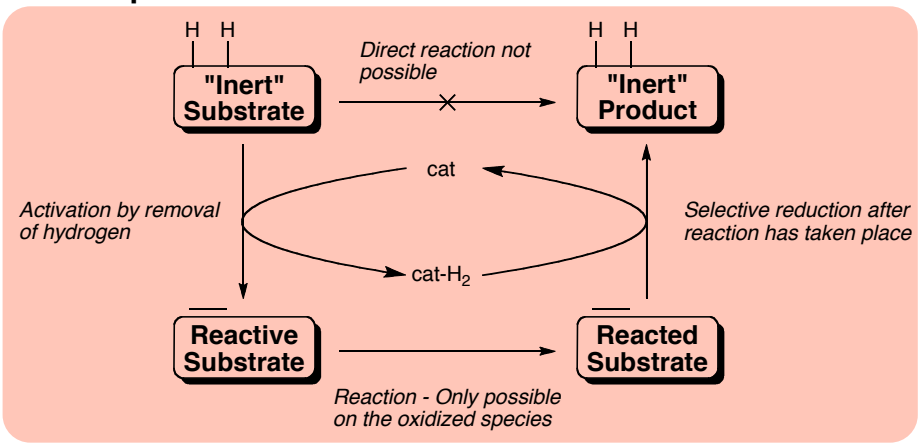
I.B. Seiple

Borrowing Hydrogen

Baran Group Meeting
1/16/2010

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 (acohols 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 $[Ru(p\text{-cymene})Cl_2]_2$.

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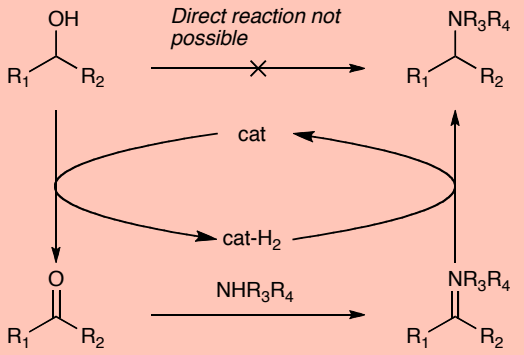
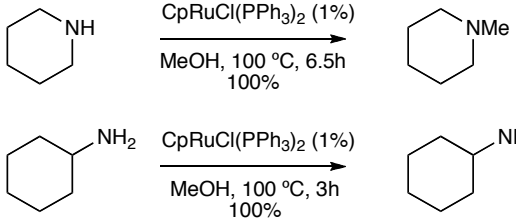
1. Ami(n/d)ation of Alcohols



Traditional Alternatives:

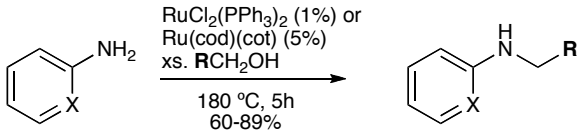
1. Reductive Amination
   :(-net *loss* of oxidation state
   :(-stoichiometric (toxic) rgts
   :) -low temperature
2. Alkyl LG displacement
   :(-must synthesize alkyl LG
   :(-stoich. byproducts
   :) -usually excellent yields
3. Hydroamination
   :(-regioselectivity issues
4. Mitsunobu
   :-/ -same net reaction
   :(-stoich. byproducts
   :(-nucleophile restrictions

Simple Amine Alkylations:



Restriction: This catalyst does not work for aryl amines

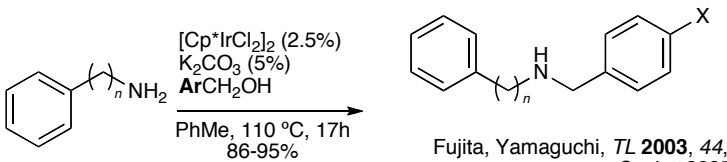
Del Zotto, *EJIC*, **2004**, 524



-Ru(cod)(cot) gave improved selectivity for mono alkylation
-addition of PR_3 and $P(OR)_3$ increased dialkylation
-Other Ru cats can be used at 110 ºC (CC **2007**, 725)

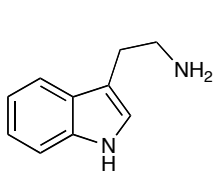
Watanabe, *JOC* **1984** *49*, 3359
Roundhill, *Polyhedron* **1990**, *9*, 2517

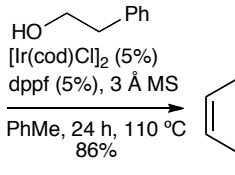
Note: $Ru_3(CO)_{12}$ with PR_3 is also a superb catalysts system for these transforms (>90%)
Beller, *Chem. Asian J.* **2007**, *2*, 403

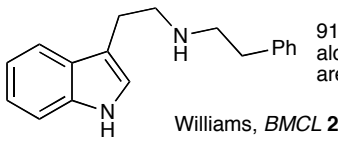


X = EDG, H, EWG
n = 0, 1, 2

Fujita, Yamaguchi, *TL* **2003**, *44*, 2687
Synlett **2005**, 560





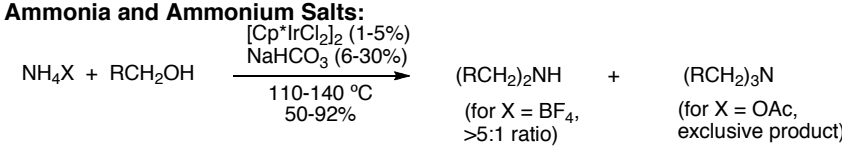


91% yield when alcohol and amine are switched

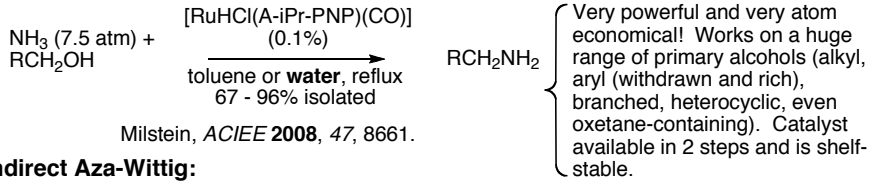
Williams, *BMCL* **2005**, *15*, 535

My vote for best amination catalyst system: $[Ru(p\text{-cymene})Cl_2]_2$ 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:



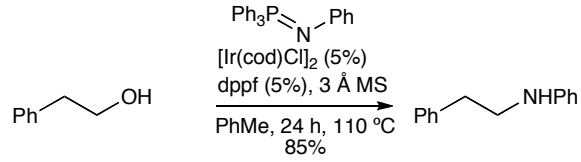
Yamaguchi, Fujita, *OL* **2008**, *10*, 181.



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.

Milstein, *ACIEE* **2008**, *47*, 8661.

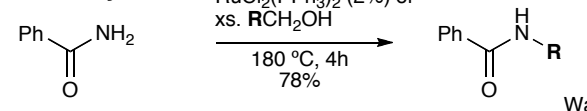
Indirect Aza-Wittig:



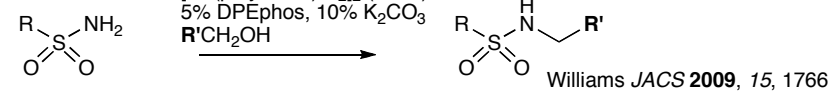
No advantage over amine coupling?

Williams, *CC* **2004**, 1072

Amide Alkylation:



Watanabe, BCSJ **1983,** *56*, 2647



Williams *JACS* **2009**, *15*, 1766

Note: Carbamates work as well with $[Cp^*IrCl_2]_2$. See Yamaguchi/Fujita *T* **2009**, *65*, 3624

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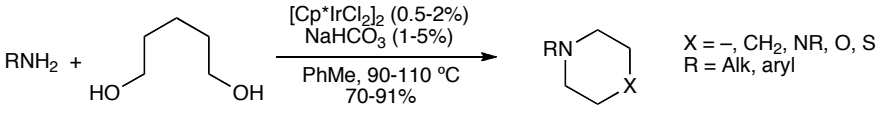
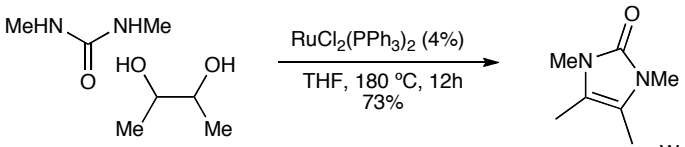
Heterocycle Formation from Diols:

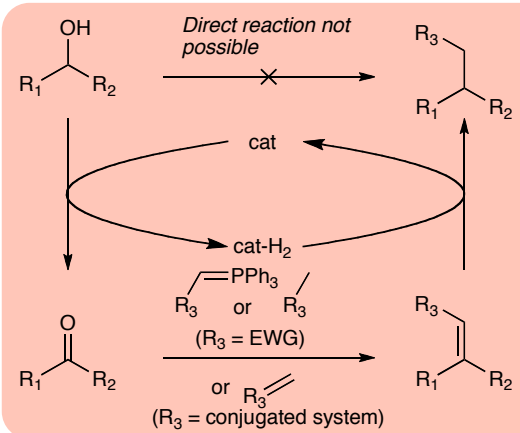


Yamaguchi, Fujita, *OS* **2006**, *83*, 217
TL **2006**, *47*, 6899



Watanabe *CC* **1992**, 1318

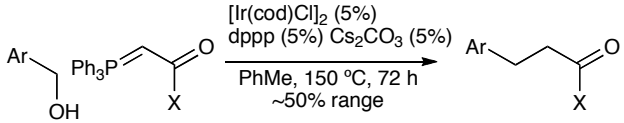
2. Alcohols as Electrophiles for Carbon Nucleophiles



Traditional Alternatives:

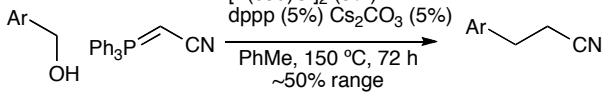
1. Wittig then Reduction
   :(-net *loss* of oxidation state
   :(-2 steps
   :) -very large scope (R3 = H)
2. Aldol then Reduction
   :(-net *loss* of oxidation state
   :(-2 steps
   :) -usually excellent yields
3. Grignard then deoxygenation
   :(-total crap
4. Olefin Metathesis then reduction
   :(-net *loss* of oxidation state
   :(-2 steps
   :) -well studied
   :) -non-polar starting materials

Indirect Wittig Reaction



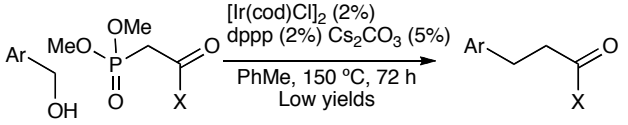
X = Or, NMe_2, NHOMe
General, but yields are often not spectacular

Williams, *EJOC* **2006**, 4367



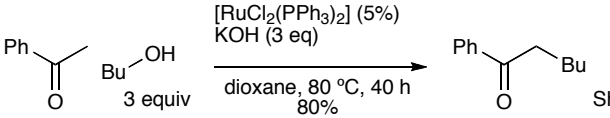
Another catalyst using an NHC ligand showed good yields even at 80 ºC for some substrates. See Williams *JACS* **2007**, *129*, 1987.

Indirect HWE Reaction



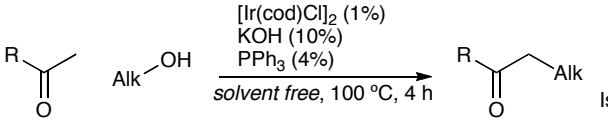
Low yields...

Indirect Aldol-type Reactions



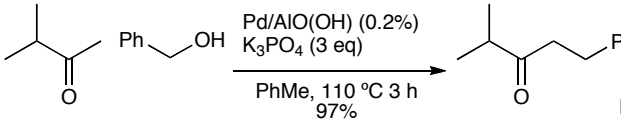
can add dodecane as hydrogen acceptor to lower alcohol loading

Shim, *JOC* **2001**, *66*, 9020
TL **2002**, 7987



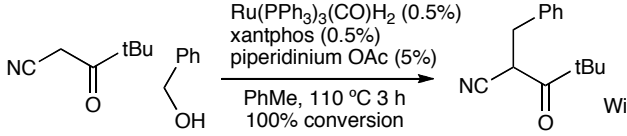
decent table with large range of R groups and alcohols

Ishii, *JACS* **2004**, *126*, 72



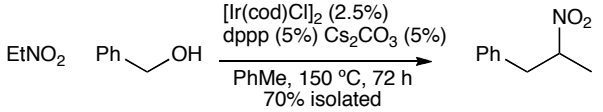
excellent yield and low catalyst loading makes this pretty hard to beat

Park, *ACIEE* **2005**, *44*, 6913.



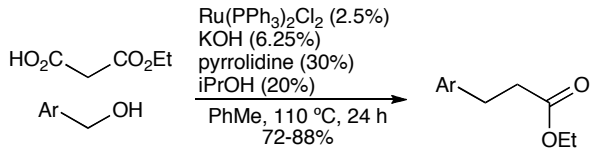
excellent yield and low catalyst loading makes this pretty hard to beat, also.

Williams, *TL* **2006**, *47*, 6787



Nitro-aldol/Henry

Williams *OBC*, **2006**, *1*, 116



Knovenagel/ -CO_2

Williams, *TL* **2008**, *49*, 7413

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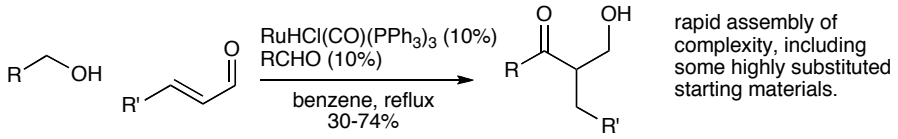
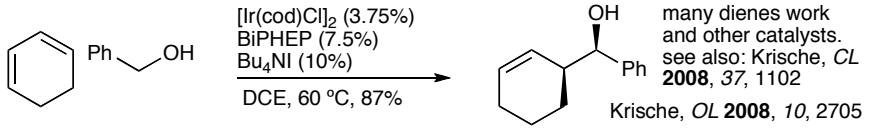


rapid assembly of complexity, including some highly substituted starting materials.

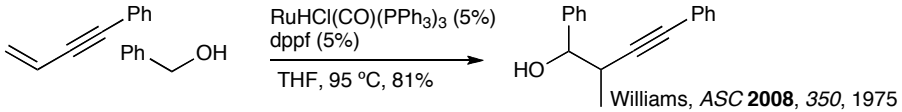
Ryu, *OL* **2010**, *12*, 1 (yes, first 2010 OL paper!)

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

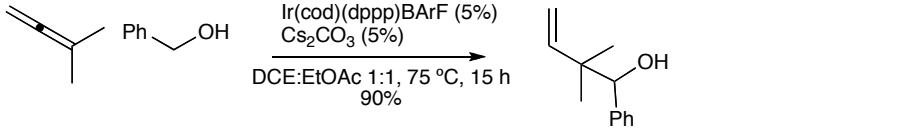


many dienes work and other catalysts. see also: Krische, *CL* **2008**, *37*, 1102

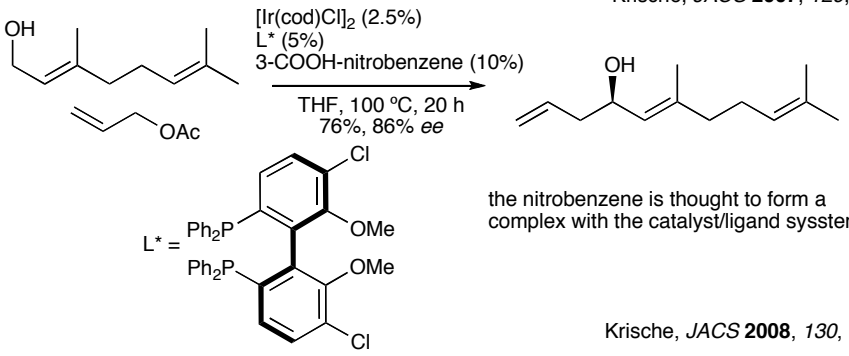
Krische, *OL* **2008**, *10*, 2705



Williams, *ASC* **2008**, *350*, 1975

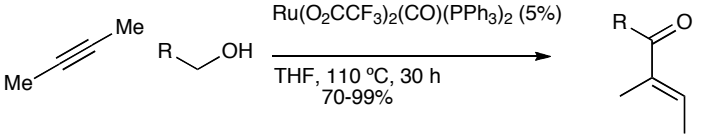


Krische, *JACS* **2007**, *129*, 15134

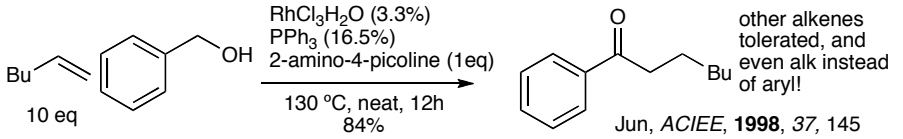


the nitrobenzene is thought to form a complex with the catalyst/ligand sysstem

Krische, *JACS* **2008**, *130*, 14891



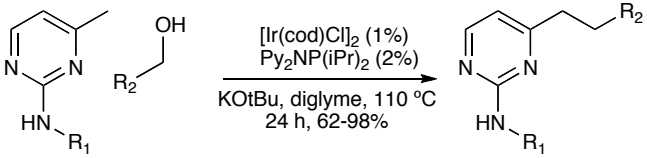
Krische, *T* **2009**, *65*, 5024



other alkenes tolerated, and even alk instead of aryl!

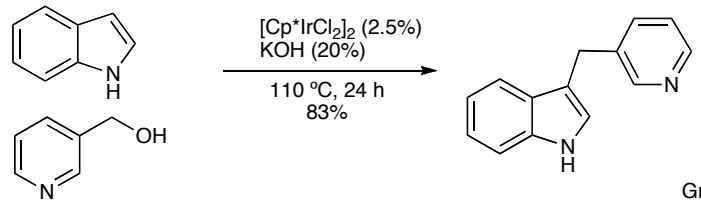
Jun, *ACIEE*, **1998**, *37*, 145

Other Carbon Nucleophiles



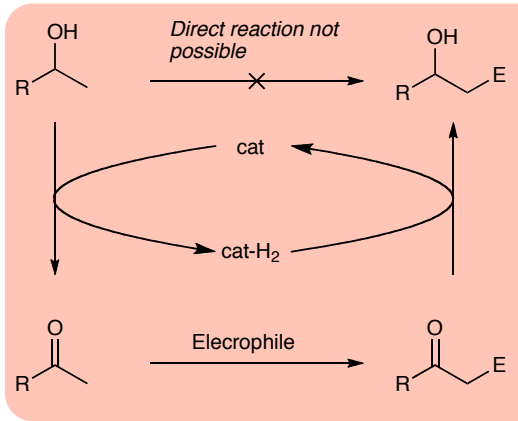
other heterocycles also examined, and several alcohols. Decent yields on all.

Kempe, *JACS* **2010**, doi: 10.1021/ja9095413



Grigg, *OL* **2007**, *9*, 3299

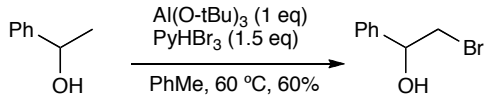
3. Alcohols as β-Nucleophiles



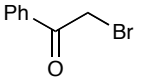
Traditional Alternatives:

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

a-Oxidation



major byproduct:



Williams, *synlett* **2003**, 124

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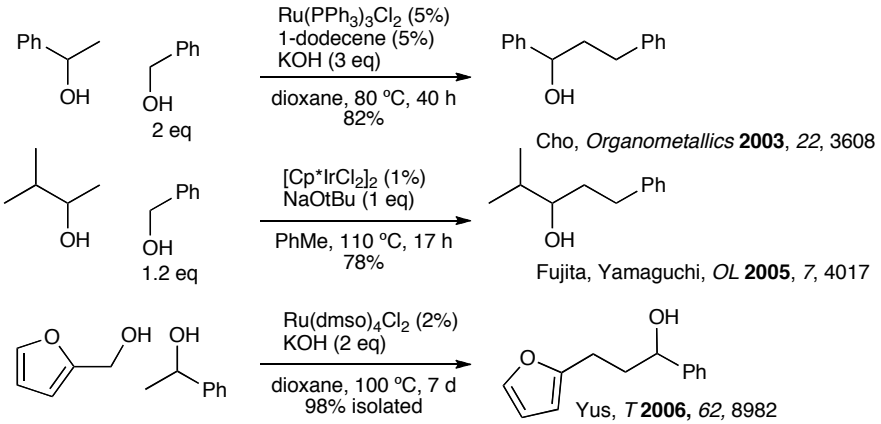
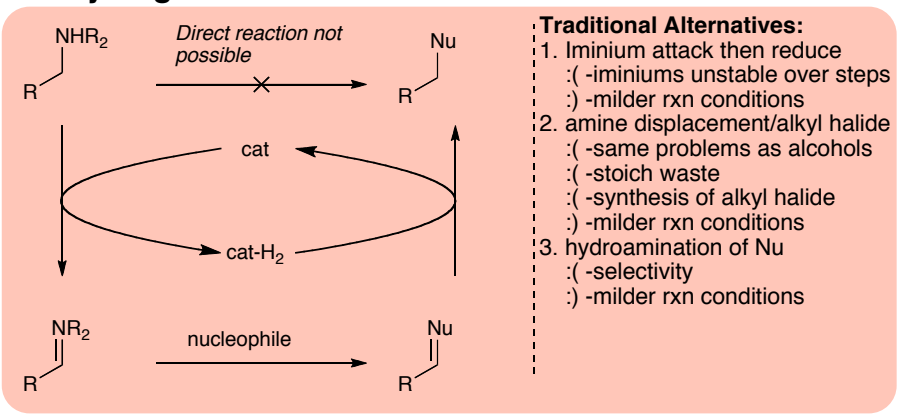
Crossed Aldol Reaction



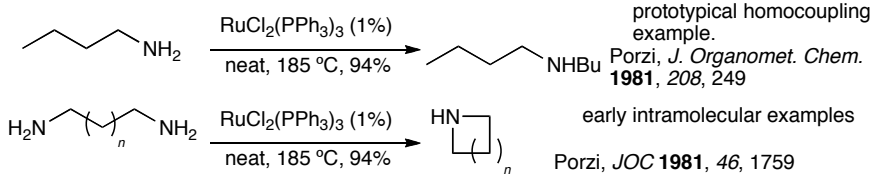
NOTE: you can also start with a ketone, and with 2+ eq of the primary alcohol, automatic reduction to the same products will occur via xfer hydrogenation!
See: Yus, *T* **2006**, *62*, 8988

4. Dehydrogenative Activation of Amines



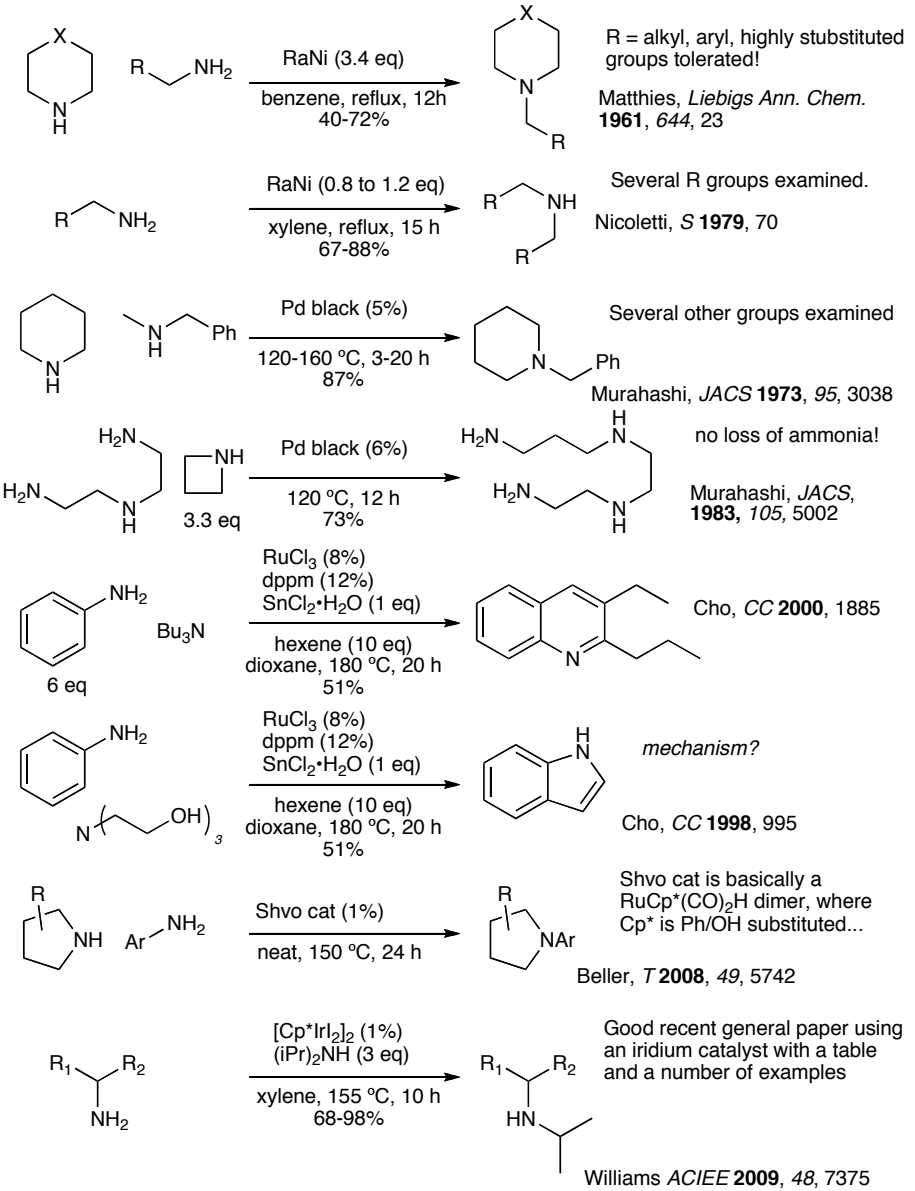
Traditional Alternatives:
1. Iminium attack then reduce
   :(-iminiums unstable over steps
   :) -milder rxn conditions
2. amine displacement/alkyl halide
   :(-same problems as alcohols
   :(-stoich waste
   :(-synthesis of alkyl halide
   :) -milder rxn conditions
3. hydroamination of Nu
   :(-selectivity
   :) -milder rxn conditions

Transamination



prototypical homocoupling example.
Porzi, *J. Organomet. Chem.* **1981**, *208*, 249

early intramolecular examples
Porzi, *JOC* **1981**, *46*, 1759



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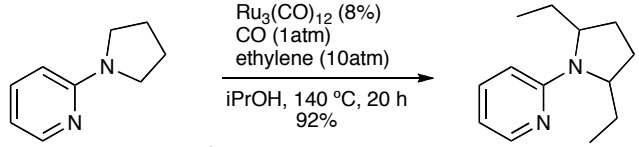
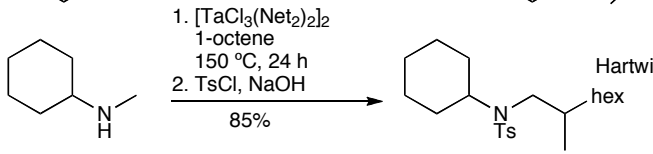
Carbon Nucleophiles



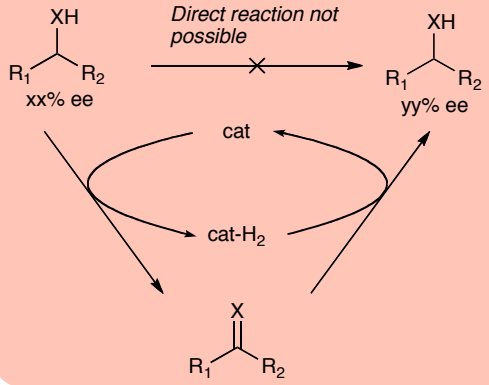
Murai, *JACS* **2001**, *123*, 10935



Hartwig, *JACS* **2007**, *129*, 6690
JACS **2008**, *130*, 14940

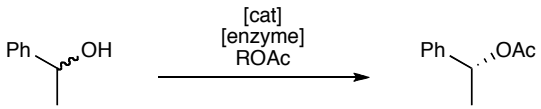
5. Miscellaneous

5A. (De)racemization Reactions



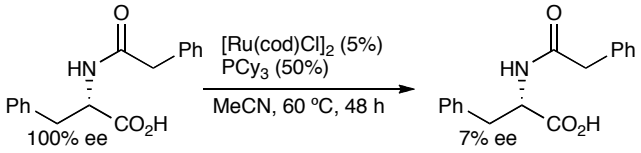
Traditional Alternatives:
1. oxidation then reduction
   :(-two very mundane steps
   :(-usually stoich. materials
   :) -hydride reductants are very versatile!
2. no traditional alternative for amines!

Briefly - Dynamic Kinetic Resolution

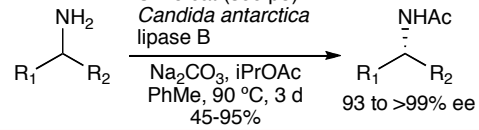


Although this fits under borrowing hydrogen, I'm sure none of you want to spend any time on it. It has been extensively reviewed. See: Bäckvall, *CR* **2003**, *103*, 3247 and references therein

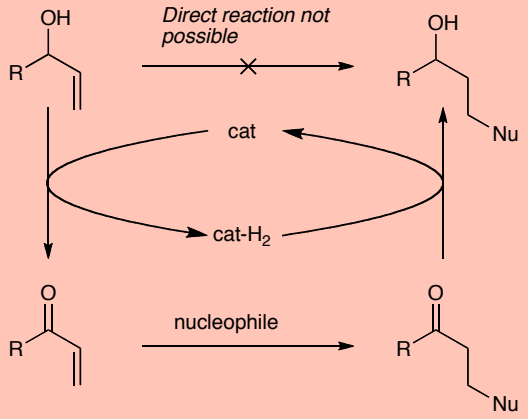
(De)racemization of Amines and Amides



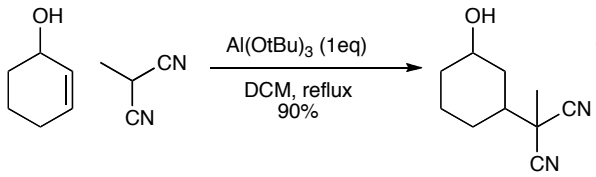
Beller, *TL* **2000**, *41*, 3821



5B. Allylic Alohols as Electrophiles



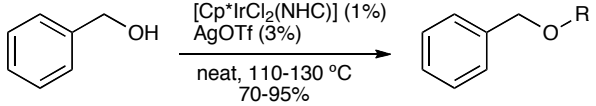
Traditional Alternatives:
1. conjugate add'n then [H]
   :(-two steps, net reduction
   :) -more control over sequence
2. directed alkene oxidation
   = -limited "Nu" selection
   :(-regioselectivity issues
3. electrophilic alkene addition
   :-/ -orthogonal approach



Williams, *ACIEE* **2001**, *40*, 4475

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



Peris, *CEJ* **2008**, *14*, 11474

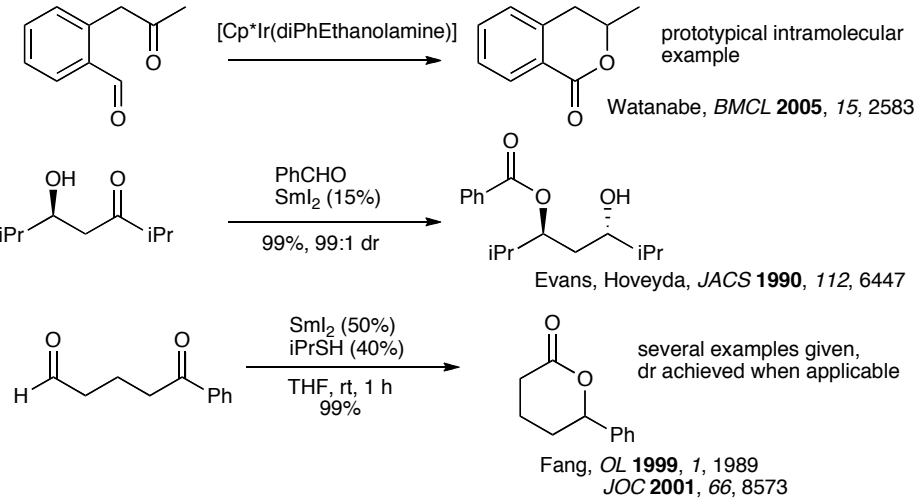
Several alcohols screened in good yield.

I.B. Seiple

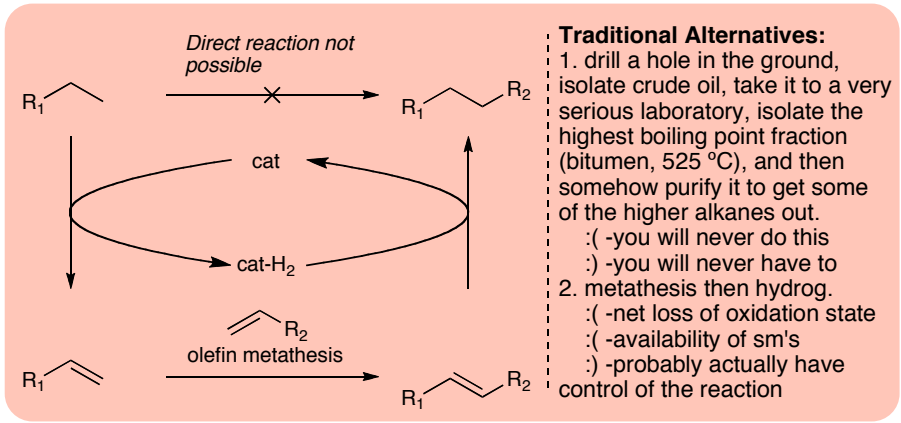
Borrowing Hydrogen

Baran Group Meeting
1/16/2010

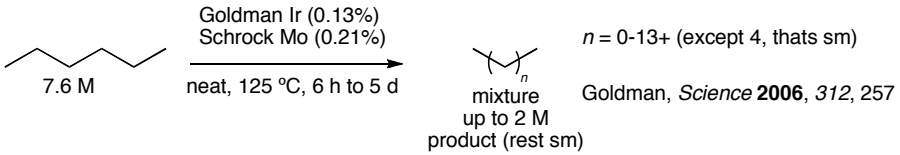
5D. Tishchenko Reaction



6. Reactions of Alkanes



Traditional Alternatives:
1. drill a hole in the ground, isolate crude oil, take it to a very serious laboratory, isolate the highest boiling point fraction (bitumen, 525 °C), and then somehow purify it to get some of the higher alkanes out.
   :(-you will never do this
   :) -you will never have to
2. metathesis then hydrog.
   :(-net loss of oxidation state
   :(-availability of sm's
   :) -probably actually have control of the reaction



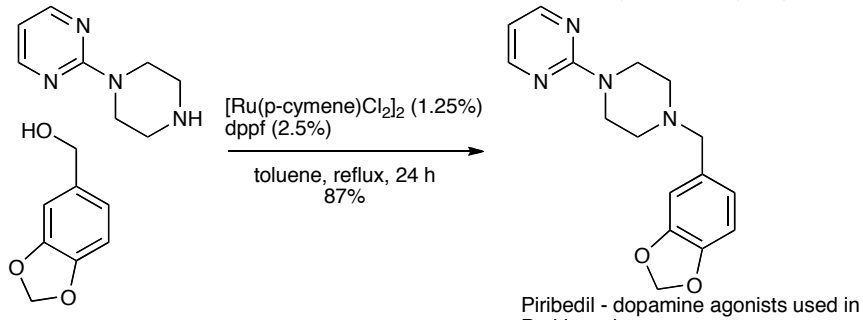
n = 0-13+ (except 4, thats sm)

Goldman, *Science* **2006**, *312*, 257

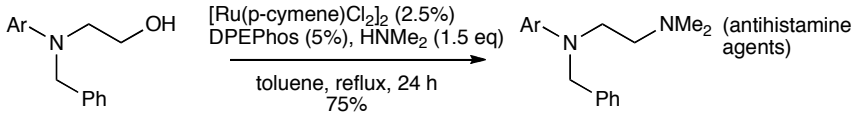
7. Applications

Synthesis of Pharmaceuticals

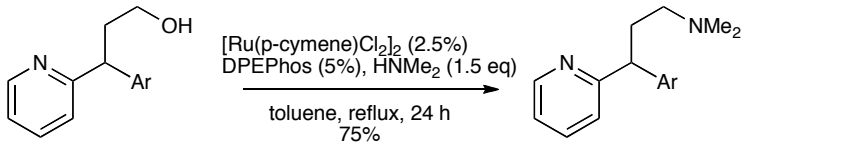
all from: Williams, *JACS* **2009**, *131*, 1767



Piribedil - dopamine agonists used in Parkinson's treatment



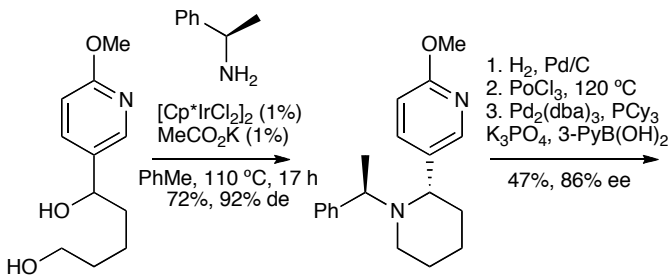
Antergan (Ar = Ph)
Tripelennamine (Ar = 2-Py)



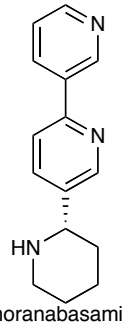
aka Chlor-Trimeton or Piriton

Pheniramine (84%, Ar = Ph)
Chlorpheniramine (81%, Ar = pClPh)

Total Synthesis



Trudell, *OL* **2009**, *11*, 1579



noranabasamine
isolated from dart frog