

Ligand-Free Suzuki–Miyaura Coupling Reactions Using an Inexpensive Aqueous Palladium Source: A Synthetic and Computational Exercise for the Undergraduate Organic Chemistry Laboratory

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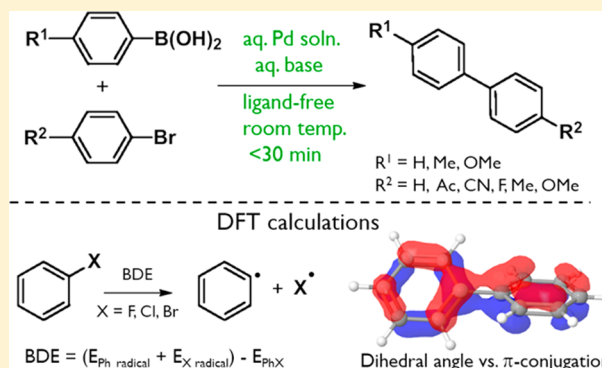
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S Supporting Information

ABSTRACT: An inexpensive procedure for introducing the Suzuki–Miyaura coupling reaction into a high-enrollment undergraduate organic chemistry laboratory course is described. The procedure employs an aqueous palladium solution as the catalyst and a range of para-substituted aryl bromides and arylboronic acids as substrates. The coupling reactions proceed rapidly at room temperature using standard glassware and do not require ligands, an inert atmosphere, or specialized equipment. Computational chemistry is used to explore the molecular and electronic structures of typical starting materials and products of the Suzuki–Miyaura coupling.

KEYWORDS: Second-Year Undergraduate, Laboratory Instruction, Organic Chemistry, Hands-On Learning/Manipulatives, Inquiry-Based/Discovery Learning, Catalysis, Green Chemistry, Molecular Modeling, Organometallics



The palladium-catalyzed coupling of organoboranes with organic halides in the presence of a base, termed the Suzuki–Miyaura coupling (SMC) reaction, is a fundamental method for the construction of C–C bonds.^{1,2} The importance of this reaction and other Pd-catalyzed couplings was recognized by the award of the 2010 Nobel Prize in Chemistry to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki.³ Introductory-level organic chemistry textbooks have only recently begun to include discussion of transition metal-catalyzed C–C bond forming reactions;⁴ in contrast, a number of instructional laboratory experiments focusing upon SMC reactions have been reported in the past decade.⁵ These procedures are excellent means by which to introduce such reactions into the undergraduate laboratory curriculum and are ideal for use in courses of relatively low enrollment. Unfortunately, these procedures also feature drawbacks, such as the requirement for expensive palladium compounds, phosphine ligands, and other additives, or the use of aryl iodides as substrates, in addition to inert atmosphere conditions or access to specialized synthesis equipment. As such, these protocols are less suited for courses of high-enrollment or at institutions operating under significant budgetary constraints.

The SMC procedure reported herein employs readily available aryl bromides and arylboronic acids as substrates and an aqueous atomic absorption standard solution as the Pd

source (~1000 ppm PdCl_2 in 5% aq HCl). A similar Pd source has been used previously in cross-coupling reactions performed under microwave heating conditions.⁶ The aqueous PdCl_2 solution is available commercially, stable indefinitely at room temperature, easy to dispense, and costs ~3¢ per reaction (~\$80 per 500 mL bottle, 200 μL per reaction, ~2500 reactions per bottle). The procedure does not require an added ligand and proceeds rapidly at room temperature under aerobic conditions using standard glassware. These aspects, along with use of a benign solvent, low catalyst loading, and ease of workup and purification, allow the reaction to be placed in the context of green chemistry. In addition to the synthetic component of the exercise, students perform computational modeling to explore the molecular and electronic structures of aryl halides and biaryl compounds. The main pedagogical goals of this lab exercise, which has been successfully completed by >1000 students in an introductory organic laboratory course, are to introduce the principles of organometallic catalysis, to use a range of spectroscopic techniques to identify starting materials and products, and to augment understanding of the electronic and molecular structures of typical starting materials and products of a SMC reaction by use of computational chemistry.

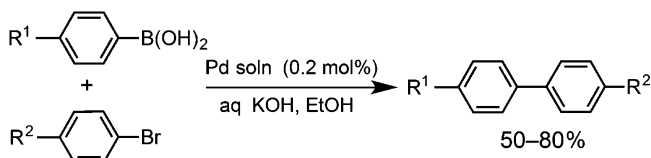
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EXPERIMENTAL OVERVIEW

Synthesis

A typical SMC reaction (Scheme 1) is performed by individual students as follows. A para-substituted aryl bromide (1.00

Scheme 1. Suzuki–Miyaura Coupling of Arylboronic Acids with Para-Substituted Aryl Bromides



R¹ = H, Me, OMe

R² = H, Ac, CN, F, Me, OMe

mmol) is dissolved in 95% aq EtOH solution (5–10 mL) in a round-bottom flask, followed by addition of the arylboronic acid (1.05 mmol). Complete dissolution of the starting materials is followed by sequential addition of aqueous Pd catalyst solution (approx 0.2 mol %) and 1 M aq KOH solution. A white solid precipitates from the rapidly stirred solution within 15 min of addition of the base solution, following which water is added and the crude product is isolated by vacuum filtration. A CH₂Cl₂ solution of the crude product is then passed through a column of anhydrous MgSO₄ in a Pasteur pipet to remove precipitated Pd and residual water. The biaryl product obtained upon evaporation of the solvent is sufficiently pure for characterization by ¹H NMR, ¹³C NMR, and IR spectroscopy. Students use ¹H NMR, ¹³C NMR, EI-MS, IR, and elemental composition data to identify the specific aryl bromide assigned as a starting material.

Computational Molecular Modeling

The use of computational molecular modeling in the organic chemistry curriculum is increasingly common.⁷ Students in our introductory laboratory course perform density functional theory (DFT) calculations on molecules relevant to each reaction studied. Analysis of these data comprises a significant portion of the grade for each laboratory report. This dual synthetic–computational approach provides students with an authentic combination of experimental and theoretical data to understand the outcomes of reactions performed in the laboratory. In the context of the SMC reaction, the computations focused upon the relative reactivity of the carbon–halogen bond of aryl halides and the three-dimensional structure of some simple biaryl compounds. All calculations were performed in the Gaussian 09 program via the WebMO interface using B3LYP/6-31G(d) (see Supporting Information for references and details of computational exercises).

HAZARDS

Arylboronic acids, aryl bromides, and substituted biaryl compounds are irritants and harmful by inhalation. Specific safety information can be obtained by consulting the MSDS for each compound. Aqueous potassium hydroxide solution is corrosive. Ethanol is flammable. Dichloromethane is an irritant and harmful by inhalation and if swallowed. Deuterated chloroform is toxic, an irritant, and a suspected carcinogen. Solid and liquid waste should be disposed into sealed and appropriately labeled containers. Appropriate personal protective equipment, such as disposable gloves, goggles, and a lab

coat, should be worn at all times and the procedures performed in a fume hood or similarly ventilated workspace.

DISCUSSION

The coupling reaction was readily completed by individual students within a typical 3-h laboratory session, furnishing the solid biaryl product in sufficient yield and purity for characterization by ¹H NMR, ¹³C NMR, and IR spectroscopy and melting point. The coupling product occasionally failed to precipitate from the reaction mixture even after prolonged stirring but was obtained upon addition of water to the reaction mixture. Only rarely did a coupling reaction fail to produce any biaryl compound, and in such rare cases, the student was allowed to repeat the experiment, always with a successful outcome. Representative student ¹H NMR, ¹³C NMR, and IR spectroscopic data and average percent yield values of the biaryl products are available in the Supporting Information.

The nature of the C–X bond (X = F, Cl, Br) of prototypical halobenzenes used in Pd-catalyzed coupling reactions was explored using computational chemistry. By calculation of the homolytic C–X bond dissociation energies⁸ and C–X bond distances⁹ of each geometry-optimized molecule, students observed a relationship between bond length and energy (i.e., longer C–X bonds are of lower energy) (Table 1). When

Table 1. Calculated Bond Dissociation Energies and Bond Distances for Halobenzenes

C–X bond ^a	Bond Dissociation Energy/(kcal/mol) ^b	Bond distance/Å ^c
C–F	122 (127)	1.36 (1.36)
C–Cl	90 (97)	1.75 (1.74)
C–Br	78 (84)	1.91 (1.90)

^aIodine is not available in the 6-31G(d) basis set. ^bB3LYP/6-31G(d) values followed by literature values in parentheses.⁸ ^cB3LYP/6-31G(d) values followed by literature values in parentheses.⁹

considered in the context of the oxidative addition step of the SMC reaction, students concluded that the C–Br bond was the most susceptible to oxidative addition of Pd (see Supporting Information for discussion of the catalytic cycle). These data illustrated for students why aryl bromides are common starting materials for Pd-catalyzed couplings rather than the less expensive and environmentally more favorable aryl chlorides.

The two-dimensional representation of biaryl compounds often instills within students the misconception that such molecules adopt a planar structure. The simplest biaryl compound, biphenyl, is, in fact, not planar but adopts a twisted structure with a significant inter-ring dihedral angle.^{10,11} To explore this structural feature, students computed the optimized geometry of biphenyl and measured the dihedral angle between the two benzene rings. Students rationalized the dihedral angle of 38.4° as a result of the competing effects of steric repulsions between the H atoms in the four ortho positions of the two benzene rings and the drive toward extended conjugation of the two π systems. Students were guided to visualize the extent of π conjugation between the rings by inspection of the π molecular orbitals (MOs) of the molecule. In the case of biphenyl, MO #32 revealed that significant conjugation remains between the two neighboring π systems despite the nonplanar structure (Figure 1). Students further explored the steric and electronic factors of biaryl compounds by calculating and rationalizing the inter-ring dihedral angle in the ortho-substituted compounds 2-

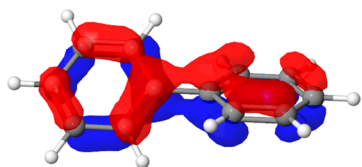


Figure 1. π -Symmetry MO of the optimized B3LYP/6-31G(d) structure of biphenyl.

methylbiphenyl and 2,6-dimethylbiphenyl (see Supporting Information for details).

The practical and technical aspects of the SMC reaction were assessed via a lab report, quiz, and exam questions. The questions required students to identify various steps in a typical catalytic coupling cycle, recognize key reaction conditions, use the coupling reaction in a multistep synthesis, and predict the identity and detailed molecular structure of biaryl products. A similar approach to the introduction of transition metal-catalyzed couplings in the instructional laboratory has recently been described.⁴

SUMMARY

An inexpensive and operationally simple procedure for introducing SMC reactions into a high-enrollment undergraduate organic chemistry laboratory course has been described. The reaction was effective for a range of commercially available aryl bromides and arylboronic acids. The exercise introduced to students the principles of organometallic chemistry and catalysis as applied to synthetic organic chemistry. In addition, via computational modeling, students gained enhanced understanding of the molecular and electronic structures of typical starting materials and products of the Suzuki–Miyaura coupling reaction.

ASSOCIATED CONTENT

Supporting Information

Student laboratory manual chapter, instructor notes, experimental procedures and spectroscopic data, and details of computational molecular modeling exercises. 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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REFERENCES

- (1) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457–2483 and references therein.
- (2) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical

Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062–5085.

(3) Suzuki, A. Cross-Coupling Reactions of Organoboranes: An Easy Way To Construct C–C Bonds. *Angew. Chem., Int. Ed.* **2011**, *50*, 6723–6737.

(4) Ballard, C. E. Green Reductive Homocoupling of Bromobenzene. *J. Chem. Educ.* **2011**, *88*, 1148–1151. See reference 2 for a list of introductory-level organic chemistry textbooks in which transition metal-catalyzed reactions are mentioned.

(5) (a) Callam, C. S.; Lowary, T. L. Suzuki Cross-Coupling Reactions: Synthesis of Unsymmetrical Biaryls in the Organic Laboratory. *J. Chem. Educ.* **2001**, *78*, 947–948. (b) Hoogenboom, R.; Meier, M. A.; Schubert, U. S. The Introduction of High-Throughput Experimentation Methods for Suzuki–Miyaura Coupling Reactions in University Education. *J. Chem. Educ.* **2005**, *82*, 1693–1696. (c) Grove, T.; DiLella, D.; Volker, E. Stereospecific Synthesis of the Geometrical Isomer of a Natural Product. *J. Chem. Educ.* **2006**, *83*, 1055–1057. (d) Leadbeater, N. E.; McGowan, C. B. *Clean, Fast Organic Chemistry-Microwave Assisted Laboratory Experiments*; CEM Publishing: Matthews, N.C., 2006; pp 27–32. (e) Novak, M.; Wang, Y.-T.; Ambrogio, M. W.; Chan, C. A.; Davis, H. E.; Goodwin, H. S.; Hadely, M. A.; Hall, C. M.; Herrick, A. M.; Ivanov, A. S.; Mueller, C. M.; Oh, J. J.; Soukup, R. J.; Sullivan, T. J.; Todd, A. M. A Research Project in the Organic Instructional Laboratory Involving the Suzuki–Miyaura Cross Coupling Reaction. *Chem. Educ.* **2007**, *12*, 414–418. (f) Aktoudianakis, E.; Chan, E.; Edward, A. R.; Jarosz, I.; Lee, V.; Mui, L.; Thatipamala, S.; Dicks, A. P. “Greening Up” the Suzuki Reaction. *J. Chem. Educ.* **2008**, *85*, 555–557. (g) Pantess, D. A.; Rich, C. V. Aqueous Suzuki Reactions: A Greener Approach to Transition Metal-Mediated Aryl Couplings in the Organic Instructional Laboratory. *Chem. Educ.* **2009**, *14*, 258–260. (h) Costa, N. E.; Pelotte, A. L.; Simard, J. M.; Syvinski, C. A.; Deveau, A. M. Discovering Green, Aqueous Suzuki Coupling Reactions: Synthesis of Ethyl (4-Phenylphenyl)acetate, a Biaryl with Anti-Arthritic Potential. *J. Chem. Educ.* **2012**, *89*, 1064–1067. (i) Hamilton, A. E.; Buxton, A. M.; Peeples, C. J.; Chalker, J. M. An Operationally Simple Aqueous Suzuki–Miyaura Cross-Coupling Reaction for an Undergraduate Organic Chemistry Laboratory. *J. Chem. Educ.* **2013**, *90*, 1509–1513.

(6) (a) Leadbeater, N. E.; Williams, V. A.; Barnard, T. M.; Collins, M. J., Jr. Open-Vessel Microwave-Promoted Suzuki Reactions Using Low Levels of Palladium Catalyst: Optimization and Scale-Up. *Org. Process Res. Dev.* **2006**, *10*, 833–837. (b) Arvela, R. K.; Leadbeater, N. E. Microwave-Promoted Heck Coupling Using Ultralow Metal Catalyst Concentrations. *J. Org. Chem.* **2005**, *70*, 1786–1790.

(7) (a) Clauss, A. D.; Nelsen, S. F. Integrating Computational Molecular Modeling into the Undergraduate Organic Chemistry Curriculum. *J. Chem. Educ.* **2009**, *86*, 955–958. (b) Rowley, C. N.; Woo, T. L.; Mosey, N. J. A Computational Experiment of the Endo vs. Exo Preference in a Diels–Alder Reaction. *J. Chem. Educ.* **2009**, *86*, 199–201. (c) Skonieczny, S.; Staikova, M. G.; Dicks, A. P. Molecular Orbital Analysis of Diels–Alder Reactions: A Computational Experiment for an Advanced Organic Chemistry Course. *Chem. Educ.* **2010**, *15*, 55–58.

(8) Blanksby, S. J.; Ellison, G. B. Bond Dissociation Energies of Organic Molecules. *Acc. Chem. Res.* **2003**, *36*, 255–263.

(9) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. Tables of Bond Lengths Determined by X-ray and Neutron Diffraction. Part 1. Bond Lengths in Organic Compounds. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1–S9.

(10) The most recent gas-phase experimental value for the dihedral angle of biphenyl is $44.4 \pm 1.2^\circ$. See Almenningsen, A.; Bastiansen, O.; Fernholt, L.; Cyvin, B. N.; Cyvin, S. J.; Samdal, S. Structure and Barrier of Internal Rotation of Biphenyl Derivatives in the Gaseous State: Part 1. The Molecular Structure and Normal Coordinate Analysis of Normal Biphenyl and Perdeuterated Biphenyl. *J. Mol. Struct.* **1985**, *128*, S9–76.

(11) The optimized dihedral angle of biphenyl is underestimated by $\sim 1^\circ$ compared to the most recent computational data. See Johansson, M. P.; Olsen, J. Torsional Barriers and Equilibrium Angle of Biphenyl:

Reconciling Theory with Experiment. *J. Chem. Theory Comput.* **2008**, 4, 1460–1471.