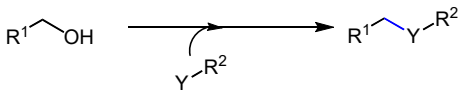
Borrowing Hydrogen Catalysis
(Hydrogen Autotransfer)

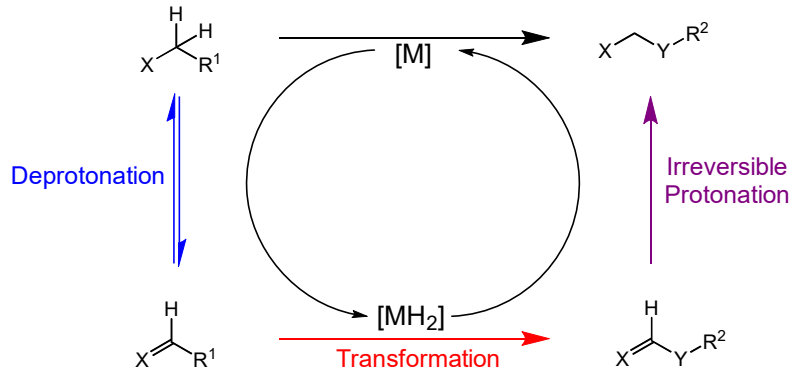
Literature Review
May Group
5/22/18
Sasha Oleynichenko

Borrowing Hydrogen (BH) Overview



- First reported in 1908
  Hebd. Seances Acad. Sci. **1908,** *146,* 298.
- Much progress in the last 20 years
- Direct combination of transfer hydrogenation with an intermediate reaction
- Can form complex molecules without separation/isolation

Borrowing Hydrogen (BH) Overview

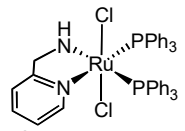


Chem. Rev. **2018**, *118*, 1410-1459

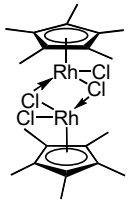
Catalyst Identity

Any metal used must form a sufficiently unstable hydride - walk the line

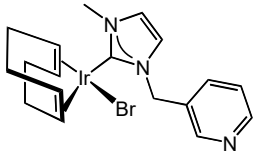
- Most common catalysts are [Ru], [Rh], and [Ir]
- [Os], [Mo] and [W] have been reported but are less common



Coord. Chem. Rev. **2017,** *331,* 1-36

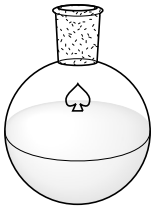


Angew. Chem. Int. Ed. **2014,** *53,* 761 –765
(Hot paper)



Chem. - Eur. J. **2015,** *21,* 17877-17889

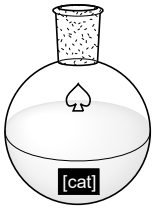
Homogenous vs Heterogenous Catalysis



Homogenous

Advantages:
Lower temperatures
Potential for more active catalyst systems
Great deal of research in the field

Disadvantages:
Generally requires additives (ligands)
Less atom economical



Heterogenous

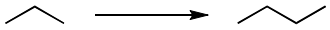
Advantages:
More atom economical (additive free)
Can use multi-functional solid catalysts
Green chemistry appealing to industry

Disadvantages:
High temperatures
Origin of BH methodology, but much less developed

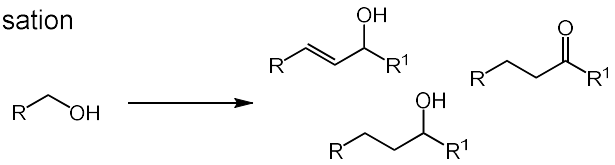
Chem. Rev. **2018**, *118*, 1410-1459

C-C Bond Formation

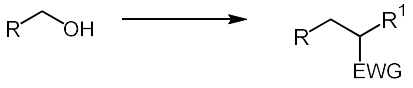
Olefin Metathesis



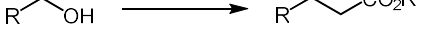
Aldol Condensation



Knoevenagel Reaction

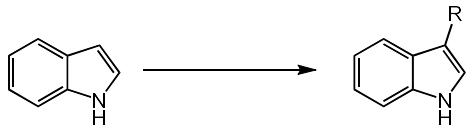


Decarboxylative Knoevenagel

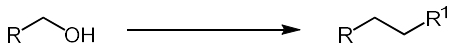


C-C Bond Formation

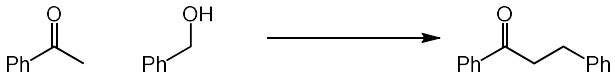
C_3 Alkylation



Wittig Reaction

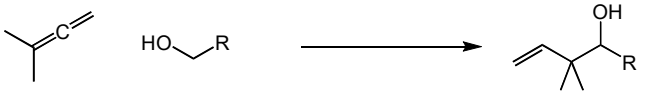


Condensation



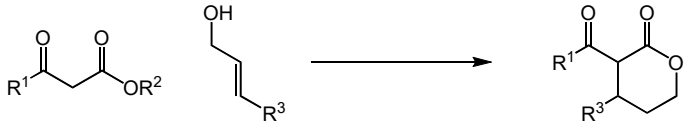
C-C Bond Formation

Allylation



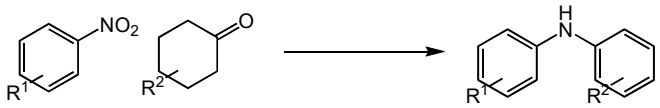
Krische JACS 2007

δ-Lactonization

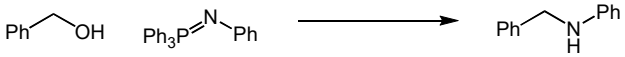


C-N Bond Formation

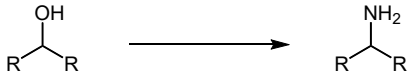
Condensation



Aza-Wittig

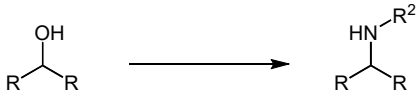


Amination

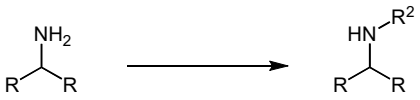


C-N Bond Formation

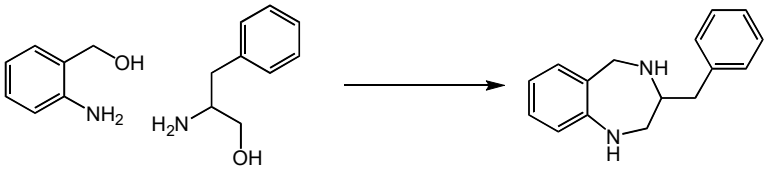
N-Alkylation



Many examples

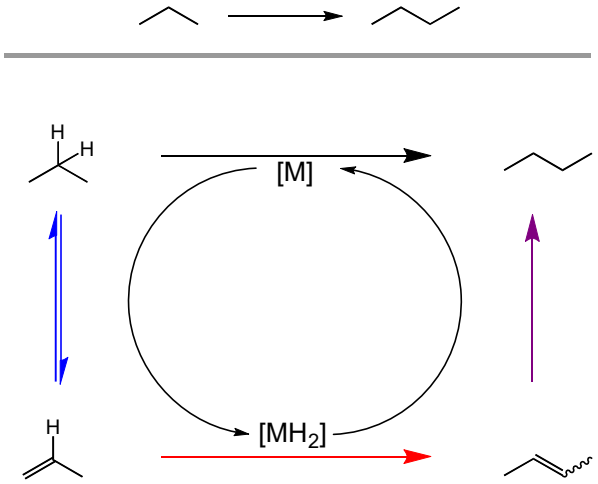


Condensation/N-Heterocyclization

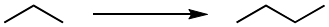


Carbon-Carbon Bond Formation

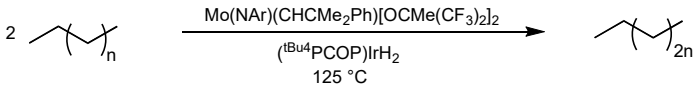
Olefin Metathesis

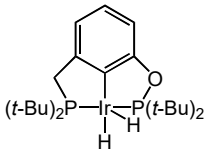


Olefin Metathesis

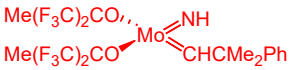


Homogenous Catalysis





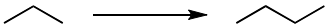
Borrowing Hydrogen



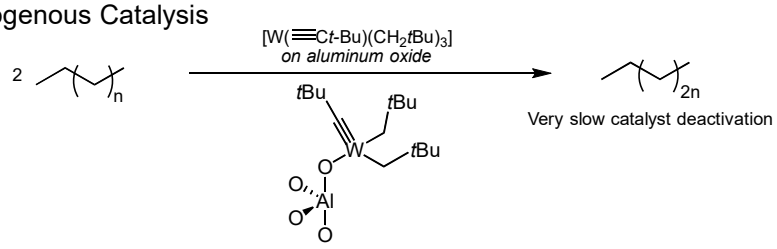
Olefin Metathesis

Schrock, Brookhart, et. al. *Organometallics* **2009,** *28*, 355-360
Brookhart, et. al. *ACS Catal.* **2013,** *3,* 2505-2514

Olefin Metathesis



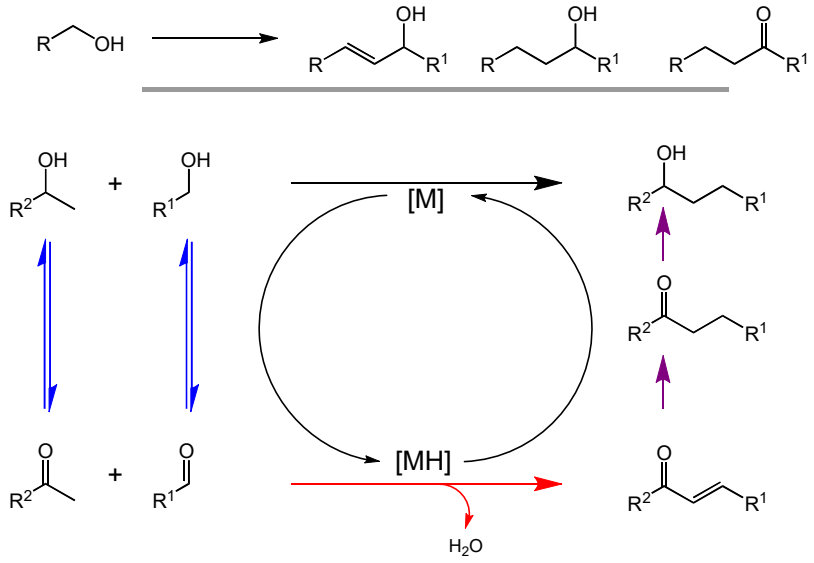
Heterogenous Catalysis



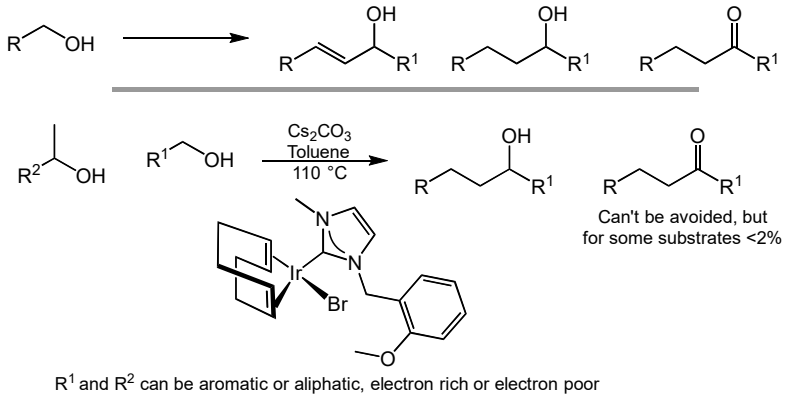
Very slow catalyst deactivation

Basset, et. al. *Angew. Chem. Int. Ed.* **2005,** *44,* 6755 – 6758

Aldol Condensation



Aldol Condensation

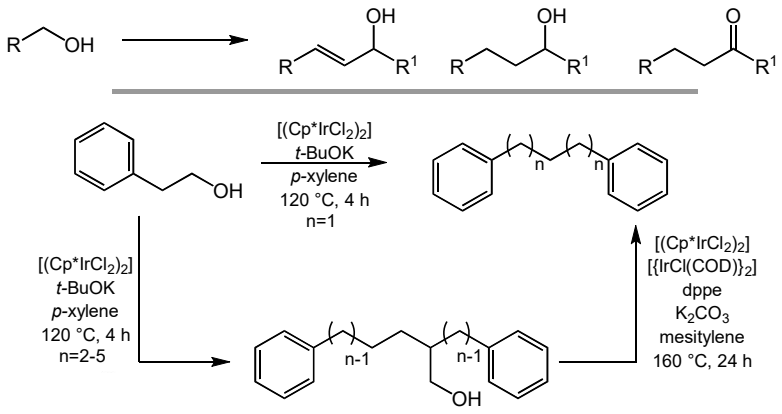


Can't be avoided, but for some substrates <2%

R^1 and R^2 can be aromatic or aliphatic, electron rich or electron poor

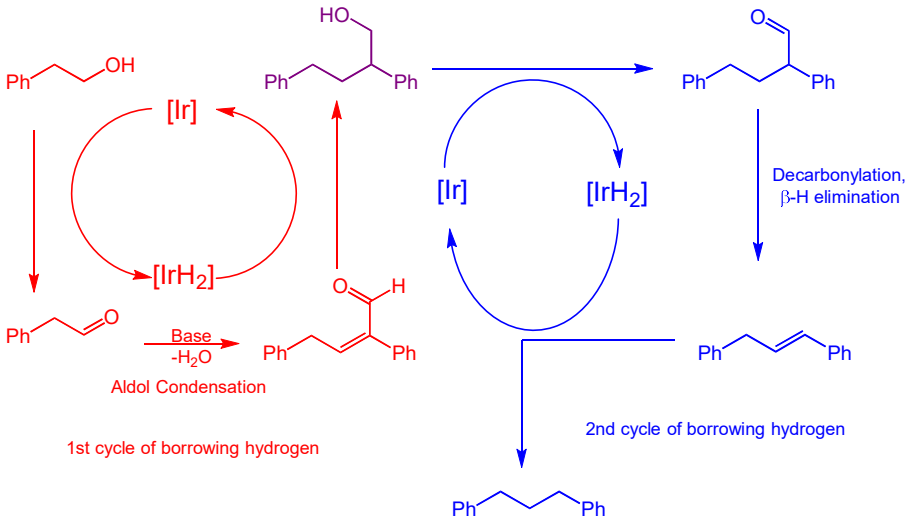
Chem. - Eur. J. **2015,** *21,* 17877-17889

Aldol Condensation



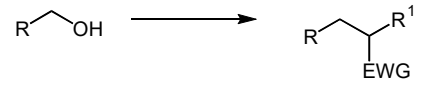
Angew. Chem., Int. Ed. **2011,** *50,* 8618-8622
Chem. Commun. **2008,** 6215

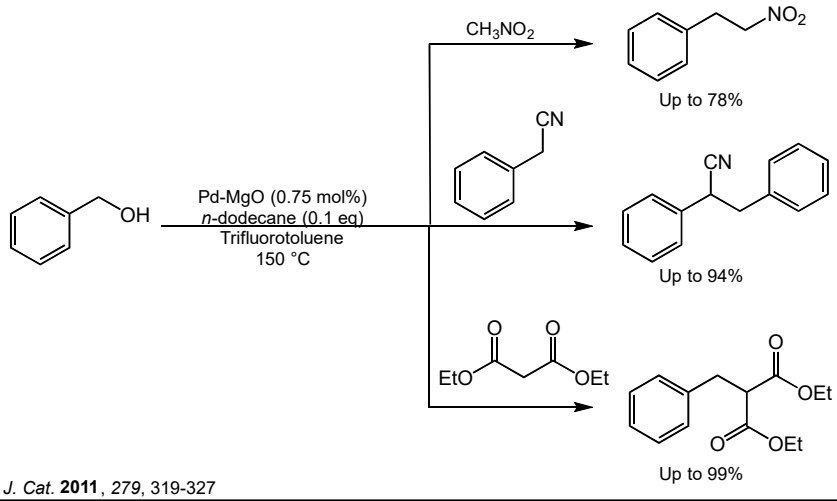
Mechanism



Angew. Chem., Int. Ed. **2011,** *50,* 8618-8622

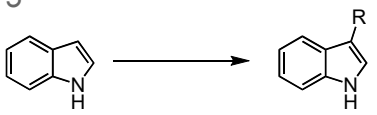
Knoevenagel Condensation

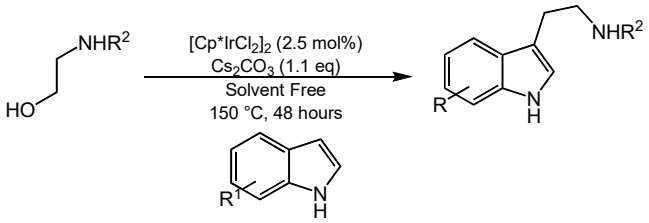




J. Cat. **2011**, *279*, 319-327

C_3 Activation of Indoles

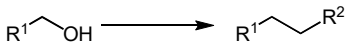


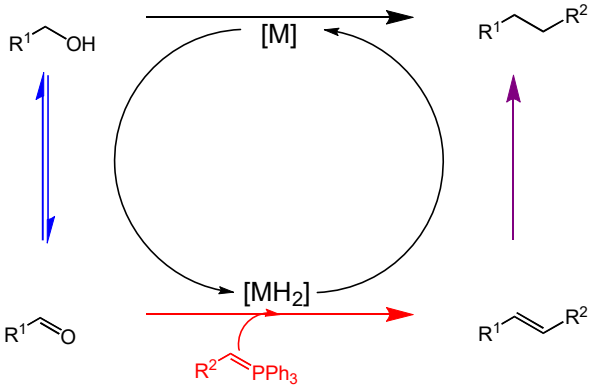


- After deprotection, gives access to many tryptamine homologues, including serotonin
- Branched alcohols are just as reactive
- Longer chains equally reactive

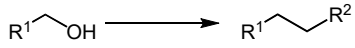
Tetrahedron **2016**, *72,* 2233-2238

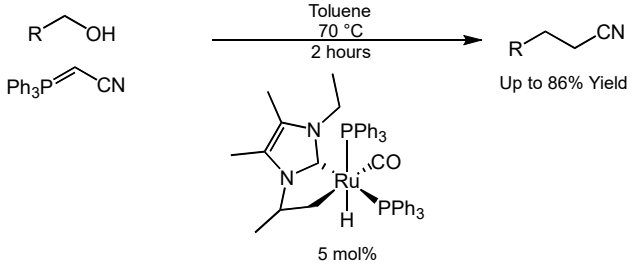
Indirect Wittig

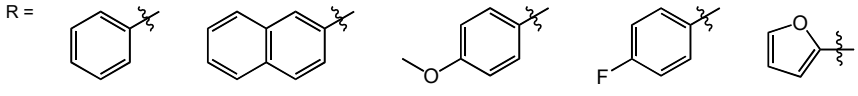




Indirect Wittig

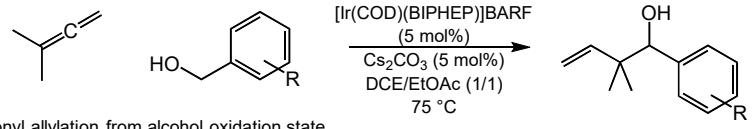






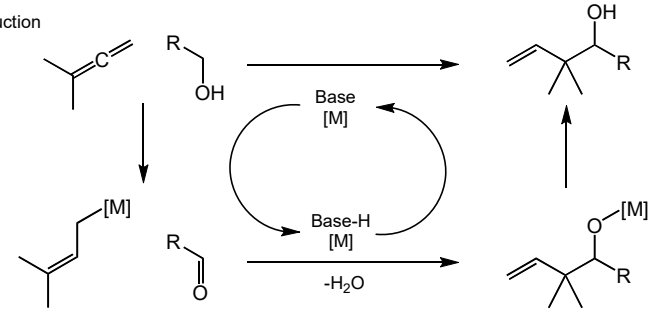
J. Am. Chem. Soc. **2007,** *129*, 1987-1995

Allylation



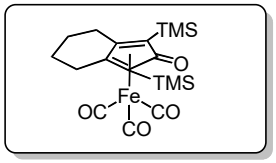
70-92% Yield

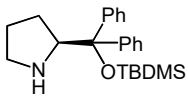
- Carbonyl allylation from alcohol oxidation state
- No byproducts are formed
- No over-reduction

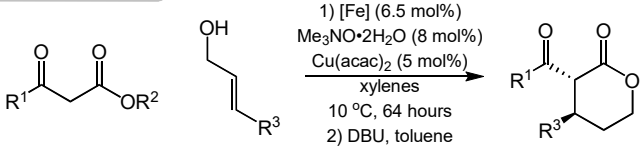


Krische, et. al. *J. Am. Chem. Soc.* **2007**, *129*, 15134-15135

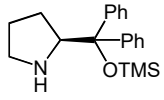
δ-Lactonization

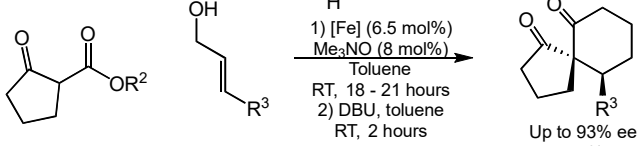






>99:1 dr
52% Yield



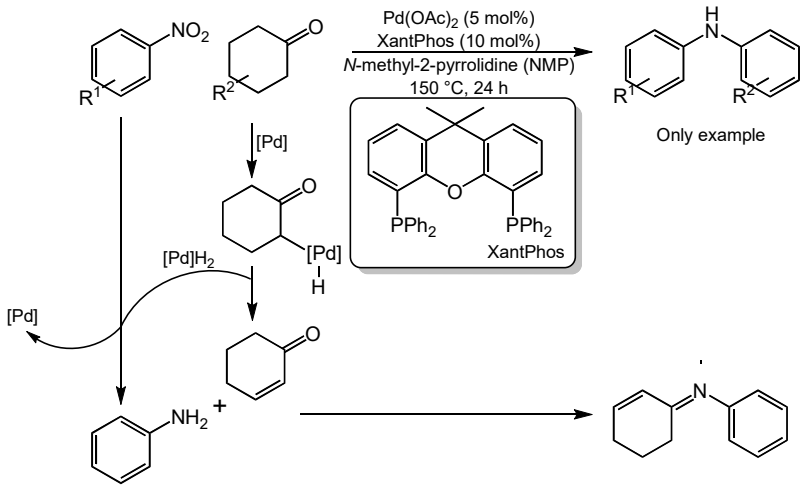


Up to 93% ee
Up to 90% yield

Synthesis **2018**, *50*, 785-792

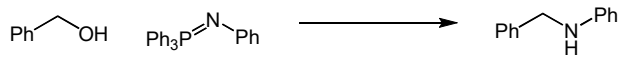
Carbon-Nitrogen Bond Formation

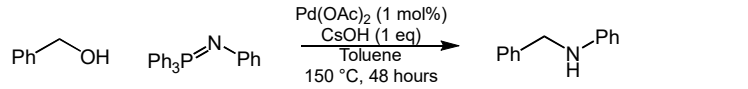
Condensation/ N-Arylation



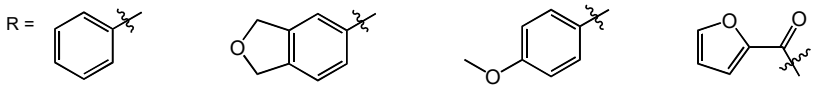
Org. Lett. **2012**, *14*, 1692-1695

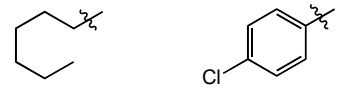
Aza-Wittig





R =



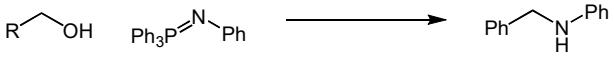


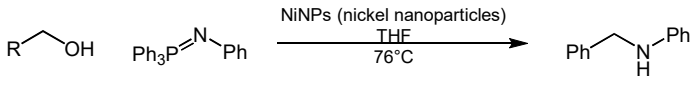
46% Yield

65% Yield

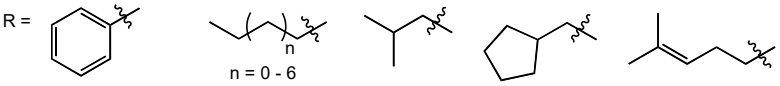
Synthesis, **2011**, *22*, 3730-3740

Aza-Wittig





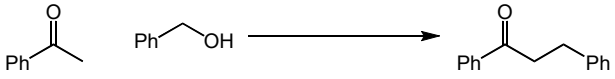
R =



n = 0 - 6

Only examples of heterogenous Aza-Wittig BH

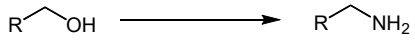
All yields below 60%

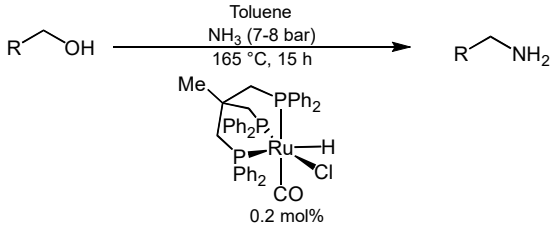


Pd/AlO(OH), K_3PO_4, toluene	92%
$[Ir(COD)Cl]_2PPh_3$, KOH, neat	86%
NiNPs, THF, 6 hrs	85%

Eur. J. Org. Chem. **2008,** 4908–4914

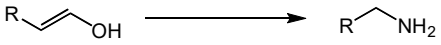
Amination of Alcohols

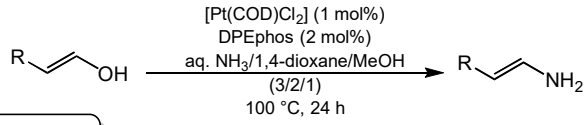


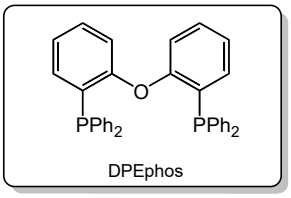


Dalton Trans., **2016,** *45,* 6856–6865

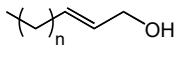
Amination of Allylic Alcohols

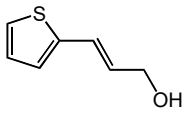


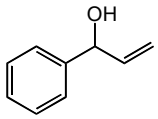


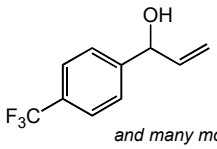


Alcohol scope:





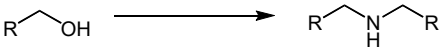


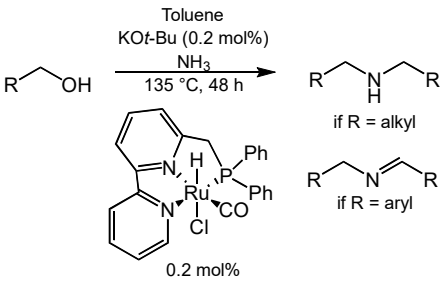


and many more

Angew. Chem. Int. Ed. **2012,** *51,* 150 –154

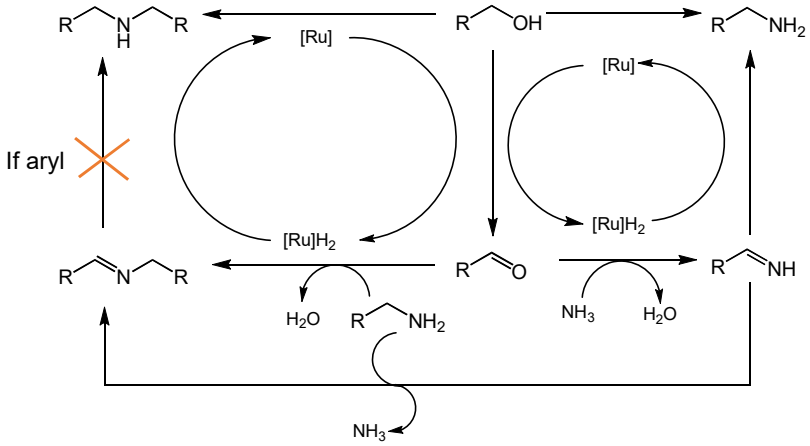
Amination to 2° Amines



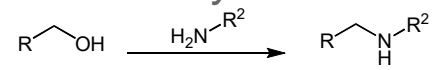


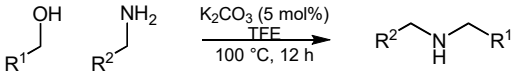
Catal. Lett. **2015**, *145*, 139-144

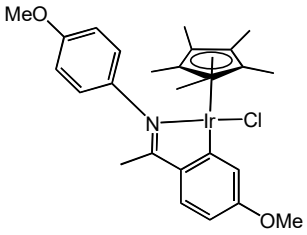
Mechanism



N-Alkylation

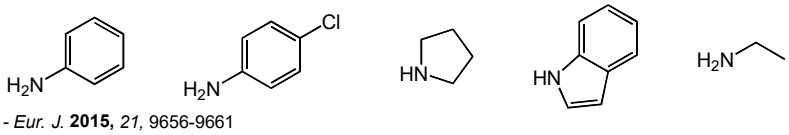






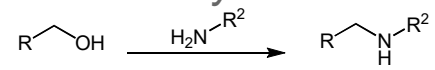
1 mol%

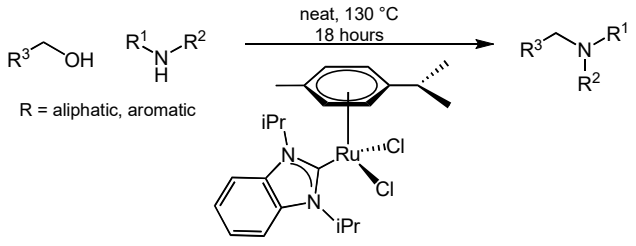
Amine scope



Chem. - Eur. J. **2015,** *21,* 9656-9661

N-Alkylation

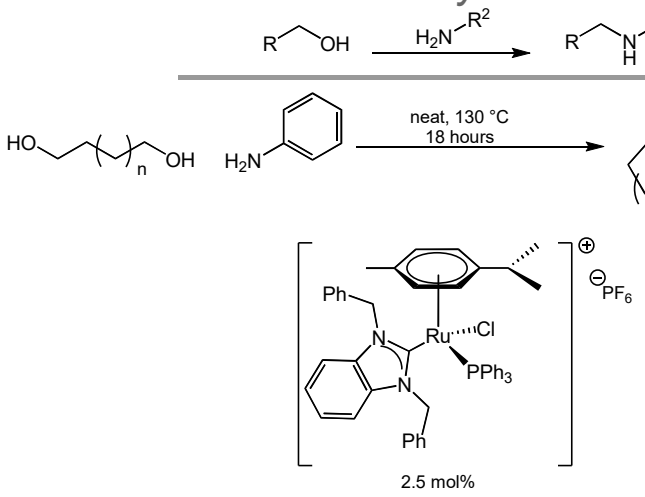




5 mol%

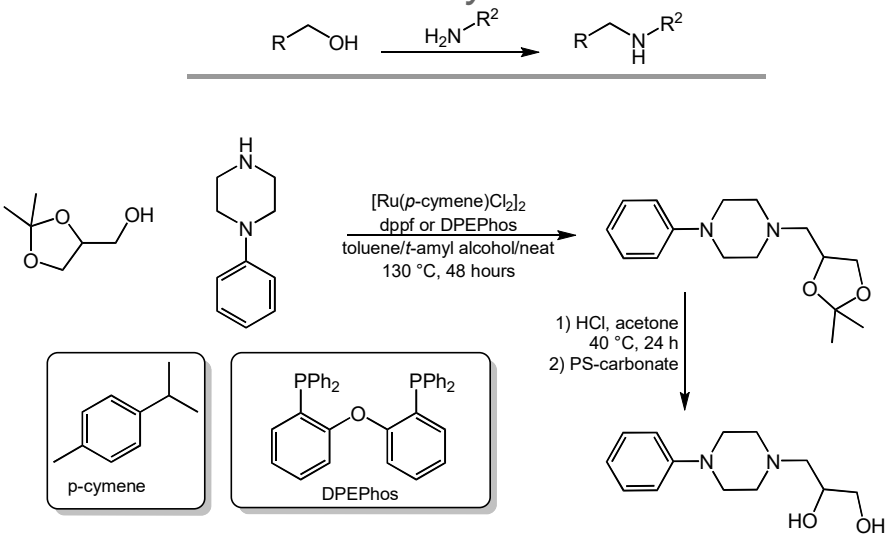
RSC Adv. **2015**, 4434-4442

N-Alkylation



RSC Adv. **2015**, 4434-4442

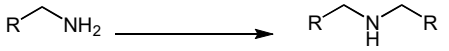
N-Alkylation

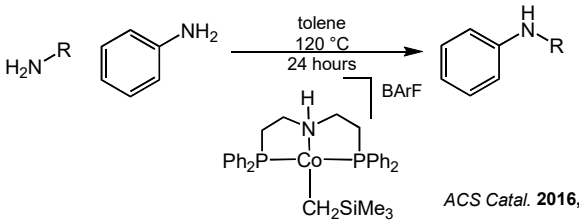


86% overall yield
Dropropizine (cough supressant)

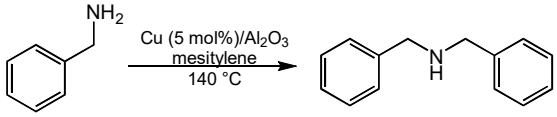
ACS Sustainable Chem. Eng. **2016,** *4, 5730-5736*

N-Alkylation



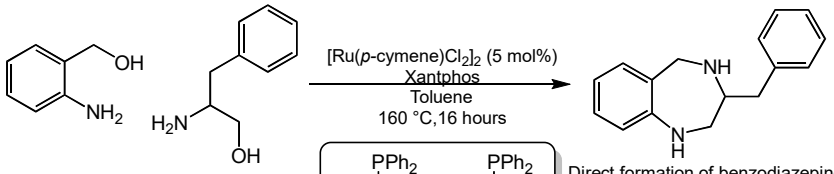


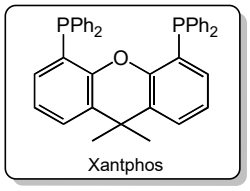
ACS Catal. **2016,** *6*, 6546-6550



Catal. Sci. Technol. **2013,** *3*, 2397-2403

Condensation/N-Heterocyclization

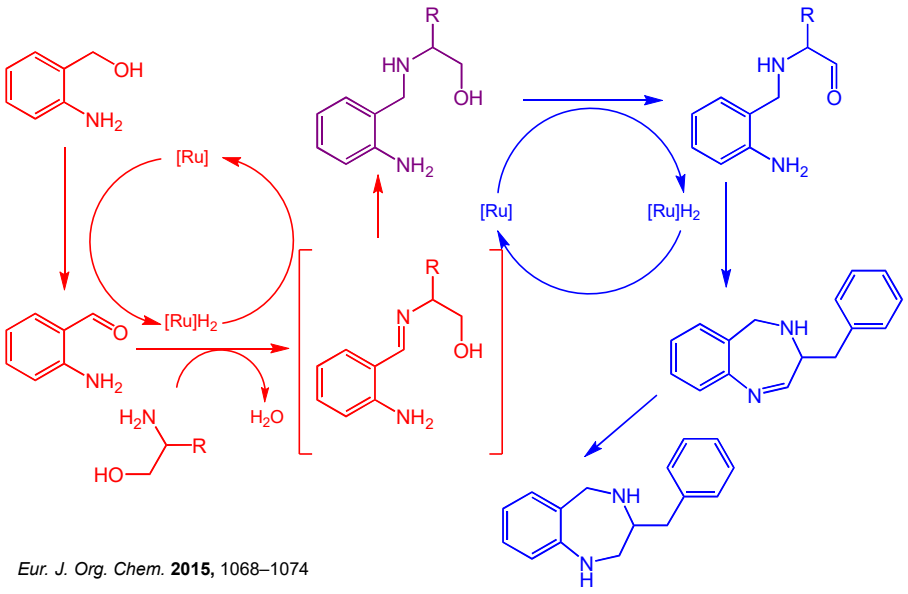




Direct formation of benzodiazepines without external hydrogenation source

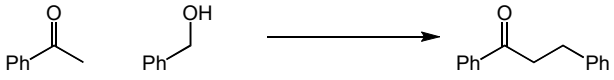
Eur. J. Org. Chem. **2015,** 1068–1074

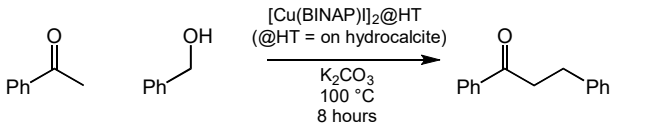
Condensation/N-Heterocyclization



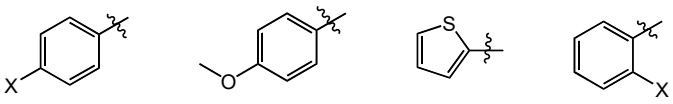
Eur. J. Org. Chem. **2015,** 1068–1074

Current Work: Condensation





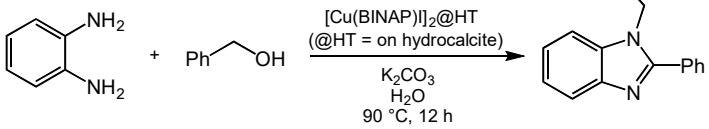
Ph =



X = Br, Cl, I

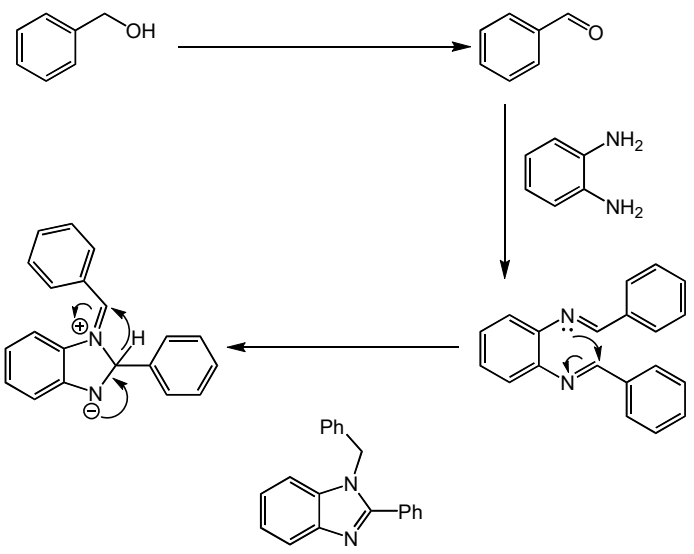
X = Br, Cl, I

Dehydrogenation - Cyclization

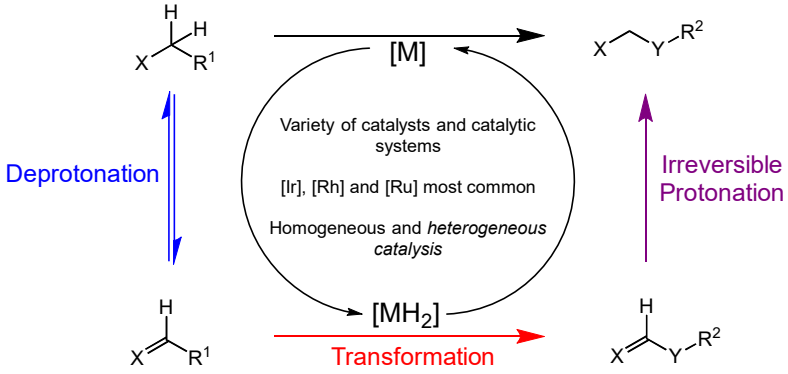


Green Chem. **2018,** Advance Article
DOI 10.1039/C8GC00557E

Mechanism



Borrowing Hydrogen (BH) Summary



C-C bond formation:
Olefin metathesis, **Aldol and Knoevenagel condensation**, Wittig reaction, indole C_3 alkylation, allylation, δ-lactonization
C-N bond formation:
Condensation, Aza Wittig reaction, amination, **N-alkylation**, condensation/N-heterocyclization