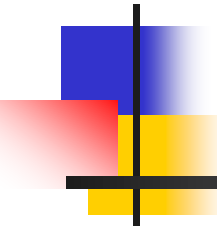


CHEMISTRY 4000

Topic #1: Introduction

Spring 2022

Dr. Susan Findlay

Introduction to Retrosynthetic Analysis

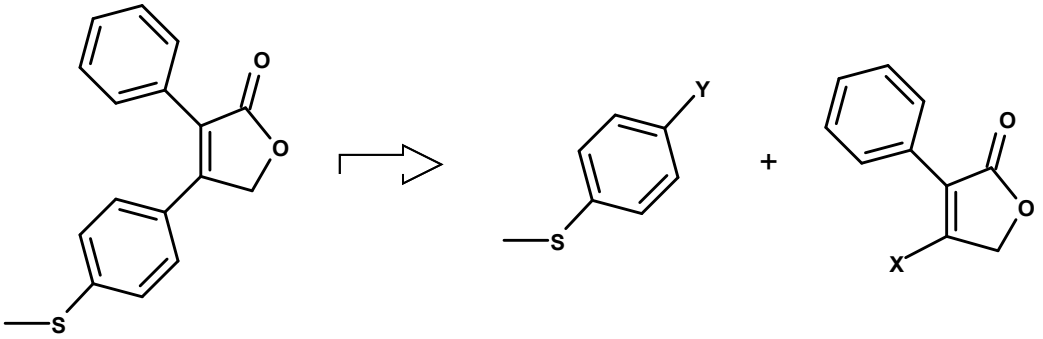
- Any synthesis of a specific target molecule must account for three main factors:
  - Skeletal structure
  - Functional groups
  - Stereochemistry (relative and absolute)

Introduction to Retrosynthetic Analysis

- Syntheses are typically developed via **retrosynthesis**, a mental exercise in which the chemist works backward from the target molecule to manageable starting materials.

- The process of breaking the target molecule into two pieces is referred to as a **retrosynthetic disconnection**.

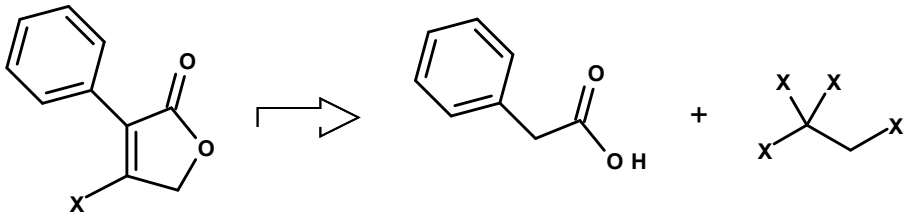
  e.g. When rofecoxib was originally analyzed, it is likely that a key retrosynthetic disconnection was identified between the substituted benzene ring and the lactone:



This gives two smaller targets rather than one large one.

Introduction to Retrosynthetic Analysis

- Retrosyntheses often use multiple retrosynthetic disconnections. In the previous example, more retrosynthetic disconnections would have been identified for the lactone intermediate:

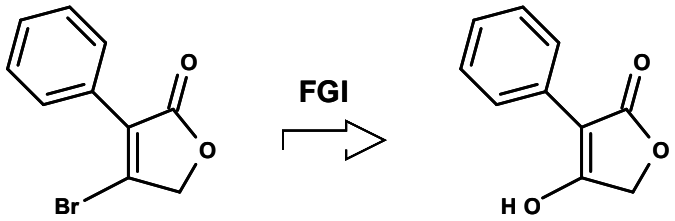


- Note that, while the chemist has to be reasonably sure that a reaction exists to perform the corresponding connection in the forward direction, specific leaving groups, etc. are not necessarily identified since there may be a number of possibilities. The X in the sketch above are not all intended to be the same as each other!
- Also, note that, for a target of any complexity, there are many good retrosyntheses, and there is rarely (if ever) such thing as a "best" retrosynthesis.

Introduction to Retrosynthetic Analysis

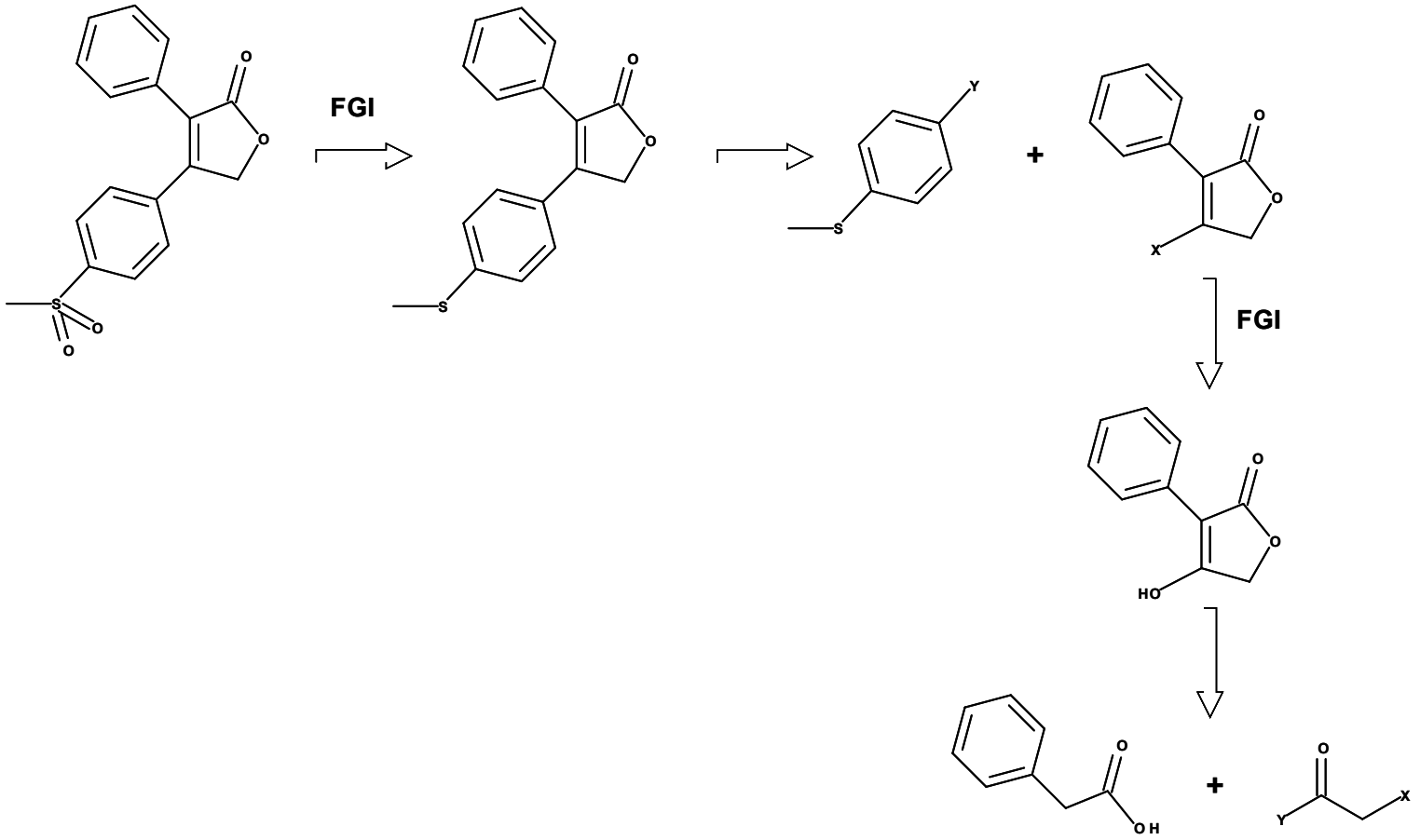
- It would be extremely unusual for a chemist to be able to use a series of retrosynthetic disconnections to arrive at commercially available starting materials directly from the target. Usually, it is necessary to manipulate the functional groups somewhat between disconnections.
- A **functional group interchange** (FGI) is exactly what it sounds like – a retrosynthetic transformation in which one functional group is converted into another.

  e.g. In the rofecoxib retrosynthetic analysis, it would have been obvious to an experienced chemist that a vinyl bromide would not be the immediate product of the lactone-forming reaction. If a vinyl bromide was desired for the final coupling reaction, a FGI would have been planned:



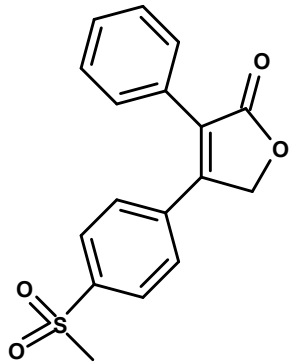
Introduction to Retrosynthetic Analysis

- The overall retrosynthetic analysis giving rise to the synthesis we saw in the first problem set might look like:



Introduction to Retrosynthetic Analysis

- When a target is subjected to retrosynthetic analysis, a bond-set is generated (a set of the bonds which will be formed via reactions in the forward synthesis). For this synthesis of rofecoxib, the bond set would be:



- Note that the resulting pieces are small enough that they should either be commercially available or easy to make from something commercially available (sometimes easier said than done!)

Introduction to Retrosynthetic Analysis

- Hoffmann suggests that choice of bond-set will be dictated by four considerations:
  - Functional groups
  - Skeletal structure
  - Available building blocks
  - Expertise in particular reactions or reaction classes

- Choosing disconnections based on functional groups:

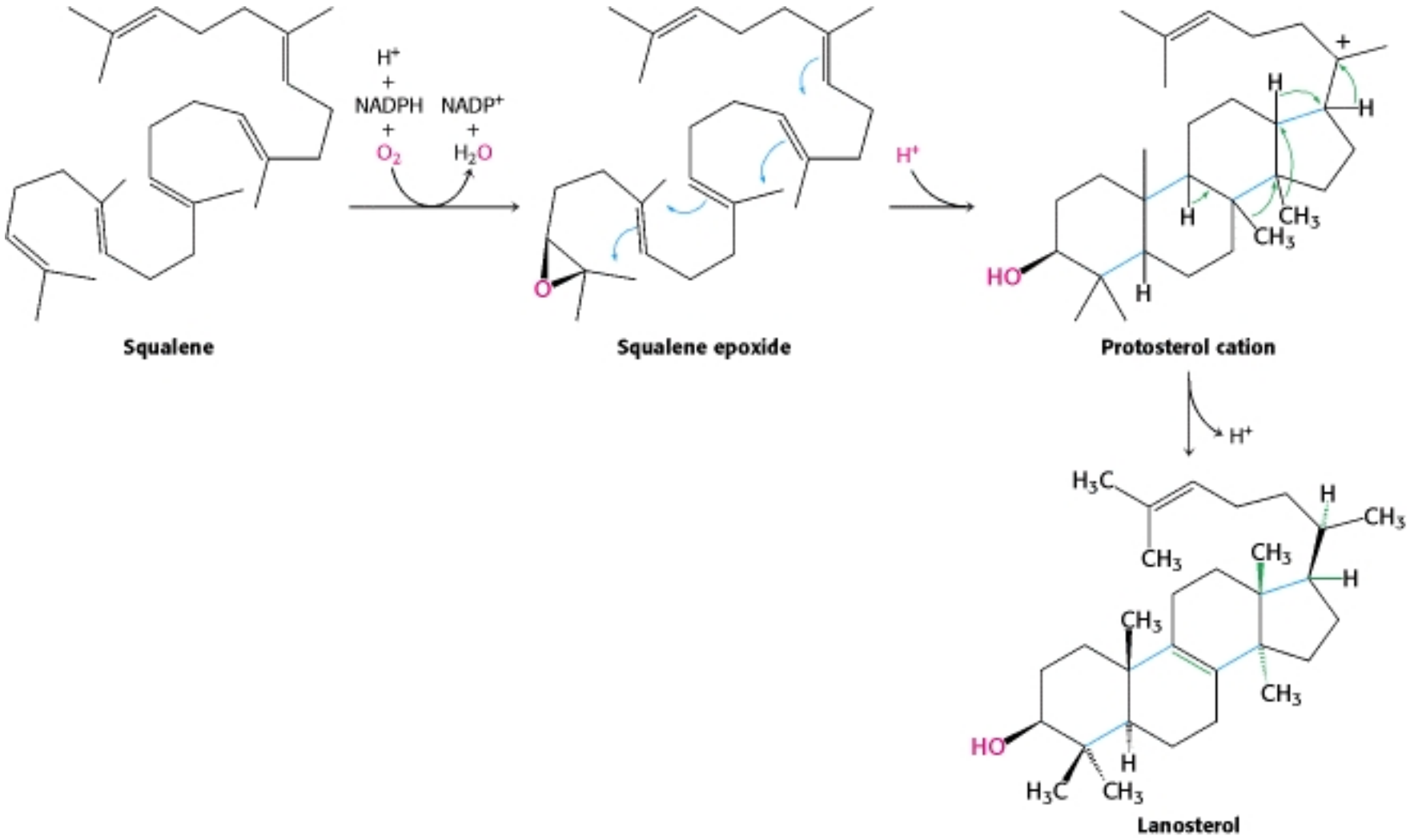
Introduction to Retrosynthetic Analysis

- Choosing disconnections based on skeletal structure:

Introduction to Retrosynthetic Analysis

- Choosing disconnections based on available building blocks:

Introduction to Retrosynthetic Analysis



Introduction to Retrosynthetic Analysis

- Choosing disconnections (or even synthetic targets) based on expertise in particular reactions or reaction classes is common, but not really something I can teach you. ☺

- It would be rare for a retrosynthesis not to be influenced by all four considerations, but sometimes one or two will dominate. Which consideration(s) appear to have dominated the retrosynthetic analysis on page 6 of these notes?

Sidenote – Suzuki Cross-Coupling Reactions

- The medicinal chemists at Merck published several studies on the Suzuki cross-coupling reaction. So, they did have a fair amount of expertise with that methodology, and that may have influenced their choice of reaction (or, alternatively, they may have become experts once the reaction became important to them).

- What is a Suzuki cross-coupling reaction?
  - It couples two molecules at aryl (or vinyl) carbon atoms.
  - One of the molecules must have a good leaving group bonded to the carbon to be coupled. It is traditionally a halide (usually ArBr or ArI) but can sometimes be a triflate ($ArOSO_2CF_3$) or diazonium salt (ArN_2BF_4 or ArN_2PF_6)
  - The other molecule must have a boronic acid group bonded to the carbon to be coupled. (Alternatively, a boronic ester can be used as long as the reaction conditions hydrolyze it to a boronic acid so that the reaction can proceed.)
  - A Pd[0] catalyst is required. $Pd(PPh_3)_4$ is a popular choice.

Sidenote – Suzuki Cross-Coupling Reactions

- A few examples of Suzuki cross-coupling reactions:

Sidenote – Suzuki Cross-Coupling Reactions

- Trickier cases need better catalysts:

Sidenote – Suzuki Cross-Coupling Reactions

- The catalytic cycle:

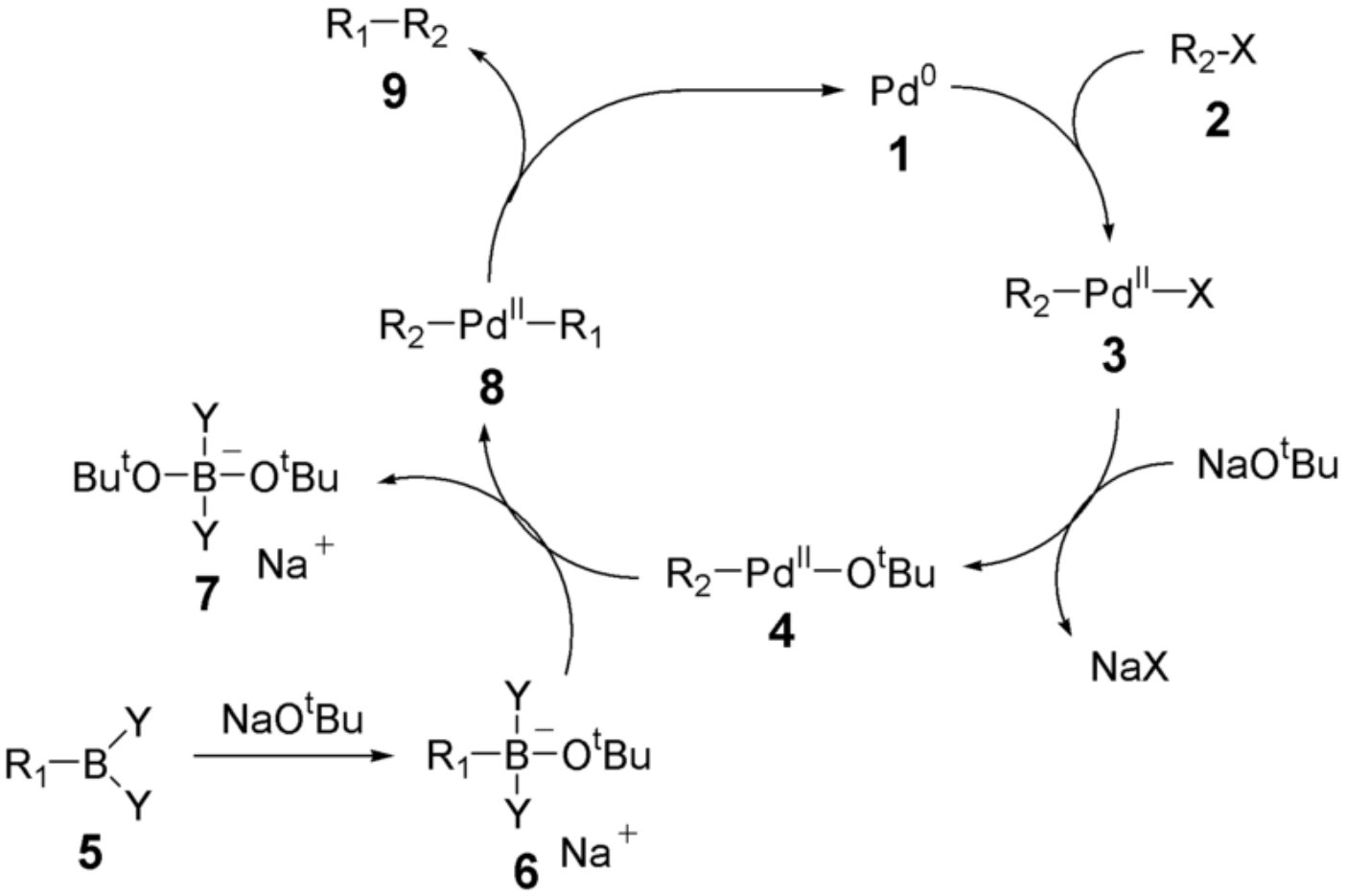


Image from Wikimedia Commons: http://en.wikipedia.org/wiki/File:Suzuki_Mechanism_Pd_Cycle.png

Sidenote – Suzuki Cross-Coupling Reactions

- What the catalytic cycle looks like with real molecules: