URIECA Module 6: Organic Structure Determination – Final Report

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INTRODUCTION

Carbon-carbon bond formation is critical in the synthesis of many organic compounds, as these reactions are necessary for the construction of the carbon "backbone". Palladium-catalyzed coupling reactions are a powerful class of carbon-carbon bond forming reactions that allow for coupling of an organic halide to an organometallic compound to yield the metal halide and the cross-coupled product.

$$R_1 - X + R_2 - M \rightharpoonup R_1 - R_2 + M - X$$

Examples of such reactions include the Heck Reaction, the Stille Reaction, the Sonagashira Reaction, and, of importance in this report, the Suzuki-Miyaura reaction.

The Suzuki-Miyaura reaction is a palladium-catalyzed reaction that couples organic halides and organoboron compounds.[1] In general, the palladium is complexed to phosphine-based ligands that increase catalytic efficacy, but the ligands are omitted in the equations below.

Like many reactions of this form, the reaction follows a mechanism consisting of three major steps. The first is oxidative addition, where Pd(o) is oxidized as it adds to the bond to the halogen.

$$R_1 - X + Pd^0 \rightharpoonup R_1 - Pd^{\mathrm{II}} - X$$

Oxidation addition is fastest when X is a relatively good leaving group, and when the bond to X is relatively weak. For halides, the activity decreases in the order I > Br >> Cl.[1]

Transmetalation is the second step. It involves the nucleophilic attack of the organoboron compound on the Pd(II) halide.

$$R_1 - Pd^{II} - X + R_2 - \mathrm{B} \rightharpoonup R_1 - Pd^{II} - R_2 + BX$$

This step is slowed by the fact that boron is a poor nucleophile. Indeed, the electrophilic character of boron is important in the most common syntheses of organoboron compounds (via nucleophilic attack by a Grignard or hydroboration of alkenes), and organoborons in general are relatively stable, not reacting with water nor oxygen.[1] The Suzuki-Miyaura reaction is generally carried out under basic conditions, which converts the organoboron to an organoborate, which is a better nucleophile.

Reductive elimination is the final step of the mechanism. In this step, the palladium is reduced and eliminated to yield the final coupling product and Pd^0.

$$R_1 - Pd^{II} - R_2 \rightharpoonup Pd^0 + R_1 - R_2$$

Palladium, like platinum, tends to form low spin d^8 square planar complexes (the two ligands are omitted in the equations). The reductive elimination proceeds only when the complex is *cis*, as interactions between the two R groups is necessary for elimination to proceed. Isomerization is relatively fast. In particular, π-orbital interaction is believed to be important, as reactivity decreases in the order diaryl- > (alkyl)aryl- > dialkyl.[1]

In general, either the oxidative addition or the transmetalation steps are rate-limiting.[1,2]

The design of ligands for palladium in the Suzuki-Miyaura coupling reaction is an important problem, as ligands can have an enormous effect on the rate and yield of the reaction. One especially useful ligand, designed by Buchwald et al., is S-Phos FIGURE, which allows for efficient, high yield Suzuki-Miyaura coupling of sterically hindered substrates, alkyl and aryl chlorides, and more.[2, A]

In particular, S-Phos can be used as a ligand for palladium to carry out efficient, room temperature Suzuki-Miyaura coupling of aryl halides and aryl boronic acids to generate biaryls.[2]

This reaction uses three equivalents of $K_3PO_4 \cdot H_2O$ as a base, one equivalent of S-Phos ligand, a catalytic amount of $Pd(OAc)_2$ as a source of Pd(o)[B]

In this report, we discuss the use of the room-temperature Buchwald reaction to couple an unknown aryl halide to an unknown boronic acid. Then, ^{1}H NMR of the aryl halide and EA/MS, ^{1}H NMR, ^{13}C NMR, and FT-IR spectra of the coupling product were used to determine the structures of the aryl halide and the boronic acid.

A. One question I have is why Buchwald et al. seem to imply that activated aryl halides are more effective as Suzuki-Miyaura substrates, as Miyaura et al. talked about electron-withdrawing substituents increasing reaction rate (and being necessary for reaction of aryl chlorides)

B. The phosphine ligand acts as a reducing agent, generating Pd(0). Some phosphine ligand is converted to the corresponding phosphine oxide, but this isn't a huge issue because only a catalytic amount of palladium is added, so there is still plenty of phosphine ligand left.

EXPERIMENTAL PROCEDURE

The procedure developed by Buchwald et al. for room temperature Suzuki-Miyarura cross-coupling is used to couple an unknown aryl halide to an unknown boronic acid. Prior to the preparative-scale reaction, 469.8 mg of impure aryl halide was purified using flash column chromatography to yield 308.5 mg of pure aryl halide (purity confirmed using ^{1}H NMR, see **DIAGRAM #**). At room temperature and pressure, the aryl halide is a white, crystalline solid.

The preparative scale-reaction procedure is as follows. A 10x3 mm Teflon stir bar is placed in a 10-mL round-bottomed flask.

Sequentially, the following solids are added to the flask using filter paper after weighing on an Ohause Explorer E12140 Balance: 0.2305 g boronic acid, 0.0055 g $Pd(OAc)_2$, 0.0080 g S-Phos, 0.2107 g aryl halide. A glass stirring rod is used to grind up solids into a finely powdered form. Solid remaining on the glass stirring rod after crushing is removed by tapping on the walls of the flask. A 14/20 rubber septum is used to close the flask, and the flask is securely clamped above a magnetic stirrer (VWR Model 220 Mini-Hot Plate Stirrer).

One end of a piece of rubber tubing is attached to a manifold N_2 outlet, and the other is connected to a disposable PrecisionGlide™ 16Gx1 ½ in needle via a Luer adaptor. The needle is inserted through septum, and another needle (open to the air) is inserted through the septum to act as an outlet. The pressure of N_2 is adjusted until roughly one bubble per second is seen in an oil bubbler attached to the manifold. The flask is flushed with N_2 for 5 minutes, to create an inert atmosphere for reaction to proceed. After 5 minutes, the outlet needle is removed, and subsequently, the nitrogen needle is removed from the septum.

1 mL of anhydrous THF is drawn into a 2 mL disposable plastic syringe using a clean long needle, and added rapidly dropwise along the walls of the reaction flask. This is repeated once more, so a total of 2 mL of THF is added to the reaction flask.

The rubber septum is quickly replaced by a ground glass stopper, and the joint is wrapped with Parafilm. The reaction mixture is stirred vigorously at room temperature for ca. 20 hours.

After 20 hours, the contents of the reaction flask are black in color. TLC with 20% EtOAc-Hexanes as a solvent is used to analyze reaction completeness by spotting aryl halide, authentic reaction product (provided separately), boronic acid, and crude reaction product. The TLC is analyzed under UV light. The desired product (R_f = 0.3) fluoresces blue under UV light, and both the aryl halide (R_f = 6.2) and boronic acid (R_f = 0.0) are UV active.

What is apparently unreacted aryl halide is observed in the TLC, along with desired product.

Crude reaction product is vacuum filtered into a 125 mL Erlenmeyer Flask using a 30x67 mm Buchner funnel and large piece of fluted filter paper to remove solids from crude product mixture. The filter paper is washed with ca. 15 mL EtOAc to ensure complete removal of product. This yields a brown-orange filtrate with some visible solid flecks.

ca. 10 mL EtOAc is used to wash the flask and transfer the filtrate to a 50 mL round-bottomed flask. This flask is closed with a ground glass stopper, the joint wrapped with Parafilm, and stored overnight in a fume hood.

The crude reaction product was dried under rotary evaporation (40° C, ca. 20 mmHg) to remove EtOAc and subsequently dissolved in the minimum amount of CH_2Cl_2. Then, the product was charged on a 3.8x30 cm column of 32.3 g of silica gel and binary gradient of 10-30% CH_2Cl_2-Hexanes is used to elute and fractions of ca. 5 mL are collected. Unreacted aryl halide is observed in fractions 36-90 and desired product in fractions 92-138, based on TLC (again with 20% EtOAc-Hexanes).

The large number of fractions and wide breadth of peaks suggests that this is not the optimal solvent system for the column.

After combining fractions into a 500 mL round bottom flask, rotary evaporation (40° C, ca. 20 mmHg) is used to remove solvent. A white powder is left, and some bumping occurs. When removing the bump trap from the rotary evaporator in order to collect any lost product, flask containing dried product is knocked onto ground and flask shatters.

The bump trap and the shards from the flask are collected and washed with EtOAc into a 90x50 recrystallization dish, to salvage remaining product. Glass shards are held using forceps when they are washed.

Solution is transferred to a 20 mL scintillation vial fitted with a 14/20 rubber adaptor. A disposable PrecisionGlide™ 16Gx1 ½ in needle is inserted through the adaptor, to allow for rotary evaporation (40° C, ca. 20 mmHg) of the solution.

TLC analysis of this product using 15% EtOAc-Hexanes as a solvent system and Ceric Ammonium Molybdate for visualization reveals that there is a nonnegligible amount of nonpolar, UV-inactive, (presumably) nonvolatile impurity in the sample (R_f ~ 1.0).

Sample is dried using rotary evaporation (40° C, ca. 20 mmHg), dissolved in the minimum amount of CH_2Cl_2, and charged onto a microscale column in a short-tipped Pasteur pipette with enough silica gel to fill ca. two-thirds of the volume of the pipette. The column is eluted with hexanes, and fractions of ca. 5 mL are taken. After ca. 20 mL of hexane has been used, elution is continued with ca. 20 mL of EtOAc. Fractions 5 and 6 contain desired product with no noticeable nonpolar impurity (based on TLC using using 15% EtOAc-Hexanes as a solvent system and Ceric Ammonium Molybdate for visualization).

Combining these fractions into a 20 mL scintillation vial and rotary evaporating (40° C, ca. 20 mmHg) yields 0.0192 g of a pale brown solid. The percent yield of the reaction, based on the molar masses determined in the next section, is **6.003%**. Needless to say, spilling and contaminating product is not the best way to get high yields.

STRUCTURE DETERMINATION

The structure of both the aryl halide and the final coupling product were both proposed initially only on the basis of ^{1}H NMR spectra and EA/MS data (for the latter) only, and ^{13}C, DEPT, and FT-IR spectra were used to validate and correct these results where needed, as they were taken largely after the fact.

Determining the structure of the aryl halide

The first step is determination of the structure of the aryl halide based on the ^{1}H NMR data. We will assume that the normalization of the integrals given above is correct (the proof that it is so is straightforward)[C].

An aryl ring has six carbons, each of which can be attached to at most one functional group. Looking in the aromatic region of the spectrum (6.5-8.5 ppm), we see signals corresponding to four hydrogen atoms: 7.99-7.96 (2H, dd, J = 8.7), 7.42-7.40 (2H, dd, J = 8.4). Thus, there are four hydrogen atoms directly bound to the aryl ring. One of the remaining two positions is occupied by the halogen atom X, and there is one substituent whose identity we do not know yet. Call this R.

Because there are two signals for four protons, there must be bilateral symmetry within the substituents of the aryl ring. The only way that four protons can arrange on an aryl ring in a bilaterally symmetric fashion is if R and X are *para* to each other. This is also implied by the pattern of splitting. Both peaks are doubled doublets with coupling constants of ~8.5 and 1-2 Hz. Because there are no signals in the spectrum with these coupling constants outside the aromatic region, the protons must be coupling with other aromatic protons. Thus, the coupling constant of 1-2 Hz suggests *meta*-coupling (the other possibility, allylic coupling, requires coupling outside the aromatic ring), and the coupling constant of ~8.5 Hz suggests *ortho*-coupling. This is consistent with a *para*-substituted aryl ring **(Figure 1).** [D]

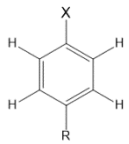

Figure 1
Aryl Halide

Now we must determine the identity of R. We have assigned the two peaks in the aromatic region, and one peak remains – a singlet corresponding to 3H at 3.92 ppm. The simplest group producing three identical protons is a methyl group[E]. The peak is very downfield, suggesting that it is a methyl ester (~3.9 ppm), an aryl ether (Ar – O – CH_3, ~3.4 ppm) or another similarly deshielding functionality[F]. For now, we will leave this question unanswered.

Determining the structure of the coupling product

First, we can use the EA data to find the empirical formula for the compound, and the MS data to find the molecular formula. Based on the EA, the empirical formula is $\mathbf{C_{5.883}H_{4.763}O_{1.542}} \approx \mathbf{C_{15}H_{12}O_4}$, which is consistent with the observed molecular mass (from the MS) of 256.07. The remaining peaks in the MS result from other isotopes of carbon, hydrogen, and oxygen (mostly carbon). Also, note that there are 15*2+2-12 = **10 degrees of unsaturation.**

We again look to the ^{1}H NMR. We note that the peaks at: 8.07-8.05 ppm (2H, dd, J = 2.1, 6.7) and 7.57-7.55 ppm (2H, dd, J = 2.1, 6.6) likely correspond to the aromatic protons in the original aryl halide, as the reaction merely replaced the halogen substituent with another substituent. We cannot tell which is which without knowledge of what R is, so we will set this aside for now.

The peak at 3.93 (3H, s) definitely corresponds to the methyl group in the original aryl halide, because there are no other methyl groups in the spectrum of the product.

There are three other protons in the aromatic region, presumably from the newly added group (call it R')[G]. Thus, the newly added group is some sort of aromatic group. We ignore annulenes and heterocyclic rings with more than 6 atoms for now. We also know that there is no nitrogen in the final product based on the EA data. Thus, R' is either a phenyl or a furanyl (pyran is not aromatic, nor is any annulene with less than 6 carbons).

R' cannot be a furanyl. We know that there are three aromatic protons in R'. This occupies 3 of the four carbons in furan, and the fourth forms the bond to our aryl ring. If this were the case, then there could be no other groups on the furanyl, and the molecular formula would not have enough oxygens.

Thus, R' is likely a phenyl.

The aromatic-region peaks appear rather unusual on the spectrum, but close analysis suggests that what appears to be an extremely asymmetric doubled doublet 7.11-7.08 ppm (2H) is in fact a doubled overlapping with a doubled doublet. These are the peaks labelled at 7.11-7.08 ppm (1H, dd, J = 1.5, 6.9) and 7.08 ppm (1H, d, J = 1.5 Hz), which are apparently *meta*-coupled to each other. The former signal (dd) is also *ortho*-coupled to a different proton, which is by process of elimination the peak at 6.89-6.87 ppm (1H, dd, J = 1.8, 6.8). It cannot be any other peak because there are no other split peaks with a coupling constant of 6.8 ppm in R'. Thus, we know the arrangement of protons on the phenyl substituent is **(Figure 2).**

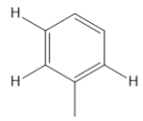

Figure 2
Aromatic Hydrogens in R'

C. Assuming that there is only one aryl ring, the integral of each dd is either 1, 2, or 3. It isn't 3 because then the putative methyl peak would integrate to 4.5, and it isn't 1 because otherwise it couldn't be a doubled doublet (not enough protons to couple to).

D. Indeed, the same result can be derived from the splitting alone, by noting that each proton is *ortho* to one proton, *meta* to another, and by elimination *para* to a third

E. I'm sure there are counterexamples, although no likely ones come immediately to mind.

F. The ^{1}H NMR shift of a methyl group can be computed to some accuracy based on the empirically additive nature of shifts. For an aryl ether, we expect a shift of roughly 0.9 + 2.5 = 3.4 pp, and for a methyl ester, 0.9 + 3 = 3.9 ppm. There aren't any other things that come immediately to mind that have the correct proton shifts

G. We must also consider the possibility that the protons are in fact alkene protons that are further downfield than normal due to conjugation with the aryl system. This could also explain the new signal at 6.00 ppm (2H, s). However, this is unlikely, because an alkene structure could not have enough symmetry to explain the multiple 2H peaks that we are observing.

Now we must figure out where R' couples to the aryl halide, and what the two other substituents on the R' are. We will figure out what they are first.

We still have to account for 2-3 oxygens (depending on whether the substituent on the original aryl halide is a methyl ester, a methoxy, or something else altogether), 1-2 degrees of unsaturation, 2 hydrogens, and 1-2 carbons.

There are only two hydrogens left in the molecular formula that we haven't assigned– they must correspond to the peak at 6.00 ppm (2H, s). These are both on the substituents of the aryl ring of R'. Because they have the same chemical shift, they are identical. There are three possibilities:

The first is that both hydrogens are on one substituent of the aryl ring of R'. This is false because then the second substituent would be a hydrogen, and it would produce an aromatic hydrogen signal in the NMR (we've already assigned all the aromatic peaks).[H]

The second is that there is one hydrogen on each substituent, and that they are equivalent. This is false because R' is asymmetric, so the two hydrogens would not show up at the same shift.

The third is that the "two" substituents are actually connected to each other, forming a ring. Because our casework has been exhaustive, this must be the case by elimination.

At this point, we put forth an assumption – R (the substituent on the original aryl ring) is either a methoxy or a methyl ester.

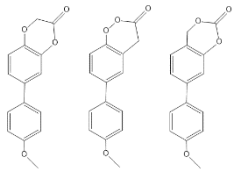

Figure 3
Possibilities if R = OMe

If it is a methoxy, then the ring substituent on the aryl ring of R' has three oxygens, one degree of unsaturation (because the ring itself is a degree of unsaturation), two carbons, and two hydrogens. None of the possibilities are likely, so we put this case aside for now **(Figure 3)**.

The second possibility is that R is a methyl ester. Then, the ring on the aryl ring of R' has two oxygens, no degrees of unsaturation, one carbon, and two hydrogens. Ignoring the peroxide, this suggests a **diether (Figure 4)**. This is consistent with the ^{1}H NMR spectrum. Now, we must confirm that it is consistent with the other spectroscopic data, by trying to assign all the peaks in the spectra.

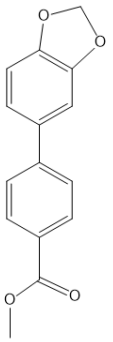

Figure 4
Tentative Structure

At this point, we (grudgingly) look to the ^{13}C NMR spectrum. We refer to carbons in the spectrum by their assignment number in the spectroscopic data table. First, we note that there are only 13 peaks in the spectrum, while there should be 15 carbons. The two "missing" peaks correspond to the symmetric carbons in the original aryl ring.

The DEPT counts are in accordance with our structure: there is 1 CH_3, 1 CH_2, and 7 CH carbons (there are only 5 CH signals because two of them in fact correspond to 2 carbons each, as mentioned earlier). This also allows us to assign some of the peaks in the ^{13}C NMR spectrum (see spectrum). We can assign the methyl and methylene carbons, which are at 101.4 ppm (#12) and 52.2 ppm (#13). In addition, given that the protons on the symmetric carbons are the most downfield protons in the ^{1}H NMR spectrum, it is reasonable to surmise that the two most downfield CH carbons (#8 and #6) are the symmetric carbons, although this is not certain. If they are, then #6 should correspond to the carbons *ortho* to the methyl ester. This is because the methyl ester is an electron withdrawing substituent, and thus withdraws electron density from the *ortho* and *para* positions due to resonance with structures with positive charges on these carbons. Then, #8 corresponds to the carbons *meta* to the methyl ester. This is akin to what is seen in the ^{13}C NMR spectrum of methyl benzoate.[3]

Carbon #1, with no protons at 167.1 ppm, corresponds to the carbon in the carbonyl group of the methyl ester.

There are two other unsaturated carbons adjacent to oxygen in the structure (the two aryl carbons bonded to the oxygens of the diether in R'). These likely correspond to peaks #3 and #2. Because phenyl groups are generally weakly activating, *ortho-para* directing groups, it is likely that the carbon *para* to the original aryl ring is more upfield than the carbon *meta* to the original aryl ring. This suggests that #3 is *para* to the original aryl ring, and #2 is *meta* to the original aryl ring.

Now, we see that #5 and #7 must be the carbons connecting the two aryl rings, as they are the only remaining carbons in the aromatic range of the spectrum that do not have any attached hydrogens. Because the carbon in R' is closer to an electron-donating group (the diether) and farther from an electron-withdrawing group (the methyl ester) it is likely that it is further upfield than the other "linking" carbon, which is on the aryl ring of the original aryl halide. Thus, #5 is on R', and #7 is on the aryl ring of the original aryl halide, *para* to the methyl ester.

Now, all we have left is the assignment peaks #9, #10, and #11. These correspond to the only three CH carbons in R'. Numbering the carbons of R' **(Figure 5)** such that the diether is 1,2-, the three carbons we are interested in are at positions 3, 5, and 6.

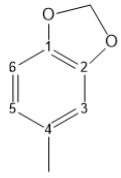

Figure 5
Numbering of carbons in R'

H. Theoretically, this could be an unusually upfield aromati s unlikely given that all the other aromatic protons are in the normal range.

I. These are the three possible functionalities (there a all of the cases are either carbonate lactones, acyl acetals, or peroxides, none of which are especially stable. I wouldn't have known that the acyl acetal was unstable if Mr. Michael W. Gribble Jr. hadn't told me, though, although I would've likely eliminated it using the ^{13}C NMR later.

The carbon at position 6 is *meta* to two electron donating group and *ortho* to a third.

The carbon at position 5 is *meta*, to one electron donating group, *ortho* to another, and *para* to a third

H. Theoretically, this could be an unusually upfield aromatic proton, but it's unlikely given that all the other aromatic protons are in the normal range.

I. These are the three possible functionalities (there are isomers, but I think all of the cases are either carbonate lactones, acyl acetals, or peroxides, none of which are especially stable. I wouldn't have known that the acyl acetal was unstable if Mr. Michael W. Gribble Jr. hadn't told me, though, although I would've likely eliminated it using the ^{13}C NMR later.

The carbon at position 3 is *ortho* to one electron donating group and *meta* to a third

Thus, the carbon at position 6 is the most deshielded of the three, and likely corresponds to peak #9 (the most downfield).

Now, we must decide whether being *para* or *ortho* to an ether confers greater shielding to a carbon, in order to assign peaks #10 and #11 to carbons 3 and 5. Looking at the ^{13}C NMR spectrum of anisole, we see that the carbon *para* to the ether is further downfield than that *ortho* to the ether.[3] This is true of the ^{13}C NMR spectrum of biphenyl as well.[3] Thus, carbon 3, which is *ortho* to both an ether and a phenyl, is likely further upfield than carbon 5, which is *para* to an ether and *ortho* to a phenyl. Thus, carbon 3 is assigned #11, and carbon 5 is assigned #10.

Now, we have assigned every peak in the ^{13}C NMR and DEPT.

Consider the FT-IR spectrum. There are no peaks in the 3600-3500 cm^{-1} region, which means that there are no non-H-bonded alcohol groups. The absence of a broad peak in the range 3500-3000 cm^{-1} tells us that there are no H-bonded hydroxyls. We do not need to worry about amines, as there are no nitrogens in the final product. We see small peaks in the 2850-3200 cm^{-1}, suggesting the presence of C-H bonds, but this is relatively minor.

The absence of a sharp peak around 3300 cm^{-1} tells us that there are no terminal alkynes in the molecule, and the absence of sharp peaks in the 2500-2000 cm^{-1} tells us that there likely are no triple bonds in the molecule at all. The strong absorbance at 1717.70 cm^{-1} indicates the presence of a carbon-oxygen double bond (carbonyl).

The multiple other peaks in the double bond region (1607.4 cm^{-1}, 1527.6 cm^{-1}, 1500.59 cm^{-1}) are consistent with the numerous double bonds in the aryl rings.

There is not much to be said about the fingerprint region (<1500 cm^{-1}).

Thus, the FT-IR spectrum is consistent with the structure that we have proposed.

As it turns out, the boronic acid that we are proposing, $R'B(OH)_2$, was used by Buchwald et al. for Suzuki-Miyaura reactions, albeit under different conditions.[2] We are also given that the halogen is a chlorine from the start, and that the boronic acid has structure $R_2B(OH)_2$.

The last thing we need to do is assign the hydrogens *meta* and *ortho* to the methyl ester to the peaks at 8.07-8.05 ppm (2H, dd, J = 2.1, 6.7) and 7.57-7.55 ppm (2H, dd, J = 2.1, 6.6). The pair of hydrogens that is *meta* to the phenyl (a weakly activating group) and *ortho* to the methyl ester (a deactivating group) will be further downfield than the pair of hydrogens that is *meta* to the methyl ester and *ortho* to the phenyl. Thus, we are done assigning protons.

I don't believe that there are any other possible structures. If R (the functional group originally *para* to the halogen in the aryl chloride) is not a methyl ester, then it is possible that there is another, better structure. However this seems to be the most likely, and many possibilities have been excluded. The structure that we have proposed is in affirmation with all of the experimental results.

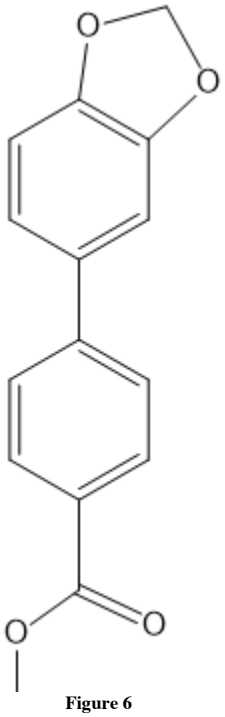

Figure 6
Suzuki-Miyaura Coupling Product

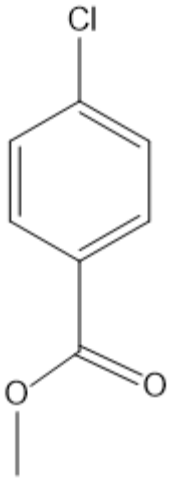

Figure 7
Structure of Aryl Halide

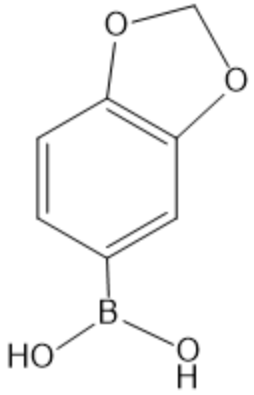

Figure 8
Boronic Acid

REFERENCES

(1) Miyaura, N; Suzuki, A, *Chem. Rev*. **1995**, 95, 2457-2483
(2) Walker, S; Barder, T; Martinelli, J; Buchwald, S, *Angew. Chem. Int. Ed*. **2004**, 43, 1871 –1876
(3) www.chemicalbook.com

SYNOPSIS TOC (Word Style "SN_Synopsis_TOC"). If you are submitting your paper to a journal that requires a synopsis graphic and/or synopsis paragraph, see the Instructions for Authors on the journal's homepage for a description of what needs to be provided and for the size requirements of the artwork.

To format double-column figures, schemes, charts, and tables, use the following instructions:

Place the insertion point where you want to change the number of columns
From the **Insert** menu, choose **Break**
Under **Sections**, choose **Continuous**
Make sure the insertion point is in the new section. From the **Format** menu, choose **Columns**
In the **Number of Columns** box, type **1**
Choose the **OK** button

Now your page is set up so that figures, schemes, charts, and tables can span two columns. These must appear at the top of the page. Be sure to add another section break after the table and change it back to two columns with a spacing of 0.33 in.

Table 1. Example of a Double-Column Table

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8

Authors are required to submit a graphic entry for the Table of Contents (TOC) that, in conjunction with the manuscript title, should give the reader a representative idea of one of the following: A key structure, reaction, equation, concept, or theorem, etc., that is discussed in the manuscript. Consult the journal's Instructions for Authors for TOC graphic specifications.

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