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Michael additions utilizing transition-metal-catalysts, Scope and limitations

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Abstract

The effect that organic solvents have on the environment and the intrinsic risk that come with using them should be limited. By replacing organic solvents with less harmful solvents, such as water, and with more effective catalysts can risks intrinsic to organic solvents be minimized or eliminated. The focus of this project is testing if Michael addition using transition metal salt catalysts with Zr or Hf are viable. Several conditions were tested to determine the optimal conditions. With limited time for testing conditions were the best result found to not use solvent. Tests performed gave insight into the limitations of the catalyst. Limitations such as solidification, unwanted side product and what methods are not applicable for quantification. This has given insight into what conditions and methods that should be avoided or circumvented can be used for future studies.

1. Introduction

1.1 Green Chemistry

The environmental consequences of using organic solvents have been understood for a long time. With regulations dictating the proper way of disposing of organic solvent in to minimize the damage to the surrounding water, air or soil. This should not come as a surprise for any chemist that encounters dangerous solvents and substrates during the daily work. Possibilities to minimize the risk to the environment by substituting organic solvent for less dangerous ones is a sensible way to circumvent those regulations. Thereby is the possibility of performing the same reaction without dangerous solvent the optimal outcome for a green chemistry. Green chemistry is not only limited to changing solvents but the entire synthesis. From minimizing the amount of steps a reaction require, too looking into more effective catalyst for synthesis. What connects these substitutions is the underlying motivation to reduce waist by making reactions more effective. [1]

Specifically for solvent has one reusable alternative been found, namely water. Because water is not as dangerous to handle or to dispose of, compared to organic or fossil-based solvents, is a large risk factor avoided. Phasing out specifically fossil-based solvents is required when water solvents become contaminated, as removing fossil-based solvents can be difficult and in turn counteracts all benefits gained. By using non contaminated water as solvent has handling of waist become less demanding with less risk to the environment. On top of that has further studies into water as a solvent found that specifically Diels Alder reaction performs faster in water that in organic solvent. [2] [3] Due to uncertainty of the scope and limitations of waters role as a solvent is more research required. This research would clarify the best and worst implementations for water as a solution. One point of interest is implementing water tolerant Lewis acids to water based solutions. These catalyzing, specifically metal salts, contain transition metals Ni, [4] Fe, [5] [6] Pb, [7] Cu [8] but also rare earth metals such as Yb. [9] [10] Yb will be a point of comparison, or more specifically $Yb(OTf)_3$. With studies showing that the same $Yb(OTf)_3$ can be reused five times resulting in a high yield [11] is it ideal as a point of comparison to other catalyst. Yb will be compared to Zr and Hf containing metal salts, which have not been rigorously tested but could acts as Lewis acids.

The goal of this thesis is to build on already optimized Michael additions utilizing $Yb(OTf)_3$ [10] by testing less tested transition metal salt catalyst, containing Zr or Hf. Problems with starting material, quantification method and unwanted side reaction limits the amount of test that could be performed.

1.2 Michael addition

A very useful tool in the organic chemist's box is the ability to create carbon-carbon bonds. One of the most useful methods of creating carbon-carbon bonds is the Michael addition. Michael addition can be implemented with a wide variety of substrates and is thereby widely used, with some limitations. The limitations are primarily focused on what substates can be used. With Michael acceptors, that are electrophiles, is a double bonded α, β-double bonded carbon bond and a carbonyl group required. The reason for this limitation is the proportionally larger LUMO at the β carbon, which is an attractive electrophile for Michael donors in 1.4-additions. This is best illustrated in the delocalization of electrons, see the example of acrolein in figure 1. Nucleophiles are less limited, with Michael donators only needing a deprotonated carbon to act as a nucleophile. The other limitation is the deprotonation, often being performed with stoichiometric amount of base in alkaline or neutral conditions.[12] [13] [14] Other methods for deprotonating include Lewis acids delocalizing elections to create nucleophiles or connecting to nitrogen that already has available free election pair.

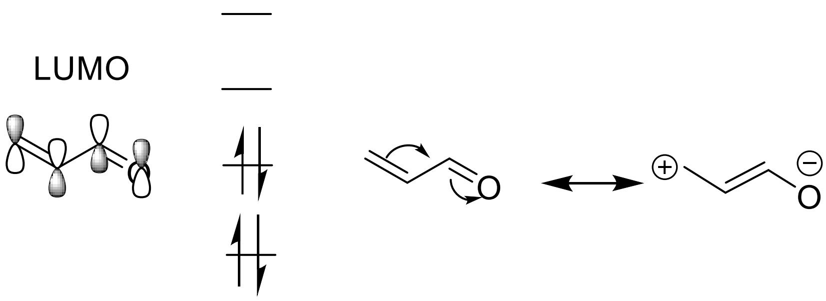

Figure 1: LUMO for acrylaldehyde, illustrating the orbital configuration for possible 1.4-addtion and 1.2-addition.

After creating a nucleophilic centre can it be attached to the electrophile. The substrates have two methods of reacting, the thermodynamic 1.4-reaction and kinetic 1.2-reaction, see figure 2. Thermodynamic reactions, or 1.4 additions, has a high activations energy. This high activation energy requires higher temperature or the use of catalyst. Usually does this result in longer reaction time, but the high activation energy makes the reactions non reversable. In contrast to kinetic reaction, or 1.2-reacions, that has a lower activation energy. This lower activation energy makes additions possible at lower temperature with shorter reaction time. Low activation energy has the downside of reversable reactions, which makes the products of 1.2-additons less stable compared to 1.4-additions.

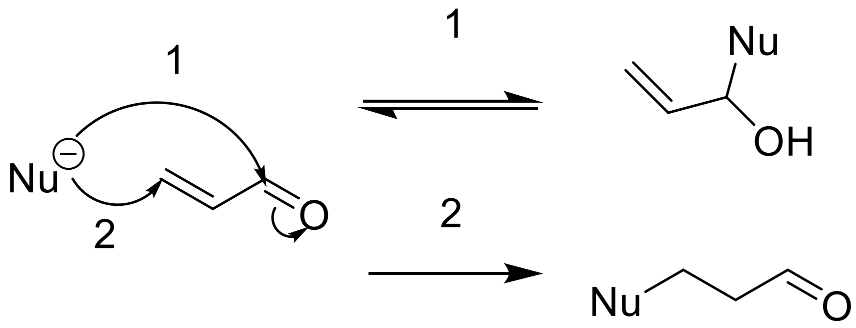

Figure 2: Illustration of Michael addition 1) kinetic reaction, reversible, low temperature and shorter reaction time. 2) Thermodynamic product, not reversable, high temperature and longer reaction time.

2. Results and discussion

2.1 Methodology

Accurate comparisons between reactions require a standardised method for all reactions. Previous rapports that performed Michael additions determined optimal proportions between Michael donors and acceptors, 1.3-dicarbonyl group respectively α, β-unsaturated carbonyl. [10] With excess Michael acceptors to Michael donors in proportions 1.1:1. The catalyst utilized can vary from 1 to 10 mol% of equivalent dissolved in 1.0 mL of a solvent that does not destroy the catalyst. To ensure that reactions conducted in solvents, that does not dissolve the reagent, can react properly is intensive stirring implemented. Previous rapports have come to a general metal salt Lewis acid catalysed mechanism for Michael addition, se figure 3. [15] With the catalyst connecting to the Michael donor 1.3-dicarbonyl group is a carbanion created between the carbonyl groups. This carbanion acts as a nucleophile to the α, β-unsaturated carbonyl LUMO and attaches itself. After the addition is performed is the catalyst removed from the final product, leaving the catalyst to attach itself to another Michael donor. To ensure that Michael additions has occurred were qualitative testing conducted with NMR, TLC and GC. When it is established that Michael additions had occurred were quantitative testing performed by comparing it to a known amount of internal standard. With internal standard added was quantification through qNMR, quantitative NMR, and GC possible. By comparing yields with yields from $Yb(OTf)_3$ catalysed reactions can results for tested conditions be determined to be worse, just as good or better that $Yb(OTf)_3$ catalysed reactions.

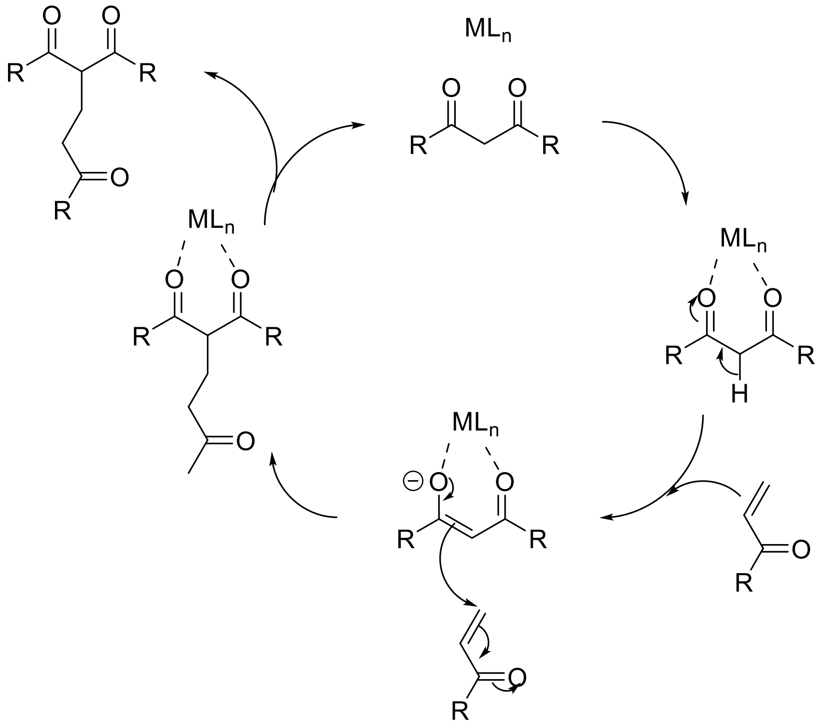

Figure 3: Proposed mechanism for Michael addition catalysed with metal-salt Lewis acid. Requiring a Michael donor with 1.3-dicarbonyl group and a Michael acceptor with a α, β-unsaturated carbonyl compound.

2.1.1 Internal standard

2.1.2 qNMR 1.3.5-trimethoxybenzene

The first method for quantification of Michael addition product was qNMR. To determine the yields of a product were known amounts of internal standard added to the reaction solution. This internal standard cannot have overlap with other peaks in NMR and should not be able to react with staring material, product, or solvent. The proposed internal standard 1.3.5-trimethoxybenzene (1) was thereby implemented, with no overlapping peaks in NMR and no expectation of reacting with the substrates involved. Before adding starting material was 0.1 equivalent of the internal standard added. With the internal standard present from the beginning of the reactions could reactions in tetrahydrofuran (THF) or without solvent have samples taken periodically to determine when the reaction had progressed. When the reaction has concluded, and all starting material have been consumed, can a reaction time and yield be determined.

The problem with this method was discovered after 6 hours, in a 10 mol% $ZrCl_4$ catalysed reaction at 60 °C dissolved in THF. Unreasonably high yields were achieved. With a yield of 176.6% that only increased to 185.4% after 6 hours and 31 minutes was it apparent that quantification was not possible, se table 1. The yield did not level out and instead decreased to 98.4% after 30 hours and 21 minutes. A separate reaction with 5 mol% $ZrCl_4$ reached similar unreasonable yields of 163.7% after 30 hours and 20 minutes, se table 2.

Table 1: Yields for 10mol% $ZrCl_4$ reaction in THF.

Time	**Yield %**
11 min	7.1
32 min	15.0
1 h 1 min	24.3
2 h 1 min	44.6
6 h 1 min	176.6
6 h 31 min	185.4
30 h 22 min	98.4
31 h 1 min	97.1

Table 2: Yields for 5mol% $ZrCl_4$ reaction in THF.

Time	**Yield %**
10 min	2.4
31 min	5.3
1 h	10.0
2 h	16.9
6 h	31.4
6 h 30 min	33.9
30 h 20 min	163.7
31 h	173.0

The reason for this unreasonably high yield was determined after a reaction with added internal standard (1) was observed through GC-MS. GC-MS showing that an unwanted side addition had occurred between (1) and the Michael acceptor methyl vinyl ketone (MVK, 2). This unwanted side reaction removed both internal standard (1) and MVK (2), creating side react to Michael addition. The proposed side reaction is illustrated in figure 4, with the product of 4-(2,4,6-trimethoxyphenyl)butan-2-amine (3) after addition. Reason for the loss of (1) can be attributed to the electron rich structure and good conditions for delocalization of electrons with the three methoxy groups. All that culminates in an effective Michael donor that competes for MVK (2). This side reaction was confirmed by setting up four separate 10 mol% $ZrCl_4$ catalysed reaction in THF at 60 °C. These four reactions were stopped after a set amount of time to determine when all internal standard (1) had reacted. Result of this is that after between 21 and 45 hours had all internal standard reacted according to ^{1}H NMR. Reports with the goal of producing the unwanted side product (3) had come to similar reaction time utilizing $AuCl_3$ could yields of 99% be reached after 24 hours at room temperature. [16] [17] With the difference in temperature and change in catalyst is it still possible that this addition occurred under similar time frames. Due to the loss of internal standard (1) to side reactions was the quantification method of qNMR reconsidered. With qNMR not being viable were priorities shifted to utilizing GC for quantification.

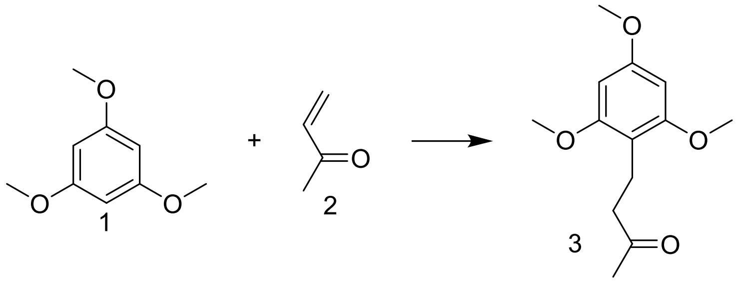

Figure 4: Reaction between 1.3.5-trimethoxybenzene (1) and MVK (2) to produce 4-(2,4,6-trimethoxyphenyl)butan-2-amine (3).

2.1.3 GC dodecane

To ensure that no unwanted side reactions could occur dodecane (4) was chosen as internal standard. With no clear possibility to react unexpectedly with starting material or product could quantification be performed without issues. For further reassurance of no unwanted side reactions was dodecane (4) added after workup, removing catalyst so it can not react unexpectedly. Due to the presence of 1.3.5-trimethoxybenzene (1) in the previous reactions were all reaction performed again without (1). Quantification of the Michael addition was done with a $Yb(OTf)_3$ catalysed reaction. The $Yb(OTf)_3$ catalyzed reaction resulted in a high yield sample that was added in equal amounts to separate solvent. These solvents had increasing amounts of internal standard (4) but with the same concentration of high yield sample. This created a calibration curve that can be used to determine the concentration of expected product be measuring proportions of area of sample peak to internal standard (4) peak. For the product ethyl 2-acetyl-5-oxohexanoate (5) will the calibration curve in figure 5 be utilized. With less-than-ideal R^2 value of 0.9781 should yields determined from this be scrutinised. But this gave a good method for quantification moving forward to evaluate tested conditions compared to optimised $Yb(OTf)_3$ catalysed yield.

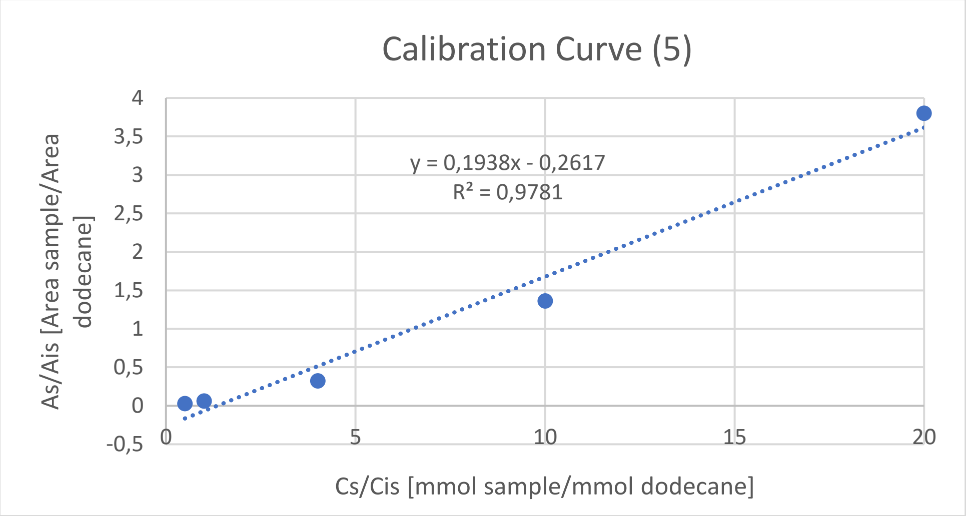

Figure 5: Calibration curve correlation of area of correlation between ethyl 2-acetyl-5-oxohexanoate (5) peak by area of dodecane (4) peak on the y-axis compared to concentration of (5) to concentration of dodecane (4).

2.2 Synthesised starting material

2.2.1 Methyl 2-nitroacetate

The first proposed Michael donator was methyl 2-nitroacetate (6). Choosing methyl 2-nitroacetate required synthesis of the starting material. Synthesis was performed utilizing two methods. One method from Organic synthes [18] which is more reliable compared to a newer but greener method. [19] The General schematic for both methods is similar with the same starting material, se figure 6, but has different workup methods. The Organic synthesis method utilizes benzene compared to the newer version substituting it with ethyl acetate. After repeating both methods could not enough starting material (6) be produced. The reason for the trace amount of yield has not been determined, but tree possible reason has been proposed. The reasons include too low temperature to form intermediate product, loss of staring material nitromethane or to high temperature when adding H_2SO_4 in the second step. Without enough methyl 2-nitroacetate (6) were other commercially available substitutions for Michael donators chosen.

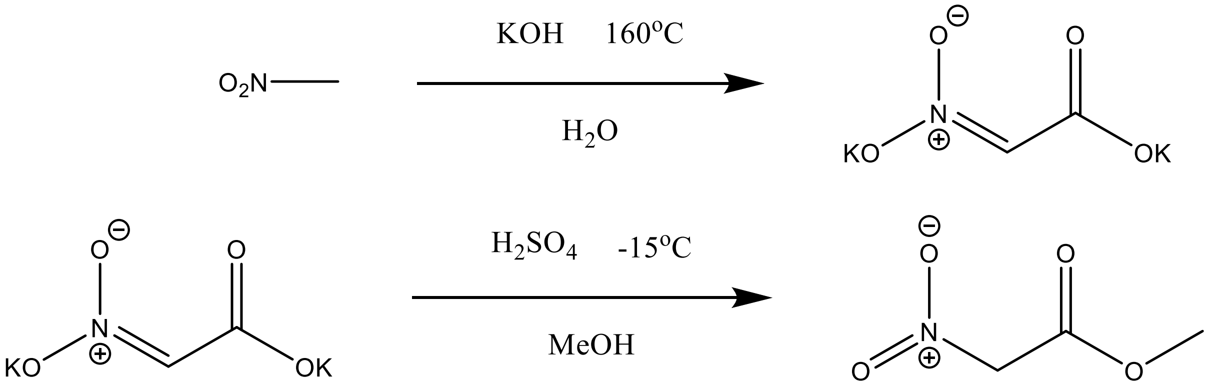

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Figure 6: Reaction for synthesis of methyl 2-nitroacetate (6) from nitromethane.

2.3 Purchased Starting material

2.3.1 Diethyl malonate

Commercially available Michael donator does not require synthesis and could thereby be implemented in Michael additions directly. One of the proposed Michael donors was diethyl malonate (7) which was tested under optimized conditions with $Yb(OTf)_3$ as catalyst. Tested conditions with other catalyst will be compared to the yields of $Yb(OTf)_3$ catalyst reaction. The chosen Michael acceptor methyl vinyl ketone (MVK, 2) was commercially available. But complications with the choice of staring material were discovered after neither TLC nor NMR could observe any product. TLC gave unreliable results giving no indication that (7) and MVK (2) had reacted. ^1H NMR after workup confirmed the TLC result, with only starting material (7) remaining with no indication of the expected product diethyl 2-(3-oxobutyl)malonate (8), se figure 7. No apparent structural limitation with either Michael donor or acceptor would hinder addition. With previous reports utilizing (7) catalysed with $ZrCl_4$ for Mannich-type reaction instead of Michael additions with $Yb(OTf)_3$ [20] Similar mechanisms between Mannich-type Reactions and Michael additions would indicate that $Yb(OTf)_3$ could catalyse the addition. This was disproven with several attempts leading to substituting (7) with another commercially available Michael donor.

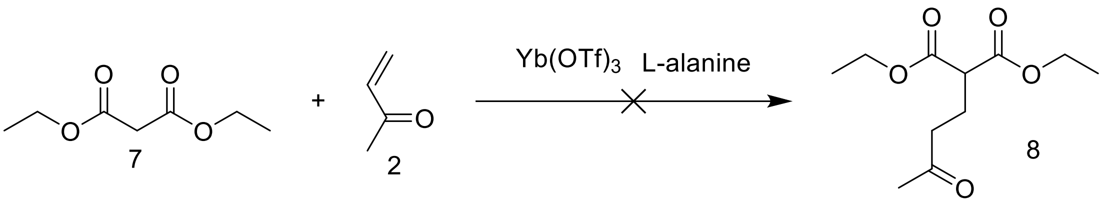
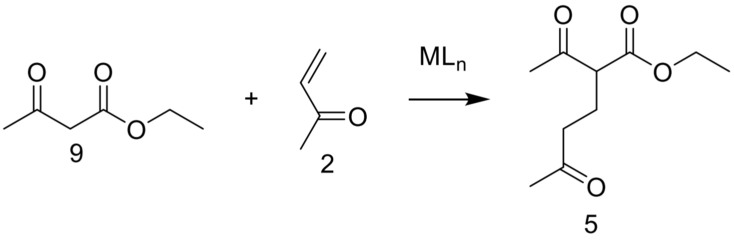


Figure 7: Proposed starting material of diethyl malonate (7) did not react with MVK (2) to form diethyl 2-(3-oxobutyl)malonate (8) through Michael addition.

2.3.2 Ethyl acetoacetate

The choice of ethyl acetoacetate (9) is primarily because of the prevalence of optimized conditions for $Yb(OTf)_3$ catalysed reactions. [10] With a reliable reaction at optimized conditions, resulting in high yields, can the product be used for calibration curves for quantifications in GC. This calibration curve can then be utilized for quantification of reactions at different conditions, se figure 5 for calibration curve. $Yb(OTf)_3$ catalysed reactions between (9) and MVK (2) resulted in the expected product ethyl 2-acetyl-5-oxohexanoate (5), with distinct peaks in NMR and GC. TLC results were unconclusive, making distinction between (5) and unwanted side products not possible. Quantification of (5) was conducted using GC calibration curve and dodecane (4) as internal standard added after workup, see figure 5. All results and conditions for Michael additions performed can be found in table 3.

Table 3: Result of all tested conditions for Michael addition utilizing 1.0 mmol ethyl acetoacetate (9), 1.1 mmol MVK (2) to produce ethyl 2-acetyl-5-oxohexanoate (5) after quenching and workup. Qualitative testing of Michel addition was conducted with ^{1}H NMR and quantification was performed with GC. Se figure 5 for calibration curve used for quantification.



Entry	Catalyst	Mol%	Temp °C	Time	Solvent (1.0 ml)	Yield %
1	$ZrCl_4$	10	60	68 h	THF	23
2a)	$Yb(OTf)_3$	10	60	68 h	H_2O	93
3	$ZrCl_4$	2	22	15 min	Neat	21
4	$ZrCl_4$	10	100	20 min	THF	41
5	$ZrCl_4$	10	100	20 min	Neat	30
6	$ZrCl_4$	10	100	19 h	THF	16

7	$ZrCl_4$	10	100	19 h	Neat	16
8	$ZrCl_4$	10	100	69 h	THF	15
9	No	0	100	69 h	THF	18
10	No	0	100	69 h	H_2O	16
11	$ZrCl_4$	10	4	3 h	THF	14
12	$ZrCl_4$	10	4	3 h	H_2O	14
13	$ZrCl_4$	10	4	3 h	Neat	57
14	$Hf(OTf)_4$	10	60	2.5 h	Neat	14
15	$Hf(OTf)_4$	5	60	2.5 h	Neat	17
16	$Hf(OTf)_4$	10	60	3 h	THF	21
17	$Hf(OTf)_4$	5	60	3 h	THF	49
18	No	0	60	3 h	THF	30
19	No	0	60	3 h	H_2O	15
20b)	No	0	60	3 h	Neat	30
21	$Hf(OTf)_4$	10	60	69 h	THF	13
22	No	0	60	69 h	THF	14
23	$ZrCl_4$	10	60	69 h	H_2O	14
24	$Hf(OTf)_4$	10	60	69 h	H_2O	14
25	$ZrOCl_2 \bullet 8H_2O$	10	22	18 h	Neat	36
26	$ZrCl_4$	10	22	18 h	Neat	34
27	$Hf(OTf)_4$	10	22	1 h	Neat	31
28b)	No	0	60	3 h	Neat	17
29	$ZrOCl_2 \bullet 8H_2O$	10	60	3 h	Neat	30
30	$ZrOCl_2 \bullet 8H_2O$	10	60	3 h	THF	32
31 c)	$ZrOCl_2 \bullet 8H_2O$	10	60	18 h	Neat	45
32 c)	No	0	80	8 h	Neat	87

a) Additional 12 mol% L-alanine, 12 mol% NaOH
b) Only duplicate.
c) Possible aqua regia contaminated stirrer.

2.4 Catalyst tested

All catalyst were tested under similar conditions, se table **3**, with some noteworthy exemptions. Exemptions include addition of 12 mol% L-alanine and 12 mol% NaOH for Yb(OTf)3 catalized reaction (entry 1). Washing of stir bars was done more thoroughly for the last tested conditions using aqua regia (entry 31 and 32). To ensure that any metal catalyst was removed was sir bars left in aqua regia solution, a mixture of 3:1 hydrocloric acid to nitric acid. Effects of aqua regia washed stirrers will be discussed when relevant. Possible contaminated stir bar could have a detrimental effect on yields. But, without comparing aqua regia washed stirrer with stirrer that wash not washed with aqua regia at similar conditions could the effect of washing not be determined.

2.4.1 $ZrCl_4$

With limited testing of $ZrCl_4$ as a Michael addition catalyst [21] were there no optimised conditions. Instead, were there promising results with Mannich-type reactions. [20] Mannich-type reactions substitute the Michael acceptor for a secondary aldimine as electrophile. But, with the same Michael donor and mechanism for addition should Michael addition be possible. Michael addition was observed with the best result at 4 °C without solvent and a reaction time of 3 hours (entry 13) resulting in 57% yeild. Adding the solvents THF or H_2O (entry 11 respectively 12) counteracts any benefit of the lower temperature resulting in 14% yield. Same trace amount of product (5) can be obtained with additional time in H_2O at 60 °C (entry 23). These are the highest respectively lowers yields that were quantified with $ZrCl_4$ as catalyst.

Several problems were observed, with the major problem of utilizing $ZrCl_4$ as a catalyst for Michael additions was solidification. This has been linked with the exothermic reactions that is observed after addition of MVK (2) to reactions. To mitigate the solidification were reactions dissolved in H_2O or THF, making reactions over nigh possible. But as previously stated will the additions of solvents reduce yields dramatically (entry 11 and 12 compared to 13). Decreased yield might be due to $ZrCl_4$ reacting with H_2O to create HCl, se figure 8. This was collaborated with solutions utilizing H_2O as solvent creating acidic conditions, pH 2. Reactions dissolved in water and thereby at low pH, will not be ideal for Michael additions, se table 3. Reactions without solvent would thereby not be acidic and thereby not affected. Additional time for reaction in solvent does not indicate that the 3 hours reaction time being the limiting factor (entry 1 and 8). With 41% yield at 100 °C after 20 minutes dissolved in THF indicating that higher yields can be accomplished without extensive reaction time dissolved in solvent (entry 4). All result could not be compared to previous reports [21] 94% yields at room temperature after 15 minutes. A 1/10 scale reaction compared to the rapport only resulted in 21% yield (entry 3) indicating that additional reagents can result in enough activation energy for successful Michael addition. The high yield in previous rapports could not be confirmed or denied as all reactions were performed at the same 1.0 mmol scale.

$$ZrCl_4 \quad + \quad 2\ H_2O \quad \longrightarrow \quad ZrO_2 \quad + \quad 4\ HCl$$

Figure 8: Reaction between catalyst $ZrCl_4$ and H_2O resulting in HCl which decrease the pH of the solution.

2.4.2 $Hf(OTf)_4$

$Hf(OTf)_4$ have less implementation as Lewis acid catalyst in Michael additions compared to $ZrCl_4$. The expectation that $Hf(OTf)_4$ would perform similar to $ZrCl_4$ is primarily due to them being in the same group but in different periods. Testing concluded that the main similarity between the catalyst was the problem of solidification. Going one period down resulted in reactions solidifying at room temperature after 1 hour compared to $ZrCl_4$ taking over night. With a more extreme exothermic reaction to addition of MVK (2) was solvents required for any rection over 1 hour. With these limitations accounted for was the highest yield 49% at 60 °C, with 5 mol% catalyst dissolved in THF after 3 hours (entry 17). The lowest yield of 13% at 60 °C, 10 mol% dissolved in THF after 69 hours (entry 21). With similarly low yield for when catalyst was dissolved in H_2O (entry 24) giving a clear indication that excessive reaction time is not ideal. Shorter reactions without solvent at room temperature (entry 27) resulted in yields of 31% after one hour. This indicates that the initial exothermic reaction with MVK (2) can catalyse the reaction better then additional time at elevated temperature could.

Longer reaction time at 60 °C has only resulted in trace amount of expected product (5). Similar low yields for longer reaction times have been observed for $ZrCl_4$ (entry 1 and 8). Both $Hf(OTf)_4$ and $ZrCl_4$ differ from $Yb(OTf)_3$ catalysed reaction (entry 2) with longer reactions times not leading to higher yields that form a level given enough time. These stronger group four metal Lewis acid catalysts are thereby not ideal for longer reaction times. Differences between $ZrCl_4$ and $Hf(OTf)_4$ was clearer with the reliance on solvents for $Hf(OTf)_4$. With the higher yield of 49% (entry 17) having a low concentration of catalyst in reaction solution. Yields differing from 21% to 49% by reducing the amount of $Hf(OTf)_4$ in the reaction from 10 mol% to 5 mol% (entry 16 compared to 17) indicating that less $Hf(OTf)_4$ is required for optimized conditions.

2.4.3 $ZrOCl_2 \cdot 8H_2O$

Working with $ZrOCl_2 \cdot 8H_2O$ had less requirements than working with $ZrCl_4$. With no exothermic reaction after addition of MVK (2) and thereby no solidification could longer time reactions be performed without solvent. Similar sentiments of $ZrOCl_2 \cdot 8H_2O$ being easier to work with, excluding solidification, was found in literature working with both catalysts. [22] [23] The literature does however not focus on carbon-carbon Michael additions, but instead carbon-nitrogen bonds or Mannich-type reactions with promising results without solvent.

With a more limited amount of tested conditions compared to $ZrCl_4$ or $Hf(OTf)_4$ was a clear picture of limitations not possible. With the best result of 45% yield (entry 31) at 60 °C with 10 mol% catalyst without solvent after 18 hours. Possible aqua regia contaminated stirrer could have influenced the yield. But if acidic conditions are detrimental for Michael additions with $ZrCl_4$ reactions dissolved in solvent, would yields be lower rather than higher due to lower pH from aqua regia. The worse condition observed resulted in 30% yield (entry 29) at 60 °C, 10 mol% after 3 hours without solvent. Adding THF had a negligible effect with a 32% yield (entry 30). But additional time and temperature are required for higher yields, only longer reaction time at room temperature results in 36% yield (entry 25).

2.4.4 No catalyst added

To ensure that the addition of catalyst was beneficial for Michael addition were several conditions tested without catalyst. After testing several conditions were yield comparable and, in some cases, higher than metal salt catalysed reactions. Of note is the 87% yield at 80 °C after 8 hours without solvent (entry 32). Same problem with aqua regia contamination could play a role in higher yield (entry 31). This could not be confirmed or denied but previous low yields with low pH from $ZrCl_4$ indicate that contamination would lower yield. Lowest yield observed was 14% (entry 22) at 60 °C after 69 hours dissolved in THF. Similarly low yields were observed for both $ZrCl_4$ and $Hf(OTf)_4$ indicating that added catalyst has no clear benefit for reactions with excessive reaction time. Increasing temperature to 100 °C and replacing solvent with H_2O resulted in 16% yield (entry 10) which corroborate that solvents are detrimental to Michael addition. All tested conditions are better than literary values of <1% yield at 25 °C dissolved in H_2O after 16 hours for the same product (5).[24] The trend observed for both transition metal salt and no catalyst are that longer reaction times at increased temperatures has a positive effect that is limited when using solvents.

2.5 Unwanted side reactions

A consistent result of all tested conditions was that yields were lower than $Yb(OTf)_3$ catalysed reaction at optimised conditions. This has been attributed to unwanted side reactions competing with Michael addition. Unwanted side reactions that were considered were cyclization of product (5), formation of unidentified higher molarity products and MVK (2) becoming the limiting reagent.

2.5.1 Cyclization or Hagemann's ester

Cyclization of product (5) was considered after entry 1 and 2 in table 3 were tested in GC-MS. Both the $ZrCl_4$ and $Yb(OTf)_3$ catalysed reactions had indications that the expected product (5) had reacted with itself to produce a Hagemann's ester (10). [25] The expected method for how a Lewis acid, in this case $ZrCl_4$, could catalyse the cyclization is illustrated in figure 9. The problem with this explanation for the low yields is that ^1H NMR did not collaborate that Hagemann's ester (10) was the major product. Attempts at propagating cyclization with higher temperatures at longer reaction time were unsuccessful with the major product always being (5). Low yields can thereby not be because of cyclization. More likely reasons for low yields are through MVK (2) becoming the limiting reagent and unwanted higher molar product.

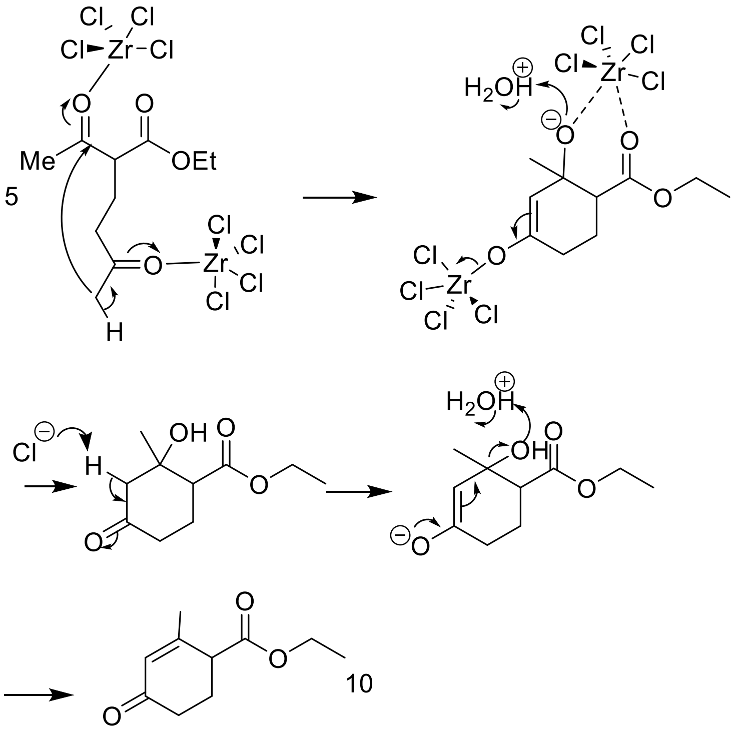


Figure 9: Proposed mechanism for cyclisation of (5) to produce Hagemann's ester (10) utilizing the Lewis acid $ZrCl_4$.

2.5.2 High molar weight side product

Problem with impurities in reactions without extensive workup is expected. But, without clear indication to why yields were low, and with previous experience of unwanted side reactions could the possibility not be overlooked. With no clear separation between expected product (5) and unwanted side product in TLC, was separation through HPLC not viable. Without workup with HPLC could side products be observed in GC and ^{1}H NMR but could not be identified. With no clear sample of a side product could no identification or quantification be performed. These unidentified side products could only be labelled as impurities. A neglectable amount of impurities was observed with the reactions not using any catalyst compared to those with metal salt catalyst. As the impurities never exceeded the expected product (5) or starting materials (2) (9) ^{1}H NMR peaks, was it deterred that these impurities were not the major factor for low yields. The reason that remains is the possibility of MVK (2) becoming the limiting reagent for Michael additions.

2.5.3 Limiting reagent MVK

Polymerisation of MVK (2) is the most likely reason for low yields. This assumption is based on the exothermic reaction after adding MVK (2) to $ZrCl_4$ and $Hf(OTf)_4$ leading to solidification. As illustrated in figure 1 and 2 is additions to MVK (2) not limited to only Michael donors but any nucleophile. For polymerization is a sizable overlap between orbitals between MVK (2) molecules competing with Michael addition. [26]

This is not a confirmed reason for why yields are low. But remnants of ethyl acetoacetate (9) in GC indicate that the limiting reagent being MVK (2). Another explanation for remnants of (9) is the difference in boiling point between starting material. Ethyl acetoacetate (9) has a bp of 181 °C, compared to MVK (2) with bp 81 °C is it possible that remaining MVK might have been removed during workup. Both explanations to remnants of (9) come to the same conclusion, that reaction has not concluded. Reasons for the absence of MVK (2) can thereby be polymerization or evaporation during workup. If polymerization of MVK (2) is the primary reason for low yields, is it because MVK (2) became the limiting factor. Extraction of the polymerised product could not be identified, but from the limited information available is polymerisations the most likely reason for low yields. [26]

3. Future work

To ensure that the results in table 3 are replicate of the conditions tested needed, before any conclusions can be drawn. With the only condition duplicated indicating a wide range in yield from 30% to 17%, table 3 (entry 20) respectively (entry 28), can no clear conclusions bee draw. The tested conditions must be replicated to ensure that yields are reproducible. Whit this established is it possible for other conditions to be tested, such as expanding the tested Michael donor, Michael acceptor and other metal salt catalyst.

A limited time frame resulted in only testing ethyl acetoacetate (9) and MVK (2). Other substitutes could not be tested to see if tested conditions worked better or worse for the tested conditions. Differences were apparent for $Yb(OTf)_3$ catalysed reactions that had a varying reaction time from 2.5 hours to 24 hours by substituting the Michael donors. [24] To determine if other starting material would be preferable to (9) and (2) would further testing with other starting material and comparing reaction times be performed. Ideal method for determining reaction time would be qNMR but with a less reactive internal standard.

For the conditions tested could the found optimized conditions be explored further, to determine if they can be improved. Different metal salt catalysts had different optimized conditions that could be pursued further. For $ZrCl_4$ were lower temperatures and longer reaction times promising. $Hf(OTf)_4$ should be tested with lower concentrations of catalyst, either with more solvent or less metal salt. $ZrOCl_2•8H_2O$ can have more promising result with longer reaction times at higher temperatures. Lastly are the reactions without catalyst that has similar optimized conditions to $ZrOCl_2•8H_2O$, were possible better conditions with longer reaction times at higher temperatures would be ideal.

These tested conditions unfortunately have some blind spots. Such as how lower than 10 mol% equivalence of $ZrCl_4$ in reactions were never tested in the same way compared to $Hf(OTf)_4$. A similar blind spot for lower than room temperature reactions for $Hf(OTf)_4$ were never tested. This results in a possible optimal conditions of low temperature and low concentration of catalyst for $ZrCl_4$ and $Hf(OTf)_4$ can be tested in future work. With only four conditions tested for $ZrOCl_2•8H_2O$ and yields consistently over 30% is it the most promising catalyst with much more work required to identify optimized conditions. One condition is how $ZrOCl_2•8H_2O$ reactions in H_2O and if it performs better than no catalyst. If similarly low yields are consistent for all tested transition metal salt catalyst in H_2O, should focus instead be redirected to the use of no solvent. For reactions without catalyst are reactions at lower than room temperature still a blind spot. If similar yields to $ZrCl_4$ catalysed reactions at 4 °C can be replicated without the $ZrCl_4$, would the limitations of the transition metal catalyst be more apparent. If all these conditions have been tested and compared can a better understanding of both scope and limitations for Michael additions using these tested transition metal salt catalysts be understood.

With that in mind is the most promising result of all tested conditions from reaction without catalyst. Prioritising replicating conditions to ensure that 87% yield (entry 32) is reproducible. If it is reproducible can the reliance on both solvents and catalyst be reduced, which is in the interest of green chemistry. This might not seem as exciting as optimizing already tested transition metal salt catalyst or testing other metal salt catalysts. But, by testing the reaction without catalyst or solvent can a better understanding of the catalyst or solvent's role in the reaction be understood. This understanding includes giving a baseline of how staring material would behave without any assistance and if catalyst hinders or helps reactions. If this baseline only results in a <1% yield [24] is it still informative of how imperative the catalyst is to the reaction.

4. Conclusion

Several tests of conditions of metal salt catalysts as Lewis acids in Michael additions between Michael donator ethyl acetoacetate (9) and Michael acceptor MVK (2) were performed. These test illustrated the scope and limitations of the catalyst $ZrCl_4$, $Hf(OTF)_4$ and $ZrOCl_2•8H_2O$. The primary limitation was speculated to be unidentified side reactions limiting yield. To account for this was conditions such as lower temperatures, lower concentrations of catalyst and shorter reaction time implemented with varying result. The best result observed circumvented limitations by not using a metal salt catalyst. Yields comparable to optimised conditions for $Yb(OTf)_3$ Michael addition was not achieved. More optimal conditions could not be found due to complications with the choice of starting material. For more definitive result is additional testing required of the transition metal salt catalyst $ZrCl_4$, $Hf(OTF)_4$ and $ZrOCl_2•8H_2O$.

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6. Experimental Section

All commercial reagent was used without further purification. NMR data was collected from a Bruker 400MHz instrument. Chemical shifts are reported in parts per million relative to internal standard for ^{1}H: CDCl3 (7.26ppm). GC data was collected from a Bruker 430-GC with BR-5ms non polar column, 5% phenyl 95% dimethyl arylene siloxane.

Synthesis of methyl 2-nitroacetate (6) according to 1/3 scale of Johnson E. C. et al. [19]: Nitromethane (0.2 mol) was added to KOH (44.8 g, 0.8 mol) dissolved in deionized H_2O (22.4mL). The solution was heated to 140 °C for 1 hour. The solution was cooled to room temperature, filtered and rinsed with MeOH until crystal were clear. The still wet crystals were added to MeOH (90 ml) and cooled to -5 °C. H_2SO_4 (0.23 mol, 12 ml) was added dropwise under vigorous stirring over 2 hours. The solution was heated to 20 °C and filtered to remove MeOH from the white crystals. White crystals were added to H_2O (40 ml) and neutralised with $NaHCO_3$ powder. Solution was separated with ethyl acetate (4 x 50 ml) and washed with brine. Ethyl acetate was removed, and solution was distilled under reduced pressure. Resulting yield was 0% (0 g, 0 mol) of methyl 2- nitroacetate.

Synthesis of methyl 2-nitroacetate (6) according to 1/3 scale of organic synthes [18]: Nitromethane (14.0 ml, 0.26 mol) was added dropwise to KOH (56.4 g, 1.01 mol) dissolved in deionized H_2O (29 ml). The solution was heated to 130 °C for 1 hour under reflux. The solution was cooled overnight at 3.0 °C. The solution was filtered and rinsed with MeOH until clear. The crystals collected were placed under vacuum to dry overnight. Intermediate product dipotassium aci-nitroacetate 34.6% yield (16.4 g, 0.09 mol) was produced.

Finely grounded dipotassium aci-nitroacetate (16.0 g, 0.088 mol) was suspended in MeOH (106 ml) and cooled to -30 °C. Dropwise addition of H_2SO_4 (14.0 ml, 25.8 g, 0.26 mol) over 1 hour under vigorous stirring. The brown solution was heated up to room temperature from -15 °C under stirring. Resulting brown solution was filtered. MeOH was removed from yellow filtrate under reduced pressure. Reduced solution was diluted with toluene, separated, and cleaned with distilled H_2O. The organic phase was reduced and distilled under reduced pressure, resulting in a clear liquid. Resulting yield was 14.4% (1.5 g, 0.013 mol) of methyl 2-nitroacetate.

Synthesis of diethyl 2-(3-oxobutyl)malonate (8): L-Alanine (6.3 mg, 0.07 mmol) and $Yb(OTf)_3$ (36.5 mg, 0.06 mmol) added to NaOH water based solution (0.06 M, 1.2 mL) in a sealed glass vial. Solution was stirred at room temperature for 15 minutes. To the heterogeny solution was diethyl malonate (89.6µL, 0.59 mmol) and methyl vinyl ketone (53µL, 0.79 mmol). The yellow solution was put under vigorous stirring and heated to 60 °C for 3 hours. Extraction utilizing ethyl acetate (3 x 2 mL). Solution was separated and organic layer dried with Na_2SO_4. Organic layer was reduced under reduced pressure. Resulting solvent is a yellow tinted clear oil. Resulting yield 0% (0 g, 0 mol) of diethyl 2-(3-oxobutyl)malonate

General synthesis Michael addition table 3: ML_n (0.10mmol) was dissolved in THF (1.0 mL) in sealed glass vials. Solution was stirred at room temperature for 15 min. Michael donator (1.0 mol) and Michael acceptor (1.1mmol) was added. Solution was put under intense stirring and heated to 60 °C for 3 h. Solution was removed from heating and quenched with water-based sodium hydrogen carbonate solution (1.0 ml, 0.1 M). Solution was extracted with ethyl acetate (3x2 ml), washed with brine and dried over Na_2SO_4. Solvent was extracted under reduced pressure. Final solution was a yellow brown viscus oil. Dodecane (0.10 mmol) was added to solution and dissolved in MeOH. Quantification through GC gave resulting yield from Michael addition.

Synthesis of ethyl 2-acetyl-5-oxohexanoate (5) (entry 6): $ZrCl_4$ (0.10mmol, 23.3mg) was dissolved in THF (1.0 mL) in sealed glass vials. Solution was stirred at room temperature for 15 min. Ethyl acetoacetate (1.0 mmol, 126.5 µL) and methyl vinyl ketone (1.1mmol, 90.7µL) was added. Solution was put under intense stirring and heated to 100 °C for 19 h. Solution was removed from heating and quenched with water-based sodium hydrogen carbonate solution (1.0 ml, 0.1 M). Solution was extracted with ethyl acetate (3x2 ml), washed with brine and dried over Na_2SO_4. Solvent was extracted under reduced pressure. Final solution was a yellow brown viscus oil. Dodecane (23.7 µL, 0.10mmol) was added to solution and dissolved in MeOH. Quantification through GC gave resulting yield 16% (0.17mmol, 33.1 mg) ethyl 2-acetyl-5-oxohexanoate.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, 3H, CH_3 J = 0,0178 Hz), 2.09 (m, 2H, CH_2), 2.14 (s, 3H, CH_3) 2.24 (s, 3H, CH_3), 2.50 (m, 2H, CH_2), 3.50 (t, J=0.0181, 1H, CH), 4.2 (q, J = 0.0179, J = 0.0244, 2H, CH_2).

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8. Populärvetenskaplig förklaring

Behovet av lösningsmedel som kan byta ut farliga organiska eller fossil-baserade lösningsmedel har uppstått för att minimera utsläpp av farliga restprodukter. En lösning till detta behov är att istället använda vatten. Vad man har hittat är att vissa rektioner i vatten kan sker snabbare än i organiska lösningsmedel. Att byta ut lösningsmedel är inte den enda lösningen på att minimera slöseri i kemi. En annan aveny är att använda effektivare katalysatorer för att göra rektioner effektivare, kunde användas flera gånger om och kanske även i vatten. Flera katalysatorer som innehåller ”rare earth metals” har redan visat sig vara lovande och har optimerats för att binda samman molekyler. Vad detta projekt vill undersöka är mer lättillgängliga ”transition metal” katalysatorer och se om det fungerar lika bra eller bättre än de redan testade katalysatorerna. Efter flera tester med att höja och sänka temperatur och byta ut i vilket lösningsmedel rektionen sker i kom vi fram till att det testade ”transition metal” katalysatorerna inte fungerade lika bra som de ”rare earth metals” katalysatorerna. Det testade katalysatorerna kunde inte återanvändas och kunde inte utföra rektionerna lika effektivt som det redan optimerade. En överraskning var att det mest lovande reaktioner som gjordes inte hade någon katalysator alls. Att testa olika rektioner utan katalysator kan vara minder spännande än att testa nya metall katalysatorer, men det är nyttigt för att se om en katalysator hjälper eller hindrar reaktioner från att ske. Slutsatsen vi kom fram till var att det behövs fler tester för att hitta optimala förhållanden för det testade ”transiton metal” katalysatorerna så de kan fungera lika bra som det redan optimerade ”rare earth metal” katalysatorerna.