A FACILE METHOD FOR THE SYNTHESIS OF THIAZOLIUM SALTS USING P_2S_5-PY_2 COMPLEX AND THEIR APPLICATION IN INTERMOLECULAR STETTER REACTIONS

A Thesis Submitted to the

College of Graduate and Postdoctoral Studies

In Partial Fulfillment of the Requirements

For the Degree of Master of Science

In the Department of Chemistry

University of Saskatchewan

Saskatoon

By

Tianqi Ji

PERMISSION TO USE

In presenting this thesis in partial fulfilment of the requirements for a Postgraduate degree from the University of Saskatchewan, I agree that the Libraries of this University may make it freely available for inspection. I further agree that permission for copying of this thesis in any manner, in whole or in part, for scholarly purposes may be granted by the professor or professors who supervised my thesis work or, in their absence, by the Head of the Department or the Dean of the College in which my thesis work was done. It is understood that any copying or publication or use of this thesis or parts thereof for financial gain shall not be allowed without my written permission. It is also understood that due recognition shall be given to me and to the University of Saskatchewan in any scholarly use which may be made of any material in my thesis.

DISCLAIMER

Reference in this thesis/dissertation to any specific commercial products, process, or service by trade name, trademark, manufacturer, or otherwise, does not constitute or imply its endorsement, recommendation, or favouring by the University of Saskatchewan. The views and options of the author expressed herein do not state or reflect those of the University of Saskatchewan and shall not be used for advertising or product endorsement purposes.

Requests for permission to copy or to make other use of material in this thesis in whole or part should be addressed to:

Dean

College of Graduate and Postdoctoral Studies

University of Saskatchewan

116 Thorvaldson Building, 110 Science Place

Saskatoon, Saskatchewan, S7N 5C9

Canada

The head of the Department

Department of Chemistry

University of Saskatchewan

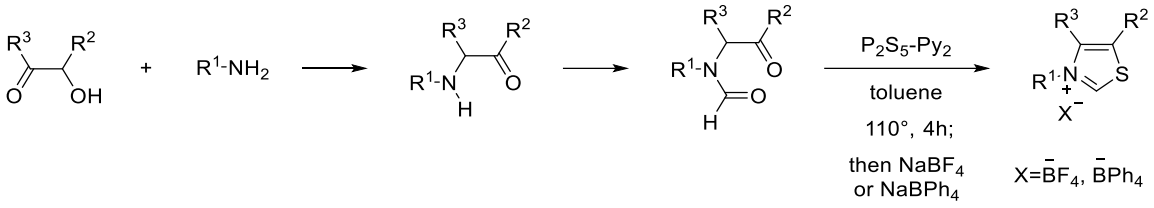
110 Science Place

Saskatoon, SK S7N 5C9

Canada

ABSTRACT

An expedient method to prepare thiazolium salts using the P_2S_5-Py_2 complex has been studied. A variety of thiazolium salts can be rapidly accessed by the clean reaction between readily available α-formamido ketones and the P_2S_5-Py_2 complex. Following salt metathesis with sodium tetrafluoroborate or sodium tetraphenylborate, the pure thiazolium salts are obtained via simple filtration. This method is suitable for a variety of substituents on the heterocycle. Reactions using the P_2S_5-Py_2 complex have been compared with other commonly used thionating methods including Lawesson's reagent and phosphorus decasulfide.



The thiazolium precatalysts were then applied in the intermolecular Stetter reaction to test their catalytic activity and to identify the most active thiazolium salt. As a result, the *N*-Cy thiazolium salts were obtained in the highest yield following the above synthetic pathway, whereas the intermolecular Stetter reaction was catalyzed by *N*-mesityl thiazolium salts in the highest yield.

ACKNOWLEDGEMENT

It was very fortunate for me to join the group of Prof. Michel Gravel, which has always been full of the atmosphere of welcoming, caring, and studying.

First I would like to express gratitude to my supervisor Prof. Gravel who is kind, and has been caring about all members of the group. He is very knowledgeable, and I have learned so much from Prof. Gravel to support my research project. He is of high academic achievement, and I always acquire the creative suggestions and instructions from Prof. Gravel while I face academic difficulties during my work. He is supportive and I always receive good advice when I make decisions on my academic development. Moreover, his rigorous scientific approach, sense of humour, and insights into chemistry are admirable and change me a lot. I'm very grateful to Prof. Gravel, my supervisor, for his patience, instructions and kindness to me and all members of the group.

I appreciate the members of the group for their help and support. Thanks a lot to Venkata, from whom I learn many lab techniques and always get answers to my questions. Thanks to Hemkalyan, whose openness made me integrate into the group in short time. Especially, I know well that details will mean success or failure in lab work from Hemkalyan. Thanks to Karn and Mehran, who often put forward creative suggestions on my project. Thanks to Rohith, who is talented, and to Mehrdad, who is very dependable. They are all my brothers.

I would like to say thanks to Dr. Jianfeng Zhu for helping with NMR and Mr. Ken Thoms for help with IR and MS. I would also like to thank Dr. Marcelo Sales, from whom I know many lab skills. I should say thanks to Ms. Amber Bornhorst for her help during my graduate program and my advisory committee member Dr. Ed Krol.

Many people at the University gave me help or assistance in the impressive and beautiful time at the University. I should say thanks to all of them.

The biggest gratefulness should be given to my dear parents for their constant love, care and support.

I thank Miss Junhan Li, my best friend, who lifted my spirits when I had serious emotional problems during the difficult pandemic isolation period. We have known each other for more than twenty years and will be best friends and family forever.

Thanks to all teachers, friends, and all people who ever helped me.

TABLE OF CONTENTS

PERMISSION TO USE i

DISCLAIMER i

ABSTRACT iii

ACKNOWLEDGEMENT iv

CHAPTER I 1

INTRODUCTION 1

1.1 The NHC-catalyzed benzoin and Stetter reactions 2

1.2 Stetter Reactions 3

1.2.1 Intramolecular Stetter reactions 3

1.2.2 Intermolecular Stetter reactions 5

1.3 Introduction to thiazolium precatalysts 10

1.4 Commonly used thionation reagents 13

1.4.1 P_2S_5-pyridine complex 16

1.4.2 Mechanistic study 17

1.5 Research objective 18

Chapter II 21

RESULTS AND DISCUSSION PART I: A Facile Method for the Synthesis of Thiazolium Salts Using P_2S_5-Py_2 Complex 21

2.1 Synthesis of cyclization precursors 21

2.1.1 Synthesis of α-amino ketones 21

2.1.2 Synthesis of α-formamido ketones 25

2.2 Synthesis of thiazolium salts using P_2S_5-Py_2 complex 30

2.2.1 Synthesis of P_2S_5-Py_2 complex 30

2.2.2 Reaction optimization 33

2.2.2.1 Solvent selection 33

2.2.2.2 Purification method 37

2.2.2.3 Optimization of temperature, P_2S_5-Py_2 loading, and reaction time 38

2.2.3 Comparison between Lawesson's reagent, $P_4S_{10,}$ and P_2S_5-Py_2 41

2.2.4 Scope of the thionation/cyclization reaction..... 43

2.3 Conclusions 47

Chapter III..... 48

RESULT AND DISCUSSION PART II: Application of Thiazolium Precursors in Intermolecular Stetter Reactions..... 48

3.1 Research objective..... 48

3.2 Development of intermolecular Stetter reaction..... 48

3.2.1 Optimization of the reaction solvent 48

3.2.2 Optimization of base..... 50

3.2.3 Scope of the reaction 52

3.2.4 Scope of aldehyde..... 54

3.3 Conclusion..... 57

CHAPTER IV..... 58

CONCLUSIONS AND FUTURE WORK..... 58

CHAPTER V 61

EXPERIMENTAL SECTION..... 61

5.1 General method 61

5.2 Experimental procedures for the synthesis of thiazolium precursors 62

5.2.1 General procedure for the preparation of α-acylamino ketones 62

5.2.2 General procedure for the preparation of thiazolium precursors..... 70

5.3 Experimental procedures for the Stetter reaction 82

5.3.1 General procedure for the Stetter reaction..... 82

LIST OF REFERENCES 84

LIST OF TABLES

Table 2.1 Summary of synthesis of α-amino ketones[a] 22

Table 2.2 Summary of synthesis of α-formamido ketones in two steps 27

Table 2.3 Solvent optimization for the synthesis of thiazolium salt with P_2S_5-Py_2[a] 34

Table 2.4 Optimization of temperature, P_2S_5-Py_2 loading, and reaction time..... 38

Table 2.5 Comparison between Lawesson's reagent, P_4S_{10}, and P_2S_5-Py_2[a]..... 41

Table 2.6 Synthesis of Thiazolium Salts with dimethyl backbone by P_2S_5-Py_2 Complex (3 equivalent) and P_4S_{10} (1 equivalent) in toluene at 110 ℃ for 2 h..... 44

Table 3.1 optimization of reaction condition with diffenent thiazolium precatalyst and chalcone. [a] 48

Table 3.2 Optimization of reaction base with N-Bn and N-Cy thiazolium precatalyst and chalcone [a] 50

Table 3.3 Scope of reaction with hetero-aromatic aldehyde and chalcone as Michael acceptor [a] 52

Table 3.4 Scope of Aldehyde of Intermolecular Stetter reactions with chalcone..... 54

LIST OF FIGURES

Figure 1. 1 Precatalysts used in intramolecular Stetter reaction 5
Figure 1.2 Precatalysts used in intermolecular Stetter reactions 7
Figure 1.3 Several NHC precatalysts..... 10
Figure 1.4 Structures of the two most common thiolation reagents.[20]..... 15
Figure 1.5 Structure of P_2S_5-Py_2 reagent 16

Figure 2.1 ^{31}P NMR spectrum of P_2S_5-Py_2 obtained from Karaghiosoff's procedure..... 31
Figure 2.2 Two conformers of $P_2S_8^{2-}$ explored by Karaghiosoff[71] 32
Figure 2.3 ^{31}P NMR spectrum of P_2S_5-Py_2 obtained from Svensson's procedure 33
Figure 2.4 ^{1}H NMR spectrum of the unpurified dithionated species **62**..... 35

LIST OF SCHEMES

Scheme 1.1 Acyl anion equivalents 2

Scheme 1.2 Proposed mechanism of benzoin and Stetter reaction 2

Scheme 1.3 The first enantioselective Stetter reaction 6

Scheme 1.4 Recent applications of Stetter reaction in the synthesis of natural products 9

Scheme 1.5 Using a thiazolium salt in a three-component coupling reaction by the Glorius group[37] 11

Scheme 1.6 Thiazolium-catalyzed Morita-Baylis-Hilman reaction reported by the Ye group 11

Scheme 1.7 Thiazolium-catalyzed [4+2] cycloaddition by the Ye group 12

Scheme 1.8 Application of polymer-supported thiazolium salt in the benzoin reaction..... 12

Scheme 1.9 General routes to the synthesis of thiazolium salts[43, 44] 13

Scheme 1.10 Some examples of thionation reagents that transform carbonyl compounds into thiocarbonyl compounds 14

Scheme 1.11 P_2S_5-Py_2 employed in chemoselective thionation.[20] 17

Scheme 1.12 Common accepted thionation mechanism of Lawesson's reagent and P_2S_5-Py_2[47] 17

Scheme 1.13 Computational mechanistic study by Merino's group (copied from reference 52) 18

Scheme 1.14 Robinson-Gabriel procedure analogous to the synthesis oxazoles from α-amidoamides 19

Scheme 1.15 Robinson-Gabriel procedure analogous to the synthesis thiazoles from α-amidoamides 19

Scheme 1.16 First synthesis of a thiazolium salt using the P_2S_5-Py_2 complex by Venkata Krishna Garapati 20

Scheme 2.1 Route for the synthesis of α-amino ketones 21

Scheme 2.2 Synthesis of α-formamido ketones 25

Scheme 2.3 Proposed mechanism of formylation of the α-amino ketones 26

Scheme 2.4 Major reaction pathways when treating an N-Ph substituted α-amino ketone with the Vilsmeier reagent 27

Scheme 2.5 Synthesis of the P_2S_5-Py_2 complex by Svensson's group 31

Scheme 2.6 Possible route for $P_2S_8^{2-}$ dianion by Minshall 32

LIST OF ABBREVIATIONS

ACN	Acetonitrile
Ada	Adamantyl
Ar	aryl
Bn	benzyl
Boc	tert-butyloxycarbonyl
tBu	tert-butyl
℃	degrees Celsius
C	concentration
Cy	cyclohexyl
δ	chemical shift (in parts per million)
d	doublet(spectral)
DBU	1,8-diazabicycl[5.4.0]undec-7-ene
DIPEA	*N*,*N*-diisopropylethylamine
DIPP	1,3-di(4-imidazolinophenoxyl)propane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact-ionization
equiv.	equivalent
FTIR	Fourier transform infrared
HPLC	high performance liquid chromotography
Hz	hertz
J	coupling constant
M	molar(mol/L)
$[M]^+$	parent molecular ion
Me	methyl
Mes	mesityl (2,4,6-trimethylphenyl)
mmol	millimole(s)
mol	mole(s)

m/z	mass-to-charge ratio
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
nr	no reaction
PEG	polyethylene glycol
Ph	phenyl
ppm	parts per million
Pr	propyl
py	pyridine
q	quartet(spectral)
R_f	retention factor
rt	room temperature
s	singlet(spectral)
TCE	trichloroethylene
t	time; triplet(spectral)
TBDPS	tert-butyldiphenylsilyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TS	transition state

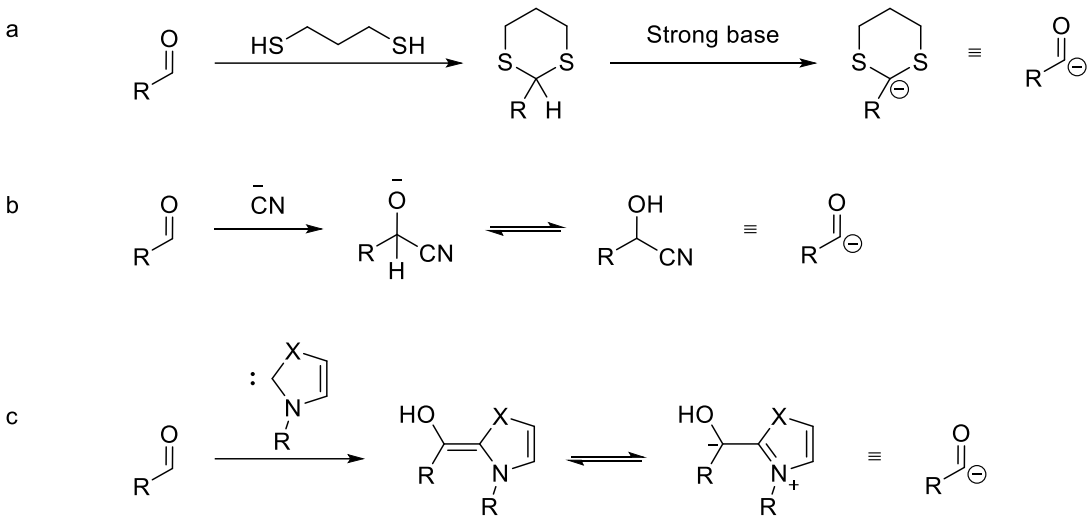
CHAPTER I

INTRODUCTION

N-Heterocyclic carbenes (NHCs) have been explored as organocatalysts, coordination to p-block elements, and transition-metal-catalyzed reactions for many years.[1] One of the most important applications is the NHC catalyzed umpolung reactions, in which intermediate acyl anion equivalents play a crucial role.[2-5] Seebach defined the nomenclature of umpolung for the first time in 1979, who mentioned that a process interchanging the normal polarity of an atom was called umpolung.[6]

The most well-known methods to form acyl anion equivalents are shown in Scheme 1. In 1977, Seebach and Corey first explored the route to reverse the electrophilic acyl carbon by dithiane and a strong base (Scheme 1.1 a).[7,8] The cyanide ion was the first catalyst used for the benzoin reaction by Wöhler and Liebig in 1832 (Scheme 1.1 b),[9] although the presence of an acyl anion intermediate was only established later. Several years later, Ukai and his colleagues explored the reaction and catalyzed the reaction using thiazolium salts for the first time in 1943 (Scheme 1.1c).[10]

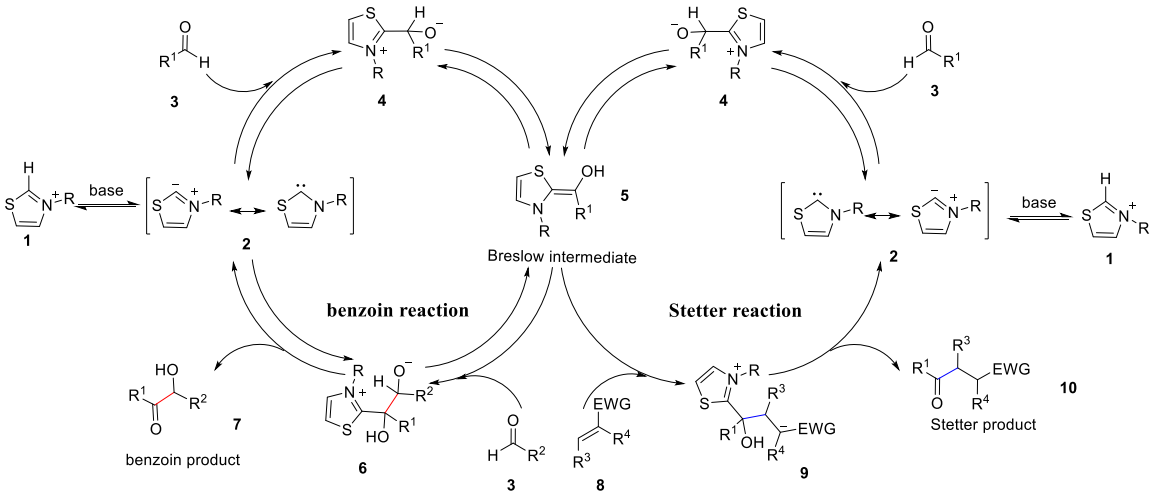
Compared with two classical methods, route a, b (Scheme 1), NHCs can lead to the umpolung of aldehydes under mild reaction conditions in a catalytic amount. Moreover, the development of NHCs opens up a new way to form a new carbon-carbon bond, especially in an enantioselective way.



Scheme 1.1 Acyl anion equivalents

1.1 The NHC-catalyzed benzoin and Stetter reactions

After Ukai explored the benzoin reaction catalyzed by thiazolium salts,[10] Breslow proposed the mechanism of benzoin reaction in 1958.[11] In 1973, Stetter and coworkers observed that the nucleophilic intermediate not only could react with another equivalent of aldehyde but also could be reacted by conjugate addition to a Michael acceptor.[12,13]



Scheme 1.2 Proposed mechanism of benzoin and Stetter reaction

Breslow proposed that thiazolium salts could be deprotonated to generate a carbene (NHC) *in situ*, which was able to reverse the polarity of an aldehyde from electrophile to the nucleophile. An acyl anion equivalent (nucleophilic carbonyl group) **5** is formed after a proton transfer, which is known as the Breslow intermediate.[11]

In the benzoin reaction (Scheme 1.2), the Breslow intermediate will attack another equivalent of aldehyde **3**. A proton transfer is followed by a catalyst regeneration to give the benzoin product **7**. On the other hand, in the Stetter reaction, the acyl anion (Breslow intermediate) reacts with a Michael acceptor **8** (EWG such as α, β - unsaturated ketone, ester or nitrile) to form a Stetter product **10** (Scheme 1.2). This type of reaction allows for the synthesis of 1,4 - dicarbonyls, which are useful in complex natural product synthesis.[14]

NHCs as organocatalysts now are extensively employed on both the benzoin and Stetter reactions as well as several other reactions. This reactivity has opened many avenues of research and has contributed to the development of new synthesis methods.

1.2 Stetter Reactions

1.2.1 Intramolecular Stetter reactions

In 1976, Stetter explored the first Stetter reaction with thiazolium salts and pointed out that the application of NHCs could largely expand the scope of 1,4-addition reactions.[12] Since the Stetter reaction can generate a new stereocenter, many chiral NHC precatalysts have been developed to induce enantioselectivity in the reaction (Figure 1.1).

The first enantioselective intramolecular Stetter reaction was revealed by Enders' group in 1996 using **11a** (EWG=CO_2Me) to form the corresponding cyclized product with 22-73% yield and 41-74% ee.[15] In 2002, Rovis' group explored the more rigid chiral triazolium precatalyst **11b**, which afforded the chroman-4-one derivative (EWG=CO_2Et) in 94% yield and 94% ee.[16] Two years later, the Rovis group reported the electron-deficient

triazolium salt **11c** to form a quaternary center-containing product (EWG=CO_2Me) enantioselectively in high yield under mild reaction conditions (85% yield, 99% ee).[17] In contrast to chiral triazolium salts, chiral thiazolium salts have not been used widely in enantioselective Stetter reactions. This situation is perhaps due to the difficulty in synthesizing chiral thiazolium salts possessing a well-defined three-dimensional structure. In 2004, Bach and his colleagues showed the use of the axially chiral thiazolium precatalyst **11d** in the Stetter reaction would result in a chroman-4-one (EWG=CO_2Me) with 85% yield and 40% ee.[18] Miller's group inserted a thiazolium moiety into a small peptide **11e** thereby improving the enantioselectivity of chroman-4-one (EWG=CO_2t-Bu) formation dramatically (67% yield and 73% ee).[19]

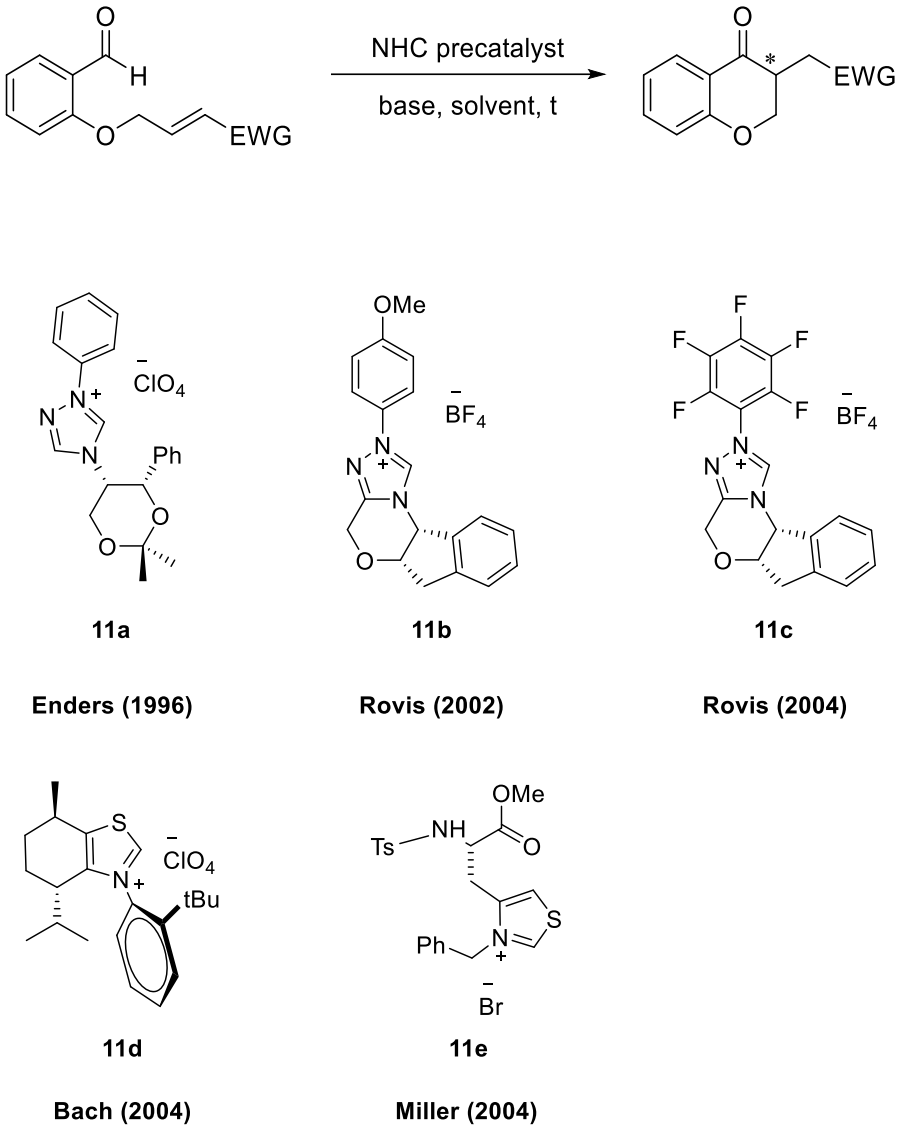


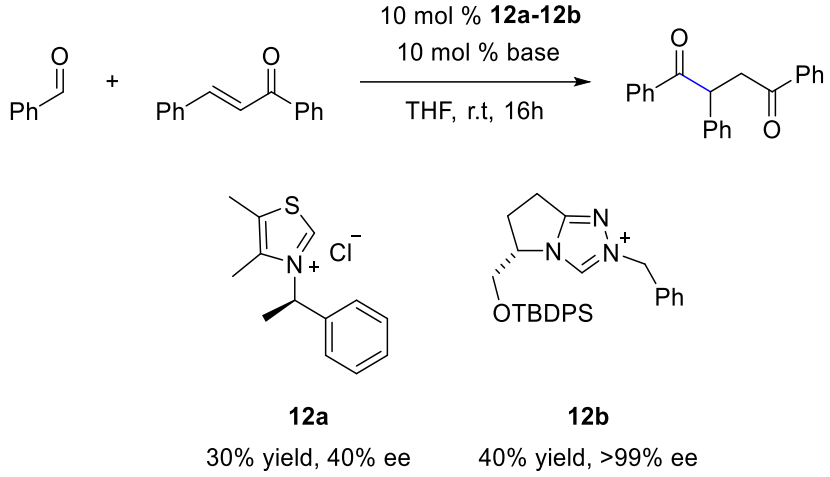
Figure 1. 1 Precatalysts used in intramolecular Stetter reaction

1.2.2 Intermolecular Stetter reactions

On the other hand, the development of the enantioselective intermolecular Stetter reaction has been relatively slower. Compared with the intramolecular Stetter reaction, the intermolecular Stetter reaction is more challenging. The Stetter product (lower entropy) is

made from the mixture of two molecules (higher entropy), so it is entropically disfavourable.

In 1993, Enders' group explored the first enantioselective intermolecular Stetter reaction. The use of chiral thiazolium salt **12a** resulted in modest yield and enantioselectivity (30% yield and 40% ee).[3] With subsequent use of a chiral triazolium salt **12b**, yields up to 40% could be obtained with >99% ee following recrystallization of the enantioenriched product (Scheme 1.3).[20]



Scheme 1.3 The first enantioselective Stetter reaction

In 2009, a new fluorinated triazolium salt **13a** was reported by Rovis, catalyzing Stetter reactions on nitroolefins with up to 95% yield and 95% ee.[21] Despite these impressive results, this catalyst proved ineffective in Stetter reactions of unsaturated ketones such as *trans*-chalcone.[22] Thus, the search for new highly active catalysts continues. In 2016, Cheng's group designed a thiazolium salt **13b** that catalyzed the intermolecular Stetter reaction with aldehyde and (E)-(2-nitrovinyl)cyclohexane in up to 79% yield.[23] In 2017, the use N-substituted itaconimides as Michael acceptor with thiazolium precatalyst **13c** was reported by Mhaske and his colleagues.[24] Very recently, the oxazolium salt **13d** was explored by Gravel's group for the first time in 2018. This new type of organocatalyst activated both benzoin and Stetter reactions in excellent yield (up to 99%).[25] Finally, the

Gravel group reported bis(diethylamino)cyclopropenylidene (EtBAC) **13e** as an excellent catalyst for the Stetter reaction.[26] Chiral BACs **13f** were also shown to catalyze the Stetter reaction on unsaturated ketones enantioselectively.[27]

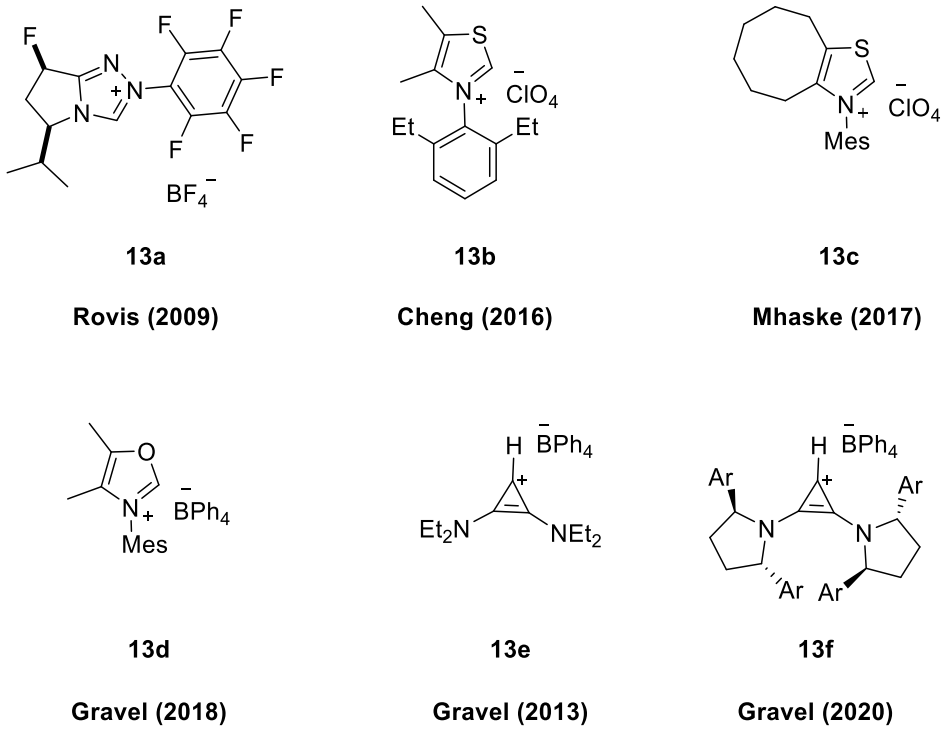


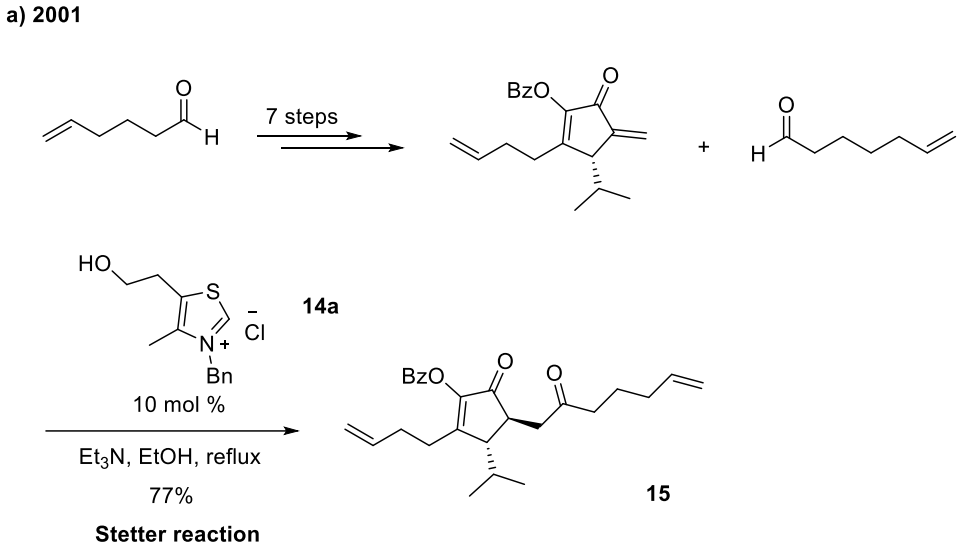
Figure 1.2 Precatalysts used in intermolecular Stetter reactions

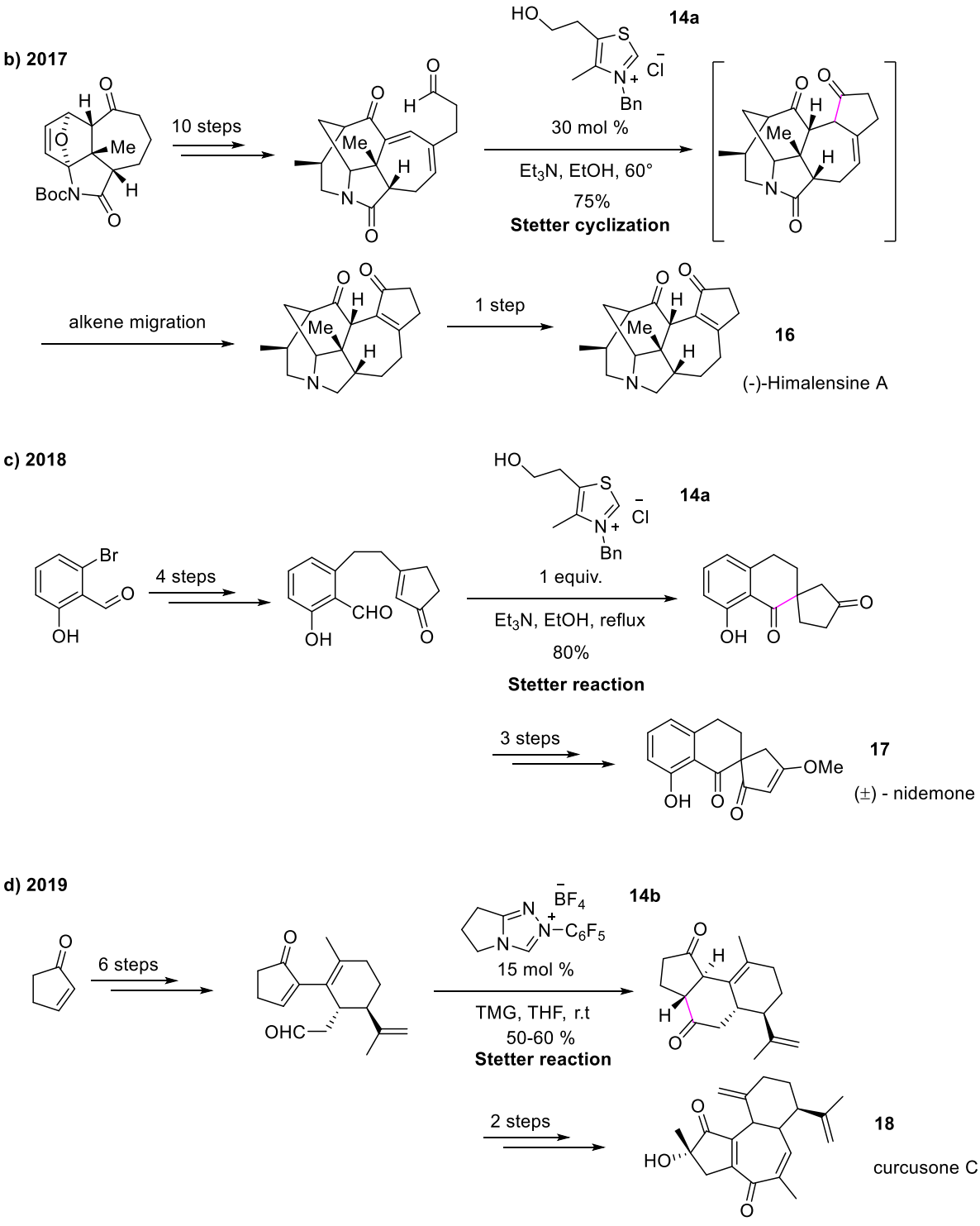
1.2.3 Stetter reaction in natural product synthesis

The Stetter reaction can be used as a critical step in the synthesis of natural products. The first use of a Stetter reaction in a total synthesis of a natural product (**15**) was published in 2001. Tius' group conveniently synthesized the 1,4-diketone intermediate through Stetter reaction using *N*-Bn thiazolium salt **14a** (Scheme 1.4 a).[28] Paton's group explored the first enantioselective synthesis of (-)-himalensine A **16** in 2017. The Stetter reaction using thiazolium salt **14a** as precatalyst enabled construction of the cyclopentanone present in the skeleton of the desired natural product **16** in 75% yield (Scheme 1.4 a).[29]

In 2018, Hsu and coworkers used the intramolecular Stetter reaction as a key step to build the spiro core in (±)-nidemone **17** with a stoichiometric amount of thiazolium precatalyst **14a** (Scheme 1.4 c, 80% yield).[30] In 2019, Stoltz's group used the fluorinated triazolium salt **14b** in the Stetter annulation to synthesize curcusone C's tricyclic skeleton **18** (Scheme 1.4 d, 50-60% yield, 2:1 dr).[31]

Although the Stetter reaction has recently been applied to total syntheses, the examples are mostly limited to the less challenging intramolecular version. The benzoin and Stetter reactions still require much catalyst development, in particular with respect to the intermolecular version.





Scheme 1.4 Recent applications of Stetter reaction in the synthesis of natural products

1.3 Introduction to thiazolium precatalysts

In general, NHCs may be easily formed by deprotonation of azolium salts. The most commonly employed of these can be represented by five precatalyst parent structures: imidazolium, imidazolinium, thiazolium, triazolium and oxazolium salts (Figure 1.3). These precatalysts are deprotonated to form active carbene species which are electron-rich because of adjacent heteroatoms.[1]

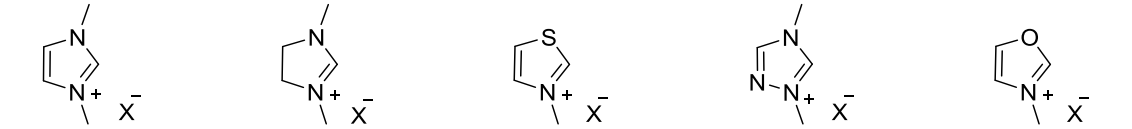
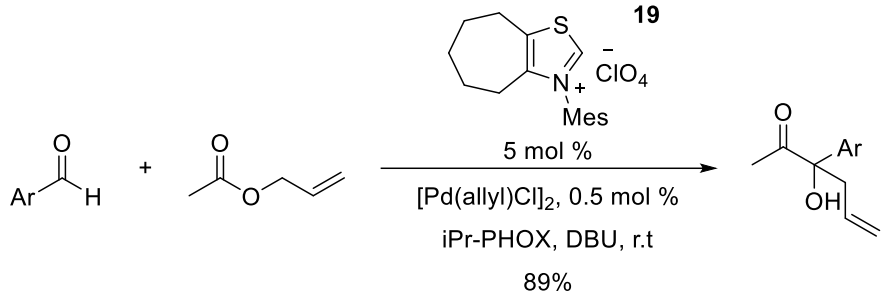


Figure 1.3 Several NHC precatalysts

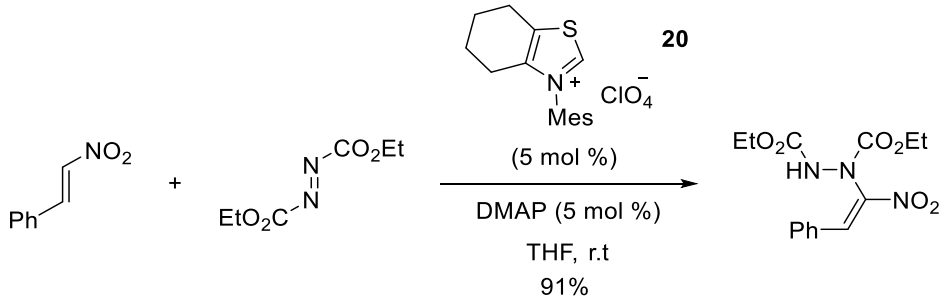
Thiazolium salts were the first kind of NHC catalysts to be explored. As the oldest of the azolium salts, they have been synthesized and used in various types of benzoin and Stetter reactions, including cross-benzoin reactions,[32] intramolecular benzoin reactions,[33] intermolecular Stetter reactions,[34] and sila-Stetter reactions.[35] Compared with other NHCs, thiazolium precatalysts, have had limited success with respect to enantioselectivity but often higher yields than triazolium and imidazolium-derived precatalysts.[2] However, only limited types of thiazolium salts have been employed in organocatalysis. Notably, the nature of the backbone and of *N*-substituent may be altered to modify the catalytic properties. The influence of the backbone and *N*-substituent on the efficiency of azolium salt could be predicted by quantifying the electronic properties and steric properties of NHCs. Normally, smaller ring sizes, bulkier and electron-donating *N*-substituent azolium salts were supposed to be more efficient. But there are some exceptions. To expand NHC-catalyzed transformations, it is desired to further synthesize thiazolium precatalysts to display a broader variety of substitution patterns.

One of the applications for which thiazolium salts have been employed is in dual organocatalysis and transition metal catalysis. Because NHCs can be coordinated to transition metals as a ligand,[36] it's difficult for azolium salts to exist with the transition-metal-based catalyst in the same catalyst system. However, the Glorius group made attempts to handle this difficulty in 2008 for the first time. Various NHC precatalysts were tried, such as thiazolium, triazolium and imidazolium salts in the tandem catalytic system. Finally, the group found that the thiazolium precatalyst **19** had an excellent capability with palladium cocatalyst, which achieved the desired reaction in 89% yield (Scheme 1.5).[37]

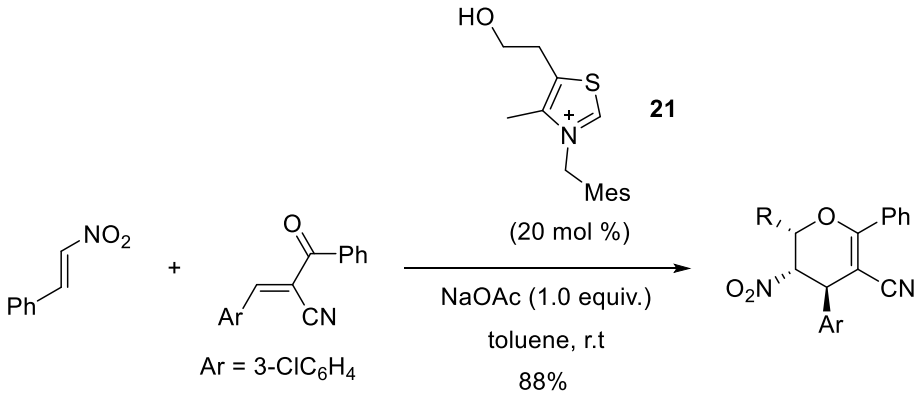


Scheme 1.5 Using a thiazolium salt in a three-component coupling reaction by the Glorius group[37]

In 2013, Ye's group used thiazolium salt **20** in the Morita-Baylis-Hilman reaction with an excellent yield (Scheme 1.6).[38] Using thiazolium salt **21** in a [4+2] cycloaddition between nitroalkenes and oxodienes was explored by Ye's group in the same year (Scheme 1.7).[39]

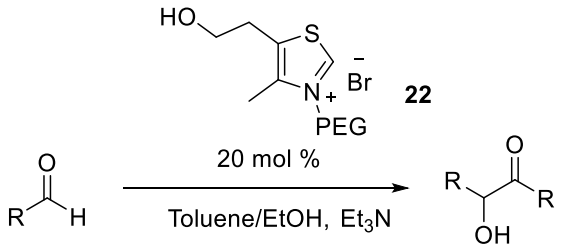


Scheme 1.6 Thiazolium-catalyzed Morita-Baylis-Hilman reaction reported by the Ye group



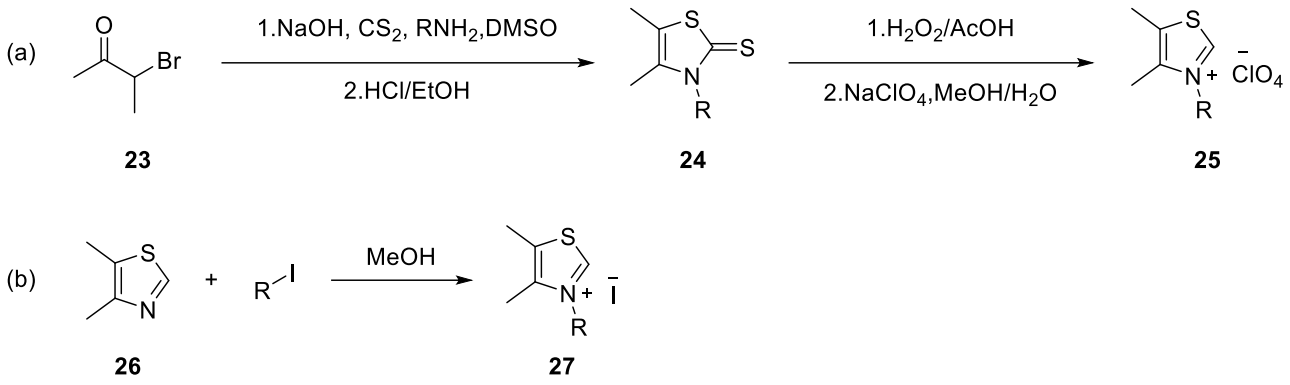
Scheme 1.7 Thiazolium-catalyzed [4+2] cycloaddition by the Ye group

In addition to the monomeric azolium salts, polymer-supported azolium salts were shown to be reusable and enhanced reactivity in acyloin condensation in some cases.[40, 41] Karimian and his coworkers published in 2021 the method of synthesizing *N*-PEGylated thiazolium bromide **22**. Finally, the catalyst activity of precatalyst was tested and resulted in the formation of the desired product in 79-82% yield (Scheme 1.8).[42]



Scheme 1.8 Application of polymer-supported thiazolium salt in the benzoin reaction

As the first explored classical NHCs, the synthesis of thiazolium salts has relied on a limited number of approaches. There are two main pathways for thiazolium synthesis (Scheme 1.9).[43]



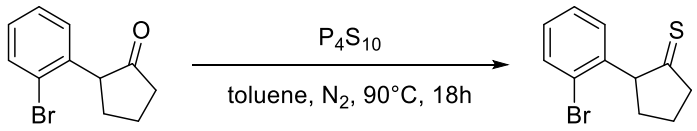
Scheme 1.9 General routes to the synthesis of thiazolium salts[43, 44]

A general way to build thiazolium precatalysts consists in the one-pot substitution and condensation of an α-halo-ketone with a primary amine and carbon disulfide to form a thione (Scheme 1.9a). Different kinds of amines react with 3-bromobutan-2-one (**23**) to form an amino ketone, and subsequent addition of NaOH and CS_2 in DMSO results in a cyclocondensation product, which dehydrates upon addition of HCl to yield thione products **24**. H_2O_2 is used for desulfurization followed by exchanging the counterion with $NaClO_4$ or another salt to form the thiazolium precatalyst **25.**[18, 45] Another common route used to synthesize thiazolium salt with dimethyl backbone is through alkylation reaction directly with 4,5-dimethylthiazole **26** and an alkyl halide (Scheme 1.9b).[46]

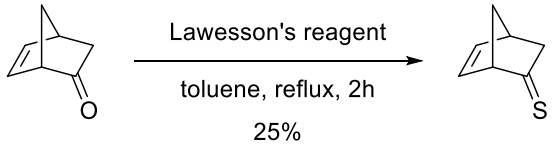
1.4 Commonly used thionation reagents

Many thionation reagents can transform a carbonyl group into a thiocarbonyl compound, such as P_4S_{10},[47] Lawesson's reagent,[48] Belleau's reagent,[49] H_2S,[50] bis(tricyclohexylstannyl) sulfide and BCl_3 (Scheme 1.10).[51]

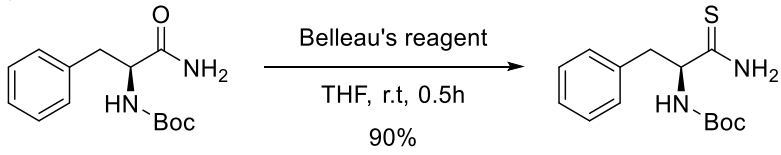
a) P_4S_{10}

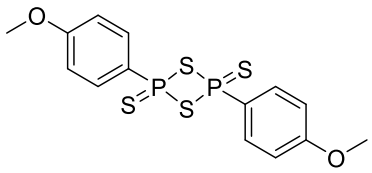


b) Lawesson's reagent

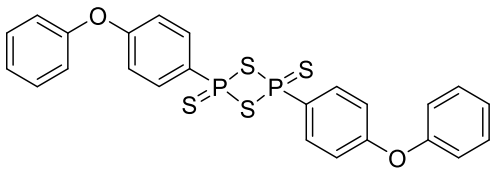


c) Belleau's reagent



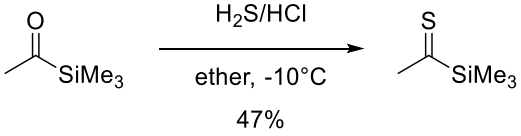


Lawesson's regent

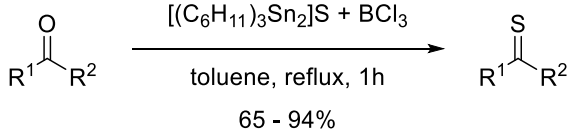


Belleau's reagent

d) H_2S

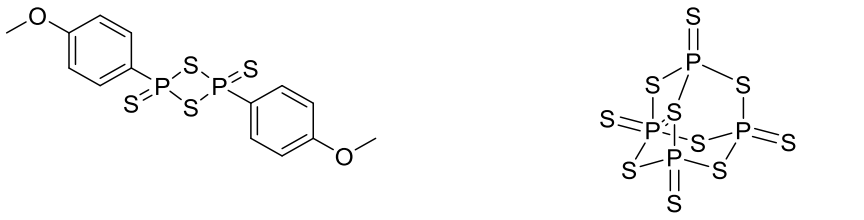


e) $[(C_6H_{11})_3Sn_2]S + BCl_3$



Scheme 1.10 Some examples of thionation reagents that transform carbonyl compounds into thiocarbonyl compounds

Among these reagents, the most convenient and commonly used are Lawesson's reagent **28** and tetraphosphorus decasulfide **29** (Figure 1.4). In 1892, Hoffman introduced P_4S_{10} as a thionation reagent for the first time. After several decades, Lawesson's Group studied the reagent **28** in depth, the so-called Lawesson's reagent.[52]



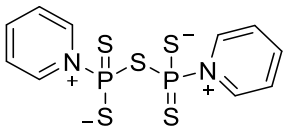
28 Lawesson's regent

29 Tetraphosphorus decasulfide

Figure 1.4 Structures of the two most common thiolation reagents.[20]

Considering these two reagents, Lawesson's reagent has been studied and applied more widely. It can thionate carboxylic acids, amides, ketones, and esters in good to excellent yield.[52] However, the reagent has its own disadvantages. Firstly, it starts to decompose around 110 °C. Moreover, the side-product and by-product of Lawesson's reagent generated during the reaction have to be removed by chromatography.[53] On the other hand, P_4S_{10} is poorly soluble in organic solvents, which limits the scope of this reagent. In recent years, combinations of reagents have been reported, such as P_4S_{10}/HMDO,[54] P_4S_{10}/Al_2O_3,[55] and P_2S_5-Py_2,[53], which often result in better yields than using Lawesson's reagent or P_4S_{10} alone.

1.4.1 P_2S_5-pyridine complex

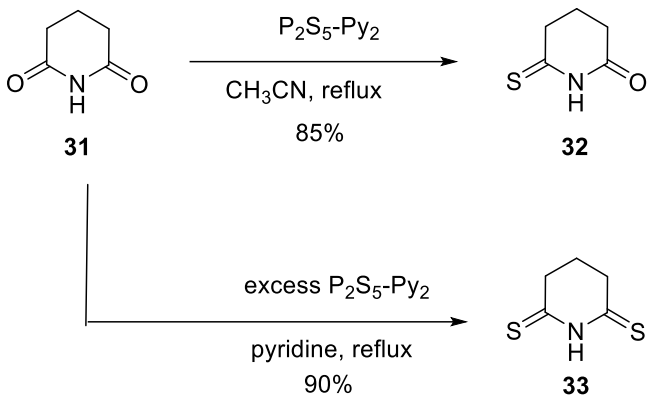


30

P_2S_5-Py_2 Complex

Figure 1.5 Structure of P_2S_5-Py_2 reagent

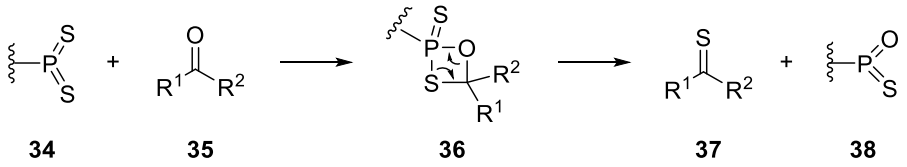
P_2S_5-Py_2 is a common thionation reagent for heterocycle construction (Figure 1.5). It can be obtained by refluxing P_4S_{10} reagent in dry pyridine.[53] Unlike Lawesson's reagent, which is also a popular thionation reagent, using P_2S_5-Py_2 reagent to achieve thionation to construct a heterocycle is advantageous because of its stability in high temperature (~180 °C),[56] ease of synthesis and good solubility in hot pyridine and acetonitrile.[53] Because the cyclization of thionated products to thiazolium salts normally requires relatively high temperatures, the thionation and cyclization reactions can be produced in one pot if the thionation reagent remains stable at high temperatures. Moreover, high chemoselectivity can sometimes be achieved by using the P_2S_5-Py_2 reagent.[53] For example, if there are multiple carbonyls in a target (e.g., **31**), the mono-thionated product **32** can be obtained by using 1 equivalent of the reagent in hot acetonitrile (Scheme 1.11). If excess thionation reagent is added in hot pyridine, the doubly thionated product **33** can be obtained in good yield. Because P_2S_5-Py_2 can quickly degrade in water, it can also simply be removed by aqueous workup.[53] On the other hand, chromatography is normally necessary for reactions using Lawesson's reagent.



Scheme 1.11 P_2S_5-Py_2 employed in chemoselective thionation.[20]

1.4.2 Mechanistic study

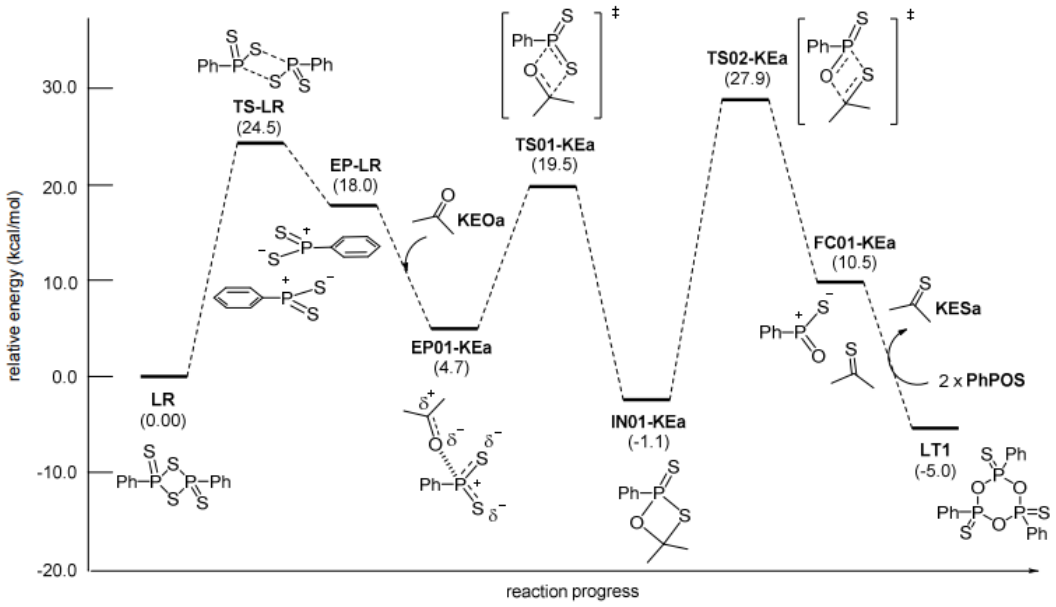
The mechanism of thionation using Lawesson's reagent or P_2S_5-Py_2 is generally accepted, in which the reagents are dissociated firstly and then undergo a formal [2+2] cycloaddition with the carbonyl group to form a four-membered ring (**36**) (Scheme 1.12). The P=O bond is known to be a much stronger bond than P-O single bond, so the four-membered ring will collapse to form a more thermodynamically stable product containing **38** a P=O bond, along with the desired thionated product **37**.[47]



Scheme 1.12 Common accepted thionation mechanism of Lawesson's reagent and P_2S_5-Py_2[47]

In 2016, Merino and his colleagues performed computations at the M06-2X/6-311+G(d,p)/PCM=DCM level of theory to support the mechanism of the thionation reaction with Lawesson's reagent (Scheme 1.13).[57] Unexpectedly, they found that the transformation of the encounter pair **EP01-KEa** to the desired products **FC01-KEa** and

KESa is endergonic. Moreover, the products **FC01-KEa** and **KESa** are higher in energy (by 10.5 kcal/mol) than the starting materials **LR** and **KEOa**, which contradicts the conclusion that the driving force of the reaction is to form a strong P=O bond.



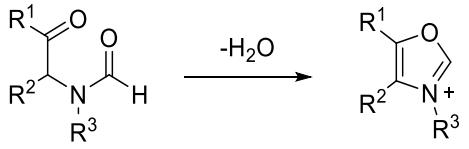
Scheme 1.13 Computational mechanistic study by Merino's group (copied from reference 52)

Via further study and calculations, they finally hypothesized that the monomer **FC01-KEa** will continue to react and form the trimer **LT1** in the end. This process releases energy, which can be the driving force to push the global reaction. As interesting as this mechanism involving Lawesson's reagent is, it is still uncertain whether reactions involving P_4S_{10} operate via a similar mechanism.

1.5 Research objective

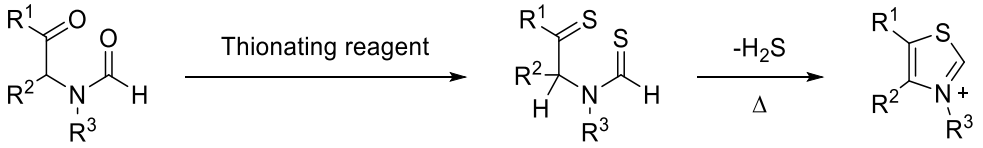
As mentioned earlier, there are two general routes to synthesize thiazolium salts, both of which can easily introduce various *N*-aryl and *N*-alkyl substituents (Scheme 1.9). However, these methods have their disadvantages. Route a is normally used for *N*-Ar

thiazolium salt synthesis. On the other hand, although Route b is the easiest method to synthesize thiazolium salt, it is limited to the synthesis of *N*-alkyl thiazolium precatalysts from primary organohalides. It was thus hoped to find a more general route to thiazolium salts that would be both concise and convenient.



Scheme 1.14 Robinson-Gabriel procedure analogous to the synthesis oxazoles from α-amidoamides

The designed route was inspired by the Robinson-Gabriel synthesis of oxazolium salts (Scheme 1.14).[58-60] In a similar manner, thiazolium salts should accessible upon treating α-formamido ketones with a thionating reagent followed by cyclization upon heating (Scheme 1.15).

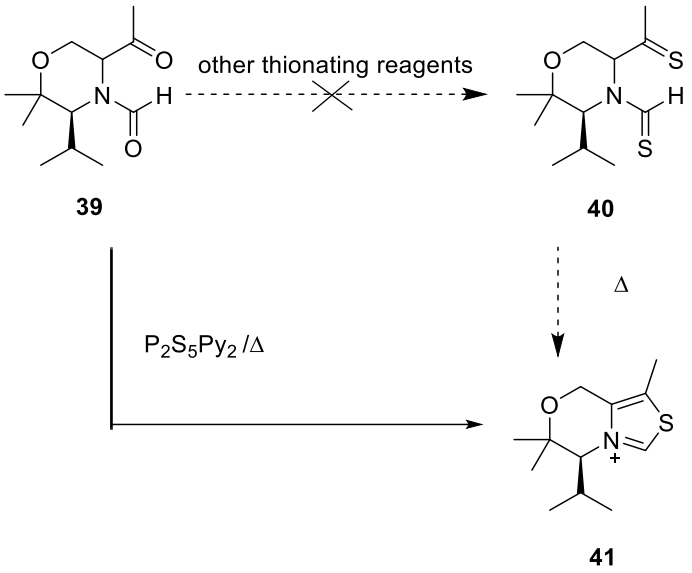


Scheme 1.15 Robinson-Gabriel procedure analogous to the synthesis thiazoles from α-amidoamides

At the beginning of this project, the only reported examples of this method for the synthesis of thiazolium salts were performed by my colleague Venkata Krishana Garapati (Scheme 1.16).[61] After trying different thionating reagents such as P_4S_{10} **29** and Lawesson's reagent **28**, the desired product was difficult to purify from complex mixture. Based on Svensson et al.'s report revealing that the P_2S_5-Py_2 complex could thionate carbonyl compounds efficiently, it was decided to investigate this reagent.

After initial trials, there were two significant advantages observed with this reagent. First, compared to the use of other P_4S_{10} modified reagents such as P_4S_{10}/Al_2O_3,[55] and P_4S_{10}/HMDO,[54] etc. the use of P_2S_5-Py_2 could afford the desired product in a much cleaner reaction. Moreover, instead of obtaining the di-thionated carbonate compound **40**, the thionation followed by cyclization could be accomplished in one pot with mild heat.

Based on the above work, the central objective of this project was to explore the synthesis of thiazolium salts bearing different types of substituents using the P_2S_5-Py_2 complex. To achieve this objective, the first step would be the optimization of the method of using the P_2S_5-Py_2 complex, and the next step would be the scope exploration (Chapter II).



Scheme 1.16 First synthesis of a thiazolium salt using the P_2S_5-Py_2 complex by Venkata Krishna Garapati

Following the synthesis of various thiazolium salts, the next objective was to determine their catalytic potential in a representative Stetter reaction through a short survey using standard conditions (Chapter III).

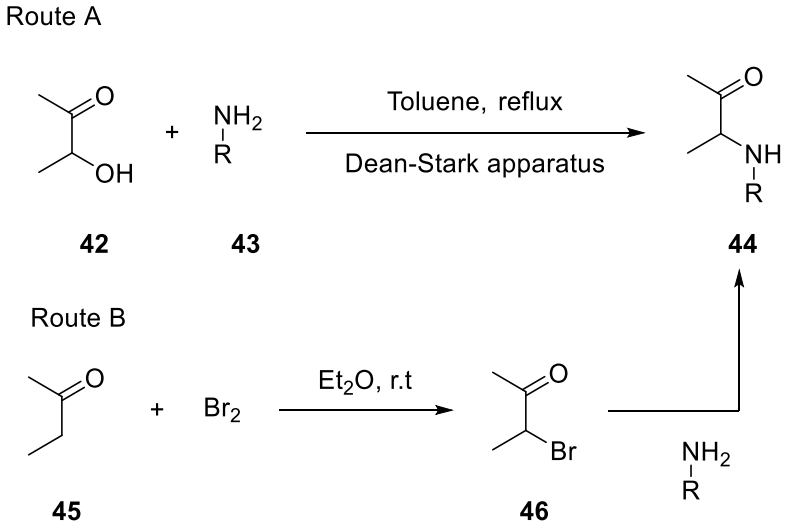
Chapter II

RESULTS AND DISCUSSION PART I: A Facile Method for the Synthesis of Thiazolium Salts Using P_2S_5-Py_2 Complex

2.1 Synthesis of cyclization precursors

2.1.1 Synthesis of α-amino ketones

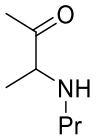
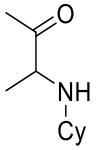
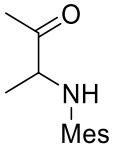
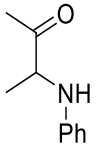
The thiazolium salts preparation started with the condensation between an amine and an α-hydroxy ketone **42** (Scheme 2.1, Route A) or with the nucleophilic substitution of an α-bromo-ketone by an amine (Route B).[62] After several trials, it was found that Route b was more practical when α-hydroxy ketones were not commercially available. However, for the simple dimethyl backbone thiazolium, the yield would decrease sharply with Route b due to the volatility of α-bromo-ketone **46**. On the other hand, the α-hydroxy ketone **42** was commercially available and could afford α-amino ketones **44** in one step using Route a. Thus, this route was selected to prepare numerous dimethyl backbone thiazolium salts.

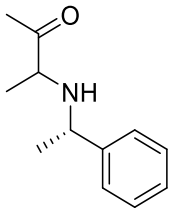
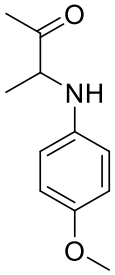
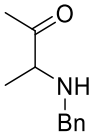
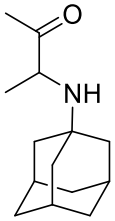
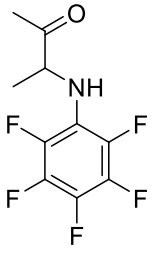


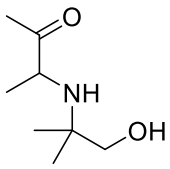
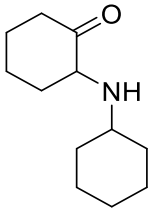
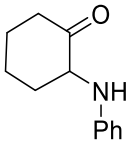
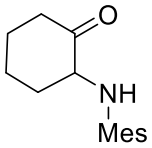
Scheme 2.1 Routes for the synthesis of α-amino ketones

The results for the synthesis of α-amino ketones are presented in Table 2.1. It was found that the α-amino ketones' isolation was difficult because of their slow elution upon column chromatography, accompanied by slow decomposition. In most cases, the α-amino ketones were directly converted to α-formamido ketones without purification. The yields for their preparation indicated in Table 2.1 were thus determined from ^{1}H NMR analysis. In some cases, it proved too difficult to determine a yield in this manner and the combined yield for this step and the subsequent formylation step was determined instead (*vide infra*).

Table 2.1 Summary of synthesis of α-amino ketones[a]

entry	α-amino ketone product	route of synthesis	yield of α-amino ketone (%)[b]
1	 **44a**	A	32
2	 **44b**	A	n.d. [c]
3	 **44c**	A	n.d.
4	 **44d**	A	70

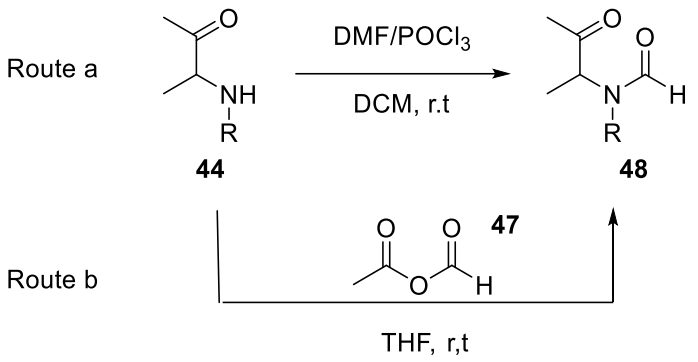
5	 **44e**	A	n.d.
6[d]	 **44f**	A	86
7	 **44g**	A	57
8	 **44h**	A	25
9[d]	 **44i**	A	82

10	 **44j**	A	14
11	 **44k**	A	67
12[d]	 **44l**	B	53
13[d]	 **44m**	-	63

[a] For the synthesis of α-amino-ketones, conc. HCl was added to a solution of amine (1 equiv.) and α-hydroxyketone (1.5 equiv.) in toluene (0.3 M) at 120 °C with Dean-Stark apparatus. [b] isolated yield. [c] n.d.: Not determined. [d] Reaction performed by Venkata Krishna Garapati.

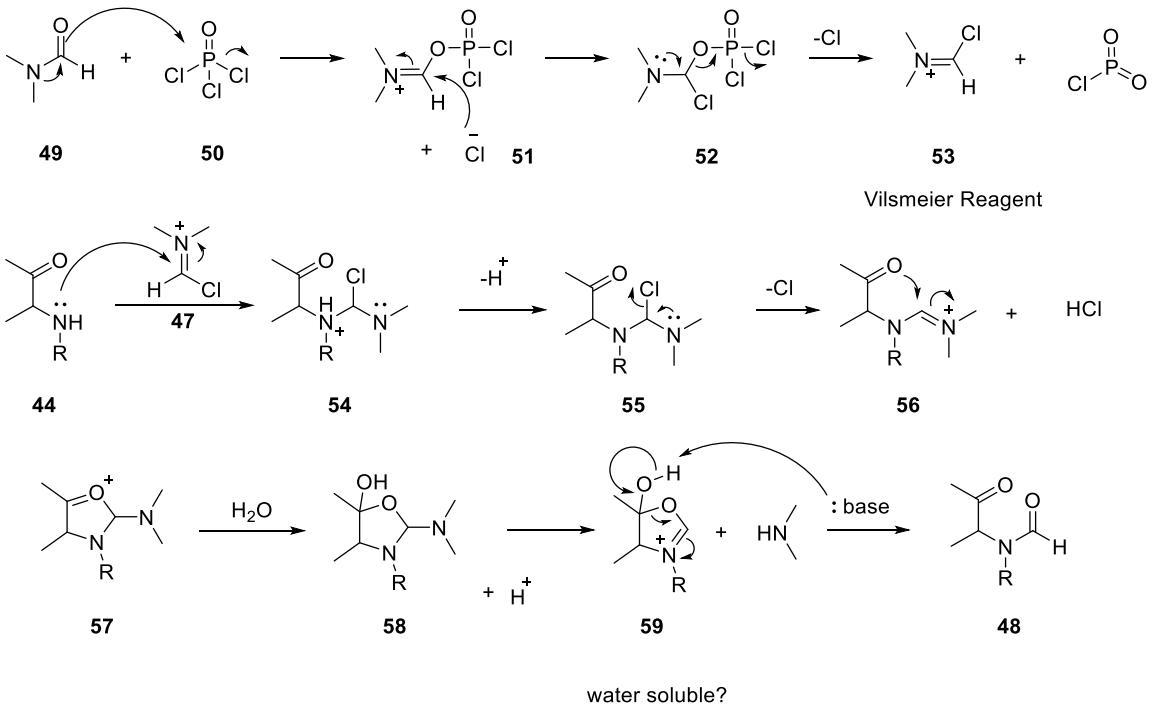
2.1.2 Synthesis of α-formamido ketones

The α-amino ketones were then formylated prior to the crucial thionation step. Two possible methods for the formylation of the α-amino ketones were identified: using the Vilsmeier reagent or a mixed formyl anhydride (Scheme 2.2).



Scheme 2.2 Synthesis of *α*-formamido ketones

The Vilsmeier reagent (Scheme 2.2, Route a) was studied first. Surprisingly, the desired product was found to stay in the aqueous layer while the other organic side-products were found in the organic layer. Gratifyingly, the pure formylated product **48** was obtained in the organic phase upon treatment with aqueous $NaHCO_3$. This led to the transformation of α-amino ketone **44** to α-formamido ketone **48** with Vilsmeier reagent with no required purification. The reason for the unexpected water solubility of the formylation products is not clear at this point. However, a possible rationale is presented in Scheme 2.3.

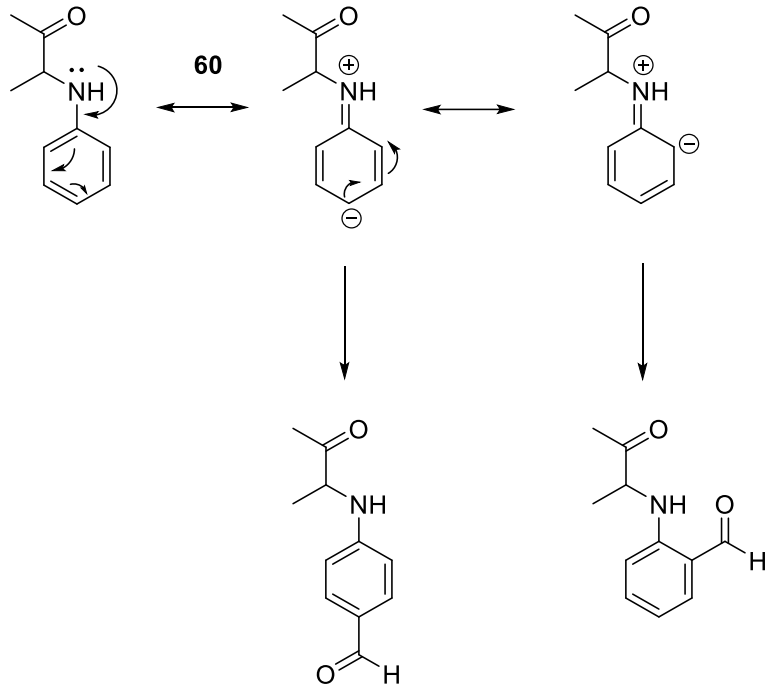


Scheme 2.3 Proposed mechanism of formylation of the α-amino ketones

The formylation product is presumably not present under the strongly acidic reaction conditions. Instead a water soluble species must be formed. This species is proposed to be a charged cyclization product (**59**). Upon treatment with base, the desired neutral formylated product **48** is then formed.

Unfortunately, the Vilsmeier method was not suitable for most substrates, including *N*-Ph substituted amino-ketones **60**. This substrate mainly underwent a Vilsmeier-Hack reaction at the ortho or para position of the phenyl ring (Scheme 2.4). For these substrates found unsuitable using the Vilsmeier reagent, Route b was followed.

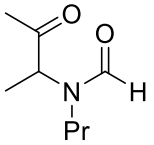
This alternative method involved the use of the mixed anhydride **47** as a versatile reagent. Although it worked acceptably for most substrates studied, chromatography was required to obtain the pure products.

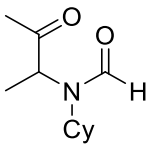
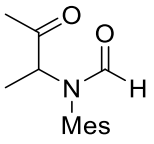
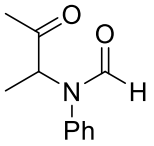
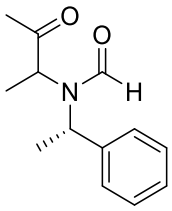
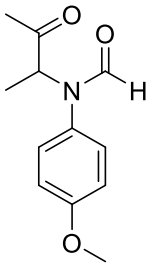


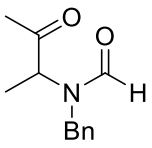
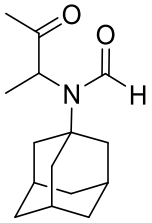
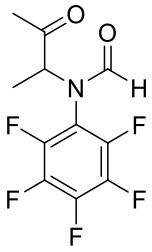
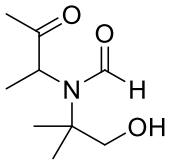
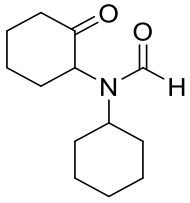
Scheme 2.4 Major reaction pathways when treating an *N*-Ph substituted α-amino ketone with the Vilsmeier reagent

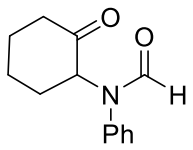
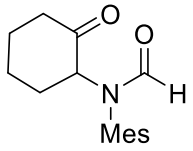
The yields for the formylation reaction, as well as the combined yields for the amination/formylation sequence are presented in Table 2.2.

Table 2.2 Summary of synthesis of α-formamido ketones in two steps

entry	α-formamido ketone product	route [a]	yield of α-formamido ketone (%)[b]	combined yield of first two steps(%)[b]
1	 **48a**	a	45	15

2	 **48b**	a	n.d.[c]	34
3	 **48c**	a	n.d.	40
4	 **48d**	b	55	39
5	 **48e**	b	n.d.	42
6[d]	 **48f**	b	74	64

7	 **48g**	b	20	11
8	 **48h**	b	13	3
9	 **48i**	a	76	62
10	 **48j**	b	80	11
11	 **48k**	b	32	21

12[d]	 **48l**	b	83	44
13[d]	 **48m**	b	34	21

[a] Route a: Vilsmeier reagent (2 equiv.) was added to a solution of amino ketone (1 equiv.) in CH_2Cl_2 at ambient temperature. Route b: the mixed anhydride **47** (2 equiv.) was added to a solution of amino ketone (1 equiv.) in CH_2Cl_2 at ambient temperature. [b] Isolated yield. [c] n.d.: Not determined. [d] Reaction performed by Venkata Krishna Garapati.

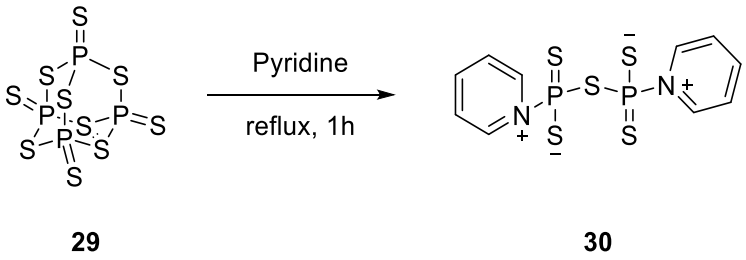
As a result of the two-step sequence, alkyl- and aryl-substituted α-formamido ketones were obtained in relatively low yields. Most of the formylated products were stable under the reaction conditions, except for the α-formamido ketone **48i** obtained from the *N*-pentafluorophenyl-substituted α-amino ketone **44i**. Indeed, α-formamido ketone **48i** was formed quickly within two hours, but prolonging the reaction time would generate by-products, thereby decreasing the yield sharply (entry 9).

2.2 Synthesis of thiazolium salts using P_2S_5-Py_2 complex

2.2.1 Synthesis of P_2S_5-Py_2 complex

Svensson's group first explored the preparation of the P_2S_5-Py_2 complex **30** and its structure[53] (Scheme 2.5). After three years, Karaghiosoff and his colleagues modified Svensson's method to improve the purification (*vide infra*).[63] They mentioned that Svensson's process could increase $Py_2P_2S_4O$ as a side-product. In order to find the best

route for P_2S_5-Py_2 complex preparation, both approaches were tried and both were monitored by ^{31}PNMR spectroscopy (Figure 2.1).



29 **30**

Scheme 2.5 Synthesis of the P_2S_5-Py_2 complex by Svensson's group

Karaghiosoff made a conclusion that the pure product could be obtained as colourless needles in up to 93% yield after stirring P_4S_{10} **29** with pyridine at ambient temperature, followed by crystallization overnight. In my hands, the result was inconsistent with Karaghiosoff's conclusion. Despite repeated attempts, dissolving P_4S_{10} in pyridine at ambient temperature did not result in the appearance of needles unless a non-polar solvent (i.e., hexanes) was added. The resulting ^{31}P NMR spectrum of the solid following filtration is shown in Figure 2.1.

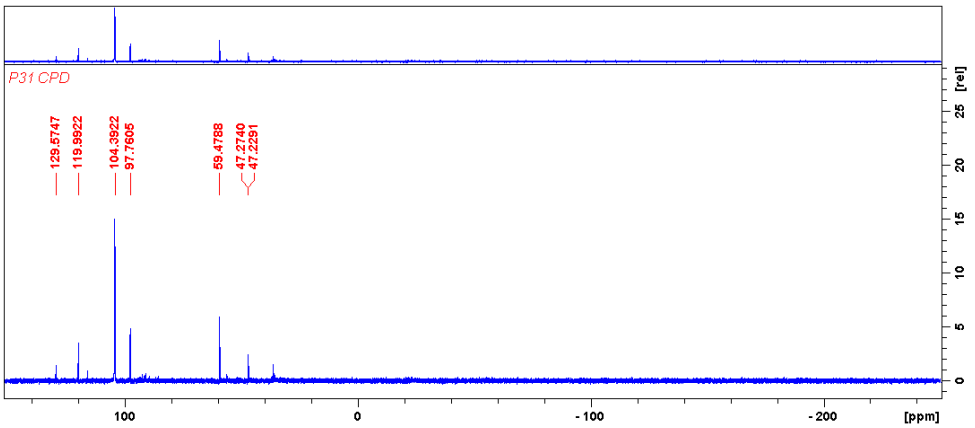
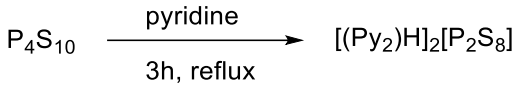


Figure 2.1 ^{31}P NMR spectrum of P_2S_5-Py_2 obtained from Karaghiosoff's procedure

Via Karaghiosoff's method, in addition to the desired P_2S_5-Py_2 (δ=104.4 ppm), there were at least five side-products. One probably was the dianion $P_2S_8^{2-}$ (δ=119.5 ppm), also observed by Minshall et al. (Scheme 2.6).[64] Karaghiosoff's group determined that $P_2S_8^{2-}$ in fact existed as a twist conformer (δ=119.5 ppm) and a chair conformer (δ=55.5 ppm), and that the two conformers interconvert spontaneously (Figure 2.2). However, no chair conformer was visible in my ^{31}P NMR spectrum. Another side product at 97.8 ppm was identified as $Py_2P_2S_4O$, which was also mentioned by Karaghiosoff. The identity of the other three side-products was not determined.



Scheme 2.6 Possible route for $P_2S_8^{2-}$ dianion by Minshall

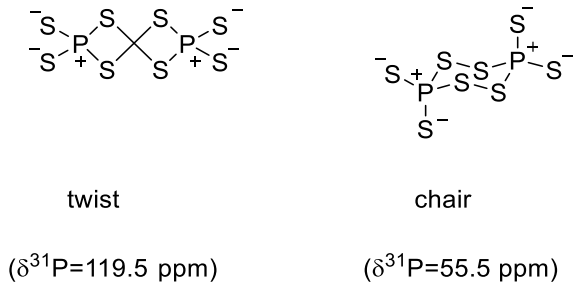


Figure 2.2 Two conformers of $P_2S_8^{2-}$ explored by Karaghiosoff[65]

On the other hand, following Svensson's original method resulted in the formation of light yellow needles in the reaction mixture. Following filtration, these needles were analyzed by ^{31}P NMR spectroscopy (Figure 2.3). This analysis revealed a cleaner P_2S_5-Py_2 reagent, although three significant side-products were still observed. Nevertheless, this reagent was successfully used in the thionation reactions (*vide infra*).

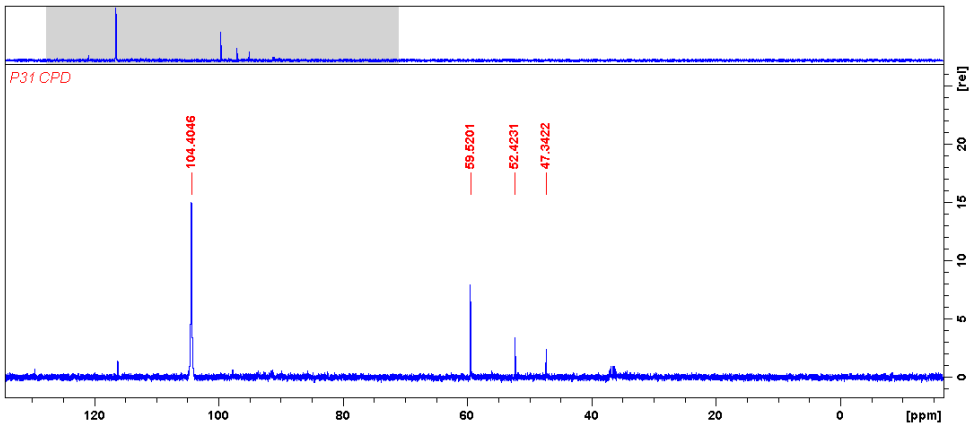


Figure 2.3 ^{31}P NMR spectrum of P_2S_5-Py_2 obtained from Svensson's procedure

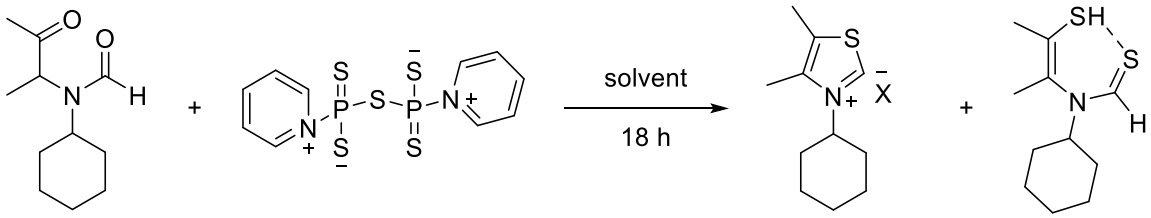
2.2.2 Reaction optimization

2.2.2.1 Solvent selection

As mentioned by Svensson,[53] the transformation of carbonyl groups into thiocarbonyl groups by P_2S_5-Py_2 (**30**) is commonly performed with pyridine or acetonitrile as solvent, both of which are miscible with water. However, this could complicate purification because of an inefficient removal of both organic-soluble and water-soluble impurities and because the desired thiazolium salts cannot generally be purified using column chromatography. Accordingly, a screening of solvents was conducted to identify suitable conditions for the thionation of α-formamido ketone **48b** (Table 2.3). The results using pyridine as the solvent showed that increasing the temperature helped convert the thionated intermediate to the final product (entries 1-2). However, a complex mixture was observed in both cases and only a low yield of the desired thiazolium salt was obtained. Attempted purification by crystallization or chromatography was unsuccessful. The use of acetonitrile as solvent resulted in a complete conversion of an as-yet unidentified thionated intermediate into the thiazolium salt, although the yield remained low (entry 3). Toluene was then selected with the hope that it would be able to dissolve most organic side-products formed during the reaction, while the less soluble thiazolium salt would form a precipitate. Gratifyingly, this hope was realized and a thiazolium-containing precipitate was obtained. Remarkably, the

pure product **61b** could be isolated by filtration, followed by dissolution in warm water, addition of $NaBF_4$, and extraction with CH_2Cl_2. Further details on this purification method are provided in section 2.2.2.2. This procedure resulted in a dramatically increased 70% yield (entry 4). For this reaction, the toluene-soluble portion of the reaction mixture was concentrated and analyzed by ^1H NMR spectroscopy. This analysis revealed the previously observed thionated intermediate to be a di-thionated species (**62**), although it is not clear if double thionation represents the main pathway toward thiazolium formation.

Table 2.3 Solvent optimization for the synthesis of thiazolium salt with P_2S_5-Py_2[a]



48b **30** **61b** **62**

entry	solvent	concentration (M)[b]	temperature (°C)	**61b**:**62**[c]	yield (%)[d]
1	pyridine	0.3	22	0.6:1	10
2	pyridine	0.3	115	100:0	5
3	acetonitrile	0.3	85	100:0	25
4	toluene	0.3	110	9:1	70

[a] P_2S_5-Py_2 (1 equiv.) and α-formamido ketone (1 equiv.) **48b** were stirred in the indicated solvent for 18 hours, followed by concentration *in vacuo*. [b] Concentration of α-formamido ketone. [c] Ratio of product **61b** to intermediate **62**, as determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Yield of **61b** was determined by ^{1}H NMR analysis of the crude reaction mixture with TCE as internal standard. [e] Isolated yield following filtration, dissolution of the precipitate in warm water, addition of $NaBF_4$ (3 equiv.), extraction with CH_2Cl_2, and concentration *in vacuo*.

The ^{1}H NMR spectrum of the unpurified di-thionated species **62** is shown in Figure 2.4. The large downfield shift of the thioformamide signal at 9.44 ppm is clear evidence that the formamide moiety underwent thionation, as this signal appeared at 8.20 ppm in the starting material. The evidence for thionation of the ketone moiety is visible from the broad signal at 5.80 ppm, which is presumably due to the hydrogen-bonded S-H.[66, 67]

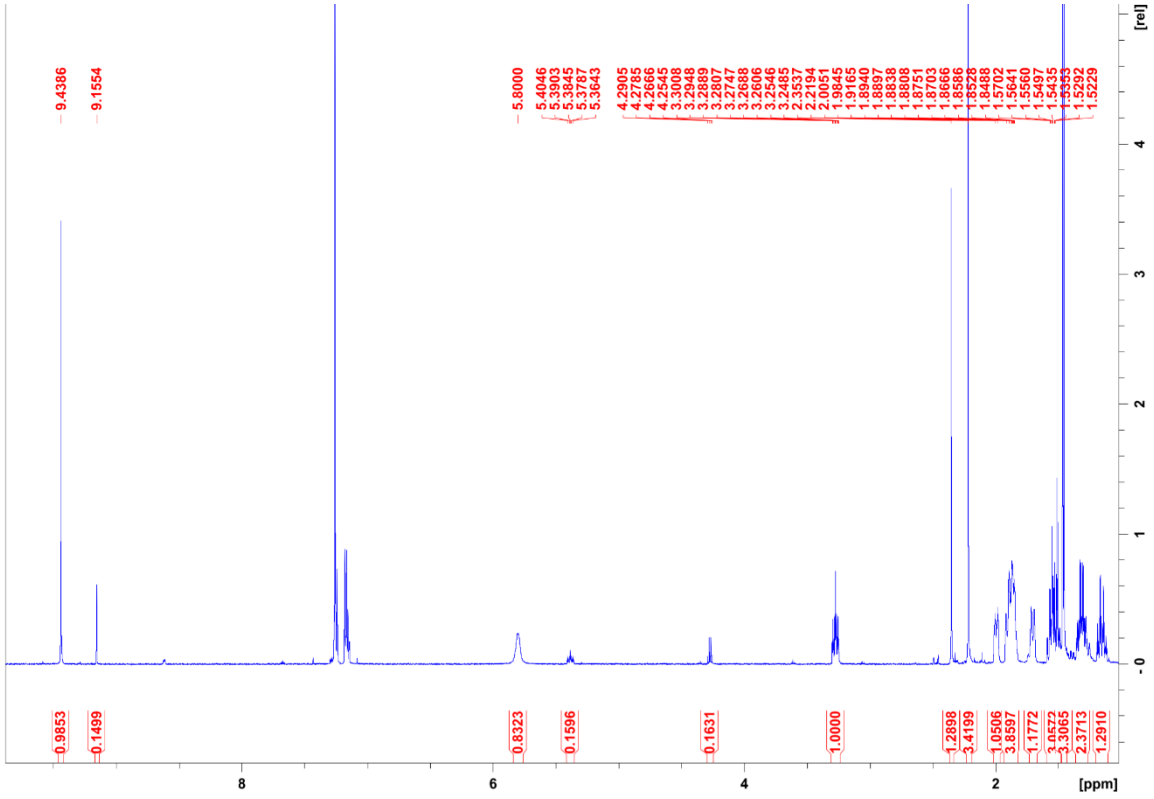
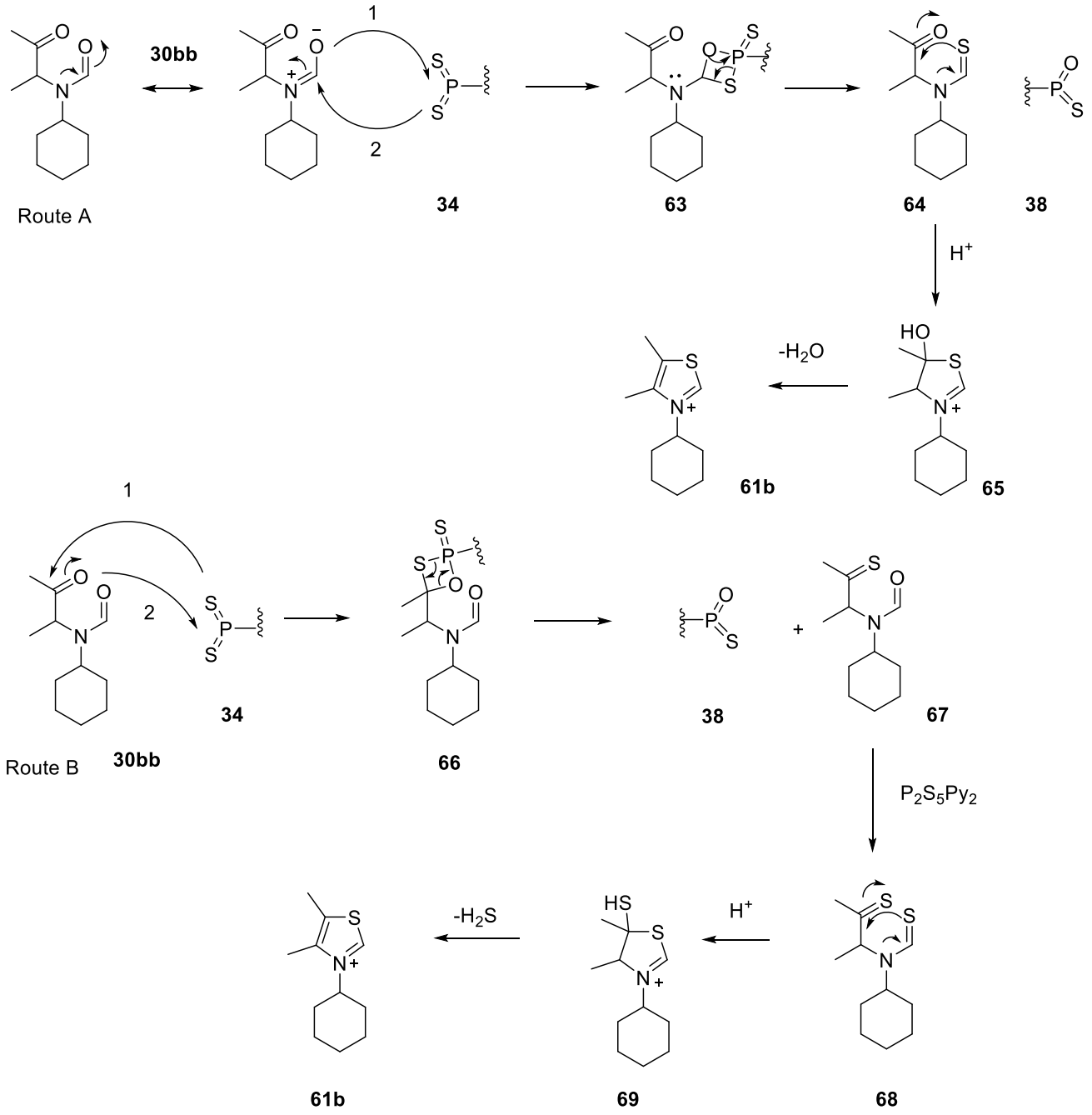


Figure 2.4 ^{1}H NMR spectrum of the unpurified dithionated species **62**

The significance of this di-thionated species is not clear. As shown in Scheme 2.7, both the mono-thionated intermediate **64/67** and the di-thionated species **68** could lead to the desired thiazolium salt. Nevertheless, the search for optimal conditions toward thiazolium synthesis was continued.

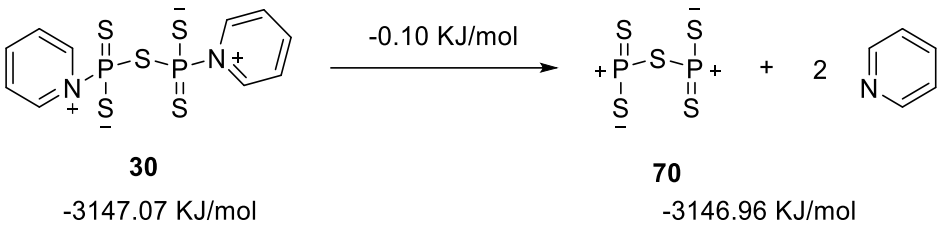


Scheme 2.7 Possible mechanisms for formation of thiazolium salt

2.2.2.2 Purification method

After determining that the precipitate from the reaction mixture contained the desired thiazolium salt, purification was the next difficulty (Table 2.3). Recrystallization attempts using two-solvent systems either failed to form any crystals or did not result in the removal of impurities. After much experimentation, it was determined that a precipitate would form from the reaction mixture without addition of $NaBF_4$. Following filtration, this precipitate could be slowly dissolved in warm water (65 °C). Any insoluble impurities could be removed by filtration at this step. The thiazolium salt could then be removed from the aqueous layer by addition of $NaBF_4$ and extraction using CH_2Cl_2, resulting in a pure product **61b** in 70% yield. It should be noted that using boiling water during the dissolution would result in the final product being contaminated with large amounts of P_2S_5-Py_2 or a related by-product.

Surprisingly, small amounts of the contaminants could be removed from the product by dissolving the mixture in hot hexanes followed by concentration under reduced pressure while hot. This observation could be related to a computational study conducted by Karaghiosoff's group.[68] In that study, the products resulting from the dissociation of P_2S_5-Py_2 (**30**) were found to have a similar enthalpy as that of the starting material (Scheme 2.8). At elevated temperature, a rapid equilibrium could be formed between these species, and both P_2S_5 (**70**) and pyridine could be removed due to their volatility, unlike the solid P_2S_5-Py_2 (**30**). Another, simpler explanation may be that some of the impurities decompose and release pyridine when exposed to boiling water. This pyridine would be extracted in the organic layer along with the thiazolium salt and contaminate the final product. Co-evaporation using hot hexanes would be sufficient to remove it.

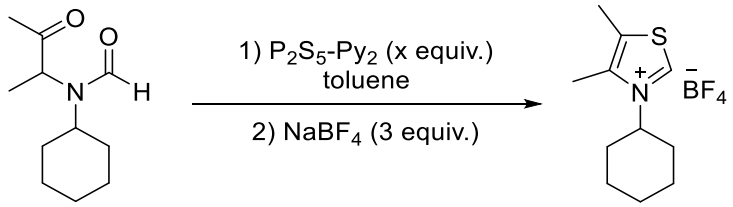


Scheme 2.8 Enthalpies of P_2S_5-Py_2 and P_2S_5/Py at the CBS-4M//MPW1PW91/aug-cc-pVTZ level, as calculated by Karaghiosoff's group

2.2.2.3 Optimization of temperature, P_2S_5-Py_2 loading, and reaction time

Optimal reaction conditions were determined by varying the temperature, the P_2S_5-Py_2 loading, and the reaction time (Table 2.4). Employing lower temperatures (entries 1-2) or a higher oil bath temperature (entry 4) did not improve the isolated yield relative to the initially employed temperature (entry 3). Although it is difficult to gain much insight due to the complex heterogeneous mixtures obtained, it was presumed that lower temperatures resulted in incomplete cyclization. On the other hand, the higher temperature led to a more complex mixture and this may be due to the P_2S_5-Py_2 starting to decompose at elevated temperatures.

Table 2.4 Optimization of temperature, P_2S_5-Py_2 loading, and reaction time



48b **61b**

entry	temperature (°C)	time (h)	P_2S_5-Py_2 loading (equiv.)	yield (%)[a]

1	90	18	0.6	34
2	100	18	0.6	50
3	110	18	0.6	70
4	130	18	0.6	31
5	110	4	1	62
6	110	4	2	69
7	110	4	3[b]	76
8	110	4	3	82
9	110	1	3	59
10	110	2	3	88
11	110	6	3	83

[a] yield of isolated, pure product. [b] Added in three portions.

To determine whether an increased amount of P_2S_5-Py_2 would result in an improved yield, the reaction was performed with 1-3 equivalents of the reagent (entries 5-8). To gain further insight into the transformation, an aliquot of the toluene-soluble portion of the reaction mixture was analyzed by ^{1}H NMR spectroscopy. Using 2 equivalents of P_2S_5-Py_2 resulted in a somewhat higher isolated yield of thiazolium salt **61b** compared to the use of 1 equivalent (entries 5-6). In both cases, the acyclic intermediate **64**/**67** was still present in solution after 4 hours. It is not clear whether the presence of additional P_2S_5-Py_2 increases the rate of formation of the acyclic intermediate, or of the cyclization step, or both.

In the next experiment, 3 equivalents of P_2S_5-Py_2 complex was added in 3 portions, with ^1H NMR analysis of an aliquot after each addition. As expected, the acyclic intermediate **64**/**67** was still present in mixture after the first two portions were added. Nevertheless, more precipitate was observed after the second addition. Upon addition of the third and final portion, the transformation of the α-formamido ketone to the final product was complete, resulting in an improved yield (entry 7). These studies also established that extended reaction time is not required to achieve a good conversion to the final product.

The reaction time was then reduced further. A short time of only 1 hour resulted in a noticeably lower yield (entry 9). Based on this, the reaction time was extended to 2 and 6 hours, respectively. The reaction was completed quickly within 2 hours, resulting in the highest yield of 88% (entry 10), whereas a longer reaction time caused a slight decrease in yield (entry 11).

In conclusion, the optimized reaction conditions and purification technique to synthesize thiazolium salts from α-formamido ketones precursors was established as the following:

1) The α-formamido ketone is stirred with 3 equivalents of P_2S_5-Py_2 complex in toluene at 110 °C for 2h hours.

2) The precipitate containing the thiazolium salt is separated by filtration.

3) The residue is dissolved in warm water (65 °C) for at least 10 minutes, then any insoluble residue is removed by filtration.

4) $NaBF_4$ (3 equiv.) is added to the filtrate, the aqueous solution is extracted with CH_2Cl_2, and the combined organic layers are then dried over Na_2SO_4 and concentrated *in vacuo*.

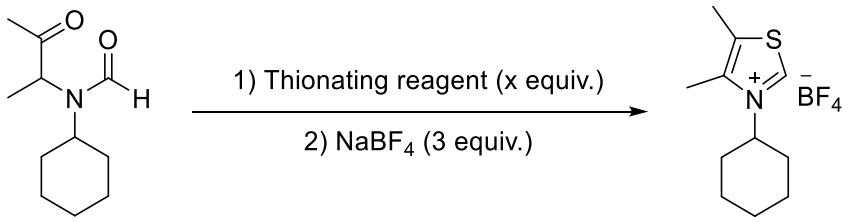
5) If small amounts of P_2S_5-Py_2 or other P_2S_5 derivatives are present, they could be removed by stirring the product in hot hexane for 5 minutes, followed by concentration *in vacuo*.

Although it was satisfying to invent a process for the reliable synthesis and purification of thiazolium salt **61b**, it was quickly realized that modifications were often required to obtain acceptable yields of pure product when other thiazolium salts were targeted.

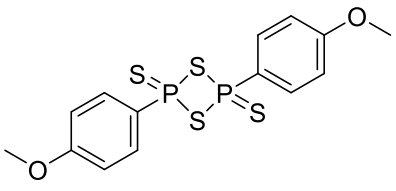
2.2.3 Comparison between Lawesson's reagent, P_4S_{10}, and P_2S_5-Py_2

Lawesson's reagent and P_4S_{10} are the most common reagents used to synthesize thiocarbonyl compounds. In order to figure out the advantages and disadvantages of each reagent and their potential application in the synthesis of thiazolium salts, a direct comparison between these reagents and P_2S_5-Py_2 was performed on the test substrate **61b** (Table 2.5).

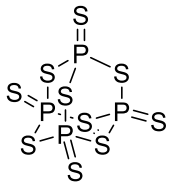
Table 2.5 Comparison between Lawesson's reagent, P_4S_{10}, and P_2S_5-Py_2[a]



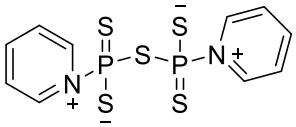
48b **61b**



28



29



30

entry	thionating reagent	loading (x)	solvent	time (min)	temperature (°C)	yield (%)

1	**28**	1	THF	120	22	<5[a]
2	**28**	1	-	5	250	18[a]
3	**28**	1	toluene	120	110	72[a]
4	**29**	1	toluene	120	110	68[b]
5	**30**	1	toluene	240	110	62[b]

[a] Yield determined by ^{1}H NMR analysis of the crude reaction mixture with TCE as internal standard. [b] Isolated yield

The use of Lawesson's reagent resulted in a low yield with the most commonly used solvent THF at room temperature (entry 1). Seed's group revealed a route to synthesize 1,3-thiazoles from 1,4-dicarbonyl compounds with Lawesson's reagent under microwave heating, resulting in up to 93% yield within minutes.[69] Subjecting substrate **48b** to these conditions resulted in a low yield of the thiazolium salt, but a significant amount of the mono-thionated intermediate was detected in the reaction mixture (entry 2). Ironically, the conversion to the desired thiazolium salt could be increased dramatically using conditions similar to those optimized earlier for the P_2S_5-Py_2 complex (entry 3). However, it proved difficult to purify the product due to the presence of undetermined side-products and chromatography proved necessary. After a quick test with 2D TLC and an attempt at using aluminum oxide, it was evident that the desired thiazolium salt was decomposing during chromatography.[70] Thus, Lawesson's reagent shows a distinct disadvantage for the purpose of synthesizing thiazolium salts. The use of P_4S_{10} also resulted in a similar conversion to that obtained when using P_2S_5-Py_2, although the product could be more easily purified in those cases (entries 4-5).

2.2.4 Scope of the thionation/cyclization reaction

With the optimal reaction conditions in hand, the scope was explored using various *N*-substituted α-formamido ketones (Table 2.6). The results using the P_2S_5-Py_2 complex were contrasted with those under similar conditions but using P_4S_{10}. Although the two sets of conditions did not use the same stoichiometry with respect to sulfur (15 S equivalents for P_2S_5-Py_2 and 10 S equivalents for P_4S_{10}), the results nevertheless provide a qualitatively useful comparison. The *N*-propyl thiazolium salt **61a** was firstly synthesized in good yield using P_2S_5-Py_2, showing unbranched *N*-alkyl substituents are well tolerated (entry 1). The use of P_4S_{10} resulted in a much lower yield. In these cases, extraction into the organic layer proved more effective using $NaBPh_4$ instead of $NaBF_4$. However, the $NaBPh_4$ salt is somewhat soluble in CH_2Cl_2 and only one equivalent was used in order to avoid this salt contaminating the final product following extraction. Use of a stoichiometric amount of $NaBPh_4$ may have limited the yields ultimately obtained. All other substrates tested featured larger *N*-substituents and extraction of the BF_4^- salt proved efficient, obviating the use of $NaBPh_4$.

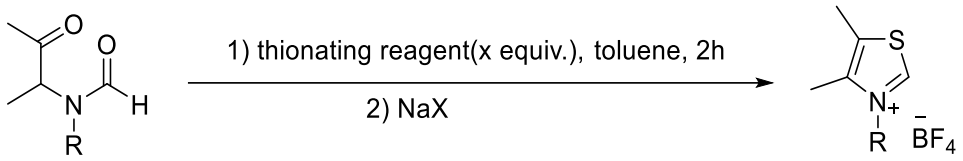
As previously mentioned, the *N*-Cy thiazolium **61b** was obtained in an excellent yield of 88% (entry 2). The use of P_4S_{10} also led to a good yield in this case. Substrates featuring benzylic *N*-substituents, both branched and unbranched, led to the desired product in modest yield (entries 3-4). This also showed that chiral thiazolium salts bearing a stereogenic center close to the catalytic site could be synthesized, although the use of P_4S_{10} proved more efficient in that case. Gratifyingly, a substrate featuring the very bulky *N*-adamantyl substituent performed well with both P_2S_5-Py_2 and P_4S_{10} (entry 5). In contrast, the use of another substrate bearing a tertiary *N*-substituent (**61j**) did not furnish the desired product (entry 6). This result suggests the incompatibility of unprotected alcohols with the thionation/cyclization reaction.

In addition to *N*-alkyl substituents, the thiazolium synthesis proved tolerant to *N*-aryl substituents. Indeed, reactions with substrates bearing *N*-Ph as well as the bulky *N*-mesityl and the electron-rich *N*-(4-$MeOC_6H_4$) delivered the desired products in satisfactory yields using both reagents (entries 7-9). Unfortunately, a substrate featuring the very electron-

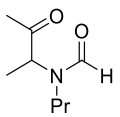
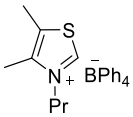
poor *N*-C_6F_5 substituent proved unreactive to the P_2S_5-Py_2 reagent and instead underwent decomposition over extended reaction time (entry 10). The P_4S_{10} reagent proved better suited to this substrate, furnishing the thiazolium salt in modest yield.

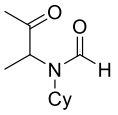
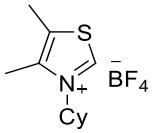
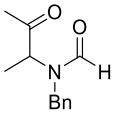
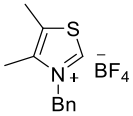
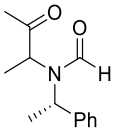
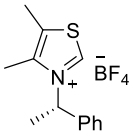
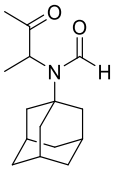
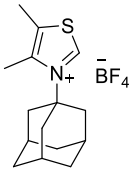
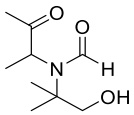
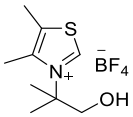
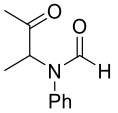
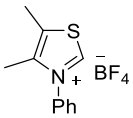
Next, substrates derived from 2-bromocyclohexanone were tested in the thionation/cyclization reaction. Surprisingly, the substrates featuring the previously well-tolerated *N*-Cy substituent failed to deliver any thiazolium product using either P_2S_5-Py_2 or P_4S_{10} (entry 11). It is possible that steric hindrance plays a role in this disappointing result. On the other hand, the corresponding *N*-Ph substrate behaved as expected with both thionation reagents (entry 12). In contrast, the bulkier *N*-Mes substrate failed to undergo the desired reaction, perhaps again due to increased steric hindrance between the *N* substituent and the cyclohexyl moiety (entry 13).

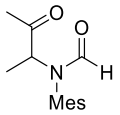
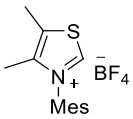
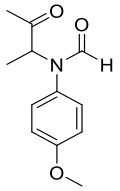
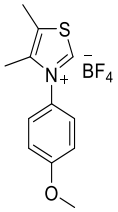
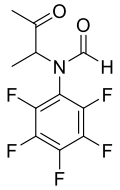
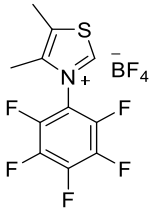
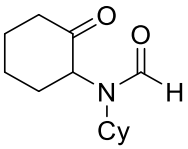
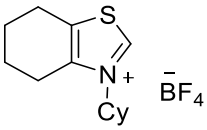
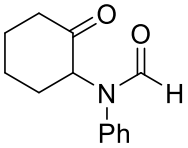
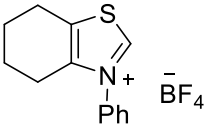
Table 2.6 Scope of the Synthesis of Thiazolium Salts Using P_2S_5-Py_2 Complex (3 equiv.) and P_4S_{10} (1 equiv.) in Toluene at 110 ℃ for 2 h

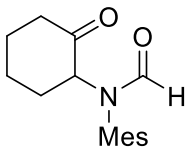
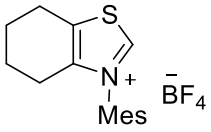


48a-m **61a-m**

entry	substrate	product	yield using P_2S_5-Py_2 (%)[a]	yield using P_4S_{10} (%)[a]
1	**48a** 	**61a** 	57	29
2	**48b**	**61b**	88	68

				
3	**48g** 	**61g** 	42	n.d.
4	**48e** 	**61e** 	36	69
5	**48h** 	**61h** 	67	63
6	**48j** 	**61j** 	0	0
7	**48d** 	**61d** 	52	54
8	**48c**	**61c**	55	70

				
9	**48f** 	**61f** 	33	72
10	**48i** 	**61i** 	0	30
11	**48k** 	**61k** 	0	0
12	**48l** 	**61l** 	54	79
13	**48m**	**61m**	0	0

				
[a] yield of isolated pure product				

2.3 Conclusions

The study described in this chapter details the successful synthesis of 10 thiazolium salts out of the 13 that were initially targeted. Despite low overall yields in some cases, the generality of the *N*-formylation/thionation/cyclization of α-amino ketones was demonstrated. The concise route was suitable for synthesizing thiazolium salts containing aliphatic, aromatic, hindered, unhindered, chiral, and achiral *N*-substituents. Exploration of the scope revealed that both P_2S_5-Py_2 and P_4S_{10} are competent reagents for the key thionation/cyclization step.

In the process, a purification method was developed for isolating the thiazolium salt formed in the presence of the P_2S_5-Py_2 reagent.

Chapter III

RESULT AND DISCUSSION PART II: Application of Thiazolium Precursors in Intermolecular Stetter Reactions

3.1 Research objective

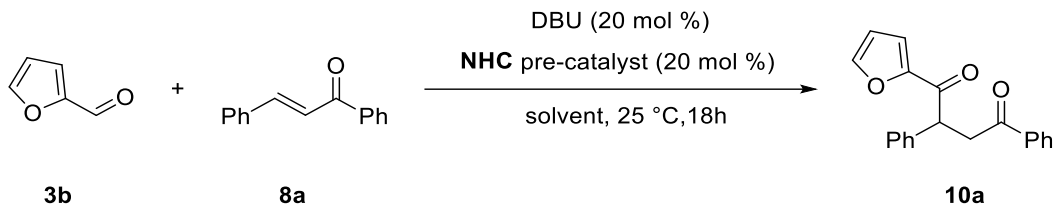
With a variety of NHC-precursors in hand, the next objective was to determine their catalytic activity in the intermolecular Stetter reaction. The most efficient pre-catalyst determined in that survey would then be used to study its generality using various aldehydes in their Stetter reaction with chalcone as a standard acceptor.

3.2 Development of intermolecular Stetter reaction

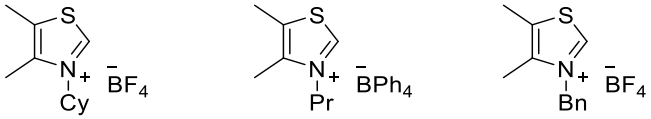
3.2.1 Optimization of the reaction solvent

A screening of solvents was conducted to identify suitable conditions for the intermolecular Stetter reaction catalyzed by thiazolium salts **61a**, **61b**, and **61g** (Table 3.1). The use of THF, toluene and diethyl ether led to no or only a trace amount of Stetter product (entries 2-5, 7, 9), while that of the alcoholic solvent methanol resulted in a solidified mixture which may have been formed from a polymerization event (entry 4). Compared with other solvents, the use of dichloromethane resulted in a higher yield with all three catalysts (entry 1,6,8), and it was selected as the optimal solvent for further optimization.

Table 3.1 Optimization of reaction solvent with different thiazolium pre-catalysts and chalcone. [a]



3b **8a** **10a**



61b **61a** **61g**

entry	NHC-precatalyst	solvent	yield (%) [b]
1	**61b**	CH_2Cl_2	< 5 [c]
2	**61b**	THF	0
3	**61b**	toluene	0
4	**61b**	MeOH	0
5	**61b**	ether	0
6	**61a**	CH_2Cl_2	< 5 [c]
7	**61a**	toluene	0
8	**61g**	CH_2Cl_2	18
9	**61g**	toluene	< 5 [c]

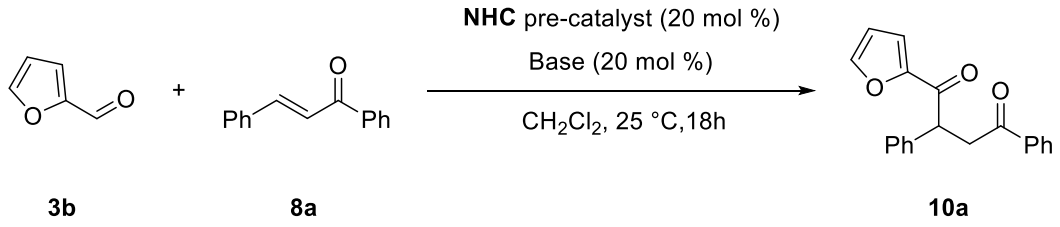
[a] DBU (20 mol %), chalcone **8a** (0.05 mmol), aldehyde **3b** (0.06 mol), pre-catalyst **61a**, **61b**, or **61g** (20 mol %). [b] Isolated yield. [c] Yield of **10a** was determined by ^{1}H NMR analysis of the crude reaction mixture with TCE as internal standard.

3.2.2 Optimization of base

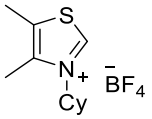
To determine which base would result in an improved yield, the most commonly used bases DIPEA and DBU were employed in the intermolecular Stetter reaction catalyzed by thiazolium salts **61b** and **61g** (Table 3.3).

Using catalytic amounts of DIPEA, the reactions were found inefficient, resulting in low yield (entries 3, 9). No desired product was observed after increasing the DIPEA loading (entries 4, 10). On the other hand, DBU could afford an improved yield (entries 1, 5) when used in catalytic amounts. Increasing the loading of DBU did not result in significant improvements (entries 2, 6). Finally, the reaction time could be reduced down to 3h without a deleterious effect on the yield (entries 7, 8).

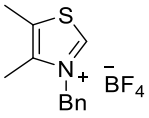
Table 3.2 Optimization of reaction base with *N*-Bn and *N*-Cy thiazolium pre-catalysts and chalcone [a]



3b **8a** **10a**



61b



61g

entry	NHC- precatalyst	time (h)	base	yield (%) [b]
1	**61b**	18	DBU(20 mol %)	< 5 [c]
2	**61b**	18	DBU(30 mol %)	0
3	**61b**	18	DIPEA(20 mol %)	0
4	**61b**	18	DIPEA(100 mol %)	0
5	**61g**	18	DBU(20 mol %)	18
6	**61g**	18	DBU(100 mol %)	20
7	**61g**	1	DBU(20 mol %)	6
8	**61g**	3	DBU(20 mol %)	19
9	**61g**	18	DIPEA(20 mol %)	< 5 [c]
10	**61g**	18	DIPEA(100 mol %)	< 5 [c]

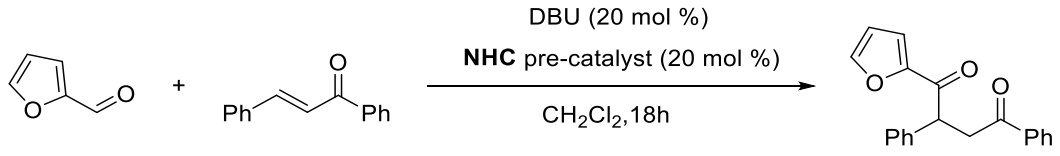
[a] Chalcone **8a** (0.05 mmol), aldehyde **3b** (0.06 mmol), NHC-precatalysts **61b** or **61g** (20 mol %). [b] Isolated yield. [c] Yield was determined by ^{1}H NMR analysis of the crude reaction mixture with TCE as internal standard.

3.2.3 Scope of the reaction

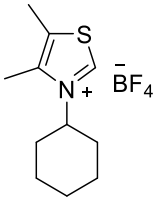
With optimal reaction conditions in hand, the scope was explored using various NHC pre-catalysts (Table 3.3). As determined previously, using *N*-Cy thiazolium carbene resulted in a relatively low yield (entry 1). No increase of yield was observed when the counterion was changed from BF_4^- to BPh_4^- (entry 2). On the other hand, increasing the reaction temperature to 45 °C with *N*-Bn thiazolium salt resulted in a dramatically increased 89% yield (entry 3-4). The use of **61a** or **61c** resulted in moderate yield (entries 5, 6). However, the use of pre-catalysts bearingstrongly electron-rich or electron-deficient *N*-substituents (**61f**, **61i**) did not furnish the desired product at all (entries 7, 8). The use of *N*-phenyl substituted thiazolium precursor **61d** only led to a trace amount of the desired product (entry 9). As using *N*-Cy thiazolium salts led to unsatisfactory yields (entries 1, 2), it is possible that steric hindrance obstructed the generation of the Breslow intermediate. This hypothesis is consistent with the observation that when a pre-catalyst bearing an *N*-adamantyl substituent was employed, it did not furnish the desired final product (entry 10).

Under the optimal reaction conditions, the *N*-Bn thiazolium salt **61g** was observed to be the most efficient pre-catalyst among all thiazolium salts for the intermolecular Stetter reaction.

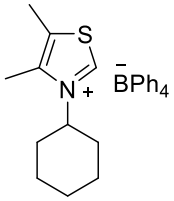
Table 3.3 Screen of pre-catalysts under optimized conditions [a]



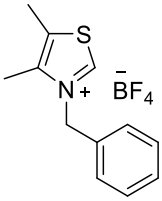
3b **8a** **10a**



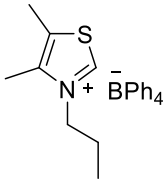
61b



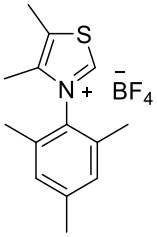
61b (BPh_4)



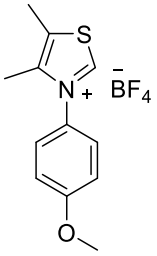
61g



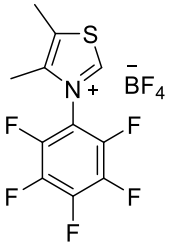
61a



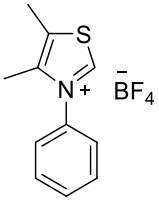
61c



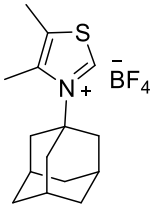
61f



61i



61d



61h

entry	NHC-precatalyst	temperature (℃)	yield(%)
1	**61b**	25	5
2	**61b (BPh_4)**	25	< 5 [c]
3	**61g**	25	22
4	**61g**	45	89
5	**61a**	25	11
6	**61c**	25	22
7	**61f**	25	0
8	**61i**	25	0
9	**61d**	25	< 5 [c]

10	**61h**	25	0

[a] DBU (20 mol %), chalcone **8a** (0.065 mmol), furfural **3b** (0.06 mmol), NHC-precatalysts (20 mol %). at 25 ℃ to 45 ℃ for 3h. [b] isolated yield. [c] Conversion was determined by ^{1}H NMR analysis of the crude reaction mixture with TCE as internal standard.

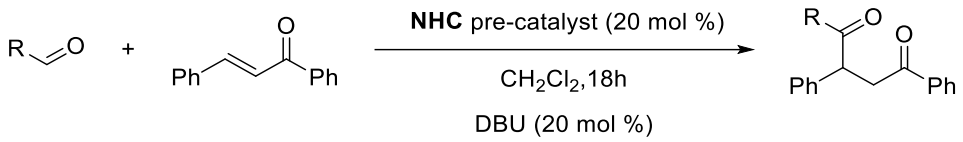
3.2.4 Scope of aldehyde

With the selected thiazolium salt **61g** in hand, the scope of the intermolecular Stetter reaction was further explored using various aldehydes. Although not as efficient, the results using the easily available thiazolium salts **61b**, and **61d** are also provided for comparison purposes (Table 3.4).

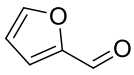
Reactions with furfural afforded an excellent yield with the optimal pre-catalyst **61g**, but low yields with the other two thiazolium salts even at 45 ℃ (entries 1-3). The use of benzaldehyde did not furnish the desired product with any of the three thiazolium salts (entries 4-6). The use of the more electron-poor aldehyde methyl 4-formylbenzoate with *N*-Bn thiazolium **61g** delivered the desired product in moderate yield (entry 7). However, no desired product was observed in the reaction of methyl 4-formybenzate with *N*-Cy thiazolium **61b** and only a low yield was obtained with *N*-Ph thiazolium **61d** (entries 8-9).

Based on this initial survey, the use of the aromatic aldehyde bearing an electron-withdrawing group (**3d**) afforded a higher yield than the reaction utilizing benzaldehyde **3c**. This is fully consistent with prior observations in our group, as is the observation that furfural was found to be the most efficient aldehyde.

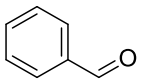
Table 3.4 Scope of aldehyde in the intermolecular Stetter reactions with chalcone[a]



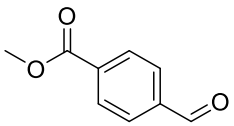
3 **8a** **10a-c**



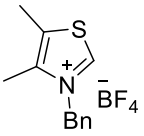
3b



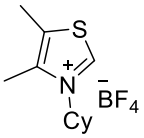
3c



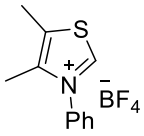
3d



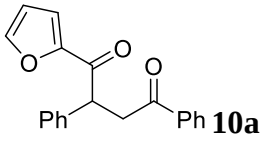
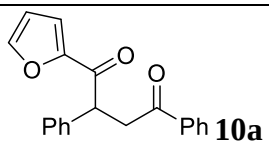
61g

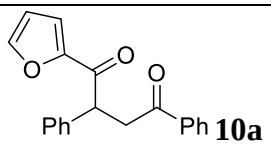
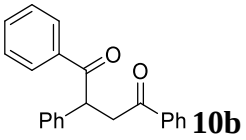
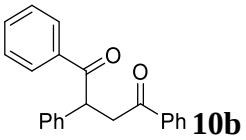
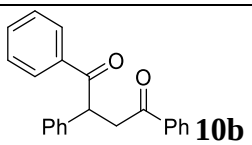
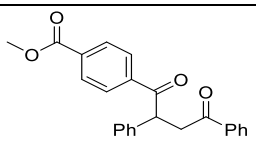
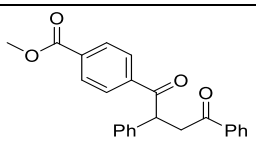
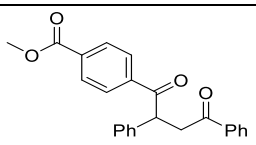


61b



61d

entry	aldehyde	pre-catalyst	temperature (°C)	product	yield (%)[b,c]
1	**3b**	**61g**	45	 **10a**	89
2	**3b**	**61b**	45	 **10a**	5

3	**3b**	**61d**	45	 **10a**	5
4	**3c**	**61g**	25	 **10b**	0
5	**3c**	**61b**	25	 **10b**	0
6	**3c**	**61d**	25	 **10b**	0
7	**3d**	**61g**	25	 **10c**	35
8	**3d**	**61b**	25	 **10c**	0
9	**3d**	**61d**	25	 **10c**	< 5

[a] DBU (20 mol %) chalcone **8a** (1.0 equiv.), aldehyde **3** (1.2 equiv.), NHC-precatalyst **61g, 61b, 61d** (20 mol %.). [b] Isolated yield. [c] Yield was determined by ^{1}H NMR analysis of the crude reaction mixture with TCE as internal standard.

3.3 Conclusion

The intermolecular Stetter reaction with various achiral thiazolium salts and chalcone as Michael acceptor was explored. The pre-catalyst **61g** bearing an *N*-Bn substituent proved to be the most efficient for this reaction. The scope of aldehyde proved fairly limited in this preliminary study. Further exploration is warranted to determine the suitability of these pre-catalysts in intermolecular Stetter reactions.

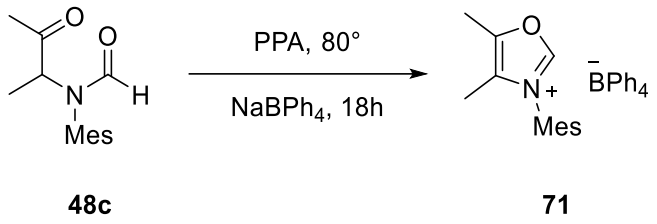
CHAPTER IV

CONCLUSIONS AND FUTURE WORK

In this thesis, a new method for synthesizing thiazolium salts from simple starting materials was investigated. The key step involved the use of P_2S_5-Py_2 complex as a thionation reagent in the final cyclization. The results obtained with this reagent were mixed. Indeed, the yields obtained were superior to those obtained with other, more common thionation reagents in some cases, but lower yields were obtained for some substrates. Nevertheless, it was found that purification of the thiazolium salts was facilitated in all cases. This aspect proved quite important as column chromatography on silica gel, a purification technique commonly employed in organic synthesis, proved unsuitable for thiazolium salts.

A variety of thiazolium salts that were made easily accessible using the P_2S_5-Py_2 complex were then used in a model intermolecular Stetter reaction. Although the results did not point toward any groundbreaking direction for this reaction, the ability to rapidly screen a large number of thiazolium salts was made evident through this limited study.

With a synthetic route and our experience preparing thiazolium salts, the Gravel group applied this knowledge to the synthesis of related oxazolium salts (Scheme 4.1).[25] The oxazolium pre-catalysts proved very efficient compared to thiazolium catalysts, but the study of their properties and applications are pretty limited at present. After screening by V K. Garapati, the *N*-mesityl oxazolium salt **71** catalyzed umpolung reactions in high yield, including benzoin and Stetter reactions. Inspired by this result, we hope to isolate the corresponding oxazole-2-ylidene (the carbene catalyst) and its olefin dimer. Such isolation would allow a more thorough understanding of its bonding, catalyst reactivity and structural characteristics.



48c **71**

Scheme 4.1 Synthesis route of oxazolium precatalyst by Venkata

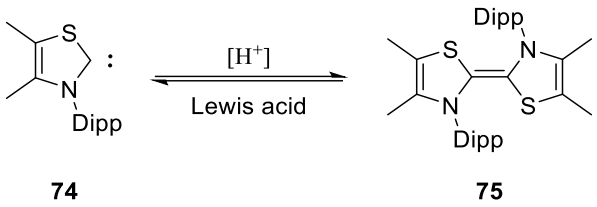
In 1991, Arduengo and his coworkers published the synthesis route of isolate imidazol-2-ylidenes, which can be stable at ambient temperature under an inert atmosphere (Figure 4.1).[71] After several years, they isolated and characterized the stable thiazol-2-ylidene **74** and its dimer **75** for the first time in 1997 (Scheme 4.2).[72] They obtained four critical conclusions. Firstly, isolable thiazol-2-ylidenes are only stable in a strictly anaerobic and anhydrous environment, and they are less stable than imidazol-2-ylidenes. Secondly, the increased steric hindrance on the nitrogen atom can increase the stability of singlet carbenes. Thirdly, NMR spectroscopy on imidazol-2-ylidene, imidazolin-2-ylidene, and thiazol-2-ylidene indicate the latter's carbene center is shifted downfield, which shows decreased π donation from the nitrogen atom to the C_2 carbene center. Fourth, they also synthesized the olefin dimer of thiazol-2-ylidene successfully, forming under acid catalyst from carbene and dissociating back to carbene under Lewis acid. [72]

72 **73**

imidazol-2-ylidenes
Arduengo (1991)

thiazole-2-ylidenes
Arduengo (1997)

Figure 4. 1 stable carbene isolated by Arduengo group



74 **75**

Scheme 4.2 The reversible dimerization of a thiazol-2-ylidene

The isolation and structural investigation of *N*-heterocyclic carbenes in the form of imidazol-2-ylidenes, thiazol-2-ylidenes, and triazolylidenes[73] has been accomplished. However, no oxazolylidene has been isolated yet.

In 2013, Nyulászi's group compared the properties of oxazol-2-ylidene with other stable carbenes by computational study. As they found, the electrophilicity of oxazol-2-ylidenes is slightly higher than that of imidazol-2-ylidenes, while thiazol-2-ylidenes have the highest electrophilicity. On the other hand, the nucleophilicity of oxazol-2-ylidenes is much less than that of imidazol-2-ylidenes.

Their conclusions are based purely on theoretical calculations and suggest further experimental investigation of oxazol-2-ylidenes. We hope to use the computational study to design a series of potential stable carbenes and experiments to prove its properties and reactivities in the future work. Moreover, the results will be compared with those for imidazol-2-ylidenes, thiazol-2-ylidenes and triazol-2-ylidenes, which have been published. The objective is to increase the number of carbene options available, and further study the stability of oxazolylidenes and their reactivity in umpolung reactions.

Based on our results and on extensive investigations in the field, it is known that the substitution on nitrogen plays an important role in the stabilities of *N*-heterocyclic carbenes. For example, the less sterically hindered *N*-substituents allow the formation of the olefin dimer for thiazol-2-ylidenes.[72] Accordingly, we plan to compare the catalytic activity of the extremely hindered *N*-adamantyl oxazolium salts with that of the previously reported *N*-mesityl oxazolium salt.

CHAPTER V

EXPERIMENTAL SECTION

5.1 General method

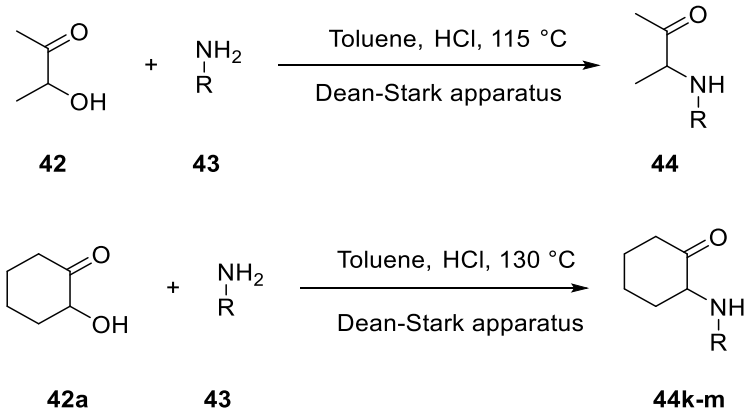
Anhydrous solvents including CH_2Cl_2, Toluene, THF, diethyl ether, MeOH were distilled using a Braun Solvent Purification System and stored under nitrogen over 3 Å molecular sieves. Pyridine and acetonitrile were purified by refluxing with CaH_2 for 2h followed by distillation. The other commercially available reagents, including DBU, DIPEA, furfural and benzaldehyde, were purified by distillation in a Büchi Glass Oven B-585.

Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F_{254} and was visualized with UV light and iodine, ninhydrin or $KMnO_4$. Silica gel 60 (40-63 mm) used for column chromatography was purchased from Silicycle Chemical Division. NMR spectra were measured in $CDCl_3$ or DMSO-d_6 at 500 MHz or 600 MHz for ^1H and 125 MHz for ^{13}C. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards for chemical shifts: $CDCl_3$ (7.26 ppm ^1H, 77.23 ppm ^{13}C); DMSO-d_6 (2.50 ppm ^1H, 39.51 ppm ^{13}C); Pyridine-d_5 (8.74 ppm, 7.58 ppm, 7.22 ppm ^1H, 150.35 ppm, 135.91 ppm, 123.87 ppm ^{13}C). High-resolution mass spectra (HRMS) were obtained on a VG 70E double focusing high resolution spectrometer. EI ionization was accomplished at 7 eV and Cl at 50 eV with ammonia as the reagent gas. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. Unless otherwise stated, all samples were prepared as a film on a KBr pellet for IR analysis. For some of the reactions, the yield was determined by ^1H NMR with trichloroethylene (TCE) as an internal standard.

5.2 Experimental procedures for the synthesis of thiazolium precursors

5.2.1 General procedure for the preparation of α-acylamino ketones

Preparation of α-amino ketone



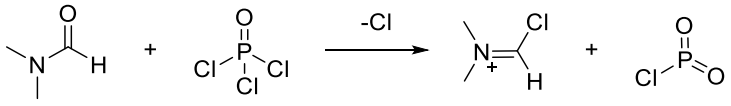
42 **43** **44**

42a **43** **44k-m**

Scheme 5. 1 Preparation of α-amino ketone

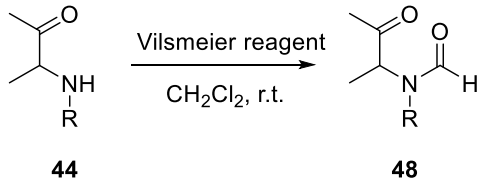
The appropriate amine (9.5 mmol) and α-hydroxy ketone (1.0 g, 11.4 mmol) were stirred in toluene (31.5 mL) at reflux temperature for 6 h with a Dean-Stark apparatus and 0.1 mL of conc. HCl as the catalyst. The obtained reaction mixture was concentrated, then the yield was determined by ^{1}H NMR spectroscopy using TCE as an internal standard. The α-amino ketone product was used in the formylation reaction without further purification.[25, 74-79]

Preparation of α-acylamino ketones with Vilsmeier reagen (Route a)



49 **50** **53** **54**

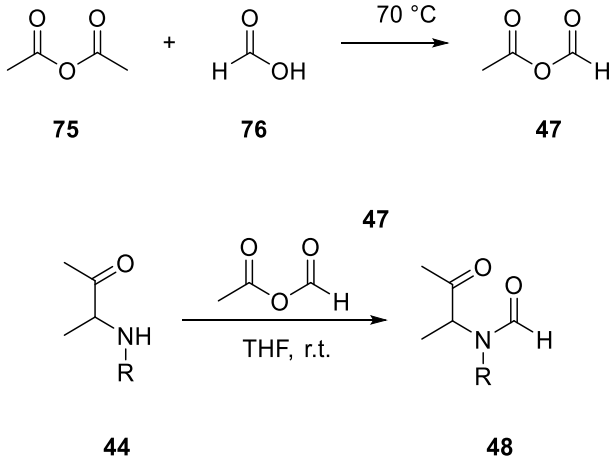
Vilsmeier Reagent



Scheme 5. 2 Preparation of α-acylamino ketones with Vilsmeier reagent

$POCl_3$ (0.4 mL, 5.0 mmol) was added into DMF (0.2 mL, 2.0 mmol) at 0 ℃ under argon, followed by stirring at room temperature for 30 min. The resulting Vilsmeier reagent was added dropwise to the appropriate α-amino ketone (1.0 mmol) in CH_2Cl_2 (3.4 mL) at 0 ℃ under argon. Generally, the reaction mixture turned dark brown over 4 hours. Once the reaction was completed as determined by TLC analysis, it was quenched with ice and then stirred until it warmed up to room temperature. 10 mL of CH_2Cl_2 and 20 mL of H_2O were added to the flask for extraction. The aqueous layer first was washed with CH_2Cl_2 (5 × 10 mL). The aqueous layer was then basified to pH 8-9 using aq. Na_2CO_3 (sat.). The desired product was then extracted with CH_2Cl_2 (5 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure.

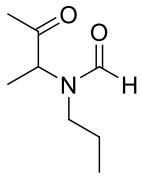
Preparation of α-formamido ketones using mixed anhydride (Route b)



Scheme 5. 3 Preparation of α-formamido ketones using mixed anhydride

The acetic anhydride (0.6 mL, 5.9 mmol) and formic acid (0.4 mL, 11.8 mmol) were stirred at 70 ℃ for 2h. The obtained mixed anhydride was then added to the appropriate α-amino ketone solution (2.94 mmol) in THF (9.8 mL) followed by stirring at ambient temperature for 18 hours. The resulted crude compound was purified by column chromatography on silica gel, then concentrated under vacuum.

_N_-(3-oxobutan-2-yl)-_N_-propylformamide (48a)

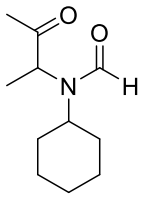


Sticky brown liquid (45% yield, Route a)

The Vilsmeier reagent was prepared from DMF (0.75mL, 9.67 mmol) and $POCl_3$ (0.36 mL, 3.87 mmol) according to Route a. The prepared Vilsmeier reagent was added to the solution of 3-(propylamino)butan-2-one **44a** (250mg, 1.93 mmol) in CH_2Cl_2 (4.2 mL) under argon, after stirring at rt for 12h. The reaction mixture was quenched by ice. 10 mL of CH_2Cl_2 and 20 mL of H_2O were added to the flask for extraction. The aqueous layer first was washed with CH_2Cl_2 (5 × 10 mL). The aqueous layer was then basified to pH 8-9 using aq. Na_2CO_3 (sat.). The desired product was then extracted with CH_2Cl_2 (5 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give 137mg (45%) of α-formamido ketones 48a as a sticky brown liquid.

R_f = 0.3 (20% MeOH/ CH_2Cl_2) ; **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 8.14 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 1H), 3.30-3.23 (m, 2H), 3.16 (dt, *J* = 14.7, 7.5 Hz, 1H), 2.16 (s, 3H), 1.64-1.56 (m, 2H), 1.38 (d, *J* = 7.08 Hz, 3H), 0.95 (t, *J* = 7.38 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 205.9, 205.6, 163.1, 62.5, 58.3, 48.7, 45.0, 26.9, 26.8, 23.6, 21.8, 15.7, 13.3, 11.5, 11.2

_N_-cyclohexyl-_N_-(3-oxobutan-2-yl)formamide (48b)

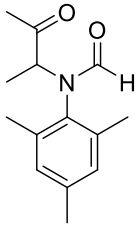


Light brown solid (38% yield for two steps, Route a)

Acetic anhydride (3.24mL, 34.3 mmol) and formic acid (2.59mL, 68.5mmol) were stirred at 70 ℃ for 2 hours under argon. The prepared mixed anhydride was added to a stirred solution of unpurified 3-(cyclohexylamino)butan-2-one **44b** (2.9g) in dry THF (35 mL) and then stirred continuously at rt for 12 hours. The crude compound was purified by column chromatography (20% MeOH/CH_2Cl_2) to give 1.3g light brown solid (38% yield for two steps).

R_f = 0.3 (15% EtOAc/ CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 8.20 (s, 1H), 3.07-4.02 (q, *J* = 6.9 Hz, 1H), 3.27 (tt, *J* = 12.1, 3.6 Hz, 1H), 2.16 (s, 3H), 2.01-1.94 (m, 1H), 1.94-1.83 (m, 3H), 1.74 – 1.63 (m, 1H), 1.58-1.44 (m, 3H), 1.42 (d, *J* = 6.9 Hz, 3H), 1.40-1.27 (m, 3H), 1.13 (qt, *J* = 13.2, 3.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 205.3, 162.3, 162.0, 58.6, 57.6, 57.6, 52.3, 33.8, 33.1, 30.6, 30.6, 26.9, 26.7, 25.9, 25.9, 25.7, 25.70 25.3, 25.1, 18.4, 14.5; **FTIR** (KBr thin film) υmax (cm^{-1}): 3397, 3302.05, 2939, 2926, 1076, 1658, 1448, 1428, 500; **HRMS** (EI^+) m/z calculated for $C_{11}H_{19}NO_2$ $[M]^+$: 198.1416; found: 198.1495

***N*-mesityl-*N*-(3-oxobutan-2-yl)formamide (48c)**[25]

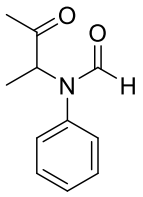


Yellow solid (40% for two steps, Route a)

Acetic anhydride (0.46 mL, 4.87 mmol) and formic acid (0.37 mL, 9.74 mmol) were stirred at 70 ℃ for 2 hours under argon. The prepared mixed anhydride was added to a stirred solution of unpurified 3-(mesitylamino)butan-2-one **44c** (500mg) in dry THF (4.9 mL) and then stirred continuously at rt for 12 hours. The crude compound was purified by column chromatography (2% MeOH/CH_2Cl_2) to give 170 mg yellow solid (40% yield for two steps).

R_f = 0.25 (1% MeOH/Hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.98 (s, 1H), 6.96 (s, 1H), 6.91(s, 1H), 4.52 (q, *J* = 7.4 Hz, 1H), 2.40 (s, 3H), 2.38 (s, 3H), 2.30 (s, 3H), 2.14 (s,3H), 0.97 (d, *J* = 7.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 205.5, 163.8, 138.9, 138.9, 137.9, 133.3, 129.9, 129.2, 59.6, 27.9, 21.1, 18.9, 18.6, 13.7

***N*-(3-oxobutan-2-yl)-*N*-phenylformamide (48d)**[25]

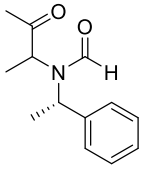


Yellow liquid (55% yield, Route b)

Acetic anhydride (0.6 mL, 6.44 mmol) and formic acid (0.32 mL, 8.52 mmol) were stirred at 70 ℃ for 2 hours under argon. The prepared mixed anhydride was added to a stirred solution of 3-(phenylamino)butan-2-one **44d** (700mg, 4.29 mmol) in dry THF (14.3 mL) and then stirred continuously at rt for 16 hours. The crude compound was purified by column chromatography (2% MeOH/CH_2Cl_2) to give 465 mg (55%) yellow solid.

R_f = 0.3 (30% EtOAc/Hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 8.38 (s, 1H), 7.42 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.38 – 7.31 (m, 1H), 7.20 (dd, *J* = 7.5, 1.8 Hz, 2H), 4.87 (q, *J* = 7.3 Hz, 1H), 2.28 (s, 3H), 1.34 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 205.4, 162.7, 139.1, 129.7, 127.9, 126.3, 60.4, 26.9, 13.8;

***N*-(3-oxobutan-2-yl)-*N*-((S)-1-phenylethyl)formamide (48e)**

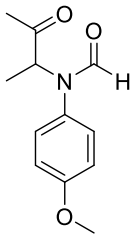


Yellow liquid (42% yield for two steps, Route b)

Acetic anhydride (1.9 mL, 20.4 mmol) and formic acid (1.3 mL, 34.0 mmol) were stirred at 70 ℃ for 2 hours under argon. The prepared mixed anhydride was added to a stirred solution of unpurified 3-(((S)-1-phenylethyl)amino)butan-2-one **44e** (1.3 g) in dry CH_2Cl_2 (13.6 mL) and then stirred continuously at rt for 16 hours. The crude compound was purified by column chromatography (2% MeOH/CH_2Cl_2) to give 700 mg yellow liquid (42% yield for two steps).

R_f = 0.3 (5% MeOH/ CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 8.41 (d, *J* = 16.7 Hz, 2H), 8.25 (d, *J* = 6.9 Hz, 1H), 7.43 – 7.29 (m, 15H), 7.26 (s, 1H), 6.00 (d, *J* = 7.3 Hz, 1H), 4.87 (q, *J* = 7.4 Hz, 1H), 4.80 (q, *J* = 7.3 Hz, 1H), 3.88 (q, *J* = 7.2 Hz, 1H), 3.80 (q, *J* = 7.5 Hz, 1H), 3.72 (dq, *J* = 13.8, 7.2 Hz, 2H), 2.21 (s, 1H), 2.15 (d, *J* = 2.3 Hz, 3H), 1.73 (t, *J* = 6.7 Hz, 7H), 1.57 – 1.53 (m, 4H), 1.44 (p, *J* = 8.5 Hz, 7H), 1.22 (d, *J* = 7.5 Hz, 1H), 1.09 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 205.8, 205.1, 204.8, 162.8, 162.5, 162.0, 161.9, 139.9, 139.5, 139.3, 139.0, 129.0, 129.0, 128.7, 128.7, 128.3, 128.2, 128.1, 127.9, 127.56, 127.0, 58.2, 58.0, 57.8, 57.3, 56.7, 56.5, 49.6, 49.5, 26.8, 26.7, 26.5, 26.2, 19.9, 19.7, 19.0, 18.3, 16.4, 16.1, 14.4, 13.8; **FTIR** (KBr thin film) υmax (cm^{-1}): 3320, 3064, 2938,2886, 1718, 1672, 1594, 1494, 1357, 1285, 1160, 1098, 700, 623 ; **HRMS** (EI^+) m/z calculated for $C_{13}H_{17}NO_2$ $[M]^+$: 219.1259; found: 219.1252

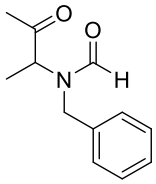
***N*-(4-methoxyphenyl)-*N*-(3-oxobutan-2-yl)formamide (48f)**



Yellow liquid (74% yield, Route b)

R_f = 0.3 (20% EtOAc/ CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 8.29 (s, 1H), 7.17 – 7.11 (m, 2H), 6.93 – 6.83 (m, 2H), 4.90 (q, *J* = 7.3 Hz, 1H), 3.82 (s, 3H), 2.28 (s, 3H), 1.28 (d, *J* = 7.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ:205.6, 162.9, 159.3, 131.4, 128.6, 114.6, 59.9, 55.5, 27.0, 13.8; **FTIR** (KBr thin film) υmax (cm^{-1}): 3045, 2989, 2938, 1721, 1671, 1511, 1355, 1245, 1030, 836, 562; **HRMS** (EI^+) m/z calculated for $C_{12}H_{15}NO_3$ $[M]^+$: 221.1052; found: 221.1050

***N*-benzyl-*N*-(3-oxobutan-2-yl)formamide (48g)**

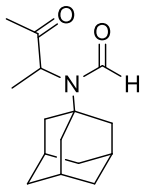


Yellow liquid (20% yield, Route b)

Acetic anhydride (1.6 mL, 16.9 mmol) and formic acid (1.3 mL, 33.9 mmol) were stirred at 70 ℃ for 2 hours under argon. The prepared mixed anhydride was added to a stirred solution of unpurified 3-(benzylamino)butan-2-one **44g** (1.0 g) in dry THF (11.3 mL) and then stirred continuously at rt for 16 hours. The crude compound was purified by column chromatography (5% MeOH/CH_2Cl_2) to give 233 mg yellow liquid (20% yield for two steps).

R_f = 0.4 (5% MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 8.33 (s, 1H), 7.40-7.24 (m, 5H), 4.59-4.45 (m, 1H), 4.44-4.36(m, 1H), 2.01 (s, 3H), 1.27 (d, *J* = 7.1 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 205.6, 205.2, 175.0, 163.2, 163.2, 136.6, 136.2, 129.0, 128.8, 128.7, 128.5, 128.4, 128.0, 127.8, 127.7, 61.9, 58.3, 50.7, 46.4, 42.2, 26.7, 26.7, 20.8, 15.9, 13.2; **FTIR** (KBr thin film) υmax (cm^{-1}): 3324, 2988, 1720, 1666, 1428, 1357, 1206, 703, 590; **HRMS** (EI^+) m/z calculated for $C_{12}H_{15}NO_2$ $[M]^+$: 205.1103; found: 205.1109

_N_-((3s,5s,7s)-adamantan-1-yl)-_N_-(3-oxobutan-2-yl)formamide (48h)[77]

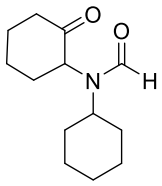


Yellow solid (13% yield, Route b)

Acetic anhydride (0.55 mL, 5.78 mmol) and formic acid (0.44 mL, 11.6 mmol) were stirred at 70 ℃ for 2 hours under argon. The prepared mixed anhydride was added to a stirred solution of 3-(((3s,5s,7s)-adamantan-1-yl)amino)butan-2-one **44h** (640 mg) in dry THF (5.8 mL) and then stirred continuously at rt for 16 hours. The crude compound was purified by column chromatography (2% MeOH/CH_2Cl_2) to give 135 mg (13%) yellow solid.

R_f = 0.3 (2% MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 8.31 (s, 1H), 3.62 (q, *J* = 6.7, 1H), 2.22 (brs, 3H), 2.14 (s, 3H), 2.02-1.96 (m, 6H), 1.76-1.67 (m, 6H), 1.47 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 205.4, 160.7, 57.1, 57.0, 42.4, 35.8, 29.40, 26.4, 15.5

***N*-cyclohexyl-*N*-(2-oxocyclohexyl)formamide (48k)**

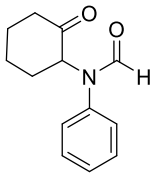


White solid (32% yield, Route b)

Acetic anhydride (0.27 mL, 2.87 mmol) and formic acid (0.22 mL, 5.74 mmol) were stirred at 70 ℃ for 2 hours under argon. The prepared mixed anhydride was added to a stirred solution of 2-(cyclohexylamino)cyclohexan-1-one **44k** (280 mg) in THF (4.8 mL) and then stirred continuously at rt for 16 hours. The crude compound was purified by column chromatography (100% EtOAc) to give 103 mg (32%) white solid.

R_f = 0.3 (2% MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.80 (s, 1H), 6.91 – 6.81 (m, 1H), 4.17 – 4.07 (m, 1H), 2.57 (td, *J* = 6.5, 4.6 Hz, 4H), 2.09 (p, *J* = 6.0 Hz, 2H), 1.97 – 1.86 (m, 1H), 1.84 – 1.69 (m, 4H), 1.68 – 1.57 (m, 1H), 1.40 – 1.13 (m, 5H), 1.03 (qt, *J* = 13.1, 3.8 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 138.2, 56.6, 40.2, 26.4, 24.6, 23.4, 22.9, 22.3, 21.4

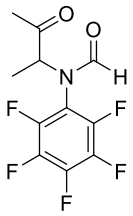
***N*-(2-oxocyclohexyl)-*N*-phenylformamide (48l)**



White solid (83% yield, Route b)

R_f = 0.3 (2% MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 8.34 (s, 1H), 7.40-7.36 (m, 2H), 7.35-7.32 (m, 1H), 7.27-7.24 (m, 2H), 4.98 (dd, *J* = 12.3, 6.1 Hz, 1H), 2.26-2.58 (m, 1H), 2.47 (td, *J* = 14.1, 6.1 Hz, 1H) , 2.12-2.00 (m, 2H), 1.99-1.89 (m, 1H), 1.84-1.69 (m, 2H), 1.67-1.54 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 205.3, 162.3, 162.0, 58.6, 57.6, 57.6, 52.3, 33.8, 33.1, 30.6, 30.6, 26.9, 26.7, 25.9, 25.9, 25.7, 25.7, 25.3, 25.1, 18.4, 14.5; **FTIR** (KBr thin film) υmax (cm^{-1}):2940, 2867, 1681, 1594, 1494, 1270, 702; **HRMS** (EI^+) m/z calculated for $C_{13}H_{15}NO_2$ $[M]^+$: 217.1103; found: 217.1096

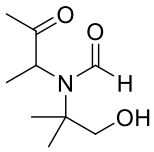
***N*-(3-oxobutan-2-yl)-*N*-(perfluorophenyl)formamide (48i)**



White solid (76% yield, Route a)

R_f = 0.4 (20% EtOAc/Hexane); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 8.15 (s, 1H), 4.70(q, J=7.14 Hz, 1H), 2.31(s, 3H), 1.33(d, J=7.14 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 203.4, 203.3, 162.3, 161.9, 146.2, 144.2, 139.2, 114.2, 63.7, 60.4, 27.2, 27.0, 17.0, 13.3; **FTIR** (KBr thin film) υmax (cm^{-1}):2985, 2325, 1731, 1710, 1361, 1264, 1108, 798; **HRMS** (EI^+) m/z calculated for $C_{11}H_8F_5NO_2$ $[M]^+$: 281.0475; found: 281.0482

***N*-(1-hydroxy-2-methylpropan-2-yl)-*N*-(3-oxobutan-2-yl)formamide (48j)**



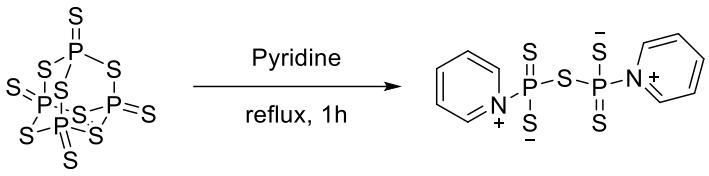
White solid (80% yield)

Acetic anhydride (0.3 mL, 3.14 mmol) and formic acid (0.24 mL, 6.28 mmol) were stirred at 70 ℃ for 2 hours under argon. The prepared mixed anhydride was added to a stirred solution of 3-((1-hydroxy-2-methylpropan-2-yl)amino)butan-2-one **44j** (280 mg) in toluene (3.1 mL) and then stirred continuously at rt for 16 hours. The crude compound was purified by column chromatography (20% MeOH/DCM) followed by recrystallization with hot EtOAc to give 239 mg (81%) white solid

R_f = 0.4 (20% MeOH/CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.50 (s, 1H), 3.99 (d, *J* = 12.5 Hz, 1H), 3.34 (q, J = 6.7 Hz, 1H), 3.29 (d, *J* = 12.5 Hz, 1H), 1.46 (s, 3H), 1.42 (s, 3H), 1.30 (d, *J* = 6.7 Hz, 3H), 1.27 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 169.3, 95.0, 66.0, 63.8, 53.8, 53.1, 25.5, 23.6, 20.4, 14.1

5.2.2 General procedure for the preparation of thiazolium precursors

Preparation of P_2S_5-Py_2 *complex with Svensson's procedure*



29 **30**

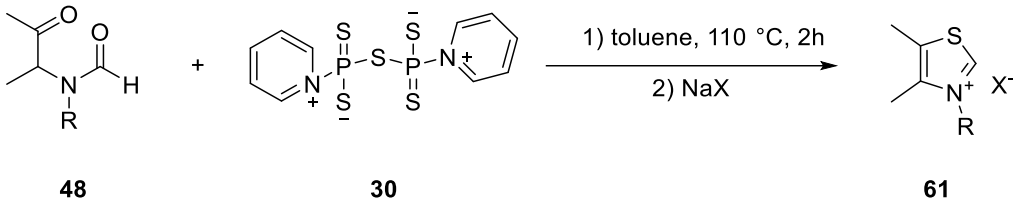
Scheme 5. 4 Preparation of P_2S_5-Py_2 complex

The P_4S_{10} (4.5 g, 0.01mmol) was refluxed in dry pyridine (56mL) at 80 ℃ for 2 hours. The obtained clear yellow solution was left standing at ambient temperature overnight for crystallization. The resulting crystals were filtered and washed with dry acetonitrile (15 mL × 3) followed by dry hexane (15 mL), then dried under high vacuum for 2 hours to obtain a pale yellow solid (6.4 g reaction mixture).

Preparation of P_2S_5-Py_2 *complex with Karaghiosoff's procedure*

The P_4S_{10} (889 mg, 2.0 mmol) was stirred in dry pyridine (40 mL) at 25 ℃ for 1h. The obtained yellow solution was left standing at ambient temperature overnight for crystallization. The resulting crystals were filtered, then dried under high vacuum for 2 hours to obtain a sticky yellow solid (230mg reaction mixture).

Preparation of thiazolium pre-catalysts with P_2S_5-Py_2 *complex*

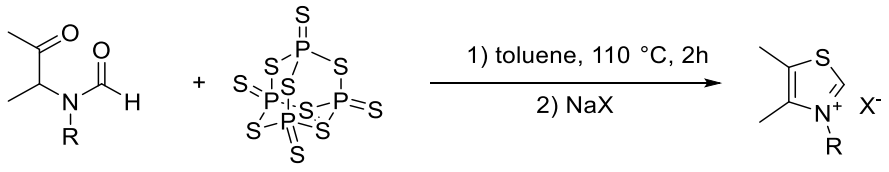


48 30 61

Scheme 5. 5 Preparation of thiazolium pre-catalysts with P_2S_5-Py_2 complex

The appropriate α-formamido ketone (0.25 mmol) and P_2S_5-Py_2 complex (0.75 mmol) were stirred in toluene at 110 ℃ for 2 hours. Over this period, the solution turned to yellow colour, and a sticky slurry precipitate formed. The soluble portion was then removed using a Pasteur pipette, and the precipitate was washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear yellow solution. $NaBF_4$ (0.75 mmol) or $NaBPh_4$ (0.22 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was stirred at room temperature for x minutes. After extraction with CH_2Cl_2 (10 mL × 3), the combined organic extracts were dried over Na_2SO_4 then concentrated under vacuum. If the obtained compound quickly turned green upon exposure to air, hexane (3 mL) was added to the product, then heated at 100 ℃ for 5 min, then concentrated while hot. This treatment was repeated three times.

Preparation of thiazolium precursors with P_4S_{10} *reagent*

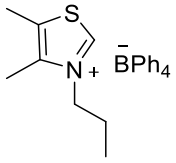


48 29 61

The appropriate α-formamido ketones (0.22 mmol) and P_4S_{10} (100 mg, 0.22 mmol) were stirred in toluene at 110 ℃ for two hours. Over this period, the solution turned to yellow, and a sticky slurry precipitate formed. The soluble portion was then removed using a Pasteur pipette, and the precipitate was washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear yellow solution.

$NaBF_4$ (0.66 mmol) or $NaBPh_4$ (0.20 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was stirred at room temperature for 30 minutes. After extraction with CH_2Cl_2 (10 mL × 3), the combined organic extracts were dried over Na_2SO_4 then concentrated under vacuum. If the obtained compound quickly turned green upon exposure to air, hexane (3 mL) was added to the product, then heated at 100 ℃ for 5 min, then concentrated while hot. This treatment was repeated three times.

4,5-dimethyl-3-propylthiazol-3-ium tetraphenylborate (61a)



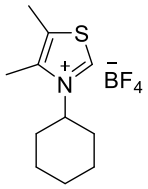
Light brown solid (57% yield with P_2S_5-Py_2 complex; 29% yield with P_4S_{10})

P_2S_5-Py_2 complex (198.9 mg, 0.52 mmol) was added to a solution of *N*-(3-oxobutan-2-yl)-*N*-propylformamide **48a** (137.0mg, 0.87 mmol) in dry toluene (2.9 mL) and then stirred at 90℃ for 16 hours. The mother liquor was removed using a Pasteur pipette, and the precipitate washed with Et_2O (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBPh_4$ (0.27g, 0.78 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) followed by recrystallization with EtOAc to give 235mg (57%) light brown solid.

P_4S_{10} (141 mg, 0.32 mmol) was added to a solution of *N*-(3-oxobutan-2-yl)-*N*-propylformamide **48a** (50 mg, 0.32 mmol) in dry toluene (1.06 mL) and then stirred at 110 ℃ for 2 hours. The mother liquor was removed using a Pasteur pipette, and the precipitate washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (105 mg, 0.95 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 22 mg (29 %) light brown liquid.

^{1}H NMR (600 MHz, DMSO-d_6) δ: 9.96 (s, 1H), 7.19-7.14 (m, 8H), 6.92 (t, *J* = 7.4 Hz, 8H), 6.78 (t, *J* = 7.17 Hz, 4H), 4.40 (t, *J* = 7.4 Hz, 2H), 2.43(s, 3H), 1.85-1.78 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 164.4, 164.0, 163.6, 155.9, 142.1, 136.0, 133.6, 125.8, 125.8, 125.8, 122.0, 54.7, 22.8, 12.4, 11.4, 10.8.

3-cyclohexyl-4,5-dimethylthiazol-3-ium tetrafluoroborate (61b)



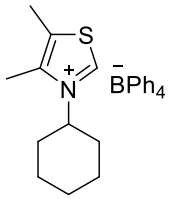
Pale yellow solid (82% yield with P_2S_5-Py_2 complex; 68% yield with P_4S_{10})

P_2S_5-Py_2 complex (289 mg, 0.76 mmol) was added to a solution of *N*-cyclohexyl-*N*-(3-oxobutan-2-yl)formamide **48b** (50 mg, 0.25 mmol) in dry toluene (2.9 mL) and then stirred at 110 ℃ for 2 hours. The mother liquor was removed using a Pasteur pipette, and the precipitate was washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (83.5 mg, 0.76 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 60 mg (82 %) pale yellow solid.

P_4S_{10} (225.3 mg, 0.51 mmol) was added to a solution of *N*-(3-oxobutan-2-yl)-*N*-propylformamide **48b** (100 mg, 0.51 mmol) in dry toluene (1.70 mL) and then stirred at 110 ℃ for 2 hours. The mother liquor was removed using a Pasteur pipette, and the precipitate was washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (55.6 mg, 0.51 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 49 mg (68 %) pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.84 (s, 1H), 4.31 (tt, *J* = 12.1, 3.4 Hz, 1H), 2.54 (s, 3H), 2.50 (s, 3H), 2.16 (d, *J* = 11.9 Hz, 2H), 2.00 (dt, *J* = 13.7, 3.3 Hz, 2H), 1.88 (qd, *J* = 12.3, 3.5 Hz, 2H), 1.78 (dt, *J* = 13.2, 3.3 Hz, 1H), 1.48 (qt, *J* = 12.9, 3.3 Hz, 2H), 1.37 (qt, *J* = 13.2, 3.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 152.5, 141.4, 133.6, 63.9, 33.2, 25.4, 24.4, 12.5, 11.6; **FTIR** (KBr thin film) υmax (cm^{-1}): 2932, 2858, 1453, 1109, 533; **HRMS** (EI^+) m/z calculated for $C_{11}H_{18}NS^+$ $[M]^+$: 196.1154; found: 196.1151.

3-cyclohexyl-4,5-dimethylthiazol-3-ium tetraphenylborate (61b(BPh_4))

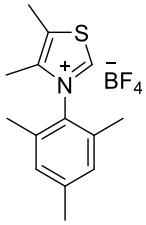


White solid (38% yield with P_2S_5-Py_2 complex)

P_2S_5-Py_2 complex (185 mg, 0.50 mmol) was added to a solution of *N*-cyclohexyl-*N*-(3-oxobutan-2-yl)formamide **48b** (160 mg, 0.81 mmol) in dry toluene (2.5 mL) and then stirred at 110 ℃ for 2 hours. The mother liquor was removed using a Pasteur pipette, and the precipitate was washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBPh_4$ (0.3 g, 0.89 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) followed by recrystallization with EtOAc to give 158 mg (38 %) white solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.03 (s, 1H), 7.17 (br s, 8H), 6.92 (t, *J* = 7.3 Hz, 8H), 6.78 (t, *J* = 7.1 Hz, 4H), 4.49 (t, *J* = 11.9 Hz, 1H), 2.49 (s, 3H), 2.07 (d, *J* = 11.4 Hz, 2H), 1.86 (d, *J* = 13.5 Hz, 2H), 1.82 – 1.66 (m, 3H), 1.53 – 1.42 (m, 2H), 1.30 - 1.19 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ:163.9, 163.5, 163.1, 162.8, 153.1, 135.5, 132.6, 125.3, 125.3, 125.3, 125.3, 121.5, 62.3, 24.7, 24.3, 12.0, 11.2; **FTIR** (KBr thin film) υmax (cm^{-1}):3089, 3051, 2995, 2938, 2860, 1577, 1477, 751, 734, 706, 612, 470; **HRMS** (EI^+) m/z calculated for $C_{11}H_{18}NS^+$ $[M]^+$:196.1154; found: 196.1161

3-mesityl-4,5-dimethylthiazol-3-ium tetrafluoroborate (61c)



White solid (55% yield with P_2S_5-Py_2 complex; 70% yield with P_4S_{10})

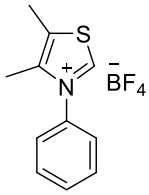
P_2S_5-Py_2 complex (490 mg, 1.29 mmol) was added to a solution of *N*-mesityl-*N*-(3-oxobutan-2-yl)formamide **48c** (50 mg, 0.21 mmol) in dry toluene (1.4 mL) and then stirred at 110 ℃ for 2 hours. The mother liquor was removed using a Pasteur pipette, and the precipitate was washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (83.5 mg, 0.76 mmol) was added to the solution, followed by CH_2Cl_2.

The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 38 mg white solid (55 %).

P_4S_{10} (95.3 mg, 0.21 mmol) was added to a solution of *N*-mesityl-*N*-(3-oxobutan-2-yl)formamide **48c** (50 mg, 0.21 mmol) in dry toluene (1.07 mL) and then stirred at 110 ℃ for 2 hours. The upper solution mother liquor was removed using a Pasteur pipette, and the precipitate was washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (25.5 mg, 0.21 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 50 mg white solid (70 %).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.79 (s, 1H), 7.08 (s, 2H), 2.66 (s, 3H), 2.38 (s, 3H), 2.12 (s, 3H), 1.97 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 156.9, 142.3, 141.7, 135.1, 133.8, 132.9, 130.4, 21.3, 17.3, 13.0, 11.4; **FTIR** (KBr thin film) υmax (cm^{-1}): 3124, 2919, 1486, 1441, 1100, 1065, 533; **HRMS** (EI^+) m/z calculated for $C_{14}H_{18}NS^+$ $[M]^+$: 232.1154; found: 232.1148

4,5-dimethyl-3-phenylthiazol-3-ium tetrafluoroborate (61d)



Pale yellow solid (52% yield with P_2S_5-Py_2 complex; 54% with P_4S_{10})

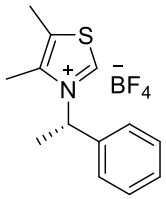
P_2S_5-Py_2 complex (90 mg, 0.24 mmol) was added to a solution of *N*-(3-oxobutan-2-yl)-*N*-phenylformamide **48d** (50 mg, 0.26 mmol) in dry toluene (1.3 mL) and then stirred at 110 ℃ for 2 hours. The upper solution mother liquor was removed using a Pasteur pipette, and the precipitate was washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (57.4 mg, 0.50 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 37 mg pale yellow solid (52 %).

P_4S_{10} (95.3 mg, 0.21 mmol) was added to a solution of *N*-(3-oxobutan-2-yl)-*N*-phenylformamide **48d** (50 mg, 0.21 mmol) in dry toluene (1.07 mL) and then stirred at

110 ℃ for 2 hours. The upper solution mother liquor was removed using a Pasteur pipette, and the precipitate was washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (25.5 mg, 0.21 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 39 mg pale yellow solid (54 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.38 (s, 1H), 7.45-7.39 (m, 2H), 7.38-7.33 (m, 1H), 7.22-7.18 (m, 2H), 4.88 (q, *J* = 7.3 Hz, 1H), 2.29 (s, 3H), 1.35 (d, *J* = 7.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 155.6, 142.5, 136.9, 134.2, 131.9, 130.6, 126.0, 12.8, 12.5; **FTIR** (KBr thin film) υmax (cm^{-1}):3104, 2955, 1450, 1040, 706; **HRMS** (EI^+) m/z calculated for $C_{11}H_{12}NS^+$ $[M]^+$: 190.0658; found: 190.0694

(S)-4,5-dimethyl-3-(1-phenylethyl)thiazol-3-ium tetrafluoroborate (61e)



Brown liquid (36% yield with P_2S_5-Py_2 complex; 69% with P_4S_{10})

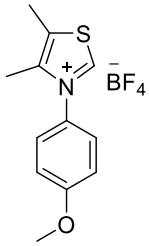
P_2S_5-Py_2 complex (298 mg, 0.78 mmol) was added to a solution of *N*-(3-oxobutan-2-yl)-*N*-((S)-1-phenylethyl)formamide **48e** (50 mg, 0.26 mmol) in dry toluene (1.3 mL) and then stirred at 110 ℃ for 2 hours. The upper solution mother liquor was removed using a Pasteur pipette, and the precipitate was washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (28.7 mg, 0.26 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 28 mg brown liquid (36 %).

P_4S_{10} (101.3 mg, 0.23 mmol) was added to a solution of of *N*-(3-oxobutan-2-yl)-*N*-((S)-1-phenylethyl)formamide **48e** (50 mg, 0.23 mmol) in dry toluene (1.07 mL) and then stirred at 110 ℃ for 2 hours. The upper solution mother liquor was removed using a Pasteur pipette, and the precipitate was washed with hexane (3 mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (25.0

mg, 0.23 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 44 mg (69 %) brown liquid.

^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.16 (s, 1H), 7.43 (dd, *J* = 8.2, 6.7 Hz, 2H), 7.40 – 7.35 (m, 1H), 7.30 (dd, *J* = 7.1, 1.8 Hz, 2H), 6.05 (q, *J* = 6.9 Hz, 1H), 2.47 (s, 3H), 2.29 (s, 3H), 1.93 (d, *J* = 7.0 Hz, 3H); **^{13}CNMR** (125 MHz, $CDCl_3$) δ: 153.1, 142.6, 137.5, 134.0, 129.8, 129.3, 126.2, 64.4, 22.4, 12.6, 11.9

3-(4-methoxyphenyl)-4,5-dimethylthiazol-3-ium tetrafluoroborate (61f)



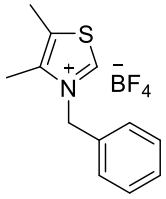
Pale yellow solid (33% yield with P_2S_5-Py_2 complex; 72% yield with P_4S_{10})

P_2S_5-Py_2 complex (258 mg, 0.68 mmol) was added to a solution of *N*-(4-methoxyphenyl)-*N*-(3-oxobutan-2-yl)formamide **48f** (50 mg, 0.23 mmol) in dry toluene (0.75 mL) and then stirred at 110 ℃ for 2 hours. The upper solution mother liquor was removed using a Pasteur pipette, and the precipitate was washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (99.3 mg, 0.90 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 23 mg (33 %) pale yellow solid.

P_4S_{10} (100 mg, 0.23 mmol) was added to a solution of of N-(4-methoxyphenyl)-N-(3-oxobutan-2-yl)formamide **48f** (50 mg, 0.23 mmol) in dry toluene (0.75 mL) and then stirred at 110 ℃ for 2 hours. The upper solution mother liquor was removed using a Pasteur pipette, and the precipitate washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (75 mg, 0.67 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 50 mg (72 %) pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.12 (s, 1H), 7.56 (d, *J* = 8.96 Hz, 2H), 7.14 (d, *J* = 8.96 Hz, 2H), 3.80 (s, 3H), 2.50 (s, 3H), 2.13 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 161.8, 155.7, 142.6, 133.8, 129.5, 127.3, 115.6, 56.0, 12.9, 12.5.

3-benzyl-4,5-dimethylthiazol-3-ium tetrafluoroborate (61g)



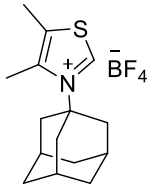
Light brown solid (43% yield with P_2S_5-Py_2 complex; 65% yield with P_4S_{10})

P_2S_5-Py_2 complex (278 mg, 0.73 mmol) was added to a solution of *N*-benzyl-*N*-(3-oxobutan-2-yl)formamide **48g** (50 mg, 0.24 mmol) in dry toluene (1.2 mL) and then stirred at 110 ℃ for 2 hours. The upper solution mother liquor was removed using a Pasteur pipette, and the precipitate was washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (107 mg, 0.95 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 30 mg (43 %) light brown liquid.

P_4S_{10} (108 mg, 0.24 mmol) was added to a solution of of *N*-benzyl-*N*-(3-oxobutan-2-yl)formamide **48g** (50 mg, 0.24 mmol) in dry toluene (0.8 mL) and then stirred at 110 ℃ for 2 hours. The upper solution mother liquor was removed using a Pasteur pipette, and the precipitate was washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (27 mg, 0.24 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 45 mg (65 %) brown liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.79 (s, 1H), 7.42-7.35 (m, 3H), 7.31-7.26 (m, 2H), 5.64 (s, 2H), 2.48 (s, 3H), 2.37 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 154.9, 142.4, 133.8, 131.5, 129.8, 129.7, 128.5, 57.8, 12.7, 11.8.

3-((3s,5s,7s)-adamantan-1-yl)-4,5-dimethylthiazol-3-ium tetrafluoroborate (61h)



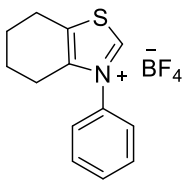
Pale yellow solid (67% yield with P_2S_5-Py_2 complex; 63% yield with P_4S_{10})

P_2S_5-Py_2 complex (229 mg, 0.60 mmol) was added to a solution of *N*-((3s,5s,7s)-adamantan-1-yl)-*N*-(3-oxobutan-2-yl)formamide **48h** (50 mg, 0.20 mmol) in dry toluene (1.2 mL) and then stirred at 110 ℃ for 2 hours. The upper solution mother liquor was removed using a Pasteur pipette, and the precipitate was washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (88 mg, 0.80 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 46 mg (67 %) pale yellow solid.

P_4S_{10} (27 mg, 0.06 mmol) was added to a solution of of N-((3s,5s,7s)-adamantan-1-yl)-N-(3-oxobutan-2-yl)formamide **48h** (15 mg, 0.06 mmol) in dry toluene (0.2 mL) and then stirred at 110 ℃ for 2 hours. The upper solution mother liquor was removed using a Pasteur pipette, and the precipitate was washed with hexane (1mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (20 mg, 0.18 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 43 mg (63 %) pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.91 (s, 1H), 2.73 (s, 3H), 2.51 (s, 3H), 2.40 (s, 9H), 1.80 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 154.2, 141.5, 135.4, 70.3, 41.1, 35.1, 30.0, 15.5, 13.0; **FTIR** (KBr thin film) υmax (cm^{-1}): 3170, 2921, 2855, 1251, 1057, 802; **HRMS** (EI^+) m/z calculated for $C_{15}H_{22}NS^+$ $[M]^+$: 248.1467; found: 248.1461

3-phenyl-4,5,6,7-tetrahydrobenzo[d]thiazol-3-ium tetrafluoroborate (61l)



Pale yellow solid (49% yield with P_2S_5-Py_2 complex; 79% with P_4S_{10})

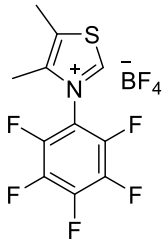
P_2S_5-Py_2 complex (175 mg, 0.46 mmol) was added to a solution of *N*-(2-oxocyclohexyl)-*N*-phenylformamide **48l** (50 mg, 0.23 mmol) in dry toluene (0.77 mL) and then stirred at 110 ℃ for 2 hours. The upper solution mother liquor

was removed using a Pasteur pipette, and the precipitate was washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (25 mg, 0.23 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 35 mg (49 %) pale yellow solid.

P_4S_{10} (102.3 mg, 0.23 mmol) was added to a solution of of *N*-(2-oxocyclohexyl)-*N*-phenylformamide **48l** (50 mg, 0.23 mmol) in dry toluene (0.8 mL) and then stirred at 110 ℃ for 2 hours. The upper solution mother liquor was removed using a Pasteur pipette, and the precipitate was washed with hexane (1mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (25.3 mg, 0.23 mmol) was added to the solution, followed by CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 55 mg (79 %) pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.76 (s, 1H), 7.67-7.59 (m, 3H), 7.54 (t, *J* = 7.5 Hz, 2H), 2.99 (t, *J* = 6.00 Hz, 2H), 2.58 (t, *J* = 6.09 Hz, 2H), 2.02-1.96 (m, 2H), 1.96-1.89 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 155.9, 144.2, 136.6, 136.1, 131.8, 130.6, 125.7, 24.2, 24.0, 21.6, 21.1; 522; **FTIR** (KBr thin film) υmax (cm^{-1}): 3421, 2940, 1492, 1031, 771, 696, 621, **HRMS** (EI^+) m/z calculated for $C_{13}H_{14}NS^+$ $[M]^+$: 216.0841; found: 216.0848

4,5-dimethyl-3-(perfluorophenyl)thiazol-3-ium tetrafluoroborate (61i)



Dark brown solid (30% yield with P_4S_{10})

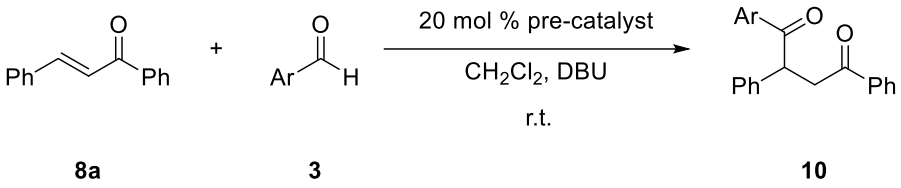
P_4S_{10} (47 mg, 0.11 mmol) was added to a solution of *N*-(3-oxobutan-2-yl)-*N*-(perfluorophenyl)formamide **48i** (30 mg, 0.11 mmol) in dry toluene (0.36 mL) and then stirred at 110 ℃ for 2 hours. The upper solution mother liquor was removed using a Pasteur pipette, and the precipitate was washed with hexane (3mL × 3). The precipitate was then dissolved in water at 65 ℃ over 20 min until it turned into a clear solution. $NaBF_4$ (35 mg, 0.33 mmol) was added to the solution, followed by

CH_2Cl_2. The biphasic mixture was purified by extraction with CH_2Cl_2 (10 mL × 3) to give 12 mg (30 %) dark brown liquid.

^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.47 (s, 1H), 2.60 (s, 3H), 2.34 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 161.9, 135.4, 12.6, 11.2; **FTIR** (KBr thin film) υmax (cm^{-1}): 3120, 2960. 1526, 1073, 1040, 730, 522; HRMS (EI^+) m/z calculated for $C_{11}H_7F_5NS^+$ $[M]^+$: 280.0214; found: 280.0221

5.3 Experimental procedures for the Stetter reaction

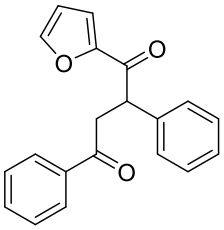
5.3.1 General procedure for the Stetter reaction



Scheme 5. 6 General procedure for the intermolecular Stetter reaction with chalcone

Chalcone (10 mg, 0.05 mmol), DBU (11.8 mmL, 0.05 mmol) and pre-catalyst (0.05 mmol) were added to a Schlenk tube. After filling the tube with argon, aldehyde (0.06 mmol), CH_2Cl_2 (0.12 mL) were added to the Schlenk tube successively. The reaction mixture was stirred at room temperature or 45℃ for 6h. The obtained mixture then passed through a Pasteur pipette with 1cm silica gel followed by washing with 5% MeOH/ CH_2Cl_2 as eluent. The mixture was monitored by TLC then concentrated.

1-(furan-2-yl)-2,4-diphenylbutane-1,4-dione (10a)



White solid (13 mg, 89%)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.98 - 7.96 (m, 2H), 7.57 – 7.54 (m, 2H), 7.46 – 7.40 (m, 4H), 7.34 – 7.31(m, 2H), 7.26 – 7.23 (m, 2H), 6.48 (dd, *J* = 3.6, 1.7 Hz, 1H), 5.14 (dd, *J* = 10.2, 3.8 Hz, 1H), 4.18 (dd, *J* = 18.1, 10.2 Hz, 1H), 3.33 (dd, *J* = 18.1, 3.8 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 198.0, 187.9, 153.3, 146.7, 138.4, 136.5, 133.4, 129.2, 128.8, 128.7, 128.6, 128.5, 128.3, 128.1, 127.6, 118.3, 112.4, 48.8, 42.9

LIST OF REFERENCES

1. Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F., An overview of N-heterocyclic carbenes. *Nature* **2014,** *510*, 485-496.

2. Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T., Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes. *Chemical Reviews* **2015,** *115*, 9307-9387.

3. Enders, D.; Niemeier, O.; Henseler, A., Organocatalysis by N-Heterocyclic Carbenes. *Chemical Reviews* **2007,** *107*, 5606-5655.

4. Thai, K. S.-L., E.; Gravel, M, *N-Heterocyclic Carbenes in Organocatalysis. In Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications; Dalko, P. I., Ed.; Wiley-VCH: Weinheim*. 2013; p 495-522.

5. Hopkinson, M. N.; Glorius, F., An Overview of NHCs. In *N-Heterocyclic Carbenes in Organocatalysis*,2018; pp 1-35.

6. Seebach, D., Methods of Reactivity Umpolung. *Angewandte Chemie International Edition in English* **1979,** *18*, 239-258.

7. GrÖBel, B.-T.; Seebach, D., Umpolung of the Reactivity of Carbonyl Compounds Through Sulfur-Containing Reagents. *Synthesis* **1977,** *1977*, 357-402.

8. Seebach, D.; Corey, E. J., Generation and synthetic applications of 2-lithio-1,3-dithianes. *The Journal of Organic Chemistry* **1975,** *40*, 231-237.

9. Wöhler; Liebig, Untersuchungen über das Radikal der Benzoesäure. *Annalen der Pharmacie* **1832,** *3*, 249-282.

10. Ukai, T.; Tanaka, R.; Dokawa, T. J. J. P. S. J., A new catalyst for acyloin condensation. **1943,** *63*, 296-300.

11. Breslow, R., On the Mechanism of Thiamine Action. IV.1 Evidence from Studies on Model Systems. *Journal of the American Chemical Society* **1958,** *80*, 3719-3726.

12. Stetter, H., Catalyzed Addition of Aldehydes to Activated Double Bonds—A New Synthetic Approach. *Angewandte Chemie International Edition in English* **1976,** *15*, 639-647.

13. Stetter, H.; Schreckenberg, M., A New Method for Addition of Aldehydes to Activated Double Bonds. *Angewandte Chemie International Edition in English* **1973,** *12*, 81-81.

14. Stetter, H.; Kuhlmann, H., The Catalyzed Nucleophilic Addition of Aldehydes to Electrophilic Double Bonds. In *Organic Reactions*,1991; Vol. 40, pp 407-496.

15. Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H., The First Asymmetric Intramolecular Stetter Reaction. Preliminary Communication. *Helvetica Chimica Acta* **1996,** *79*, 1899-1902.

16. Kerr, M. S.; Read de Alaniz, J.; Rovis, T., A Highly Enantioselective Catalytic Intramolecular Stetter Reaction. *Journal of the American Chemical Society* **2002,** *124*, 10298-10299.

17. Kerr, M. S.; Rovis, T., Enantioselective Synthesis of Quaternary Stereocenters via a Catalytic Asymmetric Stetter Reaction. *Journal of the American Chemical Society* **2004,** *126*, 8876-8877.

18. Pesch, J.; Harms, K.; Bach, T., Preparation of Axially Chiral N,N′-Diarylimidazolium and N-Arylthiazolium Salts and Evaluation of Their Catalytic Potential in the Benzoin and in the

Intramolecular Stetter Reactions. *European Journal of Organic Chemistry* **2004,** *2004*, 2025-2035.

19. Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J., A peptide-catalyzed asymmetric Stetter reaction. *Chemical Communications* **2005**, 195-197.

20. Enders, D.; Han, J.; Henseler, A., Asymmetric intermolecular Stetter reactions catalyzed by a novel triazolium derived N-heterocyclic carbene. *Chemical Communications* **2008**, 3989-3991.

21. DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T., Catalytic Asymmetric Intermolecular Stetter Reaction of Heterocyclic Aldehydes with Nitroalkenes: Backbone Fluorination Improves Selectivity. *Journal of the American Chemical Society* **2009,** *131*, 10872-10874.

22. Sánchez-Larios, E. G., M. , *unpublished results.*

23. Cheng, Q.-F.; Wang, J.-W.; Wang, Q.-F.; Liu, Z., Intermolecular Stetter reaction of aromatic aldehydes with (E)-(2-nitrovinyl)cyclohexane induced by N-heterocyclic carbene and thiourea. *Chinese Chemical Letters* **2016,** *27*, 1032-1035.

24. Ahire, M. M.; Mhaske, S. B., Synthesis of Succinimide Derivatives by NHC-Catalyzed Stetter Reaction of Aromatic Aldehydes with N-Substituted Itaconimides. *ACS Omega* **2017,** *2*, 6598-6604.

25. Garapati, V. K. R.; Gravel, M., Oxazolium Salts as Organocatalysts for the Umpolung of Aldehydes. *Organic Letters* **2018,** *20*, 6372-6375.

26. Wilde, M. M. D.; Gravel, M., Bis(amino)cyclopropenylidenes as Organocatalysts for Acyl Anion and Extended Umpolung Reactions. *Angewandte Chemie International Edition* **2013,** *52*, 12651-12654.

27. Rezazadeh Khalkhali, M.; Wilde, M. M. D.; Gravel, M., Enantioselective Stetter Reactions Catalyzed by Bis(amino)cyclopropenylidenes: Important Role for Water as an Additive. *Organic Letters* **2021,** *23*, 155-159.

28. Harrington, P. E.; Tius, M. A., Synthesis and Absolute Stereochemistry of Roseophilin. *Journal of the American Chemical Society* **2001,** *123*, 8509-8514.

29. Shi, H.; Michaelides, I. N.; Darses, B.; Jakubec, P.; Nguyen, Q. N. N.; Paton, R. S.; Dixon, D. J., Total Synthesis of (−)-Himalensine A. *Journal of the American Chemical Society* **2017,** *139*, 17755-17758.

30. Hsu, D.-S.; Liou, C.-Y., Total synthesis and structural revision of (±)-nidemone. *Organic & Biomolecular Chemistry* **2018,** *16*, 4990-4995.

31. Wright, A. C.; Stoltz, B. M., Enantioselective construction of the tricyclic core of curcusones A–D via a cross-electrophile coupling approach. *Chemical Science* **2019,** *10*, 10562-10565.

32. Jin, M. Y.; Kim, S. M.; Han, H.; Ryu, D. H.; Yang, J. W., Switching Regioselectivity in Crossed Acyloin Condensations between Aromatic Aldehydes and Acetaldehyde by Altering N-Heterocyclic Carbene Catalysts. *Organic Letters* **2011,** *13*, 880-883.

33. Ema, T.; Oue, Y.; Akihara, K.; Miyazaki, Y.; Sakai, T., Stereoselective Synthesis of Bicyclic Tertiary Alcohols with Quaternary Stereocenters via Intramolecular Crossed Benzoin Reactions Catalyzed by N-Heterocyclic Carbenes. *Organic Letters* **2009,** *11*, 4866-4869.

34. Bortolini, O.; Fantin, G.; Fogagnolo, M.; Giovannini, P. P.; Massi, A.; Pacifico, S., Thiazolium-catalyzed intermolecular Stetter reaction of linear and cyclic alkyl α-diketones. *Organic & Biomolecular Chemistry* **2011,** *9*, 8437-8444.

35. Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A., The Thiazolium-Catalyzed Sila-Stetter Reaction: Conjugate Addition of Acylsilanes to Unsaturated Esters and Ketones. *Journal of the American Chemical Society* **2004,** *126*, 2314-2315.

36. Zhang, D.; Zi, G., N-heterocyclic carbene (NHC) complexes of group 4 transition metals. *Chemical Society Reviews* **2015,** *44*, 1898-1921.

37. Lebeuf, R.; Hirano, K.; Glorius, F., Palladium-Catalyzed C-Allylation of Benzoins and an NHC-Catalyzed Three Component Coupling Derived Thereof: Compatibility of NHC- and Pd-Catalysts. *Organic Letters* **2008,** *10*, 4243-4246.

38. Chen, X.-Y.; Xia, F.; Ye, S., Catalytic MBH reaction of β-substituted nitroalkenes with azodicarboxylates. *Organic & Biomolecular Chemistry* **2013,** *11*, 5722-5726.

39. Chen, X.-Y.; Sun, L.-H.; Ye, S., N-Heterocyclic Carbene Catalyzed [4+2] Cycloaddition of Nitroalkenes with Oxodienes. *Chemistry – A European Journal* **2013,** *19*, 4441-4445.

40. Powell, A. B.; Suzuki, Y.; Ueda, M.; Bielawski, C. W.; Cowley, A. H., A Recyclable, Self-Supported Organocatalyst Based on a Poly(N-Heterocyclic Carbene). *Journal of the American Chemical Society* **2011,** *133*, 5218-5220.

41. Yamashita, K.; Shimizu, Y.; Tokuda, H.; Kuromiya, T.; Tsuda, K., Acyloin condensation by polymer supported thiazolium salt: Relation between the catalytic activity and the degree of quarternization. *Journal of Polymer Science Part A: Polymer Chemistry* **1989,** *27*, 4389-4395.

42. Haghighi, A. J.; Mokhtari, J.; Karimian, K., N-PEGylated Thiazolium Salt: A Green and Reusable Homogenous Organocatalyst for the Synthesis of Benzoins and Acyloins. *Catalysis Letters* **2021,** *151*, 1646-1652.

43. Pesch, J.; Harms, K.; Bach, T., Preparation of Axially Chiral N,N′-Diarylimidazolium and N-Arylthiazolium Salts and Evaluation of Their Catalytic Potential in the Benzoin and in the Intramolecular Stetter Reactions. **2004,** *2004*, 2025-2035.

44. Chen, Y. T.; Jordan, F., Reactivity of the thiazolium C2 ylide in aprotic solvents: novel experimental evidence for addition rather than insertion reactivity. *The Journal of Organic Chemistry* **1991,** *56*, 5029-5038.

45. Piel, I.; Pawelczyk, M. D.; Hirano, K.; Fröhlich, R.; Glorius, F., A Family of Thiazolium Salt Derived N-Heterocyclic Carbenes (NHCs) for Organocatalysis: Synthesis, Investigation and Application in Cross-Benzoin Condensation. *European Journal of Organic Chemistry* **2011,** *2011*, 5475-5484.

46. Vu, N. D.; Bah, S.; Deruer, E.; Duguet, N.; Lemaire, M., Robust Organocatalysts for the Cleavage of Vegetable Oil Derivatives to Aldehydes through Retrobenzoin Condensation. **2018,** *24*, 8141-8150.

47. Ozturk, T.; Ertas, E.; Mert, O., A Berzelius Reagent, Phosphorus Decasulfide (P4S10), in Organic Syntheses. *Chemical Reviews* **2010,** *110*, 3419-3478.

48. Vallée, Y.; Masson, S.; Ripoll, J.-L., New routes to thioketenes and propadienethione by flash vacuum thermolysis. *Tetrahedron* **1990,** *46*, 3921-3928.

49. Lajoie, G.; Lépine, F.; Maziak, L.; Belleau, B., Facile regioselective formation of thiopeptide linkages from oligopeptides with new thionation reagents. *Tetrahedron Letters* **1983,** *24*, 3815-3818.

50. Bonini, B. F.; Mazzanti, G.; Zani, P.; Maccagnani, G., Chemistry of silyl thioketones. Part 5. Synthesis and properties of alkyl α-silyl thioketones: a comparison with aryl derivatives. *Journal of the Chemical Society, Perkin Transactions 1* **1989**, 2083-2088.

51. Steliou, K.; Mrani, M., Reagents for organic synthesis. Tin-assisted sulfuration: a highly potent new method for the conversion of carbonyl units into their corresponding thiocarbonyl analogs. *Journal of the American Chemical Society* **1982,** *104*, 3104-3106.

52. Ozturk, T.; Ertas, E.; Mert, O., Use of Lawesson's Reagent in Organic Syntheses. *Chemical Reviews* **2007,** *107*, 5210-5278.

53. Bergman, J.; Pettersson, B.; Hasimbegovic, V.; Svensson, P. H., Thionations Using a P4S10−Pyridine Complex in Solvents Such as Acetonitrile and Dimethyl Sulfone. *The Journal of Organic Chemistry* **2011,** *76*, 1546-1553.

54. Curphey, T. J., Thionation with the Reagent Combination of Phosphorus Pentasulfide and Hexamethyldisiloxane. *The Journal of Organic Chemistry* **2002,** *67*, 6461-6473.

55. Polshettiwar, V.; Kaushik, M. P., Alumina encapsulated phosphorus pentasulfide (P4S10/Al2O3) mediated efficient thionation of long chain amides. *Tetrahedron Lett.* **2006,** *47*, 2315-2317.

56. Kingi, N.; Bergman, J., Thionation of Tryptanthrin, Rutaecarpine, and Related Molecules with a Reagent Prepared from P4S10 and Pyridine. *The Journal of Organic Chemistry* **2016,** *81*, 7711-7716.

57. Legnani, L.; Toma, L.; Caramella, P.; Chiacchio, M. A.; Giofrè, S.; Delso, I.; Tejero, T.; Merino, P., Computational Mechanistic Study of Thionation of Carbonyl Compounds with Lawesson's Reagent. *The Journal of Organic Chemistry* **2016,** *81*, 7733-7740.

58. Wasserman, H. H.; Vinick, F. J., Mechanism of the Robinson-Gabriel synthesis of oxazoles. *The Journal of Organic Chemistry* **1973,** *38*, 2407-2408.

59. Robinson, R., CCXXXII.—A new synthesis of oxazole derivatives. *Journal of the Chemical Society, Transactions* **1909,** *95*, 2167-2174.

60. Gabriel, S., Eine Synthese von Oxazolen und Thiazolen. I. **1910,** *43*, 134-138.

61. Garapati, V. K. R. Synthesis and Study of Oxazolium and Thiazolium Salts as Organocatalysts. University of Saskatchewan**,2021**.

62. Hinderling, R.; Prijs, B.; Erlenmeyer, H., Über α-Alkylamino-ketone. *Helvetica Chimica Acta* **1955,** *38*, 1415-1420.

63. Schönberger, S.; Jagdhuber, C.; Ascherl, L.; Evangelisti, C.; Klapötke, T. M.; Karaghiosoff, K., New Acyclic Neutral Phosphorus Sulfides and Sulfide Oxides. *Zeitschrift für anorganische und allgemeine Chemie* **2014,** *640*, 68-75.

64. Minshall, P. C.; Sheldrick, G. M., Pyridinium 2,2,5,5-tetrathio-cyclo-di(phosphadithianate), [(pyridine)2H]22+[P2S8]2−. *Acta Crystallographica Section B* **1978,** *34*, 1378-1380.

65. Rotter, C. Matching Phosphorus and Chalcogens - New Chemistry with Old Elements. Ludwig-Maximilian University of Munich**2009**.

66. Selzer, T.; Rappoport, Z., Triphenylethenethiol. Structure, Equilibria with the Thioketone, Solvation, and Association with DMSO. *The Journal of Organic Chemistry* **1996,** *61*, 5462-5467.

67. Paquer, D. V., J, *J. Bull. Soc. Chim. Fr.* **1971**, 4407.

68. Schönberger, S. Phosphorus, Sulfur and Pyridine: a Unique Combination to a Great Structural Diversity Ludwig-Maximilian University of Munich**2013**.

69. Kiryanov, A. A.; Sampson, P.; Seed, A. J., Synthesis of 2-Alkoxy-Substituted Thiophenes, 1,3-Thiazoles, and Related S-Heterocycles via Lawesson's Reagent-Mediated Cyclization under Microwave Irradiation: Applications for Liquid Crystal Synthesis. *The Journal of Organic Chemistry* **2001,** *66*, 7925-7929.

70. Kolodziej, K.; Romanowska, J.; Stawinski, J.; Kraszewski, A.; Sobkowski, M., The case of triethylammonium cation loss during purification of certain nucleotide analogues: a cautionary note. *Analytical and Bioanalytical Chemistry* **2015,** *407*, 1775-1780.

71. Arduengo, A. J.; Harlow, R. L.; Kline, M., A stable crystalline carbene. *Journal of the American Chemical Society* **1991,** *113*, 361-363.

72. Arduengo III, A. J.; Goerlich, J. R.; Marshall, W. J., A Stable Thiazol-2-ylidene and Its Dimer. **1997,** *1997*, 365-374.

73. Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.-P.; Ebel, K.; Brode, S., Preparation, Structure, and Reactivity of 1,3,4-Triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene, a New Stable Carbene. **1995,** *34*, 1021-1023.

74. Laks, J. A. S.; Ross, J. R.; Bayomi, S. M.; Sowell Sr, J. W., Synthesis of N-1-Substituted 2-Amino-3-t-butoxycarbonyl-4,5- dimethylpyrroles. *Synthesis* **1985,** *1985*, 291-293.

75. Mattson, R. J.; Wang, L.-C.; Sr., J. W. S., Synthesis of substituted 2-amino-3-(alkyl or aryl)sulfonylpyrroles. **1980,** *17*, 1793-1795.

76. Bunescu, A.; Piemontesi, C.; Wang, Q.; Zhu, J., Heteroannulation of arynes with N-aryl-α-aminoketones for the synthesis of unsymmetrical N-aryl-2,3-disubstituted indoles: an aryne twist of Bischler–Möhlau indole synthesis. *Chemical Communications* **2013,** *49*, 10284-10286.

77. Fürstner, A.; Alcarazo, M.; César, V.; Lehmann, C. W., Convenient, scalable and flexible method for the preparation of imidazolium salts with previously inaccessible substitution patterns. *Chemical Communications* **2006**, 2176-2178.

78. Vankar, Y. D.; Shah, K.; Bawa, A.; Singh, S. P., Chemistry of α-nitroepoxides : Synthesis of useful intermediates via nucleophilic ring opening of α-nitroepoxides. *Tetrahedron* **1991,** *47*, 8883-8906.

79. Li, X.; Chen, M.; Xie, X.; Sun, N.; Li, S.; Liu, Y., Synthesis of Multiple-Substituted Pyrroles via Gold(I)-Catalyzed Hydroamination/Cyclization Cascade. *Organic Letters* **2015,** *17*, 2984-2987.