JOURNAL OF CHEMICAL EDUCATION

Laboratory Experiment

pubs.acs.org/jchemeduc

Synthesis and Characterization of Copper Complexes with a Tridentate Nitrogen-Donor Ligand: An Integrated Research Experiment for Undergraduate Students

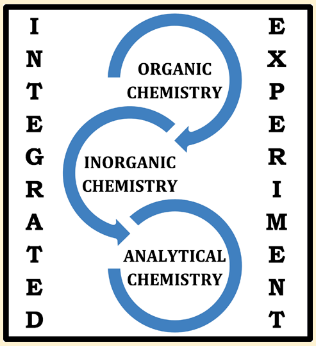
Katherine A. Bussey,[†] Annie R. Cavalier,[†] Jennifer R. Connell,[†] Margaret E. Mraz,[†] Ashley S. Holderread,[†] Kayode D. Oshin,[*,†] and Tomislav Pintauer[‡]

[†]Department of Chemistry and Physics, Saint Mary's College, Notre Dame, Indiana 46556, United States

[‡]Department of Chemistry and Biochemistry, Duquesne University, Pittsburgh, Pennsylvania 15282, United States

Ⓢ *Supporting Information*

ABSTRACT: An integrated laboratory experiment applying concepts and techniques developed in organic chemistry, inorganic chemistry, and instrumental analysis is presented for use by students interested in undergraduate research. The experiment incorporates some advanced laboratory practices such as multistep organic synthesis and purification, detailed reaction mechanism, air-sensitive metalation techniques, variable-temperature NMR experiments, cyclic voltammetry, and single crystal X-ray crystallography. Subsequently, students are presented with an experience that mirrors fundamental inorganic chemistry research practices found in laboratories throughout the world.



KEYWORDS: *Upper-Division Undergraduate, Analytical Chemistry, Inorganic Chemistry, Organic Chemistry, Interdisciplinary/Multidisciplinary, Inquiry-Based/Discovery Learning, NMR Spectroscopy, Crystals/Crystallography, IR Spectroscopy, Synthesis*

INTRODUCTION

As students advance through the undergraduate chemistry curriculum, exposure to laboratory exercises showcasing the integration of concepts and techniques from different disciplines of chemistry is important to their development. Several studies have been published detailing the importance of incorporating integrated, research-based experiments in the undergraduate chemistry curriculum.[1−6] The common thread found in these studies is a desire to prevent segmented thinking by students and encourage conjugated thinking at the interface between different disciplines. This is a valuable skill for students to learn as they transition to research at the graduate level or industry, which typically require similar integration between disciplines.[7,8] Many integrated laboratory experiments have been developed that can be implemented into an existing or new chemistry curriculum.[9−18] To add to this collection, an interdisciplinary experiment is described herein that can serve as an introduction for students interested in undergraduate research. This experiment develops fundamental laboratory skills that will be useful as students take on more advanced faculty-specific research projects. Critical skills such as how to conduct literature searches; interpreting experimental procedures; ligand synthesis, purification, and isolation; complexation reactions (air-sensitive/air-stable); and characterization techniques are presented. This experiment also provides students with an opportunity to communicate their results through written or oral formats. The primary goal is to synthesize and characterize simple copper complexes incorporating a tridentate bis(2-pyridylmethyl)amine (BPMA) ligand precursor. The BPMA ligand is considered tridentate because of the three (tri-) nitrogen donor groups present that can coordinate to a metal, in this case copper.

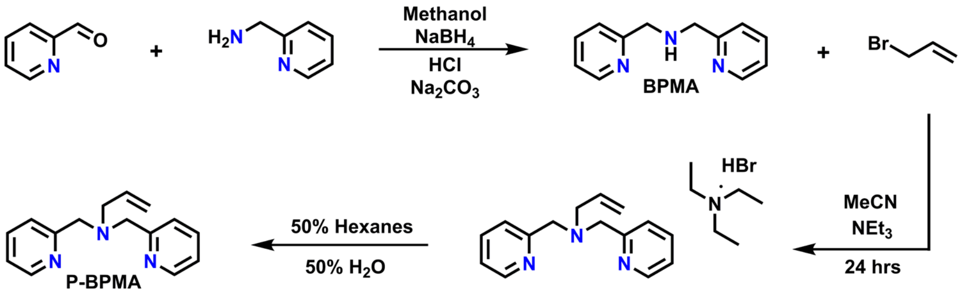
EXPERIMENT

Literature Searches, Ligand Synthesis, and Reaction Mechanism

This experiment is broken up into eight research periods and carried out over an eight-week block (meeting once a week); it can also be conducted over a four-week block (meeting twice a week). The first period is used to discuss the concept of reaction mechanisms and effective literature searches using SciFinder, as well as journal article archives found online. Three periods are devoted to synthesis, purification, and isolation of the tridentate ligand, utilizing articles found from the literature search. Two periods are used to perform complexation reactions with the ligand and different copper salts. The final two periods are used to characterize and interpret spectra obtained from all precursors, ligands, and complexes using a variety of techniques. Faculty can elect to use future research

DOI: 10.1021/acs.jchemed.5b00175
J. Chem. Educ. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis and Extraction of Propene-bis(2-pyridylmethyl)amine (P-BPMA)



periods to work on developing formal report writing, poster, and oral presentation skills utilizing results from this experiment.

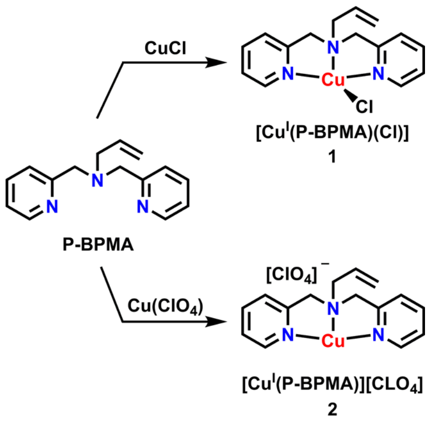
A general reaction mechanism for the desired ligand, propene-bis(2-pyridylmethyl)amine (P-BPMA), is outlined in Scheme 1. There are two contributing reactions: (i) synthesis and purification of the ligand precursor BPMA, employing literature procedures obtained in period one (recommended is the procedure developed by Antunes et al.[19]). BPMA is also available commercially and can be purchased ahead of time to use as a reference or substitute if the synthesis is unsuccessful.[20,21] (ii) Synthesis/purification of the P-BPMA ligand utilizing modified literature procedures.[22−24]

Complexation Reactions: Air-Sensitive, Air-Stable, and Salt Metathesis Reactions

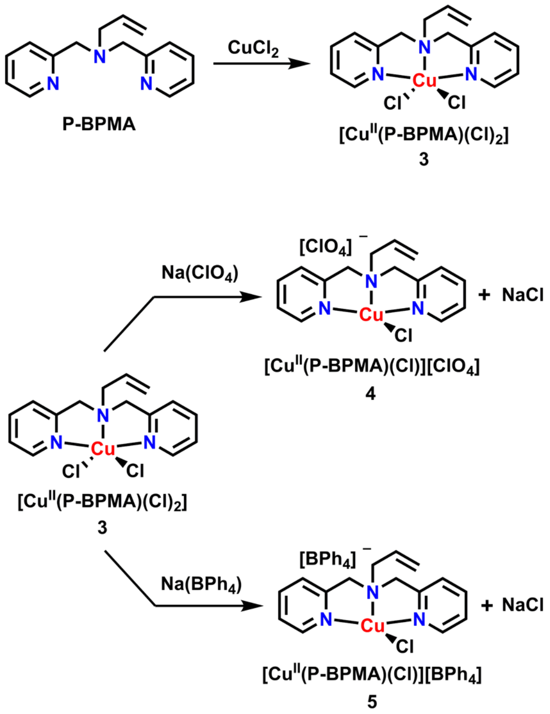
This section integrates the fields of organic and inorganic chemistry, demonstrating to students that the product isolated in the previous section serves as a crucial starting material for reactions discussed in this section. Students also learn about air-sensitive reaction techniques and equipment, a staple in modern inorganic chemistry. Air-sensitive reactions outlined in this section are carried out in a glovebox or on a standard Schlenk line utilizing solvent transfer between ports. Two reactions incorporating 1 equiv of P-BPMA with 1 equiv each of copper(I) chloride and copper(I) perchlorate in anhydrous acetonitrile are set up under an inert atmosphere. Addition of anhydrous pentane to the reaction mixtures affords precipitates of complexes [Cu^{I}(P-BPMA)(Cl)] (**1**) and [Cu^{I}(P-BPMA)][ClO_4] (**2**) (Scheme 2).

Air-stable copper(II) complexes are synthesized from the primary complex [Cu^{II}(P-BPMA)(Cl)$_2$] (**3**) (Scheme 3), made by reacting 1 equiv of P-BPMA with 1 equiv of copper(II) chloride in acetonitrile at room temperature. Slow addition of pentane to the reaction mixture generates precipitates of **3**. Students are introduced to the technique of salt metathesis at this point, demonstrating the ability to exchange one or all counterions in a complex with a different counterion. This portion of the experiment can be used to complement lectures explaining the concept behind anion metathesis. As shown in Scheme 3, students perform a reaction between 1 equiv of Na(A) salt ($A^- = ClO_4^-$ or BPh_4^-) and 1 equiv of complex **3** in acetonitrile at room temperature, producing complexes [Cu^{II}(P-BPMA)(Cl)][ClO_4] (**4**) and [Cu^{II}(P-BPMA)(Cl)][BPh_4] (**5**). A side product from this reaction is sodium chloride (NaCl), which is separated by cooling the mixture to facilitate precipitation; centrifuging aliquots of the mixture and filtering isolates the desired copper complex.

Scheme 2. Reaction of P-BPMA with CuCl and Cu(ClO_4) To Give Complexes 1 and 2

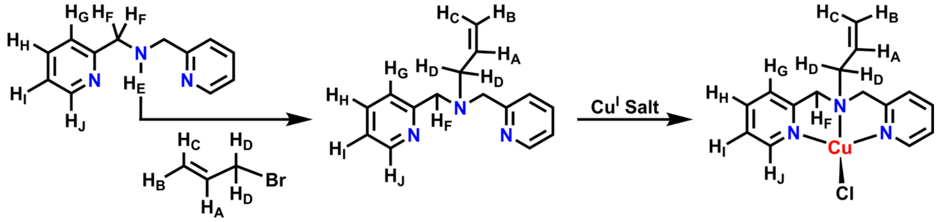


Scheme 3. Synthesis and Salt Metathesis Reactions Produce the Desired Copper(II) Complexes: [Cu^{II}(P-BPMA)(Cl)$_2$] (3), [Cu^{II}(P-BPMA)(Cl)][ClO_4] (4), [Cu^{II}(P-BPMA)(Cl)][BPh_4] (5)[a]



[a] Students characterize the complexes by IR spectroscopy, UV−vis spectroscopy, cyclic voltammetry, and X-ray crystallography.

Scheme 4. Synthetic Reaction Pathway for Copper(I) Complexes with Protons Labelled



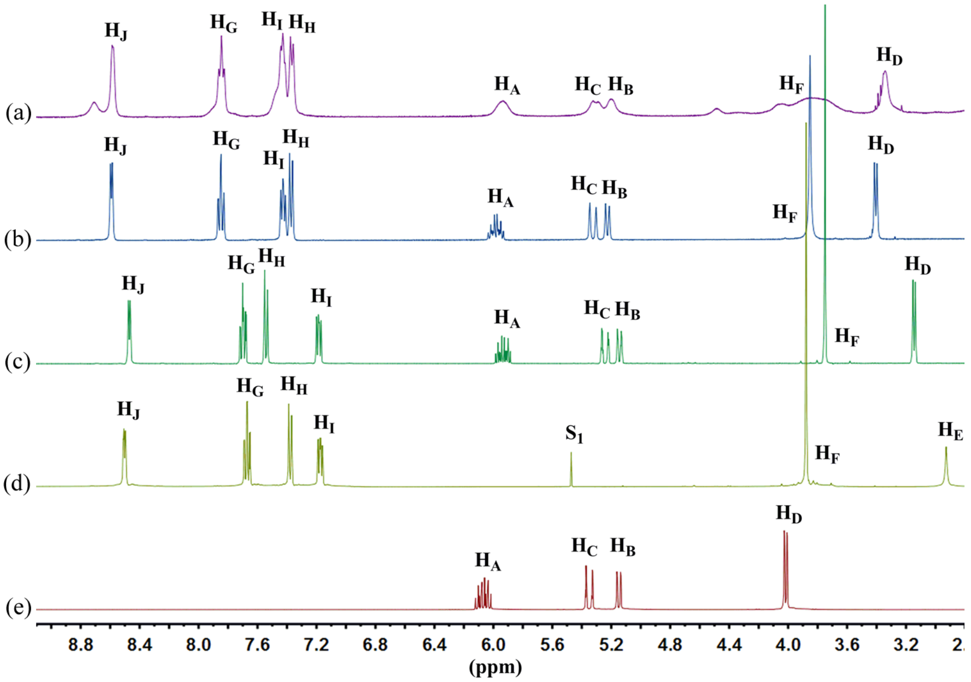


Figure 1. Room temperature ^{1}H NMR spectra (400 MHz, CD_3CN) of (a) allyl bromide precursor, (b) BPMA ligand precursor, (c) P-BPMA ligand, (d) **2**, and (e) **1**. NMR solvent peaks are omitted for clarity and CH_2Cl_2 solvent peak is denoted as **S_1**.

■ HAZARDS

Standard laboratory precautions should be taken when handling all chemicals, working with a Schlenk line, rotary evaporator, and glovebox. Students should wear personal protective equipment including lab coats, gloves and safety glasses. Solvents used are flammable and should be stored in appropriate storage cabinets. 2-Pyridine-carboxaldehyde and 2-(aminomethyl)pyridine should be stored in a refrigerator once opened. Copper(I) perchlorate [$Cu^I(ClO_4)$] salts are potentially explosive and should be handled in small quantities. Sodium borohydride ($NaBH_4$) is hygroscopic and should be stored in a desiccator. Ligands and complexes synthesized are relatively safe and stable, although copper(I) complexes should be stored under inert atmosphere to prevent oxidation. NMR solvents are suspected carcinogens and should be handled with care; samples should be prepared in a laboratory outside of the instrument room. If liquid nitrogen is used on traps for the Schlenk line, care should be taken when handling its transfer into dewars by wearing appropriate cryogenic gloves and goggles.

■ RESULTS AND DISCUSSION

Synthesis Results

The synthetic portion of this experiment has been successfully carried out six times by five undergraduate students (second-year and upper-division) and one high school student in a research chemistry course. Synthesis results are as follows;

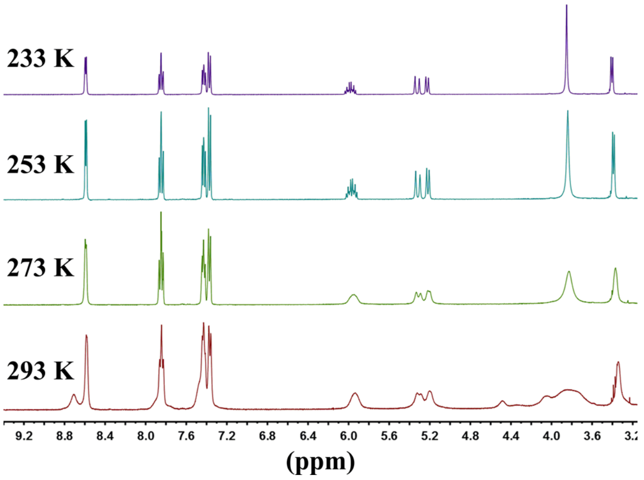
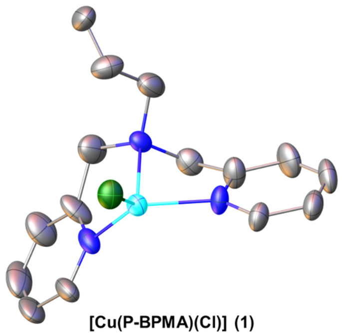
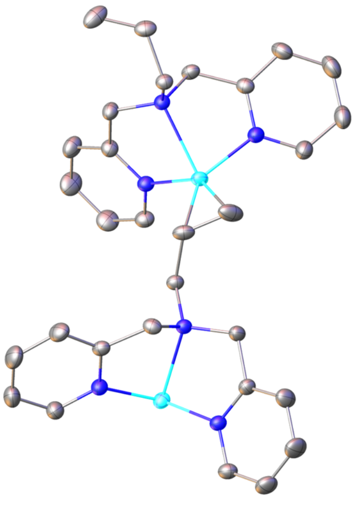


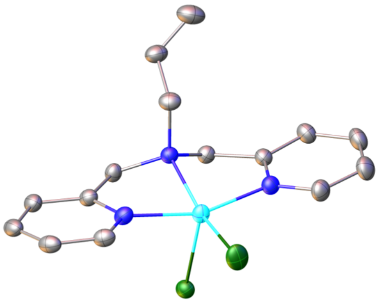
Figure 2. Variable temperature NMR spectra (400 MHz, CD_3CN) of **1**.

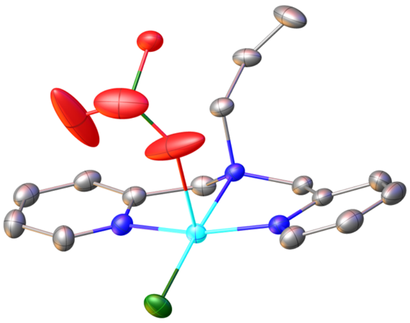
Nuclear Magnetic Resonance Spectroscopy

Students tracked proton positions for compounds involved in the reaction pathway (Scheme 4) using progressive ^{1}H NMR spectra (Figure 1). The ^{1}H NMR spectrum obtained for P-


[Cu(P-BPMA)(Cl)] (1)


[Cu(P-BPMA)][ClO$_4$] (2)


[Cu(P-BPMA)(Cl)$_2$] (3)


[Cu(P-BPMA)(Cl)] [ClO$_4$](4)

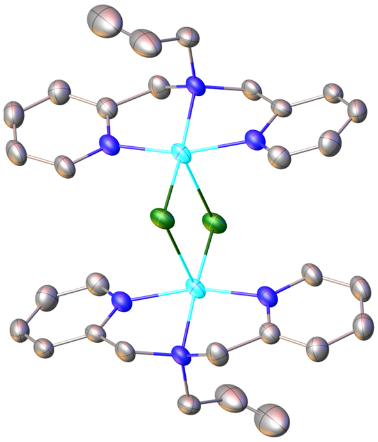

[Cu(P-BPMA)(Cl)] [BPh$_4$](5)

Figure 3. Solid-state structures for copper(I) and copper(II) complexes. (ClO_4) and (BPh_4) counterions are omitted from complexes **2** and **5** for clarity.

BPMA (Figure 1c) displayed a significant upfield shift for protons **H$_D$** compared to the allyl bromide precursor (Figure 1a). This was due to a loss of the bromide anion during the coupling process, with BPMA now attached via a nitrogen atom to the allyl carbon. The pyridyl protons of P-BPMA (**H$_G$**, **H$_H$**, **H$_I$**, **H$_J$**) appear between 7.00 and 9.00 ppm, and the methylene protons (**H$_F$**) appear collectively around 3.75 ppm. Protons corresponding to the aliphatic arm in the ligand and complexes (**H$_A$**, **H$_B$**, **H$_C$**, **H$_D$**) are located between 3.00 and 6.00 ppm, with the characteristic methine proton (**H$_A$**) displayed at 6.10 ppm.

A spectrum displaying well resolved peaks was obtained for **2** (Figure 1d), and one displaying coalescing peaks, indicative of some exchange, was obtained for **1** (Figure 1e). This exchange for **1** could be between a monomeric and dimeric structure of the complex, or solvent coordination and dissociation at room temperature. Proton peak positions in both spectra are analogous, with most signals experiencing a deshielding effect relative to the free ligand. All proton signals shifted downfield with the exception of **H$_G$**, which experienced a shielding effect from the metal, consequently moving upfield. To study the coalescing peaks obtained for **1**, a variable temperature NMR experiment was performed by students to slow down the exchange process, producing a spectrum displaying better resolved peaks at 233 K (Figure 2) (see Supporting Information for VT-NMR experiment details). This spectrum resembled that obtained for the room temperature ^{1}H NMR spectrum of **2**, which suggests that solvent coordination and dissociation in acetonitrile may be the more likely exchange occurring at room temperature. This solvent coordination to copper(I) centers is well documented in the literature and has been rationalized using ligand electronic effects, where acetonitrile molecules can act as ligands and provide more electron density to the metal center when bound, disfavoring coordination of other ligands.[25] In this experiment, the competing ligand was the chloride anion.

X-ray Crystallography

Utilizing the vapor diffusion method,[26] single crystals suitable for X-ray analysis were grown for all complexes and solved by students using the free Olex^2 crystal solution software.[27] The structural results are highlighted in Figure 3 with a more detailed analysis provided in the Supporting Information. It is interesting to note that a solid state polymeric structure was obtained for **2** and a dimeric structure was obtained for complex **5**, which are most likely due to the noncoordination nature of their counterions. If there is access to an X-ray

DOI: 10.1021/acs.jchemed.5b00175
J. Chem. Educ. XXXX, XXX, XXX−XXX

diffractometer, this experiment provides different exercises of varying difficulty that can be carried out by students. They can grow crystals for all complexes and collect diffraction data to generate crystallographic information files (CIFs), which can then be used to solve respective structures. The air-sensitive complexes require the use of an inert atmosphere glovebox or chamber to facilitate crystal growth. Alternatively, students can use a simpler procedure to grow crystals and collect diffraction data for the air-stable copper complexes alone. A third option can be to provide students with some or all CIFs already collected (provided as Supporting Information), so they can learn to use free crystal solution software such as Olex^2,[27] and SHELX.[28,29]

CONCLUSION AND ASSESSMENT

An integrated laboratory experiment on the synthesis and characterization of copper complexes with a tridentate nitrogen-donor ligand has been presented for use as an undergraduate research component. Concepts and techniques from organic, inorganic, instrumental, and analytical chemistry were incorporated in this experiment. Two areas of the experiment could potentially stand in the way of student success: (i) synthesis of the ligand precursor (BPMA), and (ii) growing crystals suitable for X-ray analysis. Solutions to these potential issues were provided: (i) ligand precursor (BPMA) can be purchased commercially ahead of time in case the synthesis is unsuccessful, and (ii) CIFs for all complexes were provided in the Supporting Information if single crystal growth is unsuccessful.

Faculty can design variations of this experiment to fit shorter or longer research time frames, for example, (i) if a purely inorganic focus is desired for students, faculty can purchase the BPMA precursor, synthesize the ligand in one step and provide that to students; (ii) the experiment can be conducted using different metals of interest to the instructor or student, producing a variety of complexes that can be made collectively or each time that the experiment is attempted; and (iii) several lecture concepts can be incorporated in the experiment, such as crystal field theory to explain color difference observed in the copper complexes; the paramagnetic nature of copper(II) complexes and its effect on NMR spectroscopy results; Jahn–Teller effects (if observed); and geometry differences between copper(I) and copper(II) complexes.

Students were assessed on: (i) percent yields obtained relative to literature values; (ii) purity of isolated compounds determined from characterization results, which tied into; (iii) laboratory techniques such as equipment handling and spectra acquisition; and (iv) the ability to interpret spectra properly and to communicate results. Above all, they were able to grasp and articulate the importance of integration between subdisciplines because of their experience with this experiment.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00175.

> Experiment procedures, cyclic voltammetry results, crystallographic information, infrared spectra results, and instructor's notes (PDF, DOCX)
> Complex **1** [Cu^{I}(P-BPMA)(Cl)] (CIF)
> Complex **2** [Cu^{I}(P-BPMA)][ClO_4] (CIF)
> Complex **3** [Cu^{II}(P-BPMA)(Cl_2)] (CIF)
> Complex **4** [Cu^{II}(P-BPMA)(Cl)][ClO_4] (CIF)
> Complex **5** [Cu^{II}(P-BPMA)(Cl)][BPh_4] (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: koshin@saintmarys.edu.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The corresponding author would like to thank all students listed for their contribution to this experiment; Saint Mary's College, Duquesne University and University of Notre Dame for instrumentation support; American Chemical Society, Cambridge Isotope Laboratories Inc., Eli Lilly & Company, The Weber Foundation, and Saint Mary's College for funding support. National Science Foundation Grants (CHE-0844131), (CHE-1360886), and (CHE-0443233) are also gratefully acknowledged.

REFERENCES

(1) Gron, L. U.; Hales, D. A.; Teague, M. W. Creating a Research-Rich Chemistry Curriculum with an Integrated, Upper-Level Undergraduate Laboratory Program. *J. Chem. Educ.* **2007**, *84* (8), 1343–1349.

(2) Lunsford, S. K. Integrated Lecture and Laboratory Chemistry Components of Science Education Program for Early and Middle Childhood Education Majors. *J. Chem. Educ.* **2004**, *81* (5), 685–691.

(3) Bailey, C.; Kingsbury, K.; Kulinowski, K.; Paradis, J.; Schoonover, R. An Integrated Lecture-Laboratory Environment for General Chemistry. *J. Chem. Educ.* **2000**, *77* (2), 195–197.

(4) Van Hecke, G. R.; Karukstis, K. K.; Haskell, R. C.; McFadden, C. S.; Wettack, F. S. An Integration of Chemistry, Biology, and Physics: The Interdisciplinary Laboratory. *J. Chem. Educ.* **2002**, *79* (7), 837–840.

(5) Teo, T. W.; Coh, M. T.; Yeo, L. W. Chemistry Education Research Trends: 2004–2013. *Chem. Educ. Res. Pract.* **2014**, *15* (4), 470–487.

(6) Sevian, H.; Talanquer, V. Rethinking Chemistry: A Learning Progression on Chemical Thinking. *Chem. Educ. Res. Pract.* **2014**, *15* (1), 10–23.

(7) Hurd, P. D. Why We Must Transform Science Education. *Educ. Leader.* **1991**, *49* (2), 33–35.

(8) McCurdy, S. M.; Zegwaard, K. E.; Dalgety, J. Evaluating the Development of Science Research Skills in Work-Integrated Learning Through the Use of Workspace Science Tools. *Asia-Pac. J. Coop. Educ.* **2013**, *14* (4), 233–249.

(9) Hayes, J. M. An Integrated Visualization and Basic Molecular Modeling Laboratory for First-Year Undergraduate Medicinal Chemistry. *J. Chem. Educ.* **2014**, *91* (6), 919–923.

(10) Kulczynska, A.; Johnson, R.; Frost, T.; Margerum, L. D. How Do Structure and Charge Affect Metal-Complex Binding to DNA? An Upper-Division Integrated Laboratory Project Using Cyclic Voltammetry. *J. Chem. Educ.* **2011**, *88* (6), 801–805.

(11) Kirk, S. R.; Silverstein, T. P.; McFarlane-Holman, K. L.; Taylor, B. L. Probing Changes in the Conformation of $tRNA^{Phe}$: An Integrated Biochemistry Laboratory Course. *J. Chem. Educ.* **2008**, *85* (5), 666–673.

(12) Clark, C. A.; Schwinefus, J. J.; Schaefle, N. J.; Muth, G. W.; Miessler, G. L. Lysozyme Thermal Denaturation and Self-Interaction: Four Integrated Thermodynamic Experiments for the Physical Chemistry Laboratory. *J. Chem. Educ.* **2008**, *85* (1), 117–120.

(13) Works, C. F. Synthesis, Purification, and Characterization of μ–(1,3-propanedithiolato)-hexacarbonyldiiron. Laboratory Experiment or Mini-Project for Inorganic Chemistry or Integrated Laboratory. *J. Chem. Educ.* **2007**, *84* (5), 836–838.

(14) Gravelle, S.; Langham, B.; Geisbrecht, B. V.; Photocatalysis, A. Laboratory Experiment for an Integrated Physical Chemistry-Instrumental Analysis Course. *J. Chem. Educ.* **2003**, *80* (8), 911−913.

(15) de Mattos, M. C. S.; Nicodem, D. E. Soap from Nutmeg: An Integrated Introductory Organic Chemistry Laboratory Experiment. *J. Chem. Educ.* **2002**, *79* (1), 94−95.

(16) Logan, J. W.; Wicholas, M. 1,5-Cyclooctadiene Complexes of Iridium: Synthesis, Characterization, and Reaction with Dihydrogen. An Experiment for an Integrated Physical-Inorganic Laboratory Course. *J. Chem. Educ.* **2001**, *78* (9), 1272−1274.

(17) *The Integrated Approach to Chemistry Laboratory: Selected Experiments*, 4th ed.; Basu, P., Johnson, M. E., Eds.; DEStech Publications, Inc.: Lancaster, 2009.

(18) Anderson, C. D.; Macaulay, D. B.; Bloomfield, M. M.; Bauer, J. M. *Laboratory Experiments to Accompany General, Organic, & Biological Chemistry An Integrated Approach*, 3rd ed.; Wiley: Hoboken, NJ, 2013.

(19) Carvalho, N. F.; Horn, A.; Bortoluzzi, A. J.; Drago, V.; Antunes, O. A. Synthesis and Characterization of Three Mononuclear Fe(III) Complexes Containing Bipodal and Tripodal Ligands: X-ray Molecular Structure of the Dichloro[N-propanamide-N,N-bis-(2-pyridylmethyl) amine]iron(III) perchlorate. *Inorg. Chim. Acta* **2006**, *359* (1), 90−98.

(20) Di-(2-picolyl)amine. http://www.sigmaaldrich.com/catalog/product/aldrich/385638?Lang=en&region=US.html (accessed Sep 2015).

(21) Bis(2-pyridylmethyl)amine. http://www.tcichemicals.com/eshop/en/us/commodity/D2228/ (accessed Sep 2015).

(22) Rodriguez, M. C.; Lambert, F.; Morgenstern-Badarau, I.; Cesario, M.; Guilhem, J.; Keita, B.; Nadjo, L. Selective Metal-Assisted Oxidative Cleavage of a C−N Bond: Synthesis and Characterization of the Mononuclear Iron(III) $[Fe(BPG)Cl_2]$ Complex and its Two $[Fe(BPA)Cl_3]$ and $[Fe(BPE)Cl_3]$ Derivatives. *Inorg. Chem.* **1997**, *36* (16), 3525−3531.

(23) Mandal, S. K.; Que, L. Models for Amide Ligation in Nonheme Iron Enzymes. *Inorg. Chem.* **1997**, *36* (24), 5424−5425.

(24) Hayes, T. R.; Lyon, P. A.; Silva-Lopez, E.; Twamley, B.; Benny, P. D. Photo-initiated Thio-ene Click Reactions as a Potential Strategy for Incorporation of $[M^I(CO)_3]^+$ (M = Re, ^{99m}Tc) Complexes. *Inorg. Chem.* **2013**, *52* (6), 3259−3267.

(25) Zhang, C. X.; Kaderli, S.; Costas, M.; Kim, E.; Neuhold, Y. M.; Karlin, K. D.; Zuberbuhler, A. D. Copper(I)-Dioxygen Reactivity of $[(L)CuI]^+$ (L = Tris(2-pyridylmethyl)amine): Kinetic/ Thermodynamic and Spectroscopic Studies Concerning the Formation of $Cu-O_2$ and Cu_2-O_2 Adducts as a Function of Solvent Medium and 4-Pyridyl Ligand Substituent Variations. *Inorg. Chem.* **2003**, *42* (6), 1807−1824.

(26) Forsythe, E. L.; Maxwell, D. L.; Pusey, M. Vapor Diffusion, Nucleation Rates and the Reservoir to Crystallization Volume Ratio. *Acta Crystallogr., Sect. D: Biol. Crystallogr.* **2002**, *58* (10), 1601−1605.

(27) Olex^2 crystallography Software. http://www.olexsys.org/Software (accessed Sep 2015).

(28) SHELX Download. http://shelx.uni-ac.gwdg.de/SHELX/download.php (accessed Sep 2015).

(29) Sheldrick, G. M. *SHELXTL*, Crystallographic Computing System 6.1, Bruker Analytical X-Ray System: Madison, WI, 2000.

DOI: 10.1021/acs.jchemed.5b00175
J. Chem. Educ. XXXX, XXX, XXX−XXX