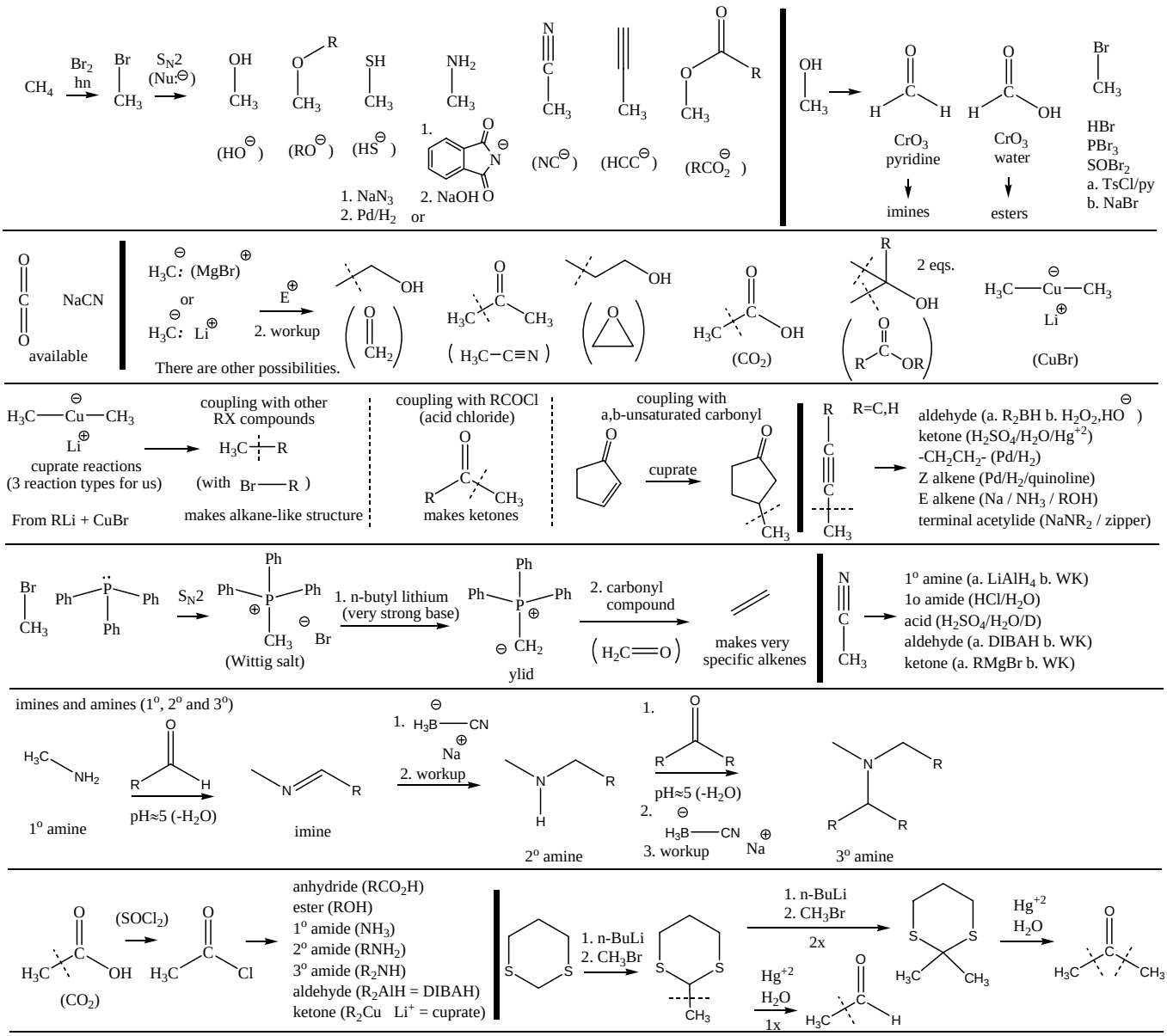
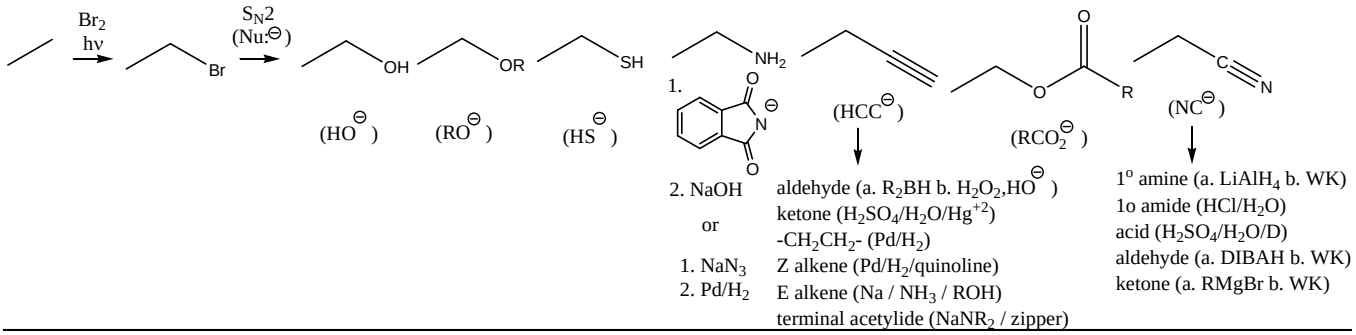
Chem 315/316 (Beauchamp) Name _____

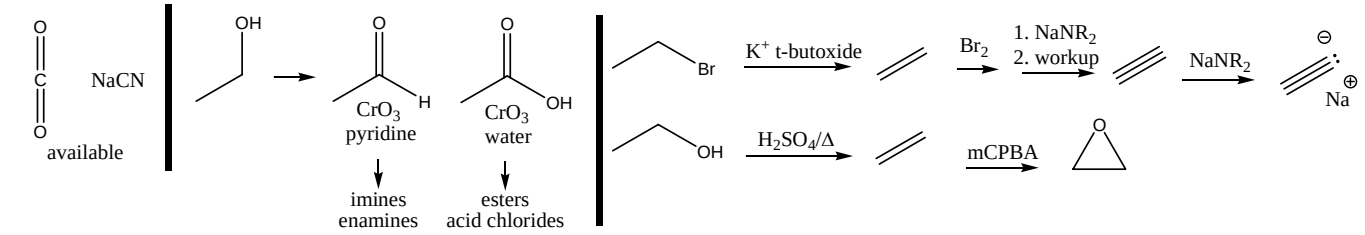
Some important 1C, 2C and 3C building blocks. You need to know these reactions. A fair amount of alkene chemistry is not covered in these pages.

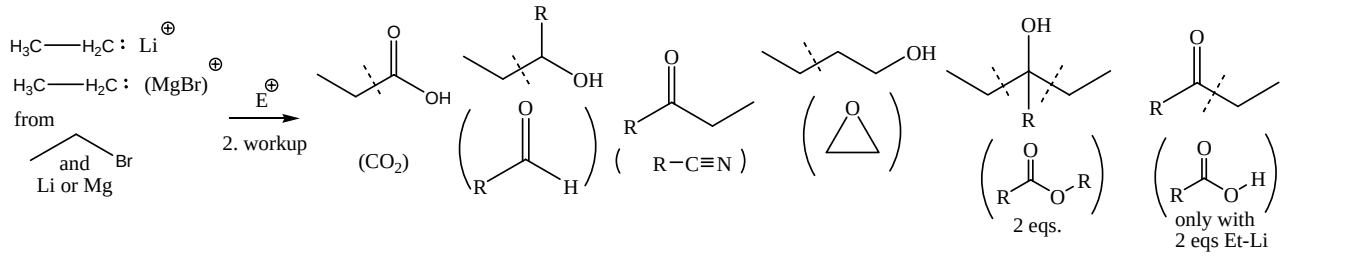
1 Carbon – you need to know reagents to allow synthetic transformations among these structures. Just a sampling.

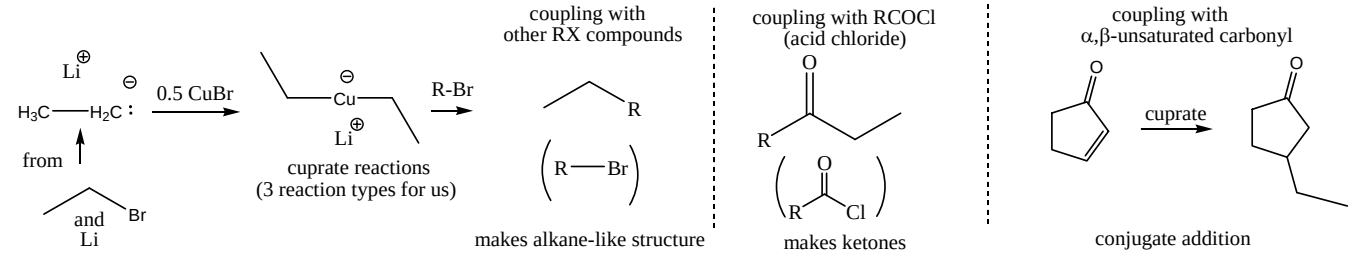


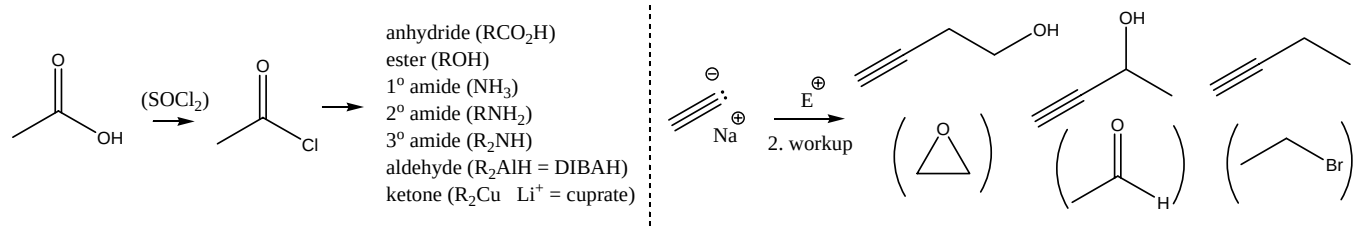
2 Carbons – you need to know reagents to allow synthetic transformations among these structures. Just a sampling

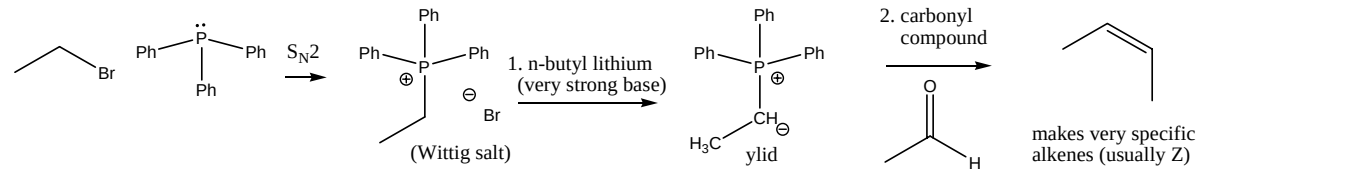


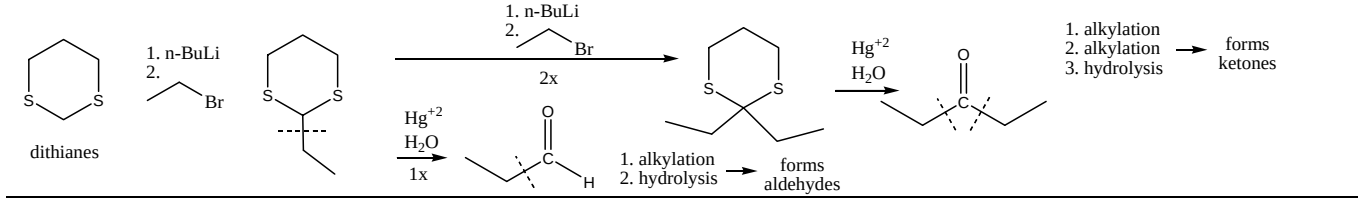

NaCN
available
CrO_3 pyridine
imines enamines
CrO_3 water
esters acid chlorides
K^+ t-butoxide
Br_2
1. $NaNR_2$ 2. workup
$NaNR_2$
H_2SO_4/Δ
mCPBA

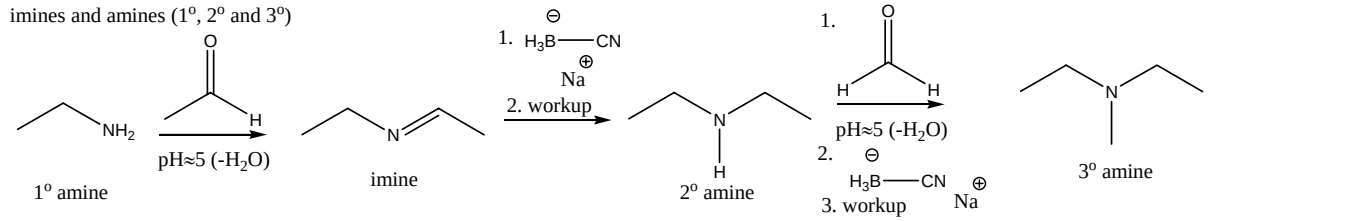

from
and Li or Mg
2. workup
(CO_2)
$R-C\equiv N$
2 eqs.
only with 2 eqs Et-Li


0.5 CuBr
from
and Li
cuprate reactions (3 reaction types for us)
R-Br
coupling with other RX compounds
makes alkane-like structure
coupling with RCOCl (acid chloride)
makes ketones
coupling with α,β-unsaturated carbonyl
cuprate
conjugate addition

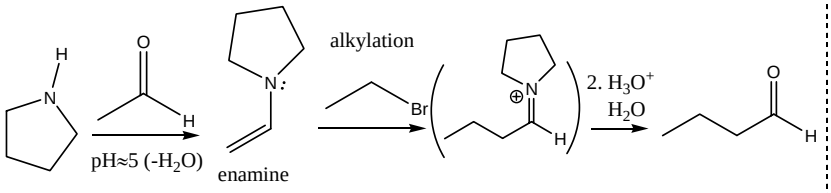

$(SOCl_2)$
anhydride (RCO_2H)
ester (ROH)
1° amide (NH_3)
2° amide (RNH_2)
3° amide (R_2NH)
aldehyde (R_2AlH = DIBAH)
ketone (R_2Cu Li^+ = cuprate)
2. workup

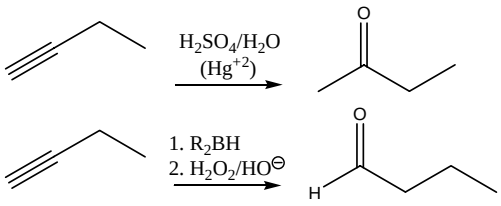

S_N2
(Wittig salt)
1. n-butyl lithium (very strong base)
ylid
2. carbonyl compound
makes very specific alkenes (usually Z)


dithianes
1. n-BuLi 2.
2x
1x
Hg^{+2} H_2O
1. alkylation 2. hydrolysis
forms aldehydes
1. alkylation 2. alkylation 3. hydrolysis
forms ketones

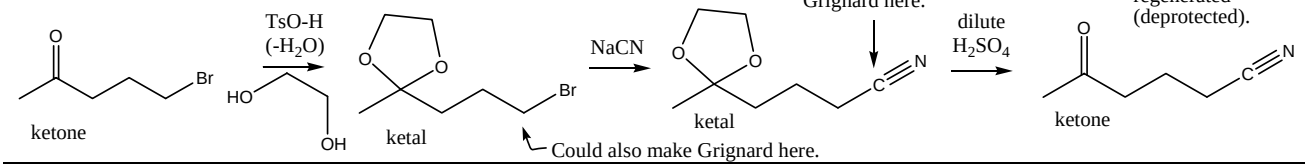

imines and amines (1°, 2° and 3°)
1° amine
pH≈5 (-H_2O)
imine
2. workup
2° amine
3. workup
3° amine

enamines

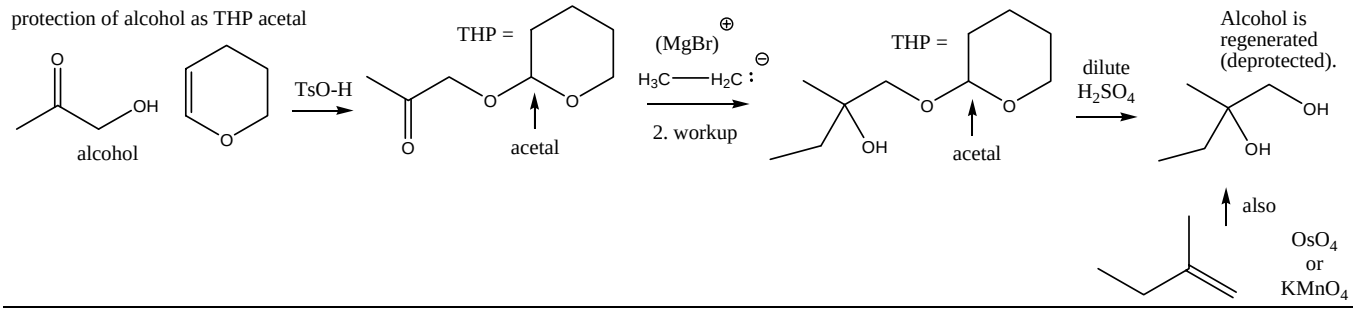




protection of aldehyde as acetal and ketone as ketal

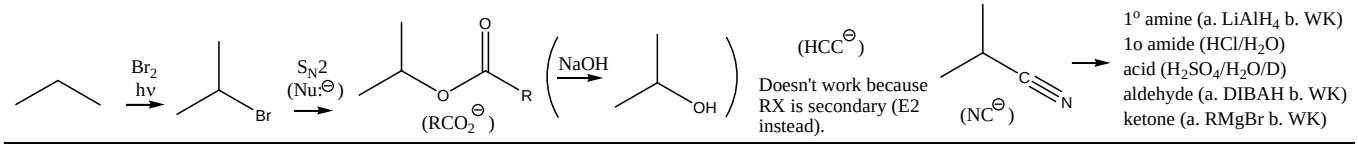


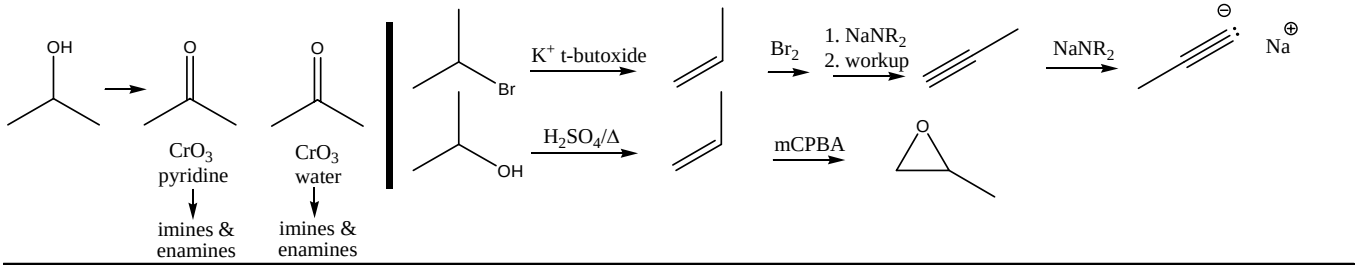
protection of alcohol as THP acetal

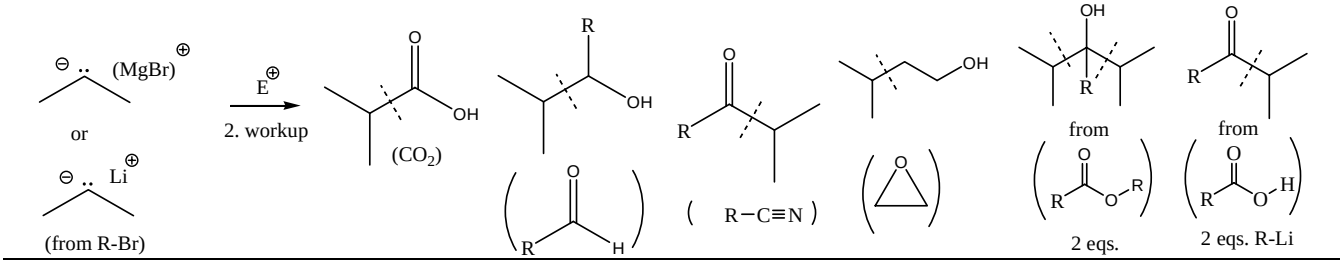


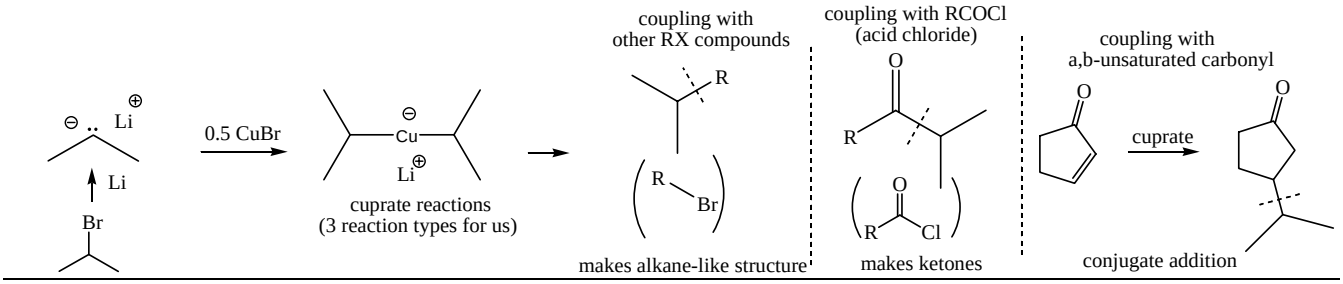
3 Carbons – Just a few selective examples. Too many possibilities to be comprehensive (2X and 1X possibilities).

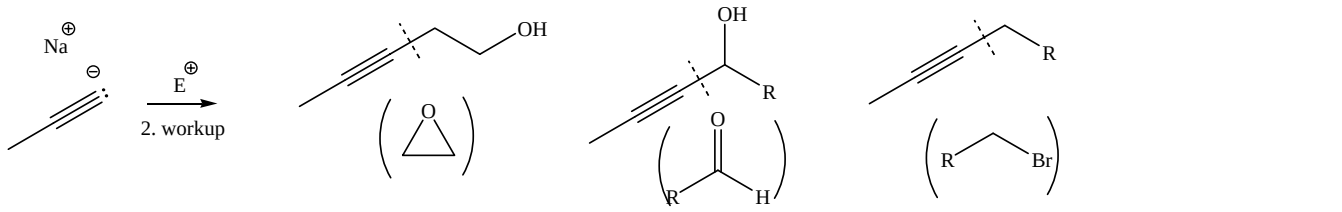
2X propane (some examples)



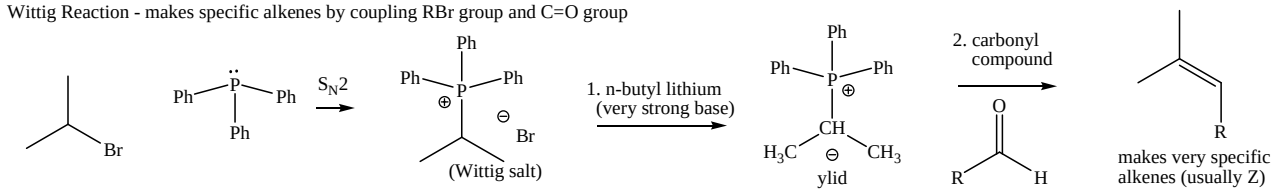




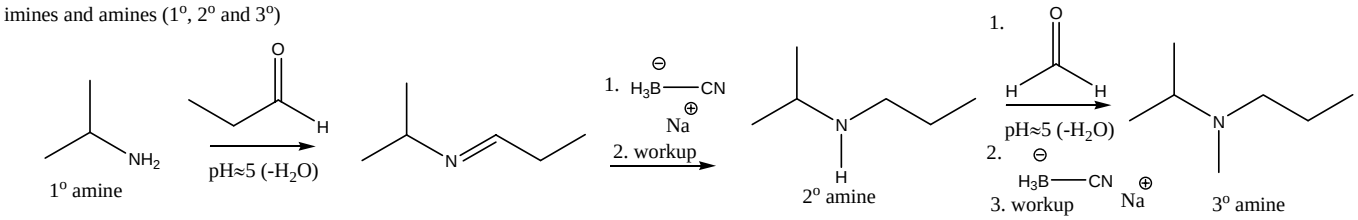




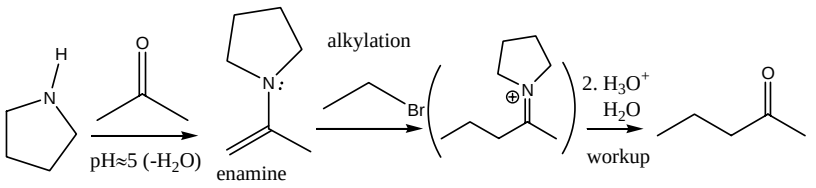
Wittig Reaction - makes specific alkenes by coupling RBr group and C=O group

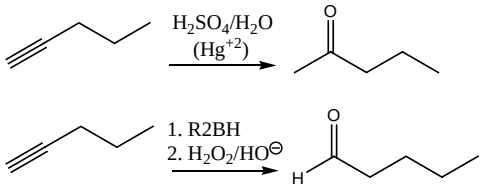


imines and amines (1°, 2° and 3°)

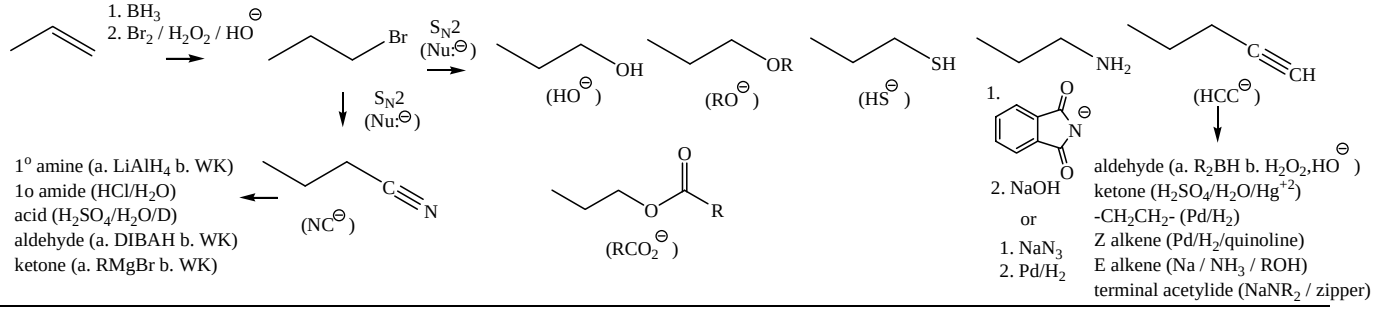


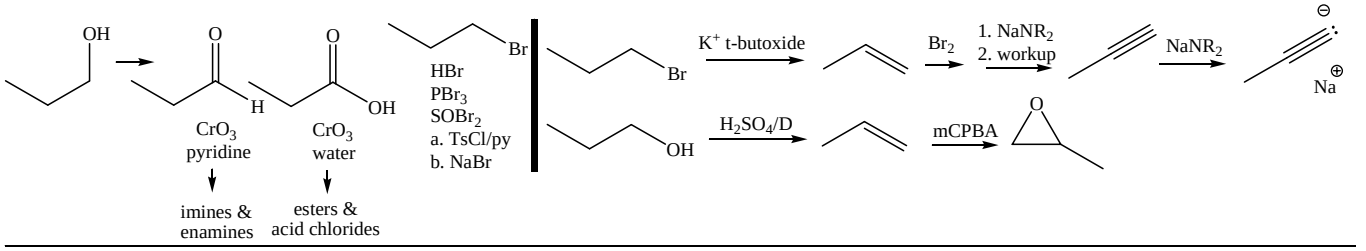
enamines

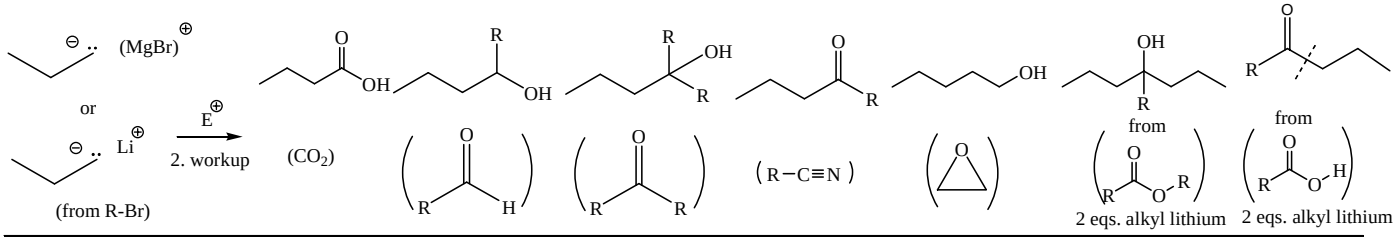


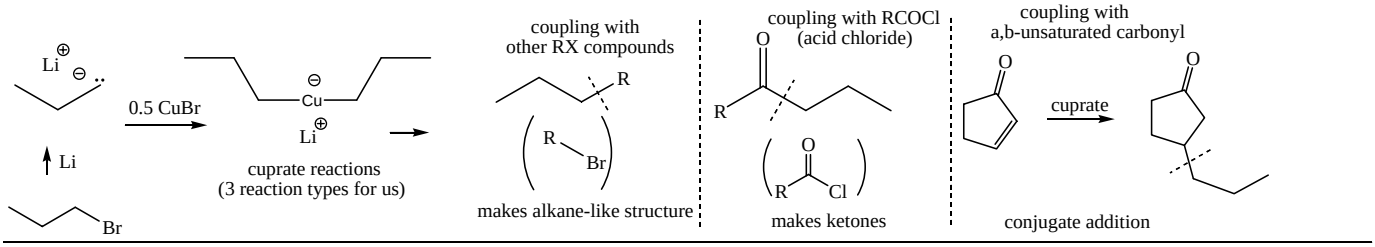


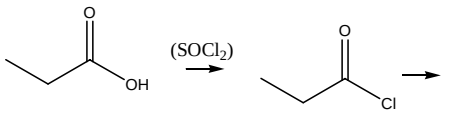
1X propane (some examples)











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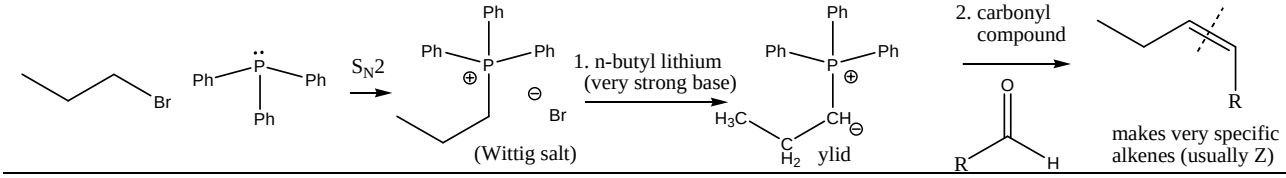
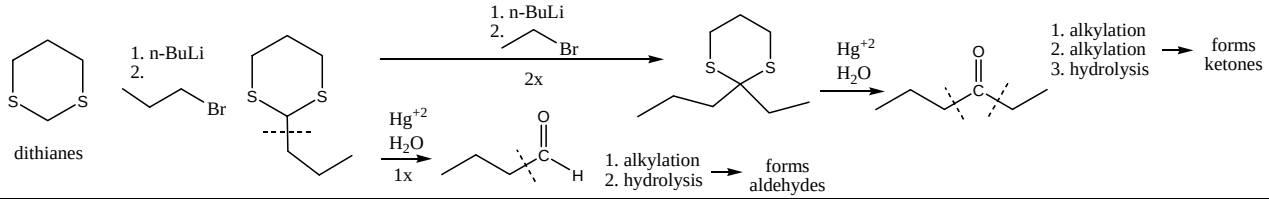
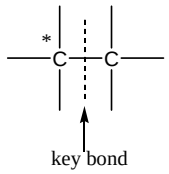




^{14}C Synthesis Strategies

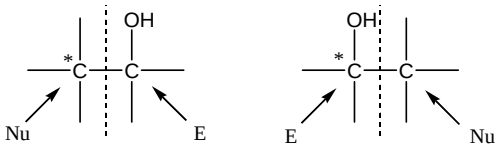
In our course every carbon-carbon bond made with asterisked carbon must be made created using a nucleophile/electrophile reaction.



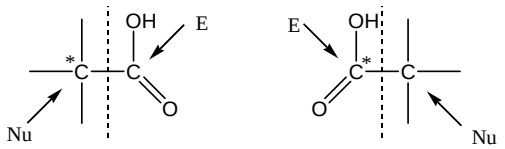
nucleophile (Nu) = ?

electrophile (E) = ?

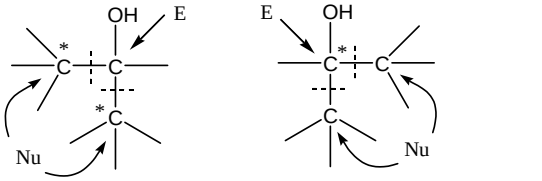
Which is the nucleophile and which is the electrophile depends on clues in the target molecule.



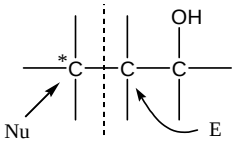
clue: COH group could have been C=O group (aldehyde or ketone).



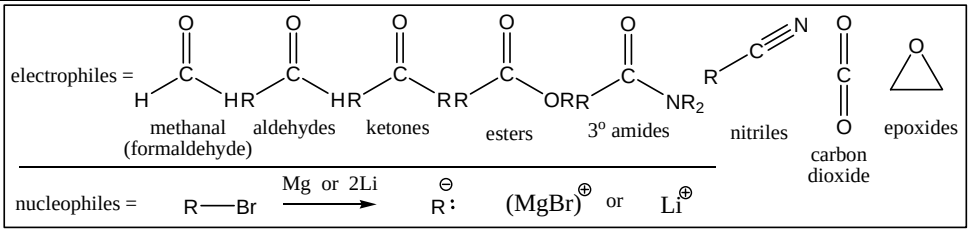
clue: COH group could have been C=O group (carbon dioxide).



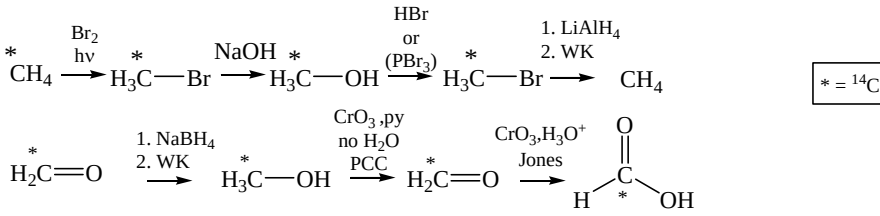
clue: When two COH groups are identical C=O group could be ester.



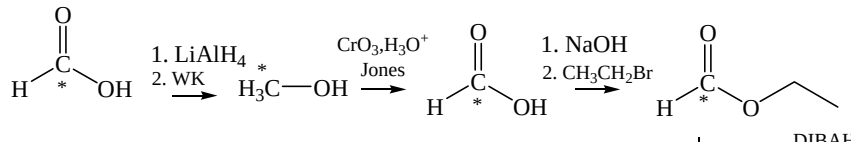
clue: COH group could have been an epoxide group.



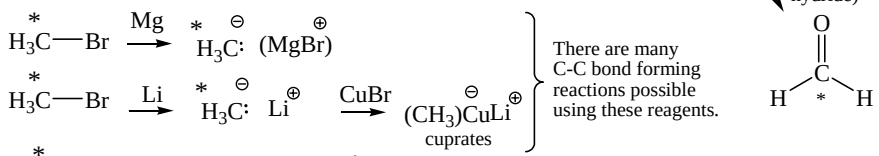
Some useful interconversions in ^{14}C syntheses (using one carbon functional group transformations).



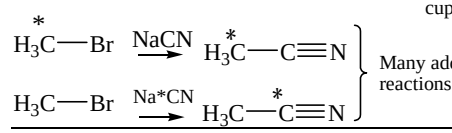
* = ^{14}C labeled carbon atom



DIBAH (diisobutyl-aluminium hydride)



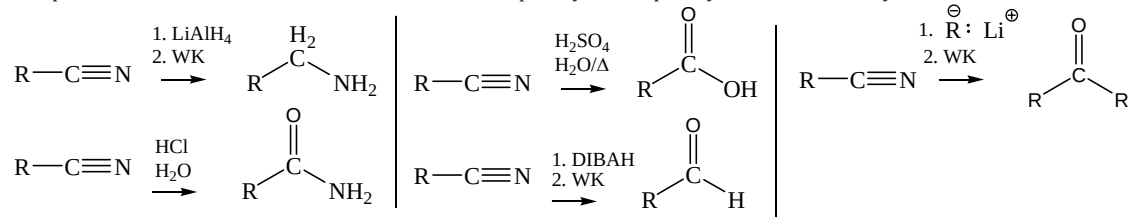
There are many C-C bond forming reactions possible using these reagents.



Many additional reactions (see below).

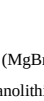
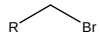
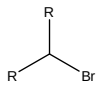
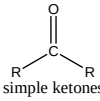
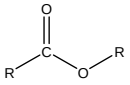
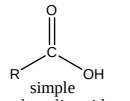
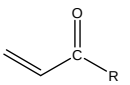
WK = workup (often necessary for final protonation)

Sample reactions of nitriles. Further transformation can make primary amines, primary amides, acids, aldehydes and ketones.

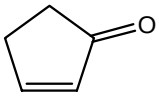


Products from reactions of carbon nucleophiles and carbon electrophiles used in the ^{14}C Game and our course:

Carbon and hydrogen nucleophiles

Carbon electrophiles	R: $Li^{\oplus}$ organolithium reagents	R: $(MgBr)^{\oplus}$ organolithium reagents	RCC $Na^{\oplus}$ acetylides	$Na^{\oplus}$:CN: cyanide	R_2Cu $Li^{\oplus}$ cuprates	$Li^{\oplus}$ AlH_4 (LAH)	$Na^{\oplus}$ BH_4	 diisobutylaluminium hydride (DIBAH)
 methyl RX	NR	NR	alkynes	nitriles	2 RX coupling reaction	alkyls	alkyls	NR
 primary RX	NR	NR	alkynes	nitriles	2 RX coupling reaction	alkyls	alkyls	NR
 secondary RX	NR	NR	E2	nitriles	2 RX coupling reaction	alkyls	alkyls	NR
 ethylene oxide	1° ROH	1° ROH	1° ROH alkynes	1° ROH nitriles	1° ROH	1° ROH	1° ROH	NR
 propylene oxide	2° ROH	2° ROH	2° ROH alkynes	2° ROH nitriles	2° ROH	2° ROH	2° ROH	NR
 isobutylene oxide	3° ROH	3° ROH	3° ROH alkynes	3° ROH nitriles	3° ROH	3° ROH	3° ROH	NR
 methanal	1° ROH	1° ROH	1° ROH alkynes	cyanohydrin	NR	methanol	methanol	NR
 simple aldehydes	2° ROH	2° ROH	2° ROH alkynes	cyanohydrin	NR	1° ROH	1° ROH	NR
 simple ketones	3° ROH	3° ROH	3° ROH alkynes	cyanohydrin unless sterically hindered	NR	2° ROH	2° ROH	NR
 simple esters	3° ROH (Nu: twice)	3° ROH (Nu: twice)	NR	NR	1° ROH (Nu: twice)	1° ROH	NR	aldehydes
 simple carboxylic acids	ketones (B: once Nu: once)	acid/base no net rxn	acid/base no net rxn	NR	acid/base no net rxn	acid/base no net rxn	acid/base no net rxn	acid/base no net rxn
 simple acid chlorides	3° ROH (Nu: twice)	3° ROH (Nu: twice)	NR	NR	ketones	1° ROH	1° ROH	NR
simple nitriles	ketones	ketones	NR	NR	NR	1° amines (also amines from amides)	NR	aldehydes (also aldehydes from 3° amides)
carbon dioxide	carboxylic acids	carboxylic acids	carboxylic acids	NR	NR	NR	NR	NR
 α,β-unsaturated ketones	3° ROH	3° ROH	NR	NR	conjugate addition	alcohols	alcohols	NR

WK = normal workup to neutralize the reaction conditions. For the basic reactions (like above) above this would require mild acid neutralization (H_3O^+).
NR = no reaction or no productive result or not emphasized

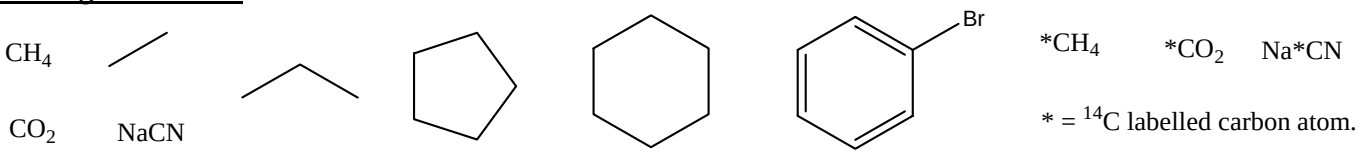
	$R'^{\ominus}\ Li^{\oplus}$	$R'^{\ominus}\ (MgHBrH)^{\oplus}$	$R'_2Cu^{\ominus}\ Li^{\oplus}$	$RCC^{\ominus}\ Na^{\oplus}$	$NC^{\ominus}\ Na^{\oplus}$	$Li^{\oplus}\ AlH_4^{\ominus}$	$Na^{\oplus}\ BH_4^{\ominus}$
1^o RCH_2Br primary RX	NA	NA	**alkyl coupling**	alkyne	nitriles	1^o RCH_2-H	1^o RCH_2-H
2^o R_2CHBr secondary RX	NA	NA	**alkyl coupling**	E2	nitriles	2^o R_2CH-H	2^o R_2CH-H
 epoxides	ROH (+2C+OH)	ROH (+2C+OH)	ROH (+2C+OH)	ROH (+2C+OH)	ROH (+2C+OH)	ROH	ROH
$H_2C{=}O$ methanal	1^o ROH	1^o ROH	NA	1^o ROH	1^o ROH	methanol	methanol
$RHC{=}O$ aldehydes	2^o ROH	2^o ROH	NA	2^o ROH	2^o ROH	1^o ROH	1^o ROH
$R_2C{=}O$ ketones	3^o ROH	3^o ROH	NA	3^o ROH	3^o ROH	2^o ROH	2^o ROH
$O{=}C{=}O$ carbon dioxide	carboxylic acids	carboxylic acids	NA	NA	NA	NA	NA
RCO_2R' esters	3^o ROH (twice)	3^o ROH (twice)	NA	NA	NA	1^o ROH	**NA**
RCO_2H carboxylic acids	ketones acid/base x 1 nucleophile x 1	NA	NA	acid/base	acid/base	1^o ROH	**NA**
$R{-}C{\equiv}N$ nitrils	ketones	ketones	NA	NA	NA	1^o RNH_2	**NA**
$RCONR_2$ 3^o amides	ketones	ketones	NA	NA	NA	1^o,2^o,3^o RNH_2	**NA**
RCOCl acid chlorides	3^o ROH	3^o ROH	ketones	NA	NA	1^o ROH	**NA**
 α,β-unsaturated carbonyls	1,2-addition	1,2-addition	**conjugate addition (1,4-addition)**	1,2-addition	**conjugate addition (1,4-addition)**	1,2-addition	**NA**

WK = workup reaction with electrophilic/acidic H_3O^+

NA = not applicable to our course (no reaction, not productive or not emphasized)

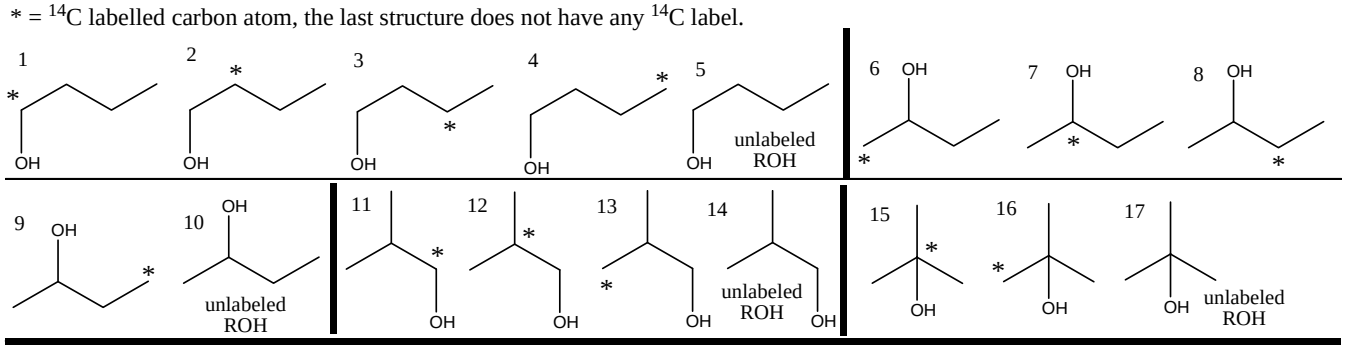
Use clues in the target molecule to determine what the last step could have been. Once you work back one step, use clues in that molecule to determine how you could work back one additional step. Repeat this process until you get to the necessary starting conditions, i.e. allowable ^{14}C starting units ($*CH_4$, $*CO_2$, Na*CN where "*" indicates a radioactive ^{14}C isotope). Until aromatic chemistry is covered bromobenzene is also available.

Starting Structures:

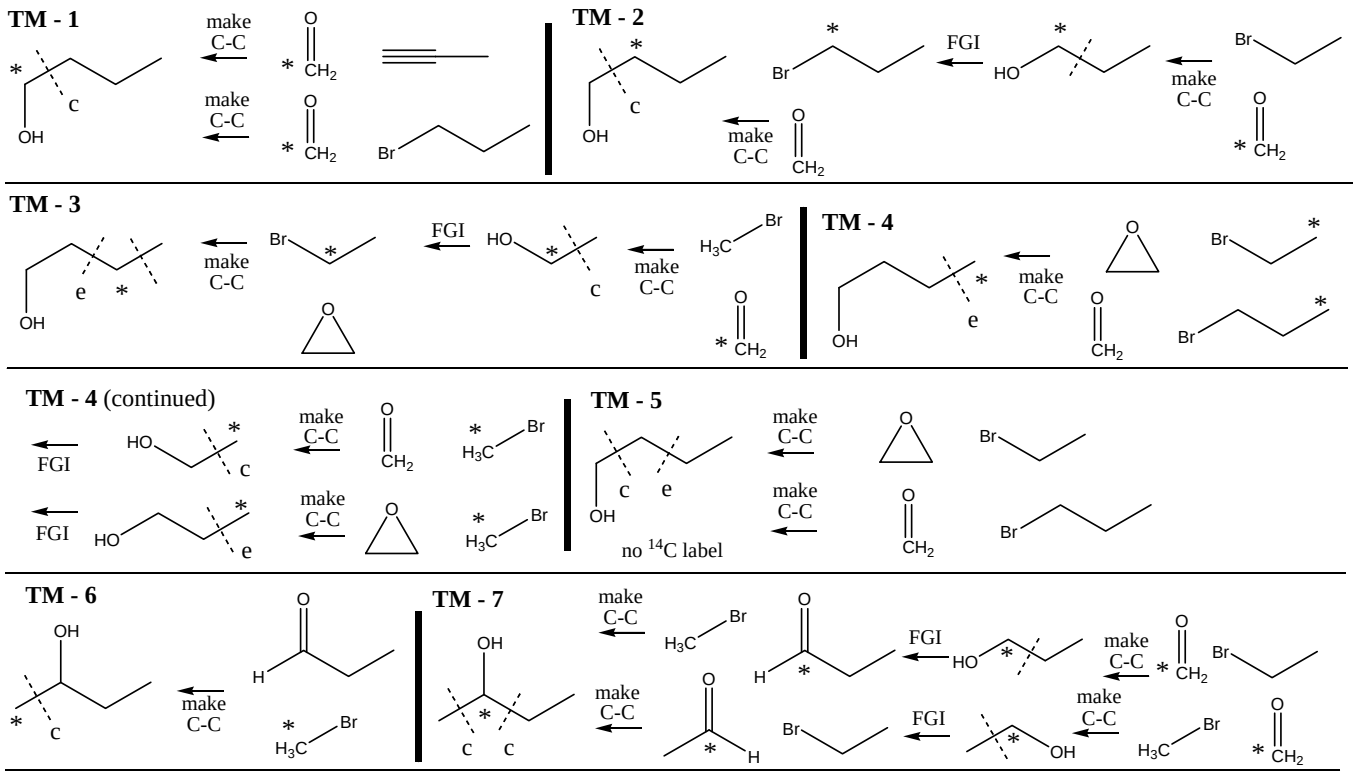


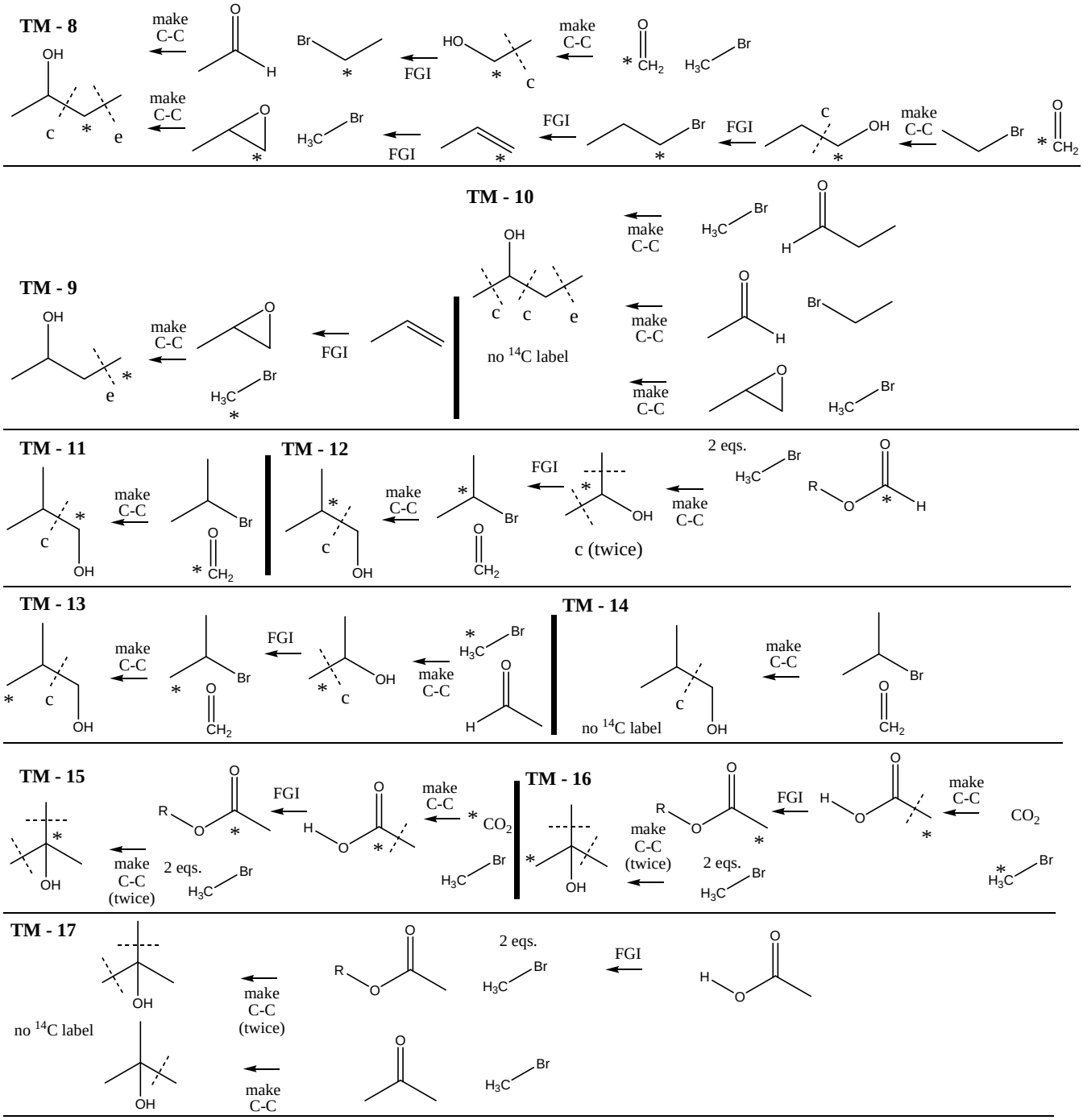
Examples – Target Molecules (TM - #)

C4 alcohols - Two carbon skeletons, Four alcohols patterns possible, Many ^{14}C labeled target molecules (TM)

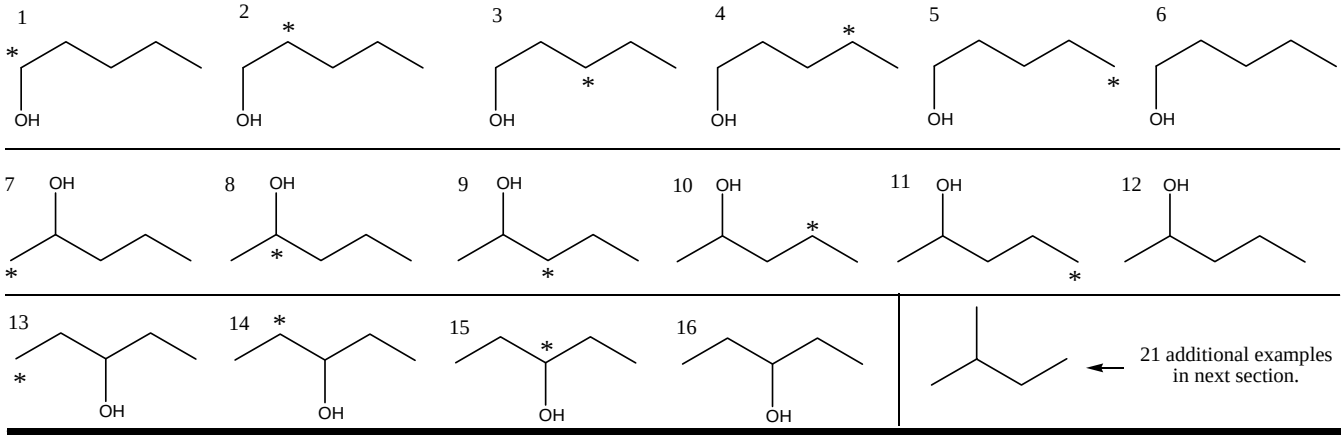


C4 unlabelled examples shown below. Reacting materials are traced back until they are 3 carbons or less, where it is assumed you can make them (see start of this handout for several 1C, 2C and 3C functional group interconversions = FGI). [c = carbonyl strategy, e = epoxide strategy, a = alkyne strategy]

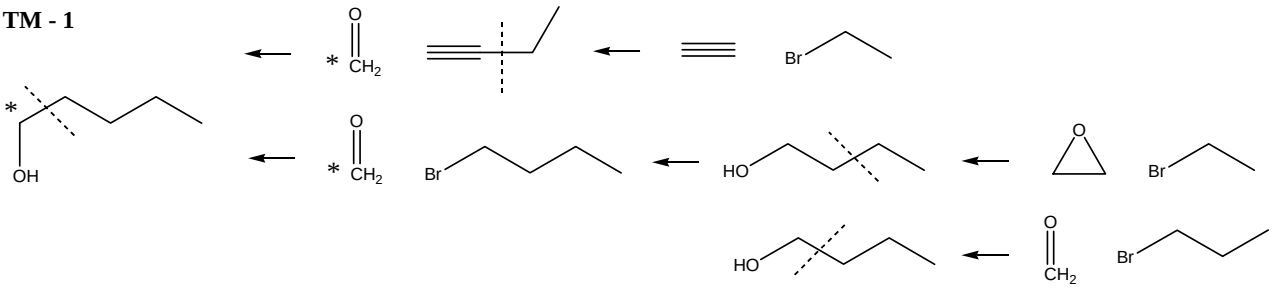



TM - 8
make C-C
FGI
make C-C
make C-C
FGI
FGI
FGI
make C-C
TM - 9
make C-C
FGI
TM - 10
no 14C label
make C-C
make C-C
make C-C
TM - 11
make C-C
TM - 12
make C-C
FGI
make C-C
2 eqs.
c (twice)
TM - 13
make C-C
FGI
make C-C
TM - 14
make C-C
no 14C label
TM - 15
make C-C (twice)
2 eqs.
FGI
make C-C
TM - 16
make C-C (twice)
2 eqs.
FGI
make C-C
TM - 17
make C-C (twice)
make C-C
no 14C label
2 eqs.
FGI

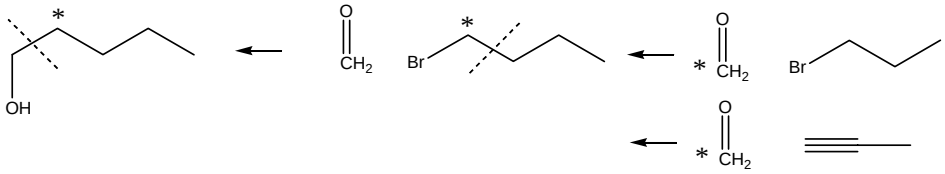
Straight chain C5 alcohols (branched possibilities are not shown, but you can always ask.)



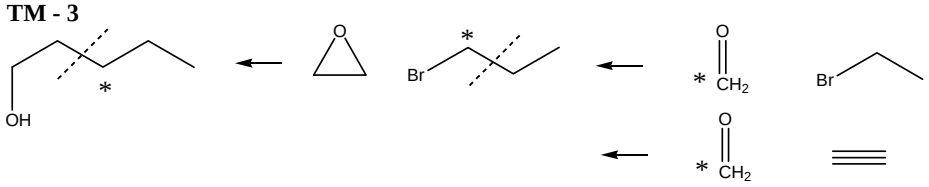
TM - 1



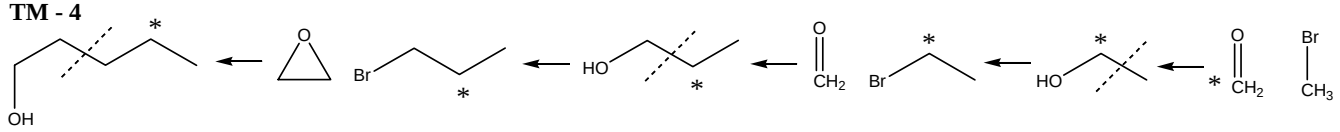
TM - 2



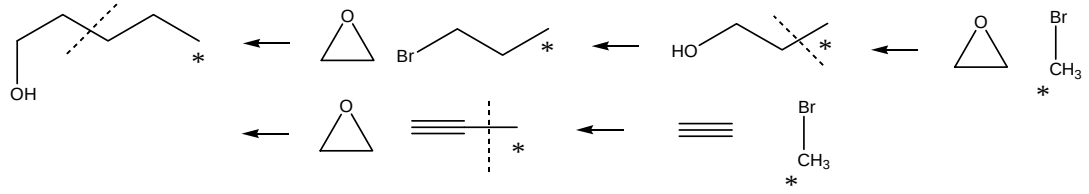
TM - 3



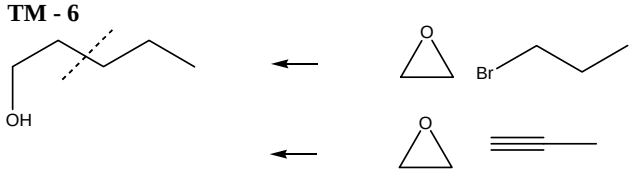
TM - 4



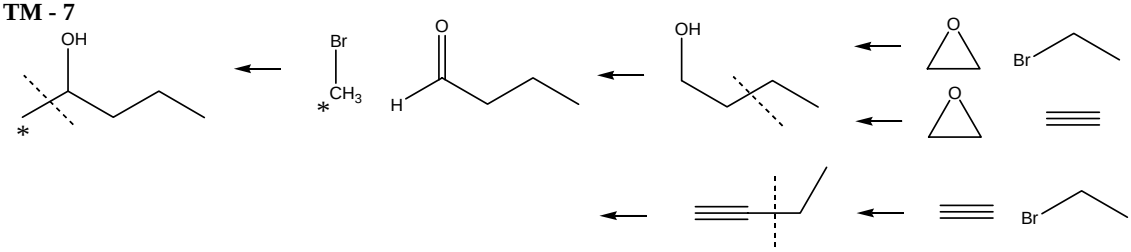
TM - 5



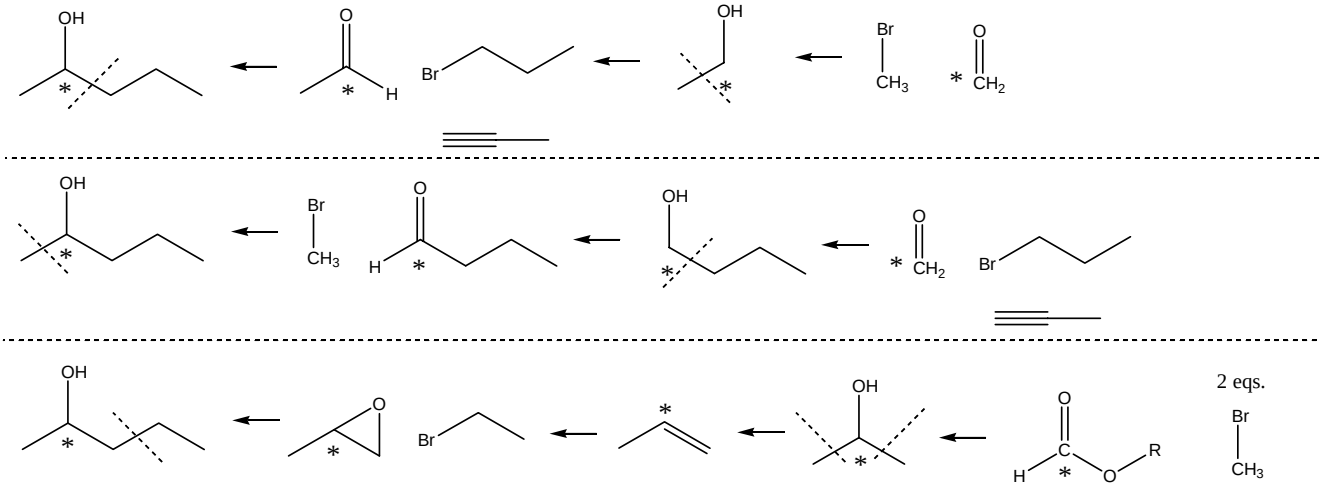
TM - 6



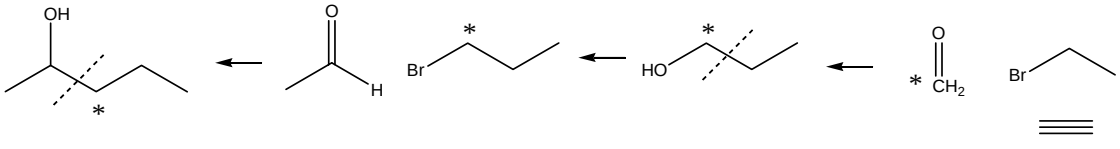
TM - 7



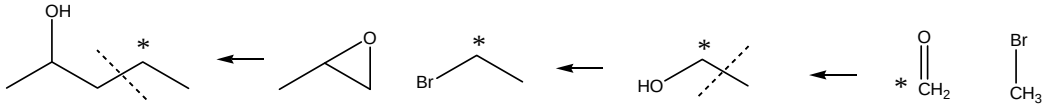
TM - 8



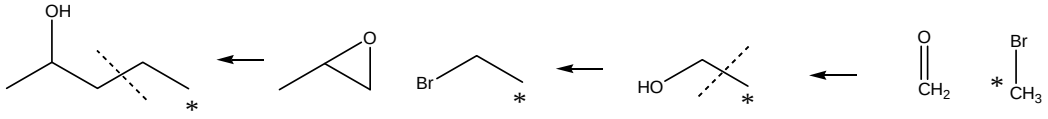
TM - 9



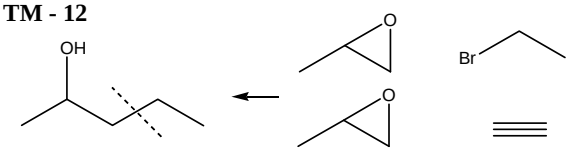
TM - 10



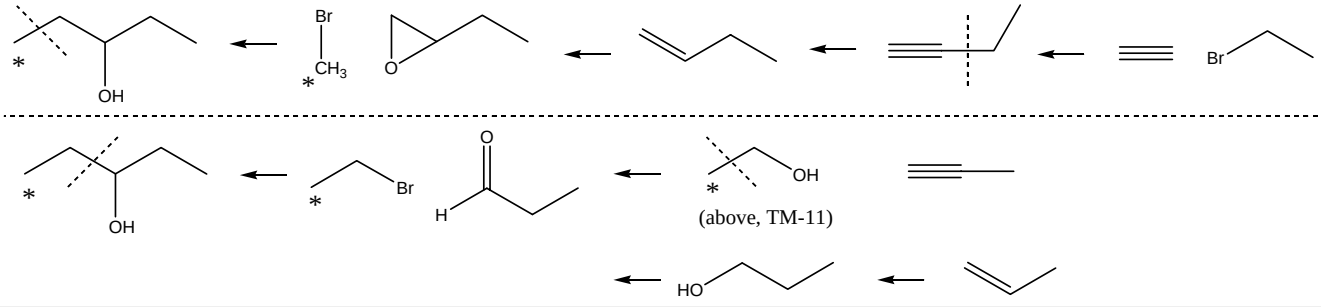
TM - 11



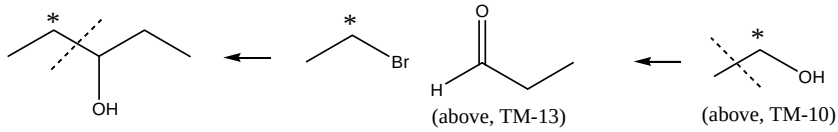
TM - 12



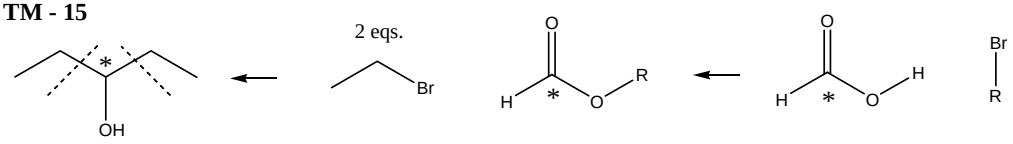
TM - 13



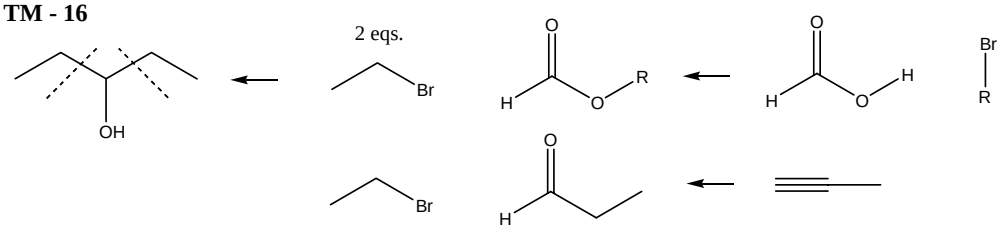
TM - 14



TM - 15

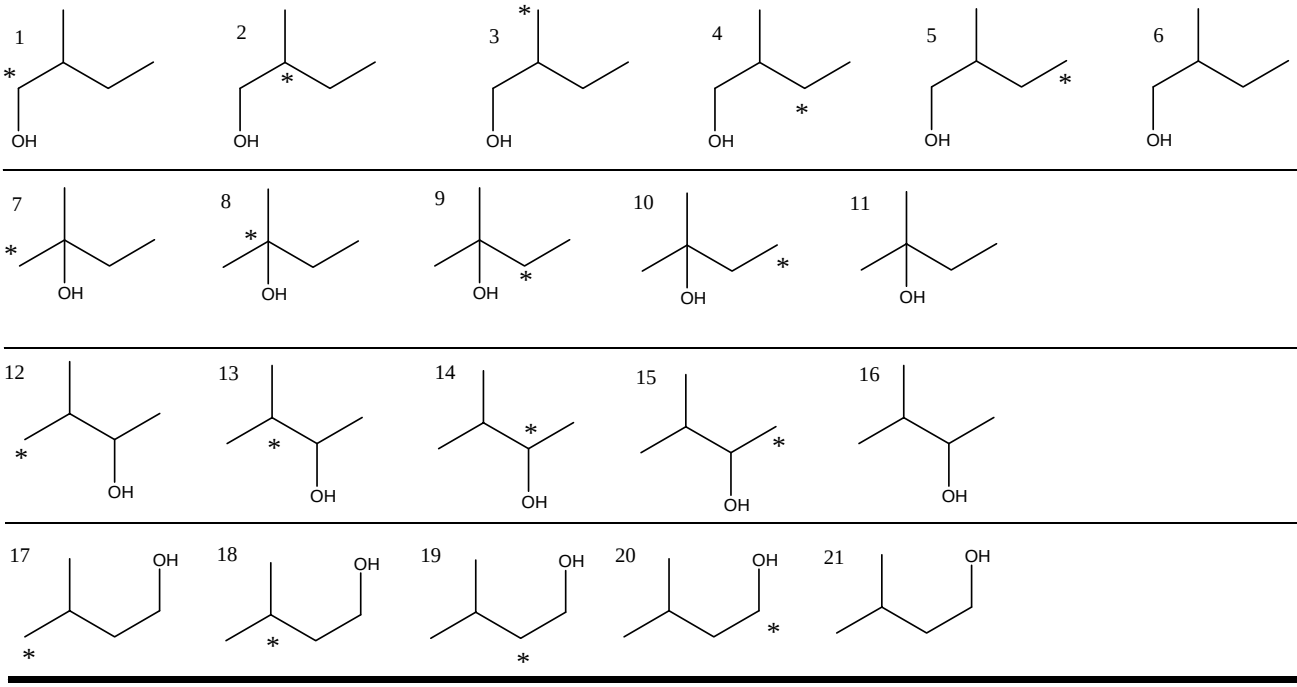


TM - 16

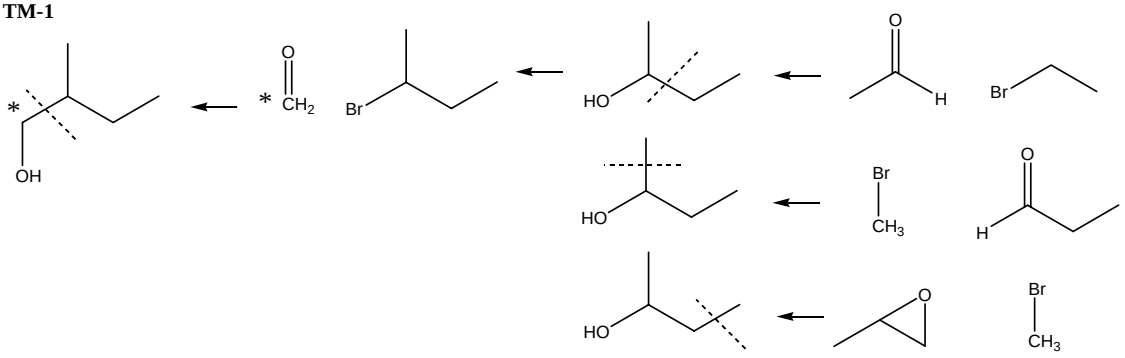


Examples – Target Molecules (TM - #)

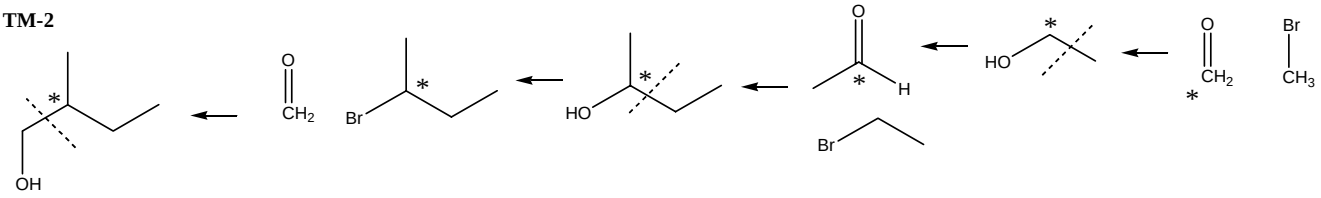
4C chain with methyl branch alcohols



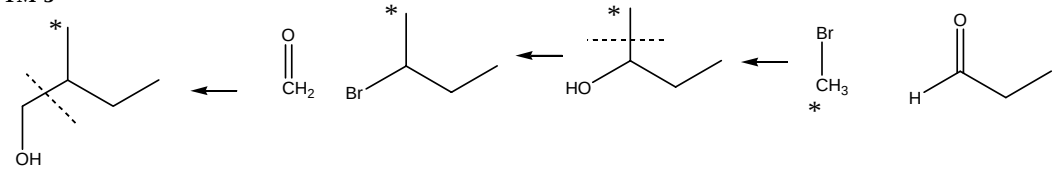
TM-1



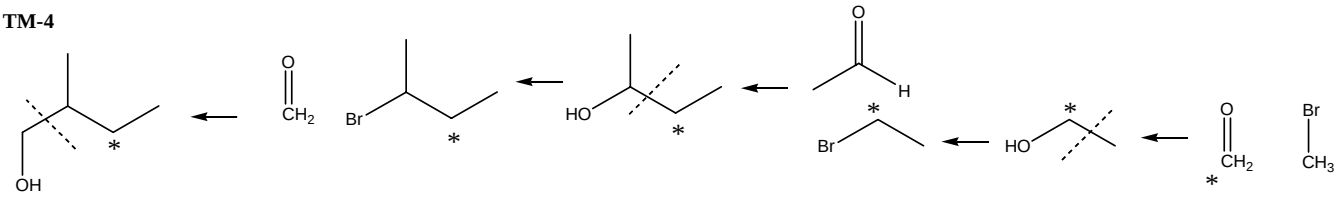
TM-2



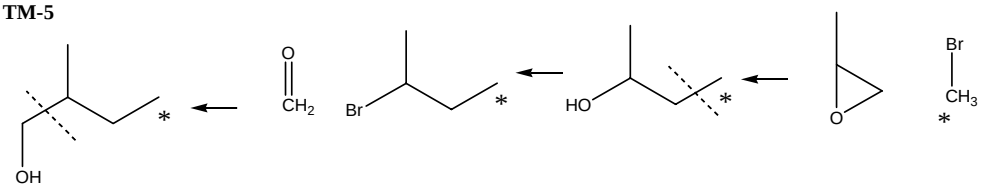
TM-3



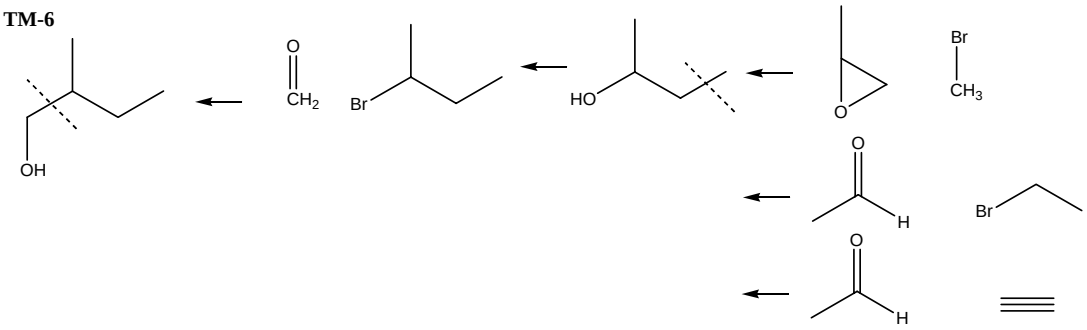
TM-4



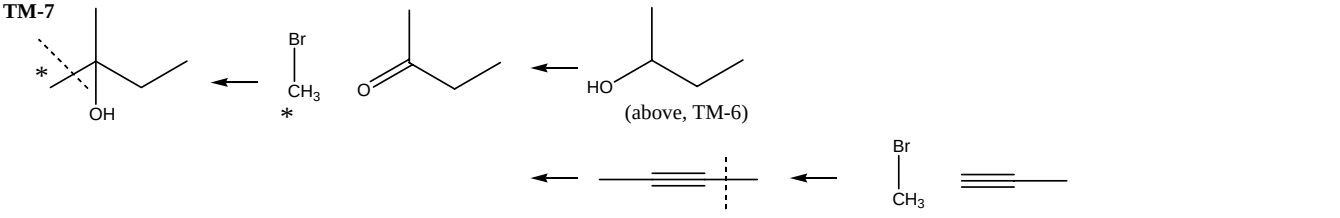
TM-5

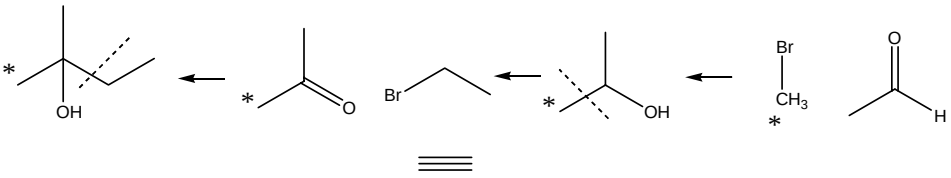


TM-6

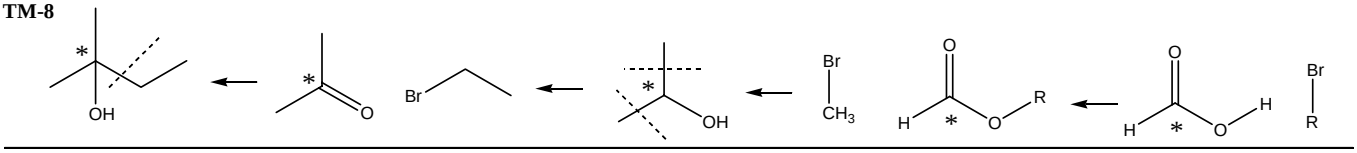


TM-7

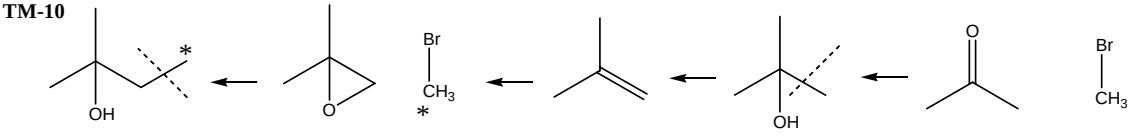




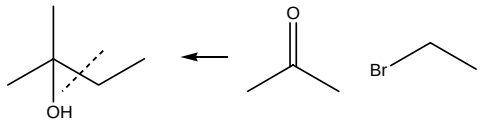
TM-8



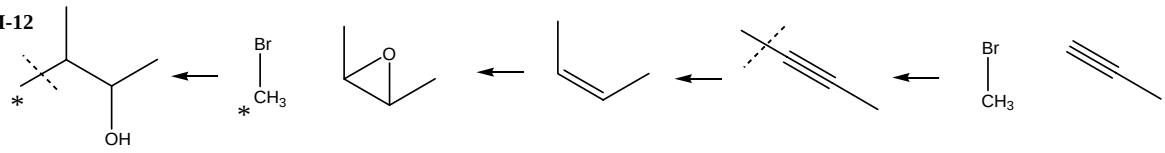
TM-10

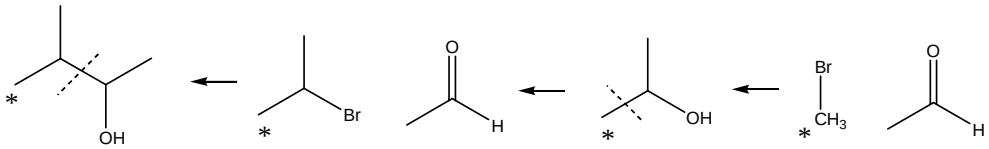


TM-11

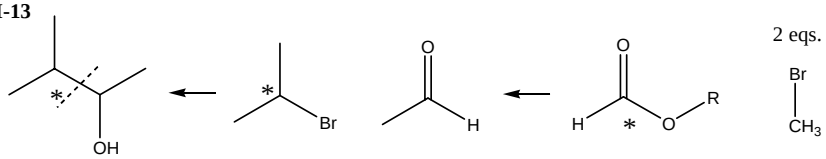


TM-12

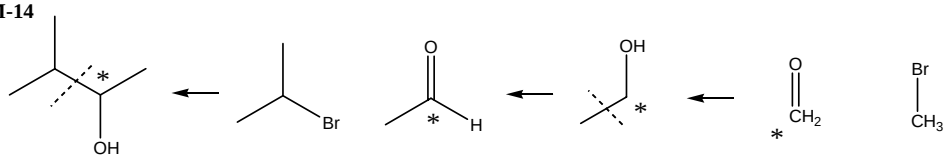




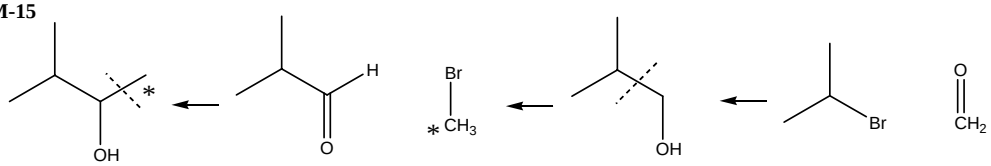
TM-13



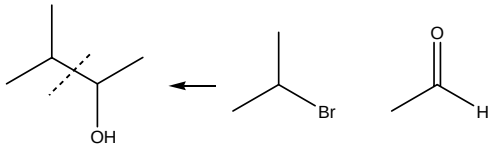
TM-14



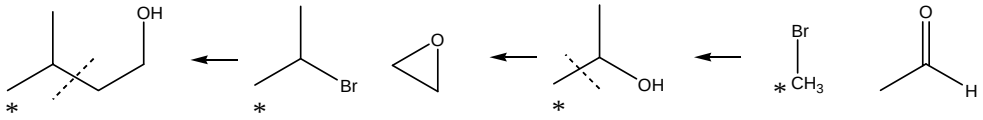
TM-15



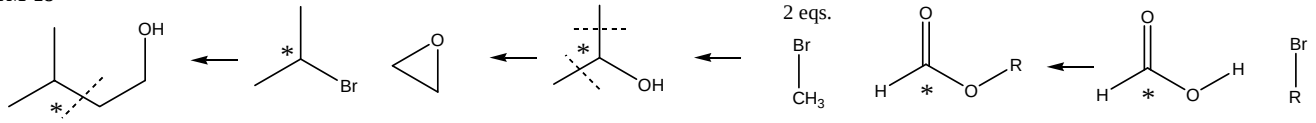
TM-16



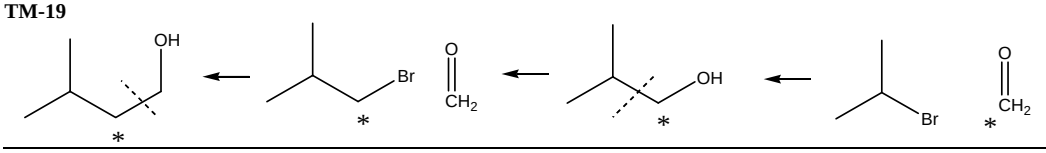
TM-17



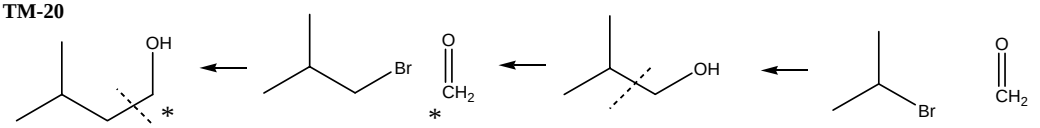
TM-18



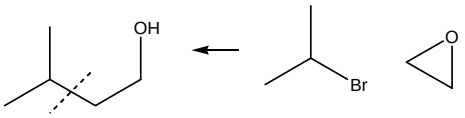
TM-19



TM-20



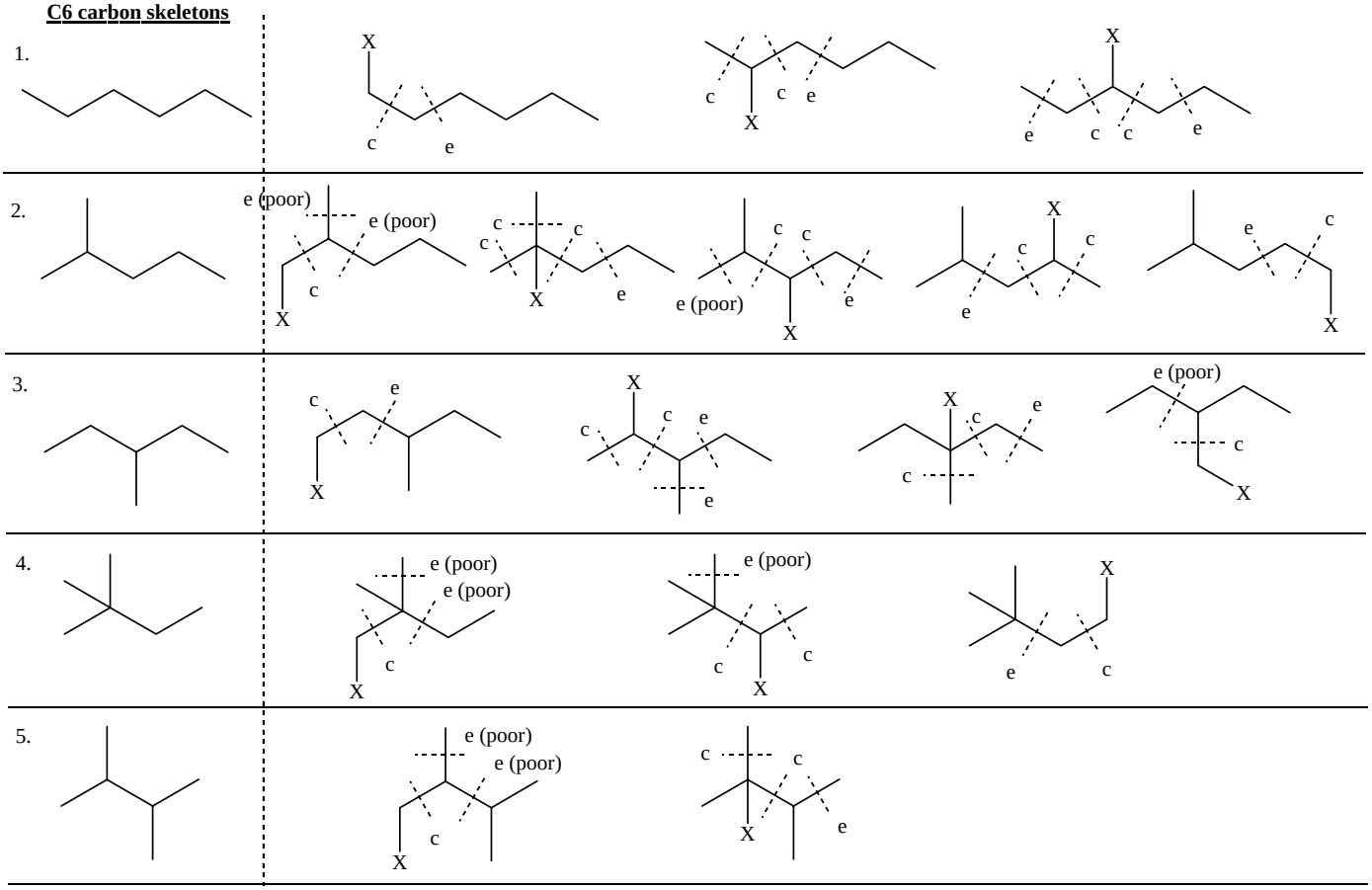
TM-21



C6 carbon isomers of various single bonding functional groups (HO-, H_2N-, Cl-, Br-, I-, RO-, TsO-, NC-, etc.)

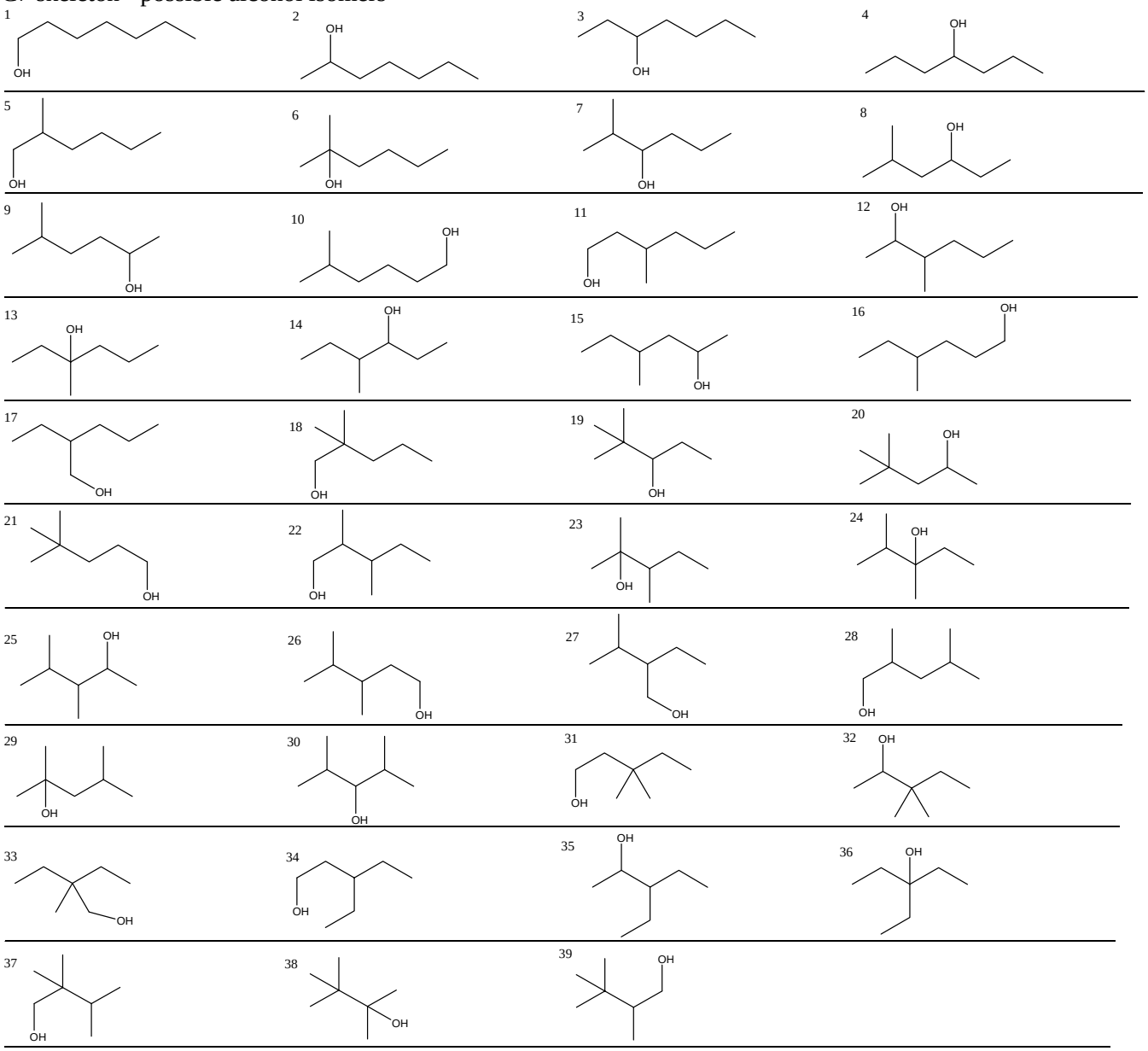
Possible substituton patterns of C6 carbon skeletons. Dashed lines represent disconnections between two carbon atoms. One carbon would be a nucleophile and supply two electrons, while the other carbon would be an electrophile and accept two electrons. If X = "OH", it would represent a key clue for these possible disconnections. A disconnection between the CX carbon and its neighbor carbon represents a carbonyl/carbanion dissonnection (symbolized with "c" by the dashed lines). A disconnection between the next two carbon atoms over (C2-C3 from CX) represents a epoxide/carbanion disconnection (symbolized with "e" by the dashed lines). When epoxides are secondary on both sides, with different groups, or a more substituted carbon would have to be attacked they represent a poor strategy and are listed as “poor” in the examples below. Carbanion nucleophiles that we have used so far in our course are terminal acetylides (from alkynes, must be linear) and Mg and Li organometallic reagents (from R-Br, linear or branched).

C6 carbon skeletons



Propose a synthesis for the following C7 alcohols using only our given starting materials (methane, ethane and propane). Work backwards from the target. The last step of the synthesis should be your first step. Since you only have C1, C2 and C3 starting materials, you will have to construct at least two carbon-carbon bonds and in many cases more than two. Useful strategies include Mg and Li organometallic nucleophiles joined with carbonyl or epoxide electrophiles, or if there is a straight chain segment, alkyne nucleophiles can be joined with carbonyl, epoxide or RX electrophiles. Many of useful transformations are provided in the 1C, 2C and 3C examples above. Do not show mechanisms, but do show each synthetic step, with reagents, back to an allowed starting material. Remember that "OH" could be substituted for many other functional groups, such as -Br, -NH_2, -OR, -O_2CR, -CN, -CCR. Primary OH can be oxidized to an aldehyde or a carboxylic acid (which could be made into an ester, acid chloride or amide). This is only a sampling of what is possible.

C7 skeleton - possible alcohol isomers



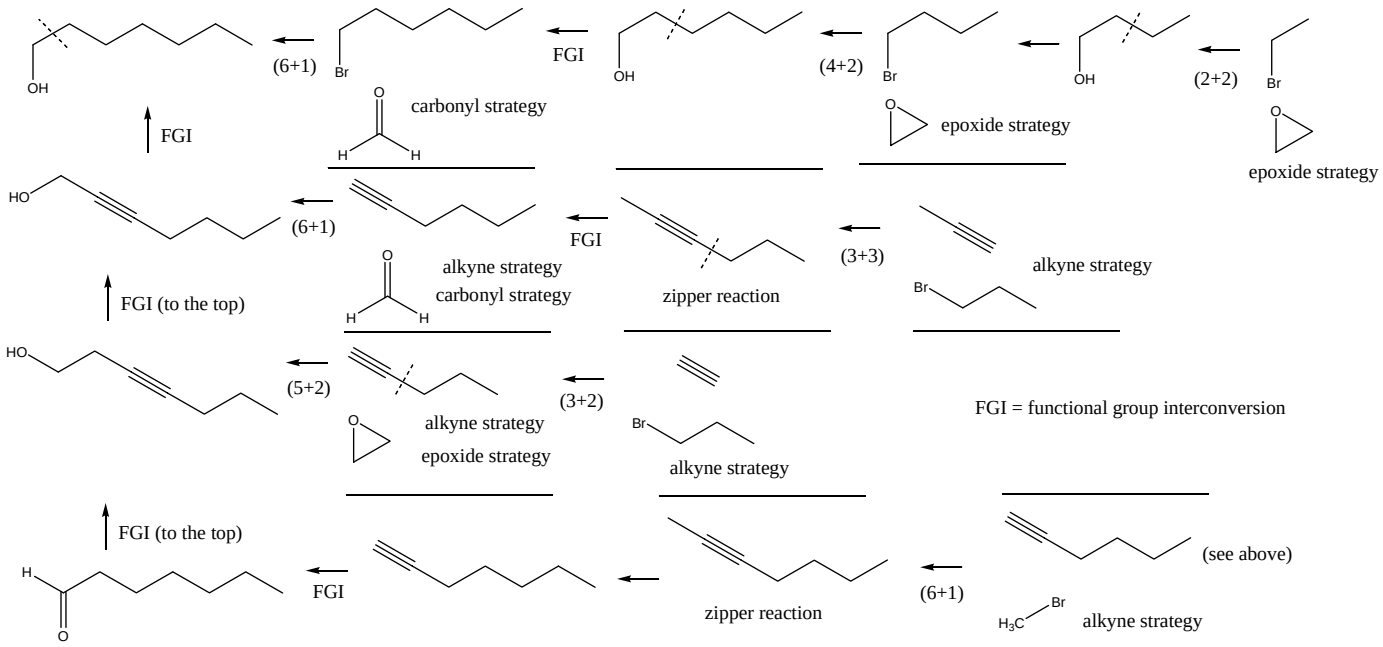
C7 isomeric synthesis examples

Several basic plans of attack are shown below for the first molecule above (#1). Each step of the example syntheses is NOT shown, rather the key steps to construct the skeleton are shown, without reagents, along with a few functional group interconversions (FGI). The number of carbons joined together are listed in parenthesis. RBr is often assumed to make a nucleophile carbon using Mg or Li (essential equivalent in our course, except for one reaction not covered yet) when reacted with a carbonyl group or epoxide. However, when RBr is reacted with a nucleophilic terminal acetylide it is assumed to be an electrophile. I assume you can make routine functional groups of C1, C2 and C3 (many examples are listed in the first 5 pages of this document). If this is not the case, then you need to learn these FGI's. We will cover synthesis of some of the above target molecules in class (#1 → #39). Why not try a few yourself outside of class, and if you have problems ask me to try some in class. Once a structure has 3 or fewer carbon atoms it is not continued. You can probably find a synthesis for any or those molecules in the beginning pages of this handout. If you find one is missing, then ask me.

Some points to remember:

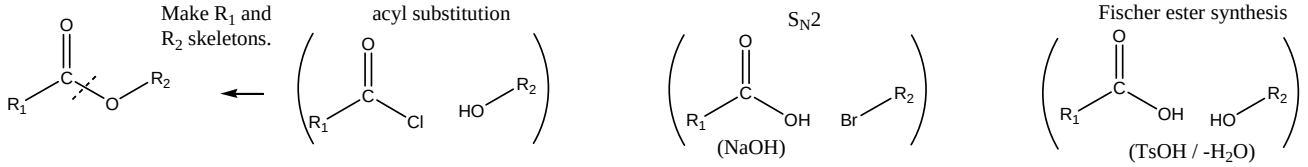
1. OH can be oxidized to aldehydes (from 1^o ROH) or carboxylic acids (from 1^oROH, which can be made into esters or acid chlorides and more), or ketones (from 2^o ROH).
2. OH can be made into a leaving group (Cl, Br, I, OTs), which can be made into amines, esters, nitriles, ethers, alkynes, thiols, thioethers, replaced with "H/D" and much more.
3. OH can be eliminated in H_2SO_4/Δ, but rearrangements could be a problem. Br can be eliminated with potassium t-butoxide, but regioselectivity can be a problem (requires anti C_β-H/C_α-X conformation).

TM-1

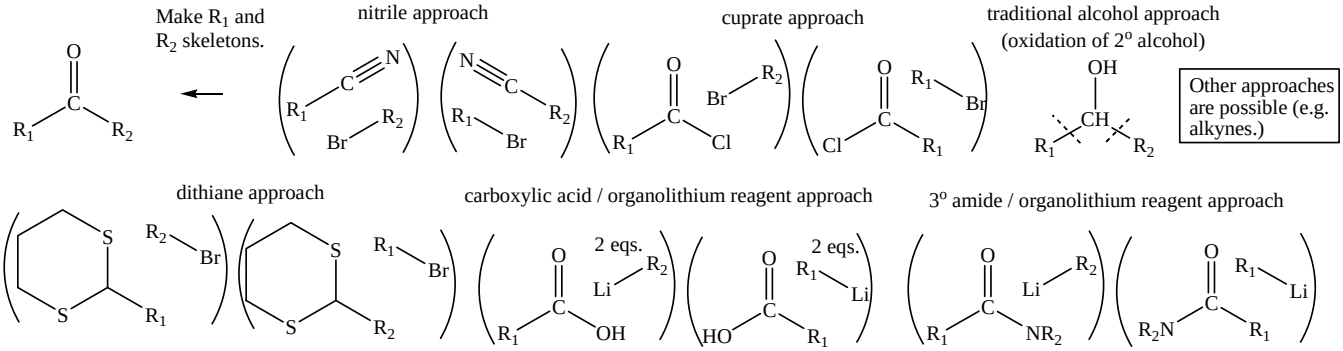


Combination Problems – Two structures (or more) in one target molecule.

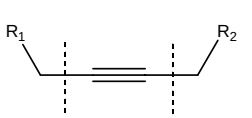
Esters



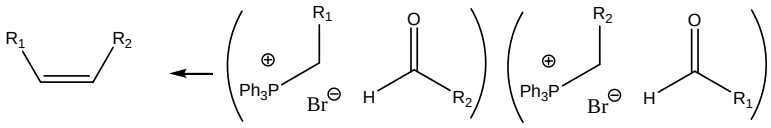
Ketones



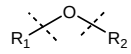
Alkynes



Wittig Reactions

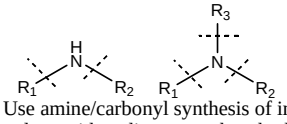


Ethers



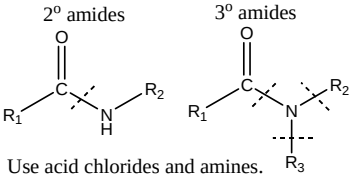
Join in S_N1, S_N2 and addition reactions to alkenes.

Amines



Use amine/carbonyl synthesis of imine and reduce with sodium cyanoborohydride.

Amides

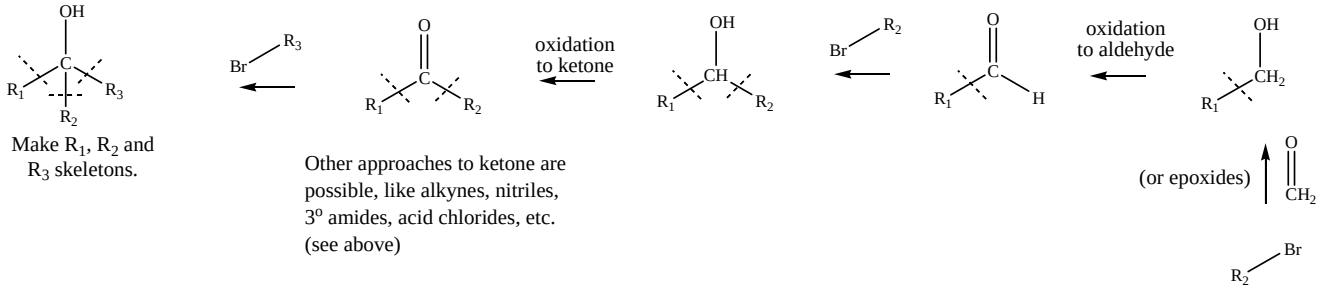


Use acid chlorides and amines.

Cuprate Couplings

Both R_1 and R_2 come from R-Br compounds. One is made into lithium reagent to react with other as RBr. Hardest to see, because there are no clues.

3° Alcohols



Other approaches to ketone are possible, like alkynes, nitriles, 3° amides, acid chlorides, etc. (see above)