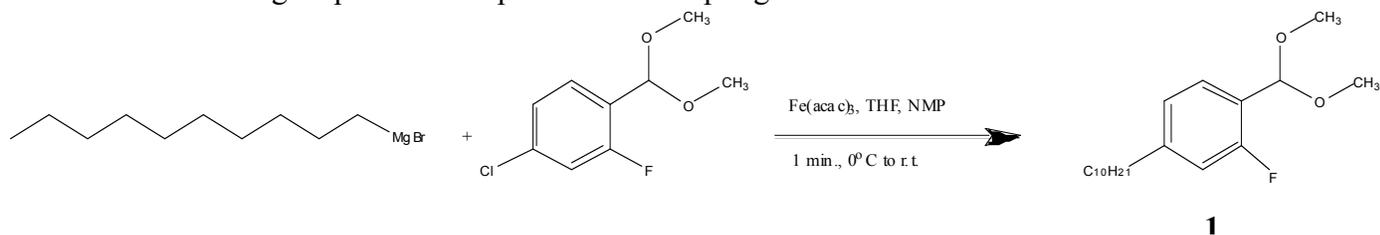# A Comparison of Cross-Coupling Reactions Involving an Aryl Group and an R Group

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Abstract: A number of cross-coupling reactions involving the iron catalyst, Fe(acac)$_3$, were performed in order to couple an aryl group and a decyl chain. Cross-coupling of decylmagnesium bromide and an aryl chloride, for example, 4-chloro-2-fluorobenzaldehyde dimethyl acetal, was efficiently achieved via a one pot reaction as exemplified by the preparation of compound **1**. Although the coupling was compatible with an ester group on the ring, coupling with an aldehyde group or a ketone group on the ring was difficult to obtain due to direct attack by the Grignard at the carbonyl. In addition, it was also discovered that having a fluorine substituent on the ring helps to further promote the coupling.

Synthesis of 4-decyl-2-fluorobenzaldehyde dimethyl acetal.

Introduction

The use of cross-coupling reactions is an important part of organic synthesis, especially in the formation of carbon-carbon bonds and carbon-heteroatom bonds.[1] These cross-coupling reactions require the use of a variety of organometallic reagents and catalysts, nickel and palladium being the most widely used catalysts in the field. However, many of these nickel and palladium complexes are expensive and are sensitive to oxygen and air.

Recently, there has been a growing interest in the study, improvement, and use of cheaper and readily-available organometallic reagent and catalyst combinations that also are effective cross-coupling reagents. Fürstner proposed the use of simple iron salts, such as FeCl$_n$ and Fe(acac)$_n$ (n=2,3), to effectively cross-couple alkyl and aryl Grignard reagents with aryl and heteroaryl chlorides.[1,2] In addition, Cahiez also proposed the use of the same iron catalyst for the alkylation of aromatic Grignard reagents.[3,4]

For this project, two methods were implemented and examined. The first method tested was Fürstner's cross-coupling procedure that involved a reaction between an alkyl Grignard and an aryl chloride (Figure 1). The second method was Cahiez's cross-coupling procedure that involved a reaction between an aryl Grignard and an alkyl chain (Figure 2).
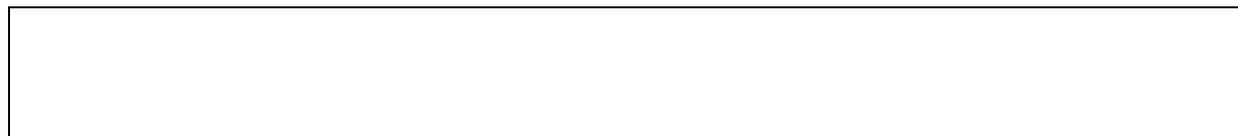
Figure 1. Fürstner method.
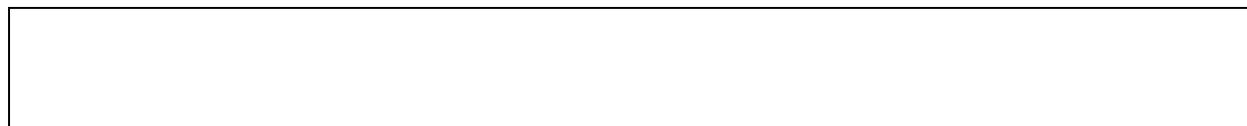
Figure 2. Cahiez method.

Experimental Procedure

General

Prior to each reaction, all glassware was oven-dried and cooled under nitrogen. All reactions were carried out under a nitrogen atmosphere. All starting materials were purchased from Sigma-Aldrich Chemical Co. with the exception of 4-chloro-2-fluorobenzaldehyde (Matrix Scientific).

Preparation of Decylmagnesium Bromide

A 1.5171 g portion (61.73 mmole) of magnesium turnings was placed in a three-necked flask equipped with a magnetic stirbar, glass stopper on the left neck, addition funnel fitted with a rubber septum on the middle neck, and a condenser fitted with a nitrogen inlet on the right neck. About 60 mL of anhydrous THF (with BHT as inhibitor) was added through the septum into the addition funnel from its Sure Seal bottle via a metal cannula and dry nitrogen to pump the liquid. From the addition funnel, enough THF was added to the flask to just cover the magnesium turnings. 1-bromodecane, (12.31 mL, 59.31 mmole) was measured with a 10 mL syringe (2 aliquots of about 6.1 mL of 1-bromodecane) and injected into the addition funnel in such a way that it concentrated in the bottom of the funnel. About 20 drops of 1-bromodecane were added to the magnesium and THF in the funnel and stirred with the heat turned on in order to start the reaction. Within a few minutes, the solution became cloudy and grey with bubbles forming. The whole apparatus was then picked up and swirled in order for the THF and 1-bromodecane in the addition funnel to mix thoroughly. The rest of the 1-bromodecane/THF mixture was then added in the span of 45 minutes to maintain gentle reflux. Once the addition was complete, the mixture was allowed to stir and reflux for an additional period of 20 minutes. Most of the Mg turnings were greatly reduced in size. After reflux, the colorless mixture was then cooled and transferred to a storage flask via a polymer tube and filter. About 10 mL of anhydrous THF was pumped into the storage flask via dry nitrogen to prevent Grignard reagent from precipitating. The storage flask was flushed with nitrogen and stored.

Titration of Decylmagnesium Bromide

Decylmagnesium bromide (10 mL) was added to a 250-mL volumetric flask that contained 20 mL de-ionized H_2O (dI H_2O). A 150 mL portion of a 0.1088 M solution of HCl was then transferred to the volumetric flask via burette. The Grignard solution was then diluted to the 250 mL mark with dI H_2O. One 50 mL aliquot of this quenched Grignard solution was then used to wash a clean burette for delivery of the Grignard. Then, four 50 mL aliquots of the quenched Grignard solution were then transferred to 4 separate 250-mL Erlenmeyer flasks equipped with magnetic stirbar. Three drops of phenolphthalein were then added to each flask and each was titrated with 0.1045 M NaOH.

Cross-Coupling Reaction between Decylmagnesium Bromide and 4-chlorobenzaldehyde

An oven dried, 100 mL, three-necked, round-bottomed flask equipped with a magnetic stirbar, rubber septum, and a nitrogen inlet was flushed with nitrogen and charged with 4-chlorobenzaldehyde (0.6639 g, 4.723 mmole), ferric acetylacetonate [Fe(acac)$_3$] (0.0838 g, 0.2373 mmole), 30 mL anhydrous THF (with inhibitor), and 1.60 mL of N-methylpyrrolidinone (NMP). The whole apparatus was maintained under N$_2$ atmosphere throughout the duration of the reaction. The flask was immersed in an ice bath and the solution of decylmagnesium bromide (9.905 mL, 6.012 mmole) was immediately added from the storage flask within one minute via syringe. This caused a color change from red to pale yellow with solid white precipitate suspended in solution. The ice bath was removed and the resulting mixture was stirred for 7-10 minutes, then diluted with 12.40 mL of Et$_2$O, and carefully quenched by addition of 18.60 mL of 1 M HCl. The mixture was transferred into a separatory funnel (the flask was rinsed with Et$_2$O), and the aqueous phase was separated and extracted with 12.40 mL of Et$_2$O. The combined organic phases were washed with 18.60 mL of saturated NaHCO$_3$, dried over anhydrous MgSO$_4$, and concentrated by rotary evaporation, which resulted in a crude, orange product.

Purification of Crude Product for All Cross-Coupling Reactions

About one-third of the crude product was then dissolved in an equal volume of cyclohexane. A one-inch silica gel column was then prepared by mixing silica with cyclohexane and pouring the slurry into a plastic column. The dissolved crude product was run through the column, and finally the mobile phase was used to collect separate fractions. These fractions were then evaporated under nitrogen and analyzed.

Cross-Coupling Reaction between Decylmagnesium Bromide and 4-chlorobenzaldehyde dimethyl acetal

An oven dried, 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirbar, rubber septum, and a nitrogen inlet was flushed with nitrogen and charged with 4-chlorobenzaldehyde dimethyl acetal (0.7699 g, 4.126 mmole), Fe(acac)$_3$ (0.0740 g, 0.2095 mmole), 25 mL anhydrous THF (with inhibitor), and 1.40 mL NMP. The whole apparatus was maintained under N$_2$ atmosphere throughout the duration of the reaction. The flask was immersed in an ice bath and the solution of decylmagnesium bromide (8.65 mL, 5.252 mmole) was immediately added from the storage flask within one minute via syringe. This caused a color change from red to dark red/brown with solid white precipitate suspended in solution. The ice bath was removed and the resulting mixture was stirred for 7-10 minutes, then diluted with 11 mL of Et$_2$O, and carefully quenched by addition of 16.50 mL of 1 M HCl. The mixture was transferred into a separatory funnel (the flask was rinsed with Et$_2$O), and the aqueous phase was separated and extracted with 11 mL of Et$_2$O. The combined organic phases were washed with 16.50 mL of saturated NaHCO$_3$, dried over anhydrous MgSO$_4$, and concentrated by rotary evaporation, which resulted in a crude, red-orange product.

Preparation of 4-chlorobenzaldehyde dimethyl acetal[5,6]

A 3.6601 g (26.04 mmole) portion of 4-chlorobenzaldehyde was placed in an oven-dried 100-mL round bottom flask that had been cooled with nitrogen and equipped with a magnetic stir bar. Next, 4.740 mL (44.67 mmole) of distilled trimethyl orthoformate, 7 mL of methanol, and 0.1592 g (0.8369 mmole) of *p*-toluenesulfonic acid monohydrate were then added to flask and the mixture was stirred overnight. The acid was then neutralized by the addition of 1.8 mL of a

0.5 M solution of sodium methoxide in methanol. The solvents were then removed on a rotary evaporator to produce a crude oil. Cyclohexane (10 mL) was added to the flask for azeotropic formation with the last traces of methanol and further evaporated. Precipitate was present in mixture after addition of cyclohexane. The solid product, which was most likely the salt of *p*-toluenesulfonic acid, and the liquid product were separated through vacuum filtration. The liquid product was then dried over K_2CO_3.

Preparation of 4-chloro-2-fluorobenzaldehyde dimethyl acetal

A 4.1986 g (26.49 mmole) portion of 4-chloro-2-fluorobenzaldehyde was placed in an oven-dried 100 mL round bottom flask which had been cooled with nitrogen and equipped with a magnetic stir bar. Next, 4.740 mL (44.67 mmole) of distilled trimethyl orthoformate, 7 mL of methanol, and 0.1390 g (0.7307 mmole) of *p*-toluenesulfonic acid monohydrate were then added to flask and the mixture was stirred overnight. The acid was then neutralized by the addition of 1.8 mL of a 0.5 M solution of sodium methoxide in methanol. The solvents were then removed on a rotary evaporator to produce a clear layer on bottom, which was the protected ring, and a milky layer on top. Two 10 mL aliquots of cyclohexane were added to the flask for azeotropic formation with the last traces of methanol and further evaporated. The colorless liquid product was then dried over K_2CO_3.

Cross-Coupling Reaction between Decylmagnesium Bromide and 4-chloro-2-fluorobenzaldehyde dimethyl acetal

An oven dried, 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirbar, rubber septum, and a nitrogen inlet was flushed with nitrogen and charged with 4-chloro-2-fluorobenzaldehyde dimethyl acetal (0.7789 g, 3.808 mmole), Fe(acac)$_3$ (0.0682 g, 0.1931 mmole), 23 mL anhydrous THF (with inhibitor), and 1.25 mL of NMP. The whole apparatus was maintained under N_2 atmosphere throughout the duration of the reaction. The flask was immersed in an ice bath and the solution of decylmagnesium bromide (7.13 mL, 4.85 mmole) was immediately added from the storage flask within one minute via syringe. This caused a color change from red to dark orange/brown with one single mass of white precipitate. The ice bath was removed and the resulting mixture was stirred for 7-10 minutes, then diluted with 10 mL of Et$_2$O, and carefully quenched by addition of 15 mL of 1 M HCl. The mixture was transferred into a separatory funnel (the flask was rinsed with Et$_2$O), and the aqueous phase was separated and extracted with 10 mL of Et$_2$O. The combined organic phases were washed with 15 mL of saturated NaHCO$_3$, dried over anhydrous MgSO$_4$, and concentrated by rotary evaporation. The resulting crude product was red/orange-yellow.

Cahiez Method

Preparation of 4-(benzaldehyde dimethyl acetal) magnesium bromide

A 0.9809 g portion (40.35 mmole) of magnesium turnings was placed in a three-necked flask equipped with a magnetic stirbar, glass stopper in the left neck, addition funnel fitted a rubber septum on the middle neck, and a condenser fitted with a nitrogen inlet on the right neck. The whole apparatus was maintained under N_2 atmosphere throughout the duration of the reaction. About 40 mL of anhydrous THF (with inhibitor) was added through the septum into the addition funnel from its Sure Seal bottle via a metal cannula and dry nitrogen to pump the liquid. From the addition funnel, enough THF was added to the flask to just cover the magnesium

turnings. 4-bromobenzaldehyde dimethyl acetal, (6.35 mL, 38.00 mmole) was measured with a 10 mL syringe and injected into the addition funnel in such a way that it concentrated in the bottom of the addition funnel. About 20 drops of 4-bromobenzaldehyde dimethyl acetal were added to the magnesium and THF in the funnel and stirred with the heat turned on in order to start the reaction. Within a few minutes, the solution became darker with a yellow-green color. The whole apparatus was then picked up and swirled in order for the THF and 1-bromodecane in the addition funnel to mix thoroughly. Next, the rest of the 4-bromobenzaldehyde dimethyl acetal/THF mixture was added in the span of 45 minutes to maintain gentle reflux. Once the addition was complete, the mixture was allowed to stir and reflux for a period of 20 minutes. Most of the Mg turnings reduced in size. After reflux, the dark brown/violet mixture was then cooled and transferred to a storage flask via a polymer tube and filter.

Titration of 4-(benzaldehyde dimethyl acetal) magnesium bromide

A 10 mL portion of 4-(benzaldehyde dimethyl acetal) magnesium bromide was added to 250-mL volumetric flask that contained 20 mL dI H_2O. Next, a 150 mL portion of a 0.1088 M solution of HCl was then transferred to the volumetric flask via burette. The Grignard solution was then diluted to the 250 mL mark with dI H_2O. One 50 mL aliquot of the Grignard solution was then used to wash a clean burette for delivery of the Grignard. Then, four 50 mL aliquots of the Grignard solution were then transferred to 4 separate 250 mL Erlenmeyer flasks equipped with magnetic stirbar. Three drops of phenolphthalein were then added to each flask and titrated with 0.1045 M NaOH.

Cross-Coupling Reaction between 4-(benzaldehyde dimethyl acetal) magnesium bromide and 1-bromodecane

An oven dried, 100 mL, three-necked, round-bottomed flask equipped with a magnetic stirbar, rubber septum on the left neck, addition funnel on the middle neck, and a nitrogen inlet on the right neck was flushed with nitrogen and charged with anhydrous THF (8 mL), 1-bromodecane (1.5 mL, 7.168 mmole), Fe(acac)$_3$ (0.1259 g), TMEDA (0.108 mL), and HMTA (0.0584 g). The whole apparatus was maintained under N_2 atmosphere throughout the duration of the reaction. The reaction mixture was cooled to 0°C then 4-(benzaldehyde dimethyl acetal) magnesium bromide (12 mL) was slowly added over a period of 60 minutes. After the completion of the addition, the reaction was stirred for an additional 30 minutes and then quenched with 1 M HCl (18 mL). The aqueous phase was extracted with diethyl ether (3 x 14.3 mL). The combined organic layers were then washed with 1 M HCl (18 mL), washed with saturated NaHCO$_3$ (24 mL), dried over anhydrous MgSO$_4$, and concentrated by rotary evaporation. The crude residue was purified by flash chromatography using a mobile phase of 20:19 cyclohexane/ethyl acetate mixture and a stationary phase of silica gel (width: 5 cm, height: 10 cm), which yielded a colorless oil.

Reactions with X-Substituted Aryl Chlorides with Decylmagnesium Bromide

Cross-Coupling Reaction Between Decylmagnesium Bromide and 1-chloro-3-fluorobenzene

An oven dried, 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirbar, rubber septum on the left neck, glass stopper on the middle neck and a nitrogen inlet on the right neck was flushed with nitrogen and charged with 1-chloro-3-fluorobenzene (0.5651 g, 4.329 mmole), Fe(acac)$_3$ (0.0768 g, 0.2175 mmole), 26 mL anhydrous THF (with inhibitor), and

1.43 mL of NMP. The whole apparatus was maintained under N_2 atmosphere throughout the duration of the reaction. The flask was immersed in an ice bath and the solution of decylmagnesium bromide (8.11 mL, 5.150 mmole) was immediately added from the storage flask within one minute via syringe. This caused a color change from red to brown with white precipitate. The ice bath was removed and the resulting mixture was stirred for 7-10 minutes, then diluted with 11.5 mL of Et_2O, and carefully quenched by addition of 17.1 mL of 1 M HCl. The mixture was transferred into a separatory funnel (the flask was rinsed with Et_2O), and the aqueous phase was separated and extracted with 11.5 mL of Et_2O. The combined organic phases were washed with 17.1 mL of saturated $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated by rotary evaporation, which resulted in a crude, orange product.

Cross-Coupling Reaction Between Decylmagnesium Bromide and 1-bromo-4-chlorobenzene

An oven dried, 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirbar, rubber septum on the left neck, glass stopper on the middle neck, and a nitrogen inlet on the right neck was flush with nitrogen and charged with 1-bromo-4-chlorobenzene (0.7926 g, 4.140 mmole), $Fe(acac)_3$ (0.0754 g, 0.2145 mmole), 25 mL anhydrous THF (with inhibitor), and 1.36 mL of NMP. The whole apparatus was maintained under N_2 atmosphere throughout the duration of the reaction. The flask was immersed in an ice bath and the solution of decylmagnesium bromide (7.60 mL, 5.160 mmole) was immediately added from the storage flask within one minute via syringe. This caused a color change from red to dark brown. The ice bath was removed and the resulting mixture was stirred for 7-10 minutes, then diluted with 11 mL of Et_2O, and carefully quenched by addition of 16.3 mL of 1 M HCl. The mixture was transferred into a separatory funnel (the flask was rinsed with Et_2O), and the aqueous phase was separated and extracted with 11 mL of Et_2O. The combined organic phases were washed with 16.5 mL of saturated $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated by rotary evaporation, which resulted in a crude, red-orange product.

Cross-Coupling Reaction Between Decylmagnesium Bromide and 1,4-dichlorobenzene

An oven dried, 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirbar, rubber septum on the left neck, glass stopper on the middle neck, and a nitrogen inlet on the right neck was flush with nitrogen and charged with 1,4-dichlorobenzene (0.7470 g, 5.081 mmole), $Fe(acac)_3$ (0.0948 g, 0.2684 mmole), 30 mL anhydrous THF (with inhibitor), and 1.70 mL of NMP. The whole apparatus was maintained under N_2 atmosphere throughout the duration of the reaction. The flask was immersed in an ice bath and the solution of decylmagnesium bromide (9.52 mL, 6.468 mmole) was immediately added from the storage flask within one minute via syringe. This caused a color change from red to dark brown. The ice bath was removed and the resulting mixture was stirred for 7-10 minutes, then diluted with 13.5 mL of Et_2O, and carefully quenched by addition of 20 mL of 1 M HCl. The mixture was transferred into a separatory funnel (the flask was rinsed with Et_2O), and the aqueous phase was separated and extracted with 13.5 mL of Et_2O. The combined organic phases were washed with 20 mL of saturated $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated by rotary evaporation, which resulted in a crude, red product.

Results and Discussion

Analyses of all reaction mixtures were performed with TLC, FT-IR, ^{1}H NMR, and GC-FID. As described in the experimental section, the extracted product mixtures were evaporated via rotary evaporation to an oil residue and then purified through a one-inch, silica gel column. Multiple fractions were collected. The first two fractions collected the rinse with cyclohexane. Fractions 3 through 6 were where the majority of the product was found; therefore, these fractions were analyzed.

Results for Fürstner Method

It was first important to note GC peak retention times of standards as well for alcohols produced by ordinary Grignard reactions that were likely formed during the cross-coupling (Table 1).

Standards	Retention Time (min)
Decane	2.595
4-chlorobenzaldehyde	3.661
4-chlorobenzaldehyde dimethyl acetal	5.156
4-chloro-2-fluorobenzaldehyde	2.439
4-chloro-2-fluorobenzaldehyde dimethyl acetal	4.016

Table 1. List of standards and their retention times.

The first cross-coupling reaction that was carried out was between decylmagnesium bromide and 4-chlorobenzaldehyde. The IR spectrum showed peaks at 3356.21 cm^{-1} (-OH Group), a peak at 2920.51 cm^{-1} (sp[3]C-H), and a peak at 1449.78 (aromatic ring). The ^{1}H NMR showed a singlet peak at 7.235 ppm (aromatic region), a broad peak at 1.402 ppm (-CH$_2$), and a distorted triplet at 0.832 ppm (-CH$_3$). The GC-FID results showed 4 major peak retention times (Table 2).

Retention Time (min.)	Corresponding Standards
2.556	Decene
2.607	Decane
10.814	--------------------
11.921	--------------------

Table 2. GC-FID analysis for the cross-coupling reaction between decylmagnesium bromide and 4-chlorobenzaldehyde obtained from fraction 4. The corresponding standards section correlates to matches in retention times between compounds found in the coupling reaction and that of known standards.

The late-eluting peaks at 10.814 min. and 11.921 min. (the most product present in the fraction) suggested that coupling occurred; however, the IR chromatogram showed no evidence of a strong carbonyl peak. Instead, a broad –OH peak was observed, which suggested that the alkyl Grignard attacked the carbonyl instead of displacing the chlorine.

To further prove that this side reaction occurred, a straightforward Grignard reaction was done to produce the suspected alcohol as a control. A 1:1 ratio of Grignard reagent and 4-

chlorobenzaldehyde was used in this experiment. Since no Fe(acac)$_3$ and NMP was used during this reaction, it was certain that the Grignard would react with the carbonyl. The IR spectrum showed peaks at 3331.75 cm^{-1} (-OH Group), a peak at 2853.78 cm^{-1} (sp^{3}C-H), and at 1466.09 (aromatic ring). The ^{1}H NMR showed chemical shifts at 7.244 ppm (aromatic region); a triplet centered at 4.596 ppm; 1.060 ppm (-CH$_2$ in the decyl chain); and 0.839 ppm (terminal carbon at the end of decyl chain). The GC-FID results showed 3 major peak retention times (Table 3).

Retention Time (min.)	Standards
2.561	Decene
2.612	Decane
11.925	**Alcohol Product**

Table 3. GC-FID analysis of Grignard reaction used as a control.

The most dominant product, presumably the alcohol obtained from a Grignard reaction had a retention peak time of 11.925 minutes. This peak retention time closely matches the retention time of the decylmagnesium bromide/4-chlorobenzaldehyde cross-coupling reaction. It was then concluded that the major product of the cross-coupling reaction between decylmagnesium bromide and 4-chlorobenzaldehyde was indeed the alcohol product (Figure 3). The peak at 10.814 min. also suggested that the coupling product may have been achieved; however, due to the majority of the Grignard reagent attacking the carbonyl, the coupling reaction wasn't effective and efficient enough in synthesizing the target molecule.
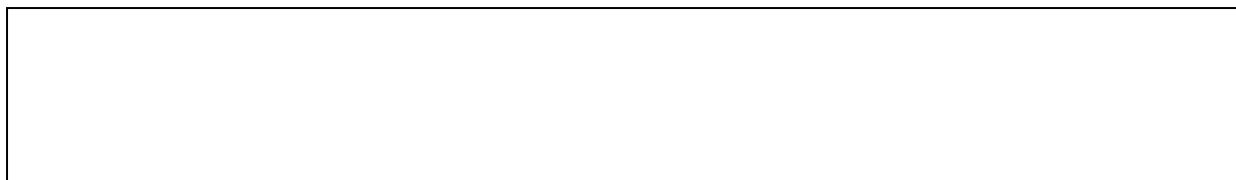
Figure 3. Results of cross-coupling reaction between decylmagnesium bromide and 4-chlorobenzaldehyde.

Due to the reactivity of the Grignard with the carbonyl on the aldehyde, it was then imperative to perform the cross-coupling reaction between decylmagnesium bromide and 4-chlorobenzaldehyde dimethyl acetal. The IR spectrum of the reaction product showed a peak at 2924.06 cm^{-1} (sp^{3}C-H), a peak at 1709.33 cm^{-1} (C=O), and a peak at 1466.58 cm^{-1} (aromatic ring). The ^{1}H NMR showed peaks at the following chemical shifts: singlet at 9.927 ppm (aldehyde), 7.309 ppm (aromatic region), small singlet 5.692 ppm (H connected to the C connected to the aryl ring), strong singlet at 3.257 ppm (-CH$_3$ groups of the acetal), and at 1.215 ppm (-CH$_2$ as part of the long decyl chain). Most significantly, there was a faint triplet at about 1.8 ppm. This meant that the decyl chain was connected to the aryl ring. This triplet represents the H's on the carbon connected to the aryl ring. The GC-FID results showed 5 major peak retention times (Table 4).

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Retention Time (min.)	Standards
2.610	Decane
3.665	4-chlorobenzaldehyde
5.141	4-chlorobenzaldehyde dimethyl acetal
10.813	----------------------
10.965	----------------------

Table 4. GC-FID results for the cross-coupling reaction between decylmagnesium bromide and 4-chlorobenzaldehyde dimethyl acetal obtained from fraction 3.

Decane was the most dominant peak in the fraction. Furthermore, both 4-chlorobenzaldehyde and 4-chlorobenzaldehyde dimethyl acetal were present in the fraction as well, the latter having the more dominant peak. The 4-chlorobenzaldehyde was present because of unreacted starting material being quenched with acid, which deprotected the dimethyl acetal into the corresponding aldehyde, thus giving rise to the 4-chlorobenzaldehyde peak. Along with the two different peaks corresponding to both the starting material and its corresponding aldehyde, there are two late-eluting peaks, suggesting that some coupling did occur in the reaction. It was presumed that these two late-eluting peaks were the coupling product with the dimethyl acetal still protecting the aldehyde or the aldehyde itself. This was the result of the coupled product being partly deprotected to its corresponding aldehyde during the quenching of the Grignard with 1 M HCl. Though coupling did occur, it was not the major product of the reaction since the majority of the products in the reaction were both 4-chlorobenzaldehyde and 4-chlorobenzaldehyde dimethyl acetal.

After these two coupling reactions, it was necessary to modify certain conditions for the experimental procedures just to experiment and see if the desired product may be achieved. One modification was done was the 4-chlorobenzaldehyde/decylmagnesium bromide coupling reaction. The previous coupling reaction used excess Grignard (about 120% Grignard) to ensure all the starting aryl chloride was used in the reaction. In this variation, the 4-chlorobenzaldehyde was used in excess and the percent of Grignard used was 80%.

The product IR spectrum showed peaks at 3400.81 cm^{-1} (-OH), 2924.49 cm^{-1} (-sp^{3}C-H), 1709.39 cm^{-1} (C=O), and 1596.12 cm^{-1} & 1488.90 cm^{-1} (aromatic ring). The ^{1}H NMR showed peaks at the following chemical shifts: singlet at 9.979 ppm (aldehyde); 7.902 ppm, 7.774 ppm, 7.585 ppm, 7.925 ppm (aromatic region); a faint triplet at 4.544 ppm (benzylic carbon); a very faint triplet at about 2.050 (CH$_2$ connected to aryl ring); and at 1.284 ppm (-CH$_2$ as part of the long decyl chain). GC-FID results are listed in Table 5.

| Retention Time (min.)	Standards
2.503	Decene
2.555	Decane
3.638	4-chlorobenzaldehyde
10.815	-----------------------
11.925	**Alcohol Product**

Table 5. GC-FID results for the cross-coupling reaction with altered experimental conditions between decylmagnesium bromide and 4-chlorobenzaldehyde obtained from fraction 4.

The dominant peak for this reaction was the late-eluting peak at 11.925 minutes. As in the previous coupling reaction with these two reactants, a majority of the Grignard attacked the carbonyl carbon, which resulted in the same late-eluting retention time peak as previously seen in the original decylmagenisum bromide/4-chlorobenzaldehyde reaction. In addition, the use of excess starting material translated to unreacted aryl chloride as seen by the early-eluting peak in the chromatogram results. There was some coupling product (10.815 min.), but the amount present in fraction 4 was negligible.

      The other modification implemented was the with 4-chlorobenzaldehyde dimethyl acetal/decylmagnesium bromide coupling reaction. After the addition of the Grignard reagent to the starting aryl chloride in ice, the solution was warmed to about 50°C to 60°C for a period of 30 minutes under reflux to drive the reaction to see if this method promoted the coupling. Through GC-FID analysis, the retention times showed that the majority of components found in each of the fractions obtained and analyzed (fractions 4-7) were the unreacted dimethyl acetal and its corresponding aldehyde. More importantly, there was little or no coupling at all for this type of reaction, making this method impractical.

      A cross-coupling reaction between decylmagnesium bromide and 4-chloroacetophenone was also performed and yielded the same results as with the 4-chlorobenzaldehyde – the Grignard reagent attacked the carbonyl instead of displacing the chlorine (Figure 4).
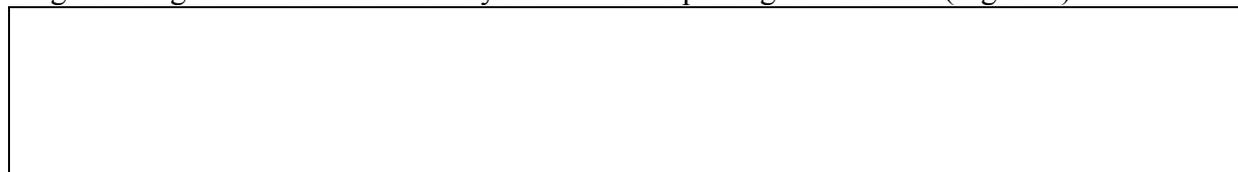
Figure 4. Results of cross-coupling reaction between decylmagnesium bromide and 4-chloroacetophenone.

      Both the aldehyde and ketone function groups serve as moderate electron withdrawing groups. However, through these experiments, it was determined that the Grignard reaction with the carbonyl is more favorable and faster than the desired cross-coupling reaction.

Cross-Coupling Reaction Between 4-chloro-2-fluorobenzaldehyde dimethyl acetal and 1-bromodecane
   It was then necessary to attempt the Fürstner method again with the knowledge that a fluorine group *ortho* to the benzaldehyde on the aryl ring may help to promote the cross-coupling. The preparation of 4-chloro-2-fluorobenzaldehyde dimethyl acetal was successfully achieved and identified through IR, NMR, and GC-FID analysis.

The IR spectrum of the protected aryl ring showed dominant peaks at 2935.69 cm^{-1} (-sp^{3}C-H) and 1611.87 cm^{-1} & 1487.01 cm^{-1} (aromatic ring). The ^{1}H NMR showed peaks at the following chemical shifts: 7.638 ppm, 7.478 ppm, 7.360 ppm, 7.154 ppm, and 6.986 ppm (aromatic region); a singlet at 5.532 ppm (H connected to the C of the dimethyl acetal connected to the aryl ring); and a strong singlet at 3.330 ppm (6 H's connected to the two C's representing the two methyl groups connected to the acetal). GC-FID results showed a major retention time peak at 4.016 minutes, which was the protected product.

The actual cross-coupling reaction between the prepared dimethyl acetal and the Grignard reagent was also successfully done. The IR spectrum of fraction 4 showed peaks at 2925.52 cm^{-1} (-sp^{3}C-H), and 1611.84 cm^{-1} & 1487.01 cm^{-1} (aromatic ring). More importantly, the ^{1}H NMR showed peaks at the following chemical shifts labeled in figure 5: 7.447 ppm, 7.195 ppm, 7.018 ppm, 6.790 ppm (C); a singlet at 5.577 ppm (E); a strong singlet at 3.372 ppm (D); a triplet at 2.794 ppm, 2.595 ppm, 2.483 ppm (B); a broad peak at 1.272 ppm (-CH$_2$ as part of the long decyl chain); and a peak at 0.891 ppm (A). The GC-FID chromatogram is shown in Graph 1 and the major retention time peaks are listed in Table 6.

Retention Time (min.)	Standards
1.901	Decane
3.967	4-chloro-2-fluorobenzaldehyde dimethyl acetal
10.756	**Coupled Product**

Table 6. GC-FID results for the cross-coupling reaction between decylmagnesium bromide and 4-chloro-2-fluorobenzaldehyde dimethyl acetal obtained from fraction 4.
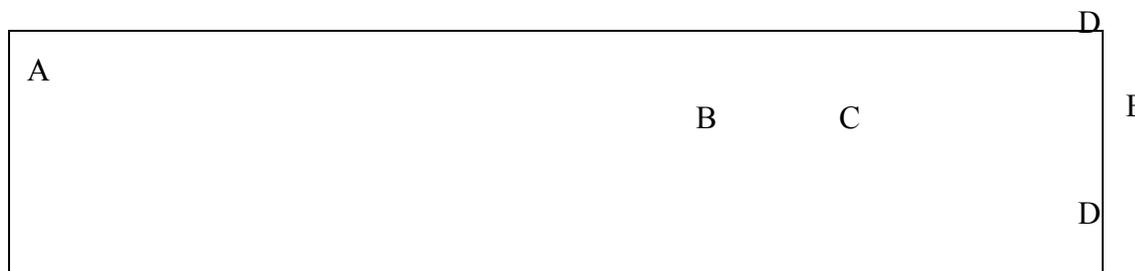
Figure 5. Structure of 4-decyl-2-fluorobenzaldehyde dimethyl acetal with labeled NMR chemical shifts.

A.

B.

C.

Graph 1. GC-FID results of the cross-coupling reaction between decylmagnesium bromide and 4-chloro-2-fluorobenzaldehyde dimethyl acetal. A) GC of 4-chloro-2-fluorobenzaldehyde dimethyl acetal. B) GC of decane. C) GC of fraction 4. The peak at 10.756 min. is presumably the target compound, 4-decyl-2-fluorobenzaldehyde dimethyl acetal.

By having the fluorine atom attached *ortho* to the dimethyl acetal, electron density was delocalized to both the dimethyl acetal and the fluorine, making the carbon attached to the chlorine even more electrophilic. This electron withdrawing allows the coupling to occur more efficiently.

Results for Cahiez Method

Cross-Coupling Reaction Between 1-bromodecane and 4-(benzaldehyde dimethyl acetal) magnesium bromide
After flash chromatography, liquid product was obtained in fractions 24 through 27 and analyzed. The IR spectrum of fraction 24 showed peaks at 2918.21 cm^{-1} (-sp^{3}C-H), 2729.18 cm^{-1} (aldehyde), 1704.75 cm^{-1} (C=O), and 1606.45 cm^{-1} & 1465.77 cm^{-1} (aromatic ring). The ^{1}H NMR showed peaks at the following chemical shifts: singlet at 9.985 ppm (aldehyde); 7.889 ppm, 7.751 ppm, 7.408 ppm, 7.080 ppm (aromatic region); a singlet at 3.343 ppm (3 H's connected to the C on the dimethyl acetal); a triplet at about 2.804 ppm, 2.698 ppm, 2.583 ppm, (benzylic H's of decyl chain); and at 1.279 ppm (-CH$_2$ as part of the long decyl chain). The GC-FID results showed one major retention time peak at 10.990 minutes, which was the coupled product.
The Cahiez method showed that coupling did occur; however, the yield was low. It was also established that one major product of the reaction was 4,4'-biphenyldicarboxaldehyde and/or the dimethyl acetal still attached to the biphenyl compound (Figure 6). This was due to

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unreacted 4-bromobenzaldehyde dimethyl acetal which had reacted with the Grignard, 4-(benzaldehyde dimethyl acetal) magnesium bromide, to form the biphenyl compound during the preparation of the Grignard reagent.

+

Figure 6. Self-coupling between 4-(benzaldehyde dimethyl acetal) magnesium bromide and 4-bromobenzaldehyde dimethyl acetal.

The formation of these biphenyl compounds thus compromised the yield of the coupled product, which made the Cahiez method impractical for the synthesis of the target compound. Also, this method was less practical since a dfferent aryl Grignard reagent must be prepared prior to each coupling reaction. In addition, the Grignard reagent preparation is not compatible with many other functional groups on the ring.

Reactions with Halogen-Substituted Aryl Chlorides and Decylmagnesium Bromide
    Through the research, cross-coupling reactions were also attempted between decylmagnesium bromide and different aryl rings that contained a second halogen atom along with the Cl to be substituted. Cross-coupling reactions were done with 1-chloro-3-fluorobenzene, 1-bromo-4-chlorobenzene, and 1,4-dichlorobenzene (Table 7).

Compound Name	Structure
1-chloro-3-fluorobenzene	
1-bromo-4-chlorobenzene	
1,4-dichlorobenzene	

Table 7.

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The cross-coupling reaction between decylmagnesium bromide and 1-chloro-3-fluorobenzene promoted the coupling the most, which suggested that an electron withdrawing substituent, such as fluorine, is needed for the nucleophilic Grignard to react with the electrophilic carbon and displace the chlorine.

The results for the reaction with 1-bromo-4-chlorobenzene provided results that were inconclusive. Some coupling may have occurred, but there were also other retention time peaks present when analyzed through GC-FID and these could not be identified.

Finally, the results for the reaction with 1,4-dichlorobenzene showed that some coupling did occur primarily through GC-FID and NMR analysis; however there was still some starting material present in the collected fractions.

Through these experiments, it was determined that promotion of the coupling depends on the halogen substituent and its electron withdrawing capabilities. Since fluorine is a very electronegative atom, electron density is pulled toward the fluorine atom, making the carbon connected to the chlorine partially positive. This partially positive carbon is then susceptible to nucleophilic attack of the Grignard, allowing the coupling to occur. Chlorine was also electron-withdrawing enough for the coupling to occur; however, there was still some starting material present, suggesting that coupling is not as effective as coupling reaction between decylmagnsium bromide and 1-chloro-3-fluorobenzene. As for the bromine substituent, more analysis is needed for an explanation.

In addition, the location of the electron-withdrawing group on the ring may have been important for the coupling to occur. Since the fluorine was located *meta-* to the chlorine, this may have allowed the coupling to occur more efficiently. More research needs to be done to determine whether the position of electron-withdrawing halogen subsituents on the ring, relative to the chlorine being substituted, affects the cross-coupling between these two molecules.

Conclusion

Through the use of the cheap and nonhygroscopic iron catalyst Fe(acac)$_3$, a comparison of cross-coupling reactions was made. The target compound, 4-decyl -2-fluorobenzlaldehyde, was nearly achieved. All that needs to be done is to deprotect the dimethyl acetal to get the corresponding aldehyde, thus finally obtaining the target compound. More importantly, what was also found was that the fluorine attached to the aryl ring is an important aspect in terms of promoting the coupling. Fluorine's electronegative character makes it an electron-withdrawing group, which appears to be necessary for the coupling reaction. By having a fluorine *ortho* to the benzaldehyde dimethyl acetal, this makes the carbon connected to the chlorine even more eletrophilic because electron density is being pulled toward both the fluorine and the dimethyl acetal, which permits the coupling to occur in good yield.

In addition, using different halogen substituents on the ring promoted the coupling to occur. The more electron-withdrawing halogen, the more likely the coupling occurs effectively and in great yield. More research can be done to study these halogens and their specific nature in promoting the cross-coupling reaction. More research must also be done on the use of certain protecting groups for the aldehyde on the ring. It may be possible that by having a protecting group that has a powerful electron-withdrawing capability will promote the coupling even further.

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