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Investigation of Kumada Cross Coupling Reaction for Large Scale Production of (2R, 7R, E)-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy) benzyl)-N, N, 8-trimethylnon-4-enamide

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Investigation of Kumada Cross Coupling Reaction for Large Scale Production of (2*R*, 7*R*, E)-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy) benzyl)-*N*, *N*, 8-trimethylnon-4-enamide

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Abstract

Investigation into Kumada cross coupling reaction was conducted by developing the reliable, efficient procedure for Grignard Reagent and its subsequent cross coupling reaction. Safe Mg metal activation as well as moisture free system was created by using MeMgCl reagent and improved the efficiency of Grignard reaction. The established coupling reaction was successfully demonstrated at multi kilogram (50 Kg) scale and the coupling product was purified by using Agitated Thin Film Evaporator (ATFE) technique.

Introduction

The transition metal-catalyzed cross-coupling reactions of organic electrophiles and organometallic reagents have emerged as a tremendously powerful synthetic tool in combining a wide variety of coupling partners.[1-3] In organic chemistry the Kumada coupling is a type of cross coupling reaction, useful for generating the carbon-carbon bonds by the reaction of a Grignard reagent and an organic halide.[4] The group of Robert Corriu and Makoto Kumada reported the reaction independently in 1972. The reaction is notable for being among the first reported catalytic cross coupling methods.[5-6] Despite the subsequent development of alternative reactions (Suzuki, Sonogashira, Stille, Hiyama and Negishi couplings), the Kumada coupling continues to enjoy many synthetic applications, including the industrial scale production of Aliskiren (Figure 1).[7] Furthermore the kumada coupling using commercially readily available Fe catalyst, which is more environmental friendly and most abundant inexpensive metal on earth.

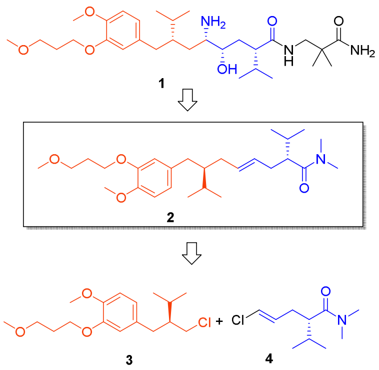
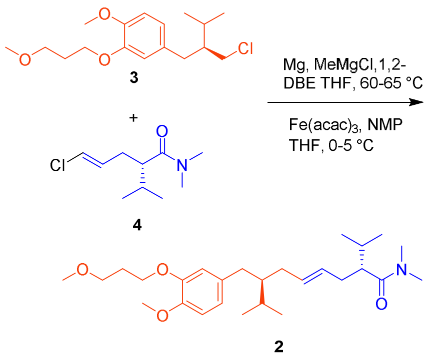


Figure 1. Disconnection Approach to Aliskiren (1)

Grignard reaction is one of the most versatile organometallic transformations, well supported with the following quotation: "*Each chemist has carried out the Grignard reaction at least once in his lifetime*".[8] Grignard reagents are normally prepared through addition of an organic halide into a stirred suspension of magnesium turnings in diethyl ether or THF. The reaction occurs on the surface of the turnings. After the Grignard reagent forms on the reactive metal surface, it gets dissolved and sets the site available to interact with the organic halide. After the initiation, the organic halide transferred to the Mg reactive site *via* the oxidative insertion event and this is considered to be the rate-limiting step of Grignard reagent formation.[9] The potential hazard associated with the manufacturing of the Grignard reagents occurs at the initiation stage. Oxidative insertion event onset is found to be highly exothermic which leads to run-away situation if there is no appropriate temperature control through effective cooling.[10-12] Many methods have been developed to initiate Grignard reaction e.g. crushing the Mg pieces in situ, rapid stirring, sonication of the suspension, Iodine, methyl iodide, and 1, 2-dibromoethane.

In our approach, to support our ongoing project Aliskiren **1**, we need to prepare multi kilogram quantities of (2*R*, 7*R*, *E*)-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy) benzyl)-*N*, *N*, 8-trimethylnon-4-enamide intermediate **2**.[13] In order to produce compound **2**, the following synthetic Scheme 1 (Kumada cross coupling reaction) was considered.



Scheme 1. Synthesis of Compound **2** *via* Kumada cross coupling reaction

Although some of the methods are available in the literature for these reactions however we encountered difficulty in reproducing the Grignard reagent and its subsequent cross couplings. All our attempts to prepare the Grignard reagent were unsuccessful and the reactions ended up with no reaction leaving behind alkyl chloride (**3**) or corresponding alkane compound. Hence we intended to establish a large scale suitable safer process for formation Grignard reagent of **3** and its subsequent Kumada cross coupling reaction.

Results and Discussion

In order to carry out the formation of the Grignard reagent and the subsequent coupling, extensive process investigation considering different process parameters was conducted and described.

Solvent Study for Grignard Reagent

The nature of solvent and its concentration plays a major role in preparation and stabilization of Grignard's. Moreover, the two electron pair short lived Grignard reagent was stabilized with co-ordination of solvent. In addition, the Grignard reagents undergo a redistribution reaction to give diorgano magnesium species *via* Schlenk equilibrium (Fig 2).[14]

$$\mathrm{R\text{-}Cl} + \mathrm{Mg} \longrightarrow \mathrm{R\text{-}Cl}^{-\bullet} + \mathrm{Mg}^{+\bullet}$$

$$\mathrm{R\text{-}Cl}^{-\bullet} \longrightarrow \mathrm{R}^{\bullet} + \mathrm{Cl}^{-}$$

$$\mathrm{R}^{\bullet} + \mathrm{Mg}^{+\bullet} \longrightarrow \mathrm{RMg}$$

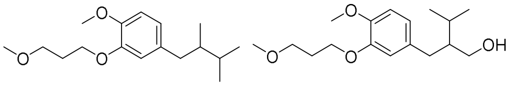
$$\mathrm{RMg}^{+} + \mathrm{Cl}^{-} \longrightarrow \mathrm{RMgCl}$$

$$2\ \mathrm{RMgCl} + \mathrm{THF} \rightleftharpoons \mathrm{R_2Mg} + \mathrm{MgCl_2}\ (\mathrm{THF})$$

Figure 2. Schlenk Equilibrium of Grignard Reagent

In our attempts, tetrahydrofuran (THF) was chosen as reaction solvent and also we studied the solvent concentration effect. This study revealed that more dilution did not favor Grignard reagent which is probably due to more moisture content and peroxides in higher volumes of solvent leading to deactivation of Grignard reagent. Moreover, it was also found that Grignard reagent of **3** was highly unstable towards moisture and oxygen. In this context, we observed degradation to form alkane (**5**), hydroxyl (**6**) impurities (Figure 3). Alkane **5** is expected in

Grignard reagent of **3** preparation but we were also surprised to observe the formation of significant amount of hydroxy impurity **6**.



5 **6**

Figure 3: Impurities and their structures **(5 & 6)**

As shown in Figure 4, we suspect that the Grignard reagent would have reacted with oxygen and generated the peroxy Grignard reagent leading to a formation of impurity **6** after hydrolytic quenching. Hence it is essential to ensure that the moisture and oxygen free system for Grignard reaction is in place.

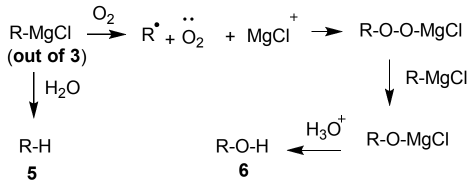
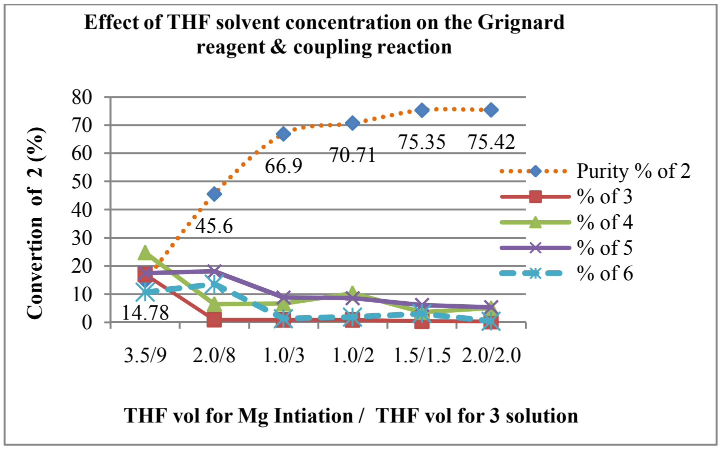


Figure 4. Plausible mechanism for impurity **5 & 6**

Extensive process investigation suggested that the minimum volume of THF is superior for Mg initiation and as well as for better coupling. Hence the optimal 6 volumes of THF (2 vol for Mg initiation, 2 vol for **3** solution and 2 volumes for dissolving **4** into solution) were chosen for Grignard reagent and coupling reaction (Graph 1).



Graph 1. Effect of THF solvent concentration on the Grignard reagent and coupling (**2**)

Also in DOE analysis of data of this reaction clearly evidenced that increase in the solvent volume for Grignard preparation led to decrease in purity of **2** (Figure 5). Moreover, with higher volume of THF, the degradation of Grignard reagent to corresponding alkane **5** and rise in hydroxy impurity **6** were observed.

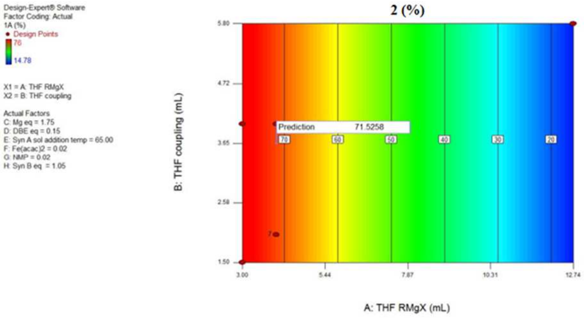


Figure 5. Effect of solvent concentration on Purity of **2 (%)**

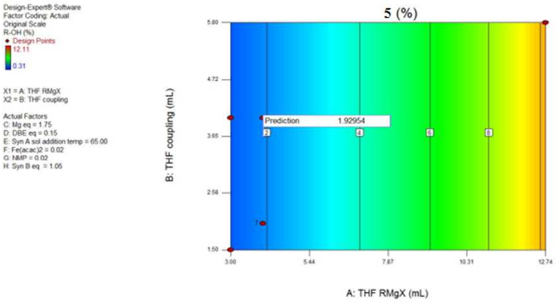


Figure 6. Effect of solvent concentration on content of **5 (%)**

Study of Mg Metal for Grignard Reagent

In our hands, utilization of Mg turnings for preparation of Grignard reagent was unsuccessful. Because utilization of Mg turnings require higher temperature (70-75 °C) for initiation, moreover prolonged maintenance of the reaction at this temperature lead to degradation of reagent and resulted in **5** along with other impurities. Interestingly, when using Mg powder, the initiation was achieved at 50-55 °C and improved the efficiency of Grignard reagent formation. This reflects that the high surface area of Mg powder could have complemented in its activation/initiation at low temperature and thus avoided the degradation of the Grignard reagent. After the Grignard reagent forms on the reactive Mg surface, it dissolves away from the site and sets the site free, exposing it to the organic halide. This phenomenon was more suitable for Mg powder.[15] Furthermore, it was realized that the quantity of Mg is playing significant role in initiation as well as in stabilization of the Grignard reagent. Relatively high amount of 1, 2 dibromo ethane (DBE) initiator, have been utilized liberating $MgBr_2$ that would have hampered the performance of the coupling reaction. DOE analysis revealed that the lowering of the equivalence of DBE, increase in Mg purity of **2** was increased (Figure 7).

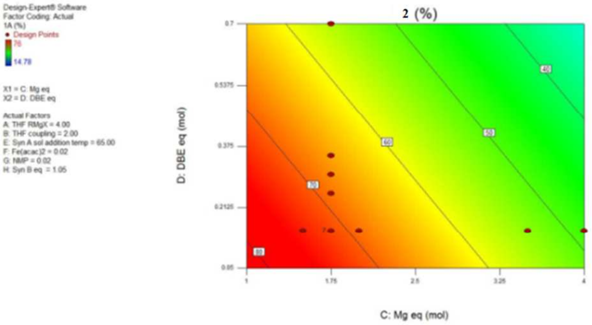
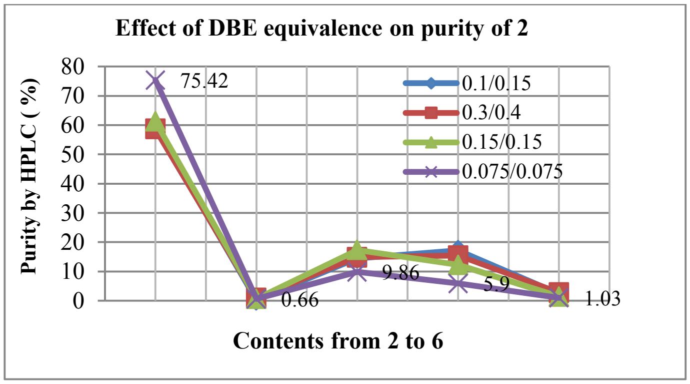


Figure 7. Effect of Mg equivalence on Purity of **2**

In order to avoid the interference of un-reacted Mg and $MgBr_2$ byproducts, the Grignard reagent was filtered and the filtrate was taken into the coupling reaction. Although some of the experiments afford superior coupling results, in further experimentation very low reproducibility was observed. This may be attributed to the exposure of the Grignard reagent to moisture and air effecting the coupling reaction. Moreover, the filtration of Grignard reagent is a highly undesirable operation at production scale. In subsequent investigation the optimal 1.75 equivalence of Mg was chosen for preparation of the Grignard reagent.

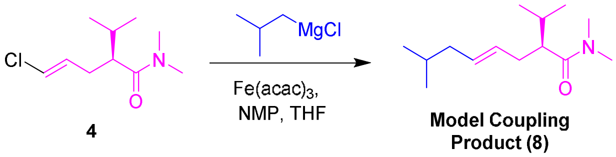
Mg Activation with Methyl Magnesium Chloride (MeMgCl)

Further the Mg activation study revealed that different batches of Mg gave different results in Grignard formation and subsequent coupling reaction. Moreover the reaction was not reproducible when Iodine and 1, 2-dibromoethane (DBE) were used to activate the newer batches of Mg. Since different lots and types of Mg did not afford reliable results, a more reproducible method for the Mg activation was investigated. In this study it was found that 0.15 equivalents of 1, 2-dibromoethane is viable for activation of magnesium. On the other hand excess moles of (0.3) DBE or its fast addition lead to a sudden rise of the temperature to 70 °C and that subsequently effected the Grignard reagent and the coupling reaction. Hence the viable 0.15 equivalence of DBE was used as 0.075 equivalence for Mg initiation and 0.075 moles was mixed with alkyl halide **3** and slowly added to Mg and thus ensured the continuous Mg initiation and achieved the Grignard reagent formation (Graph 2).



Graph 2**.** Effect of DBE equivalence on Grignard and Coupling Reaction (**2**)

Although these conditions were able to reproduce the Grignard formation and coupling reactions on lab scale, we were not able to succeed at pilot scale batches (5 kg), because in pilot scale batch only 5-10 % of coupling product was observed. In addition to this, the batch HPLC analysis revealed that un-reacted **4** and impurity **5** as major side products and raised the concerns about the efficiency of the coupling conditions.



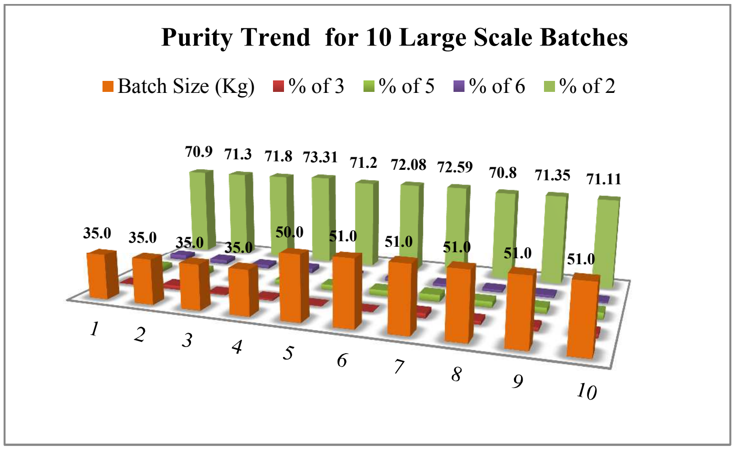
Scheme 2: Model study for coupling reaction

Further to evaluate the efficiency of coupling conditions, the Isopropyl magnesium halide (Model Grignard/known quality) was coupled with **4** under pilot scale conditions. In this experiment, 80-85% conversion of isopropyl coupled product **8** was observed (Scheme 2) and proved the efficiency of the coupling conditions. Further it was understood that during the batch execution of the prepared Grignard reagent was exposed to moisture present in the system it dissociated to **5** and was thus not involved in the subsequent coupling reaction. In the laboratory, initiation of Mg is often confirmed by observation of increased foaming or vigorous bubbles emanating from the Mg chips and darkening of the solution (Figure 8). However these visual observations are often difficult to ascertain on large industrial scale. Moreover, the Mg activation has to be performed under reflux conditions, the temperature remains relatively constant and therefore the detection of the initiation of the reaction based on temperature measurements becomes difficult for pilot scale batches. In order to render a more efficient process for large scale Mg activation, moisture free methods were investigated for the Grignard reaction.

Figure 8. Typical Mg activation snaps shots

In our study a safer Mg metal activation as well moisture free system was created by using MeMgCl reagent and improved the efficiency of Grignard formation. In order to ensure the moisture free reactor set up for the Grignard reaction, before starting the batch, the reaction solvent THF was refluxed in the reactor and re circulated through the transferring lines and alkyl halide addition receivers. Further prior to charging the Mg into the reactor, the Mg in the reactor was dried and the reactor was evacuated with vacuum and filled with nitrogen gas. Thereafter, **3** was dissolved in THF solvent (2 vol) and to this solution was added DBE (0.075 equiv.) and MeMgCl solution. In this method the MeMgCl reacted with moisture and liberated methane gas. Thus the alkyl halide **3** solution was ensured moisture free. Addition of moisture free alkyl halide solution not only quenched the moisture present in the Grignard system but also weakens the MgO layer and exposed the reactive Mg surface to alkyl halide **3**. As a result, of the reactive surface of Mg the initiation was achieved at low temperature (50-55 °C) and stabilized the Grignard reagent. During the initiation of Mg, increased foaming and vigorous bubbles emanating from the Mg chips was observed, in addition to a darkening of the solution (Figure 8). After the initiation, the **3** solution was slowly added to magnesium at 60-65 °C and stirred at the same temperature for 45-60 min. In this investigation, the selection of Mg powder (instead of Mg turnings) could be able to avoid the higher temperature exposure to Grignard preparation and thus avoided the dissociation of the Grignard reagent. Introduction of MeMgCl solution could exterminate the moisture present in the reaction and made the Grignard system moisture free and that helped in getting reproducible coupling results. This moisture free controlled strategy not only succeeded in the gram scale (lab) but also demonstrated the process robustness in the large scale (50 kg) batches (Graph 3).

Graph 3: Purity Trend for 10 Large Scale Batches of **2**



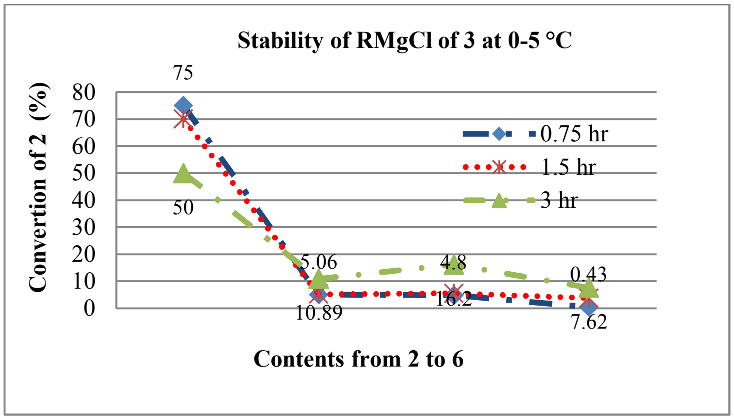
Study of Alkyl Chloride 3 addition time and temperature

Another important parameter for Grignard reagent preparation is the addition time and temperature of alkyl halide (**3**) solution. Moreover it is necessary to maintain continuous initiation of Mg during the preparation of the Grignard reagent. Further, continuous Mg initiation is dependent on the supply of alkyl halide. Fast addition (~15-20 min) of alkyl solution at 55-60 °C lead to uncontrolled exothermic and incomplete Grignard reaction whereas slow addition (45-

60 min) of alkyl chloride solution at 55-60 °C and subsequent maintenance at 65-68 °C for 60-70 min afforded the best results. After completion of RMgCl formation from **3**, it was cooled to 0-5 °C and added to the **4** solution and formed the coupling product **2**.

Study of Grignard Stirring Time at 0-5 °C

At this point stirring the Grignard at 0-5 °C for longer time has shown effect on stability of Grignard reagent as it is clearly evidenced (Graph 4) that the higher the maintenance the (3 h) higher the dissociation of Grignard leading to formation of corresponding alkane impurity (**5**) which also affected the subsequent coupling event, Thus 0.75 h was preferred for maintenance of Grignard reagent formation.



Graph 4. Effect of Grignard stirring time on conversion of **2**

Investigation of the Cross Coupling Reaction of 2

In general, metal-catalyzed cross-coupling reactions proceed through three critical organo metallic processes: oxidative addition of an electrophilic carbon-heteroatom bond into the lowvalent transition metal, transmetalation and reductive elimination to form a new C-C bond (Figure 9).[16-18]

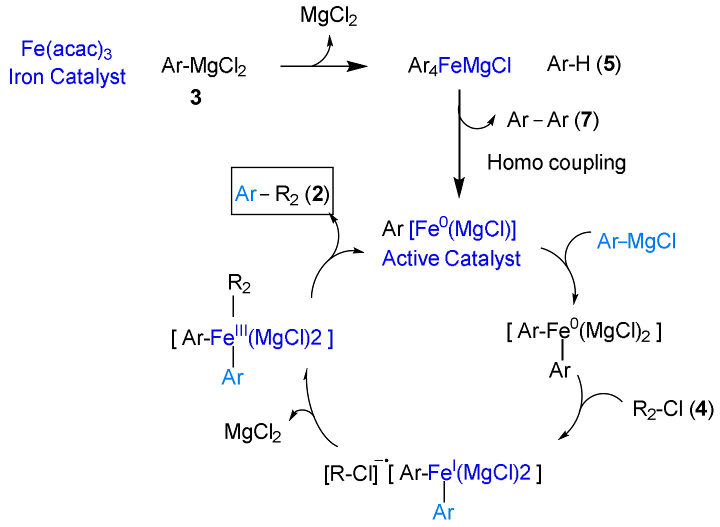
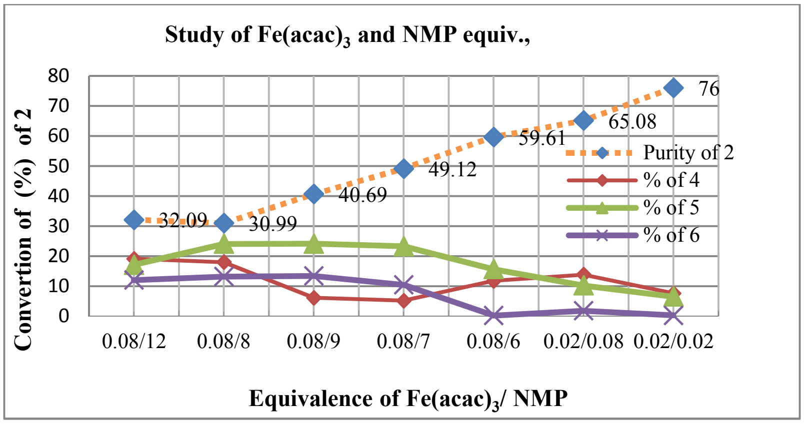


Figure 9. Plausible Mechanism for Kumada Cross Coupling **(2)**

As shown Figure 9, in this coupling reaction after addition of **4** solution, the Fe(acac)$_3$ and NMP[19]catalyst spontaneously react with Grignard regent of **3** and generate the active catalyst Ar [Fe^0(MgCl)]. Subsequently the active catalyst reacts with **4** and transmetalation followed by reductive elimination reactions take place affording the coupling product **2**. In this cycle the active Fe catalyst regenerates and is continuously involved in the coupling reaction produces the coupling product **2**.

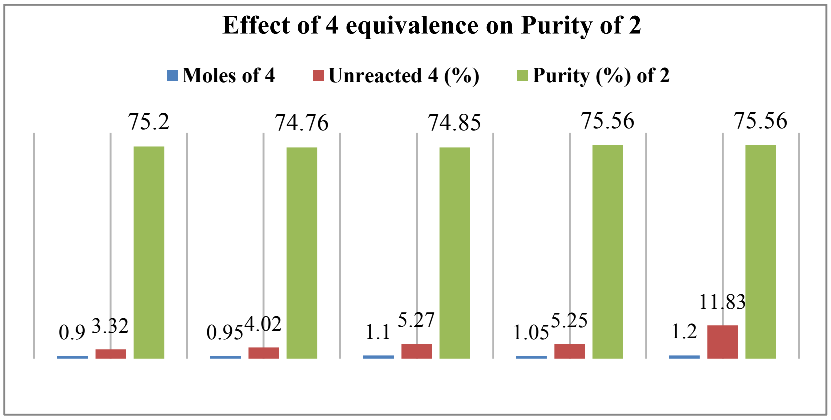
Study of Fe (acac)$_3$ and NMP equivalence

In this reaction generation of the active complex (Inorganic Grignard) is crucial for the success of the coupling reaction. In the initial development 0.08 eq of Fe (acac)$_3$ and 9.0 eq of NMP was employed and most of the time it offered poor conversions. Moreover, close inspection of Fe (acac)$_3$ and NMP equiv, the 0.02 and 0.02 eq catalytic systems afforded the best conversion. On the other hand varying the above catalytic system irreproducible results were noticed with lower or higher equivalences. Hence, 0.02 eq of Fe (acac)$_3$ and 0.02 eq of NMP were chosen for further study (Graph 5).



Graph 5. Effect of Fe (acac)$_3$ and NMP equivalences on purity of **2**

Further we screened the equivalence of **4**. In this study 0.9, 1.0, 1.05 and 1.1 equivalents were tested. With this study it was found the 1 and 1.05 equivalence of **4** gave the best yield and purity results. Although higher equivalents of **4** (1.1 equiv.,) afford similar results concerns over the difficulty in purging of residual **4**, the optimal 1.05 equivalence of **4** was selected for coupling (Graph 6).

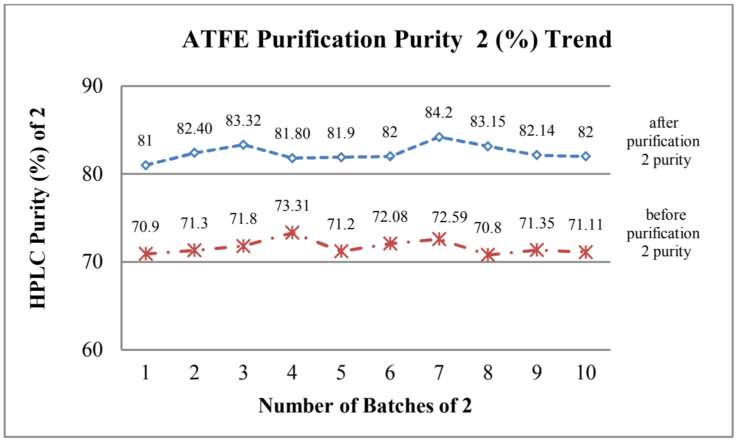


Graph 6. Effect of **4** equivalence on purity of **2**

Further, the conversion of **2** is temperature dependent. Evidently, the addition of **4** is exothermic and at higher temperature the regeneration of active catalyst and subsequent coupling reaction is not efficient. Hence the addition time was studied and optimal conditions identified as addition of **4** at 0-5 °C and maintenance at 25-35 °C for 1.0 to 1.5 h.

Agitated Thin Film Evaporator (ATFE) for Purification of 2:

After completion of the reaction it was quenched with aqueous HCl solution and the product was extracted into toluene. Thereafter the toluene layer was concentrated and crude **2** was obtained with ~70-75 % HPLC purity. We proceeded with this crude **2** for subsequent reactions (i.e., bromolactonization, azidation and amynolysis); we experienced difficulty in consistency of the reaction performance and isolations. Since the coupled product **2** and its impurities are of liquid, it was difficult to purify. Hence, the high vacuum distillation (HVD) was opted for the purging of the impurities (**3** to **6**). Although the HVD purification process (Temperature: 240 - 250 °C, 1-2 torr vacuum) was successful at lab scale, in subsequent pilot scale batch HVD distillations created issues in the assay of the **2**. Because of the increased time, high temperature distillations in a stirred tank (SS) reactor, compound **2** gets degraded and resulted in lower assays (~ 60-65 %). Therefore large scale suitable thin film evaporation technologies were studied and Agitated Thin Film Evaporator (ATFE) technology was chosen. In this technology the coupled product **2** was purified by the film evaporation at low temperatures (Graph 7).



Graph 7.ATFE purification purity trend (before /after) of 10 large scale batches of **2**

Further the continuous feed increased the rate of production of compound **2**. Moreover because of the short surface contact residence time of the compound with higher temperature, the assay and purity of the compound was improved and produced the coupled compound with high consistency.

Conclusion

In conclusion we have under taken a detailed study of the Kumada cross coupling reaction and developed a reliable, efficient procedure for Grignard Reagent formation and its subsequent cross coupling reaction. A safer Mg metal activation as well as a moisture free system was achieved by using MeMgCl reagent and this improved the efficiency of Grignard reagent formation. The established Kumada coupling reaction was successfully demonstrated at multi kilogram (4 x 35 & 6 x 50 Kg) scale and the coupling product was purified by using an Agitated Thin Film Evaporator (ATFE) technique.

Experimental Section:

Step 1 : Mg (6.754 Kg, 277mol) was charged in a dry reactor and stirred at 85-90 °C for 45-60 min under inert atmosphere (*in order to expel moisture and oxygen*). Thereafter, it was cooled and charged with THF (100 L).

Step 2 : Preparation of alkyl halide 3 solution

1, 2-Dibromoethane (DBE lot 1, 1.02 L) and methyl magnesium chloride [MeMgCl, 10 L (*to quench the traces of solvent moisture*)] were added to a solution of alkyl halide **3** (50 kg, 158.8 mol) in THF (100 L).

Step 3 : Thereafter, the solution of alkyl halide **3** in THF (500 mL only) along with first lot of DBE (*prepared in step 2*) and DBE lot-2 (1.02 L) were added to the reactor containing Mg in

THF (*managed in step 1*) at 55-60 °C. After completion of the addition, Mg activation was initiated (*bubbles observed*) and temperature was raised to 60-65 °C. Subsequently to this Mg suspension, the remaining quantity of alkyl halide (**3**) solution was added over period of 45-60 min at 60-65 °C. After that, the reaction mass was stirred at 60-65 °C for 50-60 min (formation of Grignard reagent out of alkyl halide **3**) and then cooled to 0-5 °C.

Step 4 : Preparation of 4 solution

Compound **4** (33.85 kg, 166 mol) along with the *N*-Methyl 2- Pyrrolidinone (NMP) (0.32 Kg, 166 mol) and Iron (III) acetylacetonate (Fe (acac) $_3$) (1.121 kg, 3.1 mol) was dissolved in THF (100 L). After that, the **4** solution was added to the above Grignard reagent at 0-5 °C (*prepared in step 3*) and then allowed the reaction mass temperature to rise to 30-35 °C. Further the reaction was stirred at same temperature for 60-90 min and then cooled to 0-5 °C.

Step 5: Quenching Solution (work up)

Subsequently, another reactor was charged with 10 % HCl solution (0.7 L) and cooled to -5-0 °C. Thereafter, the above cooled reaction mass (*processed in step 4*) was slowly added to the aq. HCl solution (quenched) and stirred at 25-35 °C for 15-20 min. Thereafter, the product (**2**) was extracted with toluene (3 x 250 L) and washed with 10 % aq. HCl solution (0.4 L) and followed by water (2 x 150 L) washings. Subsequently, the toluene layer was distilled and obtained the crude **2** with 72.6 % HPLC purity and 82 % yield (57.99 kg).

Step 6 : ATFE purification

The crude (**2)** (*from step 5*) was subjected to thin film evaporation at 160 -170 °C under vacuum (1 Torr). During this thin film evaporation the low boiling impurities were separated from compound **2** and the compound **2** was collected in a separate receiver with 78.8 % (55.72 kg) yield. HPLC purity details of compound **2**: 84.2 % , **3**: 2.5 % , **6**: 1.5 % and other 12 %

accounted for minor impurities. ^{1}H-NMR (500 MHz, $CDC1_3$): 0.81-0.90 (m, 6H), 0.97 (d, 6H), 1.52 (m, 1H), 1.70 (m, 1H), 1.84 - 1.91 (m, 1H), 1.93-2.03 (m, 2H), 2.08 (m, 2H), 2.31-2.39 (m, 2), 2.41-2.59 (m, 3H), 3.29 (dd,1H), 3.36 (s, 3H), 3.57 (t, 2H), 3.80 (s, 3H), 3.78-3.85 (m, 1H), 4.03-4.16 (m, 4H), 4.67 (m,1H), 5.37-5.5, (m, 2H), 6.63 (dd,1H), 6.67 (d, 1H), 6.70 (d,1H), 7.14-7.34 (m, 5H) ppm.

Acknowledgments

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(19) *N*-methylpyrrolidinone (NMP) likely used to stabilize the active iron species.

Table of Contents Graphic

Large Scale Production of Fe Catalyzed Kumada Cross Coupling Reaction