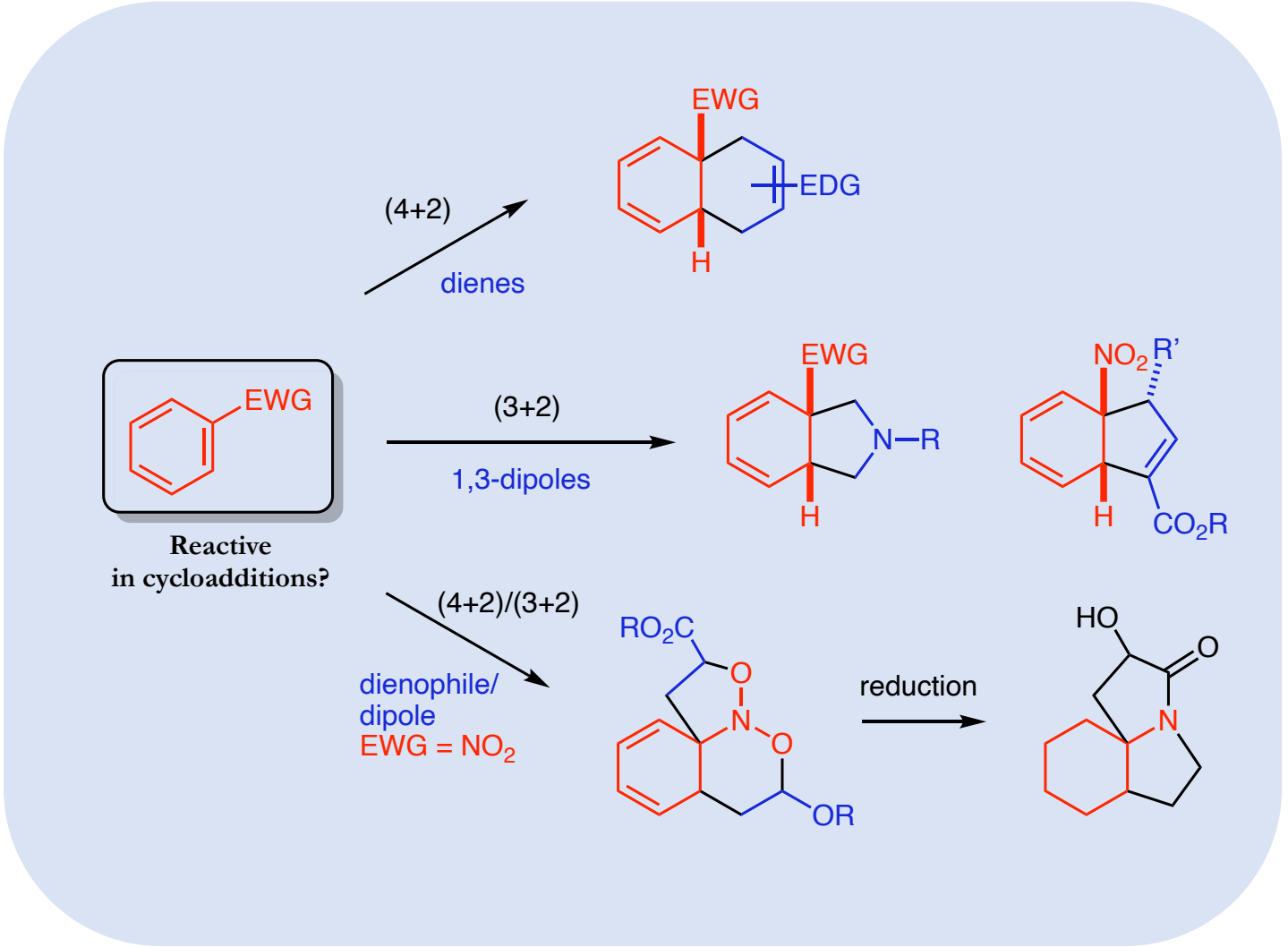
Photocatalysed (3+2) cycloaddition for the dearomatization of electron-poor arenes under flow conditions

Y. Faye, B. Rkein, A. Bigot, T. Lequeux, J. Legros and I. Chataigner

June 28th 2023

Group Interest in Dearomative Cycloadditions



From easily accessible substrates
Polycyclic functionnalized cycloadducts
Tetrasubstituted carbon center
Ring junction stereochemistry

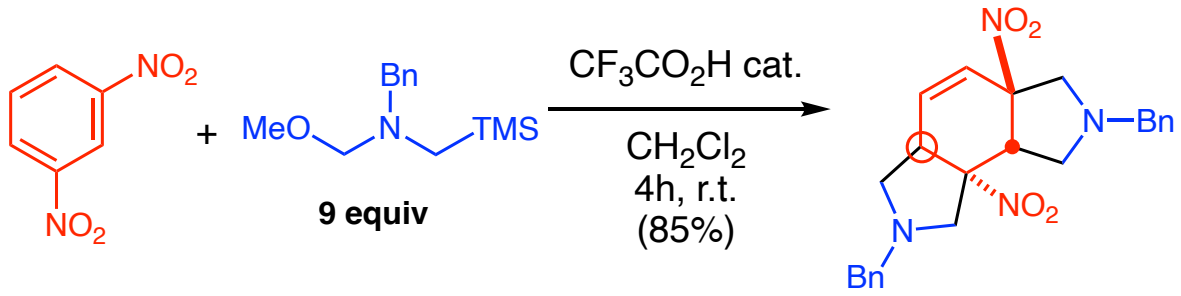
But … Inertness of arenes
And Prevent re-aromatization

See for instance:

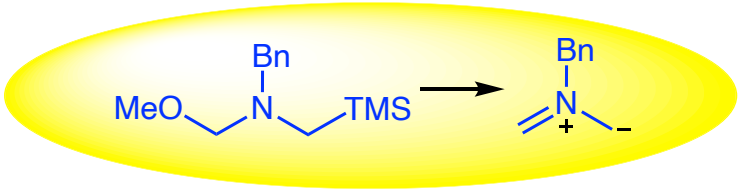
Chem. Commun. **2022**, *58*, 11807
Chem. Commun., **2021**, *57*, 10071
Chem. Eur. J. **2019**, *25*, 13688
Chem. Commun. **2019**, *55*, 7494
Org. Lett. **2007**, *9*, 4159
Chem. Commun., **2005**, 1351
J. Org. Chem. **2003**, *68*, 7990

State of the Art (3+2) Cycloadditions

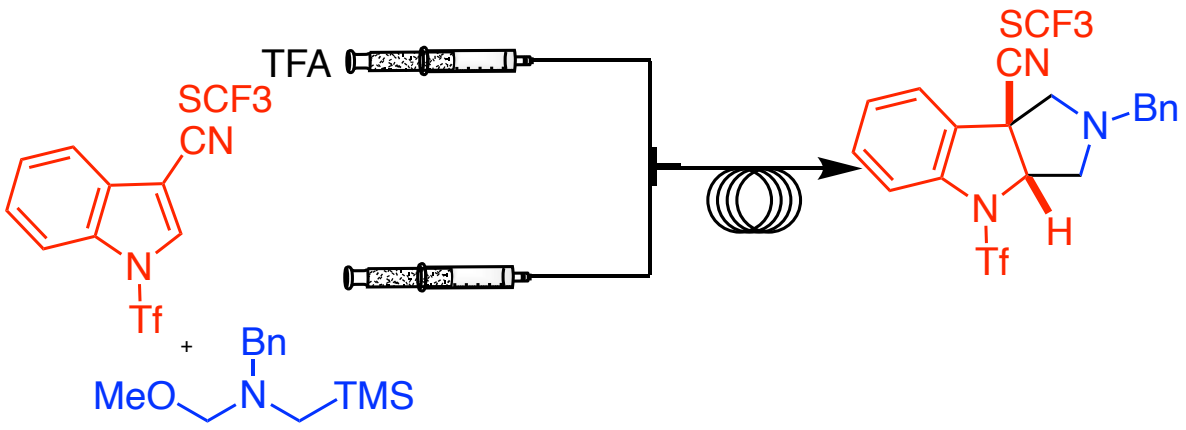
In acidic conditions
At r.t., from benzenes



Angew. Chem. Int. Ed. **2011**, *50*, 4068
Chem. Eur. J. **2013**, *19*, 7181

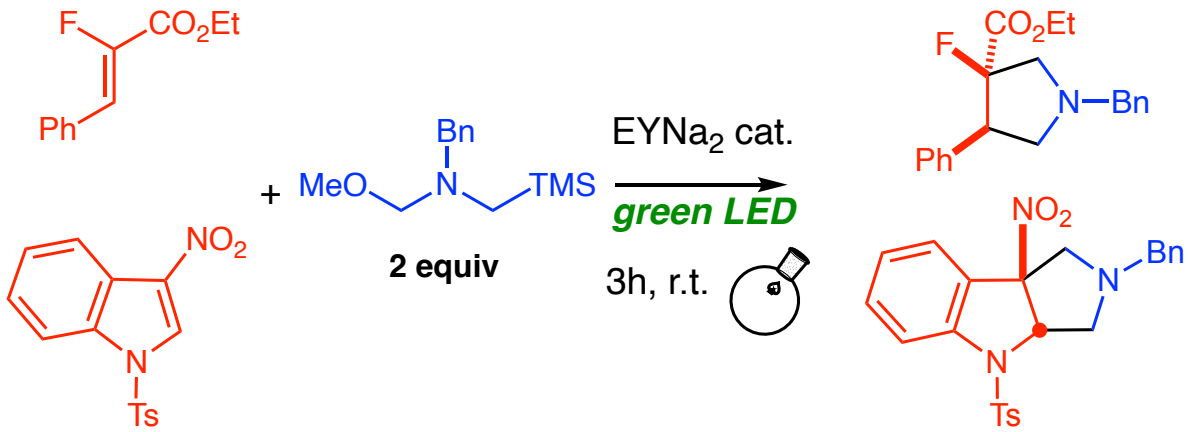


Flow conditions



Org. Biomol. Chem. **2020**, *18*, 3481
J. Flow Chem. **2022**, *12*, 141

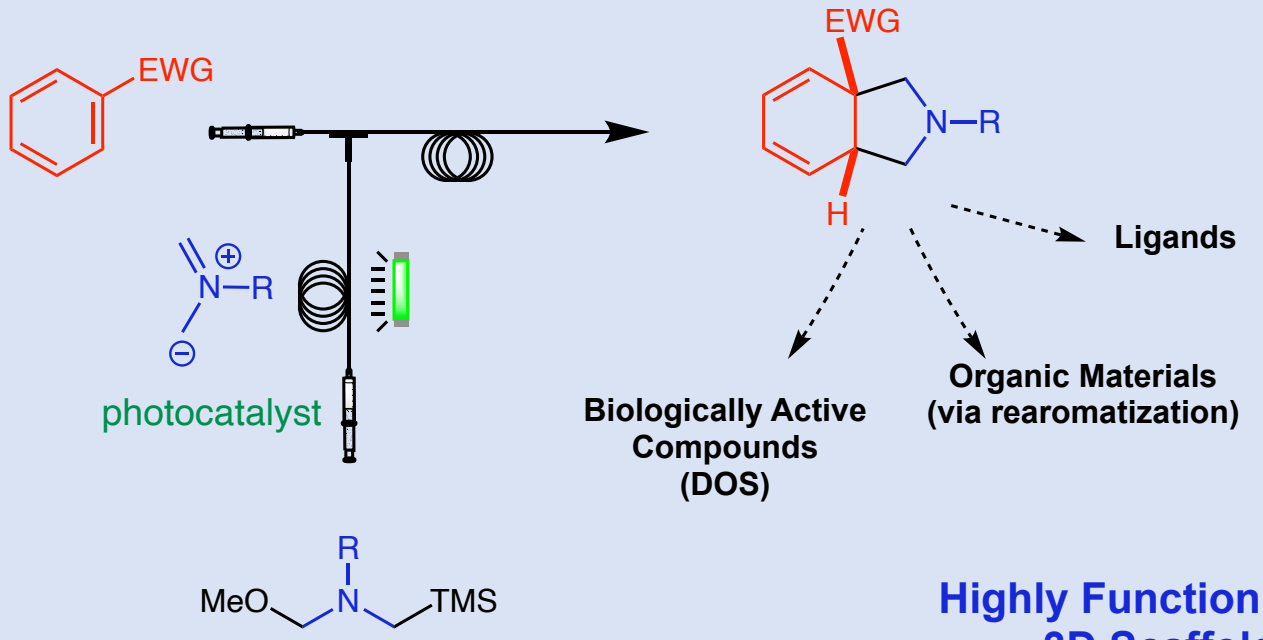
Photocatalysis



Lequeux, et coll. *J. Org. Chem.* **2019,** *84*, 5877

Mixing Photocatalytic and Flow Conditions….

Dearomative (3+2) Cycloadditions
Under non acidic conditions?

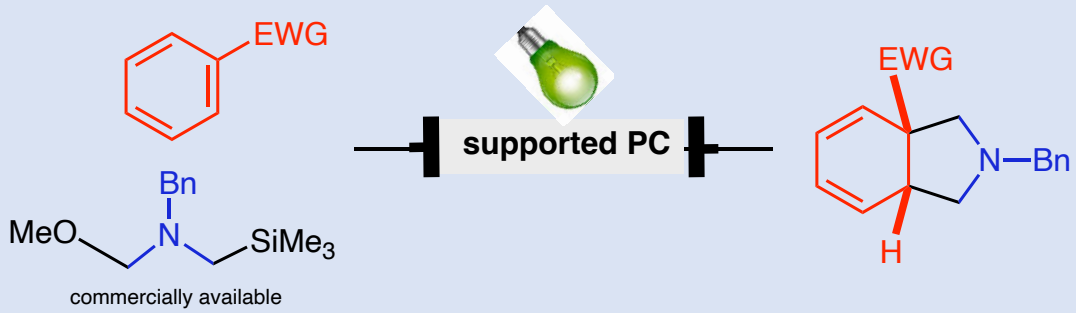


Highly Functionnalized 3D Scaffolds

From Different Arenes easily accessible

Youssou Faye's PhD

Supported Photocatalysis



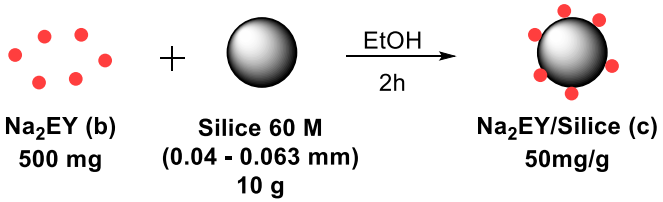
supported PC :

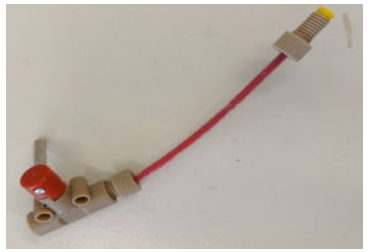
$EYNa_2@SiO_2$

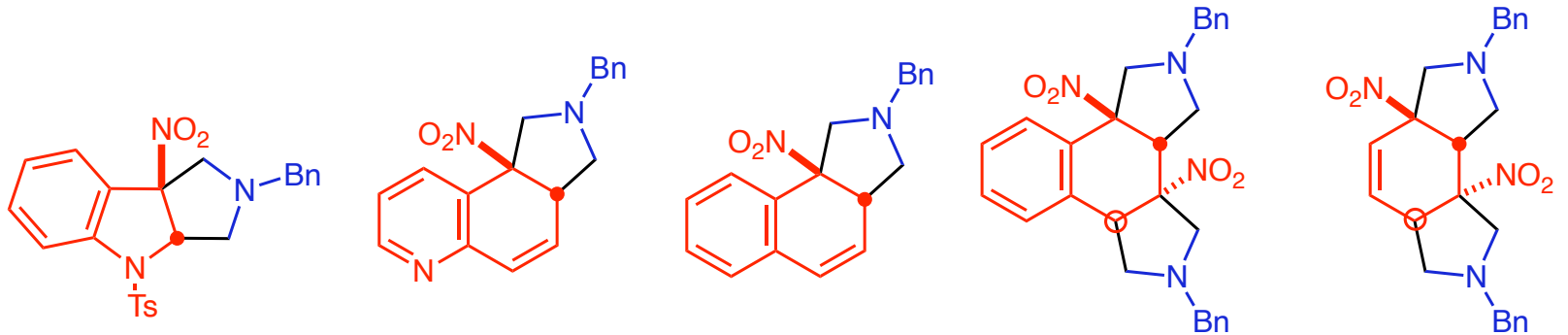
or

$EYNa_2@IRA900$

conversion (isolated yield)







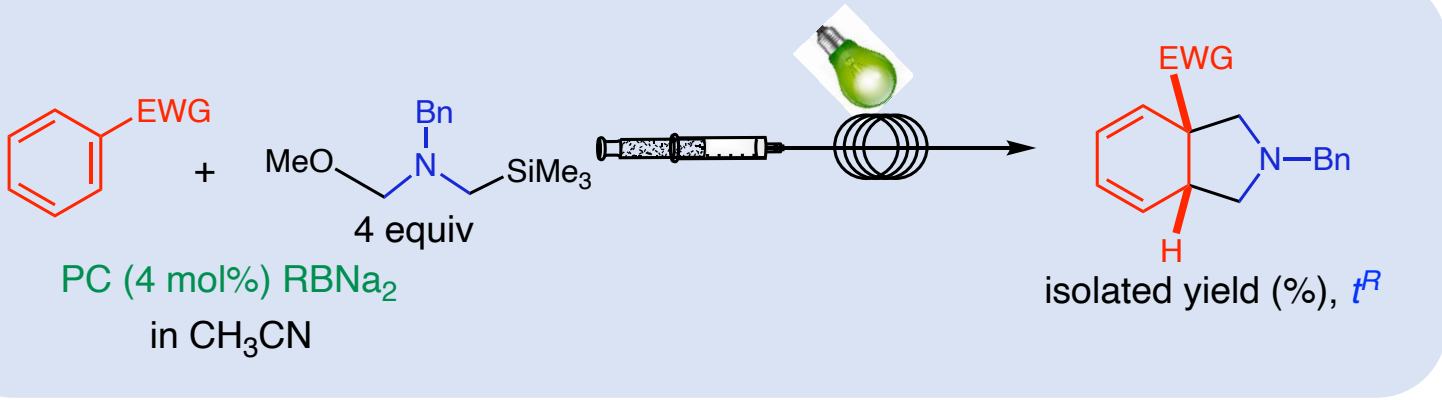
100% (85%) 100% (62%) 100% (85%) 100% (40%) 55%

100% (85%) 0% 0% 0% 0%

But leaching

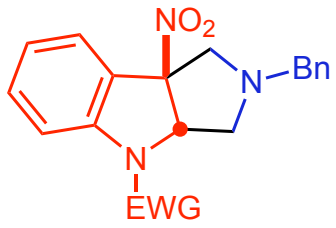
Faye, Y.; Rkein, B.; Bigot, A.; Lequeux, T.; Legros, J.; Chataigner, I. *Chem. Eur. J.* **2023**, e202301567 (DOI : 10.1002/chem.202301567)

Homogeneous Conditions

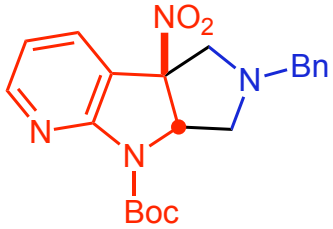


Heteroarenes
5-membered ring

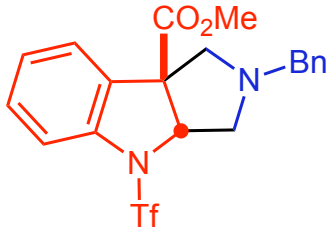
NO_2, CO_2Me, CN



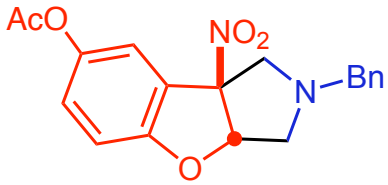
EWG = Ts 85%, 10 min
EWG = Boc 89%, 10 min



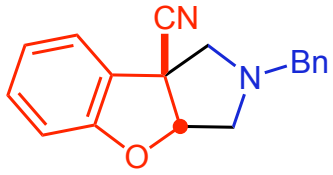
87%, 10 min



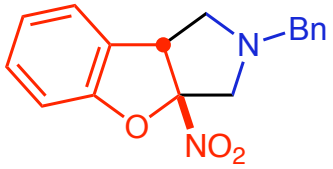
68%, 20 min



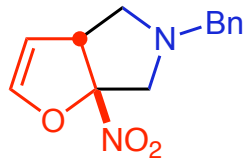
95%, 10 min



72%, 20 min



72%, 20 min



57%, 40 min

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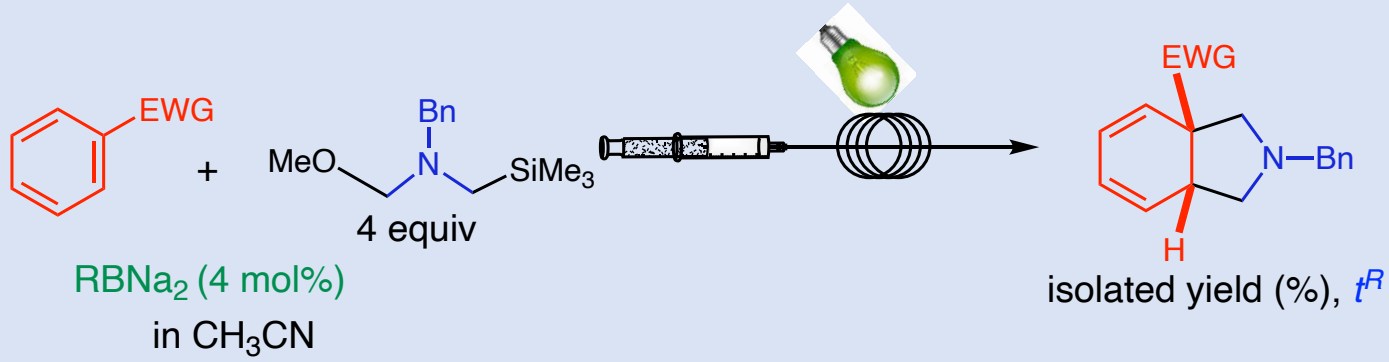
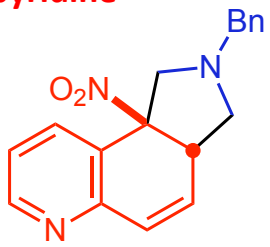
Homogeneous Conditions

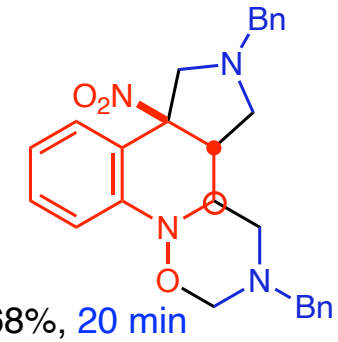
Electron-poor 6-membered rings



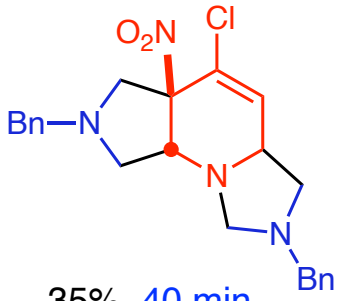
quinolines, pyridine



64%, 20 min

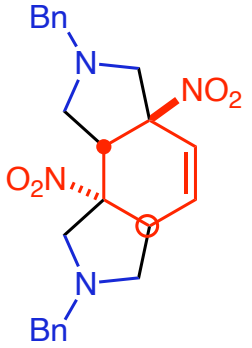


68%, 20 min



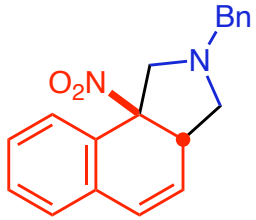
35%, 40 min

benzenes

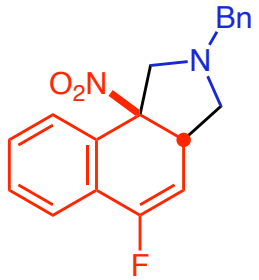


75%, 40 min

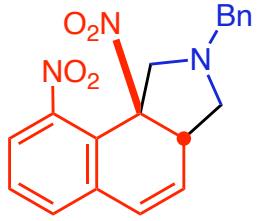
naphthalenes



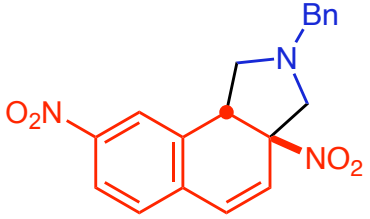
85%, 20 min



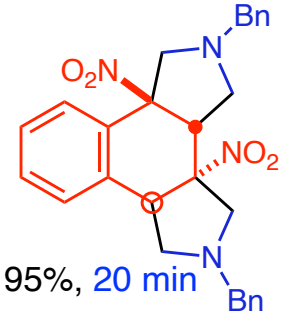
80%, 40 min



77%, 20 min



80%, 20 min



95%, 20 min

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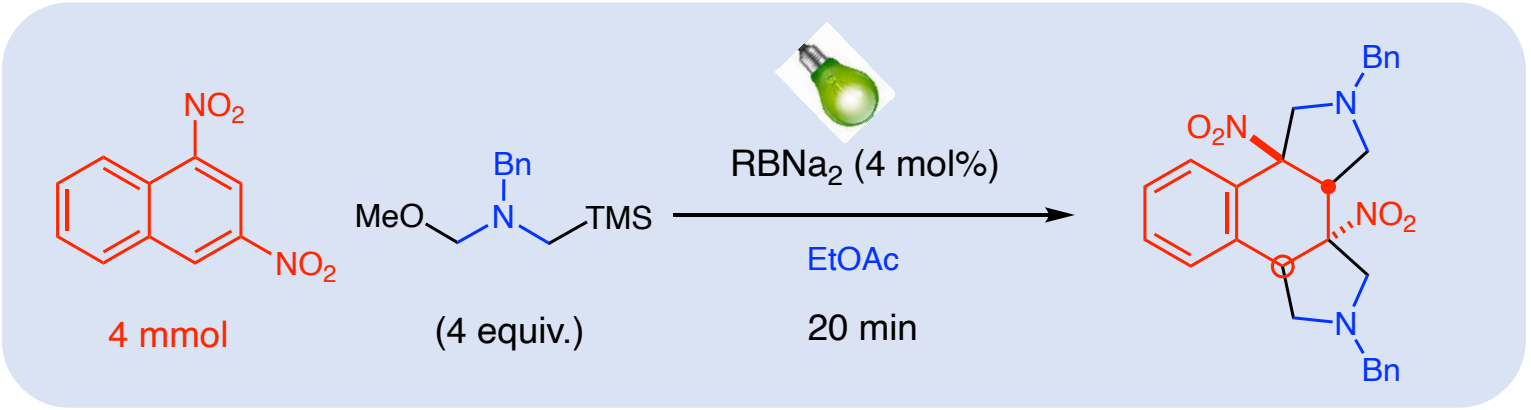
In EtOAc, on larger scale



batch traces

flow 100% conversion
(62% yield on 4 mmol scale)

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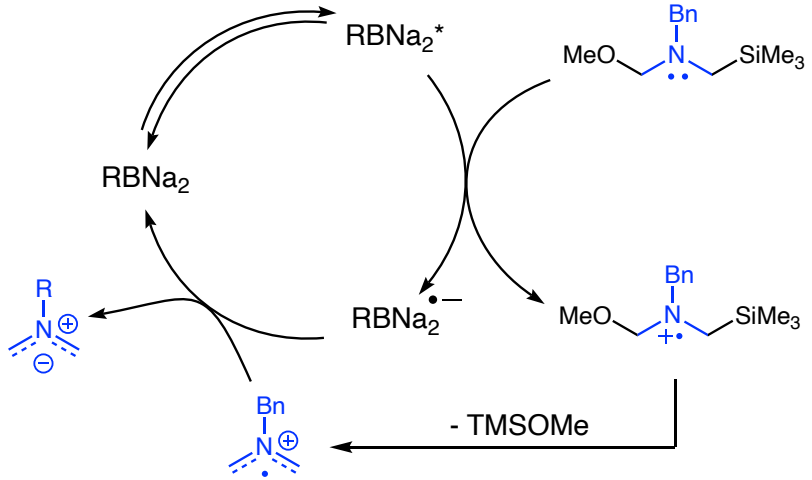
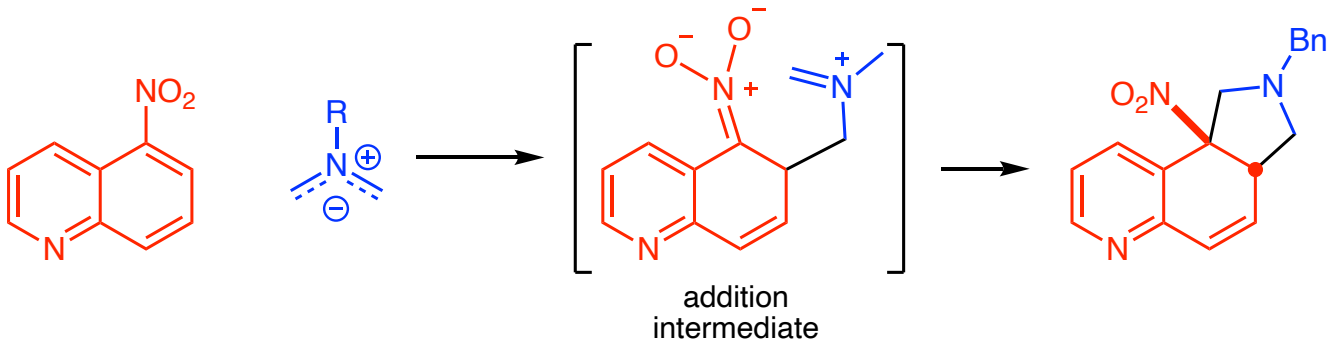
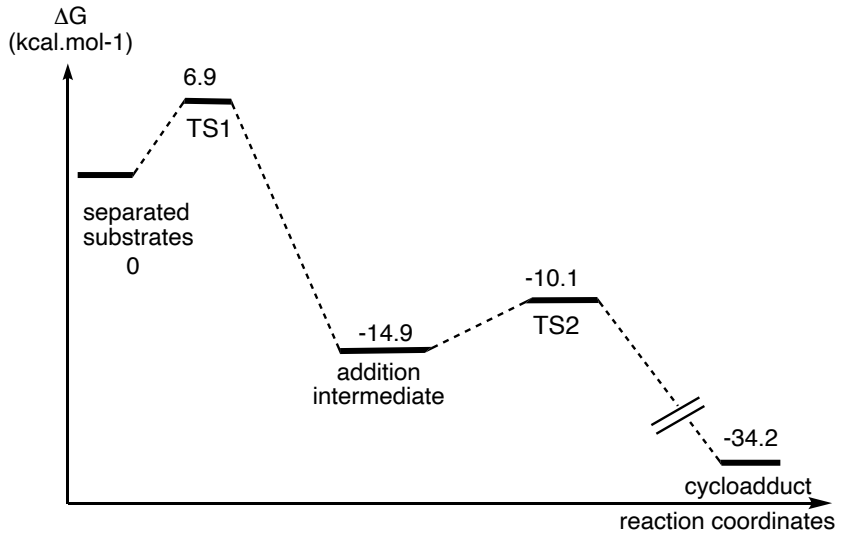
Photoredox Mechanism proposed

1- Formation of the azomethine ylide by photocatalysis



2- Reaction of the azomethine ylide with the electrophilic arene





DFT (Gaussian 16) at the (SMD:CH3CN) M062X/6-31G(d,p) level

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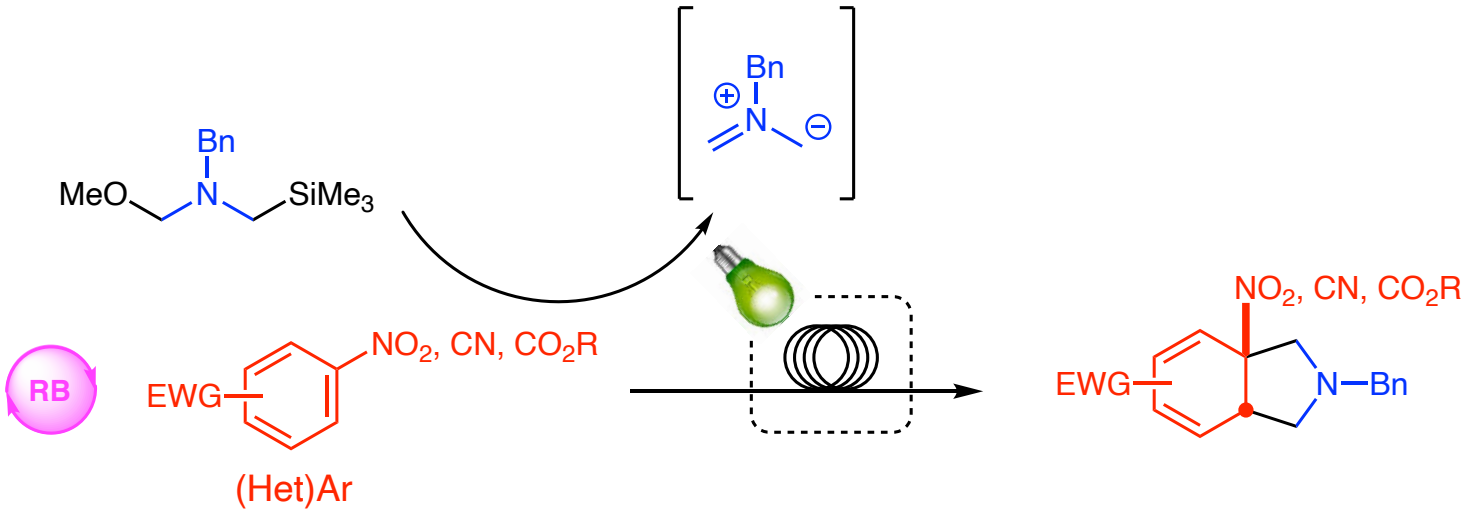
Conclusion



- Efficient dearomative photocatalyzed (3+2) Cycloaddition
- Variety of (het)arenes
- 3D Structures prone to post-functionnalizations
- Tetrasubstituted center at ring junction
- Mild conditions (no acid, no metal, at r.t.)
- Flow conditions (intensification)
- Friendly EtOAc solvent

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Acknowledgments

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Prof. T. Lequeux (LCMT, Univ Caen)
Dr Julien Legros

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Thank you for your kind attention!