THE STETTER REACTION: SYNTHESIS OF COMPLEX SPIRO BIS-INDANES AND STUDIES ON QUATERNARY CENTER FORMATION

A Thesis Submitted to the College of

Graduate Studies and Research

In Partial Fulfillment of the Requirements

For the Degree of Master of Science

In the Department of Chemistry

University of Saskatchewan

Saskatoon

By

JANICE M. HOLMES

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.

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

The Head

Department of Chemistry

University of Saskatchewan

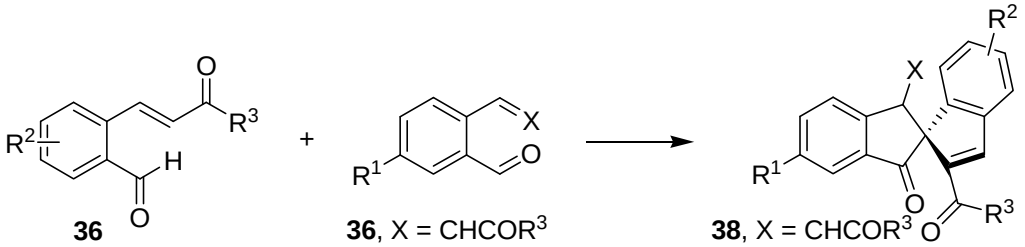
Saskatoon, SK S7N 5C9

CANADA

ABSTRACT

This work covers recent advances in the Stetter reaction, including two novel domino Stetter reactions and preliminary studies on quaternary center formation via the intermolecular Stetter reaction.

The *N*-heterocyclic carbene (NHC) catalyzed domino Stetter-aldol-Michael dimerization of *o*-formyl chalcone derivatives **36** affords spiro bis-indane homo-dimers **38** in good yields and moderate to high diastereomeric ratios. Three carbon-carbon bonds, including the hindered quaternary center at the spiro ring junction, form at a remarkable rate under mild reaction conditions. Spiro bis-indanes **39** are also produced in moderate to good yields through the Stetter-aldol-aldol reactions of *o*-formyl chalcones **36** with phthalaldehyde derivatives **27**. The scope, limitations, and potential applications of these remarkable complexity-generating domino reactions are discussed.



Preliminary results in the formation of quaternary centers via the intermolecular Stetter reaction are also disclosed. The viability of β,β-disubstitued Meldrum's acid, diethyl malonate, and malononitrile alkylidenes as well as diphenylcyclopropenone and 3-phenylcyclobutenone as acceptors in the Stetter reaction are discussed.

ACKNOWLEDGMENTS

I wish to express my sincere appreciation to my supervisor, Dr. Michel Gravel, for his amazing wisdom, patience, and encouragement. I would like to thank the members of my advisory committee, Dr. Soledade Pedras and Dr. Ed Krol for their valuable guidance. I am grateful for a postgraduate scholarship received from the Natural Sciences and Engineering Research Council of Canada and funding received from the Department of Chemistry.

I would like to express my gratitude to Eduardo for his instruction and collaboration, to Karen for her guidance and friendship, to Li for his remarkable insight and unending anecdotes, to Khalil for his impressive knowledge and incredible spirit, Dr. Marcelo Sales for his guidance, and to Dr. Majewski for sharing his lab. I am also grateful for the friendship of the remaining members of the Gravel Group: Craig, Crystal, Myron, Pouyan, Eric, Sida, and Steven.

I am truly grateful for my wise, loving parents, Linda and Dennis; my intelligent, talented, beautiful sisters, Cynthia, Kelly, and Heather; their incredible partners, Daryl and Matt; my adorable, creative, precious nieces and nephews, Ben, Sam, Des, Sloan, and Charlotte; and my dear Grandma Marg for a lifetime of love and support.

Among all my friends, I would particularly like to thank Kristen and Dave, Megan and Tyler, Kristen W., Deandra, Cara, Suzanne, and Rob for their amazing support and wonderful company; my former managers Darren, Petros, and Omar for their kindness; and my former co-workers Lisa, Joel, Kendra, Bevan, Andy, and Sam for sharing their amazing spirits.

This work is dedicated to my dear Grandmother,

Margaret Beryl Morrison

on the occasion of her 99th birthday.

TABLE OF CONTENTS

LIST OF TABLES

Table page

LIST OF FIGURES

LIST OF SCHEMES

Scheme page

LIST OF ABBREVIATIONS

Ar – aryl

Bn – benzyl

BuLi – butyl lithium

cat. - catalyst

d – days

DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene

DCC - *N*,*N*'-Dicyclohexylcarbodiimide

DMAP – 4-dimethylaminopyridine

DME - dimethoxyethane

DMF – dimethylformamide

dr – diastereomeric ratio

E^+ – electrophile

ee – enantiomeric excess

Et – ethyl

equiv. – equivalents

EWG – electron withdrawing group

FG – functional group

h - hours

IBX – 2-iodoxybenzoic acid

iPr – isopropyl

KHMDS – Potassium bis(trimethylsilyl)amide

LA – Lewis acid

LAH – lithium aluminum hydride

MCPBA – *meta*-chloroperoxybenzoic acid

Me – methyl

mol – mole

MW – microwave

NHC – *N*-heterocyclic carbene

NMR – nuclear magnetic resonance

nr – no reaction

o – ortho

Ph – phenyl

PTSA – *para*-toluenesulfonic acid

rt – room temperature

SAA – Stetter-aldol-aldol

SAM – Stetter-aldol-Michael

S_N2 – bimolecular nucleophilic substitution reaction

T – temperature

t – time

TBS – *tert*-butyldiphenylsilyl

TFAA – trifluoroacetic anhydride

THF – tetrahydrofuran

TMEDA - tetramethylethylenediamine

TMG – tetramethylguanidine

TLC – thin layer chromatography

PART I - INTRODUCTION

CHAPTER ONE

INTRODUCTION

1.1 N-Heterocyclic Carbene Catalysis of Aldehydes

Umpolung, the reversal of a functional group's innate reactivity, is a powerful tool in organic synthesis. Classical modes of reactivity only permit carbon-carbon bond formation of electron acceptors with electron donors. These electronic requirements inherently restrict the structure of the resulting molecule to an alternating acceptor-donor pattern. For this reason, disubstituted structures containing 1,3- and 1,5- functional group (FG) relationships are easily obtained by classical modes of reactivity, whereas 1,2- and 1,4- functional group relationships cannot be easily accessed (Figure 1-1). In contrast to classical reactivity, the *umpolung* of a formal acceptor permits the formation of a carbon-carbon bond between two classical acceptors. The bond formed between these two electron deficient carbons affords molecular structures with either 1,2- or 1,4-relationships of functional groups.[1]

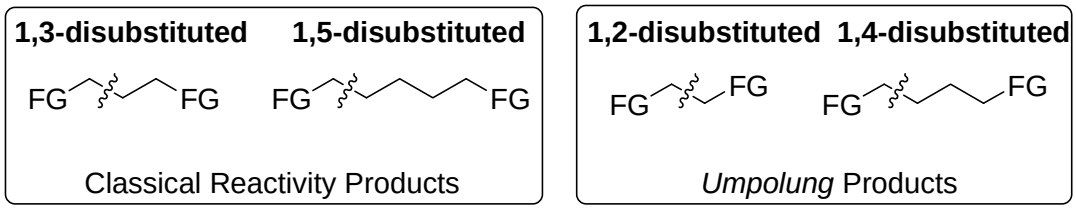
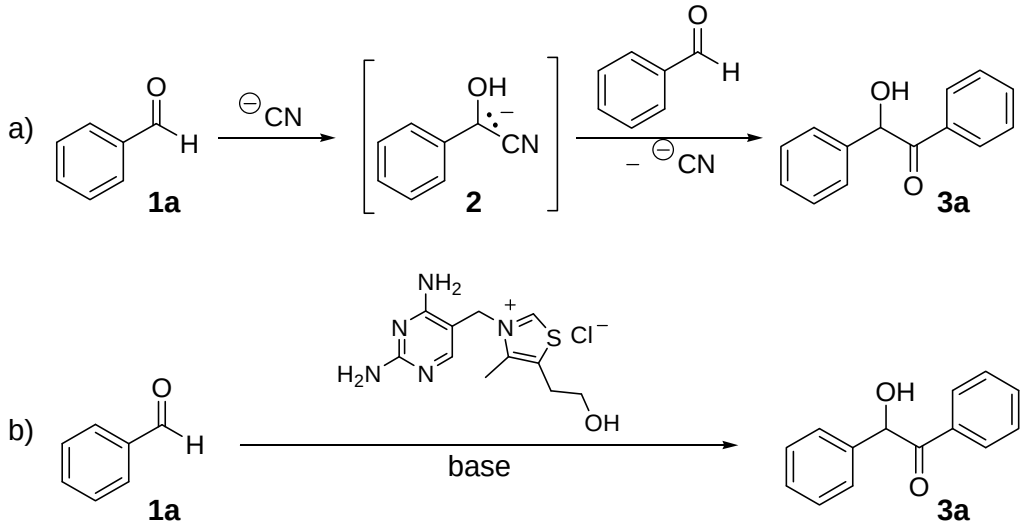


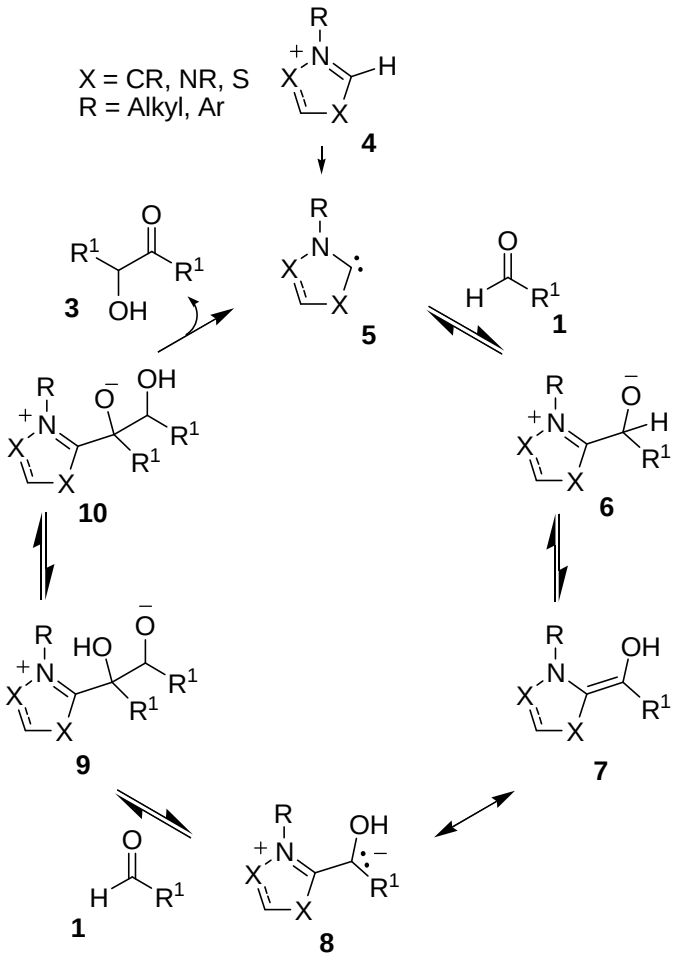
Figure 1-1 Products of Classical Reactivity and *Umpolung.*

A class of organic catalysts, known as *N*-heterocyclic carbenes (NHCs), has become increasingly popular in recent years, particularly for their use in *umpolung* reactions of aldehydes.[2] These remarkable catalysts effectively reverse the typical reactivity of an aldehyde from electron acceptor to electron donor, allowing for unique bond formation.

One of the most common NHC-catalyzed *umpolung* reactions is the coupling of aldehydes in the benzoin reaction. The self-condensation of benzaldehyde **1a** to produce the α-hydroxyketone, benzoin **3a**, was first reported in 1832 by Wöhler and Liebig (Scheme 1.1a).[3] This early example of the benzoin reaction employed cyanide to induce the *umpolung* of benzaldehyde. In 1903, Lapworth laid the groundwork for the elucidation of aldehyde *umpolung* mechanisms with his proposed mechanism for the cyanide promoted benzoin reaction.[4] Lapworth postulated that cyanide attack onto the carbonyl of **1a** followed by proton transfer would produce intermediate **2**. This resonance stabilized intermediate accounts for the nucleophilic reactivity of the formerly electron deficient carbon. In 1943, the first NHC-catalyzed benzoin reaction was reported (Scheme 1.1b).[5] Ukai and co-workers observed that in the presence of a base, thiamine promoted the coupling of benzaldehyde **1a** to produce benzoin **3a**.



Scheme 1.1 a) Lapworth's Proposed Intermediate for Wöhler and Liebig's Cyanide Catalyzed Benzoin Reaction. b) Ukai's NHC-Catalyzed Benzoin Reaction.

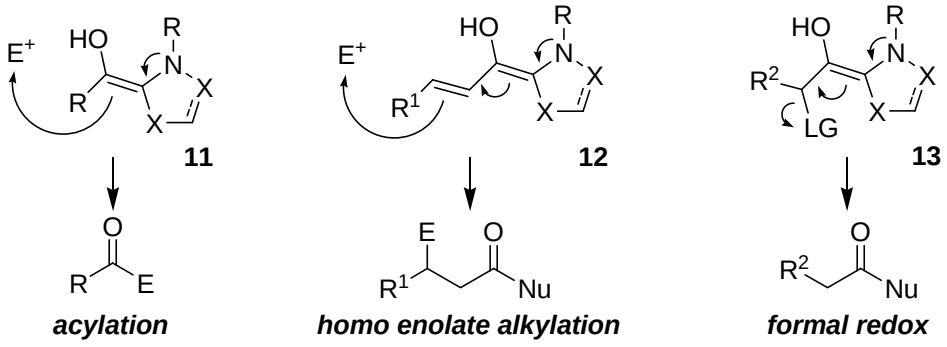


Scheme 1.2 NHC-Catalytic Cycle of Benzoin Reaction.

The NHC's reactivity is best rationalized by the mechanism for the benzoin reaction proposed by Breslow in 1958.[6] First, the highly reactive NHC species **5** is generated *in situ* by deprotonation of the thiazolium pre-catalyst **4** (Scheme 1.2). Then the carbene carbon of **5** attacks the electron deficient carbonyl of the aldehyde **1** to produce intermediate **6**. Subsequent intermolecular proton transfer affords the reactive Breslow Intermediate **7**. The newly nucleophilic carbon, best represented by resonance structure **8**, then reacts with another equivalent of aldehyde to form intermediate **9**. Proton transfer and the subsequent collapse of the tetrahedral alkoxide of **10** produces the α-

hydroxyketone product **3** and regenerates the NHC. As this reaction affords the same product as the reaction of the corresponding acyl anion, Breslow intermediate **7** is effectively an "acyl anion equivalent".

Since Ukai's discovery, NHC catalysis has been employed in a number of transformations. In addition to the acyloin reaction, the NHC-catalyzed acylation of conjugate addition acceptors in the Stetter reaction has also been extensively studied. However, NHC-catalyzed reactions of aldehydes are not limited to acylation reactions. Depending on the structure of the aldehyde, a number of reactions may occur following the formation of the Breslow intermediate.[2] The combination of an α,β-unsaturated aldehyde with an appropriate NHC affords a^3-d^3 *umpolung* of the enal allowing for alkylation of the β carbon of **12** (Scheme 1.3).[7] If the aldehyde possesses a leaving group on its α carbon, a formal redox reaction may occur (Scheme 1.3). Following the ejection of the leaving group of **13**, the keto form of the resulting species is attacked by a nucleophile and the NHC is ejected.[8]

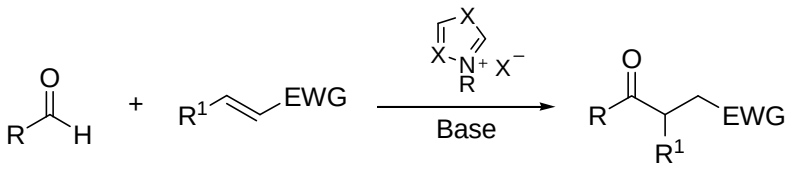


Scheme 1.3 NHC-Catalyzed Reactions of Aldehydes

1.2 The Stetter Reaction

The conjugate addition of an "acyl anion equivalent" onto an electron poor olefin was first reported by Stetter in 1973. Stetter's seminal work employed cyanide as the

umpolung inducing catalyst.[9] The first NHC-promoted Stetter reaction was reported in the following year (Scheme 1.4).[10] Stetter reactions employing NHCs have been reported with aliphatic, aromatic, and heteroaromatic aldehydes. NHC catalysts proved to be superior to cyanide catalysts in the promotion of the Stetter reactions of both aliphatic aldehydes and *o*-substituted benzaldehyde derivatives. The reactivity of the Stetter reaction is best rationalized through a mechanism analogous to the previously discussed mechanism for the benzoin reaction. In fact, the kinetically favoured yet reversible, benzoin reaction often competes with the Stetter pathway, and thus the benzoin products are often observed as intermediates in the Stetter reaction.

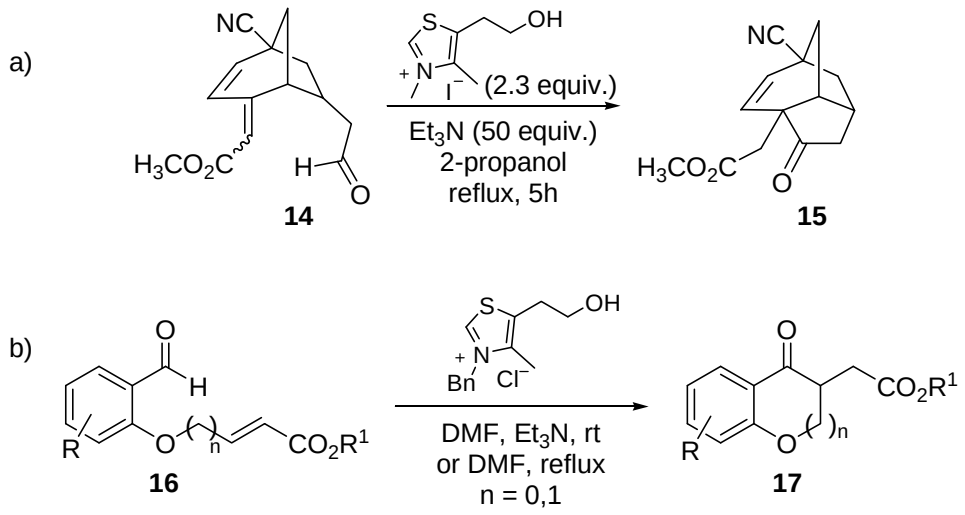


Scheme 1.4 The NHC-Catalyzed Stetter Reaction

1.2.1 The Intramolecular Stetter Reaction

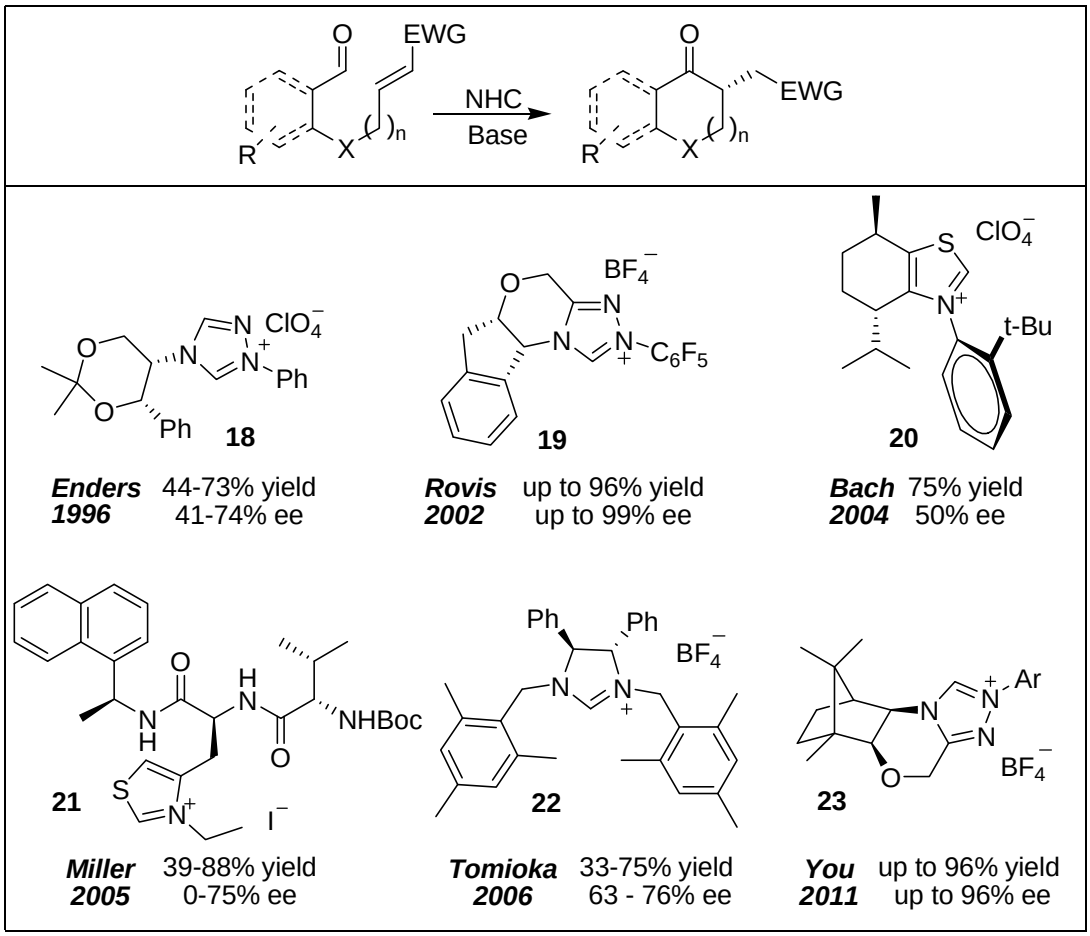
In his 1979 total synthesis of (±)-hirsutic acid, Trost reported the first intramolecular Stetter reaction (Scheme 1.5a). Notably, this seminal work was also the first synthesis of a quaternary center via the Stetter reaction.[11] The difficult transformation of compound **14** to key intermediate **15** required excess amounts (2.3 equivalents) of the thiazolium pre-catalyst to afford a 67% yield of **15** (Scheme 1.5a). The first intramolecular Stetter reaction performed catalytically was reported by Ciganek in 1995. By tethering Stetter acceptors *ortho* to aromatic aldehydes, Ciganek was able to efficiently access 4-chromanones (Scheme 1.5b, n = 1). Benzo-annulated furanones were also obtained in

modest yield from base sensitive starting materials when DMF and heat were employed to deprotonate the thiazolium pre-catalyst (Scheme 1.5b, n = 0).[12]



Scheme 1.5 a) Trost's Stoichiometric NHC Intramolecular Stetter Reaction. b) Ciganek's Catalytic Intramolecular NHC Stetter Reaction.

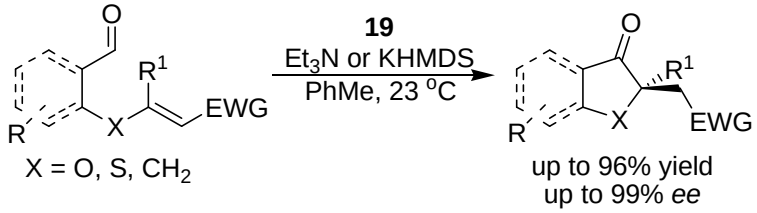
Immediately following Ciganek's report, Enders reported the first enantioselective, intramolecular Stetter reaction. By employing chiral triazolium salt **18** and potassium carbonate as base, Enders was able to access 4-chromanones in modest enantioselectivity (up to 74% ee) (Scheme 1.6).[13] In 2002, Rovis emerged as the frontrunner in the field of asymmetric intramolecular Stetter reactions. In Rovis' seminal report, highly enantioenriched benzo-annulated products (X = O, NR, S, CH_2; n = 0, 1) and 2-substituted cyclopentanones were produced in good yield when chiral triazolium salt **19** was employed (Scheme 1.6).[14]



Scheme 1.6 NHC Precursors Employed in the Asymmetric Intramolecular Stetter Reaction

In 2004, Bach reported the use of axially chiral thiazolium catalyst **20** in the modestly enantioselective synthesis of 4-chromanones (Scheme 1.6). The poor stereoselectivity of Bach's methodology is attributed to the conversion of **20** to its atropisomer in the presence of base.[15] Miller and co-workers screened a number of peptide substituted thiazolium salts for their ability to promote a stereoselective intramolecular Stetter reaction. Thiazolium salt **21** afforded the best results, producing 4-chromanones in moderate enantioselectivity and modest to good yields (Scheme 1.6).[16] In 2006, Tomioka reported the use of chiral C2 symmetric imidazolinium **22** in the moderately

enantioselective synthesis of cyclopentanones.[17] Recently, You and co-workers reported highly enantioselective syntheses of 4-chromanones employing camphor derived triazolium salt **23** to promote the Stetter reaction (Scheme 1.6).[18]

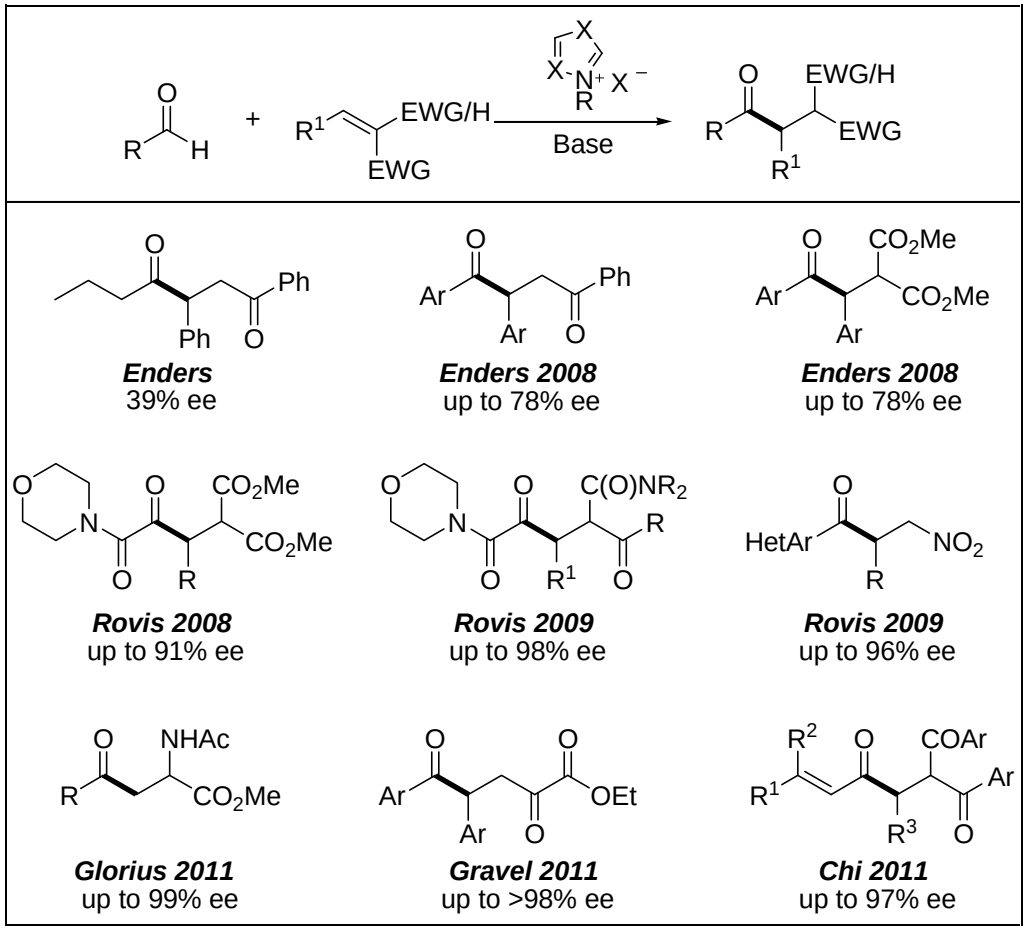


Scheme 1.7 Rovis' Catalytic Asymmetric Intramolecular Stetter Quaternary Center Formation

In the past decade, Rovis has made significant advances in the asymmetric intramolecular Stetter reaction. In 2004, Rovis reported the first formation of a quaternary center through a catalytic asymmetric Stetter reaction (Scheme 1.7).[19] The same method was employed for the enantioselective preparation of tertiary ethers and thioethers. While his early work focused on the effects of the different length and types of tethers, Rovis has also extensively studied the scope of the reaction with different Michael acceptors and substituents on the aromatic backbone.[20] In general, substrates with small groups *meta* or *para* to the formyl group on the aromatic backbone were well tolerated. However, electron-withdrawing groups on the aromatic ring required less basic catalysts, in order to avoid epimerization of the product. Highly enantioenriched products were generally obtained when *E* α,β-unsaturated ketones, esters, amides, phosphonates, and phosphine oxides were employed as Michael acceptors.[21] On the other hand, α,β-unsaturated thioesters and nitriles resulted in a slightly lower enantioselectivity (70-80% *ee*). The use of α,β-unsaturated aldehyde or *Z* α,β-unsaturated methyl ester acceptors afforded products in low enantiomeric excess (22 and 30% *ee*, respectively).[22]

1.2.2 The Intermolecular Stetter Reaction

In recent years, significant progress has been made in the asymmetric intermolecular Stetter reaction. An early example reported by Enders employed a chiral thiazolium catalyst in the Stetter reaction of butanal and *trans*-chalcone. The Stetter adduct was obtained in 39% ee and 4% yield.[23] In 2008, Enders reported the first moderately enantioselective intermolecular Stetter reaction, employing a chiral triazolium pre-catalyst in the Stetter reaction of aromatic aldehydes with chalcone derivatives and later, β-aryl malonate alkylidenes (up to 78% ee) (Scheme 1.8).[24] In 2008, Rovis reported the first synthesis of highly enantioenriched intermolecular Stetter adducts. Despite this significant accomplishment, the scope of Rovis' method was limited to the reaction of glyoxamide with β-alkyl malonate alkylidenes and shortly afterward, β-alkyl ketoamide alkylidenes.[25] In 2009, Rovis augmented his previous work with the highly enantioselective Stetter reaction of heteroaromatic aldehydes and β-alkyl nitroalkenes.[26] In 2011, Glorius contributed the enantioselective synthesis of amino acid derivatives via the asymmetric intermolecular Stetter reaction of dehydroamino esters.[27] Around the same time, Gravel and co-workers reported the first highly enantioselective intermolecular Stetter reaction on substrates bearing aryl substituents on the reactive site of the acceptor. β,γ-Unsaturated α-ketoesters afforded enantioenriched Stetter adducts when combined with heteroaromatic and aromatic aldehydes.[28] Recently, Chi reported the preparation of highly enantioenriched Stetter adducts from β-alkyl enals and modified chalcones. β-Aryl and β,β-disubstituted enals afforded slightly lower enantiomeric excesses.[29]

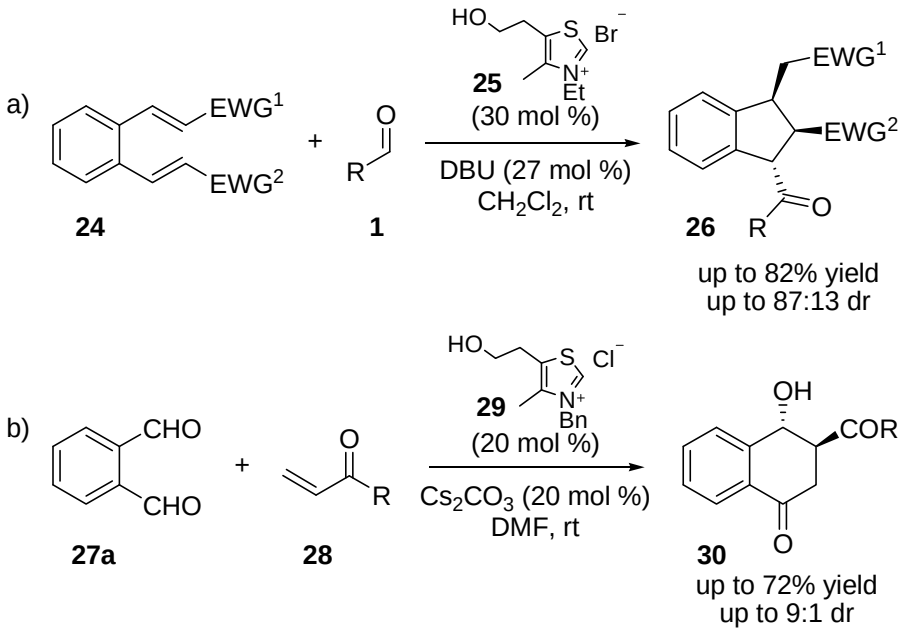


Scheme 1.8 Adducts Formed in the Intermolecular Stetter Reaction

1.2.3 Domino Stetter Reactions

In recent years, the area of domino NHC-catalyzed reactions has grown in interest.[30] In 2009, Gravel and Sánchez-Larios reported a unique domino Stetter-Michael reaction. This methodology traps the enolate produced in the Stetter reaction of **24** and **1** in an intramolecular Michael reaction (Scheme 1.9a). The reaction produces indanes **26** bearing three contiguous stereogenic centres. Good yields and diastereomeric ratios were obtained when electron-poor, unhindered aldehydes were employed.[31] Early in 2010, Ye et al. published a paper employing similar methodology to produce 4-hydroxytetralones **30** in a domino Stetter-aldol reaction (Scheme 1.9b). Following the Stetter reaction of *o*-

formyl aromatic aldehyde **27** and electron poor olefin **28**, the enolate produced in the reaction undergoes an aldol reaction with the free formyl group. Two contiguous stereocentres are formed.[32] Good yields and diastereomeric ratios are obtained for mono-substituted olefins. The use of α-disubstituted olefins as acceptors was also well tolerated, however the reaction of β-substituted olefins failed completely.

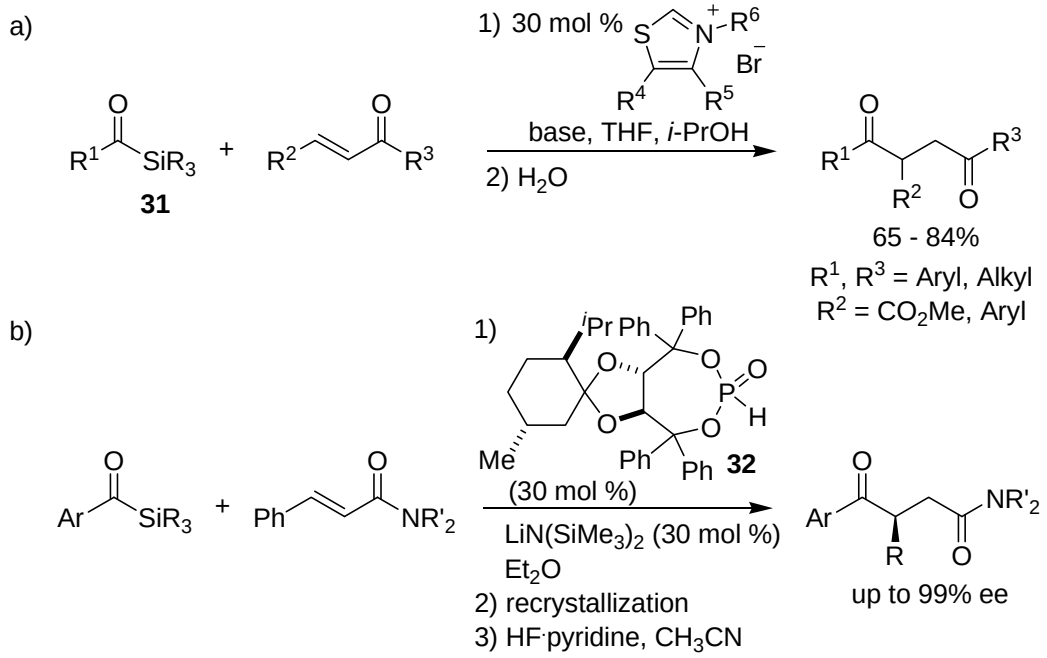


Scheme 1.9 Domino Stetter Reactions a) Sánchez-Larios and Gravel's Stetter-Michael Reaction Pathway. b) Ye's Stetter-Aldol Reaction.

1.2.4 Formal Stetter Reactions

In 2004, Scheidt reported the first NHC promoted formal Stetter reaction of acyl silanes.[33] This methodology circumvents the formation of the competing benzoin products typically observed in the Stetter reaction. Following the addition of the NHC onto the carbonyl of **31**, a [1,2]-Brook rearrangement produces the silylated Breslow intermediate. The additive isopropanol serves to desilylate the Breslow intermediate (Scheme 1.10). In 2006, the enantioselective formal Stetter reaction of acyl silanes was

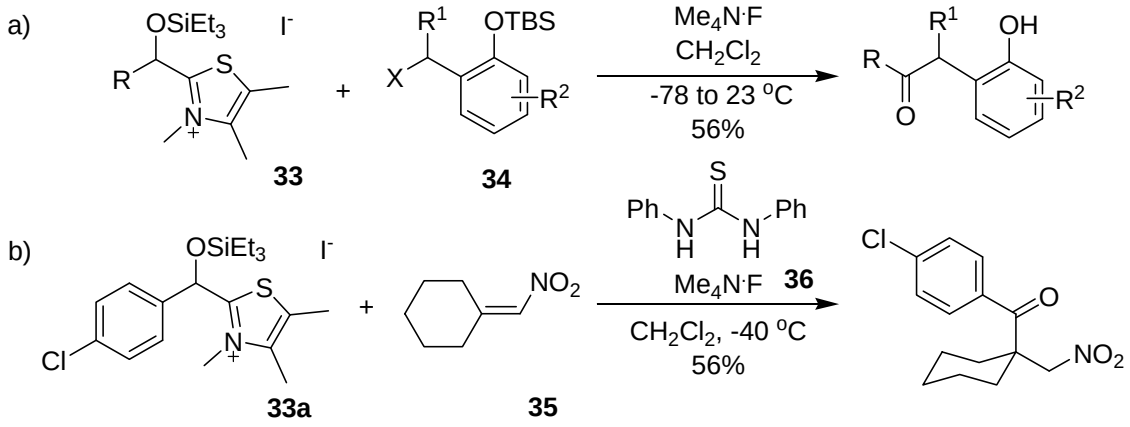
reported by Johnson.[34] Previously, Johnson had employed this methodology in an enantioselective cross silyl benzoin reaction.[35] The metallophosphite derived *in situ* from **32** was employed to activate the acyl silanes and direct the stereoselectivity of the silyl Stetter reaction. Recrystallization of the adduct followed by desilylation afforded the formal Stetter product in enantiomeric excesses superior to any intermolecular Stetter reaction reported at the time (Scheme 1.10).



Scheme 1.10 Formal Stetter Reaction of Acyl Silanes a) Scheidt's NHC-Promoted b) Johnson Enantioselective Metallophosphite-Promoted

A formal Stetter reaction employing silylated thiazolium carbinols as the "acyl anion equivalents" has been reported by Scheidt. In Scheidt's reaction, a fluoride source deprotects **33** and proton transfer affords the corresponding Breslow intermediate. Scheidt combined this methodology with the fluoride promoted *in situ* generation of *o*-quinone methides from *o*-silylated phenols **34** in the synthesis of α-aryl ketones (Scheme 1.11a).[36] This unique process also permitted a formal Stetter reaction to be performed on

base sensitive β-alkyl nitro olefins.[37] Superior results were obtained when thiourea **36** was employed as co-catalyst to activate the nitroalkene. In one example, the reaction of the silylated carbinol **33a** with nitro methylenecyclohexane **35** forms a new quaternary centre (Scheme 1.11b). As Scheidt's reaction goes through the same addition step as the Stetter reaction, these results suggest that formation of a quaternary centre through the intermolecular Stetter reaction is possible. Despite this achievement, quaternary centre formation via the intermolecular Stetter reaction has yet to be reported.



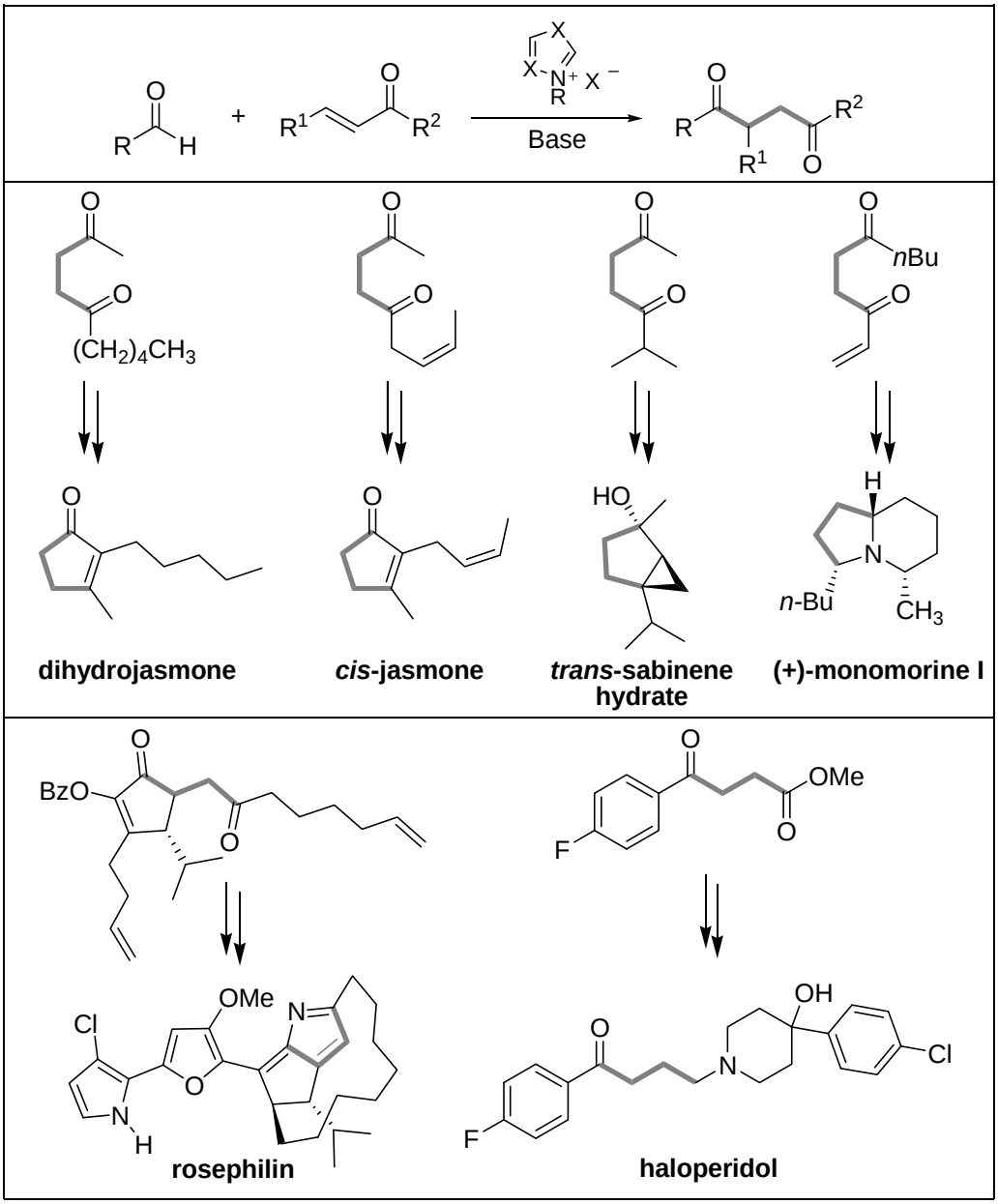
Scheme 1.11 Scheidt's Silyl Thiazolium Carbinols as Acylating Agents in a) α-Aryl Ketone Synthesis b) Quaternary Centre Formation.

1.2.5 Application of the Stetter Reaction in Natural Product Synthesis

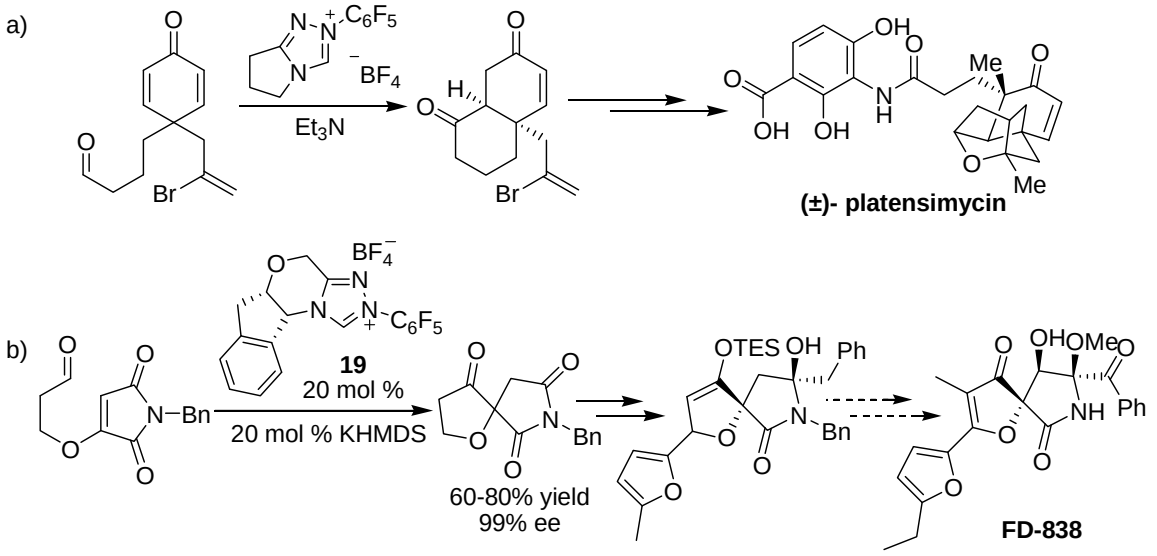
The unique 1,4-dicarbonyl relationship of the Stetter adduct has been exploited in a number of total syntheses. In 1975, Stetter reported the first application of the intermolecular Stetter reaction in natural product synthesis. Both dihydrojasmone and *cis*-jasmone were prepared by an intermolecular Stetter reaction and subsequent intramolecular aldol condensation of the Stetter adducts (Scheme 1.12).[38] A similar methodology was also employed by Galopin to form the five-membered ring in the synthesis of (±)-*trans*-sabinene hydrate (Scheme 1.12).[39] Blechert also exploited the

Stetter adduct's 1,4-dicarbonyl relationship to form the pyrrolidine ring in (+)-monomorine I (Scheme 1.12).[40] In the synthesis of the natural product, roseophilin, Tius employed a diastereoselective intermolecular Stetter reaction to access the pyrrole precursor (Scheme 1.12).[41] Grée employed a Stetter adduct in his concise synthesis of haloperidol (Scheme 1.12).[42] As the intermolecular Stetter reaction remains limited to specific substrate combinations, only structurally simple Stetter adducts have been employed in natural product synthesis, to date.

The intramolecular version of the Stetter reaction has also been employed in natural product synthesis. As previously discussed, Trost employed an intramolecular Stetter reaction in the synthesis of hirsutic acid (Scheme 1.4a).[11] In 2007, Nicolaou reported the formal synthesis of antibiotic (±)-platensimycin employing a diastereoselective intramolecular Stetter reaction to produce the intermediate *cis*-decalin (Scheme 1.13a).[43] Rovis reported a stereoselective intramolecular Stetter reaction to produce the spirobicyclic core of antibiotic FD-838 (Scheme 1.13b).[44]



Scheme 1.12 Application of the Intermolecular Stetter Reaction in Total Synthesis



Scheme 1.13 Application of the Intramolecular Stetter Reaction a) Nicolaou's Formal Synthesis of Platensimycin b) Rovis' Synthesis of the Core of FD-838.

1.3 Summary

The NHC-promoted *umpolung* of aldehydes allows for unique bond formation. In particular, the addition of an "acyl anion equivalent" onto an electron poor olefin in the Stetter reaction affords products with a 1,4 relationship of functional groups. In recent years, a number of highly enantioselective intermolecular Stetter reactions have been reported. The intramolecular Stetter reaction has provided access to enantioenriched benzo-annulated products and cyclopentanones. Domino Stetter reactions have been employed in the preparation of more highly substituted benzo-annulated products. The development of formal Stetter reactions has provided access to the Stetter adducts of base sensitive material. Despite these recent advances, the application of the intermolecular Stetter reaction in natural product synthesis is limited. A number of natural product syntheses have exploited the 1,4 relationship of the functional groups, however, only structurally simple substrates were employed. To improve the synthetic utility of the

Stetter reaction, the scope of the reaction must be extended to permit the formation of more complex products.

PART II – RESULTS AND DISCUSSION

CHAPTER TWO

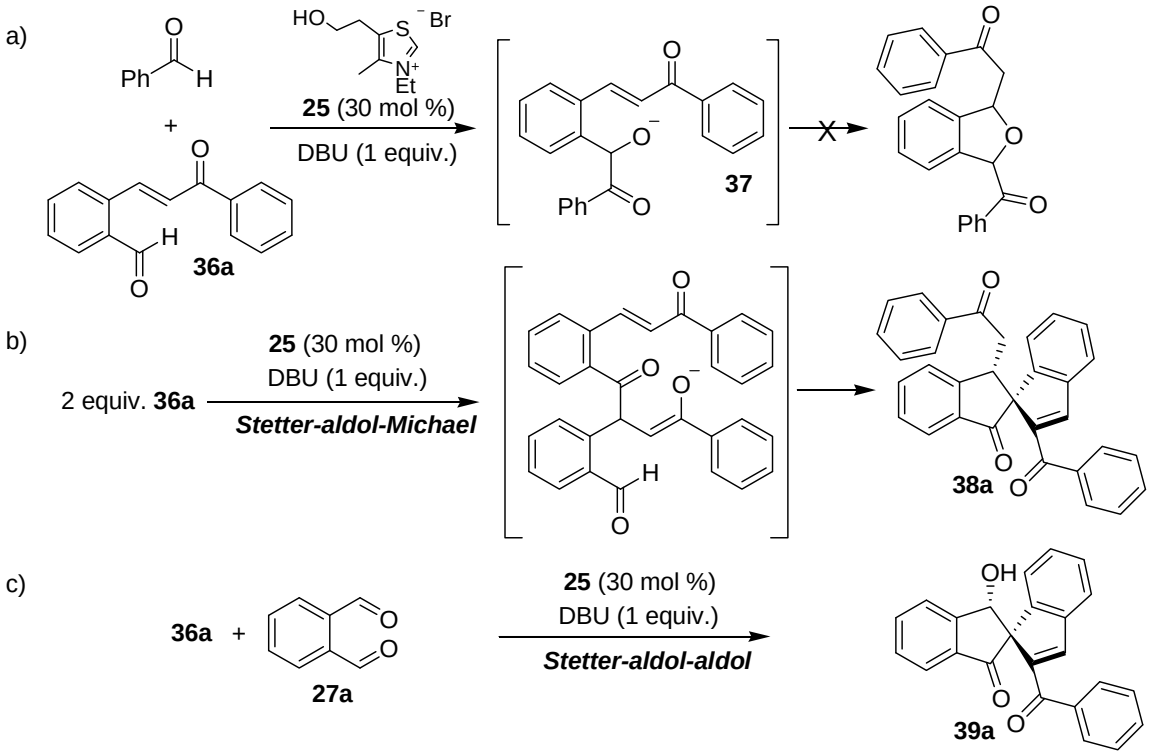
SPIRO BIS-INDANE FORMATION FROM STETTER-ALDOL-MICHAEL AND STETTER-ALDOL-ALDOL REACTIONS

2.1 Introduction

Under Eduardo Sánchez-Larios' supervision, undergraduate student Crystal Daschner commenced studying domino NHC-catalyzed reactions in September 2008. By employing *o*-formyl chalcone, **36a**, as acceptor in a cross-benzoin reaction, Crystal hoped to trap the cross-benzoin product **37** by intramolecular conjugate addition of the resulting alkoxide (Scheme 2.1a). However, Crystal observed that under standard NHC reaction conditions, only **36a** was consumed and a complex product, **38a**, was obtained. Presumably, the spiro bis-indane **38a** is formed from the aldol, Michael, and dehydration reaction of the Stetter adduct of two equivalents of **36a**. This unique domino Stetter-aldol-Michael (SAM) dehydration reaction produces three new carbon-carbon bonds and a spiro ring junction in high diastereoselectivity (Scheme 2.1b). Following Crystal's discovery, Dr. Michel Gravel employed similar methodology in the hetero-dimerization of phthalaldehyde **27a** and *o*-formyl chalcone, **36a** (Scheme 2.1c) in a Stetter-aldol-aldol (SAA) reaction.

In addition to the remarkable efficiency of these reactions, the possible synthetic applications of the SAM and SAA reaction were intriguing. These two novel domino Stetter pathways produce spiro ring junctions, structures present in biologically active natural products, such as fredericamycin A[45] and acutumine[46] (Figure 2-1). In particular, minor modifications may be made to the SAA spiro indane product to produce the core

structure of fredericamycin A, a natural product that possesses antifungal, antibacterial, cytotoxic, and antitumour activity.[47]



Scheme 2.1 Previous Research: a) Crystal Daschner's Attempted Cross-Benzoin Reaction b) Crystal Daschner's Stetter-aldol-Michael Reaction of **36a**. c) Dr. Michel Gravel's Stetter-aldol-aldol Reaction of **27a** and **36a**.

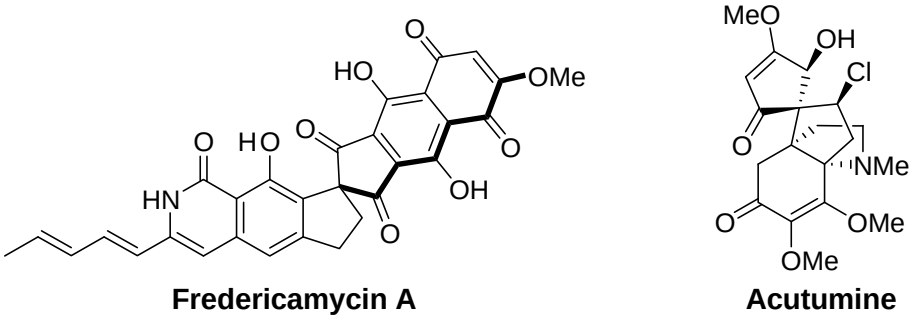
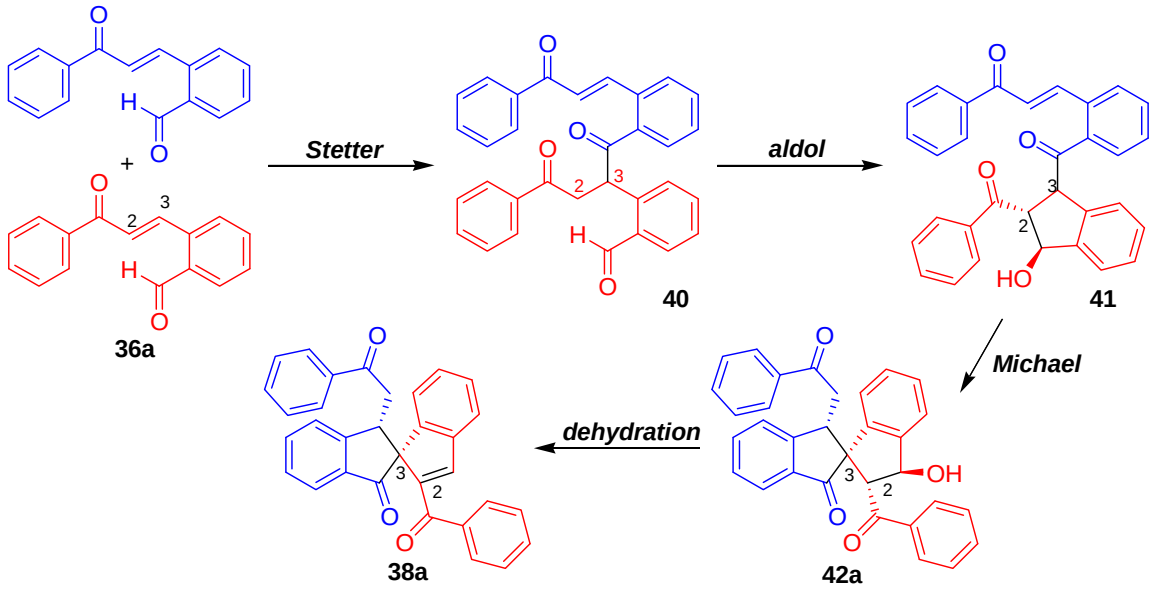


Figure 2-1 Structures of Spiro Bis-Indane Natural Products Fredericamycin A and Acutumine.

In the summer of 2009, the optimization of both the SAM and the SAA pathways was investigated by the author. Various NHC pre-catalysts and bases were screened for their ability to promote the two reactions. At this point, the isolation of the advanced intermediate, spiro bis-indane alcohol **42a** permitted further insight into the exact order of the four reactions in the SAM pathway (Scheme 2.2). Addition of the formyl group of **36a** onto C3 of a second equivalent of **36a** produces Stetter adduct **40**. Then aldol reaction of the formyl group of **40** forms indane **41**. Subsequently, a diastereoselective Michael reaction affords the spiro ring junction in intermediate **42a**. Finally, base promoted dehydration affords the major product, spiro bis-indane **38a**.

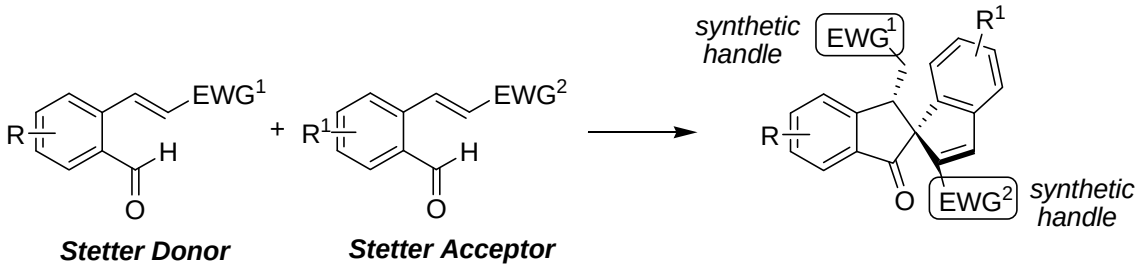


Scheme 2.2 Reaction Pathway of Stetter-Aldol-Michael Dehydration Reaction of **36a**.

2.2 Research Objectives

The primary goal for both the SAM and SAA pathway was to improve the efficiency of the reaction by determining the reaction conditions that would afford the best yield and ratio of diastereomers, while employing the least amount of NHC pre-catalyst possible.

More specifically, a method to prevent the formation of side products was investigated. Various reaction conditions were also screened in order to suppress the base promoted isomerization of the product. Furthermore, to improve the synthetic utility of the method, the reactivity of acceptors bearing electron withdrawing groups other than ketones were screened for reactivity in both the SAM and SAA pathways. In order to provide more diverse synthetic handles within the structure of the product, a cross SAM was investigated (Scheme 2.3).

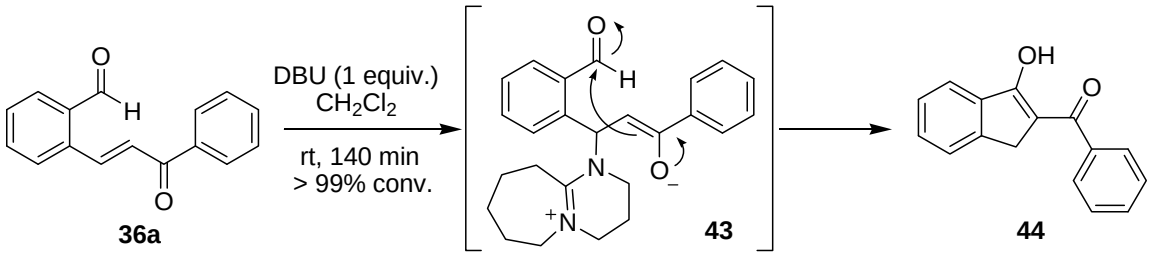


Scheme 2.3 Synthetic Plan for the Preparation of Structurally Diverse Spiro Bis-Indanes

2.3 Reaction Optimization

2.3.1 Competing Baylis-Hillman Reaction

During preliminary studies, an undesirable side product, **44** was often observed. As **44** is likely produced from the intramolecular Baylis-Hillman of **36a**, either the carbene or the base, 1,8-diazabicycloundec-7-ene (DBU), could be the nucleophile promoting the side reaction. A control experiment carried out without the addition of the NHC pre-catalyst revealed that DBU itself promotes the unwanted transformation (Scheme 2.4). Presumably, conjugate addition of DBU onto **36a** creates enolate **43** which then attacks the nearby formyl group in an intramolecular aldol reaction. Elimination of DBU and subsequent double bond migration affords the observed side product, **44**.

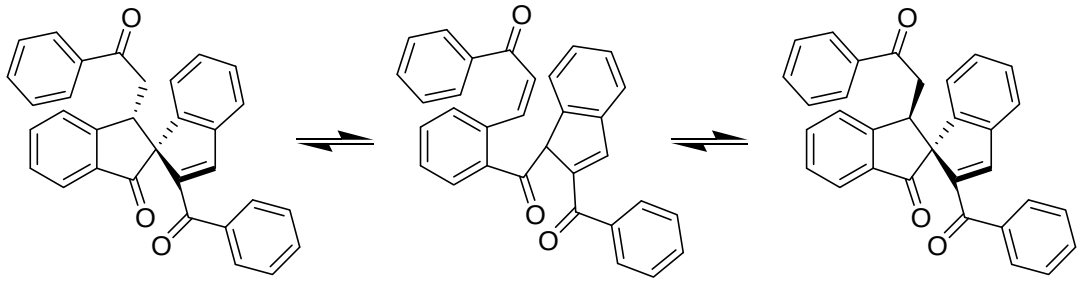


Scheme 2.4 DBU Control Experiment of Baylis-Hillman Reaction of **36a**

If the Baylis-Hillman pathway was reversible, side product **44** could be converted back to **36a** and subsequently be consumed by the SAM pathway. A sample of **44** was re-subjected to reaction conditions to determine if it could be converted into the desired spiro bis-indane product. However, no reaction was observed after 3 hours, suggesting that **44** is not formed reversibly (results not shown).

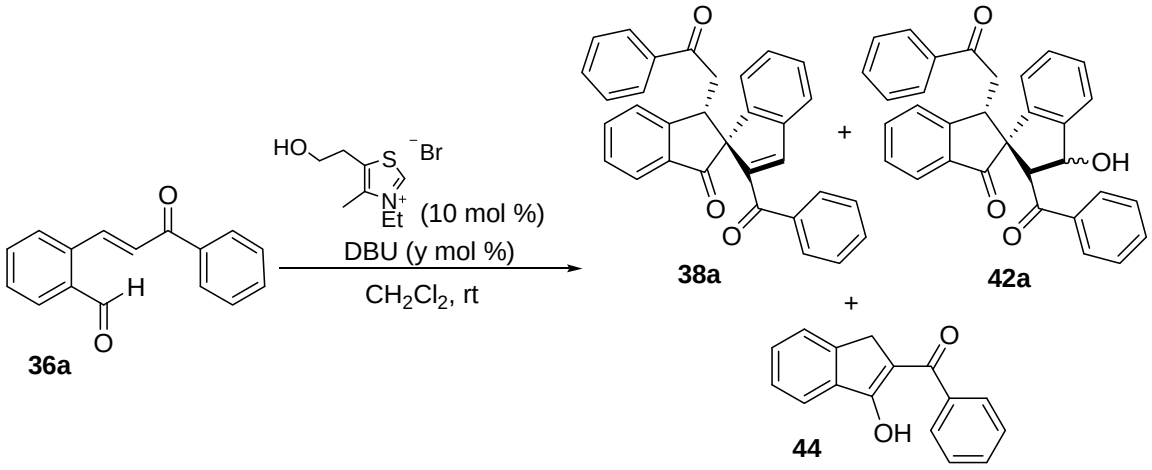
2.3.2 Optimization of Base

All SAM reactions were performed by the dropwise addition of the base to a solution of the substrate and pre-catalyst in dichloromethane (CH_2Cl_2), unless otherwise noted. Reactions were quenched with an aqueous solution of saturated ammonium chloride following the complete consumption of the substrate as determined by thin-layer chromatography (TLC). The amount of excess DBU remaining after the deprotonation of the pre-catalyst greatly affects the chemoselectivity and diastereomeric ratio of the reaction. Small amounts of DBU proved to be insufficient for the complete dehydration of alcohol **42a**, resulting in prolonged reaction time and incomplete conversion (Table 2-1, entry 1). In addition to increasing the amount of Baylis-Hillman side product, **44**, stoichiometric amounts of the DBU were observed to decrease the diastereomeric ratio of **38a** (entry 5). The loss in the diastereomeric ratio suggests that DBU promotes the retro-Michael-Michael isomerization of **38a** (Scheme 2.5).



Scheme 2.5 Retro-Michael-Michael Isomerization of Spiro Bis-Indane **38a**

Table 2-1 Effects of the Amounts of Base on the Stetter-Aldol-Michael Reaction of **36a**



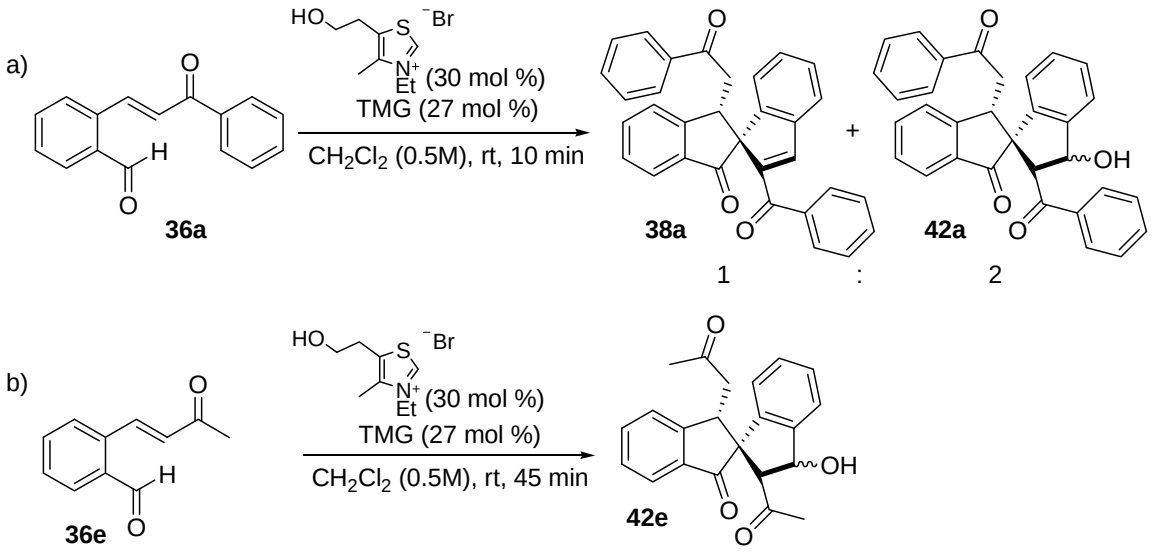
entry	DBU (y mol %)	t (min)	38a : 42a : 44[a]	dr of 38a[b]
1	15	30	20 : 20 : < 1	> 20 : 1
2	20	15	20 : 2 : < 1	> 20 : 1
3	25	15	20 : 1 : < 1	17 : 1
4	30	15	20 : < 1 : 1	17 : 1
5	100	10	20 : <1 : 2	7 : 1

[a] Product distribution determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Diastereomeric ratio determined by ^{1}H NMR analysis of the crude reaction mixture.

Under the conditions outlined in Table 2-1, the optimal amount of DBU was determined to be 30 mol% as this amount was sufficient to dehydrate **42a** without

significantly decreasing the ratio of **38a** or greatly increasing the production of the side product **44** (entry 4).

Tetramethylguanidine (TMG) was also screened for its ability to promote the SAM pathway. As excess base is detrimental to the diastereomeric ratio and overall yield of the SAM reaction and as TMG is a stronger base than DBU, the ratio of base to pre-catalyst was adjusted so that excess base was not present in the reaction mixture. Surprisingly, the reaction conditions outlined in Scheme 2.6a were insufficient to dehydrate alcohol **42a**. As excess base would be detrimental to the diastereomeric ratio of **38a**, the effects of TMG were not investigated any further. Notably, the Baylis-Hillman side product was not observed in the crude reaction mixture of this experiment. These results suggest that neither TMG nor the NHC promote the Baylis-Hillman pathway.



Scheme 2.6 a) Tetramethylguanidine (TMG) Promoted Stetter-Aldol-Michael Reaction of **36a** b) TMG Promoted Stetter-Aldol-Michael Reaction of **36e**.

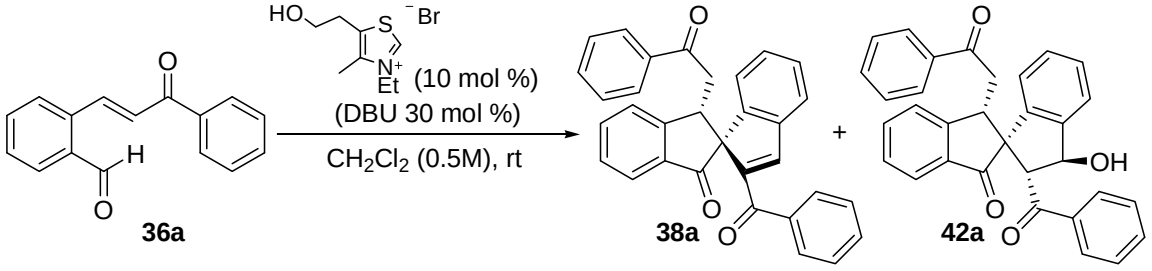
As methyl ketone substrate **36e** was likely base sensitive, **36e** was subjected to additional base screening. When standard reaction conditions were accompanied by a full

equivalent of iPr_2NEt and 30 mol % catalytic loading of the NHC precursor, a complex mixture with only trace amounts of product was obtained (not shown). The use of substoichiometric amounts of TMG only afforded the alcohol **42e** amongst a complex mixture of side products (Scheme 2.6b).

2.3.3 Reaction Time Study

To determine the effects of reaction time on the product distribution and yield, three experiments employing the same reaction conditions were quenched at different times. In entry 1, (Table 2-2) the reaction was quenched upon complete consumption of the starting material. This short reaction time afforded an excellent ratio of diastereomers, yet was insufficient to fully dehydrate alcohol **42a**. Thus, the reaction time was extended to allow for the full conversion of **36a** to the desired product, **38a**. A reaction time of 15 minutes was sufficient to fully eliminate **42a**, thereby affording a higher yield of **38a** with only a slight decrease in the diastereomeric ratio (entry 2). As there are a number of possible diastereoisomers of **42a** that were not identified by ^{1}H NMR, it is possible that trace amounts of these alcohols could partially account for the less than quantitative yield of **38a**. If these diastereomers of **42a** eliminated at a slower rate than **42a**, a longer reaction time would produce a higher yield of **38a**. However, increasing the reaction time to 60 minutes resulted in a drastic decrease in the diastereomeric ratio. As a low diastereomeric ratio would ultimately result in a low yield of the desired diastereomer, isolation of the product was deemed unnecessary. All subsequent reactions were quenched within minutes of the starting material's consumption (as determined by TLC).

Table 2-2 The Effects of Reaction Time on the Stetter-Aldol-Michael Pathway of **36a**.



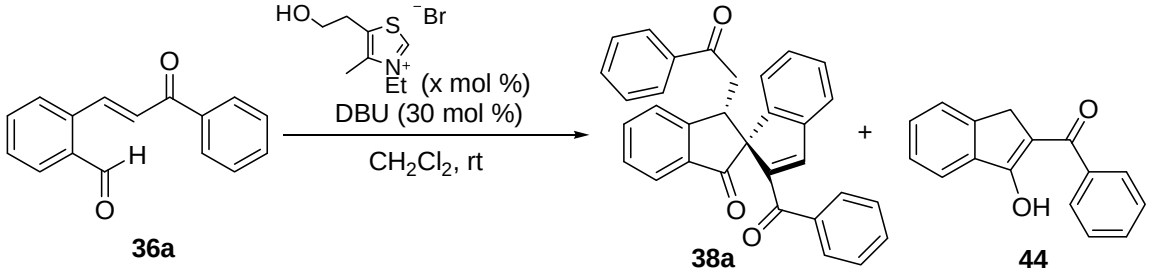
entry	t (min)	38a : 42a[a]	dr of 38a[b]	yield (%)[c]
1	12	20 : 1	> 20 : 1	76
2	15	> 20 : 1	17 : 1	79
3	60	> 20 : 1	8 : 1	nd

[a] Production distribution determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Diastereomeric ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Combined yield of pure isolated product diastereomers.

2.3.4 Optimization of NHC-Catalytic Loading

Under the conditions outlined in Table 2-3, a catalytic loading of 1 mol % was insufficient to promote the SAM pathway. As a result, only side product **44** was observed in the crude reaction mixture (entry 1). Although a catalytic loading of 5 mol % was observed to promote the reaction, significant amounts of the Baylis-Hillman product formed. A low diastereomeric ratio was also obtained, presumably due to the product's prolonged exposure to DBU (entry 2). The ideal catalytic loading was determined to be 10 mol% as this amount promoted the reaction efficiently without compromising the diastereomeric ratio of **38a** (entry 3).

Table 2-3 The Effects of Catalytic Loading on the Stetter-Aldol-Michael Reaction of **36a**



36a **38a** **44**

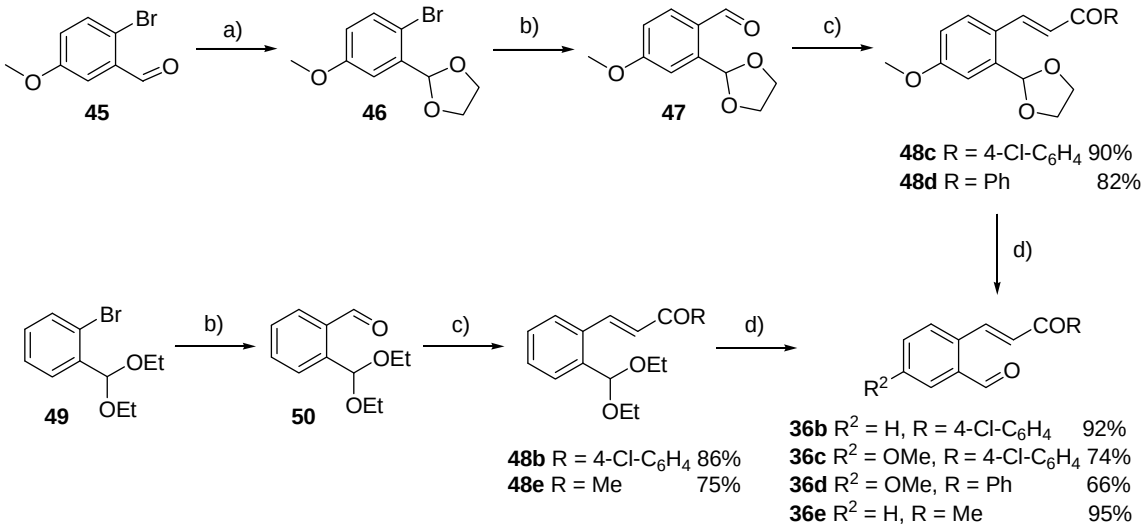
entry	cat. loading (x mol %)	t (min)	38a : 44[a]	dr of 38a[b]	yield of 38a (%)
1	1	(18 h)	1 : > 20	-	-
2	5	35	1 : 1.2	7 : 1	59[c]
3	10	15	> 20 : 1[d]	17 : 1	79[e]

[a] Product distribution determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Diastereomeric ratio determined by ^{1}H NMR analysis of the crude reaction mixture.[c] Yield of pure isolated major diastereomer. [d] Trace amount of **44** detected by ^{1}H NMR analysis. [e] Yield of combined pure isolated diastereomers.

2.4 Stetter-Aldol-Michael Homo-Dimers

2.4.1 Preparation of O-Formyl Chalcone Derivatives

The preparation of the *o*-vinylketone benzaldehyde derivatives required that a Wittig reaction be carried out on phthalaldehyde derivatives. To ensure the reaction proceeded selectively, the Wittig reaction was carried out on mono-protected dialdehydes (Scheme 2.7). Aldehyde **45**[48] was protected as a dioxolane using acid catalysis under Dean-Stark conditions to produce **46**. The installation of the vinyl ketone was then carried out over two steps. Lithium-halogen exchange of aryl bromides **46** and **49** and subsequent nucleophilic attack on dimethylformamide (DMF) afforded the desired mono-protected dialdehydes **47** and **50**, respectively. The Wittig reaction of the free formyl groups of **47** and **50** produced the desired vinyl ketones. Finally, removal of the aldehyde protecting groups using silica supported iron (III) chloride afforded the desired *o*-formyl ketone derivatives **36b-e**.[49]



Reaction Conditions: a) $(CH_2OH)_2$ (5 equiv.), PTSA (3 mol %), PhMe [0.2M], Dean-Stark, 25h, 82% b) THF (0.2M), nBuLi (1.5 equiv.) then DMF (2 equiv.), -78 ^{o} - 0 ^{o}C, 95% c) $Ph_3PCHCOR$ (1.5 - 2 equiv.), CH_2Cl_2 [0.3M], MW, 100 ^{o}C, 5 - 25h d) 10% $FeCl_3 \cdot SiO_2$, (1 equiv, by mass), Acetone [0.15M], rt, 15 min - 5h

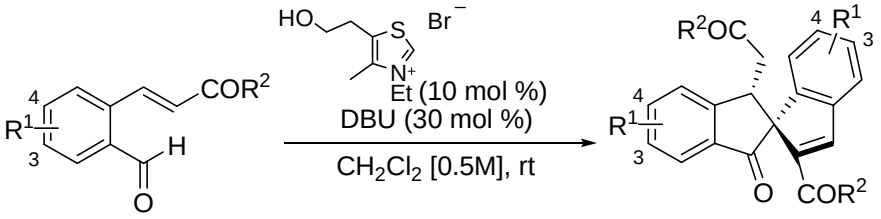
Scheme 2.7 Synthesis of *O*-Formyl Chalcone Derivatives

2.4.2 Scope of Stetter-Aldol-Michael Reaction

The *o*-vinylketone benzaldehyde derivatives were subjected to the optimized reaction conditions for model substrate **36a** (Table 2-4, entry 1). The *p*-methoxy group on the phenyl ketone deactivated the Michael acceptor of **36f** relative to the model substrate **36a**, resulting in a long reaction time yet an excellent diastereomeric ratio (entry 2). Conversely, the installation of a *p*-chloro substituent on the phenyl ketone of **36b** and **36c** required shorter reaction times and afforded the products in good yield yet slightly lower diastereomeric ratios (entries 3, 4 and 7). Substrate **36d**, featuring an activating *m*-methoxy group produced **38d** in good yield with an excellent diastereomeric ratio (entry 5). A *p*-fluoro group on the backbone of substrate **36g** also required a short reaction time but afforded the product in only a moderate yield and a lower diastereomeric ratio. The methyl ketone on **36e** deactivated the vinyl ketone towards conjugate addition, resulting in a prolonged reaction time and a low diastereomeric ratio of **38e** (entry 8). Gratifyingly,

ethyl thioester **36i** also favoured the SAM pathway, affording the product in modest yield and a good diastereomeric ratio.

Table 2-4 Scope of the Stetter-Aldol-Michael Reaction



36a-i **38a-i**

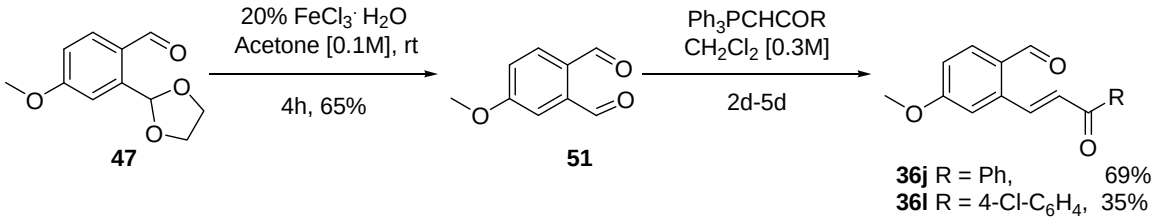
entry	R^1	R^2	t (min)	product[a]	yield (%)[b]	dr of 38[c]
1	H	Ph	15	**38a**	79	17 : 1
2[d]	H	4-MeO(C_6H_4)	45	**38f**	68	> 20 : 1
3	H	4-Cl(C_6H_4)	5	**38b**	86	12 : 1
4	3-MeO	4-Cl(C_6H_4)	5	**38c**	81	10 : 1
5	3-MeO	Ph	9	**38d**	85	> 20 : 1
6[d]	4-F	Ph	5	**38g**	64	11 : 1
7[d]	4-F	4-Cl(C_6H_4)	15[e]	**38h**	80	16 : 1
8	H	Me	195	**38e**	75	7 : 1
9[d]	H	SEt	120	**38i**	31	13 : 1

[a] Relative configuration determined by X–ray crystallography. [b] Combined yield of pure isolated product diastereomers. [c] Diastereomeric ratio determined by ^{1}H NMR analysis of crude reaction mixture. [d] Experiments performed by Eduardo Sánchez-Larios [e] Reaction concentration = 0.1 M.

2.5 Cross Stetter-Aldol-Michael Reactions

2.5.1 Synthesis of Substrates for the Cross Stetter-Aldol-Michael Reaction

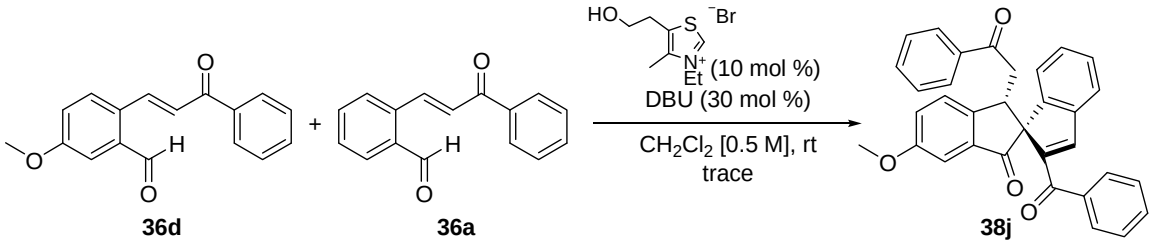
Following the successful isolation of many SAM homo-dimers, optimization of a cross-dimerization SAM was investigated. Two new substrates were prepared for the SAM cross-dimerization study (Scheme 2.8). Cleavage of the protecting group of **47** afforded the desired dialdehyde **51** in satisfactory yield. A moderately selective Wittig reaction served to install the conjugate addition acceptor *meta* to the methoxy substituent in **36j** and **36l**.



Scheme 2.8 Synthesis of Substrates for the Cross Stetter-Aldol-Michael Reaction

2.5.2 Reaction Optimization of the Cross Stetter-Aldol-Michael Reaction

Presumably, a methoxy group *meta* to the formyl group would activate **36d** towards the attack by the NHC, thereby making **36d** the preferred donor over **36a** in the Stetter reaction. The increased reactivity of the formyl group on **36d** should therefore result in the chemoselective formation of **38f**. The optimized conditions for the SAM homo-dimerization were employed for the initial investigation of SAM cross-dimerization (Scheme 2.9). However, these conditions yielded only minimal conversion after 30 minutes. In the optimized homo-dimerization, the molar ratios were calculated relative to substrate **36a** which behaved as both Stetter acceptor and donor. However, in the cross-dimerization, the molar ratios are calculated relative to the species behaving solely as the Stetter acceptor, therefore it was necessary to effectively double the amount of catalyst and base in order to obtain the ideal ratios of reagents. All further reactions were carried out according to the scheme outlined in Table 2-5.



Scheme 2.9 Initial Trial of Stetter-Aldol-Michael Cross-Dimerization

A preliminary reaction carried out at room temperature produced four major spiro bis-indane products, indicating that the reaction proceeded with poor regioselectivity (Table 2-5, entry 1). However, as the product distribution was not the unselective statistical distribution (1 : 1 : 1 : 1), the results suggested a selective cross-dimerization would be possible with further modifications. Decreasing the temperature of the reaction slowed the rate of the reaction without improving the product distribution (entry 2), thus all further reactions were carried out at room temperature. To prevent **36d** from behaving as a Stetter acceptor, it was necessary to employ a substrate that would be more activated towards reacting with the Breslow Intermediate than **36d**.

A methoxy group *meta* to the vinyl ketone on **36j** could potentially activate the vinyl ketone towards accepting Stetter donors. The same methoxy group would also be positioned *para* relative to the formyl group, which should deactivate the formyl group towards the NHC (Figure 2-2a). Indeed, employment of **36j** as Stetter acceptor increased the selectivity of the cross reaction (entry 3). Activation of Stetter acceptor **36b** with a chloro substituent *para* to the vinyl ketone produced slightly higher chemoselectivity than when unactivated substrate **36a** was employed (entry 4, Figure 2-2a).

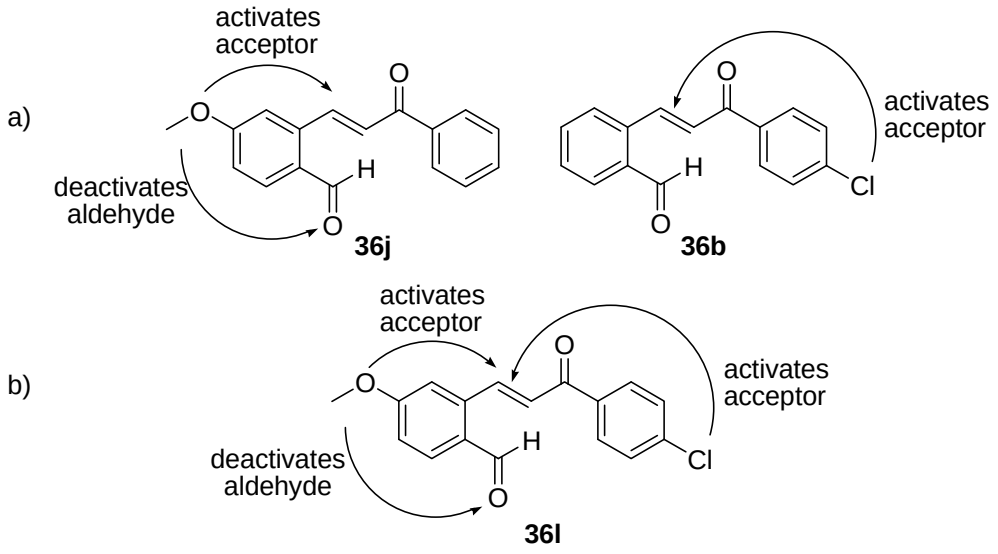
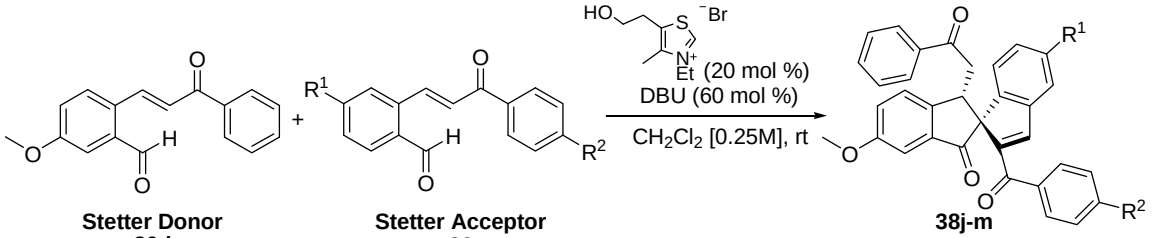


Figure 2-2 Proposed Effects of Aromatic Substituents on a) Activated Acceptors **36j** and **36b** b) Doubly Activated Acceptor **36l**.

Table 2-5 Cross Stetter-Aldol-Michael Optimization



entry	R^1	R^2	T (°C)	t (min)	product distribution[a]
1	H	H	rt	11	3 : 2 : 2 : 1
2	H	H	0	40	3 : 2 : 2 : 1
3	OMe	H	rt	60	17 : 10 : 7 : 1
4	H	Cl	rt	22	2 : 1[b]
5	OMe	Cl	rt	60	10 : 1 : 1 : 1

[a] Product distribution determined by ^{1}H NMR analysis of crude reaction mixture. Reported in the following order: **38j-m** (major diastereomer) : homo-dimer from Stetter donor : homo-dimer from Stetter acceptor : **38j-m** (minor diastereomer) [b] **36b** did not react completely, thus only the major cross dimer and homo-dimer of **36d** formed.

Finally, substrate **36l** was prepared so that both the chloro activated vinyl ketone and the dual effects of the methoxy group on the aromatic backbone could be exploited

(Figure 2-2b). Gratifyingly, the reaction of the activated Michael donor **36d** and electronically tuned **36l** proceeded with high chemoselectivity producing the desired product **38g** in 42% yield (entry 5). These results demonstrate that chemoselective cross SAM reactions are possible when strongly biased starting materials are employed.

2.6 Stetter-Aldol-Aldol Reaction

2.6.1 Reaction Optimization

Employing similar methodology used in the SAM reaction, spiro bis-indanes were prepared through the Stetter-aldol-aldol (SAA) reaction of *o*-formyl chalcones and phthalaldehydes. A model study was carried out using *o*-formyl chalcone **36a** and phthalaldehyde **27a**. The major diastereomer of the SAA product, **39a**, was difficult to separate on column chromatography from the product of the competing SAM reaction. However, a pure sample of ***epi*-39a** could easily be isolated. Therefore the yield of ***epi*-39a** was used to compare the efficiency of the different reaction conditions. To minimize the amount of acceptor lost to SAM homo-dimerization, preliminary studies were carried out with three equivalents of **27a**. The high concentration of the dialdehyde was expected to deter the formation of the Breslow intermediate of **36a**, thereby preventing the acceptor from entering the SAM pathway.

Surprisingly, the optimized conditions of the SAM did not facilitate the desired SAA reaction (Table 2-6, entry 1). Increasing the amount of the NHC pre-catalyst to 30 mol% from 10 mol% and the amount of DBU from 0.3 to one equivalent produced trace amounts of the SAA product in a complex mixture containing the unreacted dialdehyde **27a** and the Baylis-Hillman product **44** (entry 2). Similar results were observed for the reaction carried out at 0˚C (entry 3). Presumably, at such high concentrations of aldehyde, the benzoin and retro-benzoin reactions of **27a** are greatly favoured over the

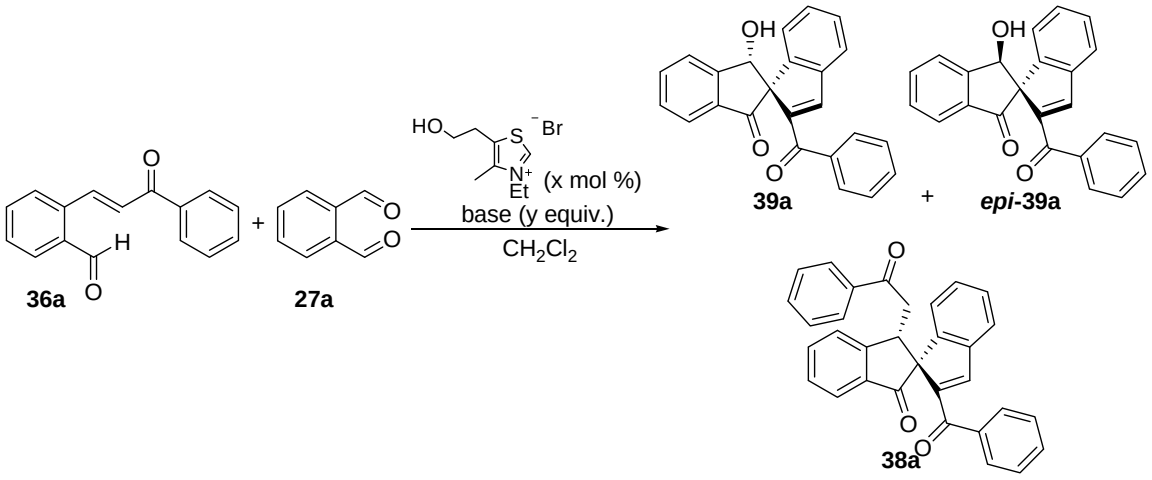
SAA pathway. Meanwhile, the acceptor **36a** is consumed by the DBU-catalyzed Baylis-Hillman reaction.

Reduction of the amount of **27a** from three equivalents to one equivalent afforded the desired product in 25% yield of the minor diastereomer. Decreasing the amount of **27a** further, to 2/3 the molar amount of the acceptor, resulted in a 30% yield of the minor diastereomer. When 0.5 equivalents of the dialdehyde were employed, the yield of ***epi*-39a** was increased to 34%, with a 66% yield of the combined diastereomers (based on the dialdehyde) (entry 6).

As the low diastereomeric ratio of **39a** to ***epi*-39a** was likely due to a base-promoted retro-aldol reaction, a number of base studies were performed. When only enough DBU was added to deprotonate the NHC pre-catalyst, only trace amounts of product were observed (entry 7). Similar results were obtained when only a slight excess of DBU was employed (entry 8). When the weak base iPr_2NEt was employed, only a trace amount of product was observed after 3 hours (entry 9). An experiment employing TMG as base afforded yields similar to those obtained with DBU (entry 10).

To determine the thermodynamic equilibrium of the two SAA products, a single diastereomer, ***epi*-39a** was exposed to basic conditions. DBU promoted the retro-aldol reaction of ***epi*-39a** to afford a 1 : 0.9 mixture of **39a** to ***epi*-39a** after 24 hours (Scheme 2.10). Ultimately, it was determined that it was impossible to avoid isomerization under basic conditions.

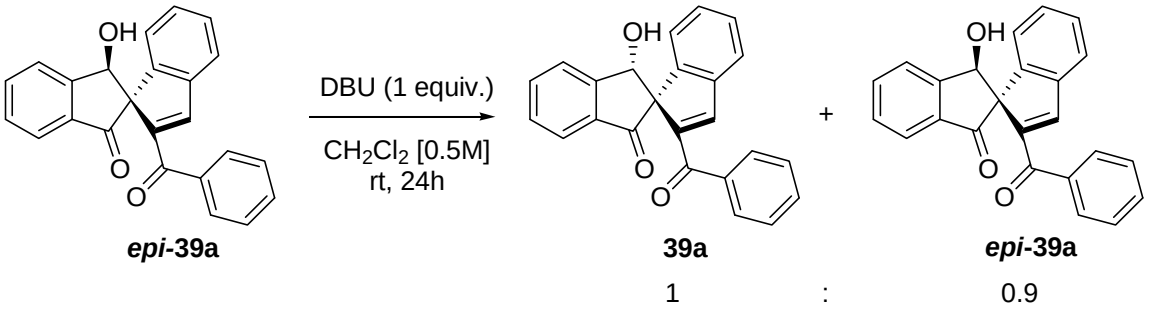
Table 2-6 Optimization of the Model Stetter-Aldol-Aldol Reaction of **27a** and **36a**



entry	equiv. 27	pre-cat. loading (x mol%)	base (y equiv.)	T (˚C)	t (min)	39a : *epi*-39a[a]	yield[b] {conv.}[c] (%)
1	3	10	DBU (0.3)	rt	30	-	{nr}[d]
2	3	30	DBU (1)	rt	35	-	{trace}
3	3	30	DBU (1)	0	30	-	{trace}
4	1	30	DBU (1)	0	90	1 : 0.6	25
5	0.7	20	DBU (0.7)	0	60	1 : 0.6	30
6	0.5	15	DBU (0.5)	0	60	1 : 0.8	34
7	0.5	15	DBU (0.1)	0	35	-	{trace}
8	0.5	15	DBU (0.2)	0	60	-	{trace}
9	0.5	15	iPr_2NEt (0.5)	0	180	-	{trace}
10	0.5	15	TMG (0.5)	0	60	1 : 1.2	36

[a] Diastereomeric ratio determined by ^1H NMR analysis of the crude reaction mixture. [b] Yield of pure isolated ***epi*-39a**.[c] Conversion determined by ^1H NMR analysis of the crude reaction mixture. [d] No reaction (nr)

In order to deter the acceptor **36a** from entering the competing SAM pathway, a number of order of addition experiments were carried out. Neither the dropwise addition nor the portionwise addition of the acceptor improved the ratio of SAA product to SAM product (not shown). Both reactions afforded a high conversion of **36a** to the Baylis-Hillman side product. Presumably, the low concentration of the acceptor resulted in prolonged exposure to DBU, thereby promoting the Baylis-Hillman pathway.



Scheme 2.10 Isomerization Experiment of ***epi*-39a** in DBU.

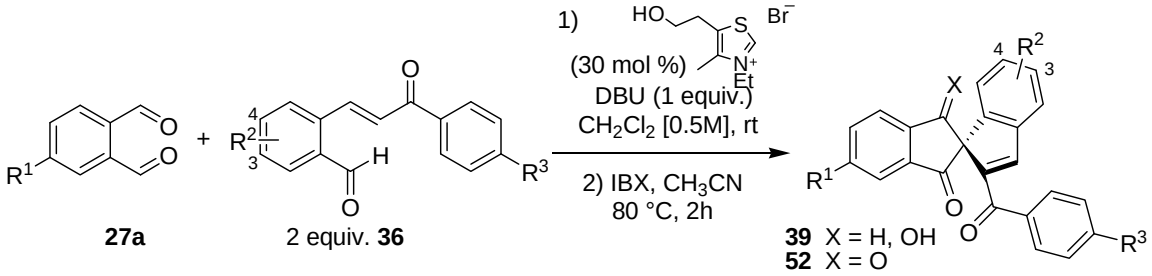
2.6.2 Scope of the Stetter-Aldol-Aldol Reactions

The discrepancy between the diastereomeric ratio of the SAA products in the ^{1}H NMR spectrum of the crude reaction mixture and the ratio of the masses of the two products following isolation by flash column chromatography (FCC) suggested that some of the product was being lost during the purification process. Indeed, destruction of the stereogenic center of the secondary alcohol by 2-iodoxybenzoic acid (IBX) oxidation of the crude SAA reaction mixture, afforded one product in a combined yield higher than the isolated yield of just the SAA reaction (Table 2-6, entry 6 and Table 2-7 entry 1). All further SAA products were isolated following IBX oxidation of the crude material.

To determine the scope of the SAA reaction, a number of electronically biased *o*-formyl chalcone derivatives and phthalaldehydes derivatives were screened for reactivity. A *m*-methoxy group served to activate the formyl group of **36d** towards the NHC, promoting the competing SAM reaction and consequently, affording a low yield of the SAA product (entry 2). The reaction of **27a** with the *p*-chloro activated acceptor **36b** produced the spiro bis-indane product in satisfactory yield (entry 3). Deactivation of the substrate's formyl group and activation of the acceptor moiety through strategic placement of aromatic substituents on **36g** resulted in a high yield of the SAA product

(entry 4). Remarkably, the SAA reaction of the methoxy substituted dialdehyde **27b** proceeded chemoselectively, indicating that the methoxy group selectively activated the *meta* formyl group and deactivated the *para* formyl group towards the NHC. Following oxidation, the product was isolated in a modest yield (entry 5). A *para* methoxy substituent on the phenyl ketone served to deactivate the acceptor moiety resulting in a poor yield (entry 6). A fluoro substituent *meta* to the acceptor moiety on the phenyl ketone afforded a fast reaction time and good yield (entry 7). Fluoro substituted phthalaldehyde required the use of the highly activated acceptor **36h** to afford the product in moderate yield (entry 8).

Table 2-7 Scope of the Stetter-Aldol-Aldol Reaction



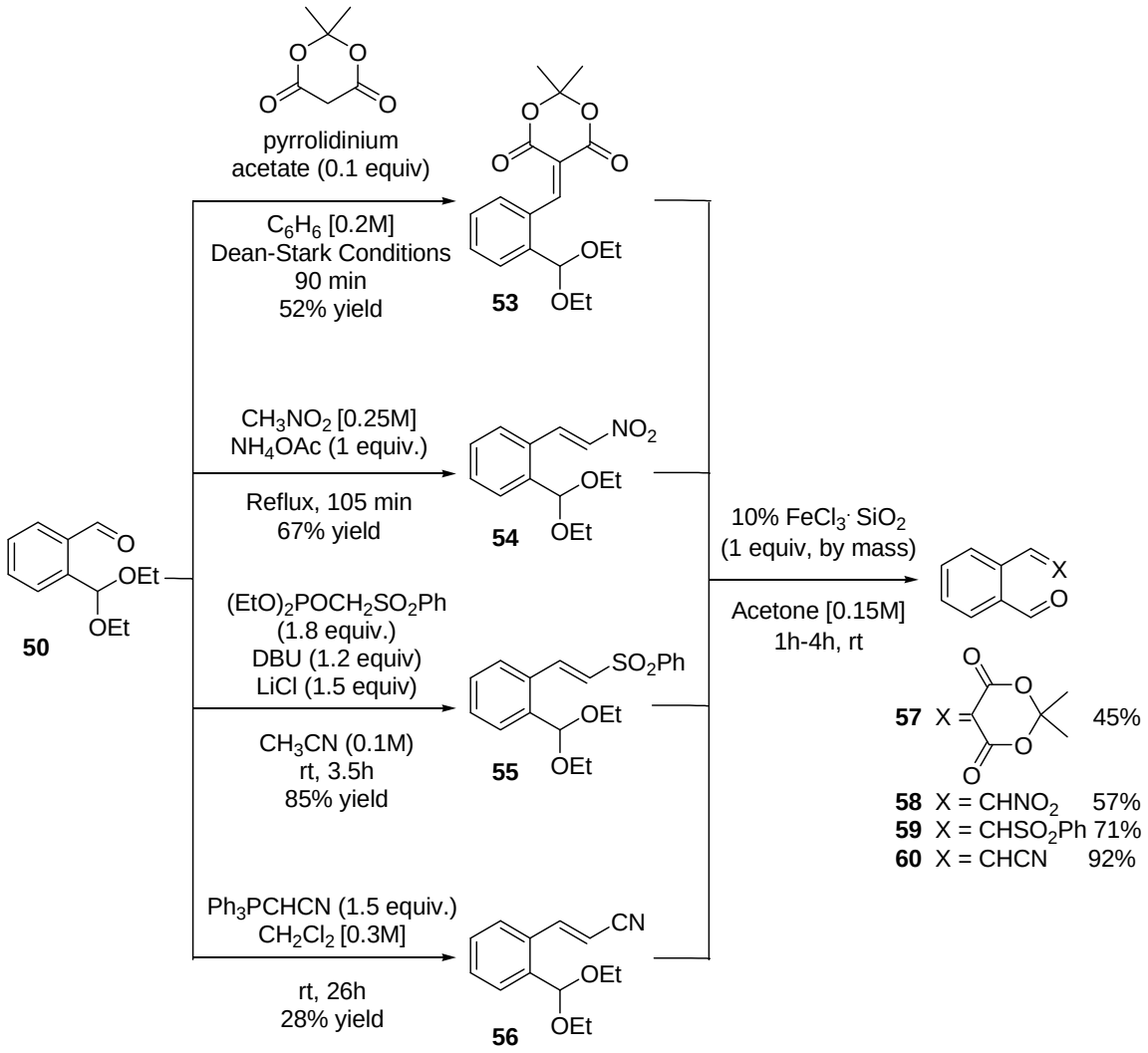
entry	R^1	R^2	R^3	t[a] (min)	product	yield[b] (%)
1	H	H	H	20	**52a**	71
2	H	3-MeO	H	100	**52b**	36
3	H	H	Cl	30	**52c**	58
4	H	4-MeO	Cl	15	**52d**	75
5	MeO	H	H	35	**52e**	42
6[c]	H	H	MeO	60	**52f**	25
7[c]	H	4-F	H	5	**39g**	72[d]
8[c]	F	4-F	Cl	60	**52h**	50

[a] Reaction time of Stetter-aldol-aldol reaction. [b] Yield of pure isolated product over two steps. [c] Experiments performed by Eduardo Sánchez-Larios. [d] Yield of **39g**.

2.7 Other Acceptors Screened in the Stetter-Aldol-Michael and Stetter-Aldol-Aldol Reactions

2.7.1 Preparation of Substrates

Substrates with a variety of electron withdrawing groups such as, nitro, sulfone, nitrile, and malonate groups were screened for reactivity in the SAM and SAA reactions.



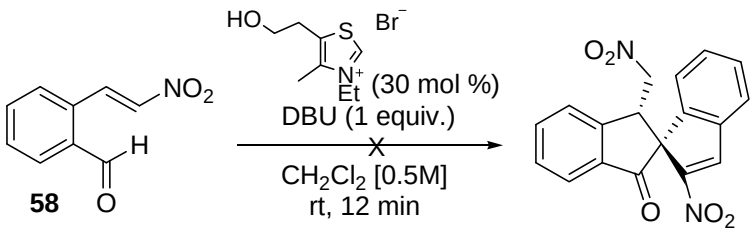
Scheme 2.11 Synthesis of Substrates for Domino Stetter Reactions

All substrates were prepared from the mono-protected dialdehyde, **50** in two steps (Scheme 2.11). Substrate **53** was prepared from the Knoevenagel condensation of

Meldrum's acid onto **50**. Henry reaction of **50** with nitromethane followed by dehydration afforded protected intermediate **54**. Substrate **55** was prepared by an efficient Horner-Wadsworth-Emmons reaction. A moderately *E* selective Wittig reaction afforded the desired intermediate **56**. Iron(III) chloride acetal deprotection of intermediates **53-56** afforded the desired substrates **57-60** for the spiro bis-indane pathway.

2.7.2 Stetter-Aldol-Michael Reactions

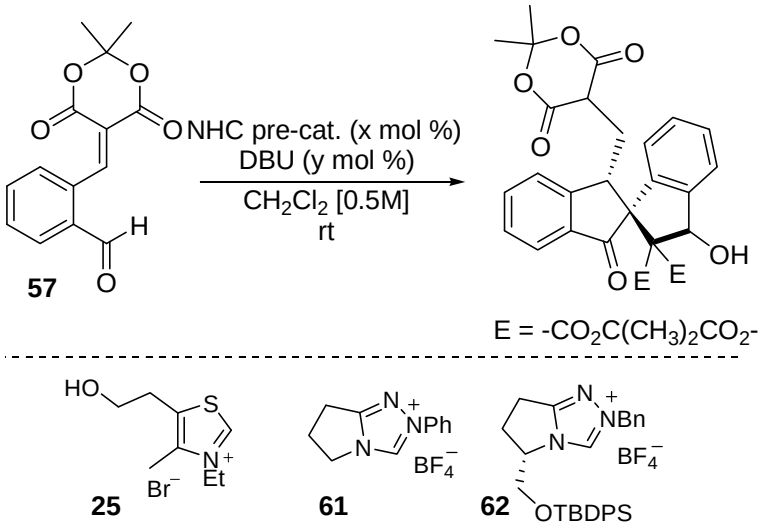
Under standard SAM reaction conditions, nitroalkene **58** was completely consumed within 12 minutes, as determined by TLC. ^{1}H NMR analysis of the crude reaction mixture revealed that a complex mixture had formed, without a trace of the desired product (Scheme 2.12). As **58** appeared to be unstable under reaction conditions, no further experiments were conducted.



Scheme 2.12 Attempted Stetter-Adol-Michael Reaction of **58**.

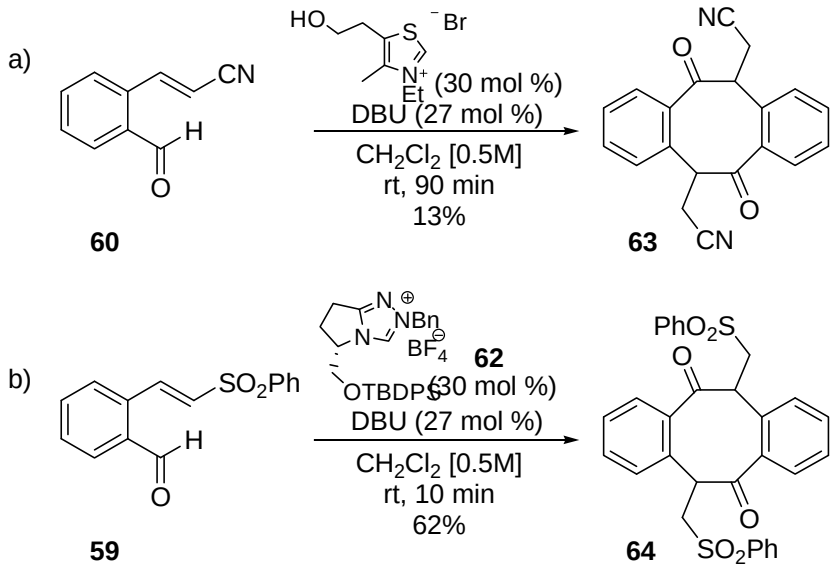
Meldrum's acid alkylidene **57** was unreactive under the optimized reaction conditions for the SAM of model substrate **36a** (Table 2-8, entry 1). Neither triazolium pre-catalyst **61** nor **62** promoted the reaction (entries 2 and 3). These results are likely due to the irreversible addition of the NHC onto the Michael acceptor. When stoichiometric amounts of DBU were employed, TLC detection revealed that **57** was completely consumed within one hour. However, ^{1}H NMR analysis of the crude reaction mixture revealed that the substrate had decomposed to a complex mixture of products (entry 4).

Table 2-8 Attempted Stetter-Aldol-Michael Reactions of **57**.



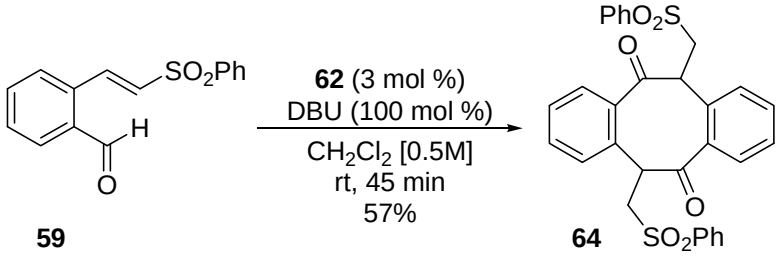
entry	NHC pre-cat.	NHC (x mol%)	DBU (y mol%)	t	results
1	**25**	10	30	90 min	nr
2	**61**	30	27	3 d	nr
3	**62**	30	27	3 d	nr
4	**62**	30	100	55 min	complex mixture of products

Substrates **59** and **60** had been screened for their reactivity in the SAM reaction by the author in the summer of 2009. Under standard reaction conditions both substrates underwent double Stetter reactions to produce eight-membered rings, **61** and **63** (Scheme 2.13). Although the desired SAM products had not been observed, the formation of the double Stetter products clearly indicates that the first step in the SAM pathway, the Stetter reaction is possible for both **59** and **60**.



Scheme 2.13 Undergraduate Research: a) Double Stetter Reaction of **60** b) Double Stetter Reaction of **59**.

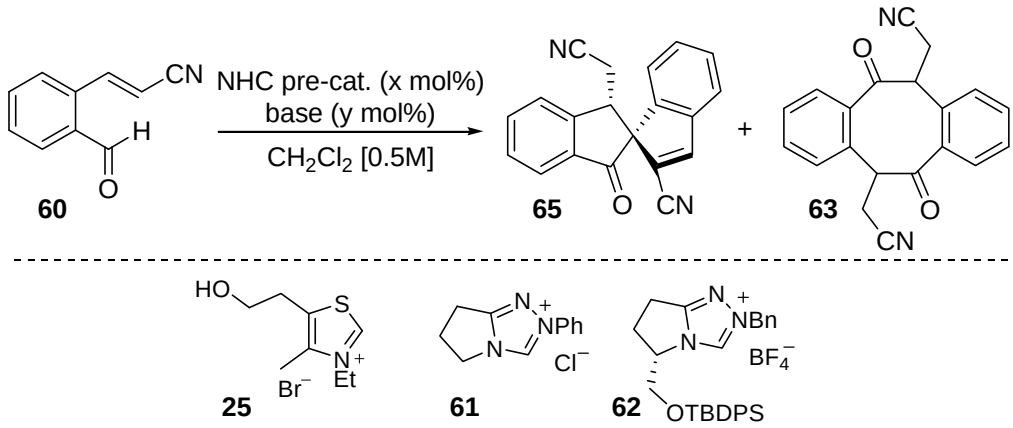
In the double Stetter pathway, the adduct from the first Stetter reaction must form the Breslow Intermediate with the NHC before undergoing the second Stetter reaction. In contrast, the Stetter adduct forms an enolate and then undergoes an aldol reaction in the desired SAM pathway. Thus, the loading of NHC was dropped to 3 mol % and the amount of base was increased to 1 equivalent in order to favour the SAM pathway over the double Stetter pathway of **59**. Regrettably, the double Stetter product was still obtained under these conditions (Scheme 2.14).



Scheme 2.14 Double Stetter Reaction of **59**.

The use of TMG as base did not assist in the promotion of the SAM reaction of **60** (Table 2-9, entry 1). Triazolium pre-catalysts were also screened for their ability to promote the SAM reaction of **60**. While **62** afforded trace amounts of the double Stetter product amongst a complex mixture, **61** completely failed to activate the aldehyde (entries 2 and 3). Once again, lower catalytic loading did not promote the SAM pathway (entry 4).

Table 2-9 Attempted Stetter-Aldol-Michael Reactions of **60**.



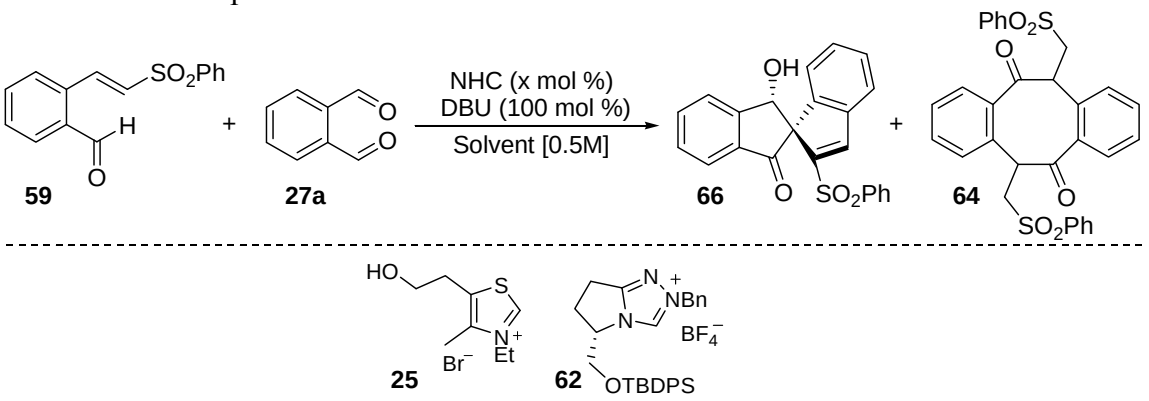
entry	NHC pre-cat.	NHC (x mol%)	base	base (y mol%)	t (h)	results
1	**25**	30	TMG	27	17	trace **63**
2	**61**	30	DBU	27	18	nr
3	**62**	30	DBU	27	(10 min)	trace **63**
4	**62**	3	DBU	2.7	19	nr

2.7.3 Stetter-Aldol-Aldol Reactions

Substrate **59** was also screened for its reactivity in the SAA reaction. The optimized reaction conditions for the model substrate left **59** partially unreacted with trace amounts of the double Stetter product. The use of dichloroethane as solvent permitted heating of the reaction mixture to reflux (84˚C). However, only a complex mixture with trace amounts of the double Stetter product was obtained under these conditions. Despite the

low catalytic loading, when triazolium pre-catalyst **62** was employed; only the double Stetter product was obtained.

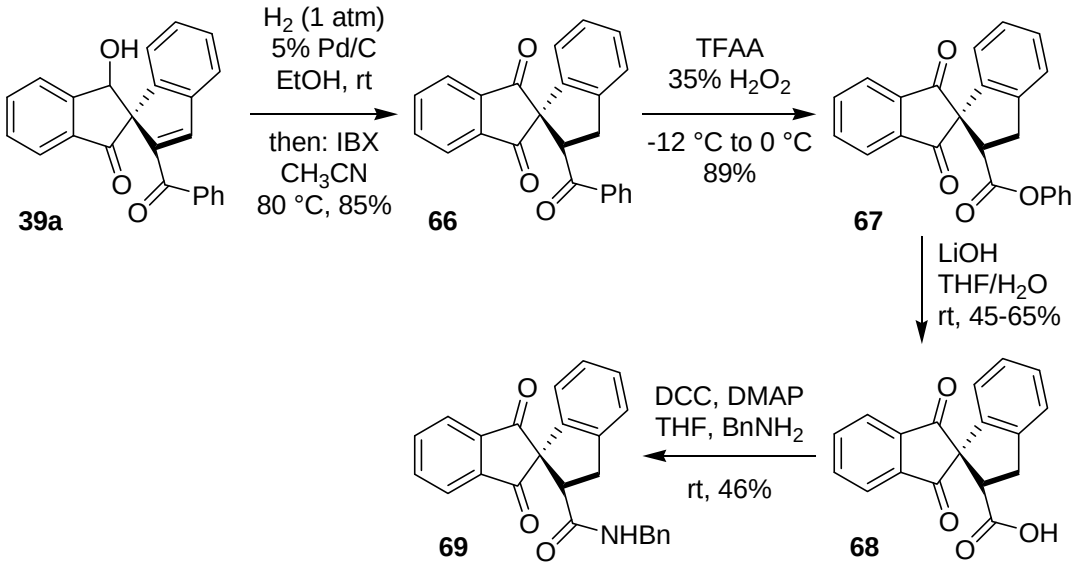
Table 2-10 Attempted Stetter-Aldol-Aldol Reactions of **59** and **27**.



entry	NHC pre-cat.	NHC (x mol%)	solvent	T (˚C)	t	product
1	**25**	30	CH_2Cl_2	23	5 d	complex mixture
2	**62**	30	$(CH_2Cl)_2$	reflux	4 d	complex mixture
3	**62**	3	CH_2Cl_2	23	20 min	**64**

2.8 Synthesis of Fredericamycin A Analog

To demonstrate one of the possible synthetic applications of the SAA reaction, Eduardo Sánchez-Larios prepared an analog of fredericamycin A from SAA adduct **39a** (Scheme 2.15).[50] The enone of **39a** was reduced to the corresponding saturated ketone using palladium on carbon (Pd/C) and an atmosphere of hydrogen gas. Oxidation of the secondary alcohol using IBX afforded triketone **66**. A selective Baeyer-Villiger oxidation produced ester **67**. Subsequent hydrolysis followed by amidation afforded the desired fredericamycin A analog, **69**.



Scheme 2.15 Preparation of Fredericamycin A Analog from Stetter-Aldol-Aldol Adduct **39a**.

2.9 Conclusions

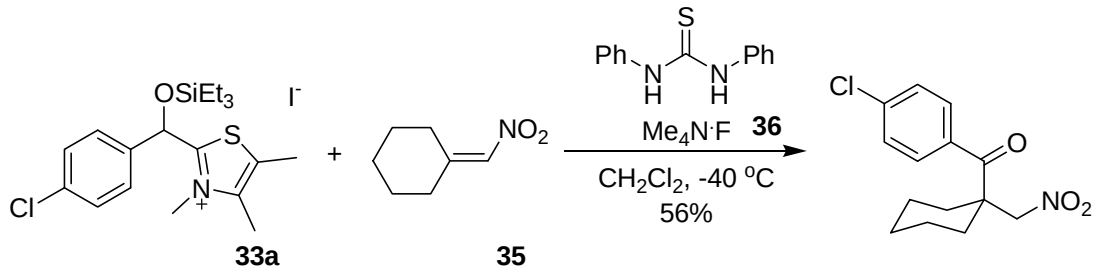
A variety of spiro bis-indanes were prepared in good yield and moderate to high diastereoselectivity through both the SAA and SAM pathways. A SAM cross-dimerization was carried out with remarkable regioselectivity, demonstrating the electronic effects of substituents on the starting materials. Under standard NHC reaction conditions, substrates bearing nitrile and sulfone withdrawing groups readily underwent double Stetter reactions to produce eight-membered rings. The above results were published in collaboration with Eduardo Sánchez-Larios' preparation of a derivative of the core of fredericamycin A from a SAA product.[51]

CHAPTER THREE

INTERMOLECULAR STETTER REACTIONS TOWARDS QUATERNARY CENTRE FORMATION

3.1 Introduction

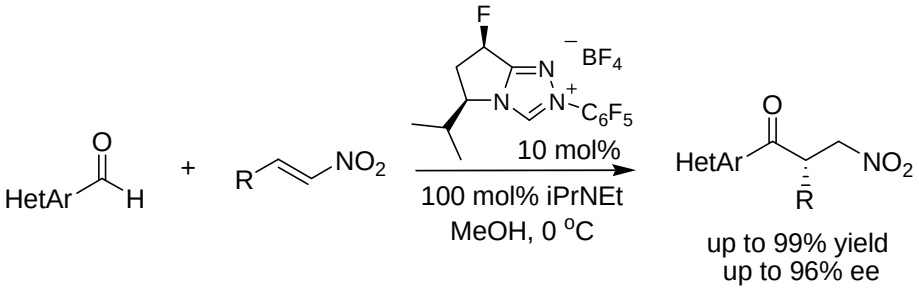
In 2006, Scheidt et al. reported the formal Stetter reaction of silylated thiazolium carbinols and base sensitive β-alkyl nitroalkenes.[37] In one example, a new quaternary centre is formed from the formal Stetter reaction of silylated thiazolium carbinol **33a** and nitro methylenecyclohexane (Scheme 3.1). As the proposed addition step in the formal Stetter reaction is the same as in the intermolecular Stetter reaction, these results indicate that quaternary centre formation through the intermolecular Stetter reaction is possible.



33a **35**

Scheme 3.1 Scheidt's Quaternary Centre Formation via the Formal Stetter Reaction of **35**

Following Scheidt's contribution, Rovis demonstrated that intermolecular Stetter reactions could be performed on β-alkyl nitroalkenes when the weak base, iPr_2NEt, was employed at 0˚C (Scheme 3.2).[52] Despite this achievement, the scope of this reaction is limited to the formation of tertiary centers. Presumably, the relatively greater steric bulk of a triazolium based Breslow intermediate compared to a thiazolium based intermediate prevented the formation of quaternary centres.



Scheme 3.2 Rovis' Stetter Reaction of β-Alkyl Nitroalkenes

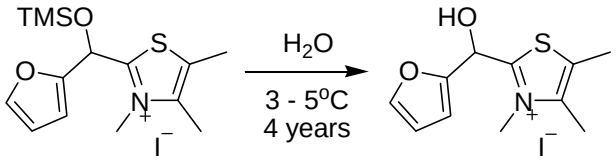
3.2 Research Objectives

In order to extend the scope of the intermolecular Stetter reaction to permit the formation of quaternary centers, β,β-disubstituted olefins were screened for reactivity in the formal Stetter reaction of thiazolium carbinols. As the ultimate goal of this project was to develop a method for quaternary centre formation through the intermolecular Stetter reaction, promising candidates were subjected to further screening under standard Stetter reaction conditions.

3.3 Formal Stetter Optimization

The formal Stetter reaction of thiazolium carbinols offered certain advantages in the screening of Stetter acceptors. The absence of excess unreacted aldehyde completely circumvents the Stetter reaction's competing benzoin reaction. Additionally, the addition of the NHC onto the Stetter acceptor is also avoided. Therefore, to improve the efficiency of the investigation, all β,β-disubstituted olefins were subjected to the reaction conditions for the formal Stetter reaction of thiazolium carbinols. Silylated thiazolium carbinol **33b** had been previously prepared by Dr. Michel Gravel[i] in 2007 following Scheidt's protocol.[37] Surprisingly, since its preparation, the moisture in air had completely hydrolyzed **33b** to thiazolium carbinol **70** (Scheme 3.3).[53]

[i] Gravel, M *unpublished results*.

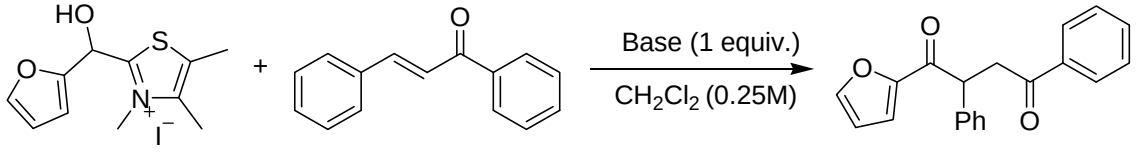


33b **70**

Scheme 3.3 Hydrolysis of Silylated Thiazolium Carbinol **33b**

As the use of thiazolium carbinol **70** in the formal Stetter reaction would more closely reproduce the reaction conditions of the Stetter reaction, its ability to participate in the formal Stetter reaction was briefly investigated. Bases DBU and iPr_2NEt both promoted the formal Stetter reaction of **70** and *E*-chalcone (Table 3-1, entries 1 and 2). As DBU afforded superior results, it was employed for further investigations. ^{1}H NMR analysis of reaction mixture aliquots revealed that **70** is completely consumed within 15 minutes of its subjection to DBU (not shown).

Table 3-1 Optimization of the Formal Stetter Reaction of Thiazolium Carbinol **70**



70 **71** **72**

entry	equiv. of 70	equiv. of 71	base	time (min)	conv. (%)[a]
1	1	1	iPr_2NEt	(7.5h)	20
2	1	1	DBU	15	66
3	1.5	1	DBU	10	52
4	1	2	DBU	5	66
5	1	2	Cs_2CO_3	130	10

[a] Conversion determined by ^{1}H NMR analysis of crude reaction mixture.

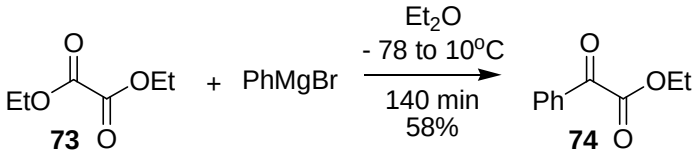
Neither the use of excess **70** nor excess **71** improved the conversion beyond 66% (entries 2 and 4). The use of Cs_2CO_3 also did not improve the conversion, likely due to the limited solubility of both **70** and Cs_2CO_3 in dichloromethane (entry 5). As the

conversion could not be easily improved beyond 66%, the reaction conditions outlined in entries 2 and 4 were employed in the screening of Stetter acceptors.

3.4 Doubly Activated Alkylidene Acceptors

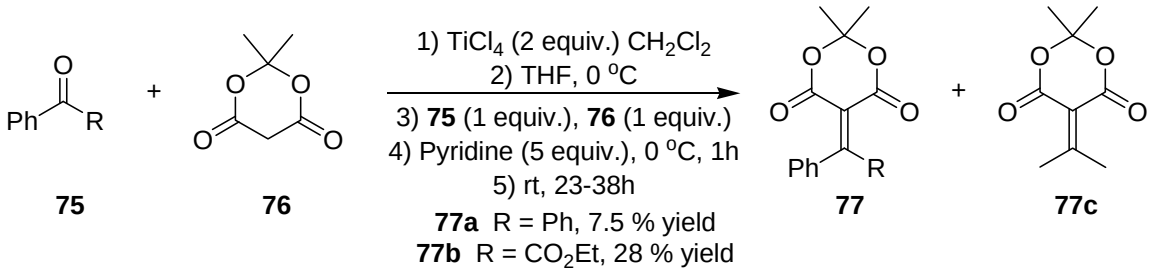
3.4.1 Meldrum's Acid Alkylidene Acceptors

In an effort to compensate for the negative steric effects of the β,β-disbustituted acceptor, highly electrophilic acceptors, such as Meldrum's acid derived alkylidenes, were prepared. Meldrum's acid alkylidene **77b**'s precursor, **74** was prepared from diethyl oxalate **73** and phenylmagnesium bromide following a literature procedure (Scheme 3.4).[54]



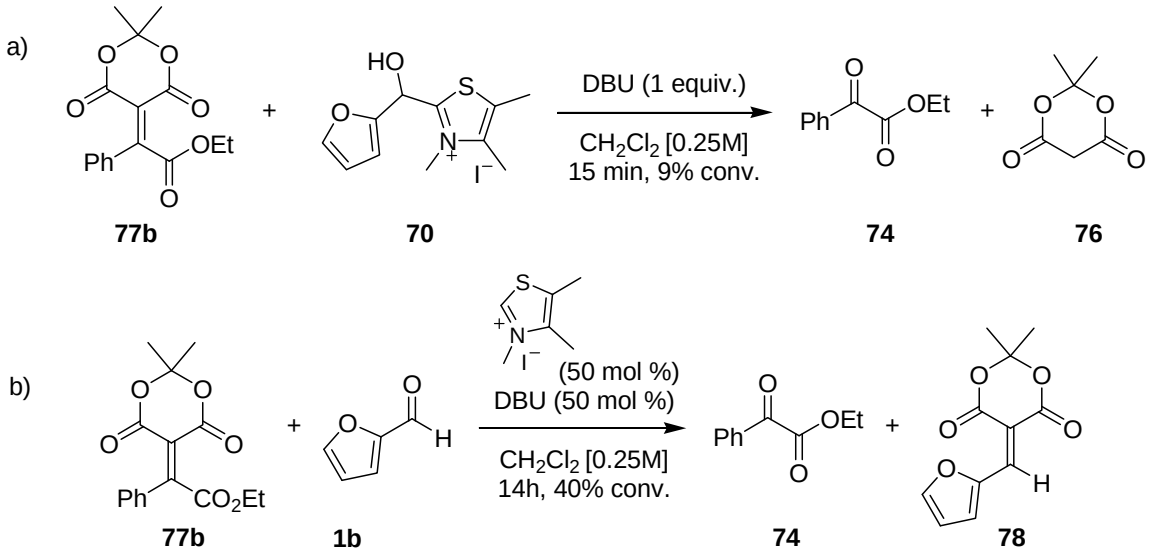
Scheme 3.4 Synthesis of α-Ketoester **74**

Meldrum's acid alkylidenes were prepared from Brown's procedure for the Knoevenagel condensation of Meldrum's acid **76** and the carbonyl of **75** (Scheme 3.5).[55] Regrettably, the formation of side product **77c** from two equivalents of Meldrum's acid, resulted in low yields of **77a** and **77b**.



Scheme 3.5 Synthesis of Meldrum's Acid Alkylidenes

Both substrates **77a** and **77b** were screened for reactivity in the formal Stetter reaction with thiazolium carbinol **70**. Under standard reaction conditions substrate **77a** was completely unreactive (not shown) whereas substrate **77b** partially hydrolyzed to the corresponding α-ketoester **74** (Scheme 3.6). When the corresponding Stetter reaction was attempted, α-ketoester **74** and 2-furaldehyde derived Meldrum's acid alkylidene, **78** were obtained as the major products (Scheme 3.6). Presumably, the hydrolysis of **77b** to Meldrum acid and α-ketoester **74**, is followed by the condensation of 2-furaldehyde with Meldrum's acid to produce **78**.

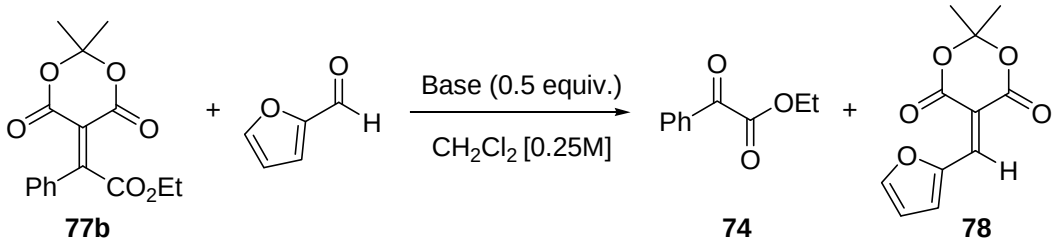


Scheme 3.6 Formal Stetter Reaction of Substrate **77b**

To determine the cause of substrate **77b**'s sensitivity to the reaction conditions, three control experiments were performed. When substrate **77b** and 2-furaldehyde were dissolved in dichloromethane, the Meldrum's acid alkylidene did not hydrolyze (Table 3-2, entry 1). However, when the same reagents were exposed to DBU, substrate **77b** almost completely hydrolyzed over a period of 14 hours (entry 2). When activated 4Å powdered molecular sieves were employed to remove residual water from the reaction

mixture, partial hydrolysis was still observed (entry 3). As Meldrum's acid alkylidenes proved to be unstable to standard Stetter reaction conditions, their use in the Stetter reaction was not investigated any further.

Table 3-2 Base Control Experiments Performed on **77b**



77b **74** **78**

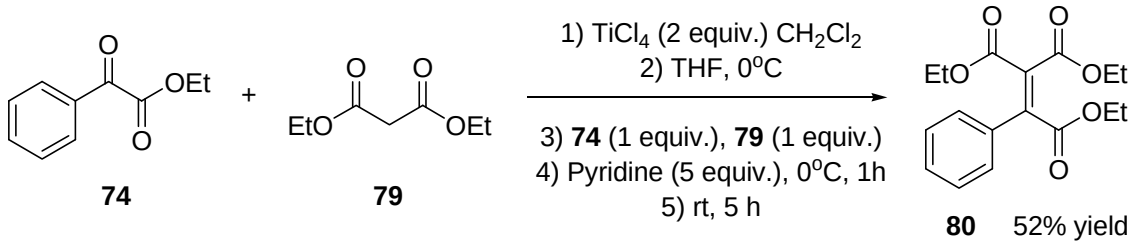
entry	base	additive	time (h)	conv. to 74 (%)[a]	conv. to 78 (%)[a]
1	-	-	5	-	-
2	DBU	-	14	87	50
3	DBU	molecular sieves	20	7	-

[a] Conversion determined by ^{1}H NMR analysis of the crude reaction mixture.

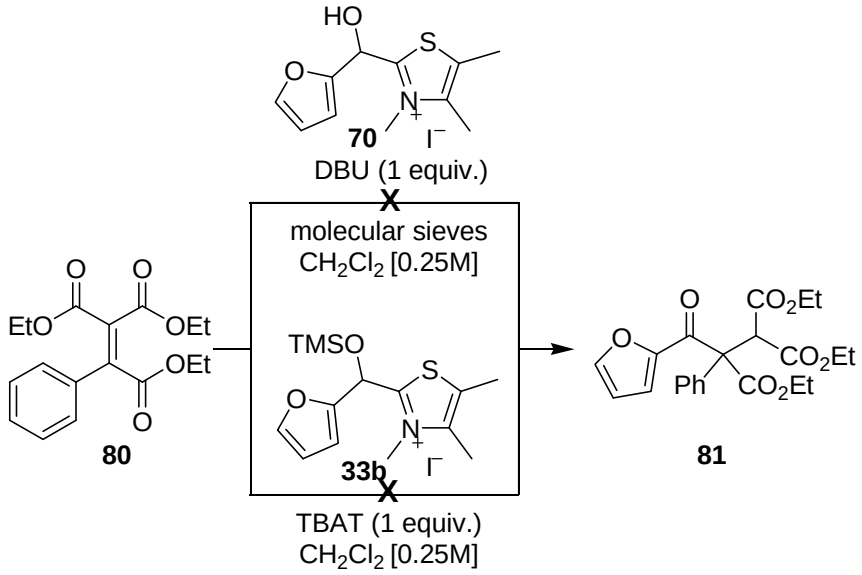
3.4.2 Diethyl Malonate Alkylidene Acceptors

Gravel group member, Karen Thai, recently developed a method for the production of tertiary alcohols through the keto-aldehyde cross benzoin of α-ketoesters, such as **74**.[56] These results clearly indicate that attack of the Breslow intermediate is not hindered by the bulky reactive site of the α-ketoester. Presumably, an olefin bearing the same substituents and possessing similar electrophilicity as the carbonyl, would exhibit similar reactivity in the Stetter reaction to produce a quaternary centre. As recent reports from Mayr suggest that ketones and diethyl malonate derived alkylidenes exhibit similar electrophilicity,[57] acceptor **80** was prepared. Starting from α-ketoester **74**, titanium tetrachloride promoted Knoevenagel condensation with diethyl malonate **79** afforded the desired acceptor in 52% yield (Scheme 3.7).

Prior to screening for reactivity in the Stetter reaction, it was necessary to determine if substrate **80** were stable under reaction conditions. Thus, **80** was exposed to a solution of DBU in dichloromethane in the presence of activated 4Å powdered molecular sieves for 24 hours (not shown). As no decomposition of the acceptor was observed under these conditions, **80** was subjected to further tests. Initially, two formal Stetter reactions were attempted. However, **80** did not form the Stetter adduct with the silylated thiazolium carbinol or the unprotected thiazolium carbinol (Scheme 3.8).

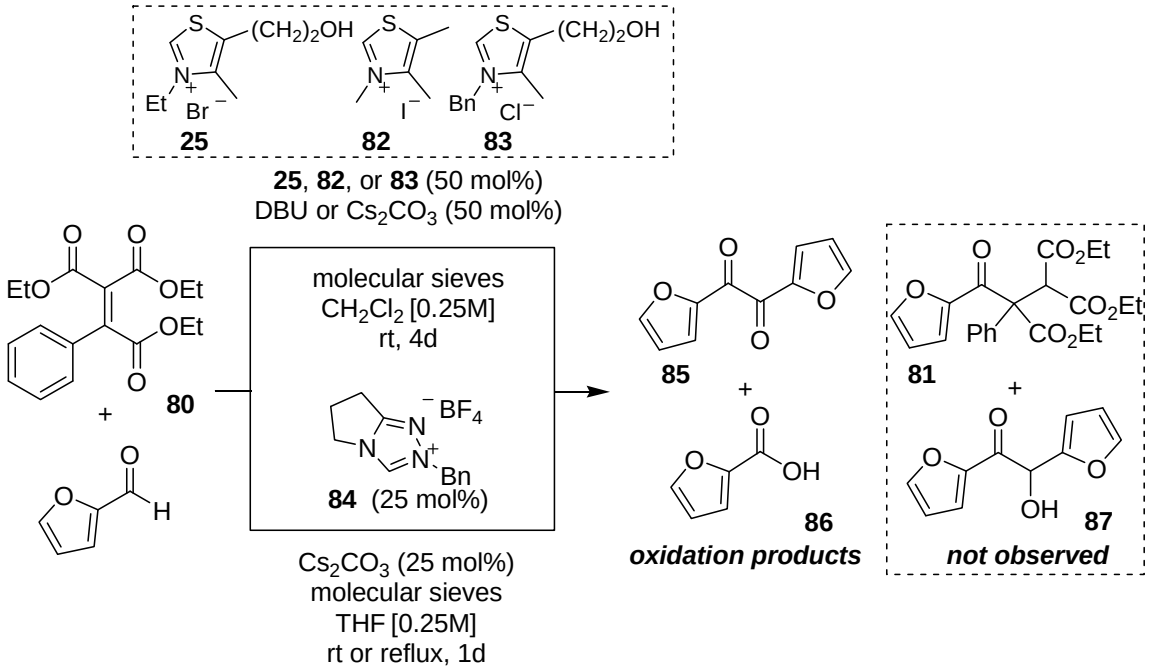


Scheme 3.7 Synthesis of Diethyl Malonate Alkylidene **80**



Scheme 3.8 Attempted Formal Stetter Reactions of Diethyl Malonate Alkylidene **80**

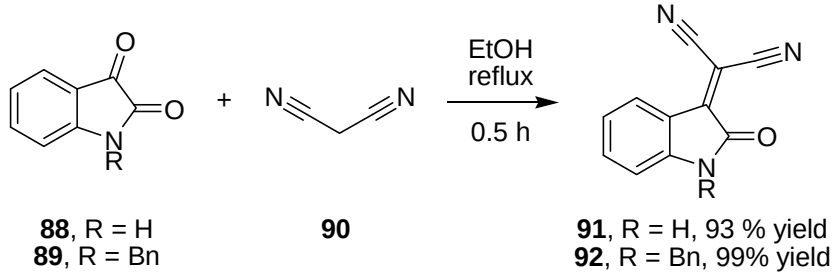
Thiazolium NHC pre-catalysts **25, 82,** and **83** were screened with both DBU and Cs_2CO_3 separately (Scheme 3.9). Under the conditions outlined in Scheme 3.9 none of the thiazolium derived NHCs promoted the desired Stetter reaction. ^{1}H NMR analysis of the crude reaction mixture indicated almost complete consumption of the aldehyde under all reaction conditions. However, the expected benzoin product, furoin (**87**) was not detected in the crude ^{1}H NMR which suggests that the aldehyde was lost to NHC promoted oxidation. Triazolium based NHC pre-catalyst **84** was also screened for its ability to promote the Stetter reaction of substrate **80** (Scheme 3.9). Tetrahydrofuran was employed as solvent to permit the reaction to be performed at reflux as well as ambient temperature. Once again all the aldehyde was consumed, yet no Stetter or benzoin product was obtained, likely due to the oxidation of the aldehyde.



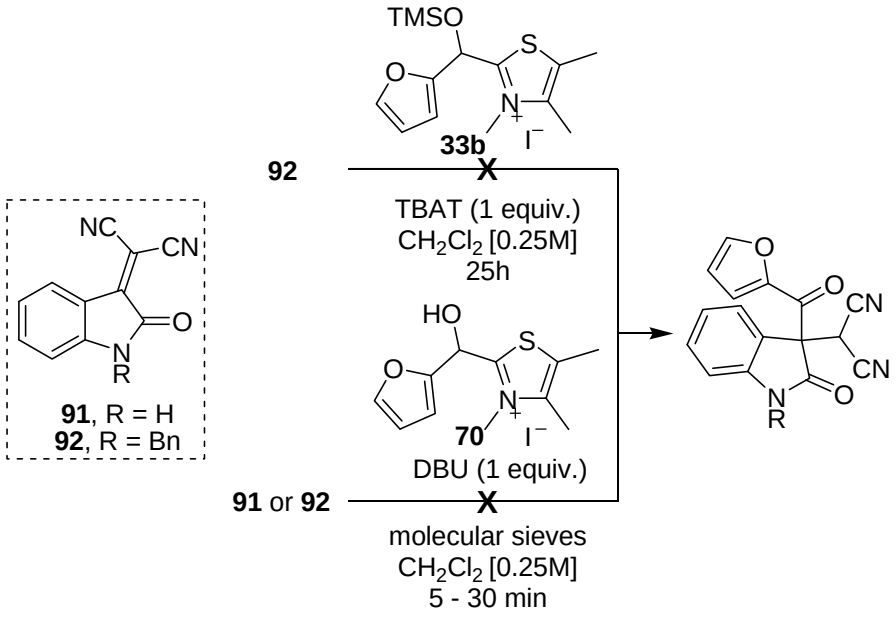
Scheme 3.9 Attempted Stetter Reactions of Substrate **80**

3.4.3 Malononitrile Alkylidene Acceptors

In an effort to reduce the steric hindrance at the reactive site of the Stetter acceptor, malononitrile alkylidenes **91** and **92** were prepared from isatin **88** and *N*-benzyl isatin **89**, respectively (Scheme 3.10). Substrate **92** was screened for reactivity in the formal Stetter reaction with silylated thiazolium carbinol **33b**. **91** and **92** were also screened for reactivity with thiazolium carbinol **70**. All reaction conditions outlined in Scheme 3.11 resulted in a complex mixture of products.



Scheme 3.10 Synthesis of Malononitrile Alkylidenes **91** and **92**



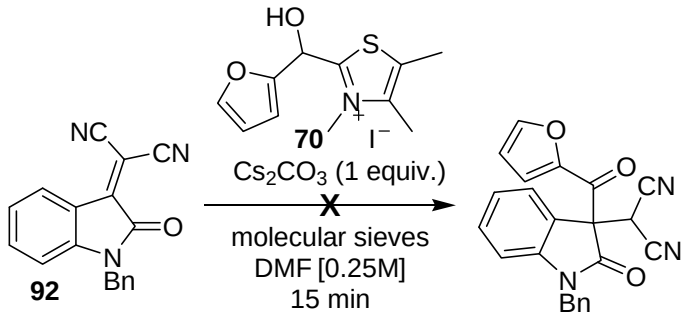
Scheme 3.11 Attempted Formal Stetter Reactions of Substrates **91** and **92**

As the acceptors were unstable under formal Stetter reaction conditions, a series of control reactions were performed employing one equivalent of base in dichloromethane (0.25M). Subjection of substrate **91** to DBU resulted in a complex mixture of products (Table 3-3, entry 1). Similar results were observed when activated 4Å powdered molecular sieves were introduced (entry 2). No reaction occurred when **91** was subjected to the less basic, non-nucleophilic base, Cs_2CO_3 in the presence of 4Å powdered molecular sieves (entry 3). **92** was determined to be unstable in the presence of nucleophilic bases DBU and iPr_2NEt (entries 4 and 5). No reaction was observed when **92** was subjected to the non-nucleophilic base, Cs_2CO_3 (entry 6). As iPr_2NEt is a weaker base than Cs_2CO_3, these results suggested that iPr_2NEt's ability to behave as a nucleophile is responsible for the decomposition of the acceptors. All further investigations on substrates **91** and **92** were performed with the non-nucleophilic base, Cs_2CO_3.

Table 3-3 Base Control Experiments Performed on Substrates **91** and **92**

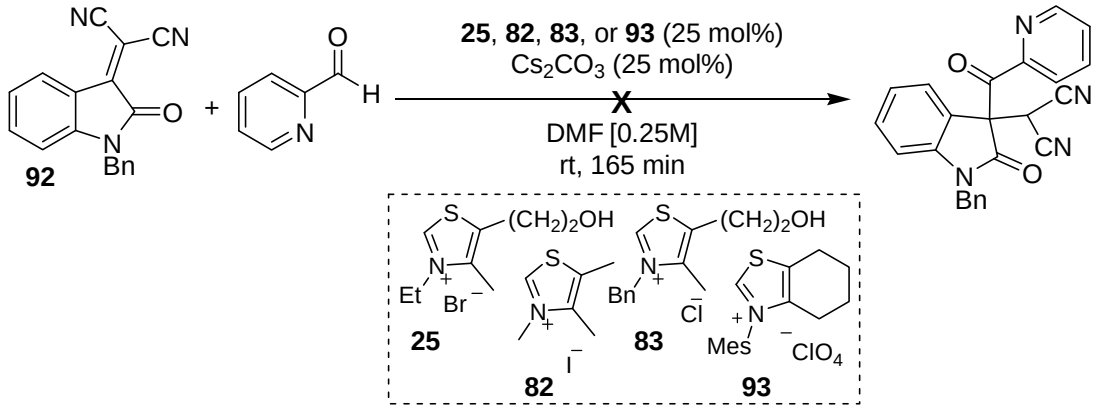
entry	acceptor	base	additive	time (h)	results
1	**91**	DBU	-	24	complex mixture
2	**91**	DBU	molecular sieves	24	complex mixture
3	**91**	Cs_2CO_3	molecular sieves	24	no reaction
4	**92**	DBU	-	2	complex mixture
5	**92**	iPr_2NEt	-	2	complex mixture
6	**92**	Cs_2CO_3	-	2	no reaction

A second formal Stetter reaction was attempted with substrate **92** using Cs_2CO_3 as base (Scheme 3.12). To improve the solubility of both the base and the thiazolium carbinol, DMF was employed as solvent. Despite complete consumption of the thiazolium carbinol **70**, the Stetter adduct was not obtained.



Scheme 3.12 Attempted Cs_2CO_3 Formal Stetter Reaction of Substrate **92**

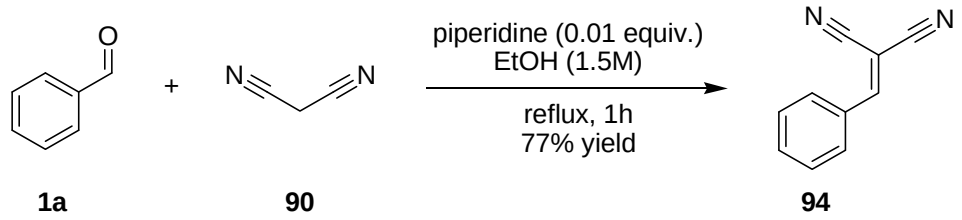
A series of thiazolium catalyzed Stetter reactions employing Cs_2CO_3 as base and DMF as solvent were also attempted on substrate **92** (Scheme 3.13). When thiazolium NHC pre-catalyst **82**, **83**, and **93** were employed, a complex mixture of products derived from the acceptor was obtained. The aldehyde, however, was largely unreacted, not even the benzoin product was detected. These results suggest that the NHC derived from **82**, **83**, and **93** promote the decomposition of **92**. When NHC pre-catalyst **25** was employed, the benzoin product was obtained and only partial decomposition of **92** was observed. Similar results were obtained when the reaction was repeated in CH_2Cl_2 (not shown).



Scheme 3.13 Attempted Stetter Reactions of Substrate **92**

Following these disappointing results, the viability of malononitrile alkylidenes as acceptors in the Stetter reaction was investigated using **94**. A simple Knoevenagel

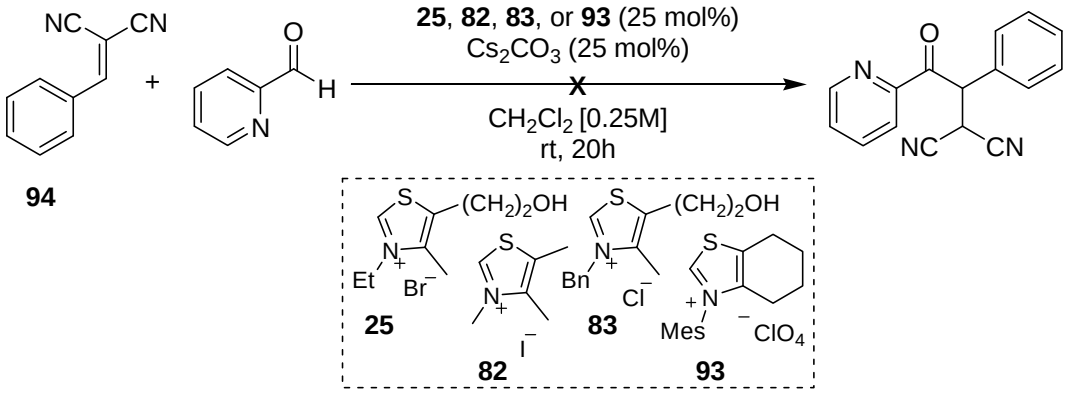
coupling between benzaldehyde and malononitrile afforded **94** in a 77% yield (Scheme 3.14).



1a **90** **94**

Scheme 3.14 Preparation of Malononitrile Derived Alkylidene **94**

When **94** was subjected to the reaction conditions outlined in Scheme 3.15, the acceptor and aldehyde formed a complex mixture of products. These results suggested that malononitrile derived alkylidenes are not viable acceptors in the Stetter reaction.



94

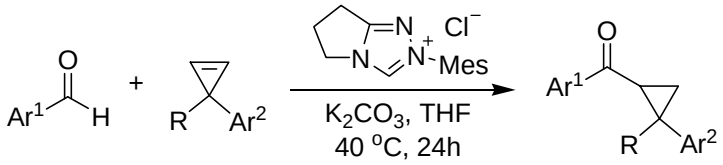
25 **82** **83** **93**

Scheme 3.15 Attempted Stetter Reactions of Malononitrile Derived Alkylidene **94**

3.5 Cycloenone Acceptors

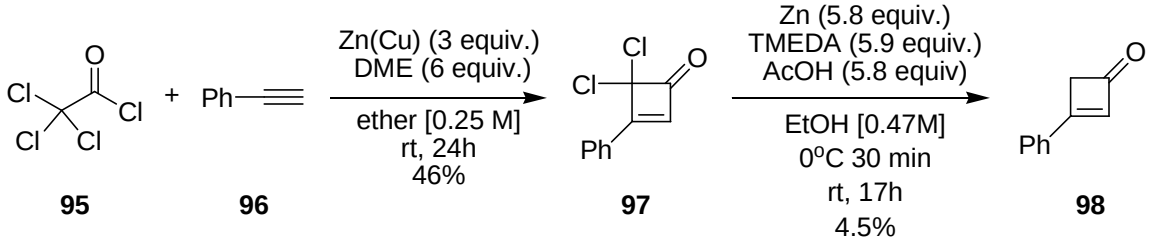
As doubly activated β,β-disubstituted alkenes were generally unstable under standard Stetter reaction conditions, it was necessary to develop another method of activation for the acceptors. In 2011, Glorius reported the NHC-promoted hydroacylation of unactivated cyclopropenes (Scheme 3.16).[58] Presumably, the cyclopropene's ring strain enhanced its reactivity as acceptor relative to other unactivated acceptors. In the hopes that this strategy could be exploited in the quaternary centre forming intermolecular

Stetter, 3-phenylcyclobutenone and diphenylcyclopropenone substrates were investigated.



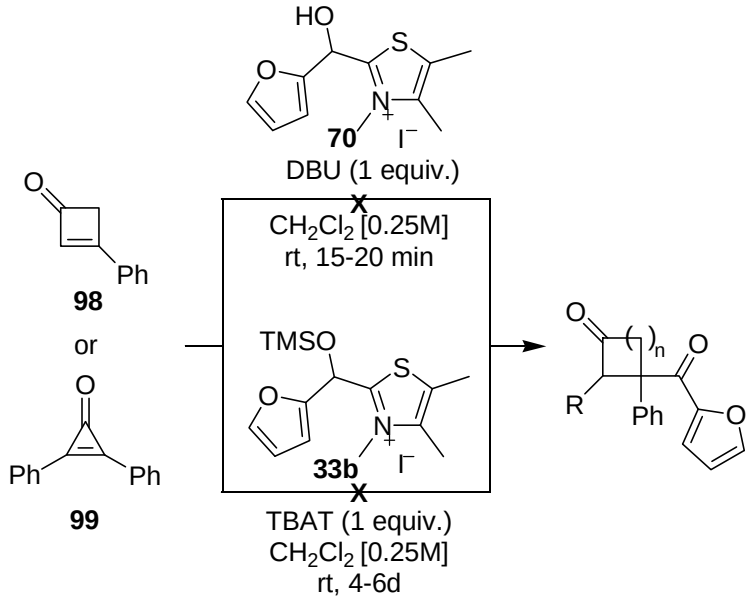
Scheme 3.16 Glorius' Hydroacylation of Unactivated Cyclopropenes

3-Phenylcyclobutenone **98** was prepared from trichloroacetyl chloride **95** and phenylacetylene **96**, following a literature procedure (Scheme 3.17).[59]



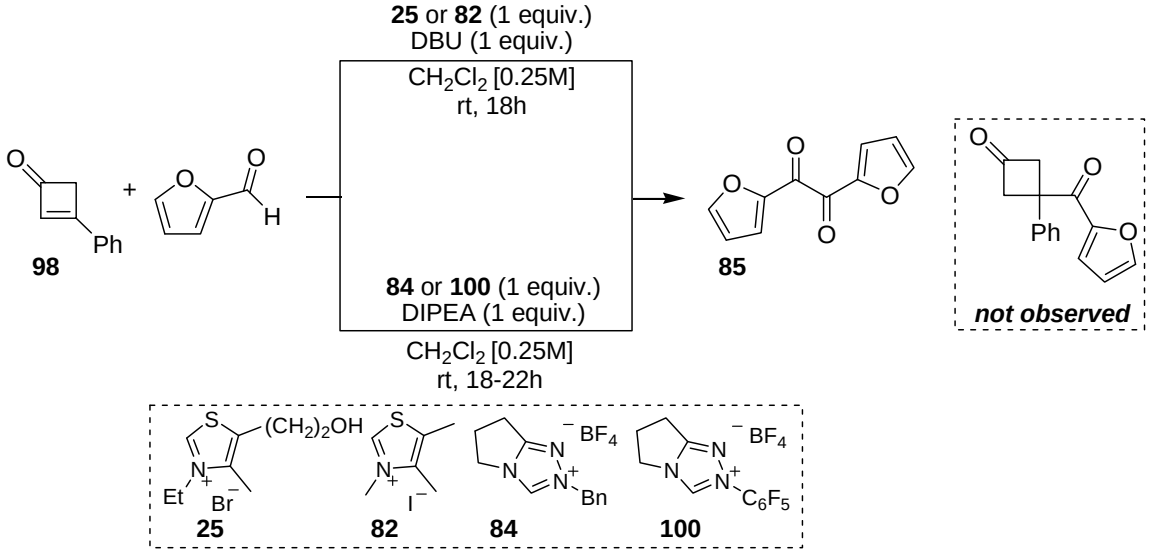
Scheme 3.17 Preparation of Cyclobutenones **98**

Neither 3-phenylcyclobutenone **98** nor diphenylcyclopropenone **99** were reactive in the formal Stetter reactions of silylated thiazolium carbinol **33b** and thiazolium carbinol **70** (Scheme 3.18).



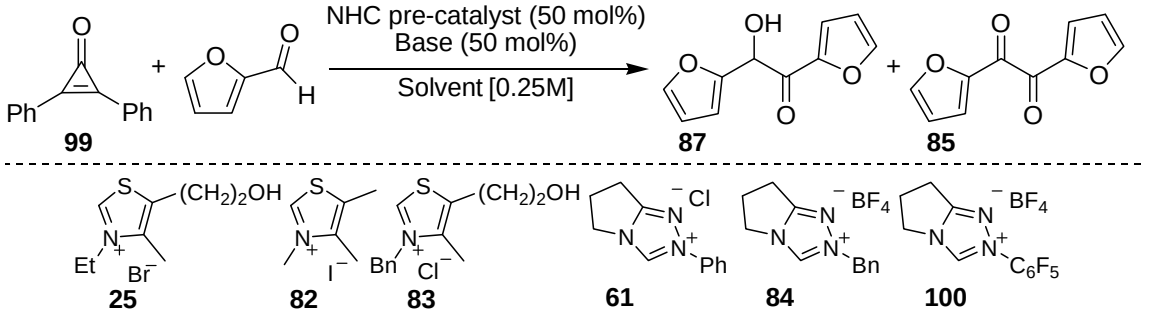
Scheme 3.18 Attempted Formal Stetter Reaction of **98** and **99**

As substrate **98** was unreactive under the conditions outlined in Scheme 3.19, only the oxidation product, **85** was obtained.



Scheme 3.19 Attempted Stetter Reactions of 3-Phenylcyclobutenone

Table 3-4 Attempted Stetter Reactions of Diphenylcyclopropenone **99**



entry	NHC	base	solvent	T (˚C)	t (d)	products
1	**25**	Cs_2CO_3	CH_2Cl_2	rt	4	**85**
2	**82**	Cs_2CO_3	CH_2Cl_2	rt	4	nr
3	**83**	Cs_2CO_3	CH_2Cl_2	rt	4	**85**
4	**61**	iPr_2NEt	CH_2Cl_2	rt	4	**85**
5	**84**	iPr_2NEt	CH_2Cl_2	rt	4	**85**
6	**84**	iPr_2NEt	CH_2Cl_2	rt	4	**85**
7	**100**	iPr_2NEt	DMF	80	1	**85**
8	**100**	iPr_2NEt	THF	80	1	**85, 87**
9[a]	**100**	iPr_2NEt	THF	80	2	**85**, **87**

[a] Reaction was performed in sealed pressure vessel.

Diphenylcyclopropenone **99** was unreactive under standard NHC conditions for thiazolium (Table 3-4, entries 1-3) and triazolium (entries 4-6) pre-catalysts, thus oxidation product **85** was obtained. An increase in temperature from ambient temperature to 80˚C did not promote the reaction in either DMF or THF (entries 7 and 8). In an effort to minimize the formation of oxidation side products a sealed vessel was employed (entry 9). Regrettably, under these conditions the Stetter adduct did not form and oxidation product **87** was still obtained.

3.6 Conclusions

β,β-Disubstituted Meldrum's acid-, diethyl malonate-, and malononitrile-derived alkylidenes were screened for reactivity in both the formal and catalytic Stetter reaction. These acceptors were generally unstable under standard reaction conditions. 3-Phenylcyclobutenone and diphenylcyclopropenone were also screened for reactivity in

the formal and catalytic Stetter reaction. None of the reaction conditions screened promoted the Stetter reaction of 3-phenylcyclobutenone or diphenylcyclopropenone.

CHAPTER FOUR

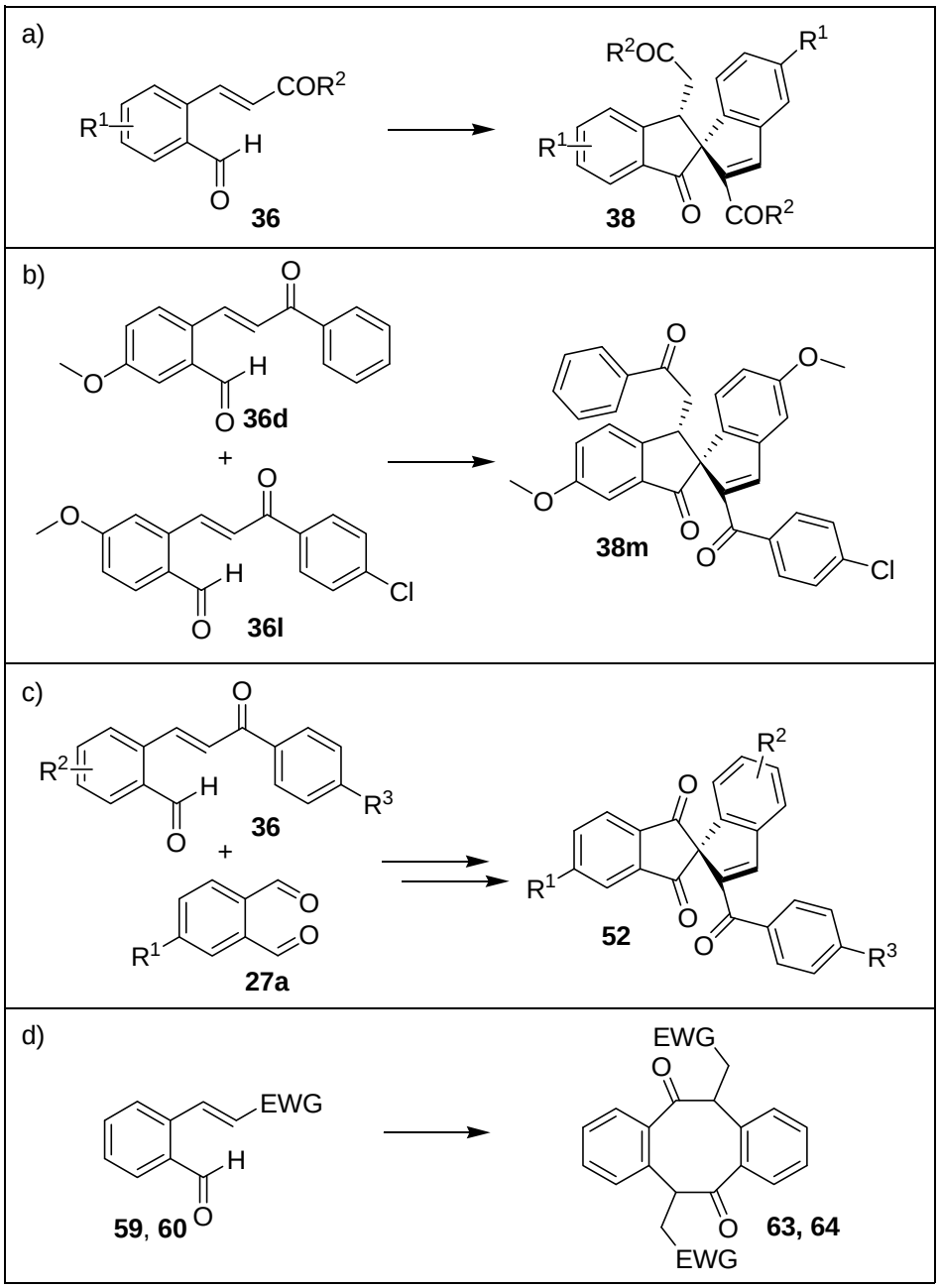
SUMMARY

4.1 Development of Stetter-Aldol-Michael and Stetter-Aldol-Aldol Reactions

The development of a unique domino Stetter reaction, the Stetter-aldol-Michael reaction of *o*-formyl chalcone derivatives, provided access to structurally complex spiro bis-indanes (Scheme 4.1a). The results of the SAM were highly dependent on the amount of base in the reaction mixture and the reaction time. The base, DBU, was observed to promote the competing Baylis-Hillman reaction of *o*-formyl chalcones. Large excesses of DBU also resulted in low diastereomeric ratios due to the retro-Michael-Michael isomerization of the product. Long reaction times also resulted in lower diastereomeric ratios, presumably due to prolonged exposure to the base. Under optimized conditions, the SAM of *o*-formyl chalcones generally afforded products in high diastereomeric ratios and good yields. Substrates bearing electron poor acceptor moieties underwent the SAM pathway rapidly, affording products with high diastereomeric ratios. Comparatively more electron rich acceptors required longer reaction times and generally resulted in lower diastereomeric ratios. A chemoselective cross Stetter-aldol-Michael reaction demonstrated the ability of the substrates to be electronically tuned towards accepting or donating in the Stetter reaction (Scheme 4.1b).

Spiro bis-indanes were also prepared through the Stetter-aldol-aldol reaction of phthalaldehydes and *o*-formyl chalcone derivatives (Scheme 4.1c). Optimization of the Stetter-aldol-aldol pathway required the *o*-formyl chalcone's competing Stetter-aldol-Michael pathway to be suppressed. Ultimately, it was determined that the SAM pathway could not be completely circumvented. Thus the transformation of the phthalaldehyde derivative in the SAA reaction was improved by employing an excess of the *o*-formyl

chalcone. As the retro-aldol-aldol reaction resulted in poor diastereomeric ratios, one of the two stereogenic centres was destroyed by oxidation prior to the isolation of the product. The SAA reaction followed by oxidation afforded spiro bis-indanes in moderate to good yield.

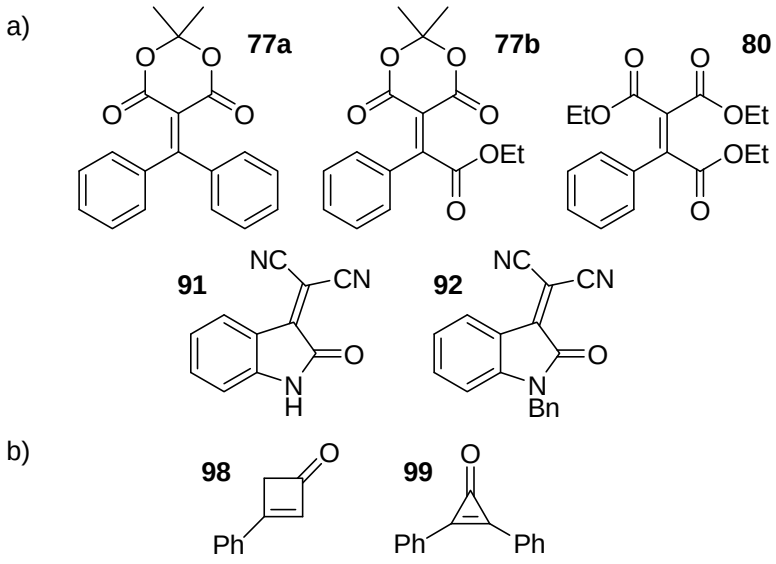


Scheme 4.1 Domino Stetter Reactions *o*-Formyl Chalcone Derivatives.

Under standard reaction conditions, substrates bearing nitrile and sulfone electron withdrawing groups on the acceptor moiety did not undergo the Stetter-aldol-Michael or the Stetter-aldol-aldol pathway. Following the initial Stetter reaction of these substrates, the Stetter adduct underwent a second Stetter reaction to produce dibenzo[8]annulene products.

4.2 Studies on Quaternary Center Formation

Quaternary center formation via the intermolecular Stetter reaction has yet to be reported. As this development would greatly increase the synthetic utility of the Stetter reaction, a number of β,β-disubstitued electron poor olefins were screened for reactivity in the Stetter reaction. As the steric bulk of the reactive site was expected to make the conjugate addition acceptors unreactive, acceptors doubly activated in the α position were employed. Unfortunately, β,β-disubstitued Meldrum's acid- , diethyl malonate-, and malononitrile- derived alkylidenes were generally observed to be unstable under standard reaction conditions (Scheme 4.2a).

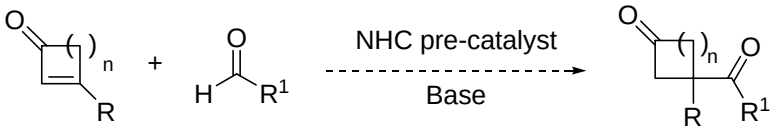


Scheme 4.2 β,β-Disubstitued Acceptors Screened For Reactivity in the Stetter Reaction

As alleviation of steric strain has been previously shown to promote the reaction of cyclopropenes, the Stetter reactions of 3-phenylcyclobutenone and diphenylcyclopropenone were investigated (Scheme 4.2b). To date, all reaction conditions screened have not promoted the Stetter reaction of these substrates.

4.3 Future Directions

To date, the cyclobutenones and cyclopropenones appear to be stable under standard Stetter reaction conditions. However, the acceptors have not been observed to undergo the Stetter reaction prior to the loss of the aldehyde to oxidation reactions. These results warrant further investigations. Employing more reactive acceptors or changing the reaction conditions may serve to promote the Stetter reaction prior to the oxidation of the aldehyde.



Scheme 4.3 Proposed Stetter Reaction of Substituted Cycloenones

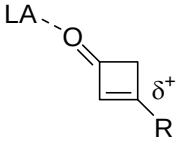


Figure 4-1 Proposed Lewis Acid Activation of Substituted Cyclobutenone

Cycloenones bearing smaller substituents in the β position may prove to be more reactive in the Stetter reaction due to a decrease of steric bulk around the reactive site (Scheme 4.3). Increased concentrations and elevated reaction temperatures may serve to overcome the energy barrier prior to the oxidation of the Breslow intermediate. Co-

operative catalysis, such as Lewis acid (LA) activation of the acceptor may also serve to promote the desired Stetter reaction (Figure 4-1).

PART III – RESULTS, APENDIX, AND DISCUSSION

CHAPTER FIVE

EXPERIMENTAL SECTION

5.1 General Methods

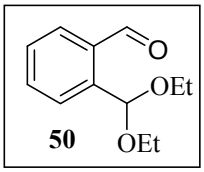
Anhydrous solvents were dried using a Braun Solvent Purification System and stored under nitrogen over 3 Å molecular sieves. The powdered 4 Å molecular sieves used in reaction mixtures were activated by heating at 300 ˚C for 18h under a pressure of 0.25 Torr. Benzaldehyde and 2-furaldehyde were distilled prior to use and stored under an atmosphere of nitrogen at – 4 ˚C. Unless otherwise noted, all other commercial reagents were used without further purification. All reactions were performed under an atmosphere of nitrogen gas, unless otherwise noted. Thin layer chromatography (TLC) was performed using glass plates pre-coated (0.25 cm) with silica gel 60 F_{254}. Detection methods include: UV light (254 nm) visualization and staining with 5% phosphomolybdic acid (PMA) followed by charring on a hot plate. Silica gel SI 60 (40-63 μm) from Silicycle Chemical Division was used for column chromatography.

Nuclear magnetic resonance spectra were recorded on Bruker NMR in $CDCl_3$ solution at 500 MHz for ^{1}H and 125 MHz for ^{13}C. The residual solvent protons (^{1}H, 7.26 ppm) or the solvent carbons (^{13}C, 77.23 ppm) were used as internal standards for chemical shifts. High-resolution mass spectra (HRMS) were obtained on a double focusing high resolution spectrometer. EI ionization was accomplished at 70 eV and CI at 50 eV with ammonia as the reagent gas. FTIR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. All samples submitted for IR analysis were prepared as a film on a

KBr pellet. Melting points were measured on a Gallenkamp melting point apparatus. All melting points are uncorrected.

5.2 Preparation of Chalcone Derivatives

2-(Diethoxymethyl)benzaldehyde (50)

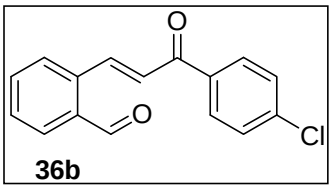


50

A modified literature procedure was employed for the synthesis of the title compound.[60] A 250-mL round bottom flask containing 2-bromobenzaldehyde diethyl acetal (3.1 mL, 15 mmol, 1.0 equiv.) and anhydrous THF (77 mL, 0.2M) was cooled to –78 °C prior to the dropwise addition of *n*-butyllithium (9.7 mL, 23 mmol, 1.5 equiv.). After stirring at –78 °C for 20 minutes, dimethylformamide (2.4 mL, 31 mmol , 2.1 equiv.) was added dropwise. The reaction mixture was slowly warmed up to 0°C and subsequently quenched with saturated ammonium chloride solution (30 mL). The resulting mixture was diluted with ethyl acetate and an aqueous saturated sodium chloride solution (20 mL). The organic layer was isolated and washed with water and an aqueous saturated sodium chloride solution then dried over sodium sulfate and concentrated. The product was obtained without the need for further purification in a 95% yield (3.05g). ^{1}H NMR data agrees with previously reported values.[61] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.49 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.58 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.48 (dd, *J* = 7.4, 7.4 Hz, 1H), 5.96 (s, 1H), 3.73-3.67 (m, 2H), 3.60-3.54 (m, 2H), 1.23 (t, *J* = 7.05 Hz, 6H).

(*E*)-2-(3-(4-Chlorophenyl)-3-oxoprop-1-enyl)benzaldehyde (36b)

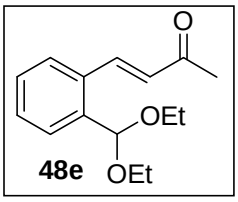
2-(diethoxymethyl)benzaldehyde (**50**) (500 mg, 2.4 mmol, 1 equiv) and (chlorophenacylidene)triphenyl phosphorane (1.49 g, 3.6 mmol, 1.5 equiv) were dissolved in dichloromethane (8 mL, 0.3 M) in a 20 mL vial. The vial was subsequently



36b

crimped and submitted to the microwave reactor at 100 °C for 25 h at normal absorption. The reaction mixture was then concentrated under reduced pressure and purified by FCC using 2.5% ethyl acetate in toluene to afford **48b** in 86% yield (712 mg). In a 50-mL round bottom flask, **48b** (712 mg, 2.1 mmol 1 equiv.) was dissolved in acetone (21 mL, 0.1M) to which $FeCl_3 \bullet 6H_2O$ (111 mg, 0.41 mmol, 0.2 equiv.) and two drops of distilled water were added. After stirring for 15 minutes, the reaction mixture was concentrated and passed through 4 cm of silica using 50% ethyl acetate and hexanes. Following concentration, the crude reaction mixture was purified by FCC employing 20% ethyl acetate in hexanes. The pure product **36b** was obtained in a 92% yield (0.512g).[62] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.56 (d, *J* = 15.8 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 2H), 7.90 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.65 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.60 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 15.7 Hz, 1H).

(*E*)-4-(2-(Diethoxymethyl)phenyl)but-3-en-2-one (36e)

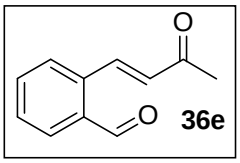


48e

In a 10-mL microwave vial 2-(diethoxymethyl) benzaldehyde (**50**) (299 mg, 1.44 mmol, 1 equiv) was dissolved in dry dichloromethane (3.6 mL, 0.4 M). To the resulting solution 1-(triphenylphosphoranylidene)-2-propanone (0.917 g, 2.88 mmol, 2 equiv), was added. The vial was crimped and subjected to the microwave reactor at 100 °C for 24 h at normal absorption. The reaction was concentrated and flashed through 4 cm of silica using 50% ethyl acetate in hexanes. The resulting mixture was then purified by FCC using 20% ethyl acetate in hexanes to afford a yellow oil in 75% yield (267 mg). **FTIR**

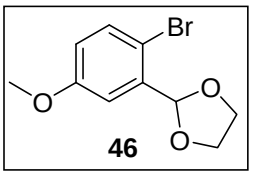
(KBr film) ν_{max} (cm^{-1}): 2976, 1673, 1611, 1359, 1254, 1177, 1059, 758; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 16.3 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 2H), 7.39 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.35 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.58 (d, *J* = 16.3, 1H), 3.64 – 3.60 (m, 2H), 3.56 – 3.50 (m, 2H), 2.40 (s, 3H), 1.22 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.0, 141.8, 138.1, 133.5, 129.9, 129.1, 129.0, 127.7, 127.0, 100.9, 62.0, 27.2, 15.4; **HRMS** (EI^+) *m/z* calculated for $C_{11}H_{11}O_2$: 174.0680 $[M - C_4H_{10}O]^+$; Found: 174.0674.

(*E*)-2-(3-Oxobut-1-enyl)benzaldehyde (36e)



In a 25-mL round-bottom flask (*E*)-4-(2-(diethoxymethyl)phenyl)but-3-en-2-one (**48e**) (0.267g, 1.08 mmol, 1 equiv.) was dissolved in acetone (10mL, 0.1M). $FeCl_3$•SiO_2 (58.1mg, 0.215 mmol $FeCl_3$, 0.20 equiv. of $FeCl_3$) was added to the flask. After 30 minutes the reaction mixture was concentrated and passed through a plug of silica using 50% ethyl acetate in hexanes to yield a pure sample of the desired product as a yellow oil (99% yield, 185 mg). Rf = 0.3 (30% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^1): 1749, 1697, 1609, 1567, 1482, 1360, 1287, 1254, 1206; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.47 (d, *J* = 16.3 Hz, 1H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.66-7.57 (m, 3H), 6.58 (d, *J* = 16.4 Hz, 1H), 2.43 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.9, 192.8, 140.8, 136.6, 134.1, 134.0, 131.9, 130.7, 130.3, 128.1, 27.2; **HRMS** (EI^+) *m/z* calculated for $C_{11}H_{10}O_2$: 175.0752 $[M+1]^+$; Found: 172.0759.

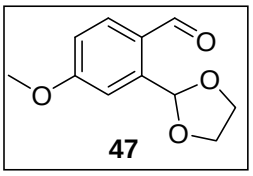
2-(2-Bromo-5-methoxyphenyl)-1,3-dioxolane (**46**)



46

The title compound was prepared by a slightly modified literature procedure.[63] To a solution of 2-bromo-5-methoxybenzaldehyde (**45**)[64] (5.16 g, 24.0 mmol, 1 equiv.) in toluene (147 mL, 0.16M) in a 250-mL round-bottom flask was added ethylene glycol (8.20 mL, 147 mmol, 6.1 equiv.) and *para*-toluenesulfonic acid monohydrate (168 mg, 0.88 mmol, 0.037 equiv.), sequentially. After 24.5h of heating under Dean-Stark conditions, the reaction mixture was cooled to room temperature and washed with water in a separatory funnel. The aqueous layer was separated and washed twice with ethyl acetate (2 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated. The resulting mixture was purified by FCC using in 10% ethyl acetate in hexanes then in 20% ethyl acetate as eluent. The product was obtained as a yellow oil (82% yield, 5.16g). ^{1}H NMR data agreed with literature data.[63] Rf = 0.5 (30% ethyl acetate in hexanes) **^{1}H NMR** (500 MHz, $CDCl_3$) δ7.45 (d, *J* = 8.7 Hz, 1H), 7.15 (d, *J* = 3.0 Hz, 1H), 6.79 (dd, *J* = 8.7, 3.1 Hz, 1H), 6.04 (s, 1H), 4.17-4.06 (m, 4H), 3.80 (s, 3H).

2-(1,3-Dioxolan-2-yl)-4-methoxybenzaldehyde (**47**)

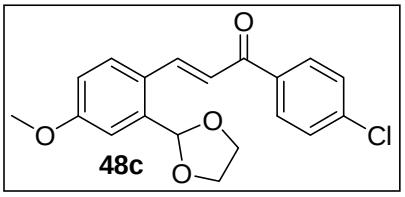


47

A modified literature procedure was used to prepare the title compound.[65] In a 250-mL round-bottom flask 2-(2-bromo-5-methoxyphenyl)-1,3-dioxolane (**46**) (4.93g, 19.2 mmol) was dissolved in dry tetrahydrofuran (105 mL) prior to cooling to –78°C. The addition of *n*-butyllithium (2.22M in hexanes, 14.2 mL, 31.6 mmol) was followed by stirring for 20 minutes. *N,N*-Dimethylformaldehyde (3.26 mL, 42.1 mmol) was carefully added,

dropwise. The mixture was slowly warmed to room temperature before quenching with saturated ammonium chloride. The organic layer was separated, washed once with brine, dried over sodium sulfate, and then concentrated. Purification by flash column chromatography using 40% ethyl acetate in hexanes yielded **47** as an orange oil (95% yield, 3.80g). ^{1}H NMR data agreed with literature data, albeit with improved resolution.[65] Rf = 0.3 (30% ethyl acetate in hexanes) **FTIR** (KBr film) ν_{max} (cm^{-1}): 2890, 1687, 1601, 1285, 1244, 1169, 1120, 1077, 828; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 6.97 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.14 - 4.10 (m, 2H), 4.09 - 4.06 (m, 2H), 3.88 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.4, 164.1, 141.9, 133.4, 127.9, 114.5, 112.4, 100.6, 65.6, 55.8; **HRMS** (EI^+) m/z calculated for $C_{11}H_{12}O_4$: 208.0736 [M^+]; Found: 208.0734.

(*E*)-3-(2-(1,3-Dioxolan-2-yl)-4-methoxyphenyl)-1-(4-chlorophenyl)prop-2-en-1-one (48c)

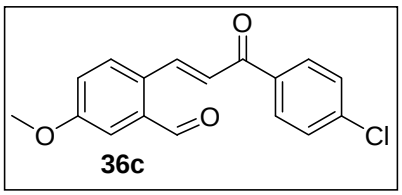


48c

In a 20-mL microwave vial, 2-(1,3-dioxolan-2-yl)-5-methoxybenzaldehyde (**47**) (500 mg, 2.40 mmol, 1 equiv) was dissolved in dry dichloromethane (8.0 mL, 0.3 M). To the resulting solution (4-chlorophenacylidene)triphenyl phosphorane (1.99 g, 4.80 mmol, 2 equiv), was added. The vial was crimped and subjected to the microwave reactor at 100 °C for 22 h at normal absorption. The reaction was concentrated and passed through 4 cm of silica using 50% ethyl acetate in hexanes. The resulting mixture was purified by FCC using 30% ethyl acetate in hexanes to afford an orange solid in 90% yield (742 mg). m.p. = 65-67 °C, Rf = 0.3 (30% ethyl acetate in hexanes). **FTIR** (KBr

film) ν_{max} (cm^{-1}): 2890, 1660, 1593, 1495, 1399, 1298, 1215, 1173, 1091, 1037, 1011, 816; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 15.5 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.7 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 15.5 Hz, 1H), 7.20 (d, *J* = 2.6 Hz, 1H), 6.92 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.05 (s, 1H), 4.17–4.12 (m, 2H), 4.10 – 4.05 (m, 2H), 3.85 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 189.3, 161.6, 142.1, 139.1, 136.9, 130.7, 130.1, 129.0, 128.9, 126.4, 121.5, 115.4, 112.0, 101.5, 65.6, 55.6; **HRMS** (EI^+) *m/z* calculated for $C_{19}H_{17}O_4Cl$: 344.0815 [M^+]; Found: 344.0811.

(*E*)-2-(3-(4-Chlorophenyl)-3-oxoprop-1-enyl)-5-methoxybenzaldehyde (36c)

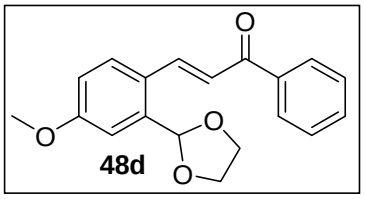


36c

In a 50-mL round-bottom flask (*E*)-3-(2-(1,3-dioxolan-2-yl)-4-methoxyphenyl)-1-(4-chlorophenyl)prop-2-en-1-one (**48c**) (0.638g, 1.85 mmol, 1 equiv.) was dissolved in acetone (12.3mL, 0.15M). $FeCl_3$•SiO_2 (640mg, 0.474 mmol $FeCl_3$, 0.255 equiv of $FeCl_3$) was added to the mixture. After 4 h the reaction had ceased to progress by TLC analysis. The reaction mixture was concentrated and passed through 4 cm of silica using 50% ethyl acetate in hexanes. As the reaction had only reached 71% conversion, the crude was re-subjected to the reaction conditions outlined above for an additional 5 h. The mixture was once again concentrated and passed through a plug of silica. Purification by FCC using 4% ethyl acetate in toluene afforded a pure sample of the desired product as a yellow solid (67% yield, 374 mg). m.p. = 99-101 °C, Rf = 0.4 (10% ethyl acetate in toluene). **FTIR** (KBr film) ν_{max} (cm^{-1}): 1691, 1592, 1496, 1298, 1092, 1011; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.53 (d, *J* = 15.6 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.41 (d,

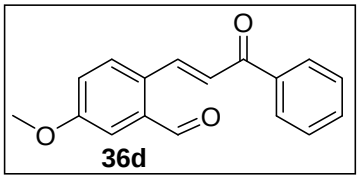
J = 2.7 Hz, 1H), 7.30 (d, *J* = 15.6 Hz, 1H), 7.18 (dd, *J* = 8.6, 2.6 Hz, 1H), 3.92 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 191.2, 189.4, 161.6, 140.9, 139.6, 136.5, 135.9, 130.3, 129.8, 129.8, 129.2, 125.0, 120.9, 115.2, 56.0; **HRMS** (CI^+-NH_3) *m/z* calculated for $C_{17}H_{14}ClO_3$: 301.0631 $[M+H]^+$; Found: 301.0635.

(*E*)-3-(2-(1,3-Dioxolan-2-yl)-4-methoxyphenyl)-1-phenylprop-2-en-1-one (48d)



In a 20-mL microwave vial 2-(1,3-dioxolan-2-yl)-5-methoxybenzaldehyde (**47**) (500 mg, 2.40 mmol, 1 equiv) was dissolved in dry dichloromethane (8.0 mL, 0.3 M). To the resulting solution (phenacylidene)triphenyl phosphorane (1.83 g, 4.80 mmol, 2 equiv), was added. The vial was crimped and subjected to the microwave reactor at 100°C for 31 h at normal absorption. The reaction was concentrated and passed through 4 cm of silica using 50% ethyl acetate in hexanes. The resulting mixture was purified by FCC using 30% ethyl acetate in hexanes to afford **48d** as a light yellow solid in 98% yield (731 mg). m.p. = 75-78 °C, Rf = 0.3 (30% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 2890, 1660, 1590, 1496, 1296, 1217, 1120, 1069, 1017, 781, 695; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 15.5 Hz, 1H), 8.01 (d, *J* = 7.4 Hz, 2H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.48 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.40 (d, *J* = 15.5 Hz, 1H), 7.20 (d, *J* = 2.6 Hz, 1H), 6.93 (dd, *J* = 8.6, 2.5 Hz, 1H), 4.17 – 4.04 (m, 4H), 3.85 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.7, 161.4, 141.6, 138.8, 138.6, 132.7, 128.8, 128.7, 128.6, 122.1, 115.4, 112.0, 101.6, 65.6, 55.6; **HRMS** (EI^+) *m/z* calculated for $C_{19}H_{18}O_4$: 310.1205 $[M^+]$; Found: 310.1197.

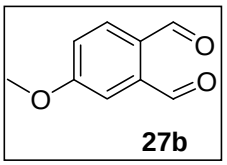
(*E*)-5-Methoxy-2-(3-oxo-3-phenylprop-1-enyl)benzaldehyde (36d)



36d

In a 50-mL round-bottom flask (*E*)-3-(2-(1,3-dioxolan-2-yl)-4-methoxyphenyl)-1-phenylprop-2-en-1-one (**48d**) (0.731g, 2.36 mmol, 1 equiv.) was dissolved in acetone (24mL, 0.1M). $FeCl_3 \bullet 6H_2O$ (128 mg, 0.472 mmol, 0.2 equiv.) was added to the mixture, followed by 2 drops of distilled water. After 3.5 h the reaction had long ceased to progress by TLC analysis. The reaction mixture was concentrated and flashed through 4 cm of silica using 50% ethyl acetate in hexanes. Having only reached 85% conversion, the crude was resubjected to the reaction conditions outlined above for an additional 2 h. The mixture was once again concentrated and the new catalyst was removed over a plug of silica. Purification by FCC using 20% ethyl acetate in hexanes afforded a pure sample of the desired product as a yellow solid (65% yield, 409mg). An additional sample of the product was isolated contaminated with 10% starting material (132mg). m.p. = 69-72 °C, Rf = 0.2 (20% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 1690, 1598, 1496, 1294, 1217, 1016, 693; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.52 (d, *J* = 15.6 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 1d), 7.59 (t, *J* = 7.1 Hz, 1H), 7.51 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.36 (d, *J* = 15.6 Hz, 1H), 7.18 (dd, *J* = 8.6, 2.6 Hz, 1H), 3.19 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 191.1, 190.5, 161.4, 140.2, 138.1, 135.8, 133.1, 130.2, 129.7, 128.9, 128.8, 125.6, 121.0, 114.6, 55.9; **HRMS** (CI^+-NH_3) *m/z* calculated for $C_{17}H_{15}O_3$: 267.1021 $[M+1]^+$; Found: 267.1025.

4-Methoxyphthalaldehyde (27b)

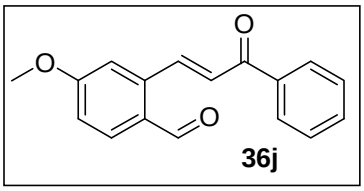


27b

In a 50-mL round-bottom flask 2-(1,3-dioxolan-2-yl)-4-methoxybenzaldehyde (**47**) (0.500 g, 2.40 mmol, 1 equiv.) was dissolved in acetone (24 mL, 0.1M). $FeCl_3$•$6H_2O$ (195 mg, 0.720 mmol, 0.300 equiv.) was added to the mixture. After 40 minutes the reaction had ceased to progress by TLC. An additional $FeCl_3$•$6H_2O$ (0.05 equiv.) was added. As no change was visible after 1 h the reaction mixture was concentrated and flashed through 4 cm of silica using 50% ethyl acetate in hexanes. The reaction had only reached 85% conversion, and thus the crude was re-subjected to the reaction conditions outlined (0.1 M in acetone, 0.1 equiv. $FeCl_3$) for an additional 2.5 h. The mixture was once again concentrated and passed through a plug of silica. Purification by FCC using 20% ethyl acetate in hexanes afforded a pure sample of the desired product as a yellow solid (80% yield, 315 mg). m.p. = 75-78 °C, Rf = 0.2 (20% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 1765, 1694, 1595, 1568, 1501, 1430, 1323, 1286, 1255, 1208, 1164, 1095, 1028, 938, 832; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.65 (s, 1H), 10.32 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 1 H), 7.44 (d, *J* = 2.2 Hz, d), 7.21 (dd, *J* = 8.5, 2.1 Hz, 1H), 3.94 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.2, 191.2, 164.1, 138.9, 134.8, 129.7, 119.0, 115.0, 56.2; **HRMS** (EI^+) *m/z* calculated for $C_9H_8O_3$: 164.0473 [M^+]; Found: 164.0476.

(*E*)-2-(3-Phenyl-3-oxoprop-1-enyl)-4-methoxybenzaldehyde (36j)

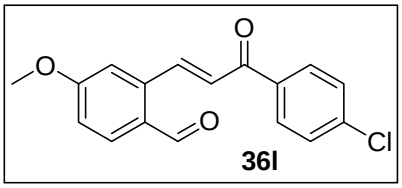
In a 10-mL round-bottom flask 4-methoxyphthalaldehyde (**27b**) (200 mg, 1.22 mmol, 1 equiv.) was dissolved in dry dichloromethane (3.6 mL). An additional 1.1 mL of dichloromethane (total 0.3M) was added following the addition of phenacylidene



36j

triphenylphosphorane (460 mg, 1.22, 1 equiv.). After 47h the reaction mixture was concentrated then passed through 4 cm of silica using 50% ethyl acetate in hexanes. Following concentration, the mixture was separated by FCC using 5% ethyl acetate in toluene as eluent. The pure desired isomer was isolated as a yellow solid in a 69% yield (223 mg). **FTIR** (KBr film) ν_{max} (cm^{-1}) 1687, 1607, 1562, 1447, 1287, 1117, 1016, 694; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.53 (d, *J* = 15.7 Hz, 1H), 8.02 (d, *J* = 7.5 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.51 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.31 (d, *J* = 15.7, 1H), 7.17 (d, *J* = 2.0 Hz, 1H), 7.05 (dd, *J* = 8.6, 2.2 Hz, 1H), 3.93 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.0, 190.4, 164.0, 141.7, 139.8, 137.8, 135.1, 133.2, 129.0, 128.8, 128.1, 127.7, 115.1, 113.6, 55.9; **HRMS** (EI^+) m/z calculated for $C_{17}H_{14}O_3$: 266.0943 [M^+]; Found: 266.0945.

(*E*)-2-(3-(4-Chlorophenyl)-3-oxoprop-1-enyl)-4-methoxybenzaldehyde (36l)



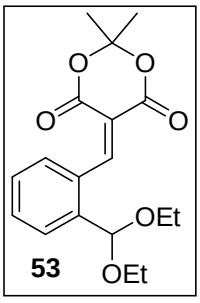
36l

In a 10-mL round-bottom flask 4-methoxyphthalaldehyde (**27a**) (93 mg, 0.57 mmol, 1 equiv.) was dissolved in dry dichloromethane (1.4 mL). An additional 0.5 mL of dichloromethane (total 0.3M) was added following the addition of (4-chlorophenacylidene)triphenylphosphorane (235 mg, 0.57, 1 equiv.). After 24 h an additional 0.20 equiv. of (4-chlorophenacylidene)triphenyl phosphorane was added (47 mg, 0.11 mmol). After five days the reaction mixture was concentrated and passed through a plug of silica using 50% ethyl acetate in hexanes. FCC with 5% ethyl acetate of toluene served to isolate a pure sample of the two isomers (134 mg). The sample was

then flashed twice with 20% ethyl acetate in hexanes to afford a pure sample of the desired *E* isomer as a white solid (60 mg, 35% yield). m.p.: 150-152 °C, Rf = 0.2 (20% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 1666, 1597, 1306, 1245, 1093; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.69 (d, *J* = 15.7 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 15.7 Hz, 1H), 7.17 (s, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 3.93 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.6, 189.9, 164.0, 142.5, 139.6, 139.4, 136.13, 135.6, 130.4, 129.2, 128.1, 127.2, 115.1, 113.8, 56.0; **HRMS** (EI^+) *m/z* calculated for $C_{17}H_{13}O_3Cl$: 300.0553 [M^+]; Found: 300.0553.

5.3 Preparation of Substrates With Other Electron Withdrawing Groups

5-(2-(Diethoxymethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (53)

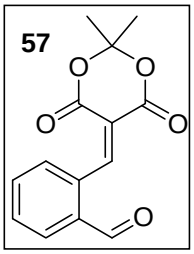


53

The aforementioned compound was prepared according to a literature procedure for the preparation of Meldrum's acid alkylidenes.[66] In a 25-mL round bottom flask, 2-(diethoxymethyl)benzaldehyde (**50**) (0.21 g, 1.0 mmol. 1.0 equiv.) and 2,2-dimethyl-1,3-dioxane-4,6-dione (0.14 g, 1.0 mmol, 1.0 equiv.) were dissolved in benzene (5 mL, 0.2M). A 0.20 ml aliquot of a 0.5 M solution of pyrrolidinium acetate (0.10 mmol, 0.10 equiv.) in benzene was added. After heating at 50 ˚C for 14.5h, the reaction mixture was cooled to room temperature. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate (5 mL). The layers were separated and the aqueous layer was back extracted with ethyl acetate (6 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification by FCC using 15% ethyl acetate as eluent afforded 0.11g of the product as an orange oil (34% yield). **FTIR** (KBr

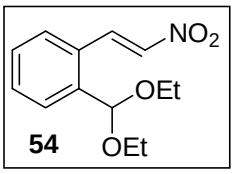
film) ν_{max} (cm^{-1}) 2978, 1736, 1615, 1480, 1393, 1381, 1353, 1280, 1202, 1107, 1058, 1026, 934; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.53, (d, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.36 (dd, *J* = 7.6, 7.6 Hz, 1H), 5.53 (s, 1H), 3.63-3.57 (m, 2H), 3.54-3.48 (m, 2H), 1.81 (s, 6H), 1.19 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 162.7, 159.5, 138.7, 131.5, 131.0, 130.0, 128.2, 127.4, 116.1, 104.9, 101.1, 61.9, 27.9, 15.3; **HRMS** (EI^+) *m/z* calculated for $C_{18}H_{22}O_6$: 334.1416 [M^+]; Found: 334.1417.

2-((2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)benzaldehyde (57)



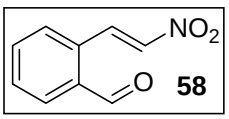
In a 25-mL round-bottom flask 5-(2-(diethoxymethyl)benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**53**) (0.17 g, 0.52 mmol, 1.0 equiv.) was dissolved in acetone (3.5 mL, 0.15M). 10% $FeCl_3$•SiO_2 (0.17 g, 0.077 mmol $FeCl_3$, 0.15 equiv of $FeCl_3$) was added to the mixture. After 1 hour the reaction mixture was concentrated and passed through 4 cm of silica using 50% ethyl acetate in hexanes. Following concentration, the solid was recrystallized using ethyl acetate and hexanes. Filtration afforded the product in a 45% yield (61 mg). **FTIR** (KBr film) ν_{max} (cm^{-1}) 3000, 1735, 1695, 1622, 1568, 1482, 1394, 1352, 1280, 1195, 1122, 1030, 1001, 934; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.85 (s, 1H), 7.91-7.89 (m, 1H), 7.69-7.65 (m, 2H), 7.52-7.51 (m, 1H), 1.80 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.3, 162.2, 159.4, 159.2, 134.2, 134.0, 133.9, 133.6, 130.8, 130.1, 118.0, 105.3, 27.9.

(*E*)-1-(Diethoxymethyl)-2-(2-nitrovinyl)benzene (54)



The title compound was prepared by a modified literature procedure.[67] Ammonium acetate (77 mg, 1,0 mmol, 1 equiv.) was added to a 25-mL round bottom flask containing 2-(diethoxymethyl)benzaldehyde (**50**) (0.21 g, 1.0 mmol, 1.0 equiv.) in nitromethane (4 ml, 0.25M). The reaction mixture was stirred for 105 min prior to concentration under reduced pressure. The product was purified twice by FCC using 10% ethyl acetate as eluent. The yellow solid was obtained in a 67% yield (0.17 g). **FTIR** (KBr film) ν_{max} (cm^{-1}) 2977, 2881, 1634, 1521, 1342, 1213, 1342, 1213, 1109, 1059, 967, 766; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.62 (d, *J* = 13.6 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 13.5 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 1H), 7.39 (dd, *J* = 7.5 Hz, 1H). 5.60 (s, 1H), 3.68-3.62 (m, 2H), 3.58-3.52 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 139.5, 137.9, 137.5, 131.4, 129.2, 129.0, 128.2, 128.0, 100.9, 62.3, 15.3.

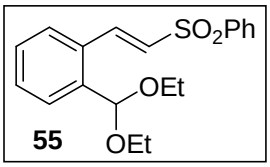
(*E*)-2-(2-Nitrovinyl)-benzaldehyde (58)



In a 25-mL round-bottom flask name (**54**) (0.17 g, 0.66 mmol, 1.0 equiv.) was dissolved in acetone (4.4 mL, 0.15M). 10% $FeCl_3$•SiO_2 (0.17 g, 0.074 mmol $FeCl_3$, 0.11 equiv of $FeCl_3$) was added to the mixture. After 90 min the reaction had ceased to progress by TLC. The reaction mixture was concentrated and passed through 4 cm of silica using 50% ethyl acetate and hexanes. Purification by FCC using 20% ethyl acetate in hexanes afforded the pure product in 57% yield (67 mg). **FTIR** (KBr film) ν_{max} (cm^{-1}) 1690, 1556, 1518, 1344, 1201, 970; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.95 (d, *J* = 13.6 Hz, 1H), 7.94 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.74-

7.67 (m, 2H), 7.62 (d, *J* = 7.1 Hz, 1H), 7.48 (d, *J* = 13.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.3, 139.9, 136.9, 135.0, 134.6, 134.3, 131.8, 131.2, 128.8.

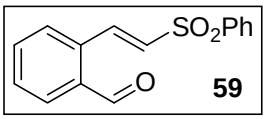
(*E*)-1-(Diethoxymethyl)-2-(2-(phenylsulfonyl)vinyl)benzene (55)



55

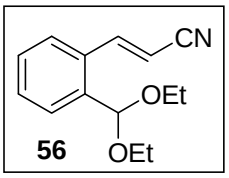
Lithium chloride (76 mg, 1.8 mmol, 1.5 equiv.) was suspended in acetonitrile (7 mL) in a 25-mL round bottom flask. Diethyl phenylsulfonylmethylphosphonate (0.63 g, 2.2 mmol, 1.8 equiv.) was added as a solution in acetonitrile (3 mL). DBU (0.22 mL, 1.4 mmol, 1.2 equiv.) and a solution of 2-(diethoxymethyl)benzaldehyde (**50**) (0.25 g, 1.2 mmol, 1 equiv.) in acetonitrile (3 mL, total 0.1 M) were added sequentially. After 3.5h of stirring at ambient temperature, the reaction was quenched with an aqueous solution of saturated ammonium chloride (10 mL). The organic layer was concentrated under reduced pressure. The resulting solution was then extracted with dichloromethane (5 x 6 mL). The combined organic layers were dried over sodium sulfate. Following concentration, FCC purification using 30% ethyl acetate in hexanes as the eluent afforded the product in an 85% yield (0.35g). **FTIR** (KBr film) ν_{max} (cm^{-1}) 2976, 1447, 1307, 1147, 1086, 1059, 855, 813, 754, 688, 620. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 15.3 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.61-7.58 (m, 2H), 7.53 (dd, *J* = 7.9, 7.9 Hz, 2H), 2H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.39 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.29 (t, *J* = 7.5 ,7.5 Hz, 1H), 6.78 (d, *J* = 15.3 Hz, 1H), 5.60 (s, 1H), 3.63-3.59 (m, 2H), 3.55-3.50 (m, 2H), 1.20 (t, *J* = 7.0, 7.0 Hz, 6H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ 140.9, 138.5, 133.4, 131.4, 130.5, 129.4, 128.9, 128.8, 127.8, 127.5, 100.6, 62.2, 15.3.

2-[(1*E*)-2-(Phenylsulfonyl)ethenyl]-benzaldehyde (59)



In a 25-mL round-bottom flask (*E*)-1-(diethoxymethyl)-2-(2-(phenylsulfonyl)vinyl)benzene (**55**) (0.35 g, 1.0 mmol, 1 equiv.) was dissolved in acetone (6.7 mL, 0.15M). 10% $FeCl_3$•SiO_2 (0.31 g, 0.14 mmol $FeCl_3$, 0.14 equiv of $FeCl_3$) was added to the mixture. After 135 min the reaction had long ceased to progress by TLC analysis. An additional 55 mg of 10% $FeCl_3$•SiO_2 (0.025 mmol $FeCl_3$, 0.025 equiv of $FeCl_3$) was added. After an additional 105 min, the reaction mixture was concentrated and flashed through 4 cm of silica using 50% ethyl acetate in hexanes. Purification by FCC employing 30% ethyl acetate in hexanes as the eluent afforded the off white product **59** in a 71% yield (0.20 g). **FTIR** (KBr film) ν_{max} (cm^{-1}) 1696, 1615, 1594, 1569, 1481, 1447, 1308, 1199, 1147, 1085, 872, 852, 779, 752, 723, 688, 651, 618, 569, 547; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.54 (d, *J* = 15.4 Hz, 1H), 8.01-7.99 (m, 2H), 7.84-7.84 (m, 1H), 7.63-7.53 (m, 6H), 6.81 (d, *J* = 15.4 Hz, 1H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.1, 192.1, 140.4, 140.4, 134.1, 133.9, 133.7, 131.8, 131.7, 130.9, 129.5, 128.5, 128.1.

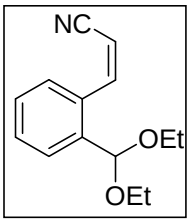
(*E*)-3-((2-Diethoxymethyl)phenyl)acrylonitrile (56)



To a vial containing 2-(diethoxymethyl)benzaldehyde (0.25 g, 1.2 mmol, 1.0 equiv.) in dichloromethane (4 mL, 0.3M) was added 2-(triphenylphosphoranylidene)-acetonitrile (0.54 g, 1.8 mmol, 1.5 equiv.). After 26h the reaction mixture was concentrated. An initial separation by FCC using 10% ethyl acetate afforded a moderately pure sample of each isomer. Each sample was subsequently purified using FCC and 10% ethyl acetate as eluent to afford the *E*

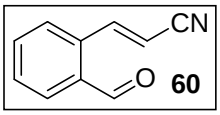
isomer in a 22% yield and *Z* in a 35% yield. **FTIR** (KBr film) ν_{max} (cm^{-1}) 2979, 2218, 1618, 1445, 1109, 1058, 758; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 16.6 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.41 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H), 7.36 (ddd, *J* = 7.5, 7.5, 0.9 Hz, 1H), 5.79 (d, *J* = 16.6 Hz, 1H), 5.52 (s, 1H), 3.63-3.58 (m, 2H), 3.53-3.47 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 149.1, 137.8, 132.5, 130.5, 129.1, 128.0, 126.4, 118.5, 100.9, 97.6, 62.0, 15.3.

(*Z*)-3-((2-Diethoxymethyl)phenyl)acrylonitrile



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93-7.82 (m, 1H), 7.80 (d, *J* = 12.0 Hz, 1H), 7.59-7.56 (m, 1H), 7.42-7.40 (m, 1H), 5.50 (d, *J* = 12.0 Hz, 1H), 5.49 (s, 1H), 5.59-3.51 (m, 2H), 3.51 (m, 2H), 1.20 (t, *J* = 7.7 Hz, 6H).

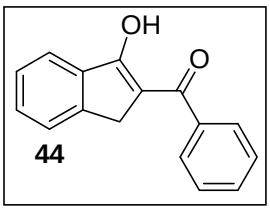
(*E*)-3-(2-Formylphenyl)acrylonitrile (60)



In a vial fitted with septum **(*E*)**-3-((2-diethoxymethyl) phenyl)acrylonitrile (**56**) (59 mg, 0.26 mmol, 1 equiv.) was dissolved in acetone (1.7 mL, 0.15M). 10% $FeCl_3$•SiO_2 (60 mg, 0.027 mmol $FeCl_3$, 0.1 equiv of $FeCl_3$) was added to the mixture. After 135 min the reaction was concentrated under reduced pressure and passed through 4 cm of silica using 50% ethyl acetate in hexanes. The solution was concentrated and the resulting white solid was further purified by FCC using 20% ethyl acetate in hexanes as eluent. The product was obtained in a 92% yield (37 mg). ^{1}H NMR data agrees with previously reported values.[68] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.42 (d, *J* = 16.6 Hz, 1H), 7.87-7.86 (m, 1H), 7.66-7.65 (m, 2H), 7.59-7.57 (m, 1H), 5.86 (d, *J* = 16.6 Hz, 1H).

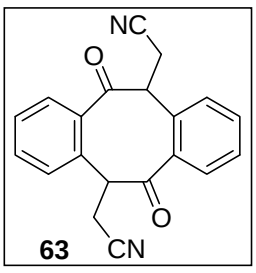
5.4 Products of Competing Reactions

(3-Hydroxy-1H-inden-2-yl)phenyl-methanone (44)



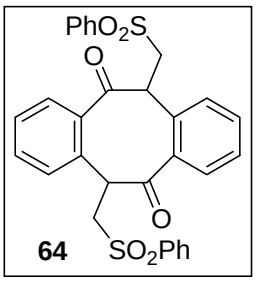
A 5-mL Schlenk tube containing (*E*)-2-(3-phenyl-3-oxoprop-1-enyl)benzaldehyde (**36a**) (50 mg, 0.21 mmol, 1.0 equiv.) was charged with dry dichloromethane (0.5 M). The dropwise addition of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) (32 µL, 0.21 mmol, 1.0 equiv.) resulted in the yellow solution turning dark brown in colour. After stirring the mixture at ambient temperature for 160 minutes, the reaction was quenched with a saturated solution of ammonium chloride (aq) (2 mL) and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were dried over sodium sulfate anhydrous and the solvent was removed under reduced pressure. **FTIR** (KBr film) ν_{max} (cm^{-1}) 1610, 1570, 1494, 1468, 1448, 1381, 1324, 1303, 1287, 1270, 1207, 1187, 1165, 1151, 1094, 917, 847, 741, 692, 551; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 15.01 (s, 1H), 7.96-7.95 (m, 2H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.59 (dd, *J* = 6.8, 6.8 Hz, 1H), 7.55-7.51 (m, 4H), 7.45 (dd, *J* = 7.2, 7.2 Hz, 1H), 3.95 (s, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 196.1, 171.0, 148.8, 138.1, 135.0, 133.6, 131.5, 128.8, 128.4, 127.7, 125.8, 123.7, 109.7, 32.5.

2,2'-(3,4,7,8-Tetrahydrodibenzo[8]annulene)diacetonitrile (63)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.6 Hz, 2H), 7.78 (dd, *J* = 7.7, 7.4 Hz, 2H), 7.68-7.64 (m, 4H), 5.67 (dd, *J* = 6.4, 5.7 Hz, 2H), 3.11 (dd, *J* = 16.8, 5.2 Hz, 2H), 2.95 (dd, *J* = 16.8, 7.0 Hz, 2H). **HRMS** (EI^+) *m/z* calculated for $C_{20}H_{14}N_2O_3$: 314.1055 [M^{+1}]; found: 314.104.

2,2'-Bis(phenylsulfonylmethyl)(3,4,7,8-tetrahydrodibenzo[8]annulene) (64)



64

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.6, 7.0, 4H), 7.77-7.73 (m, 2H), 7.64 (dd, *J* = 7.4, 7.2 Hz, 4H), 7.23-7.23 (m, 6H), 7.02-7.01 (m, 2H), 6.14-6.12 (m, 2H), 3.65-3.54 (m, 4H).

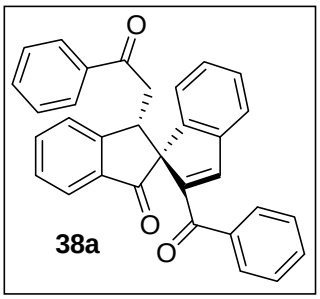
5.5 Synthesis of spiro bis-indanes via a Stetter-Aldol-Michael (SAM) sequence

General procedure for the preparation of spiro bis-indanes (38)

An oven-dried 5-mL Schlenk tube fitted with a septum containing *o*-formyl chalcone (**36a-e**) (1 equiv.) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazol-3-ium bromide (**25**) (0.1 equiv.) was purged under high vacuum for 15 minutes. The vessel was subsequently subjected to three vacuum-nitrogen gas cycles and left under an atmosphere of nitrogen gas. The addition of dry dichloromethane (0.5 M) was followed by the dropwise addition of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) (0.3 equiv.). After stirring the mixture at ambient temperature for 5-195 min (see Table 2-4 for reaction time), the reaction was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over sodium sulfate anhydrous and the solvent was removed under reduced pressure. The crude product was purified by FCC.

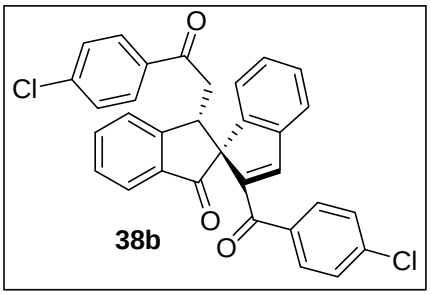
Rel-(1S,1'R)-2'-benzoyl-1-(2-phenyl-2-oxoethyl)-1,2'-spirobi[inden]-3(1H)-one (38a)

The aforementioned compound was characterized by Crystal Daschner.[69] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 – 7.89 (m, 3H), 7.73 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.63 – 7.49 (m,



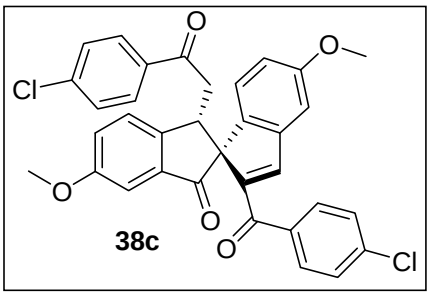
9H), 7.45 (dd, *J* = 7.4, 7.4, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.30 (dd, *J* = 7.8, 7.4 Hz, 2H), 7.20 (dd, J = 7.4, 7.4 Hz, 1H), 7.14 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.82 (d, *J* = 7.4 Hz, 1H), 4.93 (dd, *J* = 8.6, 5.7 Hz, 1H), 3.40 (dd, *J* = 17.0, 9.3 Hz, 1H), 3.34 (dd, *J* = 17.1, 5.4 Hz, 1H).

Rel-(1S,1'R)-2'-(4-chlorobenzoyl)-1-(2-(4-chlorophenyl)-2-oxoethyl)-1,2'-spirobi[inden]-3(1H)-one (38b)



0.185 mmol scale, dr 12:1, white solid, 86% yield, m.p.= 191-193°C. Rf = 0.4 (5% ethyl acetate in toluene). (major diastereomer) **FTIR** (KBr film) ν_{max} (cm^{-1}): 1717, 1684, 1630, 1589, 1461, 1400, 1347, 1265, 1209, 1091, 1014, 812, 761; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.6 Hz, 2H), 7.89 (d, *J* = 8.4 Hz, d), 7.74 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.54 – 7.43 (m, 6H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.20 dd, *J* = 7.4, 7.4 Hz, 1H), 7.14 (dd, *J* = 7.4, 7.4, 1H), 6.81 (d, *J* = 7.5, 1H), 4.88 (dd, *J* = 10.2, 4.5 Hz, 1H), 3.43 (dd, *J* = 17.1, 10.2 Hz, 1H), 3.31 (dd, *J* = 17.1, 4.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.5, 196.3, 190.4, 155.0, 148.8, 145.3, 144.4, 143.6, 139.7, 138.7, 135.5, 135.1, 130.9, 129.2, 128.9, 128.6, 128.4, 128.3, 125.7, 125.5, 124.8, 123.4, 72.3, 40.6, 38.9; **HRMS** (EI^+) *m/z* calculated for $C_{32}H_{20}Cl_2O_3$: 522.0790 [M^{+1}]; found: 522.0792.

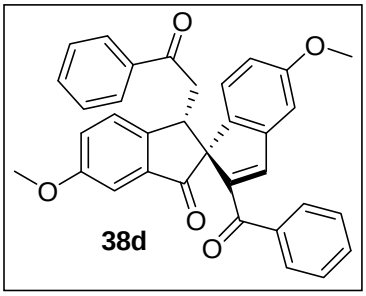
Rel-(1S,1'R)-2'-(4-chlorobenzoyl)-1-(2-(4-chlorophenyl)-2-oxoethyl)-5,5'-dimethoxy-1,2'-spirobi[inden]-3(1H)-one (38c)



38c

0.166 mmol scale, dr 10:1, yellow solid, 81% yield, m.p.= 154-156 °C. Rf = 0.2 (5% ethyl acetate in toluene). (major diastereomer) **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 2940, 1714, 1685, 1628, 1588, 1492, 1430, 1400, 1348, 1280, 1237, 1175, 1091, 1029, 982, 911, 804, 733; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 2H) 7.50 – 7.47 (m, 5H), 7.35 (s, 2H), 7.31- 7.26 (m, 3H), 6.83 (d, *J* = 1.7 Hz, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 6.67 (dd, *J* = 8.3, 2.0 Hz, 1H), 4.73 (dd, *J* = 10.3, 4.5 Hz, 1H), 3.89 (s, 3H), 3.70 (s, 3H), 3.39 (dd, *J* = 16.8, 10.4 Hz, 1H), 3.24 (dd, *J* = 16.8, 4.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.7, 196.4, 190.2, 160.3, 160.1, 149.8, 147.6, 144.9, 144.2, 139.5, 138.6, 138.5, 137.7, 135.1, 130.9, 129.2, 128.9, 128.8, 125.6, 124.6, 124.0, 115.1, 110.0, 106.9, 71.9, 56.0, 55.6, 40.1, 39.0; **HRMS** (EI^+) *m/z* calculated for $C_{34}H_{24}Cl_2O_5$: 582.1001 [M^+]; found: 582.0985.

Rel-(1S,1'R)-2'-benzoyl-5,5'-dimethoxy-1-(2-oxo-2-phenylethyl)-1,2'-spirobi[inden]-3(1H)-one (38d)

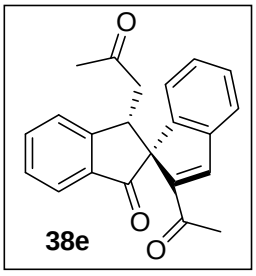


38d

0.188 mmol scale, dr >20:1, white solid, 85% yield, m.p.= 89-91 °C. Rf = 0.3 (10% ethyl acetate in toluene). (major diastereomer) **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 1715, 1628, 1492, 1347, 1280, 1237, 1027, 810, 728; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.1 Hz, 2H), 7.59 – 7.57 (m,

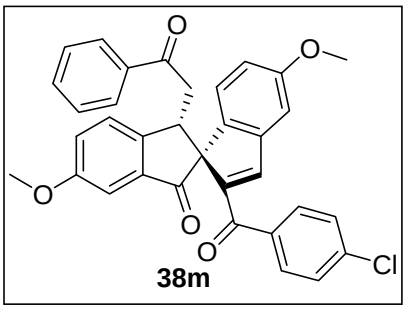
3H), 7.52 – 7.49 (m, 3H), 7.45 (t, *J* = 7.4, 7.4 Hz, 1H), 7.42 (s, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.34 – 7.29 (m, 3H), 6.86 (d, *J* = 2.2 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 6.67 (dd, *J* = 8.4, 2.3 Hz, 1H), 4.78 (dd, *J* = 9.4, 5.3 Hz, 1H), 3.89 (s, 3H), 3.70 (s, 3H), 3.37 (dd, *J* = 16.9, 9.6 Hz, 1H), 3.27 (dd, *J* = 16.9, 5.2 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 201.0, 197.7, 191.5, 160.2, 160.0, 149.9, 148.0, 145.1, 144.4, 138.9, 138.6, 137.9, 136.9, 133.0, 132.2, 129.5, 128.5, 128.5, 127.9, 125.8, 124.5, 124.0, 114.9, 110.0, 106.9, 72.0, 55.9, 55.7, 40.1, 39.3; **HRMS** (EI^+) *m/z* calculated for $C_{34}H_{26}O_5$: 514.1780 [M^+]; found: 514.1781.

Rel-(1'R,3S)-2'-acetyl-3-(2-oxopropyl)-1,2'-spirobi[inden]-1(3H)-one (38e)



0.287 mmol scale, dr 7:1, white solid, 75% yield, m.p.= 207-209 °C. Rf = 0.15 (40% ethyl acetate in hexanes). (major diastereomer) **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 1709, 1650, 1461, 1368, 1075; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.6 Hz, 1H), 7.69 (s, 1H), 7.69 (t, *J* = 7.5, 7.5 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.47 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.33 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.18 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1d), 4.71 (dd, *J* = 8.8, 6.0 Hz, 1H), 2.84 (dd, *J* = 17.5, 5.7 Hz, 1H), 2.54 (dd, *J* = 17.4, 9.2 Hz, 1H), 2.53 (s, 3H), 1.68 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 205.8, 194.4, 155.4, 149.5, 145.9, 143.3, 142.7, 137.1, 135.4, 128.6, 128.3, 128.1, 125.4, 125.2, 125.0, 123.5, 121.5, 71.4, 43.9, 40.3, 30.1, 26.8; **HRMS** (EI^+) *m/z* calculated for $C_{22}H_{18}O_3$: 330.1256 [M^+]; found: 330.1254.

Rel-(1S,1'R)-2'-(4-chlorobenzoyl)-5,6'-dimethoxy-1-(2-oxo-2-phenylethyl)-1,2'-spirobis[inden]-3(1H)-one (38m)



0.094 mmol scale ca. dr >10:1, white solid, 42% yield, m.p.= 232-235 °C. Rf = 0.35 (10% ethyl acetate in toluene). (major diastereomer) **FTIR** (KBr pellet) ν_{max} (cm^{-1}): 1714, 1683, 1598, 1551, 1492, 1430, 1348, 1284, 1232, 1140, 1088, 1027, 910, 807, 732, 689; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.51 – 7.40 (m, 4H), 7.36 (s, 1H), 7.33 (s, 1H), 7.31 – 7.27 (m, 4H), 6.71 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.37 (s, 1H), 4.79 (dd, *J* = 9.4, 5.1 Hz, 1H), 3.89 (s, 3H), 3.68 (s, 3H), 3.40 (dd, *J* = 16.9, 9.6 Hz, 1H), 3.30 (dd, *J* = 16.9, 5.1 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.7, 197.5, 189.9, 160.5, 160.0, 148.0, 147.8, 146.9, 144.8, 138.4, 138.3, 137.4, 136.8, 136.4, 133.2, 130.9, 128.8, 128.6, 127.9, 126.4, 125.8, 124.6, 113.4, 110.6, 107.0, 72.7, 55.9, 55.8, 40.0, 39.0; **HRMS** (EI^+) *m/z* calculated for $C_{34}H_{25}ClO_5$: 548.1391 [M^+]; found: 548.1390.

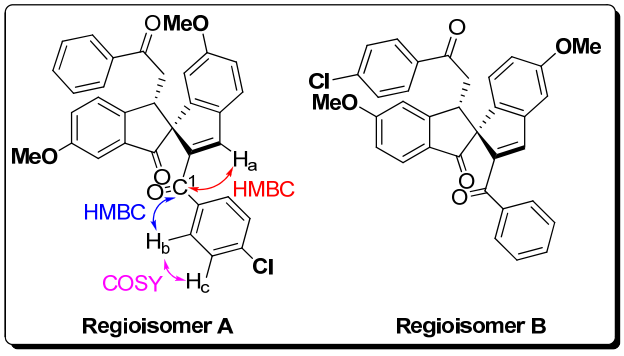
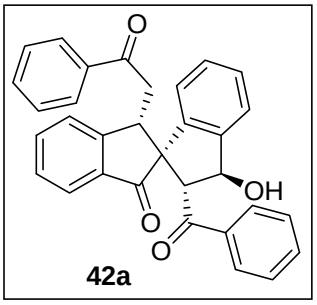


Figure 5-1 Regioisomers Formed in the Cross-Stetter-Aldol-Aldol Reaction

The identity of the products was determined as follows: H_a having been identified in the ^{1}H NMR (7.36 ppm, s, ^{1}H) was observed to correlate to a carbonyl carbon (189.9

ppm), C^1, and thus the carbonyl of the enone was identified. C^1 was also observed to possess a HMBC correlation with an aromatic doublet of integration two (H_b, 7.86 ppm, d, J = 8.3 Hz, 2H). Thus, it follows that if the major product was regioisomer A the observed signal for H_b would possess a COSY correlation with another aromatic doublet of integration two. However, if the isolated product was regioisomer B, H_b would possess a COSY correlation with an aromatic doublet of doublets of integration two, which would further correlate to a aromatic triplet of integration one. As H_b was observed to correlate to an aromatic doublet of integration two (H_c, 7.47 ppm, d, J = 8.4 Hz, 2H) it was determined that regioisomer A was the product isolated.

Rel-(1'S,2'R,3S,3'S)-2'-benzoyl-3'-hydroxy-3-(2-oxo-2-phenylethyl)-2',3'-dihydro-1,2'-spirobi[inden]-1(3H)-one (42a)



42a

The aforementioned compound was prepared and characterized by the author prior to commencing graduate studies.[70] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.85 (d, J = 7.7 Hz, 2H), 7.78 (d, J = 7.4 Hz, 2H), 7.68 (dd, J = 7.7, 7.7 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.56 (dd, J = 7.4, 7.4 Hz, 1H), 7.52 – 7.48 (m, 3H), 7.43 – 7.32 (m, 5H), 7.22 (t, J = 7.5 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 6.62 (d, J = 7.7 Hz, 1H), 5.85 (dd, J = 6.7, 6.7, 1H), 4.60-4.57 (m, 2H), 3.55 (d, J = 6.4 Hz, 2H), 3.31-3.29 (m, 1H).

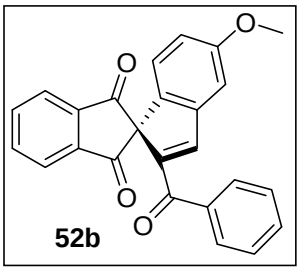
5.6 Synthesis of spiro bis-indanes via a Stetter-Aldol-Aldol (SAA) Oxidation sequence

General procedure for the preparation of spiro bis-indanes (52)

An oven-dried 5-mL Schlenk tube fitted with a septum containing phthaldialdehyde **27** (1 equiv.), *o*-formyl chalcone derivative **36** (2 equiv.) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazol-3-ium bromide (**25**) (0.3 equiv.) was purged under high vacuum for 15 minutes. The vessel was subsequently subjected to three vacuum-nitrogen gas cycles and left under an atmosphere of nitrogen gas. The addition of dry dichloromethane (0.5 M) was followed by the dropwise addition of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) (1 equiv.). After stirring the mixture at ambient temperature for 15-100 min (see Table 2-7 for reaction times) the reaction was quenched with a saturated solution of ammonium chloride (aq) (4 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over sodium sulfate anhydrous and the solvent was removed under reduced pressure. The crude reaction mixture was subsequently dissolved in acetonitrile (0.1M) in a 25-mL round bottom flask. 2-Iodoxybenzoic acid (IBX) (2 equiv) was added and the mixture was heated to 80°C for 2 hours. After cooling to ambient temperature the crude mixture was diluted with ethyl acetate and filtered through a fritted funnel and the filter-cake was washed with a mixture of 20% methanol in dichloromethane (5x). The solvent was evaporated under reduced pressure. The product was purified by FCC.

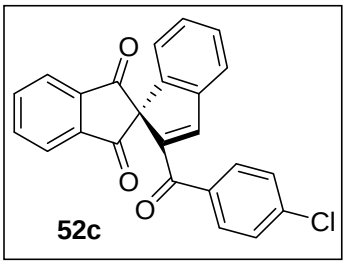
2'-Benzoyl-5'-methoxy-1,2'-spirobi[indene]-1,3-dione (52b)

0.209 mmol scale (28.9 mg, 36% yield), yellow oil, Rf = 0.3 (0.5% methanol in dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 1708, 1625, 1557, 1446, 1341, 1237, 1029, 963, 775, 728.; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 5.6, 3.1 Hz, 2H), 7.93



(dd, *J* = 5.6, 3.1 Hz, 2H), 7.81 (d, *J* = 7.3 Hz, 2H), 7.77 (s, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.46 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.13 (d, *J* = 1.8 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.82 (dd, *J* = 8.4, 2.1 Hz, 1H), 3.81 (s, 3H).; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 196.9, 190.5, 160.7, 147.8, 147.0, 145.1, 143.6, 137.7, 137.6, 136.0, 132.7, 129.1, 128.7, 124.6, 123.0, 116.0, 110.6, 72.3, 55.8.; **HRMS** (EI^+) *m/z* calculated for $C_{25}H_{16}O_4$: 380.1049 [M^+]; found: 380.1044.

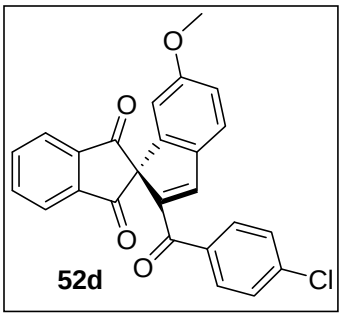
2'-(4-Chlorobenzoyl)-1,2'-spirobi[indene]-1,3-dione (52c)



0.209 mmol scale (46.5 mg, 58% yield), yellow solid, m.p.= 248-250 °C. Rf = 0.3 (0.5% methanol in dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 1704, 1626, 1337, 1258, 1090, 847, 762, 699, 622, 558; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.96 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.41 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.29 (d, *J* = 7.5, 7.5 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, d); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 196.5, 189.3, 148.1, 145.6, 145.2, 143.6, 143.6, 139.1, 136.0, 130.6, 130.4, 130.0, 129.1, 129.0, 125.8, 125.6, 124.7, 122.3; **HRMS** (EI^+) *m/z* calculated for $C_{24}H_{13}ClO_3$: 384.0553 [M^+]; found: 384.0561

2'-(4-Chlorobenzoyl)-6'-methoxy-1,2'-spirobi[indene]-1,3-dione (52d)

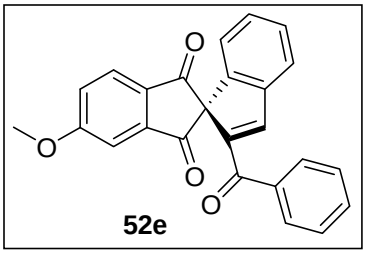
0.05 mmol scale (15.6 mg, 75% yield), yellow solid, m.p.= 167-170 °C, Rf = 0.3 (30% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm^{-1}): 1708, 1599, 1548, 1432, 1338,



52d

1288, 1143, 1091, 1014, 910, 817, 757, 731; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.95 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.75 (s, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 6.93 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.45 (d, *J* = 1.5 Hz, 1H), 3.72 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 196.6, 188.9, 161.8, 148.2, 147.5, 143.9, 143.6, 138.8, 136.3, 136.2, 136.1, 130.4, 129.0, 126.7, 124.7, 114.9, 108.9, 72.8, 55.9; **HRMS** (EI^+) *m/z* calculated for $C_{25}H_{15}ClO_4$: 414.0659 [M^{+1}]; found: 414.0648.

2'-Benzoyl-5-methoxy-1,2'-spirobi[indene]-1,3-dione (52e)

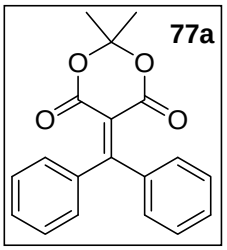


52e

0.116 mmol scale (18.4 mg, 42% yield), yellow solid, m.p.= 189-192 °C, Rf = 0.3 (1% methanol in dichloromethane). **FTIR** (KBr film) ν_{max} (cm^{-1}): 1704, 1627, 1599, 1557, 1490, 1341, 1294, 1261, 1082, 1020, 757, 739; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.5 Hz, 1H), 7.83-7.80 (m, 3H), 7.61 (d, *J* = 8.6 Hz, 1H), 7.56 (t, *J* = 7.5, 7.5 Hz, 1H), 7.52 (d, *J* = 2.1 Hz, 1H), 7.47 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.43 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.39 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 4.01 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 196.7, 194.9, 190.7, 166.3, 147.8, 146.6, 145.9, 145.5, 143.7, 137.8, 137.1, 132.7, 129.7, 129.2, 129.1, 128.7, 126.3, 125.5, 124.9, 122.3, 106.0, 56.5; **HRMS** (EI^+) *m/z* calculated for $C_{25}H_{16}O_4$: 380.1049 [M^+]; found: 380.1047.

5.7 Preparation of β,β-Disubstituted Stetter Acceptors

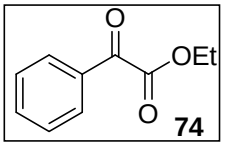
5-(Diphenylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (77a)



The title compound was prepared from a modified literature procedure.[71] A solution of titanium tetrachloride (0.22 mL, 2.0 mmol, 2.0 equiv.) in dichloromethane (0.5 mL) at 0 ˚C was added dropwise to a 25-mL round bottom flask containing dry tetrahydrofuran (THF) (3 mL), also at 0 ˚C. To the resulting suspension, a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (0.14 g, 1.0 mmol, 1.0 equiv.) and benzophenone (0.18 g, 1.0 mmol, 1.0 equiv.) in THF (1 mL) was added. Following the dropwise addition of pyridine (0.40 mL, 5.0 mmol, 5.0 equiv.) in THF (1 mL, 0.2M total), the solution was stirred at 0 ˚C for 1 h. The round bottom flask was removed from the ice bath and stirred at ambient temperature for 39h. The reaction mixture was then quenched with distilled water (2 mL) and ether (2 mL). The separated organic layer was washed with brine (5 mL) and an aqueous solution of saturated sodium bicarbonate (5 mL), then dried over sodium sulfate and concentrated under reduced pressure. FCC with 7.5% ethyl acetate in toluene served to isolate a moderately pure sample of the product. Recrystallization from methanol afforded the desired product in as a white solid in 8% yield (23 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 (t, *J* = 7.6, 7.6 Hz, 2H), 7.38 (dd, *J* = 7.3, 7.3 Hz, 4H), 7.23-7.22 (m, 4H), 1.91 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.0, 160.8, 140.1, 130.8, 130.0, 128.1, 116.4, 104.1, 27.8.

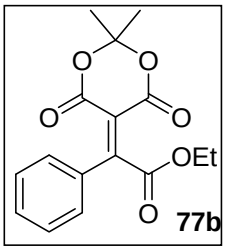
Ethylbenzoylformate (74)

The title compound was prepared following a slightly modified literature procedure.[72] A 50-mL round bottom flask containing diethyl oxalate (1.0 mL, 7.4 mmol, 1.0 equiv.) in diethyl ether (25 mL, 0.3M) was charged with a 1.0 M solution of phenylmagnesium



bromide in THF (8.8 mL, 8.8 mmol, 1.2 equiv.) at -78 ˚C. The reaction mixture was allowed to warm up to 10 ˚C over 140 min before it was quenched with a saturated aqueous solution of ammonium chloride. The layers were separated and the aqueous layer was washed with ether (3 x 25 mL). The combined organic layers were washed with 50 mL of brine, dried over sodium sulfate, and concentrated under reduced pressure. Bulb-to-bulb distillation at 160 ˚C under a pressure of 0.25 torr afforded the product with minor impurities. FCC using 10% ethyl acetate in hexanes as eluent afforded the desired product in 58% yield (0.76 g). ^{1}H NMR data agrees with previously reported values, albeit with improved resolution.[73] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.66 (dddd, *J* = 7.5, 7.5, 1.2, 1.2 Hz, 1H), 7.51 (dd, *J* = 8.0, 7.8 Hz, 2H), 4.45 (q, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H).

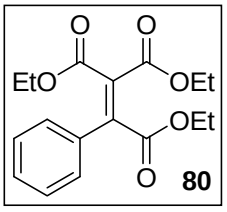
Ethyl 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-2-phenylacetate (77b)



The title compound was prepared using Fillion's[74] modification to Brown's procedure.[71] A solution of titanium tetrachloride (0.68 mL, 6.2 mmol, 2.1 equiv.) in dichloromethane (1.5 mL) at 0 ˚C was added dropwise to a 50-mL round bottom flask containing dry tetrahydrofuran (THF) (10.7 mL), also at 0 ˚C. To this suspension, a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (0.42 g, 2.9 mmol, 1.0 equiv.) and ethylbenzoylformate (0.58 g, 3.2 mmol, 1.1 equiv.) in THF (4 mL, total 0.22M) was added. Following the dropwise addition of pyridine (1.2 mL, 15 mmol, 5.0 equiv.), the solution was stirred at 0 ˚C for 1 h. The round bottom flask was removed from the ice bath and stirred at ambient

temperature for 23h. The reaction mixture was quenched with distilled water (6 mL) and diluted with ether (2 mL). The organic layer was separated and dried over sodium sulfate and concentrated. To prevent acid promoted decomposition on column, the resulting mixture was purified by FCC (25% ethyl acetate in hexanes) with a fast flow rate. The product was further purified by titration with methanol to afford the product in a 28% yield (0.25g). ^{1}H NMR data agrees with previously reported values.[74] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 – 7.42 (m, 5H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.85 (s, 6H), 1.33 (t, *J* = 7.1 Hz, 3H).

Triethyl 2-phenylethene-1,1,2-tricarboxylate (80)

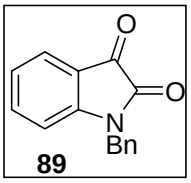


80

A solution of titanium tetrachloride (0.95 mL, 8.7 mmol, 2.1 equiv.) in dichloromethane (1.9 mL) at 0 ˚C was added dropwise to a 50-mL round bottom flask containing dry tetrahydrofuran (THF) (11 mL), also at 0 ˚C. To the resulting suspension, a solution of diethylmalonate (0.64 mL, 4.2 mmol, 1.0 equiv.) and ethylbenzoylformate (0.75 g, 4.2 mmol, 1.0 equiv.) in THF (8 mL, total 0.22M) was added. Following the dropwise addition of pyridine (1.7 mL, 21 mmol, 5.0 equiv.), the solution was stirred at 0 ˚C for 1 h. The round bottom flask was removed from the ice bath and stirred at ambient temperature for 4h. The reaction was quenched with 19 mL of water. The organic layer was separated, dried over sodium sulfate, and concentrated. The product was isolated by FCC using 10% ethyl acetate in hexanes followed by 20% ethyl acetate in hexanes. The pure product was obtained as a colourless oil in 52% yield (0.71 g) following further purification by FCC using 0.8% ethyl acetate in hexanes as eluent. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 5H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 6H), 1.03

(t, J = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.0, 164.8, 163.0, 147.0, 133.4, 130.1, 128.8, 127.9, 127.7, 62.3, 62.2, 61.9, 14.2, 14.1, 13.8.

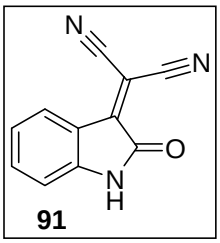
***N*-Benzyl isatin (89)**



89

N-Benzyl isatin was prepared according to a literature procedure.[75] Isatin (0.37 g, 2.5 mmol, 1.0 equiv.) was dissolved in *N*,*N*-dimethylformamide (4.6 mL, 0.54M) in a 25 mL round bottom flask at 0 ˚C. The addition of a suspension of sodium hydride in mineral oil (57 – 63%, 0.11 g, 2.6 mmol, 1.1 equiv.) turned the reaction mixture dark purple. After 10 minutes, gas evolution ceased. Benzyl bromide (0.35 mL, 2.9 mmol, 1.2 equiv.) was then added, dropwise resulting in a deep red reaction mixture. After 15 minutes, 22 mL of distilled water was added to the reaction mixture. A bright orange precipitate formed. The solid was isolated by vacuum filtration and then recrystallized from hot ethanol. The product was isolated as deep orange needle-like crystals in a 58% yield (0.35 g). ^{1}H NMR data agreed with previously reported data, albeit with improved resolution.[75] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 (d, J = 7.4 Hz, 1H), 7.48 (ddd, J = 7.8, 7.8, 0.9 Hz, 1H), 7.37 – 7.29 (m, 5H), 7.09 (dd, J = 7.5, 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.93 (s, 2H).

2-(1,2-Dihydro-2-oxo-3H-indol-3-ylidene)propanedinitrile (91)

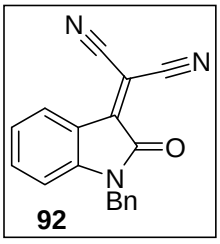


91

The title compound was prepared according to a slightly modified literature procedure.[76] Isatin (0.36 g, 2.5 mmol, 1.0 equiv.) and malononitrile (0.16 g, 2.5 mmol, 1.0 equiv.) were dissolved in ethanol (25 mL, 0.1M) in a 50-mL round bottom flask equipped with a water

condenser. The resulting solution was refluxed for 30 minutes. The reaction mixture was then concentrated under reduced pressure and placed under high vacuum for 90 min at 90 ˚C. The pure product was obtained as a red solid in a 93% yield (0.45 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.6 Hz, 1H), 7.57 (br s, 1H,), 7.56 (ddd, *J* = 7.8, 7.8, 1.1 Hz, 1H), 7.17 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H).

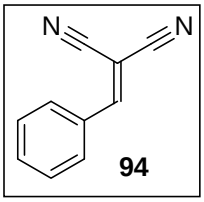
2-[1,2-Dihydro-2-oxo-1-(phenylmethyl)-3H-indol-3-ylidene]-propanedinitrile (92)



92

N-Benzyl isatin (0.35 g, 1.5 mmol, 1.0 equiv.) and malononitrile (96 mg, 1.5 mmol, 1.0 equiv.) were dissolved in ethanol (14.5 mL, 0.1M) in a 25-mL round bottom flask equipped with a water condenser. The resulting solution was refluxed for 40 minutes. The reaction mixture was then concentrated under reduced pressure and placed under high vacuum for 2h at 75 ˚C. The pure product was obtained as a dark purple solid in a 99% yield (0.41 mg). ^{1}H NMR data agrees with previously published values, albeit with higher resolution.[77] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.8 Hz, 1H), 4.67 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H), 7.37 – 7.30 (m, 5H), 7.11 (ddd, *J* = 7.8, 7.8, 0.7 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H).

2-(Phenylmethylene)-propanedinitrile (94)

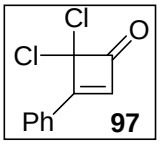


94

The title compound was prepared according to a literature procedure.[78] Malononitrile (0.32 g, 4.8 mmol, 1.02 equiv.) was dissolved in anhydrous ethanol (3 mL, 1.5M) in 10-mL round bottom flask. Benzaldehyde (0.48 mL, 4.7 mmol, 1.0 equiv.) and piperidine (5 μL, 0.05 mmol, 0.01 equiv.) were added sequentially. The reaction flask was then equipped with a water

condenser and heated to reflux for 1h. Cooling of the reaction vessel afforded a fine, fibrous beige precipitate. The product was isolated by vacuum filtration in a 77% yield (0.56 g). ^{1}H NMR data agrees with previously reported values.[79] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.7 Hz, 2H), 7.78 (s, 1H), 7.64 (t, *J* = 7.5, 7.5 Hz, 1H), 7.55 (dd, *J* = 7.8, 7.6 Hz, 2H).

4,4-Dichloro-3-phenylcyclobuten-1-one (97)

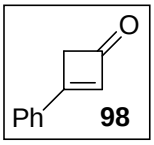


97

The title compound was prepared from a modified literature procedure.[80] Zinc (2.0 g, 30 mmol, 3 equiv.) was suspended in 10 mL of degassed, distilled water. Copper sulfate (0.15 g, 0.94 mmol, 0.094 equiv.) was added, and nitrogen gas was bubbled through the solution. After 15 minutes the water was decanted and the black solid was rinsed with acetone (2 x 5mL). The zinc-copper couple was then dried under high vacuum for 2h. The material was then transferred to a 100-mL round bottom flask and placed under an atmosphere of nitrogen gas. The flask was charged with ether (40 mL, 0.25M) and phenylacetylene (1.1 mL, 10 mmol, 1 equiv.) and equipped with an addition funnel with gas equilibrator and water condenser. A solution of trichloroacetyl chloride (2.2 mL, 20 mmol, 2 equiv.) and 1,2-dimethoxyethane (12.5 mL) were added via the addition funnel over one hour. After 22 hour the slurry was filtered. The filtrate was sequentially washed with aqueous solutions of saturated ammonium chloride, saturated sodium bicarbonate and saturated sodium chloride (20 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The product was isolated by FCC employing 5% ethyl acetate in hexanes followed by 10% ethyl acetate in hexanes and further purified by recrystallization from

hot 5% ethyl acetate in hexanes. The title compound was obtained in a 46% yield (0.99g). ^{1}H NMR data agrees with previously reported values albeit with improved resolution.[81] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 – 7.92 (m, 2H), 7.65 (dddd, *J* = 7.5, 7.3, 1.3, 1.3 Hz, 1H), 7.61-7.58 (m, 2H), 6.62 (s, 1H).

3-Phenylcyclobutenone (98)



The title compound was prepared from a modified literature procedure.[80] In a 25-mL round bottom flask, 1.8 g of zinc (27 mmol, 5.9 equiv.) was suspended in ethanol (8 mL). The reaction flask was cooled to 0 ˚C prior to the addition tetramethylethylenediamine (4.1 mL, 27 mmol, 5.9 equiv.). Acetic acid (1.5 mL, 27 mmol, 5.9 equiv.) was added over 5 minutes. A solution of 4,4-dichloro-3-phenylcyclobuten-1-one in ether (1 mL) and ethanol (3 mL, total 0.5M) was added over 10 minutes. The reaction mixture was stirred at 0 ˚C for another 15 minutes prior to removal from the ice bath. After 17h at ambient temperature, the reaction mixture was filtered. The filtrate was washed with saturated aqueous solutions of ammonium chloride, sodium chloride and sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. Purification by FCC using 5% ethyl acetate as eluent afforded the title compound as a bright yellow solid in a 4.5% yield (30 mg) and 3-phenylcyclobutanone in a 34% yield (0.23 g). ^{1}H NMR data agrees with previously reported values albeit with improved resolution.[80] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 – 7.61 (m, 2H), 7.51 – 7.49 (m, 3H), 6.39 (s, 1H), 3.54 (s, 2H).

5.8 General Procedures for Acceptor Screening

General Procedure for Formal Stetter Reaction of Thiazolium Carbinol

In a small vial the acceptor (1 equiv.) was dissolved in CH_2Cl_2 (0.25M). 2-(Hydroxy-2-furanylmethyl)-3,4,5-trimethyl-thiazolium iodide **70** (1 equiv.) was added in one portion followed by the dropwise addition of DBU (1 equiv.). After 5 – 30 minutes, a saturated aqueous solution of ammonium chloride was added. The organic layer was diluted with CH_2Cl_2 prior to extraction. The aqueous layer was further extracted with CH_2Cl_2 (3x). The organic layers were combined and dried over sodium sulfate prior to concentration.

General Procedure for Formal Stetter Reaction of Silylated Thiazolium Carbinol

In a small vial, 3,4,5-trimethyl-2-[2-furanyl[(trimethylsilyl)oxy]methyl]-thiazolium iodide **33b** (1 equiv.) and the acceptor (1 equiv.) were dissolved in CH_2Cl_2 (0.25M). Tetrabutylammonium difluorotriphenylsilicate (1 equiv.) was added in one portion. After 1 – 6 days, the reaction was quenched by the addition of distilled water. The organic layer was diluted with CH_2Cl_2 prior to extraction. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over sodium sulfate prior to concentration.

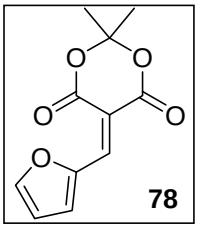
General Procedure for Stetter Reactions of β,β-Disubstitued Olefins

In a small vial the acceptor (1 equiv.) and NHC pre-catalyst (0.5 equiv.) were dissolved in CH_2Cl_2. The addition of the aldehyde (1 equiv.) was followed by the portionwise addition of base (0.5 equiv.) After 18h – 4 days, a saturated aqueous solution of ammonium chloride was added. The organic layer was diluted with CH_2Cl_2 and

extracted. The aqueous layer was further extracted with CH_2Cl_2 (3x). The combined organic layers were dried over sodium sulfate and concentrated.

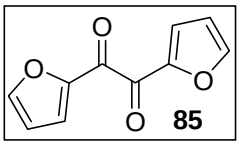
5.9 Products of Competing Reactions

5-(2-Furanylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (78)



^{1}H NMR data agrees with previously reported values.[82] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 3.8 Hz, 1H), 8.35 (s, 1H), 7.84 (d, *J* = 1.4 Hz, 1H), 6.75-6.74 (m, 1H), 1.76 (s, 6H).

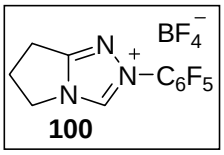
1,2-Di-2-furanyl-1,2-ethandione (85)



^{1}H NMR data agrees with previously reported values, albeit with improved resolution.[83] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78 (br s, 2H), 7.65 (d, *J* = 3.6 Hz, 2H), 6.64 (dd, *J* = 3.4, 1.3 Hz, 2H).

5.10 Preparation of *N*-Heterocyclic Carbene 100

6,7-Dihydro-2-(2,3,4,5,6-pentafluorophenyl)-5H-pyrrolo[2,1-c]-1,2,4-triazolium tetrafluoroborate (100)

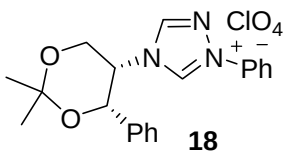


The aforementioned compound was prepared following a modified literature procedure.[84] An improved procedure was published shortly after this experiment was performed.[85] In 50-mL round bottom flask containing 2-pyrrolidone (0.38 mL, 5.1 mmol, 1.0 equiv.) was charged with dichloromethane (25 mL, 0.2M). Trimethyloxonium tetrafluoroborate (0.82 g, 5.6 mmol, 1.1 equiv.) was added and the reaction was stirred for 20h at ambient temperature. The

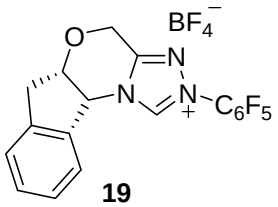
addition of pentafluorophenylhydrazine (1.0 g, 5.1 mmol, 1.0 equiv.) afforded a cloudy, dark orange reaction mixture. After 24h of stirring at ambient temperature, the reaction mixture was concentrated under reduced pressure then place under high vacuum for 1h. Chlorobenzene (25 mL) and triethylorthoformate (1.7 mL, 10 mmol, 1 equiv.) was added. The reaction mixture was then heated to reflux for 24h. A second equivalent of triethylorthoformate (1.7 mL, 10 mmol, 1 equiv.) was then added and the solution was once again heated to reflux for 24h. After cooling to room temperature the reaction mixture was diluted with toluene (25 mL) and stirred for 1h. The product was isolated as a light brown precipitate in 8% yield (0.15g). ^{1}H NMR data agrees with previously reported values.[84] **^{1}H NMR** (500 MHz) δ 10.28 (s, 1H), 4.78 (t, *J* = 7.5 Hz, 2H), 3.43 (t, *J* = 7.7 Hz, 2H), 3.03 (q, *J* = 7.5 Hz, 2H).

APPENDIX

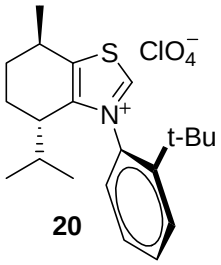
N-HETEROCYCLIC CARBENE PRECURSORS



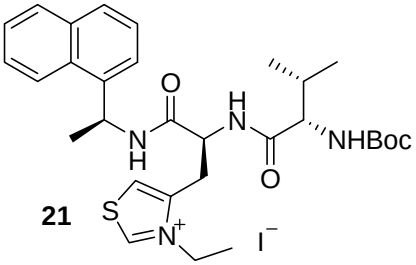
18



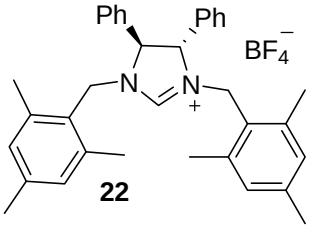
19



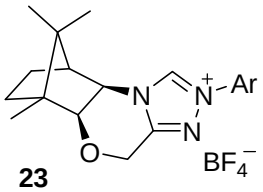
20



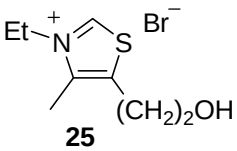
21



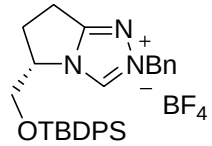
22



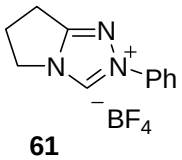
23



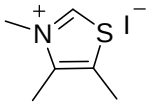
25



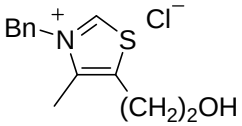
62



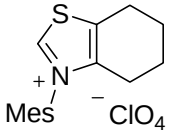
61



82

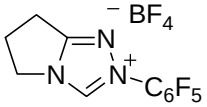


83



93

84



100

REFERENCES

1. Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239-258.

2. For a recent review of NHC reactivity see: Bugaut, X., Glorius, F. *Chem. Soc. Rev*., **2012**, *41*, 3511–3522.

3. Wöhler, F., Liebig, J. *Ann. Pharm*., **1832**, *3*, 249-282.

4. Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995-1005.

5. Ukai, T., Tanaka, R., Dokawa, T. *J. Pharm. Soc. Jpn*, **1943**, *63*, 296–300.

6. Breslow, R. *J. Am. Chem. Soc.***1958**, *80*, 3719-3726.

7. For a recent review of homoenolate reactivity see: Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev*., **2008**, *37*, 2691–2698.

8. For a review on NHC-catalyzed redox reactions of α-functionalized aldehydes see: Rong, Z.-Q.; Zhang, W.; Yang, G.–Q.; You, S.-L. *Curr. Org. Chem*., **2011**, *15*, 3077–3090.

9. Stetter, H.; Schreckenberg, M. *Angew. Chem., Int. Ed. Engl*. **1973**, *12*, 81.

10. Stetter, H.; Kuhlmann, H. *Angew. Chem.* **1974**, *16*, 589.

11. Trost, B.; Shuey, C.D.; DiNinno, F.; McElvain, C.D. *J. Am. Chem. Soc.* **1979**, *101*, 1284-1285.

12. Ciganek, E. *Synthesis* **1995**, 1311- 1314.

13. Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta.***1996**, *79*, 1899-1902.

14. Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc*. **2002**, *124*, 10298-10299.

15. Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem*. **2004**, 2025-2035.

16. Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun*. **2005**, 195-197.

17. Matsumoto, Y.; Tomioka, K. *Tetrahedron Lett*. **2006**, *47*, 5843-5846.

18. Rong, Z.-Q.; Li, Y.; Yang, G.-Q.; You, S.-L. *Synlett* **2011**, *7*, 1033–1037.

19. Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876-8877.

20. Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc*. **2002**, *124*, 10298-10299.

21. Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934–1936.

22. Read de Alaniz, J.; Rovis, T. *Synlett* **2009**, 1189–1207.

23. Enders, D.; Balensiefer, T. *Acc. Chem. Res*. **2004**, *37*, 534-541.

24. a) Enders, D.; Han, J.; Henseler, A. *Chem. Commun*. **2008**, 3989-3991; b) Enders, D.; Han, *J. Synthesis* **2008**, 3864-3868.

25. a) Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066-14067; b) Liu, Q.; Rovis, T. *Org. Lett*. **2009**, *11*, 2856-2859.

26. DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc*. **2009**, *131*, 10872-10874.

27. Jousseaume, T.; Wurz, N. E.; Glorius, F. *Angew. Chem. Int. Ed*. **2011**, *50*, 1410 – 1414.

28. Sánchez-Larios, E.; Thai, K.; Bilodeau, F.; Gravel, M *Org. Lett.* **2011**, *13*, 4942–4945.

29. Fang, X.; Chen, X.; Lv, H.; Chi, Y. R. *Angew. Chem. Int. Ed*. **2011**, *50*, 11782 – 11785.

30. Grossman, A.; Enders, D. *Angew. Chem. Int. Ed*. **2012**, *51*, 314 – 325.

31. Sánchez-Larios, E.; Gravel, M. *J. Org. Chem.* **2009**, *74*, 7536-7539.

32 . Sun, F.-G.; Huang, X.-L.; Ye, S. *J. Org. Chem*. **2010**, *75*, 273–276.

33 . Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314-2315.

34. Nahm, M. R.; Potnick, J. R.; White, P. S.; Johnson, J. S. *J. Am. Chem. Soc.* **2006**, *128*, 2751-2756.

35. Linghu, X.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070-3071.

36. Mattson, A. E.; Scheidt, K. A *J. Am. Chem. Soc.* **2007**, *129*, 4508–4509.

37. Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc*. **2006**, *128*, 4932-4933.

38. Stetter, H.; Kuhlmann, H *Synthesis* **1975**, 379.

39. Galopin, C. C. *Tetrahedron Lett.* **2001**, *42*, 5589–5591.

40. Randl, S.; Blechert, S. *J. Org. Chem.* **2003**, *68*, 8879-8882.

41. Tius, M. A.; Harrington, P. E. *J. Am. Chem. Soc.* **2001**, *123*, 8509-8514.

42. Anjaiah, S.; Chandrasekhar, S.; Grée, R. *Adv. Synth. Catal*. **2004**, *346*, 1329 –1334.

43. Nicolaou, K. C.; Tang, Y.; Wang, J. *Chem. Commun*., **2007**, 1922–1923.

44. Orellana, A.; Rovis, T. *Chem. Commun*., **2008**, 730–732.

45. Pandey, R. C.; Toussaint, M. W.; Stroshane, R. M.; Kalita, C. C.; Aszalos, A. A.; Garretson, A. L.; Wei, T. T.; Byrne, K. M.; Geoghegan, R. F.; White, R. J. *J. Antibiot*. **1981**, *34*, 1389-1401.

46. a) Goto, K.; Sudzuki, H. *Bull. Chem. Soc. Jpn.* **1929**, *4*, 220-224. b) Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. *Tetrahedron Lett.* **1967**, *8*, 2421-2424. c) Tomita, M.;

Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. *Tetrahedron Lett.* **1967**, *8*, 2425-2430.

47. Warnick-Pickle, D. J.; Byrne, K. M.; Pandey, R. C.; White, R. J. *J. Antibiotics.* **1981**, *34*, 1402.

48. Aldehyde **45** was prepared from commercially available starting material by Eduardo Sánchez-Larios see: Sánchez-Larios, E. Enantioselective and Domino Intermolecular Stetter Reactions. Ph.D. Thesis, University of Saskatchewan, 2011.

49. Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.*, **1986**, *51*, 404–407.

50. Sánchez-Larios, E. Enantioselective and Domino Intermolecular Stetter Reactions. Ph.D. Thesis, University of Saskatchewan, 2011.

51. a) Sánchez-Larios, E.; Holmes, J. M.; Daschner, C. L.; Gravel, M., *Org. Lett.* **2010**, *12*, 5772-5775. b) Sánchez-Larios, E.; Holmes, J. M.; Daschner, C. L.; Gravel, M., *Synthesis* **2011**, 1896-1904.

52. DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc*. **2009**, *131*, 10872-10874.

53 . Triazolium carbinols have been studied previously. See: Teles, J. H.; Melder, J. – P., Ebel, K.; Schneider, R.; Gehrer, E.; Harder, W.; Brode, S. *Helv. Chim. Acta.* **1996**, *79*, 75 – 83.

54. Creary, X. J. Org. Chem., 1987, 52, 5026–5030.

55. Baxter, G. J.; Brown, R. F. C. *Aust. J. Chem*. **1975**, *28*, 1551 – 1557.

56. Thai, K. NHC-Catalyzed Transformations: Stetter, Benzoin, and Ring Expansion Reactions. Ph.D. Thesis, University of Saskatchewan, 2012.

57. Appel, R.; Mayr, H. *J. Am. Chem. Soc*. **2011**, *133*, 8240–8251.

58. Bugaut, X.; Liu, F.; Glorius, F. *J. Am. Chem. Soc*. **2011**, *133*, 8130–8133.

59. Danheiser, R. L.; Savariar, S.; Cha, D. D. *Org. Synth.* **1990**, *68*, 32-40.

60. Chezal, J. M.; Moreau, E.; Desbois, N.; Blache, Y.; Chavignon, O.; Teulade, J. C. *Tetrahedron Lett*. **2004**, *45*, 553-556.

61. Ueda, M.; Kawai, S.; Hayashi, M.; Naito, T.; Miyata, O. *J. Org. Chem*. **2010**, *75*, 914–921.

62. For complete characterization data see reference 50.

63. Koepf, M.; Melin, F.; Jaillard, J.; Weiss, J. *Tetrahedron Lett*. **2005**, *46*, 139 – 142.

64. 2-Bromo-5-methoxybenzaldehyde (**45**) was prepared by Eduardo Sánchez-Larios: Sánchez-Larios, E. Enantioselective and Domino Intermolecular Stetter Reactions. Ph.D. Thesis, University of Saskatchewan, 2011.

65. Remy, C. C.; King, S. W.; Cochran, D.; Springer, J. P.; Hirshfield, J. *J. Org. Chem*. **1985**, *50*, 4120-4125.

66. Dumas, A. M.; Seed, A.; Zorzitto, A. K.; Fillion, E. *Tetrahedron Lett.*, **2007**, *48*, 7072-7074.

67. Runyon, S. P.; Peddi, S.; Savage, J. E.; Roth, B. L.; Glennon, R. A.; Westkaemper, R. B. *J. Med. Chem.* **2002**, *45*, 1656-1664.

68. Bryan, C. S.; Lautens, M. *Org. Lett*., **2010**, *12*, 2754–2757.

69. For full characterization see: Sánchez-Larios, E.; Holmes, J. M.; Daschner, C. L.; Gravel, M., *Org. Lett.* **2010**, *12*, 5772-5775.

70. For synthesis and full characterization see: Sánchez-Larios, E.; Holmes, J. M.; Daschner, C. L.; Gravel, M., *Org. Lett.* **2010**, *12*, 5772-5775.

71. Baxter, G. J.; Brown, R. F. C. *Aust. J. Chem*. **1975**, *28*, 1551 – 1557.

72. Creary, X. *J. Org. Chem*., **1987**, *52*, 5026–5030.

73. Meng, Q.; Sun, Y.; Ratovelomanana-Vidal, V.; Genêt, J. P.; Zhang, Z. *J. Org. Chem*., **2008**, *73*, 3842–3847.

74. Wilsily, A.; Fillion, E. *Org. Lett*., **2008**, *10*, 2801 – 2804.

75. Marti, C.; Carreira, E. M. *J. Am. Chem. Soc*., **2005**, *127*, 11505–11515.

76. Liu, H.; Guolan Dou, G.; Shi, D. *J. Comb. Chem*., **2010**, *12*, 292–294.

77. Deng, H.-P. Wei, Y,; Shi, M. *Org. Lett*., **2011**, *13*, 3348–3351.

78. Chang, L. C. W.; von Frijtag Drabbe Künzel, J. K.; Mulder-Krieger, T.; Spanjersberg, R. F.; Roerink, S. F.; van den Hout, G.; Beukers, M. W.; Brussee, J.; IJzerman A. P. *J. Med. Chem*. **2005**, *48*, 2045-2053.

79. Yamashita, K.; Tanaka, T.; Hayashi, M. *Tetrahedron*, **2005**, *61*, 7981–7985.

80. Danheiser, R. L.; Savariar, S.; Cha, D. D. *Org. Synth.* **1990**, *68*, 32.

81. Hassner, A.; Dillon, J. L. *J. Org. Chem*. **1983**, *48*, 3382-3386.

82. Yeagley, A. A.; Lowder, M. A.; Chruma, J. J. *Org. Lett.* **2009**, *11*, 4022-4025.

83. Wang, X.; Zhang, Y. *Tetrahedron* **2003**, *59*, 4201–4207.

84. Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem*., **2005**, *70*, 5725–5728.

85. Vora, H. U.; Lathrop, S. P.; Reynolds, N. T.; Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *Org. Synth*. **2010**, *87*, 350-361.