

Name: Anh Ngo

Iron-Catalyzed Direct Aryl-Alkyl Cross-coupling Reactions

Researcher: Anh Ngo

Advisor: Dr. Phalguni Ghosh

Date: 12/18/2014

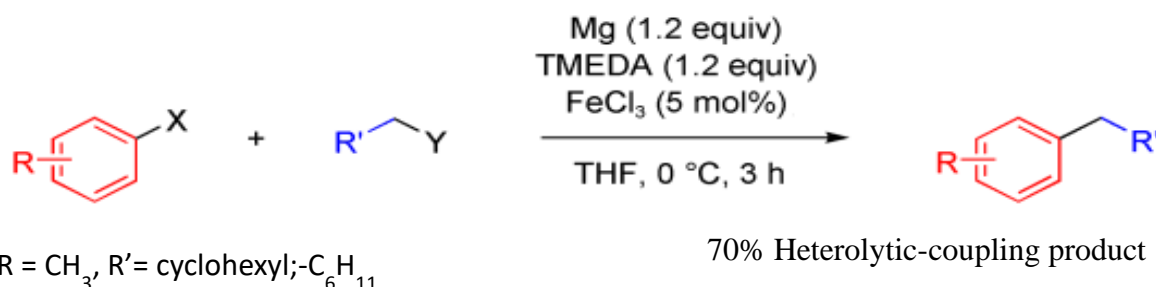
Department of Natural Sciences, Middlesex County College, Edison, NJ 08818

Abstract:

This research was done to replicate the recent advancement of the use of “Inorganic Grignard reagent” for aryl-alkyl cross-coupling reaction developed by Professor Alois Fürstner during the past decade. The experiment was attempted twice following the procedure which written in the article but did not success. Therefore, the Grignard reagent was decided to form first before proceeding with the catalyst, Fe(acac)₃/ TMEDA. As the result, extracted the Bitolyl as a major product instead of cross-coupling aryl-alkyl product and an unknown product as minor.

Introduction

This study was done to reproduce the progression of the use of “Inorganic Grignard reagent” in aryl-alkyl cross-coupling reaction. The general Grignard reactions are not catalyzed (mean 1 to 1). However, here the large quantities of hard-to handle and sensitive Grignard reagent which had been developed by professor Alois Fürstner group used the various Iron compounds called “Inorganic Grignard reagent” [Fe(MgX)₂] as a catalyst to form similar type of C-C bond formation reaction.

Reported by Axel Jacobi von Wangelin et.al, **Angew. Chem. Int. Ed** 2009,48, 607-610

Experimental

Name: Anh Ngo

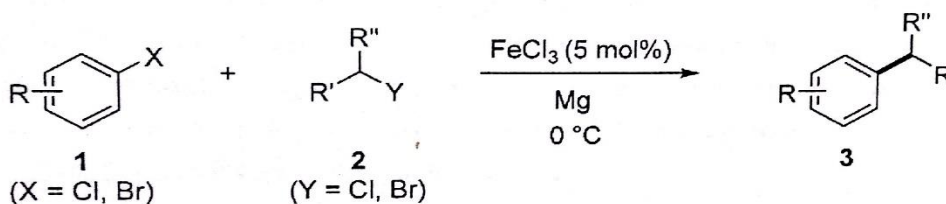
Intrumentaion: NMR were recorded using Nanalysis (Model NMReady 60). IR spectra were recorded using Perkin Elmer Infrared Spectrophotometer (Motel 710 B Serial 132636)

1. First reaction:

Could use $\text{Fe}(\text{acac})_3$ instead of FeCl_3 to get the same formation.

Reported by Axel Jacobi von Wangelin et.el, **Angew. Chem. Int. Ed** 2009,48, 607-610.

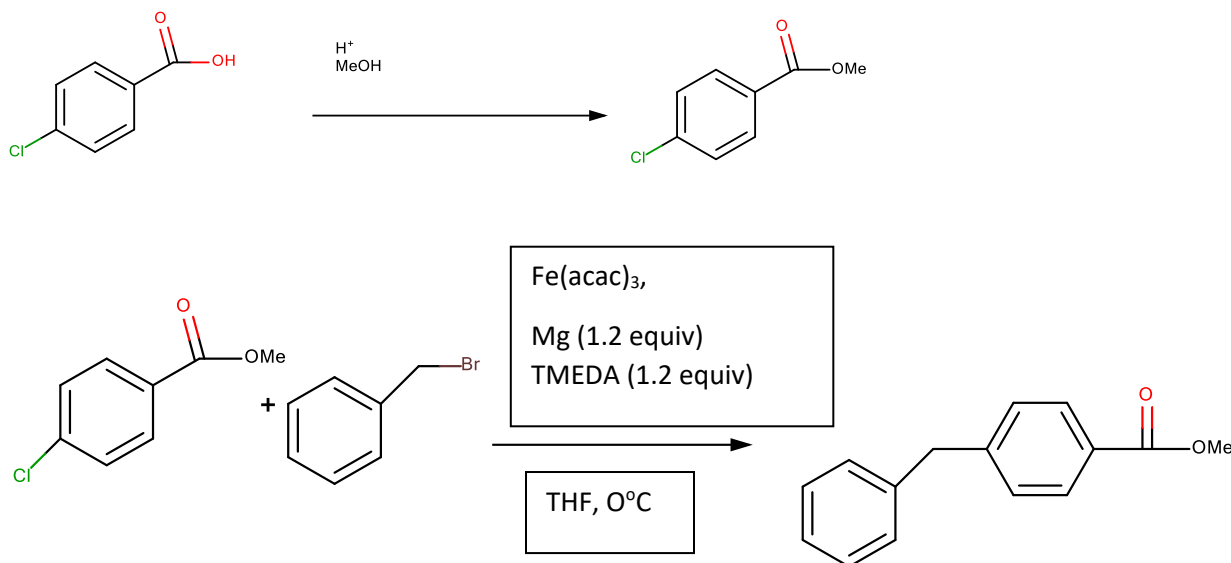
Attempted the following reaction using Iron(acetolactone)₃ complex as a catalyst in dried THF.



Ran the experiment following the procedure which written on the article for 2 times but **the reaction did not show any coupling products**. Therefore, the Grignard reagent was decided to form first before proceeding with the catalyst, $\text{Fe}(\text{acac})_3$ / TMEDA.

2. Second reaction:

Used $\text{Fe}(\text{acac})_3$ instead of FeCl_3 and Benzyl bromide instead long chain alkyl.



Procedure:

Name: Anh Ngo

1. First reaction:

THF was freshly distilled over sodium with 47 mg of benzophenone. The colorless color of solvent turned blue after few hours which mean a dried THF solvent was distilled of.

Note: No air, no moisture, no O₂ allowed during the procedure.

Magnesium (1.2mmol, 0.0333g) was added into a 3 necks round bottom flask then dry THF solvent (4mL) was added. After added Fe(acac)₃ (0.05mmole, 0.0177g), solution turned into orange brown solution. Added Tolybromide (0.1932g) and TMEDA (1.2 mmole, 0.181 mL). Stirred the solution for 45 minutes, solution's color turned to dark green. Then added cyclohexylbromide (0.148 mL) and stirred for few hours in water bath (20°C) color turn light yellow.

Saturated with ammonium chloride (NH₄Cl 5ml) and extracted with cyclohexane.

Did filtration, TLC and column chromatography for the mixture products.

2. Second reaction:

Preparation of para-chlorobenzoic acid methyl ester:

2g of 4-chlorobenzoic acid was added into a round bottom flask with 35mL of methanol 99.9% and 2.00mL of H₂SO₄. After stirred solution for few hours, the reaction was completely done. TLC test was done in solvent of 1:4 ethyl acetate: hexan. After filtered and dried the product over Na₂SO₄, extracted a clear oil yellow product. Ran column chromatography and extracted 2 products. Used the rotavap and vacuum to dry the compound then did the NMR test. Got 76% yield of para- chloromethyl benzoate product.

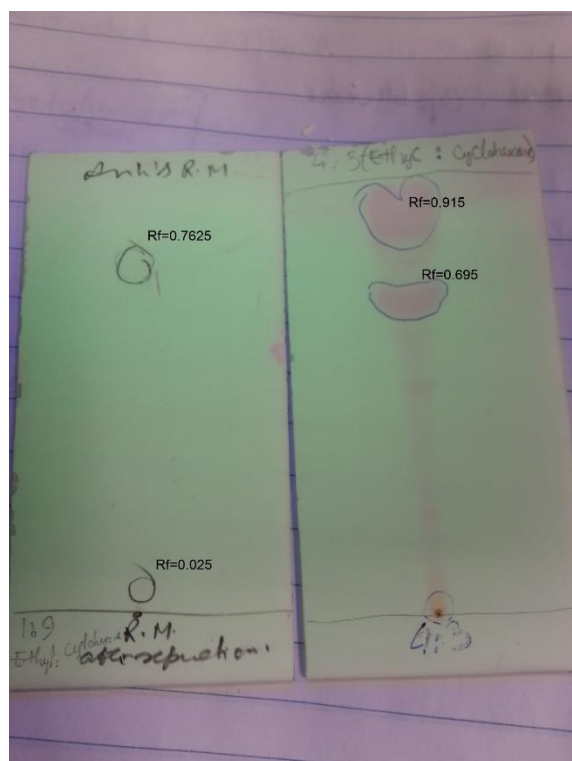
Aryl- alkyl cross-coupling reaction: (page 24)

0.3039g magnesium (12.1 mmol) and THF (20mL) were added into a 3 necks round bottom flask. After added Iodine, colorless color of the solution turned to brown. Added benzyl bromide (0.7184 mL), color of solution turned into oily yellow. Color of solution turned to yellow when ferric acetylacetonate (0.135 g) was added. Added para-chloro methyl benzoate (1.30 g), solution's color turned into brown orange. Diluted it with 20 mL Et₂O and 20mL HCl. Filtrated, washed mixture (30mL NaHCO₃), and dried over Na₂SO₄. Rotary evaporation the compound.

Results and discussion:

TLC:

Name: Anh Ngo



Extracted 2 products by using column chromatography.

1:9 ethyl acetate: cyclohexane (first product)

4:3 ethyl acetate: cyclohexane (second product)

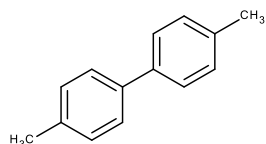
Dried products by rotavap R-3

percent yield:

1st product: 52.87%

2nd product: 24.33%

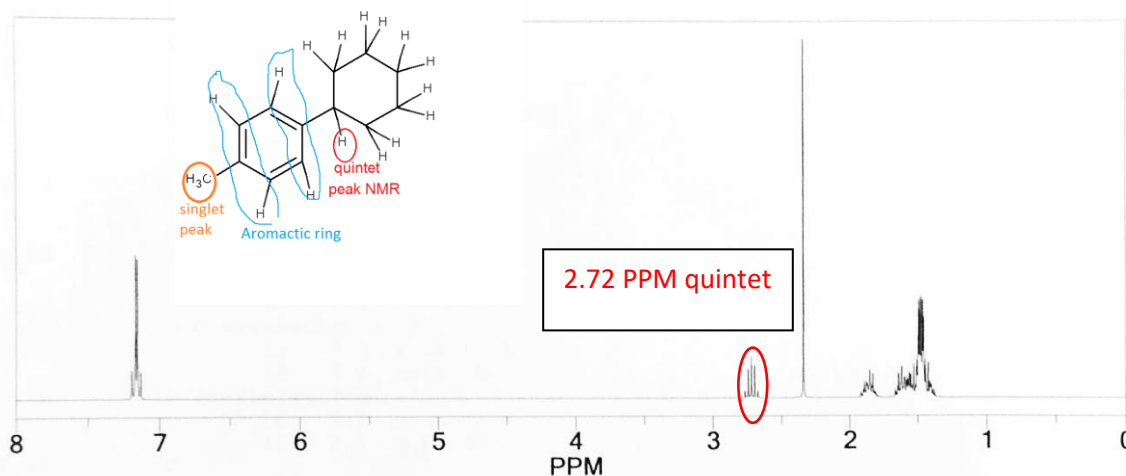
First product: Bitolyl product



Homolytic-coupling product

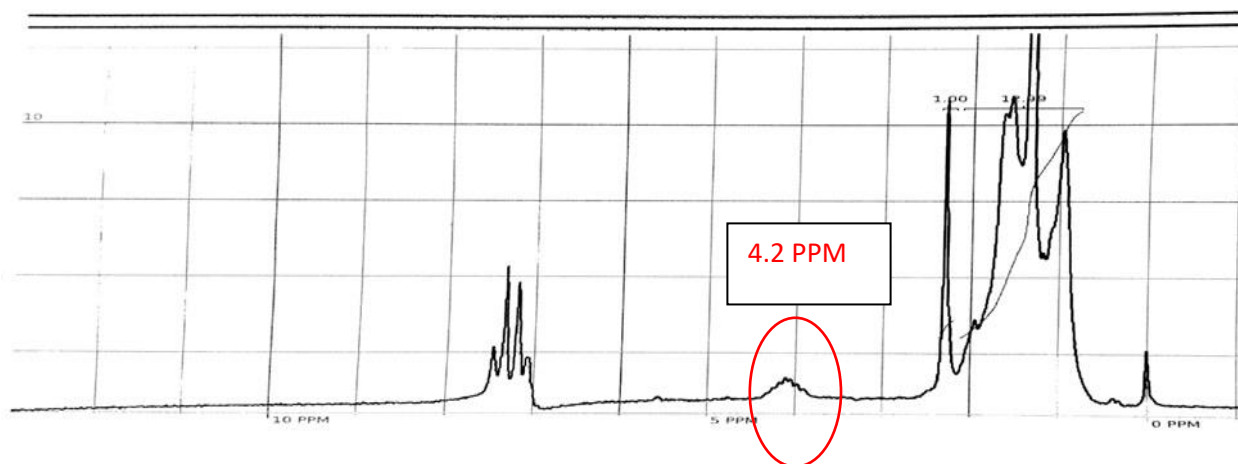
Second product: unknown.

Name: Anh Ngo



Predicted NMR for aryl-alkyl cross-coupling product:

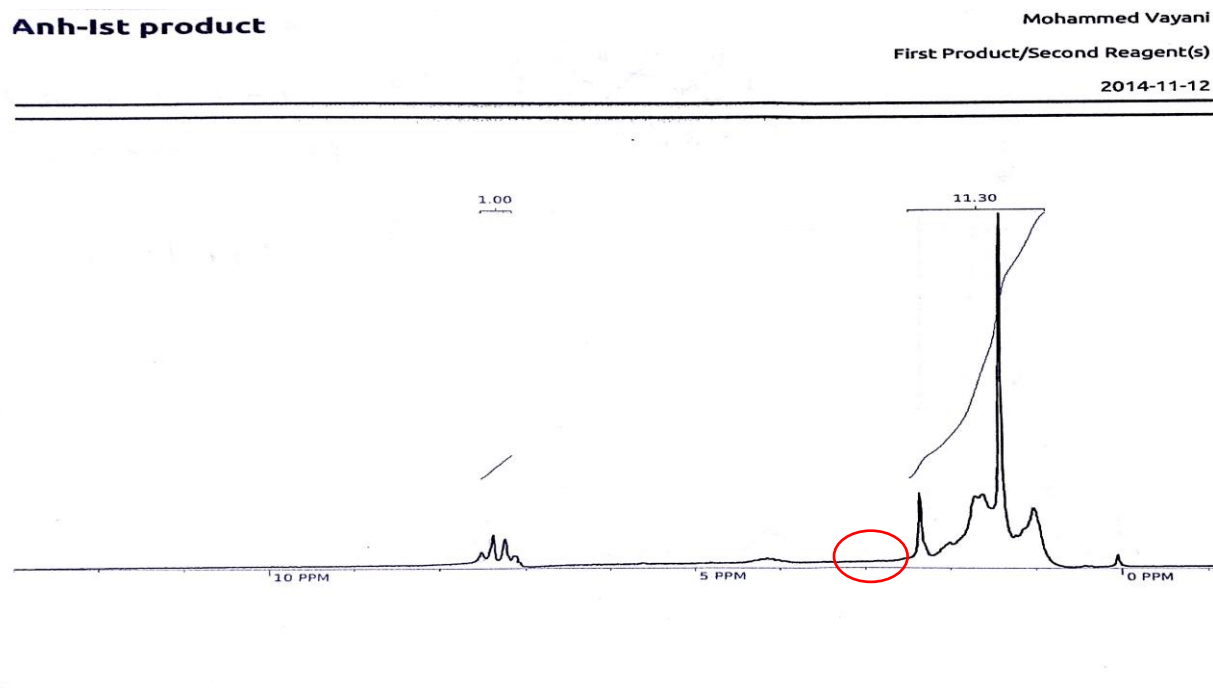
NMR test for 1st product:



All the peaks were there (10 protons and 1 quintet proton) but the NMR the quintet at 4.2 PPM should be at 2.72ppm to compare with the predicted NMR one. The integral ratio did not match. It looks very high when compared to the predicted one. M

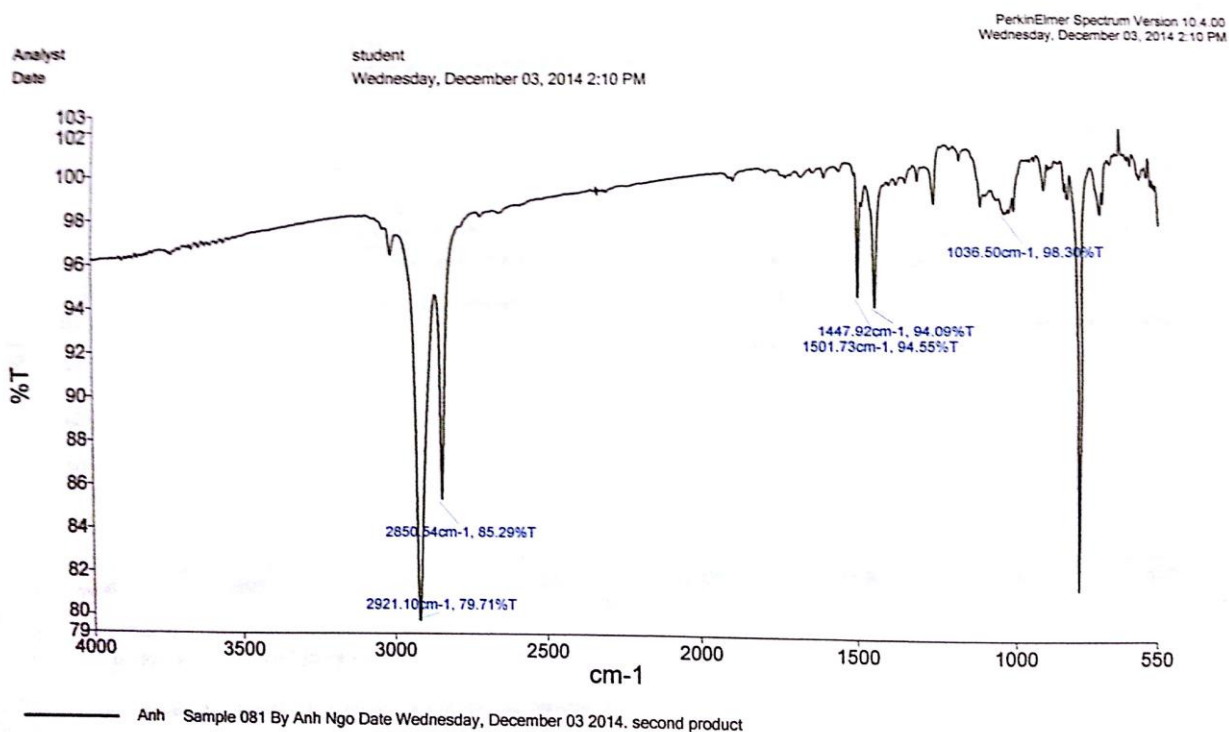
NMR after dry product for several times:

Name: Anh Ngo



There was no quintet peak at 2.72 PPM.

IR of the first product: only show aromatic C=C peak at 1447.92cm^{-1} , and C-H₂ peak 2921.10cm^{-1} - 2850.54cm^{-1}

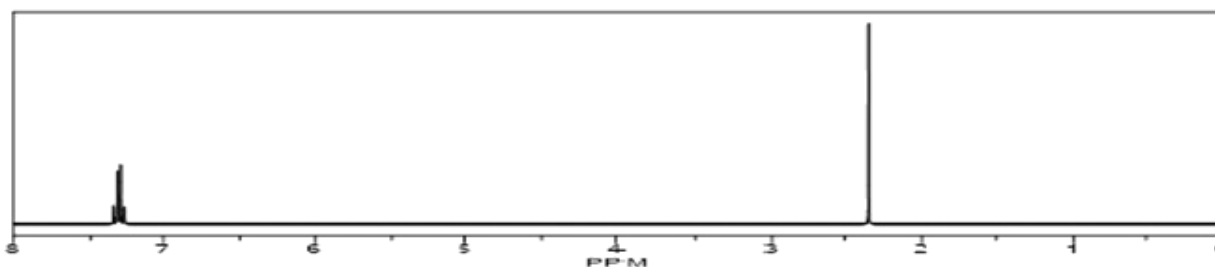
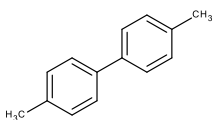


Name: Anh Ngo

After did 2nd Column chromatography to remove solvent impurities.

Solvent 1:9 Ethyl acetate: Pentane

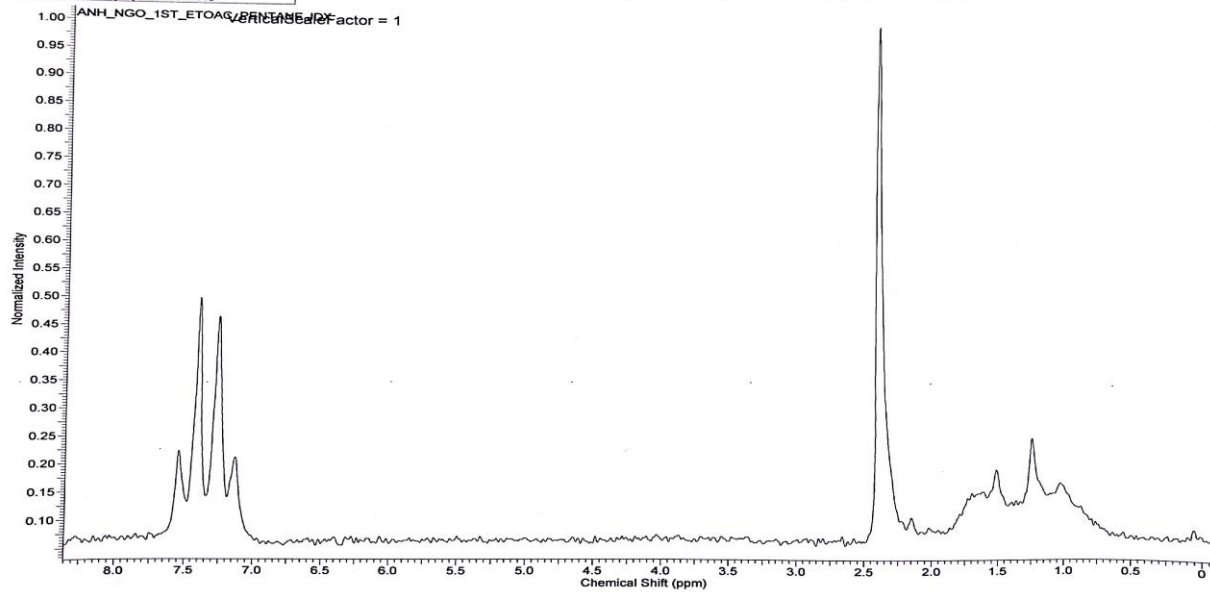
NMR of first product match with Bitolyl predicted NMR: therefore the first product is Bitolyl.



This report was created by ACD/NMR Processor Academic Edition. For more information go to www.acdlabs.com/nmrproc/

12/10/2014 2:26:57 PM

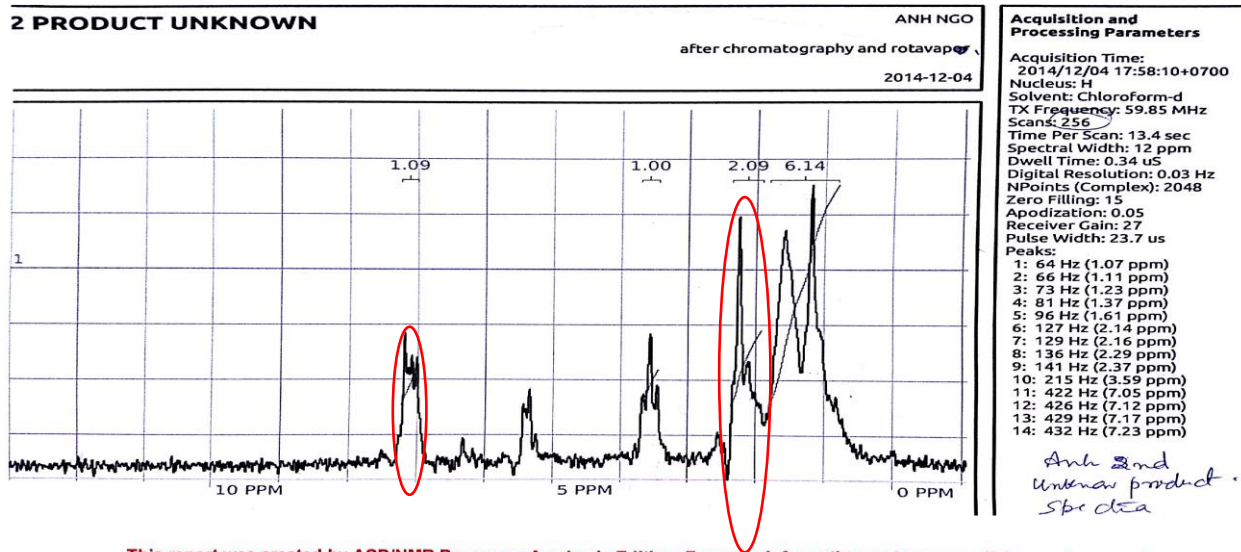
Acquisition Time (sec)	38.6674	Comment	Anh Ngo 1st product Etoac: Pentane jdx	Date	2014/12/03 18:54:47-0700
Date Stamp	2014/12/03 18:54:47-0700	File Name	E:\ANH_NGO_1ST	ETOAC_PENTANE_JDX	
Frequency (MHz)	59.85	Nucleus	1H	Origin	Nanalysis Corp.
Owner	Nanalysis	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	847.43	Original Points Count	32768	Spectrum Offset (Hz)	359.0763



Name: Anh Ngo

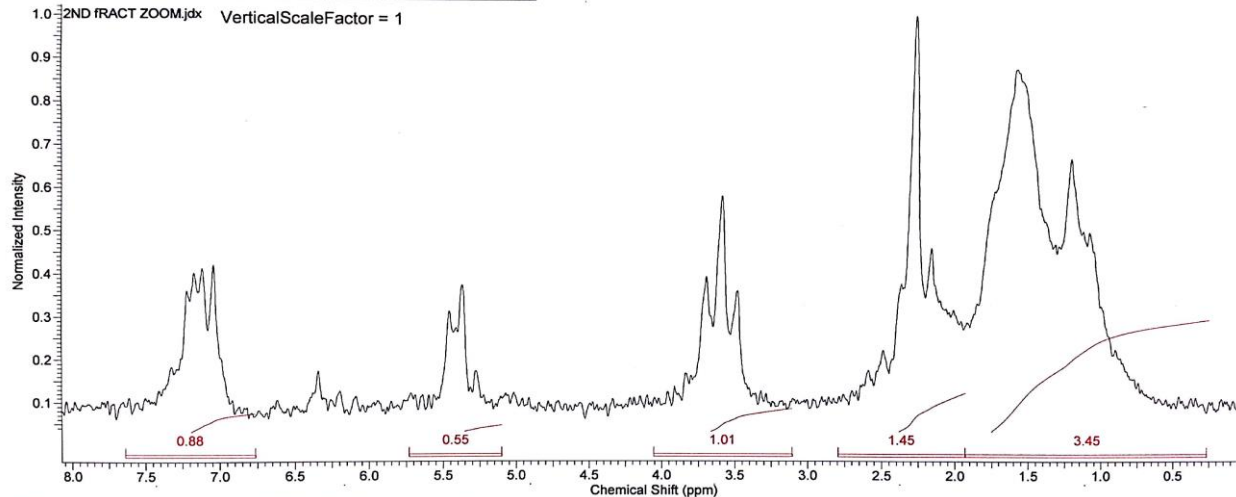
NMR of second product:

NMR showed aromatic peak, methyl peak, a triplet peak at 3.58PPM and triplet peak at 5.5 PPM.



This report was created by ACD/NMR Processor Academic Edition. For more information go to www.acdlabs.com/nmrproc/

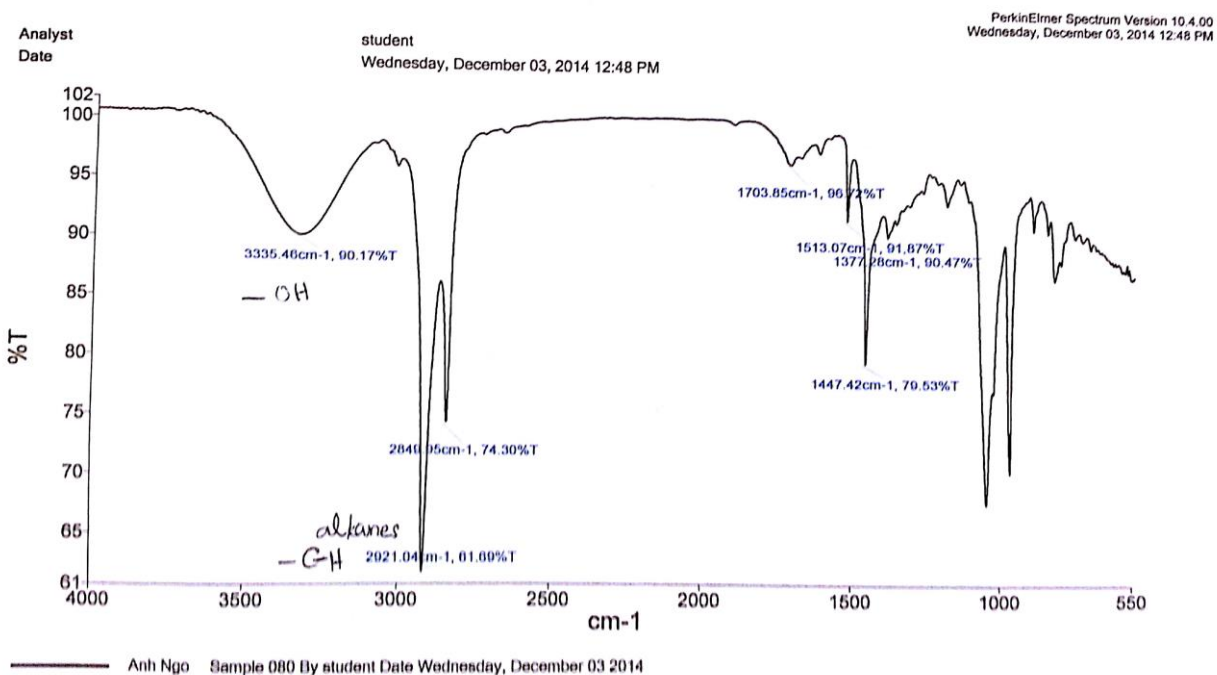
Acquisition Time (sec)	19.3343	Comment	2ND FRACT ZOOM.jdx	Date	2014/12/05 09:11:09 AM
Date Stamp	2014/12/05 09:06:00-0700	File Name	F:\2ND FRACT ZOOM.jdx		
Frequency (MHz)	59.85	Nucleus	1H	Origin	Nanalysis Corp.
Owner	Nanalysis	Points Count	16384	Solvent	CHLOROFORM-d
Spectrum Offset (Hz)	359.0637	Sweep Width (Hz)	847.41	Original Points Count	16384



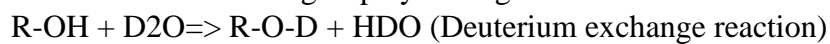
No.	(ppm)	Value	Absolute Value	Non-Negative Value
1	2665 .. 1.930	4.5185471	2.26695337e+3	3.45185471
2	3305 .. 2.791	1.44599009	9.49632141e+2	1.44599009
3	1087 .. 4.051	1.01233160	6.64833435e+2	1.01233160
4	1007 .. 5.730	0.55301851	3.63186554e+2	0.55301851
5	7648 .. 7.630	0.87822562	5.76761414e+2	0.87822562

IR of second product showed -OH peak and alkane-C-H peak

Name: Anh Ngo

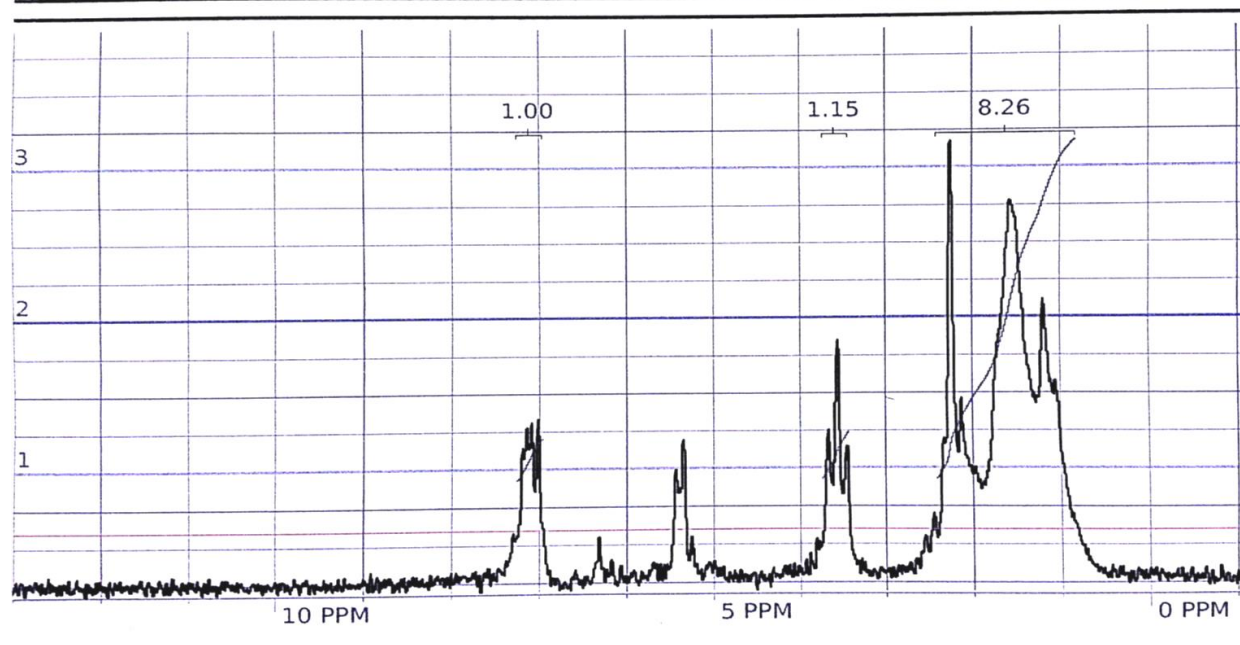


Tried to take out -OH group by adding D₂O:



NMR of second product after adding D₂O: couldn't identify the structure of second product.

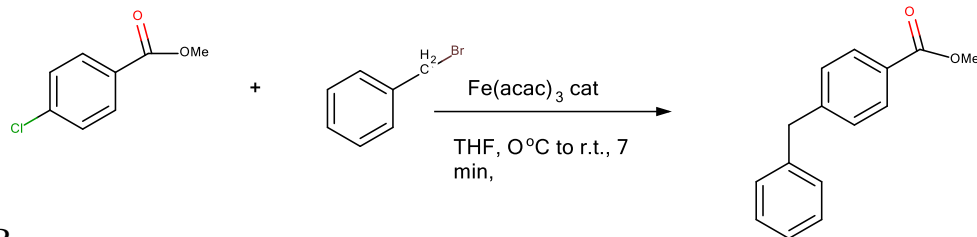
2014-12-05



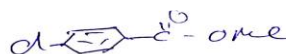
Name: Anh Ngo

3. Second reaction:

Used Fe(acac)₃ instead of FeCl₃ and Benzyl bromide instead long chain alkyl.

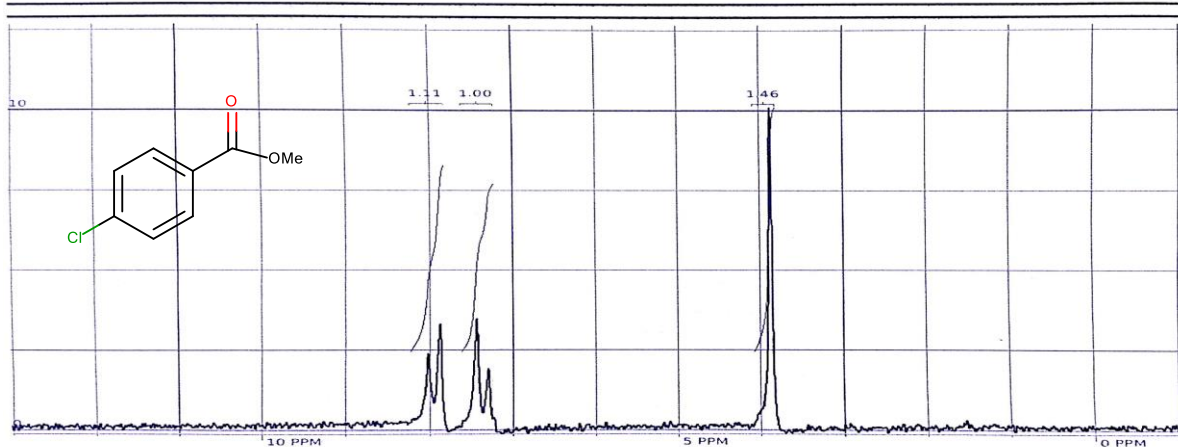


NMR
4-Chlorobenzoic acid methyl ester



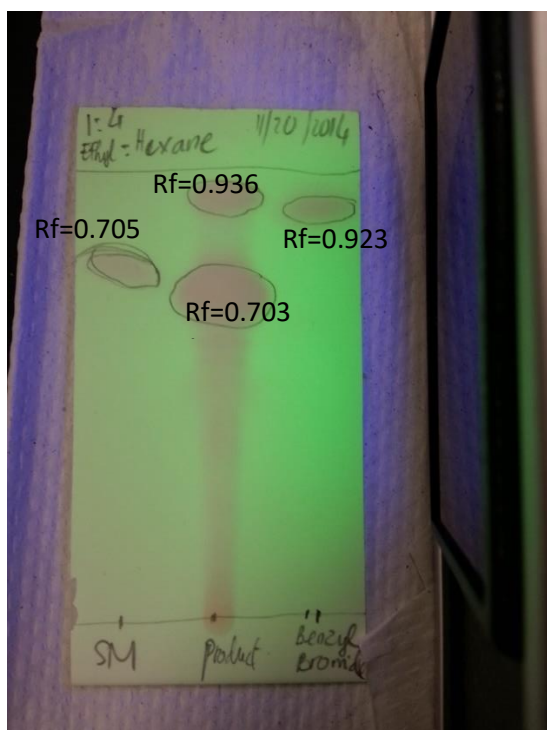
Anh Ngo

2014-11-25

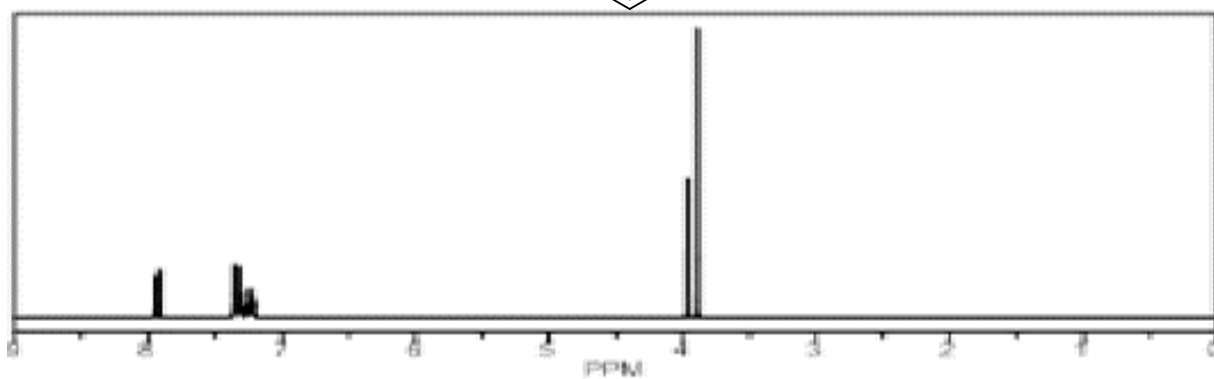
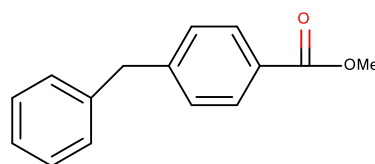


TLC:

Name: Anh Ngo

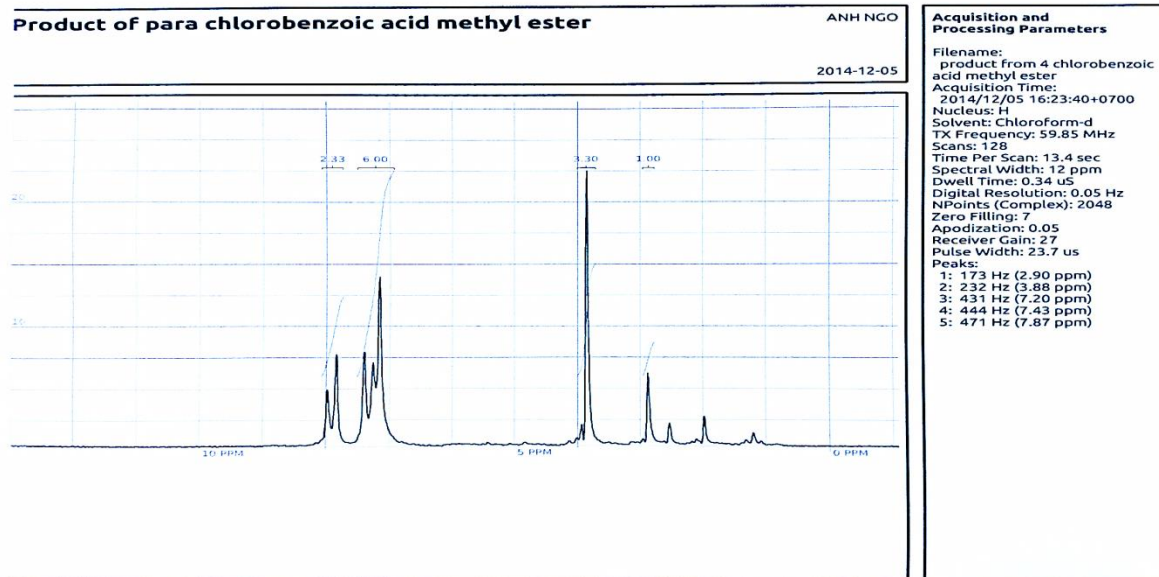


NMR:
predicted NMR for major product:



NMR of product:

Name: Anh Ngo



NMR for the product didn't match with the predicted NMR but match with NMR of the Chlorobenzoic acid methyl ester. So the reaction did not successfully occur.

Conclusion

Extracted Bitolyl as a major product instead of cross-coupling aryl- alkyl product.

Unable to identify the structure of the second product.

Attempted second reaction using the para-Cl-methyl benzoate following the procedure of JACS paper but could not successfully make the reaction going.

Most likely may not be able to generate proper "inorganic Grignard reagent" in MCC laboratory to get the product.

Possible reasons could be either THF is not completely dry or we are unable to reproduce the exact experimental condition, because we did not have the facilities of running the reaction under strictly an aerobic atmosphere.

Acknowledgements

Dr. Phalguni Ghosh

Dr. Steven Rowley

Dr. Brian Lavey

Chairperson: Dr. Parag Muley

Name: Anh Ngo

Dean: David Edward

Bristol-Myers Squibb (for funding this project)

Doug Reardon and Aubry (Chemistry Lab personnel)

Peer Students: Tram Tran, Devin Lubin, Mohammed Vayani

References

- 1 Waldemar Maximilian Czaplak, Matthias Mayer, and Axel Jacobi von Wangelin.

Angew.Chem.Int.Ed. 2009, 48, 607-610

- 2 Alois Fürstner*, Andreas Leitner, Maria Mendez, and Helga Krause.

J.AM.CHEM.SOC.2002, 124, 13856-13983.