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# Organometallic approach to the taxane skeleton involving new iron tricarbonyl complexes

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**Thesis no 1446**

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**University of Fribourg**

**Switzerland**

**Group Meeting 09-13-2005**

# Plan

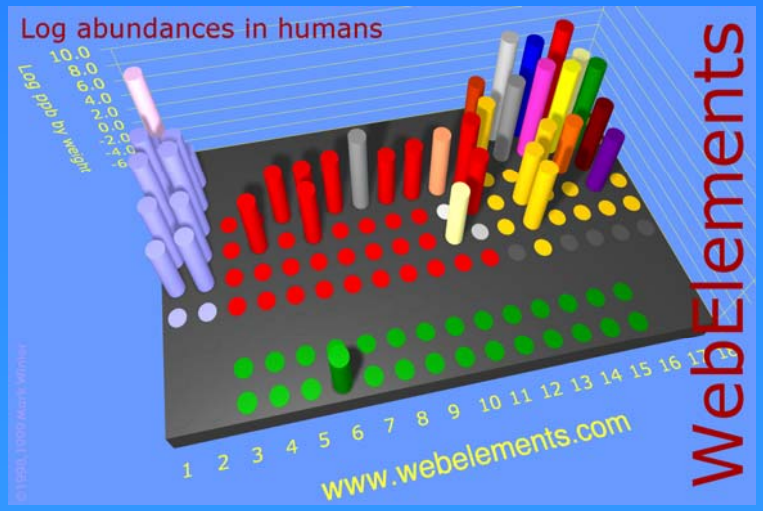
- Introduction
- Aim of this work
- Results
  - Synthesis of the triene complex
  - Study of the coupling reaction on a model case
  - Synthesis of cyclohexadienyl complexes
  - Application of the coupling coupling reaction
- Conclusion

# Iron complexes

Among the large variety of transition metals, the use of organo iron complexes is limited compared to, for example, palladium, rhodium or iridium.

However iron has a high potential :

- It is the second most abundant metal after aluminum and it is omnipresent in nature
- It is an environmentally friendly metal and it plays a vital role in animal and vegetal life



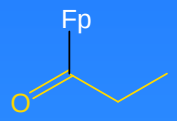
# Iron carbonyl complexes

## Iron carbonyl complexes :

They can be classified in different groups according to the number of coordinated carbon centers, the type of bonding between the organic ligand and the metal center and the nature of the organic ligand.

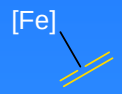
$\eta^1$- :

σ-allyl-




σ-acyl-

$\eta^2$- :



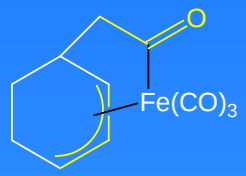

[Fe] = $Fe(CO)_4$ or $Fp^+$

π-alkene-

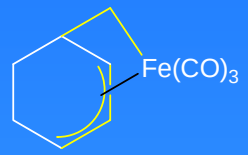
$\eta^3$- :

X = halogene, etc.

π-allyl-




σ-acyl-π-ally

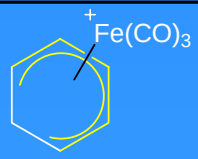



σ-alkyl-π-allyl-

$\eta^4$- :

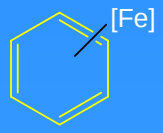
diene-

$\eta^5$- :




dienyl-

$\eta^6$- :



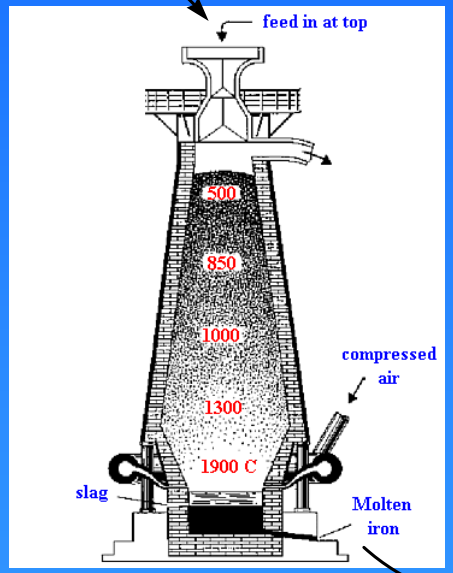

[Fe] = FeCp, FeCp*, FeAr

arene-

# Iron carbonyl complexes

## From iron ore to iron pentacarbonyl

$$2\ Fe_2O_3 + 3\ C \xrightarrow{\Delta} 4\ Fe + 3\ CO_2$$

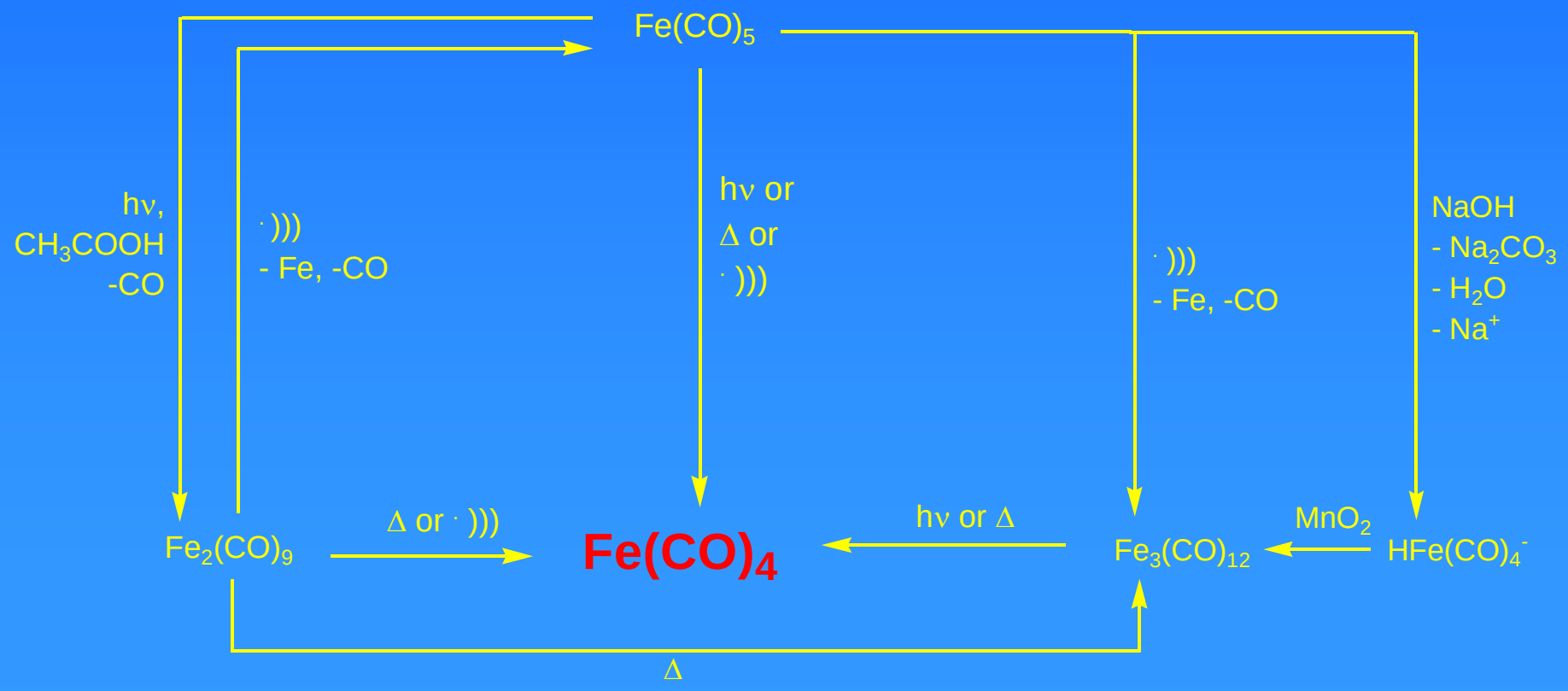


## Formation of iron pentacarbonyl

$$Fe + 5\ CO \longrightarrow Fe(CO)_5 \longrightarrow Fe + 5\ CO$$

# Iron complexes

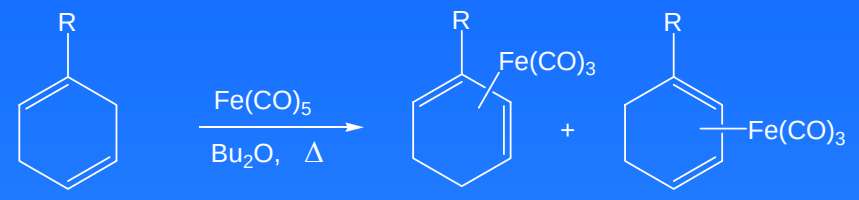
## Synthesis of iron tricarbonyl complexes



# Iron carbonyl complexes

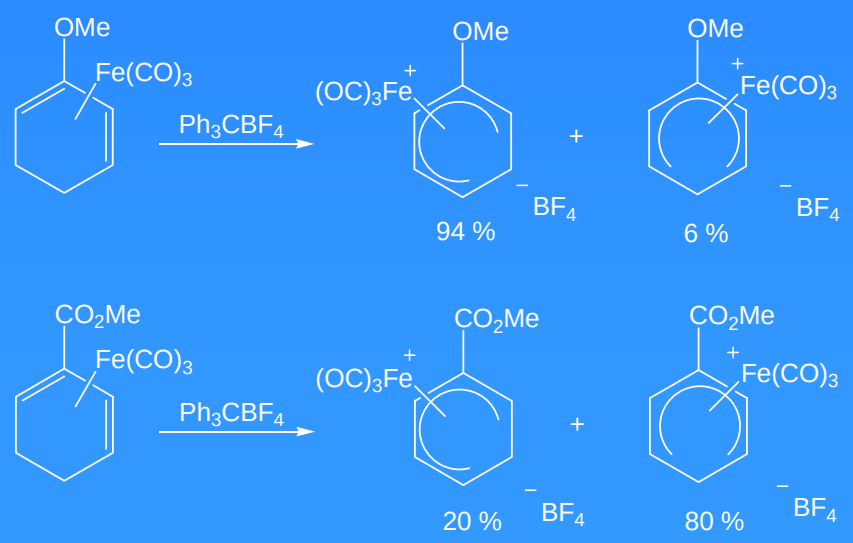
## Synthesis of iron tricarbonyl complexes

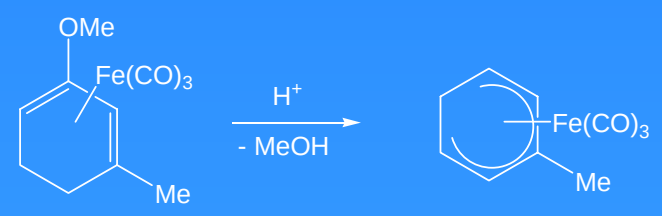
### ➢ diene complexes :




Reihlen et al., *Liebigs Ann. Chem.*, **1930**. 482, 161

### ➢ cationic dienyl complexes :



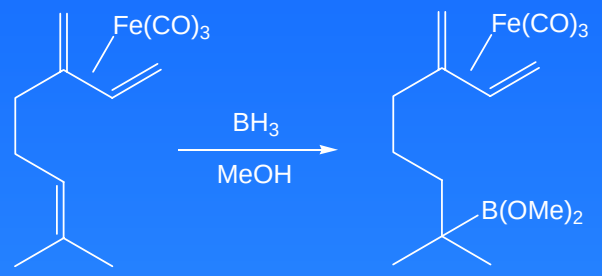




A. J. Pearson, *Iron Compound in Organic Synthesis*, Academic Press, London, **1994**

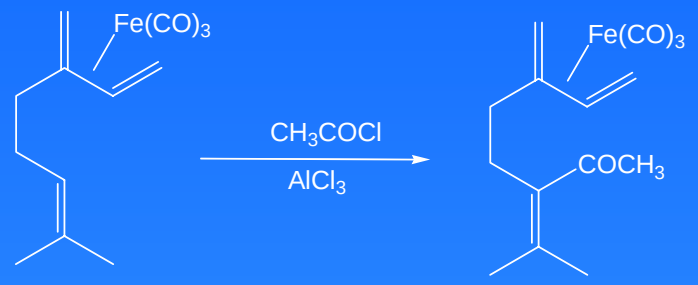
# Iron carbonyl complexes

## Synthetic applications of iron tricarbonyl complexes

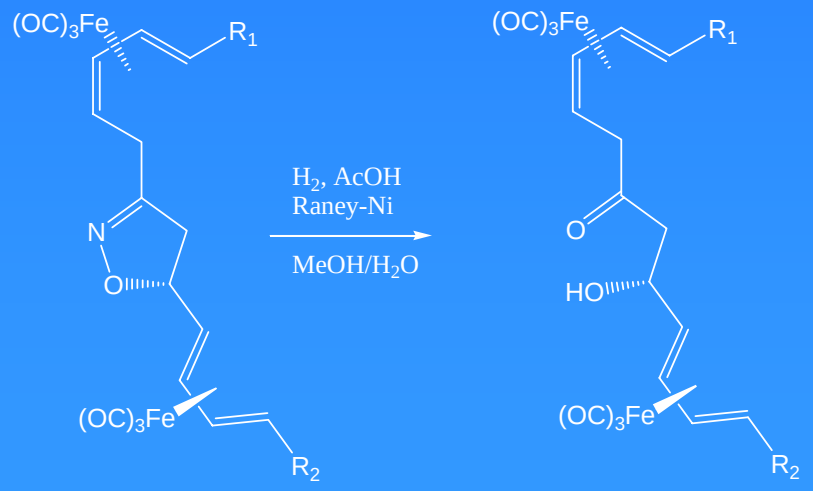
- **protection or stabilization of dienes :**




G. Evans et al., *J. Organomet. Chem.*, **1975**. 102, 507




M. Franck-Neumann et al., *Angew. Chem.*, **1986**. 98, 1138




W. A. Donaldson et al., *Synthesis*, **2003**. 13, 2064

# Iron carbonyl complexes

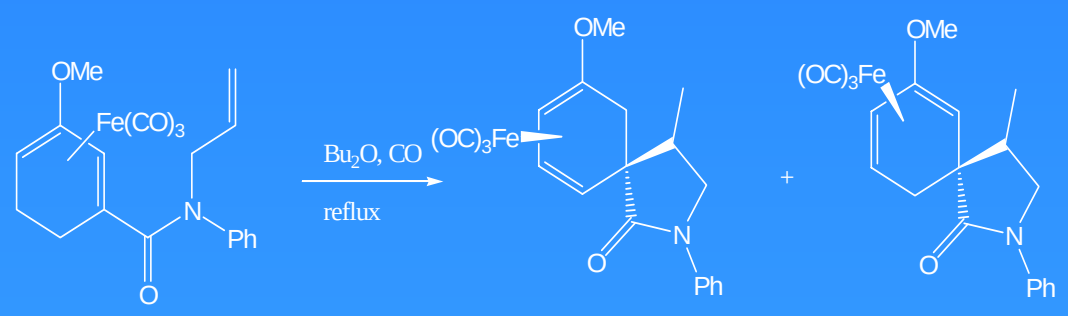
## ➢Asymmetric applications :

### • addition of nucleophile

M. Franck-Neumann, P. Chemla, D. Martina, *Synlett*, **1990**, 641

A. J. Birch, et al, *J. Chem. Soc. Chem. Commun.*, **1980**, 857

### • intramolecular spiroannelation




A. J. Pearson et al, *J. Org. Chem*, **2001**, 66, 3140

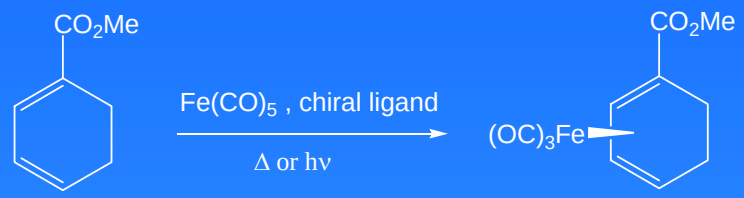
# Iron carbonyl complexes

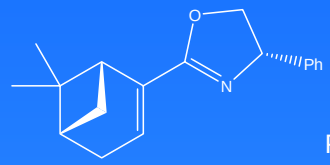
## Enantioselective complexation :

### ➢ Chiral transfert agents

30 % ee

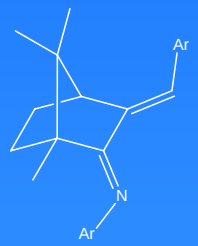
A. J. Birch et al, *Organometallics*, 1984, 3, 1075




88 % ee

P. Aspari, Thesis n° 1256, University of Fribourg

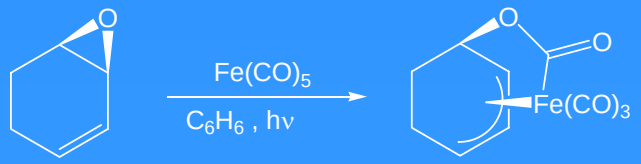



Ar = 4-$MeOC_6H_4$

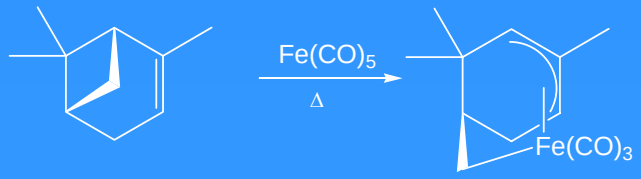
86 % ee

H.-J. Knölker et al, *Pure Appl. Chem.* 2001, 73, 7, 1075

### ➢ From a chiral ligand via ring opening complexation




A. J. Pearson, *Iron Compound in Organic Synthesis*, Academic Press, London, **1994**

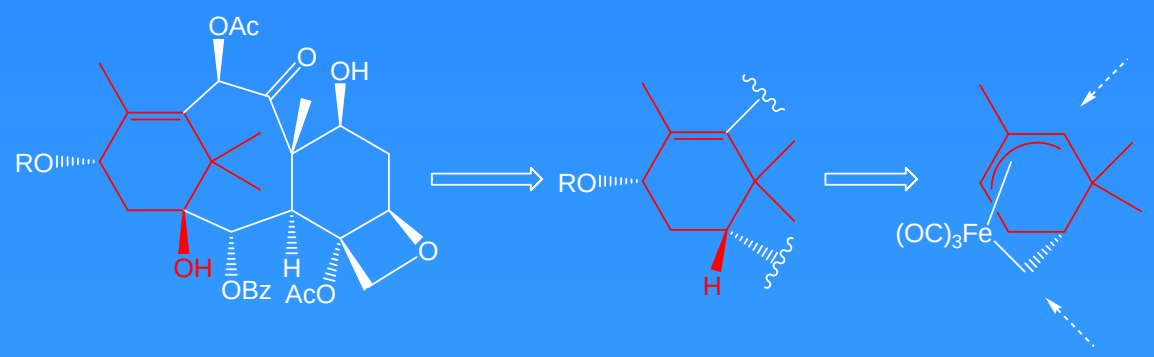



T.A. Jenny, L. Ma, *Tetrahedron Lett.*, **1991**, 32, 6101

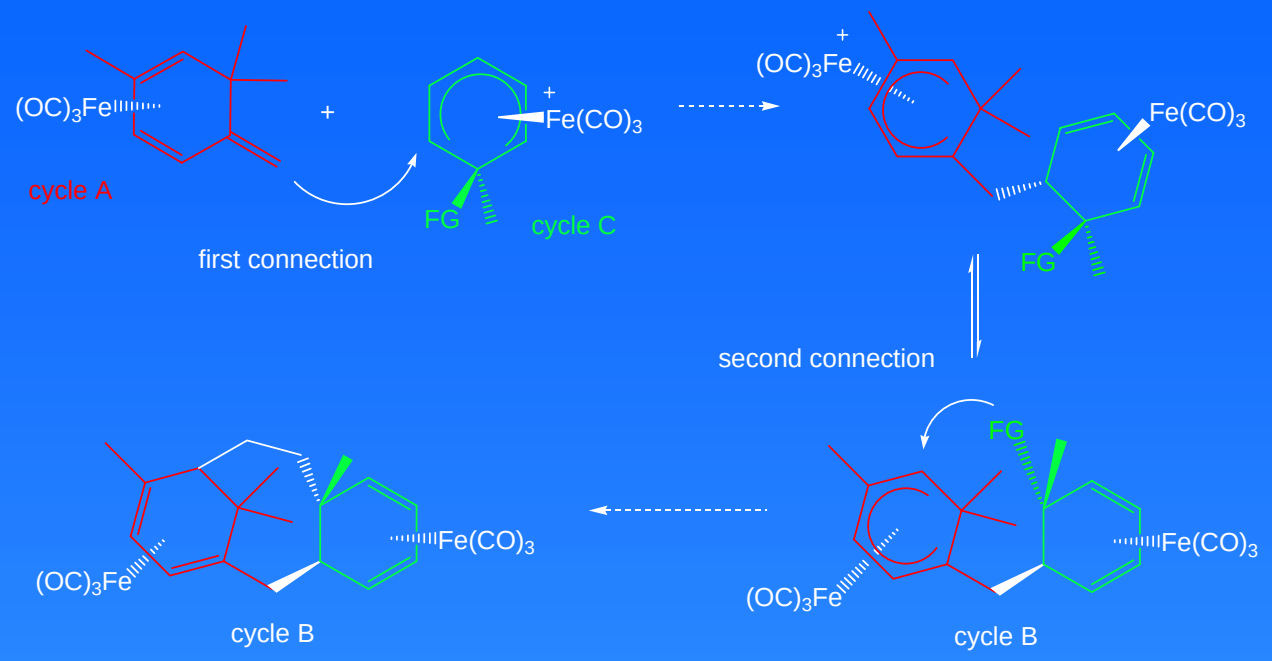
# Seco-pinene complex

This so called seco-pinene complex is the starting point of this work

This optically active complex has been proposed as an interesting building block for ring A of the Taxane skeleton.



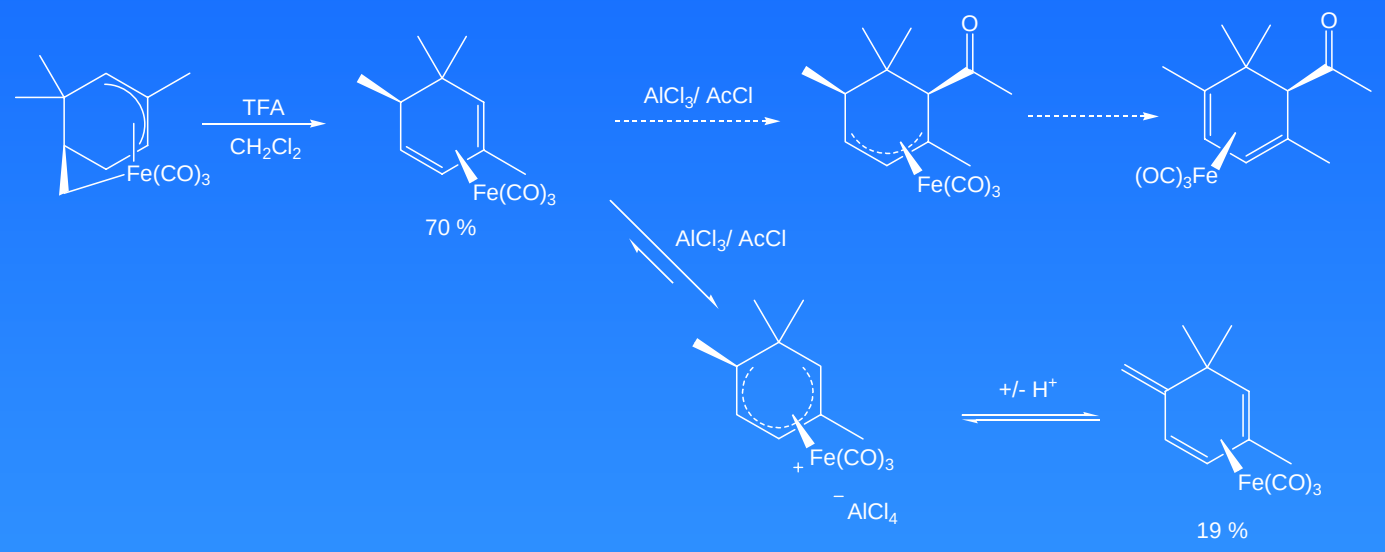
# Aim of this work




- Synthesis of a nucleophilic complex from seco-pinene (cycle A)
- Synthesis of a suitably functionalized cyclohexadienyl complex (cycle C)
- Investigation of the conditions needed to achieve the connections between the two building blocks (cycle B)

# Synthesis of the triene complex

- Synthesis

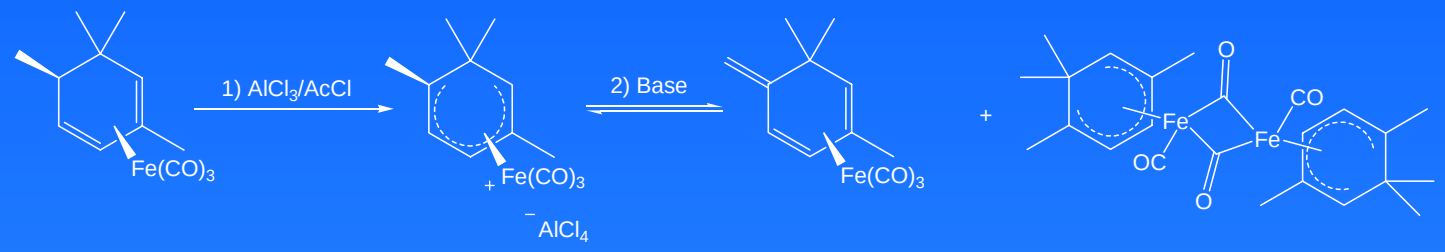



Optimization of the conditions :

- Addition of a base
- Amount of Perrier's reagent

# Synthesis of the triene complex

- **Addition of an aqueous base solution**



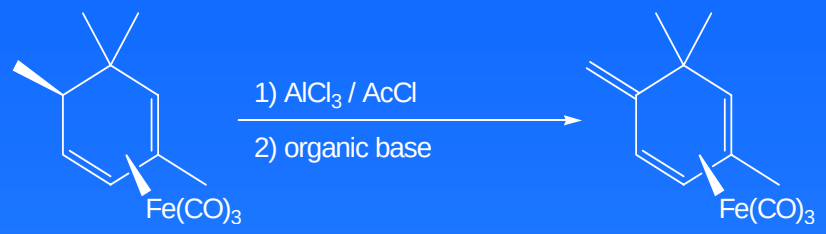

| Entry | Base | diene | triene | dimer |
|---|---|---|---|---|
| 1 | $NaHCO_{3\ sat}$ | 5 % | 10 % | - |
| 2 | $Na_2CO_{3\ sat}$ | 5 % | 38 % | 6 % |
| 3 | NaOH 30 % | 5 % | 20 % | 27 % |

**NMR analysis shows that the transformation of the diene complex into the cationic intermediate is complete but a back-reaction takes place during the aqueous work-up**

⇒ **Use of organic base instead of aqueous solution to prevent the in situ formation of HCl**

# Synthesis of the triene complex

- Addition of an organic base




| Entry | Base | diene | triene |
|---|---|---|---|
| 1 | $Et_3N$ (4) | 20 % | 39 % |
| 2 | $Et_3N$ (8) | 15 % | 49 % |
| 3 | $Et_3N$ (16) | 9 % | 55 % |
| 4 | TMEDA (1) | 22 % | 33 % |
| 5 | TMEDA (2) | 18 % | 45 % |
| 6 | TMEDA (4) | - | 70 % |

4 equivalents of TMEDA are needed

⇒ Complexation of the aluminum

⇒ Reaction with the excess of acetyl chloride

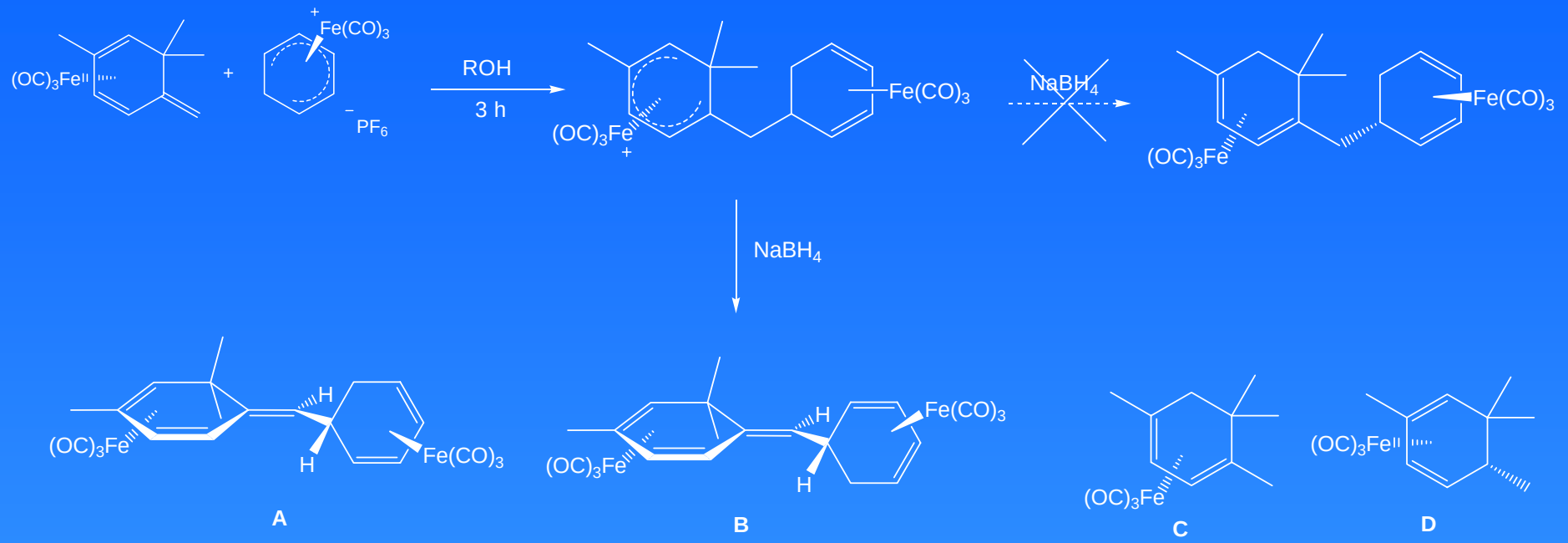
## ➢ Amount of Perrier's reagent

| Entry | $AlCl_3$ (eq) | AcCl (eq) | TMEDA (eq) | diene | triene |
|---|---|---|---|---|---|
| 1 | 4 | 2 | 4 | - | 70 % |
| 2 | 3 | 1.5 | 3 | 11 % | 53 % |
| 3 | 2 | 1 | 2 | 20 % | 41 % |

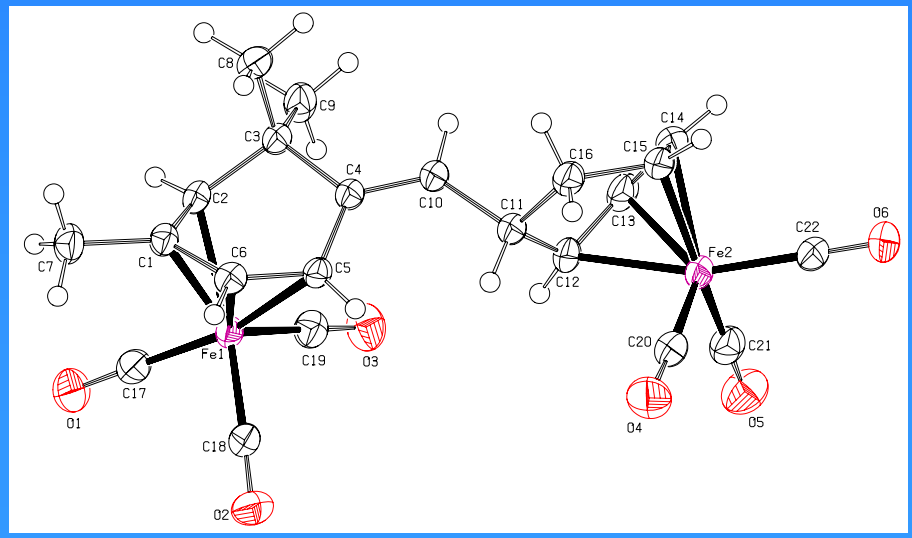
**⇒ Two equivalents of Perrier's reagent are needed**

# Coupling reactions

## Study on a model case

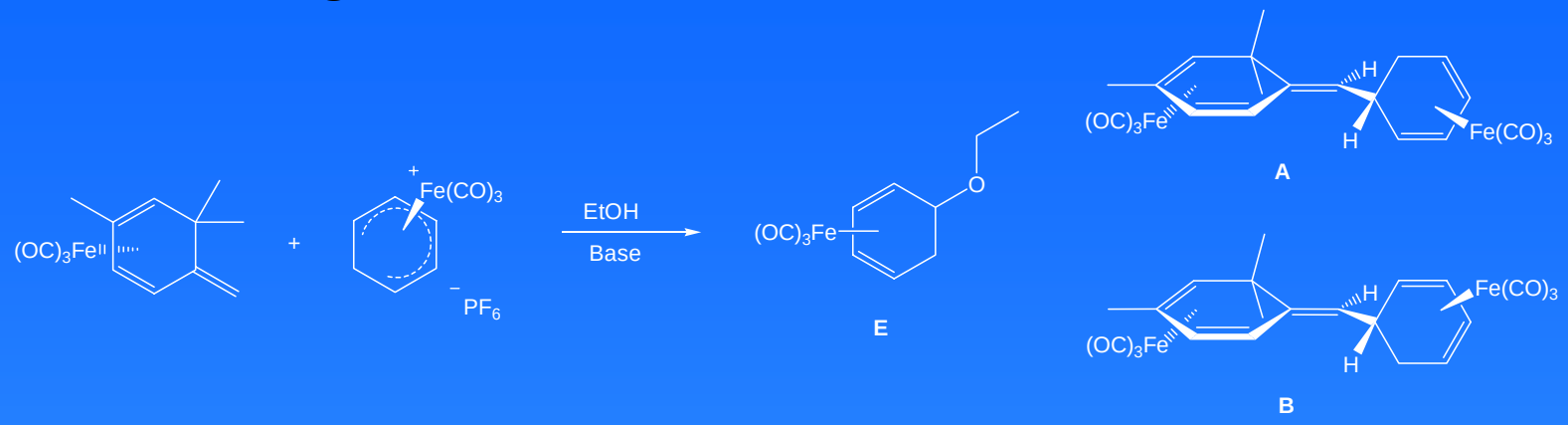


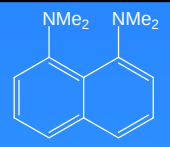
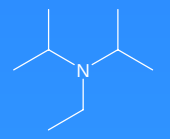
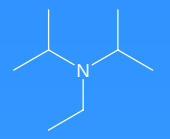

| Entry | Solvent (temperature) | Products (yield) |
|---|---|---|
| 1 | EtOH (85°C) | A / B (50 %)<br>C / D (50 %) |
| 2 | MeOH (40°C) | A / B (traces)<br>C / D (78 %) |
| 3 | *t*-BuOH (60°C) | A/ B (50 %)<br>C / D (40 %) |



# Coupling reactions

## Addition of an organic base

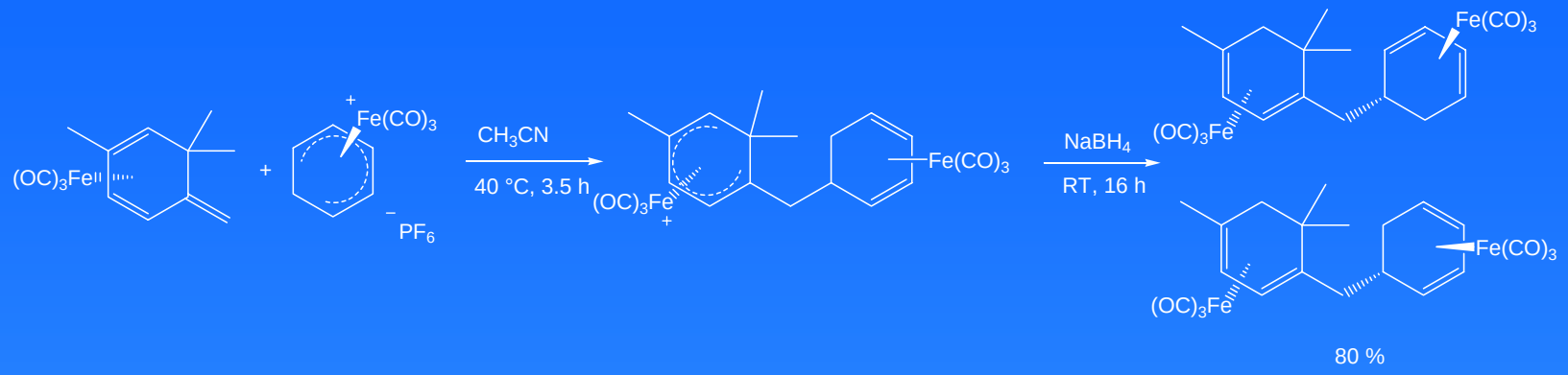



| Entry | Base | Products (yield) |
|---|---|---|
| 1[a] |  | triene (90 %), E (98 %) |
| 2[a] |  | triene (80 %), E (90 %) |
| 3[b] |  | triene (45 %), A/B (45 %), E (38 %) |

a: addition of the base simultaneously
b: addition of the base after 3.5 h

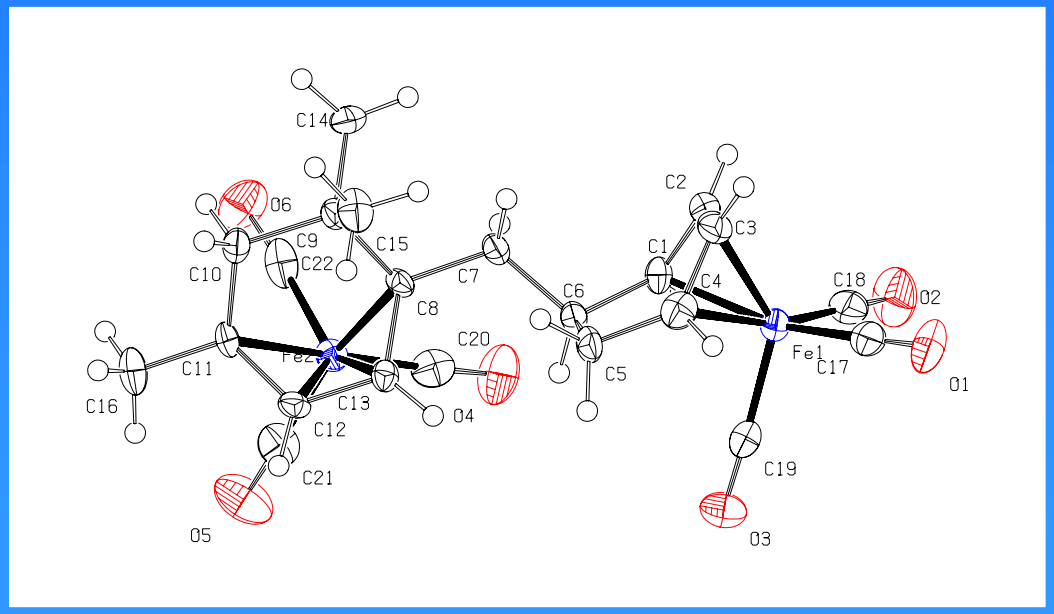
# Coupling reactions

## Influence of the solvent



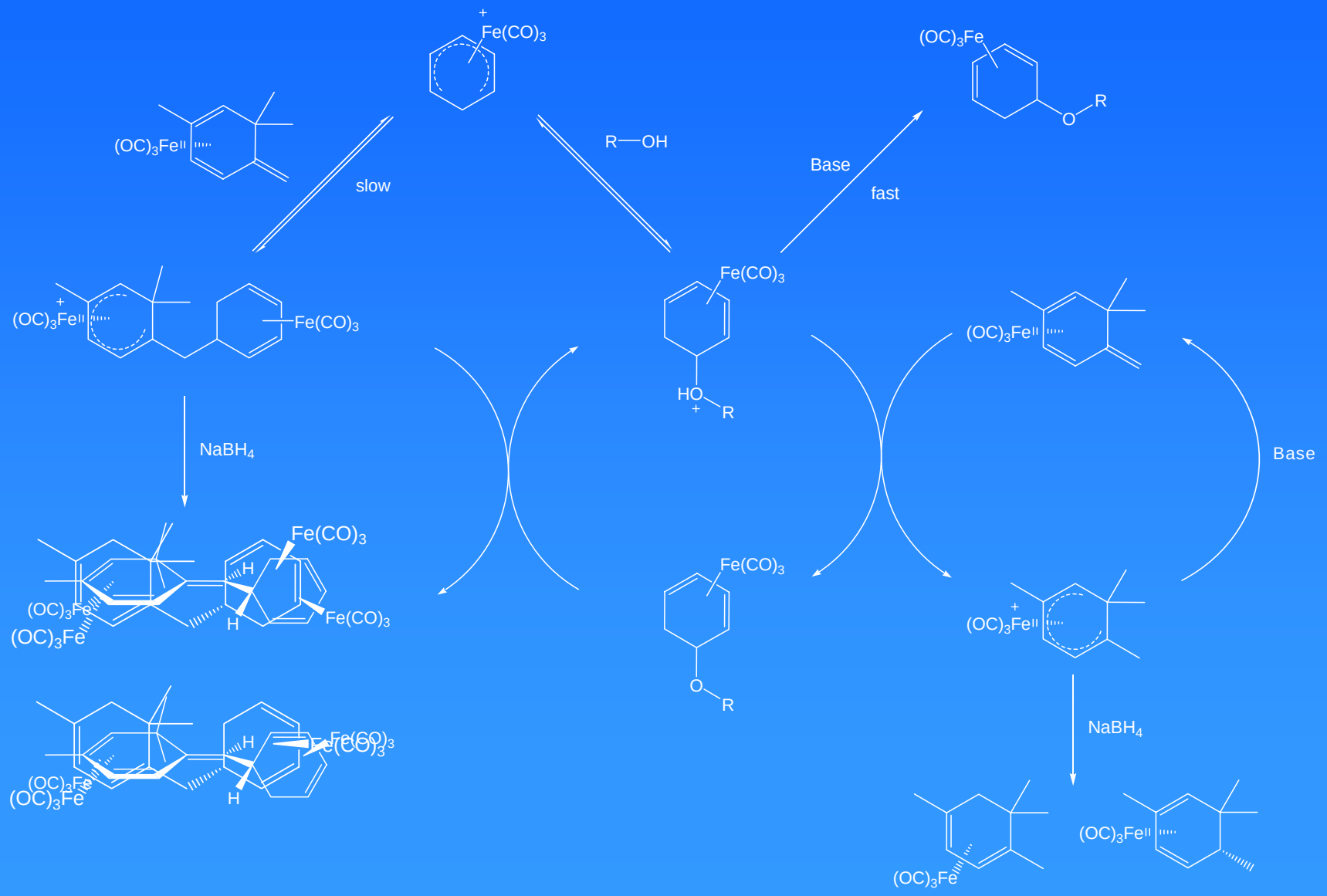

NMR spectra of the mixture show a 1 :1.7 ratio between the two isomers

The stereochemistry was confirmed by an X-Ray analysis of the minor isomer

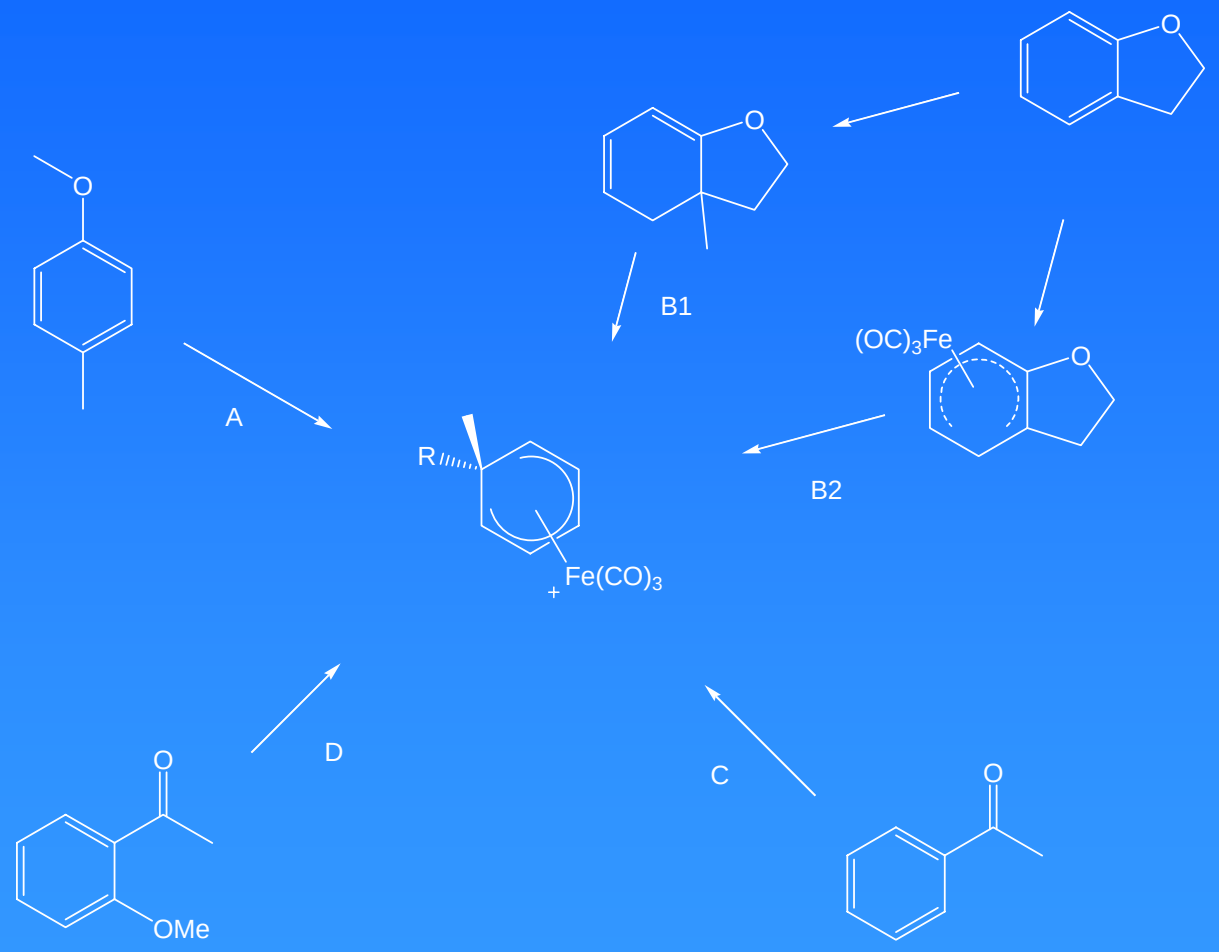


# Coupling reactions

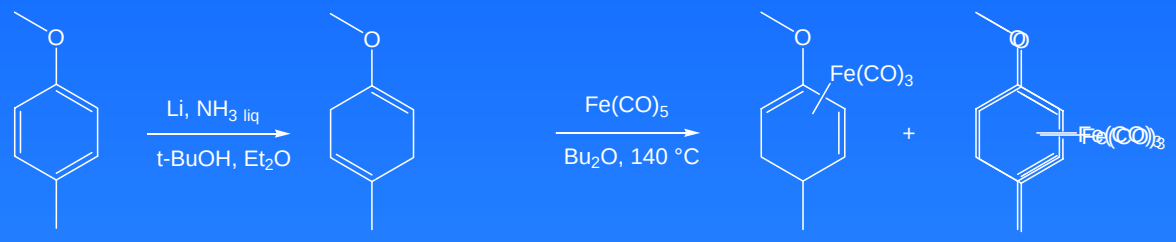
## Rationalization



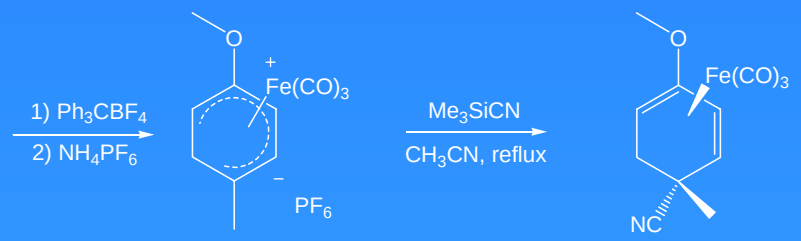
# Synthesis of cyclohexadienyl complexes



## Synthesis of a cyano substituted complex

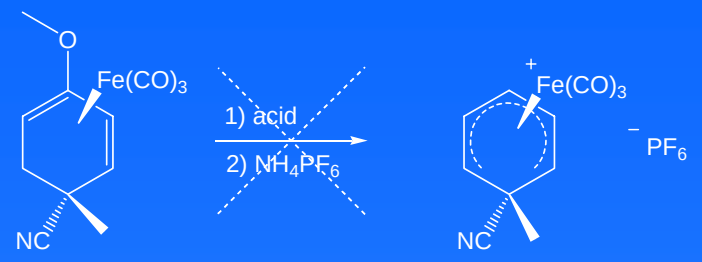



91 % 23 % 32 %




95 % 70 %

# Methylanisol pathway



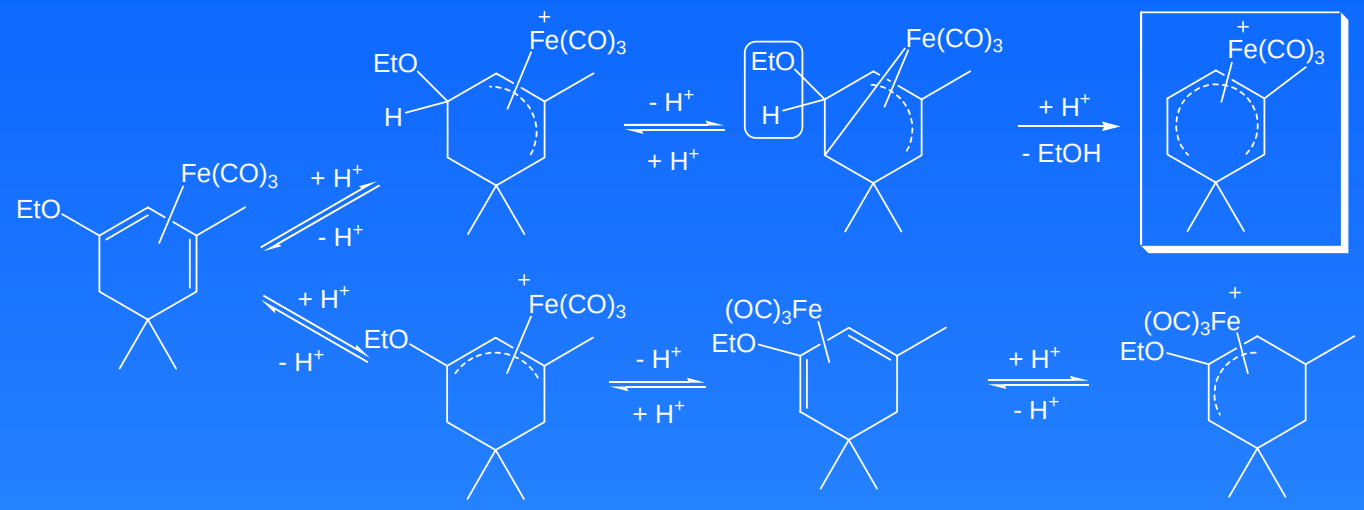

| Entry | Acid | Conditions | Product |
|---|---|---|---|
| 1 | $H_2SO_4$ | RT, 2.5 h | degradation |
| 2 | TFA | RT, 2.5 h | no reaction |
| 3 | TFA | RT, 48 h | no reaction |
| 4 | TFA | $CH_2Cl_2$, reflux, 5 h | no reaction |

- The relative position of the quaternary center with respect to the methoxy group does not allow the ionization to take place

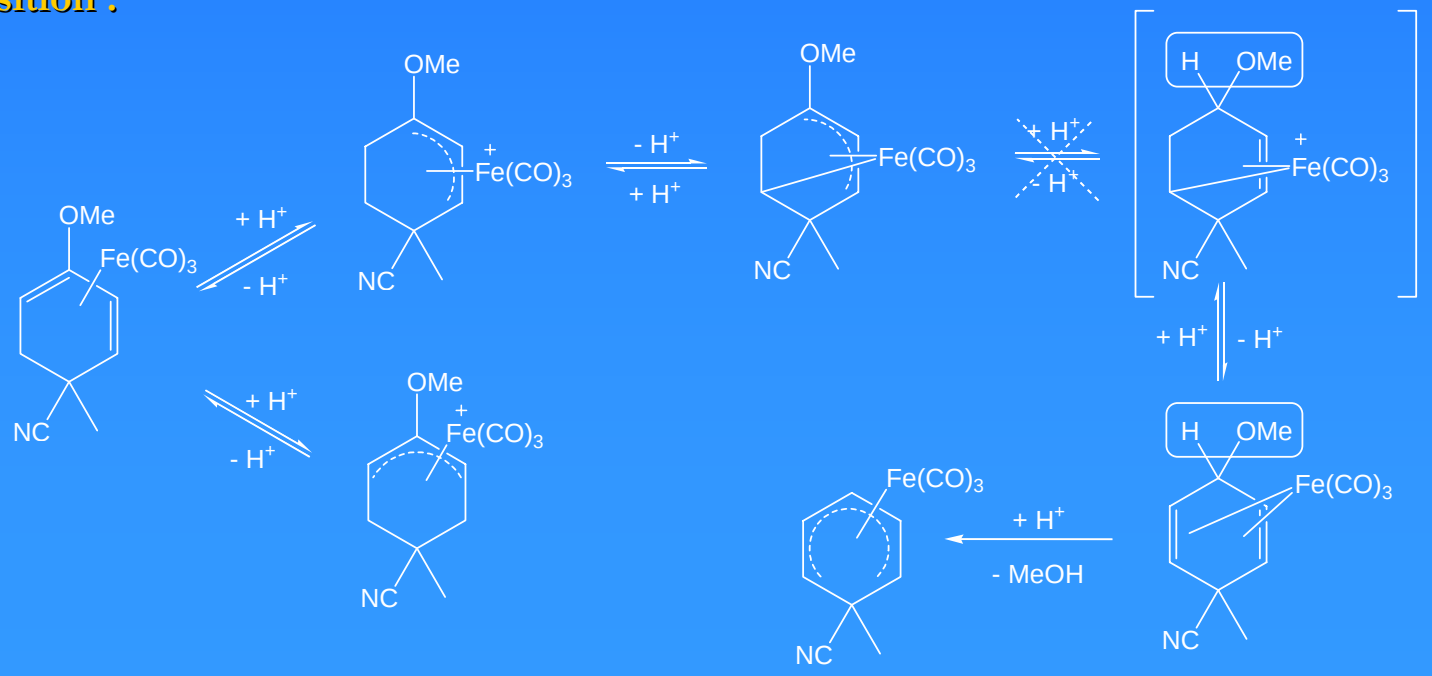
# Methylanisol pathway

## Rationalization :

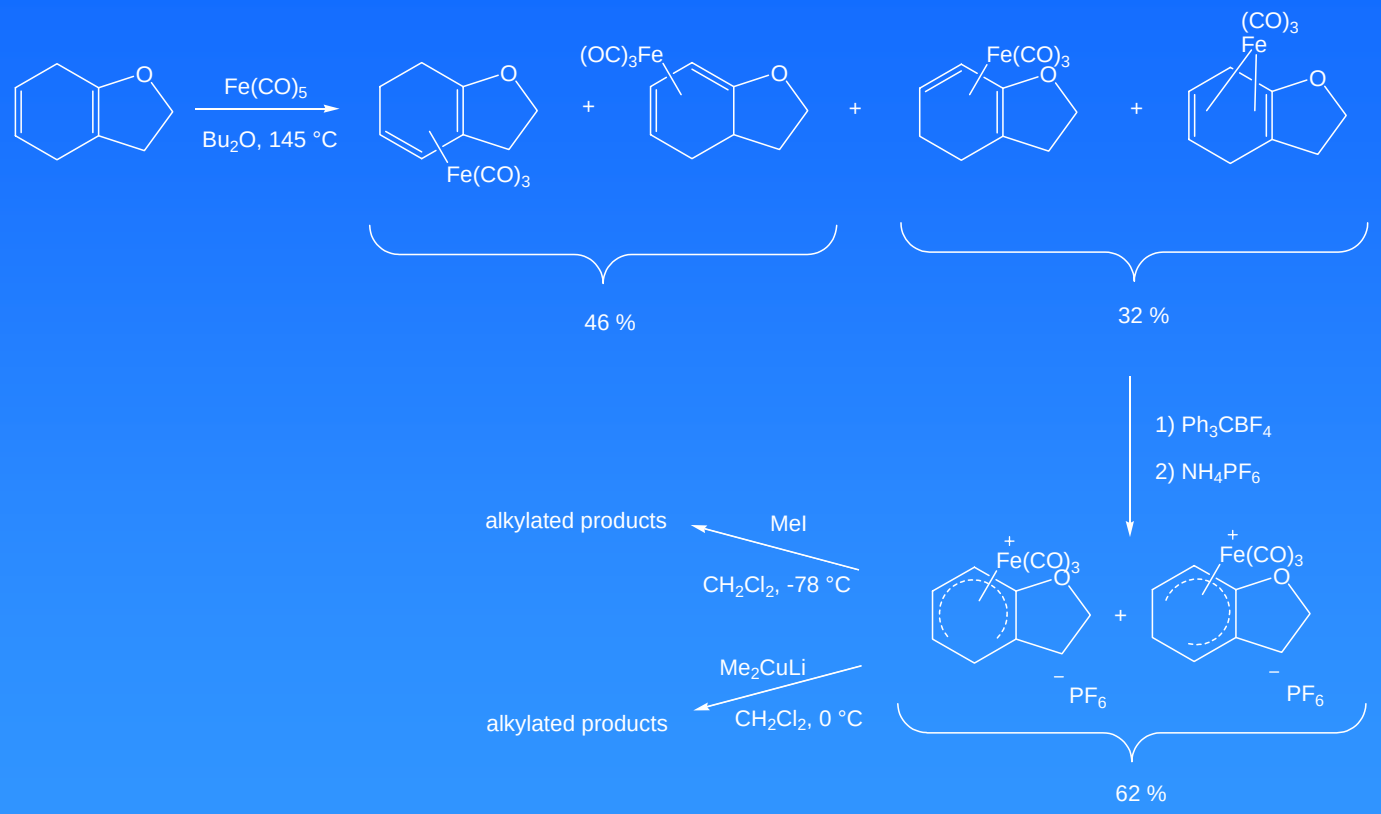
### Alkoxy in meta position :




### Alkoxy in para position :



## First strategy

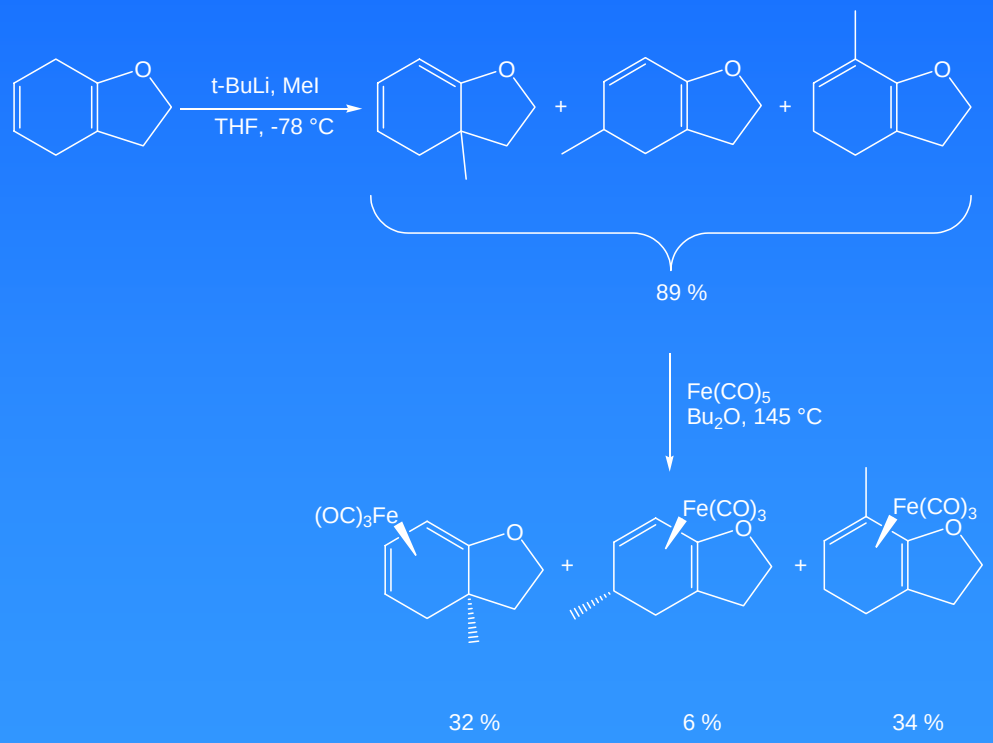



**Both alkylation procedures lead to a mixture of at least three inseparable alkylated products in less than 30 % yield**

**⇒ Inversion of the reaction sequence**

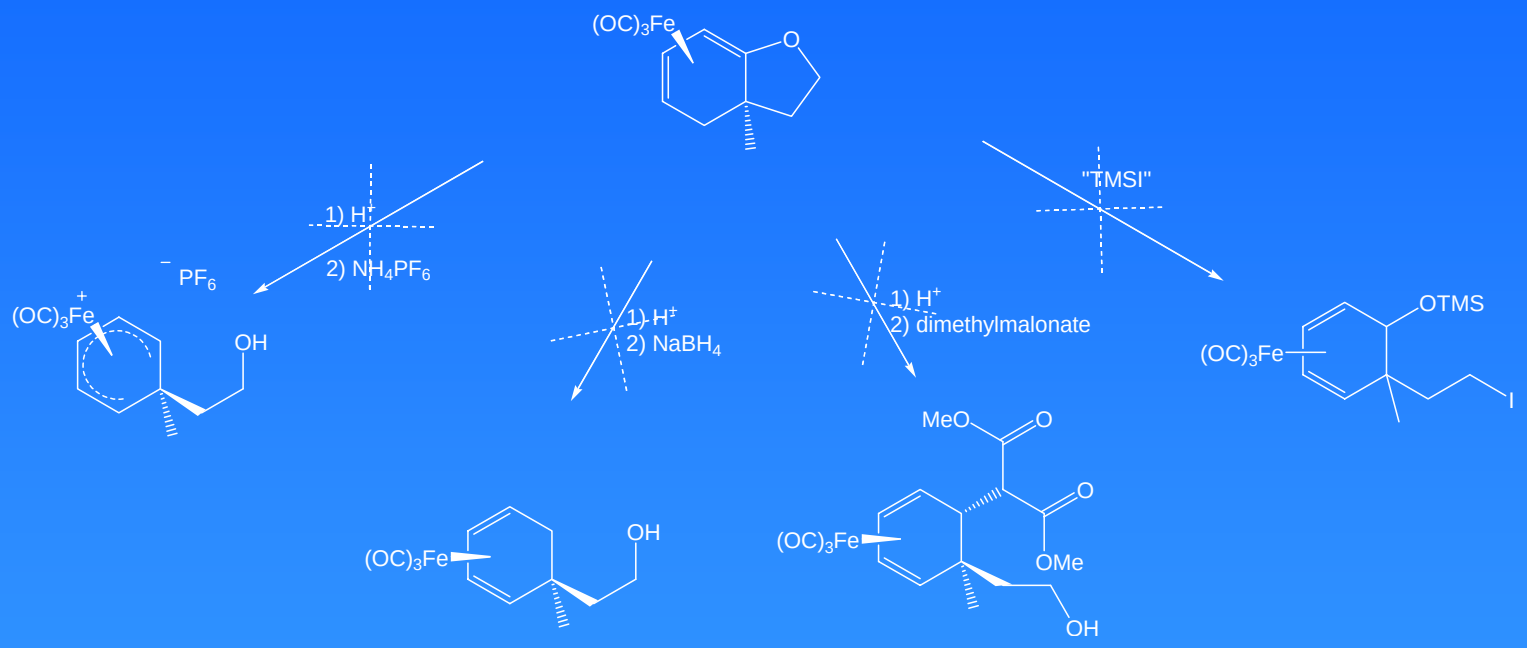
# Benzofuran pathway

## Second strategy



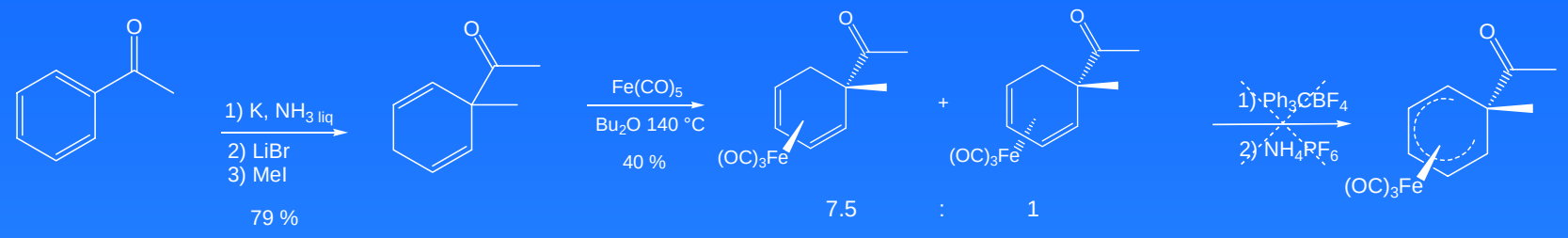
# Benzofuran pathway

**All attempts to open the furan ring were unsuccessful :**




- Ionization under acidic conditions
- Addition of nucleophiles to trap in situ the cationic complex
- Ring opening reaction using TMSI

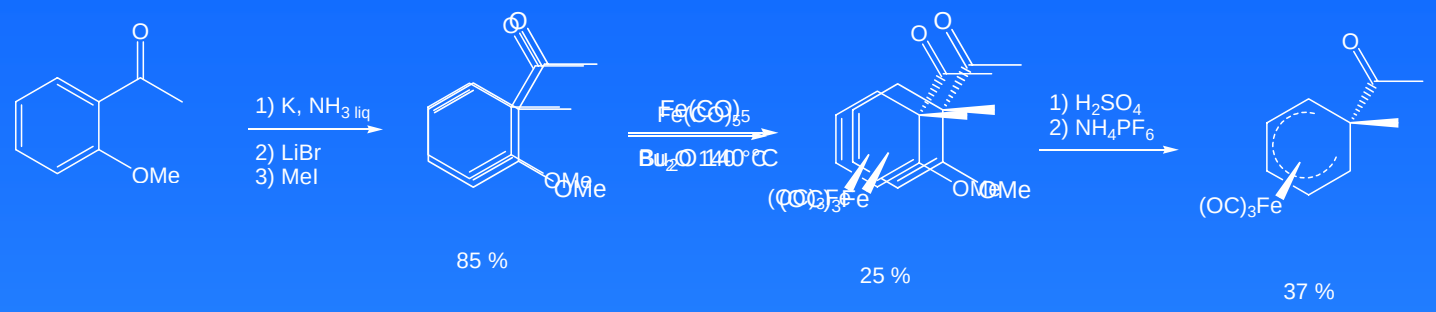
## Synthesis of an acetyl substituted cyclohexadienyl complex




The hydride abstraction with triphenylcarbenium tetrafluoroborate on the α-position of a quaternary center has not been reported so far

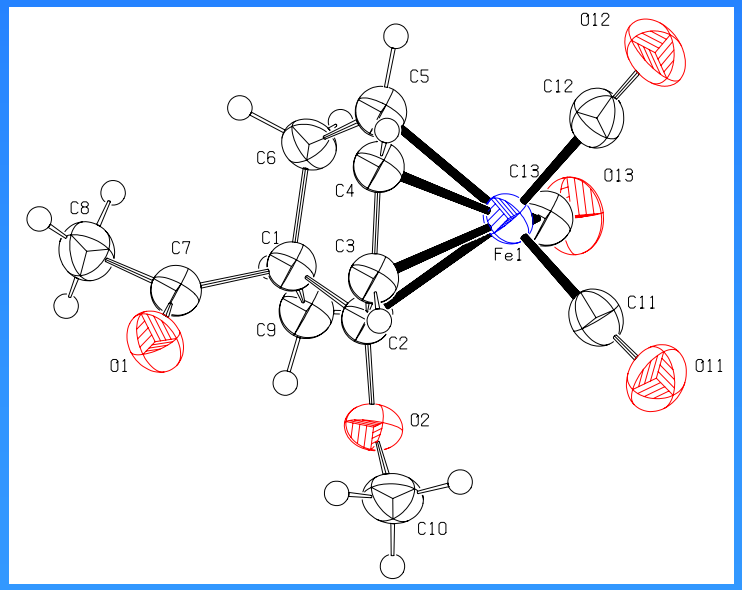
- The steric hindrance of the quaternary center may prevent the approach of the bulky trityl cation and consequently the hydride abstraction

# Synthesis of an acetyl substituted cyclohexadienyl complex




The complexation reaction shows an unexpected "selectivity", only one diastereomer was observed in the NMR spectra

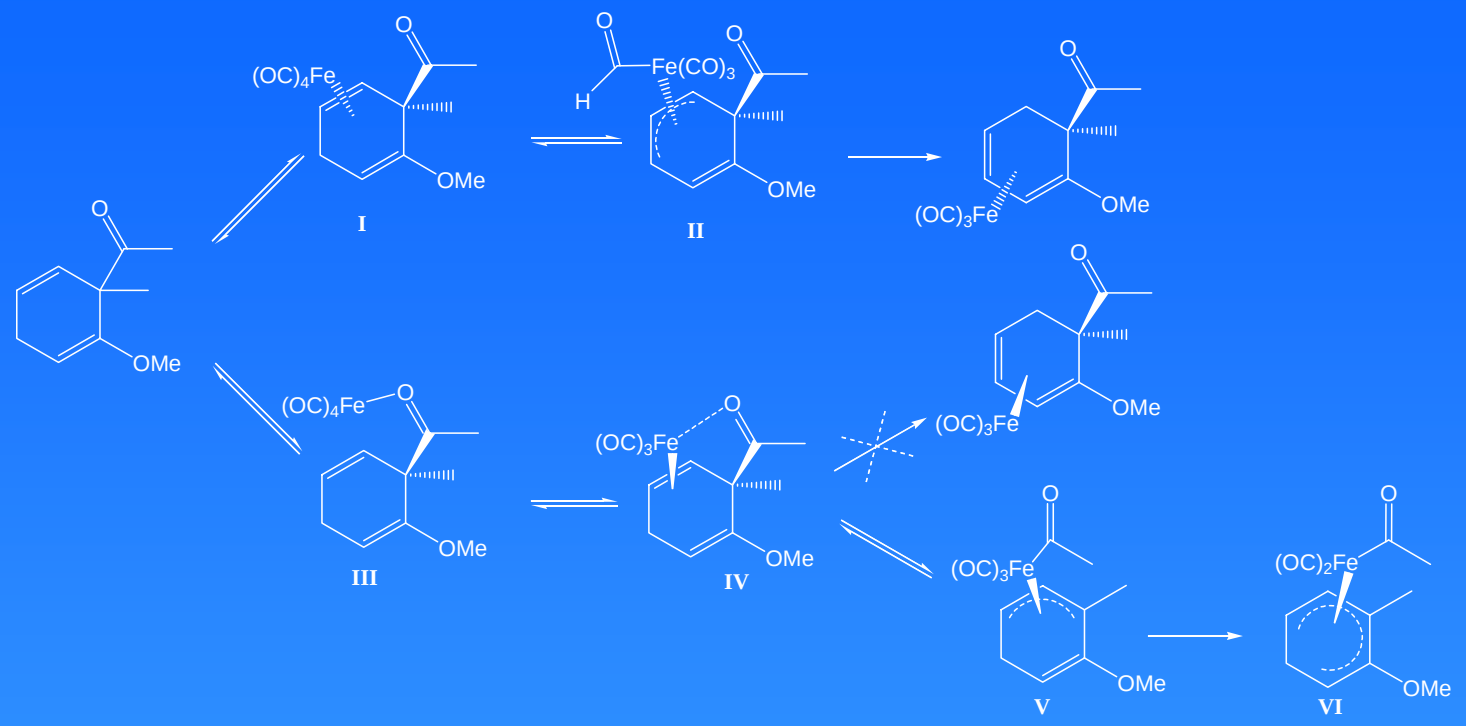
X-ray structure was obtained




- ⇨ Only the 2,4 diene complex was formed
- ⇨ The compexation occurs anti with respect to the acetyl group

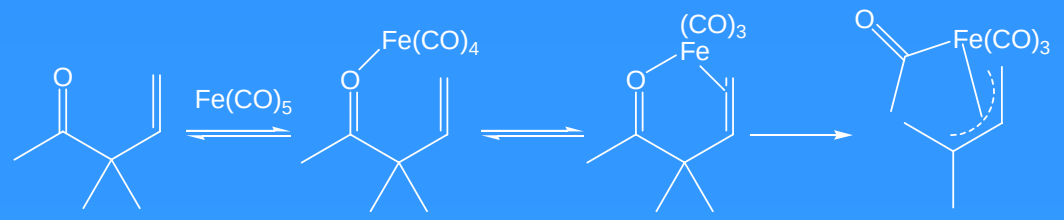
# Methoxyacetophenone pathway

The low yield and the unexpected "selectivity" can be explained as follows :



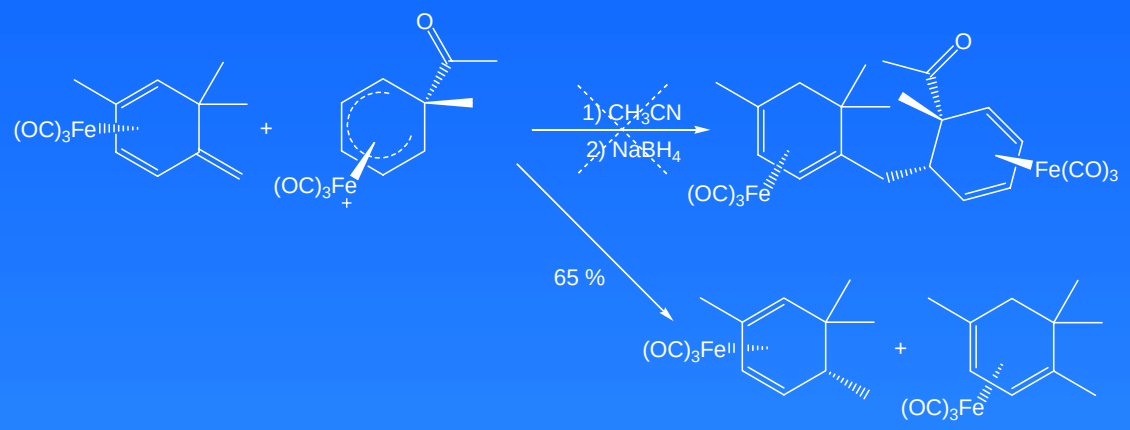

The complexation occurs preferentially on the acetyl side of the diene due to an initial complexation of the iron on the oxygen but instead of the isomerization, a fragmentation occurs leading to an unstable σ-acyl cyclohexadienyl complex

⇨ This type of fragmentation has been observed during the complexation of dimethylpentenone



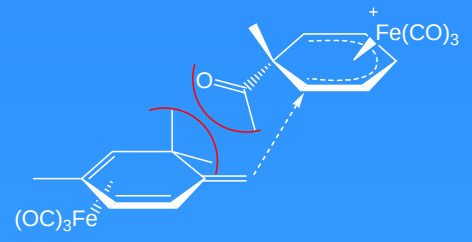
# Coupling reactions

## Application on the taxane skeleton synthesis

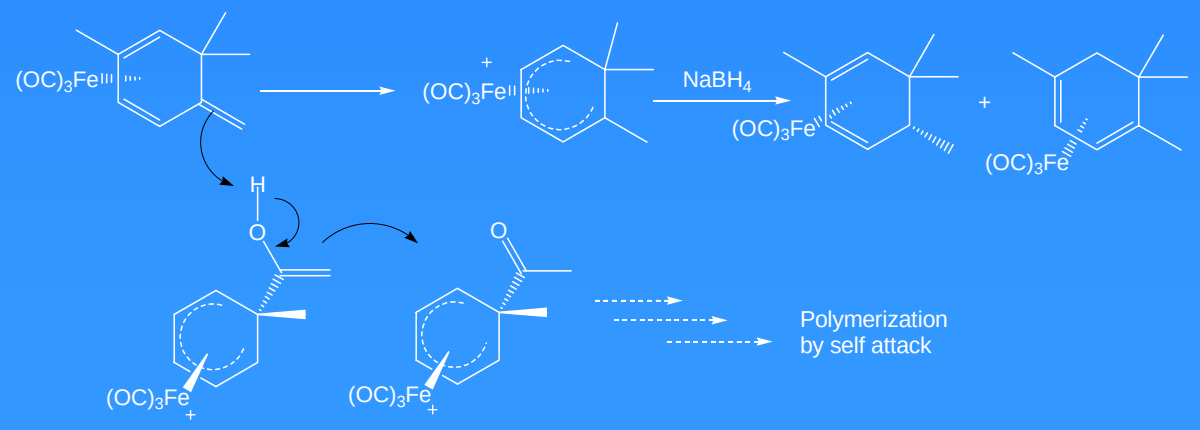



## Possible explanations :

### Steric hindrance :

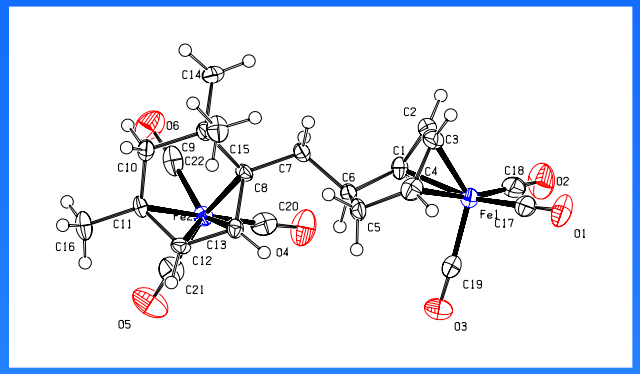



### Side reaction :

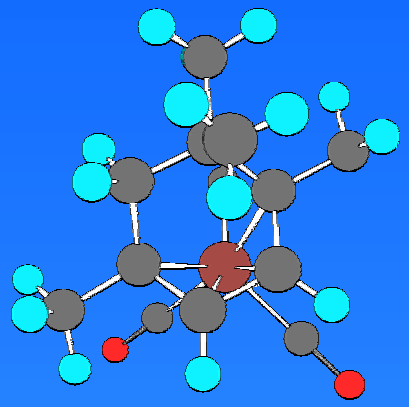


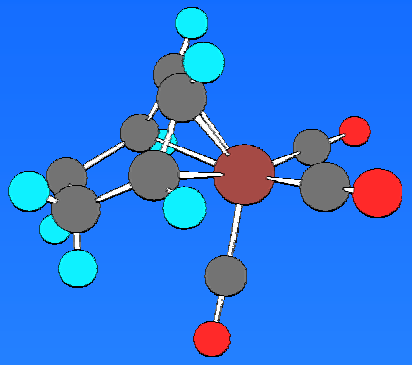
# Outlook

## Modelization of the other isomer

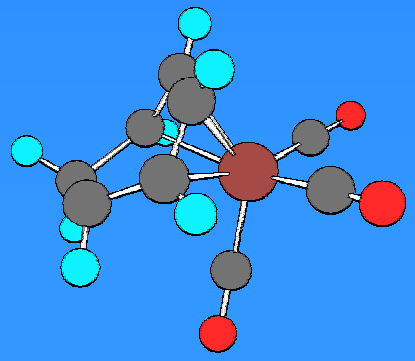



Dissociation

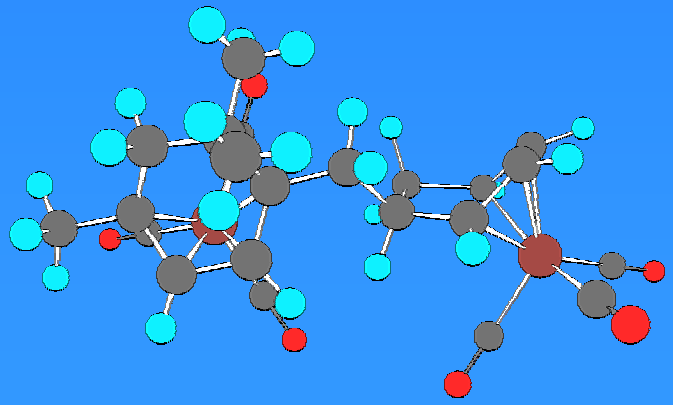




Mirror image

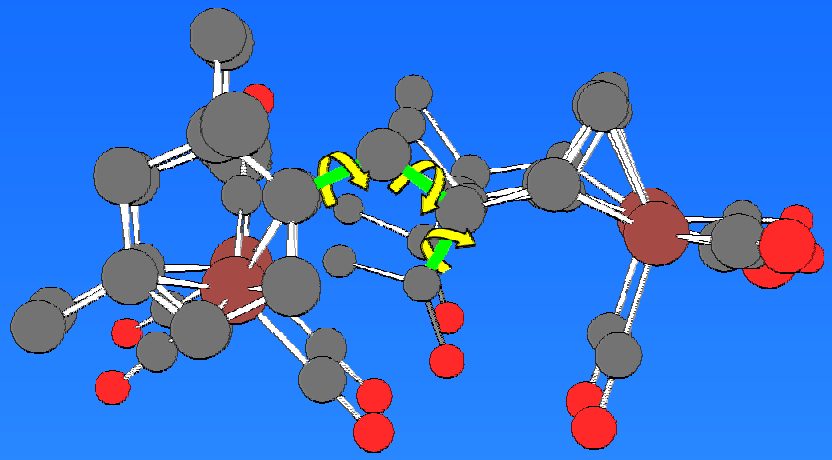


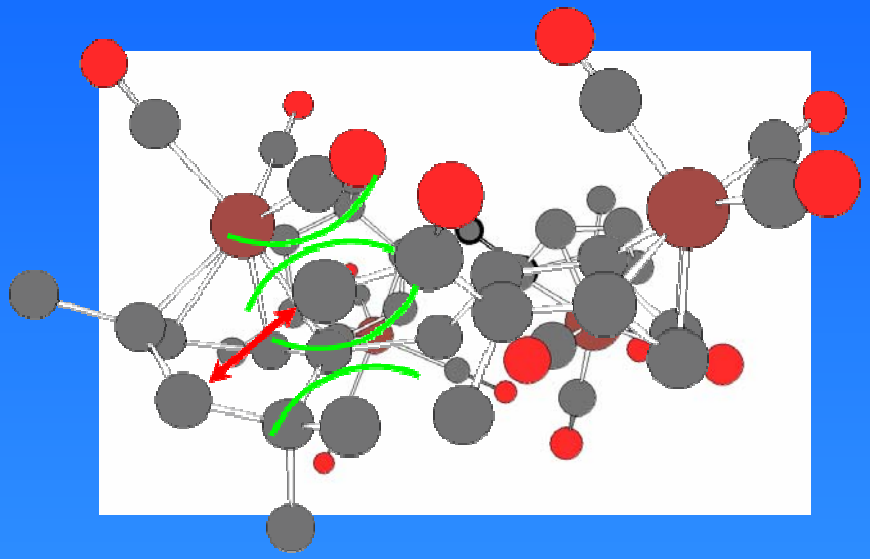
Recombination



# Outlook

Addition of the functional groups and modelization of the postulated final B ring closure





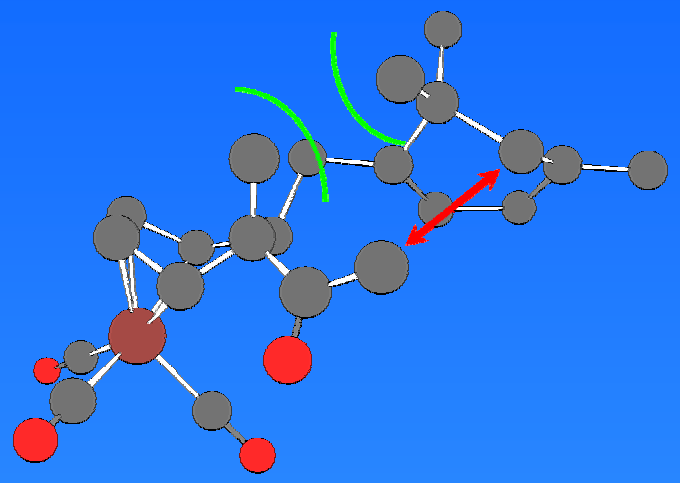
Such approach will be difficult :

- Steric interaction
- Addition has to occur in a syn fashion with respect to iron

Two strategies could be proposed :

# Outlook

⇒ A selective decomplexation of one of the two cycles

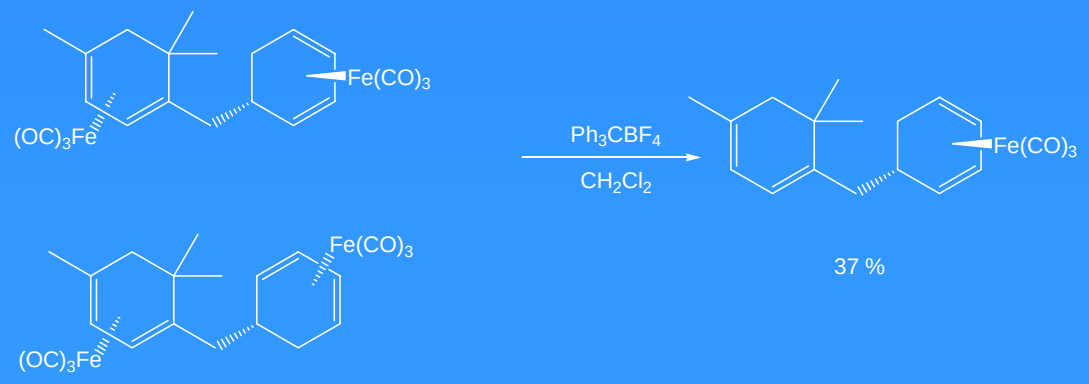


A decomplexation will decrease the steric interactions

But

1. A method to achieve such selective reaction has to be found
2. A new synthetic strategy has to be devised to achieve the final ring closing reaction

Surprisingly a selective decomplexation of the triene part has been observed during an ionization attempt :

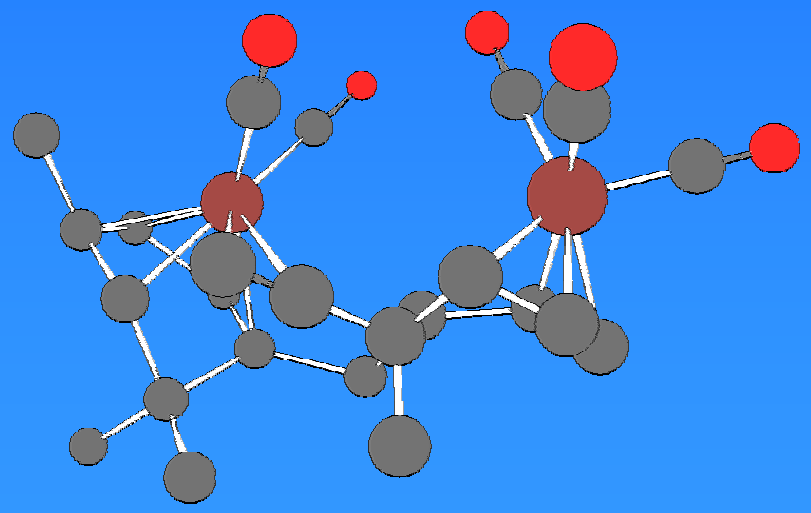


# Outlook

⇒ **The insertion of the incoming group in the coordination sphere of iron complexed to cycle A**

Additions of acetylenes or alkenes derivatives on iron tricarbonyl complexes via insertion in the iron coordination sphere have been reported

⇒ The synthesis of an acetylenic analogue of the binuclear complex could be envisaged



- Linear geometry and the small size of the acetylene group would decrease the steric interactions
- Photolytical exchange of one of the CO by the acetylenic moiety would permit the insertion
- Upon activation, the syn addition could take place leading the a tricyclic product possessing a taxane skeleton

# Conclusion

- ✓ The conditions for the synthesis of the triene complex have been optimized
- ✓ The synthesis of a suitably functionalized cyclohexadienyl complex has been achieved
- ✓ Even its application in the taxadiene skeleton synthesis could not be achieved, the coupling reaction has been studied on a model case :
  - ➢ The reactivity of the triene complex as nucleophile has been studied permitting the synthesis of a binuclear complex in an excellent yield and with a moderate selectivity
  - ➢ The influence of the solvent and of the addition of a base has been investigated allowing the understanding of the mechanism of this reaction
- ✓ A modelization of the expected binuclear complex has been done permitting the proposition of two possible strategies to apply this reaction in the taxadiene synthesis

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