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Laboratory Experiment

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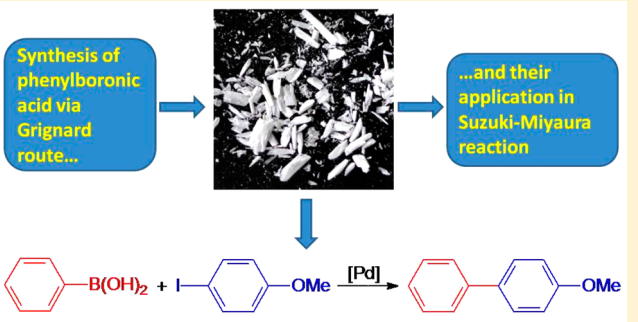
Introducing Undergraduates to Research Using a Suzuki–Miyaura Cross-Coupling Organic Chemistry Miniproject

Deyvid G. M. Oliveira, Clarissa H. Rosa, Bruna P. Vargas, Diego S. Rosa, Márcia V. Silveira, Neusa F. de Moura, and Gilber R. Rosa*

Escola de Química e Alimentos, Universidade Federal do Rio Grande - FURG, Campus Santo Antônio da Patrulha. Rua Barão do Cahy, 125, Cidade Alta, CEP 95500-000, Santo Antônio da Patrulha, Rio Grande do Sul, Brazil

Supporting Information

ABSTRACT: A five-week miniproject is described for an upper-division experimental organic chemistry course. The activities include synthesis of a phenylboronic acid via a Grignard reaction and its use in a Suzuki–Miyaura cross-coupling reaction. Technical skills and concepts normally presented in practical organic chemistry courses are covered, including the use of an inert atmosphere (Schlenk tube technique), separation of mixtures (filtration), melting range determination, infrared (IR) spectrum, stoichiometric calculations and gas chromatography techniques.



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INTRODUCTION

For thorough training in organic chemistry, students need to know complex, current reactions. Because more complex organic syntheses require several laboratory periods, the idea of using miniprojects presents a good method for thorough training in organic chemistry.[1] Additionally, traditional and basic technical training can also be addressed during miniprojects.

The Suzuki–Miyaura cross-coupling reaction is widely used in modern organic synthesis, and therefore, it must be included in the training of chemistry professionals.[2] The development of practical laboratory experiments involving this reaction has been reported that also illustrates the importance of "green" processes.[3]

To provide students with this experience, a 5-week experiment (lab period = 3 h/week) is described based on the Suzuki–Miyaura cross-coupling reaction of phenylboronic acid (**1**) with 4-iodoanisole (**2**) catalyzed by tetrakis(triphenylphosphine)-palladium(0) ($Pd(PPh_3)_4$) or Dupont's catalyst (NCP pincer palladacycle, Figure 1) to synthesize 4-methoxybiphenyl (**3**) (Scheme 1) under an inert atmosphere (Schlenk tube technique). The synthesis of **1** is done via the Grignard route under an inert atmosphere (Scheme 2),[4] although **1** is commercially available.

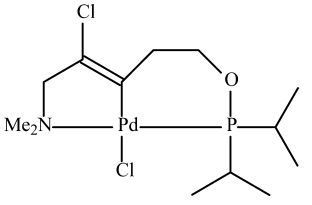
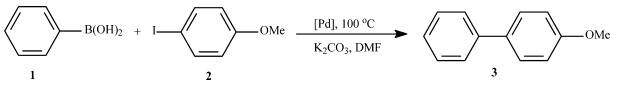
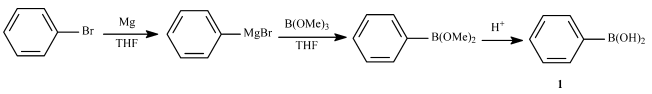


Figure 1. Dupont's catalyst (NCP pincer palladacycle).

Scheme 1. Suzuki-Miyaura Cross-Coupling Performed by Students



Scheme 2. Synthesis of Phenylboronic Acid Using a Grignard Reagent



The primary goal for this experiment is to introduce students to a research-like environment by familiarizing them with the scientific literature and more detailed laboratory routines. At the conclusion of this five-week miniproject, students should be more comfortable synthesizing organic compounds and identifying reaction products using GC techniques in addition to reporting their results in a journal-ready format.

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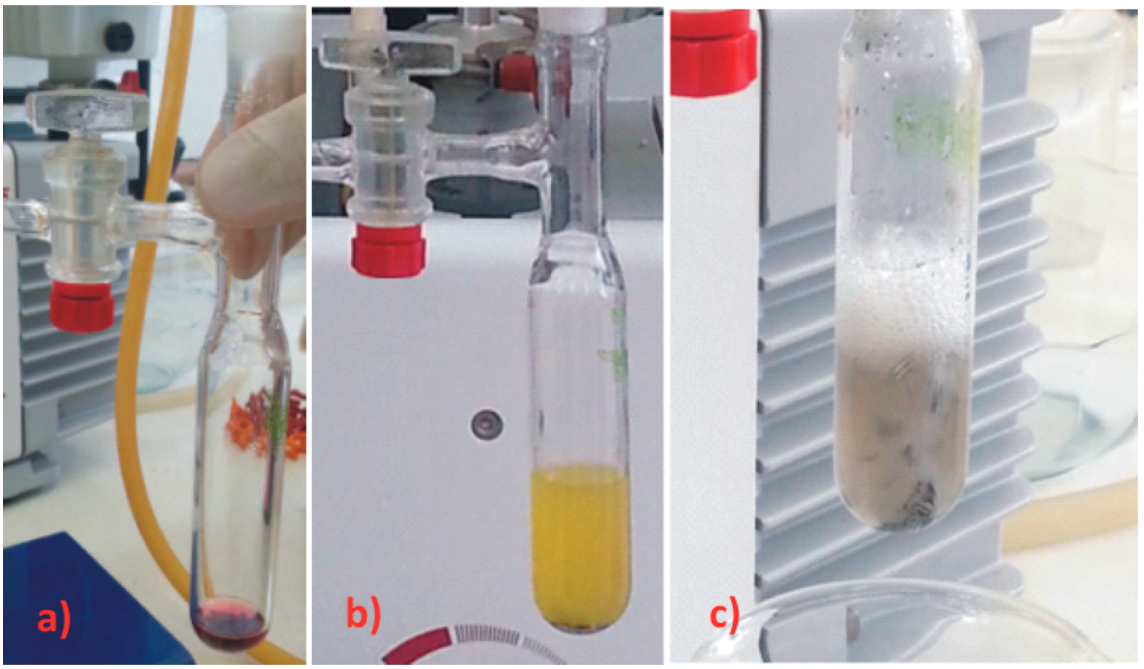

Figure 2. (a) Bromobenzene, iodine, and magnesium in the flask; (b) after THF addition; (c) beginning of the Grignard reaction.

EXPERIMENT

Students work in groups of three. Prior to the initial laboratory period, students read two papers related to the experiment.[4,5] In week one, a quick introduction to the Schlenk tube technique is provided. Students synthesize the phenylboronic ester via the Grignard route.[4] Bromobenzene (10 mmol), iodine (small crystal), and magnesium (10.8 mmol) in 10 mL of tetrahydrofuran (THF) is refluxed under N_2; after completion of the reaction, the solution is transferred to an addition funnel under N_2 and the solution is added dropwise to a solution of trimethylborate (10 mmol) in THF (10 mL) cooled in a dry ice/ethanol bath. After the addition is complete, the reaction mixture containing the phenylboronic ester is stored in a Schlenk flask under N_2 atmosphere at room temperature until the next class.

In week two, the phenylboronic ester is hydrolyzed and worked up to give **1** that crystallizes over the next week. In week three, students collect **1** as white, needle-like crystals, determine its melting range, and obtain an IR spectrum. The expected yield for the synthesis of **1** is of the order of 80%.

Week four focuses on the synthesis of **3**.[5] Each group is assigned a catalyst and a reaction time; phenylboronic acid (1.5 mmol), 4-iodoanisole (1.0 mmol), catalyst ($Pd(PPh_3)_4$ or Dupont's catalyst, 0.2 mol %), and potassium carbonate (2 mmol) in dimethylformamide (DMF) are heated at 100 °C for the assigned time (1, 2, 3, or 4 h) under N_2.

In week five, the yield of the Suzuki−Miyaura cross-coupling reaction is determined by GC analysis using an internal standard (undecane). Detailed procedures are in the Supporting Information.

HAZARDS

Magnesium, trimethylborate, THF, methanol and DMF are flammable. H_2SO_4 and KOH are corrosive. $Pd(PPh_3)_4$ and 4-iodoanisole are harmful if inhaled. 4-Methoxybiphenyl and biphenyl (byproduct) are irritants. Dupont's catalyst must be handled with care because its hazards are not known; however, it is thermal and air stable. The use of low quantities of catalyst (0.2 mol %) and small amount of byproduct generated show that the proposed catalytic system (for Suzuki−Miyaura cross-coupling) is of low toxicity to students. All experiments are conducted with students wearing eye protection, lab coats, nitrile gloves, and fume hood (for harmful reagents).

RESULTS AND DISCUSSION

The miniproject was implemented with 15 students in 2013 in an upper-division undergraduate course, Experimental Organic Chemistry, Course of Agroindustrial Engineering - Emphasis on Agrochemical. The course covers basic techniques of synthesis and characterization of organic compounds.

The formation of phenylmagnesium bromide in the Grignard reaction for the synthesis of phenylboronic acid had a significant color change and was effervescent (Figure 2), which students found interesting. Subsequent reaction with trimethylborate, hydrolysis of the phenylboronic ester, and workup gave crystals of **1**. The yield ranged from 17 to 70% (Table 1). Low yields of phenylboronic acid were associated with variables related to the preparation of the Grignard reagent (inert atmosphere and anhydrous THF), as well as those during the adjustment of the pH of the reaction mixture and crystallization. However, even with unsatisfactory results from the reaction, a fruitful discussion

Table 1. Results Obtained for Each Group in Miniproject[a]

Group	Melting Range, °C	Yield of **1**, %	Catalyst	Time, h	Yield of **3**, %
1	215−218	58	$Pd(PPh_3)_4$	1	44
2	216−217	67	$Pd(PPh_3)_4$	2	69
3	216−220	70	$Pd(PPh_3)_4$	3	78
4	215−218	17	$Pd(PPh_3)_4$	4	99
5	216−219	63	Dupont's	3	93

[a]Suzuki−Miyaura cross-coupling conditions: 4-iodoanisole (1 mmol), phenylboronic acid (1.5 mmol), catalyst (0.2 mol %), K_2CO_3 (2 mmol), DMF (2 mL), 100 °C, GC yields.

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concerning technical errors can occur. The reported melting range of pure phenylboronic acid is 214−216 °C.[4] Each student group reported melting points that fell within this range (Table 1). Moreover, students in each group analyzed an IR spectrum of the phenylboronic acid synthesized for two major bands at ±3230 cm^{-1} (υOH) and ±1340 cm^{-1} (υBO). A representative spectrum from a student group is in the Instructor's Notes in the Supporting Information.

The Suzuki−Miyaura cross-coupling reaction between phenylboronic acid and 4-iodoanisole was performed under an inert atmosphere for different reaction times. Four groups used the classical catalyst, $Pd(PPh_3)_4$, and one group used Dupont's catalyst. The reactions were analyzed by gas chromatography using the internal standard technique; the peaks of interest appeared at ±3 min (undecane, the internal standard), ± 5 min (4-iodoanisole), and ±8 min (4-methoxybiphenyl). Information about the use of the internal standard technique, GC equipment, and a representative chromatogram is given in the Instructor's Notes in the Supporting Information. The results obtained by the students for the Suzuki−Miyaura cross-coupling reaction only are provided in Table 1.

Longer reaction times resulted in a higher yield when $Pd(PPh_3)_4$ was used as the catalyst (groups 1−4).[2] When Dupont's catalyst was used with a reaction time of 3 h (group 5), a higher yield was obtained than for the classical catalyst for the same reaction time. This result was explained using the classic catalytic cycle for the Suzuki−Miyaura cross-coupling reaction (Figure 3). Dupont's catalyst benefits from a partial dissociation

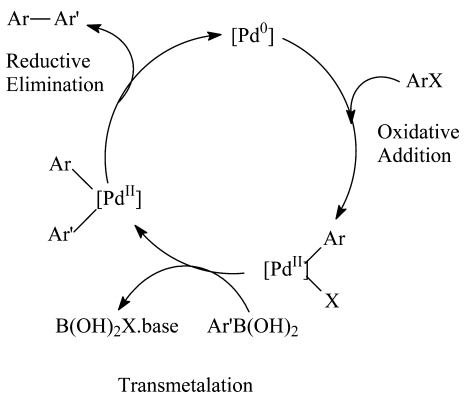

Figure 3. Catalytic cycle of Suzuki−Miyaura cross-coupling reaction.

of phosphinite ligand that does not occur with the classical catalyst, and this facilitates the oxidative addition of substrates (the limiting step of the Suzuki-Miyaura cross-coupling reaction).[5]

Although the synthesis chosen for this miniproject promotes the generation of a byproduct, biphenyl (Ph-Ph) for this Suzuki−Miyaura reaction, it enables the development of many essential skills to the student of organic chemistry. This study was designed as a low-cost, practical class and promoting the use of materials and reagents available in laboratories with limited resources, so, even being a synthesis that does not adhere to atom economy, the waste generated (THF, $Mg(OH)_2$, MeOH, DMF, K_2CO_3, and traces of Pd) is of low toxicity. However, handling non eco-friendly reactions and treating waste is also a part of learning for future professionals in chemistry. The choice of a low amount of catalyst (0.2 mol %) denotes, on the other hand, the search for more efficient catalytic systems that facilitate purification of products.

CONCLUSION

This five-week miniproject introduced advanced undergraduate students to a complex organic synthesis process. Starting with basic information, students prepared a phenylboronic acid using an air sensitive reaction, purified it by crystallization, determined its melting range and obtained an IR spectrum to confirm its purity, and used it as a starting material in a Suzuki−Miyaura cross-coupling reaction. In addition, students used gas chromatography to quantify the biaryl formed in the last reaction, which illustrates a common procedure in organic chemistry laboratories. To conclude this miniproject, students determined the differences in reaction yield obtained by changing the catalyst and provided an explanation for the phenomenon in a laboratory report (paper format).

The pedagogical objectives proposed for this miniproject were fully achieved. The sequence of related activities motivated and effectively engaged all students, creating a cooperative spirit between workgroups. The skills developed during this miniproject are valuable for professionals in the field of organic synthesis. Students participating in similar activities exhibited outstanding performance in research groups.

ASSOCIATED CONTENT

Supporting Information

Student handout (procedures for the synthesis and characterization of phenylboronic acid and 4-methoxybiphenyl) and Instructor's Notes. This material is available via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: gilberrosa@furg.br.

Notes

The authors declare no competing financial interest.

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