24th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-24)

15 November – 15 December 2020

Theoretical study of the Aza-Wittig reaction, Me3P=NR (R = Methyl or Phenyl) with aldehyde by the DFT and DFT-D methods (dispersion correction)

Dr. Abdelghani Adda & **Dr. Hayat Sediki**

Presentation plan

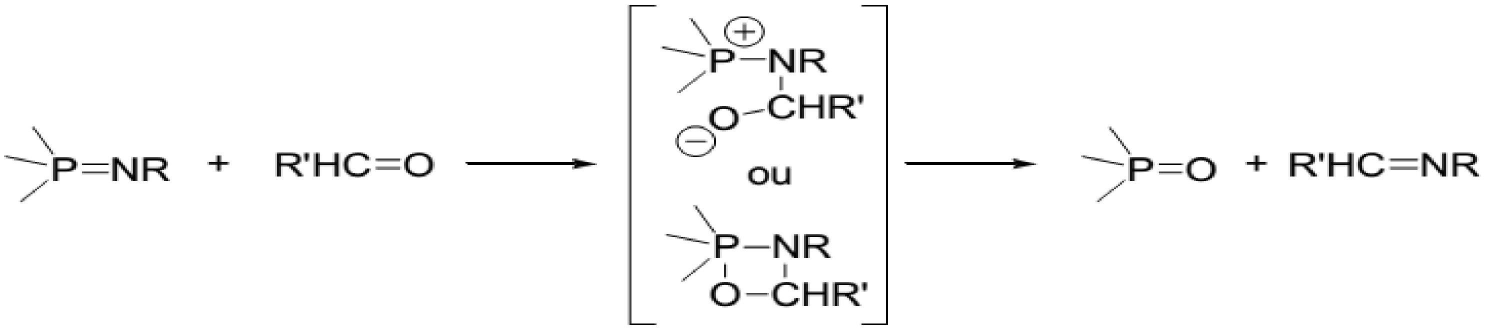
- Introduction
  - Role of aza-Witting reaction
  - Mechanism of the aza-Wittig reactions
- Goal of study
- Theoretical methods
- Results & discussion
- Conclusion

Introduction

Role of the aza-wittig reaction

- The aza-Wittig reaction plays an important role in organic transformations.
- Such a reaction can introduce in carbonyl compounds the imine bond C = N and can be easily reformed.

- Today, the use of iminophosphoranes (Phosphazenes) has become a powerful tool in organic synthesis strategies directed towards the construction of nitrogenous heterocycles.

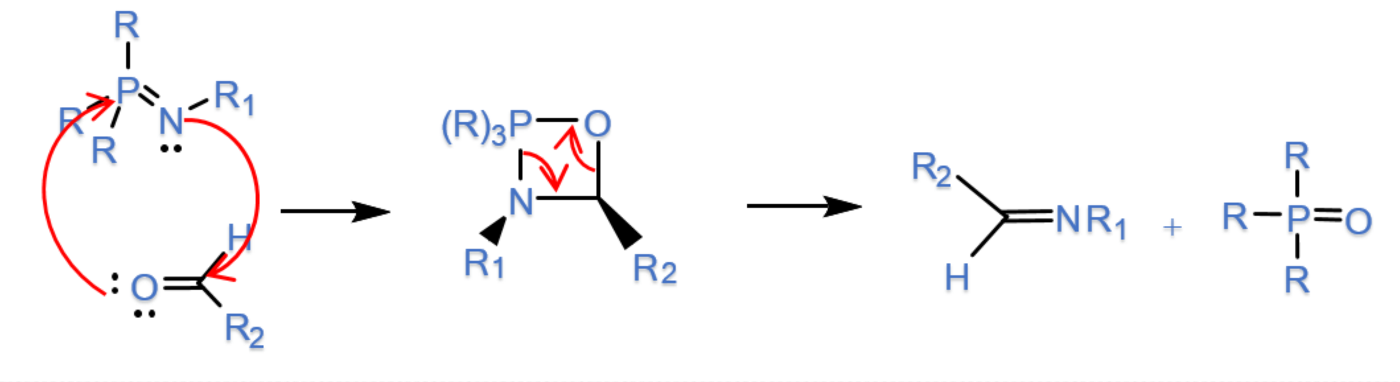


Mechanism of the aza-Wittig reaction

- This is arguably the most important reaction in the iminophosphorane reactivity panel.

- This reaction consists of a nucleophilic attack of the iminophosphoranes on the carbonyl (or thio-carbonyl) derivatives., followed by the removal of phosphine oxide (or phosphine sulfide).

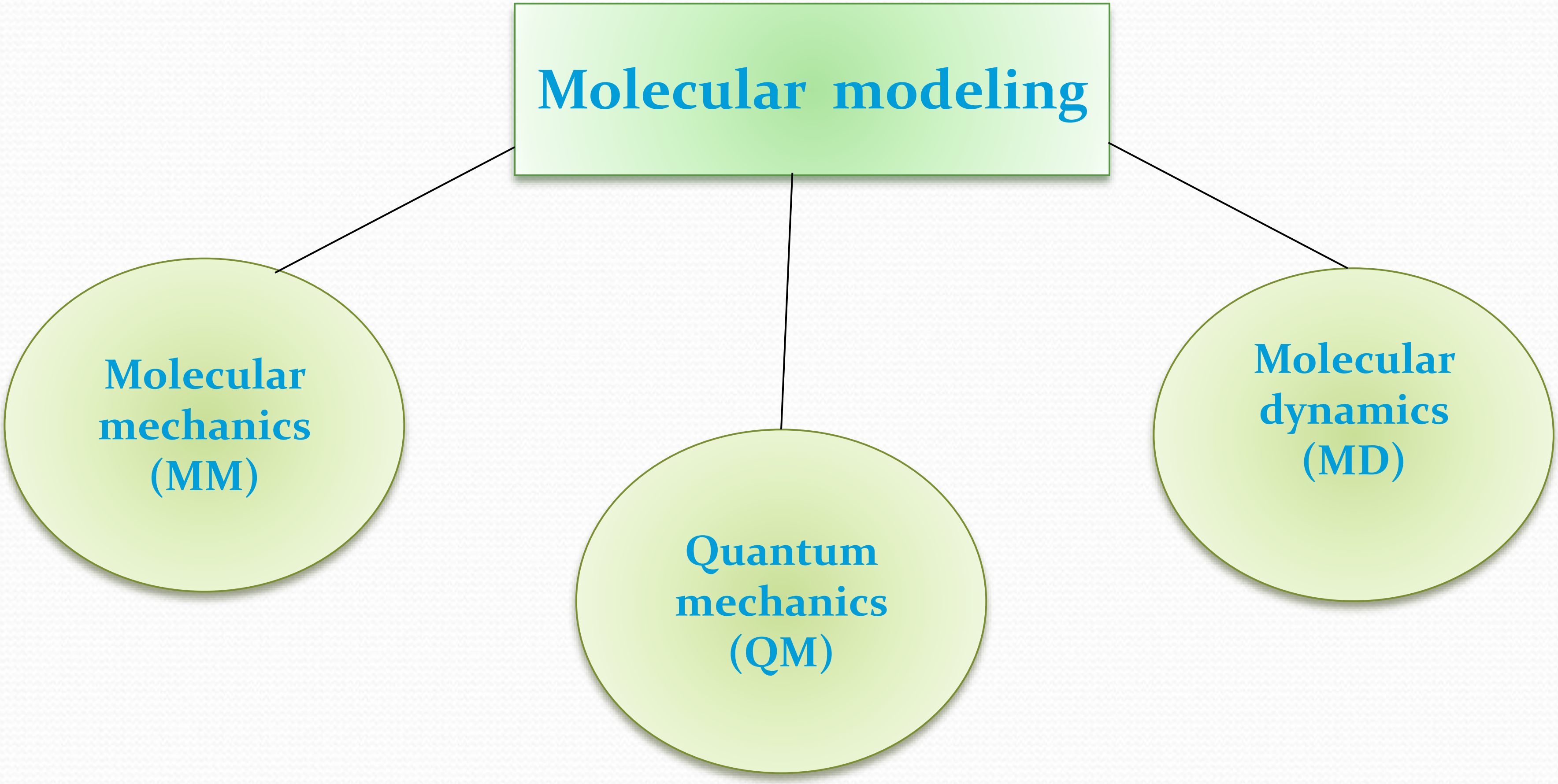
- This reactivity very clearly resembles that of phosphorus ylides, hence its name.



Mechanism of the aza-Wittig reaction
(R = CH3, R1 = CH3 or phenyl, R2 = CH3,)

Goal of the study

- Theoretical study of the Aza-Wittig reaction using molecular modeling software, using the DFT quantum method.
- In this work we have studied the aza-Wittig reaction for the two substituents of R, methyl and phenyl, (CH3) 3 = NR with ethanal (C2H4O).
- To our knowledge, no theoretical study on the DFT-D calculation (van der Walls dispersion correction) has yet been published on the aza-Wittig reaction.



Molecular modeling

Molecular mechanics (MM)

Quantum mechanics (QM)

Molecular dynamics (MD)

Theoretical methods

Density Functional Theory ‘DFT’

✓ DFT is a method of quantum computation that allows the study of electron density and energy in an exact way.

✓Most widely used method in chemistry and physics due to its efficiency.

- The main drawback is the lack of attractive long-distance interactions,
- The local density approximation (LDA) and the generalized gradient approximation (GGA) do not take into account dispersion interactions.

❖ The improvement of DFT calculations therefore requires the inclusion of :

- Van der Waals forces,
- and dispersion in the exchange-correlation functional.

➢ Adding a DFT-D corrective term or through a dedicated VdW-DFT function.

Empiric correction ‘DFT-D’

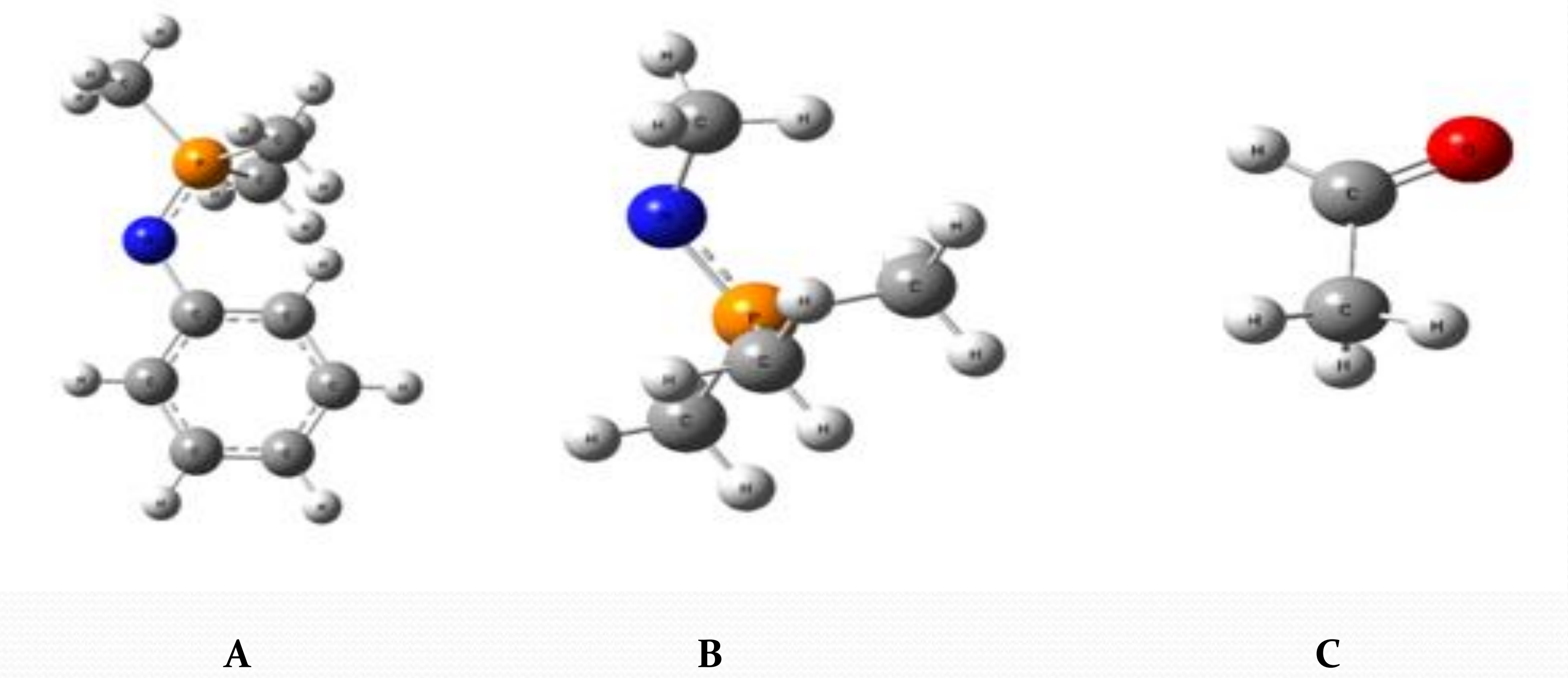
- Among the different implementations of DFT-D, those of Grimme and Tkatchenko Scheffler are among the most popular.
- The approach taken by Grimme in 2006 (and subsequently noted as G06) is to add a corrective term to the Kohn-Sham energy.

$$E = E_{KS-DFT} + E_{DISP}$$

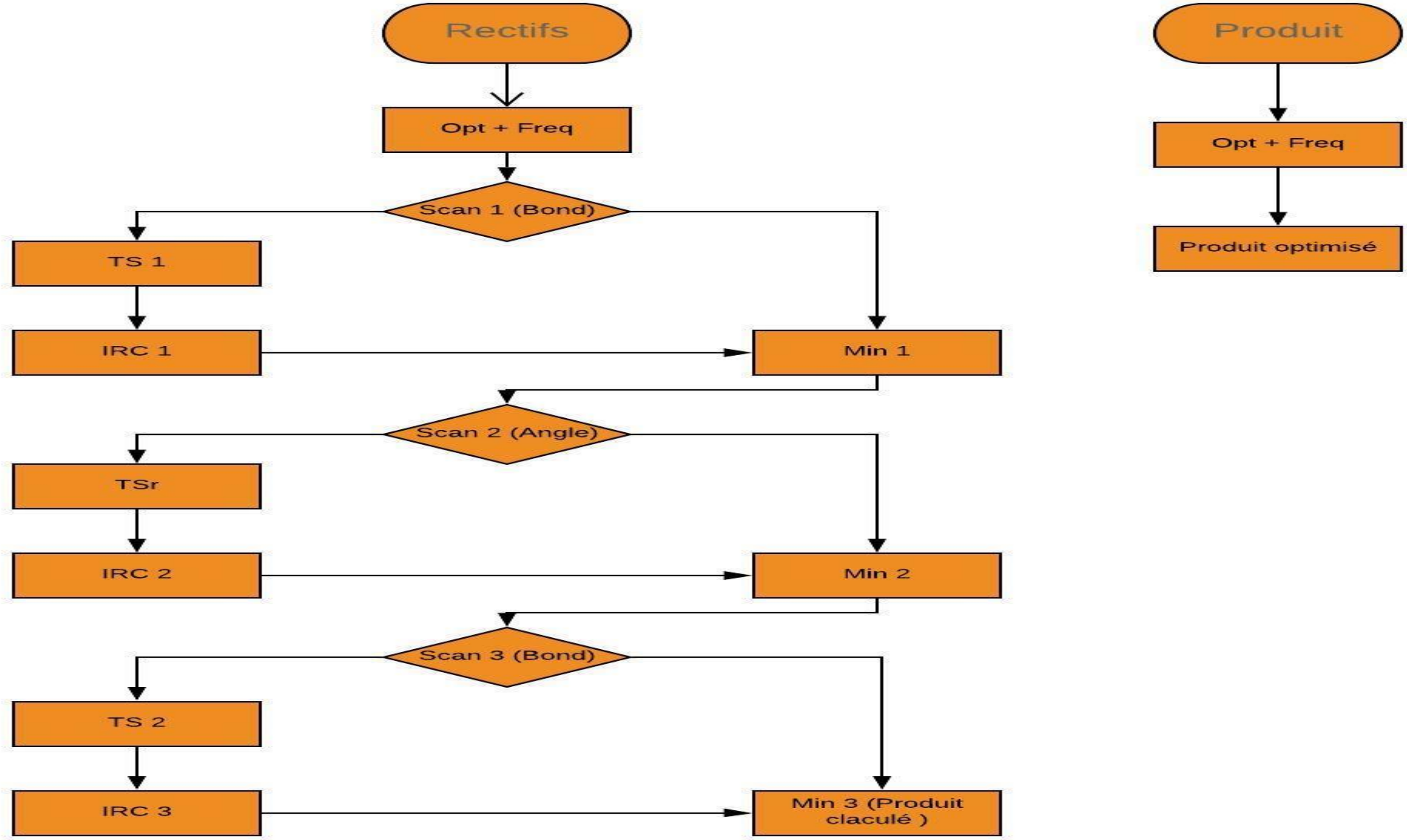
Results & discussion

Calculation methods

DFT study using the functional B3LYP and B3LYP-GD3BJ (Empirical dispersion) with a base 6-31G (d, p).



Optimized geometries of the reagents used in the Aza-Wittig reaction mechanism :
A: phosphazene with phenyl , **B:** phosphazene with methyle , **C:** Ethanal



Calcul steps

Étude de la réaction Méthylimino(triméthyl)phosphorane avec l'éthanal.

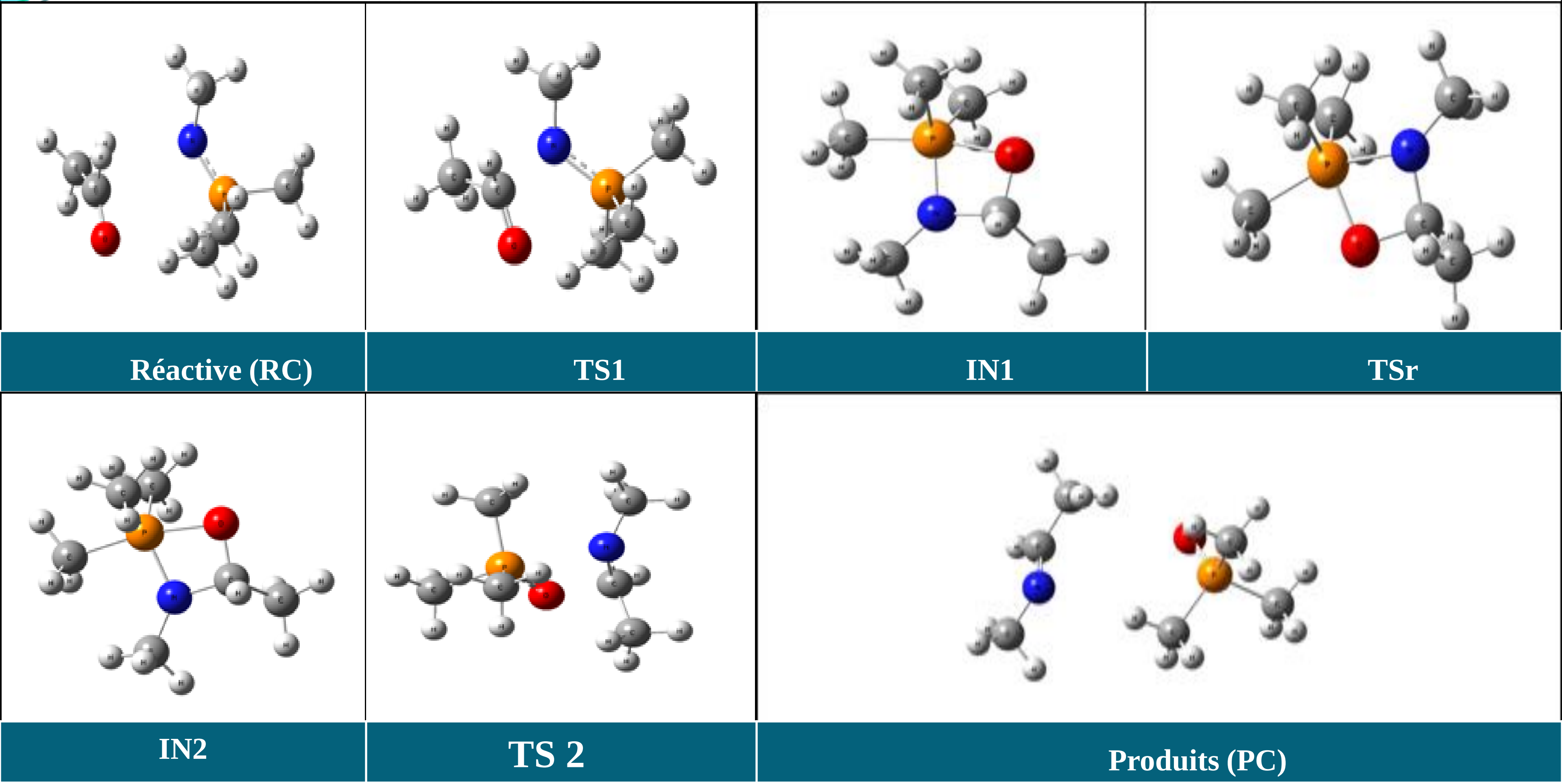
Using DFT calculations at B3LYP / 6-31G (d, p) and B3LYP-D / 6-31G (d, p) level, it is shown that the reaction of the Aza-Wittig titer continues via

$(CH_3)_3P{=}NCH_3 + O{=}CH_2CH_3 \rightarrow RC \rightarrow TS1 \rightarrow IN1 \rightarrow TSr \rightarrow IN2 \rightarrow TS2 \rightarrow PC \rightarrow (CH_3)_3P{=}O + CH_3N{=}CH_2CH_3$

RC: reactif complexe **PC:** product complexe , **TS:** transition state , **IN:** intermediate

Bond lengths (in Å) and dihedral angles (in degrees) of the Aza-Wittig reaction of methylimino(trimethyl)phosphorane with Acetaldehyde $(CH_3)_3P{=}NCH_3$.

B3LYP/6-31G(d,p) B3LYP-D/6-31G(d,p)	$d_{P\text{-}N}$ Angström	$d_{C\text{-}O}$ Angström	$d_{P\text{-}O}$ Angström	$d_{N\text{-}C}$ Angström	Φ_{PNCO}
Réactive (RC)	1.58 1.58	1.22 1.22	3.63 3.45	3.07 2.84	-2.42 -0.50
TS1	1.64 1.63	1.28 1.28	2.69 2.70	1.76 1.76	-7.30 -6.75
IN 1	1.72 1.71	1.40 1.40	1.84 1.84	1.47 1.46	-6.73 -6.95
TSr	1.81 1.81	1.42 1.43	1.73 1.73	1.45 1.45	-11.76 -11.66
IN2	1.72 1.71	1.40 1.40	1.84 1.84	1.47 1.46	-6.75 -6.95
TS2	2.42 2.41	1.69 1.69	1.59 1.59	1.36 1.36	8.58 10.20
Produit (PC)	4.13 3.89	3.76 3.53	1.51 1.51	1.27 1.27	-2.11 -2.01



Réactive (RC) **TS1** **IN1** **TSr**

IN2 **TS 2** **Produits (PC)**

Optimized geometries of structures involved in the reaction pathway.

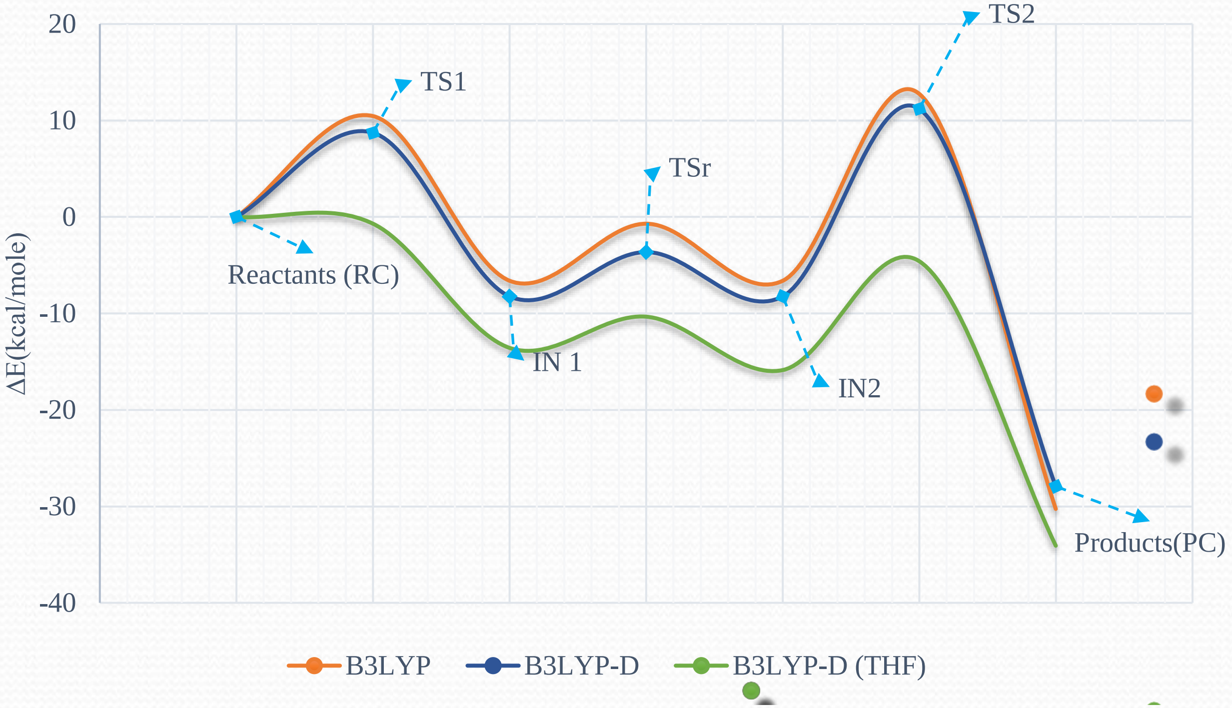
‘Methylimino (trimethyl) phosphorane with ethanal’

Structures	**B3LYP**			**B3LYP-D**		
	ΔE (Kcal/mol)	**ΔG (Kcal/mol)**	**ΔH (Kcal/mol)**	**ΔE (Kcal/mol)**	**ΔG (Kcal/mol)**	**ΔH (Kcal/mol)**
Reactant(CR)	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
TS1	**10.44**	**14.77**	**10.28**	**8.73**	**12.17**	**8.52**
IN 1	**-6.63**	**-0.05**	**-5.01**	**-8.23**	**-2.46**	**-6.62**
TSr	**-0.71**	**6.44**	**-0.98**	**-3.63**	**2.75**	**-2.85**
IN2	**-6.63**	**-0.05**	**-5.01**	**-8.23**	**-2.46**	**-6.62**
TS2	**12.75**	**17.97**	**12.80**	**11.20**	**16.06**	**11.32**
Product (CP)	**-30.27**	**-29.31**	**-29.53**	**-27.94**	**-26.90**	**-27.15**

- Relative energies, enthalpy and Gibbs free energy (kcal/mol) calculated by the DFT, at the theoretical level B3LYP and B3LYP-D3 with a base of 6-31G**.

- (D: Dispersion corrections of Grimme).

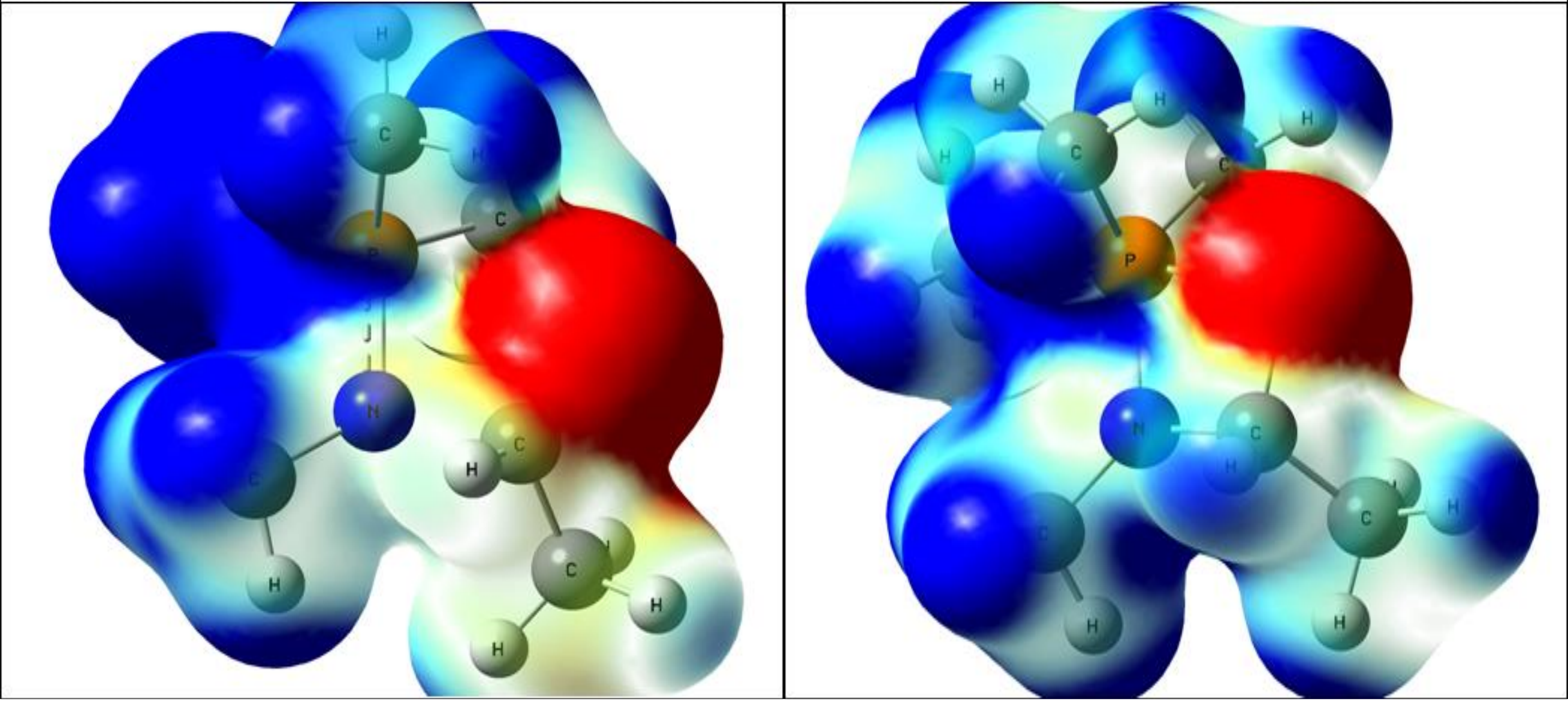
- Potential energy diagram of the reaction of Aza-Wittig of Methylimino(trimethyl) phosphorane with Acetaldehyde in gas phase B3LYP, B3LYP-D3 and with solvent B3LYP-D3 (THF).



	$\Delta G^{\neq}_{B3LYP}$	$\Delta G^{\neq}_{B3LYP-D}$
RC → TS1	**14.77**	**12.17**
IN2 → TS2	**18.01**	**18.52**

Activation energy corresponds to Cycloaddition-Cycloreversion of Oxazaphosphetidine for functional B3LYP, B3LYP-D3.

Molecular electrostatic potential



TS1

IN1

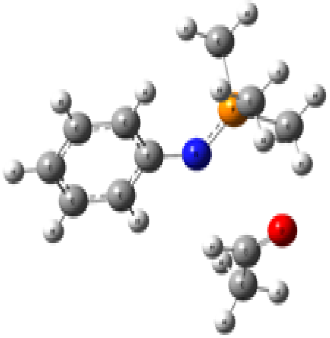
Maps of total electron density, calculated electrostatic potential for TS1 and intermediates IN1, regions of highest electron density distribution are displayed in intense red -16.31 kcal/mol and regions of density distribution lower electronics in intense blue +16.31 kcal/mol.

Study of the reaction of Phenylimino (trimethyl) phosphorane with Acetaldehyde

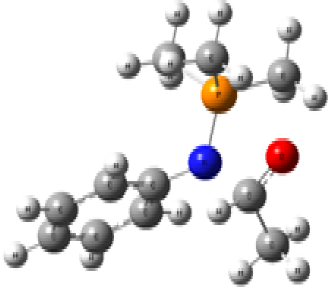
- To better understand the variables of the Aza-Wittig reaction, we performed a theoretical analysis on another substituent of R1 = Phenyl.

B3LYP/6-31G(d,p) B3LYP-D/6-31G(d,p)	**d_{P-N} Angström**	**d_{C-O} Angström**	**d_{P-O} Angström**	**d_{N-C} Angström**	**Φ_{PNCO}**
Reactant (CR)	1.59 1.59	1.22 1.22	3.60 3.46	3.12 2.89	-3.38 0.72
TS1	1.65 1.64	1.29 1.29	2.55 2.57	1.74 1.73	-7.29 -8.33
IN 1	1.73 1.72	1.40 1.40	1.84 1.84	1.47 1.47	-5.42 -5.35
TSr	1.93 1.91	1.45 1.45	1.68 1.68	1.44 1.43	-4.88 -5.37
IN2	1.92 1.90	1.44 1.44	1.68 1.69	1.44 1.44	-3.55 -3.71
TS2	2.60 2.50	1.62 1.58	1.59 1.60	1.38 1.39	1.77 8.90
Product (CP)	4.05 3.75	3.21 2.97	1.51 1.51	1.28 1.28	9.05 11.62

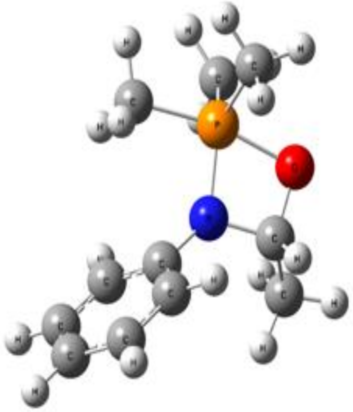
Bond lengths (in Å) and dihedral angles (in degrees) of the Aza-Wittig reaction of methylimino(trimethyl)phosphorane with Acetaldehyde $(CH_3)_3P=NPh$.



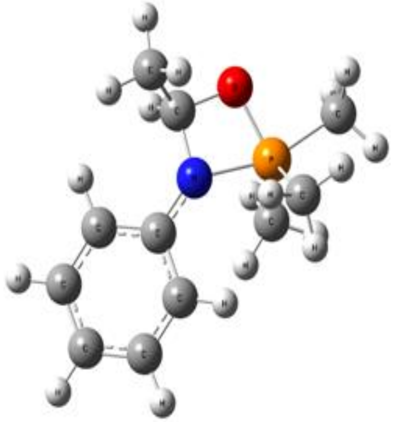
Réactive (RC)



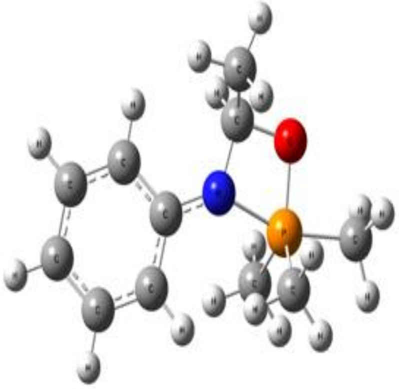
TS1



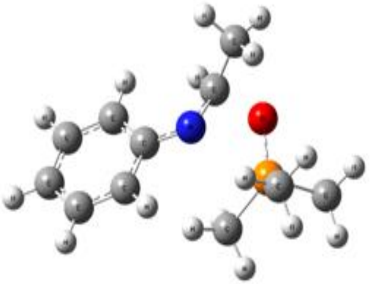
IN1



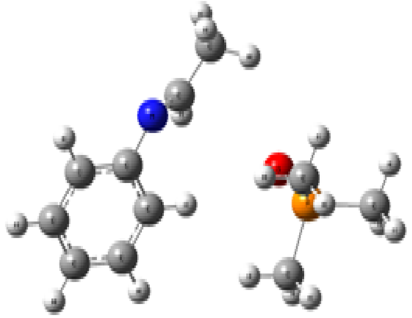
TSr



IN2



TS 2



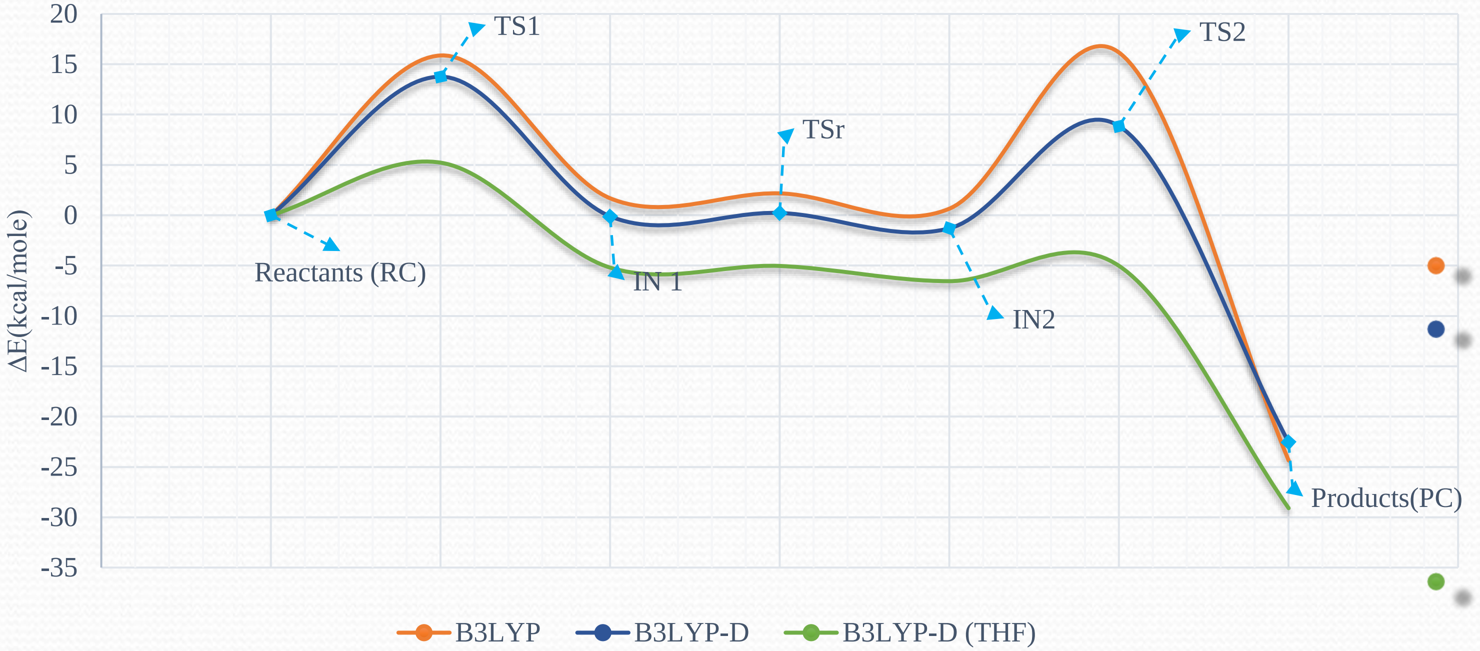
Produits (PC)

Optimized geometries of structures involved in the reaction pathway.

Structures	**B3LYP**			**B3LYP-D**		
	ΔE (Kcal/mol)	**ΔG (Kcal/mol)**	**ΔH (Kcal/mol)**	**ΔE (Kcal/mol)**	**ΔG (Kcal/mol)**	**ΔH (Kcal/mol)**
Reactant (CR)	**0**	**0**	**0**	**0.00**	**0.00**	**0.00**
TS1	**15.88**	**19.05**	**15.59**	**13.76**	**16.30**	**13.40**
IN 1	**1.69**	**7.36**	**3.03**	**-0.11**	**3.69**	**1.15**
TSr	**2.18**	**9.21**	**3.00**	**0.23**	**6.08**	**0.99**
IN2	**0.66**	**7.51**	**2.15**	**-1.30**	**4.37**	**0.14**
TS2	**10.23**	**14.87**	**10.24**	**8.85**	**13.31**	**8.98**
Product (CP)	**-24.35**	**-23.29**	**-23.67**	**-22.55**	**-21.48**	**-21.89**

Relative energies, enthalpy and Gibbs free energy (kcal/mol) calculated by the DFT, at the theoretical level B3LYP and B3LYP-D3 with a base of 6-31G.**

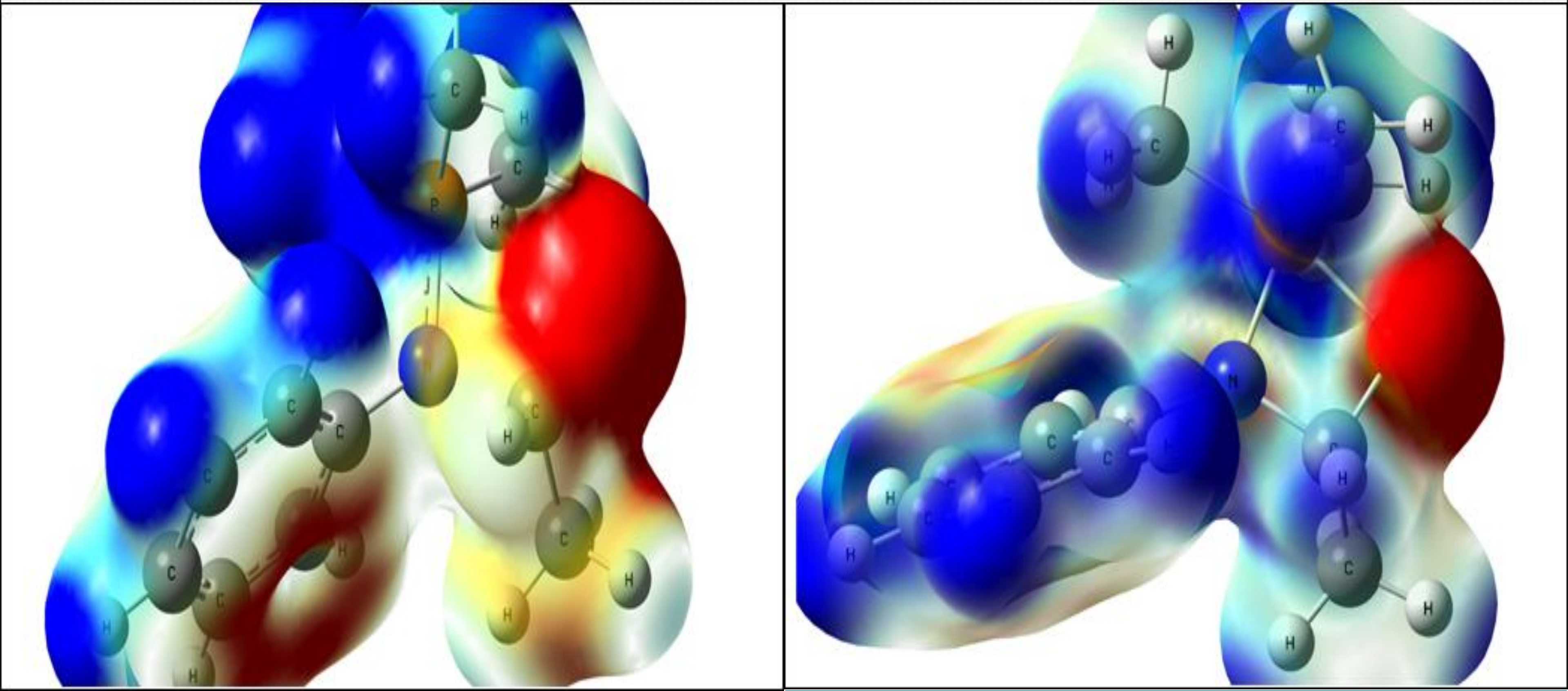
Potential energy diagram of the reaction of Aza-Wittig of Phenylimino(trimethyl) phosphorane with Acetaldehyde in gas phase B3LYP, B3LYP-D3 and with solvent B3LYP-D3 (THF).



	$\Delta G^{\neq}_{B3LYP}$	$\Delta G^{\neq}_{B3LYP-D}$
RC → TS1	**19.05**	**16.30**
IN2 → TS2	**7.35**	**8.93**

Activation energy corresponds to Cycloaddition-Cycloreversion of Oxazaphosphetidine for functional B3LYP, B3LYP-D3.

Molecular electrostatic potential



TS1

IN1

Maps of total electron density, calculated electrostatic potential for TS1 and intermediates IN1, regions of highest electron density distribution are displayed in intense red -16.31 kcal/mol and regions of density distribution lower electronics in intense blue +16.31 kcal/mol.

Conclusion

- The aza-Wittig reaction between phosphazenes and aldehydes takes place by a [2+2] Cycloaddition-Cycloreversion mechanism, with Oxazaphosphetidines being the reaction intermediates. The two processes [2+2] are associated with thermally authorized asynchronous processes.

- Methylimino(trimethyl)phosphorane is more reactive than phenylimino(trimethyl)phosphorane and less reactive in the second stage of elimination, Cyclorevision, of imine

- The energy barriers associated with the rotational movement are localized between the two intermediates, therefore, only the second stage leading to the imines and phosphine oxides.

- The addition of the term dispersion correction brings a new description of the reaction and the path of the chemical reaction, because it makes it possible to find a better description of the dispersion interactions in the description of the corrected functions and of the DFT method.

THANK YOU FOR YOUR ATTENTION