



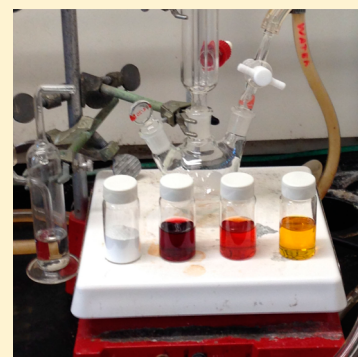
Template Effect and Ligand Substitution Methods for the Synthesis of Iron Catalysts: A Two-Part Experiment for Inorganic Chemistry

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Supporting Information

ABSTRACT: Asymmetric transfer hydrogenation is an important transformation for the production of fine chemicals. Traditionally, platinum group metals are used to catalyze this reaction, but recent pressure for greener practices has driven the development of base-metal catalysts. Due to the growing interest in this area of research, the underlying concepts for this type of chemistry are suitable for an undergraduate laboratory. A two-part experiment was adapted from original research and tested for use in an upper-division undergraduate inorganic chemistry laboratory. The first part of the experiment explores the template synthesis of a *trans*-bis-acetonitrile iron complex with a tetradentate ligand. The product from the first laboratory period is used as the starting material in the second laboratory period that focuses on the synthesis of a green catalyst mimic. Students learn about multi-step synthesis, specifically the synthesis of a catalyst for green chemistry, and key inorganic chemistry concepts to help reinforce topics introduced during lectures.



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

The asymmetric transfer hydrogenation (ATH) of prochiral ketones is an important process that is used by the pharmaceutical, perfume, and food industries in the synthesis of enantiopure alcohols.¹ This transformation makes use of a sacrificial reductant, such as isopropanol or formic acid, to provide a hydride and proton equivalent for the hydrogenation of unsaturated substrates. A major advantage of transfer hydrogenation (TH) is that it does not require the specialized equipment and safety measures needed to work with high pressures of hydrogen gas. Despite extensive study in this area, most of the catalysts developed to date employ expensive, as well as toxic, platinum group metals, such as ruthenium.^{1–5} Economic and political pressure for sustainable practices, however, has prioritized the development of greener catalysts that incorporate cheap, abundant metals.⁶ Iron is an attractive substitute for ruthenium not only for these reasons, but also because of its low toxicity and environmental impact.^{7,8} Recently, exceptional iron ATH catalysts were reported with turnover frequencies (TOF) that rival those of naturally occurring enzymes (TOF up to 243 s^{–1}).⁹

To synthesize such iron complexes, a template approach was adopted because traditional techniques to first generate the ligand and then coordinate it to a metal center proved unsuccessful.¹⁰ In addition, a ligand substitution reaction with CO gas and KBr to replace the acetonitrile ligands on the initial complexes was needed to produce active precatalysts (Scheme 1).^{11–14}

Despite the growing academic and commercial interest in developing greener organometallic catalysts, there are very few undergraduate laboratory experiments that cover this growing field.^{15–18} Moreover, metal templating is a powerful synthetic

tool in inorganic chemistry, but this concept is also under-represented in undergraduate laboratories.^{19–22} A practical experiment is presented here for synthesis of an iron catalyst in an upper-division undergraduate inorganic chemistry laboratory that exposes students to both of these important concepts.^{10–14}

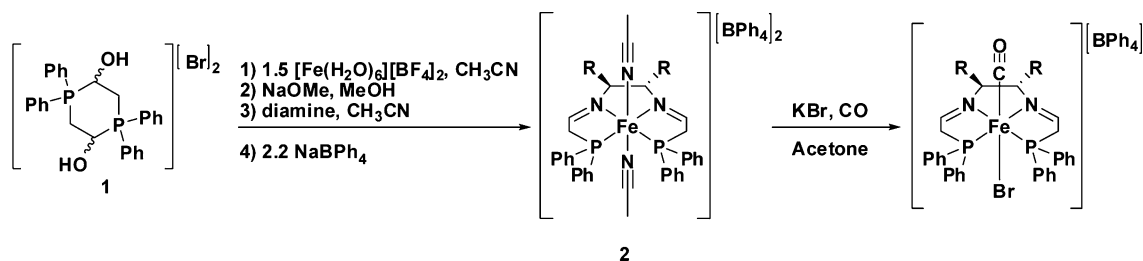
The experiment has two parts and can be performed over two, 4-h laboratory periods. The product from the first laboratory period is used as the starting material in the second laboratory period and students learn about multistep syntheses in which the yield and purity of a previous reaction directly influences those of the end product. The experiment was successfully performed, individually, by 24 advanced students in an inorganic chemistry course during the 2013/2014 academic year. The experiment is also designed to reinforce content and topics discussed in lectures.^{10–14}

■ EXPERIMENTAL OVERVIEW

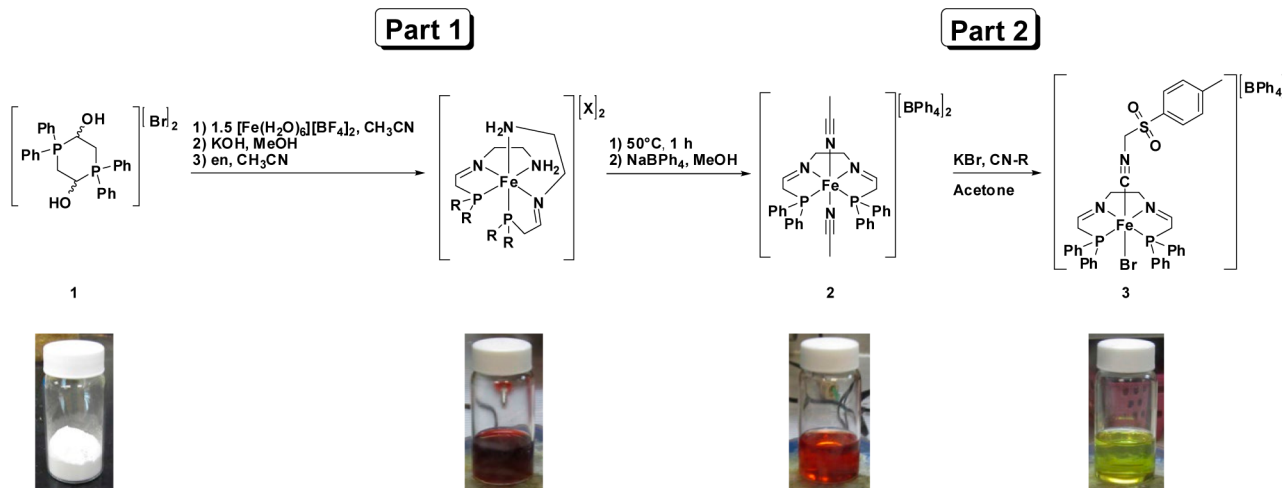
2,5-Dihydroxy-1,1,4,4-tetraphenyl-1,4-diphosphonocyclohexane dibromide, **1**, is synthesized for students.^{23,24} Detailed procedures for the experiment are in the Supporting Information.

Part 1: Template Synthesis

In a one-pot reaction, the phosphonium dimer precursor **1**, [Fe(H₂O)₆][BF₄]₂, and KOH are combined in methanol under a nitrogen atmosphere (schematic of experimental setup in Supporting Information Figure S1). It should be noted, however, that the apparatus used to exclude oxygen is not crucial for the success of the experiment (more details in the

Scheme 1. Synthesis of Iron Precatalysts Using Metal Templating and Ligand Substitution.^{10,11,14}

Scheme 2. General Synthetic Scheme for Parts 1 and 2 of the Experiment and Representative Pictures of the Starting Materials, Intermediates, and Products



Supporting Information). After several minutes, a small amount of acetonitrile is added, and after several more minutes ethylenediamine is added. The solution rapidly turns a dark wine-red color, forming a “bis-tridentate” intermediate (vide infra). After a heating time of approximately 1 h, the solution turns a reddish-orange color, indicating the formation of the desired tetradentate product 2. Salt metathesis with NaBPh₄ in methanol gives the product as a pink precipitate. After a wash with methanol and ether, and a drying step under vacuum, the pink product is isolated in yields ranging from 50 to 90% (average student yield was approximately 80%).

Part 2: Ligand Substitution To Generate a Catalyst Mimic

In continuation from Part 1, 2 is dissolved in acetone along with an excess of KBr under a nitrogen atmosphere (schematic of experimental setup in Supporting Information Figure S1). Once again, the nitrogen atmosphere is not crucial for the success of the experiment (more details in the Supporting Information). The reaction mixture is stirred for several minutes and then a solution of *para*-toluenesulfonylmethyl isocyanide in acetone is added dropwise. The reaction is heated for 20–30 min until the solution turns yellow (usually accompanied by the formation of a large amount of precipitate). A large amount (25 mL) of hexanes is added to encourage precipitation of the final product, 3, which is collected as a yellow powder by filtration. After a wash with water, methanol, and ether, and a drying step under vacuum, the yellow product is isolated in yields ranging from 60 to 85% (average student yield was approximately 75%). The synthesis and structure of 3 (Scheme 2) has been reported.²⁵ IR spectra of 3 are run as nujol mulls.

HAZARDS

Proper protective equipment (i.e., gloves, lab coat, and safety goggles) should be worn at all times throughout this experiment. Ethylenediamine is harmful if swallowed, inhaled or absorbed through the skin; it has an irritating ammonia odor; manipulate in a fumehood. Iron(II) tetrafluoroborate hexahydrate is highly corrosive and a severe irritant; it is harmful if swallowed, inhaled or absorbed through the skin. Potassium hydroxide is highly corrosive and hygroscopic. Sodium tetraphenylborate is toxic if ingested and may be harmful if inhaled or absorbed through skin; it may cause eye, skin and respiratory tract irritation. *para*-Toluenesulfonylmethyl isocyanide is toxic if ingested. Potassium bromide is not normally considered harmful, but take normal precautions. Acetone is extremely flammable; it is not normally considered dangerous, but take normal precautions. Hexane is extremely flammable, hazardous in case of skin contact, ingestion, and inhalation, and slightly hazardous in case of eye contact; *n*-hexane is a neurotoxin. Acetonitrile is a lachrymator and direct inhalation should be avoided; it may cause skin irritation. Deuterated acetonitrile has the same hazards as the non-deutero form. Diethyl ether is an extremely flammable solvent, and a potent narcotic. Deuterated dimethyl sulfoxide may be harmful if swallowed or inhaled; it may cause eye, skin, and respiratory tract irritation. Dimethyl sulfoxide solutions are readily absorbed through the skin; avoid contact with solutions containing toxic materials. For compounds 1–3 the hazards are not clearly known; take normal precautions: avoid ingestion, inhalation, and contact with skin or mucous membranes.

■ DISCUSSION

Preparation

A crucial ligand precursor for this experiment is **1**, which needs to be prepared in advance. This compound is not currently commercially available, but can be synthesized in 1 day using well-known literature procedures (included in Supporting Information).^{23,24} This starting material is incredibly convenient because it is an air- and moisture-stable solid that can be easily stored and weighed. Moreover, these compounds do not exhibit a strong odor, like many other phosphine starting materials and, thus, are more easily handled by students than air-sensitive, malodorous oils. In the future, **1** is expected to be available through common chemical suppliers; all other starting materials can be readily obtained from commercial sources. In addition, stock solutions of many starting materials were prepared ahead of time.

Part 1: Template Synthesis

In the first part of the experiment, metal templating was presented to the students and the principles of this phenomenon were discussed. When performing the experiment, initially, a kinetic product was formed that has two tridentate ligands (Scheme 2). This “bis-tridentate” complex was a deep wine-red color, and formed rapidly upon addition of the diamine. With heating, however, the kinetic product converted to the desired iron complex with a tetradentate ligand, **2**, which was, in fact, the thermodynamic product. This synthetic route was presented to students and the various color changes explained. It was stressed that, in the absence of the metal center, the same ligand precursors react to make different products, and in this way the experiment served as a practical example of metal templating. Kinetic versus thermodynamic control of reaction products was only briefly discussed.

To isolate product **2**, salt metathesis was introduced as a means to purify inorganic compounds. The principles of salt metathesis were presented, as well as some predictions that could be made based on ion size and solubility. Students used NaBPh₄ in order to precipitate the desired product **2**, which acted as a practical demonstration of this concept and its utility. It was explained that salt metathesis was necessary due to a mixture of counterions in solution (tetrabromoferrate formed during the reaction, which persisted in solution along with tetrafluoroborate). To isolate a pure compound, salt metathesis was used to remove the other counterions.

Although students did not run NMR spectra of their compounds for financial reasons, to characterize product **2**, students were introduced to phosphorus-31 nuclear magnetic resonance (³¹P NMR) spectroscopy. An analogy was made to hydrogen and carbon-13 NMR spectroscopy, and it was stressed that much can be learned about a complex from its ³¹P NMR spectrum. Many of the postlab questions for the first part of the experiment were centered on interpreting ³¹P NMR spectra and examining the trends observed. Prepared NMR spectra were given to students to interpret (Supporting Information). Student laboratory reports indicated that an understanding of ³¹P NMR spectroscopy was achieved and students were capable of interpreting simple ³¹P NMR spectra.

Part 2: Ligand Substitution To Generate a Catalyst Mimic

In the second part of the experiment, the main focus was placed on green chemistry and the synthesis of a catalyst mimic. The importance of ATH in the context of fine chemical synthesis was discussed with students, along with a brief background of

the field. In addition, the push for more sustainable, environmentally friendly practices and the green chemistry movement were presented with respect to highly active iron carbonyl ATH catalysts. A comparison of these catalysts with the isocyanide product **3**, which is a very close mimic of these reported catalysts, was made to link it with cutting-edge catalytic research (the two ligands have similar coordination properties; an isocyanide was used in place of carbon monoxide for safety reasons).

In addition, the second part of the experiment also afforded an opportunity to discuss ligand substitution reactions, and the two main classes of mechanisms for this type of transformation.^{26,27} The steps for associative and dissociative mechanisms were described, along with the factors affecting them.^{26,27} The experiment served as a practical example of a ligand substitution reaction with an octahedral complex, and a post-lab question on the subject was given to students. Student reports showed a good understanding of the two different mechanisms, and in this way the lab report reinforced concepts taught in lectures.

To characterize **3**, students ran IR spectra of their products. An analogy between carbonyl ligands as strong π acceptor ligands and isocyanide ligands was made, and the bonding characteristics of these compounds were discussed. It was stressed that the weakening of the C–O triple bond in carbonyl ligands, as well as the weakening of the C–N triple bond in isocyanide ligands, was reflected in the IR spectrum of complexes bearing these ligands.²⁷ Furthermore, the bonding characteristics of π donor ligands, such as a bromide ligand, were also presented. The concepts of π donors and π acceptors, crucial in the interpretation of the IR spectrum of the final product, were addressed in a post-lab question. Students showed a good understanding of the ideas presented and were able to justify the decrease in stretching frequency seen in **3**.

It should be noted that the isocyanide species generated is not catalytically active. This, along with financial considerations, was the reason why an achiral ethylenediamine backbone was chosen in place of other chiral diamines. The procedure can be easily modified, however, to include another diamine of choice. In addition, if a catalytically active species is desired, a literature procedure for the synthesis of a carbonyl species has been included in the Supporting Information, along with the procedure for a standard catalytic run. For catalysis, the active species is extremely air and moisture sensitive, and requires rigorous solvent drying and degassing, as well as advanced Schlenk-line techniques (further details in Supporting Information).

■ SUMMARY

A two part experiment adapted from original research was successfully employed in an advanced undergraduate inorganic chemistry course with a very high success rate. This report represented one of the only experiments available in the literature that covered the areas of green organometallic catalysts and transition metal templating. Moreover, the pedagogical value of this experiment was very high because it covered a large number of inorganic chemistry concepts, and reinforced content and topics discussed in lectures. Lastly, this experiment was fairly robust and flexible, in that it can be adapted for other uses, such as kinetic versus thermodynamic control of reactions or for a kinetic analysis, as well as for lower year courses.

■ ASSOCIATED CONTENT

■ Supporting Information

Instructions for students, student handouts, notes for demonstrators, notes for instructors, including additional and complementary activities, a procedure for the synthesis of the phosphonium dimer precursor, a procedure for the synthesis of the active catalytic species with a carbonyl ligand, and a procedure for the transfer hydrogenation of acetophenone. 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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