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CoEBio3

Towards Total Biocatalytic Synthesis

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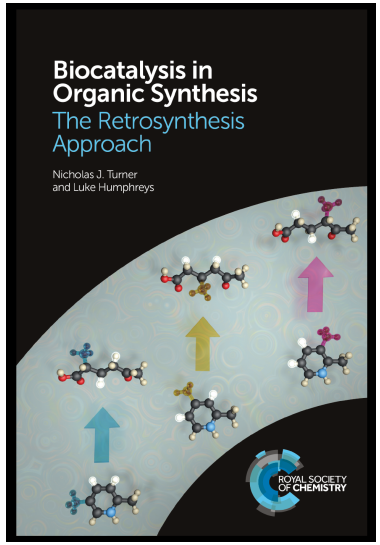
Merck
Rahway, NJ, USA
22nd Aug 2018



Biocatalytic retrosynthesis

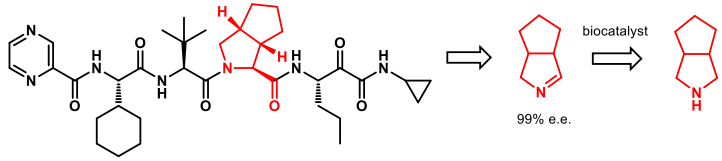
commentary

Biocatalytic retrosynthesis

Nicholas J Turner & Elaine O'Reilly

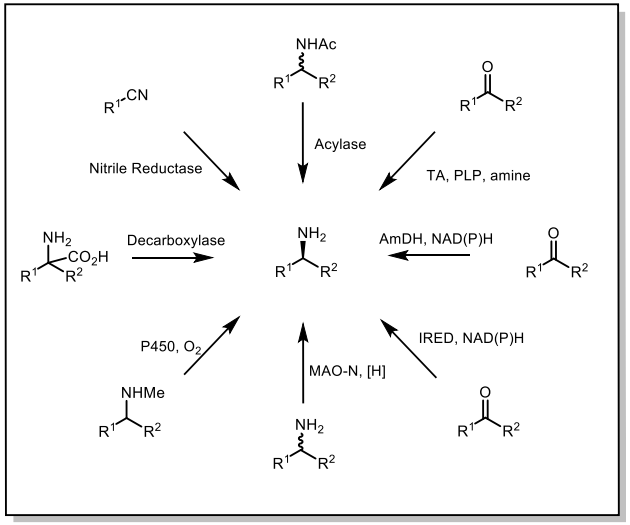
The recent development of a broad range of biocatalysts that can be applied in organic synthesis has brought into focus the need to rethink the way in which organic target molecules might be constructed in the future. To aid synthetic chemists in identifying where biocatalysts might be usefully applied, we propose that guidelines and rules for 'biocatalytic retrosynthesis' be developed and that this new approach be embedded in the future training and education of organic chemists.

Telaprevir (Incivek) launched May 2011 for Hepatitis C



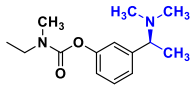
***Nature Chem. Biol.*, 2013, *9*, 285-288; *Angew. Chem. Int. Ed.*, 2017, *56*, 8942-8973 (with Erick Carreira).**

Retrosynthesis: 1º amines

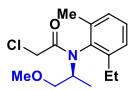


***Biocatalysis in organic synthesis: The retrosynthesis approach*, RSC. 2018, p.279.**

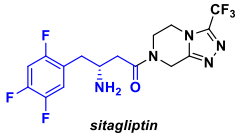
1º, 2º, 3º – acylic amines



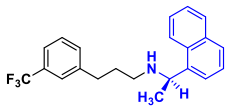
rivastigmine (Parkinson's)



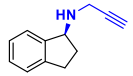
metolachlor (agrochemical)



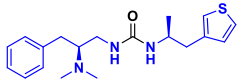
sitagliptin (diabetes)



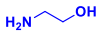
cinacalcet (renal disease)



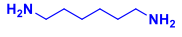
rasagiline (Parkinson's)



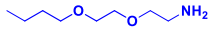
PZM21 (opioid)



ethanolamine (monomer)



hexamethylene diamine (nylon)

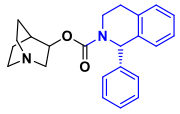


BDG-amine (BASF)

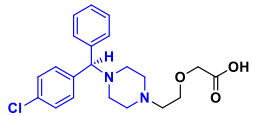
N-heterocycles (saturated and unsaturated)

DABCO (polyurethane)

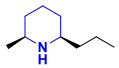
N-methyl pyrrolidine (solvent)



solifenacin (urinary tract)

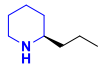


levocetirizine (anti-histamine)

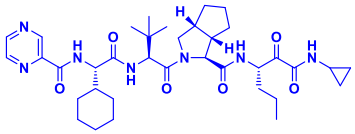


dihydropinidine (pheromone)

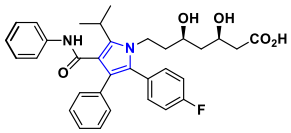
(S)-eleagnine (chocolate, cocoa)



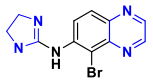
(R)-coniine (hemlock)



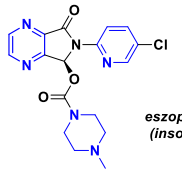
telaprevir (hepatitis C)



atorvastatin (cholestrol lowering)

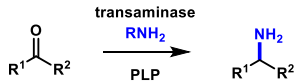


brimonidine (glaucoma)

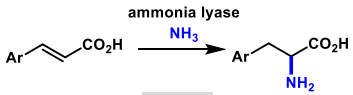


eszopiclone (insomnia)

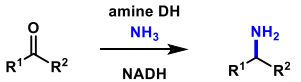
(Asymmetric) biocatalytic amine toolbox



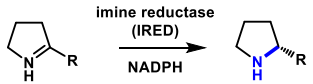
202-(*S*) & 9-(*R*)



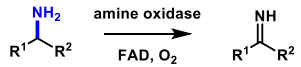
21-(*S*)



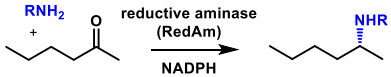
10-(*S*)



280-(*S*) & 120-(*R*)



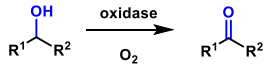
97-(*S*) & 38-(*R*)



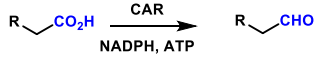
5-(*S*) & 5-(*R*)

CoEBio3 collection
Prozomix

Biocatalytic toolbox



20 (3 families)



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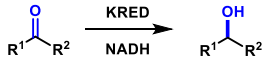
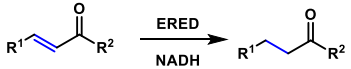


(*S*) & (*R*) Prozomix



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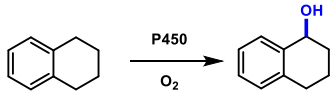
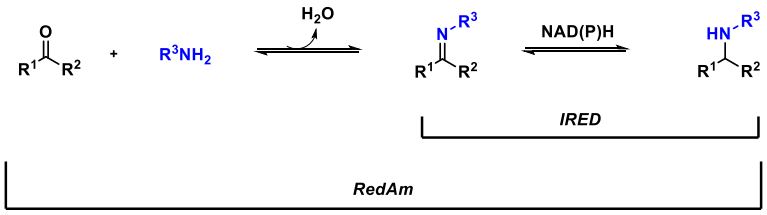


50

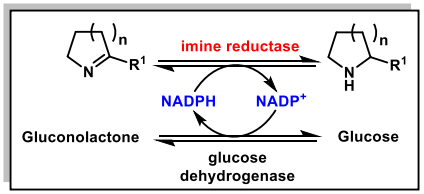
CoEBio3 collection
Prozomix

Imine Reductases (IREDs)
&
Reductive Aminases (RedAms)

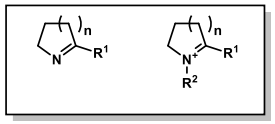


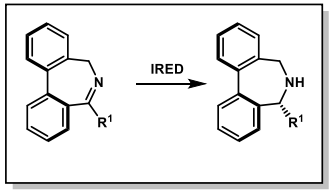
Imine reductases (IREDs)

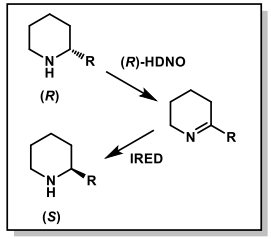
Whole cell and isolated enzyme imine reduction

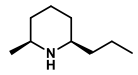


K. Mitsukura *et al.*, *Org. Biomol. Chem.*, 2010, *8*, 4533.

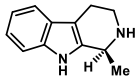




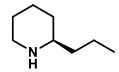




dihydropinidine (pheromone)



(*S*)-Eleagnine (chocolate, cocoa)

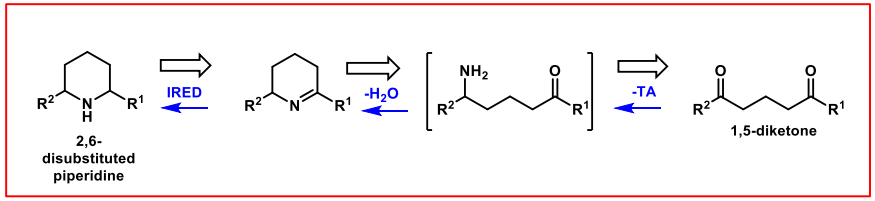


(*R*)-coniine (hemlock)

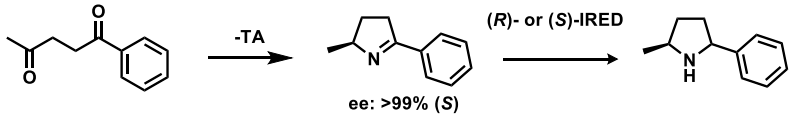
ChemCatChem, 2013, *5*, 3505.

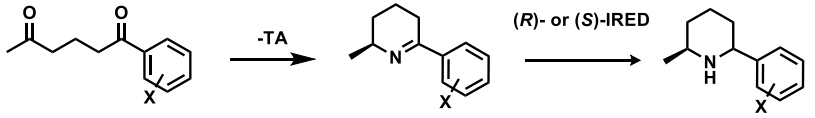
ACS Catal, 2016, *6*, 3753.
ACS Catal, 2016, *6*, 3880.

Cascade reactions with IREDs



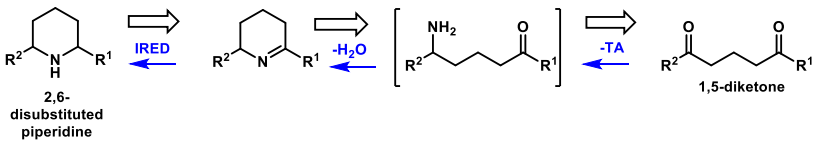
ω-TA - IRED tandem reactions

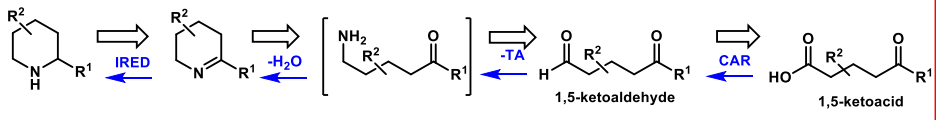




S.P. France, S. Hussain, F. Leipold, A. Hill *et al.*, *ACS Catal.*, 2016, *6*, 3753.

Cascade reactions with IREDs

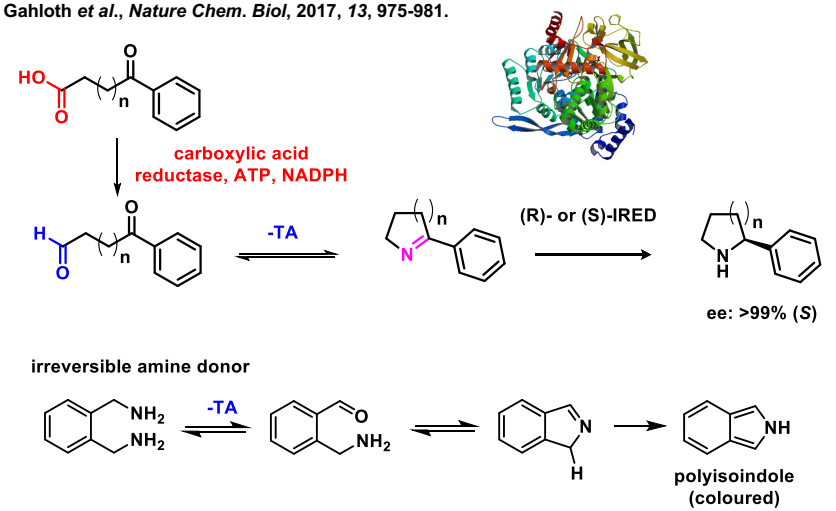




S.P. France, S. Hussain, F. Leipold, A. Hill *et al.*, *ACS Catal.*, 2016, *6*, 3753.

CAR - ω-TA - IRED tandem reactions

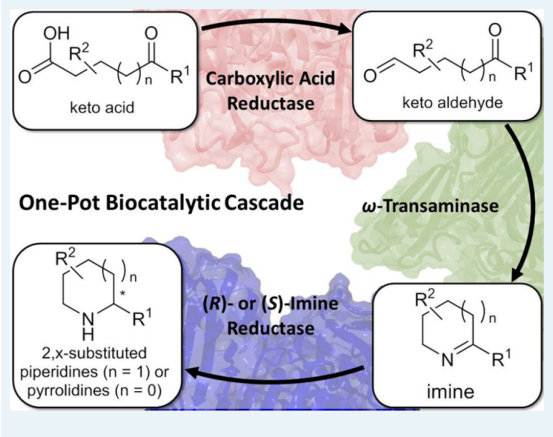
D. Gahloth *et al.*, *Nature Chem. Biol*, 2017, *13*, 975-981.



O'Reilly *et al.*, *Angew. Chem. Int. Ed.* 2014, 53, 10714 - 10717 (VIP).

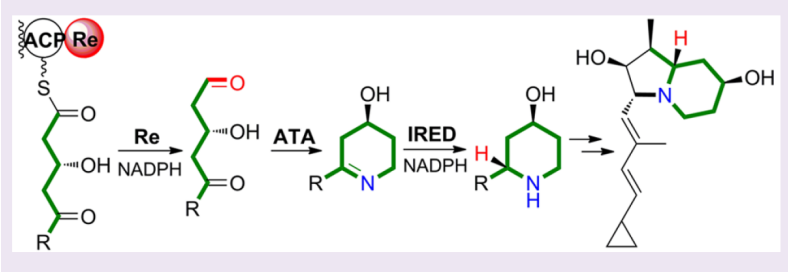
S.P. France, S. Hussain, F. Leipold, A. Hill *et al.*, *ACS Catal.*, 2016, *6*, 3753.

Synthesis of chiral piperidines (laboratory)



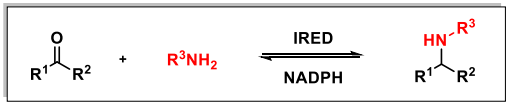
S.P. France, S. Hussain, F. Leipold, A. Hill *et al.*, *ACS Catal.*, 2016, *6*, 3753.

Biosynthesis of chiral piperidines (Nature)



H. Peng, *et al.*, ACS *Chem. Biol.*, 2016, *11*, 3278-3283.

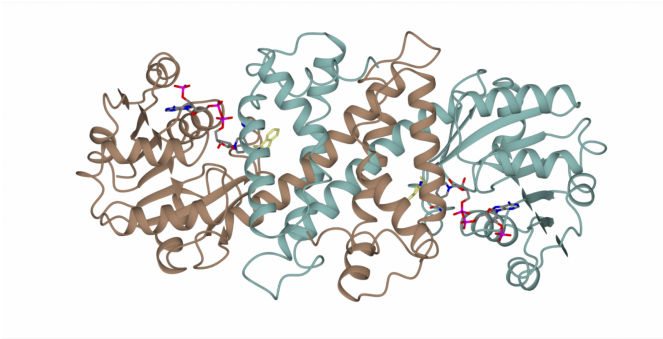
Reductive amination using IREDs?



- high enzyme loading
- high amine concentration (>20:1)
- narrow substrate scope
- imine formation not enzyme catalysed

1. T. Huber *et al.*, *ChemCatChem*, 2014, *6*, 2248.
2. P.N. Scheller *et al.*, *ChemCatChem*, 2015, *7*, 3239.
3. D. Wetzl *et al.*, *ChemCatChem*, 2016, *8*, 2023.

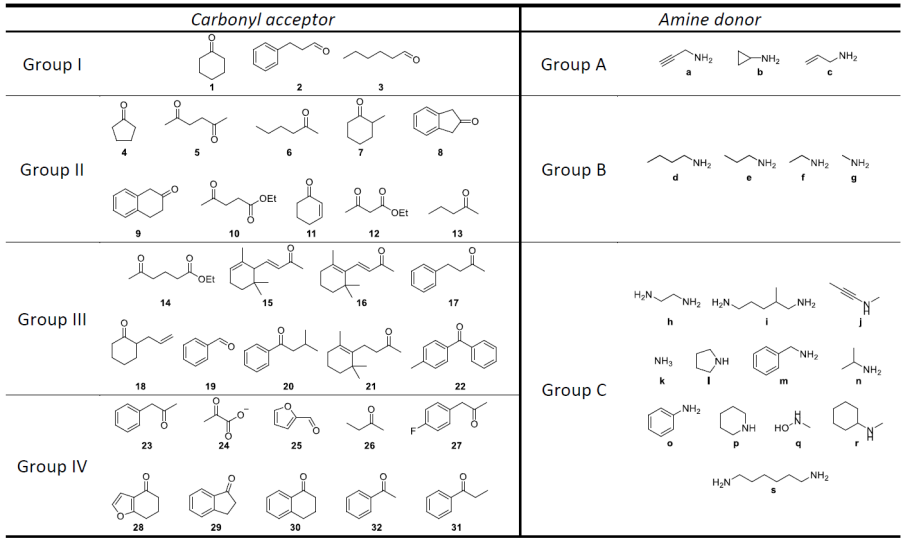
AspRedAm = Reductive Aminase



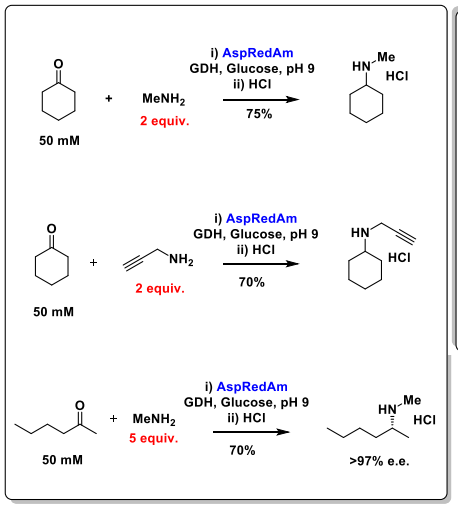
- 'IRED' from *Aspergillus oryzae*
- NADPH dependent oxidoreductase
- Sequence similarity and structural homology to IREDs

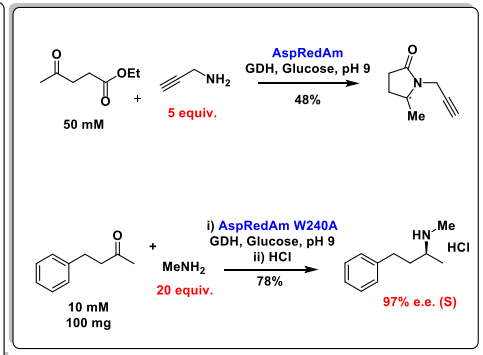
G. Aleku, S.P. France *et al.*, *Nature Chem.*, 2017, *9*, 961-969.

Reactivity chart



Reductive Aminase (RedAm) from A. oryzae





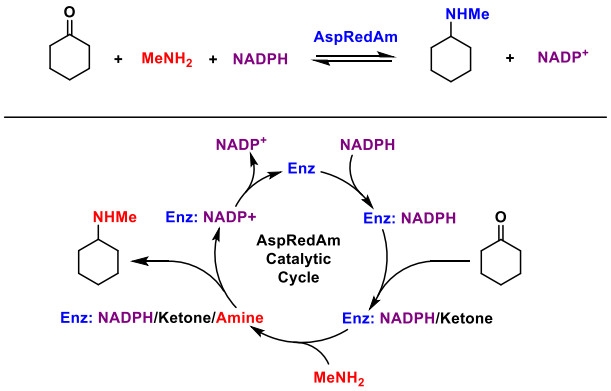
Turnover number (TON) of >30,000

Turnover frequency (TOF) of up to 300 min^{-1}

[S] up to 0.4M amine & 0.2M ketone with new homologues

G. Aleku, S.P. France *et al.*, *Nature Chem.*, 2017, *9*, 961-969.

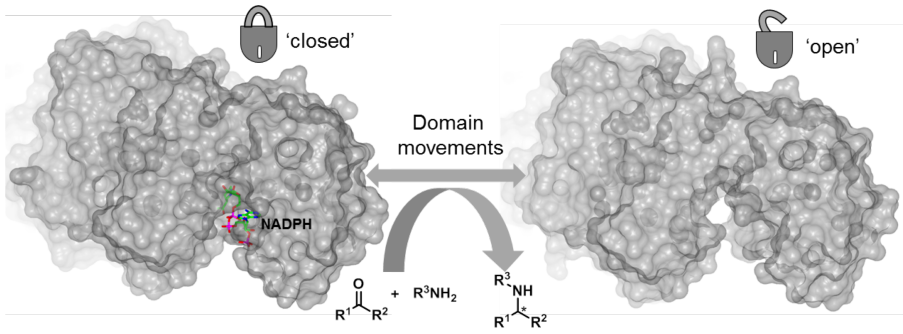
Kinetics of reductive amination with AspRedAm



Formation of ternary complex - sequential binding – ordered Ter bi mechanism

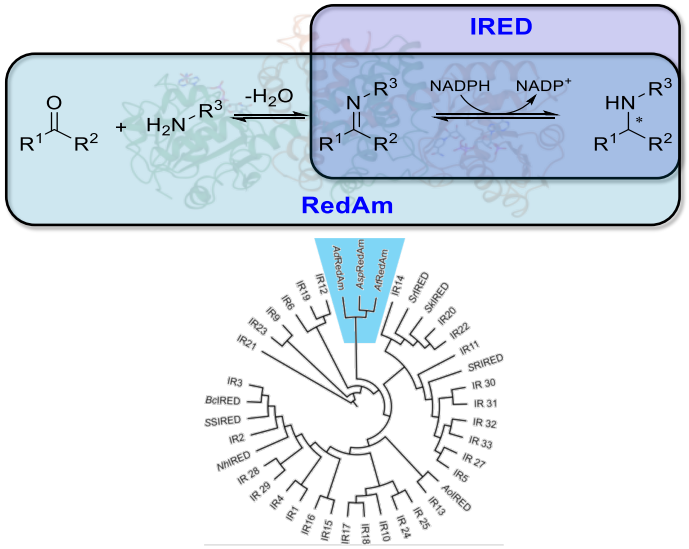
G. Aleku, S.P. France *et al.*, *Nature Chem.*, 2017, *9*, 961-969.

Mechanism of AspRedAm?



Mahima Sharma, Juan-Mangas-Sanchez, Gideon Grogan

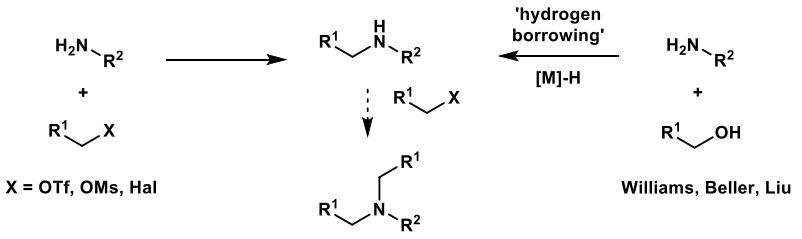
Relationship of RedAms to IREDs

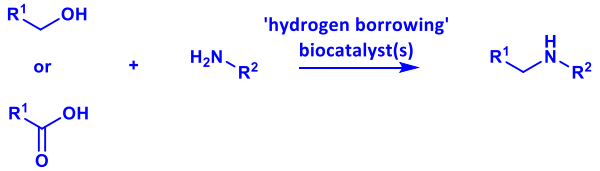


G.-D. Roiban *et al.*, *ChemCatChem.*, 2017, DOI: 10.1002/cctc.201701379 (GSK).
S.P. France *et al.*, *ChemCatChem.*, 2017, DOI: 10.1002/cctc.201701408 (Pfizer).

Redox neutral cascades for amine alkylation

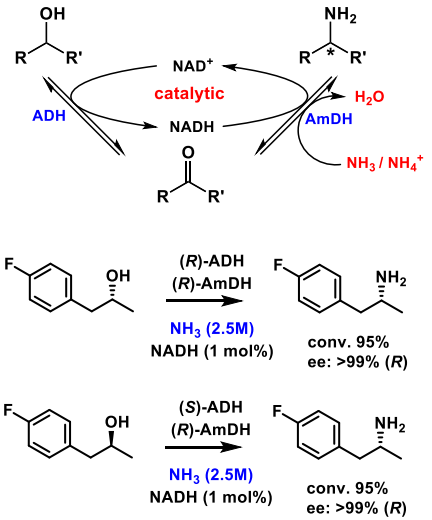
- Genotoxic alkylating reagents
- Further alkylation of amine product





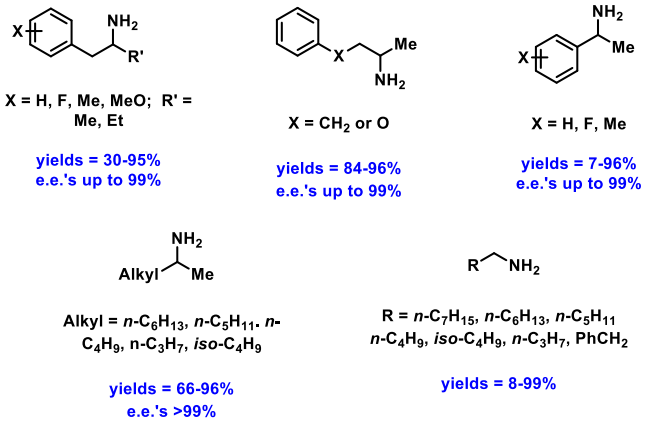
review on 'hydrogen borrowing': J. Leonard *et al.*, *Org. Proc. Res. Dev.*, 2015, *19*, 1400 - 1410.

Biocatalytic asymmetric hydrogen borrowing



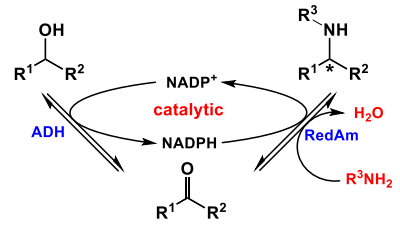
F.G. Mutti. T. Knaus, N.S. Scrutton, M. Breuer and N.J. Turner, *Science*, 2015, *349*, 1525-1529.
See also: F.-F. Chen, Y.-Y. Li, G.-W. Zheng, J.-H. Xu, *ChemCatChem*, 2015, *7*, 3838-3841.

Biocatalytic asymmetric hydrogen borrowing



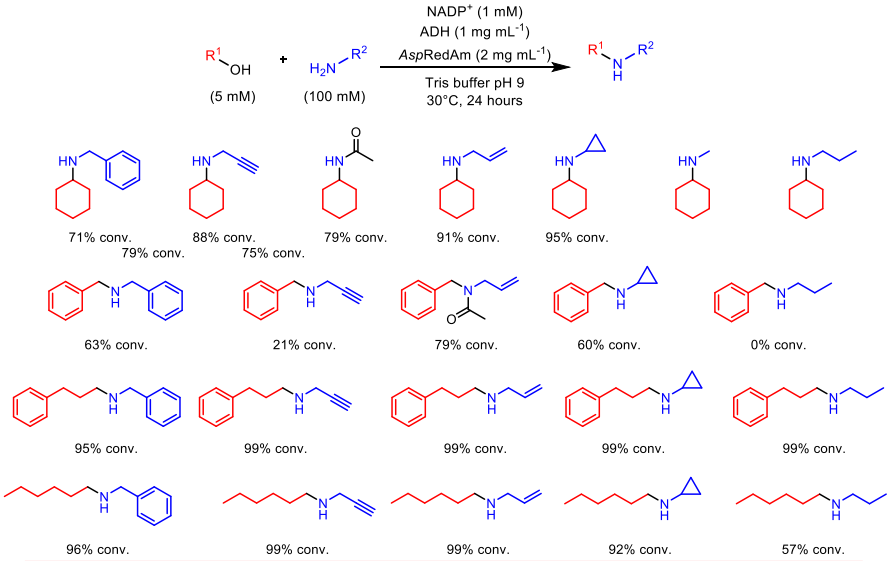
F.G. Mutti. T. Knaus, N.S. Scrutton, M. Breuer and N.J. Turner, *Science*, 2015, *349*, 1525-1529.

2º Amine synthesis via hydrogen borrowing?



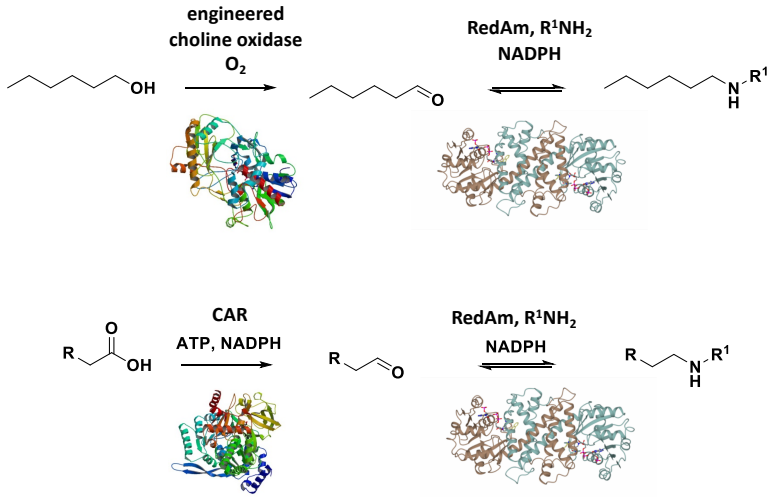
S.L. Montgomery, J. Mangas-Sanchez *et al.*, *Angew. Chem. Int. Ed.*, 2017, *56*, 10491-10494.

ADH/AspRedAm hydrogen borrowing



S.L. Montgomery, J. Mangas-Sanchez *et al.*, *Angew. Chem. Int. Ed.*, 2017, *56*, 10491-10494.

Choline oxidase or CAR + RedAm



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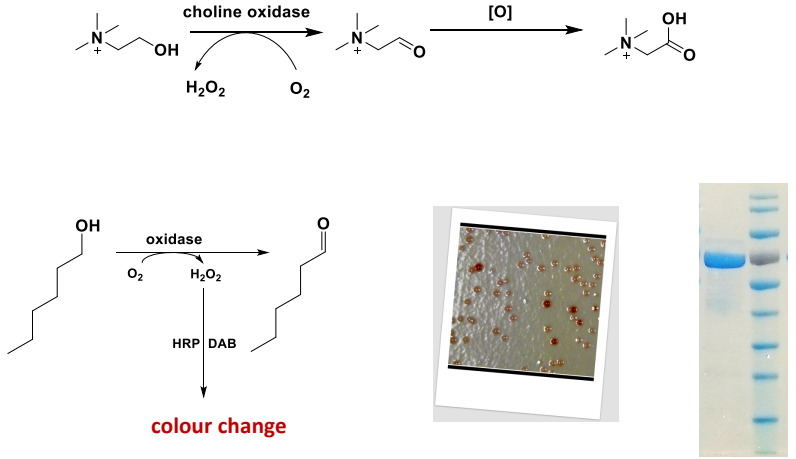
Engineering choline oxidase



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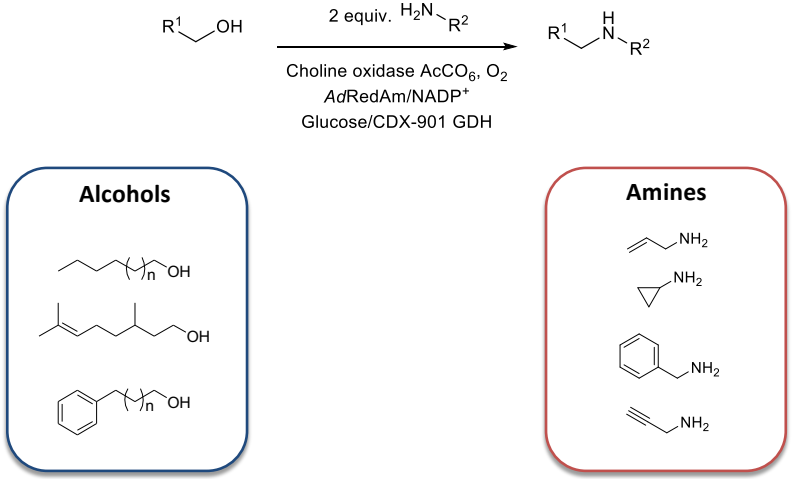
Choline oxidase + RedAm



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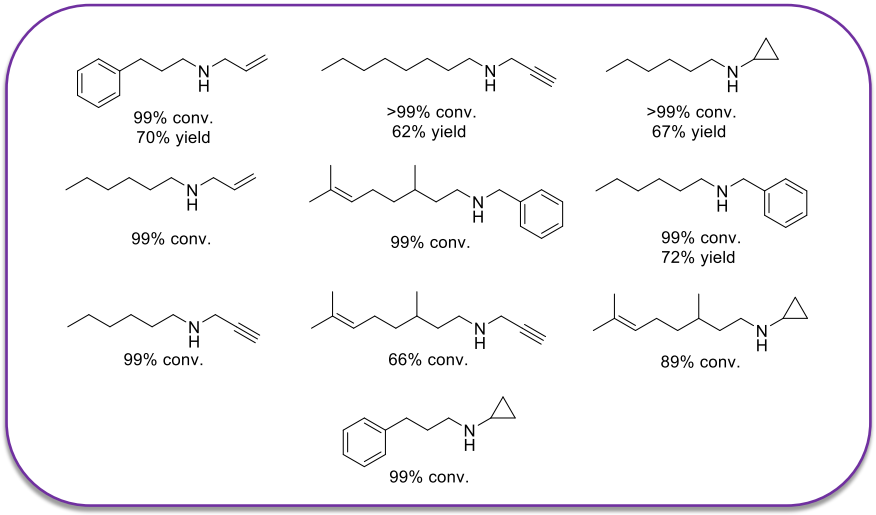
Choline oxidase + RedAm



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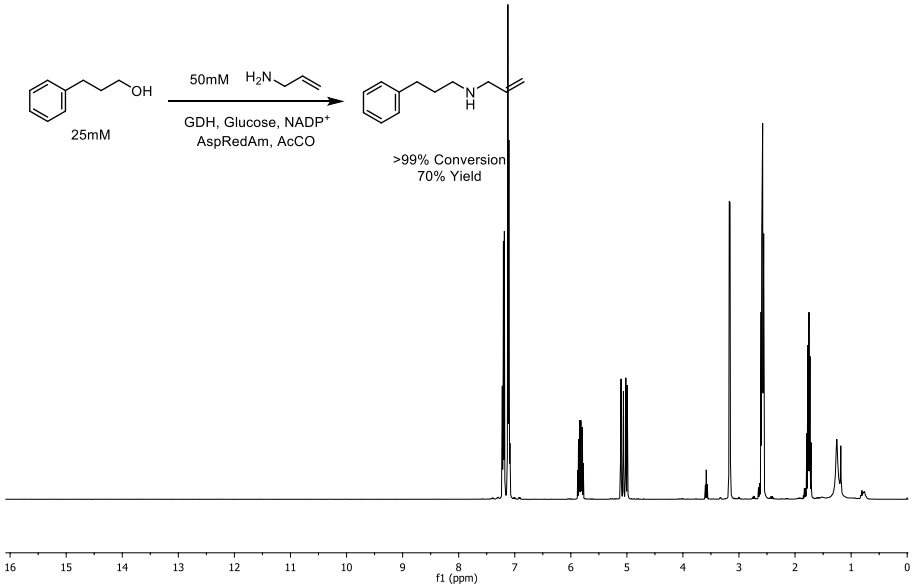
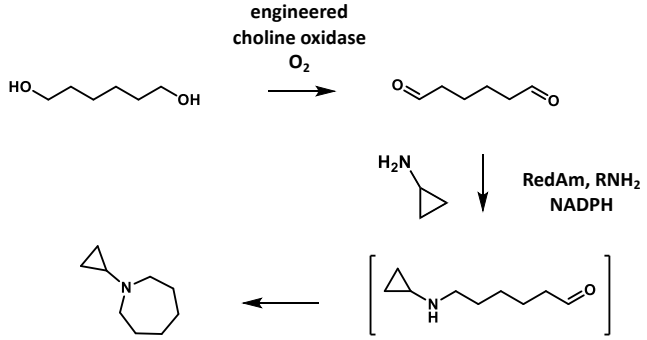
Preparative scale reactions



1,n-diols with choline oxidase + RedAm



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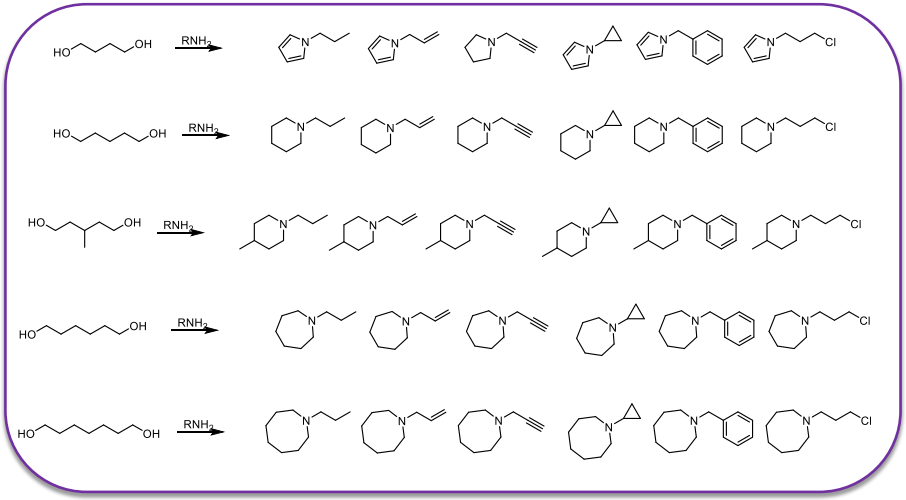
Synthesis of 5-, 6-, 7-, 8-membered heterocycles



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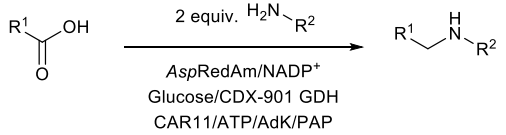
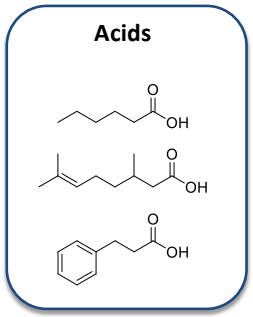
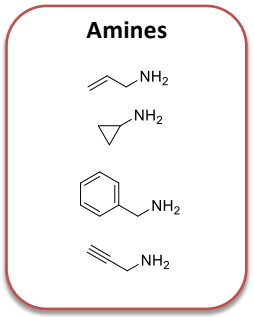
N-Alkylation of amines with carboxylic acids







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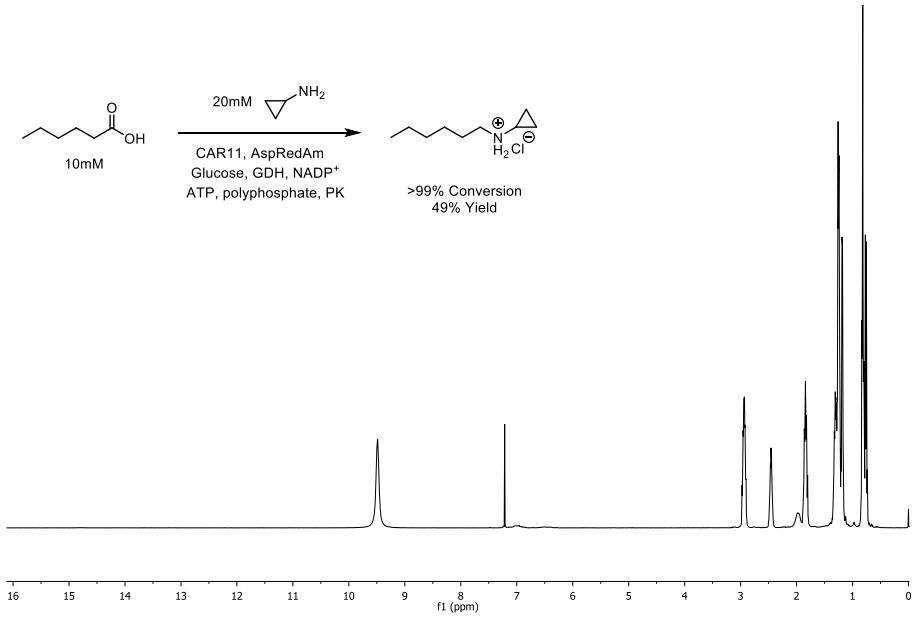
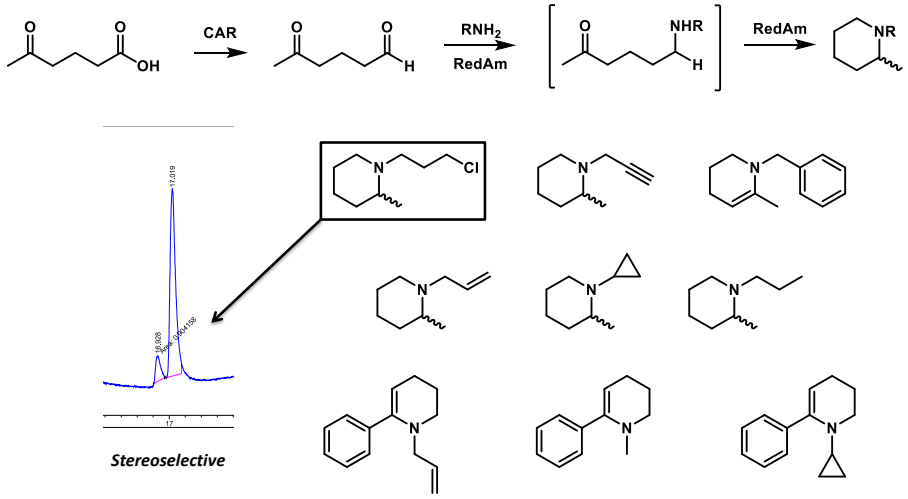
Preparative scale reactions



Heterocyclic synthesis using CAR/RedAm



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Challenges and opportunities for biocatalysis

- **Need to imbed guidelines for route design into synthetic chemistry (biocatalytic retrosynthesis).**
- **How many different biocatalyst classes do we have/need to be able to do multi-step organic synthesis? 50 />250.**
- **How many distinct retrosynthetic disconnections? (ca. 250).**
- **Where are the gaps in biocatalysis – which reactions are under-represented in the biocatalysis toolbox (C-X bond formation)?**
- **Cascade reactions present real opportunity for biocatalysis (difficult with conventional organic reagents/catalysts).**
- **Need to increase application of biocatalysis in discovery chemistry.**

Acknowledgements

BBSRC 20 Years of Pioneering Great British Bioscience

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