Supporting Information

Multistep Reaction Based *De Novo* Drug Design: Generating Synthetically Feasible Design Ideas

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- Sonogashira

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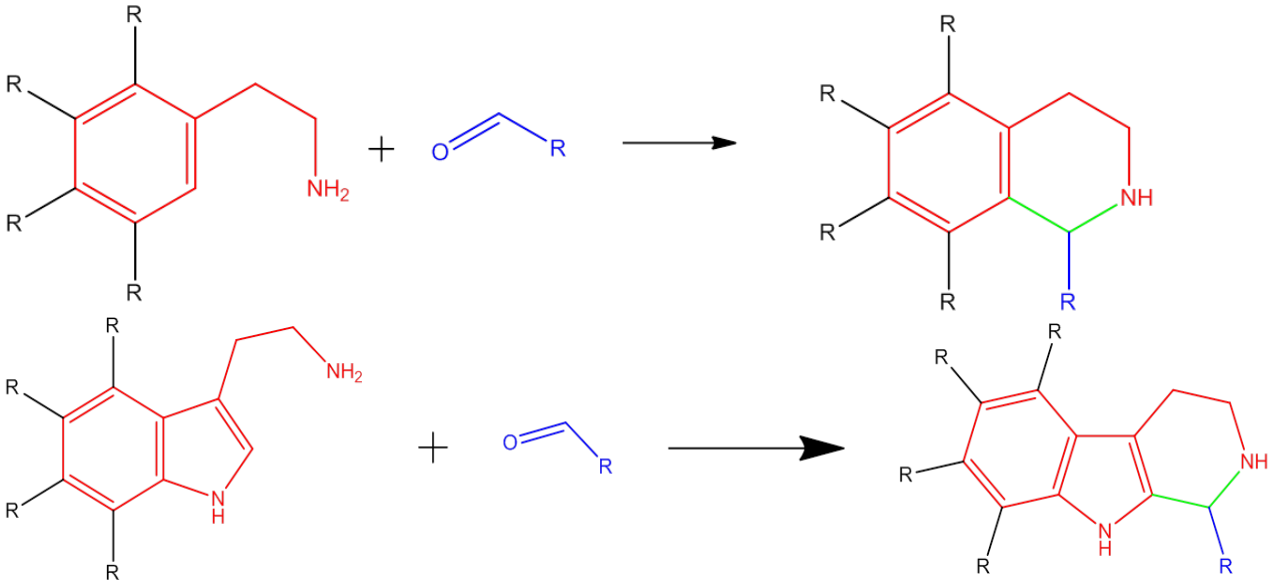

Reaction Notes:

- This reaction can produce regioisomers for some reagents.

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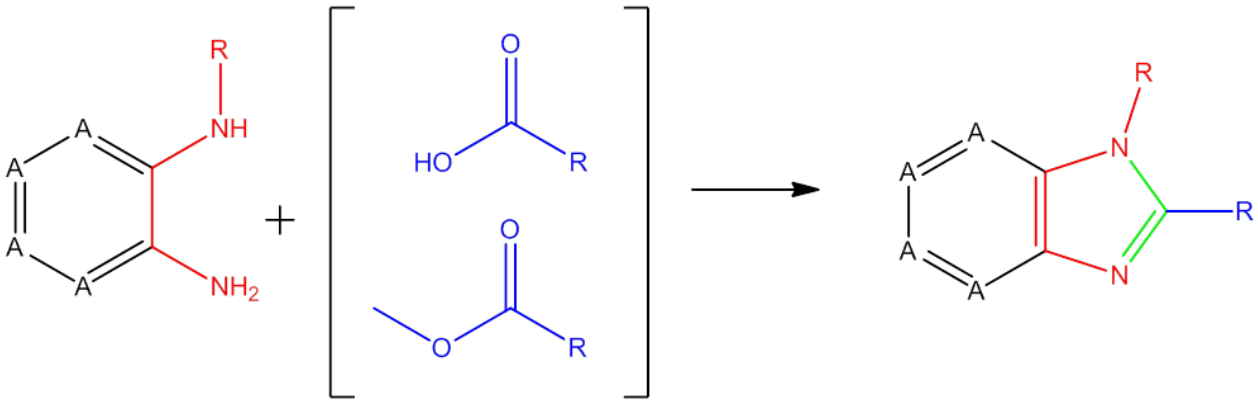
Benzimidazole via Condensation with Carboxylic Acid/Ester[1,8]



Reaction Notes:

- This reaction is possible with any six-membered aromatic heterocycle.

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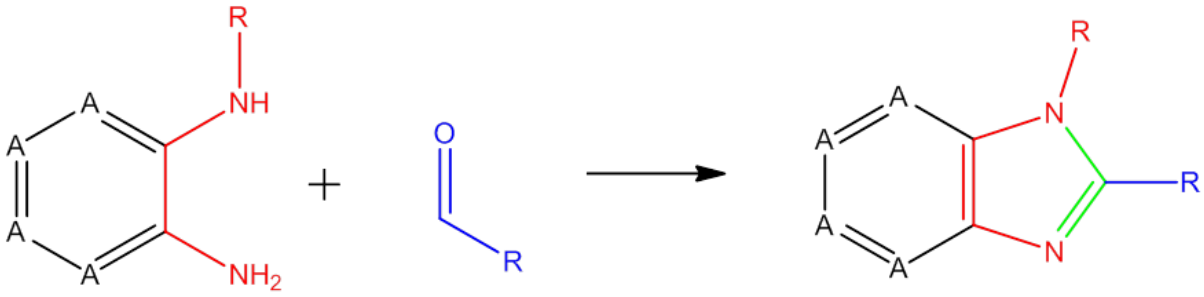
Benzimidazole via Condensation with Aldehyde[1,8,9,10]



Reaction Notes:

- This reaction is possible with any six-membered aromatic heterocycle.

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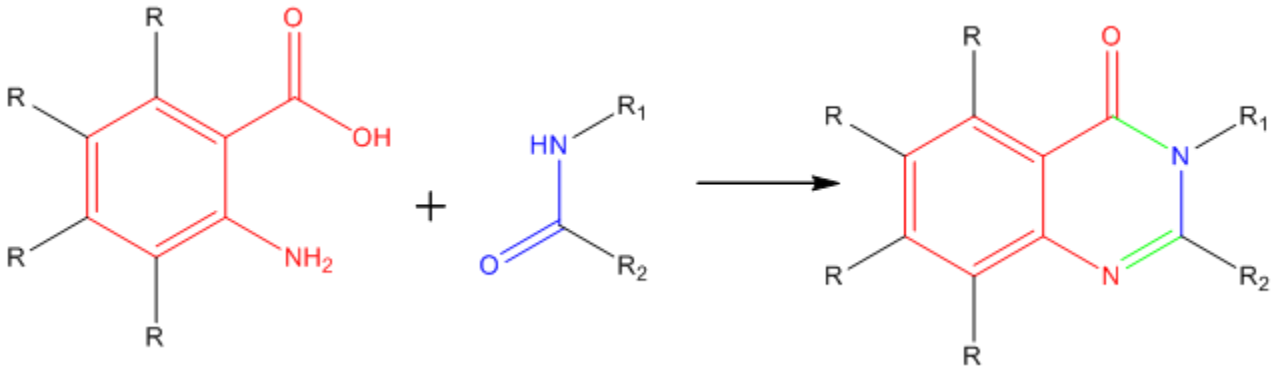
Niementowski Quinazoline Synthesis[1,11]



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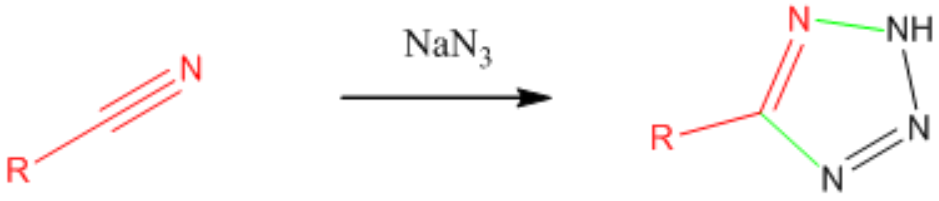
Terminal Tetrazole via Cycloaddition[1,12,13]



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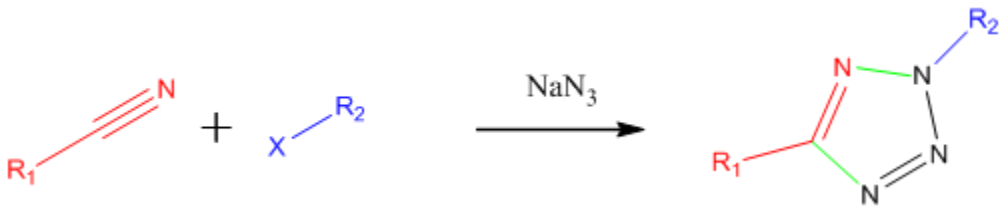
2,5-Tetrazole via Cycloaddition[1]



Reaction Notes:

- This reaction is not regioselective, but has an alternative product. There is an additional step where the halogen (X) is substituted with azide (NaN_3).

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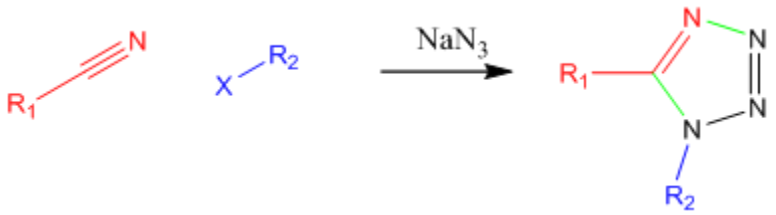
1,5-Tetrazole via Cycloaddition[1]



Reaction Notes:

- This reaction is not regioselective, but has an alternative product. There is an additional step where the halogen (X) is substituted with azide (NaN_3).

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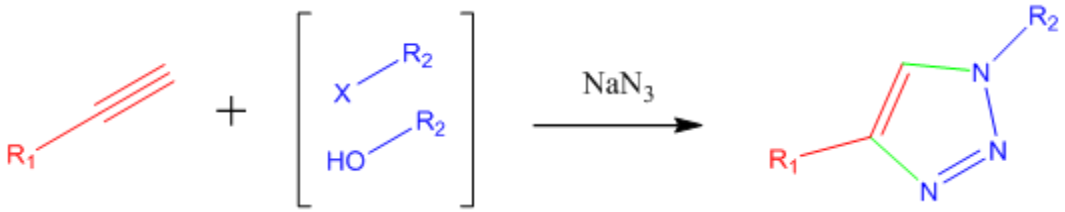
1,4-Subst Cu Catalyzed Huisgen[1,14,15]



Reaction Notes:

- X = Cl, Br, I
- R1 = aryl, alkyl
- R2 = aliphatic carbon
- The halogen or hydroxyl group is substituted under Mitsunobu conditions with NaN_3. The stereochemistry must be considered at the secondary halides/alcohols.

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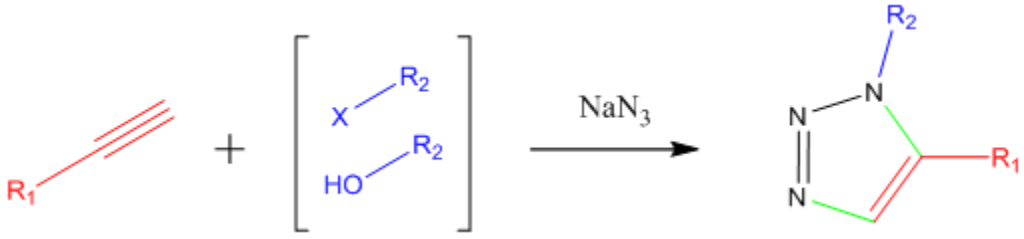
1,5-Subst Ru Catalyzed Huisgen[1,14]



Reaction Notes:

- X = Cl, Br, I
- R1 = aryl, alkyl
- R2 = aliphatic carbon
- The halogen or hydroxyl group is substituted under Mitsunobu conditions with NaN_3. The stereochemistry must be considered at the secondary halides/alcohols.

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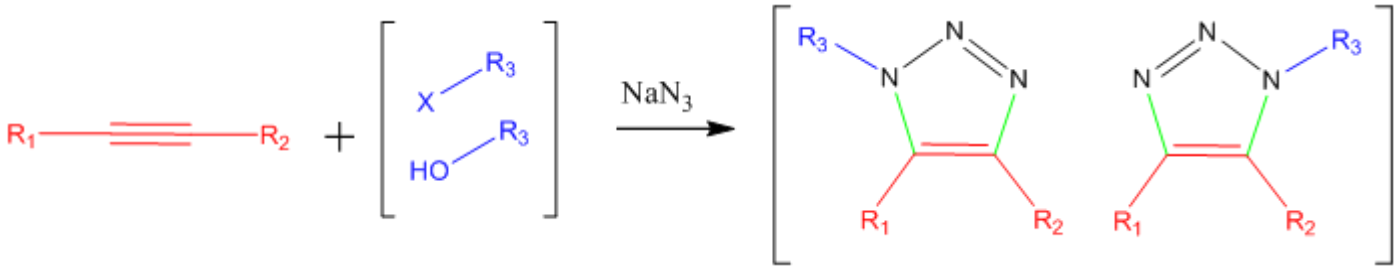
Huisgen with Disubstituted Alkyne[1,14]



Reaction Notes:

- X = Cl, Br, I
- R1 = aryl, alkyl
- R2 = aliphatic carbon
- This reaction is not regioselective rather asymmetrically substituted alkynes form both regioisomers. The halogen or hydroxyl group is substituted under Mitsunobu conditions with NaN_3. The stereochemistry must be considered at the secondary halides/alcohols.

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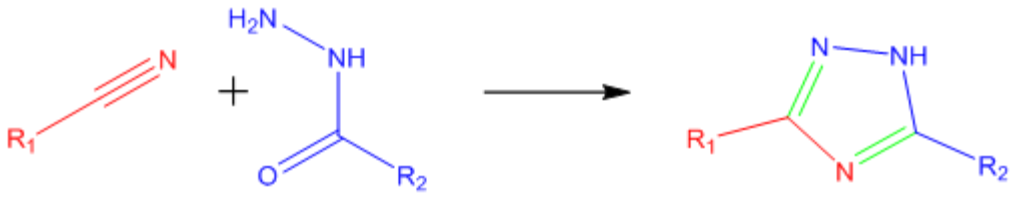
1,2,4-Triazole via Condensation with Acetohydrazide[1]



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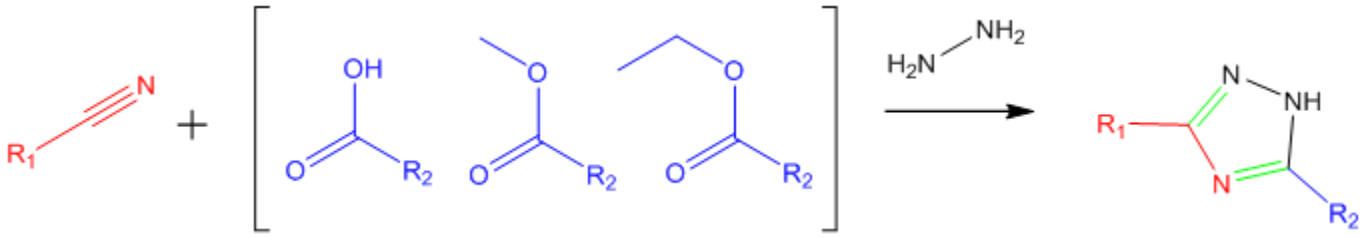
1,2,4-Triazole via Condensation with Carboxylic Acid/Ester[Error! Reference source not found.]



Reaction Notes:

- There is an additional nucleophilic substitution with hydrazine step.

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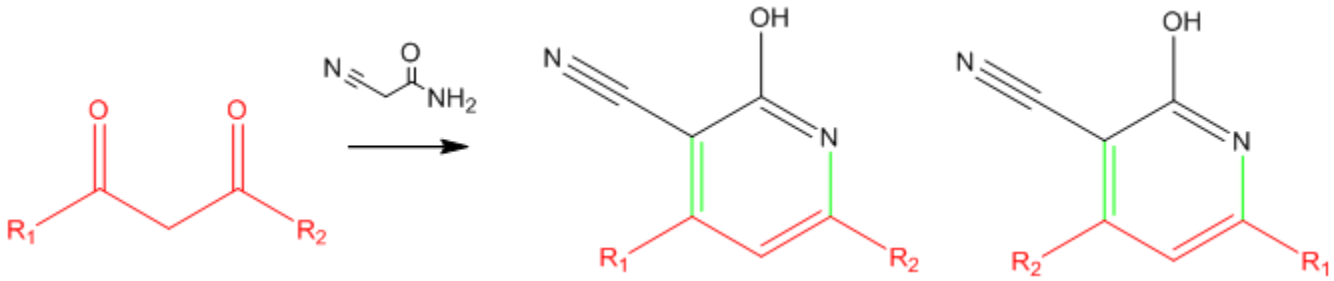
3-Nitrile Pyridine via Condensation[1]



Reaction Notes:

- R1 and R2 must be an aromatic or aliphatic carbon and not carbonyl/carboxylic acid.
- Central carbon of reactant must have at least one hydrogen atom attached.
- Only one of the carbonyl groups of the reactant can be part of the product ring.
- This reaction has the potential to produce regioisomers due to symmetric substructure definition.

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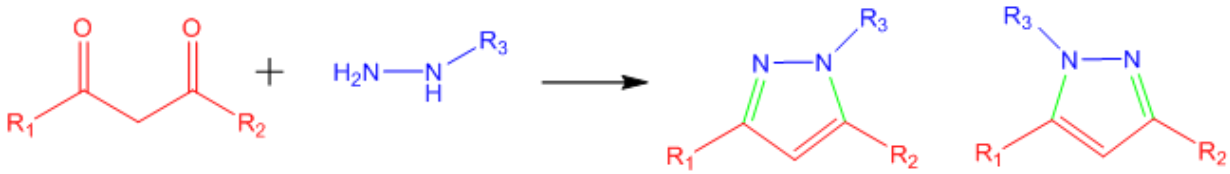
1,3,5-Pyrazole via Condensation[1]



Reaction Notes:

- R1 and R2 must be an aromatic or aliphatic carbon and not carbonyl/carboxylic acid.
- R3 = H, C, or possibly even C=O
- Central carbon of reactant must have at least one hydrogen atom attached.
- Only one of the carbonyl groups of the reactant can be part of the product ring.
- This reaction has the potential to produce regioisomers due to symmetric substructure definition.

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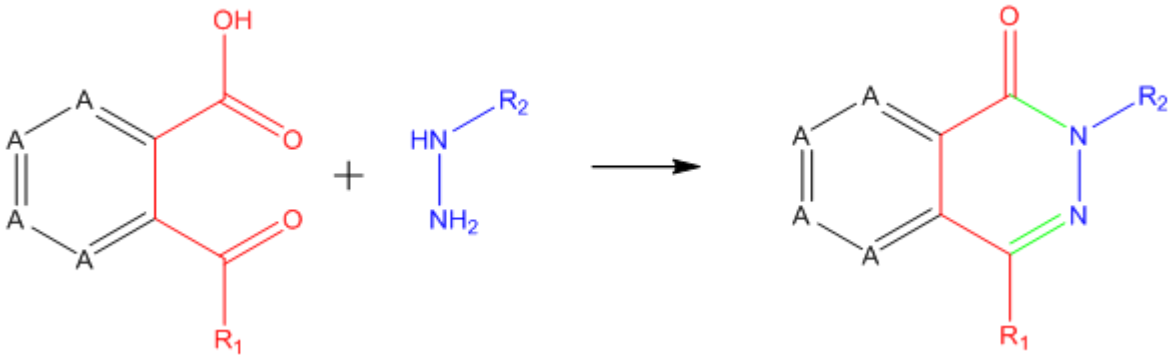
2,4-Phthalazinone via Condensation[1]



Reaction Notes:

- R2 must be C, but not a C=O, C=S, or C=N
- This reaction is possible with any six-membered aromatic heterocycle, even if it is substituted.

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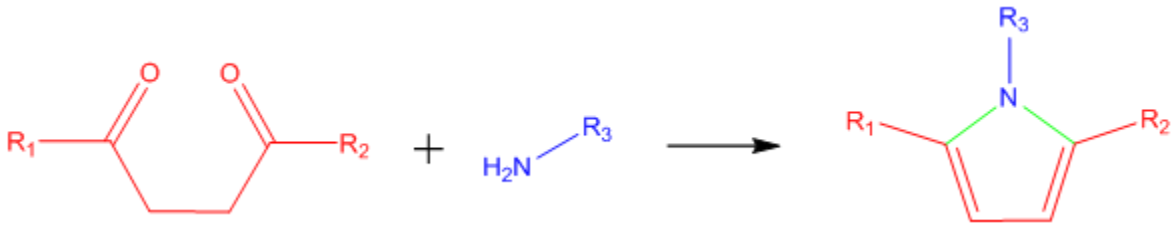
Paal-Knorr[1,16,17,18]

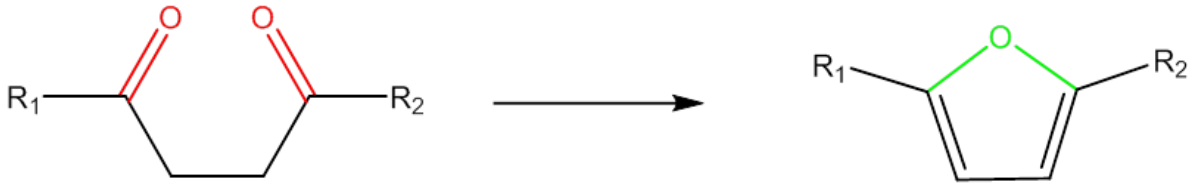
Pyrrole



Reaction Notes:

- The two central carbons of first reactant may be substituted, but must contain at least one hydrogen atom.
- The second reactant must be a primary amine.

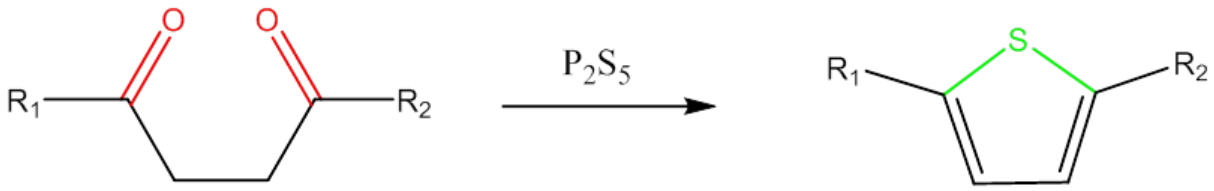
Furan



Reaction Notes:

- Acid-catalyzed synthesis results in hemiacetal intermediate followed by furan formation.

Thiophene



Reaction Notes:

- Addition of sulfonization agent P_2S_5 is required to produce intermediate thioketone.
- Acid-catalyzed reaction results in thiophene.

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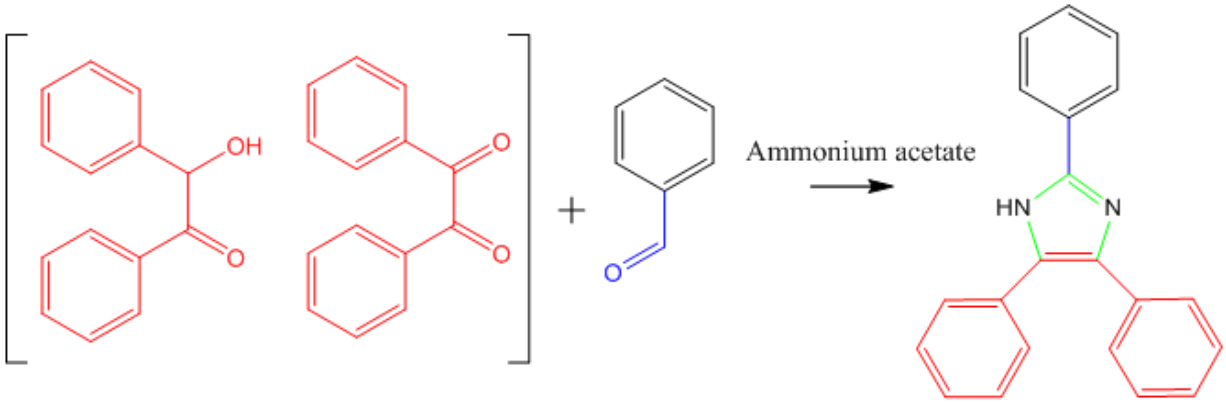
Triaryl Imidazole via Condensation[1]



Reaction Notes:

- The first reactant may be a keto or a hydroxyl group.
- The second reactant must be an aldehyde connected to any aromatic system.

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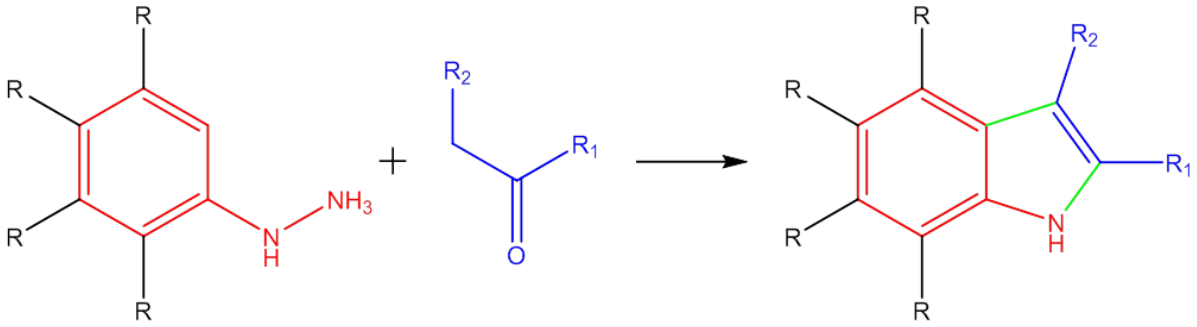
Fischer Indole Synthesis[1]



Reaction Notes:

- This reaction can produce regioisomers for some reagents.

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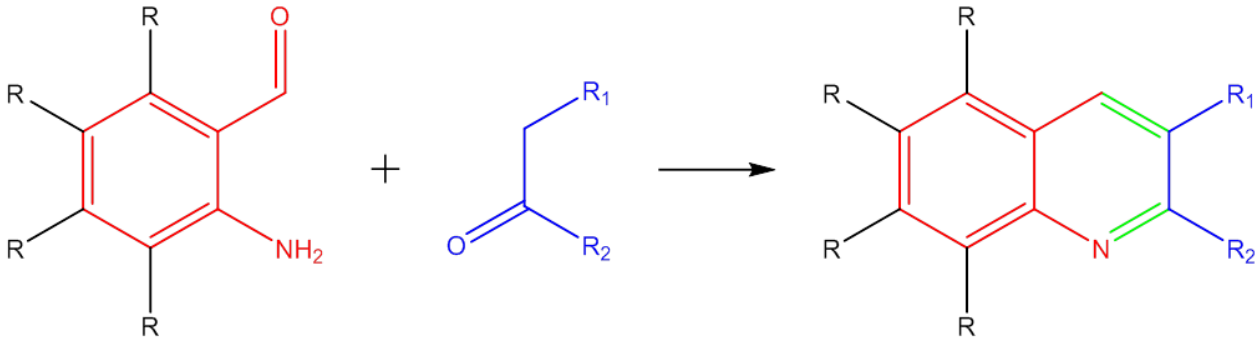
Friedlaender Quinoline[1,19]



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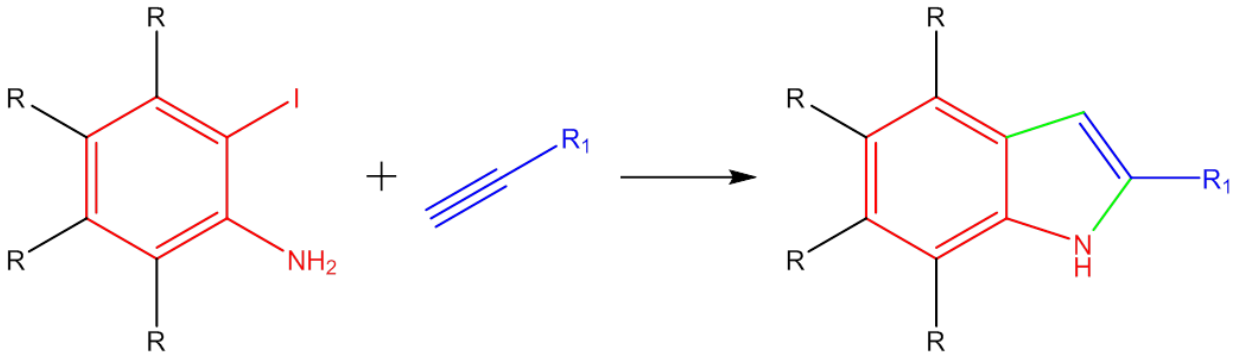
Indole Synthesis[1,20]



Reaction Notes:

- Br or I allowed on the heterocyclic reactant.

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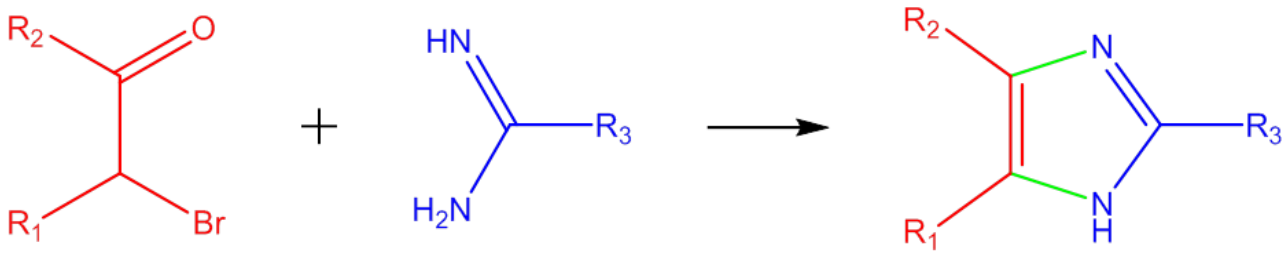
Imidazole via Condensation[1]



Reaction Notes:

- R1 and R2: The first atom must be a C
- R3: aryl, N

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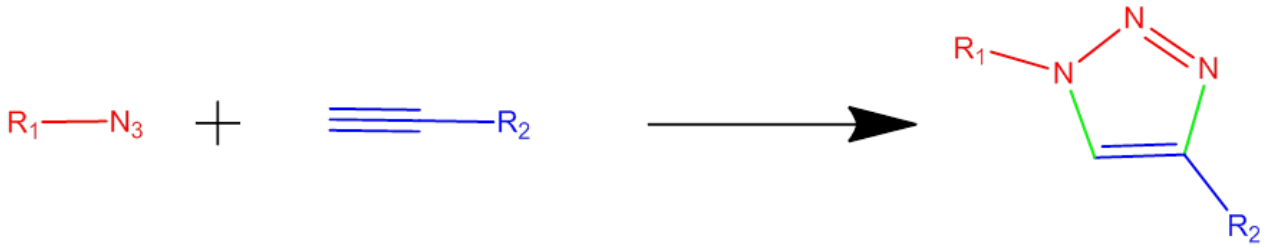
Copper-Catalyzed Azide-Alkyne Cycloaddition[21,22]



Reaction Notes:

- R1: Alkyl or CH_2OBn
- R2: Ph or CO_2H

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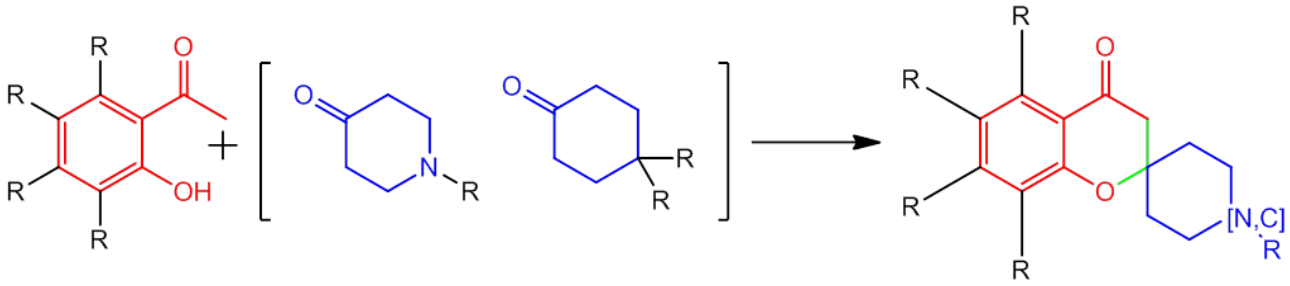
Spiro Chromanone via Condensation[1]



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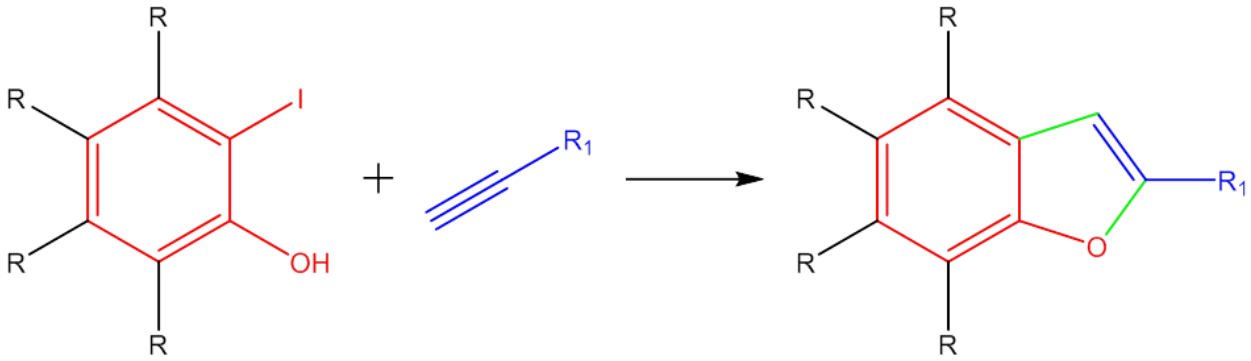
Benzofuran via Cycloaddition[1]



Reaction Notes:

- Br or I are allowed on the heterocyclic reactant.

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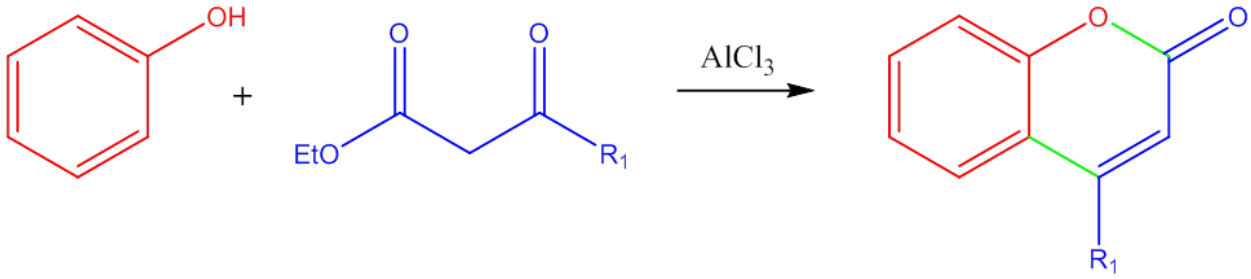
Pechmann Condensation[23]



Reaction Notes:

- Requires addition of Lewis Acid $AlCl_3$.

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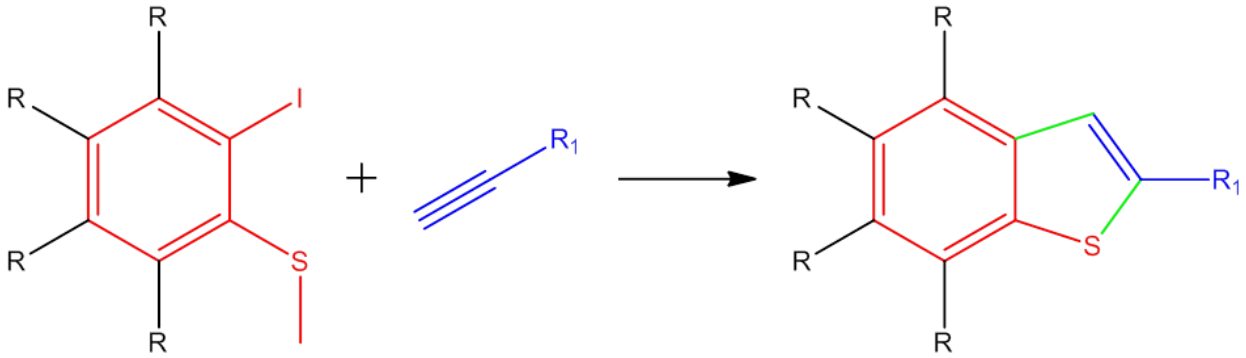
Benzothiophene via Condensation[1]



Reaction Notes:

- Br or I are allowed on the heterocyclic reactant.

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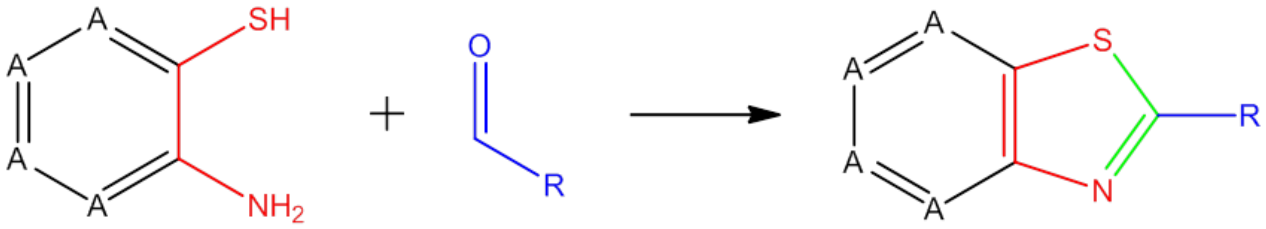
Benzothiazole via Condensation[1]



Reaction Notes:

- This reaction is possible with any six-membered heterocycle.

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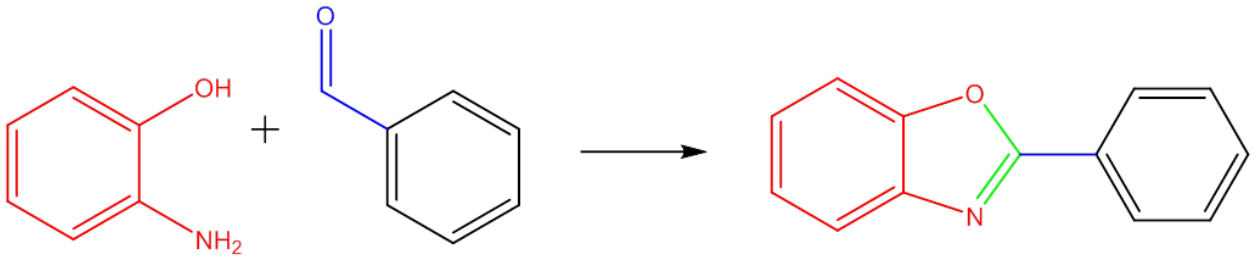
Benzoxazole via Condensation with Aromatic Aldehyde[1]



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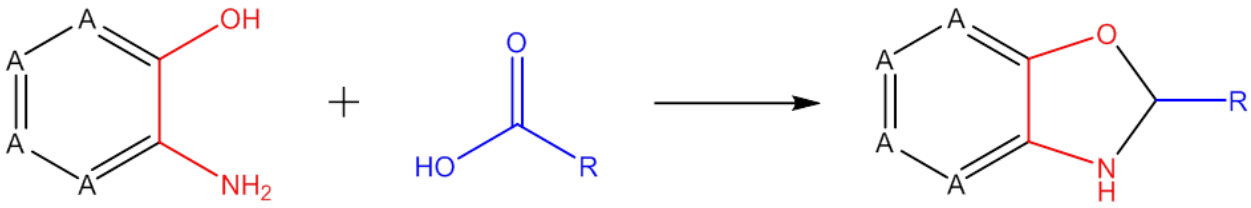
Benzoxazole via Condensation with Carboxylic Acid[1]



Reaction Notes:

- This reaction is possible with any six-membered heterocycle.

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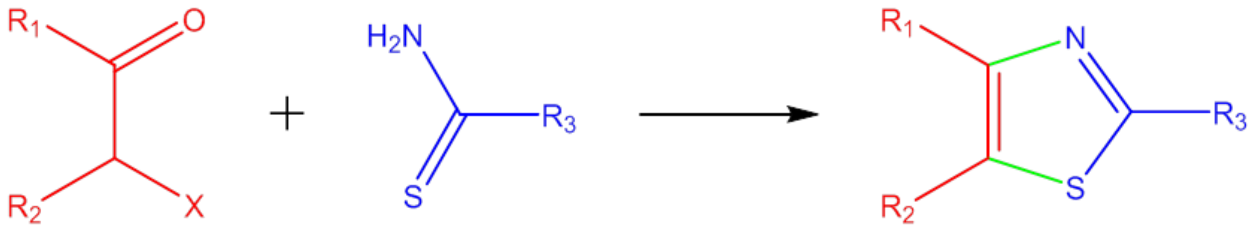
Hantzsch Thiazole[1]



Reaction Notes:

- X: Cl, Br, or I
- Neither carbons in the C=O or C-X groups cannot be part of a ring

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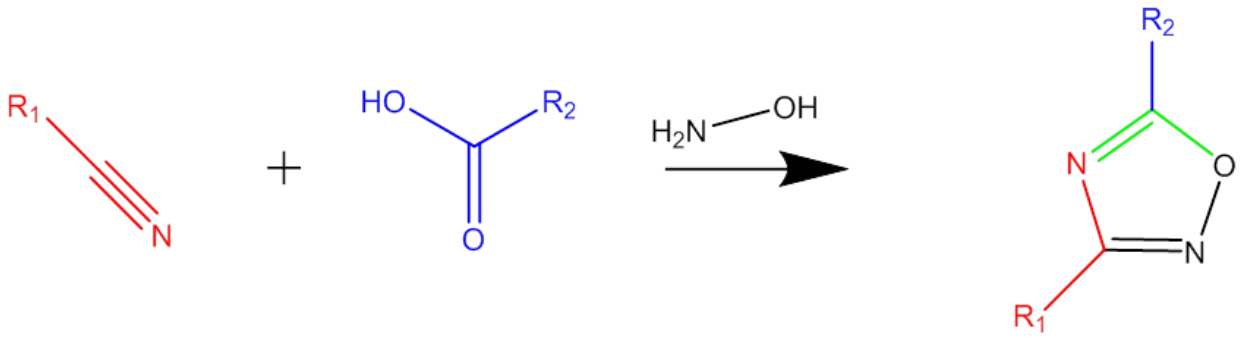
Oxadiazole via Condensation[1]



Reaction Notes:

- The nitrile must be converted to an amidoxime by the hydroxylamine reagent prior to the reaction.

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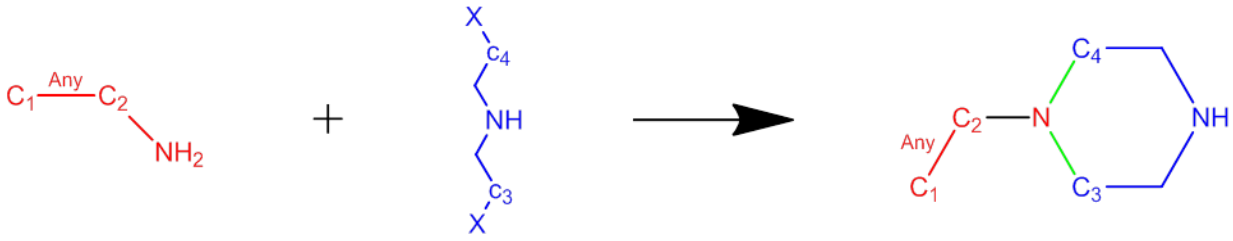
Heterocycle Ring Formation[24]



Reaction Notes:

- C1 should not have a =O, =S, or a halogen attached.
- C2 should not have a =O, =S, or =N attached.
- C3 & C4 should have 2 hydrogens attached.
- The other carbon and nitrogen in the second reagent can be substituted and be a C, N, O, or S.
- X can be a Cl or Br.

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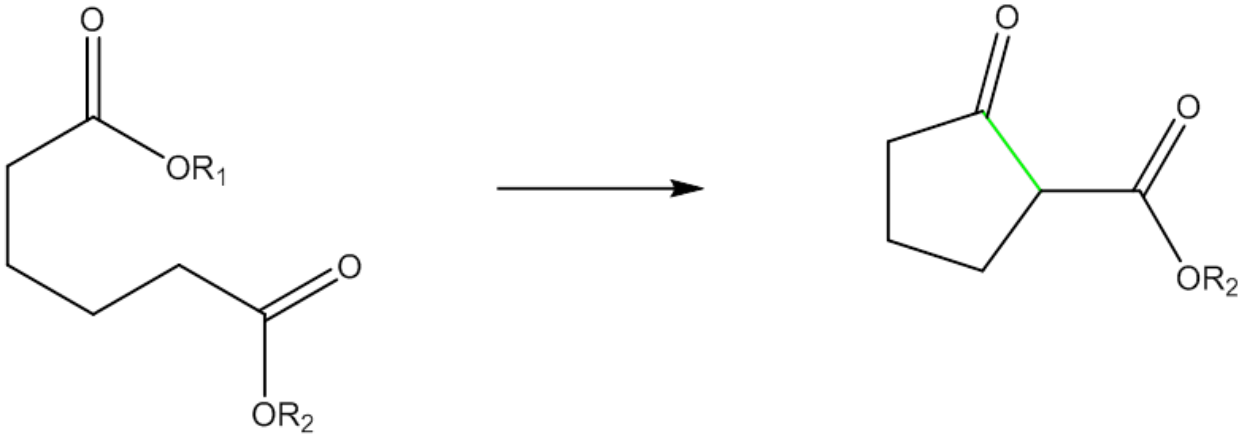
Dieckmann Condensation[25,26,27]



Reaction Notes:

- Intramolecular condensation reaction.
- R groups can be alkyl or aryl.
- Addition of alkoxide base necessary to drive reaction.

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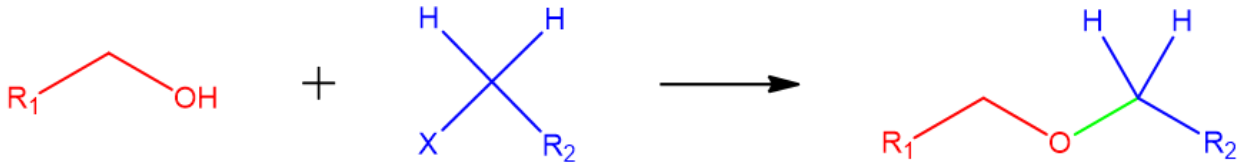
Williamson Ether[1]



Reaction Notes:

- X: Must be a Cl, Br, or I primary alkyl halide.
- The hydroxy group may be attached to an aromatic or aliphatic (1^0, 2^0, or 3^0) carbon.

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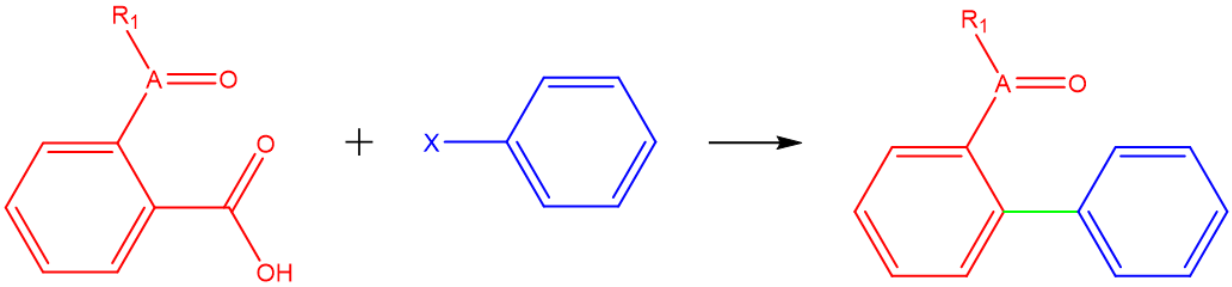
Biaryl via Decarboxylative Coupling[1,28]



Reaction Notes:

- A: C, S, or N
- X: Cl, Br, or I

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Migita-Kosugi-Stille Coupling[1,29]

Reaction Notes:

- Reactant one must be transformed into organotin (stannane) first.
- R1: vinyl (C=C), aryl
- X1: Br, I
- Ar: any aromatic system
- X2: Cl, Br, I

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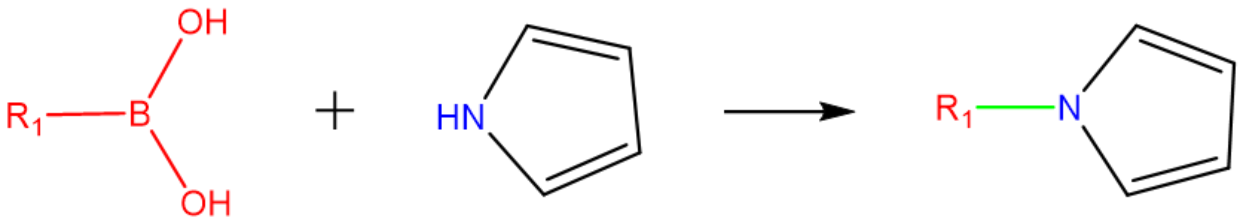
Chan-Lam Coupling[1,30]



Reaction Notes:

- This reaction works with various 5-membered aromatic rings that contain NH even if they are fused to other rings.
- Regioisomers are likely to be produced in the case where protomers of the 5-membered heterocycle exist.
- R1: aryl

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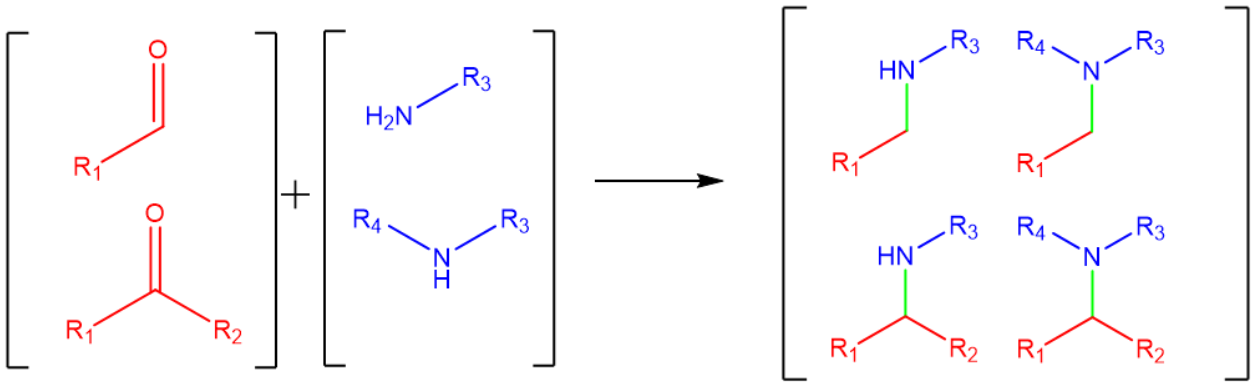
Reductive Amination[1]



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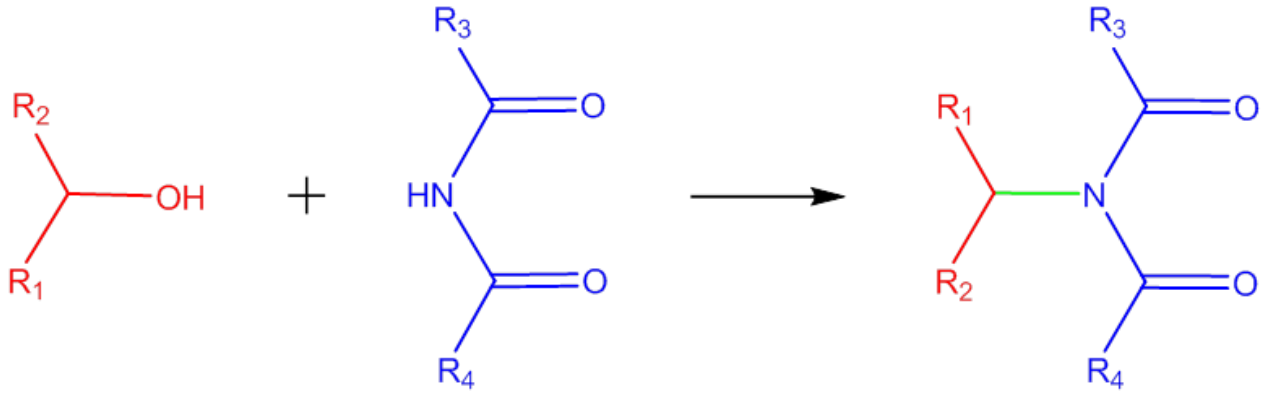
Mitsunobu Imide[1]



Reaction Notes:

- This reaction causes an inversion of stereochemistry at chiral centers.
- There are no restrictions on R1, R3, and R4; however, R2 must be either hydrogen or carbon.

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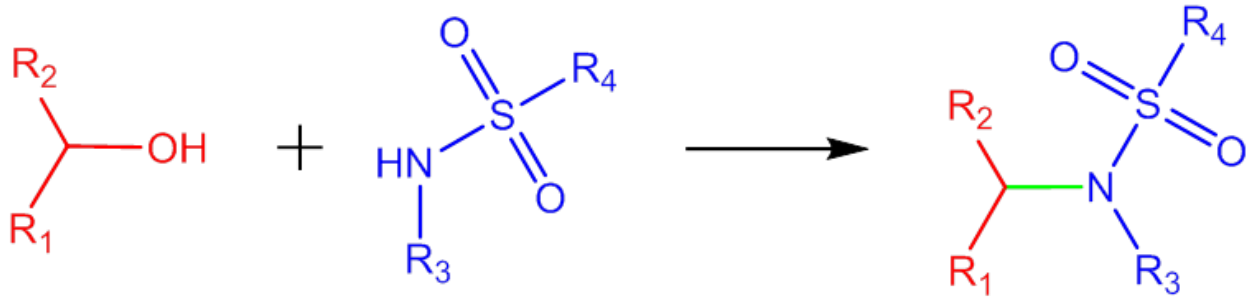
Mitsunobu Sulfonamide[1]



Reaction Notes:

- This reaction causes an inversion of stereochemistry at chiral centers.
- There are no restrictions on R1, R3, and R4; however, R2 must be either hydrogen or carbon.

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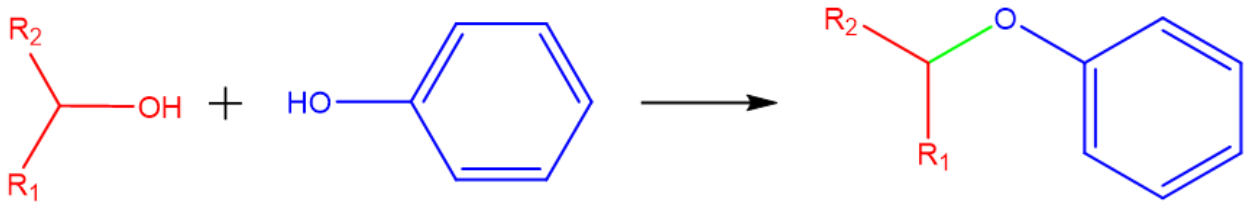
Mitsunobu Phenol[1]



Reaction Notes:

- This reaction causes an inversion of stereochemistry at chiral centers.
- There are no restrictions on R1; however, R2 must be either hydrogen or carbon.

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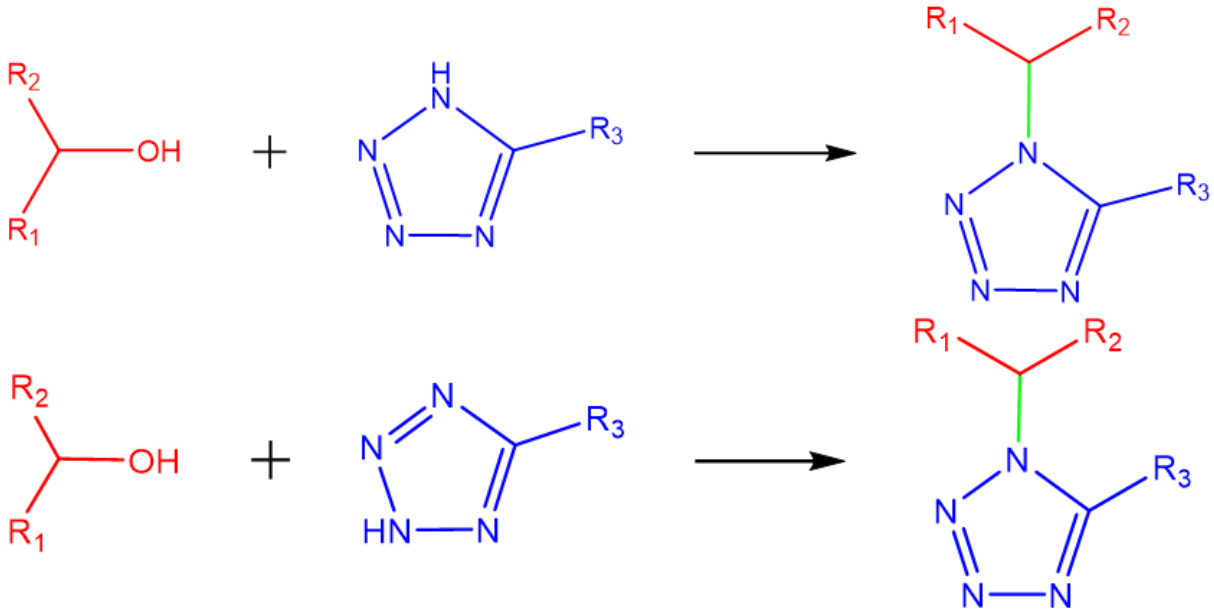
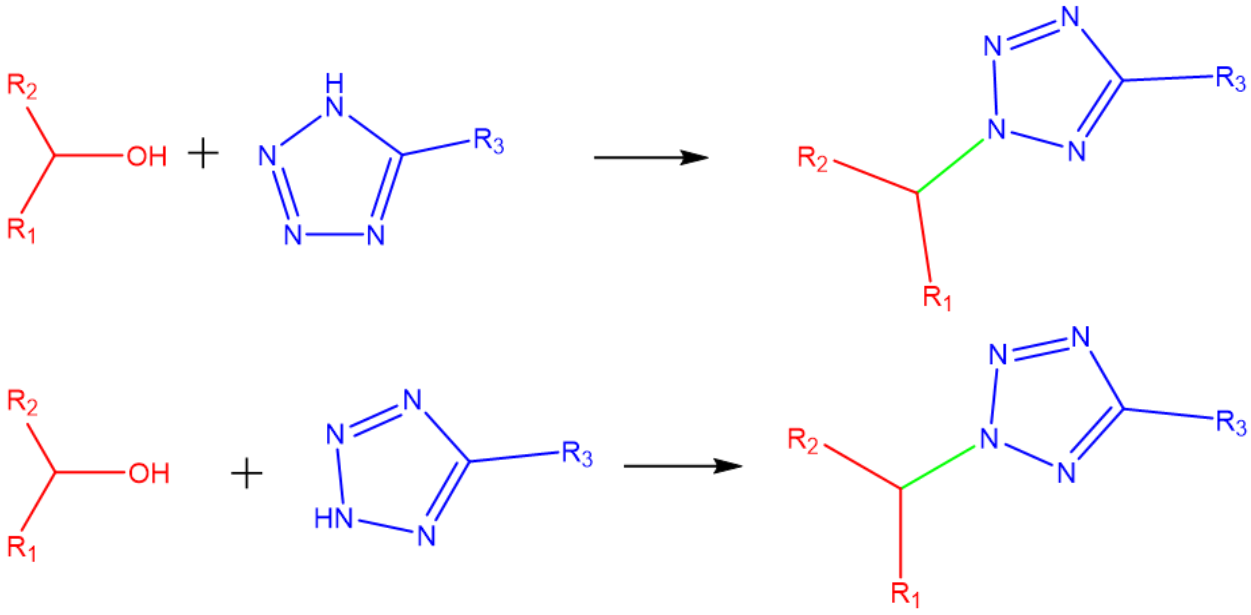
Mitsunobu Tetrazole[1]

Mitsunobu 1,5-Tetrazole (tautomers)



Mitsunobu 2,5-Tetrazole (tautomers)



Reaction Notes:

- This reaction causes an inversion of stereochemistry at chiral centers.
- This reaction is not regioselective. An alternative product is substituted at the N at position 2 instead of 1.
- There are no restrictions on R1 or R3; however, R2 must be either hydrogen or carbon.

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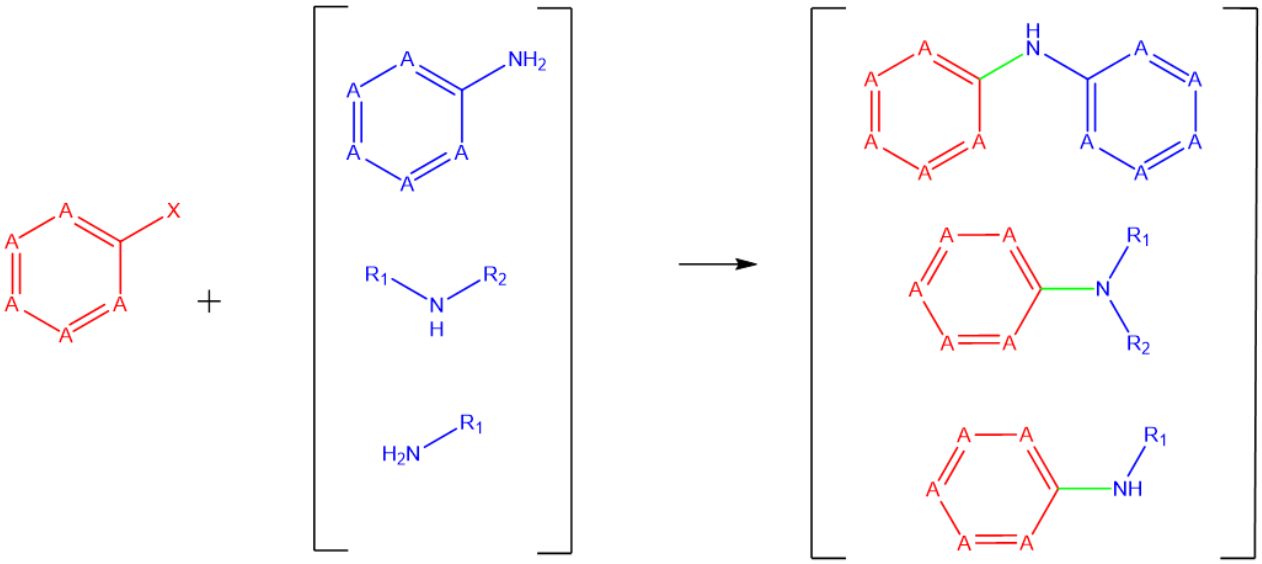
Buchwald-Hartwig[1]



Reaction Notes:

- X: Cl, Br, I
- A: N,C

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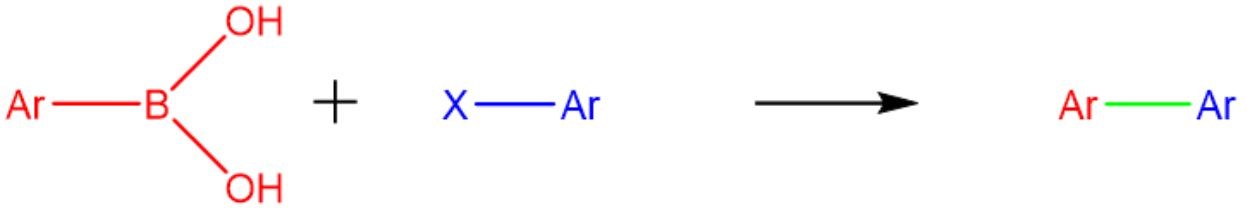
Suzuki[1]



Reaction Notes:

- Any boronic acid (including cyclic structures)
- X: Cl, Br, I

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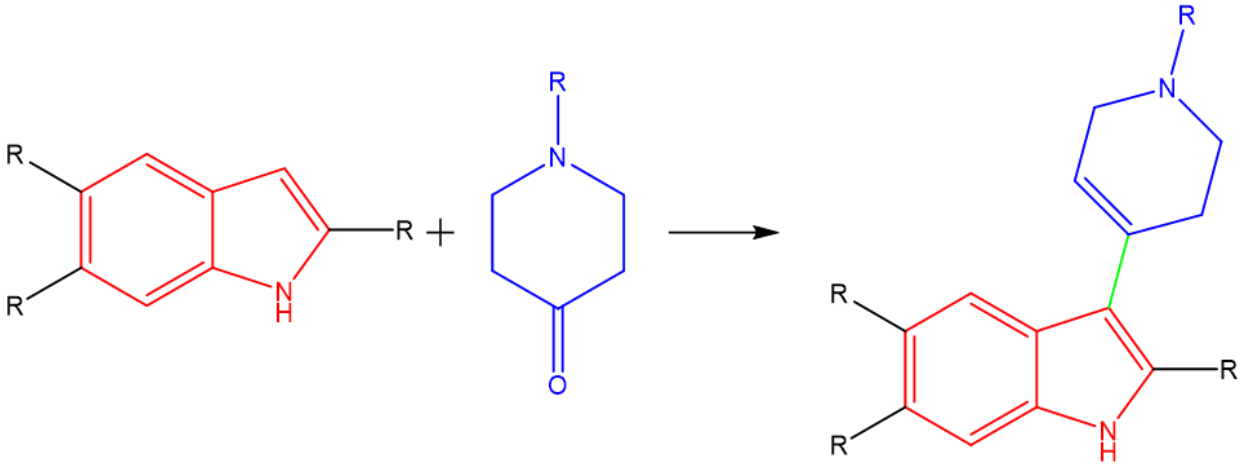
Piperidine Indole via Condensation[1]



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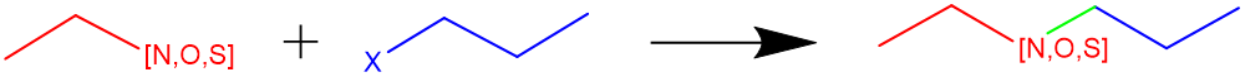
Heteroatom Alkylation via Nucleophilic Attack[1]



Reaction Notes:

- X is a halogen
- The nucleophile can be 1^0, 2^0, or 3^0.

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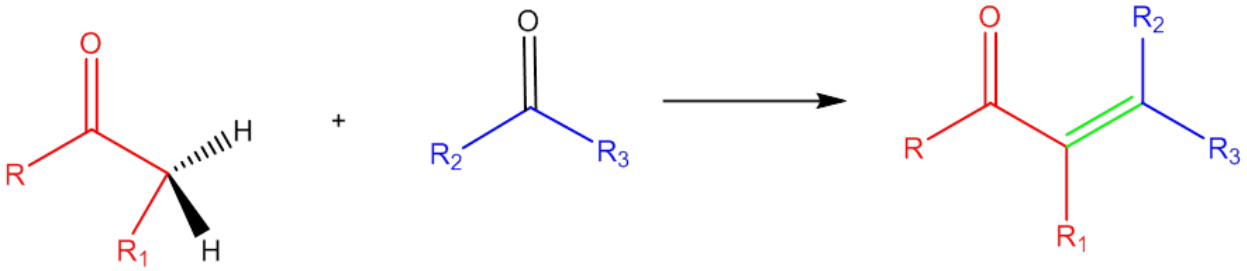
Aldol Condensation[31,32,33]



Reaction Notes:

- R groups can be aryl or alkyl.

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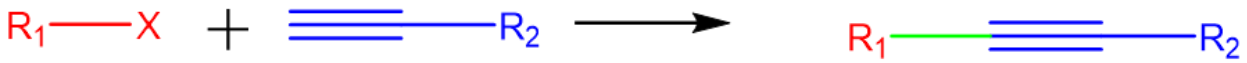
Sonogashira[1,34]



Reaction Notes:

- R1: aryl, vinyl
- X: Br, I
- R2: any C

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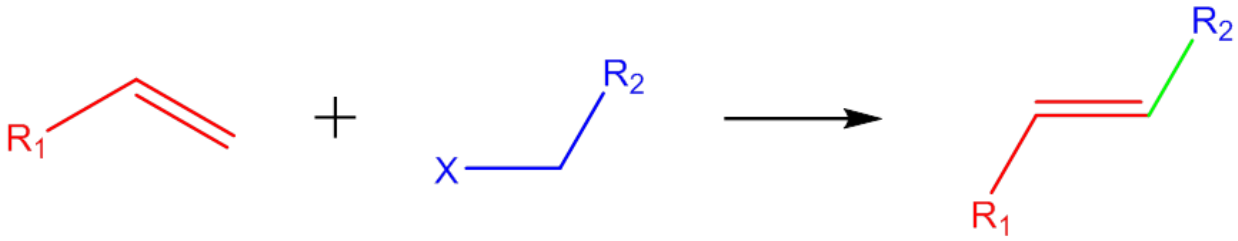
Mizoroki-Heck Terminal Vinyl[1]



Reaction Notes:

- R1: aryl, COO, CN (electron withdrawing groups yield trans selectivity)
- R2: aryl, vinyl
- X: Cl, Br, I

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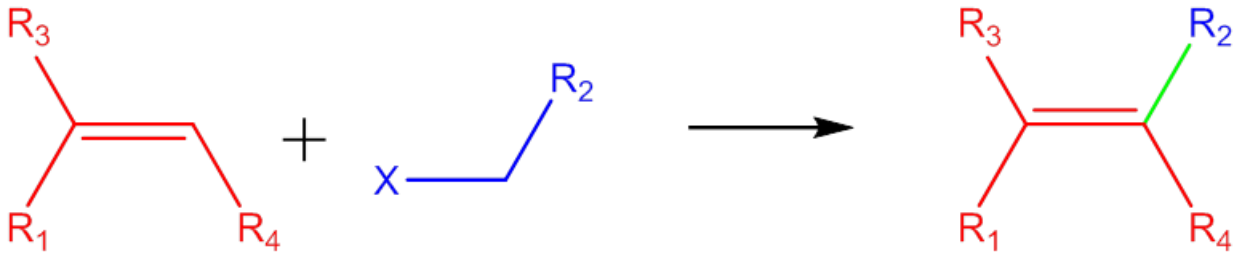
Mizoroki-Heck Non-Terminal Vinyl[1]



Reaction Notes:

- R1: aryl, COO, CN
- R2: aryl, vinyl
- X: Cl, Br, I

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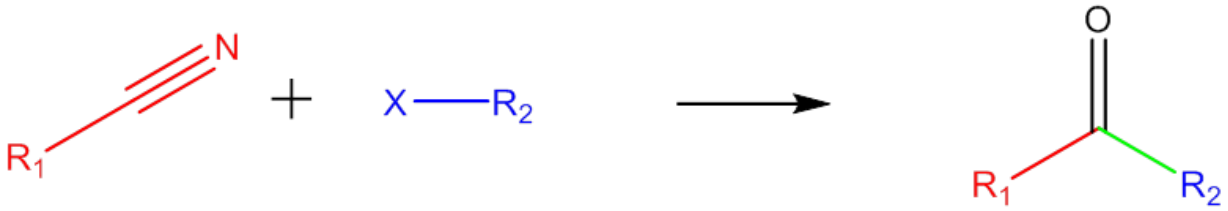
Grignard Carbonyl[1,35,36]



Reaction Notes:

- Reactant 2 must be transformed into Grignard (RMgX) reagent first.
- R2: aryl, alkyl
- X: Cl, Br, I

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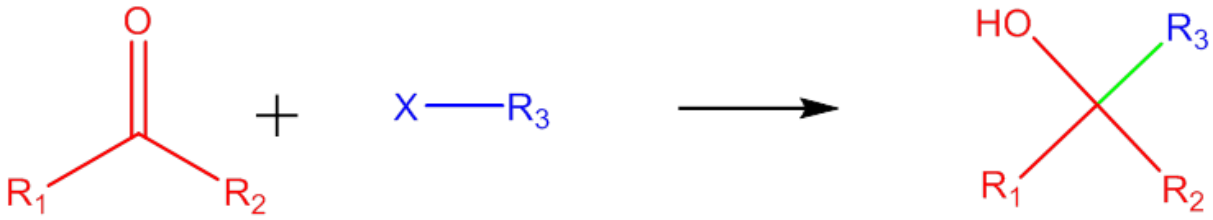
Grignard Alcohol[1,37,38]



Reaction Notes:

- Reactant 2 must be transformed into Grignard (RMgX) reagent first.
- It is possible that this reaction will create a stereocenter.
- R2: H, C
- X: Cl, Br, I

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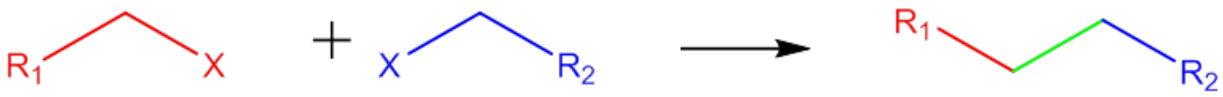
Negishi[1,39]



Reaction Notes:

- Formation of Zn halide is required as an additional step.

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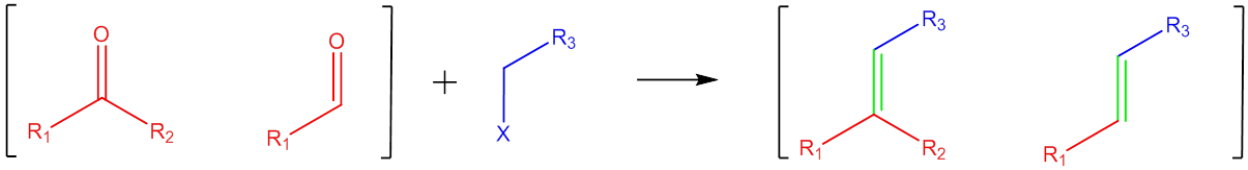
Wittig[1,40,41]



Reaction Notes:

- This reactions requires the formation of ylide from the alkyl halide by adding triaryl phosphine.
- Not stereoselective: both E/Z isomers can be formed depending on reaction conditions.
- R1 and R2: aryl, alkyl, vinyl, many functional groups tolerated here.
- X: Cl, Br, I
- Only primary alkyl halides allowed for second reactant.
- R3: must be a carbon, but not attached to Br, I, or OMet (eliminates ylide).

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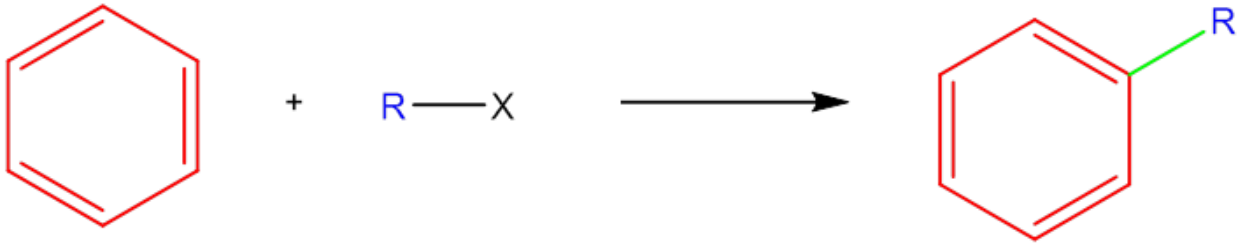
Friedel-Crafts Alkylation[42,43,44]



Reaction Notes:

- This reaction must utilize an arene.
- R: any alkyl group.
- Requires $FeCl_3$ catalyst.
- X: Cl, Br

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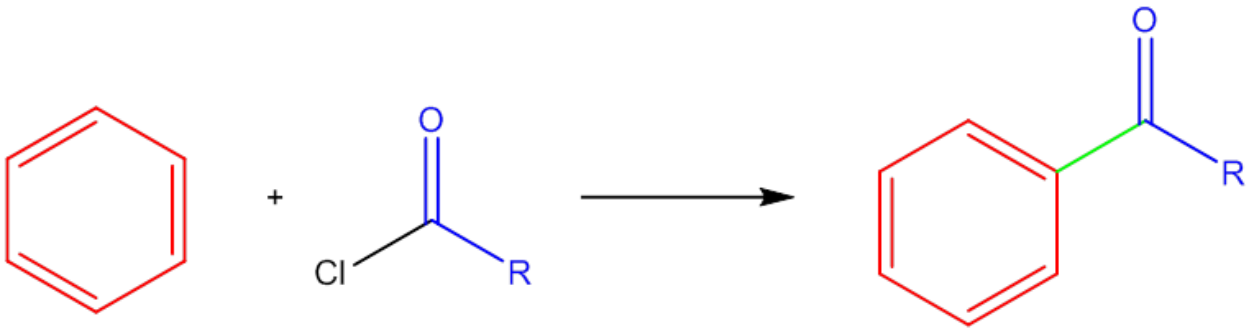
Friedel-Crafts Acylation[45,46,47]



Reaction Notes:

- This reaction must utilize an arene.
- R: any alkyl group.
- Requires Lewis Acid Catalyst $AlCl_3$.

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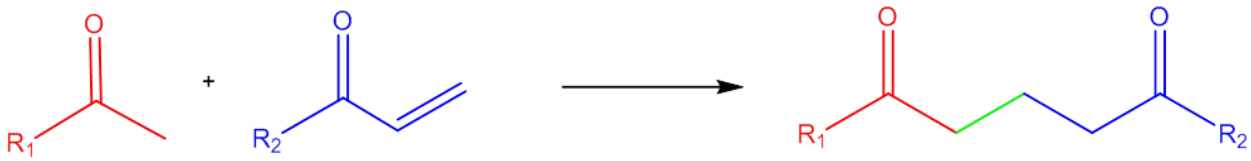
Michael-Addition[48]



Reaction Notes:

- This reaction requires a base (NaOH or KOH) to drive the reaction.
- R groups may be alkyl or aryl.

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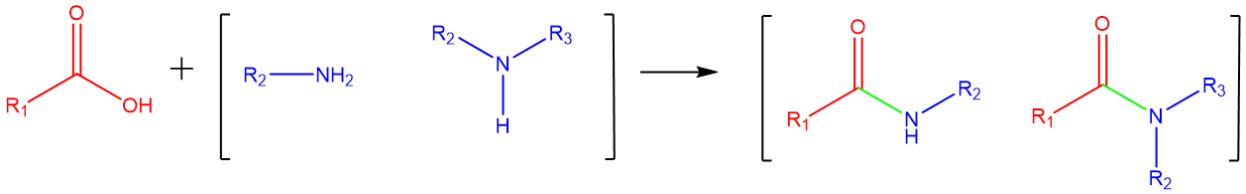
Schotten-Baumann Amide[1]



Reaction Notes:

- Activation of carboxy group (COOH→COCl) required as additional step.
- R1, R2, and R3: aryl allowed

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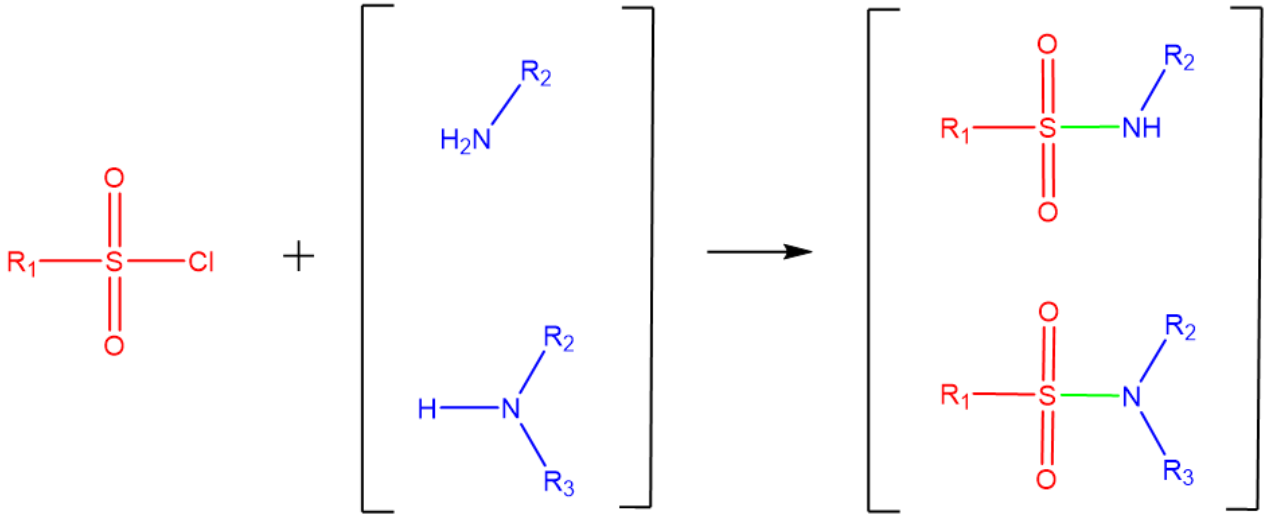
Sulfonamide[1]



Reaction Notes:

- R1: C, N

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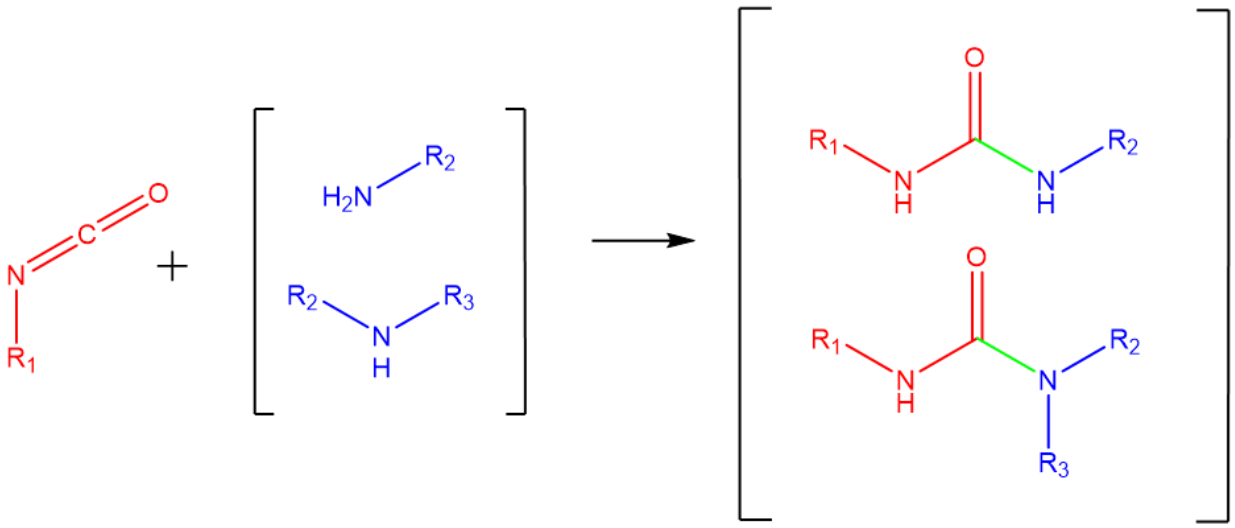
Wöhler[1]



Reaction Notes:

- R1: C, aryl, alkyl
- R2: C, aryl, alkyl
- R3: C, aryl, alkyl

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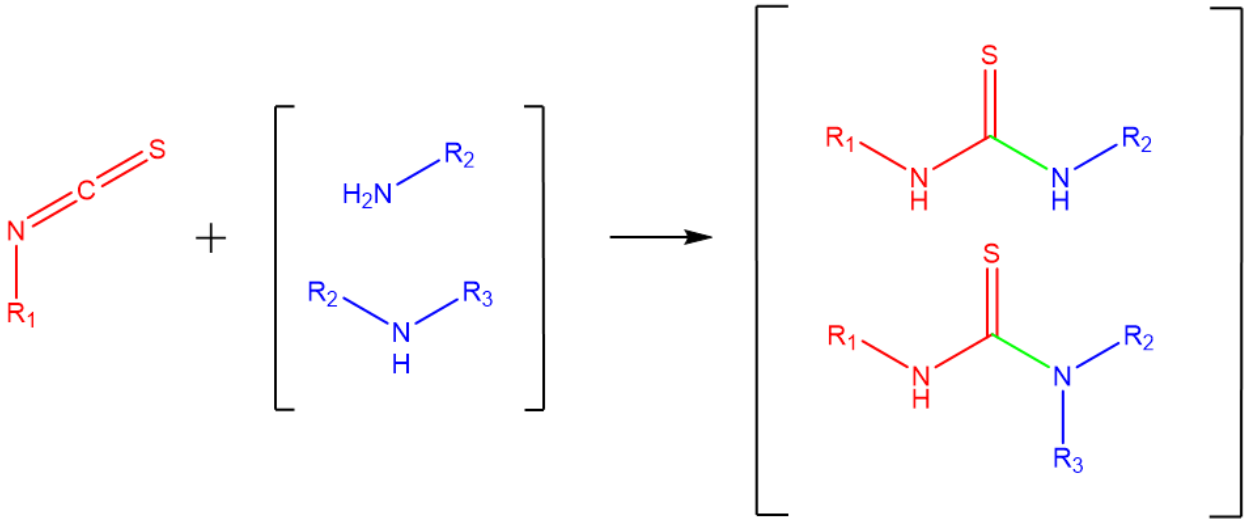
Thiourea via Nucleophilic Addition[1]



Reaction Notes:

- R1: C, aryl, alkyl
- R2: C, aryl, alkyl
- R3: C, aryl, alkyl

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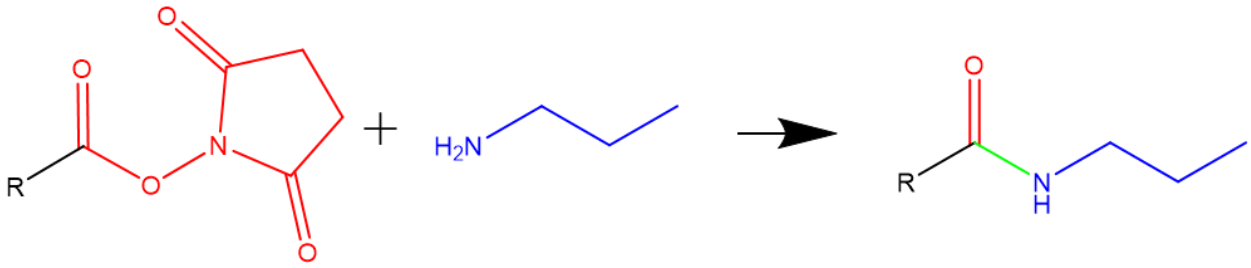
NHS Ester Reaction[49]



Reaction Notes:

- Requires the NHS (N-Hydroxysuccinimide) ester reagent.
- The R-group needs to start with an oxygen or carbon.
- The amine needs to be a primary amine.

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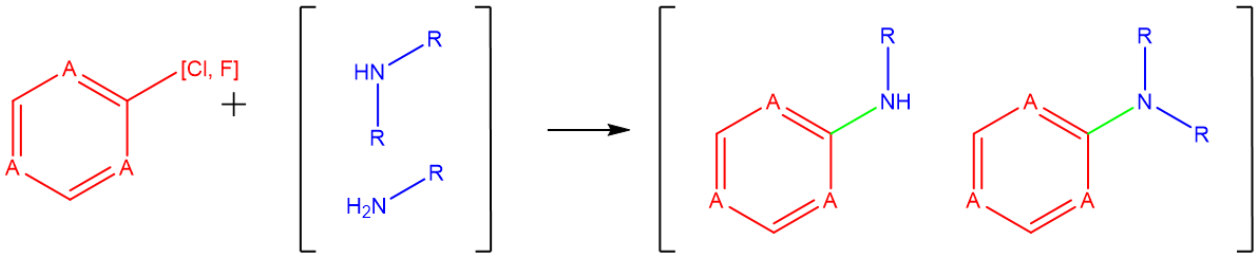
Heteroaromatic via Nucleophilic Substitution[1,50]



Reaction Notes:

- The heteroatoms activate the para and ortho positions for substitution.
- A: C or N of a pyridine, pyrimidine, or triazine.
- The N cannot be double bonded, triple bonded, or bonded to 3 heavy atoms.

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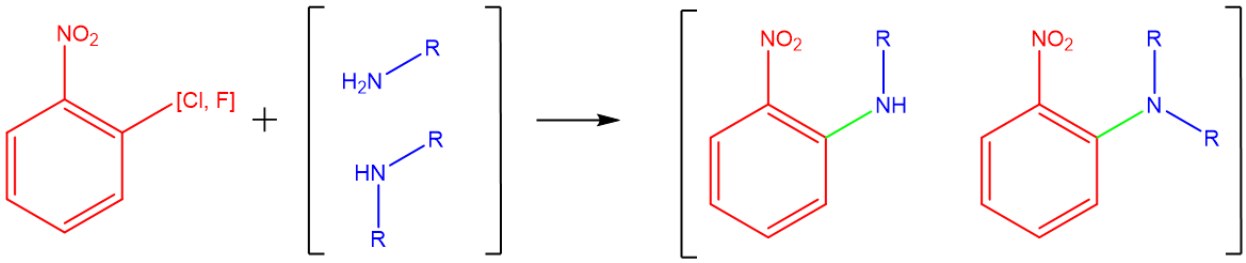
Ortho Substituted Nitroaniline via Nucleophilic Substitution[1,50]



Reaction Notes:

- The ortho nitro group has an activating effect on nucleophilic substitution.
- The N must not be charged, double bonded, or triple bonded.

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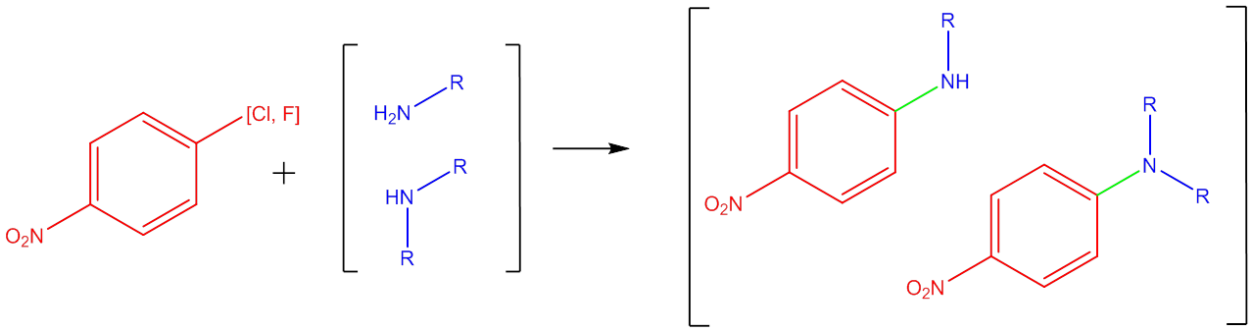
Para Substituted Nitroaniline via Nucleophilic Substitution[1]



Reaction Notes:

- The para nitro group has an activating effect on nucleophilic substitution.
- The N must not be charged, double bonded, or triple bonded.

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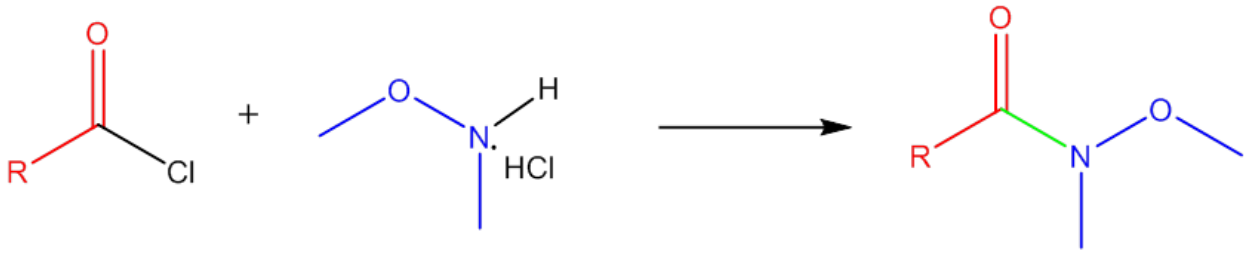
Weinreb-Nahm Amide[51,52]



Reaction Notes:

- R: aryl or alkyl.

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Staudinger Reaction[53,54]

Reaction Notes:

- Addition of PPh_3 is required to react with the azide.
- R: any alkyl or aryl group.

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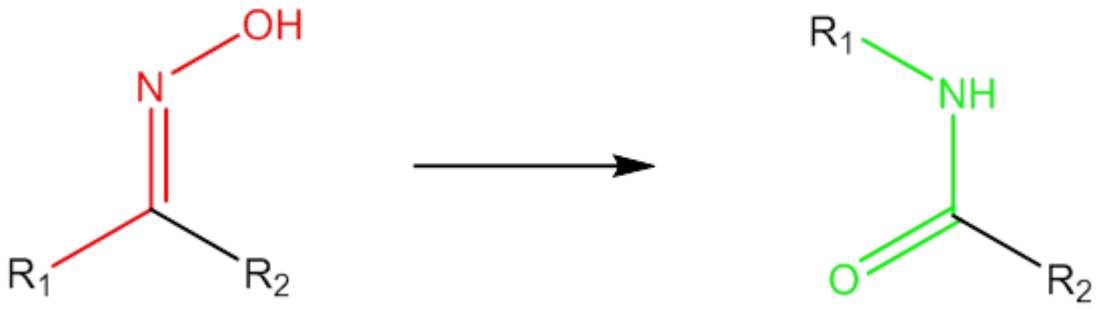
Beckmann Rearrangement[55,56]



Reaction Notes:

- Amide synthesis via oxime rearrangement.
- Requires acid catalyst H_2SO_4.

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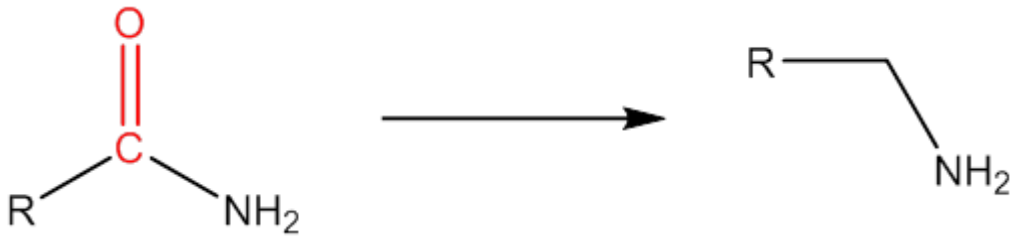
Amide Reduction[57,58]



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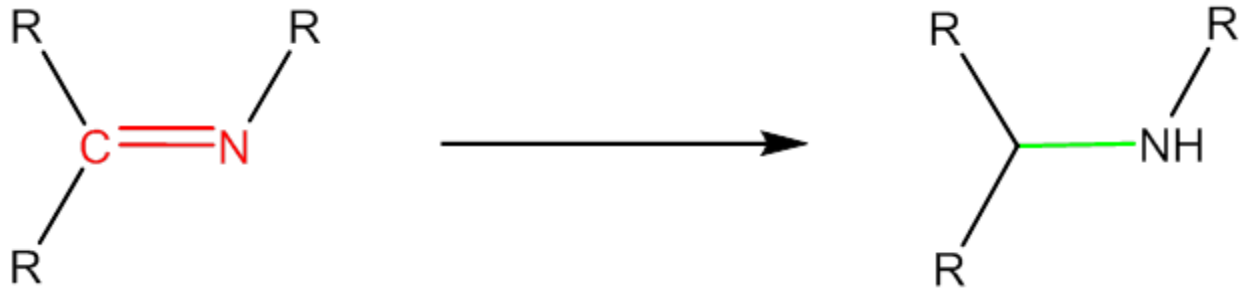
Imine Reduction[59,60]



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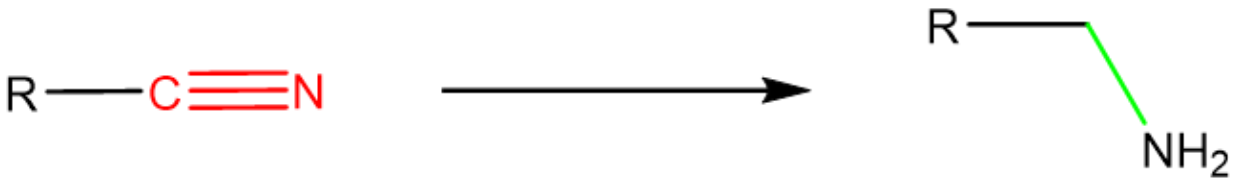
Nitrile Reduction[61]



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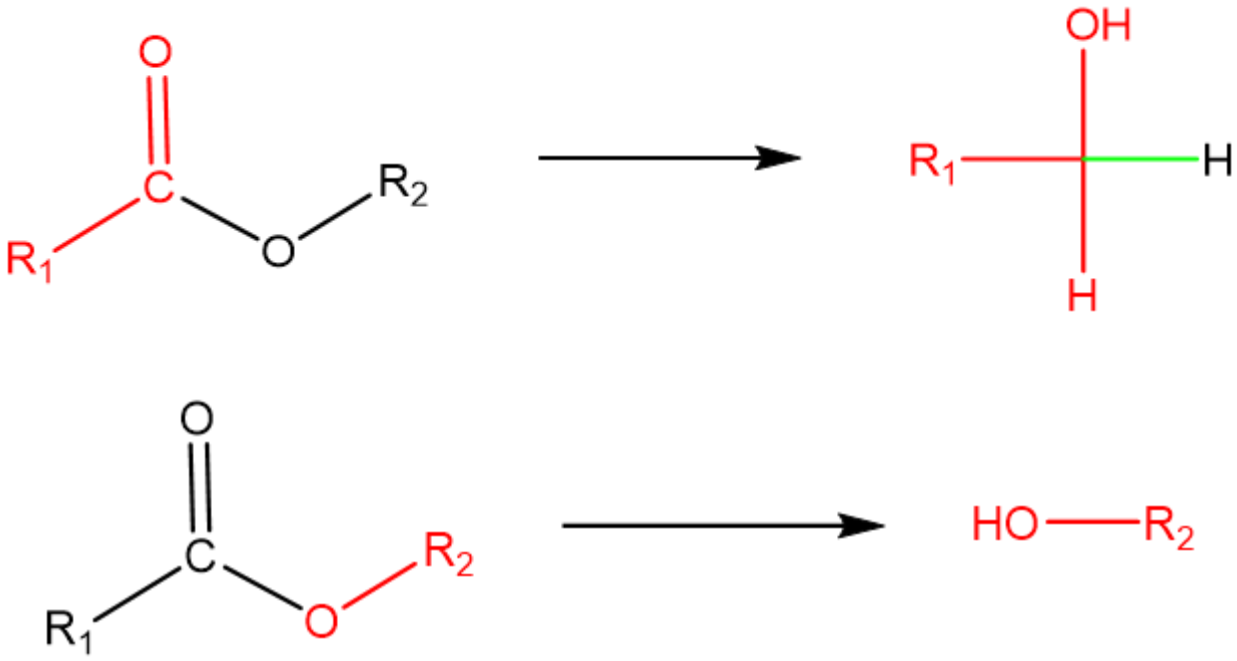
Ester Reduction[62]



Both products are formed; however, only one is randomly selected to be included in the synthesis.

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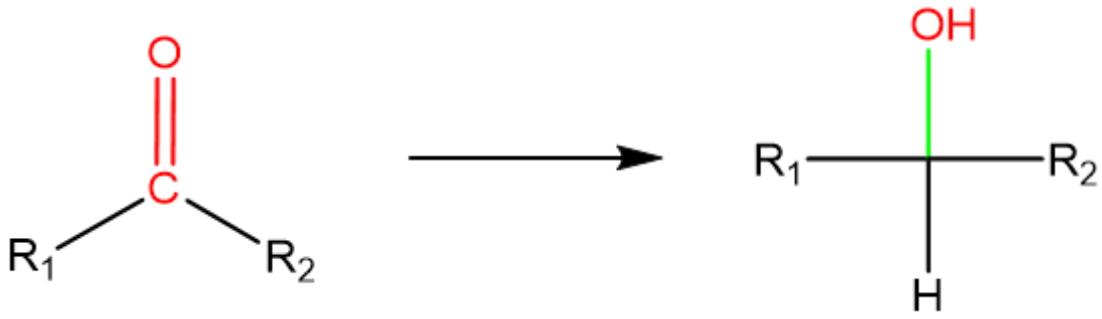
Ketone Reduction[63,64]



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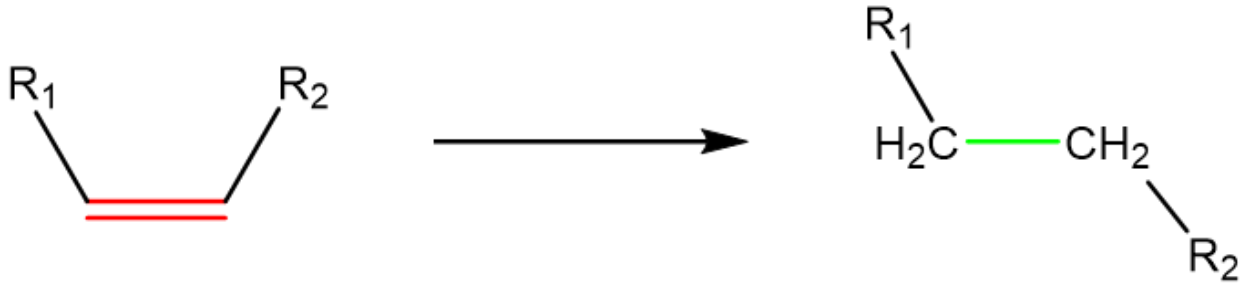
Alkene Reduction[65]



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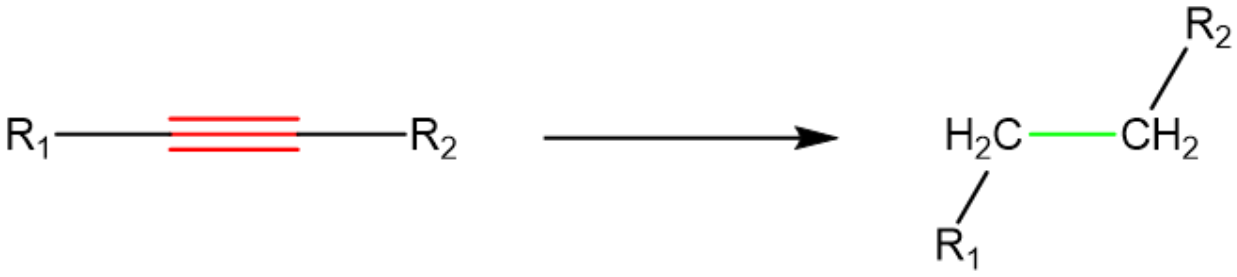
Alkyne Reduction



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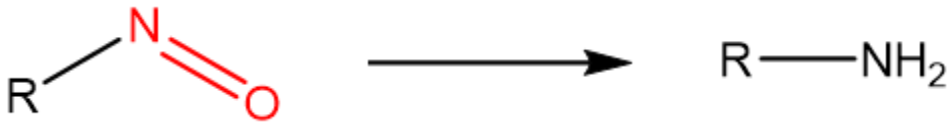
Nitroso_Reduction[66,67]



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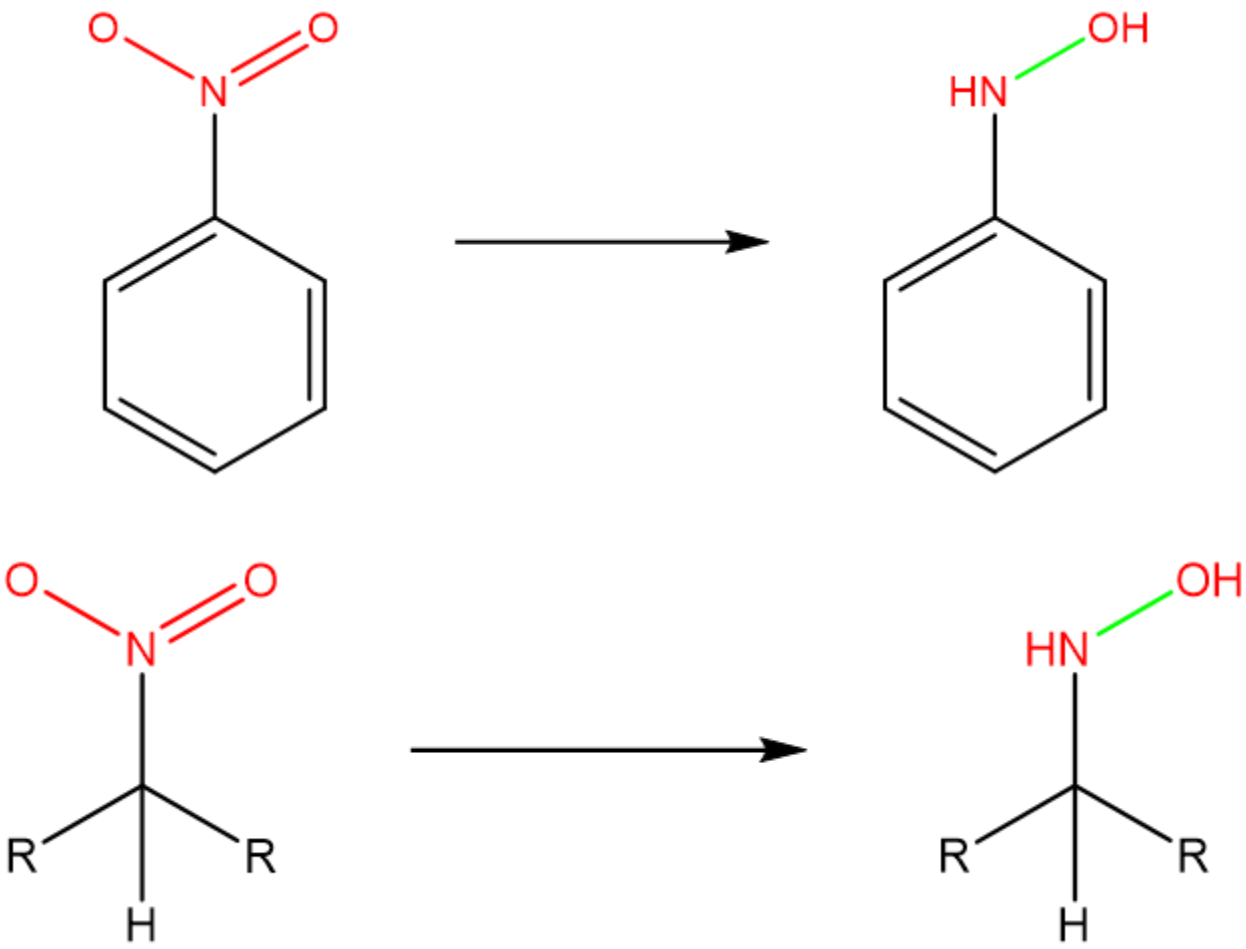
Nitro to Hydroxylamine[68,69]



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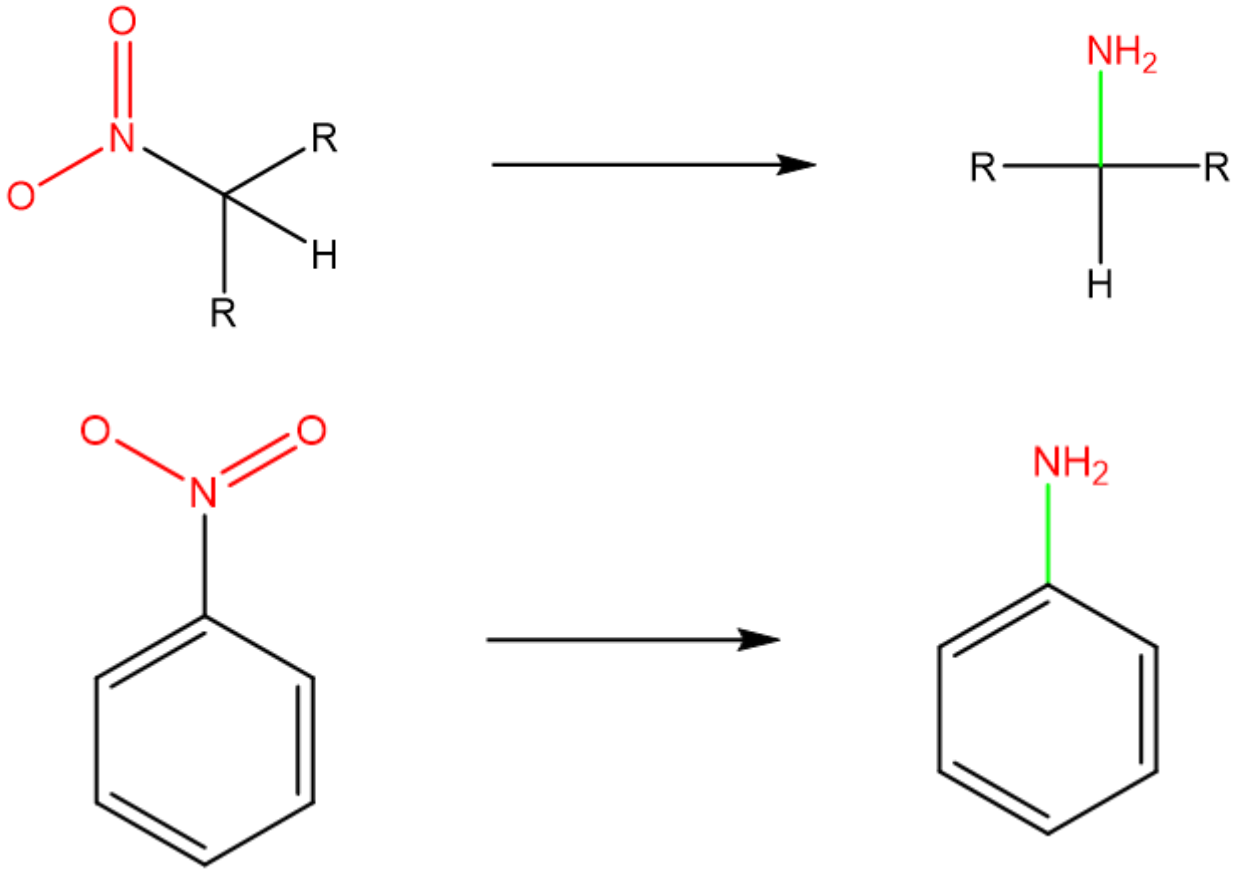
Nitro to Amine/Aniline[70,71]



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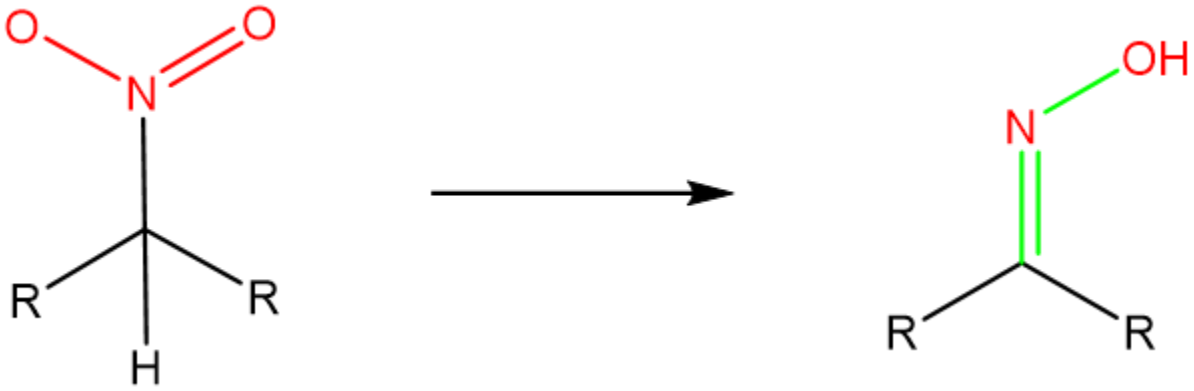
Aliphatic Nitro to Oxime[72,73]



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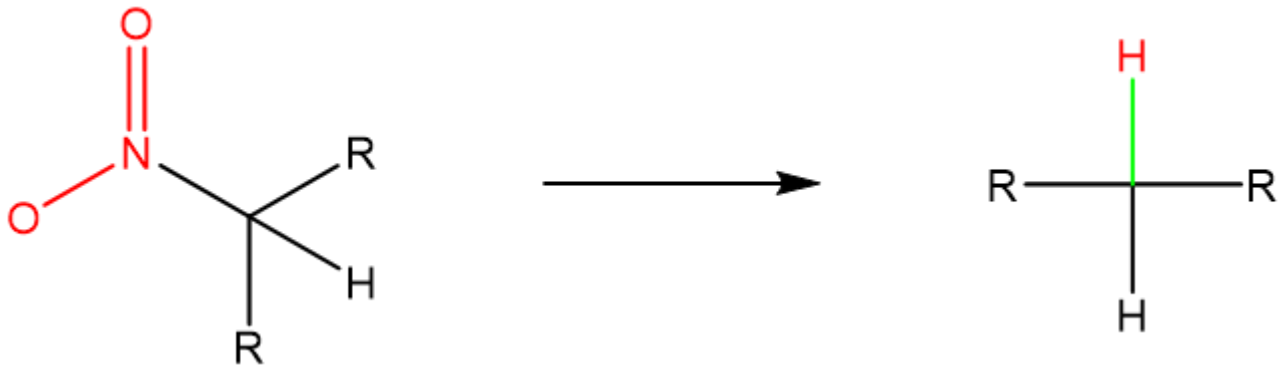
Aliphatic Nitro to Hydrocarbon[74,75]



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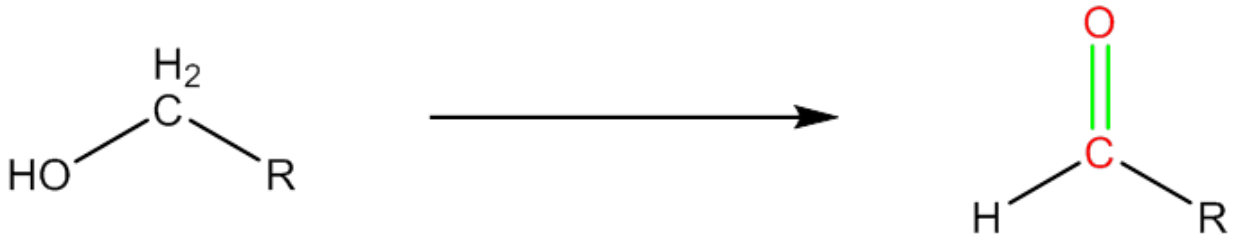
Primary Alcohol [O] to Aldehyde[57,76]



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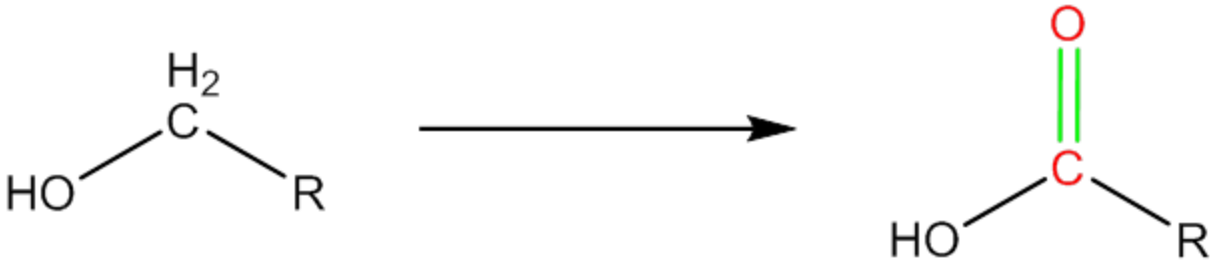
Primary Alcohol [O] to Carboxylic Acid[57,77]



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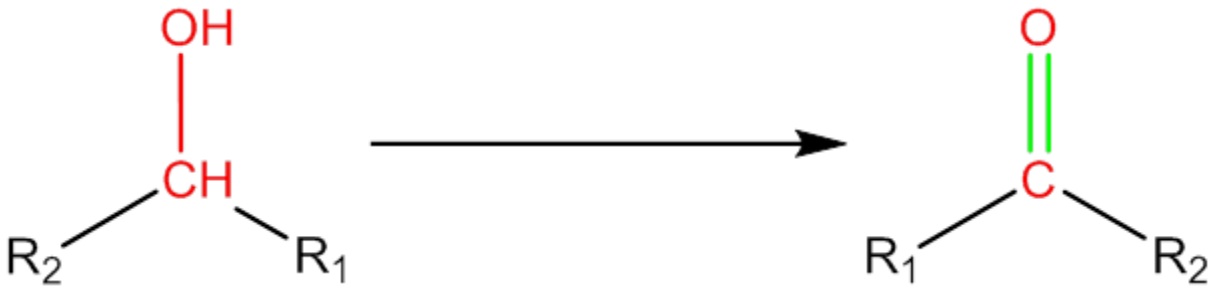
Secondary Alcohol [O] to Ketone[57,78]



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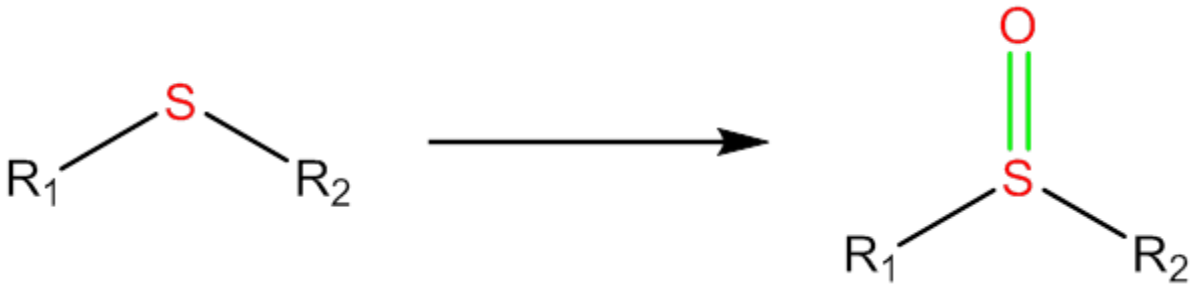
Sulfide to Sulfoxide[79,80]



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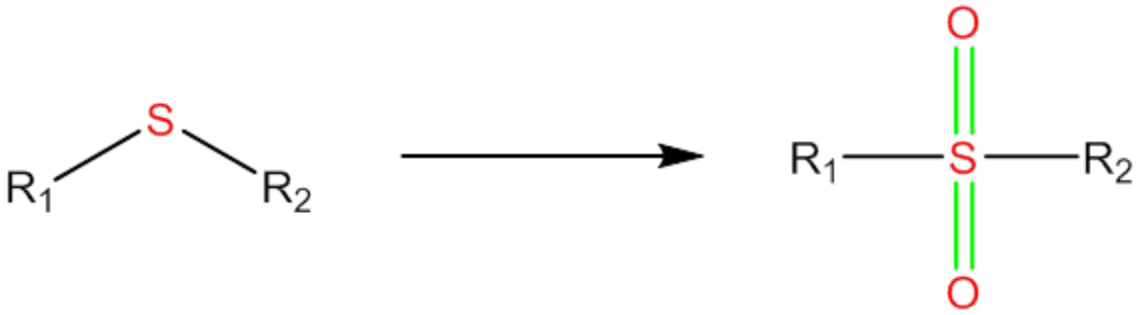
Sulfide to Sulfone[81]



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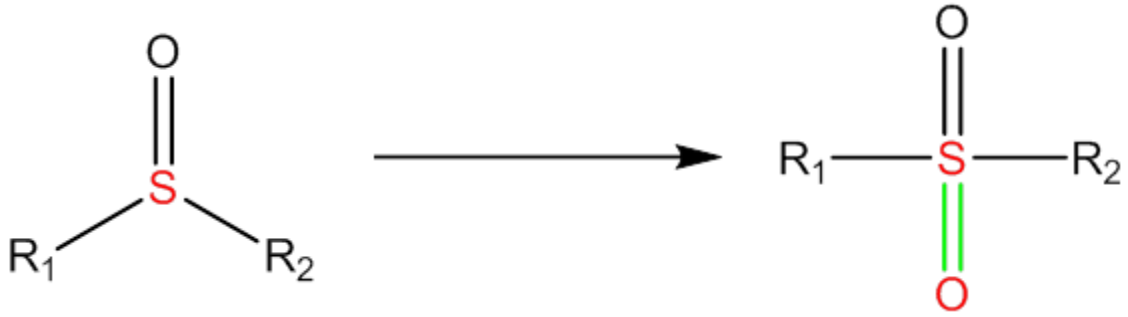
Sulfoxide to Sulfone[81]



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