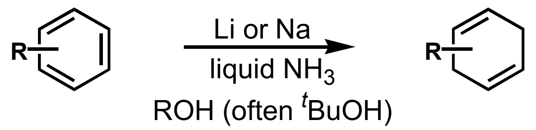
Functional Group Interconversions - Lecture 4

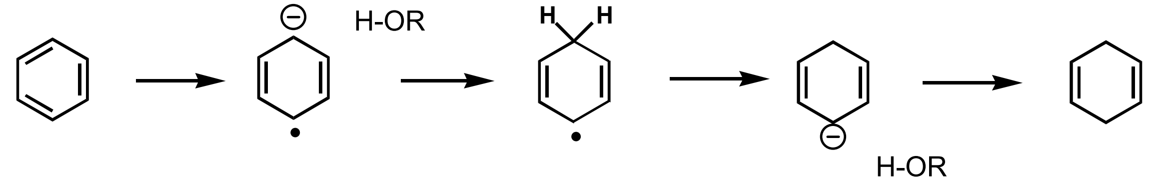
3.4 *Reduction of aromatic systems*

We can reduce aromatic systems to cyclohexanes under very forcing hydrogenolytic conditions, though this isn't a generally useful process. More interesting is the partial reduction of arenes to skipped 1,4-cyclohexadienes by dissolving metal reduction - the Birch reduction. When the starting benzene ring is substituted, the Birch reduction displays useful regioselectivity. Thus, electron withdrawing groups end up deconjugated from the alkenes (since they stabilise the anionic intermediates) while electron donating groups end up on the alkenes - they avoid being adjacent to negative charge.

Birch reduction

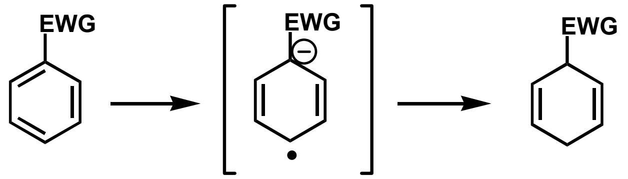
· Partial reduction of an aromatic ring to a non-conjugated, 1,4-diene





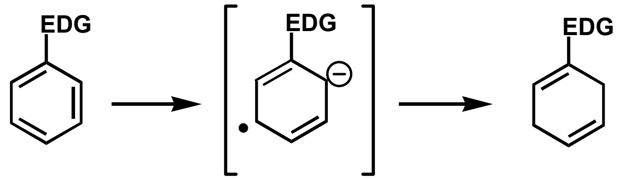
EWG =
CO$_2$R, CN, *etc*.

(relatively fast reaction)

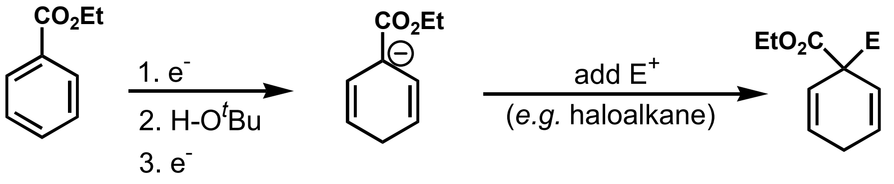


EDG =
alkyl, OMe, NR$_2$, *etc*.

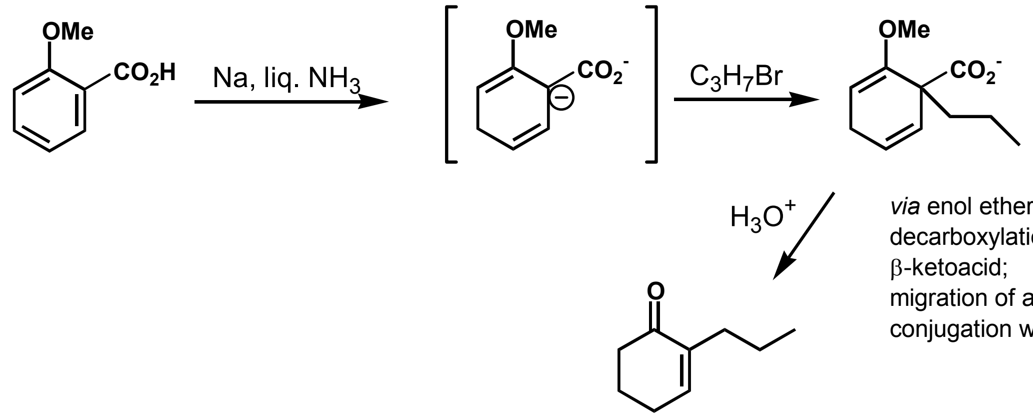
(relatively slow reaction)



It is sometimes possible to trap the intermediate anions with electrophiles. For example, if the amount of added alcohol is limited to 1 equivalent, then the enolate formed by reduction of benzoate esters can be trapped with alkyl halides:



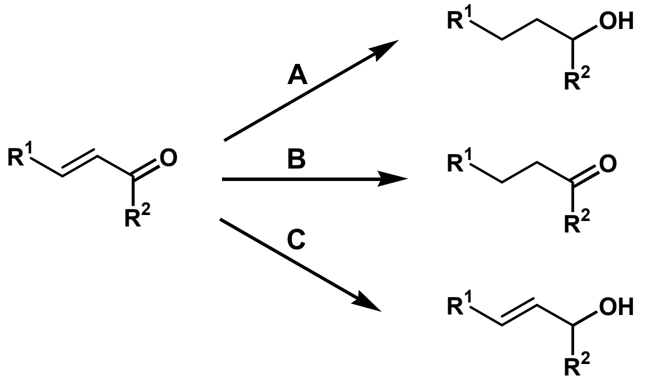
e.g.



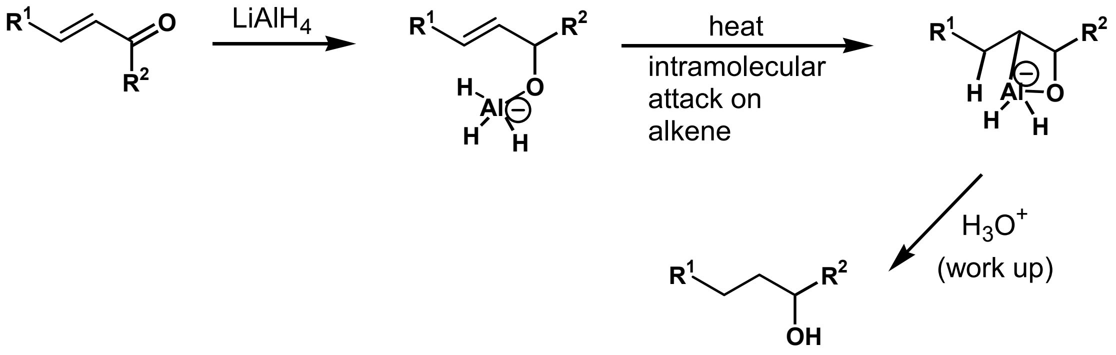
via enol ether hydrolysis;
decarboxylation of
β-ketoacid;
migration of alkene into
conjugation with carbonyl

3.5 *Reduction of α,β-unsaturated carbonyl compounds*

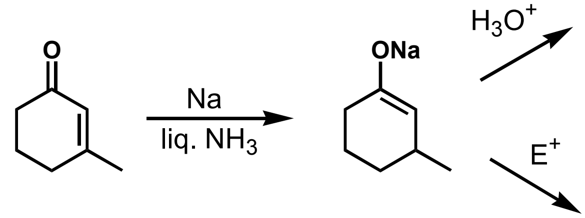
There are three possible outcomes to this: total reduction to the saturated alcohol; partial reduction to the unsaturated ketone; and partial reduction to the allylic alcohol:



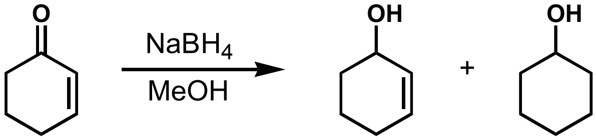
Outcome **A** – total reduction – can be accomplished by using $LiAlH_4$ at elevated temperatures:



Outcome **B** – reduction of the alkene – can often be done by using H_2 and a catalyst (*e.g.* Pd/C). Alternatively, we can use Na in liquid NH_3, which allows the useful possibility of trapping the intermediate enolate with electrophiles. This process allows **regiospecific enolate formation** from the enone.



For outcome **C** – reduction of the carbonyl group only - one of the most reliable methods involves the use of $NaBH_4$ along with $CeCl_3$ in MeOH (known as the Luche reduction). (Mechanistically, the $CeCl_3$ is believed to accelerate the reaction between $NaBH_4$ and MeOH to give alkoxyborohydrides (see Lecture 1), as well as increasing the ability of the MeOH to undergo hydrogen bonding to the carbonyl group in the enone).



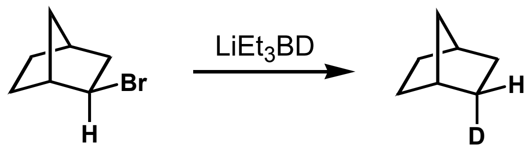
with **no** $CeCl_3$: 59:41
with $CeCl_3$: 99:1

Section 4: Reductive cleavage of C-X bonds

4.1 *Hydride displacements*

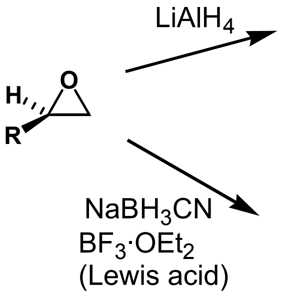
$LiAlH_4$, $NaCNBH_3$ and $LiEt_3BH$ (sold as "Super hydride"!) can all displace halides, tosylates and mesylates from primary and secondary alkyl positions. Since the reactions are S_N2 in nature, this is a useful way of making stereospecifically deuterated compounds through the corresponding deutero reducing agents. This is of much use in biosynthetic studies.

e.g.



(D = deuterium = ^2H)

Epoxides are a special class of C-X species: there are two possible sites of attack and we can tailor our reaction conditions to gain access to either. Thus, nucleophilic conditions give rise to attack at the less hindered carbon, while the use of a Lewis acid promotes attack at the best cation-stabilising centre (usually more substituted) on account of the polarised transition state. (Again, inversion of stereochemistry is seen at the centre being attacked by "H^-").

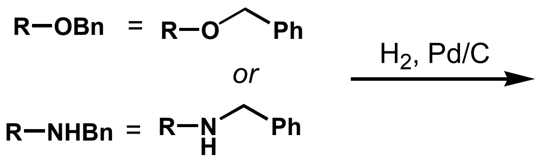


4.2 *Radical reactions*

Don't need to worry about these at the moment (await 3rd year!) but they are very useful, and not just for C-X reductions. Much of the work was pioneered by the Nobel Laureate Sir Derek Barton, who spent most of his career at Imperial College.

4.3 *Hydrogenolysis*

Cleavage of benzylic ethers and amines by hydrogenolysis gives rise to useful protecting groups for synthesis (see later in the course!)



Next time (**Monday 15th Dec** at 9am): Oxidation of C-H bonds, alcohols

AA 11.12.03

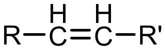
REFERENCE SECTION!

Functional Group Reactivity with Various Reducing Agents

Reagent Reaction	$NaBH_4$/EtOH	$LiAlH_4$	$LiAlH(O^tBu)_3$	BH_3-THF	$(i\text{-}Bu)_2AlH$ (DIBALH)	Catalytic hydrogenation
$RCHO \longrightarrow RCH_2OH$	+	+	+	+	+	+
$RCOR' \longrightarrow RCH(OH)R'$	+	+	+	+	+	+
$RCOCl \longrightarrow RCHO$	n/a	n/a	n/a	-	+*	n/a
$RCOCl \longrightarrow RCH_2OH$	n/a	+	+	-	+	+
Lactone ⟶ Diol	-	+	±	+	+	+
Epoxide ⟶ Alcohol	-	+	±	+	+	+
$RCOOR' \longrightarrow RCH_2OH + R'OH$	-	+	±	±	+	+
$RCOOH \longrightarrow RCH_2OH$	-	+	-	+	+	-
$RCONR'R'' \longrightarrow RCH_2NR'R''$	-	+	-	+	+	+
$RCONR'R'' \longrightarrow RCHO$	-	+	-	n/a	+	+
$R{-}C{\equiv}N \longrightarrow RCH_2NH_2$	-	+	-	+	+	+
$RNO_2 \longrightarrow RNH_2$	-	+	-	-	+	+
$RCH{=}CHR \longrightarrow RCH_2CH_2R$	-	-	-	+	-	+

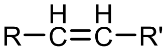
+ = gives reaction shown
- = does not give reaction shown
n/a = gives other reaction
± = borderline case
* = if one equivalent used

*Ease of reduction of various functional groups by lithium aluminium hydride**

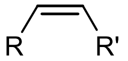
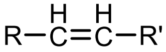
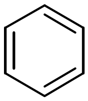
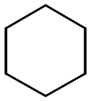
Substrate	Product	Ease of reaction
RCHO	RCH_2OH	Easiest
RCOR'	RCHOHR'	
RCOCl	RCHO	
lactone	diol	
epoxide	alcohol	
RCOOR'	RCH_2OH	
RCOOH	RCH_2OH	
$RCOO^-$	RCH_2OH	
RCONHR'	RCH_2NHR'	
$R-C\equiv N$	RCH_2NH_2	
RNO_2	RNH_2	Most difficult
 $R-\overset{H}{C}=\overset{H}{C}-R'$	- - - -	Inert

* - lithium aluminium hydride is VERY reactive, so discrimination between functional groups in the same reaction may be difficult - see notes for use of modified hydride reagents

Ease of reduction of various functional groups by borane

Substrate	Product	Ease of reaction
RCOOH	RCH_2OH	Easiest
 $R-\overset{H}{C}=\overset{H}{C}-R'$	RCH_2CH_2R'	
RCOR'	RCHOHR'	
$R-C\equiv N$	RCH_2NH_2	
epoxide	alcohol	
RCOOR'	RCH_2OH	Most difficult
RCOCl	- - - -	Inert

Ease of reduction of various functional groups by catalytic hydrogenation

Substrate	Product	Ease of reaction
RCOCl	RCHO	Easiest
RNO_2	RNH_2	
$R-\equiv-R'$		
RCHO	RCH_2OH	
 $R-\overset{H}{C}=\overset{H}{C}-R'$	RCH_2CH_2R	
RCOR'	RCHOHR'	
$ArCH_2OR$	$ArCH_3$ + ROH	
$R-C\equiv N$	RCH_2NH_2	
RCOOR'	RCH_2OH	
RCONHR'	RCH_2NHR'	
		Most difficult
$RCOO^-$	- - - -	Inert