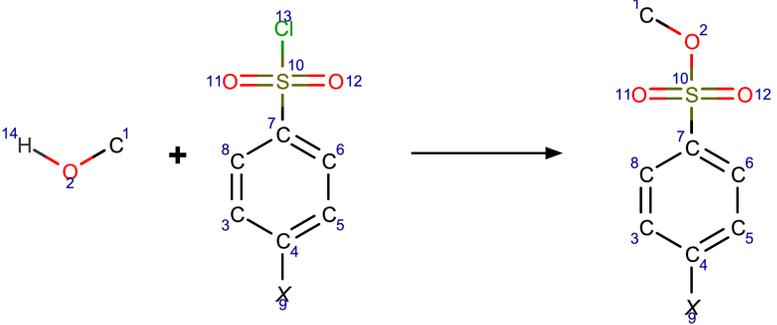
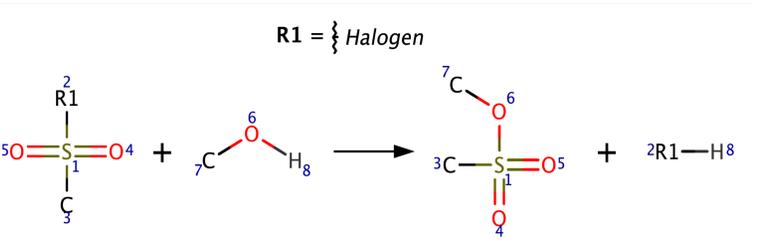
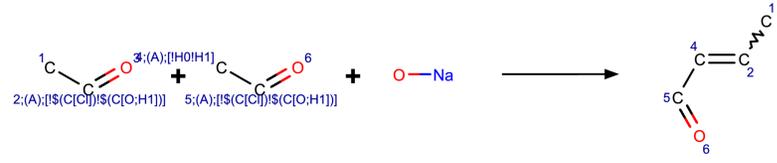
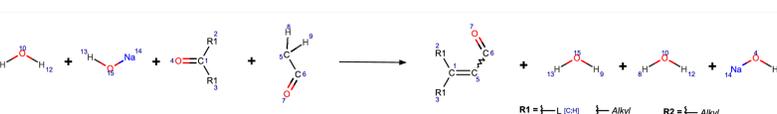
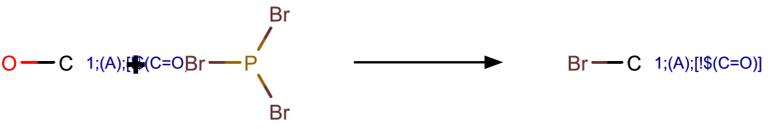


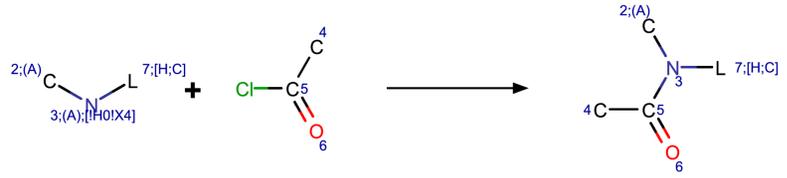
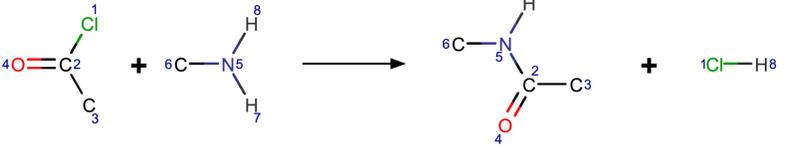
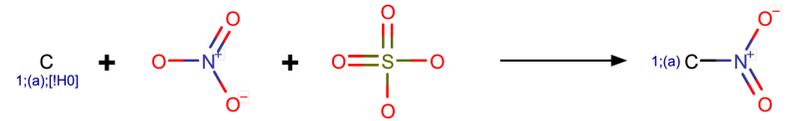
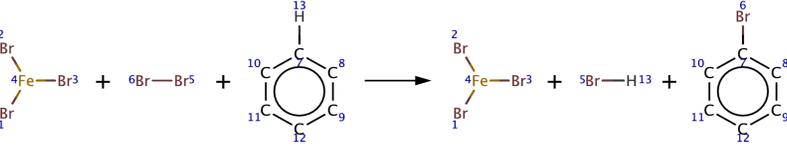
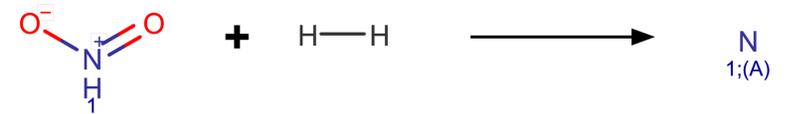
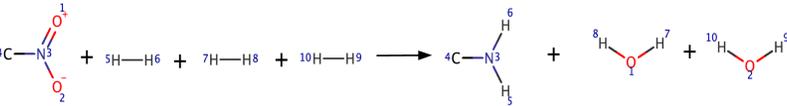
## Acknowledgements

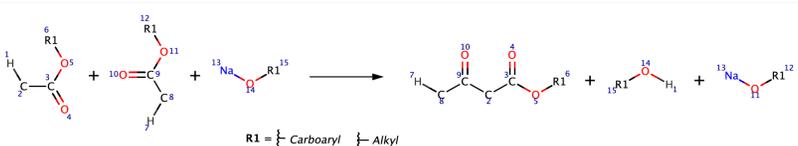
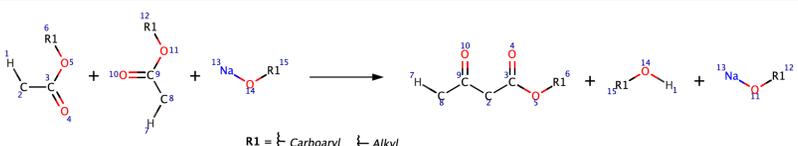
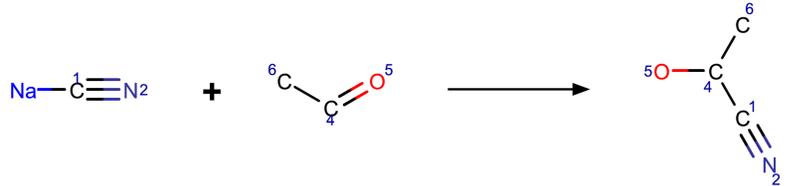
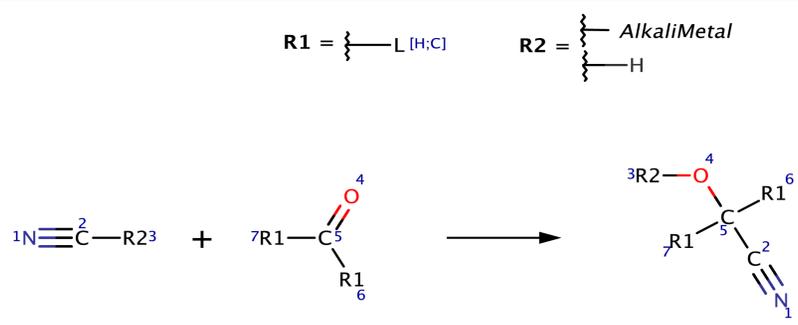
- SMARTS are taken from [A.Heifets](#) benchmark available from his [Chemical Planning](#) Web page at the Univ. of Toronto.
- RXN are implemented using [ChemAxon](#)'s graphical reaction editor Marvin Sketch that provides Atom Mapping. This work has been done at the Ryerson University by the CS students supervised by [Mikhail Soutchanski](#) (Computer Science) and [Anne Johnson](#) (Chemistry).
- For each SMARTS file matched to RXN, there is (the list of) the corresponding benchmark problem number(s). Note that multiple SMARTS files can be mapped into the same more generic RXN file, but these more specific SMART files may appear in the different benchmark problems listed in the right-most column.
- The reactions appear as images in the publicly available solutions to the [MIT 5.13 Organic Chemistry 2](#) exams.
- Annotations, references and external links can be provided in any column where there is space available.
- This documents is distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 license: <http://creativecommons.org/licenses/by-nc-sa/3.0/us/>

## SMARTS to RXN Mapping

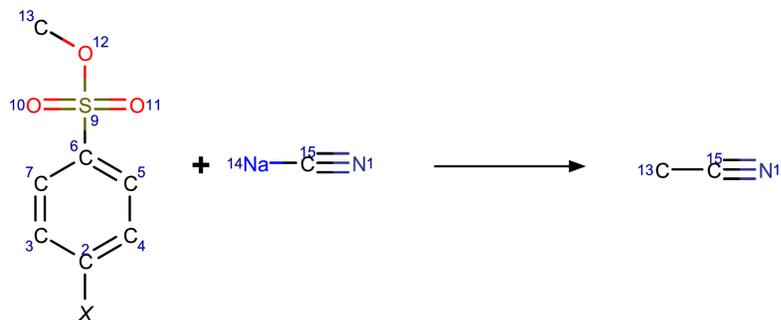
	SMARTS	RXN	PROBLEM NO.
1	Acid_chlorides_from_carboxylic_acids.smarts 	ThionylChlorideConversionOfCarboxylicAcidsToAcidChlorides.rxn <p>The 8th atom C in carboxylic acid stands for alkyl. Thionyl chloride has the chemical formula SOCl<sub>2</sub>.</p>	6, 7, 8, 11, 12, 19, 20
2	Alcohol_from_alkene.smarts $2:(A) C=C 1:(A) + O (H2:A) + O=S(=O)(O)O \longrightarrow 1:(A) C-C_2 O$ <p>Sulphuric acid H<sub>2</sub>SO<sub>4</sub> is a catalyst for this reaction. Any strong acid is fine.</p>	HydrationOfAlkenes.rxn 	20 1 <sup>st</sup> step

3	<p>Alcohol_to_4-chlorobenzene_sulfonate.smarts</p> 	<p>TosylationOfAlcohols.rxn</p>  <p><math>R1 = \{ \text{Halogen} \}</math></p> <p>4-Toluenesulfonyl chloride is an organic compound with the formula <math>CH_3C_6H_4SO_2Cl</math>. This reagent is widely used in organic synthesis. Abbreviated TsCl or TosCl, it is a derivative of toluene and contains a sulfonyl chloride (<math>-SO_2Cl</math>) functional group. See details in <a href="https://en.wikipedia.org/wiki/4-Toluenesulfonyl_chloride">https://en.wikipedia.org/wiki/4-Toluenesulfonyl_chloride</a></p>	<p>1</p> <p>In RXN, 3<sup>rd</sup> carbon can be alkyl or aryl. RXN is more generic than SMARTS with benzene ring. In R1, halogen is usually chlorine.</p>
4	<p>Aldol_condensation_with_ketone_and_base.smarts</p>  <p>The SMARTS reaction uses a specific aldehyde, formaldehyde, but not a ketone. The more generic RXN uses R1 that can be a hydrogene or an alkyl.</p> <p>“An <a href="#">aldol condensation</a> is an organic reaction in which an enol or an enolate ion reacts with a carbonyl compound to form a <math>\beta</math>-hydroxyaldehyde or <math>\beta</math>-hydroxyketone followed by a dehydration to give a conjugated enone”.</p>	<p>AldolCondensation.rxn</p>  <p>Textbooks:  F. Carey, R. Giuliano "Organic Chemistry", 8th edition, 2011. Ch 20 "Enols and Enolates", Section 20.3 "The Aldol Condensation", p.873  Clayden J., Greeves N., Warren S. Organic Chemistry, 2nd edition, 2012  Ch 26 "Reactions of enolates with carbonyl compounds: the aldol and Claisen reactions".</p>	<p>5, 14.1, 16, 17</p> <p>To make it usable, added Na-OH and H<sub>2</sub>O to the initial state.</p>
5	<p>Alkyl_bromide_with_PBr3.smarts</p> 	<p>PBr3ConversionOfAlcoholsToAlkylBromides.rxn</p>  <p>7<sup>th</sup> carbon can be any alkyl since any primary alcohol can be a reactant.</p>	<p>3, 6, 7, 11, 14, 15, 20</p>

6	<p>Amine_addition_to_acid_chloride.smarts</p>  <p>This is a nucleophilic addition/elimination reaction between acyl (acid) chloride and primary or secondary amines to form amides. RXN is designed for primary amines, but in SMARTS amine can be primary or secondary.</p>	<p>AmideSynthesisFromAcidChloride.rxn (7, 11)</p>  <p><a href="https://en.wikipedia.org/wiki/Amine#Alkylation.2C_acylation.2C_and_sulfonation">https://en.wikipedia.org/wiki/Amine#Alkylation.2C_acylation.2C_and_sulfonation</a> The 6<sup>th</sup> carbon can be alkyl or aryl, see reaction image at <a href="https://upload.wikimedia.org/wikipedia/commons/1/1a/Amide_formation_from_amine.gif">https://upload.wikimedia.org/wikipedia/commons/1/1a/Amide_formation_from_amine.gif</a></p>	7, 11
7	<p>Aromatic_nitration.smarts</p> 	<p>AromaticNitration.rxn</p>  <p>The 2<sup>nd</sup> carbon has an aromatic bond with the 3<sup>rd</sup> carbon to represent an aryl. This aromatic bond is preserved by this reaction, but shown for clarity.</p>	2, 4, 11
8	<p>Bromination_of_benzene.smarts</p>  <p><a href="https://www.khanacademy.org/science/organic-chemistry/aromatic-compounds/reactions-benzene/v/bromination-of-benzene">https://www.khanacademy.org/science/organic-chemistry/aromatic-compounds/reactions-benzene/v/bromination-of-benzene</a></p> <p><a href="https://en.wikipedia.org/wiki/Electrophilic_halogenation">https://en.wikipedia.org/wiki/Electrophilic_halogenation</a></p>	<p>AromaticBromination.rxn</p>  <p>This can be generalized to halogenation of benzene. <a href="http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch23/ch23-2-1.html">http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch23/ch23-2-1.html</a></p>	11, 12
9	<p>Catalytic_hydrogenation_of_nitro_group.smarts</p> 	<p>CatalyticHydrogenationOfNitroGroup.rxn</p>  <p>Common catalysts: Pt or Pd. The 4<sup>th</sup> carbon is aryl or alkyl.</p>	2, 4, 11

10	<p>Claisen_condensation_with_ethyl_esters.smarts</p>  <p><a href="https://en.wikipedia.org/wiki/Claisen_condensation">https://en.wikipedia.org/wiki/Claisen_condensation</a></p> <p>Clayden et al, Organic Chemistry, 2<sup>nd</sup> Ed, pages 640-647.</p>	<p>ClaisenCondensation.rxn</p>  <p>R1 = <math>\begin{cases} \text{Carboxyl} \\ \text{Alkyl} \end{cases}</math></p> <p>F. Carey, R.Giuliano, Organic Chemistry, Section 20.5, p.882</p>	13 Carbons 6 <sup>th</sup> and 12 <sup>th</sup> are alkyls or aryls.
11	<p>Claisen_condensation_with_methyl_esters.smarts</p>  <p><a href="https://upload.wikimedia.org/wikipedia/commons/thumb/0/01/Claisen_condensation_overall.png/1050px-Claisen_condensation_overall.png">https://upload.wikimedia.org/wikipedia/commons/thumb/0/01/Claisen_condensation_overall.png/1050px-Claisen_condensation_overall.png</a></p> <p>Animation of reaction mechanism is available at <a href="https://upload.wikimedia.org/wikipedia/commons/9/92/C-K_startAnimGif_2.gif">https://upload.wikimedia.org/wikipedia/commons/9/92/C-K_startAnimGif_2.gif</a></p>	<p>ClaisenCondensation.rxn</p>  <p>R1 = <math>\begin{cases} \text{Carboxyl} \\ \text{Alkyl} \end{cases}</math></p> <p>The <b>Claisen condensation</b> is a <u>carbon-carbon bond forming reaction</u> that occurs between two <u>esters</u> or one ester and another <u>carbonyl</u> compound in the presence of a <u>strong base</u>, resulting in a <math>\beta</math>-keto ester or a <math>\beta</math>-diketone. At least one of the <u>reagents</u> must be <u>enolizable</u> (have an <math>\alpha</math>-<u>proton</u> and be able to undergo <u>deprotonation</u> to form the <u>enolate anion</u>).</p>	9 Carbons 6 <sup>th</sup> and 12 <sup>th</sup> are alkyls or aryls.
12	<p>Cyanide_addition_to_carbonyl.smarts</p>  <p><a href="https://en.wikipedia.org/wiki/Cyanohydrin_reaction">https://en.wikipedia.org/wiki/Cyanohydrin_reaction</a></p> <p>A <b>cyanohydrin reaction</b> is a reaction by an <u>aldehyde</u> or <u>ketone</u> with a <u>cyanide anion</u> or a <u>nitrile</u> to form <u>cyanohydrin</u></p> <p>See mechanism and animation of cyanide addition to the carbonyl group at <a href="http://www.chemtube3d.com/Nucleophilic%20substitution%20at%20the%20carbonyl%20group%20-%20Cyanohydrin%20formation.html">http://www.chemtube3d.com/Nucleophilic%20substitution%20at%20the%20carbonyl%20group%20-%20Cyanohydrin%20formation.html</a></p>	<p>CyanohydrinFormation.rxn</p>  <p>R1 = <math>\begin{cases} \text{L [H;C]} \end{cases}</math>      R2 = <math>\begin{cases} \text{AlkaliMetal} \\ \text{H} \end{cases}</math></p> <p>F.Carey and R.Giuliano Organic Chemistry, Section 17.7 "Cyanohydrin formation", page 739-741.</p> <p>J.Clayden et al Organic Chemistry, Ch 6 "Nucleophilic addition to the carbonyl group", section "Attack of cyanide on aldehydes and ketones", pages 125-128.</p>	19

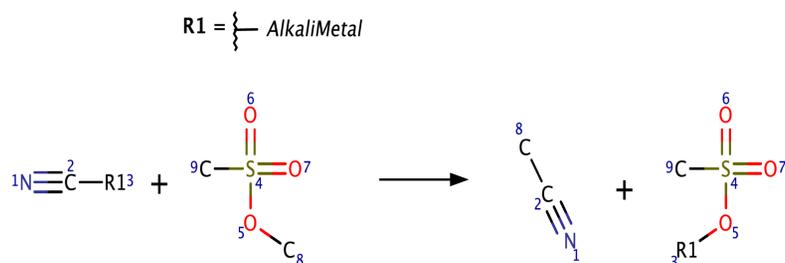
13 Cyanide\_displacement\_of\_halo-benzenesulfonates.smarts



CIC6H4SO2Cl is 4-Chlorobenzenesulfonyl chloride, it is a starting material in Problem 1. It is a [sulfonyl halide](#). After reacting with alcohol it produces the molecule shown on the left-hand-side. Do **not** confuse this reagent with tosyl chloride (TsCl).

Toluene (methylbenzene) consists of a phenyl group attached to a methyl group. A tosyl group (abbreviated Ts or Tos) is CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>. This group is usually derived from the compound tosyl chloride, CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>Cl (abbreviated TsCl).

CyanideDisplacementOfTosylGroupSN2.rxn



Sulfonyl groups have general formula R-S(=O)<sub>2</sub>-R', where there are 2 double bonds between the sulfur and oxygen. A sulfonic acid refers to a compound with the general formula R-S(=O)<sub>2</sub>-OH, where R is an organic alkyl or aryl group and the S(=O)<sub>2</sub>-OH group a sulfonyl hydroxide. Sulfonic acids can be converted to esters. This class of organic compounds has the general formula R-SO<sub>2</sub>-OR'. Salts or esters of sulfonic acids are called sulfonates.

[https://en.wikipedia.org/wiki/Sulfonic\\_acid](https://en.wikipedia.org/wiki/Sulfonic_acid)

1  
This is the 2<sup>nd</sup> reaction in Problem 1.

The 8<sup>th</sup> carbon stands for R' group in the sulfonic ester. The 9<sup>th</sup> carbon represents the key carbon atom in chlorobenzene

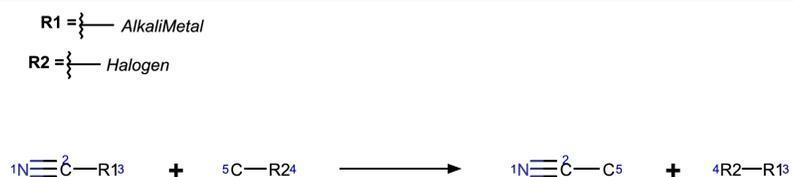
This reaction forms the C-C bond between 8<sup>th</sup> and 2<sup>nd</sup> carbons, which is the main product.

14 Cyanide\_formation\_from\_alkyl\_bromide.smarts

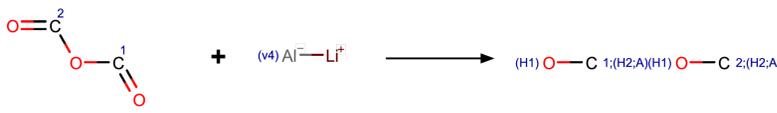
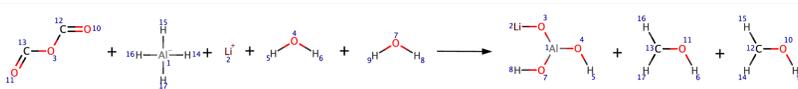
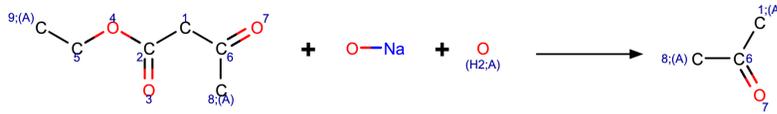
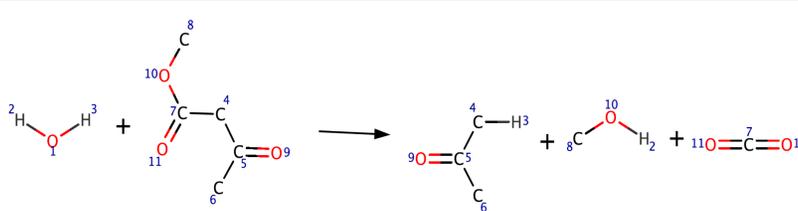
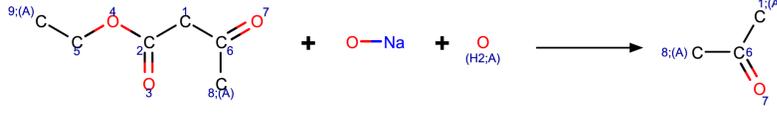
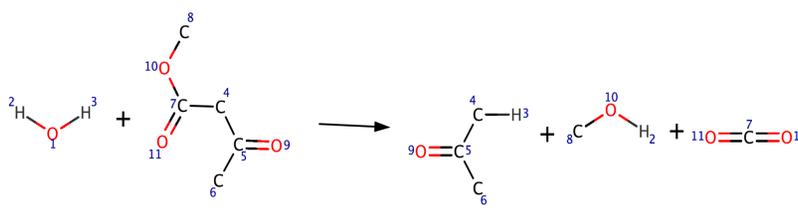
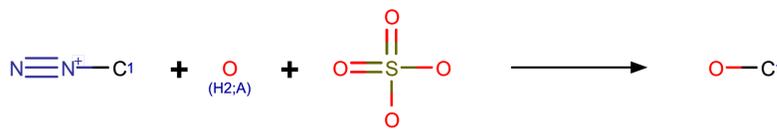


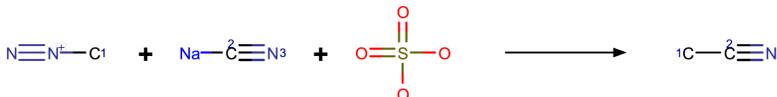
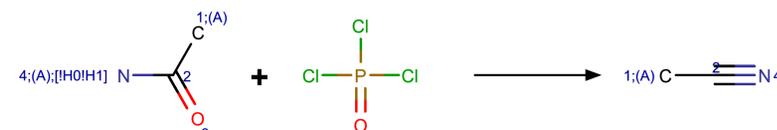
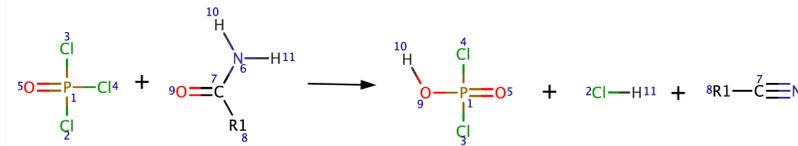
Usually, the 5<sup>th</sup> carbon in RXN is primary or secondary alkyl, but it can be also phenyl bonded with CH<sub>2</sub>. DMSO (dimethyl sulfoxide) is typical solvent. See F.Carey& R. Giuliano, Section 18.12, 8<sup>th</sup> Ed., p793. See also their Table 19.6 "Preparation of nitriles" (p.849), Table 8.1 "Reactions of Alkyl halides" (p.325).

CyanideDisplacementOfBromideSN2.rxn

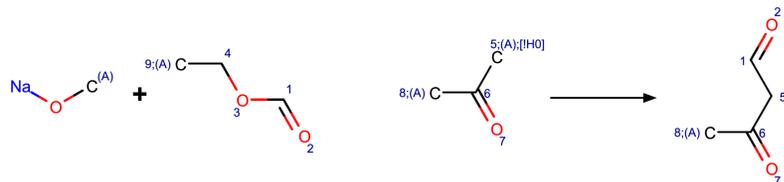


7, 11, 15

15	<p>Cyclic_anhydride_reduction.smarts</p> 	<p>LAHReductionOfAnhydrides.rxn</p>  <p>This reaction never happens in one step. In reality, it is a sequence of two reactions. Water is added only when the 1<sup>st</sup> step has been completed.</p> <p>Lithium aluminium hydride, commonly abbreviated to LAH, is an inorganic compound with the chemical formula LiAlH<sub>4</sub>. It is used as a reducing agent in organic synthesis, especially for the reduction of esters, carboxylic acids, and amides.</p> <p><a href="https://en.wikipedia.org/wiki/Lithium_aluminium_hydride">https://en.wikipedia.org/wiki/Lithium_aluminium_hydride</a></p>	10, 18
16	<p>Decarboxylation_of_beta_keto_esters.smarts</p> 	<p>DecarboxylationOfBetaKetoEsters.rxn</p> 	13
17	<p>Decarboxylation_of_beta_keto_ethyl_esters.smart</p> 	<p>DecarboxylationOfBetaKetoEsters .rxn</p> 	16
18	<p>Dediazoniatio_n_to_hydroxy.smarts</p>  <p><u>Diazo</u> refers to a type of organic compound called diazo compound that has two linked nitrogen atoms (azo) as a terminal functional group. The general formula is R<sub>2</sub>C--N<sub>2</sub>.</p>	<p>HydroxylSubstitutionOfDiazoniumIonSN1.rxn</p>  <p>“Reduction of a diazonium group (dediazotiation) provides an indirect method for the removal of an amino group from an aromatic ring”: quoted from M.Smith “March’s Advanced Organic Chemistry”, 7<sup>th</sup> Ed, 2013, section 19-69, p.1549.</p>	2

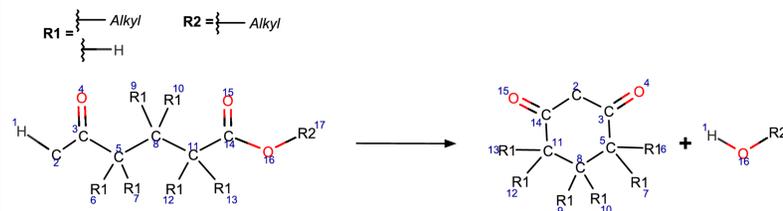
19	<p>Dediazotiation_to_nitrile.smarts</p>  <p>A <a href="#">nitrile</a> is any organic compound that has a <math>-C\equiv N</math> functional group. The prefix cyano- is used interchangeably with the term nitrile in industry.</p>	<p>NitrileSubstitutionOfDiazoniumIonSN1.rxn</p> $R_1 = \begin{cases} \text{AlkaliMetal} \\ \text{Cu} \end{cases}$ $2N\equiv\overset{1}{N}-C^3 + 4N\equiv\overset{5}{C}-R_{16} \longrightarrow R_6 + 1N\equiv N^2 + 4N\equiv\overset{5}{C}-C^3$ <p>3<sup>rd</sup> Carbon can be alkyl or aryl. This is one of Sandmeyer reactions.</p>	11
20	<p>Dehydration_of_amide_to_nitrile.smarts</p>  <p><a href="#">Carboxamides</a> (or amino carbonyls) are functional groups with the general structure <math>R-CO-NR'R''</math> with R, R', and R'' as organic substituents, or hydrogen.</p>	<p>DehydrationOfAmides.rxn</p> $R_1 = \text{Alkyl}$  <p><a href="#">Amide to nitrile mechanism</a> using POCl3 - <a href="#">phosphoryl chloride</a>.</p>	8
21	<p>Diazotization.smarts</p>  <p><a href="#">Diazonium compounds</a> or diazonium salts are a group of organic compounds sharing a common functional group <math>R-N_2^+X^-</math> where R can be any organic group, such as an alkyl or an aryl, and X is an inorganic or organic anion, such as a halogen.</p>	<p>Diazotization.rxn</p>  <p>Diazotisation is the nitrosation of primary aromatic <a href="#">amines</a> with <a href="#">nitrous acid</a> generated in situ from <a href="#">sodium nitrite</a> and a strong acid, e.g., <a href="#">hydrochloric acid</a>. The process of forming diazonium compounds is called "diazotation", "diazonation", or "diazotization".</p>	2, 4, 11

## 22 Dieckmann\_condensation\_with\_ketone.smarts



The [Dieckmann condensation](#) is the [intramolecular](#) chemical reaction of [diesters](#) with base to give [β-ketoesters](#). F.Carey & R.Giuliano "Organic Chemistry", 8<sup>th</sup> Ed., 2011, Section 20.6 "The Dieckman Cyclization" (p.884), and Section 20.7 "Mixed Claisen Condensations" (p. 885). See also Table 20.3 "Carbonyl Condensation", pages 914-915. SMARTS reaction is actually mixed Claisen condensation

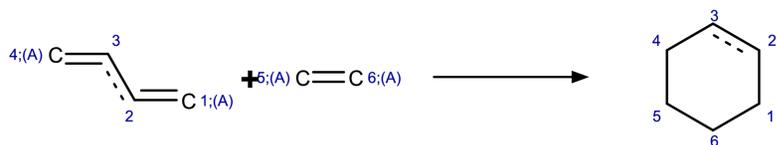
## DieckmannCyclization.rxn



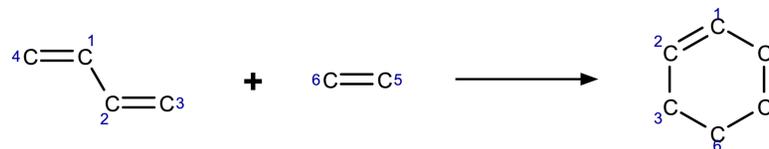
We use a more specific case of the Dieckmann-type cyclization for a six-membered ring to match the example in Problem 16. This is to cover the cases where the carbon chain connecting the nucleophilic moiety and the electrophilic ester is or is not substituted. In MIT solutions, aldol condensation on the left is the 1<sup>st</sup> step in 16.

16  
The MIT solution of this problem implies 3<sup>rd</sup> step is a ring-forming [Dieckmann condensation](#), not mixed Claisen reaction shown in SMARTS. There are errors in this MIT solution. We implement left pathway only.

## 23 Diels-Alder\_cycloaddition\_0.smarts



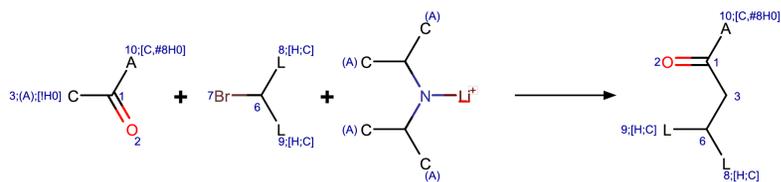
## DielsAlderCycloaddition.rxn



The [Diels-Alder](#) reaction is an [organic chemical reaction](#) (specifically, a [4+2] [cycloaddition](#)) between a conjugated [diene](#) and a substituted [alkene](#), commonly termed the [dienophile](#), to form a [cyclohexene](#) system.

10, 12, 18

## 24 Enolate\_SN2\_attack\_on\_alkyl\_bromide.smarts

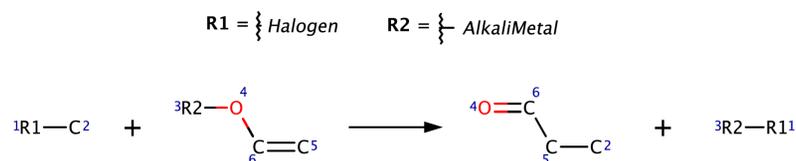


The carbonyl in SMARTS has [keto](#) form, but RXN uses [enol](#) form of this molecule: see [keto-enol tautomerism](#). SMARTS reaction merges 2 different steps: ketone and LDA followed by enol SN2 attack on alkyl halide.. However, the MIT solution to Problem 14 shows both steps separately in sequence. Therefore, RXN implements each step individually.

Solution to Problem 13 includes both `Enolate_SN2_attack_on_alkyl_bromide.smarts` followed by the ring forming `intramolecular_Enolate_SN2_attack_on_alkyl_bromide.smart`

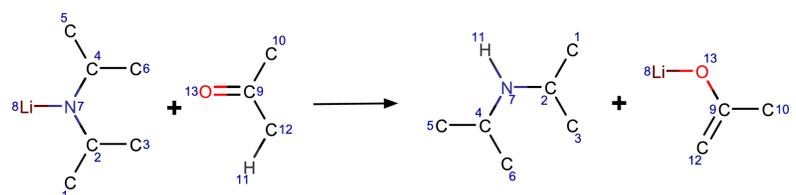
Lithium diisopropylamide (commonly abbreviated LDA) is a chemical compound with the molecular formula  $[(CH_3)_2CH]_2NLi$ . It is used as a strong base and has been widely accepted due to its good solubility. [https://en.wikipedia.org/wiki/Lithium\\_diisopropylamide](https://en.wikipedia.org/wiki/Lithium_diisopropylamide)

## EnolateAttackOnAlkylHalideSN2.rxn (14)

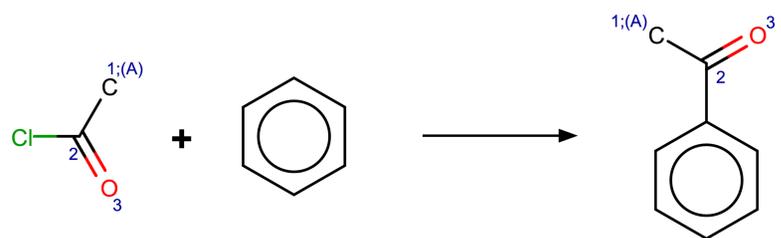


The 2<sup>nd</sup> carbon is primary or secondary alkyl. See [Alkylation of Enolates](#) in F.Carey and R.Giuliano, 8<sup>th</sup> Ed, 20.9, p.887

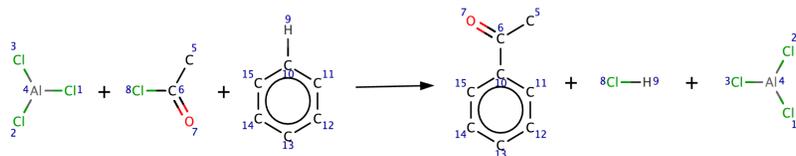
## EnolateFormation.rxn (14)



## 25 Friedel-Crafts\_acylation.smarts

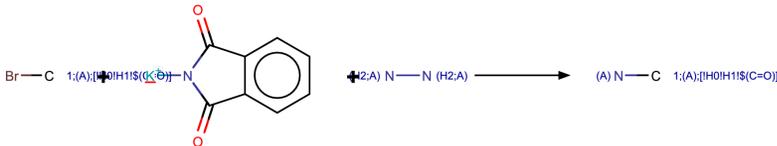
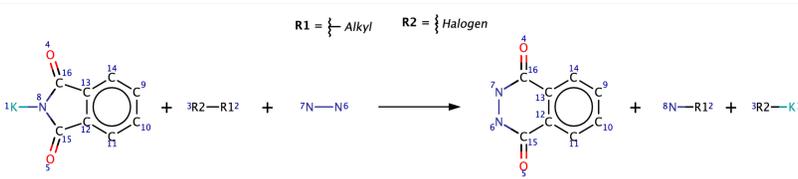
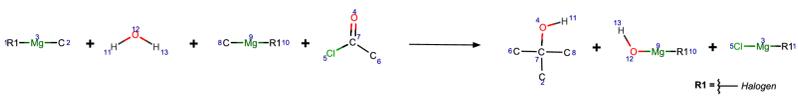
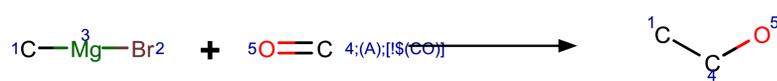
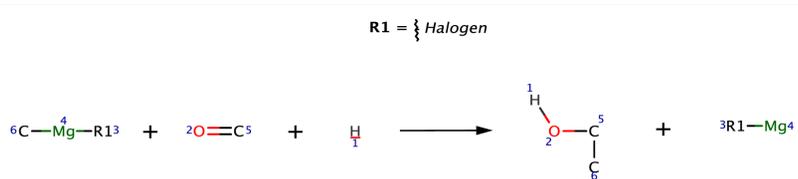


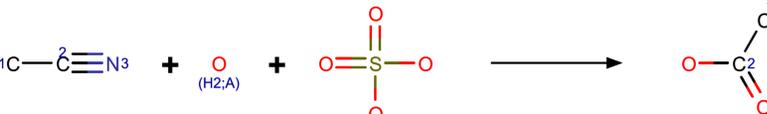
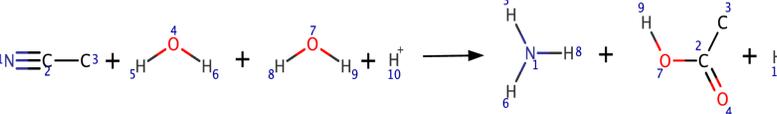
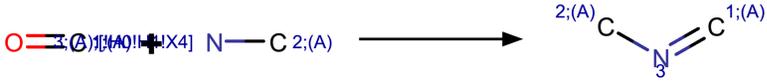
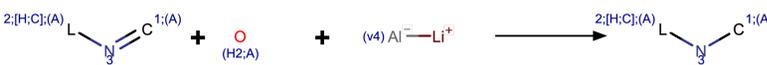
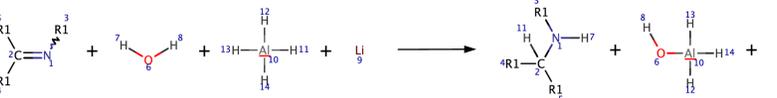
## FriedelCraftsAcylation.rxn



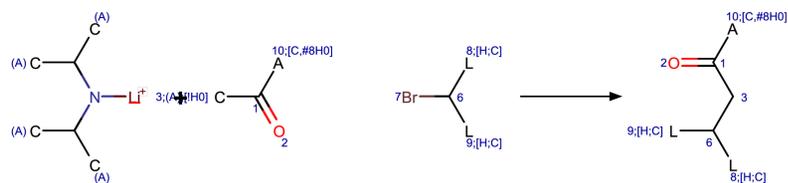
13, 14

19

<p>26 Gabriel_synthesis_from_alkyl_bromide.smarts</p>  <p>The <a href="#">Gabriel synthesis</a> is a chemical reaction that transforms primary <a href="#">alkyl halides</a> into primary <a href="#">amines</a>. Traditionally, the reaction uses <a href="#">potassium phthalimide</a>.</p>	<p>GabrielSynthesis.rxn</p>  <p>This reaction is using <a href="#">hydrazine</a> H<sub>2</sub>NNH<sub>2</sub>. See F.Carey &amp; R.Giuliano Organic Chemistry, 8<sup>th</sup> Ed, 2011, Section 21.8, "Gabriel synthesis of primary alkylamines", pages 946-947.</p>	<p>3</p>
<p>27 Grignard_addition_to_acid_chloride.smarts</p>  <p>This reaction happens in 2 steps. Water added only when the 1<sup>st</sup> step has completed. An <a href="#">acyl chloride</a> (or acid chloride) is a compound with the <a href="#">functional group -COCl</a>.</p>	<p>GrignardAdditionToAcidChlorides.rxn</p> 	<p>12, 20</p>
<p>28 Grignard_addition_to_carbonyl.smarts</p>  <p>The <a href="#">Grignard reaction</a> is an <a href="#">organometallic chemical reaction</a> in which <a href="#">alkyl</a>, <a href="#">vinyl</a>, or <a href="#">aryl-magnesium halides</a> (Grignard reagents) add to a <a href="#">carbonyl</a> group in an aldehyde or ketone. In RXN, aldehyde and ketone are represented implicitly as carbonyl C=O. The product can be primary, secondary or tertiary alcohol.</p>	<p>GrignardReaction.rxn</p>  <p>F.Carey and R.Giuliano, 8<sup>th</sup> Ed, 2011, Section 14.6 "Synthesis of alcohols using Grignard reagents", p. 614-615, and Table 14.2 "Reactions of Grignard reagents with aldehyde and ketones". J.Clayden et al, Organic Chemistry, 2<sup>nd</sup> ed, 2012, Chapter 9 "Using organometallic reagents to make C-C bonds", Section "Secondary and tertiary alcohols: which organometallic, which aldehyde, which ketone", p.192-193.</p>	<p>6, 12, 15, 20 The 1<sup>st</sup> hydrogen atom is from water added in the 2<sup>nd</sup> step of this two step reaction.</p>

29	<p>Grignard_reagent_formation.smarts</p>  <p>F.Carey &amp; R.Giuliano, 8<sup>th</sup> Ed, Section 14.4 "Preparation of Organomagnesium Compounds: Grignard Reagents", p610. J.Clayden et al, Organic Chemistry, 2<sup>nd</sup> ed, 2012, Chapter 9 "Using organometallic reagents to make C-C bonds",</p>	<p>GrignardReagentFormation.rxn</p>  <p><math>R2 = \{ \text{Halogen} \}</math></p> <p>see Section "How to make Grignard reagents", p.184-185.</p>	6, 12, 15, 20
30	<p>Hydrolysis_of_nitriles.smarts</p> 	<p>HydrolysisOfNitriles.rxn</p> 	11
31	<p>Imine_formation.smarts</p> 	<p>ImineFormation.rxn</p> <p><math>R1 = \{ \text{---L [H;C]} \}</math></p> 	3, 7, 15
32	<p>Imine_reduction_to_amine.smarts</p> 	<p>ImineReductionToAmine.rxn</p>  <p><math>R1 = \{ \text{---L [H;C]} \}</math></p>	3, 7, 15

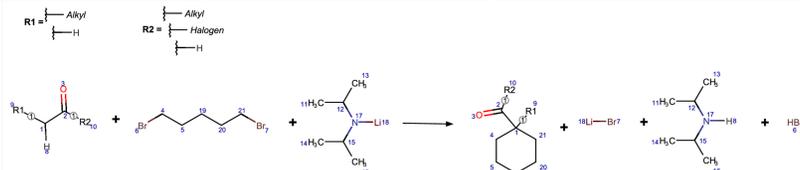
33 intramolecular\_Enolate\_SN2\_attack\_on\_alkyl\_bromide.smarts



This SMARTS does not form a ring, but the MIT solution to Problem 13 includes enolate alpha alkylation with cyclization reaction on the 3rd step that should form a 6 member ring. In total, solution to p13 is composed from these 4 SMARTS reactions:

Claisen\_condensation\_with\_ethyl\_esters.smarts #10  
 Enolate\_SN2\_attack\_on\_alkyl\_bromide.smarts #24  
 intramolecular\_Enolate\_SN2\_attack\_on\_alkyl\_bromide #33  
 Decarboxylation\_of\_beta\_keto\_esters.smarts #16  
 [On the right, you see numbers in the enumeration of SMARTS reactions in this Matching document.]

enolateC-alkylationToForm6ring.rxn

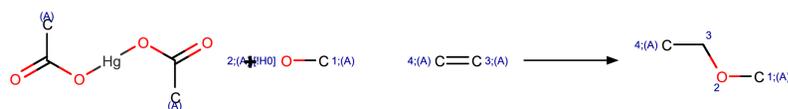


As we explained in Item 24 above, the SMARTS reaction in #24 is replaced with EnolateFormation.rxn followed by EnolateAttackOnAlkylHalideSN2.rxn. In our implementation here, we merge these 2 reactions together with enolate alpha alkylation with cyclization reaction to obtain the single enolateC-alkylationToForm6ring.rxn

Therefore, our solution to p13 consists of 3 steps only: #10, #33, #16. However, note that in the MIT solution, there are 4 steps.

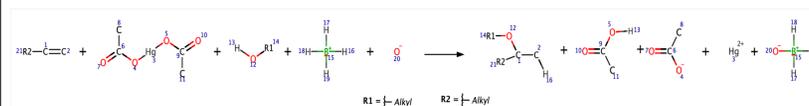
13

34 intramolecular\_Oxymercuration-reduction.smarts

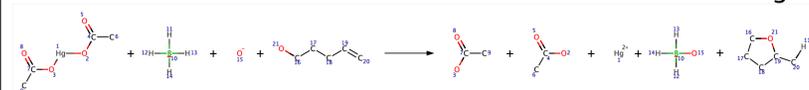


SMARTS is *not* intramolecular version, but inter-molecular version with primary alcohol. An oxymercuration-reduction reaction consists of two different steps: [oxymercuration](#) followed by [reductive demercuration](#). See details at F.Carey & R. Giuliano, 8<sup>th</sup> Ed, 2011, Ch6, page 275

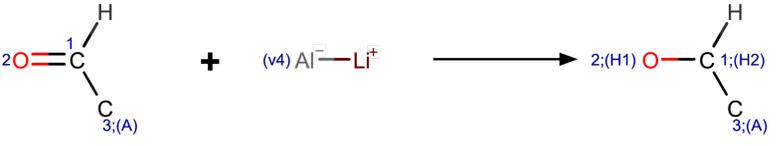
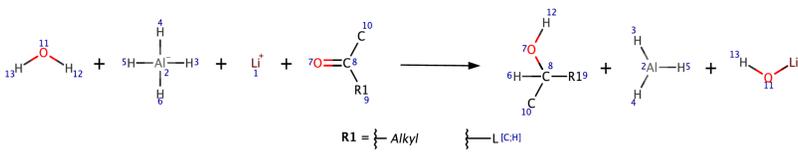
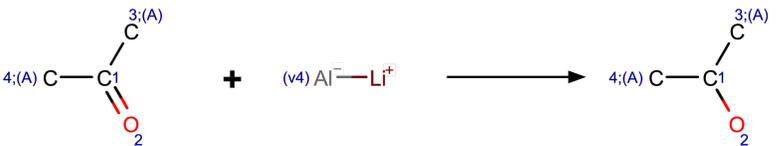
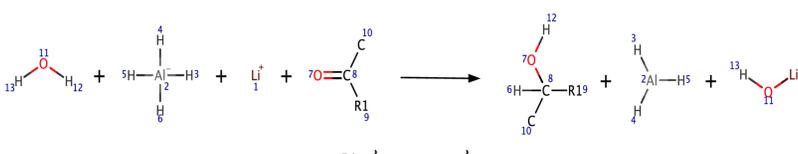
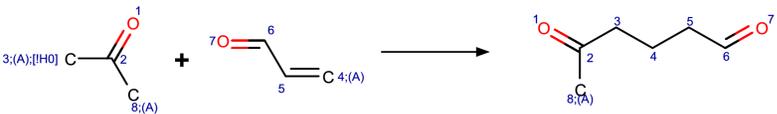
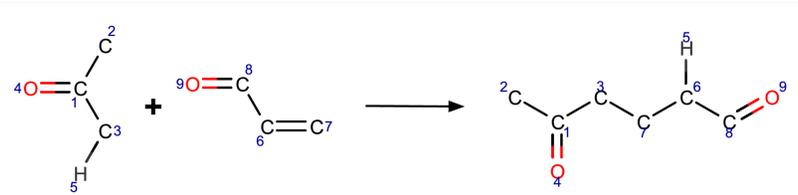
IntramolecularOxymercurationReduction.rxn



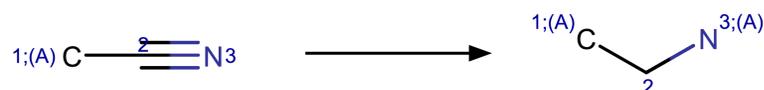
The above image corresponds to SMARTS file. The image below is a correct intramolecular RXN for a 5-membered ring.



10  
 The intramolecular oxymercuration on reduction is the last step in MIT's solution to Problem 10.

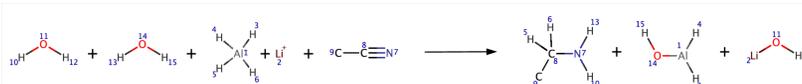
35	<p>LiAlH<sub>4</sub>_reduction_of_aldehydes.smarts</p>  <p>See details in F.Carey &amp; R.Giuliano, Section 15.2, p.648-654 ("Preparation of alcohols by reduction of aldehydes and ketones"). Water is used only in the 2nd operation. The reduction is carried out in diethyl ether solvent. When it is completed, then water is added to the reaction mixture. In the 1<sup>st</sup> step, <a href="#">lithium aluminum hydride</a> (LiAlH<sub>4</sub>) and <a href="#">sodium borohydride</a> (NaBH<sub>4</sub>) are the most common reagents.</p>	<p>LAHReductionOfAldehydesAndKetones.rxn</p>  <p>Despite its name, this RXN covers both <a href="#">aldehyde</a> and <a href="#">ketone</a> reduction (SMARTS #35 and #36) since R1 (9<sup>th</sup> atom) can be either a hydrogen or an alkyl. Aldehydes yield <a href="#">primary alcohol</a>. Ketones yield <a href="#">secondary alcohols</a>. In chemical reality, this is combination of two separate reaction: the reduction and hydrolysis operations. A balanced equation: 4R<sub>2</sub>C=O+LiAlH<sub>4</sub> + H<sub>2</sub>O → 4R<sub>2</sub>CHOH + Al(OH)<sub>4</sub>. (see p. 654)</p>	18
36	<p>LiAlH<sub>4</sub>_reduction_of_ketone.smarts</p> 	<p>LAHReductionOfAldehydesAndKetones.rxn</p> 	14
37	<p>Michael_addition_with_ketone.smarts</p>  <p>The Michael reaction or <a href="#">Michael addition</a> is the nucleophilic addition of a Michael donor - generally a <a href="#">carbanion</a> (a <a href="#">nucleophile</a>), to a Michael donor - generally a conjugated system with an electron withdrawing group such as cyano, keto or ester (an <a href="#">electrophile</a>), e.g., an <a href="#">α,β-unsaturated carbonyl compound</a> (a class of carbonyl compounds with the general structure (O=CR')-C<sup>α</sup>=C<sup>β</sup>-R''). It belongs to the larger class of <a href="#">conjugate additions</a>. This is a useful method for formation of new carbon-carbon bonds.</p>	<p>MichaelAdditionToUnsaturatedKetones.rxn</p>  <p>F. Carey and R. Sundberg "Advanced Organic Chemistry", Part B "Reactions and Synthesis", 5<sup>th</sup> Ed, 2007, Section 2.6.1 "Conjugate Addition of Enolates" (pages 183-189). F. Carey and R. Giuliano, Organic Chemistry, 8<sup>th</sup> Ed, Section 20.19 "Addition of Carbanions to α,β-unsaturated ketones", pages 910-911.</p>	16, 17

## 38 Nitrile\_reduction\_to\_amine.smarts

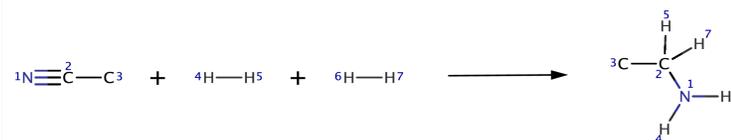


The top RXN is a sequence of 2 reactions; water is added when the 1<sup>st</sup> reaction completed. The bottom RXN requires a catalyst from Group 10 metals such as Pt or Pd. See [catalytic hydrogenation of nitriles](#) in Wikipedia for details.

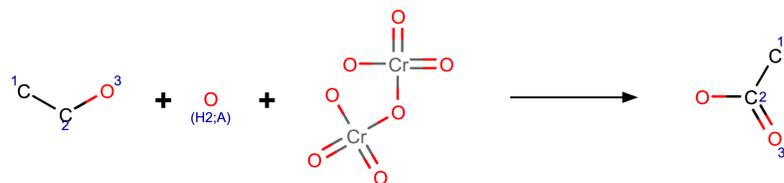
## LAHReductionOfNitriles.rxn (7, 11, 15, 19)



## CatalyticHydrogenationOfNitriles.rxn (1)

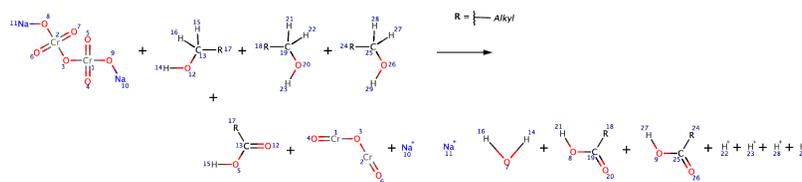
1, 7, 11,  
15, 19

## 39 Oxidation\_of\_alcohols\_to\_carboxylic\_acids.sma(9)

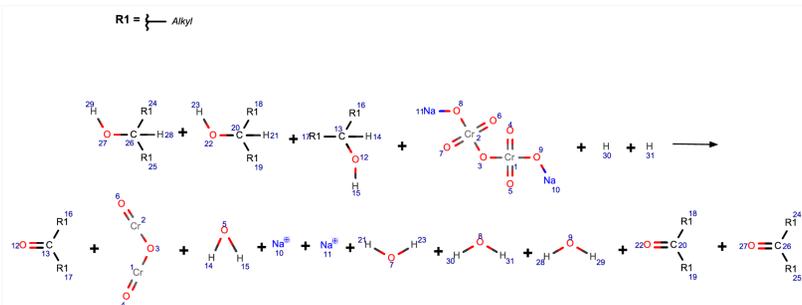


SMARTS uses the [chromic acid](#), but the MIT solution mention explicitly [sodium dichromate](#) reagent. In SMARTS, it is not clear whether an alcohol reagent is [primary](#) or secondary.  
 $3R_2CHOH + NaCr_2O_7 + 2H^+ \rightarrow 3R_2C=O + Cr_2O_3 + 2H_2O + 2Na^+$   
 $3RCH_2OH + 2NaCr_2O_7 + 4H^+ \rightarrow 3RC=OOH + Cr_2O_3 + 5H_2O + 4Na^+$

## SodiumDichromateOxidationOfPrimaryAlcohol.rxn

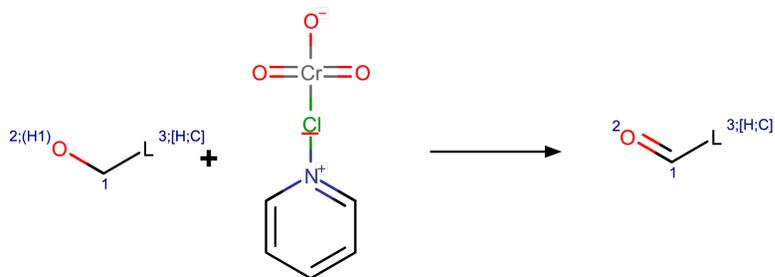


## SodiumDichromateOxidationOfSecondaryAlcohol.rxn



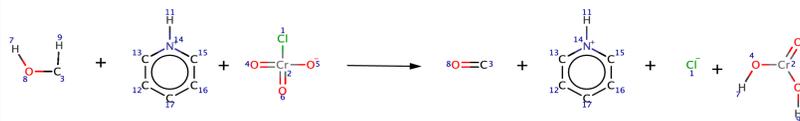
8, 9, 12  
MIT solutions use primary alcohol, so only the top RXN is useful. The bottom RXN is for secondary alcohols. This reaction is rarely used now due to toxicity of Cr. We focus on the major products, but ignore the ions going in solution

## 40 Oxidation\_of\_alcohols\_with\_PCC.smarts

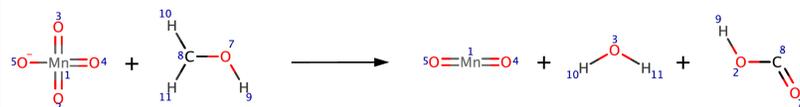


This SMARTS reaction is used in solutions to the MIT problems (3,5,7,9,14,15,17,19). However, in the Problems 7 and 19 actually another reagent  $\text{KMnO}_4$  is shown explicitly. For this reason, there are 2 RXN reactions matching this SMARTS reaction. PCC means [pyridinium chlorochromate](#). It is a yellow-orange salt with the formula  $[\text{C}_5\text{H}_5\text{NH}][\text{CrO}_3\text{Cl}]$ . PCC is used primarily for oxidation of alcohols to form carbonyls. The C-C bonds in [pyridinium](#) are aromatic.

## OxidationOfAlcoholsWithPCC.rxn (3,5,7,14,15,17)



## OxidationOfPrimaryAlcoholWithPotassiumPermanganate.rxn (7, 19)

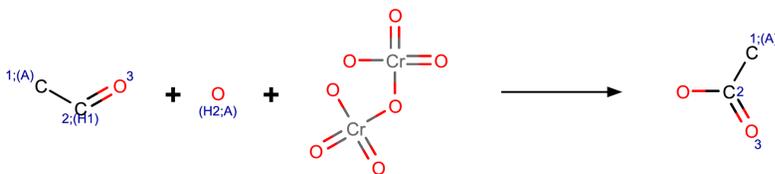


[Potassium permanganate](#)  $\text{KMnO}_4$  is a [salt](#) consisting of  $\text{K}^+$  and  $\text{MnO}_4^-$  ions. Since  $\text{KMnO}_4$  is a strong oxidizing reagent, it is difficult to stop this reaction; usually, it proceeds to carboxylic acids. In RXN, for simplicity, potassium ion K is not shown explicitly.

3, 5, 7, 14, 15, 17, 19

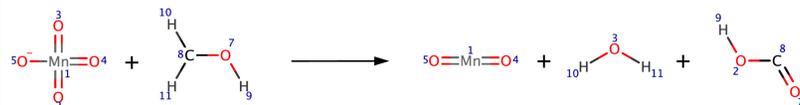
Since the MIT solutions to problems 7 and 19 use  $\text{KMnO}_4$  the RXN solution uses [oxidationOfPrimaryAlcoholWithPotassiumPermanganate](#) when needed. If the MIT solution is using PCC too, then this is replicated by [oxidationOfAlcoholsWithPCC.rxn](#)

## 41 Oxidation\_of\_aldehydes\_to\_carboxylic\_acids.smarts (7,8,12,19)

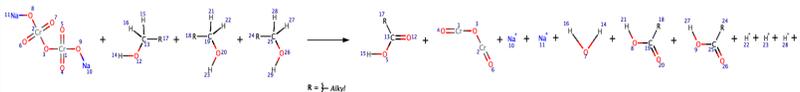


This SMARTS reaction is used in solutions to the MIT problems (7,8,12,19). In the MIT solutions to 7, 19, we see that  $\text{KMnO}_4$  is supposed to be used instead, while in 8, 12 sodium dichromate was intended. For this reason, this SMARTS file is matched to 2 different RXN files.

## OxidationOfPrimaryAlcoholWithPotassiumPermanganate.rxn (7,19)

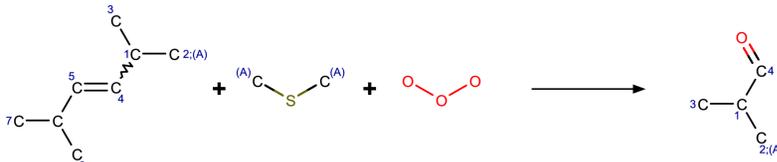
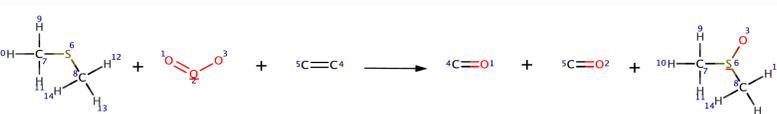
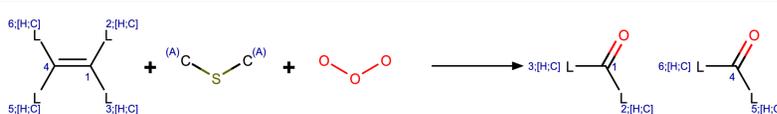
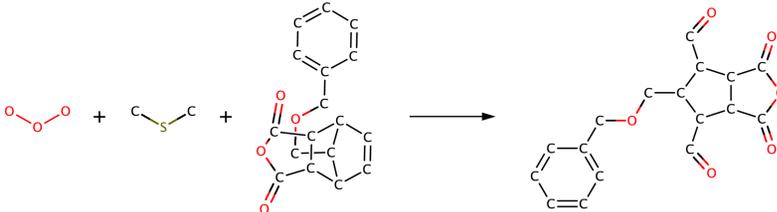
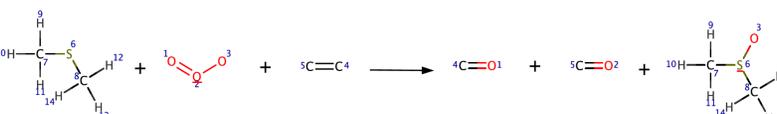
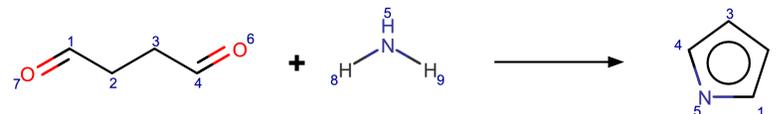
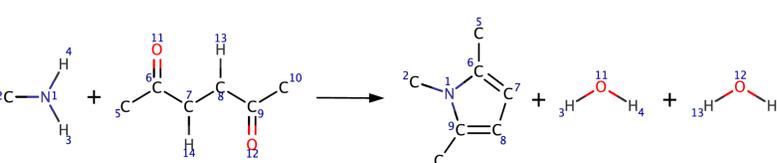


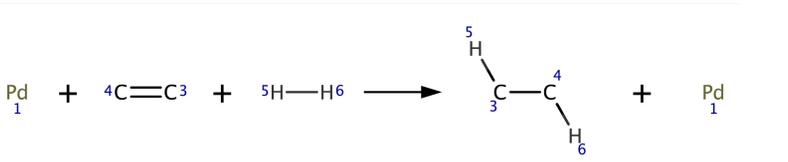
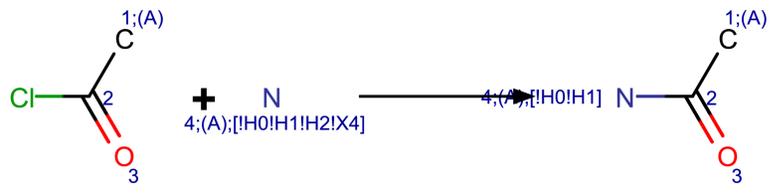
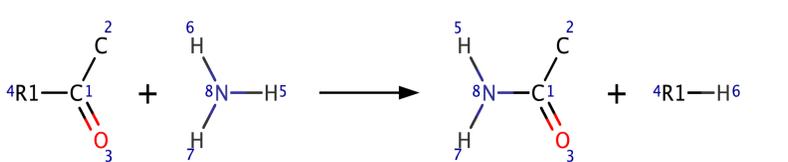
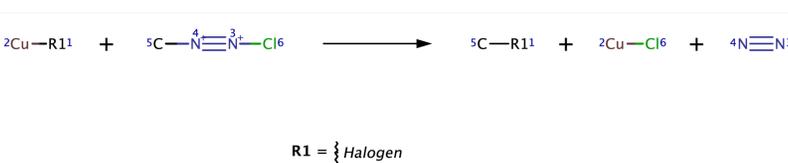
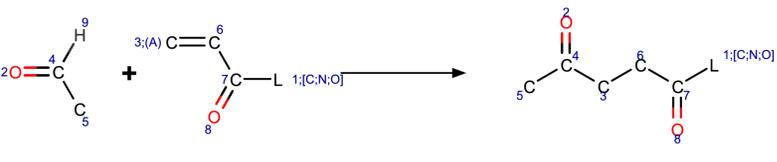
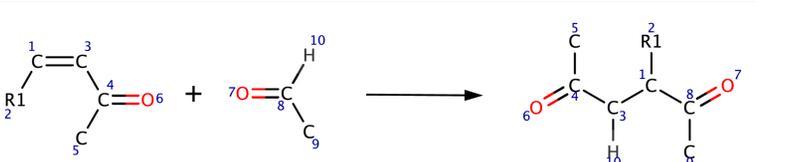
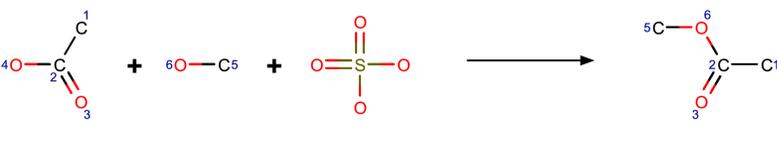
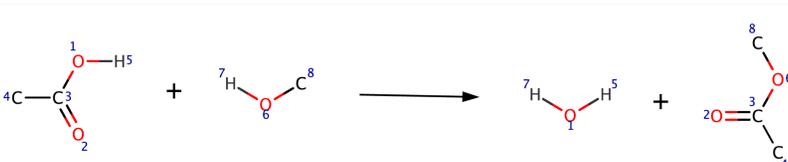
## SodiumDichromateOxidationOfPrimaryAlcohol.rxn

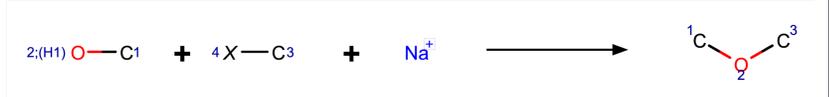


Used in RXN solution to 8,12.

7, 8, 12, 19

<p>42 Ozonolysis_with_reductive_workup.smarts</p>  <p>Ozonolysis is an organic reaction where the unsaturated bonds of <a href="#">alkenes</a> or <a href="#">alkynes</a>, are cleaved with ozone. In the product, the multiple carbon-carbon bond has been replaced by a carbonyl group. The outcome of the reaction depends on the type of multiple bond being oxidized and the work-up conditions. SMARTS shows <a href="#">ozonolysis of alkenes</a> with <a href="#">dimethyl sulphate</a> (DMS) used in reductive work-up.</p>	<p>ReductiveOzonolysis.rxn</p>  <p>The shown possibility accounts for about 50% of the product. About 25% of the product mixture will be carbonyl C=O formed by the 4<sup>th</sup> carbon and the 1<sup>st</sup> oxygen and carbonyl between the 5<sup>th</sup> carbon and the 2<sup>nd</sup> oxygen, with the sulfur in DMS forming bond with the 3<sup>rd</sup> oxygen. The other 25% of the product mixture will be the carbonyl compound formed by the 4<sup>th</sup> carbon and the 2<sup>nd</sup> oxygen, another carbonyl formed by the 5<sup>th</sup> carbon and the 3<sup>rd</sup> oxygen, while DMS is bonded with the 1<sup>st</sup> oxygen atom.</p>	8
<p>43 Ozonolysis_with_reductive_workup_on_cyclic_systems.smarts</p>  <p>Solution to Problem 18 actually has a ring:</p> 	<p>ReductiveOzonolysis.rxn</p> 	18
<p>44 Paal_Knorr_pyrrrole_synthesis_0.smarts</p> 	<p>PaalKnorrPyrroleSynthesis.rxn</p> 	1

45	<p>Palladium_catalyst_hydrogenation_of_alkene.smarts</p> $2;(A) C=C 1;(A) + H-H \longrightarrow 2;(A) C-C 1;(A)$ <p>Known as catalytic hydrogenation of alkene. Platinum can also be used as a catalyst.</p>	<p>CatalyticHydrogenationOfAlkenes.rxn</p> 	12
46	<p>Primary_amide_from_acid_chloride.smarts</p> 	<p>AmideSynthesisFromAcidHalides.rxn</p> <p>R1 = { Halogen</p> 	8
47	<p>Sandmeyer_with_cuprous_halide.smarts</p> $N\equiv N^+ - C1 \quad 2;[H;Cl] \quad L - Cu \longrightarrow 1C - L \quad 2;[Br;I;Cl]$ <p>This is one many reactions called Sandmeyer reactions.</p>	<p>SandmeyerReaction.rxn</p>  <p>R1 = { Halogen</p>	4
48	<p>Stetter_gamma_ketone_synthesis.smarts</p> 	<p>StetterReaction.rxn</p>  <p>R1 = { Alkyl      { —Ph</p>	1
49	<p>Transesterification_with_methanol.smarts</p> 	<p>FischerEsterification.rxn</p> 	9

50	<p>Williamson_Ether_Synthesis.smarts</p> 	<p>WilliamsonEtherSynthesis .rxn</p> <p>R1 = { Halogen</p> 	18
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### **RXN to SMARTS Mapping**

1	AldolCondensation.rxn	Aldol_condensation_with_ketone_and_base.smarts	5, 16, 17
2	AmideSynthesisFromAcidChloride.rxn	Amine_addition_to_acid_chloride.smarts	7, 11
3	AmideSynthesisFromAcidHalides.rxn	Primary_amide_from_acid_chloride.smarts	8
4	AromaticBromination.rxn	Bromination_of_benzene.smarts	11, 12
5	AromaticNitration.rxn	Aromatic_nitration.smarts	2, 4, 11
6	CatalyticHydrogenationOfAlkenes.rxn	Palladium_catalyst_hydrogenation_of_alkene.smart s	12
7	CatalyticHydrogenationOfNitriles.rxn	Nitrile_reduction_to_amine.smarts	1
8	CatalyticHydrogenationOfNitroGroup.rxn	Catalytic_hydrogenation_of_nitro_group.smarts	2, 4, 11
9	ClaisenCondensation.rxn	Claisen_condensation_with_ethyl_esters.smarts (13)Claisen_condensation_with_methyl_esters.smar ts (9)	9, 13
10	CyanideDisplacementOfBromideSN2.rxn	Cyanide_formation_from_alkyl_bromide.smarts	7, 11, 15
11	CyanideDisplacementOfTosylGroupSN2.rxn	Cyanide_displacement_of_halo- benzenesulfonates.smarts	1
12	CyanohydrinFormation.rxn	Cyanide_addition_to_carbonyl.smarts	19
13	DecarboxylationOfBetaKetoEsters.rxn	Decarboxylation_of_beta_keto_esters.smarts (13) Decarboxylation_of_beta_keto_ethyl_esters.smarts (16)	13, 16
14	DehydrationOfAmides.rxn	Dehydration_of_amide_to_nitrile.smarts	8
15	Diazotization.rxn	Diazotization.smarts	2, 4, 11
16	DieckmannCyclization.rxn	Dieckmann_condensation_with_ketone.smarts	16
17	DielsAlderCycloaddition.rxn	Diels-Alder_cycloaddition_0.smarts	10, 12, 18

18	EnolateAttackOnAlkylHalideSN2.rxn(2 <sup>nd</sup> part of smart)	Enolate_SN2_attack_on_alkyl_bromide.smarts	14
19	EnolateFormation.rxn (this reaction is 1 <sup>st</sup> part in SMARTS reaction)	Enolate_SN2_attack_on_alkyl_bromide.smarts	14
20	FischerEsterification.rxn	Transesterification_with_methanol.smarts	9
21	FriedelCraftsAcylation.rxn	Friedel-Crafts_acylation.smarts	19
22	GabrielSynthesis.rxn	Gabriel_synthesis_from_alkyl_bromide.smarts	3
23	GrignardAdditionToAcidChlorides.rxn	Grignard_addition_to_acid_chloride.smarts	12, 20
24	GrignardReaction.rxn	Grignard_addition_to_carbonyl.smarts	6, 12, 15, 20
25	GrignardReagentFormation.rxn	Grignard_reagent_formation.smarts	6, 12, 15, 20
26	HydrationOfAldehydesAndKetones.rxn		
28	HydrationOfAlkenes.rxn	Alcohol_from_alkene.smarts	20
29	HydrolysisOfNitriles.rxn	Hydrolysis_of_nitriles.smarts	11
30	HydroxylSubstitutionOfDiazoniumIonSN1.rxn	Dediazoniatio_n_to_hydroxy.smarts	2
31	ImineFormation.rxn	Imine_formation.smarts	
32	ImineFormation.rxn	Imine_formation.smarts	3, 7, 15
33	ImineReductionToAmine.rxn	Imine_reduction_to_amine.smarts	3, 7, 15
34	IntramolecularOxymercurationReduction.rxn	intramolecular_Oxymercuration-reduction.smarts	10
35	LAHReductionOfAldehydesAndKetones.rxn	LiAlH4_reduction_of_aldehydes.smarts	18
36	LAHReductionOfAldehydesAndKetones.rxn	LiAlH4_reduction_of_ketone.smarts	
37	LAHReductionOfAnhydrides.rxn	Cyclic_anhydride_reduction.smarts	10, 18
38	LAHReductionOfNitriles.rxn	Nitrile_reduction_to_amine.smarts	7, 11, 15, 19
39	MichaelAdditionToUnsaturatedKetones.rxn	Michael_addition_with_ketone.smarts	16
40	NitrileSubstitutionOfDiazoniumIonSN1.rxn	Dediazoniatio_n_to_nitrile.smarts	11
41	OxidationOfAlcoholsWithPCC.rxn	Oxidation_of_alcohols_with_PCC.smarts	3, 5, 7, 14, 15, 17
42	OxidationOfPrimaryAlcoholWithPotassiumPermanganate.rxn		7,19
43	PaalKnorrPyrroleSynthesis.rxn	Paal_Knorr_pyrrole_synthesis_0.smarts	1
44	PBr3ConversionOfAlcoholsToAlkylBromides.rxn	Alkyl_bromide_with_PBr3.smarts	3, 6, 7,11, 14,15, 20
45	ReductiveOzonolysis.rxn	Ozonolysis_with_reductive_workup.smarts (8) Ozonolysis_with_reductive_workup_on_cyclic_systems.smarts (18)	8, 18
46	SandmeyerReaction.rxn	Sandmeyer_with_cuprous_halide.smarts	4

47	SodiumDichromateOxidationOfPrimaryAlcohol.rxn & SodiumDichromateOxidationOfSecondaryAlcohol.rxn	Oxidation_of_alcohols_to_carboxylic_acids.smarts	8, 9
49	StetterReaction.rxn	Stetter_gamma_ketone_synthesis.smarts	1
50	ThionylChlorideConversionOfCarboxylicAcidsToAcidChlorides.rxn	Acid_chlorides_from_carboxylic_acids.smarts	6, 7, 8, 11, 12, 19, 20
51	TosylationOfAlcohols.rxn	Alcohol_to_4-chlorobenzene_sulfonate.smarts	1
52	WilliamsonEtherSynthesis.rxn	williamsonEtherSynthesis.rxn	18