Méthodes et stratégies en synthèse totale et asymétrique

Applications of transition metal complexes in cascade cyclization reactions

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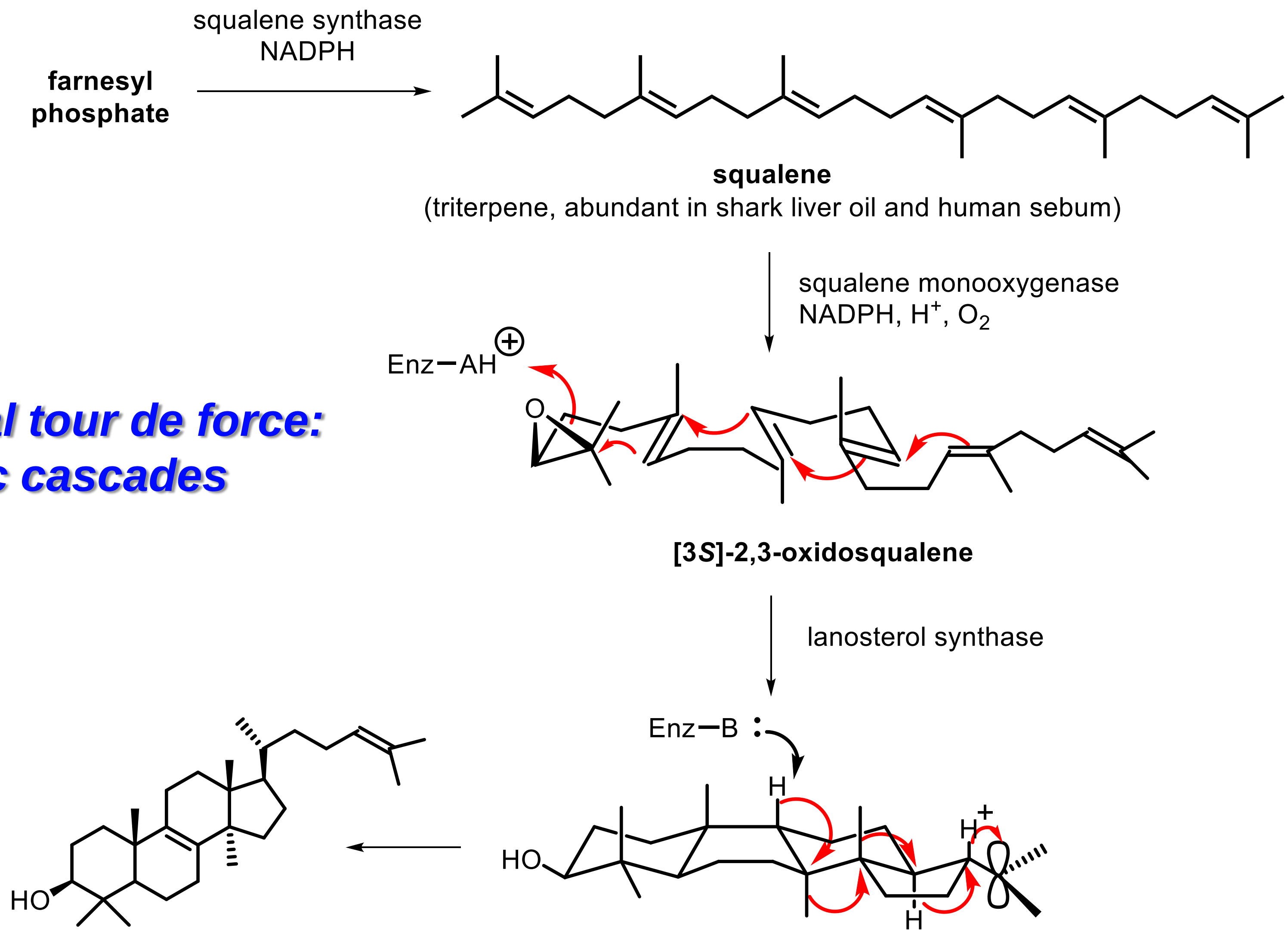
Introduction

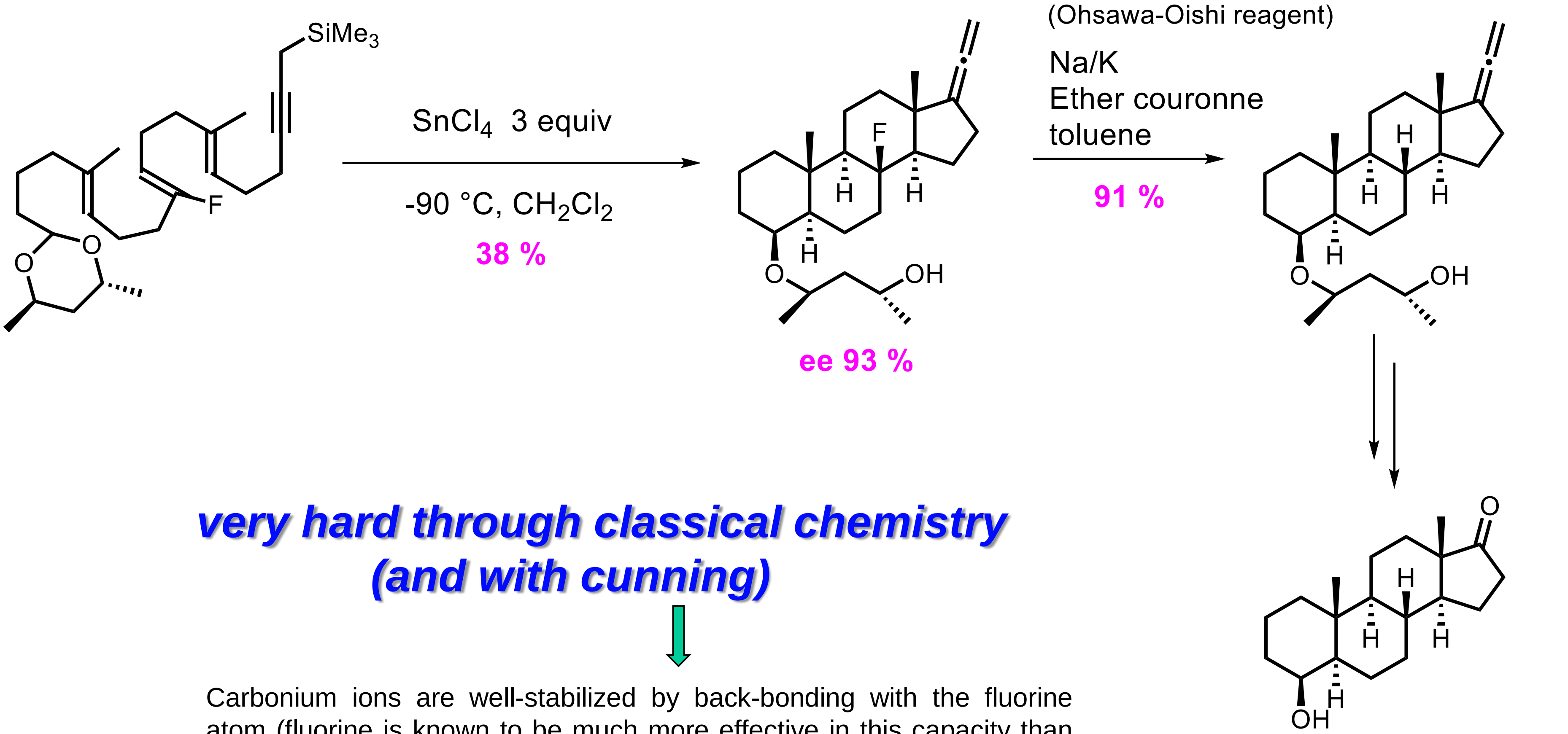
biological tour de force: cationic cascades



Lanosterol
(triterpenoid, all steroids
derive from it (cholesterol, estradiol,
testosterone ...))

Introduction

Biomimetic cyclizations?



4β-hydroxyandrostan-17-one

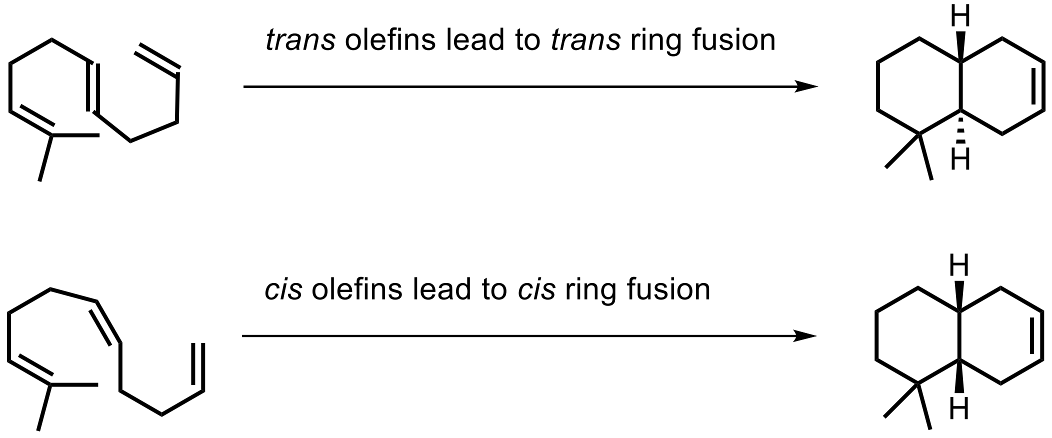
very hard through classical chemistry (and with cunning)

Carbonium ions are well-stabilized by back-bonding with the fluorine atom (fluorine is known to be much more effective in this capacity than the other halogen atoms: Olah, G. A.; Mo, Y. K. *Adv. Fluorine Chem.* **1973**,*7*, 69.

W. S. Johnson *et al J. Am. Chem. Soc.* **1993,** *115*, 493; 497; 504; 515

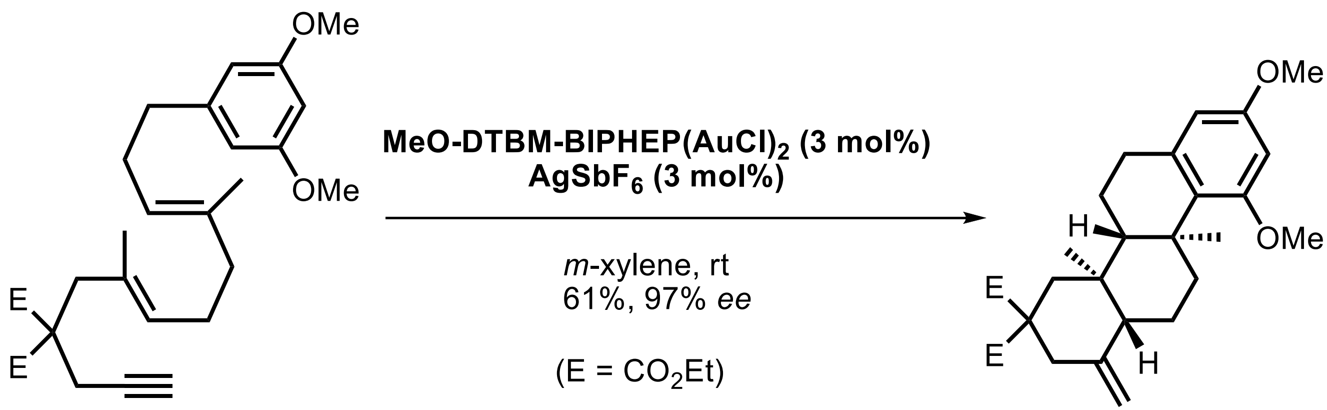
Introduction

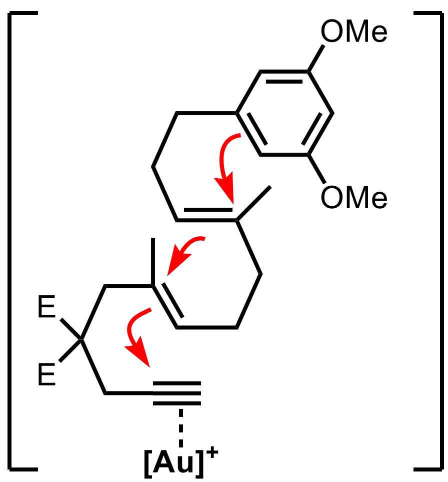
Stork-Eschenmoser postulate (1955)



Introduction

emerging methods





- ***How did we come to this?***
- ***what are the other polycyclization methods?***

Toste, F. D. *et al J. Am. Chem. Soc.* **2010**, 8276

Table of Contents

Transition-Metal Catalyzed Cyclization Reactions

Tandem and Cascade Processes

Helpful knowledge:

- Woodward-Hoffmann rules
- *Gem*-disubstituent effect (Thorpe-Ingold Effect, reactive rotamer effect)
- Baldwin's rules
- Bredt rule

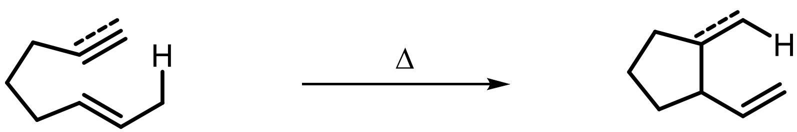
1. Cycloisomerizations

CYCLIZATIONS THAT INVOLVE A SIMPLE ISOMERIZATION OF AN ACYCLIC SUBSTRATE

ex :

→ Intramolecular **Diels-Alder**

→ Intramolecular **Alder-ene** (group transfer reaction)



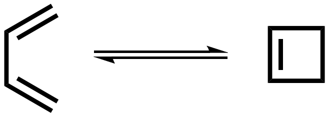
Limitations : - high temperature required

- low chemoselectivity of the thermal process

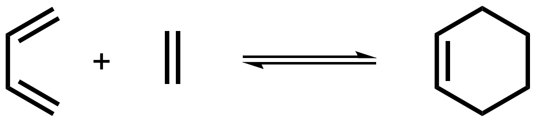
⇨ **Solution** : (TRANSITION)-METAL CATALYSIS

5 main categories of pericyclic reactions:

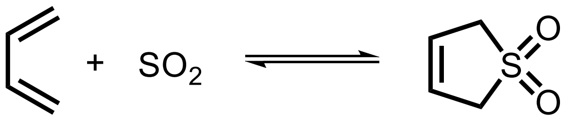
- Electrocyclic ring opening/closure



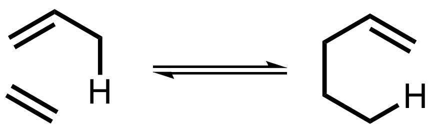
- Cycloaddition/cycloreversion reactions



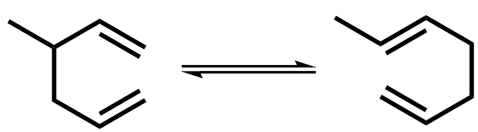
- Cheletropic reactions



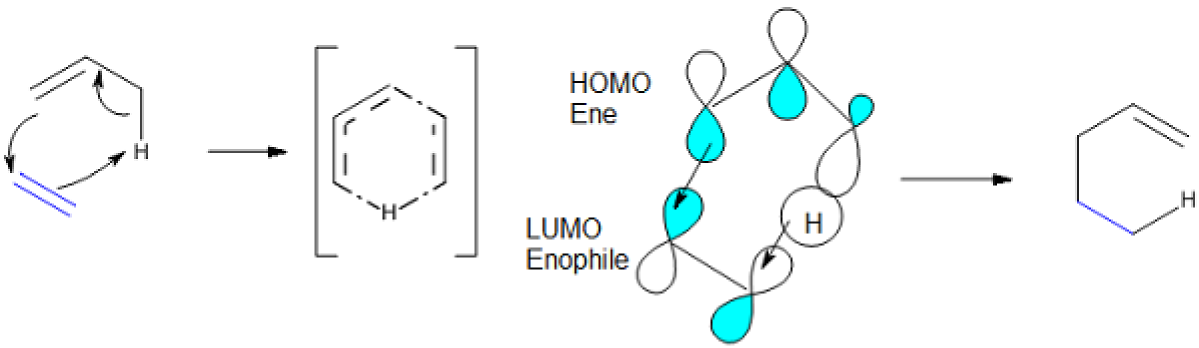
- Group transfer reactions



- Sigmatropic rearrangements



Ene-reactions are also known as the Alder-ene reaction (1943)
(same Alder as in Diels-Alder (1928), Nobel prize 1950)



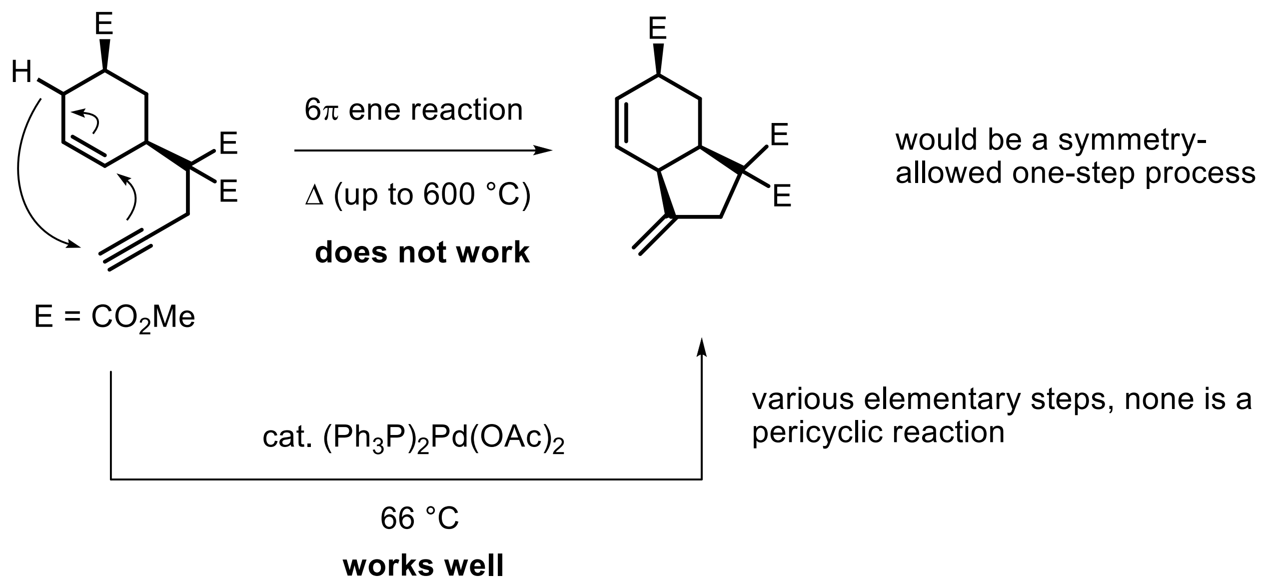
The main frontier-orbital interaction occurring in an ene reaction is between the HOMO of the ene and the LUMO of the enophile.

The HOMO of the ene results from the combination of the π-bonding orbital in the vinyl moiety and the C-H bonding orbital for the allylic H. Concerted, all-carbon-ene reactions have, in general, a high activation barrier, which was approximated at 33 kcal/mol in the case of propene and ethene, as computed at the M06-2X/def2-TZVPP level of theory. However, if the enophile becomes more polar (going from ethane to formaldehyde), its LUMO has a larger amplitude on C, yielding a better C–C overlap and a worse H–O one, determining the reaction to proceed in an asynchronous fashion. This translates into a lowering of the activation barrier until 14.7 kcal/mol (M06-2X/def2-TZVPP), if S replaces O on the enophile (Bieckelhaupt et al*, J. Comput Chem*. **2012**, *33*, 509).

Intramolecular ene reactions benefit from less negative entropies of activation than their intermolecular counterparts, so they are usually more facile, occurring even in the case of simple enophiles, such as unactivated alkenes and alkynes

1. Cycloisomerizations

The pericyclic reaction is symmetry allowed but too energetically demanding anyway. A metal-catalyzed reaction can provide the desired product through a stepwise (not pericyclic) mechanism, from the same substrate.



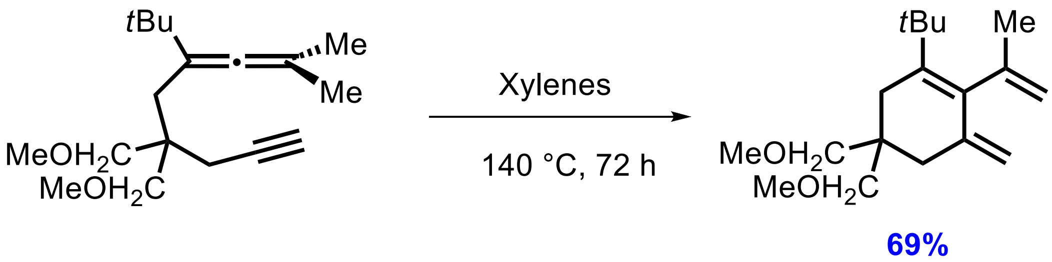
Formal pericyclic reaction

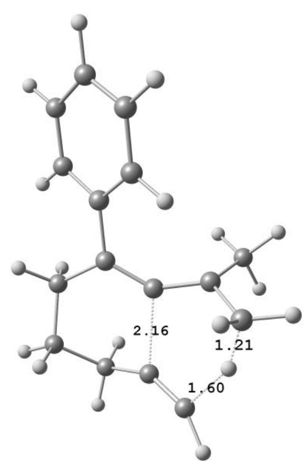
Trost, B. M. *et al.* (NB: Pd(0) does not work)

1. Cycloisomerizations

Thermal Alder-ene reaction

High temperatures, long time

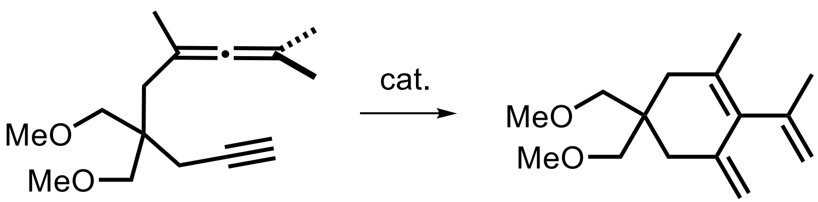




$\Delta H^{\ddagger}_{298}$ = 33 kcal/mol

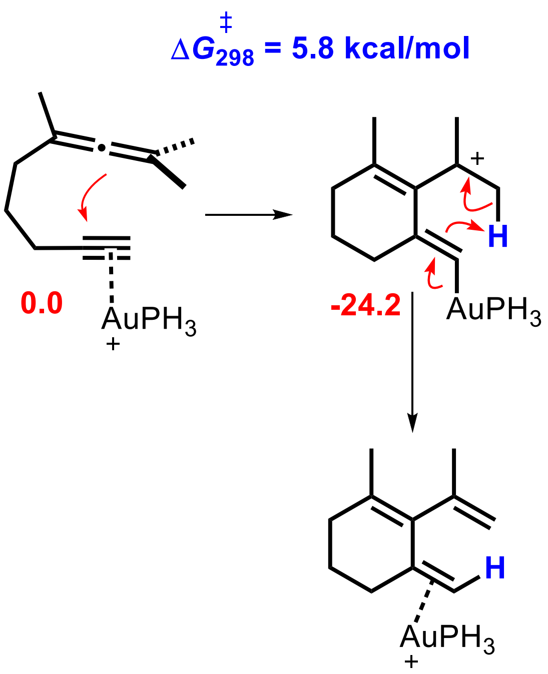
1. Cycloisomerizations

Formal Alder-ene reaction: in the presence of a catalyst, milder conditions, lower activation barriers

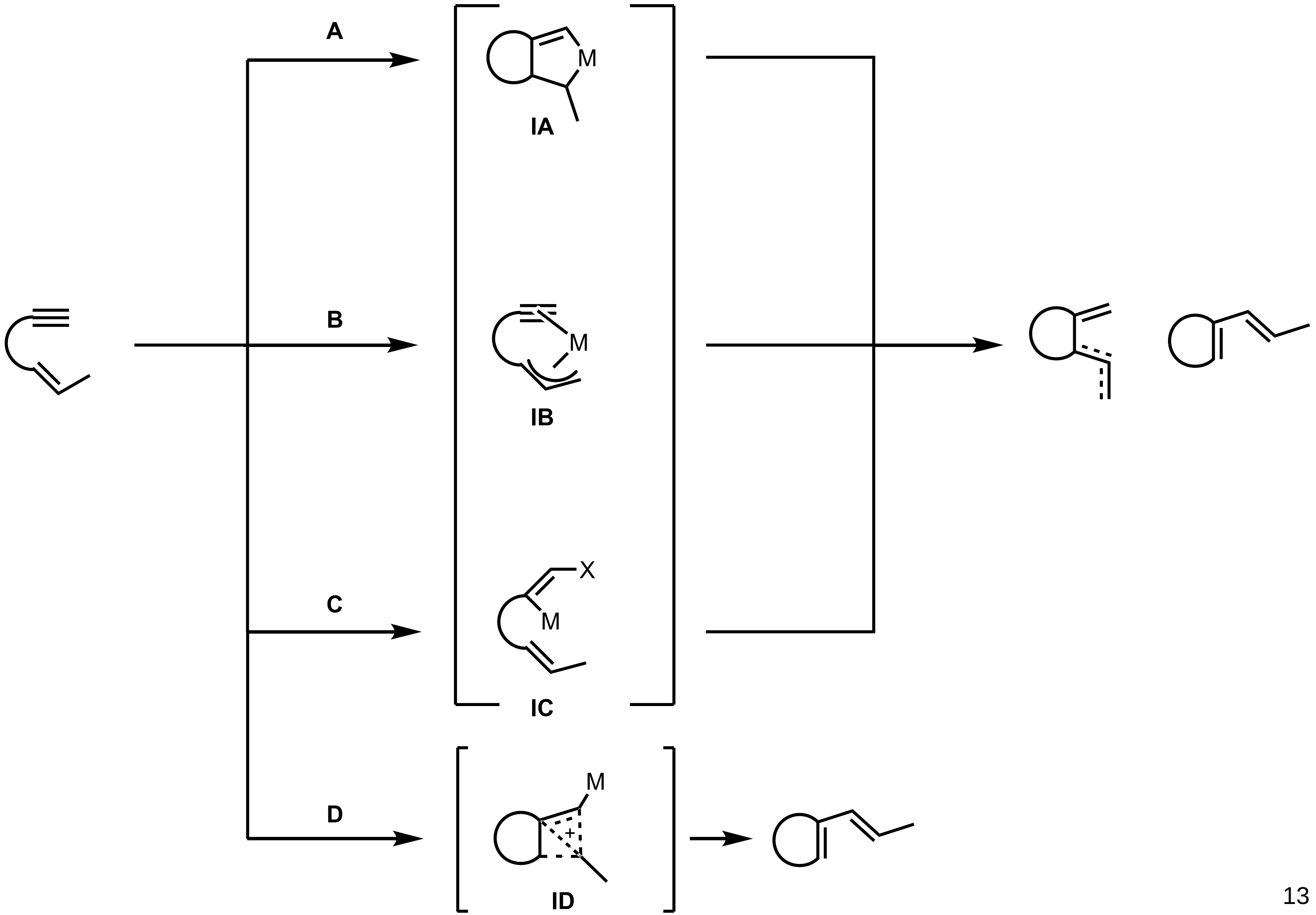


cat.[a]	T (°C)	Time (h)	Yield (%)
Ph_3PAuCl / $AgSbF_6$	0	0.5	70
Ph_3PAuCl / $AgPF_6$	0	0.5	70
Ph_3PAuCl / $AgBF_4$	0	0.5	72
Ph_3PAuCl / AgOTf	0	0.5	84
$Ph_3PAuNTf_2$	0	0.5	70
Ph_3PAuCl / $AgClO_4$	0	0.5	75
$Pt(PhCN)_2dppp(BF_4)_2$	35	0.3	57

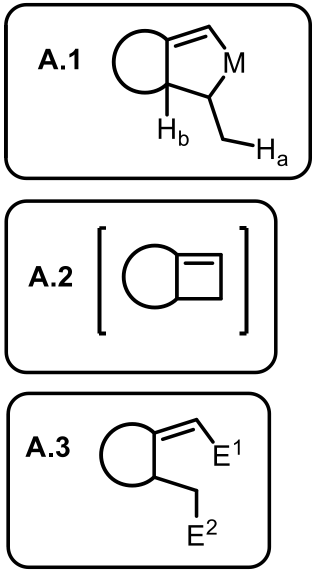
[a] [Au] / [Ag] (1 mol%), CH_2Cl_2; [Pt] (5 mol%), toluene.

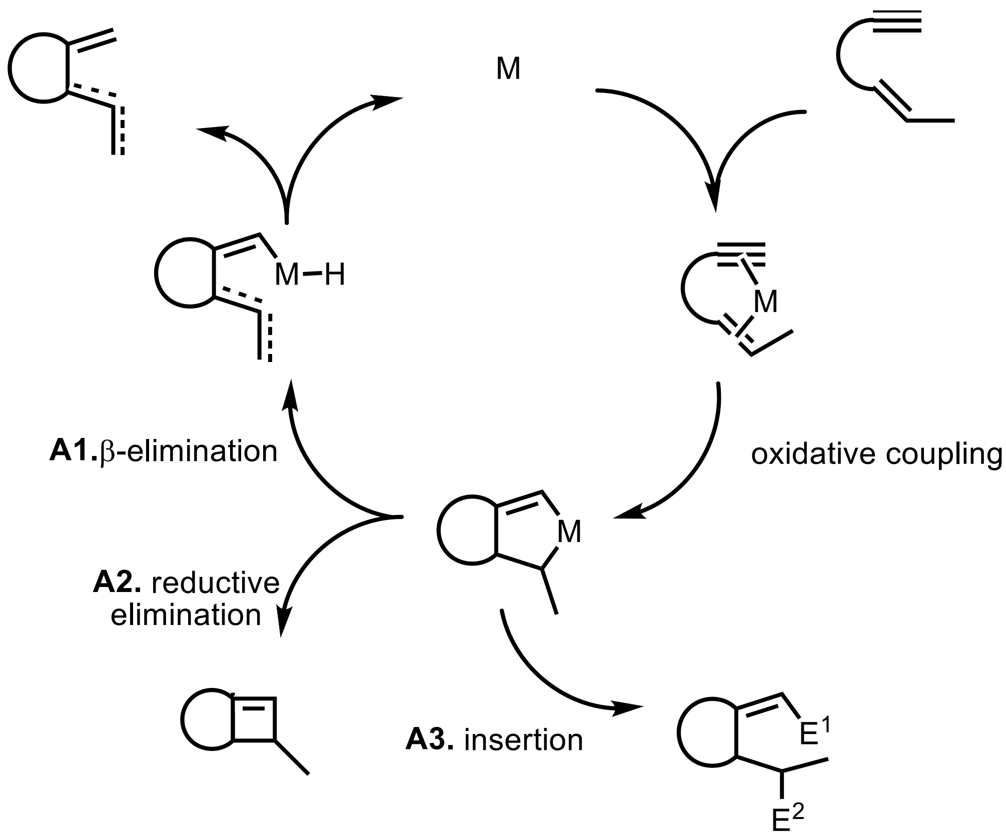


1. MECHANISTIC POSSIBILITIES WITH ENYNES



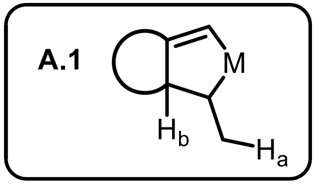
1. A. METALLACYCLOPENTENE PATHWAY



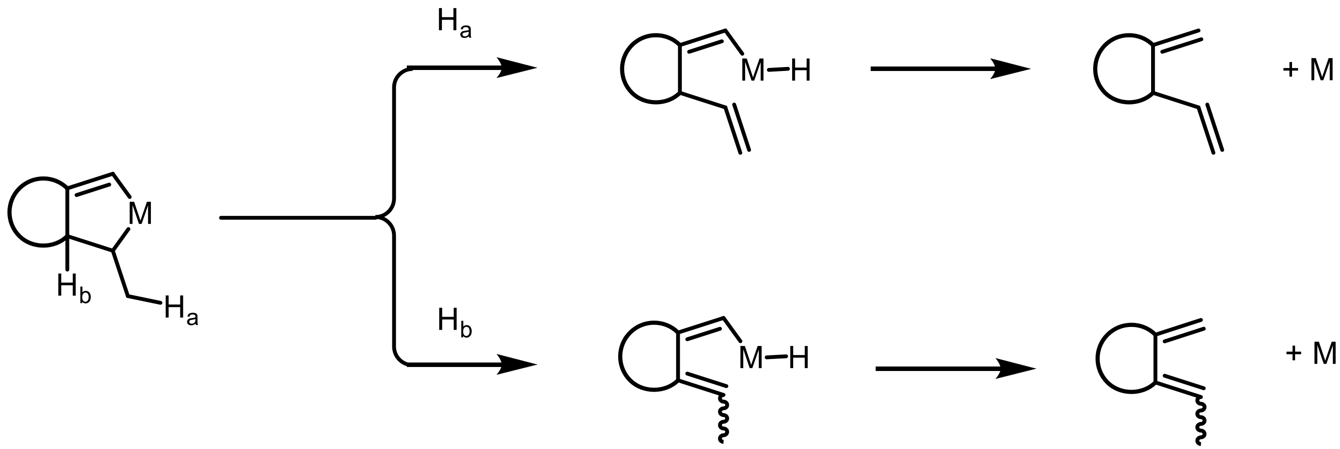


Alkyne = enophile
Alkene = ene

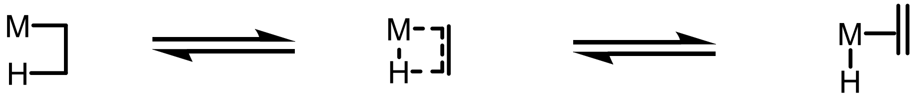
1. A. METALLACYCLOPENTENE PATHWAY



A1. β-Elimination



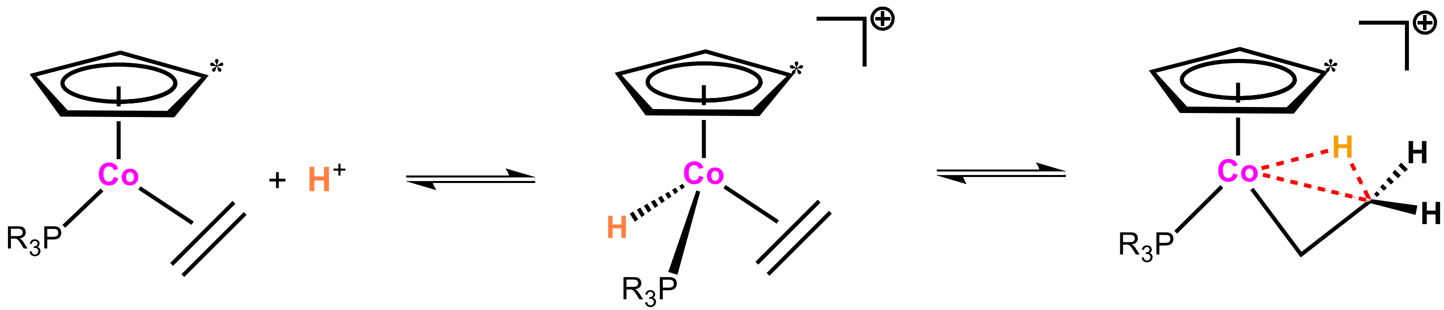
β-Elimination



M = Pd, Ru, Co ...

Alkenes and hydrides:

It is possible sometimes to isolate complexes in which the vacant orbital is partially filled by the electrons of the C^{β}–H bond. These species that are pre-organized for β-H elimination are usually transition states only. There existence demonstrate nonetheless the possible coordination of the C^{β}–H bond. The σ C–H bond serves as ligand. The metal gives electrons back in the σ* C–H. Therefore, the C–H bond elongates (1.20 Å instead of 1.09 Å)

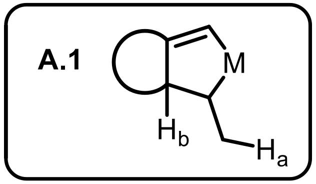


This type of interaction is called agostic (Brookhardt, Green, 1983)
This is a case of *3-center 2-electron* bonding (delocalization of 2 e over three atoms)

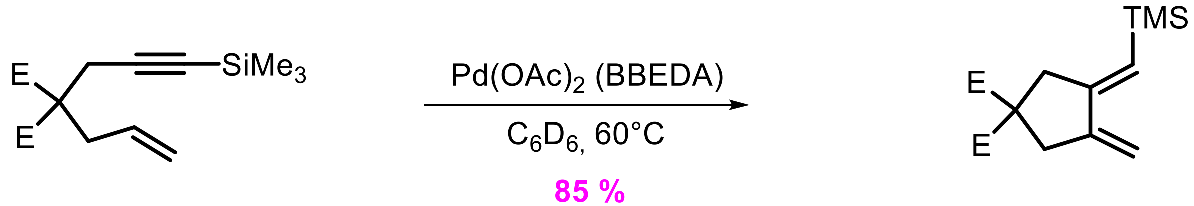
Original definition: “to refer specifically to situations in which a hydrogen atom is covalently bonded to both a carbon and to a transition metal atom.”

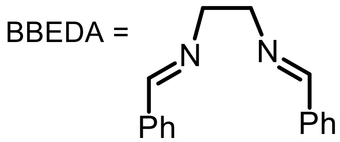
Brookhart, M.; Green, M. L. H. *J. Organometal. Chem*. **1983**, *250*, 395

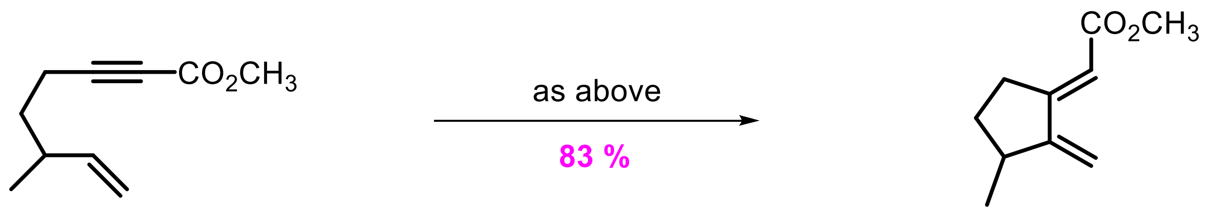
1. PALLADIUM-CATALYZED CYCLOISOMERIZATION OF 1,6-ENYNES

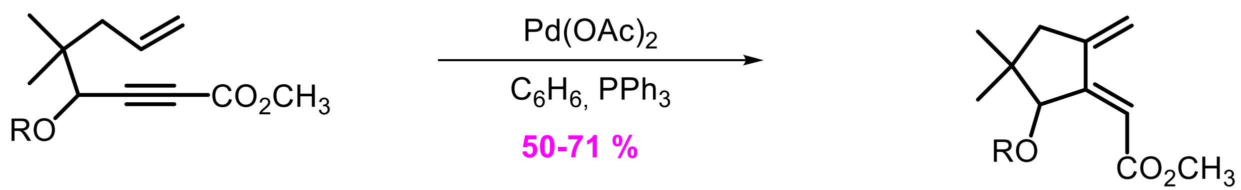


ene partner is a terminal double bond ⇒ only H_b can be eliminated





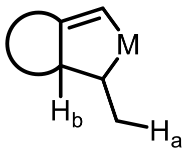




R = H, TMS, TBDMS, Ac

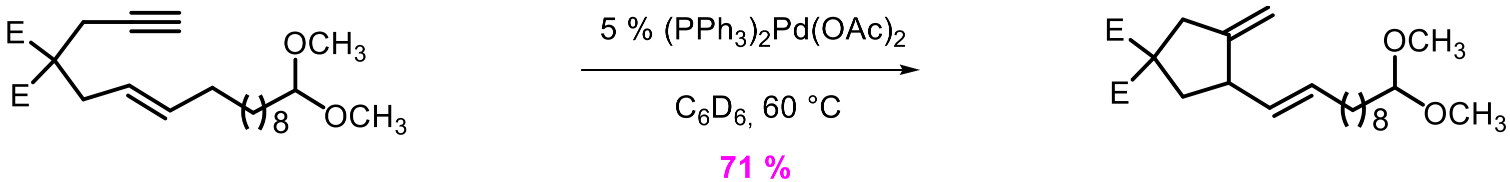
1. PALLADIUM-CATALYZED CYCLOISOMERIZATION OF 1,6-ENYNES

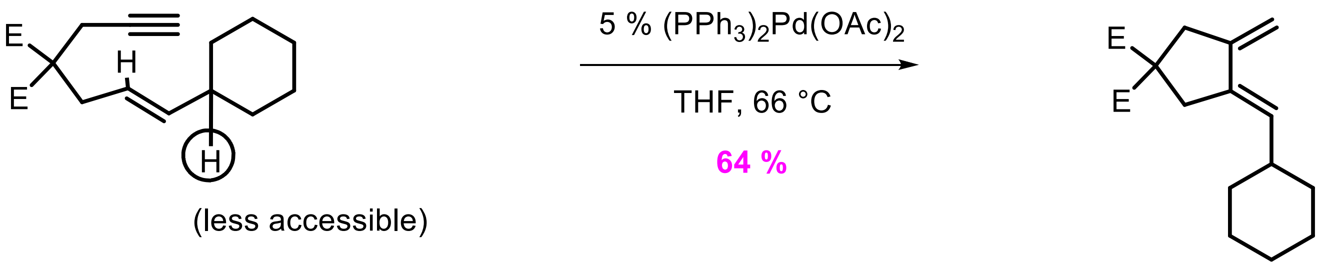
A.1



ene partner is a substituted double bond ⇒ H$_a$ and H$_b$ are able to β-eliminate

Hard to predict, but selective





(no longer true with Ru$^+$, see later)

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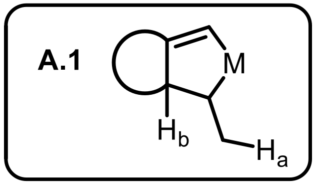
1. PALLADIUM-CATALYZED CYCLOISOMERIZATION OF 1,6-ENYNES



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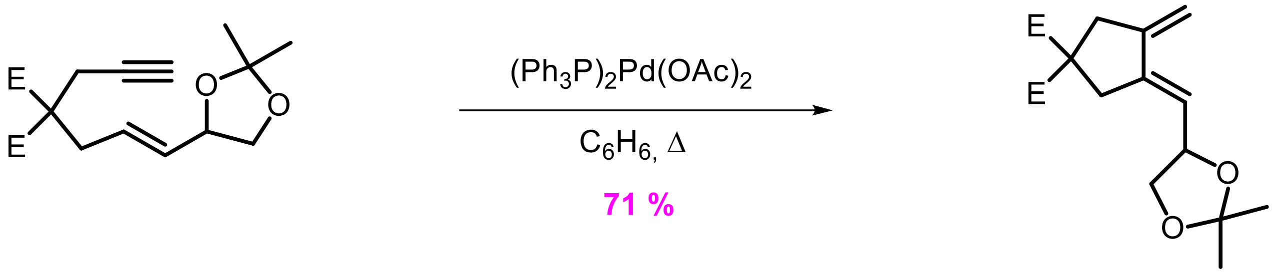
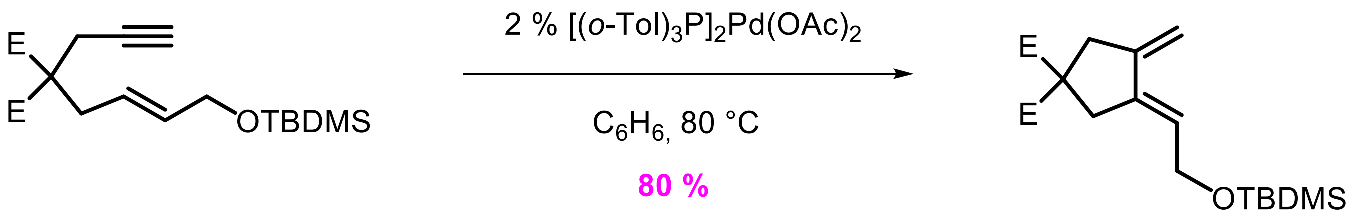
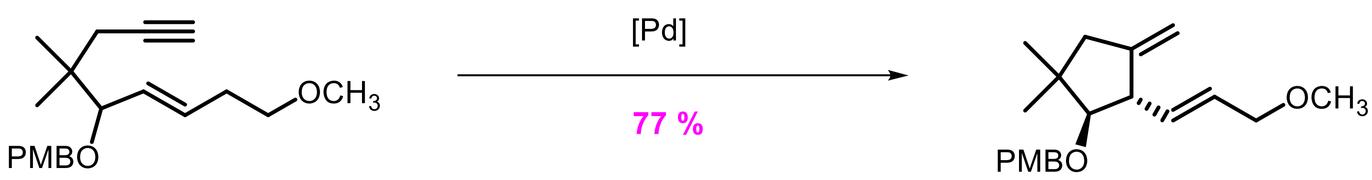
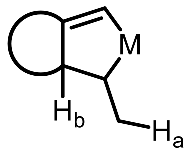


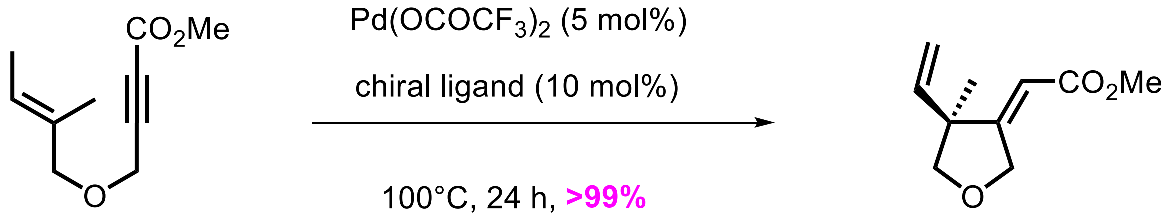




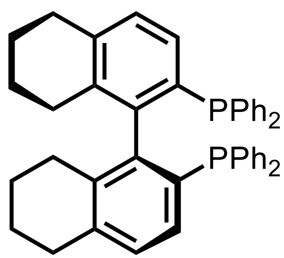
1. PALLADIUM-CATALYZED CYCLOISOMERIZATION OF 1,6-ENYNES

A.1

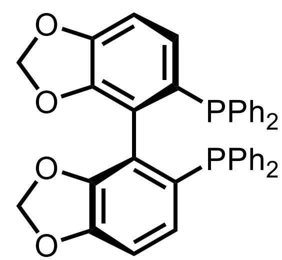




(R)-segphos, 99% ee
(S)-H_8-binap, 95% ee



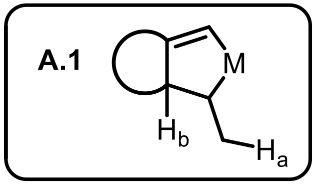
(S)-H_8-binap

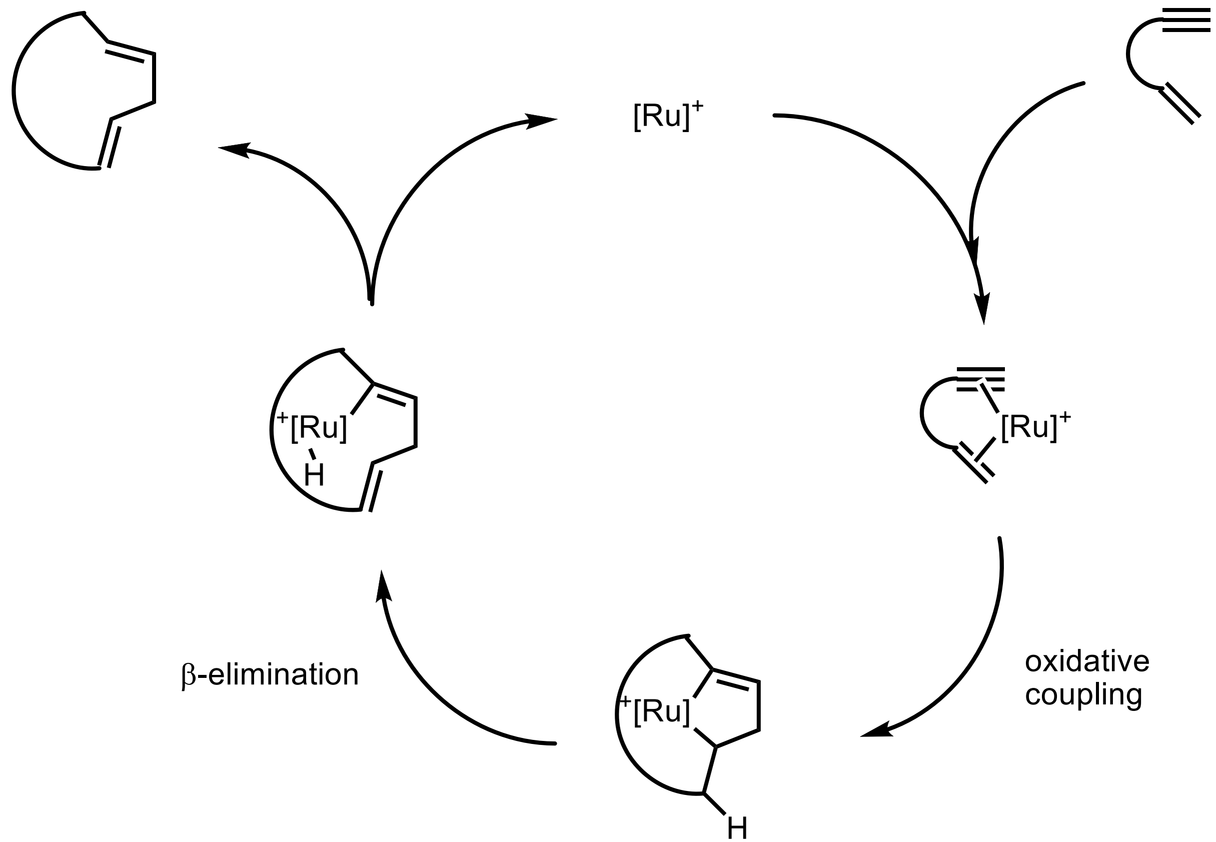


(R)-segphos

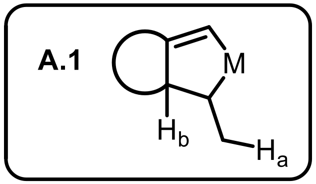
Mikami, K. *et al*

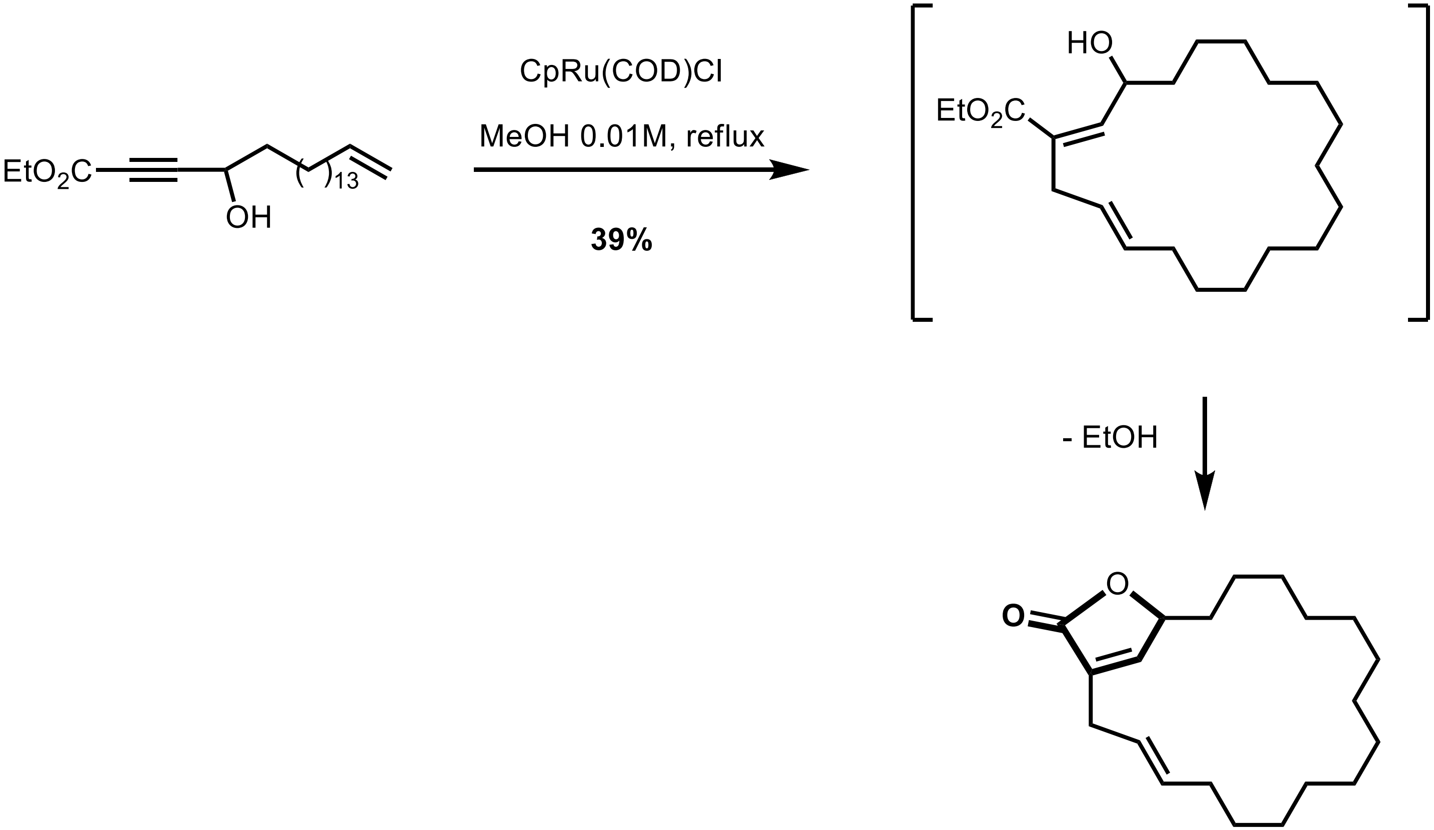
1. RUTHENIUM-CATALYZED CYCLOISOMERIZATION OF 1,n-ENYNES





1. RUTHENIUM-CATALYZED CYCLOISOMERIZATION OF 1,n-ENYNES

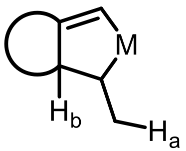


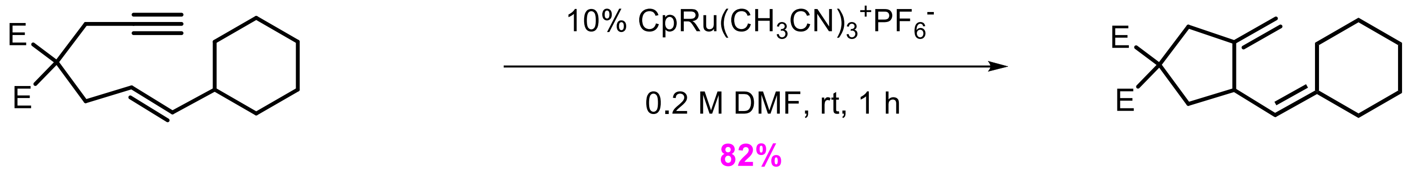


synthesis of butenolides

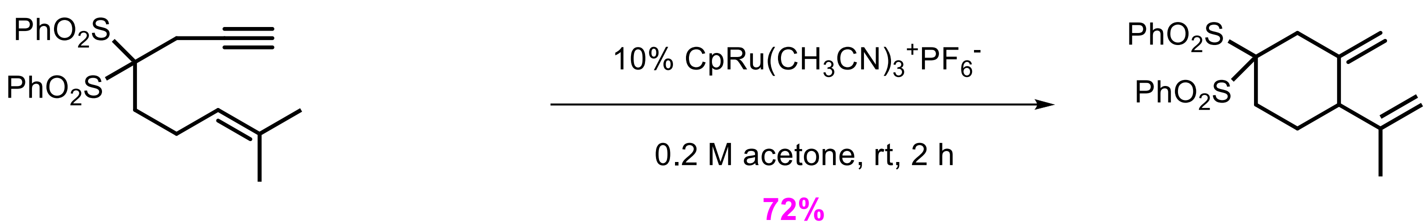
1. RUTHENIUM-CATALYZED CYCLOISOMERIZATION OF 1,n-ENYNES

A.1





E = CO_2Me



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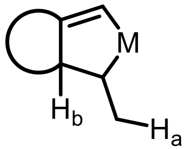
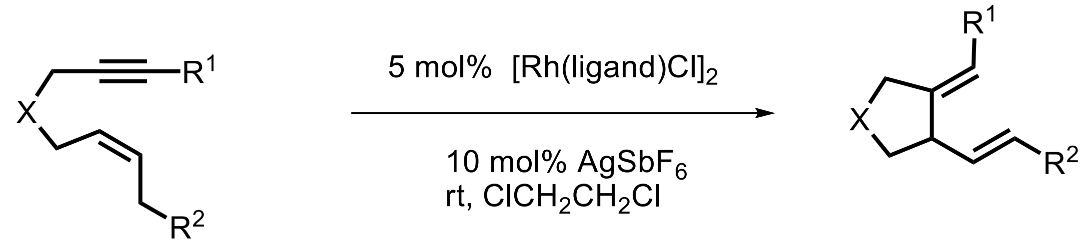
1. RHODIUM-CATALYZED CYCLOISOMERIZATION OF 1,6-ENYNES

A.1

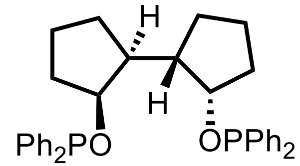


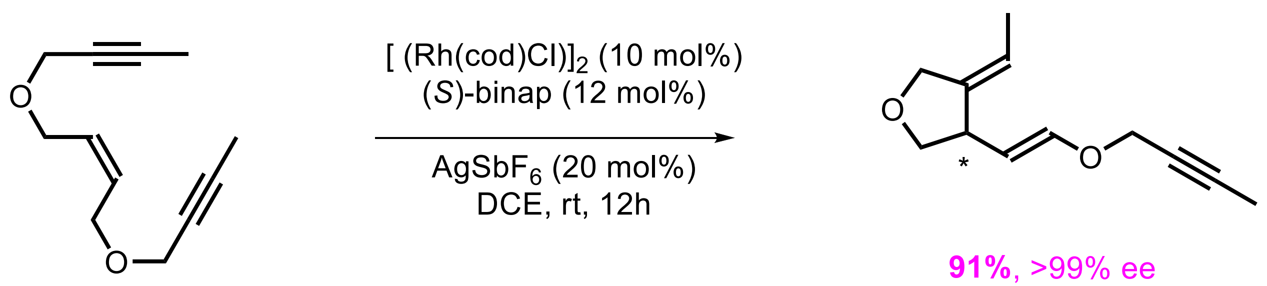


X = O, Ar-N, $(EtO_2C)_2C$

50%-quant.

Ligand
- dppb = 1,2-bis(diphenylphosphino)butane
- BICPO = (2*R*,2*R*)-bis(diphenylphosphinite)-(1*R*,1'*R*)-dicyclopentane





91%, >99% ee

Zhang, X. *et al.*

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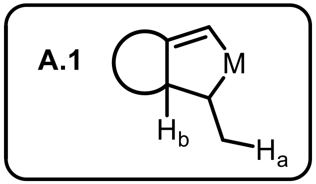
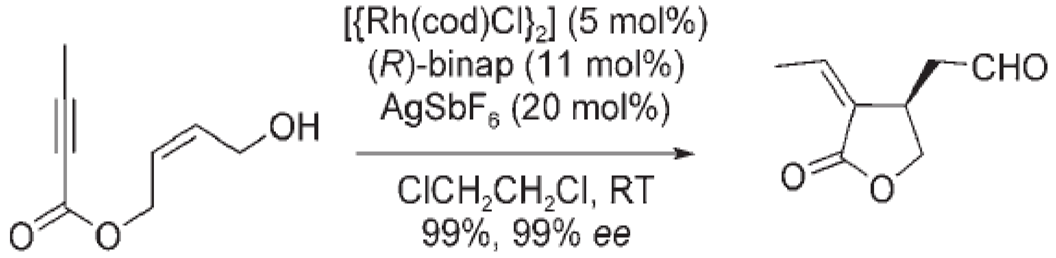
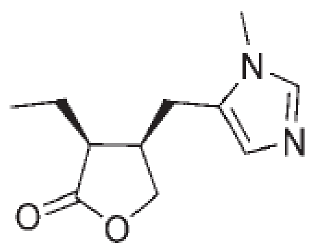




203 **204**



(+)-pilocarpine **205**

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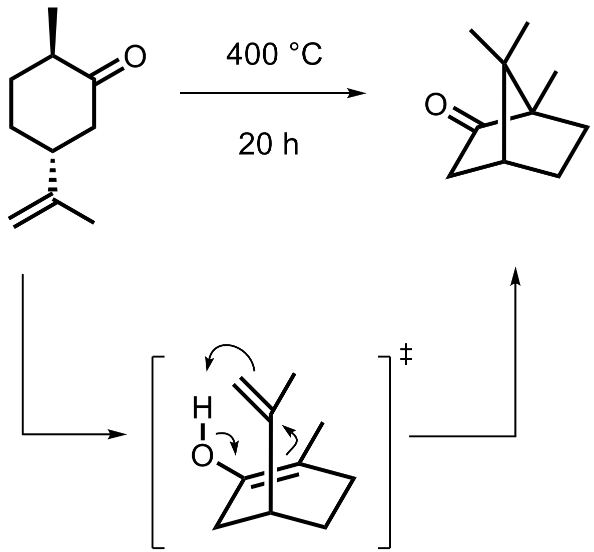
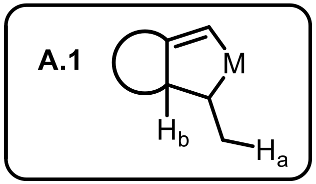
1. CONIA-ENE TYPE REACTIONS

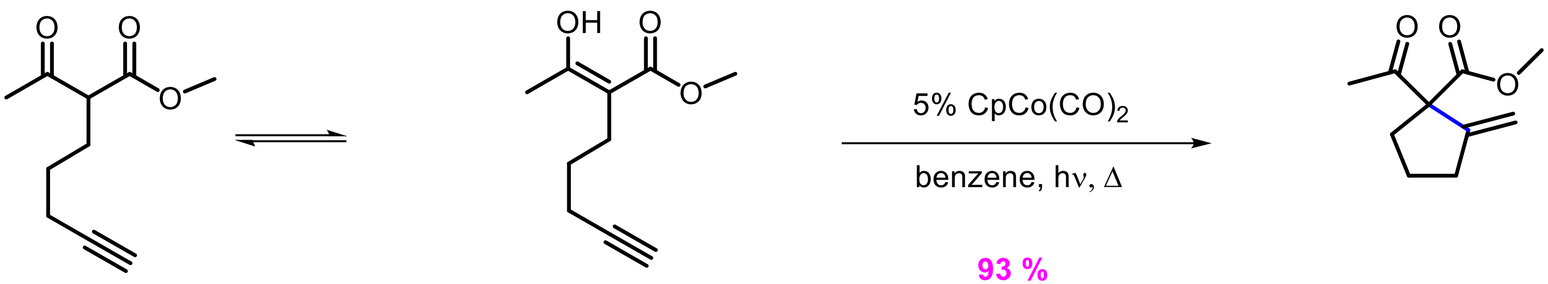
Thermal Conia-ene reaction (1967)



Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1



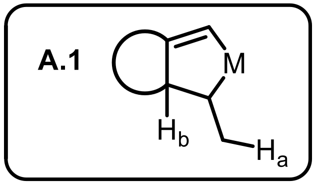
Formal Conia-ene reaction



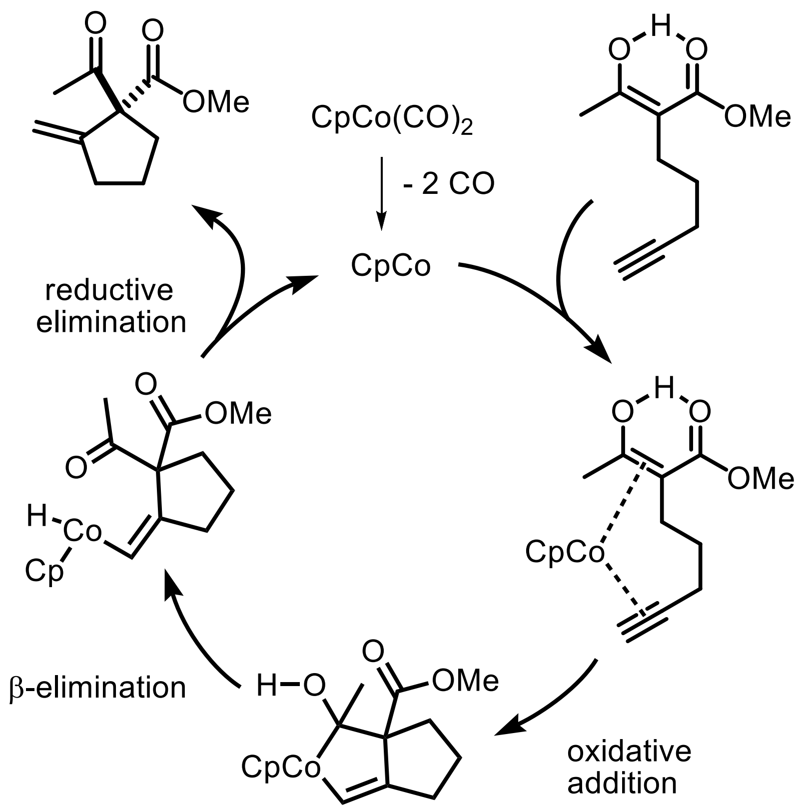
enol form = ene partner

alkyne = enophile

(NB: Enol form more favored from the ketone than from the ester)

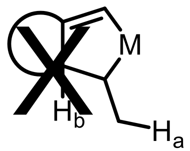


Formal Conia-ene reaction

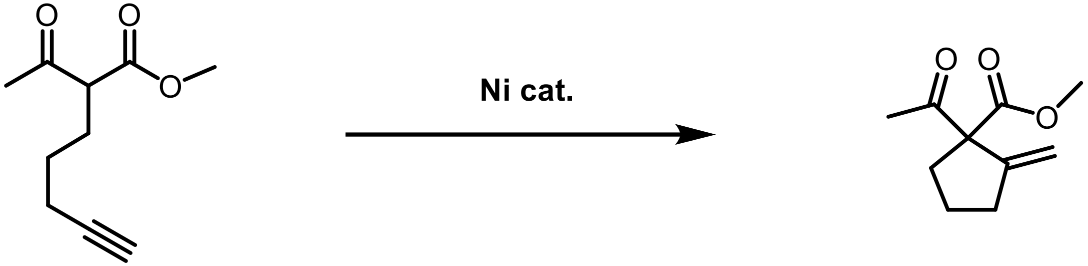


1. CONIA-ENE TYPE REACTIONS

A.1



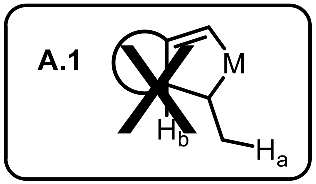
Formal Conia-ene reaction



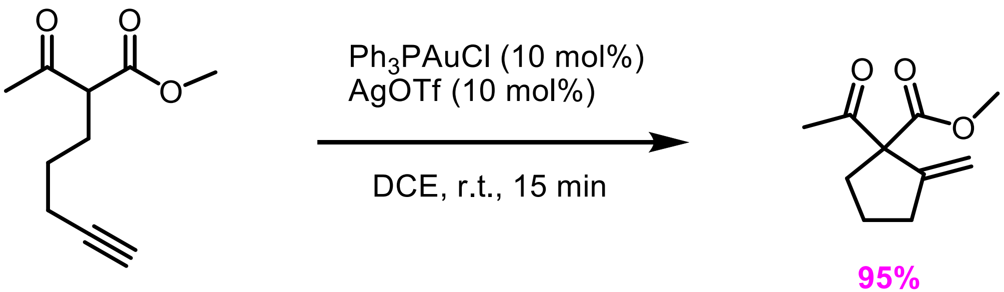
10 mol% $Ni(PPh_3)_4$, 50 mol% $Yb(OTf)_3$	dioxane, 50 °C, 15 h	**0%**
10 mol% $Ni(acac)_2$, 20 mol% $Yb(OTf)_3$	dioxane, 50 °C, 12 h	**83%**

Yang, D. *et al*

1. CONIA-ENE TYPE REACTIONS

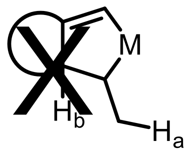


Formal Conia-ene reaction

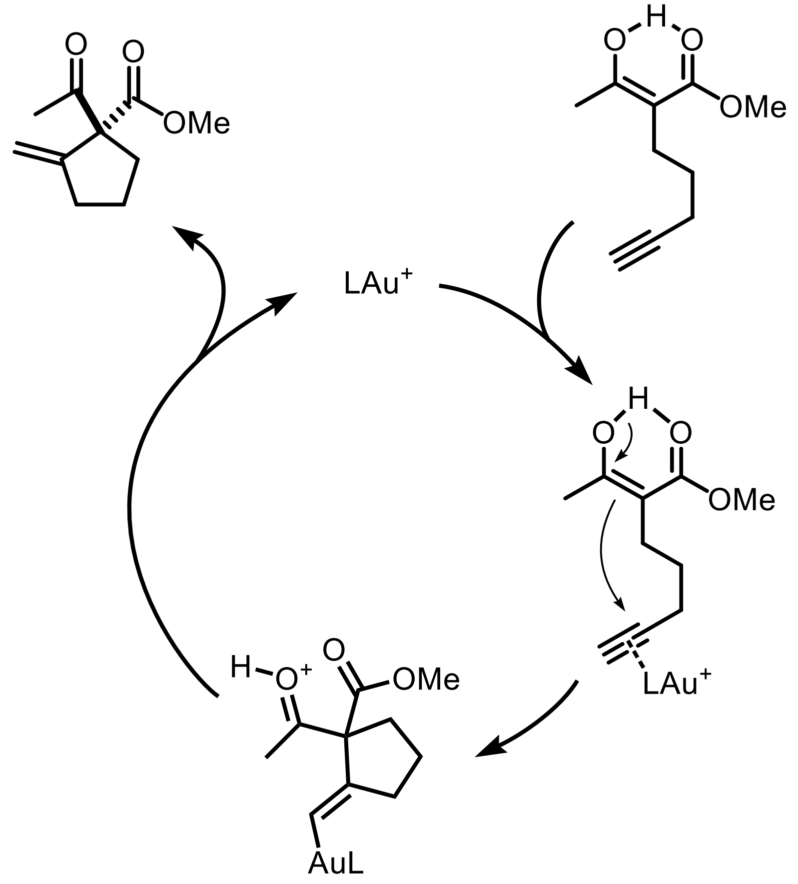


Toste F. D. *et al*

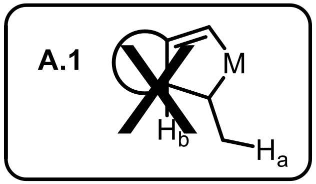
1. CONIA-ENE TYPE REACTIONS

A.1 

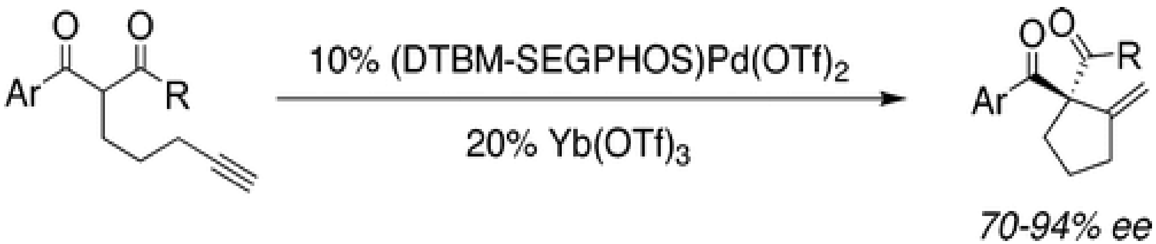
Formal Conia-ene reaction

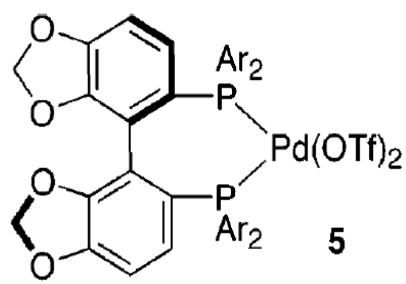


1. CONIA-ENE TYPE REACTIONS



Formal Conia-ene reaction

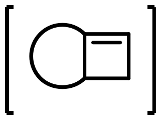




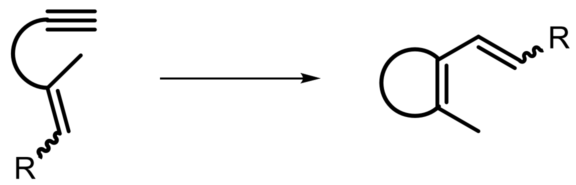
Ar = 3,5-di(*tert*-butyl)-4-methoxyphenyl:
(*R*)-DTBM-SEGPHOS

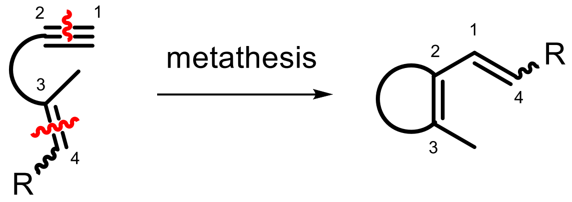
Toste, F. D. *et a*l

1. ENYNE METATHESIS

A.2 

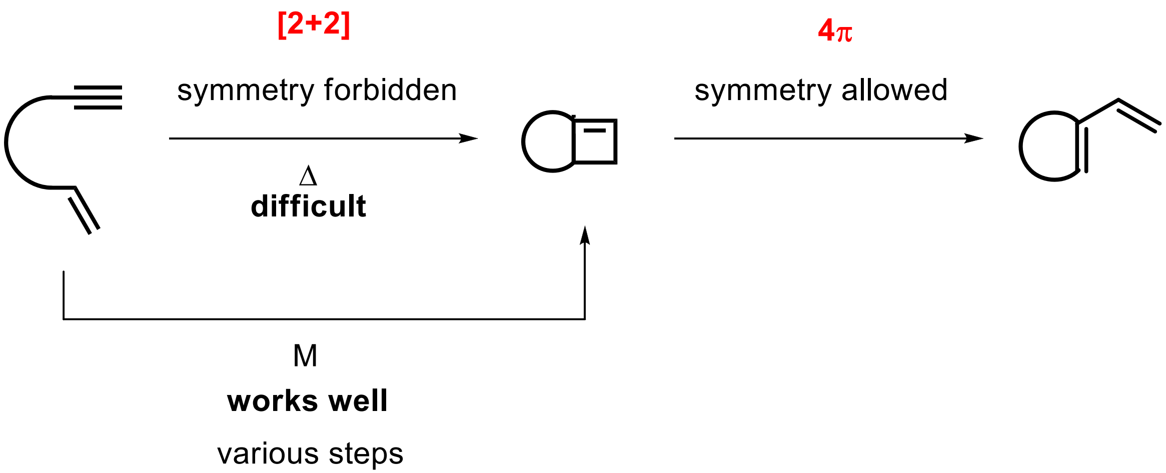
Some enyne cycloisomerizations can hide 4π electrocyclic ring opening/closure



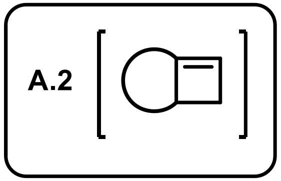


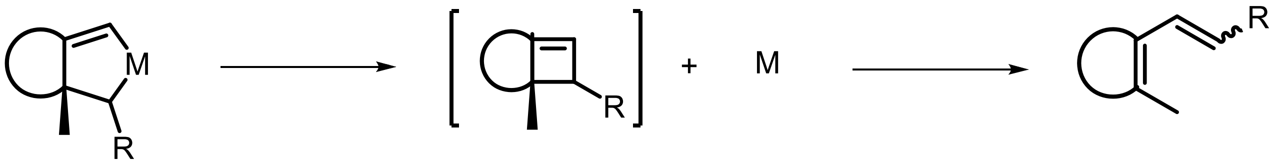
1. ENYNE METATHESIS

The first pericyclic reaction is symmetry forbidden. A metal-catalyzed reaction can provide the desired product anyway, from the same substrate.



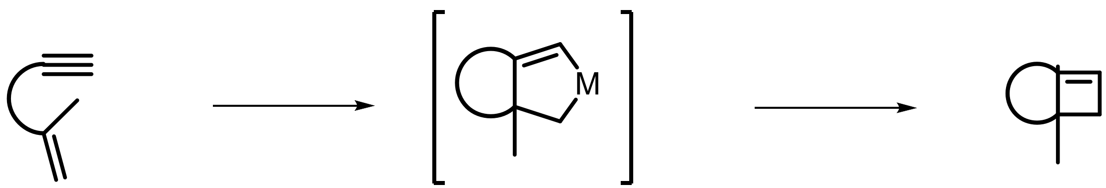
1. ENYNE METATHESIS



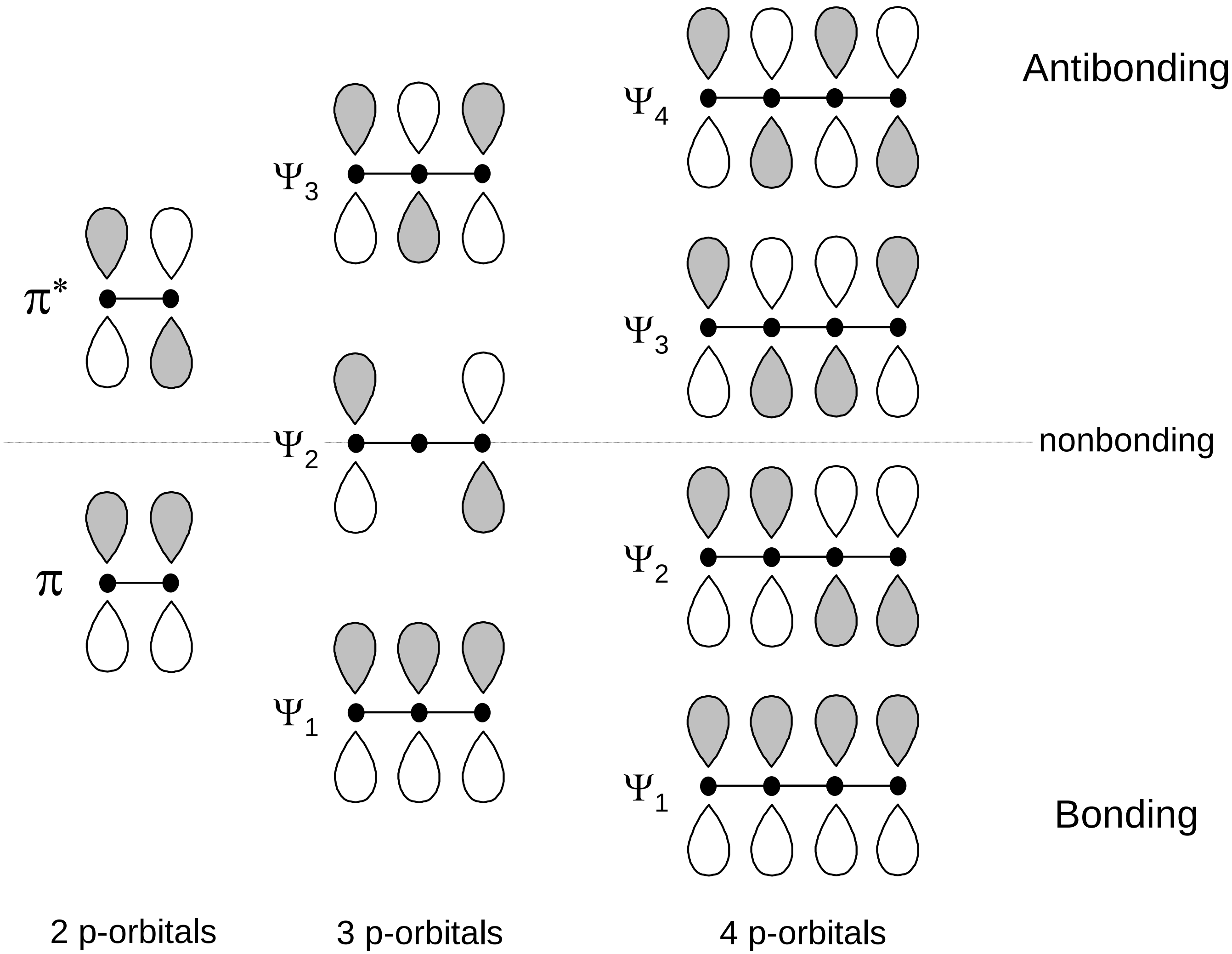


When : • the rate of the β-elimination slows down for geometric, steric and electronic reasons

• no β-hydrogens are available

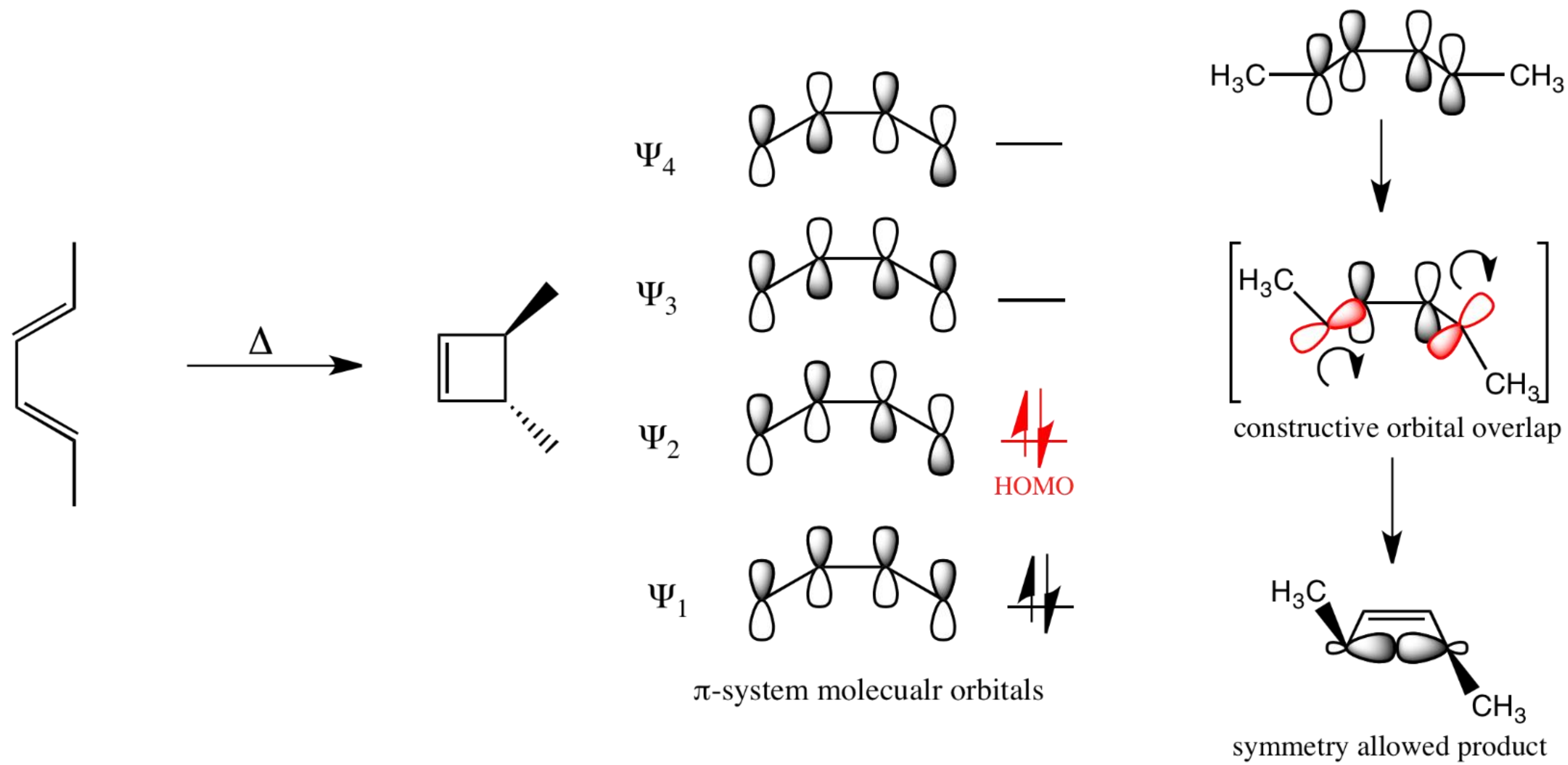


Pericyclic reactions involve conjugated π systems as substrates or transition states

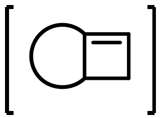


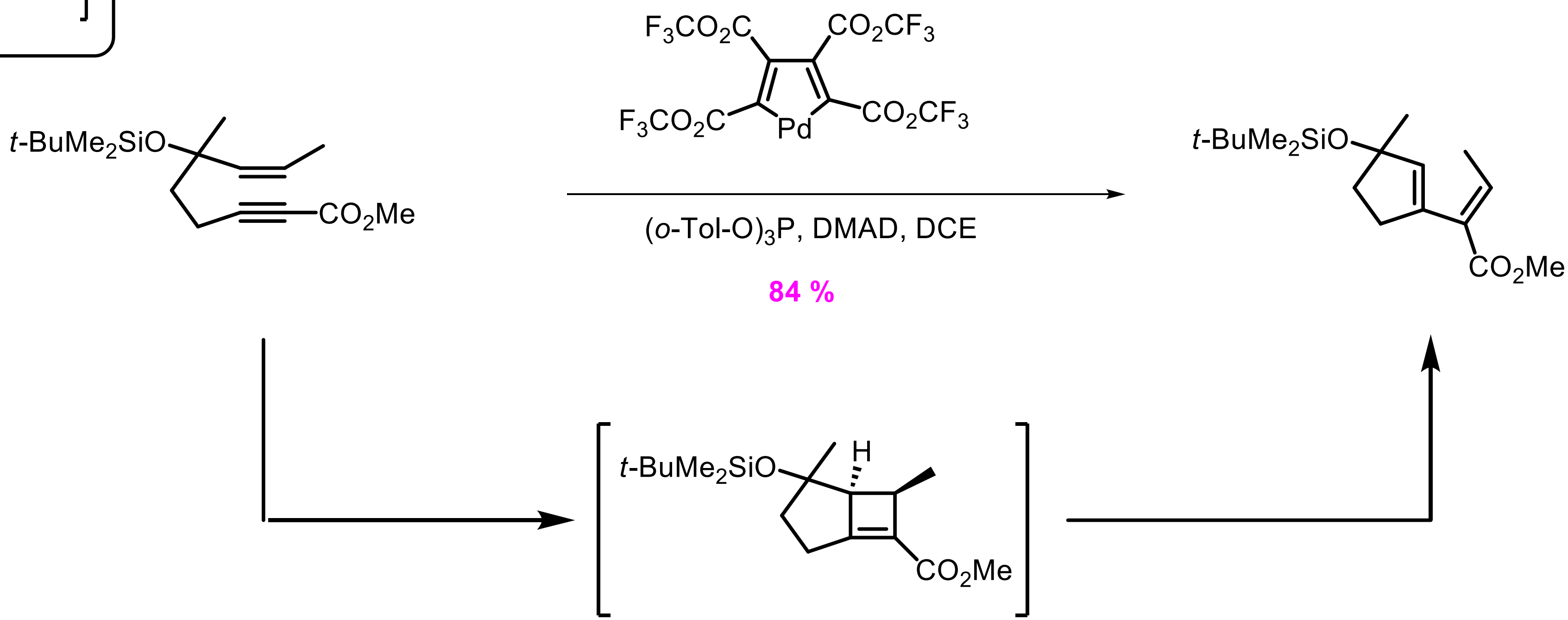
They usually obey Woodward-Hoffmann rules

set of rules in organic chemistry predicting the barrier heights of pericyclic reactions based upon conservation of orbital symmetry

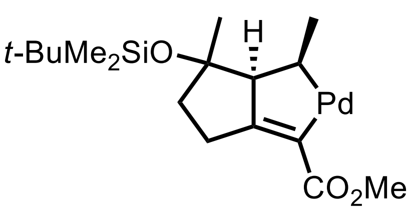


1. ENYNE METATHESIS

A.2 

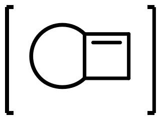


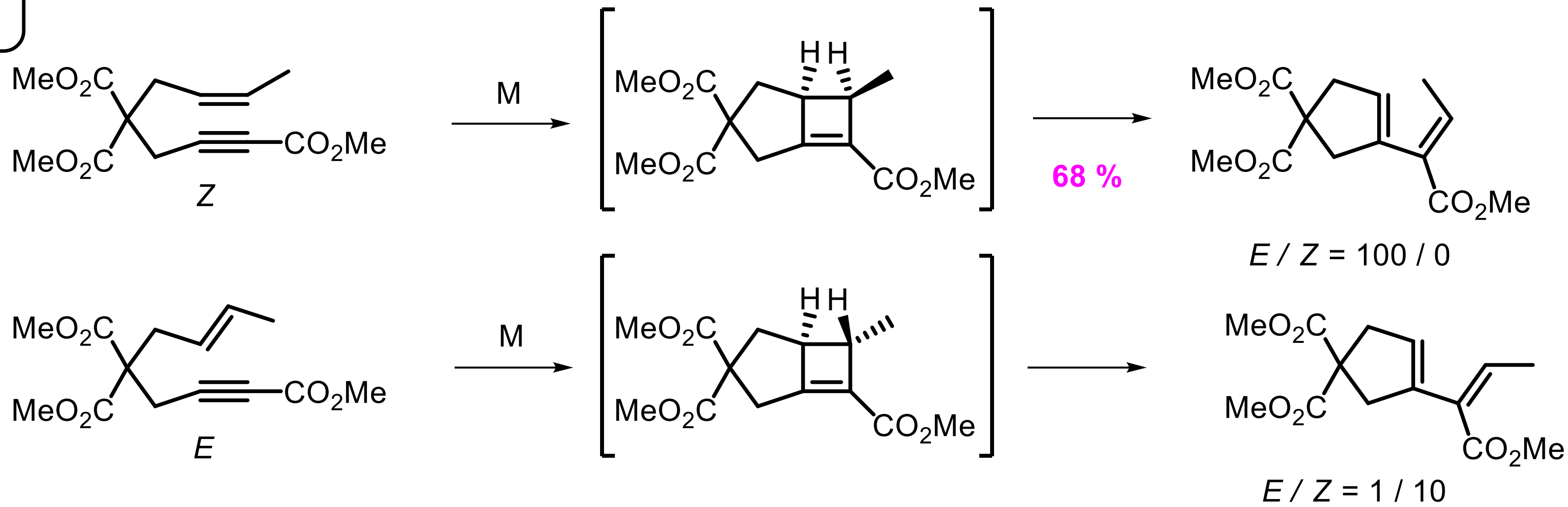
NB: the oxidative cyclization is stereoselective



Trost, B. M. *et al*

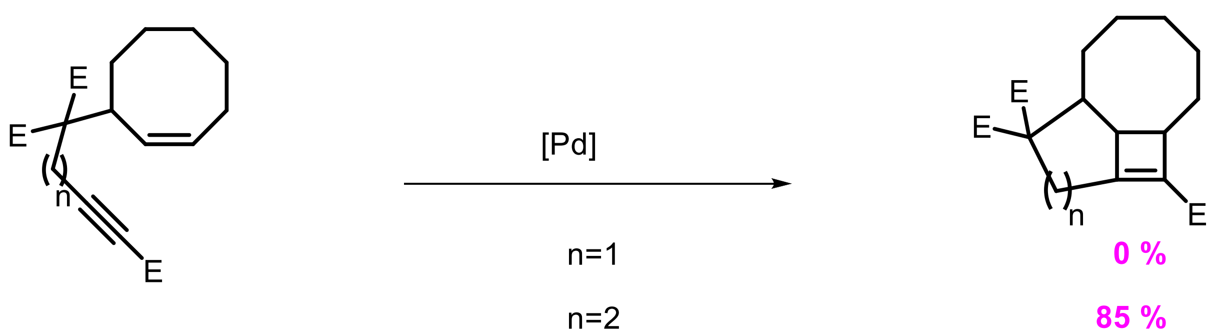
1. ENYNE METATHESIS

A.2 



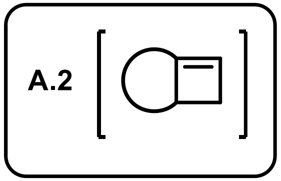
The thermal conrotatory opening of the cyclobutene explains the ratio of the cycloadducts

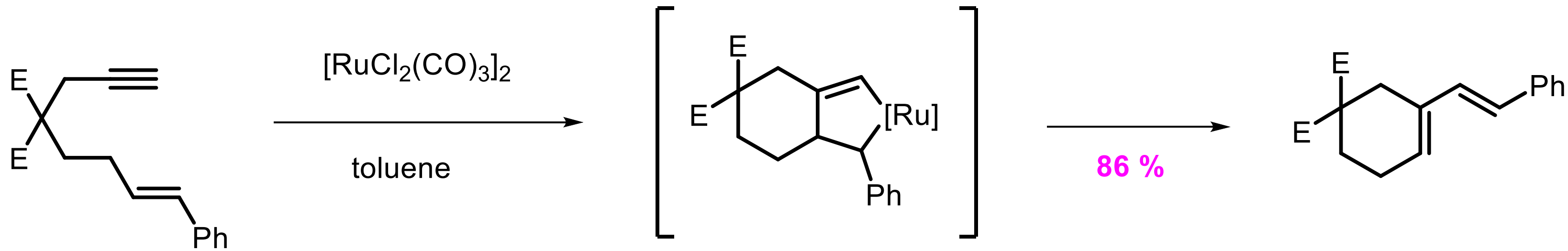
In some cases, the opening of the cyclobutene is not possible :



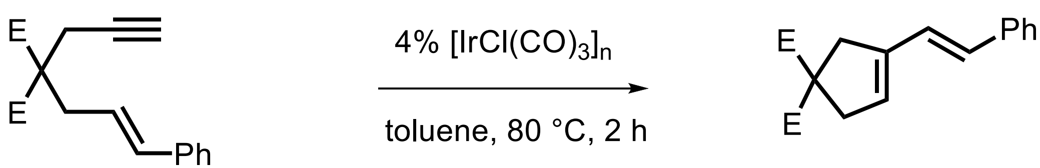
Trost, B. M. *et al*

1. ENYNE METATHESIS





Trost, B. M. *et al*

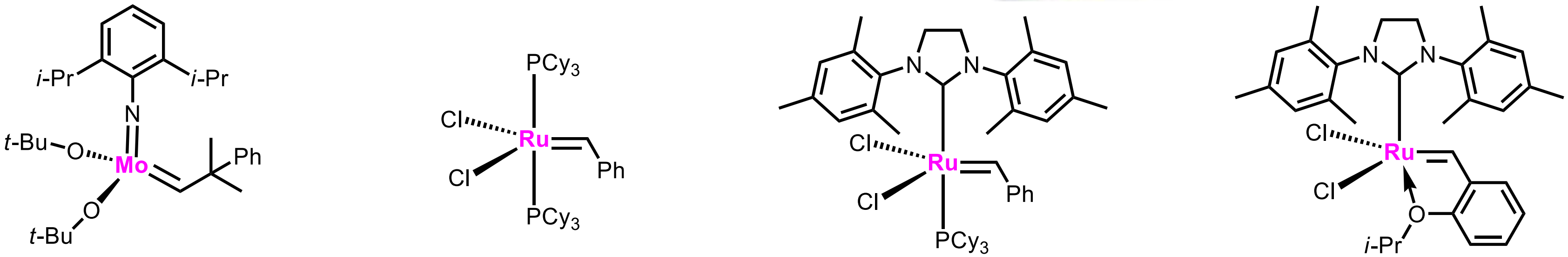


E = CO_2Et

Murai, S. *et al*

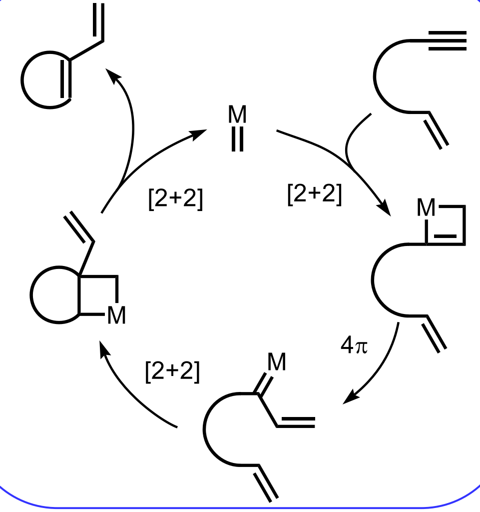
1. ENYNE METATHESIS

Classical olefin metathesis catalysts such as …

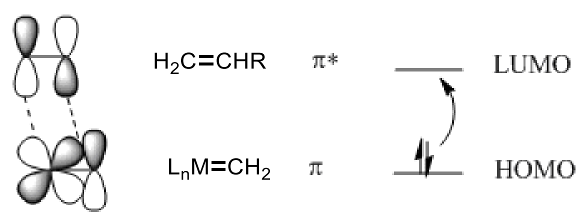


(Schrock) (Grubbs I) (Grubbs II) (Hoveyda-Grubbs II)

… would follow a mechanism such as this:



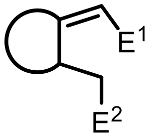
The direct [2+2] cycloaddition of two alkenes or one alkene and one alkyne is formally symmetry forbidden (HOMO S /LUMO A) and thus has a high activation energy. The Chauvin mechanism (1971) involves the **[2+2] cycloaddition** of a π bond to a transition metal alkylidene. The resulting 4-membered ring complex then **cyclorevert**. Interaction with the *d*-orbitals on the metal catalyst lowers the activation energy enough that the reaction can proceed rapidly at modest temperatures

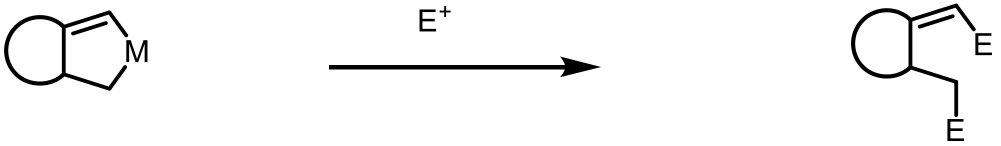


Because it starts from an enyne, there is a 4π cycloreversion here

1. A. METALLACYCLOPENTENE PATHWAY / ELECTROPHILIC INSERTIONS

A.3





C*sp*^{2}-metal bond
C*sp*^{3}-metal bond
} could react selectively with one or two electrophiles

With transition metals from column 8, 9, 10 : β-elimination and reductive elimation are favored

With transition metals from column 4 (Ti, Zr) : No vacant site of coordination

Inert towards β-elimination

→ Intermolecular reactions

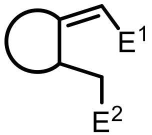
- Carbonylation
- Hydrolysis, halogenolysis
- Transmetalation
- Alkylation of aldehydes

→ Intramolecular reactions

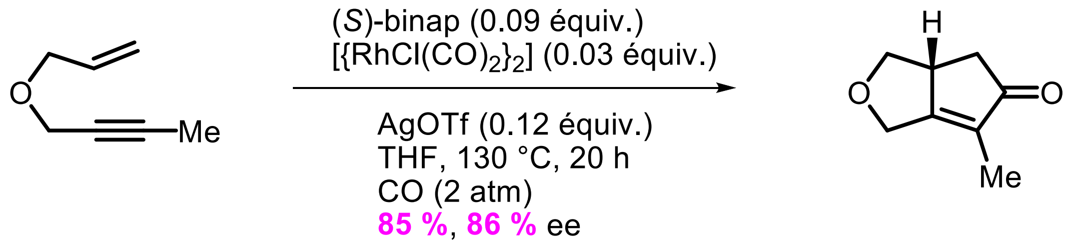
- Rearrangements

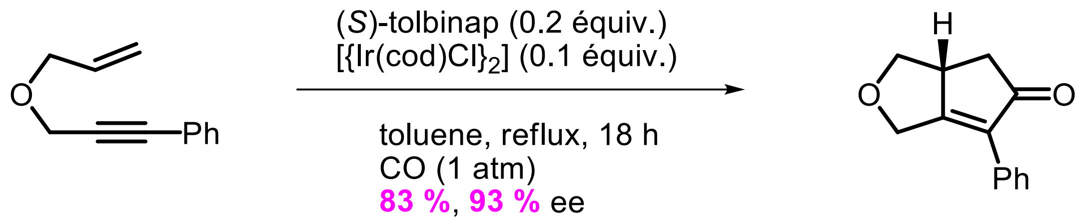
1. A. METALLACYCLOPENTENE PATHWAY / ELECTROPHILIC INSERTIONS

A.3



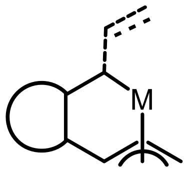
The Pauson-Khand reaction





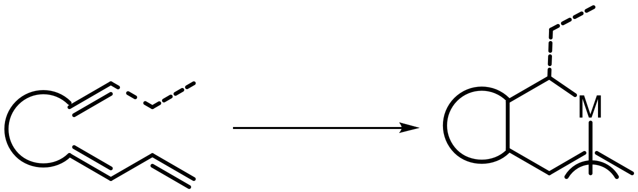
1. **B. π-ALLYL PATHWAY**

B.1



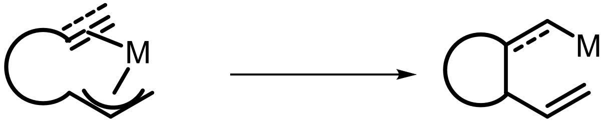
Two modes of cyclization :

1. The cyclization of 2 unsaturated partners generates the π-allyl complex

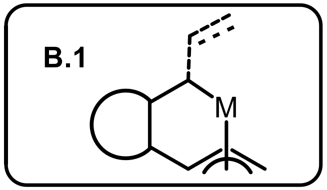


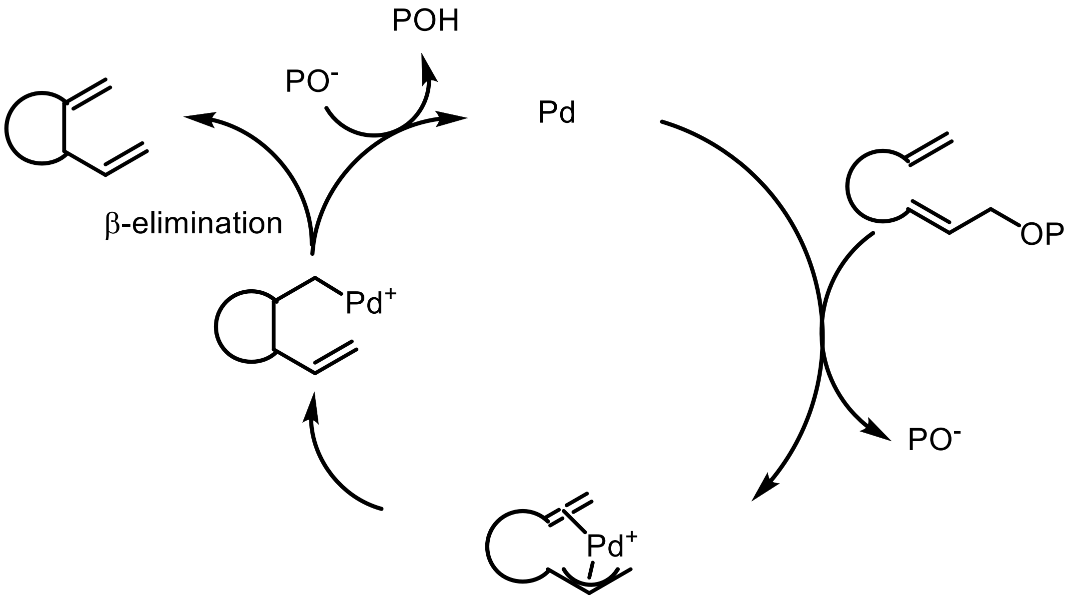
In intramolecular version , two metals are able to mediate such a reaction : Fe , Pd

2. The π-allyl complex is generated before the cyclization



1. PALLADIUM-CATALYZED CYCLIZATION OF A π-ALLYL COMPLEX



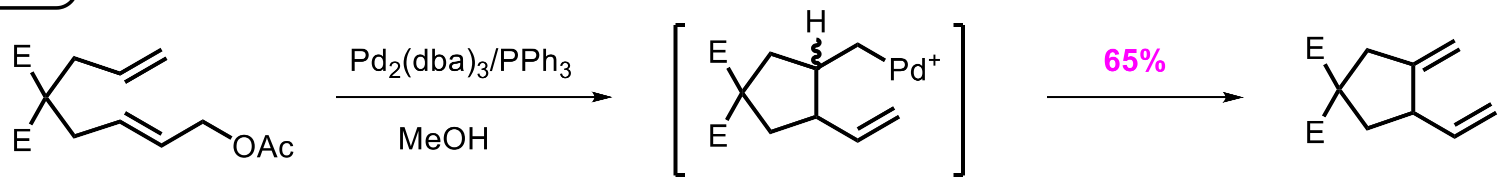


Echavarren, A. M. *et al*

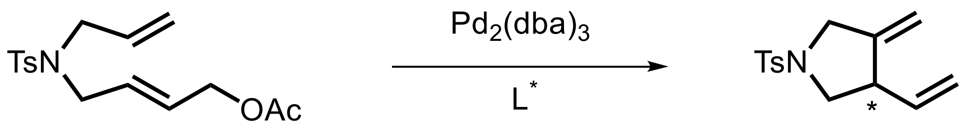
1. PALLADIUM-CATALYZED CYCLIZATION OF A π-ALLYL COMPLEX

The enophile is a double bond: β-elimination is possible

B.2



Asymmetric version :

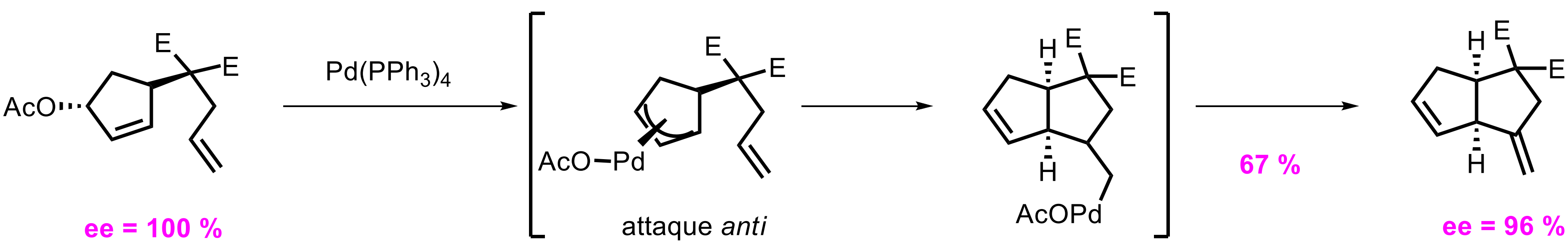


0 - 79 %

ee = 0 - 20 %

L^* = *(S, S)*-DIOP, *(R)*-BINAP, *(R)*-MOPI

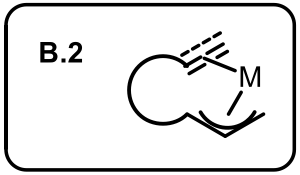
Oppolzer, W. *et al*

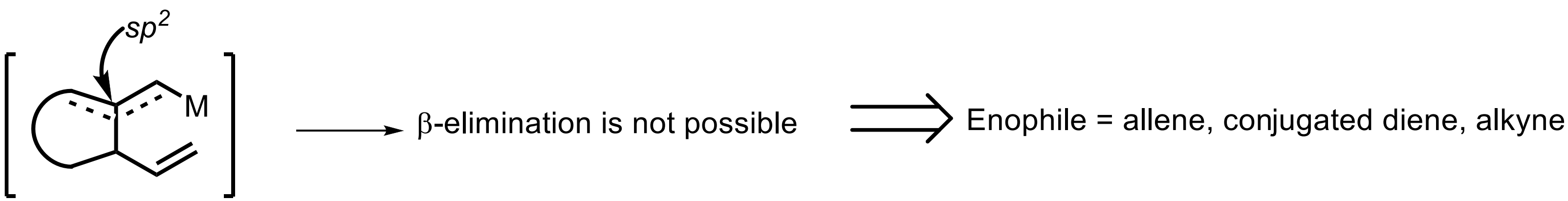


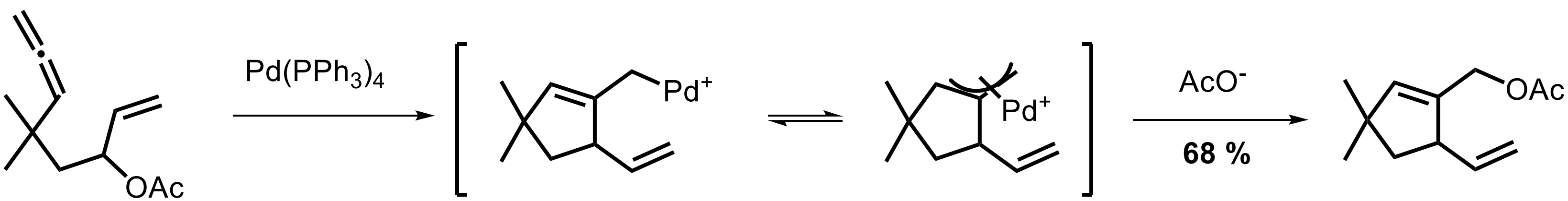
1.

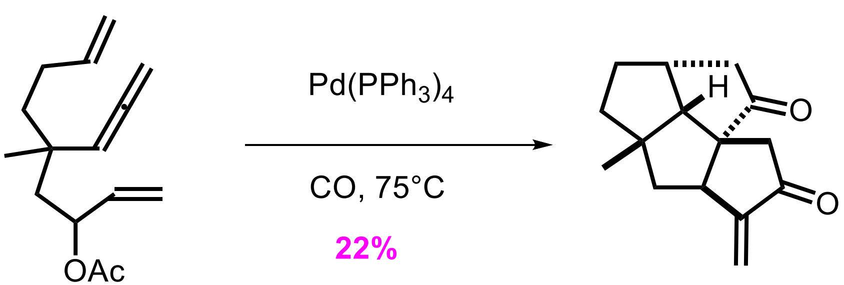
PALLADIUM-CATALYZED CYCLIZATION OF A π-ALLYL COMPLEX

The enophile is not a double bond: β-elimination is not possible



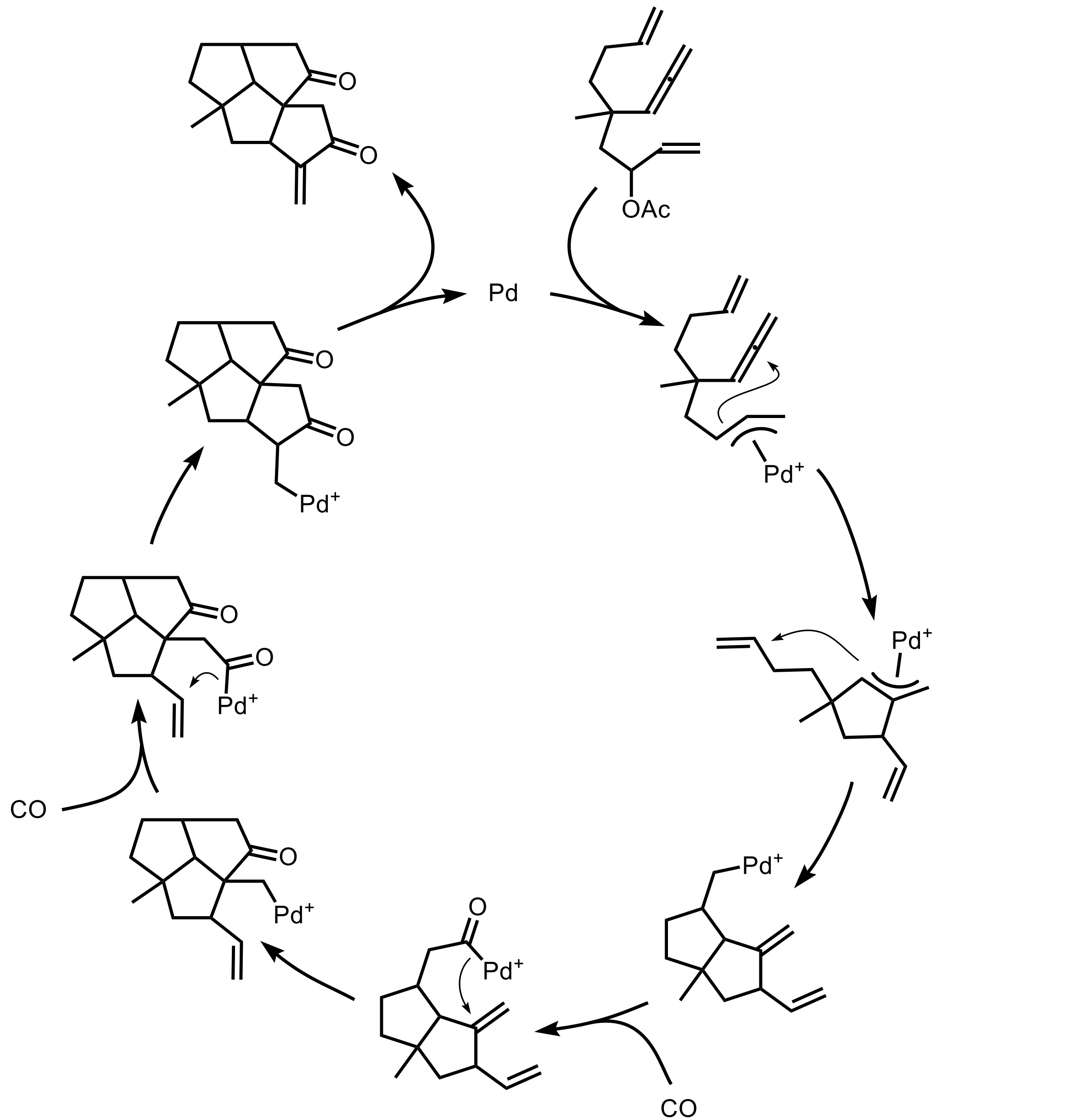




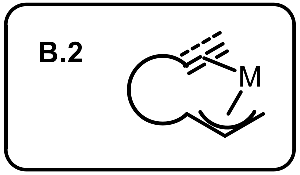


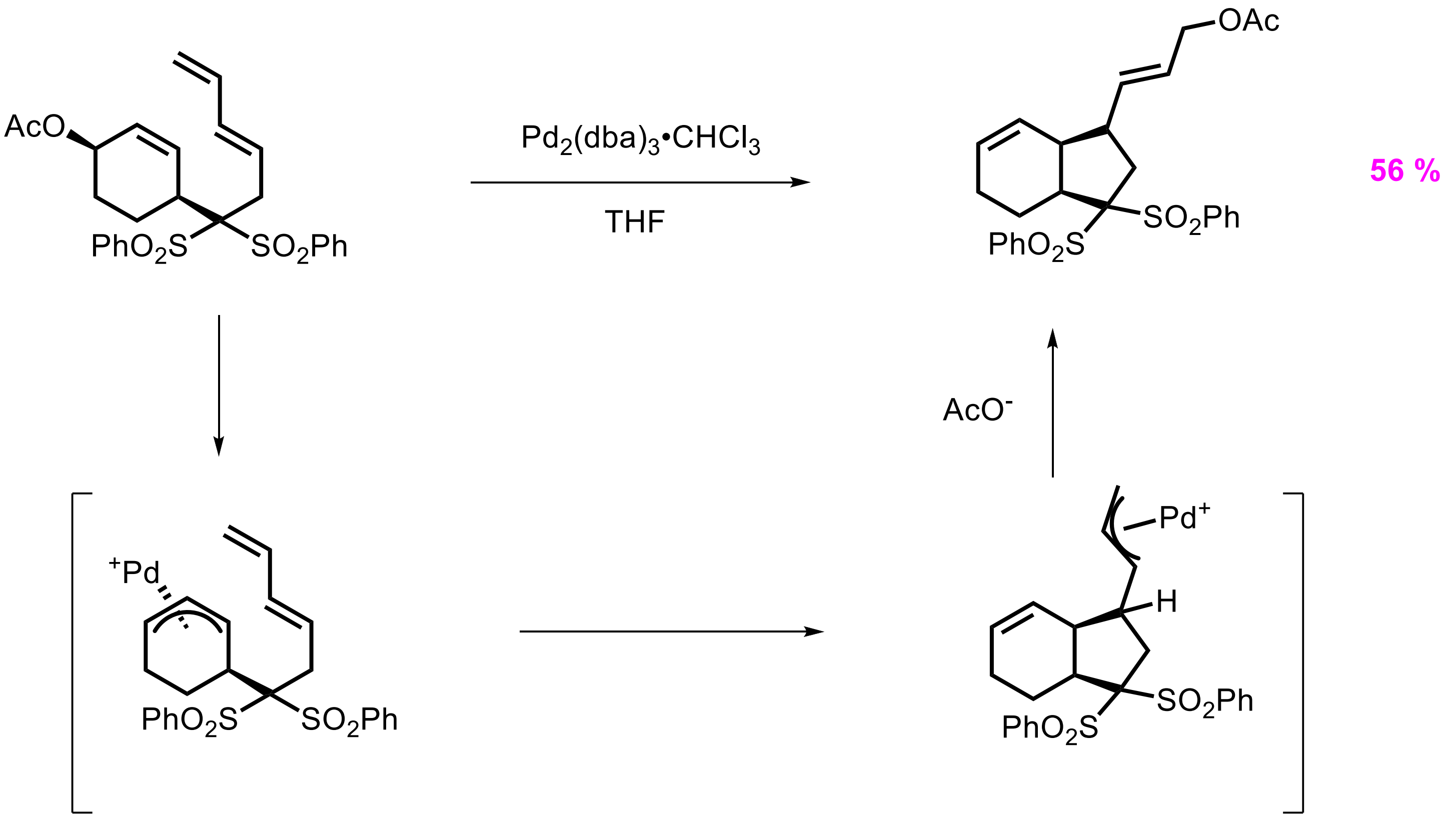
Yamamoto, K. *et al*

1. PALLADIUM-CATALYZED CYCLIZATION OF A π-ALLYL COMPLEX



1. PALLADIUM-CATALYZED CYCLIZATION OF A π-ALLYL COMPLEX

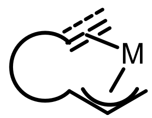


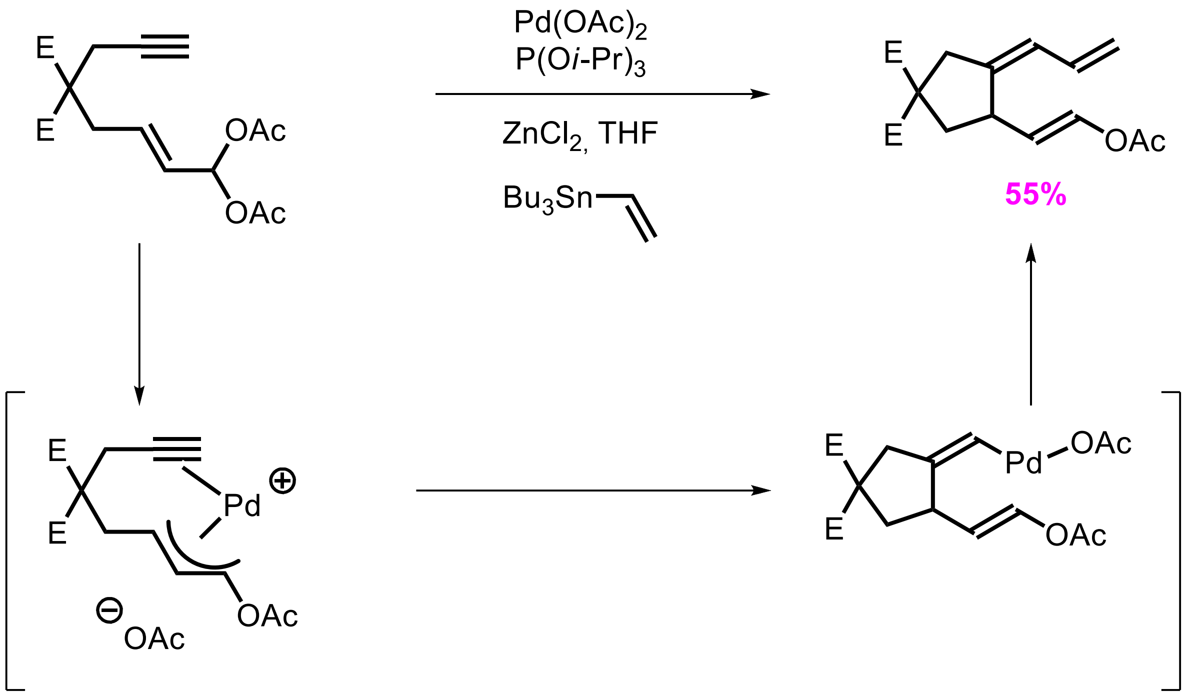


Trost, B. M. *et al*

1. PALLADIUM-CATALYZED CYCLIZATION OF A π-ALLYL COMPLEX

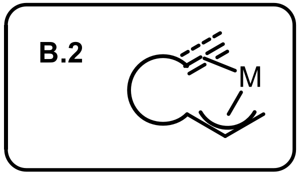
B.2

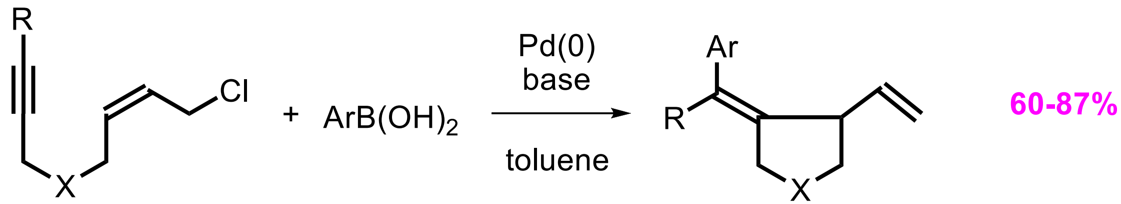




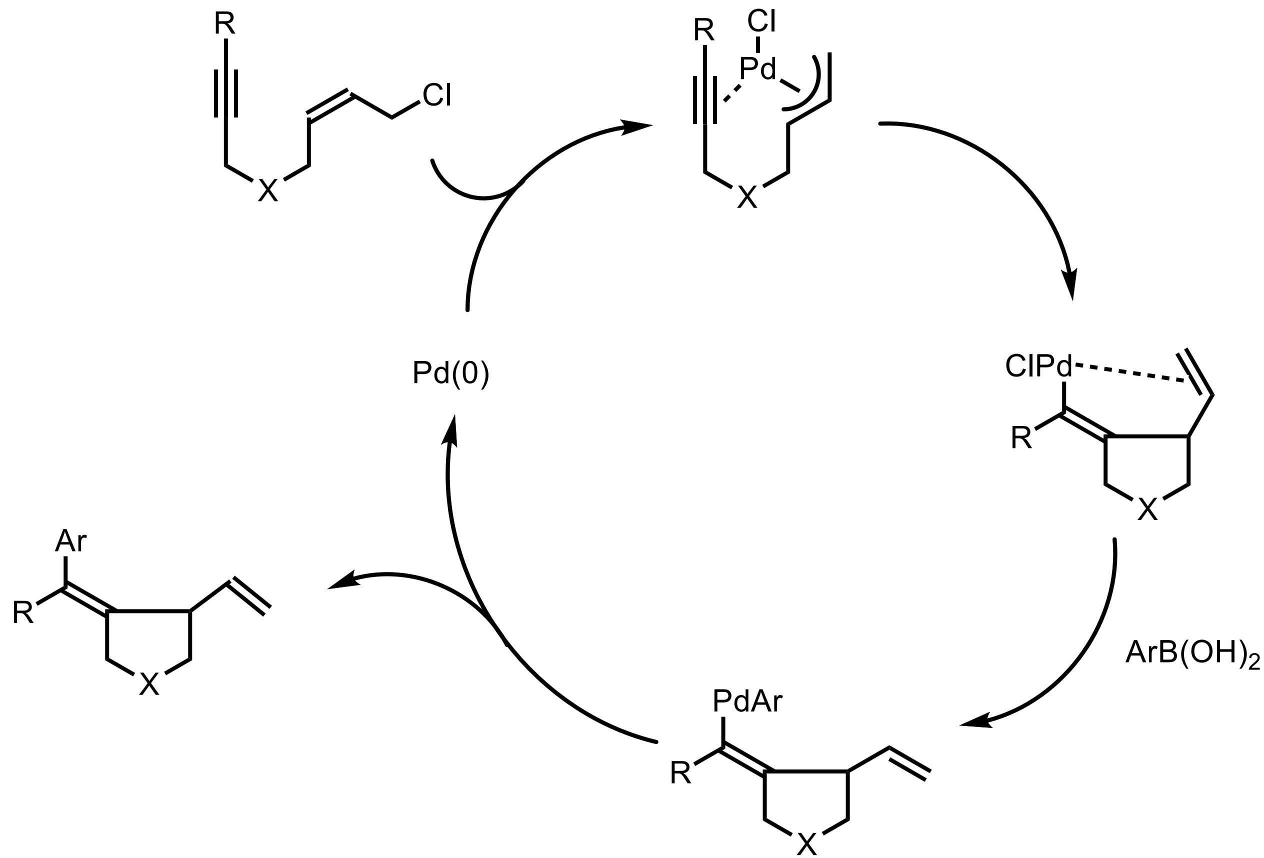
Holzhapfel, C. W. *et al*

1. PALLADIUM-CATALYZED CYCLIZATION OF A π-ALLYL COMPLEX





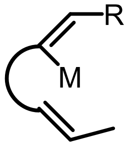
R= Ph, Bu, CH_3OCH_2 ; X = O, NBn, NTs

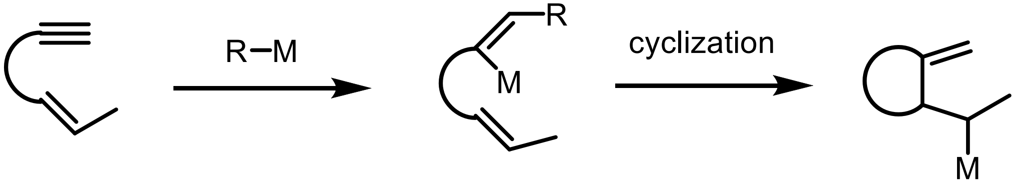


Zhang, Z. *et al*

1. VINYLMETAL PATHWAY

C.1





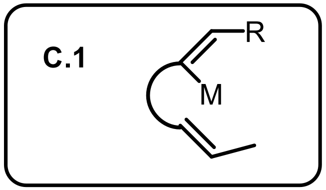
R = H, SnR'$_{3,}$ BR'$_2$......   M = Pd, Ru, Rh

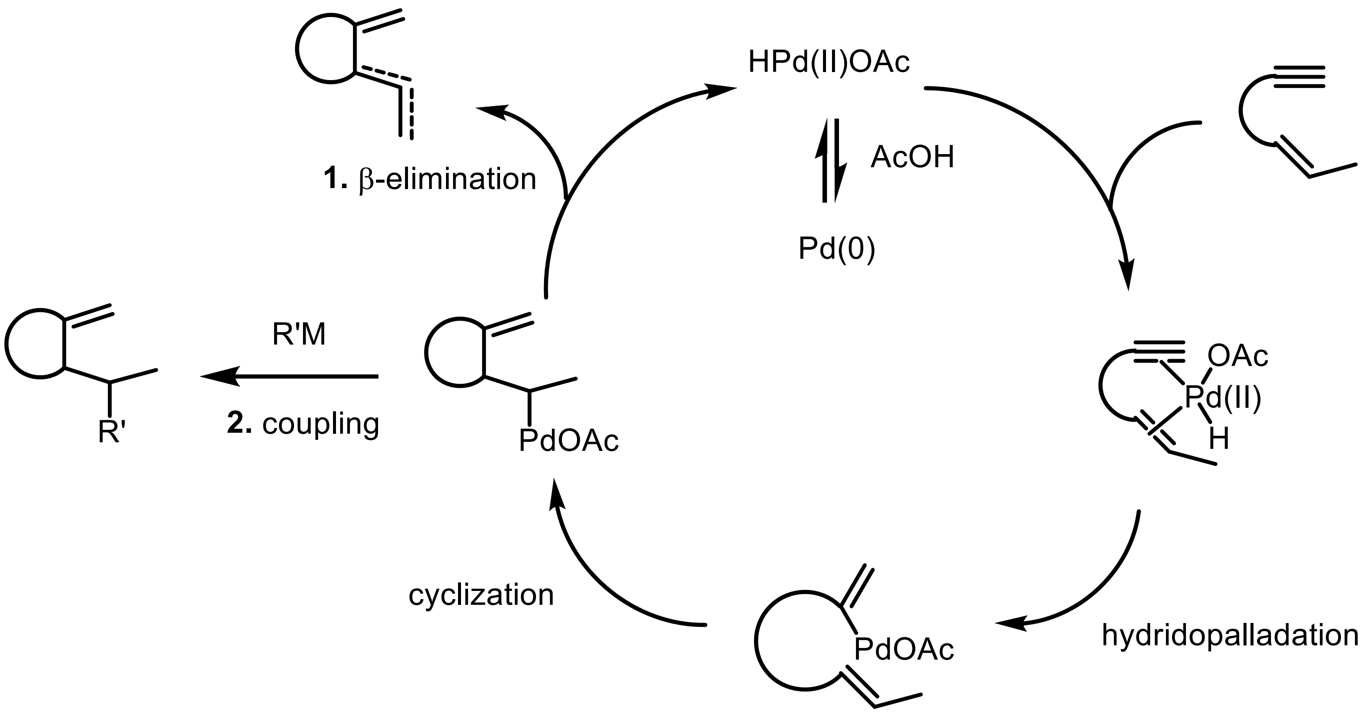
We will limit to R = H and palladium

Hydridometallation : Palladium - Ruthenium

Stanno- and Borometallation : Palladium

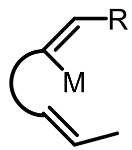
1. HYDRIDOPALLADATION

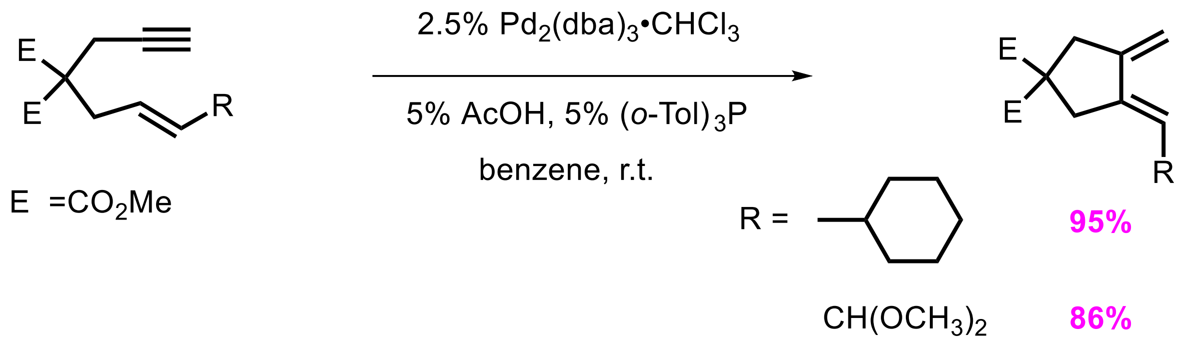


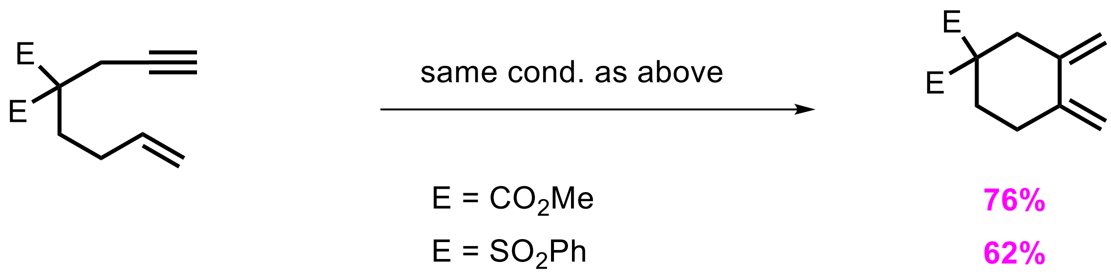


1. HYDRIDOPALLADATION / β-ELIMINATION

C.1



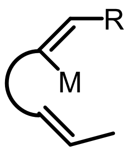


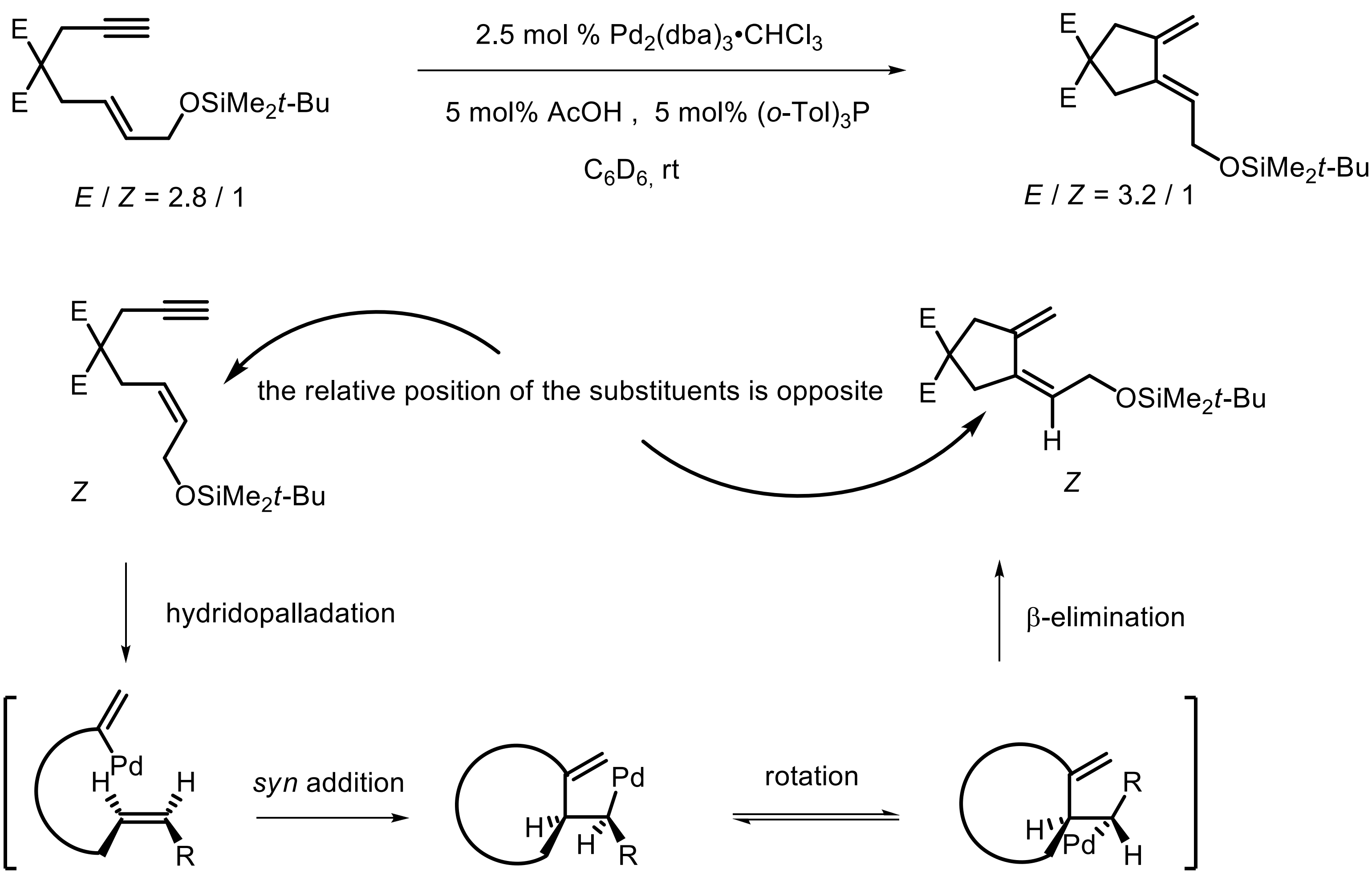


Trost, B. M. *et al*

1. HYDRIDOPALLADATION / β-ELIMINATION

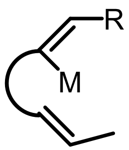
C.1



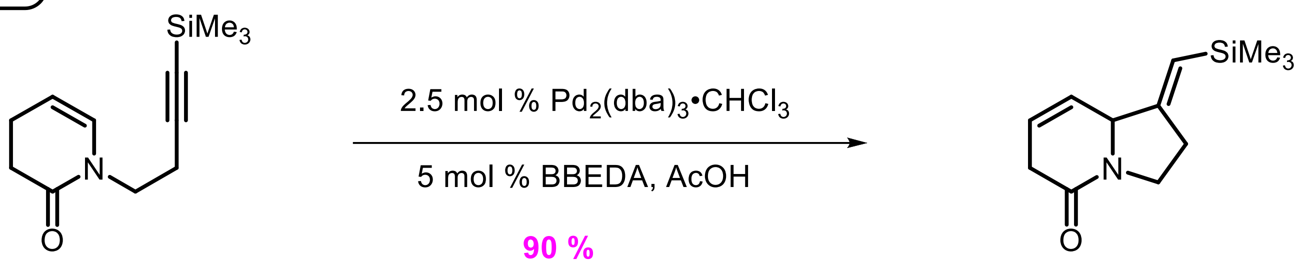


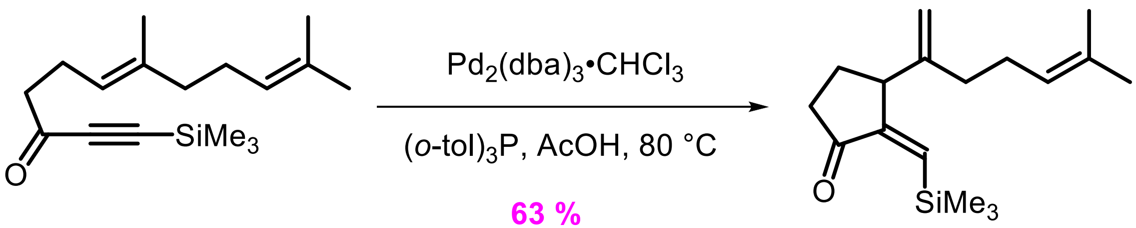
1. HYDRIDOPALLADATION / β-ELIMINATION

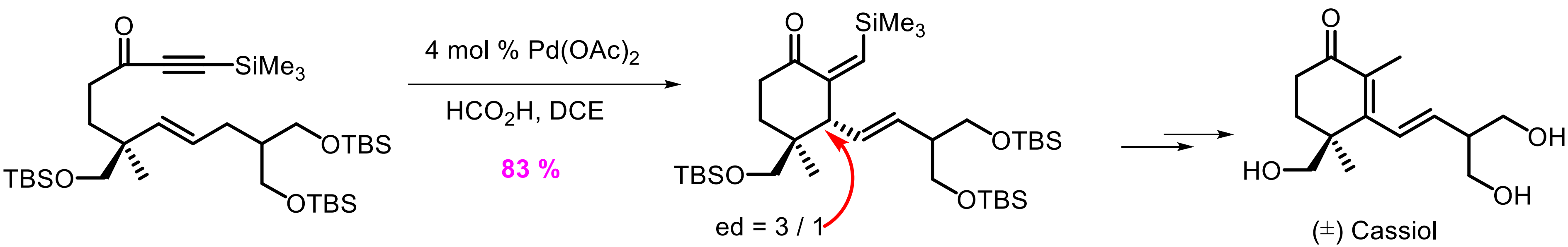
C.1



Applications



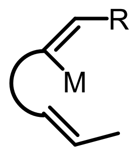


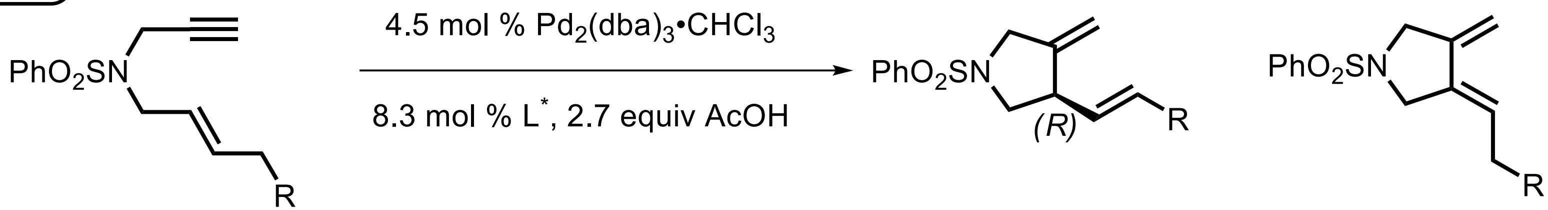


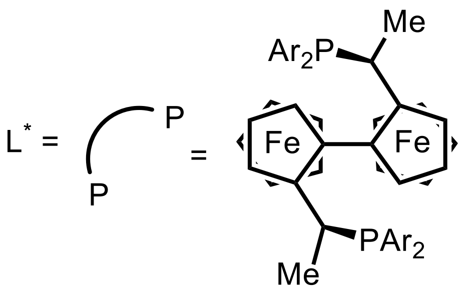
Trost, B. M. *et al*

1. HYDRIDOPALLADATION / β-ELIMINATION: ENANTIOSELECTIVITY

C.1

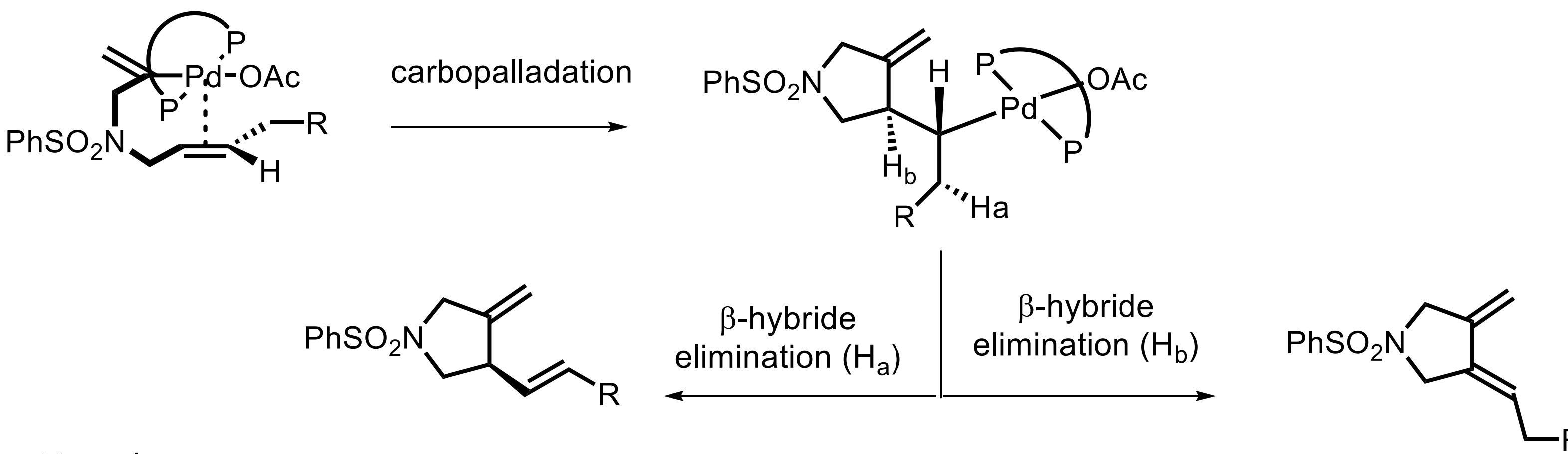






(*S*,*S*)-(*R*,*R*)-trap
Ar = *p*-$CF_3C_6H_4$

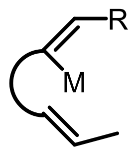
R		
$SiMe_3$	**24 %** (ee = 76 %)	-
CH_2SiMe_3	**53 %** (ee = 95 %)	**15 %**
CH_2Ph	**62 %** (ee = 75 %)	**13 %**

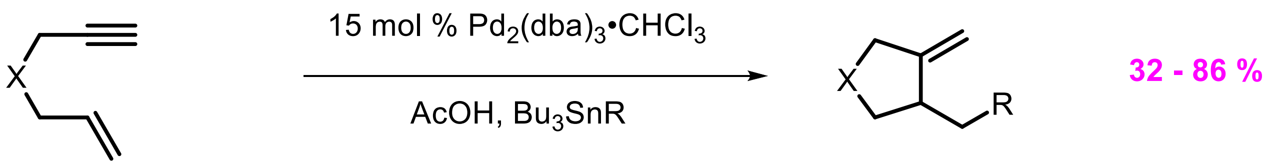


Ito, Y. *et al*

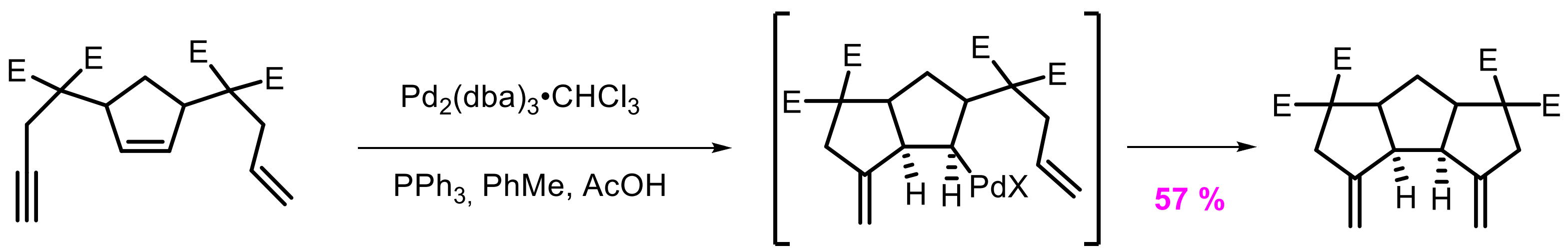
1. HYDRIDOPALLADATION / COUPLING REACTIONS

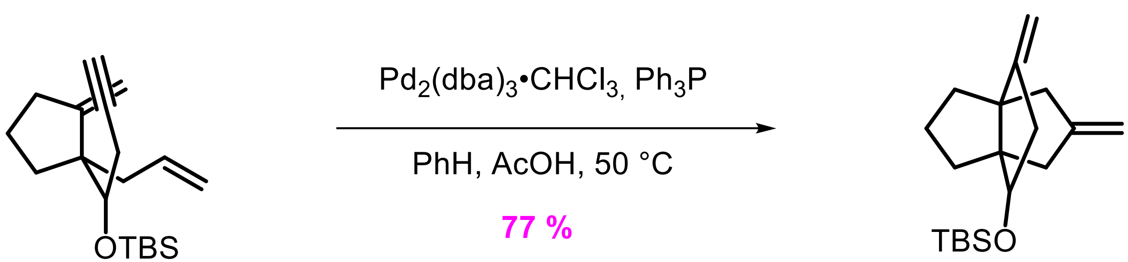
C.1





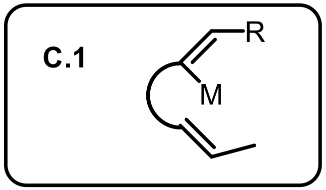
Insertion of alkene is also possible : cascade of cyclizations

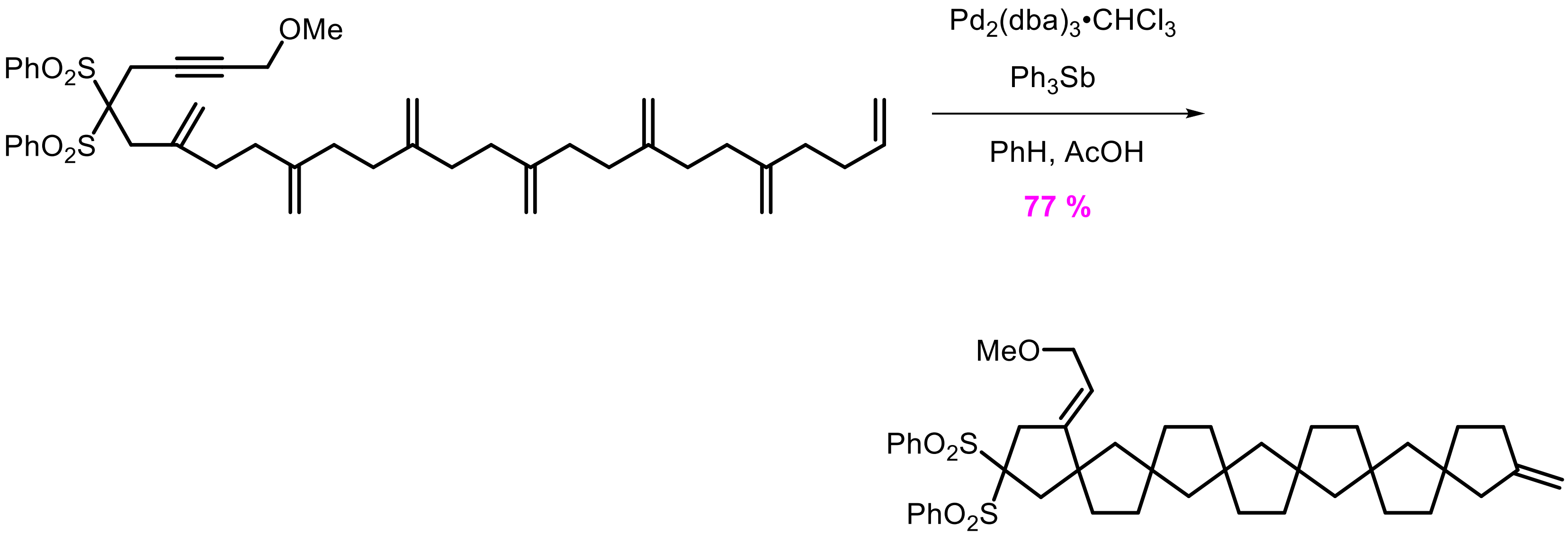




Trost, B. M. *et al*

1. HYDRIDOPALLADATION / COUPLING REACTIONS

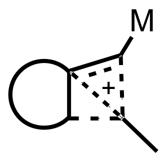




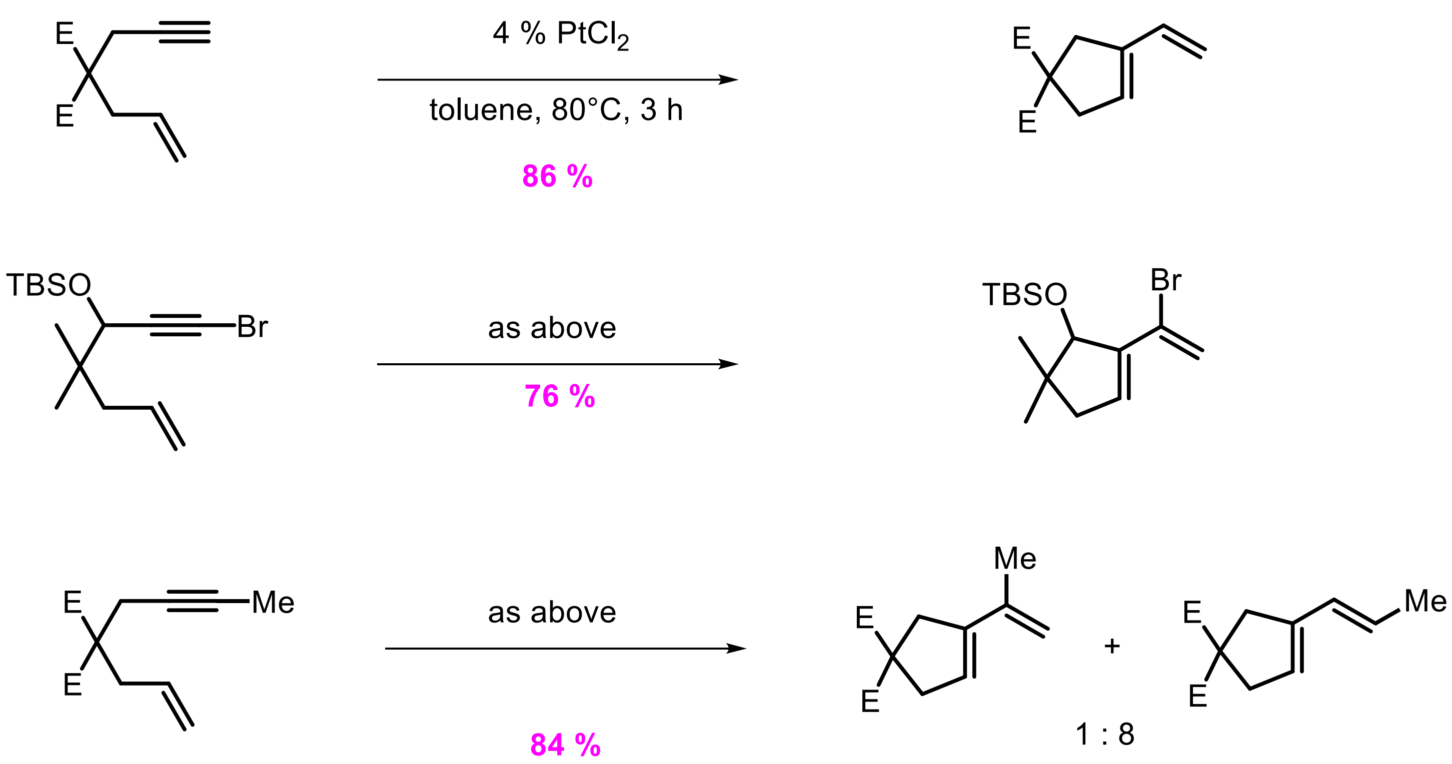
Trost, B. M. *et al*

1. PLATINUM-CATALYZED CYCLOISOMERIZATIONS OF 1,6-ENYNES

D.



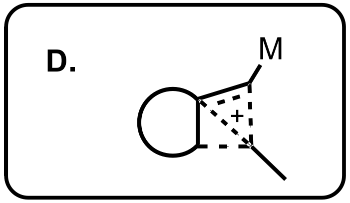
Enyne metathesis

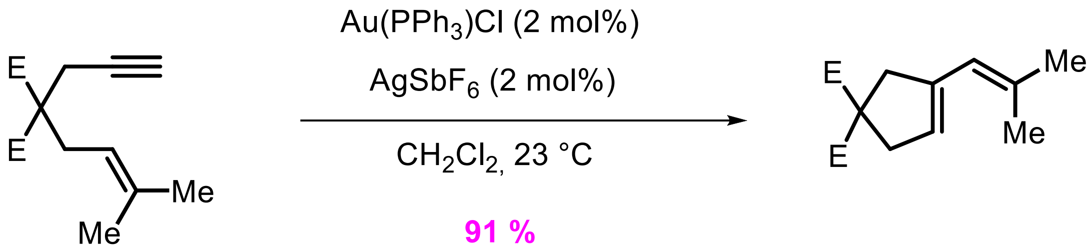


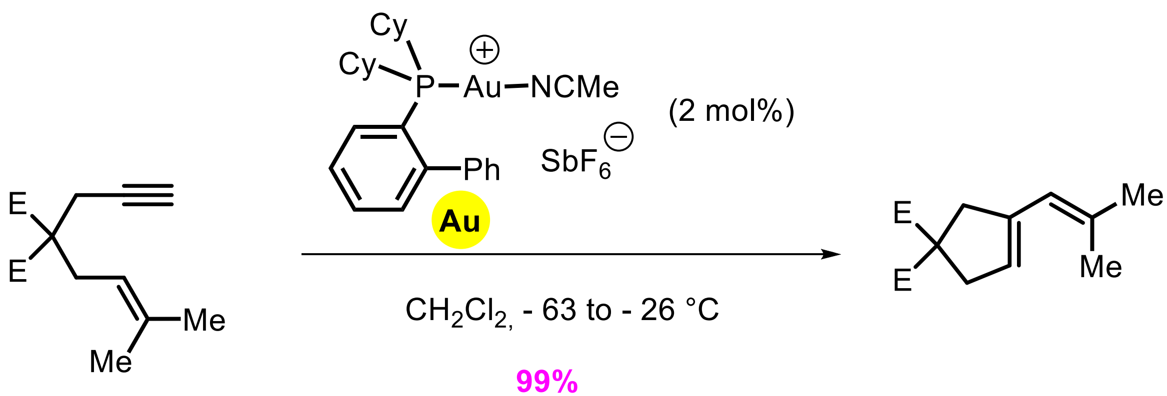
The reaction works with $PtCl_4$ as well

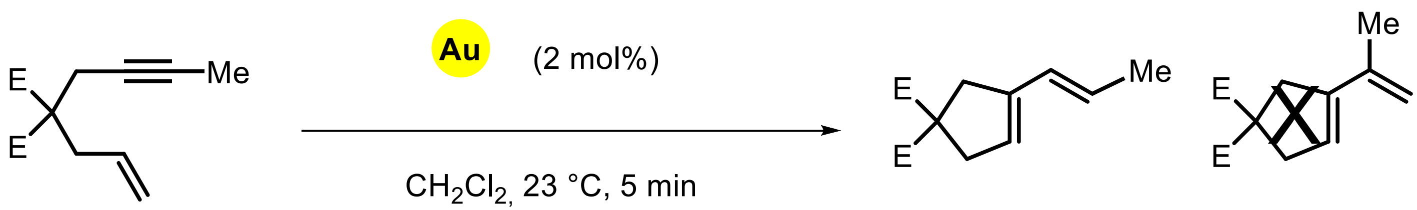
Murai, S. *et al*

1. GOLD-CATALYZED CYCLOISOMERIZATIONS OF 1,6-ENYNES





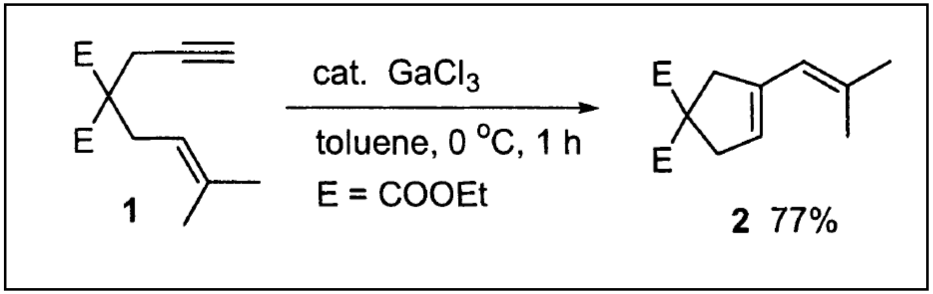


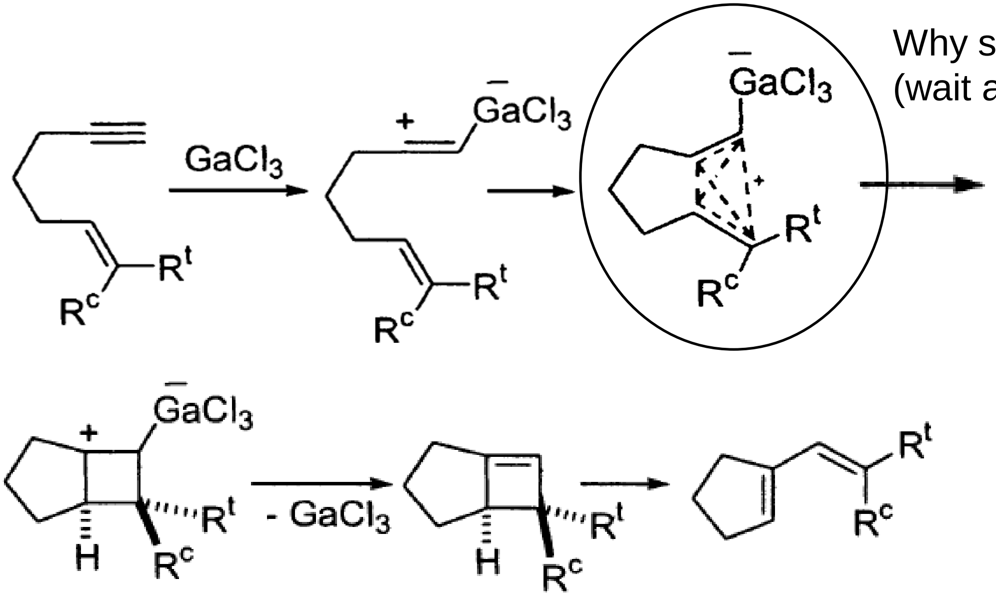


?? Not the expected product (see double cleavage)

Echavarren, A. M. *et al*

1. GALLIUM-CATALYZED CYCLOISOMERIZATIONS OF 1,6-ENYNES

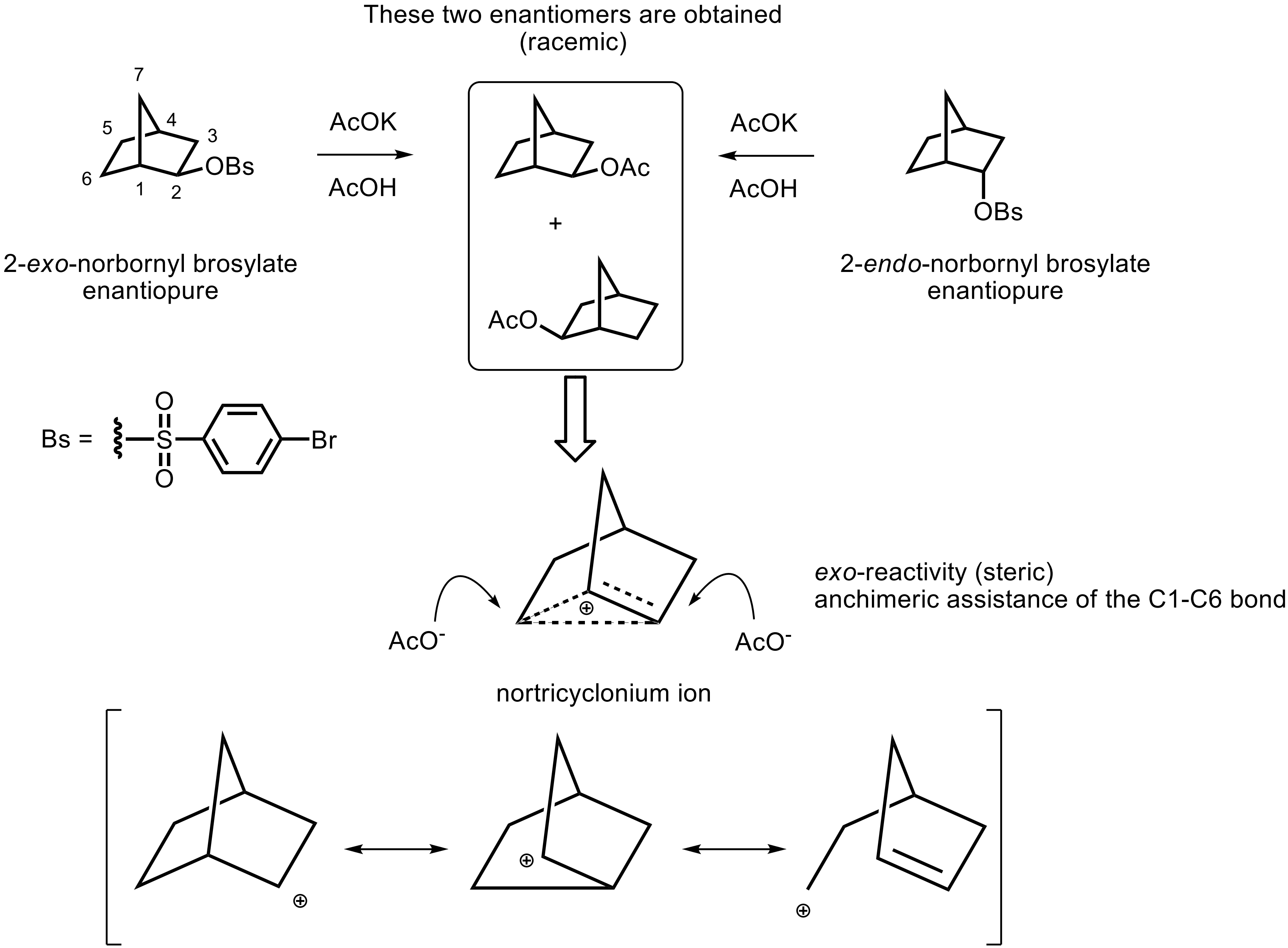




Why such a crazy intermediate??
(wait a few slides)

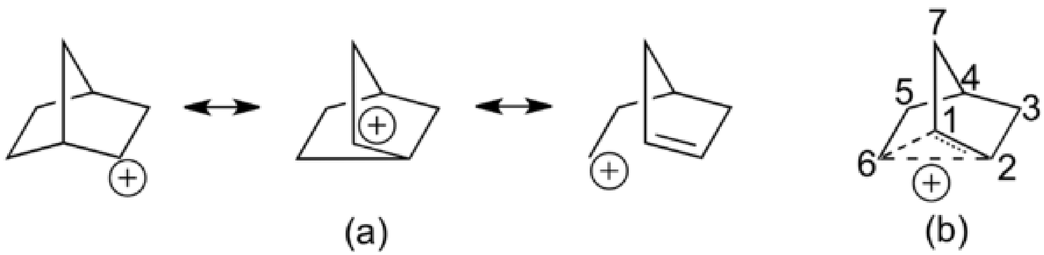
Chatani *et al*

1.



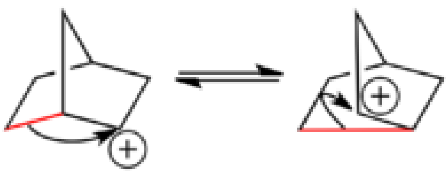
Saul Winstein's reaction (1949): coined the term « non-classical ion » (but also anchimeric assistance, homoaromaticity, intimate ion pair …)

2-norbornyl carbocation: non-classical view (greater stabilization)

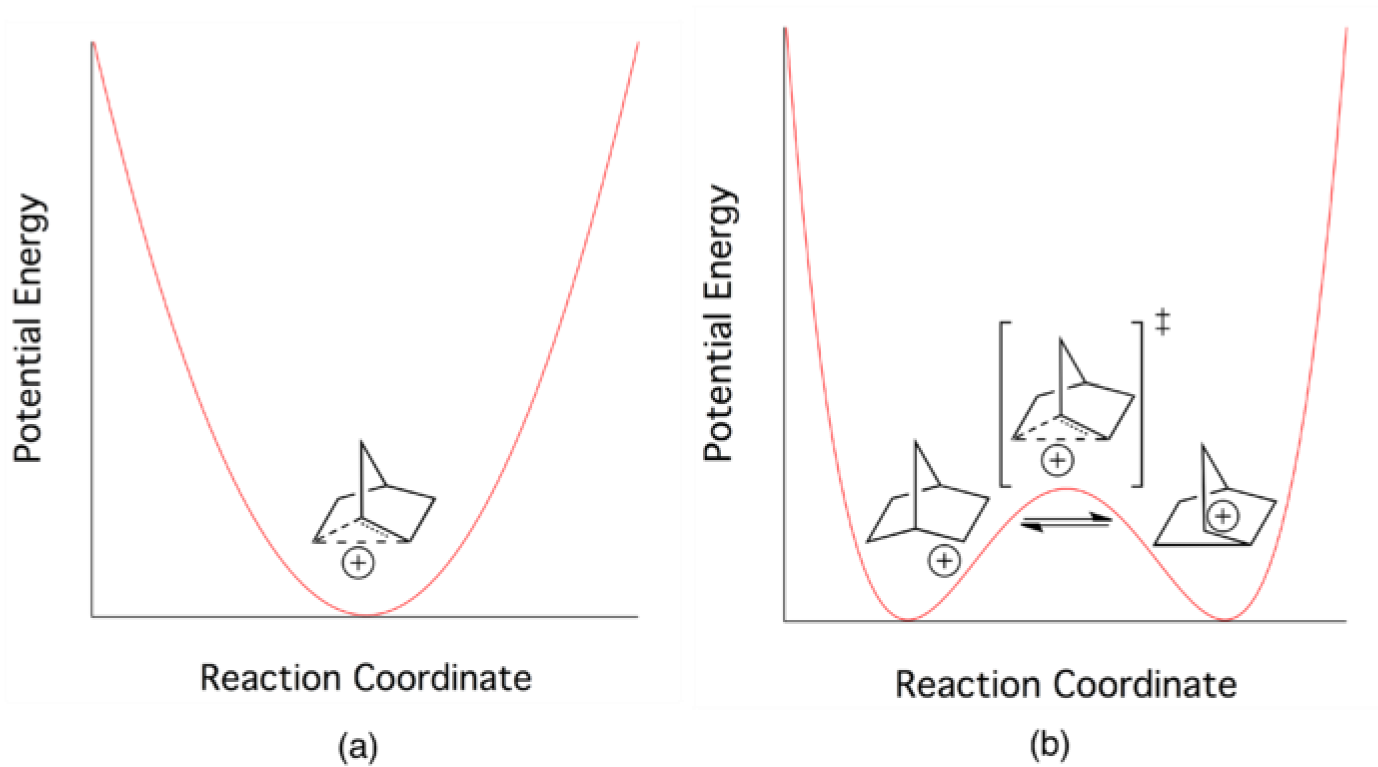


(a) Explicit resonance structures for the non-classical 2-norbornyl cation. (b) Common depiction of the 2-norbornyl cation, using dashed lines for partial bonds.

classical view:



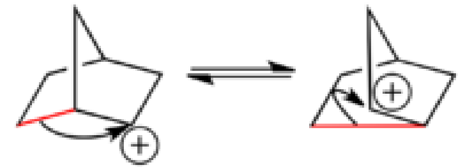
In the classical depiction of the 2-norbornyl cation, there is a rapid equilibrium between two asymmetric enantiomeric structures.



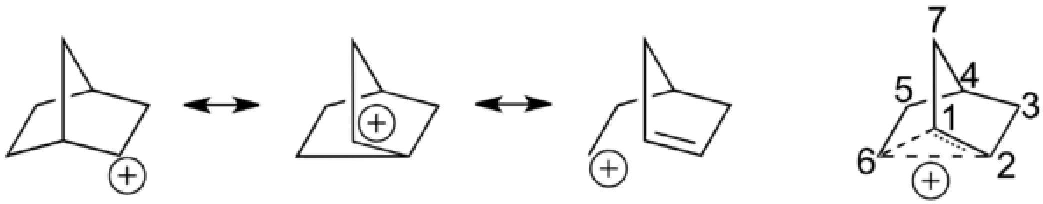
(a) In the non-classical view, the delocalized cation is the stable potential energy minimum. (b) In the classical view, it is instead a low-lying transition state between two enantiomers of the asymmetric species

2-norbornyl carbocation:

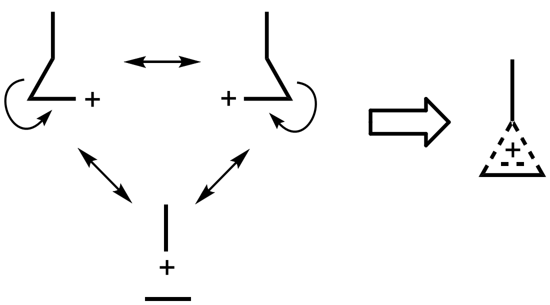
classical view:



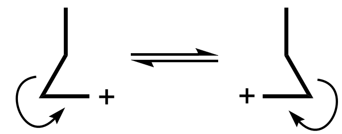
non-classical view (greater stabilization)



(a) Explicit resonance structures for the non-classical 2-norbornyl cation. (b) Common depiction of the 2-norbornyl cation, using dashed lines for partial bonds.



non-classical carbocation:
- resonance hybrid
- stable potential energy minium
- hypovalent ***3-center 2-electron*** interaction

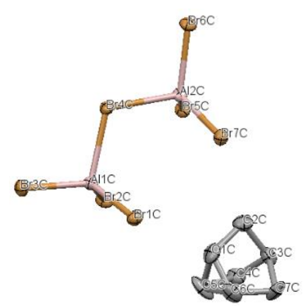


classical carbocation: rapidly equilibrating pairs of cations (Wagner-Meerwein rearrangement)

Cons: H. C. Brown *Acc. Chem. Res.* **1986**, *19*, 34

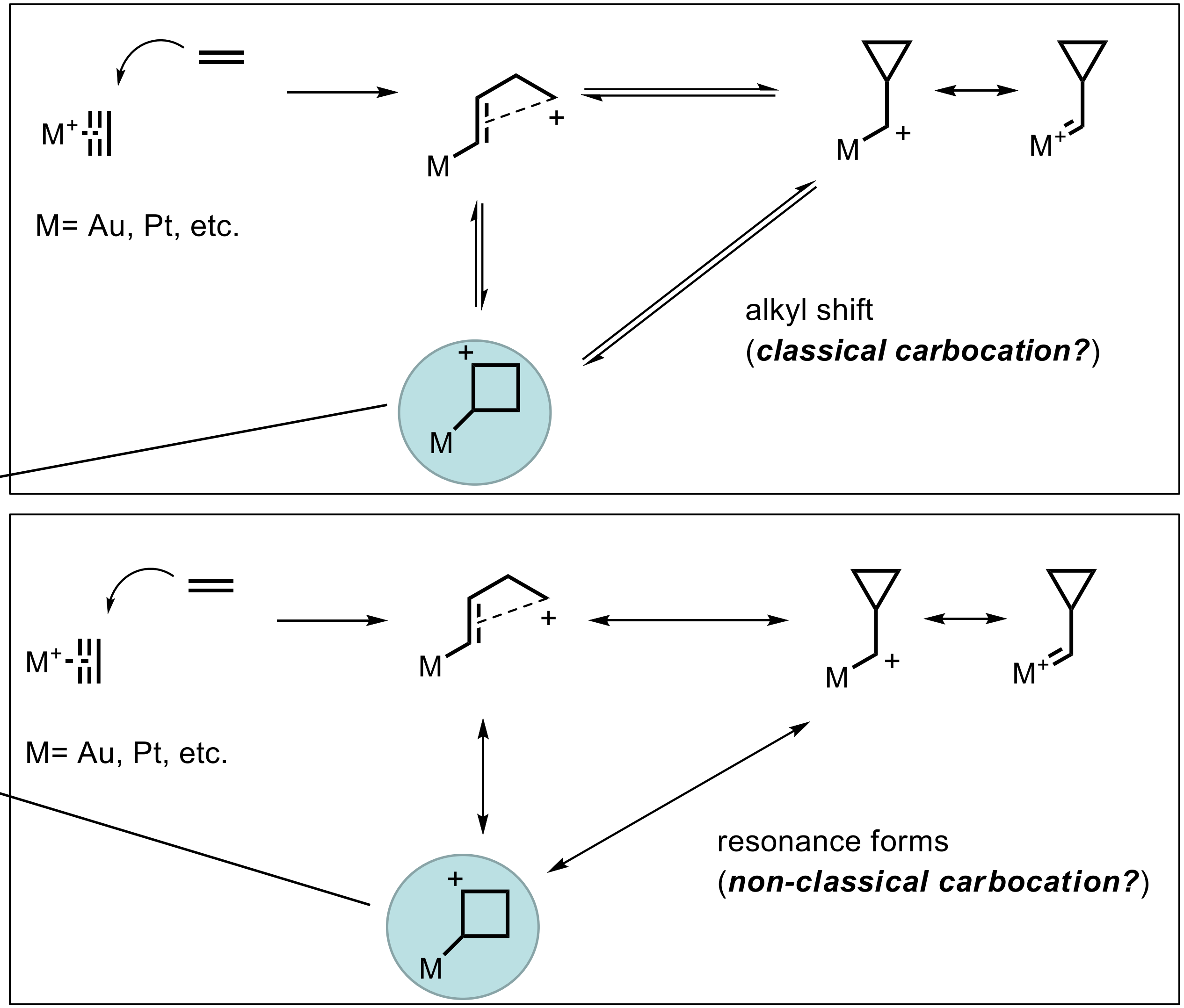
Pros: S. Winstein *et a*l *J. Am. Chem. Soc.* **1949**, *71*, 2953
G. Olah et al *J. Am. Chem. Soc.* **1972**, *94*, 2529

End game: cristal structure determination of the nonclassical 2 norbornyl carbocation, K. Meyer, I. Krossing *et al*, *Science* **2013**, *341*, 62

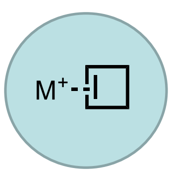


1.

Attack of an alkene onto an alkyne activated by a π-acidic metal

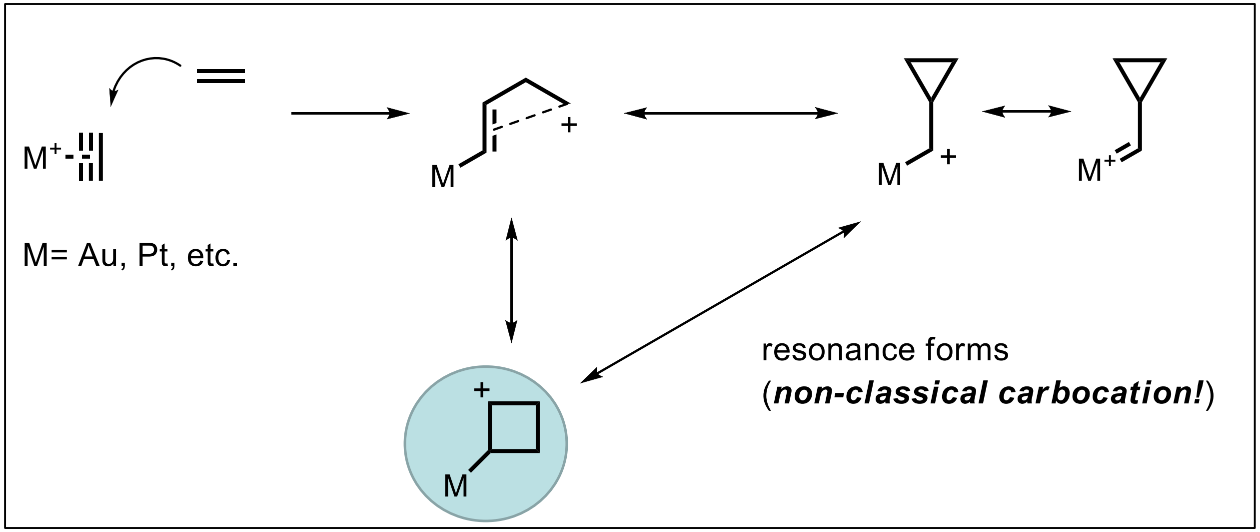


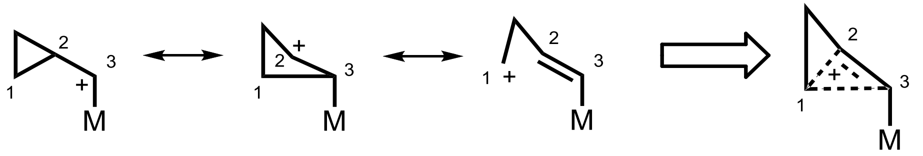
This is no less than the [2+2] cycloaddition product complexed in a κ^1 fashion (now depicted κ^2 for clarity)



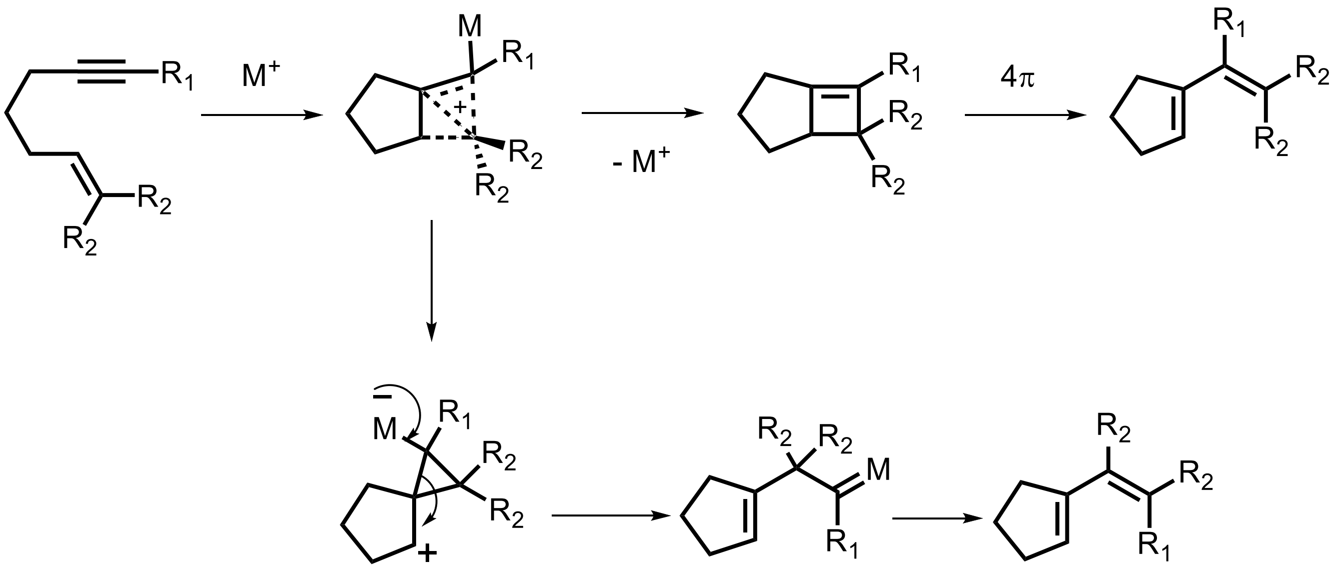
1.

Attack of an alkene onto an alkyne activated with a π-acidic metal



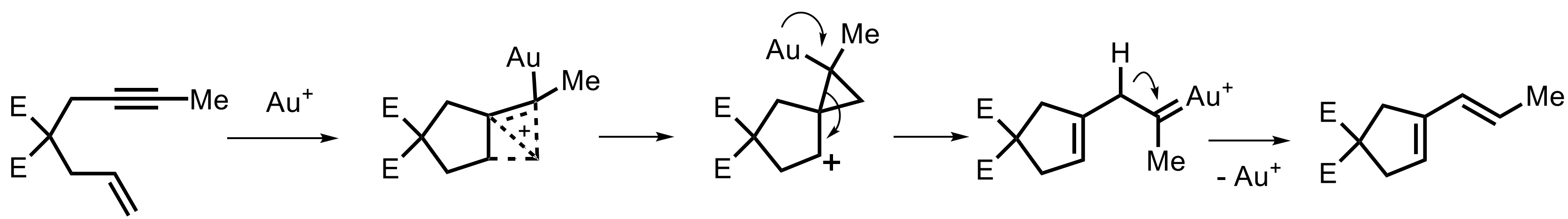


1.

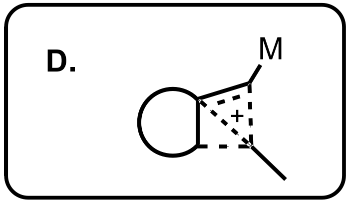


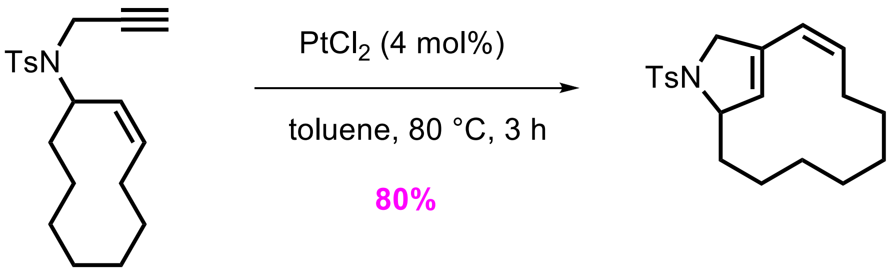
Single cleavage (enyne metathesis)

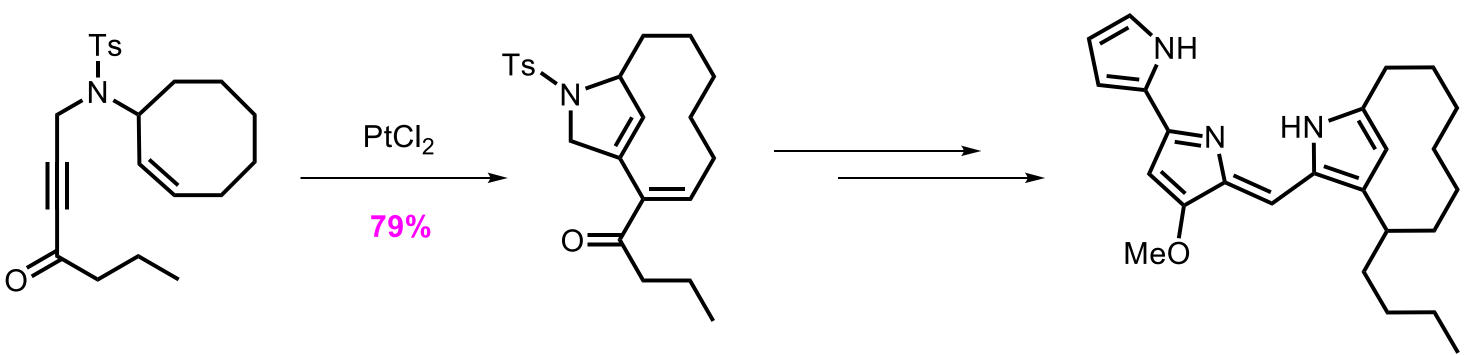
Double cleavage (no 4π)



1. APPLICATIONS IN SYNTHESIS



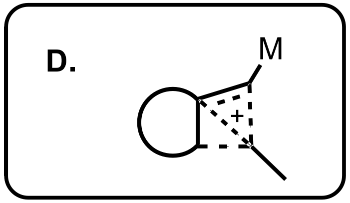


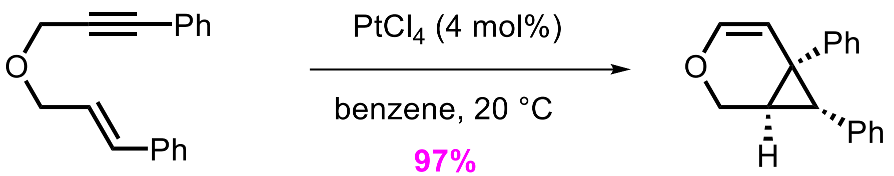


Streptorubine B

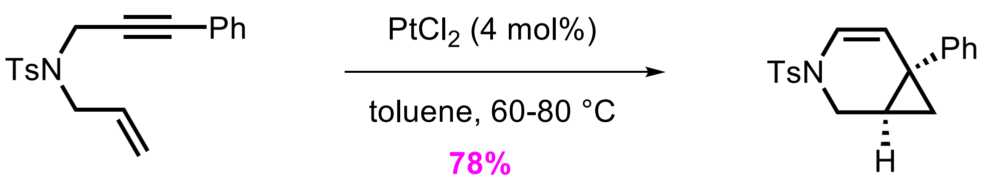
Fürstner, A. *et al*

1. FORMATION OF BICYCLO[4.1.0]HEPTENES

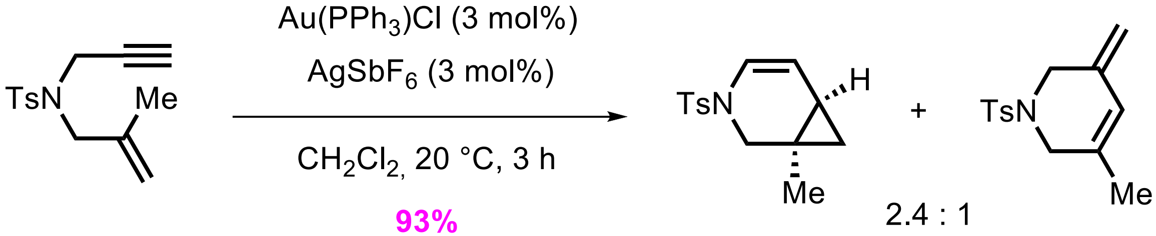




Blum, J. *et al*



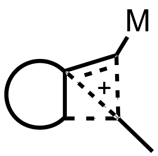
Fürstner, A. *et al*



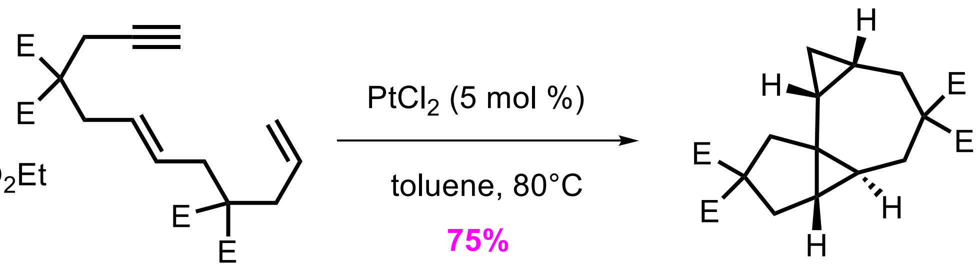
Echavarren, A. M. *et al*

1. CYCLOISOMERIZATION OF DIENYNES

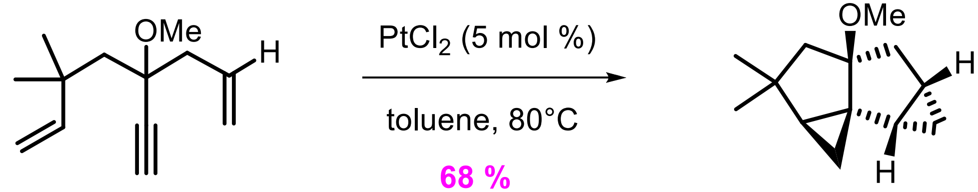
D.



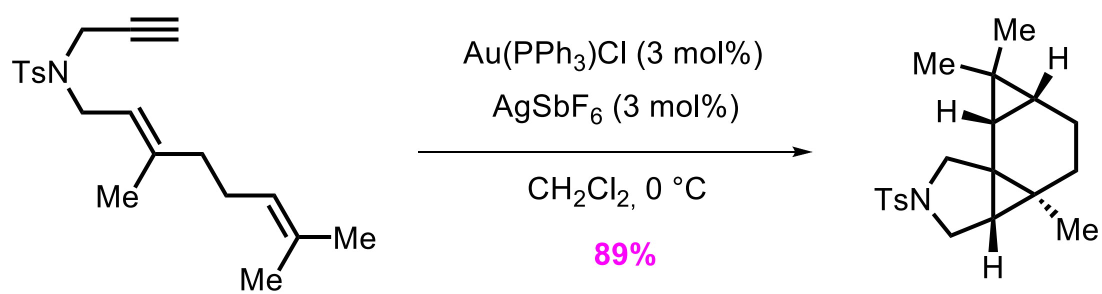
E = CO_2Et



Murai, S. *et al*

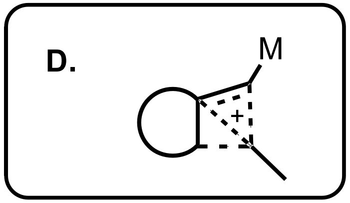


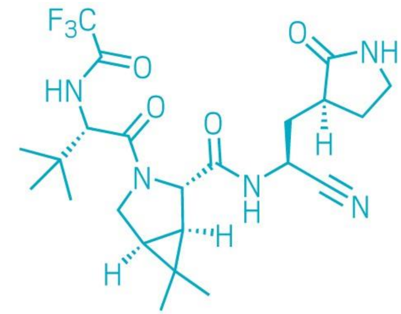
Fensterbank, L.; Malacria, M. *et al*



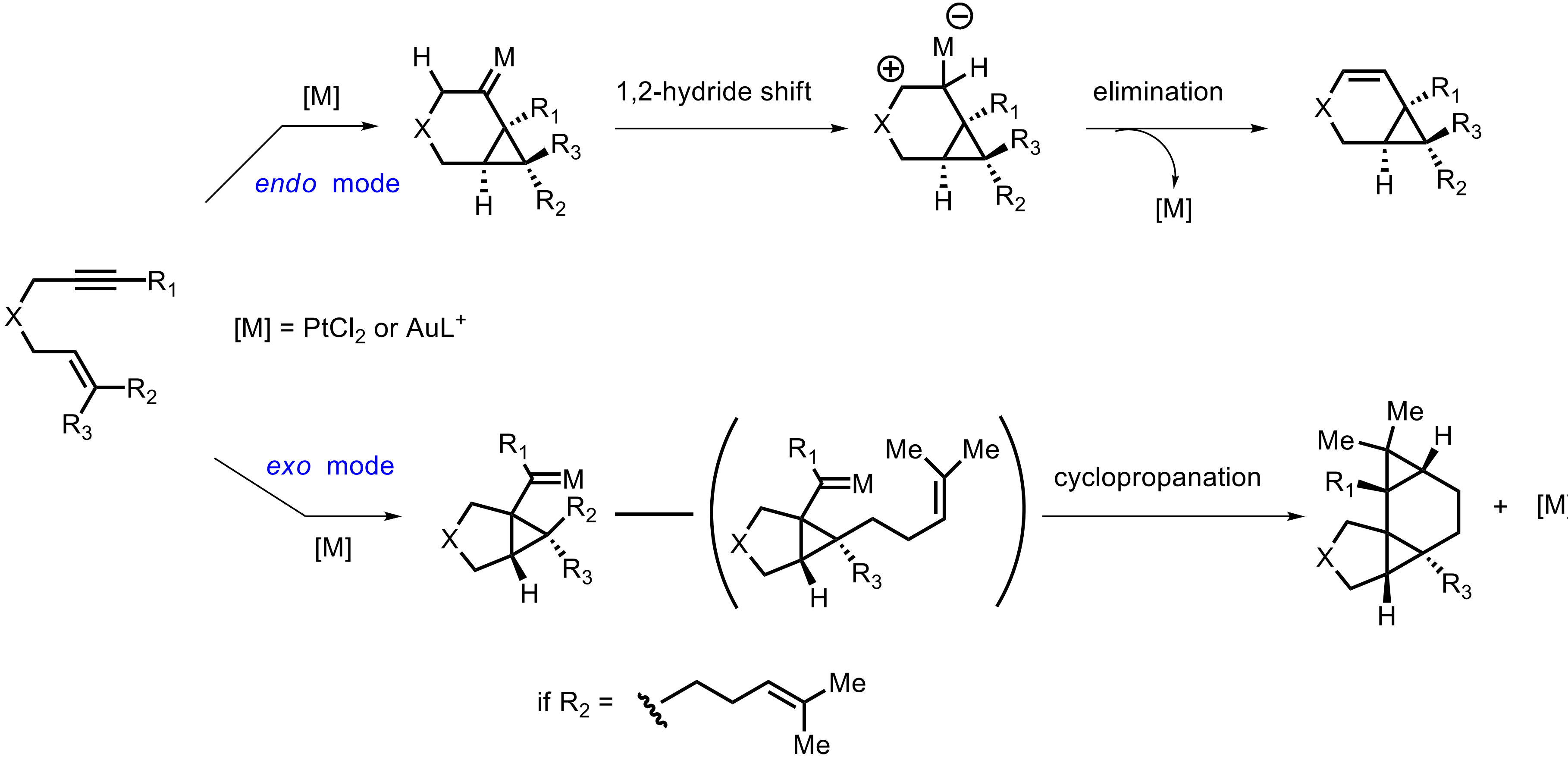
Echavarren, A. M. *et al*

1. PROPOSED MECHANISM

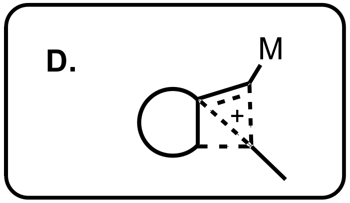


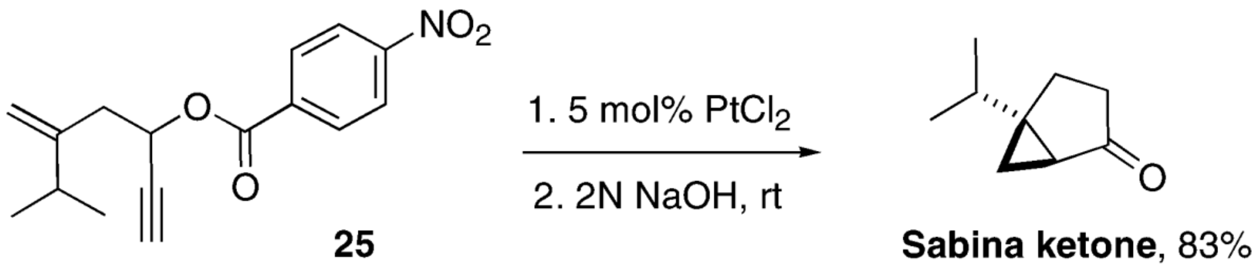


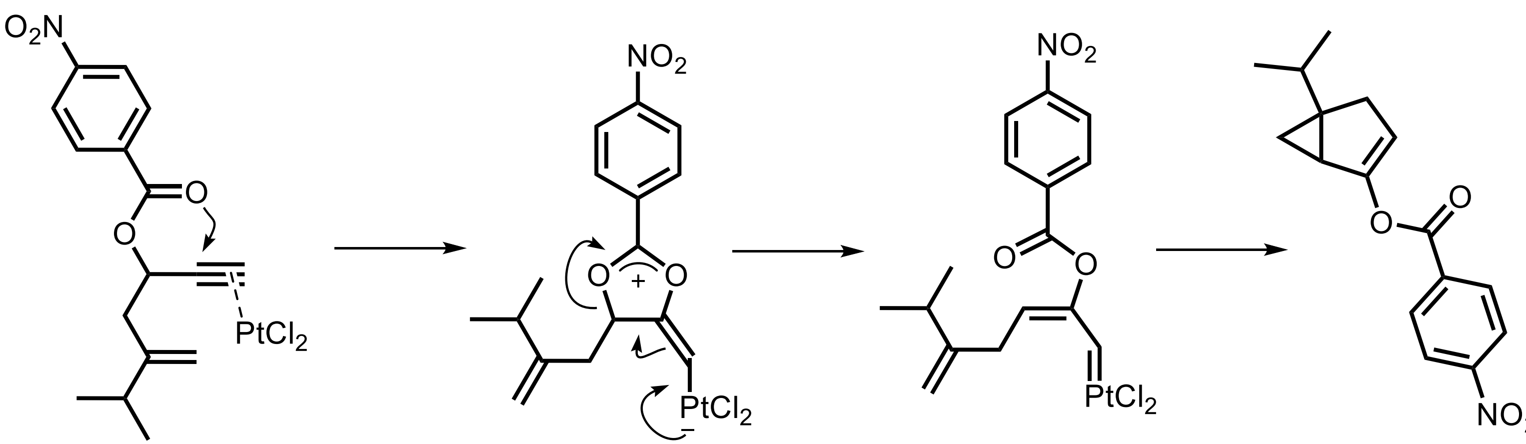
PF-07321332



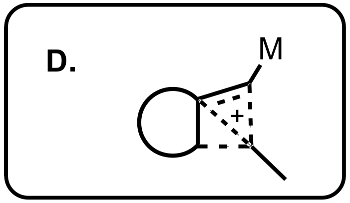
1.

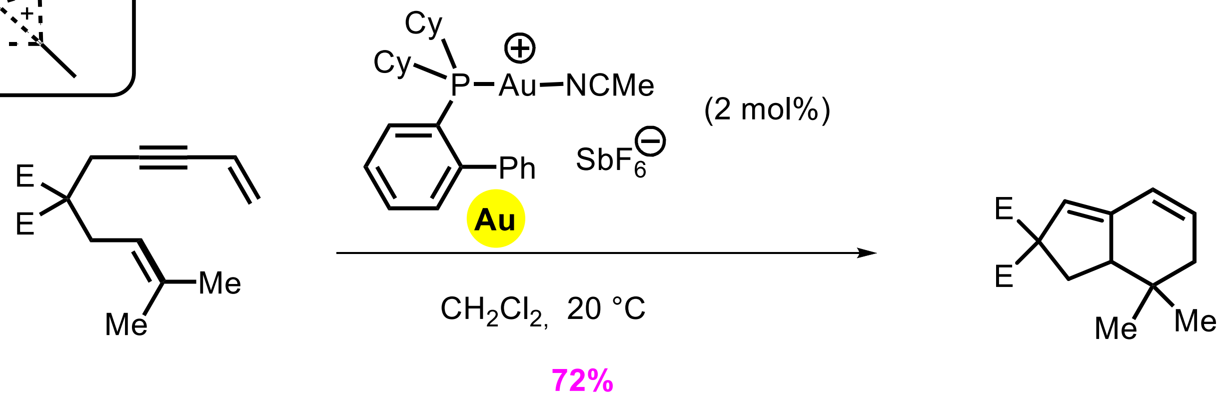

D.
M
+

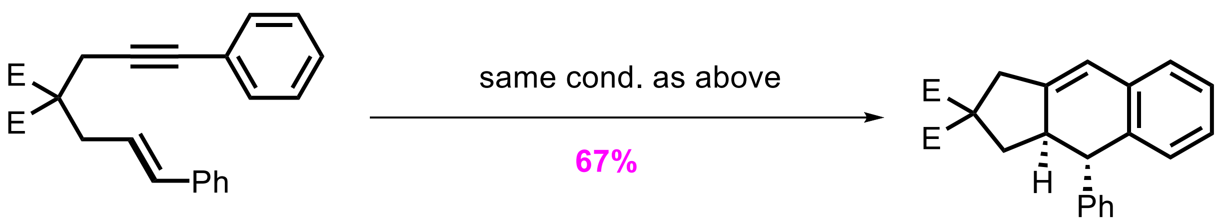

NO_2
O
O
25
1. 5 mol% $PtCl_2$
2. 2N NaOH, rt
O
Sabina ketone, 83%


O_2N
O
O
$PtCl_2$
NO_2
O
+
O
$PtCl_2$
−
NO_2
O
O
$PtCl_2$
O
O
NO_2

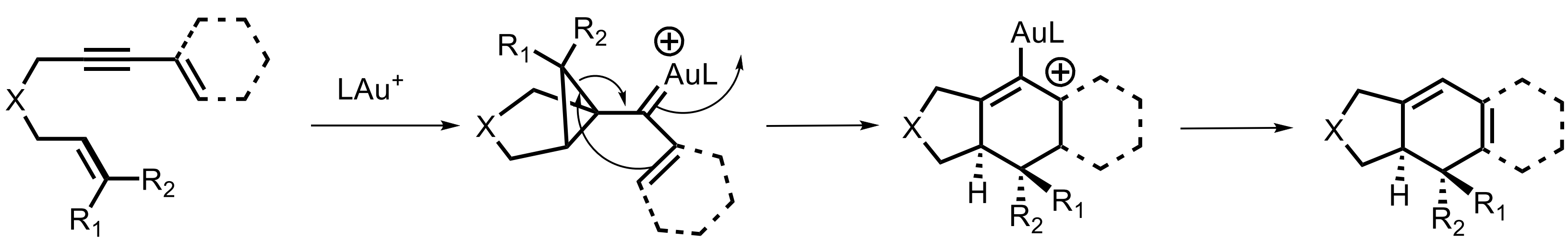
1. INTRAMOLECULAR [4+2] CYCLOADDITION OF ALKENES WITH ENYNES







Proposed mechanism:

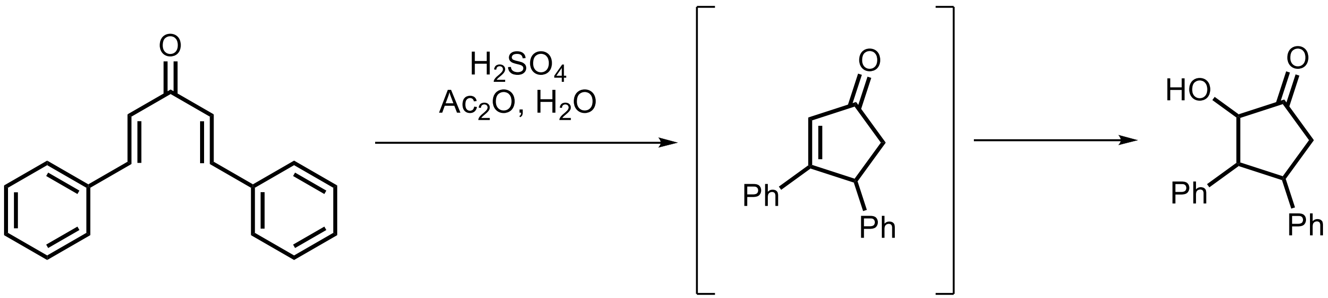


Echavarren, A. M. *et al*

1. NAZAROV TYPE REACTIONS

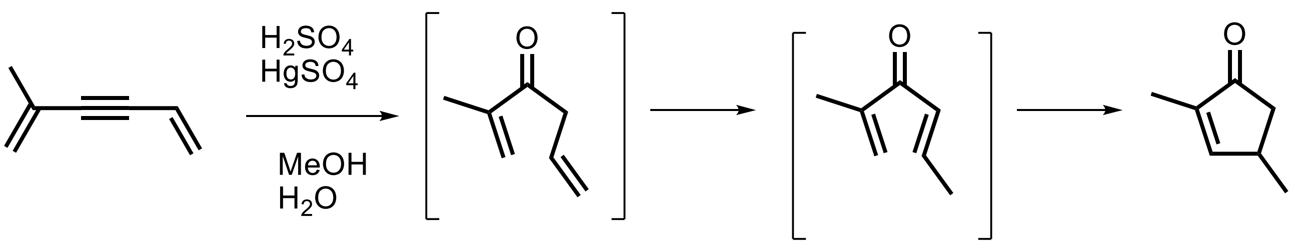
The Nazarov reaction

Discovered by Vorländer (1903)



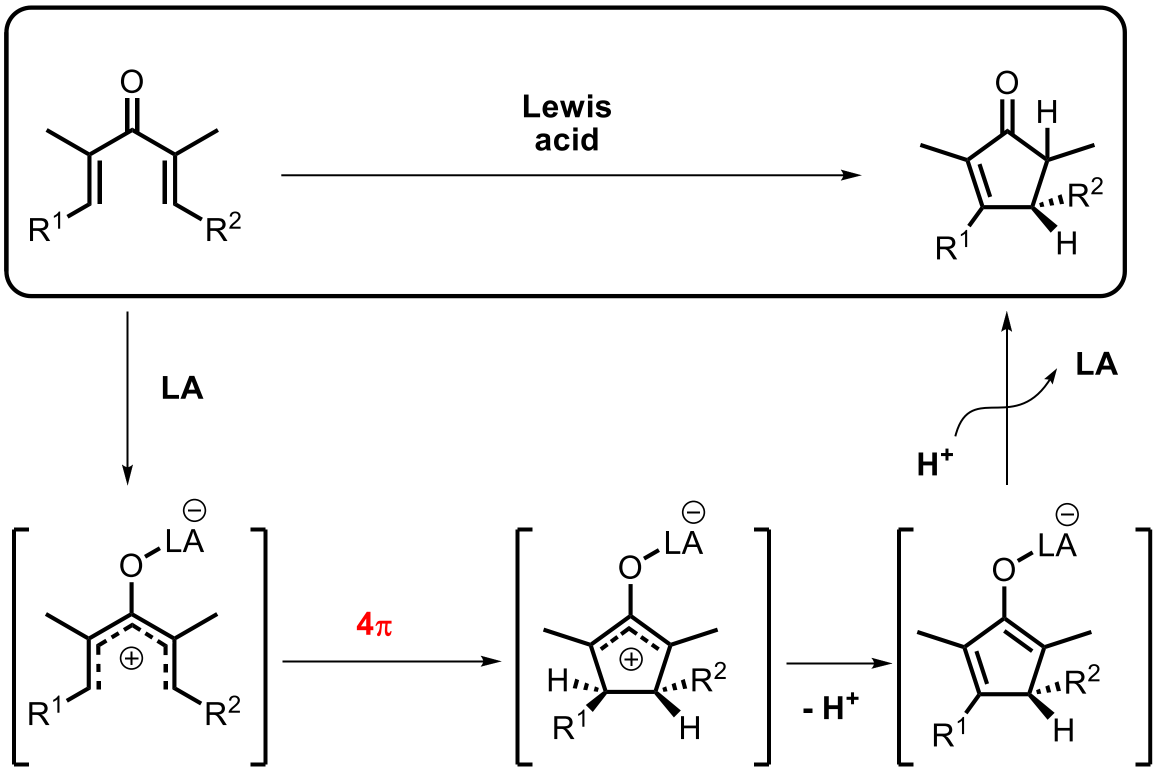
(enol oxidation took place)

Rediscovered by Nazarov (1941)

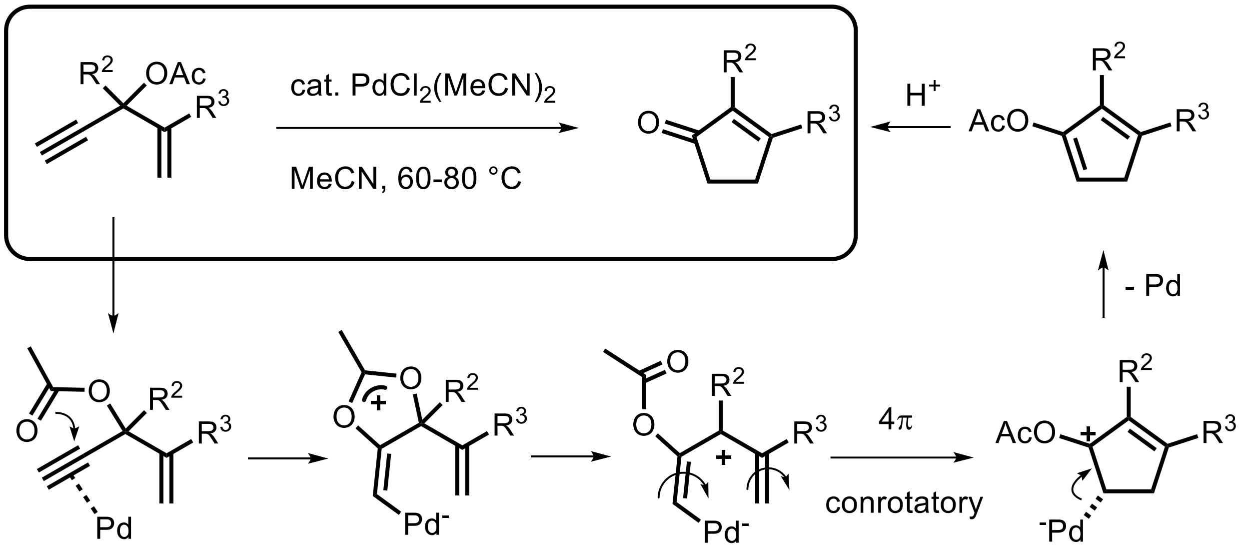


1. NAZAROV TYPE REACTIONS

The Nazarov reaction

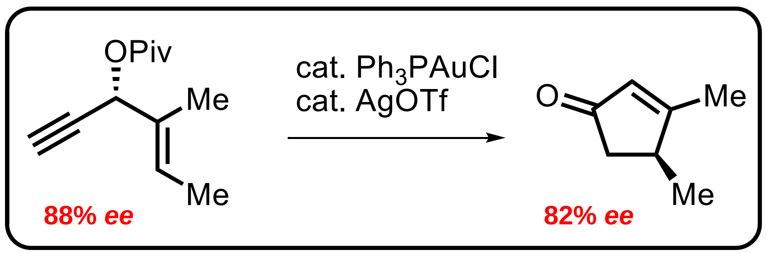


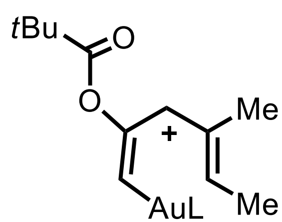
the Rautenstrauch rearrangement



1. NAZAROV TYPE REACTIONS

the Rautenstrauch rearrangement



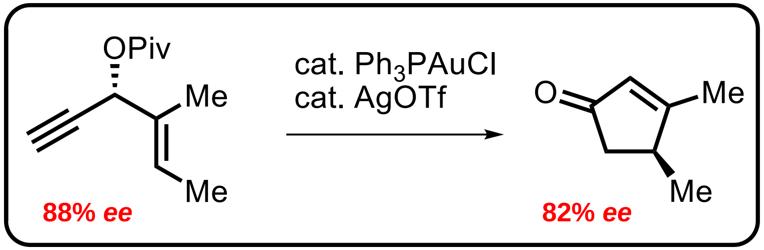


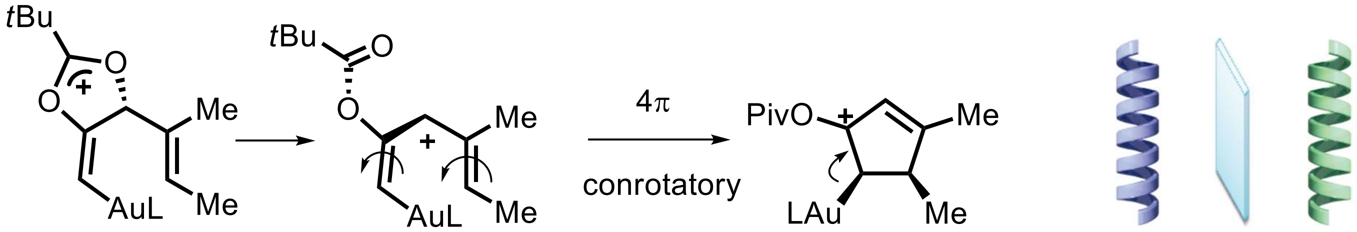
Chirality transfer is possible, how can this be if a carbocation is involved??

Toste F. D. *et al*

1. NAZAROV TYPE REACTIONS

the Rautenstrauch rearrangement



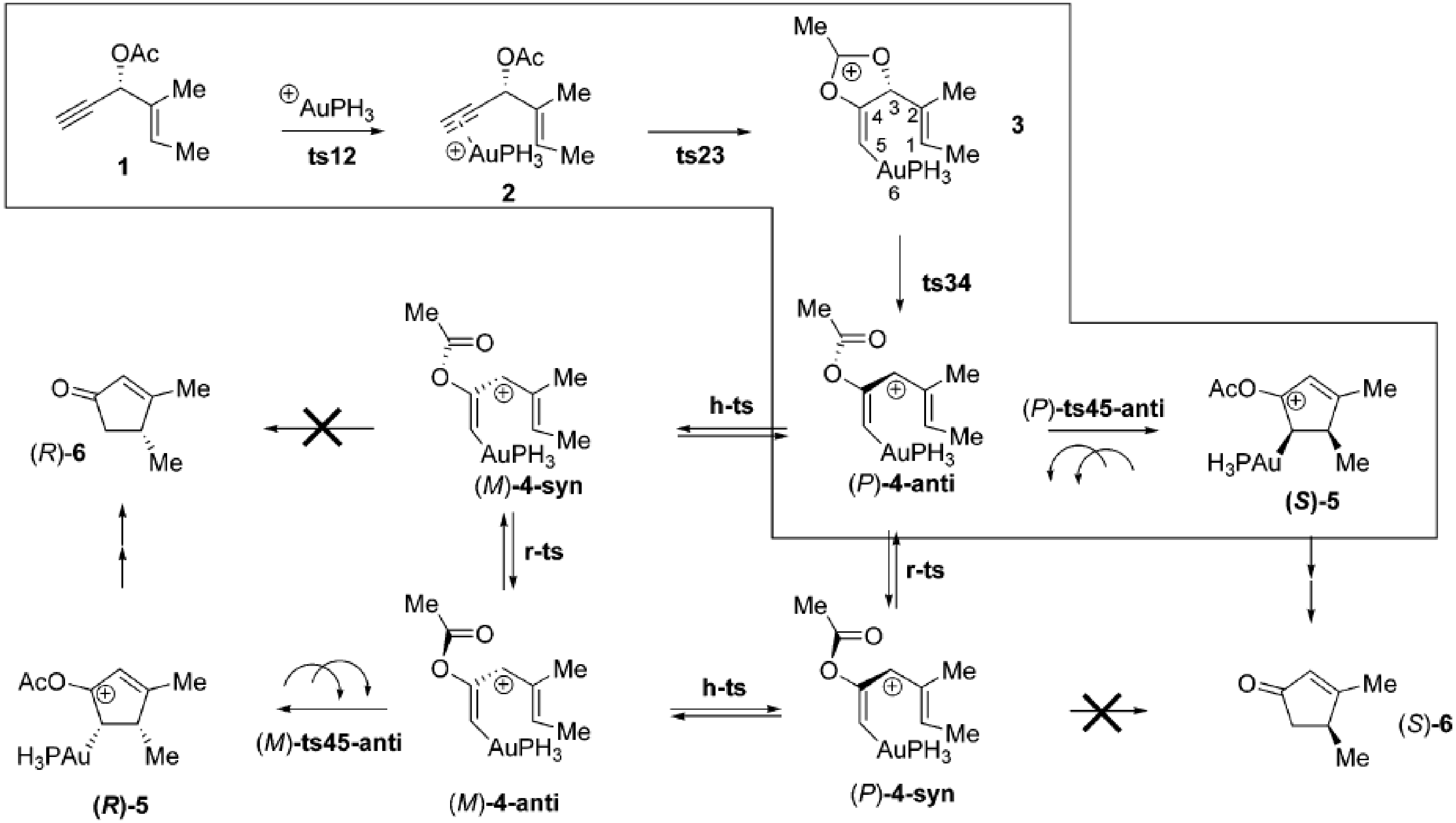


Not planar, chiral

Center-to-Helix-to-Center Chirality Transfer

Toste F. D. *et al*

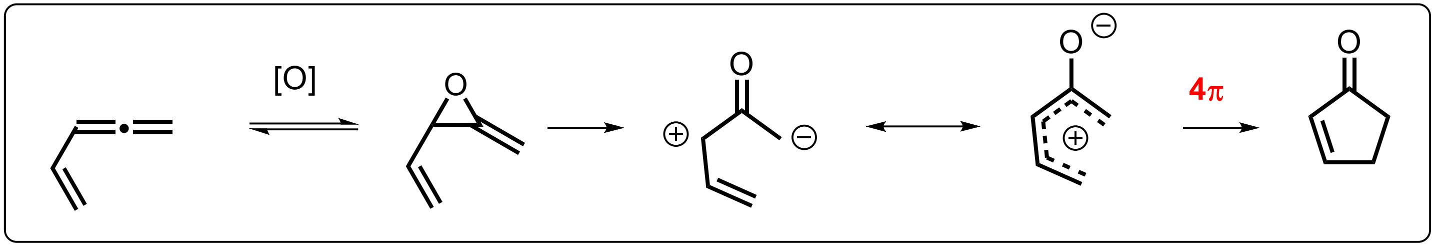
the Rautenstrauch rearrangement

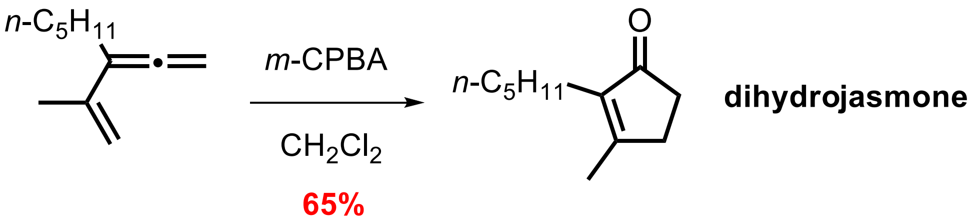


de Lera *et al*

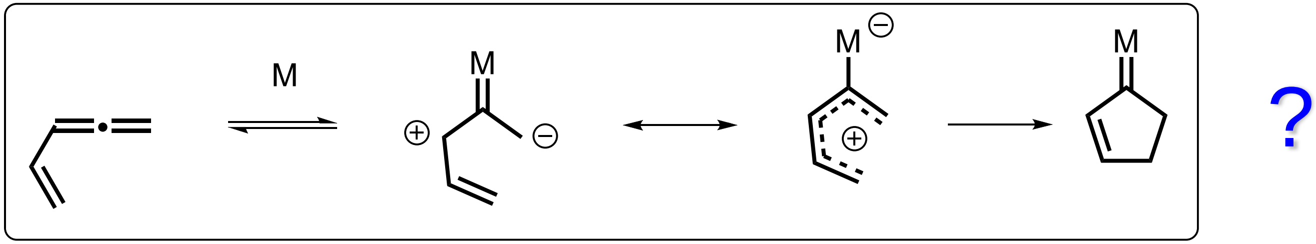
1. NAZAROV TYPE REACTIONS

Metalla-Nazarov reactions



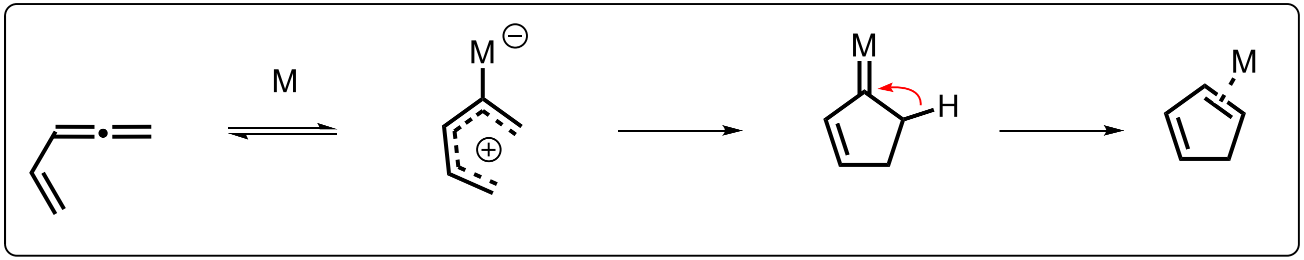


M. L. Roumestant, M. Malacria, J. Goré. J. Grimaldi, M. Bertrand, *Synthesis* **1976**, 755.

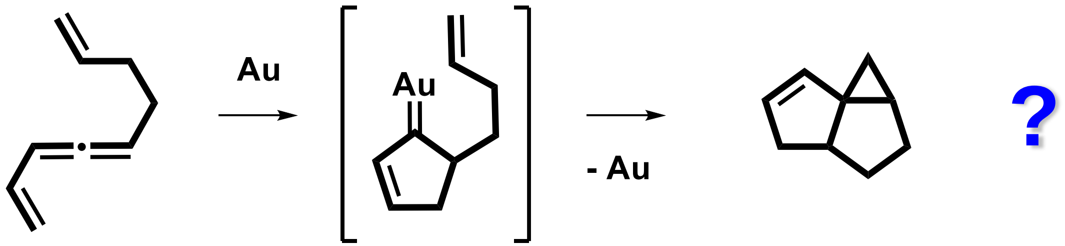


1. NAZAROV TYPE REACTIONS

Metalla-Nazarov reactions

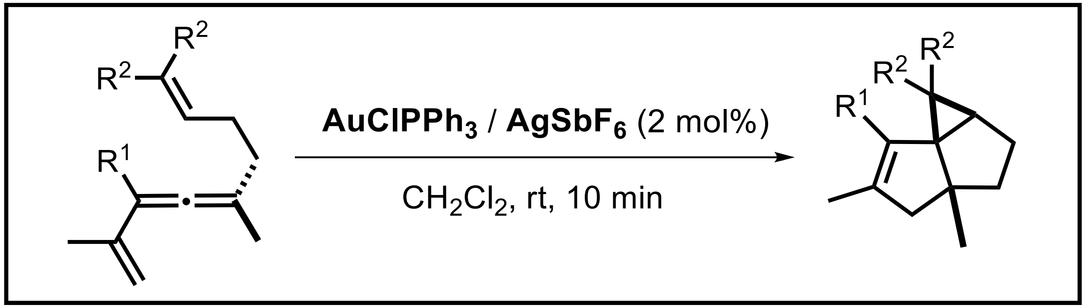


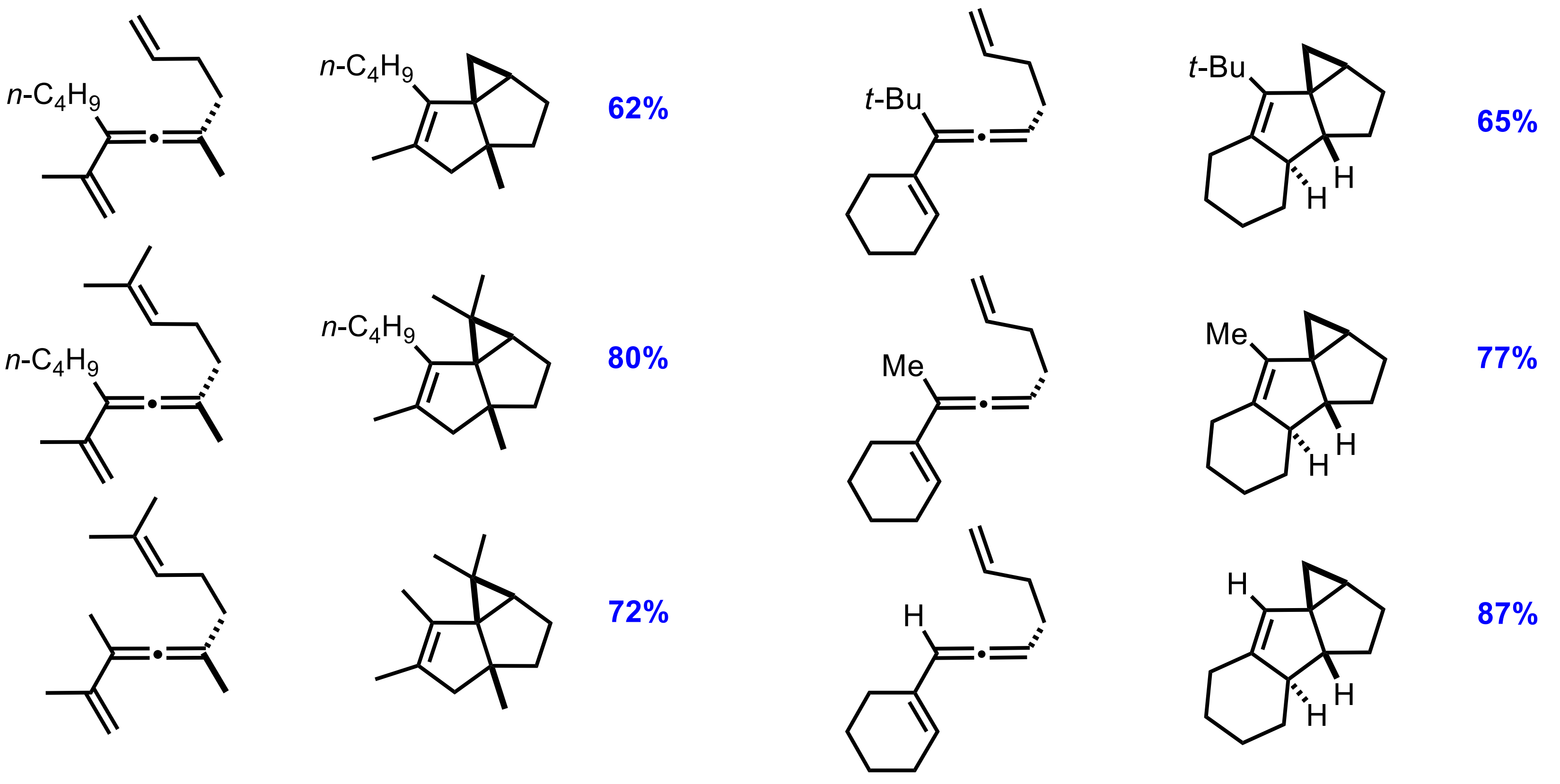
A. Buzas, F. Gagosz, *J. Am. Chem. Soc*. **2006**, *128*, 12614;
Zhang, L.; Wang, S. *J. Am. Chem. Soc*. **2006**, *128*, 1442;
Huang, X.; Zhang, L. *J. Am. Chem. Soc*. **2007**, *129*, 6398;
Lee, J. H.; Toste, F. D. *Angew. Chem. Int. Ed*. **2007**, *46*, 912;
Funami, H.; Kusama, H.; Iwasawa, N. *Angew. Chem. Int. Ed*. **2007**, *46*, 909;
Trillo, B.; López, F.; Gulías, M.; Castedo, L.; Mascareñas, J. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 951
….



Fensterbank, Malacria *et al*

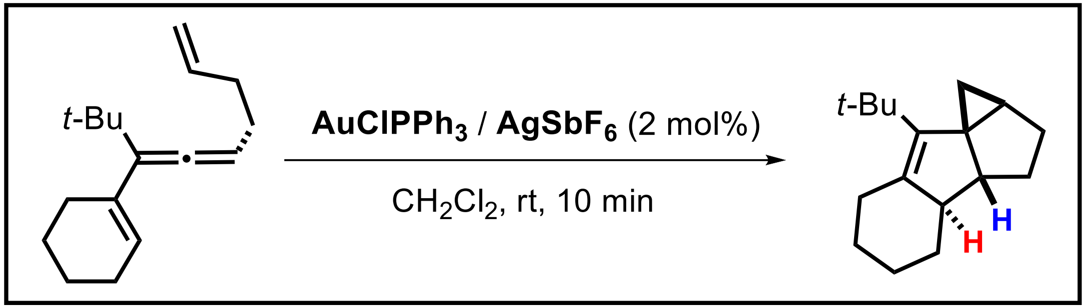
1. NAZAROV TYPE REACTIONS

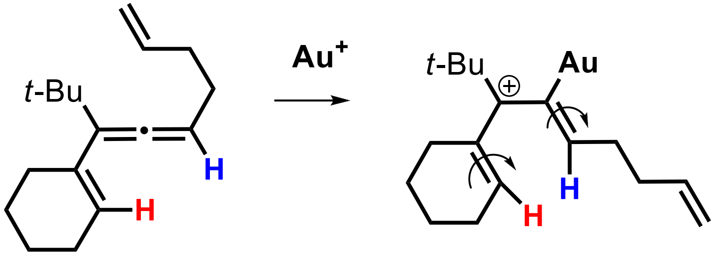




Fensterbank, Malacria *et al*

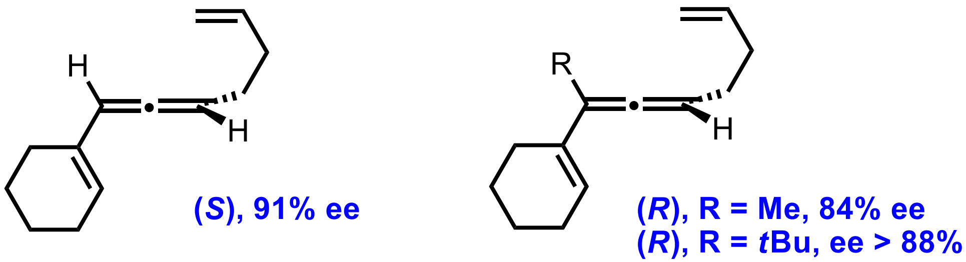
Metalla-Nazarov reactions





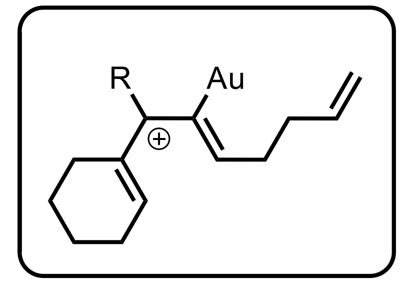
Fensterbank, Malacria *et al*

Metalla-Nazarov reactions



AuCl(PPh$_3$) (2 mol%)
AgSbF$_6$ (2 mol%)
CH_2Cl_2, –20 °C, 2 h

How can a chirality transfer (axis to center) be possible through a carbocation??



0% ee

R = Me, 84% ee
R = *t*Bu, 88% ee

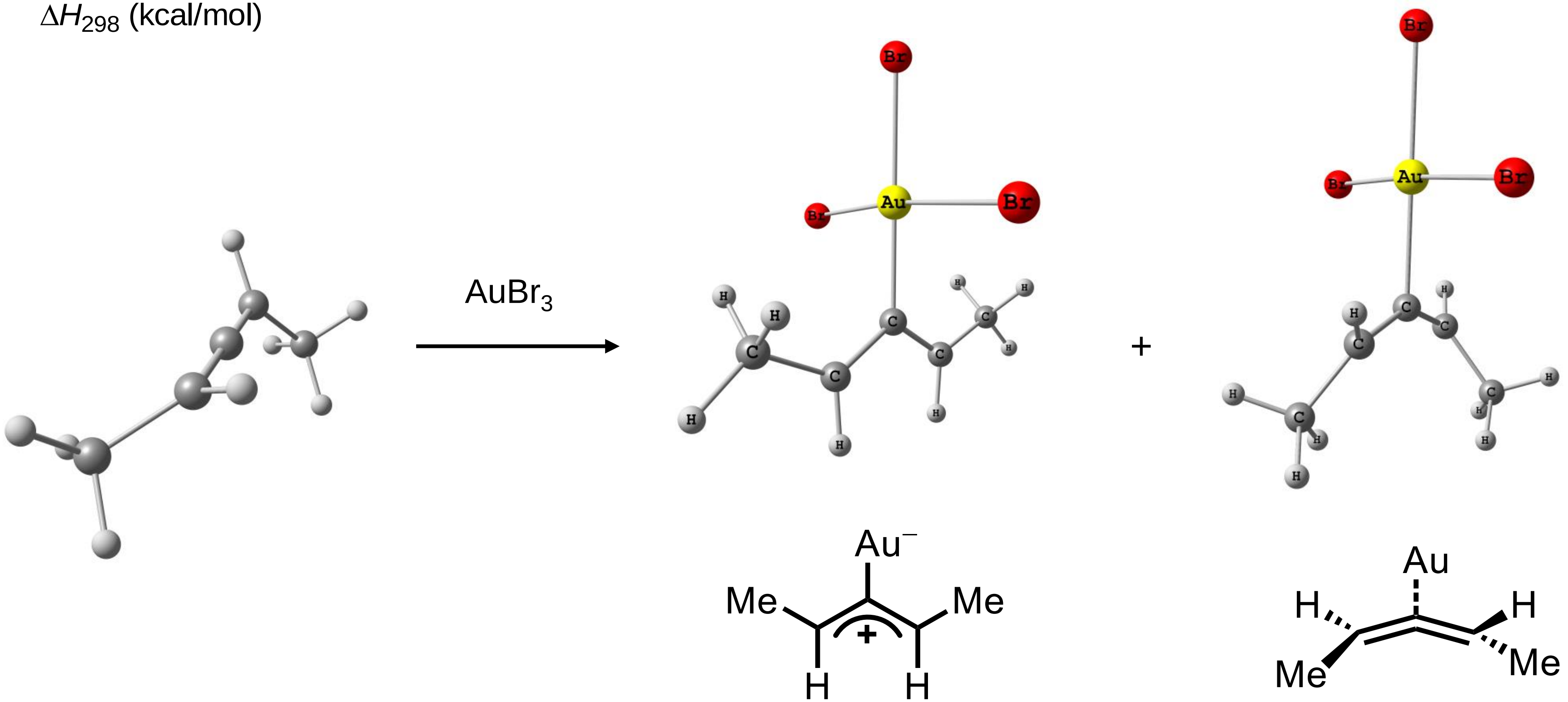
Fensterbank, Malacria *et al*

1. NAZAROV TYPE REACTIONS

DFT/B3LYP LACVP(d,p)

ΔH_{298} (kcal/mol)

Vinyl Cations *vs* Bent Allene Complexes

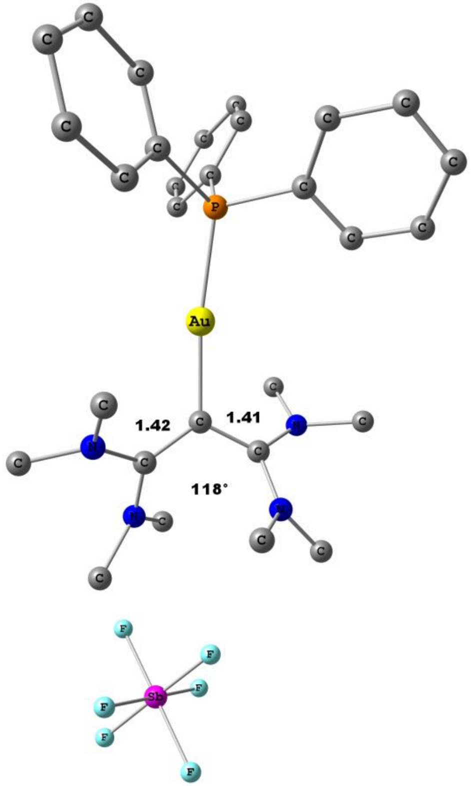


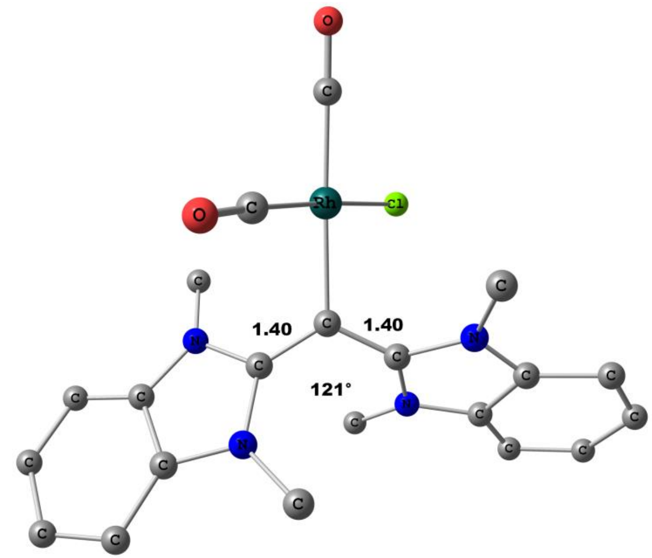
0.0
(achiral)

1.4 (helically chiral but racemizes rapidly)

Fensterbank, Malacria *et al*

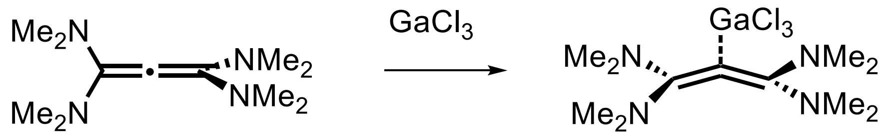
Bent Allenes Are Not Just Computational Curiosities

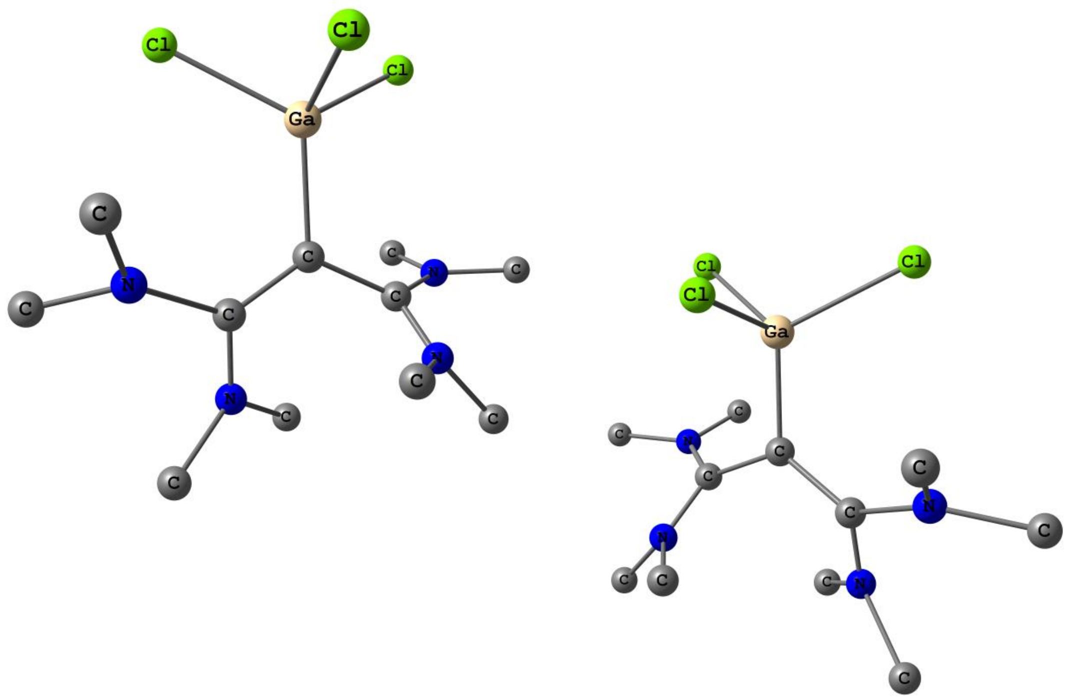




G. Bertrand *et al*
A. Fürstner *et al*

Bent Allenes Are Not Just Computational Curiosities



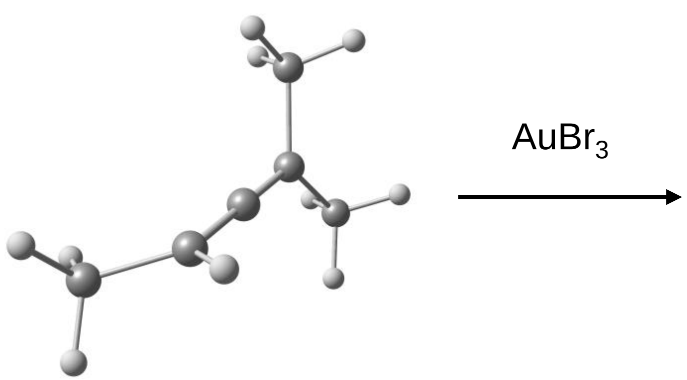


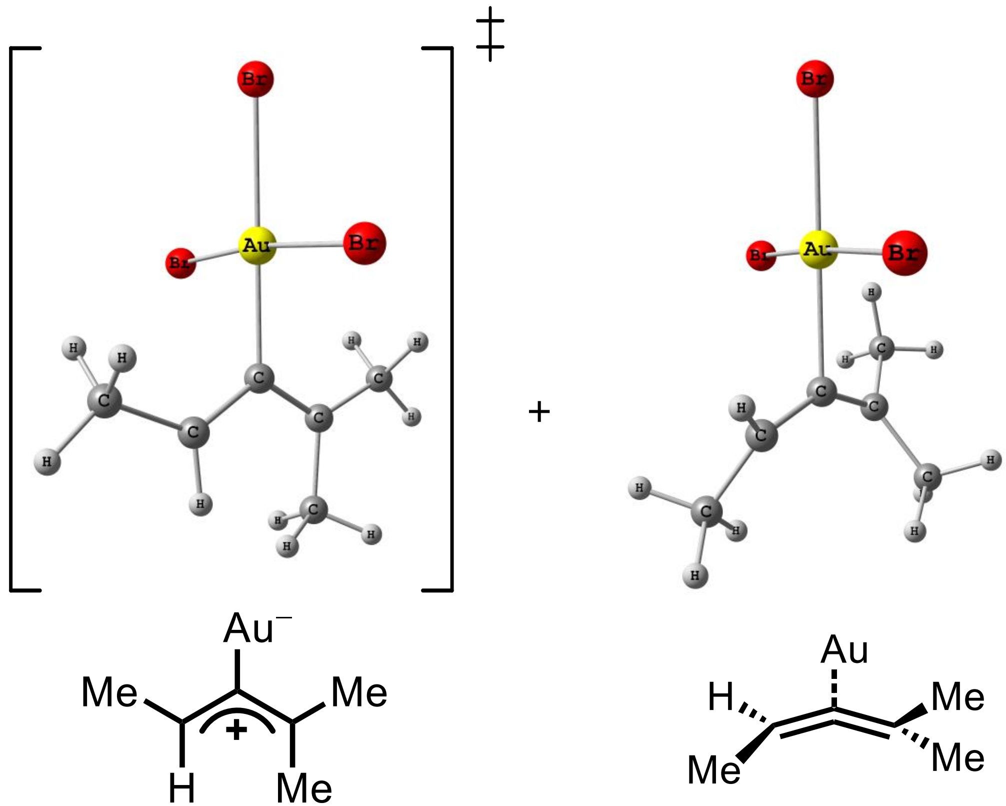
“The unit cell of this bent allene complex contains two enantiomers, which is consistent with the fact that bent allene complexes can be helically chiral”

Vinyl Cations *vs* Bent Allene Complexes

DFT/B3LYP LACVP(d,p)

ΔH_{298} (kcal/mol)



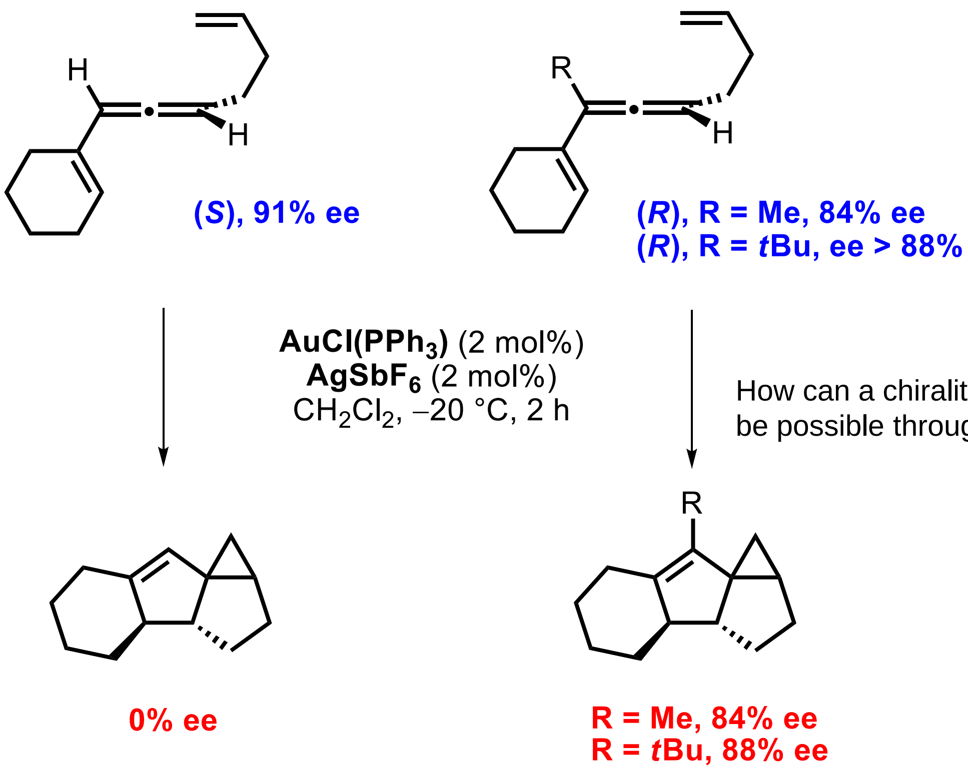


10.0
(racemization TS of the bent allene complex)

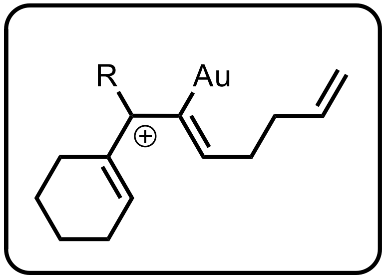
0.0
(helically chiral)

Fensterbank, Malacria *et al*

Metalla-Nazarov reactions



How can a chirality transfer (axis to center) be possible through a carbocation??



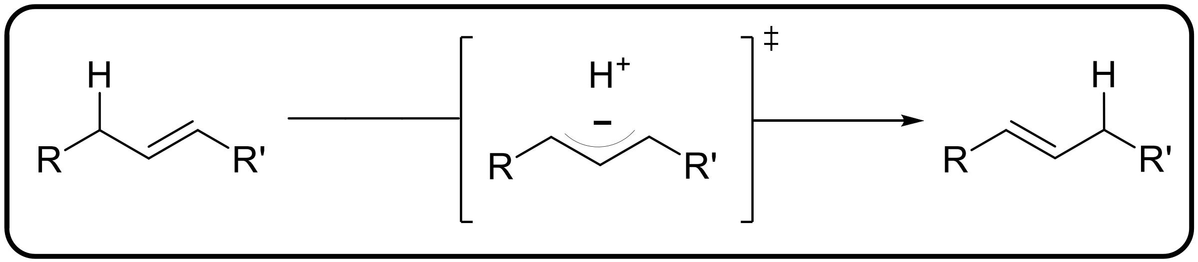
Not planar, chiral

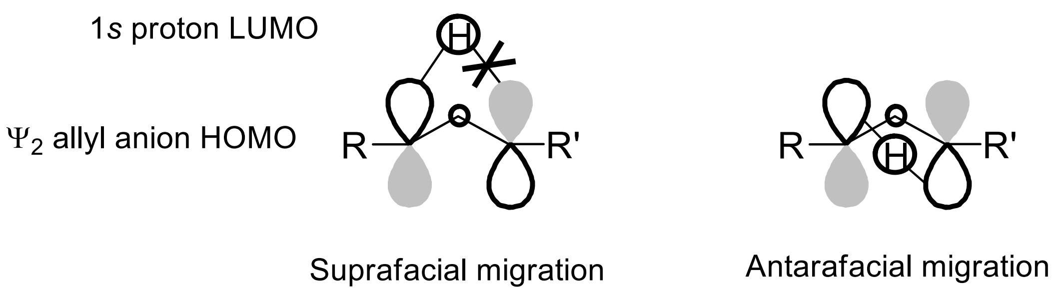
Axial-to-Helix-to-Center Chirality Transfer

Fensterbank, Malacria *et al*

1. CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS

- *[1,3] Sigmatropic Rearrangements: H migration*

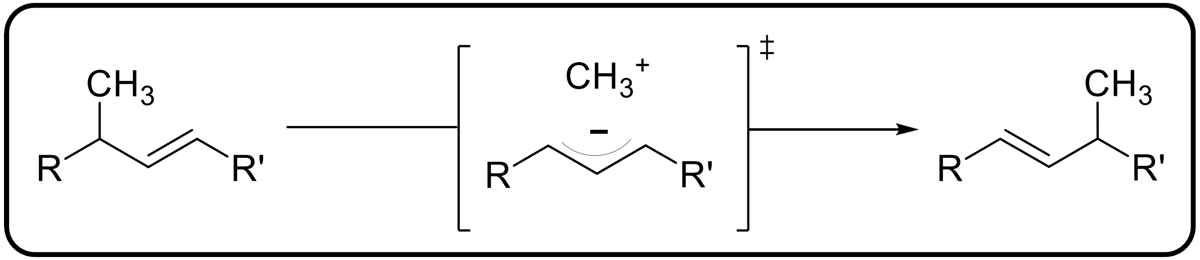


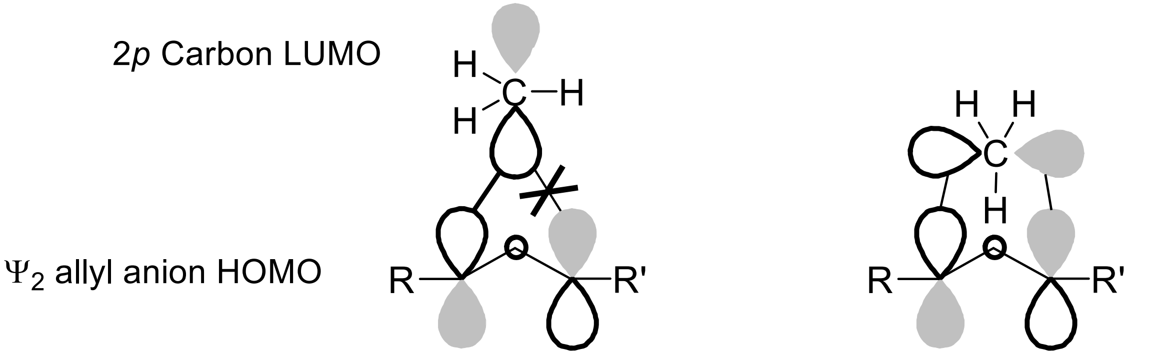


FORBIDDEN

ORBITALLY ALLOWED BUT H CANNOT BRIDGE DISTANCE

- ***[1,3] Sigmatropic Rearrangements: C migration***





Suprafacial migration
Retention at carbon

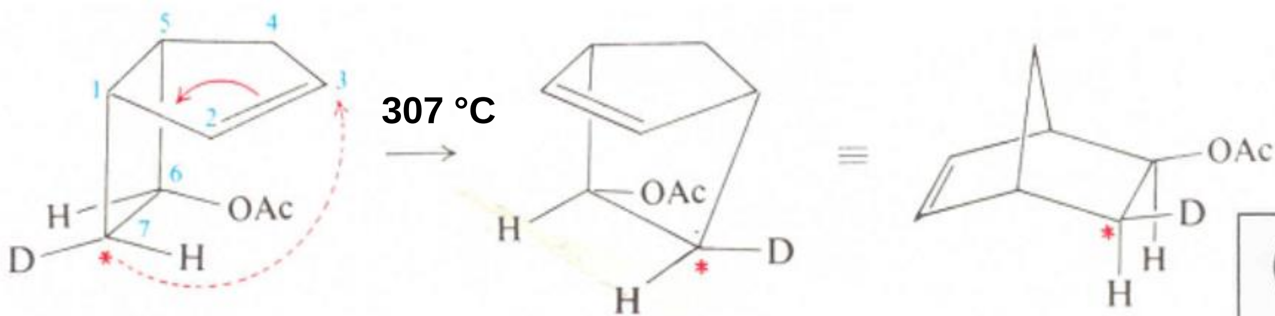
FORBIDDEN

Suprafacial migration
Inversion at carbon

ALLOWED

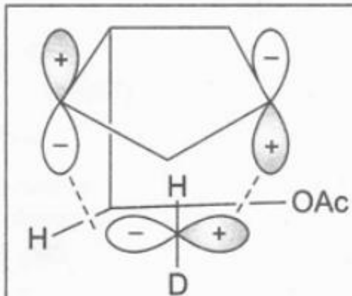
CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS

classical example: [1,3] carbon migration



V VI

Figure 33.25 The deuterium-labeled bicyclo[3.2.0]heptene V rearranges via a [1,3]-C shift to the norbornene VI. There is *inversion of configuration* at C–7: from *R* to *S*. (Or, using C–6 as our standard, we see that H eclipses OAc in V, and D eclipses OAc in VI.)

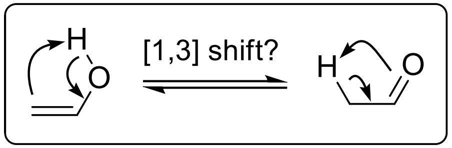


(II)
Transition state

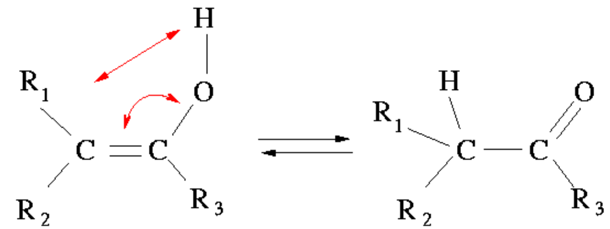
➢ This reaction proceeds by a [1,3] migration and with *complete inversion of configuration in the migrating group*.[1]

Berson et al *J. Am. Chem. Soc*. **1967**, *89*, 1043 (with a timid citation of Woodward and Hoffmann)

Keto-enol tautomerism, a [1,3] sigmatropic shift?

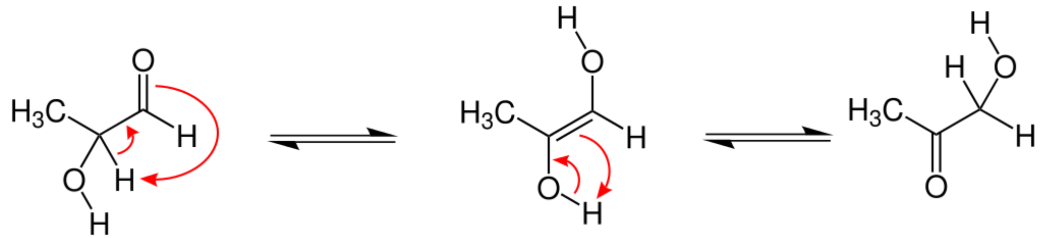


Wikipedia in French:

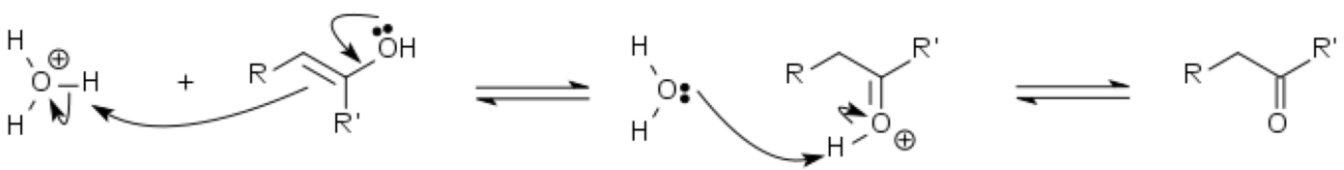


Enfin corrigé en 2019 …

Wikipedia in German:



Wikipedia in English:

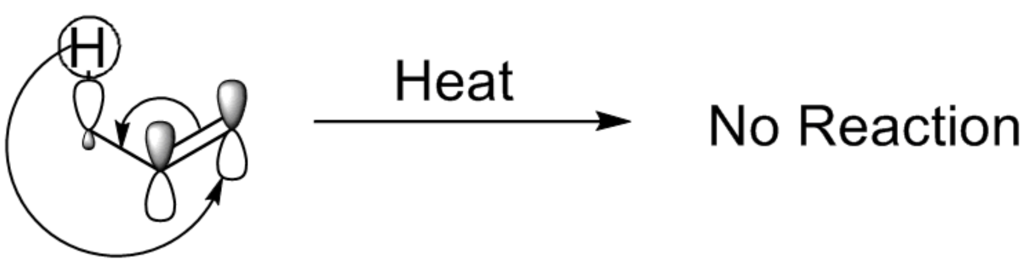


Keto-enol tautomerism, a [1,3] sigmatropic shift?

Wikipedia in English:

In a thermal [1,3] hydride shift, a hydride moves along three atoms. The Woodward–Hoffmann rules dictate that it would proceed in an antarafacial shift. Although such a shift is symmetry allowed, the Mobius topology required in the transition state prohibits such a shift because it is geometrically impossible, which accounts for the fact that enols do not isomerize without an acid or base catalyst.

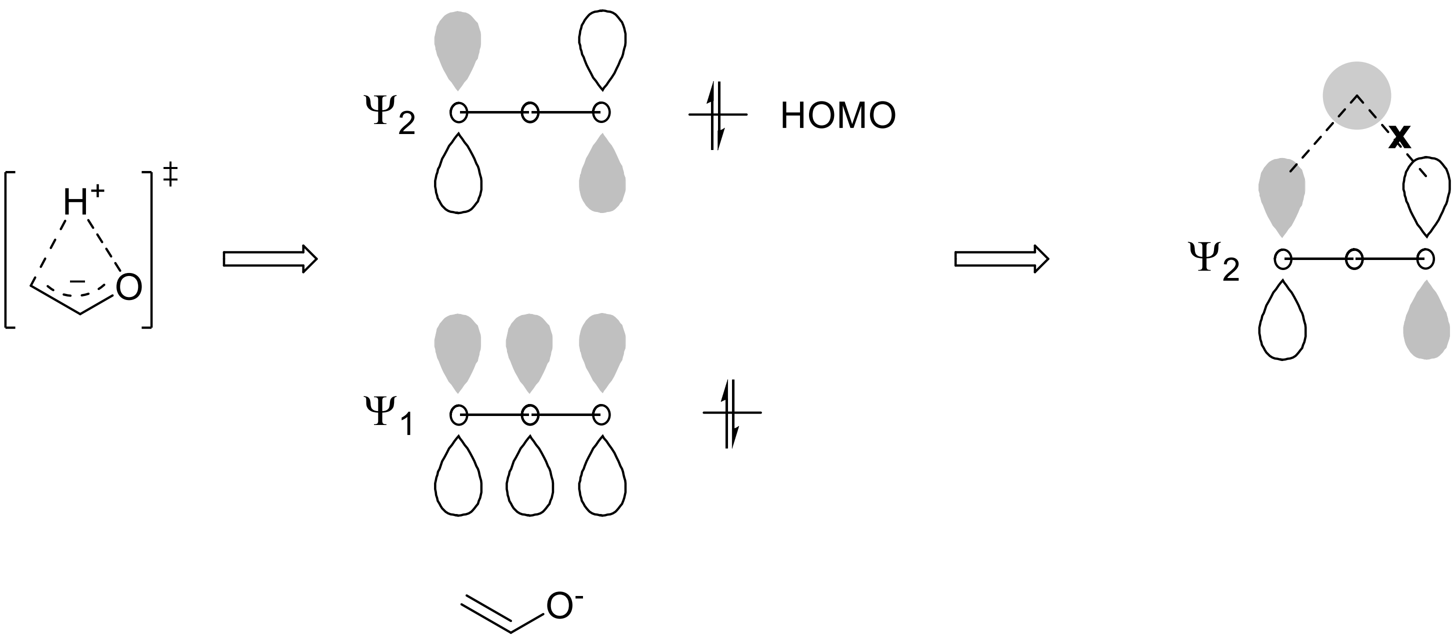
Geometrically impossible [1,3] Hydride Shift



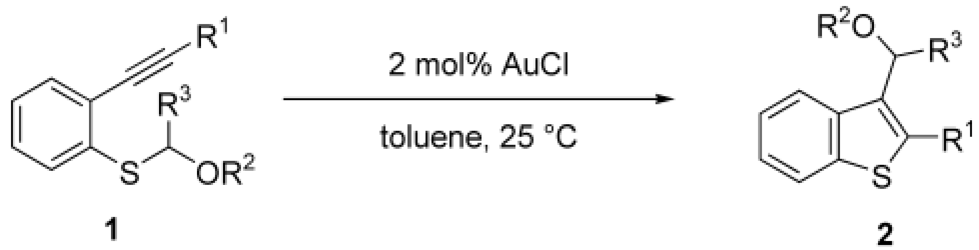
Keto-enol tautomerism, no arrows!

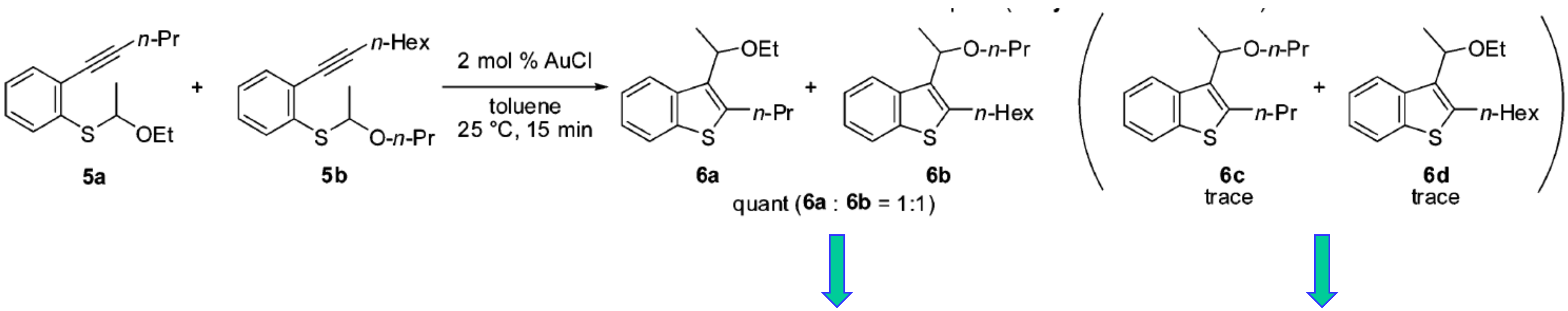
Wikipedia in English:

In a thermal [1,3] hydrogen shift, a hydrogen moves along three atoms. The Woodward–Hoffmann rules dictate that it would proceed in an antarafacial shift. Although such a shift is symmetry allowed, the Mobius topology required in the transition state prohibits such a shift because it is geometrically impossible, <u>which accounts for the fact that enols do not isomerize without an acid or base catalyst.</u>



1. CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS



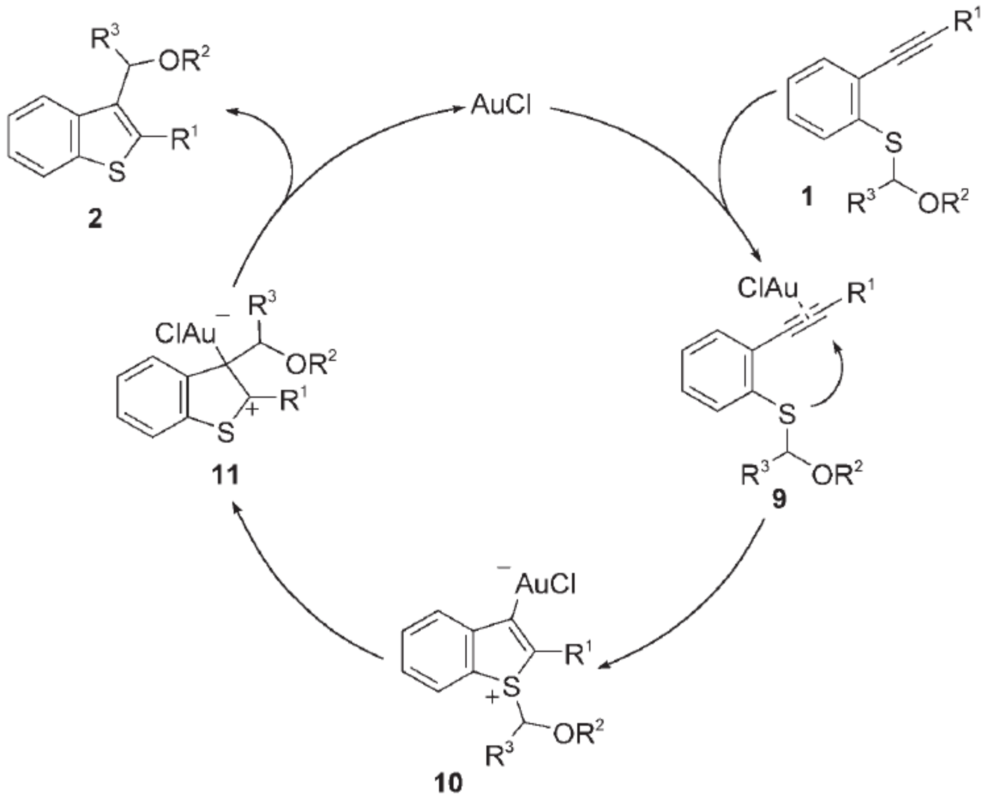


Normal products

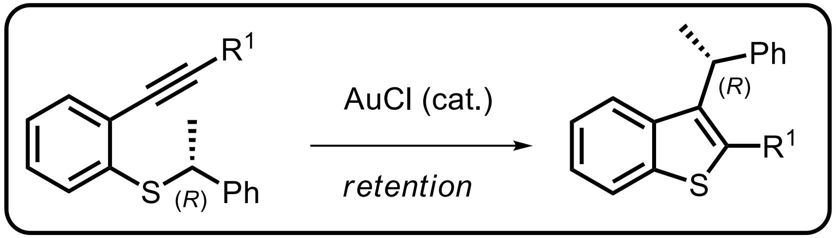
Crossover products

Yamamoto, Y. *et al*

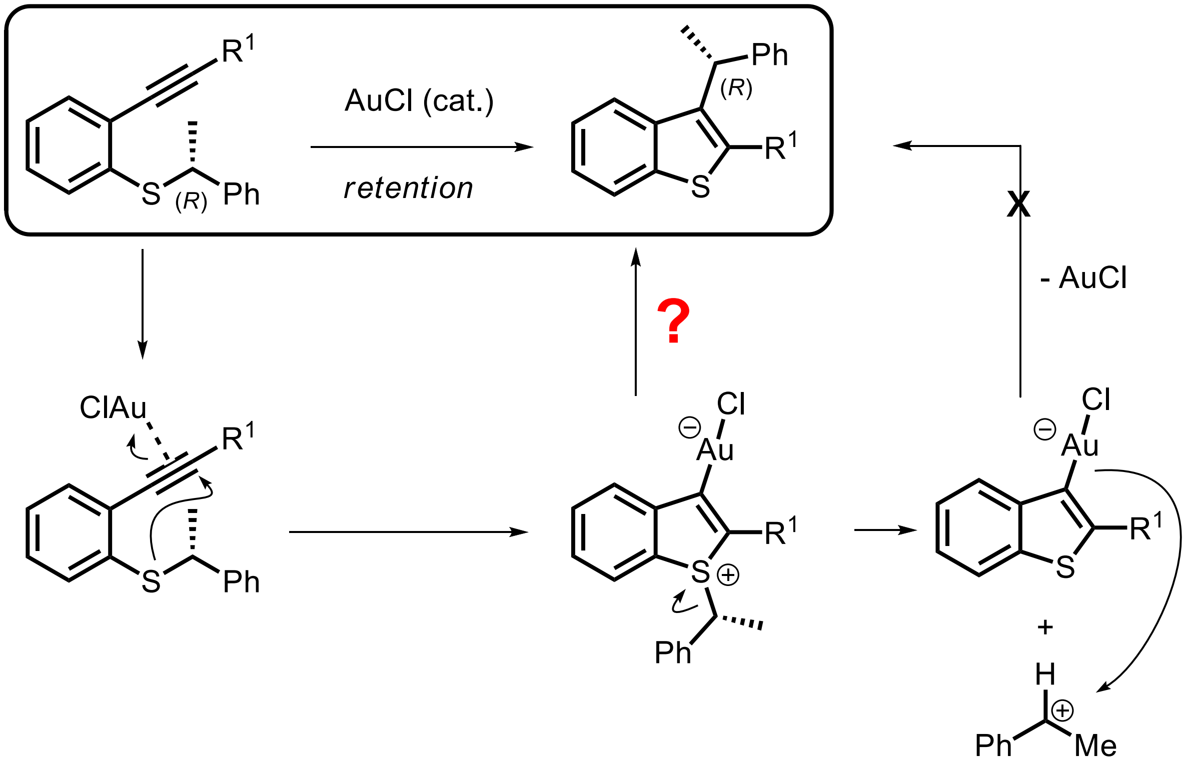
CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS



1. CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS

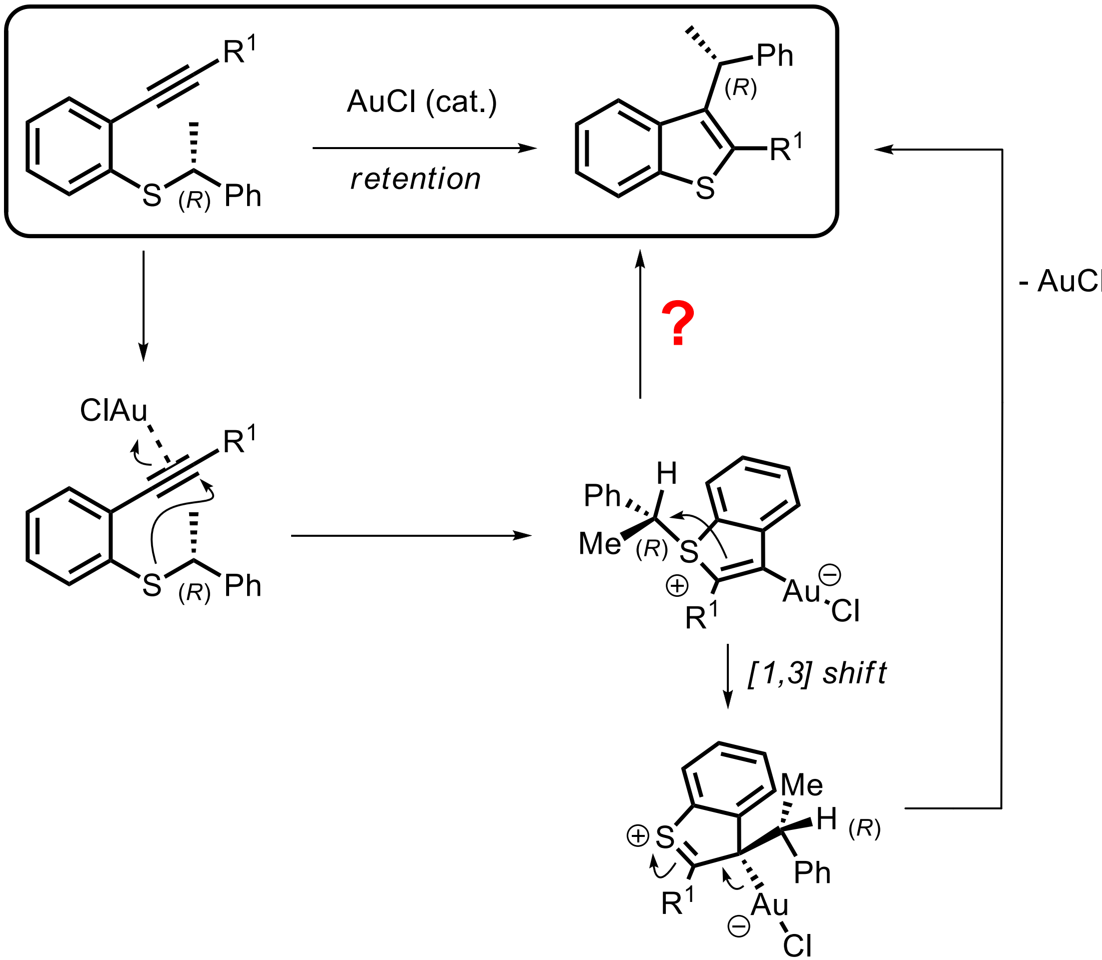


1. CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS

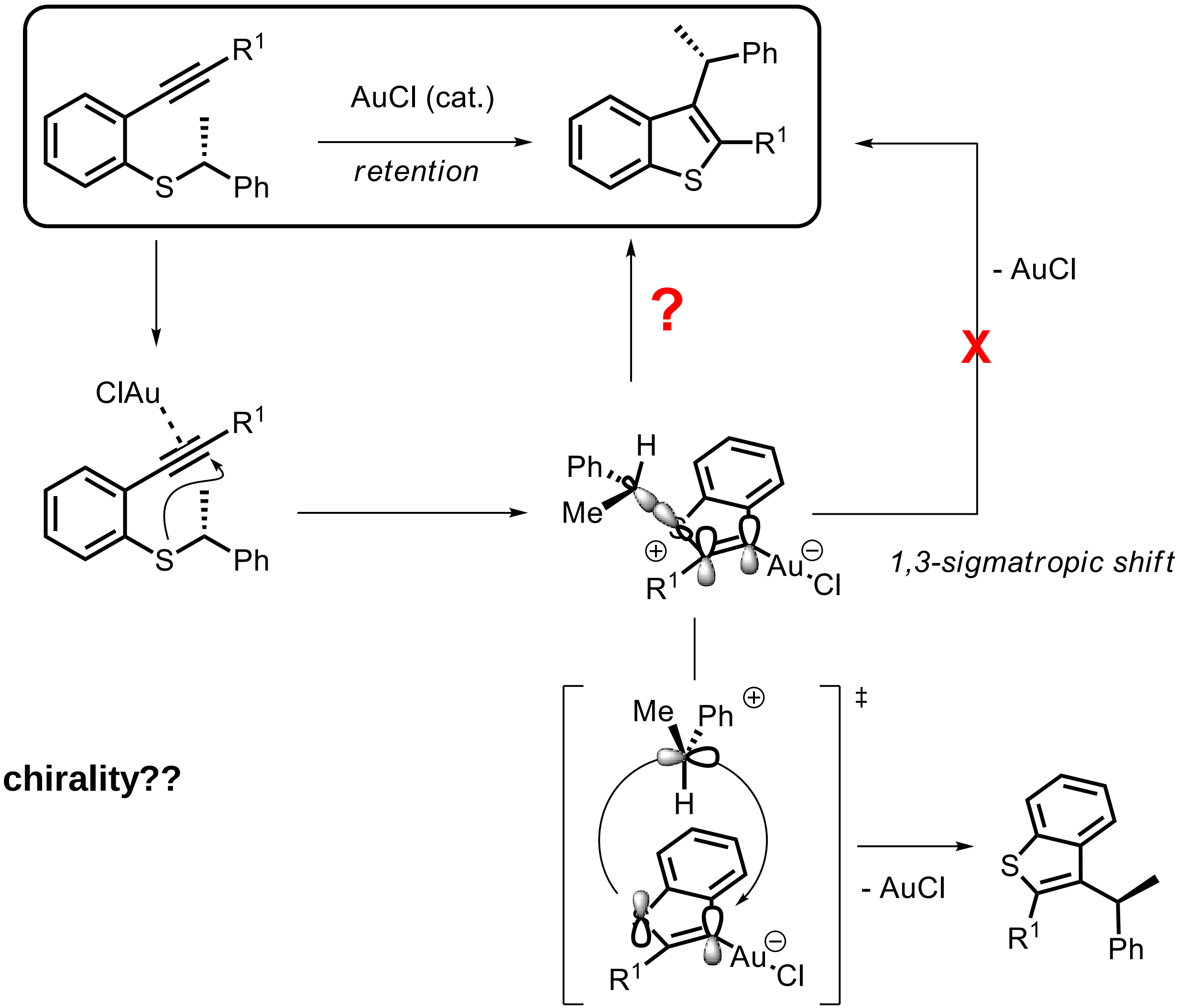


Walden retention seems impossible

1. CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS

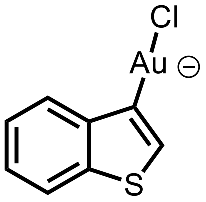


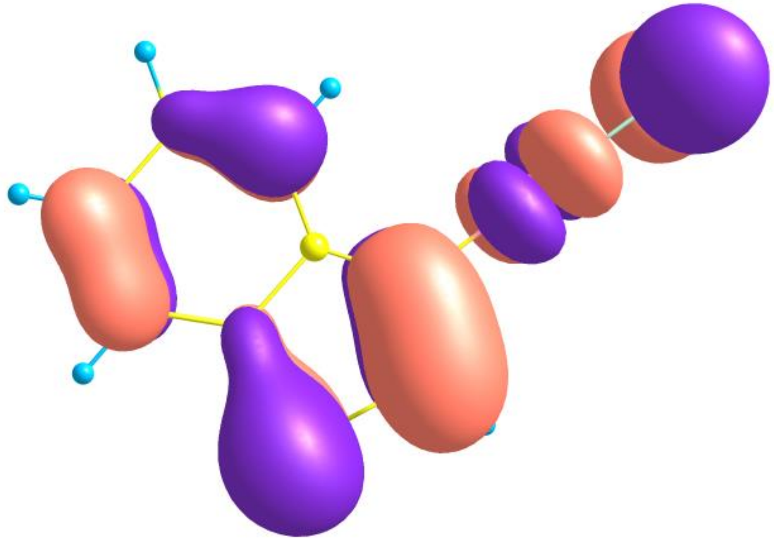
1. CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS



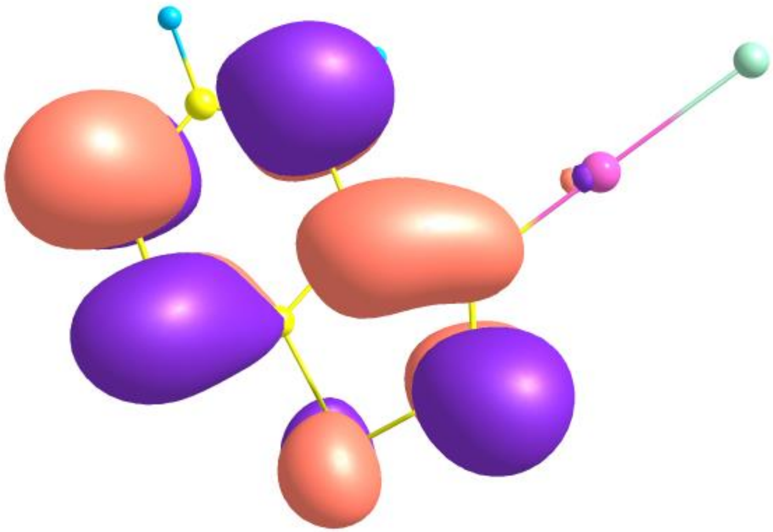
Memory of chirality??

CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS



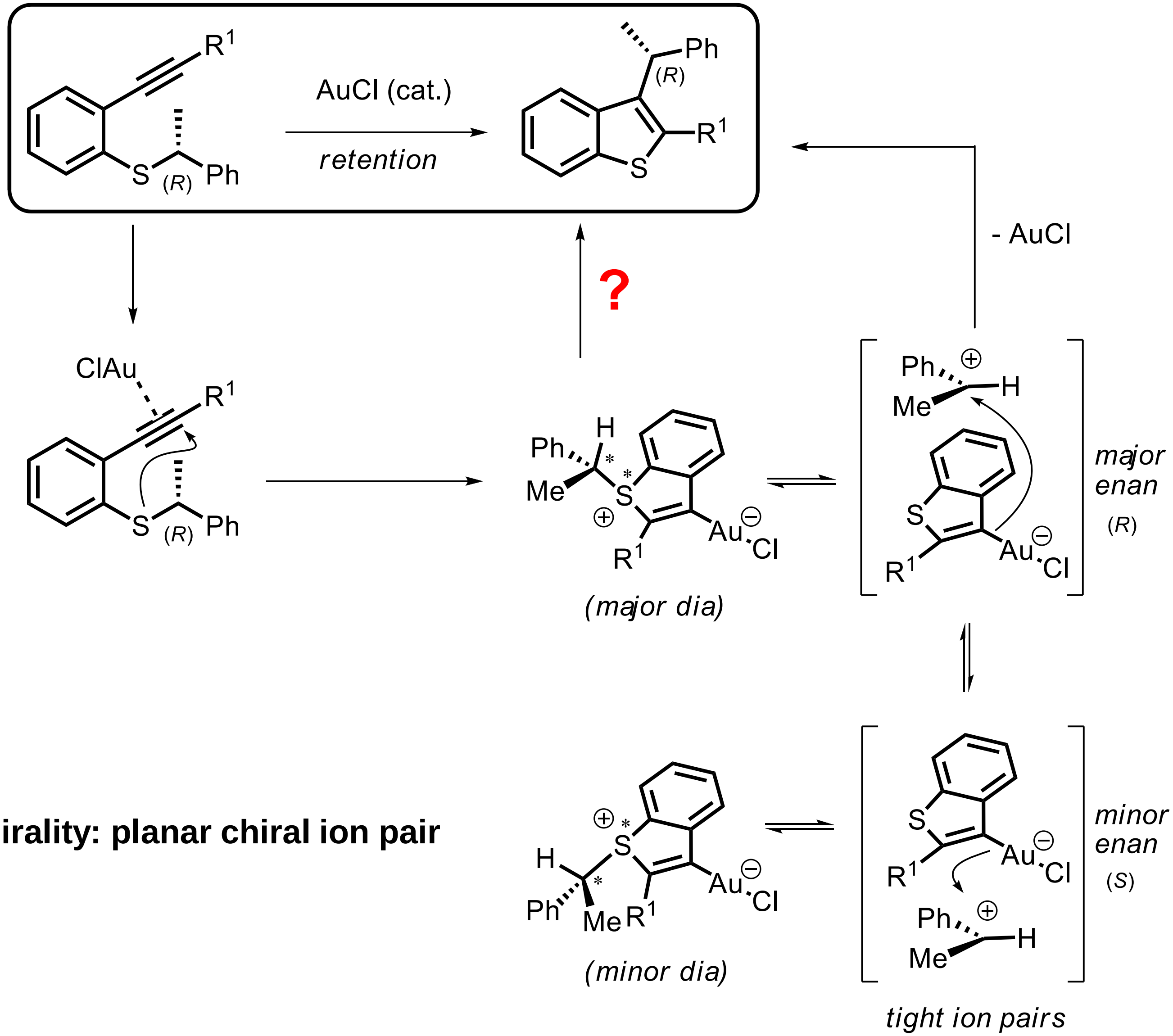


HOMO

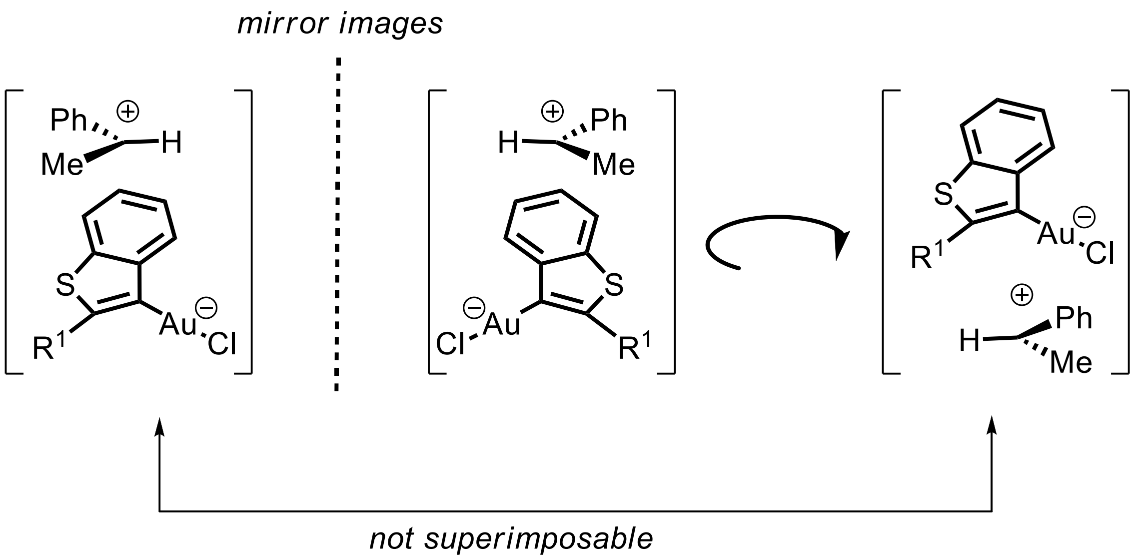


LUMO

CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS



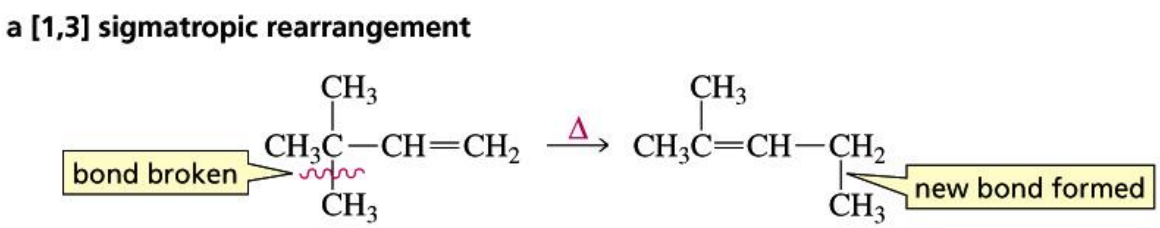
Memory of chirality: planar chiral ion pair



Memory of chirality: planar chiral ion pair

1. CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS

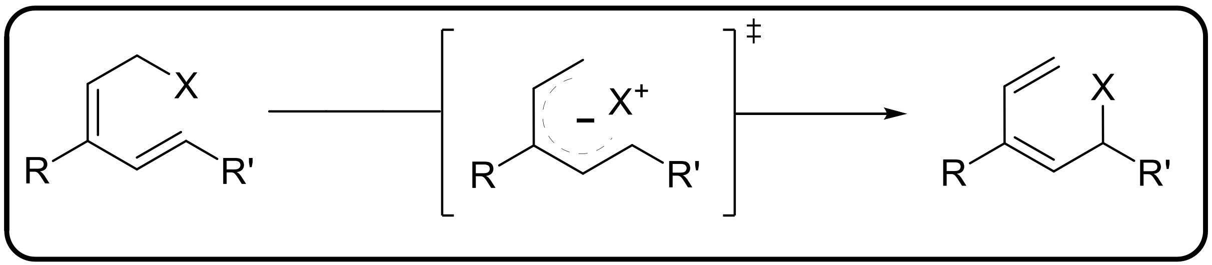
The [1,3]-sigmatropic rearragement appears in many textbook …



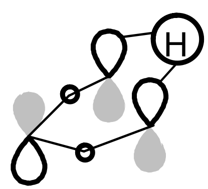
… but it is suspicious

CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS

- ***[1,5] Sigmatropic Rearrangements***



Ψ_3 pentadienyl anion HOMO

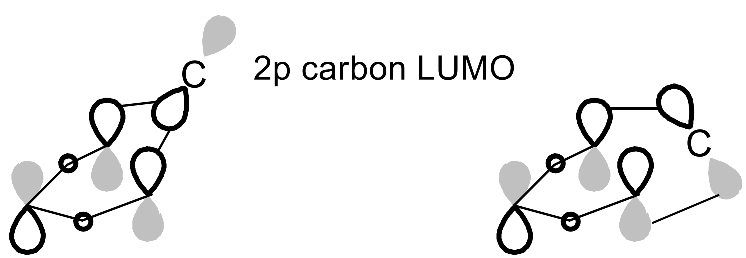


1s proton LUMO

Suprafacial migration
ALLOWED

Antarafacial migration
FORBIDDEN

Ψ_3 pentadienyl anion HOMO

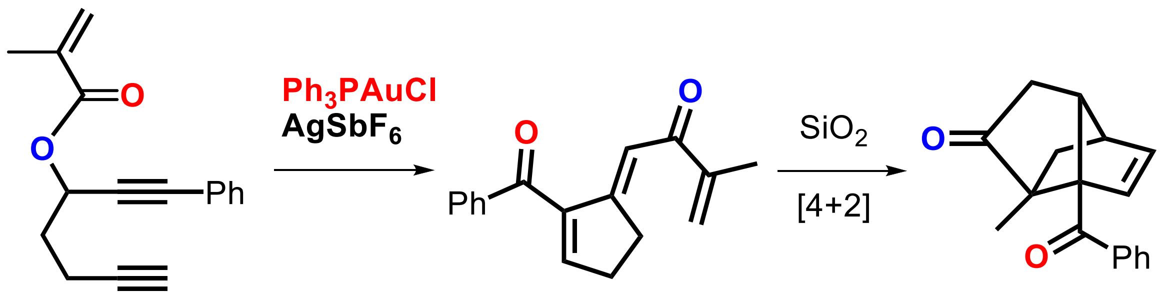


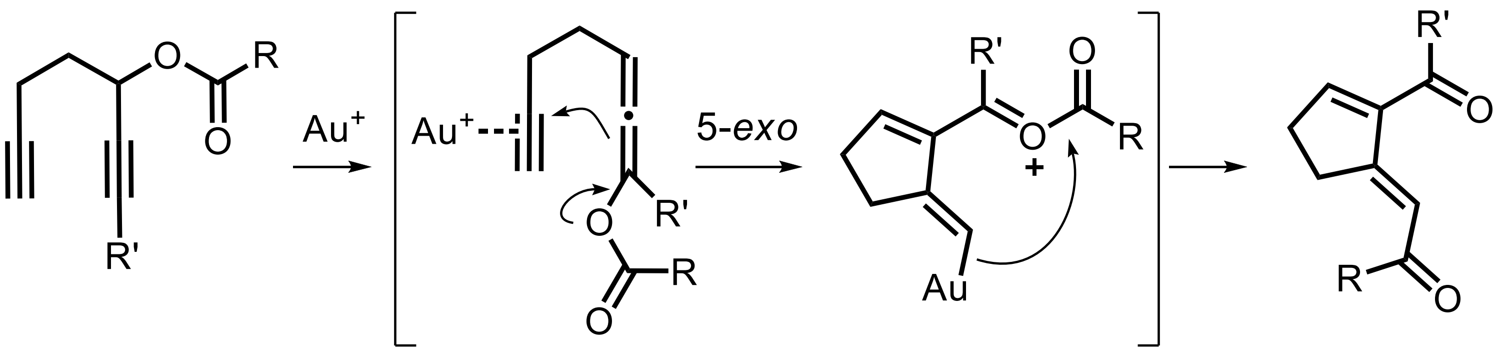
2p carbon LUMO

Suprafacial migration
Retention at Carbon
ALLOWED

Antarafacial migration
Inversion at Carbon
ALLOWED

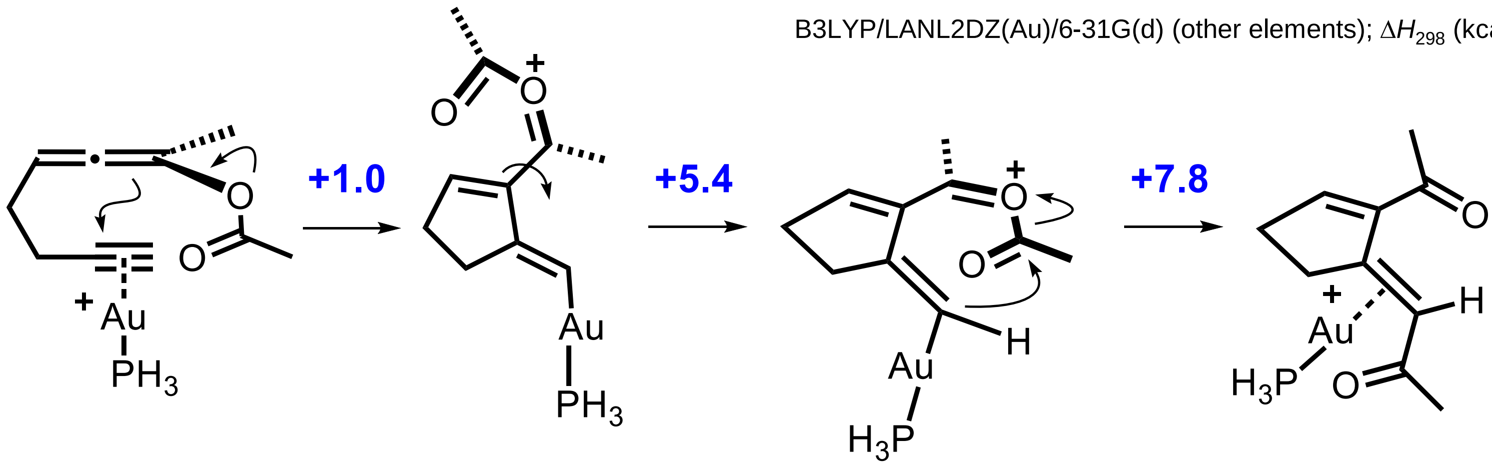
- *[1,5] Sigmatropic Rearrangements*



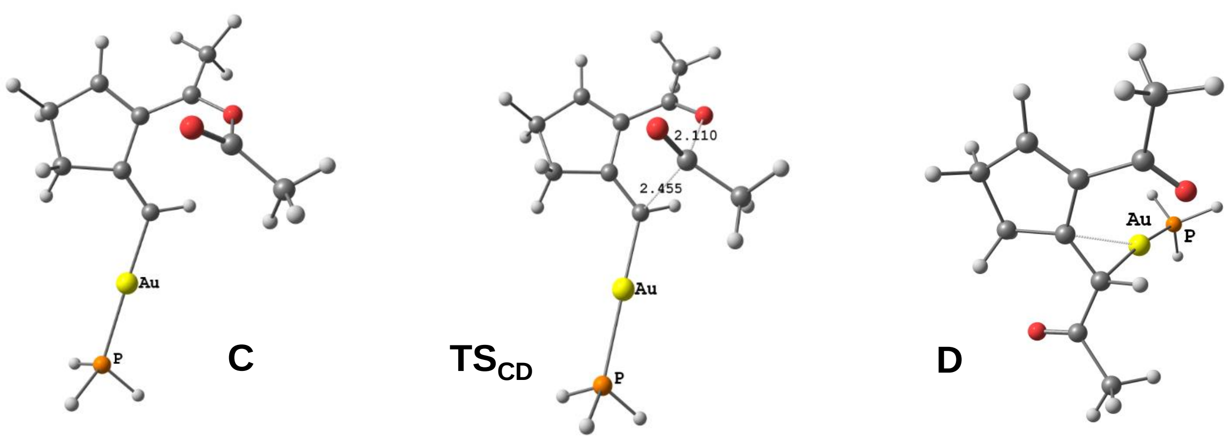


- ***[1,5] Sigmatropic Rearrangements***

B3LYP/LANL2DZ(Au)/6-31G(d) (other elements); ΔH_{298} (kcal/mol)



A (0.0) **B (-28.2)** **C (-29.5)** **D (-57.8)**

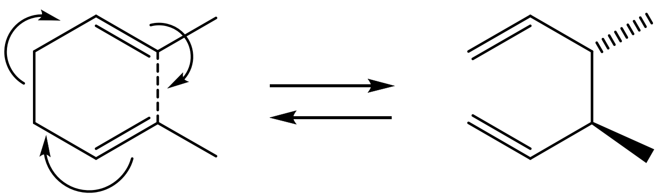


C TS$_{CD}$ D

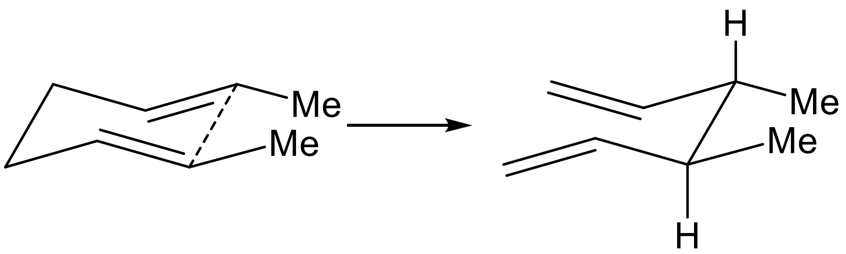
CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS

- *[3,3] Sigmatropic Rearrangements*

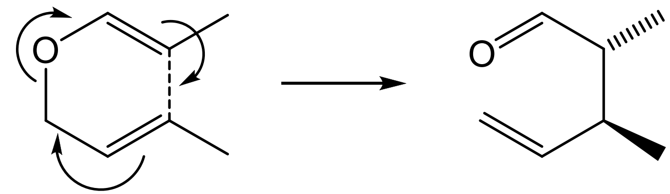
COPE rearrangement



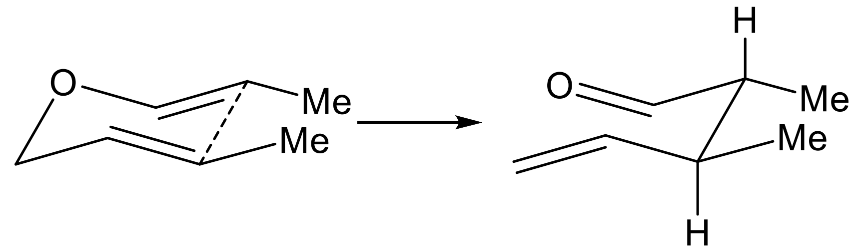
often reversible



CLAISEN rearrangement



usually irreversible



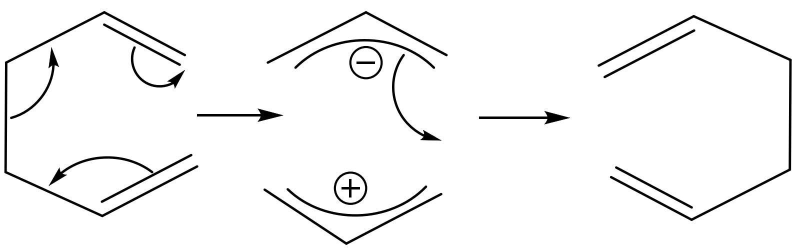
Both reactions proceed via a chair-like transition state.

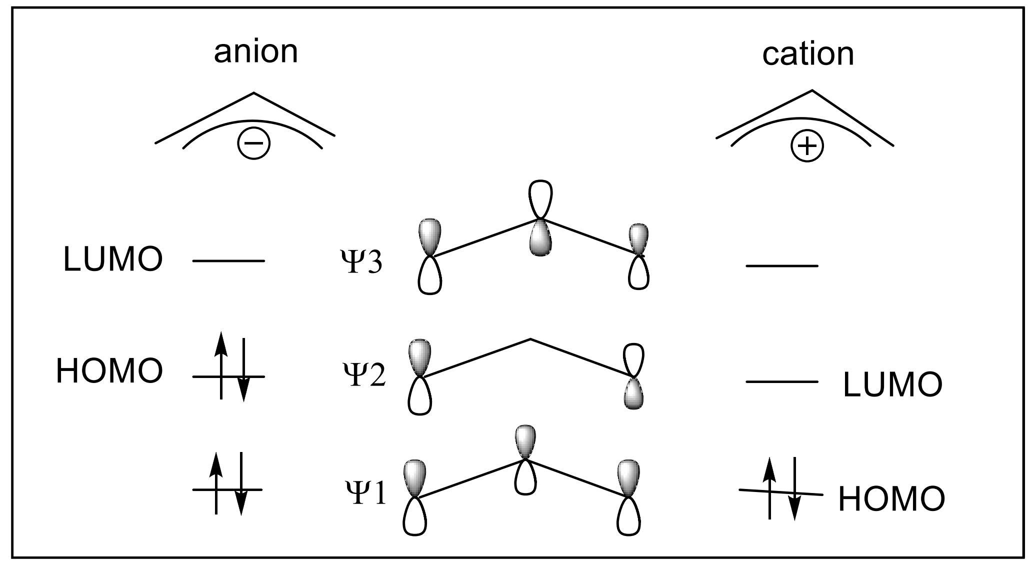
Suprafacial/suprafacial

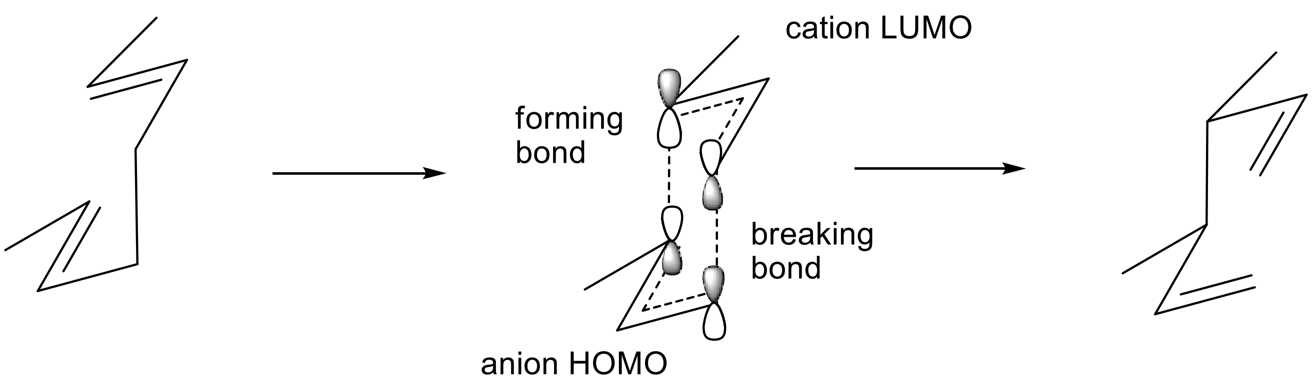
1. CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS

- ***[3,3] Sigmatropic Rearrangements***

Think of reaction as cation + anion:



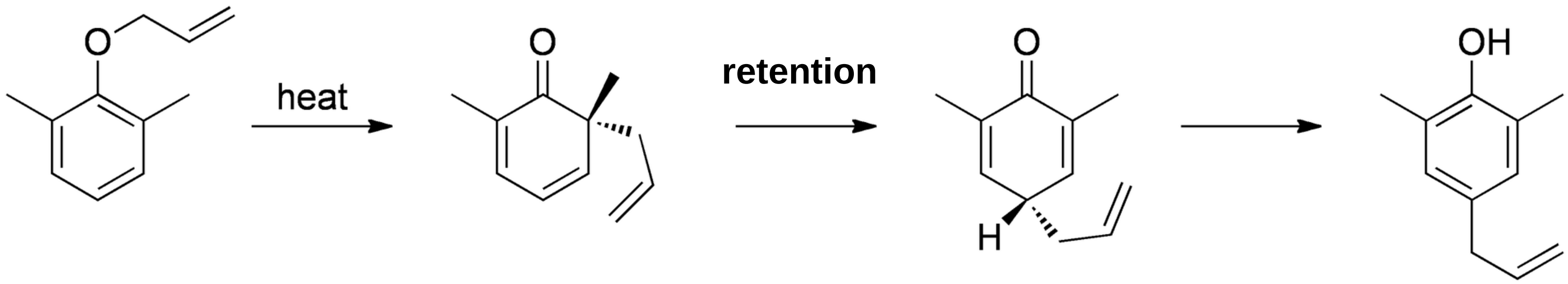




Suprafacial/suprafacial

1. CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS

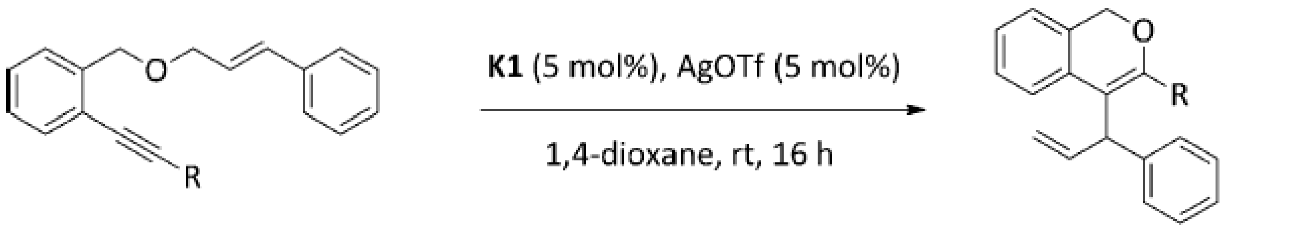
- *[3,3] Sigmatropic Rearrangements*



Suprafacial/suprafacial

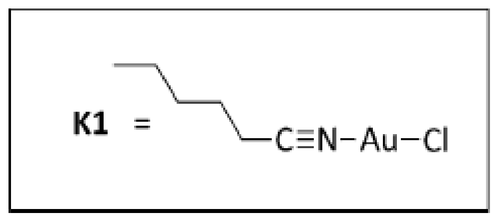
1. CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS

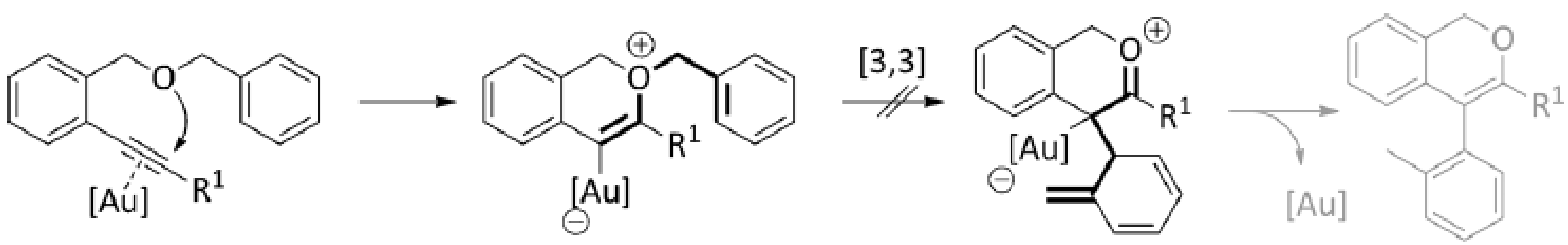
- *[3,3] Sigmatropic Rearrangements*



20a
20b

21a R = Ph, 18 %
21b R = *n*Bu, 66 %

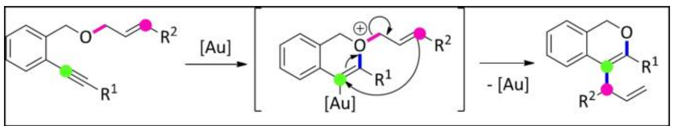


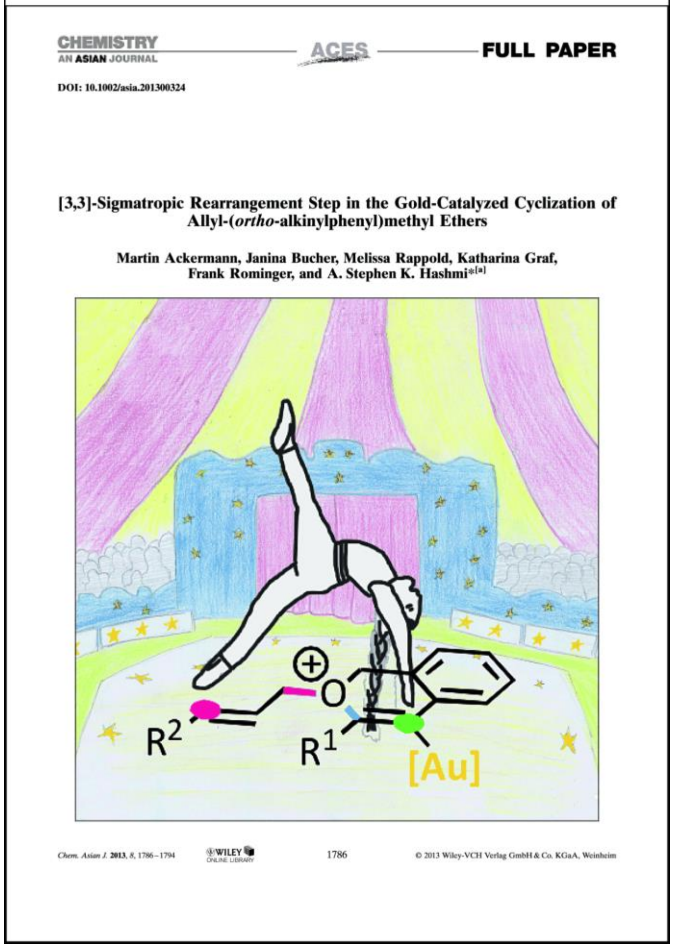


25 **26** **27** **28**

1. CYCLOISOMERIZATIONS INVOLVING SIGMATROPIC SHIFTS

- *[3,3] Sigmatropic Rearrangements*



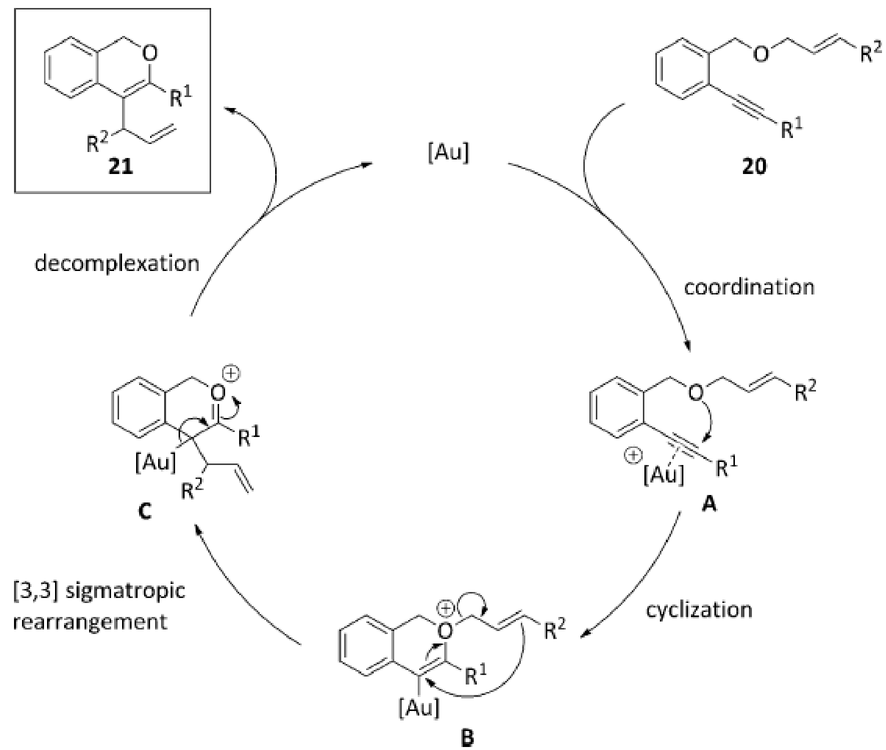

CHEMISTRY
AN ASIAN JOURNAL
ACES
FULL PAPER

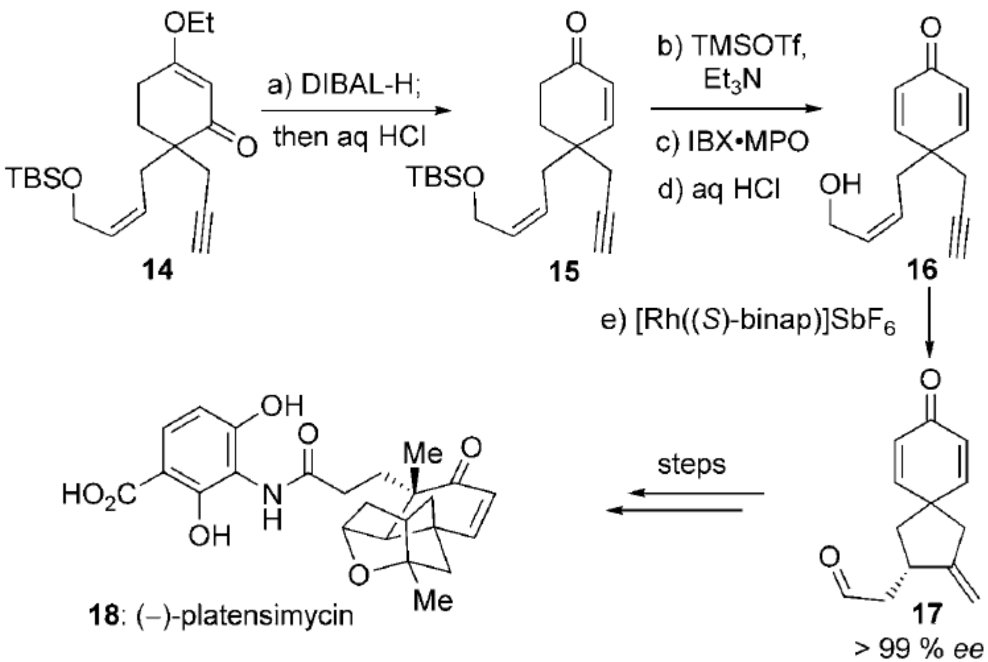
DOI: 10.1002/asia.201300324

[3,3]-Sigmatropic Rearrangement Step in the Gold-Catalyzed Cyclization of Allyl-(*ortho*-alkinylphenyl)methyl Ethers

Martin Ackermann, Janina Bucher, Melissa Rappold, Katharina Graf, Frank Rominger, and A. Stephen K. Hashmi*[a]

Chem. Asian J. 2013, 8, 1786–1794 · WILEY ONLINE LIBRARY · 1786 · © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

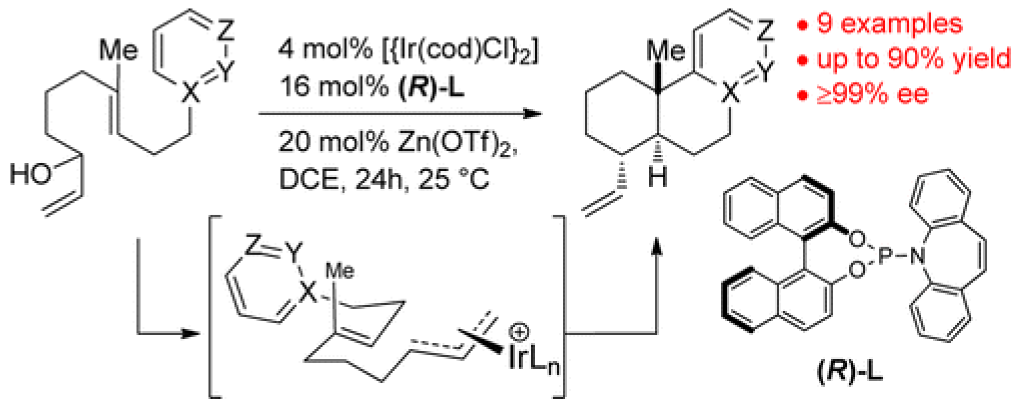




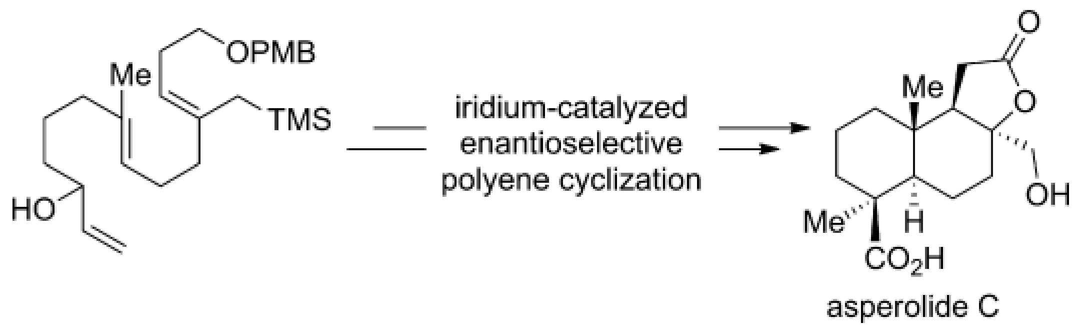
Scheme 3. Formal total synthesis of (−)-platensimycin. Reagents and conditions: a) DIBAL-H (1.0 M in hexanes, 1.2 equiv), THF, −78→ −20 °C, 1 h; then 2 N aq HCl, 0 °C, 30 min, 88 %; b) TMSOTf (1.2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C, 30 min; c) IBX (1.2 equiv), MPO (1.2 equiv), DMSO, 23 °C, 3 h; d) 1 N aq HCl, THF, 0 °C, 1 h, 68 % over three steps; e) $[Rh((S)\text{-binap})]SbF_6$ (0.05 equiv), DCE, 23 °C, 12 h, 86 %, > 99 % *ee*. DIBAL-H = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, IBX = *o*-iodoxybenzoic acid, MPO = 4-methoxypyridine-*N*-oxide, TBS = tert-butyldimethylsilyl, TMS = trimethylsilyl.

Nicolau et al.

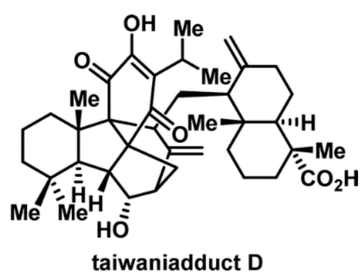
1. SELECTED APPLICATIONS OF WHAT WE HAVE SEEN IN CHAPTER 1



Carreira et al.

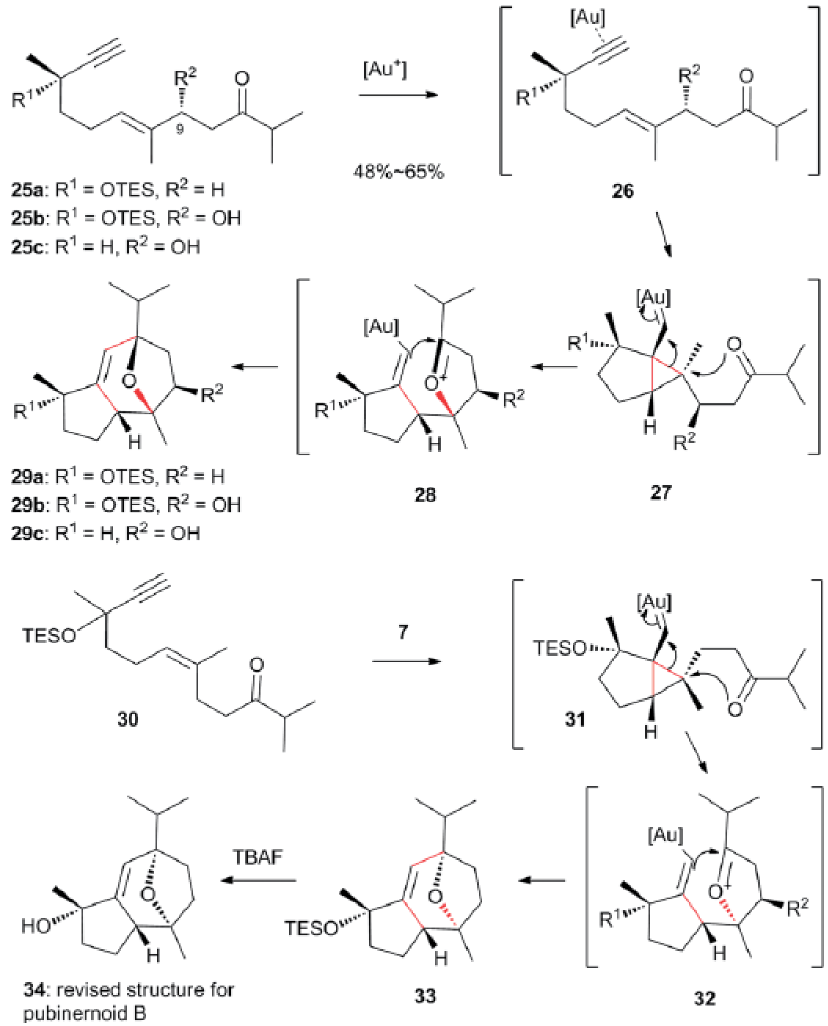


Carreira et al.



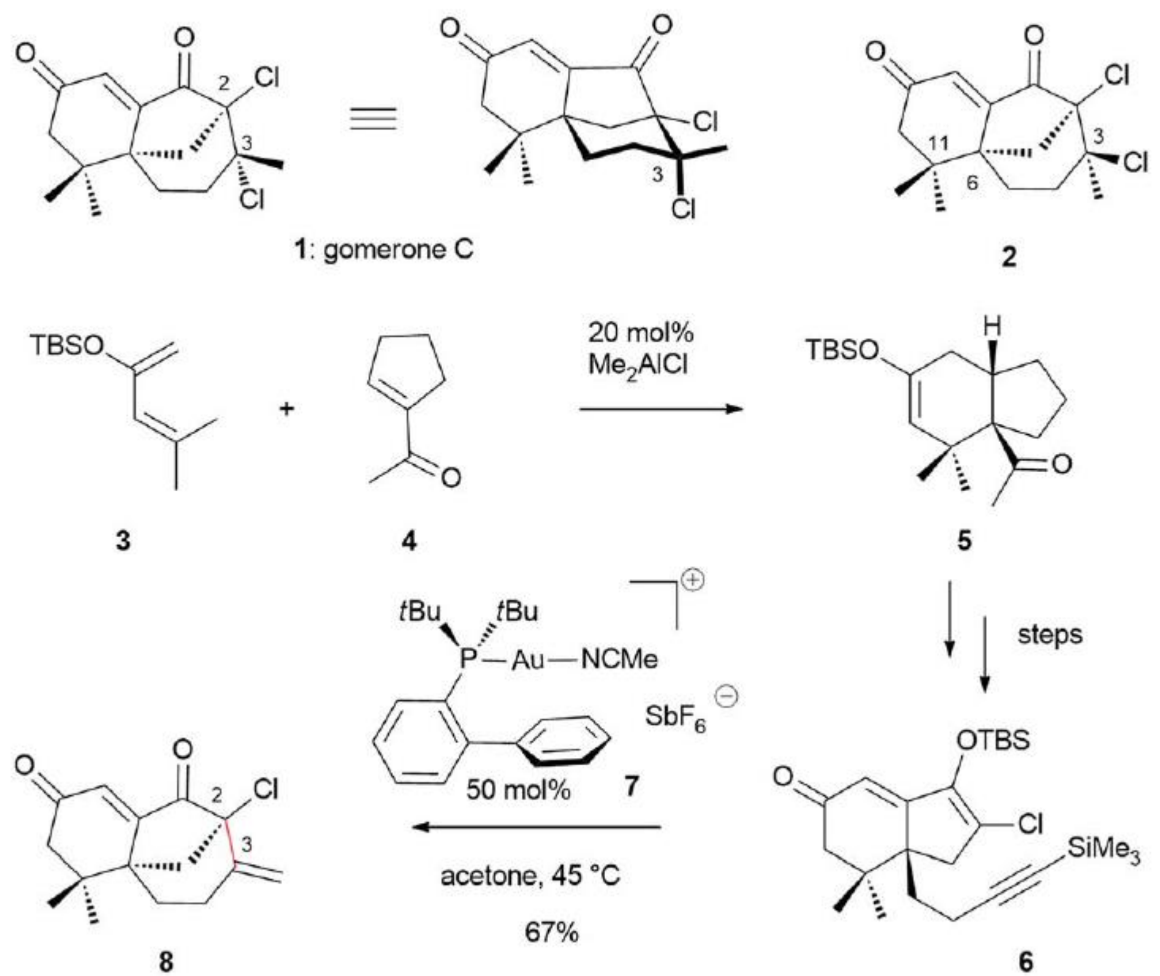
Li et al.

1. SELECTED APPLICATIONS OF WHAT WE HAVE SEEN IN CHAPTER 1



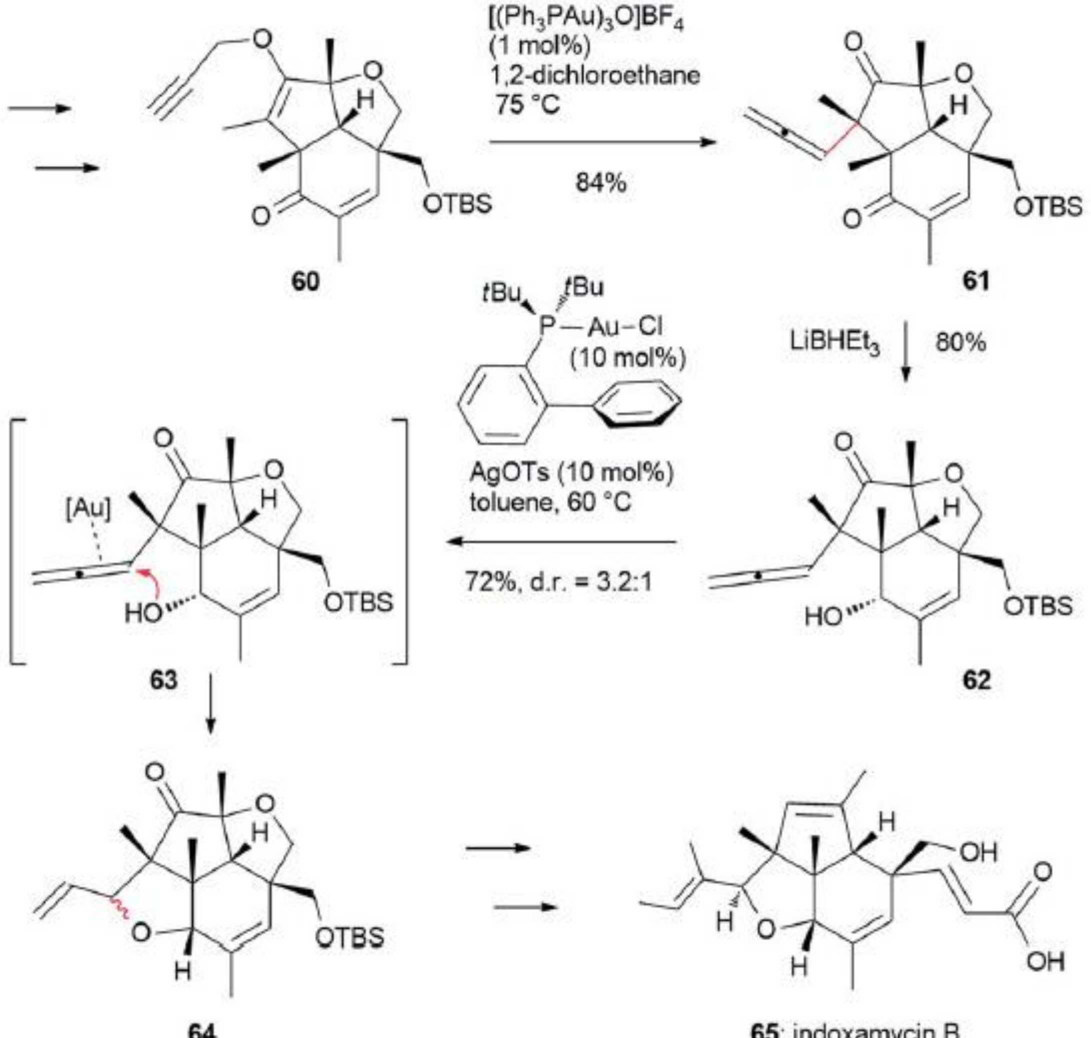
Scheme 4 Total syntheses of pubinernoid B, orientalol F and englerin A.

1. SELECTED APPLICATIONS OF WHAT WE HAVE SEEN IN CHAPTER 1



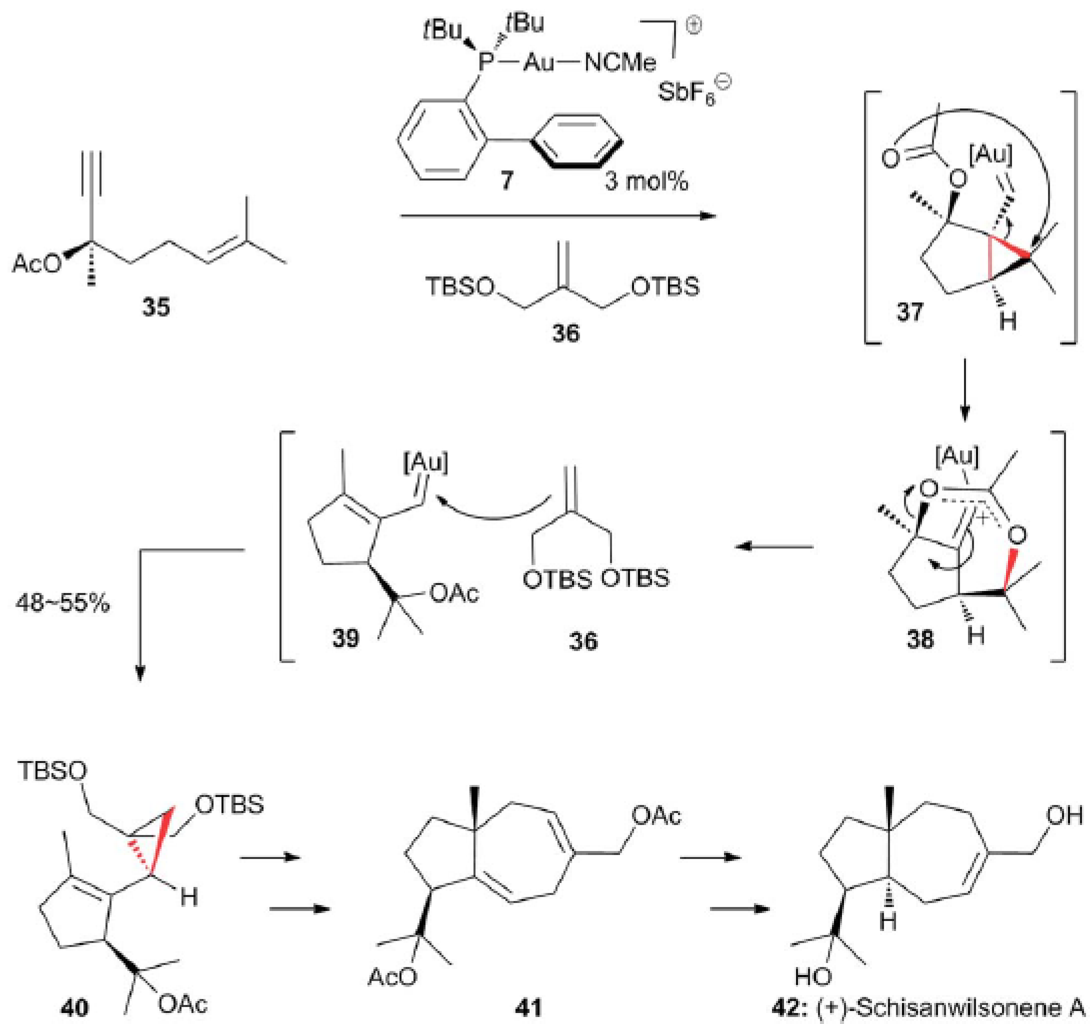
Conia-ene

Scheme 1 The total synthesis of gomerone C.



Scheme 8 The total synthesis of indoxamycin B.

Carreira et al.

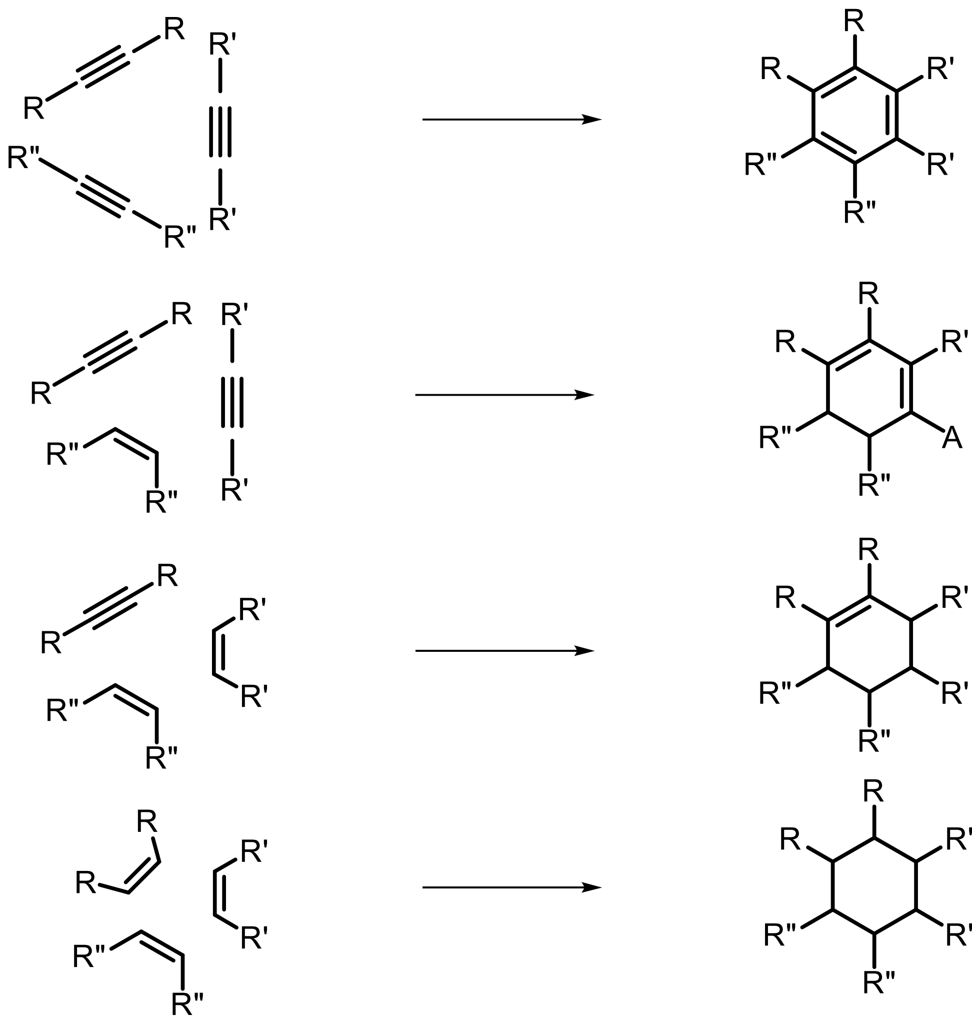


Scheme 5 The total synthesis of (+)-schisanwilsonene A.

Echavarren et al.

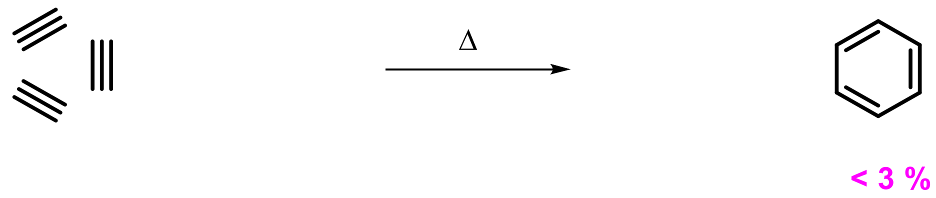
2. [2+2+2] Cycloadditions

[2+2+2] cyclizations of three unsaturated moieties : A very powerful strategy for the construction of six-membered rings



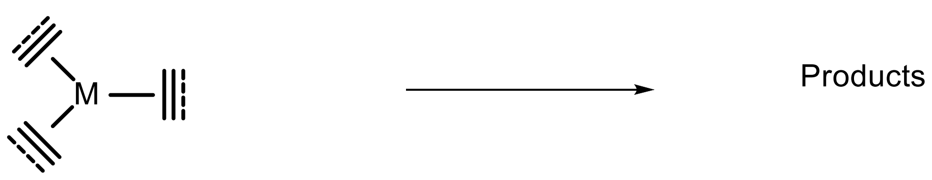
2. [2+2+2] Cycloadditions

1st example of cyclotrimerization:

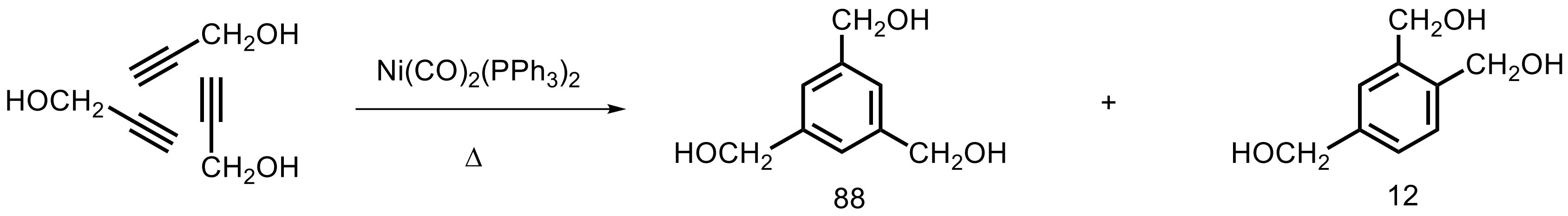


Berthelot, M. *C.R. Acad. Sci.* **1866**, 62.

Transition-metals can promote the reaction by templating the reactants:



2. [2+2+2] Cycloadditions

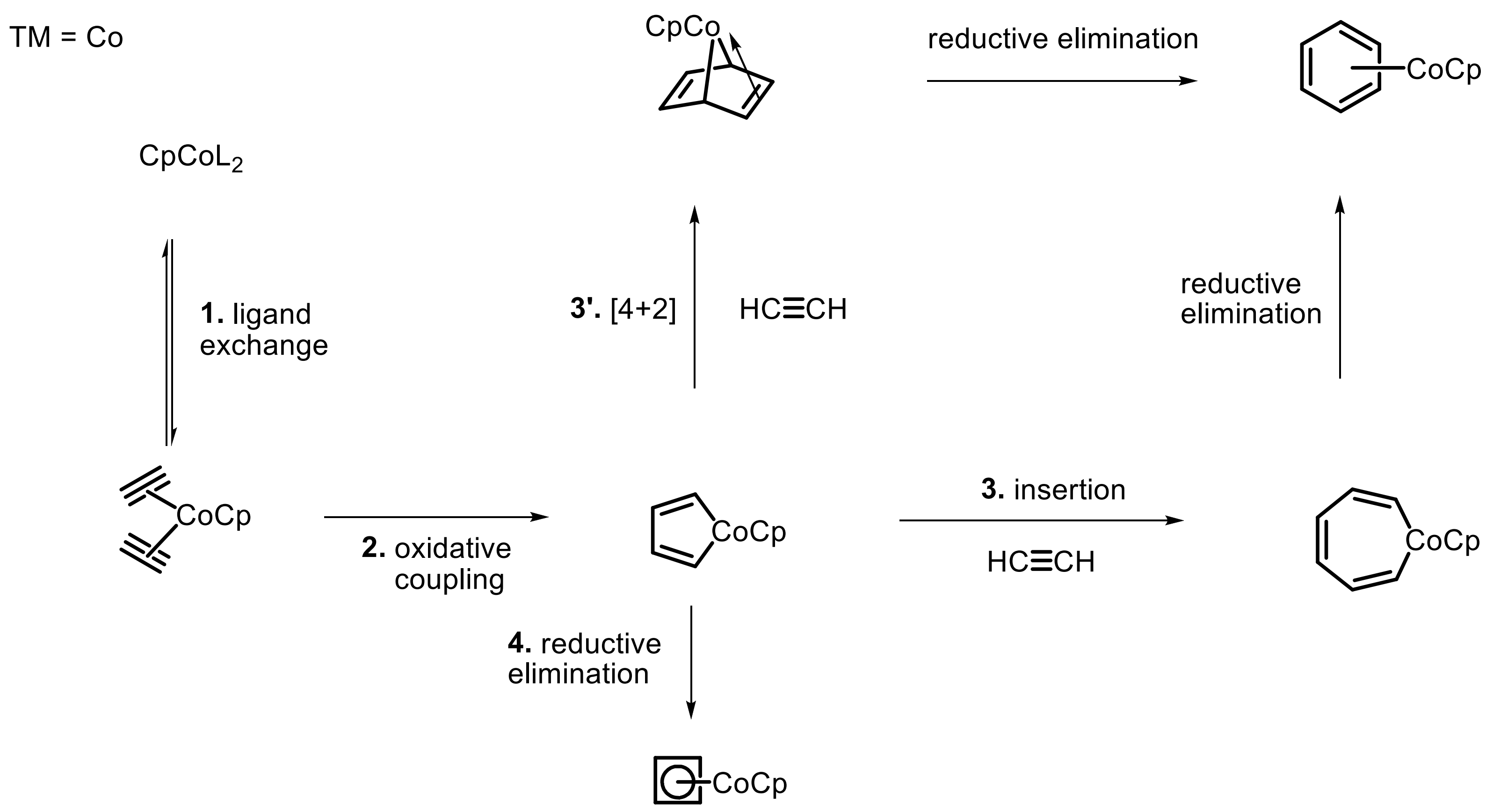


Reppe, W. *et al Justus Liebigs Ann. Chem.* **1948**, *560*, 1 and 116

⇨ Almost all the transition metals can catalyze the cyclotrimerization of alkynes to benzene derivatives

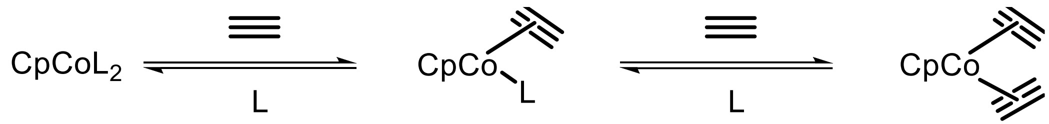
⇨ Many unsaturated moities can take part: alkynes, alkenes, allenes, nitriles, isocyanates, aldehydes, ketones, CO ....

2. [2+2+2] CYCLOADDITION OF ALKYNES: MECHANISTIC ASPECTS



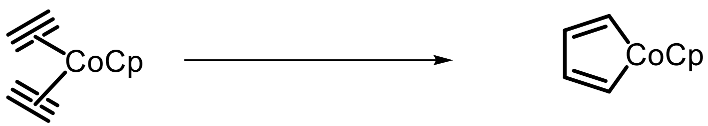
2. [2+2+2] CYCLOADDITION OF ALKYNES: MECHANISTIC ASPECTS

1. Ligand exchange :



If L = CO heating and/or irradiation are required

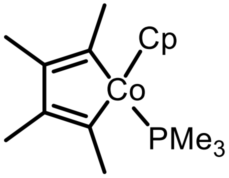
2. Oxidative coupling :



18 e$^-$

16 e$^-$: coord. unsaturated

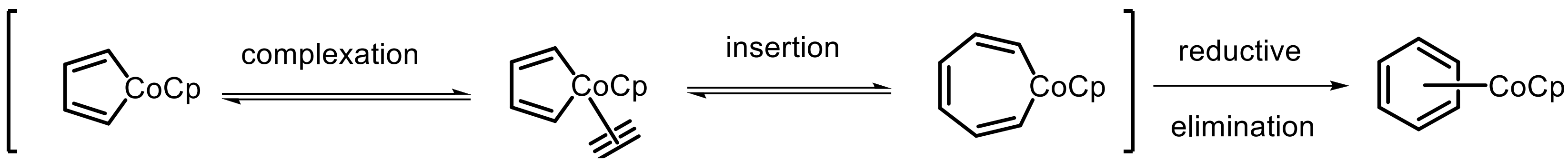
In presence of strong σ-donor ligands (PR_3), the reactivity of the metallacycle decreases and it can be isolated



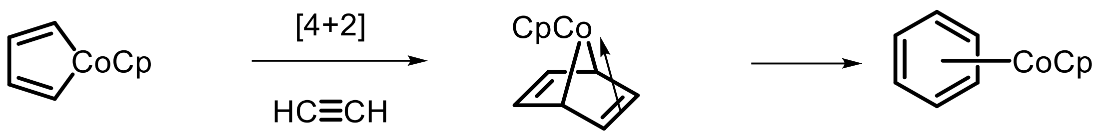
Bergmann, R. G. *et al*

2. [2+2+2] CYCLOADDITION OF ALKYNES: MECHANISTIC ASPECTS

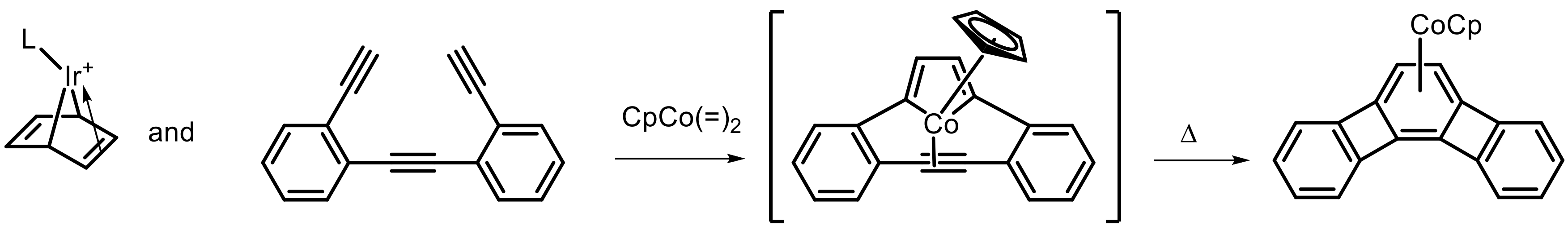
3. Complexation /Insertion/ Reductive elimination



3'. [4+2]



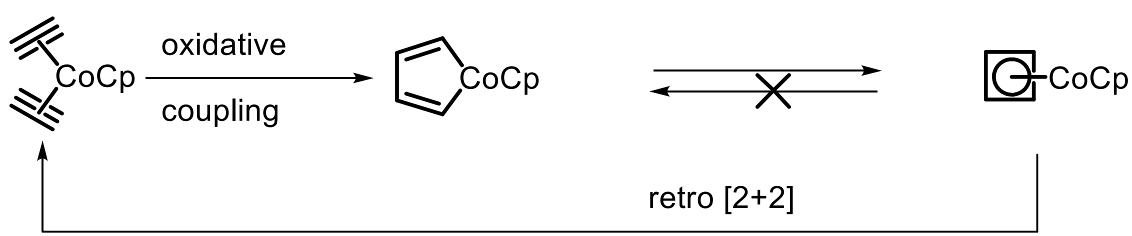
Some proofs for a [4+2] reaction :



Eisenstein, O.

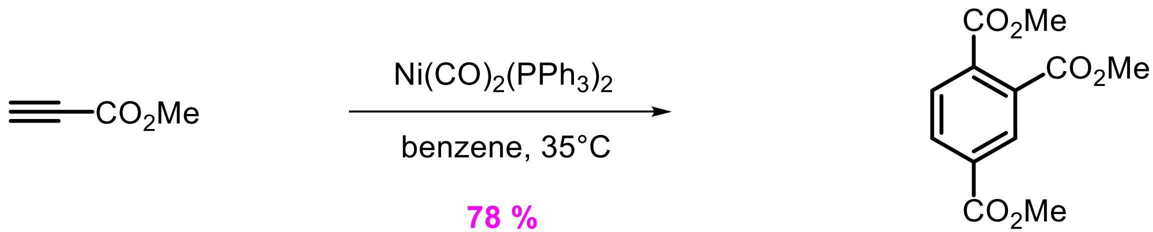
Vollhardt, K. P. C.

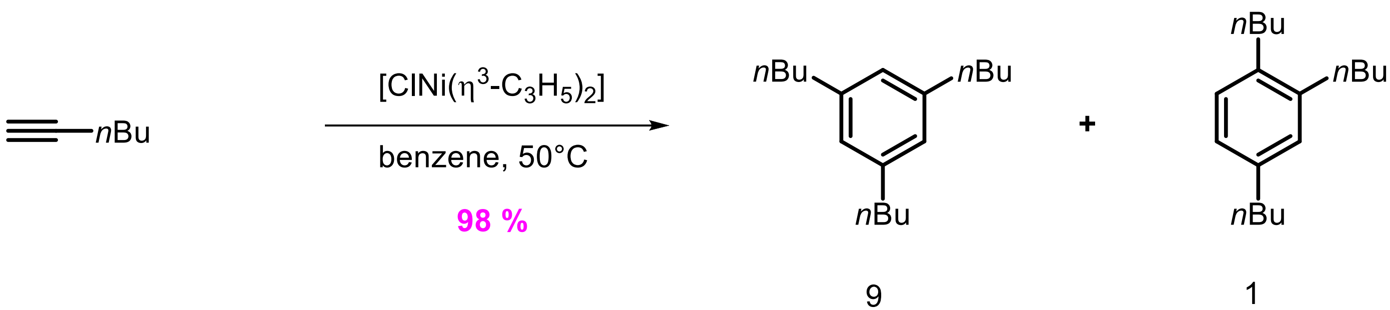
4. Redutive Elimination:



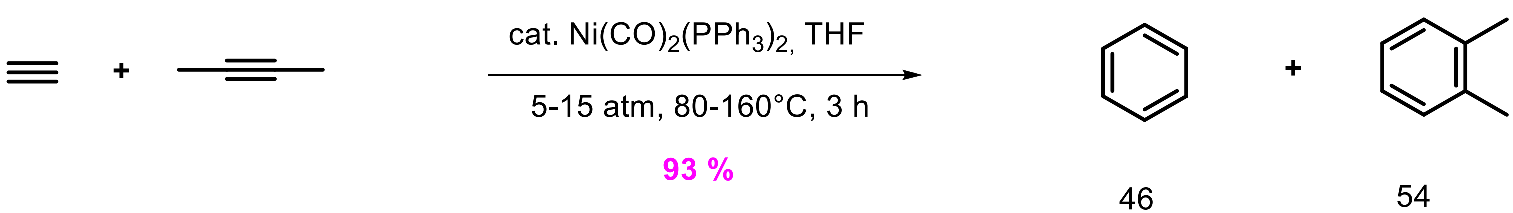
2. [2+2+2] CYCLOADDITION OF ALKYNES: CHEMOSELECTIVITY

Regioselectivity :

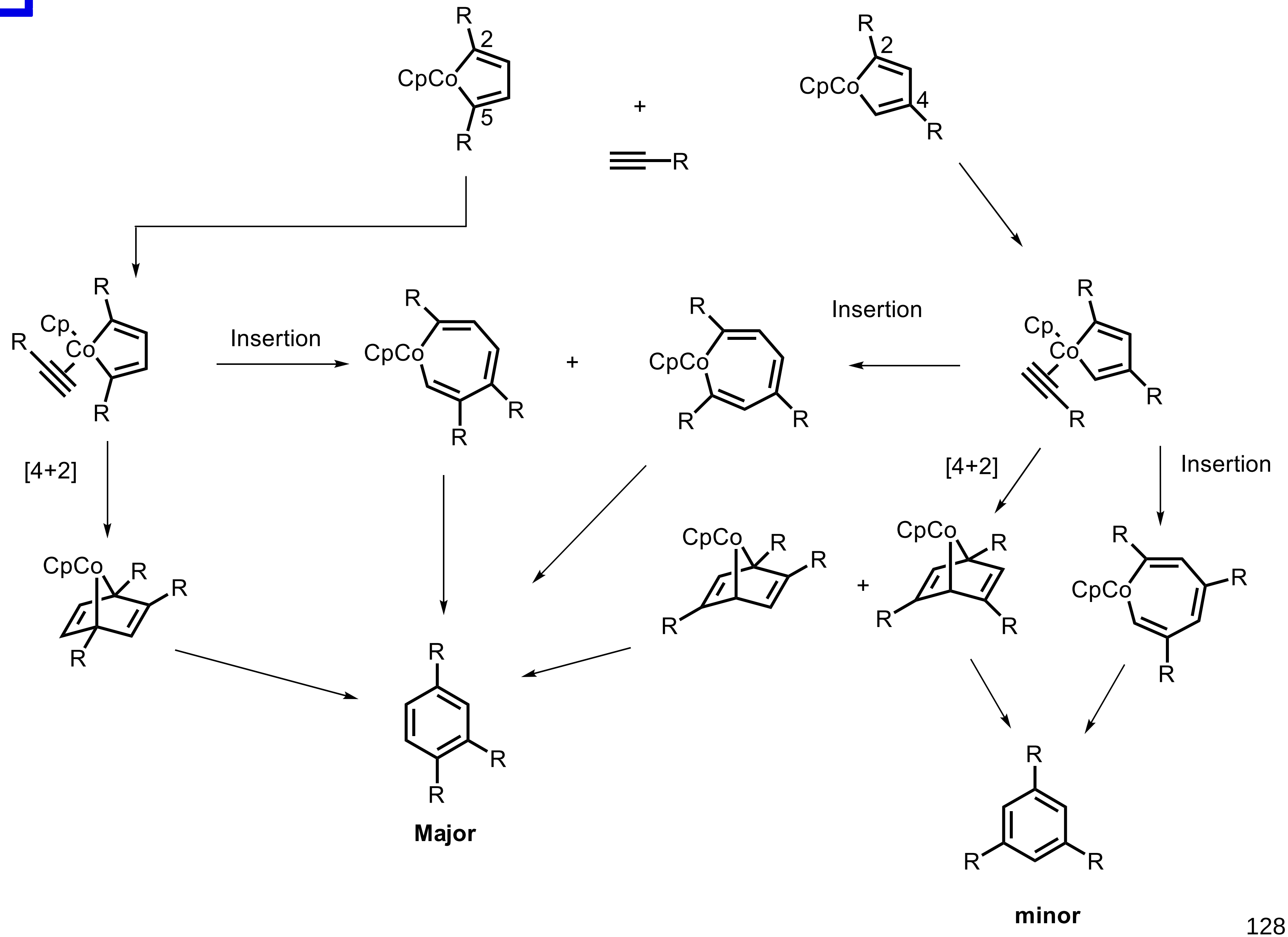




Chemoselectivity :

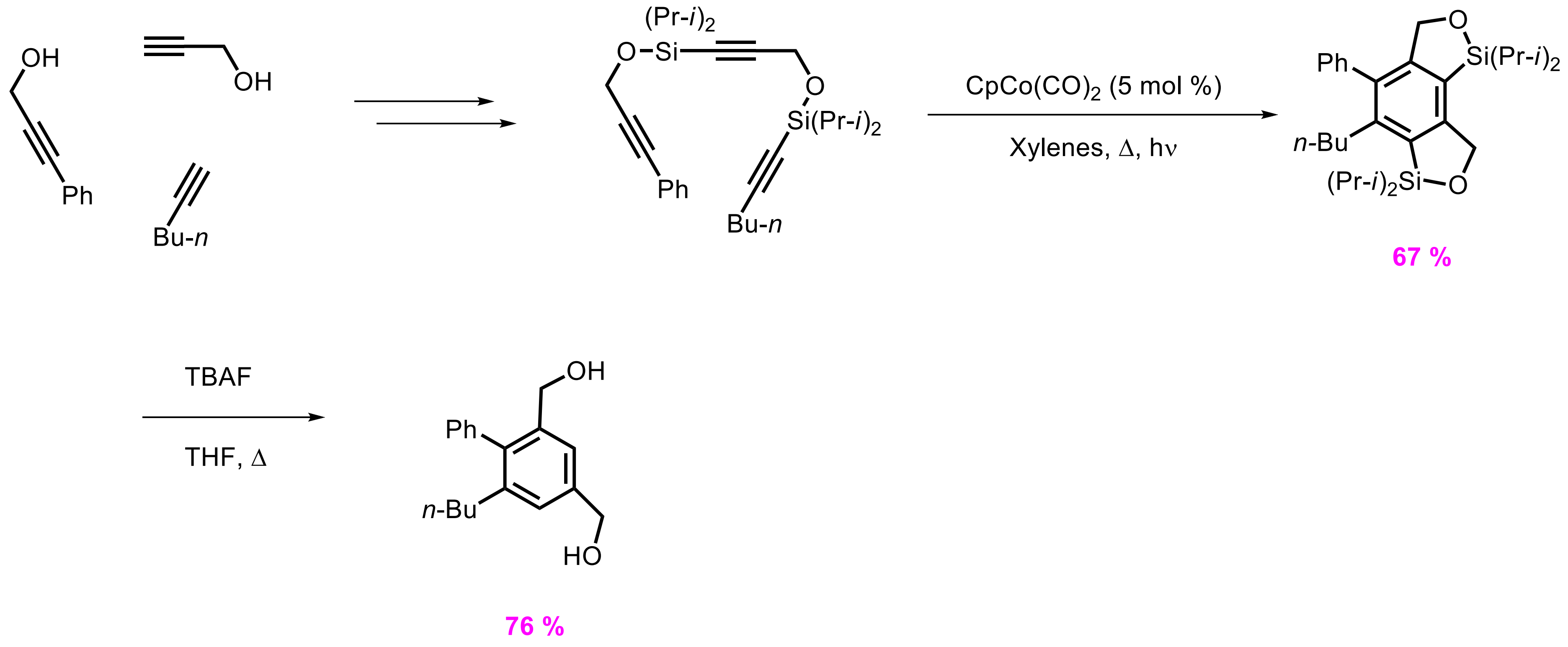


2. [2+2+2] CYCLOADDITION OF ALKYNES: REGIOSELECTIVITY



2. REGIO- AND CHEMOCONTROLLED INTERMOLECULAR REACTIONS

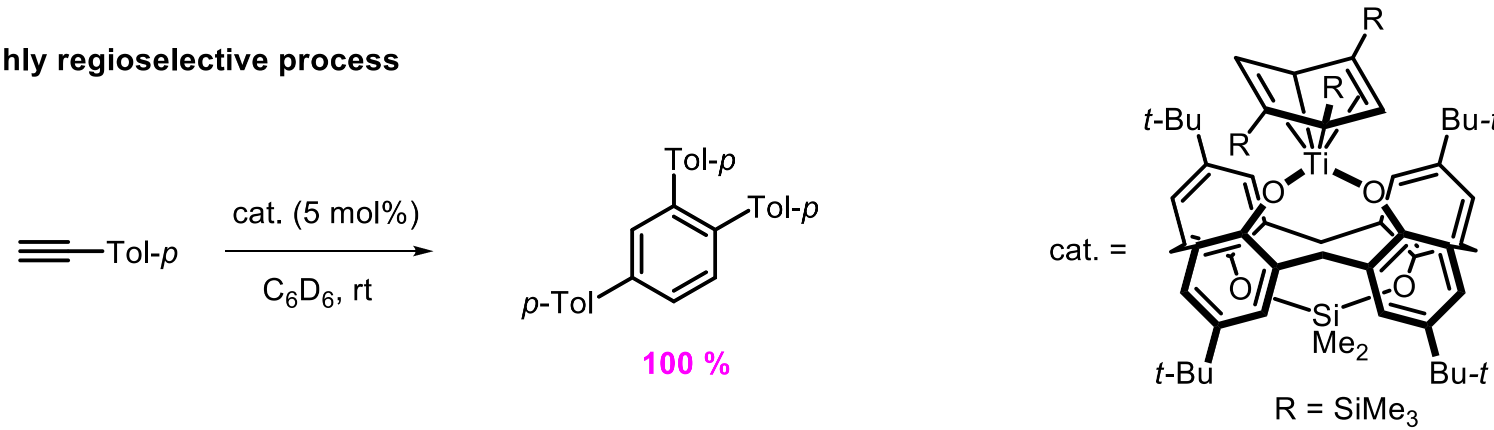
Disposable silyl-tether for a regio- and chemoselective process



Malacria *et al*

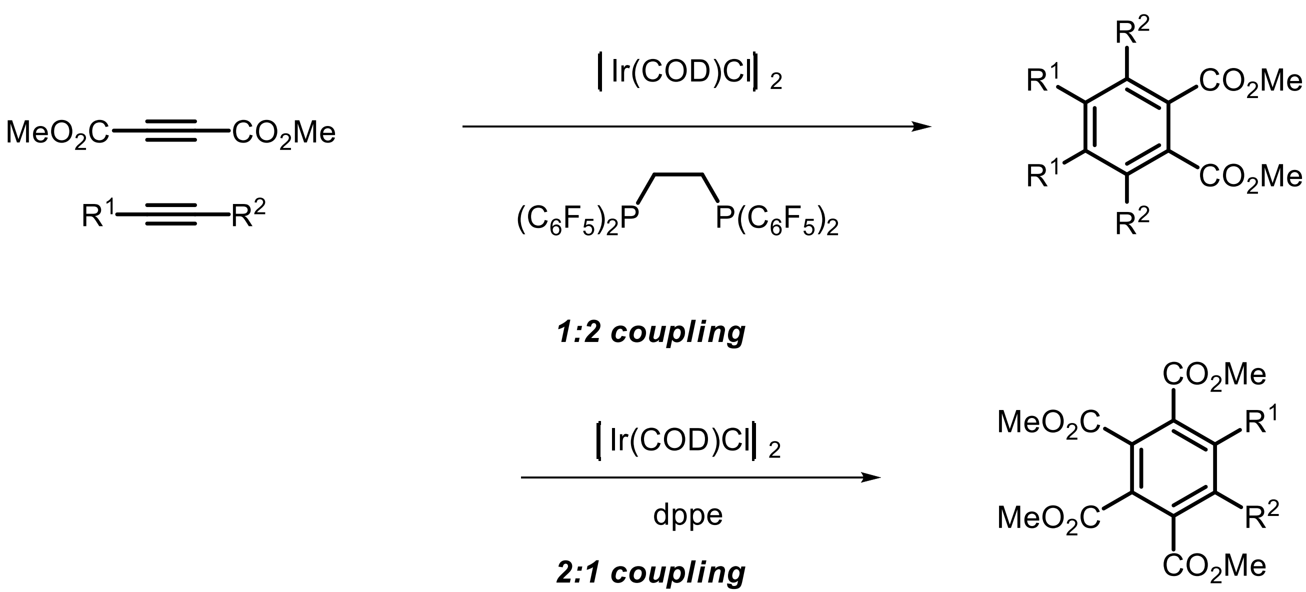
2. REGIO- AND CHEMOCONTROLLED INTERMOLECULAR REACTIONS

Highly regioselective process



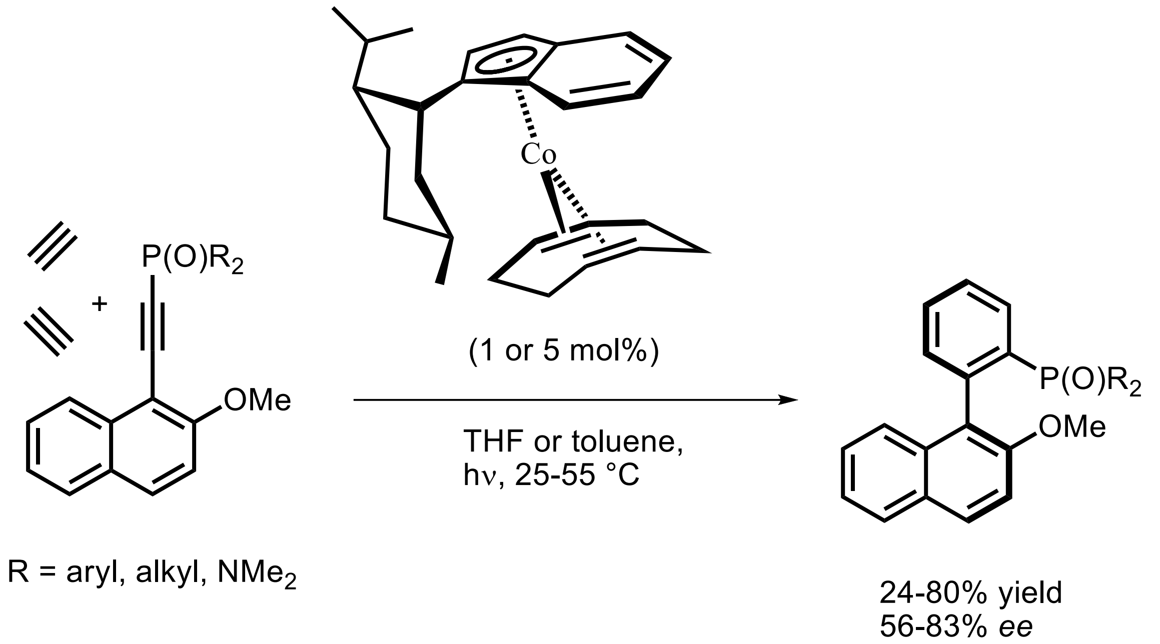
Ozerov *et al*

Highly chemoselective process



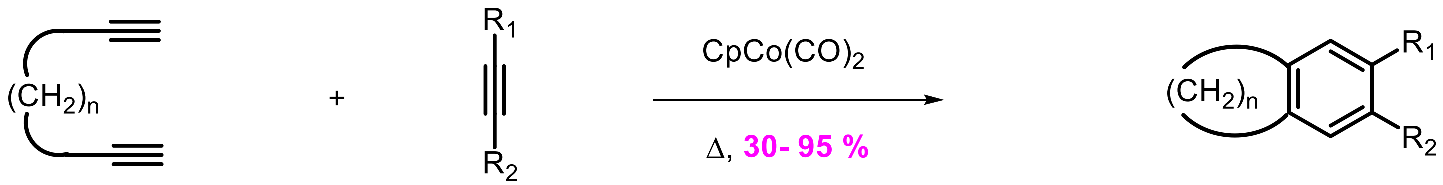
Takeuchi *et al*

2. [2+2+2] CYCLOADDITION OF ALKYNES

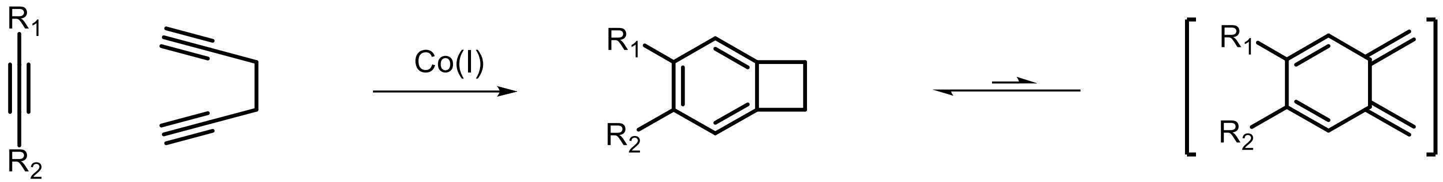


B. Heller *et al*

2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES



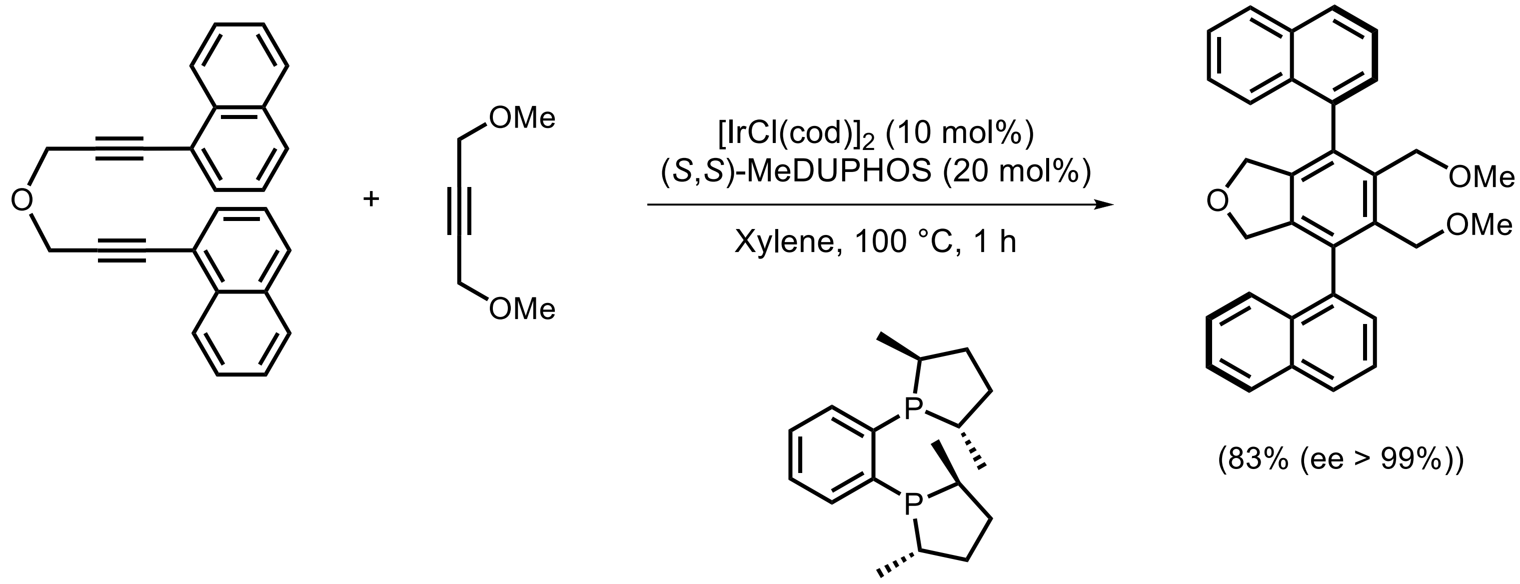
n = 2, 3, 4, 5 ; R_1, R_2 = H, alkyl, aryl, vinyl, ester, ether, ketone, amine , $SiMe_3$



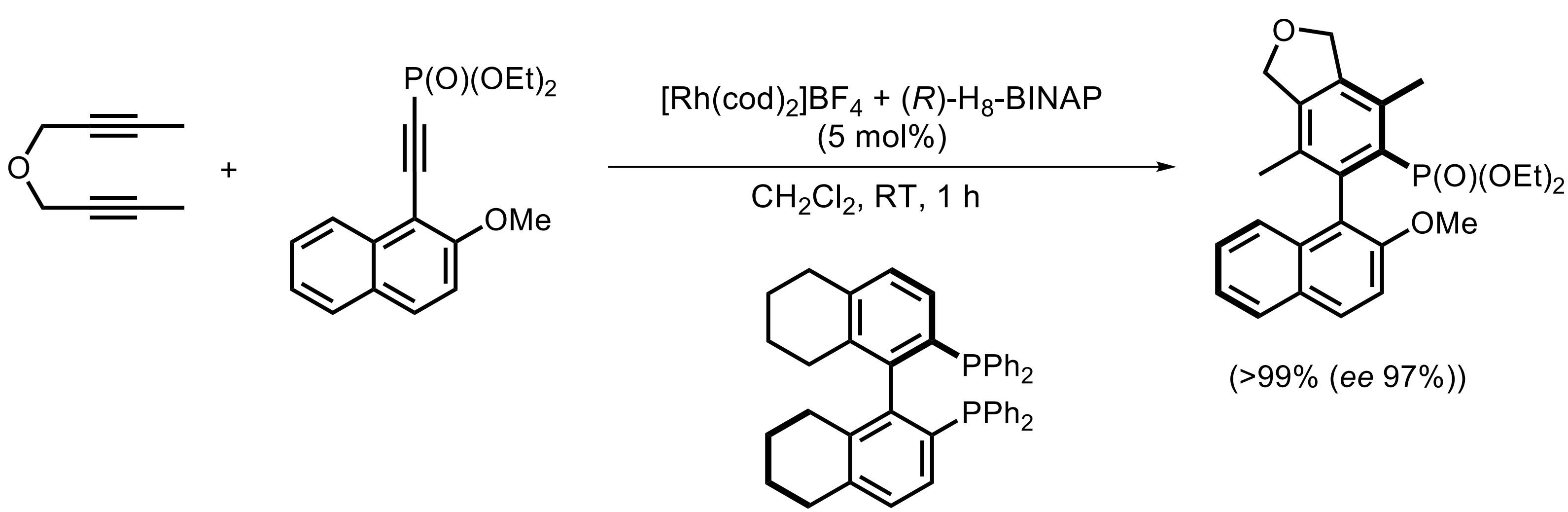
o-quinodimethane

Vollhardt, K. P. C.

2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES



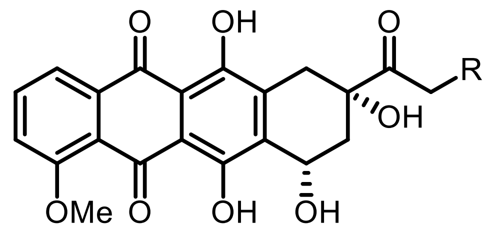
K. Takagishi *et al*



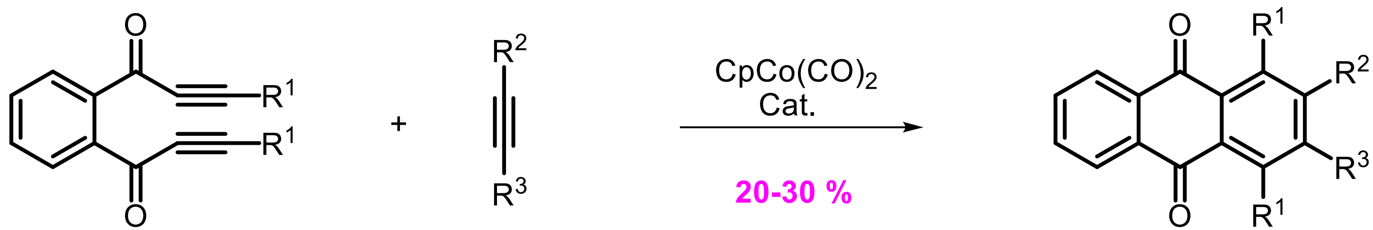
K. Tanaka *et al*

2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES

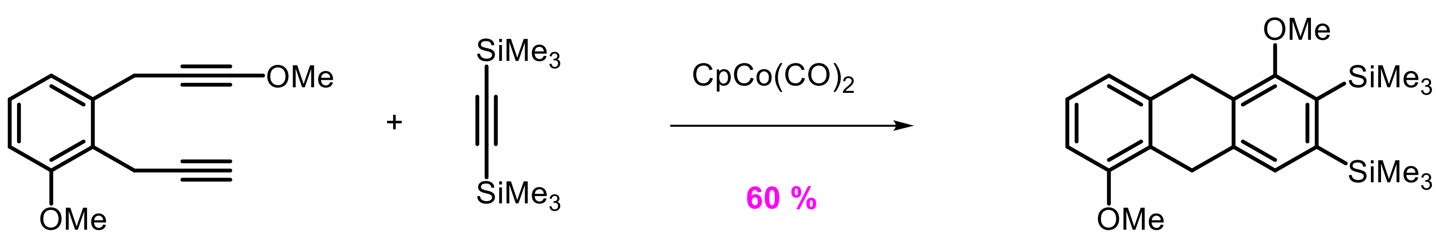
Access to the Anthracycline aglycones



Two Strategies



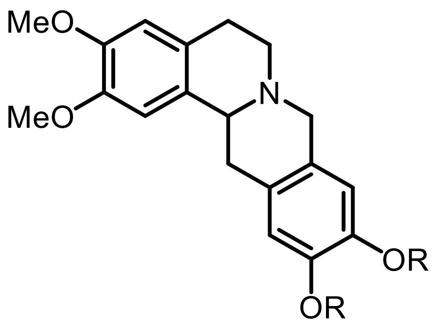
R^1 = H, $SiMe_3$ R^2, R^3 = H, alkyl, $SiMe_3$

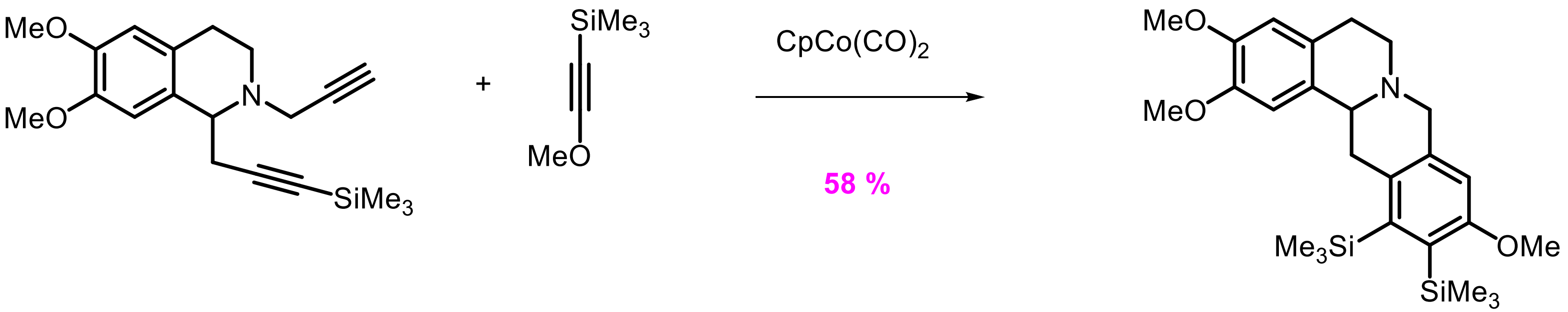


Vollhardt, K. P. C. *et al*

2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES

Access to the Protoberberine alkaloids



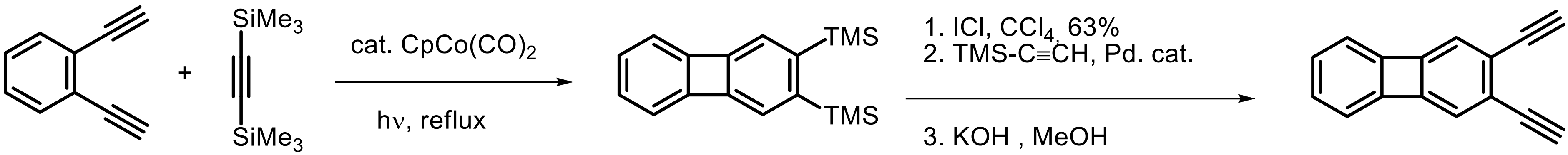


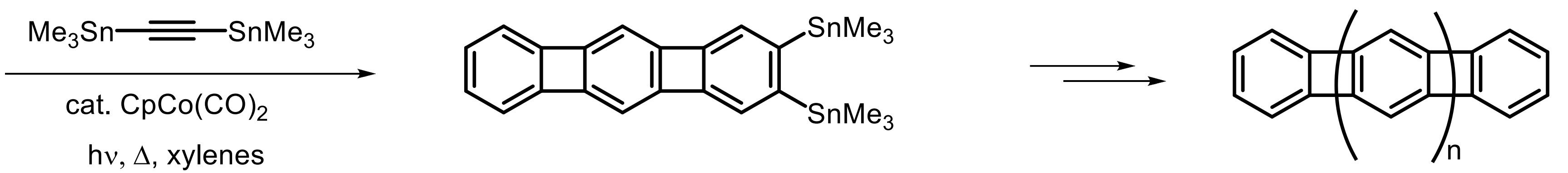
The more crowded is regioselectively generated

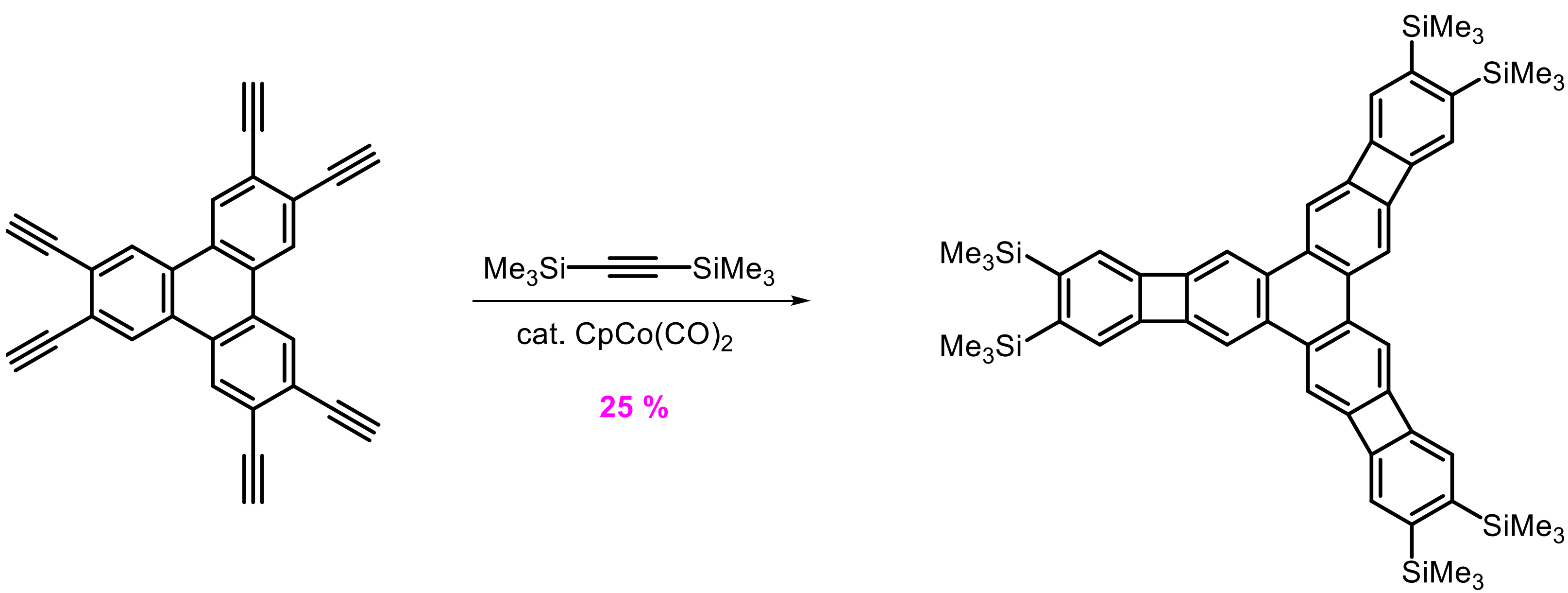
Vollhardt, K. P. C. *et al*

2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES

Access to Multiphenylenes: Iterative approach



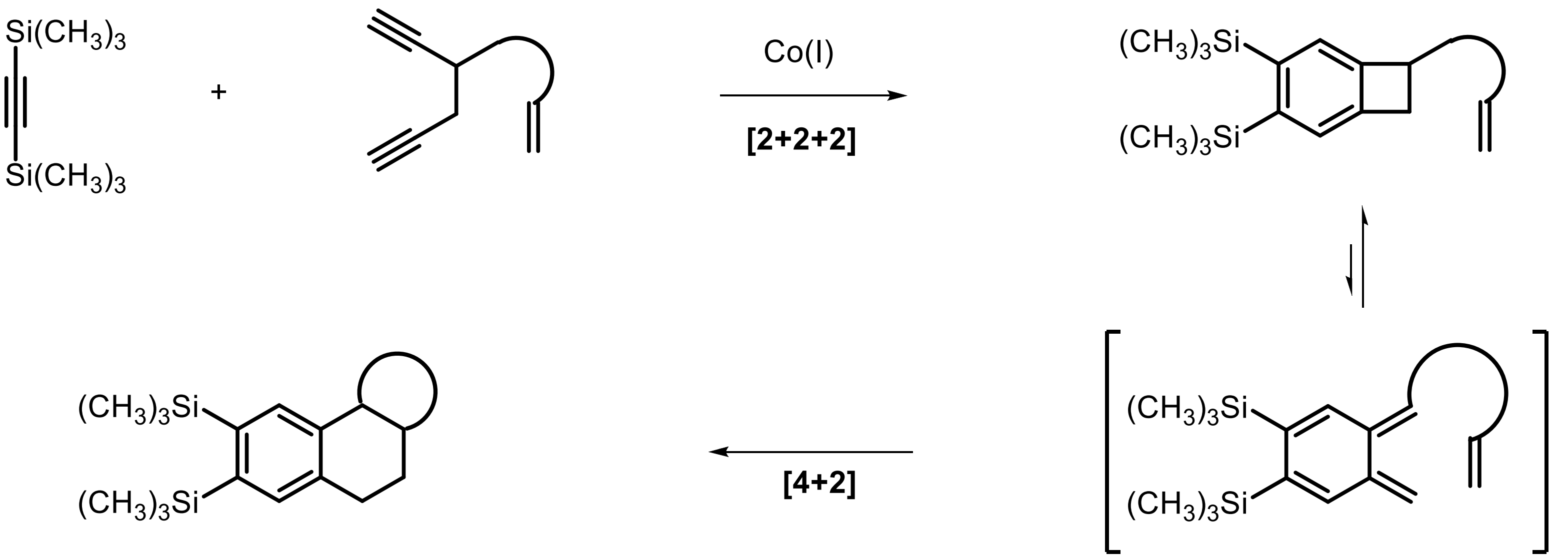




Vollhardt, K. P. C. *et al*

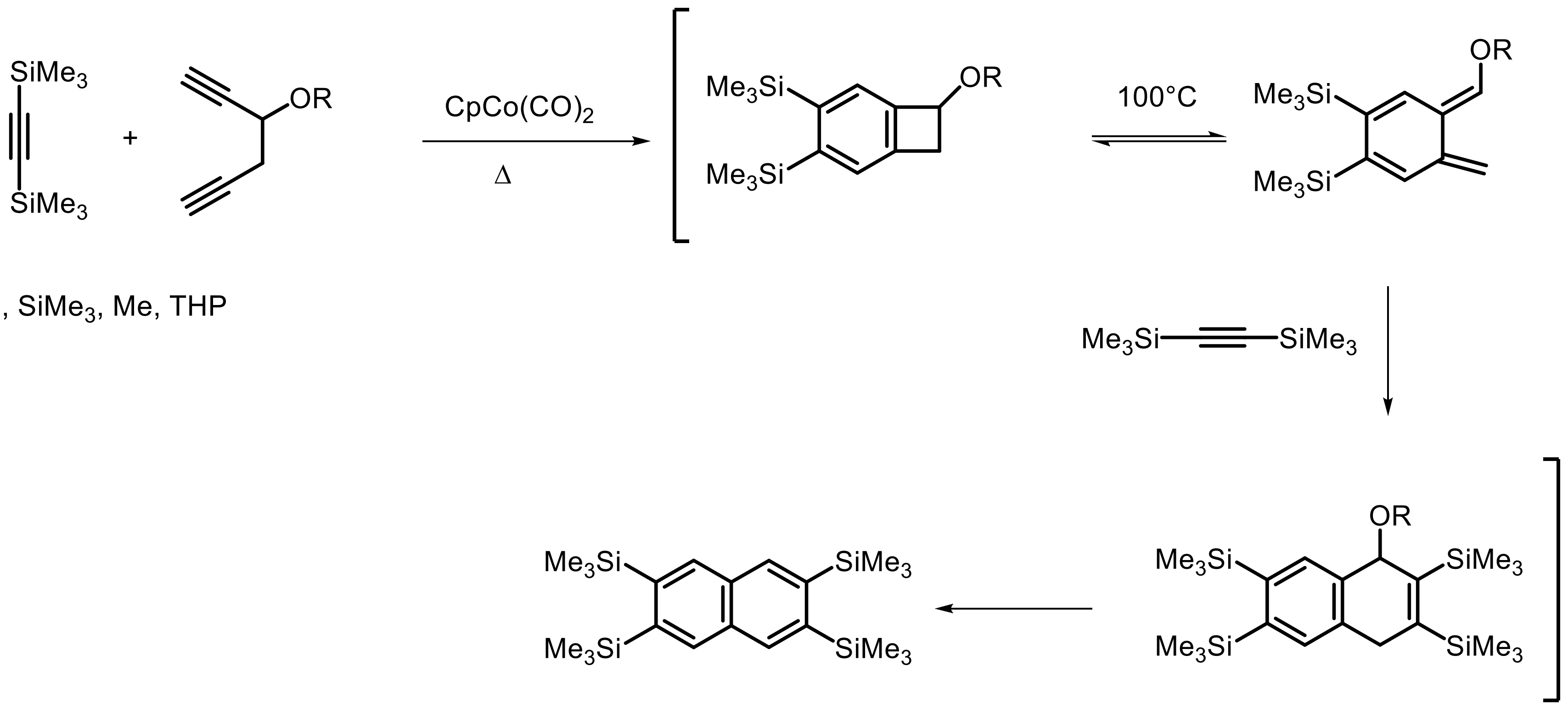
2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES / [4+2]

TANDEM REACTION [2+2+2] - [4+2] :



2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES / [4+2]

TANDEM PRINCIPLE



R = H, $SiMe_3$, Me, THP

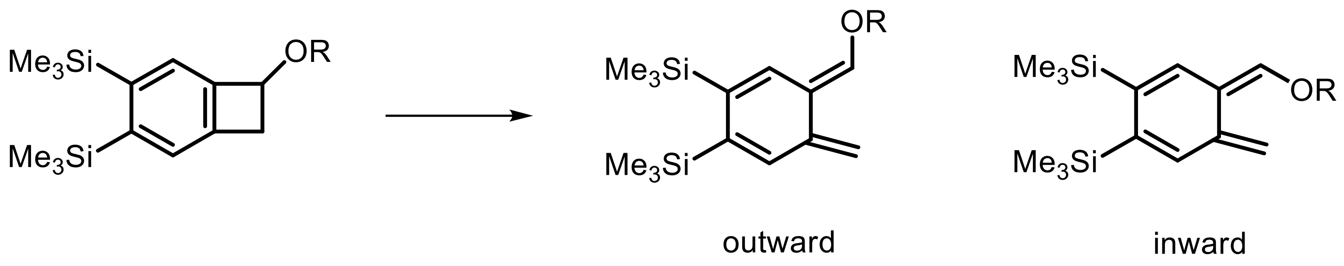
5 carbon-carbon bonds are created in one step

Vollhardt, K. P. C. *et al*

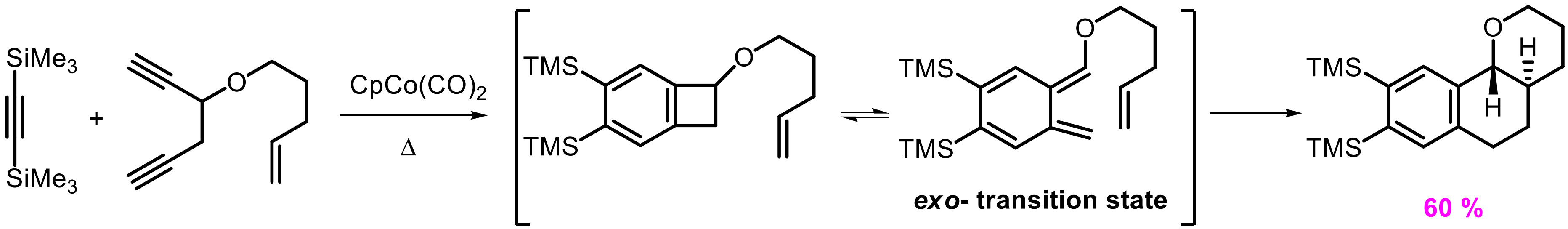
2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES / [4+2]

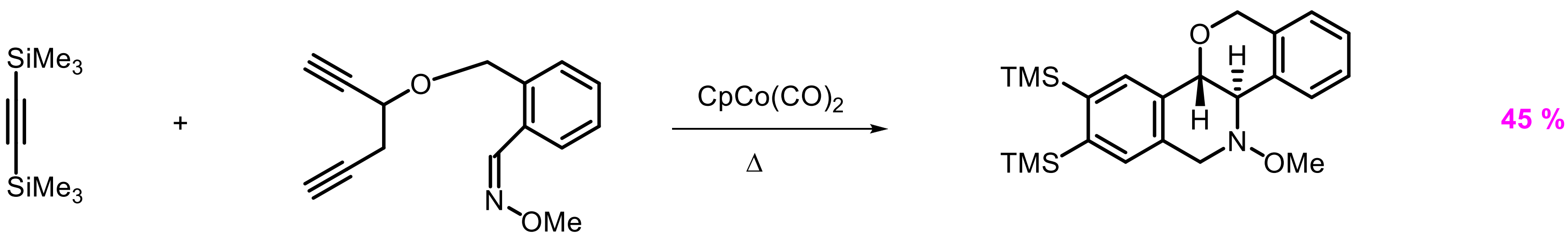
TANDEM PRINCIPLE

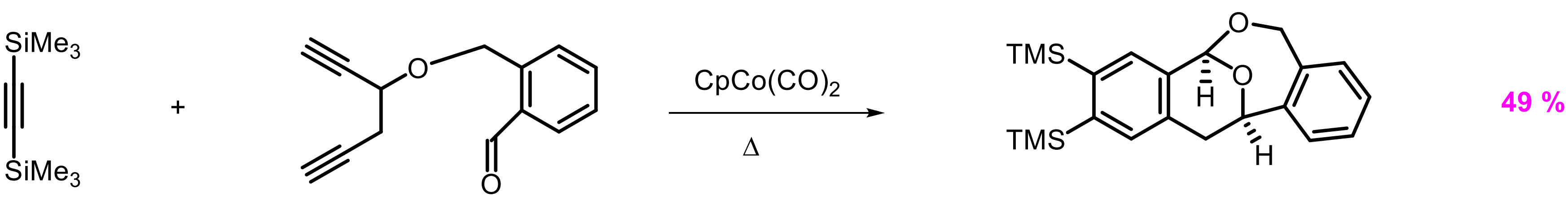
NB: outward and inward isomers are allowed by conrotatory ring opening. The stereoselectivity is controlled by torquoselectivity



2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES / [4+2]





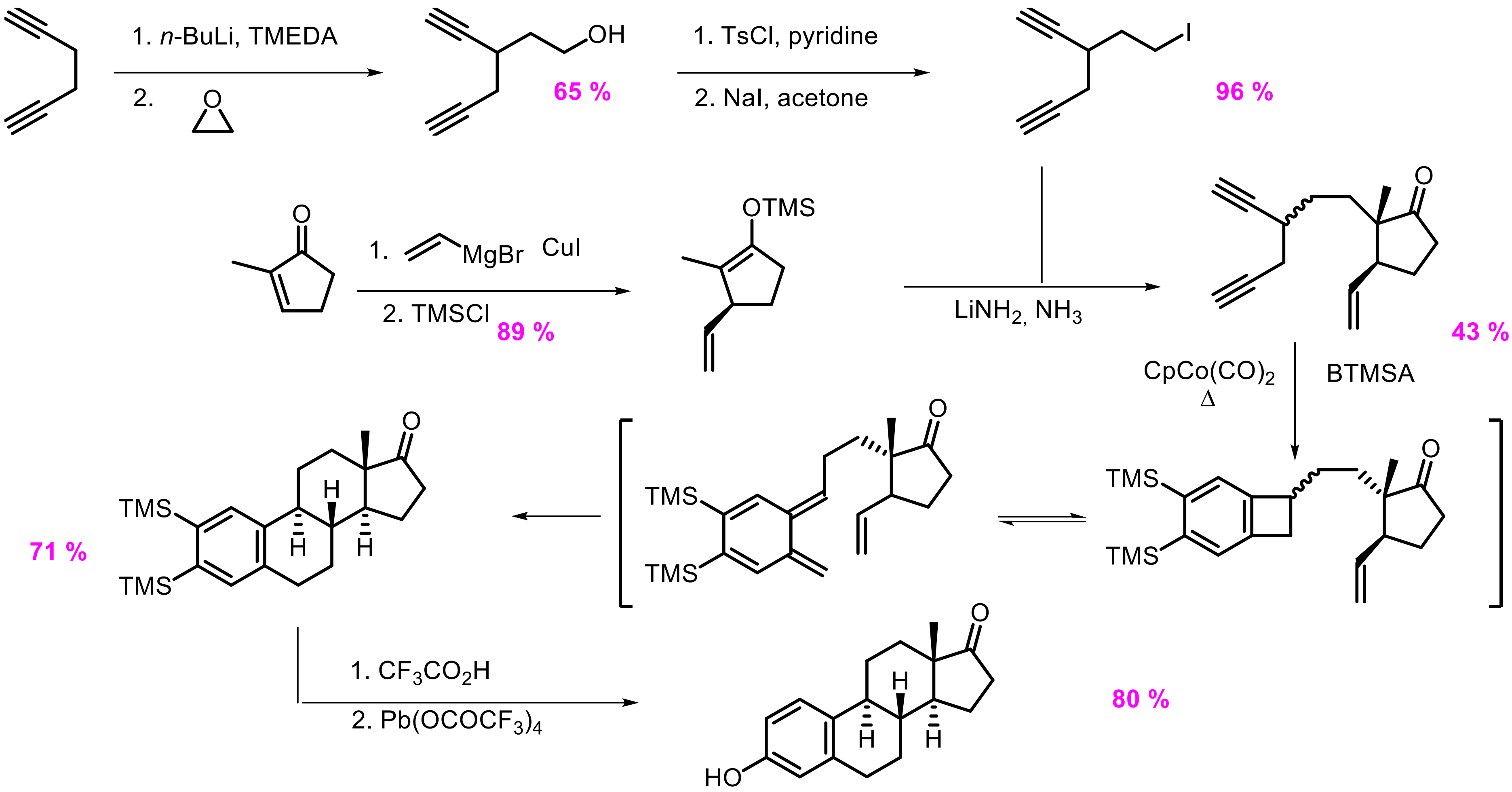


It has been shown that the metal is not involved in the Diels-Alder closure

Vollhardt, K. P. C.

2. TANDEM PRINCIPLE: THE COBALT WAY TO (±) ESTRONE

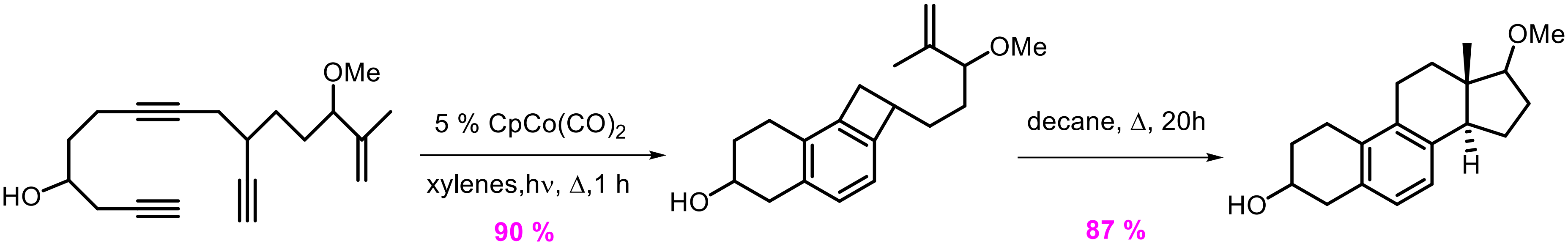
THE D → ABCD approach



Vollhardt, K. P. C.

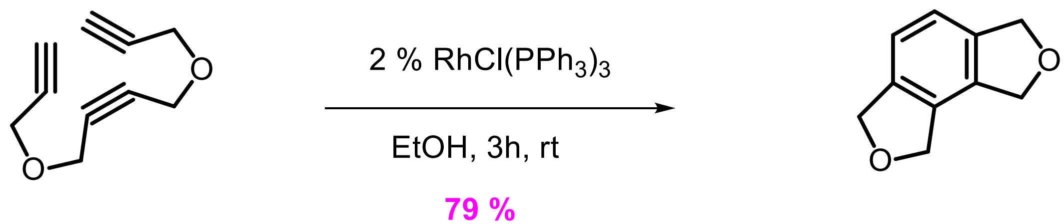
2. INTRAMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES

With Cobalt :



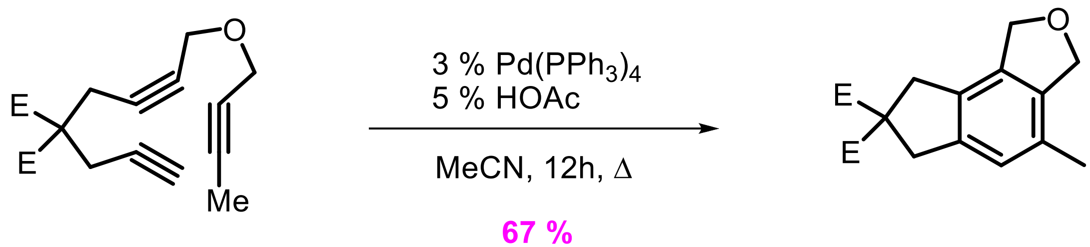
Vollhardt, K. P. C. *et al*

With Rhodium



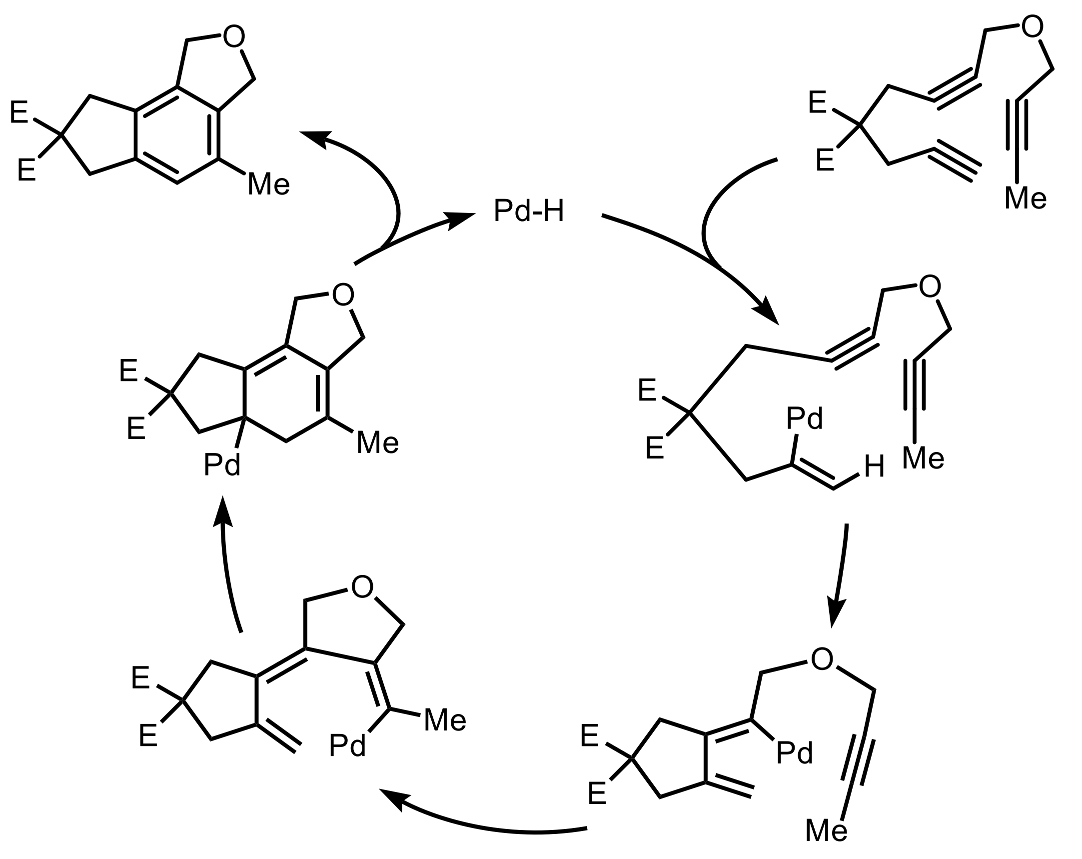
Grigg, R. *et al*

With Palladium

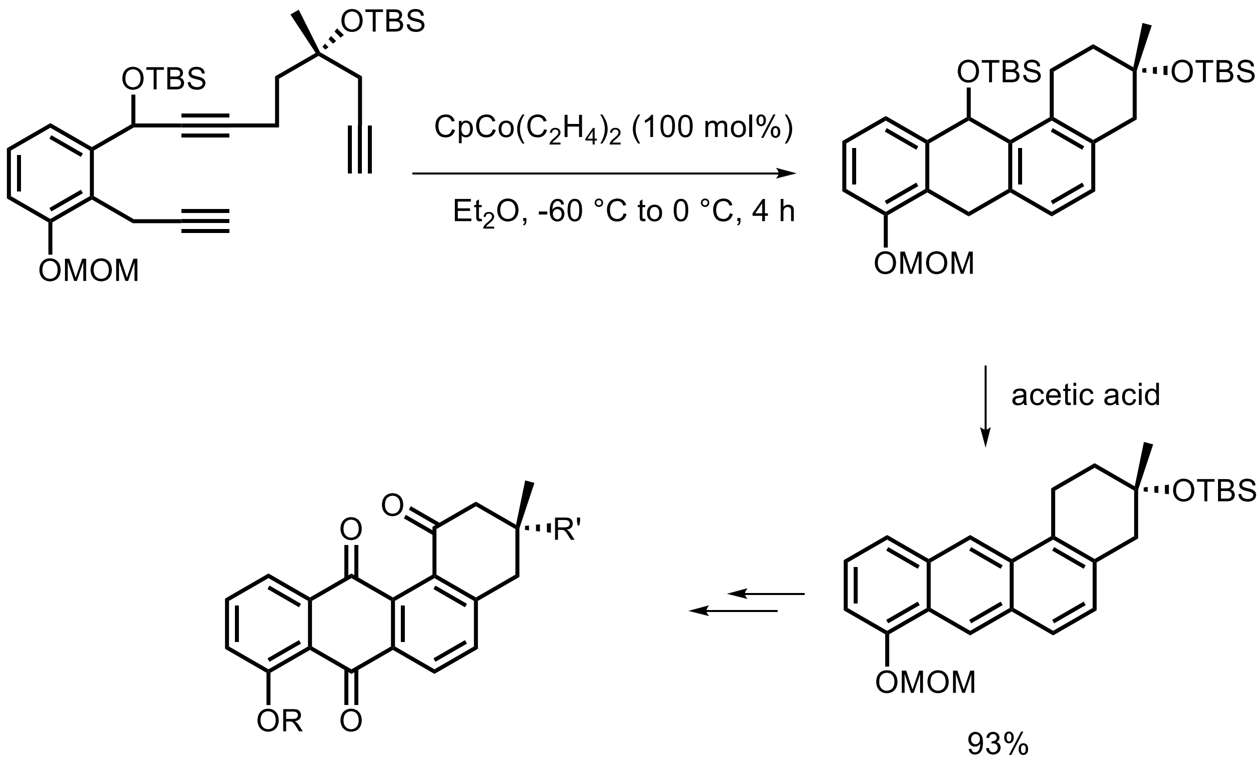


Negishi, E. -i *et al*

2. INTRAMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES



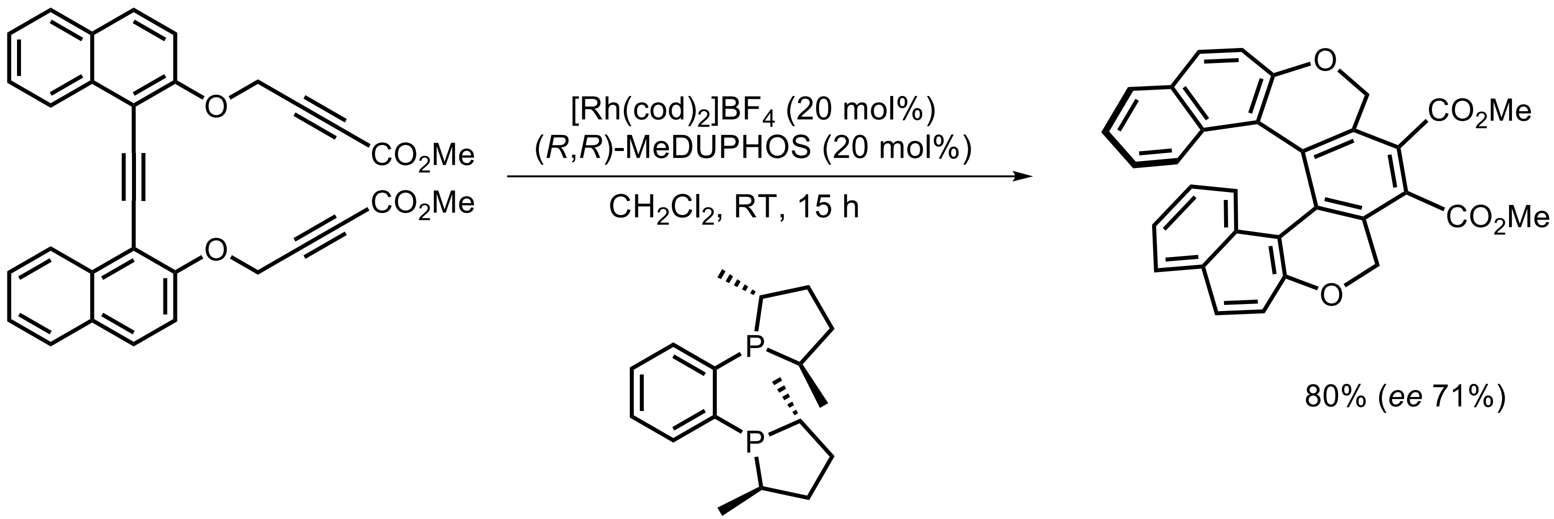
2. INTRAMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES

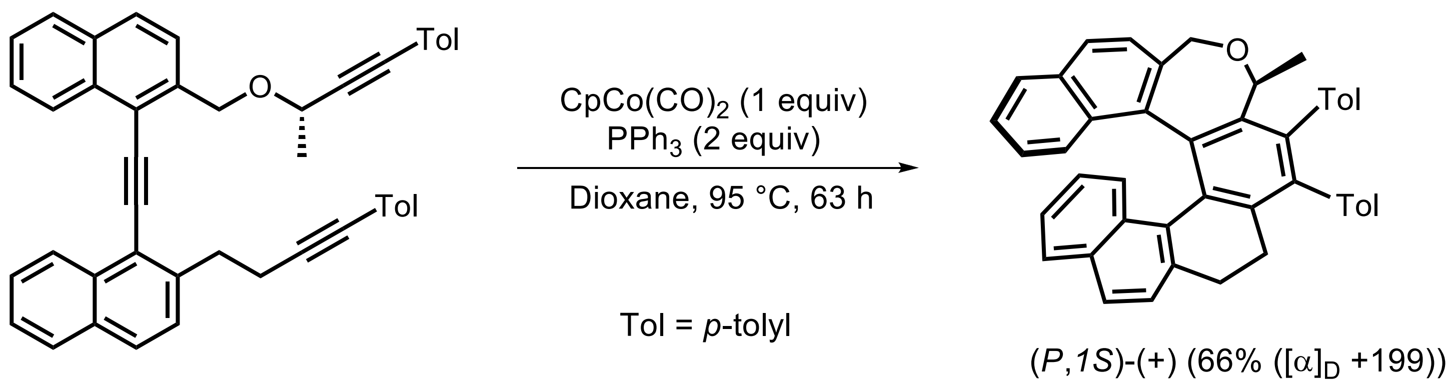


R = Me, R' = H ((+)-rubiginone B2)
R = Me, R'= OH ((-)-tetrangomycin)
R = H, R' = OH ((-)-8-*O*-methyltetrangomycin)

U. Groth *et al*

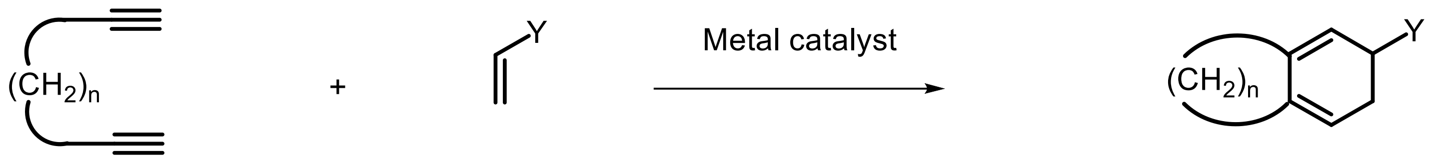
2. INTRAMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES





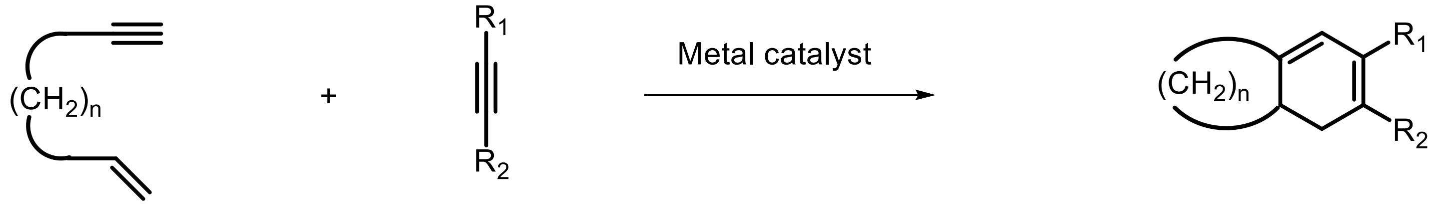
2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES AND ALKENES

Type 1 : Diyne-monoalkene cyclization



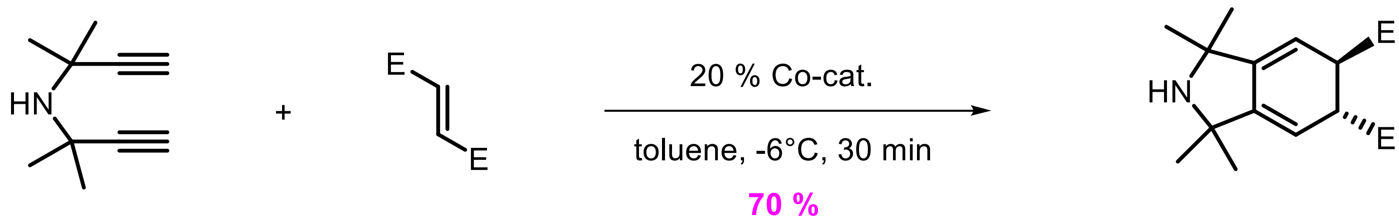
Cobalt and rhodium are effective

Type 2 : Enyne-monoalkyne cyclization



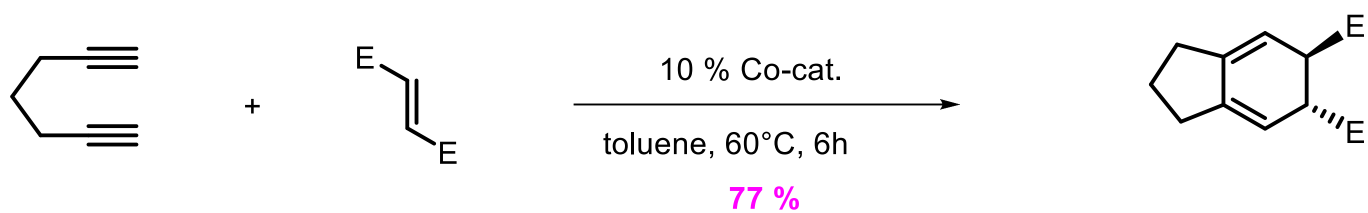
Co and Rh are not very efficient even inert in this cyclization
Pd is effective

2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES AND ALKENES

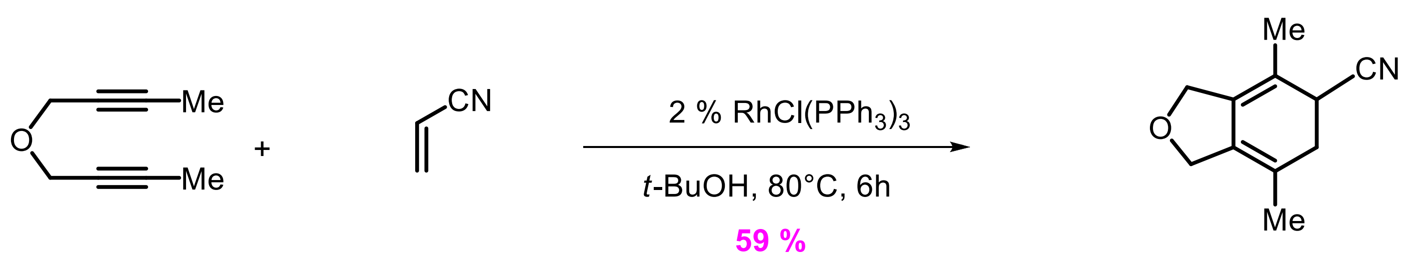


E = CO_2Et

Co-cat : $Co(CH_3CN)_2$(*trans* ECH=CHE)$_2$



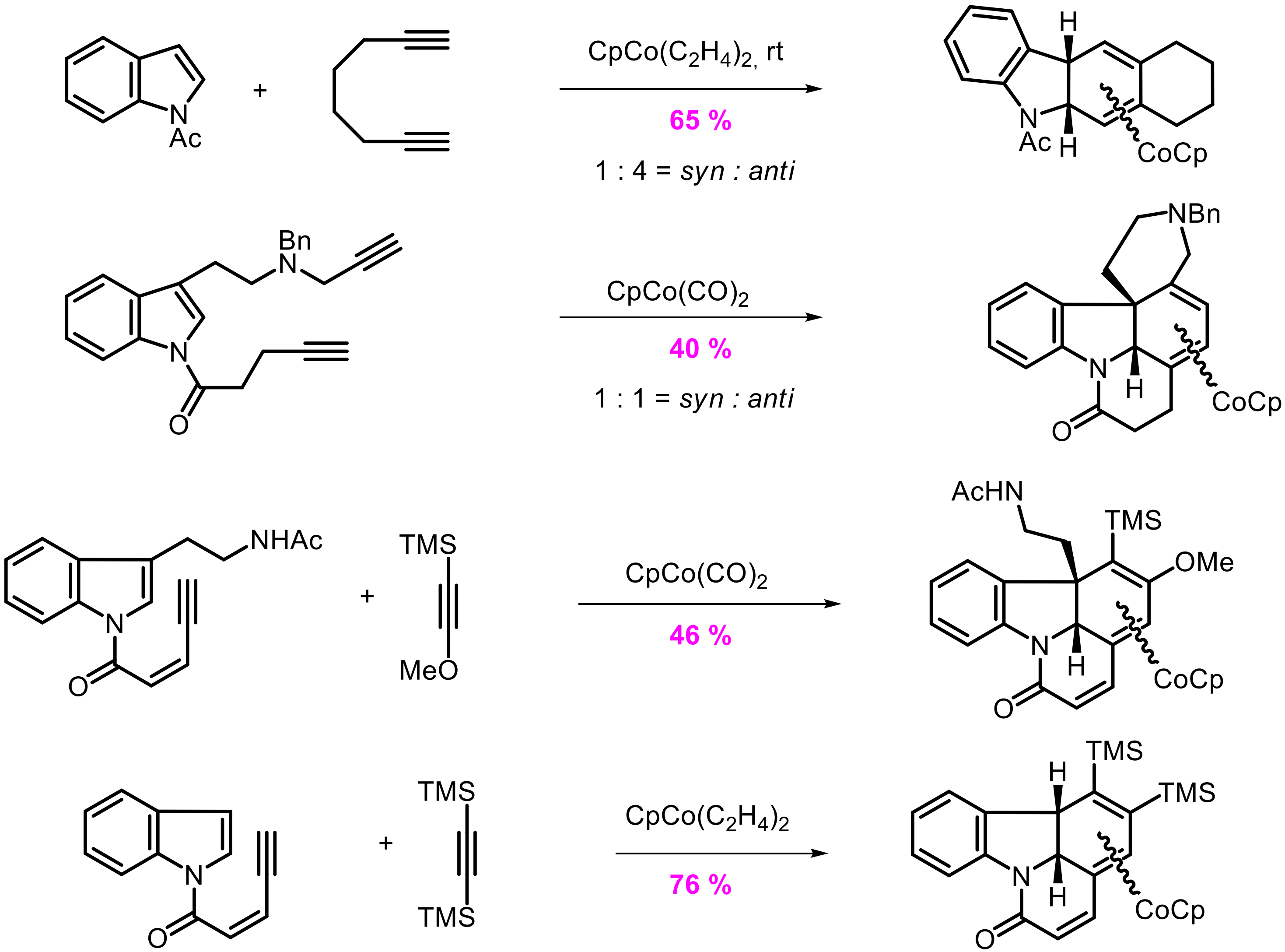
Chiusoli, G. P. *et al*



Grigg, R. *et al*

2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES AND ALKENES

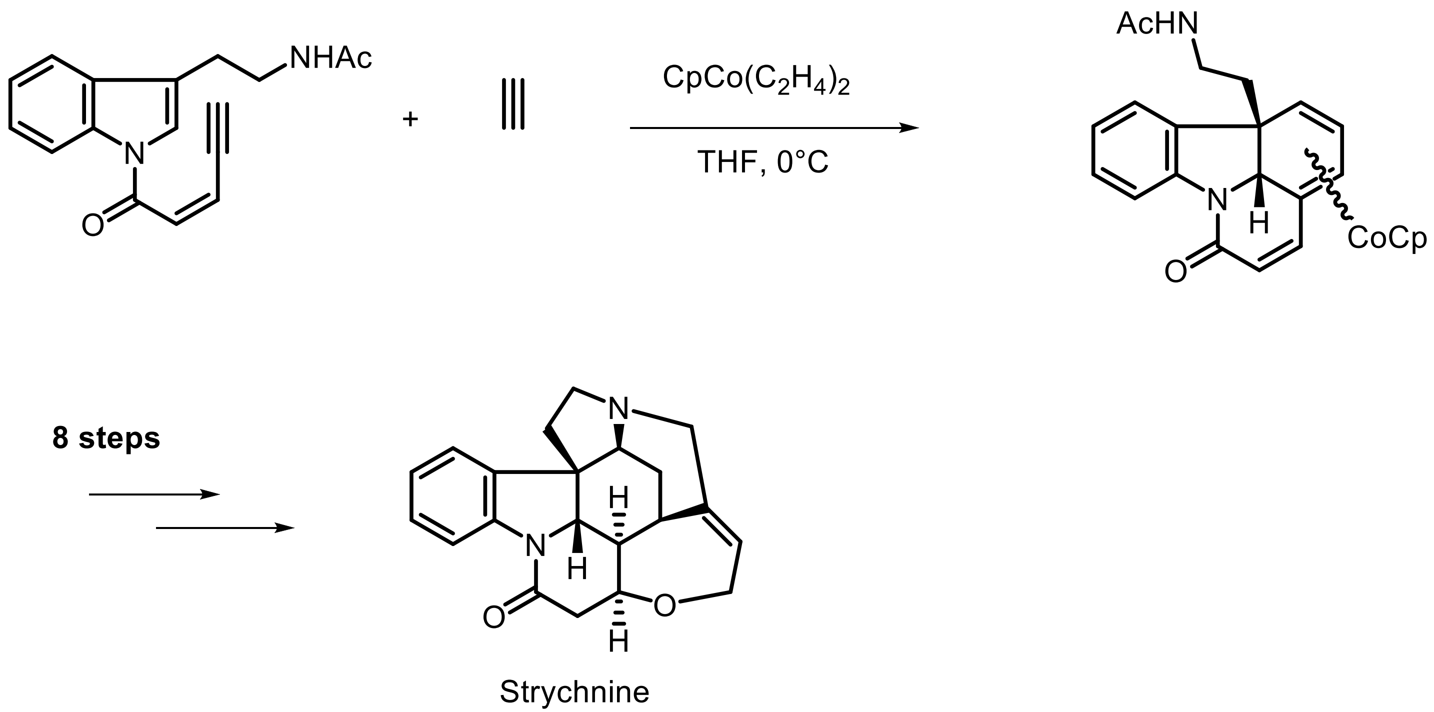
Cyclization of alkynes with the Indole 2, 3 double bond



Vollhardt, K. P. C. *et al*

2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES AND ALKENES

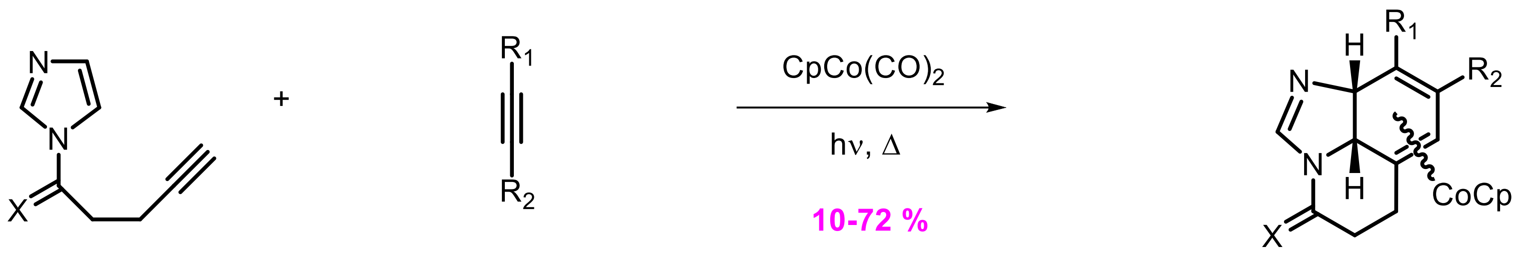
Cyclization of alkynes with the Indole 2, 3 double bond : formal synthesis of Strychnine



Vollhardt , K. P. C. *et al*

2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES AND ALKENES

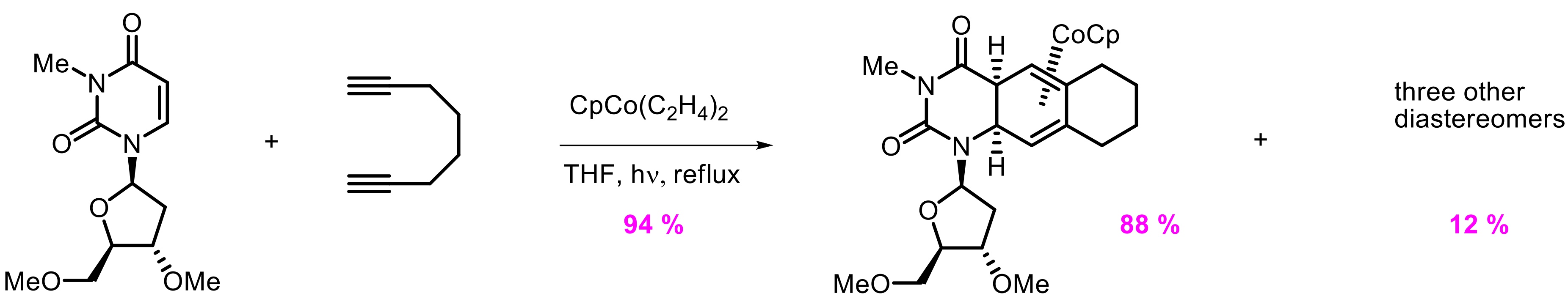
Cyclization of alkynes with the Imidazole 4, 5 double bond



X = O, CH_2 R_1, R_2 = TMS, OMe, CO_2Me

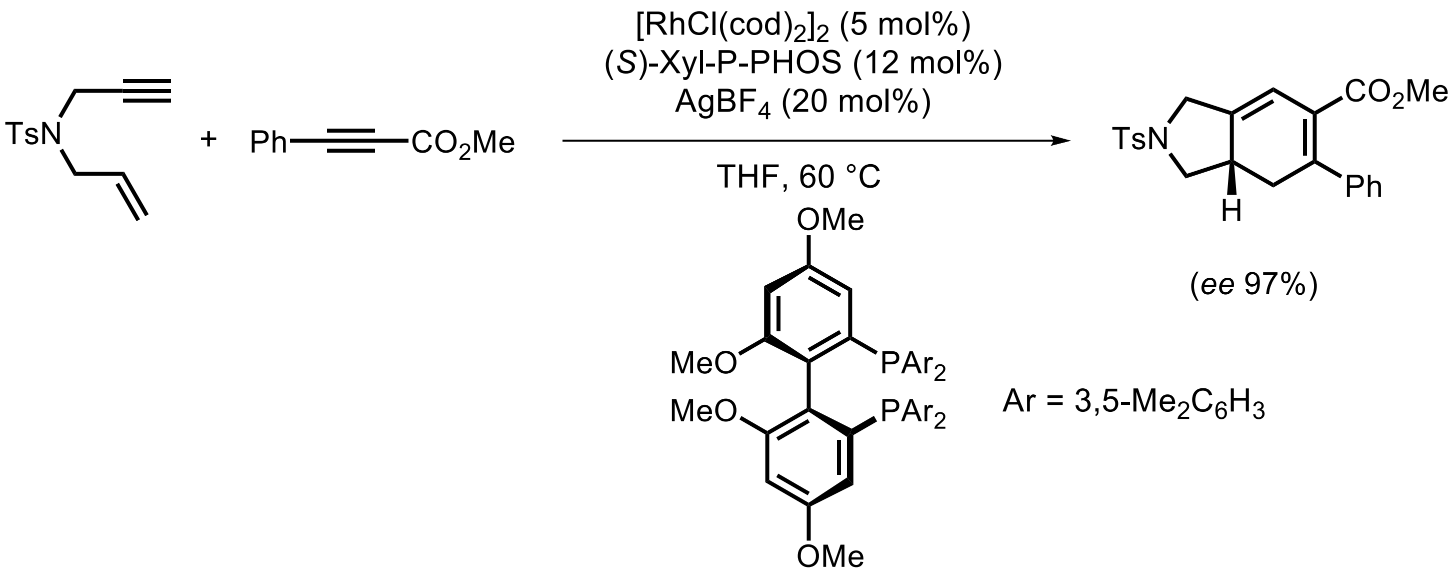
Vollhardt, K. P. C. *et al*

Cyclization of alkynes with Uracil derivatives



Vollhardt, K. P. C. *et al*

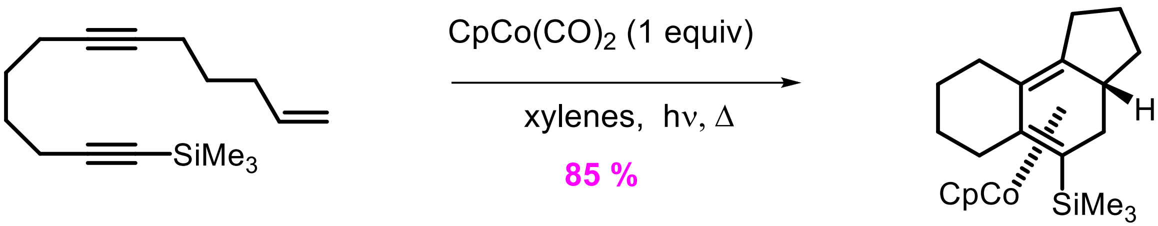
2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES AND ALKENES



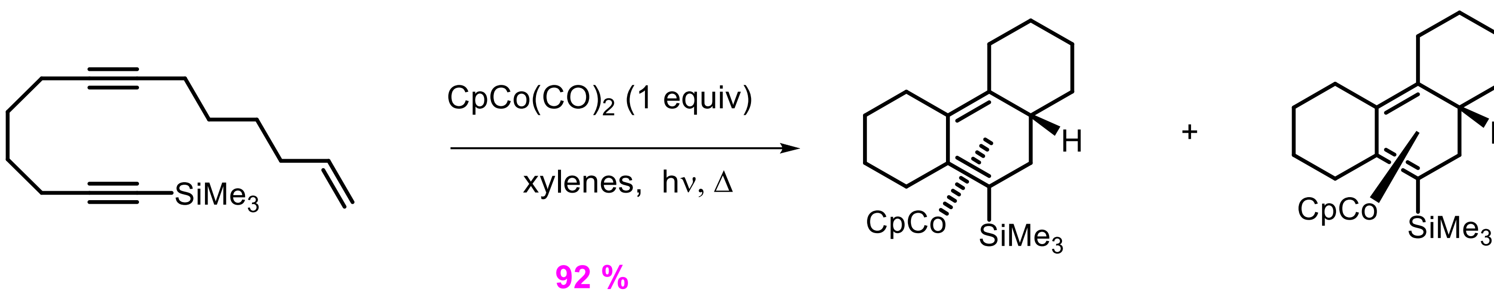
P. A. Evans *et al*

2. INTRAMOLECULAR [2+2+2] CYCLOADDITION OF ENEDIYNES

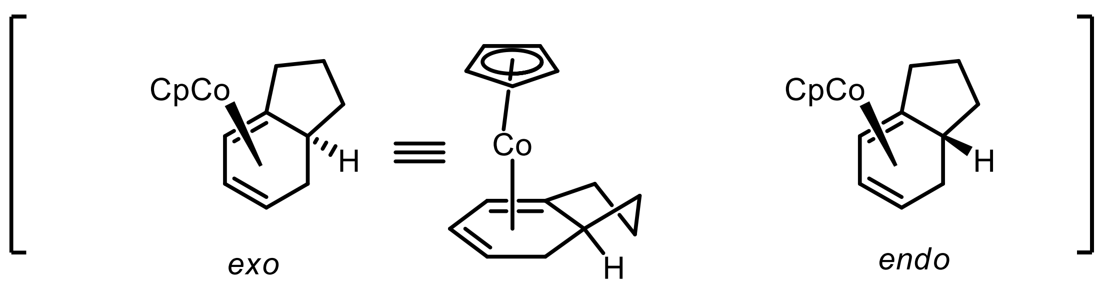
Enediynes with a terminal double bond :



only *exo*



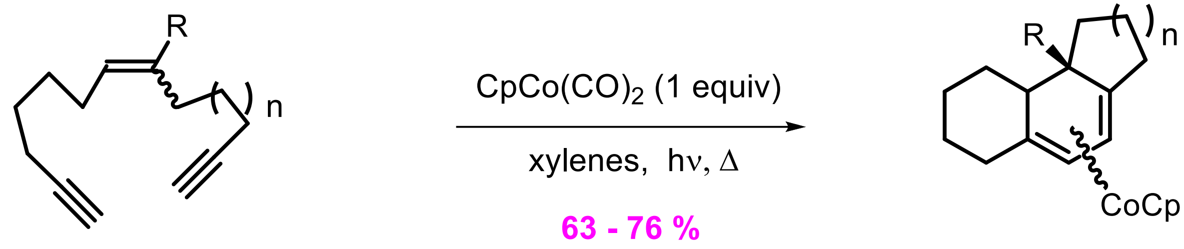
exo 1 : 1 ***endo***



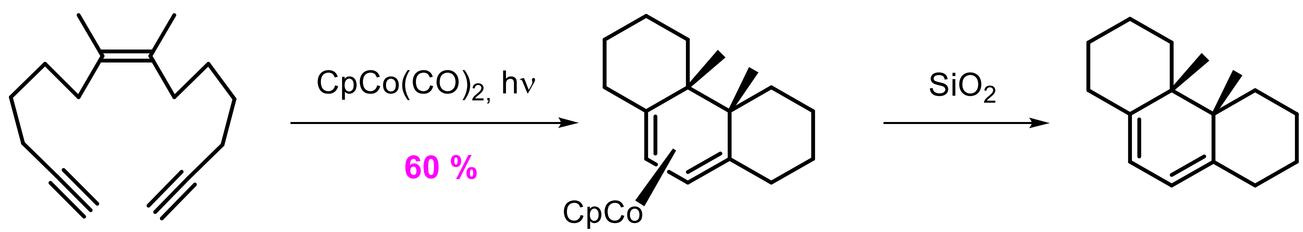
Vollhardt, K. P. C. *et al*

2. INTRAMOLECULAR [2+2+2] CYCLOADDITION OF ENEDIYNES

Enediynes with an internal double bond :

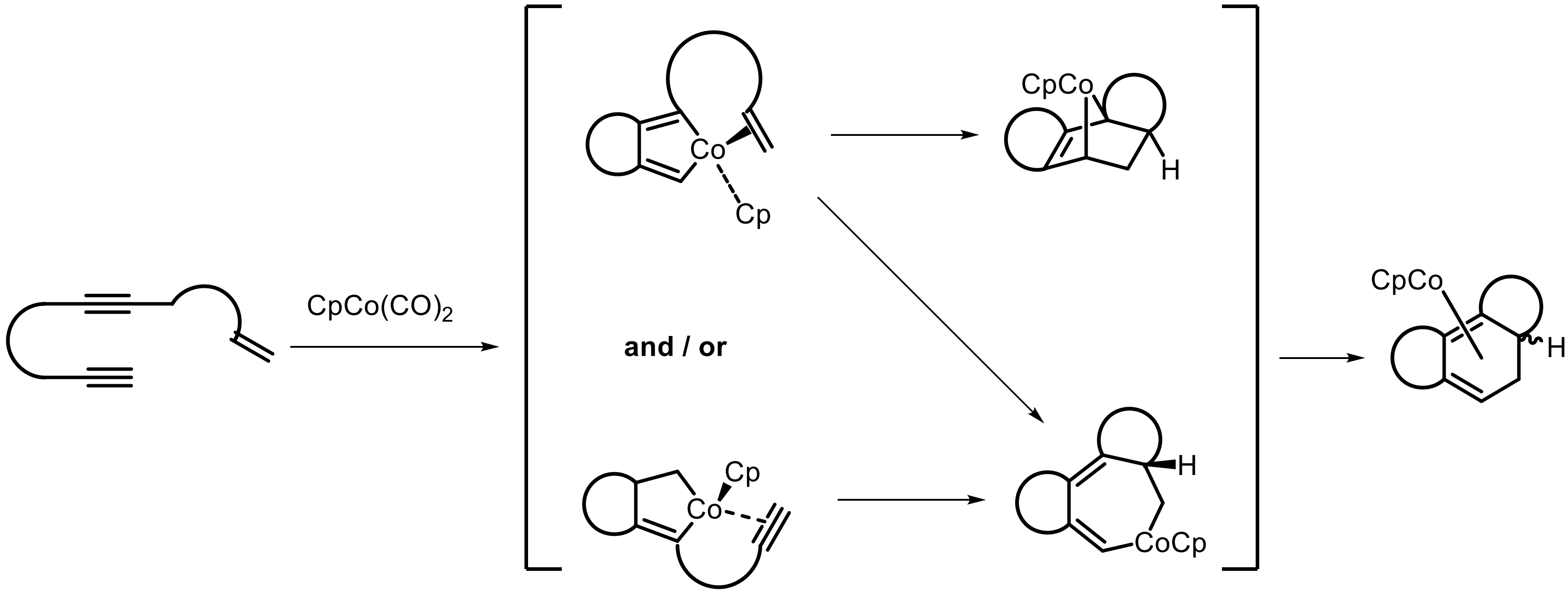


R = H or Me ; n = 1, 2



Vollhardt, K. P. C. *et al*

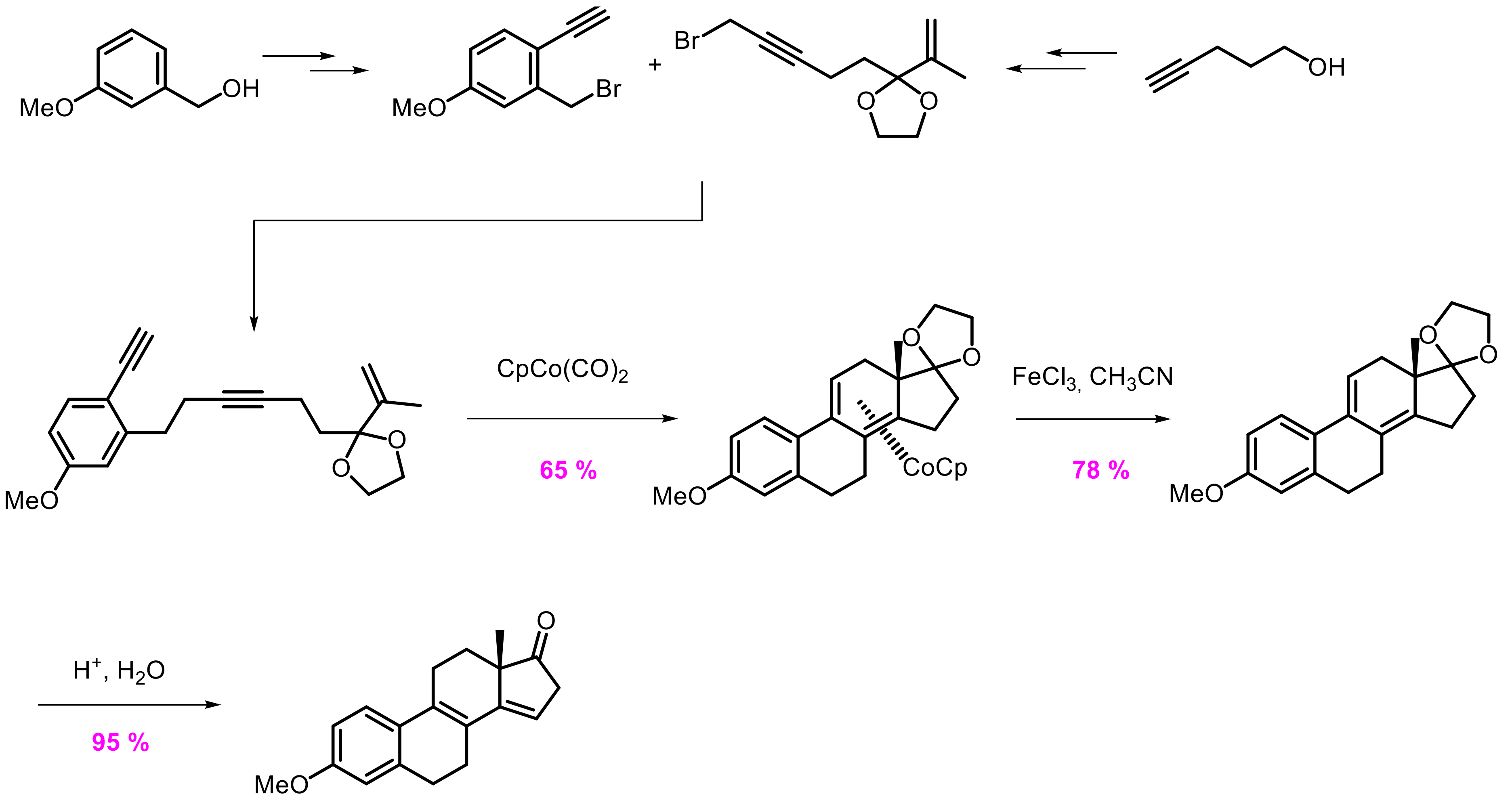
2. INTRAMOLECULAR [2+2+2] CYCLOADDITION OF ENEDIYNES: MECHANISTIC ASPECTS



Isolation of cobaltacyclopentenes: Wakatsuki, Y. *et al J. Am. Chem. Soc.* **1979**, *101*, 1123

2. [2+2+2] CYCLIZATIONS OF ENEDIYNES : THE COBALT WAY TO (±)-ESTRONE

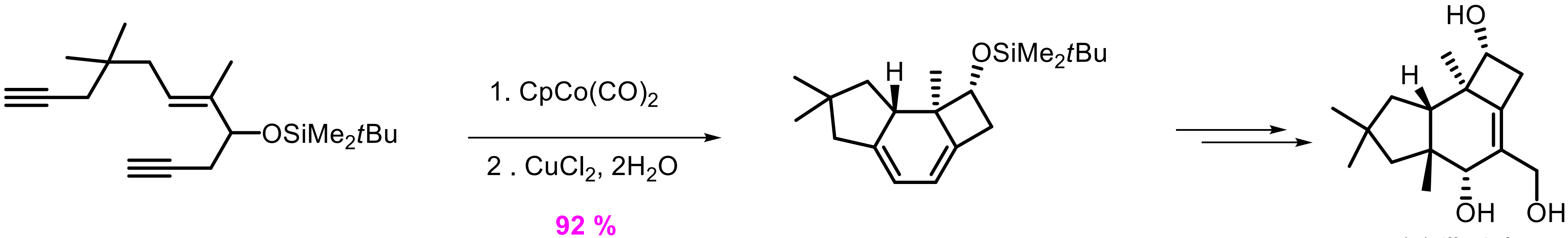
The A → ABCD approach



Vollhardt, K. P. C. *et al*

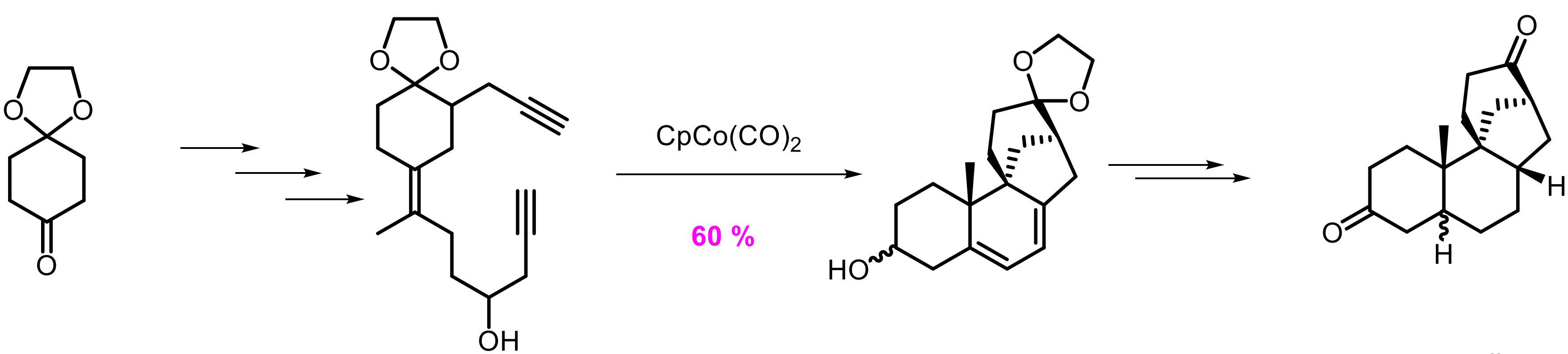
2. INTRAMOLECULAR [2+2+2] CYCLOADDITION OF ENEDIYNES

Stereoselective synthesis of the sesquiterpene Illudol



(±)-illudol

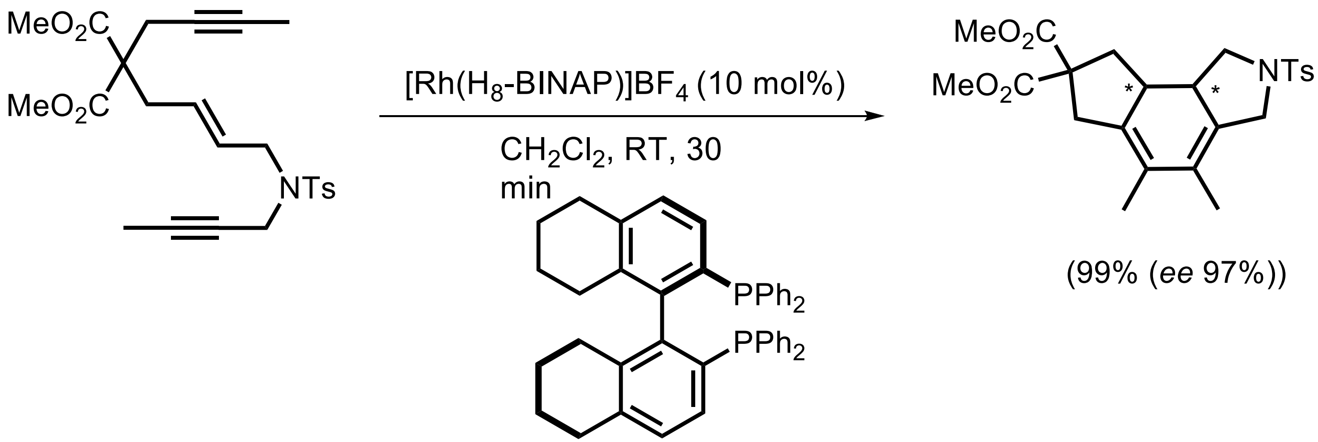
Synthesis of the diterpene Stemodine



stemodine

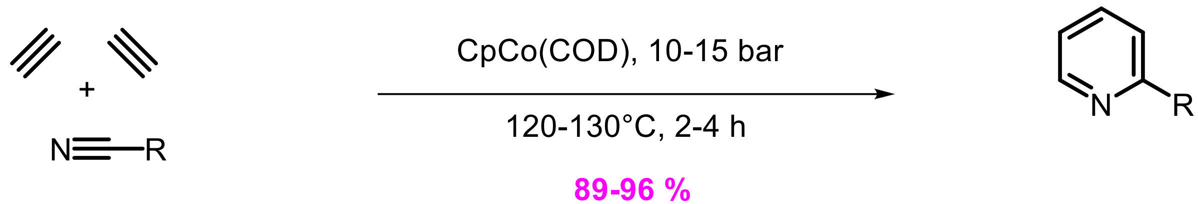
Vollhardt, K. P. C. *et al*

2. INTRAMOLECULAR [2+2+2] CYCLOADDITION OF ENEDIYNES

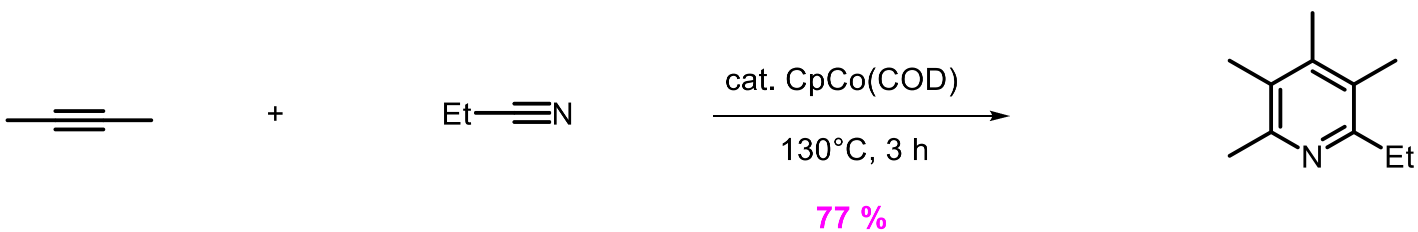


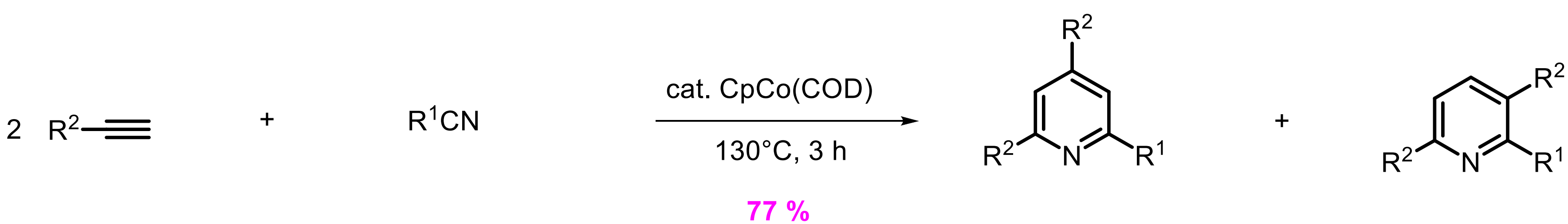
T. Shibata, *et al*

2. INTERMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES AND NITRILES



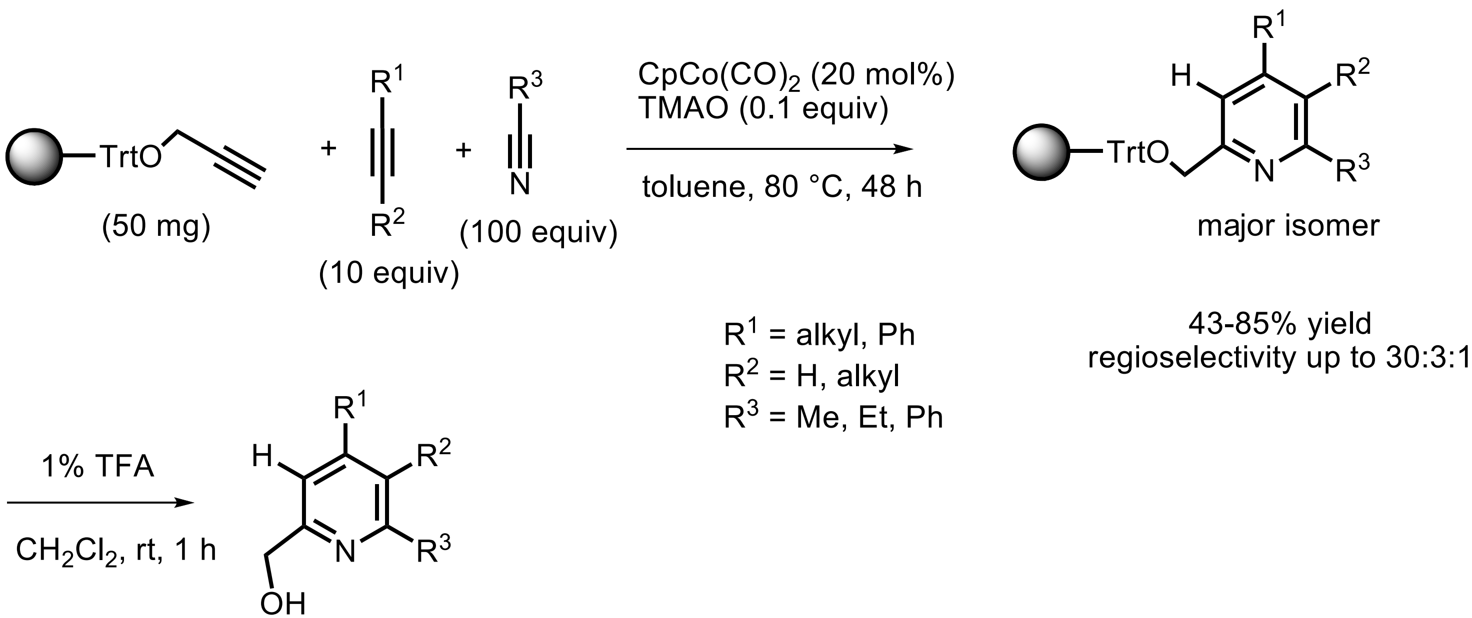
R = H, alkyl, cyclopropyl, $CH=CH_2$, thien-2-yl, aryl





Wakatsuki, Y. *et al*

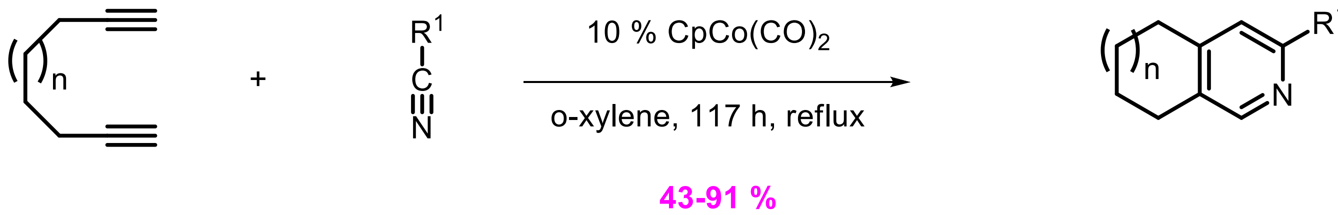
2. INTERMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES AND NITRILES



A. Deiters *et al*

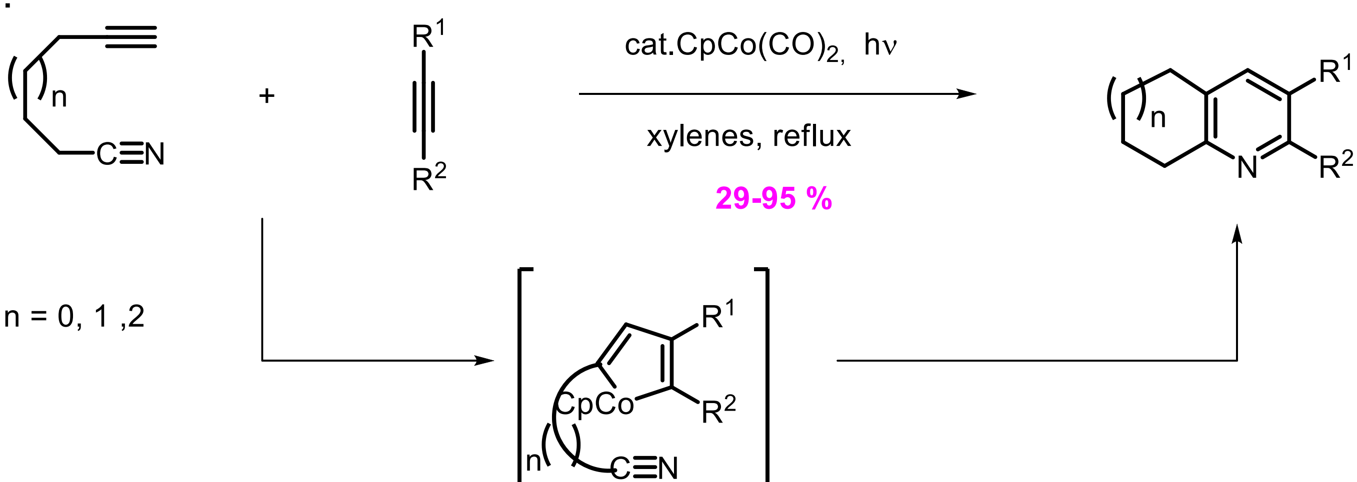
2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES AND NITRILES

Diyne and nitrile :



n =0, 1, 2 ; R^1 = alkyl, aryl, CH_2OCH_3, $CH_2CO_2C_2H_5$

Cyanoyne and alkyne :

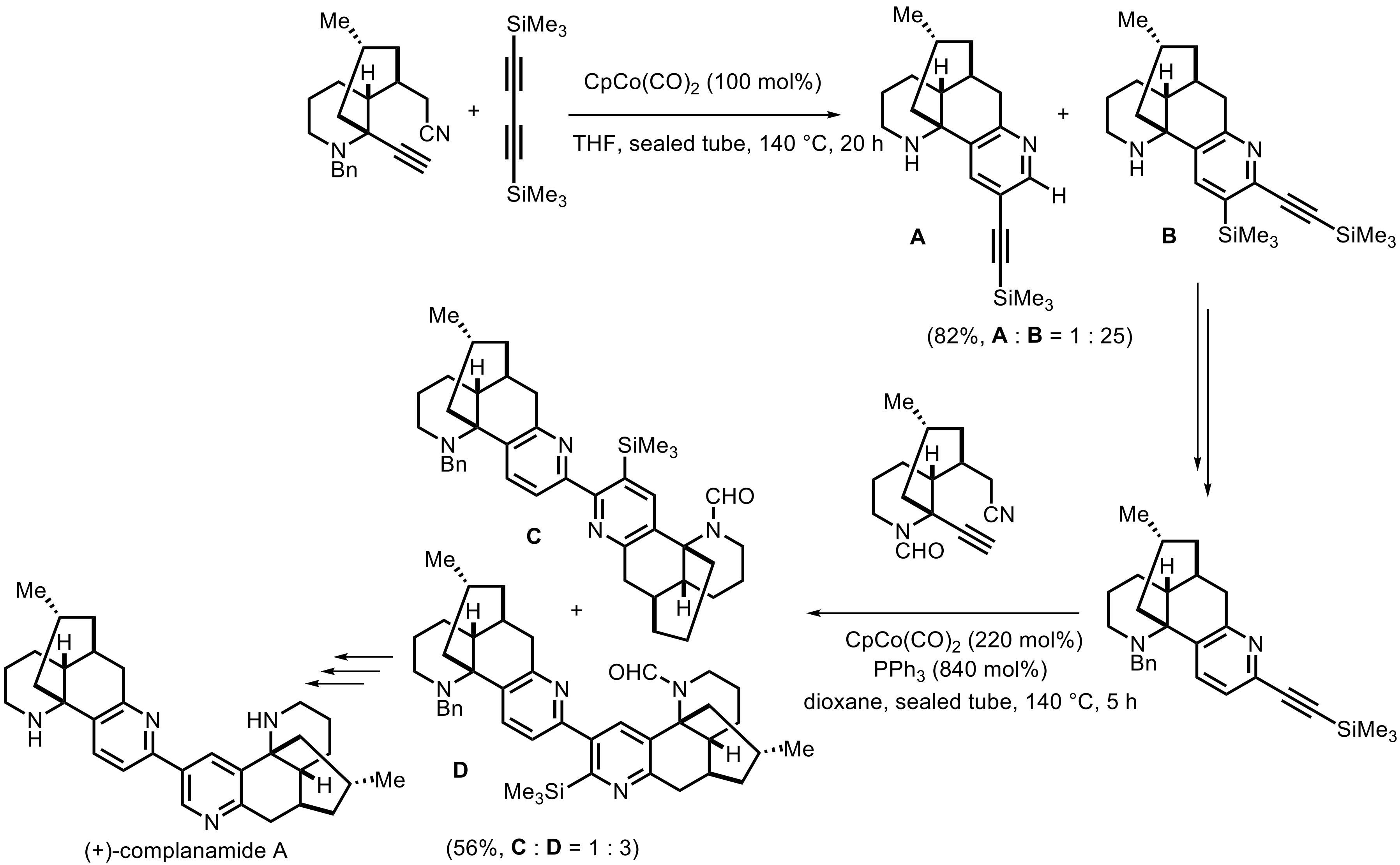


n = 0, 1 ,2

R^1, R^2 = $SiMe_3$, CO_2Me, CH_2OMe, H, alkyl, aryl

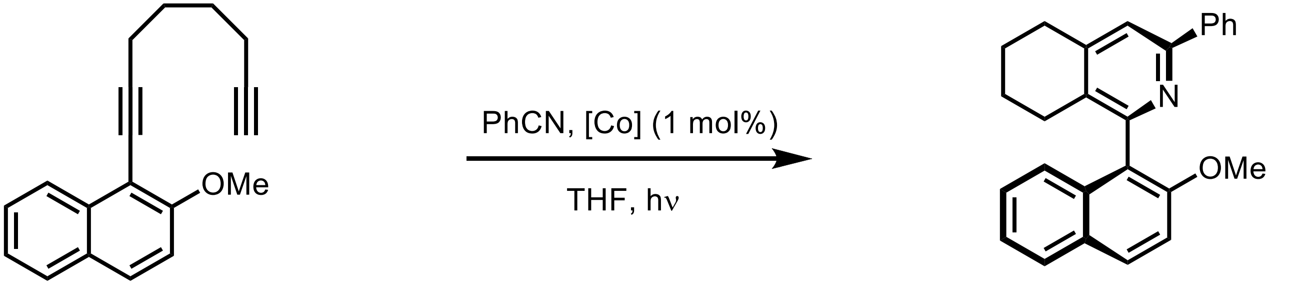
Vollhardt, K. P. C. *et al*

2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES AND NITRILES



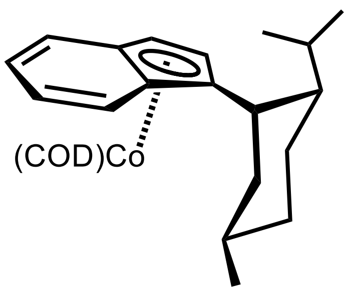
D. Siegel *et al*

2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES AND NITRILES



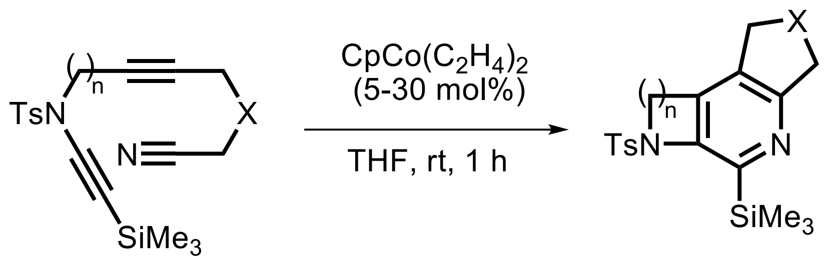
86 % yield , **93 %** ee

[Co] =



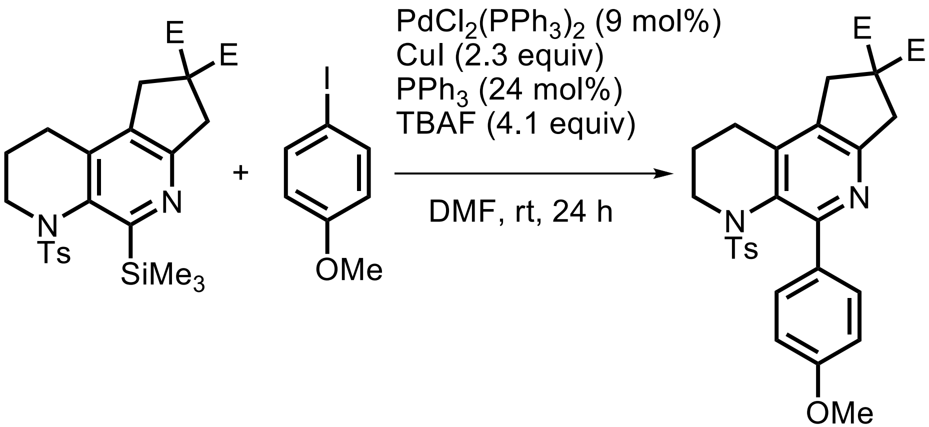
Gutnov *et al*

2. INTRAMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES AND NITRILES



50-100% yield

X = NCbz, CH_2, $(CH_2)_2$, $C(CO_2Me)_2$, O
n = 1, 2, 3

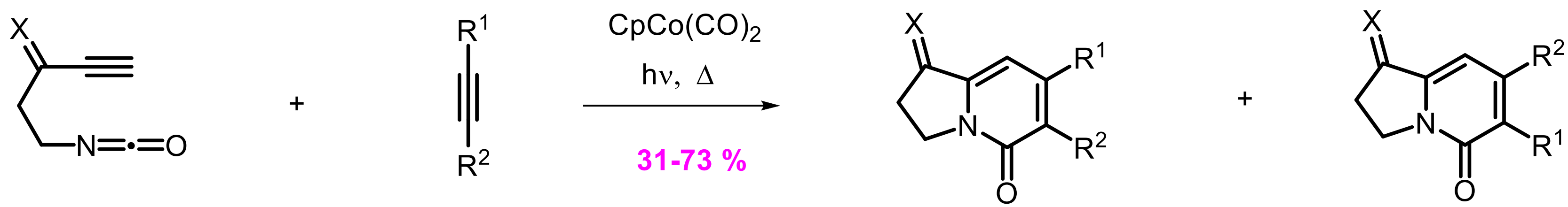


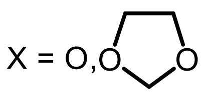
(77%)

C. Aubert, M. Malacria *et al.*

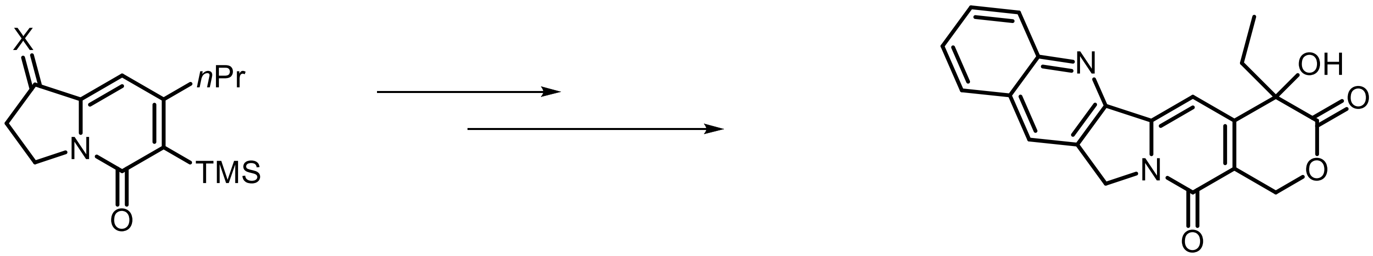
2. BIMOLECULAR [2+2+2] CYCLOADDITION OF ALKYNES AND ISOCYANATES

Cyclization of alkynes with isocyanates : formal total synthesis of Camptothecin





R^{1}, R^{2} = alkyl, ketal , $SiMe_3$, CH_2OR

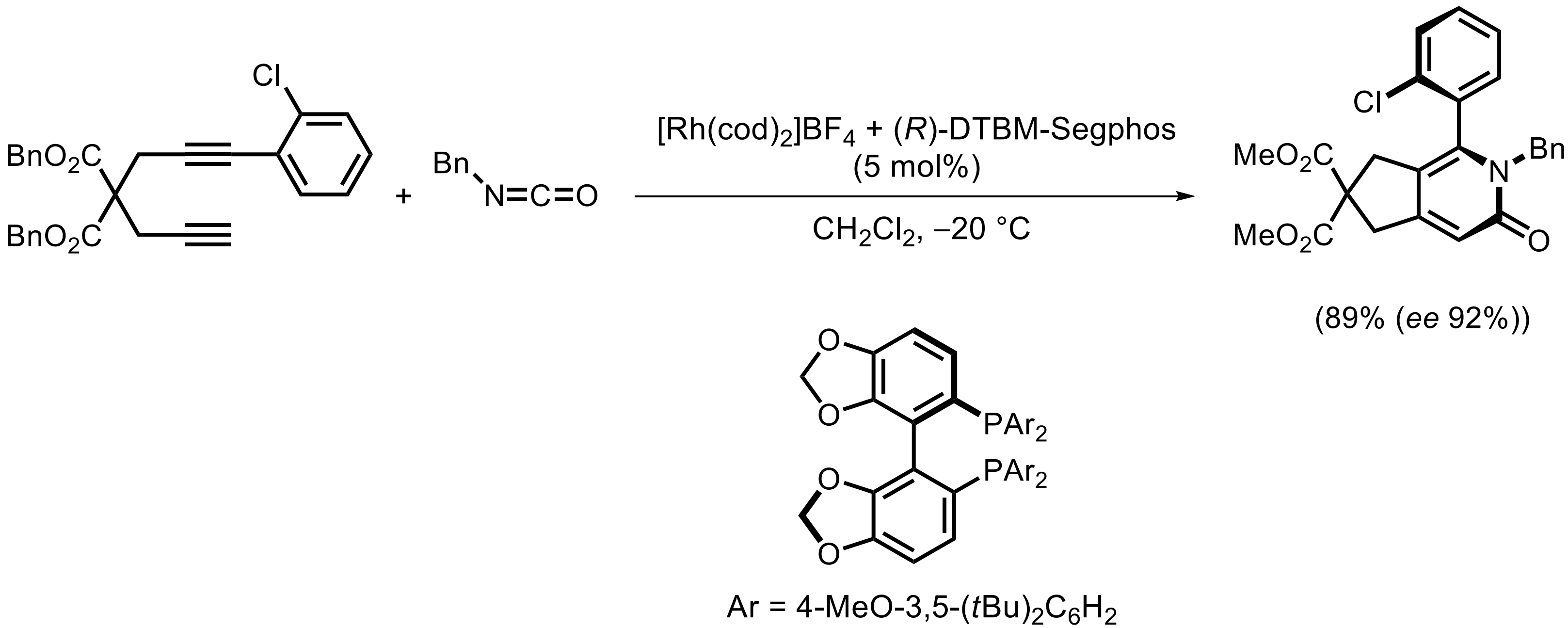


Camptothecin

Vollhardt, K. P. C. *et al*

Anticancer drug: topotecan®, irinotecan®

2. BIMOLECULAR [2+2+2] CYCLOADDITIONS INVOLVING ISOCYANATES

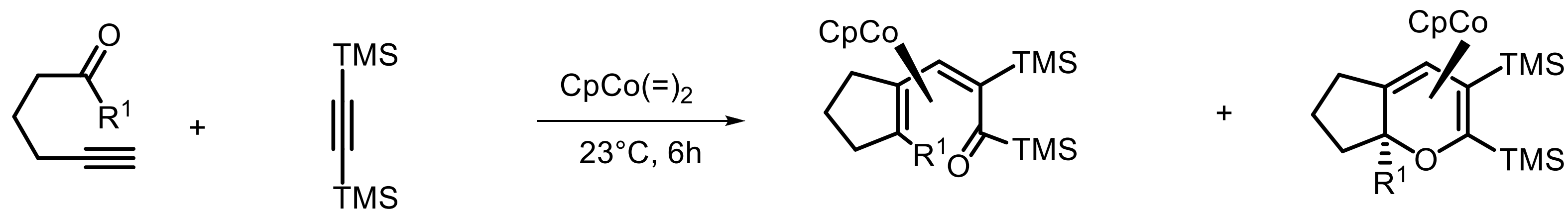


K. Tanaka *et al*

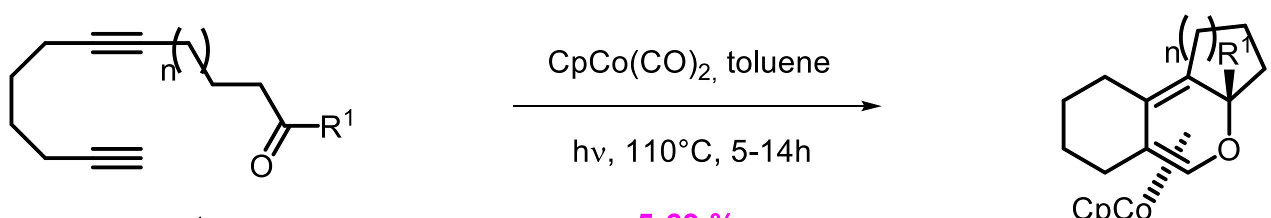
2. [2+2+2] CYCLOADDITIONS INVOLVING ALDEHYDES AND KETONES

Enamine double bond could also react and allow the formal total synthesis of γ-Lycorane: Vollhardt, K. P. C. *et al* *Synthesis* **1993**, 579

Inter- and intramolecular cyclizations of alkynes with aldehydes and ketones :



R^1 = H	18 %	**100**	0
R^1 = Me	86 %	0	**100**

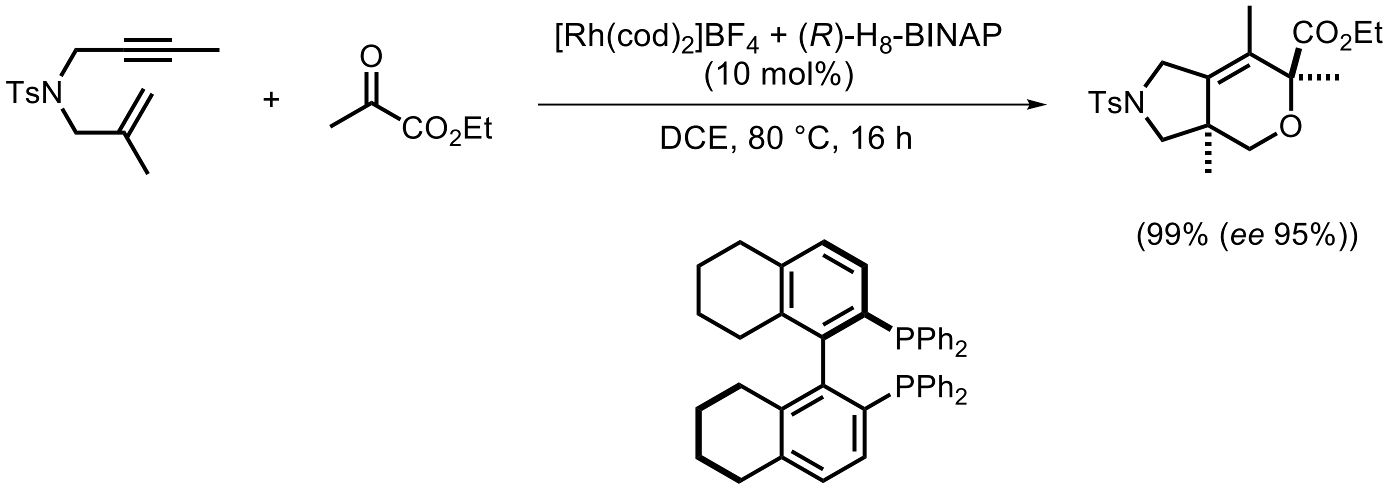


n = 1, 2 ; R^1 = H, Me

5-69 %

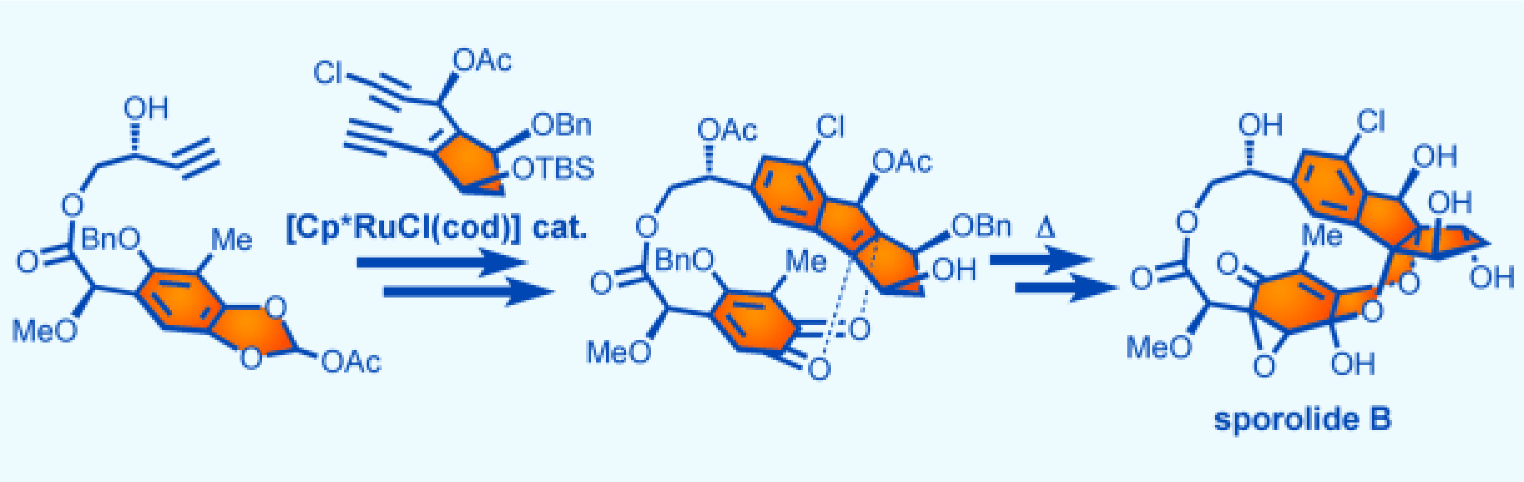
Vollhardt, K. P. C. *et al*

2. [2+2+2] CYCLOADDITIONS INVOLVING ALDEHYDES AND KETONES



(99% (*ee* 95%))

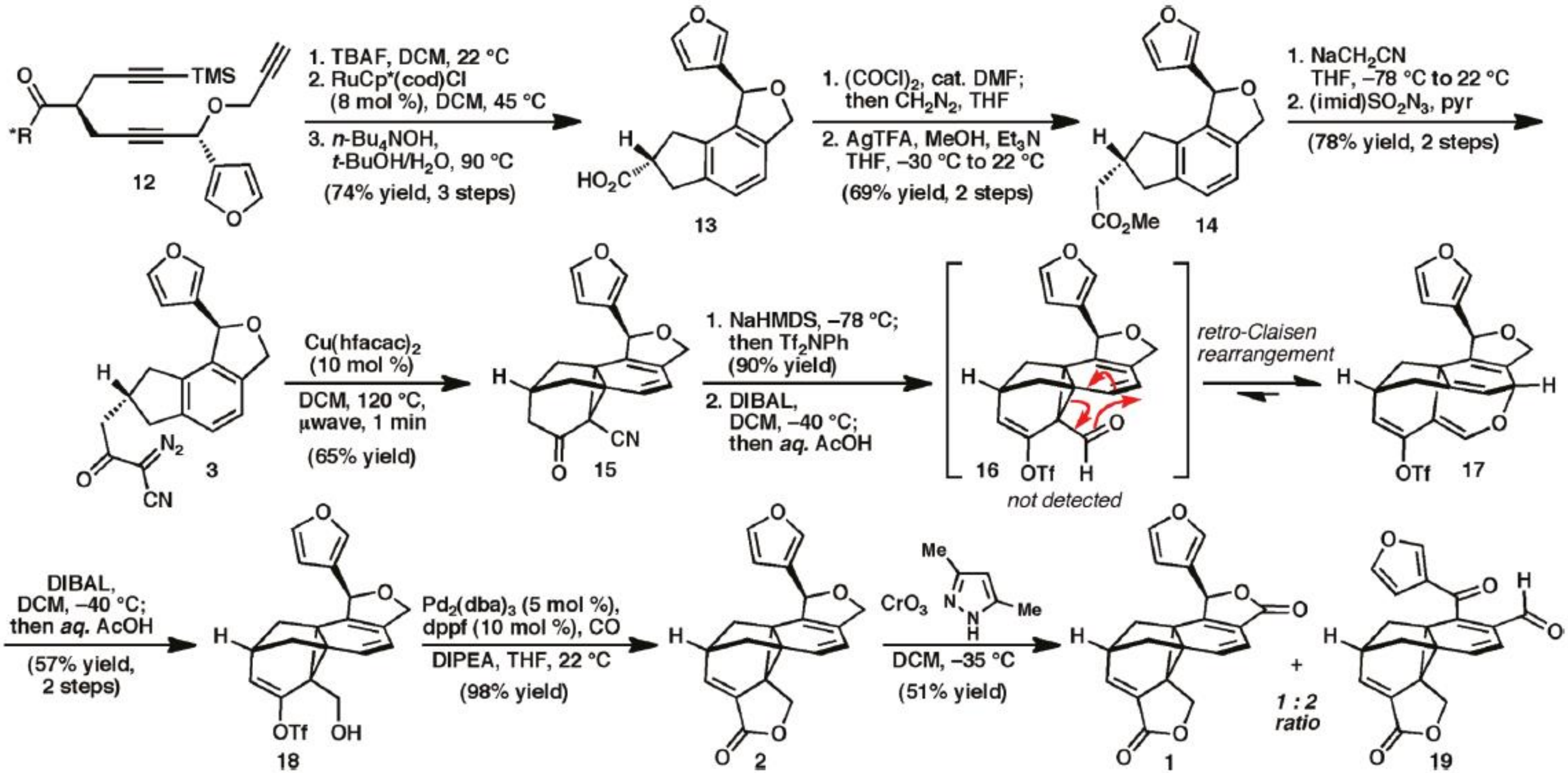
2. SELECTED APPLICATIONS OF WHAT WE HAVE SEEN IN CHAPTER 2



Nicolau, K. C. *et al*

2. SELECTED APPLICATIONS OF WHAT WE HAVE SEEN IN CHAPTER 2

Scheme 2. Synthesis of (+)-Salvileucalin B (1)

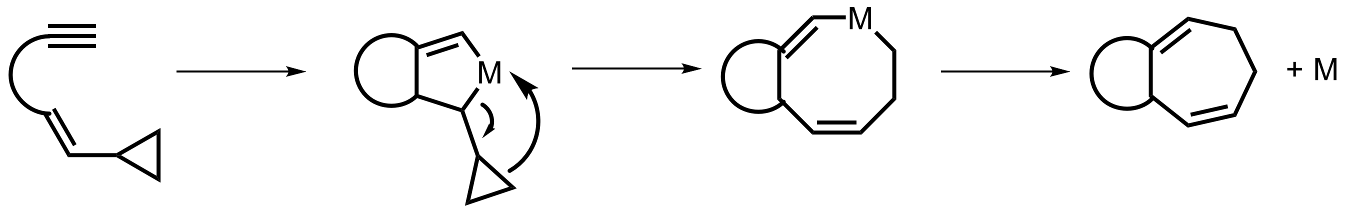


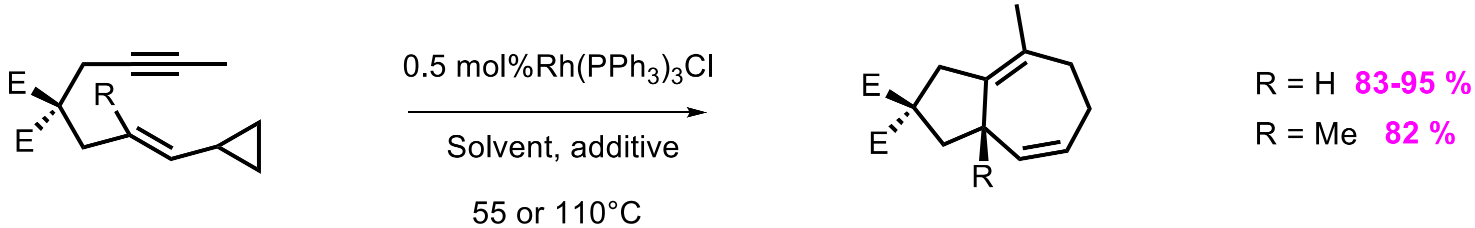
Reisman, S. E. *et al*

3. High Order Cycloadditions

Ex: [5+2] CYCLOADDITIONS

Access to seven-membered rings



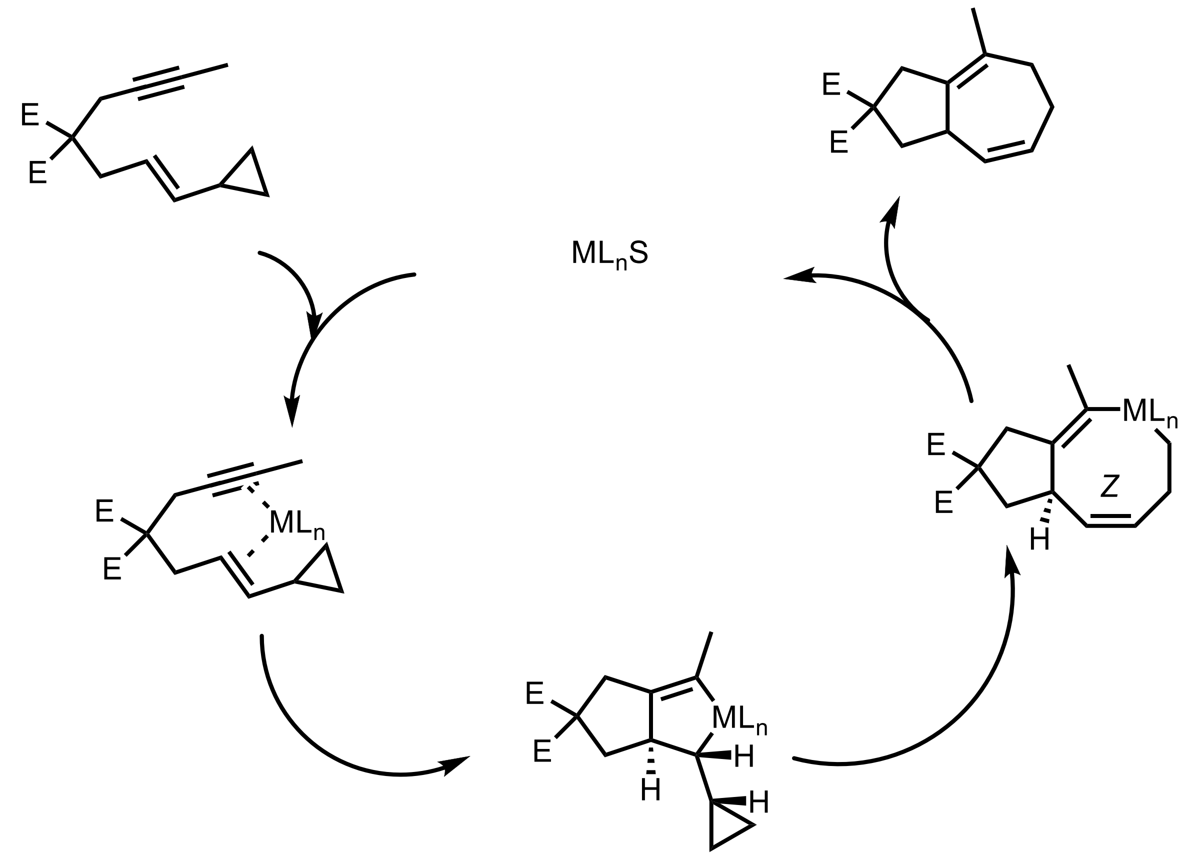


R = H, Me   solvent = toluene, CF_3CH_2OH additive = AgOTf

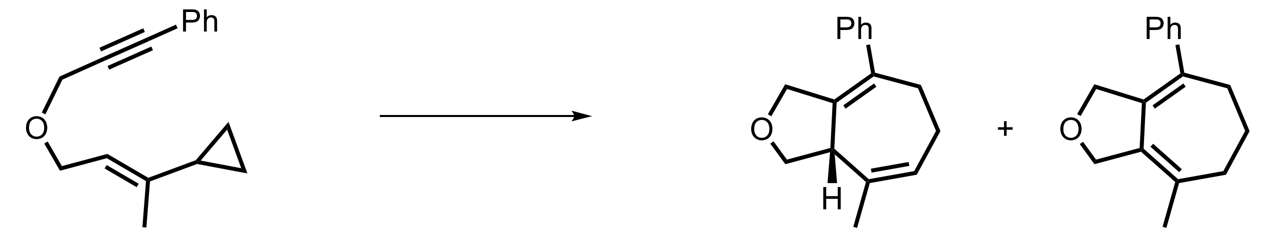
when the polarity of the solvent increases, the reaction proceeds more rapidly (20 min At 110 °C)

Wender, P. A. *et al*

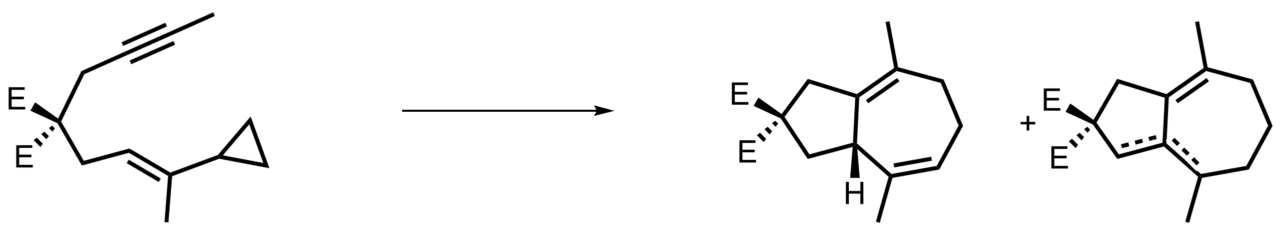
3. [5+2] CYCLOADDITIONS: MECHANISTIC ASPECTS



3. [5+2] CYCLOADDITIONS: CHOICE OF THE CATALYST



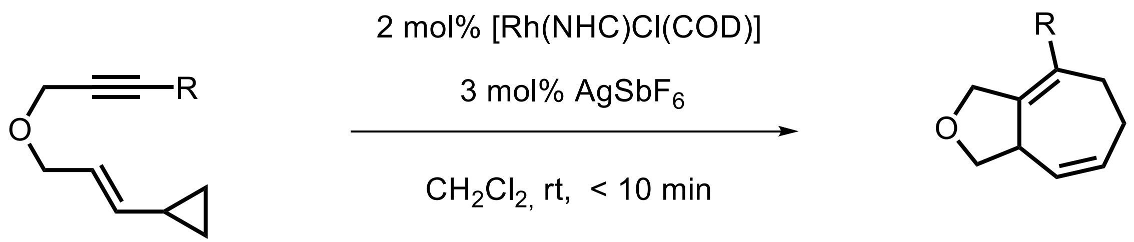
$[Rh(CO)_2Cl]_2$	5 mol % 110°C, 20 min	**80 %**	0 %
$Rh(PPh_3)_3Cl/AgOTf$		0 %	0 %



$[Rh(CO)_2Cl]_2$	5 mol % 110°C, 3 h	**80 %**	0 %
$Rh(PPh_3)_3Cl/AgOTf$	10 mol % 110°C, 2 d	**69 %**	**20 %**

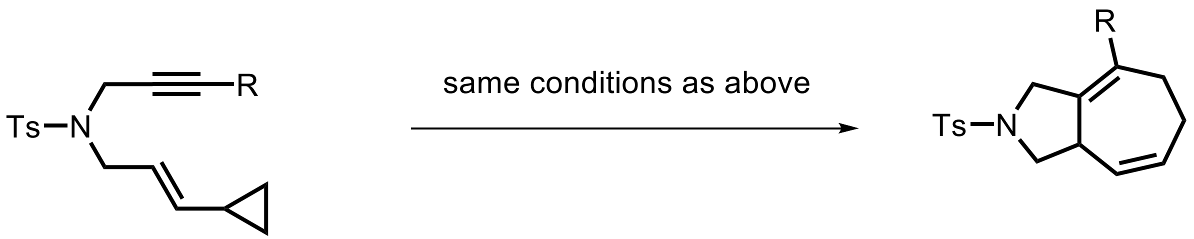
Wender, P. A. *et al*

3. [5+2] CYCLOADDITIONS: NHC-Rh CATALYST



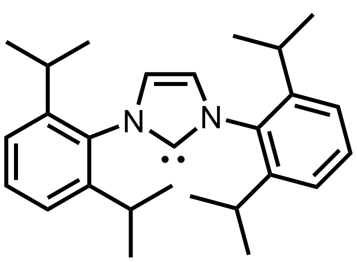
R = H, Ph

R = H **91%**
R = Ph **96%**



R = H, Ph, Me, Et

R = H **98%**
R = Ph **95%**
R = Me **93%**
R =Et **94%**



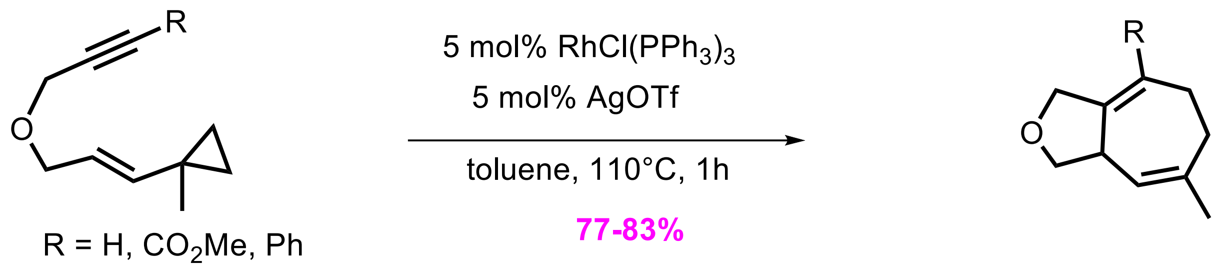
NHC

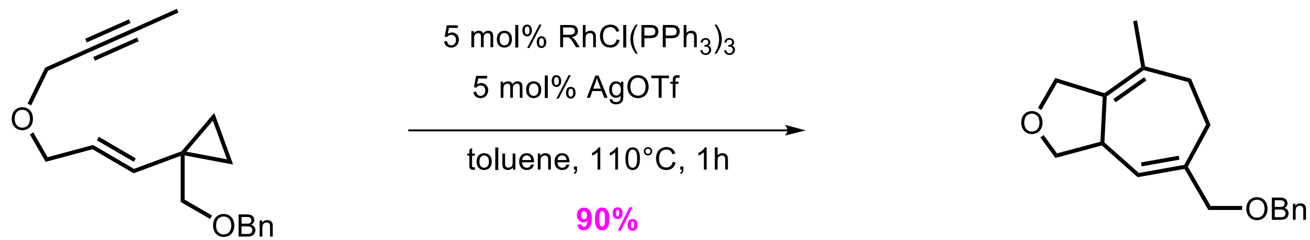
With this catalyst, intermolecular reaction does not work

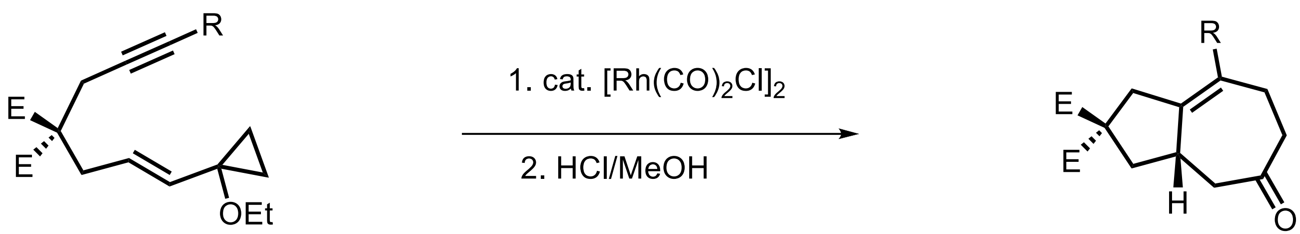
Chung, Y. K. *et al*

3. [5+2] CYCLOADDITIONS: REGIO- and STEREOSELECTIVITY

1-Substituted 1-vinylcyclopropanes





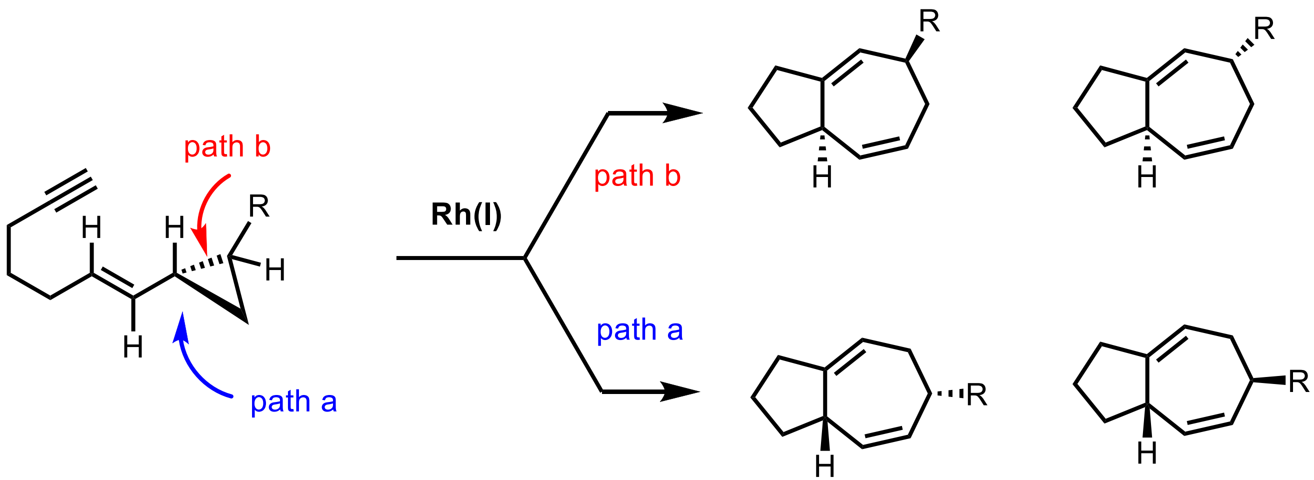


R = H	5 mol% cat., $CDCl_3$, 30°C, 40h	81%
R = Me	0.5 mol% cat., CH_2Cl_2, rt, 30h	73%

Wender, P. A. *et al*

3. [5+2] CYCLOADDITIONS: REGIO- and STEREOSELECTIVITY

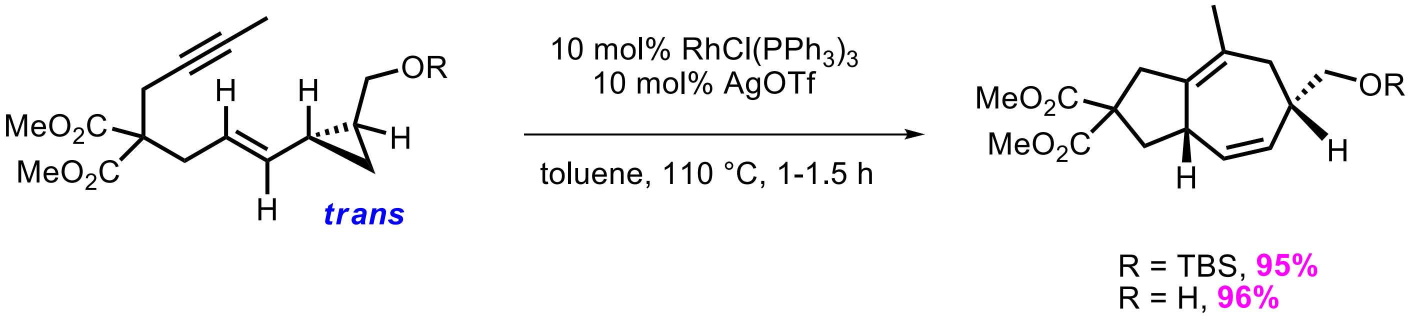
1,2-Disubstituted 1-vinylcyclopropanes:

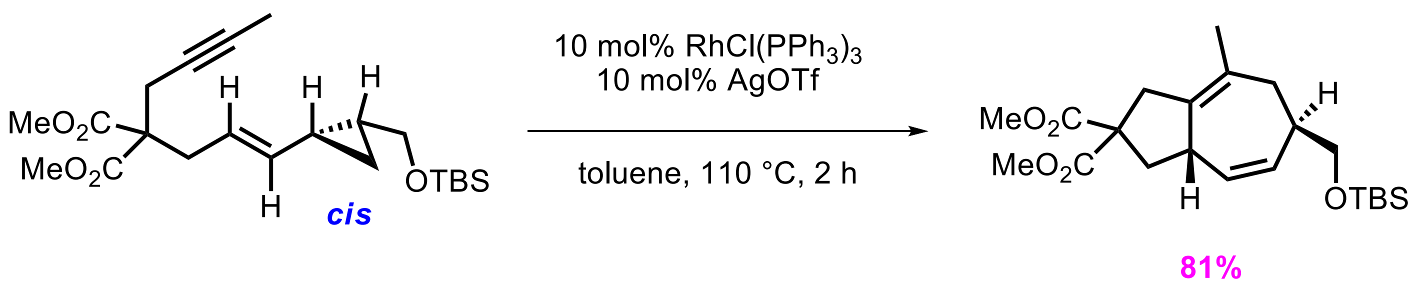


Wender, P. A. *et al*

3. [5+2] CYCLOADDITIONS: REGIO- and STEREOSELECTIVITY

1,2-Disubstituted 1-vinylcyclopropanes:

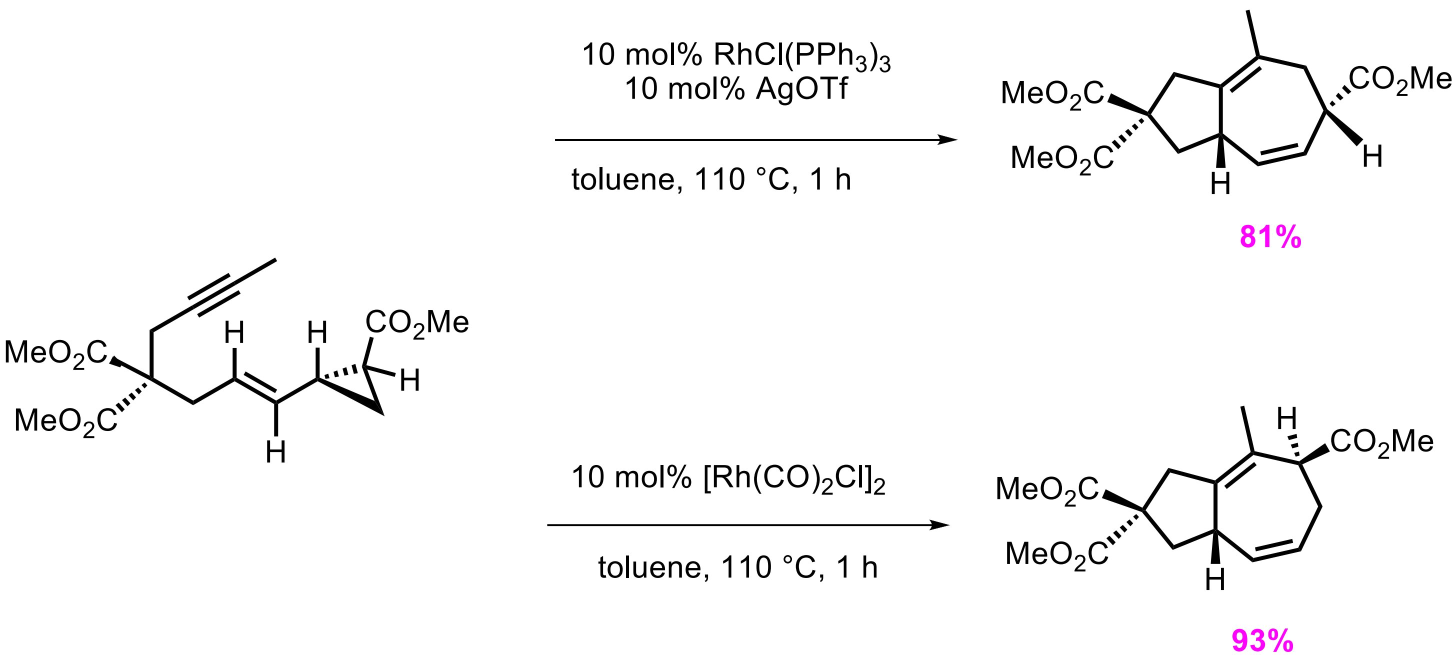




The product arises from the cleavage of the less substituted cyclopropane bond

3. [5+2] CYCLOADDITIONS: REGIO- and STEREOSELECTIVITY

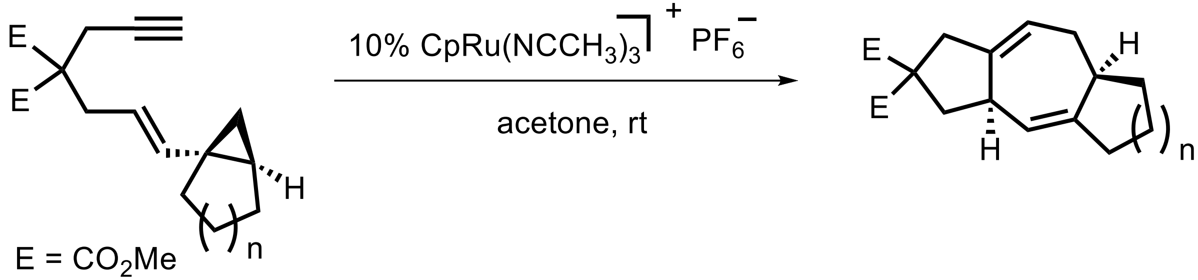
1,2-Disubstituted 1-vinylcyclopropanes:



Wender, P. A. *et al*

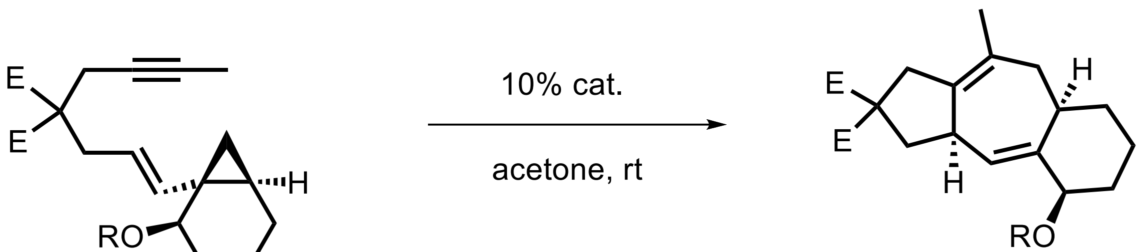
3. RUTHENIUM-CATALYZED [5+2] CYCLOADDITIONS

Construction of tricyclic compounds containing a seven-membered ring



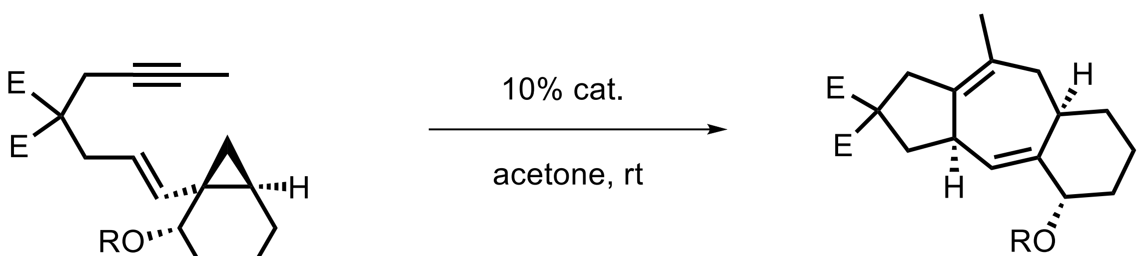
n = 1 **85%**

n =2 **81%**



R = H **81%** dr > 20:1

R =TBS **81%** dr > 20:1

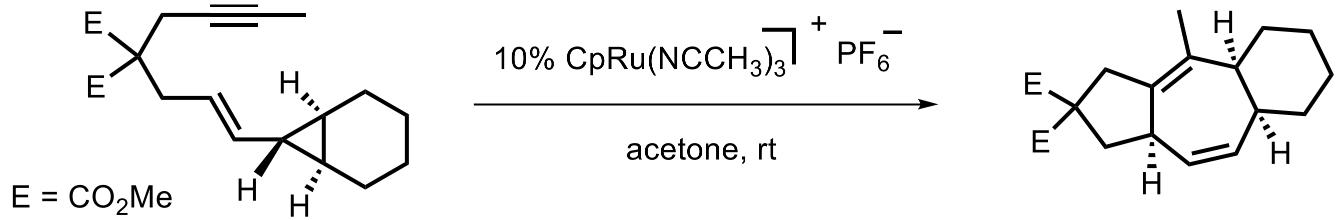


R = H **80%** dr > 20:1

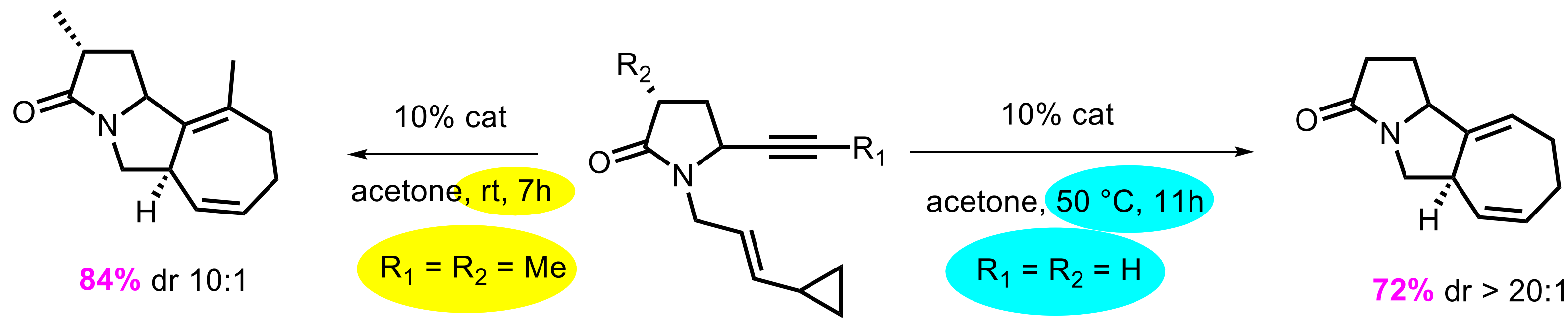
R =TBS **69%** dr > 10:1

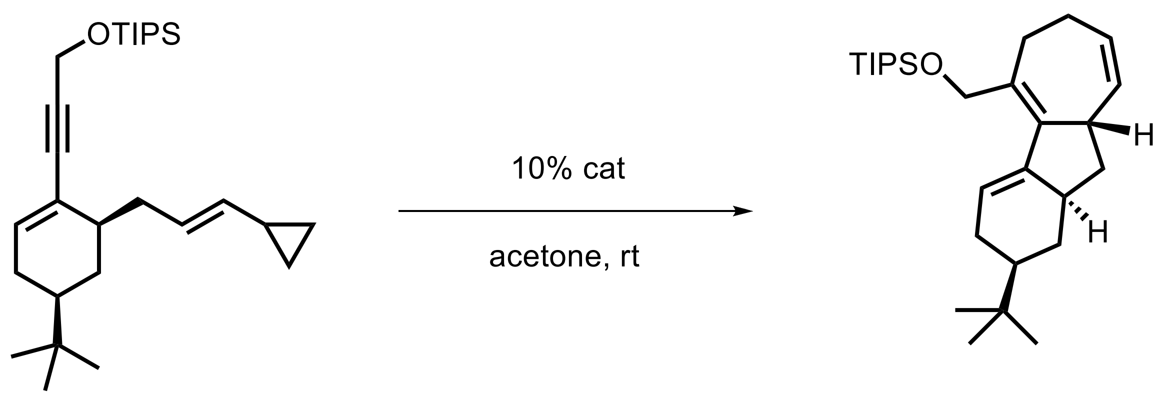
Trost, B.M. *et al*

3. RUTHENIUM-CATALYZED [5+2] CYCLOADDITIONS



93% dr > 20:1

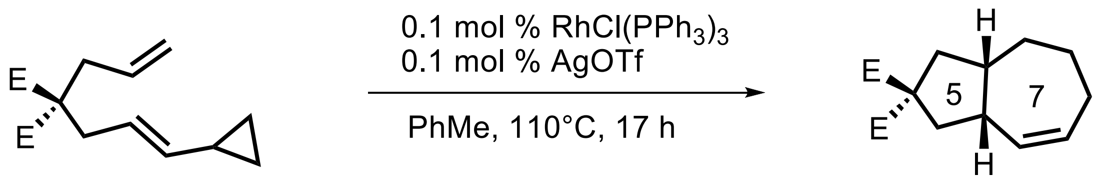




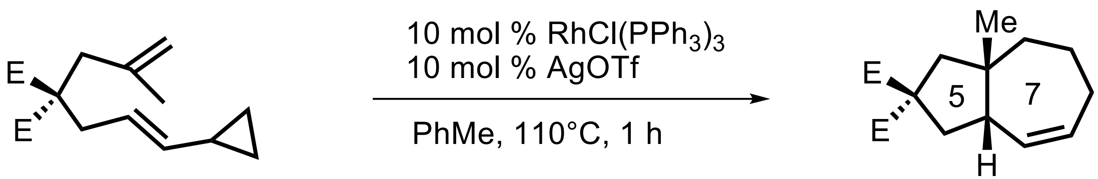
91% dr = 10:1

Trost, B.M. *et al*

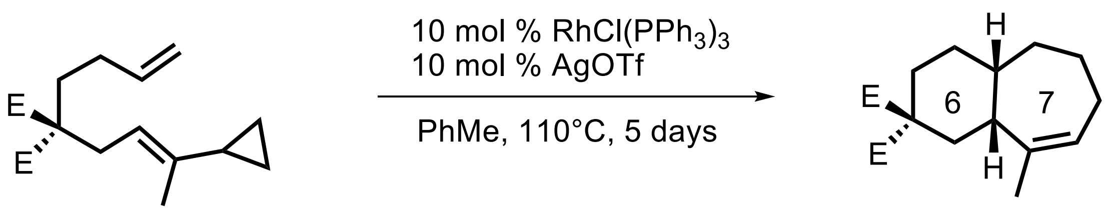
3. [5+2] CYCLOADDITIONS OF ENE-VINYLCYCLOPROPANES



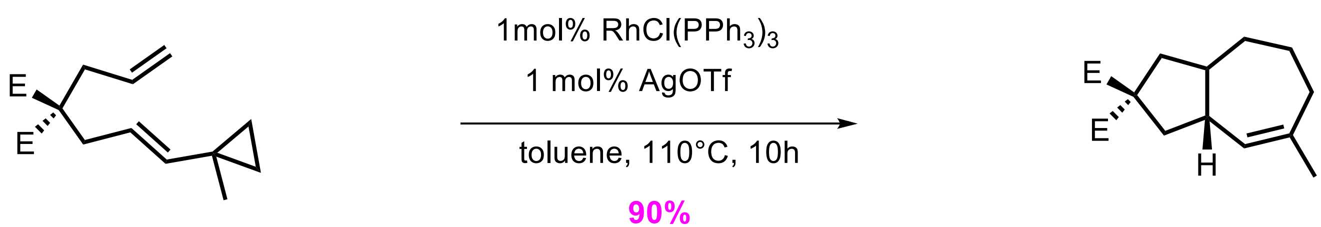
86-91 %, only one isomer



94 %, only one isomer

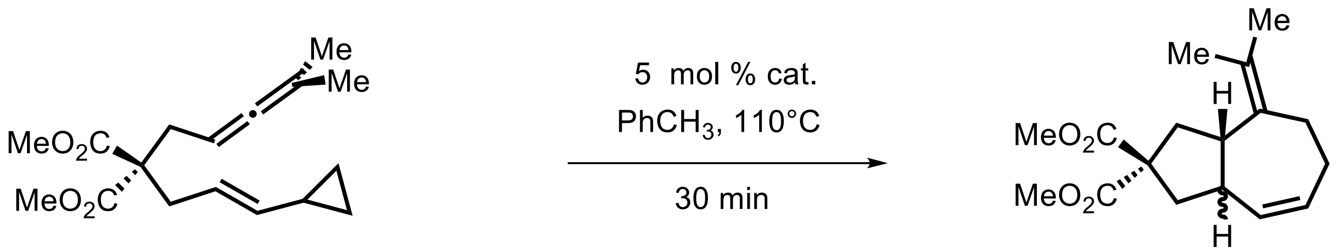


77 %, only one isomer



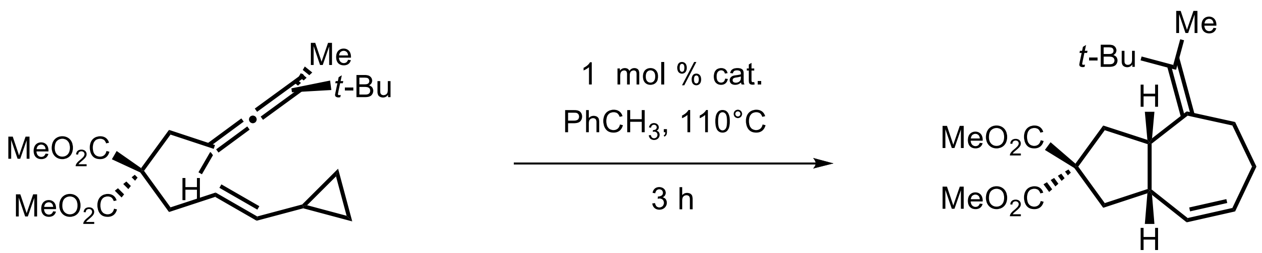
Wender, P. A. *et al*

3. [5+2] CYCLOADDITIONS OF ALLENE-VINYLCYCLOPROPANES



with $RhCl(PPh_3)_3$ + AgOTf	**92 %**	*cis* / *trans* = 2/1
$[Rh(CO)_2Cl]_2$	**90 %**	*cis* / *trans* >10:1

Total transfer of axial chirality to centered chirality



96 %

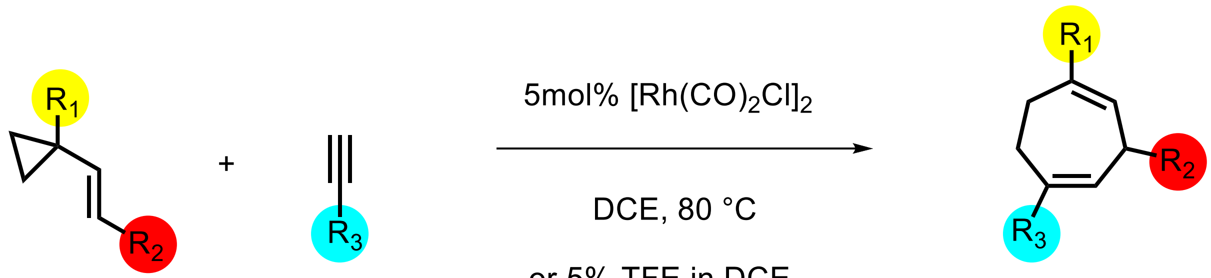
ee 91%

ee 92%

Wender, P. A. *et al*

3. RHODIUM-MEDIATED INTERMOLECULAR [5+2] CYCLOADDITIONS

Unactivated vinylcyclopropanes



R1 = *i*-Pr, Me, H, TMS, CH_2OTBS, CHMeOTBS

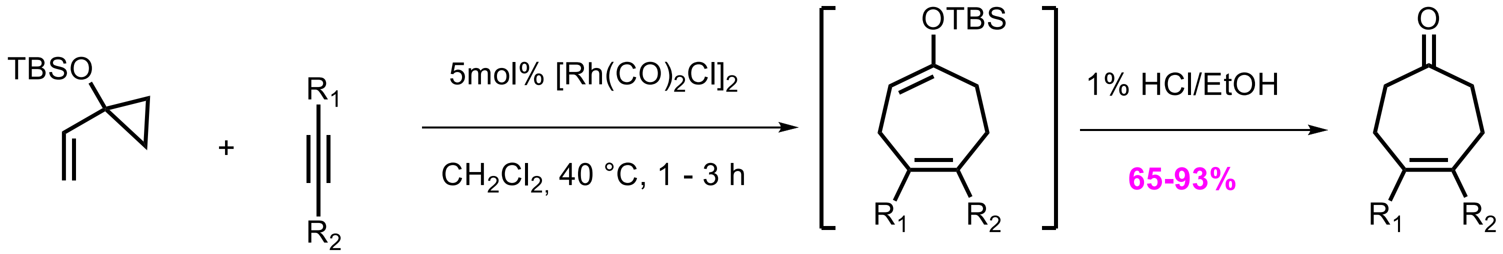
R2 = H, CH_2OH, CH_2OTBS, CH_2OMe

R3 = CO_2Me, Ph, TMS, CH_2OMe, CH_2OH

53-95%

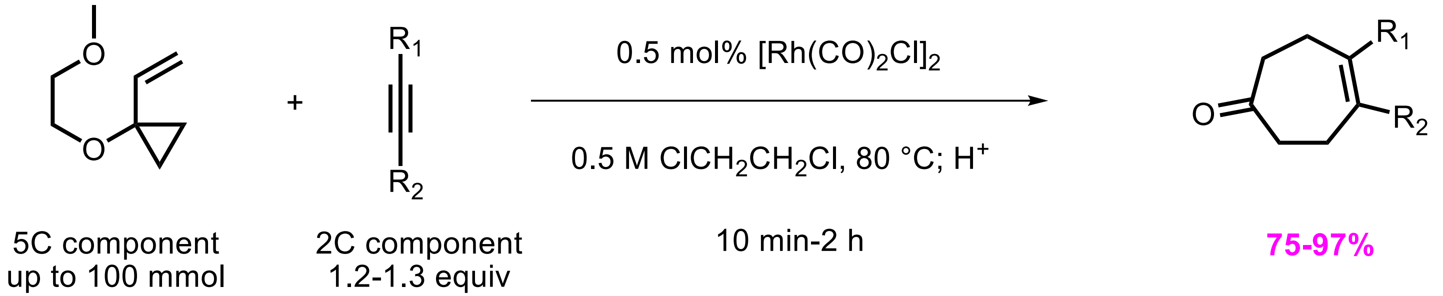
Wender, P. A. *et al*

3. RHODIUM-MEDIATED INTERMOLECULAR [5+2] CYCLOADDITIONS



R_1 = CO_2Me, CH_3CO, CH_2OH, $SiMe_3$, *i*-Pr, H ; R_2 = CO_2Me, H, Me

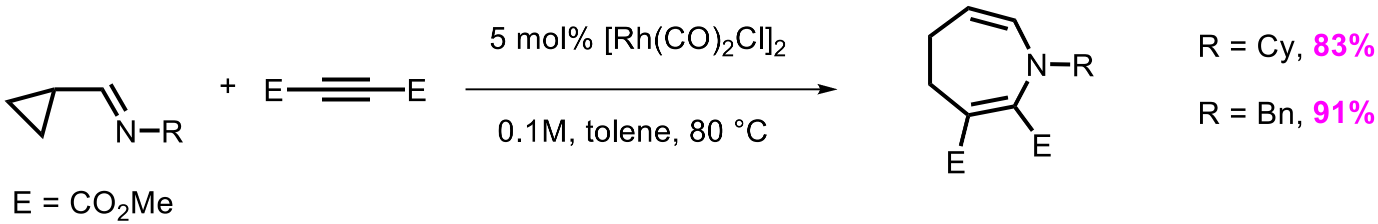
Preparative scale syntheses by using a practical five carbon component

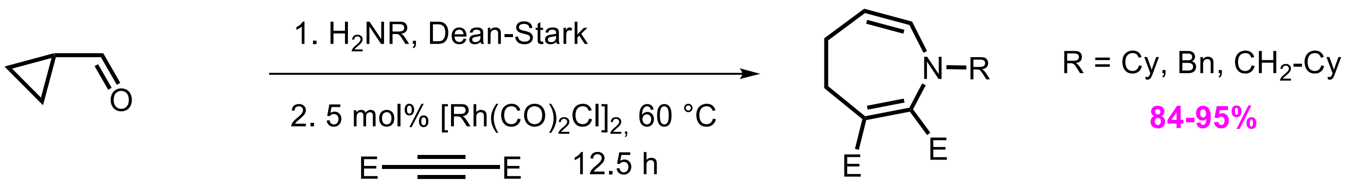


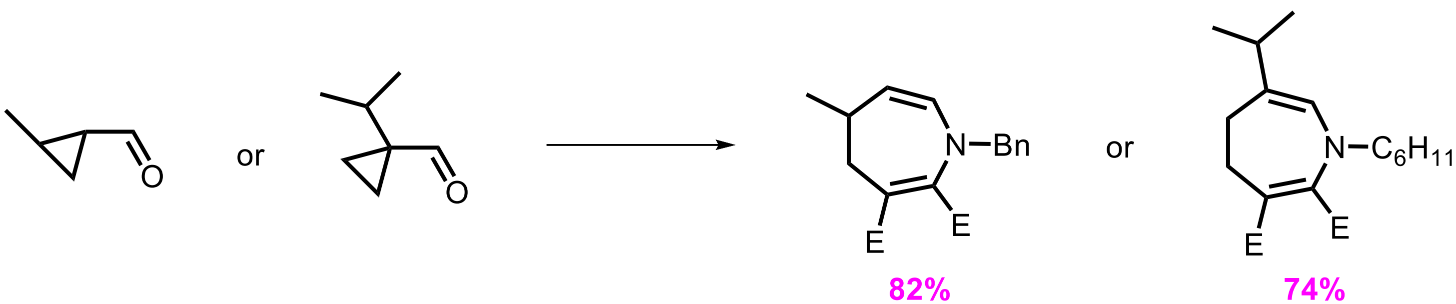
Wender, P. A. *et al*

3. INTERMOLECULAR AZA-[5+2] CYCLOADDITIONS

Synthesis of dihydroazepines

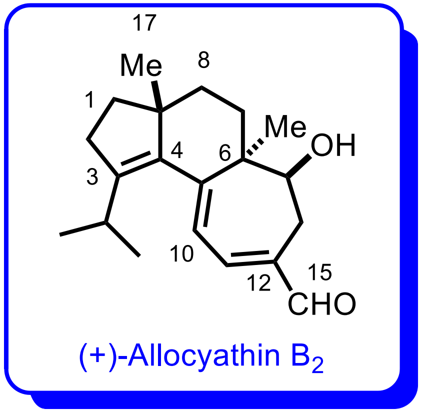


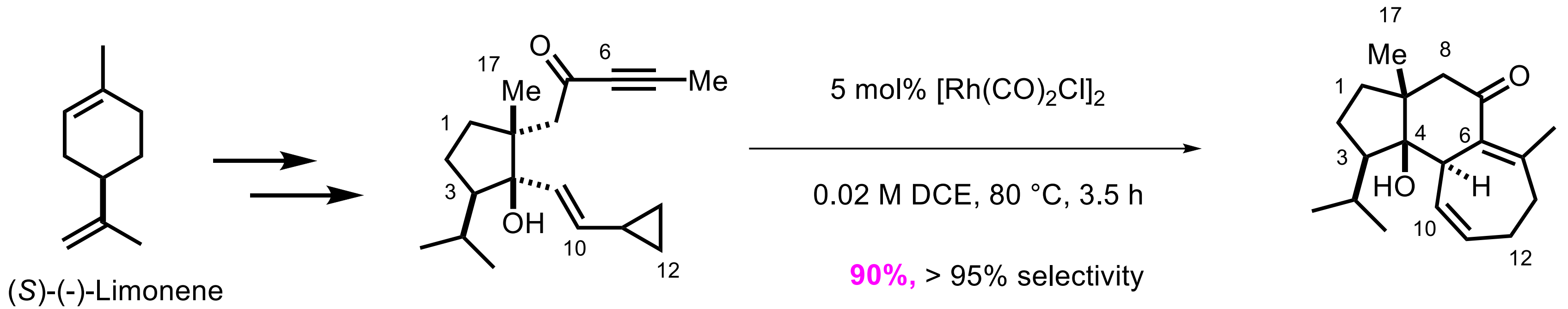




Wender, P. A. *et al*

Asymmetric synthesis of the tricyclic core of NGF-inducing cyathane diterpene
(NGF = Nerve Growth Factor)
Antifungal, antibacterial

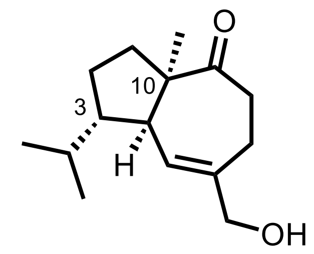




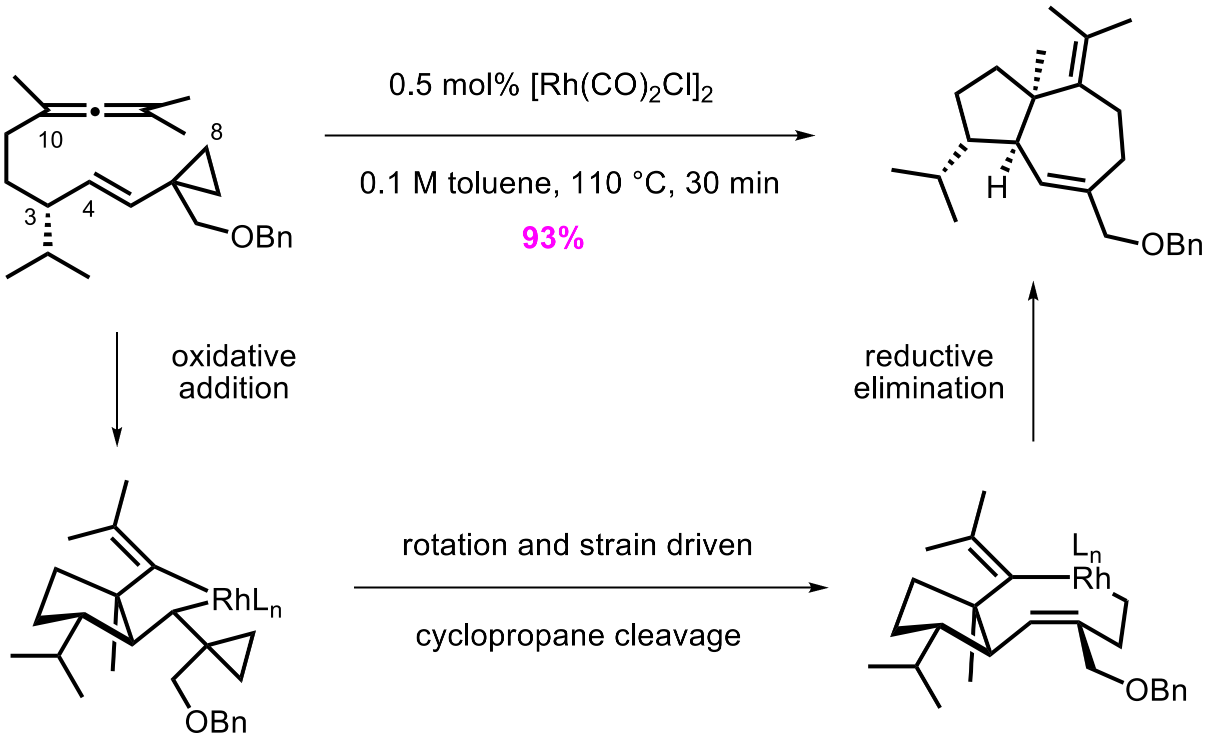
Wender, P. A. *et al*

3. APPLICATIONS IN SYNTHESIS

Asymmetric total synthesis of (+)-Aphanamol I
Toxic componant of the fruit aphanamixis grandifolia

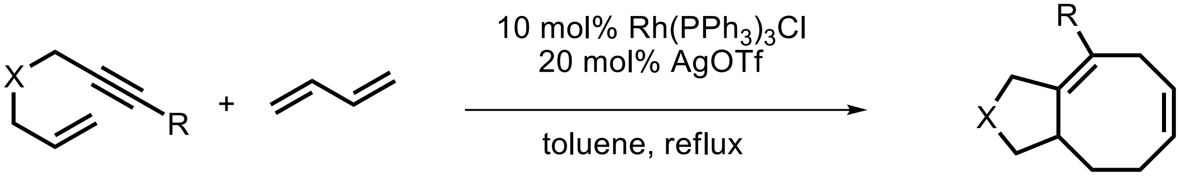


(+)-Aphanamol I



3. [4+2+2] CYCLOADDITIONS

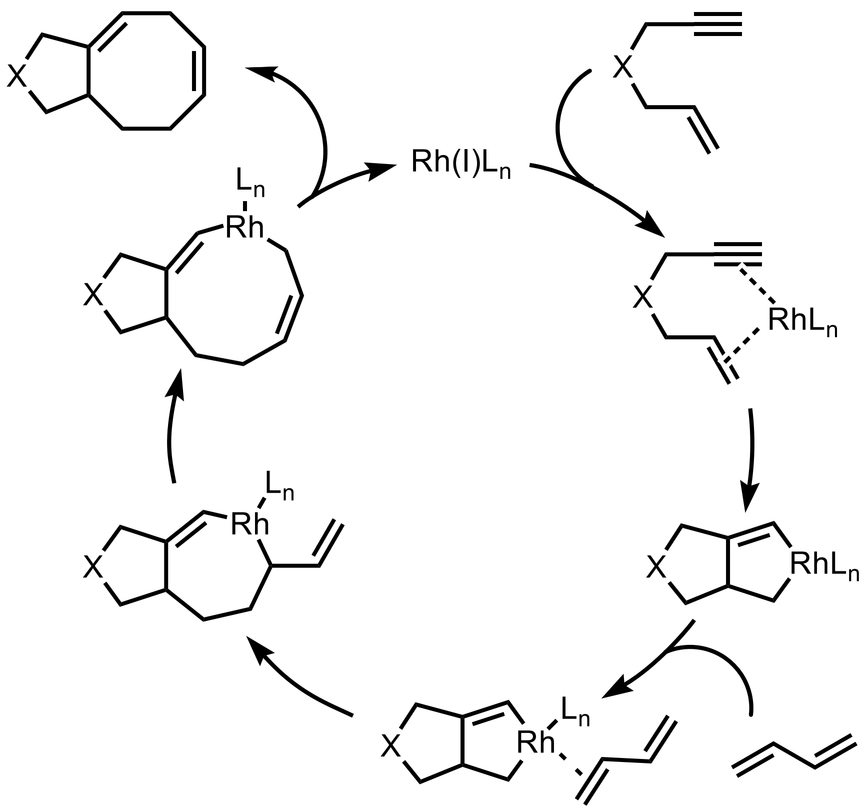
Access to eight-membered rings



X = NTs, SO_2, O ; R = H, Me, Ph

71-92%

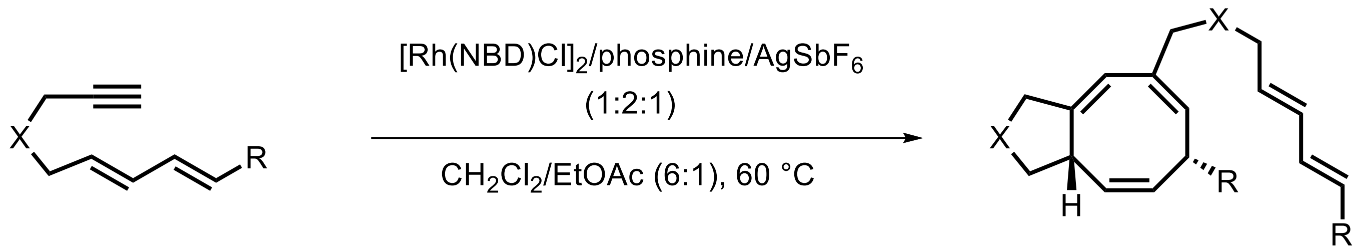
Proposed mechanism:



Evans, P. A. *et al*

3. [4+2+2] CYCLOADDITIONS

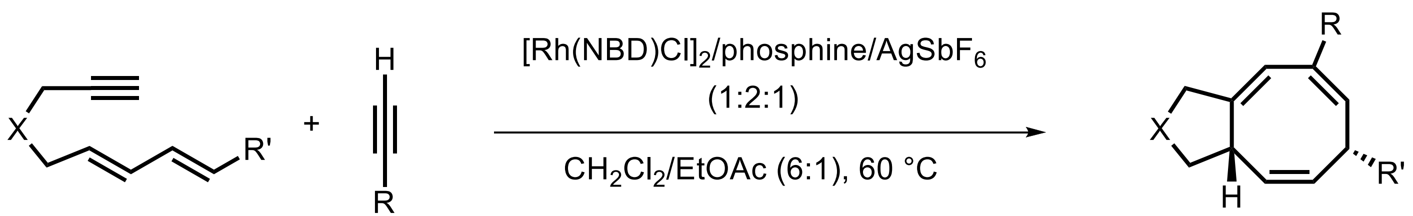
Dimer formation



X = O, NTs; R' = Me, H

10-80%

[4+2+2] cycloaddition

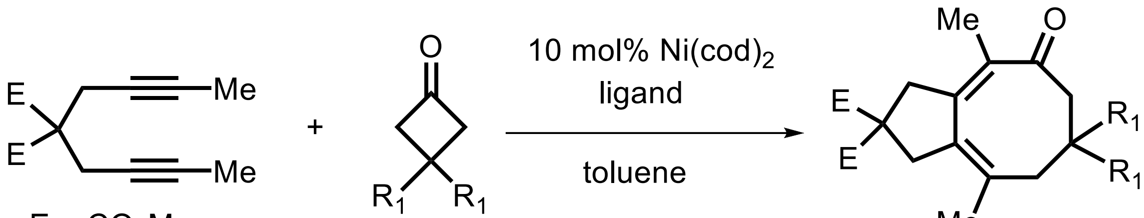


X = O, NTs; R' = Me, H   R = CH_2OBn, *n*-Pr, H

10-73%

Gilbertson, S. R. *et al*

3. [4+2+2] CYCLOADDITIONS

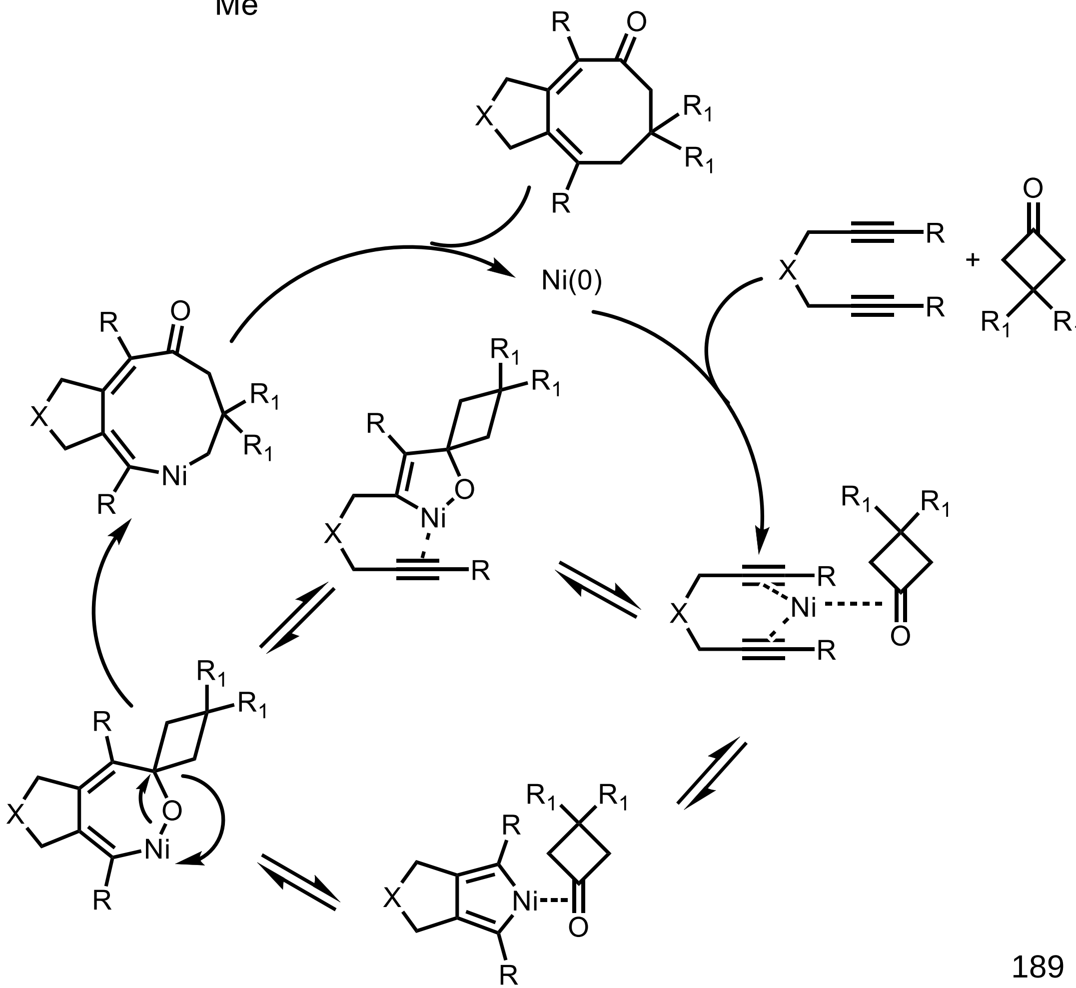


E = CO_2Me
R_1 = Ph, Et

20 mol% P(*n*-Bu)$_3$, 100 °C, 3h **91%**

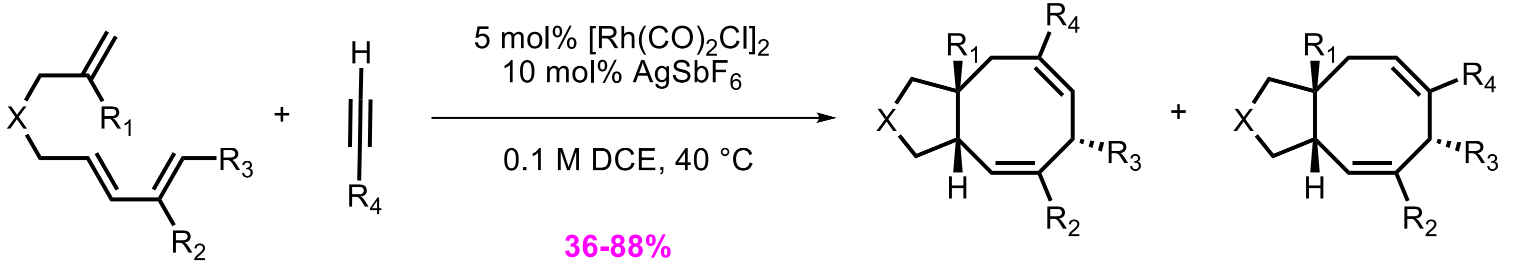
10 mol% IPr, rt, 1h **92%**

Proposed mechanism:



Murakami, M. *et al*

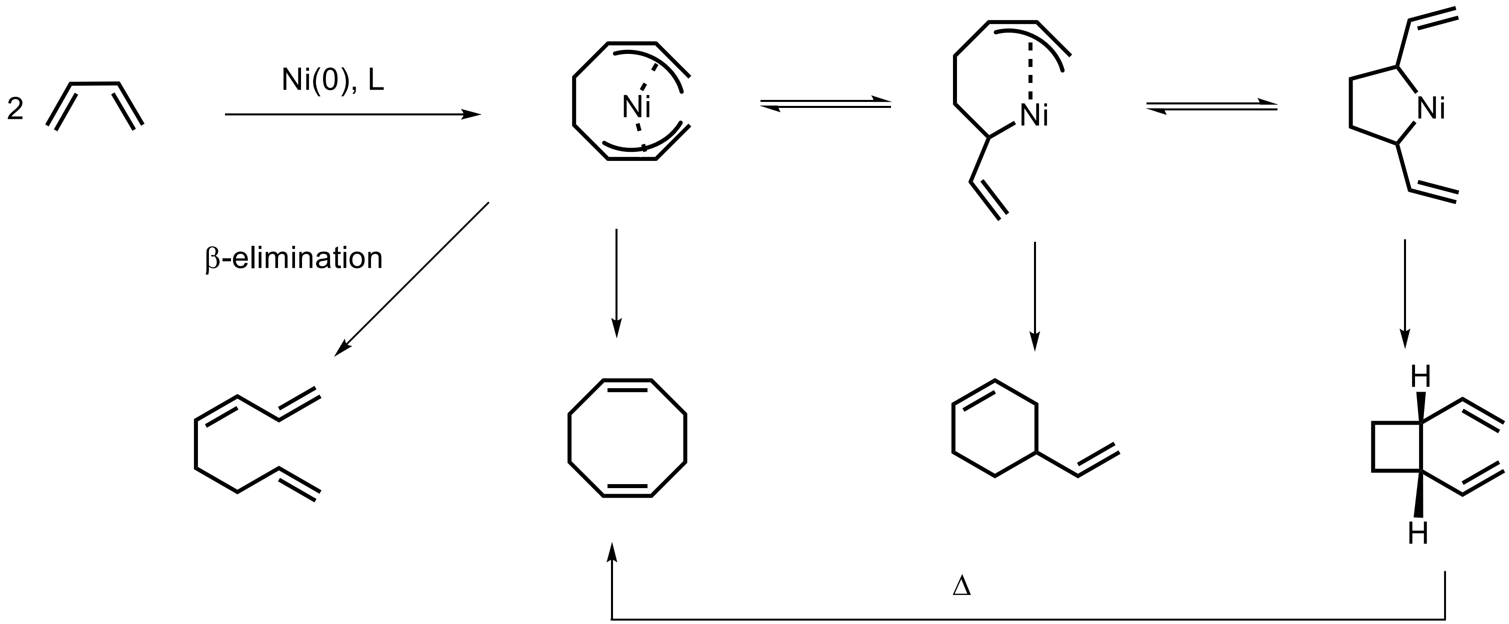
3. [4+2+2] CYCLOADDITIONS



Wender, P. A. *et al*

[4+4] CYCLOADDITIONS

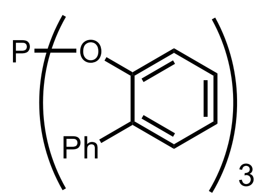
Intermolecular version



Cope (σ[3,3])

Ni(0) = $Ni(cod)_2$

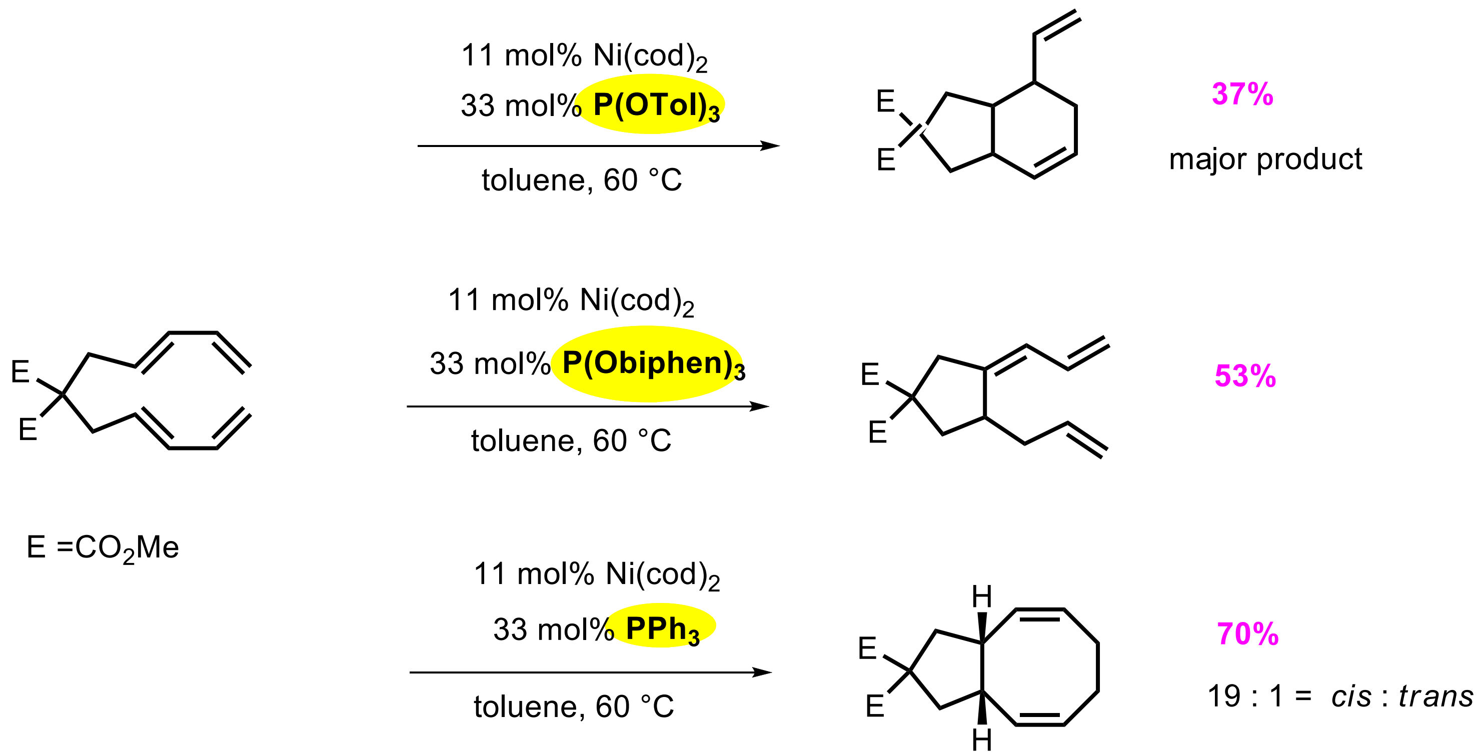
$Ni(acac)_2$ /Et_2AlOEt

L = 

Heimbach, P. *et al*

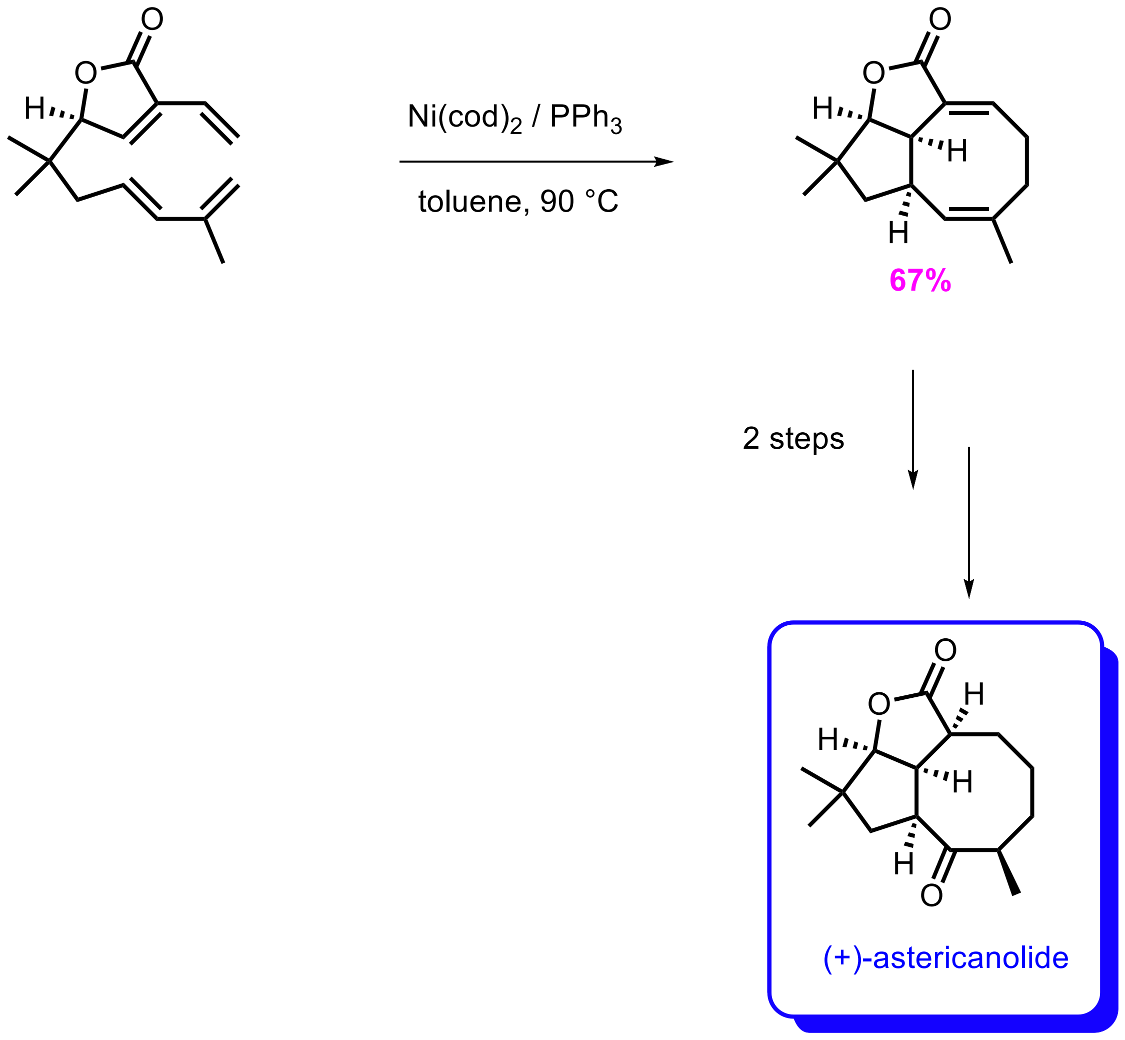
3. [4+4] CYCLOADDITIONS

Intramolecular version: effect of the ligand



Wender, P. A. *et al*

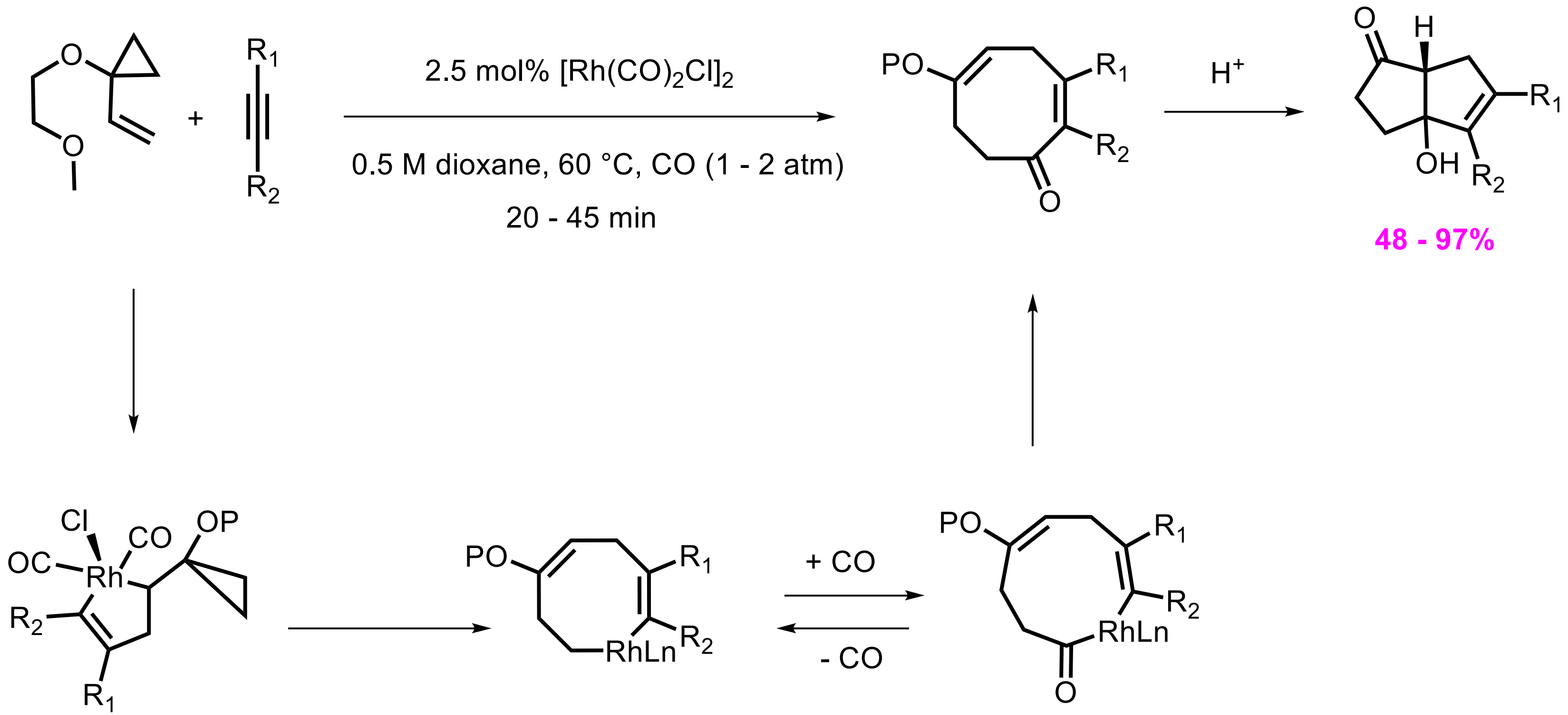
3. [4+4] CYCLOADDITIONS



Wender, P. A. *et al*

3. CARBONYLATIVE [x+y+z+1] CYCLOADDITIONS

Intermolecular [5+2+1] cycloadditions

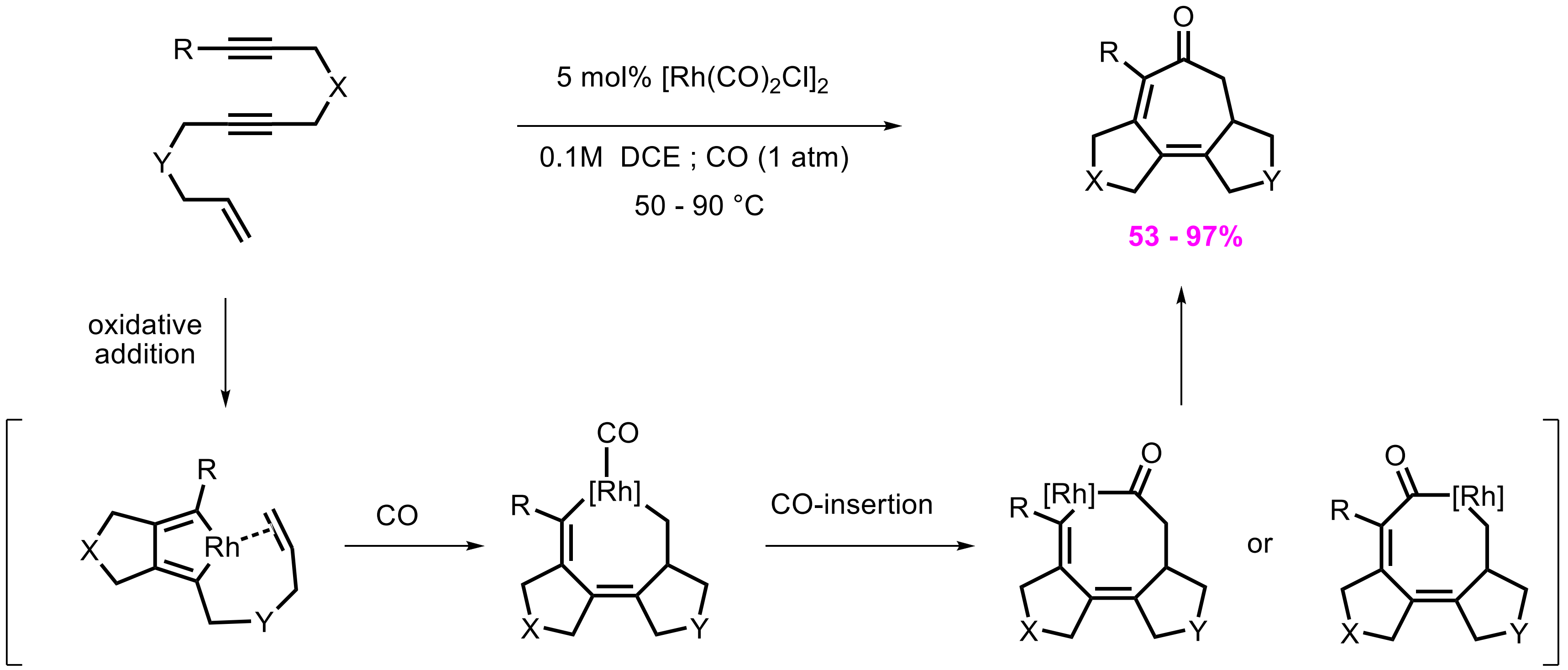


R_1 = COMe, $CONH_2$, CHO, CO_2Me ; R_2 = alkyl, Ph, TMS

Wender, P. A. *et al*

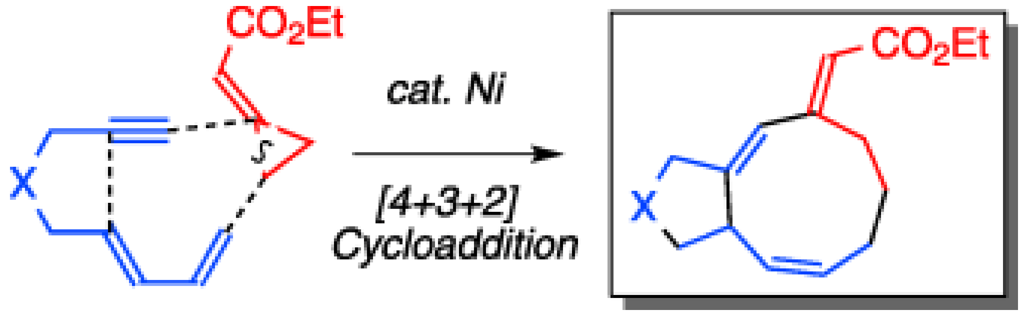
3. CARBONYLATIVE [x+y+z+1] CYCLOADDITIONS

Intramolecular [2+2+2+1] cycloadditions



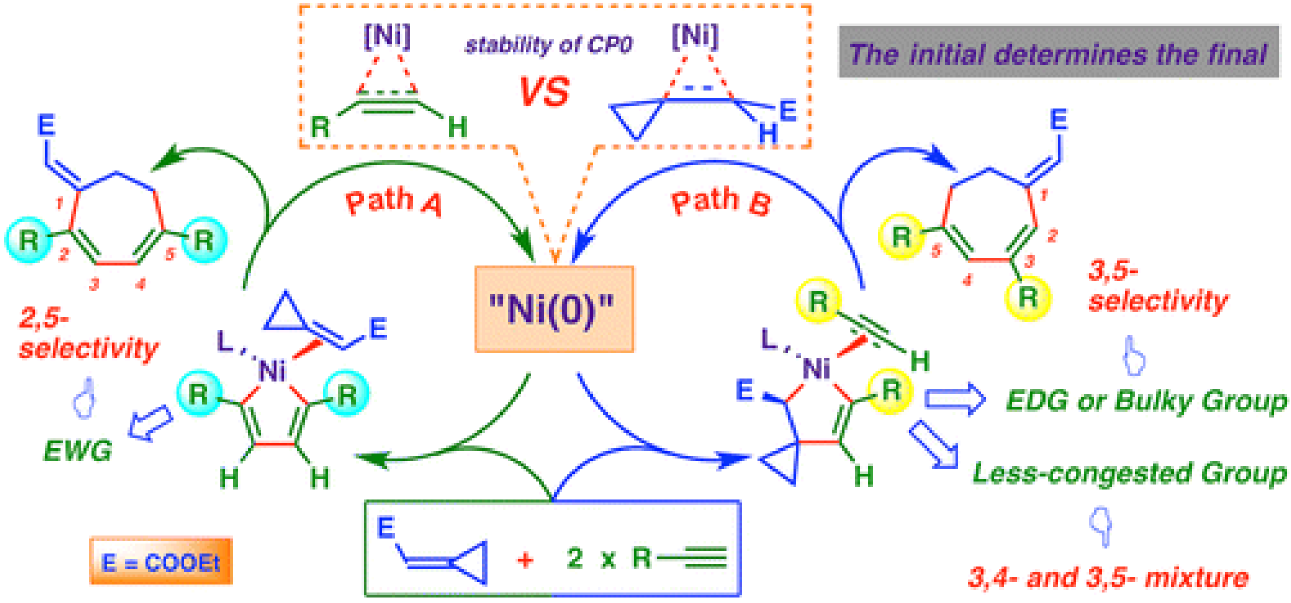
Ojima, I. *et al*

3. SELECTED APPLICATIONS OF WHAT WE HAVE SEEN IN CHAPTER 3



Ogoshi, Saito *et al*

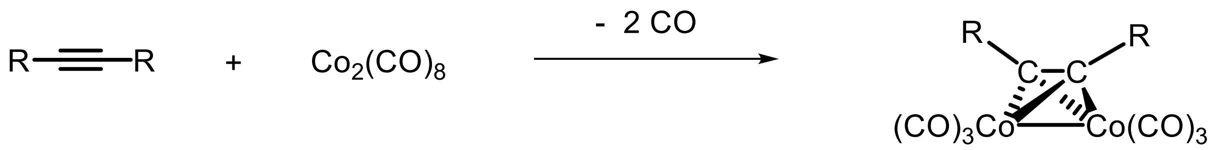
[3+2+2]

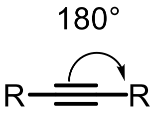


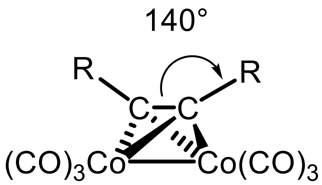
Komagawa, Uchiyama *et al*

4. The Nicholas Reaction

INTRODUCTION: ALKYNE/DICOBALT HEXACARBONYL COMPLEXES





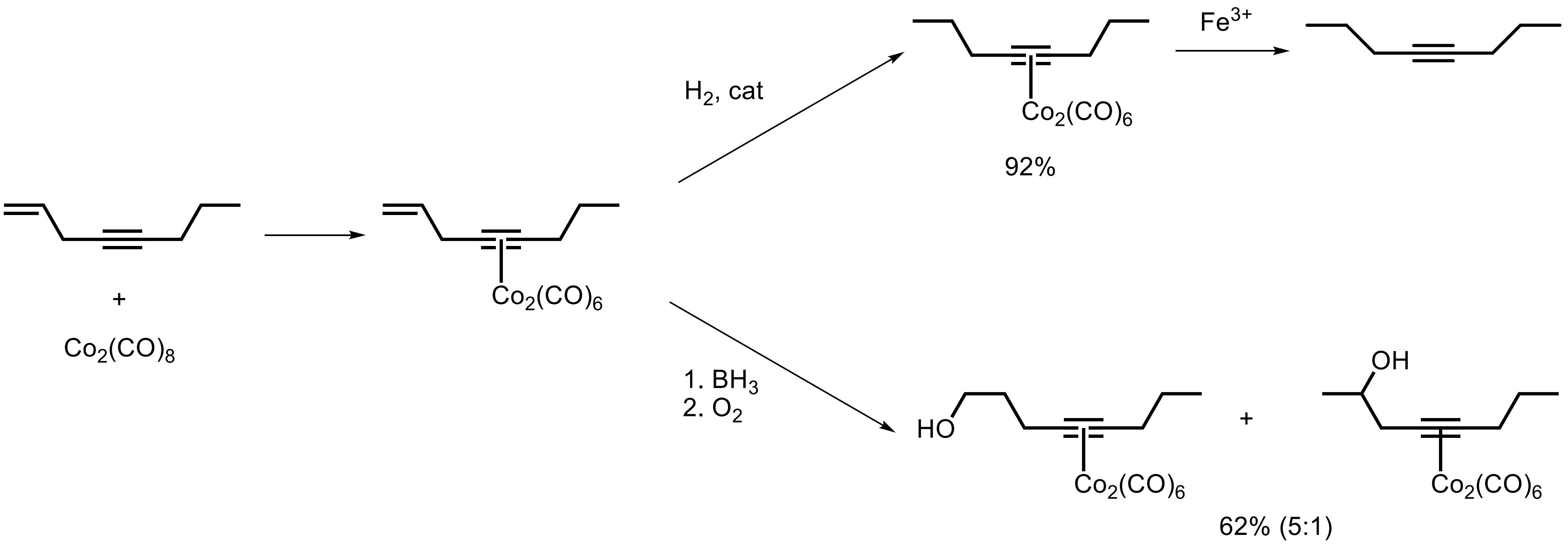


d (C≡C) = 1.18Å

d (C—C) = 1.37Å

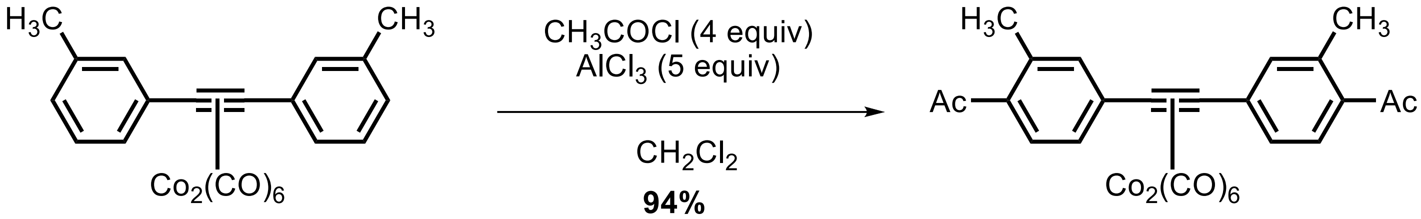
Dickson, R. S.; Fraser, P. J.

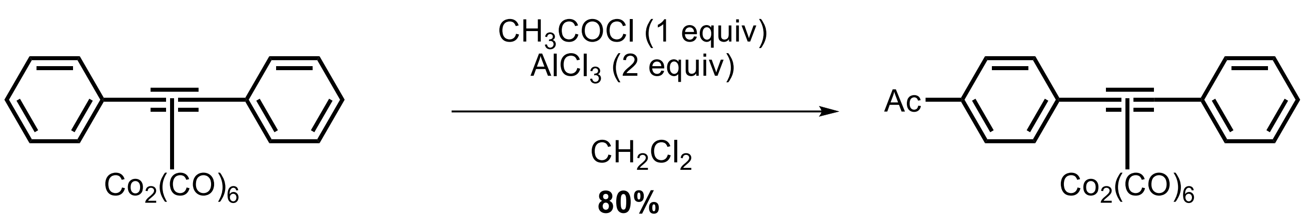
4. INTRODUCTION: $Co_2(CO)_6$ PROTECTING GROUP



Nicholas, K. M.; Pettit, R.

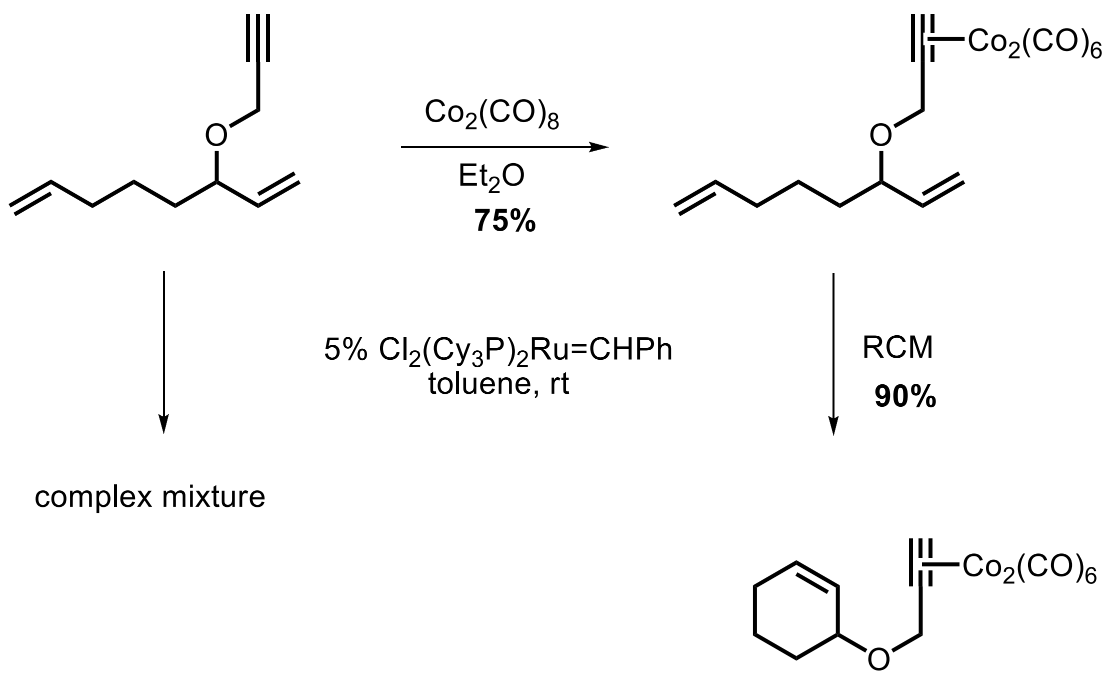
4. INTRODUCTION: $Co_2(CO)_6$ PROTECTING GROUP





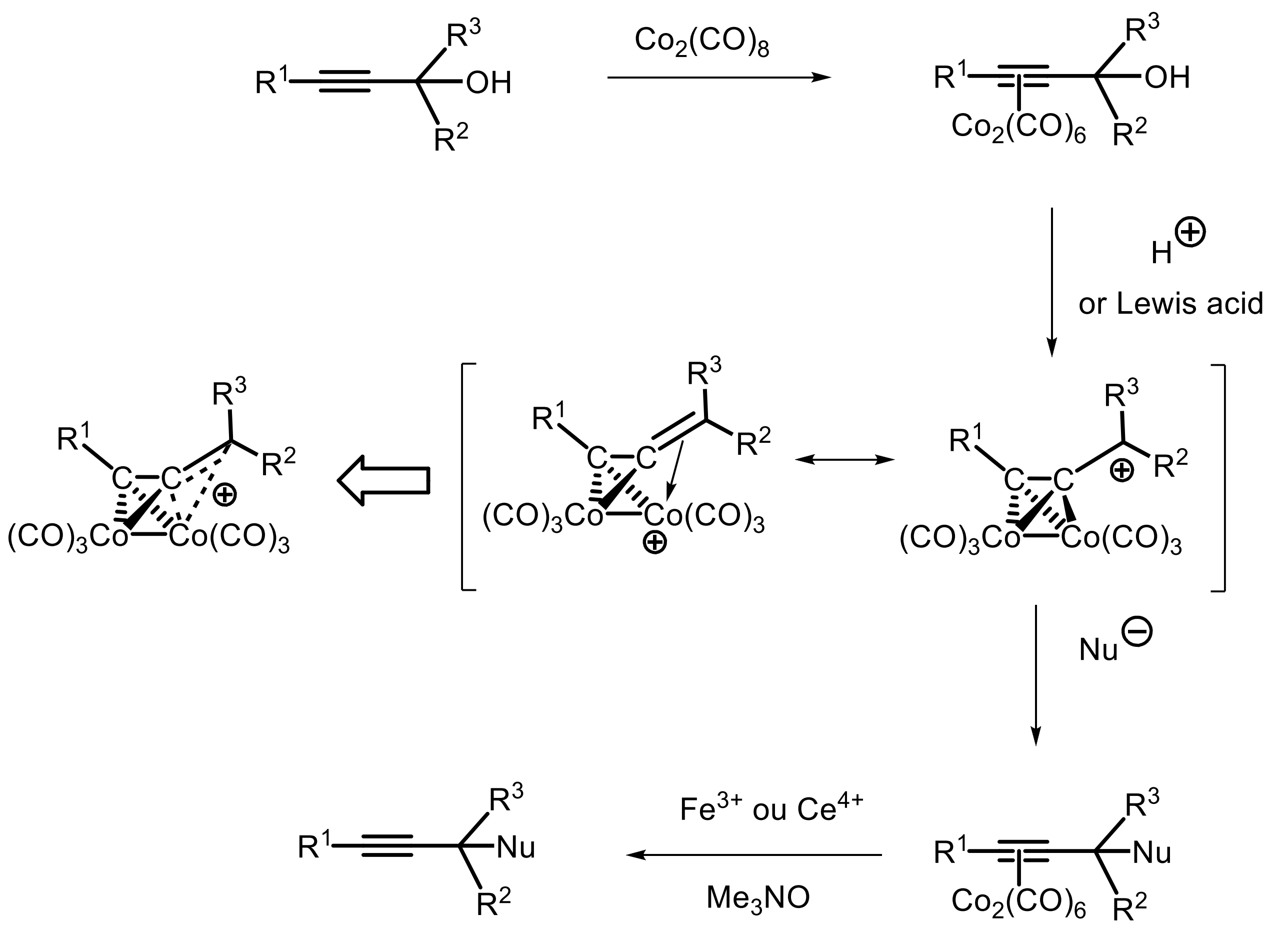
Seyferth, D. *et al*

4. INTRODUCTION: $Co_2(CO)_6$ PROTECTING GROUP

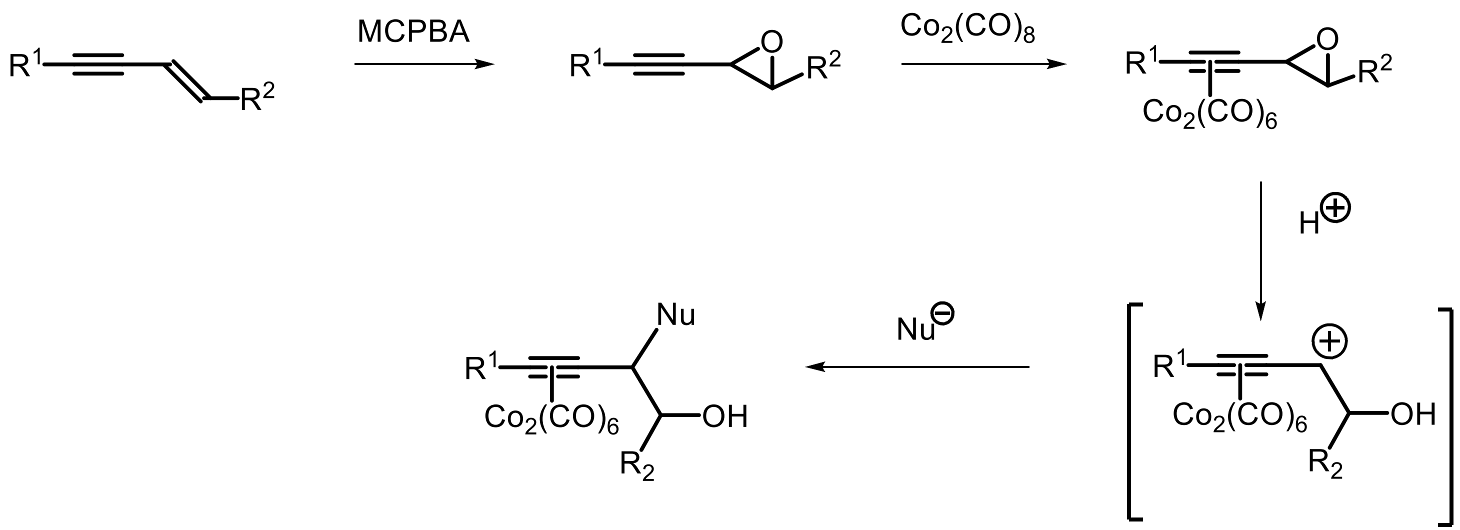


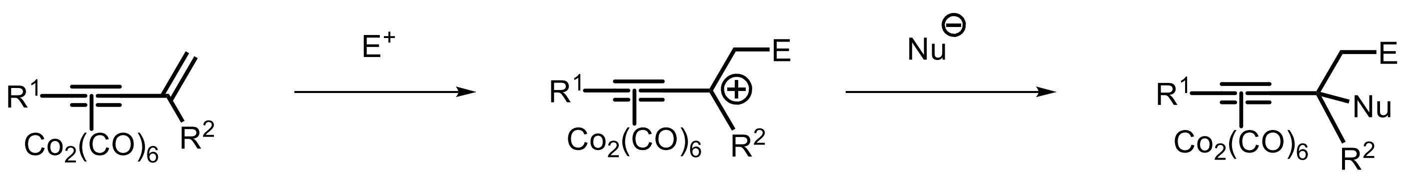
Pérez-Castells, J. *et al*
Danishefsky, S. J. *et al*

4. THE NICHOLAS REACTION



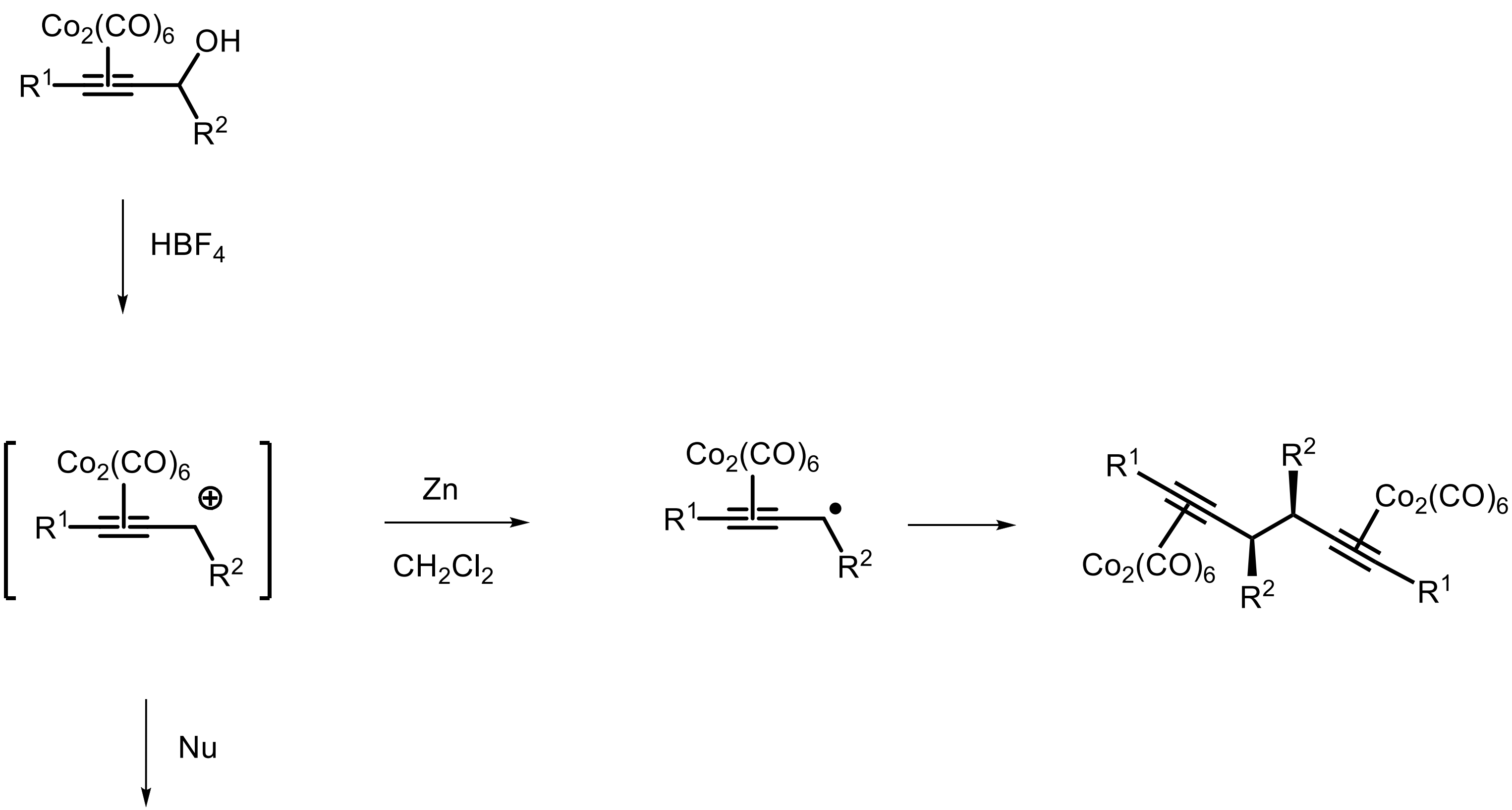
4. THE NICHOLAS REACTION

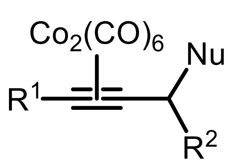




Smit, W. A.; Caple, R. *et al*

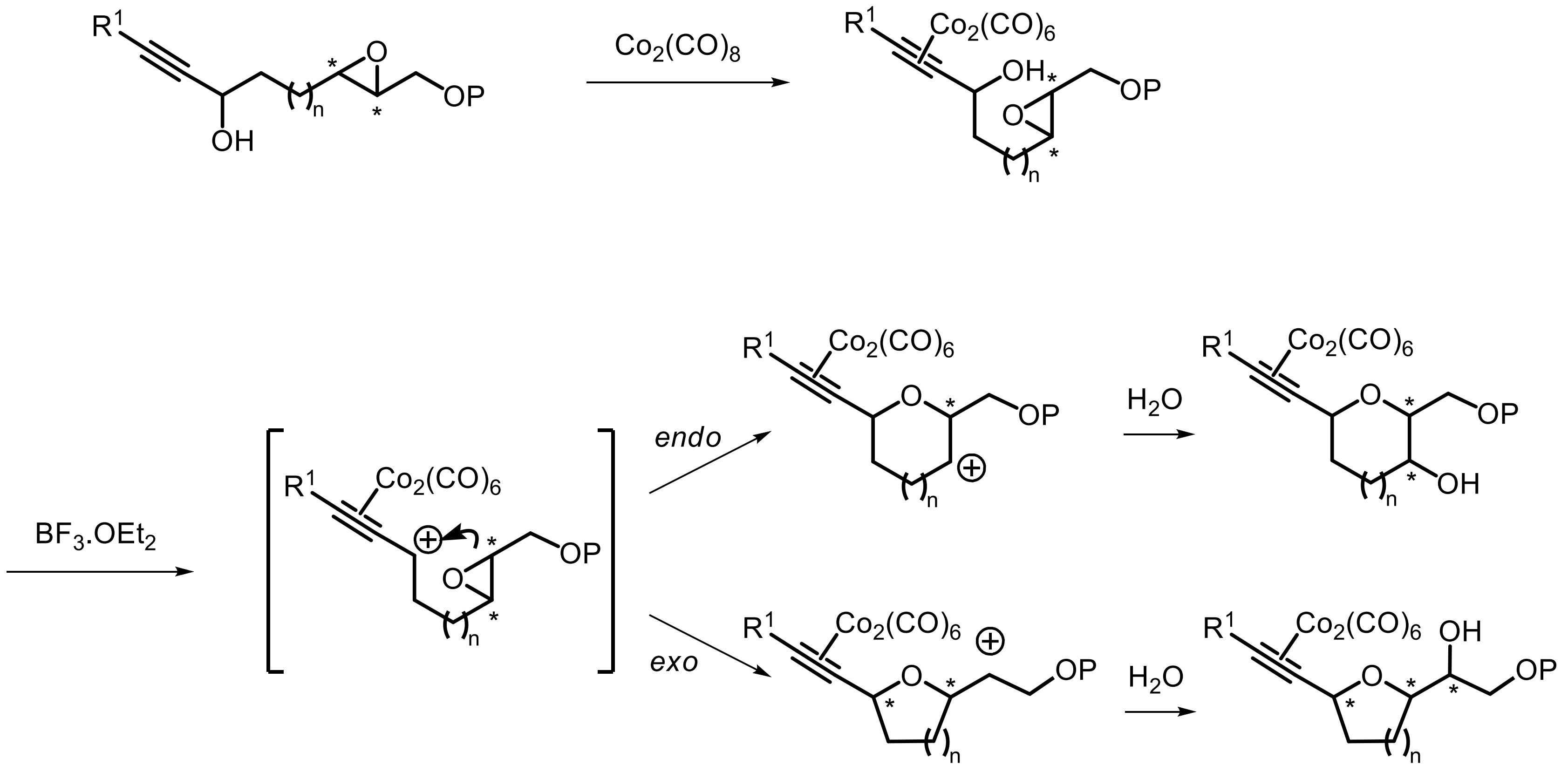
4. ACTIVATION - STABILISATION OF THE α CARBOCATION





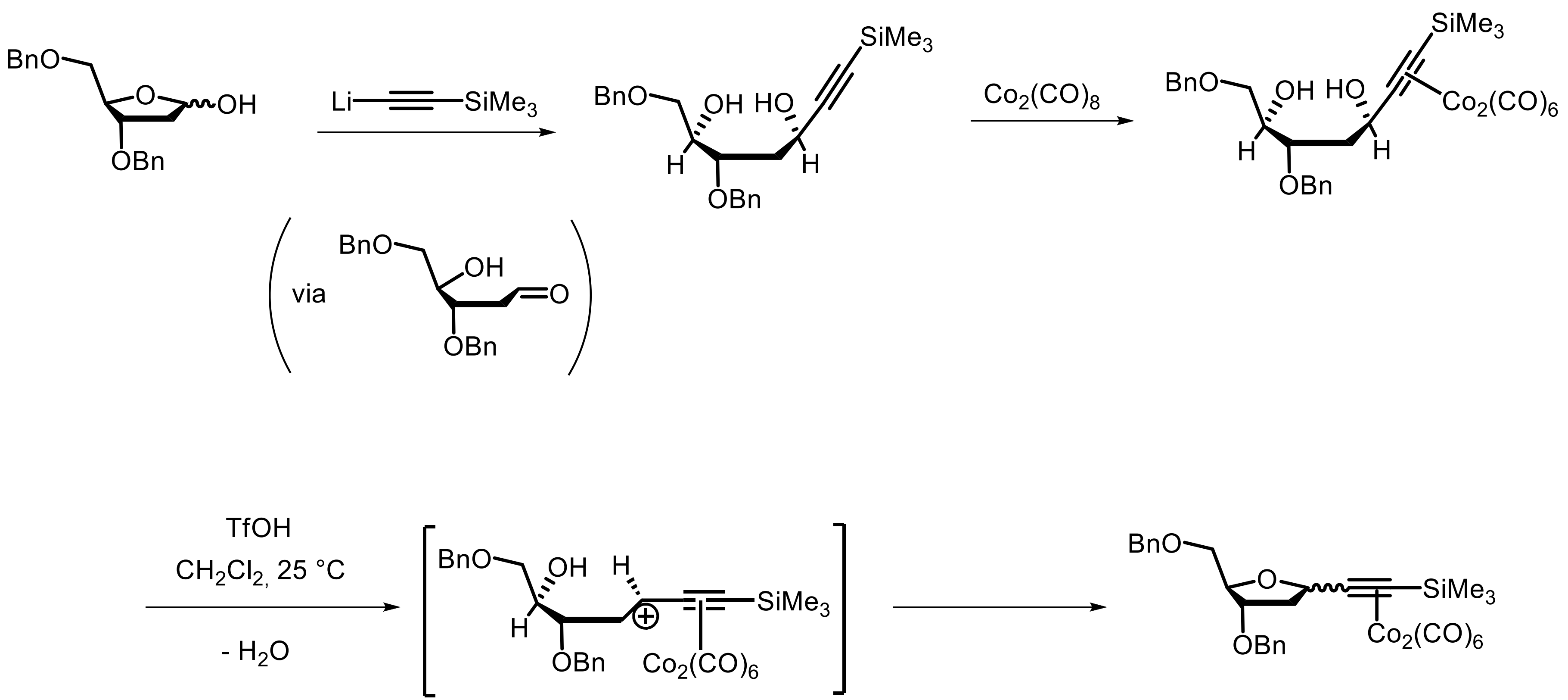
Nu = ROH, R_2,NH, RMgX,R_1R_2CO, aromatics, β-dicarbonyls

4. EPOXIDES AS NUCLEOPHILES



Crisostomo, F. R. P *et al*

4. ALCOHOLS AS NUCLEOPHILES

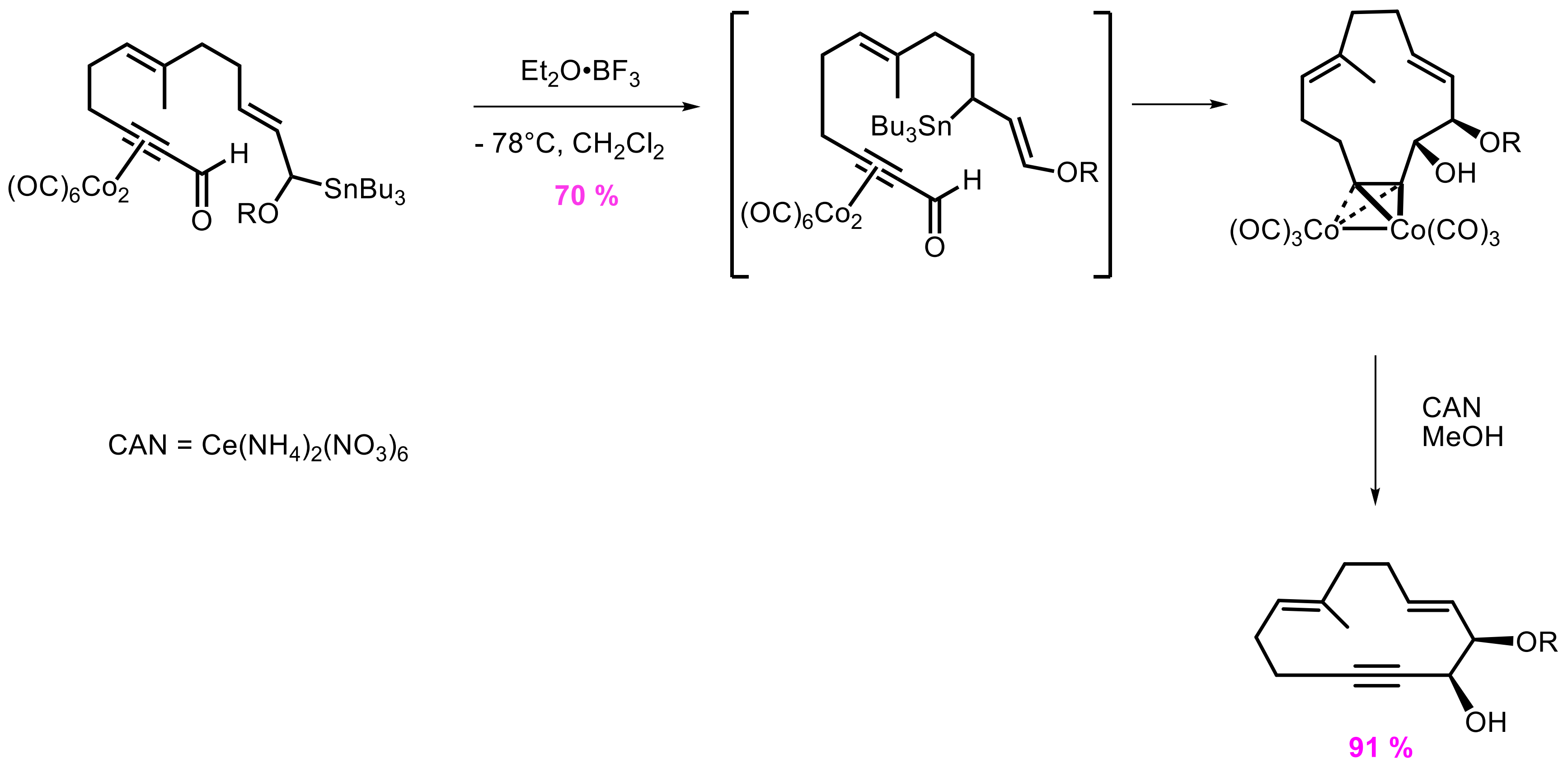


$\beta/\alpha > 99$

Easy access to *C*-nucleosides

Inouye, M. *et al*

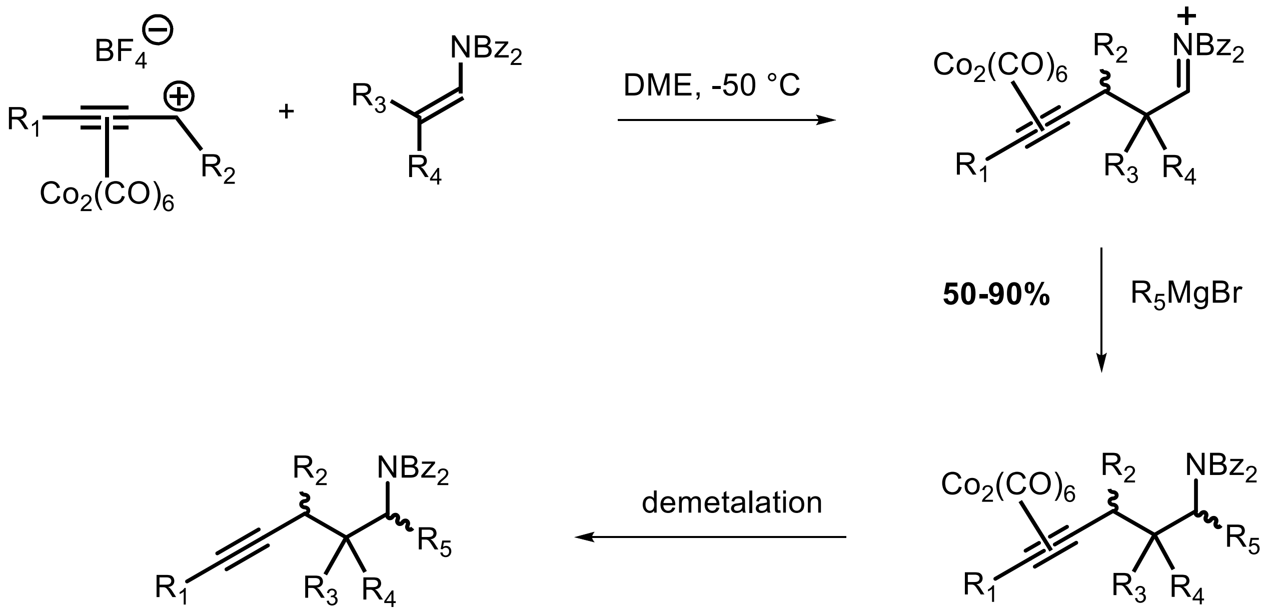
4. ALKENES AS NUCLEOPHILES



CAN = $Ce(NH_4)_2(NO_3)_6$

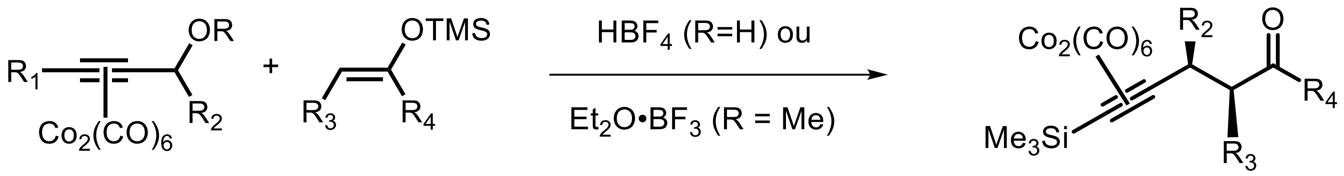
J.A. Marshall, J. A.; Gung, W. Y.

4. ENAMINES AS NUCLEOPHILES

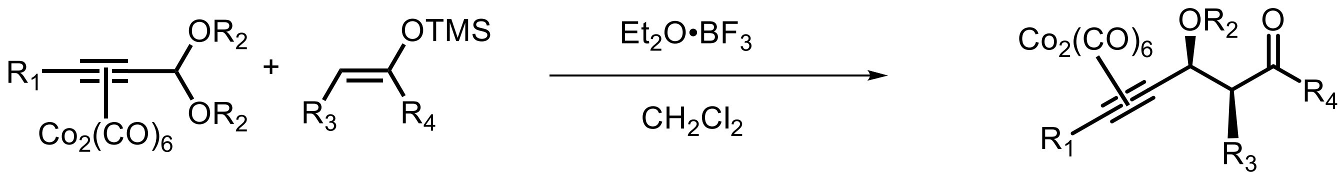


Roth, K. D.

4. ENOL ETHERS AS NUCLEOPHILES

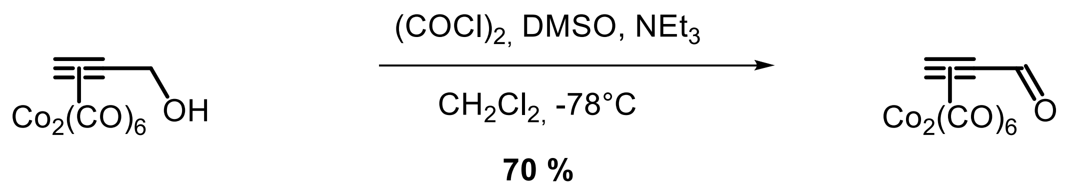


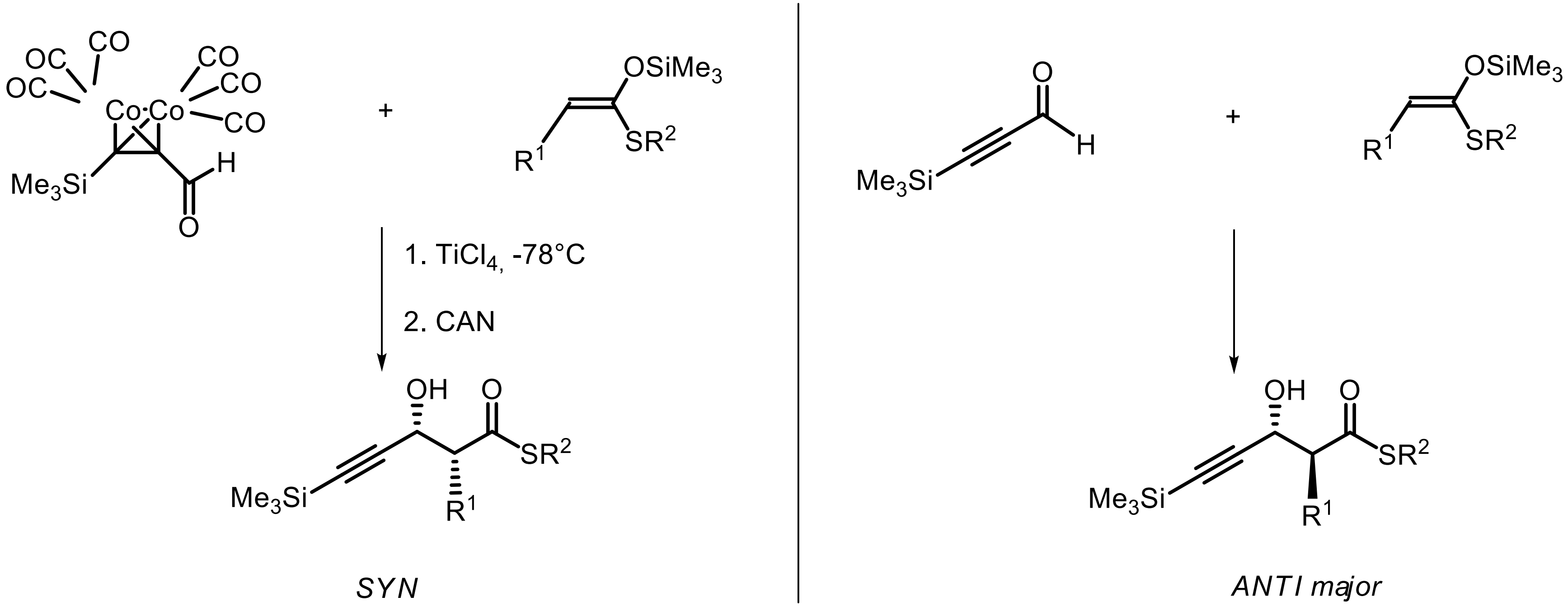
Schreiber, S. L. *et al*



Nicholas, K. M. *et al*

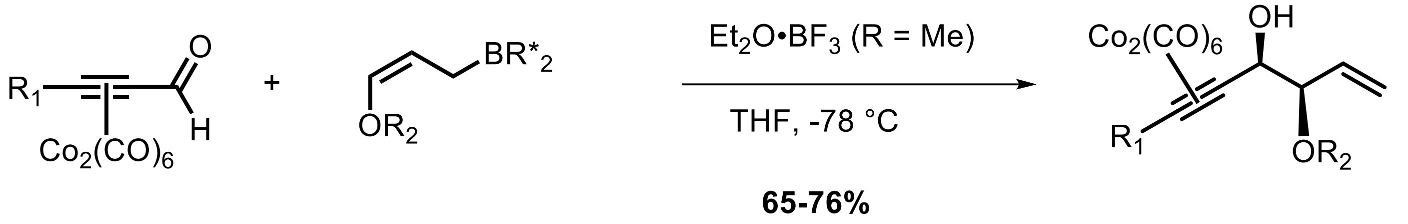
4. MODIFICATION OF THE STEREOSELECTIVITY





Hanaoka, M. *et al*

4. ALLYL METALS AS NUCLEOPHILES

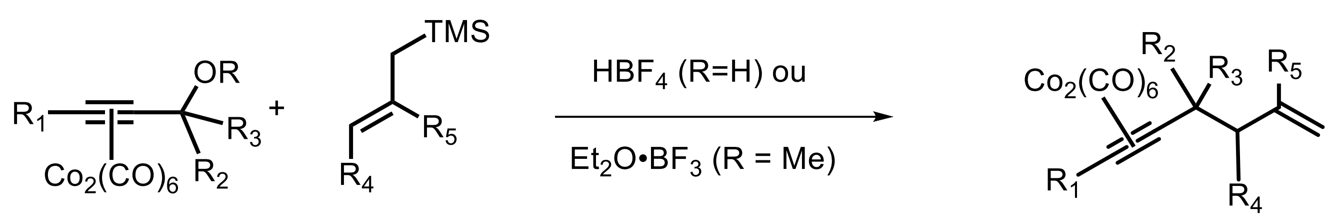


R_1 = Ph, Me, H
R_2 = Me, CH_2OMe
R* = isopinocampheyl

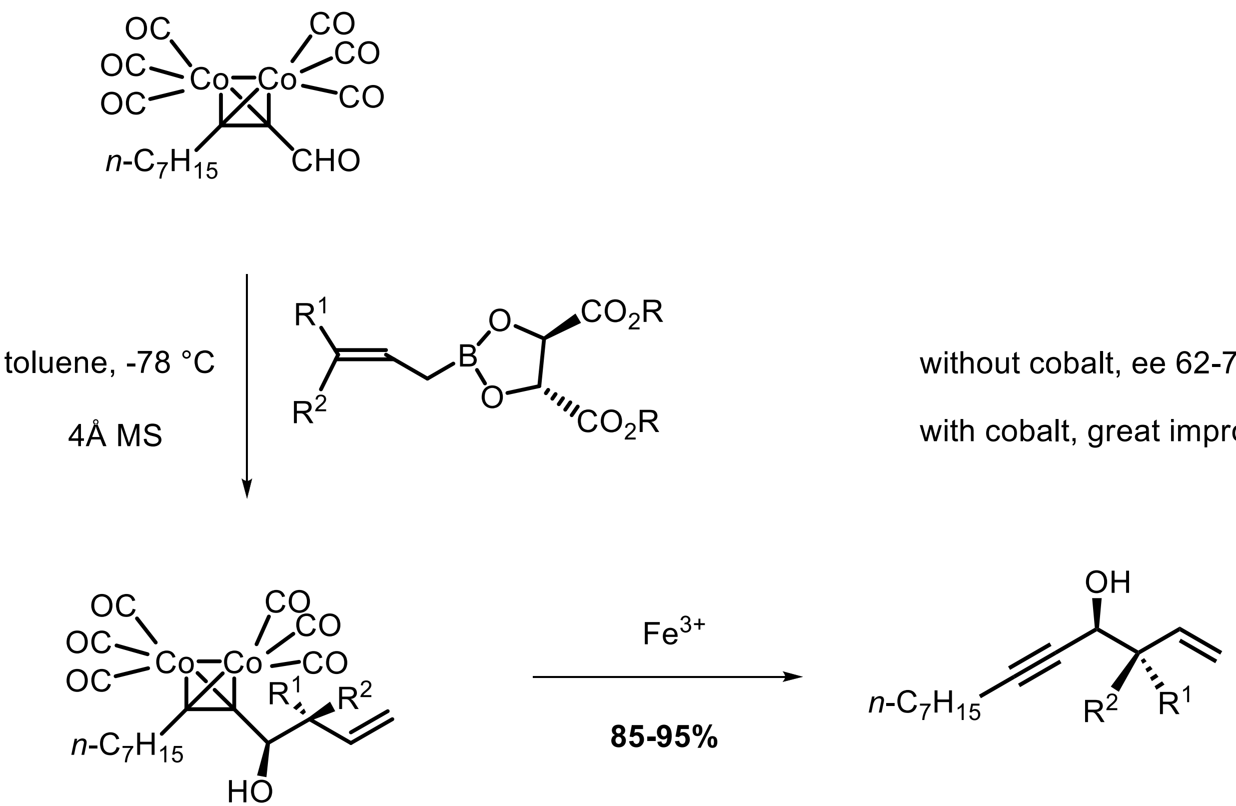
R* = isocampheyl

de : 88 jusqu'à 95%
ee > 96%
(sans cobalt, 65% ee)

Ganesh, P.; Nicholas, K. M.



4. MODIFICATION OF THE STEREOSELECTIVITY



without cobalt, ee 62-74%

with cobalt, great improvement

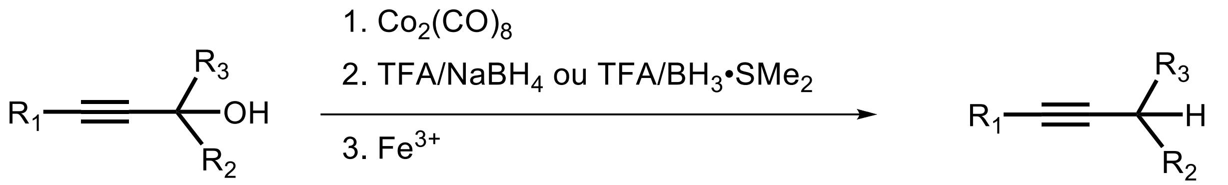
$R_1 = R_2 = H$; 92 % ee

R_1 = Me : R_2 = H ; 97:3 = *anti:syn* ; 96% ee

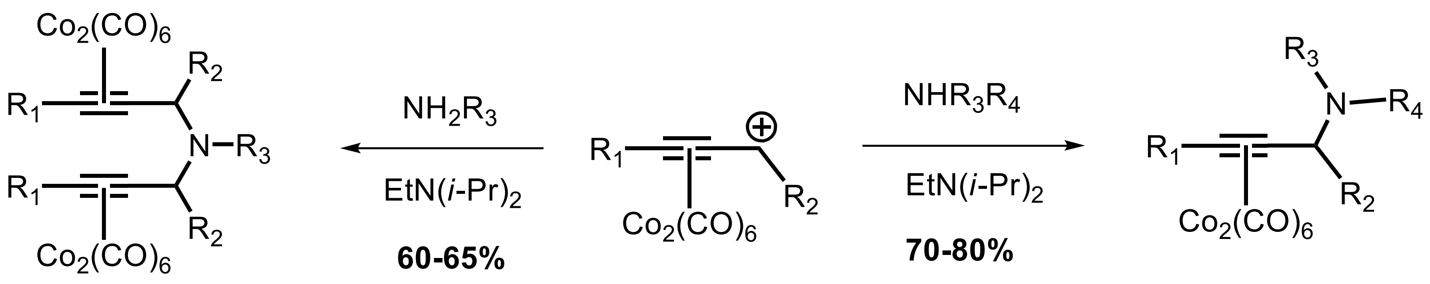
R_1 = H ; R_2 = Me ; 97:3 = *syn:anti* ; 86% ee

Roush, W. R.; Park, J. C.

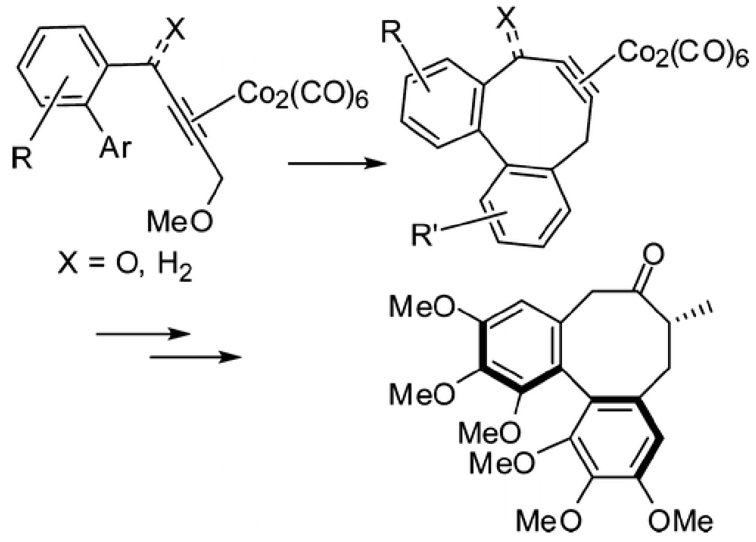
4. OTHER NUCLEOPHILES



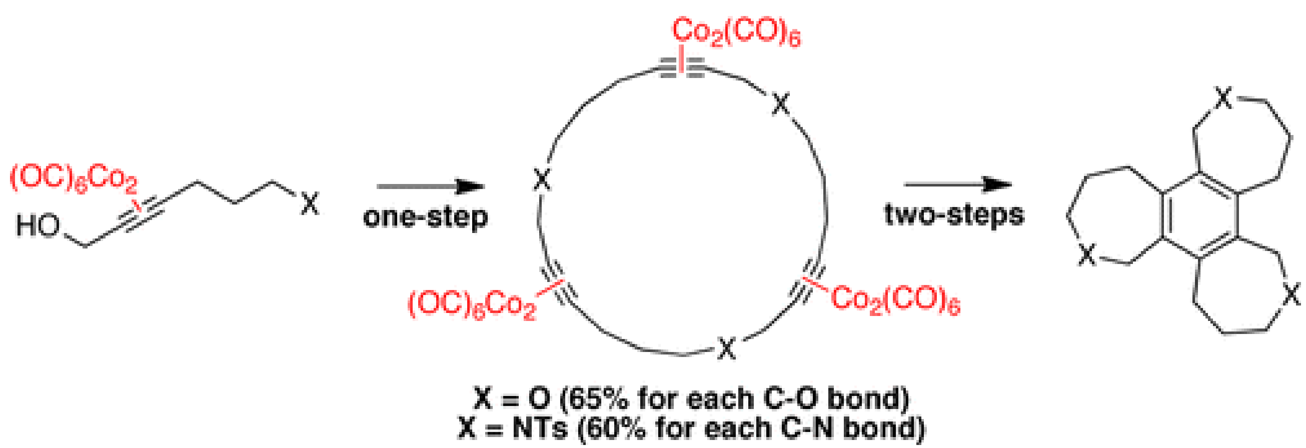
Nicholas, K. M.; Siegel, J.



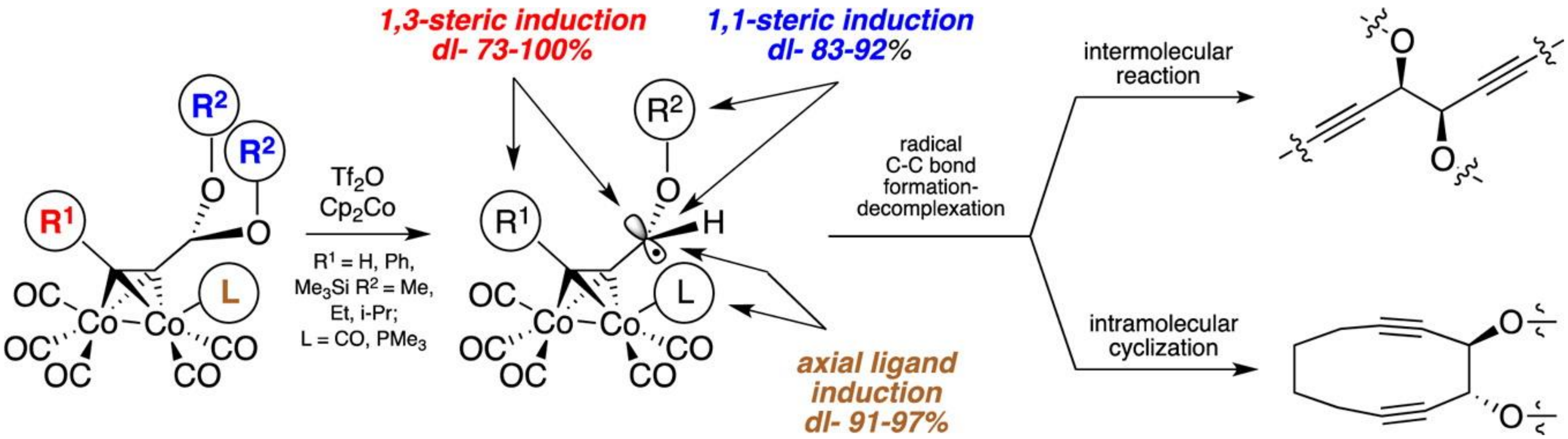
Roth, K. D.; Müller, U.



Green *et al*.



Crisostomo *et al*.



Melikyan *et al*.