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Laboratory Experiment

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Nickel-Catalyzed Suzuki–Miyaura Cross-Coupling in a Green Alcohol Solvent for an Undergraduate Organic Chemistry Laboratory

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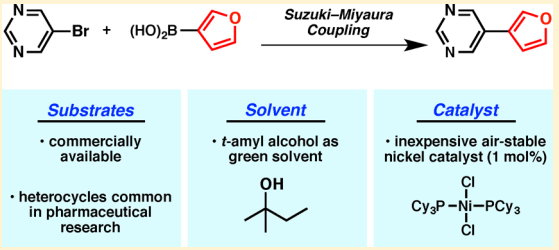
Supporting Information

ABSTRACT: A modern undergraduate organic chemistry laboratory experiment involving the Suzuki–Miyaura coupling is reported. Although Suzuki–Miyaura couplings typically employ palladium catalysts in environmentally harmful solvents, this experiment features the use of inexpensive nickel catalysis, in addition to a "green" alcohol solvent. The experiment employs heterocyclic substrates, which are important pharmaceutical building blocks. Thus, this laboratory procedure exposes students to a variety of contemporary topics in organic chemistry, including transition metal-catalyzed cross-couplings, green chemistry, and the importance of heterocycles in drug discovery, none of which are well represented in typical undergraduate organic chemistry curricula. The experimental protocol uses commercially available reagents and is useful in both organic and inorganic instructional laboratories.



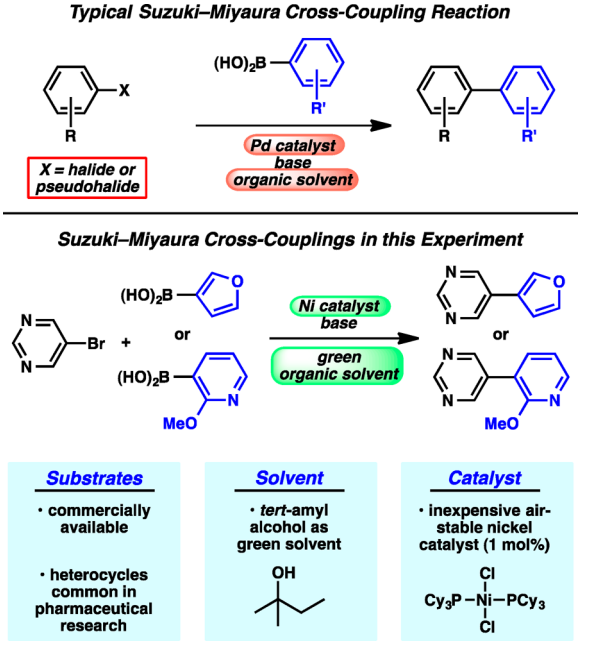
KEYWORDS: *Second-Year Undergraduate, Upper-Division Undergraduate, Organic Chemistry, Laboratory Instruction, Hands-On Learning/Manipulatives, Organometallics, Green Chemistry, Heterocycles*

Methods for the assembly of carbon–carbon (C–C) bonds are a cornerstone of any undergraduate organic chemistry course. Most commonly, textbooks and curricula prominently feature classical reactions such as Grignard additions[1] and Friedel–Crafts acylations,[2] which serve as excellent pedagogical tools. The incorporation of more modern C–C bond forming reactions into the undergraduate curriculum has been a topic of interest, such that many new textbooks at least briefly mention new tactics for C–C bond construction that are commonly used in research laboratories.[3]

One particularly attractive class of transformations that has seen increased attention in undergraduate organic chemistry curricula is transition metal-catalyzed cross-coupling reactions.[4] Reactions such as the Suzuki–Miyaura, Negishi, and Heck couplings provide indispensable tools in academia and industry for C–C bond formation. The importance of these transformations is underscored by the awarding of the 2010 Nobel Prize in Chemistry to Suzuki, Negishi, and Heck for their pioneering studies of these key reactions.[5] In an effort to expose undergraduate students to these couplings, new experimental procedures have been put forth with much success.[6] For example, Deveau and co-workers recently reported a palladium-catalyzed Suzuki–Miyaura coupling suitable for undergraduate laboratories,[6a] which also features important lessons involving medicinal chemistry and green chemistry.[6a–c,7]

An operationally simple variant of the Suzuki–Miyaura cross-coupling (Scheme 1) is described.[8] Analogous to a typical Suzuki–Miyaura coupling, an aryl electrophile is joined to an aryl boronic acid fragment using a transition metal catalyst to give a biaryl product. In the protocol described herein, several features are highlighted: (A) The substrate and the boronic acids used are commercially available heterocycles.[9] Oxygen- and nitrogen-containing heterocycles are common building

Scheme 1. Typical Suzuki–Miyaura Cross-Coupling and a Modern Variant Featuring the Use of a Green Solvent, Heterocyclic Substrates, and a Nickel Catalyst



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blocks used in pharmaceutical research for the preparation of new medicines.[10] (B) The solvent utilized is *tert*-amyl alcohol,[11,12] which is considered a "green" alternative to typical organic solvents.[13,14] It is estimated that 20−85 kg of organic solvent waste is produced per kilogram of drug produced in a six- to eight-step drug manufacturing process, so the use of green solvents is especially desirable.[15] (C) The catalyst employed is a commercially available and air-stable nickel complex,[16−19] which compares well to more commonly used palladium catalysts. Furthermore, nickel is a nonprecious metal and is, therefore, more abundant and less expensive compared to its precious metal counterpart palladium.[20]

This laboratory experiment exposes students to a variety of contemporary topics in organic chemistry, including cross-coupling reactions, catalysis, and the importance of heterocycles in drug discovery. Moreover, this experiment introduces the critical concepts of green chemistry,[13] which are often overlooked in traditional undergraduate organic chemistry curricula.

PEDAGOGICAL GOALS

- To develop a contemporary undergraduate instructional laboratory experiment involving the Suzuki−Miyaura cross-coupling reaction as a means to expose students to typical reaction sequences encountered by academic and industrial researchers.
- To bring attention to current and important topics in organic chemistry, including cross-couplings, transition metal catalysis, green chemistry, and heterocycles in pharmaceutical research.
- To provide students with training in standard organic chemistry laboratory techniques, including reaction setup, reaction monitoring, compound purification, and structure elucidation by ^{1}H and ^{13}C NMR analysis.

OVERVIEW OF LABORATORY EXPERIMENT

This experiment is designed for an upper-division undergraduate organic chemistry laboratory but is also appropriate for second-year undergraduate organic and advanced inorganic chemistry laboratories. The experiment requires 4−5 h to complete and can be performed over two laboratory periods, if necessary. Students complete a prelaboratory worksheet before conducting the experiment to ensure they understand the experiment and any safety concerns. A postlaboratory worksheet further promotes student understanding and helps students perform a critical analysis of their results.

EXPERIMENT

Students work individually and complete a prelaboratory worksheet. Each student is assigned an unknown heterocyclic boronic acid as a coupling partner whose identity is determined after the coupling reaction using NMR spectroscopy. Students weigh the substrate (5-bromopyrimidine), boronic acid, base (K_3PO_4), and catalyst (1 mol %) and combine them in a 1 dram (∼4 mL) vial. After adding a stir bar and *tert*-amyl alcohol, the reaction is stirred at room temperature for 30 min, and then heated to 80 °C using a preheated heating block or an oil bath. After heating for 1 h, students use thin-layer chromatography (TLC) to determine if the reaction is complete and gauge the purity of the product. The mixture is subjected to aqueous workup and the crude product is purified via flash column chromatography on silica gel. The isolated product is then analyzed via ^{1}H and ^{13}C NMR spectroscopy using a postlaboratory worksheet. A detailed description of the experiment is described in the Supporting Information.

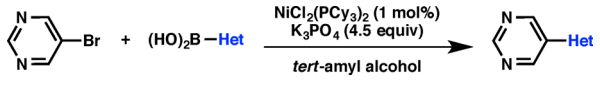
HAZARDS

Closed-toed shoes, long pants, safety glasses, gloves, and flame-resistant laboratory coats should be worn at all times. All hazardous materials should be handled and disposed of in accordance with the recommendation of the materials' safety data sheet and EH&S. Bis(tricyclohexylphosphine)nickel(II) dichloride ($NiCl_2(PCy_3)_2$) and heterocyclic boronic acids may be harmful if inhaled, swallowed, or absorbed through skin. 5-Bromopyrimidine and potassium phosphate are irritants and may be harmful if inhaled, swallowed, or absorbed through skin. *Tert*-amyl alcohol is an irritant and may, therefore, cause skin and eye irritation; it is also flammable and may be harmful if inhaled, swallowed, or absorbed through skin. Hydrochloric acid and sodium hydroxide are corrosive and can cause burns to the skin, eyes, and respiratory tract. Ethyl acetate and hexanes are flammable and volatile organic solvents. The *n*-hexane in hexanes is a neurotoxin. $CDCl_3$ is toxic and a cancer suspect agent. The products of the coupling are not considered harmful, but care should be taken to avoid inhalation or contact with skin.

RESULTS AND DISCUSSION

The nickel-catalyzed Suzuki−Miyaura coupling using green solvents was recently described.[21] Despite the promise of this protocol, some efforts were necessary to render this transformation suitable for an undergraduate instructional experiment (see the Instructors' Notes in the Supporting Information for further details). We first examined several heterocyclic substrates and heterocyclic boronic acids.[9] The substrates shown in Scheme 1 were found to be optimal based on their commercial availability and ability to react using low loadings of the nickel catalyst in *tert*-amyl alcohol as the solvent. A brief selection of our optimization efforts using conventional heating or microwave heating is highlighted in Table 1. The conditions shown in entries 3 and 7 (conventional heating) were identified as optimal conditions. It should be noted that the experiment could be performed in a microwave reactor with comparable yields (see entries 4 and 8).

Table 1. Survey of Reaction Conditions



Entry[a]	Het	Temp. (°C)	Time	Product (%)[b]
1		50	1 h	49
2		80	0.5 h	75
3		80	1 h	98
4[c]		150	10 min	96
5		50	1 h	95
6		80	0.5 h	89
7		80	1 h	100
8[c]		150	10 min	91

[a]Conditions: 5-bromopyrimidine (1.0 equiv), heterocyclic boronic acid (2.5 equiv), *tert*-amyl alcohol (0.3 M). [b]Yield was determined by ^{1}H NMR analysis of the crude reaction mixtures using hexamethylbenzene as an internal standard. [c]The reaction was conducted in a microwave reactor.

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The optimized experimental protocol was implemented during one term of an advanced undergraduate organic chemistry lecture and laboratory course, which mainly consisted of students majoring in Chemistry or Biochemistry. Students were briefly introduced to cross-coupling reactions, including the Suzuki–Miyaura coupling,[8] and green chemistry during the course lecture meeting. They then read the laboratory handout, which covered experimental details and various background information on cross-couplings, green chemistry, and heterocycles. Students completed a prelaboratory worksheet, which was designed to make sure students understood the chemistry, the experimental protocol, and safety considerations. Completion of the prelaboratory worksheet satisfactorily was required for students to carry out the experiment.

Each student was given one of the two unknown boronic acids and carried out the Suzuki–Miyaura coupling experiment. The main aspects of this experiment included reaction setup, monitoring, purification, and spectroscopic analysis. Of the 30 students who carried out the experiment, 29 of them were able to isolate their desired product after chromatography. Students used ^{1}H NMR and ^{13}C NMR analysis (student spectra are given in the Supporting Information) to determine the identity of their unknown boronic acids and their cross-coupled products. Yields ranged from 28–95% for those who used the furanyl boronic acid, whereas yields were in the 39–100% range for those who employed the pyridyl boronic acid. Average yields were 61% and 76%, respectively. Lower yields were likely caused by the loss of product during workup or purification. Residual solvent was seen in several cases during ^{1}H NMR analysis of products. However, other notable impurities, such as unreacted boronic acid, were rarely seen. A required postlaboratory worksheet was used to facilitate data analysis and further expand on the key chemical concepts from this experiment.

Discussion Topics

This experiment provided the opportunity to discuss a range of important topics relevant to undergraduate organic chemistry lecture material and modern laboratory practices. With regard to organic chemistry, discussion topics included, but were not limited to, transition metal-catalyzed cross-couplings,[4] the mechanism of the Suzuki–Miyaura coupling,[8] and heterocycles.[10] Moreover, this experiment provided an opportunity to address modern, big picture topics, such as pharmaceutical research and the growing importance of green chemistry. In the laboratory, students were exposed to a contemporary experimental protocol and gained experience in a variety of methods and techniques. This included reaction setup on a small scale (e.g., 100 mg of substrate and only 4.4 mg of the nickel catalyst), reaction analysis using thin layer chromatography (TLC), aqueous workup, flash column chromatography, and NMR analysis. An anonymous student evaluation of the experiment indicated that students recognized the concepts emphasized in the experiment (see Supporting Information).

CONCLUSIONS

A modern protocol was developed for the Suzuki–Miyaura coupling that is suitable for use in undergraduate instructional laboratories. The experimental procedure was straightforward and provided student training in modern laboratory methods and techniques. In addition, the laboratory exposed students to a variety of contemporary topics in organic chemistry, including transition metal-catalyzed cross-couplings, the importance of heterocycles in drug discovery, and green chemistry. This experiment will allow educators to introduce a variety of topics efficiently into their undergraduate organic chemistry curricula, which are otherwise often neglected in conventional undergraduate organic chemistry laboratories.

ASSOCIATED CONTENT

Supporting Information

Detailed student handout; prelaboratory worksheet; postlaboratory worksheet; notes for instructors; NMR spectra of products, including spectra from students. This material is available via the Internet at http:/pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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