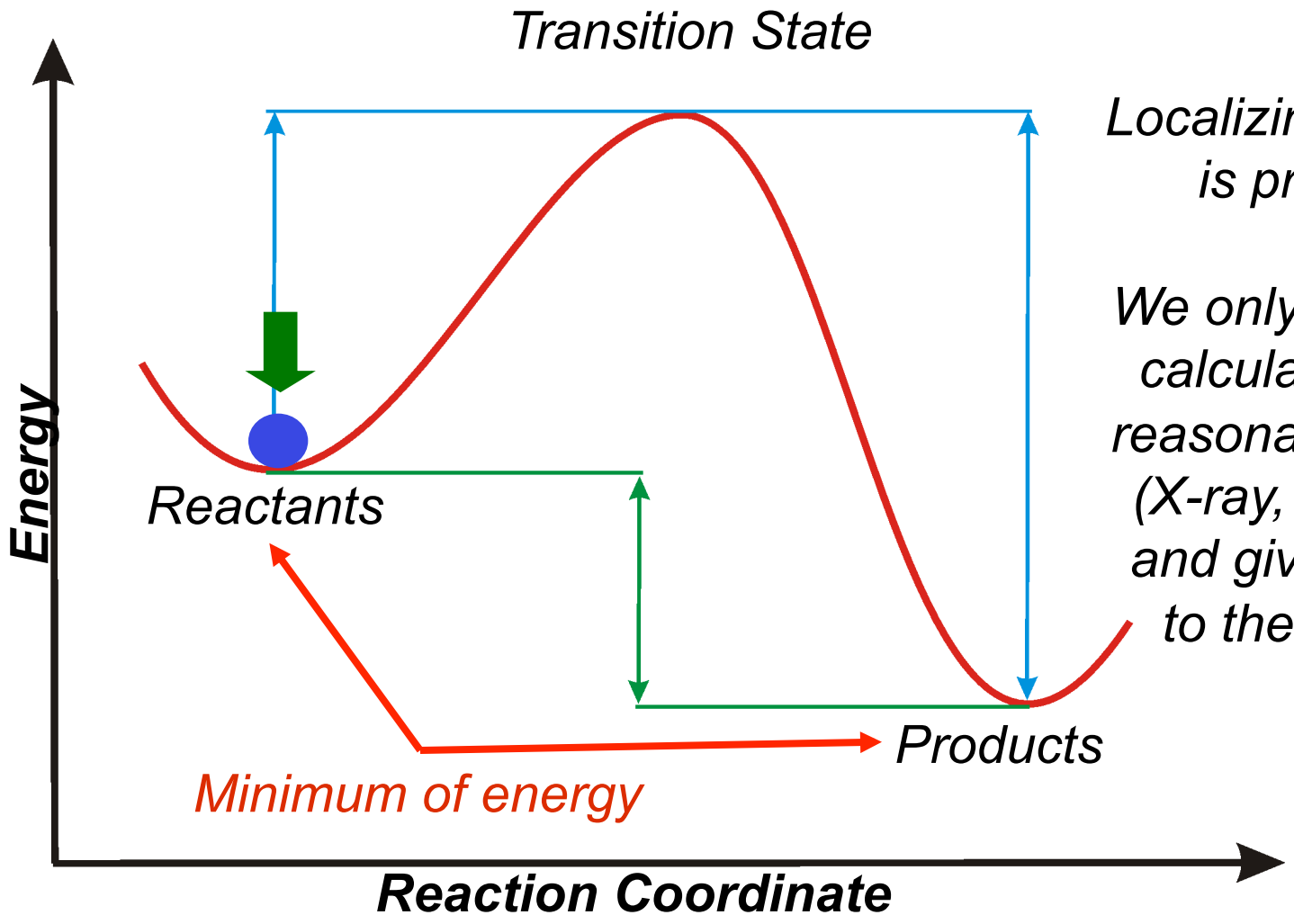
Finding intermediates



Localizing a minimum is pretty easy.

We only have to start calculations from a reasonable structure, (X-ray, hand-made) and give some time to the computers

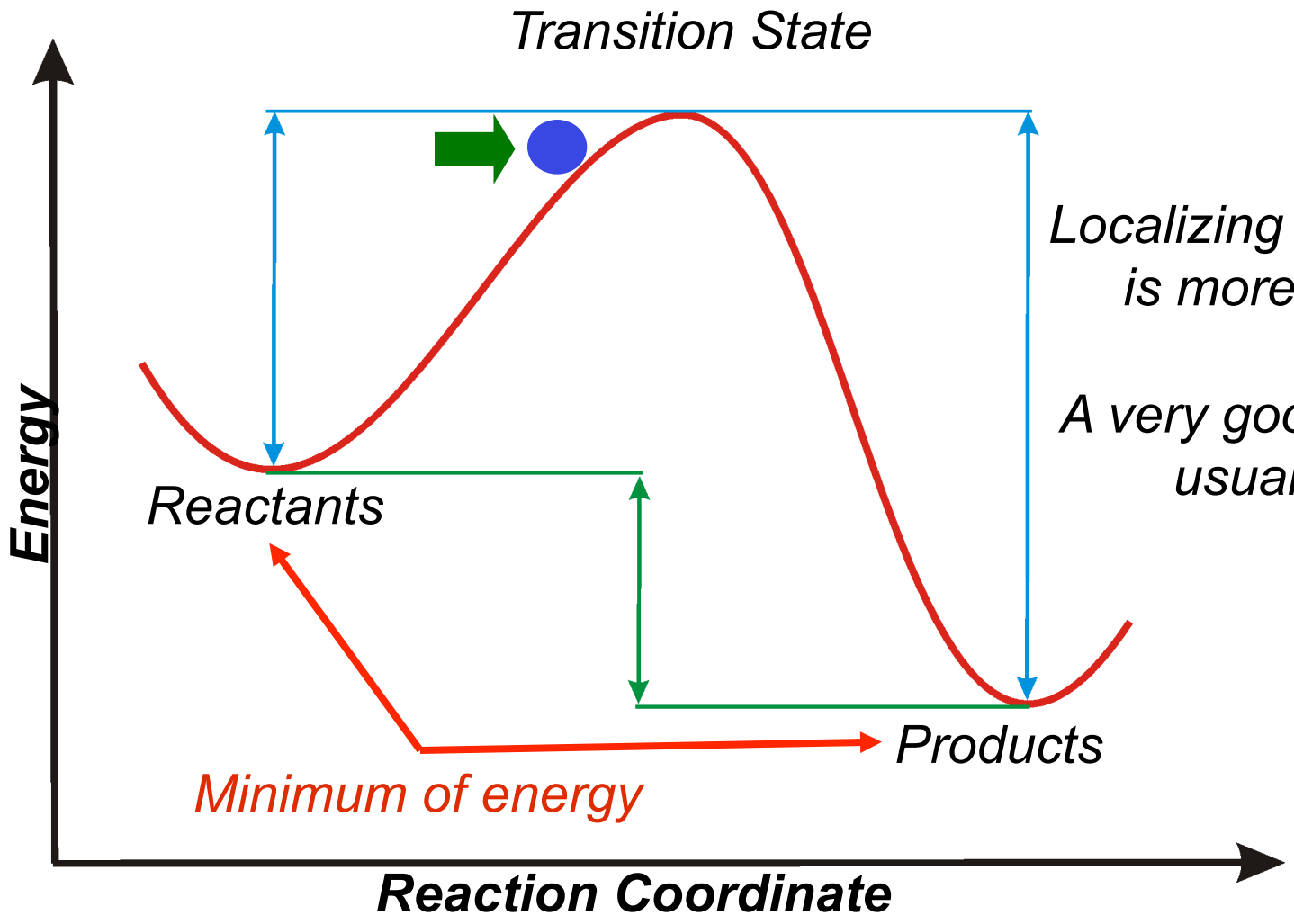
Finding intermediates



Localizing a minimum is pretty easy.

We only have to start calculations from a reasonable structure, (X-ray, hand-made) and give some time to the computers

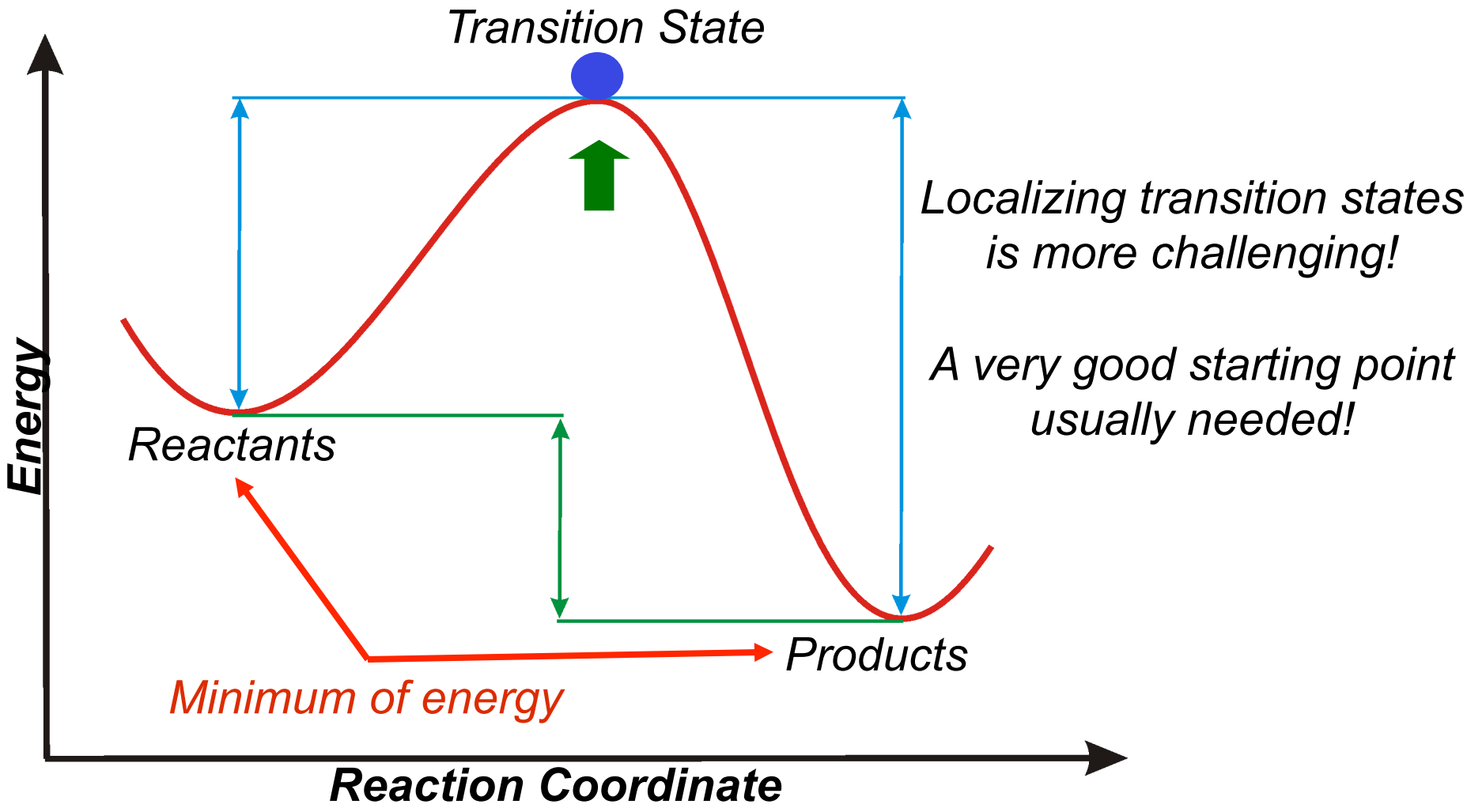
Finding transition states



Localizing transition states is more challenging!

A very good starting point usually needed!

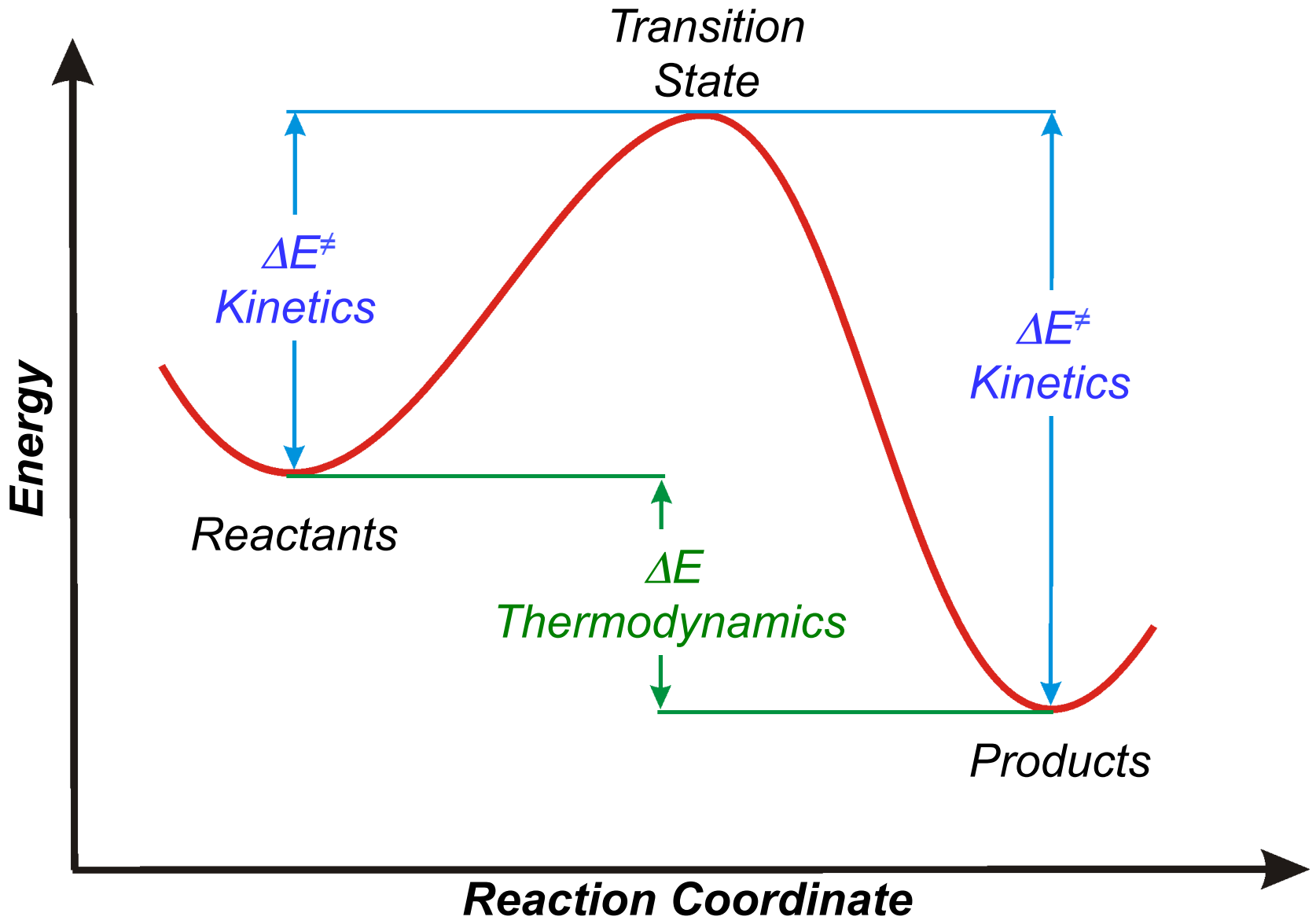
Finding transition states



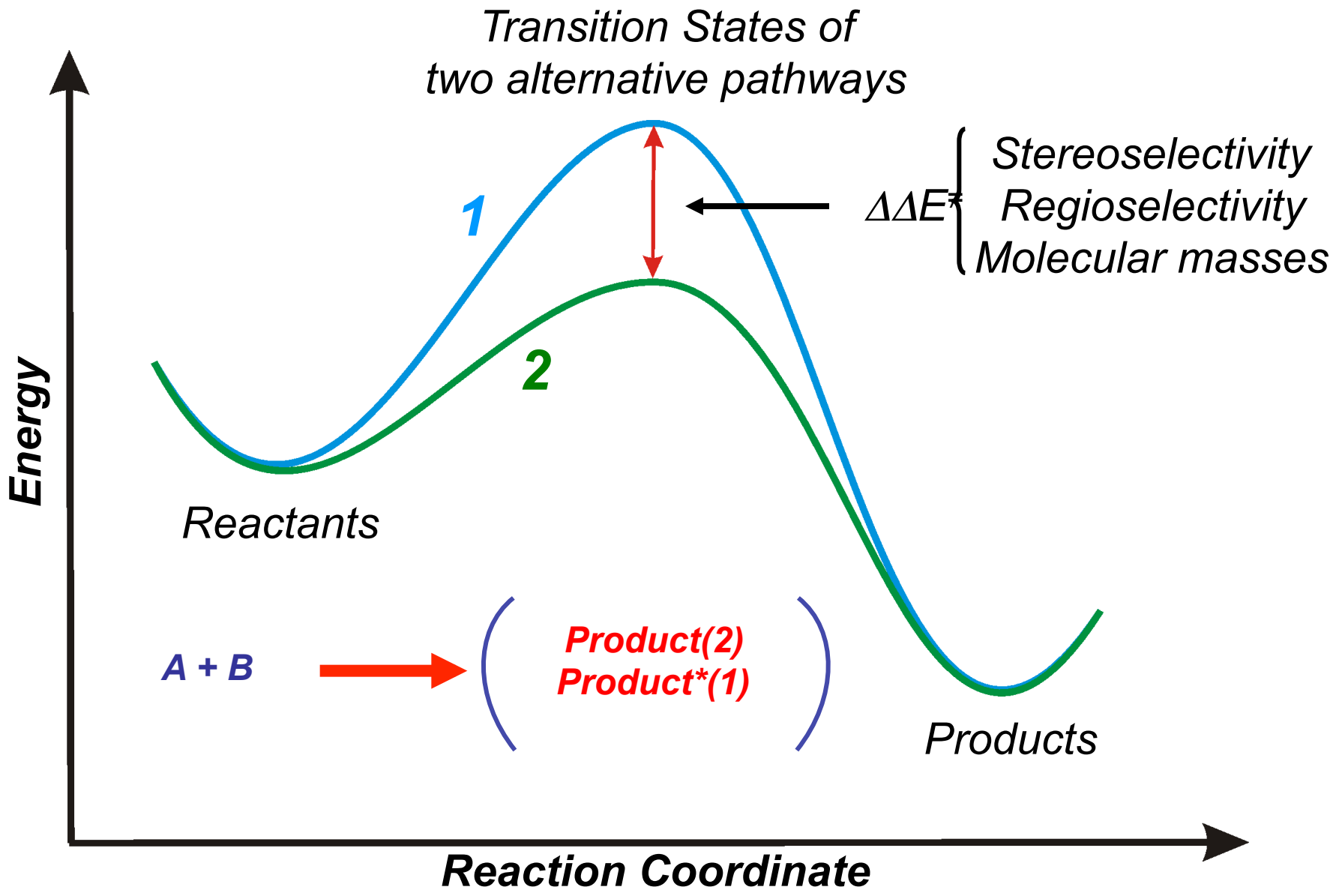
Localizing transition states is more challenging!

A very good starting point usually needed!

What we get from an energy plot



Understanding selectivities



Looks easy… where are the problems ?

Geometries obtained from DFT calculations are extremely reliable.
But… are you sure that you get the right structure ? **(Quiz 1)**

DFT energies are usually quite accurate.
But… how to trust this 12.3 kcal/mol barrier you get ? **(Quiz 2)**

Selectivity is usually played within 1-3 kcal/mol.
How to know if this *in silico* designed catalyst is selective ? **(Quiz 3)**

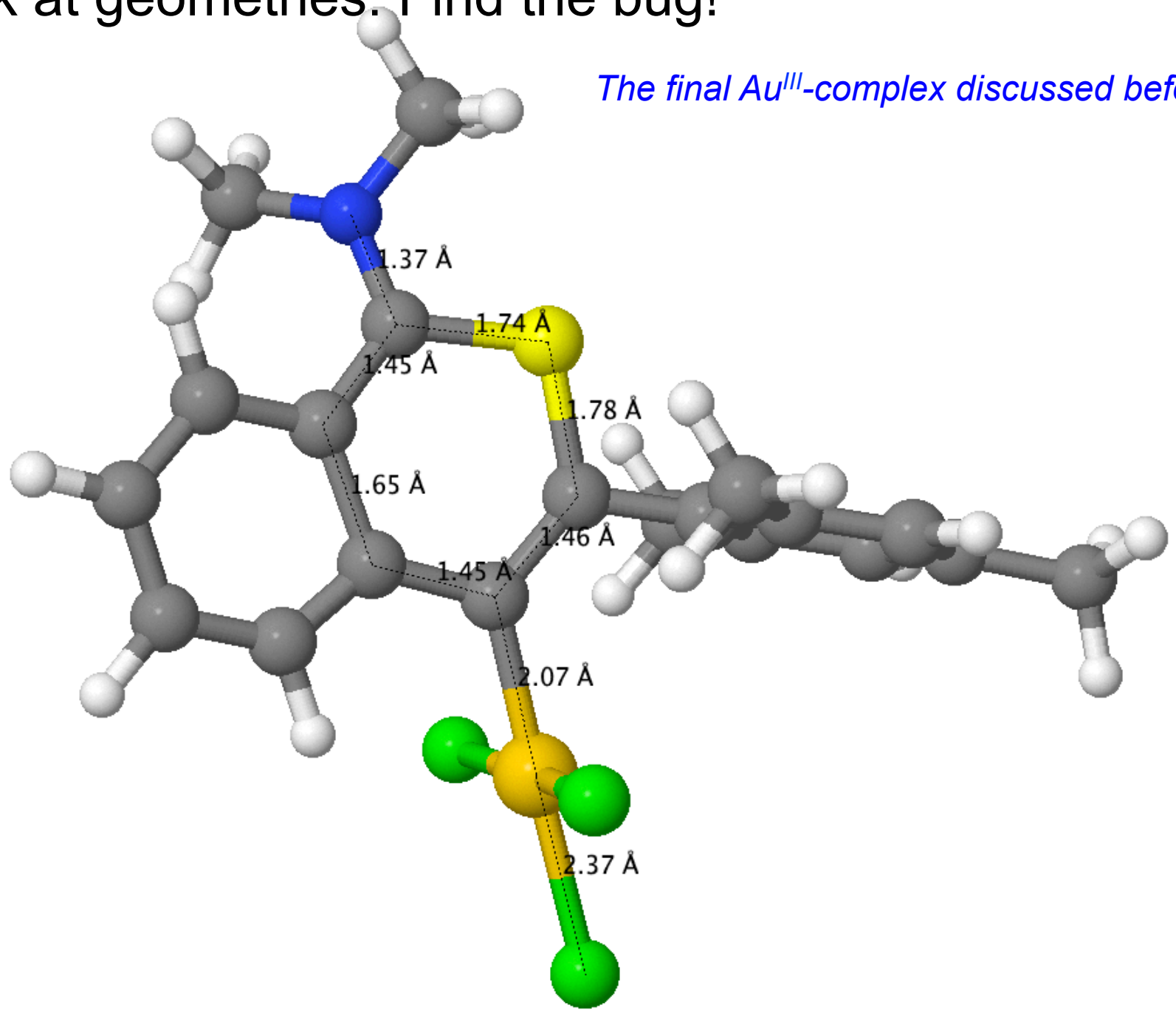
Selectivity is usually determined by steric and electronic effects.
How to understand what plays a role for my reaction ? **(Quiz 4)**

Outline

- Introduction
- Quiz 1 : Geometries
- Quiz 2 : Energies
- Quiz 3 : Predicting selectivity
- Quiz 4 : Understanding selectivity
- Conclusions

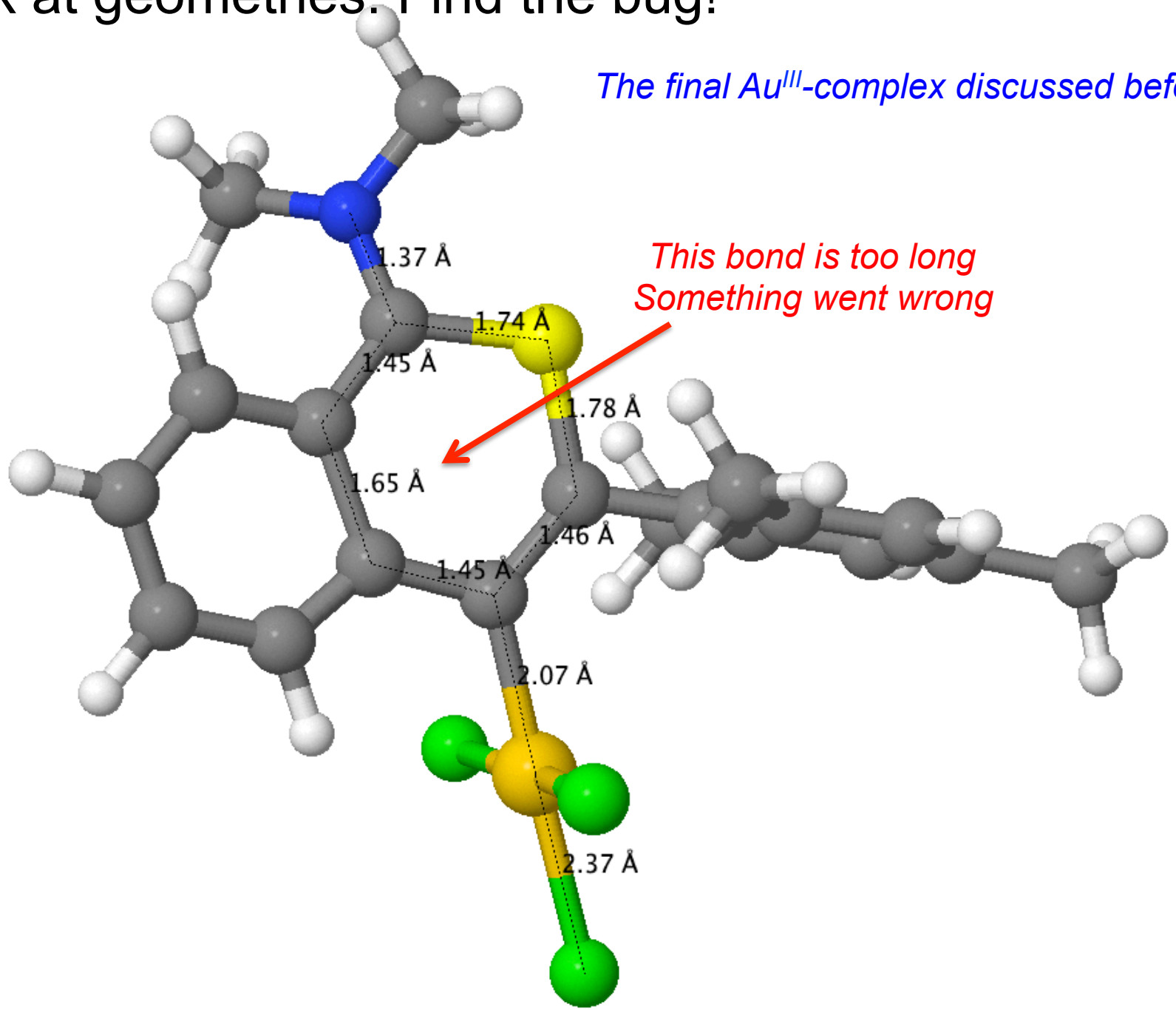
Look at geometries: Find the bug!

The final Au^{III}-complex discussed before



Look at geometries: Find the bug!

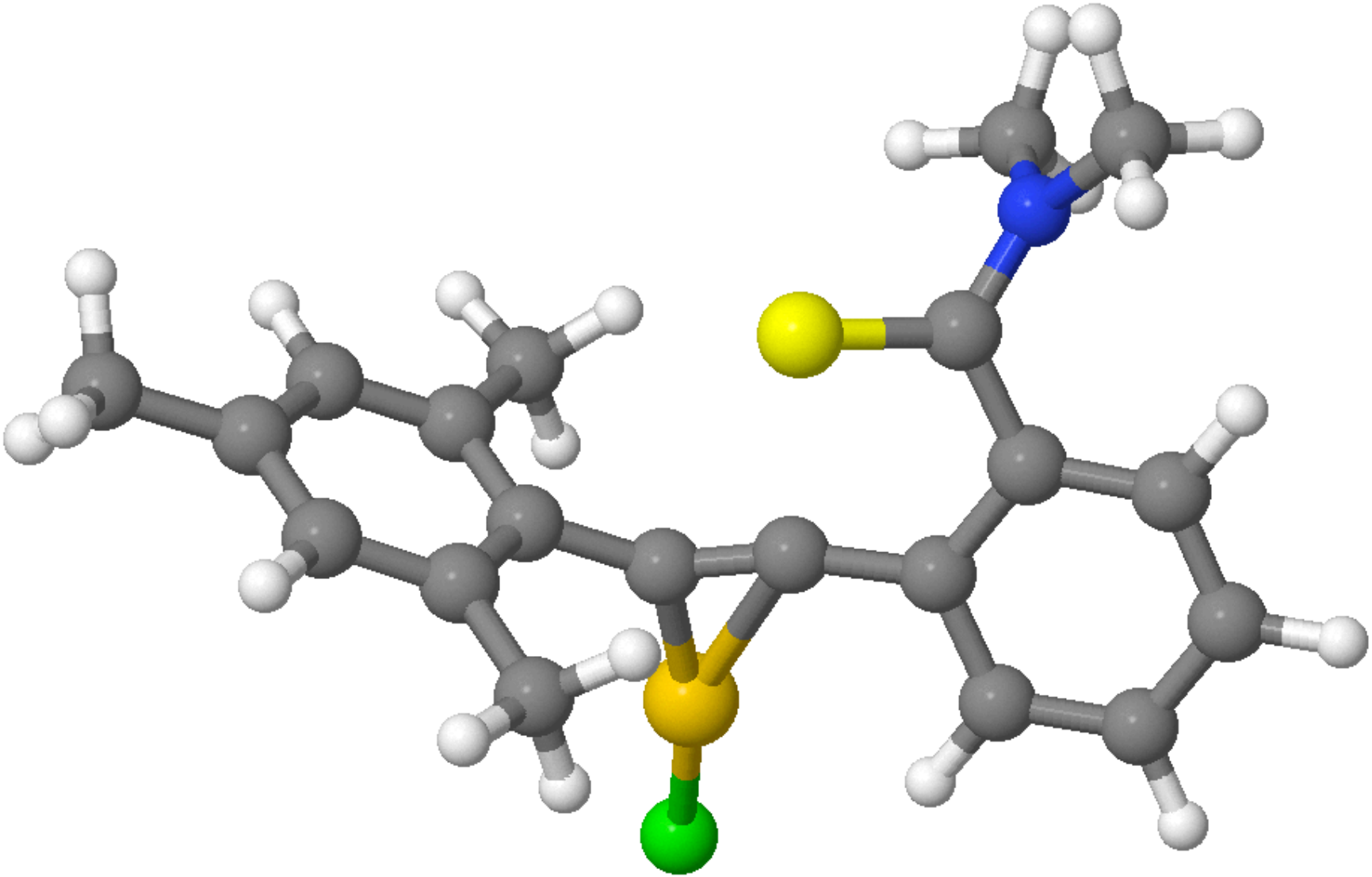
The final Au^{III}-complex discussed before



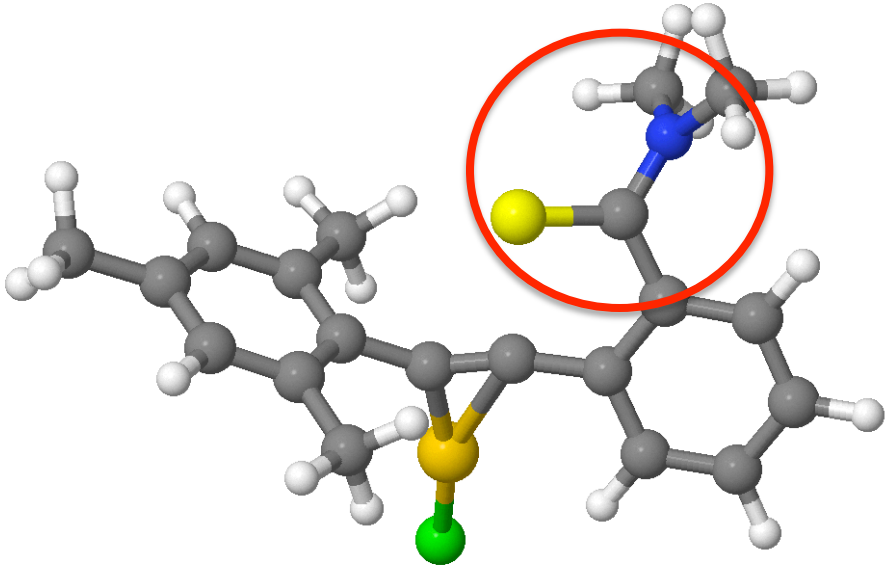
This bond is too long
Something went wrong

Look at geometries: Find the bug!

The Au^{I} transition state for the 5-endo cyclization discussed before

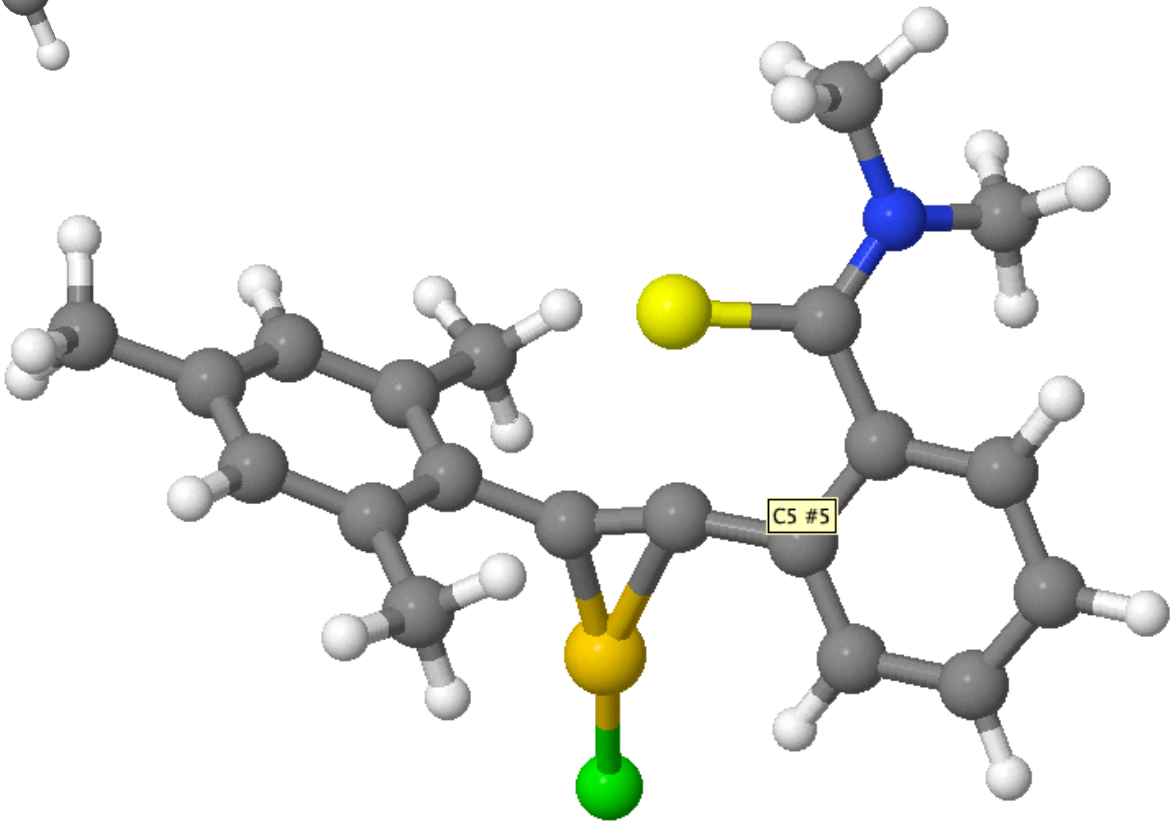


Look at geometries: Find the bug!



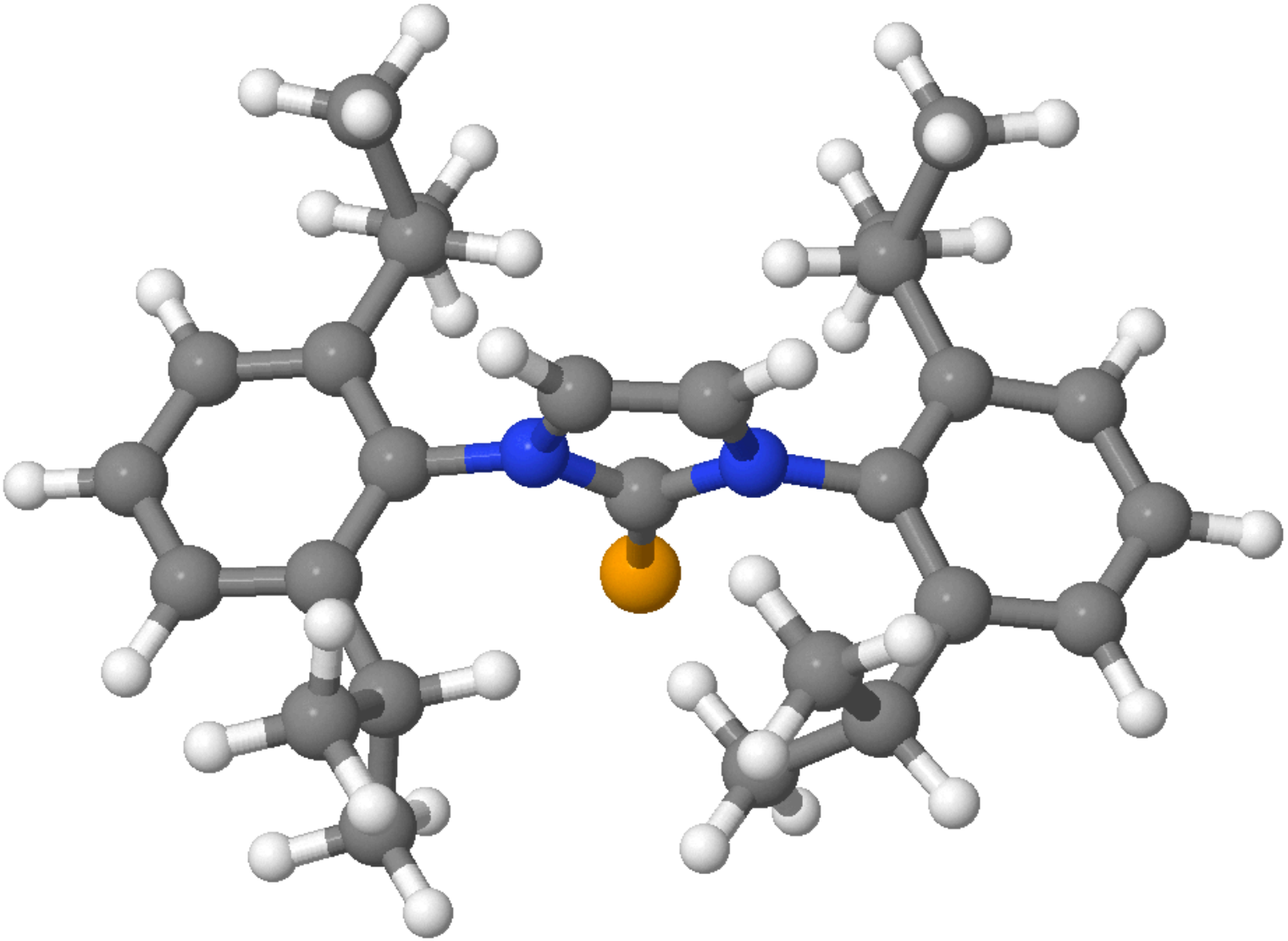
You know that amide bonds are planar
The challenge is spotting this bug
by quick visual inspection

Correct (common) conformation
of a (thio)amide group

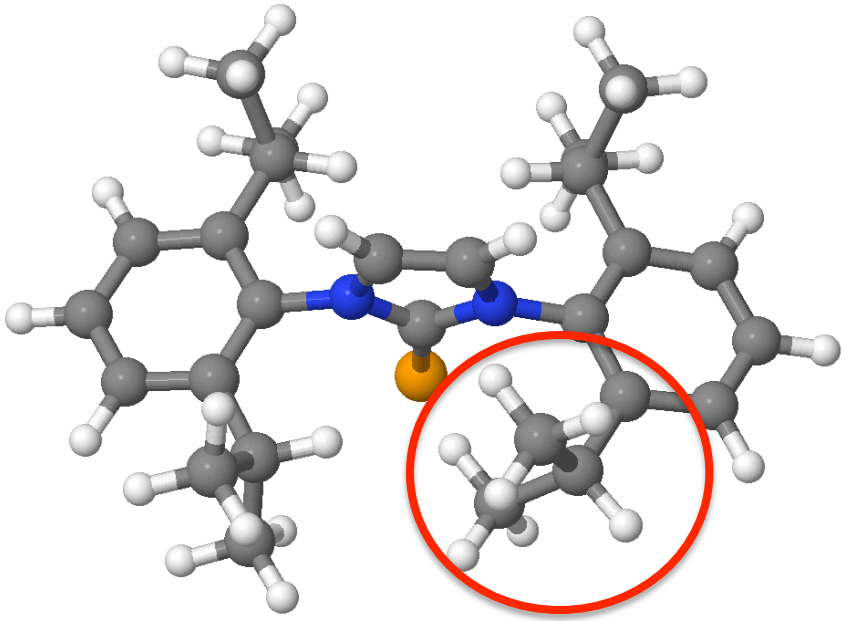


Look at geometries: Find the bug!

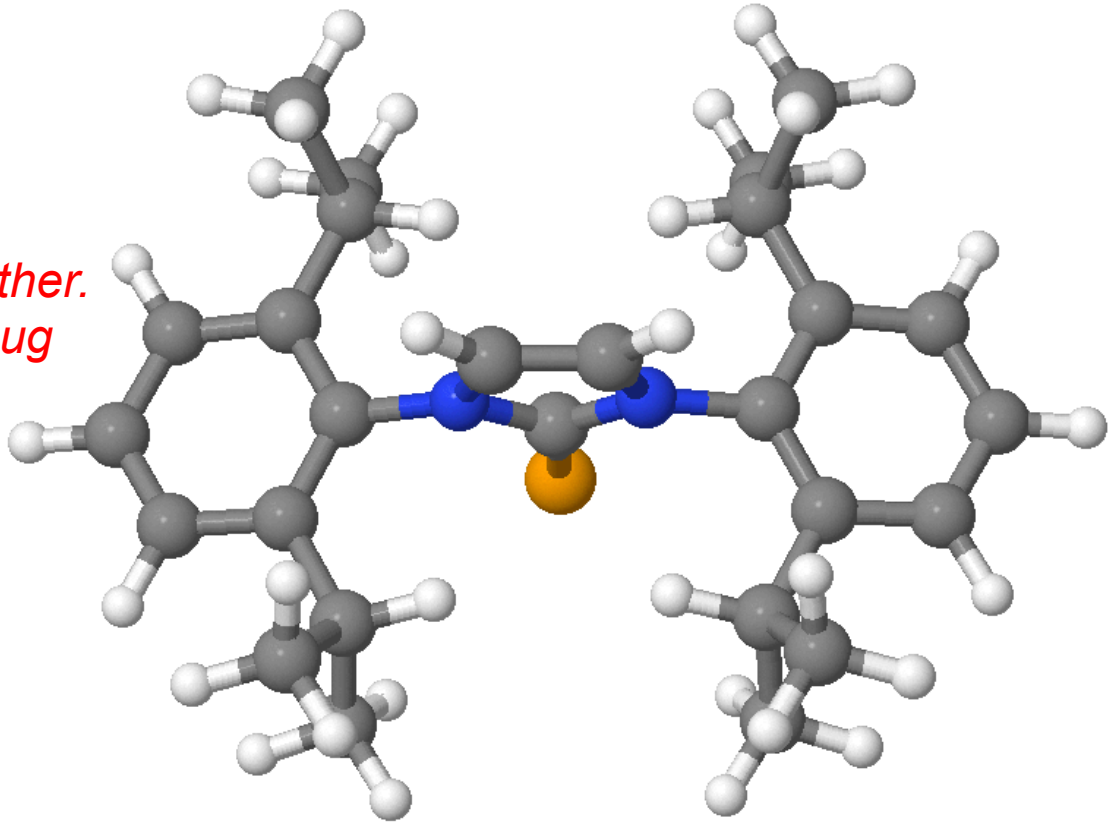
Structure of a NHC-Au^{I} complex



Look at geometries: Find the bug!



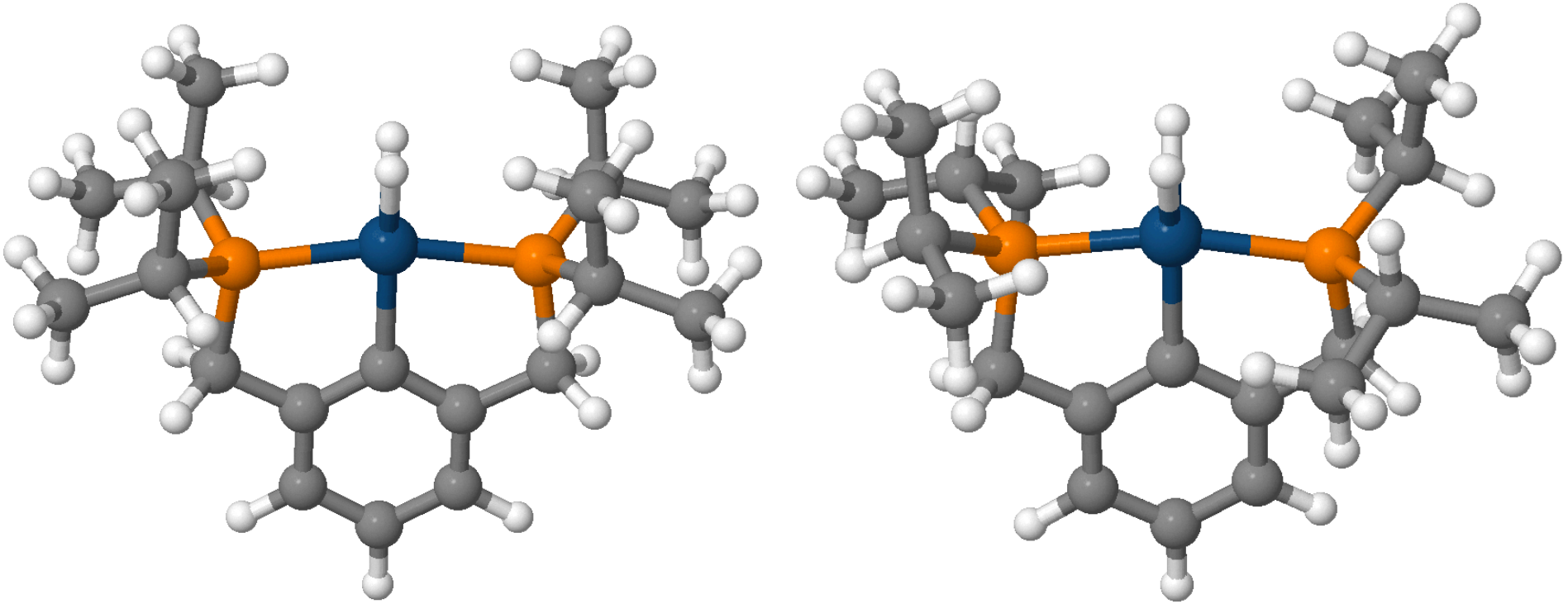
i-Pr C-H bonds normally face each other.
You need trained eye to spot this bug



Correct (common)
Orientation of the iPr group

Look at geometries: Find the bug!

One of the winning Brookhart catalysts for ethylene to aromatics
Nature Chemistry 2011, 3, 167

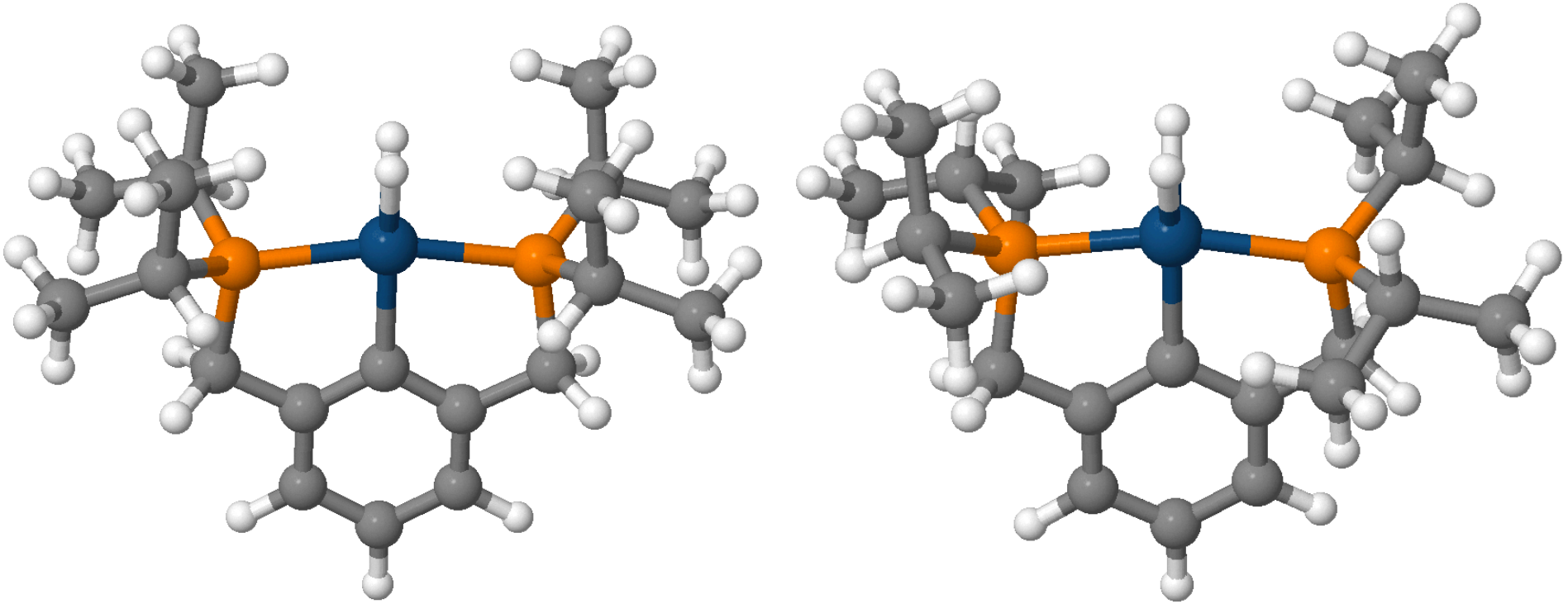


Look at geometries: Find the bug!

Sorry no bug…

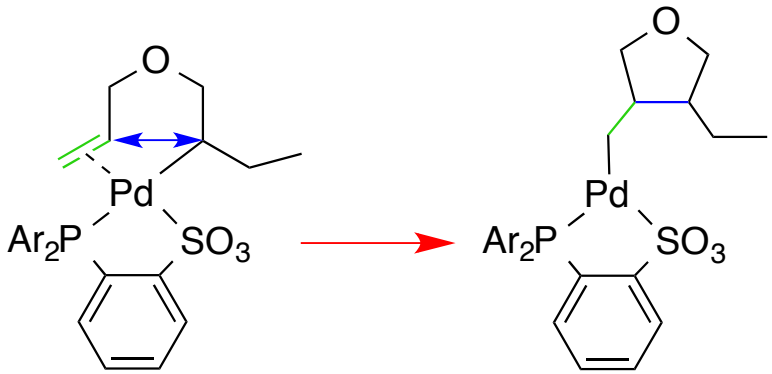
the iPr groups can assume a plethora of different conformations of similar energy

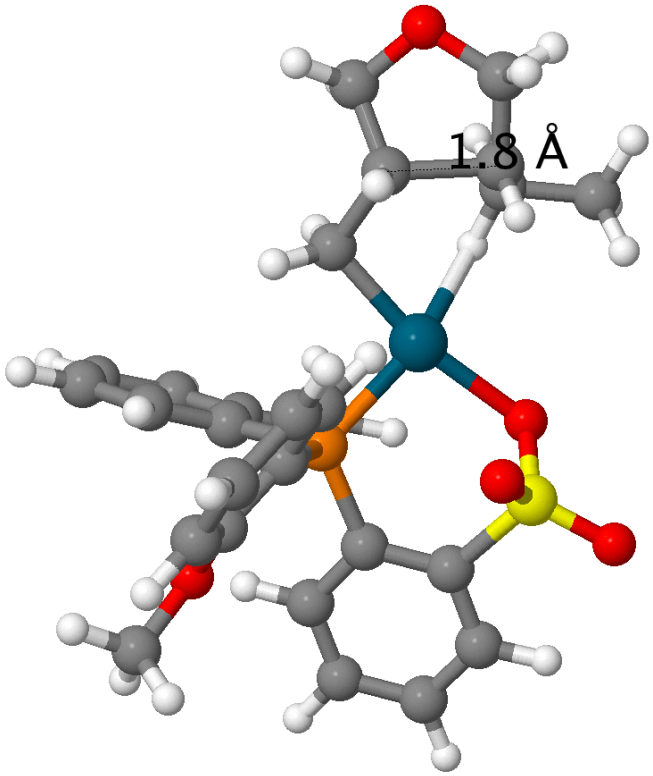
You have to consider all of them to characterize properly a reaction pathway



Additional issues in transition states location

You are searching for the TS corresponding to insertion of the C=C into the Pd-C bond. Before going home you run a job to find this TS. You ask to calculate freqs after TS localization to be check for a single negative freq.

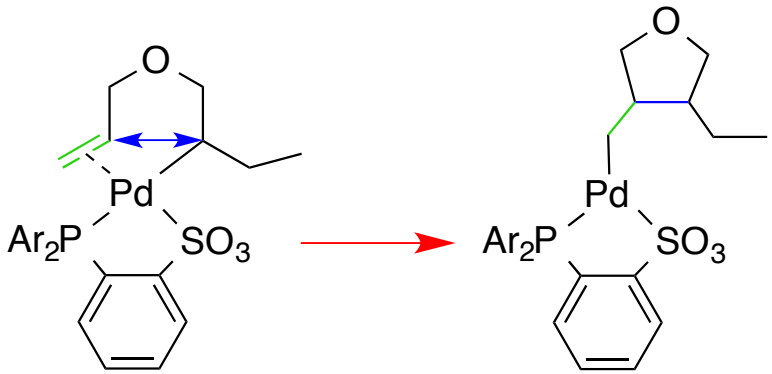


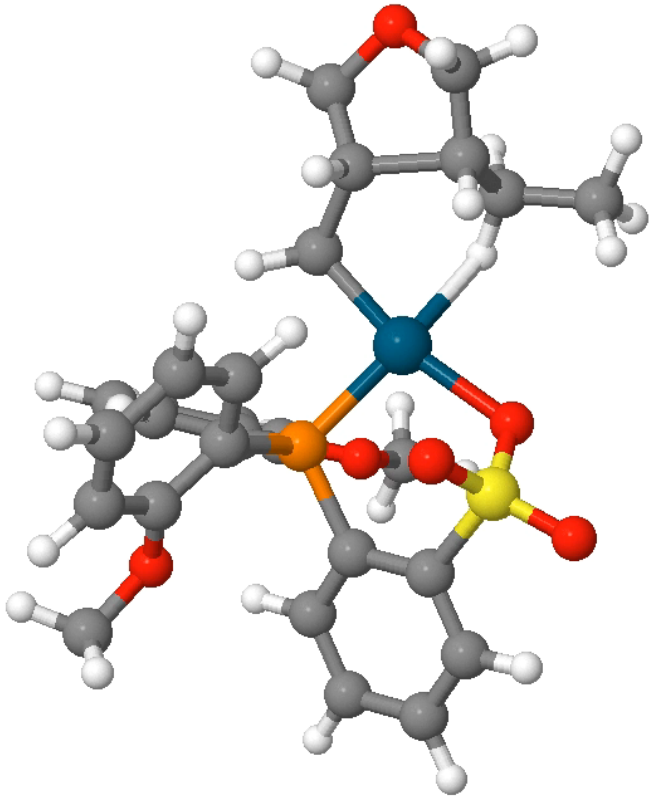


The next morning the the job is completed and it has a single imaginary freq at -83 cm^{-1}. The emerging C-C bond is definitely longer than a standard C-C single bond. *Can you consider the job done ?*

Additional issues in transition states location

No, the story is not over yet, as the imaginary freq at -83 cm^{-1} has nothing to do with the formation of a C-C bond. Go back and try again.

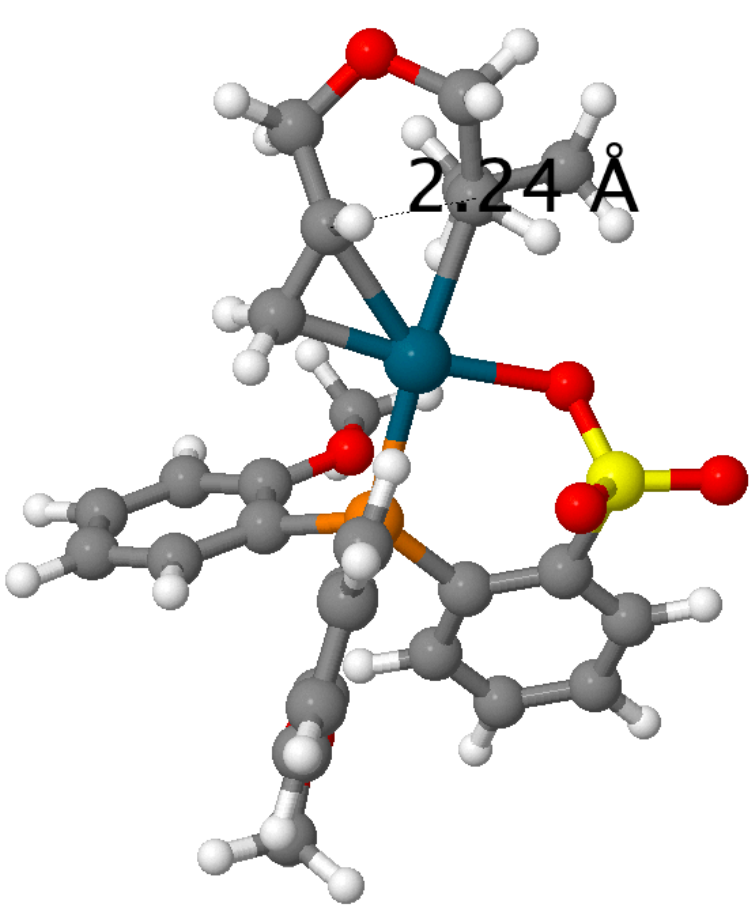


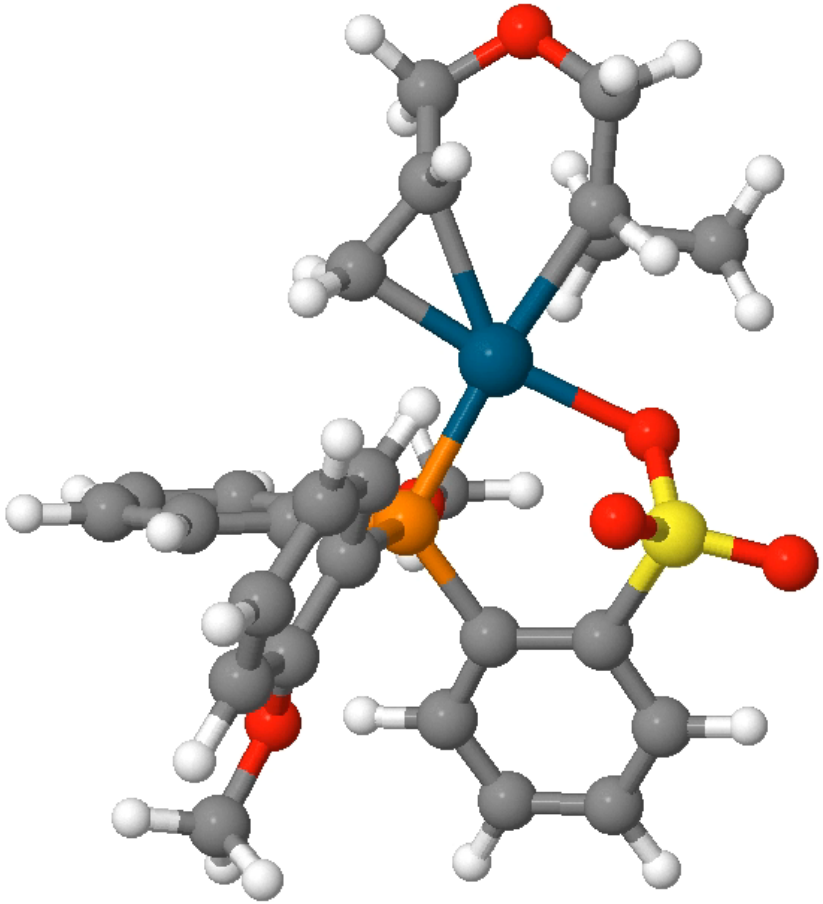


Before going home you run a job to find again this TS, you changed the starting geometry.

Additional issues in transition states location

The next morning the the job is completed and it has a single imaginary freq at -210 cm^{-1}, and the emerging C-C bond is 2.10 Å. The negative freq clearly corresponds to the forming C-C bond. *Mission completed !*

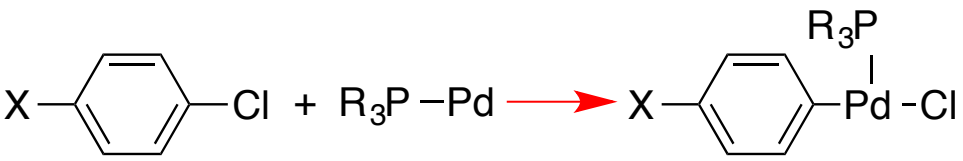




Outline

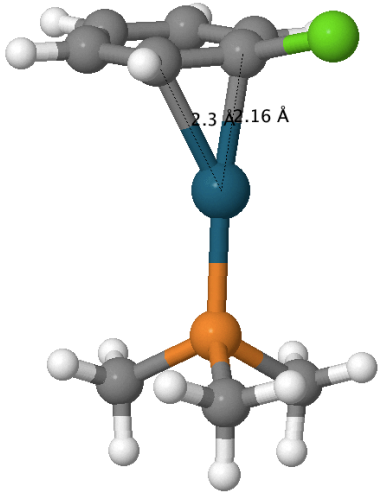
- Introduction
- Quiz 1 : Geometries
- Quiz 2 : Energies
- Quiz 3 : Selectivities
- Quiz 4 : Building a reaction pathway
- Quiz 5 :
- Conclusions

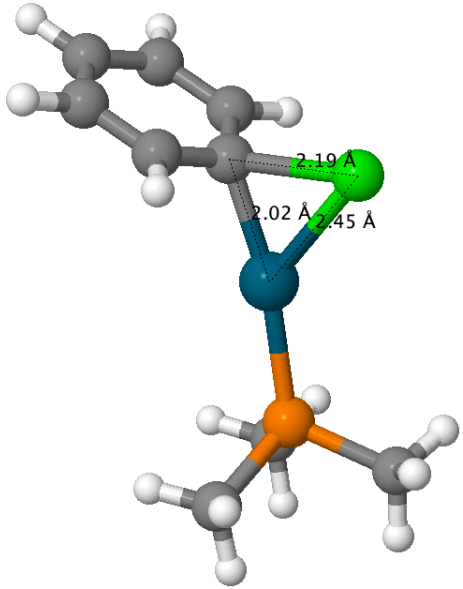
Aryl-X activation by Pd

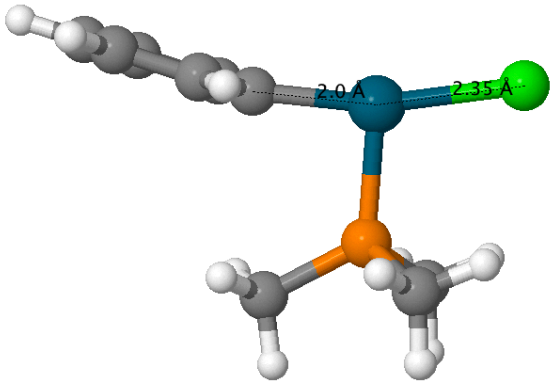


X = H, NMe_2, NO_2

Asking 3 PhD students
to calculate this reaction
E in kcal/mol







	H	NMe_2	NO_2
PhD 1 :	0	0	0
PhD 2 :	0	0	0
PhD 3 :	0	0	0

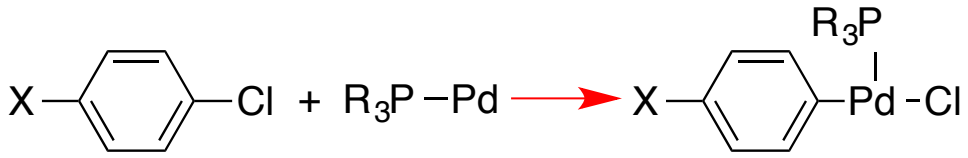
	H	NMe_2	NO_2
PhD 1 :	7.8	9.9	9.6
PhD 2 :	7.9	4.6	9.8
PhD 3 :	7.9	15.4	9.9

	H	NMe_2	NO_2
PhD 1 :	-16.5	-16.9	-16.2
PhD 2 :	-16.8	-16.8	-16.3
PhD 3 :	-16.7	-17.0	-16.5

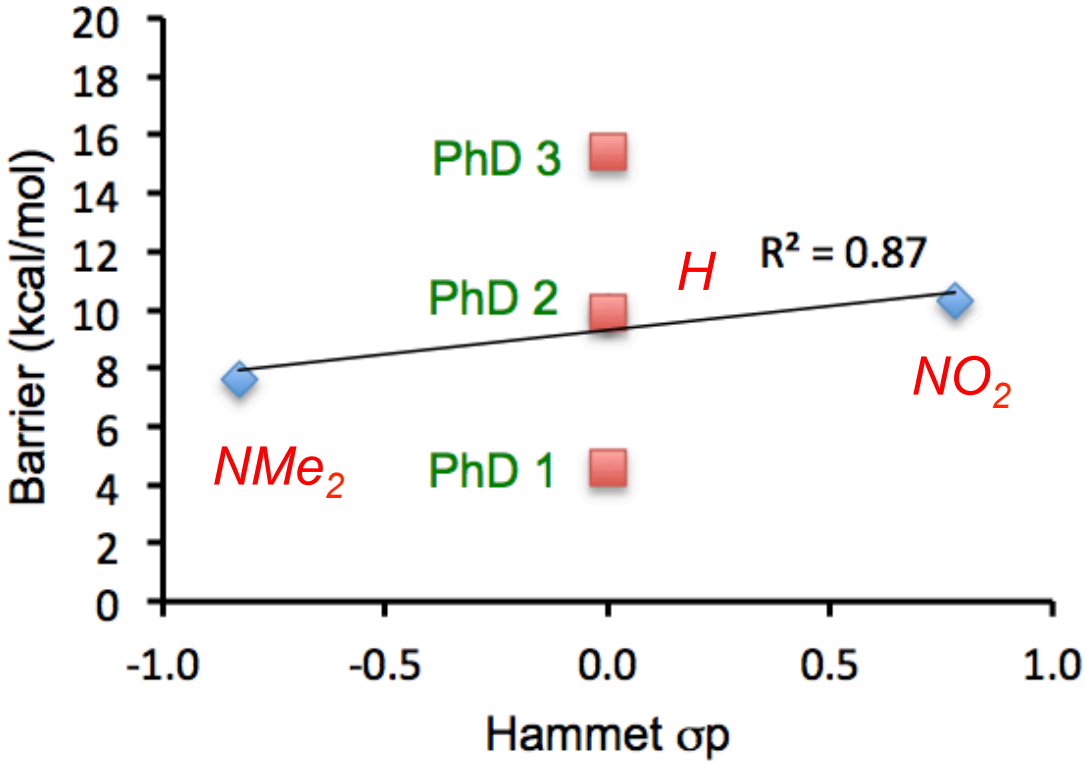
Who is right ? (if any)
aka
How to know if a number is correct or not ?

Aryl-X activation by Pd

One usual trick is comparing strictly related systems with a descriptor



X = H, NMe_2, NO_2



Whenever possible, don't rely on a single number but try to get trends

One number whispers, **many numbers talk loud!**

Outline

- Introduction
- Quiz 1 : Geometries
- Quiz 2 : Energies
- Quiz 3 : Predicting selectivity
- Quiz 4 : Understanding selectivity
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Stereoselective reactions

Bolm & Gladysz, Chem. Rev. 2003, 103, 2761

Enantioselective Catalysis : selective, and reproducible generation of a given enantiomer of a chiral product from achiral reactants.

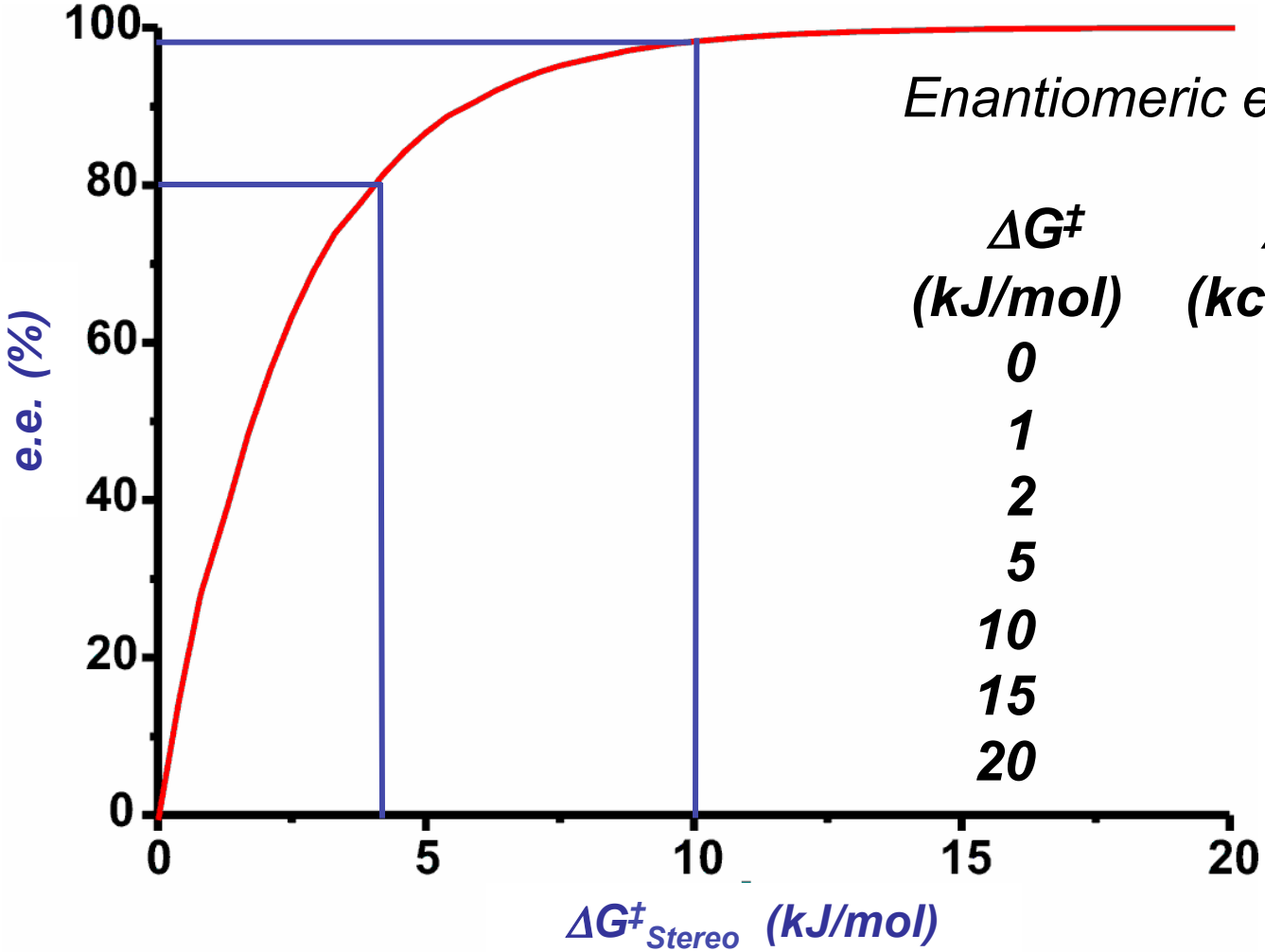
Enantioselective catalysts are with no exception chiral and non racemic.

The reaction efficiency is measured as : enantiomeric excess (e.e.) = %A - %A*

The enantiomeric excess is determined by: $\Delta G^{\ddagger} = G^{\ddagger}(A^*) - G^{\ddagger}(A)$

The connection is : $$\frac{\%A^*}{\%A} = e^{-\Delta G/RT}$$

How much $\Delta G^{\ddagger}$ do we need ?



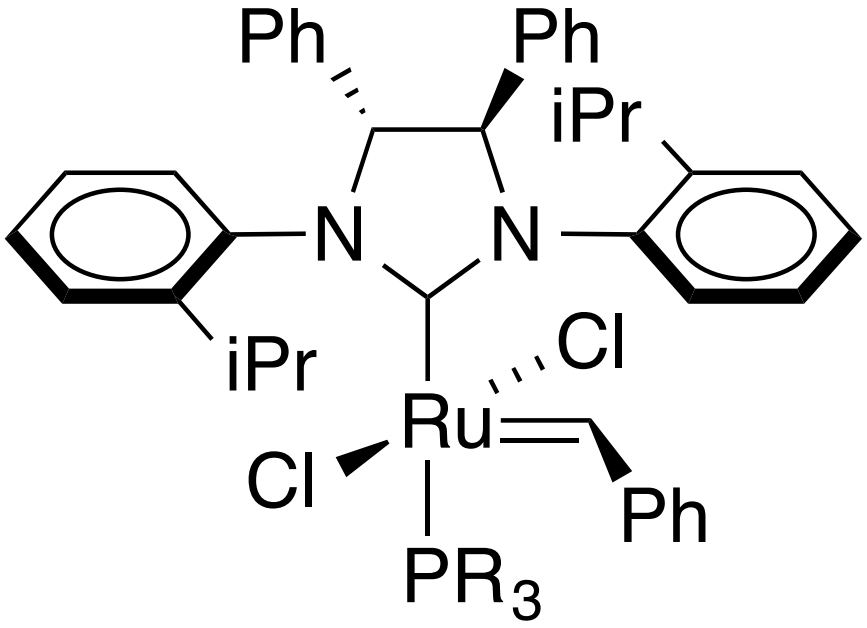
Enantiomeric excess at 25 °C

$\Delta G^{\ddagger}$ (kJ/mol)	$\Delta G^{\ddagger}$ (kcal/mol)	e.e (%)
0	0.0	0.0
1	0.2	18.4
2	0.5	35.6
5	1.2	73.1
10	2.4	95.3
15	3.6	99.3
20	4.8	99.9

Stereoselectivity usually played with $\Delta G^{\ddagger} \approx 10$ kJ/mol or 2 kcal/mol
This is smaller than the rotation around a single C-C bond, but enough to roll 95% of the reactants along the favored pathway.

These energy differences are at the limit of DFT accuracy

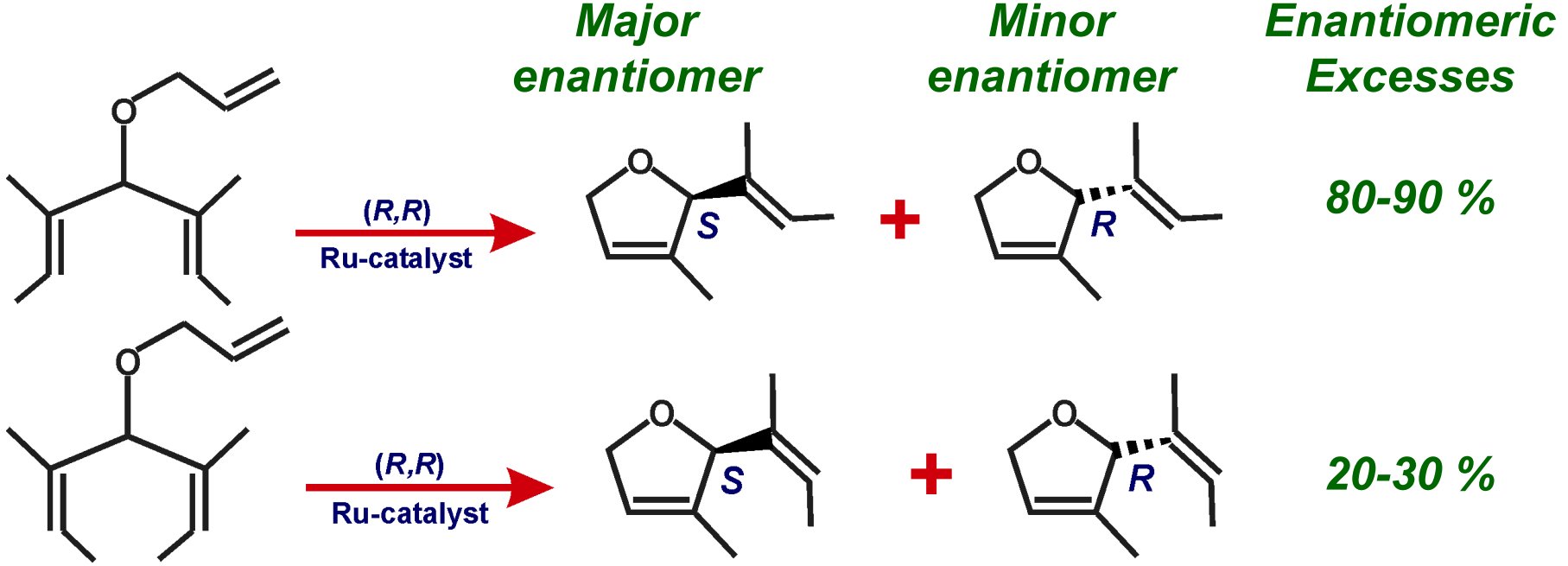
Asymmetric olefin metathesis



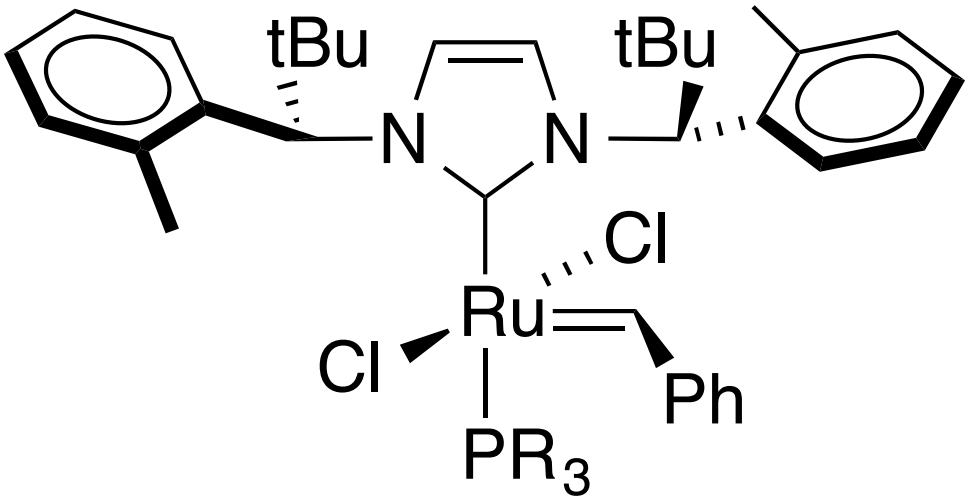
Best Grubbs catalyst so far

Still space for improvements.

Extremely hot area
suppose you want to invent a new catalyst. Rather than blind testing, you try to design it in silico.



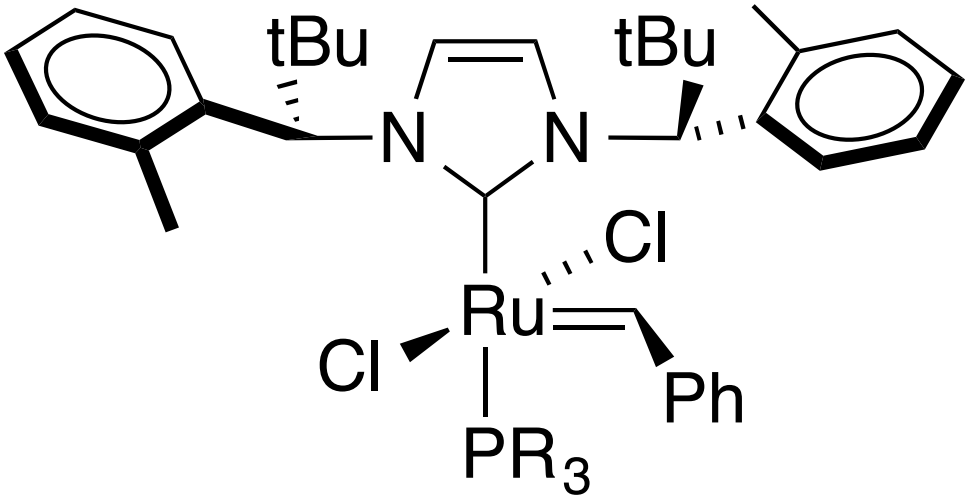
Asymmetric olefin metathesis

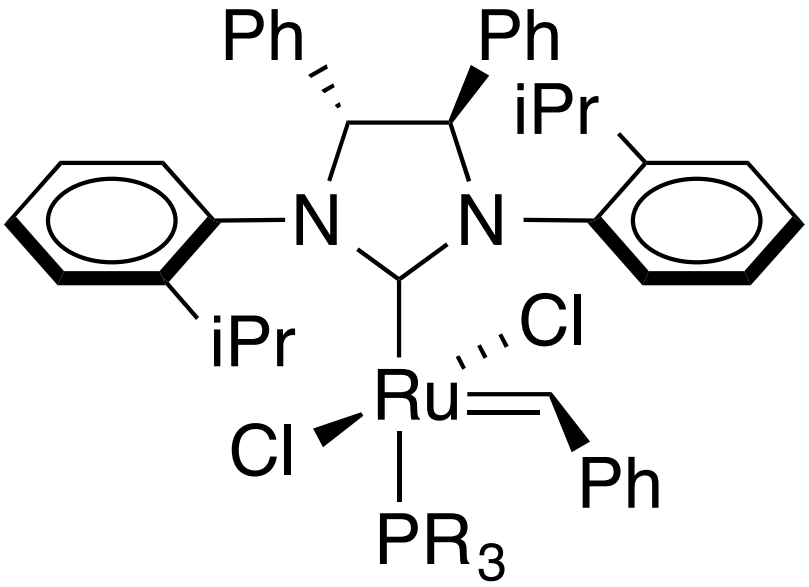


You predict this catalyst to result in a ΔE_{Stereo} of 2.6 kcal/mol, which means more than 95% e.e.

Would you be happy ?
How to trust this prediction ?

Asymmetric olefin metathesis





You predict this catalyst to result in a ΔE_{Stereo} of 2.6 kcal/mol, which means more than 95% e.e.

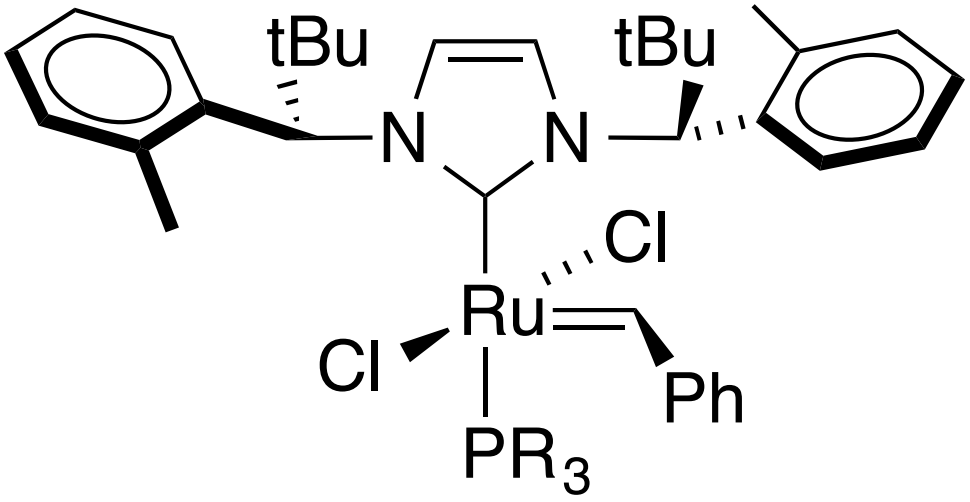
Would you be happy ?
How to trust this prediction ?

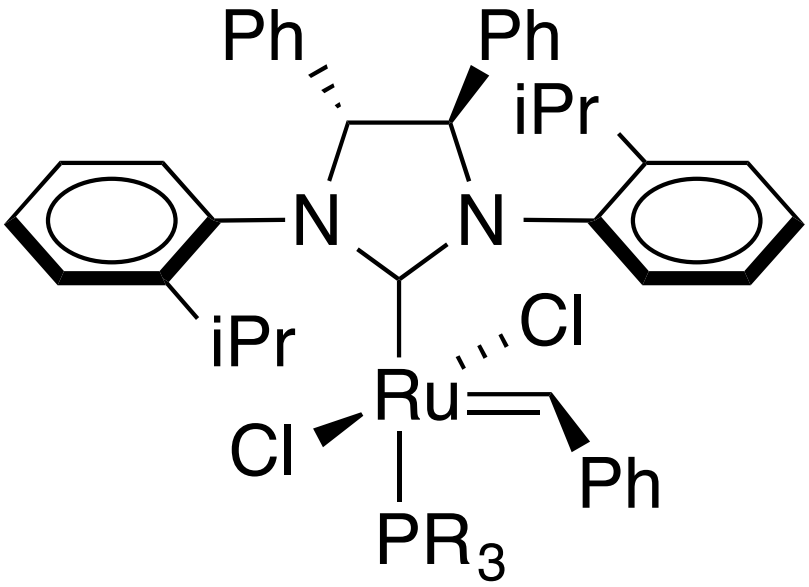
Testing prediciton on a known system

For the known system I predict a ΔE_{Stereo} of 3.2 kcal/mol, which means I am overestimating the selectivity

***No, I am not happy**!*
My new catalyst should perform even worse than the old one

Asymmetric olefin metathesis





You predict this catalyst to result in a ΔE_{Stereo} of 2.6 kcal/mol, which means more than 95% e.e.

Would you be happy ?
How to trust this prediction ?

Testing prediciton on a known system

For the known system I predict a ΔE_{Stereo} of 0.7 kcal/mol, which means that my selectivity calculation is OK.

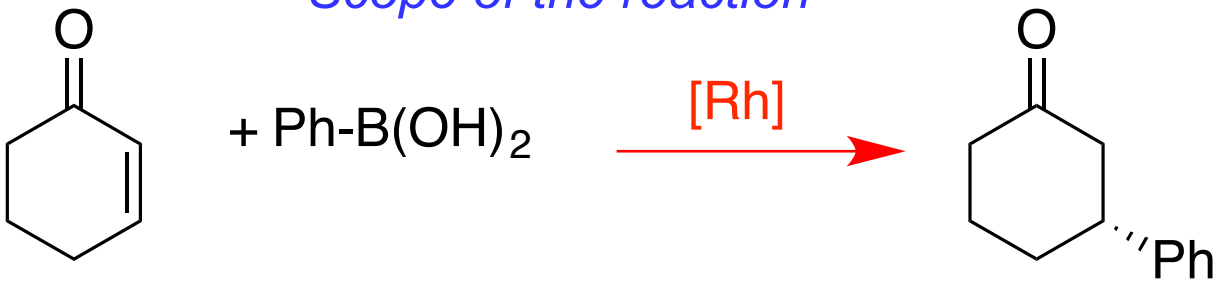
Yes, I am happy!
My new catalyst should perform much better than the old one!

Outline

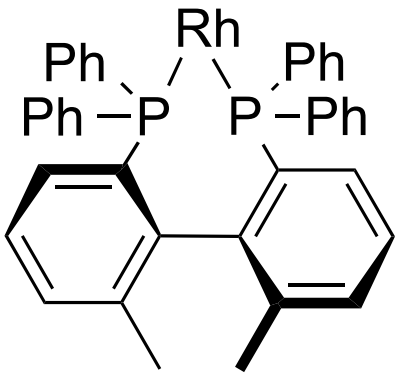
- Introduction
- Quiz 1 : Geometries
- Quiz 2 : Energies
- Quiz 3 : Predicting selectivity
- Quiz 4 : Understanding selectivity
- Conclusions

Understanding selectivities

Scope of the reaction



The catalyst investigated



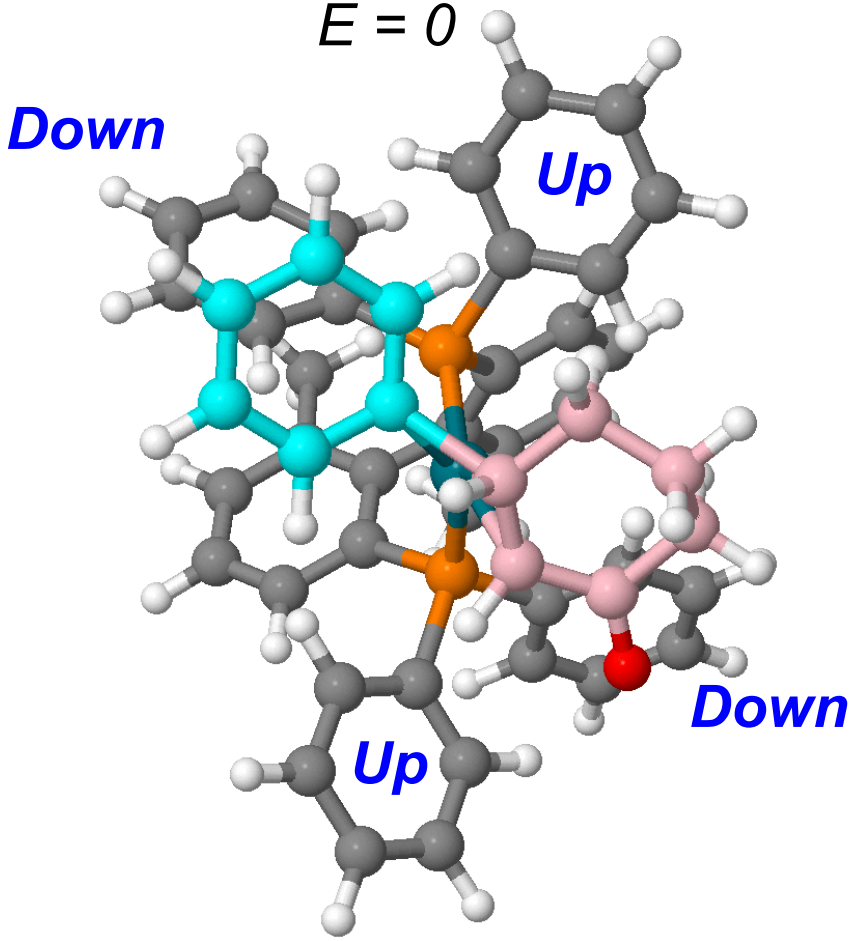
The enantioselective performance

ee = 90%

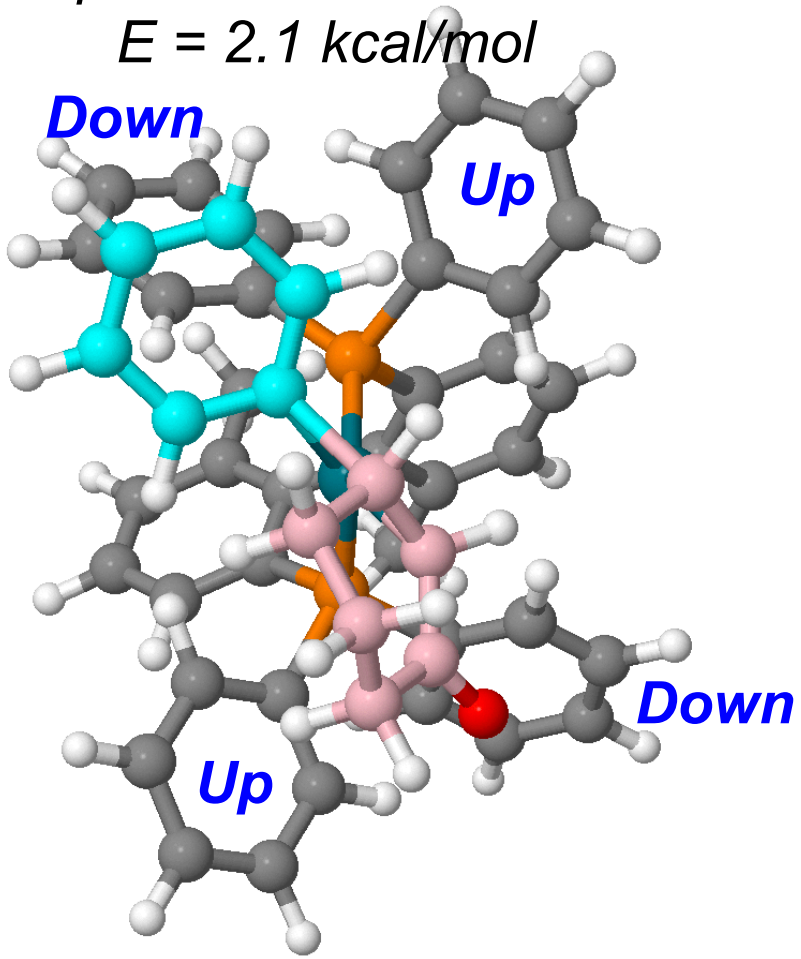
Understanding selectivities

DFT reproduces experiments

E = 0



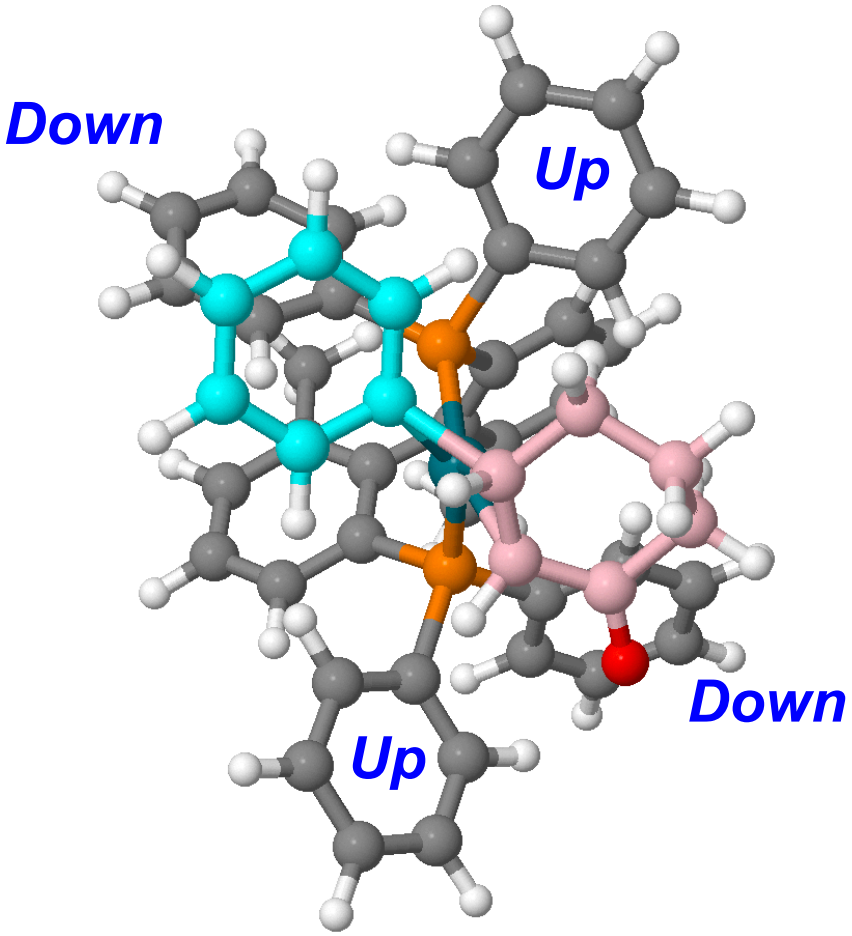
E = 2.1 kcal/mol

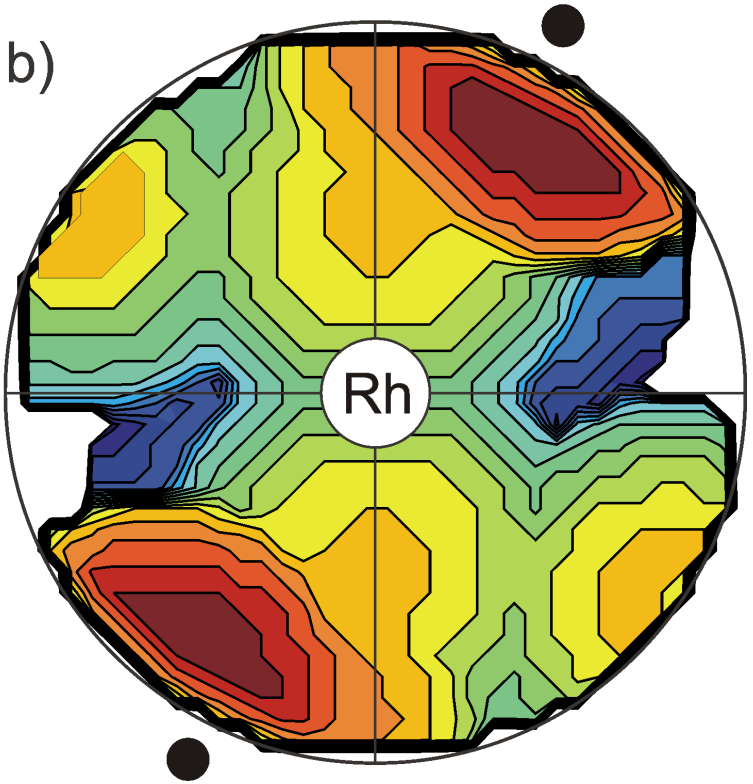


Now the question: Why is this better ?
This is the answer that experimental people need.
They already know that the one on the left is preferred ☺

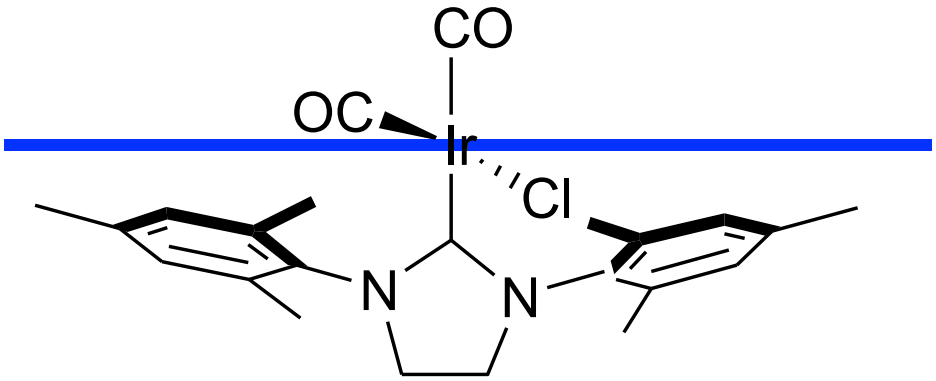
Understanding selectivities

Selectivity is steric in nature. The favored TS has the substrate placed in the groove between the "Up" phenyl rings of the ligand



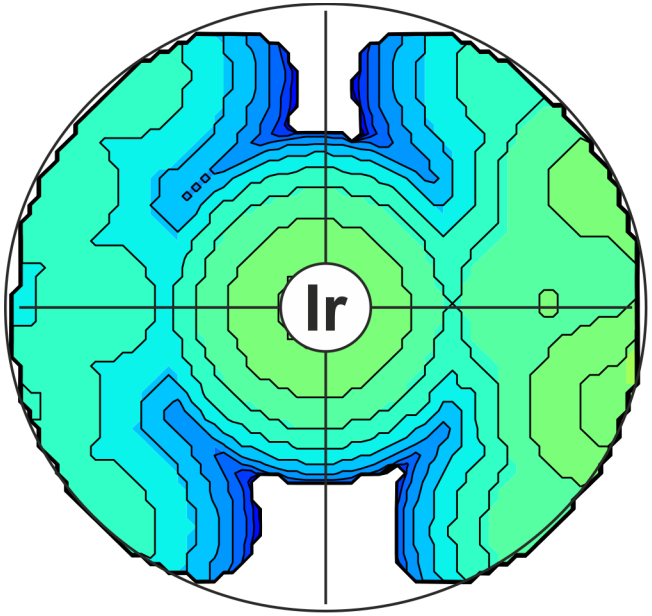


Topographic steric maps of ligands



3D-view
Physical map

3D-view
Physical map



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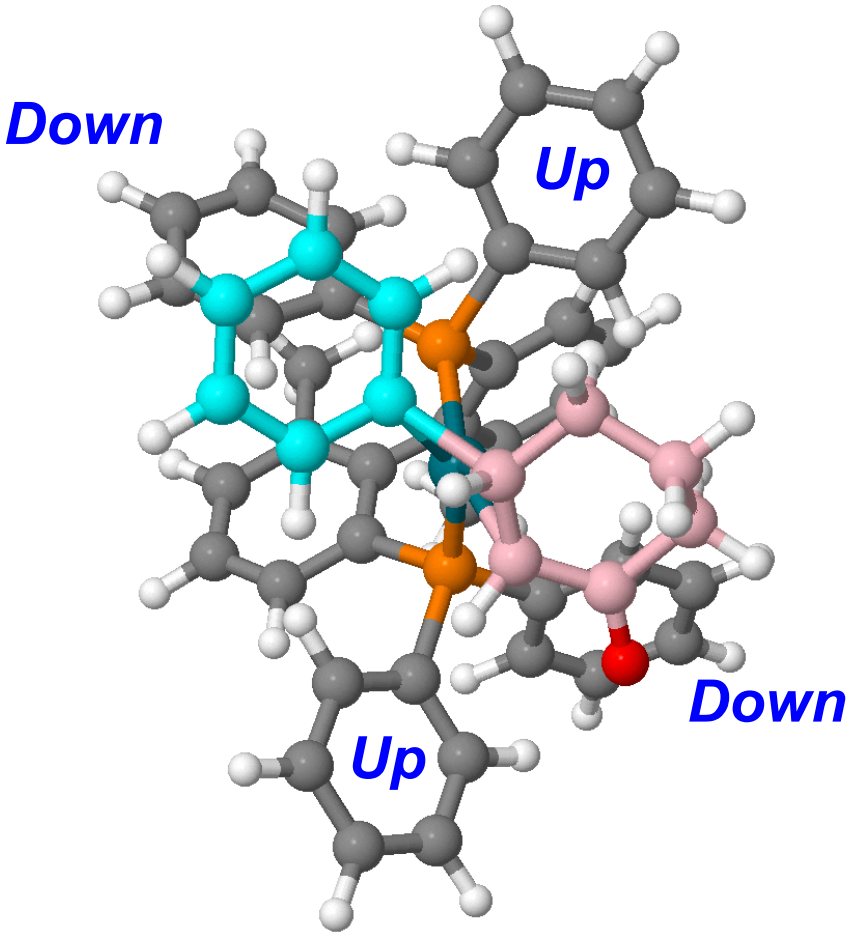
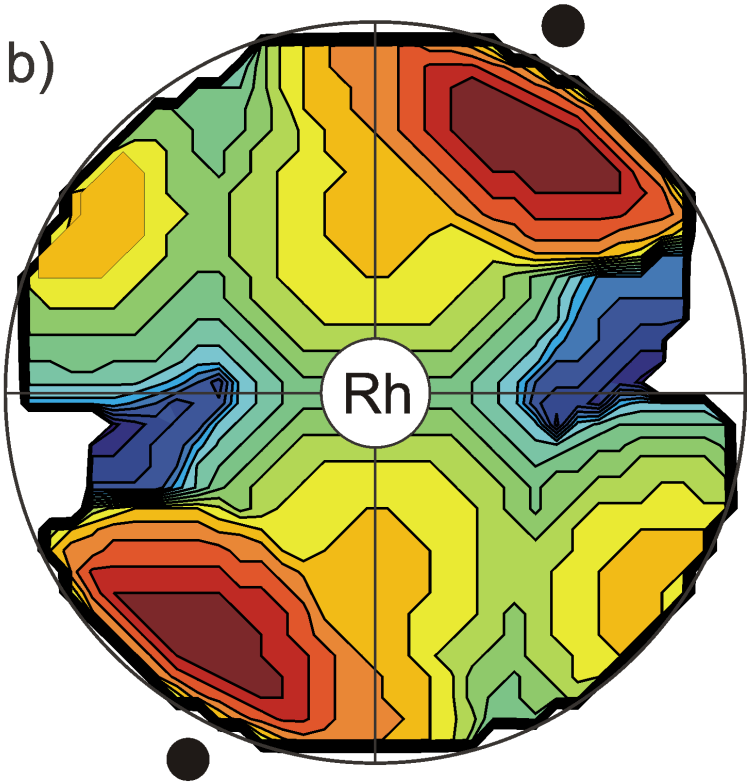
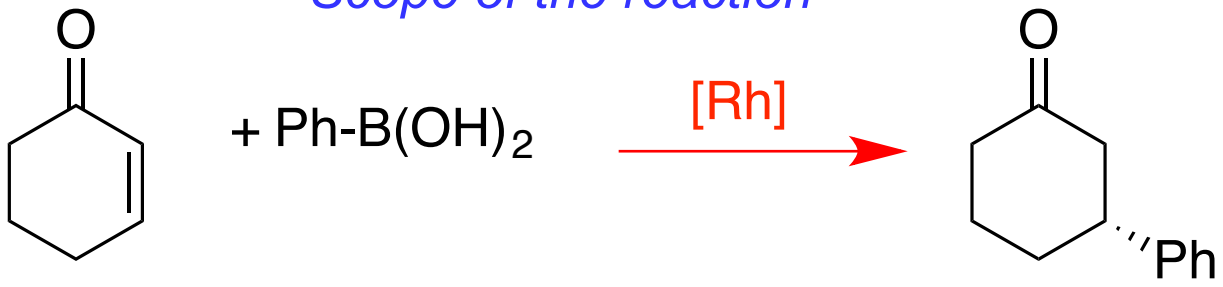




Understanding selectivities

Scope of the reaction



The catalyst compared

The enantioselective performance

ee = 99%

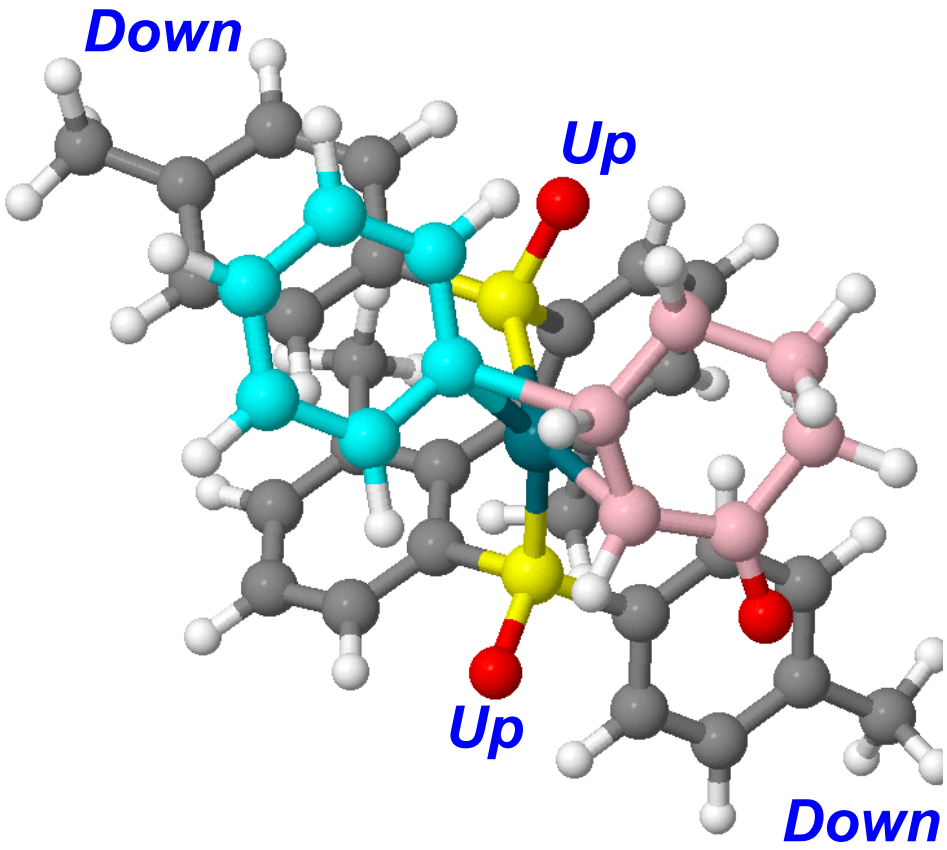
ee = 90%

Cavallo Dorta et al. Chem. Eur. J. ***2010****, 16, 14348. Ibid.* ***2010****, 16, 14335.*

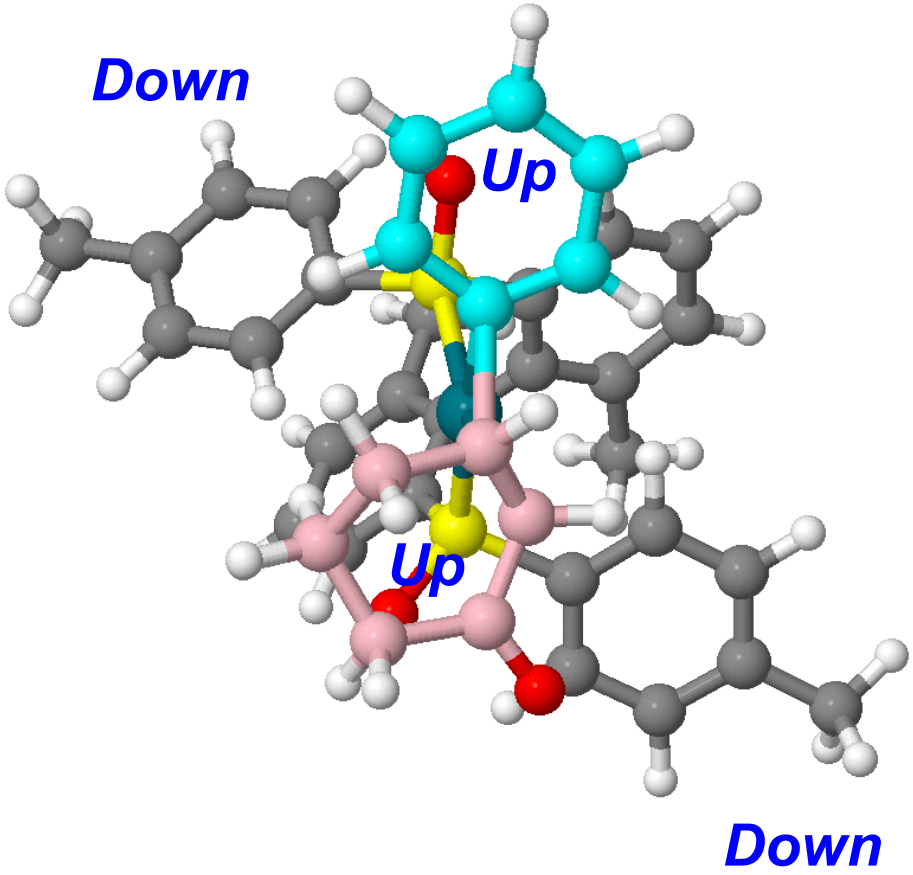
Understanding selectivities

DFT reproduces experiments

E = 0



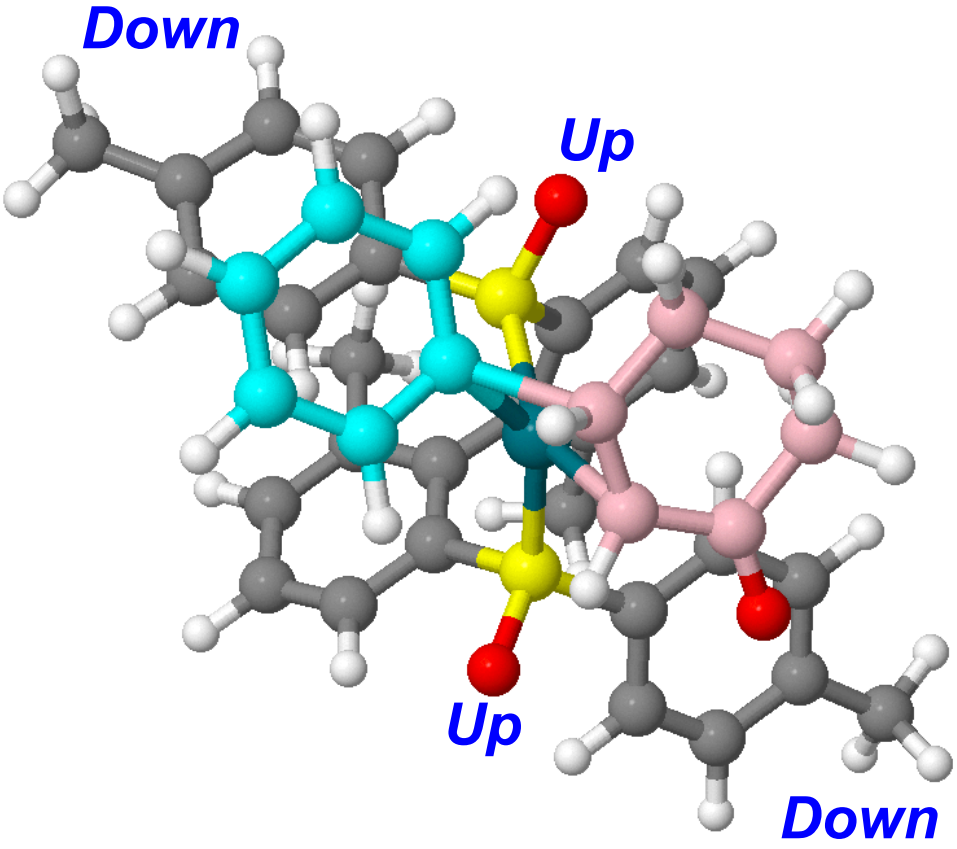
E = 3.4 kcal/mol

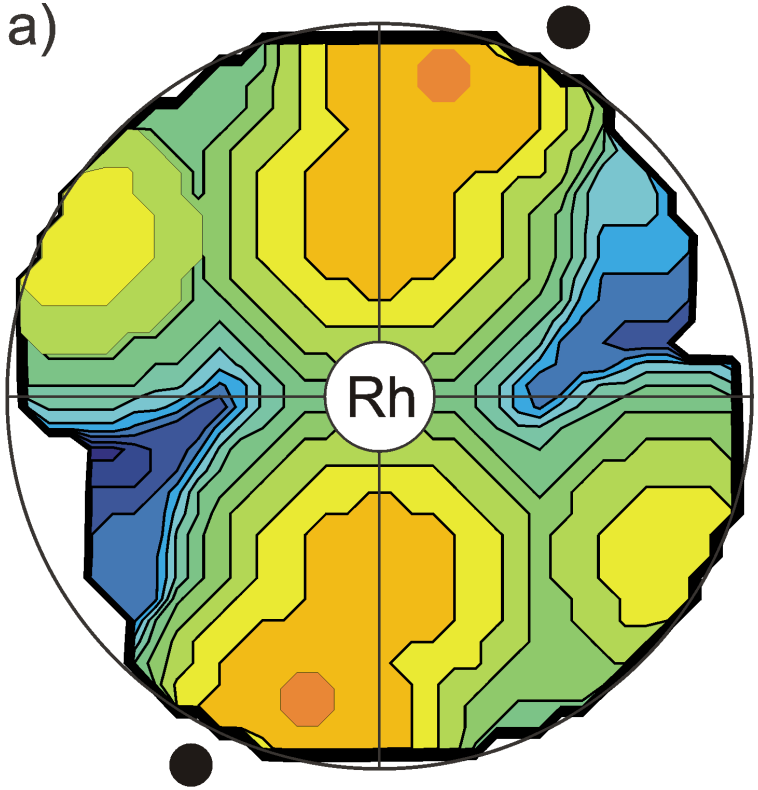


The same question again:
Why is this better ?

Understanding selectivities

Steric interaction is not the reason. The steric map is totally flat, the O atom is too small to give steric hindrance





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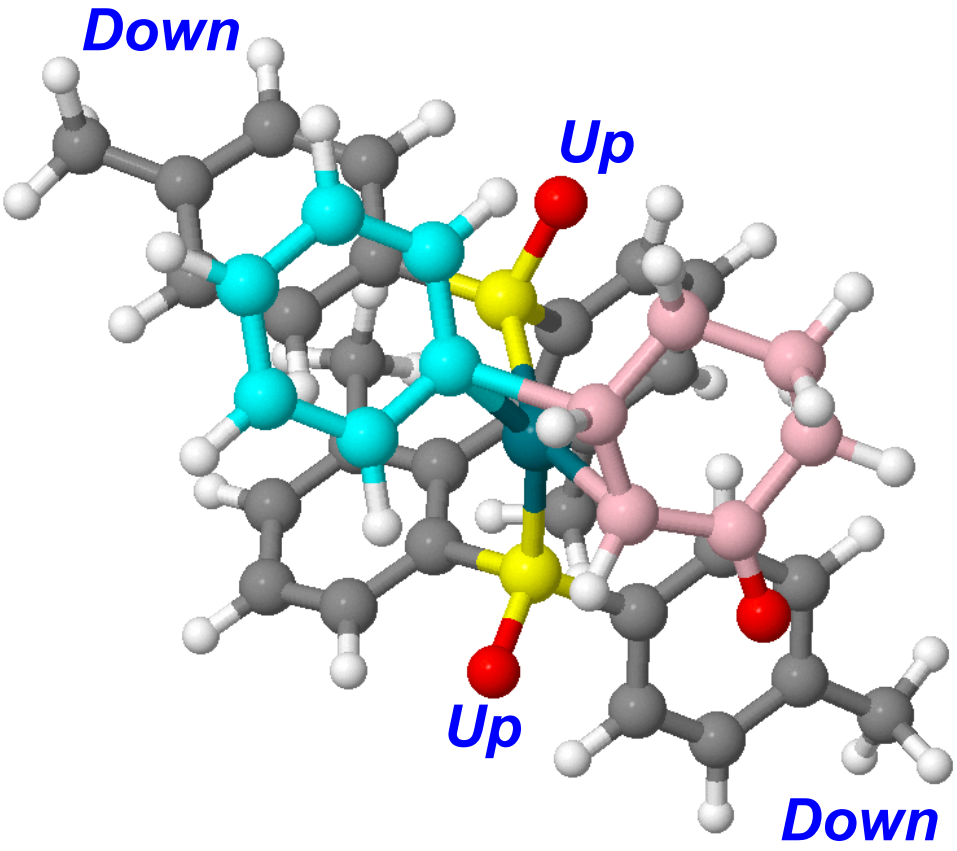
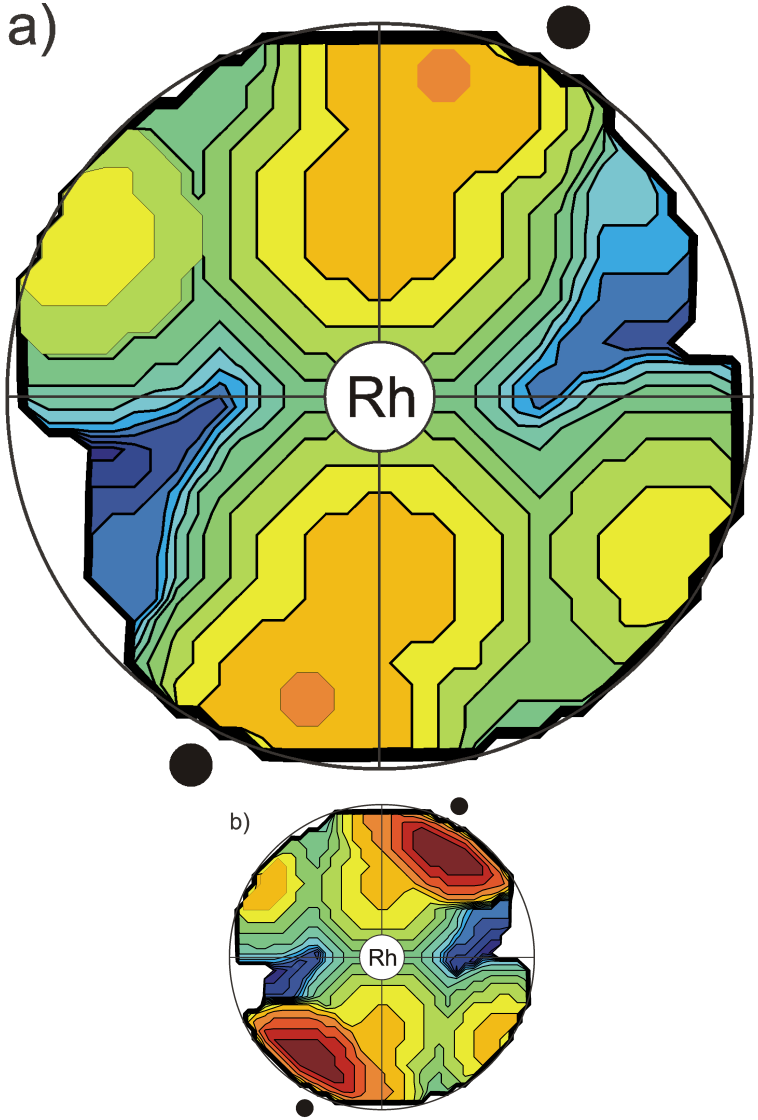


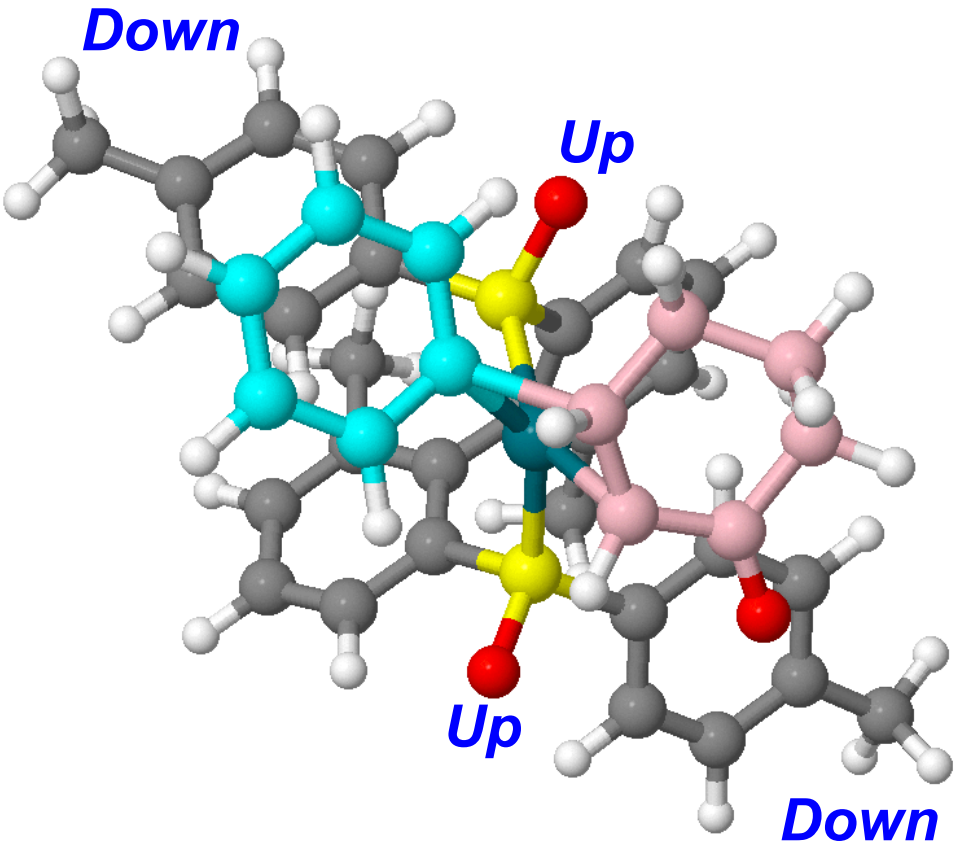


The same question again:
Why is this better ?

Understanding selectivities

DFT reproduces experiments

E = 0



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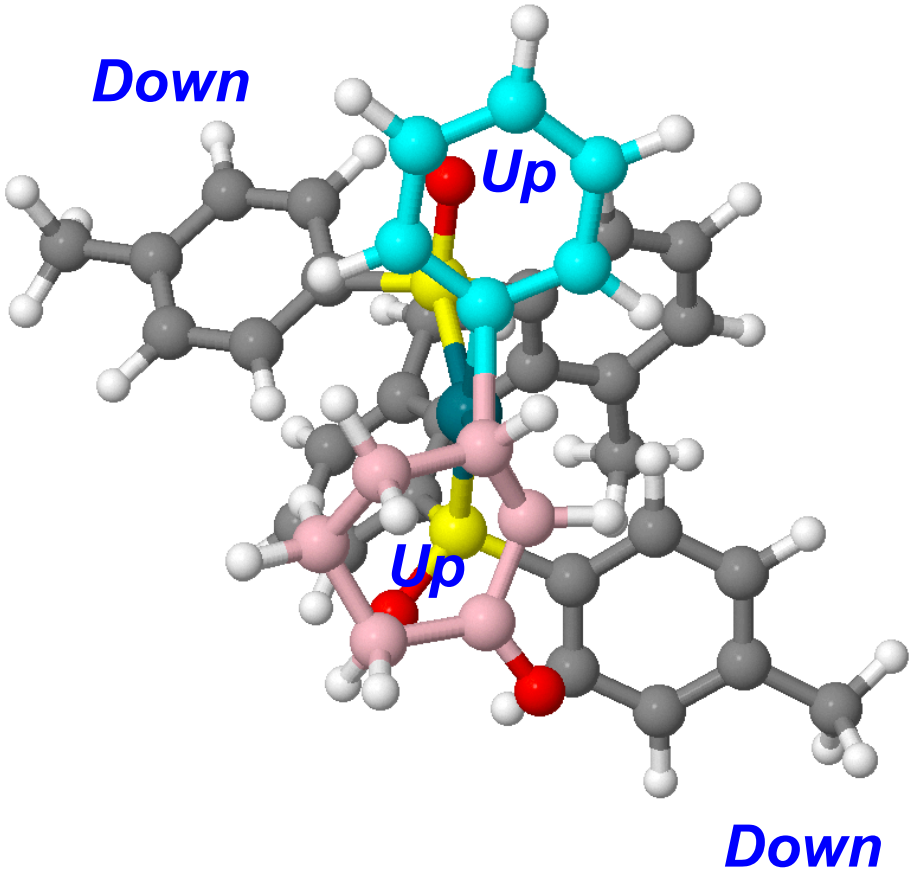
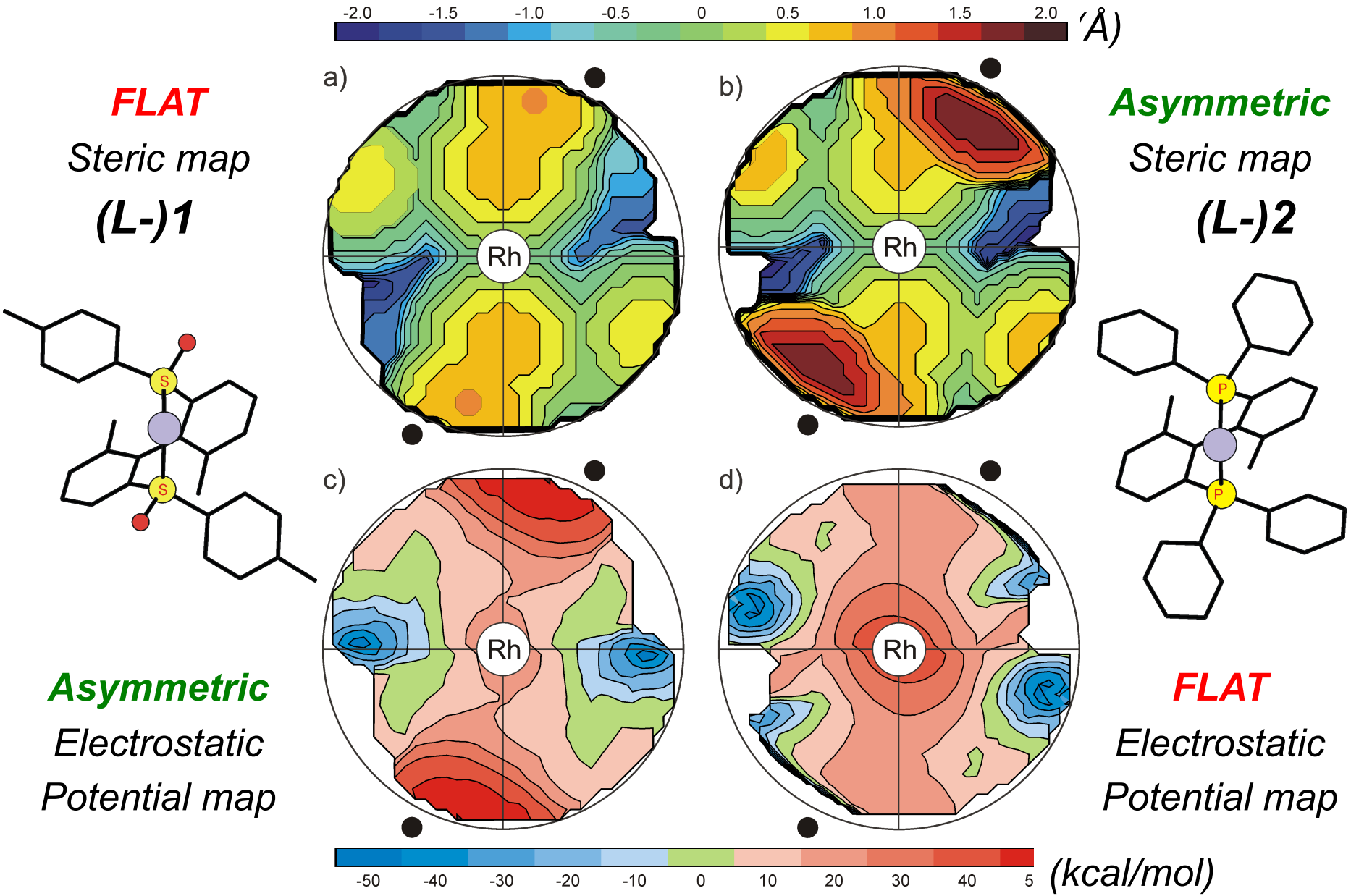


The question remains the same:
Why is this better ?

Understanding selectivities



FLAT

Steric map

(L-)1

Asymmetric

Steric map

(L-)2

Asymmetric

Electrostatic

Potential map

FLAT

Electrostatic

Potential map

Cavallo Dorta et al. Chem. Eur. J. ***2010****, 16, 14348. Ibid.* ***2010****, 16, 14335.*

Some tips…

1. Never trust your computer
2. Computers have no brain, only muscles
3. Trust your brain
4. Be always suspicious
5. Look for trends rather than single values
6. Use good chemical sense
7. Try to go beyond numbers, often they are already known
8. Select the best computational cost/accuracy compromise

Grazie