Azolium-based compounds and materials for catalytic applications

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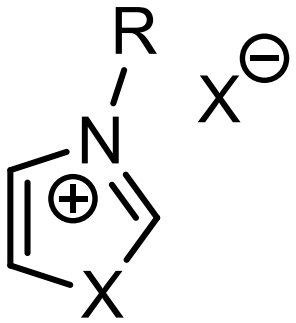
Main focus theme:

"Organic Synthesis for Probing the Chemistry-Biology Interface"



Azolium-based compounds and materials for catalytic applications

Organocatalysis

Metal-based catalysis

Water as reaction medium

Biomimetic synthesis

C-C and C-X bond forming reactions

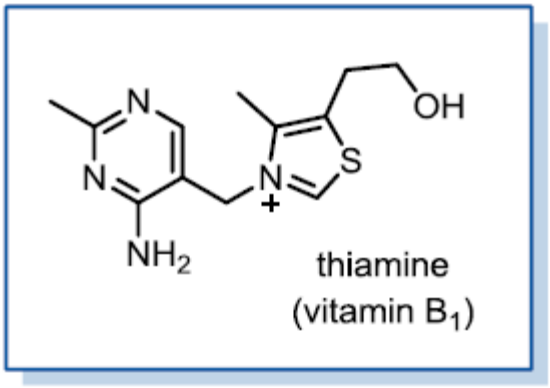
Synthesis of biologically useful compounds

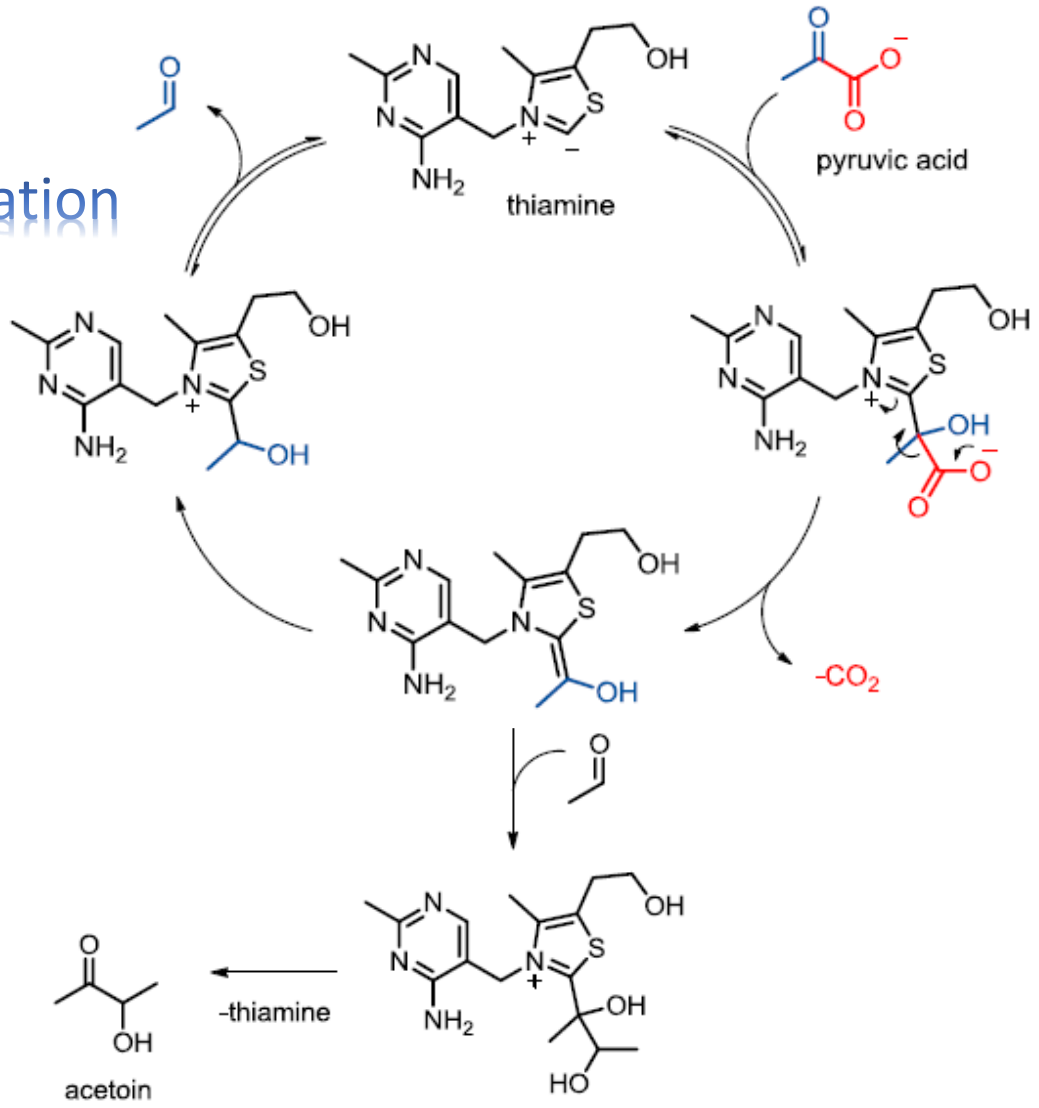
Cooperative catalysis

chemistry-biology interface

Biological applications

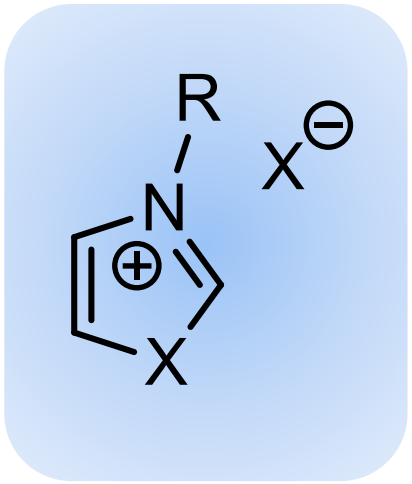
Pyruvic acid decarboxylation





Acetoin synthesis

Outline



Pre-catalysts (NHC)

- NHC
- chiral-NHC
- supported-NHC
- metal-NHC

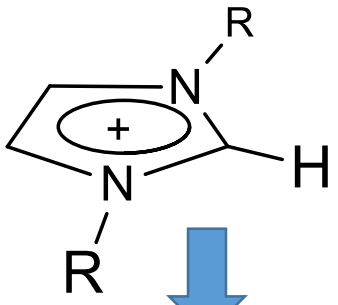
Azolium Catalysts

Azolium Support

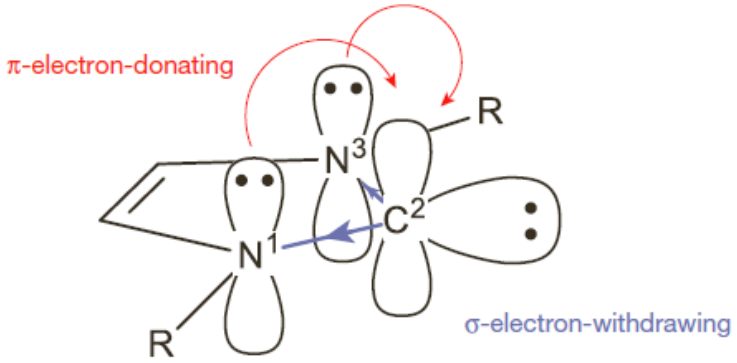
Azolium Tags

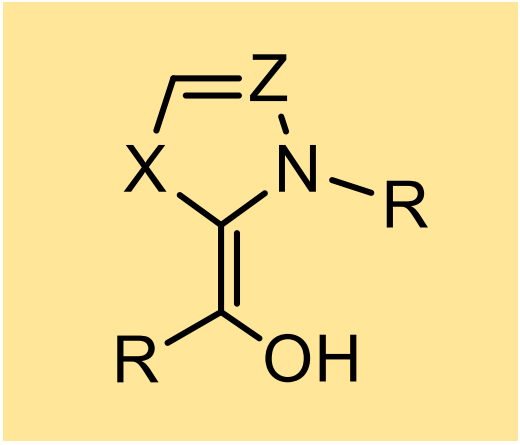
Biological applications

Azolium salts

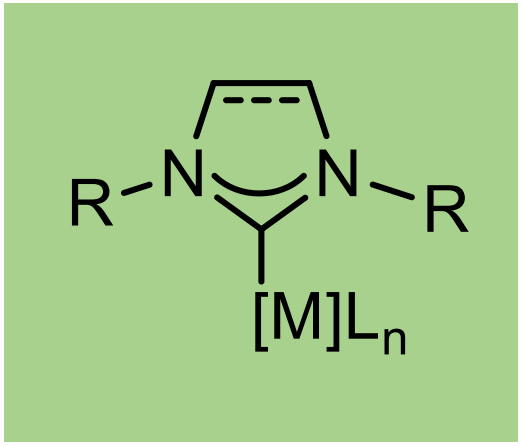


N-heterocyclic carbenes



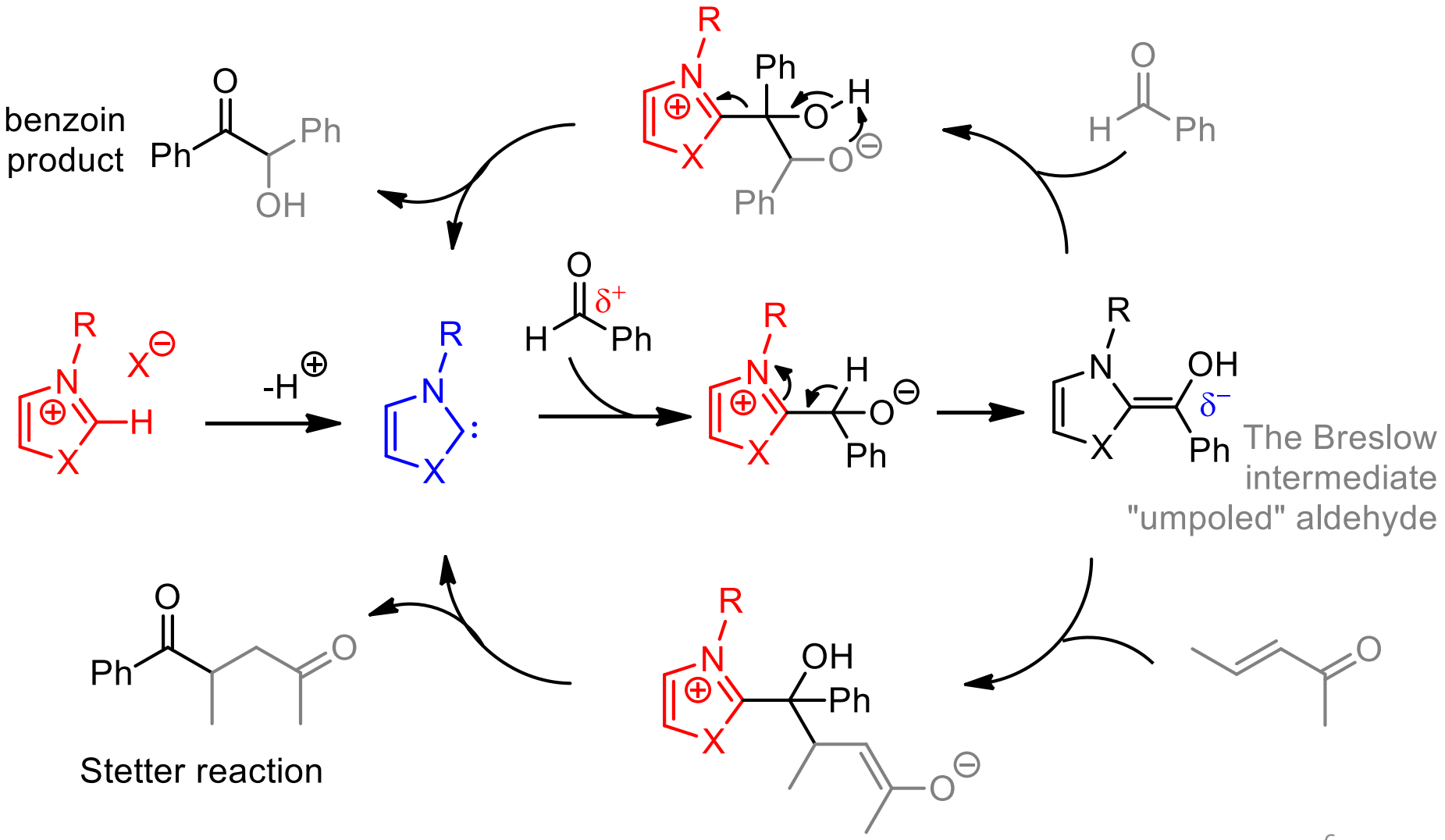


Organocatalysts

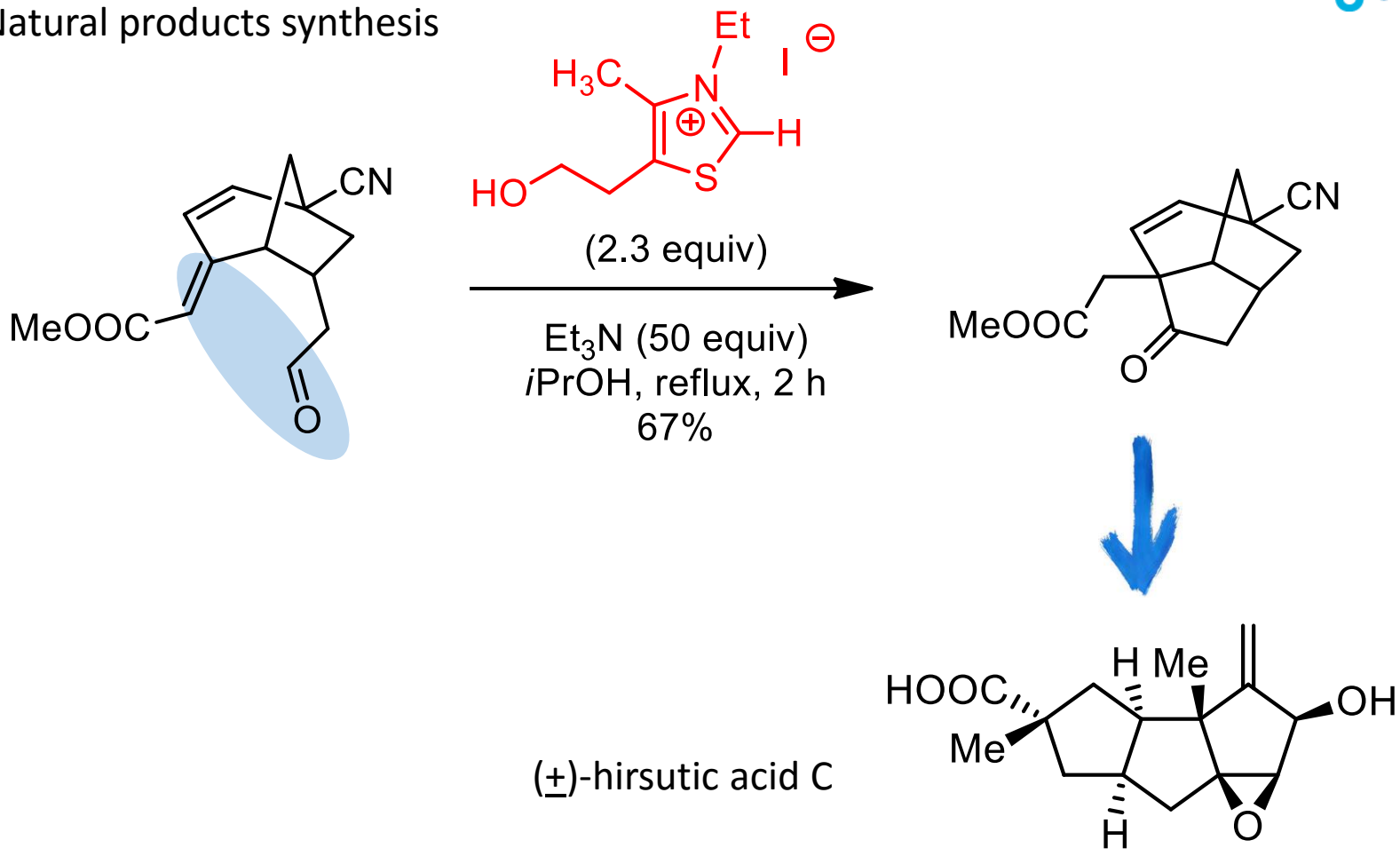


Metal-based catalysts

- *Basic applications: Benzoin formation, Stetter Reaction*
  - *Role of the azolium moiety*



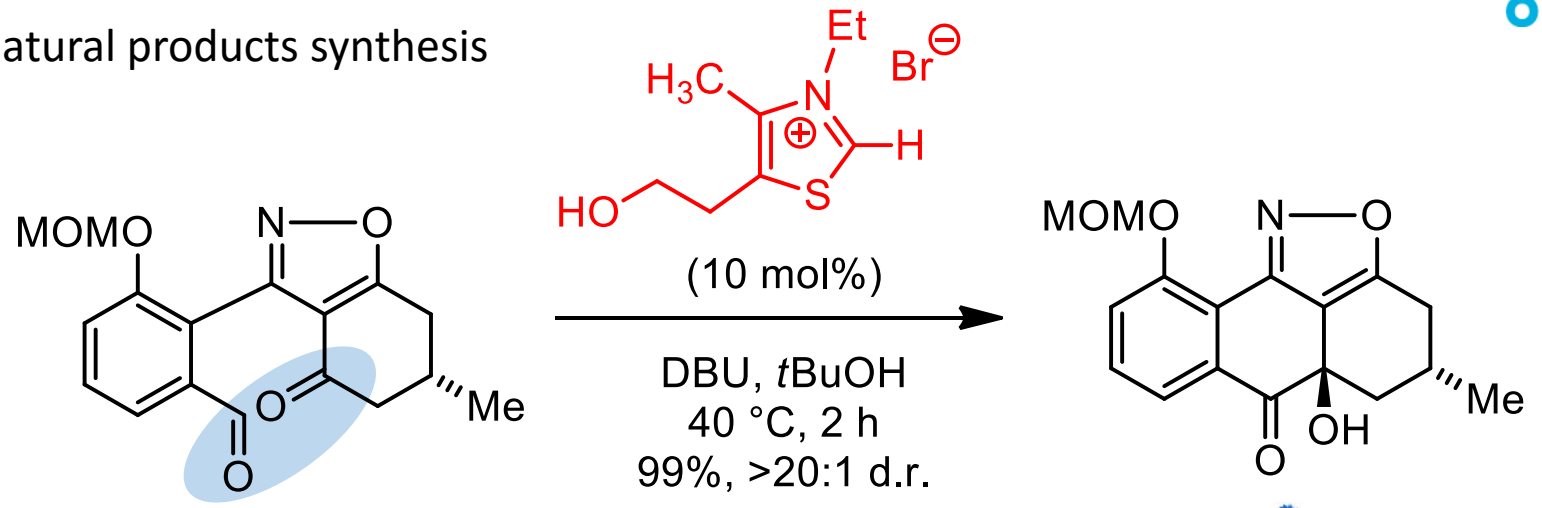
- Natural products synthesis



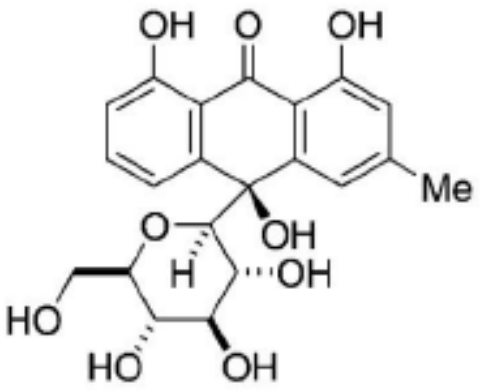
(±)-hirsutic acid C

B. Trost et al. *J. Am. Chem. Soc.* **1979**, *101*, 1284

- Natural products synthesis

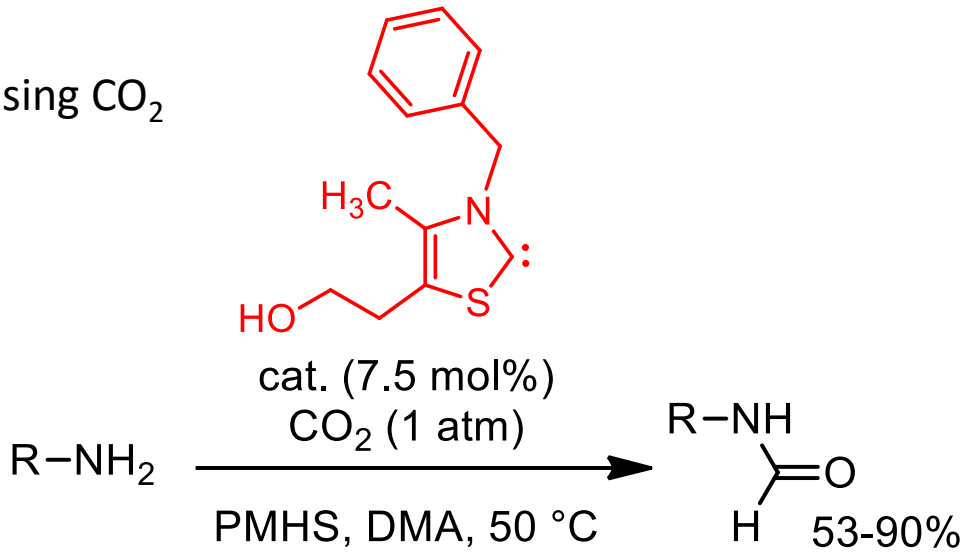


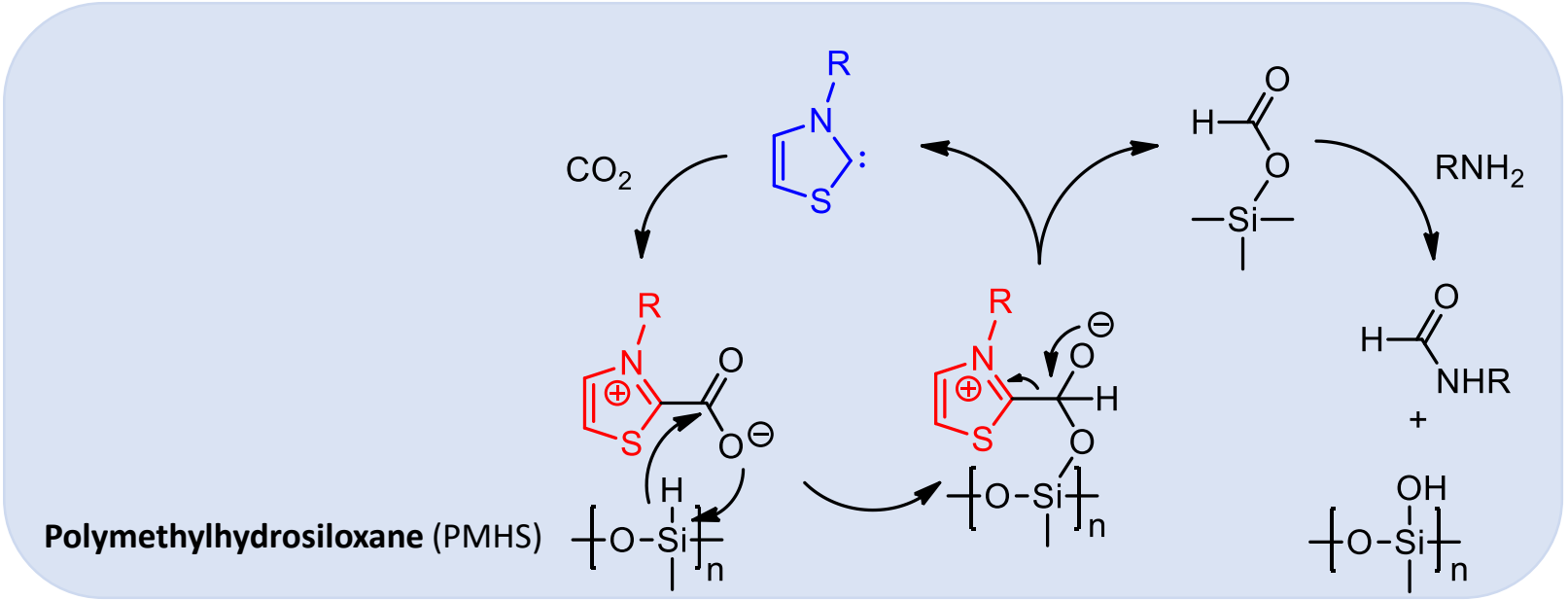
cassialoin



K. Suzuki et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 1084-1087

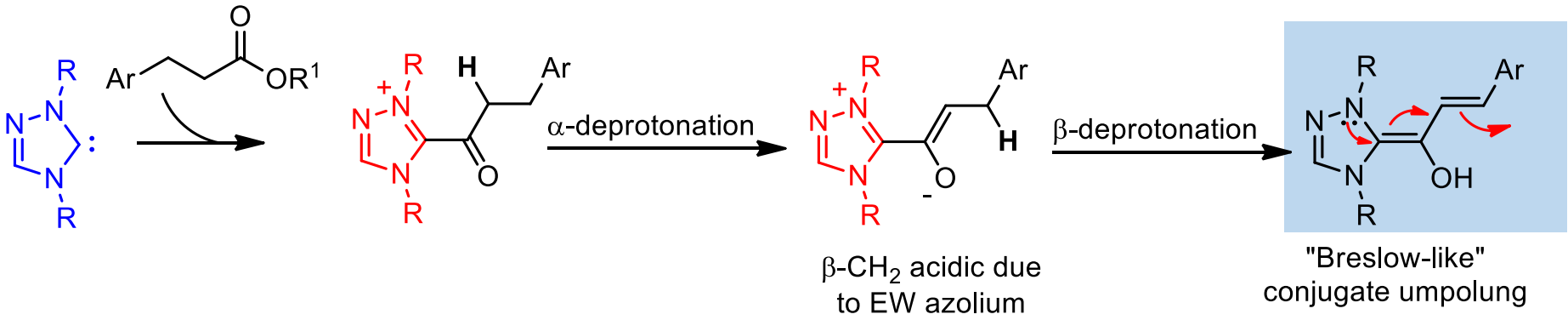
- *N*-formylation of amines using CO_2



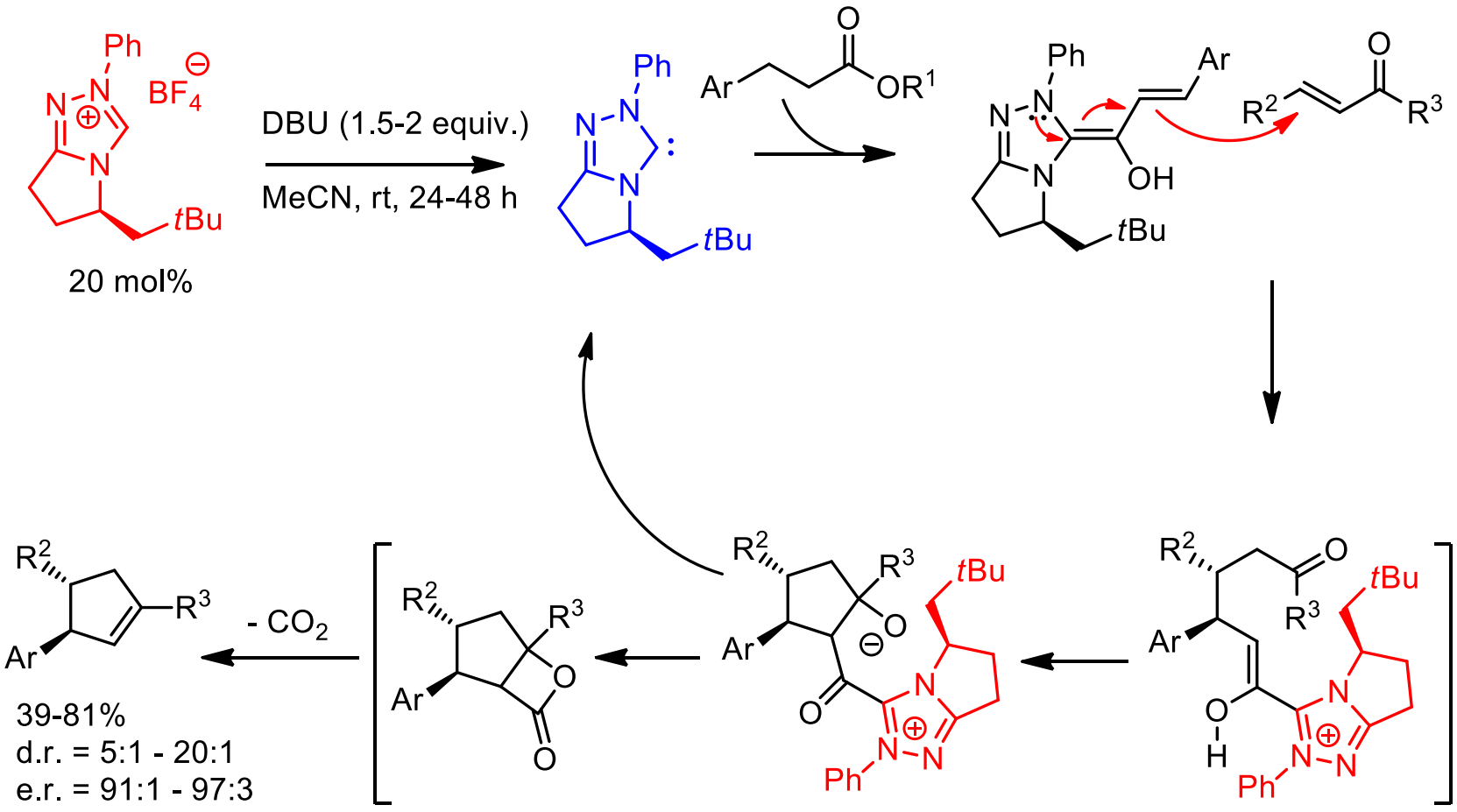


P. J. Dyson et al. *Chem. Commun.* **2016**, *52*, 2497-2500

- Advanced applications

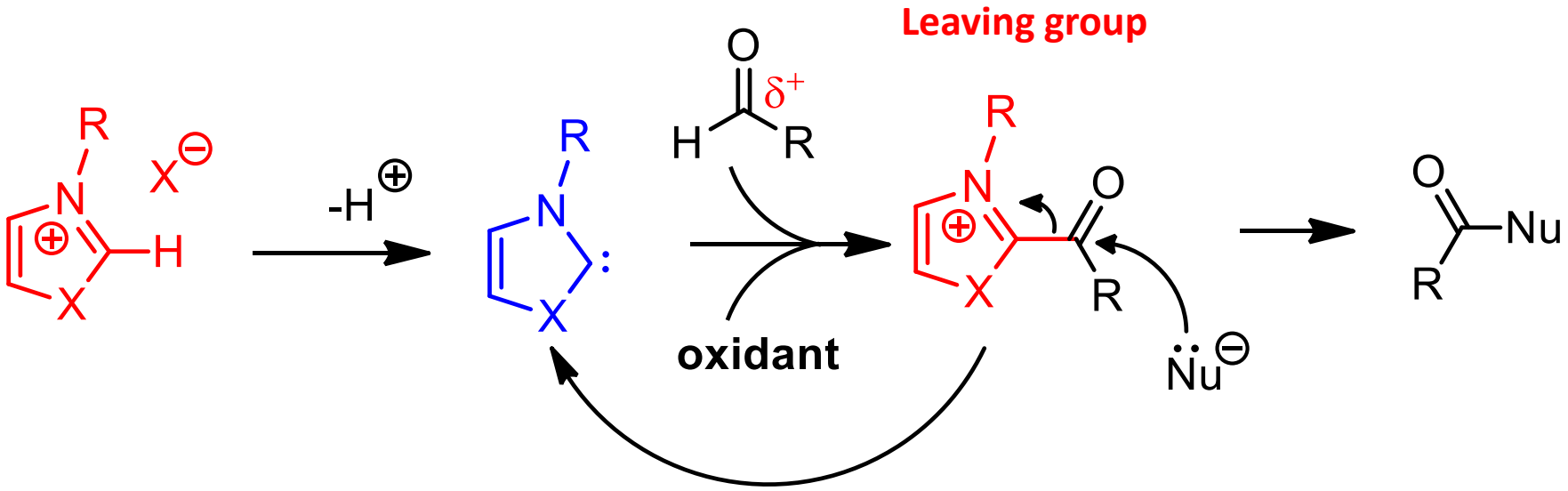


- Enantioselective synthesis

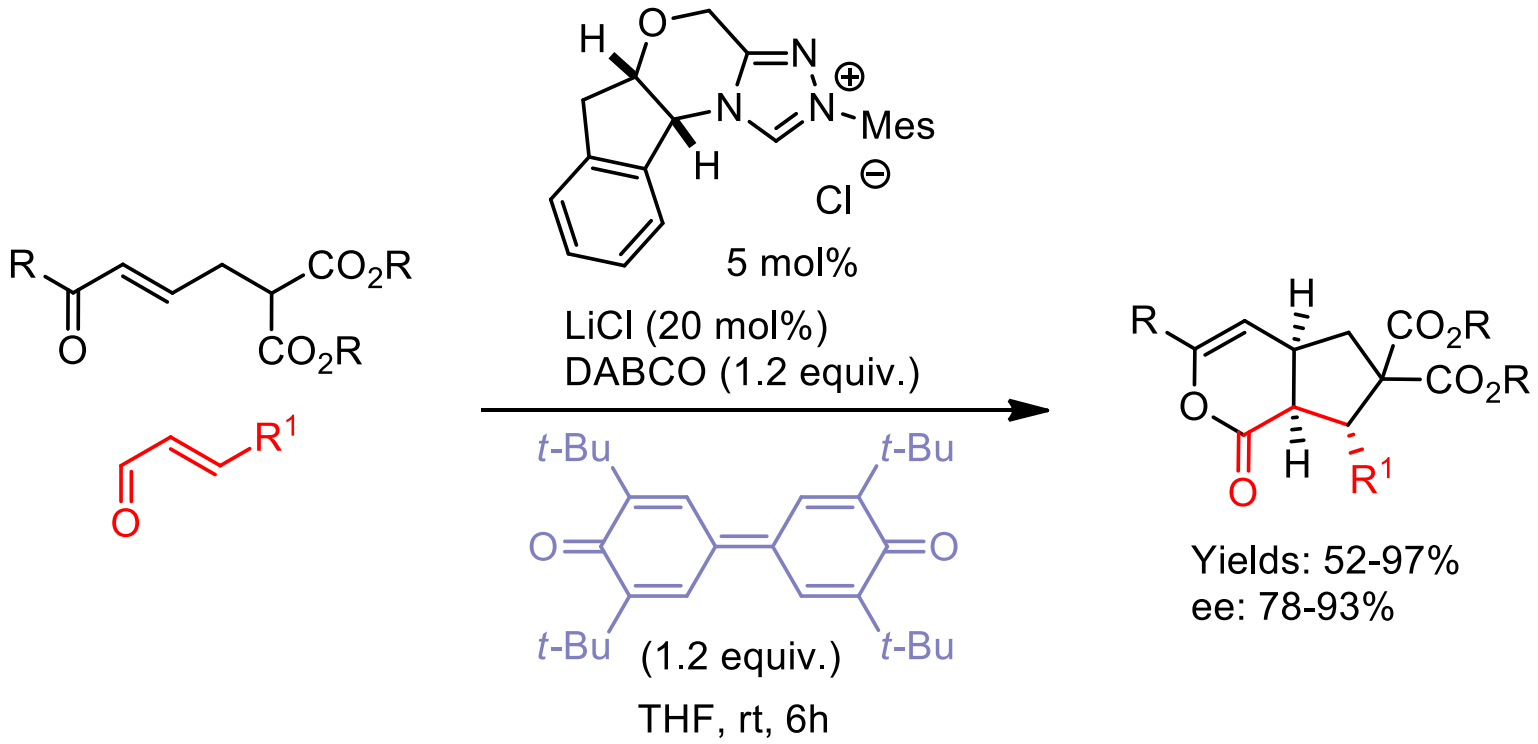


Y. R. Chi et al. *Nature Chem.* **2013**, *5*, 835-839

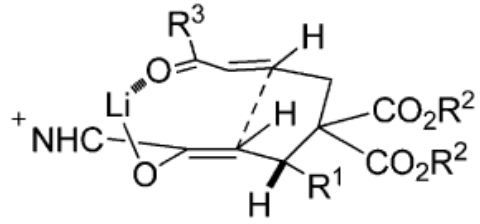
- Advanced applications

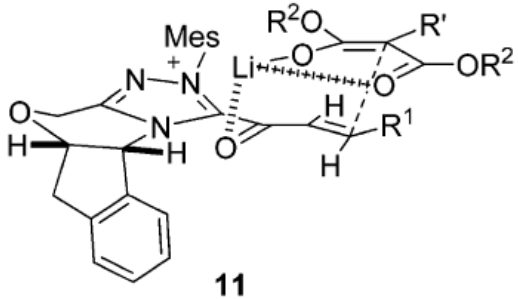


- Enantioselective synthesis
- Cooperative catalysis



A. Studer et al. *Org. Lett.* **2015**, *17*, 4940–4943





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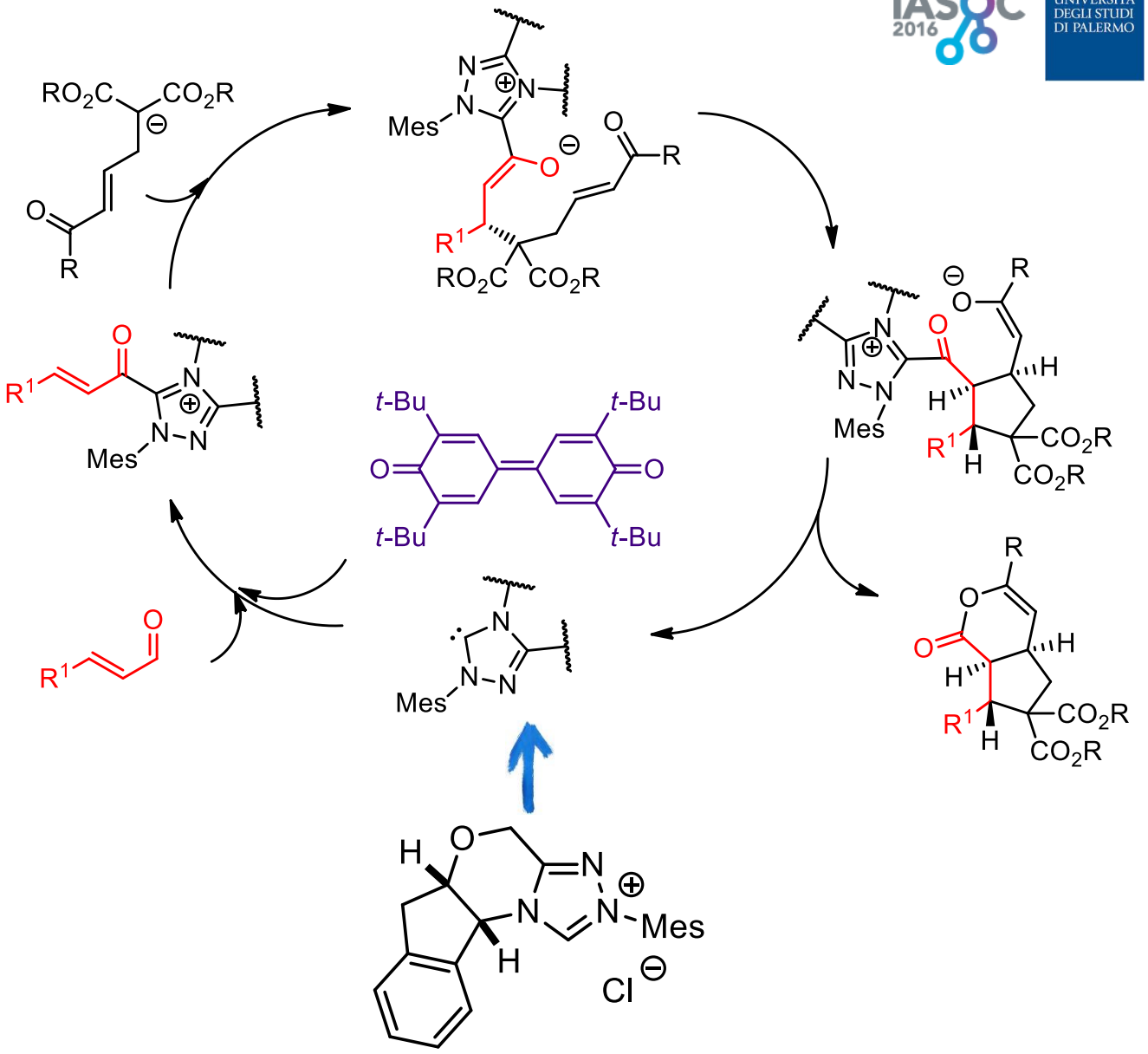
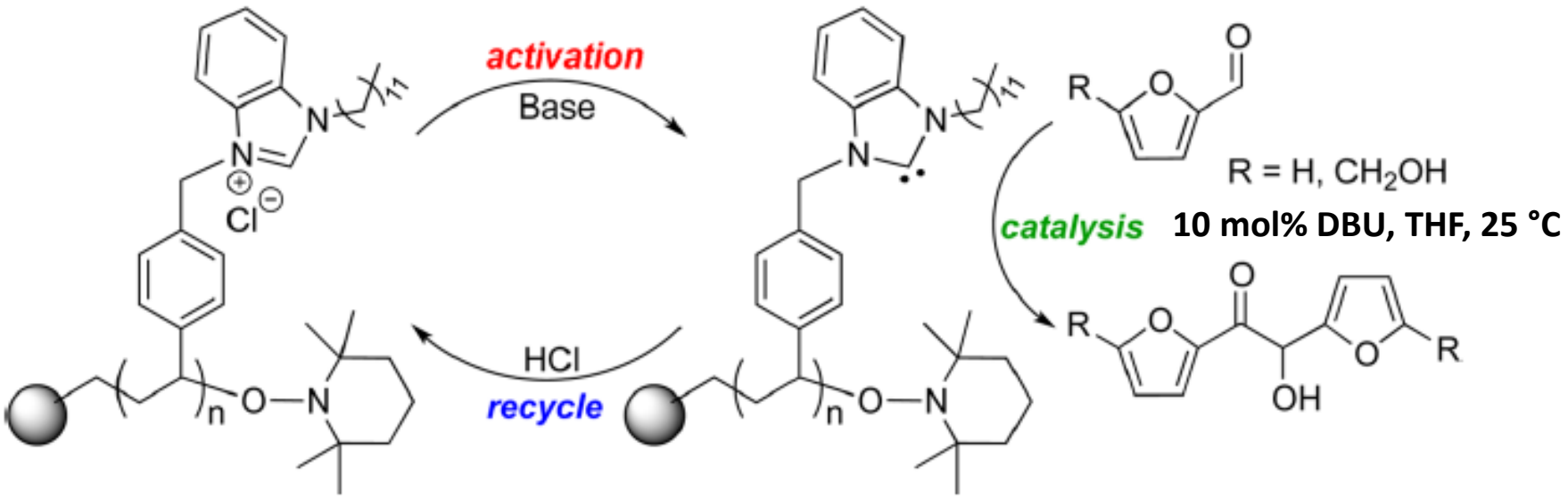
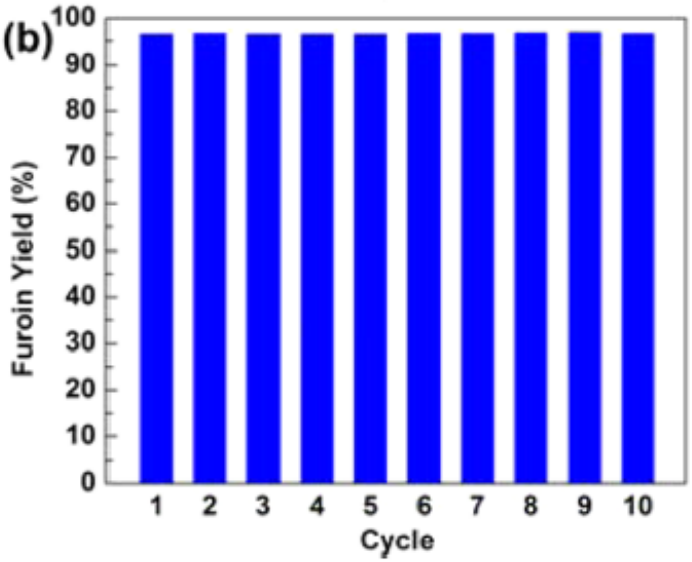


A. Studer *et al., Org. Lett.* **2015**, *17*, 4940–4943

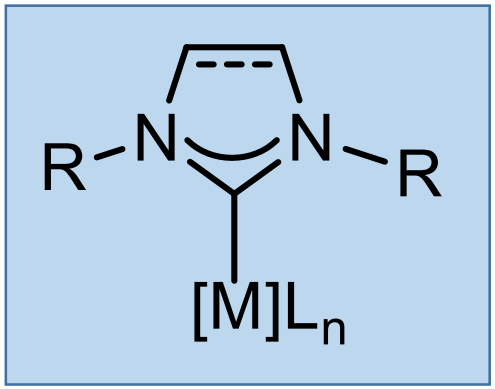
- Supported NHC

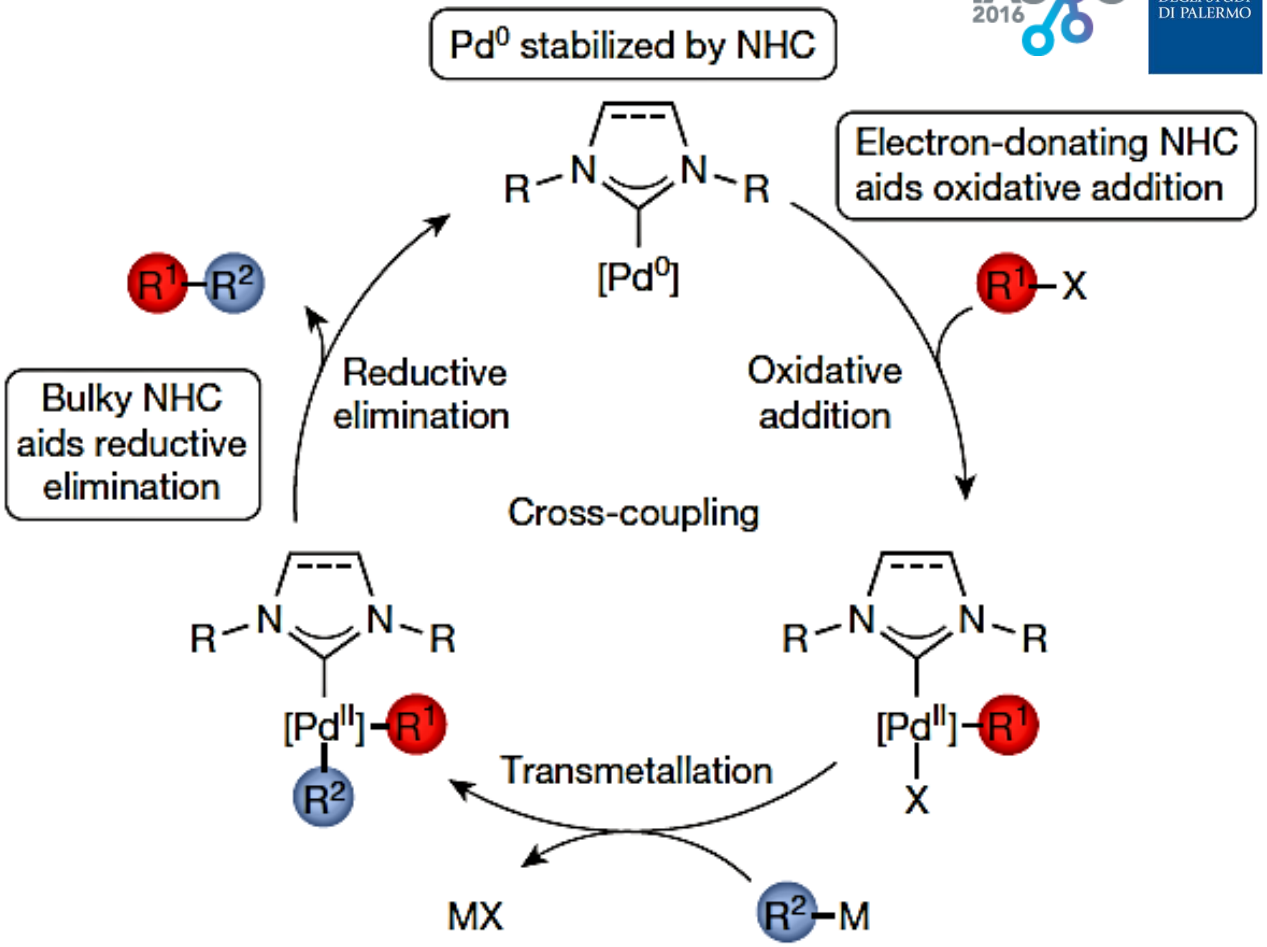




Y. X. Chen et al. *ACS Catal.* **2015**, *5*, 6907-6917

- Metal-NHC

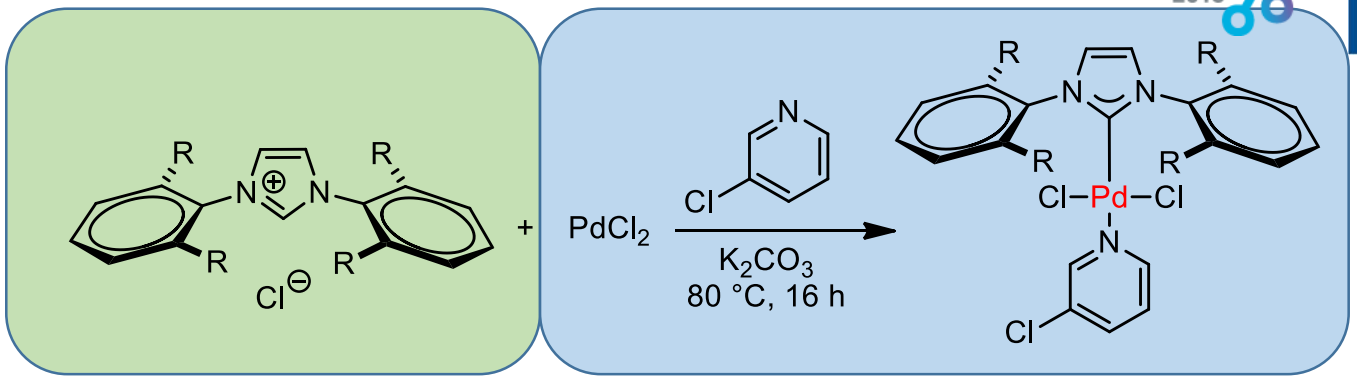


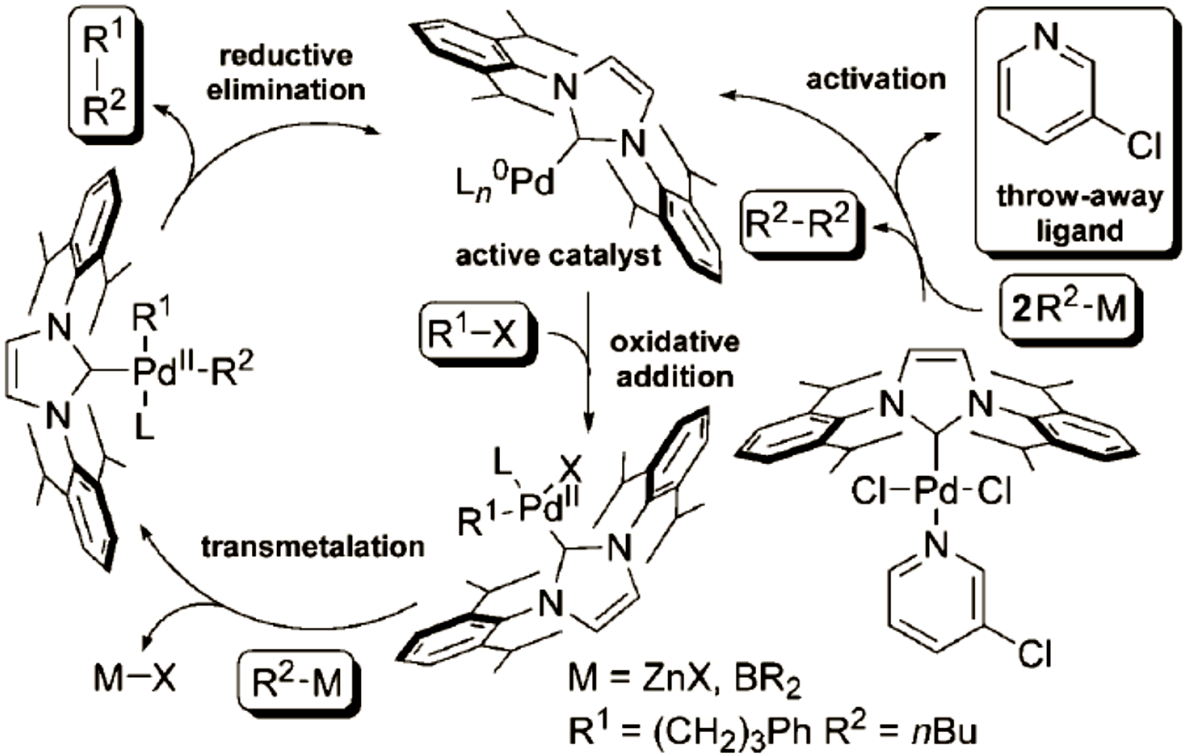


R^1, R^2 = aryl, heteroaryl, alkyl
X = halide, pseudohalide
M = $B(OR)_2$ (Suzuki–Miyaura), SnR_3 (Stille), ZnR (Negishi) and also heteroatom coupling partners such as HNR_2 (Buchwald–Hartwig)

F. Glorius et al. *Nature* **2014**, *510*, 485-496

- Metal-NHC



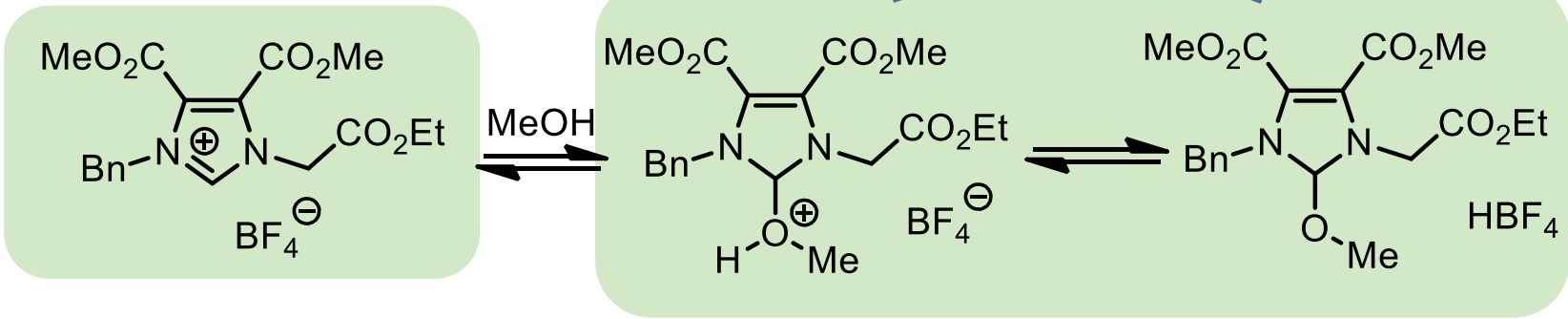


M. G. Organ et al. *Chem. Eur. J.* **2006**, *12*, 4743-4748

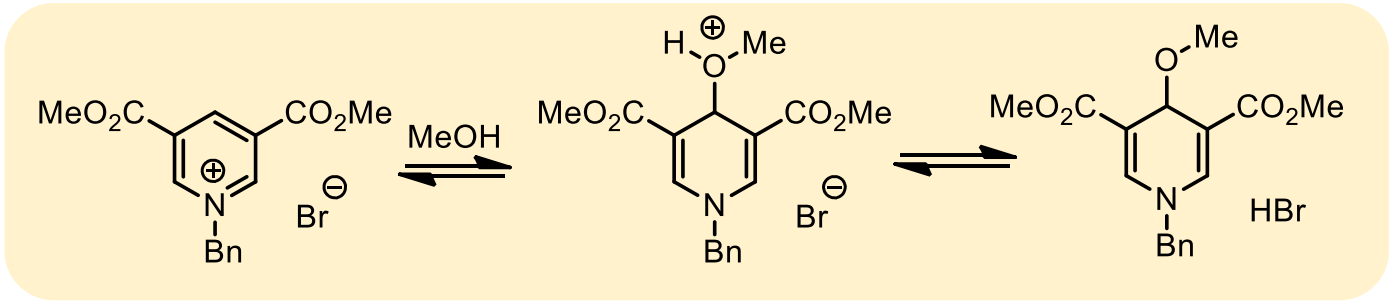
- Aldehyde protection and deprotection

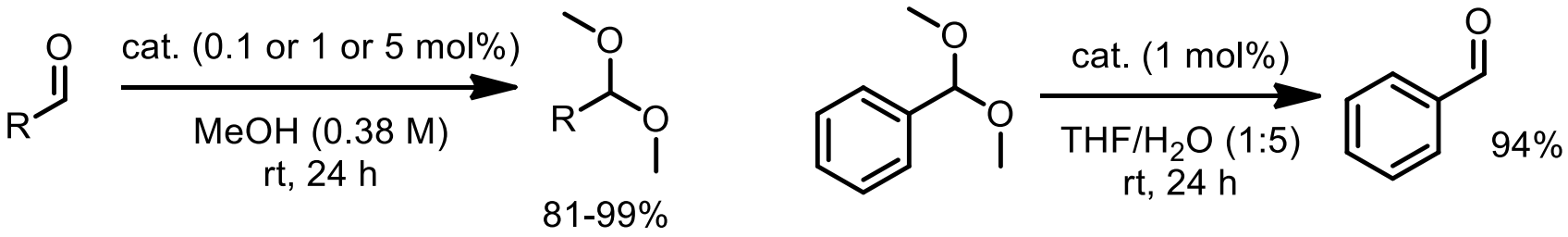
Aprotic salt as acidic catalyst when used with a protic additive

Acidic species



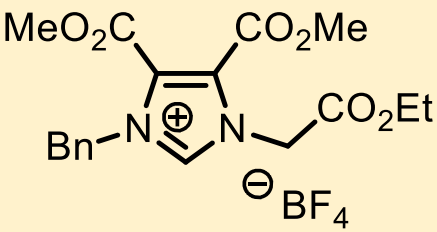
NAD⁺ ⟷ **NADH**

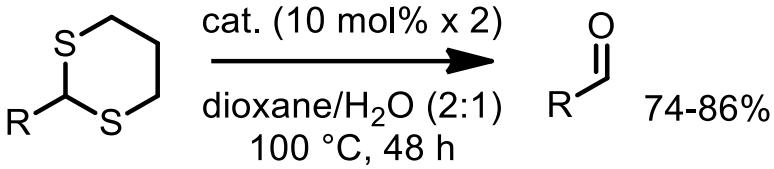


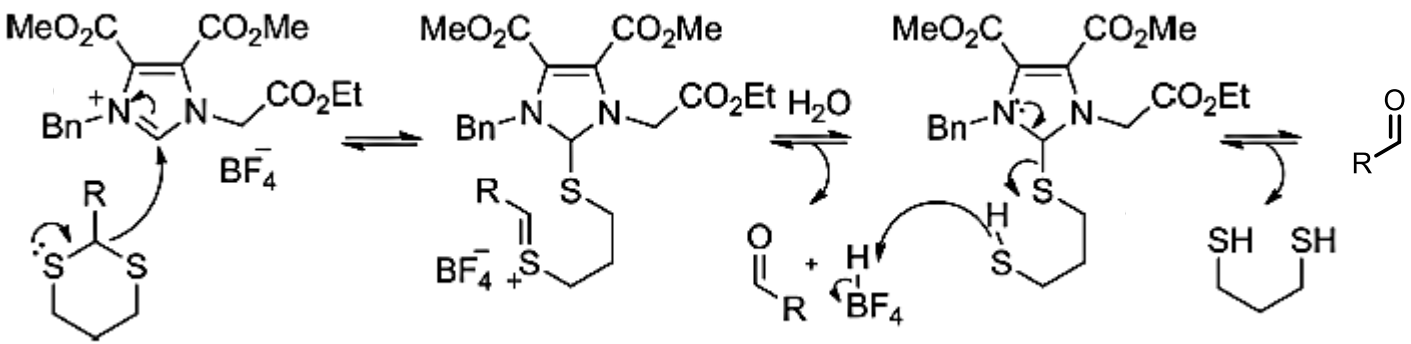


S. J. Connon et al. *Org. Lett.* **2008**, *10*, 4935-4938; N. Gathergood, S. J. Connon et al. *Green Chem.* **2013**, *5*, 5000-5007

- 1,3-Dithiane deprotection

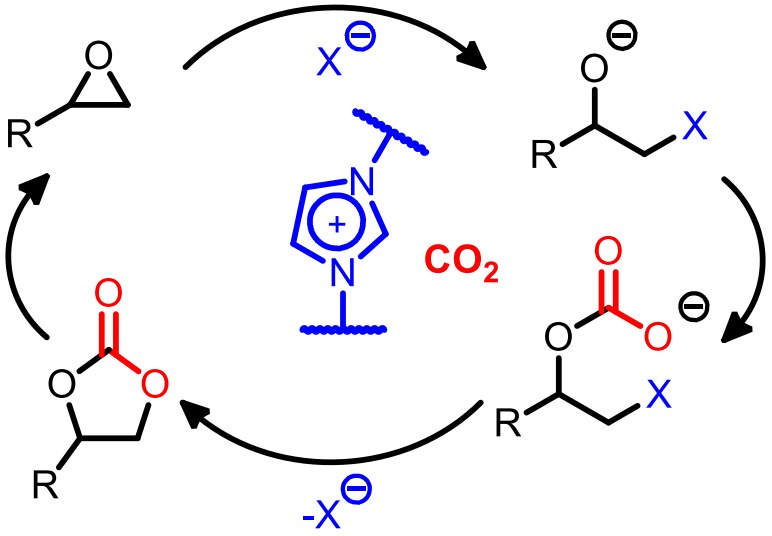


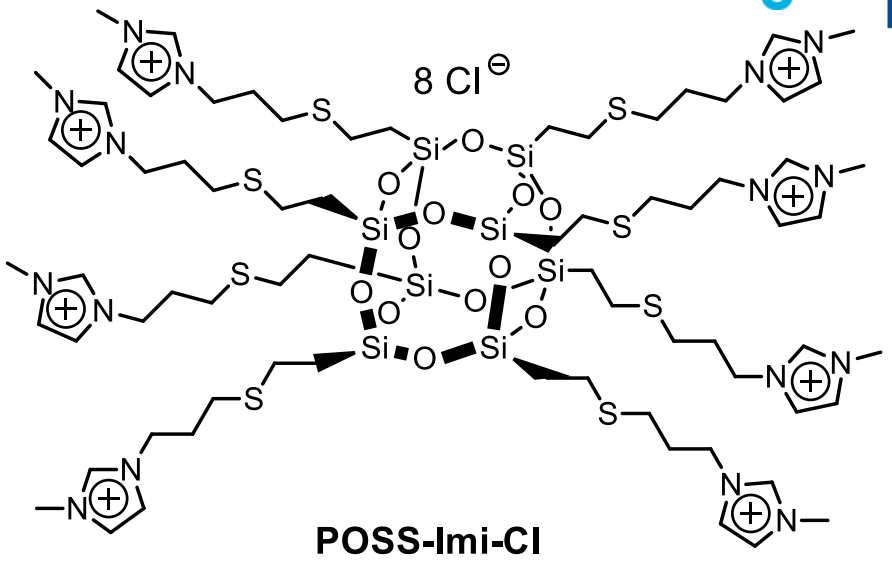




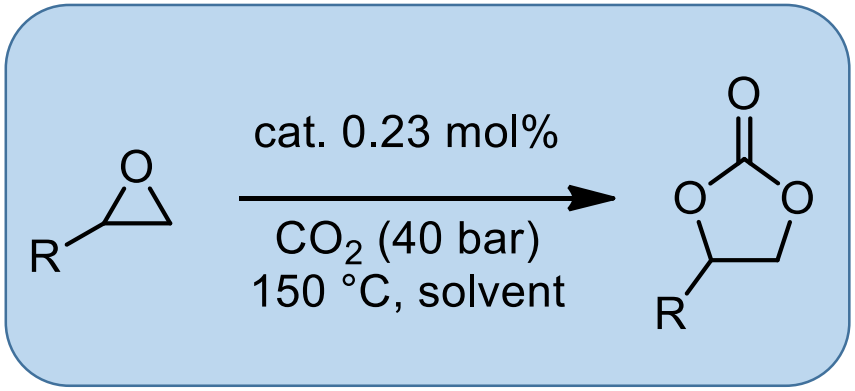
N. Gathergood, S. J. Connon et al. *Eur. J. Org. Chem.* **2015**, 188-194

- Cyclic carbonate synthesis
- Phase transfer catalysis





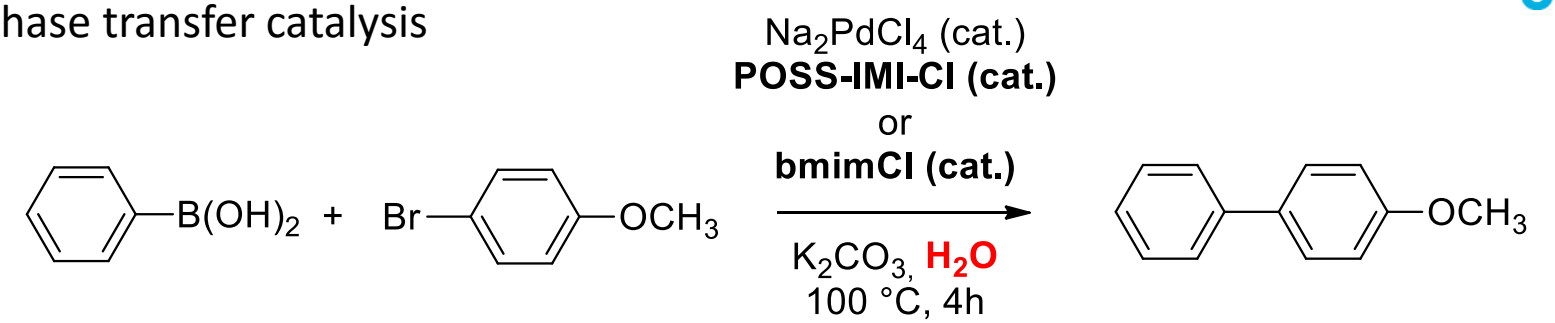
polyhedral oligomeric silsesquioxanes (POSS)

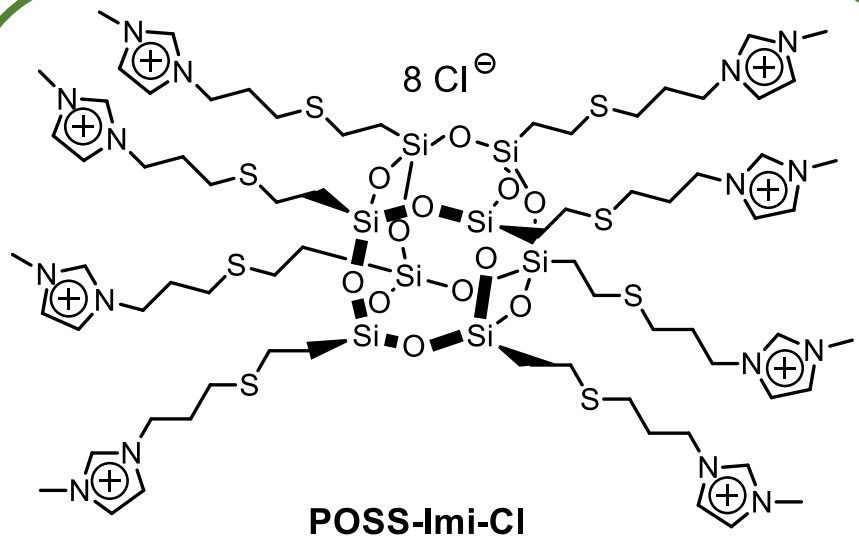


Cat	R	Solvent	T(°C)	TON
POSS-Imi-Cl	Ph	iPrOH	150	553
BmimCl	Ph	iPrOH	150	326
POSS-Imi-Cl	CH_2Cl	EtOH	100	479
BmimCl	CH_2Cl	EtOH	100	342

M.G. et al. *Catal. Sci. Technol.* **2015**, *5*, 5000-5007

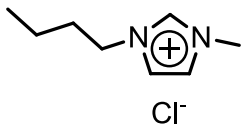
- Phase transfer catalysis





POSS-Imi-Cl

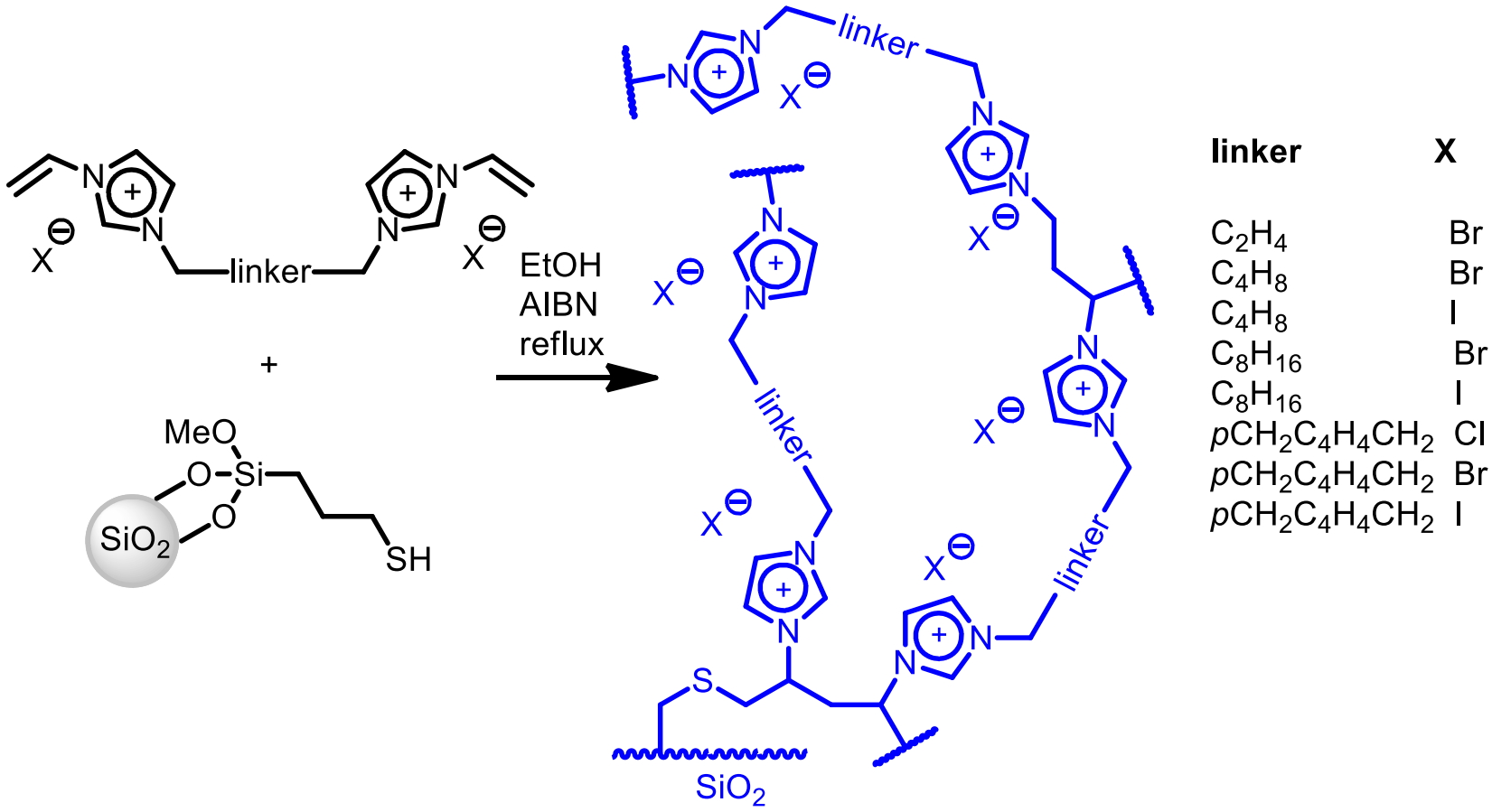
Na_2PdCl_4 (3.2 μmol) +
POSS-Imi-Cl (0.8 μmol) Conv. 90%



Na_2PdCl_4 (3.2 μmol) +
bmimCl (6.4 μmol) Conv. 30%

M.G. et al. *ChemCatChem* **2016**, *8*, 1685-1691

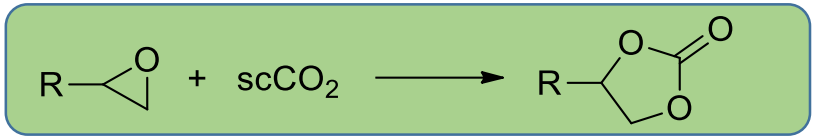
- Covalently linked ionic liquid phase

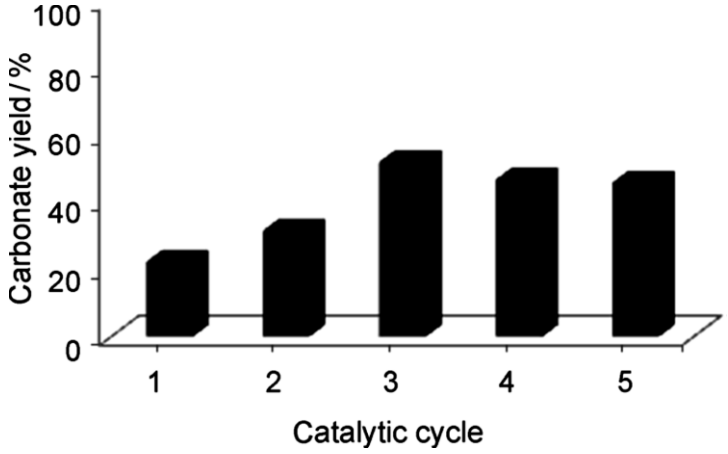


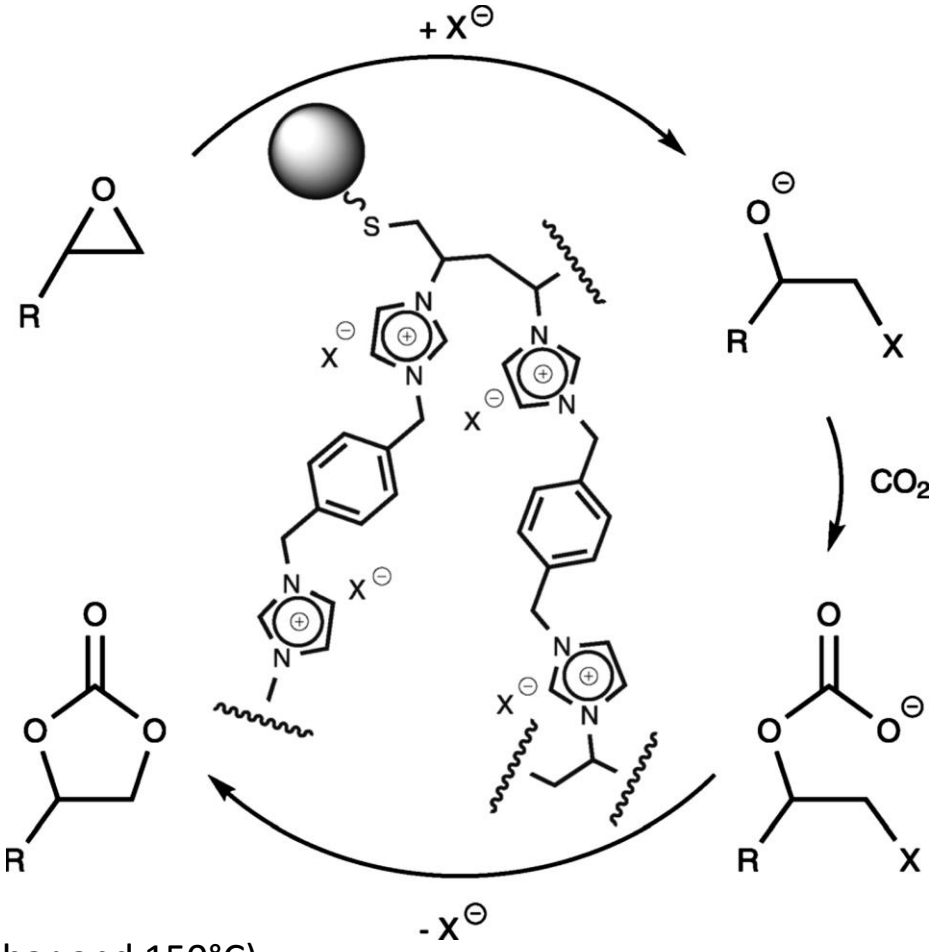
linker	X
C_2H_4	Br
C_4H_8	Br
C_4H_8	I
C_8H_{16}	Br
C_8H_{16}	I
$pCH_2C_4H_4CH_2$	Cl
$pCH_2C_4H_4CH_2$	Br
$pCH_2C_4H_4CH_2$	I

M.G. et al. *ChemSusChem* **2011**, *4*, 1830-1837; *Catal. Sci. Technol.* **2014**, *4*, 1598-1607

- Cyclic carbonate synthesis



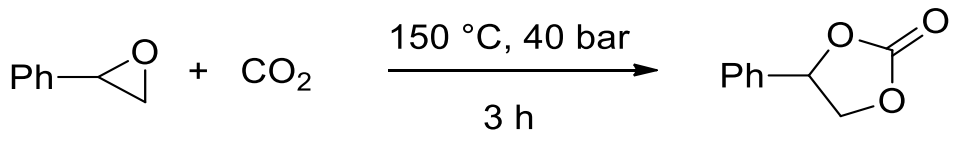


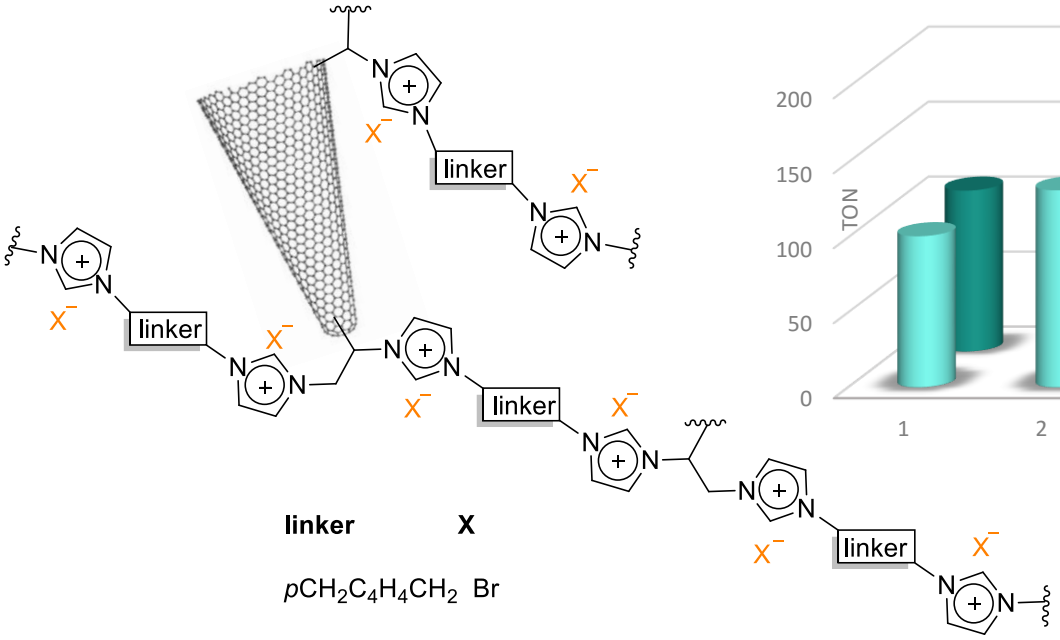


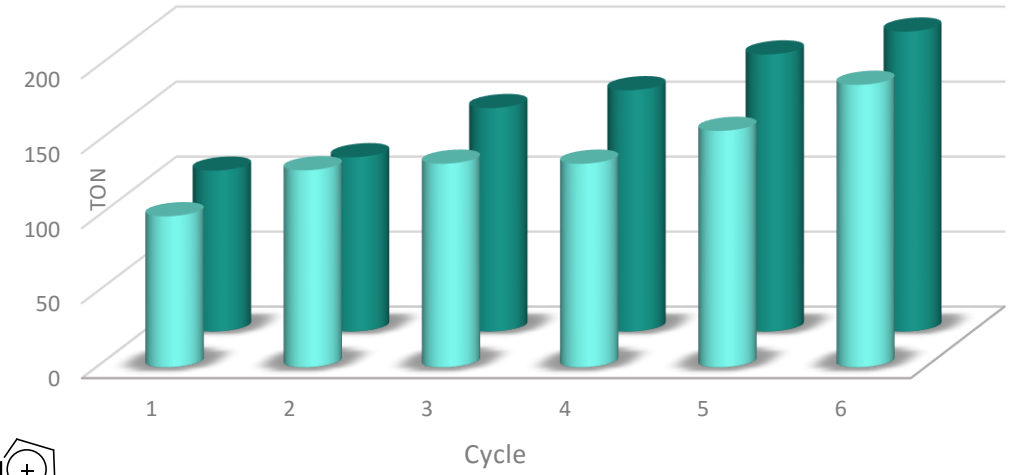
high values of productivity:
45 g of styrene carbonate/g catalyst (3 h at 80 bar and 150°C)
25 g of propylene carbonate/g catalyst (3 h at 100 bar and 150°C)

M.G. et al. *ChemSusChem* **2011**, *4*, 1830-1837; *Catal. Sci. Technol.* **2014**, *4*, 1598-1607

- Cyclic carbonate synthesis
- Increased catalytic activity upon recycling

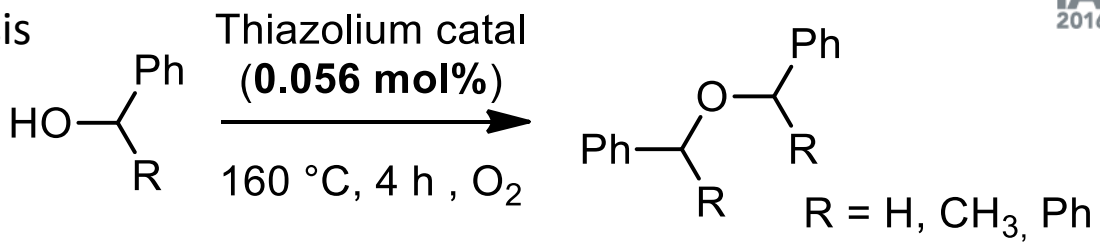


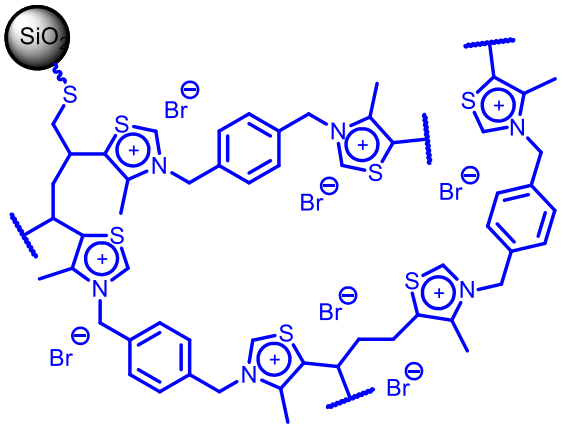


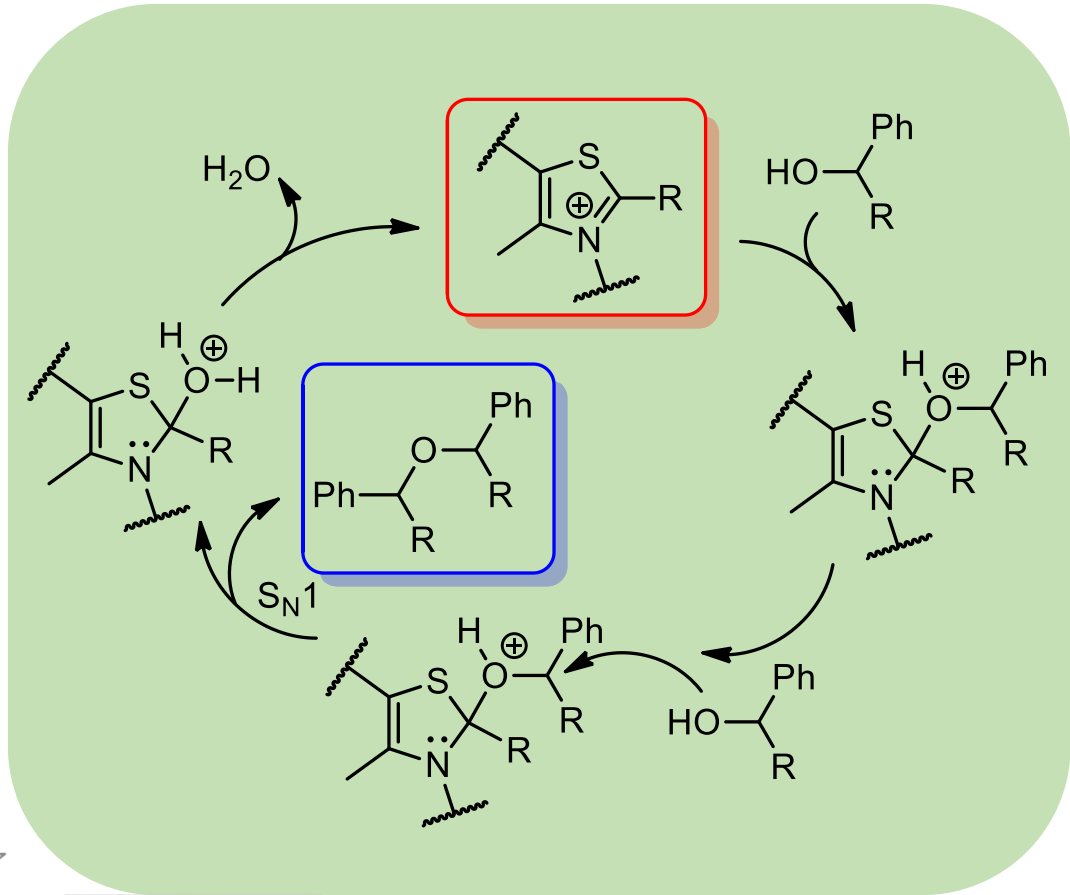


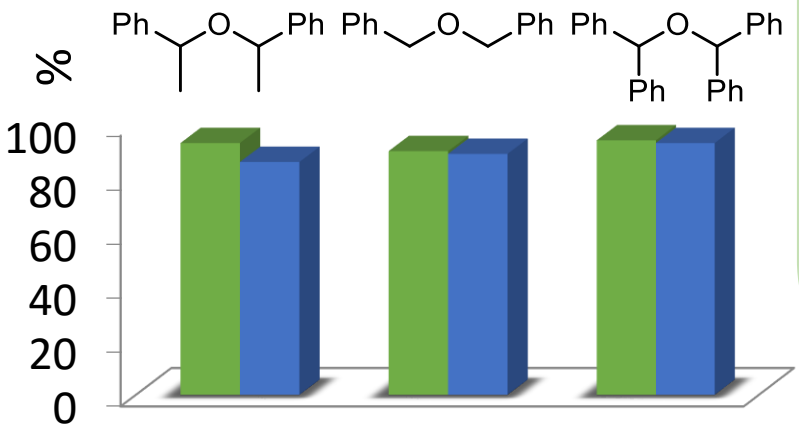
M.G. et al. *ChemSusChem submitted* ; *Catal. Sci. Technol.* **2016**, accepted

- Benzyl ethers synthesis





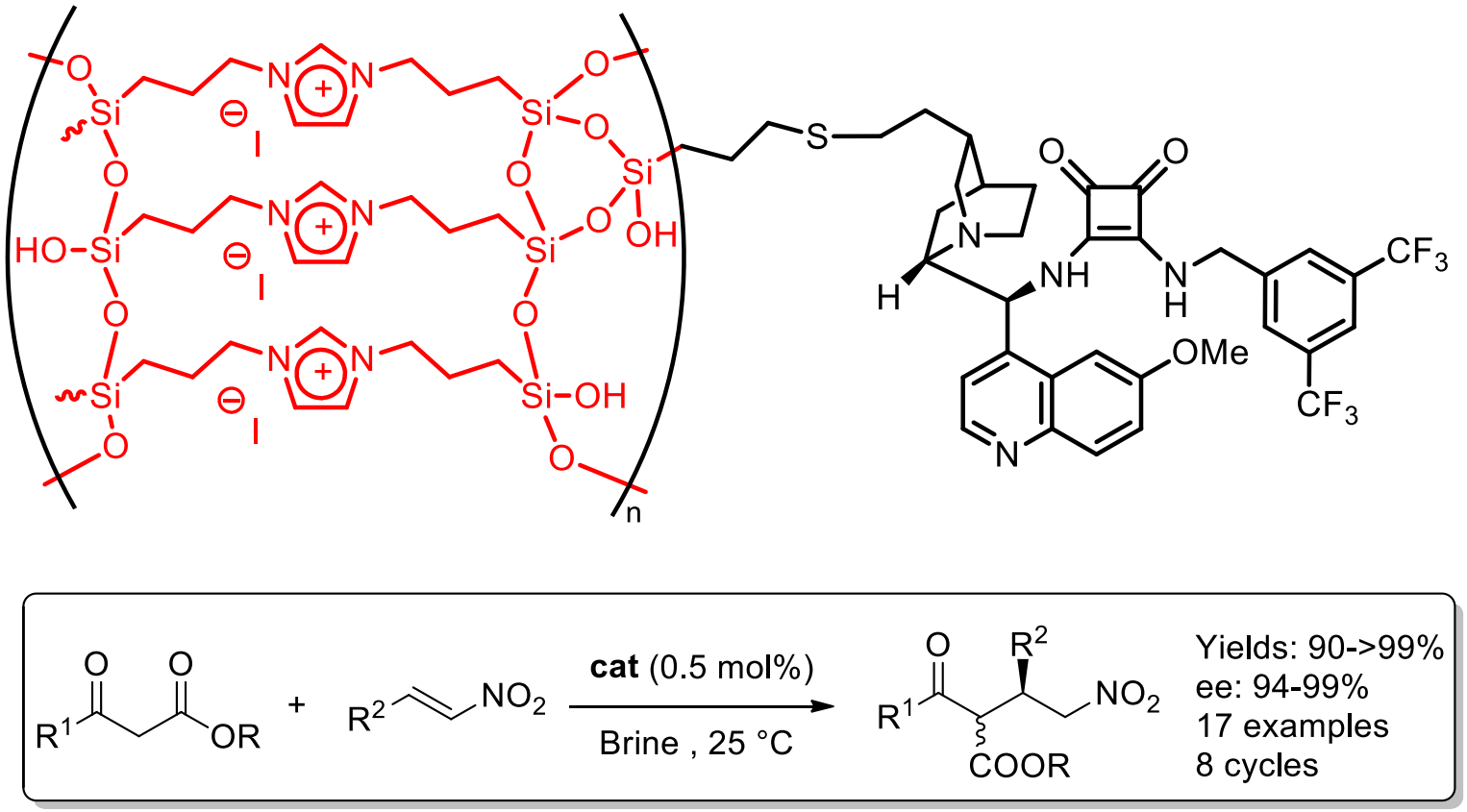




M.G. et al. *Adv. Synth. Catal.* **2015**, *357*, 800-810

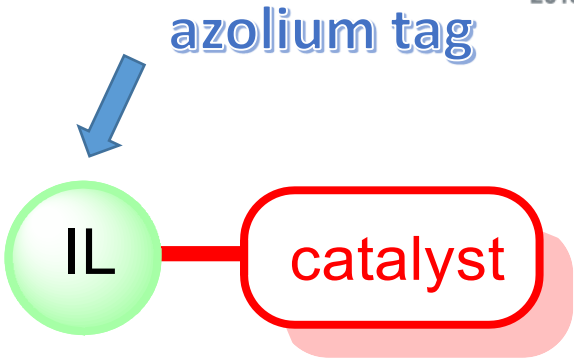
Conversion
Selectivity

- Phase transfer catalysis



G. Liu et al. *ACS Catalysis* **2014**, *4*, 2137-2142

- Azolium tag strategy

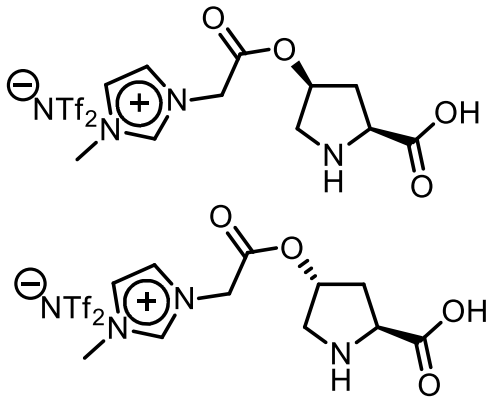


✓ Ion tag makes easier the immobilization of the catalyst in an ionic liquid or water, with an improved product/catalyst separation. The counterion allows for the solubility profile of the catalyst.

✓ Ion tag may increase the reaction rate (electrosteric activation)

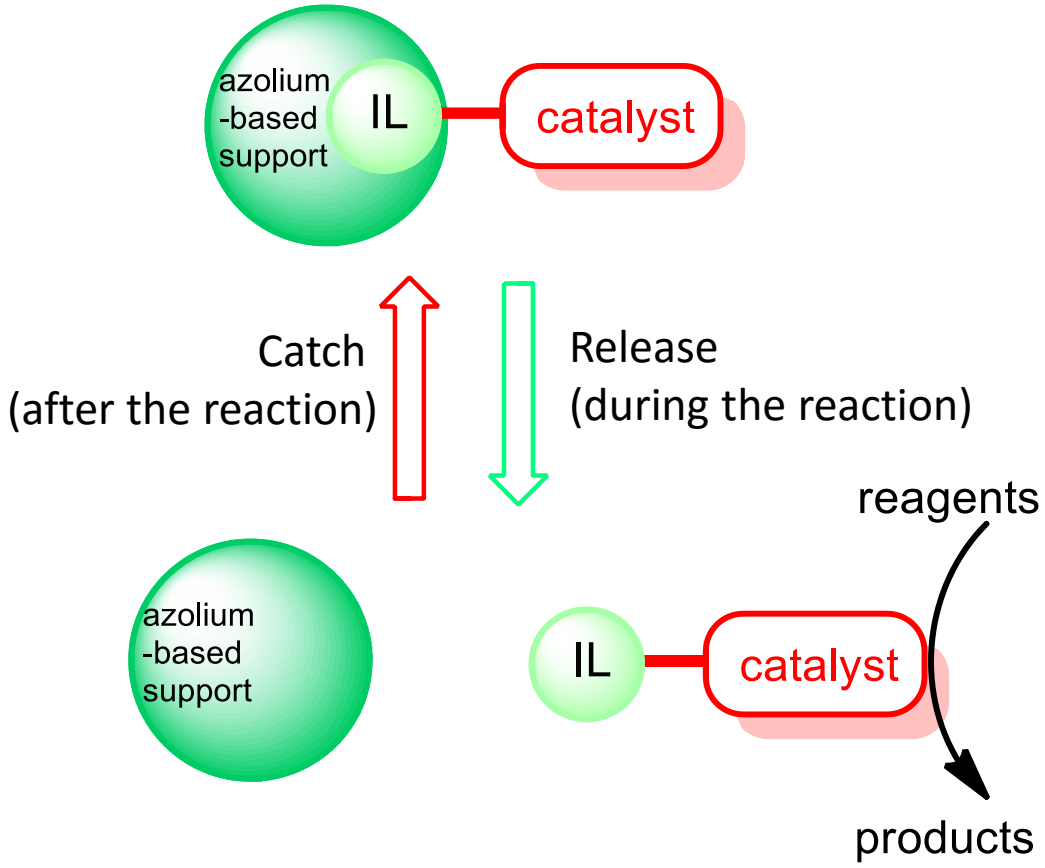
«Electrostatic stabilization of a transition state by an ion tag could be considered a simplified version of the electrostatic activation of enzymatic reactions»

The higher activity of the *cis* catalysts could be the closer proximity of the charges in the TS due to the *cis*-oriented ion tag



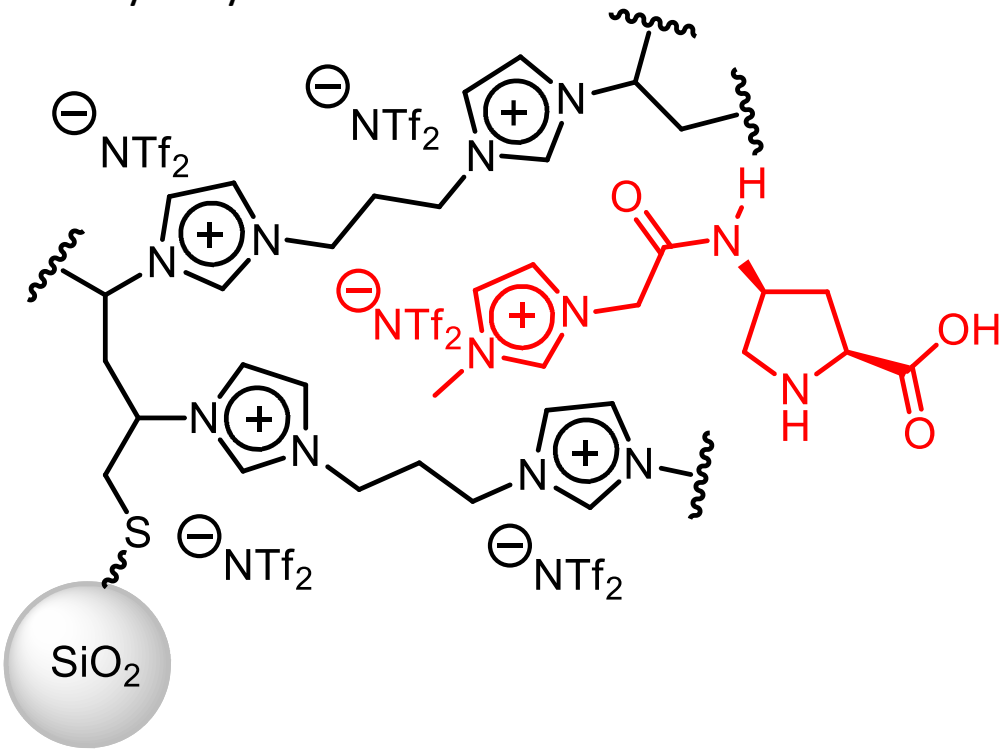
M. Lombardo, C. Trombini *ChemCatChem* **2010**, *2*, 135-145

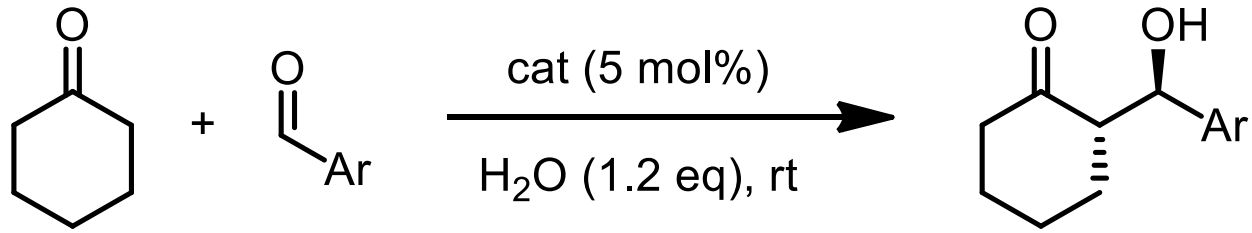
- "release and catch" catalytic systems



M.G. et al. *Green Chem.* **2013**, *15*, 2608-2618

- "release and catch" catalytic systems



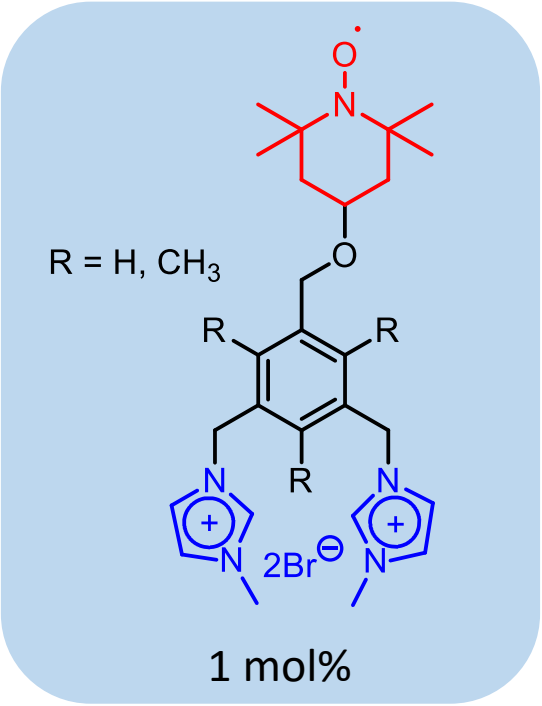


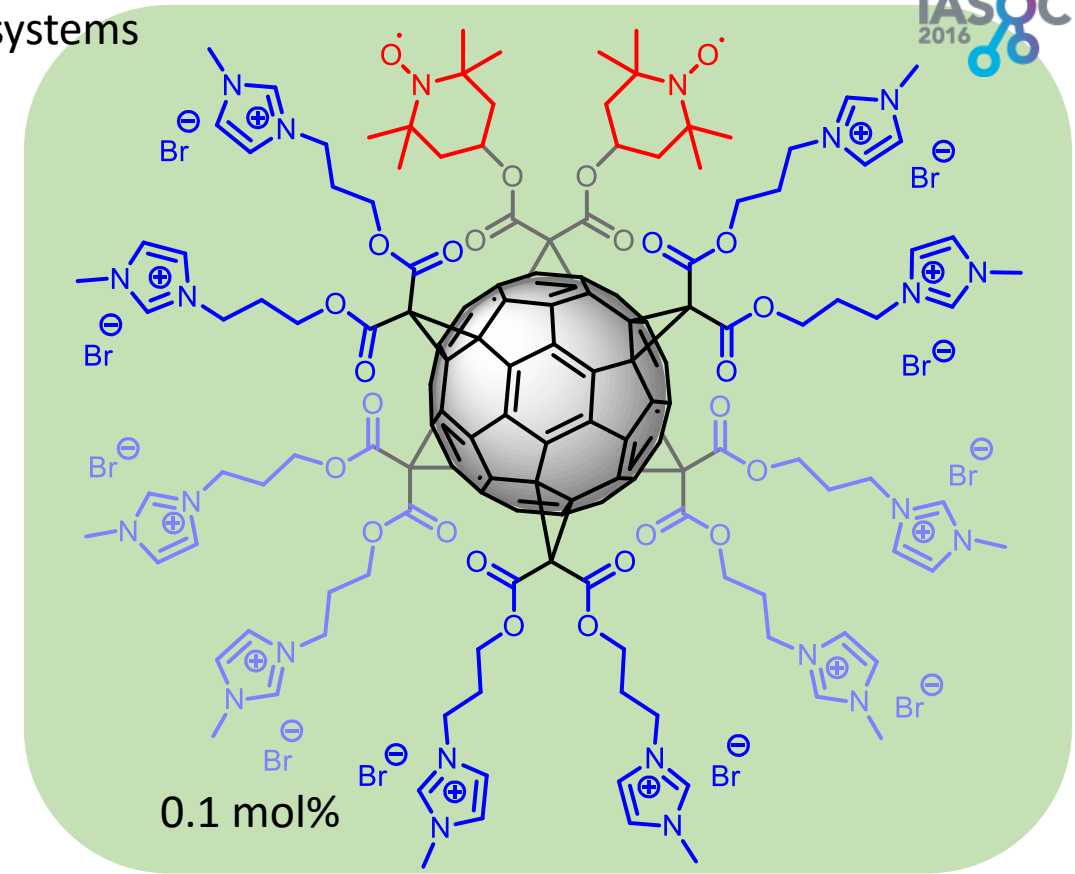
5 equiv.

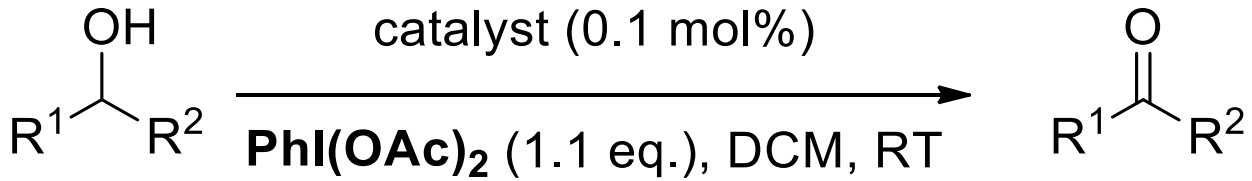
Yields up to >99%
d.r. up to 97:3
e.e. up to >99%
5 examples
15 cycles

M.G. et al. *ChemCatChem* **2012**, *4*, 1000-1006; M. Lombardo, C. Trombini et al. *Adv. Synth. Catal.* **2011**, *353*, 3234-3240

- "release and catch" catalytic systems
- Cooperative catalysis



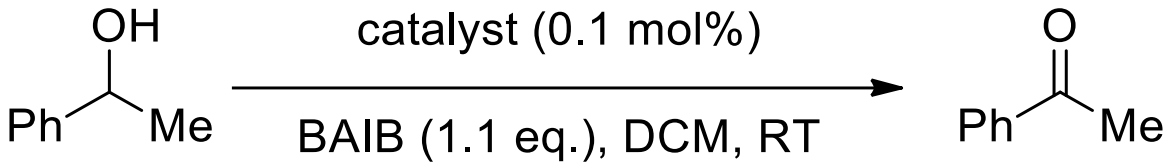


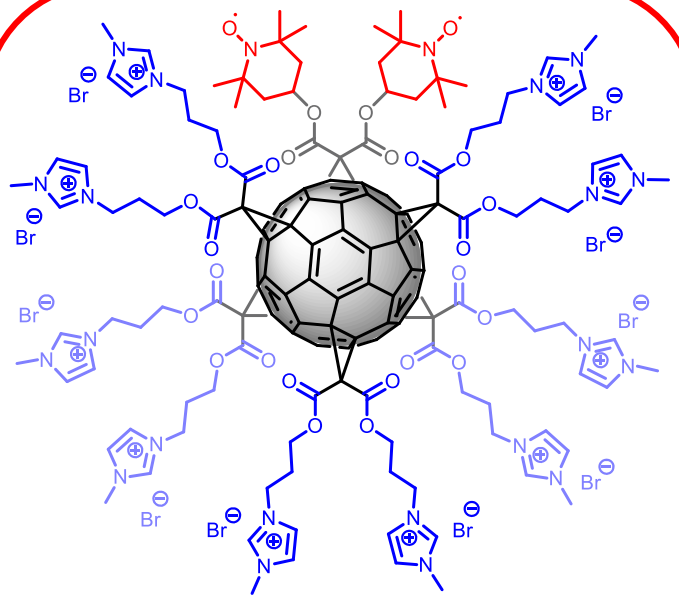


Primary and secondary aliphatic and benzylic alcohols. *15 examples, yields >95%*

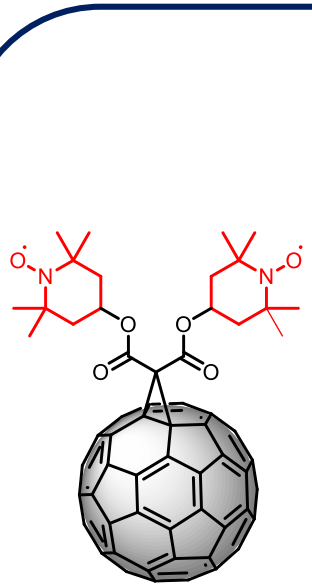
M.G. et al. *ChemCatChem* **2013**, *5*, 2991-2999; *Adv. Synth. Catal.* **2015**, *357,* 51-58

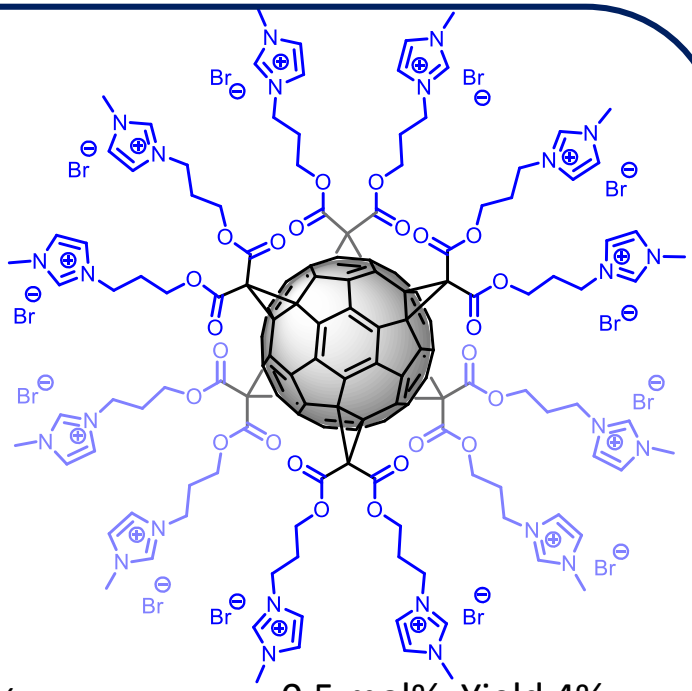
- Cooperative catalysis





0.1 mol% Yield >95%



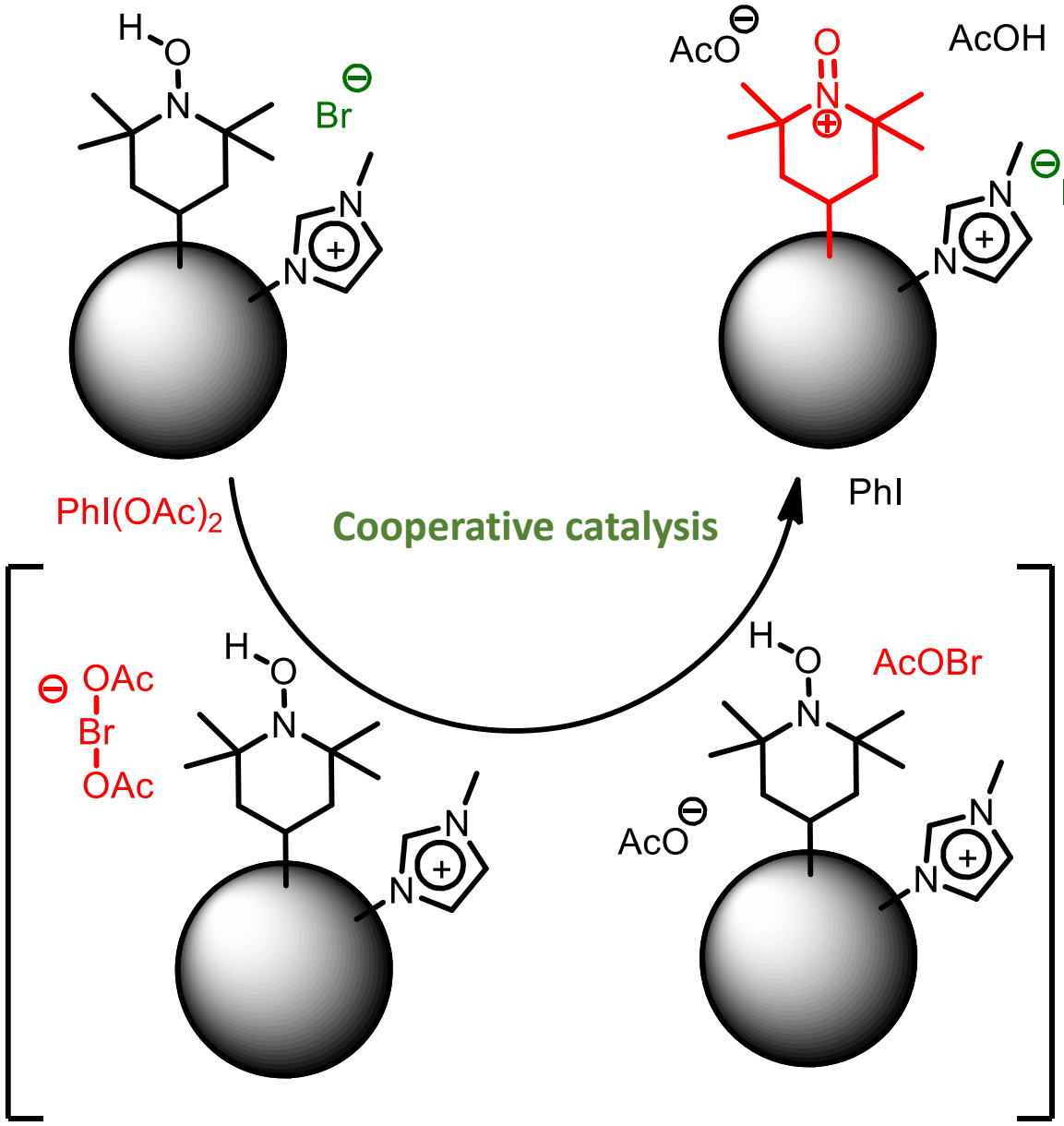


0.1 mol% Yield 8%

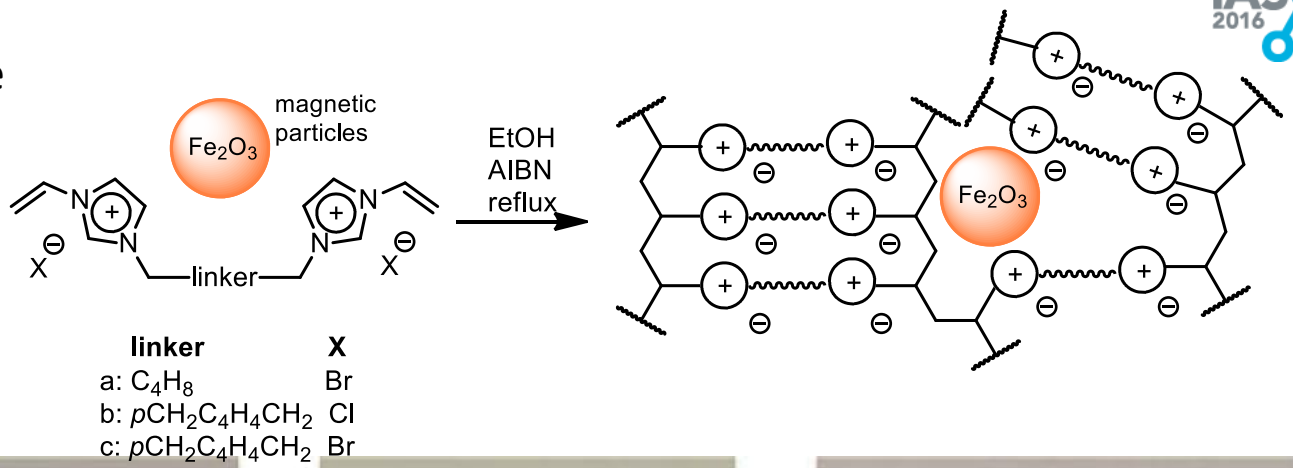
0.5 mol% Yield 4%

Yield 36%

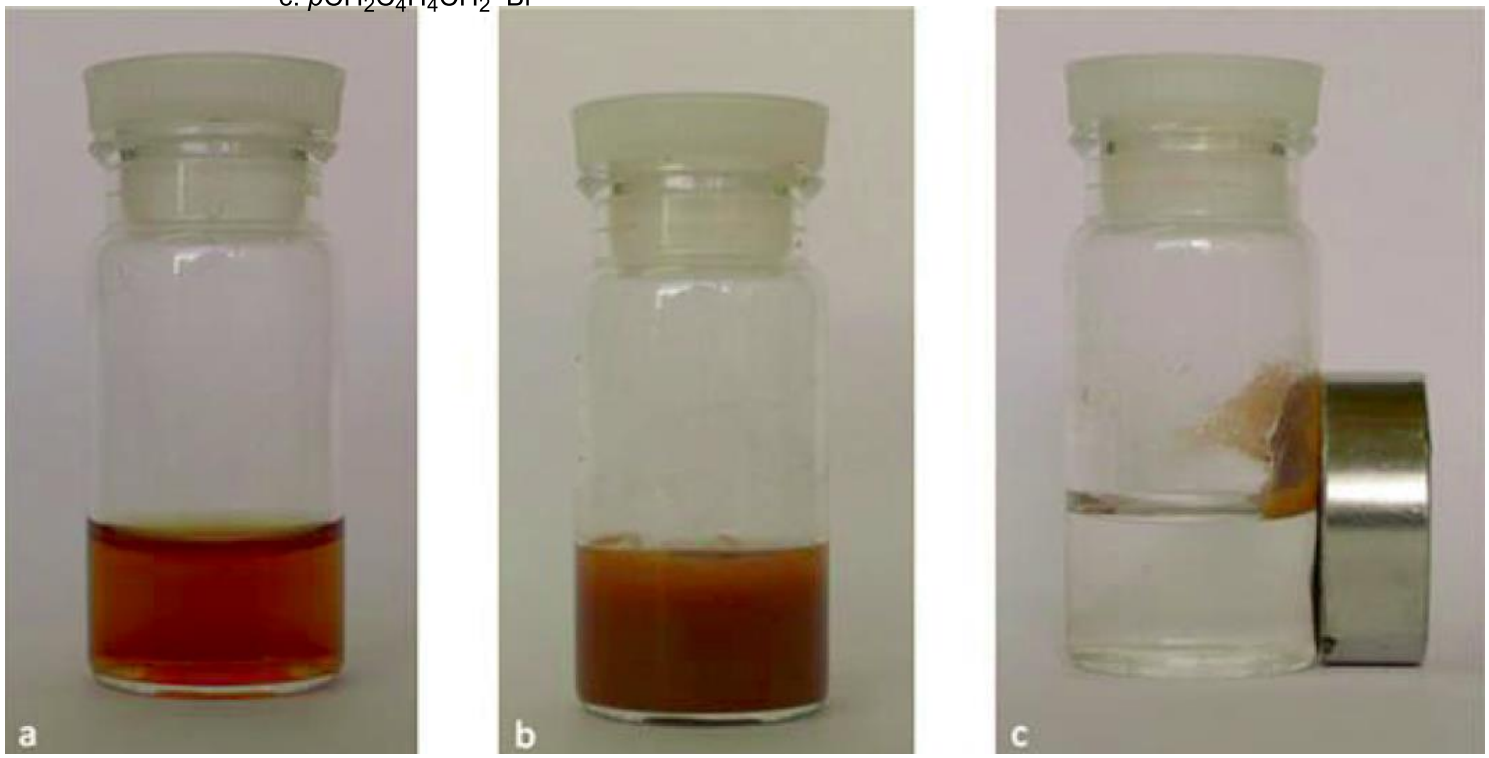
Adv. Synth. Catal. **2015**, *357,* 51-58


PhI(OAc)2
Cooperative catalysis
PhI
AcOH
AcOBr
OAc
Br
OAc
AcO
Br

- $PdCl_4^{2-}$ capture

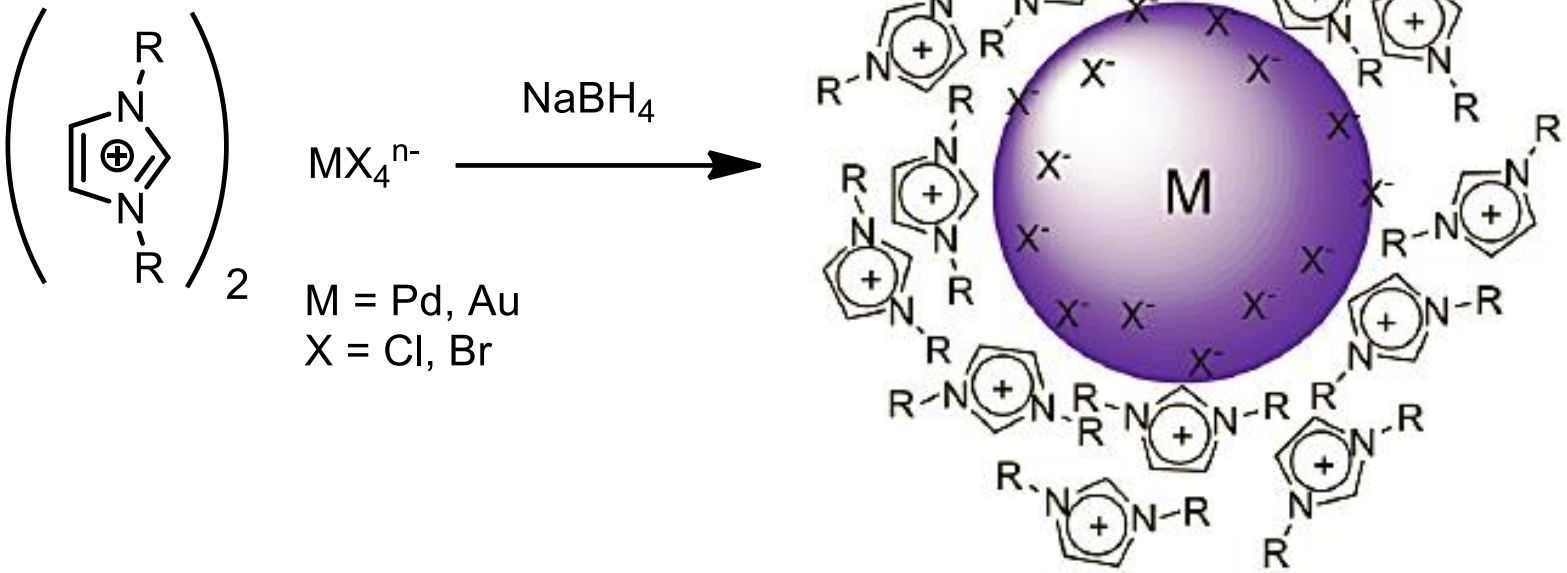


linker	X
a: C_4H_8	Br
b: $pCH_2C_4H_4CH_2$	Cl
c: $pCH_2C_4H_4CH_2$	Br



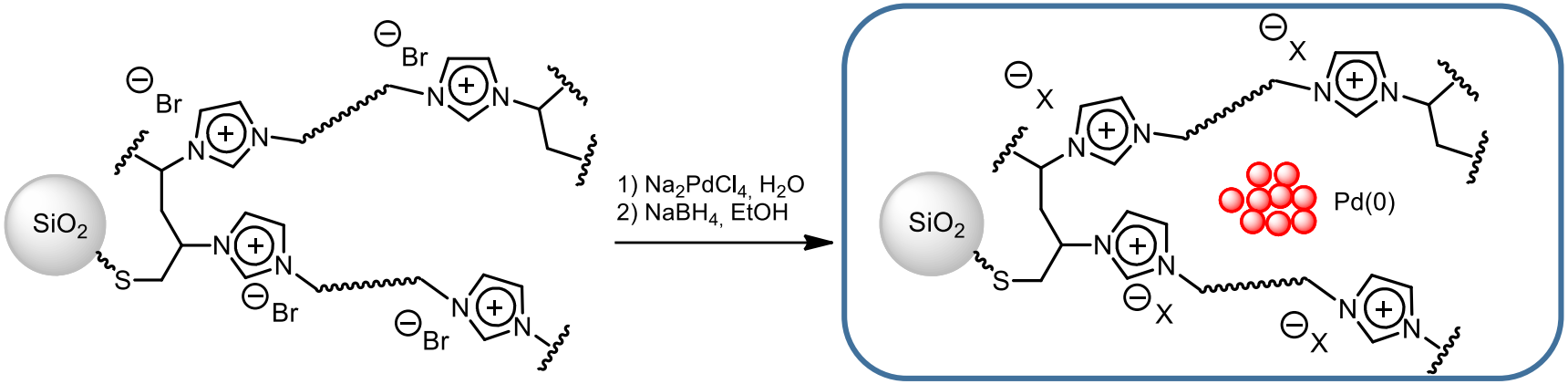
M.G. et al. *J. Mat. Chem.* **2012**, *22*, 20728-20735; *ChemPlusChem* **2014**, *79*, 421-426

- Metal nanoparticles stabilisation

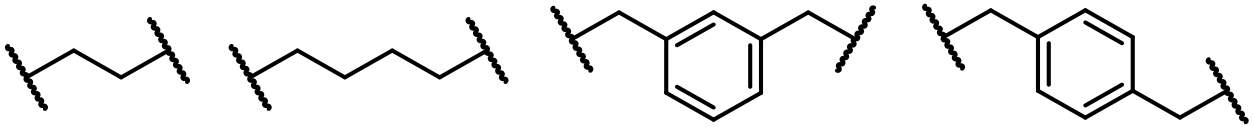


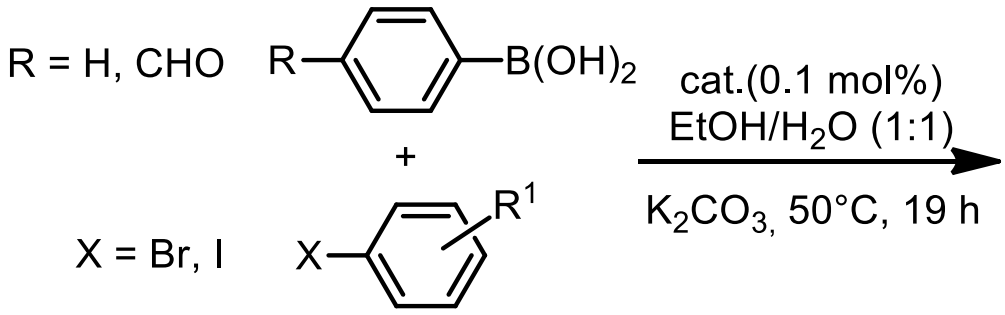
P. D. Beer et al. *Dalton Trans.* **2013**, *42*, 1385-1393

- C-C coupling reactions (Suzuki)



= linker:

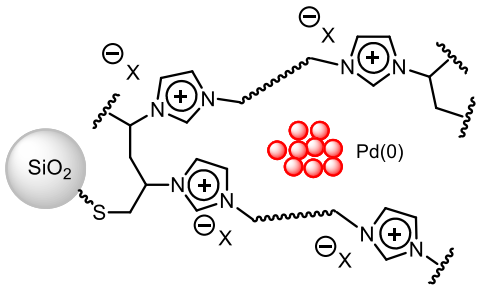


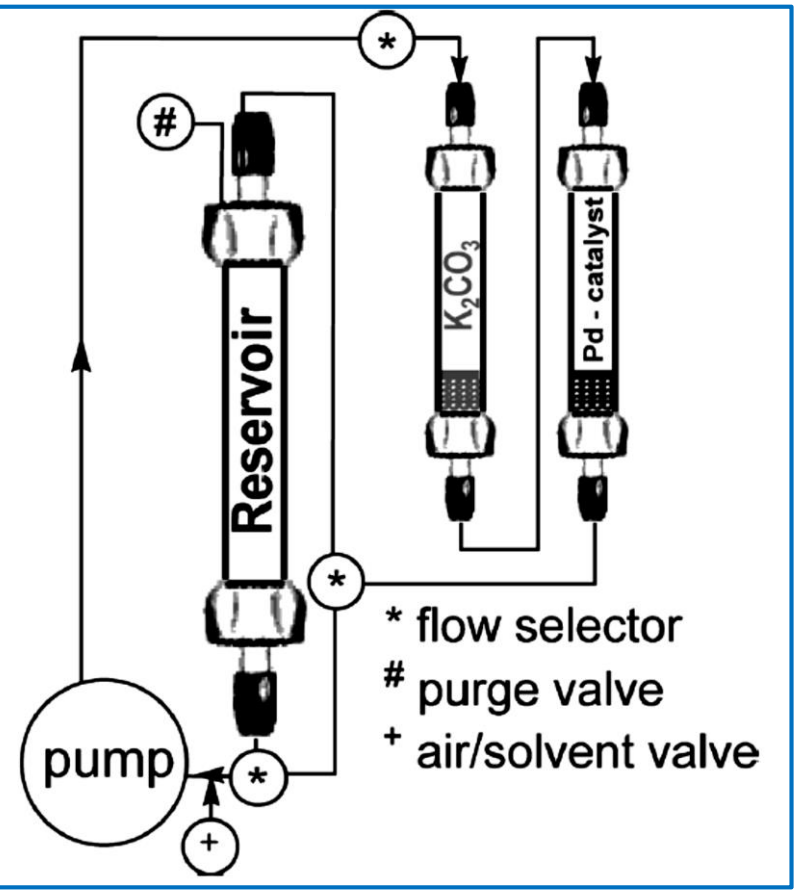


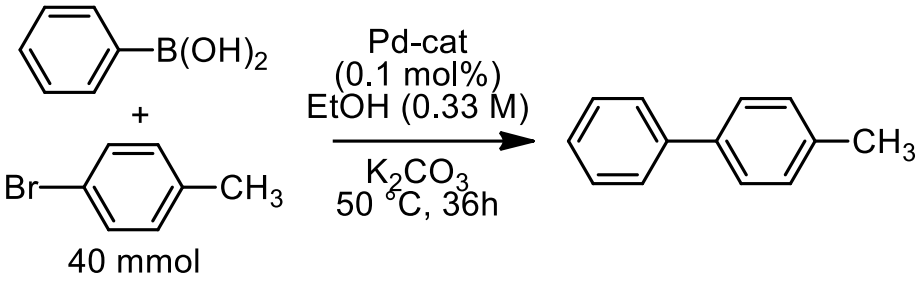
30 examples
Yields up to 99%

M.G. et al. *Adv. Synth. Catal.* **2011**, *353*, 2119-2130; *Adv. Synth. Catal.* **2013**, *355*, 2007-2018

- C-C coupling reactions (Suzuki) under flow condition







Cycle	Yield [%]
1	96
2	96
3	94
4	95

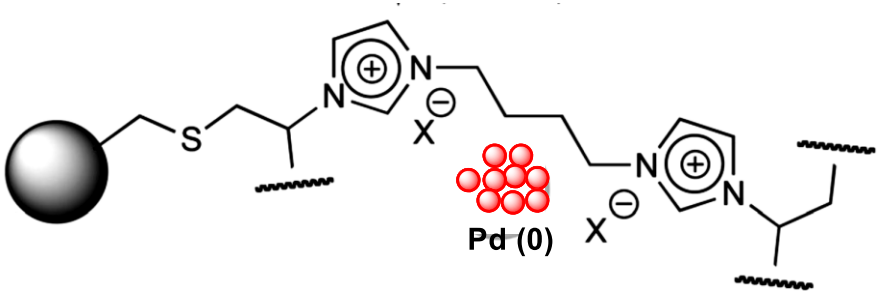
TON 3800 after 4 cycles

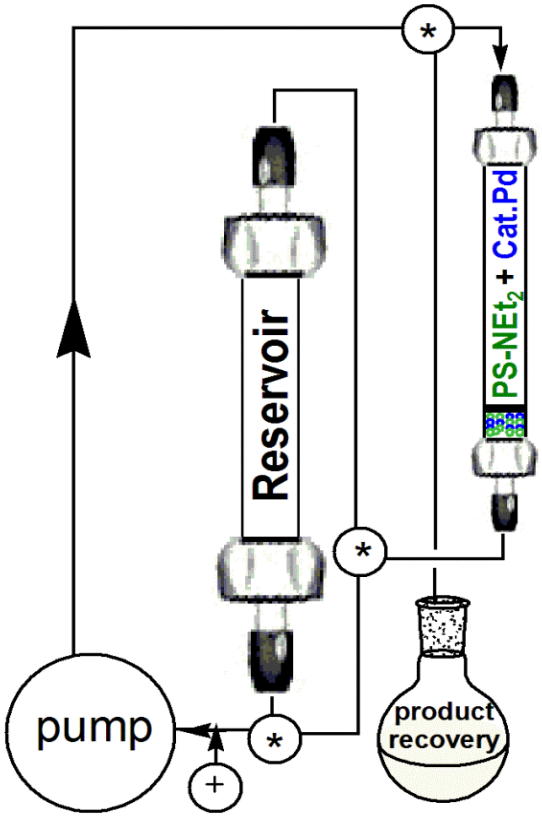
42 mg of catalyst → 27 g of 4-bromotoluene

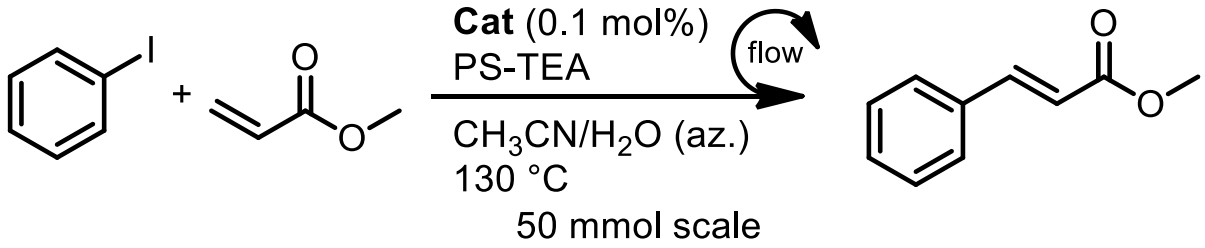
E factor = 3.55 (under flow), E factor = 3431 (under batch)

M.G. et al. *Adv. Synth. Catal.* **2011**, *353*, 2119-2130; *Adv. Synth. Catal.* **2013**, *355*, 2007-2018

- C-C coupling reactions (Heck) under flow condition

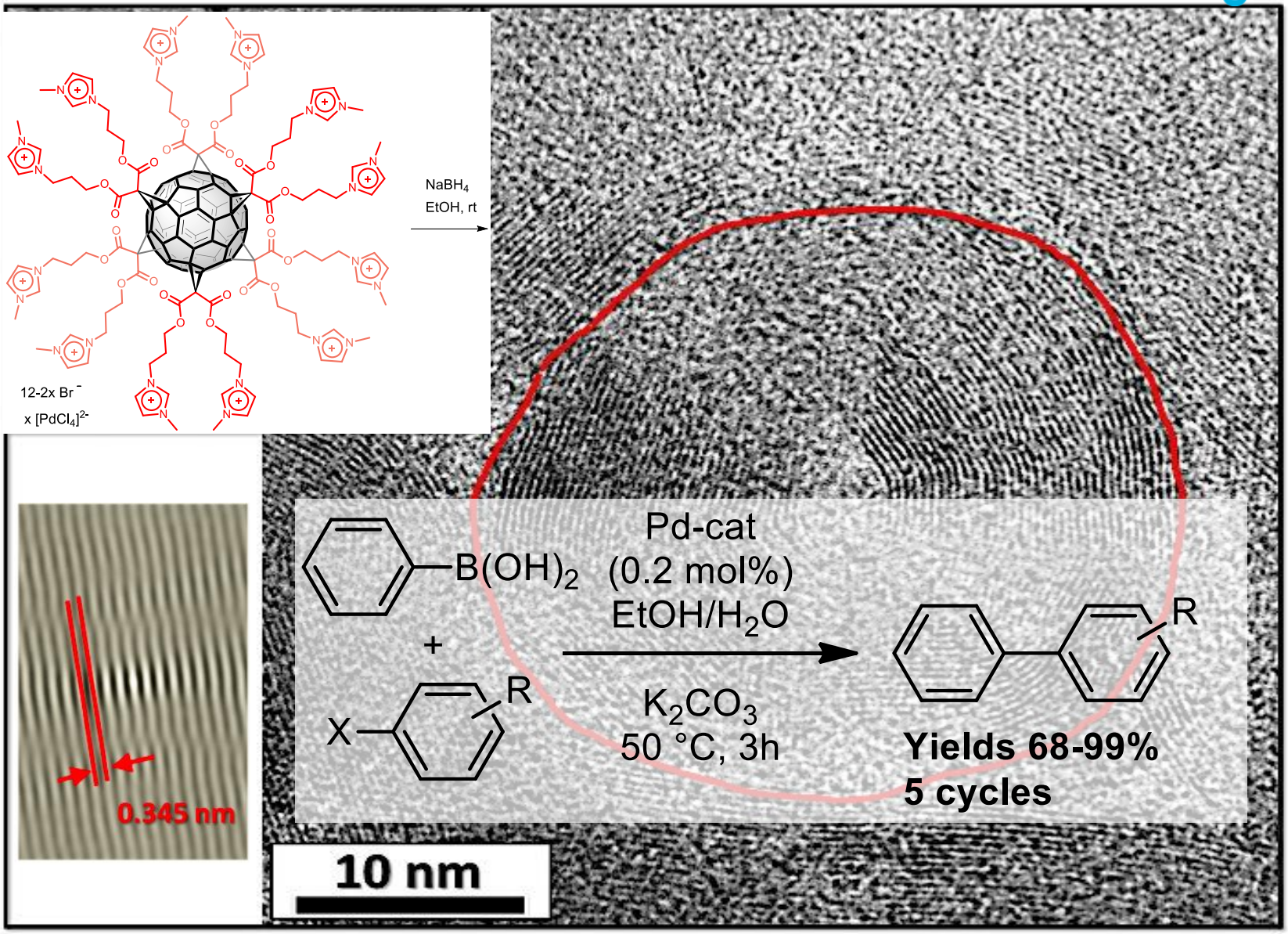






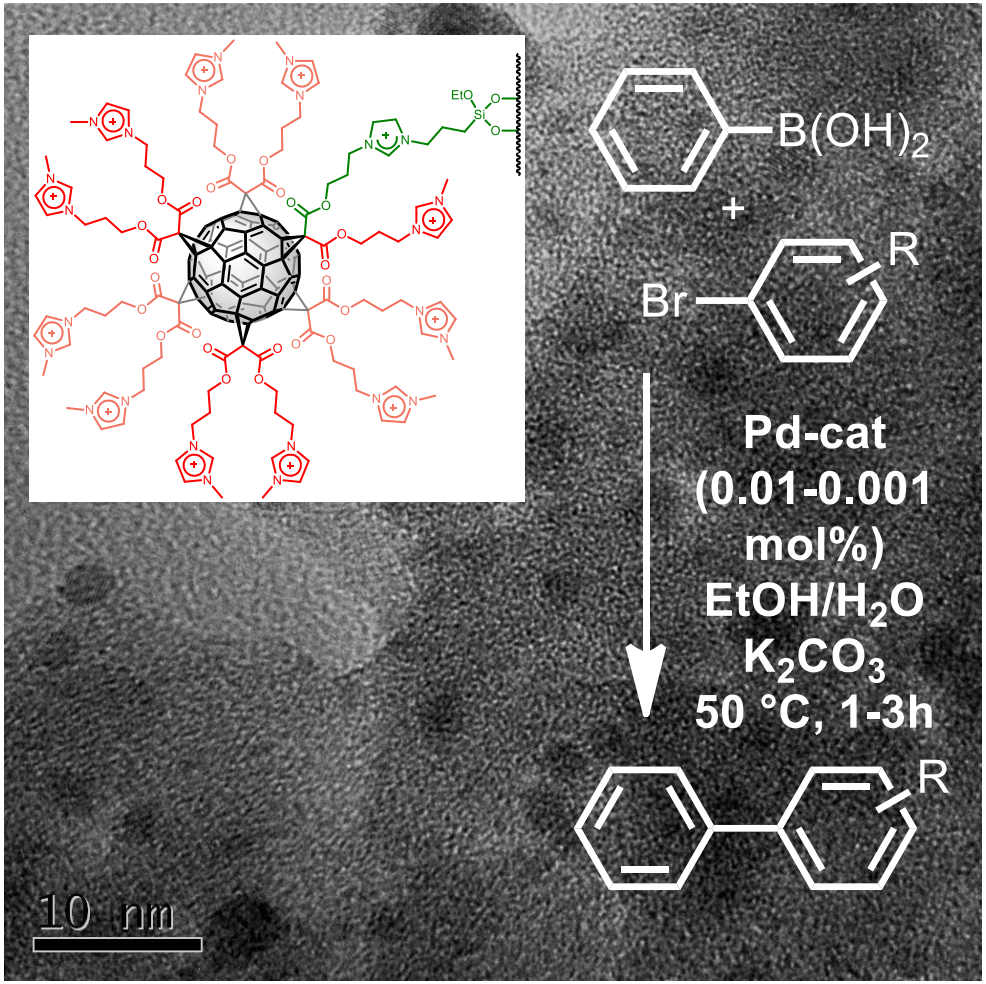
Entry	Cycle	Time (h)	Yield (%)	Pd content (ppm)
1	1	4.5	80	4.5
2	2	3	90	4.3
3	3	3	88	4.2
4	4	3	89	4.3

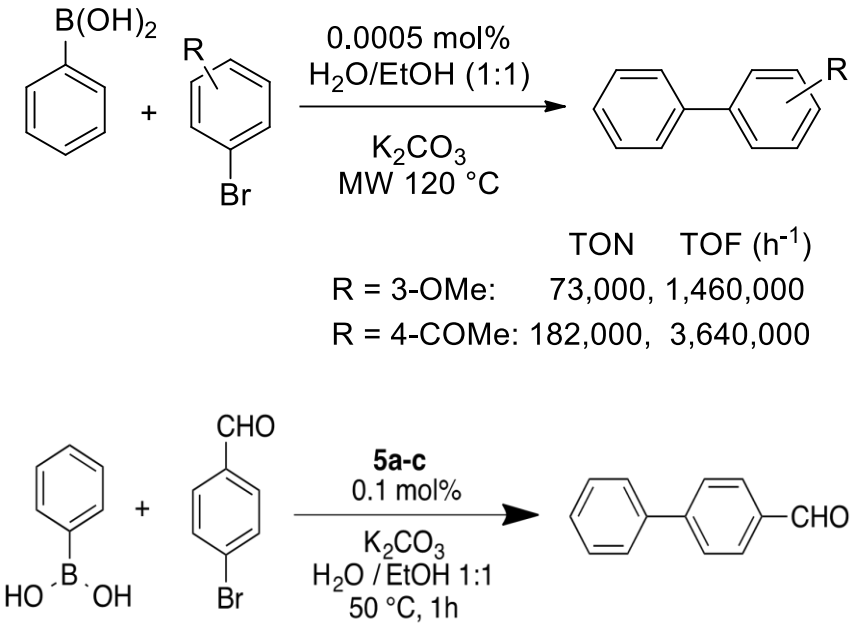
M.G. et al. *ACS Sustainable Chem. Eng.*, **2014**, *2*, 2813-2819

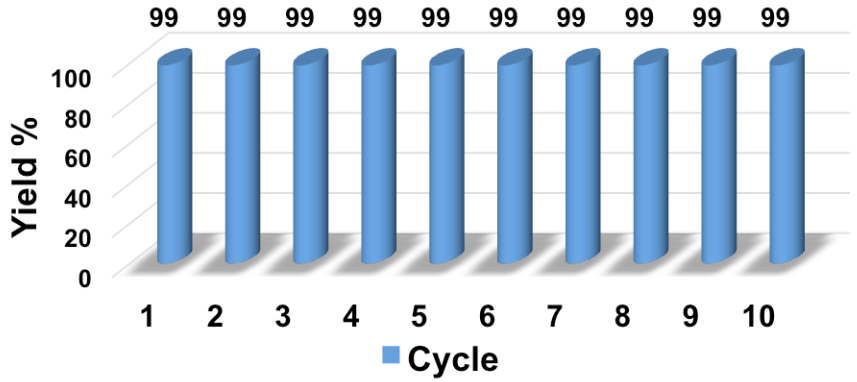


M.G. et al. *Chem. Eur. J.* **2015**, *21,* 3327-3334

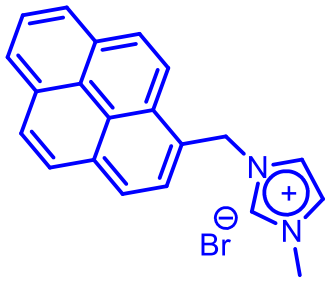
- C-C coupling reactions (Suzuki)

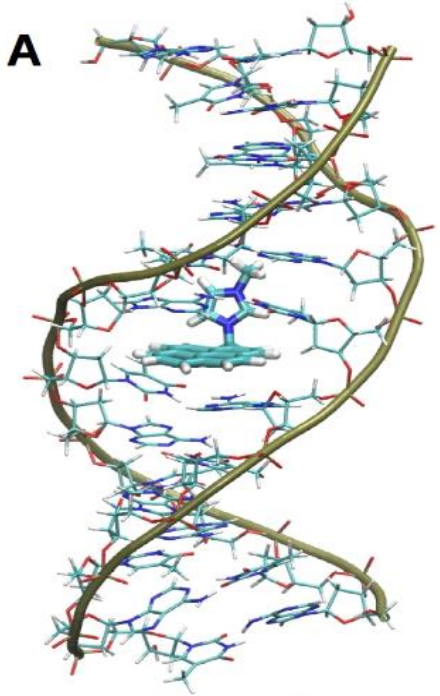


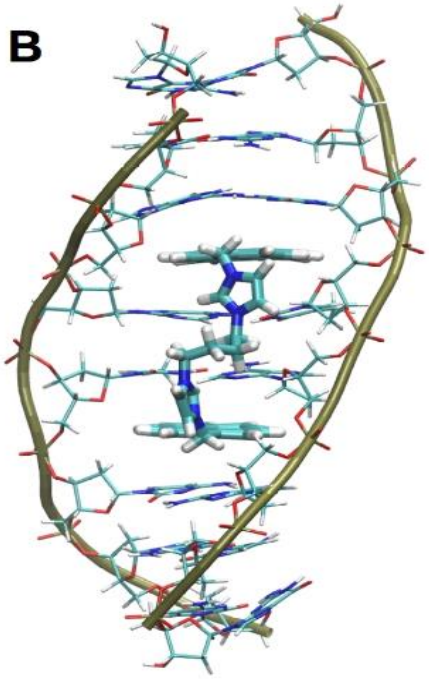


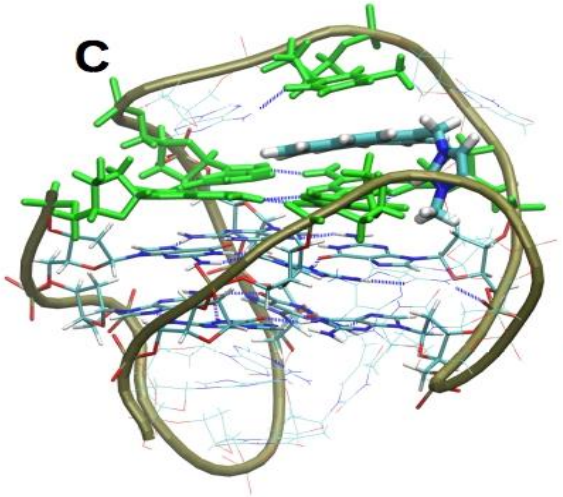


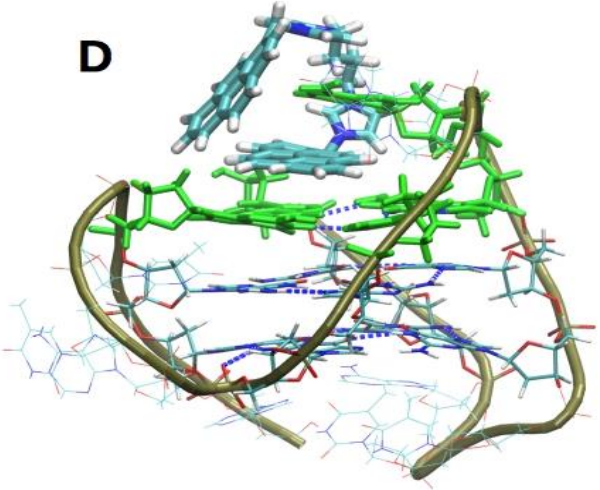
- Azolium salts as antitumor agents

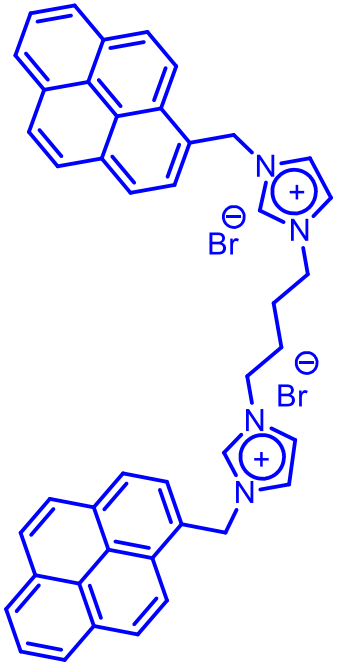












Submitted.