

# **Iron or Copper?**

## **– Method Development and Mechanistic Studies on Cross-Coupling Reactions**

Per-Fredrik Larsson



UNIVERSITY OF GOTHENBURG

Department of Chemistry and Molecular Biology

University of Gothenburg

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# **Iron or Copper? – Method Development and Mechanistic Studies on Cross-Coupling Reactions**

Per-Fredrik Larsson

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*Per aspera ad astra*

In memory of Per Larsson (1949-2008)



## Abstract

The area of catalysis has had an immeasurable impact on modern society. This has been acknowledged through several Nobel prizes during the 20<sup>th</sup> century ranging from Haber (1918) for the synthesis of ammonia to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki (2010) for palladium-catalyzed cross-coupling reactions.

The development of efficient cross-coupling reactions has made this transformation a vital instrument in the method library of organic synthesis. Today, cross-coupling reactions are widely used in industrial applications in areas such as fine chemical production and pharmaceutical industry. With increasing demands on environmentally friendly and cheaper alternatives to the commonly used palladium and nickel catalysts several alternative metals have been evaluated. Among these, both iron and copper have experienced a revival during the past two decades.

The iron-catalyzed cross-coupling reaction has proved successful for a range of transformations but the mechanistic picture behind these reactions is still not entirely comprehensive. Several important mechanistic features for this reaction are presented in this thesis based on experimental studies such as titration, kinetic, and competitive Hammett study. Several of these experimental results are supported by computational studies done by Dr. Kleimark.

In the pursuit of finding alternative catalysts for known transformations one has to consider the presence of potential trace-metal contaminants. The case presented in this thesis concerns the “iron” catalyzed C-N cross-coupling reaction which turned out to be catalyzed by traces of copper present in the commercially available iron source.

The discovery that many copper-catalyzed cross-coupling reactions could be run with much lower catalytic loadings than previously reported further strengthened the role of copper as a viable catalyst in cross-coupling reactions. Method development, kinetic studies and ligand synthesis for sub-mol% copper-catalyzed transformations are presented in this thesis.

**Keywords:** iron, copper, transition metal, cross-coupling, reaction mechanism, kinetic investigation, Hammett study, sustainable catalysis, trace-metal, mass-transfer, ligand development, ligand scope.

**ISBN:** 978-91-628-8505-2



## List of Publications

This thesis is based on the following papers, which are referred to in the text by their Roman numerals. Reprints were made with permission from the publishers.

- Paper I: *Mechanistic Investigation of Iron-Catalyzed Coupling Reactions*  
J. Kleimark, A. Hedström, P.-F. Larsson, C. Johansson, P.-O. Norrby  
*ChemCatChem*, 2009, *1*, 152-161
- Paper II: *Low Temperature Studies of Iron-Catalyzed Cross-Coupling of Alkyl Grignards with Aryl Electrophiles*  
J. Kleimark, P.-F. Larsson, P. Emamy, A. Hedström, P.-O. Norrby  
*Adv. Synth. Catal.*, 2012, *354*, 448-456
- Paper III: *Copper-Catalyzed Cross-Couplings with Part-per-Million Catalyst Loadings*  
P.-F. Larsson, A. Correa, M. Carril, P.-O. Norrby, C. Bolm  
*Angew. Chem., Int. Ed.*, 2009, *48*, 5691-5693
- Paper IV: *Mechanistic Aspects of Sub-mol% Copper-Catalyzed C-N Cross-Coupling Reactions*  
P.-F. Larsson, P.-O. Norrby  
*Manuscript*
- Paper V: *Kinetic Investigation of a Ligand-Accelerated Sub-mol% Copper-Catalyzed C-N Cross-Coupling Reaction*  
P.-F. Larsson, C. Bolm, P.-O. Norrby  
*Chem. Eur. J.*, 2010, *16*, 13613-13616
- Paper VI: *New Efficient Ligand for Sub-mol% Copper-Catalyzed Heteroatom Cross-Coupling Reactions Running Under Air*  
P.-F. Larsson, P. Astvik, P.-O. Norrby  
*Manuscript*

## Contributions to the Papers

- I. Contributed to the outline of the study. Performed parts of the experimental work. Contributed to the interpretation of the results. Wrote parts of the manuscript.
- II. Outlined the study. Planned and performed large part of the kinetic study. Contributed to the interpretation of the results. Wrote parts of the manuscript.
- III. Outlined the study and performed parts of the experimental work. Contributed to the interpretation of the results. Wrote parts of the manuscript.
- IV. Outlined the study and performed all experimental work. Contributed to the interpretation of the results. Wrote the manuscript.
- V. Outlined the study and performed all experimental work. Contributed to the interpretation of the results. Wrote the manuscript.
- VI. Outlined the study. Performed parts of the experimental work. Contributed to the interpretation of the results. Wrote the manuscript.



## Abbreviations

|                     |   |
|---------------------|---|
| acac                | acetylacetonate   |
| DBM                 | dibenzoylmethane  |
| DETA                | diethylene triamine   |
| DFT                 | density functional theory   |
| DMDETA              | dimethyldiethylene triamine   |
| DMEDA               | dimethylethylene diamine  |
| DMF                 | dimethylformamide   |
| DMSO                | dimethylsulfoxide   |
| EDA                 | ethylene diamine  |
| ESIMS               | electrospray ionization mass spectroscopy   |
| IAT                 | iodine atom transfer  |
| ICP-AES             | inductively coupled plasma atomic emission spectroscopy   |
| ICP-MS              | inductively coupled plasma mass spectroscopy  |
| KHMDS               | potassium hexamethyldisilazane  |
| NHC                 | N-heterocyclic carbene  |
| NMP                 | N-methylpyrrolidone   |
| NMR                 | nuclear magnetic resonance  |
| P <sub>4</sub> -tBu | 1-tert-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylidenamino]-2λ5,4λ5-catenadi(phosphazene)                             |
| P <sub>2</sub> -Et  | 1-ethyl-2,2,4,4,4-pentakis(dimethylamino)-2λ5,4λ5-catenadi(phosphazene), tetramethyl(tris(dimethylamino)phosphoranylidene)phosphorictriamid-et-imin |
| SET                 | single electron transfer  |
| S <sub>RN</sub> 1   | unimolecular radical nucleophilic substitution  |
| TBAA                | tetrabutylammonium adipate  |
| TBPE                | tetrabutylphosphonium ethanoate   |
| TBPM                | tetrabutylphosphonium malonate  |
| TEMPO               | (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl  |
| THF                 | tetrahydrofuran   |
| TMEDA               | tetramethylethylene diamine   |
| Ts                  | tosyl   |
| UV                  | ultraviolet   |

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# 1. Introduction

## 1.1 Transition Metal Catalyzed Cross-Coupling Reactions

### 1.1.1 Catalysis

A catalyst is defined as a substance that lowers the free energy barrier of a given reaction without itself being consumed, hence increasing the rate of the transformation.<sup>1</sup> The situation is depicted in Figure 1 where substrates A and B react to form product C. Without the presence of the catalyst (cat.), the activation barrier for the reaction is too high for the reaction to proceed. Adding the catalyst enables a different reaction pathway which lowers the total activation energy and facilitates the product formation.

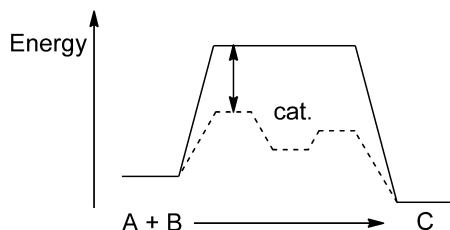
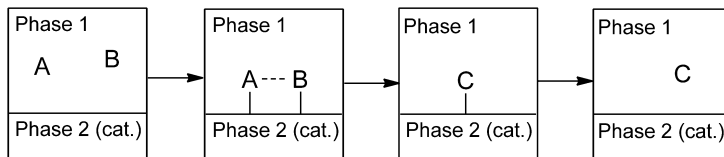


Figure 1 General principle of catalysis

Catalysis can be classified as either heterogeneous or homogeneous. In heterogeneous catalysis the reaction occurs near or at the interface between phases whereas in the case of homogeneous catalysis the reaction occurs in one phase (Figure 2). The phases can either be gas, liquid or solid state. There are several subcategories of homogeneous catalysis where the most prominent are transition metal-, enzyme-, organo- and Lewis acid-catalysis

### Heterogeneous Catalysis



### Homogeneous Catalysis

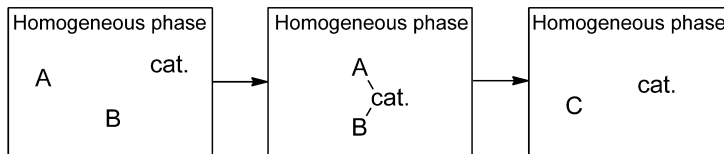


Figure 2 Homogeneous versus heterogeneous catalysis

There are numerous important processes in chemistry that utilize catalysis as a mean of forming desired products. The Haber-Bosch process is one of the most prominent heterogeneous catalytic processes, fixating nitrogen and hydrogen to produce ammonia. From this process over 500 million tons of fertilizer is produced each year (2004).<sup>2</sup> These fertilizers have been estimated to have supported around 27% of the world's population during the past century. The process alone is so important that predications show that the world's population in 2008 would have peaked at approximately 3 billion instead of 6 billion, in the absence of its development.<sup>3</sup> One example of an important homogeneous catalytic processes is the Monsanto process in which 2 million tons of acetic acid is produced from methanol every year.<sup>4</sup>

## 1.1.2 Transition Metals

Transition metals is a group of elements that are situated in the group 3-12 in the periodic table (Figure 3). Transition metals are characterized by their electronic structure  $[(n-1)d^m ns^2]$  with incomplete d sub-shell giving rise to the exceptional ability to form a vast variety of complexes.<sup>5</sup>

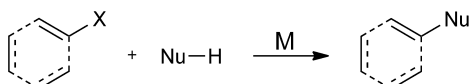
| 1<br>IA                  | 2<br>IIA                 | The transition metals     |                          |                          |                          |                          |                          |                          |                          |                          |                          | 13<br>IIIA               | 14<br>IVA                 | 15<br>VA                  | 16<br>VIA                 | 17<br>VIIA                | 18<br>VIIIA               |                            |                            |                            |                            |                            |                            |                            |                            |                            |                            |                            |                            |                            |                            |                            |                            |                          |                           |
|--------------------------|--------------------------|---------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|--------------------------|---------------------------|
| 1<br><b>H</b><br>1.01    | 2<br><b>He</b><br>4.00   |                           |                          |                          |                          |                          |                          |                          |                          |                          |                          | 5<br><b>B</b><br>10.81   | 6<br><b>C</b><br>12.01    | 7<br><b>N</b><br>14.01    | 8<br><b>O</b><br>16.00    | 9<br><b>F</b><br>19.00    | 10<br><b>Ne</b><br>20.18  |                            |                            |                            |                            |                            |                            |                            |                            |                            |                            |                            |                            |                            |                            |                            |                            |                          |                           |
| 3<br><b>Li</b><br>6.94   | 4<br><b>Be</b><br>9.01   | 3<br><b>Na</b><br>22.99   | 4<br><b>Mg</b><br>24.31  | 5<br><b>Al</b><br>26.98  | 6<br><b>Si</b><br>28.09  | 7<br><b>P</b><br>30.97   | 8<br><b>S</b><br>32.07   | 9<br><b>Cl</b><br>35.45  | 10<br><b>Ar</b><br>39.95 | 11<br><b>K</b><br>39.1   | 12<br><b>Ca</b><br>40.08 | 13<br><b>Sc</b><br>44.96 | 14<br><b>Ti</b><br>47.88  | 15<br><b>V</b><br>50.94   | 16<br><b>Cr</b><br>52.00  | 17<br><b>Mn</b><br>54.94  | 18<br><b>Fe</b><br>55.85  | 19<br><b>Co</b><br>58.93   | 20<br><b>Ni</b><br>58.69   | 21<br><b>Cu</b><br>63.55   | 22<br><b>Zn</b><br>65.39   | 23<br><b>Ga</b><br>69.72   | 24<br><b>Ge</b><br>72.61   | 25<br><b>As</b><br>74.92   | 26<br><b>Se</b><br>78.96   | 27<br><b>Br</b><br>79.90   | 28<br><b>Kr</b><br>83.80   |                            |                            |                            |                            |                            |                            |                          |                           |
| 19<br><b>K</b><br>39.1   | 20<br><b>Ca</b><br>40.08 | 21<br><b>Sc</b><br>44.96  | 22<br><b>Ti</b><br>47.88 | 23<br><b>V</b><br>50.94  | 24<br><b>Cr</b><br>52.00 | 25<br><b>Mn</b><br>54.94 | 26<br><b>Fe</b><br>55.85 | 27<br><b>Co</b><br>58.93 | 28<br><b>Ni</b><br>58.69 | 29<br><b>Cu</b><br>63.55 | 30<br><b>Zn</b><br>65.39 | 31<br><b>Ga</b><br>69.72 | 32<br><b>Ge</b><br>72.61  | 33<br><b>As</b><br>74.92  | 34<br><b>Se</b><br>78.96  | 35<br><b>Br</b><br>79.90  | 36<br><b>Kr</b><br>83.80  | 37<br><b>Rb</b><br>85.47   | 38<br><b>Sr</b><br>87.62   | 39<br><b>Y</b><br>88.91    | 40<br><b>Zr</b><br>91.22   | 41<br><b>Nb</b><br>92.91   | 42<br><b>Mo</b><br>95.94   | 43<br><b>Tc</b><br>(98)    | 44<br><b>Ru</b><br>101.07  | 45<br><b>Rh</b><br>102.91  | 46<br><b>Pd</b><br>106.42  | 47<br><b>Ag</b><br>107.87  | 48<br><b>Cd</b><br>112.41  | 49<br><b>In</b><br>114.82  | 50<br><b>Sn</b><br>118.71  | 51<br><b>Sb</b><br>121.76  | 52<br><b>Te</b><br>127.6   | 53<br><b>I</b><br>126.9  | 54<br><b>Xe</b><br>131.29 |
| 55<br><b>Cs</b><br>132.9 | 56<br><b>Ba</b><br>137.3 | 57<br><b>La*</b><br>138.9 | 58<br><b>Ce</b><br>140.1 | 59<br><b>Pr</b><br>140.9 | 60<br><b>Nd</b><br>144.2 | 61<br><b>Pm</b><br>(145) | 62<br><b>Sm</b><br>150.4 | 63<br><b>Eu</b><br>152.0 | 64<br><b>Gd</b><br>157.3 | 65<br><b>Tb</b><br>158.9 | 66<br><b>Dy</b><br>162.5 | 67<br><b>Ho</b><br>164.9 | 68<br><b>Er</b><br>167.3  | 69<br><b>Tm</b><br>168.9  | 70<br><b>Yb</b><br>173.0  | 71<br><b>Lu</b><br>175.0  | 72<br><b>Rn</b><br>(222)  | 73<br><b>Fr</b><br>(223)   | 74<br><b>Ra</b><br>(226)   | 75<br><b>Ac^</b><br>(227)  | 76<br><b>Rf</b><br>(261)   | 77<br><b>Db</b><br>(262)   | 78<br><b>Sg</b><br>(263)   | 79<br><b>Bh</b><br>(264)   | 80<br><b>Hs</b><br>(265)   | 81<br><b>Mt</b><br>(268)   | 82<br><b>Ds</b><br>(271)   | 83<br><b>Rg</b><br>(272)   | 84<br><b>Tl</b><br>204.4   | 85<br><b>Pb</b><br>207.2   | 86<br><b>Bi</b><br>209     | 87<br><b>Po</b><br>(209)   | 88<br><b>At</b><br>(210)   | 89<br><b>Rn</b><br>(222) |                           |
| 87<br><b>Fr</b><br>(223) | 88<br><b>Ra</b><br>(226) | 89<br><b>Ac^</b><br>(227) | 90<br><b>Th</b><br>232.0 | 91<br><b>Pa</b><br>(231) | 92<br><b>U</b><br>238.0  | 93<br><b>Np</b><br>(237) | 94<br><b>Pu</b><br>(244) | 95<br><b>Am</b><br>(243) | 96<br><b>Cm</b><br>(247) | 97<br><b>Bk</b><br>(247) | 98<br><b>Cf</b><br>(251) | 99<br><b>Es</b><br>(252) | 100<br><b>Fm</b><br>(257) | 101<br><b>Md</b><br>(258) | 102<br><b>No</b><br>(259) | 103<br><b>Lr</b><br>(260) | 104<br><b>Uu</b><br>(285) | 105<br><b>Uub</b><br>(286) | 106<br><b>Uut</b><br>(287) | 107<br><b>Uuq</b><br>(288) | 108<br><b>Uur</b><br>(289) | 109<br><b>Uus</b><br>(290) | 110<br><b>Uuh</b><br>(291) | 111<br><b>Uuq</b><br>(292) | 112<br><b>Uuo</b><br>(293) | 113<br><b>Uuq</b><br>(294) | 114<br><b>Uur</b><br>(295) | 115<br><b>Uus</b><br>(296) | 116<br><b>Uuh</b><br>(297) | 117<br><b>Uuq</b><br>(298) | 118<br><b>Uuo</b><br>(299) | 119<br><b>Uuq</b><br>(300) | 120<br><b>Uur</b><br>(301) |                          |                           |

Figure 3 Periodic table of the elements

Due to these characteristics, many transition metals are used as catalysts in organic chemistry to make or break organic bonds. The flexible environment also makes it possible to design the surrounding of the transition metals by using ligands which bind to the metal center and change the steric bulk and/or the electronic properties of the desired catalyst.

### 1.1.3 Cross-Coupling Reactions

The transition metal catalyzed cross-coupling is in principle a nucleophilic substitution reaction between an electrophile, for example aromatic or vinylic halide and/or sulfonate, and a nucleophile, that can be an activated carbon or heteroatom compound, with a metal as catalyst (Scheme 1).<sup>5</sup>



Scheme 1 Cross-coupling reaction

This category of reactions is an immensely important tool in organic chemistry enabling a diverse set of otherwise inaccessible advanced molecular transformation. The history of these reactions stretches from the late 19th century up until today. Some notable cross-coupling reactions and the year of their discovery are shown in Figure 4.<sup>6-24</sup>

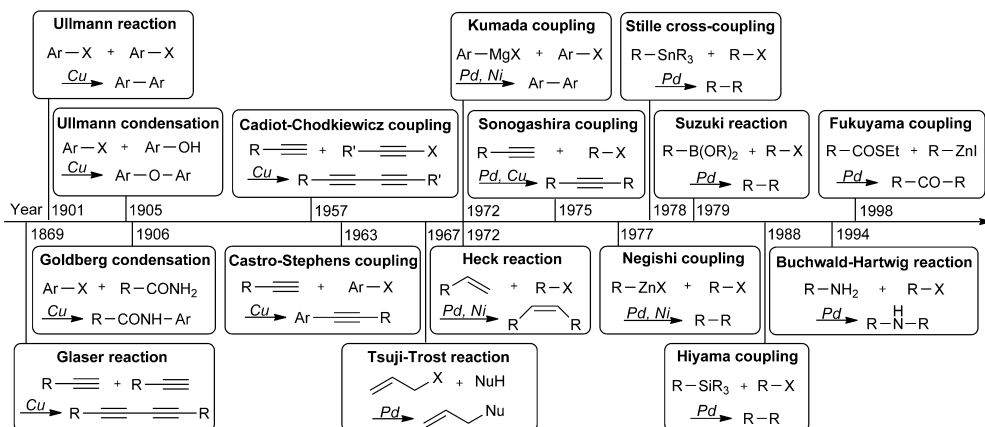


Figure 4 Time-line of notable cross-coupling reactions

Since the 1990's the number of publications and patents for palladium catalyzed cross-couplings have grown steadily (Figure 5).<sup>25</sup> A total of approximately 16 000 publications and patents have been published during 1991-2010 for seven of these reactions: Suzuki, Heck, Sonogashira, Stille, Negishi, Buchwald-Hartwig, and Kumada reaction.



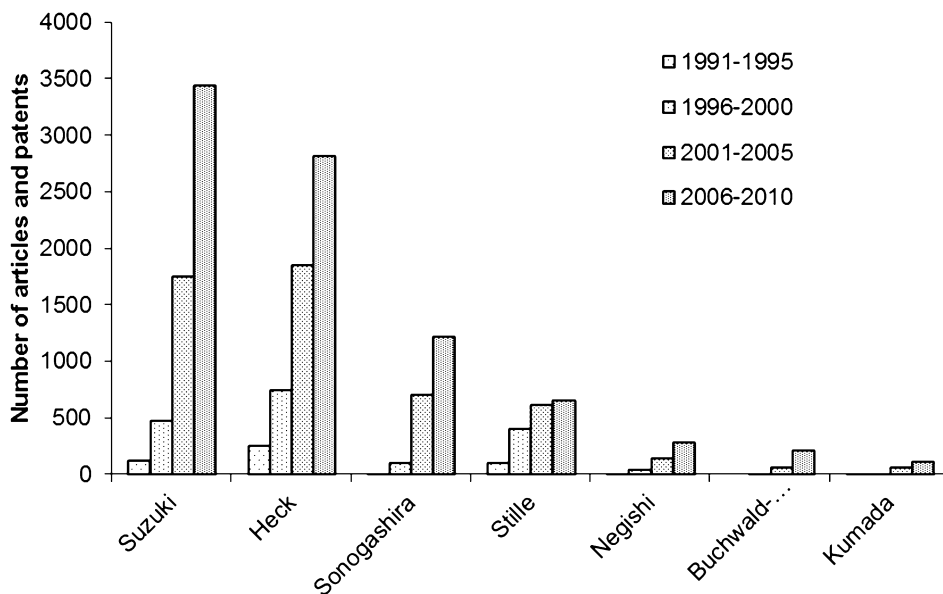


Figure 5 Total number of publications and patents for some palladium catalyzed cross-coupling reactions<sup>a</sup>

The Suzuki reaction is one of the most common reactions used in large scale fine chemical production world-wide today.<sup>26</sup> The importance of the area was acknowledged in 2010 by the awarding of the Nobel Prize in chemistry to three pioneers in the area of palladium catalyzed cross-coupling reactions: Richard F. Heck, Ei-ichi Negishi and Akira Suzuki.

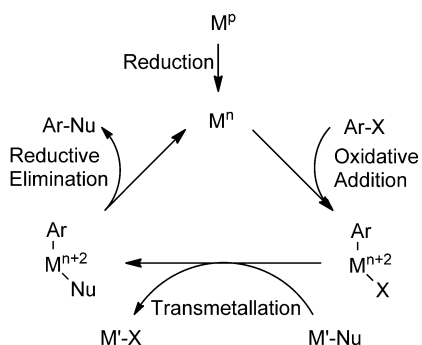
The scope and application of transition metal catalyzed cross-coupling reactions in organic chemistry is immense.<sup>25,27-33</sup> Even though the progression pace has steadily been increasing and the area has been referred to as “mature” there is still much to be discovered.<sup>34</sup>

<sup>a</sup> Numbers taken from Web of Science data base ([www.isiknowledge.com](http://www.isiknowledge.com)) 2012-07-15

### 1.1.4 Mechanism

Increased mechanistic knowledge is the key for effective method development and ligand design and hence a fundamental part of organic chemistry.

Numerous mechanistic studies have been done on cross-coupling reactions.<sup>25,27,28,30,31,33</sup> The most commonly evoked catalytic cycle for cross-coupling reactions starts with an oxidative addition followed by a transmetalation and finally ending with a reductive elimination (Scheme 2).<sup>15</sup>



Scheme 2 General catalytic cycle for cross-coupling reactions

In many cases the pre-catalyst is reduced *in-situ* to form the active catalyst such as Pd(II) to Pd(0) and Ni(II) to Ni(0). This can be achieved through several different pathways, such as double transmetalation to the pre-catalyst followed by reductive elimination to form the active catalyst (Scheme 3).



Scheme 3 Formation of the active catalyst

## 1.2 Kinetic Methods

### 1.2.1 Reaction Kinetics

Reaction kinetics studies the rate ( $v$ ) at which the reactant/reactants disappear and the product is formed in a given reaction system. A kinetic study is often used by chemists as a first means to study a reaction in general. Although the kinetics does not usually prove a mechanism it is a powerful tool for excluding possible mechanism and hence narrows down the plausible pathways for a given system. A given stoichiometric reaction where  $n_A$  molecules of A reacts with  $n_B$  molecules of B to produce  $n_C$  molecules of C can be expressed as Equation 1.<sup>35,36</sup>



Equation 1

The rate of the reaction is the change in concentration and depends on the concentrations of the involved species. The rate can be expressed as a differential rate equation (Equation 2).

$$v = \frac{1}{n_C} \frac{d[C]}{dt} = -\frac{1}{n_A} \frac{d[A]}{dt} = -\frac{1}{n_B} \frac{d[B]}{dt} = k_r [A]^a [B]^b$$

Equation 2

In Equation 2,  $k_r$  is the rate constant for the reaction, and  $a$  and  $b$  are the reaction orders in A and B, respectively. The reaction order is often a whole number or zero. A common exception from this is multi-step reactions where more than one energy barrier is rate limiting during the reaction. Another example is when off-cycle equilibrium is present in a catalytic cycle. In these cases fractional reaction orders can be found. Single step reaction orders give information about the number of molecules involved in the transition state of the reaction. For example, a first order reaction in A means that one molecule of A is present in the rate determining transition state of the reaction.

To determine the reaction order for a unimolecular reaction the logarithm of the differential rate equation (Equation 2) gives us Equation 3.

$$v = k_r[A]^a \Rightarrow \log(v) = \log(k_r) + a \log[A]$$

Equation 3

By plotting  $\log[A]$  against  $\log(v)$  the slope of the linear correlation is equal to the reaction order  $a$  with  $\log(k)$  as intercept. For more complex reaction systems involving several reactants for example A, B and C, the pseudo-first order assumption can be used (Equation 4). The assumption is based on varying the concentration of just one of the reactants, keeping the others at high enough concentration and hence effectively constant. This gives an apparent rate constant,  $k_{app}$ , instead of the actual  $k_r$  (Equation 4).

$$v = k_r[A]^a[B]^b[C]^c = k_{app}[A]^a$$

Equation 4

Through this, the reaction order and hence the rate law for the specific reaction, can be determined by a stepwise procedure for all the components by using the logarithmic expression shown in Equation 3. Note that this assumption is also only true for the initial stage of the reaction when the variations of the concentration for the reaction components are negligible.

The differential rate equation (Equation 2) may also be expressed as an *integrated rate equation*, which allows comparison between experimental concentration data and that predicted by the rate expression. The integrated rate equation for a first order reaction is expressed in Equation 5.

$$\ln[A] = \ln[A]_0 - k_1 t$$

Equation 5

$[A]_0$  is the value of  $[A]$  at  $t = 0$ . Plotting the logarithm of  $[A]$  should then produce a linear correlation with slope  $-k_1$ .

### 1.2.2 Hammett Equation

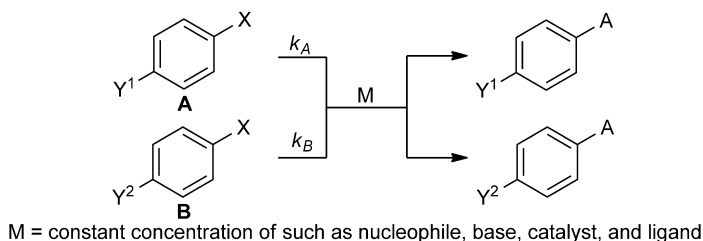
The Hammett equation, developed in 1937 by Louis Plack Hammett, is a linear free-energy relationship which relates the reaction rate or the equilibrium constant for meta- and para-substituted aromatic compounds (Equation 6).<sup>37</sup>

$$\log\left(\frac{K}{K_H}\right) = \rho\sigma \quad \text{or} \quad \log\left(\frac{k}{k_H}\right) = \rho\sigma$$

Equation 6

$K$  and  $k$  are the equilibrium or rate constants for a reaction. The  $\sigma$ -constants were originally defined by fitting to known ionization constants of para- and meta-substituted benzoic acids. Different  $\sigma$ -values have been tabulated for a selected few model reactions. A large positive  $\sigma$ -constant for a specific substituent generally implies a high electron withdrawing power relative to H and a large negative  $\sigma$ -constant implies a high electron donating power relative to H. The value of  $\rho$  (the reaction constant) gives information about the electronic properties of the rate limiting transition state in the reaction mechanism. If  $\rho > 0$ , the transition state is stabilized by electron-withdrawing substituents, hence indicating that the charge of the transition state at the benzylic position becomes more negative. In the situation when  $\rho < 0$  the transition state is stabilized by electron donating substituents, indicating that the charge of the transition state at the benzylic position becomes more positive. Large magnitudes of  $\rho$  indicate that the reaction is going through an ionic-type mechanism.

A simple and efficient variant for gaining insight into a reaction mechanism is to construct a competitive Hammett study. Instead of relying on absolute kinetics this method competes two substrates in the same reaction vessel, reacting with rate constants  $k_A$  and  $k_B$  (Scheme 4).



Scheme 4 Competitive Hammett study

The assumption that both the substrates follow the same mechanism with the same selectivity determining step has to be made to make this method valid. As opposed to the regular Hammett study, a competitive Hammett study does not give the individual rate constants for each substrate but rather the relative rate constants. The rate expression for **A** and **B** are shown in Equation 7.

$$-\frac{d[A]}{dt} = k_A[M][A] \text{ and } -\frac{d[B]}{dt} = k_B[M][B]$$

Equation 7

Dividing  $-\frac{d[A]}{dt}$  by  $-\frac{d[B]}{dt}$  gives the following expression (Equation 8).

$$\frac{d[A]}{d[B]} = \frac{k_A [A]}{k_B [B]} \Rightarrow \frac{d[A]}{[A]} = \frac{k_A}{k_B} \frac{d[B]}{[B]}$$

Equation 8

Through this both the time- and temperature-dependence together with most other reaction condition variables cancel out. Integration of Equation 8 gives Equation 9.

$$\ln \frac{[A_0]}{[A]} = \frac{k_A}{k_B} \ln \frac{[B_0]}{[B]}, k_{rel} = \frac{k_A}{k_B}$$

Equation 9

The competitive Hammett plot is then constructed through Equation 10.

$$\log \frac{k_A}{k_H} = \log k_{rel} = \rho\sigma$$

Equation 10

Instead of  $\rho$  giving the nature of the rate limiting transition state it is instead giving information about the selectivity-determining step of the reaction. Due to the experimental simplicity it is a very powerful and useful method for mechanistic studies, especially in combination with computational and absolute kinetic studies.

### 1.3 Aim of the Thesis

The area of iron and copper-catalyzed cross-coupling reactions has experienced a renaissance during the last two decades due to firmer demands on cost-reduction, environment concerns and sheer scientific curiosity. Although iron and copper have now proved to be useful tools in organic chemistry these areas are still underdeveloped compared to the more commonly used palladium counterpart.

The aim of this thesis is to give a comprehensive summary of the scientific development in the area of iron- and copper-catalyzed cross-coupling reactions ultimately leading up to the work done in our research group (**Paper I-VI**). Methods used include reaction and ligand development, mechanistic studies and computational work. The thesis also includes an intermezzo, discussing the impact and consequences of trace-metal catalysis in organic chemistry.





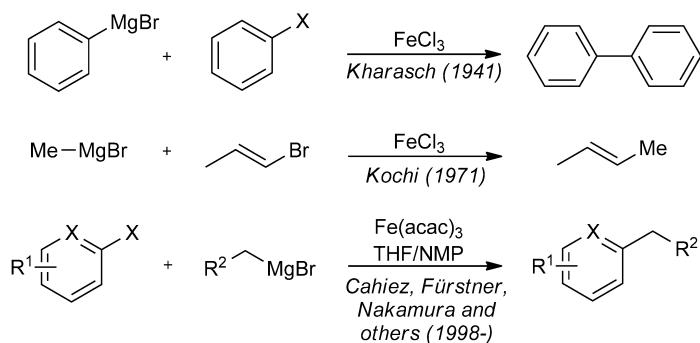
## 2. Iron-Catalyzed Cross-Coupling Reactions

### 2.1 Iron-Catalyzed C-C Cross-Coupling Reaction

#### 2.1.1 Background

Transition metal catalyzed C-C cross-coupling reactions are a fundamental part of organic chemistry and the development of new methods is still a growing field. Since the introduction of palladium (Heck, Suzuki, Sonogashira, Negishi, Stille, Hiyama) and nickel (Kumada) as effective catalysts for these transformations in the 1970's it has had a dominant position in the area of homogeneous catalysis.<sup>25,30-33</sup> Economic and environmental demands, as well as scientific curiosity, has led to development of less studied alternative catalysts for these transformations, among which iron has proved very efficient.<sup>38-42</sup>

The history of iron-catalyzed cross-coupling reactions dates back to the pioneering work done by Kharasch and Fields during the 1940's.<sup>10</sup> During the 1970's, Kochi further developed this area and performed extensive mechanistic studies on iron-catalyzed cross-coupling reaction of vinyl halides using Grignard reagents as nucleophile.<sup>43-49</sup> Since then the area has been more or less dormant until the groups of Fürstner, Cahiez, Nakamura and others revived the area in the late 1990's and early 2000's (Scheme 5).<sup>50-55</sup>

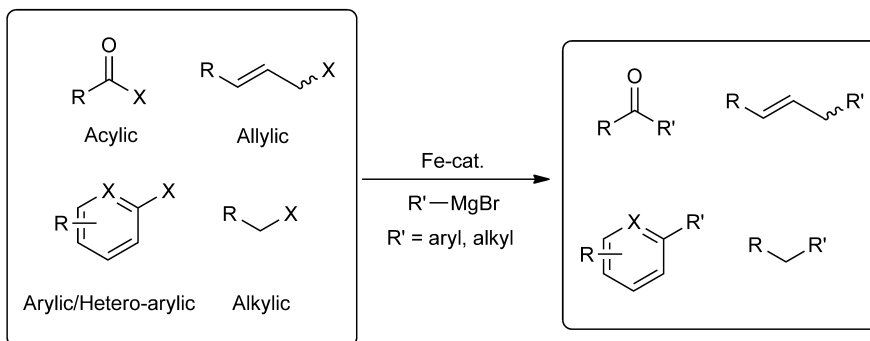


Scheme 5 Iron-catalyzed cross-coupling reactions from 1941 until today

Iron-catalyzed cross-coupling reaction has today established itself as a solid complement to other traditional transition metal catalysts, such as Pd, Cu, and Ni. The reaction scope has broadened greatly and much effort has been made to expand the mechanistic knowledge for these reaction systems.

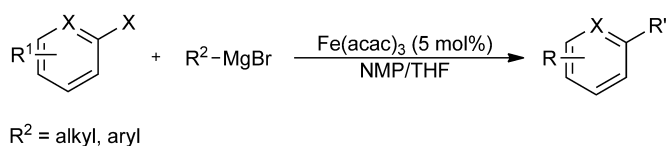
### 2.1.2 Reaction Scope

The scope of electrophiles for iron-catalyzed cross-coupling reactions has grown extensively (Scheme 6). Some notable work with acyclic and allylic electrophiles has been summarized in several reviews.<sup>38,39,41,42</sup>



Scheme 6 Range of electrophiles for iron-catalyzed cross-coupling reaction

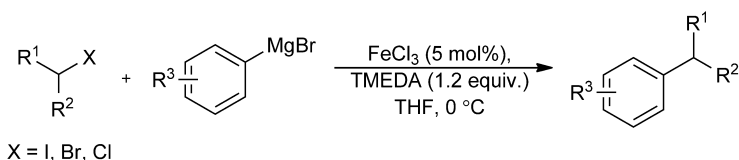
The introduction of N-methylpyrrolidone (NMP) as co-solvent in iron-catalyzed cross-coupling reactions by Cahiez and Avedissian was a great breakthrough which broadened the field immensely.<sup>50</sup> Fürstner and co-workers have worked extensively on iron-catalyzed cross-couplings on aryl electrophiles with alkyl/aryl Grignards (Scheme 7).<sup>38</sup>



Scheme 7 Iron-catalyzed cross-coupling of alkyl/aryl Grignards with aryl/hetero-aryl electrophiles

The reaction is more or less instantaneous at room temperature and the scope includes simple para- and meta-substituted aryl chlorides and triflates as well as more challenging hetero-aryl substrates. Contrary to the palladium systems the order of efficiency for the aryl electrophiles in cross-coupling reactions are  $ArOTf > ArCl > ArBr > ArI$ . The reaction can be run using simple iron(II) or iron(III)-salts of which the most commonly used are  $FeCl_2$ ,  $Fe(acac)_2$ ,  $FeCl_3$  and  $Fe(acac)_3$ .

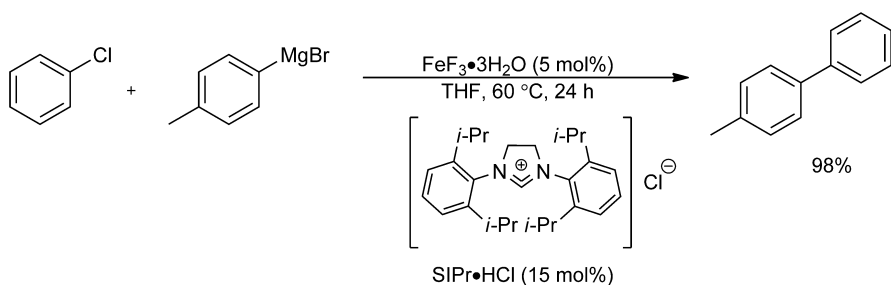
The ligand development for iron-catalyzed cross-coupling reactions has been scant but Nakamura *et al.* have successfully applied simple diamines, like tetramethylethylene diamine (TMEDA), for the coupling of aryl Grignards with alkyl electrophiles (Scheme 8).<sup>54</sup>



Scheme 8 Iron-catalyzed cross-coupling of aryl Grignards with alkyl electrophiles

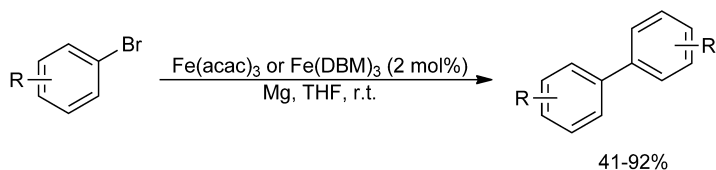
The risk of  $\beta$ -hydrogen elimination, when using primary and secondary alkyl halides, was avoided by slow addition of the Grignard reagent. Bedford and co-workers have also showed that salen is a valid ligand for these transformations.<sup>52</sup> Further work by the same group expanded the ligand scope to include phosphane, phosphite, arsine, or NHC ligands.<sup>56</sup>

One of the primary issues with the iron-catalyzed biaryl cross-coupling reaction is suppression of the homo-coupling of the Grignard reagent caused by either oxidation with the aryl halide or the iron-catalyzed halide-metal exchange. Nakamura *et al.* have developed a method, based on  $\text{FeF}_3 \cdot 3\text{H}_2\text{O}$  and NHC ligands, which successfully gives the biaryl cross-coupling product as major outcome (Scheme 9).<sup>57,58</sup>



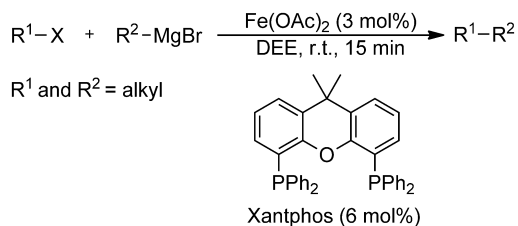
Scheme 9 Iron-catalyzed biaryl cross-coupling reaction

Methods for selective iron-catalyzed homo-coupling reactions have been developed by Pei and co-workers, by mixing metallic magnesium and aryl bromides in THF using  $\text{Fe}(\text{acac})_3$  or  $\text{Fe}(\text{DBM})_3$  as catalyst (Scheme 10).<sup>59</sup>



Scheme 10 Iron-catalyzed homo-coupling of aryl bromides

The issue with  $\beta$ -hydride elimination is most notable for the  $\text{sp}^3\text{-sp}^3$  couplings and hence one of the most difficult transformations. Chai and co-workers have proved that iron is capable of catalyzing this type of reactions using Xantphos as the most successful ligand (Scheme 11).<sup>60</sup>



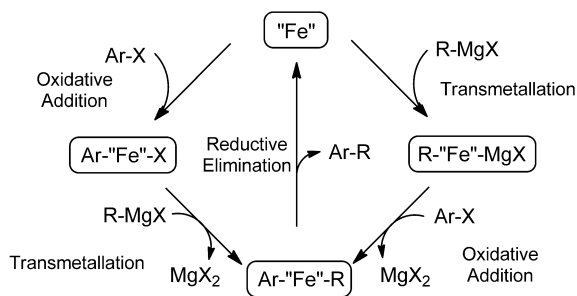
Scheme 11 Iron-catalyzed cross-coupling of alkyl Grignard reagents with alkyl electrophiles

The  $\text{sp}^3\text{-sp}^3$  transformation shows the great potential of iron catalysis even though the yields are low to moderate for the reactions studied. Nakamura and co-workers have just recently developed a successful iron-catalyzed alkyl-alkyl Suzuki-Miyaura coupling reaction.<sup>61</sup> Also in this case, Xantphos proved to be the most efficient ligand.

The promising features of the iron-catalyzed cross-coupling chemistry has been proven in several complex synthetic applications.<sup>38,62-65</sup> Together with the development of highly functionalized Grignard reagents the area of iron catalysis has the potential to grow even further.<sup>66</sup>

### 2.1.3 Mechanistic Studies

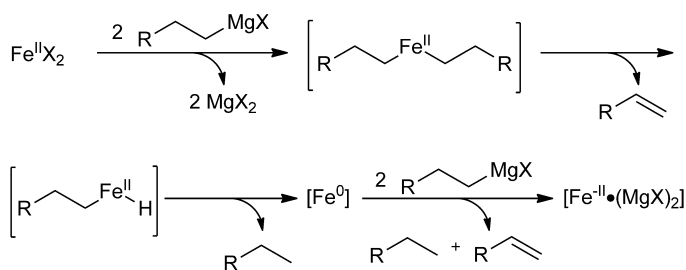
The first mechanistic contributions to iron-catalyzed cross-coupling reactions were made by Kochi during the 1970's.<sup>67-69</sup> Based on the results given, Kochi proposed a mechanism involving oxidative addition, transmetalation and reductive elimination. However, the order of the oxidative addition and transmetalation could not be determined (Scheme 12).



Scheme 12 A proposed mechanism for iron-catalyzed cross-coupling based on Kochi's results

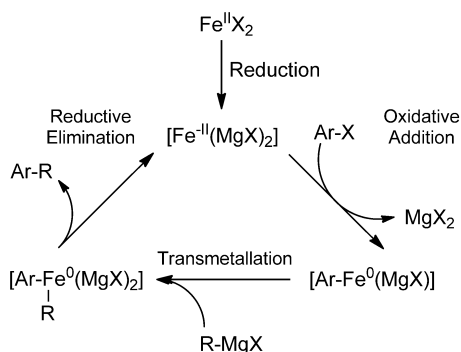
The oxidation state of the active iron catalyst was never fully determined but Fe(I) was suggested as highly probable. However, low-valent alternatives such as Fe(0) could not be ruled out.

The revival of the iron-catalyzed cross-coupling reactions has caused renewed interest into the mechanism behind these transformations. One of the major discussions in recent literature has been the oxidation state of the active iron catalyst. Fürstner and co-workers have published extensive mechanistic work suggesting the involvement of low-valent iron species as the active catalyst for the iron-catalyzed cross-coupling of aryl halides with alkyl Grignard reagents using excess magnesium. Together with the work done by Bogdanovic *et al.*, these results indicate that the *in-situ* reduction of iron does not stop at Fe(I)/Fe(0) but rather generates "inorganic Grignard reagents" with the formal composition of  $[\text{Fe}(-\text{II})(\text{MgX})_2]$  (Scheme 13).<sup>38,51,70-72</sup>



Scheme 13 *In-situ* formation of low-valent iron based "inorganic Grignard reagents"

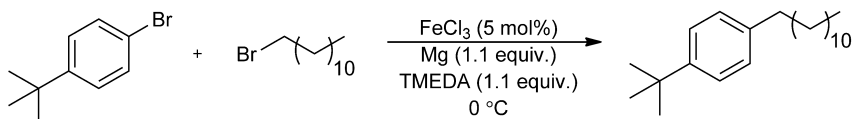
Fürstner and co-workers have proposed a mechanistic cycle based on the low-valent iron species (Scheme 14).



Scheme 14 Fürstner's proposed mechanism based on low-valent iron species

The low-valent iron complex  $[\text{Li}(\text{tmeda})_2][\text{Fe}(\text{C}_2\text{H}_4)_4]$ , first prepared by Jonas *et al.*, was used successfully as active catalyst for these transformations.<sup>71,73</sup> Fürstner later showed that iron in a range of oxidation states from -II to III proved to be efficient pre-catalysts in these reactions.<sup>72</sup> The oxidation state of Fe(-I) was however not included, due to issues with acquiring a stable Fe(-I) complex. Wolf and co-workers have recently prepared a number of Fe(-I) complexes and used them in cross-coupling reactions giving moderate yields.<sup>74</sup>

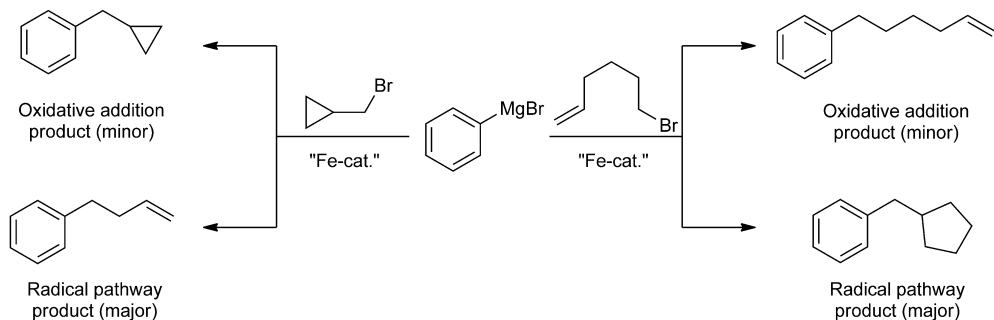
Wangelin and co-workers have studied the direct iron-catalyzed aryl-alkyl cross-coupling reaction forming the Grignard reagent *in-situ* by using metallic magnesium (Scheme 15).



Scheme 15 Iron-catalyzed direct aryl-alkyl cross-coupling reaction

The postulated mechanistic proposal is similar to Fürstner's, involving low-valent iron species, and is based mainly on the product formation pattern and UV-data. The authors have however not excluded the possibility for other mechanistic pathways.

Concerning the iron-catalyzed cross-coupling of alkyl halides with aryl Grignard reagents several authors propose a radical type mechanism. Bedford and co-workers have argued towards a radical pathway based on the observed product formation from the reaction of phenylmagnesium bromide with (bromomethyl)-cyclopropane (Scheme 16).<sup>56,75</sup>

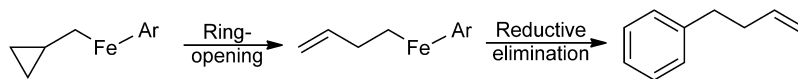


Scheme 16 Product distribution indicating radical mechanism

The expected product from an oxidative addition mechanism was not observed; instead the ring-opened product was obtained as major product, hence indicating a radical pathway. Further support for the radical mechanism was given from the reaction of phenylmagnesium bromide with 6-bromohexene, which gave the ring-closed product as the predominant product (Scheme 16). Similar results were observed by Nakamura and co-workers for the same substrates when generating  $\text{Fe}(\text{tmEDA})(\text{mesityl})_2$  *in-situ* as active catalyst.<sup>76</sup> Cahiez and co-workers have also speculated on a radical mechanism based on their results.<sup>77</sup> There are, however, alternative explanations for the outcome of the radical-clock experiments. The (bromomethyl)-cyclopropane ring-opening could

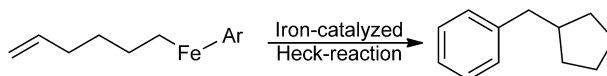


occur in the complex succeeding the oxidative addition and transmetalation, due to steric strain (Scheme 17).



Scheme 17 Ring-opening due to steric strain

An iron-catalyzed Heck-reaction could explain the ring-closed product from 6-bromohexene (Scheme 18).<sup>78</sup>



Scheme 18 Iron-catalyzed Heck-reaction

In summary, although low-valent iron complexes have been shown to be effective pre-catalysts for cross-coupling reactions the mechanistic support for this is far from conclusive. Several inconsistencies are also present concerning the radical mechanistic proposals.

## 2.2 Limitations and Challenges

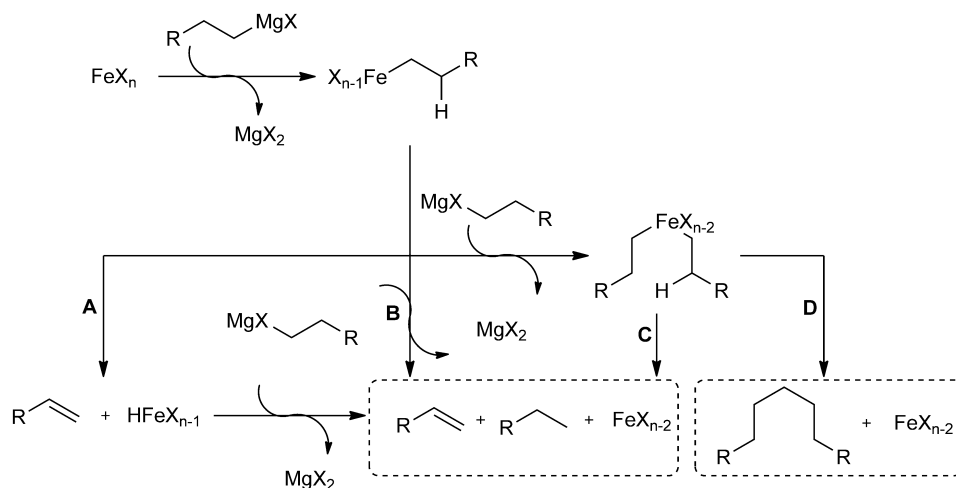
Recent work on iron-catalyzed cross-coupling reactions has proved that iron is a valid supplement to palladium and nickel in various C-C cross-coupling transformations. The lack of mechanistic knowledge behind the iron catalysis is however a major drawback for further method and ligand development. The fact that the reaction is extremely fast makes mechanistic studies, such as determining the active catalyst and kinetic studies, especially troublesome. Most of the mechanistic conclusions, since Kochi's first kinetic studies, are based mainly on product distribution or variation of the pre-catalyst.

The increasing growth of computational power has made it possible to study otherwise inaccessible systems, such as transition states of transition metal catalyzed reactions.<sup>79</sup> The combination of kinetic and computational studies is a powerful tool that will give some insights into the iron-catalyzed cross-coupling reactions in this thesis.

## 2.3 Mechanistic Investigation of Iron-Catalyzed Coupling Reactions (Paper I)

The mechanistic work done by Fürstner and co-workers on iron-catalyzed cross-coupling reactions have gained a lot of attention and generated a renewed interest regarding the fundamental understanding of these transformations. Indirect evidence that low-valent iron species are valid catalysts for some cross-coupling reactions has been presented, but it is still too early to exclude other mechanistic pathways. The lack of knowledge concerning the oxidation state and the nature of the active iron catalyst is a pressing issue. To gain more insight into the mechanism of iron-catalyzed cross-coupling reaction a combination of experimental (titration and competitive Hammett study) and computational studies were performed.

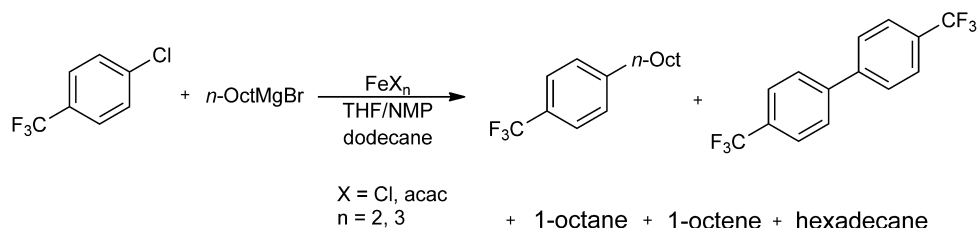
The iron-catalyzed cross-coupling reaction of aryl halide with alkyl Grignard reagents forms not only the desired cross-coupling product but also other organic compounds, namely alkanes, alkenes and homo-coupling of two alkyls, through different pathways (Scheme 19). Most of these by-products are associated with the reduction of iron to generate the active catalyst.



Scheme 19 Activation pathways for iron

The first alkyl iron complex is formed through a transmetalation to the iron salt. The oxidized by-products (alkene, alkane and homo-coupling) are subsequently formed through four possible routes (A-D). The alkane and alkene adducts can be formed directly either from a  $\beta$ -hydride elimination followed by a reductive elimination (A) or by a direct elimination pathway (B). An alternative pathway is the formation of a dialkyl iron complex from which an internal elimination gives the alkane and alkane product (C) or the homo-coupling product through reductive elimination (D). Each of these pathways reduce the iron by two electrons. From titrating the reaction and measuring the amounts of oxidized by-products some information of the amount of electrons transferred to iron and hence the oxidation state of the active catalyst could be gathered.

The cross-coupling of 1-chloro-4-(trifluoromethyl)benzene with *n*-octylmagnesium bromide was chosen as the standard reaction for the titration experiment (Scheme 20).



Scheme 20 Standard reaction for the titration experiment

The titration was performed through adding small portions of the Grignard reagent to the reaction mixture (intervals of 5 minutes) and taking out samples after each addition followed by GC-analysis. The mass-balance for the aryl was found to be constant to within a few percent and a linear relationship between the sum of all alkyl by-products and the added Grignard reagent was confirmed. The oxidized by-products were plotted against the added Grignard reagent. The resulting titration plot contains three phases (Figure 6);

1. The initiation phase, where iron is reduced to the active form.
2. The linear phase, where all the Grignard reagent is consumed to form the cross-coupling product.
3. The deactivation phase, where the catalytic activity is severely reduced, indicated by the increased amount of *n*-octane in the work-up due to unreacted Grignard reagent. This phase is characterized by notable precipitation in the reaction mixture.

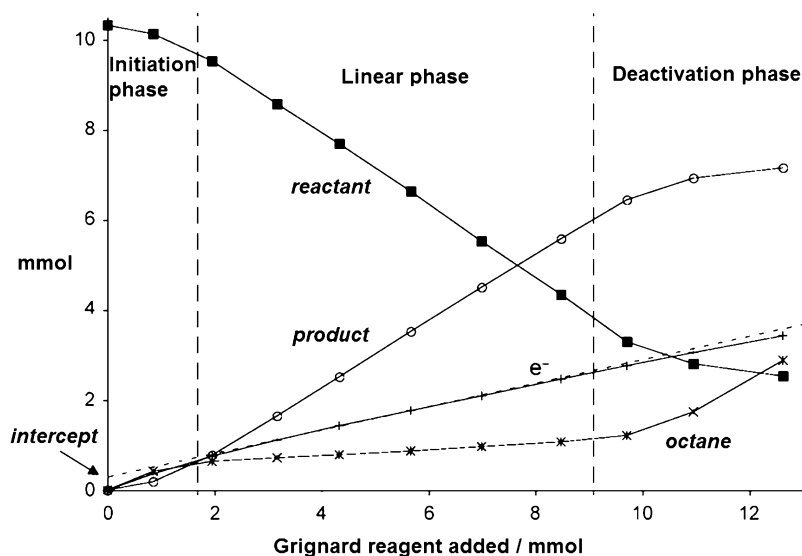


Figure 6 Representative example of a titration plot

In an ideal situation, the way to proceed would be to just extrapolate the linear region in phase 2 to the x-axis and note the amount of Grignard reagent needed for the reduction of the iron. Unfortunately this does not account for the impurities present in the Grignard reagent or the sensitivity for acidic impurities such as water protonating the Grignard reagent. To circumvent this issue the analysis is instead based on the sum of the oxidized products, *n*-octene and hexadecane. Each molecule of formed *n*-octene and hexadecane accounts for two electrons transferred to iron. The total amount of transferred electrons to iron are then plotted as two times the amount of formed *n*-octene and hexadecane (dotted line in Figure 6). Ideally this concentration should be constant in the linear region but since *n*-octene and hexadecane are present as impurities in the Grignard reagent this is not the case. The correct amount of electrons is instead given by extrapolating the linear

region to the y-axis. Dividing this number with the amount of iron complex added gives the amount of electron added to each iron atom (Table 1).

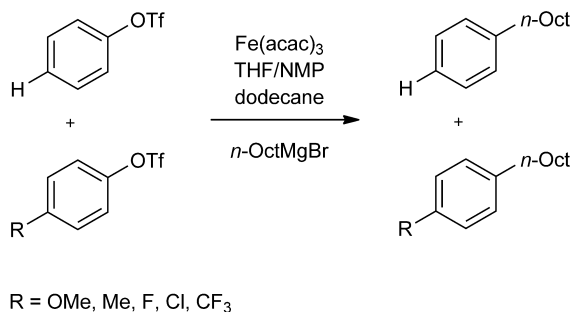
Table 1 Number of electrons added to each atom of iron

| Entry | Catalyst                    | Fe (mol%) | THF (mL) | Ratio e <sup>-</sup> /Fe <sup>a</sup> |
|-------|-----------------------------|-----------|----------|---------------------------------------|
| 1     | <b>FeCl<sub>2</sub></b>     | 5         | 35       | 0.256 ± 0.004                         |
| 2     |                             | 10        | 35       | 0.146 ± 0.004                         |
| 3     |                             | 15        | 35       | 0.237 ± 0.006                         |
| 4     | <b>Fe(acac)<sub>2</sub></b> | 5         | 70       | 0.566 ± 0.007                         |
| 5     |                             | 5         | 105      | 0.699 ± 0.067                         |
| 6     |                             | 5         | 35       | 0.684 ± 0.001                         |
| 7     | <b>Fe(acac)<sub>2</sub></b> | 10        | 35       | 0.705 ± 0.010                         |
| 8     |                             | 15        | 35       | 0.695 ± 0.013                         |
| 9     |                             | 5         | 70       | 0.809 ± 0.010                         |
| 10    | <b>FeCl<sub>3</sub></b>     | 5         | 105      | 0.736 ± 0.063                         |
| 11    |                             | 5         | 35       | 0.605 ± 0.006                         |
| 12    |                             | 10        | 35       | 0.614 ± 0.005                         |
| 13    | <b>FeCl<sub>3</sub></b>     | 15        | 35       | 0.642 ± 0.014                         |
| 14    |                             | 5         | 70       | 1.094 ± 0.039                         |
| 15    |                             | 5         | 105      | 1.026 ± 0.029                         |
| 16    | <b>Fe(acac)<sub>3</sub></b> | 5         | 35       | 0.991 ± 0.011                         |
| 17    |                             | 10        | 35       | 0.903 ± 0.040                         |
| 18    |                             | 15        | 35       | 1.127 ± 0.021                         |
| 19    | <b>Fe(acac)<sub>3</sub></b> | 5         | 70       | 1.123 ± 0.023                         |
| 20    |                             | 5         | 105      | 1.169 ± 0.031                         |

<sup>a</sup> Standard error from the regression analysis

As can be seen from the data gathered the interpretation is not trivial. At high concentrations both the Fe(II) and Fe(III) pre-catalysts gives substantially lower e<sup>-</sup>/Fe-ratios than expected. There is however a dilution effect that increases the amount of electrons transferred closer to 1 equivalents for Fe(II). This could indicate that the pre-catalyst is less prone to oligomerize at lower concentrations. The data is more consistent for the Fe(acac)<sub>2</sub> and Fe(acac)<sub>3</sub> pre-catalysts probably due to the fact that the acetylacetonate ligand prevents oligomerization by coordinatively saturating the iron catalyst. The Fe(III)-salts would be expected to consume 1 equivalent more electrons than Fe(II), but this is not observed. Our interpretation is that only a partial amount of the pre-catalyst is reduced to the active catalyst and most of the iron is present as either Fe(II) or Fe(III). By this reasoning, the presence of low-valent iron species such as Fe(-II) is highly unlikely due to the fact that these would readily comproportionate with the remaining iron in oxidation state +II or +III.

To gain further mechanistic information a competitive Hammett study was performed. Due to the low reactivity for the aryl chlorides with electron withdrawing groups, the more reactive aryl triflates were chosen as substrates (Scheme 21).



Scheme 21 Competitive Hammett study

The relative rates were fitted against  $\sigma$ ,  $\sigma^-$  and  $\sigma^\bullet$  (Table 2).<sup>80,81</sup>

Table 2 Relative rates and  $\sigma$ -values

| <b><i>p</i>-substituents</b> | <b><i>k</i><sub>rel</sub></b> | <b><math>\sigma</math></b> | <b><math>\sigma^-</math></b> | <b><math>\sigma^\bullet</math></b> |
|------------------------------|-------------------------------|----------------------------|------------------------------|------------------------------------|
| OMe                          | 0.32                          | -0.268                     | -0.26                        | 0.24                               |
| Me                           | 0.51                          | -0.17                      | -0.17                        | 0.11                               |
| F                            | 3.2                           | 0.062                      | 0.062                        | -0.08                              |
| Cl                           | 17.7                          | 0.227                      | 0.227                        | 0.12                               |
| CF <sub>3</sub>              | 165 <sup>a</sup>              | 0.54                       | 0.65                         | 0.08                               |

<sup>a</sup> Determined in competition with the *p*-Cl substrate,  $k(\text{CF}_3)/k(\text{Cl}) = 9.34$

The best correlation was found for  $\sigma$  alone with a large  $\rho$ -value of +3.8 indicating a significant building up of negative charge in the transition state in the aromatic ring, hence indicating that the oxidative addition is an effectively irreversible step in the catalytic cycle (Figure 7).

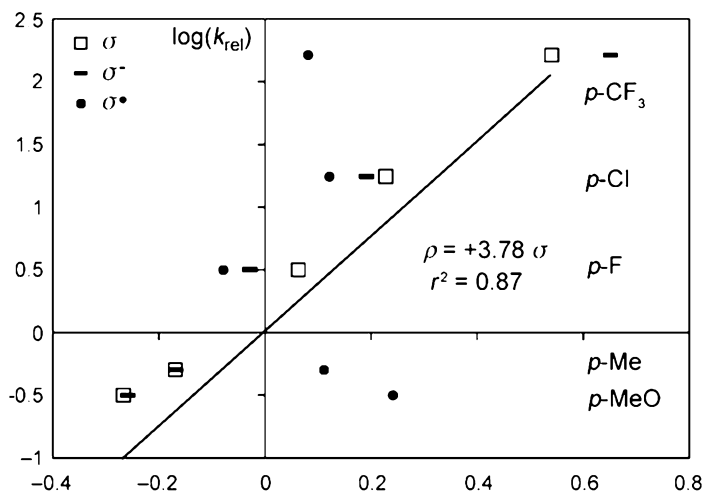


Figure 7 Competitive Hammett correlation plot for  $\sigma$ ,  $\sigma^-$  and  $\sigma^\bullet$

Despite the large buildup of negative charge the correlation to  $\sigma^-$  is far worse than to  $\sigma$ . The correlation to  $\sigma^\bullet$  was not satisfactory either. The alternative SET pathway for the oxidative addition involving an aryl radical anion could be ruled out since a correlation to a combination of  $\sigma^-$  and  $\sigma^\bullet$  should be present. The threefold acceleration for  $\sigma_F$  is also something only found for the standard  $\sigma$ -scale. However, few reactions correlate to  $\sigma^\bullet$  alone. With this in consideration, a combination of  $\sigma$  and  $\sigma^\bullet$  were constructed giving a considerable improvement in correlation ( $r^2 = 0.956$  compared to 0.870) (Figure 8).



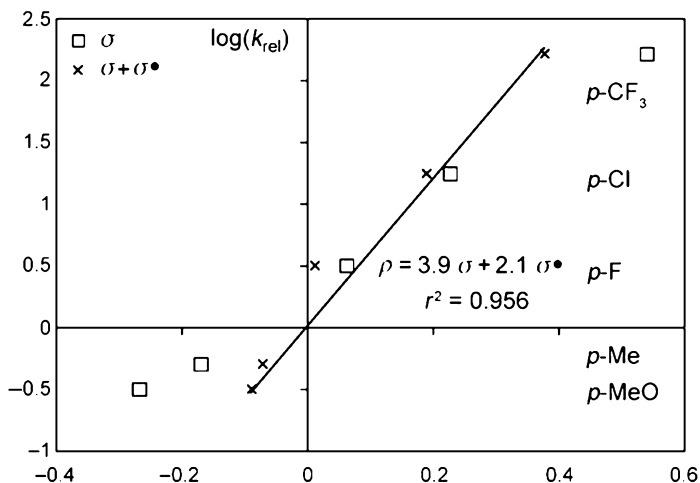


Figure 8 Competitive Hammett correlation for  $\sigma$  and the combination of  $\sigma$  and  $\sigma^\bullet$

The interpretation of the combined  $\sigma$  and  $\sigma^\bullet$  correlation is that there is a transfer of spin from iron to the aromatic ring during the oxidative addition transition state.

Several more factors that proved beneficial for keeping the catalyst active were the use of NMP, TMEDA, dilution and excess substrate. The use of excess Grignard reagent did however deactivate the catalyst.

The experimental results from this study do not give conclusive answers concerning the oxidation state of the active iron catalyst or the nature of the catalytic cycle. However they do give important indications concerning both these factors. Even though a Fe(III)/Fe(I) or Fe(II)/Fe(0) cycle could not be confirmed, through the titration experiment, the results are not in agreement with the presence of low-valent iron species. The combined correlation of  $\sigma$  and  $\sigma^\bullet$  in the competitive Hammett plot and the given interpretation was further supported by the computational work done by Dr. Kleimark.

Several important results were given from the computational study. One of the most firm evidences against low-valent iron species as active catalyst could be found from the calculated barriers for the reductive elimination (Table 3).

Table 3 Free-energy ( $\text{kJmol}^{-1}$ ) for the reductive elimination

| "Fe"   | No. sol <sup>a</sup> | Ox. State <sup>b</sup> | $\Delta G$ | $\Delta G^*$ |
|--------|----------------------|------------------------|------------|--------------|
| FeMg   | 3                    | -II                    | 195        | -            |
| FeMgCl | 3                    | -I                     | 94         | -            |
| Fe     | 2                    | 0                      | 30         | 191          |
| FeCl   | 2                    | +I                     | -181       | 10           |

<sup>a</sup> Number of explicit solvent molecules used in the calculations ( $\text{Me}_2\text{O}$ )

<sup>b</sup> Oxidation state of iron after reductive elimination

The unfavorable thermodynamics for the reductive elimination giving the low-valent iron species -II and -I is far too high to be a valid pathway. Concerning the other two possible pathways, the calculated barrier for the reductive elimination is highly in favor for the Fe(III)/Fe(I) catalytic cycle with a barrier of just  $10 \text{ kJmol}^{-1}$  compared to  $191 \text{ kJmol}^{-1}$  for the Fe(II)/Fe(0) cycle. The computational results could not discriminate whether or not the transmetallation occurs prior or after the oxidative addition. This is however not an imperative issue since both pathways has the oxidative addition as the rate limiting step in the catalytic cycle (Figure 9).

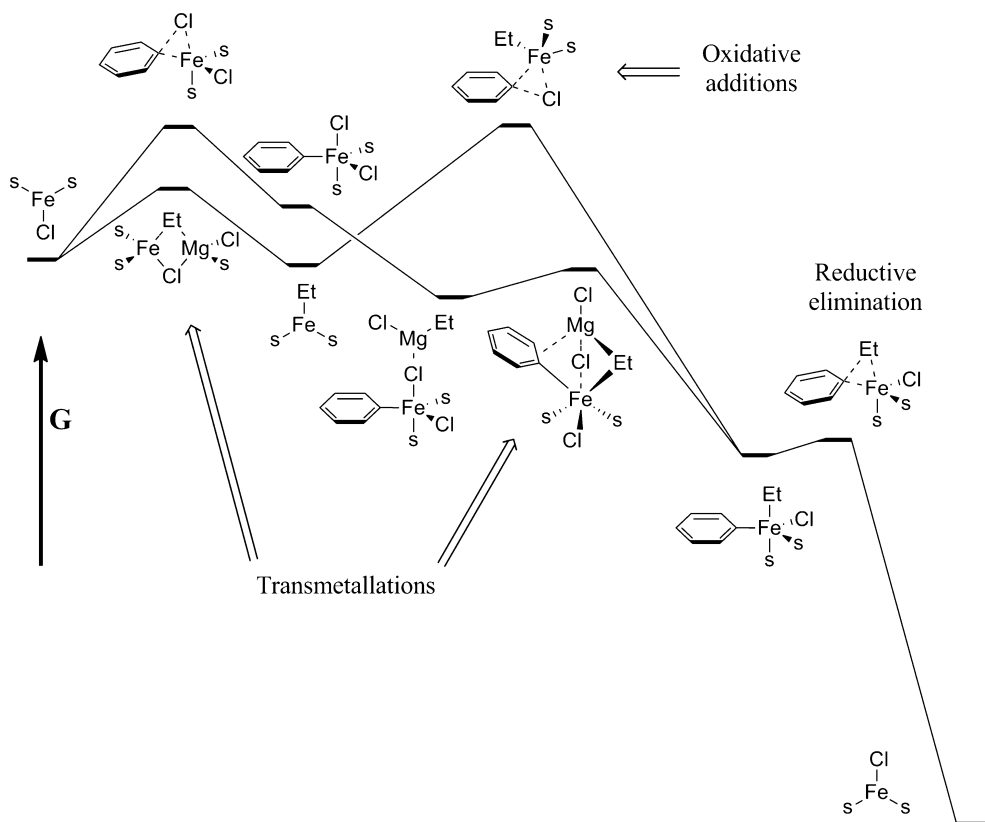
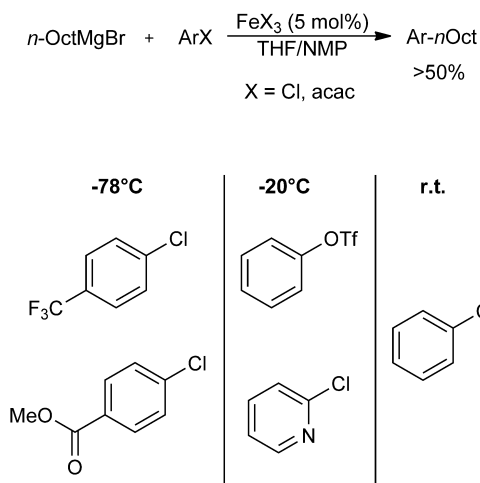


Figure 9 Free-energy surface for the Fe(III)/Fe(I) catalytic cycle

The combined results from the experimental and computational study clearly supports the Fe(III)/Fe(I) catalytic cycle with oxidative addition as rate limiting step, in good agreement with the competitive Hammett results. The low-valent iron species have been shown to work as pre-catalysts in previous studies, but the computational results indicate that the regeneration of these compounds cannot occur under these reaction conditions due to the unfavorable thermodynamics.

## 2.4 Low Temperature Studies of Iron-Catalyzed Cross-Coupling of Alkyl Grignard with Aryl Electrophiles (Paper II)

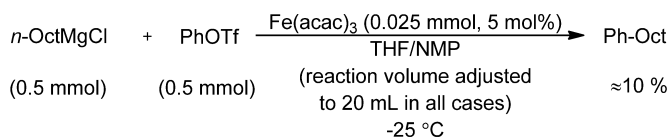
One of the features of iron-catalyzed cross-coupling reactions that differentiate them from their palladium and nickel equivalents is the ability to be run at low temperature. A screening of aryl electrophiles showed that strong electron withdrawing groups are imperative for the reaction to run at  $-78\text{ }^{\circ}\text{C}$ . At  $-20\text{ }^{\circ}\text{C}$  the unsubstituted aryl triflate and chloropyridine reacts and at ambient temperature, even the unsubstituted aryl chloride gives satisfactory yield (Scheme 22).



Scheme 22 Low temperature screening

The trend is in agreement with the previously proposed hypothesis that the oxidative addition is the rate limiting step in the catalytic cycle. The trend was confirmed by the calculations done by Dr. Kleimark with the exception of chloropyridine which showed a high calculated reactivity. The reason for the low experimental reactivity could be due to coordination of the nitrogen electron lone pair to either magnesium or iron, inhibiting the oxidative addition.

With the aim of gaining further mechanistic insights on iron-catalyzed cross-coupling a kinetic study was performed on the reaction between *n*-octylmagnesium chloride and phenyl triflate at low temperature ( $-25\text{ }^{\circ}\text{C}$ ) (Scheme 23).



Scheme 23 Standard reaction for the low temperature kinetic study

The initial concentration of each component (Grignard reagent, phenyl triflate,  $\text{Fe(acac)}_3$ ) were varied systematically and the reaction progress was followed by GC up to approximately 10 % yield. Under these reaction conditions, we expect linear plots if the reaction occurs via a single mechanism. Non-linear plots in this region could be interpreted as major changes in the mechanism during the reaction.

### Phenyl Triflate

One of the most surprising results from the kinetic study was the reaction behavior when varying the concentration of the phenyl triflate. Contrary to the previous study (Paper I) where large excess of the substrate increased the stability of the catalyst, the opposite was observed here when increasing the phenyl triflate concentration from 0.025 M – 0.20 M (Figure 10).

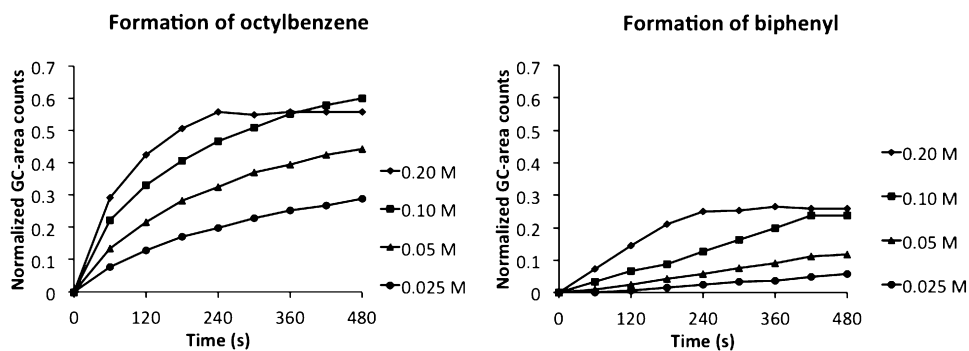
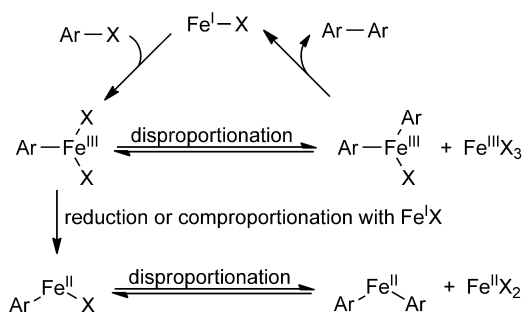


Figure 10 Formation of octylbenzene and biphenyl at different phenyltriflate concentrations

A steady increase of the reaction rate was observed when increasing the substrate concentration but at high concentration the catalyst suddenly deactivates. Compared to the titration experiments where the Grignard reagent is added in small portions which ensures that the Grignard reagent is never in

large excess with respect to the catalyst, this is not the case here. However, this does not fully explain the deactivation at high concentration of phenyl triflate. During the course of the reaction an increase of biphenyl was observed. The postulated hypothesis to explain this behavior could be the presence of a deactivation pathway involving less active poly-arylated iron species (Scheme 24).



Scheme 24 Deactivation pathway producing less active poly-arylated iron species

The proposed deactivation pathway could explain the increased production of biphenyl and also account for the abrupt deactivation occurring after approximately 3 minutes at 0.20 M when all the iron is effectively converted to less active poly-arylated iron(III or II) complexes. Poly-arylated iron species have been isolated as stable complexes and should not be able to act as effective catalysts for these transformations.<sup>82,83</sup>

### Grignard Reagent

The initial concentration of the Grignard reagent was varied from 0.025 – 0.50 M (Figure 11).

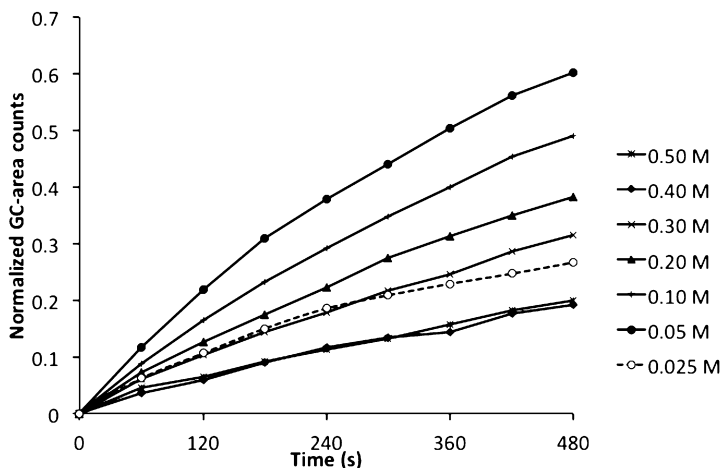


Figure 11 Formation of octylbenzene at different Grignard reagents concentrations

The reaction rate is doubled going from 0.025 M to 0.05 M indicating that the Grignard reagent is involved in the rate limiting step in the catalytic cycle. The curvatures for both these plots however indicate a slow deterioration of the active catalyst. As the concentration is increased beyond 0.05 M, the catalytic activity is decreased reaching a minimum at 0.40 M. Comparative F-test analysis on the 0.50 M plot shows that starting the analysis at 60 sec gives the most significant line. From 1 minute and onwards the reaction is independent of the Grignard reagent concentration and no further deactivation occurs. The same is true for 0.40 M concentration. The deactivation is less significant for the lower concentration span. These results are a strong indication of dual catalyst activity where the highly active catalyst is converted to a less active form with increasing concentration of the Grignard reagent. The deterioration increases as the concentration of the Grignard reagent increases. One plausible explanation for this behavior is the strong reducing power of the Grignard reagent that reduces the iron to less active low-valent species.

## Iron

The initial iron concentration was varied from 0.25 mM – 5.0 mM which corresponds to 1 – 20 mol% catalytic loading (Figure 12).

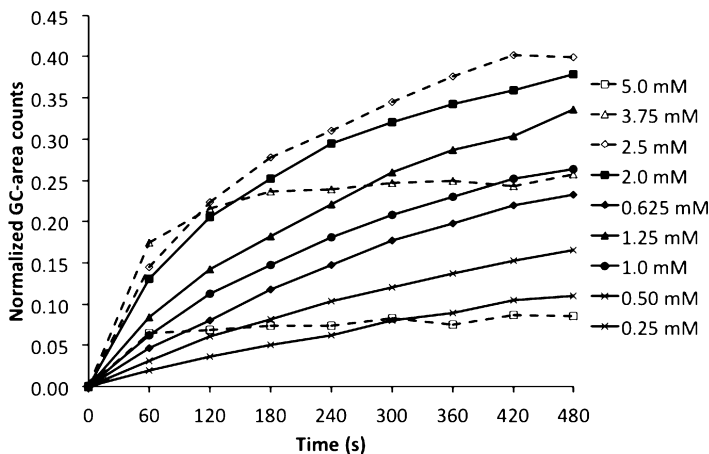


Figure 12 Formation of octylbenzene at different iron concentrations

Similar to the other components studied, the iron also showed positive reaction order at low concentrations, reaching a maximum rate at 2.5 mM. The curvature, due to decreased activity, is more notable as concentration of iron increases. Above 2.5 mM a rapid catalyst death was observed. The decreased activity could be due to the formation of Fe(II) via comproportionation between Fe(I) and Fe(III) (Scheme 24). This bimolecular process is much slower than the Fe(III)/Fe(I) cycle and should form inactive poly-arylated iron species. This is supported by the observed increase of biphenyl as the concentration of iron increases (Figure 13).



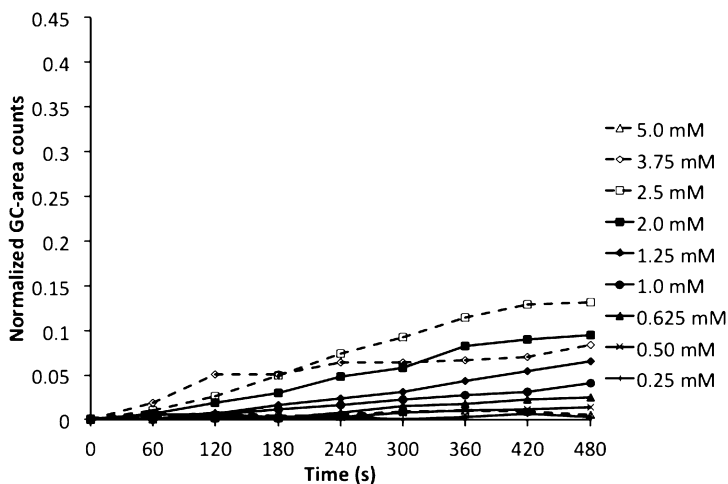
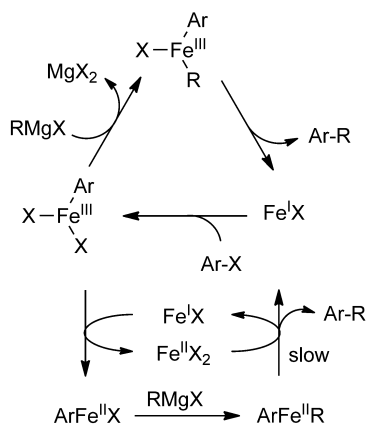


Figure 13 Formation of biphenyl at different iron concentrations

This catalytic death can be interpreted as a bimolecular catalyst deactivation occurring at high concentration of iron resulting in precipitation of iron. The precipitation could occur via disproportionation producing insoluble Fe(0) or Fe(I) species.

From the results of the kinetic study in combination with the computational work done a plausible mechanism for the iron-catalyzed cross-coupling under reducing environment has been proposed (Scheme 25).



Scheme 25 Plausible catalytic cycle under reducing environment

From our results the deactivation of the iron catalyst at high Grignard reagent concentrations could not be explained by addition to Fe(III) or Fe(I) since this catalytic cycle is very fast. Instead the explanation could be a reduction of  $\text{ArFe(III)X}_2$  either by SET reduction by the Grignard reagent or through comproportionation with Fe(I) to form Fe(II) species that would slowly return to the normal catalytic cycle through a bimetallic pathway. The proposed catalytic cycle does not account for the deactivation at high concentration of phenyltriflate. Transmetalation among iron complexes could however produce inactive poly-arylated iron species.

## 2.5 Summary and Outlook

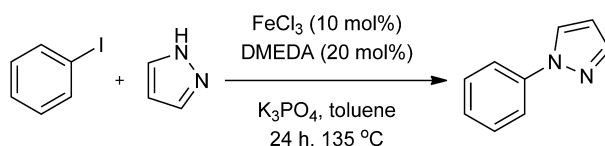
Concerning the iron-catalyzed cross-coupling reaction the most pressing issue has been the lack of mechanistic knowledge. Our experimental and computational studies on iron-catalyzed cross-coupling reactions have revealed several interesting features concerning the oxidation state of the active iron catalyst and the overall catalytic cycle. In contrast to the widely assumed catalytic cycle involving low-valent iron species, our results support a Fe(III)/Fe(I) catalytic cycle. From the kinetic results several different complex deactivation pathways have been suggested such as a dual-catalytic system, oligomerization and over-reduction of the catalyst.

Future endeavors in the area of iron catalysis might include a more thorough kinetic study based on calorimetric methods. This method has been shown to be an effective approach for studying the kinetics for catalytic systems.<sup>84,85</sup>



### 3. Intermezzo – Trace-Metal Catalysis

Due to the steady progression of iron-catalyzed C-C cross-coupling reactions our interest shifted towards C-X bond formation (X = N, O, S). As of 2007, this area was more or less a black spot on the map of iron chemistry. However, during the autumn of 2007 Bolm and co-workers published a paper on iron-catalyzed C-N cross-coupling reactions (Scheme 26).<sup>86</sup>



Scheme 26. Iron catalyzed C-N cross-coupling reaction

Our groups initiated a collaboration with the aim to conduct mechanistic and computational studies to elucidate the mechanism behind this reaction. During 2008 several more papers were published claiming iron-catalyzed C-O, C-S and C-C (Sonogashira) cross-coupling reactions.<sup>87-90</sup> However, several inconsistencies with the reaction system (*e.g.* varying yields, inconsistent reaction time and optimized reaction data) raised our suspicion that something was wrong. In an attempt to achieve reproducibility, equivalents of deionized water were added. The reaction gave consistent yields adding 1-4 equivalents of water. For safety, the deionized water was distilled, and to our surprise adding this water instead gave no effect at all resulting in zero to low yield. Apparently, something in the deionized water was essential for the reaction to work. The iron salt that was used, FeCl<sub>3</sub>, had a purity level of 98 %. The data sheet from the supplier indicated that the batch could contain a maximum of 0.1 % Cu-traces. With this in mind, 0.01 mol% CuCl<sub>2</sub> was used instead of 10 mol% FeCl<sub>3</sub>. Copper catalysis has been associated with problems such as high catalytic loading, moderate yields, and high temperatures for a long time.<sup>91</sup> Therefore, we were surprised that the reaction worked. The actual catalyst was not iron but instead traces of copper.<sup>92,93,b</sup>

These results sparked a renewed interest in copper-catalyzed cross-coupling reactions in the scientific community and also raised questions concerning other papers claiming iron or even “metal free” catalyzed reactions.

<sup>b</sup> prof. Bolm was contacted by prof. Buchwald who suggested the same conclusion concerning copper traces.

One important question concerning trace-metal contaminants is: “Is it important to know what catalyzes the reaction if the reaction works?” In the discussion following the proposed “metal-free” Suzuki reaction, which turned out to be palladium catalyzed after all, Leadbeater concludes that from a pure synthetic point of view this might not be important.<sup>94</sup> On the other hand one cannot optimize a reaction effectively in a “black-box” environment and issues with reproducibility arise. Even though many of the reported papers on “metal-free” catalyzed reactions take rigorous precautions and use highly sensitive analytical methods to claim their case, the level of uncertainty still is notable. In the case of the Suzuki reaction, as little as 50 ppb palladium is enough to catalyze the reaction. One issue with many of these cases is that the reactions are known reactions for copper or palladium chemistry. Working with “metal-free” or “alternative metal” catalyzed systems that are not orthogonal to copper or palladium chemistry is highly unreliable. One notable case is the Sonogashira reaction. Bolm and co-workers published, in 2008, an iron-catalyzed version of this reaction.<sup>90</sup> After the joint publication of the sub-mol% copper-catalyzed C-N reaction, the claimed iron-catalyzed Sonogashira reaction was re-visited. Also this reaction proved to work with sub-mol% amount of copper as catalyst.<sup>95</sup> However, in 2010, Novák *et al.* published a paper claiming that the actual catalyst in the “copper”-catalyzed Sonogashira was ppb levels of palladium.<sup>96</sup>

One recent reaction that has been under review is the proposed metal-free catalyzed C-H bond arylations using *t*-BuOK.<sup>97-102</sup> The system is however strikingly similar to the copper-catalyzed C-X (X = N, O, S) cross-coupling reactions with DMEDA as the most efficient ligand (in these papers, DMEDA is termed organocatalyst). The authors have taken some measures to prove their point such as radical trapping experiments, purification of the *t*-BuOK by sublimation, trapping of K<sup>+</sup>-ions by 18-crown-6, ICP-AES and ICP-MS analysis, and DFT-calculations. Although the reaction is supported by these control experiments there is still room for some criticism. The radical trapping experiment is a blunt tool in this case. The observation that the reaction stops when adding for example TEMPO, does not exclude the possibility that a copper catalyst is present, since support for radical pathways exist for copper as well. 18-crown-6 does not only complex with K<sup>+</sup>-ions but also Cu(II) hence inhibiting the copper pre-catalyst. The ICP-AES and ICP-MS analysis of the *t*-BuOK does not exclude the possibility of contamination from other sources for example glassware, magnetic stirring bars, or other reagents used. In the case of C-N cross-coupling reaction even leaching from the magnetic stirring-bar is enough to catalyze the reaction. (*vide infra* and Paper IV) However interesting these results might appear, great care and more studies has to be done to draw

any further conclusions. Yet another case that has been under some criticism is the proposed Lanthanum(III) Oxide-Catalyzed C-N Cross-Coupling by Nageswar and co-workers. Buchwald bases his criticism, to some degree, on the close similarities with the sub-mol% copper-catalyzed version of the C-N cross-coupling reaction.<sup>103</sup> There are more examples in the literature of similar situation regarding uncertainties about the active catalyst.<sup>104</sup>

So why have reports in literature of using ppm-ppb levels of palladium and copper been so scarce up until now? As I see it, it can be a question of practical issues and lack of time, the human factor. It is much simpler to add 5-10 mol% of copper or palladium salts just using the scale, for the every-day chemist, compared to ppm-ppb amounts. Many of these catalysts have low solubility in the solvent used; hence stock-solutions are not easily made. The increasing pressure of publishing papers due to toughened competition in a growing scientific community results in less time to investigate discoveries more thoroughly than necessary. Again, if something works, it works. The different approaches to chemical science are not in conflict but complimentary and essential for the growth of the scientific area. These stated examples are just a proof that the “self-correcting” character of science actually works. An anonymous author, to some degree, blames these published “errors” on the scientific journals peer-review system.<sup>105</sup> This is a system that relies on the fact that the reviewers trusts the results presented in good faith. The author suggests a hybrid system in which the paper is open for discussion by any interested part, supervised by the editors, following the classical peer-reviews. The authors then have an opportunity to respond to any eventual criticism. This sounds good, but the pressure on the scientific community is already high enough that adding even more workload would not be beneficial. The authors concluding remarks, paraphrasing Winston Churchill, “Peer review is the worst form of assessing science, except all the others that have been tried”, is on the mark.

As Buchwald points out, there is also a trend today to publish “new” metal catalysts for old reaction systems, hence when the reaction actually is shown to be catalyzed by traces of the “old” metal catalyst it gets a lot of attention.<sup>106</sup> The attention is well deserved and has led to a growing understanding and cautions, in the scientific community, when proposing “metal- free” or “new metal catalysts”. To revisit old reaction systems and optimize these with “homeopathic” amounts of catalyst is not only interesting from a scientific point of view, but also from an industrial, due to cost reduction and environmental benefit.



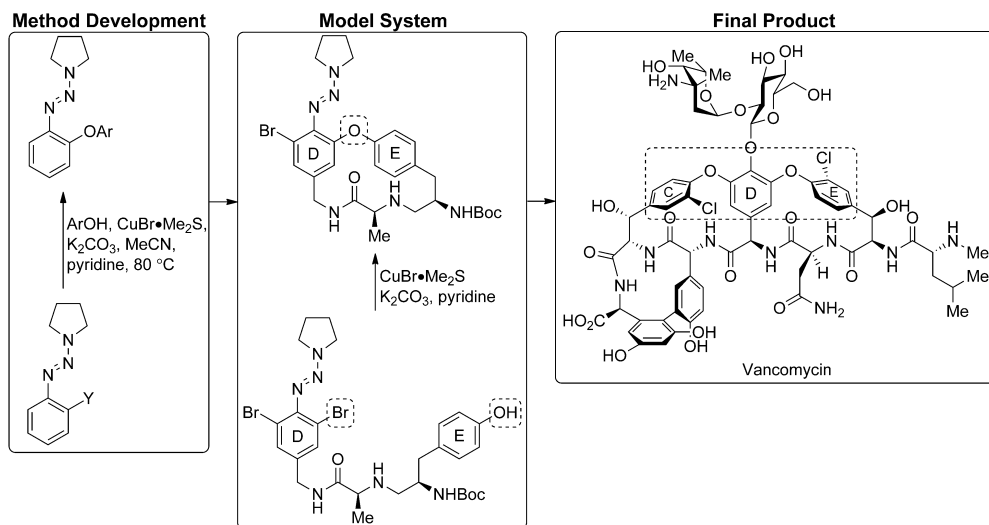


## 4. Copper-Catalyzed Cross-Coupling Reactions

### 4.1 Copper-Catalyzed C(aryl)-X (X = N, O, S) Cross-Coupling Reaction

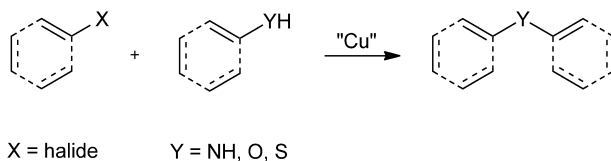
#### 4.1.1 Background

C(aryl)-X-C(aryl) (X = N, O, S) are important structural moieties in a vast amount of naturally occurring molecules of importance for example vancomycin and chloropetines. Vancomycin is considered as one of the most valuable antibiotics of today due to the high bactericidal effectiveness it possesses. It is still considered one of the “last resort” drugs for the treatment of bacterial infections. Nicolau and co-workers have developed an Ullmann-type reaction for the construction of the C-O-D and D-O-E connections in Vancomycin. The reaction is based on the possible coordination of copper to a triazene moiety. The method was later successfully used in the total synthesis of Vancomycin (Scheme 27).<sup>107,108</sup>



Scheme 27 Ullmann-type coupling for the construction of the C-O-D and D-O-E connections in Vancomycin

There are various other examples of applications in fine chemical production and total synthesis where copper-catalyzed cross-coupling reactions have proved successful.<sup>91,109</sup> The development of methods to create these bonds is therefore imperative (Scheme 28).

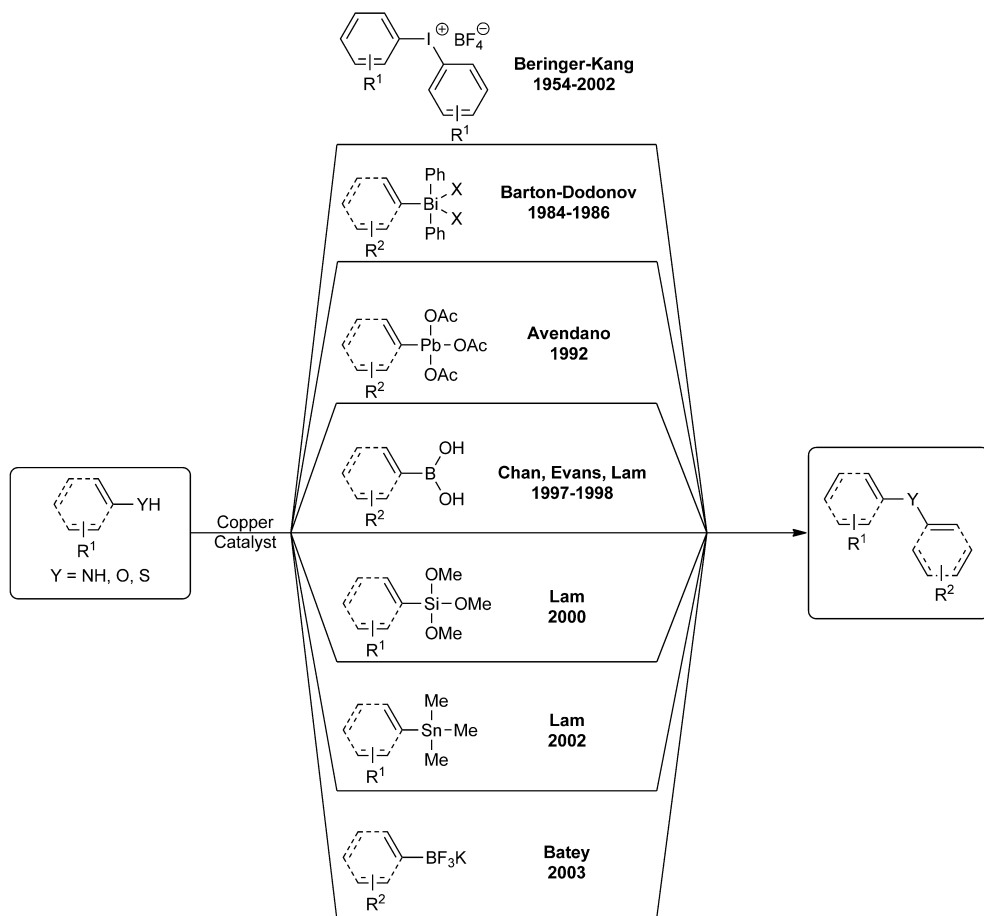


Scheme 28 Copper-catalyzed cross-coupling

Since Ullmann's and Goldberg's work on copper mediated reactions in the early 20<sup>th</sup> century the area has been more or less dormant until the late 1980's/early 1990's when several authors published new and efficient methods for these type of reactions. Today copper has proven to be a versatile and effective catalyst for numerous model reactions, hence moving away from the older systems that demanded high temperature, stoichiometric amounts of copper and limited substrate scope.<sup>30,91</sup>

### 4.1.2 Reaction Scope

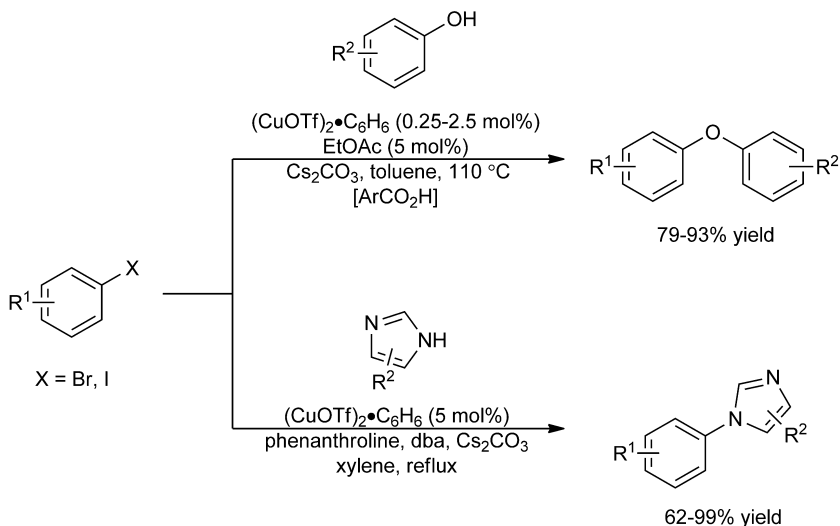
The number of arylating reagents that can be utilized in copper-catalyzed cross-coupling reactions is spans from simple aryl halides (Cl, Br, I) to potassium aryltrifluoroborates (Scheme 29).<sup>110-119</sup>



Scheme 29 Reagent scope for Ullmann reaction

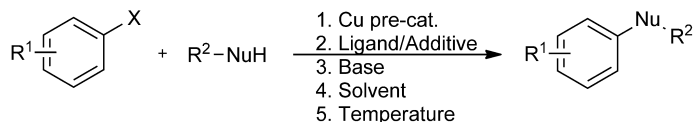
Despite the developed methods using these more exotic coupling partners the most common choice is still the aryl halides with the reactivity order of  $\text{ArI} > \text{ArBr} \gg \text{ArCl}$ . Buchwald and co-workers are one of the major contributors to this area following the earlier work done in palladium-catalyzed C-N cross-coupling reactions. Their publications in 1997 and 1999, presenting the  $(\text{CuOTf})_2$  catalyzed

cross-coupling of aryl halides with phenols and imidazoles proved that copper could be a feasible catalyst for these systems, and sparked a renewed interest in copper catalysis (Scheme 30).<sup>120,121</sup>



Scheme 30  $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$  catalyzed C-N and C-O cross-coupling reaction

The subsequent enormous expansion of the copper chemistry evoked several important reaction condition optimizations, broadening of the nucleophile scope and ligand discovery. There is an impressive range of N/O/S-nucleophiles that can be effectively arylated through copper catalysis today, such as pyrazoles, indoles, imidazoles, amides, anilines, aliphatic amines, phenols, aliphatic alcohols, and thiols.<sup>30,91,109,122-125</sup> All the methods share similar features but rely on careful optimization of the involved reaction components, namely; 1. Copper pre-catalyst, 2. Ligand/Additive, 3. Base, 4. Solvent, and 5. Temperature (Scheme 31).



Scheme 31 General copper-catalyzed cross-coupling reaction

The most common choice of copper pre-catalyst is CuI, but other sources like CuCl, CuBr,  $\text{Cu}_2\text{O}$ , CuOAc,  $\text{Cu}(\text{OAc})_2$ , CuO,  $\text{CuCl}_2$  are often efficient alternatives.<sup>5,30,91</sup> A notable exception from this is

the intramolecular amination of aryl halides where the use of in-situ formed CuOAc greatly improved the reaction rate and enabled the temperature to be lowered to as low as 35 °C compared to 100 °C when using CuI.<sup>126</sup> The catalytic loading is often in the range of 5-20 mol% but there are a few isolated examples where much less catalyst is needed.<sup>127,128</sup> It is widely assumed that the oxidation state of the active copper catalyst is +I even when using Cu(II)-salts. Since Cu(I) is sensitive to oxidation most reactions are performed under inert atmosphere, either argon or nitrogen.

There are several classes of ligands that have proven effective in copper-catalyzed cross-coupling, for example diphosphines (**1**), phenanthrolines (**2**), diamines (**3**), amino acids (**4**), iminophenols (**5**), hydroxyquinolines (**6**), carbenes (**7**),  $\beta$ -diketones (**8**), and glycols (**9**) (Figure 14).<sup>30,91,109,122</sup>

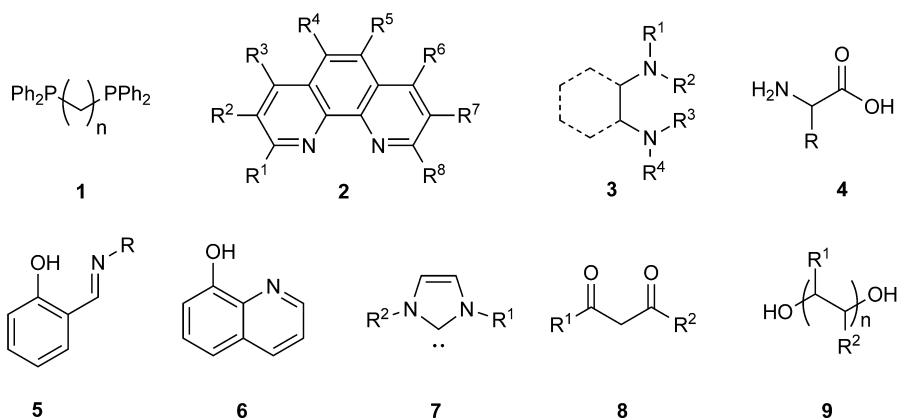
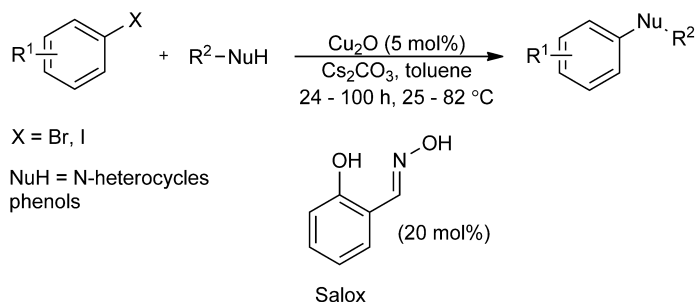


Figure 14 Ligands for copper-catalyzed cross-coupling

Since the introduction by Buchwald and co-workers in 2001/2002, the aliphatic diamine ligands (**3**) have proven to be very effective in a range of copper-catalyzed cross-coupling reactions.<sup>109,129,130</sup> One of the key feature with these ligands is their simplicity compared to other ligand system, and also that most of these are commercially available and hence suitable for industrial scale use. From the coupling reaction of iodobenzene with indole, using 5 mol% of CuI as catalyst,  $N^1,N^2$ -dimethylethane-1,2-diamine (DMEDA), trans-cyclohexane-1,2-diamine and trans- $N^1,N^2$ -dimethylcyclohexane-1,2-diamine proved to be the most efficient ligands.<sup>130</sup> These three diamines have been singled out as the most successful ligands in a range of coupling reactions including arylation of 1° and 2° amides, carbamates, lactames, NH heterocycles, hetero anilines, inter- and intramolecular C-O bond formation, and C-S bond formation. Despite the success of the diamines in

copper-catalyzed cross-coupling reactions, the high temperature, usually around 80-120 °C, is still a notable problem. Taillefer *et al.* have synthesized a range of iminophenol-based ligands that have proven to be very effective in copper-catalyzed C-N and C-O arylations, significantly reducing the reaction temperature (Scheme 32).<sup>127,131,132</sup>



Scheme 32 Oxime-ligands for C-N and C-O copper-catalyzed cross-coupling

Using Salox instead of diamines in these transformations has made it possible to run the reaction at room temperature for some substrates. Another class of ligands that has proved successful in copper-catalyzed C-N cross-coupling reactions is phenanthrolines. Buchwald and co-workers have found 4,7-dimethoxy-1,10-phenanthroline to be a highly effective ligand for the arylation of a range of imidazoles.<sup>128</sup> With catalytic loadings down to 0.025 mol% and temperatures at 60 °C this is one of the most efficient methods available for this kind of transformation. Ma and co-workers have successfully used simple amino acids such as L-proline as ligand for a number of copper-catalyzed C-X cross-coupling reactions.<sup>133</sup>

The choice of solvent is an important factor in copper-catalyzed cross-coupling reactions. At elevated temperatures the high boiling solvents are preferred but introduction of new ligand systems have made it possible to move away from polar solvents like DMF and DMSO towards less-polar alternatives, for example toluene and dioxane.<sup>109</sup>

In the majority of the copper-catalyzed cross-coupling methods, simple inorganic bases, for example  $\text{K}_3\text{PO}_4$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{Cs}_2\text{CO}_3$  and  $\text{CaCO}_3$ , have been the most effective choices, together with sodium and potassium alkoxides. One key issue with these bases is the low solubility, hence introducing mass-transfer effects. On the other hand using a strong soluble base such as KHMDS requires slow addition to give satisfying yields, as have been shown for the Goldberg reaction. The same study also

successfully used a phosphazene base for this transformation.<sup>134</sup> There are some other examples in the literature of using phosphazene bases, such as P<sub>4</sub>-*t*Bu and P<sub>2</sub>-Et, for the arylation of phenols and thiophenols but the high catalytic loadings (20 – 100 mol%) render these methods less useful (Figure 15).<sup>135,136</sup>

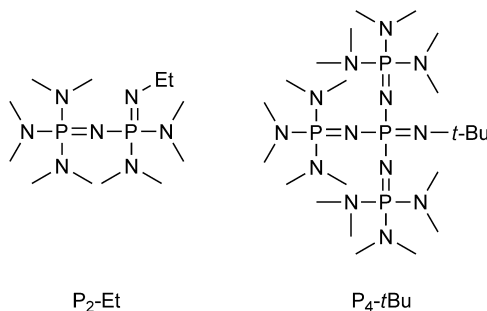


Figure 15 The phosphazene bases P<sub>2</sub>-Et and P<sub>4</sub>-*t*Bu

A more successful approach has been to use organic ionic liquids as bases for CuI catalyzed arylation of benzylic amines, anilines, N-heterocycles and a limited scope of aliphatic amines. TBAA, TBPE and TBPM were among the most efficient in the studied systems and allowed the reaction to run at room temperature (Figure 16).<sup>137,138</sup>

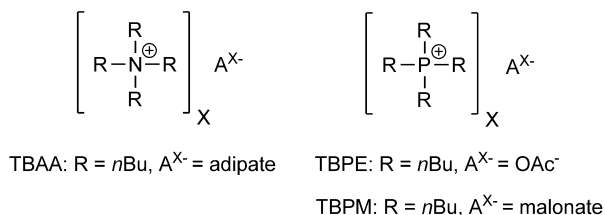


Figure 16 Ionic liquid bases for copper-catalyzed cross-coupling

The major drawbacks with using ionic liquid bases are the cost and regeneration. The price for the commercially available monobasic tetrabutylammonium phosphate is currently more than 30 times as high per gram compared to tribasic potassium phosphate.<sup>6</sup>

<sup>6</sup> Numbers taken from [www.sigmaaldrich.com](http://www.sigmaaldrich.com) 2012-07-15

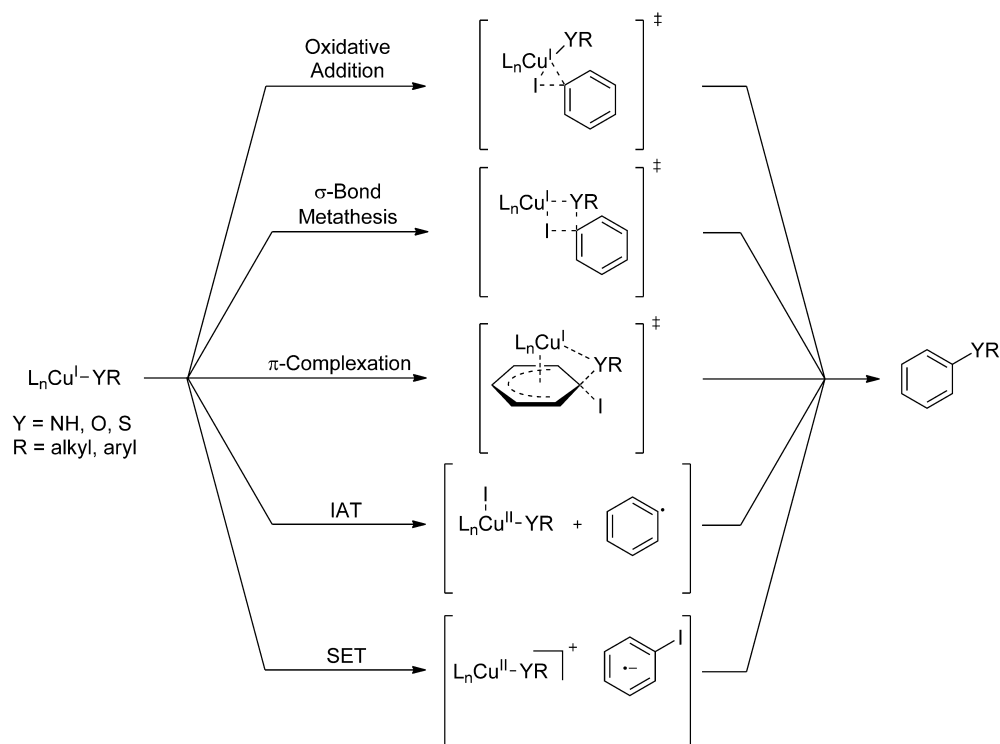
The requirement for elevated temperatures (around 80-120 °C) is one of the major drawbacks with copper-catalyzed cross-coupling reactions. As mentioned above ligand development has made it possible to run at lower temperatures for some systems and the use of ionic liquid bases enables reactions at room temperature. Some examples of microwave assisted copper-catalyzed cross-coupling reactions have been published.<sup>139,140</sup> These reactions requires more polar solvents such as NMP and very high temperatures in some cases (195 °C).

Going beyond the C-X (X = N, O, S) cross-coupling reactions, copper has been found effective at several other transformations, most recently for oxidative trifluoromethylation.<sup>141-143</sup> The steady progression and development of copper catalysis proves that the area is far from depleted and that we can expect more to come in the future.



### 4.1.3 Mechanistic Studies

Even though the Ullman condensation and Goldberg reaction have been known for over a century the mechanism is still under investigation. Several different proposals have been published but none has been met with full support from the scientific community. The mechanistic proposals can be narrowed down to five different pathways; oxidative addition,  $\sigma$ -bond metathesis,  $\pi$ -complexation, iodine atom transfer (IAT), and single electron transfer (SET) (Scheme 33).<sup>144</sup>

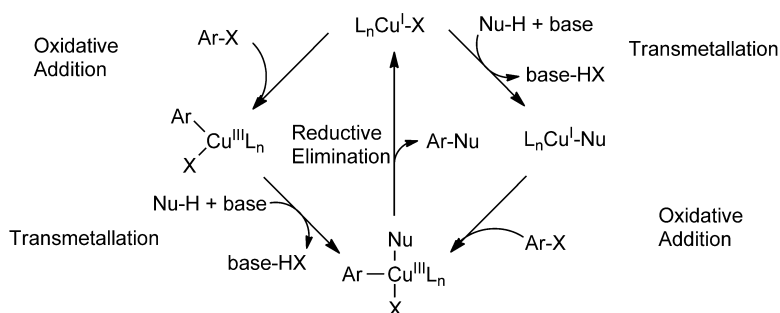


Scheme 33 Mechanistic proposals for the Ullmann condensation and Goldberg reaction

Almost any copper salt of any stable oxidation state can be used as pre-catalysts. There is, however, a consensus that  $Cu(I)$  is the most probable oxidation state of the active catalyst. Due to the electrochemical potential of copper there exists a disproportionation equilibrium ( $2 Cu(I) \rightarrow Cu(II) + Cu(0)$ ) which is greatly influenced by the solvent and ligand used.<sup>145</sup>

### Oxidative Addition

The oxidative addition mechanism involves a Cu(III) species which is formed through the oxidative addition of the aryl halide to the active Cu(I)-catalyst. The existence of Cu(III)-complexes has been a subject for some debate for decades. Through mechanistic studies, NMR-studies and computational methods the support for Cu(III) is of today undisputable in some cases.<sup>146-177</sup> One should take into consideration that in many situations where Cu(III) has been suggested as the formal oxidation state in the catalytic cycle, the actual charge is closer to Cu(I)/Cu(II) due to donation of negative charge from ligands.<sup>178</sup> A general catalytic scheme is shown in Scheme 34.



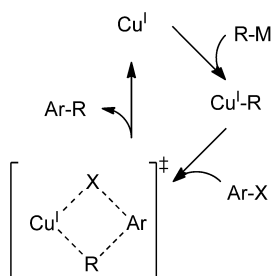
Scheme 34 Catalytic cycle through oxidative addition

Compared to the palladium-catalyzed counterpart, where the oxidative addition precedes the transmetalation, the order and nature of the steps for the copper-catalyzed reaction is uncertain.<sup>5,28</sup> The oxidative addition mechanism were suggested by Cohen and co-workers during their studies on organocuprates.<sup>179-181</sup> The subsequent work by others also pointed towards the oxidative addition mechanism.<sup>182,183</sup> Even more support for this was given by Bethell and co-workers working on the copper-catalyzed amination of halogenoanthraquinone with primary amines.<sup>184</sup> More recent work by Taillefer and co-workers supports the oxidative addition/reductive elimination pathway based on experimental observations. All together, the reactivity order of the aryl halides ( $ArI > ArBr \gg ArCl$ ), higher reactivity with electron-withdrawing groups on the aryl (competitive Hammett study) and decreased reactivity due to steric hindrance on the substrates, all supports the proposed mechanism. The radical pathway was excluded mainly based on two experiments. The first was the observation that radical scavengers and electron acceptors did not hamper the reaction and secondly that the reaction with 1,4-diiodobenzene exclusively gave the mono-substituted product.<sup>127,185</sup>

Further work by Jutand and co-workers and Taillefer and co-workers on the diaryl ether formation comes to the same conclusion.<sup>186</sup> Hartwig *et al.* have studied the cross-coupling of amides with aryl iodides and diaryl ether formation and also proposed the oxidative addition/reductive elimination as the most probable mechanism based on their experimental results.<sup>187-189</sup>

### $\sigma$ -Bond Metathesis

The  $\sigma$ -bond metathesis mechanism has only been suggested occasionally.<sup>190-194</sup> Contrary to the oxidative addition mechanism the formal oxidation state of copper remains +I. The mechanism involves a four-centered intermediate from which the product is formed directly (Scheme 35).

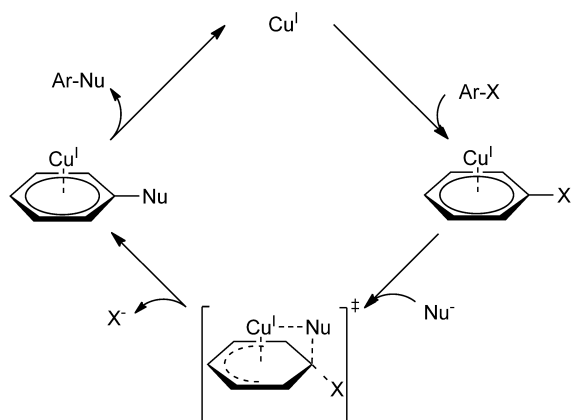


Scheme 35  $\sigma$ -bond metathesis

Multi-centered intermediates are difficult to distinguish from ionic or radical counterparts and hence most of the proposals are not supported by mechanistic studies but rather by plausible suggestions.

### $\pi$ -Complexation

Similar to the  $\sigma$ -bond metathesis the  $\pi$ -complexation mechanism has not found any wide support in the literature. The core of this mechanism is the polarization of the Ar-X bond through the interaction with Cu(I) and the  $\pi$ -system, enabling the nucleophile to attack a Meisenheimer complex (Scheme 36). The oxidation state of copper remains +I through the catalytic cycle.

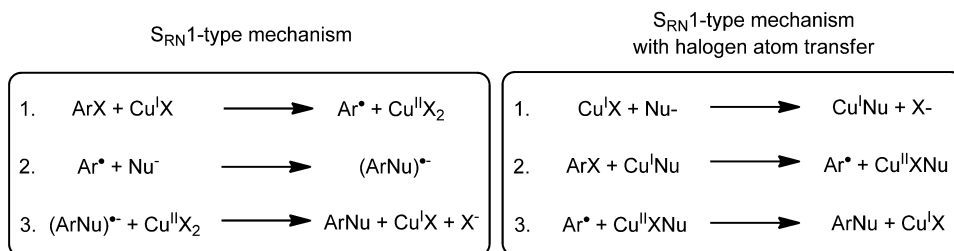


Scheme 36  $\pi$ -complexation mechanism

In the 1960's, Weingarten proposed this type of mechanism based on kinetic studies made on copper-catalyzed cross-coupling with phenoxide.<sup>195,196</sup> The order of reactivity for the aryls ( $\text{ArI} > \text{ArBr} > \text{ArCl}$ ) together with the known structure of Cu(I)-benzene complexes supported their proposal. Although most Cu(I)-benzene complexes prefer  $\eta$ -2 arrangement some computational work have shown that  $\eta$ -6 is actually preferred over  $\eta$ -1 or  $\eta$ -2.<sup>197</sup> In more recent work by Ma and co-workers, using amino acids as ligands for C-N cross-couplings, the  $\pi$ -complex mechanism was also proposed although this was later altered towards a oxidative addition/reductive elimination pathway.<sup>133,198</sup>

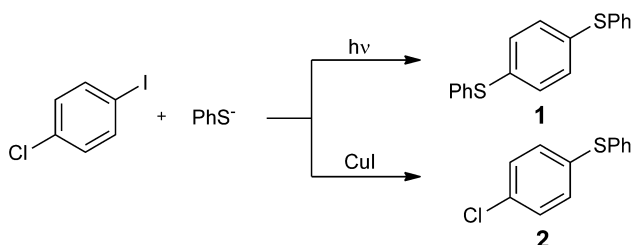
#### *Single electron transfer (SET) and Iodine Atom Transfer (IAT)*

Speculations on a SET mechanism in the Ullmann reaction was proposed in 1937 by Waters.<sup>199</sup> During the 1970's Bunnett published several papers in the area of radical nucleophilic substitution and defined the type of mechanism known as unimolecular radical nucleophilic substitution ( $\text{S}_{\text{RN}}1$ ).<sup>200</sup> In light of these studies Kochi and Jenkins showed that free radicals could react with catalytic amounts of Cu(II) via atom transfer to produce the desired coupling product.<sup>201,202</sup> Two different mechanisms were proposed (Scheme 37).



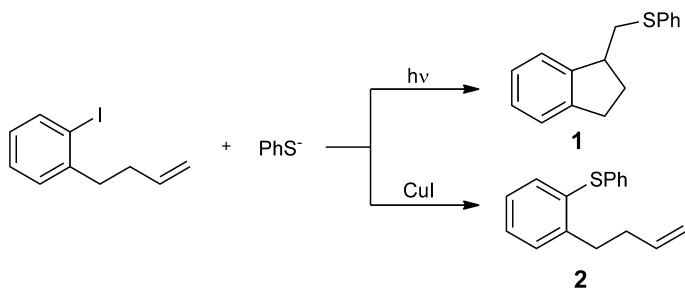
Scheme 37  $S_{RN}1$ -type mechanism for Ullmann reactions

Although several authors after Kochi have proposed the SET/IAT-pathways for Ullmann-type reactions the mechanism has been met with skepticism.<sup>203–205</sup> Bowman and co-workers published results to disprove the  $S_{RN}1$ -mechanism based on photostimulation and radical-clock experiments. The first reaction that was studied was the C-S copper-catalyzed cross-coupling between phenylthiolate and 1-chloro-4-iodobenzene. An  $S_{RN}1$ -mechanism should give the disubstituted product as was the case when photostimulation was used on the reaction system. When CuI was used as catalyst, the only detected product was the monosubstituted product **2** (Scheme 38).<sup>183</sup>



Scheme 38 Photostimulation versus copper catalysis

The radical-clock experiment was designed in a similar fashion as shown in Scheme 39. The expected cyclisation product involving a radical-type mechanism was formed using photostimulation but only the substituted product was formed using CuI as catalyst.

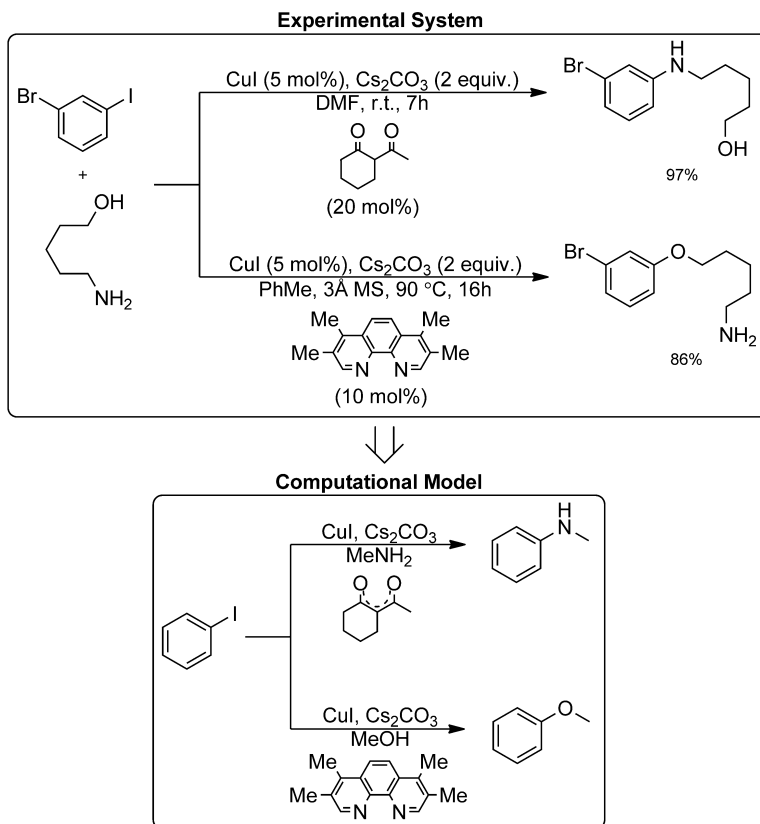


Scheme 39 Radical-clock experiment

For both these results, it can be argued whether they really disprove a radical-type mechanism. In the case of the mono- versus disubstituted product distribution the explanation could just be that the energy barrier for the C-Cl bond cleavage is too high for the copper catalytic system and hence does not compete with the C-I cleavage. In the case of radical-clock experiment results from studies like this must be taken with great care. Although photostimulation clearly forms the product expected from a radical-pathway contrary to the copper-catalyzed reaction, this does not disprove the S<sub>RN</sub>1-mechanism. In the copper-catalyzed case, the reaction is competing between ring-closure and reaction with the copper thiolate complex. The copper thiolate complex is most probably in close vicinity of the electrophile hence out-competing the ring-closing pathway. This clearly shows that experiments pro or against radical mechanisms should be interpreted with great care.

#### *Computational Studies*

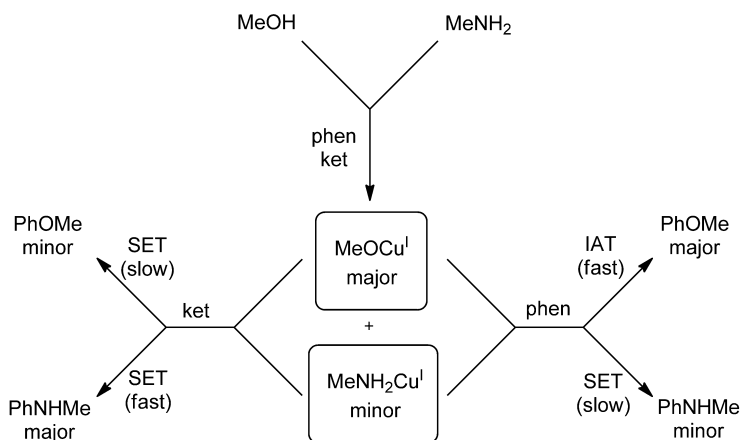
With the increasing capacity of computational technologies new insights to the copper-catalyzed cross-coupling mechanism has been presented.<sup>206,207</sup> One of the most thorough investigations up until today has been done by Houk and Buchwald where they studied the competing cross-coupling on an amino-alcohol substrate based on earlier experimental results (Scheme 40).<sup>208</sup>



Scheme 40 Buchwald's experimental system and Houk's computational model

Four different reaction pathways were investigated, oxidative addition / reductive elimination, sigma-bond metathesis, iodine atom transfer (IAT) and single electron transfer (SET). The result from the study suggests that the N- versus O-selectivity is not determined at the nucleophile formation step but rather at the activation of the aryl halide. The oxidative addition / reductive elimination and sigma bond metathesis were ruled out as possible reaction pathways due to their large energy barriers compared to the SET- and IAT-pathways. A rather complex mechanistic pathway involving SET- and IAT-mechanism constitutes an explanation for the experimental N- and O-selectivity. Both ligands, phenanthroline (phen) and beta-ketone (ket), favor the formation of the  $\text{MeOCu}^{\text{I}}$  intermediate (Scheme 41). The electron-rich beta-ketone favor a SET-mechanism at the aryl halide activation step, which differentiates between the two intermediates,  $\text{MeOCu}^{\text{I}}$  and  $\text{MeNHCu}^{\text{I}}$ ,

by their electronic character. The  $\text{MeNHCu}^{\text{I}}$  intermediate reacts faster than the  $\text{MeOCu}^{\text{I}}$  due to it being more electron-rich, hence explaining the N-selectivity when using the beta-ketone ligand. In the case of the much less electron-rich phenanthroline ligand, the formation of PhNHMe is still suggested to go through a SET-pathway, but the formation of PhOMe is going via a much faster IAT-mechanism, hence explaining the O-selectivity when using phenanthroline-ligand.



Scheme 41 Mechanistic results from Houk's computational study

This thorough computational study not only gives a valid explanation for the N- and O-selectivity for copper-catalyzed cross-coupling reaction through a SET- and IAT-mechanistic pathway but also shows the high degree of complexity for these reactions compared to earlier results from experimental-only studies. The authors have however excluded the  $\pi$ -complexation pathway from the study due to scarce support in the literature. Furthermore the computational study does not account for Bowman's radical clock experiment which does not support a SET mechanism (*vide supra*).

Although much work has been done to elucidate the mechanism behind copper-catalyzed cross-coupling the picture today is still not entirely clear. The recent results from computational studies imply more than anything that the mechanistic behavior of these reactions is very complicated and therefore hard to study by experimental methods. The fact that the reactions often are inhomogeneous and runs at elevated temperatures does not make it less complicated.



## 4.2 Limitations and Challenges

The progress in the area of copper-catalyzed cross-coupling chemistry since the revival in the late 1990's has had a major impact in organic synthesis. By expanding the substrate scope, development of new ligand systems, optimization of reaction conditions, bases, additives, time, solvent and reaction temperatures, copper has proved to be an efficient and important tool alongside the more studied and established palladium chemistry. Copper does not only have environmental benefits compared to palladium but is also a lot cheaper, particularly if ligand prices are also considered. Both these factors offer a competitive advantage in industrial scale chemistry compared to palladium. However bright the future for copper chemistry might seem there still are several unsolved problems.

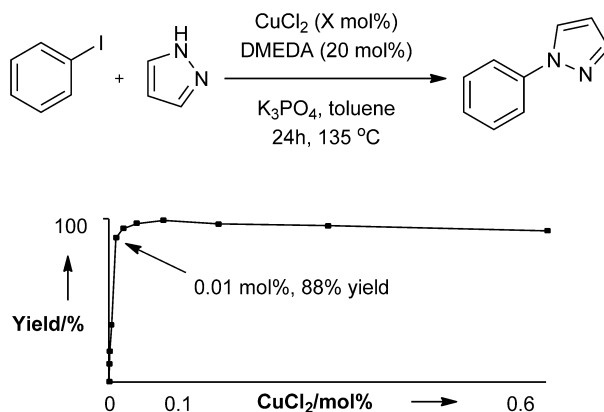
Even though the substrate scope has been widely broadened there still is room for improvement mostly due to the inefficient "trial and error" experiments that is needed in many cases. The reason for this is mainly due to the low insight in the mechanistic behavior of copper-catalyzed cross-coupling reactions. The increasing demand for lowering the metal residues in the final product on industrial scale production of fine chemicals is a costly and challenging process. This is one of the most prominent complications in copper chemistry today; when low turn-over numbers for the catalytic cycles often require high catalytic loadings in the range of 5-30 mol%.

The results presented in this thesis will shed some light on the issue with high catalytic loading and bring some insights to the mechanism behind the copper-catalyzed C-N cross-coupling reaction, as well as introducing a catalytic system working at very low copper concentrations.

### 4.3 Copper-Catalyzed Cross-Couplings with Part-per-Million Catalyst Loadings (Paper III)

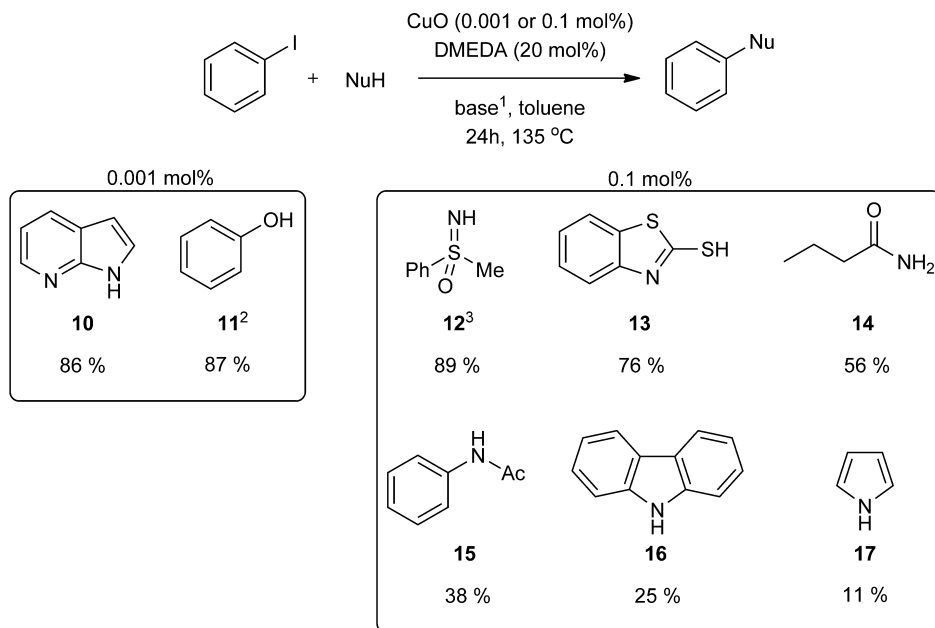
The discovery, during our work with iron-catalyzed C-N cross-coupling, that the reaction actually was catalyzed by sub-mol% copper was a great surprise. In light of the demand for more efficient turn-over numbers and frequencies for copper-catalyzed cross-coupling reactions the findings that using DMEDA as ligand allowed the concentration of copper to be reduced to as low as 0.001 mol% was a welcome contribution to this area.

The standard reaction that was used for optimization was the C-N cross-coupling between pyrazole and iodobenzene (Scheme 42).



Scheme 42 C-N cross-coupling with varying amounts of copper

As can be seen from Figure 5, 0.01 mol% of CuCl<sub>2</sub> is enough to give satisfactory yields. The choice of CuCl<sub>2</sub> as catalyst was made purely out of practical reasons; it is one of the few soluble copper salt, hence allowing preparation of stock solutions. Similar results were also found using benzamide and indole as nucleophiles. However, both tolylsulfonamide and aniline proved unreactive using sub-mol% copper catalyst. Our co-workers broadened the scope of the reaction using copper oxide as catalyst (Scheme 43).



<sup>1</sup> K<sub>3</sub>PO<sub>4</sub>•H<sub>2</sub>O was used for **10-12**. K<sub>2</sub>CO<sub>3</sub> was used for **13** and **15**.

CsCO<sub>3</sub> was used for **14** and **16**. NaO*t*-Bu was used for **17**.

<sup>2</sup> 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD) was used instead of DMEDA with DMF as solvent.

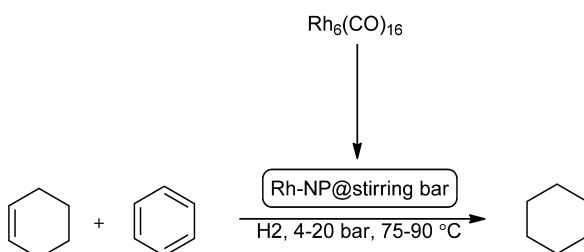
<sup>3</sup> Used 40 mol% DMEDA

Scheme 43 Examples of sub-mol% catalyzed C-N cross-coupling with various nucleophiles

These results show that the system is somewhat unpredictable but shows promising features for further investigation and optimization.

One important remark that has to be made considering working with catalytic loadings down to ppm amounts has been to reproduce the conditions that give zero yields. Several factors have shown to greatly influence the reactions and hence prohibit the reproduction of zero yields, which is essential for the understanding of these transformations. One such issue is cleaning the glass-ware. It is imperative that the glass-ware is cleansed in a KOH/*i*-PrOH bath for approximately 24h, washed with deionized water and dried at 150 °C prior to use. Our co-workers also showed that using new glass-ware in all reactions was a feasible way to avoid contamination. Another issue is the magnetic stirring-bar. Using stirring-bars with a thin layer of teflon cover leads to leaching of metal impurities

into the reaction mixture and hence issues with zero-yield reproduction (Paper IV). Recently, Janiak and co-workers have showed that nano-particles are easily deposited onto teflon-coated magnetic stirring-bars.<sup>209</sup> As a proof they treated a magnetic stirring-bar with  $\text{Rh}_6(\text{CO})_{16}$  and then used it as catalyst for the hydrogenation of cyclohexene or benzene (Scheme 44).



Scheme 44 Using nano-particle coated magnetic stirring bars for Rh-catalyzed hydrogenation

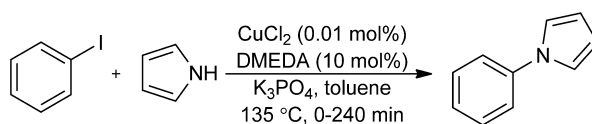
This could be a potential source for trace-metal contaminations. In our case, however, we were able to reproduce zero yields for the standard cross-coupling reaction of pyrazole with iodobenzene using magnetic stirring-bars with thicker teflon-coating. To exclude the possibility of catalysis by traces of palladium in the sub-mol% copper-catalyzed cross-coupling reaction of pyrazole and iodobenzene, 0.001 mol% of PdOAc (20  $\mu\text{L}$ , 1 mM in dry THF) was added instead of  $\text{CuCl}_2$ . No product formation was observed after 24 h at 135 °C, hence it is highly unlikely that traces of palladium is present as active catalyst in the sub-mol% copper-catalyzed C-N cross-coupling reactions studied (Paper IV).

In summary, these results did not only show that the copper chemistry still has much to offer but that great care should be taken when working with catalysis in organic chemistry due to the risk of trace-metal catalysis.

## 4.4 Mechanistic Aspects of Sub-mol% Copper-Catalyzed C-N Cross-Coupling Reactions (Paper IV)

The role of diamine ligands in the initial formation of the copper-nucleophile complex has been studied in several mechanistic and computational studies.<sup>188,207,208,210-213</sup> Buchwald and co-workers have presented a theory based on kinetic data that conclude that the role of DMEDA is to hamper multiple ligation of the nucleophile to the copper catalyst.

To investigate the initiation phase of the sub-mol% copper system a standard cross-coupling reaction of pyrrol with iodobenzene was chosen (Scheme 45).



Scheme 45 Sub-mol% copper-catalyzed cross-coupling of pyrrol with iodobenzene

The experiment was run by pre-equilibrating mixtures (30 min at 135 °C) including all reaction components but one and subsequently starting the reaction with the missing component. The initial kinetic profile gave some important information about the initiation phase (Figure 17).

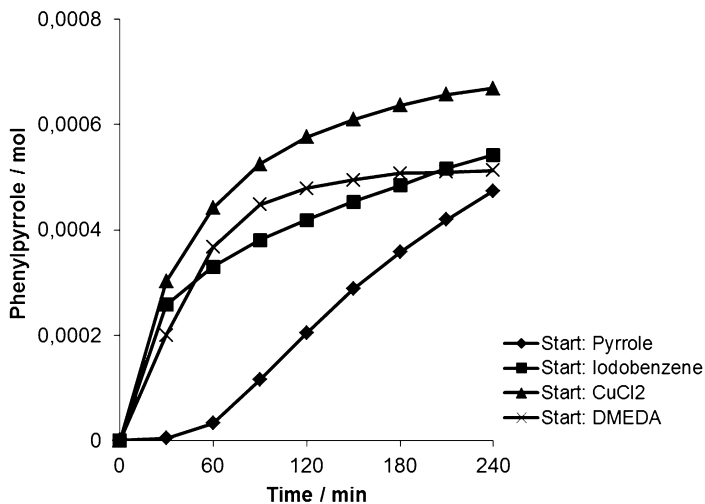
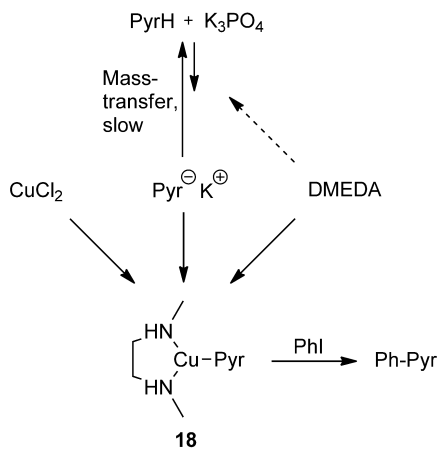


Figure 17 Starting the reaction with different reaction components

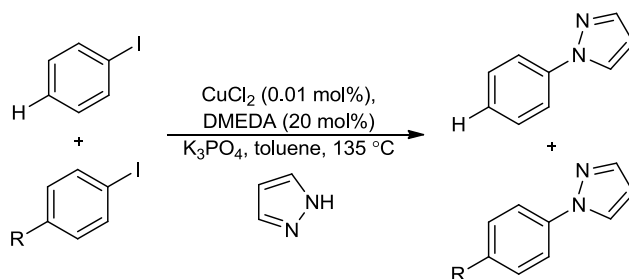
The most obvious effect is the initiation time with pyrrole. Other effects may not be significant. The lag time could possibly be due to the mass transfer for the deprotonation of the pyrrole by the heterogeneous  $K_3PO_4$  (Scheme 46).



Scheme 46 The mass-transfer for the deprotonation of pyrrole

The steady-state point for the mass-transfer equilibrium is reached after approximately 40 minutes. When starting the reaction with iodobenzene the steady-state for the mass-transfer has already been reached and hence the preformed complex **18** is converted to product in less than 30 minutes.

A competitive Hammett study was also performed to gain further mechanistic information. The copper-catalyzed cross-coupling of pyrazole with various para-substituted iodobenzenes were chosen as reaction system (Scheme 47).



| R               | $k_{\text{rel}}$ | $\sigma$ | $\sigma^\bullet$ |
|-----------------|------------------|----------|------------------|
| OMe             | 0,8291           | -0,27    | 0,24             |
| tBu             | 0,8235           | -0,2     | 0,13             |
| Me              | 0,8857           | -0,17    | 0,11             |
| Cl              | 1,1802           | 0,23     | 0,12             |
| CF <sub>3</sub> | 1,4862           | 0,54     | 0,08             |

Scheme 47 The reaction for the competitive Hammett study including  $k_{\text{rel}}$ ,  $\sigma$ , and  $\sigma^\bullet$ -values

The results showed good correlation to  $\sigma$  but not to  $\sigma^\bullet$  (Figure 18).

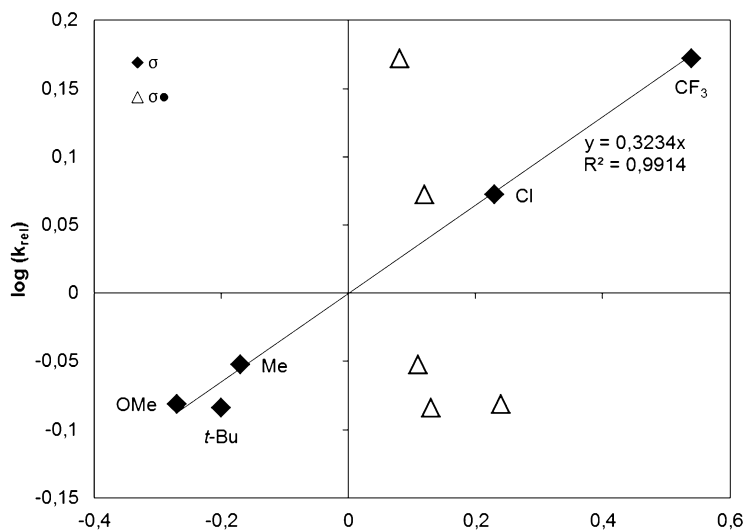


Figure 18 Competitive Hammett correlation for  $\sigma$  and  $\sigma^*$

Taillefer and co-workers have performed a comparable study using 5 mol% of  $\text{CuO}_2$  and Salox as ligand with similar result.<sup>131</sup> Neither of these results support the SET/IAT mechanism proposed by Houk and Buchwald.<sup>208</sup> Both the SET and IAT mechanism involves radical intermediates which are stabilized by both electron withdrawing and donating substituents, resulting in increased rate of product formation. This was not observed in our, as well as Taillefer's, case.

Altogether the influence of DMEDA on sub-mol% copper-catalyzed cross-coupling reactions cannot be fully elucidated. One can only speculate if the diamine ligand is only part of the active catalyst or if it has more roles such as facilitating the mass-transfer for the deprotonation of the nucleophile. The results from the competitive Hammett study is in agreement of Taillefers study and do not agree with a SET/IAT as have been proposed by Houk and Buchwald. Taillefer suggests that the oxidative addition pathway is the most probable mechanism based on their results (*vide supra*).





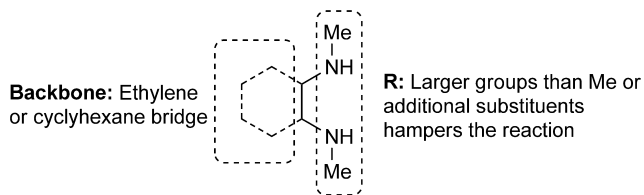


Figure 20 Beneficial structural motifs for diamine ligands

One important observation regarding these structural motifs is that they have all been examined using approximately 5-10 mol% of copper catalyst. It is clear from our results that when using sub-mol% copper, the ligand design is much narrower than using higher amounts of copper. As can be seen from Figure 19, just adding one more methyl group to DMEDA greatly hampers the reaction. One of the disadvantages of using diamines in copper-catalyzed C-N cross-coupling reaction has been the issue with arylation of the ligand producing unwanted byproducts (up to 17%).<sup>130,134</sup> Surprisingly, this is not a concern when low concentration of copper is used.

To gain further mechanistic insight behind this unique behavior, a kinetic study was performed. The unexpected result from the kinetics of DMEDA was that the rate of the reaction actually increased even though the ratio DMEDA/CuCl<sub>2</sub> > 1000 (Figure 21).

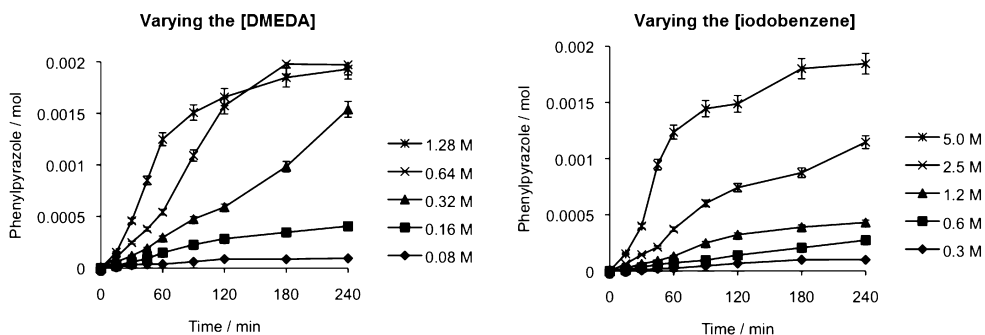


Figure 21 Kinetic profile for DMEDA and iodobenzene

Running the reaction in neat DMEDA results in 91 % yield within 1 h at 135 °C, and 88 % yield at 65 °C after 16 h. The reason for the high efficiency of DMEDA has been speculated to origin from

the fact that the role of DMEDA is not only to coordinate to the active copper catalyst but might also help to solubilizing  $K_3PO_4$ , hence eliminating the mass-transfer issue otherwise present.

The reaction order in iodobenzene was found to be approximately one in agreement with previous studies.<sup>95,210,213</sup> This confirms that the iodobenzene is involved in the rate limiting step of the reaction. The reaction order in  $K_3PO_4$  was determined to be zero. This is not surprising due to the fact that the heterogeneous base remains in constant equilibrium in solution independent of the amount used.

One of the most interesting findings from this study was that the reaction order of copper at low concentration is one, but at the breaking point of 1 mM and above the reaction order is zero (Figure 22).

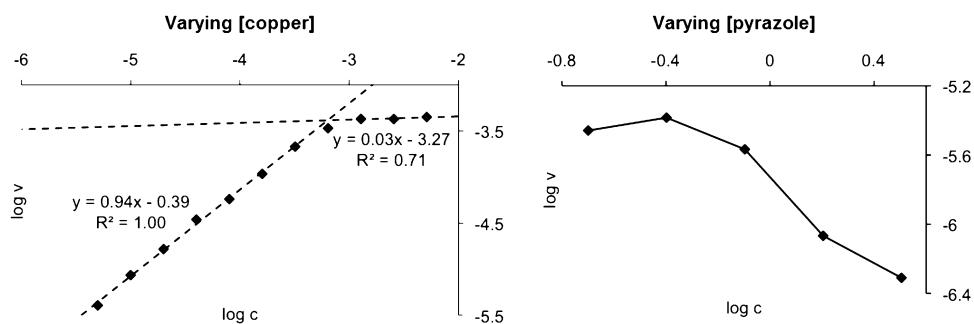
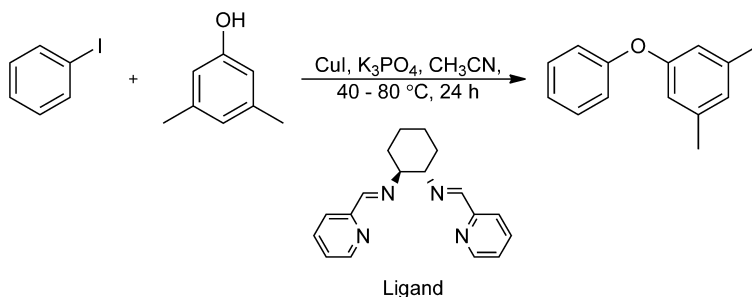


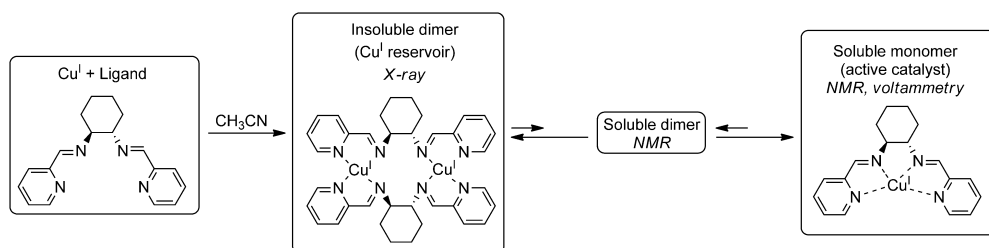
Figure 22 Kinetics for copper and pyrazole

The hypothesis is that the copper below 1 mM is homogeneous, whereas, above 1 mM the copper forms inactive heterogeneous species, possibly nanoparticles or insoluble copper aggregates.<sup>214</sup> Taillefer has studied this “reservoir” behavior for the copper-catalyzed cross-coupling of phenols using tetra-dentate ligands (Scheme 48).<sup>215</sup>



Scheme 48 Tetra-dentate ligands for copper-catalyzed C-O cross-coupling

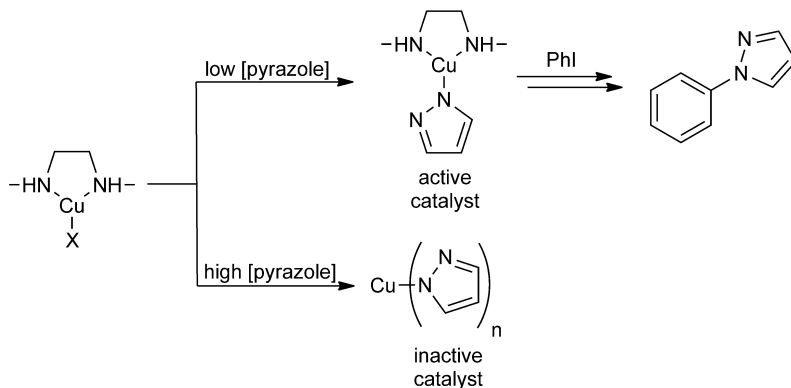
The results from X-ray crystallography, electrospray ionization mass spectroscopy (ESIMS), NMR and cyclic voltammetry concluded that the copper/ligand-complex exists in two different forms of aggregation; one soluble monomer (active catalyst) and one insoluble dimer (inactive catalyst) (Scheme 49).



Scheme 49 Aggregation of CuI with the tetra-dentate ligand

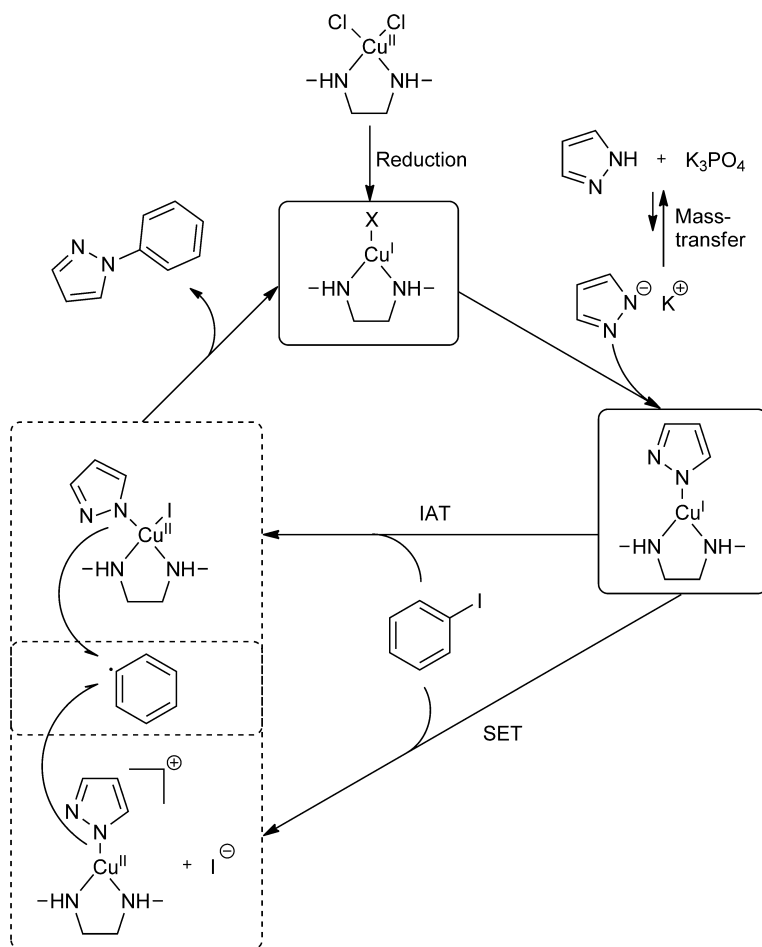
Similar conclusions were drawn by Bolm and co-workers for the sub-mol% copper-catalyzed Castro-Stephens reactions. The partial reaction order in copper was explained by a reversible coordination of the ligand to a polymeric resting state of the catalyst, forming the monomeric active catalyst.<sup>95</sup> These interesting results could also apply to the CuCl<sub>2</sub>/DMEDA system for copper-catalyzed C-N cross-coupling reactions.

The negative reaction order in pyrazole at high concentrations is most probably due to over-ligation of the copper catalyst (Scheme 50).



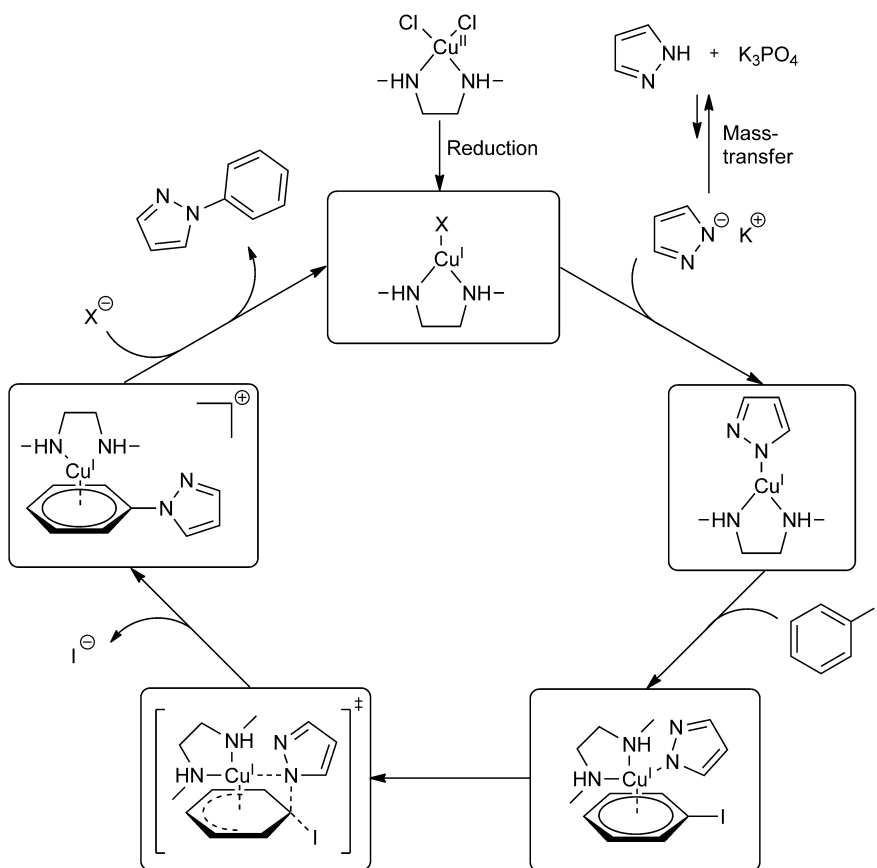
Scheme 50 Catalyst deactivation through multi-ligation

The combined mechanistic results from our work with sub-mol% copper-catalyzed cross-coupling reaction do not give a full mechanistic picture. We can however speculate and exclude some mechanistic pathways. Based on the kinetic results and the computational work done by Houk a plausible mechanism can be drawn (Scheme 51). This mechanistic proposal does not fit all of our gathered experimental data. The most obvious is that the Hammett study does not correlate to  $\sigma^\bullet$  which should be the case for this proposal. It should, however, be noted that few reactions correlate to  $\sigma^\bullet$  alone.



Scheme 51 A plausible mechanism for the sub-mol% copper-catalyzed C-N cross-coupling reaction

One pathway that has been excluded from Houk's and Buchwald's extended mechanistic studies, based on scarce support in the literature, is the  $\pi$ -complexation mechanism (Scheme 52).



Scheme 52 Plausible  $\pi$ -complexation mechanism

Although the  $\pi$ -complexation mechanism has found little support it has not been disproved and could be an alternative mechanistic pathway alongside the more commonly proposed oxidative addition or SET/IAT mechanism. One should however expect a much higher  $\rho$ -value for this type of mechanism than 0.3.

## 4.6 New Efficient Ligand for Sub-mol% Copper-Catalyzed Heteroatom Cross-Coupling Reactions Running Under Air (Paper VI)

From the knowledge gathered from the sub-mol% copper-catalyzed C-N cross-coupling using DMEDA as ligand we set out to expand the ligand scope for this type of reactions. Since the reaction is extremely sensitive towards substitution patterns on the ligand the choice fell upon synthesizing N,N''-dimethyl diethylenetriamine (DMDETA) starting from diethylenetriamine (Figure 23).

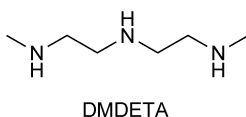
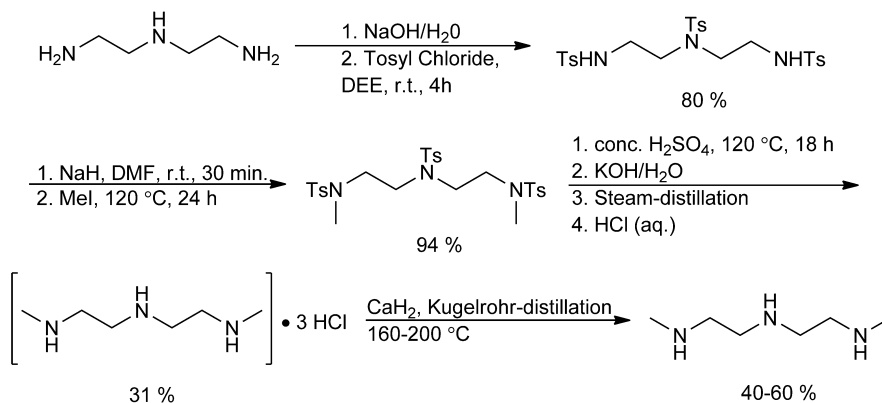


Figure 23 N,N''-dimethyldiethylene triamine (DMDETA)

This simple ligand has not been tested in copper-catalyzed C-N cross-couplings and contains the same features known to be effective in this type of reaction, namely ethylene-bridge and mono-methylated amines. The synthetic procedure was based on published recipes (Scheme 53).<sup>216,217,d</sup>

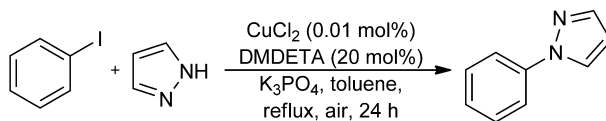


Scheme 53 Synthetic procedure for N,N''-dimethyldiethylene triamine

<sup>d</sup> Synthetic work done by Peter Astvik



As standard reaction for DMDETA the copper-catalyzed cross-coupling of pyrazole with iodobenzene was chosen (Scheme 54).



Scheme 54 Sub-mol% copper-catalyzed reaction run under air

DMDETA was as efficient as DMEDA giving yields of approximately 80-90 % after 24 h, with one major difference: air stability. The sub-mol% copper/DMEDA system is sensitive to air and must be run under inert atmosphere. The copper/DMDETA system however is stable under reflux in the presence of air (Figure 24).

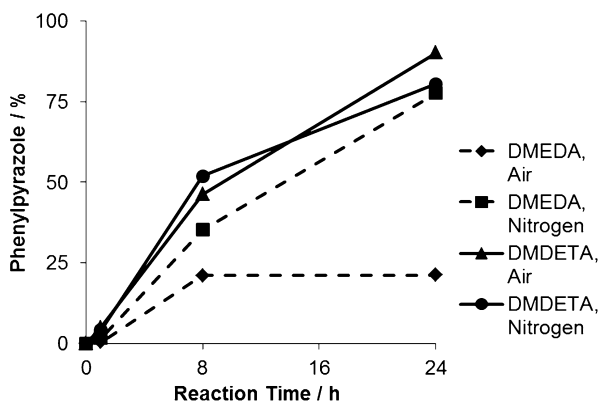


Figure 24 DMEDA and DMDETA performance under nitrogen and air atmosphere

To further explore the efficiency of DMDETA a kinetic study was performed by varying the concentration of DMDETA for the standard reaction (Figure 25).

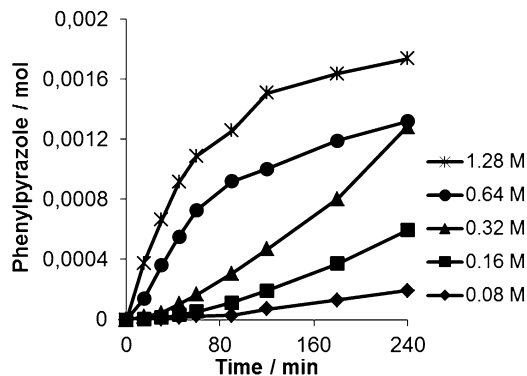


Figure 25 Kinetic profile for DMDETA ranging from 10 - 160 mol%

The kinetic profile is similar to that for DMEDA within measurement accuracy.

The reaction order in copper was also determined (Figure 26).

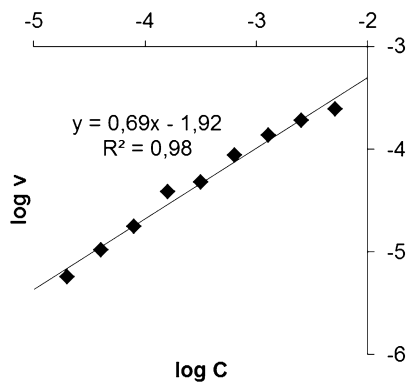
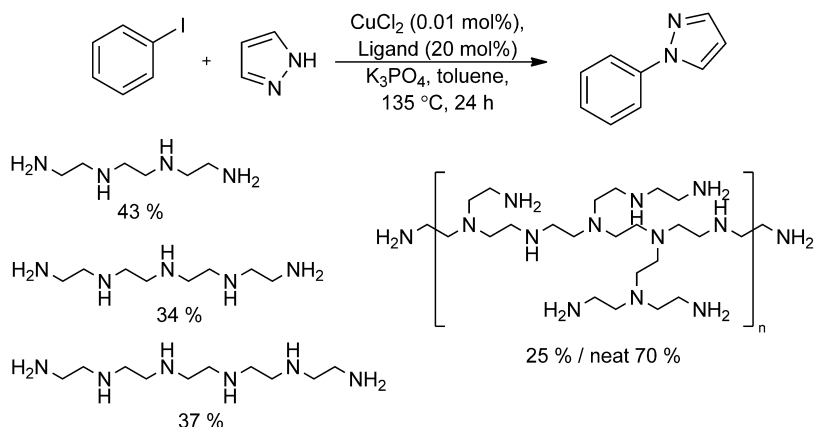


Figure 26 Reaction order in copper ranging from 0.0025 - 0.64 mol%

The reaction order lacks the non-linear behavior observed for the DMEDA-system, hence indicating that DMDETA is more effective at solubilizing the active catalyst and preventing oligomerization.

A range of other long-chained aliphatic amines were also tested as ligands for the standard reaction but none gave satisfying yields (Scheme 55). The polyethyleneimine, however, gave 70 % yield if the reaction was run without solvent.



Scheme 55 Long-chained aliphatic amines as ligands for sub-mol% copper-catalyzed C-N cross-coupling reactions

Some selected solid-supported aliphatic amines (StratoSphere™ PL-EDA resin, StratoSphere™ PL-DETA, tris(2-aminoethyl)-amine polymer bound) were also tried as ligands but gave zero yield under standard reaction conditions. The fact that polymer-bound aliphatic amines were unsuccessful as ligands in sub-mol% copper-catalyzed C-N cross-coupling reactions indicates that the ligand needs to be present as free amine and could be involved in the mass-transfer of the heterogeneous base.

DMDETA has proved not only to be a competitive ligand for sub-mol% catalyzed C-N cross-coupling reactions but also air stable compared to the DMEDA-system.

## 4.7 Summary and Outlook

As in the case of iron, copper has also experienced a revival as catalyst in cross-coupling reaction. One of the issues with copper has been the high catalytic loading, typically 5-30 mol%. The discovery that a range of transformations could actually be catalyzed by sub-mol% copper by using an excess of diamine ligand has further strengthened the position of copper as a competent catalyst. In contrast to using 5-10 mol% of copper when almost any diamine is usable as ligand, at sub-mol% amounts DMEDA and DMDETA are the only efficient choices. The kinetic data shows the extraordinary efficiency of DMEDA with positive reaction order even when the concentration of DMEDA is greater than 1000 relative to the copper concentration. Several explanations for the behavior of this system have been proposed. From the kinetic data and in conjunction with literature a plausible mechanism has been proposed. The ligand scope has been broadened by adding DMDETA as a working ligand for sub-mol% copper catalysis with the most notable feature of being an air stable system.

To further broaden the scope and gain valuable mechanistic information for sub-mol% copper-catalyzed chemistry a competitive Hammett study on the nucleophile could be a future project. As mentioned before, the  $\pi$ -complexation pathway has not been accounted for in any computational study. However unlikely this pathway might seem it is vital to explore all possibilities before making any final conclusions.

## 5. Concluding Remarks

The impact of the transition metal catalyzed cross-coupling reaction in organic chemistry has been enormous and the field is steadily growing. With the most commonly used catalysts, palladium and nickel, reaching its peak in success, the scientific community has moved towards non-conventional alternative catalytic systems. Among these, iron and copper have reappeared as valid alternatives. Although the progress has been successful there are still some unresolved topics as have been mentioned in this thesis.

The increasing endeavors to find valid alternative metal catalysts to old transformations pose an increasing demand on experimental accuracy for avoiding trace-metal contaminations. The discovery that iron-catalyzed C-N cross-coupling reaction was instead catalyzed by small traces of copper raised several important questions among scientists. How could this happen? Is it important? How could this be avoided? The answers to questions like these are not easily given. Several factors could add to situations like this occurring such as time-pressure and laboratory practice. From a purely experimental point of view this may not be an issue but from a mechanistic point of view it is imperative to know the nature of the reaction that is studied. The increased knowledge and cautiousness in the scientific community concerning trace-metals in catalysis should be enough to avoid situations like this occurring in the future.



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