**Catalysis: Iron-catalyzed Arylation of Alkyl Halides**

*Based on reports by Kozak and co-workers.*6

**Objectives**

To explore the use of transition metal complexes as homogeneous catalysts for an organic transformation. As a group, to identify the possible influence of spectator ligands on catalytic performance by pooling data. Specific technical and educational objectives are:

* Students will be able to operate the inert atmosphere glovebox and block reactor to conduct a (mostly) air-free reaction
* Students will be able to analyze gas chromatographic (GC) data to determine the percent conversion, TON, and TOF for a catalytic system
* Students will be able to use data from *in situ* experiments to propose a structure for an active catalyst
* Students will be able to draw conclusions about the relationship between steric and electronic parameters of ligands and catalyst performance

**Background**

Metal-mediated cross coupling reactions are an increasingly important class of carbon-carbon bond forming transformations. Because of the ease with which complex organic structures can be assembled using this class of transformation, they have become a standard tool for the construction of natural products, as well as in the manufacturing of pharmaceuticals, and fine and commodity chemicals. In 2010, the Nobel prize in chemistry was awarded jointly to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki "for palladium-catalyzed cross couplings in organic synthesis.”1,2 Numerous variants of these cross coupling reactions are possible, with functional groups or hydrocarbon fragments differing in each case.

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**Scheme 1**. A general scheme for the cross coupling of two hydrocarbon fragments, R and R’.

Palladium complexes are the most popular homogeneous catalysts for many cross coupling reactions, in part due to their excellent air and moisture tolerance, and compatibility with many functional groups. However, Pd is somewhat rare, and quite expensive when compared to base metal counterparts. The moderate toxicity of Pd residuals, coupled with the difficulty of removing all trace metal (including colloidal Pd formed as a deactivation pathway for many catalyst systems), have prompted several research groups to investigate the use of alternate metals as catalysts for cross coupling reactions. Of these, catalysts derived from cheap, abundant, and non-toxic metals such as iron are demonstrating their utility in a number of applications.3-6 This experiment will focus on the development of such a catalyst system using iron to effect a Kumada-type coupling of an aryl grignard and an alkyl halide.

In this lab, you will explore the Kumada coupling of phenyl magnesium bromide and a chloroalkane using an iron catalyst system. You will generate the catalyst *in situ*, rather than adding a pre-formed complex to the reaction mixture. This experiment is part of a multi-year project to explore the competency of these catalyst systems, and your group’s data will be incorporated into a master catalyst survey table. By compiling the data from all groups, we may make statements about the general effects that spectator ligands may play on catalyst activity.

**Before You Come to Lab...**

Read this lab handout carefully, and decide on a plan (no more than one page!) for your time in the laboratory and submit this to your instructor no later than 8:00 AM on the day of lab. You may find it helpful to construct a flowchart describing the steps you will take to set up and monitor the catalysis.

For this lab, all groups will be working with slightly different spectator ligands, but using the same organic transformation and conditions. Find and consult the GoogleDoc spreadsheet with catalysis data, and make sure that you are aware of the quantities of each reagent or solvent used, and the times at which you will assay the reaction. Read and understand the safety document located at the end of this lab manual, in which proper safety and operating procedures for using the glovebox are described.

To ensure that all groups have a chance to get their catalysis running within the time allotted for lab, you should come to lab with a completed table showing the quantities (volumes or masses) of each reagent or solid to be used. In addition, respond to the following question:

1. In your own words, describe the process of initiating and evaluating a catalytic reaction. What is the role of the metal complex in this reaction? How will you know if the reaction is complete (provide specific details)?

**Safety, Hazards & Waste**

All procedures should be conducted in a fumehood, and gloves should be worn when handling all reagents. Always wash your hands thoroughly before leaving the laboratory. A lab coat is recommended, and should be worn at all times when handling hazardous compounds. All organic reagents and solvents are flammable, and may be hazardous in some cases (avoid inhalation). In addition, metals salts and organic reagents are irritants, and some are cancer-suspect agents.

You will be preparing some solutions for your catalytic reactions in the glovebox for this experiment, and special precautions are required to protect both you and the reactive chemicals stored in this piece of equipment. Before using the glovebox, read and understand the safety document included at the end of this lab manual, in which proper safety and operating procedures for the Inorganic laboratory are described. Before using the glovebox, you **must** be checked out by your instructor.

**Procedure**

You will be weighing your metal precursor and ligand in the glovebox, then adding solvent and substrates via syringe on the benchtop, and immediately transferring the vial to the aluminum block reactor on the bench. To ensure that all groups have a chance to get their catalysis running within the time allotted for lab, you should come to lab with a completed table showing the quantities (volumes or masses) of each reagent or solid to be used. The glovebox will be used on a first-come, first-(self)served basis, under your instructor or TA’s supervision. While other groups are in the glovebox, you can prepare GC vials with each of your starting materials (for comparison runs), or begin answering the questions at the end of this experiment.

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**Scheme 2.** Kumada coupling of phenyl magnesium bromide and chlorocyclohexane.

All groups will be following the same general procedure, as described in Scheme 2. As shown, the phenyl and cyclohexyl fragments are joined via the formation of a carbon-carbon bond. Since the product of this reaction is achiral we will not concern ourselves with measuring the enantioselectivity, and instead focus on the percent conversion of chlorocyclohexane. Each group will be assigned a different spectator ligand (L), and form their catalyst complex in situ prior to adding substrates.

Tare a small screw-capped vial, and weigh 0.05 mmol of the appropriate ligand (see handout) and 0.05 mmol of the metal precursor (Fe(OAc)2) into the vial. Add a small stir bar (~1 cm length), and seal the vial with a red cap fitted with a PTFE septum before bringing it and your trash out through the antechamber. Make sure to wipe your spatula and leave both it and the balance clean for the next person.

On the benchtop, add 5 mL Et2O to your vial via a syringe (through the PTFE septum). Place your vial in the 30°C heating block, and ensure that your reaction stirs for 5 minutes. This time is important for the formation of the catalyst complex. After 5 minutes has elapsed, add 2.0 mmol of chlorocyclohexane and 4.0 mmol of PhMgBr via syringe (through the septum top). Stir your reaction for 30 minutes at 30°C in the heating block.

After 30 minutes has elapsed, add 2.0 mmol dodecane, and quench the reaction by adding 5 mL of 1.0 M HCl. Remove the organic layer using a pipette, and extract the residual aqueous layer using 5 mL of Et2O. Dry the combined organic layers using MgSO4 or Na2SO4, and prepare a sample for GC-MS by filtering your solution through a small plug of silica (~0.5 cm high) contained in a pasteur pipet (see **Figure 1**, see your instructor or TA for instructions on how to prepare these), into a GC vial. The total volume of your filtered solution in the vial should be approximately 0.5 mL, adding Et2O to dilute to ~1.5 mL . Label your GC vial, and run it on the GC-MS instrument located in the analytical lab, using the method Xcoupling.mth (we will set up an autosampler queue for the entire lab class).



**Figure 1**. Pasteur pipette filter.

Integrate the peaks, and by comparison with the reference data provided for the starting materials, determine the identity of each of the peaks in your catalytic mixture, the relative distribution of products (i.e. which products are formed, relative to each other), and the percent conversion. Note that chlorocyclohexane is the limiting reagent, and the area corresponding to the products **and** chlorocyclohexane must always be equal to 100% of the ‘substrate’. Use the dodecane peak to standardize the quantity of chlorocyclohexane in the reaction mixture.

**For Your Report (Full)**

Summarize the results of your catalytic reaction in a table showing the percent conversion and relative distribution of products. You should also calculate the TON and TOF for your catalytic system using methods discussed in the lecture. We will be pooling data to look at the effects across all ligands; report your numbers in the google doc ([click here to access this document](https://docs.google.com/spreadsheets/d/1eDJwwmvW7gzj9q_GhO1g7IOmedwKko0CcOVGVyvS_O8/edit?usp=sharing)) shared by your instructor by the end of the week. Answer the questions below in your report, then draw some general conclusions about the reaction, and summarize your results.

1. What did you learn about catalysis from this experiment? What you might do differently if you were conducting this experiment another time? Your response to this question should take into account your response to the pre-lab question, and specifically address any misconceptions you had prior to the experiment.
2. Compare your data to that obtained by the group as a whole. Which ligand(s) generated the most effective catalyst? Explain (using the numerical data for the entire class) why you think this was the most effective catalyst. Make a sketch of your proposed complex.
3. Suggest a different organic molecule that might serve as a good ligand for this experiment. Use the results obtained by the entire class to make an informed guess about what might be effective. Your response should include a structure showing structural reasons for choosing the molecule you did, a CAS number, and the price for this molecule from a reputable chemical supply company such as Aldrich or Acrōs. (You may find it helpful to use the “substructure” or “similarity search” features in SciFinder)
4. Propose an alternate substrate that would yield a chiral coupling product. How might you modify the ligand or complex in order to control the ratio of enantiomers formed via such a reaction? Explain.
5. Why is it important to stir the ligand and metal for five minutes before adding the substrate?
6. Find an original research article in the primary chemical literature (i.e. not a review) describing a catalytic system for the Kumada coupling. Determine which metal(s) and ligands are used to accomplish this transformation. Compare the percent conversion and TOF/TON for the reported system with that obtained by the class. If your paper does not calculate these values, calculate them from the data provided! How do the numbers compare? What conclusions might you draw from this paper that might help you improve the catalytic reaction?

**References**

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3. Kochi, J. K. “Electron-Transfer Mechanisms for Organometallic Intermediates in Catalytic Reactions.” *Acc. Chem. Res.* **1974**, *7*, 351-360.
4. Frisch, A. C.; Beller, M. “Catalysts for Cross-Coupling Reactions with Non-activated Alkyl Halides.” *Angew. Chem. Int. Ed.* **2005**, *44*, 674-688.
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6. Qian, X.; Dawe, L. N.; Kozak, C. M. “Catalytic alkylation of aryl Grignard reagents by iron(III) amine-bis(phenolate) complexes.” *Dalton Trans.* **2011**, *40*, 933-943.