Sustainability and Green Chemistry at Evotec

K. Spielmann[a], C. Keignart[a], E. Taroni[a], D. Caputo[a], J. Malassis[a], S. Périé[a], S. Veau[a], J. Toum[a], E. Scherer[b]
[a]Evotec, 195 route d'Espagne, 31100 Toulouse, [b]Evotec, 40 Avenue Tony Garnier, 69007 Lyon

At Evotec – a world leading R&D partnering organization – we are committed to reduce the environmental impact of our activities, by adopting the green chemistry principles[1]. The aim is to design chemical products and processes that reduce or eliminate the use or generation of hazardous substances. Green chemistry applies across the life cycle of a chemical product (from design to disposal). Moreover, we are also engaged in energy saving to decrease the global carbon footprint of the company. Sustainability and green chemistry are implemented while maintaining our level of excellence in drug discovery.

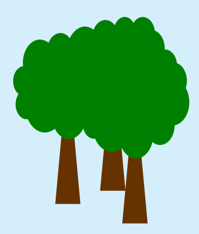
To reach our objectives, we have identified four areas of improvements. Our chemists are committed to adopt more responsible practices. We are always looking for new technologies, greener and safer alternatives. This poster is focused on two areas in continuous improvement at Evotec: solvent alternatives and purification.

SOLVENTS	PLASTIC WASTE RECYCLING	ENERGY	RAISING AWARENESS
Use safer solvents from biosources	Reduce/re-use plastic consumables	Reasonable use of electricity	12 principles of Green Chemistry[1]
Reduce use of chlorinated solvents	Encourage recycling when possible	Shut the sash when not used	Communication, posters sessions

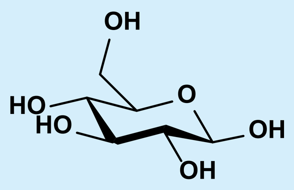
2-MeTHF (2-mehytletrahydrofuran)

Properties:
- MW: 86.14 g/mol
- BP: 80°C
- MP: -136 °C
- Aprotic solvent

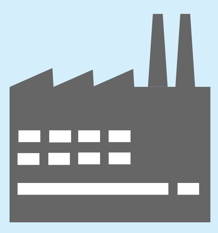
Lignocellulosic Biomass



Acid hydrolysis of cellulose and hemicellulose

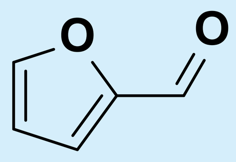


Biofine Process

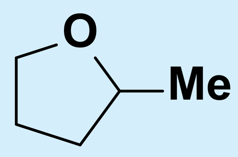


H_2 Natural gas

Hydrogenation

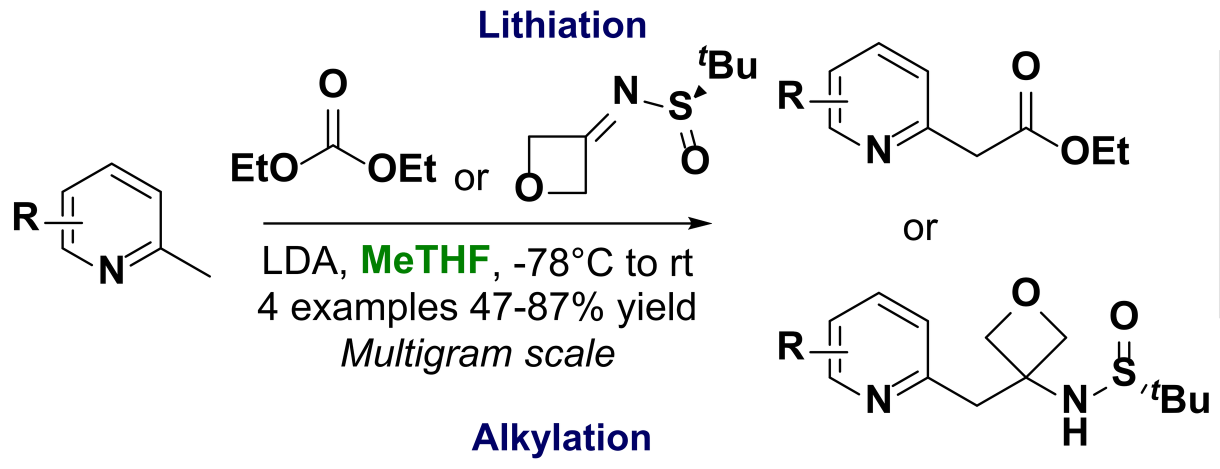


2-MeTHF

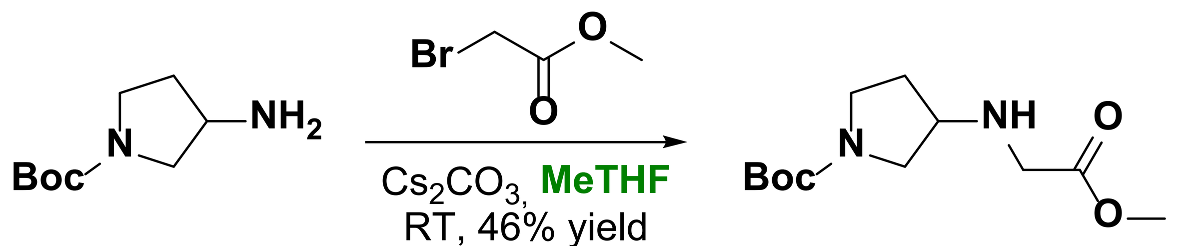


Alternative to DCM, Dioxane and THF[2]
Benefits:
- Lower peroxide formation than THF (safe alternative)
- Limited miscibility with water (easier work-up)
- Compatible with scale-up
- Low heat vaporization (less solvent loss during reaction reflux)
- Derived from renewable resources such as corncobs

Lithiation

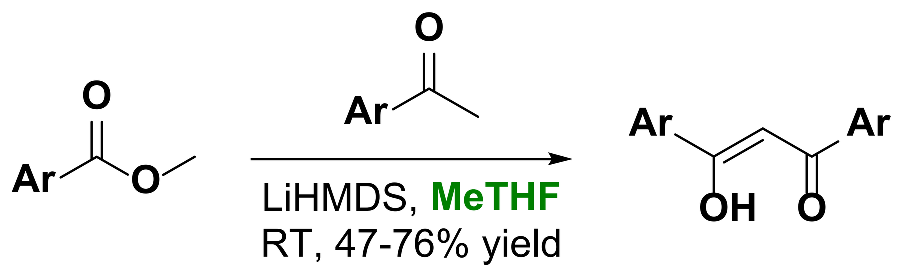


Alkylation

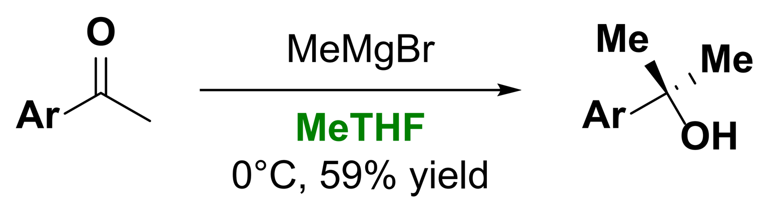


Reaction reported in DMF on SciFinder (no yield)

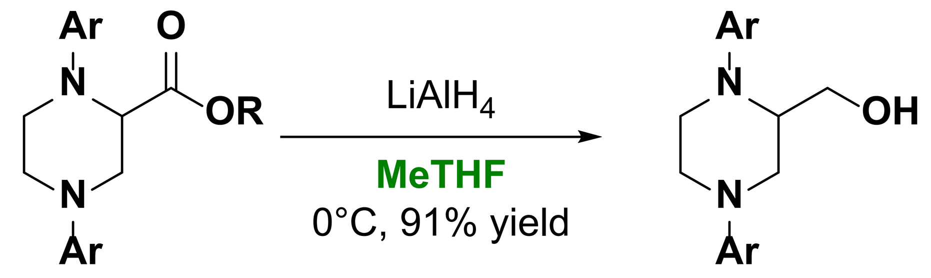
Claisen condensation



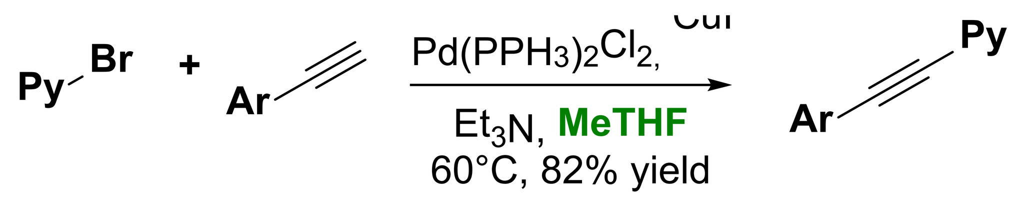
Grignard addition



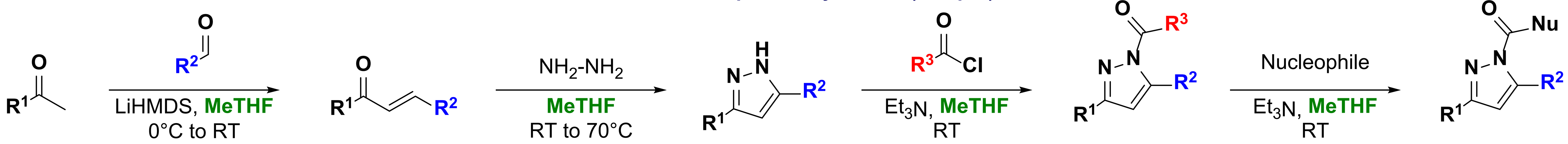
Reduction



Sonogashira cross coupling



Sequential synthesis (one pot)

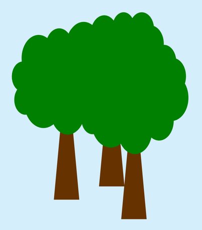


- 5 steps carried out
- 9 examples
- Overall yield: 5-55%

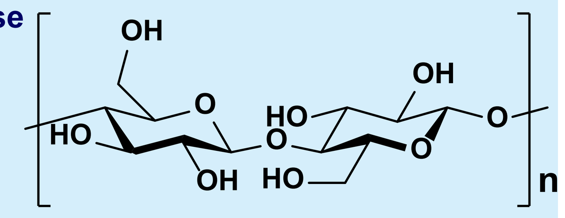
DMI (Dimethyl isosorbide)

Properties:
- MW: 174.19 g/mol
- BP: 235 °C
- MP: -70 °C
- Aprotic solvent

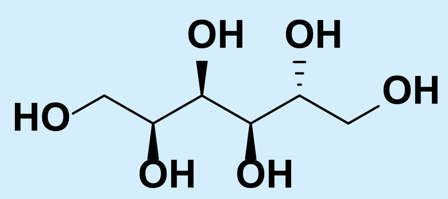
Biomass



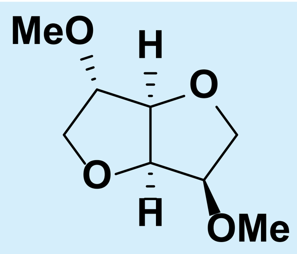
Cellulose



Sorbitol



DMI

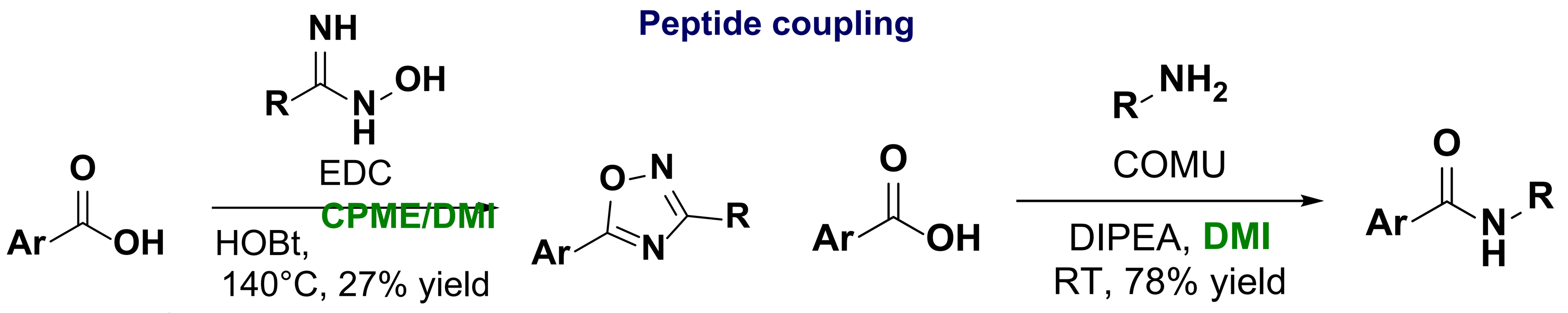


Hydrolysis/hydrogenation

Dimethyl carbonate

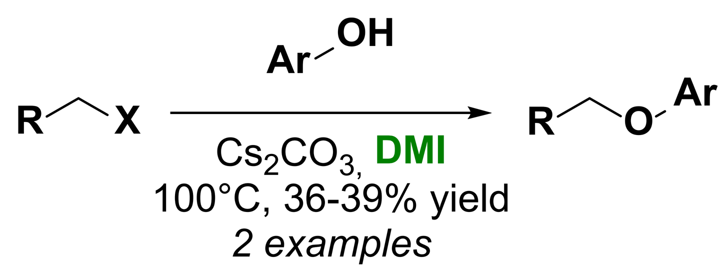
Alternative to DMSO, DMF and NMP[3]
Benefits:
- Water soluble (easily removed during work-up)
- Dipolarity/polarizability similar to DMF, DMAc (close properties)
- Compatible with strong bases (e.g. NaH) and strong acids
- Low toxicity (used in cosmetic and formulation)
- Derived from renewable feedstocks (cellulose, sorbitol)

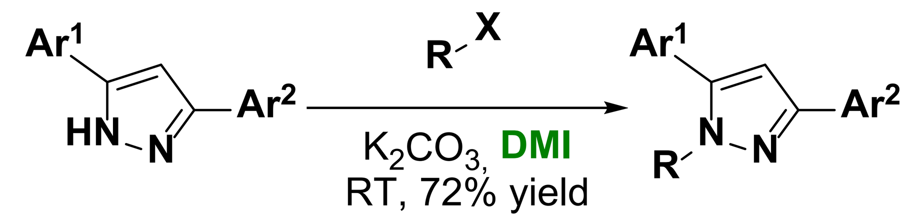
Peptide coupling



Similar yield obtained with DMF

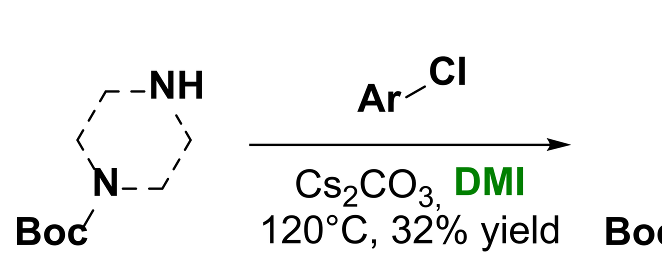
Alkylation



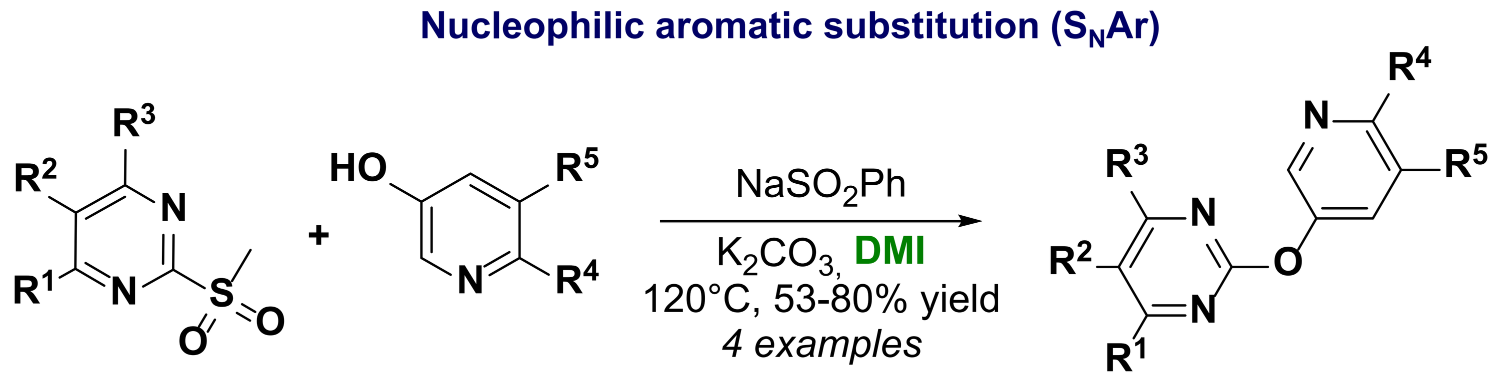


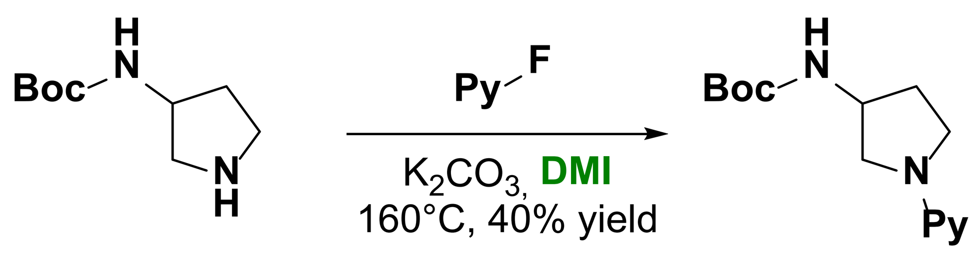
Product collected by precipitation after water addition

Nucleophilic aromatic substitution (S_NAr)



Improved yield compared to DMF



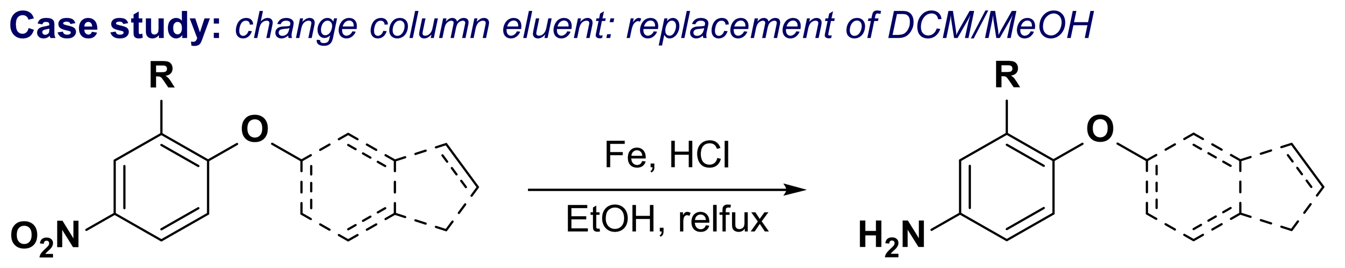


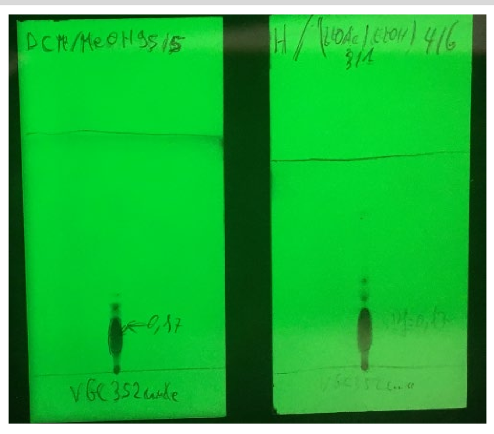
Similar yield obtained with DMF, faster conversion

Rethinking purification, DCM reduction[4]

Avoiding Chromatography		
One pot or telescope?	Recrystallization / Trituration	
Alternative to traditional Flash Chromatography		
SFC	Reverse-phase chromatography	Ion exchange resins
Making Flash Chromatography more sustainable		
Solvent choice	Efficiency	Reuse and recycling

Case study: *change column eluent: replacement of DCM/MeOH*





DCM free Challenge!

1st batch: 0 to 6% MeOH in DCM → impure product
2nd batch: 10-60% (EtOAc/EtOH 3:1) in Heptane → pure product
Work-up: *Avoid the use of DCM for extraction (good alternatives: EtOAc, MeTHF or EtOAc/iPrOH (3:1) for difficult extraction)*

1) Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press: New York, **1998**, 30, By permission of Oxford University Press
2) [a]Coby J. Clarke, Wei-Chien Tu, Oliver Levers, Andreas Bröhl, and Jason P. Hallett *Chemical Reviews* **2018**, 118, 747 [b]Pace, V., Hoyos, P., Castoldi, L., Domínguez de María, P. and Alcántara, A.R. *ChemSusChem* **2012**, 5, 1369 [c]Andrew Jordan, Callum G. J. Hall, Lee R. Thorp, and Helen F. Sneddon *Chemical Reviews* **2022**, 122, 6749
3) [a]Aricò, F.; Tundo, P. *Beilstein J. Org. Chem.* **2016**, *12*, 2256 [b]F. Aricò, A. S. Aldoshin, P. Tundo, *ChemSusChem* **2017**, 10, 53 [c]Russo F., Galiano F., Pedace F., Aricò F., and Figoli A. *CS Sustainable Chem. Eng.* **2020**, 8, 1, 659
4) [a]Peterson E.A., Dillon B., Raheem I., Richardson P., Richter D., Schmidte R. and Sneddon H.F. *Green Chem.*, **2014**, 16, 4060 [b]Taygerly J.P., Miller L.M., Yeec A. and Peterson E.A. *Green Chem.*, **2012**, 14, 3020 [c]MacMillan D.S., Murray J., Sneddon H.F., Jamiesona C. and Watson A.J.B. *Green Chem.*, **2012**, 14, 3016