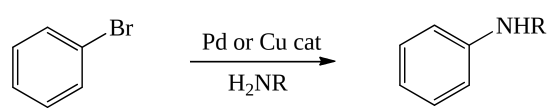
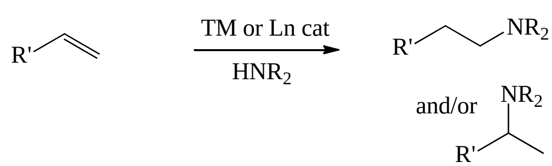
Catalytic synthesis
of
amines and amides

Jonathan Williams
University of Bath

Catalytic approaches to amine synthesis

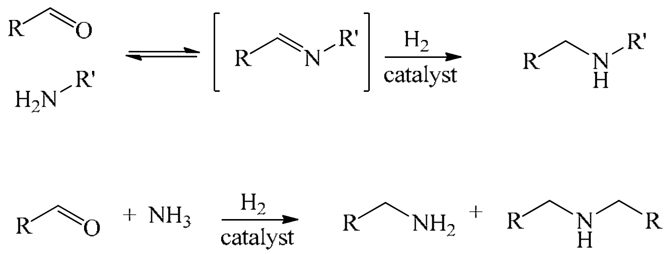


Chem. Sci., **2011**, 27



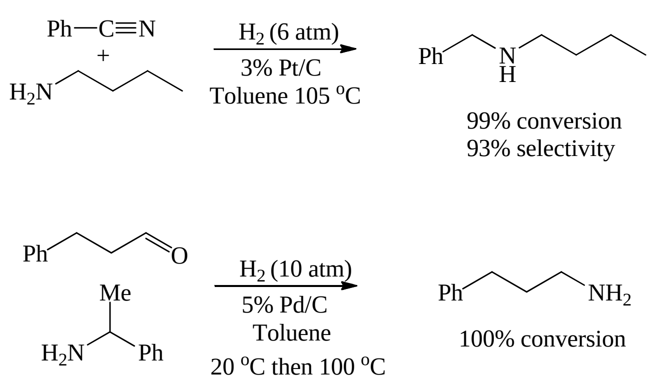
Org. Biol. Chem., **2005**, 1819
ChemCatChem, **2010**, 1192

Reductive amination



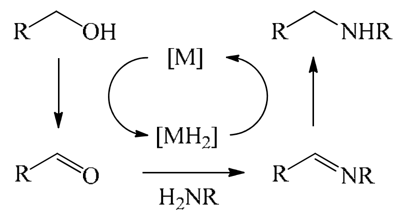
Current Org. Chem., **2008**, 1093

Reductive amination in a flow reactor



Collaboration with Pawel Plucinski, Sumeet Sharma and Anna Sobolewska

Borrowing hydrogen methodology for amine alkylation



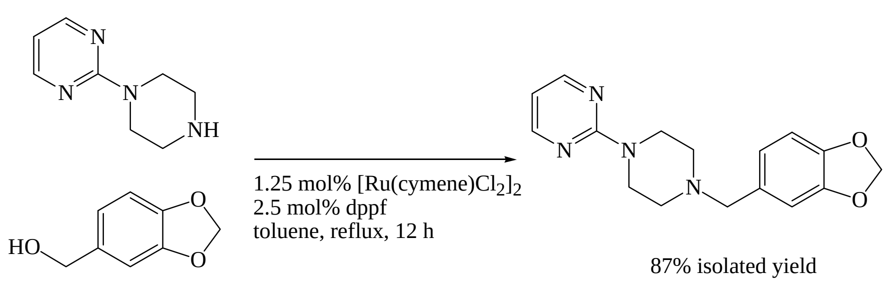
Ruthenium and iridium catalysts have been widely used for this reaction

Avoids the use of alkyl halides

Water is the only by-product

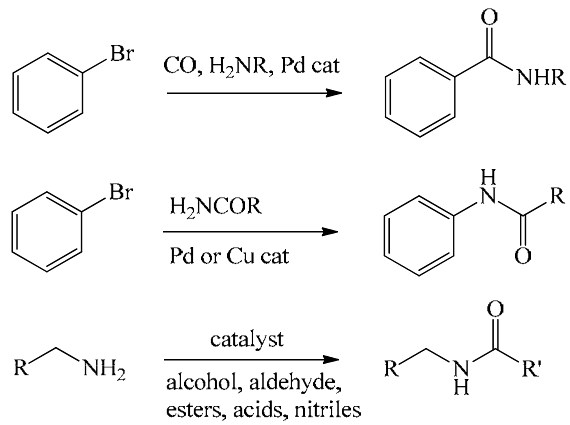
Adv. Synth. Catal., **2007**, 1555, *Dalton Trans.*, **2009**, 753

One pot synthesis of Piribedil



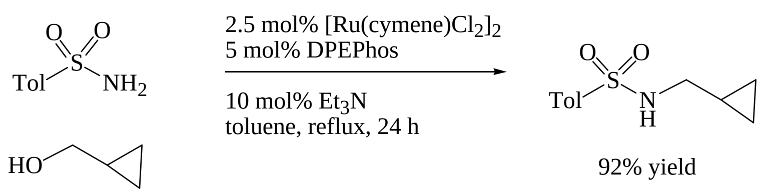
Tetrahedron Lett., 2007, 8263, Haniti Hamid

Catalytic approaches to amide synthesis



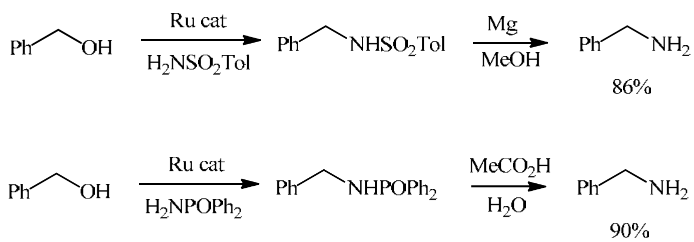
Metal-catalysed approaches to amide bond formation
C. L. Allen and J. M. J. Williams, *Chem. Soc. Rev.*, **2011**, *40*, 3405

Alkylation of Sulphonamides with Alcohols



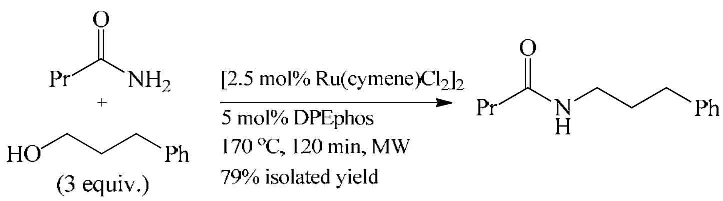
Gareth Lamb, *J. Am. Chem Soc.*, 2009, 1766
See also, Beller et al., *J. Am. Chem Soc.*, 2009, 1775

Sulphonamides/Phosphonamides for Primary Amine Synthesis



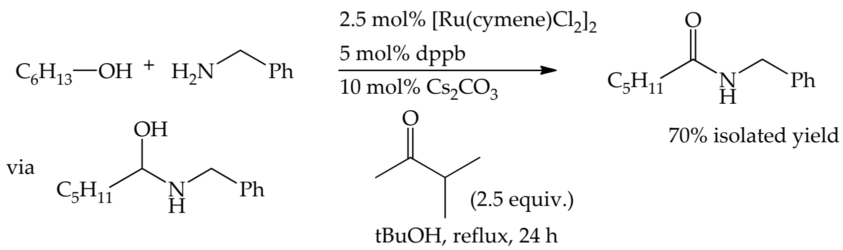
Gareth Lamb, *Tetrahedron Lett.*, 2009, 3374

Amide alkylation requires fairly forcing conditions



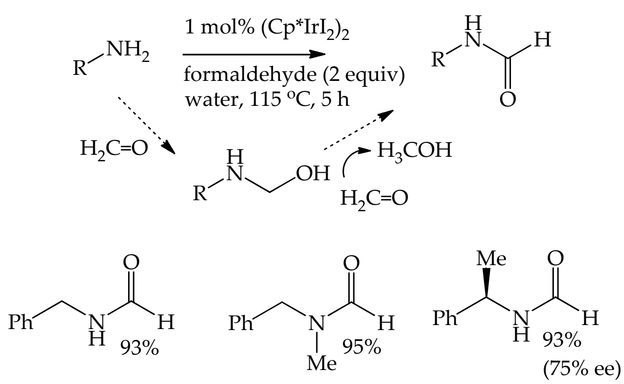
Andrew Watson, *J. Org. Chem*., **2011** , 76, 2328

Amide formation from alcohols



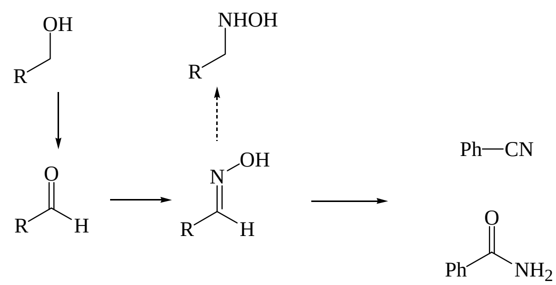
Andrew Watson, *Org. Lett.*, **2009**, 2667
See also; Milstein et al., *Science*, **2007**, 317, 790
Gruzmacher et al., *Angew. Chem.*, **2008**, 559

Formylation using formaldehyde as oxidant and reagent

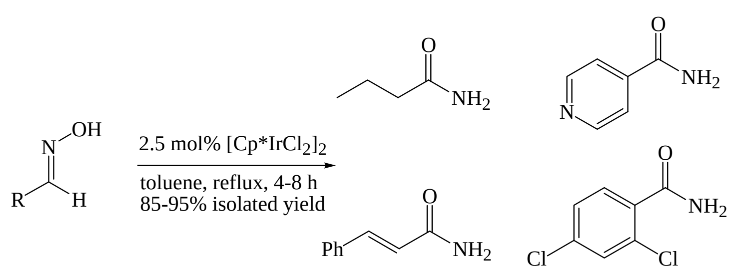


Ourida Saidi

Elimination / re-arrangement reactions with H_2NOH

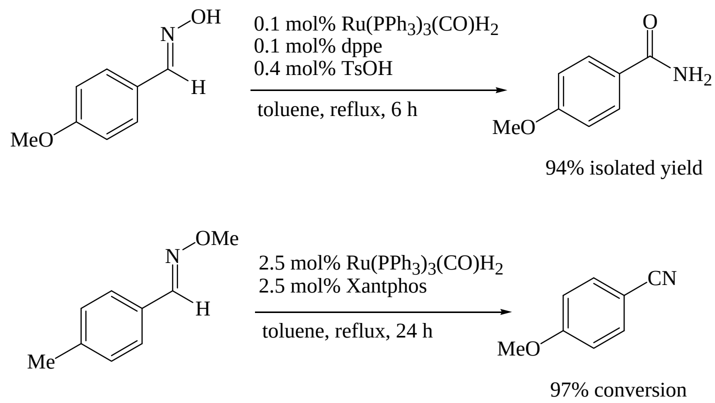


Ir catalysed rearrangement of oximes into amides



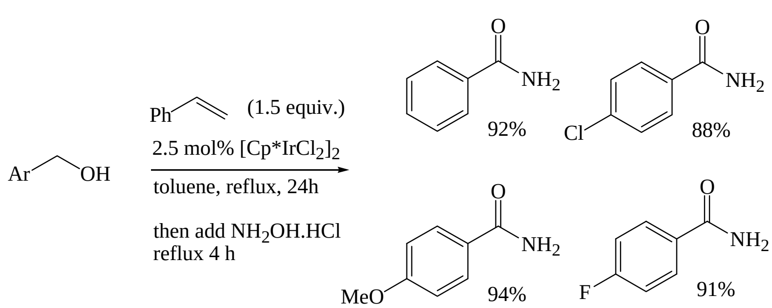
Nathan Owston, *Org. Lett.*, **2007**, 73.

Ru catalysed reactions of oximes



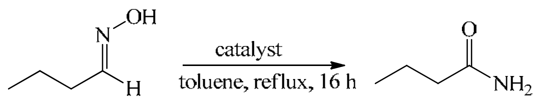
Nathan Owston, *Org. Lett.*, **2007**, 3599. *Tetrahedron Lett.*, **2007**, 7761.

One pot conversion of alcohols into amides



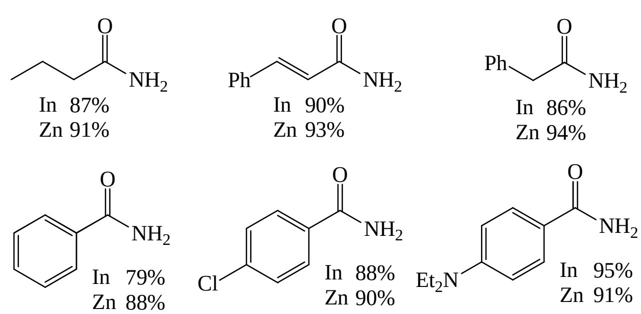
Nathan Owston, *Org. Lett.*, **2007**, 73.

Cheaper metals are also effective for oxime rearrangement



	conv (%)
2.5 mol% In $(OTf)_3$	98
2.5 mol% CuBr	84
2.5 mol% $NiCl_2$	98
2.5 mol% ZnI_2	80

Some examples of Zn and In catalysed amide formation



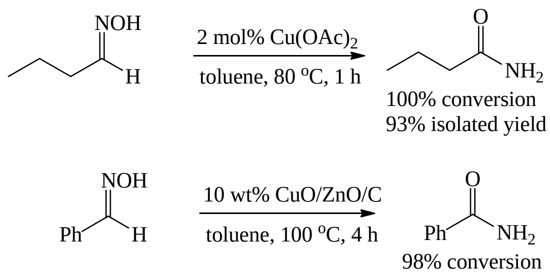
In = 0.4 mol% $In(NO_3)_3$
Zn = 10 mol% $ZnCl_2$

Catalyst cost
(to convert 1 mol of substrate)

$ZnCl_2$	100 mmol = £0.20
$In(NO_3)_3$	4 mmol = £4.00
$Ru(PPh_3)_3(CO)H_2$	1 mmol = £63.00

Liana Allen, *Tetrahedron Lett.*, **2010**, 2724

Simple copper salts also provide good reactivity

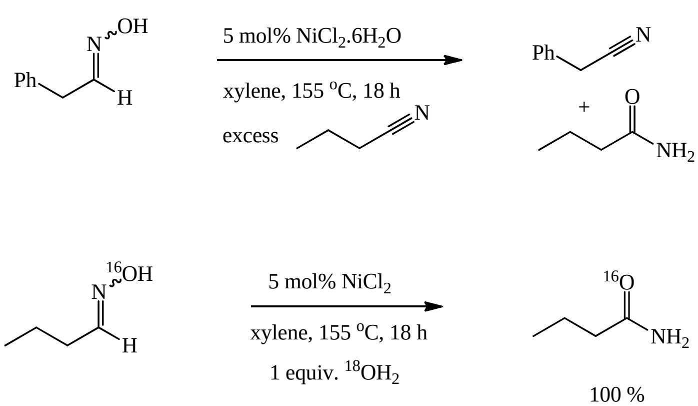


Heterogeneous catalyst can be successfully reused
and also works well in an X-cube flow reactor

Catalyst cost of $Cu(OAc)_2$ (to convert 1 mol of substrate) = £0.26

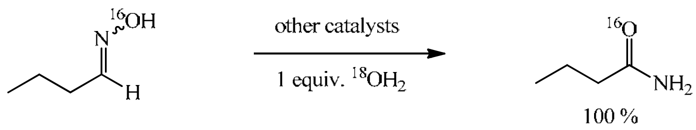
Simon Bishopp and Sumeet Sharma, *Tetrahedron Lett.* **2011**, 4252

Some mechanistic studies



Liana Allen, *Org. Lett.*, **2010**, 5096

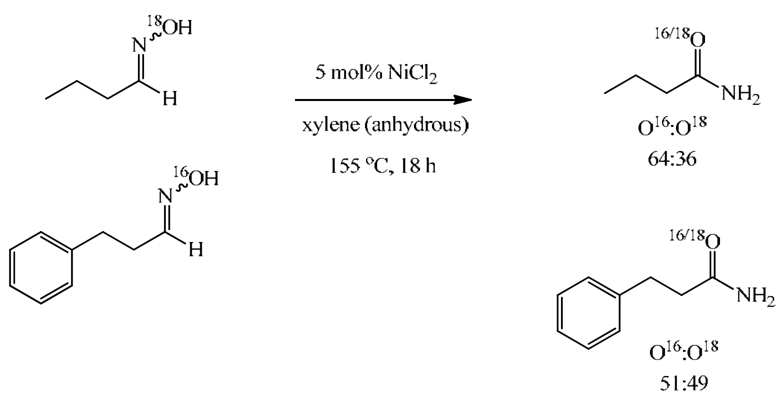
Lack of ^{18}O incorporation with other catalysts



$ZnCl_2$, $In(NO_3)_3$, $RuH_2(PPh_3)_3(CO)$/dppe/HOTs, $RhCl(PPh_3)_3$

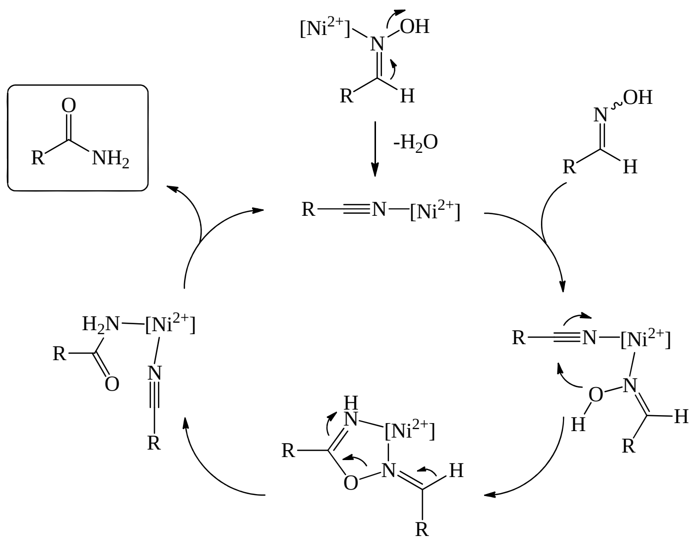
Ruth Lawrence

Crossover experiment suggests a bimolecular O transfer



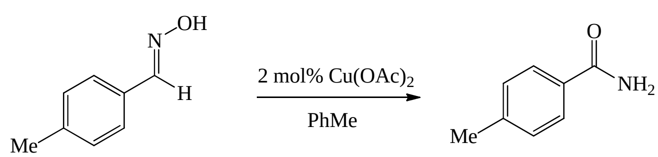
Liana Allen, *Org. Lett.*, **2010**, 5096

One possibility for the mechanism of oxime re-arrangement



Liana Allen, *Org. Lett.*, **2010**, 5096

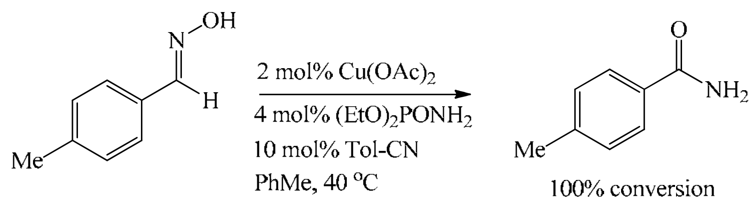
Formation of the intermediate nitrile appears to be slow



10 min, 110 °C	17
15 min, 110 °C	34
30 min, 110 °C	100
30 min, 80 °C	43
60 min, 80 °C	100
10 min, 110 °C (+ 10 mol% Tol-CN)	100

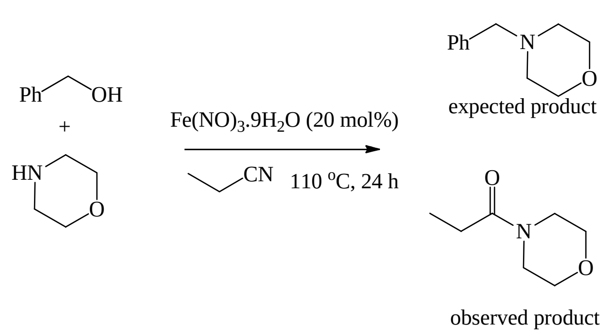
Liana Allen, Liam Emmett, Ruth Lawrence, *Adv. Synth. Catal.*, **2011**, in press

Working towards room temperature amide formation



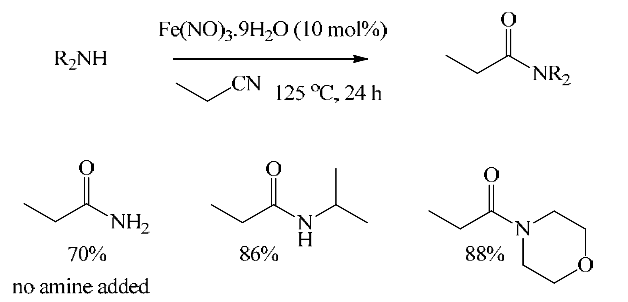
James Lynch

Attempted Borrowing Hydrogen reaction with iron catalysts



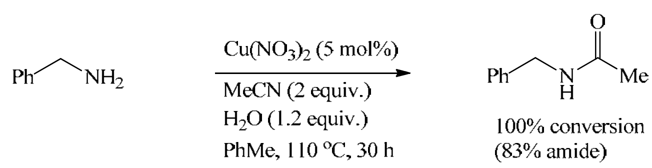
Liana Allen, *Tetrahedron Lett.*, **2009**, 4262

Iron-catalysed conversion of nitriles into amides



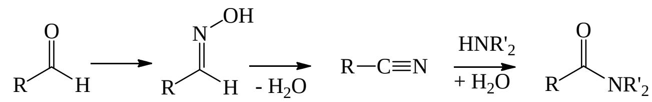
Liana Allen, *Tetrahedron Lett.*, **2009**, 4262

Other catalysts may be more effective for this reaction

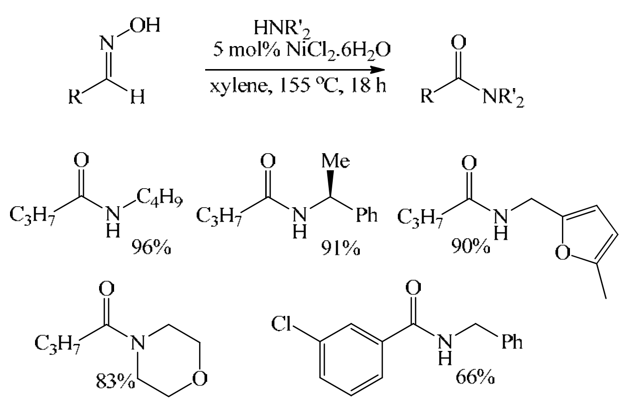


Simge Davulcu

Conversion of aldehydes into amides?

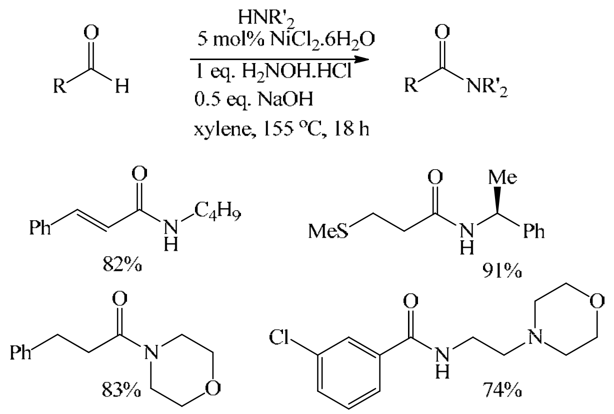


Ni salts catalyse formation of secondary/tertiary amides



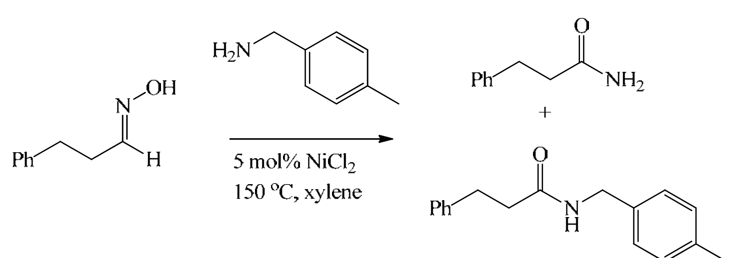
Liana Allen, *Org. Lett.*, **2010**, 5096

Conversion of aldehydes into secondary and tertiary amides



Liana Allen, *Org. Lett.*, **2010**, 5096

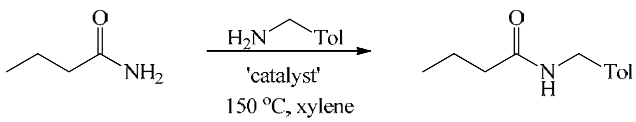
Secondary amide formation goes via the primary amide



2 h	35% primary	18% secondary
6 h	26% primary	74% secondary
16 h	2% primary	98% secondary

Liana Allen and Liam Emmet

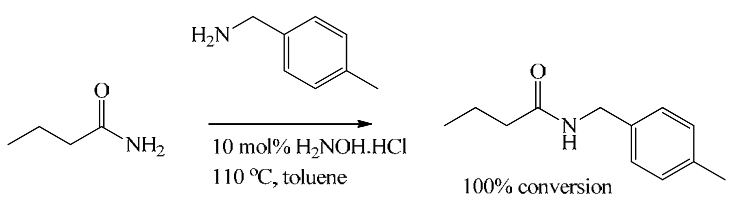
What catalyses secondary amide formation?

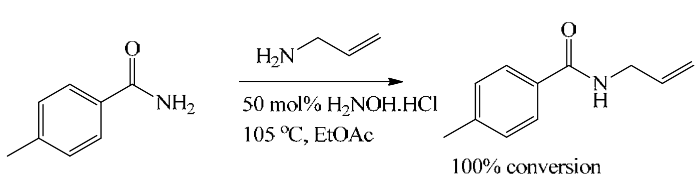


$NiCl_2$ (10 mol%)	39%
$Ph(CH_2)_2CH{=}NOH$ (10 mol%)	69%
both	78%

Liana Allen

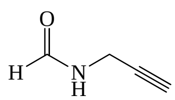
Hydroxylamine catalyses transamidation



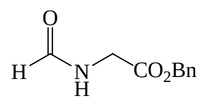


Liana Allen

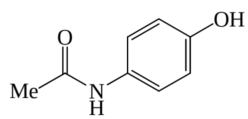
More amides from hydroxylamine catalysed transamidation



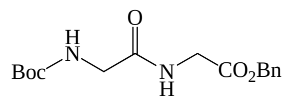
87% yield, 10 mol% cat



91% yield, 10 mol% cat



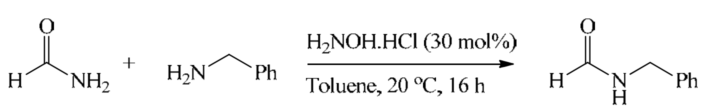
76% yield, 50 mol% cat



71% yield, 50 mol% cat

Liana Allen

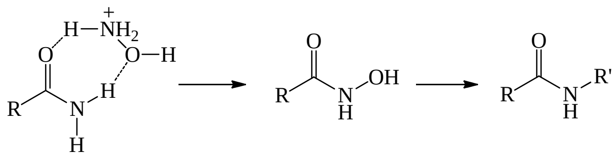
Room temperature catalytic transamidation



100% conversion
0% conversion with no 'catalyst'

Liana Allen

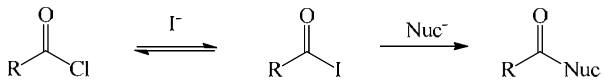
Mechanism of amide activation by hydroxylamine?



Secondary amides do not undergo transamidation

NMR concentration studies show association between hydroxylamine hydrochloride and primary amide

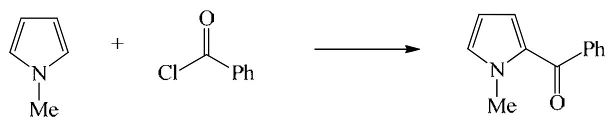
Iodide as an alternative inorganic catalyst



Are acyl iodides more electrophilic than acyl chlorides?

James Taylor and in collaboration with Steve Bull

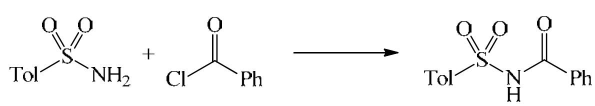
Iodide 'catalysed' acyl transfer



80 °C, EtOAc, 1 h	0% conversion
80 °C, 1 equiv. LiI, EtOAc, 1 h	100% conversion
Reflux, toluene, DBN, 4 h	96% conversion

Org. Lett., **2010**, 5740, James Taylor and in collaboration with Steve Bull

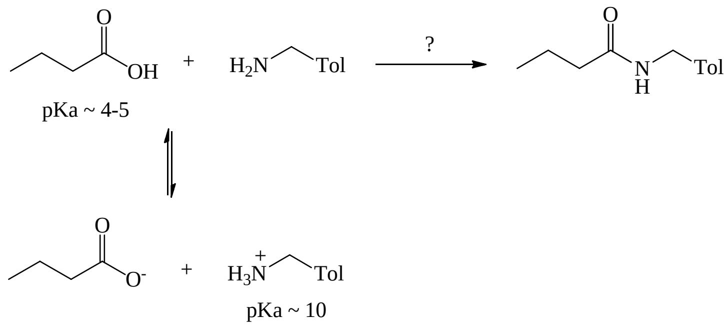
Iodide 'catalysed' formation of acylsulphonamides



82 °C, MeCN, 24 h, no KI	12% conversion
82 °C, MeCN, 24 h, 60 mol% KI	100% conversion

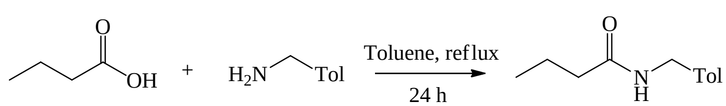
Russ Wakeham

Towards direct amide formation from acids and amines?



March: When carboxylic acids are treated with amines, salts are obtained. The salts can be pyrolyzed to give amides

Uncatalysed amide formation

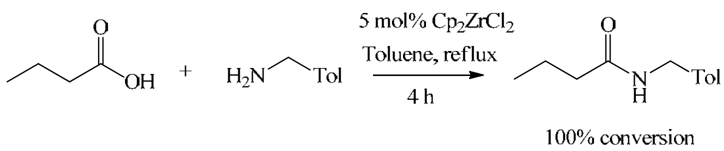


100% conversion

93% yield, 93 g

Liana Allen, *Chem. Commun.*, **2011**, in the press

Catalytic direct amide formation



Liana Allen, Rosie Chhatwal *Chem. Commun.*, **2011**, in the press

Acknowledgements

Liam Emmett
Haniti Hamid
Gareth Lamb
Nathan Owston
Ourida Saidi
Andrew Watson

Steven Bull
James Taylor

Simon Bishopp
Pawel Plucinski
Sumeet Sharma
Anna Sobolewska

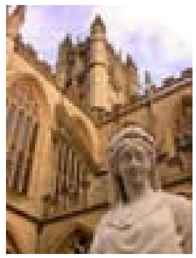
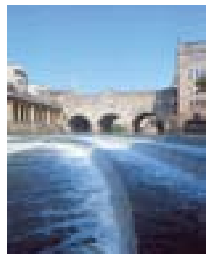
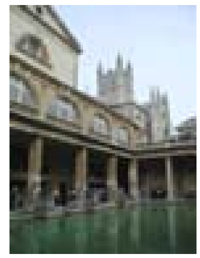
Liana Allen
Rosie Chhatwal
Simge Davulcu
Ruth Lawrence
James Lynch
Russ Wakeham

Sarah Abou-Shehada
Ben Atkinson
Helen Lomax
Winson Ma
Dominic van der Waals

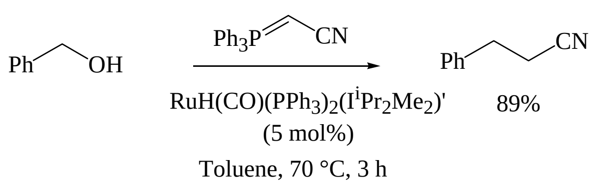
EPSRC
University of Bath
GlaxoSmithKline
AstraZeneca
Syngenta
Pfizer
Brunei Government


2011-
UNIVERSITY

The Beautiful Buildings of Bath

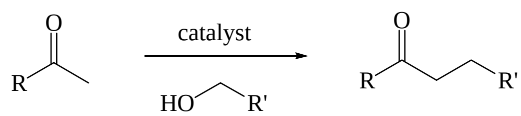




Milder conditions with ruthenium complexes



J. Am. Chem. Soc., 2007, 1987, Belinda Paine

Chemistry from other groups

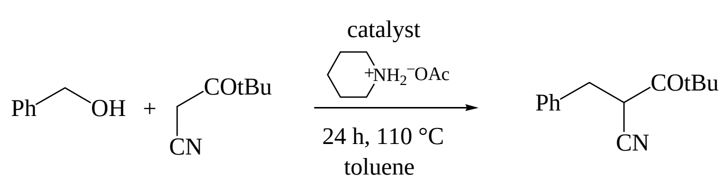


Cho	$RuCl_2(PPh_3)_3$	*J. Org. Chem*, 2001, 9020
Yus	$Ru(dmso)_4Cl_2$	*Tetrahedron*, 2006, 8982
Ishii	$[Ir(cod)Cl]_2/PPh_3$	*J. Am. Chem. Soc.*, 2004, 72
Park	Pd(heterogeneous)	*Angew. Chem. Int.*, 2005, 6913

Kaneda	Ru (heterogeneous)	*J. Am. Chem. Soc.*, 2004, 5662
Grigg	Cp^*IrCl_2	*J. Org. Chem.*, 2006, 8023

Angew. Chem. Int., 2007, 2358. *Adv. Synth. Cat.*, 2007, 1555

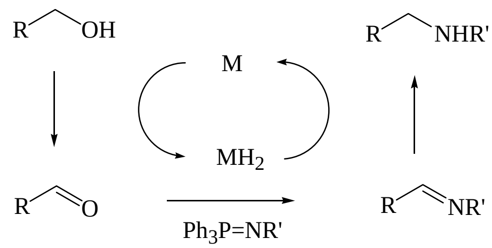
Ruthenium complexes for aldol chemistry



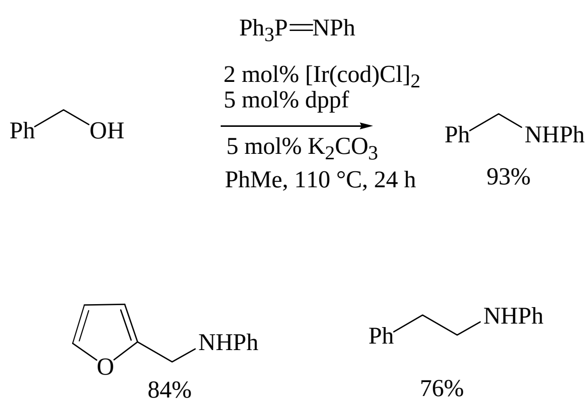
2.5 mol% $[Ir(cod)Cl]_2$, 5 mol% dppf, 5 mol% K_2CO_3	55%
5 mol% $Ru(PPh_3)_3(CO)H_2$	56%

Paul Slatford

Amine formation via the Aza-Wittig reaction

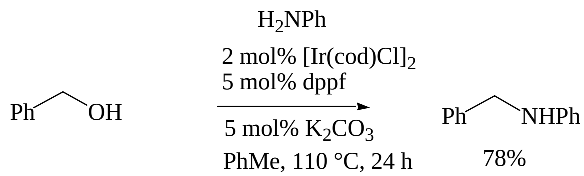


Indirect Aza-Wittig reactions



Chem. Commun., 2004, 1072, Gerta Cami-Kobeci

Simple amines are also successful



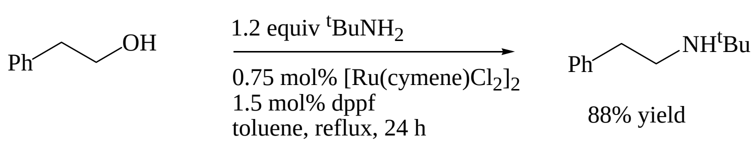
Related chemistry

Grigg, $Ru(PPh_3)_4H_2$ Chem Comm, 1981, 611

Beller, $Ru_3(CO)_{12}$ /R_3P Tetrahedron Lett, 2006, 8881

Yamaguchi, Cp^*IrCl_2 Synlett, 2005, 560

Ruthenium complexes are more active



Chem. Commun. 2007, 725, Haniti Hamid