

Student Manual for
Aerobic Alcohol Oxidation Using a Copper(I)/TEMPO Catalyst System

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15 Aerobic oxidation of a 1° alcohol

15.1 Introduction

Earlier in the course you oxidized 4-*tert*-butylcyclohexanol (a 2° alcohol) to the corresponding ketone using a mixture of bleach and acetic acid (Chapter 8, p. 67). In this experiment, you will use a recently discovered Cu-based aerobic oxidation catalyst system to convert a 1° alcohol to the corresponding aldehyde.

15.2 Oxidizing agents

In addition to the bleach/acetic acid oxidation system, you may have heard of metal-based oxidizing agents such as pyridinium chlorochromate (PCC), CrO₃ in conc. H₂SO₄ (Jones reagent), KMnO₄ and OsO₄ in CHEM 343 lecture. Such reagents are traditionally used in organic synthesis research labs to accomplish a range of oxidations; however, despite their utility, they feature a number of disadvantages:

- a) the reagents are often highly toxic, environmentally harmful and difficult to dispose;
- b) they are typically used in stoichiometric amounts (*i.e.* the same molar amount as the substrate that is being oxidized);
- c) they yield by-products (such as inorganic salts) that have to be separated from the desired product;
- d) they often promote over-oxidation, in which the desired product undergoes further oxidation before it can be isolated. For example, aldehydes are often over-oxidized to carboxylic acids.

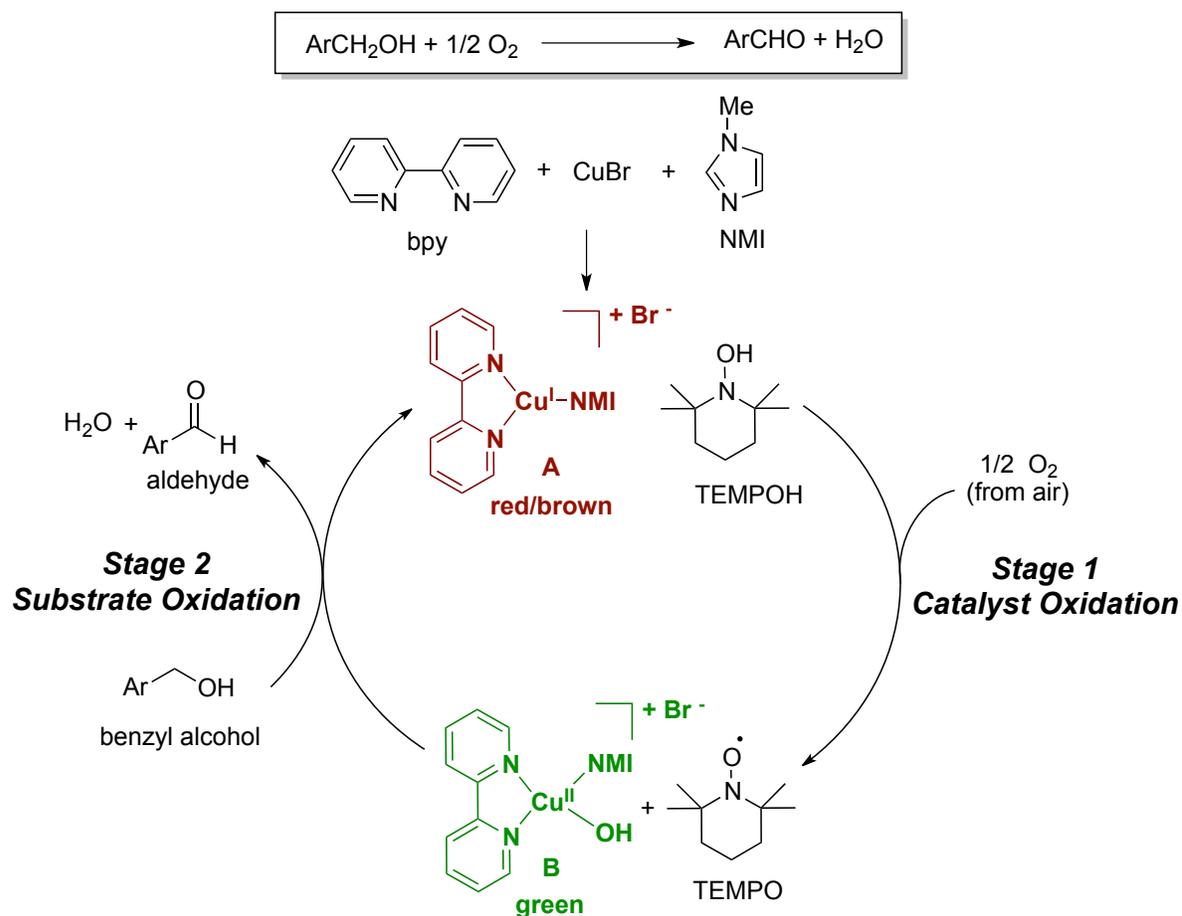
These and other factors often make it difficult to scale-up stoichiometric metal-based oxidation reactions for use in the synthesis of fine-chemicals and pharmaceuticals.

Instead of using stoichiometric oxidants alone, many research groups are focused upon the development of *catalytic* systems that enable the use of atmospheric O₂ as the stoichiometric oxygen source. Recall that a catalyst is an additive used in a sub-stoichiometric amount that increases the rate of a chemical reaction without itself being consumed or undergoing a net chemical change. In other words, a catalyst lowers the activation energy of a chemical process by lowering the energy of the transition state (ΔG^\ddagger) for conversion of reactants to products. The catalyst does not alter the energy of the reactants or products!

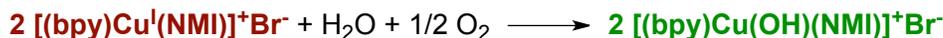
You have already used a simple transition metal catalyst in CHEM 344 in order to perform the Suzuki coupling reaction (Chapter 14, p. 119).

In this experiment you will use a catalytic system consisting of copper(I) bromide (CuBr), 2,2'-bipyridine (bpy), *N*-methyl imidazole (NMI) and a stable organic radical (TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy) in combination with atmospheric oxygen as the stoichiometric oxidant to convert an unknown primary alcohol to the corresponding aldehyde. You will determine the identity of the unknown alcohol using a combination of ¹H- and ¹³C-NMR, GC-MS, and % elemental composition data (see p. 131). The identity of the product will be determined by ¹H-NMR and EI-MS data.

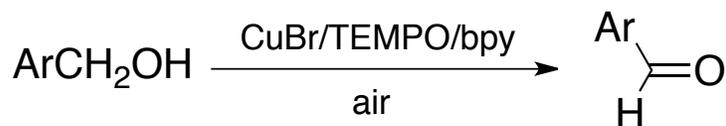
The catalytic oxidation system used in this experiment was recently reported by UW-Madison chemists Dr. Jessica Hoover and Prof. Shannon Stahl (see *J. Am. Chem. Soc.* **2011**, *133*, 16901-16910 for details). A simplified version of the catalytic cycle of this reaction is shown below – it will be discussed further in the pre-lab discussion session.



Initiation step (TEMPOH is not present at the beginning of the reaction):



Procedure



You need to calculate the mass (g) of unknown alcohol to use - have your TA check the calculation before you begin the experiment.

Work in pairs. To a 125 mL Erlenmeyer flask containing a stir bar add the unknown alcohol (2.5 mmol) and acetone (15 mL). Weigh CuBr (35 mg), bpy (40 mg) and TEMPO (40 mg) into separate small glass vials.

To the rapidly stirred solution of the unknown alcohol add sequentially CuBr, bpy and TEMPO as solids, following each addition with ~3 mL rinse of solvent (for total of ~25 mL solvent volume). Add NMI (4 drops, the color of the reaction solution will fade) and stir the mixture rapidly until you observe a significant color change, then stir for a further 5 min.

Transfer the reaction mixture to a 250 mL separatory funnel. Add water (25 mL) and pentane (25 mL) and extract the organic product into the organic solvent with vigorous shaking. Remove the aqueous layer (think about which layer is which!) and extract it with pentane (10 mL). Combine the organic layers and stir over anhydrous MgSO₄ for ~10 min.

Remove the MgSO₄ by filtration (think about which type of filter funnel to use) and transfer the filtrate into a weighed beaker or flask. Evaporate the solvent in a fume hood using a rotary evaporator or under a stream of dry nitrogen. After the solvent is removed, note the appearance of the product. Determine the % yield and submit a sample of the product for ¹H-NMR and GC-MS analysis.

Lab Report

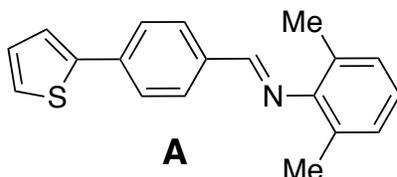
In addition to answering the post-lab questions below, your report should include:

- calculations showing the molecular formula of your unknown starting alcohol;
- clear drawings of the ¹H- and ¹³C-NMR spectra of the alcohol based on the provided data;
- the structure of the starting alcohol based upon the fully interpreted NMR and MS data (assign all signals in the ¹H-NMR spectrum, assign ¹³C-NMR signals as either alkyl or aromatic, and draw fragments for the most likely molecular ion and the base peak in the EI-MS);
- the structure of the product based upon your fully assigned experimental ¹H-NMR and MS data (assign all integrated signals in the ¹H-NMR spectrum, and draw fragments for the most likely molecular ion and the base peak in the EI-MS).

Post-lab questions

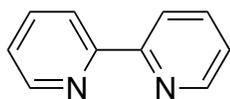
1) What evidence would appear in the $^1\text{H-NMR}$ and IR spectra indicating over-oxidation of the aldehyde?

2) Show how compound **A** could be synthesized from 4-bromobenzaldehyde using a combination of reactions that you have studied in CHEM 344. Clearly draw and name the reactions you propose (you do not need to show the mechanism for each reaction).

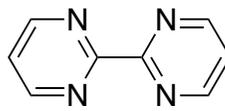


3) In the Suzuki-coupling lab report you used computational modeling to analyze the competing effects of π -conjugation and steric repulsion in a series of simple biphenyl compounds.

The oxidation catalyst component 2,2'-bipyridine (bpy) is essentially a biphenyl molecule substituted by an N-atom at one of the *ortho* positions on each ring.



2,2'-bipyridine



2,2'-bipyrimidine

a) Repeat the calculations you performed in the Suzuki-coupling lab report on 2,2'-bipyridine (*cis* and *trans* isomers) and 2,2'-bipyrimidine. Record the dihedral angle between the two rings of each molecule and visualize (and show in your answer) the molecular orbitals responsible for cross-ring conjugation.

b) Provide a brief explanation for the observed geometry of the above molecules that considers how the competing effects of π -conjugation and steric repulsion influence the structure, and compare the structures to that of the biphenyl molecules modeled in Chapter 14.

Unknown A

Molecular mass: 142.64 g/mol

Elemental composition: 58.95 % C; 4.97 % H; 11.23 % O, 24.85 % X (X= halogen)

$^1\text{H-NMR}$: δ 2.70 (s, 1H); 4.50 (s, 2H); 7.29 (d, 2H); 7.21 (d, 2H).

$^{13}\text{C-NMR}$: δ 64.13; 128.23; 128.63; 133.22; 139.12

EI-MS: m/z 144 (23%); 142 (70%) 107 (100%)

Unknown B

Molecular mass: 122.18 g/mol

Elemental composition: 78.64% C; 8.27% H; 13.09% O

$^1\text{H-NMR}$: δ 2.31 (s, 3H); 2.35 (s, 1H); 4.55 (s, 2H); 7.10 (d, 2H); 7.21 (d, 2H).

$^{13}\text{C-NMR}$: δ 21.09; 64.58; 127.12; 129.01; 136.89; 138.04

EI-MS: m/z 122 (87%); 107 (100%), 91 (53%)

Unknown C

Molecular mass: 187.04 g/mol

Elemental composition: 44.95 % C; 3.78 % H; 8.55 % O, 42.72 % X (X= halogen)

$^1\text{H-NMR}$: δ 2.44 (s, 1H); 4.54 (s, 2H); 7.17 (d, 2H); 7.44 (d, 2H)

$^{13}\text{C-NMR}$: δ 64.28; 121.35; 128.54; 131.52; 139.73

EI-MS: m/z 188 (56%); 186 (58%); 157 (18%); 155 (10%); 107 (100%)

Unknown D

Molecular mass: 150.24 g/mol

Elemental composition: 79.94 % C; 9.41 % H; 10.65 % O

$^1\text{H-NMR}$: δ 1.23 (d, 6H); 2.28 (s, 1H); 2.89 (sept, 1H); 4.57 (s, 2H); 7.18 (d, 2H); 7.26 (d, 2H)

$^{13}\text{C-NMR}$: δ 24.04; 34.02; 64.92; 126.56; 127.24; 138.44; 148.28

EI-MS: m/z 150 (49%); 135 (100%); 119 (31%)

Unknown E

Molecular mass: 138.18 g/mol

Elemental composition: 69.53 % C; 7.31 % H; 23.16 % O

$^1\text{H-NMR}$: δ 2.58 (s, 1H); 3.75 (s, 3H); 4.53 (s, 2H); 6.83 (d, 2H); 7.23 (d, 2H).

$^{13}\text{C-NMR}$: δ 55.32; 64.83; 114.20; 128.48; 133.73; 159.50

EI-MS: m/z 138 (100%); 107 (26%)

CHEM 344 Oxidation of a 1° alcohol

Name:

Partner:

TA:

Unknown _____

Structure of starting material:

Mass of product _____

% Yield of product (show calculation below) _____

Structure of product:

CHEM 344 Oxidation of a 1° alcohol

Name:

Pre-lab

Descriptive title
Purpose statement
Balanced reaction
Reagent table
Answer(s) to pre-lab questions
Outline of lab procedure

Total _____/5

Report

Coversheet present and complete _____/1

Observations _____/7

Discretionary pts (legibility, organization etc.) _____/2

Total _____/10

Pre-lab + Report Total _____/15

Results

Unknown alcohol Calculation of formula _____/2

Sketches of ¹H-/¹³C-NMR spectra _____/2

Assignment of ¹³C-NMR data _____/2

Assignment of ¹H-NMR data _____/4

EI-MS fragments _____/4

Product Assignment of ¹H-NMR data _____/4

EI-MS fragments _____/2

%Yield calculation _____/1

Post-lab question 1 _____/2

Post-lab question 2 _____/4

Post-lab question 3 _____/8 (2+6)

Total _____/35

Pre-lab + Report +Results Total _____/50

Hazards

The substituted benzyl alcohols and benzaldehydes used in this experiment are irritants and harmful if ingested.

Copper(I) bromide, TEMPO, and NMI are corrosive.

2,2'-Bipyridine is toxic if ingested.

Acetone and pentane are flammable.

Appropriate personal protective equipment such as protective gloves, goggles and lab coats should be worn at all times.

Solid and liquid waste should be disposed into appropriately labeled containers.

The aerobic oxidation reactions presented herein employ organic solvents in the presence of air; therefore, precautions appropriate for the handling of flammable solvents (acetone, pentane) should be employed