Reviews:

Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1-334.

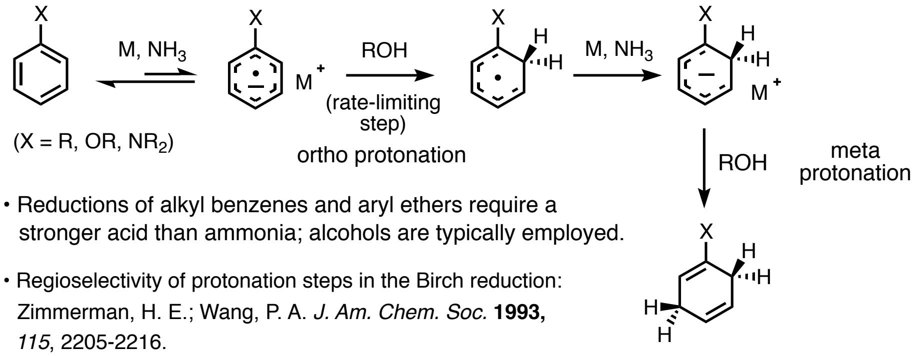
Mander, L. N. In *Comprehensive Organic Synthesis*; Trost, B. M. and Fleming, I., Ed.; Pergamon: Oxford, **1991**, Vol. 8, pp. 489-521.

Hook, J. M.; Mander, L. N. *Natural Prod. Rep.* **1986**, *3*, 35-85.

Propects for Stereocontrol in the Reduction of Aromatic Compounds: Donohoe, T. J.; Garg, R.; Stevenson, C. A. *Tetrahedron: Asymmetry* **1996**, *7*, 317-344.

Mechanism:

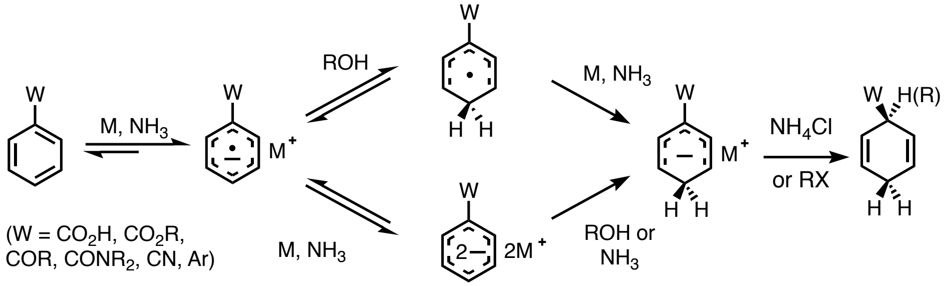
Electron-Donor Substituents (X):



- Reductions of alkyl benzenes and aryl ethers require a stronger acid than ammonia; alcohols are typically employed.
- Regioselectivity of protonation steps in the Birch reduction: Zimmerman, H. E.; Wang, P. A. *J. Am. Chem. Soc.* **1993,** *115*, 2205-2216.

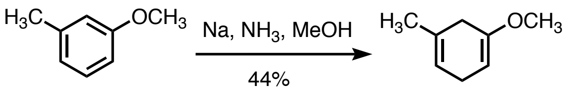
- Protonation of cyclohexadienyl anions is kinetically controlled and occurs at the central carbon.

Electron-Withdrawing Substituents (W):

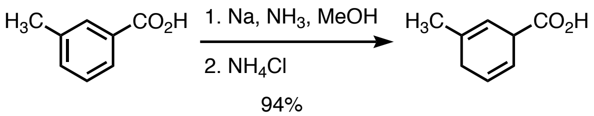


- Aromatic carboxylic acids and carboxylates are readily reduced with Li/NH_3 in the absence of alcohol additives.

Additivity of Substituent Effects:



Birch, A. J. *J. Chem. Soc.* **1944**, 430-436.



Chapman, O. L.; Fitton, P. *J. Am. Chem. Soc.* **1963**, *85*, 41-47.

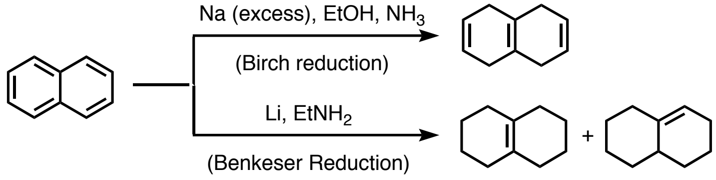
Conditions:

- Metals: Li, K, Na, occasionally Ca or Mg.
- Co-solvents: diethyl ether, THF, glymes.
- Proton sources (where appropriate): *t*-BuOH and EtOH are most common, also MeOH, NH_4Cl, and water.

Metal	Solubility in NH_3 at –33 °C (mol Metal/mol NH_3)	Normal reduction potential at –50 °C in NH_3 (V)
Li	0.26	–2.99
Na	0.18	–2.59
K	0.21	–2.73

From: Briner, K. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A., Ed.; John Wiley and Sons: New York, **1995**, Vol. 5, pp. 3003-3007.

- Reduction in low molecular weight amines (Benkeser reduction):



- Reduction in low molecular weight amines (in the absence of alcohol additives) furnishes more extensively reduced products than are obtained under Birch conditions (M, NH_3, ROH).

A Comparison of Methods Using Lithium/Amine and Birch Reduction Systems: Kaiser, E. M. *Synthesis* **1972**, 391-415.

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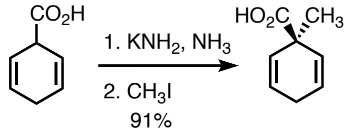
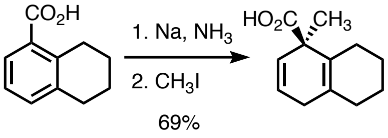
Reductive alkylation:

- Enolates derived from 1,4-dihydrobenzoic acids are selectively alkylated at the α-carbon.



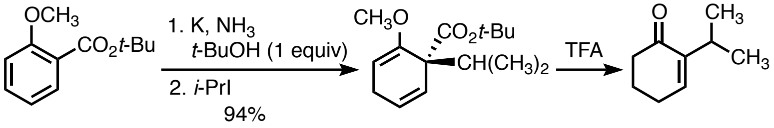
Nelson, N. A.; Fassnacht, J. H.; Piper, J. U. *J. Am. Chem. Soc.* **1961**, *83*, 206-213.
See also: Birch, A. J. *J. Chem. Soc.* **1950**, 1551-1556.

- Loewenthal and co-workers first demonstrated single step reductive alkylation of aromatic compounds:

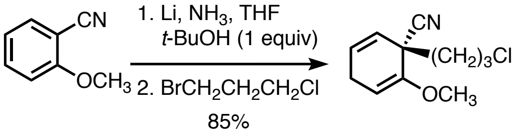


Bachi, M. D.; Epstein, J. W.; Herzberg-Minzly, Y.; Loewenthal, H. J. E. *J. Org. Chem.* **1969**, *34*, 126-135.

- Reductive alkylations of aromatic esters, amides, ketones, and nitriles typically are conducted in the presence of one equivalent of an alcohol:



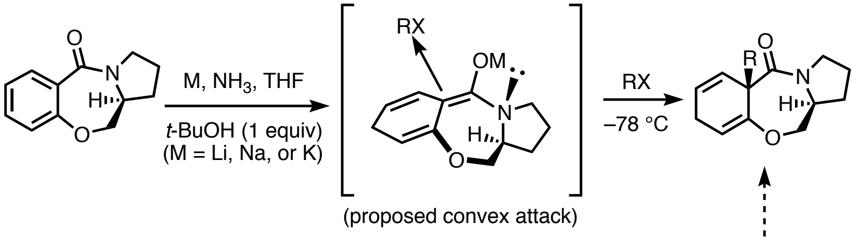
Hook, J. M.; Mander, L. N.; Woolias, M. *Tetrahedron Lett.* **1982**, *23*, 1095-1098.



Schultz, A. G.; Macielag, M. *J. Org. Chem.* **1986**, *51*, 4983-4987.

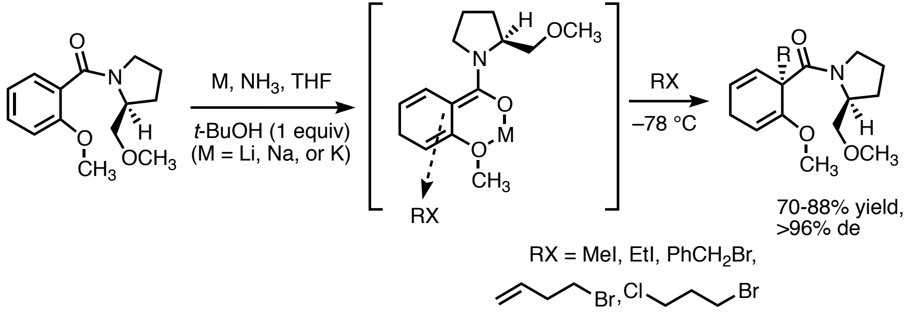
Asymmetric Birch Reduction:

Reviews: Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207-213; Schultz, A. G. *Chem. Commun.* **1999**, 1263–1271.



RX	yield (%)	de (%)
MeI	67	60
EtI	82	>98
$CH_2{=}CH_2CH_2Br$	75	>96
$PhCH_2Br$	73	>96
$CH_2{=}CH_2CH_2CH_2Br$	89	96
$ClCH_2CH_2CH_2Br$	91	(n.d.)

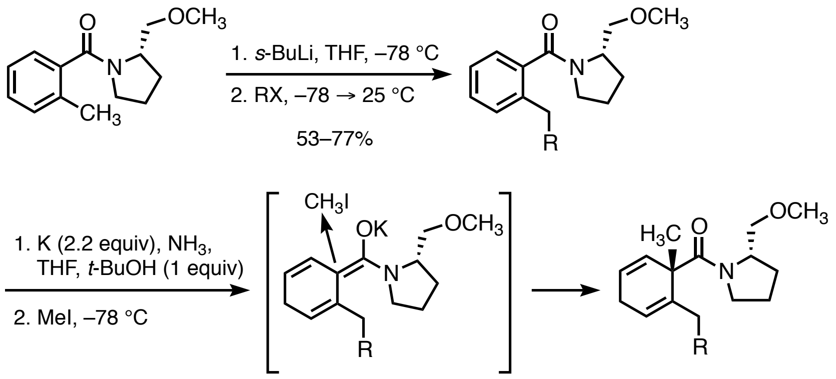
opposite
facial
selectivity



- Transition state may be complex, viz., enolate aggregation and nitrogen pyramidalization.
- Schultz proposes that Birch reduction results in kinetically controlled formation of a dimeric enolate aggregate wherein the metal is chelated by the aryl ether; the side chain of the chiral auxiliary is proposed to block the β-face of the enolate.

Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828-7841.

- 1,6-Dialkyl-1,4-cyclohexadienes are accessible by asymmetric Birch alkylation:

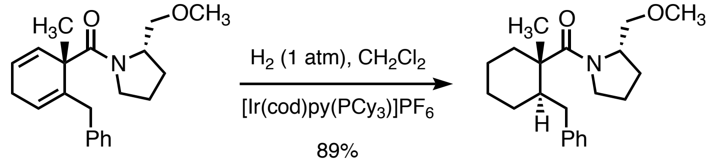


R	yield (%)	de (%)
H	90	> 98
Me	66	93
Et	79	90
$CH_2CH{=}CH_2$	76	93
$CH_2CH_2CH{=}CH_2$	69	90
CH_2Ph	62	95
CH_2CH_2Ph	77	93
$CH_2OCH_2CH_2SiMe_3$	71	94
CH_2CH_2OTBS	88	96
CH_2CH_2OMe	79	95

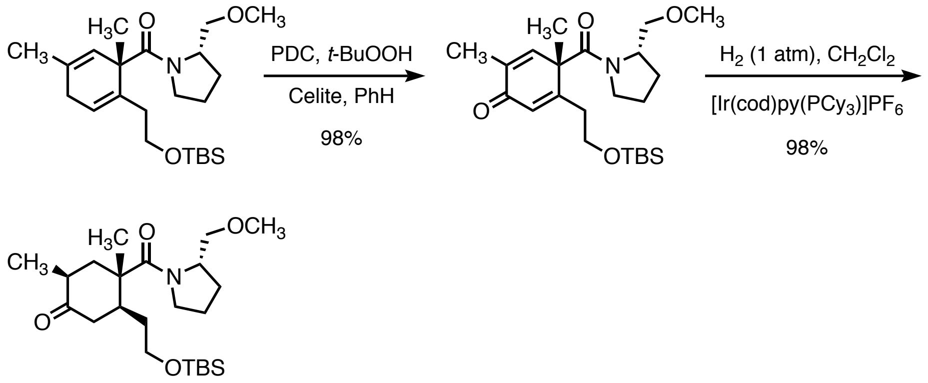
Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1991**, *113*, 4931–4936.

Transformations of asymmetric Birch alkylation products:

- Amide-directed hydrogenation with Crabtree's catalyst:

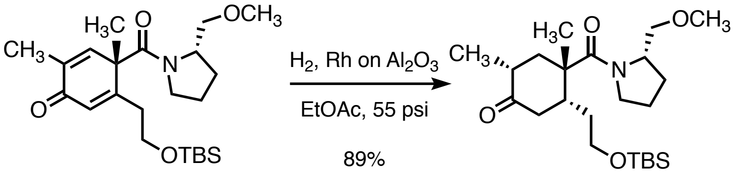


Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1991**, *113*, 4931–4936.



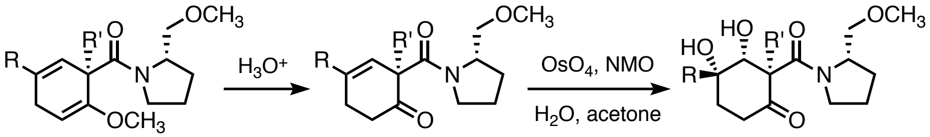
Schultz, A. G.; Hoglen, D. K.; Holoboski, M. A. *Tetrahedron Lett.* **1992**, *33*, 6611–6614.

- Heterogenous hydrogenation with rhodium on alumina occurs *anti* to the bulky amide, presumably due to steric factors.



Schultz, A. G.; Hoglen, D. K.; Holoboski, M. A. *Tetrahedron Lett.* **1992**, *33*, 6611–6614.

- Dihydroxylation of 3-cyclohexen-1-ones obtained by Schultz's asymmetric Birch alkylation occurs exclusively *anti* to the amido substituent:



R	R'	yield (%)
H	Me	91
H	CH_2Ph	86
H	$(CH_2)_3N_3$	88
H	$(CH_2)_3Cl$	94
CH_2Ph	Et	73
Me	Et	76

Schultz, A. G.; Dai, M.; Tham, F. S.; Zhang, X. *Tetrahedron Lett.* **1998**, *39*, 6663–6666.

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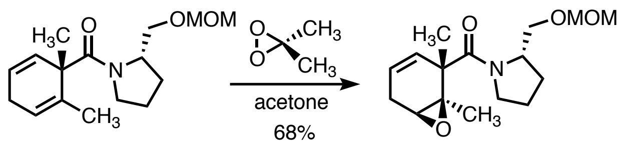
- Regio- and stereo-selective epoxidation has been demonstrated:

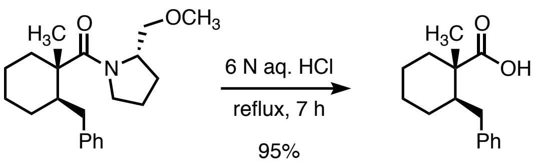


>13 : 1 diastereoselectivity

Schultz, A. G.; Harrington, R. E.; Tham, F. S. *Tetrahedron Lett.* **1992**, *33*, 6097–6100.

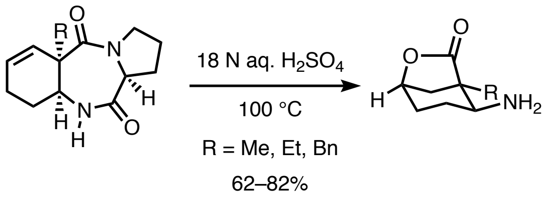
Methods of cleavage of Schultz's chiral auxiliaries:

- Acid catalyzed cleavage of the alkylation products requires harsh conditions:



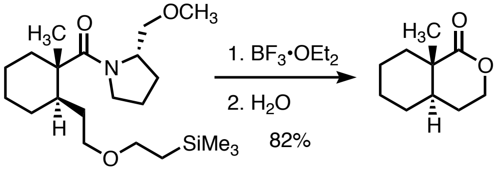
Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1991**, *113*, 4931–4936.

- Olefinic substrates undergo protiolactonization under the conditions of acidic hydrolysis:

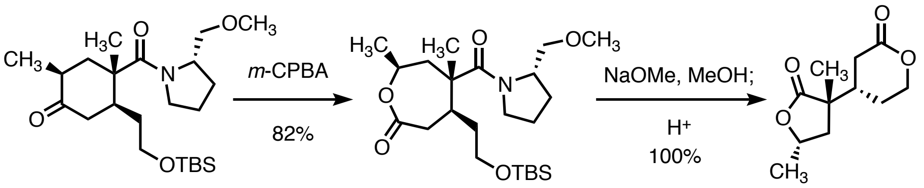


Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, 109, 6493–6502.

- Lactonization can be effectively employed for amide cleavage:

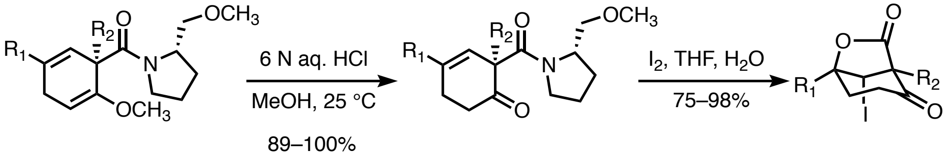


Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1991**, *113*, 4931–4936.



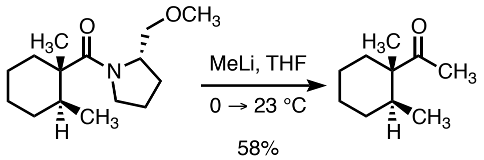
Schultz, A. G.; Hoglen, D. K.; Holoboski, M. A. *Tetrahedron Lett.* **1992**, *33*, 6611–6614.

- Iodolactonization:



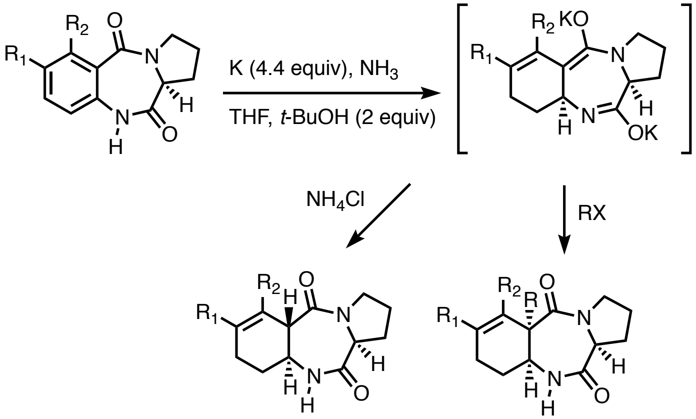
Schultz, A. G.; Dai, M.; Khim, S.-K.; Pettus, L.; Thakkar, K. *Tetrahedron Lett.* **1998**, *39*, 4203–4206.

- Addition of alkyllithium reagents:



Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828-7841.

Asymmetric synthesis of amino-substituted cyclohexenes:



R_1		RX	yield (%)	de (%)
H	H	MeI	54	70
H	H	EtI	68	82
H	H	NH_4Cl	73	not reported
H	Me	MeI	53	> 88
Me	H	NH_4Cl	84	one diastereomer
Me	H	MeI	78	52
Me	H	EtI	87	78
Me	H	CH_2=$CHCH_2Br$	68	> 95 : 5
Me	H	BnBr	78	> 95 : 5

Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, 109, 6493–6502.

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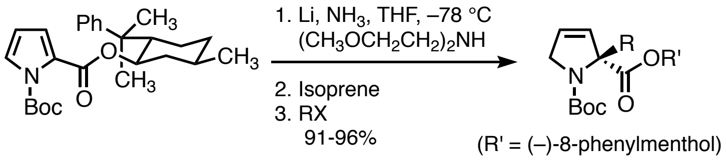
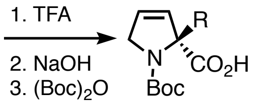
Asymmetric Birch Reduction of heterocycles:



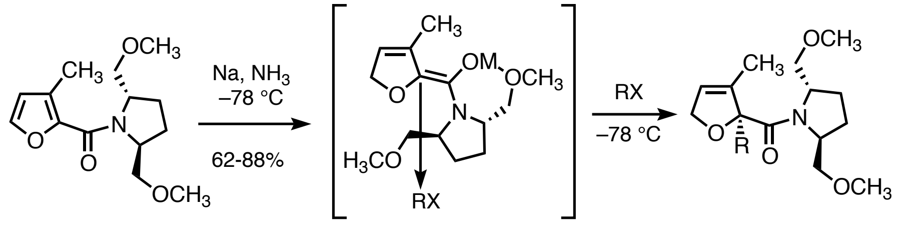
(R' = (–)-8-phenylmenthol)



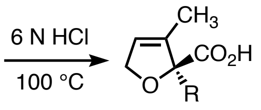
R	yield(%)	ee(%)
Me	79	78
Et	71	86
i-Bu	70	90
CH_2Ph	67	90

- Addition of the chelating amine $(CH_3OCH_2CH_2)_2NH$ was found to increase yields; the anion derived from this amine is less basic and less nucleophilic than $LiNH_2$, suppressing byproduct formation.

Donohoe, T. J.; Guyo, P. M.; Helliwell, M. *Tetrahedron Lett.* **1999**, *40*, 435-438.



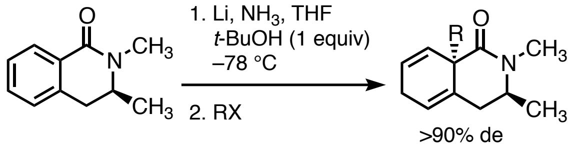
(proposed TS geometry)



R	yield(%)	ee(%)
Me	86	>94
Et	74	>94
i-Bu	68	>94

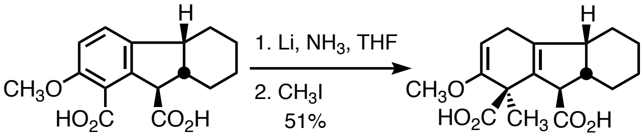
Donohoe, T. J.; Helliwell, M.; Stevenson, C. A. *Tetrahedron Lett.* **1998**, *39*, 3071-3074.

Chiral substrates:



R = CH_3 72%
R = $CH_2CH{=}CH_2$ 66%
R = CH_2Ph 68%

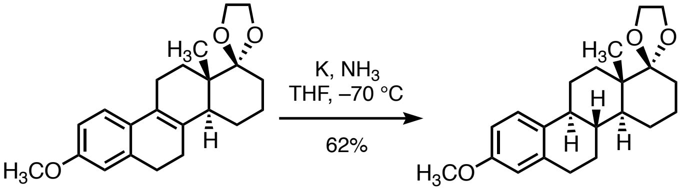
Schultz, A. G.; Kirinich, S. J.; Rahm, R. *Tetrahedron Lett.* **1995**, *36*, 4551-4554.



House, H. O.; Strickland, R. C.; Zaiko, E. J. *J. Org. Chem.* **1976**, *41*, 2401-2408.

Dissolving metal reductions of conjugated alkenes:

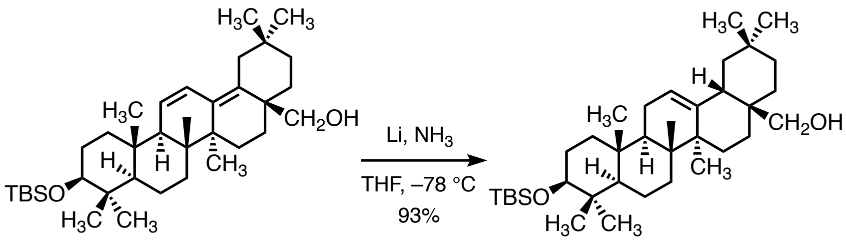
- Styrenes, conjugated dienes, and enones are more readily reduced under dissolving metal conditions than are aromatics; reduction occurs at low temperature without alcohol additives.



Ananchenko, S. N.; Limanov, V. Y.; Leonov, V. N.; Rzheznikov, V. N.; Torgov, I. V. *Tetrahedron* **1962**, *18*, 1355-1367.

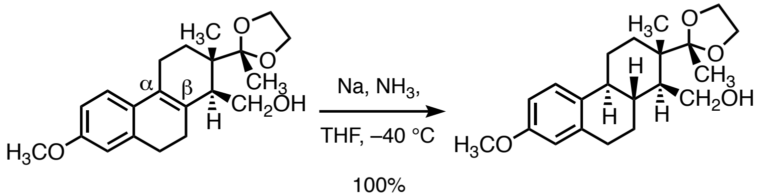
- Trans-fused products are favored, carbon pyramidalization is proposed in the transition state.

Stereochemical and/or regiochemical control by intramolecular protonation:

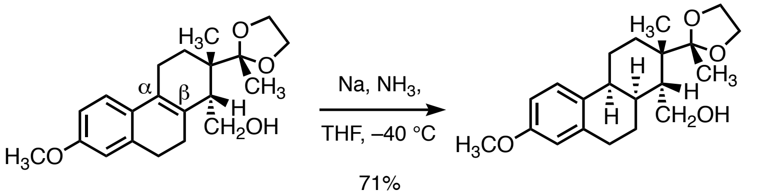


- It is proposed that the stereochemical outcome is the result of intramolecular protonation of the radical anion.

Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873-8874.

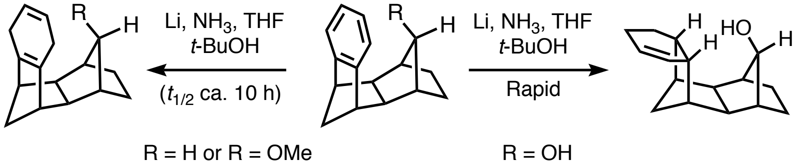


whereas:



- Initial intramolecular protonation at the β-position is proposed.

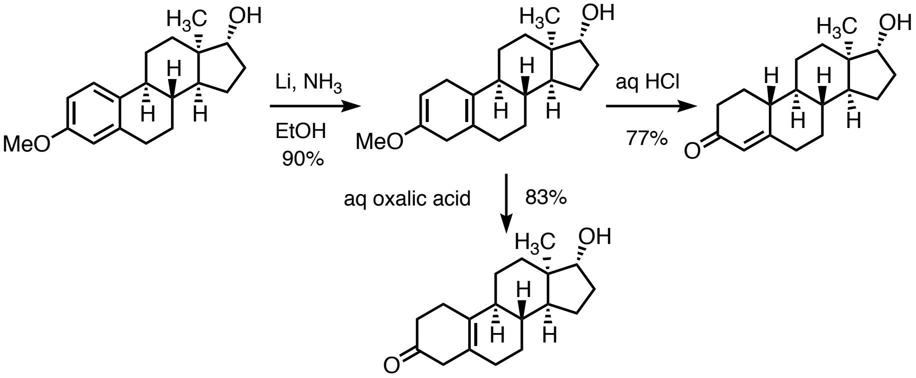
Lin, Z.; Chen, J.; Valenta, Z. *Tetrahedron Lett.* **1997**, *38*, 3863-3866.



Cotsaris, E.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1982**, 1206-1208.

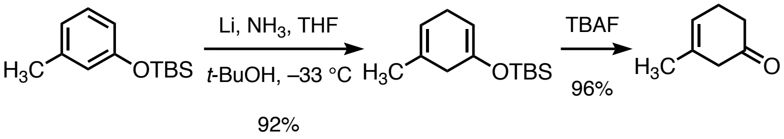
Transformations of Birch Reduction products:

- Synthesis of α,β or β,γ-unsaturated cyclohexanones



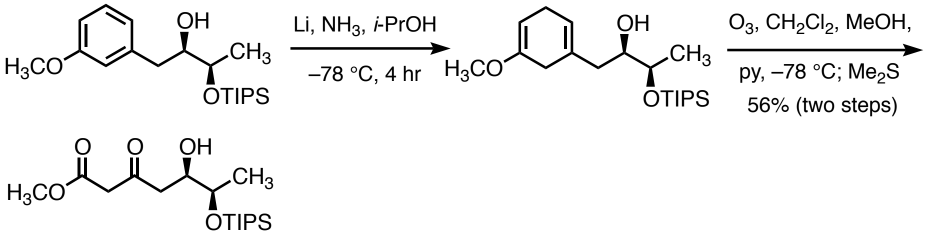
Nelson, N. A.; Wilds, A. L. *J. Am. Chem. Soc.* **1953**, *75*, 5366-5369.

- Reduction of aryl silyl ethers and synthesis of β,γ-unsaturated cyclohexanones:



Fuchs, P. L.; Donaldson, R. E. *J. Org. Chem.* **1977**, *42*, 2032-2034.

- Ozonolysis of Birch reduction products:



Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741-750.

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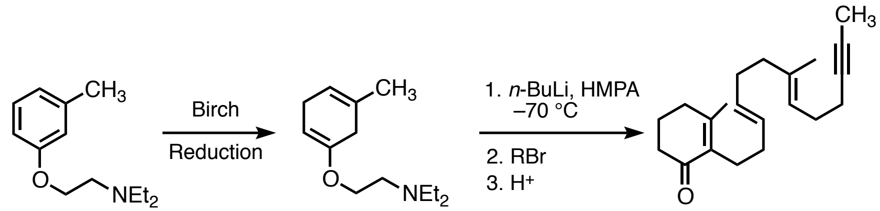
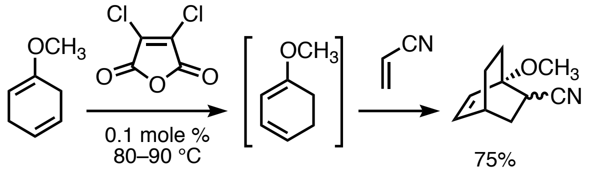
- Reductive alkylation of aromatics without electron-withdrawing groups is unsuccessful.
- Directed metalation of Birch products is possible:



Amupitan, J.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1978**, 852-853.
Bishop, P. M.; Pearson, J. R.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1983**, 123-124.

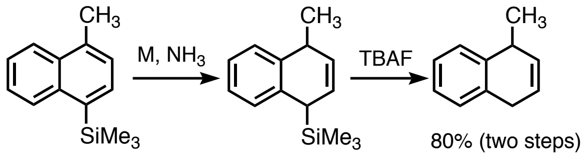
- Diels-Alder cycloaddition by isomerization of 1,3-dienes in situ:



- Isomerization is proposed to occur through a charge-transfer complex.

Birch, A. J.; Dastur, K. P. *Tetrahedron Lett.* **1972**, *41*,4195-4196.

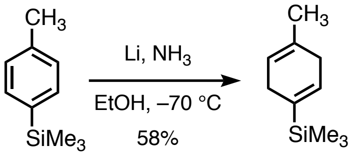
- Silyl substituents can be used to modify the regiochemistry of Birch reduction:



Rabideau, P. W.; Karrick, G. L. *Tetrahedron Lett.* **1987**, *28*, 2481-2484.

- In the absence of competing factors, allylic silanes are generally produced from Birch reduction of aryl silanes; this is attributed to stabilization of negative charge at the α-carbon by silicon.

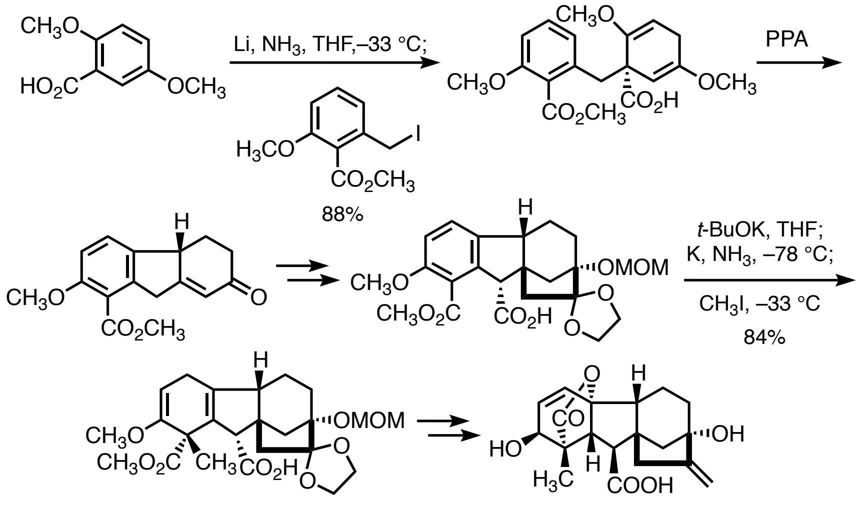
But:



Eaborn, C.; Jackson, R. A.; Pearce, R. *J. Chem. Soc., Perkin Trans. I* **1975**, 470-474.

Birch Reduction – Application in Synthesis:

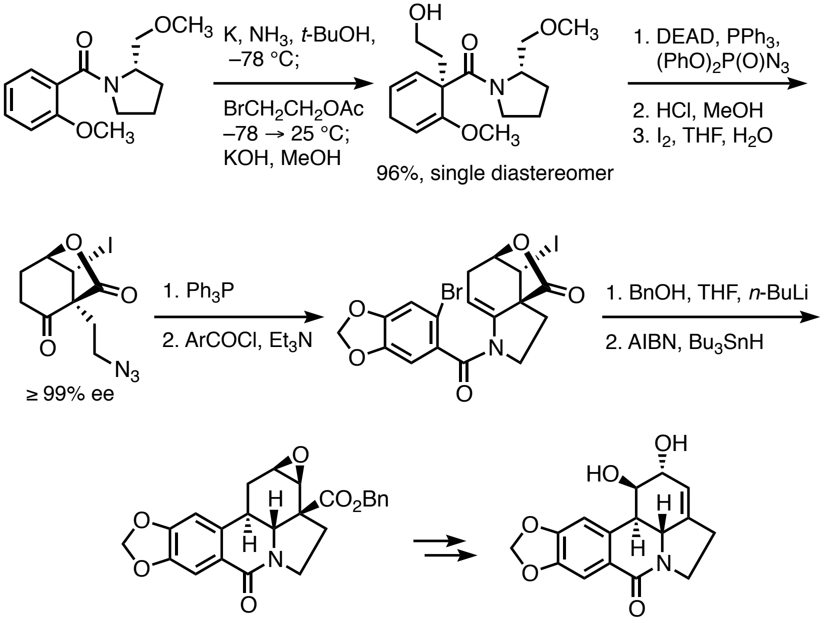
(±)-Gibberellic Acid:



(±)-Gibberellic Acid

Hook, J. M.; Mander, L. N.; Urech, R. *J. Org. Chem.* **1984**, *49*, 3250-3260.

(+)-Lycorine:



(single diastereomer)

(+)-Lycorine

Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1996**, *118*, 6210-6219.

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