Lisa M. Barton

The Birch Reduction

Baran Group Meeting
3/10/18

Helpful Resources:

Literature seminar, B. Hafensteiner (2005) [**Group Meeting**]
Organic Reactions, **1992**, *42*, 1 [**review**]
Nat. Prod. Rep., **1986**, *3*, 35 [**review**]
Curr. Org. Chem., **2015**, *19*, 1491 [**review**]
Targerts in heterocycic systems, **1999**, *3*, 117 [**review - heterocyclic Birch**]
Recl. Trav. Chim. Pays-Bas., **1995**, *114*, 259 [**review - electrochemical Birch**]

Background

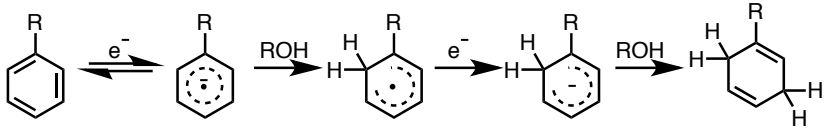
• Originally discovered by Wooster and Godfrey in 1937 in the reduction of toluene in NH_3 using either Na or K *JACS*, **1937**, *59*, 596

• Extensively developed by Arthur J. Birch and is therefore named after him

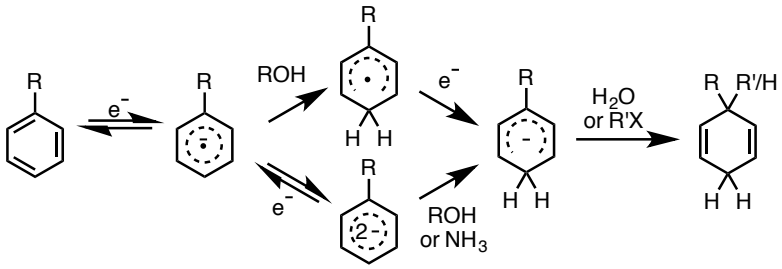
First Publication on: *J. Chem. Soc.*, **1944**, 430
Complete list of contributions: *Tetrahedron*, **1988**, *44*, No. 10, pp. v-xviii

Mechanism

1) Electron-Donating Substituents



2) Electron-Withdrawing Substituents



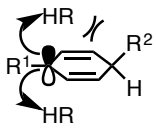
• In both cases reduction will occur 1,4 across the aromatic ring

• Initial protonation takes place at position with highest electron density andprotonation of the dianion will usually occur at the site that will give the most stable monoanion (exceptions exist)

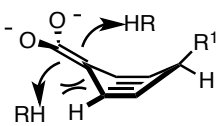
• Most common side reactions: bond cleavage, dimerization (pyridine), and substituent reduction (esters, amides, ketones)

Stereochemistry

• Determined by the protonation of the final monoanion
• reductive alkylation leads greater selectivity due to increased sterics



• When $R^{1,2}$ is H no steric preference and protonation occurs equally from either face
• When $R^{1,2} \neq H$ Cis product predominates



• When there is a π substituent, a boat conformation is adopted
• vinyl hydrogens block bottom lobe of anion orbital and protonation comes from top face

Procedures

Solvents: Ammonia* ∗ = Most commonly used

Metals: Sodium*, Lithium*, Potassium*, Calcium, Magnesium
• Li most reactive but can therefore lead to overreduction, in which case Na best

Cosolvents (used to aid in solubility): Diethyl Ether*, Tetrahydrofuran*, Glymes*

Proton Sources: Ethanol*, *tert*-butyl alcohol*, H_2O

Concentration: Often run under dilute conditions (0.1–0.5 g metal per 100 mL NH_3)

Temperature: Most commonly ran at –78 ºC, due to low bp of NH_3. highest at reflux (–33 ºC)

Purity of Reagents: Not necessary but recommended

Order of Addition: Often very important and empirically determined
• Substrate dissolved in cosolvent with alcohol can be added to NH_3 and metal solution
• Metal added last to solution containing all other reagents
• Alcohol added last to solution containing all other reagents

Quenching Materials: either can use acidic materials (alcohols, water, NH_4Cl, $FeCl_3$),electron-transfer reagents (sodium benzoate/dienes then water), or alkyl halides in the case of reductive alkylations
• Most commonly the fast addition of saturated NH_4Cl (frothing occurs) is used

Organic Reactions, **1992**, *42*, 1

Comparison with Other Methods

Benskeser Reduction: reduction of arenes using Li in 1° amines, ethylenediamine, or a mix of 1° and 2° amines; more powerful than Birch conditions and can lead to reduction beyond dihydro stage and mixture of products

Catalytic Hydrogenation: procedes far past Birch reduction

Not Discussed in this group meeting:

• Birch reduction of non-aromatic compounds (*ie* protecting group removal, alkenes, alkynes)
• Birch reduction for functionalization of nanotubes

The Birch Reduction

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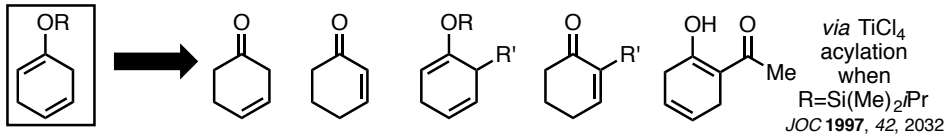
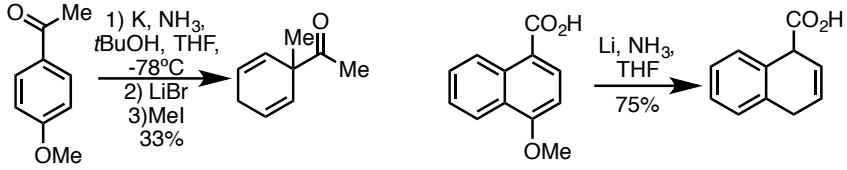
Aryl Ethers

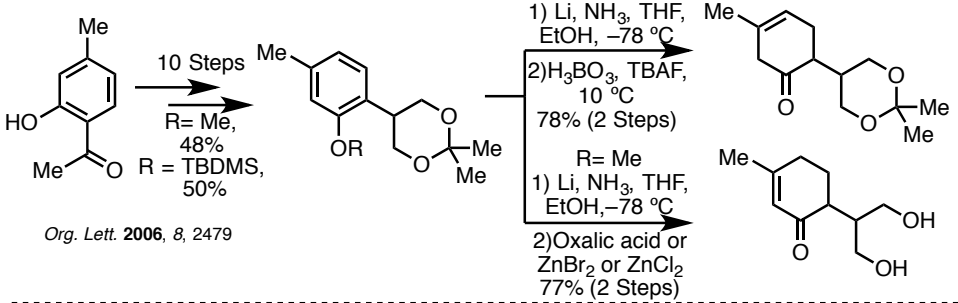


• Limitations: Partial or complete loss of alkoxy group (usually when *para* or *ortho* to EWG)

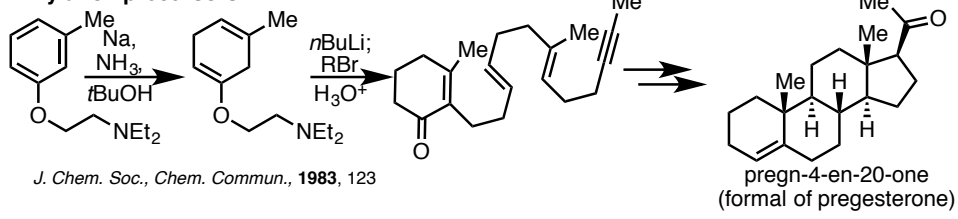


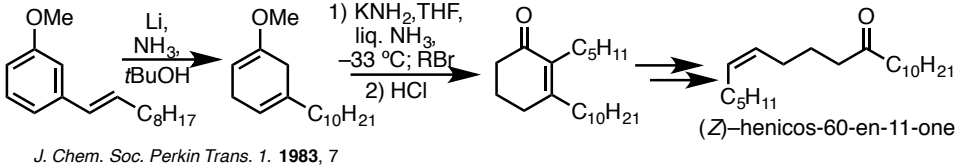
Na instead of Li, MeOH as a H$^+$ donor, addition *t*BuOK prior to reduction, or quenching with $FeCl_3$ instead of NH_4Cl can limit loss of OMe

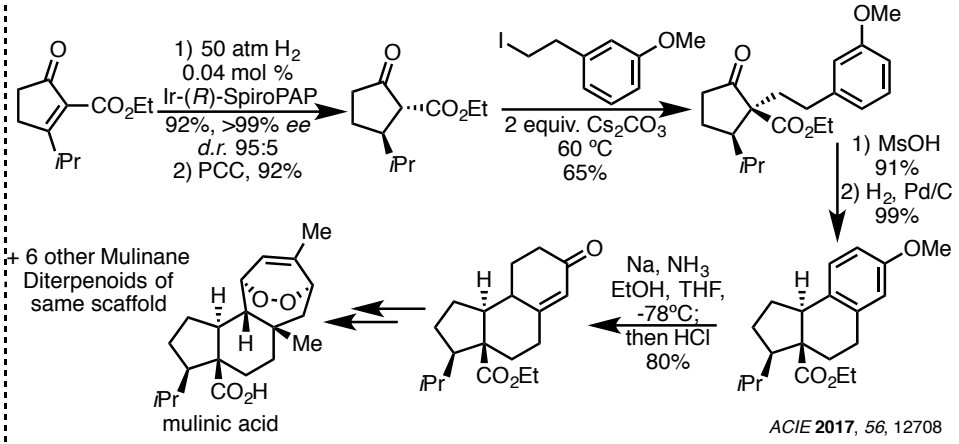
•β,γ-unsaturated ketones often isomerize into conjugation



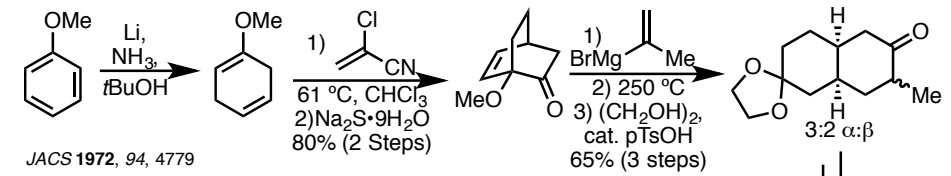
Alkylation precursors

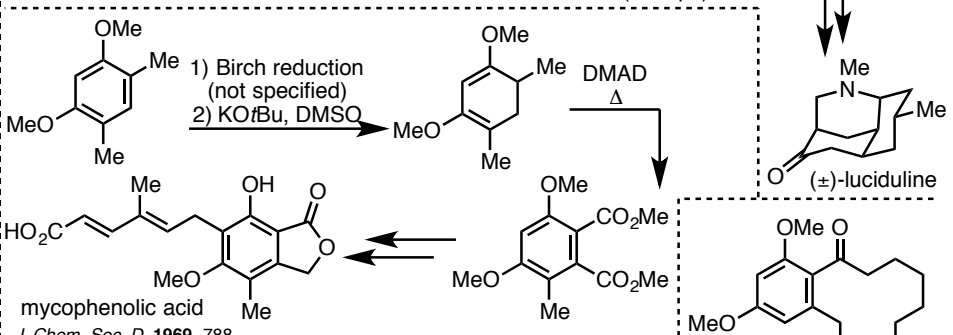


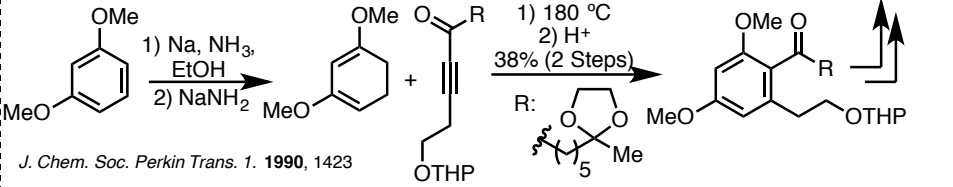




Cycloaddition precursors







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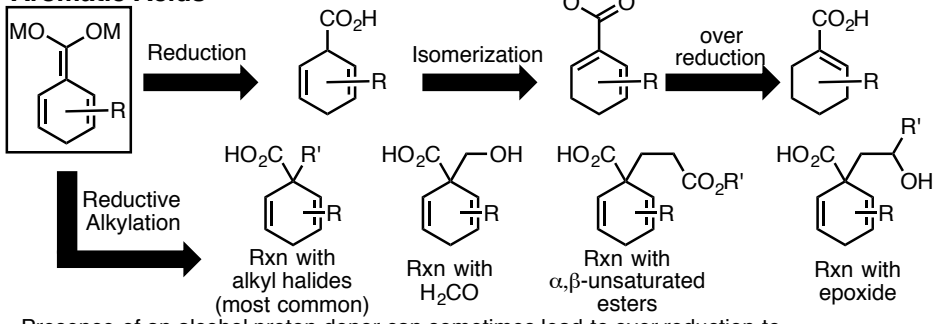
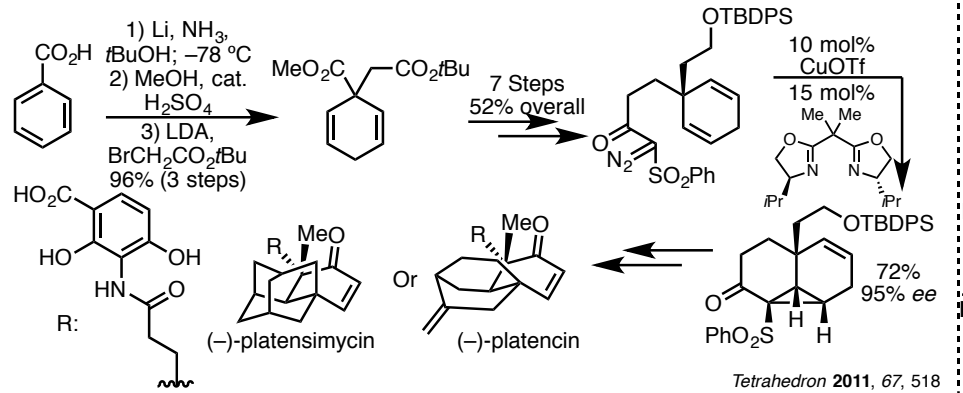
Aromatic Acids

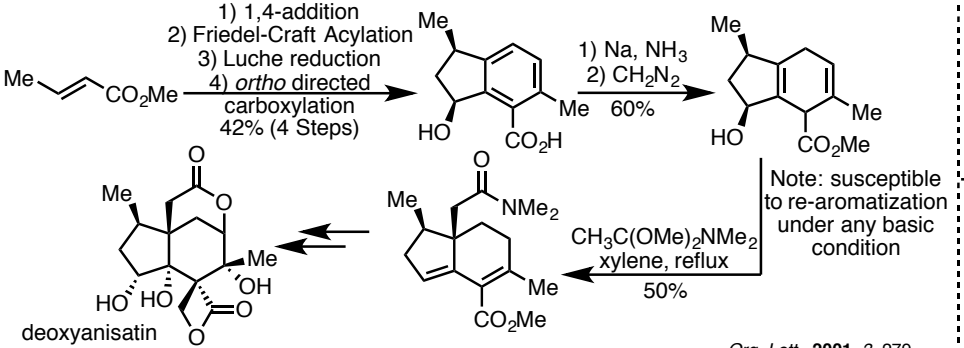


- Presence of an alcohol proton donor can sometimes lead to over reduction to dihydrobenzoic acid and/or conjugate product
  - Use of NH_4Cl in absence of alcohol can prevent
- If arene is *para* substituted will often get a mixture of *cis* and *trans* isomers largely influenced substituent sterics

Annulation

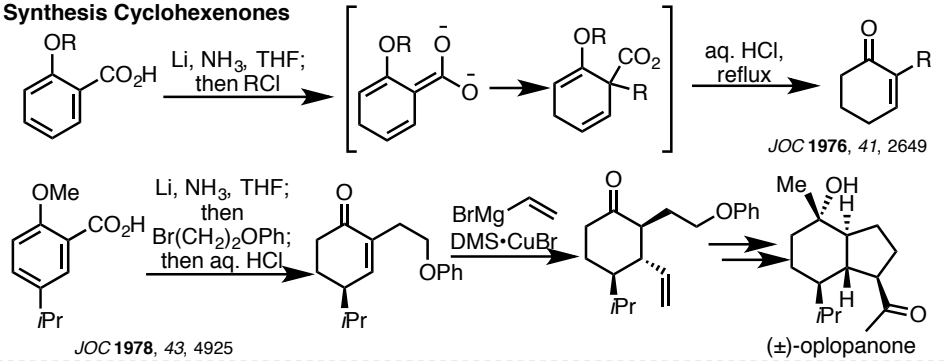


Tetrahedron **2011**, *67*, 518

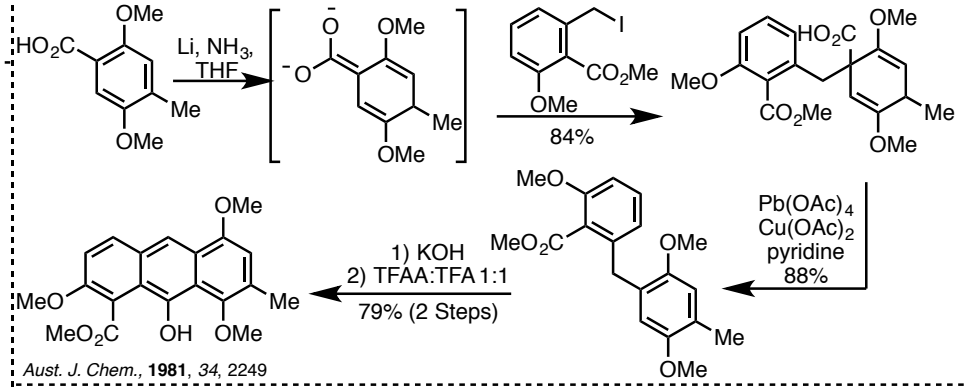


Org. Lett., **2001**, *3*, 279

Synthesis Cyclohexenones

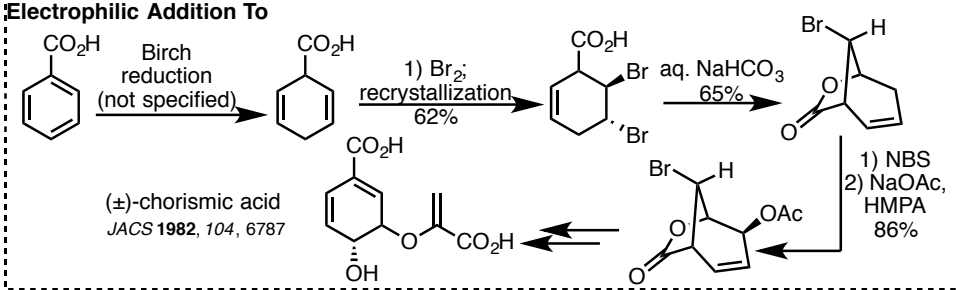


Re-aromatization

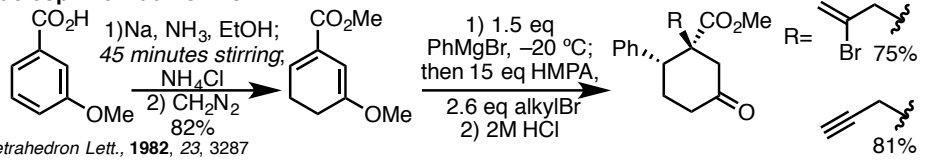


Aust. J. Chem., **1981**, *34*, 2249

Electrophilic Addition To



Nucleophilic Addition To



Tetrahedron Lett., **1982**, *23*, 3287

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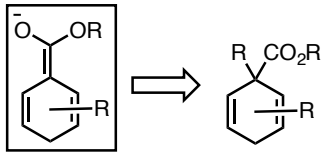
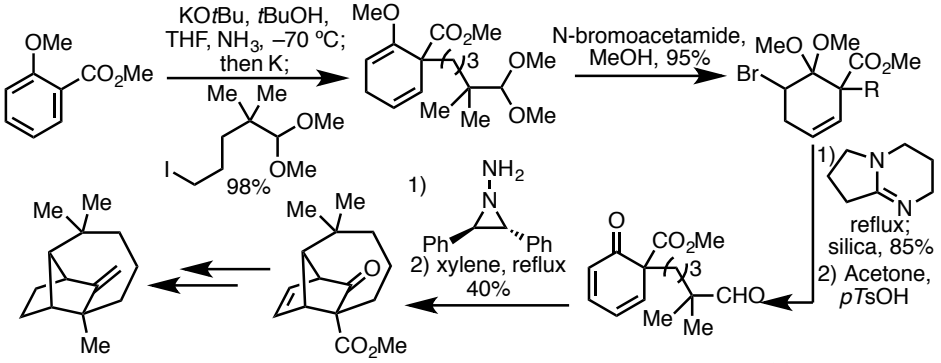
Aromatic Esters

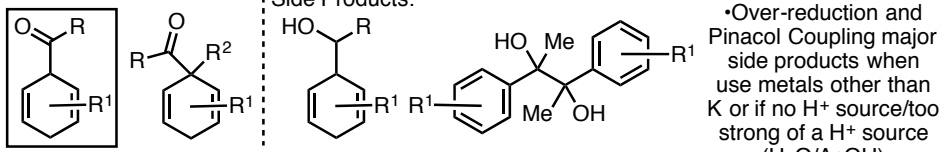


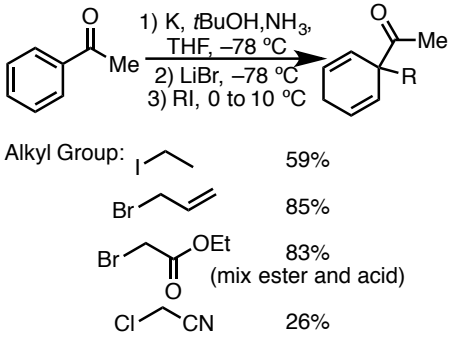
- Limitations include competitive carbonyl reduction
  - 1-2 equiv. H_2O or *t*BuOH added *before* Na in NH_3 can prevent (doesn't work for methyl esters or those with 4-alkyl substituents)
  - *t*BuOH with Li/K in NH_3 work with methyl esters and some 4-alkyl substituted
- Unlike aromatic acids, for reductive alkylation esters are usually more soluble, resistant to isomerization, rearomatization and decarboxylation



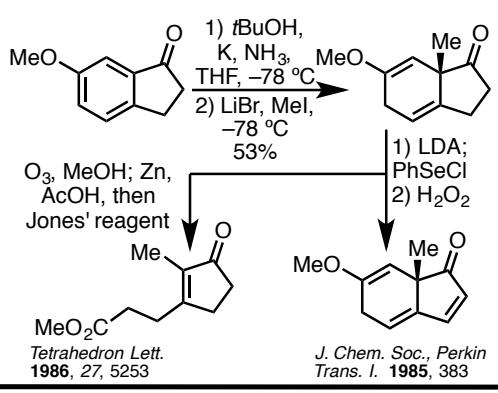
JOC **1985**, *50*, 915

Aromatic Ketones





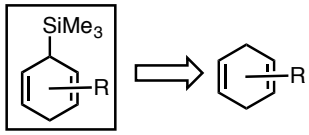
JOC **1973**, *38*, 3887



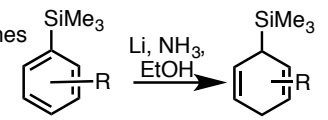
Tetrahedron Lett. **1986**, *27*, 5253

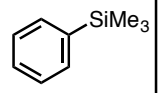
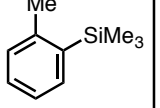
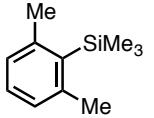
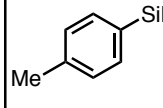
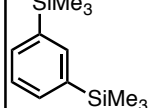
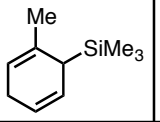
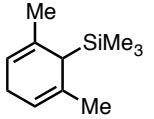
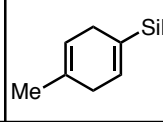
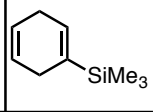
J. Chem. Soc., Perkin Trans. I. **1985**, 383

Arylsilanes



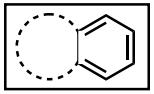
- Most commoly used to control regiochemistry of reduction as give allylic silanes
- Many times C–Si bond cleaved directly using standard conditions



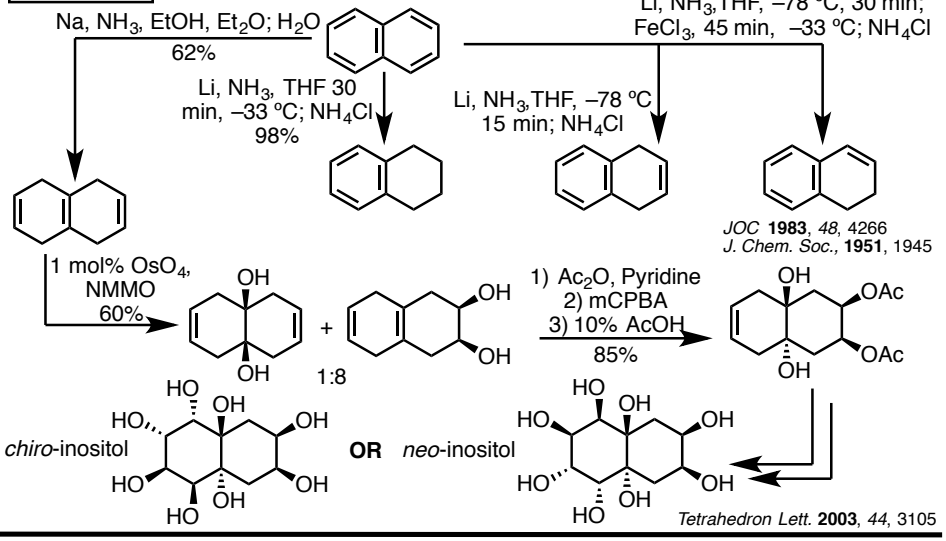
R					
Product (major)					
Yield	76%	60%	70%	70%	96%

J. Chem. Soc., Perkin Trans. I. **1975**, 470

Polyaromatic



- more reactive than simple benzenes
- site of reduction controled by distribution of e^- density in anionic intermediates
- mixture products common



JOC **1983**, *48*, 4266
J. Chem. Soc., **1951**, 1945

Tetrahedron Lett. **2003**, *44*, 3105

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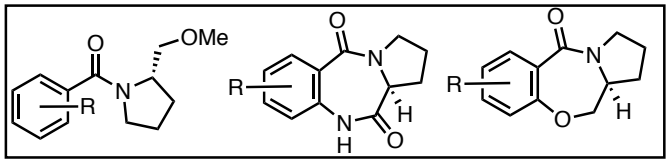
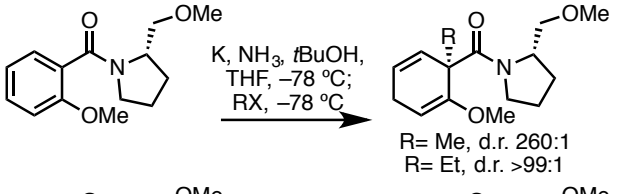
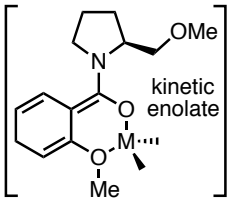
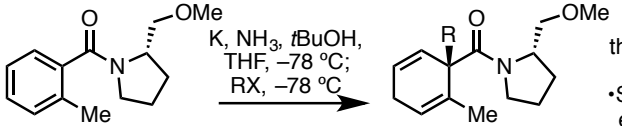
Asymmetric Methods: Amides



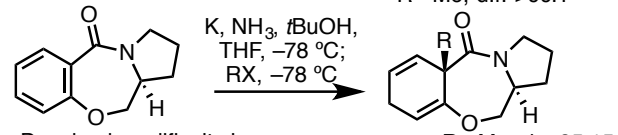
- Most methods use *L*-proline derivatives as a chiral auxiliary for diastereoselective reductive alkylation
- Procedures use K instead of Li to prevent F.G. reduction



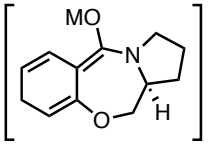




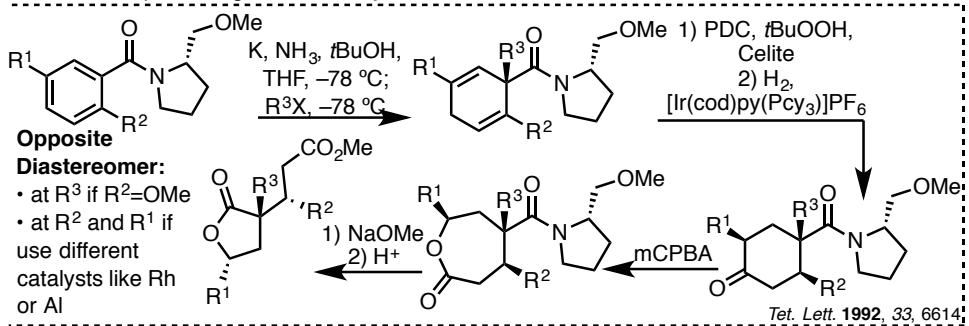
- Opposite selectivity arises though chelation enolate to OMe as well as NH_3
- Selectivity reversed by allowing equilibration to thermodynamic enolate before addition RX



Drawbacks: •dificulty in remove aux.
•Need *o*–substituent to promote good selectivity

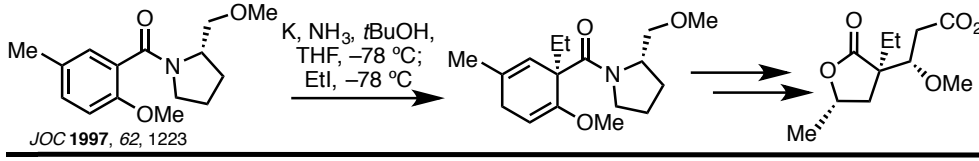


JACS **1988**, *110*, 7828

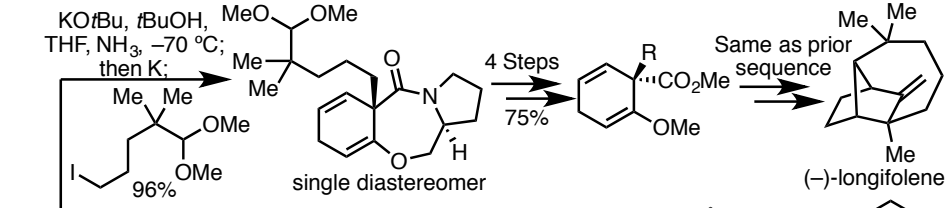


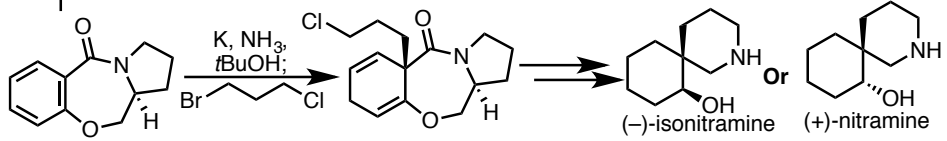
Opposite Diastereomer:
- at R^3 if R^2=OMe
- at R^2 and R^1 if use different catalysts like Rh or Al

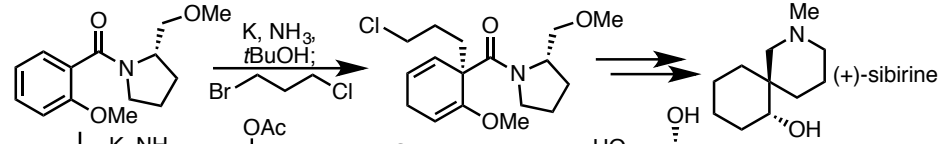
Tet. Lett. **1992**, *33*, 6614

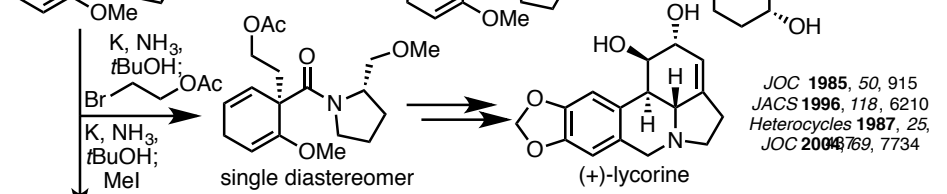


JOC **1997**, *62*, 1223

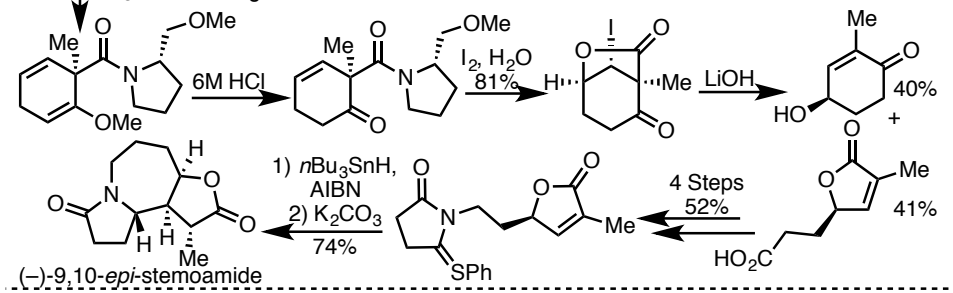


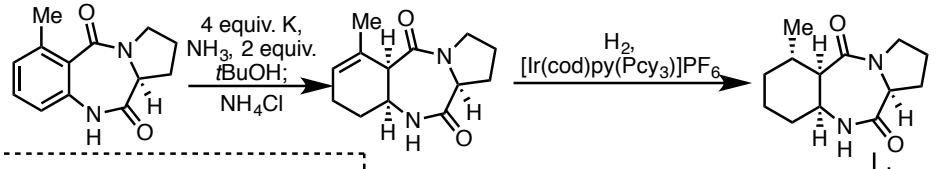


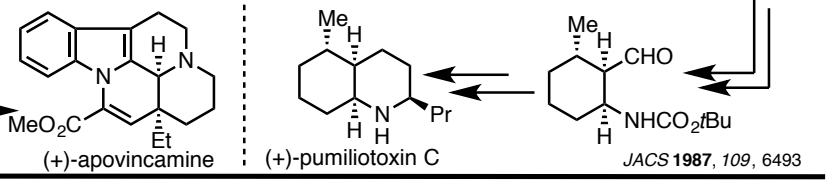




JOC **1985**, *50*, 915
JACS **1996**, *118*, 6210
Heterocycles **1987**, *25*, *JOC* **2004**, *69*, 7734







JACS **1987**, *109*, 6493

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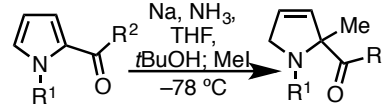
Heterocycles

- Just as with carbocycles, co-solvents can be used to increase solubility (Dioxane, THF, Et_2O, DME) and order of addition can impact yield and product
- Alcohol addition depends on substrate (*i.e.* moderately activated usch as e^--deficient pyrroles and furans don't need)

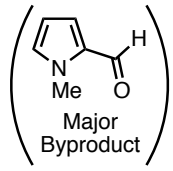
Pyrroles

Unactivated or with only Electron Donating substituents: No desired products

2-substituted



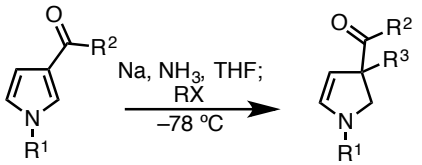
	Yield
R^1 = Me, R_2 =	25-30%
R^1 = Me, R_2 = O*i*Pr	20%
R^1 = Boc, R_2 =	85% (*t*BuOH excluded) *



∗ = Optimized conditions; can also be used with EtI, BuI, *i*BuI, BnBr and AllylBr

JOC **1996**, *61*, 7664

3-substituted

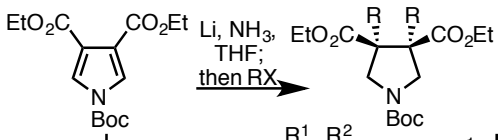


10 eq. $(MeOCH_2CH_2)_2NH$ needed to prevent loss of R^1 group when = Adoc

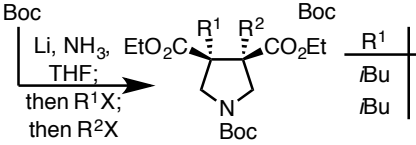
R^1	R^2	R^3	Yield
Boc		Me	70%
Boc		Bn	69%
Adoc	OCy	Me	72%
Adoc	OCy	H	74%

Tetrahedron Lett. **1998**, *39*, 3075

3,4-disubstituted



R	Me	Et	Allyl	*i*Bu
cis:*trans*	>20:1	>10:1	>10:1	>10:1
Yield	77%	82%	70%	79%

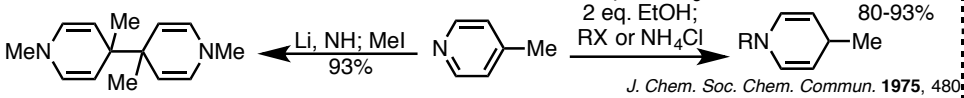


R^1	R^2	*cis*:*trans*	Yield
*i*Bu	Me	only cis	82%
*i*Bu	Bn	only cis	77%

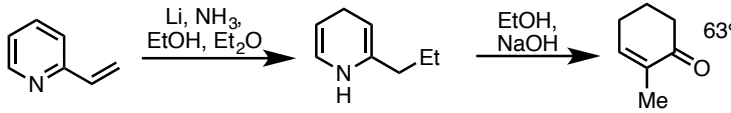
J. Chem. Soc. Chem. Commun. **1999**, 141

Pyridines

Very sensitive to rxn conditions

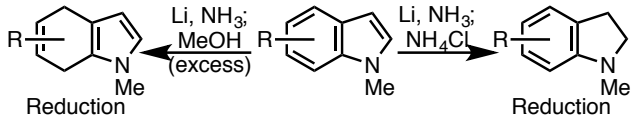


J. Chem. Soc. Chem. Commun. **1975**, 480



JOC, **1975**, *40*, 3606

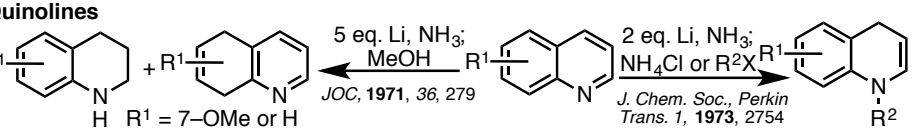
Indoles



JOC, **1971**, *36*, 279

•It is thought that MeOH is acidic enough to rapidly protonate the radical anion as it forms in equilibrium with the N-alkylindole but NH_3 is not acidic enough and can only protonate the dianion

Quinolines



JOC, **1971**, *36*, 279

J. Chem. Soc., Perkin Trans. 1, **1973**, 2754

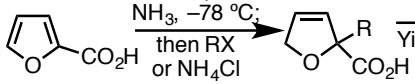
Furans

As with pyrroles unactivated or furans with electron donating substituents cannot be reduced under Birch conditions

When R^1=H

R^2	Me	*i*Pr	Bn	CH_2OMe	CO_2Me
Yield	88%	78%	45%	79%	78%

2-substituted

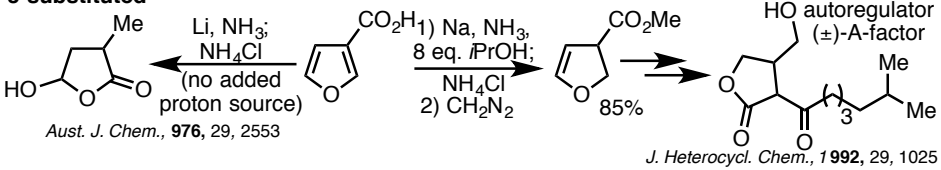


R^2	Me	*i*Pr	Bn	H
Yield	75%	95%	75%	80%

Tetrahedron Lett., *1***975,** 9, 627

• Note if too large an excess of metal isused dimeric and ring openned side products predominate
• Amides as EWG also work

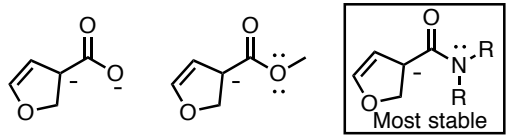
3-substituted

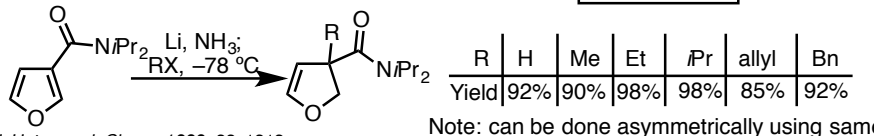


Aust. J. Chem., **976,** 29, 2553

J. Heterocycl. Chem., *1***992,** 29, 1025

Theorized ring opening do to the instability of carbanion intermediate:



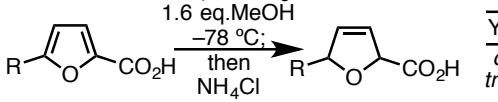


R	H	Me	Et	*i*Pr	allyl	Bn
Yield	92%	90%	98%	98%	85%	92%

J. Heterocycl. Chem., *1***996,** 33, 1313

Note: can be done asymmetrically using same L-proline derived amides as previously shown

2,5-disubstituted



R	Me	Et	*n*Pr	*t*Bu	Bn	(*p*-MeO)Bn
Yield	83%	85%	64%	71%	40%	40%
cis:*trans*	(1:1)	(1:1)	(1:1)	(1:1)	(3:2)	(3:2)

Bull. Chem. Soc. Jpn., *1***975,** 48, 491

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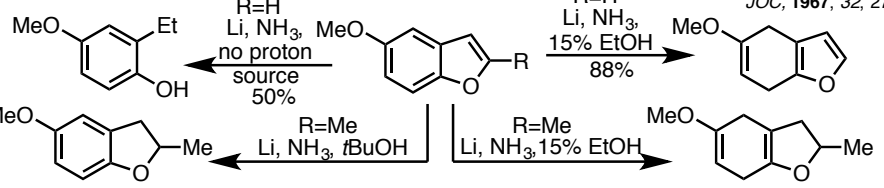
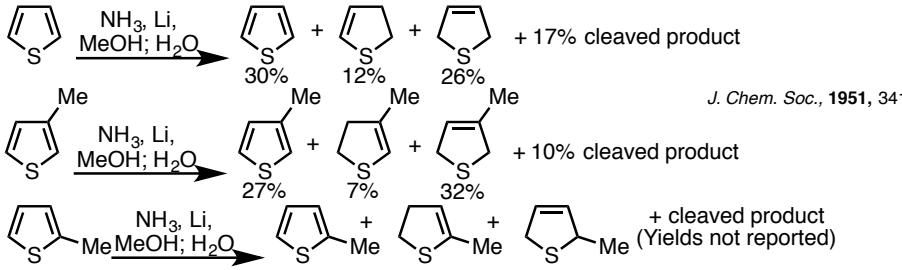
Benzofurans Very sensitive to reaction conditions.



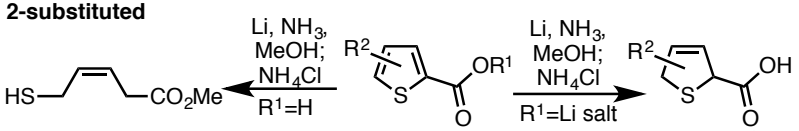
JOC, **1967**, *32*, 2794

Thiophenes Unlike furans and pyrroles, unactivated thiophenes has been reported but gives a mixtures of over-reduced and ring cleaved products

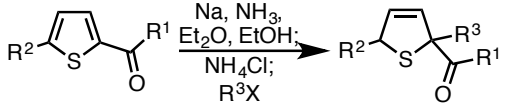


J. Chem. Soc., **1951**, 3411

2-substituted



J. Chem. Soc., **1951**, 3411

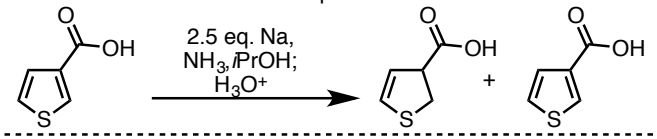


R^1	*n*Pr	*n*Pr	Cy	*n*Pr	nC_7H_{15}
R^2	H	H	H	*n*Bu	Me
R^3	Bn	allyl	Bn	Bn	Me
Yield	82%	68%	80%	76%	44%

No comment on *cis*:*trans* selectivity

Chem. Lett., **1981**, 1341

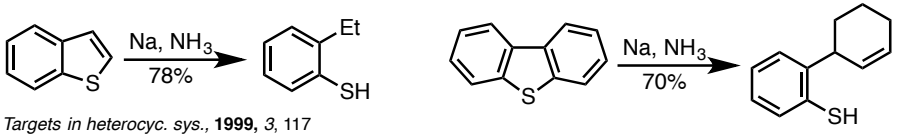
3-substituted - almost no examples



3:2 mix product to starting material; low yielding

Tetrahedron Lett., **1985**, *26*, 1791

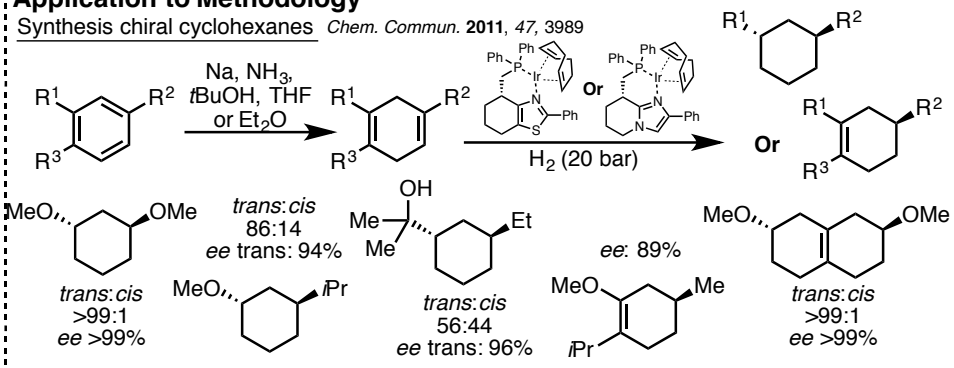
Benzothiophenes and Dibenzothiophenes - very few examples



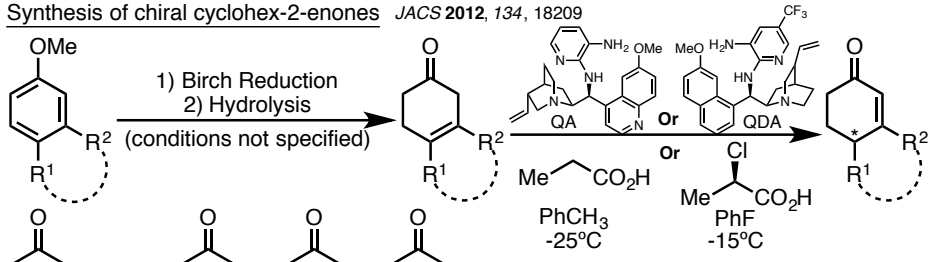
Targets in heterocyc. sys., **1999**, *3*, 117

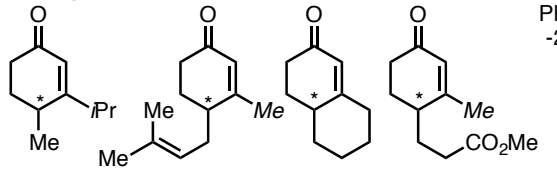
Application to Methodology

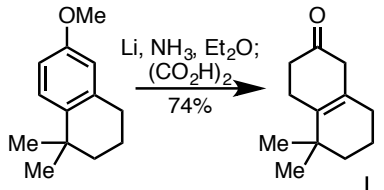
Synthesis chiral cyclohexanes *Chem. Commun.* **2011**, *47*, 3989



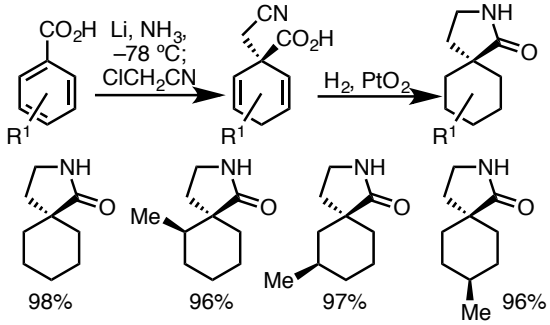
Synthesis of chiral cyclohex-2-enones *JACS* **2012**, *134*, 18209

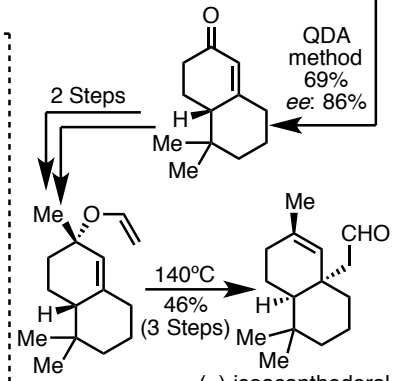






Synthesis of Spiral Lactams *Eur. J. Org. Chem.* **2017**, *6*, 1074





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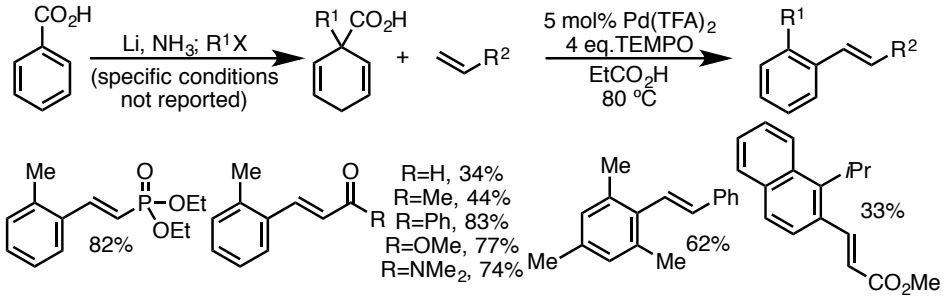
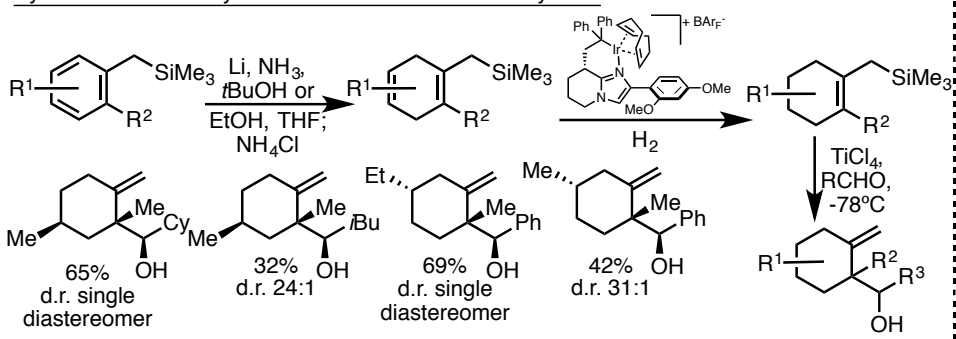
Synthesis *ortho*-alkylated vinylarenes

ACS Catal. **2018**, *8*, 1213



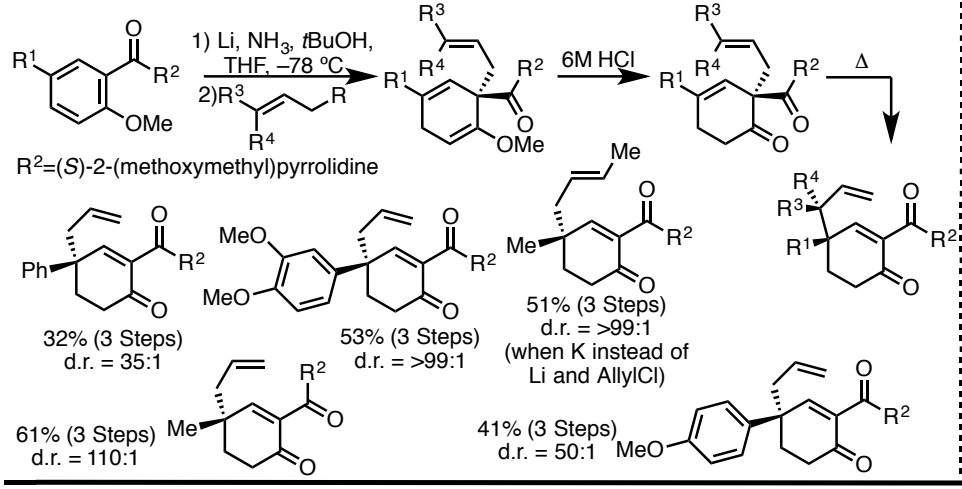
Synthesis of chiral allylsilanes for Hosomi–Sakurai allylation

Chem. Eur. J. **2018**, *24*, 1681



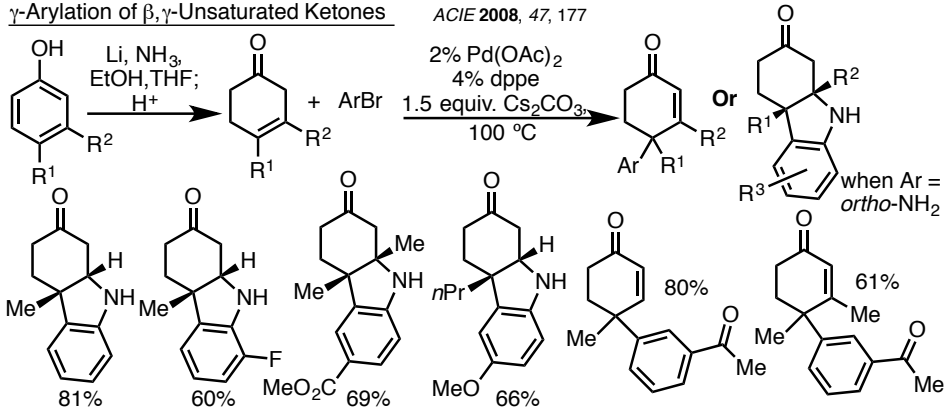
Enantioselective Birch-Cope Sequence for Quaternary Stereocenters

JOC **2007**, *72*, 930



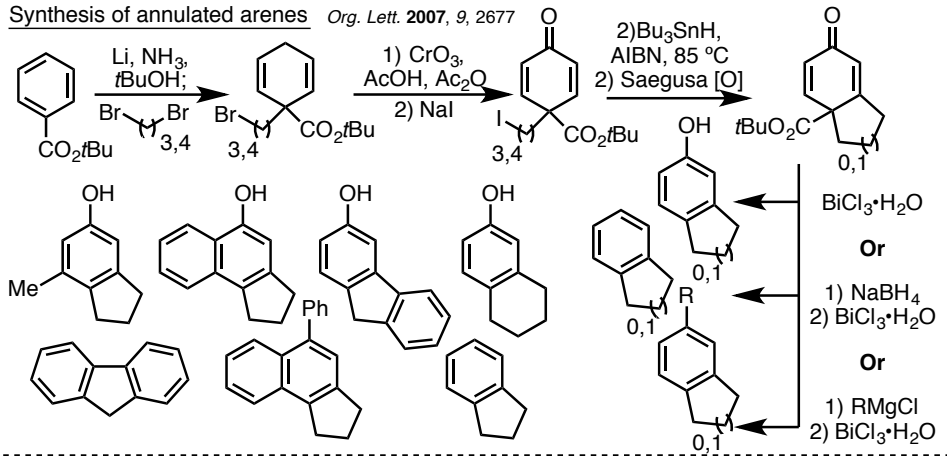
γ-Arylation of β,γ-Unsaturated Ketones

ACIE **2008**, *47*, 177



Synthesis of annulated arenes

Org. Lett. **2007**, *9*, 2677



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Electrochemical Birch Reduction

•First reported by Birch himself:

Other reported procedures:

• Pt, LiCl, $MeNH_2$
JACS **1963**, *85,* 2858;

• Pt, Graphite or C; LiCl, ethylenediamine: major product cyclohexene
J. Electrochem. Soc., **1963**, *110,* 425

•Al, LiCl, EtOH:HMPA 67:33, undivided: major product cyclohexane
Bull. Chem. Soc. Jpn., **1982**, *55,* 347

•Hg, $(Bu_3EtN)OH$, H_2O, 60ºC,
J. Electrochem. Soc., **1981**, *128,* 322

•Hg, $(TBA)BF_4$, THF/H_2O, rt
JOC., **1985**, *50,* 556

Electrolytic Reduction in Liquid Ammonia

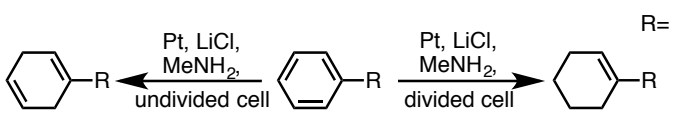
BENZENOID compounds have been reduced to dihydro-derivatives by means of sodium and alcohol in liquid ammonia[1]. The process has now been carried out electrolytically on *m*-tolyl methyl ether at a smooth copper cathode with a current density of 0·04 amp./sq. cm. in a saturated solution of sodium ethoxide in liquid ammonia containing 5 per cent of ethyl alcohol, the temperature being maintained at about − 40° by means of a solid carbon dioxide – alcohol bath. The dihydro-*m*-tolyl methyl ether, probably the 2 : 5-, was identified (see ref. 1) by conversion to the 2 : 4-dinitrophenyl-hydrazone of 3-methyl-Δ²-*cyclo*hexenone, m.p. 174°, undepressed by an authentic specimen. The current efficiency of the reduction was low, but can probably be improved, and the process may be of general utility for similar reactions.

ARTHUR J. BIRCH

Dyson Perrins Laboratory,
Oxford.
June 7.

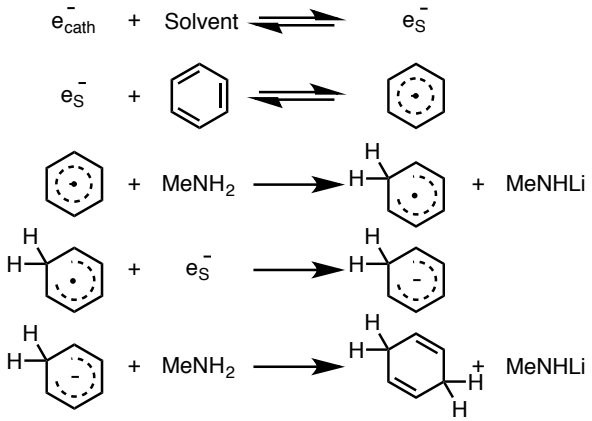
[1] Birch, *J. Chem Soc.*, 430 (1944).

Nature, **1946,** *158,* 60



R=	Divided	Undivided
H	49%	49%
Me	44%	64%
Et	63%	73%
*i*Pr	75%	82%
*t*Bu	81%	85%

Mechanism



• methylamide serves as proton source forming LiNHMe

• in undivided cell methylamine HCl can quench LiNHMe; in divided two are seperated so LiNHMe isn't neutralized and isomerizes to conjugated 1,3-diene which can be further reduced

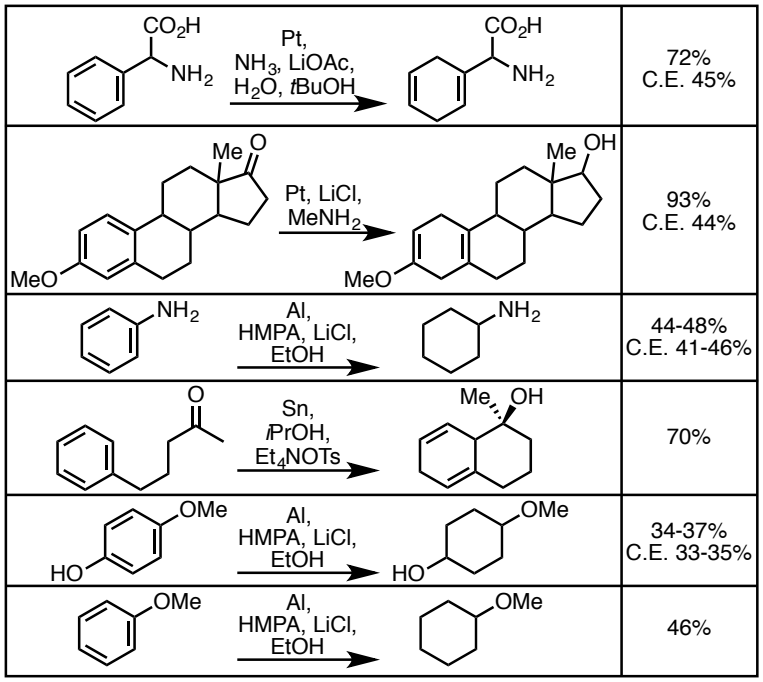
JACS **1963**, *85,* 2858;
JACS **1964**, *86,* 5272;
J. Electrochem. Soc., **1966**, *113,* 1060

•The observed differences in product distribution (cyclohexadiene vs. cyclohexene vs cyclohexane) has been attributed to proton availability

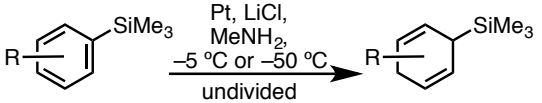
Control by lowering current density, temperature and EtOH concentration

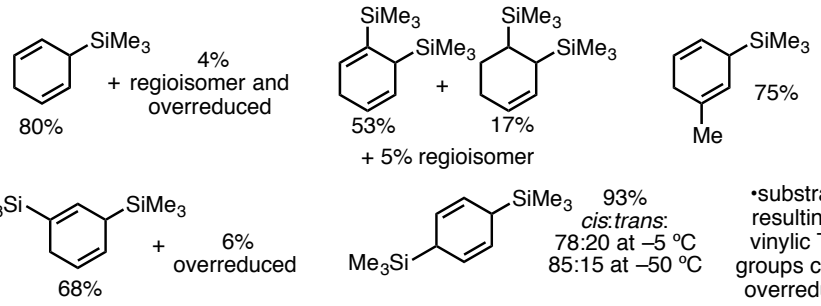
JACS **1969**, *91,* 4194

Electrochemical Birch reductions



Red. Trav. Chim. Pays-Bas. **1995**, *114*, 259





•substrates resulting in vinylic TMS groups can be overreduced

Note that unlike under standard Birch conditions no loss of Si reported

J. Chem. Soc., Perkin Trans. 1 **1974**, 2055