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Synthesis of Chiral N-Heterocyclic Carbene Precursors and Key Intermediates for Catalytic Enantioselective Cyclizations of Conjugated Trienes

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SYNTHESIS OF CHIRAL *N*-HETEROCYCLIC CARBENE PRECURSORS AND KEY INTERMEDIATES FOR
CATALYTIC ENANTIOSELECTIVE CYCLIZATIONS OF CONJUGATED TRIENES

by

PHILLIP D. WILKERSON

Under the Direction of Professor Hao Xu

ABSTRACT

Cocatalyzed reactions using Brønsted acids and chiral *N*-heterocyclic carbenes to yield highly enantioselective products have been reported recently in many journals. The development of new chiral *N*-heterocyclic carbenes is a competitive field among synthetic chemist. In a recent study we found that conjugated trienes could be cyclized using Brønsted acids and chiral *N*-heterocyclic carbenes. The synthesis of novel chiral *N*-heterocyclic carbene precursors, and the precursors to novel conjugated trienes are reported herein.

INDEX WORDS: Asymmetric Catalysis, Catalyst Design, *N*-heterocyclic carbenes

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CATALYTIC ENANTIOSELECTIVE CYCLIZATIONS OF HIGHLY CONJUGATED TRIENES

by

PHILLIP D. WILKERSON

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Science

in the College of Arts and Sciences

Georgia State University

2012

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2012

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College of Arts and Sciences

Georgia State University

May 2012

DEDICATION

I would like to dedicate my thesis to my loving mother, Belenda Wilkerson. After the death of my father, Mickey Wilkerson, when I was 13 years old, she has made sure I had every opportunity possible to further my education. By her love, encouragement, and support, I have been able to pursue my own personal endeavors, which has led me to successfully obtain my goals. Thank you “Woman”, I love you.

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I would first like to acknowledge Professor Hao Xu, for allowing me to work and grow as a chemist in his lab. I would also like to thank Dr. Guansai Liu for his help, patience, and inspiration as a chemist in the lab. He represented what a true friend and colleague were with his actions and motivation in our lab group. I would also like to thank Dr. Al Baumstark and Dr. Jeremiah Harden for their words of guidance and inspiration throughout my graduate track. I would also like to thank Chris Toth for being an excellent friend and coworker throughout our graduate pursuit.

TABLE OF CONTENTS

| | |
|--|-----------|
| ACKNOWLEDGEMENTS | v |
| LIST OF FIGURES | vii |
| 1 INTRODUCTION (LITERATURE REVIEW)..... | 1 |
| 1.1 Carbenes | 1 |
| 1.2 N-Heterocyclic Carbenes | 2 |
| 1.3 Cooperative Catalysis | 4 |
| 2 PROPOSED SYNTHESIS OF PRECURSORS FOR BIFUNCTIONAL CHIRAL NHCs | 7 |
| 2.1 Bifunctional Chiral NHCs | 7 |
| 2.2 Results of Synthesis of Precursors to Bifunctional Triazole Carbenes..... | 7 |
| 3 PROPOSED SYNTHESIS OF THE BUILDING BLOCKS TO VINYL SUBSTRATES..... | 11 |
| 3.1 Stetter Cyclization | 11 |
| 3.2 Results of the Synthesis of Precursors to Vinyl Substrates..... | 12 |
| 3.3 Results of the Synthesis of Precursors to Vinyl Iodide Substrates | 13 |
| 4 CONCLUSIONS..... | 15 |
| 5 EXPERIMENTAL..... | 16 |
| 5.1 General Information..... | 16 |
| 5.2 General Synthesis of the Building Blocks to Bifunctional NHCs | 17 |
| 5.3 General Synthesis to the Precursors of Vinyl Tin Substrates..... | 21 |
| 5.4 General Synthesis to the Precursors of Vinyl Iodide Substrates | 22 |
| 5.5 Compound Characterization | 25 |
| 6 REFERENCES..... | 31 |
| 7 SPECTRA..... | 32 |

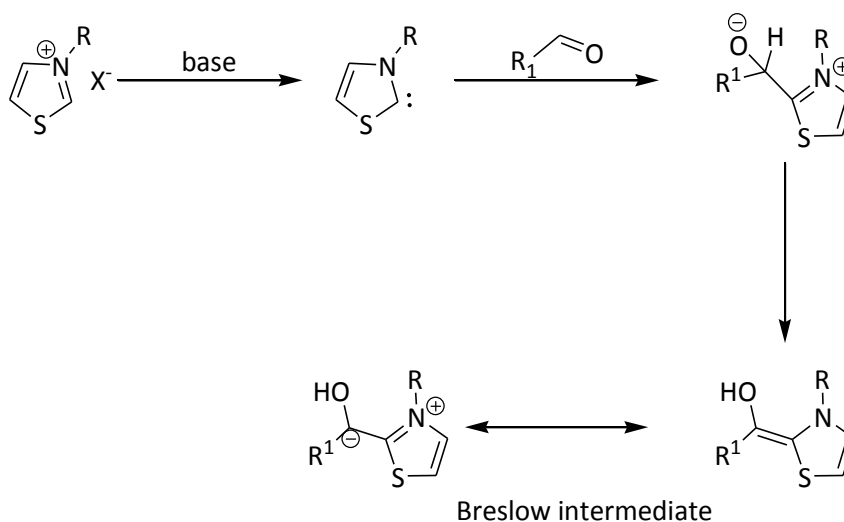
LIST OF FIGURES

| | |
|--|----------|
| Figure 1. 1,3-Di-1-adamamtyl-imidazol-2-ylidene..... | 2 |
| Figure 2. Benzoin Condensation of Ar. Aldehydes, Catalyzed by Triazolium Chiral Catalyst..... | 3 |

1 INTRODUCTION (LITERATURE REVIEW)

In 1943 Ukai¹ showed that acyl anions could be generated from aldehydes when in the presence of stoichiometric amounts of thiazolium salts which would then yield benzoin products. In 1958 Breslow² later demonstrated that the thiazolium salt is deprotonated to yield a carbene which then adds to the aldehyde to form an acyl anion, now commonly called the Breslow intermediate (Scheme 1).³

Scheme 1



1.1 Carbenes

A carbene is a neutral carbon atom that has two valence bonds and two unshared valence electrons. The carbene's lone pair is considered to either be in a singlet state, where the two unshared electrons are in the same orbital with antiparallel spins, or they are in a triplet state, where the unshared electrons are in different orbitals but have parallel spins. In the early 1960's Wanzlick⁴ was able to show that carbenes may not be unstable intermediates; by using vicinal amino substituents, Wanzlick greatly increased the stability of carbenes. This discovery would eventually lead Fischer⁵ to synthesize an electrophilic carbenic carbon that was completely stable in a transition metal complex in 1964. Years later Schrock⁶ synthesized a nucleophilic carbenic carbon, in which the polarization of the metal to carbon bond was found to be inverted. Between the time period of Fisher's first discovery and Schrock's later

nucleophilic carbenic carbon, Wanzlick⁷ and Öfele⁸ reported their independent research discoveries on the first *N*-heterocyclic carbene (NHC) complexes with transition metals. It would be another 20 years before Bertrand⁹ isolated the first stable carbene.¹⁰

1.2 *N*-Heterocyclic Carbenes

In 1991 Arduengo¹¹ *et al.* published the characterization of the first crystalline carbene, 1,3-adamantyl imidazole-2-ylidene. This carbene species was capable of forming complexes with transition metals, as seen in Figure 1. The stability of the imidazole-2-ylidene carbenes and their analogs proved to open the door for many transition metal carbene complexes and opened up new fields of research.¹⁰

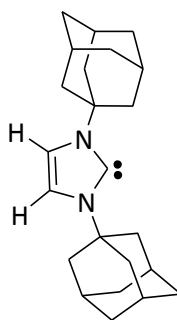


Figure 1.¹¹ 1,3-Di-1-adamantyl-imidazol-2-ylidene

Since Arduengo's crystalline carbene characterization, many researchers have made it their mission to not only discover new NHCs but to better understand the nature and reactivity of the NHCs.¹⁰ Recent studies have shown that carbene's reactivity can be controlled through steric manipulation and electronic parameters using heterocyclic rings.³

Development of NHCs with metal-catalyzed reactions was one of the directions that researchers used to better understand the reactivity potential of carbenes. One of the major contributions to NHC-metal catalysis was the discovery of NHC-ruthenium complexes. The stable NHC-ruthenium complexes would prove to be important in ring-closing metathesis of acyclic diene precursors to yield functionalized carbocycles and heterocycles.¹⁰ In the early 2000's, Hartwig¹², Cloke¹³, and Nolan¹⁴ proposed the importance of NHC-palladium complexes in the synthesis of forming carbon-carbon bonds through

known reactions like the Heck reaction, the Suzuki-Miyaura cross-coupling reactions and through telomerizations of alkenes.¹⁵ More recently Ghosh¹⁶ and co-workers proposed a new bifunctional NHC-nickel complex. These new bifunctional complexes contain both a Lewis acidic metal site and a Lewis basic amido-N site, which allows the ligands to successfully undergo base-free Michael addition reactions.

Metal-free organocatalysis offers not only reduced costs to the synthetic designs of NHCs, but could also decrease the environmental impact that metal-catalyzed reactions possess. Many synthetic chemists have approached the problem of developing organocatalyzed NHC reactions, by developing chiral carbene catalysts. Chiral catalysts are capable of producing desired products with high enantioselectivities. The growing demand for specific enantiomers or diastereomers of biologically active molecules in the pharmaceutical field has greatly increased the demand for chiral catalysts.

In 1996 Enders et al reported the first chiral triazolium-based catalyst, in which a triazolium salt catalyzes a benzoin reaction of an aromatic aldehyde to aromatic acyloin with enantioselectivities up to 86%, Figure 2.¹⁷ Enders would then shortly thereafter report the first asymmetric intramolecular Stetter reaction, a 1,4-michael addition of aldehydes to alkenes which are catalyzed by a thiazolium salt that is deprotonated by a weak base, which created a catalytic pathway to a field of enantiomerically enriched acetates.¹⁸ Since the exposure of *N*-heterocyclic carbene's ability to promote the benzoin condensation, there has been a tremendous increase in the number of publications that report NHC-catalyzed reactions.¹⁰

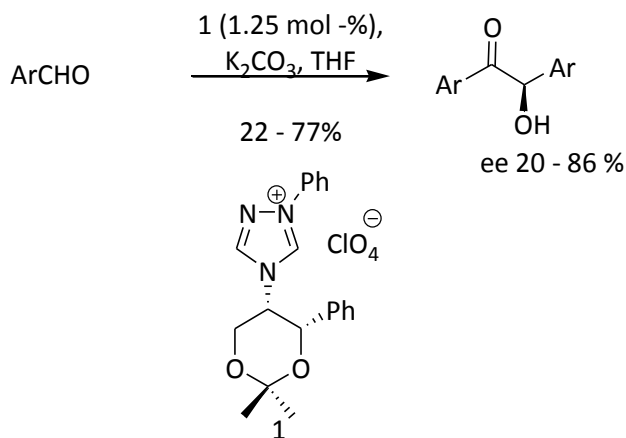


Figure 2. Benzoin Condensation of Ar. Aldehydes, Catalyzed by Triazolium Chiral Catalyst

Rovis¹⁹ and co-workers expounded greatly upon the development of NHC catalyzed intramolecular Stetter reactions. In 2004 Rovis *et al.* showed a promising enantioselective intramolecular Stetter reaction of salicylaldehyde derivatives aminoindanol and phenylalanine-derived catalyst.¹⁹ Later in 2004 Rovis and co-workers began to capitalize on the use of NHCs by generating quaternary stereocenters through a catalytic asymmetric Stetter reaction. They found that Stetter reactions of aliphatic ketones catalyzed by aminoindanol triazolium salts yielded 1,4-dicarbonyl compounds with quaternary stereocenters in high yields and selectivities.²⁰ Since Rovis NHC studies began in 2000, triazolium NHCs have shown to be more versatile than their thiazolium and imidazolium NHCs because of the available number of sites for structural and electronic modifications. Combining amino alcohols or amino acid derivatives with a variety of hydrazines, Rovis and co-workers were able to produce a variety of bench stable triazolium salts.³ Most recently, in 2011 Rovis *et al.* published their findings of cooperative NHC/Brønsted acid catalysis of α,β -unsaturated imines with enals to yield *trans*- γ -lactams with high enantioselectivities and high yields.²¹

1.3 Cooperative Catalysis

In similarity to the bifunctional NHC-nickel complexes described earlier, there has been an increase in cooperative catalysis as a strategy for asymmetric synthesis. Cooperative catalysis provides

new modes for activating molecules through the combination of Lewis base and Lewis Acid substrate activation, which can then lead to new reactivity and selectivity patterns. *N*-heterocyclic carbenes are part of a privileged class of Lewis bases in asymmetric organocatalysis.²² When NHcs are used cooperatively with Lewis acids the field of carbene catalysis is greatly enhanced.²³

The use of bifunctional catalysts has also shown to drastically increase the efficiency of asymmetric synthesis with relation to enantioselectivity and conversion rate. A bifunctional catalyst contains both a Lewis acid moiety and a Lewis Base moiety. Catalyst that contain both an electrophilic and a nucleophilic substrate could lead to stronger stereodiscrimination and higher enantioselectives. In 1997 Shibasaki demonstrated efficient carbon-carbon, C-S, C-P, C-O, and C-H bond forming reactions employing chiral heterobimetallic complexes as catalysts. Groger *et al.* were able to design monometallic and bifunctional phosphinoyl-containing catalysts. The catalysts were able to coordinate with both electrophilic substrates and nucleophilic substrates in a transition state, which enabled a highly enantioselective process.²⁴

As stated before, many synthetic chemists have demonstrated the advantages of NHC mediated organocatalysis in conjunction with Brønsted acid cocatalysts. Recently Song²⁵ and co-workers have proposed a new idea of bifunctional NHCs. Using the idea of acid/base catalysis work done by Saito²⁶ and Lectka they began the synthesis of bifunctional chiral NHCs. Starting with *L*-pyroglutamic acid, they constructed a similar triazolium salt catalyst similar to Rovis' triazole-2-ylidene. When the silyl group of the NHC precursors is deprotected, a possible site for hydrogen bonding opens. When this theory was tested by employing their novel catalyst towards the intermolecular benzoin condensation, benzoin products were obtained with > 97 % ee's.²⁵

Using the mechanistic scaffold of Rovis²¹ Stetter cyclization of enals and imines, which involves a cooperative NHC and Brønsted acid catalysis, novel bifunctional chiral NHCs were proposed to catalyze the Stetter cyclization. This cyclization would only involve the NHC catalyst and would not be syn-

thesized cooperatively with a Brønsted acid catalyst. By activating the imine with the NHC that first attacks the enal, the 1,4 addition of the enal to the imine is predicted to produce a cyclized product in high yields and with high ee's. The proposed syntheses of the precursors for these bifunctional chiral NHCs are described herein.

2 PROPOSED SYNTHESIS OF PRECURSORS FOR BIFUNCTIONAL CHIRAL NHCs

2.1 Bifunctional Chiral NHCs

Xu *et al.* cyclization of conjugated trienes used a chiral *N*-heterocyclic carbene and an acetic acid as a cocatalyst. . Similar to Rovis' synthesis of trans- γ -lactams, Xu and co-workers Stetter cyclization of trienes used Brønsted Acids to activate key intermediates.²¹⁻²² In both these publications and many others, an acid cocatalyst is needed to help facilitate the reaction. Even though Brønsted acids have shown to significantly enhance Stetter reactions by providing proton transfers and activating sights for nucleophilic attacks,²⁷ it has not been proven that the same, or better reactivity and yields could not be achieved if the intermediates are activated from another source other than the Brønsted acid.

Acknowledging the promising possibilities that bifunctional catalysts possess, the Xu group proposed a new approach towards novel bifunctional catalysts. These metal-free bifunctional catalysts offered the possibility of greater reactivity and higher enantioselectivity.

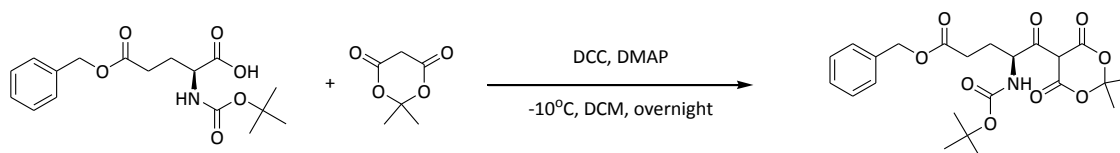
To design these catalysts a synthesis of Chiral 1,2,4-Triazolium Salts published by Rovis in 2005 was altered.²⁸ The compounds maintain a similar 1,2,4-triazolium backbone to serve as the carbene nucleophile precursor, and a chiral carbon for enantioselective reactions. A new feature of the structure would be designed to contain an area for hydrogen bonding, and activation to occur. With the novel bifunctional catalysts in mind, the synthetic route to the bifunctional catalysts left a trail of novel building blocks along the way. Each novel compound was not only a step closer to bifunctional catalysts, but a window to other syntheses yet to be explored.

2.2 Results of Synthesis of Precursors to Bifunctional Triazole Carbenes

A synthesis reported by Rovis²⁷ was slightly mimicked in the preparation of the bifunctional triazole carbene building blocks. Synthesis began with Boc-L glutamic and aspartic acid derivatives of β -benzyl esters. The butoxycarbonyl protected amino acids were reacted with *N,N'*-dicyclohexylcarbodiimide (DCC), 4-Dimethylaminopyridine(DMAP), and Meldrum's acid (Equation 1).

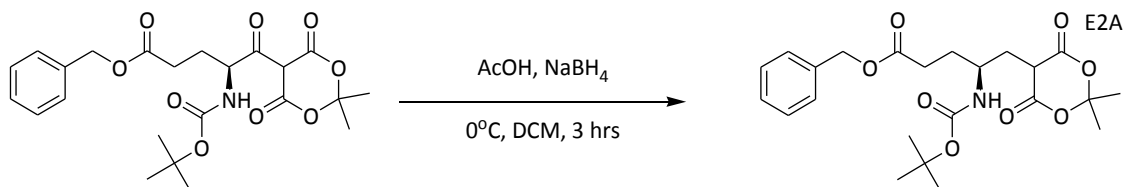
DCC and DMAP were used to activate the amino acid derivatives and promote coupling with Meldrum's acid. After filtering off the dicyclohexylurea produced during the reaction, the remaining DMAP was washed out with potassium bisulfate (KHSO_4). The organic extracts (DCM) were combined and used in the next synthesis without further purification.

Equation 1



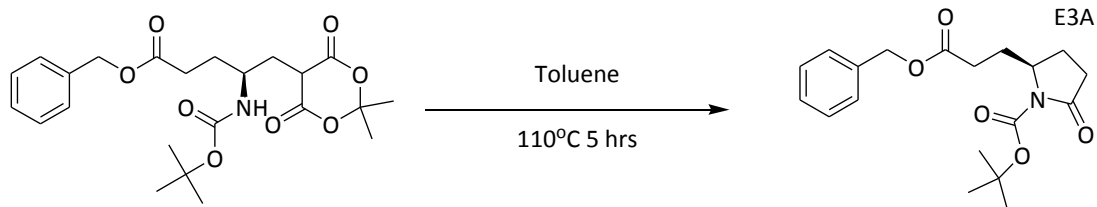
The product from Equation 1 was protonated with 98% acetic acid (11 eq AcOH) at -5°C . To this cold stirring solution was added sodium borohydride (2.5 eq NaBH_4) initiating the reduction of the acid carbonyl. The reaction continues until water is eliminated and the substrate is fully reduced (Reaction 2). The desired product **E2A** is then crystallized with ether to give a pure white solid with an overall yield of 60-75% for the two steps.

Equation 2



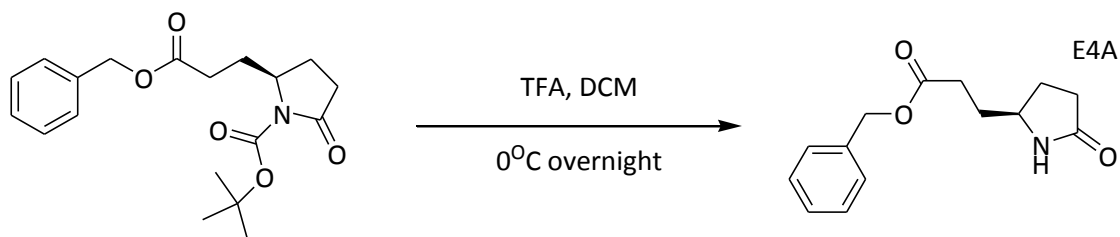
Compound **E2A** was refluxed in Toluene for 5 hours to ensure a complete decarboxylative ring closure. The reaction promotes the lone pair of the nitrogen atom to attack one of the carbonyls of the Meldrum's acid based structure. After intermolecular cleavage the cyclized product is a 5-substituted pyrrolidinone structure **E3A**, as seen in Equation 3. After flash chromatography, pure oil can be obtained with 74% yield.

Equation 3



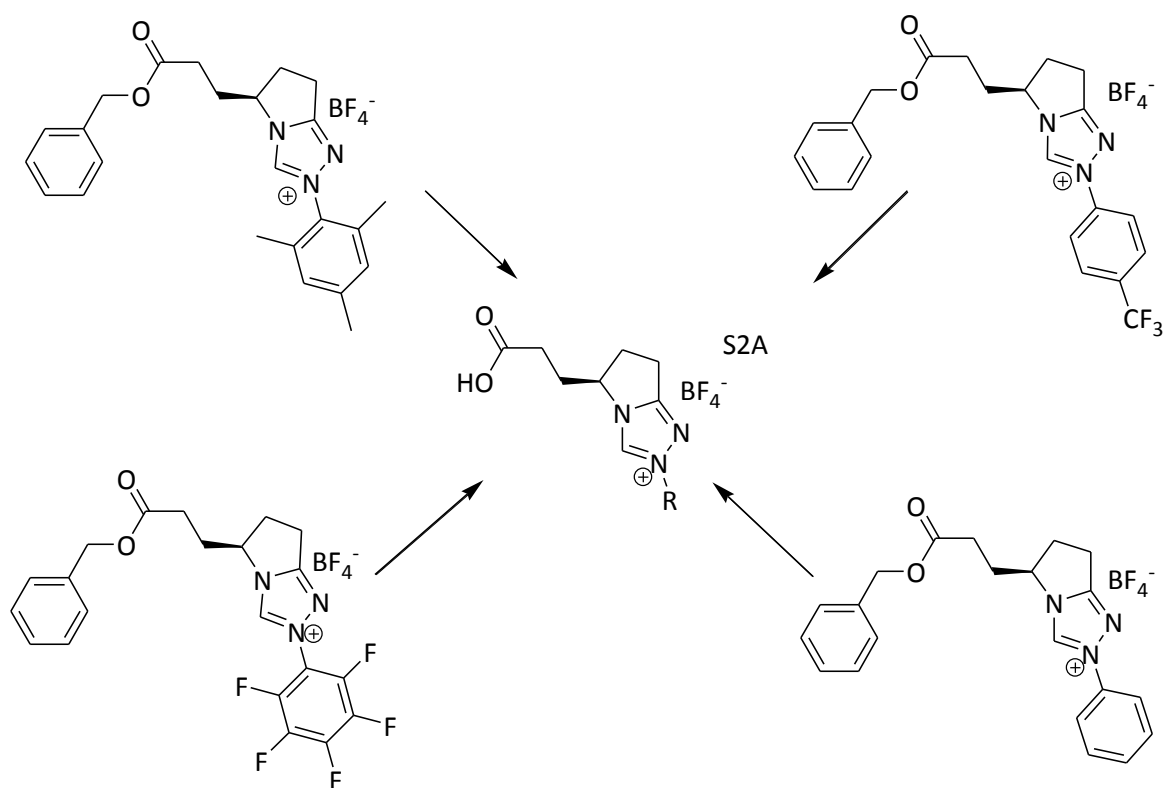
Compound **E3A** was deprotected by reacting with trifluoroacetic acid in DCM at 0 °C (Equation 4). With the Boc group removed, the product can be recovered from flash chromatography as a pure white solid with 70% yield, to give **E4A**.

Equation 4



Using Rovis'²⁷ scope of phenylhydrazine we predict that compound **E4A** can be used to synthesize an array of pyrrolidinone-derived catalyst precursors. These precursors could then be further reduced to produce potential bi-functional triazole catalysts **S2A** (Scheme 2).

Scheme 2



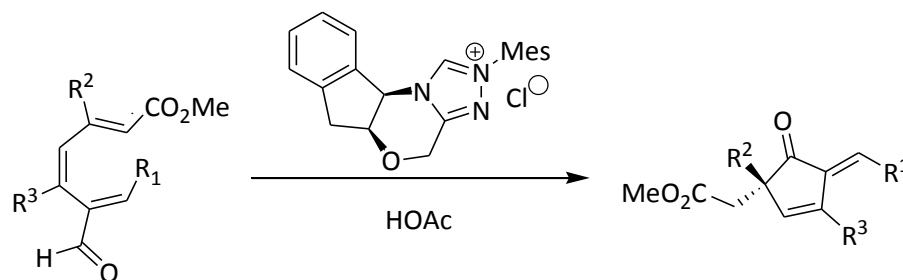
3 PROPOSED SYNTHESIS OF THE BUILDING BLOCKS TO VINYL SUBSTRATES

3.1 Stetter Cyclization

The benzoin condensation, a 1,2-addition, and the Stetter reaction, a 1,4-addition, are two known methods for forming carbon-carbon bonds. The benzoin condensation method adds aldehydes to carbonyl compounds to yield 2-hydroxy ketones, and the Stetter addition of aldehydes to unsaturated alkenes via a 1,4-michael addition yields an access pathway to form 1,4-bifunctional molecules.²⁹ The synthesis of 1,4-dicarbonyl compounds is mainly achievable from Stetter reactions.¹⁸

The selective catalysis of triene cyclizations has often eluded chemist in the synthetic field. The cyclization yields promising products that contain unique functional groups, which are often difficult to access by other syntheses. Xu *et al.* has recently shown²² that one Stetter cyclization product, a functionalized cyclopentenone, contains a quaternary stereogenic center and adjacent conjugated diene. The functionalized cyclopentenones are synthesized through highly enantioselective (98-99% ee) triene cyclizations, cocatalyzed by acetic acid and a chiral *N*-heterocyclic carbene (Equation 5).²² Screening of several privileged NHCs revealed that cooperative catalysis of aminoindanol-derived triazolium carbene and acetic acid worked best for the triene cyclizations.

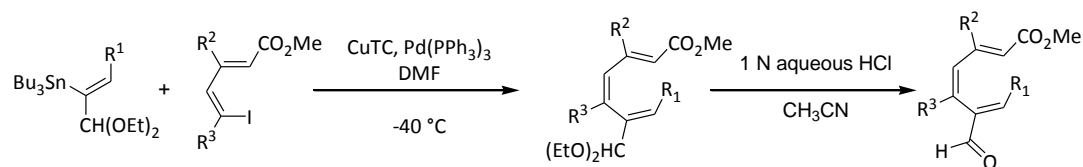
Equation 5



A Liebeskind modified Stille coupling³⁰ is used to link a vinyl tin substrates with vinyl iodide substrates, which is then deprotected to yield the conjugated triene seen in Scheme 3. By synthesizing different triene systems the chemical reactivity of the cyclopentenones could be altered. With different

substituents added the electronic effects of the allylic group could easily be changed and different groups could be synthesized for the chiral quaternary center.

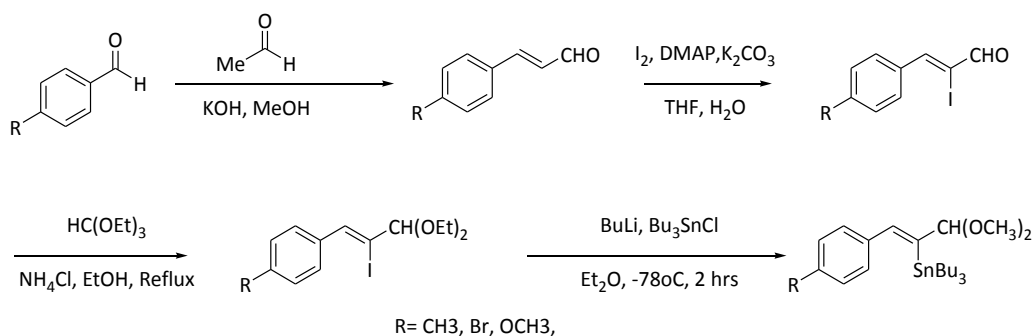
Scheme 3



3.2 Results of the Synthesis of Precursors to Vinyl Tin Substrates

As part of the research design to synthesize the conjugated trienes, several novel compounds were synthesized along the way. To synthesize the vinyl tin products, substituted benzaldehyde undergoes cross-aldol condensations to yield α,β -unsaturated aldehydes with moderate yields. The substituted benzaldehydes were chosen based on their ability to represent a wide range of substrates covering electron donating to electron withdrawing groups.³¹ The substituted α,β -unsaturated aldehydes undergo an iodination to yield substituted α -iodoaldehydes in moderate yields. These α -iodoaldehydes are then protected with triethyl orthoformate to yield the protected α -iodoaldehydes in excellent yields (Scheme 4). Lithiation of the iodoacetals, followed by a tin substitution could yield the vinyl tin substrates, which would not be isolated before further synthesis.

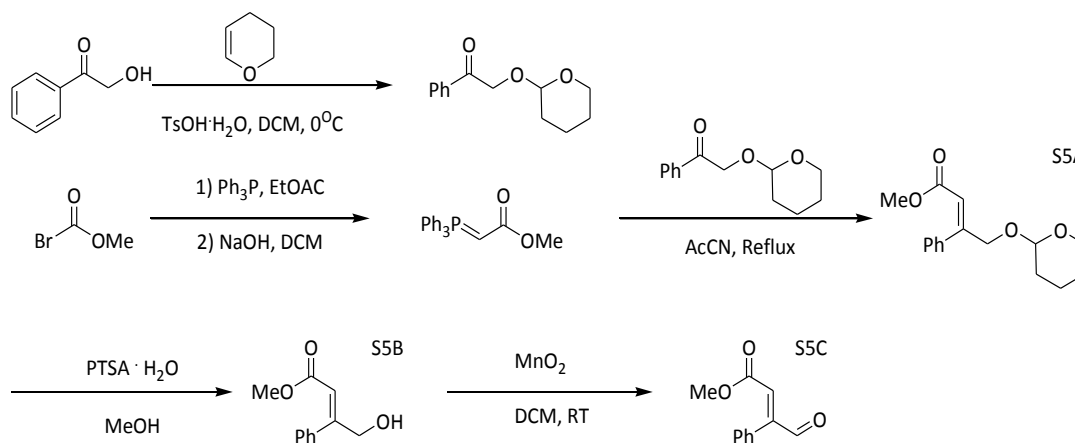
Scheme 4³²



3.3 Results of the Synthesis of Precursors to Vinyl Iodide Substrates

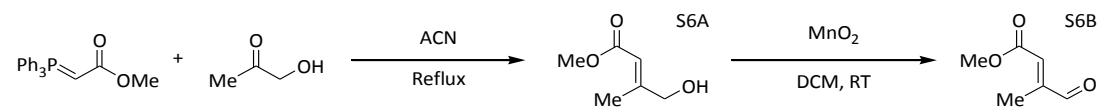
The vinyl iodide building blocks were synthesized using a Wittig reaction with a phosphorus ylide substrate followed by deprotonation of the hydroxyl group. First phosphorane is generated via addition elimination synthesis with triphenylphosphine and methyl bromoacetate.³³ The phenyl based vinyl iodide substrate was synthesized by first treating 2-hydroxyacetophenone with dihydropyran to yield a protected tetrahydropyranylation product of 2-hydroxyacetophenone.³⁴ The protected 2-hydroxyacetophenone then undergoes a Wittig reaction with the synthesized phosphorane to yield Compound **S5A** in great yields. Compound **S5A** is then deprotected with strong acid to yield Compound **S5B** in moderate yields. The hydroxyl product is then oxidized manganese dioxide to convert the allylic alcohol to yield the allyl aldehyde product, Compound **S5C** in moderate yields (Scheme 5).³⁵ A Stork-Zhao Wittig Olefination³⁶ of Compound **S5C** could then be used to synthesize the vinyl iodide substrate.

Scheme 5



The methyl substituted vinyl iodide was carried out in a similar synthesis as the phenyl substituted vinyl iodide. Hydroxyacetone was directly reacted with the phosphorus ylide in acetonitrile to yield the Wittig reaction product Compound **S6A** in moderate yields. Allylic alcohol was then treated with manganese dioxide to yield the oxidation product, **S6B**, in moderate yields (Scheme 6).³⁵ A Stork-Zhao Wittig Olefination³⁶ of Compound **S6C** could then be used to synthesize the vinyl iodide substrate.

Scheme 6



4 CONCLUSION

Since the discovery of the *N*-heterocyclic carbene, many successful synthetic routes have been developed to capitalize on the carbene's reactive ability. Much work has gone into the synthetic route to find stable complexes that are capable of sustaining the activity of the carbene. Using the triazolium salt scaffold, novel building blocks to potential new chiral bifunctional NHC catalyst have been produced. Using glutamic acid and aspartic acid derivatives, six new compounds have been synthesized and characterized. These new compounds are the precursors to chiral bifunctional NHCs, and will hopefully be successful in highly enantioselective asymmetric Stetter cyclizations. The synthesis of three novel precursors to vinyl tin substrates has also been completed and the products were fully characterized. To complete the synthesis of the trienes, two vinyl iodide substrates were synthesized to couple with the different substituted vinyl tin substrates. Three new compounds were synthesized in making the phenyl substituted vinyl iodide substrates and the synthesis of these compounds with the characterization is reported herein.

5 EXPERIMENTAL

5.1 General Information

General Procedures

All reactions were performed in oven dried or flame-dried round bottom flasks and vials. Stainless steel syringes and cannulas were used to transfer air and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230 – 400 mesh) from Sigma Aldrich.

Materials

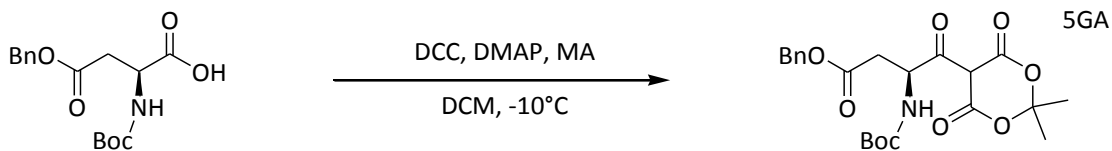
Commercial reagents were purchased from Sigma Aldrich, Fluka, EM Science, and Lancaster and used as received. All solvents were used after being freshly dispensed from SG Water anhydrous solvent system unless otherwise noted.

Instrumentation

Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker UltraShield – 400 (400 MHz) spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak (CDCl_3 : δ 7.26). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent (CDCl_3 : δ 77.0). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and integration. The mass spectroscopic data were obtained at the Georgia State University mass spectrometry facility using a Micromass Platform II single quadrupole instrument.

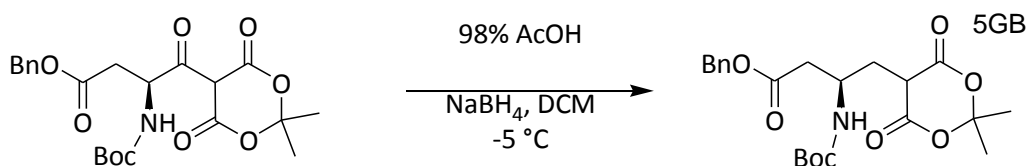
5.2 General Synthesis of the Building Blocks to Bifunctional NHCs

General procedure for synthesis of benzyl 3-(tert-butoxycarbonyl)-4-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4-oxobutanoate



Compound **5GA** is synthesized by following a reported procedure on a new molecule.²⁸ A 500 mL round bottom flask was charged with Boc-L-aspartic acid β-benzyl ester (10 g, 30.9 mmol), Meldrum's acid (4.90 g, 34.0 mmol), DMAP (5.66 g, 46.4 mmol), and CH₂Cl₂ (100 mL) and cooled to -10°C. To the cooled reaction mixture is added a solution of DCC (7.02 g, 34.0 mmol) in CH₂Cl₂ (50 mL) dropwise. The solution is stirred overnight at -10°C to completion. Upon warming to room temperature the solid, dicyclohexylurea, is filtered off and the reaction mixture is washed with 5% KHSO₄ (4 X 100 mL), brine, dried, and concentrated down to almost 200 mL and used in the next step without further purification.

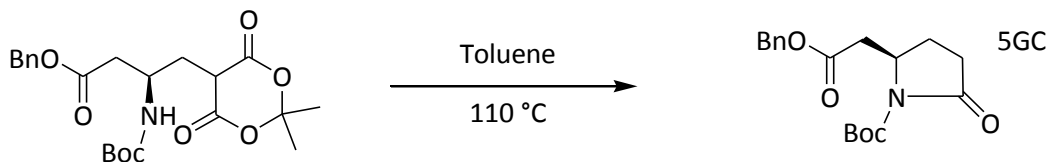
General procedure for synthesis of benzyl 3-(tert-butoxycarbonyl)-4-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)butanoate



Compound **5GB** is synthesized by following a reported procedure on a new molecule.²⁸ A 500 mL round bottom flask is charged with Compound (approximately 31 mmol, all of the material from previous step) in CH₂Cl₂ (200 mL) and 98 % AcOH (20 mL, 341 mmol). The solution is cooled to -5°C and stirred for 5 minutes. Then NaBH₄ (2.93 g, 77.5 mmol) is added to solution in portions over the next 3 hours. The reaction is then stirred at -5°C overnight until the reaction is complete. Upon completion

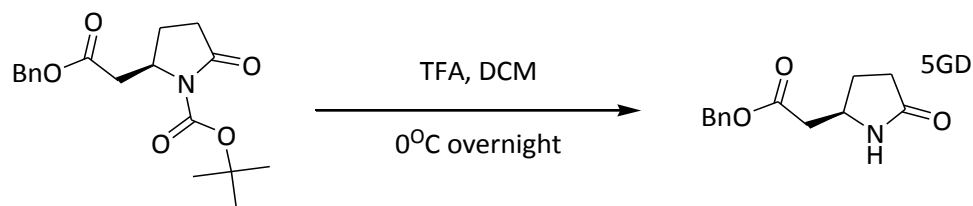
the reaction is washed, dried, and concentrated. The product is then crystallized from diethyl ether to yield Compound (8.51 g, 19 mmol, 63% from Compound, 75 % lit) a pure white solid.

General procedure for synthesis of tert-butyl 2-(2-(benzyloxy)-2-oxoethyl)-5-oxopyrrolidine-1-carboxylate



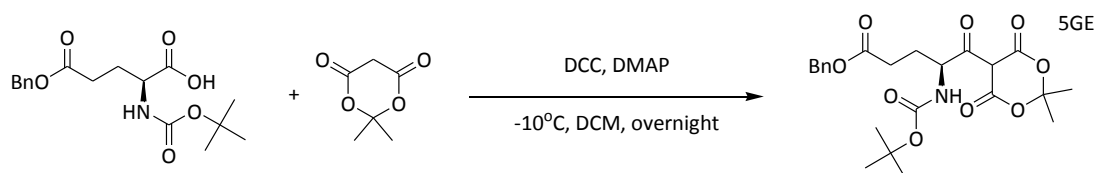
Compound **5GC** is synthesized by following a reported procedure on a new molecule.²⁸ A 250 mL round bottom flask is charged with Compound (8.51 g, 19.5 mmol) and toluene (100 mL, 940 mmol). This solution is heated to reflux for 5 hrs. or until reaction is complete. Upon completion the reaction is concentrated and purified by flash chromatography (DCM : MeOH = 20 : 1) which yields Compound (4.8 g, 14.4 mmol, 74% yield, lit did not purify) as a yellow oil.

General procedure for synthesis benzyl 3-(5-oxopyrrolidin-2-yl)propanoate



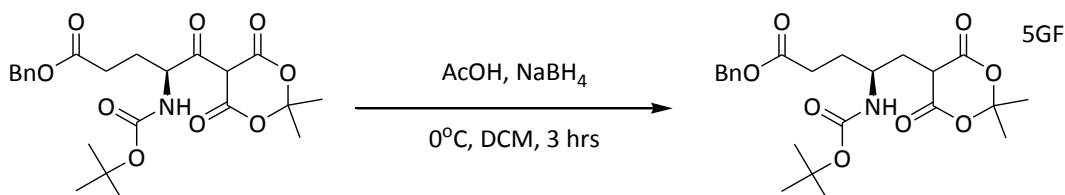
Compound **5GD** is synthesized by following a reported procedure on a new molecule.²⁸ A 250 mL round bottom flask is evacuated and refilled with argon, then compound(4.5 g, 13.5 mmol) is dissolved in CH₂Cl₂ (200 mL), and cooled to 0 °C. While stirring trifluoroacetic acid (2.27 mL, 29.7 mmol) is added dropwise to the solution. The reaction is allowed to warm to room temperature and is quenched with NaHCO₃ upon completion, washed, dried, and evacuated. Product is purified by flash chromatography (DCM : MeOH = 20 : 1) which yields Compound (2.2 grams, 9.4 mmol, 70 % yield) as a white solid.

General procedure for synthesis benzyl 4-(tert-butoxycarbonyl)-5-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-5-oxopentanoate



Compound **5GE** is synthesized by following a reported procedure on a new molecule.²⁸ A 500 mL round bottom flask was charged with Boc-L-aspartic acid β -benzyl ester (6.7 g, 20 mmol), Meldrum's acid (3.17 g, 22 mmol), DMAP (3.66 g, 30 mmol), and CH_2Cl_2 (100 mL) and cooled to -10°C . To the cooled reaction mixture is added a solution of DCC (4.53 g, 22 mmol) in CH_2Cl_2 (50 mL) dropwise. The solution is stirred overnight at -10°C to completion. Upon warming to room temperature the solid, dicyclohexylurea, is filtered off and the reaction mixture is washed with 5% KHSO_4 (4 X 100 mL), brine, dried, and concentrated down to almost 200 mL and used in the next step without further purification.

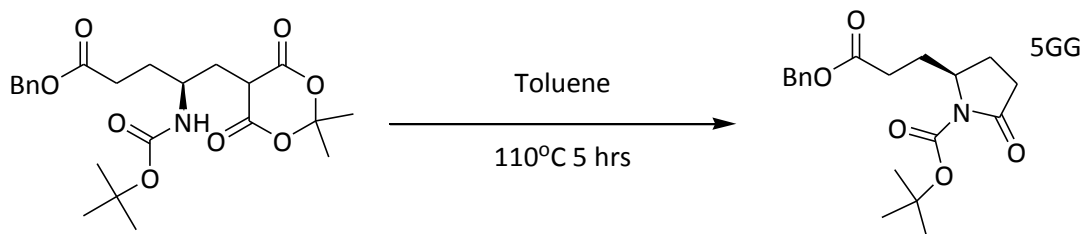
General procedure for synthesis of benzyl 4-(tert-butoxycarbonyl)-5-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)pentanoate



Compound **5GF** is synthesized by following a reported procedure on a new molecule.²⁸ A 500 mL round bottom flask is charged with Compound (approximately 20 mmol, all of the material from previous step) in CH_2Cl_2 (200 mL) and 98 % AcOH (13 mL, 225 mmol). The solution is cooled to -5°C and stirred for 5 minutes. Then NaBH_4 (1.92 g, 50 mmol) is added to solution in portions over the next 3 hours. The reaction is then stirred at -5°C overnight until the reaction is complete. Upon completion

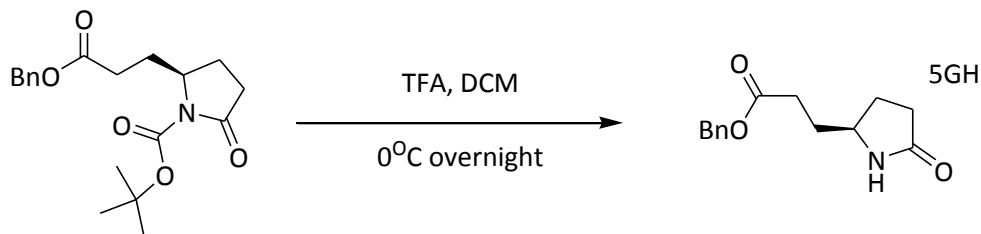
the reaction is washed, dried, and concentrated. The product is then crystallized from diethyl ether to yield Compound (6.1 g, 19 mmol, 67.5% from Compound , 75 % lit) a pure white solid.

General procedure for synthesis tert-butyl 2-(3-(benzyloxy)-3-oxopropyl)-5-oxopyrrolidine-1-carboxylate



Compound **5GG** is synthesized by following a reported procedure on a new molecule.²⁸ A 250 mL round bottom flask is charged with Compound (6.1 g, 13.5 mmol) and toluene (70 mL, 675 mmol). This solution is heated to reflux for 5 hrs. or until reaction is complete. Upon completion the reaction is concentrated and purified by flash chromatography (DCM : MeOH = 20 : 1) which yields Compound (4.4 g, 12.6 mmol, 93% yield , lit did not purify) as a yellow oil.

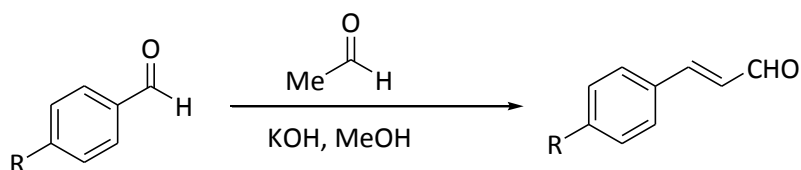
General procedure for synthesis benzyl 3-(5-oxopyrrolidin-2-yl)propanoate



Compound **5GH** is synthesized by following a reported procedure on a new molecule.²⁸ A 250 mL round bottom flask is evacuated and refilled with argon, then compound(4.4 g, 12.6 mmol) is dissolved in CH₂Cl₂ (200 mL), and cooled to 0 °C. While stirring trifluoroacetic acid (2.13 mL, 27.8 mmol) is added dropwise to the solution. The reaction is allowed to warm to room temperature and is quenched with NaHCO₃ upon completion, washed, dried, and evacuated. The concentrated compound yields (3.0 grams, 12.1 mmol, 96 % yield) a pure oil that is used without further purification.

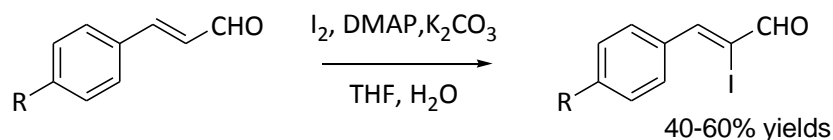
5.3 General Synthesis to the Precursors of Vinyl Tin Substrates

General procedure for Preparation of α,β -unsaturated Aldehydes



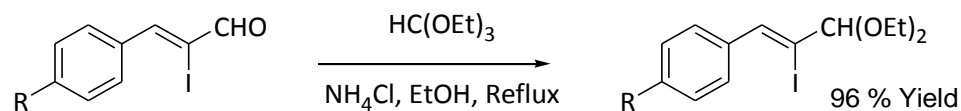
As reported in literature,³⁷ a 250 mL round bottom flask is charged with the substituted benzaldehyde (5.55 g, 30 mmol), acetaldehyde (1.98 g, 45 mmol,) and MeOH (150 mL) is stirred at 0 °C. To the stirring solution is added KOH (2.5 g, 35 mmol) dissolved in MeOH (150 mL) dropwise via graduated addition funnel of the span of four hours. The solution is allowed to slowly warm to room temperature, upon which it is quenched with 1 M HCl and extracted with CH₂Cl₂. The combined organic layers are washed with brine, dried with Na₂SO₄, and evacuated. The concentrate is purified by flash chromatography (DCM : MeOH = 100 : 1) to yield the substituted α,β -unsaturated aldehyde (2.9 g, 13.8 mmol, 46 % yield) as a pure oil.

General procedure for the preparation of α -iodoaldehydes



As reported in literature,³⁴ the aldehyde (12 mmol) was dissolved in a mixture of tetrahydrofuran/water (40 mL 1:1). Potassium carbonate (2.0 g, 14.4 mmol), iodine (4.5 g, 18 mmol), and 4-Dimethylaminopyridine (DMAP, 0.3 g, 2.4 mmol) were then added successively. After stirring at room temperature for 24 hours, the reaction mixture was diluted with CH₂Cl₂ and washed with saturated sodium thiosulfate solution. The combined organic layers were washed with brine, dried, and evacuated. Product was purified by flash chromatography (Hexanes : DCM = 1 : 2) yielded α -iodoaldehyde (40-60 % yield) as pure oils.

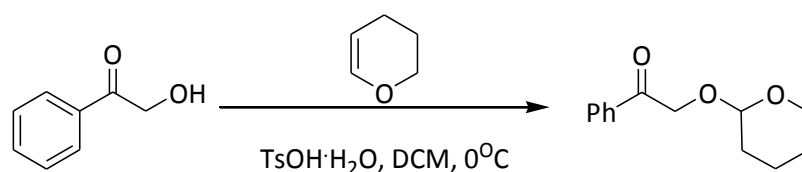
General procedure for the synthesis of α -Iodoacetals



To a stirred solution of α -iodoaldehyde (6.6 mmol) and triethyl orthoformate (1.4 g, 9.5 mmol) in ethanol (10 mL) was added ammonium chloride (15 mg, 0.26 mmol). After the addition, the mixture was stirred under refluxing condition until all the starting material was consumed. The mixture was then concentrated on rotovap. The concentrate is purified by flash chromatography (hexane : EtOAc : Et₃N = 20 : 80 : 5) to yield the z-diethoxy-2-iodoprop-1-enyl-p-benzene (6.3 mmol, 96%) as a pure oil.

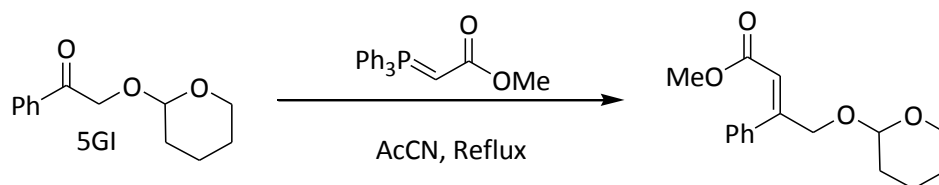
5.4 General Synthesis to the Precursors of Vinyl Iodide Substrates

General procedure for the preparation of 1-phenyl-2-(tetrahydro-2H-pyran-2-yloxy)ethanone



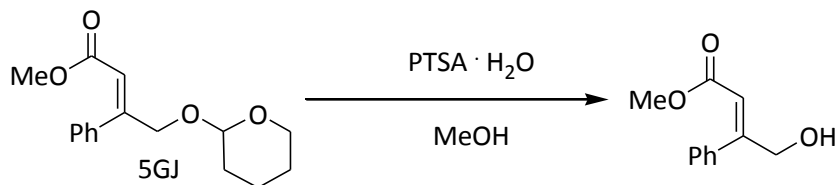
As reported in literature,³⁴ in a 250 mL round bottom flask, 2-hydroxyacetophenone (3.0 g, 22 mmol) is first mixed with toluenesulfonic acid monohydrate (.23 g, 1.1 mmol) in CH₂Cl₂ (130 mL). The solution is cooled to 0 °C and to the stirring solution is added dihydropyran (10.0 mL, 110.1 mmol,) and the solution is stirred until completion. The reaction is quenched with sodium carbonate, extracted with DCM, dried and evacuated. The concentrate is purified by flash chromatography (DCM : MeOH = 20 : 1) to yield a pure solid (3.9 g, 17.7 mmol, 80 % yield).

General procedure for the synthesis of (E)-methyl 3-phenyl-4-(tetrahydro-2H-pyran-2-yloxy)but-2-enoate



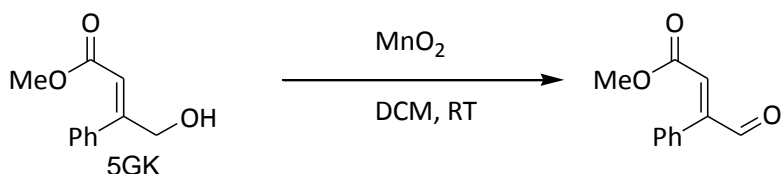
In a 100 mL round bottom flask Compound **5GI** (2.22 g, 10.07 mmol) and phosphorane (4.04 g, 12.09 mmol) is dissolved in acetonitrile (40 mL) and heated to reflux. During refluxing the condenser is raised to allow evaporation of the acetonitrile to greatly reduce the concentration. By reducing the concentration the reaction is able to go to completion. Any remainder acetonitrile is then evaporated on an oil pump. The concentration is then extracted with ether and purified by flash chromatography (hexane : ethyl acetate = 10 : 1) to yield (2.35 g, 8.5 mmol, 84 % yield) a pure oil.

General procedure for the synthesis of (E)-methyl 4-hydroxy-3-phenylbut-2-enoate



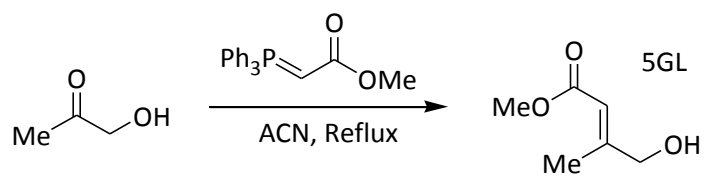
In a 100 mL round bottom flask Compound **5GJ** (2.24 g, 8.14 mmol) is dissolved in methanol (40 mL) and cooled to 0 °C. To the cooled solution is added toluenesulfonic acid monohydrate (0.077 g, 0.4 mmol) and stirred for at 4 hours. The reaction is quenched with sodium carbonate upon completion, extracted with ethyl acetate, dried, and evacuated. The concentrated solution is purified by flash chromatography (hexane : ethyl acetate = 10 : 1) to yield (1.24 g, 6.4 mmol, 80 % yield) a pure oil.

General Procedure for the synthesis of (E)-methyl 4-oxo-3-phenylbut-2-enoate



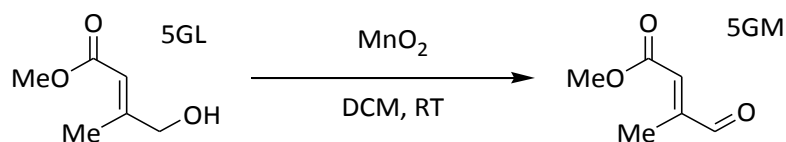
In a 100 mL round bottom flask Compound **5GK** (1.24 g, 6.4 mmol) is dissolved in CH_2Cl_2 (40 mL) and stirred at room temperature. To the stirring solution is added manganese dioxide (1.12 g, 12.9 mmol), and is allowed to stir for 2 hours. Every 2 hours another 2 equivalents of manganese dioxide is added until completion of reaction. The solution is filtered over celite, and purified by flash chromatography (hexane : ether = 10 : 1) to yield (1.09 g, 5.7 mmol, 89 % yield) a pure transparent solid.

General procedure for the preparation of (E)-methyl 4-hydroxy-3-methylbut-2-enoate



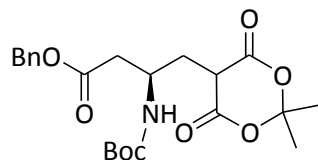
In a 100 mL round bottom flask hydroxyacetone (8.5 g, 114 mmol) and phosphorane (46 g, 137 mmol) is dissolved in acetonitrile (200 mL) and heated at reflux for four hours. The concentration is then purified by extraction with ether followed by flash chromatography (hexane : ethyl acetate = 10 : 1) to yield Compound **5GL** (12.54 g, 96.4 mmol, 84 % yield) as a pure oil.

General procedure for the preparation of (E)-methyl 3-methyl-4-oxobut-2-enoate

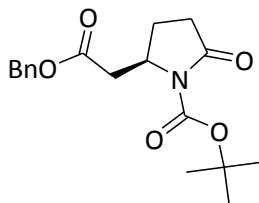


In a 100 mL round bottom flask Compound **5GL** (8.03 g, 61.7 mmol) is dissolved in CH_2Cl_2 (200 mL) and stirred at room temperature. To the stirring solution is added manganese dioxide (10.7 g, 123 mmol), and is allowed to stir for 2 hours. Every 2 hours another 1 equivalent of manganese dioxide is added until completion of reaction. The solution is filtered over celite, and purified by flash chromatography (hexane : ether = 10 : 1) to yield Compound **5GM** (5.45 g, 42.5 mmol, 69 % yield) as a pure oil.

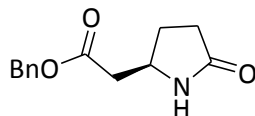
5.5 Compound Characterization



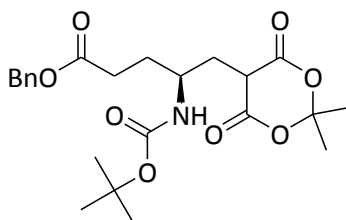
Benzyl 3-(tert-butoxycarbonyl)-4-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)butanoate: ^1H NMR (400 MHz, CDCl_3) δ ppm 7.38-7.33 (m, 5 H), 5.15 (s, 2H), 4.36-4.27 (m, 1H), 3.97 (d, 1H), 2.69-2.66 (dd, J = 8 Hz, 4 Hz, 2 H), 2.39-2.36 (m, 1H) 2.22-2.17 (m, 1 H), 1.81-1.75 (d, J = 24 Hz, 6 H), 1.41 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3): 171.06, 165.50, 165.37, 135.47, 128.65, 128.42, 128.35, 105.08, 79.82, 66.74, 46.14, 44.33, 39.47, 31.05, 28.62, 28.27, 25.89; HRMS (ESI-TOF) for $\text{C}_{23}\text{H}_{32}\text{NO}_8$ [$\text{M} + \text{Na}^+$] calculated 458.1791, found 458.1804



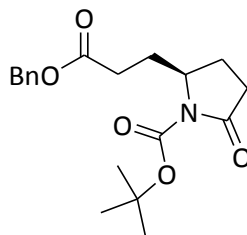
Tert-butyl 2-(2-(benzyloxy)-2-oxoethyl)-5-oxopyrrolidine-1-carboxylate ^1H NMR (400 MHz, CDCl_3) δ ppm 7.40-7.36 (m, 5 H), 5.17 (s, 2H), 4.58-4.52 (m, 1H), 3.00-2.95 (dd, J = 4 Hz, 16 Hz, 1H), 2.65-2.61 (m, 1 H), 2.60-2.55 (m, 1H) 2.50-2.42 (m, 1 H), 2.30-2.19 (m, 1 H), 1.91-1.85 (m, 1 H), 1.55 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3): 173.59, 170.23, 149.75, 135.62, 128.81, 128.42, 128.34, 83.29, 66.65, 54.57, 38.32, 30.96, 28.01, 22.99; HRMS (ESI-TOF) for $\text{C}_{18}\text{H}_{23}\text{NO}_5$ [$\text{M} + \text{Na}^+$] calculated 356.1474, found 356.1491



Benzyl 3-(5-oxopyrrolidin-2-yl)propanoate ^1H NMR (400 MHz, CDCl_3) δ ppm 7.42-7.35 (m, 5 H), 6.14, (s, 1H), 5.16 (s, 2H), 4.07-4.00 (m, 1H), 2.68-2.63 (dd, $J = 4$ Hz, 16 Hz, 1 H), 2.57-2.51 (dd, $J = 8$ Hz, 20 Hz, 1 H) 2.38-2.32 (m, 3 H), 1.79-1.68 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): 177.53, 171.03, 135.32, 128.61, 128.45, 128.29, 66.70, 50.37, 41.03, 29.51, 26.69; HRMS (ESI-TOF) for $\text{C}_{13}\text{H}_{16}\text{NO}_3$ [M^+] calculated 234.1130, found 234.1141

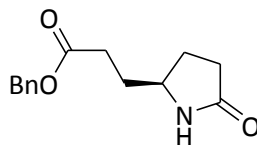


Benzyl 4-(tert-butoxycarbonyl)-5-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)pentanoate: ^1H NMR (400 MHz, CDCl_3) δ ppm 7.38-7.33 (m, 5 H), 5.13 (s, 2H), 4.56-4.54 (d, $J = 8.0$ Hz, 1H), 3.99-3.93 (d, $J = 24$ Hz, 1H), 2.51-2.47 (t, $J = 16$ Hz, 2 H), 2.30-2.23 (m, 1H) 2.19-2.16 (m, 1 H), 1.96-1.93 (m, 1 H), 1.81-1.76 (d, $J = 20$ Hz, 6 H), 1.40 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3): 172.93, 165.43, 156.50, 135.72, 128.50, 128.19, 128.17, 104.93, 79.60, 66.40, 49.34, 44.23, 32.01, 31.07, 30.50, 28.50, 28.19, 25.80; HRMS (ESI-TOF) for $\text{C}_{23}\text{H}_{32}\text{NO}_8$ [M^+] calculated 450.2128, found 450.2138

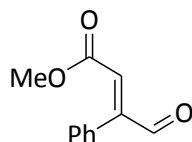


Tert-butyl 2-(3-(benzyloxy)-3-oxopropyl)-5-oxopyrrolidine-1-carboxylate: ^1H NMR (400 MHz, CDCl_3) δ ppm 7.36-7.32 (m, 5 H), 5.12 (s, 2H), 4.17-4.16 (m, 1H), 2.61-2.52 (m, 1 H), 2.45-2.38 (m, 3 H) 2.15-2.10 (m, 2 H), 1.90-1.85 (m, 1 H), 1.75-1.70 (m, 1 H), 1.51 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3): 173.85,

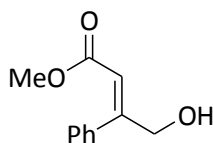
172.26, 149.82, 135.63, 128.49, 128.25, 128.21, 82.96, 66.42, 57.05, 31.16, 30.48, 28.88, 27.91, 22.38; HRMS (ESI-TOF) for $C_{19}H_{25}NO_5$ [M + Na⁺] calculated 370.1630, found 370.1648



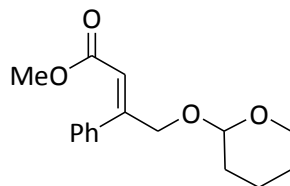
Benzyl 3-(5-oxopyrrolidin-2-yl)propanoate: 1H NMR (400 MHz, $CDCl_3$) δ ppm 7.39-7.36 (m, 5 H), 6.64, (s, 1H), 5.12 (s, 2H), 3.70-3.63 (m, 1H), 2.45-2.41 (t, $J = 16$ Hz, 2 H), 2.35-2.29 (q, $J = 24$ Hz, 2 H) 2.27-2.21 (m, 1 H), 1.88-1.83 (q, $J = 20$ Hz, 2 H), 1.72-1.69 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): 178.26, 172.65, 135.67, 128.56, 128.32, 128.28, 66.49, 53.69, 31.47, 30.58, 30.04, 26.90; HRMS (ESI-TOF) for $C_{14}H_{17}NO_3$ [M +] calculated 248.1287, found 248.1288.



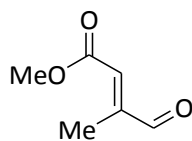
(E)-methyl 4-oxo-3-phenylbut-2-enoate: 1H NMR (400 MHz, $CDCl_3$) δ ppm 9.78 (s, 1 H), 7.44-7.42 (t, $J = 8$ Hz, 3H), 7.27-7.25 (m, 2H), 6.73 (s, 1H), 3.70 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): 192.85, 165.39, 148.76, 135.26, 131.06, 129.14, 128.88, 128.01, 52.07; HRMS (ESI-TOF) for $C_{11}H_{11}O_3$ [M +] calculated 191.0708, found 191.0709



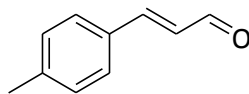
(E)-methyl 4-hydroxy-3-phenylbut-2-enoate: 1H NMR (400 MHz, $CDCl_3$) δ ppm 7.40-7.35 (m, 3H), 7.20-7.19 (d, $J = 4$ Hz, 2H), 6.21 (s, 1H), 4.36 (s, 2 H), 2.30 (s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): 166.67, 158.26, 136.97, 128.27, 128.15, 127.35, 114.96, 66.59, 51.26;



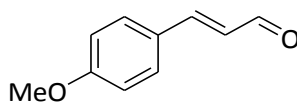
(E)-methyl 3-phenyl-4-(tetrahydro-2H-pyran-2-yloxy)but-2-enoate: ^1H NMR (400 MHz, CDCl_3) δ ppm 7.40-7.34 (m, 3H), 7.24-7.22 (m, 2H), 6.25 (s, 1H), 4.75-4.73 (t, $J = 8$ Hz, 1 H), 4.52-4.47 (dd, $J = 4$ Hz, 16 Hz, 1 H), 4.24-4.19 (dd, $J = 4$ Hz, 16 Hz, 1 H), 3.88-3.82 (m, 1 H), 3.59 (s, 3 H), 3.57-3.51 (m, 1 H), 1.81-1.69 (m, 3 H), 1.65-1.54 (m, 3 H); ^{13}C NMR (100 MHz, CDCl_3): 166.54, 158.18, 136.93, 128.13, 128.02, 127.26, 114.86, 94.40, 66.45, 63.86, 51.13, 31.87, 25.12, 20.22; HRMS (ESI-TOF) for $\text{C}_{11}\text{H}_{11}\text{O}_3$ [M +] calculated 227.1440, found 277.1446



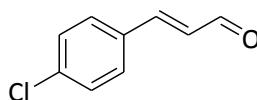
(E)-methyl 3-methyl-4-oxobut-2-enoate: known compound³⁸: ^1H NMR (400 MHz, CDCl_3) δ ppm 9.49 (s, 1 H), 6.46 (s, 1 H), 3.76 (s, 3 H), 2.09 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): 194.26, 165.76, 150.52, 134.79, 60.16, 51.79, 20.80, 14.00, 10.61



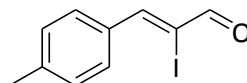
(E)-3-(p-tolyl)acrylaldehyde: known compound³⁷: ^1H NMR (400 MHz, CDCl_3) δ ppm 9.71 (d, $J = 7.6$ Hz, 1H), 7.46 (d, $J = 2.5$ Hz, 2H), 7.43 (d, $J = 16$ Hz, 1H), 7.24 (d, $J = 8$ Hz, 2H), 6.72 (dd, $J = 7.6, 16$ Hz, 1H), 2.39 (s, 3H)



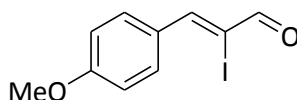
(E)-3-(4-methoxyphenyl)acrylaldehyde: known compound³⁹: ^1H NMR (400 MHz, CDCl_3) δ ppm 9.64 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 8 Hz, 2H), 7.42 (d, J = 16 Hz, 1H) 6.94 (d, J = 8 Hz, 2H), 6.60 (dd, J = 7.6, 16 Hz, 1H) 3.86 (s, 3H)



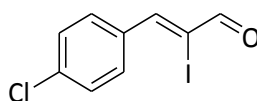
(E)-3-(4-chlorophenyl)acrylaldehyde: known compound⁴⁰: ^1H NMR (400 MHz, CDCl_3) δ ppm 9.70 (d, J = 7.6 Hz, 1H), 7.52–7.40 (m, 5H), 6.68 (dd, J = 16.0 Hz, 7.6 Hz, 1H)



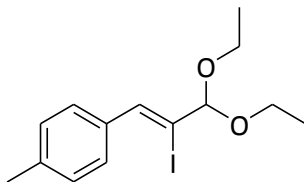
(Z)-2-iodo-3-p-tolylacrylaldehyde: known compound³⁹: ^1H NMR (400 MHz, CDCl_3) δ ppm 8.76 (s, 1 H), 8.06 (s, 1 H), 8.95 (d, J = 12.0 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H)



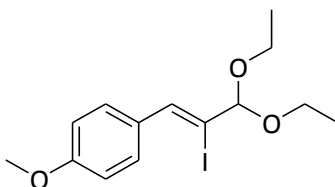
(Z)-2-iodo-3-(4-methoxyphenyl)acrylaldehyde: known compound³⁹: ^1H NMR (400 MHz, CDCl_3) δ ppm 8.74 (s, 1 H), 8.09 (d, J = 8.0 Hz, 2 H), 8.04 (s, 1 H), 7.02 (d, J = 8.0 Hz, 2 H), 3.89 (s, 3 H)



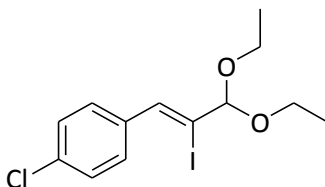
(Z)-3-(4-chlorophenyl)-2-iodoacrylaldehyde: known compound³⁹: ^1H NMR (400 MHz, CDCl_3) δ ppm 8.81 (s, 1 H), 8.07 (s, 1 H), 7.98 (d, J = 8.8 Hz, 2 H), 7.50 (d, J = 8.8 Hz, 2 H)



(Z)-1-(3,3-diethoxy-2-iodoprop-1-enyl)-4-methylbenzene : ^1H NMR (400 MHz, CDCl_3) δ ppm 7.52 (d, J = 8.0 Hz, 2 H), 7.27 (d, J = 4.0 Hz, 1 H), 7.18 (d, J = 8.0 Hz, 2 H), 4.72 (s, 1 H), 3.70–3.56 (m, 4 H), 2.36 (s, 3 H), 1.29 (t, J = 8.0 Hz, 6 H); ^{13}C NMR (100 MHz, CDCl_3): 138.4, 136.2, 133.6, 128.80, 128.76, 105.1, 103.8, 61.9, 21.4, 15.1; IR (film) ν_{max} , 3057 (w), 2975 (m), 2928 (w), 2878 (m), 1480 (w), 1445 (m), 1329 (m), 1116 (s), 1055 (s) cm^{-1} ; HRMS (ESI-TOF) for $\text{C}_{14}\text{H}_{19}\text{O}_2\text{INa}$ [$\text{M} + \text{Na}^+$] calculated 369.0328, found 369.0313



(Z)-1-(3,3-diethoxy-2-iodoprop-1-enyl)-4-methoxybenzene : ^1H NMR (400 MHz, CDCl_3) δ ppm 7.64 (d, J = 12.0 Hz, 2 H), 6.92 (d, J = 8.0 Hz, 1 H), 4.71 (s, 1 H), 3.84 (s, 3 H), 3.71–3.57 (m, 4 H), 1.30 (t, J = 8.0 Hz, 6 H); ^{13}C NMR (100 MHz, CDCl_3): 159.7, 135.7, 130.4, 128.0, 113.4, 105.2, 102.4, 61.9, 55.2, 15.1; IR (film) ν_{max} , 2829 (w), 1674 (s), 1595 (m), 1579 (s), 1557 (m), 1485 (m), 1407 (m), 1278 (m), 1078 (s), 1091 (s) cm^{-1} ; HRMS (ESI-TOF) for $\text{C}_{14}\text{H}_{19}\text{O}_3\text{INa}$ [$\text{M} + \text{Na}^+$] calculated 385.0277, found 385.0267



(Z)-1-chloro-4-(3,3-diethoxy-2-iodoprop-1-enyl)benzene: ^1H NMR (400 MHz, CDCl_3) δ ppm 7.55 (d, J = 8.8 Hz, 2 H), 7.36 (d, J = 8.0 Hz, 2 H), 7.29 (s, 1 H), 4.78 (s, 1 H), 3.74–3.56 (m, 4 H), 1.31 (t, J = 7.2 Hz, 6 H); ^{13}C NMR (100 MHz, CDCl_3): 135.16, 135.15, 134.17, 130.2, 128.3, 105.7, 104.9, 62.0, 15.1 ; IR (film) ν_{max} , 2976 (m), 2928 (w), 2879 (m), 1593 (m), 1564 (m), 1473 (m), 1409 (w), 1333 (w), 1257 (w), 1116 (s), 1055 (s) cm^{-1} ; HRMS (ESI-TOF) for $\text{C}_{13}\text{H}_{16}\text{O}_2\text{ClINa}$ [$\text{M} + \text{Na}^+$] calculated 388.9781, found 388.9777

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7 SPECTRUM

