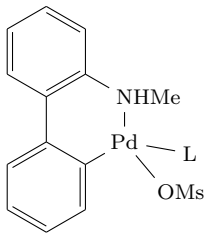
Topic 8

Exam 2

8.1 Exam 2 Review Sheet

3/20:

- Exam 1 content!
- Cross-coupling, revisited.
  - Heck reaction.
    - Mechanism: Oxidative additoin, ligand exchange, migratory insertion, β-hydride elimination, ligand exchange, reductive elimination.
    - Regioselectivity: Balance of aryl to less-substituted C (sterics), Pd to δ^- C (electronics).
      - ➢ Triflates exaggerate δ^+ on Pd.
  - Buchwald-Hartwig amination.
    - Palladium source: $Pd(OAc)_2$, $Pd_2(dba)_3$, precatalyst (e.g., the following).

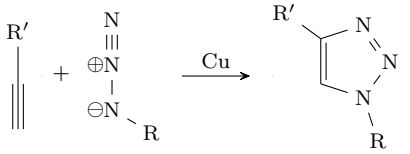


      - ➢ L = anything not super bulky, e.g., ^{t}BuBrettPhos.
    - Ligand: BINAP, Xantphos, many others.
    - Base: Weak (Cs_2CO_3) or strong (NaO^tBu) can work.
    - Solvent: Ethereal or aromatic hydrocarbon can work.
    - Temperature: RT-140 °C.
    - Mechanism: Activation then oxidative addition, binding, deprotonation and loss of X^- to give base $\cdot$ HX salt, reductive elimination.
  - Wacker oxidation.
  - Indole syntheses, promoted by Pd-catalyzed cross-coupling.
    - New mechanisms, but do not create any new substitution schemes.
  - Ullmann/Goldberg couplings.
    - Original method: Stoichiometric strong base, polar solvents, high temperatures.
    - Modern method: Ligands.
      - ➢ Heterocycle-amide couplings (Goldberg-type): Proline.

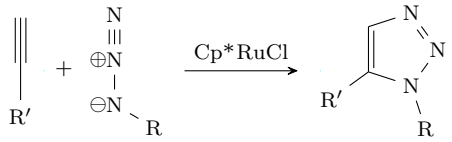
➢ Amine couplings (Ullmann-type): Oxalamides (even able heteroaryl chlorides!).
- Mechanism: Nucleophile binding, oxidative addition, reductive elimination.
  - ➢ May also be Pd-like in some cases (with oxidative addition first).
- Use sp^2-bromides and iodides (*not* sp^2-triflates).
- Catalytic CuI helpful.

- New heterocycles and their key properties.
  - 1,2,3-triazole.
    - Stability: Up to 500 °C.
    - Tautomerization: Rapid among all when unsubstituted.
    - Amphoteric, like imidazole.
    - Acidity: Protonated form ($pK_a = 1.2$).
    - 1,2,3-triazole containing chemical: Benzotriazole (chemical photography).
  - 1,2,4-triazole.
    - Tautomerization: Rapid among all when unsubstituted.
    - Acidity: Protonated form ($pK_a = 2.2$).
    - 1,2,4-triazole containing drug: Epoxiconazole (fungicide).
  - Tetrazole.
    - Tautomerization: Rapid.
    - Acidity: Comparable to a carboxylic acid.
    - Tetrazole-containing drug: Valsartan.
  - Oxazole.
    - Basicity: Mildly basic nitrogen (not great because poor resonance).
    - Acidity: C2 can be deprotonated with LDA.
    - Aromaticity: Less aromatic than thiazole.
    - Oxazole-containing drug: Neopeltolide (oncology).
  - Isoxazole.
    - Reactivity: Some EAS.
    - Isoxazole-containing drug: Valdecoxib (pain).
  - Thiazole.
    - *Reactivity, acidity, basicity, nucleophilicity, protonation, π-excessive/deficient, hydrogen bonding, tautomerization, etc.*
    - Basicity: More basic than oxazole (lower EN of S vs. O).
    - Aromaticity: Greater than oxazole.
    - Reactivity: EAS at enamine carbon (C5).
    - Thiazole-containing natural product: Thiamine aka vitamin B1.
  - 1,2,4-oxadiazole.
    - Reactivity: Explosophore.
  - 1,3,4-oxadiazole.
    - 1,3,4-oxadiazole-containing drug: Raltegravir (HIV).

- 1,2,3-triazole synthesis.
  - $[3 + 2]$ dipolar azide-alkyne cycloadditions.
    - Making aliphatic azides: Use S_N2.
    - Making aryl azides: Use 1. HONO, 2. NaN_3.



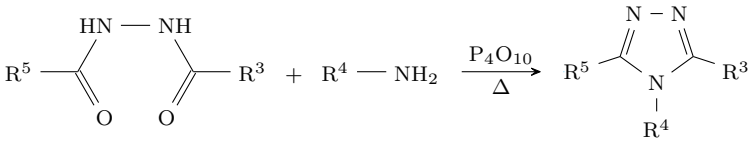
(a) CuAAC (1,4-substitution).



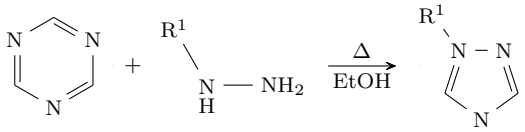
(b) RuAAC (1,5-substitution).

- Possible mechanism: Sonogashira-type copper acetylide formation, azide coordination, electrocyclization, ring contraction, elimination.

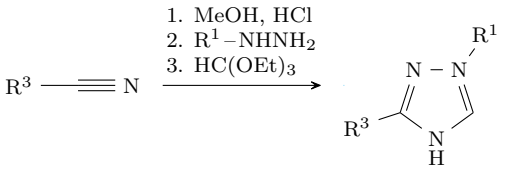
- 1,2,4-triazole synthesis.
  - **Paal-Knorr-type** (1,2,4-triazole synthesis): (3)(4)5-substitution.



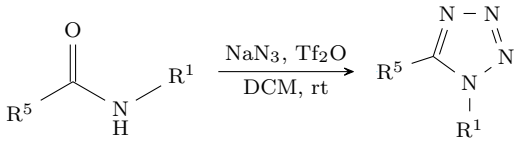
  - *sym*-Triazine-type (1,2,4-triazole synthesis): 1-substitution.



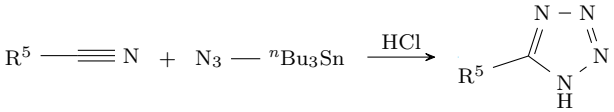
  - Acyl hydrazides and chloroimidates: Enables formation of same derivatives.
  - **Pinner-type** (1,2,4-triazole synthesis): 13-substitution.



- Tetrazole synthesis.
  - **Vilsmeier-Haack-type** (tetrazole synthesis): 15-substitution.

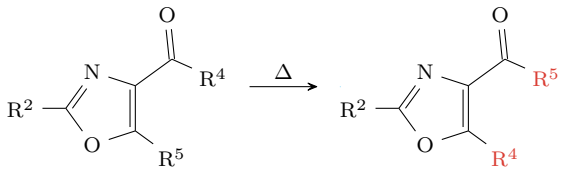


  - Tin azide-type (tetrazole synthesis): 5-substitution.

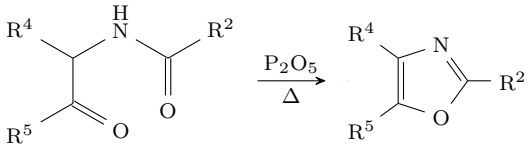


  - **Passerini** (tetrazole synthesis): Enables formation of same derivatives.

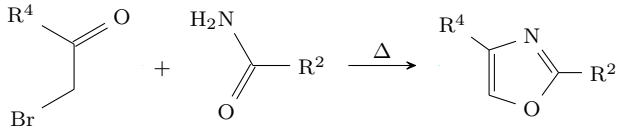
- Oxazole reactivity.
  - S_NAr at C2 with good LG (e.g., chloride).
  - C2-lithiation and electrophilic functionalization (via ring-opened isocyanide).
  - 5-addition (2-lithiation, TIPS protection, 5-lithiation, functionalization, PG removal).
  - Lateral deprotonation.
  - **Cornforth rearrangement**.



- Oxazole synthesis.
  - **Robinson-Gabriel** (oxazole synthesis): 2(4)5-substitution.

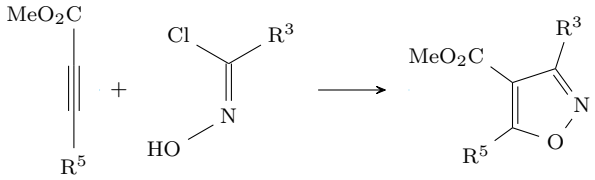


  - **Blümlein-Lewy** (oxazole synthesis): 24-substitution.



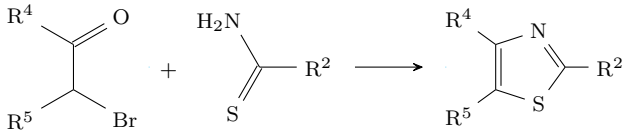
  - **Fischer** (oxazole synthesis): Enables formation of same derivatives.

- Isoxazole synthesis.
  - Dipolar cycloaddition: 5-ester-34-substitution.

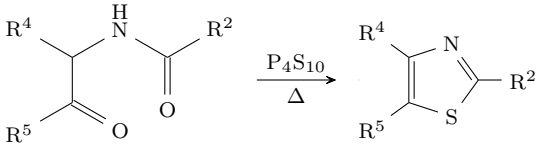


    - Nitrile oxides formed from 1,3-elimination of oximes.
    - Esters can be saponified.
    - R^5 can be bromine, and then hydrogenated.

- Thiazole synthesis.
  - **Hantzsch** (thiazole synthesis): 24(5)-substitution.

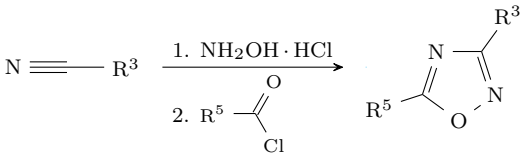


    - Other halides and pseudo-halides can be used in place of a bromide.
  - **Van Leusen** (thiazole synthesis): Enables formation of 4-tosyl-5-thioesterthiazoles.
  - **Cook-Heilbron** (thiazole synthesis): Enables formation of 2-thio-5-amino-4-substituted thiazoles.
  - **Robinson-Gabriel** (thiazole synthesis): 2(4)5-substitution.



- 1,2,4-oxadiazole synthesis.

  - **Pinner-type** (1,2,4-oxadiazole synthesis): 35-substitution.



- 1,3,4-oxadiazole sythesis.
  - **Robinson-Gabriel-type** (1,3,4-oxadiazole syntheiss): 25-substitution.