Spring 2021

Hydroamidation with Acetamides and Trifluoroacetamides

Gordon H. Whitetree

HYDROAMIDATION WITH ACETAMIDES AND TRIFLUOROACETAMIDES

by

GORDON H.WHITETREE

(Under the Direction of Hans Schanz)

ABSTRACT

The hydroamidation reaction is an attractive methodology for the construction of larger functional molecules. In our research, a baseline reactivity was established for the hydroamidation reaction using a set of N-alkyl and N-aryl (trifluoro)acetamides with methyl acrylate and acrylonitrile, various bases and varying reaction conditions. The combination of alkenes, acetamides, and trifluoroacetamides with base was crucial for reaction rate. N-aryl trifluoroacetamides exhibited near quantitative conversions in neat alkene with Diazabicycloundecene (DBU) as base. The less acidic N-aryl acetamides performed much faster in the presence of KO*t*Bu and conversions of >95% were accomplished regularly but contained a large presence of side reactions, namely polymers formed during the reaction from methyl acrylate and acrylonitrile. N-aryl acetamides unexpectedly (>95%) and reliably reacted with acrylonitrile and DBU within an hour. Somewhat surprisingly, the amount of base did not always correlate with reaction rate. In fact, reactions with KO*t*Bu often performed at similar rates between 10-25% loading with respect to amide but providing better yields with lower base concentrations. Alkyl acetamides and trifluoroacetamides exhibited significantly lower reaction rates and conversions with Hunig's base which is weaker than DBU. Also, temperatures studies demonstrated that many reactions plateaued at elevated temperatures, while room temperature reactions frequently provided the highest conversions. This can partially be attributed to the degradation of base or side product formation resulting in an inhibition of the reaction. These trends were then used to establish reaction conditions to generate a polymer based on a bifunctional amide and acrylate. The polymerization affords approximately 8% conversion of the functionalities and improved designs are needed to obtain macromolecules of relevant size.

INDEX WORDS: Hydroamidation, Amides, Conjugate addition, Alkenes

HYDROAMIDATION WITH ACETAMIDES AND TRIFLUOROACETAMIDES

by

GORDON H. WHITETREE

B.S., Georgia Southern University, 2010

A Thesis Submitted to the Graduate Faculty of Georgia Southern University

in Partial Fulfillment of the Requirements for the Degree

MASTER OF SCIENCE

COLLEGE OF SCIENCE AND MATHEMATICS

HYDROAMIDATION WITH ACETAMIDES AND TRIFLUOROACETAMIDES

by

GORDON H WHITETREE

Major Professor:	Hans Schanz
Committee:	Karelle Aiken
	Ji Wu

Electronic Version Approved:
May 2021

DEDICATION

This thesis is dedicated to my parents, Gordon and Suzanna Whitetree, for their immense support and love.

To all of my mentors both professional and academic for seeing my potential long before I did.

To my daughter, Evelyn Whitetree, who has been here only a short while but has changed my life in the most amazing ways possible.

To my wife, Cassandra Whitetree, who has been my biggest cheerleader, fan, and coach. Who has been there every step and never missed one. Without you nothing would have been possible.

ACKNOWLEDGMENTS

I would like to acknowledge Georgia Southern University and the Chemistry Department for the use of their facility, equipment, and instruments. I would like to acknowledge the Master of Science in Applied Physical Science program for the graduate teaching assistantship funding. I would like to thank the American Chemical Society and the Petroleum Research Fund for grant funding I received. I want to thank Dr. Hans Schanz for his patience and guidance through this master's program. I would like to thank my thesis committee, Dr. Aiken and Dr. Wu for their knowledge and advice bestowed upon me. I would like to thank the Master of Science in Applied Physical Science program director, Dr. Michele McGibony for her encouragement and advice over the past two years. I would like to acknowledge my fellow undergraduate and graduate research students who worked alongside me in the lab including: Tytianna Robinson, Micah Spandau, Arturo Diaz, and Nadia Singleton. I would like to thank other fellow graduate students for their support throughout my graduate career. I want to recognize the Georgia Southern University Faculty and Staff for their support. I would like to dedicate a special thanks to Dr. Orvis for his help with all NMR problems and questions I came across.

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF SCHEMES

Page

CHAPTER 1: INTRODUCTION

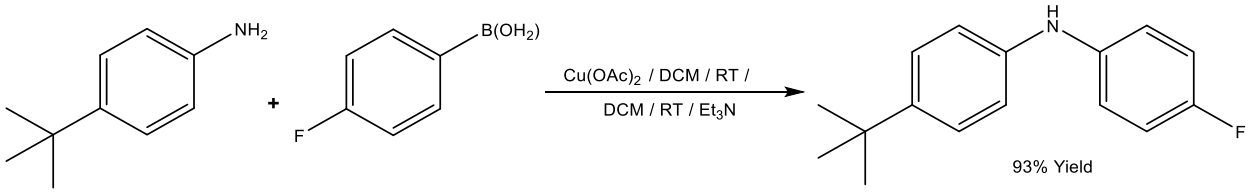
1.1 C-N Bond Formation

Carbon-nitrogen bond formation is an essential task in chemistry and biochemistry synthesis.[1-4] Polypeptides, polymers, pesticides, and pharmaceuticals are a few sections of the market that are dependent on using carbon-nitrogen bond formation methodologies.[5, 6] The formation of these bonds have been studied for over a century. Amines and aryl amines have been used to react with aldehydes and ketones to create Schiff bases. Reactions of secondary amines form enamines with aldehydes and ketones. When hydrazine is reacted with an aldehyde the product forms a C-N double bonded hydrazone.

Reductive amination is the use of a reducing agent to form a substituted amine group from the combination of a primary amine group and ketone.[7]

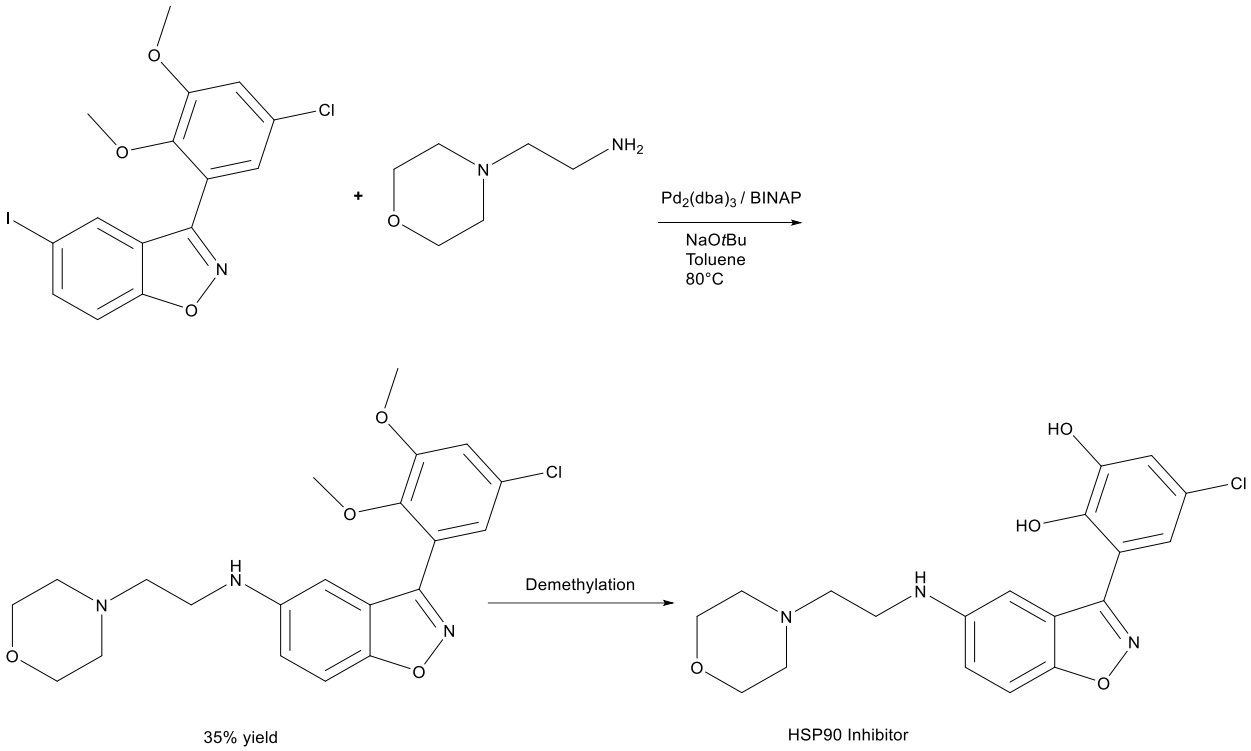
Reactions of primary and secondary amines with acyl halides proceed readily to form amides. The reaction of an ester with an amine yields an amide compound in similar fashion, however this reaction requires high heating and high concentrations of amine.

Recent contributions to C-N bond formation have been from coupling reactions. The Ullman reaction, first reported in the early 20th century, involves the use of amines and aryl halides to form aryl amines.[8] Similar coupling reactions have recently been explored to widen the scope of available copper catalysts and address problems such as harsh reaction conditions, limited substrate scope, and the use of large amounts of copper reagents.[9] In the 1990s the Chan-Lam coupling was reported that involves a bond formation of an aryl carbon to an N-H bond via oxidative coupling. This reaction is supported by copper salts and boronic acid proceeds under ambient conditions with a wider scope of substrates compared to the Ullman reaction (Scheme 1).[10] Chan *et al* successfully found a wide variety of N-containing substrates to couple with phenyl boronic acid including carbamates, sulfonamides, ureas, imides, amides, anilines, and amines.[11]



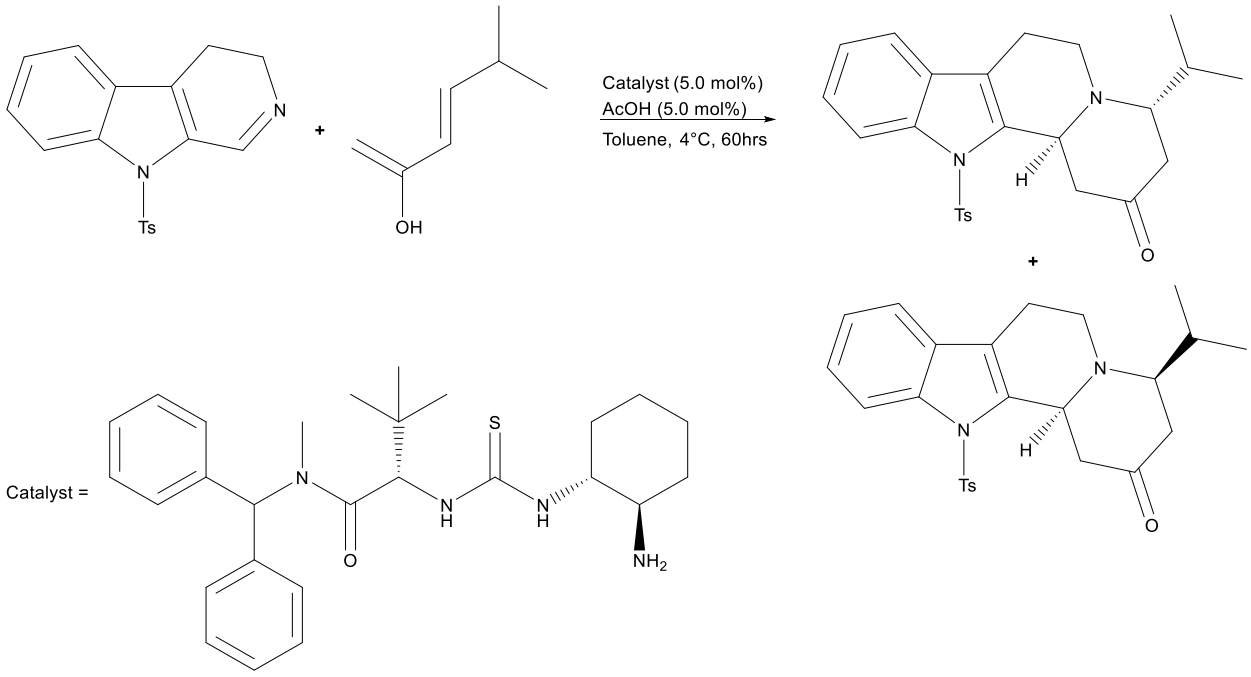
Scheme 1. Chan-Lam coupling reaction with an aniline and an aryl boronic acid.[11]

Around the same time in the late 1990's a coupling reaction via palladium based catalysts coupling was reported by Stephen Buchwald and John Hartwig. This reaction named the Buchwald-Hartwig coupling reaction provided an avenue for the arrangement of amines and aryl halides.[12] This coupling reaction has led the way in general protocols in the formation of synthetic materials, pharmaceuticals, and natural products.[13] This coupling reaction was utilized in the synthesis of an intermediate for a HSP90 inhibitor that would eventually be a drug candidate for an antitumor medication. This step was achieved by coupling 1-(2-aminoethyl)piperidine with an aryl iodide (Scheme 2).[14]



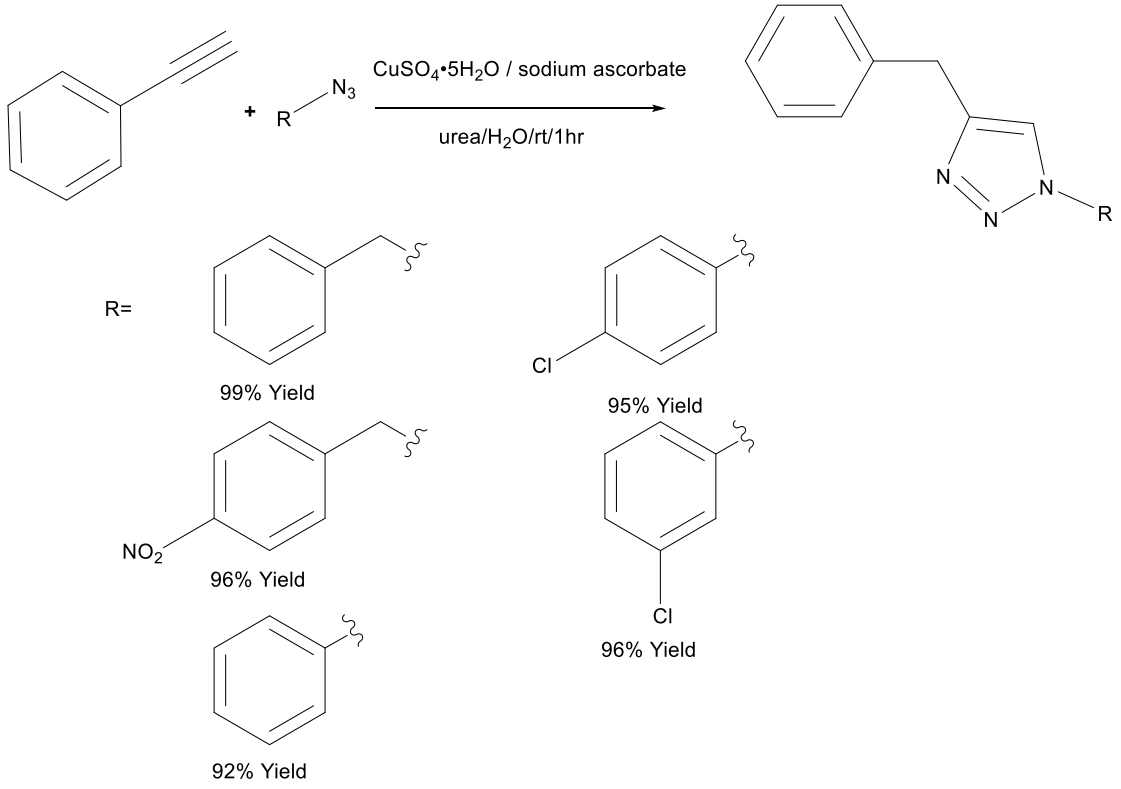
Scheme 2. A Buchwald-Hartwig coupling of an amine to an aryl halide to form HSP90 Inhibitor performed by Gopalsamy *et al.*[14]

Other notable, more recent C-N bond formation reactions include the aza Diels-Alder reactions. Much like the carbon-based Diels- Alder, this reaction results in a six membered heterocycle. However, with the introduction of an N-atom to either the diene or dienophile, this six membered ring will contain said N-atom.[15] This is a simultaneous formation of two C-N bonds. An example of this reaction was completed by Lalonde *et al*.[16] Indolo- and benzoquinolizidine compounds were synthesized via this reaction that was catalyzed by a primary aminothiourea catalyst. The experiment proceeded with an optimization of thiourea catalysts in order to achieve the desired reactivity of enones and the selected cyclic imines. (Scheme 3).



Scheme 3. An aza Robinson Annulation that forms indolo- and benzoquinolizidine.

The azide-alkyne Huisgen [3+2] cycloaddition is a reaction reported by Rolf Huisgen and group in the 1950s. The reaction between a terminal alkyne and an azide results in a 1,2,3-triazole.[17] With the more recent introduction of a copper catalyst to this system the reaction was found to require lower temperatures and an increase in selectivity. [18] This reaction has been described as a key reaction in "Click Chemistry" that is a process that gives high yields, is wide in scope, is regioselective, quantitative, and the byproducts are easily removable. The reaction also proceeds under benign conditions (low temperatures, benign solvents, or solvent-free).[19] A more recent example of the Click Chemistry process of the [3+2] cycloaddition was done by Ali *et al*. that used urea as a ligand in the copper catalyst and water as a medium (Scheme 4).[20] This experiment focused on the rate of reaction with different ligands and found that reactions with high yields could be achieved with reaction times as little as one hour.



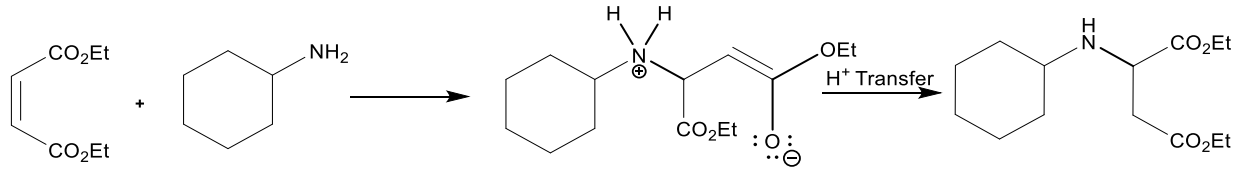
Scheme 4. Huisgen [2+3] cycloaddition reaction conducted by Ali *et al.*[20]

1.2 Conjugate Addition

The Michael addition is a conjugate addition of a nucleophile across a carbon-carbon double (alkene) or triple (alkyne) bond. This reaction has gained popularity because it is atom economic, selective, and tunable. The standard mechanism formulated for their reaction is based on the standard conjugate 1,4-addtion. The β-carbon of an α,β-unsaturated carbonyl compound is attacked by a strong nucleophile, results in an enolate intermediate. [21] This enolate tautomerizes into the Michael adduct. This reaction is commonly promoted by a base, however additions have also been accomplished using various Lewis- acids, including organometallic complexes.[22, 23] Functional groups containing oxygen, sulfur, selenium, phosphorous, and nitrogen have also been observed to perform as nucleophiles.[24-27] The alkene or alkyne is more reactive when an electron withdrawing substituent is present. Acrylate and maleate classes of alkenes have shown to be effective electrophiles in these reactions.[28, 29] Other electrophiles that have been previously investigated are conjugated aldehydes, ketones, esters, amides, nitriles, nitro olefins, vinyl sulfones or vinyl phosphonates.[30]

1.3 Hydroamination

The conjugate addition with the use of a nitrogen-based nucleophile is classified as an aza-Michael addition. The reaction can be further categorized by the use of an amine (hydroamination) or an amide (hydroamidation). The more common type is the hydroamination. During hydroamination, a primary or secondary amine is added across the C=C double or C≡C triple bond in the presence of an electron withdrawing group. The N-based nucleophile is typically directed to the β-carbon of the alkene/alkyne. The reaction or occurs both intermolecularly and intramolecularly.[31, 32] A recent study by Bláha *et al.* proposed a mechanism (Scheme 5). This mechanism suggests that a zwitterion is formed first. In the second step the transfer of hydrogen from the N-H occurs and this was determined to be the rate limiting step. This transfer of hydrogen can either proceed with assistance from another amine (low predicted activation energy) or less likely without the assistance (high predicted activation energy).[29]



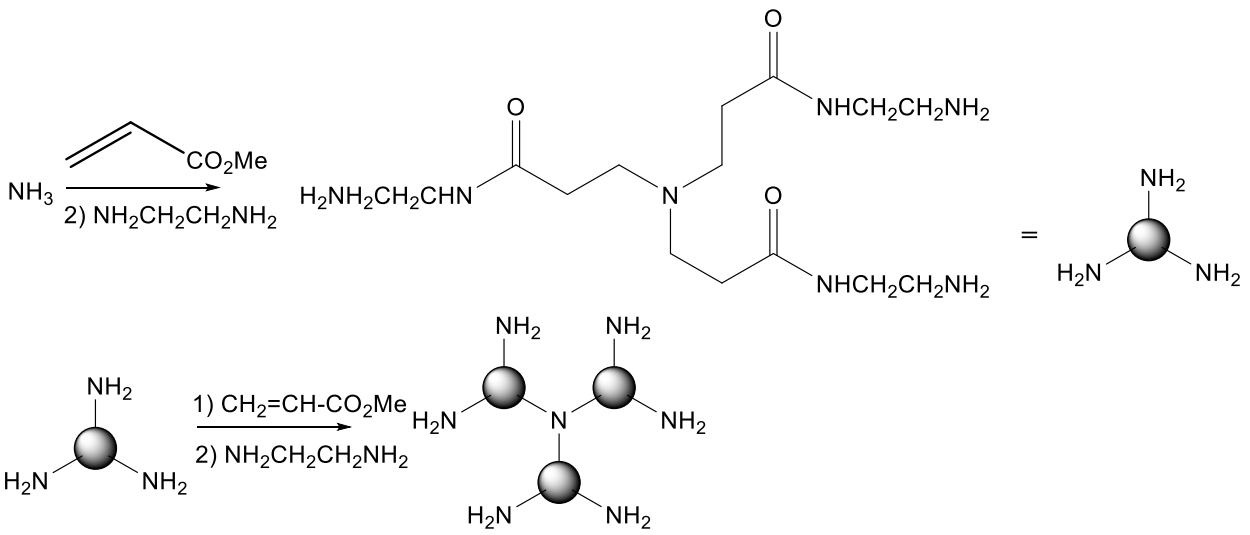
Scheme 5. A catalyst free, solvent free, hydroamination conducted by Bláha et al.[29]

Late-transition metal complexes have been intensely investigated to facilitate hydroamination reactions where the addition is not spontaneous.[33] It was noted by Kobatashi *et al.* that the use of complexes of group 7-11 transition metals were effective in the promotion of aza-Michael addition.[34] A

study of the conjugate addition of butyl acrylate and bis(amino-propyl)-terminated polydimethylsiloxane found the reaction occurred with yields of up to 90% in 8 hours with these metals.[28] Intramolecular cyclization to form N-heterocyclic structures provided straight forward access to a number of scaffolds found commonly in natural compounds.[31]

The versatility of monomers, low sensitivity to oxygen, and ability to design biodegradable polymers makes polymerization via hydroamination a meaningful technique to a stepwise polymerization process.[22] Polymers that were produced from this method ranged from elastomers to engineering thermoplastics. The success of these reactions produced polymers of various topologies such as linear, high crosslinked, hyper branched structures, cross-linked network solids, or dendrimers.

The use of the hydroamination to generate macromolecules has provided an avenue for new materials.[36] The use of hydroamination to polymerize was notably completed by Tomalia *et al*. in the formation of starburst oligomers (Scheme 6).[35]



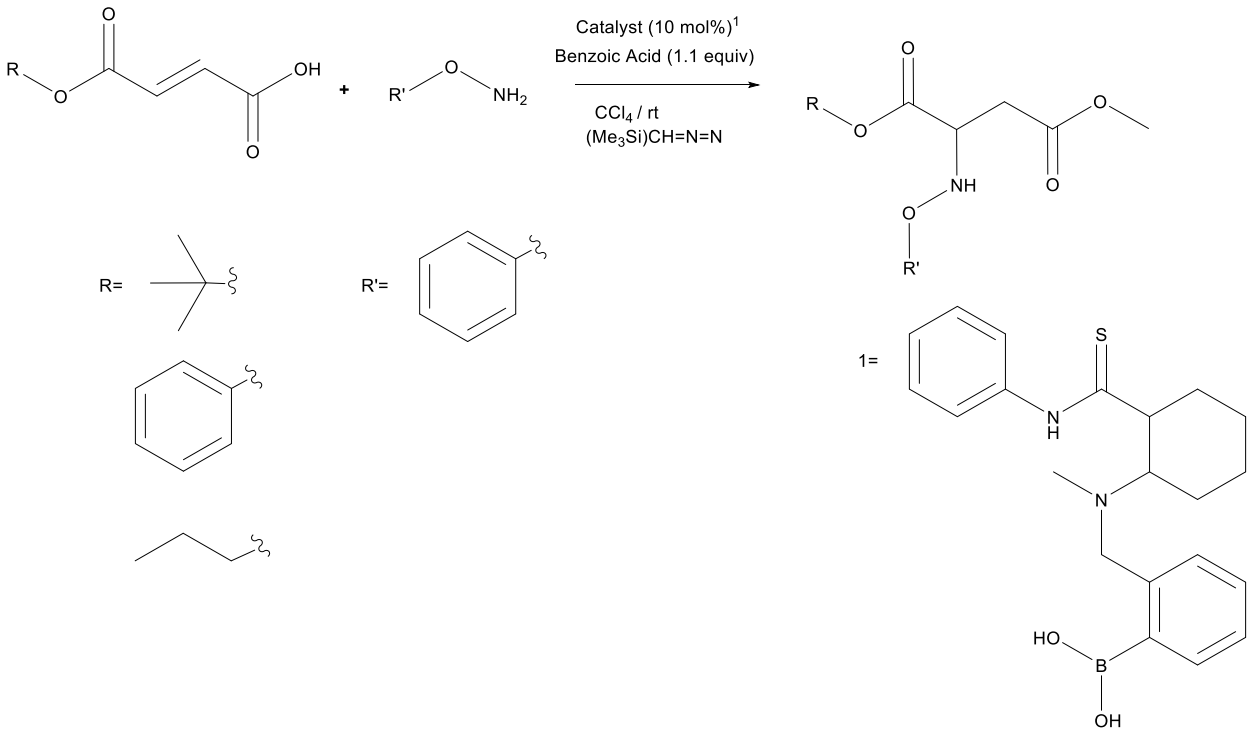
Scheme 6. The formation of dendrimers first discovered by the Tomalia group.

Organocatalysts containing thiourea/boronic acid were successfully developed by Michigami *et al.* to synthesize aspartate-derived hydroxylamine precursors.[36] Reactions were conducted at room temperature in acidic conditions by addition of various amounts of benzoic acid. The reaction was then methylated with trimethylsilyl diazomethane in order to produce the precursors suitable for ligation (Scheme 7). This reaction was stereoselective to the β-carbon for every instance. The acids that were

utilized, functioned in the catalytic cycle of the catalyst. The acidity of this reaction played a large role due to reports that use of a stronger acid inhibited the reaction entirely. If the acid was too weak it could not function as a catalyst. The use of the t-butyl ester and benzoic acid resulted in the highest yield (88%).

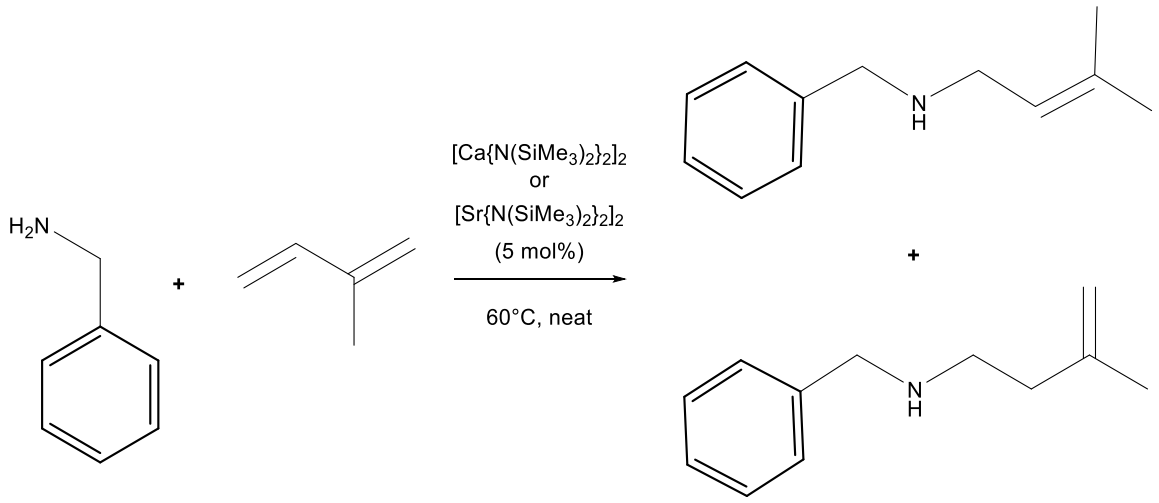
Acid	PKa	Conversion (%)
Formic Acid	3.74	0
Acetic Acid	4.76	57
Pivalic Acid	4.93	77
Benzoic Acid	4.20	88
p-Toluenesulfonic acid	-2.8	0

Figure 1. The use of different acids in the hydroamination involving a boronic acid and thiourea catalyst.



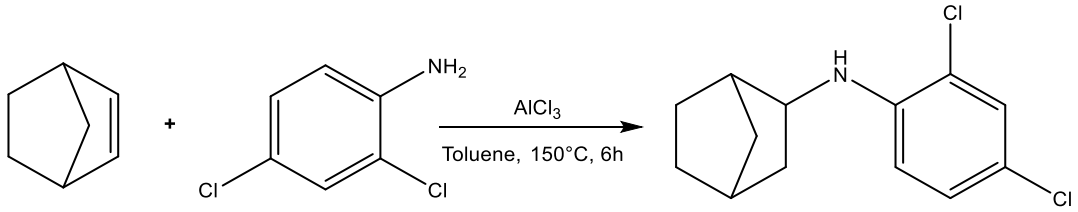
Scheme 7. A hydroamination involving the use of boronic acid and thiourea catalyst conducted by Michigami et al.[36]

The use of alkaline-earth metals to catalyze an intermolecular hydroamination was observed by Brinkmann *et al.* [37] It was found that styrenes and dienes were effectively catalyzed by calcium and strontium catalysts (Scheme 8).



Scheme 8. The hydroamination reaction catalyzed by a calcium or strontium metal catalyst.[37]

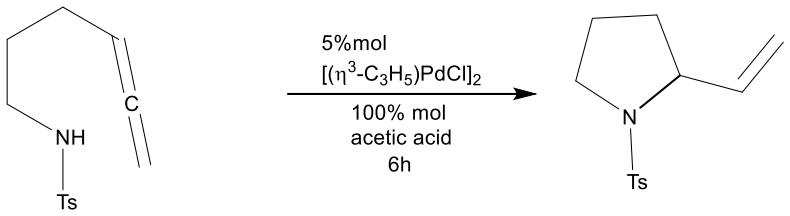
Xia *et al.* added $AlCl_3$ to study the hydroamination of anilines and non-activated alkenes. The work demonstrated that $AlCl_3$ significantly improved the yields for aromatic amines (70%-82% yield). It was also concluded that increased acidity of the aniline increased the overall success of the hydroamination (scheme 9). The group suggested a mechanism of the Lewis acid protonating the non-activated alkene and a subsequent nucleophilic attack on the resulting cation.[38]



Scheme 9. A Lewis acid catalyzed hydroamination reaction between norborene and 2,4-dichloro aniline.

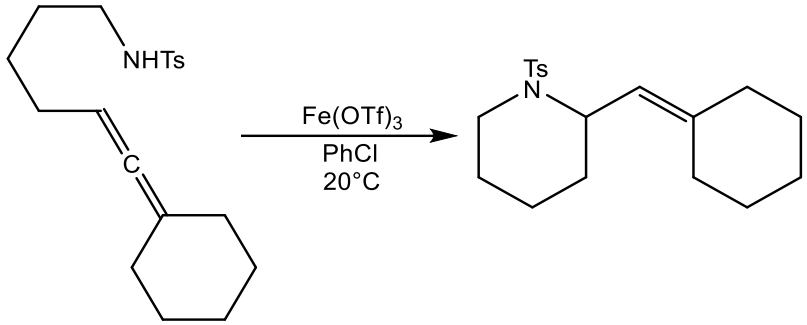
1.4 Hydroamidation

While the hydroamination reaction has been extensively investigated, little is known thus far about the hydroamidation reaction. Amides are less nucleophilic when compared to amines and thus are less researched. The ability to form hydrogen-bonds by accepting and donating makes the amide important for biomolecules and structural polymeric materials.[28] Intramolecular hydroamidation was successfully performed by the Meguro group. The reaction of tosyl amides and catalytic amounts of allyl palladium chloride yielded of up to 87% of the cyclized product (Scheme 10). It was found that the use of acetic acid promoted faster reaction times and higher yields with the amide.[39]



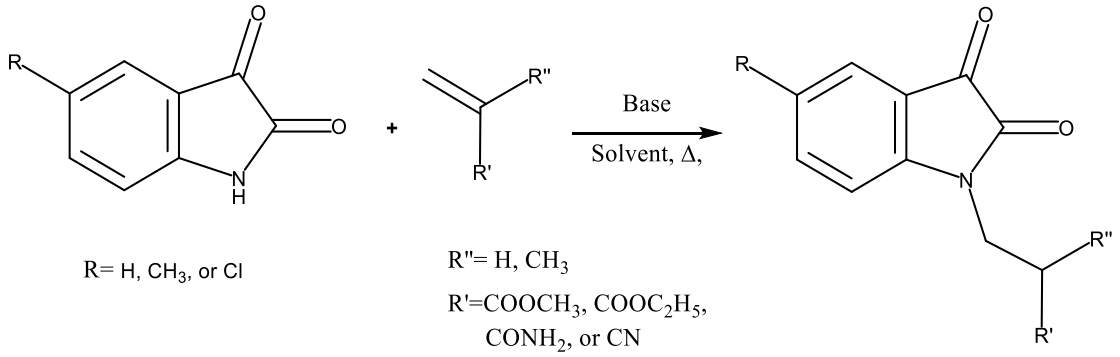
Scheme 10. An intramolecular aza-Michael addition catalyzed by a palladium catalyst.[39]

A successful hydroamidation was also performed using an iron catalyst in order to close rings intramolecularly via amide and diene functional groups. The catalyst involved optimization of Fe(III) triflate that successfully catalyzed the formation of piperidine derivatives (Scheme 11).[40]



Scheme 11. A ring-closing hydroamidation of a tosyl amide catalyzed by an iron catalyst.

The use of base as a catalyst for hydroamidation was observed by Chen *et al.* in 1994. The group conducted the hydroamidation of isatin and acrylate derivatives with the use of various combinations of base and solvents (Scheme 12). [41]



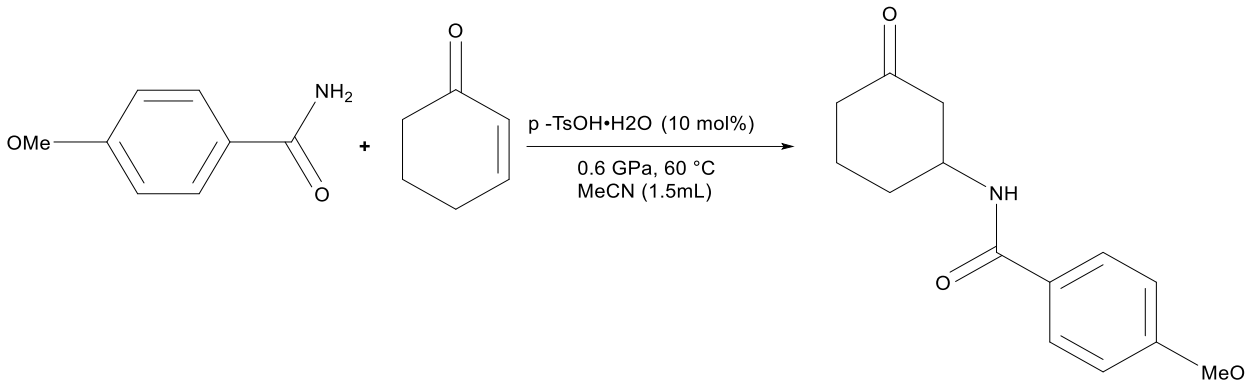
Scheme 12. The reaction of isatin derivatives with various acrylates via hydroamidation.

The scope of amides of this experiment was limited to isatin, however it demonstrates how the various use of bases, solvents, and temperatures affect the yield of a reaction. A yield of 72.5% was achieved with the use of KOH with DMF as a solvent at a temperature of 25° C (Figure 1). This experiment shows that the choice of solvent and base combinations has a distinct effect on how the reaction proceeds.[41]

Base	Solvent	Temperature	Time(h)	Yield %
NaOH	DMF	25	8	68.8
NaOH	MeOH	65	8	trace
NaOH	CH_3CN	81	8	trace
NaOH	THF	25	48	52.4
KOH	DMF	25	12	72.5
KOH	MeOH	65	24	8
KOH	CH_3CN	81	8	trace
KOH	THF	25	48	54.7
Na_2CO_3	DMF	25	12	0
K_2CO_3	DMF	25	12	trace
CaO	DMF	25	12	0
$NH(C_2H_5)_2$	DMF	25	12	0
$N(C_2H_5)_3$	DMF	25	12	8.2

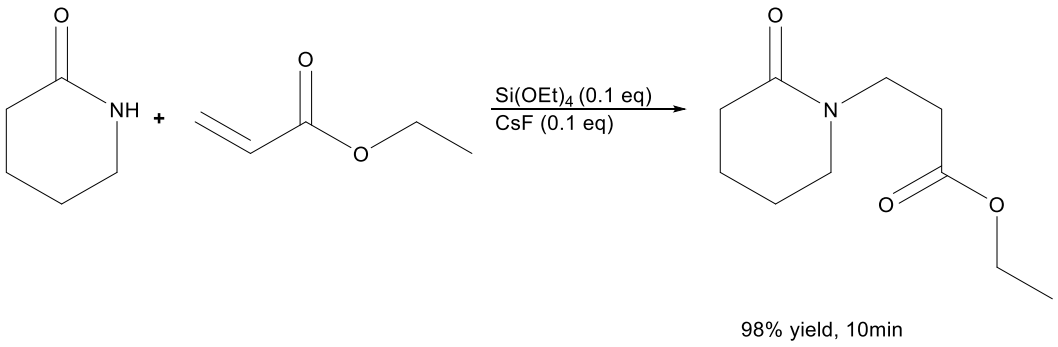
Figure 2. The results of the combinations of bases and solvents on the hydroamidation of isatin and methyl acrylate.

Another hydroamidation conducted by Azad *et al.* demonstrated that the reaction can occur with the use of a Brønsted-Lowry acid.[42] The conditions for this article included high pressure conditions and presented yields of up to 80% with 4-methoxybenzamide and 2- cyclohexen-1-one and p-$TsOH•H_2O$ (Scheme 13).[42]



Scheme 13. A hydroamidation reaction involving the use of a Brønsted-Lowry acid done by Azad *et al.*[42]

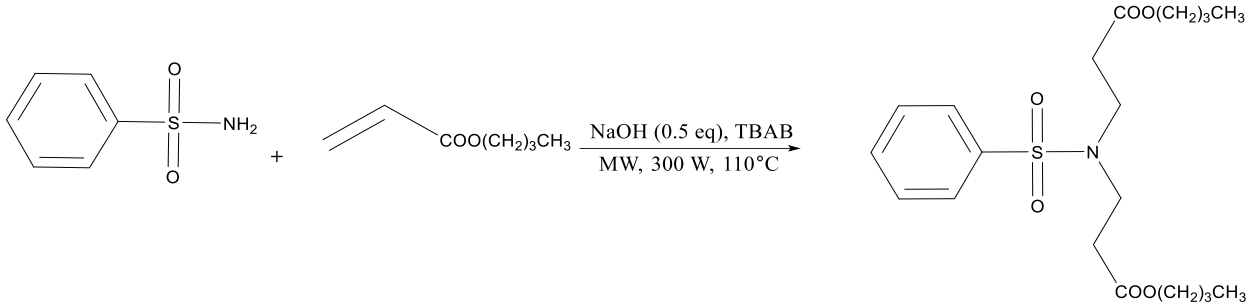
In an experiment conducted by Ahn *et al.*,. lactam derivatives were added to acrylates with various reactivity (Scheme 13).[43] The use of the CsF-$Si(OR)_4$ system was found to effectively catalyze the conjugate addition of lactams. The authors reported that the use of the catalytic system served two functions in the reaction: 1) generation of base in order to deprotonate the lactam N-H bond and 2) trapping of the enolate adduct to give the corresponding silyl enol ether. The absence the $Si(OR)_4$ resulted in low yields compared to reactions containing the siloxane. Optimization showed that only a 10mol % (to the amide) of the catalytic system was required to effectively enhance the reaction. It was found that some reactions could occur with up to 98% yield in up to 10 minutes It was also observed that addition of alkyl groups to the β-carbon of the alkene, making it more sterically hindered, resulted in no product conversion.[41]



Scheme 14. A hydroamidation of lactam by ethyl acrylate done by Ahn *et al.*[43]

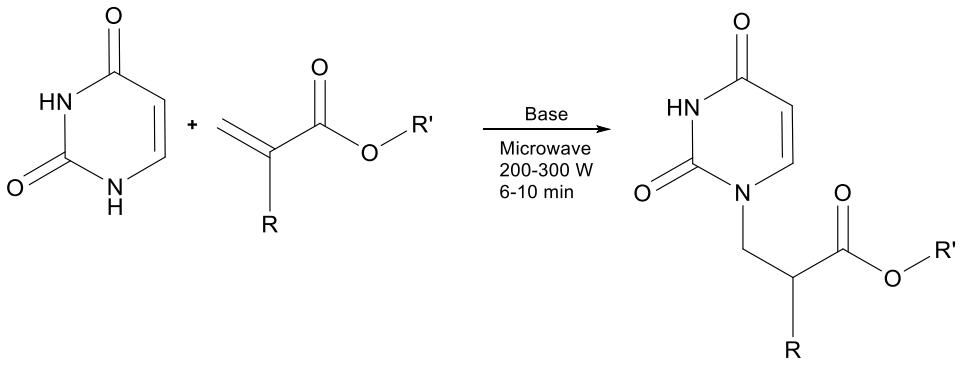
Hydroamidation has also been observed via microwave synthesis. Zare *et al*. demonstrated the importance of microwave assistance on the Michael addition of a sulfonamide to an acrylate (Scheme 14). The optimization of base in this studied showed that sodium hydroxide was the appropriate base to use versus other strong bases (91% yield compared to the next base KO*t*Bu at 69%). Another note is that the

monosubstituted product was not detected. These conditions were able to produce up to 91% isolated yields.[44]



Scheme 15. A microwave irradiation assisted hydroamidation of benzenesulfonamide and butyl acrylate.

Acyclic nucleosides and derivatives were also prepared via hydroamidation.[45] A study from Khalafi-Nezhad *et al*. demonstrated that Uracil derivatives could successfully undergo hydroamidation with acrylate derivatives using base and microwave irradiation (Scheme 15).[46]



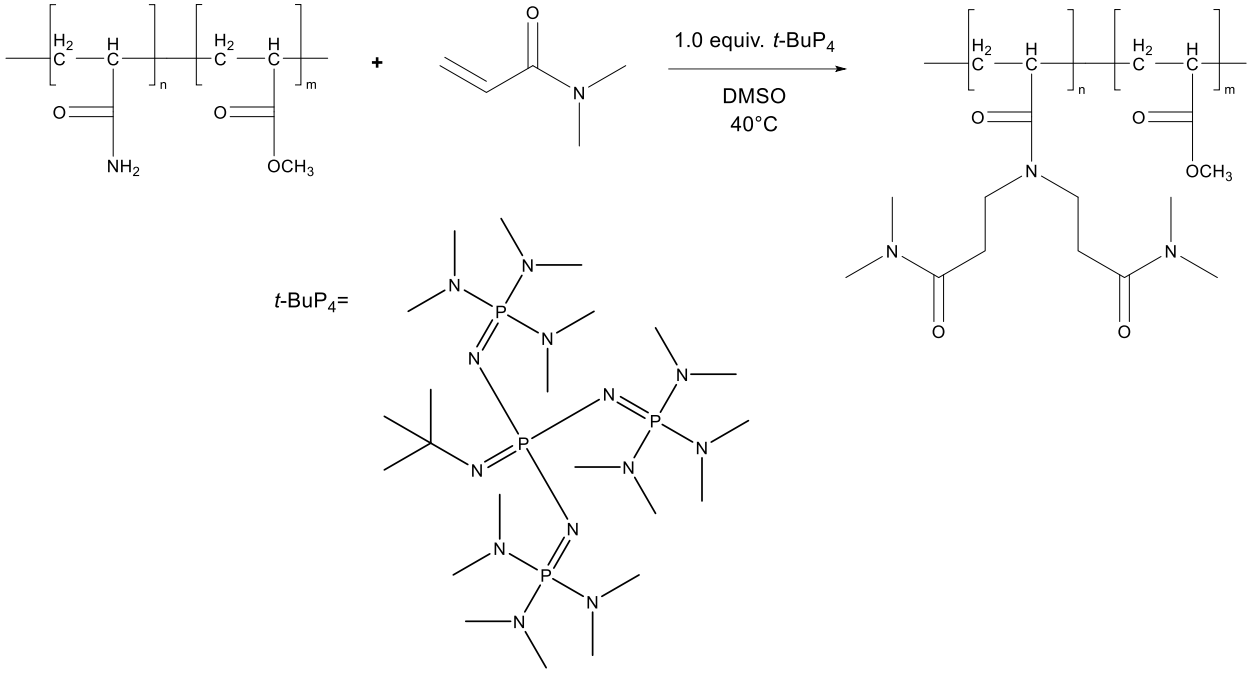
Scheme 16. The microwave synthesis of uracil and ethyl acrylate performed by Khalafi-Nexhad *et al.*[46]

This reaction is notable because of the presence of two amido functional groups. The group observed a noticeable difference in conversion when using a more sterically hindered alkene bond (ethyl acrylate 87% vs ethyl methacrylate 40%). Different bases were observed to have different yields in the reaction of uracil and ethyl acrylate (Figure 3). However, it was determined that there was no clear trend on the yields of the bases in terms of strength.[46]

Entry	Base	Microwave power (W)	Reaction time (min)	Yield (%)
1	DABCO	2006		83
2	DMAP	2008		70
3	Cs_2CO_3	2008		65
4	K_2CO_3	2008		59
5	DBU	2008		52
6	CaO	30010		41
7	MgO	30012		18

Figure 3 The yields of various bases used in hydroamidation used in the study by Khalafi-Nexhad *et al.*[46]

To date polymerization via hydroamidation has not been widely reported. Recent application of the reaction in the field of material science has been limited to post-polymerization modifications.[47] A post polymerization modification was conducted by Yang *et al.* in which N,N- dimethylacrylamide was added across a C=C double bond of a methyl acrylate and acrylamide copolymer with *t*-BuP_4, a strong non-nucleophilic base (scheme 17). This hydroamidation involves the addition of an alkene to the amide of the side chain of the polymer. This method is effective to functionalize an available primary or secondary amide found in the side chain. In contrast, this project involves using hydroamidation technology to form a novel polymer that utilizes an amide and C=C multiple bond to as the structure of the main chain.



Scheme 17. The post-polymerization modification of P(MA70-co-AM30) via hydroamidation conducted by Yang *et al.*

1.5 Hypothesis, Research Goals, Experimental Design

Thus far aza-Michael hydroamidation has not been widely reported in the use to form materials. In order to achieve high molecular weight polymers, high conversion rates of monomers are required. The goal of this project was to identify conditions that afford >99% in 30m reaction time or less. Reaction variables such as the electrophilicity of the Michael acceptor, concentration of base (catalyst), addition of Lewis acidic metals, strength of base, reaction temperature, electric properties of the amide, and steric properties of the amide were optimized. Primary amides were also investigated in this reaction that can result in monosubstituted and disubstituted products. Gathering this information was used to develop a working library of hydroamidation of acetamides and trifluoroacetamides and facilitate quantitative hydroamidation. This knowledge was used to achieve the end goal of synthesizing multifunctional monomers that can be polymerized to form materials of high interest via hydroamidation.

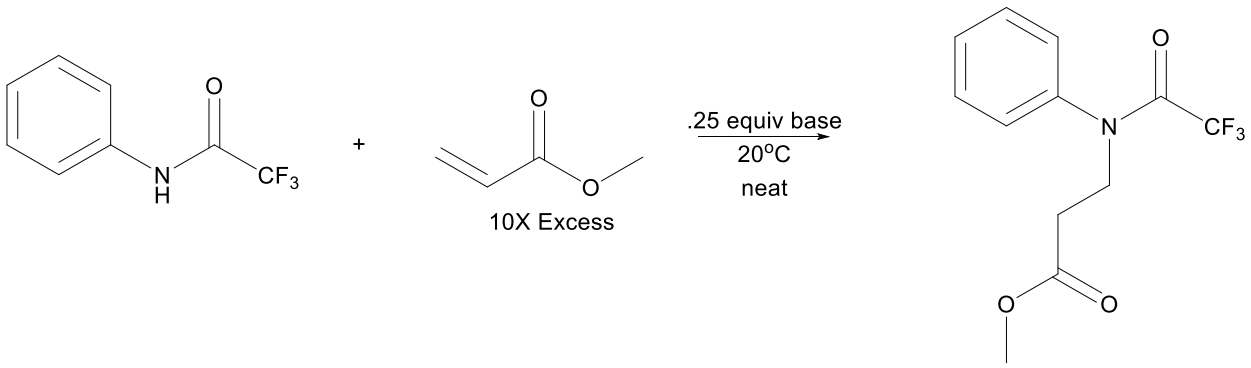
CHAPTER 2: RESULTS AND DISCUSSION

In the following studies, N-aryl and N-alkyl acetamides were reacted with α,β-unsaturated alkenes under different conditions in order to find optimal reactivities.

2.1 Hydroamidation of Acetamides

2.1.1 Establishing the Most Effective Base with Acetanilide

Base plays an essential role in the hydroamidation reaction. A base study was conducted for the reaction of acetanilide and methyl acrylate (Scheme 18, Table 1) using bases of different strengths to determine the role of base strength and establish a standard reaction. The reaction was conducted at room temperature with KO*t*Bu, DBU and Hunig's Base with the same concentration (25mol%) with methyl acrylate at a 10 fold excess. KO*t*Bu showed the highest amount of product formed after 1 day, but there were significant amounts of polyacrylate signals present in the ^{1}H NMR. KO*t*Bu is not a favorable base for hydroamidation due to the formation of a polyacrylate side product. In light of making polymers via stepwise polymerization KO*t*Bu would cause significant amounts of the chain-growth polymerization side reaction. DBU is a weaker base but showed steady conversion with little to no polyacrylate formation. However, after 8 days the base sluggishly reached only moderate conversions. Hunig's base is non-nucleophilic but a weaker base than DBU. The base was unable to reach any observable conversions after 1 day of reaction. Although not ideal for stepwise polymerization at this time KO*t*Bu lead to fast quantitative conversion that completes the first goal of this study. Other variables will be tuned to observe if the polymerization of the acrylate can be kept to a minimum.



Scheme 18. The reaction between acetanilide and methyl acrylate with various bases (25mol%) at 20°C.

Table 1. The conversion of acetanilide with methyl acrylate with various bases (25mol%) at 20°C.

Base	Time (min, h, or days)	Conversion (%)
KO*t*Bu	15min	94
KO*t*Bu	24h	Quant.
DBU	1h	0
DBU	24h	45
DBU	8 days	60
Hunig's base	1h	0
Hunig's base	24h	0

2.1.2 Base Concentration Study using KO*t*Bu and Acetanilide

After establishing that KO*t*Bu achieves quantitative rates of conversion at 20°C, a base concentration study was conducted under the same conditions (table 2). A decrease in base concentration may suppress the side reactions. This is important for the end goal of forming a polymer via stepwise polymerization. 10mol% showed fast conversions similar to 25mol% but soon the base would be consumed by polyacrylate side reactions. With the rates of reaction being similar, but 25mol% outperforming after 15 minutes the base concentration was kept at 25mol%.

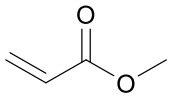
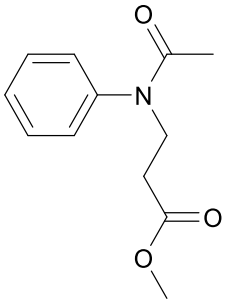
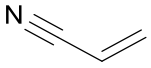
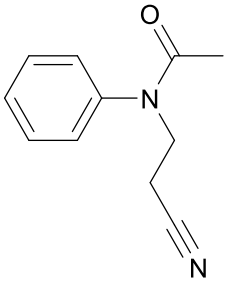
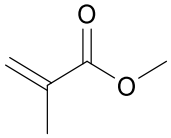
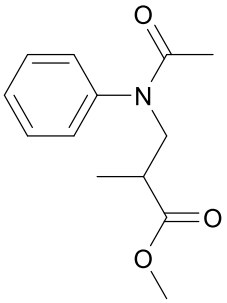
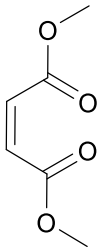
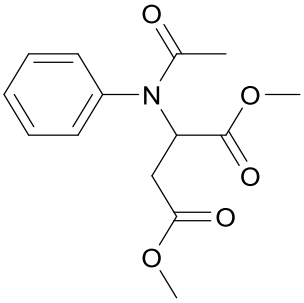
Table 2.The conversion of acetanilide with methyl acrylate with various concentrations of KO*t*Bu at 20°C.

Base loading (mol%)	Time (mine, h, or days)	Conversion (%)
10	5min	73
10	15min	83
25	15min	94
25	1h	Quant.

2.1.3 Study of Acetanilide Using Different Alkenes.

A study with alkenes of different electrophilicty and steric hindrance was done to establish the role of the alkene in the hydroamidation of acetanilide (table 3). Reactions of acetanilide with methyl acrylate and acrylonitrile at 20°C with 25mol% KO*t*Bu were able to reach quantitative conversions in 1 day or less. Acrylonitrile reached quantitative conversion in about 15min of reaction time but the formation of polyacrylonitrile was dominant. After 15min the product peaks had a larger intensity than the alkene peaks despite being at a 10-fold excess indicating that the majority of the excess of acrylonitrile has been converted into polymer. The conversion rate is desirable for the end goal of producing a high molecular weight polymer. However, the basicity of KO*t*Bu caused undesirable side reactions with the methyl acrylate and acrylonitrile that would interfere with the desirable polymer formation via hydroamidation. Methyl methacrylate (MMA) and dimethyl maleate were tested with acetanilide under the same conditions. The reactions did not yield any observable amounts of hydroamidation product with acetanilide and KO*t*Bu, even after 2 days of reaction time. It is likely that the steric hindrance of the methyl group to the C=C double bond prevents the hydroamidation reaction to occur. Hence, only methyl acrylate and acrylonitrile were used in further reactivity studies.

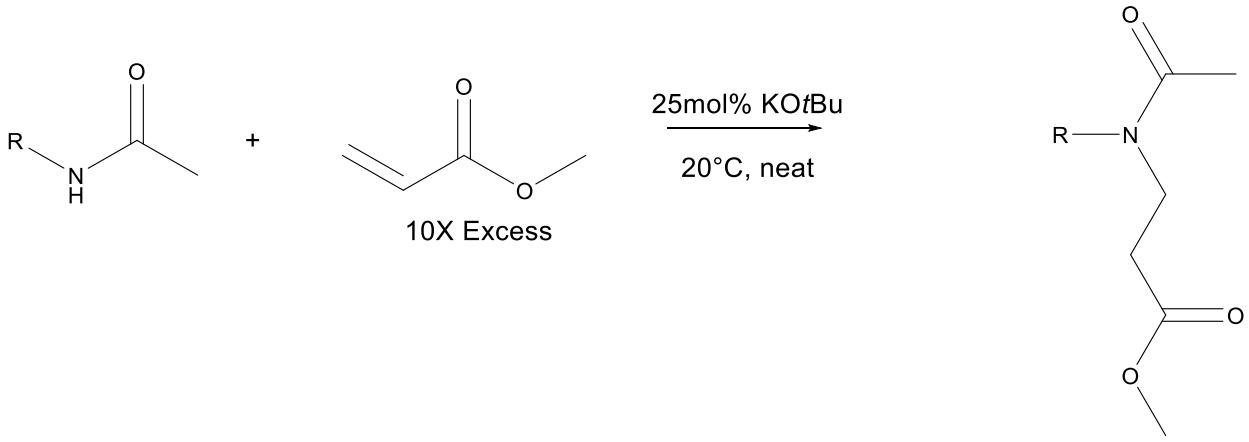
Table 3. The conversion of acetanilide with various alkenes with KOtBu (25mol%) at 20℃

Alkene	Product	Time (min, h, or days)	Conversion (%)
 methyl acrylate		15min	94
		24h	Quant.
 acrylonitrile		15m	Quant.
 methyl methacrylate		1h	0
		2 days	0
 dimethyl maleate		1h	0
		2 days	0

2.1.4 Study of Reactivity of Various Acetamides with Methyl Acrylate

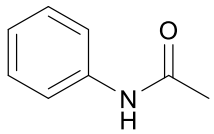
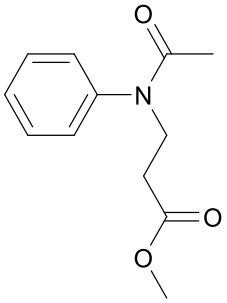
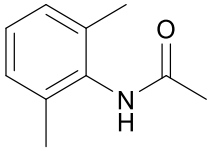
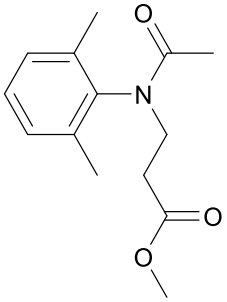
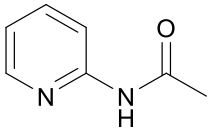
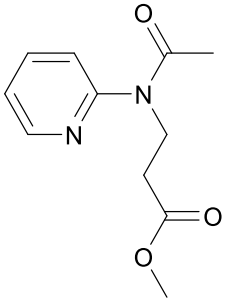
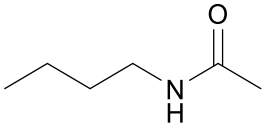
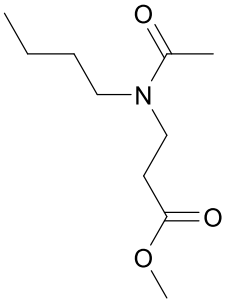
A variety of acetamides were tested with methyl acrylate in order to establish the reactivity with KO*t*Bu (25mol%) at room temperature (table 4, scheme 19). Introducing a steric hindrance in the form of two ortho methyl groups did not appear to slow the reaction. In fact, the addition of these groups enhanced the reactivity of the N-H bond. The N-pyridyl acetamide group did not perform as well as the aromatic groups. It should be noted that the N-pyridyl acetamide display low solubility in the acrylate.

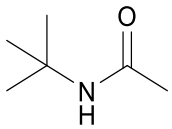
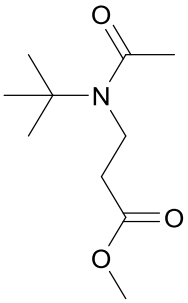
Alkyl acetamides are less acidic than arylamides, hence their reactivities in these reactions are expected to differ. N-butyl acetamide and *t*butyl acetamide were reacted with methyl acrylate under identical conditions. N-butyl acetamide reacted slowly and did not show the same reactivity as the aryl acetamides. *t*butyl acetamide showed no reactivity with regards to hydroamidation. N-aryl acetamide became the focus of this project due to their increased activity in this study. It is likely that the steric hindrance of the *t*butyl acetamide additionally affects its ability to form the conjugate addition product.



Scheme 19. The reaction between various acetamides and methyl acrylate using KO*t*Bu (25mol%) at 20°C.

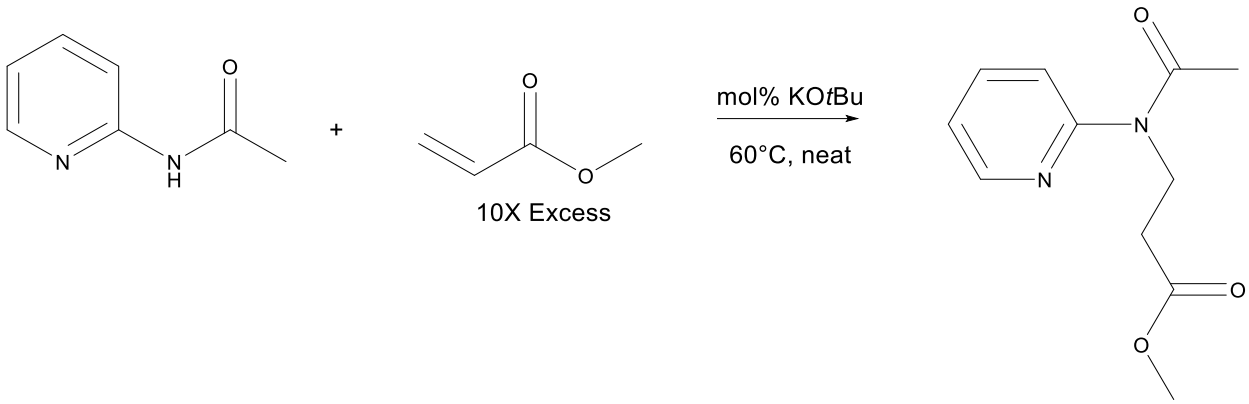
Table 4. The conversion of various acetamides and methyl acrylate using KO*t*Bu (25mol%) at 20°C.

Anilide	Product	Time (min or h)	Conversion (%)
		1h	Quant.
		5min	Quant.
		5min	69
		24h	70
		1h	30
		24h	33

		1h	0
		24h	0

2.1.5 Base Concentration Study of N-(2-pyridyl) acetamide

Using the least reactive aryl acetamide from the previous study a base concentration study was conducted on N-(2-pyridyl) acetamide with various base concentrations at 60℃ (table 5, scheme 20). The increased temperature is used to increase the solubility of the amide in the acrylate, thus hopefully increasing amide conversion. Surprisingly, the second highest conversion (80%) was found for a reaction with a low amount of base (10mol% KO*t*Bu) after 4 days of reaction time before the conversion plateaued. The most effective conversion was accomplished at 25mol% KO*t*Bu. This would indicate that the increase in temperature to increase the solubility of the acetamide in the acrylate was effective in increasing reactivity. However, as the base increases to 50% loading there is a stark decrease in reactivity and only moderate conversions achieved. 100% loading performed even worse where the reaction completely stalled after reaching 20%.



Scheme 20. The reaction of N-(2-pyridyl)acetamide with methyl acrylate with various concentrations of KO*t*Bu at 60℃.

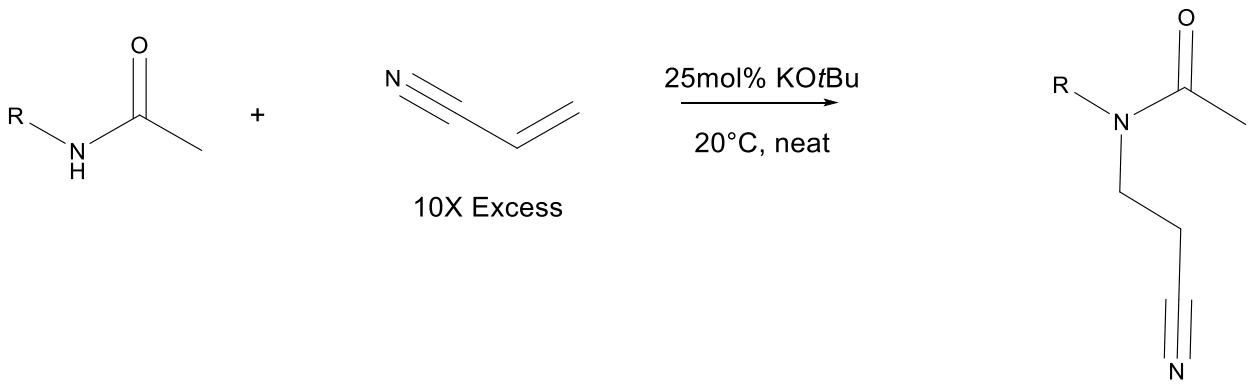
Table 5. The conversion of N-(2-pyridyl) acetamide with methyl acrylate with various concentrations of KO*t*Bu at 60°C.

Base loading (mol%)	Time (min, h, or days)	Conversion (%)
10	1.5h	44
10	24h	60
10	4 days	80
25	1h	Quant.
50	15min	13
50	1.5h	16
50	24h	29
50	4 days	63
100	1.5h	20
100	24h	20
100	4 days	20

2.1.6 Reactions of Acetamides with Acrylonitrile and DBU

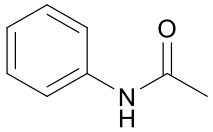
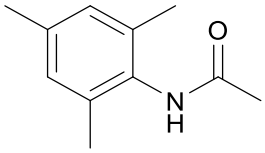
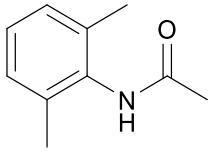
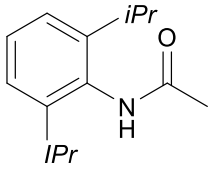
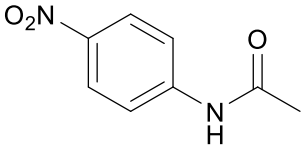
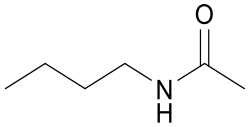
The reactivity of acrylonitrile and acetanilide with KO*t*Bu was a desired reaction riddled with polyacrylonitrile side product (table 6, scheme 21). To see if the use of a weaker base that did not previously result a large presence of side products, N-aryl and N-alkyl acetamides were reacted with acrylonitrile in the presence of 25 mol% DBU at 20˚C. Surprisingly, the N-aryl acetamides reached quantitative conversions in relatively short amounts of time. The N-alkyl acetamide did not show a high amount of reactivity. One reason could be that the N-alkyl acetamides are less acidic than the N-aryl acetamides.

It is notable because the reaction with acetamides and methyl acrylate under the same conditions produces lower yields and the reactions proceed slower by orders of magnitude. The diisopropyl anilide, where the amide group is severely sterically hindered compared to the dimethyl aniline, reacted fully in under 1h. It was shown that this steric hindrance had a rate-lowering effect in other reactions (*vide infra*). This is not the case here. The result is also surprising because methyl acrylate is the more reactive substrate with KO*t*Bu as base in comparison to acrylonitrile. At this point the reason for this surprisingly reactive combination is not known.



Scheme 21. The reaction between various acetamides and acrylonitrile with 25mol% DBU at 20°C

Table 6. Conversion of various acetamides with acrylonitrile catalyzed by DBU (25mol%) at 20℃.

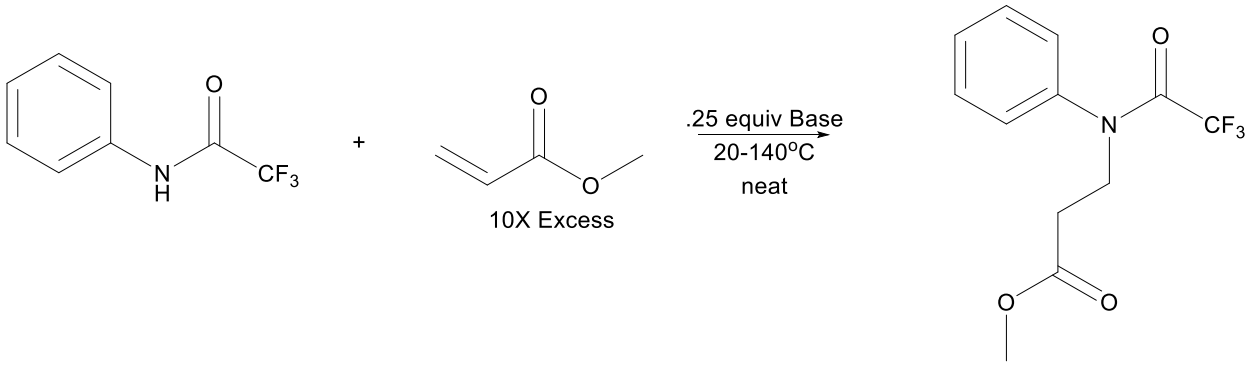
Acetamide	Time (h)	Conversion (%)
	1h	Quant.
	1h	87
	24	Quant.
	1h	88
	24h	Quant.
	1h	Quant.
	1h	97
	24h	Quant.
	1h	0
	24h	0

2.2 Hydroamidation of Trifluoroacetamides

Trifluoro acetamides are more acidic than the respective acetamides by several orders of magnitude. Hence, it can be expected that their reactivity may be superior in the presence of weaker bases (e.g. DBU vs. KO*t*Bu). The rate of conversion and yield of the reaction was tested under different conditions by selectively tuning parameters such as base, base concentration and temperature.

2.2.1 Base study of (N-phenyl)-2,2,2-trifluoroacetamide

A base study was conducted using bases of different strengths with methyl acrylate (table 7, scheme 22). The reaction was conducted at room temperature with DBU, KO*t*Bu, and Hunig's Base with the standard concentration (25mol%). KO*t*Bu showed the highest amount of product formed after 2 days, but there were significant amounts of polyacrylate present in the ^{1}H NMR. DBU showed steady conversion at room temperature. While it was a slower reaction in comparison to KO*t*Bu, DBU reached similar conversion in a longer amount of time with little to no polyacrylate formation. Hunig's base, being the weakest base of the three, did not have any amide conversion at room temperature. When the same conditions except for temperature were changed there was amide conversion at 140°C, but this temperature also caused significant amounts of side reactions (e.g. polyacrylate). The conversion at this temperature was also lower than DBU at room temperature. The steady increase in conversion of (N-phenyl)-2,2,2-trifluoroacetamide and non-nucleophilic nature that resulted in less participation in side reactions made DBU the most suitable base in the hydroamidation of trifluoroacetamides.



Scheme 22. The reaction of (N-phenyl)-2,2,2-trifluoroacetamide with methyl acrylate under various bases (25mol%) and temperatures.

Table 7. Conversion of (N-phenyl)-2,2,2-trifluoroacetamide with methyl acrylate catalyzed by different bases (25mol% loading).

Base	Temperature (°C)	Time (h or days)	Conversion (%)
DBU	20	1 h	0
DBU	20	48 h	65
DBU	20	8 days	82
KO*t*Bu	20	1 h	0
KO*t*Bu	20	48h	86
Hunig's base	20	1h	0
Hunig's base	20	48h	0
Hunig's base	140	1h	trace
Hunig's base	140	48h	29

2.2.2 Base Concentration Study of (N-phenyl)-2,2,2-trifluoroacetamide

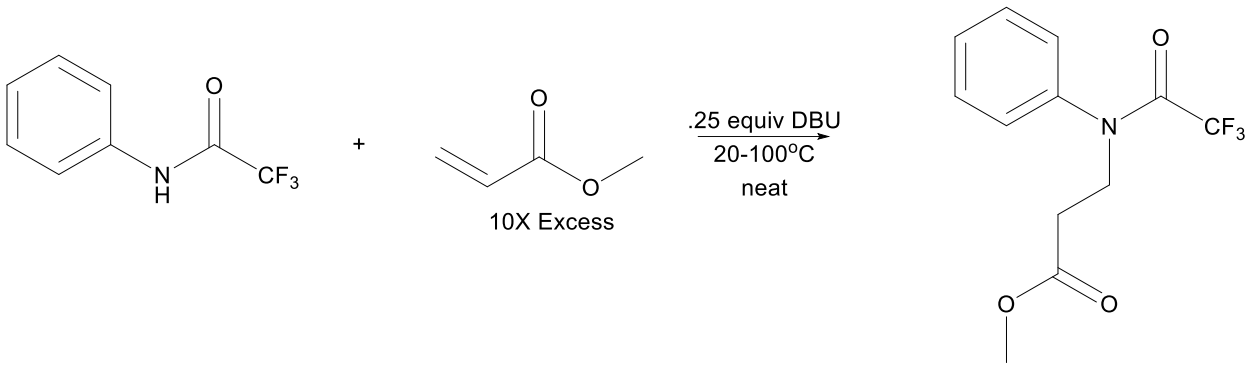
After establishing DBU as the most effective base for the reaction, a base concentration study was conducted at 60℃ with DBU at concentrations of 10, 25, and 75 mol% (table 8). The ideal base concentration should allow for high conversion in minutes in addition to keeping the presence of side reactions to a minimum. 10 mol% DBU outperformed the other concentrations and achieved high rates of conversions after 2 days of reaction. As the concentration of base increased the rate of conversion decreased compared to 10 mol% base loading. However, even under the most favorable conditions, the reactions did not reach >99% conversion.

Table 8. The conversion of (N-phenyl)-2,2,2-trifluoroacetamide with methyl acrylate and various amounts of DBU at 60 ℃

Base Loading (mol%)	Time (h or days)	Conversion (%)
10	1h	25.4
10	48h	91
10	4 days	93
25	1h	6
25	48h	91
75	1h	10
75	48h	71
75	4 days	80

2.2.3 Temperature study of (N-phenyl)-2,2,2-trifluoroacetamide with methyl acrylate

(N-phenyl)-2,2,2-trifluoroacetamide was reacted with methyl acrylate in the presence of DBU (25mol%) at various temperatures (table 9, scheme 23). The use of higher temperatures was investigated to determine if hydroamidation reaction can be accelerated without increasing side product formation. At the highest temperature of 100°C the reaction exhibited the fastest rate in the early stages, clearly outperforming the other rates at the other temperatures. Indeed, the reaction was close to proceed via pseudo first order kinetics in the first 3h. Then the reaction rate decreases significantly and plateaus significantly after 24h. 60°C appears to proceed via first order kinetics for 24h and 20°C first order for 2 days. These observations appear to coincide with a noticeable decomposition of base. 60˚C had the highest conversion that could be contributed to a temperature that is both high enough to overcome the activation barrier of the additional product and low enough to not cause great decomposition of base. Once the reactions began to plateau, the ^{1}H NMR exhibited a significant number of signals that may be attributed to the decomposition of the base. However, even after several days of reaction time, the reaction still continued to convert amide at a very slow rate. The decomposition of the base at 60°C and 100°C makes high conversion rates and quantitative conversion improbable. While the reactions at room temperature took much longer, the low temperature appears to be necessary for a sustainable reaction since, in the long- term, it is beneficial to minimize side and decomposition reactions triggered at elevated temperatures.



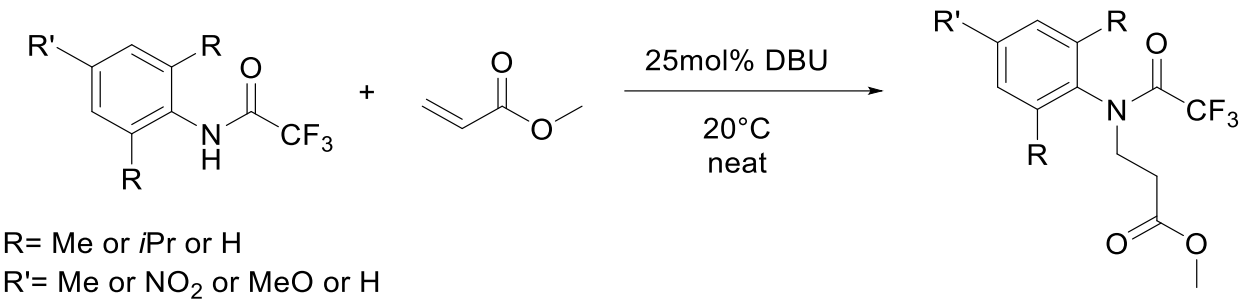
Scheme 23. The hydroamidation reaction of (N-phenyl)-2,2,2-trifluoroacetamide with methyl acrylate at various temperatures.

Table 9. Conversion of (N-phenyl)-2,2,2-trifluoroacetamide and methyl acrylate with DBU (25mol%) at various temperatures.

Temperature (°C)	Time (h)	Conversion (%)
20	24	41
	48	65
	90	73
	186	82
60	1	6
	4	20
	24	88
	48	91
	192	93
100	0.5	20
	1.25	48
	3	79
	5	83
	7	83
	120	88

2.2.4 The Influence of Various Electronic and Steric Parameters for a Variety of Trifluoroacetamides

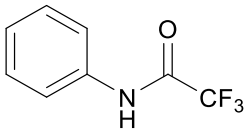
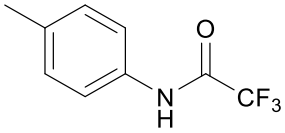
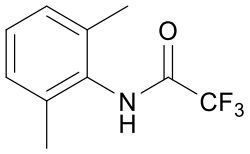
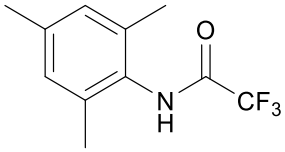
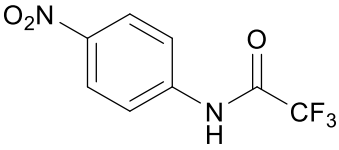
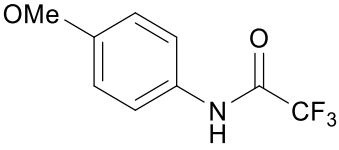
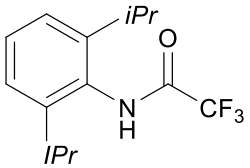
A variety of trifluoroacetanilides were tested with methyl acrylate in order to establish the influence of electronic and steric parameters of the aryl ring (table 10, scheme 24). The conversion of trifluoroacetanilide was discussed before and it did not afford complete conversion even after days. The addition of a methyl group in the para position of the anilide increased the reactivity slightly but not dramatically. Anilides with two ortho methyl groups performed the fastest hydroamidation with methyl acrylate. The addition of a third para methyl group in comparison to the 2,6-dimethyl derivative enhances the reactivity even more resulting in quantitative conversions after 68h and 72h respectively. That suggests that some of the reactivity increase is due to a slight increase of the ring electron density whereas steric factors due to the ortho CH_3 groups do not seem prohibitive. By contrast, when diisopropyl groups are introduced into the aniline the reaction is significantly slower. To support the observation that electronic properties of the aryl substituents are important to reactivity, an electron withdrawing group was added to the phenyl ring in the form of a p-nitro group. This resulted in a dramatic loss of reactivity with no conversion observed even after days. In contrast, introducing a p-methoxy group, a π- donating group, a dramatic increase of the reaction rate was expected. However, while the conversion exceeded that of p-nitro and p-methyl anilides, the di-methyl substituted amides performed faster. This would suggest that there is another factor aside from the electron density. With the addition of o-methyl groups to the aryl ring, an increase in the solubility of the amide in the acrylate and/or a potential twist of the ring plane out of the H-N-C plane due to steric reasons could be the cause of the faster conversions. It also should be noted that the rates of p-nitro and diisopropyl derivatives performed at a significantly lower rate than the di and trimethyl derivatives. Upon deprotonation, the nucleophilicity of p-nitro derivative is weaker compared to the other substituted aryl trifluoroacetamides. This is somewhat counterintuitive as the reactivity trends were reversed to the acetanilide derivatives (Table 6) in the addition reaction with acrylonitrile in the only other study where these anilides were used together. At this point, the factors resulting in these deviating activities can only be speculated about. The reactivity differences are much more pronounced in this study with trifluoroacetanilides and methyl acrylate, but a closer investigation of the influence of the aryl ring on the reactivities is warranted.



R= Me or *i*Pr or H
R'= Me or NO_2 or MeO or H

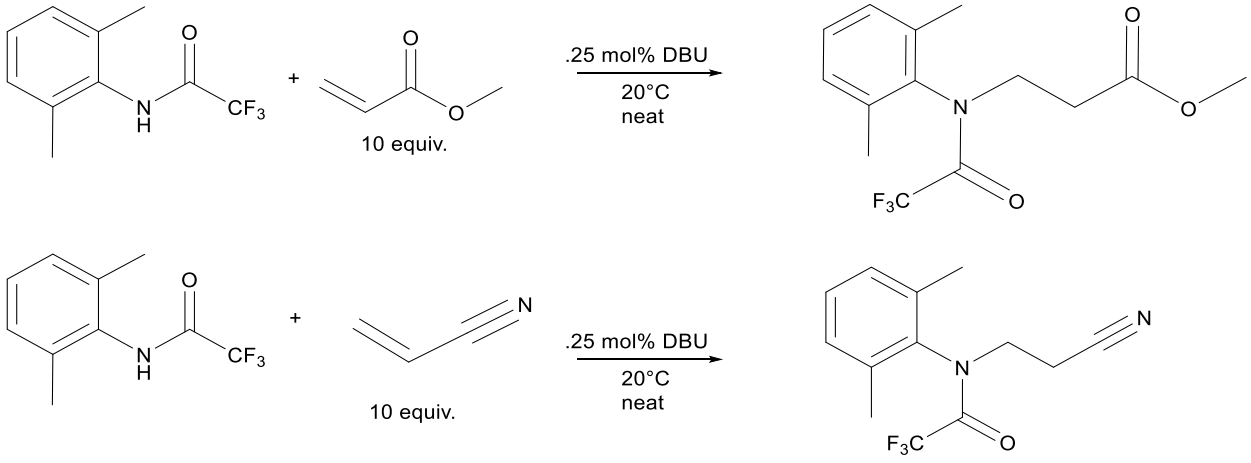
Scheme 24. The electronic and steric parameter study of trifluoroacetamides and methyl acrylate with 25mol% DBU at 20℃.

Table 10. Conversion of various trifluoroacetanilides with methyl acrylate at 20˚C with 25 mol% DBU.

Anilide	Time (h)	Conversion (%)
	24	41
	48	65
	90	73
	24	46
	48	70
	72	80
	24	80
	48	96
	72	quant.
	8	62
	24	90
	48	quant.
	24	0
	48	0
	144	0
	24	43
	48	73
	96	93
	24	37
	48	40
	72	76

2.2.5 Kinetics study of N-(2,6-dimethylphenyl)-2,2,2-trifluoroacetamide using different alkenes

For this study, the 2,6-dimethylanilide was investigated. It was demonstrated that this amide exhibited superior reactivity in hydroamidation of trifluoroacetanilides affording quantitative conversions in several instances (*vide supra*). Methyl acrylate and acrylonitrile were investigated under standard conditions 10 fold excess, 25 mol% DBU at room temperature (Scheme 25, table 11). However, for both substrates, reaction times of 24h or more were needed to reach conversions of >90%. For example the reaction of N-(2,6-dimethylphenyl)-2,2,2-trifluoroacetamide achieved 54% conversion after 14h and would achieve quantitative conversions after 72h of reaction time. The same reaction with acrylonitrile proceeded with similar reactivity achieving 50% conversion after 14h of reaction time and achieved quantitative conversion except it was not until after 87h of reaction time. In most conditions, methyl acrylate reacted a fraction faster with trifluoroacetamides than acrylonitrile, but the reactivities were not dramatically different. Both reactions exhibited pseudo first order kinetics in the first 24h with the acrylate being somewhat more reactive than acrylonitrile. This is in stark contrast to the acetanilide reactivities, when acrylonitrile appeared to be orders of magnitude more reactive. However, the long term goal is to design *bis* or multifunctional monomers to be used in stepwise polymerization reactions via hydroamidation, the acrylate reactivity is of higher relevance as bi or multifunctional acrylates are straight forwardly accessible. The fact that quantitative conversion of the acetamide with an acrylate was accomplished was a milestone in this project.



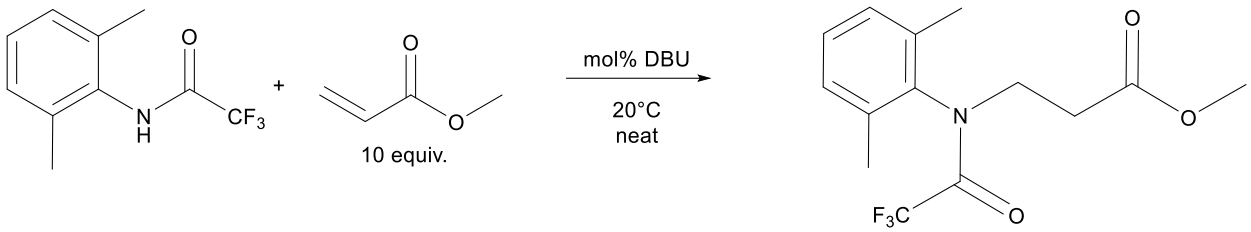
Scheme 25. Hydroamidation of N-(2,6-dimethylphenyl)-2,2,2-trifluoroacetamide with different alkenes.

Table 11. Conversion of N-(2,6-dimethylphenyl)-2,2,2-trifluoroacetamide with methyl acrylate and acrylonitrile using DBU (25mol%) at 20˚C.

Alkene	Time (h)	Conversion (%)
Methyl Acrylate	14	54
	24	79
	37	88
	48	96
	72	Quant.
Acrylonitrile	14	50
	24	72
	37	79
	48	84
	72	88
	168	Quant.

2.2.6 N-(2,6-dimethylphenyl)-2,2,2-trifluoroacetamide and DBU loading

A base loading study was completed with N-(2,6-dimethylphenyl)-2,2,2-trifluoroacetamide and DBU was added in various mol% with respect to the amide (table 12, scheme 26). This was completed to study if high base concentrations lead to faster amide conversions. A loading of 10% base with respect to the amide accomplished a conversion of 98% which is higher than the conversions for the reactions of 50% loading and higher. In fact, high base concentrations again were detrimental for the conversion after long reaction times. The most effective conversion was accomplished at 25mol% DBU. 75% and 100% DBU loading experiments demonstrated that the reaction becomes less effective, but the conversion is still higher with 10% loading (62% and 47% vs. 45%). While it can be speculated that higher base loadings may result in an increased rate for side reactions, the presence of both starting material in the reaction solution after 170h indicates that this alone cannot account for this observation. The deactivation may be caused by a side product with an inhibiting effect, e.g. via inhibition of a co-catalytic species that we may have not yet identified.



Scheme 26. A reaction between 2,6-dimethyl-trifluoroacetanilide and methyl acrylate. DBU concentrations with respect to the amide were present in various concentrations.

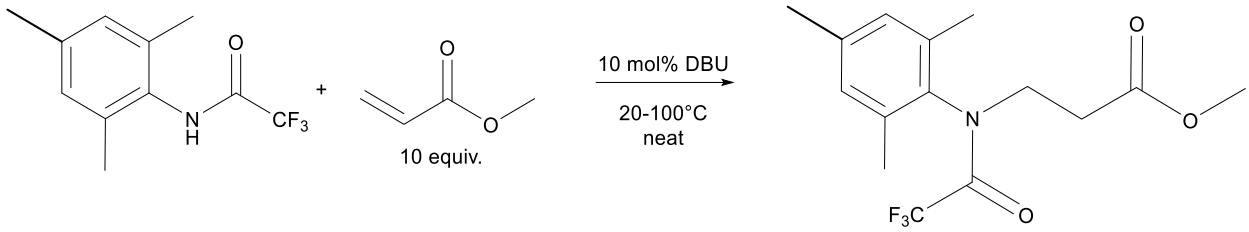
Table 12. Conversion of 2,6-dimethyl-trifluoroacetanilide and methyl acrylate using various DBU concentrations (mol%) at 20˚C.

DBU Loading (mol%)	Time (h)	Conversion (%)
10	24	45
	48	84
	170	98
25	24	79
	48	96
	72	Quant.
50	24	76
	48	85
	170	94
75	24	62
	48	77
	170	83
100	24	47
	48	67
	170	76

2.2.7 Hydroamidation of 2,2,2-trifluoro-N-mesitylacetamide at various Temperatures

2,2,2-trifluoro-N-mesitylacetamide and methyl acrylate at a 10-fold excess were reacted with DBU (10mol%) at various temperatures (Scheme 27, table 13). With previous base loading and temperature studies with less reactive trifluoroacetamides the increase in base and temperature typically lead to incomplete reactions. This study was conducted to determine if increased temperatures and lower base loading could increase the rate of reaction to achieve quantitative rates in less time.

A temperature study was conducted wherein base was decreased to 10 mol% and reaction temperatures were changed. The reaction at 100°C had a fast acceleration initially, 94% amide conversion after 7h of reaction. After 24h product formation reached a plateau and product was no longer forming. Once the reaction stopped, side reaction peaks began to appear. The ^{1}H NMR peaks of the base disappeared, and a number of new signals started to appear in the region of 1-4 ppm. This is consistent with the previous temperature studies with DBU. The conversion at 20 ˚C displayed a slow but steady increase. Quantitative conversions were obtained however, it took three times as long as at 60 ˚C. The highest rate of conversion in the shortest amount of time was again achieved using 60°C. While using an increased temperature increases the chances of side and back reactions, employing a slightly higher temperature resulted in quantitative conversion with methyl acrylate in the series of experiments that were conducted.



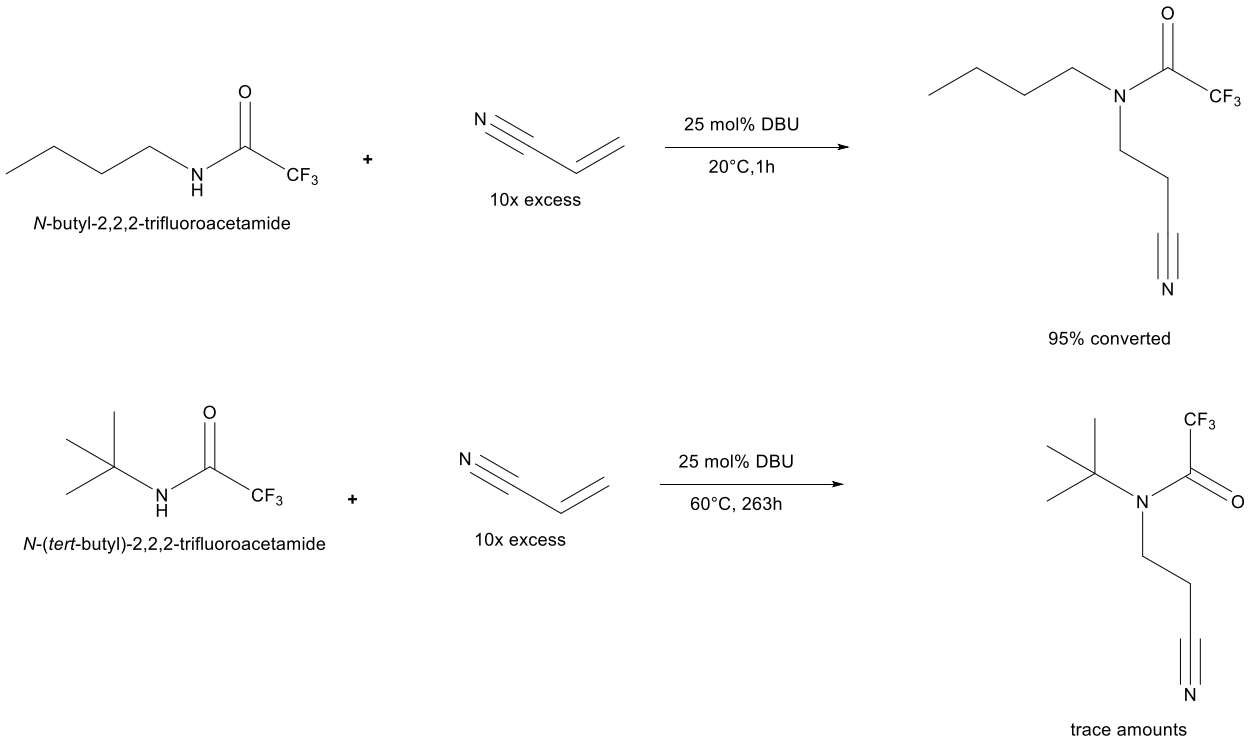
Scheme 27. The reaction of 2,2,2-trifluoro-N-mesitylacetamide and methyl acrylate with DBU (10mol%) at various temperatures.

Table 13. Conversion of 2,2,2-trifluoro-N-mesitylacetamide and methyl acrylate with DBU (10mol%) at various temperatures.

Temperature (˚C)	Time (h)	Conversion (%)
	7	19
20	24	67
	146	Quant.
	7	98
60	24	Quant.
	7	94
100	24	94
	146	92

2.2.8 Hydroamidation of alkyl trifluoroacetamides

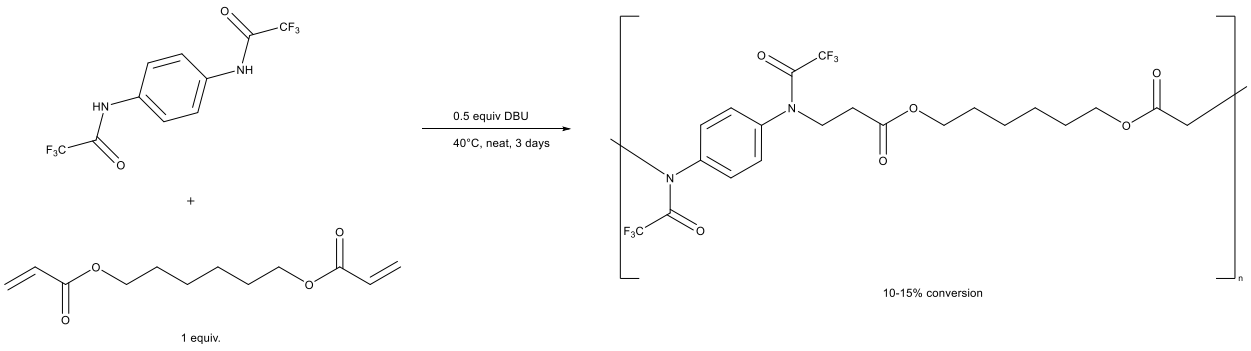
N-alkyltrifluoroacetamides (scheme 28) were reacted under various conditions with acrylonitrile. The N-butyl trifluoroacetamide reacted with acrylonitrile much faster than the *t*-butyl trifluoroacetamide affording >95% conversion in 1h. The *t*Bu derivative however, does not afford significant quantities of the product even after days at elevated temperatures. This demonstrates that the steric properties of the alkyl group dramatically affects the reactivity of the trifluoroacetamides in the hydroamidation. It stands to reason that there may be an acidity sweet spot in this reaction that is present with N-alkylacetamides and N-alkyltrifluoroacetamides. Making the amides less or more acidic could result in lower activities.



Scheme 28. The hydroamidation of alkyl trifluoroacetamides with methyl acrylate.

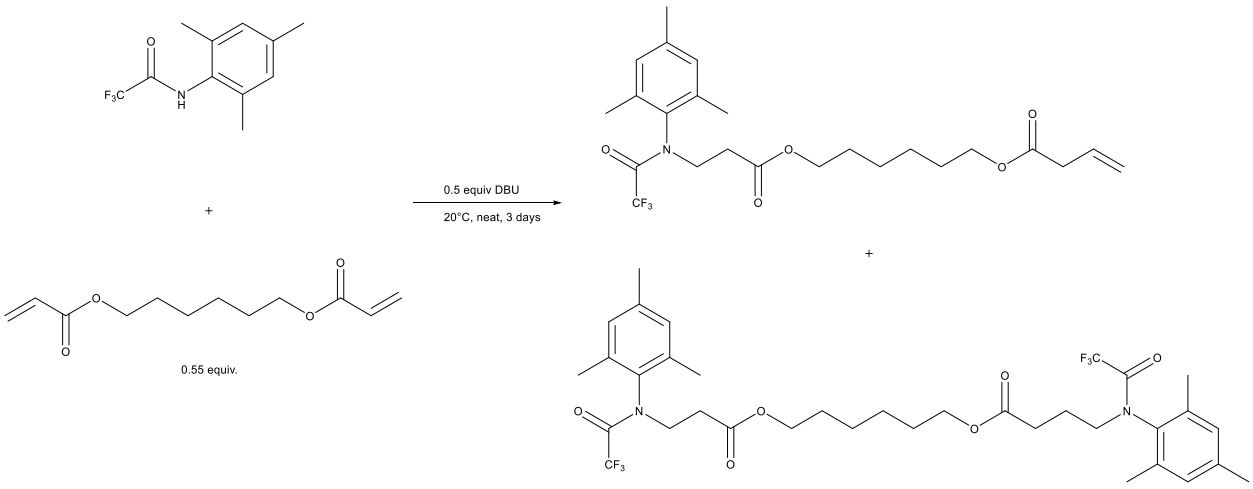
2.2.9 Synthetic strategies via hydroamidation

A polymer was attempted using parameters learned from previous studies. Bifunctional acrylate and aryl trifluoroacetamide were synthesized via a modified procedure.[48, 49] DBU was selected as the base because of its high reactivity with trifluoroacetamides and low affinity to produce side reactions. The reaction proceeded with 25mol% DBU and 1 equivalence of diacrylate at 40°C (scheme 29). The increased temperature was used to increase the solubility of the diamide, however the diamide still showed low solubility in the diacrylate. After 21 days, the conversion rate was determined to be <8%.



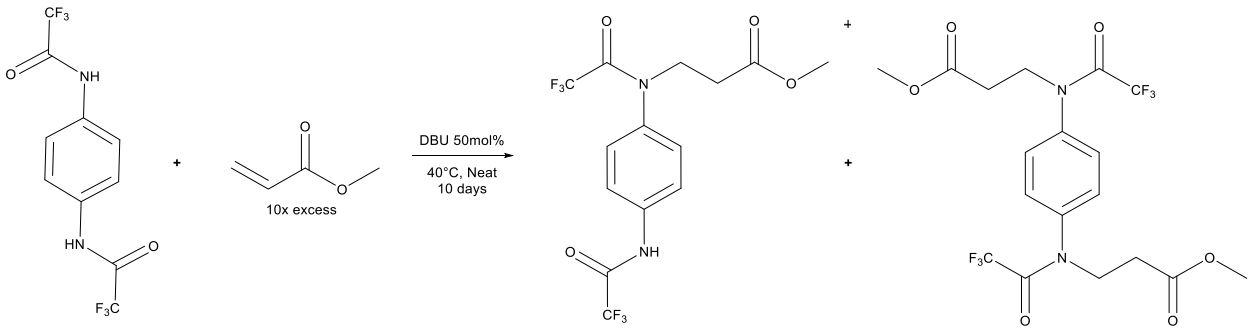
Scheme 29. The reaction between a ditrifluoroacetamide and diacrylate with DBU (50mol%) at 40°C.

We tested the reactivity of the diacrylate using 2,2,2-trifluoro-N-mesitylacetamide with DBU (25mol%) at 20℃ (scheme 30). The acrylate was in a 10mol% excess, but the acetamide was completely consumed in the reaction after 3 days. This indicates that the acrylate is reactive enough to afford high conversions.



Scheme 30. The reaction between 2,2,2-trifluoro-N-mesitylacetamide and diacrylate with DBU (25mol%) at 20℃.

The diamide was reacted with methyl acrylate at a 10-fold excess at room temperature with DBU (50 mol%). The solubility of the diamide was poor in the excess acrylate which affects its reactivity. After 10 days the conversion reached an estimated 20% conversion of the diamide or 40% (approximately 25% monosubstituted and 15% disubstituted) of the total available amide groups after 10 days (scheme 31).



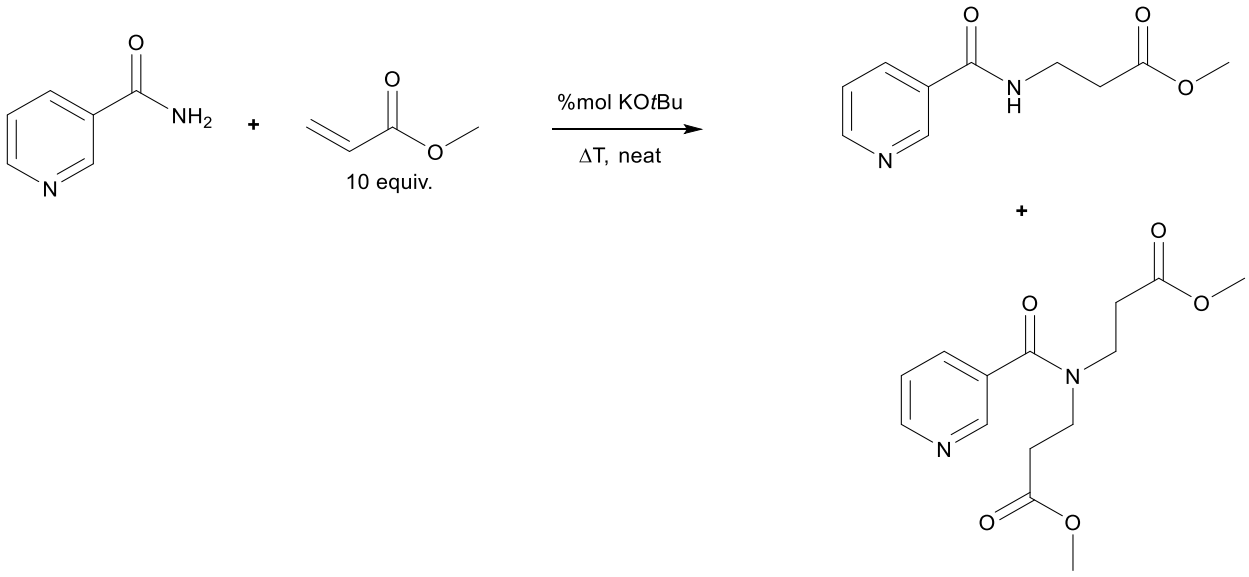
Scheme 31. The reaction between a diamide and methyl acrylate with DBU (50mol%) at 20℃.

Because the acrylate is reactive and the diamide has low solubility, thus low reactivity, further study and optimization of the functionalization of the diamide is needed in order to increase its solubility

and reactivity. However, the study also provides proof of concept that the step-wise polymerization via hydroamidation is possible.

2.3.0 Reactivity of nicotinamide

Primary amides were tested with different reaction variables to observe the kinetics of the hydroamidation reaction. Hydroamidation proceeded solvent free at higher temperatures (60-100℃) due to the low solubility of the primary amides (scheme 32, table 14). The primary amides react to form a possibility of two products: a monosubstituted and disubstituted product. The presence of both substituted products in similar distributions suggests that the activation energy for both product formations are close. However, if the base has a catalytic function the end result should be mostly disubstituted product. Reactions with KO*t*Bu were fast in the first hour, but complete conversion of the nicotinamide was never observed. In fact, the product distribution remained largely intact after that time period for reactions with 25mol% base at 60℃ and 50% base at 100℃. This signals a plateauing of the reaction as it was observed before. A study of different temperatures was conducted to observe if the reaction product distribution can be influenced. However, increasing the temperature did not follow a trend and only increased the presence of polymer. An increase in base concentration also did not significantly influence the product distribution. It should be noted that the disubstituted product is the major product at 60℃, but minor at temperatures of 80℃ and above. However, there is no clear correlation between temperature and product distribution as these results appear somewhat random in nature.

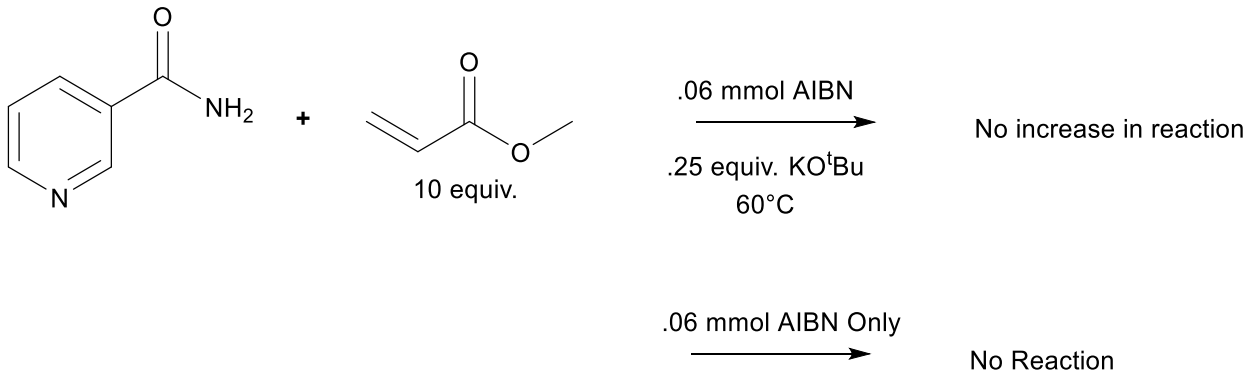


Scheme 32. The reaction of nicotinamide with methyl acrylate at various concentrations of KO*t*Bu at various temperatures

Table 14. Conversion of nicotinamide and methyl acrylate with KOtBu at different base loadings and reaction temperatures.

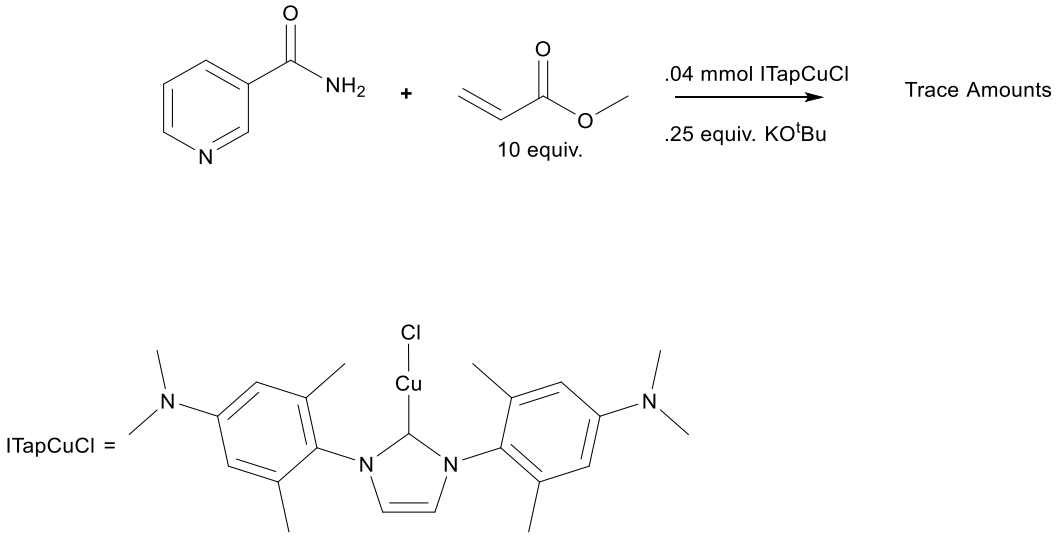
Base loading (mol%)	T (˚C)	Time (h)	Starter material (%)	Monosubstitution product (%)	Disubstitution product (%)
25	60	1	23	33	44
25	60	2	21	37	42
25	80	1	77	17	6
25	80	48	40	44	16
25	100	1	41	40	19
25	100	48	24	50	26
50	100	1	21	47	32
50	100	48	18	47	34

The random and somewhat erratic nature of the addition suggested the possibility of a radical mechanism. A radical initiator was added in order to facilitate the addition in the absence and in the presence of base (scheme 33). The addition of the radical initiator by itself showed no indication of a hydroamidation reaction. The paired reaction yielded results typical of the previous reactions. It is likely that a radical mechanism does not play a role in the hydroamidation reaction.



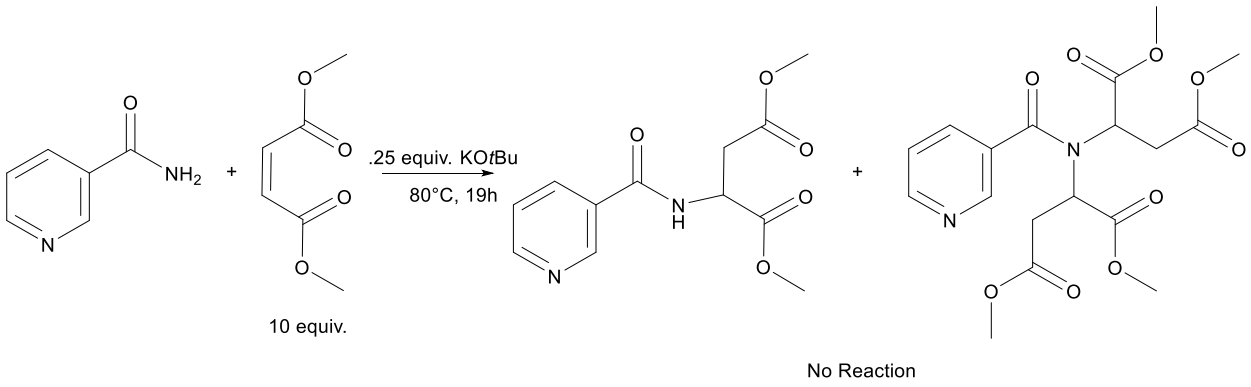
Scheme 33. Experiments used to study the mechanism of the hydroamidation reaction. All reactions were run neat at 60°C unless otherwise noted.

Another possibility was considered that the hydroamidation could be catalyzed similar to Gunnoe's hydroamination reactions.[50] In the presence of ITapCuCl the reaction showed no increase in conversion compared to the catalyst-free reaction under otherwise identical conditions (scheme 34).



Scheme 34. Experiments used to study the mechanism of the hydroamidation reaction. All reactions were run neat at 60°C unless otherwise noted.

The use of dimethyl maleate was explored as an electrophile (scheme 35). This reaction was heated to 80°C and allowed to react for up to 118 hours. No noticeable reaction was noted.



Scheme 35. The proposed reaction of nicotinamide and dimethyl maleate.

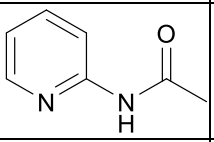
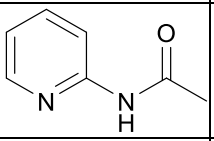
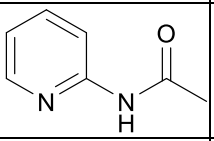
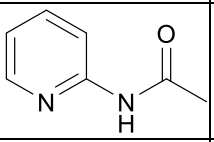
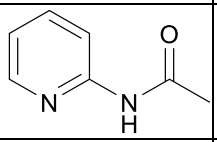
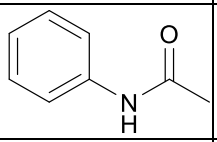
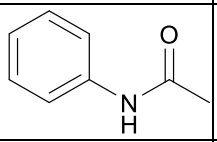
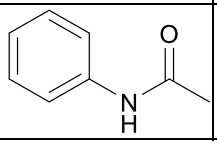
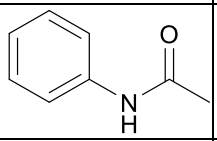
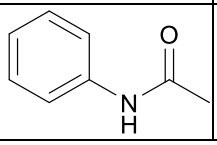
The use of primary amides were explored initially to evaluate the reactivity of the hydroamidation reaction. It was difficult to control which product was formed and high yields of the disubstituted product were inconsistent. At this time the use of secondary amides were further explored.

2.4.0 Lewis Acids as potential cocatalysts in the Hydroamidation of Acetamides

Lewis-acidic metal catalysts paired with bases have successfully facilitated aza-Michael addition reactions. Having established a baseline for catalytic activity with different reaction variables a closer investigation was conducted that focused on the reactions that converted sluggishly or inconsistently, in the presence of base (table 15). Transition and main group metals were applied, in catalytic amounts, to the hydroamidation reactions to determine their effect. The coordination may occur at the site of the electron withdrawing group or by the C=C double bond. This coordination could make the electrophile C=C bond more electron poor and will be more susceptible to an attack from the enolate ion. $Ti(OEt)_4$, $TiCl_4$, $Al(OsBu)_3$, $CaCl_2$, are hard Lewis acids. These hard acids are oxophilic in nature and should coordinate to the carboxy C=O bond of the acrylate, hence increasing the electrophilicity at the β-carbon atom of the C=C double bond. Reactions that resulted in low conversions or reacted slowly were replicated with the addition of metal catalysts. $CaCl_2$ in two different concentrations (25mol% and 50mol%) was introduced to a reaction of N-(2-pyridyl) acetamide and methyl acrylate at 20℃ with KO*t*Bu as the base (25mol). In fact, it appeared to hinder the reaction. Aluminum tri-sec butoxide was introduced to a reaction N-(2-pyridyl) acetamide and methyl acrylate at 100℃ with KO*t*Bu as the base (25mol%).

Aluminum tri-sec-butoxide was also used in the absence of an extra base. These reactions resulted in low yields and in the case metal catalyst only reaction, no yield at all. Acetanilide and acrylonitrile were used and catalyzed by Hunig's Base (25mol%) and titanium chloride (33mol%) at 20℃. However no reaction occurred indicating that the reaction may need to have a stronger base. Acetanilide was reacted with methyl methacrylate and KO*t*Bu as the base (25mol%) at 60℃. There was no noticeable reaction after 24h, however when titanium isoproxide was introduced there were signals that indicated a reaction had occurred. In summary, no experiment exhibited an increase in conversion or rate as a result of the addition of a Lewis-acid cocatalyst.

Table 15. Conversions of various acetamides with various alkenes in hydroamidation reaction in the presence of Lewis acids.

Base	Amide	Cocatalyst or Lewis Acid	Cocatalyst or Lewis Acid loading (mol%)	Temp. (˚C)	Alkene*	Time (h or days)	Conversion (%)
KO*t*Bu		-	-	20	MA	1h	69
KO*t*Bu		$CaCl_2$	25	20	MA	1h	14
						24h	14
KO*t*Bu		$CaCl_2$	50	20	MA	1h	27
						24h	27
None		Al(O*s*Bu)3	33	100	MA	3 days	0
KO*t*Bu		Al(O*s*Bu)3	33	100	MA	3 days	58
Hunig's Base		-	-	20	AN	2 days	0
Hunig's Base		$TiCl_4$	33	20	AN	24h	0
Hunig's Base		$TiCl_4$	33	20	AN	360h	0
KO*t*Bu		None	10	10	MMA	24h	0
KO*t*Bu		$Ti(OEt)_4$	10	10	MMA	24h	17

** MA= Methyl acrylate AN = acrylonitrile MMA = methyl methacrylate*

CHAPTER 3: CONCLUSION AND FUTURE OUTLOOK

Significant progress was made in determining reaction variables to achieve high rates of conversion of intermolecular hydroamidation. Accessing tertiary amides were successfully made in high yields with the optimized reaction. There are reaction conditions that need to be met in order to eliminate side reactions namely formation of polymers from the alkene substrates. While KO*t*Bu resulted in fast, quantitative conversions with amides, the significant polyacrylate or polyacrylonitrile formation are unfavorable to achieve a high molecular weight polymer using hydroamidation. The base used needs to be non-nucleophilic in order to not interact unfavorably with the alpha, beta- unsaturated alkene. The strength of the base needs to be balanced in order to deprotonate the amide and sequentially reprotonate the alpha carbon of the conjugate addition product by the conjugate acid. DBU is weaker in comparison to KO*t*Bu but when used in low concentrations (10-25% with respect to the amide) resulted in steady amide conversion with minimal side products. Quantitative conversions were achieved with the use of alkenes with different electron withdrawing groups. Reaction with trifluoroacetamides were studied and found that the alkenes result in similar reaction times. Surprisingly, reactions converting aryl acetamides or N-butyl trifluoroacetanilide and acrylonitrile with DBU as a base resulted in faster quantitative reactions while the same reaction with methyl acrylate was comparatively much slower. High temperatures were observed to degrade DBU, disfavor the addition product with KO*t*Bu, and increased the prevalence of polyacrylate side product. Steric and electronic parameters play a role in the reaction. A *t*butyl amide is less likely to react compared to a N-butyl amide. Electronic parameters were investigated by the addition of different electron donating and withdrawing substituents to the aryl ring. This resulted in greater activity with electron donating groups and a loss of activity with electron withdrawing groups. It did allow for the addition product with Hunig's base at very high temperatures, but side reactions were present. When milder temperatures were used addition was not observed. Lewis Acidic metals were not observed to increase the catalytic activity of the base.

Using the information collected from this study, a polymerization of a diamide and a diacrylate was attempted but the conversion rates were low. While the diacrylate is relatively reactive, the diamide was relatively insoluble in the reaction solution and this could be why the conversion was low.

Further research avenues may be taken to increase reactivities. Stronger bases that are non-nucleophilic like DBU may provide higher conversion rates with the reaction of acetamides and acrylonitrile with less side reactions with the alkene. Likewise, the trifluoroacetamides that did not reach quantitative conversions may find greater conversions with a stronger, non-nucleophilic base. Quantitative yields were found in this project without the use of metal catalyst, but use of these catalysts may prove to

be fruitful in future hydroamidation reactions. Polymerization of high molecular weight polymers may be possible via hydroamidation if the reactivities are sufficiently improved. Further functionalization of the diamide may result in better solubility and more electron density of the aryl component, thus greater reactivity. Likewise, further functionalization of the diacrylate may result in a more electron deficient C=C double bond that could increase the reactivity.

CHAPTER 4: DETERMINATION OF CONVERSION VIA ^{1}H NMR SPECTROSCOPY

For all amides used in this study, the presence of base is essential for the hydroamidation. Therefore prior to introduction of base, a small aliquot was obtained from the reaction vessel and a ^{1}H NMR spectrum was recorded. When the base was added the reaction was monitored at various times and the product signal peaks were identified (Figure 5). The ^{1}H NMR signal generated by the new N-CH_2 group from the acrylate or acrylonitrile after the addition (Signal X, δ = 3.7-4.2ppm) was related to the known signals of the amide starter. Figure 4 illustrates the changes of the ^{1}H NMR spectrum during the hydroamidation. For trifluoroacetanilide, the ortho-H of the phenyl ring (A) can be reliably integrated during the reaction. The new signal at δ 4.01 represents the N-CH_2 group of the product. Both signals represent the same number of H-atoms in starting material and product. It should be noted that signal Y (CH_2-COOMe) often integrates to a marginally large integral than signal X, likely because of an overlap with a signal DBU or one of its decomposition products. Hence signal X is the more reliable integral for the determination of the amount of product. In order to calculate the conversion, the integral of X was divided by the sum of A + X. For the reaction presented in figure 4 the conversion would calculate to:

$$A = 1.07$$
$$X = 2.0$$
$$Conversion = \frac{X}{A+X} \; so \; \frac{2.0}{1.07+2.0} = 65\%$$

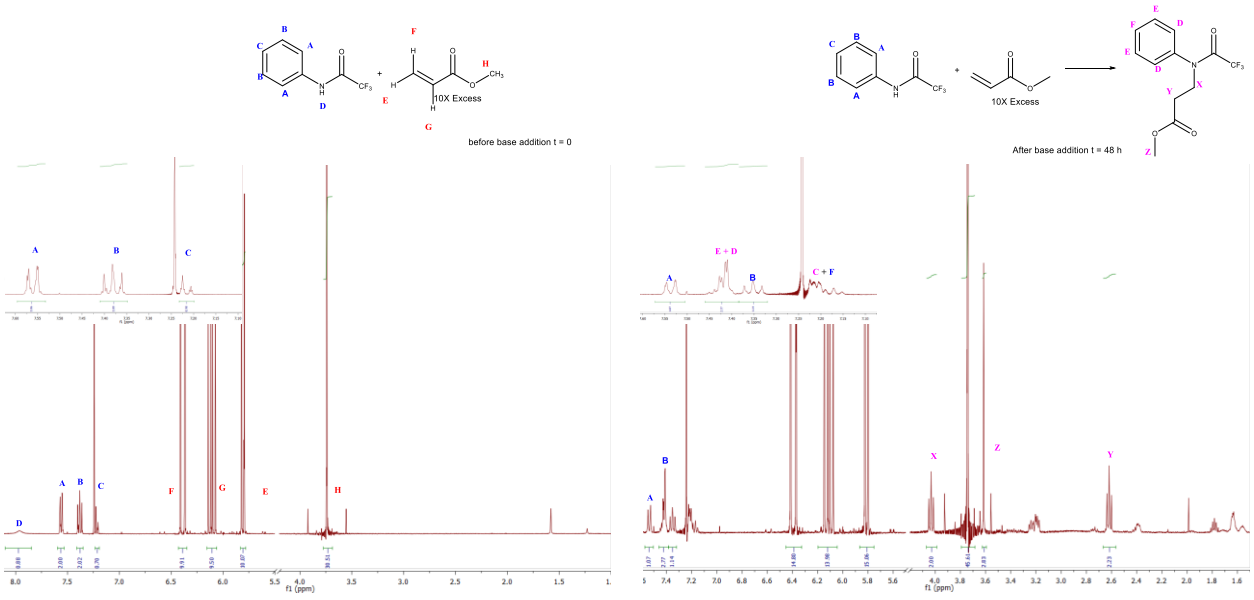


Figure 4. Two labeled NMR spectra of the reaction between trifluoroacetanilide and methyl acrylate.

In other reactions, where the aryl reactant and product groups overlap, the strategy for

conversion of the amide is adjusted. For example, in the reaction of N(2,6-dimethylphenyl)-2,2,2-trifluoro acetamide with acrylonitrile, the ^{1}H NMR signal associated with N-CH_2 proton was integrated and the aryl product signals for the reactant (signal B) and product (signal I). The signals associated with H-atoms B and I that could not be separated (δ=7.11 C-H meta to C-N of product and reactant). The combined signal has a contribution from signal I, which has the same integral as K, so that value of K can be divided by the value of the total integral to obtain conversion. For example:

$$B + I = 2.31$$

$$K = I = 2.0$$

$$Conversion = \frac{K}{I + B} \; so \; \frac{2.0}{2.31} = 87\%$$

While this is not a highly accurate method for determination of conversion in particular at high conversions, it is reliable enough to establish kinetic trends. It can be used to establish trends over time with reactions.

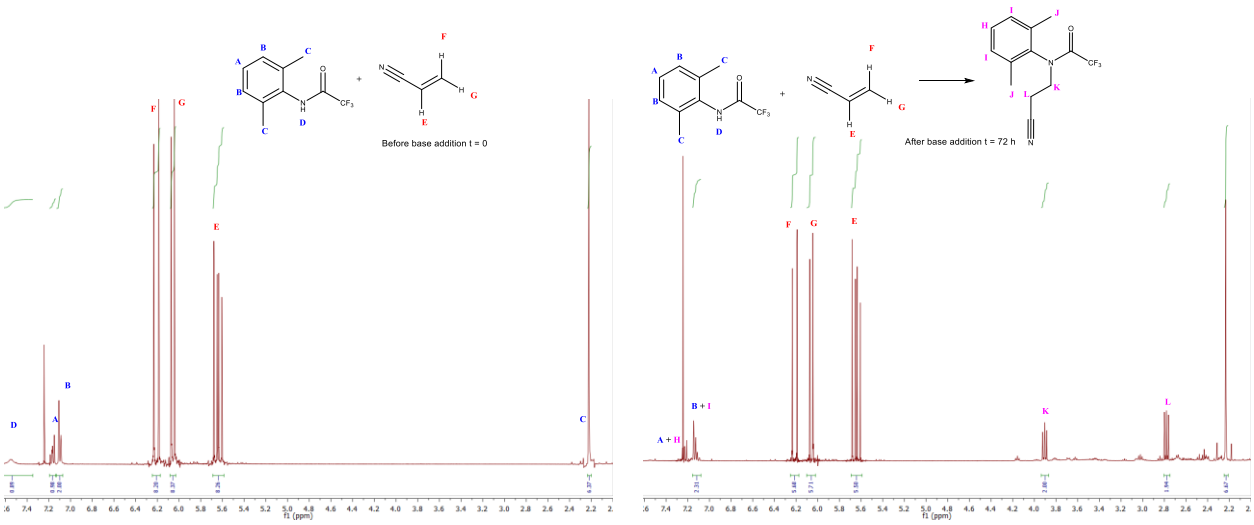


Figure 5. Two labeled NMR spectra of the reaction between dimethyl trifluoroacetanilide and acrylonitrile.

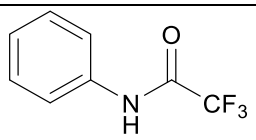
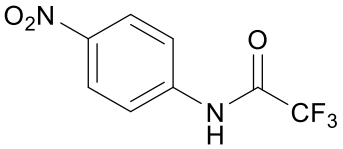
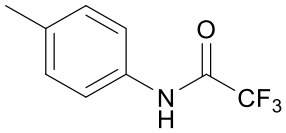
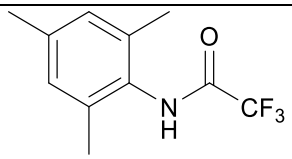
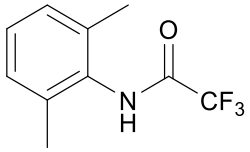
CHAPTER 5: MATERIALS AND EXPERIMENTAL

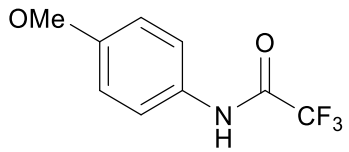
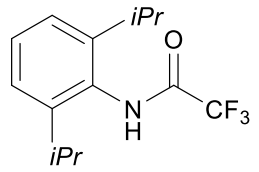
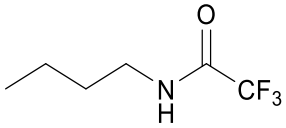
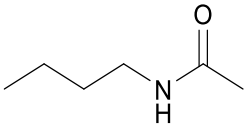
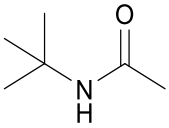
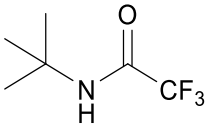
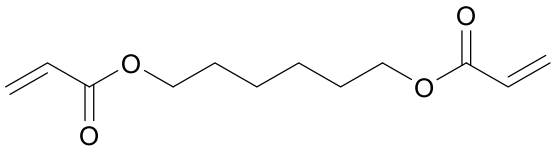
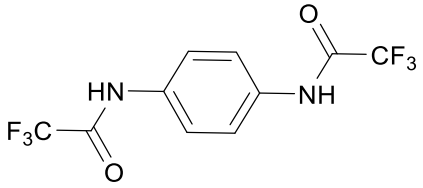
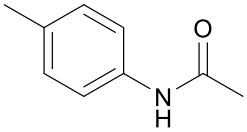
Acetanilide 99+% , aluminum tri-sec butoxide 97%, 8-Diazabicyclo[5.4.0]undec-7-ene 99% (DBU), potassium tert-butoxide 98+% (KO*t*Bu), methyl acrylate 98%, chloroform-D 99.8%, and ethyl acetate 99.6% were purchased from Acros Organics.Dichloromethane 99.5% was purchased from Fischer. Diisopropyl ethylamine (Hunig's Base) and titanium isopropoxide 98+% was purchased from Alfa Aesar. $CaCl_2$ anhydrous 96%, methyl methacrylate, and nicotinamide were purchased from Sigma Aldrich.

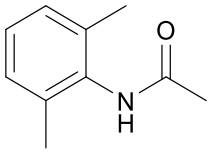
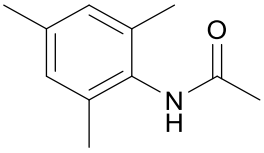
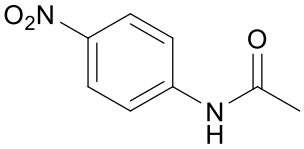
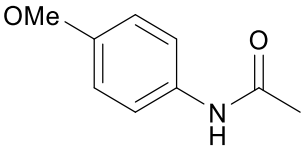
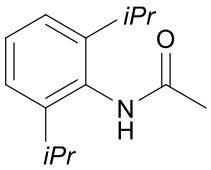
Dimethyl maleate 97.0+% Acrylamide 98.0+% and acrylonitrile were purchased from TCI America. Nuclear Magnetic Resonance (NMR) spectroscopy was performed with an Agilent Technologies 400 NMR.

Formation of amides

Formation of trifluoroacetamides were confirmed via NMR and conducted via modified procedures from:

Amide	Reference
	Penieres-Carrillo et *al.*[51]
	Penieres-Carrillo et *al.*[51]
	Watkins *et al.*[52]
	Watkins *et al.*[52]
	Kvicala *et al.*[53]

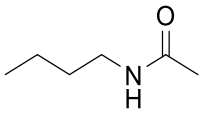
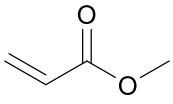
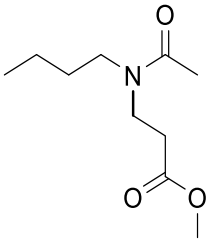
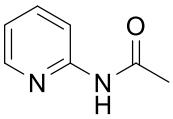
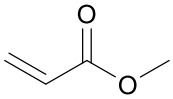
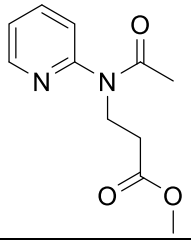
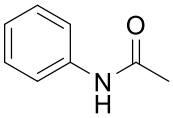
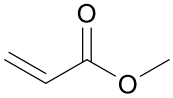
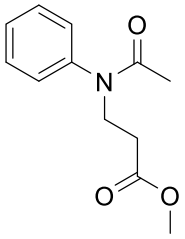
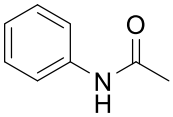
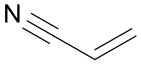
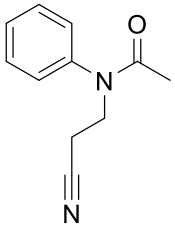
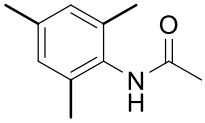
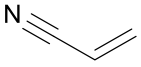
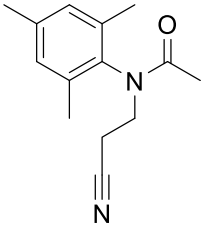
	Kawamoto *et al.*[54]
	Kambe *et al.*[55]
	Corey *et al.*[56]
	Linton *et al.*[57]
	Linton *et al.*[57]
	Linton *et al.*[57]
	Murdoch *et al.*[48]
	An *et al.*[49]
	Huo *et al.*[58]

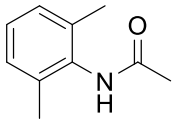
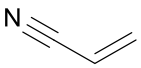
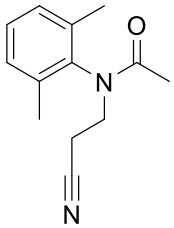
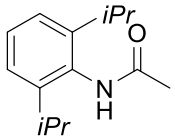
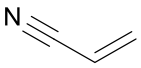
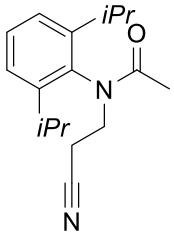
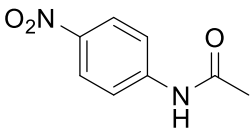
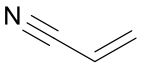
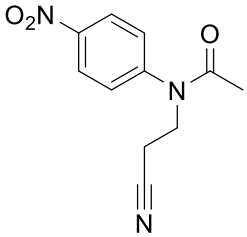
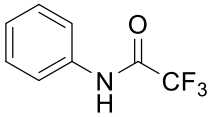
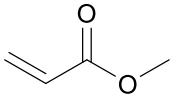
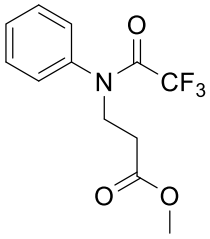
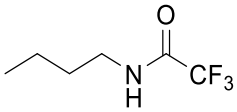
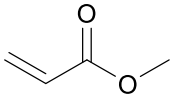
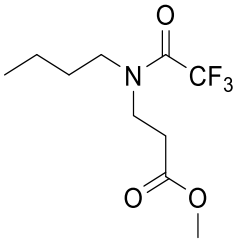
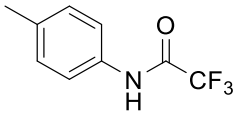
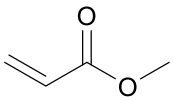
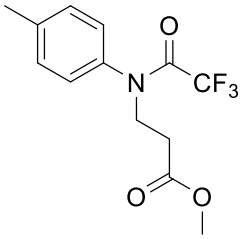
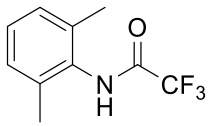
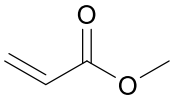
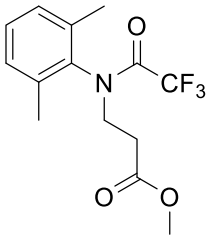
	Gowda *et al.*[59]
	Gowda *et al.*[59]
	Zhang *et al.*[60]
	Konwar *et al.*[61]
	Ford *et al.*[62]

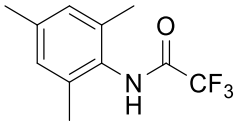
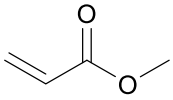
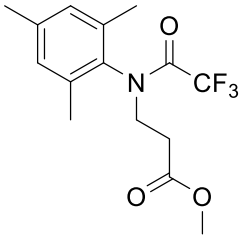
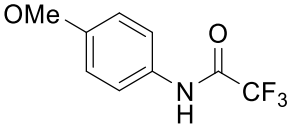
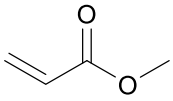
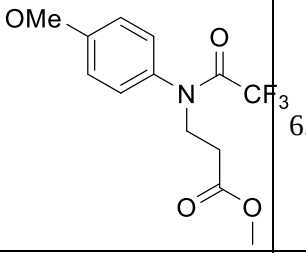
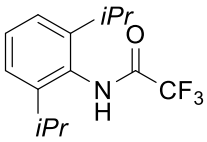
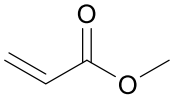
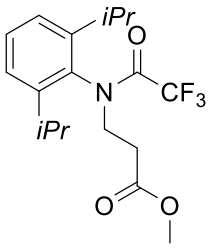
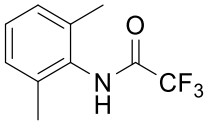
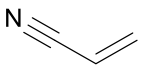
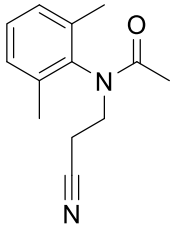
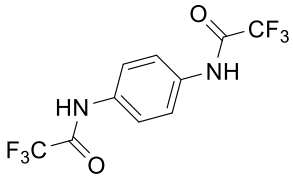
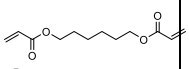
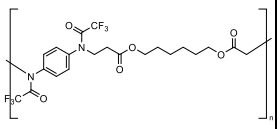
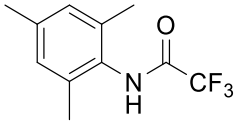
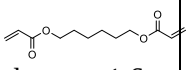
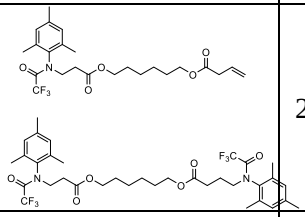
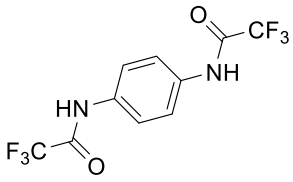
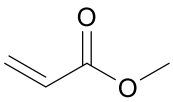
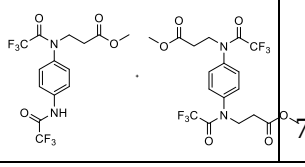
Experimental

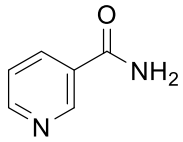
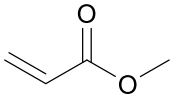
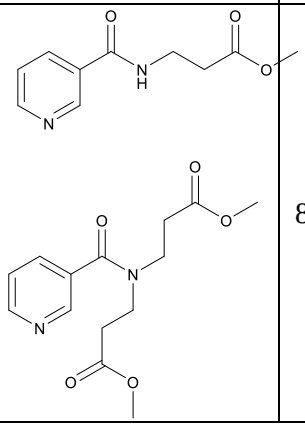
Representative procedure for the hydroamidation of alkene with amide and base

Base (KO*t*Bu, DBU, or Hunig's Base, 10-100mol% with respect to amide) was added in one portion to a mixture of amide and alkene (10x excess) in a pressure flask. The flask was closed and stirred at a predetermined temperature (20˚C-140˚C). Aliquots were taken after predetermined time intervals (5min-7days) by cooling the reaction mixture in an ice bath and removal of one drop from this mixture for ^{1}H NMR analysis. The conversion was determined by integrating the signals at … ppm (product) and … ppm (reactant).

Amide	Alkene	Product	Amide Peak	Product Peak
 N-butyl acetamide	 methyl acrylate		3.21ppm, 2H	2.56 ppm, 2H
 N-(2-pyridyl)acetamide	 methyl acrylate		8.49ppm, 1H	4.11 ppm, 2H
 acetanilide	 methyl acrylate		7.32 ppm, 2H*	3.98 ppm, 2H
 acetanilide	 acrylonitrile		7.32 ppm, 2H*	3.94 ppm, 2H
 N-mesitylacetamide	 acrylonitrile		6.95 ppm, 2H	2.69 ppm, 2H

 N-(2,6-dimethylphenyl)acetamide	 acrylonitrile		7.15 ppm, 2H	3.82 ppm, 2H
 N-(2,6-diisopropylphenyl) acetamide	 acrylonitrile		7.17 ppm, 2H	3.76 ppm, 2H
 N-(4-nitrophenyl)acetamide	 acrylonitrile		7.73 ppm, 2H	3.95 ppm, 2H
 (N-phenyl)-2,2,2-trifluoroacetamide	 methyl acrylate		7.52 ppm, 2H	4.03 ppm, 2H
 N-butyl-2,2,2-trifluoroacetamide	 methyl acrylate		3.61 ppm, 2H	1.34 ppm, 2H
 2,2,2-trifluoro-N-(p-tolyl)acetamide	 methyl acrylate		7.07 ppm, 2H*	3.61 ppm, 2H
 N-(2,6-dimethylphenyl)-2,2,2-trifluoroacetamide	 methyl acrylate		7.08 ppm, 2H*	2.72 ppm, 2H

 2,2,2-trifluoro-N-mesitylacetamide	 methyl acrylate		6.91 ppm, 2H*	3.90 ppm, 2H
 2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide	 methyl acrylate		6.91 ppm, 2H	3.99 ppm, 2H
 N-(2,6-diisopropylphenyl)-2,2,2-trifluoroacetamide	 methyl acrylate		7.12 ppm, 2H	7.18 ppm, 2H
 N-(2,6-dimethylphenyl)-2,2,2-trifluoroacetamide	 acrylonitrile		6.91 ppm, 2H*	3.99 ppm, 2H
 N ,N'-(1,4-phenylene)bis(2,2,2-trifluoroacetamide	 hexane-1,6-diyl diacrylate		7.12 ppm, 2H	6.98 ppm, 2H** 6.73 ppm, 2H***
 2,2,2-trifluoro-N-mesitylacetamide	 hexane-1,6-diyl diacrylate		2.90 ppm, 2H	3.87 ppm, 2H** 4.00 ppm, 2H***
			7.41 ppm, 2H	7.55 ppm, 2H**

N ,N'-(1,4-phenylene)bis(2,2,2-trifluoroacetamide	methyl acrylate			7.31 ppm, 2H***
 nicotinamide	 methyl acrylate		8.16 ppm, 2H	8.08 ppm, 2H** 7.72 ppm, 2H***

*= integral represents amide of starter material and product **=integral represents product signal of the monosubstituted product
***=integral represents product signal of disubstituted product

REFERENCES

1. Wen, L.; Liu, X.; Chen, W.; Yan, J., One-pot synthesis of N-confused porphyrin-dipyrrin conjugates and their optical properties. *Spectrochim. Acta A Mol. Biomol. Spectrosc.* **2020,** *227*.
2. Lundberg, H.; Tinnis, F.; Selander, N.; Adolfsson, H., Catalytic amide formation from non-activated carboxylic acids and amines. *Chem. Soc. Rev.* **2014,** *43* (8), 2714-2742.
3. Chandgude, A. L.; Fasan, R., Highly Diastereo- and Enantioselective Synthesis of Nitrile-Substituted Cyclopropanes by Myoglobin-Mediated Carbene Transfer Catalysis. *Angew. Chem. Int. Ed.* **2018,** *57* (48), 15852-15856.
4. Wang, X., Challenges and outlook for catalytic direct amidation reactions. *Nat. Catal.* **2019,** *2* (2), 98-102.
5. Tan, S. Y.; Evans, R. R.; Dahmer, M. L.; Singh, B. K.; Shaner, D. L., Imidazolinone-tolerant crops: history, current status and future. *Pest Manag. Sci.* **2005,** *61* (3), 246-257.
6. Zhuang, Y. F.; Cao, X. Y.; Zhang, J. N.; Ma, Y. Y.; Shang, X. X.; Lu, J. X.; Yang, S. L.; Zheng, K.; Ma, Y. M., Monomer casting nylon/graphene nanocomposite with both improved thermal conductivity and mechanical performance. *Compos. Pt. A-Appl. Sci. Manuf.* **2019,** *120*, 49-55.
7. Brown, W. H.; Foote, C. S.; Iverson, B. L.; Anslyn, E., *Organic Chemistry*. Cengage Learning: 2011.
8. Kantam, M. L.; Chintareddy, V. K.; Pottabathula, S.; Suresh, B., *Amination and Formation of sp2 C-N Bonds*. Spring: 2013; Vol. 46, p 119-171.
9. Bhunia, S.; Pawar, G. G.; Kumar, S. V.; Jiang, Y. W.; Ma, D. W., Selected Copper-Based Reactions for C-N, C-O, C-S, and C-C Bond Formation. *Angew. Chem. Int. Edit.* **2017,** *56* (51), 16136-16179.
10. Rao, K. S.; Wu, T. S., Chan-Lam coupling reactions: synthesis of heterocycles. *Tetrahedron* **2012,** *68* (38), 7735-7754.
11. Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P., New N- and O-arylations with phenylboronic acids and cupric acetate. *Tetrahedron Lett.* **1998,** *39* (19), 2933-2936.
12. Heravi, M. M.; Kheilkordi, Z.; Zadsirjan, V.; Heydari, M.; Malmir, M., Buchwald-Hartwig reaction: An overview. *J. Organomet. Chem.* **2018,** *861*, 17-104.
13. Ruiz-Castillo, P.; Buchwald, S. L., Applications of Palladium-Catalyzed C-N Cross-Coupling Reactions. *Chem. Rev.* **2016,** *116* (19), 12564-12649.
14. Gopalsamy, A.; Shi, M. X.; Golas, J.; Vogan, E.; Jacob, J.; Johnson, M.; Lee, F.; Nilakantan, R.; Petersen, R.; Svenson, K.; Chopra, R.; Tam, M. S.; Wen, Y. X.; Ellingboe, J.; Arndt, K.; Boschelli, F., Discovery of benzisoxazoles as potent inhibitors of chaperone heat shock protein 90. *J. Med. Chem.* **2008,** *51* (3), 373-375.
15. Cao, M. H.; Green, N. J.; Xu, S. Z., Application of the aza-Diels-Alder reaction in the synthesis of natural products. *Org. Biomol. Chem.* **2017,** *15* (15), 3105-3129.
16. Lalonde, M. P.; McGowan, M. A.; Rajapaksa, N. S.; Jacobsen, E. N., Enantioselective Formal Aza-Diels-Alder Reactions of Enones with Cyclic Imines Catalyzed by Primary Aminothioureas. *J. Am. Chem. Soc.* **2013,** *135* (5), 1891-1894.
17. Wu, P.; Fokin, V. V., Catalytic azide-alkyne cycloaddition: Reactivity and applications. *Aldrichimica Acta* **2007,** *40* (1), 7-17.
18. Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V., Copper(I)-catalyzed synthesis of azoles. DFT study predicts unprecedented reactivity and intermediates. *J. Am. Chem. Soc.* **2005,** *127* (1), 210-216.
19. Kolb, H. C.; Finn, M. G.; Sharpless, K. B., Click chemistry: Diverse chemical function from a few good reactions. *Angew. Chem. Int. Ed.* **2001,** *40* (11), 2004-2021.

20. Ali, A. A.; Chetia, M.; Sarma, D., Urea assisted copper(I)-catalyzed azide-alkyne cycloaddition reactions in water. *Tetrahedron Lett.* **2016,** *57* (15), 1711-1714.
21. Nair, D. P.; Podgorski, M.; Chatani, S.; Gong, T.; Xi, W. X.; Fenoli, C. R.; Bowman, C. N., The Thiol-Michael Addition Click Reaction: A Powerful and Widely Used Tool in Materials Chemistry. *Chem. Mat.* **2014,** *26* (1), 724-744.
22. Mather, B. D.; Viswanathan, K.; Miller, K. M.; Long, T. E., Michael addition reactions in macromolecular design for emerging technologies. *Prog. Polym. Sci.* **2006,** *31* (5), 487-531.
23. Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M., Hydroamination: Direct addition of amines to alkenes and alkynes. *Chem. Rev.* **2008,** *108* (9), 3795-3892.
24. Bittner, B.; Koppe, K.; Frank, W.; Ignat'ev, N., Michael addition catalyzed by difluorotris(pentafluoroethyl)phosphorane. *J. Fluor. Chem.* **2016,** *182*, 22-27.
25. Gunay, U. S.; Cetin, M.; Daglar, O.; Hizal, G.; Tunca, U.; Durmaz, H., Ultrafast and efficient aza- and thiol-Michael reactions on a polyester scaffold with internal electron deficient triple bonds. *Polym. Chem.* **2018,** *9* (22), 3037-3054.
26. Battistelli, B.; Lorenzo, T.; Tiecco, M.; Santi, C., "On-Water" Michael-Type Addition Reactions Promoted by PhSeZnCl. *Eur. J. Org. Chem.* **2011,** (10), 1848-1851.
27. Enders, D.; Saint-Dizier, A.; Lannou, M. I.; Lenzen, A., The phospha-Michael addition in organic synthesis. *Eur. J. Org. Chem.* **2005,** (1), 29-49.
28. Genest, A.; Binauld, S.; Pouget, E.; Ganachaud, F.; Fleury, E.; Portinha, D., Going beyond the barriers of aza-Michael reactions: controlling the selectivity of acrylates towards primary amino-PDMS. *Polym. Chem.* **2017,** *8* (3), 624-630.
29. Blaha, M.; Trhlikova, O.; Podesva, J.; Abbrent, S.; Steinhart, M.; Dybal, J.; Duskova-Smrckova, M., Solvent-free, catalyst-free aza-Michael addition of cyclohexylamine to diethyl maleate: Reaction mechanism and kinetics. *Tetrahedron* **2018,** *74* (1), 58-67.
30. Sanchez-Rosello, M.; Acena, J. L.; Simon-Fuentes, A.; del Pozo, C., A general overview of the organocatalytic intramolecular aza-Michael reaction. *Chem. Soc. Rev.* **2014,** *43* (21), 7430-7453.
31. Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A., Enantioselective phase-transfer-catalyzed intramolecular Aza-Michael reaction: Effective route to pyrazino-indole compounds. *Angew. Chem. Int. Ed.* **2008,** *47* (17), 3238-3241.
32. Tan, Z.; Li, Z.; Ma, Y.; Qin, J.; Yu, C., Potassium tert-Butoxide Prompted Highly Efficient Transamidation and Its Coordination Radical Mechanism. *Eur. J. Org. Chem.* **2019,** *2019* (28), 4538-4545.
33. Huang, L. B.; Arndt, M.; Goossen, K.; Heydt, H.; Goossen, L. J., Late Transition Metal-Catalyzed Hydroamination and Hydroamidation. *Chem. Rev.* **2015,** *115* (7), 2596-2697.
34. Ferruti, P.; Ranucci, E.; Trotta, F.; Gianasi, E.; Evagorou, E. G.; Wasil, M.; Wilson, G.; Duncan, R., Synthesis, characterisation and antitumour activity of platinum(II) complexes of novel functionalised poly(amido amine)s. *Macromol. Chem. Phys.* **1999,** *200* (7), 1644-1654.
35. Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P., A New Class of Polymers - Starburst-Dendritic Macromolecules. *Polym. J.* **1985,** *17* (1), 117-132.
36. Michigami, K.; Murakami, H.; Nakamura, T.; Hayama, N.; Takemoto, Y., Catalytic asymmetric aza-Michael addition of fumaric monoacids with multifunctional thiourea/boronic acids. *Org. Biomol. Chem.* **2019,** *17* (9), 2331-2335.
37. Brinkmann, C.; Barrett, A. G. M.; Hill, M. S.; Procopiou, P. A., Heavier Alkaline Earth Catalysts for the Intermolecular Hydroamination of Vinylarenes, Dienes, and Alkynes. *J. Am. Chem. Soc.* **2012,** *134* (4), 2193-2207.
38. Xia, Y.; Wei, H.; Xu, B.; Zhang, C., Lewis acid catalyzed intermolecular olefin hydroamination: Scope, limitation, and mechanism. *Eur. J. Org. Chem.* **2008,** (11), 1929-1936.

39. Meguro, M.; Yamamoto, Y., A new method for the synthesis of nitrogen heterocycles via palladium catalyzed intramolecular hydroamination of allenes. *Tetrahedron Lett.* **1998,** *39* (30), 5421-5424.
40. Jung, M. S.; Kim, W. S.; Shin, Y. H.; Jin, H. J.; Kim, Y. S.; Kang, E. J., Chemoselective Activities of Fe(III) Catalysts in the Hydrofunctionalization of Allenes. *Org. Lett.* **2012,** *14* (24), 6262-6265.
41. Chen, G.; Tang, Y.; Zhang, J.; Wu, Y.; Hao, X. J.; Mu, S. Z., Michael Addition between Isatin and Acrylate Derivatives. *Lett. Org. Chem.* **2011,** *8* (9), 614-617.
42. Azad, S.; Kobayashi, T.; Nakano, K.; Ichikawa, Y.; Kotsuki, H., Efficient Bronsted acid-catalyzed aza-Michael reaction of amides and ureas with alpha,beta-unsaturated enones under high-pressure conditions. *Tetrahedron Lett.* **2009,** *50* (1), 48-50.
43. Ahn, K. H.; Lee, S. J., Conjugate Addition of Amides to Alpha,beta-unsaturated Esters by CSF-SI(OET)(4) System. *Tetrahedron Lett.* **1994,** *35* (12), 1875-1878.
44. Zare, A.; Hasaninejad, A.; Zare, A. R. M.; Khalafi-Nezhad, A.; Parhami, A., An Efficient Solventless Method for the Synthesis of N,N-Dialkyl Sulfonamide Derivatives. *J. Iran Chem. Soc.* **2008,** *5* (4), 617-622.
45. Qu, G.-R.; Zhang, Z.-G.; Geng, M.-W.; Xia, R.; Zhao, L.; Guo, H.-M., Microwave-promoted Michael addition in neat water: A rapid, efficient and green method for the preparation of acyclic nucleosides. *Synlett* **2007,** (5), 721-724.
46. Khalafi-Nezhad, A.; Zarea, A.; Rad, M. N. S.; Mokhtari, B.; Parhami, A., Microwave-assisted Michael addition of some pyrimidine and purine nucleobases with alpha,beta-unsaturated esters: A rapid entry into carboacyclic nucleoside synthesis. *Synthesis-Stuttgart* **2005,** (3), 419-424.
47. Hasaninejad, A.; Zare, A.; Zare, A. R. M.; Parhami, A.; Sharghi, H.; Khalafi-Nezhad, A., Preparation of N-Arylsulfonyl Imines from Sulfonamides and Aryl Aldehydes Using Magnesium Oxide as a Heterogeneous and Reusable Catalyst Under Solvent-Free Conditions. *Phosphorous Sulfur Silicon Relat. Elem.* **2008,** *183* (11), 2769-2776.
48. Shen, Y.; Tang, H.; Zhan, Y.; Van Kirk, E. A.; Murdoch, W. J., Degradable Poly(beta-amino ester) nanoparticles for cancer cytoplasmic drug delivery. *Nanomedicine* **2009,** *5* (2), 192-201.
49. An, C.; Wu, C.; Wu, C. J.; An, C. M. Precursor composition for polyimide and use thereof. TW200821339-A; TW341851-B1.
50. Munro-Leighton, C.; Blue, E. D.; Gunnoe, T. B., Anti-Markovnikov N-H and O-H additions to electron-deficient olefins catalyzed by well-defined Cu(I) anilido, ethoxide, and phenoxide systems. *J. Am. Chem. Soc.* **2006,** *128* (5), 1446-1447.
51. Alfredo Luna-Mora, R.; Ortega-Jimenez, F.; Rios-Guerra, H.; Guadalupe Garcia-Estrada, J.; Javier Perez-Flores, F.; Gonzalez-Carrillo, J.; Torres-Reyes, A.; Moreno-Gonzalez, L.; Martinez-Zaldivar, A.; Guillermo Penieres-Carrillo, J., Simultaneous infrared-ultrasound irradiation in organic synthesis: Acylation of amines, alcohols and amino alcohols. *J. Mex. Chem. Soc.* **2019,** *63* (2), 71-81.
52. Motati, D. R.; Uredi, D.; Burra, A. G.; Bowen, J. P.; Fronczek, F. R.; Smith, C. R.; Watkins, E. B., Differential formation of nitrogen-centered radicals leading to unprecedented, regioselective bromination of N,N '-(1,2-phenylene)bisamides and 2-amidophenols. *Org. Chem. Front.* **2020,** *7* (9), 1095-1106.
53. Hosek, J.; Rybackova, M.; Cejka, J.; Cvacka, J.; Kvicala, J., Synthesis of Heavy Fluorous Ruthenium Metathesis Catalysts Using the Stereoselective Addition of Polyfluoroalkyllithium to Sterically Hindered Diimines. *Organometallics* **2015,** *34* (13), 3327-3334.
54. Okawa, T.; Aramaki, Y.; Yamamoto, M.; Kobayashi, T.; Fukumoto, S.; Toyoda, Y.; Henta, T.; Hata, A.; Ikeda, S.; Kaneko, M.; Hoffman, I. D.; Sang, B.-C.; Zou, H.; Kawamoto, T., Design, Synthesis, and Evaluation of the Highly Selective and Potent G-Protein-Coupled Receptor Kinase 2 (GRK2) Inhibitor for the Potential Treatment of Heart Failure. *J. Med. Chem.* **2017,** *60* (16), 6942-6990.

55. Zhu, L.; Le, L.; Yang, M.; Au, C.-T.; Qiu, R.; Kambe, N., Carbon-Carbon Bond Formation of Trifluoroacetyl Amides with Grignard Reagents via C(O)-CF3 Bond Cleavage. *J. Org. Chem.* **2019,** *84* (9), 5635-5644.
56. Reddy, L. R.; Reddy, B. V. S.; Corey, E. J., Efficient method for selective introduction of substituents as C(5) of isoleucine and other alpha-amino acids. *Org. Lett.* **2006,** *8* (13), 2819-2821.
57. Steffel, L. R.; Cashman, T. J.; Reutershan, M. H.; Linton, B. R., Deuterium exchange as an indicator of hydrogen bond donors and acceptors. *J. Am. Chem. Soc.* **2007,** *129* (43), 12956-12957.
58. Gao, Y.; Mao, Y.; Zhang, B.; Zhan, Y.; Huo, Y., Regioselective nitration of anilines with Fe(NO3)(3)center dot 9H(2)O as a promoter and a nitro source. *Org. Biomol. Chem.* **2018,** *16* (21), 3881-3884.
59. Gowda, B. T.; Usha, K. M.; Jyothi, K., Infrared, H-1 and C-13 NMR spectral studies on di- and tri-substituted N-aryl amides, 2,6-X2C6H3NHCOCH3-iXi and 2,4,6-X3C6H2NHCOCH3-iXi (X = Cl or CH3 and i=0, 1, 2 or 3). *Z. NaturForsch. A.* **2004,** *59* (1-2), 69-76.
60. Pan, X.-Q.; Lei, M.-Y.; Zou, J.-P.; Zhang, W., Mn(OAc)(3)-promoted regioselective free radical thiocyanation of indoles and anilines. *Tetrahedron Lett.* **2009,** *50* (3), 347-349.
61. Das Sharma, S.; Gogoi, P.; Boruah, M.; Konwar, D., SDS/Ac2O/H2O: Surfactant-mediated cleavage of Imines with acetic anhydride to carbonyls and acetanilides in water. *Synth. Comm.* **2007,** *37* (15), 2473-2481.
62. Addams, H.; Cockroft, S.; Guardigli, C.; Hunter, C. A.; Lawson, K. R.; Perkins, J.; Spey, S. E.; Urch, C. J.; Ford, R., Experimental measurement of noncovalent interactions between halogens and aromatic rings. *Chembiochem* **2004,** *5* (5), 657-665.