

A Mechanistic Study of Palladium Catalyzed Dehalogenation

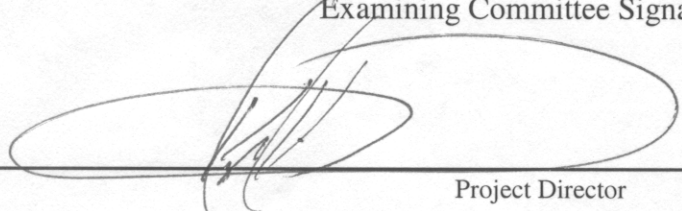
by
Sarah Sewell

Departmental Honors Thesis
The University of Tennessee at Chattanooga
Chemistry Department

Project Director: Dr. Kyle Knight
Examination Date: March 17, 2003

Gregory Grant
Kyle Knight
Joanie Sompayrac
Thomas Waddell

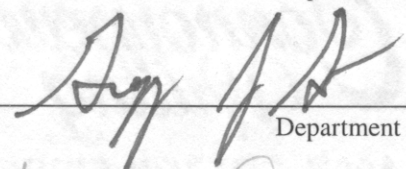
Examining Committee Signatures:



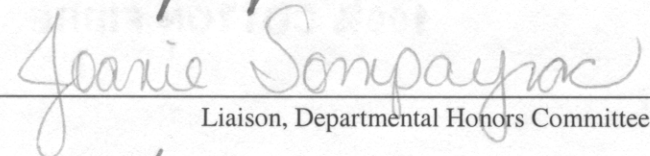
Project Director




Department Examiner



Department Examiner



Liaison, Departmental Honors Committee



Chairperson, University Departmental Honors Committee

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Abstract

A study of the mechanism of a palladium catalyzed system for the dehalogenation of alkyl halides was conducted with the goal of developing a system for kinetic resolution of alkyl halides. Pd (0) compounds generated from diphosphine palladium chloride, diisobutyl aluminum hydride, and ethyl magnesium chloride are effective for the dehalogenation of alkyl halides. A similar system containing tris(dibenzylideneacetone) diPd(0) and cesium carbonate was also studied. The mechanism of both systems will be compared.

Introduction

Enantiomers are molecules that have the same connectivity, but similar to left and right hands, they are non-super imposable mirror images.¹ This property is called chirality. When a chiral molecule is the product of a simple chemical reaction, an equal amount of the two enantiomers are produced. Because enantiomers have the same chemical and physical properties, trying to separate them can be difficult.

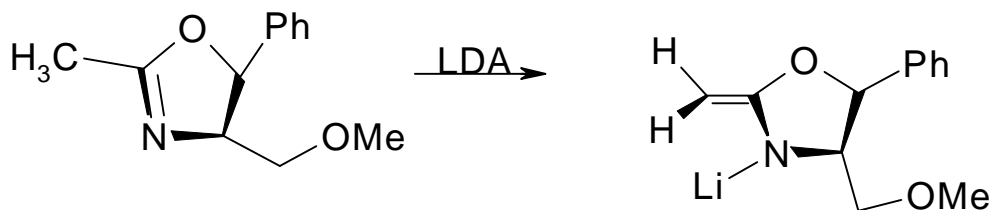
When drugs are produced in a laboratory by conventional methods, they contain both enantiomers. Each enantiomer has the potential to react differently in the body. This difference in the way enantiomers react in the body can cause harmful side effects when mixtures of enantiomers are used as drugs. An example of this can be seen in the case of Thalidomide. In 1956, Thalidomide was used as a sedative in Europe. One enantiomer of Thalidomide worked well as a sedative, but the other caused severe birth defects.² Therefore, the Federal Drug Administration has begun to require drug companies to develop and sell all new compounds in a single enantiomer form.

The goal of our research is to develop an inexpensive method of separating enantiomers that can be used in pharmaceutical synthesis. We will focus on a group of compounds called alkyl halides. Alkyl halides are used extensively in synthesis, most importantly nucleophilic alkylation reactions. Unfortunately, alkyl halides have not been used in chiral synthesis because the single enantiomeric forms are expensive and hard to obtain.³ Therefore, a method to produce alkyl halides in a single enantiomeric form would be beneficial.

Kinetic resolution is a class of reaction in which one enantiomer of a racemic mixture is selectively removed. In kinetic resolution, a chiral reagent reacts with a

racemic mixture in such a way that one enantiomer is destroyed or removed. The chiral reagent will react with the two enantiomers at different rates, resulting in the starting enantiomers being consumed in different amounts. Therefore, at the end of the reaction, one enantiomer can be recovered in excess.⁴ Previous attempts to use kinetic resolution with alkyl halides have succeeded with only a moderate yield. One example is a nucleophilic displacement reaction using chiral nucleophiles as the reagent. An oxazoline was treated with lithium diisopropylamide (LDA). Then a racemic mixture of 2-iodoalkane was added. After quenching with acid, an iodoalkane was produced that was 25-30% enantiomerically pure (Figure I).⁵

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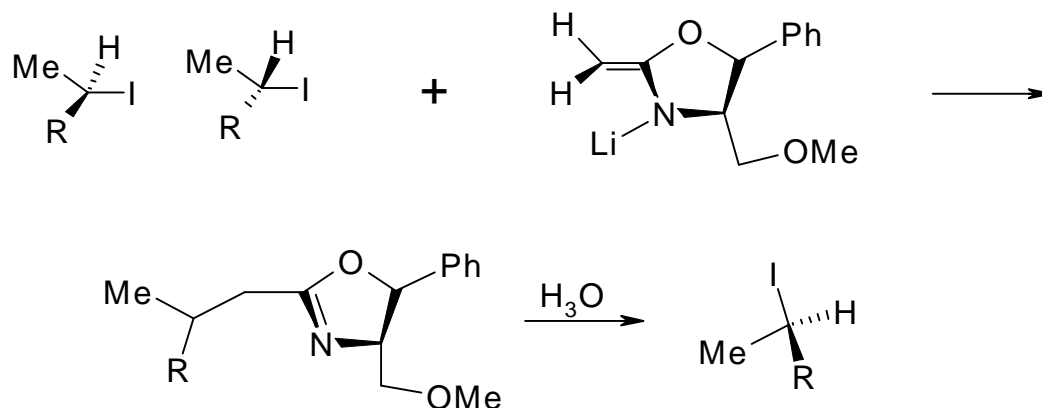


Figure I: Previous attempts to isolate alkyl halides using kinetic resolution

The goal of our research was to determine the conditions of two catalytic cycles involving palladium and to apply kinetic resolution of secondary alkyl halides using chiral ligands. One advantage of our research is there are several different types of chiral ligands that can be used.⁶ Another advantage of the systems we researched was that the complexed palladium catalyst was regenerated in the reaction, so only small amounts of expensive chiral ligands are used.

The first catalytic cycle we examined was based upon the Heck reaction. The purpose of the Heck reaction is to insert a carbon to carbon double bond (Figure II).⁷

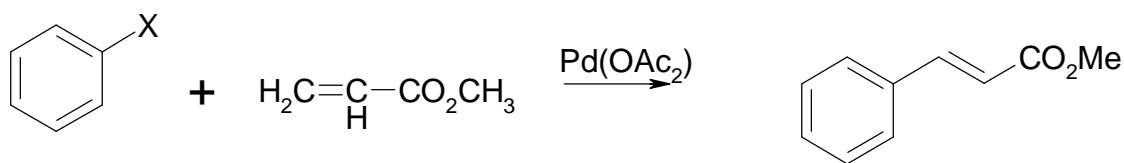


Figure II: Insertion of a double bond by the Heck reaction

The Heck reaction utilizes a palladium (0) complex bearing a donor ligand, normally a tertiary phosphine, as the catalyst to couple aryl or vinyl halides to alkenes.⁸ The catalytic cycle of the Heck reaction has several steps (Figure III). The first step is the oxidative addition of an aryl, vinyl, benzyl, or allyl halide. In the next step, an alkene is introduced into the system and a 1,2 insertion of the alkene takes place. The final step is *b*-hydride elimination..^{7,8}

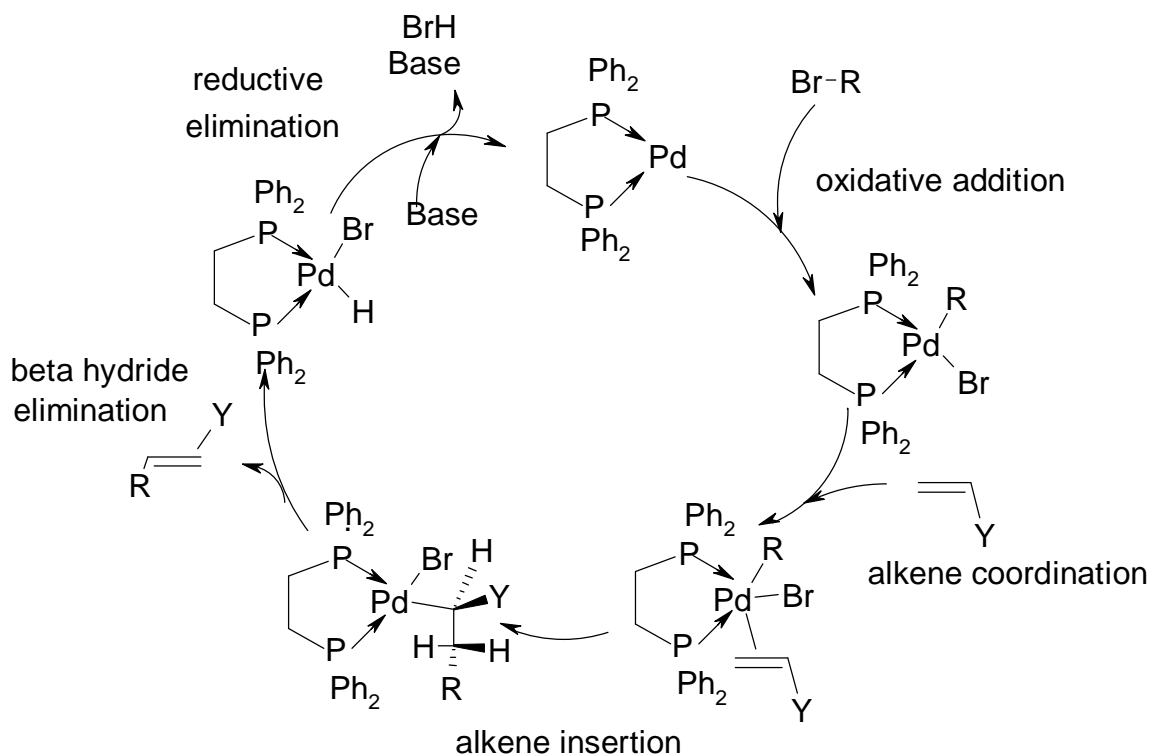


Figure III: The mechanism of the Heck reaction

The Heck reaction does not work with alkyl halides that contain *b*-hydrogens. When a compound contains *b*-hydrogens undergoes oxidative addition to a palladium complex, *b*-hydride elimination occurs at a rate faster than the alkene insertion. Therefore, a carbon to carbon bond is not inserted.⁷

This apparent disadvantage could present an opportunity to develop a new system for kinetic resolution of racemic alkyl halides. In the proposed catalytic cycle, the alkyl halide would undergo oxidative addition, *b*-hydride elimination, and reductive elimination (Figure IV).

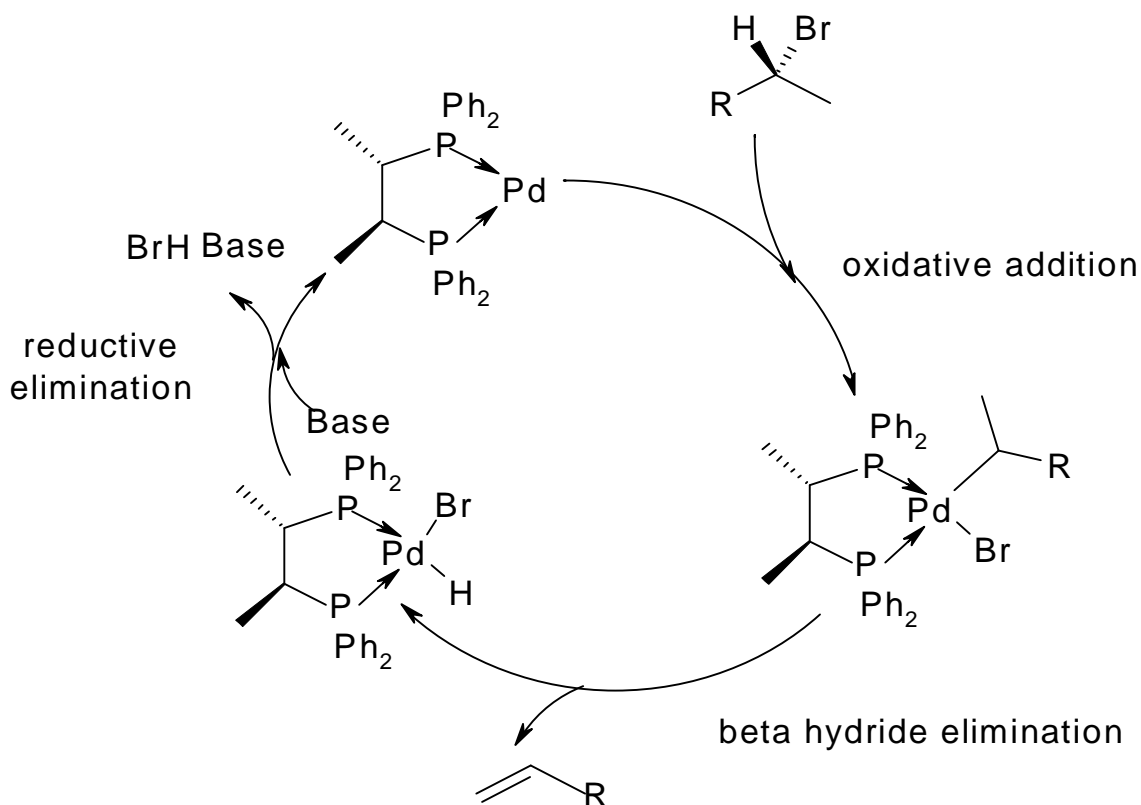


Figure IV: The mechanism of dehalogenation under Heck conditions

The second catalytic cycle we examined was a system in which alkyl halides were reduced using Grignard reagents and palladium catalysts.⁹ Palladium (II) chloride bearing a donor ligand reacts with ethyl magnesium chloride in a nucleophilic displacement and beta hydride elimination. This reduces the palladium complex to the oxidation state of (0). Then the palladium undergoes oxidative addition. Then the complex undergoes nucleophilic displacement, β -hydride elimination, and reductive elimination (Figure V).⁹

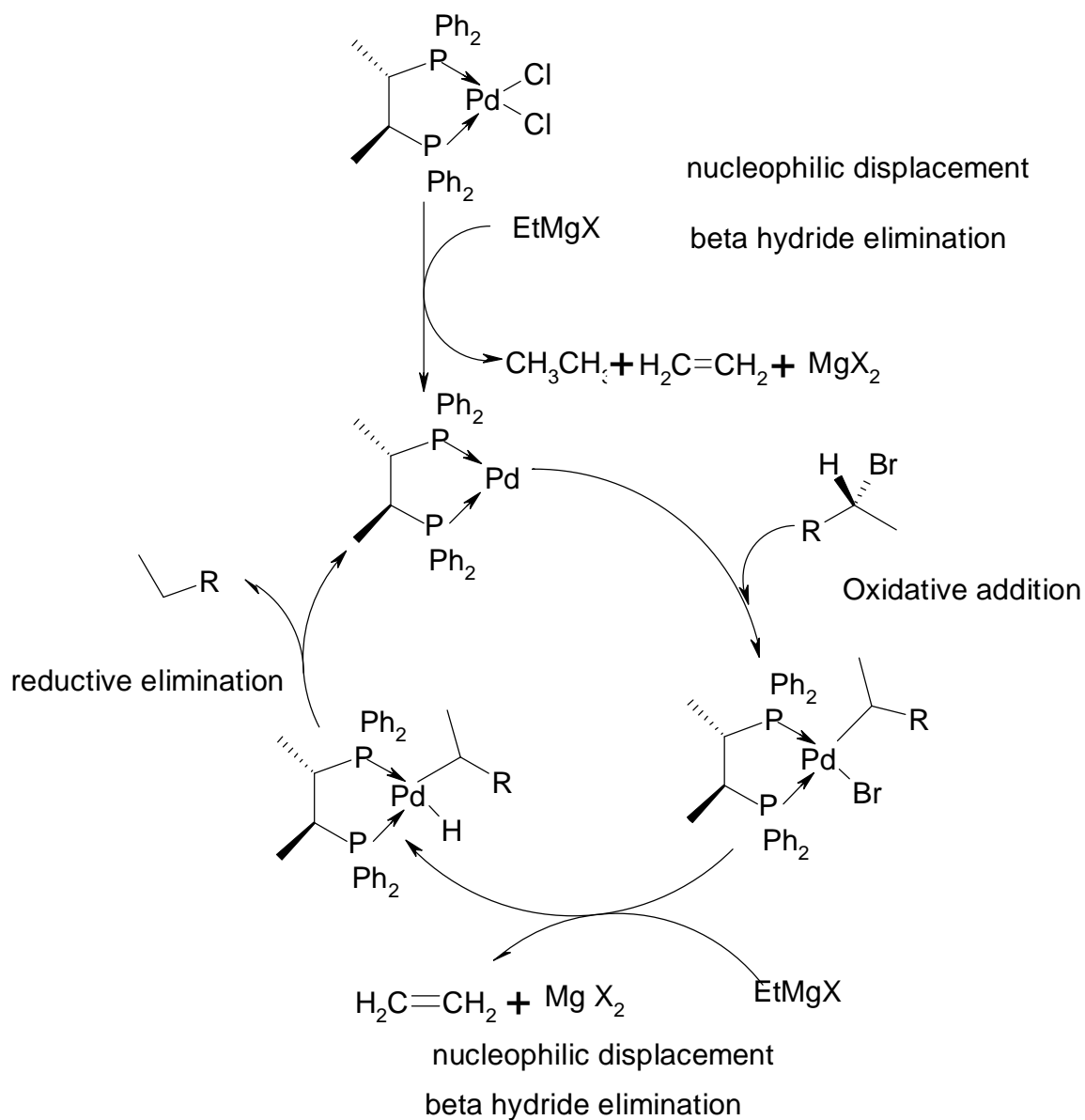


Figure V: The mechanism of dehalogenation under Grignard conditions

We determined the optimum conditions for both catalytic cycles and used several enantiomerically pure ligands with the Heck conditions in an attempt for kinetic resolution. Mechanistic experiments were performed on the dehalogenation under Grignard conditions, and the mechanisms of the two reactions were compared.

Experimental

Methods and Materials

All chemicals were purchased from Aldrich chemical company. Ethyl ether and tetrahydrofuran were dried using sodium metal and benzophenone. Standard Schlenk techniques were followed.

Dehalogenation under Heck conditions

Tris(dibenzylideneacetone)dipalladium (0.012 g, 0.0125 mmol, 2.5 mol percent), R-(+)-2,2 Bis (diphenylphosphino)1-1binaphthyl (0.016 g, 0.025 mmol, 5.0 mol percent), and the base (if solid) was placed under nitrogen using two cycles of an evacuate/quench protocol. To this mixture, the solvent (20 mL of tetrahydrofuran), bromoethylbenzene (0.068 mL, 0.50 mmol) and the GC standard (1 mL of nonane) was added via syringe. Periodically 0.5 mL samples were taken with a syringe. These were treated with 1M hydrochloric acid solution and extracted with ethyl ether and then the organic phase was analyzed using gas chromatography.

Dehalogenation under Grignard conditions

A 0.05 mmol portion of the catalyst (palladium chloride, palladium acetate, or tris(dibenzylideneacetone)dipalladium and 0.05 mmol portion of the ligand (1,1-Bis(diphenylphosphino)ferrocene) were placed under nitrogen conditions using two cycles of an evacuate/quench protocol, and the reaction vessel was cooled to -78°C. To this mixture was added solvent (10 mL of ethyl ether), diisobutyl aluminum hydride (0.5 mmol, 0.5 mL), 1 mL of the GC standard (dodecane), the alkyl halide (1.0 mmol), and then the Grignard reagent (1.0 mmol, 0.33 mL). The cooling bath temperature was then allowed to rise to room temperature over two hours. After reaching this temperature, 0.5

mL samples were periodically acquired from the reaction solution by syringe. These were treated with 1M hydrochloric acid solution and extracted with hexanes. The organic phase was analyzed with gas chromatography.

GC Analysis

Gas chromatography (GC) analysis was performed on an Agilent 6850 with a flame ionization detector. The column was packed with β -cyclodextrine sugars. For optimum separation the temperature was ramped depending upon the alkyl halide and the internal standard. When bromoethyl benzene and propylbenzene were used, the injection temperature was 50°C for 12 minutes. Then, the temperature ramped at 1°C per minute until 150°, where it remained for 30 minutes. When 2-bromopentane and propylbenzene were used, the injection temperature was 45°C for 12 minutes, and then ramped at 1°C per minute until 150°C was reached. The temperature remained at 150°C for 30 minutes. When 1-bromo-3-phenyl propane and propylbenzene were in a reaction, the injection temperature was 55°C for 12 minutes. The temperature was ramped at 2°C per minute until 150°C, where it remained for 30 minutes. When 2-bromopentane and dodecane were used the injection temperature was 45°C for 12 minutes. The temperature was ramped at 1°C per minute until 150°C, where the temperature remained constant for 30 minutes.

Results

A 0.0125 mmol portion of tris(dibenzylideneacetone) dipalladium (0), 0.025 mmol of R-(+) 2,2 Bis (diphenylphosphino) 1-1 binaphthyl (BINAP), and 1-bromoethyl benzene were reacted with several different bases at several different temperatures to obtain the optimum conditions of the dehalogenation of alkyl halides with the Heck conditions (Table I).

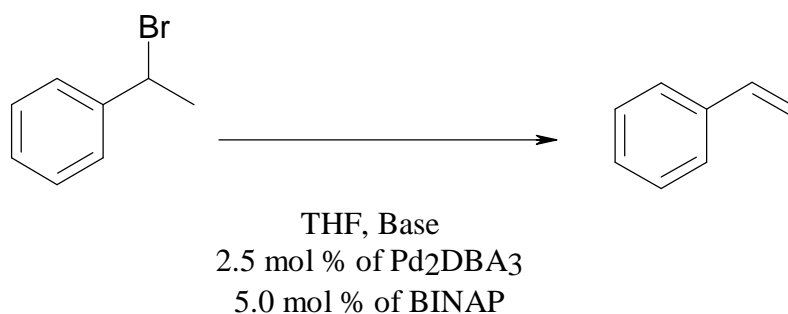


Table I: Determination of the Heck conditions for the dehalogenation of alkyl halides

Experiment	Base	Reflux	Time	Percent of the alkyl Halide consumed (%)
Book I-75	Potassium Carbonate	Yes	18 hours	0.0
Book II-77	Pyridine	Yes	1 hour	0.0
			1 week	91.0
Book I-79	Cesium Carbonate	Yes	1.5 hours	100.0
Book II-3	Cesium Carbonate	No	24 hours	32.1

Cesium carbonate was determined to be the optimum base because the alkyl halide is consumed without reflux at room temperature. A control reaction was conducted in which bromoethyl benzene and cesium carbonate were refluxed in the absence of the ligand or catalyst. This experiment required one week to convert twenty

five percent of bromoethylbenzene, confirming the necessity of the catalyst for a rapid reaction.

We used several chiral ligands in an attempt at kinetic resolution, using several different alkyl halides. A 0.0125 mmol portion of tris(dibenzylidene acetone) dipalladium (0) (Pd_2DBA_3), 6.0 mmol of cesium carbonate, 20 mL of tetrahydrofuran, and 0.07 mL of propyl benzene or was used as an internal chromatography standard (Table II).

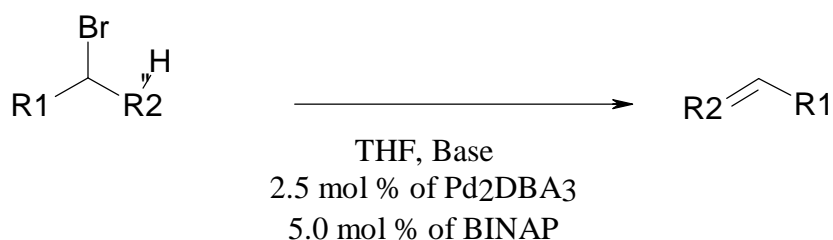


Table II: Kinetic resolution with the Heck conditions						
Experiment	alkyl halide	ligand	percent consumed (%)	enantiomeric excess	Time (hours)	Reflux
Book II-3	Bromoethyl benzene	(R)-BINAP	32.1	0.0	24	No
Book II-15	2 bromopentane	Me-BPE	8.6	0.0	24	Yes
Book II-17	2 bromopentane	(R)-BINAP	0.0	0.0	24	Yes
Book II-33	2 bromopentane	TROST	12.6	0.0	24	Yes
Book II-39	2 bromopentane	(S,S) Chiraphos	31.5	0.0	24	Yes
Book II-41	2 bromopentane	(S,S) Chiraphos	7.7	0.0	48	No
Book II-49	1 bromo 3 phenyl propane	(S,S) Chiraphos	23.2	0.0	24	Yes
Book II-51	1 bromo 3 phenyl propane	(S, S) Chiraphos	2.0	0.0	24	No

Since the dehalogenation with the Heck conditions was limited to benzyl alkyl halides and did not result in enantioselectivity with several ligands, we began to research a

catalytic system that was published by Scott and coworkers that used a Grignard reagent and diisobutylaluminum hydride (DIBAL).¹⁰

The dehalogenation of strait chain alkyl halides was successful with ethyl magnesium bromide, DIBAL, and dichloro[1-1' bis(diphenylphosphino) ferrocene] palladium (II) ((dppf)PdCl₂), and dodecane or propylbenzene as the internal chromatography standard (Table III).

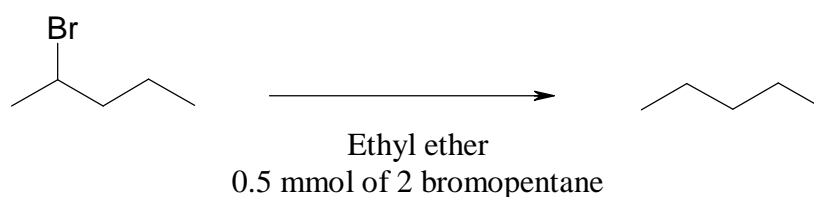


Table III: Dehalogenation of alkyl halides with Grignard Conditions

Experiment	Palladium source	alkyl halide	Time (hours)	percent consumed (%)
Book II-75	(dppf)PdCl ₂	2 bromopentane	24	94.9
Book II-79	none	2 bromopentane	24	3.1

The scope of this reaction was probed by varying Grignard reagents and sources of palladium (Table IV). In each reaction, 1.0 mmol of 2 bromopentane was used as the alkyl halide and 0.5 mmol of DIBAL was added. Dichloro[1-1' bis(diphenylphosphino) ferrocene] palladium (II) was the most reactive source of palladium. Ethyl magnesium bromide was the most effective Grignard reagent.

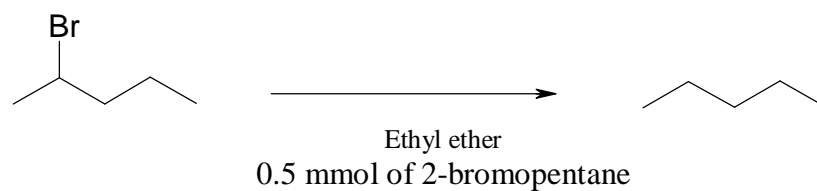


Table IV: Variation of Grignard reagents and palladium sources

Experiment	Palladium Source	Grignard Reagent	Time (hours)	Percent consumed (%)
Book II-87	Pd (II) acetate	Ethyl-MgBr	24	26.6
Book II-89	Pd ₂ DBA ₃	Ethyl-MgBr	24	49.8
Book III-27	dppf(PdCl ₂)	Methyl-MgBr	24	33.9
Book III-31	dppf(PdCl ₂)	Propyl-MgCl	24	0.0
Book III-33	dppf(PdCl ₂)	Isopropyl-MgCl	24	34.3

There were several inconsistencies in the mechanism that we wished to study. DIBAL is included in the preparation, but not in the mechanism.¹⁰ Several experiments were done to determine the exact role of DIBAL and the exact role of the Grignard reagent. In each reaction 1.0 mmol of 2 bromopentane was used as the alkyl halide (Table V).



Ethyl ether
0.5 mmol of 2-bromopentane

Table V: Mechanistic Experiments						
Experiment	Pd Source	Grignard Reagent	DIBAL	Ligand	Time (hours)	Percent consumed (%)
Book II-93	dppf(PdCl ₂)	None	Yes	N/A	72	10.3
Book III-25	dppf(PdCl ₂)	Ethyl-MgBr	None	N/A	24	18.8
Exp III-29	Pd ₂ DBA ₃	Ethyl-MgBr	None	dppf	24	100
Book III-35	Pd ₂ DBA ₃	None	Yes	dppf	72	11.6
Book II-75	(dppf)PdCl ₂	Ethyl-MgBr	Yes	N/A	24	94.9

This data suggests that DIBAL reduces the palladium from an oxidation state of Pd(II) to Pd(0). The Grignard reagent is responsible for the nucleophilic displacement.

Discussion

The optimum conditions for the dehalogenation under Heck conditions are tris(dibenzylideneacetone)dipalladium (0), $(\text{Pd}_2(\text{DBA})_3)$ as the palladium source and cesium carbonate as the base. This system only worked with benzylic halides and there was no enantioselectivity observed with several enantiomerically pure ligands. The amount of alkyl halides that were consumed were low and required reflux. The slow step in the system is oxidative addition. If the oxidative addition step could be increased the system would be more productive.

Therefore, we began to research a system presented by Scott and coworkers where the oxidative addition of alkyl halides was reported to be rapid.¹⁰ The dehalogenation of straight chain alkyl halides was successful with ethyl magnesium bromide, diisobutylaluminum hydride and dichloro[1-1'-bis(diphenylphosphino)ferrocene] palladium(II), $((\text{dppf})\text{PdCl}_2)$. In twenty-four hours without reflux, 94.9% of 2-bromopentane was consumed.

Before we began to use enantiomerically pure ligands in an attempt at kinetic resolution, we wanted to understand the mechanism. There are several inconsistencies in the published work that needed to be elucidated. Diisobutylaluminum hydride is included in the procedure, but is not present in the mechanism.¹⁰ According to the published mechanism, ethyl magnesium chloride reduces the palladium (II) to palladium(0). If this is true, then the alkyl halide should still be consumed without the addition of the DIBAL. Instead, both DIBAL and a Grignard reagent are required to enable the reaction to consume an alkyl halide. When DIBAL and $(\text{dppf})\text{PdCl}_2$ are placed

in a reaction with no Grignard reagent, the percent of alkyl halide consumed in 72 hours is 10%. When a Grignard reagent and (dppf)PdCl₂ are placed in a reaction with no DIBAL, the percent of alkyl halide consumed in 24 hours is 18.8%. When DIBAL and a palladium (0) source, Pd₂(DBA)₃, are placed in a reaction with no Grignard reagent, the percent of alkyl halide consumed in 72 hours is only 11.6%. When a Grignard reagent and Pd₂(DBA)₃ are placed in a reaction with no DIBAL, the percent of alkyl halide consumed in 24 hours is 100%. This data suggests that DIBAL is required for the reaction when the starting palladium source is palladium(II), but not necessary when the starting palladium source is palladium(0). Therefore, DIBAL reduces the palladium from an oxidation state of (II) to (0).

If the mechanism of the dehalogenation under Grignard conditions is compared to the mechanism of the dehalogenation under Heck conditions, there is another inconsistency. The oxidative addition of the alkyl halide is the slow step⁹, but oxidative addition is much faster with the Grignard conditions even though there is nothing different in that step of the mechanism from the mechanism of the Heck conditions. Since 100% of the alkyl halide was consumed when Pd₂(DBA)₃ was used, the Grignard reagent is responsible for the rapid oxidative addition. We propose that the oxidative addition step is faster because the palladium complex has become anionic (Figure VI).¹¹

In the future, different enantiomerically pure ligands will be synthesized and applied to this system in an attempt to achieve kinetic resolution.

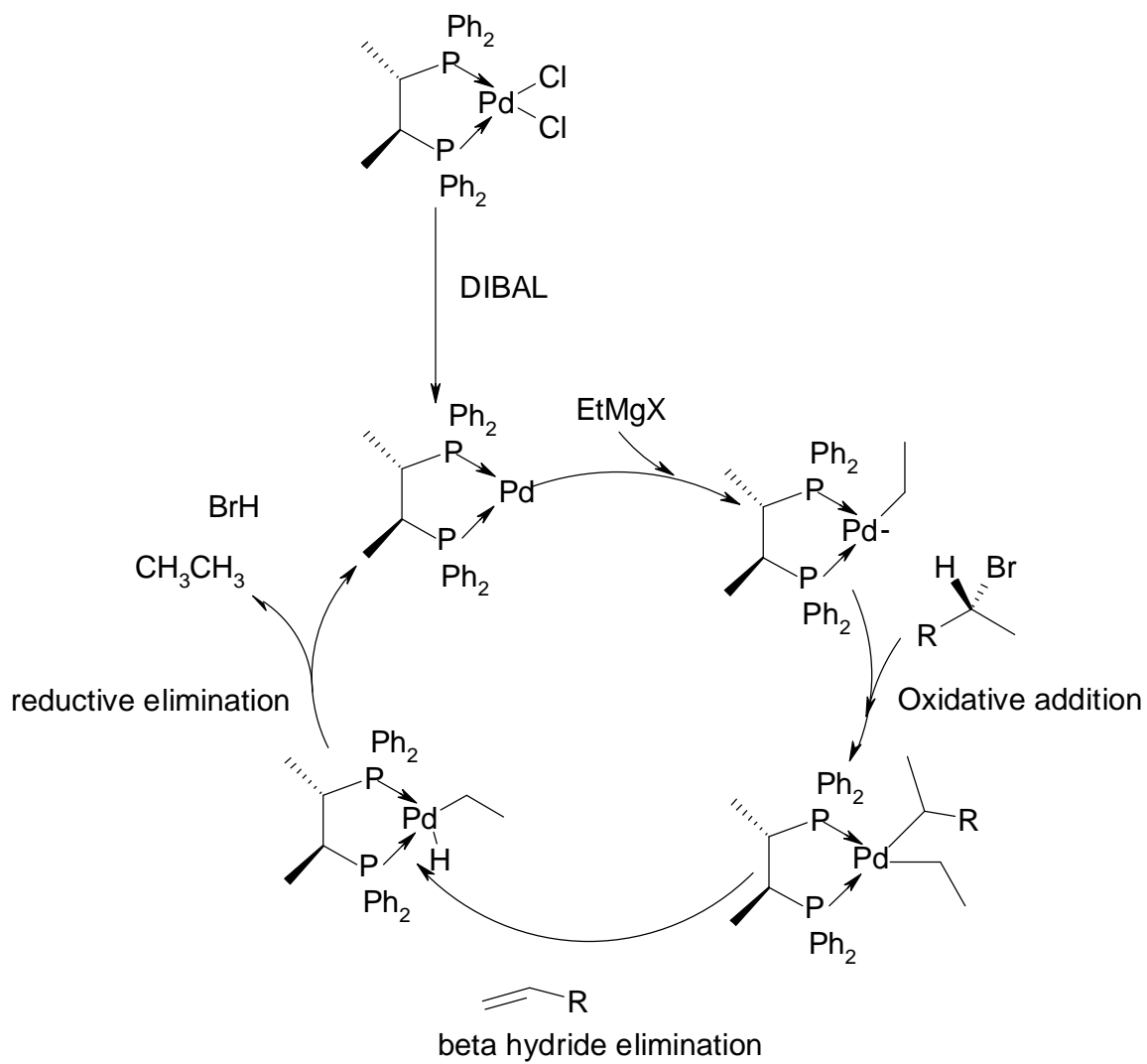


Figure VI: Proposed mechanism for the dehalogenation under Grignard conditions

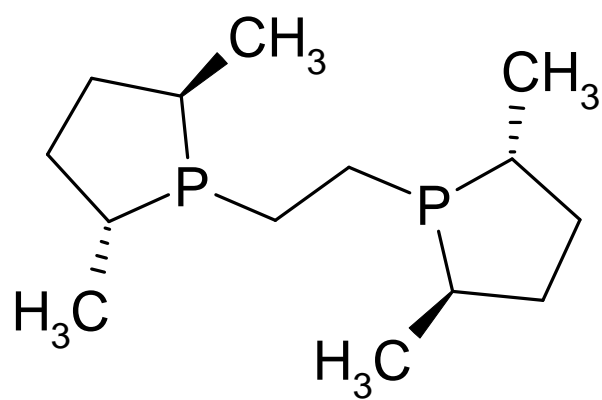
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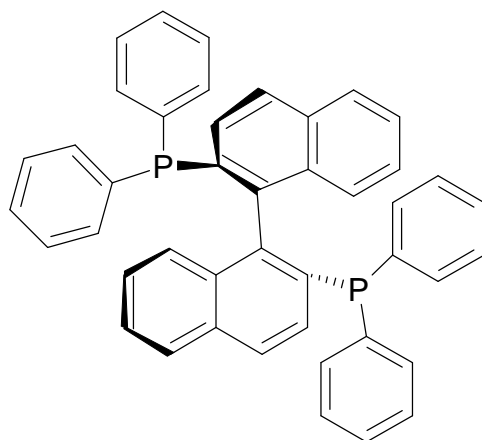
Appendix

Structures of Compounds

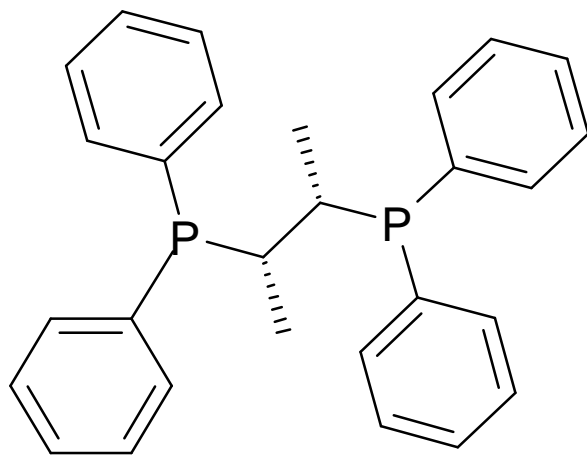
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(R)-(+)-2,2'-Bis(diphenylphosphino)-1,1'binaphthyl, (R)-BINAP.....	23
(2S,3S)-(-)-Bis(diphenylphosphino)butane, (S,S)-Chiraphos.....	24
(1R,2R)-(+)-1,2-Diaminocyclohexane-N,N'-bis(2'-diphenylphosphinobenzoyl), TROST LIGAND.....	25
Diphenylphosphinoferrocene.....	26
Dibenzylideneacetone.....	27



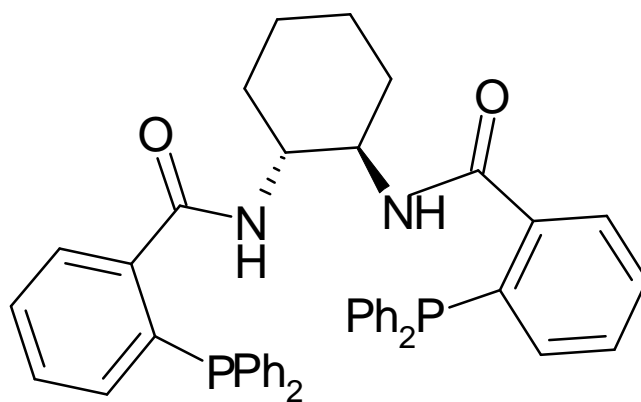
(+)-1,2-Bis((2R,5R)-2,5-dimethylphospholano)ethane, (R,R)-Me-BPE



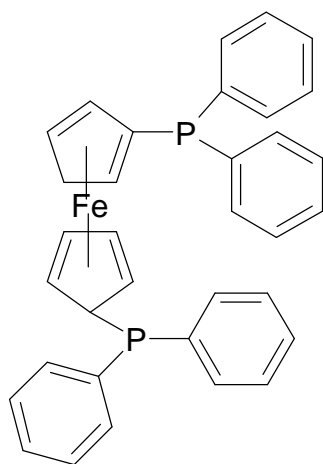
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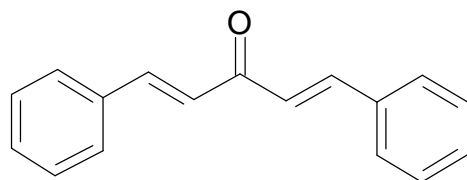
(2S,3S)-(-)-Bis(diphenylphosphino)butane, (S,S)-Chiraphos



(1R,2R)-(+)-1,2-Diaminocyclohexane-N,N'-bis(2'-
diphenylphosphinobenzoyl), TROST LIGAND



diphenylphosphinoferrocene



dibenzylideneacetone

Note: Tris(dibenzylideneacetone)dipalladium consists of three dibenzylideneacetone surrounding two palladium.

Acknowledgements

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