

SYNTHETIC TOOLBOX

Some of the reactions in this handout may not have been covered in your course. Some of the reactions covered in your course may not be included in this handout. You should come up with your own synthetic toolbox that matches the reactions covered in your course; as your course proceeds and new reactions are introduced, keep updating your toolbox.

goals	reactions
functionalize—i.e., replace a H with a functional group	radical halogenation (bromine is most selective): $\begin{array}{c} \\ -\text{C}-\text{H} \\ \end{array} + \text{X}-\text{X} \xrightarrow{\Delta \text{ or } h\nu} \begin{array}{c} \\ -\text{C}-\text{X} \\ \end{array} + \text{H}-\text{X}$
defunctionalize—i.e., replace a functional group with a H or D	$\text{RMgX} + \text{H}_3\text{O}^+ \rightarrow \text{R}-\text{H} + \text{H}_2\text{O} + \text{}^+\text{MgX}$ hydrogenation: $\begin{array}{c} \text{R}_1 \quad \text{R}_3 \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{R}_2 \quad \text{R}_4 \end{array} + \text{H}_2 \xrightarrow{\text{Pd/C}} \begin{array}{c} \text{R}_2 \quad \text{R}_1 \\ \diagdown \quad / \\ \text{C}-\text{C} \\ / \quad \diagdown \\ \text{H} \quad \text{H} \end{array} \text{ and } \begin{array}{c} \text{H} \quad \text{H} \\ \diagdown \quad / \\ \text{C}-\text{C} \\ / \quad \diagdown \\ \text{R}_1 \quad \text{R}_2 \quad \text{R}_4 \quad \text{R}_3 \end{array}$
add C's—i.e., create a C-C bond	Grignard reagent + carbonyl Grignard reagent + epoxide alkene + H_2SO_4 (cationic polymerization)
remove C's—i.e., cleave a C-C bond	ozonolysis: $\begin{array}{c} \text{R}_1 \quad \text{R}_3 \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{R}_2 \quad \text{R}_4 \end{array} \xrightarrow[2. \text{Me}_2\text{S or Zn}]{1. \text{O}_3} \begin{array}{c} \text{R}_1 \\ \\ \text{C}=\text{O} \\ \\ \text{R}_2 \end{array} + \begin{array}{c} \text{O}=\text{C} \\ \\ \text{R}_3 \\ \\ \text{R}_4 \end{array}$
synthesize an alkyl halide	radical halogenation: $\begin{array}{c} \\ -\text{C}-\text{H} \\ \end{array} + \text{X}-\text{X} \xrightarrow{\Delta \text{ or } h\nu} \begin{array}{c} \\ -\text{C}-\text{X} \\ \end{array} + \text{H}-\text{X}$ alkyl bromide from a methyl, 1°, or 2° alcohol: $\text{R}-\text{OH} + \text{PBr}_3 \rightarrow \text{R}-\text{Br} + \text{HOPBr}_2$ alkyl chloride, bromide, or iodide from a 3° alcohol ($\text{S}_{\text{N}}1$): $\text{R}-\text{OH} + \text{HX} \rightarrow \text{R}-\text{X} + \text{H}_2\text{O}$ hydrohalogenation of an alkene (X on less substituted C): $\begin{array}{c} \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \end{array} + \text{H}-\text{X} \rightarrow \begin{array}{c} \text{H} \quad \text{X} \\ \quad \\ -\text{C}-\text{C}- \\ \quad \end{array}$
synthesize a 1,2-dihalide (X's on adjacent C's)	$\begin{array}{c} \text{R}_1 \quad \text{R}_3 \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{R}_2 \quad \text{R}_4 \end{array} + \text{X}_2 \longrightarrow \begin{array}{c} \text{R}_2 \quad \text{R}_1 \\ \diagdown \quad / \\ \text{C}-\text{C} \\ / \quad \diagdown \\ \text{X} \quad \text{X} \end{array} \text{ and } \begin{array}{c} \text{X} \quad \text{X} \\ \diagdown \quad / \\ \text{C}-\text{C} \\ / \quad \diagdown \\ \text{R}_1 \quad \text{R}_2 \quad \text{R}_4 \quad \text{R}_3 \end{array}$
synthesize a carbonyl (aldehyde or ketone)	methyl, 1°, or 2° alcohol + PCC, no H_2O ozonolysis: $\begin{array}{c} \text{R}_1 \quad \text{R}_3 \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{R}_2 \quad \text{R}_4 \end{array} \xrightarrow[2. \text{Me}_2\text{S or Zn}]{1. \text{O}_3} \begin{array}{c} \text{R}_1 \\ \\ \text{C}=\text{O} \\ \\ \text{R}_2 \end{array} + \begin{array}{c} \text{O}=\text{C} \\ \\ \text{R}_3 \\ \\ \text{R}_4 \end{array}$
synthesize a Grignard reagent	$\text{RX} + \text{Mg} \rightarrow \text{RMgX}$, X = Cl, Br, or I

goals	reactions
synthesize an alcohol	<p>reduction of carbonyl (OH on attacked C):</p> $\begin{array}{c} \diagup \\ \text{C}=\text{O} \\ \diagdown \\ \text{aldehyde} \\ \text{or ketone} \end{array} \xrightarrow{\text{NaBH}_4, \text{HOR}} \begin{array}{c} \text{H}-\text{C}-\text{O}-\text{H} \\ \\ \text{alcohol} \end{array}$ $\begin{array}{c} \text{O} \quad \text{H} \\ \quad \\ -\text{C}-\text{C}- \\ \quad \end{array} \xrightarrow{1. \text{RMgX}} \begin{array}{c} \text{XMg}^{\oplus} \quad \ominus \\ \quad \\ \text{H}-\text{C}-\text{C}-\text{H} \\ \quad \\ \text{R} \quad \text{H} \end{array} \xrightarrow{2. \text{H}_3\text{O}^{\oplus}} \begin{array}{c} \text{HO} \quad \text{H} \\ \quad \\ -\text{C}-\text{C}- \\ \quad \\ \text{R} \quad \text{H} \end{array}$ <p>reduction of epoxide with LiAlH₄ or Grignard (OH on C adjacent to attacked C):</p> $\begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ -\text{C}-\text{C}- \\ \quad \end{array} \xrightarrow{1. \text{RMgX}} \begin{array}{c} \text{H} \quad \text{O}^{\oplus} \\ \quad \\ -\text{C}-\text{C}- \\ \quad \\ \text{R} \quad \text{MgX}^{\ominus} \end{array} \xrightarrow{2. \text{H}_3\text{O}^{\oplus}} \begin{array}{c} \text{H} \quad \text{OH} \\ \quad \\ -\text{C}-\text{C}- \\ \quad \\ \text{R} \quad \text{H} \end{array}$ <p>hydration of an alkene (OH on more substituted C):</p> $\begin{array}{c} \diagup \\ \text{C}=\text{C} \\ \diagdown \end{array} + \text{H}_2\text{O} \xrightarrow{\text{HA}} \begin{array}{c} \text{H}-\text{C}-\text{C}-\text{OH} \\ \quad \end{array}$ <p>hydroboration-oxidation (OH on less substituted C):</p> $\begin{array}{c} \text{R}_1 \quad \text{R}_3 \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{R}_2 \quad \text{R}_4 \end{array} \xrightarrow[2. \text{H}_2\text{O}_2, \ominus\text{OH}, \text{H}_2\text{O}]{1. \text{BH}_3} \begin{array}{c} \text{R}_2 \quad \text{R}_1 \\ \diagdown \quad \diagup \\ \text{C}-\text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{OH} \end{array} \quad \text{and} \quad \begin{array}{c} \text{H} \quad \text{OH} \\ \diagdown \quad \diagup \\ \text{C}-\text{C} \\ \diagup \quad \diagdown \\ \text{R}_1 \quad \text{R}_2 \quad \text{R}_4 \quad \text{R}_3 \end{array}$
synthesize a 1,2-haloalcohol (X and OH on adjacent C's)	$\begin{array}{c} \text{R}_1 \quad \text{R}_3 \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{R}_2 \quad \text{R}_4 \end{array} + \text{X}_2 \xrightarrow{\text{H}_2\text{O}} \begin{array}{c} \text{R}_2 \quad \text{R}_1 \\ \diagdown \quad \diagup \\ \text{C}-\text{C} \\ \diagup \quad \diagdown \\ \text{X} \quad \text{OH} \end{array} \quad \text{and} \quad \begin{array}{c} \text{X} \quad \text{R}_3 \quad \text{R}_4 \\ \diagdown \quad \diagup \\ \text{C}-\text{C} \\ \diagup \quad \diagdown \\ \text{R}_1 \quad \text{R}_2 \quad \text{OH} \end{array} + \text{HX}$
synthesize a 1,2-diol (OH's on adjacent C's)	<p>trans dihydroxylation: epoxide plus HO⁻ in H₂O (S_N2), or epoxide plus H₂O with H₂SO₄ (S_N1) osmium catalyzed dihydroxylation is cis:</p> $\begin{array}{c} \text{R}_1 \quad \text{R}_3 \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{R}_2 \quad \text{R}_4 \end{array} \xrightarrow{\text{OsO}_4, \text{H}_2\text{O}_2} \begin{array}{c} \text{R}_2 \quad \text{R}_1 \\ \diagdown \quad \diagup \\ \text{C}-\text{C} \\ \diagup \quad \diagdown \\ \text{HO} \quad \text{OH} \end{array} \quad \text{and} \quad \begin{array}{c} \text{HO} \quad \text{OH} \\ \diagdown \quad \diagup \\ \text{C}-\text{C} \\ \diagup \quad \diagdown \\ \text{R}_1 \quad \text{R}_2 \quad \text{R}_4 \quad \text{R}_3 \end{array}$

goals	reactions
synthesize an alkene	<p>E2: R-L + LDA (major product: less substituted alkene) E2: R-L (3°, 2°, or hindered 1°) + NaOH (major: more-substituted alkene) E1: R-L (2° or 3°) + H₂SO₄ + heat (major: more-substituted alkene) reduction of carbonyl, followed by E1 dehydration:</p> $ \begin{array}{c} \begin{array}{c} \text{O} \quad \text{H} \\ \parallel \quad \\ -\text{C}-\text{C}- \\ \quad \end{array} \xrightarrow{1. \text{LiAlH}_4} \begin{array}{c} \oplus \quad \ominus \\ \text{X} \text{Mg} \quad \text{O} \\ \quad \\ -\text{C}-\text{C}- \\ \quad \\ \text{H} \end{array} \xrightarrow{2. \text{H}_2\text{SO}_4, \Delta} \begin{array}{c} \text{HO} \quad \text{H} \\ \quad \\ -\text{C}-\text{C}- \\ \quad \\ \text{H} \end{array} \xrightarrow{\text{E1}} \begin{array}{c} \text{C}=\text{C}- \\ \quad \\ \text{H} \end{array} \end{array} $ $ \begin{array}{c} \begin{array}{c} \text{O} \quad \text{H} \\ \parallel \quad \\ -\text{C}-\text{C}- \\ \quad \end{array} \xrightarrow{1. \text{RMgX}} \begin{array}{c} \oplus \quad \ominus \\ \text{X} \text{Mg} \quad \text{O} \\ \quad \\ -\text{C}-\text{C}- \\ \quad \\ \text{R} \end{array} \xrightarrow{2. \text{H}_2\text{SO}_4, \Delta} \begin{array}{c} \text{HO} \quad \text{H} \\ \quad \\ -\text{C}-\text{C}- \\ \quad \\ \text{R} \end{array} \xrightarrow{\text{E1}} \begin{array}{c} \text{C}=\text{C}- \\ \quad \\ \text{R} \end{array} \end{array} $ <p>reduction of epoxide, followed by E1 dehydration:</p> $ \begin{array}{c} \begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ -\text{C}-\text{C}- \\ \quad \end{array} \xrightarrow[1. \text{LiAlH}_4 \text{ or } \text{RMgX}]{2. \text{H}_2\text{SO}_4, \Delta} \begin{array}{c} \text{HO} \quad \text{H} \\ \quad \\ -\text{C}-\text{C}- \\ \quad \end{array} \xrightarrow{\text{E1}} \begin{array}{c} \text{C}=\text{C}- \\ \quad \end{array} \end{array} $
synthesize an epoxide	<p>deprotonation followed by intramolecular S_N2:</p> $ \begin{array}{c} \text{R}_2 \quad \text{R}_1 \\ \diagdown \quad \diagup \\ \text{C}-\text{C}-\text{OH} \\ \quad \\ \text{L} \quad \text{R}_4 \quad \text{R}_3 \end{array} + \text{NaH} \longrightarrow \begin{array}{c} \text{R}_2 \quad \text{R}_1 \\ \diagdown \quad \diagup \\ \text{C}-\text{C}-\text{O}^\ominus \\ \quad \\ \text{L} \quad \text{R}_4 \quad \text{R}_3 \end{array} \longrightarrow \begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{C}-\text{C} \\ \diagdown \quad \diagup \\ \text{R}_1 \quad \text{R}_2 \quad \text{R}_4 \quad \text{R}_3 \end{array} $ <p>MCPBA oxidation of an alkene:</p> $ \begin{array}{c} \text{R}_1 \quad \text{R}_3 \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{R}_2 \quad \text{R}_4 \end{array} \xrightarrow{\text{MCPBA}} \begin{array}{c} \text{R}_2 \quad \text{R}_1 \\ \diagdown \quad \diagup \\ \text{C}-\text{C} \\ \diagdown \quad \diagup \\ \text{R}_3 \quad \text{R}_4 \end{array} \text{ and } \begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{C}-\text{C} \\ \diagdown \quad \diagup \\ \text{R}_1 \quad \text{R}_2 \quad \text{R}_4 \quad \text{R}_3 \end{array} $