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Optimization of Grignard Addition to Esters: Kinetic and Mechanistic Study of Model Phthalide using Flow Chemistry

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Abstract

The kinetics of sequential addition of a distinct Grignard species onto a lactone is studied by flow chemistry. The experimental data are shown to be consistent with a kinetic model based on four reaction steps, reaction of ester to magnesium hemiacetal, rearrangement to ketone (forward and backward) and reaction of ketone to tertiary alcohol upon quenching. The experimental derived reaction mechanism is supported by ab initio molecular computations, and the predicted activation energy is in good agreement with the experimental observations. The Grignard reaction follows a substrate-independent, reductive [2+2] cycloaddition of the Meisenheimer/Casper type. Moreover, the rearrangement equilibrium between magnesium hemiacetal and ketone is characterized and found to be feasible. Monoaddition of the ester carbonyl group is demonstrated for fluorophenylmagnesium bromide, but at reaction conditions at -40 °C with several hours of residence time. Working under cryogenic temperature conditions is essential to realizing monoaddition of the ester carbonyl group with Grignard reagents.

TOC
Introduction

Reactions of Grignard reagents with carbonyls have been intensely studied since the discovery of Grignard reactions in the early 20th century.\textsuperscript{1,2} Ketones have been the topic of many studies, while fewer have focused on aldehydes and esters.\textsuperscript{3} The Meisenheimer\textsuperscript{4} and the Swain\textsuperscript{5} mechanisms (Scheme 1 and Scheme 2, respectively) remain the most widely accepted mechanisms, despite a simplified representation that only considers the reaction between the carbonyl and the Grignard reagent.\textsuperscript{3,6} A wide variety of factors, such as the type of solvent and halide, and trace metals in the magnesium, have been found to influence the reaction. Underlying equilibria, such as the Schlenk equilibrium\textsuperscript{3,7}, are also known to have a strong influence. The Meisenheimer mechanism is a simple bimolecular reaction and entropically favored compared to the Swain mechanism. The Swain mechanism involves the formation of a bimolecular complex of the Grignard reagent and the carbonyl substrate, with a subsequently reaction of an additional Grignard reagent. Moreover, the used solvent (i.e., MeTHF) is highly coordinative, which hinders formation of higher Grignard aggregates.\textsuperscript{8,9} Therefore, our study focused on the Meisenheimer mechanism exclusively.

Scheme 1: The Grignard addition mechanism with ketone carbonyl groups as proposed by Meisenheimer and Casper.\textsuperscript{3,4}

\[
\text{R}^3\text{MgX} + \begin{array}{c}
\text{O} \\
\text{R}^1 \text{R}^2
\end{array} \rightarrow \begin{array}{c}
\text{X} \\
\text{Mg} \text{R}^1 \text{R}^2
\end{array} \rightarrow \begin{array}{c}
\text{OMgX} \\
\text{R}^3 \text{R}^1 \text{R}^2
\end{array}
\]

Scheme 2: The Grignard addition mechanism with ketone carbonyl groups as proposed by Swain and Boyles.\textsuperscript{3,5}

\[
\text{R}^3\text{MgX} + \begin{array}{c}
\text{O} \\
\text{R}^1 \text{R}^2
\end{array} \leftrightarrow \begin{array}{c}
\text{X} \\
\text{Mg} \text{R}^3 \text{R}^1 \text{R}^2 \text{X}
\end{array} \rightarrow \begin{array}{c}
\text{OMgX} \\
\text{R}^3 \text{R}^1 \text{R}^2 + \text{R}^3\text{MgX}
\end{array}
\]
Grignard addition with aldehydes, ketones and esters are generally expected to occur very fast with completion in seconds or minutes.\textsuperscript{2,10-12} Esters are known to react up to 100 times slower than aldehydes and ketones,\textsuperscript{11,12} but factors such as solvent and magnesium used cause deviation from this general trend.\textsuperscript{2,12,13} Grignard addition to either ketones or aldehydes result in the formation of monoaddition products. For esters, addition with Grignard reagent results in a mixture of mono- and diaddition products.\textsuperscript{2,14} The carbonyl oxygen in the ester forms a new ketone carbonyl group via an intramolecular rearrangement, the newly formed ketone can undergo a second addition that results in the diaddition product. The reaction can be seen as a consecutive competitive reaction, where two equivalents of Grignard reagents will result in the diaddition tertiary alcohol product upon quenching (Scheme 3).\textsuperscript{14} A few studies have demonstrated monoaddition of esters as the main product under certain conditions.\textsuperscript{15,16}

**Scheme 3:** The reaction mechanism of a Grignard addition of an ester.\textsuperscript{14} The 4-membered transition state where the Grignard addition takes place is characteristic for a \([2 +2]\) cycloaddition mechanism. The reaction of the ketone is given in Scheme 1 and Scheme 2.

Knowledge about reaction rates of a synthesis, including the main impurity formation, is valuable information when designing a reactor setup. A detailed understanding of the full reaction mechanism can sometimes be useful, but in most cases, a good understanding of the overall reactions at relevant conditions is sufficient to estimate rate constants, activation energies and pre-exponential factors needed in the design. The kinetic information about the synthesis can be used in the dimensioning of reactor setups, as well for the determination of the optimal configuration for the given chemistry. Furthermore, the knowledge can be used to select the parameter for optimal operation, and maximum performance of the chosen reactor setup, i.e. high conversion to the desired products, without formation of difficult-to-remove impurities.\textsuperscript{17,18}
Kinetic data may be generated in classic batch experiments with fast mixing of the added reactants. Upon fixed time intervals, samples from the reaction mixture are withdrawn, terminated, and analyzed. The batch method is highly efficient for slow reactions (e.g. reaction times above 30 minutes), but becomes difficult for fast. The main limitation of the batch method is the time at which samples can be withdrawn, terminated, and analyzed, which provides uncertainty to the actual reaction time. Alternative methods have been used for generating kinetic data for fast reactions (i.e. reaction times less than 5 minutes). Steady state measurements in flow chemistry were already used to some degree in the 1960s for determination of kinetics of Grignard addition reaction. The advancement of flow chemistry in the last decade and progress in the development of inline analysis has shown a growth in these alternative methods for achieving kinetic data. The use of micro reactor technology combined with inline analysis, either disrupted measurement methods (e.g. HPLC, MS) or non-disrupted methods (e.g. IR, Raman), has many advantages in comparison to traditional batch methods. Non-disrupted inline and online analyses provides sample information within seconds, which has several advantages in comparison to disruptive at-line and off-line analyses where sample time varies from minutes to hours.

Lately, a number of Grignard reactions and organometallic reactions have been demonstrated in flow reactors. Pedersen et al. transformed a routine batch process to a continuous reactor setup, where addition of a Grignard reagent to a ketone slurry suspension resulted in the formation of a key intermediate active pharmaceutical ingredient (API). Kopach et al. recently demonstrated Grignard chemistry in flow by using three coupled continuous stirred tank reactors (CSTRs). Roberge et al. utilized micro reactor technology for reaction of organometallic chemistry. The Jamison Group recently demonstrated flow setup for reaction between gasses (CO₂ and O₂) with Grignard reagents. The Ley Group covered a large number of different Grignard chemistry in flow setups. Riva et al. used flow reactor for demonstration of Grignard addition with a large number of carbonyls.

Chemistry and Strategy of Investigation

The synthesis of interest is a Grignard addition between phthalide 1, a lactone, and 4-fluorophenylmagnesium bromide (Grignard reagent 2) (Scheme 4). The phthalide 1 is chosen as a model compound based on its high solubility, and its simple structure limit the formation of
other by-products besides the diaddition. The Grignard addition between the ester carbonyl group of phthalide 1 and Grignard reagent 2, results in the formation of the ketone intermediate 4 upon rearrangement of the magnesium hemiacetal 3. The carbonyl group in the ketone intermediate 4 can undergo an additional addition with Grignard reagent 2, resulting in the formation of an undesired diaddition product 5. The desired intermediate from the first Grignard addition reaction is the monoaddition ketone 4, which subsequently reacts in a second Grignard addition reaction with 3-(N,N-dimethylamino) propylmagnesium chloride (Grignard reagent 6), to form the final product 7.

**Scheme 4:** The generation of the desired product 7, is achieved by a consecutive sequential Grignard addition reaction, where 2 fully reacts with 1 to yield 4 which then reacts with 6 to achieve 7.

Studies by Smith and Wikman⁶⁵, and Hillery and Cohen⁶⁶ suggest that substitution of hydrogen with methyl or phenyl on the carbon 3, 4 and 7 position influence the probability of the phthalide to undergo the second addition. Natelson and Pearl⁶⁷ found formation of monoaaddition phthalide, but it has not been confirmed by other researchers.⁶⁵

From a reaction engineering perspective the synthesis can be considered as a competitive consecutive reaction between phthalide 1 and ketone 4 towards the first added Grignard reagents 2. In order to have reasonable conversion, the optimization of the reaction should focus on a 1:1 ratio of reactants, and the kinetic models must therefore describe the reactivity under these conditions.
This contribution explores the kinetics of mono- and diaddition of phthalide 1 with Grignard reagents by use of a flow setup. The aim is to better understand the choice made in the legacy batch synthesis, by studying the underlying reaction rate and mechanism of the two Grignard reagents necessary to generate the desired product. The generated data are used to verify the potential of an alternative continuous production method, with a small scale-up of flow reactors in the laboratory.

**Experimental Section**

**Materials** The following materials used in this study were commercially available: Phthalide 1 (Sigma Aldrich), Naphthalene (Merck, Sigma Aldrich), Grignard reagent 2 1M in MeTHF (Alfa Aesar), anhydrous MeTHF (Sigma Aldrich). All manipulations of Grignard reagents and solution were performed in oven-dried glassware under a blanket of dry nitrogen using standard cannula and syringe techniques.

**Analytical Methods** An Agilent HP GC-MS analyzer (Agilent HP 6890 plus GC and Agilent HP 5973 MS), with an Agilent Technologies (190915-413 HP-5MS) column was used. A 0.1 μL sample was injected, using a split ratio of 100:1. The temperature program start temperature was at 70 °C, followed by a 30 °C/min ramp to 300 °C. Good separation was achieved for the main products, and no quenched Grignard reagent 2 or solvent was detectable with the MS, due to the solvent cut-off of 1.5 min elution time to protect the filament. The samples were prepared in CH₂Cl₂ (DCM), and it was not possible to distinguish between 3 and 4.

**Computational Methods** Kinetic modeling was done in Matlab using the ODE45 solver. Density Functional Theory (DFT) geometry optimizations and frequency calculations were done with Gaussian09 using the B3LYP functional. An all-electron basis set 6-311+G(d,p) was used on all involved elements. For further refining of the relative energies, single-point calculations on the 6-311++G(df,pd) level were performed. The energies of the stationary points on the potential energy surface (PES), i.e. the molecular ground states (GS) and transition states (TS), were corrected for zero-point energy (ZPE). For taking into account solvent effects, a robust two-layer approach was chosen: Calculations were performed with explicit solvent molecules, in order to satisfy the valence around the magnesium core. Additionally, a polarized-continuum model (PCM) for tetrahydrofuran (THF) was used for including solvation energies, both at the geometry optimization and the single-point level. For computational feasibility, the
explicit solvent molecules were chosen to be H₂O, since THF is too computationally expensive and attempts of using dimethyl ether failed due to the very loose degrees of freedom, introduced into the model.

**Initial Screening Experiment on Stabilization** Two Harvard PHD 2000 pumps, equipped with 8 mL stainless steel high pressure Harvard syringes, were used for the Grignard reagent 2 and phthalide 1 solutions. The two reactants streams were pre-cooled before mixed in a Valco stainless steel T-mixer (ID 0.02””) followed by a 2” stainless steel tubing (OD 1/16” ID 0.04””) connected to a 20 mL batch vessel at the target temperature. The pre-cooling consisted of 30 cm submerged PTFE tubing (OD 1/16” ID 0.02””) followed by 20 cm of coiled stainless steel tubing (OD 1/16” ID 0.02””) connecting the reactant pumps to the T-mixer. The reaction proceeded for 1 hour under stirring in the batch vessel. The reaction mixture was quenched with 0.5 M HCl at the reaction temperature, and left heating up to ambient temperature for sample preparation and analysis.

**Kinetic Experiments** The general flow setup used for the kinetic experiments is illustrated in Figure 1. Three Harvard PHD 2000 pumps were used, equipped with 8 mL stainless steel high pressure Harvard syringes. The Grignard reagent and phthalide 1 was pre-cooled before mixed in a Valco stainless steel T-mixer ID 0.02””. The pre-cooling consisted of 30 cm submerged PTFE tubing (OD 1/16” ID 0.02””) followed by 20 cm of coiled stainless steel tubing (OD 1/16” ID 0.02””) connecting the reactant pumps to the T-mixer. The reaction progressed in a 2.5 m OD 1/16” ID 0.02”” stainless steel coil, before the reaction was terminated in a second T-mixer of PEEK material ID 0.04”” at the reaction temperature before samples for off-line analysis were collected.

![Flow setup diagram](image)

**Figure 1:** The flow setup used in the kinetic experiments. Phthalide 1 and Grignard reagent 2 are mixed in a stainless steel T-mixer, before entering the SS reactor coil. The reaction is terminated
at the second T-mixer with TFA in MeOH at the reaction temperature. Samples are collected for off-line analysis.

**Results and Discussion**

**Initial Screening Experiment on Stabilization** Initially a few semi-batch experiments were carried out to identify if the magnesium hemiacetal 3 could be stabilized at low temperature conditions. Literature indicates that ester carbonyl groups can be controlled to give the monoaddition product if reaction carried out at -78 °C.\(^{15,16,72}\) The experiments were conducted with 2 equivalents of Grignard reagent 2 to the phthalide 1.

The undesired diaddition product 5 is decreasing as the temperature is lowered, and is completely absent at -40 °C (Figure 2). Full conversion of the phthalide 1 was achieved in all experiments, with the exception of -40 °C, where minor amounts were still present after 1 hour of reaction. Full conversion was achieved at -30 °C with almost no diaddition product 5 present. The kinetic experiment should therefore be carried out from -30 °C and up, as this seems more suitable for the entire reaction (i.e. very slow conversion at -40 °C). From a scaling and cost perspective, higher temperature is more desirable.

![Figure 2: The formation of the diaddition product 5 decreases with temperature (-20 °C (--), -30 °C (---), -40 °C (...)).](image)

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\(^{15}\) \(^{16}\) \(^{72}\)
A deep blue color is observed when the reaction progresses at higher temperature. The blue color is also known from the actual batch process, where it is seen near the addition point of Grignard reagent 2. The color is therefore assumed to be correlated to the formation of undesired diaddition product 5, due to local high concentration and temperature at the addition point. If the blue coloring is absent, this can serve as a good indicator that the desired monoaddition takes place. The theory is further supported from the literature, where similar color has been observed upon reaction between benzophenone and phenylmagnesium halide.6,73

**Kinetic Experiments** The kinetic experiments with Grignard reagent 2 and phthalide 1 were performed in the range from 0 °C to -30 °C, with an experiment for every 5 °C. The initial stability experiment indicated that low reaction temperature (-40 °C) was necessary to control the undesired diaddition product 5. A 1.0 M Grignard reagent 2 was used in 1.1-2.0 equivalents relative to the 0.25 M phthalide 1 solution with naphthalene as internal standard, both reactants were in MeTHF. At a temperature above -15 °C, reaction was completed after 5 minutes, but up to 1 hour residence time was necessary for the -30 °C experiment with 2 equivalents of Grignard reagent 2. The TFA quench stream was a 0.5 M TFA in MeOH with a flow rate equal to the combined flow rate of Grignard reagent 2 and phthalide 1. Due to the small volumes used to generate the kinetic data, actual yields were not isolated.

The kinetic data were fitted in MatLab with a least squared curve fit by numerical solution of the mass balance of the plug flow reactor (PFR) design equations with iteration on the rate constants. Several reaction mechanisms were (not verified) tested for their capability to describe the investigated reaction system, before the final model was chosen. The first reaction between phthalide 1 and Grignard reagent 2, illustrated by rate constant k₁ (Scheme 4), was found sufficient to a model of a second order elementary reaction (i.e. Meisenheimer mechanism). The intramolecular rearrangement between magnesium alkoxide intermediate 3 and ketone 4 is a more complex matter. Intramolecular reactions – with comparable activation energies – are generally significantly faster than the reactions that take place between two or more molecules. Moreover, an ester will normally have a reaction rate up to 100 times slower than ketones and aldehydes. Combining these general considerations requires that both a forward, k₂, and a backward, k⁻₂, reaction take place between intermediate 3 and ketone 4, establishing an equilibrium. If only the forward reaction, k₂, existed, a pseudo first order reaction for the formation of diaddition product 5 would be observed from the data as rate constant k₃. For the
reasons detailed above, the Meisenheimer mechanism was the model of choice. The final plug flow reactor (PFR) mass balances are given in Equations 1-5.

\[
\frac{d[\text{C}_1]}{d\tau} = -k_1[\text{C}_1][\text{C}_{2a}] \quad (1)
\]
\[
\frac{d[\text{C}_2]}{d\tau} = -k_1[\text{C}_1][\text{C}_2] - k_3[\text{C}_4][\text{C}_2] \quad (2)
\]
\[
\frac{d[\text{C}_3]}{d\tau} = k_1[\text{C}_1][\text{C}_2] - k_2[\text{C}_3] + k_{-2}[\text{C}_4] \quad (3)
\]
\[
\frac{d[\text{C}_4]}{d\tau} = -k_3[\text{C}_4][\text{C}_2] + k_2[\text{C}_3] - k_{-2}[\text{C}_4] \quad (4)
\]
\[
\frac{d[\text{C}_5]}{d\tau} = k_3[\text{C}_4][\text{C}_2] \quad (5)
\]

The activation energy of the reaction between Grignard reagent 2 and phthalide 1 \((k_1)\) was found to be \(52\pm8\) kJ/mol with a pre-exponential factor of \(2.53\cdot10^9\) L/(mol·s) (Figure 3). A strong correlation was found between the equilibrium rate constants \((k_2\) and \(k_{-2}\)) and the rate constant for diaddition \(k_3\). Therefore, the formation of ketone 4 was assumed to be in pseudo-steady state, which reduced the modelling equations with the following form (see supporting information):

\[
\frac{d[\text{C}_1]}{d\tau} = -k_1[\text{C}_1][\text{C}_2] \quad (6)
\]
\[
\frac{d[\text{C}_2]}{d\tau} = -k_1[\text{C}_1][\text{C}_2] - k_c[\text{C}_3][\text{C}_2] \quad (7)
\]
\[
\frac{d[\text{C}_3]}{d\tau} = k_1[\text{C}_1][\text{C}_2] - k_c[\text{C}_3][\text{C}_2] \quad (8)
\]
\[
\frac{d[\text{C}_5]}{d\tau} = k_c[\text{C}_3a][\text{C}_{2a}] \quad (9)
\]

in which \(k_c=k_3k_2/k_{-2}\).

For the combined rate constant expression \((k_c)\), the activation energy was found to be \(88\pm9\) kJ/mol with a pre-exponential factor of \(2.65\cdot10^{15}\) L/(mol·s). This pre-exponential factor is a several orders of magnitude higher than expected for a simple bimolecular reaction, since for ordinary diffusion-controlled reactions, approximate pre-factors of \(10^{10\pm1}\) L/(mol·s) are expected.\(^7\) However, the pre-factor in the current case represents the entropic contribution from not only a single bimolecular reaction \((k_3)\) but also from the \(k_2/k_{-2}\) equilibrium. Since, the ring-opened form 4 is entropically much favored over 3, the additional factor of \(~10^5\) is reasonable.
Figure 3: The Arrhenius plot of the kinetic data of Grignard reagent 2 reacting with phthalide 1. The $k_1$ (◆) is the rate constants for the monoaddition reaction, and the other terms represent the combined rearrangement equilibrium and diaddition reaction $k_c$ (▲).

To study the conversion of desired and undesired compounds as a function of relevant system or model parameters (e.g. residence time), equations (6-9) can be solved using a numerical differential equation solver with rate constants read from Figure 3 (if relevant with an added Arrhenius temperature dependency). However, this numerical exercise has not been part of the present work.

Density Functional Theory Characterization In order to better understand the molecular basis behind this process, a density functional theory (DFT) characterization of the potential energy surface was carried out. As solvation is crucial in Grignard-type chemistry, a two-level solvation model was used to account for the ether solvent: First, magnesium was coordinated with three oxygen sigma-donor ligands and second, the whole solvation complex was inserted into a polarizable continuum model of THF. This allowed a realistic description of the energetics during the reaction, e.g. by estimating activation energies or by verifying the feasibility of an equilibrium between intermediate 3 and ketone 4, for reaction with either Grignard reagent 2 or 6. The DFT results confirmed that the Grignard additions follow the Meisenheimer mechanism. Interestingly, Grignard additions were found to have a 4-membered transition state, indicative of a [2+2] cycloaddition (see Scheme 3 and Figure 4). This is in line with the early proposition.
made by Yamazaki,\textsuperscript{75} who predicted that four-membered transition states rule Grignard reactions (even though his claims included artificial multimetal aggregates, arising from incomplete treatment of solvent effects).

![Figure 4: The 4-membered transition state (TS between 1 and 3) of the monoaddition Grignard intermediate.](image)

The DFT potential energy predictions (Figure 5) reflect the reactivity differences between esters 1 and ketones 4. Furthermore, even though the transition state for rearrangement could not be localized due to complex geometries involved, an equilibrium between the cyclic 3 and open 4 configurations of the monoaddition product was found to be energetically feasible. Thus, the rate constants $k_2$ and $k_{-2}$ could be merged into an equilibrium constant $K_{eq}$, supporting the kinetic model expression used above. The DFT characterization showed that the reaction is exothermic by approximately 120 kJ/mol, with little difference between the first and the second Grignard addition. Calculations on modified Grignard reagents showed that neither the halide nor the aryl/alkyl of the Grignard reagent causes a large difference in reactivity. Though the experiment shows that there is a structure-activity relationship for the Grignard reagent with 2 being less reactive than 6, the differences are too subtle to be quantitated. In any case, the 91 kJ/mol
activation energy found by DFT for the product $k_3k_2/k_2$ (where 70 kJ/mol are from Grignard addition to ketone 4) is in good agreement with the experimentally determined value $88\pm 9$ kJ/mol. For $k_1$, the agreement is only modest, 89 kJ/mol by DFT vs. $52\pm 8$ kJ/mol by kinetic modeling. However, the $k_1$ experimental data appears to be more scattered (lower coefficient of determination (Figure 3)), and could be influenced by other factors such as steric configuration. General observation shows that esters as such are less reactive than ketones, which would require an activation energy value of at least 70 kJ/mol for the true $k_1$, underpinning the prediction by DFT.

![Figure 5: DFT characterization of the potential energy surface for reaction of ester (modeled by 2-furanone) with two equivalents of Grignard reagent (modeled by MgMeBrL3). The characterization was carried out with different Grignard reagents. Very little deviation was found when varying halide and aryl/alkyl groups of the Grignard reagent. The numbering of species is according to Scheme 4.](image)

**Conclusions**

A flow setup has been used in the generation of kinetic data of a selected Grignard addition reaction. The chemistry studied was a competitive consecutive Grignard reaction involving two different Grignard reagents reacting with an ester carbonyl functional group. The addition was studied for temperatures ranging from 0 to -30 °C. An Arrhenius plot was generated from the kinetic data based on a two-fold Meisenheimer mechanism with intramolecular rearrangement in
between. DFT analysis of the potential energy surface revealed structural and energetic insights into the molecular processes involved in Grignard additions and supported the mechanistic assumptions made in the kinetic model. At -40 °C, the competitive diaddition product could be suppressed by slowing down the intramolecular rearrangement, simultaneously causing a decrease in the reaction rate for monoaddition. The experimental kinetic data was found to be in good agreement with a DFT characterization of the potential energy surface associated with a two-fold Meisenheimer reaction.

Suppressing the formation of diaddition product from ester reacting with Grignard reagents is possible at cryogenic reaction condition, but comes with the cost of reduced reactivity towards the desired monoaddition product. The exothermic nature of Grignard addition causes a significant challenge, if the necessary cryogenic condition are to be maintained to assure the desired suppression of the undesired diaddition product. Use of multiple injection reactor technology for the Grignard reagent addition could be a rational solution to the heat problem, as this could distribute the energy release avoiding local hot spot gradients of temperature and concentration.

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Supporting Information

GC MS Mass Spectra, Steady-state derivation of kinetic equations, Cartesian coordinates of optimized transition states, IRC analysis, Photo of the reactor used for the kinetic study.
References


(45) Murray, P. R. D.; Browne, D. L.; Pastre, J. C.; Butters, C.; Guthrie, D.; Ley, S. V.


(73) Gilman, H.; Fothergill, R. E. The Constitution and the Dissociation of the Grignard
