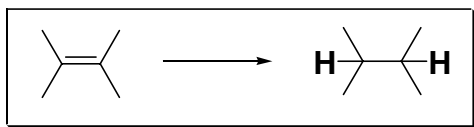


Reductions

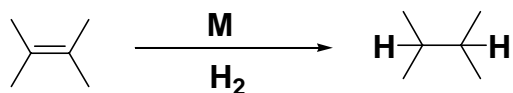
**General Resource: Trost, Comp. Org. Syn. 1991, vol 8
March, 1992, chap 19
Carey and Sundberg, vol B, Chap 5
Smith, Organic Synthesis, Chap 4**

Material organized (roughly) by transformation



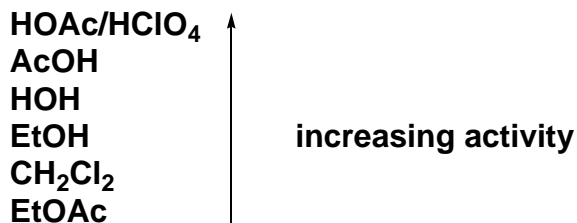
Two general classes: Transition metal hydrogenation and dissolving metal reduction

Hydrogenation: Covered in much more detail in Advanced Synthesis and Catalysis.



General trends:

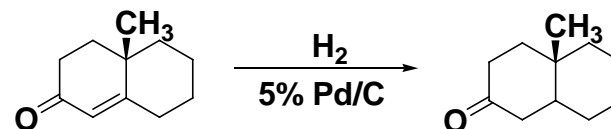
more substituted = slower
relationship of pressure:rate often not simple
many systems pose fire risk!



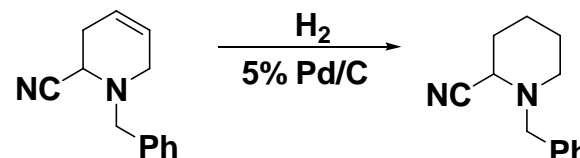
Olefin isomerization sometimes a problem

5% Pd/C

Supported metal b/c Pd \$\$\$ and tends to clump.



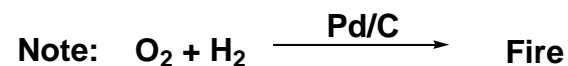
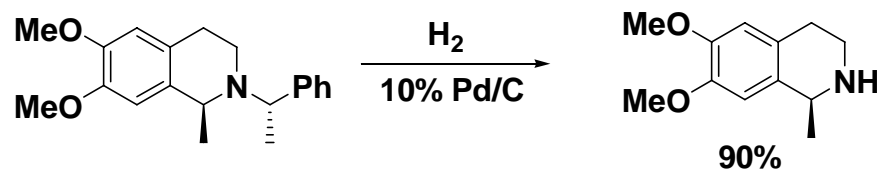
no carbonyl reduction



Benzyl survives

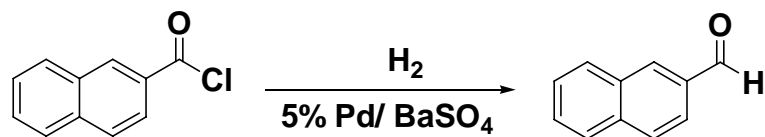
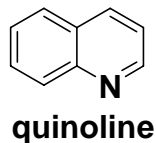
10% Pd/C

- Same deal as 5%, just more reactive
- Often used for hydrogenolysis and more difficult hydrogenations
- Mechanism of hydrogenolysis unknown

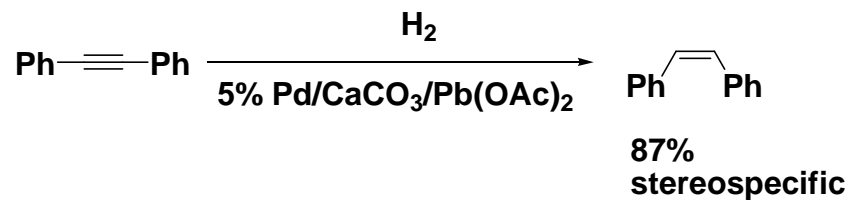


5% Pd/ BaSO₄
and
5% Pd/CaCO₃/Pb(OAc)₂ (Lindlar's cat.)
and
5% Pd/C/quinoline

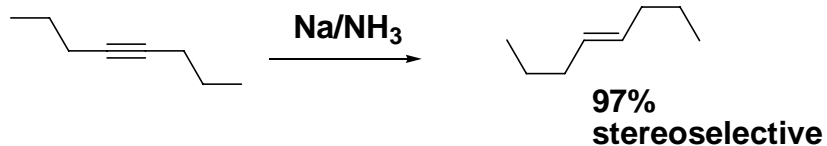
reduced activity



alkyne semi-reduction most common use:

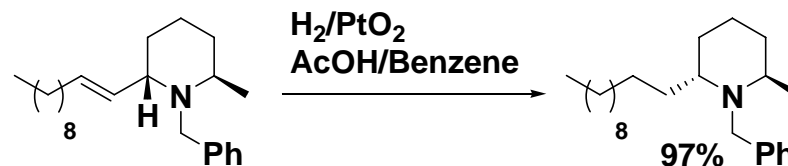


complementary method:



(more on Na to come)

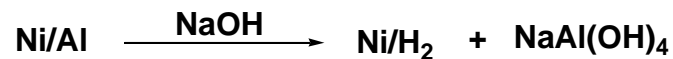
PtO₂ (Adams catalyst)
general hydrogenation cat; more active than Pd/C



Wasserman, TL, 1988, 4977

Raney Nickel (RaNi)

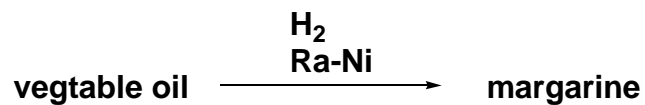
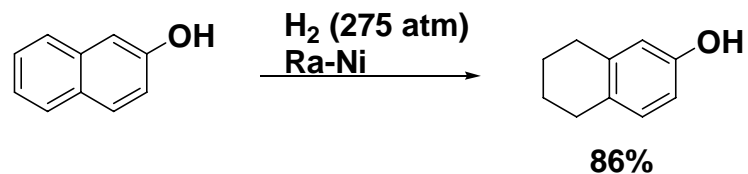
- various types available that differ in preparation
- sold as 50% wt. dispersion in water
- usually wash 5x water, 5x solvent (usually MeOH)
- Dry solid is pyrophoric!!!
- Remove by filtration under N₂ or Ar (pretty good idea for all hydrogenation catalysts)



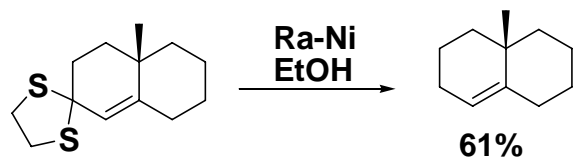
slurry has hydrogenation activity without added H₂

For some applications, can use Ni/Al in 1M NaOH/MeOH

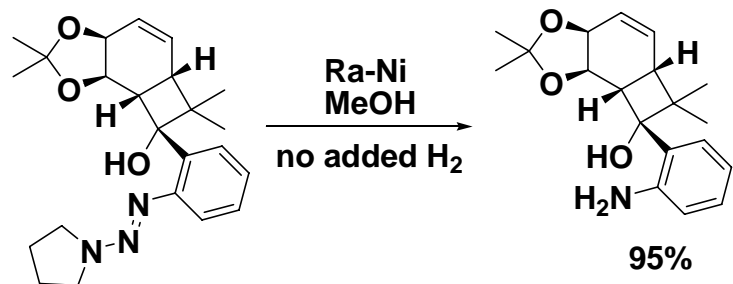
Raney Ni Applications



other uses:
desulfurization



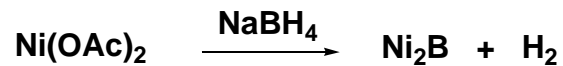
Triazene reduction



Wood, ACIEE, 2004, 1270

Ni₂B (Nickel boride)

Brown, JACS, 1963, 1004, 1005



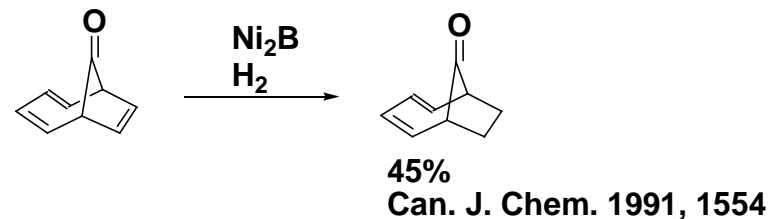
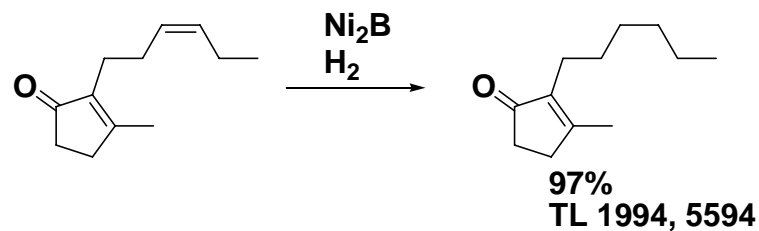
(future fuel cell technology??)

in water:

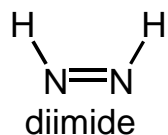
More reactive than Ra-Ni
Less double bond rearrangement

in EtOH:

Highly selective:

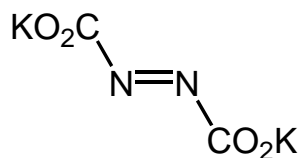


Diimide Reductions

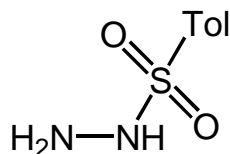
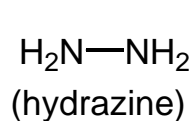


Unstable
 -generate in situ
 -use excess
 No reaction with -CN, -NO₂,
 Not poisoned by heteroatoms

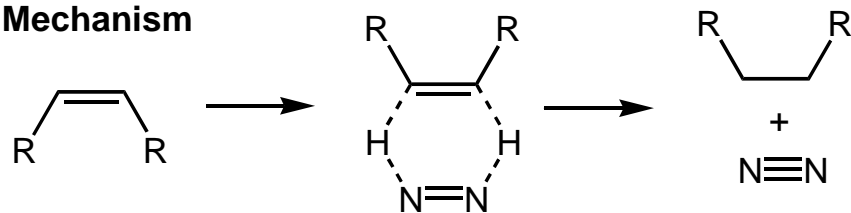
Generation



HOAc also promotes
 E-Z isomerization
JOC, **1965**, 3985



Mechanism

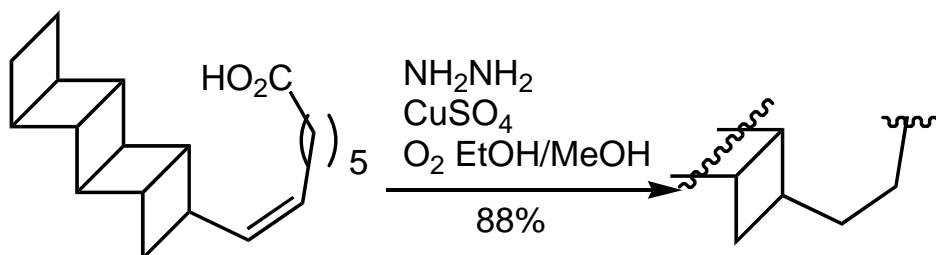


concerted hydrogen transfer
 $\Delta G^\circ \sim -50\text{kcal/mol}$

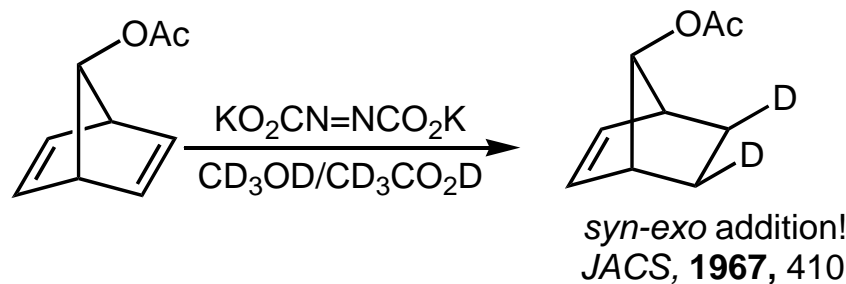
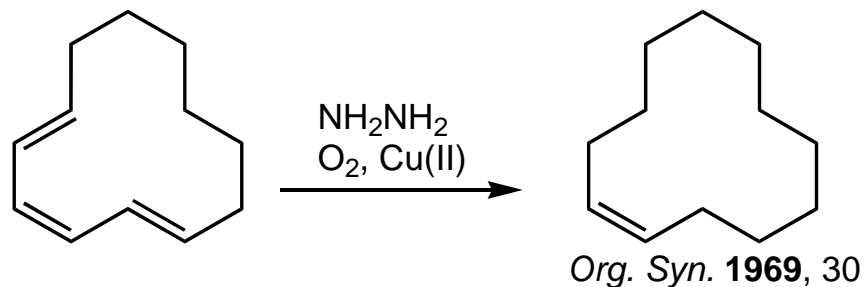
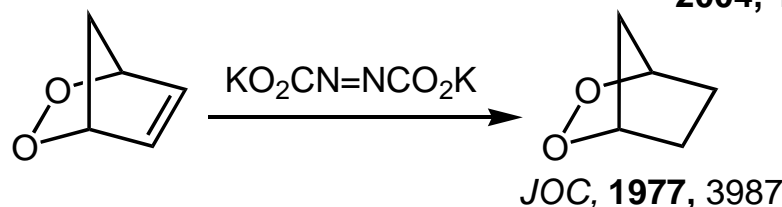
Corey, *JACS*,
1961, 2957

Examples

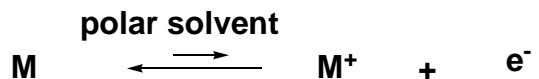
general trends: rate \uparrow as strain \uparrow
 rate \downarrow as substitution \uparrow



Corey *JACS*,
2004, 15664

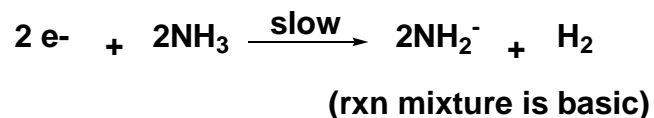


Dissolving Metal Reductions



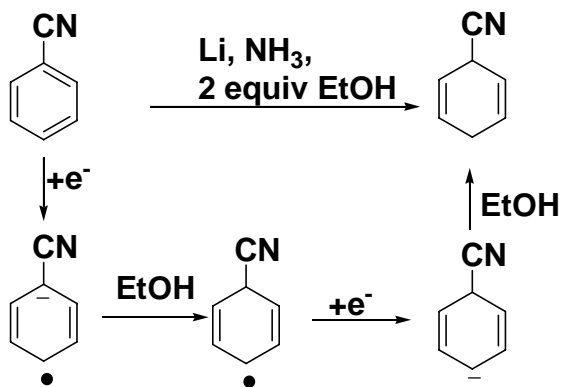
Most common solvents: NH_3 (b.p. = $-33\text{ }^\circ\text{C}$),
 MeNH_2 (b.p. = $-6.3\text{ }^\circ\text{C}$)

Competing process:

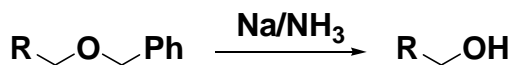
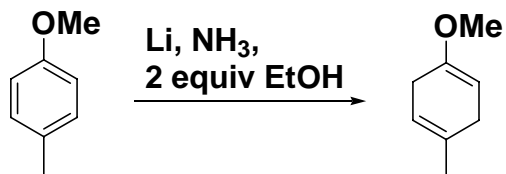


Birch Reduction

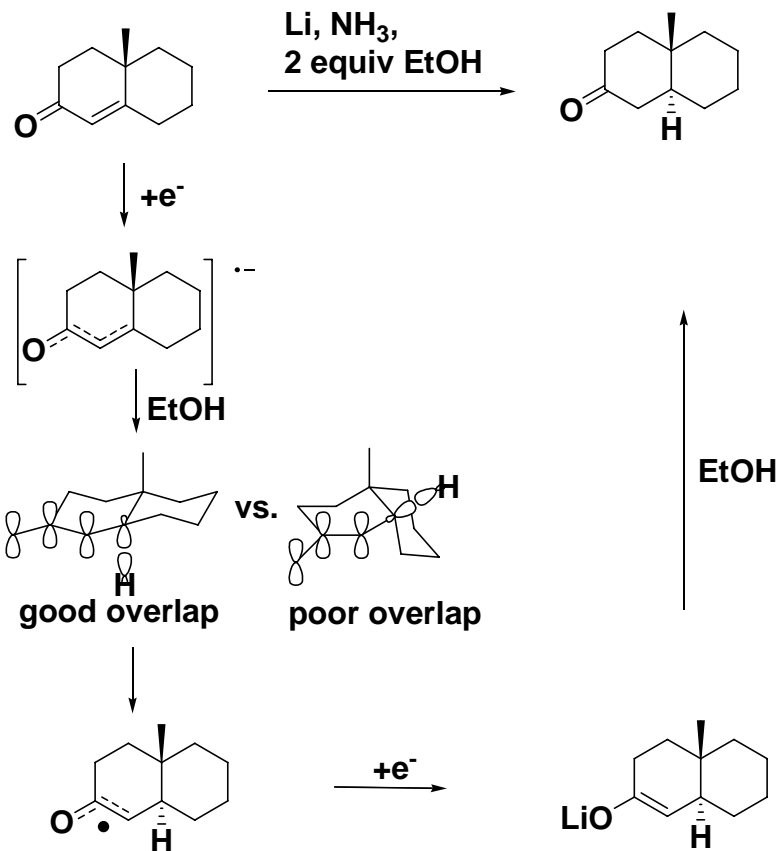
review: Rabideau, Marcinov, *Org. React*, 1992, 42, 1



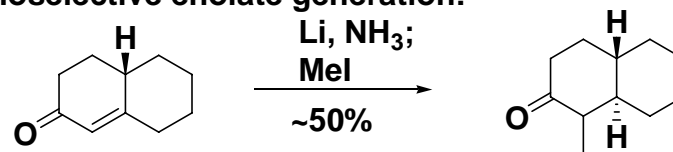
explain:



Enones

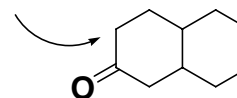


Regioselective enolate generation:



Stork, *JACS*, 1965, 275

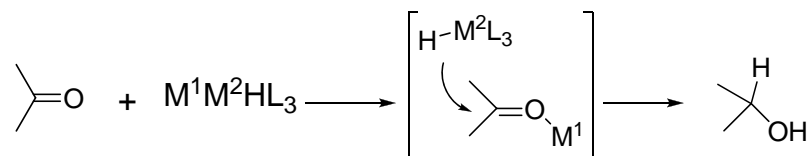
Deprotonation here



Carbonyl Reductions

Metal Hydrides-General

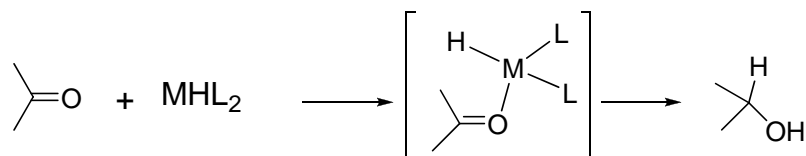
Ionic Metal Hydrides (LiAlH₄, NaBH₄, etc)



Reactivity increases with:

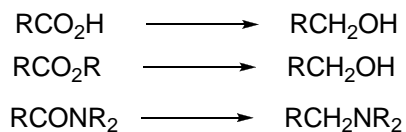
- increasing electronegative M1 (Li > Na)
- increasing electropositive M2 (Al > B)
- increasing e- donation of L (Et > H)
- increasing electrophilicity of substrate (RCHO > RCOR)

Neutral Metal Hydrides (i-Bu₂AlH, AlH₃, B₂H₆)



Reactivity increases with:

- increasing electropositive M (Al > B)
- increasing donor ability of substrate (RCO₂R > RCOR)



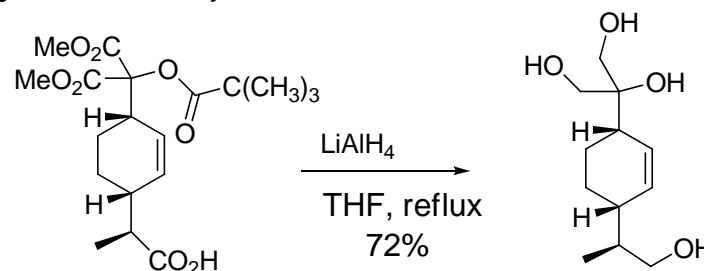
LiAlH₄

-very strong reducing agent

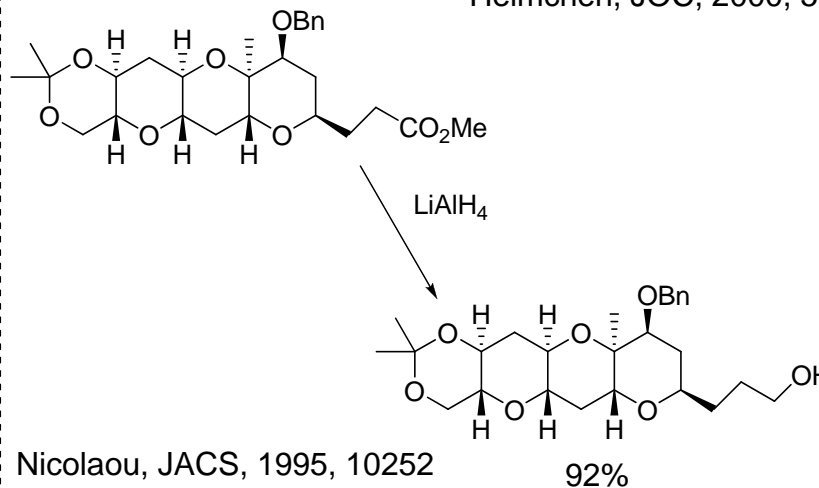
-flammable

-Workup can be trouble b/c Al salts; Feiser workup:
for ng LiAlH₄, add n mL H₂O, n mL 15% NaOH, then
3n mL H₂O, filter ppt.

-related: Red-Al [NaH₂Al(OCH₂CH₂OMe)₂]; similar reactivity but
greater solubility

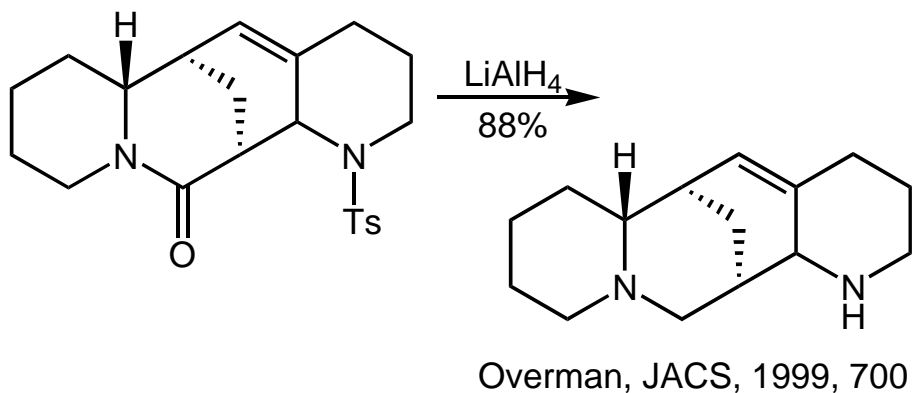


Helmchen, JOC, 2000, 5072

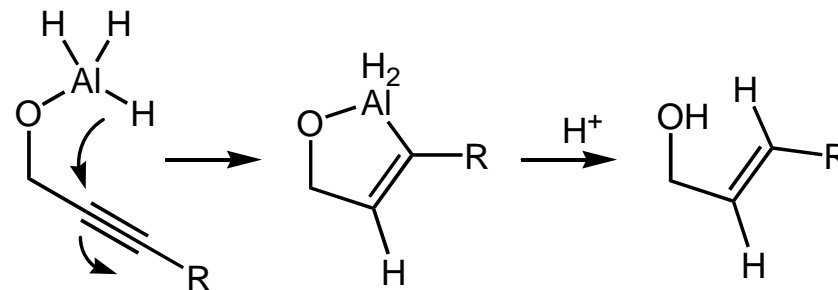


Nicolaou, JACS, 1995, 10252

92%

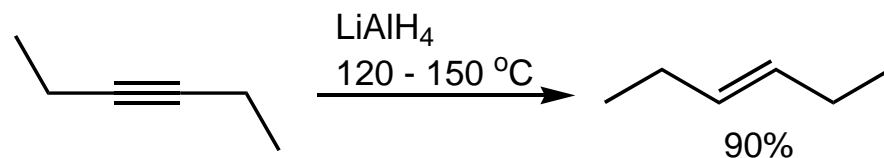


Directed reduction proceeds through intramolecular hydride delivery:

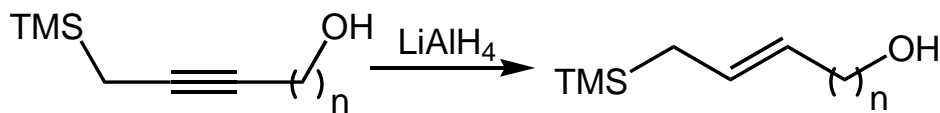


LiAlH₄ can also reduce alkynes:

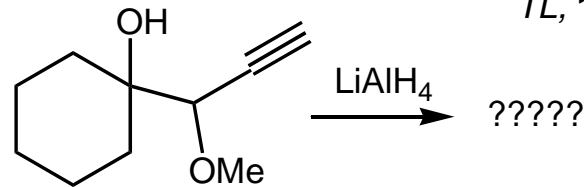
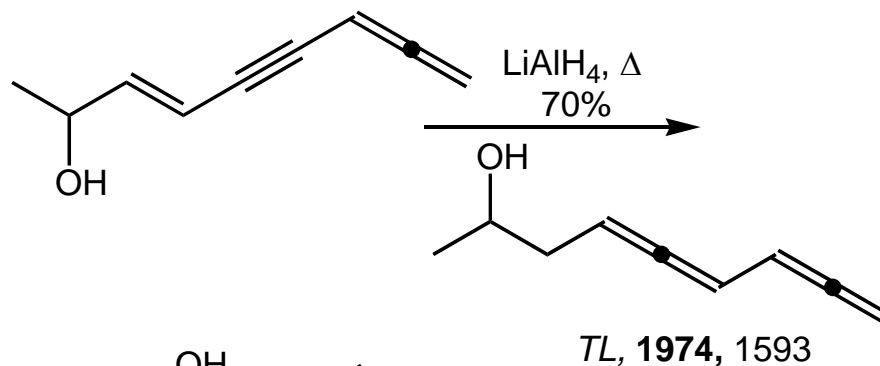
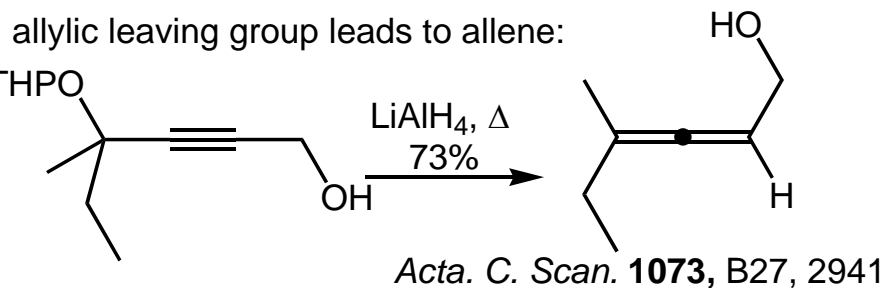
forcing conditions are required for unactivated alkynes



Nearby alcohol accelerates

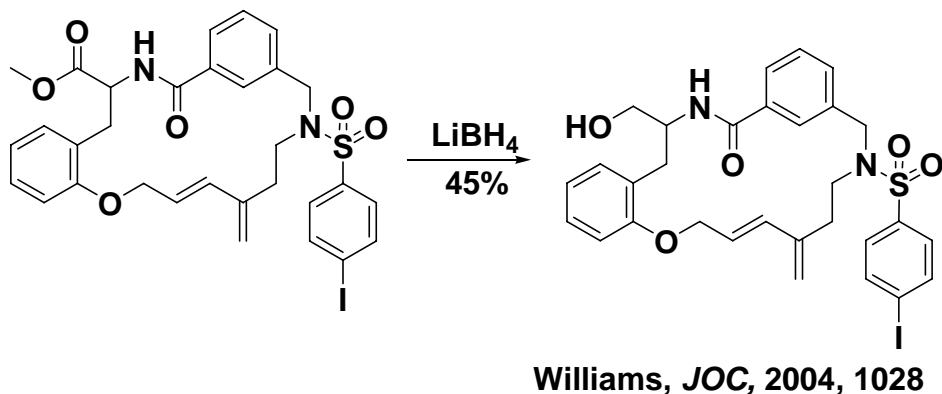
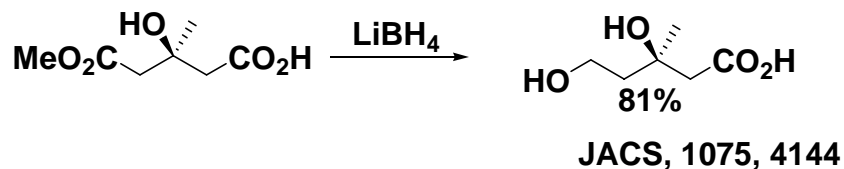


n = 1, 1h, 66 °C, 68%
JOC, **1984**, 4092
 n = 2, 48h, 85 °C, 84%
JOC, **1985**, 4014



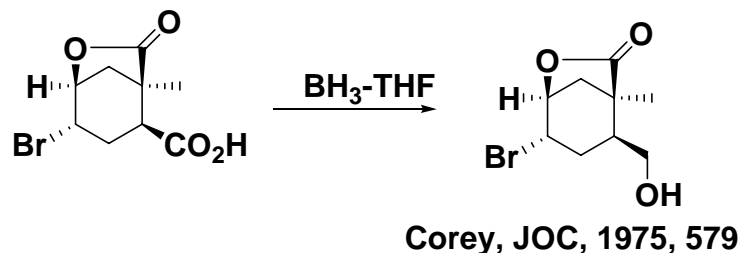
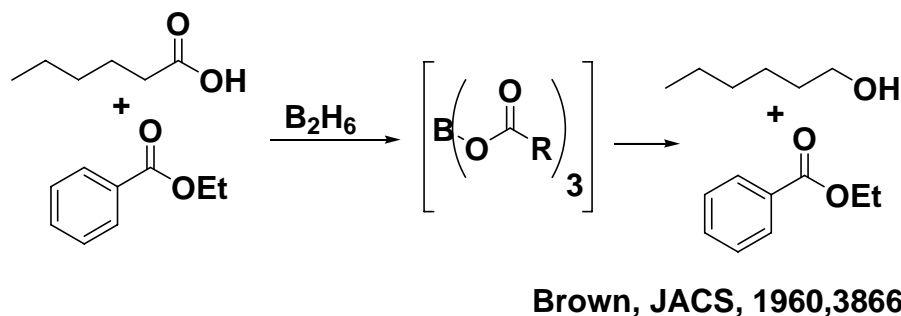
LiBH₄

- Selective reduction of esters and lactones in presence of acids
- acids 'protected' as Li salt
- solvent effects: ether>thf>iPrOH

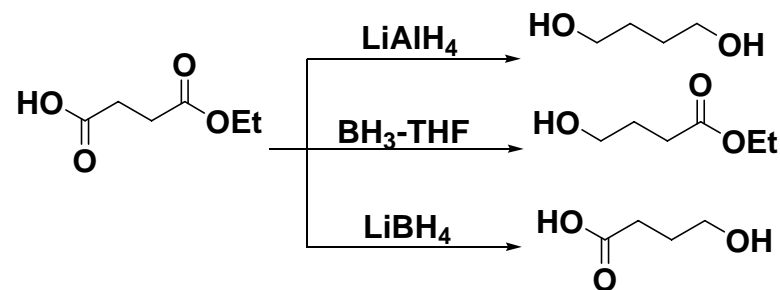


Borane complexes (BH₃-L)

- selective reduction of acids in presence of esters, amides, lactones. Will reduce ketones, aldehydes and olefins
- BH₃-THF and BH₃-Me₂S available

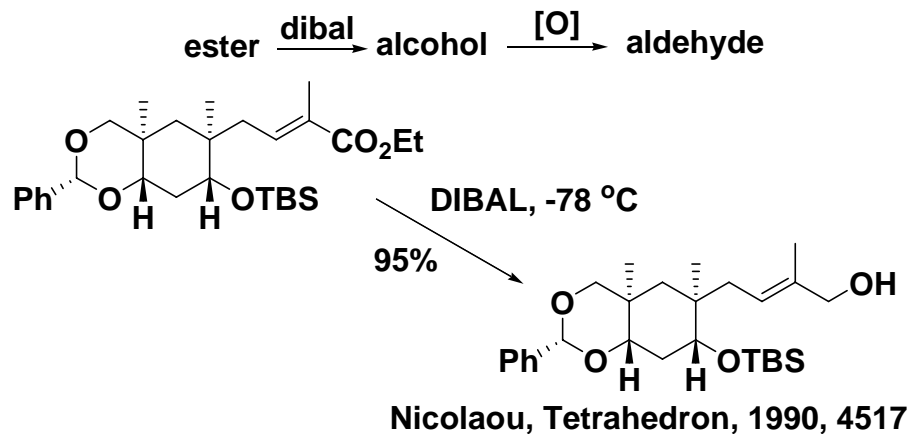


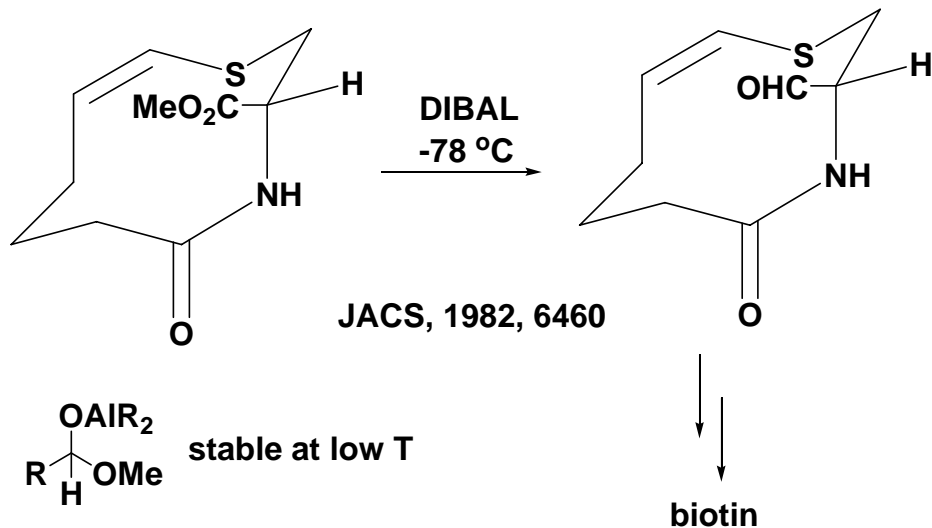
hypothetical example:



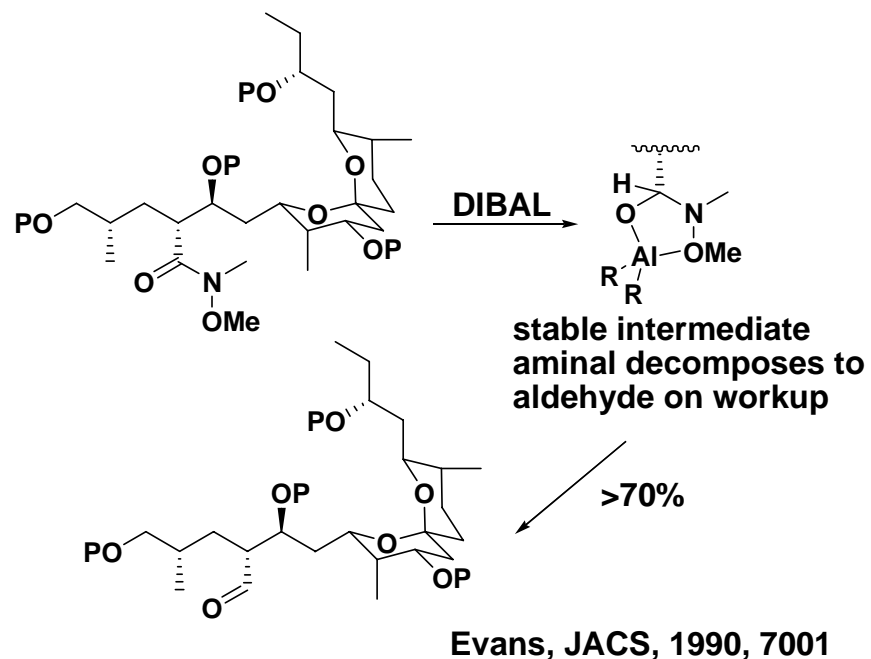
i-Bu₂AlH (aka DIBAL or DIBAL-H)

- low temp, 1 equiv, ester → aldehyde
- with XS, get alcohol
- gives 1,2 reduction of unsaturated esters
- commonly:

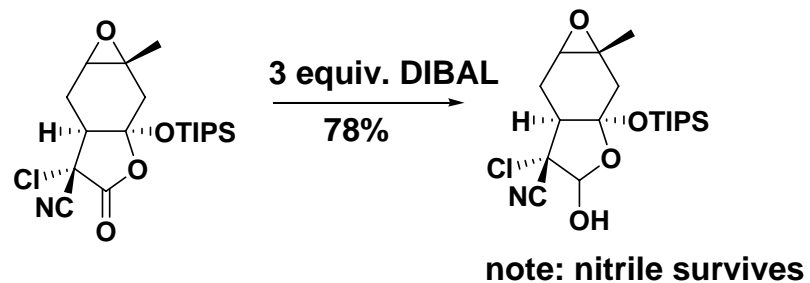




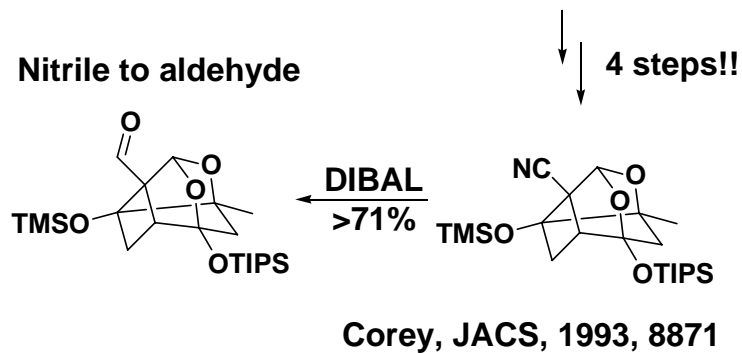
Weinreb's amide to aldehyde



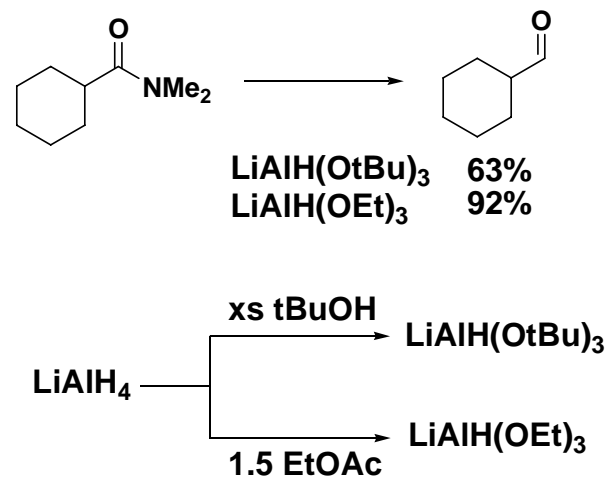
lactone to lactol



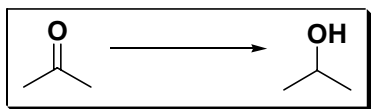
Nitrile to aldehyde



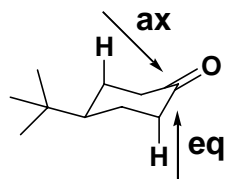
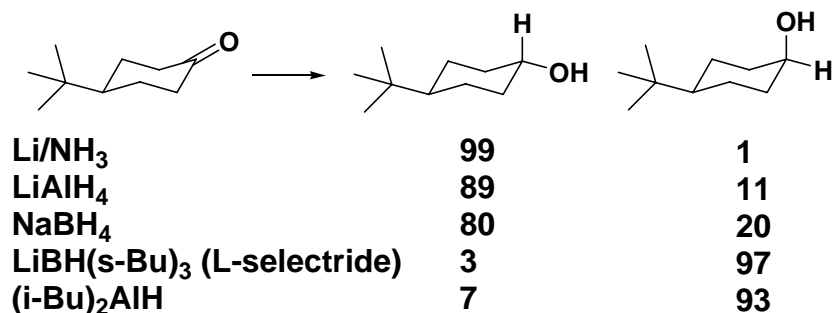
3° amides to aldehydes



Brown, JACS, 1964, 1089

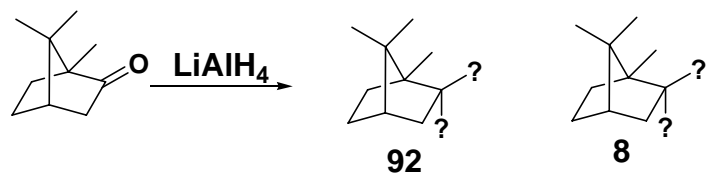
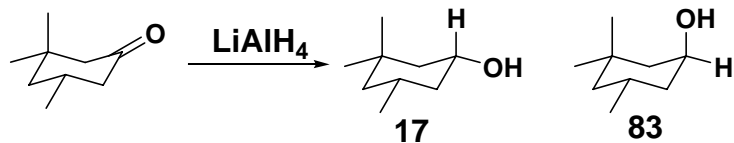


many many many ways. Focus here on selectivity issues



eq disfavored for small H-donors
b/c interaction with C2 axial H

ax disfavored for large H-donors
b/c interaction with C3 axial H

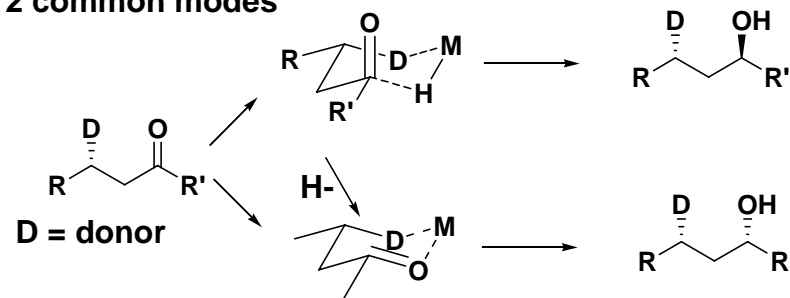


acyclic cases usually follow Felkin-Ahn model or chelate model (if chelating group nearby) to varying degrees. For a chronological presentation, see Smith, Organic Synthesis, chap 4.

Directed Reductions

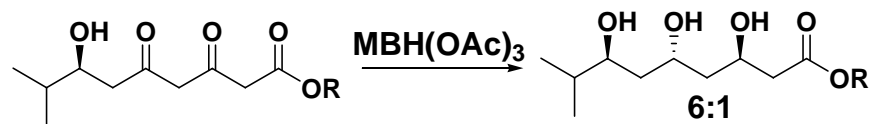
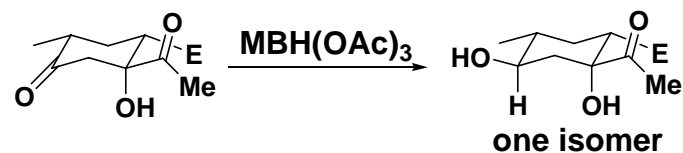
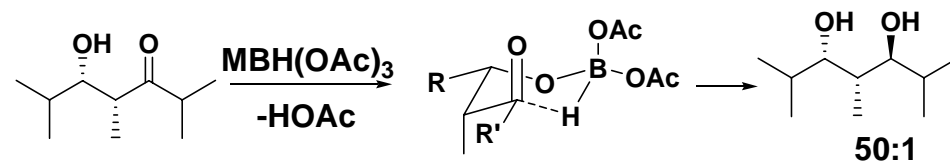
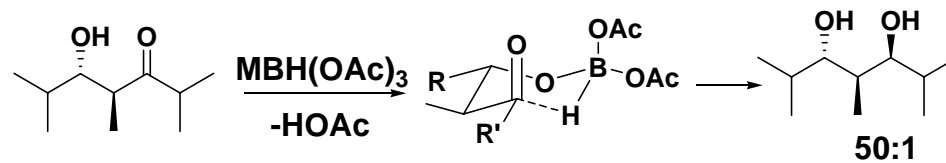
general reference for directed rxn: Hoveyda, Evans, Chem Rev. 1993, 1307

2 common modes

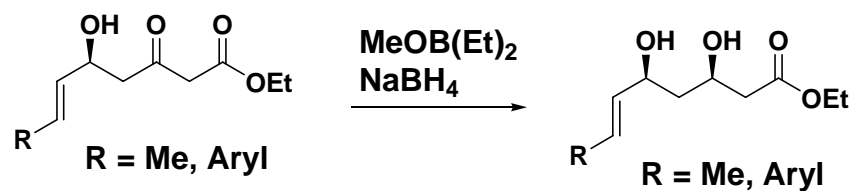
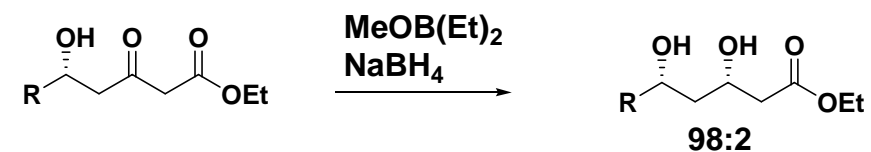
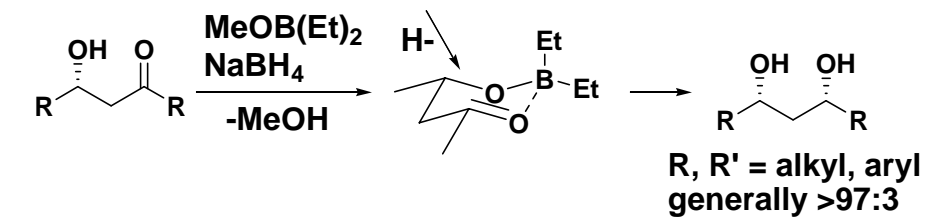


MBH(OAc)₃; M usually NMe₄

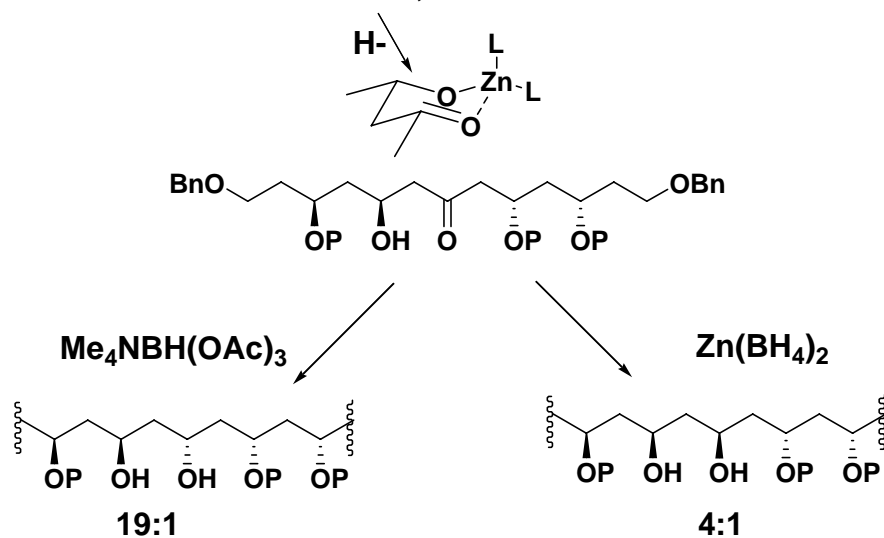
Evans, JACS, 1988, 3560



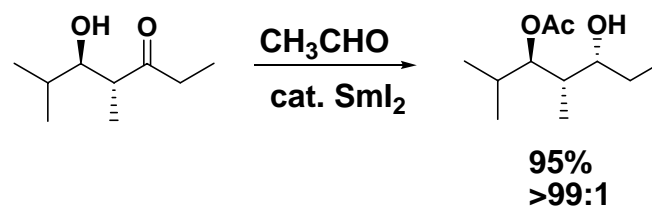
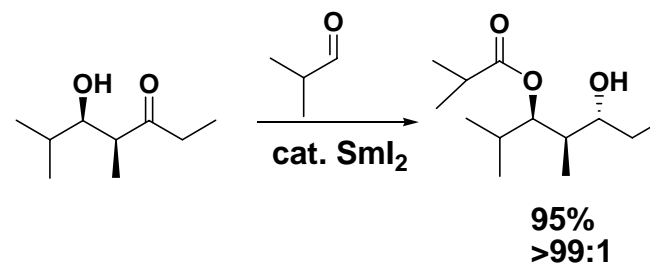
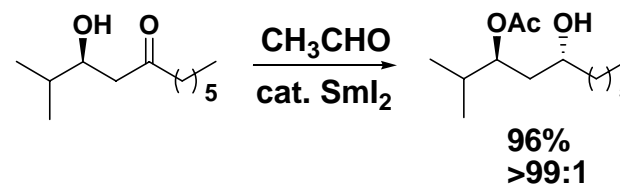
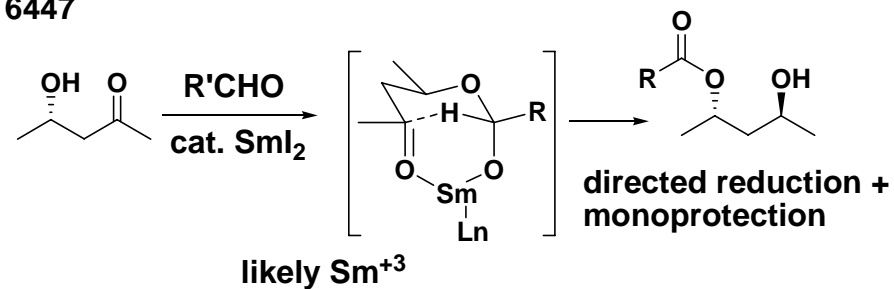
MeOB(Et)₂/NaBH₄ Prasad, TL, 1987, 155



Zn(BH₄)₂ Oishi, Nakata, Accts. Chem. Res. 1984, 338;
Evans JACS 1984, 1154



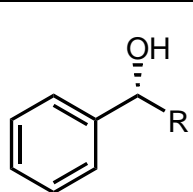
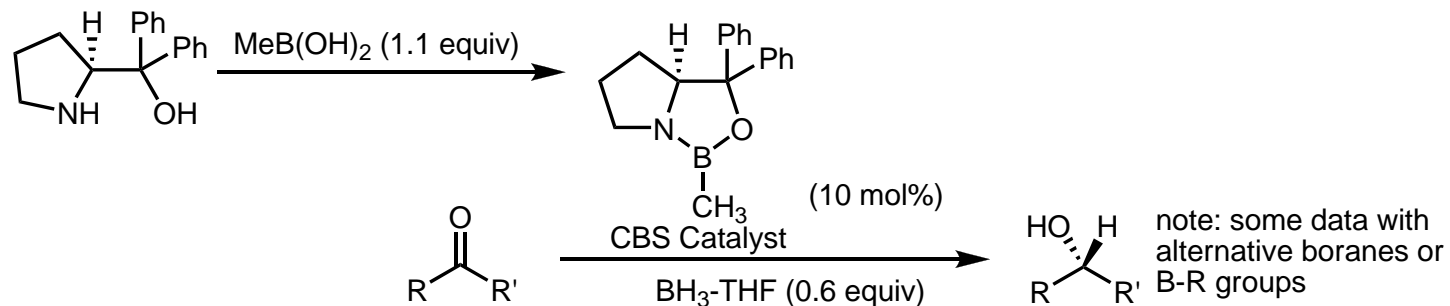
Tishchenko Reductions: Evans, Hoveyda, JACS, 1990, 6447



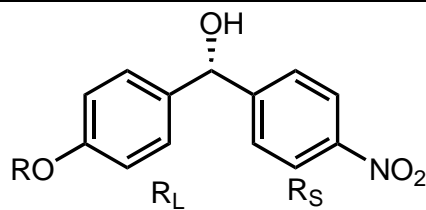
Enantioselective reductions. For metal-catalyzed, see Advanced Synthesis and Catalysis notes.

CBS Reduction: from Corey, Bakshi, and Shibata

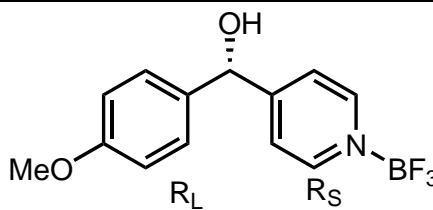
Reviews: Corey, ACIEE, 1998, p1986; Srebnik, Chem Rev, 1993, 763.



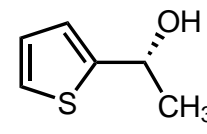
R = CH₃: 97% ee
 R = Et: 97% ee
 R = CH₂Cl: 95% ee
 R = (CH₂)₂CO₂Me: 94% ee



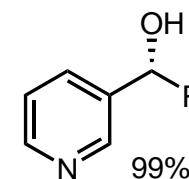
95% ee



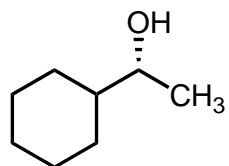
93% ee



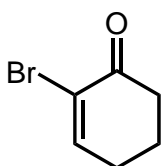
94% ee



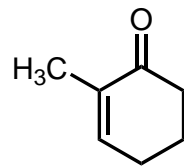
99% ee



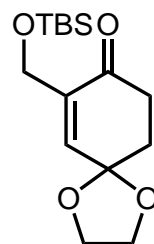
84% ee



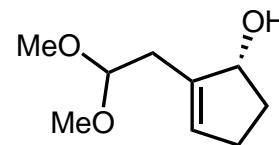
91% ee



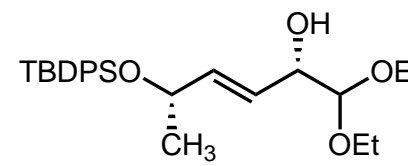
91% ee



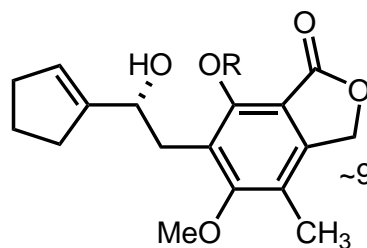
91% ee



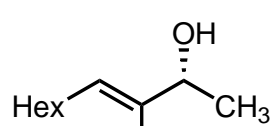
93% ee



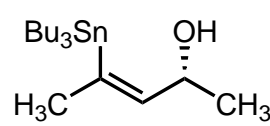
95% ee



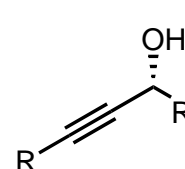
~95% ee



94% ee

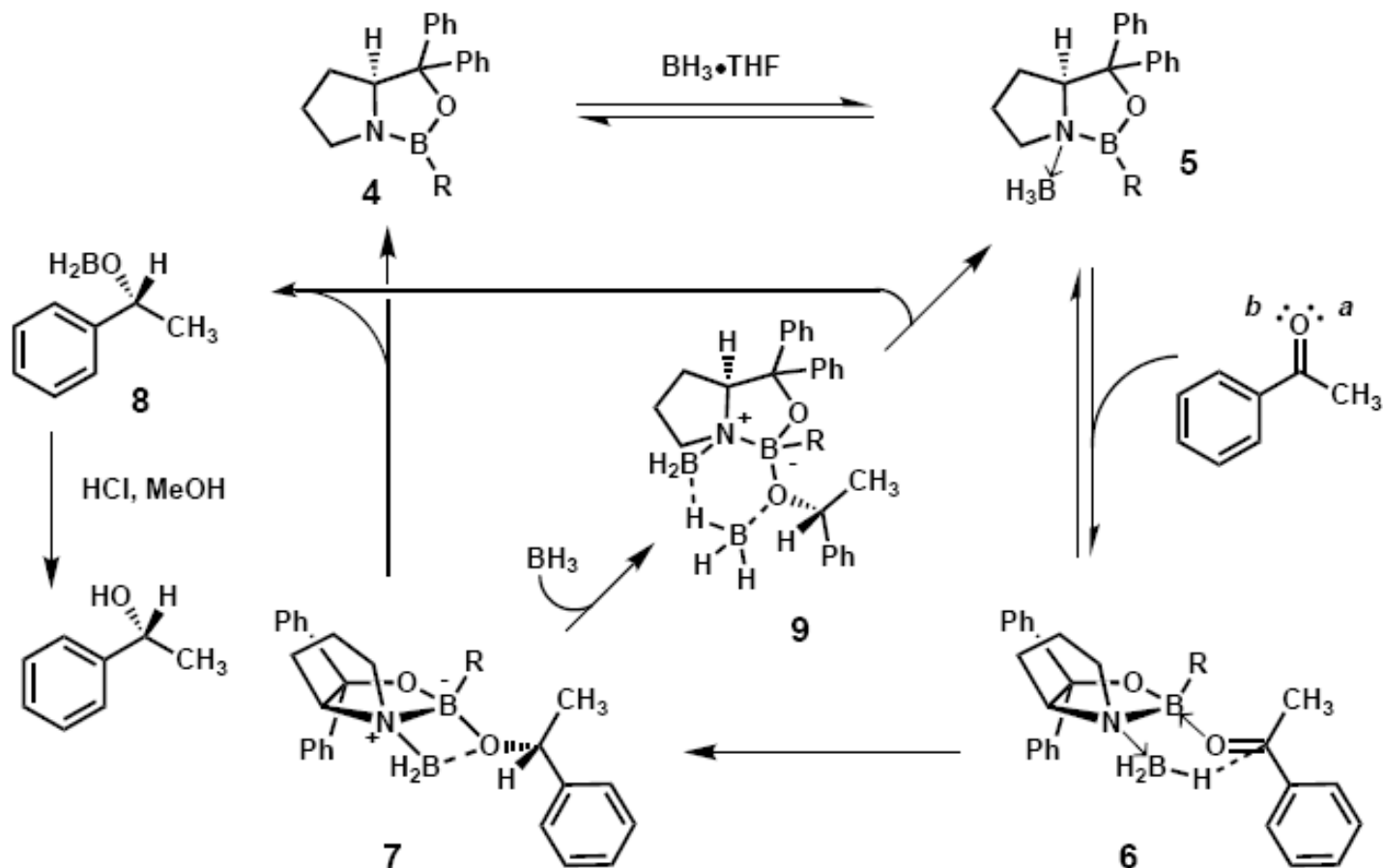


85% ee



R = Ph, R' = n-alk: 70-90 % ee
 R = Ph, R' = s-alky: 95% ee
 R = H, R' = alk: ~96% ee
 R = TIPS, R' = alk: >90% ee

Proposed mechanism for CBS reduction

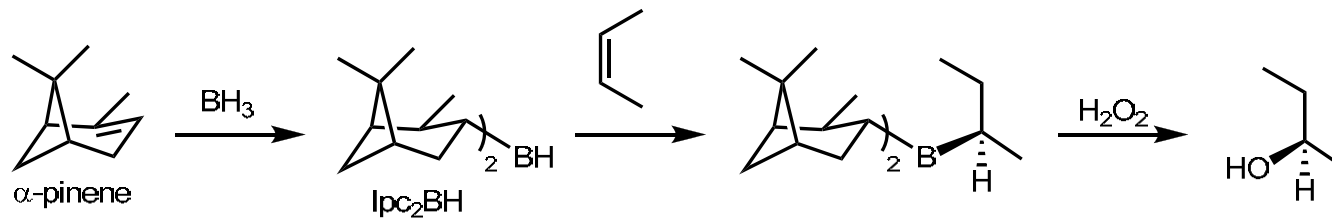


Important points:

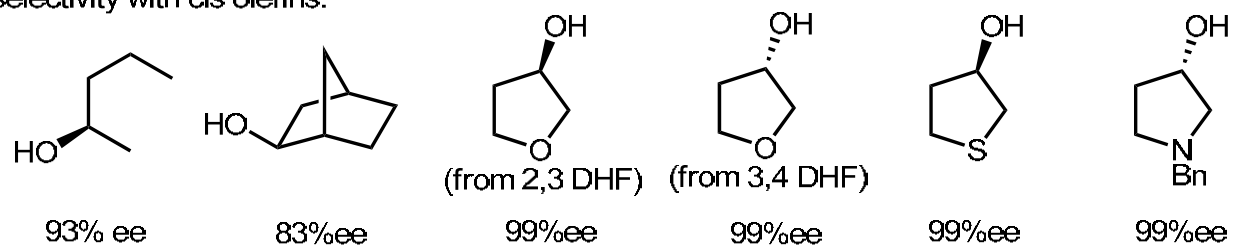
- Borane in catalyst is Lewis acid; Nitrogen is Lewis base to coordinate second borane
- Borane coordination forms cis-5,5 system (a-face in 5)
- Borane coordination increases Lewis acidity of catalyst (at B) and activates BH_3 as hydride donor
- Carbonyl coordination trans to bulky or electron rich group
- Hydride transfer via 6-membered TS
- Disproportionation between 8 and $\text{BH}_3 + (\text{RO})_2\text{BH}$ allows <1 equiv BH_3

Enantioselective reduction: Alpine borane and Dip-Cl
 Review: Brown, JOMC, 500, 1995, p1.

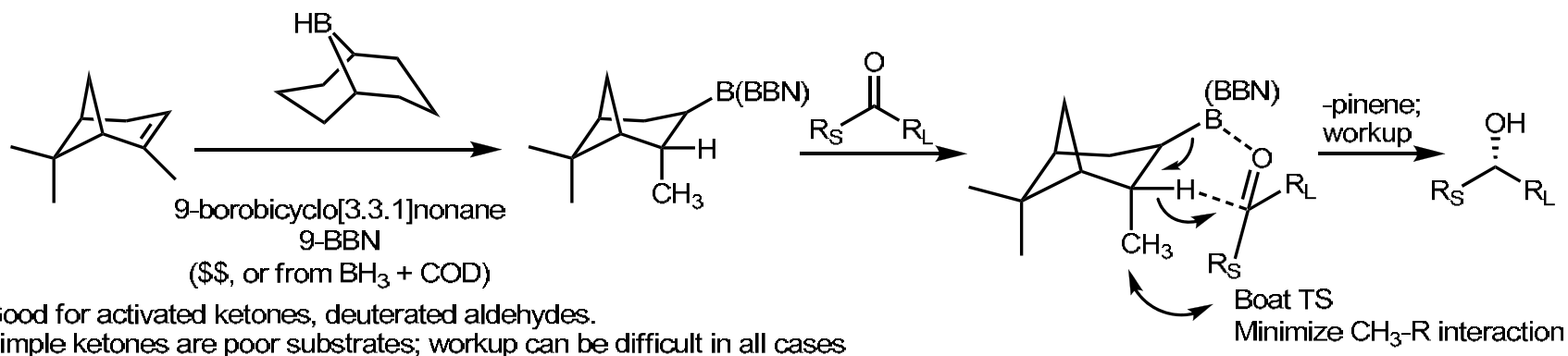
Background: asymmetric hydroboration of olefins.



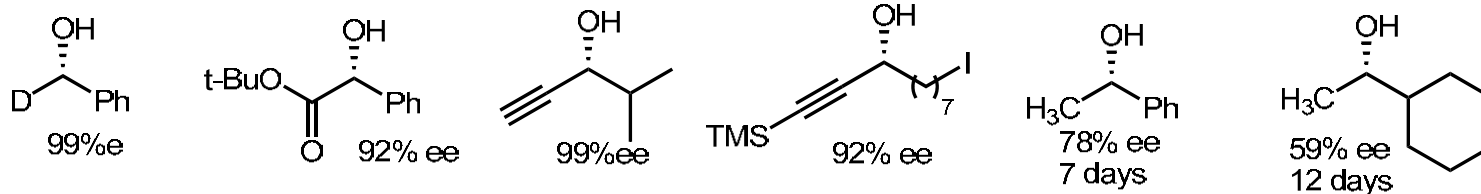
High enantioselectivity with cis olefins:



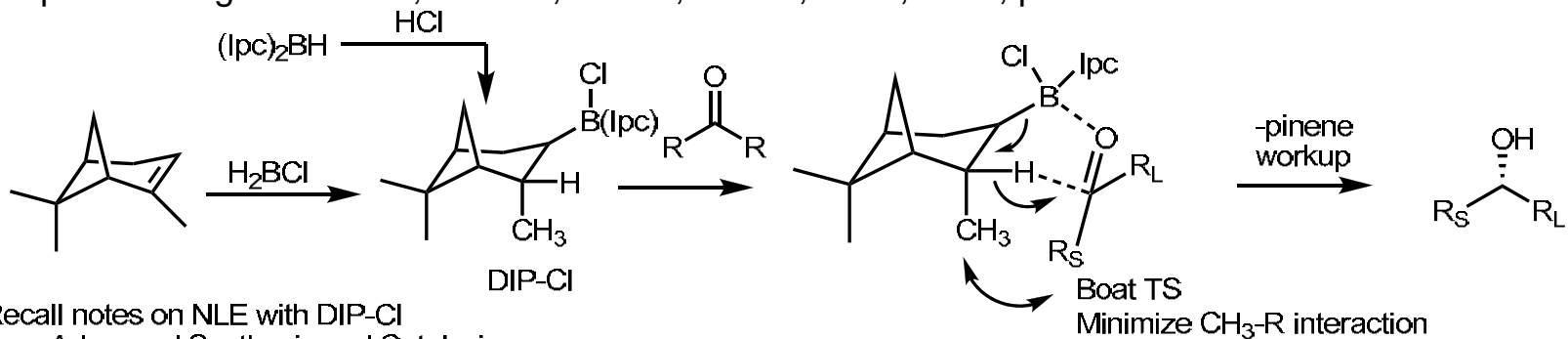
Pinene-derived reagents for asymmetric reduction of carbonyls: Alpine-Borane (from Aldrich) AKA Midland borane reduction.



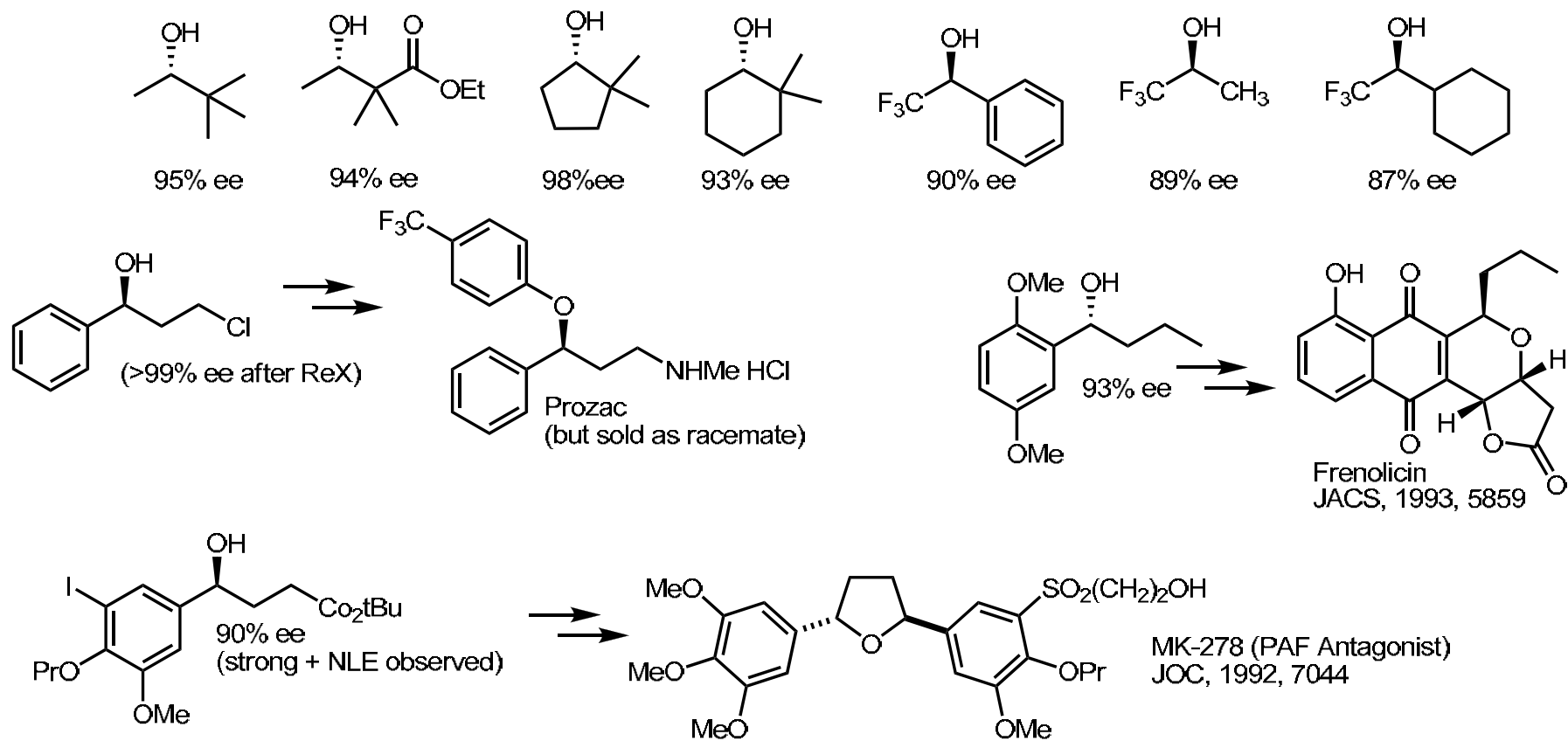
Good for activated ketones, deuterated aldehydes.
 Simple ketones are poor substrates; workup can be difficult in all cases



An improved reagent: DIP-Cl; Review, Brown, JOMC, 1995, v500, p1.



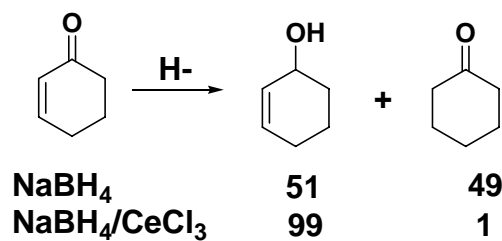
Recall notes on NLE with DIP-Cl
from Advanced Synthesis and Catalysis
See Aryl/alkyl substrates there, too



Conjugated systems:

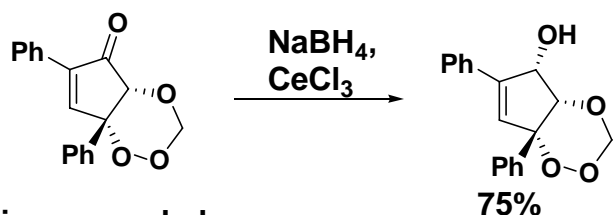
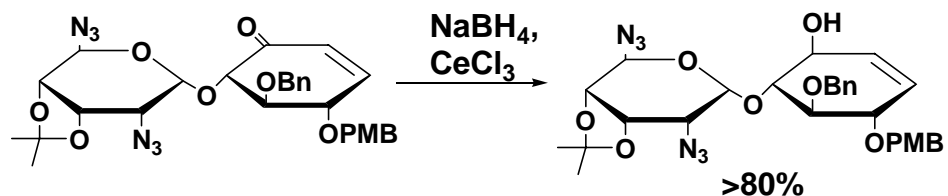
1,2 vs. 1,4

Luche reduction (original report: JACS, 1978, 2226;
review Molander, Chem Rev. 1992, 29)

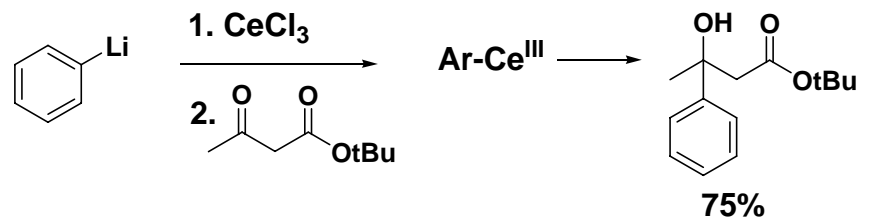


-Ce(+3) coordinates to carbonyl; promotes selective 1,2 addition.

-Requires stoichiometric quantity of ANHYDROUS CeCl_3



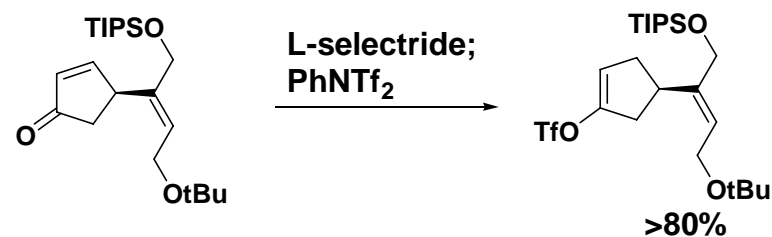
1,2 addition expanded:



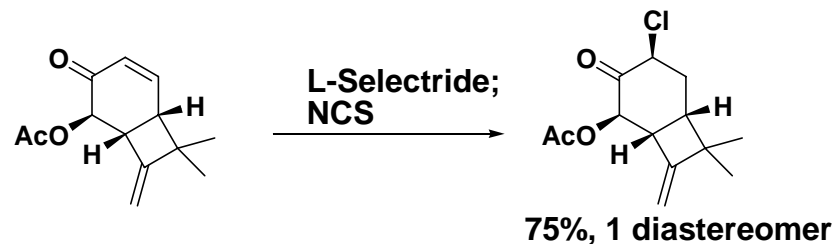
Heterocycles, 1989, 703

1,4 addition -recall Na/NH₃

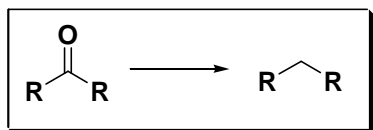
Selectrides: $\text{MBH}(\text{s-Bu})_3$; M = K, Na, Li available
-useful for regioselective enolate generation



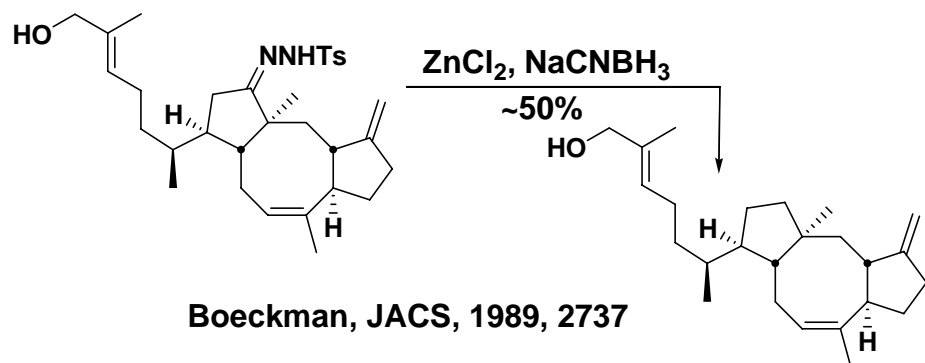
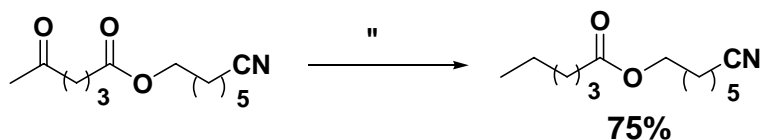
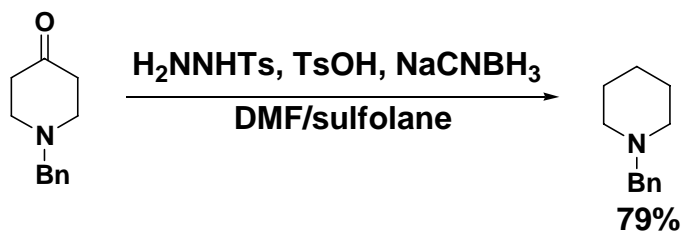
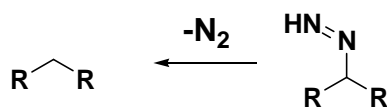
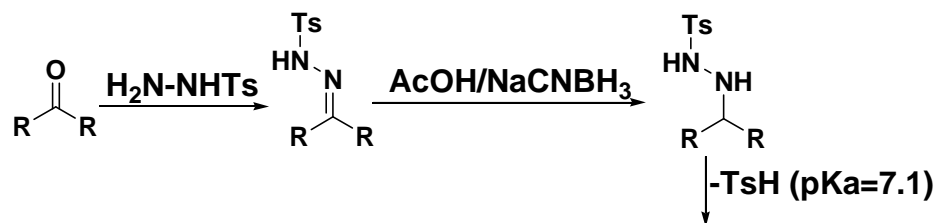
Overman, JACS, 1993, 9293



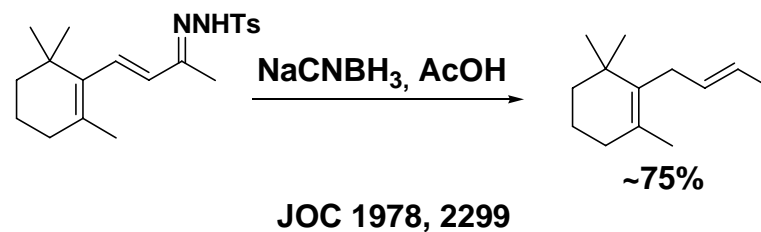
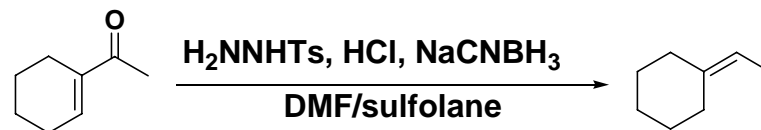
Wood, unpublished



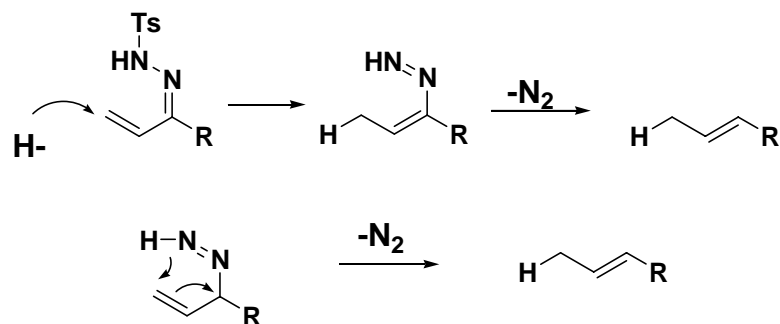
Reduction of Tosylhydrazones
 Maryanoff, JACS, 1973, 3662
 Baker, JOC, 1975, 1834



α,β -unsaturated ketones give olefin migration:

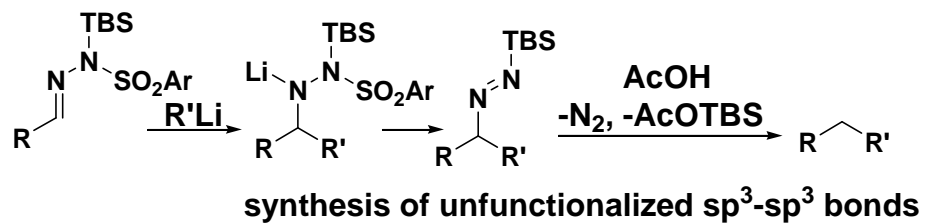


2 possible mechanisms:

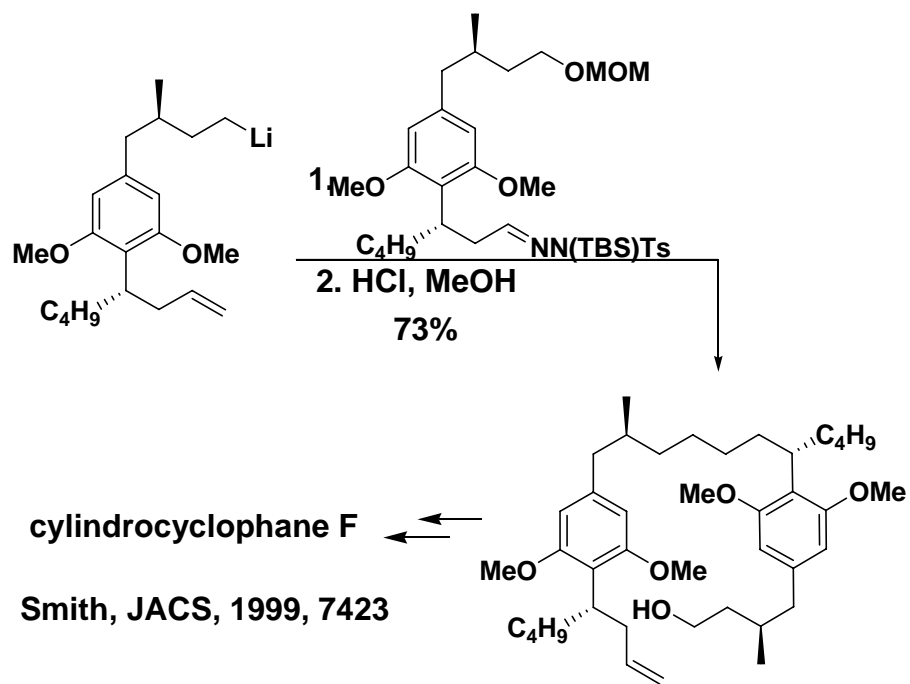


How would you distinguish between them?

Related chemistry:

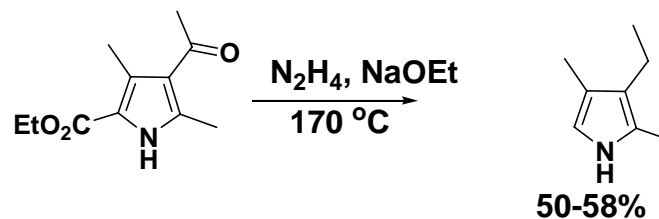


Myers, JACS, 1998, 8891

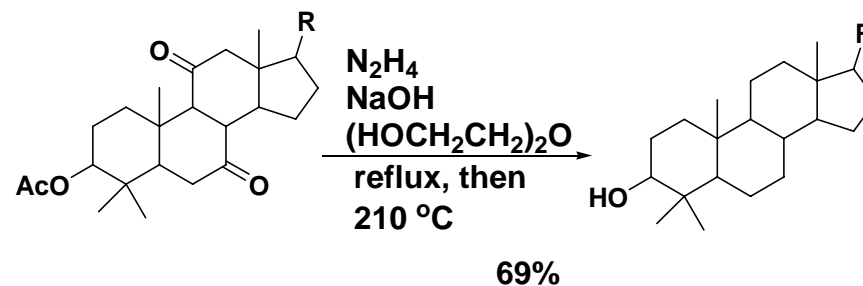


Smith, JACS, 1999, 7423

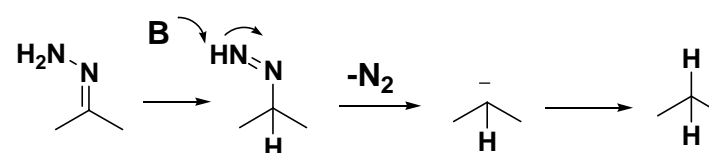
Wolf-Kishner
Brutal conditions



Org. Syn. 1995, Coll vol 3, 513



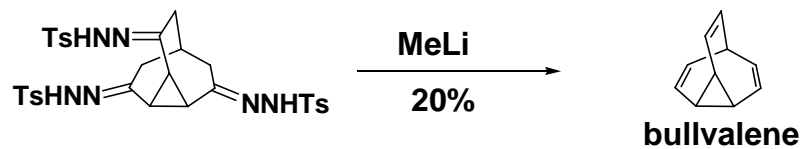
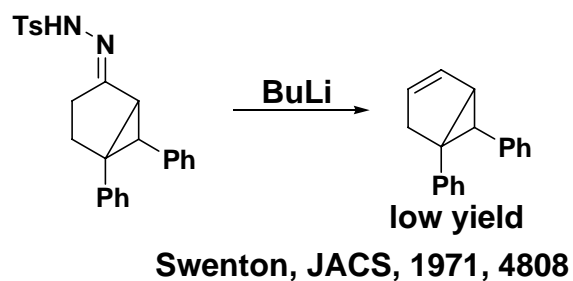
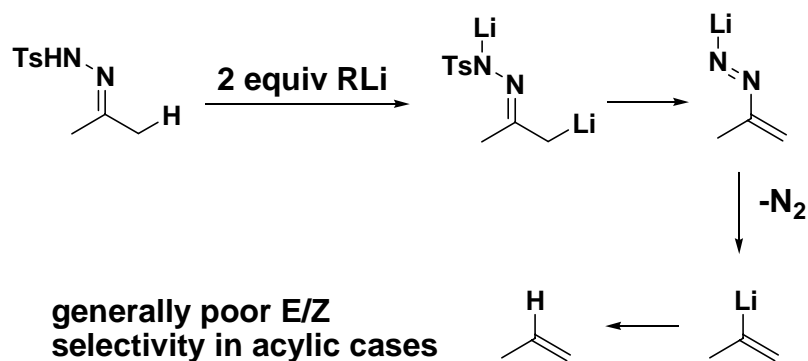
Barton, J. Chem. Soc., 1955, 2056



Shapiro reaction

useful for difficult olefins; usually low yielding with side products

review: Shapiro, Org. Rxns. 1976, 405

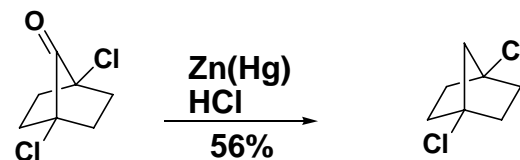


TL 1972, 2589

Other Methods

Clemmensen Reduction

review: Vedejs, Org. Rxns. 1975, 22, 401



JOC, 1969, 1109

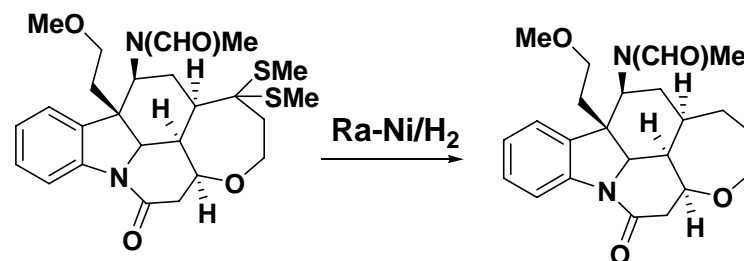
A fine method if low yields of unfunctionalized products are needed.

Desulfurization

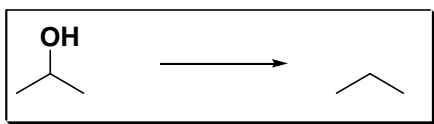
See hydrogenation above.

Ra-Ni/H₂ almost always used

Review: Org. Rxns. 1962, 356



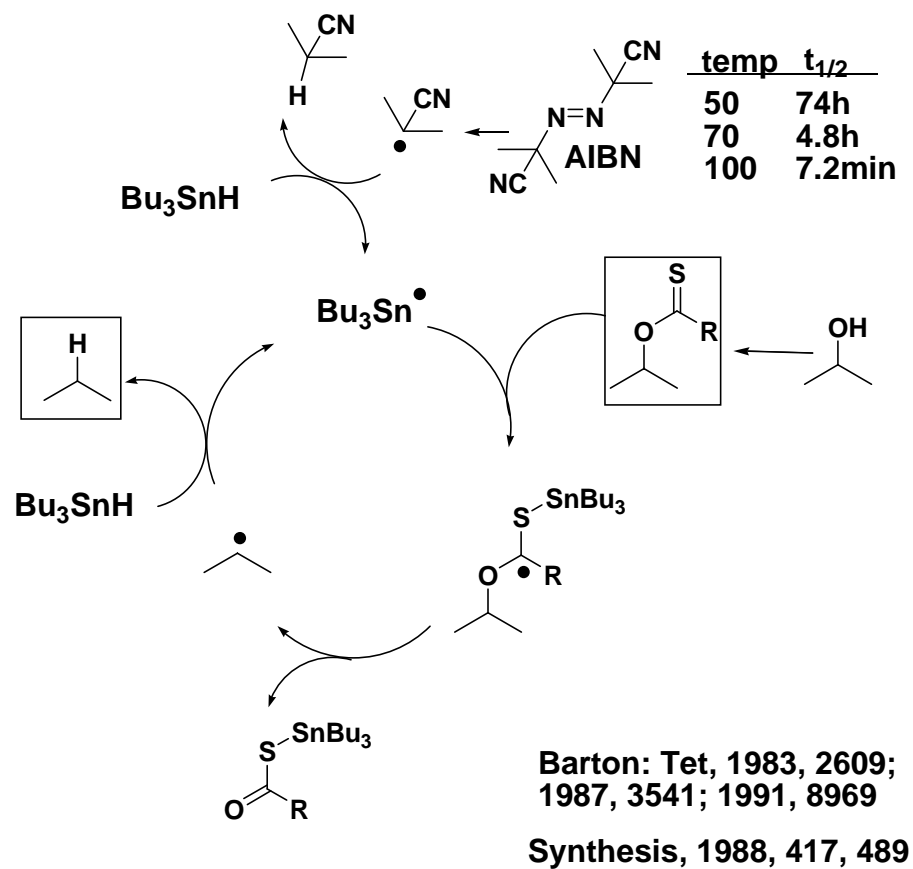
Woodward, JACS, 1948, 2107



common methods we won't cover:

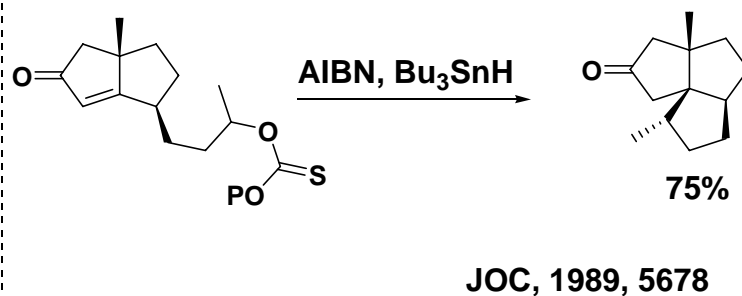
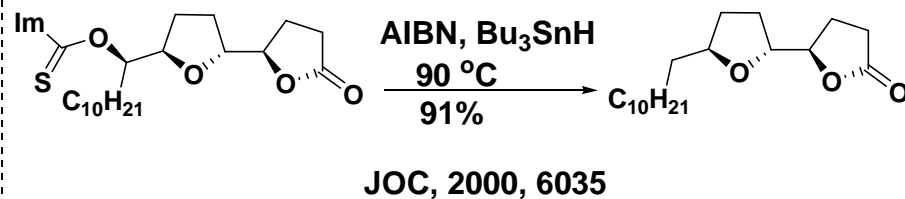
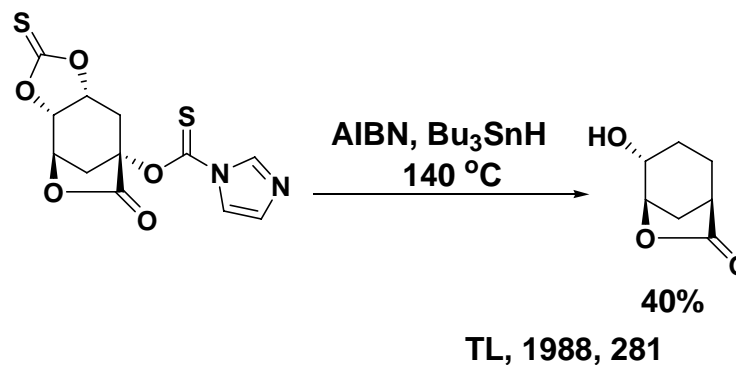
- alkyl tosylate + LiAlH₄
- conversion to halide/dehalogenation
- elimination/hydrogenation

Barton deoxygenation

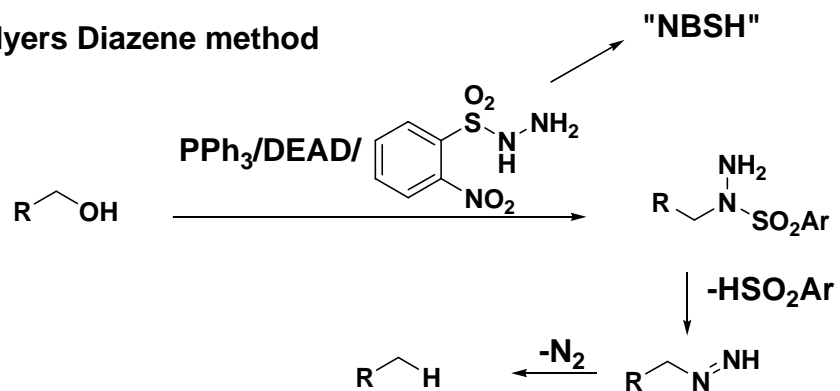


Generally useful method, but:

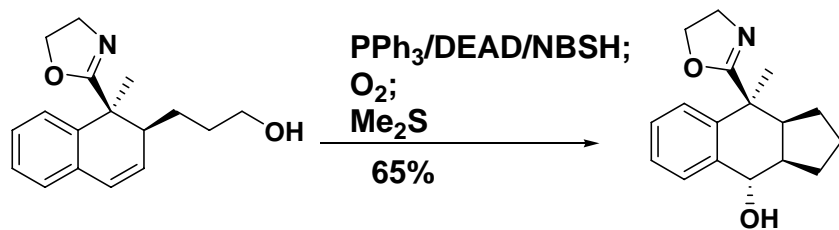
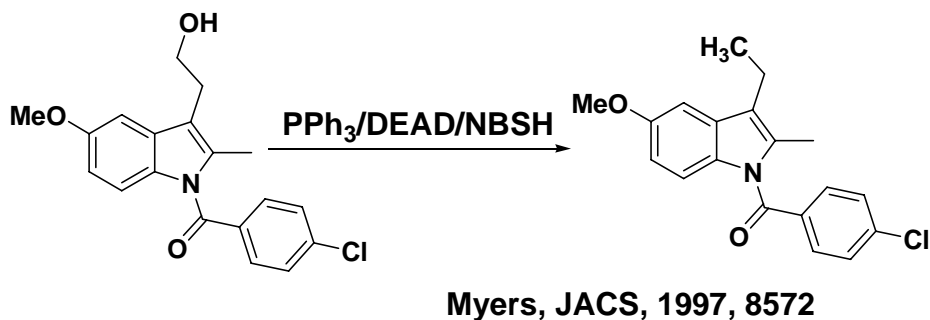
- lots tin
- 3° thiocarbamates can be difficult to make
- 1° radicals difficult to form



Myers Diazene method



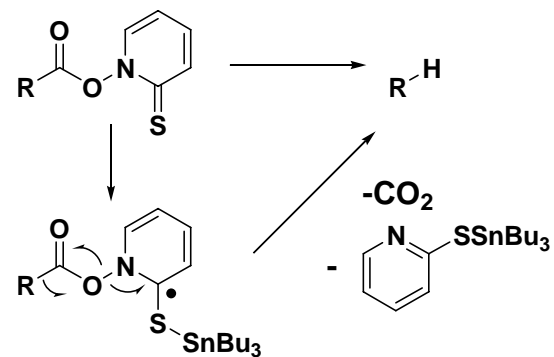
Very useful for unhindered alcohols



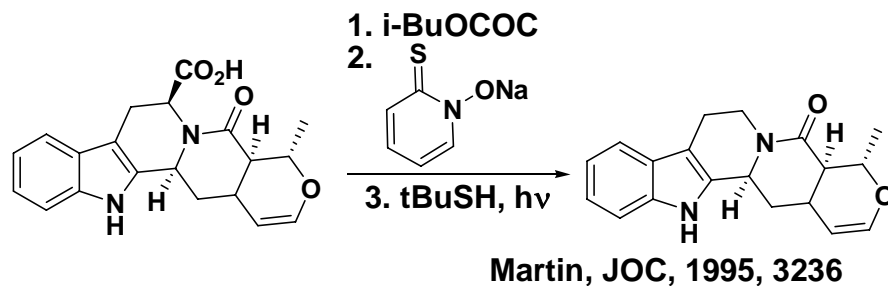
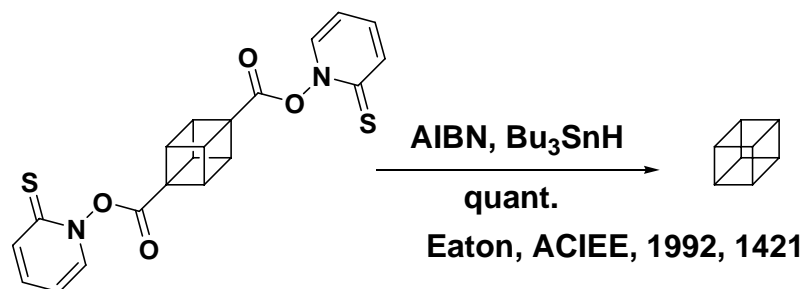
Holy cow! How does this happen?

Barton Decarboxylation

Barton, Chem. Comm. 1983, 939; Tet, 1987, 2733

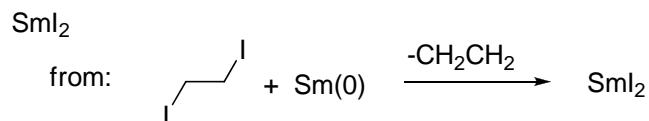


note: thiohydroxamic acid often labile enough that no Sn is needed, just ambient light. Photolysis works too.

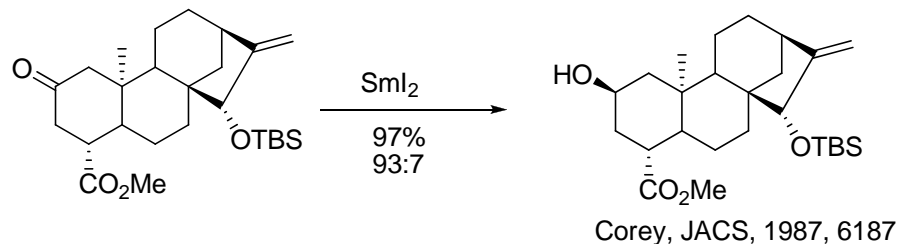
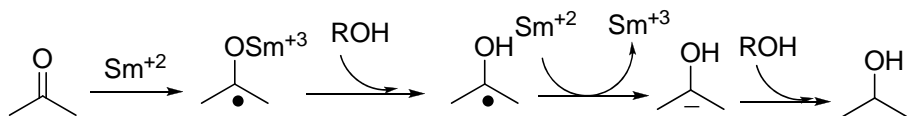


Reductive couplings and related reactions.

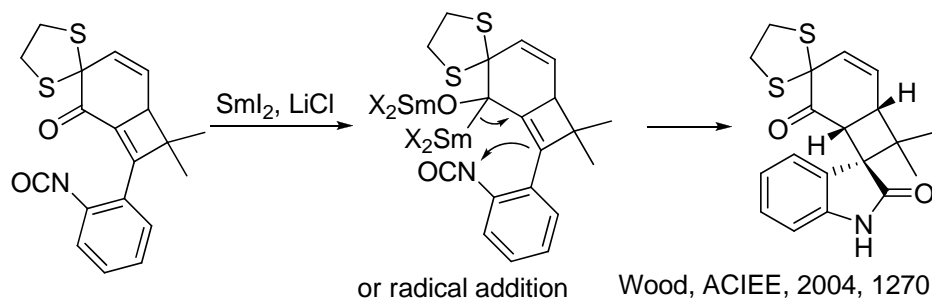
electron transfer-promoted reductions (part II)



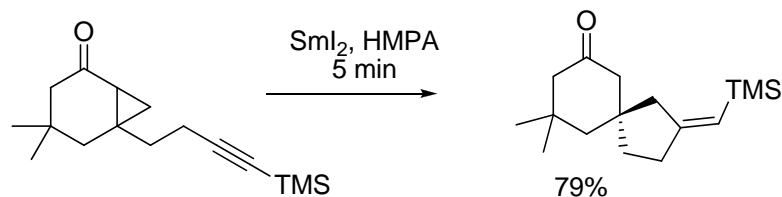
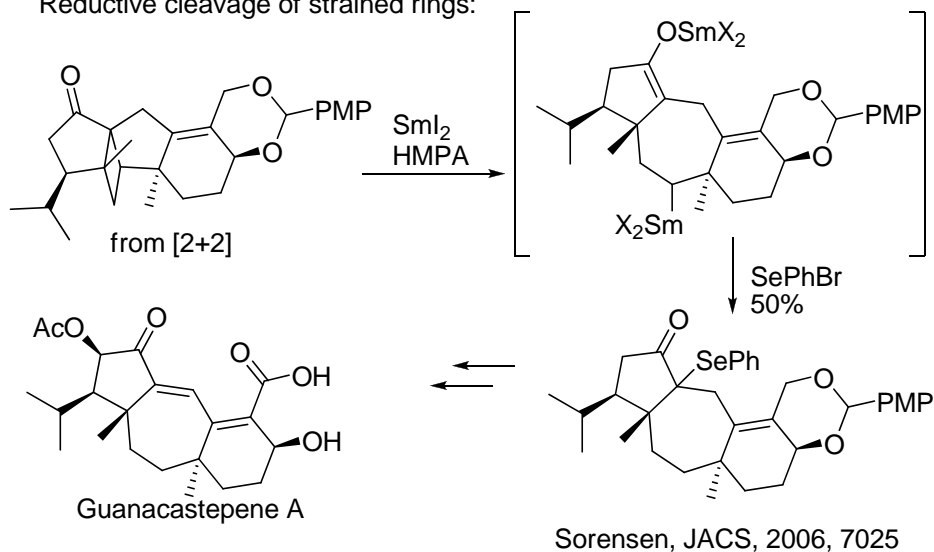
- almost always in THF (can do in Me_3CCN)
- Very air sensitive
- reactivity modulated by additives (JACS 2004, 44; JACS 2000, 7718, SYLETT, 1996, 633)
- Kagan discovered, Molander exploited, Flowers studied
- Rxn usually psycho fast
- Reviews: Molander, Chem Rev. 1992, 29; 1996, 307 (example from here).



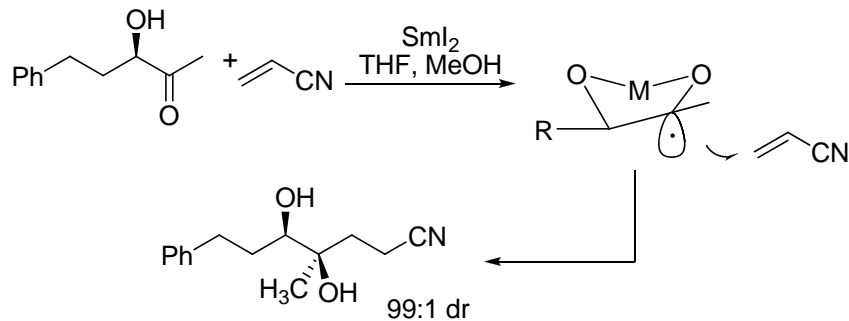
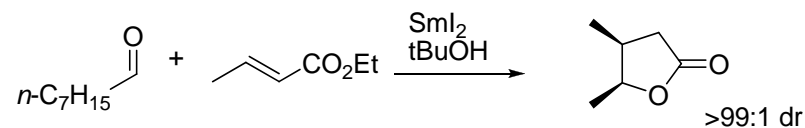
ketyl can be intercepted:



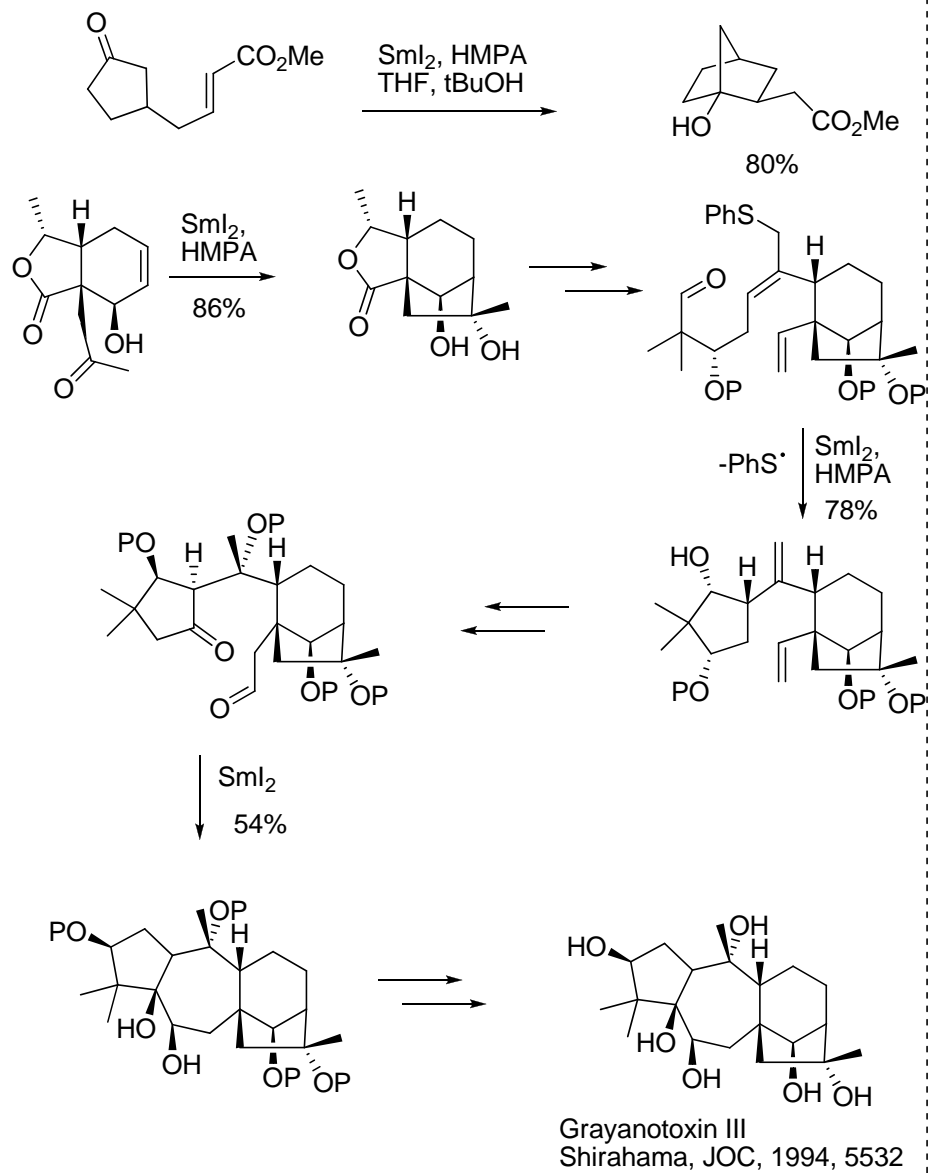
Reductive cleavage of strained rings:



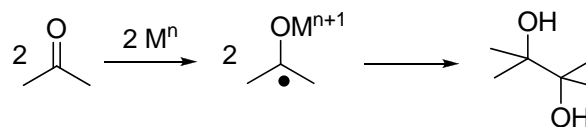
Intermolecular additions of ketyl radicals



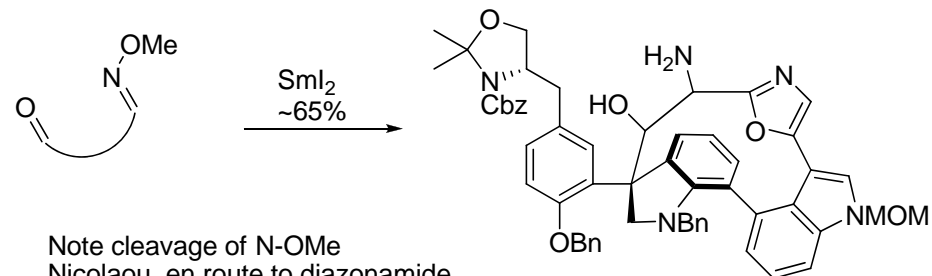
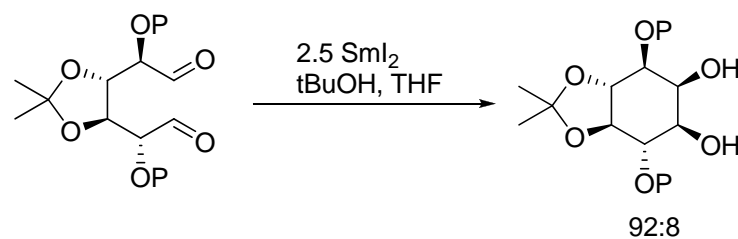
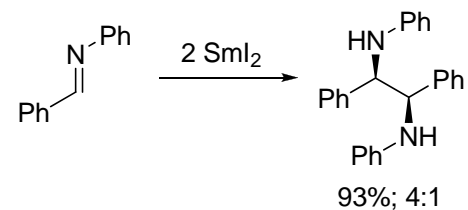
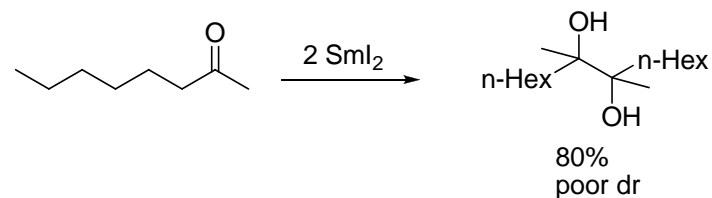
Intramolecular couplings:



Pinacol Couplings with SmI_2

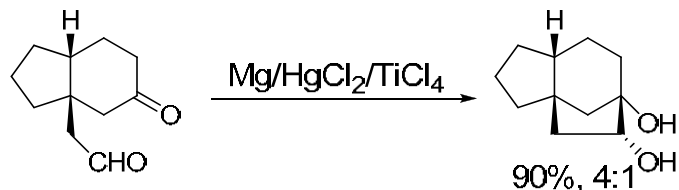
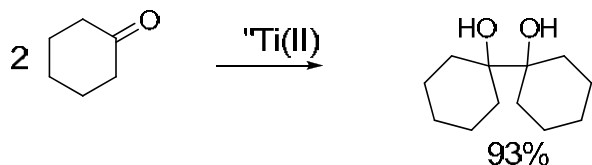


With SmI_2 (Chem Rev, 1996, 307)



With Ti

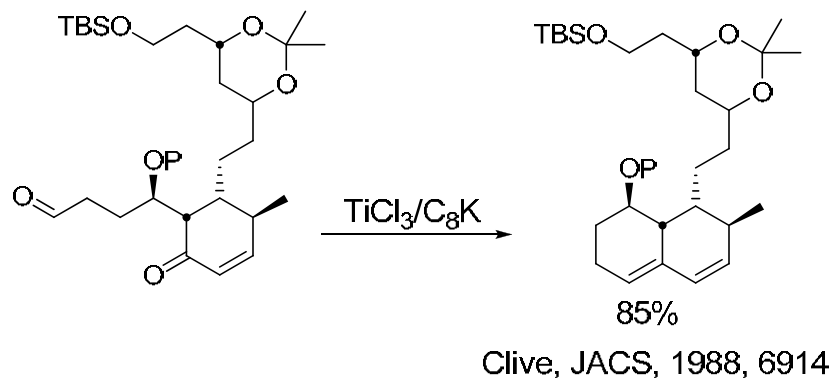
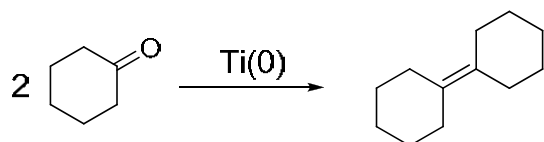
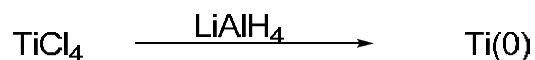
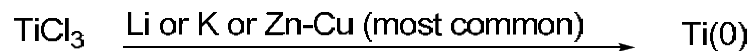
Many many ways: Larock, Comp. Org. Transformations, 1989, 547-548



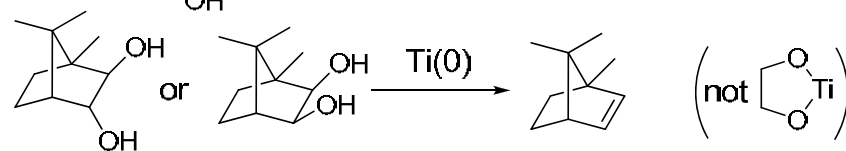
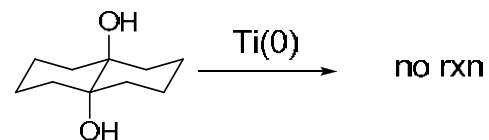
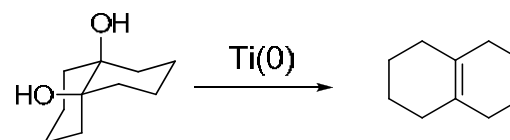
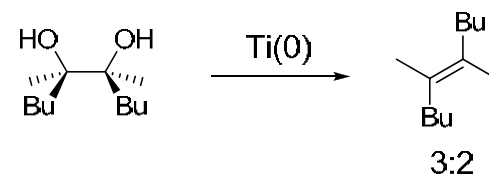
Corey, Dansheiser, JOC, 1976, 260

If access Ti(0), McMurry coupling dominates

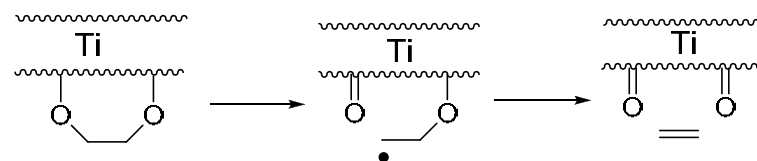
Reviews: McMurry, Chem Rev. 1989, 1513; Accts, 1983, 405



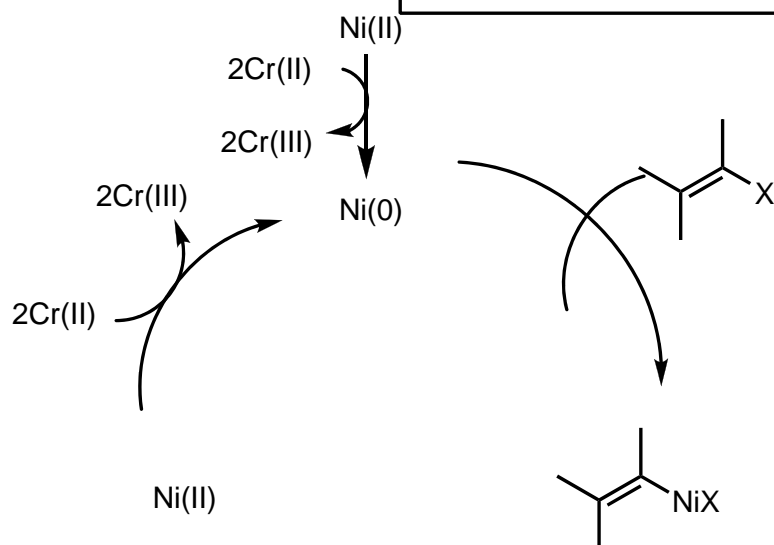
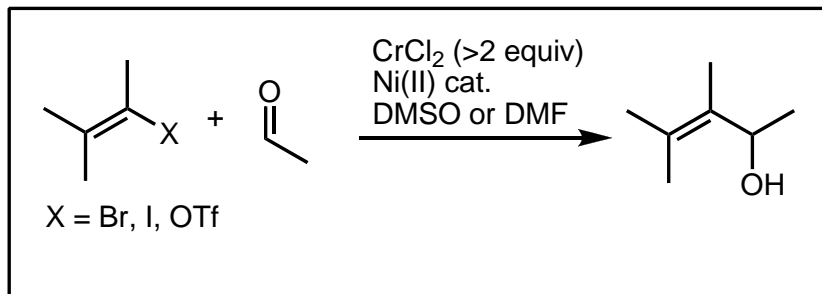
mechanistic details:



Proposed:

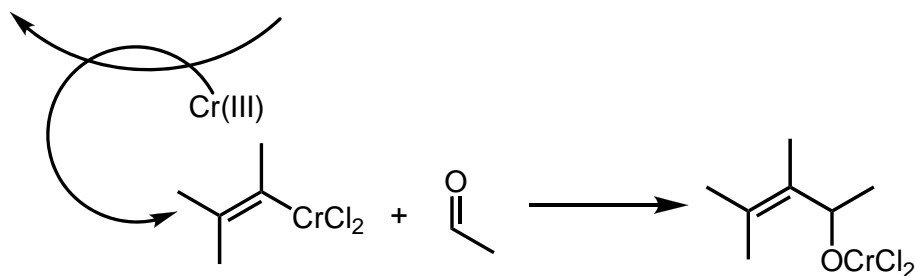


Cr-mediated reductive coupling of Sp²-X with aldehydes: the Nozaki-Hiyama-Kishi (NHK) reaction



General characteristics

- Reliable for late-stage coupling
- Broad functional group compatibility (ketones, ester, nitriles)
- Nucleophile formed in presence of electrophile (Barbier), so intramolecular (cyclizations) possible
- Often poor diastereoselectivity
- Catalytic conditions (in Cr) have been developed: Furstner, JACS, 1996, 12349
- Enantioselective versions have been developed: Kishi, JACS, 2004, 12248; OL, 2008, 3073.
- Review: Furstner, Chem Rev. 99, 991



Intermolecular additions: From Chem. Rev. 1999, 991

Table 18. Cr(II)/Ni(II)-Induced Additions of Functionalized Alkenyl Halides or Triflates to Functionalized Aldehydes

Halide	Aldehyde	Product (major isomer depicted)	Yield (%)	Ref.	Halide	Aldehyde	Product (major isomer depicted)	Yield (%)	Ref.
2-bromopropene			76	182		isobutyraldehyde		78	193
			73	182				86	194
			61	185				40	195
			70 (R = TBPDS)	185				60	196
			70 (R = H)					80	197
			d.r. = 2:1 (R = TBPDS)					d.r. = 2.5:1	
			d.r. = 1.4:1 (R = H)					80	198
			n.t.	186				80	199
			66	187				52	199
			d.r. = 10:1					d.r. = 7:3	
			66	187				80	197
			d.r. = 1:1					d.r. = 7:3	
			83	188				80	198
			d.r. = 2:1 (4:1)	(87)				80	198
			62	189				52	199
			d.r. = 2:1					d.r. = 1:1	
			100	190				23+27	200
			d.r. = 1:1 (R = PMB)					49 (33)	200
			d.r. = 2,1:1 (R = TBS)						

Intramolecular additions:

Table 21. Intramolecular Additions of Alkenyl Halides or Triflates to Carbonyl Groups Mediated by Cr(II)/Ni(II)

Substrate	Product	Yield (%)	Ref.	Substrate	Product	Yield (%)	Ref.
(Major Isomer Depicted)				(Major Isomer Depicted)			
		54	205			3b [a]	210
		81	206			76	31
		53	206			74	211
		R = H (complex mixture)	206			92	212
		53 (R = Bn)	206			d.r. = 1:1	57 + 23
		79	206			d.r. = 1:0	212
		65	207			d.r. > 20:1	60,
		30	30			d.r. = 1:1	55-65
		56	208			60 (R=Me, X=I)	60,
						0 (R=Me, X=OTf)	213
						80 (R=H, X=I)	60

Allylations and alkylations:

Table 45. Cr(II)-Mediated Addition of Various Allylic Substrates to Chiral Aldehydes

Halide	Aldehyde	Product (d.r.)	Yield (%)	Ref.
		 (5*1)	quant.	119
allyl iodide		 (10:1)	78	240
		 d.r. = 8:1	73	93
		 d.r. = 8:1	71	93
	 R = 3-indolyl	 d.r. = 8:1	64	93
		 d.r. = 8:1	55	93
		 d.r. = 53:45	71	117
		 d.r. = 53:9:3:2	67	241

Substrate	Product	CrCl ₂ (eq.)	NiCl ₂ (eq.)	Yield (%)
		3	1	26
		3	1	53
		3	1	51 (n=1) 54 (n=2)
	 d.r. = 95:5	9.7	1	41
		7	0.05	57 (X=I) 36 (X=Br)
		6	1.6	60 (R=MOM)
		8	0.06	40 (R=Me)
		8		37
		8		76