Synthesis and Characterization of a Ruthenium Photoredox Catalyst and Its Application to the Fluorination of an Aryloxyacetic Acid

(Last Revised February 2024)*

SUMMARY: Preparation and characterization of the bipyridyl ruthenium complex ruthenium-tris(2,2'-bipyridyl) dichloride hexahydrate ($Ru(bpy)_3Cl_2 \cdot 6H_2O$). Use of this complex as a photoredox catalyst in the decarboxylative fluorination of (p-phenylphenoxy)acetic acid.

INTRODUCTION

This study will be somewhat less guided than previous ones and will require some planning and creativity on your part. Your task will be to synthesize the common photoredox catalyst colloquially known as "rubpy" (pronounced "rew-bippy") and use it as a catalyst in a fluorination reaction, a very relevant synthetic transformation in medicinal chemistry and drug design.

You should read the suggested papers related to photoredox chemistry as a synthetic method to provide background as to the electronic structure of photoredox catalysts and the basics of how they behave as single electron transfer catalysts in the presence of light.

Before carrying out the fluorination reaction, you must synthesize the catalyst. Visible (blue) light-absorbing $Ru(bpy)_3^{2+}$ is one of the most common of these catalysts, which will be used here. For this project, you will be synthesizing the ruthenium complex based on the synthesis of Yu et. al. You will then follow modified procedures from Paquin et al. for the photoredox C-F bond formation using this complex as a photoredox catalyst. Note, each article is a full research paper and contains much more information than just an experimental procedure. You will look through the papers (experimental and SI's) and determine which parts of the paper/synthesis are relevant to the chemical strategy outlined below. This process of planning an experiment based on scanning through multiple papers and finding relevant sections mimics the process of designing and carrying out a synthesis in real scientific research.

EXPERIMENTAL PROCEDURES

In this study you will
(I) Synthesize and characterize a Ru photoredox catalyst
(II) Use this catalyst in a photoredox-driven fluorination reaction

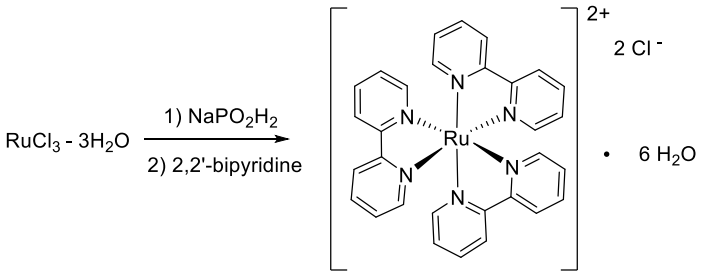
Read through the basics and some of the examples/mechanisms in the following review articles on photoredox catalysis before starting your work:

Background Information:
- Stephenson et al. *Chem. Soc. Rev.* **2011**, *40*, 102-113.
- MacMillan et al. *Chem. Rev.* **2013**, *113*(7), 5322-5363.

Use these articles and/or SI's to construct a synthetic procedure for your catalyst synthesis and your photoredox reaction:

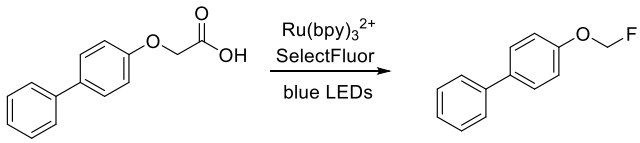
Experimental/Synthesis Information for $Ru(bpy)_3Cl_2$ and the photoredox fluorination reaction:
- Yu et. al. *Chem. Commun.* **2015**, *51*, 17443-17446.
- Paquin et. al. *J. Am. Chem. Soc.* **2014**, *136*(6), 2637-2641.

Design a synthetic protocol for ruthenium-tris(2,2'-bipyridyl) dichloride hexahydrate based on the given articles and Scheme 1 (Note that this is just a general scheme, yours in your paper should be more specific to the procedure/sequence that you use).



Scheme 1: Synthesis of the ruthenium photoredox catalyst, $Ru(bpy)_3Cl_2$.

You will then characterize your complex and use it as a photoredox in a fluorination reaction. You will use a blue 450 nm blue LED and a homemade photoreactor to carry out the reaction. (Scheme 2).



Scheme 2: Photoredox-mediated decarboxylative fluorination of (p-phenylphenoxy)acetic acid.

You should plan your ruthenium catalyst synthesis on ~100-150 mg scale (i.e. starting with ~100-150 mg of $RuCl_3$ – 3 H_2O starting material. Note that this is not the scale the paper works with; you will need to scale down all solvents and reagents accordingly). Your subsequent fluorination reaction using this catalyst will be performed on ~0.5 mmol scale of starting acid substrate. Pay particular attention to **any steps that take several hours or for any reasonable break points in your daily plans. You WILL**

*Contributed to by Jamie Neely and Rob Perkins. Testing and troubleshooting performed by Katy Piette, B.S. Chemistry SLU class of '25 and Emma Mize, B.S Chemistry SLU class of '23.

need to plan your time as efficiently as possible. Coordinate with your TA an instructor if any work needs to be done outside of the normal lab period, but you should be able to do everything in the allotted time.

This study also a good example of following a paper through the literature. Yu et. al. are one group of many who have synthesized $Ru(bpy)_3Cl_2 \cdot 6H_2O$ but use a fairly representative procedure. Paquin et al. have a very specific reaction type where this photoredox catalyst is used and that you will try to replicate (though other photoredox-mediated fluorination reactions for different functionalities have since been developed as well).

In many cases, published procedures are not optimal or do not fit the equipment or preferred techniques of your research group, and sometimes they aren't even clear or complete. For your study here, you will mainly following the provided papers, but with some minor modifications listed below. **Be sure to make these adjustments to the published procedures in your plans to ensure success.**

The following modifications to the originally published experimental procedures and tips should help you be successful in carrying out these experiments:

For the catalyst synthesis:

1. Do not dry your ruthenium chloride starting material like the procedure instructs. This step is unnecessary. That said, make sure you do your calculations of amounts of reagents correctly since you are using a hydrate instead of dried $RuCl_3$.

Trying to get a reasonable weight of the chunks of your ruthenium chloride is recommended (rather than grinding the chunks down), as the ground hydrate is a sticky paste rather than a powder. You do not need to hit an exact planned mass of starting material, just make sure that once you weigh the amount of starting ruthenium complex, you recalculate the amount of ligand you are adding to ensure the stoichiometry is corrected for your actual complex amount being slightly different from your initially calculated amount. Exact stoichiometry is important here.

2. Remember that you are not starting with exactly the same amount of starting material that the literature procedure uses. **Scale the amounts of your reagents and solvents you use accordingly**. It is rare to do a synthesis at the exact scale the original was done, so adjusting your scale is a key skill.

3. **You should degas all of your solvents** rigorously for making your catalyst and run your reaction inert, even though the procedure does not call for it. The ruthenium needs to be in a specific oxidation state for the reaction to proceed.

4. The procedure is unclear, but the "sodium hypophosphite solution" is a **saturated aqueous solution**. The water should be degassed before making the solution and the solution kept inert. This solution can be made by adding solid until it no longer dissolve (though give it time, you may come back to find it all dissolved and the solution is not yet saturated).

You should add twice the amount of this solution that is suggested in the written procedure to ensure complete reduction of your ruthenium.

5. After the desired complex is formed and solution is orange, unless you see visible insoluble impurities there is no need to filter at this point as suggested in the literature procedure.

6. After precipitation, filter with a medium rather than course frit filter funnel. It will take longer, but you will get a higher yield of catalyst product as less will sneak through the frit filter. Also note that this complex is somewhat water soluble, so DO NOT wash your filtered solid with water.

7. The process for recrystallizing the catalyst is relatively quick and painless and it is worth doing if you have the time to get more pure and extra shiny crystals. However transferring the solids to a flask to do the recrystallization is difficult while it is still wet. Letting it dry first, and then doing the recrystallization on another day may make this easier, but the choice is yours.

Recrystallize from the small amount of water listed in the procedure (provided in mL of water per gram of material).

For the photoredox-catalyzed fluorination reaction:

Safety Note: ***DO NOT LOOK AT THE BLUE LIGHT. The blue LED lamp is incredibly bright and at an unsafe wavelength for your eyes. Look away before turning it on, use the blue light protective glasses, do not look at the light coming out of the photoreaction, and shield the leaking light with a light shield to block others from looking at it. There is a pair of protective yellow glasses in lab that you may use when setting up the photoreactor box.***

You may also want to put foil over the top of the reaction area to block light AND to help reflect more escaping light back into the reactor.

1. The fluorination reaction will be carried out with 0.5 mmol of substrate in a standard 20 mL vial with a septum cap under inert atmosphere. The procedure does not specify, but you should use 5 mL of the 1:1 H_2O:MeCN solvent for this reaction (which results in a 0.1 M reaction concentration). All solvents used in this reaction and solution preparation should be rigorously degassed via sparging before adding the ruthenium complex. The reaction vial should also be kept under inert atmosphere at all times.

2. Allow some time for the reagents to stir before introducing the light (while still keeping the reaction vial under inert atmosphere). The solubility of the starting material is somewhat low, so allow time for as much of it to dissolve as possible (it will still be cloudy regardless, but

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give it some time to stir first). Keep the reaction solution under inert atmosphere at all times.

3. The lamp used will be a 50 W blue LED rather than a 500 W visible light lamp, however the light source is tuned to the absorption of the catalyst (centered around 456 nm), so the hour reaction time is still reasonable. Letting the reaction go longer than one hour won't hurt (and may help) depending on how much time you have.

4. Make sure your reaction vial is under inert atmosphere (constant light flow of nitrogen), and make sure the photoreactor is centered on the stir plate such that your reaction is stirring.

5. Perform your extraction using diethyl ether instead of dichloromethane. This will likely help avoid horrible emulsions during the extraction and will exclude some impurities that dichloromethane may dissolve while ether does not.

6. Take an ^{1}H NMR of the crude product you get after concentrating your extraction organic layers. If it looks very pure, then a simple small scale filtration through a plug of silica gel to get out some of the ruthenium and non-NMR active salts can be done.

If you notice significant impurities, you may be able to run a quick silica gel column (ask your instructor if this is viable with the given impurities) or alternatively get an "NMR yield" using the integration of an internal standard versus the integration of your product peaks to determine the amount of product actually present in your crude sample.

General Notes:

You will not need to make the ligands for synthesizing the catalyst or the fluorination substrate. The ligands were purchased, and the phenoxyacetic acid substrate was synthesized for you.

You will have to make all of the required solutions, they will not be made for you. Allow time for that, and keep in mind that making a larger stock solution as a group rather than making tiny amounts of solutions is both more accurate and more time efficient. Make sure all solutions are degassed before using.

You have more freedom with this project than others, and some steps warrant some work on days in the same week depending on your planning. **You will need to write up a full procedure and have it reviewed by the instructor before entering lab to start your synthetic work. This should include reagents and their exact amounts and a procedural plan that includes dates and times for the synthetic work. This is due before you start your synthetic work.** Note that the shorter amount of time from when you get started with the reaction to isolating the product, the more successful your synthesis will be. You have priority of using lab during your scheduled lab period over other students, but your out of lab work will have to be scheduled around limited glassware, space, other labs, and TA/instructor availability.

You should characterize your **catalyst** using the following available techniques:

• FTIR (picking out all large peaks above 1500 cm^{-1})

• ^{1}H-NMR (^{13}C-NMR is hard to get signals to show up for this one, which is generally true of electron poor aromatic rings. ^{1}H NMR is enough as long as it is consistent with a previously reported spectrum, which should be cited).

• UV-vis absorption spectroscopy. Be sure to test solubility in your chosen solvent BEFORE making your analytical sample to ensure it will dissolve. For **quantitative** analysis, the sample needs to be FULLY dissolved.

You should characterize your fluorination product using the following available techniques:

• ^{1}H-NMR

• ^{19}F-NMR

You should **not** do a formal "comparison to literature" for this. This is not something done in publications. Your data is your own and independently proves you made the compounds. You should however use a reference to cite that your NMR data is consistent with previous reports of the same compound (which allows you to get away with not doing a full characterization with high resolution mass spec, ^{13}C NMR), but that is it.

REPORT

Your report should be presented in the format of a journal article (use the communication template for Inorganic Chemistry). All characterization data should be tabulated according to journal standards in the experimental. Use everything you have learned thus far to make a complete, accurate, and professional journal article.

Include the following:

1. Experimental procedure and observations in the experimental for the synthesis of the ruthenium photoredox catalyst, including % yield. A reaction scheme should be present as well in the text that shows the reaction/conditions and the product yield.

2. Generate a master table of spectral data for the ruthenium complex similar to the example given in your past ferrocene experimental instructions. This table should concisely and accurately summarize all your characterization data for your complex. Do not include any spectra in your paper, but do include them all in your SI, fully processed and captioned well.

3. UV-vis spectra of the complex in an appropriate solvent (check to make sure it is soluble!) should be shown in the paper, as this complex's behavior as a catalyst relies on this information. Plot of molar absorption coefficient (ε, M^{-1} cm^{-1}) vs. wavelength (λ, nm). *Calculate in advance what*

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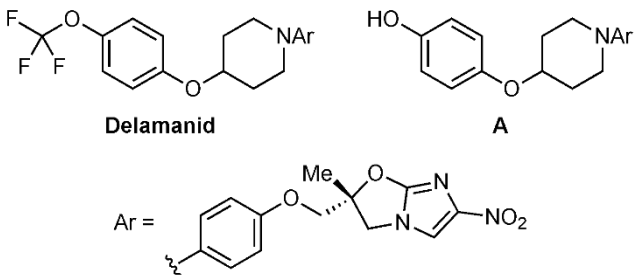
concentration sample you should make based on literature values of absorption coefficient. What electronic transitions are responsible for the observed bands, specifically the lowest energy band? How do the visible absorptions relate to the complex's color? Which absorption is taken advantage of in the fluorination reaction? Note: While UV-Vis spectra aren't usually include in the main paper (usually only in the SI) it makes sense here to publish your UV-Vis spectra in the paper since the visible absorptions of this catalyst are very important to the required discussion and is the key of how this catalyst functions.

4. Experimental procedure and observations in the experimental for the photoredox fluorination reaction. A reaction scheme should be present as well in the text that includes the reaction, reagents/conditions (including catalyst loading in mol%), and yield. You should not do a full characterization table for this (that info is all in the experimental. This paper should be focused on the ruthenium complex and its application to this reaction. After the reaction scheme, directly go to the discussion as described below:

5. Was the reaction successful? Yield? Discuss how you know the compound was fluorinated, and specifically that it was fluorinated only once. (Note: When looking at your NMRs, keep in mind that fluorine couples to protons, so you will see that unique and large coupling in your NMR if there are protons adjacent to a fluorine).

6. Any synthetic method is developed because it is useful for a particular application, however there are also usually limitations for its utility as well. Discuss the pros and cons of this method as you see it. Also discuss is limitations. This discussion needs to include professional, scientific reasoning. Think practically about what real-world situations this is a good reaction and for what applications it may be less practical

7. Demonstrate the potential of this method in medicinal chemistry by designing a synthesis (and presenting that Scheme) of a **mono**fluorinated analog of Delamanid, a treatment for tuberculosis, from the starting material **A** shown in Scheme 3 below:



Scheme 3: Anti-tuberculosis drug Delamanid and compound **A** that should be used to design the synthesis of a monofluorinated analog.

8. Briefly discuss any differences between your proposed fluorination reaction in #7 and the one performed in this experiment. Do you think your proposed fluorination reaction would work as well as in the experiment? Explain your reasoning. What would the success or failure of this theoretical reaction tell us about the utility of this fluorination chemistry in medicinal chemistry-relevant substrates?

9. In your conclusion, discuss possible future directions, in addition to summing up your results as usual. How might you modify the proposed structure of your catalyst to change its absorption wavelength and/or oxidizing/reducing ability? What other substrates (other than *aryloxy* acetic acids) might you try in the fluorination reaction?

Remember your introduction should NOT include general chemistry theory, like how photochemistry or these catalysts work (you can use references to point to that information). It should focus on and tie together some combination of applications of photoredox catalysis and the importance of fluorination reaction.

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