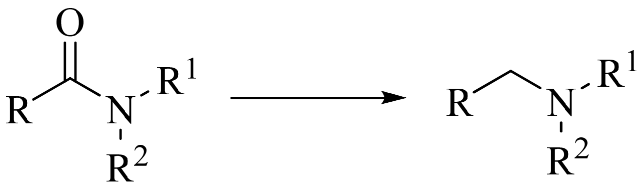
RCC (HBR)

<u>Zinc-Catalyzed Reductions of Amides:</u>

Unprecedent Selectivity and Functional Group Tolerance

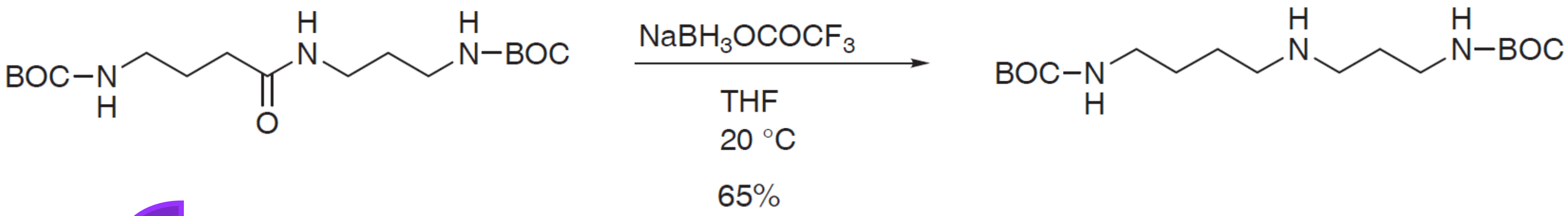
Das, S.; Addis, D.; Zhou, S.; Junge, K., Beller, M.* *J. Am. Chem. Soc.* 2010, *132*, 1770-1771

I- Precedents for reduction of amides to amines



1) Stoechiometric amounts of metal:

- Use of $LiAlH_4$,[1]
- Use of borohydrides in presence of carboxylic acids[2]



Issues:
- Air, Moisture Sensitive
- Low functional group tolerance
- Tedious purification procedures

1. Seyden-Penne, J. Reductions by the Alumino and Borohydrides in Organic Synthesis, 2nd ed.; Wiley: New York, **1997**
2. Umino, N.; Iwakuma, T.; Itoh, M. *Tetrahedron Lett.*, **1976**, 763.

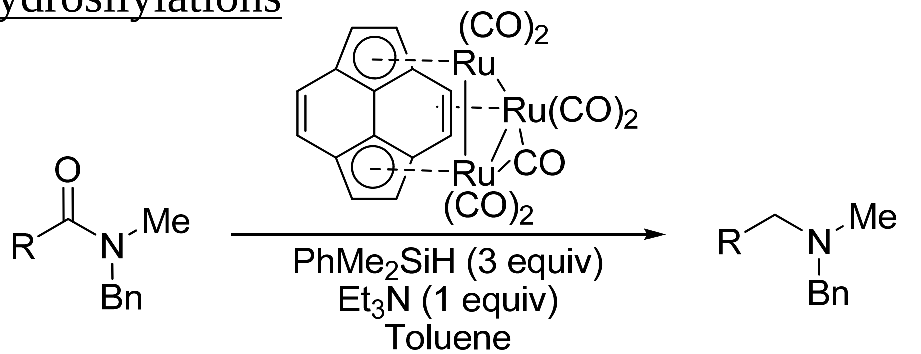
2) Catalytic amounts of metal

a) Use of molecular hydrogen: still at the beginnings (harsh conditions)

Cole-Hamilton D. J. et al. Chem. Comm. **2007**, 3154

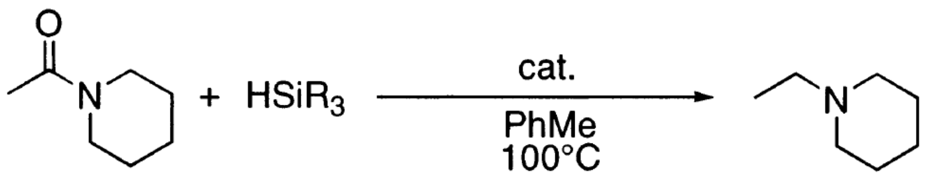
b) Metal catalyzed hydrosilylations

Ru catalysts



Sasakuma, H.; Motoyama, Y.; Nagashima, H. *Chem. Commun*. **2007**, 4916

Rh, Pt, Pd, Ir, Os Catalysts



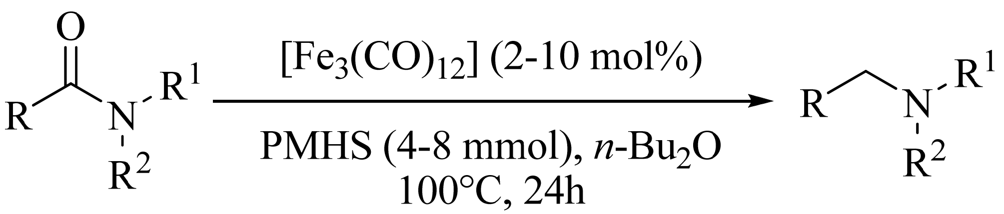
+ base in some cases

Cat: $RhH(PPh)_4$, $IrCl_3$, K_2IrCl_6, $Pd(OH)_2/C$, Pt_2Cl, $Os_3(CO)_{12}$

Igarashi, M.; Fuchikami, T. *Tetrahedron Lett.* **2001**, *42*, 1945

But: Development of cost-efficient and environmentally benign catalysts still desirable

Fe



(PMHS: PolyMethylHydroSiloxane)

28 examples, 50 to 99%

Pros:

-Tertiary and Secondary amides
- Iron: so cheap!

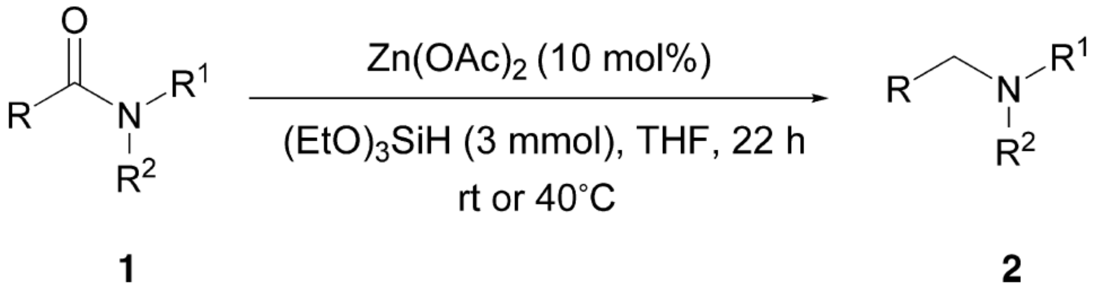
Cons:

- High temperature
- Low chemoselectivity
- 4 eq of Silanes

Beller, M. et al. *Angewandte, Chem. Int. Ed.* **2009**, *48*, 9507

II- RCC: Zn Catalyst

1) Presentation



Note that : - Room temperature or 40°C

- With other Zn catalysts (ZnX_2 (X=F, Cl, Br...): lower yields

- Other silanes ($PhSiH_3$, Ph_2SiH_2) did not react at rt

- Works with a foultitude (6) of solvents

- Highly scalable (multigrams)

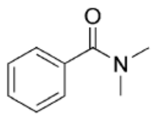
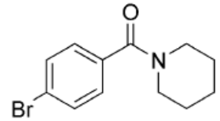
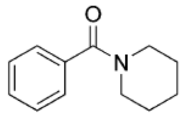
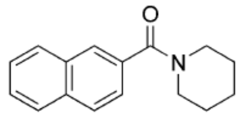
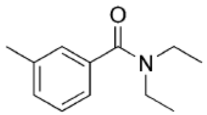
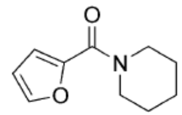
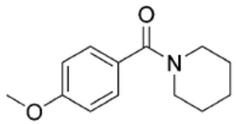
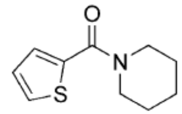
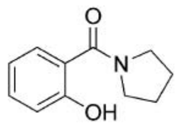
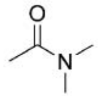
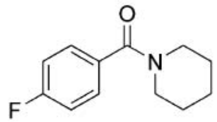
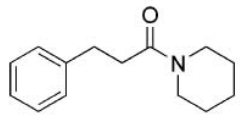
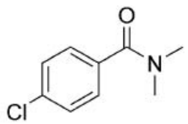
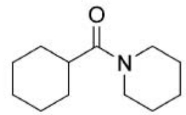
Works with ABCR®, Acros®, Sigma Aldrich® $Zn(OAc)_2$ sources !!!

For curiosity: Buchwald, S. L. *Angewandte Chem.Int. Ed.* **2009**, *48*, 5586

2) Reaction Scope

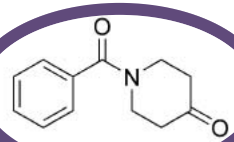
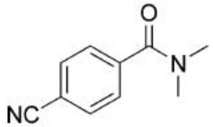
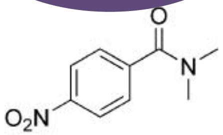
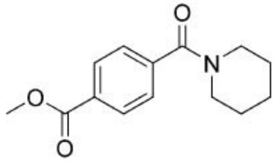
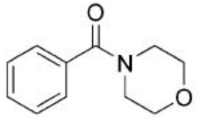
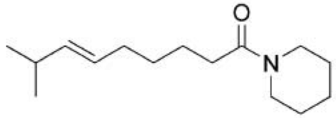
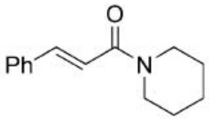
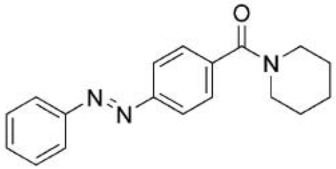
Aromatic,
Aliphatic,
and
Heterocyclic !!

Influence of
the nature of
the group on aromatics
on reaction time

entry	amide		yield (%)	entry	amide		yield (%)
1		**1a**	**2a** 97	8		**1h**	**2h** 97
2		**1b**	**2b** 85	9		**1i**	**2i** 99
3		**1c**	**2c** 75	10		**1j**	**2j** 73
4		**1d**	**2d** 80	11		**1k**	**2k** 82
5		**1e**	**2e** 87	12		**1l**	**2l** 96
6		**1f**	**2f** 92	13		**1m**	**2m** 73
7		**1g**	**2g** 87	14		**1n**	**2n** 86

[a] Reported yields are isolated yields except entries 1 and 12. [b] All reactions were performed with 1 mmol of amide except entries 3 and 10 (3 mmol). [c] Products of entries 4 and 13 were purified by column chromatography, and products of entries 3 and 10 were purified by distillation.

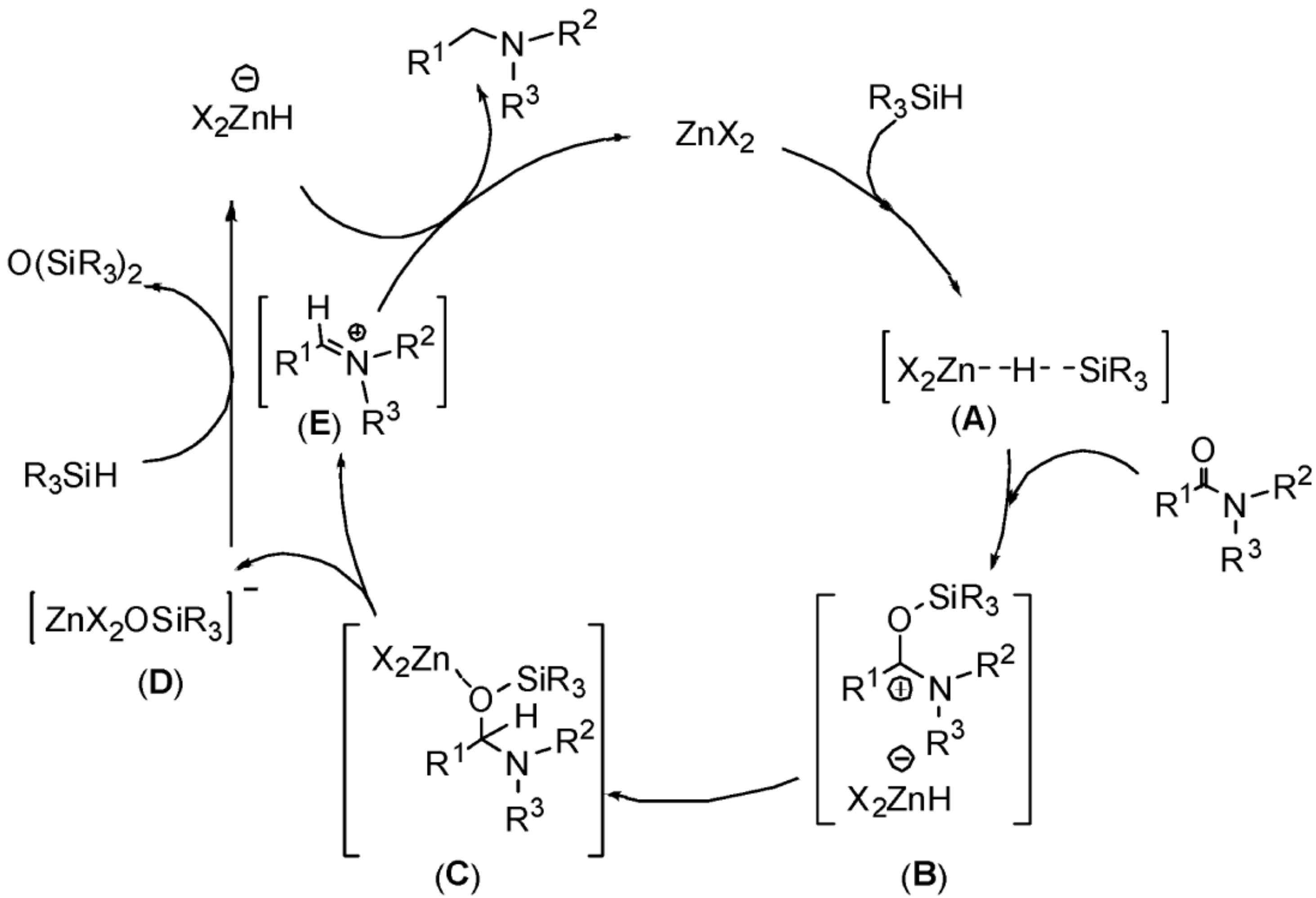
3) Functional Group Tolerance

entry	amide		yield (%)	entry	amide		yield (%)
1		**1o**	**2o** 83	5		**1s**	**2s** 72
2		**1p**	**2p** 85	6		**1t**	**2t** 65
3		**1q**	**2q** 84	7		**1u**	**2u** 87
4		**1r**	**2r** 78	8		**1v**	**2v** 91

[a] All reactions were performed on 1 mmol scale of the respective amide. [b] Entries 4−7 were purified by column chromatography.

First example of this type of selectivity

4) Mechanism



X2ZnH
R1 N R2 R3
ZnX2
R3SiH
O(SiR3)2
H R1 N R2 R3
(E)
X2Zn--H--SiR3
(A)
O R1 N R2 R3
R3SiH
ZnX2OSiR3
(D)
X2Zn O SiR3 H R1 N R2 R3
(C)
O SiR3 R1 N R2 R3 X2ZnH
(B)

III- Conclusion on this RCC

- High chemoselectivity
- Mild conditions
- Inexpensive Zn catalysts
- Might become a useful tool in synthesis if more generalizable