

SYNTH ONE POT

The Use of Diazonium Salts under Safer Conditions

Programme JCJC 2010

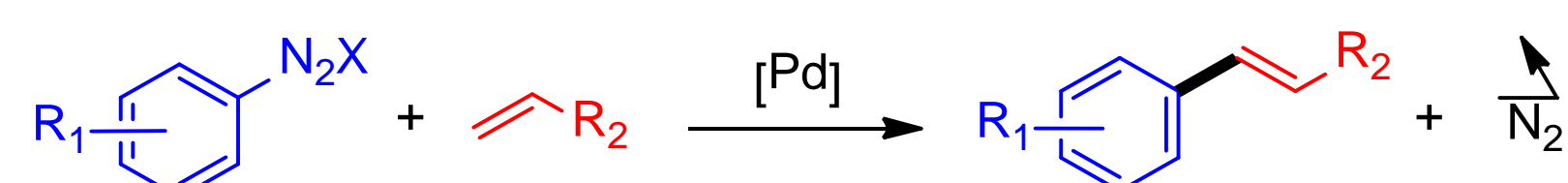


N. Oger,^a F. Le Callonnec,^b N. Susperregui,^c K. Miqueu,^c E. Fouquet,^b J.-M. Sotiropoulos,^c Erwan Le Grogneq,^a F.-X. Felpin^{*,a}

^a Université de Nantes / ^b Université de Bordeaux / ^c Université de Pau et des Pays de l'Adour

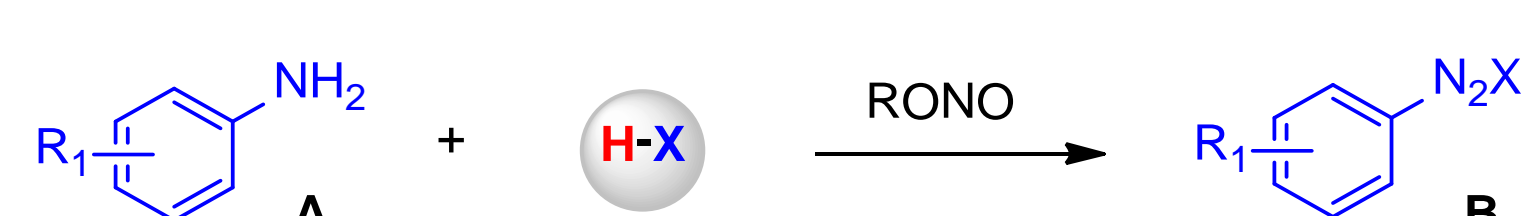
1- Introduction – A case Study, the Heck-Mastuda reaction

Aryl diazonium salts are a class of super-electrophile with the common structure of R-N₂X. The high nucleofugic properties of the diazonium function makes these compounds potentially hazardous, especially on large scale. As the stability cannot be anticipated, safety issues need to be addressed.



The Heck-Mizoroki reaction has become a standard in the toolbox of every synthetic chemist. A far less explored variant of this coupling, known as the Heck-Matsuda reaction,^[1] entails the use of aryl diazonium salts. The super-electrophile properties of aryl diazonium salts allows the reaction to proceed under mild conditions (T < 60°C), without the need of ligand, and even sometimes, base,^[2] featuring many advantages, for the development of sustainable processes.

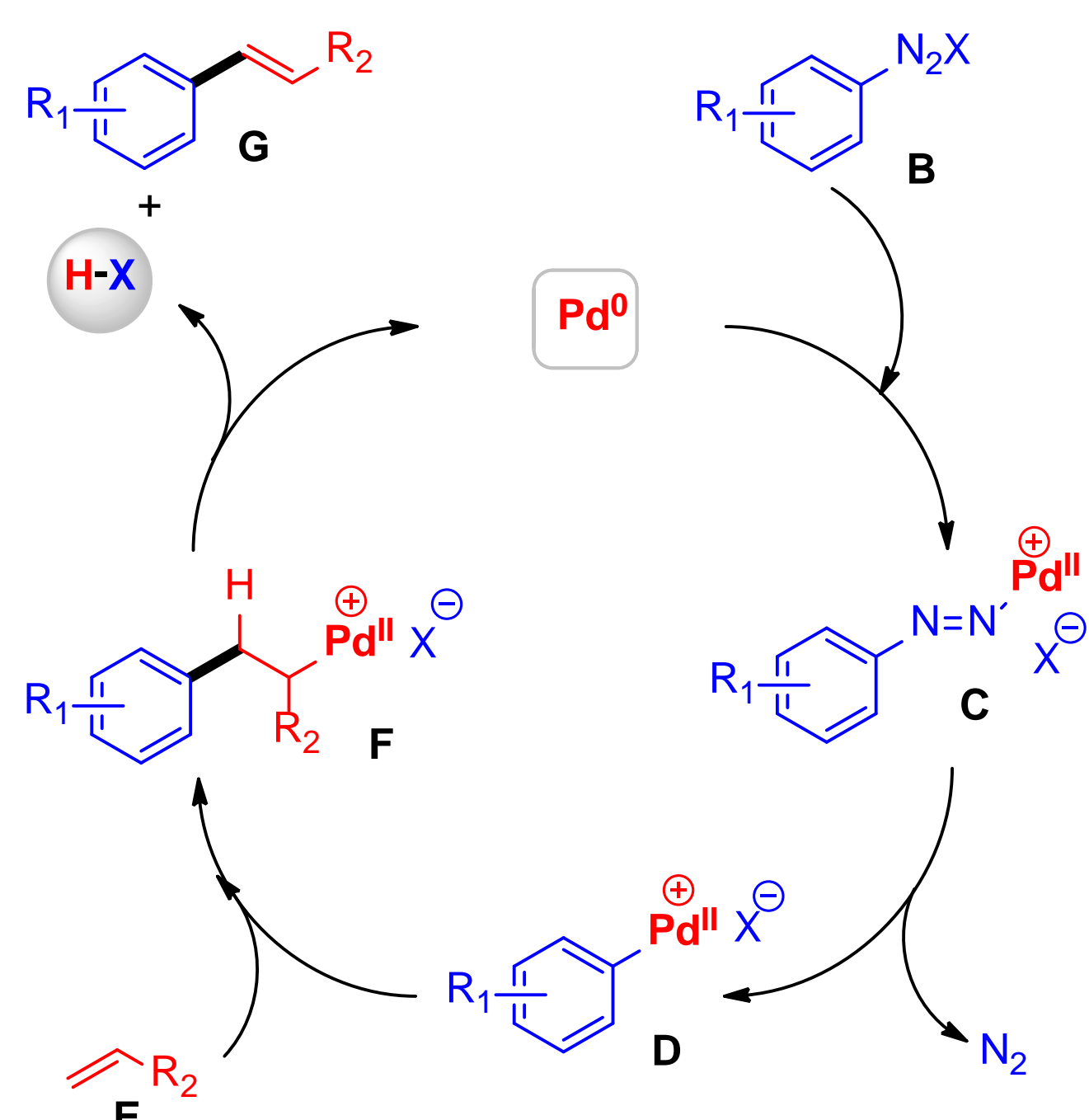
2 – Traditionnal Diazonium Salts Preparation



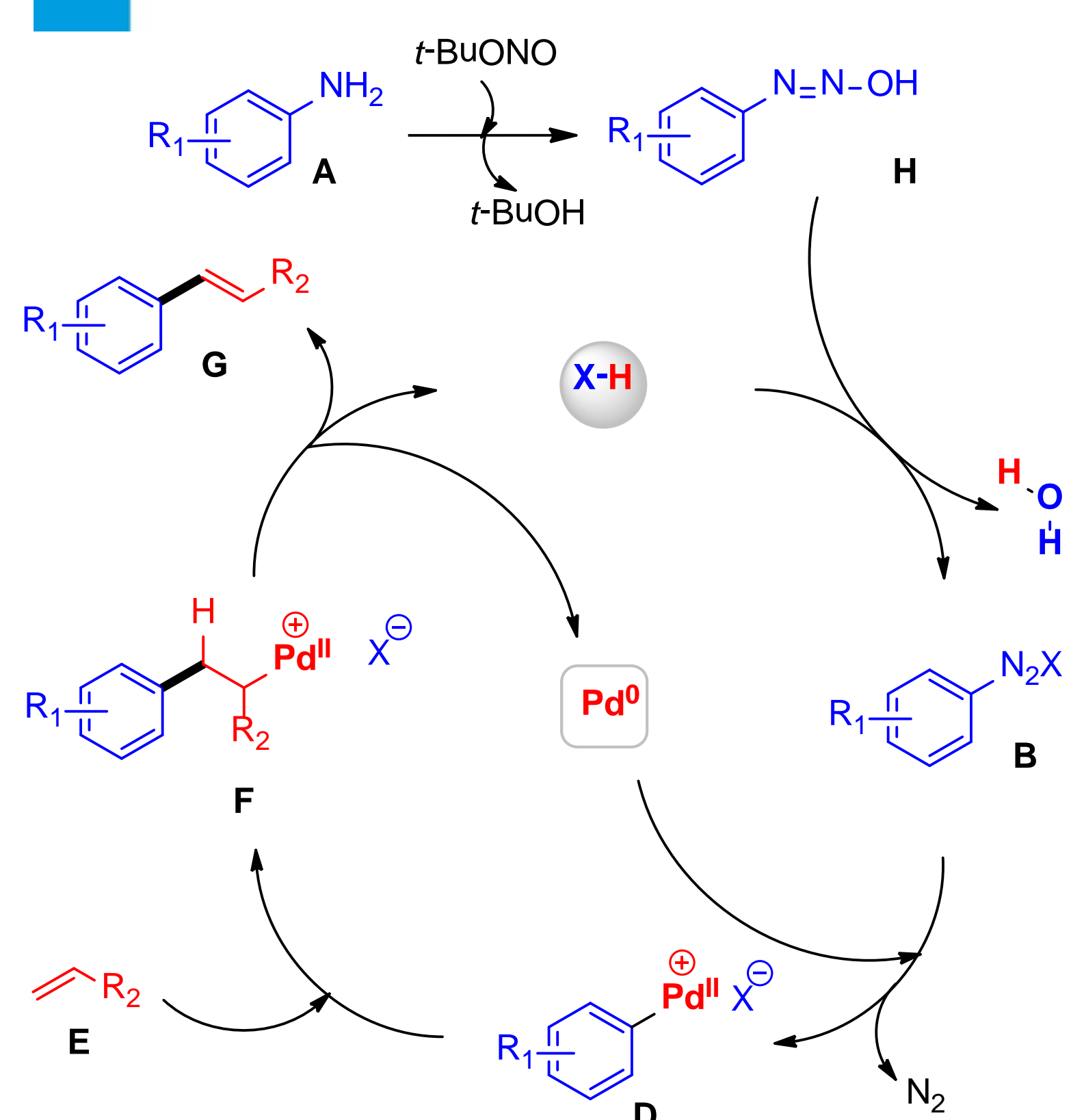
Aryl diazonium salts are commonly prepared from the corresponding aniline, by action of an alkyl nitrite or the sodium nitrite in the presence of a protic acid such as HCl or HBF₄ (H-X).

3 - Catalytic Cycle

Palladium intermediates bear a positive charge during the catalytic cycle. This uncommon feature renders very active the intermediates C, D and F, and optional the use of a base. In the absence of a base, one molar equivalent of a non trapped acid (H-X) is generated per equivalent of olefin G formed.



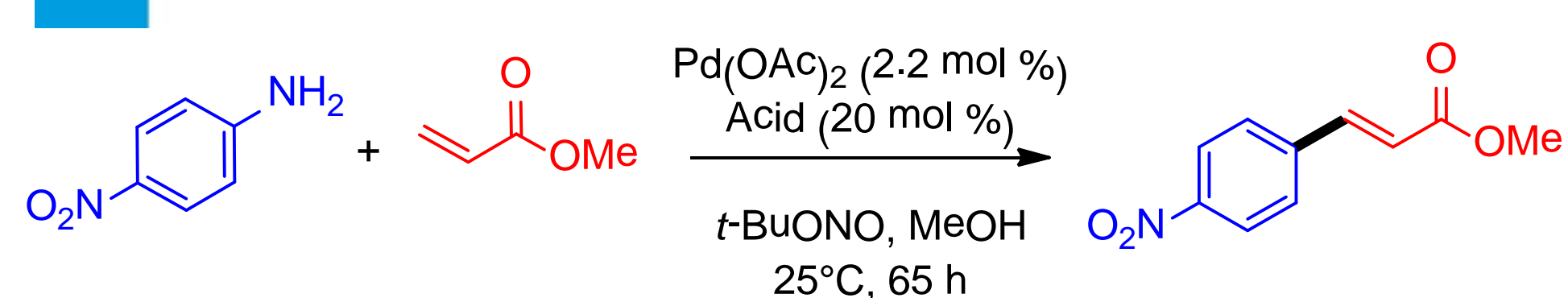
4 – Novel Strategy



With these observations in mind, we anticipated that a catalytic amount of the acid, H-X, could be used in a **cascade diazonium formation - Heck coupling process**, according to the following unprecedented double catalytic cycle.^[3]

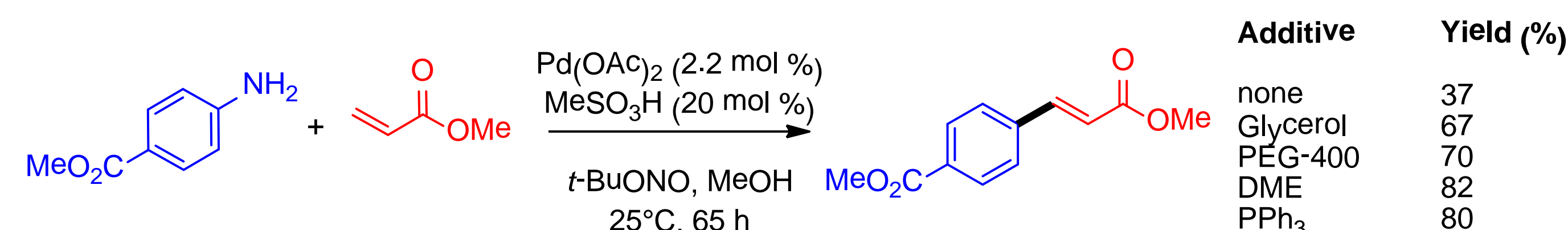
- > Only 0.2 equivalent of a non corrosive organic acid !
- > Diazonium salts is generated in situ through the reaction advancement !
- > Strategy with an unprecedented double catalytic cycle !
- > The first use of a catalytic amount of diazonium salts !
- > Only t-BuOH, H₂O and N₂ are generated as by-products !

5 – Screening - Scope



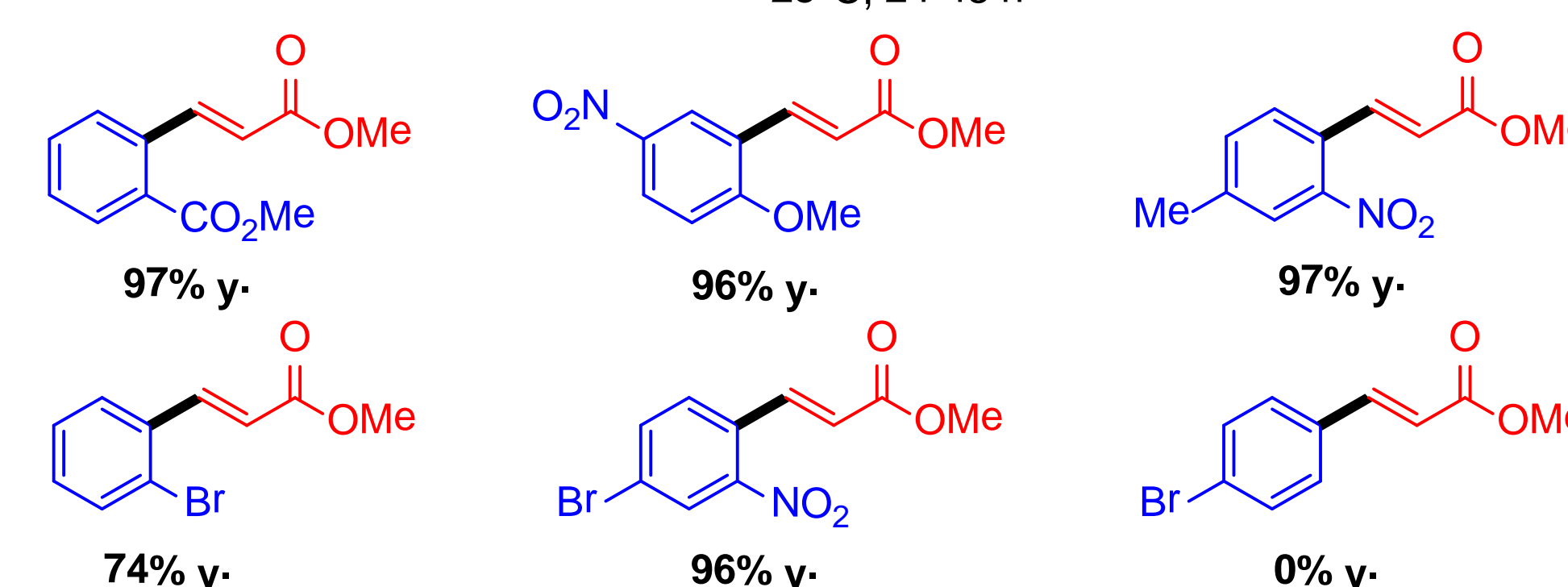
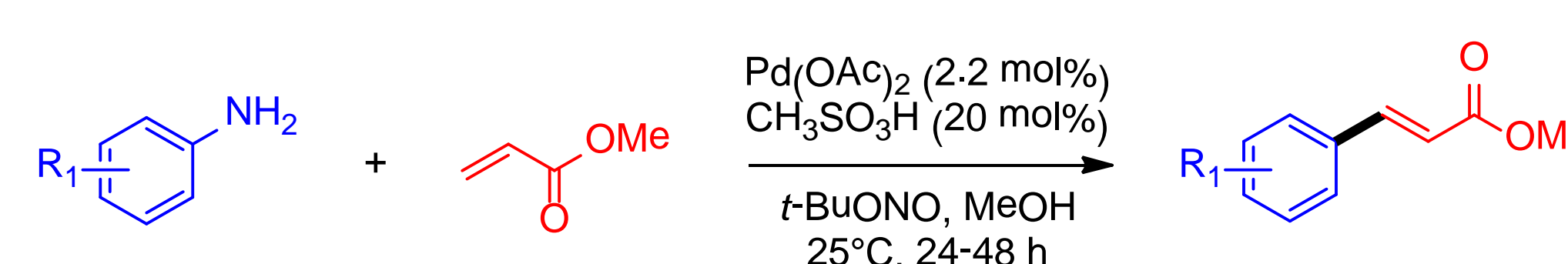
Acid	Yield (%)
HBF ₄	47
Diphénylphosphate	20
H ₃ PO ₄	12
H ₂ SO ₄	54
CH ₃ CO ₂ H	13
p-Toluènesulfonic acid	87
Camphorsulfonic acid	90
MeSO ₃ H	84

An acid screening showed that sulfonic acids were much more effective !



With many substrates we observed the beneficial effect of an additive. A rapid screening concluded that anisole was the privileged additive.

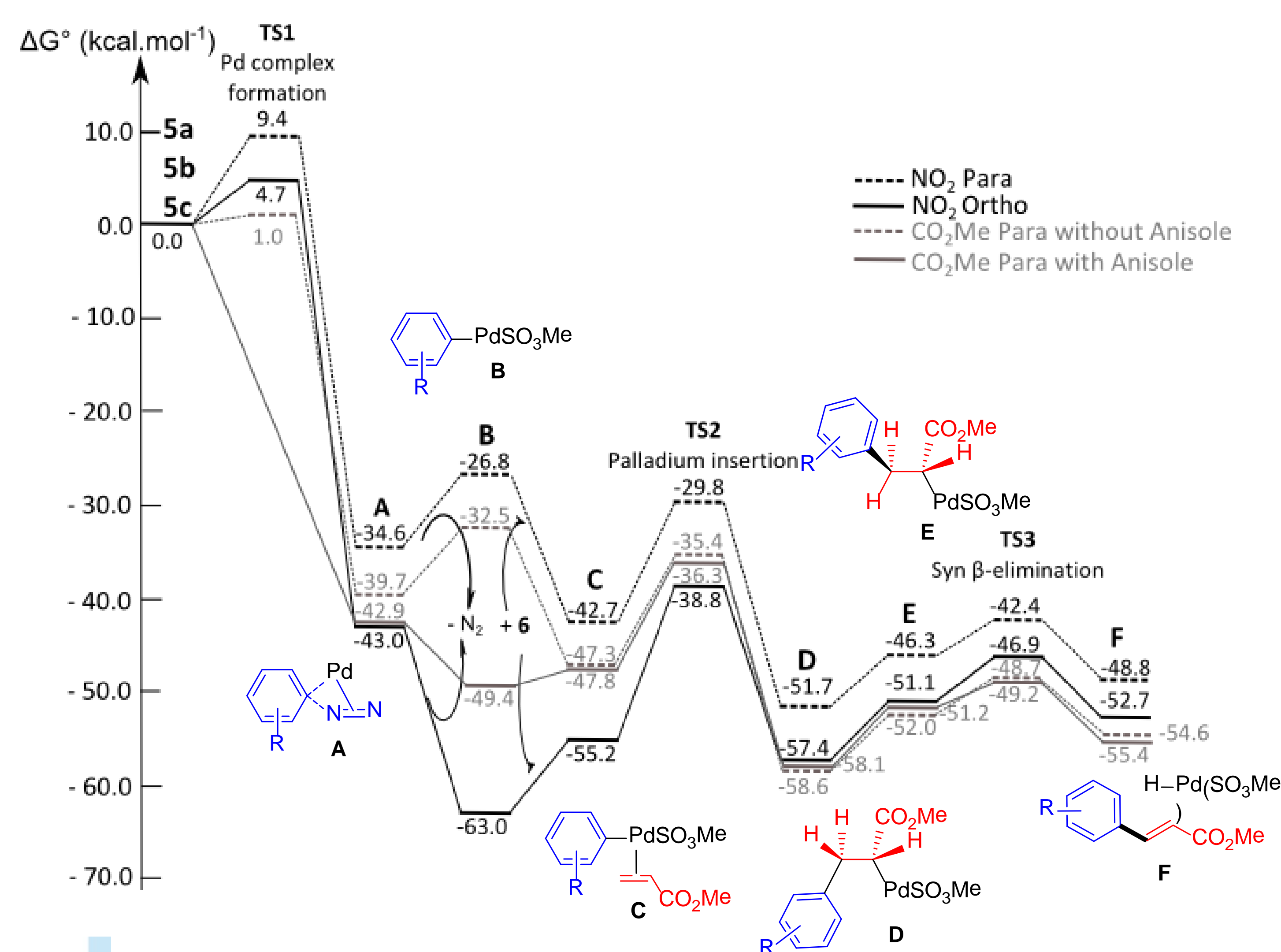
Additive	Yield (%)
none	37
Glycerol	67
PEG-400	70
DME	82
PPh ₃	80
Charcoal	59
Triethylsilane	54
Anisole	97
Thioanisole	10



The reaction scope showed that the protocol was compatible with a variety of function including ester, nitro, ether, etc. We, however, observed that ortho substituted anilines give consistently higher yields of coupling products. In order to understand this unexpected behavior, we conducted DFT calculations.^[4]

6 – Theoretical calculations at B3LYP/SDD+f (pd atom), 6-31G** (other atoms) level

We theoretically compared four reactions pathways in order to evaluate the impact of both the substituent position (*para* vs. *ortho*) and the additive on the reaction outcome. As depicted in the diagram, the product issued from the oxidative addition step (compound B) is favoured with *ortho*-substituted compounds (black full line). However, with *para*-substituted substrates, the use of anisole allows a good stabilization of intermediate B and avoids the formation of by-products (grey full line). In the absence of anisole, the destabilization of B leads to concurrent side-reactions that decrease the reaction yields (black and grey dashed lines). The beneficial effect of anisole has been confirmed with NBO analysis where a stabilizing interaction ($\Delta E_{stab} = 47.3$ kcal/mol) has been found between the methoxy group of anisole and the palladium atom



7 – Conclusion

- > First Heck-Matsuda reaction using a substoichiometric amount of diazonium !
- > Mild conditions, and only environmentally benign byproduct such as t-BuOH, H₂O, and N₂ !
- > No isolation of hazardous aryl diazonium salts !

8 – References

- [1] F.-X. Felpin, L. Nassar-Hardy, F. Le Callonnec, E. Fouquet, *Tetrahedron*, **2011**, *67*, 2815
- [2] F.-X. Felpin, K. Miqueu, J.-M. Sotiropoulos, et al., *Chem. Eur. J.* **2010**, *16*, 519
- [3] F. Le Callonnec, E. Fouquet, F.-X. Felpin, *Org. Lett.* **2011**, *13*, 2646
- [4] N. Susperregui, K. Miqueu, J.-M. Sotiropoulos, F.-X. Felpin, et al. *Chem. Eur. J.* **2012**, *18*, 7210

CONTACT :

Prof. François-Xavier Felpin, Université de Nantes, CEISAM, UMR CNRS 6230, 2 rue de la Houssinière, 44322 Nantes Cedex 3
fx.felpin@univ-nantes.fr / <http://f-x.felpin.voila.net/indexF.html>



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