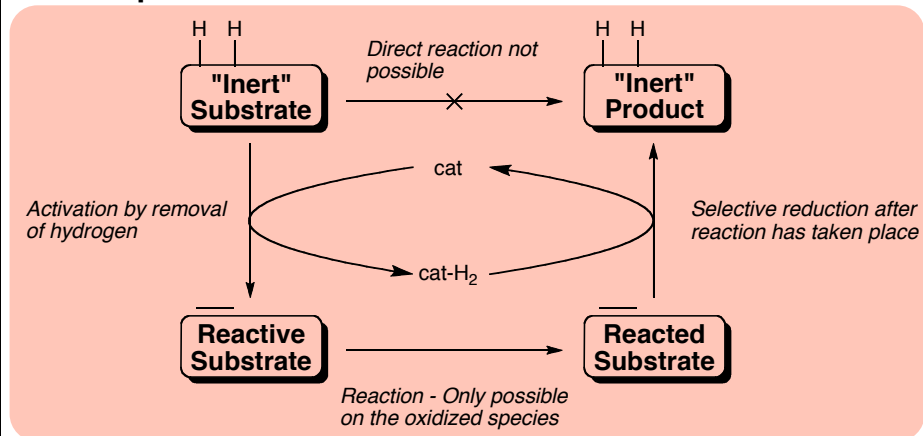


Concept



Advantages

- No net oxidation or reduction takes place in the catalytic cycle itself
- Extremely atom efficient
- "Green" - very little byproducts and waste (usually just water)
- Usually shaves off needless oxidation state fluctuations
- Allows for alternative retrosynthetic analysis

Disadvantages

- Usually high temperatures are required (110-180 °C)
- The catalyst must not interfere with reagents (not an issue with 2 step protocols)
- Selectivity of activation can be an issue

Also known as...

- hydrogen autotransfer
- dehydrogenative activation
- catalytic electronic activation

Big players in the field:

Jonathan M. J. Williams, Miguel Yus, Matthias Beller, Michael J. Krische, Rhett Kempe, Yasutaka Ishii, Ryohei Yamaguchi, Ken-ichi Fujita

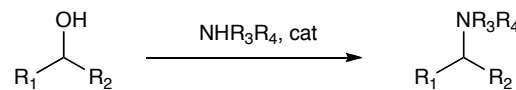
Notable Reviews:

- Williams, *Adv. Synth. Catal.* **2007**, *349*, 1555-1575 (alcohols general)
- Williams, *Dalton Trans.* **2009**, 753-762 (alcohols general, not comprehensive)
- Krische, *ACIEE* **2009**, *48*, 34-46 (Alcohols + alkenes/alkynes)
- Yus, *Chem. Rev.* **2010**, *ASAP*, doi: 10.1021/cr9002159 (classified by catalyst, general)
- Crabtree, *Chem. Rev.* **2010**, *ASAP*, doi: 10.1021/cr900202j (includes alkanes, Seiple's choice!)

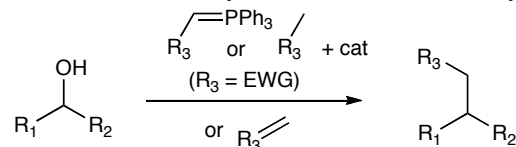
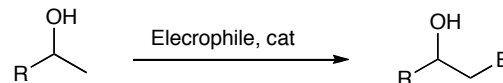
Must-Read Paper: J. M. J. Williams *et al*, *JACS* **2009**, *131*, 1766 (article on amination of alcohols. Scores of tables showing scope with the best catalyst system to date [Ru(*p*-cymene)Cl₂]₂).

Table of Contents

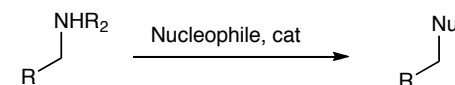
1. Ami(n/d)ation of alcohols



2. Alcohols as Electrophiles for Carbon Nucleophiles

3. Alcohols as β -nucleophiles

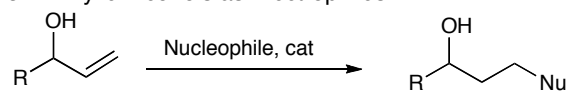
4. Dehydrogenative Activation of Amines



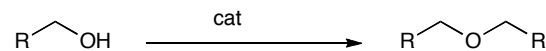
5. Miscellaneous

5A - (de)racemization

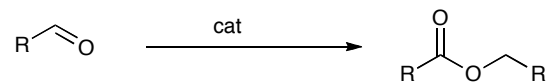
5B - Allylic Alcohols as Electrophiles



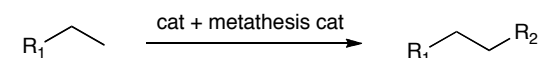
5C - Oxygen Nucleophiles



5D - Tishchenko Reaction

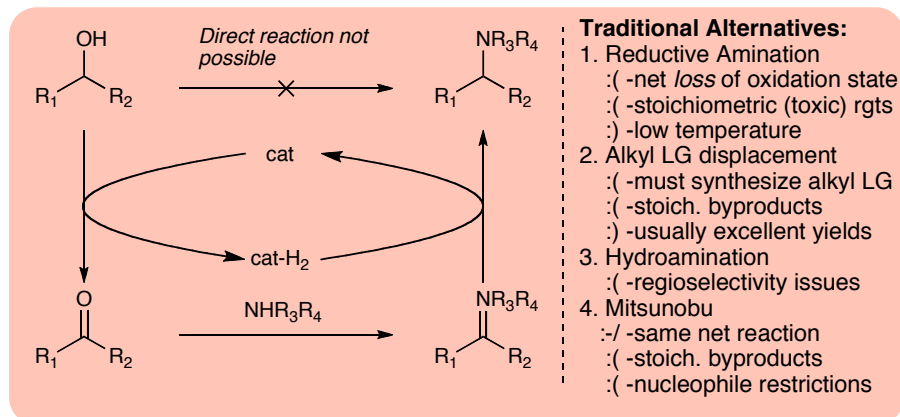


6. Reactions with alkanes

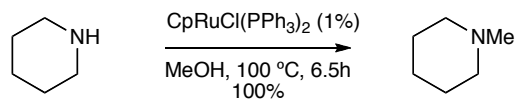


7. Applications to Pharmaceuticals and Natural Products

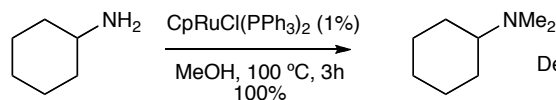
1. Ami(n/d)ation of Alcohols



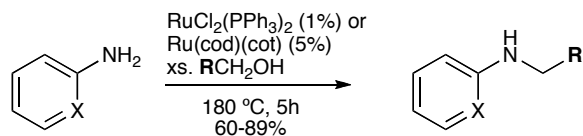
Simple Amine Alkylations:



Restriction: This catalyst does not work for aryl amines



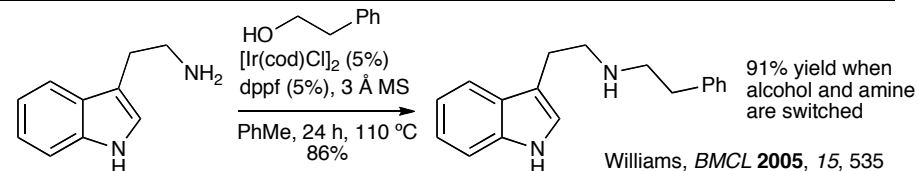
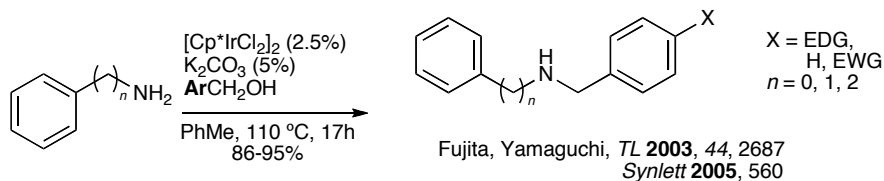
Del Zotto, *EJIC*, 2004, 524



-Ru(cod)(cot) gave improved selectivity for mono alkylation
-addition of PR₃ and P(OR)₃ increased dialkylation
-Other Ru cats can be used at 110 °C (CC 2007, 725)

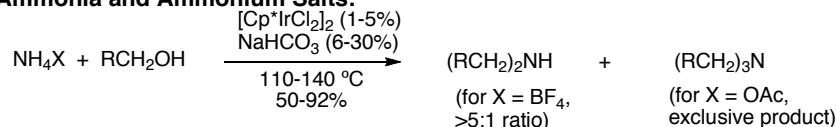
Watanabe, *JOC* 1984 49, 3359
Roundhill, *Polyhedron* 1990, 9, 2517

Note: Ru₃(CO)₁₂ with PR₃ is also a superb catalysts system for these transforms (>90%)
Beller, *Chem. Asian J.* 2007, 2, 403

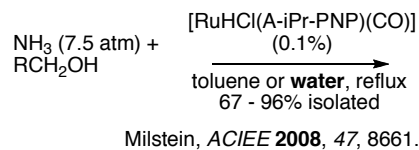


My vote for best amination catalyst system: [Ru(*p*-cymene)Cl₂]₂ with a diphosphine ligand in refluxing toluene. J.M.J. Williams had a very nice JACS full article on this last year with an enormous amount of tables and conversions that were generally 90-100% on alkyl and aryl amines and alcohols. Note that plenty of secondary alcohols are demonstrated in this article as well, and this methodology is not limited to in-situ aldehyde generation. REF: Williams *JACS*, 2009, 131, 1766.

Ammonia and Ammonium Salts:

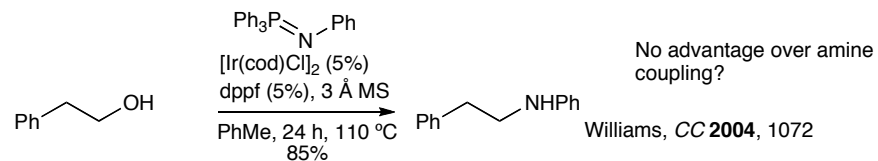


Yamaguchi, Fujita, *OL* 2008, 10, 181.

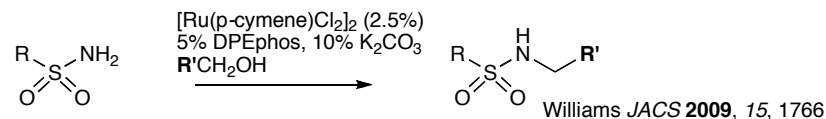
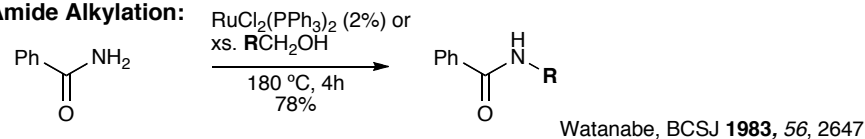


Very powerful and very atom economical! Works on a huge range of primary alcohols (alkyl, aryl (withdrawn and rich), branched, heterocyclic, even oxetane-containing). Catalyst available in 2 steps and is shelf-stable.

Indirect Aza-Wittig:

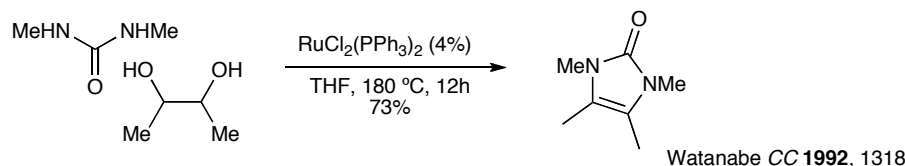
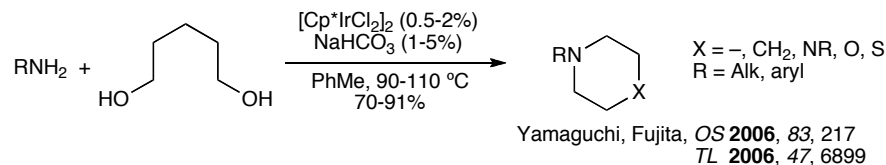


Amide Alkylation:

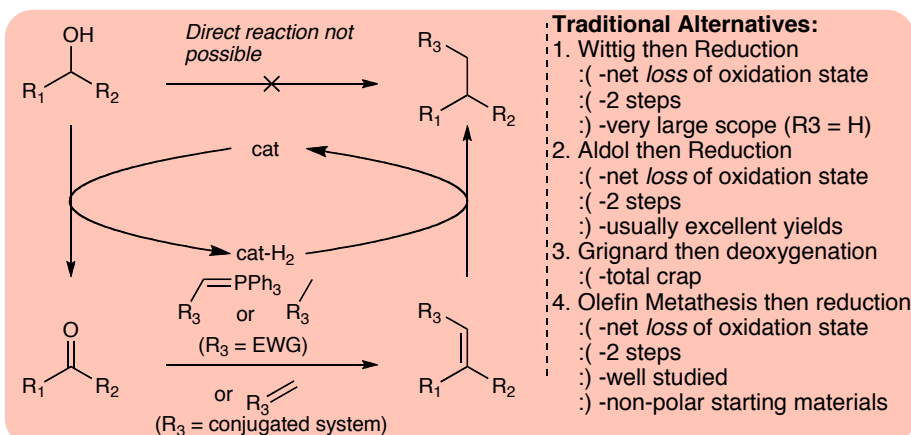


Note: Carbamates work as well with [Cp*IrCl₂]₂. See Yamaguchi/Fujita *T* 2009, 65, 3624

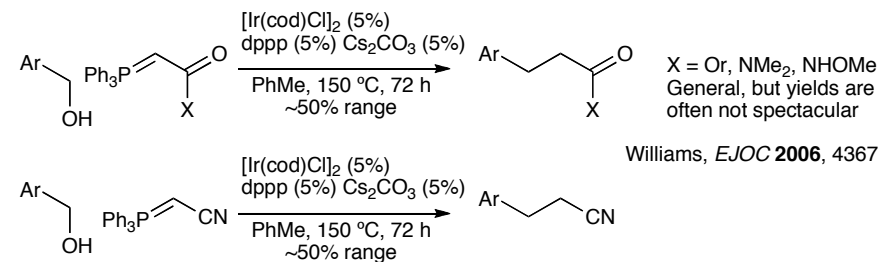
Heterocycle Formation from Diols:



2. Alcohols as Electrophiles for Carbon Nucleophiles

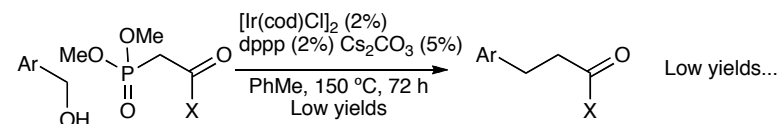


Indirect Wittig Reaction

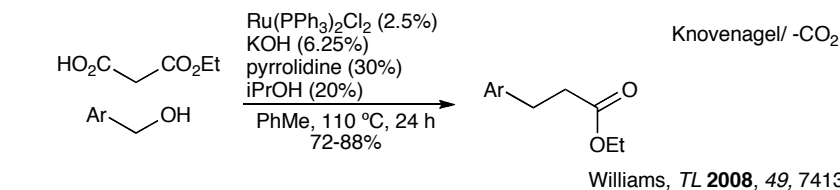
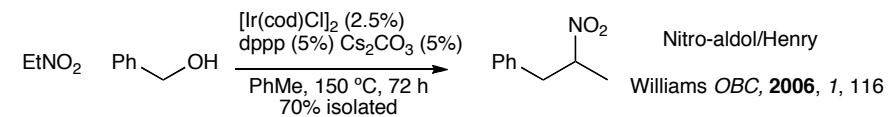
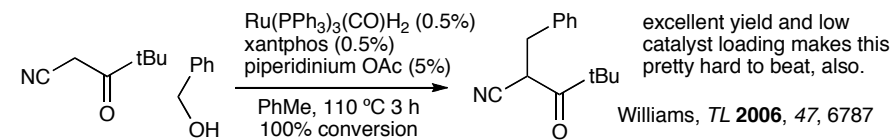
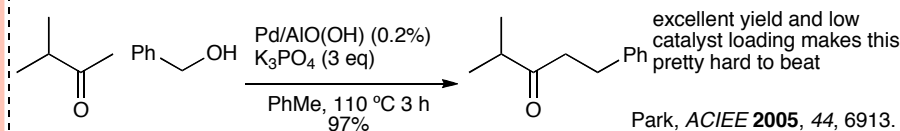
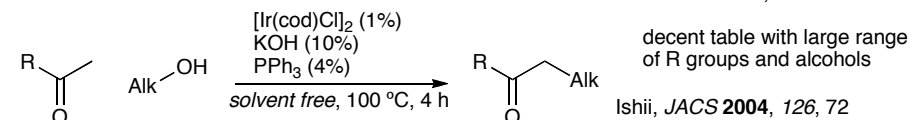
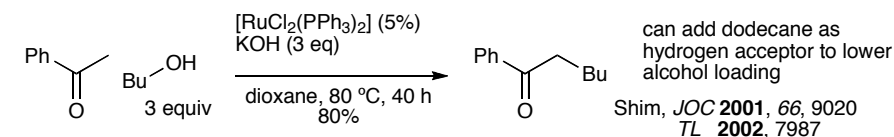


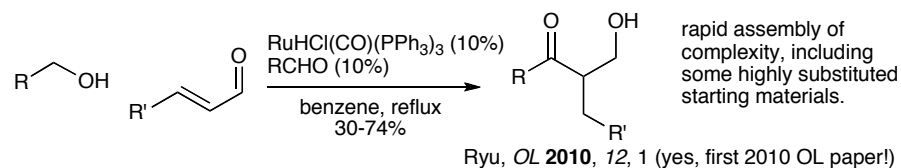
Another catalyst using an NHC ligand showed good yields even at 80 °C for some substrates.
 See Williams *JACS* **2007**, *129*, 1987.

Indirect HWE Reaction

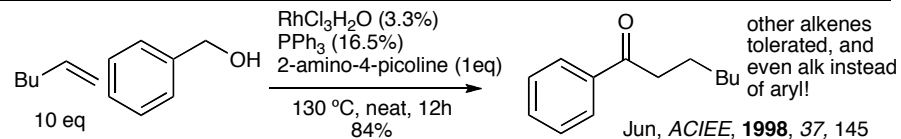
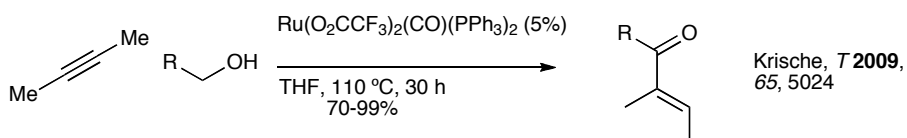
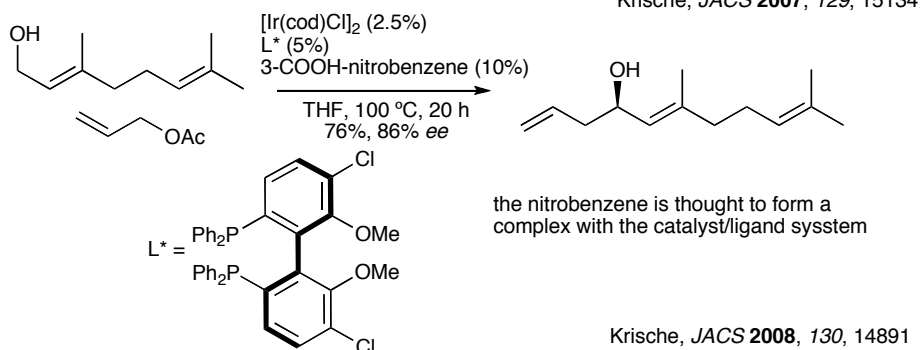
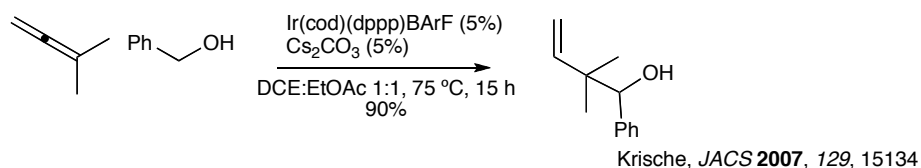
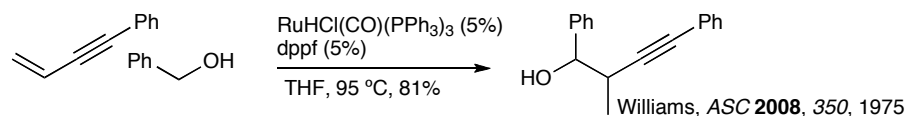
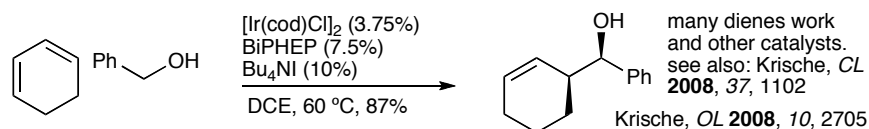


Indirect Aldol-type Reactions

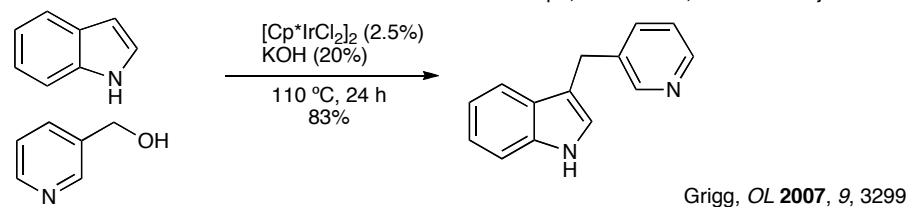
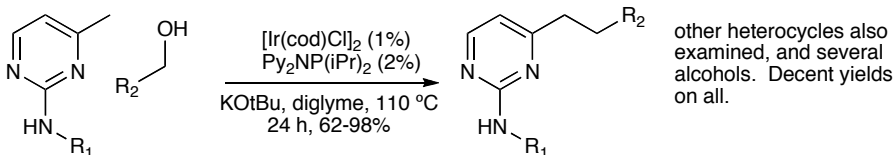




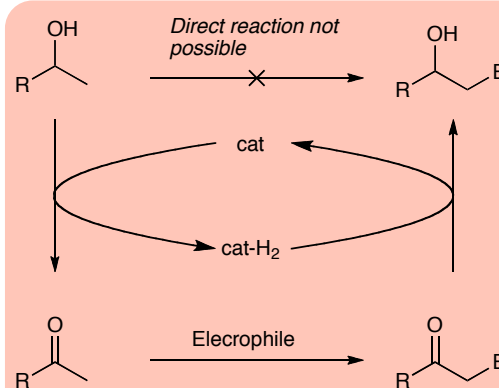
Alkene Nucleophiles - Great specific review: Krische, *ACIEE* **2009**, *48*, 34.



Other Carbon Nucleophiles



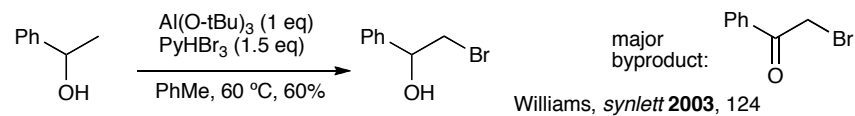
3. Alcohols as β -Nucleophiles



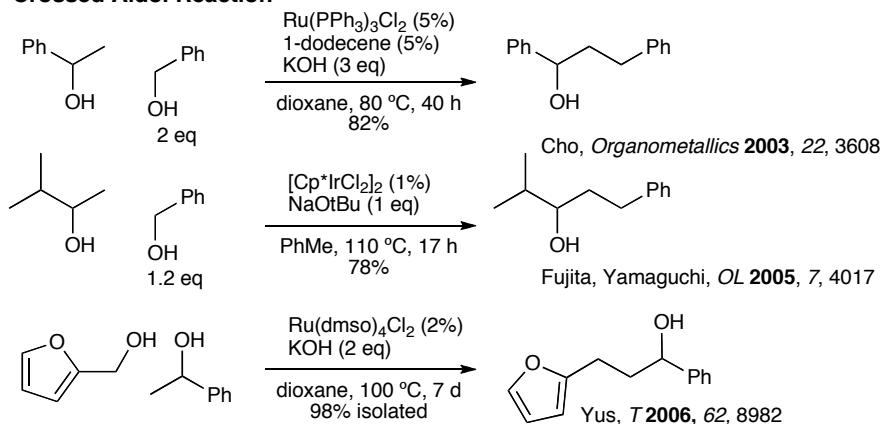
Traditional Alternatives:

1. Rxn of Carbonyl then [H]
: (-net loss of oxidation state)
: (-2 step)
2. For E = carbonyl, aldol/[H]
: (-selective reduction needed)
: (-aldols are extremely versatile)
- 3.

α -Oxidation

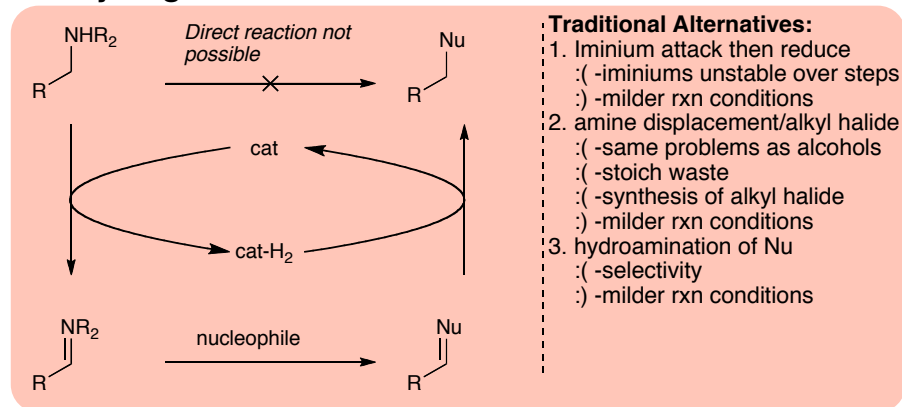


Crossed Aldol Reaction

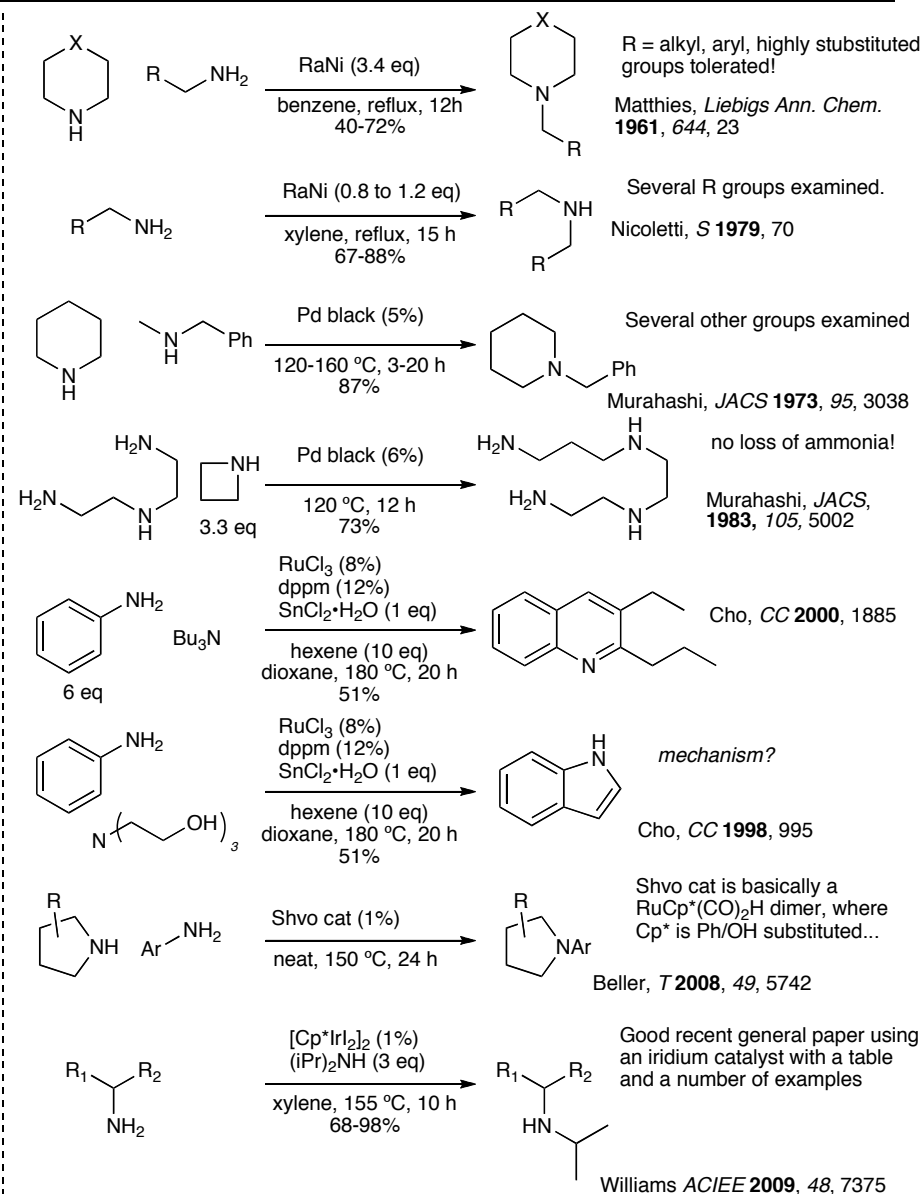
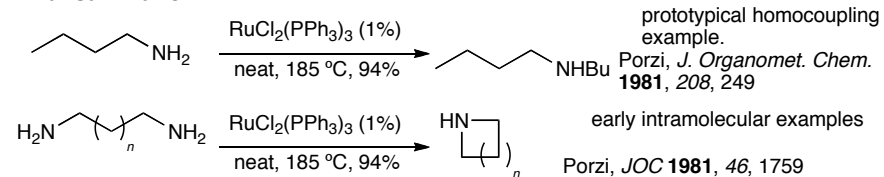


NOTE: you can also start with a ketone, and with 2+ eq of the primary alcohol, automatic reduction to the same products will occur via xfer hydrogenation!
See: Yus, *T* **2006**, *62*, 8988

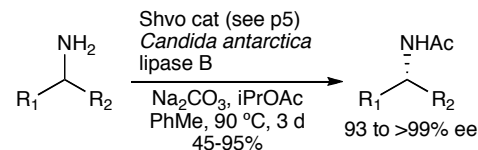
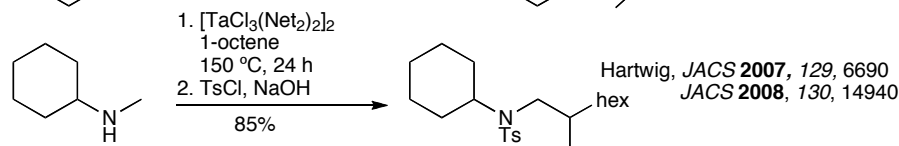
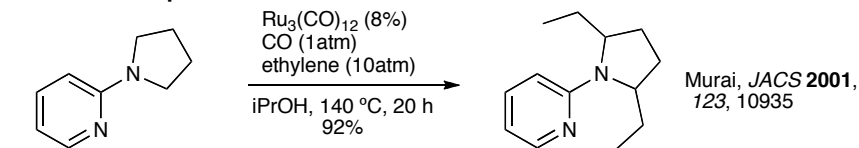
4. Dehydrogenative Activation of Amines



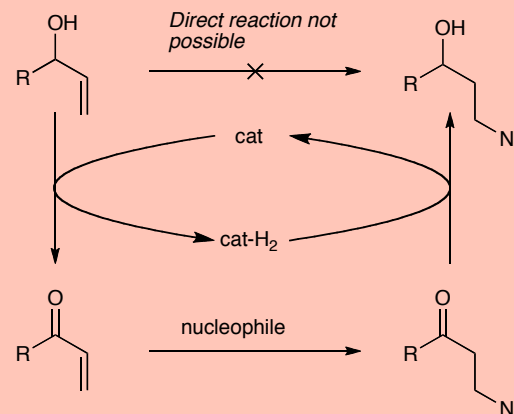
Transamination



Carbon Nucleophiles



5B. Allylic Alcohols as Electrophiles

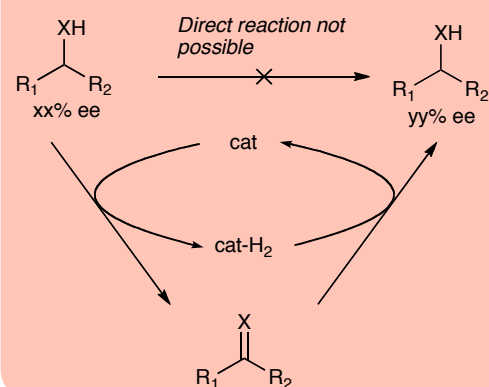


Traditional Alternatives:

- conjugate add'n then [H]
:- two steps, net reduction
:- more control over sequence
- directed alkene oxidation
= -limited "Nu" selection
:- regioselectivity issues
- electrophilic alkene addition
:- orthogonal approach

5. Miscellaneous

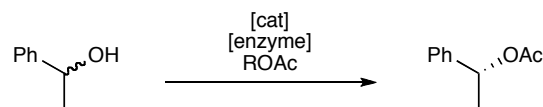
5A. (De)racemization Reactions



Traditional Alternatives:

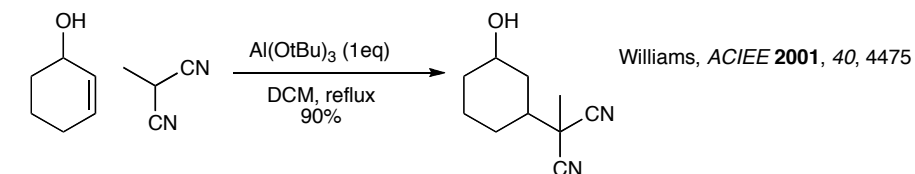
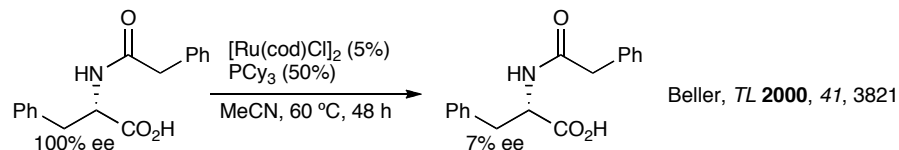
- oxidation then reduction
:- two very mundane steps
:- usually stoich. materials
:- hydride reductants are very versatile!
- no traditional alternative for amines!

Briefly - Dynamic Kinetic Resolution



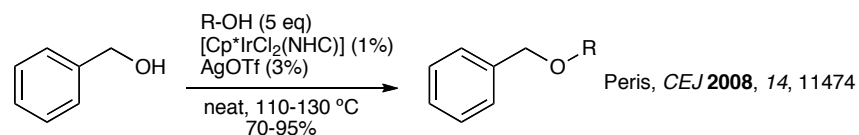
Although this fits under borrowing hydrogen, I'm sure none of you want to spend any time on it. It has been extensively reviewed. See: Bäckvall, *CR* 2003, 103, 3247 and references therein

(De)racemization of Amines and Amides



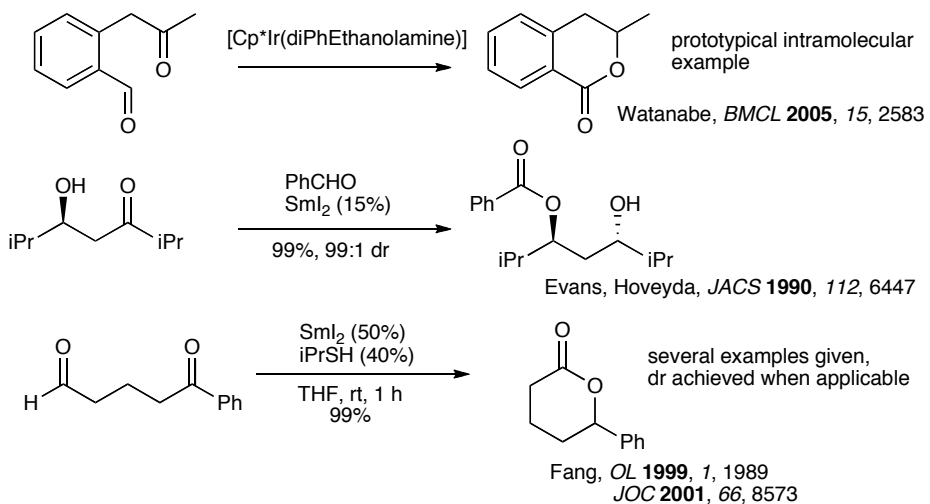
This is literally the only example I could find on this type of reaction. Needless to say, stoichiometric aluminum is not really an ideal situation, but the reaction has so much potential that I thought I would include it as a general scheme and report the example.

5C. Oxygen Nucleophiles

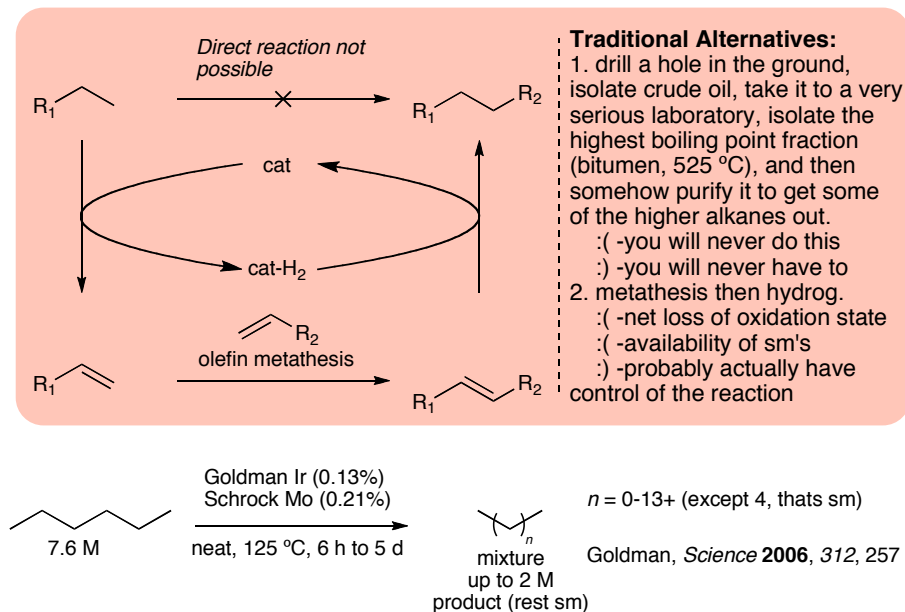


Several alcohols screened in good yield.

5D. Tishchenko Reaction

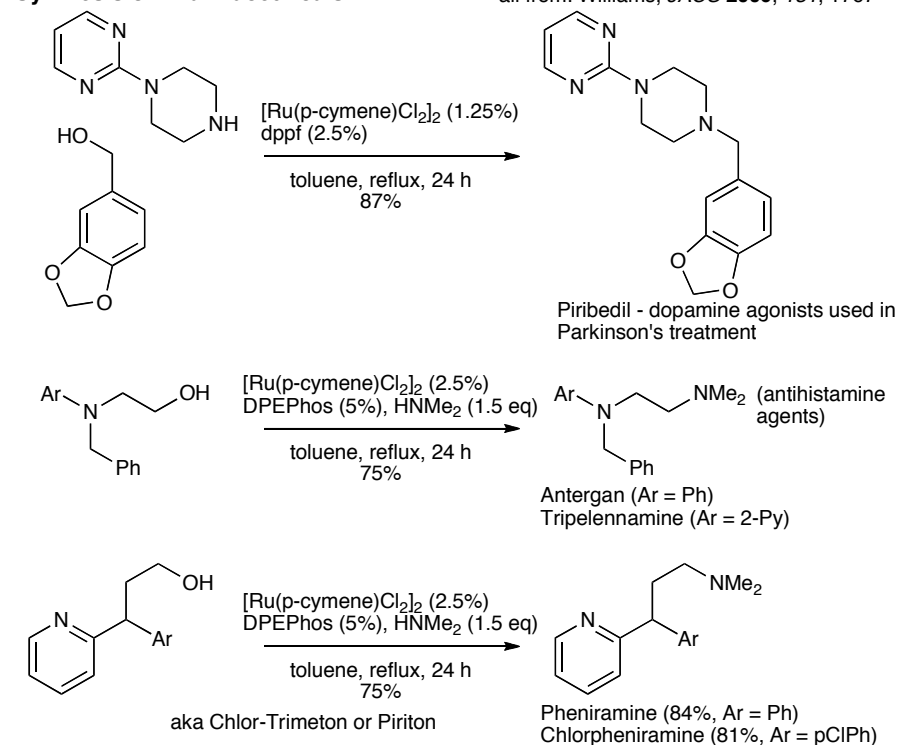


6. Reactions of Alkanes



7. Applications

Synthesis of Pharmaceuticals



Total Synthesis

