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# Safe Handling of Air-Sensitive Organometallic Reagents Using Schlenk Line Techniques: Negishi Cross-Couplings for Trainee Graduate Students

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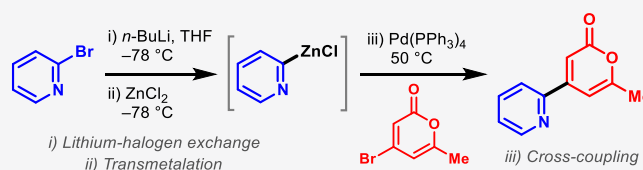
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**ABSTRACT:** A laboratory experiment has been devised to train new graduate trainees in the safe and controlled handling of air-sensitive organometallic reagents using Schlenk lines, high vacuum pumps, liquid nitrogen traps, and cannula transfers. The reaction involves the formation of air-, moisture-, and thermally sensitive 2-pyridyllithium, generated in situ by the reaction of 2-bromopyridine with *n*-butyllithium in dry THF at  $-78\text{ }^{\circ}\text{C}$ . Subsequent transmetalation with dried  $\text{ZnCl}_2$  and reaction with 4-bromo-6-methyl-2-pyrone in the presence of catalytic  $\text{Pd}(\text{PPh}_3)_4$  afforded the heterobiaryl product, 4-(2'-pyridyl)-6-methyl-2-pyrone. The many sensitivities of this experiment serve to provide an excellent practical demonstration for new graduate trainees of what can go wrong when experimental procedures are not accurately followed.

**KEYWORDS:** Graduate Education/Research, Organic Chemistry, Safety/Hazards, Hands-On Learning/Manipulatives, Problem Solving/Decision Making



Air-sensitive organometallic reagents are a fundamental component of chemical education and indispensable to research in academia and industry.<sup>1,2</sup> Good training is essential to ensure that air-sensitive reagents are handled safely.<sup>3</sup> This is especially true for pyrophoric reagents such as *t*-butyllithium, for which improper handling can be fatal<sup>4</sup> (note: the *n*-butyllithium reagent used in this experiment is considerably safer,<sup>2</sup> especially when used on a small scale). Considering this, and the routine use of air-sensitive organometallic reagents in research, the training of new graduate students in the safe handling of these reagents is a priority for many research institutions.<sup>5,6</sup> To meet this demand and develop proficiency in techniques unsuited to undergraduate laboratory courses, the creation of advanced laboratory courses for incoming graduate students is an important but underdeveloped endeavor.<sup>7</sup> When integrated into a graduate induction process, these laboratory courses also provide an excellent practical context to traditional classroom based safety seminars.

In addition to safety in the research environment, it is almost inevitable that students will encounter the use of organometallic reagents to form new C–C bonds in their studies. Training students to form new C–C bonds through transition-metal-catalyzed cross-coupling reactions<sup>8</sup> has therefore naturally become an area of great pedagogical interest.<sup>9</sup> However, the majority of the contributions in this area have focused on less sensitive cross-coupling reactions (e.g., Suzuki–Miyaura) and procedures that are more suited to undergraduate chemistry laboratories. A more operationally challenging Negishi cross-coupling reaction<sup>10</sup> procedure—involving the in situ formation of a (hetero)aryl zinc reagent—would

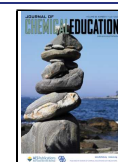
therefore provide an excellent opportunity to train new graduate research students in the safe and controlled use of air-sensitive techniques common to many research laboratories.

An example of such an air-, moisture-, and thermally sensitive Negishi cross-coupling reaction is described herein.<sup>11</sup> A brominated 2-pyrone heteroaryl electrophile is coupled to a 2-pyridyl zinc nucleophile, generated in situ, to afford a complex heterobiaryl product—a common structural motif in pharmaceutical research (note: the brominated 2-pyrone can be substituted by other organobromides, but the robustness of such new substrates would need to be rigorously tested before being tried by trainees).<sup>12</sup> Alongside teaching students the safe use of Schlenk lines, high vacuum pumps, liquid nitrogen traps, cannula transfers, and syringe techniques, this laboratory experiment has been designed to provide an important illustration of the many things that can go wrong with a sensitive reaction when improper technique is employed. This experiment therefore provides an excellent opportunity to discuss many facets of organic chemistry, such as catalysis, organolithium chemistry, drug discovery/medicinal chemistry, and lab safety.

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## ■ PEDAGOGICAL GOALS

- To provide new trainee graduate students with training in the safe use of air-sensitive organometallic reagents and high vacuum Schlenk lines, reaction setup, compound purification, and characterization using NMR and IR spectroscopy, supported by mass spectrometric characterization.
- To provide a practical context for advanced synthetic chemistry using a Negishi cross-coupling reaction to illustrate a typical C–C bond forming reaction performed in a research environment.
- To highlight topics of significant importance in modern organic and organometallic chemistry, particularly cross-coupling reactions, palladium catalysis, drug discovery/medicinal chemistry, and lab safety.
- To understand where reaction sensitivities can arise and their impact on the outcome of a reaction.

## ■ OVERVIEW OF LABORATORY EXPERIMENT

This experiment is part of an optional induction course designed for new incoming graduate students (e.g., PhD, Masters level) undertaking research in organic or inorganic chemistry laboratories. This course and experiment take place at the start of the academic year and are not formally graded. Students enroll into the course based on their planned research activities. The experiment typically requires ~6 h (including a lunch break) to complete. Students are sent the experimental procedure and an individual risk assessment to complete beforehand. The session starts with a discussion of the planned experiment, highlighting safety concerns and potential by-products that may be observed if the reagents are handled incorrectly. Upon completion of the experimental procedure, the students can purify their crude product either in a separate optional training course (in chromatographic purification methods) or in their own research laboratories (being assisted by experienced mentors in the use of flash chromatographic purification). The students then write a journal style experimental procedure with full characterization data and copies of their spectral data, which are assessed by the experiment coordinator. Finally, students receive written feedback and corrections for their work, which may be supplemented by oral feedback in an individual or group setting.

## ■ EXPERIMENT

All glassware and magnetic stirrer bars were dried in an oven (set to 70 °C) for 16 h prior to use. Students work individually or in pairs, depending on their level of prior experience. The students are instructed on the safe operation and set up of a high vacuum Schlenk line, before setting up their own apparatus and monitoring their vacuum gauge for leaks. Students attach an oven-dried Schlenk tube (with a magnetic stirrer bar) to their Schlenk line (previously setup with a liquid nitrogen cooled trap and checked thoroughly by a supporting technician professional or experienced demonstrator) and cycle between vacuum (down to 0.1 mbar or for 2 min if a vacuum gauge is not available) and nitrogen three times. Under an atmosphere of nitrogen, 2-bromopyridine (0.25 mL) and anhydrous tetrahydrofuran (THF, 14 mL) are sequentially added. The flask is cooled to –78 °C (using a dry ice acetone bath) before 2.5 M *n*-butyllithium in hexanes (1.1 mL) is added dropwise via syringe over 10 min. The reaction mixture

is stirred at –78 °C for 30 min to form the thermally sensitive lithium-halogen exchange product. During this time, students prepare an additional Schlenk tube containing ZnCl<sub>2</sub> (and a magnetic stirrer bar), which is placed under vacuum for 15 min (to partially dry the hygroscopic ZnCl<sub>2</sub>; note: a large batch of this can be dried for 24 h, prior to the experiment to assist the students, although we have found that this step can be circumvented) before being placed under nitrogen and cooled to –78 °C. The lithiated pyridine intermediate is transferred via cannula, and the reaction mixture is stirred for 20 min while allowing it to warm to ambient temperature. During this time, students prepare an additional Schlenk tube (with a magnetic stirrer bar) containing 4-bromo-6-methyl-2-pyrone (500 mg), tetrakis(triphenylphosphine)palladium(0) (Pd(PPh<sub>3</sub>)<sub>4</sub>, 153 mg), and anhydrous THF (14 mL, note: obtained from a PureSolv solvent purification system, distillation over sodium is not necessary). The pyridyl zinc intermediate is transferred via cannula (typically taking 5 min) and the reaction mixture is heated and stirred at 50 °C for 30 min. The reaction mixture is quenched by the addition of saturated aqueous NH<sub>4</sub>Cl and an aqueous workup is performed. Samples of the crude product are submitted for <sup>1</sup>H NMR spectroscopic analysis (in fresh deuterated chloroform) and gas chromatography–mass spectrometry (GC-MS). At a later date, the students purify this crude material by column chromatography (silica gel using ethyl acetate/petroleum ether with a boiling range of 40–60 °C as the eluent) and characterize all isolated products by <sup>1</sup>H/<sup>13</sup>C NMR and infrared spectroscopy and high resolution mass spectrometry. A step-by-step description of the experimental procedure is included in the [Supporting Information](#).

## ■ HAZARDS

Personal protective equipment (disposable gloves, safety glasses, and flame-resistant laboratory coat) should be worn at all times, and all experimental work should be performed in a fume hood (where all Schlenk lines and vacuum pumps were located; we do not advocate the use of this equipment on the open bench). The location of eyewash stations and safety showers should be clearly identified to the students, including any other local safety information, e.g., fire door exits. The importance of never working alone and informing your colleagues about potential hazards should be strongly stressed to all students. All Schlenk lines should be fitted with a bubbler to provide a pressure relief system. Liquid nitrogen can cause frostbite and severe cold burns and should only be handled with heavily insulated gloves. Moreover, liquid nitrogen should only be handled in well ventilated areas to avoid asphyxiation. The Schlenk vacuum line should never be opened to the air for prolonged periods when the liquid nitrogen trap is in place to avoid condensing liquid oxygen, which may cause violent explosions. Cannulas and needles are sharp and can easily puncture skin, and appropriate training is required to handle them and prevent injuries.<sup>13</sup>

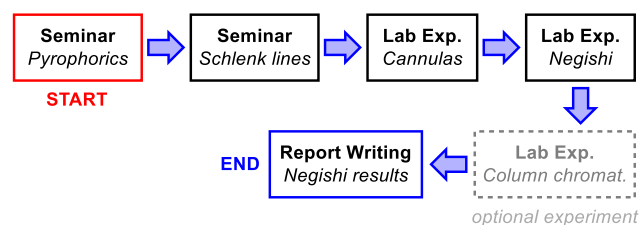
Many aryl bromides and heterobiaryl compounds do not have established toxicity profiles and should therefore be handled and treated as if they are toxic. Importantly, 2-bromopyridine is toxic if swallowed, is fatal in contact with skin, causes skin and eye irritation, and may cause respiratory irritation (note: 2-bromo-6-methoxypyridine can be used as a safer alternative if desired). *n*-Butyllithium (2.5 M in hexanes) is a highly flammable liquid, reacts with water to form flammable gases that can ignite spontaneously, may be fatal if

swallowed, causes severe skin burns and eye damage, may cause drowsiness or dizziness, is suspected of damaging fertility, and is toxic to aquatic life with long lasting effects. THF is a highly flammable liquid, is harmful if swallowed, may cause skin, eye, and respiratory irritation, may cause drowsiness or dizziness, and is suspected of causing cancer.  $\text{ZnCl}_2$  is harmful if swallowed, causes severe skin burns and eye damage, and is very toxic to aquatic life with long lasting effects.  $\text{Pd}(\text{PPh}_3)_4$  is harmful if swallowed and may cause allergic skin reactions and long lasting harmful effects to aquatic life. Ethyl acetate is a volatile and highly flammable liquid, causes serious eye irritation, and may cause drowsiness or dizziness. Deuterated chloroform is harmful if swallowed, causes skin and eye irritation, is toxic if inhaled, may cause drowsiness or dizziness, is suspected of causing cancer, is suspected of damaging the unborn child, and causes damage to organs through prolonged or repeated exposure if swallowed. All hazardous waste should be disposed of according to safety data sheet information and local regulations into labeled containers stored in an appropriately ventilated area.

## RESULTS AND DISCUSSION

Alongside a senior academic (a member of faculty with expertise in the use of Schlenk lines and high vacuum pumps)

### Scheme 1. Overview of Adaptive Lab Course Structure



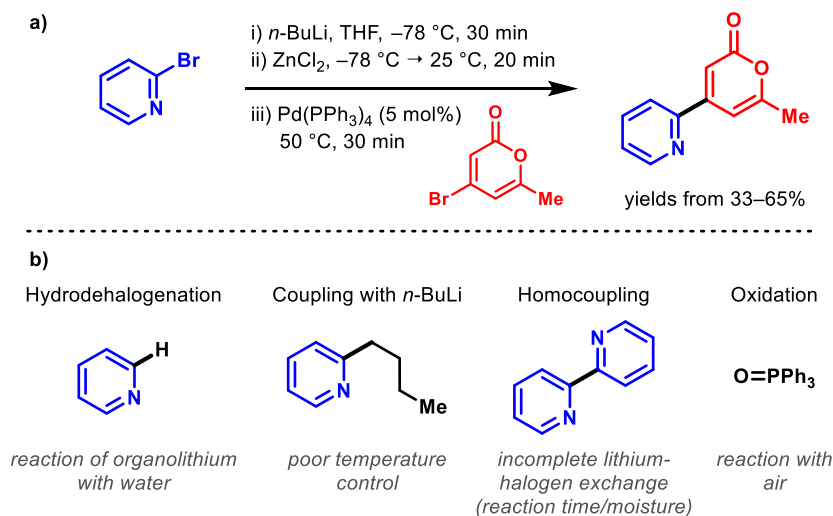
providing instruction and oversight, at least three graduate training assistants were present to provide experimental guidance and one-to-one support if necessary. This laboratory experiment has been successfully performed by different

cohorts of new graduate students since 2012 (typically 15 students per cohort, ~150 students to date). In this time, there was only one instance in which the experiment failed to afford the heterobiaryl product. Before entering the laboratory, all students attend two individual seminars (~40 min) which provide an introduction to pyrophoric reagents and the operation of a Schlenk line.<sup>14</sup> The experimental procedure is then circulated to the students to help them understand the underlying chemistry and safety considerations. Depending on the size and needs of the student cohort, this experiment has been bookended by additional experiments designed to teach the basics of (i) cannula transfer and syringe techniques and (ii) flash column chromatography using silica gel (Scheme 1). To conclude the lab course, each student writes an experimental report, including tabulated characterization data and copies of all spectral data collected, in accordance with the RSC or ACS guidelines (anonymized examples are provided in the Supporting Information).

The performance of the students and the effectiveness of this experiment are assessed based on the quality of their experimental data and submitted reports. Importantly, the students analyze their crude reaction mixtures by  $^1\text{H}$  NMR spectroscopy and/or GC-MS to provide instant feedback on the success of the experiment (conversions of starting material into product typically range from 60 to 70%). For the experimental reports, particular attention is given to the purity and assignments of spectral data as well as the identification of common impurities (e.g., solvents used during column chromatography, such as ethyl acetate, are commonly observed by  $^1\text{H}$  NMR spectroscopic analysis).

During the course of the experiment, a number of potential byproducts may be observed if the experimental procedure is not accurately followed (directly highlighting flaws in experimental technique, see Scheme 2b). To promote further learning using these byproducts, the students are challenged to isolate and identify as many products as possible and propose mechanisms for their formation and speculate what experimental error may have caused this in their experimental report. For example, pyridine is frequently observed as a hydrodehalogenation product, which is likely formed due to

### Scheme 2<sup>a</sup>



<sup>a</sup>(a) Reaction overview with yields for an exemplar cohort and (b) typical side products observed in this experiment and rationale for their formation.

reaction of the lithiated pyridine intermediate with water. Through this experiment, the students will therefore be exposed to the potential consequences of poor experimental technique for both their own personal safety and reaction performance.

## SUMMARY AND CONCLUSIONS

A Negishi cross-coupling reaction has been devised to provide new graduate research students training in the safe use of air-sensitive organometallic reagents using advanced Schlenk line techniques. In addition to lab safety, this experiment has provided excellent training in modern synthetic chemistry, reaction analysis, and reaction sensitivities.

We assessed whether the pedagogical goals of the practical experiment were met through verbal feedback. Many students went on to do air sensitive chemistry in their research laboratories and became expert in Schlenk and high vacuum line techniques. Other students, particularly from organic chemistry laboratories, were more aware of cross-coupling reaction sensitivities to oxygen and moisture, placing them in a good position to troubleshoot untested substrates facilitating access to complex molecular targets. Several students from the first two cohorts did comment on improving the overall reaction by heating the 2-bromo-6-methyl-2-pyrone with the in situ generated 2-pyridyl zinc reagent (which was introduced as an early modification). Feedback about the experiment was gathered from several cohorts of students in an open forum in a lecture room (a 30 min session, typically), where we examined spectral data and overall findings together. Within the laboratory, we reflected on the different colors (e.g., from dark green, to dark red-merlot) exhibited by the in situ generated 2-pyridyl metalated intermediates. This led to considerable critical debate in terms of the type of reactive intermediate(s) that might form under the reaction conditions (e.g., higher order metal aggregates, including mixed metal species).

Overall, approximately 150 graduate trainees from diverse training backgrounds have successfully completed this experiment as part of an adaptive training course. Alongside other induction processes, this course and laboratory experiment have been devised and used to instill a culture of proactive safety and personal responsibility in new graduate trainees.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available at <https://pubs.acs.org/doi/10.1021/acs.jchemed.2c00134>.

List of equipment and materials required to perform this experiment; experimental procedure handout; illustrations of procedure as visual aids; individual risk assessment form, and representative spectral data from students (PDF)

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## Notes

The authors declare no competing financial interest.

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(14) If these teaching materials are not already available, instructors can use informative online resources, such as <https://schlenklinesurvivalguide.com/>.

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