Exploring Green Chemistry with Aerobic Hypervalent Iodine Catalysis

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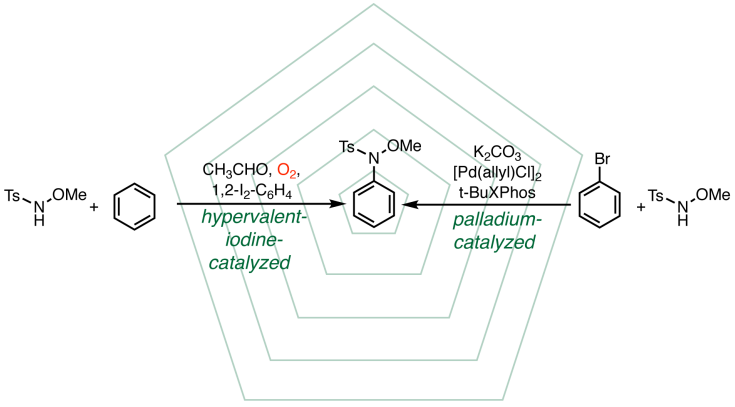
ABSTRACT

The demand for sustainable synthetic methods has motivated the development of a myriad of strategies for substrate oxidation chemistry that reflect the goals of green chemistry. Here we present a two-part laboratory module that provides undergraduate chemistry students hands-on experience with the concepts of sustainable chemistry in the context of C–N bond-forming chemistry. First, students perform a traditional Pd-catalyzed C–N cross-coupling reaction between an aryl halide and an amine (*i.e.*, C–X/N–H coupling). In the second part, students investigate a hypervalent iodine-catalyzed reaction that uses O_2 as a terminal oxidant for direct C–H/N–H coupling. Based on these two methods for accessing the same arylated amine product, students evaluate aspects of sustainability qualitatively by discussing the 12 Principles of Green Chemistry and quantitatively via green chemistry metric pentagons. These investigations highlight the complex balance of variables that must be considered when evaluating the sustainability of chemical processes. Through these activities, students explore the concepts of aerobic oxidation, hypervalency, green chemistry, and organocatalysis, while enforcing laboratory skills such as Schlenk-line technique, gas handling, and NMR spectroscopy.

GRAPHICAL ABSTRACT



KEYWORDS

Second-year undergraduate, Upper-division undergraduate, Inorganic chemistry, Organic chemistry, Inquiry-based/Discovery learning, Hands-on learning/manipulatives, Catalysis, Green chemistry, Oxidation / Reduction, Synthesis

INTRODUCTION

Oxidation reactions are critical to organic chemistry, providing opportunities to introduce new functional groups, interconvert existing functional groups, and build molecular complexity. The demand for increasingly sustainable synthetic methods[1] has motivated the development of a wide variety of new strategies for substrate oxidation.[2-7] The significant advances in sustainable oxidation chemistry that are evident in the research literature have not been reflected in the chemical education literature, which limits implementation of these new synthetic methods in the undergraduate teaching laboratory.[8-9] Given widespread recognition for the need to utilize more sustainable chemical processes, it is critical that students are both exposed to modern methods in sustainable synthesis and confront methods for the evaluation of the relative sustainability of disparate synthetic routes to a common product.

C–N bond-forming reactions are critical in fine chemicals synthesis. Aryl amines are often prepared by metal-catalyzed cross-coupling between an organohalide and an amine (often Pd-based), and C–N cross-coupling is one of the five most commonly encountered reactions in the pharmaceutical industry.[10-12] While C–N cross-coupling has evolved to be a reliable and efficient synthetic strategy, the need to pre-functionalize the aryl halide coupling partner, combined with the challenge of complete removal of transition metal species from the products, has motivated the development of alternate methods to effect C–N coupling.

Direct oxidative coupling of C–H and N–H represents a conceptually attractive approach to the construction of C–N bonds. To this end, hypervalent-iodine-catalyzed oxidative N–H / C–H coupling has been developed as a route to C–N bond-forming reactions.[13] Hypervalent iodine compounds feature iodine centers with a formally expanded valence at iodine, which is made possible by 3-center, 4-electron bonding.[14-15] Hypervalent iodine reagents display chemistry analogous to many transition metal centers

and have thus gained widespread application in synthetic organic chemistry.[16-23] Historically, hypervalent iodine chemistry required (super)stoichiometric loading of iodine-based reagents, and heavy metal-based oxidants for the synthesis of these compounds.[17, 24] Our lab has recently developed a method for the synthesis of hypervalent iodine reagents by intercepting reactive oxidants generated during aldehyde autoxidation.[24-25] We demonstrated that aerobic oxidation of aryl iodides could be coupled with C–H / N–H cross-coupling, which provides a method that uses O_2 as the terminal oxidant in the generation of aryl amines.

In this laboratory, students explore two C–N bond forming strategies: 1) Pd-catalyzed cross-coupling experiment between bromobenzene and *N*-methoxy-4-methyl-*N*-phenylbenzenesulfonamide (Figure 1a), and 2) aryliodide-catalyzed C–H / N–H coupling of *N*-methoxy-4-methylbenzenesulfonamide with benzene to afford *N*-methoxy-4-methyl-*N*-phenylbenzenesulfonamide (Figure 1b). To evaluate the relative sustainability of these two protocols, we introduce the concept of green chemistry pentagons to students, which provide a tool to evaluate a variety of important considerations, including reaction yield, atom economy (AE), reaction mass efficiency (RME), material recovery parameter (MRP), and stoichiometric factor (SF). This suite of experiments allows for students to explore concepts in hypervalency, aerobic oxidation, transition metal catalysis, and green chemistry.

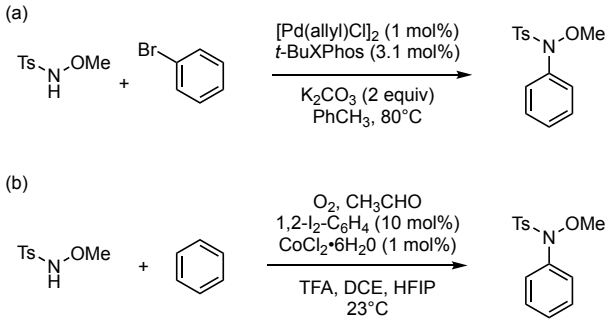


Figure 1. Summary of experiments performed by undergraduates. Undergraduate students perform (a) a traditional Pd-catalyzed cross-coupling reaction, and (b) an aryliodide-catalyzed C–H / N–H coupling reaction.

The primary learning objectives (LO) of the experiment are to

(i) illustrate the topics of aerobic oxidation, catalysis, and sustainable synthesis (LO1);

(ii) introduce students practically to sustainable synthesis through comparison of two synthetic protocols (LO2);

(iii) enforce the development of students' laboratory skills (LO3);

(iv) have students analyze experimental results through the lens of relevant chemical metrics (LO4).

LABORATORY OVERVIEW

The developed experimental module has been implemented in the Advanced Inorganic Laboratory Course (CHEM433) at Texas A&M University. Each section of CHEM433 has an enrollment between 8-12 and students work in groups of 2-3. A total of 51 students have participated in the laboratory module. The experiment was accomplished over four, three-hour long lab periods over a two-week period. Details of the laboratory preparation, experimental procedures, suggested discussion questions, and evaluation rubrics are described in the Supporting Information.

Pre-Lab

Prior to beginning laboratory work, students are provided an experiment handout, which contains a brief description of the syntheses to be performed, data that the students are expected to collect during the experiment, new techniques that the students will learn, literature references that the students are required to read, and discussion questions related to the experiment. Using the resources provided in this handout, students complete a pre-lab assignment outside of the classroom. For the pre-lab assignment, students identify appropriate procedures for the experiments they will perform, collect all relevant safety information, and answer the discussion questions. These pre-lab activities provide students the opportunity to practice searching and reading primary literature, explore the concepts of oxidase and oxygenase chemistry, and learn about the challenges inherent in using O_2 as a selective oxidant, the autoxidation of aldehydes, hypervalent iodine chemistry, and Pd-catalyzed C–N cross-couplings. The experiment handout, as well as grading rubric for the pre-lab assignment, can be found in the Supporting Information.

In the context of our course, students gather for a pre-lab oral exam, in which each student presents an answer to a question related to the pre-lab assignment. This exercise provides students with an opportunity to practice oral communication of science and provides the instructors an opportunity to correct any misconceptions about the experiment. Pre-lab assignments are also checked by the instructor or teaching assistants to ensure that all relevant safety and procedural information was correctly obtained by the students.

Weeks 1 - 2

In the first week of the experiment, students carry out the Pd-catalyzed cross-coupling reaction of *N*-methoxy-4-methylbenzenesulfonamine with bromobenzene. In the second week, students perform the 1,2-diiodobenzene catalyzed cross-coupling. In addition, to reinforce the fundamental redox chemistry that is operative during hypervalent iodine catalysis, students perform the aerobic synthesis of (diacetoxyiodo)benzene (PIDA) during the second week of the experiment. This activity 1) illustrates that the catalyst can be generated under autoxidation conditions and 2) allows for the characterization of a hypervalent iodine intermediate. If time is limited, the stoichiometric preparation of PIDA can be omitted.

Synthesis 1. Pd-catalyzed C–H amination chemistry

Skills and Techniques Learned: Schlenk-technique, degassing solvents, air-free solvent transfer, NMR spectroscopy

Synthesis 2. Aerobic C–H amination chemistry

Skills and Techniques Learned: handling compressed gasses, running reactions under a balloon atmosphere, syringe technique, utilization of reagents with low boiling points (bp < 30 °C), NMR spectroscopy

Synthesis 3. Diacetoxyiodobenzene (PIDA)

Skills and Techniques Learned: handling compressed gasses, running reactions under a balloon atmosphere, syringe technique, NMR spectroscopy

Implementation and Adaptability

The laboratory, as presented, is appropriate for an advanced organic or inorganic lab course that covers standard Schlenk technique. *Synthesis 1* utilizes anaerobic reaction conditions, and thus

requires access to the appropriate equipment (N_2 manifold or other means of delivering an inert atmosphere). *Synthesis 2* could be implemented in a Sophomore organic lab, provided access to a well-ventilated space, an O_2 tank, and two lab periods allotted for the experiment. In this case, yield data from *Synthesis 1* could be provided to allow for quantitative comparison of the two reactions using various green chemistry metrics. *Synthesis 3* could be conducted alongside *Synthesis 2*, or applied as a stand-alone experiment in either a Sophomore organic lab or introductory inorganic lab (again, provided access to a well-ventilated space, an O_2 tank, and two lab periods allotted for the experiment). Detailed safety information is provided in the Supporting Information.

In the course of developing this laboratory module, changes were made from the originally reported procedure to accommodate the experience level of the students.[24] The major modification involved increasing the reaction scale, as we found that students had trouble manipulating materials at the smaller scale. Further, in order to avoid loss of benzene during the O_2 purging step, we implemented a two-vial method detailed in the Supporting Information.

SYNTHESIS AND CHARACTERIZATION

Synthetic Summaries

Synthesis 1

In the first week of the lab students perform the Pd-catalyzed cross-coupling (Figure 1a), which requires the use of a Schlenk line. Solid K_2CO_3, *t*-Bu_2XPhos, $[Pd(allyl)Cl]_2$, and *N*-methoxy-4-methylbenzenesulfonamine are added to a Schlenk flask and placed under a nitrogen atmosphere. Degassed toluene and bromobenzene are added, the vessel is fitted with a condenser, and the reaction stirred at 80 °C overnight. The following class period the reaction is worked-up and the product is characterized by ^{1}H NMR spectroscopy.

Synthesis 2

During the second week of the lab students set-up the (diacetoxyiodo)benzene catalyzed C–N coupling reaction (Figure 1b), which has been adapted from the literature.[24] Acetaldehyde and TFA acid are added to an oxygenated solution of 1,2-diiodobenzene, benzene, and amine in a DCE:HFIP mixture with $CoCl_2$ (DCE = 1,2-dichloroethane, TFA = trifluoroacetic acid, HFIP = 1,1,1,3,3,3-

hexafluoroisopropanol). An additional portion of acetaldehyde should be added prior to the students leaving lab. The reactions are left to stir overnight and worked-up the following class period by a silica gel column and the product is characterized by ^{1}H NMR spectroscopy. Mechanistic information regarding hypervalent-iodine-catalyzed C–N couplings has been summarized in the literature.[26]

Synthesis 3

Students synthesize (diacetoxyiodo)benzene via addition of acetaldehyde to an oxygenated solution of iodobenzene in glacial acetic acid with $CoCl_2$ under an O_2 atmosphere (Figure 2).[24] The reaction is allowed to stir overnight. The mixture is worked up the following class period via extraction into CH_2Cl_2 and the compound is characterized by ^{1}H NMR spectroscopy.

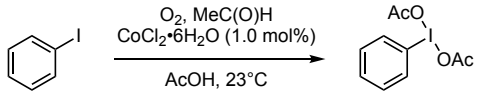


Figure 2. Aerobic generation of PIDA from iodobenzene.

Reaction Yields

Syntheses 1 – 3 have been performed by Texas A&M undergraduate students enrolled in CHEM433. The reaction yields obtained by students (working in groups) are provided below.

Table 1. Student yields obtained for synthesis.

Experiment	yield range (%)	Average (%)	n*
Synthesis 1: Pd-catalyzed cross-coupling	20 – 100	54	7
Synthesis 2: 1,2-diiodobenzene catalyzed coupling	2 – 78	27	7
Synthesis 3: PIDA	66 – 85**	73	6

* n = the number of data points; ** remaining solvent was observed in several student-collected NMR spectra

NMR Spectroscopy

Products from *Syntheses 1 – 3* are characterized by ^{1}H NMR spectroscopy, which are summarized in Tables 2 and 3.

Table 2. NMR spectroscopy chemical shift data for product of Synthesis 1 and Synthesis 2 (N-Methoxy-4-methylbenzenesulfonamide).

^{1}H shift (ppm)	Splitting	J (Hz)	# of protons	Assignment

7.41	d	-	2	-Ts/phenyl
7.24 – 7.22	m	-	5	-Ts/phenyl
7.13 – 7.09	m	-	2	-Ts/phenyl
3.88	s	-	3	-OMe protons
2.41	s	-	3	-Ts methyl protons

Table 3. NMR spectroscopy chemical shift data for product of Synthesis 3 (PIDA).

^{1}H shift (ppm)	**Splitting**	**J (Hz)**	**# of protons**	**Assignment**
8.09	d	7.3	2	*o*-phenyl protons
7.63 – 7.47	m	-	3	*m-*, *p*-phenyl protons
2.01	s	-	6	acetate

Synthetic Challenges

Leaking O_2 balloons and reaction set-ups were a problem that occurred in iodobenzene-catalyzed reactions. In order to prevent leaking, it is important to assemble the balloon so that the joints are tightly connected. In addition, it is necessary to always use a new septum and to utilize electrical tape to secure the septum to the 20-mL vial. A photograph of the apparatus is provided in the Supporting Information (Figure S1).

The appropriate amount of acetaldehyde needed for the lab section should be transferred from the bulk bottle to a secondary container before use to prevent contamination of the bulk acetaldehyde, which can undergo cyclization to form 2,4,6-trimethyl-1,3,5-trioxane.[27] Formation of 2,4,6-trimethyl-1,3,5-trioxane is indicated by the precipitation of clear, colorless crystals. It is also necessary to check bottles of acetaldehyde before each semester to ensure the acetaldehyde has not oxidized to acetic acid. Acetaldehyde is a low boiling point liquid and should be placed in an ice bath when in use to prevent the evaporation of the reagent.

Care should be taken to allow adequate time to dry the product as residual solvent was the main impurity found in student-collected NMR spectroscopy data.

RESULTS AND DISCUSSION

Application of Principles of Green Chemistry

Syntheses 1 and 2 can be compared both qualitatively and quantitatively in an effort to analyze the sustainability of each reaction. The American Chemical Society (ACS) supports the 12 Principles of Green Chemistry,[28] put forth by Paul Anastas and John Warner,[29] as a guide for making a chemical process more sustainable (Table 4). Five of these principles were selected (italicized and bolded) to be used as a qualitative baseline for comparing the Pd- and hypervalent-iodine-catalyzed cross-coupling reactions.

Table 4. The 12 Principles of Green Chemistry.

The 12 Principles of Green Chemistry
Prevention
Atom Economy
Less Hazardous Chemical Synthesis
Designing Safer Chemicals
Safer Solvents and Auxiliaries
Design for Energy Efficiency
Use of Renewable Feedstocks
Reduce Derivatives
Catalysis
Design for Degradation
Real-time Analysis for Pollution Prevention
Inherently Safer Chemistry for Accident Prevention

Prior to our in-class discussion, students are assigned reading to introduce them to the green chemistry principles above and the concept of green chemistry metrics.[30] To supplement the students reading, the instructor provides a 50-minute presentation on green chemistry. Though this topic can be discussed in a multitude of ways, the outline we chose was as follows: brief history of the field including the Pollution Prevention Act, Presidential Green Chemistry Challenge award, publication of the 12 principles, and the 2005 Nobel prize (with the work of Chauvin, Grubbs and Schrock cited as “a great step forward for “green chemistry”” in the Royal Swedish Academy of Science press release)[31]; the 12 principles of green chemistry (focusing on topics italicized and bolded in Table 2); renewability vs.

sustainability; green chemistry metrics (atom economy, reaction mass efficiency, stoichiometric factor, materials recovery parameter); and select advances in the field of green chemistry.

Class discussion was targeted at analyzing both reactions using the principles of green chemistry. For example, students were introduced to the topic of atom economy and asked to compare the atom economy of both reactions with the appropriate formula (see Supporting Information). Students were able to identify that the hypervalent-iodine-catalyzed coupling reaction has theoretically higher atom economy and therefore the reaction that should produce less waste. Our discussion of the principle of energy efficiency was focused on reaction conditions, *i.e.*, reaction temperature. The energy consequences of high temperature and pressure conditions were presented, in particular as related to industrial-scale reactions. The distinction between renewability and sustainability allows for identification of O_2 as a sustainable resource. The last principle described in detail was the need to minimize derivatized starting materials. Students successfully identified the hypervalent-iodine-catalyzed coupling reaction, which uses benzene, as the more desirable synthesis compared to Pd-catalyzed cross-coupling, which requires the derivatization of benzene (students will have also been exposed to this concept through their discussion questions, Supplemental Information Section G Q10).

Students also compared the reactions quantitatively through a simplified version of the green chemistry pentagon created by Andraos.[30] Without calculating material recovery metrics, students compared the yield, atom economy (AE), stoichiometric factor (SF), mass recovery parameter (MRP), and reaction mass efficiency (RME) of *Syntheses 1* and *2*.

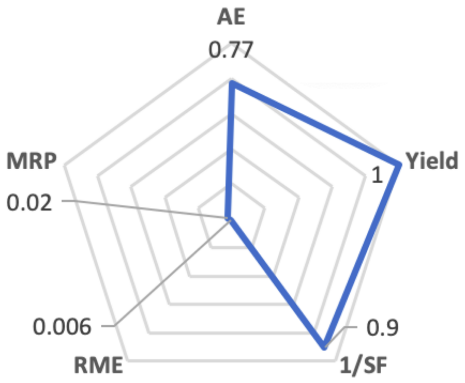


Figure 3. Example metric pentagon for Pd-catalyzed cross-coupling. AE = atom economy; SF = stoichiometric factor; MRP = materials recovery parameter; RME = reaction mass efficiency

An excel file that enables construction of the green chemistry pentagon is available as part of the Supporting Information (adapted from the materials developed by Andraos[30]). To use the adapted pentagon, students must simply know the quantity of each material used. Example pentagons for *Synthesis 1* and *Synthesis 2* are presented in Figures 3 and 4 respectively.

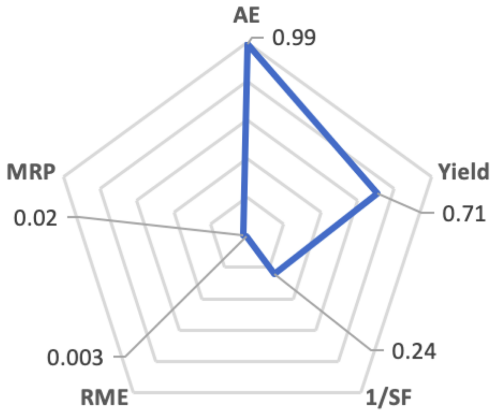


Figure 4. Example metric pentagon for 1,2-diiodobenzene-catalyzed coupling. AE = atom economy; SF = stoichiometric factor; MRP = materials recovery parameter; RME = reaction mass efficiency

When comparing the two pentagons, students should notice that the hypervalent-iodine-catalyzed reaction has a higher AE, while the Pd-catalyzed reaction has a better yield and stoichiometric factor. Both reactions have low MRP and RME values, a result of not recovering solvent or excess reagents used in the reactions.

Evaluation of Learning Objectives

Learning objectives were assessed both indirectly (student self-evaluation) and directly (group presentations post lab). For our indirect measure, students were asked to self-evaluate their comfort level with techniques covered in the experiment (LO3), as well as their understanding of green chemistry concepts (LO1, LO2, and LO4) (Table 5) before the lab module and at the end of the lab module. Specifically, the questionnaires gauged student confidence for activities in which they were well-versed — their ability to perform anaerobic manipulations (Q2), which by this point in the CHEM433 course,

students completed three lab modules that required anaerobic manipulations — as well as activities in which they were less experienced — such as their ability to work with low boiling point liquids (Q1), use compressed gas cylinders (Q3), run reactions under an O_2 atmosphere, and evaluate reactions in the context of green chemistry concepts (Q5, Q6, and Q7).

Table 5. Pre- and post-lab questionnaire. All questions were answered on a scale of 1–5.

Code	Question
Q1	Based on our laboratory activities this semester, how comfortable are you measuring and transferring low boiling point liquids (bp < 30 °C)? (LO3)
Q2	Based on our laboratory activities this semester, how comfortable are you setting up reactions under anaerobic (*i.e.*, nitrogen or argon atmosphere) conditions? (LO3)
Q3	How comfortable are you using a compressed gas cylinder? (LO3)
Q4	How comfortable are you setting up reactions under an O_2 atmosphere (not just air but using an O_2 tank of O_2 filled balloon)? (LO3)
Q5	Are you familiar with the concept of atom economy? (LO1, LO2, and LO4)
Q6	Are you familiar with the 12 Principles of Green Chemistry? (LO1, LO2 and LO4)
Q7	How comfortable would you be to compare the "greenness" of two reactions (i.e. do you know common green chemistry metrics to evaluate reactions)? (LO1, LO2 and LO4)

Student learning was also assessed through a post-lab group oral presentation. In this presentation, students were required to 1) present their experimental results, 2) generate a green chemistry metrics pentagon for each reaction, and 3) provide answers to a list of questions covering topics such as hypervalency, oxidase/oxygenase chemistry, sustainability, Pd-catalyzed C–N cross-coupling, kinetics of oxidation by O_2, and autoxidation of aldehydes (LO1, LO2, and LO4). These questions were provided to students along with their pre-lab handout. The pre-lab handout, a full list of these questions, and a model rubric for assessment of the student presentations can be found in the Supporting Information.

CONCLUSION

While advances in the development of sustainable oxidation chemistry appear in the research literature,[5-7] there has thus far been a lack of reports in the chemical education literature that introduce undergraduate students to these emerging methods.[8-9] The experiment presented herein teaches students about sustainability and catalysis through performing both a Pd-catalyzed cross-coupling

reaction and an aryliodide-catalyzed aerobic C–N bond-forming reaction. Students compare the two reactions qualitatively (12 Principles of Green Chemistry) and quantitatively (green chemistry metrics pentagon). Not only does this experiment re-enforce the development of students' laboratory skills, but it also demonstrates to students the importance of developing more sustainable synthetic methods, and emphasizes the complexity inherent in evaluating the interplay of variables that define sustainable synthesis.

ASSOCIATED CONTENT

Supporting Information

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

Experimental Procedures, Notes for Instructors, Example Rubrics (DOCX)

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