ปฏิกิริยาคู่ควบแบบไขว้ที่เร่งปฏิกิริยาด้วยสารเชิงซ้อนเหล็กของสารประกอบเฮไลด์และออร์แกโนแมกนีเซียมรีเอเจนต์

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IRON COMPLEX-CATALYZED CROSS COUPLING OF HALIDE COMPOUNDS AND ORGANOMAGNESIUM REAGENTS

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ศุภสิทธิ์ อัศวเบ็ญจาง : ปฏิกิริยาคู่ควบแบบไขว้ที่เร่งปฏิกิริยาด้วยสารเชิงซ้อนเหล็กของสารประกอบเฮไลด์และออร์แกโนแมกนีเซียมรีเอเจนต์ (IRON COMPLEX-CATALYZED CROSS COUPLING OF HALIDE COMPOUNDS AND ORGANOMAGNESIUM REAGENTS) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ดร.วรินทร ชวศิริ, 69 หน้า.

ได้ศึกษาผลของภาวะในการทำปฏิกิริยาคู่ควบแบบไขว้ของสารประกอบแอลคิลเฮไลด์และเอริลแมกนีเซียมรีเอเจนต์ที่มีสารเชิงซ้อนเหล็กเป็นตัวเร่งปฏิกิริยา พบว่าปัจจัยหลักที่ส่งผลต่อการเกิดผลิตภัณฑ์คู่ควบแบบไขว้คือระบบตัวทำละลาย การใช้โทลูอีนเป็นตัวทำละลายทำให้ได้ปริมาณผลิตภัณฑ์คู่ควบแบบไขว้สูงกว่าตัวทำละลายชนิดอื่น และสามารถละเว้นข้อกำหนดต่างๆในการทำปฏิกิริยาที่มีรายงานมาก่อนหน้า อาทิ การเติมรีเอเจนต์อย่างช้าๆ การใช้สารเติมแต่ง และลิแกนด์ที่ซับซ้อน โดยยังให้ผลได้ผลิตภัณฑ์สูง การใช้ $FeCl_3$ ซึ่งหาได้ง่ายและไม่ซับซ้อนเป็นตัวเร่งปฏิกิริยาภายใต้ภาวะที่เหมาะสมทำให้ได้ผลิตภัณฑ์คู่ควบแบบไขว้สูงถึงร้อยละ 92 จากสารตั้งต้นโบรโมไซโคลเฮกเซน และร้อยละ 76 จากสารตั้งต้นคลอโรไซโคลเฮกเซน จากการศึกษาผลของลิแกนด์พบว่าลิแกนด์ 1,3-ไดคาร์บอนิลที่มีหมู่ให้อิเล็กตรอนส่งผลให้ได้ร้อยละการเปลี่ยนแปลงของสารตั้งต้นคลอโรไซโคลเฮกเซนสูงที่สุด ในกรณีของสารตั้งต้นโบรโมไซโคลเฮกเซนสามารถเกิดการเปลี่ยนแปลงได้อย่างสมบูรณ์ในทุกประเภทลิแกนด์ แต่ลิแกนด์ที่มีหมู่ดึงอิเล็กตรอนส่งผลให้เกิดผลิตภัณฑ์ข้างเคียงปริมาณน้อยที่สุด การใช้ตัวเร่งปฏิกิริยาแบบผสมระหว่าง Fe(dbm-derivative)$_3$ และ $FeCl_3$ พบว่าให้ผลลัพธ์ดีที่สุด โดยปริมาณตัวเร่งปฏิกิริยาที่เหมาะสมคือร้อยละ 2.5 โดยโมลของ Fe(dbm-derivative)$_3$ และร้อยละ 2.5 โดยโมลของ $FeCl_3$ วิธีการนี้ให้ผลได้ของผลิตภัณฑ์จากโบรโมไซโคลเฮกเซนร้อยละ 94 และให้ผลได้ของผลิตภัณฑ์จากคลอโรไซโคลเฮกเซนสูงถึงร้อยละ 85 การศึกษาปฏิกิริยาโดยใช้สารตั้งต้นอื่นๆพบว่าความเกะกะของสารตั้งต้นที่เพิ่มขึ้นส่งผลขัดขวางการเกิดปฏิกิริยา

ภาควิชา เคมี　　　　ลายมือชื่อนิสิต ....

สาขาวิชา เคมี　　　　ลายมือชื่อ อ.ที่ปรึกษาหลัก ....

ปีการศึกษา 2557

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SUPPASITH ASSAWABENJANG: IRON COMPLEX-CATALYZED CROSS COUPLING OF HALIDE COMPOUNDS AND ORGANOMAGNESIUM REAGENTS. ADVISOR: ASST. PROF. WARINTHORN CHAVASIRI, Ph.D., 69 pp.

The effect of reaction conditions in the iron-catalyzed cross-coupling of alkyl halide and arylmagnesium reagents was studied. It was found that a solvent system was the main factor that affected the yield of cross-coupling. Using toluene as a solvent gave higher yield of cross-coupling product than other solvents. The previously reported requirements such as slow addition rate of the reagent, excessive additive, and special ligand could be omitted, while providing high product yield. Under the optimized condition, employing $FeCl_3$ as a very simple iron catalyst gave the yield of cross-coupling product up to 92% for bromocyclohexane substrate and 76% for chlorocyclohexane. In the ligand effect study, the 1,3-dicarbonyl ligand with electron-donating substituent provided the highest %conversion of chlorocyclohexane substrate. In the case of bromocyclohexane, the conversion was complete in all cases of different ligands. However, the ligand with electron-withdrawing group minimized the amount of by-products obtained. Utilizing iron precatalysts combination, containing $Fe(dbm\text{-}derivative)_3$ and $FeCl_3$, showed the best result. The appropriate catalyst loading was 2.5 mol% of $Fe(dbm\text{-}derivative)_3$ and 2.5 mol% of $FeCl_3$. This method gave 94% cross-coupling product yield from bromocyclohexane and 85% from chlorocyclohexane. Other substrates were also employed, the results showed that increasing steric hindrance of substrates could obstruct the reaction.

Department: Chemistry
Field of Study: Chemistry
Academic Year: 2014

Student's Signature ....
Advisor's Signature ....

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LIST OF ABBREVIATIONS

NMR	nuclear magnetic resonance
GC	gas chromatography
IR	infrared
J	coupling constant (NMR)
δ	chemical shift (NMR)
acac	acetylacetonate
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
Tol	toluene
Biph	biphenyl
THF	tetrahydrofuran
Et_2O	diethyl ether
DMSO	dimethyl sulfoxide
Cy	cyclohexyl
dbm	dibenzoylmethane
$CDCl_3$	deuterated chloroform
AST	additional stirring time
AI	addition interval
MB	mass balance
M	molar
mL	milliliter (s)
min	minute (s)
h	hour (s)

CHAPTER I

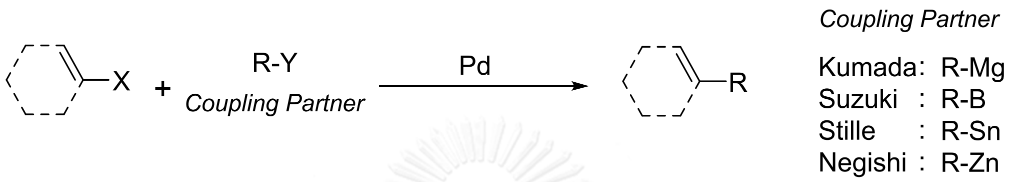
INTRODUCTION

In the world of chemistry, organic synthesis is the way to bring us a new useful organic compound, which mainly contains an array of carbon atoms connecting structure. Carbon-carbon bond formation, catalyzed by transition metal, is one of the most important reactions for organic chemists. The palladium catalyzed cross-coupling reaction is the most prominent, and becomes a basic tool in organic synthesis. It is also widely applied in medicinal and process chemistry. Despite its advantages, there are some drawbacks: the necessary ligands and palladium itself are costly, palladium compounds are regarded as highly toxic and carcinogenic [1], and trace of the palladium catalyst remains in products will be problematic. From the aspect of the environmentally friendly chemistry, 'iron' is a green metal on a spotlight due to its very low toxicity and high abundance on earth. Apart from the advantage of being a green catalyst, iron has a high catalytic reactivity in some certain cases. It promotes cross-coupling reaction to accomplish within 10 minutes of reaction time, as a practical method was demonstrated in Org. Synth. [2].

This thesis will give insight into iron catalyzed C-C coupling reactions, which have the potential to be sustainable, green alternatives to the highly utilized palladium (and nickel) catalyzed reactions. The reaction model that palladium struggles in will be studied in detail. Investigations will be undertaken to gain knowledge about the reactions, and the results will hopefully contribute to further development of new reaction protocols.

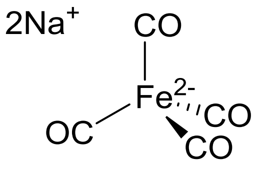
1.1 Well-Known Palladium-Catalyzed Cross-Coupling Reactions

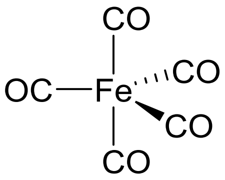
In organic synthesis, the impact of palladium and nickel catalyzed cross coupling reactions can hardly be overstated. They are applied in the synthesis of numerous natural products and biologically active compounds. One of the first catalytic cross-coupling reactions is the Kumada coupling, where a Grignard reagent couples to an organic halide in the presence of palladium or nickel salts. It was reported independently by both the groups of Kumada and Corriu in 1972. Since then this aspect of C-C bond formation has been developed, and resulted in several new coupling reactions such as Suzuki, Stille and Negishi coupling (**Scheme 1.*1***). Three of the most prominent researchers in the field, R. Heck, E. Negishi and A. Suzuki, were awarded the Nobel Prize in 2010 [3].

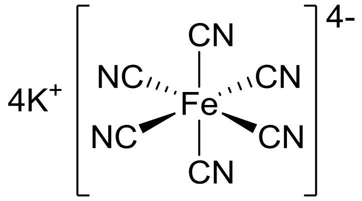


Scheme 1.1 Palladium-catalyzed cross coupling reaction

As the palladium catalyst was popularly studies and utilized in coupling reaction, other metals were also reported to have the catalytic activity in coupling reaction, one of which was iron. Iron is the fourth most abundant element in earth’s crust [4]. Iron, [Ar] $3d^6 4s^2$, exists in a several of oxidation states where the common are +II and +III. Normally, if a Fe(II)-salt exposes to air for some extent of time, it will be oxidized to Fe(III). By the way, some Fe(II) complexes with strong ligand fields are stable. Fe(II) and Fe(III) complexes prefer an octahedral coordination sphere. Fe(0) coordinates five or six electron-accepting ligands, through pi-backbonding, with trigonal bipyramidal or octahedral geometry respectively. While Fe(-II) is normally tetrahedral. Some examples of iron complexes are shown below.







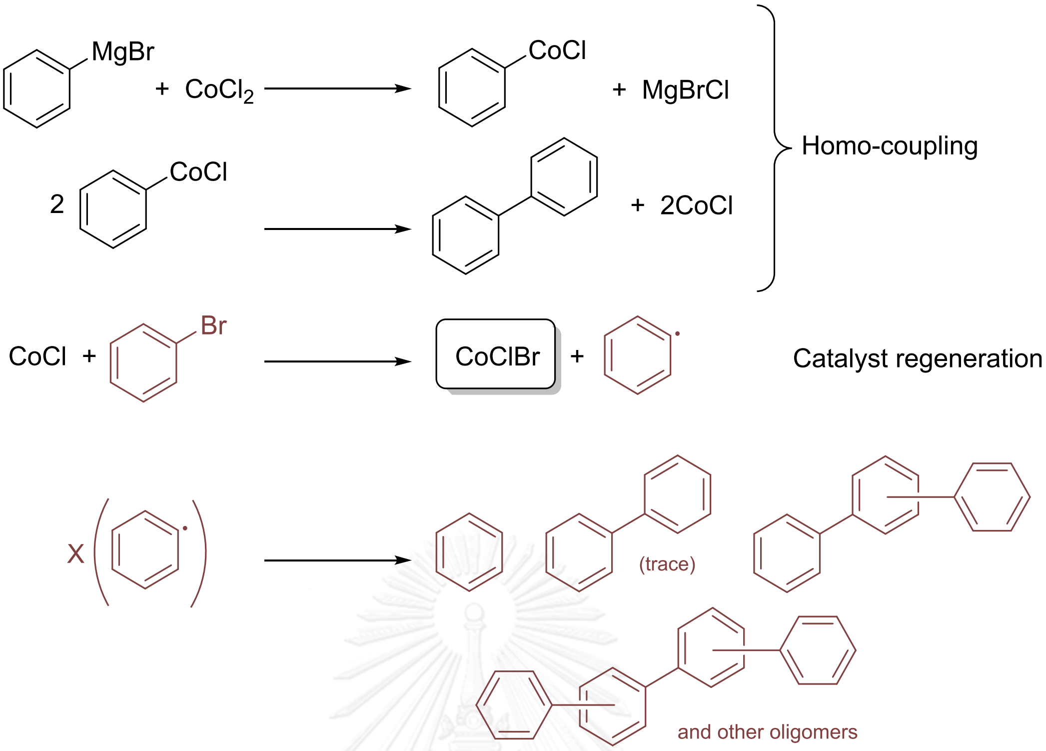
1.2 Literature Reviews on Iron Catalyzed-Coupling Reactions

The first work that can be counted as the exploration of metal catalyzed coupling reaction was in 1941, when Kharasch and coworkers investigated the effect of metal halide on the reaction of aryl Grignard reagents in the presence of organic halide [5]. Before that time it was known that contaminating transition metals in the preparation of aryl Grignard reagent led to a formation of biaryl product. Moreover, up to quantitative yield of biaryl or homo-coupling product was obtained by using a molar equivalent of metal halide in reaction with aryl Grignard reagent.

$$2RMgX + MX_2 \longrightarrow R\text{—}R + 2MgX_2 + M$$

The function of metal halide was known as an electron acceptor that it was reduced while the oxidative dimerization occurred. From the homo-coupling product synthesis point of view, Kharasch showed that metal halide can be used in a catalytic amount by adding an organohalide as an oxidant, for example bromobenzene, 4-bromotoluene, ethyl bromide or isopropyl chloride. In the model reaction, phenylmagnesium bromide was introduced to react with a catalytic amount of $CoCl_2$ in the presence of bromobenzene at almost molar-equivalent to the phenyl Grignard. The reaction was exothermic that diethyl ether was refluxing upon the addition of phenylmagnesium bromide. The analysis of products by distillation showed a good yield of biphenyl, up to 86%, along with other by-products as shown in **Scheme 1.2**.

The resulting biphenyl is quite exclusively from the organomagnesium part due to the fact that other halides can be used instead of phenyl bromide without notably decreasing the yield of biphenyl. The phenyl radical that forms in the reaction is responsible for disproportionation and oligomerization to high boiling materials. The source of that reactive phenyl radical is bromobenzene since no such high boiling materials are found when it is replaced by aliphatic alkyl halides. In the experiment shown above, 85% of bromobenzene was converted approximately to 20% benzene, 5% biphenyl, and 60% higher boiling materials.



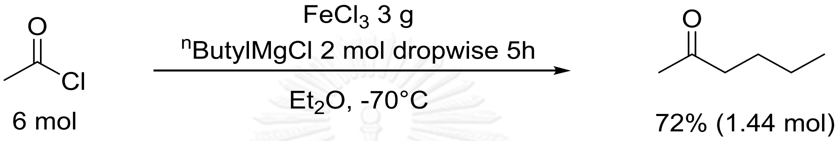
Scheme 1.2 Kharasch’s proposed mechanism of aryl Grignard homo-coupling

By the way, 3-10 mol% of **$FeCl_3$** could also give an excellent yield of biaryl coupling when reacting aryl Grignard in the presence of an organic halide, preferably a bromide one. $CuCl_2$ and $CrCl_3$ are ineffective, while $MnCl_2$ has a little effect.

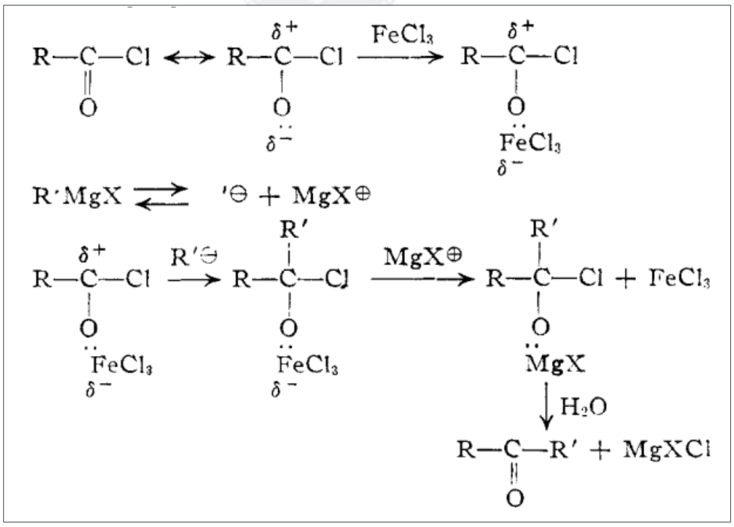
There was no mention of cross-coupling between Grignard reagent and organohalides in this work. So, anyone going to carry out this type of reaction, especially when desires a cross-coupling product, should be aware of the possibility that organic radical species from organohalide can involve in the reaction. It was presumed that the metal halide acted as an oxidation-reduction catalyst which was reduced to a lower oxidation state by Grignard reagent and oxidized back to its original (or higher) oxidation state by organic halides.

In 1953, Cook et al. reported the reaction of Grignard reagent with acyl halide to produce ketone in good yield [6]. The conditions of temperature, catalyst and molar ratios of reactants were studied. The results showed that it was possible to prepare straight chain and highly branched aliphatic ketones in good yields, with only small amounts of reduction products formed.

Anhydrous metallic halides were tested for catalytic activity in the reaction of acetyl chloride and n-butylmagnesium chloride to produce 2-hexanone. Ferric chloride was found to be superior to aluminum chloride, cuprous chloride, zinc chloride, manganese chloride, cobaltous chloride and magnesium bromide, the yields ranging from 13% with $CoCl_2$ to 47% with $FeCl_3$ at 15°C. The condition that provided maximum yield of straight chain ketone was shown below.



The product formed in this reaction was not a free ketone but a salt of magnesium halide and it needed an aqueous work-up to decompose into corresponding ketone. The mechanism was unclear but the author did not observe an evidence of radical species, so a polar mechanism was proposed, **Scheme 1.3**.

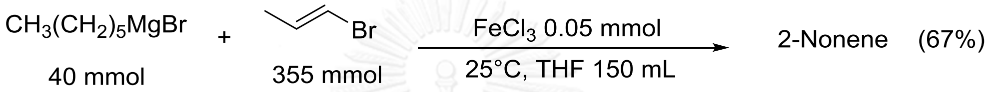


Scheme 1.3 Proposed mechanism for the iron-catalyzed ketone synthesis in 1953

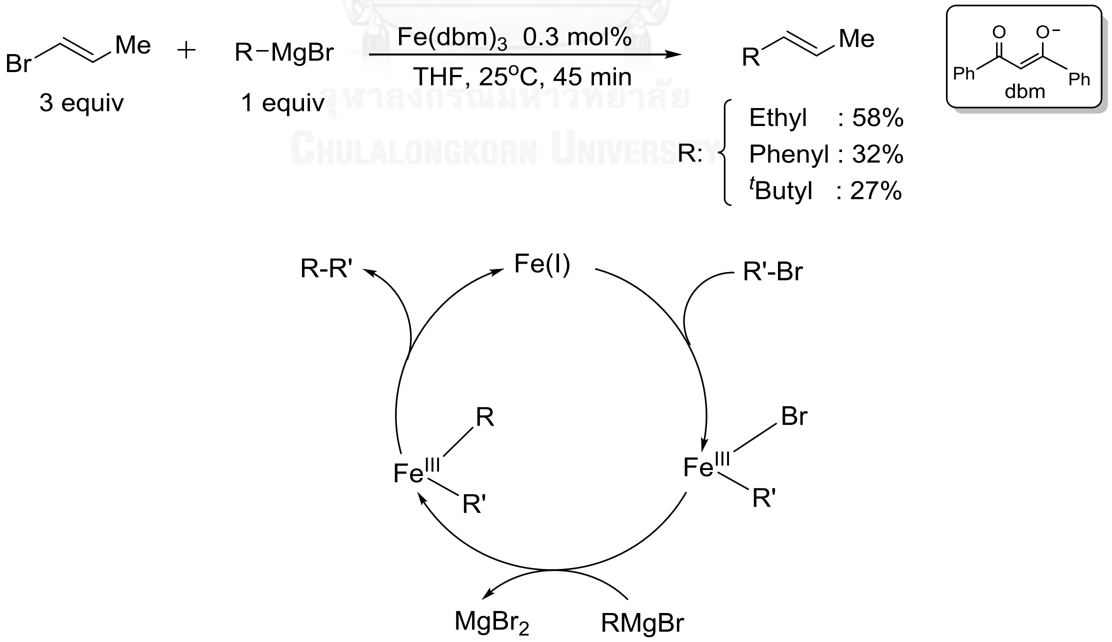
From this literature, it was proposed that ferric chloride acted as Lewis acid and the reaction went through an ionic mechanism as shown in **Scheme 1.3**.

However, the more plausible mechanism is the radical pathway involving single electron transfer (SET) and radical recombination rather than an ionic pathway. Many works supported this idea came up later [7].

In 1971, Kochi and Tamura reported a work of vinylation of Grignard reagents which was a breakthrough in iron-catalyzed cross-coupling reaction [8]. The coupling partners were alkenyl bromide and alkyl Grignard reagent. The rate of product formation was first order in alkenyl bromide but inversely related to Grignard reagent; higher concentration of Grignard reagent lowered the rate. So, the alkenyl bromide was used in excess to get higher vinylation product.

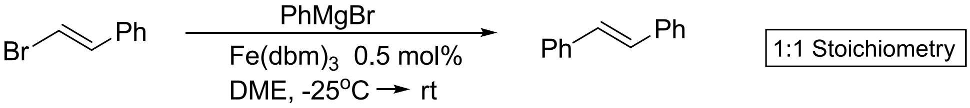


In 1975, Kochi and Neumann reported the same reaction but also studied the effect of catalyst aging with Grignard reagent [9]. An irreversible deactivation of the catalytic species was observed. Only iron tris(dibenzoylmethane) ($Fe(dbm)_3$) that was able to stand the aging time without deleterious effect; %conversion of Grignard reagent was still high. The catalytic cycle was also proposed, **Scheme 1.4**.

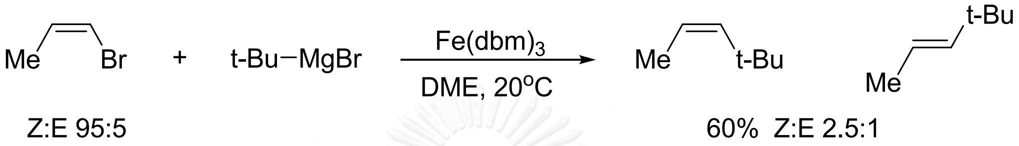


Scheme 1.4 Kochi's Fe(I)-Fe(III) cycle

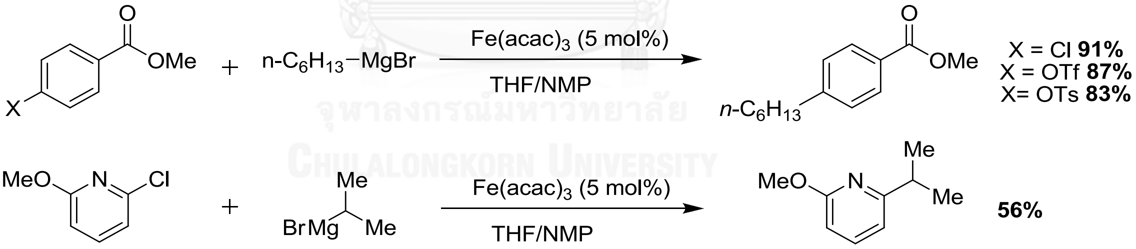
In 1983, Molander and co-workers improved the Kochi's method, alkenyl bromide was able to be used in stoichiometric amount [10].

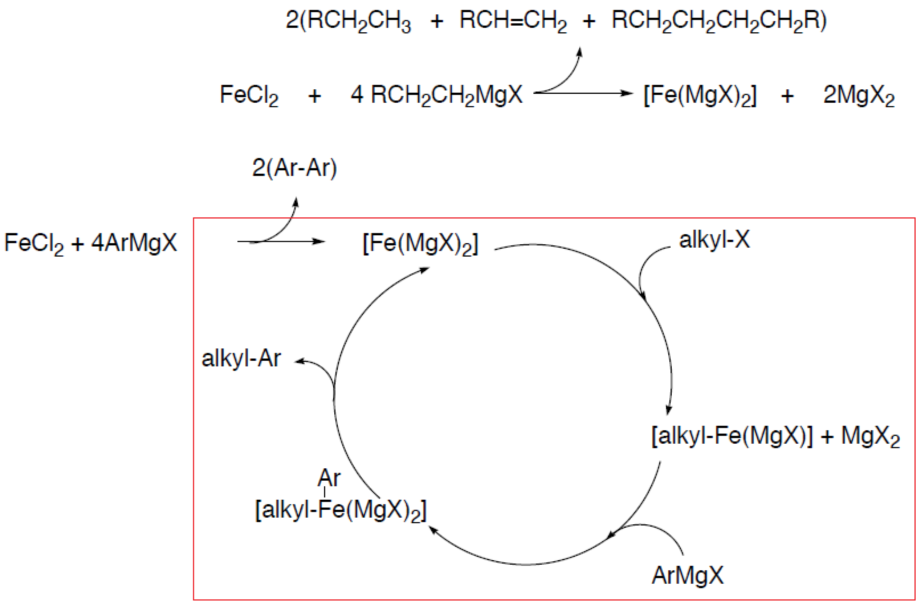


Isomerization of Z-alkene to E/Z mixture in coupling product was observed. The bulky Grignard reagent was also used.



In 2002, Fürstner et al. reported a practical route for cross-coupling of aryl halide or pseudohalide with alkyl Grignard reagent [11]. The key condition was the solvent mixture between THF and some NMP (*N*-methyl-2-pyrrolidone), while the iron precatalyst was ferric acetylacetonate. The catalytic cycle was proposed (**Scheme 1.5**).

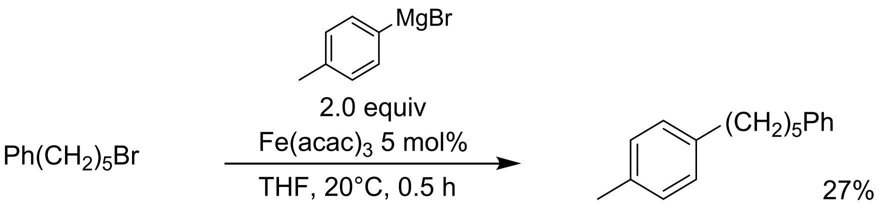




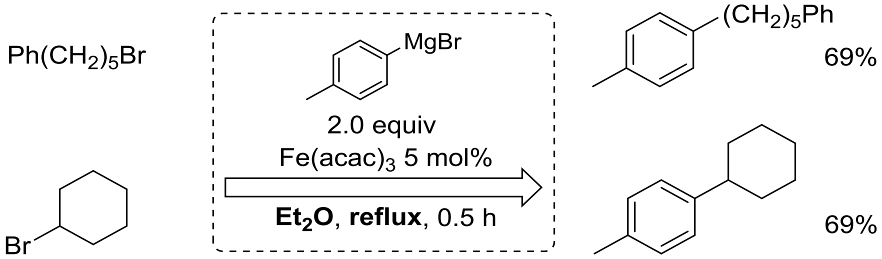
Scheme 1.5 Fürstner's proposed Fe(-II)/Fe(0) catalytic cycle [11]

Fürstner has placed a practical method for coupling alkyl Grignard reagent with activated chloroarene or non-activated arene with triflate as a leaving group. The informative synthesis procedure for the following reaction was shown in Org Synth [2].

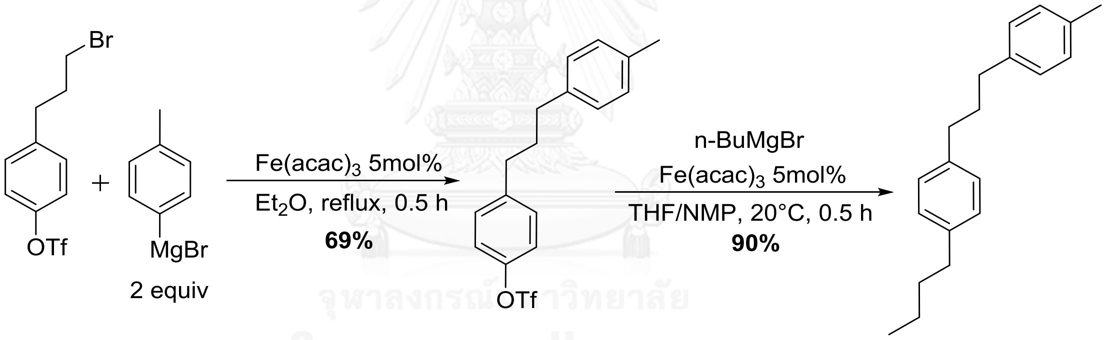
In 2004, there were three distinct works related to iron-catalyzed cross coupling of alkyl halide with aryl Grignard reagent. The first work was from Japan. Hayashi and Nagano showed that solvent choice considerably affected the cross-coupling reaction of alkyl halide [12]. The coupling product yield was low and a higher amount of by-product was obtained when using THF or THF/NMP.



While the condition that gave maximum yield of cross-coupling was refluxing diethyl ether with 2 equivalents of Grignard reagent.

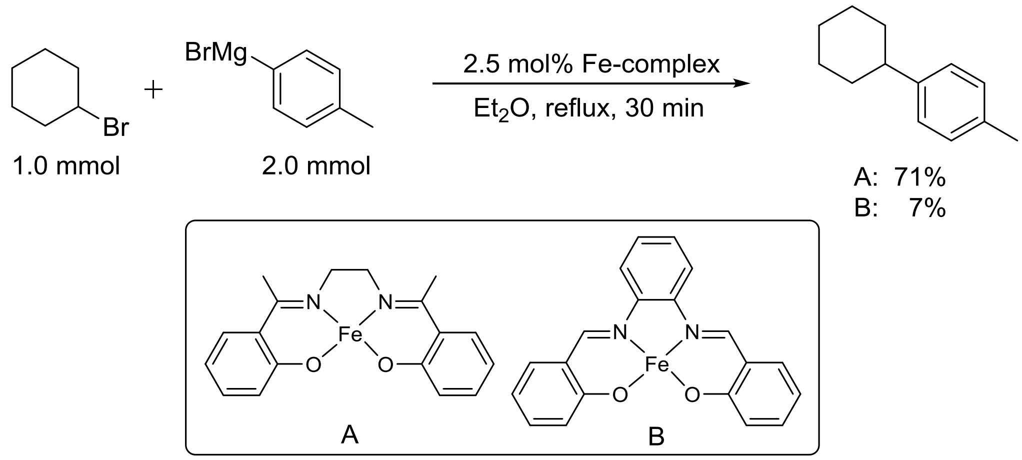


Moreover, an example of selective cross-coupling catalyzed by iron was reported (**Scheme 1.6**). The reaction condition, the solvent choice indeed, will determine which functional group will undergo coupling reaction. Both conditions used the same ferric acetylacetonate as an iron source but differed in solvent type. In diethyl ether, aryl triflate was able to stand the condition while primary alkyl bromide smoothly underwent the reaction. To coupling the triflate functional group, THF with NMP was used. This efficient method for coupling aryl triflate with primary alkyl Grignard reagent was reported by Alois Furstner [11].



Scheme 1.6 Hayashi’s selective iron-catalyzed cross-coupling [12]

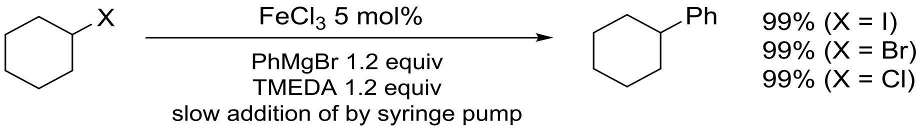
In the same year, a coherent idea of alkyl halide cross coupling was reported by Bedford’s group [13]. They studied the catalytic activity of various Fe(III)-salen complexes . The appropriate condition was under reflux of diethyl ether, which was similar to Hayashi’s work. The reaction examples are shown in **Scheme 1.7**.



Scheme 1.7 Bedford’s reaction model containing iron-salen as a catalyst [13]

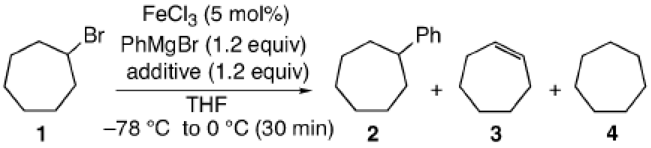
It was claimed that iron(III) salen and related complexes were able to catalyze cross-coupling of primary and secondary alkyl halide substrates with aryl Grignard reagents under mild and simple conditions.

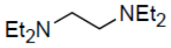
It can be seen that the yield of cross-coupling product of alkyl halide mentioned above is far from quantitative, due to the formation of by-products. However, in the same year, Nakamura reported the reaction procedure that could suppress the elimination and reduction products [14]. The reported yield was not less than quantitative even with chloro substrate. However, the reaction must be conducted with an unusual method; the Grignard reagent was mixed with the same molar amount of additive, and must be added to the reaction mixture in a very slow rate, through a syringe pump. Some reported results were shown below.

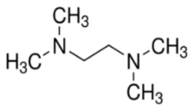


In this work, it was demonstrated that TMEDA was the most suitable additive due to the result in **Table 1.1**.

Table 1.1 The experiment set that showed that effect of TMEDA additive [14]



entry	additive	% yield				
		2	**3**	**4**	**1**	Ph–Ph
1	none	5	79	0	4	6
2	Et_3N (1.2 equiv)	3	78	0	11	5
3	*N*-methyl morpholine (1.2 equiv)	8	72	0	4	5
4	DABCO (1.2 equiv)	20	2	0	75	3
5	TMEDA (1.2 equiv)	71	19	3	trace	10
6	 (1.2 equiv)	23	48	1	11	9
7	NMP (1.2 equiv)	15	3	trace	79	4
8	PPh_3 (0.1 equiv)	6	70	trace	6	7
9	dppe (0.05 equiv)	4	8	0	81	8

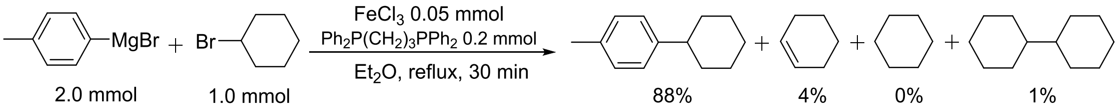


N,N,N′,N′-Tetramethylethylenediamine
(TMEDA)

Other additives including phosphine ligands and other iron catalysts (FeF_3, $Fe(BF_4)_3$, $Fe(acac)_3$, $FeCl_2$, $Fe(CO)_5$) were not effective.

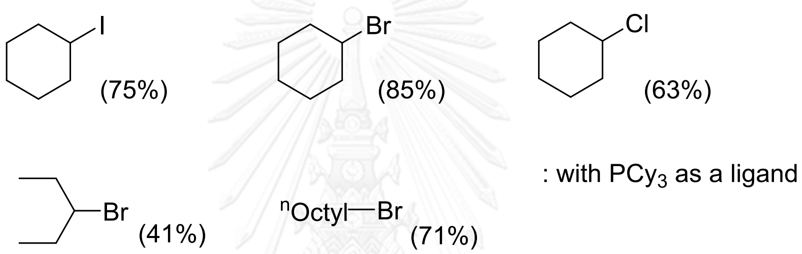
In 2006 Bedford et al. reported the work studied the effect of various types of ligands including phosphine, phosphite, arsine, and carbene [15]. It was claimed that the Nakamura method's drawbacks were surmountable; including a requirement of greater than stoichiometric amount of amine, a very slow addition of Grignard/amine mixture via syringe pump, and cooling the reaction mixture to low temperature. According to his previous work [16], amine additives can be used in catalytic amount, the reactions can be conducted at elevated temperatures, and slow addition of the Grignard reagent is unnecessary. This observation was considerably contrast to Nakamura's work, suggesting a different catalytic manifolds are operative. Even the precatalyst composition was apparently similar.

In this work, varying phosphine, phosphite, and arsine showed a range of cross-coupling yield (27 - 91%) but did not seem to have a trend from electronic or steric perspectives. An example of the reaction was as following.

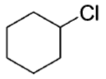
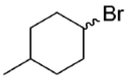


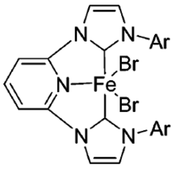
All of the reactions turned very dark brown to black upon addition of the Grignard. The steric bulk of Grignard reagent obviously affected the reaction. When o-tolylmagnesium bromide was used, the coupling product was obtained in much lower amount. It is interesting that all the results among this reaction model, utilizing phosphine phosphite and arsine ligand, showed no alkane by-product at all. The major by-product was the alkene of the alkyl halide substrate. A lower yield was obtained when the substrate was chloride or iodide. An open-chain secondary alkyl bromide gave a lower conversion to cross-coupling product, even worse than the primary alkyl bromide substrates.

Conversion to coupling product in different substrate



In variation of N-heterocyclic carbene ligands, the conversion to coupling product was generally high, comparable to the best of the previous phosphine ligand. Two carbene ligands were selected for testing the reactivity with some alkyl halides, the conversion to cross-coupling product was reported as follows.

Alkyl Halide	Conversion (%) with catalyst A	Conversion (%) with catalyst $FeCl_3$ + B
	-	73
	89	81
Br-ⁿoctyl	71	-



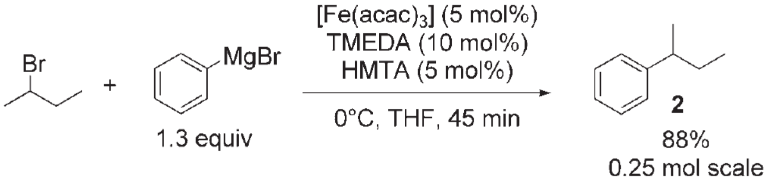
Ar = C_6H_3-2,6-$^iPr_2$

(A)

(B)

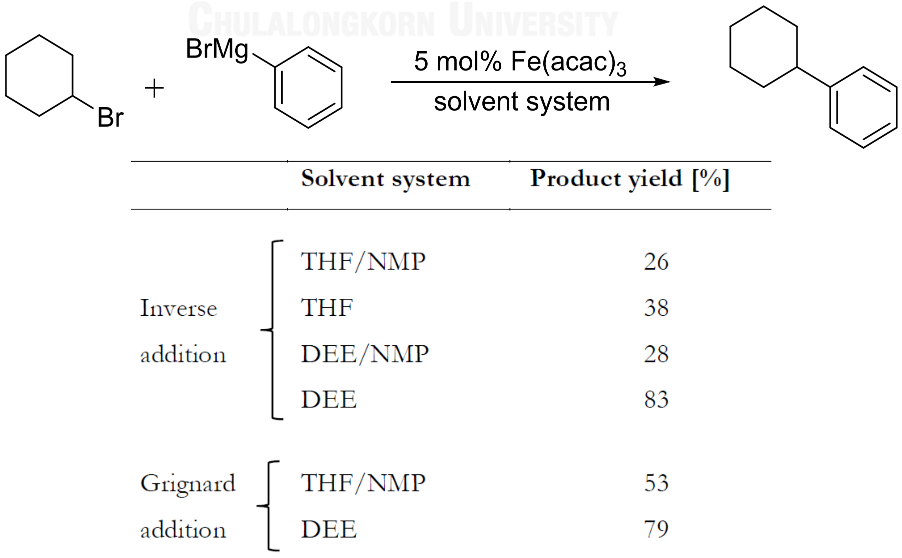
In 2007, Cahiez and co-workers reported a simpler method for iron-catalyzed cross-coupling reaction [17]. This method was inspired by Nakamura’s work, as using TMEDA in the reaction. However, the iron precatalyst was ferric acetylacetonate

($Fe(acac)_3$), which Nakamura reported to be not effective. Moreover, TMEDA and other amine ligands were used in catalytic amount, which differed from Nakamura's method where TMEDA was used more than equivalent of substrate and strictly added as a mixture in Grignard reagent.



An even simpler method was also reported, where the iron precatalyst was a complex of $FeCl_3$ and TMEDA. Iron-TMEDA complex was produced by mixing $FeCl_3$ with 1.5 equivalent of TMEDA. The resulting $[(FeCl_3)_2(tmeda)_3]$ complex would precipitate out at once. It was claimed to be an easy handling iron precatalyst comparing to hydroscopic ferric chloride, and it could be used at only 1.5 mol%. However, a chloro substrate did not react under this condition.

Hedström's doctoral dissertation [18], in the title of *Iron Catalyzed C-C Coupling Reactions Mechanistic Investigation*, reported a set of experiments that investigated the effect of reagent addition method and effect of a common additive; NMP.

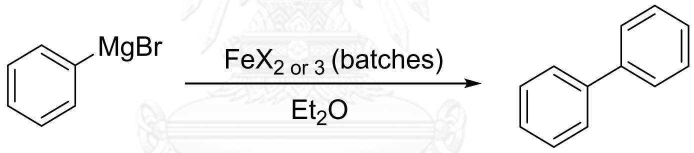


	Solvent system	Product yield [%]
Inverse addition	THF/NMP	26
	THF	38
	DEE/NMP	28
	DEE	83
Grignard addition	THF/NMP	53
	DEE	79

From this result, diethyl ether as a solvent gave the best yield of coupling product at room temperature. The presence of NMP lowered the yield in both THF and DEE. With the quick inverse addition (addition of halide solution instead of Grignard reagent), the reaction in diethyl ether had finished before the sampling started, less than 1 minute.

Generally, Grignard reagent is the last reagent to be added or even needs slowly-machine-adding in some specific condition [14]. But in this work, not only "slowly adding" could be omitted but switching the addition sequence also gives a good or even better result. It was clearly mentioned in the thesis that "The reaction does not require any additives such as NMP or TMEDA. Also, slow addition of the Grignard reagent is no longer necessary."

There was another study in this dissertation that determined the oxidation state of iron when reacting with excess phenyl Grignard reagent. The level of iron reduction was indirectly determined by an amount of biphenyl formed.



Owing to the fact that more biphenyl was produced when the reaction exposed to oxygen in air, inert work-up process was necessary to get a reproducible result.

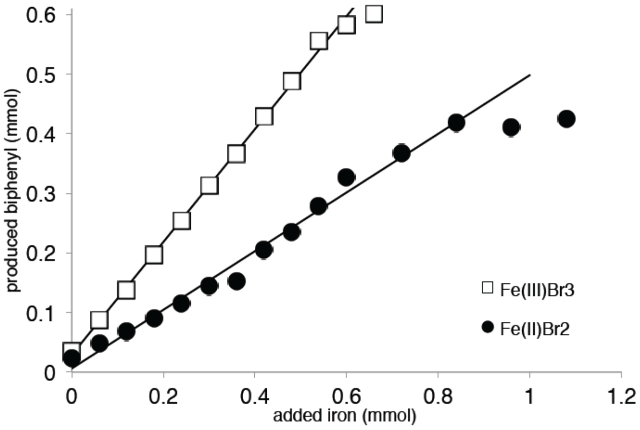
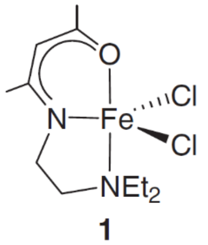


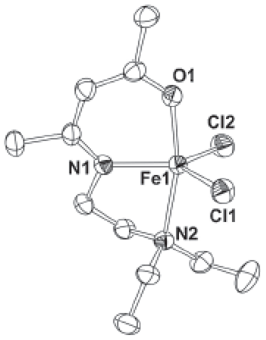
Figure 1.1 The amount of biphenyl formation upon addition of $FeBr_3$ or $FeBr_2$ [18]

One mole equivalent of biphenyl is corresponding to 2 moles of electrons in reduction of iron. So, it can be refered from this result that both Fe(III)Br_3 and Fe(II)Br_2 was reduced to Fe(I).

In 2011, Yamaguchi and co-workers reported an iron complex that was found to be an efficient catalyst for the cross-coupling reaction between aryl magnesium bromides and alkyl halides. The catalyst was iron(III) complex bearing tridentate **β**-aminoketonato ligand [19].



1

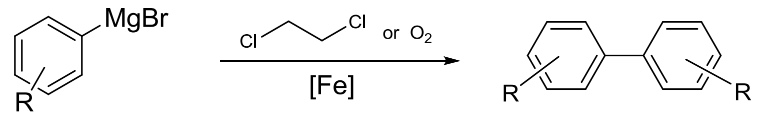


In optimization of the reaction, they varied some factors such as solvent, catalyst amount, addition rate of Grignard reagent, reaction time and temperature. It was concluded from the experiment that diethyl ether gave the best result. The fast addition of Grignard reagent resulted in the effective formation of the desired product. The product yield slightly lowered when the reaction was conducted at elevated temperature. Employments of 1.0 mol% of the catalyst and 1.2 equivalent of the magnesium reagent led to a good result. Moreover, the reaction was found to be complete within 5 min. The appropriate reaction condition is shown below.

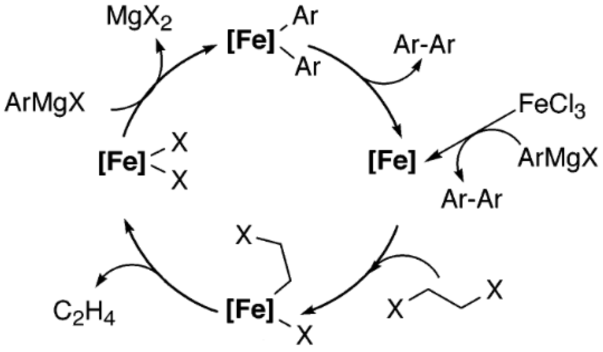
$$\text{ArMgBr} \quad + \quad \text{Cy-Br} \quad \xrightarrow[\text{Et}_2\text{O, rt ,5 min}]{\text{1 (1.0 mol\%)}} \quad \text{Cy-Ar} \qquad 87\% \text{ (Ar : Ph)}$$

This condition worked well with other substituted aryl Grignard reagents except the ortho- substituted one.

Homo-coupling of aryl Grignard reagent can be obtained in high yield if oxidants such as dichloroethane and oxygen are available [20].



The roles of dichloroethane and oxygen were similar. They were used for regeneration of the active catalyst which was the higher oxidation state of iron. Then the iron could again mediate the homo-coupling of aryl Grignard reagent. With no oxidant added, the iron was needed to be used in stoichiometric amount. Catalytic pathway was shown in **Scheme 1.8**. The by-product in the reaction using dichloroethane was gaseous ethylene, as it was trapped in bromine solution to form 1,2-dibromoethane.



Scheme 1.8 Catalytic mechanism with 1,2-dihaloethane as an oxidant [20]

1.3 Aim of Research

The aim of this research is to develop the methodology for the cross-coupling reaction utilizing the iron complex as a catalyst. By understanding the effects of reaction parameters such as solvent system, reaction time, Grignard reagent addition rate, additive and also the properties of ligands in iron complexes. The results will hopefully contribute to further development of more efficient reaction protocols.

CHAPTER II

EXPERIMENTAL

2.1 Instruments and Equipment

The ^{1}H NMR spectra were measured in deuterated chloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d_6) on Varian nuclear magnetic resonance spectrometer, model Mercury plus 400.

The FTIR spectra were recorded on attenuated total reflectance Fourier transform infrared spectrometer (ATR-FTIR), model Thermo Scientific, Nicolet 6700 /Smart iTR.

Column chromatography was performed on silica gel (Merck Grade 7734), 70-230 mesh and thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with silica gel (Merck Kieselgel 60 F254)

2.2 Chemicals

All solvents were purified by standard methodology. The solvents for cross-coupling and other moisture asensitive reactions were dried before use; Et_2O and THF were distilled from Na/benzophenone ketyl then kept over molecular sieve 4A, toluene (ACS reagent, Merck) was dried over molecular sieve 4A. Phenyl magnesium bromide (1.0 M) in THF was purchased from Sigma Aldrich (USA). Magnesium turning (Fluka) was treated with 1 M hydrochloric acid to clean the surface and dried before use. Other reagents for synthesis were purchased from Fluka or Sigma-Aldrich chemical companies and used without further purification.

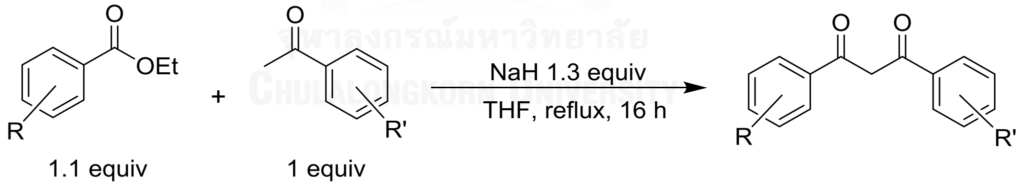
2.3 Preparation of Ligands and Complexation with Iron

2.3.1 Preparation of 1,3-Dicarbonyl Ligands

1,3-Dicarbonyl ligands, or dibenzoylmethane derivatives, were prepared by condensation reaction between substituted benzoate ester and substituted acetophenone. The products were purified by silica gel column chromatography and/or recrystallization. When doing purification by column chromatography, the spot of dibenzoylmethane can be clearly determined by ferric chloride stain which shows intense red spot upon complexation to iron. The chemical structures were confirmed by ^{1}H NMR spectroscopy. All the methods here were adapted from the reported elsewhere [21-24]. The yield of all prepared ligands were shown in **Table 2.1**.

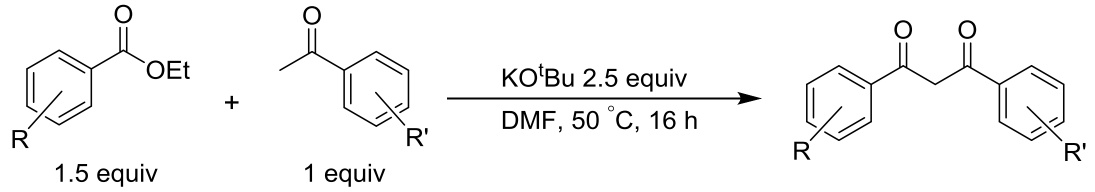
Method: A [21]

A procedure was adapted from the literature as follows: To an oven-dried round bottom flask was added NaH (60% in mineral oil, 2.5 equiv) and then anhydrous THF 3.5 mL/mmol acetophenone). This mixture was cooled to 0°C, and then the corresponding benzoate ester (1.1 equiv) and acetophenone (1 equiv) were added. The suspension was heated to reflux under N_2 for 16 h. After cooled down to room temperature, the mixture was filtered through celite and washed once with EtOH. The filtrate was treated with a mixture of ether and 1 M HCl. The ether phase was separated and washed three times with brine and dried over anhydrous $MgSO_4$. After removal of ether by evaporation, the residue was purified by column chromatography and/or recrystallization from MeOH.



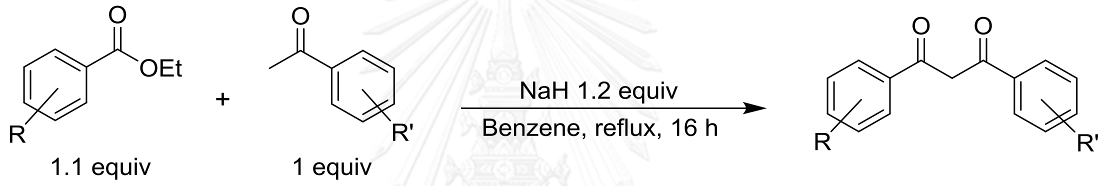
Method: B [22]

N,*N*-Dimethylformamide (DMF) (25 mL) and potassium tert-butoxide (tBuOK) (48 mmol) were heated to 50°C under N_2. Corresponding benzoate ester (28 mmol) was added, followed by a solution of acetophenone (19 mmol) in DMF (2.5 mL). After 16 h, the reaction mixture was allowed to cool and slowly neutralized with 3 M HCl solution. Water and ether were further added to separate two layers. The ether layer containing the crude diketone was washed successively with water, dried over anhydrous $MgSO_4$ and evaporated. The crude product was recrystallized from EtOH/H_2O to yield corresponding ligand.



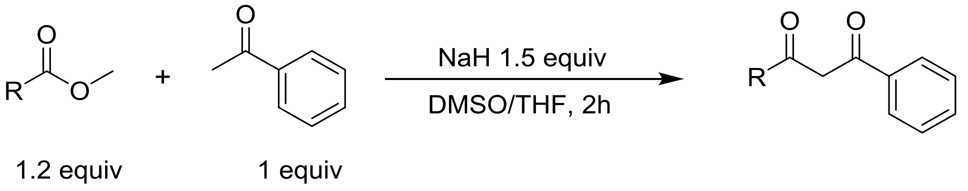
Method: C [23]

Corresponding acetophenone (10 mmol) and benzoate ester (11 mmol) in dry benzene (10 mL) was added dropwise to a suspension of 60% NaH (11 mmol) in benzene (10 mL). The mixture was refluxed for 16 h. Then the reaction mixture was cooled to room temperature and quenched with 3 HCl solution. The mixture was extracted with EtOAc, washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was recrystallized from EtOH.



Method: D [24]

NaH (suspension in mineral oil, 15 mmol) was added to a mixture of dry DMSO and anhydrous THF (1:2, 30 mL). Corresponding ester (12 mmol) and acetophenone (10 mmol) were dissolved in dry THF (4 mL) and added dropwise to the NaH-suspension while cooling with an ice bath. The brown mixture was allowed to warm up to room temperature after stirring for 2 h. THF was evaporated under reduced pressure, water was added (20 mL), and the residue was neutralized with 3 M HCl. The mixture was extracted with EtOAc (2 x 50 mL) and the combined organic layers were washed with water (8 x 20 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness. The crude product was recrystallized from EtOH.



2.3.2 Preparation of 1,3-Dicarbonyl Iron Complexes

1,3-Dicarbonyl ligand has a high affinity to iron(III) salt. It can form complex with iron without a need of any base, however heating to 40°C is required. The solvent mixture of THF, MeOH, and H_2O in 1:1:1 ratio drives the desired iron complex to precipitate out. The iron complexes generally obtained in high yield. All the complexes yields are shown in **Table 2.1**.

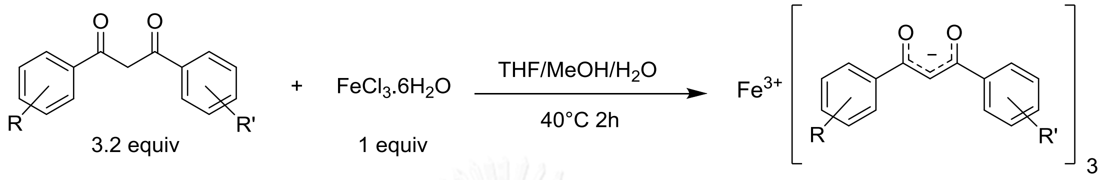
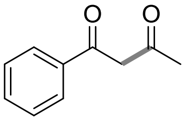
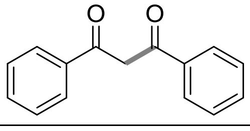
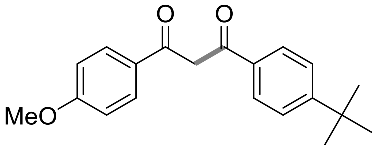
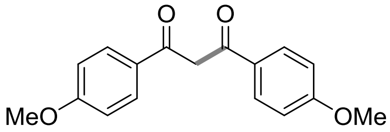
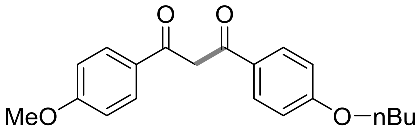
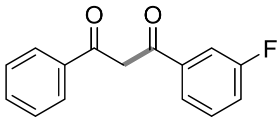
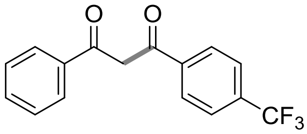
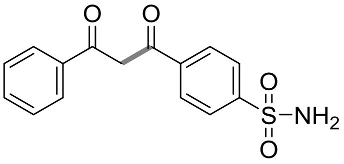
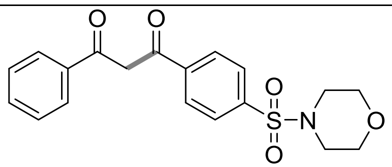


Table 2.1 Yield of 1,3-dicarbonyl ligands and corresponding iron complexes

Ligand	1,3-dicarbonyl ligands: L-H (Left Ring: acetophenone part)	Synthesis method	Yield of ligand (%)[a]	Complexation yield: L_3Fe (%)[a]
L1		D	35	56
L2		D	45	83
L3		A	41	81
L4		C	24	95
L5		A	41	88
L6		B	30	80
L7		A	37	53
L8		A	20	80[b]
L9		A	16	88[b]

a: isolated yield
b: with 2.7 equiv of triethylamine

Characterization of 1,3-Dicarbonyl ligands

1-phenylbutane-1,3-dione (L1)

1H NMR (400 MHz, CDCl3) **δ** 7.88 (d, J = 7.7 Hz, 2H), 7.65 – 7.38 (m, 3H), 6.18 (s, 1H), 2.20 (s, 3H).

1,3-diphenylpropane-1,3-dione (L2)

^{1}H NMR (400 MHz, CDCl$_3$) **δ** 8.00 (d, *J* = 7.1 Hz, 4H), 7.56 (t, *J* = 7.3 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 4H), 6.87 (s, 1H).

1-(4-*tert*-butylphenyl)-3-(4-methoxyphenyl)propane-1,3-dione (L3)

^{1}H NMR (400 MHz, CDCl$_3$) **δ** 7.97 (d, *J* = 8.8 Hz, 2H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.78 (s, 1H), 3.89 (s, 3H), 1.36 (s, 9H).

1,3-bis(4-methoxyphenyl)propane-1,3-dione (L4)

^{1}H NMR (400 MHz, CDCl$_3$) **δ** 7.96 (d, *J* = 8.7 Hz, 4H), 6.98 (d, *J* = 8.7 Hz, 4H), 6.73 (s, 1H), 3.89 (s, 6H).

1-(4-butoxyphenyl)-3-(4-methoxyphenyl)propane-1,3-dione (L5)

^{1}H NMR (400 MHz, CDCl$_3$) **δ** 8.11 – 7.87 (m, 4H), 7.08 – 6.85 (m, 4H), 6.73 (s, 1H), 4.04 (t, *J* = 6.5 Hz, 2H), 3.88 (s, 3H), 1.80 (quin, 2H), 1.54 – 1.44 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).

1-(3-fluorophenyl)-3-phenylpropane-1,3-dione (L6)

^{1}H NMR (400 MHz, CDCl$_3$) **δ** 7.99 (d, *J* = 7.7 Hz, 2H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 9.6 Hz, 1H), 7.58 (t, 1H), 7.54 – 7.42 (m, 3H), 7.32 – 7.20 (m, 1H), 6.83 (s, 1H).

1-phenyl-3-(4-(trifluoromethyl)phenyl)propane-1,3-dione (L7)

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 8.09 (d, *J* = 8.0 Hz, 2H), 8.00 (d, *J* = 7.7 Hz, 2H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.59 (t, *J* = 7.1 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 2H), 6.87 (s, 1H).

4-(3-oxo-3-phenylpropanoyl)benzenesulfonamide (L8, new compound)

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 8.12 (d, *J* = 8.5 Hz, 2H), 8.04 (d, *J* = 8.3 Hz, 2H), 8.01 (d, *J* = 8.0 Hz, 2H), 7.60 (t, *J* = 6.9 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 2H), 6.88 (s, 1H), 4.88 (s, 2H).

^{13}C NMR (100 MHz, DMSO-d_6) **δ** 186.62, 182.97, 147.70, 137.03, 134.46, 133.24, 129.19 (2C), 127.97 (2C), 127.63 (2C), 126.35 (2C), 94.19.

IR (ATR, cm^{-1}): 3316 3230 -NH_2, 1650- 1450 (very broad) enol form of **β**-diketone (**Figure A1**)

1-(4-(morpholinosulfonyl)phenyl)-3-phenylpropane-1,3-dione (L9, new compound)

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 8.14 (d, *J* = 8.3 Hz, 2H), 8.01 (d, *J* = 7.3 Hz, 2H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 6.89 (s, 1H), 3.80 – 3.72 (m, 4H), 3.06 – 3.00 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) **δ** 187.16, 182.30, 139.80, 138.24, 135.14, 132.57, 128.38 (2C), 127.97 (2C), 127.68 (2C), 127.32 (2C), 93.78, 66.35, 46.08.

IR (ATR, cm^{-1}): 1650- 1450 (very broad) enol form of **β**-diketone (**Figure A2**)

2.4 Preparation of Starting Materials

Methyl 4-Chlorobenzoate

Methyl 4-chlorobenzoate and esters of other substituted benzoic acid were prepared by Fischer esterification.

A round bottom flask was charged with 2.0 g (12.8 mmol) of 4-chlorobenzoic acid and 25 mL of MeOH. While stirring until 4-chlorobenzoic acid dissolved, 0.5 mL of H_2SO_4 was added dropwise to the solution. Then the reaction mixture was refluxed for 6 h. After cooled to room temperature, the reaction mixture was participated in hexane and 10% $NaHCO_3$ solution. The hexane layer was washed with another 2 portions of 10% $NaHCO_3$, DI water and brine. Then it was dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (10% EtOAc/ Hexane) through silica gel. Methyl 4-chlorobenzoate was obtained as white crystal (85%) which can melt in hot ambient temperature.

The procedure above was adapted to synthesize methyl and ethyl esters of other substituted benzoic acids that were needed in this work, including ethyl 3-fluorobenzoate, ethyl 4-trifluoromethylbenzoate, ethyl 4-methoxybenzoate, etc.

2.5 Cross-coupling of Aryl Halide with Alkyl Grignard Reagent

The following procedure was adapted from Org Synth [2]. An oven-dried 100 mL round-bottomed flask equipped with a magnetic stir bar, rubber septum, and flushed with N_2 and charged with 4-chlorobenzoic acid methyl ester (853 mg, 5.0 mmol), ferric acetylacetonate [$Fe(acac)_3$] (89 mg, 0.25 mmol) 30 mL of THF, and 1.98 mL of *N*-methylpyrrolidinone (NMP). The flask is immersed in an ice bath and 6 mL butylmagnesium bromide (1M) is immediately added within 20 second via a syringe. This causes an immediate color change from red to black-violet. The ice bath is removed and the resulting dark mixture is stirred for 7-10 min at ambient temperature. Then diluted with diethyl ether, and quenched by addition 1M HCl with stirring. After extraction process, the combined organic phases are dried over Na_2SO_4, and concentrated by rotary evaporator.

2.6 Optimization of Iron-Catalyzed Cross-Coupling Reaction with Selected Models

The parameter of the reaction condition, for example temperature and reaction time, can be varied to study its effect. While the general procedure was almost the same in this entire study.

2.6.1 Chlorocyclohexane and Bromocyclohexane as a Substrate

An oven-dried two-necked reaction tube was charged with 0.025 mmol selected iron precatalyst, 0.50 mmol chlorocyclohexane (or bromocyclohexane), and the solvent. The side neck was closed with septum and applied N_2 flow then closed the other neck. The reaction tube was lowered into temperature controlled bath. With stirring, 0.75 mmol of phenyl magnesium bromide (1.0 M solution in THF) was added through a syringe. The reaction was left at that temperature for a specific time. Then it was quenched with water and 40 mg of cyclododecane was added as an internal standard. The mixture was diluted with Et_2O then extracted with 2 M HCl, sat $NaHCO_3$ and dried over anhydrous Na_2SO_4. The products were determined by GC (BP1 column).

2.6.2 1-Bromohexane as a Substrate

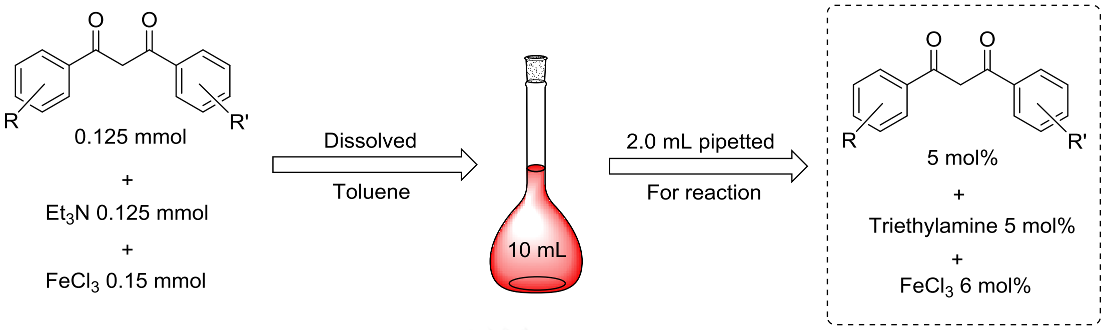
The procedure was similar to section 2.6.1, but the alkyl halide was 1-bromohexane instead.

2.7 The Effect of 1,3-Dicarbonyl Ligands

Preparation Iron-1,3-Dicarbonyl Complex Solutions

Suspension of $FeCl_3$ (anh) 24 mg (0.15 mmol) in toluene 5 mL was added the dibenzoylmethane ligand 0.125 mmol and Et_3N 17 μL. Mixed thoroughly till the entire solid dissolved. Then more toluene was added to adjust the volume of the solution to 10.0 mL. In each reaction, 2.0 mL of the iron complex solution was employed.

Therefore, all the reactions, conducted in 0.50 mmol scale, contained 6 mol% Fe and 5 mol% dibenzoylmethane ligand.



Reaction Procedure

An oven-dried two-necked reaction tube was charged with 0.50 mmol of Cy-Cl or Cy-Br. Then 2.0 mL of the previously prepared iron complex solution was added. The side neck was closed with septum and applied N_2 flow then closed the other neck. With stirring, 0.75 mmol of phenyl magnesium bromide (1.0 M solution in THF) was added through a syringe. The reactions were carried out in room temperature water bath (28°C) for appropriate reaction time, 10 min for Cy-Cl and 5 min for Cy-Br. The work-up procedure and the product determination are same as in section 2.6.1. The reaction was quenched with water and 40 mg of cyclododecane was added as an internal standard. The mixture was diluted with Et_2O then washed with 2 M HCl, sat. $NaHCO_3$ and dried over anhydrous Na_2SO_4. The reaction products were determined by GC (BP1 column).

2.8 Extended Example of Halide Coupling Partners

An oven-dried two-necked reaction tube was charged with 0.50 mmol of selected iron catalyst, 0.50 mmol alkyl halide, and 2.0 mL toluene. The side neck was closed with septum and applied N_2 flow then closed the other neck. The reaction tube was lowered into 28°C water bath. While stirring, 0.75 mmol of aryl Grignard reagent was added through a syringe. The reaction was left at that temperature for a specific time. Then quenched it with water and 40.0 mg of naphthalene was added as an internal standard. The mixture was diluted with Et_2O then extracted with 2 M HCl, sat $NaHCO_3$ and dried over anhydrous Na_2SO_4. The reaction products were determined by GC (BP1 column).

2.9 Mechanistic Studies: Reaction with the Presence of a Radical Trap

In order to investigate how (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO) may affect the reaction, various specific amounts of TEMPO were added to the standard condition, and the procedure was as follows. An oven-dried two-necked reaction tube was charged with 0.025 mmol ferric acetylacetonate, 0.50 mmol Cy-Br, and 2.0 mL toluene. The side neck was closed with septum and applied N_2 flow then closed the other neck. The reaction tube was lowered into water bath (28°C). With stirring, 0.75 mmol of phenyl magnesium bromide (1.0 M solution in THF) was added via a syringe. The reaction was left at that temperature for 5 min. Then quenched it with water then 40 mg of naphthalene was added as an internal standard. The mixture was diluted with Et_2O then extracted with 2 M HCl, sat $NaHCO_3$ and dried over anhydrous Na_2SO_4. The reaction products were determined by GC (BP1 column).

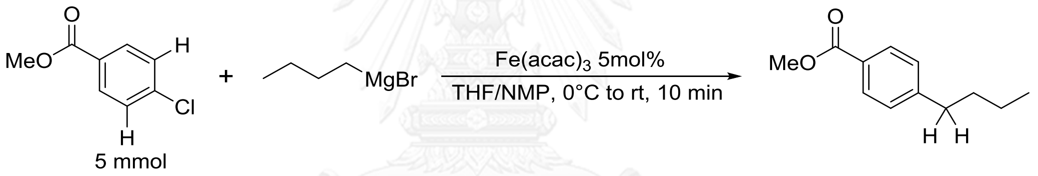
CHAPTER III

RESULTS AND DISCUSSION

3.1 Iron-Catalyzed Cross-Coupling of Aryl Halide and Alkyl Grignard Reagent

Cross-coupling of aryl chloride and n-butyl magnesium bromide was conducted by followed the reported method [2]. After work-up process the crude product was characterized by ^{1}H NMR in the presence of a specific quantity of 1,1,2,2-tetrachloroethane as an internal standard.

Table 3.1 Iron-catalyzed cross-coupling of methyl 4-chlorobenzoate and n-butyl magnesium bromide



Entry	^{n}BuMgBr	Yield^a (%)	Mass Balance (%)
1	1.2 equiv	78	115
2	1.5 equiv	93	115

a: ^{1}H-NMR yield with 1,1,2,2-tetrachloroethane as a internal standard

The ^{1}H NMR spectrum, as shown in **Figure 3.1**, gave the information of peak area. Area of peaks in rectangular sign was used for calculation. The yield of coupling product and the amount of remaining starting material were calculated and showed as %yield and %mass balance in **Table 3.1.**

The product yield was high even in the first try and increasing the amount of Grignard reagent improved the yield to 93%. It might be the moisture in NMP that made the reaction require more Grignard reagent than usual (1.2 equiv reported). Interestingly, the methyl ester functional group tolerated under the conditions. It should be noted that the reaction mixture was not cooled in ice after finished addition of Grignard reagent.

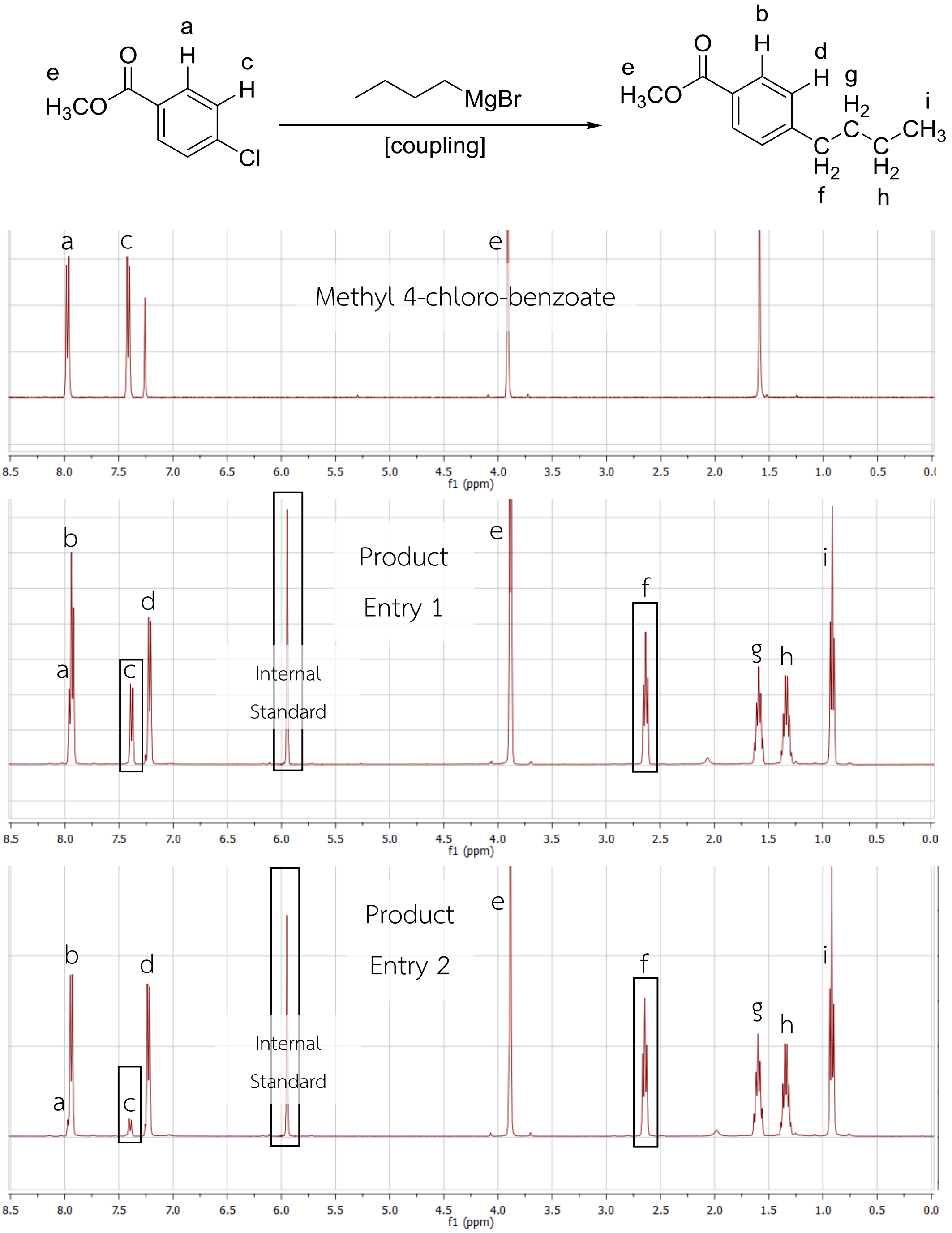
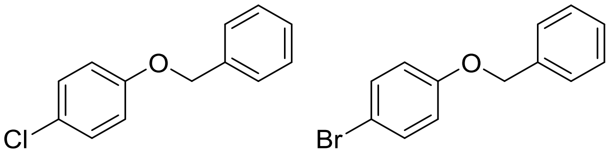


Figure 3.1 The ^{1}H NMR spectra of the starting material and reaction mixture containing 1,1,2,2,-tetrachloroethane as an internal standard

However, the following aryl halides, containing electron-donating substituent, were unreactive under this condition, as no characteristic alkyl chain proton was observed on ^{1}H NMR spectra.



These results emphasized the necessity of activating group for aryl chloride cross-coupling. The observation was very consistent with Furstner's work. It has been already showed that aryl triflate could undergo this reaction without any other substituent for activation.

In this scope, the reaction condition giving excellent yield with a very easy protocol was already established. So, the researcher moved to another scope.

3.2 Optimization of Iron-Catalyzed Cross-Coupling Reaction with Selected Models

Iron-catalyzed cross-coupling of alkyl halide and aryl Grignard reagent

Owing to the method from previously reported works, various iron complexes could be used to catalyze the coupling reaction between alkyl halide and aryl Grignard reagent. Generally, the reaction was carried out in ethereal solvents, with or without an additive or a special ligand. As a result, a wide range of product yield from the same substrate was reported, differing among the publications. Moreover, there was a lot of contradiction among the suggested procedures for conducting the reaction.

In the very preliminary study, four iron precatalysts were tested in this reaction using bromocyclohexane as a substrate. The coupling product yield ranged from 50 to 70%, which contrasted to Nakamura's work that reported a very low yield in reactions without TMEDA additive. However, sometimes the starting material was left in high portion, and the yields in the same repeating reactions, containing the same precatalyst, were very different.

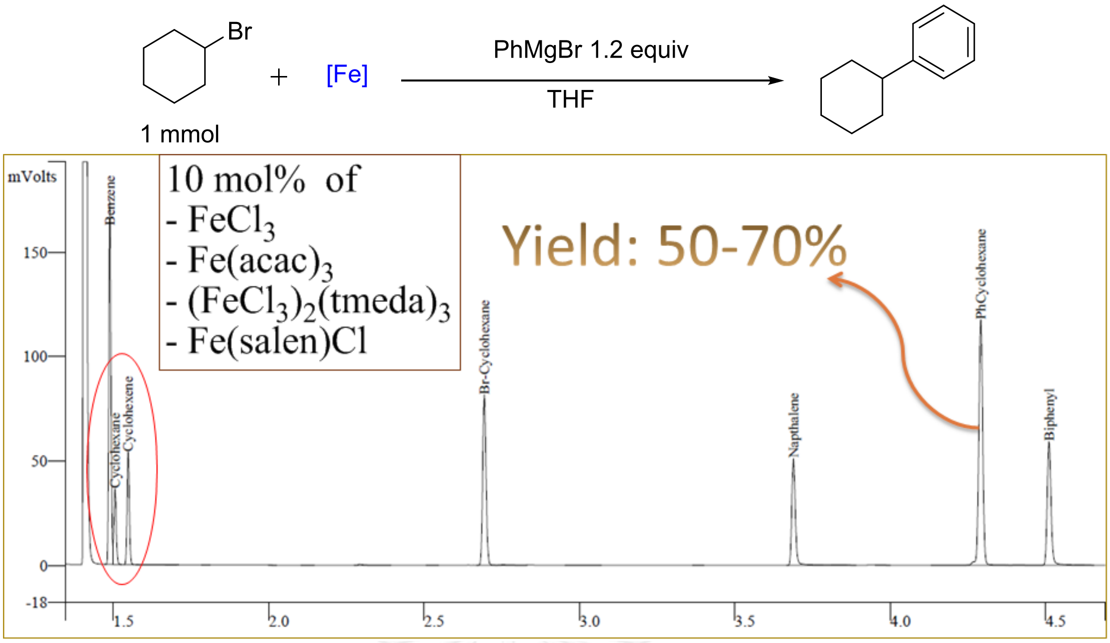


Figure 3.2 The GC chromatogram of a preliminary study of bromocyclohexane coupling

The preliminary study showed the irreproducibility and unsatisfying reaction results. Due to unknown causes, the percentage yield fluctuated even under the 'same' condition. This means the condition, in which the reaction was carried out, might not really be the same. In this chapter, experiments were designed to gain more details about the factors that really affected the reaction.

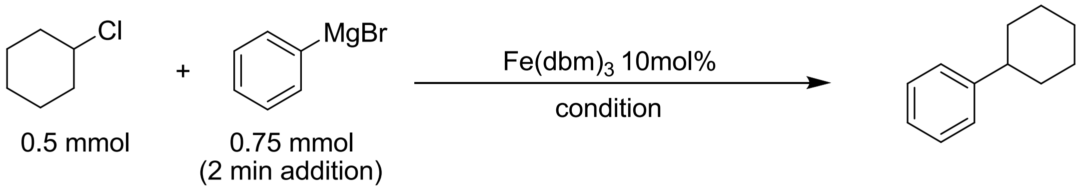
The study was separated into three parts owing to the type of substrate.

3.2.1 Reaction Optimization Using Chlorocyclohexane as a Model

Focusing on secondary alkyl halide substrate, chlorocyclohexane was chosen as a fixed starting material. It should be noted that, due to previous published work, a chloro- substrate tends to react with more difficulty to give cross-coupling product comparing with a bromo- substrate.

In **Table 3.2**, only Fe(dbm)$_3$[1] was used as a source of iron catalyst. As being the first set of experiments, these reactions were conducted in common ethereal solvents, THF and Et$_2$O.

Table 3.2 Effect of reaction temperature and solvent



Entry	Solvent : volume*	Condition	Yield (%)
1	THF: 1.2 mL	0°C, 5 min	34
2	THF: 2.7 mL	0°C, 5 min	12
3	THF: 4.2 mL	0°C, 5 min	5
4	THF: 4.2 mL	rt, 5 min	7
5	Et$_2$O: 5.0 mL	rt, 5 min	45
6	Et$_2$O: 5.0 mL	rt, 16 h	62

*Not included the volume of Grignard's reagent solution

When the reaction temperature and reaction time were kept constant, increasing the THF volume dramatically decreased the product yield (entries 1-3). While the reaction conducted at room temperature (28°C) gave comparable yield to the one at 0°C (entries 3 and 4). When Et$_2$O was used as a solvent instead of THF, the yield increased to 45% (entry 5), even the volume of Et$_2$O was much higher. The result in entry 6 implied that prolonging the reaction time, while other factors remained unchanged, could improve the yield up to 62%.

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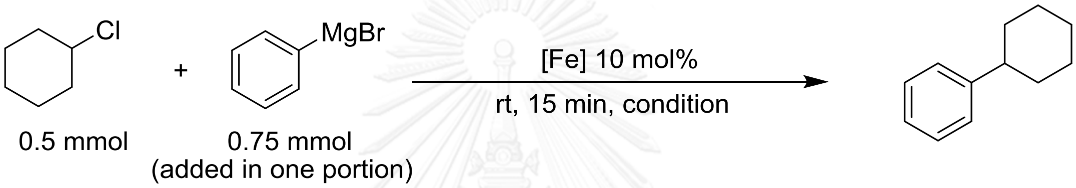
[1] Fe(dbm)$_3$ was reported as an efficient precatalyst in a certain condition [9].

This brief set of experiments suggested that the reaction was sensitive to solvent system. Moreover, the solvent that is commonly used could interrupt the reaction if it was added too much. The ambient temperature is high enough for the reaction to take place.

THF is a stronger coordinating solvent than Et_2O; perhaps it's the reason why the yield was lower in THF. So, the following experiment will bring up an example of less coordinative solvent to use in the reaction.

Table 3.3 Effect of solvent choice in the reaction of chlorocyclohexane



Entry	Solvent : volume[a]	Condition	Yield (%)
1	THF: 1.2 mL	$FeCl_3.6H_2O$	36
2	Et_2O: 3.0 mL	$FeCl_3.6H_2O$	42[b]
3	Et_2O: 3.0 mL	$Fe(dbm)_3$	49
4	Toluene 3.0 mL	$FeCl_3.6H_2O$	53[b]
5	Toluene 3.0 mL	$Fe(dbm)_3$	63
6	Toluene 3.0 mL	$Fe(acac)_3$	72

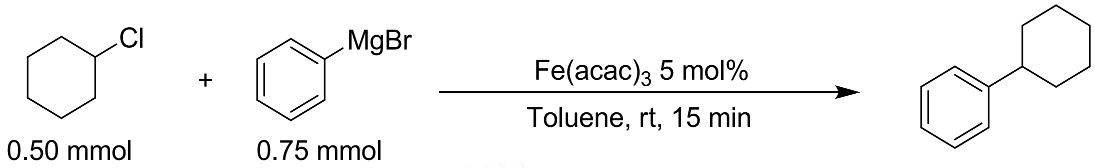
a: Not included the volume of Grignard reagent (1.0 M PhMgBr in THF).

b: $FeCl_3.6H_2O$ was not soluble in the solvent.

These reactions were conducted at room temperature for 15 minutes. In entry 1, when ferric chloride was used as an iron catalyst source, the yield was almost the same as entry 1 of table 2, which the same volume of THF was used. In entry 2, $FeCl_3.6H_2O$ was used in the solution of diethyl ether but it was sparingly soluble. Still the yield was 42% due to THF in Grignard reagent helped the solubility. When toluene was used as a solvent instead of the ethereal one, the yield improved to 72%. Even the iron catalyst was not the same; the yield that was higher than before, seemed to be higher than normal fluctuation. This result led to more investigation of the effect of solvent.

Toluene might be used as a solvent in this reaction to give better result. To determine the effect of its volume, the following set of experiment was carried out.

Table 3.4 Determination of the appropriated solvent volume



Entry	Volume of toluene (mL)	Yield (%)
1	1.0	58
2	2.0	65
3	3.0	66
4	5.0	56

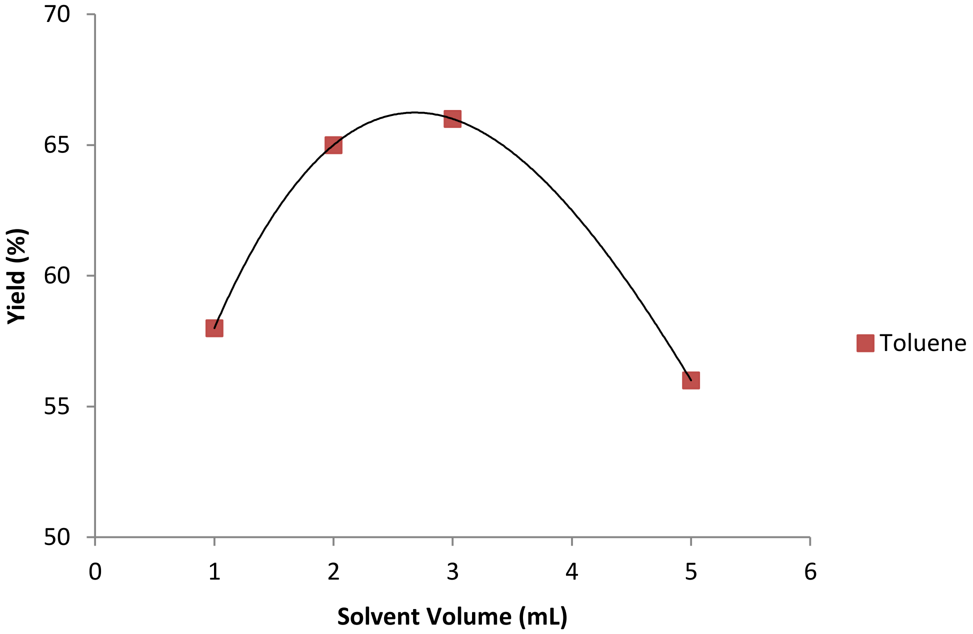


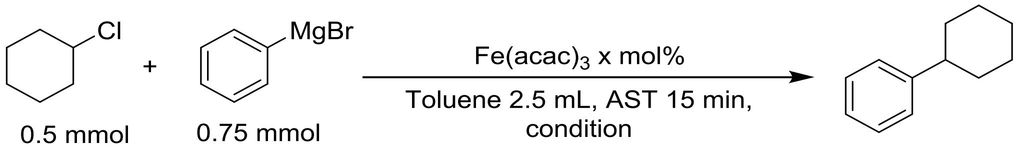
Figure 3.3 Effect of toluene volume to the cross-coupling yield

Data shown in **Figure 3.3** implied that the appropriate amount of toluene was around 2.0 to 3.0 mL in 0.50 mmol reaction scale. So the reaction conducted with this solvent system would be fixed at 2.0 mL or 2.5 mL of toluene.

Effect of Addition Interval of Grignard Reagent

It was strongly pointed out by Nakamura that rate of Grignard regent addition highly affected the yield [14]. They showed that the yield of cross-coupling could be improved from moderate to excellent (up to 99%) by slowly adding the Grignard reagent, via a syringe pump. So, in this work the effect of Grignard reagent addition rate was studied and the results were shown in **Table 3.5**.

Table 3.5 Effect of Grignard reagent addition rate to the coupling yield



Entry	mmol Fe	Condition	Yield (%)
1	5 mol%	0˚C; AI = 2-3 sec	33
2	5 mol%	0˚C; AI = 1 min	70
3	5 mol%	0˚C; AI = 5 min	67
4	5 mol%	rt; AI = 2-3 sec	63
5	5 mol%	rt; AI = 1 min	62
6	5 mol%	rt; AI = 5 min	65
7	10 mol%	0˚C; AI = 2-3 sec	23
8	10 mol%	0˚C; AI = 1 min	58
9	10 mol%	0˚C; AI = 5 min	67

*AI = Addition Interval of Grignard reagent

Table 3.5 shows the effect of Grignard reagent addition rate along with other factors such as temperature and catalyst amount. The yields of all these entries are quite similar except the case that Grignard reagent was added in a very fast manner at low temperature, entries 1 and 7. It is interesting that the reaction was not affected by fast addition when it was conducted at room temperature not at 0°C, entry 4. From these data it can be conclude that the iron-catalyzed cross-coupling reaction between aryl Grignard and alkyl halide does not require a slow addition method to improve the product yield. The normal dropwise rate, in this case equal to 1 min rate, is slow enough to do not affect the yield.

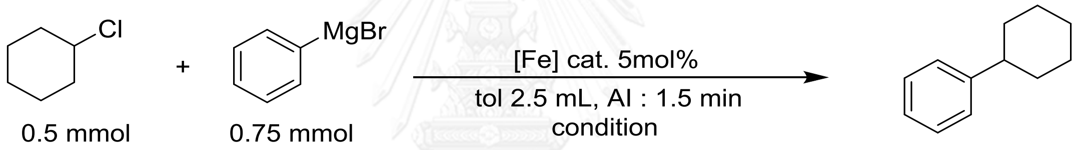
Moreover, increasing an amount of catalyst from 5 to 10 mol% did not give positive outcome. So the catalyst loading at 5mol% should be enough.

Effect of iron catalyst without special ligand

Owing to the literature review, there were many ligands reported to efficiently promote the coupling reaction of alkyl halide. But the reason why it needs ligand remains unclear. So, there is a question, “Can the reaction occur without any ligand added?” Actually, the result in **Table 3.3** showed some disappointed results using $FeCl_3$ but in those cases the reaction was done in THF which already proved to be not suitable, and the reaction in E_2O or toluene the insolubility of $FeCl_3$ might be the cause of low yield.

In order to make $FeCl_3$ clearly soluble in toluene, its solution in THF was prepared (0.5 M in THF). The $FeCl_3$ solution was pipetted for 50 μL and used in the following reactions.

Table 3.6 Cross-coupling reaction of chlorocyclohexane using ferric chloride



Entry	[Fe]	Temp; Additional stirring time	Yield	MB
1	$FeCl_3$.anh	rt; 8 min	76	95
2	$FeCl_3.6H_2O$	rt; 5 min	76	95

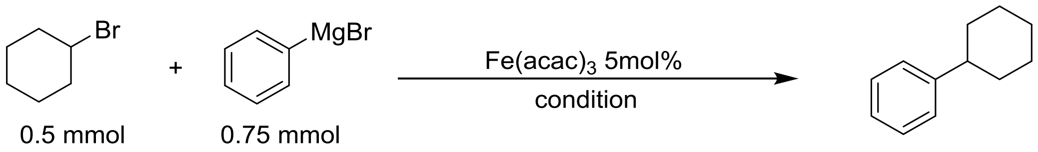
AI = addition interval of Grignard reagent

Under the optimum condition, usage of $FeCl_3$ as a very simple catalyst source provided high of cross-coupling product at 76%, regardless to the anhydrous or hydrated form. It has never been reported before that simple iron salt could efficiently mediated this reaction without any additive. These results emphasized the suitability of the reaction condition for this reaction model.

3.2.2 Reaction Optimization Using Bromocyclohexane as a Model

To study the effect of reaction condition to the coupling of bromocyclohexane, solvent choice was the first factor to be determined due to the trend from section 3.2.1.

Table 3.7 Effect of solvent to the coupling reaction of bromocyclohexane



Entry	Solvent and Volume (mL)	AI	Additional stirring time	Yield (%)	RSM[a] (%)	MB (%)
1	THF 2.0	2 min	rt; 5 min	46	33	90
2	THF 0.25	2 min	rt; 5 min	71	2	92
3	Neat[a]	2 min	rt; 5 min	73	0	89
4	Toluene 2.5	2 min	rt; 15 min	84	2	92

a: Recovery of starting material

b: 0.75 mL of THF from Grignard reagent

The use of THF as a solvent seemed to highly affect the reaction result, and it highly depended on volume. When the volume of THF was higher (entry 1), the conversion of starting material was much slower and resulted in incomplete conversion of bromocyclohexane. While the reaction in diethyl ether was reported to be finished within one minute after fast addition the Grignard reagent [18]. When the lower amount of THF was used, the conversion of starting material could be complete (entry 2 and 3). But when using toluene as a solvent the reaction was complete and gave higher yield of the expected product (entry 4).

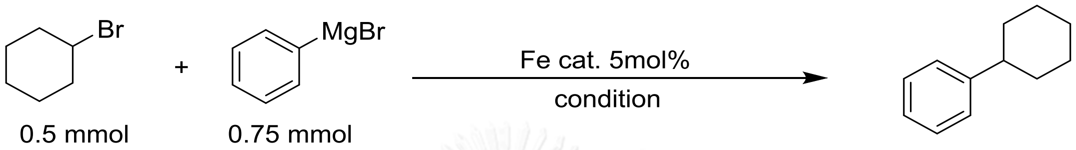
Bromocyclohexane follows the same trend as chlorocyclohexane but gives higher amount of cross-coupling product.

However there is an important factor which was reported to increase the coupling product yield, the TMEDA.

Effect of TMEDA additive to the coupling reaction of bromocyclohexane

TMEDA was reported to effectively promote cross-coupling of alkyl bromide. It was reported that when TMEDA was mixed in the same amount to the Grignard reagent and was slowly added in to the reaction, then the excellent yield was obtained. To study this effect the following set of reaction was conducted.

Table 3.8 Effect of TMEDA additive in coupling reaction of bromocyclohexane



Entry	[Fe]	Solvent (mL)	TMEDA	Temp; AST	AI	Yield	MB
1[a]	FeCl_3	THF 2.0	130 mol%	0˚C; 5 min	2 min	<0.5	85
2[a]	FeCl_3	Not added	130 mol%	0˚C; 17 min	13 min	17	90
3[a]	FeCl_3	Not added	130 mol%	0˚C; 5 min	2 min	8	89
4	Fe(acac)_3	THF 0.25	130 mol%	0˚C; 15 min	2 min	1	-
5	Fe(acac)_3	Toluene 2.5	130 mol%	˚C; 15 min	2 min	0	-
6	Fe(acac)_3	Toluene 2.5	50 mol%	˚C; 15 min	2 min	1	-
7	Fe(acac)_3	THF 2.0	Not added	rt; 5 min	2 min	46	90
8	Fe(acac)_3	THF 2.0	10 mol%	rt; 5 min	2 min	39	92
9	Fe(acac)_3	THF 2.0	50 mol%	rt; 5 min	2 min	37	88

a: Grignard reagent and TMEDA was mixed and added together

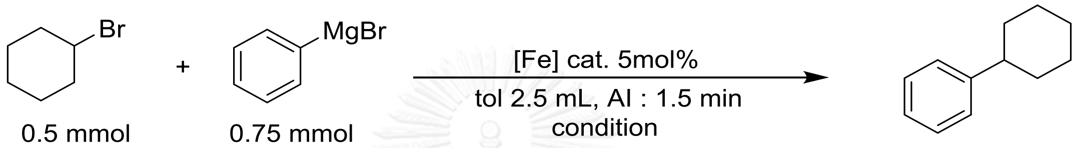
The reported condition was slow addition of Grignard/TMEDA mixture to the reaction at 0°C via a syringe pump for more than 20 min of addition interval in 1 mmol scale. Entries 1-3 was conducted to represent this condition, the PhMgBr and TMEDA was mixed before added to the reaction mixture. At low temperature (0°C) entry 2 gave the highest yield of coupling product. However, the overall yield and conversion was very low. And TMEDA seem to inhibit the reaction rather than promote the cross-coupling. The reaction at higher temperature (entries 7 - 9) showed that the more TMEDA was added the lower conversion of substrate was obtained.

Even this method might help suppress the by-product, but it needs special requirement of slow addition that cannot be done easily.

Effect of iron catalyst without special ligand

The previously prepared ferric chloride solution, used for **Table 3.6**, was also employed here. The iron salt in hydrated or anhydrous form give very little different result. However, it should be more appropriated to use anhydrous from in this reaction.

Table 3.9 Cross-coupling reaction of bromocyclohexane using ferric chloride

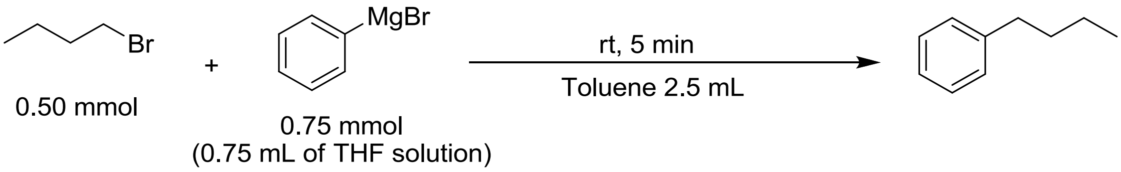


Entry	[Fe]	Temp; Additional stirring time	Yield	MB
1	$FeCl_3$.anh	rt; 5 min	91	99
2	$FeCl_3.6H_2O$	rt; 5 min	89	96

It should be noted that the coupling product yield in this ligand free system was rather higher than the same reaction employing Fe(acac)$_3$, **Table 3.7**. From this fact, the usage of iron catalyst containing chelated ligands must be cautiously considered.

3.2.3 Reaction Optimization Using 1-Bromohexane as a Model

To investigate the efficiency of this reaction with primary alkyl halide substrate, 1-bromobutane was used as a model. The reaction condition was adapted from the optimum one of section 3.2.2 with ferric acetylacetonate as a catalyst. The condition that gave highest yield in the case of bromocyclohexane yet gave just a moderate yield in this case. Varying the iron catalyst did not affect much. It should be noted that no starting material was left after 5 min of reaction time; absence of 1-bromobutane peak in GC chromatogram.



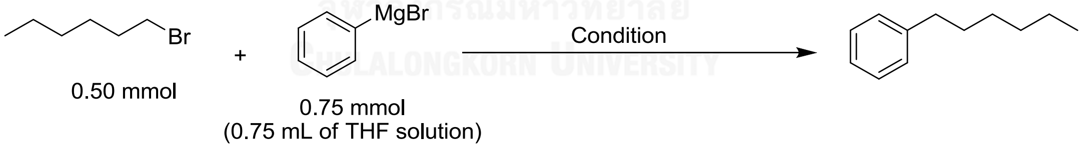
2.5mol% $Fe(acac)_3$ 5min : 40%

5.0mol% $Fe(acac)_3$ 5min : 43%

However the by-products that may form in the reactions cannot be characterized due to its low boiling nature. In order to get product distribution data the substrate must be change to the higher boiling one. For this reason, 1-bromohexane was then used as a model substrate represents the primary alkyl halide group. The by-products that should be n-hexane and 1-hexane can be quantified and the model is comparable in size to the previous part that used cyclohexane.

At the beginning, the reaction condition was adapted from the optimum of section 3.2.2. The condition that gave highest yield in the case of bromocyclohexane yet gave just a moderate yield in this case (entry 2).

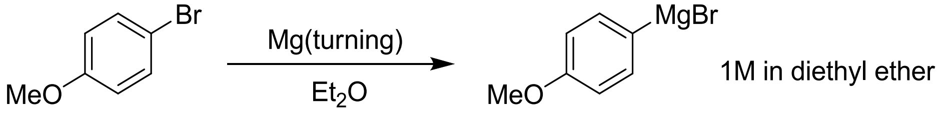
Table 3.10 Effect of reaction condition to the coupling of 1-bromohexane



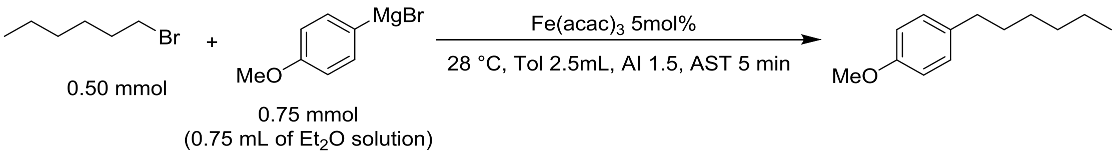
Entry	Fe Catalyst	Condition	Yield	R-Br	Alkane	Alkene	MB
1	2.5% $Fe(acac)_3$	Tol 2.5 mL, rt, 5 min	45	-	15.7	25.3	86
2	5% $Fe(acac)_3$	Tol 2.5 mL, rt, 5 min	54	-	11.0	22.2	87
3	5% $Fe(acac)_3$	THF 2.5 mL, rt, 5 min	36	34	8.2	10.3	88

4	5% $Fe(acac)_3$	No solvent added, rt	37	-	15.9	20.5	74
5	2.5% Fe(salen)Cl	Tol 2.5 mL, rt, 5 min	39	-	21.0	23.4	83
6	5% $FeCl_3$	Tol 2.5 mL, 0°C, 5 min	35	7	16.4	24.1	83
7	5% $FeCl_3$	Tol 2.5 mL, rt, 5 min	54	3	10.3	20.8	88
8	5%$FeCl_3$, 5%PPh_3	Tol 2.5 mL, rt, 5 min	49	7	11.4	18.1	86
9	5%$FeCl_3$, 15%PPh_3	Tol 2.5 mL, rt, 5 min	46	10	11.9	22.9	90
10	No [Fe] catalyst	Tol 2.5 mL, rt, 12 min	0	92	-	-	92

Varying some factors as shown in **Table 3.10** cannot improve the yield to higher than 54%. The maximum yield was obtained when $FeCl_3$ was used as a catalyst in toluene at room temperature (entry 7). But again when THF was used as a solvent instead of toluene the yield dropped to 33% (entry 3). It implies that if the THF presenting in Grignard reagent (1.0 M phenyl magnesium bromide in THF) was diminished, the yield might be higher. As a result, aryl Grignard reagent in diethyl ether was prepared by conventional way.



Then, 4-methoxy phenyl magnesium bromide in diethyl ether was used for coupling with n-hexyl bromide in a standard method (the optimum condition from section 3.2.2).



Entry	mmol Fe	Condition	Yield (%)	Alkane	Alkene	MB
1	5 mol% $Fe(acac)_3$	Toluene 2.5 mL, rt, 5 min	74	4.6	12.7	91

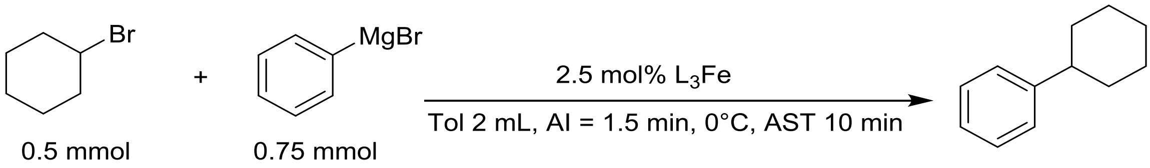
When Grignard reagent in diethyl ether was used instead of Grignard reagent in THF, the cross-coupling yield increased to 74%. Moreover, the reaction finished within 5 min, as no 1-bromohexane peak was observed in GC chromatogram. This observation are consistent with the work of Hayashi, who optimized the reaction of primary alkyl bromide and reported the diethyl ether as the most appropriated solvent [12].

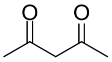
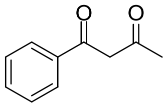
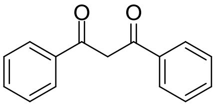
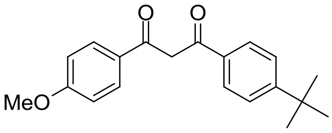
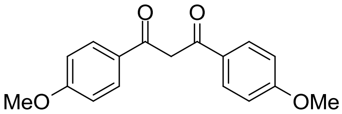
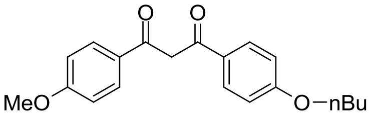
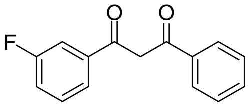
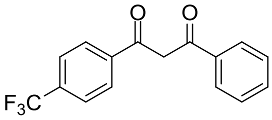
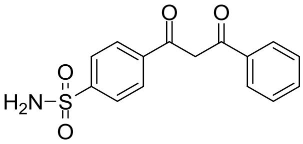
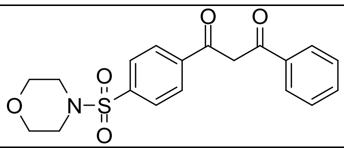
3.3 Effect of 1,3-Diketonate Ligand

3.3.1 Effect on the Reaction with Bromocyclohexane

Iron complexes of various 1,3-dicarbonyl ligands were prepared as illustrated in section 2.3 and they were used in the following reaction.

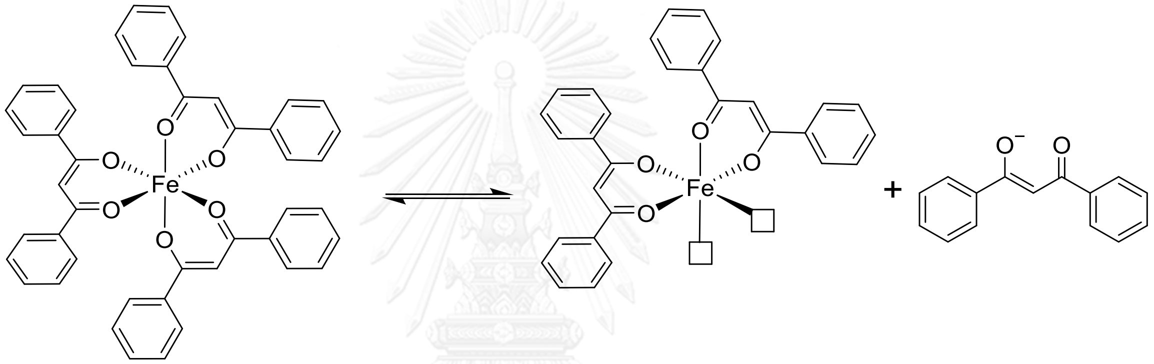
Table 3.11 Effect of 1,3-diketonate iron complexes



Entry	LH in L_3Fe complex	Yield (%)	MB (%)
1		87.0	95.9
2		87.4	95.4
3		83.9	93.7
4		84.8	92.4
5		85.3	97.4
6		80.2	96.7
7		82.0	93.1
8		85.4	94.3
9		3.9	109
10		29.6	88.8

As shown in this table, yields of cross-coupling of bromocyclohexane were relatively high except the result of entries 9 and 10. The ligands of iron complexes in these two entries contained sulfonamide substituent which had electron withdrawing property, but there were some problems. First, the complex in entry 9 was not soluble in the reaction condition. Second, the sulfonamide group may not tolerate high reactive Grignard reagent in the reaction.

Fully coordinate iron complexes with three steric bidentate ligands might result in slow down or interfering the catalytic pathways. In case the reaction occur at coordination sphere of iron, the presence of 3 folds equivalent of chelating ligand might interfere the catalytic pathway. The lower dissociation equilibrium constant of ligand from metal complex can also decrease overall rate of reaction.

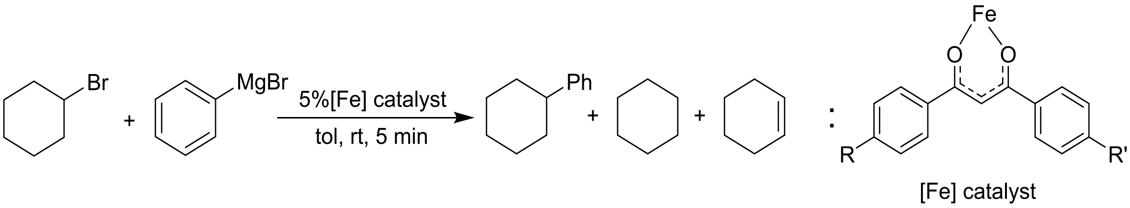


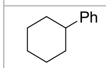
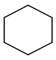
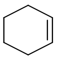
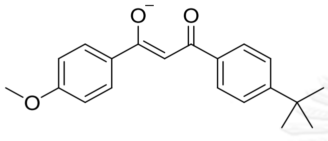
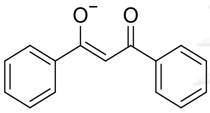
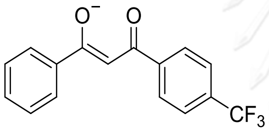
This effect can easily be observed in chloro substrate. To investigate the electronic effect of 1,3-diketonate ligands and **limit the steric hindrance** over coordination sphere, iron complex solutions were prepared and limited the ratio of iron and the ligand at 1:1 mole ratio.

Three ligands were selected to study the effect of different electron density; dibenzoylmethane with electron donating group, with no substituent, and with electron withdrawing group.

The solutions of iron complexes were prepared as shown in section 2.7.

Table 3.12 Effect of electronic property of 1,3-diketonate ligands



Entry	Ligand	Equivalent Distribution (%)				Mass Balance (%)
		Recovery of CyBr	Products			
						
1		0	90.3	2.8	6.2	99.3
2		0	90.3	2.1	4.3	96.7
3		0	91.9	1.2	3.1	96.2

In all entries, bromide starting material was completely converted to products within 5 minutes. The yield of cross-coupling product (PhCy) seemed to be a little different. But trying to compare the yield around 90% is pointless. It is more accurate to focus on the amount of unwanted cyclohexane and cyclohexene because all the by-products are only these two compounds. If the by-products are minimized, while the starting material is totally converted, that condition will be the best method.

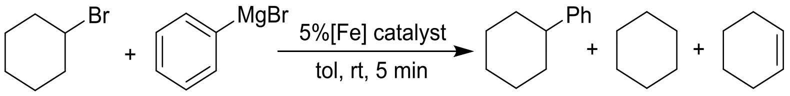
The result showed that ligand #3 gave the lowest amount of by-products; of both alkane and alkene. Ligand #3 has trifluoromethyl substituent which is strong electron withdrawing group. But when electron donating group presented (ligand #1), the by-products were obtained in highest amount. In case of no substituent on the ligand, the by-products were moderately obtained.

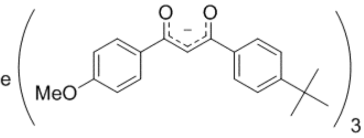
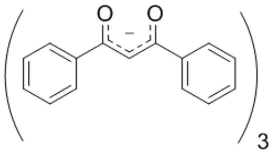
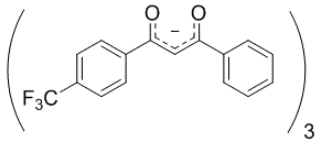
By-product amount: #1 > #2 > #3

Electron donating property: #1 > #2 > #3

There is another way to limit the ratio of Fe ligand, by using easy handling $Fe(dbm)_3$ and solution of $FeCl_3$.

Table 3.13 Effect of electronic property of 1,3-diketonate ligands



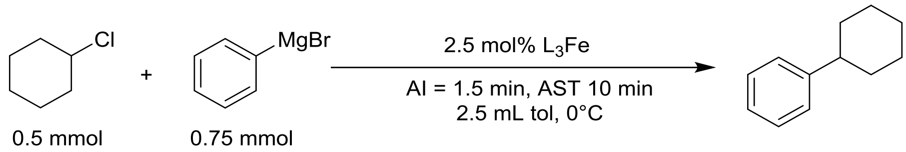
Entry	[Fe]	Yield	MB	Alkane	Alkene
1	2.5 mol% Fe  + 2.5 mol% $FeCl_3$	94.3	101.9	2.0	5.6
2	2.5 mol% Fe  + 2.5 mol% $FeCl_3$	94.4	101.9	2.0	5.5
3	2.5 mol% Fe  + 2.5 mol% $FeCl_3$	94.5	99.7	1.2	4.1
4	5 mol% $FeCl_3$	92.2	98.7	1.7	4.7
5	5 mol% $FeCl_3$ + TMEDA 15 mol%	3.7	98.9	0.7	0.4

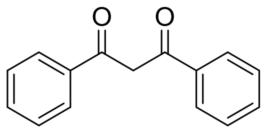
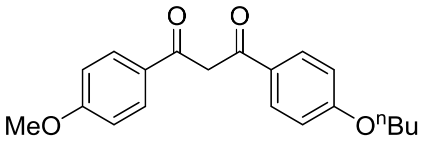
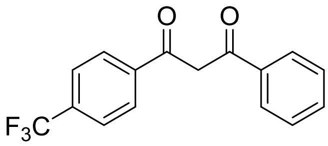
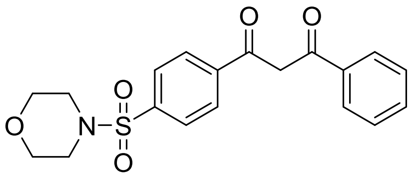
Iron complex with electron-withdrawing group on ligand gave lowest amount of by-product (entry 3). The same trend as **Table 3.12** was observed. In entry 4, ferric chloride was used as a catalyst and it also gave high yield with a little higher by-product comparing to entry 3. Entry 5 was an effort to utilize TMEDA as an additive, however $FeCl_3$ in contacted with TMEDA resulted in insoluble brown precipitate in toluene.

3.3.2 Effect on the Reaction with Chlorocyclohexane

Iron complexes of various 1,3-dicarbonyl ligands prepared from section 2.3.2 were used in the following reactions.

Table 3.14 Effect of 1,3-dicarbonyl ligands to the reaction of chlorocyclohexane



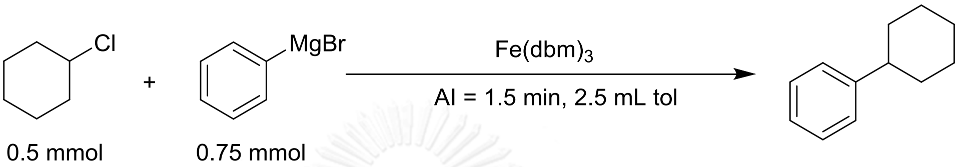
Entry	LH in L_3Fe complex	Yield (%)
1		0.4, 34^a
2		4
3		4
4		0

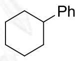
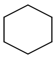
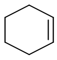
a: 1.2 mL THF was used instead of toluene

From **Table 3.14**, little yield of cross-coupling product was obtained. The result shows that the reaction of chlorocyclohexane with iron tris(dibenzoylmethane) precatalyst cannot undergo at 0°C. It might be the slower dissociation rate of dibenzoylmethane ligand that cause the iron catalyst species to be occupied and cannot react with the substrate. Comparing with the results in **Table 3.5**, chlorocyclohexane could undergo cross-coupling reaction yielding up to 70% at 0°C. In that case the ferric acetylacetonate was used. These facts indicate that when using $Fe(dbm)_3$ precatalyst, the ligand can stronger chelate to the iron active species and stabilizes it at low temperature (0°C); stabilized enough to do not react with chlorocyclohexane. The polar solvent (THF) might help dissociate the ligand resulting in 34% of product was obtained (entry 1a). For this reason, the reactions at elevated temperature were studied.

The result for Fe(dbm)$_3$ series in **Table 3.15**, showed that elevated reaction temperature (at room temperature or higher) increased the conversion of chlorocyclohexane into cross-coupling product along with formation of cyclohexene and cyclohexane as by-products.

Table 3.15 Cross-coupling of chlorocyclohexane at elevated temperature

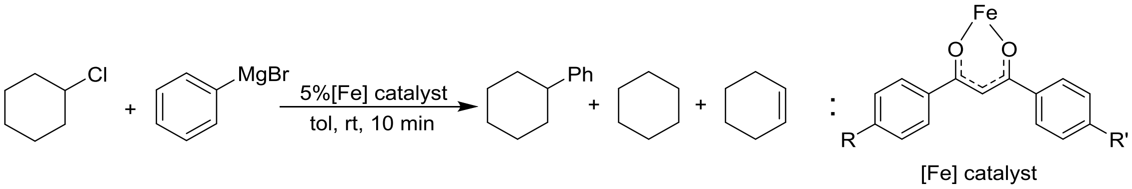


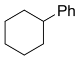
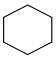
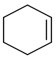
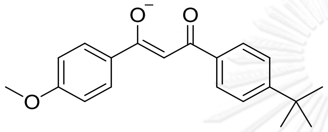
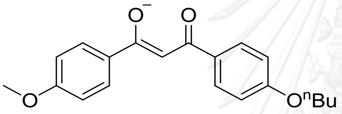
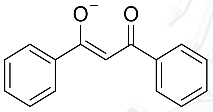
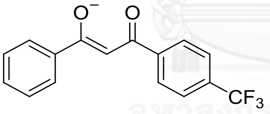
Entry	Condition			Equivalent Distribution (%)				MB (%)	Biph (%)[a]
	Fe(dbm)$_3$	Temp	AST	Recovery of CyCl	Product				
									
1	2.5 mol%	10°C	10 min	81.8	5.2	0.0	0.0	87.1	25.4
2	2.5 mol%	28°C	10 min	5.5	72.0	4.3	8.5	90.3	41.1
3	2.5 mol%	40°C	5 min	26.7	49.2	5.3	9.8	91.1	32.2
4	10 mol%	40°C	5 min	19.9	65.0	1.3	3.6	89.8	74.8
5	10 mol%	40°C	25 min	19.7	62.5	1.1	2.9	86.1	62.5

a: %mol equivalent of Ph compared to chlorocyclohexane

In presence of Fe(dbm)$_3$ as a precatalyst, the reaction at low temperature (10°C) gave a very low yield of coupling product, while a large amount of starting material remained unreacted (entry 1). When increasing the reaction temperature to 28°C, almost all the starting material was converted within 10 min (entry 2). However, when the reaction temperature was elevated to 40°C, it tended to give more alkene and alkane by-products entry 3. For unknown reason, when the catalyst loading was increased to 10 mol% and the temperature was at 40°C, the by-products occurred in very low portion (entry 4) and it did not react further after 5 minutes (entry 5).

Table 3.16 Effect of electronic property of dibenzoylmethane ligands

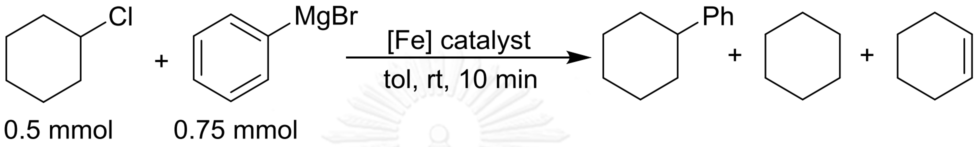


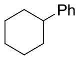
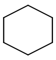
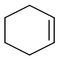
Entry	Ligand	Equivalent Distribution (%)				Mass Balance (%)
		Recovery of CyCl	Product			
						
1		1.7	80.9	4.1	14.9	101.6
2		4.1	75.4	4.8	14.5	98.9
3		14.3	62.2	5.6	9.7	91.7
4		51.6	33.6	3.5	9.0	97.7

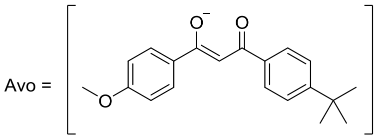
The reaction of chlorocyclohexane in the presence of ligands #1 to #4, the starting material always left in reaction mixture. The reaction with strong electron-withdrawing substituent at the para position of the benzene ring (ligand #4), chlorocyclohexane was left in 51.6 % and yield of the cross-coupling product is only 33.6 %. However, it had a tendency to complete the conversion when ligand containing electron-donating substituents at para position of benzene ring was employed. The ligand #1 which has two electron-donating groups gave the highest yield (80.9%) and starting material was left at the lowest amount at 1.7%. These results suggested that C-Cl bond breaking was the slowest step in reaction pathway. C-Cl bond breaking due to oxidative addition or single electron transfer required high electron density on metal, and in can become faster by strong donor ligand.

The other way to limit the ratio of diketone ligand to Fe was the usage of iron diketonate complex in combination with $FeCl_3$. The diketonate ligand that showed the best result in Table 3.16 was selected for this study. The iron diketonate complex ($Fe(Avo)_3$), prepared in section 2.3.2, was easy handling red powder and stable in air. The effect of iron precatalysts combination was shown in Table 3.17.

Table 3.17 The reaction using combination of iron diketonate complex and ferric chloride



Entry	Catalyst	Equivalent Distribution (%)				Mass Balance (%)
		Recovery of STM	Product			
						
#1	5mol% $Fe(Avo)_3$	0	81.0	2.0	11.9	94.9
#2	(1/3)5mol% $Fe(Avo)_3$ + (2/3)5mol% $FeCl_3$	0.6	75.6	2.9	12.0	91.1
#3	2.5mol% $Fe(Avo)_3$ + 2.5mol% $FeCl_3$	0	85.2	2.1	9.6	96.9
#4	2.5mol% $Fe(Avo)_3$	16.4	72.5	3.0	7.3	99.2
#5	5mol% $Fe(acac)_3$	0	68.5	4.3	24.5	97.3



(Avobenzone)

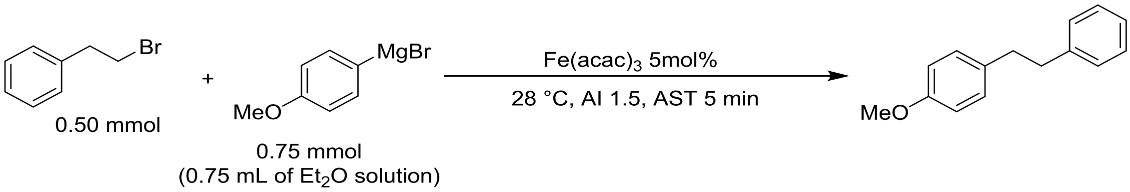
In entry 1, the reaction using 5 mol% $Fe(Avo)_3$ (red powder) gave comparable product yield to entry 1 of **Table 3.16**, which employed the same diketonate ligand. Using combination of $Fe(Avo)_3$ and $FeCl_3$ in 2.5 mol% each gave the best result at 85% product yield (entry 3). While the other iron precatalysts ratio in entry 2 gave lower product yield. The ligand to Fe ratio in entry 2 was at 1:1 and it was almost similar to the ratio in the reaction from **Table 3.16.** The iron precatalyst amount at 2.5 mol% was not enough to provide complete conversion of chlorocyclohexane (entry 4). While commercially available Fe(acac)$_3$ gave much lower yield of product (entry 5). The reaction condition in entry 5 was rather similar to the reaction in entry 6 of **Table 3.3** and can be compared to the result from **Table 3.4**.

The reason why this method of catalyst usage provided somewhat better result might be the decrease of the diketonate anion that can intervene alkyl iron intermediate in the catalytic cycle. Moreover, the appropriate ratio of diketonate ligand to Fe was 1.5:1 or 7.5 mol% of diketonate ligand per 5 mol% Fe.

3.4 Extended Example of Halide Coupling Partners

3.4.1 1°-Alkyl Halide

Table 3.18 Cross-coupling reaction of 2-Phenethyl bromide



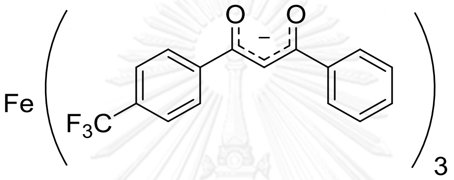
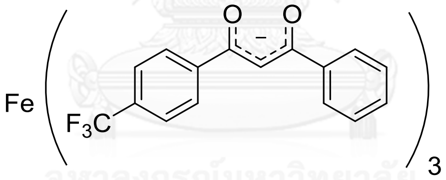
Entry	Temp	Solvent	AI	AST	Yield (%)	MB (%)	Alkane	Alkene
1	28 °C	Et_2O 2.5 mL	1.5	5	67	94	8.3	19.2
2	28 °C	Tol 2.5 mL	1.5	5	68	95	7.4	20.1

2-Phenethyl bromide underwent cross-coupling with anisylmagnesium bromide yielding the corresponding product in high yield. The yield were not different between two solvents; toluene and diethyl ether. These result were consistent to the previous observation that for primary alkyl bromide the Grignard must be in a solution of Et_2O to obtain maximum yield.

3.4.2 2°-Alkyl Halide

Cross-coupling reaction of 2-bromopropane was conducted in the optimum condition in presence of some iron precatalysts that showed the good result previous section. And the yield of cumene being the coupling product was determined by GC.

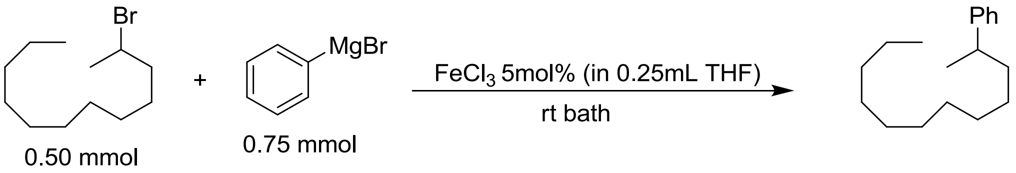
Table 3.19 Cross-coupling reaction of 2-bromopropane

Entry	Iron Catalyst	Yield*
1	2.5 mol%  + 2.5 mol% $FeCl_3$	75 %
2	5 mol% $FeCl_3$ + **THF 1.0mL**	44 %
3	5 mol% $FeCl_3$	79 %
4	1.0 mol%  + 1.0 mol% $FeCl_3$	78 %

*There was no halide starting material left in all entries.

All the entries in **Table 3.19** showed no 2-bromopropane peak on GC chromatograms. The reaction finished within 5 minutes and did not sensitive to the type of iron precatalyst (entries 1, 3 and 4). However, when 1.0 mL THF was used as a solvent instead of toluene, the yield dropped to 44% and there was no starting material left in the reaction. This result suggests that THF interferes the catalytic cycle after the substrate undergoes oxidative addition.

Table 3.20 Cross-coupling reaction of 2-bromododecane

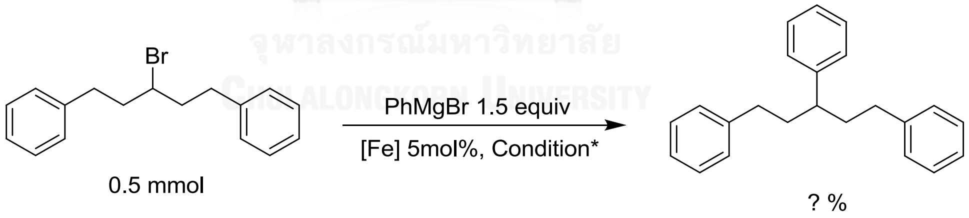


Entry	Solvent : volume*	Condition	Yield (%)
1	Toluene: 2.5 mL	AI = 1 min, AST = 10 min	40
2	Toluene: 2.5 mL	AI = 20 sec, AST = 2 min	37
3	THF: 0.5 mL	AI = 2 min, AST 10 min	trace

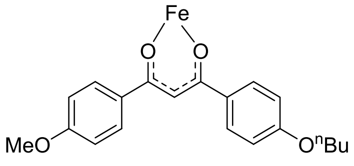
Bromo- starting material was still left after reaction in all 3 entries. The reaction slowdown after a short reaction time. Longer stirring time slightly increase product yield (entries 1 and 2). These results shows that steric hindrance of substrate might be the obstacle for this reaction.

Hence, the more steric substrate was tested in this reaction.

Table 3.21 Cross-coupling reaction of 3-bromo-1,5-diphenylpentane



Entry	Condition	Yield (%)
1	5mol% $FeCl_3$, Tol 2.5 mL, rt, 10 min	0
2	5mol% Fe[OMe,OBu-DBM]Cl_2, Tol 2.5 mL, rt, 10 min	0



[Fe] catalyst

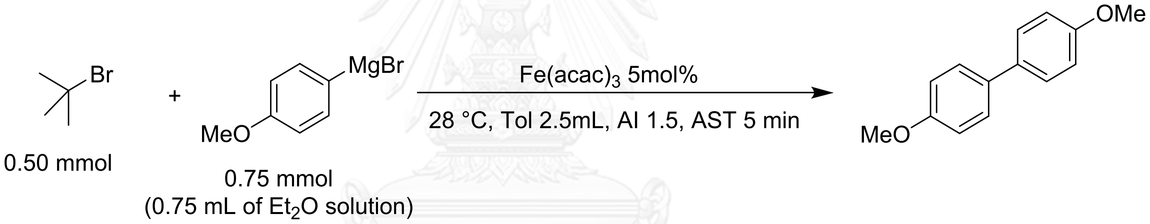
: Catalyst in entry 2

Using high steric hindrance bromo substrate, the condition in entry 1 cannot give any cross-coupling product at all. The GC chromatogram showed only unreacted substrate and small peaks which were suspected to be alkene and alkane by-products.

The reaction in entry 2 was conducted in presence of iron complex with electron donating ligand to promote the conversion of starting material. And GC chromatogram showed only more by-product occurred in the reaction but no signal of the cross-coupling at all.

3.4.3 3°-Alkyl Halide

Tert-Butyl bromide was used to represent the tertiary alkyl bromide substrate. It was allowed to react with anisyl magnesium bromide for 5 min in the following condition.



96% conversion of ^{t}Bu-Br and the only product was bianisyl

The result showed no cross-coupling of *tert*-butyl group, the only peak signal was bianisyl homo-coupling product. This result indicated that *tert*-butylbromide acted as an oxidant for homo-coupling of anisylmagnesium bromide, the same role as dichloroethane in **Scheme 1.8**. These results implied the instability of alkyl iron intermediate and it was even worse when the alkyl had high steric hindrance.

3.5 Mechanistic Studies

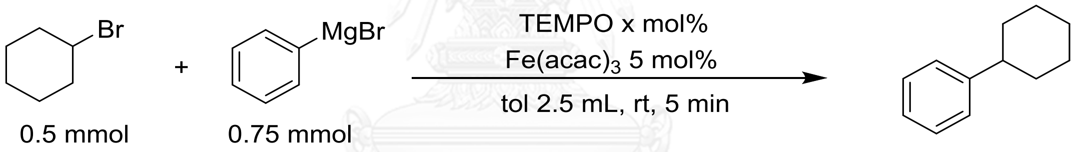
3.5.1 Effect of Tempo Radical Trap

The mechanism of this type of reaction, iron-catalyzed cross-coupling between aryl Grignard reagent and alkyl halide, has already been studied by some groups. It was reported that the catalytic cycle may involve a radical species due to the evidences such as isomerization of a radical clock and racemization in obtained product [19, 25].

Reaction Test with TEMPO

Under the optimum condition, effect of TEMPO in different amount was tested. Comparing to a blank reaction (no TEMPO added) Condition: Toluene 2.5 mL, room temperature bath, 20 sec addition time of 0.75 mL PhMgBr (1.0 M in THF).

Table 3.22 Effect of TEMPO in coupling reaction of bromocyclohexane



Entry	TEMPO	Recovery of CyBr (%)	PhCy (%)	MB (%)	Biphenyl (%)^a
1	100 mol%	90.5	4.1	96.9	152
2	50 mol%	55.4	36.0	95.6	122
3	10 mol%	0	99.2	105.8	54
4	0 mol%	0	95.6	102.0	31

a: %equivalent of phenyl part comparing with bromo substrate

From **Table 3.21**, addition of TEMPO to the reaction resulted in lowering coupling product yield. And it depended on amount of TEMPO added, the more TEMPO added the more reaction will be inhibited. However, determination of biphenyl by-product showed that when higher amount of TEMPO was added the biphenyl by-product will be obtained in higher amount. It might be the case that TEMPO reacted directly to PhMgBr instead of trapping the alkyl radical. And looking up the literature showed the following reaction [26].

$$2\ \mathrm{R{-}MgX} + 2\ \mathrm{TEMPO} \longrightarrow \mathrm{R{-}R} + 2\ \mathrm{TEMPO{-}MgX}$$

(R = aryl, alkenyl, alkynyl)

It was shown that TEMPO could react with aryl Grignard reagent giving homo-coupling product quantitatively within 5 minutes. Hence, TEMPO could not be used for radical trapping in the reaction with the presence of Grignard reagent.

3.5.2 The Plausible Catalytic Cycle

Some example of supporting evidence

Owing to Bedford's mechanistic study, it was shown that diaryl iron(II) complex had low reactivity toward alkyl halide and it could not be the part of fast catalytic cycle [27]. It was shown that ate complex presented much higher reactivity toward alkyl halide and diaryl iron(II) with less bulkiness will be reduced to lower than +II.

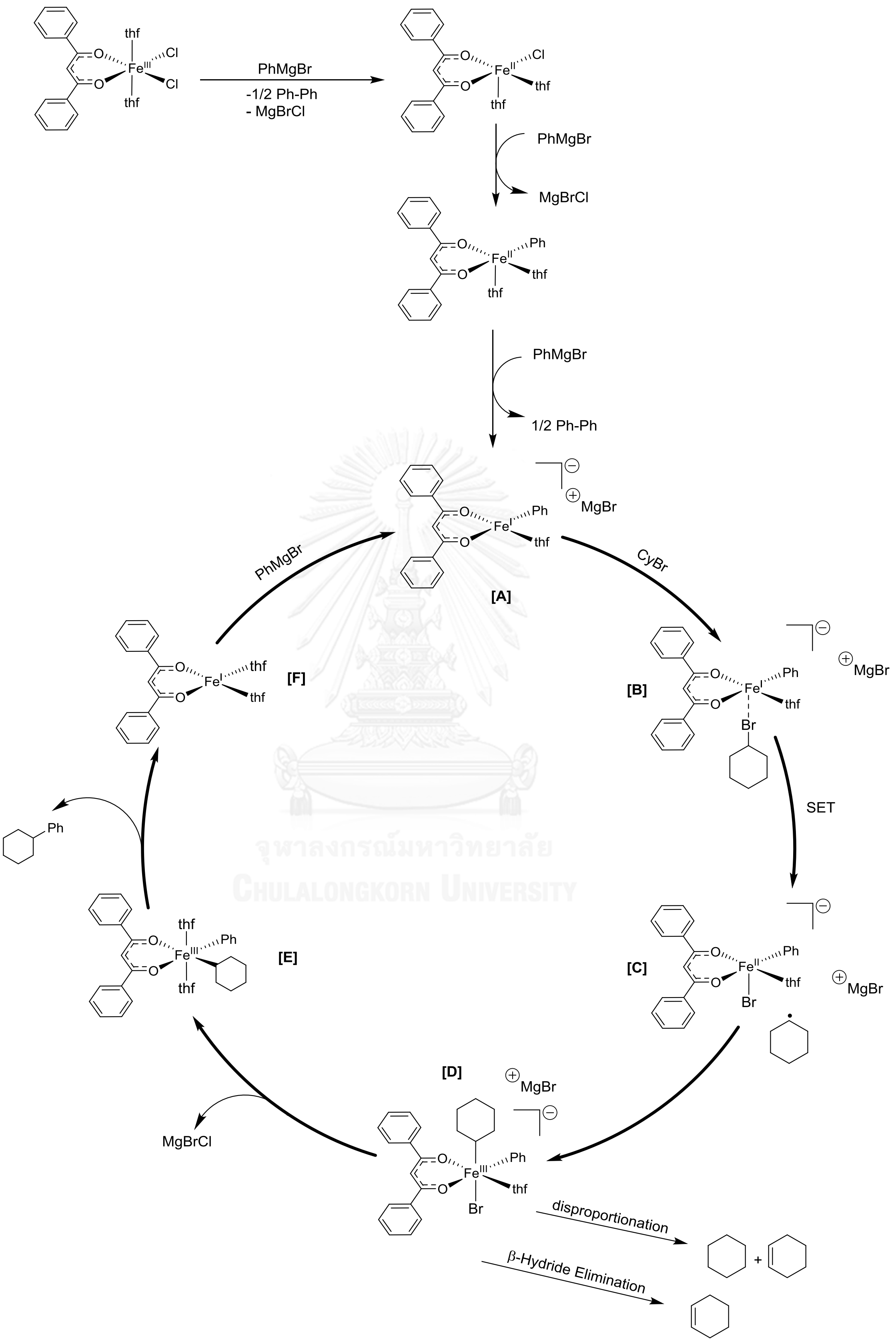
Due to, Anna's doctoral dissertation [18] the reduction of iron(III) halides by phenylmagnesium bromide was examined. The result showed that biphenyl occurred per one mole iron(III) was equivalent to the reduction by 2 moles electron. It indicated the iron(I) species.

Many works showed involvement of radical species of halide substrate [19, 25].

The plausible mechanism shown in **Scheme 3.1** was adapted from the mechanism of heteroaryl halide cross-coupling [28].

Rate of disproportionation, which can occur in step C D and E, depends on nature of substrate. Disproportionation undergoes through radical pathway and steric hindrance of radical species will make it less active. For example, the rate of disproportionation of primary alkyl is higher than the secondary and tertiary one and depends on type of metal center.

When dealing with catalysis, kinetic controlled product forms and the issue that should be concerned is the probable competitive pathways.

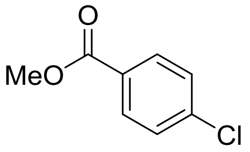
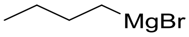
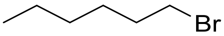
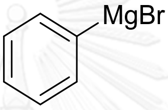
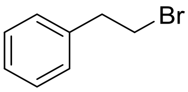
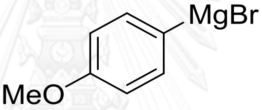
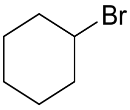
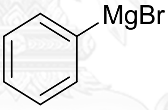
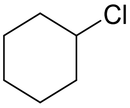
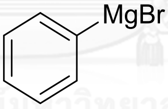
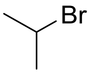
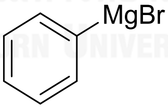
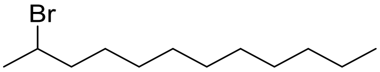
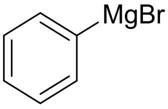
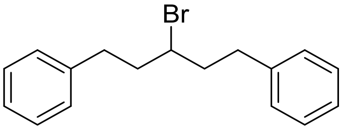
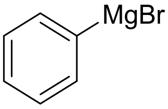
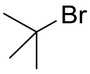
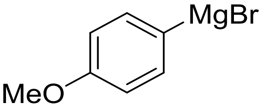


Scheme 3.1 Plausible catalytic cycle for alkyl halide and aryl Grignard cross-coupling

3.6 Summary of Substrate Scope

From all the studies in this work, the substrate scope of cross-coupling reaction catalyzed by iron was summarized.

Table 3.23 Summary of Substrate Scope

Halide Substrates	RMgBr	Yield (%)	Reference (page)
		93	28
		74	43
		68	53
		94	47
		85	51
		79	54
		40	55
		0	55
		0	56

CHAPTER IV

CONCLUSION

The iron-catalyzed cross-coupling reaction of secondary alkyl halide and aryl Grignard reagent was reported to be achieved in high yield only when an additive or a special ligand was used; for example, phosphine, *N*-heterocyclic carbene, tridentate β-aminoketonato, etc. However, in this work it was shown that high yielding of the cross-coupling product could be furnished by condition adjustment. Toluene is the most suitable solvent for this reaction. Under the optimum condition, usage of $FeCl_3$ as a very simple catalyst source provided high yield of cross-coupling up to 92% for bromocyclohexane substrate. For chlorocyclohexane substrate the reaction using $FeCl_3$ provided cross-coupling product at 76%. It has never been reported before that simple iron salt could efficiently mediated this reaction without any additive.

To study the ligand effect, the reactions with chloro- or bromocyclohexane substrate were carried out using synthesized 1,3-dicarbonyl ligands. The presence of electron-donating substituent on the 1,3-dicarbonyl ligand increased %conversion of chlorocyclohexane, while the ligand with electron-withdrawing substituent lowered the %conversion. These results suggested that for the chlorocyclohexane substrate, high electron density on iron species was needed to efficiently promote the reaction.

In the case of bromocyclohexane, conversion rate was very fast and complete in all cases of different ligands. On the other hand, the ligand with electron-withdrawing group decreased the amount of by-products, resulted in higher product yield.

The use of precatalysts combination, containing $Fe(dbm\text{-}derivative)_3$ and $FeCl_3$, to limit the ratio of ligand to iron showed the best result. The appropriate molar ratio of diketonate ligand to iron was 1.5:1 which can be performed practically by using 2.5 mol% of $Fe(dbm\text{-}derivative)_3$ and 2.5 mol% of $FeCl_3$. The result of this method gave 94% yield from bromocyclohexane and 85% yield from chlorocyclohexane.

Extending the substrate scope showed that the reaction was sensitive to the steric hindrance of halide starting material. The larger or the more steric hindrance the substrate was, the lower %conversion was obtained.

In the case of primary alkyl halide, the reaction was more sensitive to THF. Grignard reagent in THF lowered the yield comparing to one in diethyl ether. So, it is recommended to use Grignard reagent in ether and carry out the reaction in ether or toluene. On the other hand, using tertiary alkyl halide staring material resulted in side reaction without any cross-coupling product obtained.

Proposal for the Further Work

In this research concerns with the development of methodology of iron-catalyzed cross-coupling reaction. It has advantage of high reactivity that the reaction can be complete in very short reaction time. But there are also competitive pathways to generate unwanted products. Some group reported the strong sigma donor ligand to inhibit side reaction of disproportionation. It would be helpful if an efficient ligand can be utilized in the optimized reaction condition of this work.

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APPENDIX

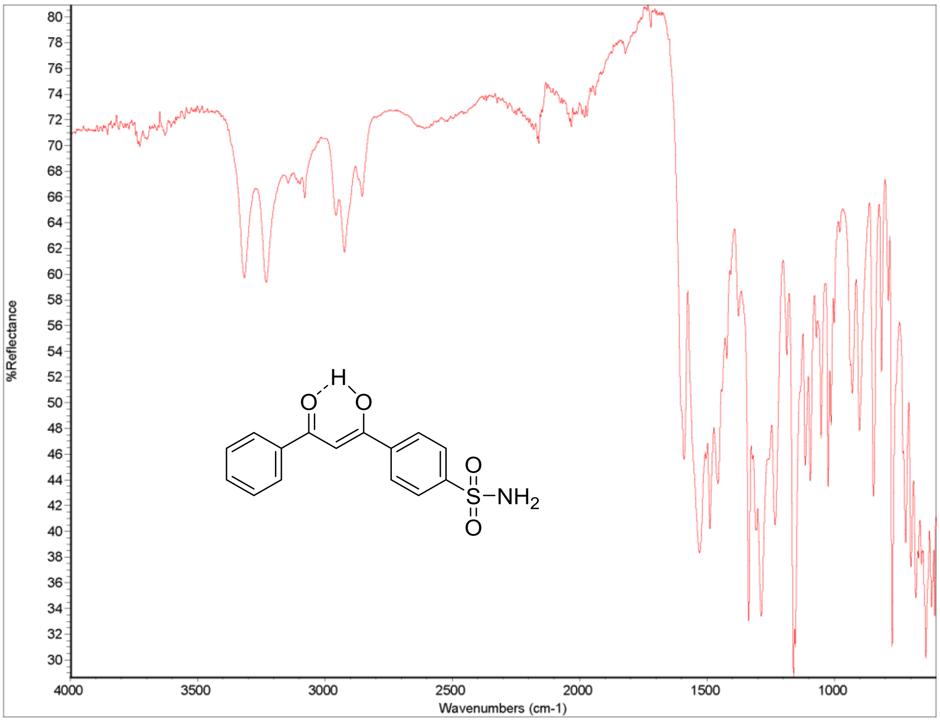

Figure A1 Infrared spectrum of L8

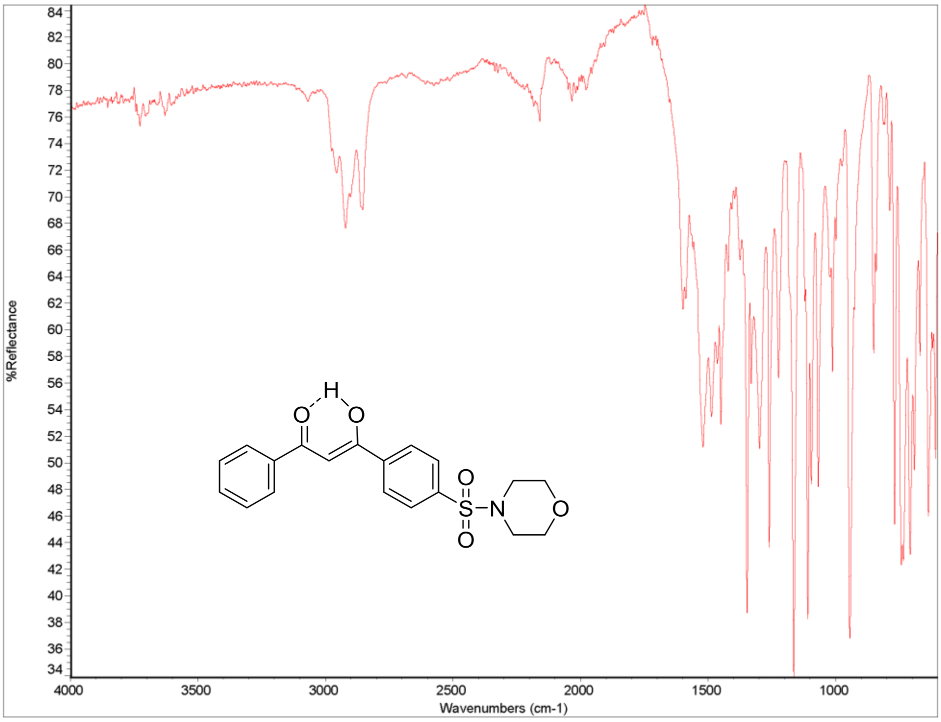

Figure A2 Infrared spectrum of L9

VITA

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