

Exercise 15 - Preparation of a Key for Reaction-Map of Organic Chemistry (see Appendix C in student manual)

Abstract:

The *Reaction -Map of Organic Chemistry* has been designed to give organic chemistry students an overview of most of the reactions needed for the organic chemistry course. The chart has been partially organized according to the periodic table on the horizontal axis and according to carbon oxidation level on the vertical axis. In addition the carboxyls are grouped vertically according to decreasing reactivity and carbon - carbon bond forming reactions are emphasized with bold arrows. The chart provides a study aide for students and should help students develop synthetic routes from one functional group to another. The chart should be especially useful for students studying for the final examination for the two semester organic chemistry course. In addition to the chart, three keys are available that organize the reactions according to mechanism, functional group preparations and functional group reactions. Chemistry can be thought of a search for order in matter and this chart attempts to provide some insight into the order that exists in organic chemistry.

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Reaction-Map as a Study Aid

At the end of a two semester course in organic chemistry, a student should be able to perform the exercises below. (Note: In addition to the exercises below, a student of organic chemistry should be able to demonstrate competency with spectroscopic, stereochemical and multistep synthetic challenges.) By performing the exercises below should result in the preparation of three keys for the *Reaction-Map of Organic Chemistry*.

1. For each numbered reaction, classify the reaction by mechanism (e.g., substitution, nucleophilic) and list the reagents, conditions, regioselectivity, stereoselectivity and restrictions associated with the reaction.
2. List all methods of preparing each functional group.
3. List all reactions of each functional group.
4. Write mechanisms for reactions: 3 (*D2*), 10 (*B13*), 19 (*C13*), 32 (*C11*), 33 (*E14*), 39 (*J3*) + 28 (*K2*), 42 (*G7*), 46 (*B13*), 47 (*C11*), 62 (*K13*), 72 (*J17*), 106 (*K19*).

The problems above should be attempted without reference to the keys but the keys can be used to help check for the correctness of answers for 1-3. The keys are available in the Instructor's Manual and to subscribers of the Journal of Chemical Education at:

http://pubs.acs.org/doi/suppl/10.1021/ed084p1224/suppl_file/jce2007p1224w.pdf

For the answers to question #4, reference to an organic chemistry textbook may be required.

KEYS TO REACTION-MAP OF ORGANIC CHEMISTRY

General Organization

Left to right, compounds in the colored or shaded regions are arranged according to the periodic table. Organolithium and Grignard reagents are under lithium and magnesium but these reagents are used elsewhere on several bold arrows for the synthesis of C-C bonds. Carbon compounds that do not contain other elements are under carbon, carbon - nitrogen (and C, N, O) compounds are under nitrogen, carbon - oxygen compounds are under oxygen and carbon - halogen (and C, O, X) compounds are under fluorine and the halogens. From top to bottom, within groups, the compounds are arranged according to the oxidation level of the compound.

The oxidation level of organic compounds is somewhat of a complex concept. Even for propane, the carbons technically have different oxidation states. For the purposes of grouping compounds by oxidation level for this chart, the general guideline used has been that oxidation involves a decrease in the number of bonds to carbon from an atom less electronegative than carbon (most frequently hydrogen) and/or an increase in the number of bonds from carbon to atoms more electronegative than carbon (most frequently N, O, X). Reduction is the reverse. If two carbons change, then the sum of the changes must be considered. When water is added to a double bond, one carbon gains a hydrogen and the other an oxygen and the net oxidation level of the molecule does not change. The increase in oxidation level is indicated by the degree of darkness in the chart in **Appendix C** and in color in the online version.

This organization results in five groups including: 1. alkanes (and organometallics), 2. alkenes (and alkene addition products such as alcohols, ethers and halides), aromatics and amines, 3. alkynes (and alkyne addition products such as carbonyls), 4. carboxyls and 5. carbon dioxide and tetrahalomethane.

For the purposes of organizing the numbering of the reactions for this key, the reactions have been grouped according to mechanism of the first step of the reaction. Many reactions fall into more than one group. The addition of hydrogen to π bonds is usually discussed in texts along with electrophilic additions to π bonds but here the hydrogen additions have been placed in the reduction category. Reductions with hydrides such as LiAlH_4 are often grouped with nucleophilic additions but here have also been included in the reduction category. The reactions are listed in the order substitution, addition, elimination, addition-elimination, oxidation, reduction, concerted and miscellaneous. To facilitate the finding of reactions from any of the keys that follow, a roadmap grid has been included. For example, the addition of HX to an alkene is represented by reaction 30 which is in grid position *B11*.

Three keys have been designed to accompany the map. The keys are arranged according to mechanism, functional group preparations and functional group reactions. Reactions in the three keys contain the reaction numbers and grid locators.

Outside of the main region, bold arrows indicate reactions that form C-C bonds. In the online version, products that result from carbon-carbon bond formation are in the grey areas. In **Appendix C**, these products are in the area with a graph grid. Dotted arrows represent reactions that result in the breaking of C-C bonds. Also included outside the main region are the reactions of aromatics and miscellaneous reactions.

Reaction-Map as a Study Aid

At the end of a two semester course in organic chemistry, a student should be able to perform the exercises below. In addition to the exercises below, a student of organic chemistry should be able to demonstrate competency with spectroscopic, stereochemical and multistep synthetic challenges.

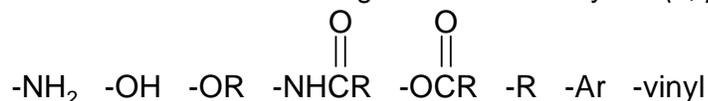
1. For each numbered reaction, classify the reaction by mechanism (e.g., substitution, nucleophilic) and list the reagents, conditions, regioselectivity, stereoselectivity and restrictions associated with the reaction.
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The problems above should be attempted without reference to the keys but the keys can be used to help check for the correctness of answers. For the answers to question #4, reference to an organic chemistry textbook may be required.

Reaction Mechanism (Listed in the order substitution, addition, elimination, addition-elimination, oxidation, reduction, concerted, miscellaneous)

SUBSTITUTION

Electrophilic (for electrophilic aromatic substitution, ortho-para directors with rate increase compared to benzene in decreasing order of reactivity are (2, p. 632):



The halides are deactivating ortho-para directors. Meta directors arranged approximately in order of decreasing reactivity are:



- 1 (D1) H_2SO_4 (can be reversed, see # 2 (E1)), aromatic \rightarrow aromatic derivatives.
- 2 (E1) $\text{H}_3\text{O}^+/\text{D}$, aromatic \rightarrow aromatic derivatives.
- 3 (D2) $\text{HNO}_3/\text{H}_2\text{SO}_4$ produces NO_2^+ , aromatic \rightarrow aromatic derivatives.
- 4 (D3) X_2/FeX_3 (or AlX_3), aromatic \rightarrow aromatic derivatives.
- 5 (D4) RX/AlCl_3 , aromatic \rightarrow aromatic derivatives, Friedel-Crafts alkylation, can rearrange and undergo multiple substitution, does not work when ring is deactivated or contains an amino group.
- 6 (D5)

$\begin{array}{c} \text{O} \\ \parallel \\ \text{RC-X}/\text{AlCl}_3 \end{array}$ or $\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{RCOCR}/\text{AlCl}_3 \end{array}$, aromatic \rightarrow aromatic derivatives, Friedel-Crafts acylation, no rearrangement or multiple substitution, does not work when ring is deactivated or contains an amino group, carbonyl can be reduced to CH_2 (see #87 (C9)).

- 7 (L2) PhY where Y is a strong activator, aromatic \rightarrow aromatic derivatives (e.g., OH or NH_2) for electrophilic aromatic substitution.
- 8 (A5) H_2O or any good proton donor, organometallic \rightarrow alkane.

Free Radical

- 9 (E3) NBS (N-bromosuccinimide), aromatics \rightarrow aromatic derivatives, good for benzylic and allylic bromination.
- 10 (B13) $\text{X}_2/h\nu$ or Δ , alkane \rightarrow alkyl halide, free radical chain reaction, multiple substitution, because of limited selectivity, useful primarily when there is only one type of hydrogen or for more reactive hydrogens (e.g., benzylic and allylic).
- 11 (I1) CuCl or CuBr , aromatics \rightarrow aromatic halides, Sandmeyer reaction.
- 12 (L4) CuCN , aromatics \rightarrow aromatic nitriles, Sandmeyer reaction.

Nucleophilic

- 13 (J1) $\text{H}_3\text{O}^+/\Delta$, aromatics \rightarrow aromatic phenols.
- 14 (J1) KI , aromatics \rightarrow aromatic iodides.
- 15 (K1) HBF_4/Δ , aromatics \rightarrow aromatic fluorides.
- 16 (L1) H_3PO_2 , aromatics \rightarrow aromatic derivatives.
- 17 (B18) CN^- , alkyl halide \rightarrow nitrile.
- 18a (C14) NH_3 , alkyl halide \rightarrow amine. The direct synthesis of amines from halides is subject to many problems including multiple substitution. Generally, alternatives (e.g., 18b, 18c) should be used.

- b (C14) 1. Phthalimide/OH⁻ 2. RX 3. NH₂NH₂, alkyl halide → amine, Gabriel synthesis of primary amines.
- c (C14) 1. NaN₃ 2. Na/ROH or LiAlH₄, alkyl halide → amine.
- 19a (C13) OH⁻, alkyl halide → alcohol, S_N2 for 1° although steric hindrance in the nucleophile or alkyl halide promotes elimination, 3° gives elimination.
- b (C13) H₂O, alkyl halide → alcohol, S_N1 for 3°, can rearrange, competes with E1.
- 20a (C15) HX, alcohol → alkyl halide, 1° usually go S_N2 (except that HCl does not work as Cl⁻ is a weak nucleophile) and 3° usually go S_N1 with rearrangement and competing elimination possible.
- b (C15) PX₃ or SOCl₂, alcohol → alkyl halide.
- c (C15) 1. TsCl/pyridine 2. X⁻, alcohol → alkyl halide.
- 21a (D13) 1. Na 2. R'X, alcohol → ether, Williamson ether synthesis, elimination possible and exclusive for 3° halide, prevalent with a 2° halide.
- b (D13) 1. TsCl/pyridine 2. OR⁻, alcohol → ether.
- c (D13) H₂SO₄, alcohol → ether, useful for symmetrical ethers and 3° ROH with 1° ROH, competes with elimination.
- 22 (C16) OR⁻, alkyl halide → ether, Williamson ether synthesis, elimination possible and prevalent for 3° halide.
- 23 (C17) 1. TsCl/pyridine 2. CN⁻, alcohol → nitrile.
- 24a (F15) H₃O⁺, oxirane → diol, overall from the alkene yields anti-addition, with an alcohol instead of water, alcohol adds to most substituted carbon (Markonikov orientation) with anti-addition.
- b (F15) OH⁻, oxirane → diol, overall from the alkene yields anti-addition, with an alcohol instead of water, alcohol adds to least substituted carbon (anti-Markonikov orientation) with anti-addition.
- 25 (F17, A2) 1. RMgX/Et₂O 2. H⁺/H₂O, oxirane → alcohol, Grignard reaction, works best on unsubstituted carbon and can give mixtures. Organocuprates (Gilman reagents) are better.

Nucleophilic or Electrophilic (depending on perspective)

- 26 (E6) 1. NH₂⁻ 2. RX, alkyne and alkyl halide → alkyne, 3° halides eliminate rather than substitute and elimination is prevalent for 2° halides.
- 27a (G7) 1. LDA (lithium diisopropylamide) 2. R''X, aldehyde or ketone → alkylated aldehyde or ketone, works best with 1° halides, multiple substitution possible, with 2 types of α hydrogens, orientation depends on conditions for kinetic vs thermodynamic control but normally gives the kinetic enolate.
- b (G7) 1. pyrrolidine (or other 2° amine)/H⁺ 2. R''X 3. H₃O⁺, aldehyde or ketone → alkylated aldehyde or ketone, alkylation usually takes place on least substituted side of the original carbonyl position, Stork enamine reaction.
- 28 (K2) H⁺/ROH, hemiacetal or hemiketal → acetal or ketal, reversible, see # 39, 40 (J3), hemiacetals and hemiketals are generally unstable and, except for sugars, not isolated.
- 29 (K3) H⁺/H₂O, acetal or ketal → hemiacetal or hemiketal, reversible, see # 28, 39, 40 (J3).

ADDITION

Electrophilic (except 30b)

- 30a (B11) HX, alkene \rightarrow alkyl halide, electrophilic Markovnikov addition.
 b (B11) HBr/peroxides, alkene \rightarrow alkyl halide, free radical mechanism yields anti-Markovnikov orientation.
- 31a (C12) H^+ (H_2SO_4 or H_3PO_4)/ROH, alkene \rightarrow ether, electrophilic Markovnikov addition with possible rearrangement and competing reactions.
 b (C12) 1. $Hg(O_2CCF_3)_2$, ROH 2. $NaBH_4$, alkene \rightarrow ether, alkoxymercuration reaction, Markovnikov addition without rearrangement.
- 32a (C11) H^+ (H_2SO_4 or H_3PO_4)/ H_2O , alkene \rightarrow alcohol, electrophilic Markovnikov addition with possible rearrangement and competing reactions.
 b (C11) 1. $Hg(OAc)_2$, THF, H_2O 2. $NaBH_4$, alkene \rightarrow alcohol, Markovnikov without rearrangement.
 c (C11) 1. BH_3 2. OH^- , H_2O_2 , H_2O , alkene \rightarrow alcohol, anti-Markovnikov¹ orientation without rearrangement.
- 33 (E14) X_2 , alkene \rightarrow dihalide, anti-addition, only practical for X = Cl or Br.
- 34 (F10) 1. H_2 /Lindlar's catalyst 2. X_2 , alkyne \rightarrow dihalide (vicinal).
- 35 (F10) HX, 2 moles, alkyne \rightarrow dihalide (geminal).
- 36a (E6) H_2O/H_2SO_4 for disubstituted alkynes, $H_2O/H_2SO_4/HgSO_4$ for terminal alkynes, alkynes \rightarrow ketones (except ethylene \rightarrow acetaldehyde), Markovnikov orientation.
 b (E6) 1. BH_3 2. H_2O_2/OH^- for disubstituted alkynes, substitute disiamylborane for borane for terminal alkynes, alkynes \rightarrow aldehydes and ketones, anti-Markovnikov orientation.
- 37,38 (I4) H^+/H_2O or OH^-/H_2O reversible formation of hydrate, aldehyde and ketones \rightleftharpoons hydrates. Equilibrium strongly favors carbonyl for ketones but is very structure dependent for aldehydes (formaldehyde - 99.99% hydrate and acetaldehyde - 58% hydrate).
- 39,40 (J3) H^+/ROH reversible formation of hemiacetal and hemiketal, aldehyde and ketones \rightleftharpoons hemiacetals and hemiketals, hemiacetals and hemiketals are generally unstable and, except for sugars, not isolated. Sugars usually exist in cyclic hemiacetal or hemiketal form. Addition of second molecule of alcohol (28 (K2), 29 (K3)) to hemiacetals and hemiketals in reversible substitution reaction yields acetal or ketal. Especially important as blocking or protecting group when ethylene glycol is used to form cyclic acetal or ketal.

Nucleophilic

- 41 (F7, A2) 1. $RMgX$ 2. H^+/H_2O , aldehyde or ketone \rightarrow alcohol, Grignard reaction.
- 42 (G7) H^+ or OH^- , aldehyde or ketone \rightarrow β -hydroxycarbonyl compound (aldol), aldol addition of conjugate base of carbonyl to carbonyl. If R's present are aromatic, addition product eliminates to give enone. If R's are not aromatic, elimination will occur with heating. If elimination occurs, the reaction is called an aldol condensation. Useful primarily when only one kind of α hydrogen is present.
- 43 (H7) $NaCN/HCl$, aldehyde or ketone \rightarrow cyanohydrin, forms cyanohydrin that can be hydrolyzed to α -hydroxycarboxylic acid.
- 44 (M7, A2) 1. $RMgX + CO_2$ 2. H^+/H_2O , carbon dioxide \rightarrow carboxylic acid, Grignard Rxn.

¹Although the orientation of the water in the product is anti-Markovnikov, since boron is more electropositive than hydrogen, the intermediate orientation is consistent with Markovnikov's rule (1, p 163).

ELIMINATION

- 45 (G4) see #42 (G7), alcohol \rightarrow alkene.
- 46a (B13) strong base, strong nucleophile such as OH⁻/ROH, alkyl halide \rightarrow alkene, Zaitsev product unless R is bulky such as *t*-butyl or X is fluorine, E2 for 1° halide competes with S_N2, E2 for 3° halide, anti elimination, thermodynamic alkene favored but decreases as base strength increases due to earlier TS .
- b (B13) poor base, poor nucleophile such as H₂O, alkyl halide \rightarrow alkene, Zaitsev product with thermodynamically favored stereochemistry dominant, doesn't work for 1° halides, competition between E1 and S_N1 for 2° and 3° halides.
- 47a (C11) H₂SO₄ or H₃PO₄, alcohol \rightarrow alkene, Zaitsev product with thermodynamically favored stereochemistry dominant, E2 for 1° halides, E1 for 2° and 3° halides, rearrangement possible.
- b (C11) POCl₃/pyridine/O°C, alcohol \rightarrow alkene, milder conditions than 47a, use of this catalyst avoids rearrangements, Zaitsev product with thermodynamically favored stereochemistry dominant, E2 reaction.
- 48 (D8) 1. CH₃I (excess) 2. Ag₂O/H₂O 3. Δ , amine \rightarrow alkene, Hofmann (least substituted) product.
- 49 (E8) NaNH₂/NH₃ or K *t*-butoxide/DMSO, (di)halide \rightarrow alkyne.

ADDITION-ELIMINATION

- 50 (E10) 1. NH₃ (or RNH₂)/H⁺ 2. H₂/Ni or hydride such as NaBH₃CN, aldehyde or ketone \rightarrow amine, reductive amination, technically this should be classed as two reactions with the addition-elimination (51 (G11)) first and the hydrogenation second.
- 51 (G11) NH₂R, aldehyde or ketone \rightarrow "imine", R's commonly used to make classic derivatives of carbonyls yield oximes (R = OH, NH₂OH = hydroxylamine), hydrazones (R = NH₂ or NHR', if 2,4-dinitrophenylhydrazine is used, a 2,4-dinitrophenylhydrazone results), semicarbazones (R = NHCONH₂, NH₂NHCONH₂ = semicarbazide).
- 52 (H15) RCOO⁻, acyl halide \rightarrow anhydride.
- 53 (K10) NH₃ (or RNH₂ or R₂NH), acyl halide \rightarrow amide.
- 54a (J15) H⁺/H₂O, acyl halide \rightarrow carboxylic acid.
- b (J15) 1. OH⁻/H₂O 2. H⁺/H₂O, acyl halide \rightarrow carboxylic acid.
- 55 (J16) ROH, acyl halide \rightarrow ester.
- 56 (K10) NH₃ (or RNH₂ or R₂NH), anhydride \rightarrow amide.
- 57a (J12) H⁺/H₂O, anhydride \rightarrow carboxylic acid.
- b (J12) 1. OH⁻/H₂O 2. H⁺/H₂O, anhydride \rightarrow carboxylic acid.
- 58 (I12) ROH, anhydride \rightarrow ester.
- 59a (J11) RCOCl (with conjugate base of acid), carboxylic acid \rightarrow anhydride.
- b (J11) Δ for formation of intramolecular anhydrides such as phthalic anhydride.
- 60 (I16) SOCl₂ or PCl₃ or PCl₅ or PBr₃, carboxylic acid \rightarrow acyl halide.
- 61 (K11) NH₃, carboxylic acid \rightarrow amide, primarily an industrial reaction as it requires extreme conditions.
- 62 (K13) H⁺/ROH, carboxylic acid \rightarrow ester, position of equilibrium important in this reaction.
- 63 (K14) H⁺/H₂O, ester \rightarrow carboxylic acid, position of equilibrium important in this reaction.
- 64 (L11) NH₃ (or RNH₂ or R₂NH), ester \rightarrow amide.
- 65a (J10) H⁺/H₂O, nitrile \rightarrow carboxylic acid.
- b (J10) 1. OH⁻/H₂O 2. H⁺/H₂O, nitrile \rightarrow carboxylic acid.

- 66a (K9) H^+/H_2O or OH^-/H_2O , nitrile \rightarrow amide, mild conditions as strong conditions yield carboxylic acids
 b (K9) H^+/ROH , nitrile \rightarrow N-substituted amide, Ritter reaction, does not work with 1° alcohols
- 67a (K11) H^+/H_2O , amide \rightarrow carboxylic acid.
 b (K11) 1. OH^-/H_2O 2. H^+/H_2O , amide \rightarrow carboxylic acid.
- 68 (H18) 1. $R'_2CuLi/Et_2O/-78^\circ C$ 2. H_2O , acyl halide and organometallic \rightarrow ketone, with Gilman reagent, addition stops at ketone level.
- 69 (K11, A3) 1. $RMgX/Et_2O$ 2. H^+/H_2O , acyl halide and organometallic \rightarrow 3° alcohol.
 70 (I17, A3) 1. $RMgX/Et_2O$ 2. H^+/H_2O , ester and organometallic \rightarrow 3° alcohol.
 71 (J7, A3) 1. $R'MgX/Et_2O$ 2. H^+/H_2O , nitrile and organometallic \rightarrow ketone.
 72 (J17) RO^- , ester \rightarrow β -keto ester, Claisen condensation, ester must have 2 α hydrogens (the 2nd one prevents a reverse reaction).

OXIDATION

- 73 (B3) 1. O_3 2. Zn/HCl , alkene \rightarrow aldehydes and/or ketones depending on alkene substitution.
- 74 (H2) $NaNO_2/HCl$, amine \rightarrow diazonium salt, for 1° aromatic amines.
- 75a (F3) $KMnO_4/H_3O^+/\Delta$, alkyl benzene with α alkyl hydrogens \rightarrow a benzoic acid.
 b (F3) $K_2Cr_2O_7/H_3O^+/\Delta$, alkyl benzene with α alkyl hydrogens \rightarrow a benzoic acid.
- 76 (D11) RCO_3H , alkene \rightarrow oxirane.
- 77a (E11) $KMnO_4/OH^-$, syn-addition, alkene \rightarrow diol.
 b (E11) 1. OsO_4 2. H_2O_2 , syn-addition, alkene \rightarrow diol.
- 78a (F12) for 2° alcohols - CrO_3/H_2SO_4 or $Na_2Cr_2O_7/H_2SO_4$ or $KMnO_4/H_2SO_4$, alcohol \rightarrow ketone.
 b (F12) for 1° alcohols - PCC (pyridinium chlorochromate), alcohol \rightarrow aldehyde.
- 79 (I13) CrO_3/H_2SO_4 or $Na_2Cr_2O_7/H_2SO_4$ or $KMnO_4/H_2SO_4$ for 1° alcohols, alcohol \rightarrow carboxylic acid.
- 80a (H12) CrO_3/H_2SO_4 or $Na_2Cr_2O_7/H_2SO_4$ or $KMnO_4/H_2SO_4$, aldehyde \rightarrow carboxylic acid.
 b (H12) 1. Ag_2O/NH_3 2. H_3O^+ Tollens test for aldehydes yields silver mirror, aldehyde \rightarrow carboxylic acid.
 c (H12) $Cu^{2+}/sodium\ tartrate$, aldehyde \rightarrow carboxylic acid, Fehling's test for aldehydes yields red Cu_2O .
 d (H12) $Cu^{2+}/sodium\ citrate$, aldehyde \rightarrow carboxylic acid, Benedict's test for aldehydes yields red Cu_2O .

REDUCTION

- 81a (A9) Mg/Et_2O , alkyl halide \rightarrow organometallic, formation of Grignard, water must be excluded.
 b (A9) Li/Et_2O , alkyl halide \rightarrow organometallic formation of organolithium compound, more reactive than Grignard, water must be excluded.
- 82 (B7) H_2/Pt or Pd or Ni , alkene \rightarrow alkane, syn-addition.
 83 (B6) H_2/Pt or Pd or Ni , alkyne \rightarrow alkane.
- 84a (D7) $H_2/Lindlar's\ catalyst$ (palladium precipitated on $CaCO_3$ and treated with $Pb(C_2H_3O_2)_2$ and quinoline), alkyne \rightarrow alkene, poisoned catalyst necessary to prevent addition of 2nd mole of H_2 , syn-addition.
 b (D7) Na or Li/NH_3 , non-terminal alkyne \rightarrow alkene, gives anti-addition resulting in trans alkene.
- 85 (B9) 1. $TsCl/pyridine$ 2. $LiAlH_4$, alcohol \rightarrow alkane.
 86 (G2) Sn/HCl , aromatic nitro compound \rightarrow aromatic amine.

- 87a (C9) Zn(Hg)/HCl/ Δ , aldehyde or ketone \rightarrow alkane, Clemmensen reduction for acid insensitive compounds.
- b (C9) $\text{NH}_2\text{NH}_2/\text{OH}^-/\Delta$, aldehyde or ketone \rightarrow alkane, Wolff-Kishner reduction for base insensitive compounds.
- c (C9) 1. $\text{HS}(\text{CH}_2)_2\text{SH}/\text{HCl}$ 2. $\text{H}_2/\text{Raney Ni}$, aldehyde or ketone \rightarrow alkane, for compounds insensitive to acid or base
- 88a (E12) 1. LiAlH_4 2. H_3O^+ , aldehyde or ketone \rightarrow alcohol.
- b (E12) 1. NaBH_4 2. H_3O^+ , aldehyde or ketone \rightarrow alcohol.
- c (E12) $\text{H}_2/\text{Raney Ni}$, aldehyde or ketone \rightarrow alcohol.
- 89 (E14) 1. LiAlH_4 2. H_2O , oxirane \rightarrow alcohol, hydride attacks least substituted carbon.
- 90a (G16) 1. LiAlH_4 2. H_3O^+ , acyl halide \rightarrow alcohol.
- b (G16) H_2/Pd , acyl halide \rightarrow alcohol.
- 91 (H15) 1. $\text{LiAlH}[\text{OC}(\text{CH}_3)_3]_3\text{H}$, -78°C 2. H^+ or $\text{H}_2/\text{partially deactivated Pd}$ similar to Lindlar's catalyst (Rosenmund reduction), acyl halide \rightarrow aldehyde
- 92a (I9) $\text{H}_2/\text{Pd}/\text{C}$, nitrile \rightarrow amine.
- b (I9) 1. LiAlH_4 2. H_2O , nitrile \rightarrow amine
- 93 (I10) 1. DIBAH (diisobutylaluminium hydride)/ -80°C 2. H^+ , nitrile \rightarrow aldehyde.
- 94 (H12) 1. LiAlH_4 2. H^+ , carboxylic acid \rightarrow alcohol.
- 95 (I13) 1. DIBAH (diisobutylaluminium hydride)/ -80°C 2. H^+ , ester \rightarrow aldehyde.
- 96 (H14) 1. LiAlH_4 2. H^+ , ester \rightarrow alcohol.
- 97 (I9) 1. LiAlH_4 2. H_2O , amide \rightarrow amine.

CONCERTED

- 98 (B4) Δ for some, alkene + diene \rightarrow cyclohexene, Diels-Alder reaction, a concerted syn addition that also falls under classifications of pericyclic and [4 + 2] cycloaddition reactions, electronic releasing groups on the diene and electron withdrawing groups on the dienophile generally increase the rate of reaction. The diene must be capable of achieving an s-cis conformation and cyclic dienes such as cyclopentadiene react rapidly. There is a stereochemical preference for electron withdrawing groups on the dienophile to end up in the endo position.

MISCELLANEOUS

- 99a (C5) 1. $\text{CH}_2\text{N}_2/\Delta$ or $h\nu$ 2. alkene, carbene + alkene \rightarrow cyclopropane, generally a syn addition, also see 107 (L18).
- b (C5) 1. $\text{CH}_2\text{I}_2/\text{Zn}(\text{Cu})$ 2. alkene, Simmons-Smith reagent, carbenoid + alkene \rightarrow cyclopropane (also see 107 (L18)).
- 100 (B18) 1. $\text{Li}/\text{Et}_2\text{O}$ 2. CuI 3. $\text{R}'\text{X}$, alkyl halide uses Gilman reagent to make symmetrical and unsymmetrical hydrocarbons.
- 101 (F6) $(\text{Ph})_3\text{P}=\text{CHR}$, Wittig reagent synthesized from 1. $\text{Ph}_3\text{P} + \text{RBr}$ 2. RLi , aldehyde or ketone \rightarrow alkene.
- 102 (H13) 1. X_2/OH^- 2. H^+ , methyl aldehydes and ketones \rightarrow haloform + carboxylic acid, haloform reaction used to test for methyl ketones (and acetaldehyde and ethanol and other 2-alcohols).
- 103 (K8) P_2O_5 or SOCl_2 , amide \rightarrow nitrile.
- 104 (L6) Br_2/OH^- , Hofmann rearrangement, amide \rightarrow amine with one less carbon.
- 105 (L12) Δ , carboxylic acid \rightarrow carbon dioxide + residue (usually aromatic or β -keto carboxylic acids, others do not easily decarboxylate).
- 106 (K19) 1. OR^- 2. $\text{R}'\text{Br}$ 3. $\text{H}^+/\text{H}_2\text{O}/\Delta$, β -keto ester \rightarrow ketone, acetoacetic ester synthesis (also consider malonic ester synthesis).
- 107 (L18) 1. *t*-butoxide 2. alkene, dichlorocarbene + alkene \rightarrow dichlorocyclopropane, a syn addition, also see 99 (C5).

Preparation of Functional Groups

Acetals and Ketals

Acid catalyzed addition of 2 moles of alcohol to aldehyde or ketone (39 *(J3)*, 28 *(K2)*).

Acyl halides

Reaction of carboxylic acid with SOCl_2 or PCl_3 or PCl_5 or PBr_3 (60 *(I16)*).

Alcohols

Reaction of an alkyl halide with OH^- (19 *(C13)*).

Reaction of an oxirane with a Grignard reagent, an organolithium reagent or a Gilman reagent (organocuprate) (25 *(F17, A2)*).

Hydration of an alkene (32 *(C11)*).

Reaction of a carbonyl compound with a Grignard reagent or an organolithium reagent (41 *(F7, A2)*).

Aldol reaction (42 *(G7)*).

Reaction of an acyl halide (69 *(K11, A3)*) or an ester (70 *(I17, A3)*) with a Grignard reagent or an organolithium reagent.

Reduction of an oxirane with LiAlH_4 (89 *(E14)*).

Reduction of carbonyl (88 *(E12)*) and carboxyl compounds (90 *(G16)*, 94 *(H12)*, 96 *(H14)*).

Aldehydes

Hydration of ethylene (36a *(E6)*) or other terminal alkynes (36b *(E6)*).

Alkylation of conjugate base with an alkyl halide (27 *(G7)*).

Formation from acetals and hemiacetals (38 *(I4)*, 40 *(J3)*).

Aldol reaction (42 *(G7)*).

Oxidation of an alkene with ozone followed by reductive workup (73 *(B3)*).

Oxidation of a primary alcohol with PCC.

Reduction of an acyl halide (91 *(H15)*) or an ester (95 *(I13)*).

Reduction of a nitrile (93 *(I10)*).

Aldehyde and ketone derivatives

Reaction of appropriate reagent with carbonyl compound (51 *(G11)*).

Alkanes

Reaction of water with a Grignard reagent or an organolithium reagent (8 *(A5)*).

Reduction of an alkene (82 *(B7)*) or an alkyne (83 *(B6)*).

Reduction of an alcohol (85 *(B9)*).

Reduction of carbonyl compounds (87 *(C9)*).

Coupling of two alkyl halides (100 *(B18)*).

Carbene and carbenoid reactions (99 *(C5)*).

Alkenes

Elimination of water from an alcohol (45 *(G4)*, 47 *(C11)*).

Elimination of HX from an alkyl halide (46 *(B13)*).

Hofmann elimination from an amine (48 *(D8)*).

Reduction of an alkyne (84 *(D7)*).

Diels-Alder reaction (98 *(B4)*).

Wittig reaction (101 *(F6)*).

Alkyl halides

Reaction of NBS at a benzylic or allylic position (9 *(E3)*).

Radical bromination or chlorination of an alkane (10 *(B13)*).

Nucleophilic substitution of an alcohol (20 *(C15)*).

Addition of HX to an alkene (30 *(B11)*) or alkyne (35 *(F10)*).

Addition of X_2 to an alkene (33 (E14)).

Haloform reaction (102 (H13)).

Addition of dichlorocarbene to an alkene (107 (L18)).

Alkynes

Alkylation of an acetylide with an alkyl halide (26 (E6)).

Elimination of 2 moles of HX from geminal or vicinal dihalides (49 (E8)).

Amides

Reaction of an acid chloride (53 (K10)) or anhydride (56 (K10)) or ester (64 (L11)) with NH_3 or a 1° or 2° amine.

Reaction of a carboxylic acid with NH_3 or a 1° or 2° amine under extreme conditions (61 (K11)).

Nitrile hydrolysis for un-substituted amide and Ritter reaction for N-substituted amide (66 (K9)).

Amines

Reaction of an alkyl halide (18 (C14)) with NH_3 , RNH_2 , or R_2NH .

Reductive amination of a carbonyl compound (50 (E10)).

Reduction of an aromatic nitro compound (86 (G2)).

Reduction of an amide (97 (I9)) or nitrile (92 (I9)).

Hofmann rearrangement starting with an amide (104 (L6)).

Anhydrides

Reaction of an acyl halide with a carboxylate ion (52 (H15), 59a (J11)).

Preparation of a cyclic anhydride by dehydration of a dicarboxylic acid (59b (J11)).

Aromatic derivatives

Sulfonation with sulfuric acid and reverse reaction (1 (D1), 2 (E1)).

Nitration with nitric acid/sulfuric acid (3 (D2)).

Reaction of aromatic with X_2 /Lewis acid (4 (D3)).

Friedel-Crafts alkylation and acylation (5 (D4), 6 (D5)).

Reaction of alkyl halide with NBS to give α -bromo aromatic (9 (E3)).

Reaction of diazonium salts to give phenols (13 (J1)), halides (11 (I1), 14 (J1), 15 (K1)), hydrocarbons (16 (L1)), nitriles (12 (L4)).

Carbon-carbon bonds

Friedel-Crafts alkylations (5 (D4)) and acylations (6 (D5)).

Reaction of a diazonium salt with $CuCN$ (16 (L1)).

Reaction of cyanide with an alkyl halide (17 (B18)).

Conversion of an alcohol to a nitrile (23 (C17)) via a tosylate.

Reaction of an acetylide with an alkyl halide (26 (E6)).

Alkylation of carbons α to a carbonyl (27 (G7)).

Reactions of carbonyls (41 (F7, A2)), carbon dioxide (44 (M7, A2)), carboxyls (68 (H18), 69 (K11, A3), 70 (I17, A3)), oxiranes (25 (F17, A2)), nitriles (71 (J7, A3)) with a Grignard reagent or an organolithium reagent.

Aldol and related reactions (42 (G7)).

Addition of cyanide to a carbonyl (43 (H7)).

Claisen condensation and related reactions (72 (J17)).

Diels-Alder reaction (98 (B4)).

Carbene and carbenoid additions to alkenes (99 (C5), 107 (L18)).

Coupling of two alkyl halides (100 (B18)).

Wittig reaction (101 (F6)).

Acetoacetic ester and malonic ester synthesis (106 (K19)).

Carboxylic acids

Reaction of carbon dioxide with a Grignard reagent or an organolithium reagent (44 (M7, A2)).

Hydrolysis of an acyl halide (54 (J15)), anhydride (57 (J12)), ester (63 (K14)), nitrile (65 (J10)) or amide (67 (K11)).

Oxidation of an alkyl benzene (75 (F3)).

Oxidation of a primary alcohol (79 (I13)) or an aldehyde (80 (H12)).

Haloform reaction of a methyl ketone (102 (H13)).

Cyanohydrins

Reaction of a carbonyl compound with cyanide (43 (H7)).

Diols (1,2)

Hydrolysis of an oxirane (24 (F15)).

Oxidation of an alkene (77 (E11)).

Esters

Reaction of an acyl halide (55 (J16)) or anhydride (58 (I12)) with an alcohol, avoids equilibrium problem involved in direct conversion from the carboxylic acid.

Acid catalyzed reaction of a carboxylic acid with an alcohol (62 (K13)).

Claisen condensation (72 (J17)).

Ethers

Williamson ether synthesis between an alkyl halide and an alkoxide ion (21 (D13), 22 (C16)).

Addition of an alcohol to an alkene including alkoxymercuration (31 (C12)).

Hemiacetals and hemiketals

Acid catalyzed addition of alcohol to a carbonyl (39 (J3)).

Ketones

Friedel-Crafts acylation (6 (D5)).

Alkylation of conjugate base with an alkyl halide (27 (G7)).

Hydration of an alkyne (36 (E6)).

Formation from ketals and hemiketals (38 (I4), 40 (J3)).

Aldol reaction and condensation (42 (G7)).

Reaction of acyl halide with Gilman reagent (68 (H18)).

Reaction of a nitrile with a Grignard reagent (71 (J7, A3)).

Claisen condensation (72 (J17)).

Oxidation of an alkene with ozone followed by reductive workup (73 (B3)).

Oxidation of a 2° alcohol (78a (F12)).

Acetoacetic ester synthesis (106 (K19)).

Nitriles

Reaction of a diazonium salt with CuCN (Sandmeyer reaction) (16 (L1)).

Nucleophilic substitution of an alkyl halide (17 (B18)).

Conversion of an alcohol (23 (C17)).

Reaction of a carbonyl compound with hydrogen cyanide (43 (H7)).

Dehydration of an amide (103 (K8)).

Organometallics

Reaction of magnesium (Grignard reagent) or lithium with an alkyl halide in ether (81 (A9)).

Formation of a Gilman reagent (organocuprate) by reacting an organolithium reagent with CuI. This procedure is used in three synthetic pathways on map (25 (F17, A2), 68 (H18), 100 (B18)).

Oxiranes

Reaction of an alkene with a peroxyacid (76 (D11)).

Reactions of Functional Groups

Acetals and Ketals

Acid catalyzed reaction to carbonyl compounds via hemiacetals and hemiketals (29 (K3)).

Acyl halides

Conversion to anhydrides (52 (H15)), amides (53 (K10)), acids (54 (J15)), esters (55 (J16)).

Reaction with Gilman reagent to give ketones (68 (H18)).

Reaction with Grignards and organolithium reagents to give 3° alcohols (69 (K11, A3)).

Reduction to 1° alcohols (90 (G16)).

Reduction to aldehydes (91 (H15)).

Alcohols

Conversion to alkyl halides (20 (C15)), ethers (21 (D13)), nitriles (23 (C17)).

Dehydration to alkenes (45 (G4), 47 (C11)).

Reaction with acyl halides (55 (J16)) and anhydrides (58 (I12)) to give esters.

Oxidation to carbonyls (78 (F12)) and carboxylic acids (79 (I13)).

Reduction to alkanes (85 (B9)).

Aldehydes

Alkylation of α -carbons (27 (G7)).

Reaction with alcohols to give hemiacetals (39 (J3)) and subsequently acetals (28 (K2)).

Reaction with water to give hydrates (37 (I4)).

Reaction with Grignards and organolithium reagents to give 2° alcohols (41 (F7, A2)).

Aldol condensation to give β -hydroxy carbonyl compounds (42 (G7)).

Reaction with cyanide to give cyanohydrins (43 (H7)).

Reductive amination to amines (50 (E10)).

Reaction with nitrogen compounds to give carbonyl derivatives (51 (G11)).

Reduction to alkanes (87 (C9)).

Reduction to 1° alcohols (88 (E12)).

Wittig reaction to give alkenes (101 (F6)).

For acetaldehyde, haloform reaction to haloform and formic acid (102 (H13)).

Alkanes

Reaction with chlorine or bromine with heat or light to give alkyl halides (10 (B13)).

Alkenes

Addition of HX to give alkyl halides (30 (B11)).

Addition of alcohols to give ethers (31 (C12)).

Addition of water to give alcohols (32 (C11)).

Addition of X_2 to give vicinal halides (33 (E14)).

Ozonolysis to give carbonyl compounds (73 (B3)).

Reaction with a peroxyacid to give an oxirane (76 (D11)).

Oxidation to a 1,2-diol (77 (E11)).

Hydrogenation to give alkanes (82 (B7)).

Reaction with a diene to give a cyclohexene, Diels-Alder reaction (98 (B4)).

Reaction with a carbene or carbenoid to give a cyclopropane (99 (C5), 107 (L18)).

Alkyl halides

Substitution to give alcohols (19 (C13)), ethers (22 (C16)), nitriles (17 (B18)).

Conversion to amines (18 (C14)).

Reaction with acetylide to give larger alkynes (26 (E6)).

Elimination to give alkenes (46 (B13)).

Elimination of dihalides to give alkynes (49 (E8)).

Reaction with magnesium or lithium to give Grignards (81a (A9)) or organolithium reagents (81b (A9)).

Coupling to give alkanes (100 (B18)).

Alkynes

Alkylation via conjugate base and alkyl halide (26 (E6)).
 Addition of H_2 , X_2 (34 (F10)), and HX (35 (F10)) to give vicinal and geminal halides
 Hydration to give carbonyl compounds (36 (E6)).
 Reduction to alkanes (83 (B6)) and alkenes (84 (D7)).

Amides

Hydrolysis to carboxylic acids (67 (K11)).
 Reduction to an amine (97 (I9)).
 Dehydration to nitriles (103 (K8)).
 Hofmann rearrangement to amines (104 (L6)).

Amines

Hofmann elimination to alkene (48 (D8)).
 Reaction with acyl halides (53 (K10)) and anhydrides (56 (K10)) to give amides.
 Reaction with nitrous acid to give diazonium ion (74 (H2)).

Anhydrides

Conversion to amides (56 (K10)), carboxylic acids (57 (J12)), esters (58 (I12)).

Aromatics

Electrophilic aromatic substitution to give sulfonates (1 (D1)), nitro compounds (3 (D2)),
 halides (4 (D3)), alkyl (5 (D4)) and acyl (6 (D5)) derivatives.
 Reaction of diazonium salts to give azo compounds (7 (L2)), phenols (13 (J1)), halides
 (11 (I1), 14 (J1), 15 (K1)), hydrocarbons (16 (L1)), nitriles (12 (L4)).
 Replacement of benzylic α -hydrogens with bromine using NBS (9 (E3)).
 Oxidation of alkyl groups (except *t*-butyl) to carboxylic acids (75 (F3)).
 Reduction of aromatic nitro compounds to give aromatic amines (86 (G2)).

Carboxylic acids

Conversion to anhydrides (59 (J11)), acyl halides (60 (I16)), amides (61 (K11)), esters
 (62 (K13)).
 Reduction to alcohols (94 (H12)).
 Decarboxylation of aromatic carboxylic acids and β -keto acids (105 (L12)).

Esters

Reaction with Grignards and organolithium reagents to give 3° alcohols (70 (I17, A3)).
 Claisen condensation to give β -keto esters (72 (J17)).
 Conversion to carboxylic acids (63 (K14)), amides (64 (L11)).
 Reduction to aldehydes (95 (I13)) and alcohols (96 (H14)).
 Decarboxylation of β -keto esters to give ketones (106 (K19)).

Hemiacetals and hemiketals

Acid catalyzed reaction with alcohol to give acetals and ketals (28 (K2)).
 Acid catalyzed reaction to give carbonyl compounds (40 (J3)).

Ketones

Alkylation of α -carbons (27 (G7)).
 Reaction with alcohols to give hemiketals (39 (J3)) and subsequently ketals (28 (K2)).
 Reaction with water to give hydrates (37 (I4)).
 Reaction with Grignard and organolithium reagents to give 3° alcohols (41 (F7, A2)).
 Aldol condensation to give β -hydroxy carbonyl compounds (42 (G7)).
 Reaction with cyanide to give cyanohydrins (43 (H7)).
 Reductive amination to amines (50 (E10)).
 Reaction with nitrogen compounds to give carbonyl derivatives (51 (G11)).
 Reduction to alkanes (87 (C9)).
 Reduction to 2° alcohols (88 (E12)).
 Wittig reaction to give alkenes (101 (F6)).
 Haloform reaction to haloform and carboxylic acid (102 (H13)).

Nitriles

Hydrolysis to give a carboxylic acid (65 (J10)) or an amide (66 (K9)).

Reduction to give an amine (92 (I9)) or aldehyde (93 (I10)).

Organometallics

Grignard and organolithium reagents

Reaction with water to give an alkane (8).

Reaction with oxiranes (25 (F17, A2)), carbonyls (41 (F7, A2)), acyl halides (69 (K11, A3)), esters (70 (I17, A3)) to give alcohols.

Reaction with carbon dioxide to give carboxylic acids (44 (M7, A2)).

Reaction with nitriles (71 (J7, A3)) to give ketones.

Gilman reagents

Reaction with oxiranes to give alcohols (25 (F17, A2)).

Reaction with acyl halides to give ketones (68 (H18)).

Reaction with alkyl halides to give alkanes (100 (B18)).

Oxiranes

Hydrolysis to 1,2-diols (24 (F15)).

Reaction with a Grignard or a Gilman reagent (organocuprate) to give an alcohol (25 (F17, A2)).

Reduction to alcohols (89 (E14)).