DISSERTATION

THE STETTER REACTION: SCOPE AND MECHANISTIC INVESTIGATION

Submitted by

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY JENNIFER LYNN MOORE ENTITLED THE STETTER REACTION : SCOPE AND MECHANISTIC INVESTIGATION BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

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ABSTRACT OF DISSERTATION

THE STETTER REACTION: SCOPE AND MECHANISTIC INVESTIGATION

Since the isolation and characterization of stable imidazolinylidene carbenes by Arduengo in 1991, chemists have been increasingly fascinated by their potential as modifying ligands on transition metals. However, it was not until Ukai demonstrated the efficacy in the benzoin reaction that the use of stable nucleophilic carbenes as catalysts was used for organic transformations. The last 10 years in particular have seen a tremendous explosion of interest in this area, with new reactivity manifolds having been developed across a range of reaction subtypes.

The highly enantioselective intramolecular Stetter reaction has been expanded to include the formation of tetrasubstituted stereocenters. The reaction is mild, general, and tolerates aromatic, aliphatic, sulfur, oxygen, and nitrogen tethering of aldehyde and Michael acceptor. The current substrate scope includes compounds with varying electronics and sterics.

A mechanistic investigation into the intramolecular Stetter reaction has been conducted. The rate law of the reaction was determined and coupled with kinetic isotope effects, competition experiments and calculations to suggest that proton transfer is rate determining. These results provide the foundation for future development of better catalysts and expansion of substrate scope. The inherent tunability of nucleophilic carbenes as catalysts promises great latitude in overcoming issues associated with functional group compatibility, turnover frequency, turnover number and, naturally,

expansion of substrate type. This suggests that nucleophilic carbene catalysts will likely remain useful tools in organic synthesis for the foreseeable future.

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through so much together and it is great to have you in my life. I promise to never forget where I came from and all of the sacrifices the past generations in my family endured to make it possible for me to be where I am today.

To my husband Joe, you have made this experience so much more fulfilling than if I did not have you. You make it possible for me to see how far we have come and what the future holds for us, thank you for your love. We do this all for you baby Turtle. I feel so blessed that you are apart of this experience and cannot wait to meet you.

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ABBREVIATIONS

Ac	acetyl
Ar	aryl
BAL	benzaldehyde lyase
BFD	benzoylformate decarboxylase
bmin	butylmethylimidazolium
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIPEA	diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl
$Eu(tfc)_3$	europium tris[3-trifluoromethylhydroxymethylene)-camphorate]
HOAt	1-hydroxy-7-azabenzotriazole
i-Pr	isopropyl
KHMDS	potassium *bis*(trimethylsilyl)amide
KIE	kinetic isotope effect
KPi buffer	potassium phosphate buffer

Me	methyl
Mes	mesityl
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
LiHMDS	lithium *bis*(trimethylsilyl)amide
n-Bu	*normal*-butyl
n-Hex	*normal*-hexyl
n-Pr	*normal*-propyl
NHC	*N*-heterocyclic carbene
PEMP	pentamethylpiperidine
Ph	phenyl
Pr	propyl
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
ThDP	thiamin diphosphate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Tol	*para*-tolyl
Ts	*para*-toluenesulfonyl (tosyl)

Chapter 1

N-Heterocyclic Carbenes : A Review of the Benzoin Reaction and Stetter Reaction

1.1 Introduction

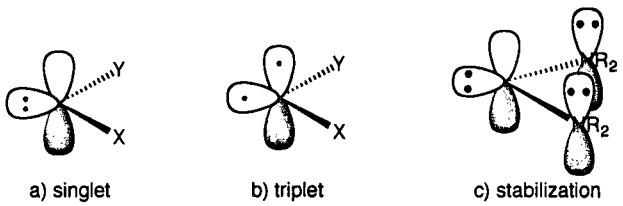
Since the isolation and characterization of stable imidazolinylidene carbenes by Arduengo in 1991,[1] chemists have been increasingly fascinated by their potential as modifying ligands on transition metals. The direct use of azolidine-based carbenes as catalysts in organic transformations, however, predates Arduengo's find by almost 50 years,[2] not to mention the role that thiamin cofactor plays in modifying a number of biochemical transformations. Even asymmetric catalysis using chiral nucleophilic carbenes is over 40 years old, with Sheehan's seminal report appearing in 1966.[3] That said, much of this early work attracted little attention from the chemical community as a whole, largely due to poor efficiency, selectivity or both. That situation has changed rather drastically in the past 10 years and the area has been reviewed both tangentially and specifically almost a dozen times.[4-14]

This review will focus on the use of chiral nucleophilic *N*-heterocyclic carbenes, commonly termed NHCs, as catalysts in organic transformations. Rather than presenting simply a laundry list of results, the focus of the current review will be to summarize and place in context the key advances made, with particular attention paid to recent and conceptual breakthroughs. These aspects, by definition, will include a heavy emphasis on mechanism. In a number of instances, the asymmetric version of the reaction has yet to be reported; in those cases, the state-of-the-art is included in order to further illustrate the broad utility and reactivity of nucleophilic carbenes.

1.2 Stable Carbenes

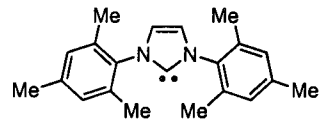
Since the 1950's carbenes have shown great potential in the field of organic and organometallic chemistry.[15-17] These neutral molecules contain a divalent carbon atom with six electrons in its valence shell and exist in either a singlet or triplet state (Scheme 1a, b). Depending on the steric and electronic environment, carbene compounds can be electrophilic or nucleophilic. NHCs contain heteroatoms on either side of the carbene atom, which donate electron density into the vacant p-orbital to enhance thermodynamic stability. For example, in carbene **2** (Scheme 1c) the nitrogen lone pairs donate electron density into the empty p-orbital of the carbene carbon perpendicular to the plane of the ring, allowing for 6π aromatic stabilization. The nitrogen atoms also stabilize the carbene via σ withdrawal of electron density from the carbene center. Steric hindrance contributes to kinetic stability. It is notable that no single characteristic is responsible for producing isolable carbenes; both electronic and steric factors are necessary for stability.[16,18]

Scheme 1



Pioneering work by Wanzlick in the 1960's established nucleophilic saturated and unsaturated carbenes as reactive intermediates, although he was unable to isolate them

due to their inherent reactivity.[19] Nearly thirty years later, Bertrand and Arduengo independently accomplished the first isolation of a carbene species, **1** and **2**, respectively.[1,20] The synthesis of bisadamantyl imidazolinylidine carbene **2** by Arduengo is considered by some to be the first isolated carbene and was unequivocally characterized by X-ray crystallography.[5] Since 1991, alkyl and aryl *N*-substitutents have both been documented to provide stable, isolable carbenes. There was concern that substituted aryl rings, which distort the plane of the carbene, would affect stability but Arduengo disproved this by synthesizing **3** and **4**.[21] The mesityl (Mes) substituted carbene prevents conjugation between the phenyl rings and the nitrogen centers, while *p*-tolyl substituents allow conjugation. Both share the same chemical characteristics and demonstrate that substitution of aryl rings has little effect on stability of the carbene compound. Since the first isolation, many groups have reported the synthesis and isolation of imidazole-, thiazole-, and triazole-derived stable carbenes, some of which are stable enough to be bottled and occasionally even commercially available.[22]



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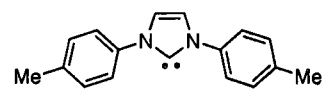

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The similarity between *N*-heterocyclic carbenes and electron-rich organophosphanes has been extensively studied and exploited in organometallic chemistry. NHC-metal complexes have been shown to outperform analogous phosphine-metal complexes in some organometallic transformations.[23,24] Both compounds are σ-donors and exhibit little backbonding character. Most notable are the advances made in coordination chemistry, olefin metathesis, and cross-coupling reactions.[25] In addition to

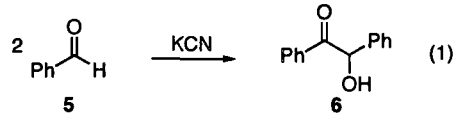
their use as ligands for transition metal catalysts, the use of NHCs as organocatalysts has experienced increased interest in the past 15 years and developed into a field of its own.

1.3 Benzoin Reaction

1.3.1 Mechanism and Catalyst Design

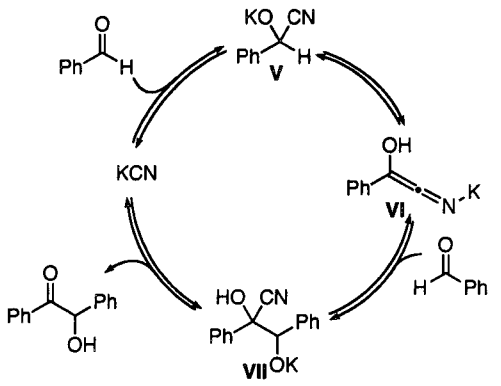
The benzoin reaction dates back to 1832 when Wöhler and Liebig reported that cyanide catalyzes the formation of benzoin **6** from benzaldehyde **5**, a seminal example in which the normal mode of polarity of a functional group was reversed (eq. 1).[26] This reversal of polarity, subsequently termed Umpolung,[27] effectively changes an electrophilic aldehyde into a nucleophilic acyl anion equivalent.

In 1903, Lapworth described his findings of the action of potassium cyanide on benzaldehyde.[28] He postulated that cyanide adds to benzaldehyde to form **V**, followed by proton transfer of the α-labile hydrogen, forming intermediate **VI** which is now referred to as an acyl anion equivalent. Addition to another molecule of benzaldehyde occurs to form **VII** (Scheme 2). The unstable cyanohydrin of benzoin **VII** then collapses to form benzoin and potassium cyanide. Additionally, Lapworth tested the reversibility of the addition of cyanide to benzaldehyde by first forming hydroxybenzyl cyanide (protonated variant of **V**) and subjecting it to benzaldehyde and base, in which benzoin was recovered.

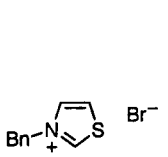


5 6 (1)

Scheme 2



In 1943, more than a century after the initial report, Ukai *et al.* showed that thiazolium salts such as **7** and **8** catalyze the homodimerization of aldehydes in the presence of base.[2] This discovery was paramount because although cyanide ions are inherently achiral, thiazolium salts can be modified to act as a source of chirality to render the reaction enantioselective.



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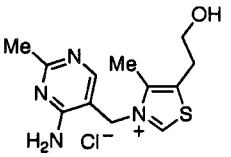

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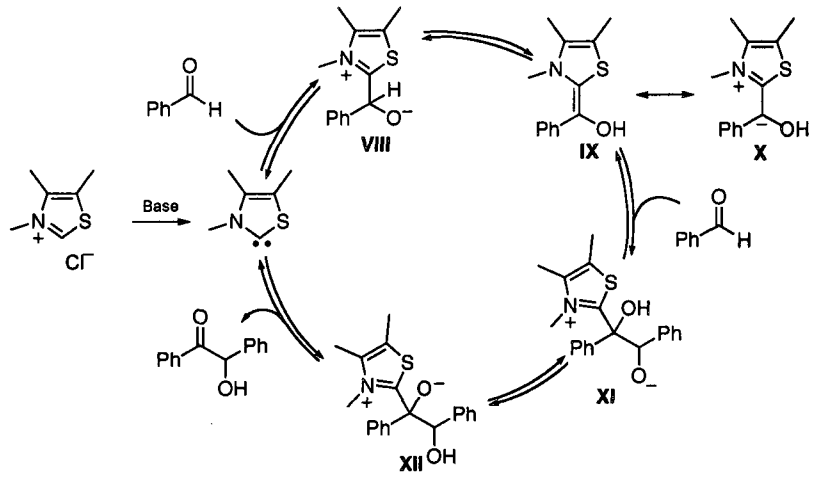
Breslow and co-workers elucidated the currently accepted mechanism of the benzoin reaction in 1958 using thiamin **8**. The mechanism is closely related to Lapworth's mechanism for the cyanide anion catalyzed benzoin reaction (Scheme 3).[28,29] The carbene, formed *in situ* by deprotonation of the corresponding thiazolium salt, undergoes nucleophilic addition to the aldehyde. A subsequent proton transfer generates a nucleophilic acyl anion equivalent known as the "Breslow intermediate" **IX**. Subsequent attack of the acyl anion equivalent on another molecule of aldehyde generates a new carbon—carbon bond **XI**. A proton transfer forms tetrahedral intermediate **XII**, allowing for collapse to produce the α-hydroxy ketone accompanied by liberation of the

active catalyst. As with the cyanide catalyzed benzoin reaction, the thiazolylidene catalyzed benzoin reaction is reversible.[30]

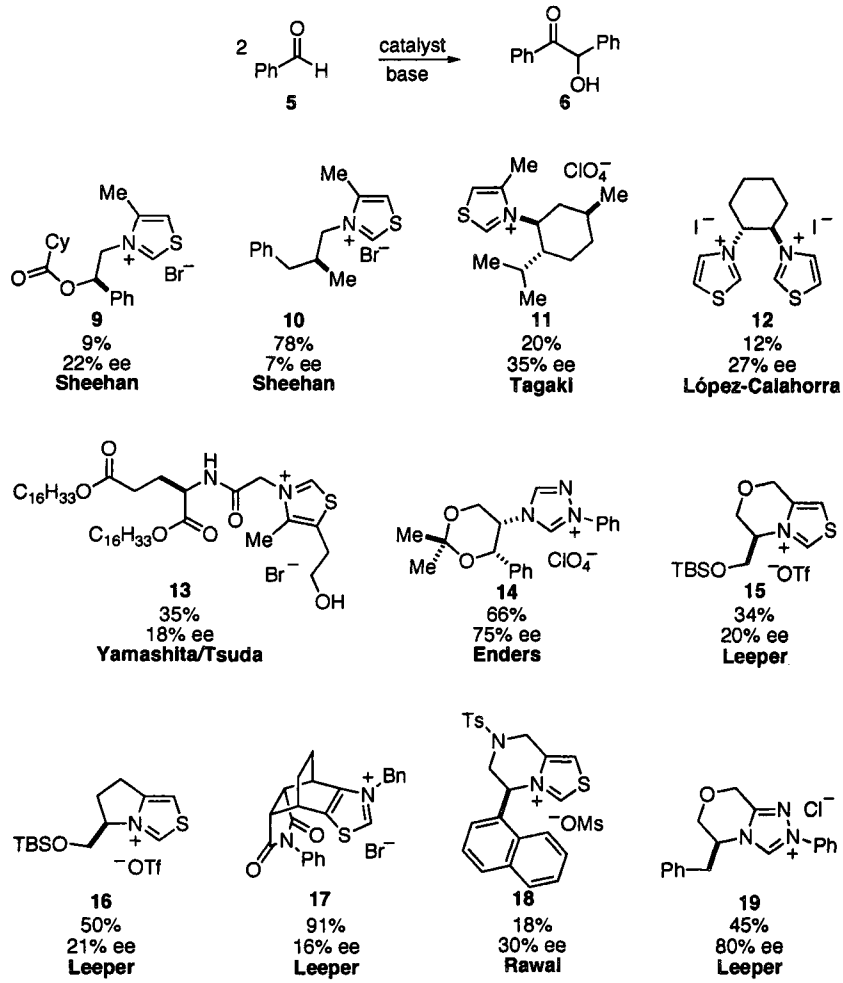
Scheme 3



In 1966, Sheehan and Hunneman reported the first example of an asymmetric benzoin reaction, using chiral thiazolium pre-catalyst **9** to yield benzoin **6** in 22% ee (Scheme 4).[3] The next significant advance occurred in 1974, when Sheehan and Hara reported that adding steric bulk around the reactive site, as shown in **10**, leads to increased asymmetric induction in benzoin formation to 29% ee, although the yields remain low.[31] Many groups have attempted to improve the enantioselectivity of the thiazolylidene catalyzed benzoin reaction with modest success. In 1980, Tagaki and co-workers synthesized thiazolium salt **11** to study the benzoin reaction in a micellar two-phase medium; despite the fact that the enantiomeric excess of 35% ee was achieved, only a slight increase in yield was observed.[32] López-Calahorra and co-workers designed the bis(thiazolin-2-ylidene) **12** in an effort to increase the rigidity of the active species, although the cyclohexyl tethered catalyst provides low yield and 27% ee.[33] Yamashita,

Tsuda, and co-workers synthesized lipid thiazolium salt **13** that produced benzoin in 18% ee.[34]

Scheme 4

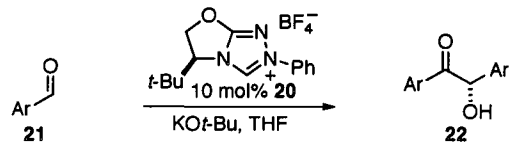


A breakthrough in the asymmetric benzoin reaction was achieved in 1996 when Enders, Teles, and co-workers introduced chiral triazolinylidene carbenes instead of thiazolylidene carbenes. They utilized a variety of chiral triazolium salts that provided increased yields and enantioselectivities, outperforming all previous thiazolium pre-catalysts.[35] The most active of these triazolium salts is **14**, which affords benzoin in 75% ee and 66% yield. In 1997, Leeper and co-workers developed a series of rigid bicylic

thiazolium salts, **15-17**, that they hypothesized would increase enantioselectivities by restraining the rotation of the chiral side chain of the catalyst.[36,37] Concurrently, Rawal and Dvorak increased the enantioselectivity of the benzoin reaction with bicyclic thiazolium salt **18** when compared to Leeper's chiral bicyclic thiazolium salts **15-17**.[38] The reactivity and enantioselectivity remained low until Leeper and co-workers exchanged the thiazolium framework for the more reactive triazolium pre-catalyst **19** and observed increased enantioselectivities, up to 80% ee.[39] In 2004, Takata and co-workers introduced the use of chiral rotaxanes as an asymmetric environment for the thiazolium catalyzed benzoin reaction, achieving modest enantioselectivities.[40]

In 2002, Enders and co-workers took advantage of the bicyclic restriction first introduced by Leeper and Rawal to develop catalyst **20**. Use of this catalyst provides a number of benzoin derivatives **22a-h** in up to 95% ee (Table 1).[41] The stereochemistry of the benzoin reaction catalyzed by thiazolium and triazolium pre-catalysts has subsequently been modeled by Houk and Dudding.[42]

Table 1



entry	22	Ar	temp (°C)	yield (%)	ee(%)
1	**a**	Ph	18	83	90
2	**b**	4-FC_6H_4	18	81	83
3	**c**	4-FC_6H_4	0	61	91
4	**d**	3-ClC_6H_4	0	85	86
5	**e**	4-MeC_6H_4	18	16	93
6	**f**	4-$MeOC_6H_4$	18	8	95
7	**g**	2-furyl	0	100	64
8	**h**	2-furyl	–78	41	88

1.3.2 Cross-Benzoin

The benzoin reaction typically consists of the homocoupling of two aldehydes, which results in the formation of inherently dimeric compounds, therefore limiting the synthetic utility. The cross-benzoin reaction has the potential to produce four products, two homocoupled adducts and two cross-benzoin products. Several strategies have been employed to develop a selective cross-benzoin reaction, including the use of donor-acceptor aldehydes, acyl silanes and acyl imines, as well as intramolecular reactions.

Müller and co-workers have developed an enantioselective enzymatic cross-benzoin reaction.[43,44] This is the first example of an enantioselective cross-benzoin reaction and takes advantage of the donor-acceptor concept. This transformation is catalyzed by thiamin diphosphate (ThDP) **23** in the presence of benzaldehyde lyase (BAL) or benzoylformate decarboxylase (BFD). Under these enzymatic reaction conditions the donor aldehyde **24** is the one that forms the acyl anion equivalent and subsequently attacks the acceptor aldehyde **25** to provide a variety of α-hydroxyketones **26** in good yield and excellent enantiomeric excesses without contamination of the other cross-benzoin products **27**. The authors chose 2-chlorobenzaldehyde **25** as the acceptor because of its inability to form a homodimer under enzymatic reaction conditions.

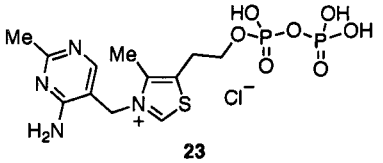


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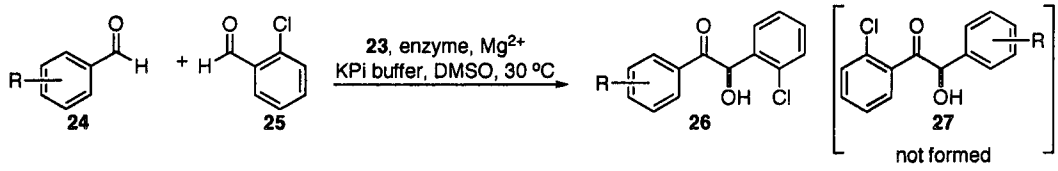
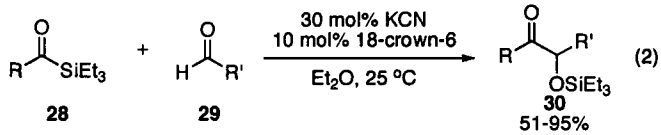
Table 2



entry	26	R	enzyme	conversion (%)	ee (%)
1	**a**	3-CN	BFD H281 A	>99	90
2	**b**	4-Br	BFD H281 A	90	95
3	**c**	4-CF_3	BFD H281 A	75	93
4	**d**	3,4-CH_2O_2	BAL	98	>99
5	**e**	3,4,5-$(CH_3O)_3$	BAL	82	>99
6	**f**	3,5-$(CH_3O)_2$	BAL	>99	>99

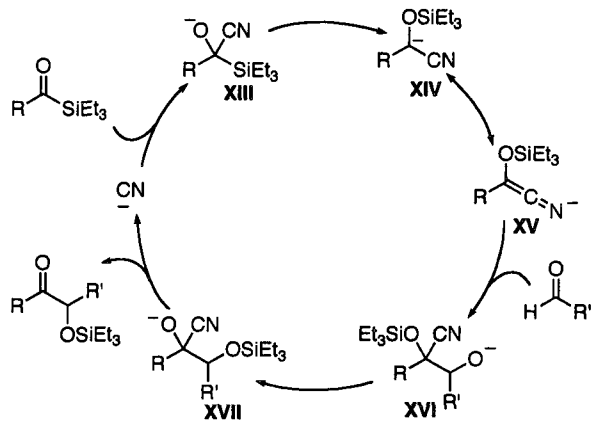
In an effort to circumvent a homodimerization event acyl silanes have been used to promote a cross-benzoin reaction. Initial reports by Johnson and co-workers employed potassium cyanide to catalyze the regiospecific cross silyl benzoin reaction to afford a single regioisomer in good yield (eq. 2).[45-47]



(2)

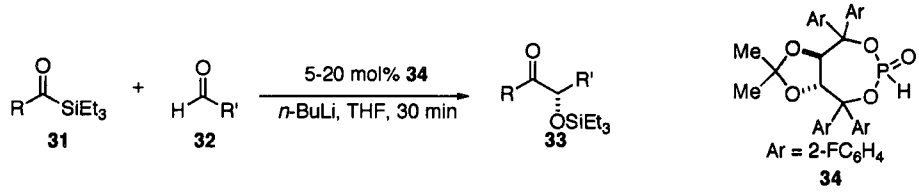
The proposed mechanism is as follows: initial cyanation of the acyl silane followed by a [1,2]-Brook rearrangement yields acyl anion equivalent **XIV** (Scheme 5). Subsequent attack by the acyl anion equivalent **XV** on the aldehyde leads to tetrahedral intermediate **XVI**. After a 1,4-silyl migration, cyanide is regenerated, and the desired α-siloxy ketone is formed.

Scheme 5



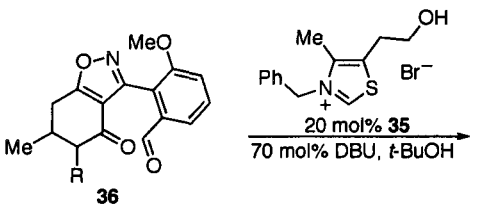
Shortly after publishing the racemic cross silyl benzoin reaction, Johnson and co-workers reported an enantioselective variant utilizing metallophosphite catalysis.[48] The lithiophosphite adds to the acyl silane and proceeds through the remainder of the mechanism in direct analogy to that observed with cyanide catalysis, with the added benefit of asymmetric induction. As illustrated in Table 3, good yields and enantioselectivities are achievable under these reaction conditions.

Table 3



entry	34	R	R'	yield (%)	ee (%)
1	**a**	Ph	Ph	84	82
2	**b**	Ph	4-ClC_6H_4	75	82
3	**c**	4-ClC_6H_4	Ph	82	87
4	**d**	Ph	4-$OMeC_6H_4$	87	91
5	**e**	4-ClC_6H_4	4-$OMeC_6H_4$	83	90
6	**f**	4-$NMe_2C_6H_4$	Ph	86	86
7	**g**	*n*-hexyl	Ph	72	67

An alternative strategy to access cross-benzoin products is to tether the two reactive partners. This approach has the disadvantages inherent to intramolecular reactions, but it provides access to products produced by the coupling of aldehydes with ketones. In 2003, Suzuki and co-workers reported the intramolecular cross-benzoin reaction utilizing thiazolium pre-catalyst **35** to obtain products such as **37** and **38** (eq. 3).[49]

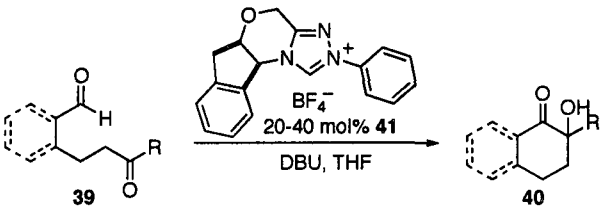


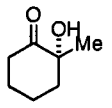
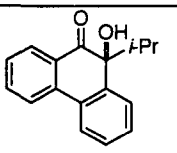
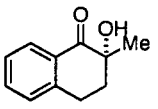
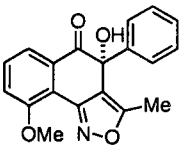
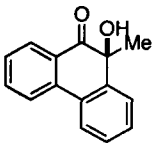
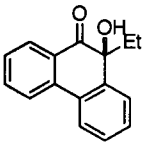
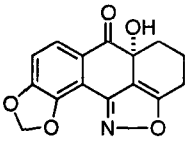
	R	yield (%)	dr
37	H	90	>20:1
38	CO_2Et	79	>20:1

(3)

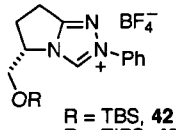
In concurrent and independent work, Suzuki and Enders found that tethered keto-aldehydes undergo highly enantioselective cross-benzoin reactions using triazolium based catalysts.[50,51] The scope includes various aromatic aldehydes with alkyl and aryl ketones. Additionally, aliphatic substrate **39a** is cyclized in excellent enantioselectivity, albeit in 44% yield.

Table 4

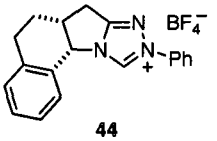


entry	40	product	yield (%)	ee (%)	entry	40	product	yield (%)	ee(%)
1	a		44	96	5	e		74	85
2	b		70	96	6	f		91	98
3	c		73	39					
4	d		47	90	7	g		73	99

In a report by Enders and co-workers, triazolium pre-catalysts **42-44** were shown to be competent in the cyclization of a variety of ketones.[50] Tetracyclic triazolium pre-catalyst **44** provides the enantioselectivities up to 98%.



R = TBS, **42**
R = TIPS, **43**

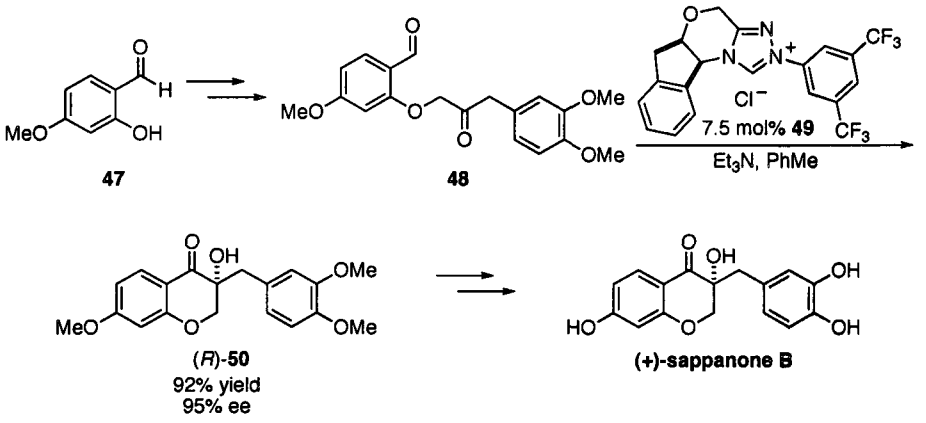


44

Suzuki and co-workers have relayed this methodology into the synthesis of (+)-sappanone B (Scheme 6).[52] The authors found that catalysts previously introduced by Rovis and co-workers led to inferior results; *N*-Ph catalyst **41** gave significant elimination

while N-C_6F_5 gave low enantioselectivities. By tuning the electronics of the N-aryl substituent these workers identified **49** as providing the optimal mix of reactivity and enantioselectivity. Commercially available 2-hydroxy-4-methoxybenzaldehyde **47** was transformed into aldehyde **48**, which upon treatment with triazolium salt **49** in the presence of base was cyclized to afford (*R*)-**50** in 92% yield and 95% ee and subsequently transformed into (+)-sappanone B.

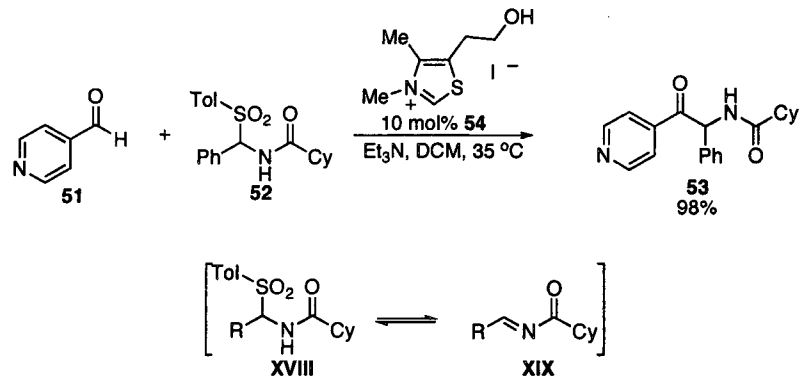
Scheme 6



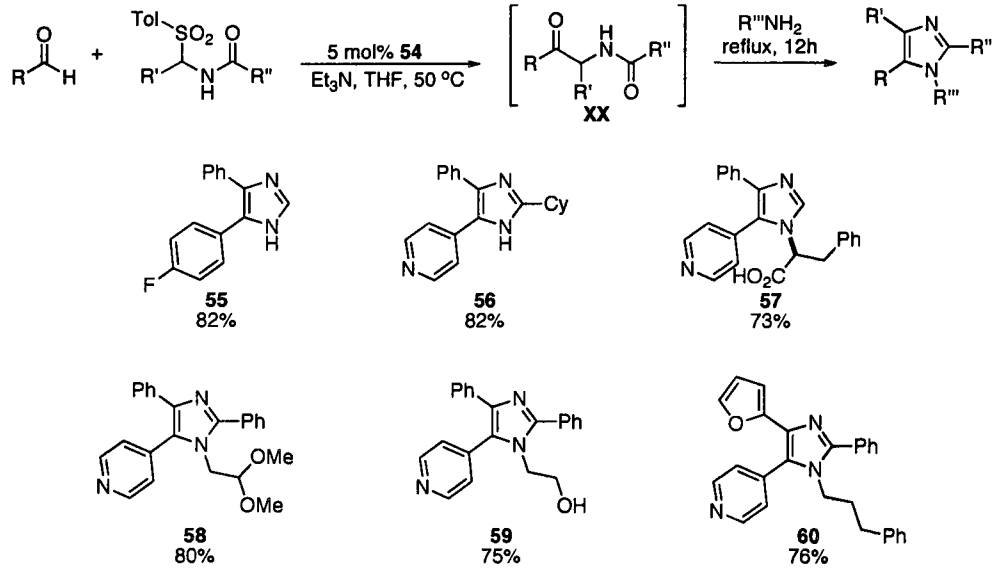
An additional means of performing a selective cross-benzoin was reported in 2001 when Murry, Frantz, and co-workers expanded benzoin methodology to include trapping of acyl imines **XIX** formed *in situ* (Scheme 7).[53] The authors chose to use α-amido sulfones due to their stability and the relative ease of acyl imine liberation. The parent reaction combines pyridine 4-carboxaldehyde **51** and tosylamide **52** in 98% yield in the presence of pre-catalyst **54** and triethylamine (Scheme 7). This method accommodates aryl aldehydes with both electron-deficient and electron-rich aryl substitutents. Acetaldehyde is also a competent coupling partner, providing the corresponding amido ketone in 62% yield. Acyl substitution of the tosyl amide varies to include hydrogen, methyl, *tert*-butoxy, and phenyl producing the desired α-amido

ketones in moderate to high yields. Expansion of this methodology to synthesize di- and tri-substituted imidazoles was reported by Murry, Frantz, and co-workers (Scheme 8).[54]

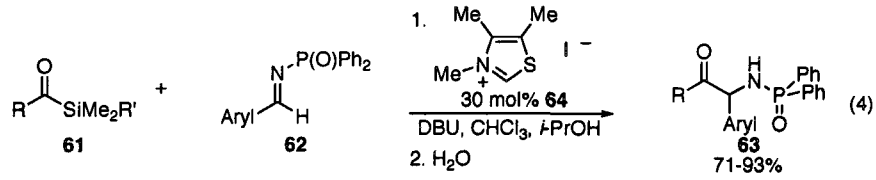
Scheme 7



Scheme 8

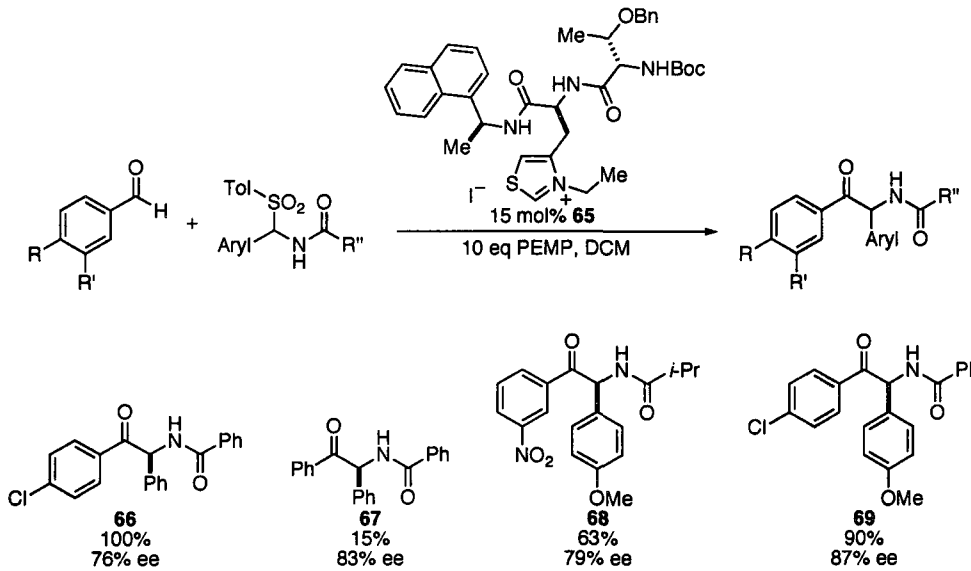


Taking advantage of the acyl silane and imine methodologies, Scheidt and co-workers illustrated the use of acyl silanes **61** and *N*-diarylphosphinoylimines **62** to form α-amino ketones **63** (eq. 4).[55] Utilizing thiazolium pre-catalyst **64**, a variety of acyl silanes, both alkyl and aryl, can be coupled efficiently. The reaction conditions are tolerant of various aryl substitutions, providing high yields.



Miller and co-workers reported the use of thiazolylalanine-derived catalyst **65** to render the aldehyde-imine cross-coupling enantioselective.[56] The authors comment on the time sensitivity of this transformation and found that racemization occurs when the reaction goes to complete conversion. Electron-deficient aldehydes are the most efficient coupling partners for various tosylamides leading to the corresponding products **66**, **68**, **69** (Scheme 9).

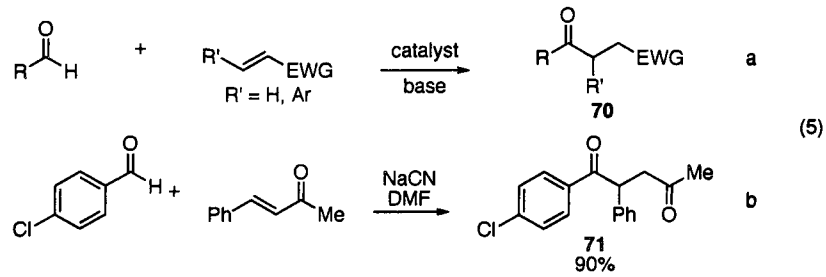
Scheme 9



1.4 Stetter Reaction

Stetter expanded Umpolung reactivity to include the addition of acyl anion equivalents to α,β-unsaturated acceptors to afford 1,4-dicarbonyls (eq. 5a).[57-60] Utilizing cyanide or thiazolylidene carbenes as catalysts, Stetter showed that a variety of aromatic

and aliphatic aldehydes act as competent nucleophilic coupling partners with a wide range of α,β-unsaturated ketones, esters, and nitriles.[61] The ability to bring two different electrophilic partners together and form a new carbon—carbon bond enhances the potential utility of this transformation. When R′ = H, the reaction is quite versatile and provides high yields of **70**. Extensive work by Stetter and others in the development of this reaction revealed that the presence of a β-substituent on the Michael acceptor is a major limitation of this methodology; generally speaking, only the most activated Michael acceptors result in synthetically useful yields (eq. 5b). It has been shown that the reaction time can be decreased significantly with microwave irradiation.[62] Also, aldehydes can add to chalcone derivatives on solid support in moderate yields.[63]

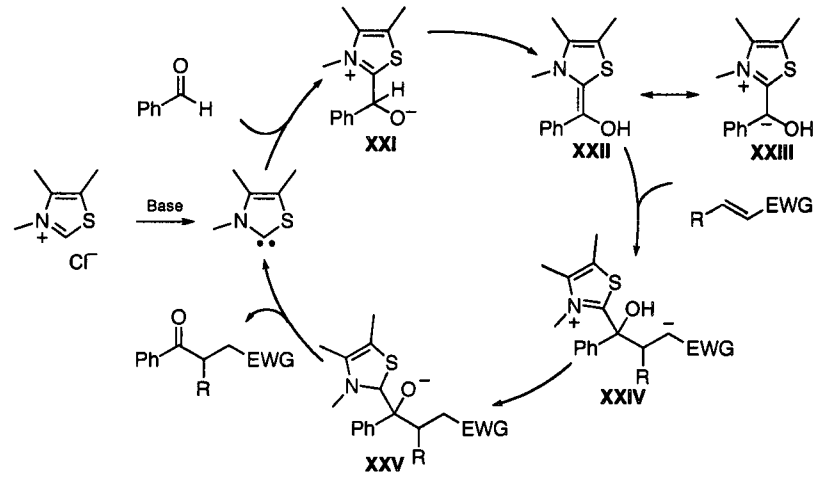


(5)

1.4.1 Mechanism

Since mechanistic studies modeling the Stetter reaction have not yet been reported, the proposed mechanism is based on that elucidated by Breslow for the thiazolium catalyzed benzoin reaction (Scheme 10). The carbene, formed *in situ* by deprotonation of the corresponding azolium salt, adds to the aldehyde to form **XXI**, which undergoes proton transfer to form the acyl anion equivalent **XXIII**. Subsequent attack into the Michael acceptor forms a new carbon—carbon bond **XXIV** and is followed by a second proton transfer. Finally, tetrahedral intermediate **XXV** collapses to form the ketone, accompanied by liberation of active catalyst.

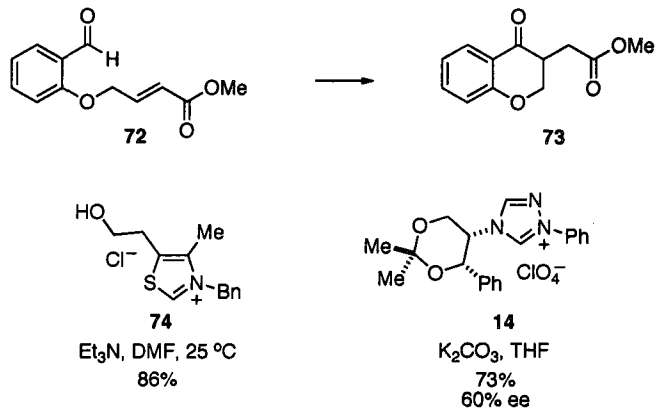
Scheme 10



1.4.2 Intramolecular Stetter Reaction

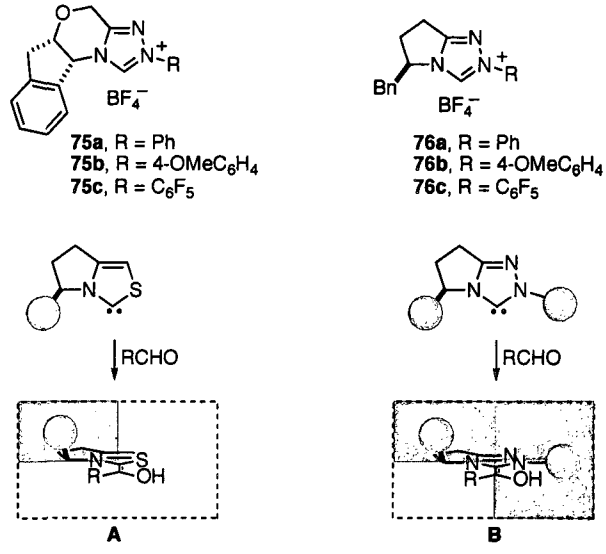
Almost 20 years after the initial report of the Stetter reaction, Ciganek reported an intramolecular variant of the Stetter reaction in 1995 with thiazolium pre-catalyst **74** providing chromanone **73** in 86% yield (Scheme 11).[64] This intramolecular substrate **72** has become the benchmark for testing the efficiency of new catalysts. Enders and co-workers illustrated the first asymmetric variant of the intramolecular Stetter reaction in 1996 utilizing chiral triazolinylidene pre-catalyst **14**.[65] Despite moderate selectivity, the implementation of a chiral triazolinylidene carbene in the Stetter reaction laid the foundation for future work.

Scheme 11



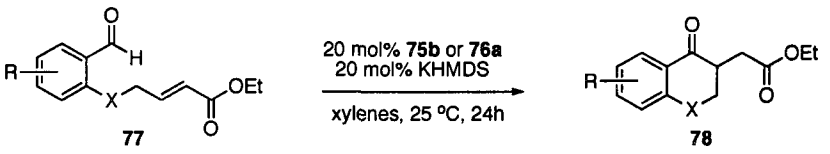
In 2002, Rovis and co-workers developed a series of triazolium pre-catalysts, **75** and **76**, and reported a highly enantioselective intramolecular Stetter reaction.[66] These structures bear a fused-ring system in order to restrict rotation, taking advantage of the concept first introduced by Leeper and Rawal, and further provide the ability to add steric bulk on both sides of the reacting site, blocking three of the four quadrants (Scheme 12, contrast Model **A** vs Model **B**).[67]

Scheme 12



These catalysts induce enantioselectivities in the resulting chromanones and derivatives **78** in up to 97% ee (Table 5). A variety of heteroatom linkers on the aldehyde tether are compatible under the reaction conditions allowing for the synthesis of a variety of desired products in high yields and enantioselectivities.

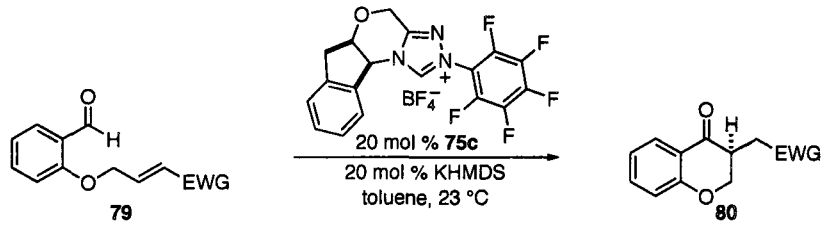
Table 5

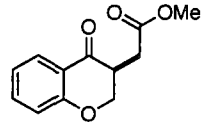
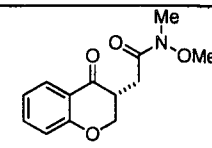
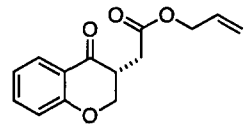
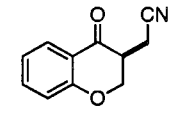
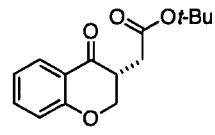
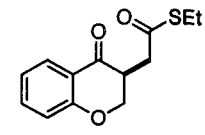
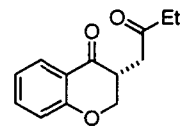
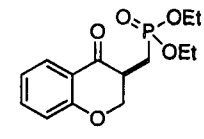
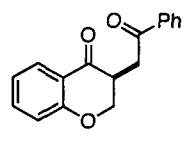
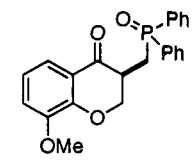


entry	78	X	R	catalyst	yield (%)	ee (%)
1	**a**	O	H	**75b**	94	94
2	**b**	CH_2	H	**76a**	90	92
3	**c**	O	2-Me	**75b**	80	97
4	**d**	S	H	**75b**	63	96
5	**e**	NMe	H	**75b**	64	82

A wide range of α,β-unsaturated acceptors work well under standard reaction conditions with pre-catalyst **75c** (Table 6). Acceptors include α,β-unsaturated esters, amides, alkyl ketones, and phosphine oxides, many of which provide the products in greater than 90% ee.[68,69] α,β-Unsaturated phenyl ketones, nitriles, and thioesters also work, albeit with lower enantioselectivity. The scope has been extended to include a variety of vinyl phosphonate precursors providing good chemical yields and moderate to high enantioselectivity (entries 9 and 10).

Table 6

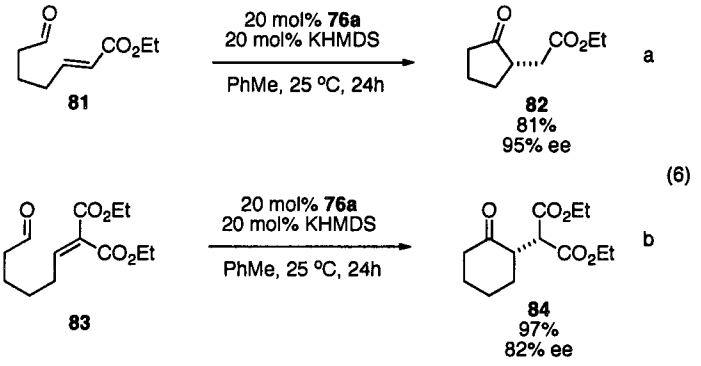


entry	80	product	yield (%)	ee (%)	entry	80	product	yield (%)	ee (%)
1	a		94	95	6[a]	f		94	92
2[a]	b		94	93	7	g		80	78
3[a]	c		94	97	8	h		85	70
4[a]	d		94	92	9	i		65	80
5	e		94	78	10	j		75	93

[a] Ent-**75c** used as pre-catalyst

Aliphatic substrates also perform well, forming five membered rings in good yield and high enantioselectivity (eq. 6a). Typical Michael acceptors, however, are not sufficiently electrophilic to induce cyclization to form six-membered aliphatic rings. In order to effect this cyclization, use of a more electrophilic Michael acceptor, such as alkylidene malonate **83**, was required (eq. 6b).[70] The difference in reactivity is presumably due to the extra conformational freedom of the aliphatic linker compared to

the fused aromatic linker of substrate **79** coupled with potential competing non-productive pathways.



Utilizing prochiral α,α-disubstituted Michael acceptors, the Stetter reaction catalyzed by **76a** has proven to be both enantio- and diastereoselective, allowing control of the formation of contiguous stereocenters (eq. 7).[71] It is noteworthy that a substantial increase in diastereoselectivity is observed, from 3:1 to 15:1, when HMDS, the conjugate acid formed upon pre-catalyst deprotonation, is removed from the reaction vessel. Reproducible results and comparable enantioselectivities are observed with free carbenes; for example, free carbene **95** provides **94** in 15:1 diastereoselectivity. The reaction scope is quite general and tolerates both aromatic and aliphatic aldehydes (Table 7).

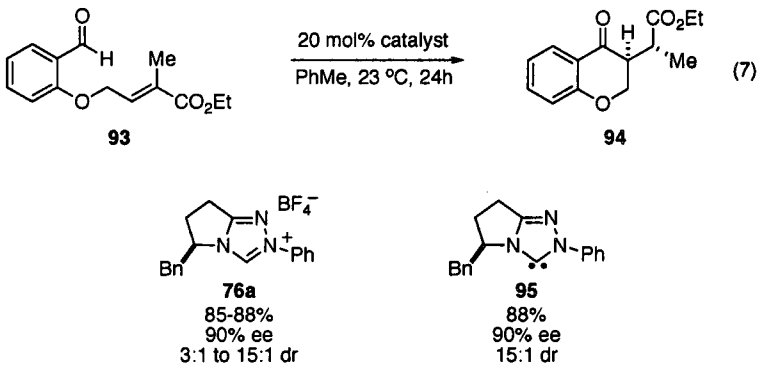
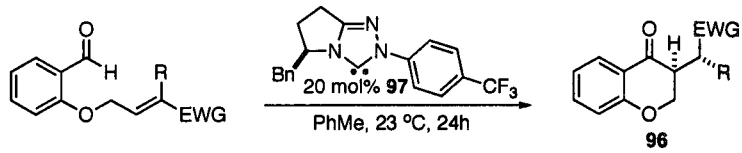
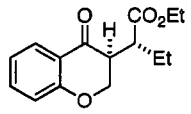
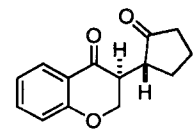
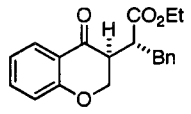
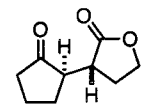
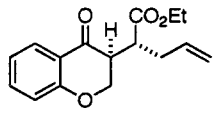
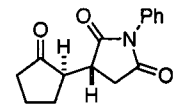


Table 7



entry	96	product	yield (%)	ee (%)	dr	entry	96	product	yield (%)	ee (%)	dr
1	a		95	92	35:1	4	d		80	95	18:1
2	b		80	84	20:1	5	e		94	99	50:1
3	c		95	83	13:1	6	f		80	88	15:1

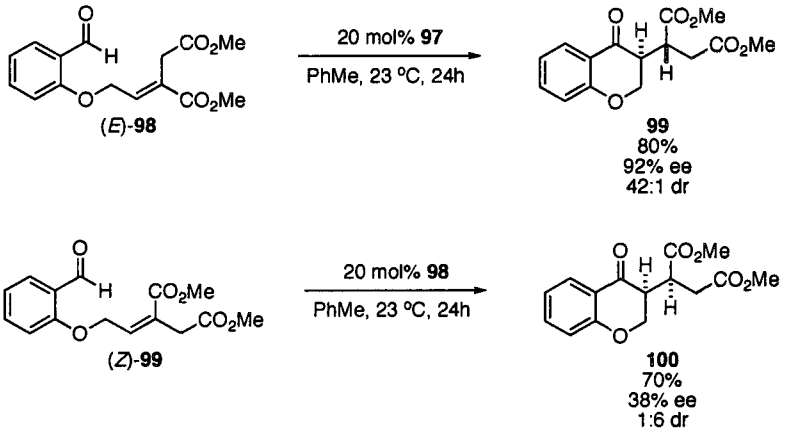
The observed diastereoselectivity of the protonation event may be explained by Model **C** (Scheme 13). In Model **C**, an intermolecular proton transfer would yield the minor diastereomer. Alternatively, the proton transfer may be intramolecular and occur from the more sterically-hindered face of the enolate, providing **D**.

Scheme 13

This mechanistic hypothesis was tested with experiments involving a pair of substrates differing only in olefin geometry about the α,β-unsaturated ester. If the assumption that proton transfer occurs faster than the bond rotation of converting **C** to **D** is valid then the (*E*)- and (*Z*)-isomers are expected to produce opposite diastereomers. In

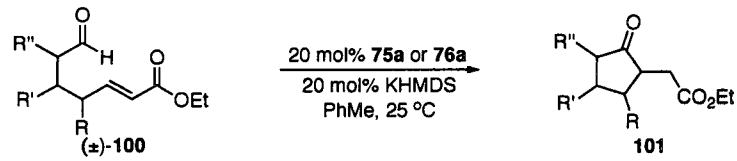
the event, (*E*)-**98** provides 42:1 dr while (*Z*)-**98** provides 1:6 dr favoring the opposite diastereomer (Scheme 14).

Scheme 14



The influence of stereocenters in the backbone has been investigated.[72] A racemic substrate **100** was subjected to standard Stetter reaction conditions leading to disubstituted cyclopentanones **101**. The reaction provided both *cis* and *trans* diastereomers in high enantiomeric excess but with very poor diastereoselectivity (Table 8). Adding steric bulk did not significantly change the outcome of the reaction (entry 2). The same trend was observed with substitution at the 3-position (entry 3 and 4). Alternatively, when substitution at 2-position was present there was little catalyst control over the diastereoselectivity and the *trans*-cyclopentanone was formed selectively in good yield (entry 5). Pre-existing stereocenters had little to no effect on the diastereoselectivity of a Stetter cyclization unless that center was alpha to the aldehyde, in which case a diminished enantioselectivity was observed (entry 5).

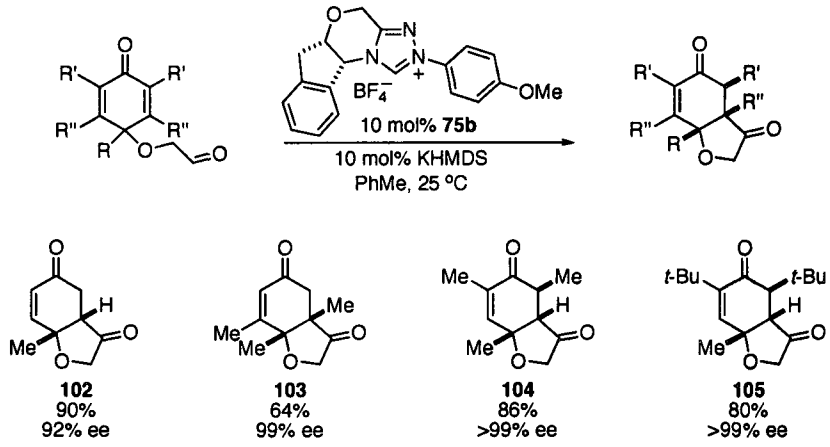
Table 8



entry	102	R	R'	R''	catalyst	yield (%)	*cis:trans*	ee (%)
1	**a**	Me	H	H	**75a**	90	50:50	95/90
2	**b**	*i*-Pr	H	H	**76a**	95	51:49	98/94
3	**c**	H	Me	H	**75a**	97	50:50	94/98
4	**d**	H	Ph	H	**75a**	96	50:50	96/98
5	**e**	H	H	Bn	**75a**	95	85:15	<5/<5

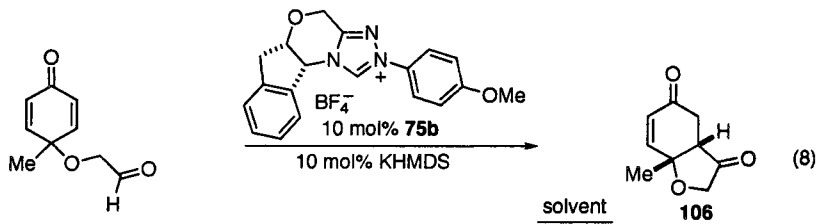
Rovis and Liu accomplished the desymmetrization of cyclohexadienones by using triazolinylidene carbene **75b** (Scheme 15).[73,74] Multiple hydrobenzofuranones **102-105** were synthesized in good yields and excellent enantio- and diastereoselectivity. Generation of three contiguous stereocenters was be achieved in >99% ee and 80% yield.

Scheme 15



In this report the authors describe a surprising solvent effect on enantioselectivities. Alcoholic solvents afford the opposite enantiomer using the same

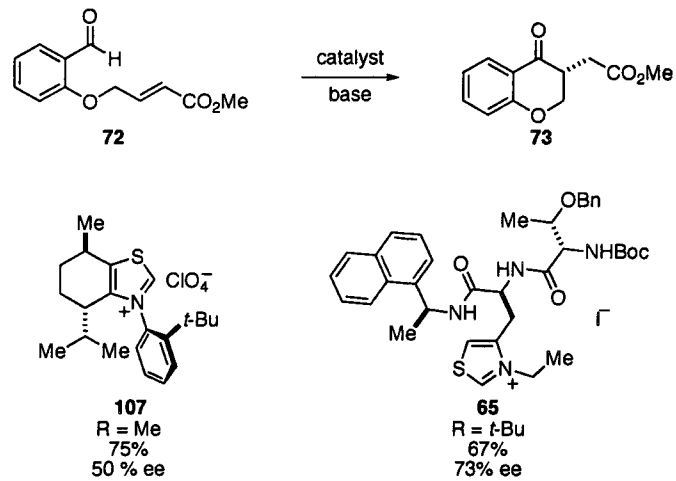
enantiomeric series of catalyst (eq. 8). This profound effect is presumably due to hydrogen bonding in the transition state on the nucleophilic enol and/or the carbonyl acceptor.



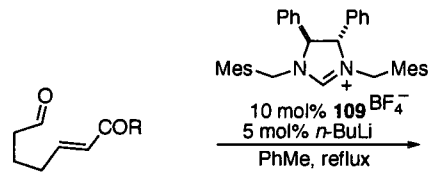
solvent	106
PhMe	90%, 88% ee
i-PrOH	65%, -63% ee

In 2004 and 2005, respectively, Bach and Miller independently described the use of chiral thiazolium salts as pre-catalysts for the enantioselective intramolecular Stetter reaction. Bach and co-workers employed an axially chiral *N*-arylthiazolium salt **107** to obtain chromanone **73** in 75% yield and 50% ee (Scheme 16).[75] Miller and co-workers found that thiazolium salts embedded in a peptide backbone **65** could impart modest enantioselectivity on the intramolecular Stetter reaction.[76] In 2006, Tomioka reported a C_2-symmetric imidazolinylidene **109** that is also effective in the aliphatic Stetter reaction, providing three examples in moderate enantioselectivities (Scheme 17).[77]

Scheme 16



Scheme 17

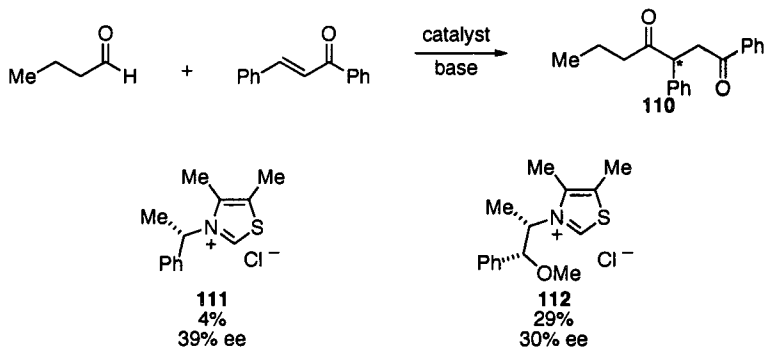


108	R	yield (%)	ee (%)
a	OMe	74	76
b	*t*-BuO	59	80
c	Ph	33	63

1.4.3 Intermolecular Stetter Reaction

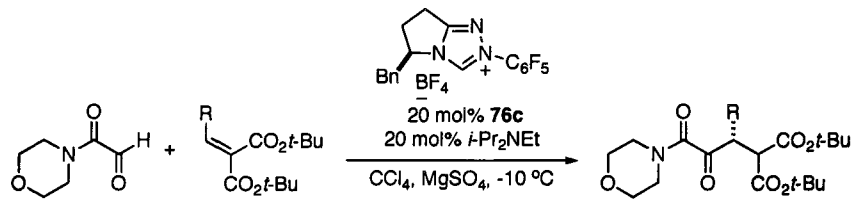
Although catalysts and reaction protocols are well-established for the enantioselective intramolecular Stetter reaction, asymmetric intermolecular Stetter products are much more difficult to obtain using known methodologies. A report by Enders and co-workers described the first asymmetric intermolecular Stetter reaction utilizing *n*-butanal and chalcone .[5] When thiazolium salt **111** is used in this system the reaction proceeds in 39% ee, albeit in 4% yield of **110**. The authors comment that both thiazolium and triazolium pre-catalysts perform poorly. The yield was increased to 29% yield with thiazolium pre-catalyst **115** although a loss in enantioselectivity was observed (Scheme 18).[78]

Scheme 18



The Rovis group has built on these early studies by Enders and co-workers to induce a catalytic asymmetric intermolecular Stetter reaction.[79] Various β-substituted alkylidenemalonates **114** undergo the Stetter reaction with glyoxamides **113** in good yields and with high asymmetric induction (Table 9). The optimal condition for the reaction to provide the highest combination of yield and enantioselectivity resulted when low temperatures and 1 equiv of Hünig's base were used.

Table 9

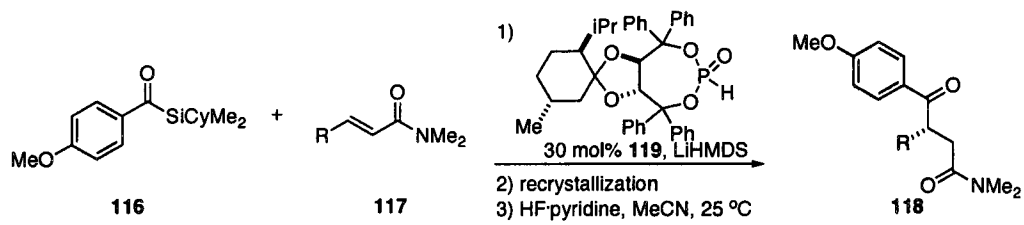


113 **114** **115**

entry	115	R	yield (%)	ee (%)
1	**a**	Et	84	90
2	**b**	Pr	83	90
3	**c**	CH_2CH_2Ph	70	88
4	**d**	$CH_2CH_2CH_2Cl$	84	81
5	**e**		97	89

In a related process, Johnson and co-workers have developed an asymmetric metallophosphite-catalyzed intermolecular Stetter-like reaction employing acyl silanes.[80,81] Acyl silanes are effective aldehyde surrogates which are capable of forming an acyl anion equivalent after a [1,2]-Brook rearrangement. The authors have taken advantage of this concept to induce the catalytic enantioselective synthesis of 1,4-dicarbonyls **118** in 89-97% ee and good chemical yields for α,β-unsaturated amides (Table 10). Enantioselectivities may be enhanced by recrystallization.

Table 10



116 117 118

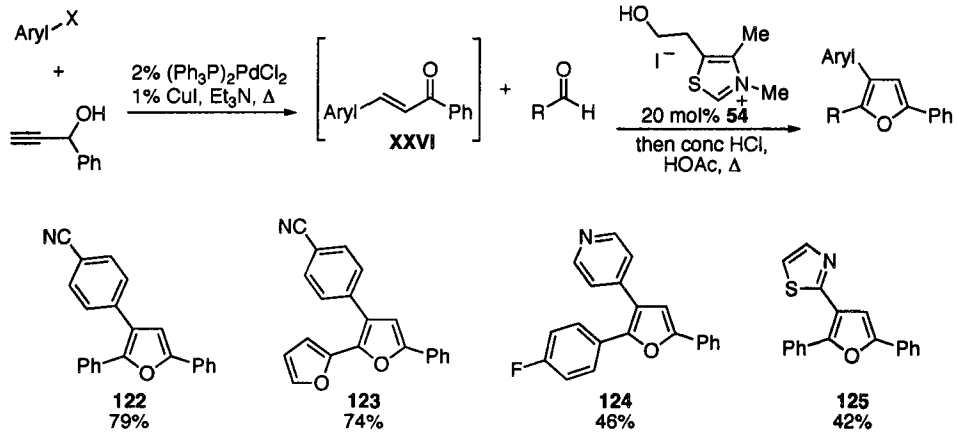
entry	118	R	yield (%)	ee[a] (%)	ee[b] (%)
1	**a**	Ph	68	90	99
2	**b**	3-MePh	67	93	99
3	**c**	4-ClPh	66	95	98
4	**d**	*N*-tosylindol-3-yl	60	97	97
5	**e**	2-naphthyl	66	89	97

a before recyrystallization
b after recrystallization

Scheidt and co-workers should that acyl silanes behave analogously to aldehydes in the Stetter manifold, ultimately forming 1,4-dicarbonyls **120** in yields up to 75%.[82,83]

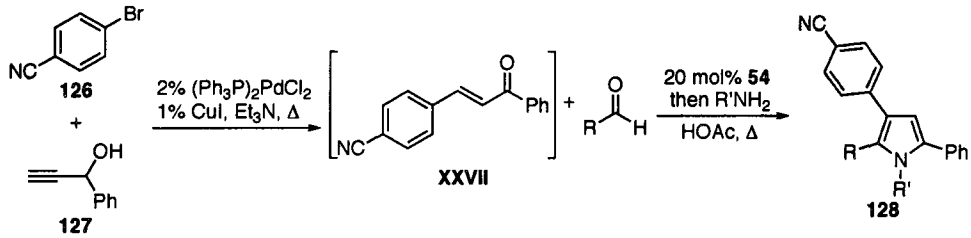
In an extension of traditional Stetter methodology, Müller and co-workers have used the Stetter reaction in a one-pot multicomponent reaction for the synthesis of furans and pyrroles (Scheme 19).[84,85] The α,β-unsaturated ketone **XXVI** is formed *in situ* and undergoes a Stetter reaction followed by a Paal-Knorr condensation.

Scheme 19



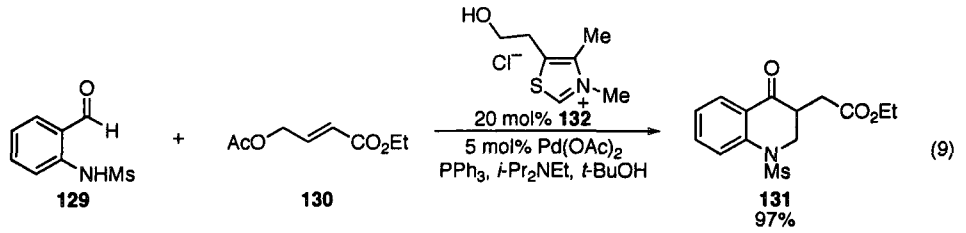
Pyrrole syntheses were more general than furan syntheses. Scheidt and co-workers have subsequently shown that acyl silanes may again be used as aldehyde surrogates in this protocol (Table 11).[82,86]

Table 11



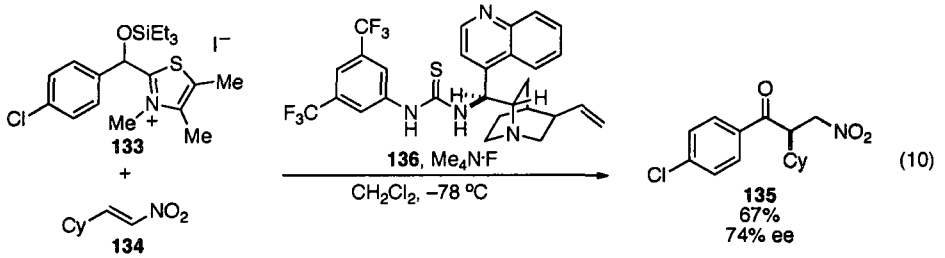
entry	128	R	R'	yield (%)	entry	128	R	R'	yield (%)
1	**a**	Ph	H	70	5	**e**	Ph	Bn	60
2	**b**	4-$OMeC_6H_4$	H	60	6	**f**	2-furyl	Bn	55
3	**c**	*n*-pentyl	H	59	7	**g**	Ph	CH_2CO_2Et	54
4	**d**	$(CH_2)_5OH$	H	53	8	**h**	Ph	CH_2CH_2OH	57

Recently, Hamada and co-workers utilized the Stetter reaction in a cascade sequence to produce dihydroquinolines, of type **131**, in excellent yields (eq. 9).[87] Although the scope of this reaction is limited to unsubstituted aryl aldehydes, the compatibility of the carbene and palladium (0) catalysis is noteworthy.



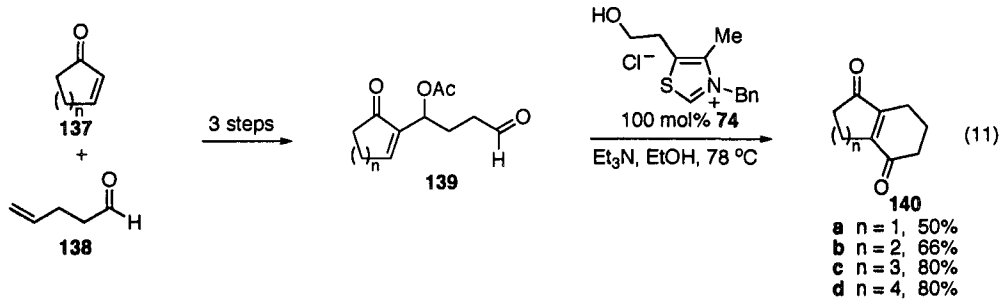
129 + 130 → 131, 97% (9)

Scheidt and co-workers have reported the application of silyl-protected thiazolium carbinols as stoichiometric carbonyl anions for the intermolecular acylation of nitroalkenes.[88] Although predominantly a discussion of racemic chemistry, a singular example illustrates that the newly formed stereocenter may be controlled by the addition of an equivalent of a chiral thiourea **136** with the desired product **135** formed in 74% ee (eq. 10).



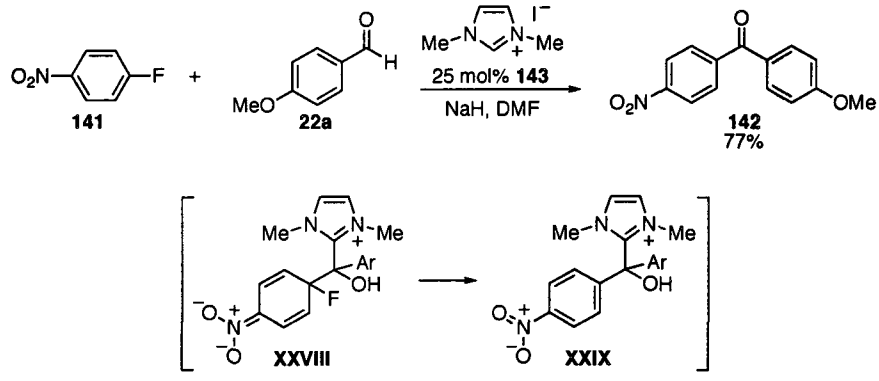
(10)

Markó and co-workers utilized the Stetter reaction in the synthesis of bicycloenediones, which proceeded in moderate yields using stoichiometric amounts of thiazolium pre-catalyst **74** (eq. 11).[89] Morita-Baylis-Hillman adducts **139** were formed in three steps from commercially available starting materials 4-pentenal **138** and the corresponding cyclic enones **137**. The carbene induces a Stetter reaction followed by acetate elimination and alkene isomerization into conjugation. The best results were obtained with **139c** and **139d** providing 1,4-dicarbonyls **140c** and **140d**, respectively, in 80% yield.



Suzuki and co-workers achieved aromatic substitution of fluoroarenes with a variety of aldehydes in good yields.[90,91] Imidazolilydene carbene formed from **143** catalyzed the reaction between 4-methoxybenzaldehyde **22a** and 4-fluoronitrobezene **141** to provide ketone **142** in 77% yield (Scheme 20). Replacement of the nitro group with cyano or benzoyl resulted in low yields of the corresponding ketones. The authors propose formation of the acyl anion equivalent and subsequent addition to the aromatic ring by a Stetter-like process forming **XXVIII**, followed by loss of fluoride anion to form **XXIX**.

Scheme 20

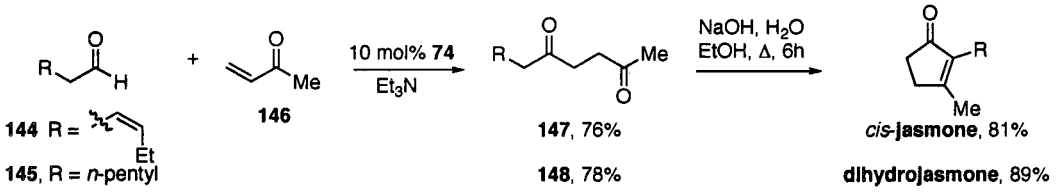


1.4.4 Applications in Total Synthesis

The first natural product synthesis that utilized the Stetter reaction was reported by Stetter and Kuhlmann in 1975 in an approach to *cis*-jasmone and dihydrojasmone

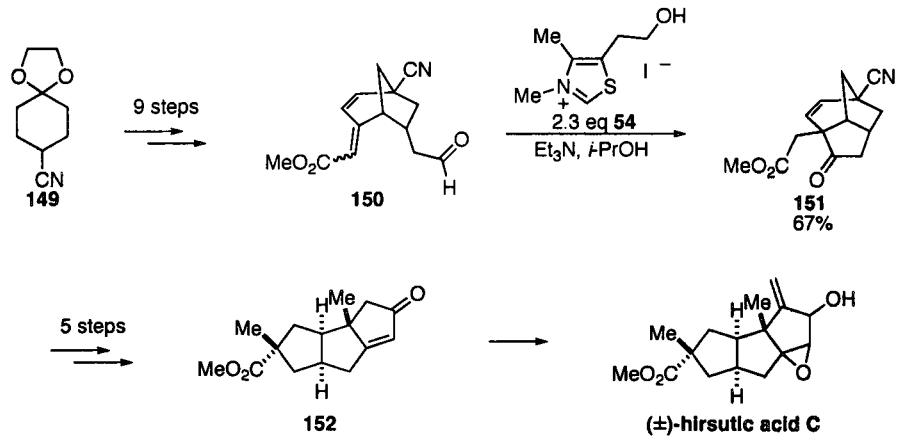
(Scheme 21).[92] Thiazolium pre-catalyst **74** was effective in catalytically generating the acyl anion equivalent with aldehydes **144** and **145**, then adding to 3-buten-2-one **146** in good yield. Cyclization followed by dehydration gives *cis*-jasmone and dihydrojasmone in 62% and 69% yield, respectively, over two steps. Similarly, Galopin coupled 3-buten-2-one and isovaleraldehyde in the synthesis of (±)-*trans*-sabinene hydrate.[93]

Scheme 21



Trost and co-workers relied on the Michael and the Stetter reaction to set the relative stereochemistry for the core of hirsutic acid C (Scheme 22).[94] The Stetter reaction was accomplished in 67% yield with 2.3 eq of 3,4-dimethyl-5-(2'-hydroxyethyl) thiazolium iodide **54** and 50 eq of triethylamine.

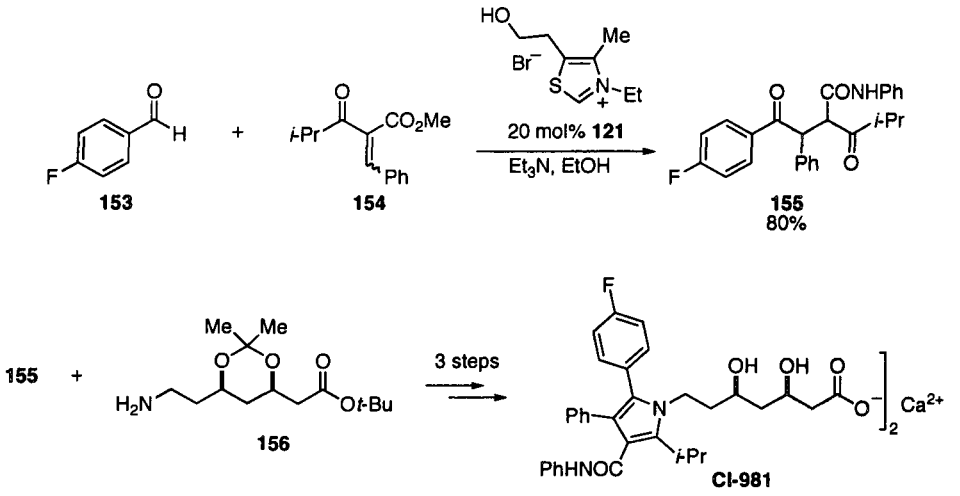
Scheme 22



The Stetter reaction is an important tool in the synthesis of CI-981, also known as LIPITOR®.[95] Roth and co-workers demonstrate the ability of commercially available

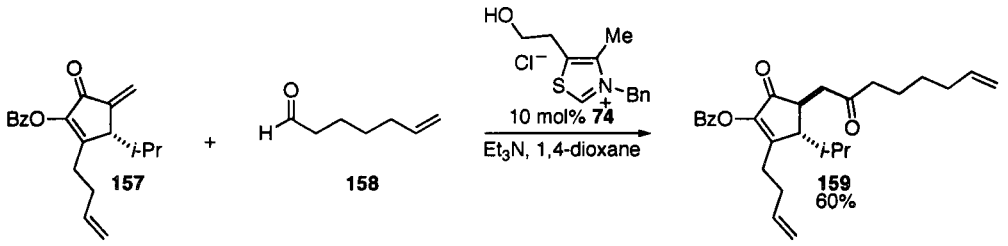
starting materials **153** and **154** to couple in the presence of 20 mol% thiazolium pre-catalyst **121** (Scheme 23).[96,97] Amide **155** was obtained in 80% yield and allowed for the convergent synthesis of CI-981 in nine steps.

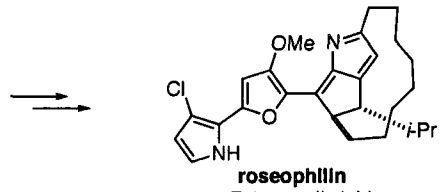
Scheme 23



In the late 1990's, Tius and co-workers described a formal total synthesis of roseophilin.[98,99] The Stetter reaction was well suited for the coupling of partners **157** and **158** in the presence of 3-benzyl-5-(hydroxyethyl)-4-methyl thiazolium chloride (Scheme 24).

Scheme 24

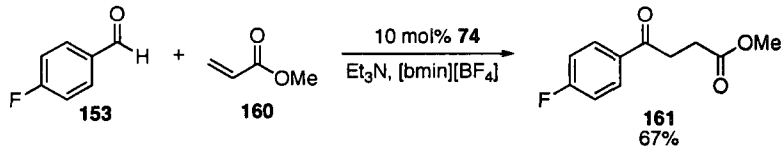


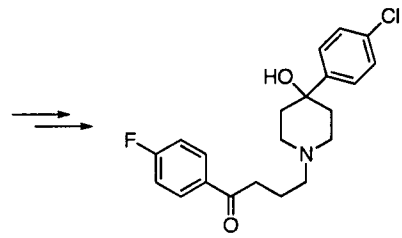


roseophilin
7% overall yield

In the process of developing the Stetter reaction in ionic liquids, Grée and co-workers applied their methodology to the synthesis of haloperidol (Scheme 25).[100] A variety of aromatic aldehydes react with methyl acrylate **160** when butylmethylimidazolium tetrafluoroborate [bmim][BF_4] is used as solvent. In the synthesis of haloperidol, electron-deficient aldehyde **153** was subjected to standard reaction conditions with **160** to provide **161** in good yield.

Scheme 25

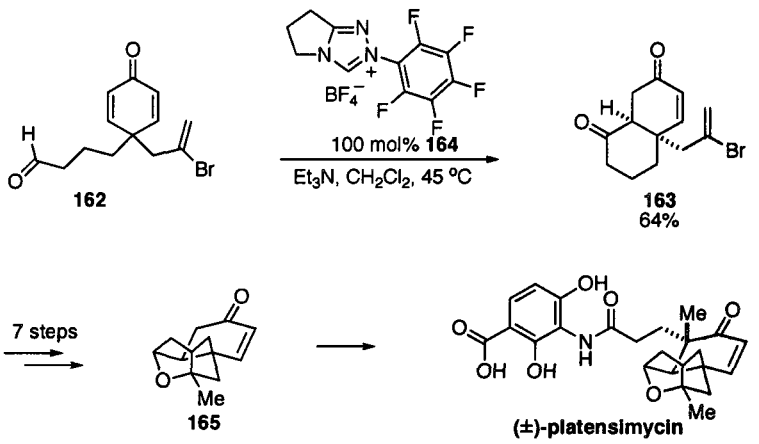




haloperidol

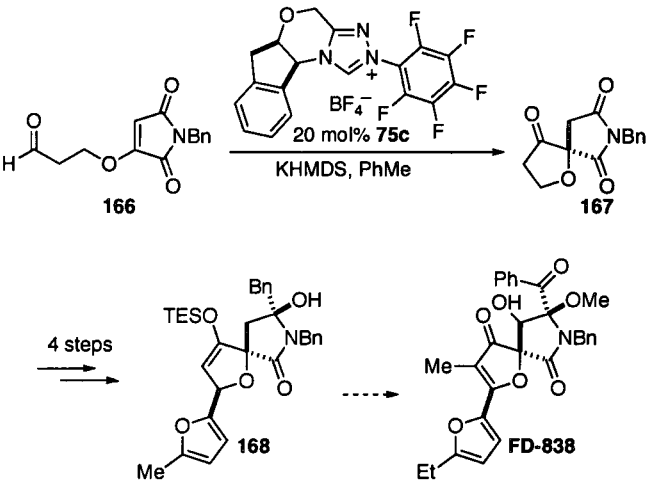
Nicolaou and co-workers recently published a formal synthesis of (±)-platensimycin utilizing Stetter methodology.[101] Aldehyde **162** was treated with achiral *N*-pentafluorophenyl pre-catalyst **164** and readily underwent cyclization to yield **163** as a single diastereomer (Scheme 26). After an additional seven steps late stage intermediate **165** was formed to complete the formal synthesis.

Scheme 26



Rovis and Orellana have reported efforts toward the synthesis of FD-838 (Scheme 27).[102] In four steps, the Stetter substrate **166** was obtained and underwent cyclization readily with aminoindanol derived pre-catalyst **75c** to produce spirocycle **167** in good yield and 99% ee.

Scheme 27



1. 8 Conclusion

The use of stable nucleophilic carbenes as catalysts for organic transformations has come a long way since Ukai's original demonstration of their efficacy in the benzoin reaction. The last 10 years in particular have seen a tremendous explosion in interest in this area, with new reactivity manifolds having been developed across a range of reaction subtypes. It is clear that with many of these shortcomings remain – functional group compatibility, turnover frequency, turnover number and, naturally, expansion of substrate type. The inherent tunability of these catalysts promises great latitude in overcoming these issues. That, coupled with an increase in new reactivity, from Umpolung type reactivity best exemplified by the benzoin and Stetter reactions to redox catalysis, nucleophilic catalysis and even Morita-Baylis-Hilman reactivity, suggests that nucleophilic carbene catalysts will likely remain useful tools in organic synthesis for the foreseeable future.

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Chapter 2

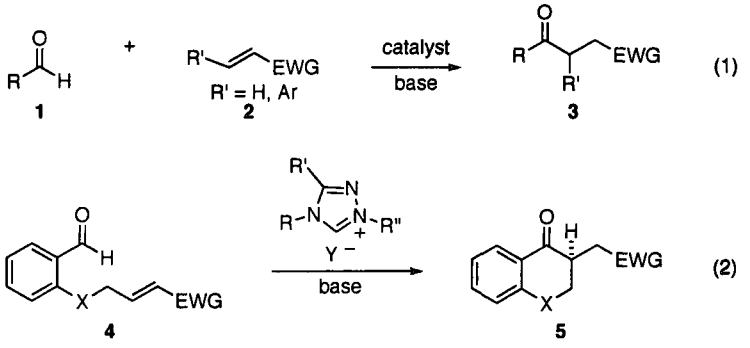
Enantioselective Formation of Quaternary Stereocenters Using the Catalytic Intramolecular Stetter Reaction and an Approach Toward a Two Step Intermolecular Stetter Reaction

2.1 Introduction

Catalytic carbon—carbon bond formation resulting in the creation of a quaternary stereocenter is a useful but challenging process in organic chemistry.[1] In addition to established approaches using chiral auxiliaries,[2] significant progress has been made in recent years developing catalytic methods for the formation of quaternary stereocenters. These methods include the intramolecular Heck reaction,[3] rearrangement of enol carbonates,[4] transition metal-mediated π-allyl chemistry,[5] copper catalyzed S_N2' displacement of allylic leaving groups[6] and conjugate additions of β-keto esters to acrylates,[1b] phase-transfer alkylation of 1-indanones,[7] arylation of ketone enolates,[8] and enantioselective alkylation of tributyl tin enolates catalyzed by Cr(salen)Cl,[9] among others. Most recently, Stoltz and Trost have each reported the deracemization of quaternary stereocenters via Pd-catalyzed decarboxylative allylation of racemic β-ketoesters.[10,11]

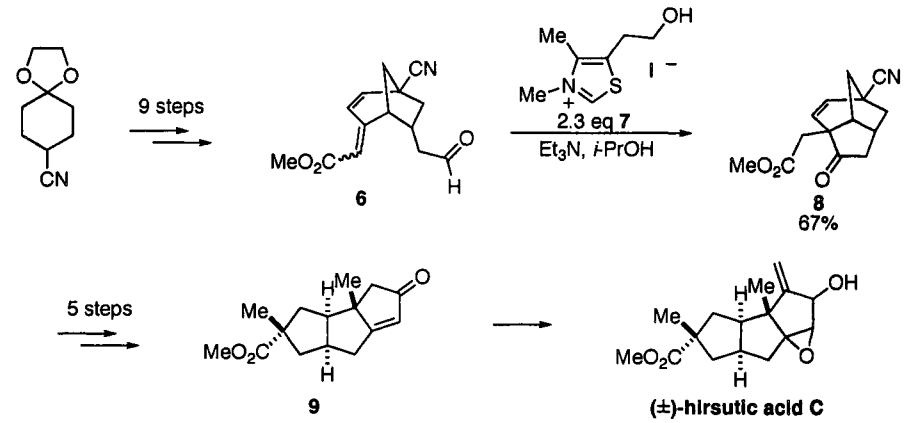
Each of these approaches is useful but limited to a specific substrate scope. We envisioned utilizing the intramolecular Stetter reaction in order to achieve a general method for the formation of quaternary stereocenters. Initial reports by Stetter and coworkers illustrated a lack of reactivity when a β-substituent on the Michael acceptor is present (**2**, R≠H, eq. 1).[12] This limitation of the Stetter methodology was overcome with

the synthesis of triazolinylidene carbenes and the tethering of the Michael acceptor to the aldehyde **4** (eq. 2).[13a, 14]

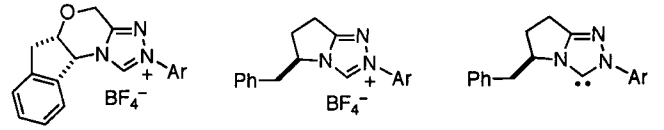


The ability of nucleophilic carbenes to perform well in the presence of a β-substitutent on the Michael acceptor was an important achievement in method development for the formation of quaternary stereocenters. The first example of this type of transformation was reported by Trost and co-workers, in which they employed the Stetter reaction to set the relative stereochemistry for the core of hirsutic acid C (Scheme 1).[15] Although the reaction was carried out with 2.3 eq of 3,4-dimethyl-5-(2'-hydroxyethyl) thiazolium iodide **7** and 50 eq of triethylamine, the Stetter product **8** was formed in 67% yield. This reaction served to highlight the potential complexity of developing a high yielding catalytic enantioselective cyclization via the Stetter reaction. We were confident that by manipulating steric and electronic factors in our reaction conditions, β,β-disubstituted Michael acceptors would be competent electrophilic partners in a catalytic intramolecular Stetter reaction with triazolinylidene carbenes.

Scheme 1



Work in our laboratory has focused on the development of chiral triazolinylidene carbenes, derived from **10**, **11** and **12**.[13] These catalysts are capable of inducing addition of aromatic and aliphatic aldehydes to α,β-unsaturated esters, ketones, and nitriles.[13a,b] My coworker, Mark Kerr, and I have expanded the scope of this reaction to include a variety of heteroatoms tethering the aldehyde and Michael acceptor as well as the generation of five- and six-membered rings in the process of forming quaternary stereocenters in high enantioselectivity.[13c,g]



10a Ar = *p*-MeOC$_6$H$_4$
10b Ar = Ph
10c Ar = C$_6$F$_5$

11a Ar = Ph
11b Ar = *p*-CF$_3$C$_6$H$_4$

12a Ar = Ph
12b Ar = *p*-CF$_3$C$_6$H$_4$

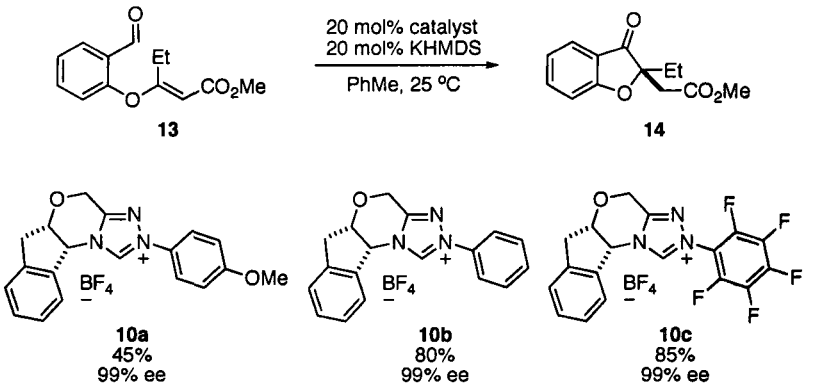
2.2 Tetrasubstituted Stereocenters

Investigation of the formation of quaternary stereocenters began with substrates such as **13** (Scheme 2), prepared via phenol alkylation of the thioacetal of salicylaldehyde, followed by deprotection. Thioether substrates were readily prepared by

reducing thiosalicylic aldehyde with lithium aluminium hydride followed by alkylation of sulfur with substituted alkynoate esters and oxidation to the desired aldehyde.

In the initial report, by Mark Kerr, a brief catalyst screen provided reaction conditions that afforded excellent yields and enantioselectivities of benzofuranone products (Scheme 2).[13c] Reaction of electron-rich *para*-methoxyphenyl-substituted aminoindanol-derived catalyst (**10a**) with **13** provides **14** in 45% yield and excellent enantiomeric excess. Catalyst **10b** provides an increase in yield and retains 99% ee. Pentafluorophenyl substituted catalyst **10c** proved to be the most efficient in terms of yield and enantioselectivity.

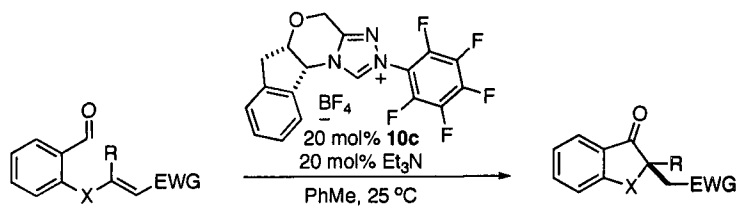
Scheme 2



Using catalyst precursor **10c** we further optimized the reaction conditions by using a mild base, triethylamine, to generate the active catalyst. Having identified an efficient catalyst system that provided desired reactivity with excellent enantioselectivity and yield, we examined the scope of this reaction beginning with substrates that contained aromatic backbones (Table 1). Benzofuranones **14** and **16** were obtained in high yields and enantiomeric excess. Thioethers were also competent substrates and reacted efficiently to provide benzothiophenone products in high yield and enantioselectivities

(entries 4 and 5). Reaction of thioether **17** provided benzothiophenone **18** in 95% yield and 92% ee. A propyl group in the β position was tolerated, providing 54% yield and 87% ee with triethylamine (entry 4). Phenethyl substitution of the thioether substrate afforded **22** in lower yield and 88% ee. A direct comparison between substrates **17** and **23** lead to the conclusion that an increase in steric bulk or electronic differences, *i.e.* ethyl vs. phenyl, suppressed reactivity while having little effect on enantioselectivity. Mark Kerr applied this methodology to an all carbon five-membered ring, which formed in 95% yield and 99% ee (entry 7).[13c] Overall, the intramolecular Stetter reaction tolerated aromatic aldehydes with varied substitution at the β-position of the Michael acceptor and heteroatom tethers.

Table 1. Scope of aromatic substrates



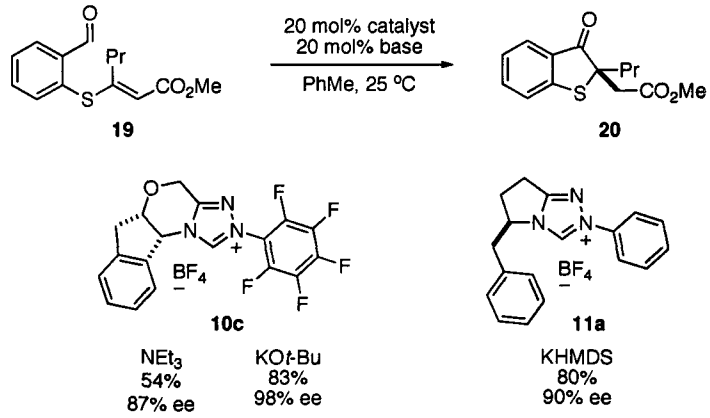
entry	substrate	product[a]	yield (%)	ee (%)[b]
1	X = H **13**	X = H **14**	96	97
2	X = Br **15**	X = Br **16**	92	89
3[c]	**17**	**18**	95	92
4	**19**	**20**	54	87
5	**21**	**22**	33	88
6	**23**	**24**	11	82
7	**25**	**26**	95	99

[a] Absolute configuration assigned by analogy to **18**.
[b] Enantiomeric excess determined by HPLC analysis on chiral stationary phase.
[c] Absolute configuration established by single-crystal X-ray analysis.

The observation that sulfur-containing compounds generally provide cyclized products in lower yields and moderate enantioselectivities prompted an additional screen of reaction conditions. A catalyst screen was performed using thioether **19** (Scheme 3),

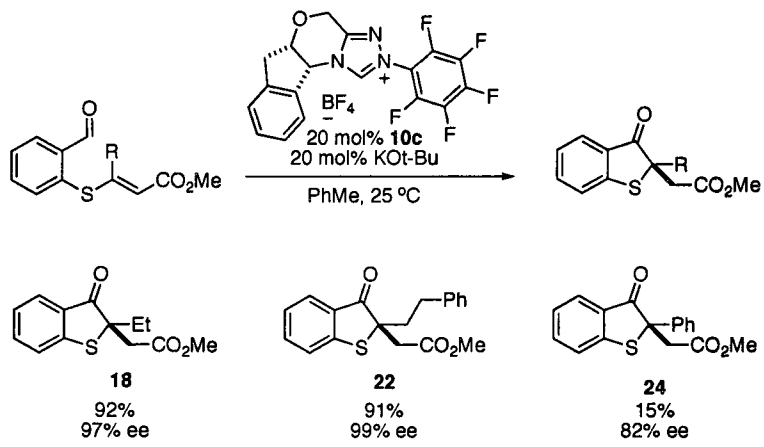
which contains propyl substitution at the β-position of the ester (Scheme 3). The aminoindanol catalyst **10c** and phenylalanine-derived catalyst **11a** afforded opposite enantiomers of the desired product in high selectivity. Exposing **19** to catalyst **11a** provided **20** in similar yield with an increase in enantioselectivity to 90%. Catalyst **10c** was then used with triethylamine but gave **20** in only moderate yield and selectivity. By changing to a bulkier base, potassium *tert*-butoxide, an increase in yield and enantioselectivity was observed.

Scheme 3



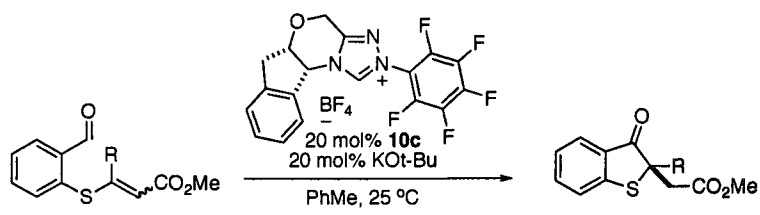
The optimum reaction conditions for thioether-containing substrates were found to be 20 mol % catalyst loading, with 20 mol % potassium *tert*-butoxide, in toluene at 25 °C (Scheme 4). Increased yields and enantioselectivities were obtained with potassium *tert*-butoxide with every sulfur-containing substrate, with the exception of **24** (Scheme 4). A slight increase in reactivity was observed with **23** while the enantiomeric excess remained at 82%. The reluctance of this substrate to participate in this reaction was ascribed to steric crowding.

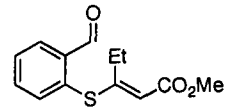
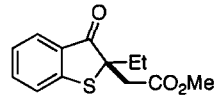
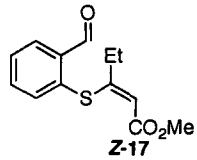
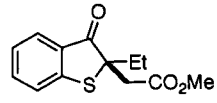
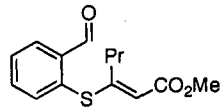
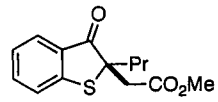
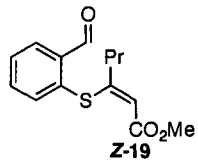
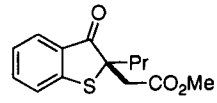
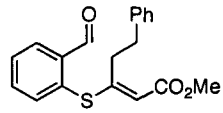
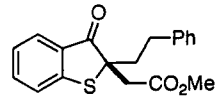
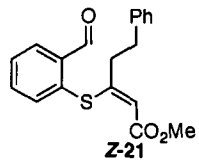
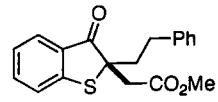
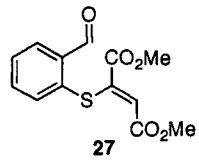
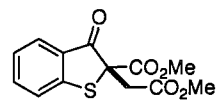
Scheme 4



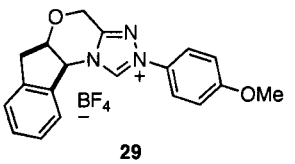
To further investigate the subtleties that dictate yield and enantioselectivity, we synthesized both alkene isomers of the Michael acceptors. The use of either (*E*)- or (*Z*)-isomer resulted in good yields and enantioselectivities. Thioether ***E*-17** gave cyclized benzothiophenone in 90% yield and 97% ee (Table 2). The reaction of the corresponding ***Z*-17** gave **18** in 89% yield and 86% ee under the same reaction conditions. The (*Z*)-isomer of the highly electrophilic *bis*-ester **27** provided cyclized product **28** in 80% yield and 90% ee when using catalyst **29**. Similar yields and lower enantioselectivities were also observed for the (*Z*)-isomer of propyl- and phenethyl- substituted Michael acceptors. Use of *(E)*-isomers provided uniformly higher yields and enantioselectivities and provided the impetus for us to focus on *(E)*-isomers for the majority of the study.

Table 2



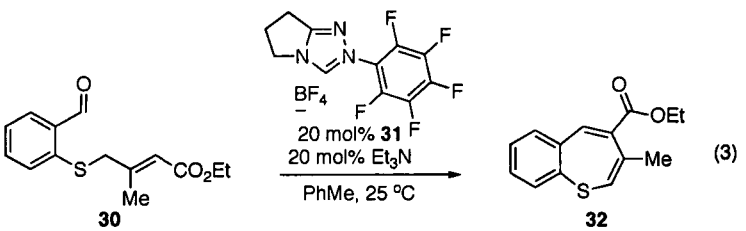
entry	substrate	product	yield (%)	ee (%)
1	 ***E*-17**	 **18**	90	97
2	 ***Z*-17**	 **18**	89	86
3	 ***E*-19**	 **20**	83	98
4	 ***Z*-19**	 **20**	85	89
5	 ***E*-21**	 **22**	91	99
6	 ***Z*-21**	 **22**	92	84
7[a]	 **27**	 **28**	85	90

a. Reaction with catalyst **29**



29

Although formation of five-membered rings and concomitant creation of quaternary stereocenters is very efficient, formation of the corresponding six-membered rings remains a challenge. When **30** is treated with achiral triazolium salt **31** and triethylamine, seven membered product **32** formed (eq. 3). This unexpected product presumably results from deprotonation γ to the ester moiety and subsequent addition into the aldehyde followed by dehydration.

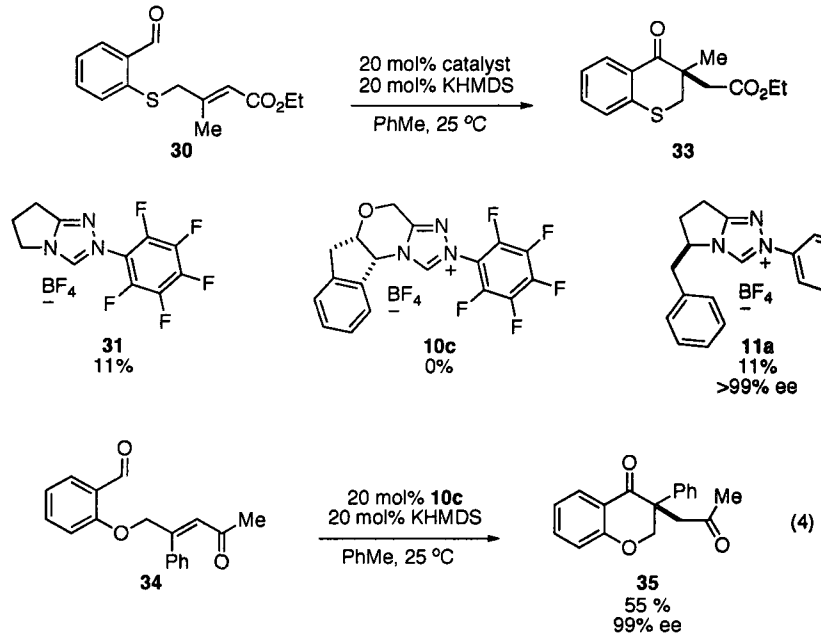


30 32 (3)

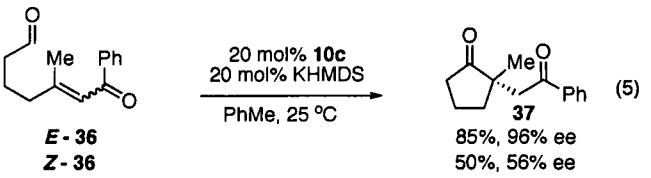
Changing the base from triethylamine to KHMDS induced cyclization of **30** to afford the desired six membered ring **33**. Treatment of thioether **30** under the standard reaction conditions (20 mol % azolium salt and 20 mol % KHMDS in toluene) with achiral catalyst **31** affords cyclized product in 11% yield (Scheme 5). Interestingly, catalyst choice is critical. Upon exposure of **30** to the same reaction conditions with chiral catalyst **10c** no desired product was formed and starting material was recovered. After investigating the most reactive catalysts, we found that catalyst **11a** provides **33** in 11% yield and >99% ee. As we have noted a higher reactivity associated with ketones vs. esters, we decided to investigate the six membered ring formation utilizing a ketone Michael acceptor. Similarly, Mark Kerr found that, by exposing methyl ketone **34**

containing phenyl substitution to our reaction conditions, the desired product was formed in 55% yield and 99% ee (eq. 4).[13c]

Scheme 5

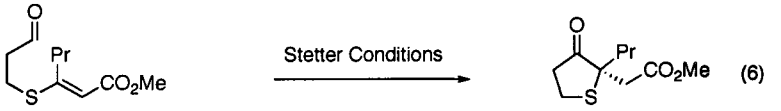


This method can be extended to substrates with aliphatic backbones, although aliphatic substrates pose a particular challenge, as they may undergo competing aldol reactions.[13a] Mark Kerr noticed that when using substrates with aliphatic backbones, enantioselectivity was affected by the geometry of the alkene in the starting material, as was the case in earlier aromatic substrates.[13c] The optimized reaction conditions were 20 mol % catalyst, and 20 mol % KHMDS in toluene. Subjecting ***E*-36** to the reaction conditions with catalyst **10c** gave cyclopentanone in 85% yield and 96% ee (eq. 5). Cyclization proceeded in lower yield and enantioselectivity for ***Z*-36**.



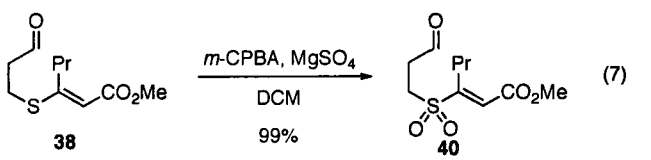
E-36
Z-36

Aldehyde **38** was subjected to a variety of Stetter reaction conditions (eq. 6). All previously investigated reaction conditions failed to provide cyclized product **39**. This observation is consistent with the work of Mark Kerr, who found a loss of reactivity with oxygen-tethered aliphatic substrates lacking a ketone as the activating group.[13c]



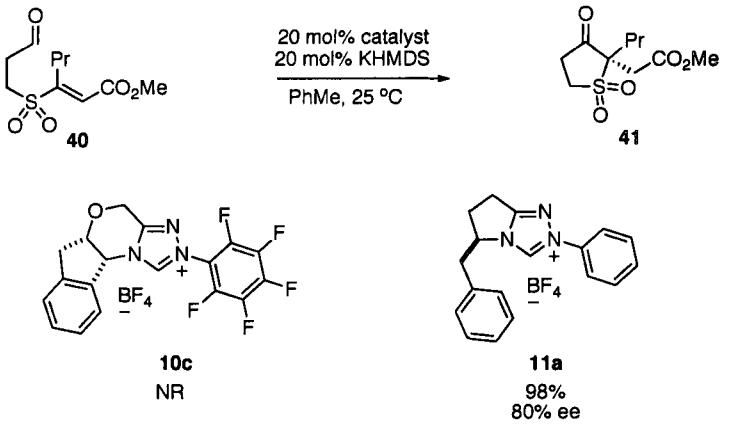
38
39

In an effort to circumvent this reactivity problem, the electrophilicity was changed by oxidizing the tether from sulfide **38** to a sulfone **40**, via *m*-CPBA oxidation (eq. 7). The reaction of the sulfone with pentafluorophenyl catalyst **10c** provided no reaction under optimized reaction conditions for thioether substrates (Scheme 6). However, use of phenylalanine precatalyst **11a** to complete conversion in an isolated yield of 98%. All attempts to separate the enantiomers by chiral HPLC failed. Chiral shift reagent $Eu(tfc)_3$ in order to observe diastereomeric species by ^1H NMR, and 80% ee was observed. The conformational restriction, due to the Thorpe-Ingold effect,[19] may account for the success of this reaction. In addition, the electron-withdrawing nature of the sulfone presumably contributes to activating the electron-deficient alkene, thus promoting cyclization.



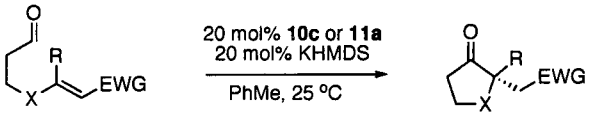
38
40

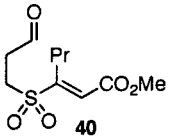
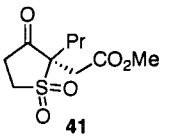
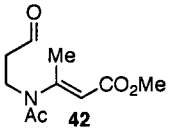
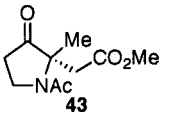
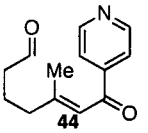
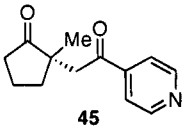
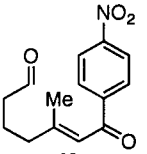
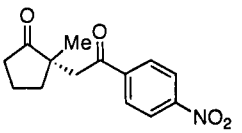
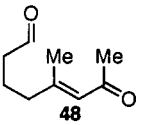
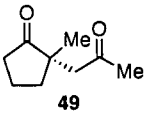
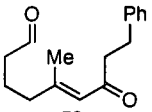
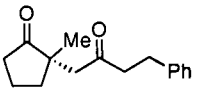
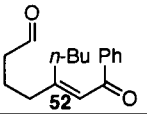
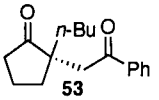
Scheme 6



The cyclization of **40** was added to the scope of aliphatic substrates that were reported by Mark Kerr in the initial paper on the formation of tetrasubstituted stereocenters.[13c] The scope of aliphatic substrates includes nitrogen-containing substrates such as **42** that provided desired product in 65% yield and 95% ee (Table 3). The α,β-unsaturated aromatic ketones **44** and **46** gave the desired product in higher yields and enantioselectivities. Excellent selectivity was observed for the formation of the quaternary stereocenter in **49** and **51** implementing aliphatic ketone Michael acceptors. Cyclization of α,β-unsaturated phenyl ketone possessing *N*-alkyl substitution **52** provided **53** in 98% ee. Aliphatic substrates with β-methyl substitution generally gave high enantioselectivity.

Table 3. Substrate scope of aliphatic aldehydes



entry	substrate	product[a]	catalyst	yield (%)	ee (%)[b]
1	 **40**	 **41**	**11a**	98	80[b]
2	 **42**	 **43**	**10c**	65	95
3	 **44**	 **45**	**10c**	85	96
4	 **46**	 **47**	**10c**	90	84
5	 **48**	 **49**	**10c**	81	95
6	 **50**	 **51**	**10c**	63	99
7	 **52**	 **53**	**10c**	71	98

[a] Absolute configuration assigned by analogy to **51**
[b] Enantiomeric excess was determined by ^{1}H NMR using chiral shift reagent Eu(hfbc)$_3$

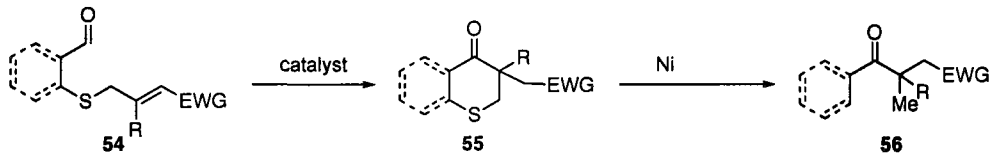
The scope of the intramolecular enantioselective Stetter reaction was expanded to afford tetrasubstituted stereocenters. The reaction is mild, general, and tolerates aromatic, aliphatic, sulfur, oxygen, and nitrogen tethering of aldehyde and Michael acceptor. The current substrate scope includes compounds with varying electronics and

sterics. Ongoing efforts include elucidating the mechanism of this reaction and discerning other important factors contributing to the reactivity of these carbene catalysts.

2.3 Two-Step Intermolecular Stetter Reaction

Asymmetric intermolecular Stetter products are difficult to obtain using known Stetter methodologies.[16] Therefore, an approach to circumvent the problems associated with the intermolecular Stetter is described. As shown in the previous section, the formation of tetrasubstituted stereocenters is accomplished with a variety of aliphatic and aromatic aldehydes containing a thioether linker between the aldehyde and the Michael acceptor (Scheme 7). With Stetter products of type **55** in hand, a reductive desulfurization can be envisioned to provide the equivalent of an intermolecular Stetter product **56**. Although this method requires a two pot procedure, it was envisioned to be a viable option for obtaining products of type **56**.

Scheme 7



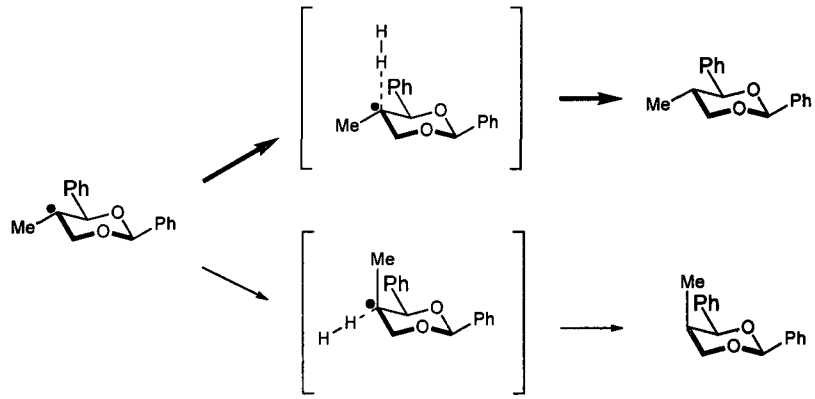
We proposed that this may be accomplished by removing the sulfur linker using a nickel species while retaining the stereochemistry of the newly formed carbon-carbon bond. The two most common species for desulfurization are Raney Ni and nickel boride complexes.

Many types of Raney nickel exist that differ by the method of preparation and the amount of hydrogen adsorbed onto nickel.[18] The activity of Raney nickel decreases in a

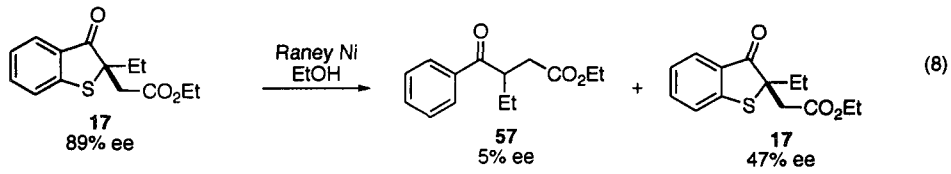
matter of months due to hydrogen loss. Raney nickel is used to replace a sulfur atom with a hydrogen atom in thiols, sulfides, and disulfides. In simple systems sulfur can be removed while leaving other functionalities untouched.

When the sulfur is attached to a carbon stereocenter the selectivity of reduction becomes important. For such a system, Shiina and coworkers found that reduction of linear aldol adducts gave poor stereoselectivity while cyclic derivatives gave good diastereoselectivity (*cis*/*trans* 11/89) (Scheme 8).[19] When starting with the *trans* benzylideneacetal no reduction product was observed. Therefore, the stereoselectivity in this reaction is dependent on the configuration of the starting material and may not hold for our substrates.

Scheme 8



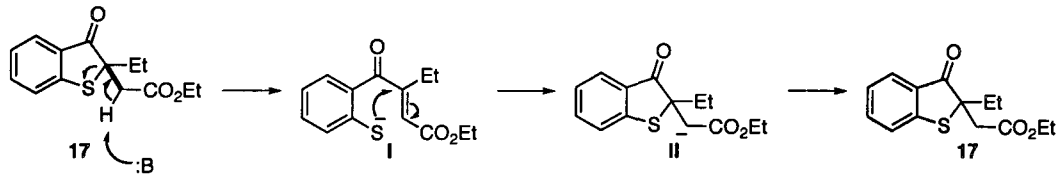
Since Shiina and coworkers observed poor selectivity with linear substrates it was not surprising that our system gave similar results. When **17** was subjected to Raney Ni in ethanol, desulfurized product was isolated in 5% ee along with recovered starting material in 47% ee (eq. 8).



(8)

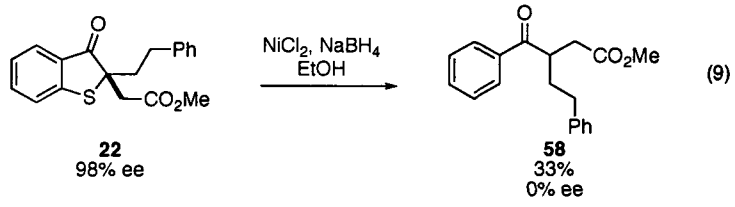
A possible path for epimerization occurs via elimination/recombination, as illustrated in Scheme 9. The hydrogen adsorbed on nickel may act as a base and eliminate sulfur **I**. Recombination provides **II**, which upon protonation yields epimerized **17**.

Scheme 9



After pursuing a variety of conditions with Raney Ni that provided low conversion and predominant epimerization, a nickel boride mediated desulfurization was undertaken. Nickel boride is generated *in situ* from nickel chloride hexahydrate and sodium borohydride.[20] Nickel boride reduction poses potential reactivity problems because nickel boride is a reducing agent for various functional groups.

When **22** was treated with *in situ* formed nickel boride, the desired product **58** was recovered in 33% yield and 0% ee (eq. 9). Variable temperatures were investigated to identify optimized conditions. These experiments proved unsuccessful, providing low yields and continued racemization of the product.



(9)

At this point, our studies shifted towards elucidating the mechanism of the Stetter reaction in order to accomplish an intermolecular Stetter reaction in one step from an aldehyde and Michael acceptor. Although the two-step intermolecular Stetter was

unsuccessful, our group has since reported the enantioselective intermolecular Stetter of glyoxamides with alkylidenemalonates.[16]

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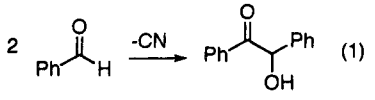
Chapter 3

Mechanistic Investigation of the Enantioselective Stetter Reaction

3.1 Introduction

The seminal example of the reversal of functional group polarity, the benzoin reaction, dates to 1832, when Wöhler and Liebig reported that cyanide anion catalyzes the formation of benzoin from two equivalents of benzaldehyde (eq. 1).[1] This reversal in polarity, subsequently termed *Umpolung*,[2] effectively changes an electrophilic aldehyde into a nucleophilic acyl anion equivalent. In 1943, more than a century after the initial report, Ukai *et al.* showed that thiazolium salts catalyze the homodimerization of aldehydes in the presence of base.[3] This discovery held enormous promise for asymmetric catalysis since thiazolium salts could be modified to act as a source of chirality to render the reaction enantioselective.



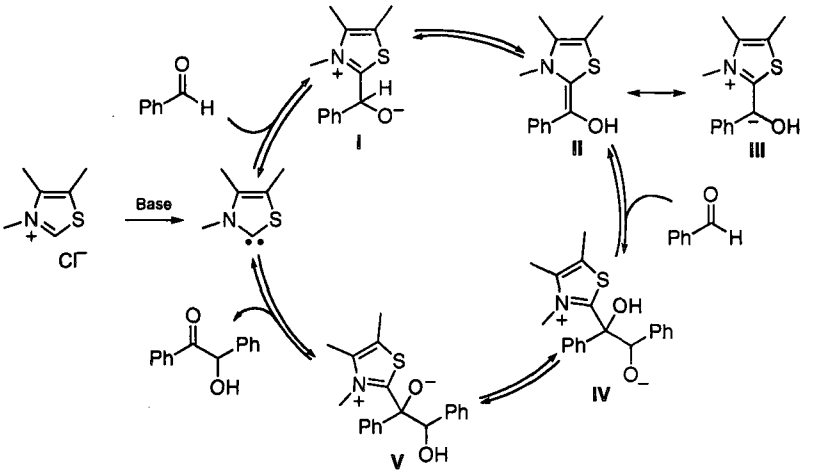
(1)

Mechanistic insight into organocatalytic reactions is important in an effort to develop general transformations. Breslow and co-workers elucidated the currently accepted mechanism of the benzoin reaction in 1958 by investigating the thiamin-catalyzed dimerization of benzaldehyde.[4] The mechanism is closely related to Lapworth's mechanism for cyanide anion catalyzed benzoin reaction (Scheme 1).[5] As proposed by Breslow, the carbene, formed *in situ* by deprotonation of the corresponding thiazolium salt, undergoes nucleophilic addition to the aldehyde to produce intermediate **I**. Subsequent intermolecular proton transfer generates a nucleophilic acyl anion equivalent **III**, also drawn in resonance with **II**, commonly known as the "Breslow

intermediate." A new carbon—carbon bond is formed upon nucleophilic attack of the acyl anion into another molecule of aldehyde. A second proton transfer forms tetrahedral intermediate **V**, which collapses to produce the α-hydroxy ketone accompanied by liberation of the active catalyst. As with the cyanide-catalyzed benzoin reaction, the thiazolinylidene catalyzed reaction is reversible.[6] Extensive kinetic studies have produced additional detail into the reaction mechanism. Breslow observed a second order dependence on aldehyde concentration and a first order dependence on the thiazolium salt during the reaction (eq. 2). This observation is consistent with the proposed rate-limiting addition of **II** to another molecule of benzaldehyde to form **IV**. This result has been confirmed in several instances.[7] We have based our working mechanism for the triazolinylidene carbene catalysted Stetter reaction on Breslow's proposed mechanism.

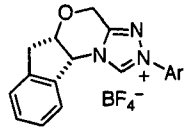
$$d[\text{benzoin}]/dt = k[\text{PhCHO}]^2[\text{catalyst}] \qquad (2)$$

Scheme 1

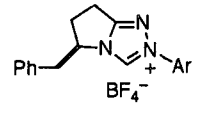


The Stetter reaction employs similar *Umpolung* reactivity wherein the acyl anion equivalent attacks a Michael acceptor to afford 1,4-dicarbonyl.[8] Utilizing cyanide or thiazolylidene carbenes as catalysts, Stetter demonstrated that a variety of aromatic and aliphatic aldehydes act as competent nucleophilic coupling partners with a wide range of α,β-unsaturated ketones, esters, and nitriles.[9] The ability to bring two different electrophilic partners together and form a new carbon—carbon bond enhances the potential utility of this transformation. Extensive work by Stetter and others in the development of this reaction revealed that the presence of a β-substituent on the Michael acceptor is a major limitation of this methodology.[10]

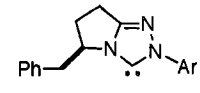
The Rovis group has focused on the development of chiral triazolinylidene carbenes and precursors, **1-3**, capable of inducing the cyclization of aromatic and aliphatic aldehydes to α,β-unsaturated esters, ketones, thioesters, amides, aldehydes, and nitriles.[11]



1a Ar = *p*-$MeOC_6H_4$
1b Ar = Ph
1c Ar = C_6F_5



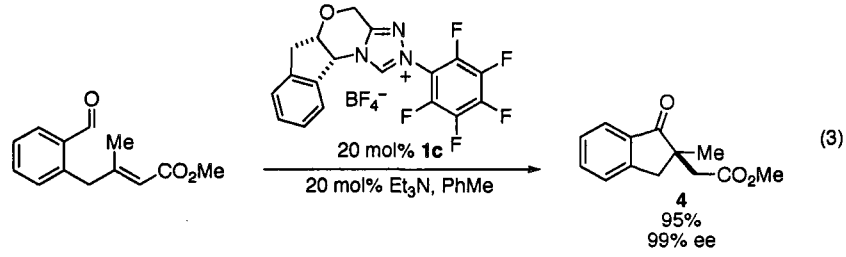
2a Ar = Ph
2b Ar = *p*-$CF_3C_6H_4$



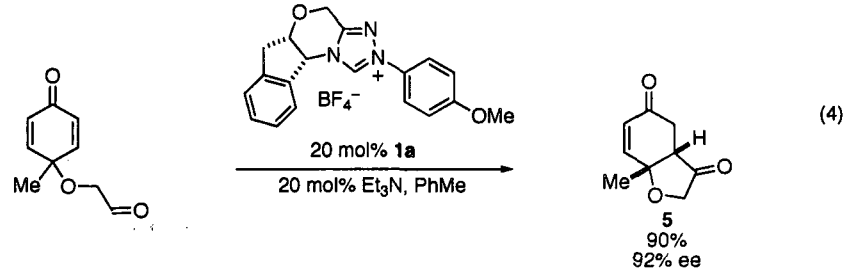
3a Ar = Ph
3b Ar = *p*-$CF_3C_6H_4$

Although recent work has greatly expanded the scope of substrates compatible with the enantioselective intramolecular Stetter reaction, the most notable advancements include the enantioselective construction of quaternary centers, the desymmetrization of cyclohexadienones, and the enantioselective and diastereoselective formation of contiguous stereocenters. Although a series of catalysts was examined, electron-deficient pre-catalyst **1c** proved the most efficient for the transformation of β,β-disubstituted Michael acceptors (eq 3).[11c,g] The desymmetrization of cyclohexadienones using

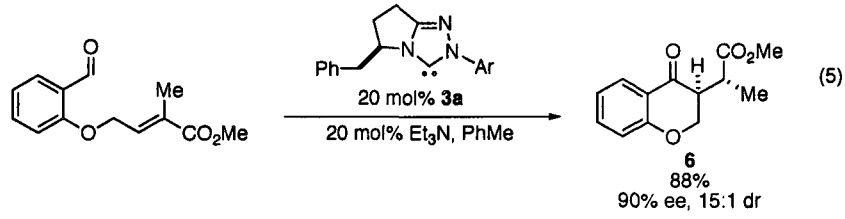
triazolinylidene carbene **1a** has been accomplished providing a variety of hydrobenzofuranones in excellent enantio- and diastereoselectivity (eq 4).[11f] Utilizing prochiral α,α,β-trisubstituted Michael acceptors, the Stetter reaction catalyzed by **2a** has proven to be both enantio- and diastereoselective, allowing control of the formation of contiguous stereocenters (eq 4).[11d] It is noteworthy that a substantial increase in diastereoselectivity is observed, from 3:1 with **2a** to 15:1 with catalyst **3a**. In order to better understand the subtle differences exhibited by catalysts **1**, **2** and **3**, we initiated an investigation into the mechanism of the intramolecular Stetter reaction.



(3)



(4)

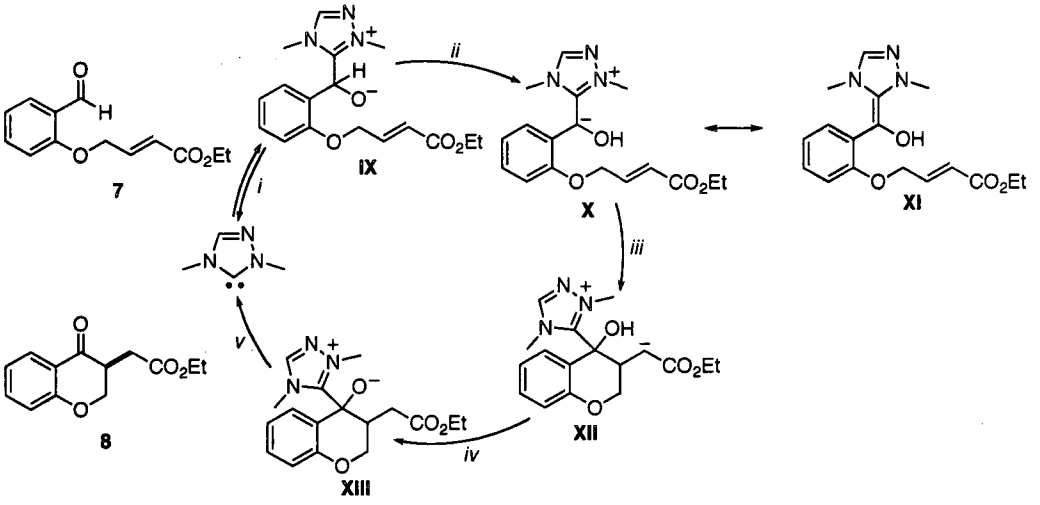


(5)

To the best of our knowledge, a detailed study probing the mechanism of the Stetter reaction catalyzed by triazolinylidene carbenes has not been reported. In the absence of such a study the working model of the Stetter reaction is based on the Breslow mechanism for the benzoin reaction. The catalytic cycle is as follows: the carbene,

formed *in situ* by base deprotonation of the corresponding azolium salt, adds to the aldehyde to form **IX**, which undergoes proton transfer to form acyl anion equivalent **X**, which is closely related to the Breslow intermediate (*vide supra*). Subsequent attack into the Michael acceptor forms a new carbon—carbon bond and is followed by a proton transfer to generate **XIII**. Finally, collapse of the tetrahedral intermediate **XIII** to form ketone **8** is accompanied by liberation of the active catalyst. As we strive to understand differences in catalysts and continue to work toward the development of the enantioselective intermolecular reactions, we believe that the results from a detailed mechanistic study may provide insight toward the rational attainment of these goals. Here we report a series of mechanistic experiments which shed light on the mechanism of triazolylidene carbene catalyzed Stetter reaction.

Scheme 2

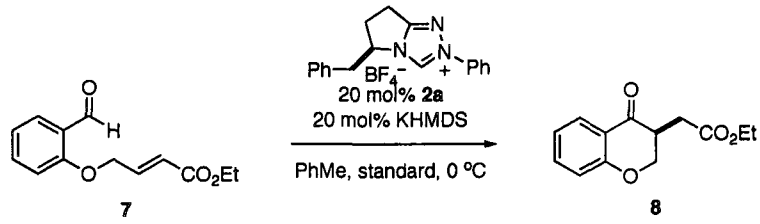


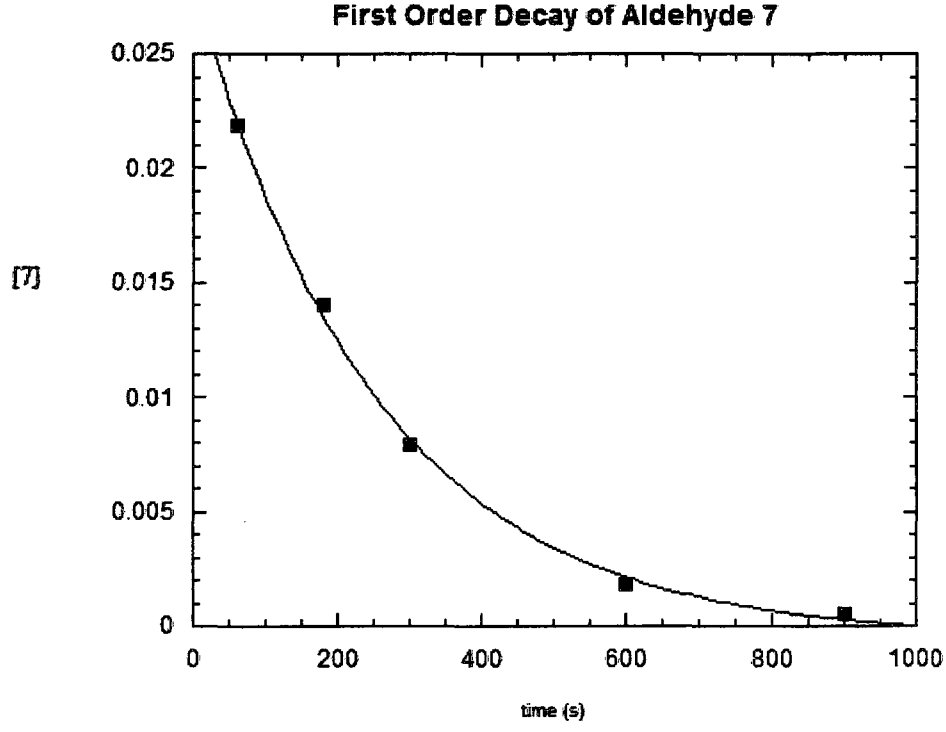
3.2 Rate Law Determination

Since salicylaldehyde derived aldehyde **7** was utilized as a benchmark to measure the efficiency and selectivity of newly-developed catalysts for the Stetter reaction, it was

chosen as the substrate for this study. Under standard reaction conditions aldehyde **7** was subjected to 20 mol% **2a**, 20 mol% KHMDS, in toluene (0.025 M) at 0 °C, under an atmosphere of argon. Gas chromatography was utilized for the analysis of cyclized product **8** by using *tert*-butyl biphenyl as an internal standard (t_R 4.9 min) and following the disappearance of aldehyde **7** (t_R 2.9 min) and concurrent appearance of keto-ester **8** (t_R 2.1 min). Standard kinetic analysis using the conversion of aldehyde **7** to keto-ester **8** exhibits a first order dependence as a function of aldehyde concentration versus time over four half lives with an observed rate of 2.65×10^{-3} s^{-1}. (Scheme 3).[6]

Scheme 3



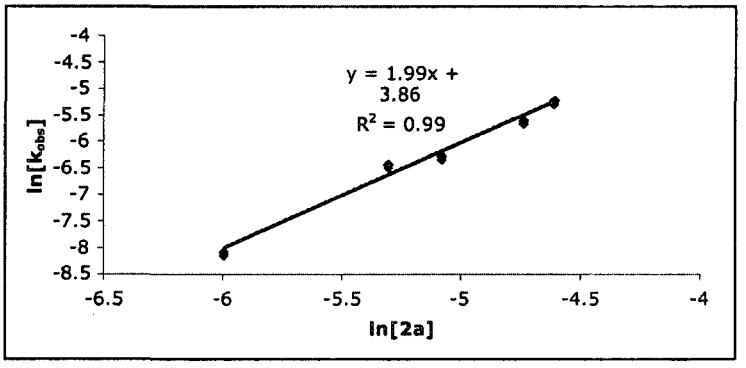


Preliminary kinetic experiments were initiated by Javier Read de Alaniz using a single batch of catalyst. The same batch was used in the following experiments to ensure that data could be used in conjunction with Javier's data to provide a better understanding of the mechanism of the Stetter reaction.

The catalyst dependence was determined by varying the concentration of catalyst from 0.0025M to 0.0100M. The data is illustrated in Figure 1 utilizing the relationship between the natural log of the observed rate constant, k_{obs}, and the natural log of the

catalyst concentration. From the slope of the line we obtain the order in catalyst concentration. In this set of experiments, a second order rate dependence on the catalyst concentration was observed. This was an unexpected result as we assumed there would only be one molecule of catalyst involved in the rate-determining step.

Figure 1



This led to a closer look at the reaction conditions. When the catalyst concentration was changed, the concentration of HMDS also changed in the same ratio. In the absence of further evidence, it was assumed the observed rate showed a first order dependence on aldehyde concentration and a second order dependence on **2a**/HMDS concentrations (eq. 6).

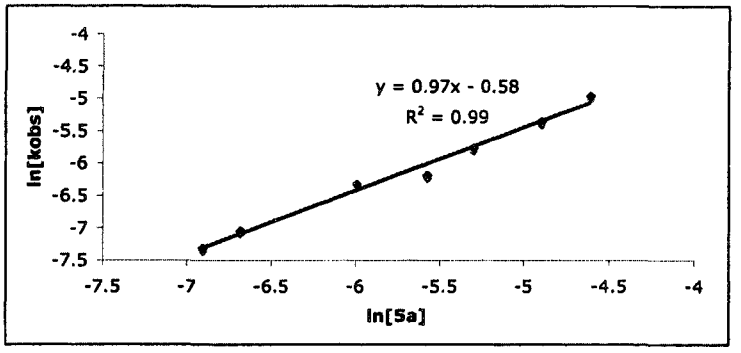
$$d[\mathbf{8}]/dt = k[\mathbf{7}][\mathbf{2a}][\text{HMDS}] \qquad (6)$$

In order to test this hypothesis we turned our attention to the same reaction with free carbene **3a**. Preformed carbene **3a** was generated by first adding 20 mol% **2a** (0.030 mmol) to a flame dried flask followed by 1 mL of toluene and 20 mol% KHMDS (0.5M solution of KHMDS was prepared before each experiment in an inert atmosphere glove box); the resulting solution was stirred for 5 min at room temperature. The volatiles were then removed under vacuum for 30 min. The residue was dissolved in 5mL fresh toluene providing free carbene **3a** followed by addition of a 1mL solution of **7** and di-

tert-butyl biphenyl (internal standard). The same method for analyzing the data, as described above, established a first order dependence on the concentration of **3a**. These experiments suggest a second order rate law (eq. 7).

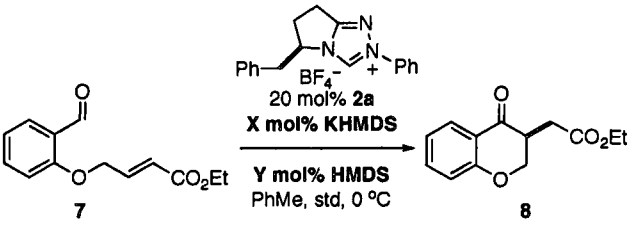
$$d[\mathbf{8}]/dt = k[\mathbf{7}][\mathbf{3a}] \qquad (7)$$

Figure 2



Encouraged by these results, the HMDS concentration was then varied to ensure our analysis was correct. The average observed rate, $k_{obs} = 3.36 \times 10^{-3}\ s^{-1}$, in the absence of HMDS was found by averaging the observed rates when **7** reacts with free carbene **3a** (Table 1, entry 1). This point is the benchmark for the reactions with varying concentrations of HMDS.

Table 1



entry	X	Y	[HMDS]	k_{obs} (s^{-1})
1	0	0	0	3.36×10^{-3}
2	20	0	0.0050	1.57×10^{-3}
3	20	5	0.0063	3.39×10^{-3}
4	20	10	0.0075	3.37×10^{-3}
5	20	20	0.0100	3.73×10^{-3}

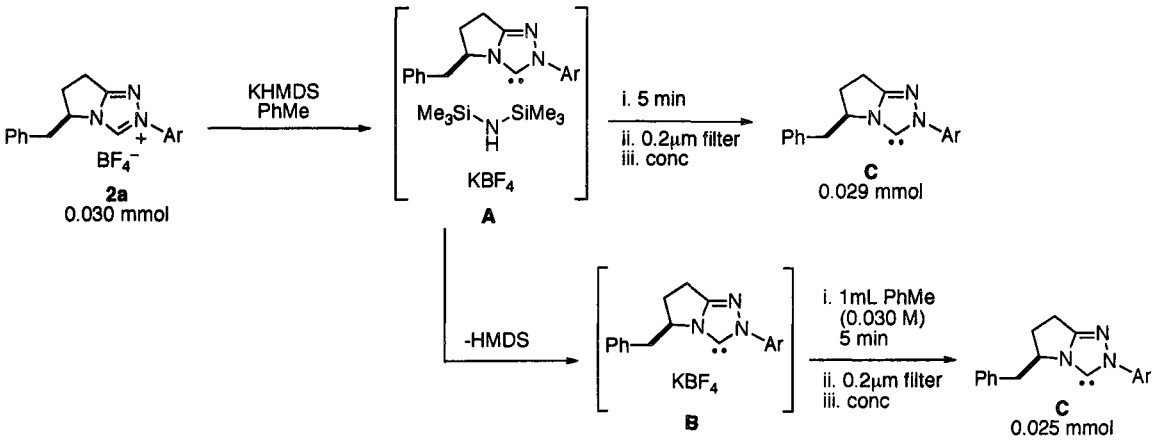
A series of experiments were initiated to determine why there is an observable change in reaction dependence on **2a** when there is a 1:1 ratio of **2a**/KHMDS. Several possibilities for this change were hypothesized. For example, we thought that water in the reaction mixture may protonate the carbene leading to less active catalyst present to mediate cyclization of **7**. Solubility of **2a** with 1 equiv of KHMDS may also lead to a decrease in activity in this system. The counter-ion BF_4^- may influence the rate of the reaction via ion pairing. Lastly, the formation of a new species may act as a proton shuttle.

If water is causing the difference in the rate of the reaction, a Karl Fisher titration should provide evidence of a higher concentration of water in one sample over another. A variety of samples were tested and difference in the concentration of water observed was negligible.

The rate difference between *in situ* carbene **2a** (Table 1, entry 2) and free carbene **3a** (Table 1, entry 1) could be attributed to the lack of solubility when 1 equivalent of KHMDS/HMDS is present in the reaction mixture. In order to establish if solubility played a role in the rate of the reaction the mass of active catalyst was determined. To a flame dried flask was added triazolium **2a** followed by the addition of toluene, forming the *in situ* carbene **A** (Scheme 4). To obtain the mass of the active catalyst, the mixture was stirred for 5 min followed by filtration, to remove the tetrafluoroborate salt, and subsequent concentration results in 0.029 mmol of **C**. The mass of **3a** was obtained by taking **A** and removing the volatiles under vacuum for 30 min followed by dissolution of the residue with 1mL of toluene, stirring for 5 min, and filtration resulting in 0.025 mmol

of active catalyst **C**. These results suggest that the solubility is not a factor in the difference in the rate of the reaction.

Scheme 4



The reaction was conducted and monitored via ^{19}F NMR to test the effect of the tetrafluroborate counter-ion. There were no visible ^{19}F resonances in the corresponding spectra, suggesting that KBF_4 is insoluble in toluene and does not effect the rate of the reaction.

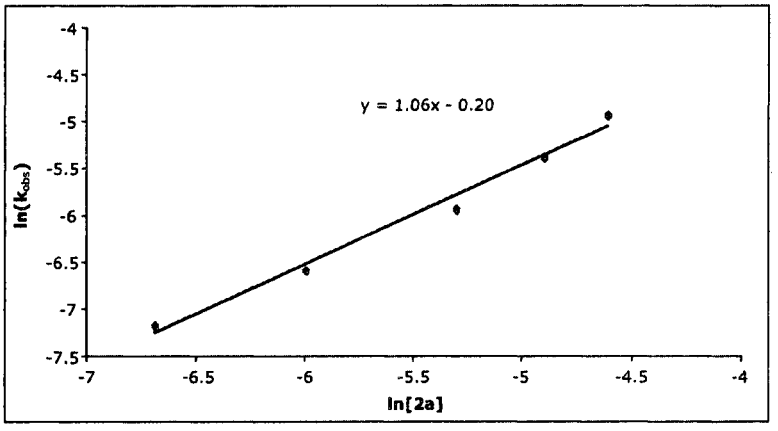
Without a clear understanding as to why **2a** behaves drastically differently from the same system with **3a**, we chose to explore a different batch of catalyst. Since this investigation began the purification of the precatalysts has evolved, largely due to my co-worker, Harit Vora. Recrystallization was the method used for purification of the triazolium salts; however, Harit found that after recrystallization, trituration provides an off white solid. This solid is in contrast to the tan solid obtained with recrystallization alone.

With the new batch of **2a** in hand, the cyclization was reevaluated in the presence of KHMDS/HMDS (Figure 3) and the absence of HMDS, *i.e.* the free carbene **3a**, under standard reaction conditions. A first order rate dependence on the catalyst concentration

is observed when **7** undergoes cyclization with **2a** (eq 8). For the initial experiments we conclude that a volatile impurity was present that inhibited the rate of the reaction. Thus, the systems of **2a** and **3a** are kinetically equivalent. The rest of the mechanistic study was completed with this newly purified batch of **2a**.

$$d[\mathbf{8}]/dt = k[\mathbf{7}][\mathbf{2a}] \qquad (8)$$

Figure 3

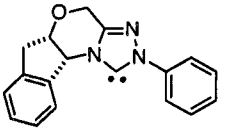


3.3 Comparison of Various Carbene Precursors

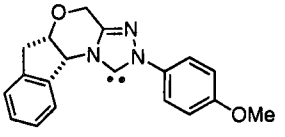
In an effort to gain a better understanding of how the structure and electronics of the carbene precursor effect the rate of the reaction a the aminoindanol derived triazolium salts were subjected to the reaction condition. These reactions were carried out with pre-catalysts that were purified with recrystallization, not recrystallization and trituration.

Preformed carbene was generated by first adding 10 mol% triazolium salt (0.030 mmol) to a flame dried flask followed by 1 mL of toluene and 10 mol% KHMDS (0.5M solution of KHMDS was prepared before each experiment in an inert atmosphere glove box); the resulting solution was stirred for 5 min at room temperature. The volatiles were

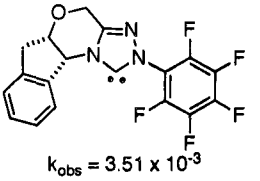
then removed under vacuum for 30 min. The residue was dissolved in 5mL fresh toluene providing free carbene followed by addition of a 1mL solution of **7** and di-*tert*-butyl biphenyl (internal standard). The aminoindanol derived carbenes provided an unexpected trend. Phenyl-substituted provides a slower rate than the *para*-methoxy-substituted carbene. This may be accounted for due to the *p*-OMe carbene being more nucleophilic than the parent phenyl catalyst. Although the pentafluorophenyl carbene is less nucleophilic than the *para*-methoxy carbene, the rate of the reaction is significantly increased. This observation may be due to an increased rate of proton transfer, i.e. the pentaflurorphenyl carbene increases the acidity of proton of the tetrahedral intermediate.



$k_{obs} = 4.17 \times 10^{-4}$



$k_{obs} = 5.39 \times 10^{-4}$



$k_{obs} = 3.51 \times 10^{-3}$

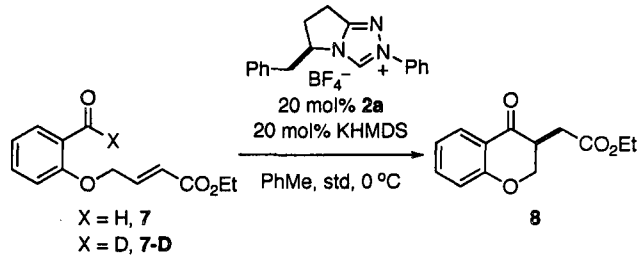
3.4 ^{2}H Kinetic Isotope Effects and Competition Experiments

To extend our understanding of the intramolecular Stetter reaction the kinetic isotope effect (KIE) of labeled aldehydes was examined. Comparison of rates of proton versus deuterium labeled aldehydes tethered to identical Michael acceptors should determine if there is a deuterium isotope effect. Three possible ^{2}H KIEs were apparent from looking at the proposed mechanism. First, if initial attack of the carbene into the aldehyde was rate-limiting we expected to see an inverse secondary KIE ($k_H/k_D < 1$). This would be indicative of a rate-determining step involving a hybridization change involving the carbon attached to the deuterium atom, from $sp^2 \rightarrow sp^3$. Second, if carbon-carbon bond formation is rate-limiting we expect to observe no appreciable deuterium

KIE ($k_H/k_D \sim 1$). Third, if proton transfer is occurring in the rate-determining step, a primary isotope should be measured ($k_H/k_D > 1$).

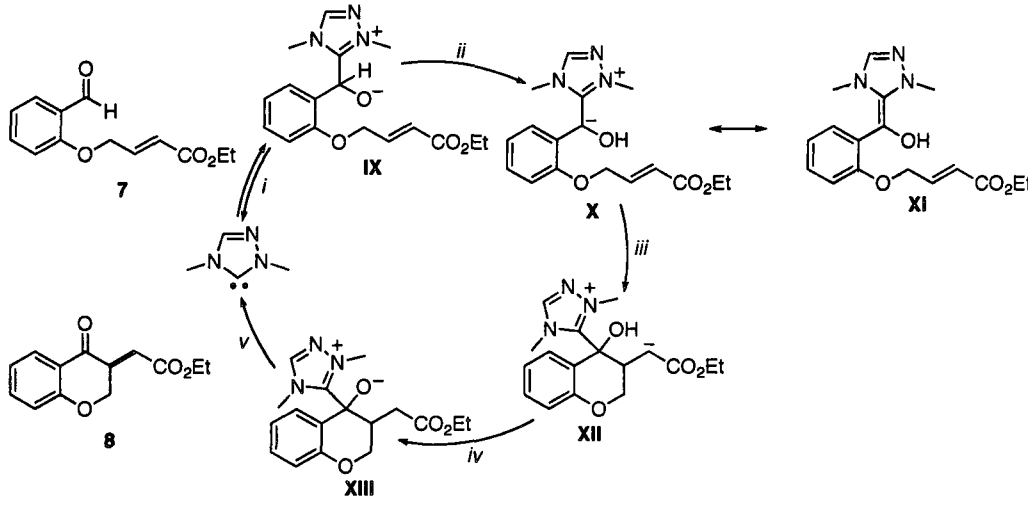
The ^2H KIE for the aldehyde was measured under standard reaction conditions from triplicate runs with **7** and its deuterated isotopologue (Ar-CDO), and the k_H/k_D found to be 2.62, thus suggesting that proton transfer is rate-limiting (Table 2).

Table 2



entry	X	k_{obs} ($x10^{-3}$)	entry	X	k_{obs} ($x10^{-3}$)
1	H	2.43	5	H	3.10
2	H	2.47	6	D	0.98
3	H	2.59	7	D	1.00
4	H	2.64	8	D	1.05

Scheme 2

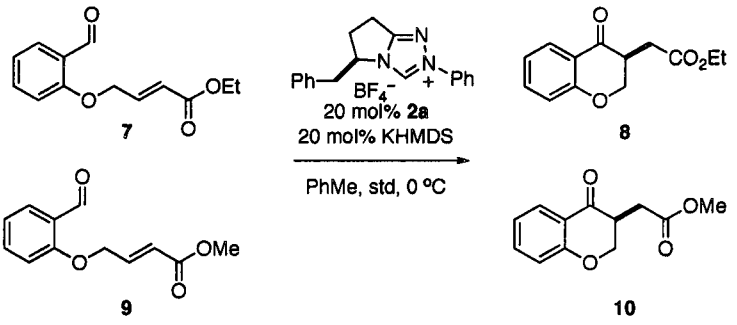


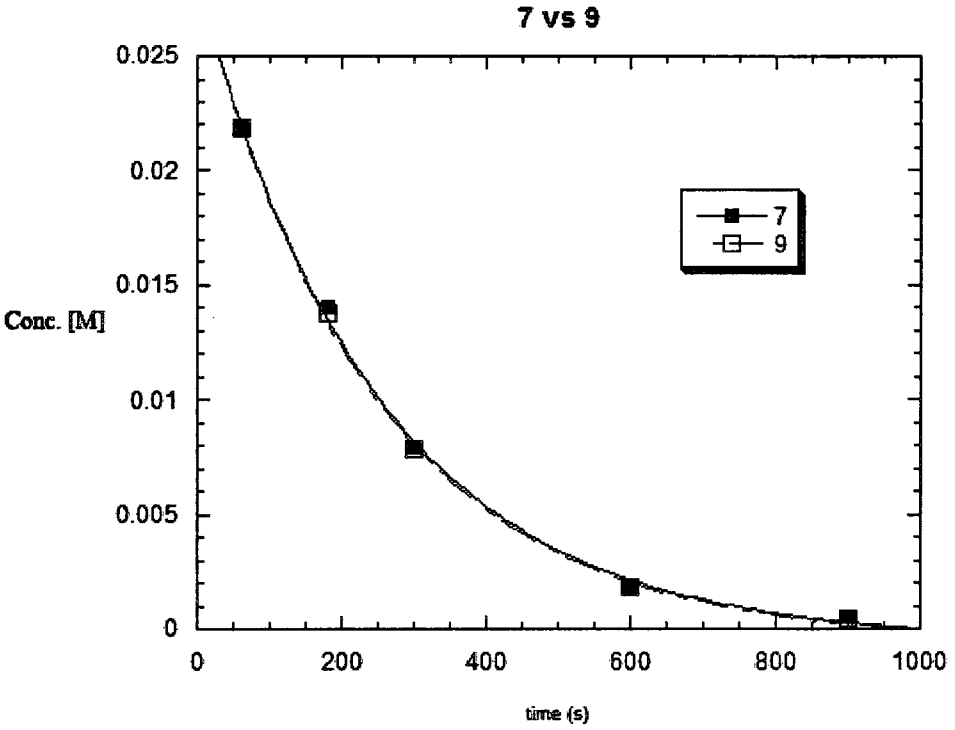
The proposed mechanism for the Stetter reaction contains two proton transfer steps (steps *ii* and *iv*, Scheme 2). Based on the magnitude of the ^{2}H KIE, two possibilities exist for the rate determining step: proton transfer from the initially generated tetrahedral intermediate **IX** from carbon to oxygen to generate nucleophilic alkene **XI** (step *ii*), or proton transfer from oxygen to the enolate generated from the conjugate addition (step *iv*). For the case in which step *ii* is rate-limiting, the nature of the Michael acceptor is expected to have no effect on the reaction rate. To elucidate the rate-determining step, a competition experiment, in which two aldehydes with different Michael acceptors were exposed to standard reaction conditions in order to observe the rate of formation of each product, was conducted. The direct competition should eliminate the variability associated with catalyst decomposition since both substrates should be equally affected by this decomposition.

A control experiment was conducted between aldehydes **7** and **9**. The only difference between these two aldehydes is an ethyl versus methyl ester and they should behave identically under the reaction conditions. To a flame dried flask was added 20 mol% of **2a** followed by 1 mL of toluene and 20 mol% KHMDS (0.5M solution of KHMDS was prepared, in a glove box, prior to each experiment). The resulting solution was stirred for 5 min at room temperature while bubbling argon. An additional 4 mL toluene was added to the reaction mixture and cooled to 0 °C for 5 min. At this point, a 1 mL toluene solution of **7**, **9**, and *tert*-butyl biphenyl (internal standard) was added. A 0.1 mL aliquot was taken at regular intervals and immediately passed through a plug of silicon gel with 100% ethyl acetate. Gas chromatography was used to determine the percent conversion of each substrate based on the internal standard. As expected,

substrates **7** and **9** behave identically under these reaction conditions (Scheme 5). The observed rates were $k_7 = 3.96 \times 10^{-3}\ s^{-1}$ and $k_9 = 4.00 \times 10^{-3}\ s^{-1}$, leading to relative rate, $k_7/k_9 = 1.01$.

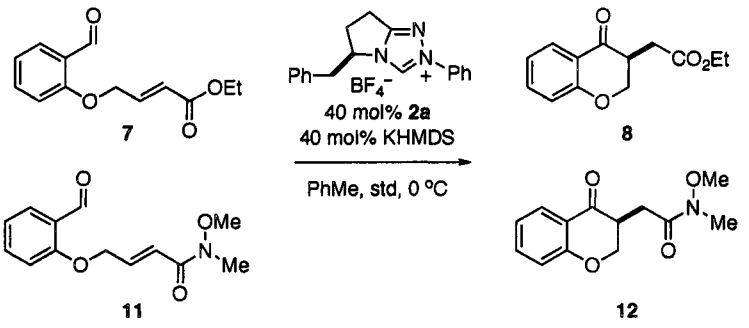
Scheme 5

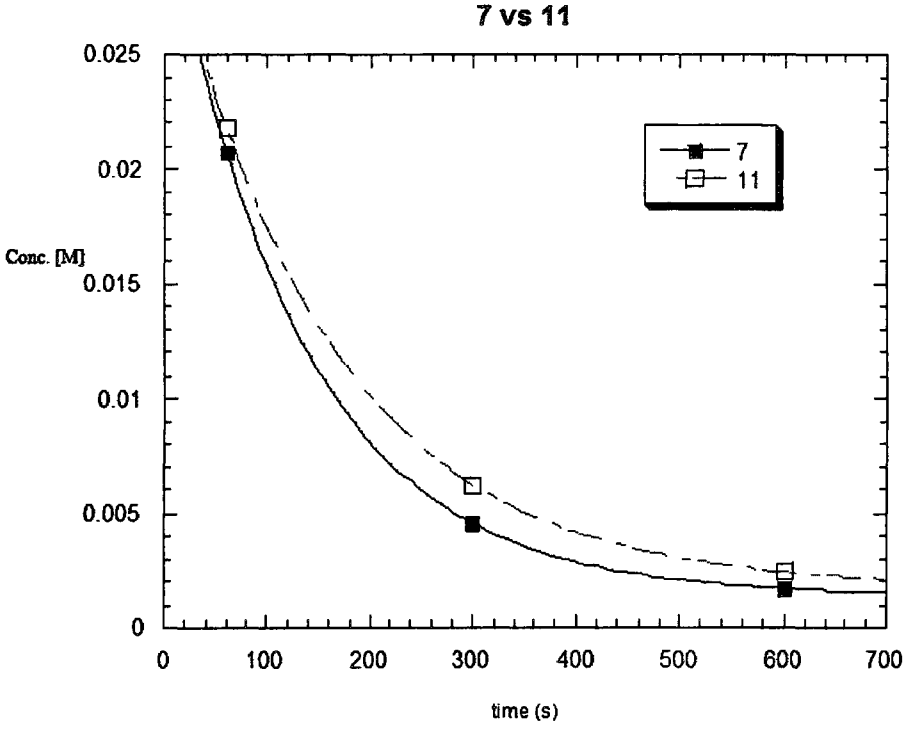




Similarly, we examined electronic changes in the Michael acceptor. Although the electronically-different Michael acceptor, Weinreb amide substrate **11**, has a decreased electrophilicity relative to the parent substrate **7**, the reaction proceeds as a similar rate (Scheme 6). In fact, there was little difference in the rate of reaction between each substrate with varying Michael acceptor. The observed rates were $k_7 = 7.56 \times 10^{-3}\ s^{-1}$ and $k_{11} = 6.24 \times 10^{-3}\ s^{-1}$, with a $k_{rel} = 1.21$.

Scheme 6

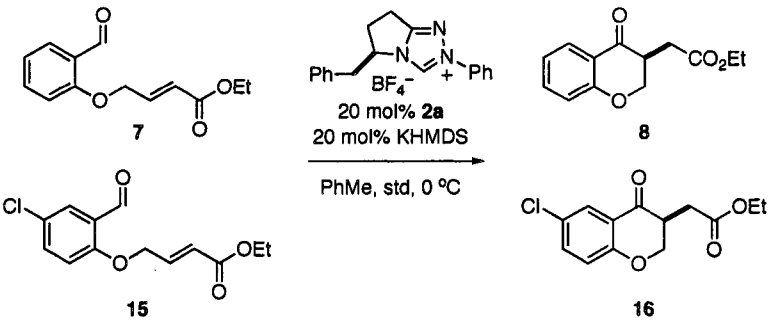


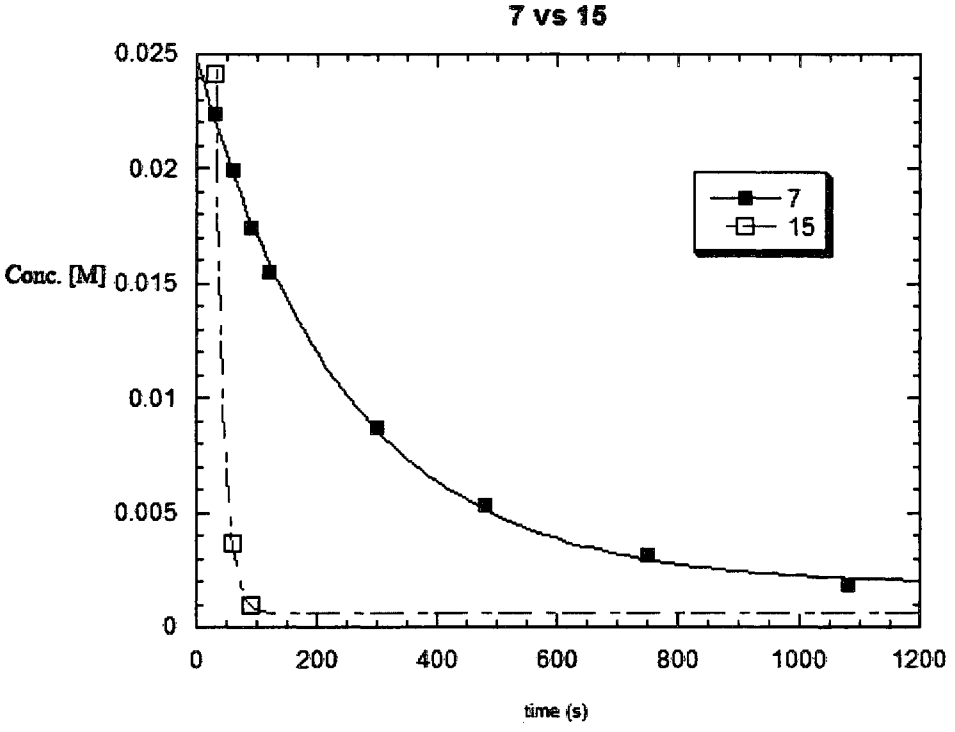


The observations compiled from these competition experiments suggest that variation of the steric and electronic nature of the Michael acceptor has little effect on the intramolecular Stetter reaction. Thus far, these competition experiments are in agreement with the first proton transfer being rate-determining (step *ii*, Scheme 2).

In the same vein, another set of competition experiments was conducted in which the environment of the aldehyde component was varied. In this case changing the aldehyde, rather than the Michael acceptor, is expected to result in different rates if step *ii* is rate-limiting. Substrate **15** was synthesized in an attempt to withdraw electron density from the tetrahedral intermediate of type **IX**, therefore increasing the acidity of the proton to be transferred. In fact, when equimolar amounts of **7** and electron poor **15** are subjected to the reaction conditions, **15** reacts at a rate 15 times faster than the parent aldehyde (Scheme 7). The observed rates are $k_7 = 4.06 \times 10^{-3}\ s^{-1}$ and $k_{15} = 6.78 \times 10^{-2}\ s^{-1}$. Electron-withdrawing groups presumably increase the acidity of tetrahedral intermediate **IX** (Scheme 2), therefore increasing the rate of the reaction.

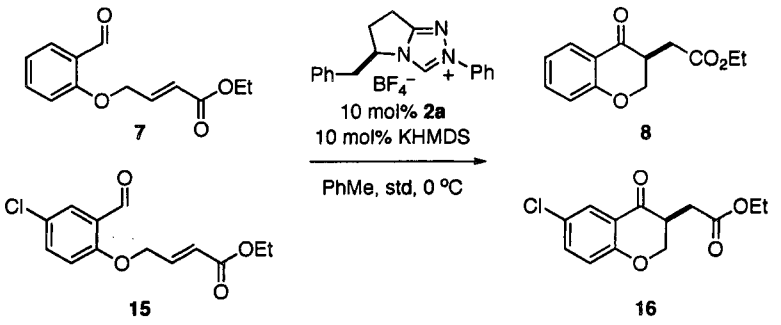
Scheme 7

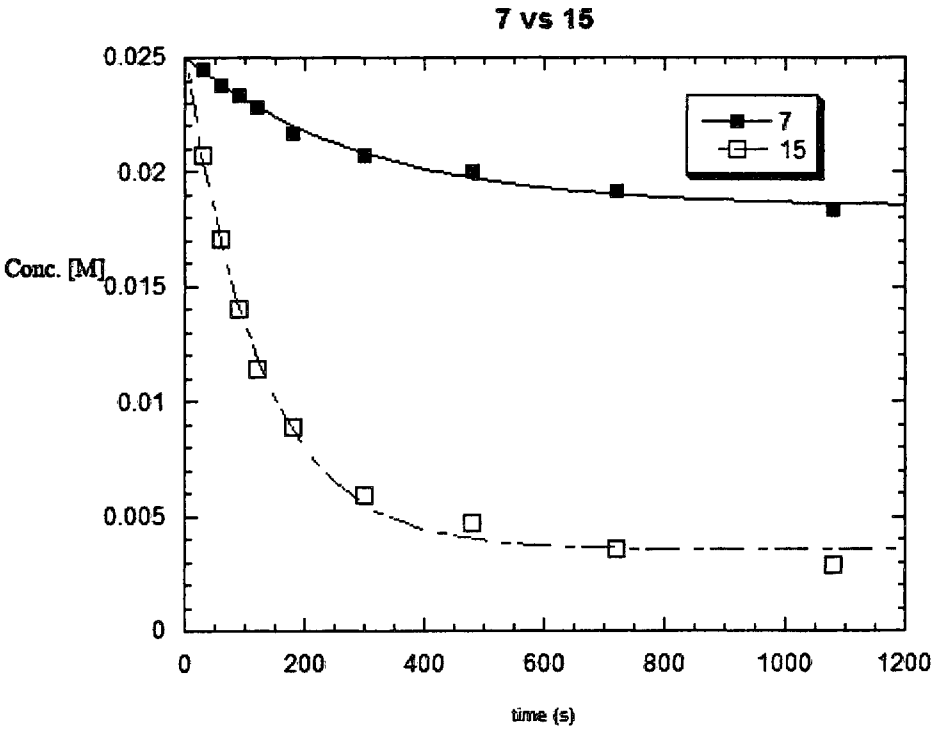

7
OEt
20 mol% 2a
20 mol% KHMDS
PhMe, std, 0 °C
8
CO2Et
15
Cl
16


7 vs 15
Conc. [M]
0.025
0.02
0.015
0.01
0.005
0
0
200
400
600
800
1000
1200
time (s)
7
15

The concentration of **2a** was cut in half in an effort to obtain a larger set of points for the disappearance of **15** (Scheme 8). Unfortunately, a number of attempts provided the same result; the reaction did not go to completion in the expected time frame, suggesting decomposition of the catalyst or product inhibition. We are confident that the result above is indicative of a drastic rate increase when the aldehyde is electron deficient.

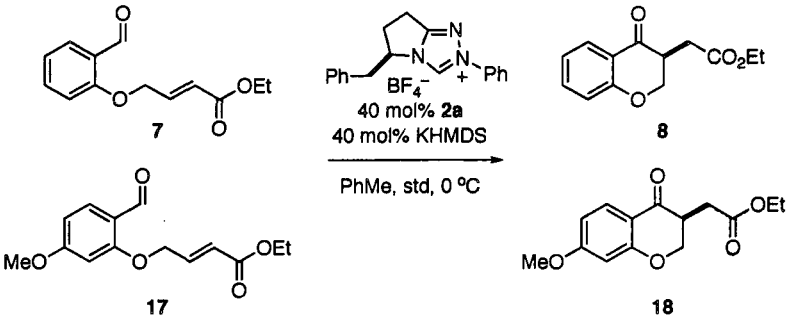
Scheme 8

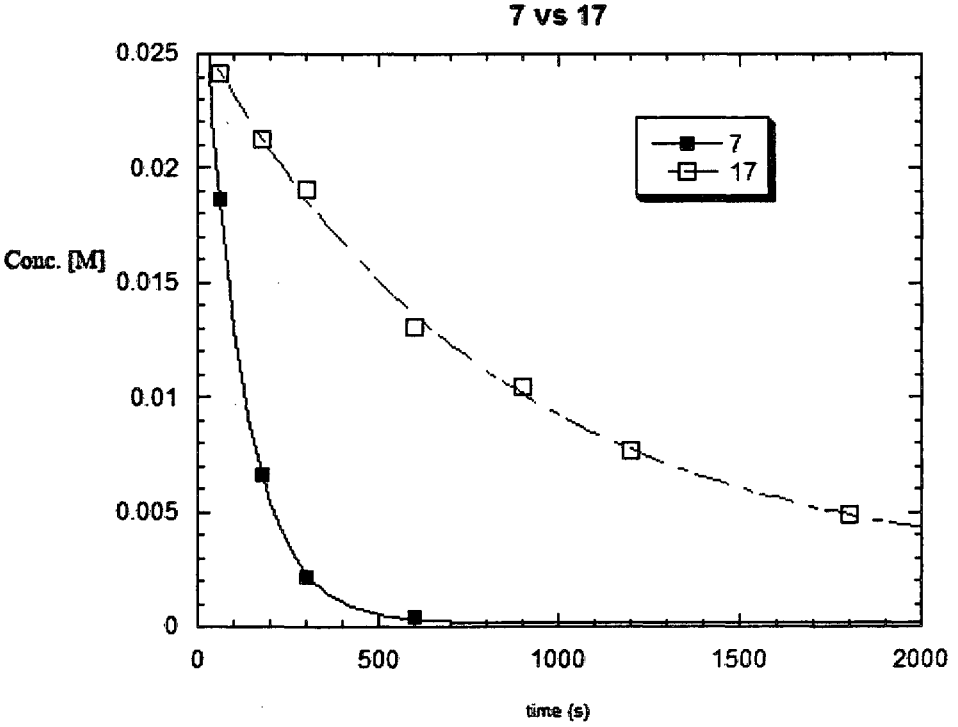




In a similar experiment, electron-rich aldehyde **17** formed product at a rate 7 times slower than **7** (Scheme 9). The observed rates are $k_7 = 8.90 \times 10^{-3}\ s^{-1}$ and $k_{15} = 1.22 \times 10^{-3}\ s^{-1}$, leading to a relative rate, $k_7/k_{17} = 7.30$. This observation can be attributed to a decreased acidity of tetrahedral intermediate **IX** formed by substrate **17**.

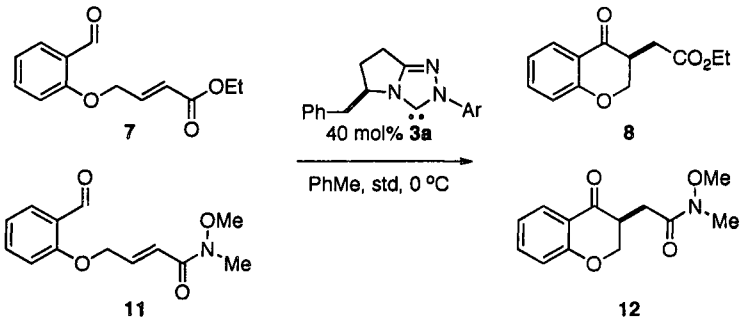
Scheme 9

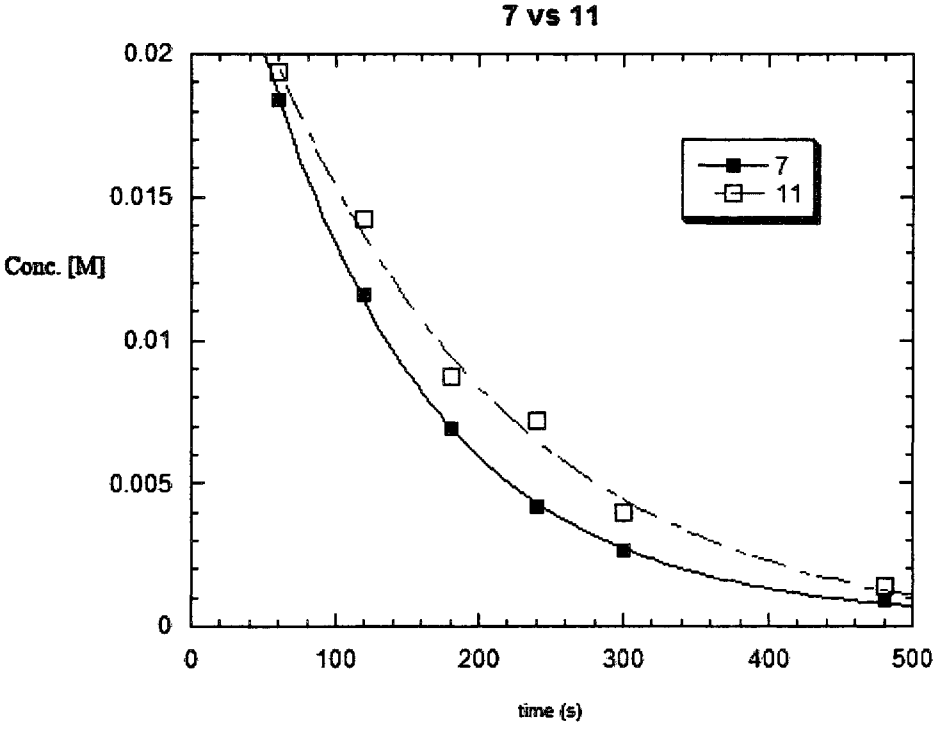




Aldehydes **11** and **15** were subjected to the same reaction conditions with catalyst **3a** to provide further evidence that **2a** and **3a** behave in the same manner. To our gratification, when the aldehyde possessing a Weinreb amide Michael acceptor **11** was reacted in competition with parent aldehyde **7**, the resulting relative rate is similar to that previously reported for **3a** (Scheme 10). The observed rates are k_7 = x 10^{-3} s^{-1} and k_{11} = 1.22 x 10^{-3} s^{-1}, leading to a relative rate, k_7/k_{11} = 1.33.

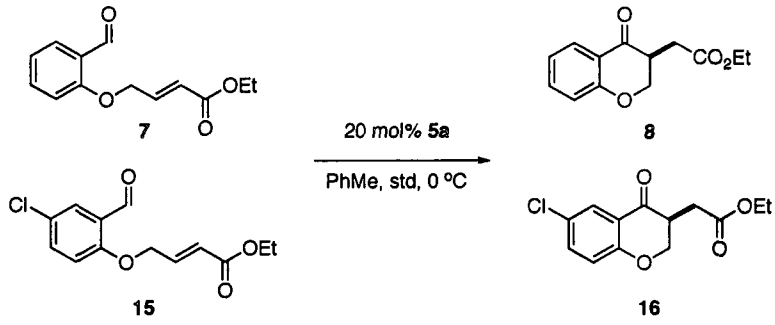
Scheme 10

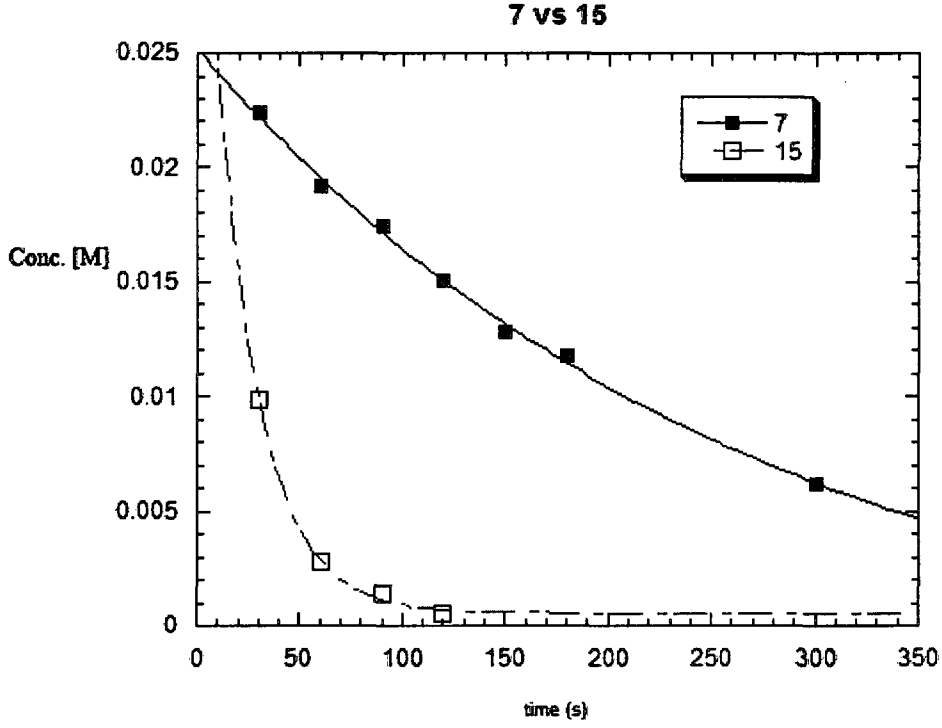




In a similar fashion, subjection of electron-poor aldehyde **15** and parent aldehyde **7** to catalyst **3a** proceeds with a rate relative rate of 11.7 (Scheme 11). The observed rates are $k_{15} = 4.33 \times 10^{-2}\ s^{-1}$ and $k_7 = 3.71 \times 10^{-3}\ s^{-1}$. The observation that **2a** and **3a** behave with little variation under the reaction conditions is consistent with the results of the competition experiments.

Scheme 11



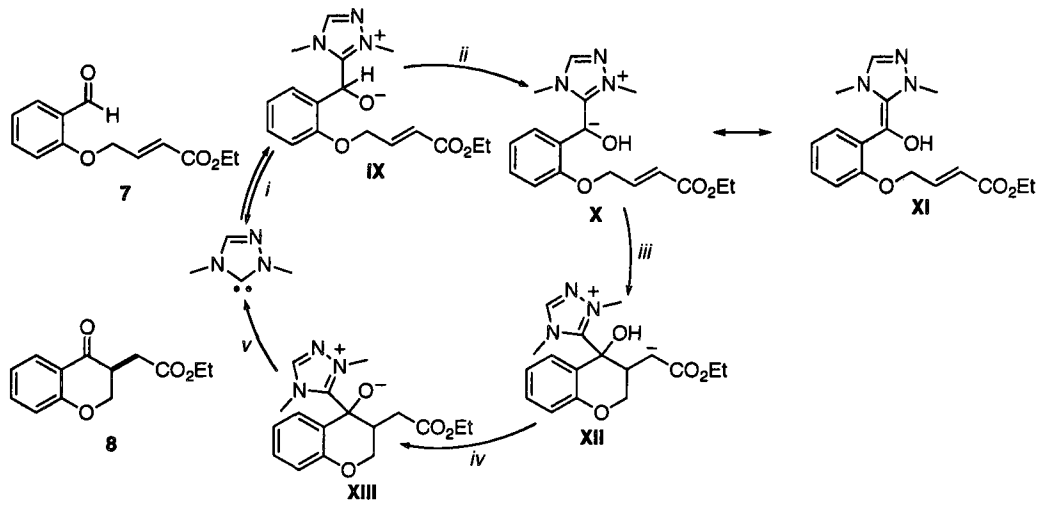


3.5 ^{13}C Kinetic Isotope Effects

Singleton and co-workers have elucidated the mechanisms for a number of concerted reactions by measuring ^{13}C kinetic isotope effects.[12] They have demonstrated that the kinetic isotope effect can be measured by integrating the natural abundance of ^{13}C in the starting material recovered from a reaction and comparing these values to the ^{13}C in the unreacted starting material. The accuracy of the integration values requires that there are no major side reactions and the reaction must be stopped at approximately 80% completion. In addition, at least 0.5 g of recovered starting material must be isolated and must be compared to starting material not submitted to the reaction but prepared from the same batch of starting material. This required the preparation of gram quantities of starting material since 2.2g of **7** is needed for the analysis.

In an effort to provide further support for our proposed mechanism, we set out to determine the ^{13}C kinetic isotope effect for this transformation, in collaboration with Daniel A. Singleton and Jacqueline Besinaiz-Thomas. Reactions of **7** mediated by 20 mol % **2a** / 3 mol % KHMDS at 0 °C were taken to ≈80% conversion. Unreacted **7** was reisolated and sent to Singleton and analyzed by ^{13}C NMR to compare with samples of the original **7**. The change in isotopic composition in each position was determined relative to the methylene group of the ethyl ester, with the assumption that isotopic fractionation of this carbon was negligible, and the KIEs were calculated as previously described.[12]

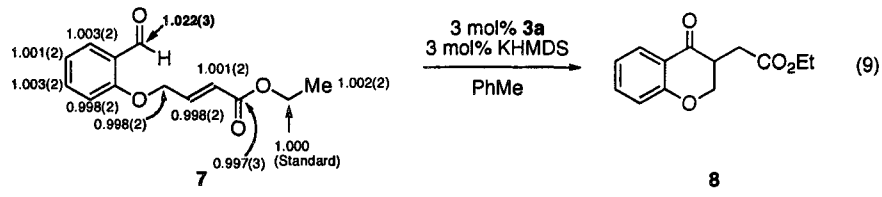
Scheme 2



If the reaction proceeds in a concerted fashion, an increase in the natural abundance of ^{13}C at the aldehyde carbon and the α carbon and β carbon of the Michael acceptor is expected. However, if addition of carbene to the aldehyde carbon (step *i*, Scheme 2) or proton transfer of the first tetrahedral intermediate **IX** (step *ii*) is rate-limiting, an increase in the natural abundance of the ^{13}C on the aldehyde carbon would be observed. Similarly, if the second proton transfer (step *iv*) is the rate determining step, a single increase in the natural abundance of ^{13}C would be observed on the carbon α to the ester. Another possibility is that carbon-carbon bond formation (step *iii*) is involved in the rate-limiting step such that both the aldehyde carbon and the β carbon of the Michael acceptor would exhibit a ^{13}C KIE.

As shown in eq. 9, the aldehydic carbon exhibits a substantial ^{13}C KIE of 1.022, but for the remaining carbons the KIE is negligible, ranging from 0.997 to 1.001. These results suggest that the aldehyde carbon is involved in the first irreversible step. Thus,

there are two possibilities for the rate determining step: carbene addition to the aldehyde or proton transfer from C→O (step *ii*, Scheme 2) is irreversible.



(9)

The results from the ^{13}C analysis cannot distinguish between these two scenarios. When coupled with the ^{2}H KIE noted above, we conclude that proton transfer occurs in rate-determining step for the intramolecular Stetter reaction under these reaction conditions.

Further ^{13}C kinetic isotopes have been conducted on the reaction in the absence of HMDS in order to confirm that a change in rate determining step does not occur. Therefore, kinetic and isotope effects in conjunction with competition experiments have established that proton transfer from **IX** → **X** (Scheme 2, step *ii*) is rate-determining.

3.6 Conclusion

A first order dependence was observed in both aldehyde concentration and triazolinylidene concentration. In addition, the ^{2}H KIE for this transformation is 2.62 suggesting a proton transfer occurs in the rate-limiting step. An investigation of various pre-catalysts is ongoing. Since proton transfer is rate-limiting, we will focus on tuning the electronics of the carbene to remove electron density from tetrahedral intermediate **IX** in an attempt to promote proton transfer, ultimately stabilizing the transition state during the proton transfer. Since the proton transfer is rate-limiting, we chose to explore

substrates in which the aldehydic proton is more acidic. This concept has provided insight into the intermolecular Stetter reaction.

We have combined facets from traditional mechanistic studies to develop a new and complete understanding of the mechanism with unprecedented detail. These results provide the foundation for the future development of better catalysts and expansion of substrate scope, and have already proven fruitful in the development of an enantioselective intermolecular Stetter reaction.

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Chapter 2 Experimental

Enantioselective Formation of Quaternary Stereocenters Using the Catalytic Intramolecular Stetter Reaction

General Methods: All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Tetrahydrofuran, diethylether, and dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, or $KMnO_4$ followed by heating. KHMDS was purchased from Aldrich Chemical Co. as a 0.5 M solution in toluene and used without purification. The purity of each compound is >95% as determined by ^1H NMR. ^1H NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometer at ambient temperature. Data is reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard (tetramethylsilane [TMS] or deuterated chloroform [$CDCl_3$]), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and bs = broad singlet), integration, and coupling constant (Hz). ^{13}C NMR were recorded on a Varian 75 or 100 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Analytical high performance liquid chromatography (HPLC) was performed on a Dynamax model SD-200 HPLC equipped with a Dynamax model UV-1 variable wavelength UV detector using a Chiracel OD-H, AD-H, or OB-H (0.46 cm X 25 cm) chiral column. Gas chromatography was performed

on a Varian Cp 3800 gas chromatograph equipped with a flame ionization detector using a Chiraldex B-DM or Chiraldex B-PH capillary gas chromatography column. Optical rotations were measured on an Autopol III automatic polarimeter in a 1 dm cell.

General procedure for the asymmetric intramolecular Stetter reaction of aromatic substrates: A flame-dried round bottom flask was charged with triazolium salt (0.02 mmol, 0.2 eq) and evacuated for 5 min, then covered with argon. Substrate (0.1 mmol, 1 eq) was added in toluene (1 mL) via syringe, followed by addition of KO*t*-Bu (0.2 mmol, 2 eq to substrate) and the solution was stirred at ambient temperature under argon for 24 h. The reaction was then poured onto a column of silica gel and eluted with a suitable solution of ethyl acetate in hexanes, to afford analytically pure product.

General procedure for the asymmetric intramolecular Stetter reaction of aliphatic substrates: A flame-dried round bottom flask was charged with triazolium salt (0.02 mmol, 0.2 eq) and toluene (1 mL) under argon. To this solution was added KHMDS (0.5M in toluene) (0.02 mmol, 0.2 eq) via syringe and the solution was stirred at ambient temperature for 5 min. Substrate (0.01 mmol, 1 eq) was added in toluene (1 mL) via syringe and allowed to stir for 24 h at ambient temperature. The reaction was then poured onto a column of silica gel and eluted with a suitable solution of ethyl acetate in hexanes, to afford analytically pure product.

Catalysts 10, 11, 12, and 29 previously reported[1]

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[1] Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, 70, 5725-5728.

Products 14, 16, 18, 26, 35, 37, 43, 45, 47, 49, 51, and 53 previously reported.[2]

General procedure for 13 and 15: The dithiane of salicylaldehyde was alkylated with the methyl pentynoate in DMF in the presence of KO*t*-Bu. The dithiane was subsequently removed with $Hg(O_2CCF_3)_2$ in acetonitrile.

General procedure for 17, 19, 21, 23, and 30: To a round bottom flask was added ether (90 mL) and cooled to 0°C followed by slow addition of lithium aluminum hydride (35.7 mmol, 2 eq). Thiosalicylic acid (17.83 mmol, 1 eq) was then slowly added. After additions were complete, the ice bath was removed and the reaction allowed to warm to room temperature overnight. The reaction was quenched with 10% sulfuric acid (30 mL) and ethyl acetate (30 mL), extracted with ethyl acetate (3 x 30 mL), washed with brine, dried with magnesium sulfate, and concentrated. The thiol was carried on immediately. The thiol (2.38 mmol, 1 eq) in acetone (24 mL) was added potassium carbonate (2.38 mmol, 1 eq). After 5 min the desired methyl propionate (2.38 mmol, 1 eq) was added and followed by TLC. The reaction mixture was concentrated and then diluted with ether, washed with ammonium chloride, and extracted with ether. The combined organics were washed with brine, dried with magnesium sulfate, and concentrated. (*E*)- and (*Z*)-isomers of alcohol were separated by flash chromatography (20% EtOAc in Hexanes) to afford 65-85% and 15-35% yields, respectively, and carried on immediately. The alcohol (1.89 mmol, 1 eq) was dissolved in methylene chloride (20 mL) followed by addition of Dess-Martin periodinate. After 3h, the reaction mixture was poured into a separatory funnel containing sodium thiosulfate (20 mL), sodium bicarbonate (20 mL), and ether (40 mL).

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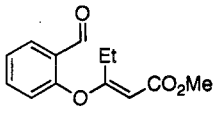
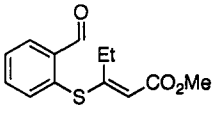
[2] Kerr, M. S. Thesis, Colorado State University, Fort Collins, CO, 2007.

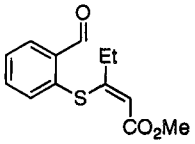
The organic layer was washed with water, brine, and dried over magnesium sulfate. The solution concentrated and purified via flash chromatography (20% EtOAc in Hexanes) to provide aldehyde in 30-75% yield, as a clear oil.



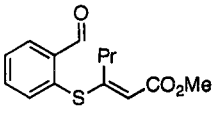
(*E*)-methyl 3-(2-formylphenoxy)pent-2-enoate (13): R_f = 0.46 (4:1 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.12 (s, 1H), 7.96-7.94 (m, 1H), 7.68-7.63 (m, 1H), 7.39-7.34 (m, 1H), 7.11-7.08 (m, 1H), 4.76 (s, 1H), 3.62 (s, 3H), 3.03 (q, 2H, *J* = 7.3 Hz), 1.33 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 177.9, 167.2, 155.9, 136.2, 129.2, 128.5, 126.5, 123.0, 96.8, 51.3, 24.9, 12.0; IR (NaCl, neat) 2948, 1715, 1691, 1631, 1452 cm^{-1}; HMRS (FAB+) calcd for $C_{13}H_{14}O_4$, 234.0892. Found 234.9698.



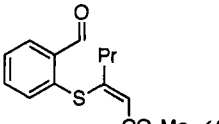
(*E*)-methyl 3-(2-formylphenylthio)pent-2-enoate (17): R_f = 0.40 (4:1 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.4 (s, 1H), 8.07-8.03 (m, 1H), 7.70-7.58 (m, 3H), 5.04 (s, 1H), 3.60 (s, 3H), 2.91 (q, 2H, *J* = 7.3 Hz), 1.29 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 166.2, 164.8, 137.6, 137.4, 135.2, 133.2, 131.0, 129.4, 111.6, 51.3, 27.5, 14.6; IR (NaCl, neat) 2945, 2836, 1690, 1582, 1182 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{14}O_3S$, 250.0664. Found 251.0746.



(*Z*)-methyl 3-(2-formylphenylthio)pent-2-enoate (*Z*-17): R_f = 0.35 (4:1 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.56 (s, 1H), 7.96-7.93 (m, 1H), 7.62-7.49 (m, 3H), 5.91 (s, 1H), 3.72 (s, 1H), 1.98 (q, 2H, *J* = 7.3 Hz), 0.91 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 166.6, 161.2, 138.2, 137.9, 134.7, 134.4, 130.4, 128.9, 112.4, 51.7, 30.8, 13.6; IR (NaCl, neat) 2975, 2948, 2853, 1701,1585 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{14}O_3S$, 250.0664. Found 250.0741.

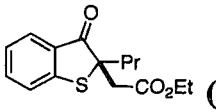


(*E*)-3-(2-Formyl-phenylsulfanyl)-hex-2-enoic acid methyl ester (19): R_f = 0.58 (7:3 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.4 (s, 1H), 8.05 (d, 1H, *J* = 7.2 Hz), 7.70-7.57 (m, 3H), 5.04 (s, 1H), 3.59 (s, 3H), 2.91-2.86 (m, 2H), 1.72 (s, 2H, *J* = 7.4 Hz), 1.03 (t, 3H, *J* = 7.3 Hz);^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 164.8, 137.5, 135.2, 133.3, 131.1, 129.4, 112.0, 51.3, 35.7, 23.6, 14.4;IR (NaCl, neat) 2961, 2871, 1697, 1600 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{16}O_3S$, 264.3400. Found 264.1874.

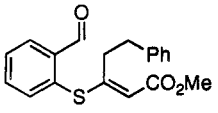


(*Z*)-3-(2-Formyl-phenylsulfanyl)-hex-2-enoic acid methyl ester (*Z*-19): R_f = 0.52 (7:3 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.6 (s, 1H), 8.00-7.97 (m, 1H), 7.64-7.54 (m, 3H), 5.94 (s, 1H), 3.76 (s, 3H), 2.02-1.97 (m, 2H), 1.33 (s, 2H, *J* = 7.4 Hz), .68 (t, 3H, *J* = 7.4 Hz);^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 166.6, 159.6, 138.1, 137.8,134.9,

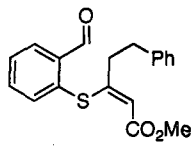
134.3, 130.3, 128.9, 113.6, 51.7, 39.2, 22.4,13.6;IR (NaCl, neat) 2962, 2872, 1698, 1585 cm^{-1}. HRMS (FAB+) calcd for $C_{14}H_{17}O_3S$, 265.0898. Found 265.0893.



(*R*) - (3-Oxo-2-propyl- 2,3 – dihydro –benzo [b] thiophen -2-yl)-acetic acid methyl ester (20). R_f = 0.43 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ = +21.2° ($CHCl_3$); HPLC analysis – Chiracel OD-H column, 90:10 hexanes to isopropanol 0.5 mL/ min, minor enantiomer : 6.0 min, major enantiomer : 7.5 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 1H, *J* = 7.7 Hz), 7.53 (t, 1H, *J* = 7.9 Hz), 7.37 (d, 1H, *J* = 7.9 Hz), 7.2 (t, 1H, *J* = 7.0 Hz), 3.56 (s, 3H), 3.07 (d, 1H, *J* = 16.7), 2.96 (d, 1H, 16.7 Hz), 1.86 (ddd, 2H, J = 5.5, 6.8, 9.6 Hz) 1.54 – 1.35 (m, 1H), 1.26 – 1.03 (m, 1H), .84 (t, 3H, *J* =7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 170.4, 152.1, 135.7, 131.3, 126.8, 124.9, 124.1, 62.7, 52.0, 42.8, 41.3, 17.9, 14.1; IR (NaCl, neat) 2958, 1741, 1699, 1591, 1449 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{17}O_3S$, 265.0898. Found 265.0885.

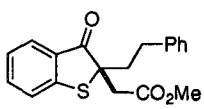


(*E*)-3-(2-Formyl-phenylsulfanyl)-5-phenyl-pent-2-enoic acid methyl ester (21): R_f = 0.54 (7:3 Hex/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 10.6 (s, 1H), 8.03-8.00 (m, 1H), 7.68-7.58 (m, 3H), 7.19-7.12 (m, 3H), 6.78-6.75 (m, 2H), 5.98 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 164.8, 163.4, 140.8, 137.6, 135.4, 131.1, 129.4, 128.8, 128.6, 126.5, 112.4, 51.4, 36.1; IR (NaCl, neat) 2947, 2856, 1697, 1601 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{19}O_3S$, 327.1055. Found 327.1044.

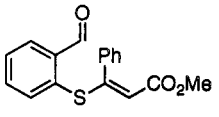


(*Z*)-3-(2-Formyl-phenylsulfanyl)-5-phenyl-pent-2-enoic acid methyl ester(*Z*-21):

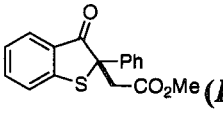
R_f = 0.45 (7:3 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.04 (d, 1H, *J* = 7.2 Hz), 7.69-7.53 (m, 3H), 7.34-7.22 (m, 5H), 5.08 (s, 1H), 3.61 (s, 1H); (100 MHz, $CDCl_3$) δ 191.6, 166.5, 158.6, 139.7, 138.2, 137.8, 134.7, 134.4, 130.5, 129.2, 128.7, 128.6, 128.4, 114.3, 51.6, 39.1, 35.7; IR (NaCl, neat) 2947, 1696, 1584, 1434 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{19}O_3S$, 327.1055. Found 327.1042.



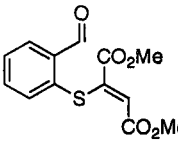
(*R*)-(3-Oxo-2-phenethyl-2,3-dihydro-benzo[b]thiophen-2-yl)-acetic acid methyl ester (22). R_f = 0.46 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ = -27.8° ($CHCl_3$): HPLC analysis - Chiracel OD-H column, 90:10 hexanes to isopropanol 0.5 mL/ min. Minor enantiomer: 9.3 min, major enantiomer: 11.8 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, 1H, *J* = 7.8 Hz), 7.57 (t, 1H, *J* = 6.9 Hz), 7.43 (d, 1H, *J* = 7.9 Hz), 7.26 – 7.10 (m, 6H), 3.59 (s, 3H), 3.12 (d, 1H, *J* = 16.8 Hz), 3.00 (d, 1H, *J* = 16.8 Hz), 2.79 – 2.67 (m, 1H), 2.47 – 2.37 (m, 1H), 2.27 – 2.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 170.3, 152.0, 140.92, 136.0, 131.3, 128.6, 126.9, 126.3, 125.1, 124.3, 62.6, 52.2, 43.1, 41.2, 31.0; IR (NaCl, neat) 2950, 1741, 1699, 1591, 1450 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{19}O_3S$, 327.1055. Found 327.1048.



(*E*)-3-(2-Formyl-phenylsulfanyl)-3-phenyl-acrylic acid methyl ester (23): R_f = 0.46 (7:3 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.49 (s, 1H), 7.65-7.62 (m, 1H), 7.35-7.21 (m, 3H), 7.05 (s, 5H), 6.15 (s, 1H), 3.81 (s, 3H); (100 MHz, $CDCl_3$) δ 191.1, 166.3, 158.2, 137.8, 136.6, 133.7, 129.1, 128.9, 128.7, 128.5, 128.3, 128.1, 117.4, 51.9, 29.9;IR (NaCl, neat) 1695, 1585, 1262 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{15}O_3S$, 299.0742. Found 299.0750.

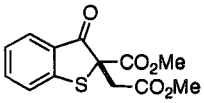


(*R*)-(3-Oxo-2-phenyl-2,3-dihydro-benzo[b]thiophen-2-yl)-acetic acid methyl ester (24). R_f = 0.46 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ = -10.3° ($CHCl_3$); HPLC analysis - Chiracel OD-H column, 90:10 hexanes to isopropanol 0.5 mL/ min. Minor enantiomer: 8.4 min, major enantiomer: 6.7 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, 1H, J = 7.9 Hz), 7.44 (t, 2 H, J = 8.1 Hz), 7.23-7.11 (m, 6H), 3.73 (s, 3H), 3.63 (d, 1H, J = 14.0 Hz), 3.56 (d, 1H, J = 14.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 169.6, 151.6, 136.1, 134.2, 130.9, 130.1, 128.0, 127.4, 127.2, 125.3, 123.9, 64.6, 53.7, 39.9; IR (NaCl, neat) 2952, 1738, 1699, 1589, 1450 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{15}O_3S$, 299.0742. Found 299.0739.

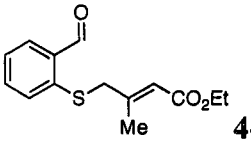


(*Z*)-2-(2-Formyl-phenylsulfanyl)-but-2-enedioic acid dimethyl ester (27): R_f = 0.45 (7:3 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.46 (s, 1H), 8.01-7.99 (m, 1H), 7.63-7.59 (m, 3H), 5.66 (s, 1H), 3.66 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (100 MHz,

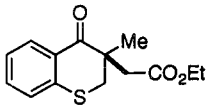
$CDCl_3$) δ 190.8, 164.8, 163.9, 137.4, 134.9, 131.2, 129.9, 117.1, 53.2, 52.3; IR (NaCl, neat) 2952, 1736, 1698, 1586,1434 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{13}O_5S$, 281.0483. Found 281.0491.



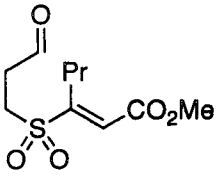
2-Methoxycarbonylmethyl-3-oxo-2,3-dihydro-benzo[b]thiophene-2-carboxylic acid methyl ester (28). R_f = 0.36 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ = +20.6° ($CHCl_3$); HPLC analysis - Chiracel AD-H column, 97:3 hexanes to isopropanol 1.0 mL/ min, minor enantiomer: 20.0 min, major enantiomer: 22.7 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, 1H, J = 7.9 Hz), 7.58 (t, 1H, J = 8.1 Hz), 7.40 (d, 1H, J = 8.1 Hz), 7.25 (m, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 3.53 (d, 1H, J = 17.3 Hz), 3.11 (d, 1H, J = 17.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 170.3, 168.5, 151.9, 136.3, 129.7, 127.7, 125.7, 124.1, 62.4, 53.9, 52.4, 39.7; IR (NaCl, neat) 2954, 1738, 1705, 1587 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{13}O_5S$, 281.0484. Found 281.0480.



4-(2-Formyl-phenylsulfanyl)-3-methyl-but-2-enoic acid ethyl ester (30): R_f = 0.41 (7:3 Hex/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 10.40 (s, 1H), 7.86 (d, 1H, J = 7.9 Hz), 7.52 (t, 1H, J = 7.9 Hz), 7.36 (m, 2H), 5.72 (s, 1H), 4.12 (q, 2H, J = 7.1 Hz), 3.60 (s, 2H), 2.29 (s, 3H), 1.25 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 166.1, 152.3, 140.2, 135.0, 134.3, 132.0, 130.3, 126.7, 119.1, 60.1, 43.9, 18.4, 14.4; IR (NaCl, neat) 2980, 1713, 1695, 1651, 1587,1560 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{17}O_3S$, 265.0898. Found 265.0895.



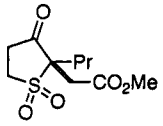
(*R*)-(3-Methyl-4-oxo-thiochroman-3-yl)-acetic acid ethyl ester (33). R_f = 0.38 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ = +41.6° ($CHCl_3$); HPLC analysis - Chiracel OD-H column, 90:10 hexanes to isopropanol 0.5 mL/ min. Minor enantiomer: 8.8 min, major enantiomer: 7.5 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, 1H, *J* = 8.6 Hz), 7.36 (t, 1H, *J* = 6.5 Hz), 7.25 – 7.14 (m, 2H), 4.13 (d, 1H, *J* = 7.1 Hz), 4.11 (q, 2H, *J* = 7.1 Hz), 3.74 (d, 1H, *J* = 13.5 Hz), 3.01 (d, 1H, *J* = 16.1 Hz), 2.98 (d, 1H, *J* = 13.5 Hz), 2.56 (d, 1H, *J* = 16.1 Hz), 1.40 (s, 3H), 1.23 (t, 3H, 7.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 171.2, 141.4, 133.2, 130.6, 130.0, 127.5,125.2, 60.8, 43.6, 41.2, 36.6, 21.2, 14.4; IR (NaCl, neat) 2978, 1732,1676, 1589, 1435 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{17}O_3S$, 265.0898. Found 265.0905.



3-(3-Oxo-propane-1-sulfonyl)-hex-2-enoic acid methyl ester (40): Thiopropanol (1.98 mmol, 1 eq) in acetone (20 mL) was added potassium carbonate (1.98 mmol, 1 eq). After 5 min, methyl 2-hexynoate (1.98 mmol, 1 eq) was added and allowed to stir overnight. Reaction mixture concentrated then diluted with ether, washed with ammonium chloride, and extracted with ether. Combined organics washed with brine, dried with magnesium sulfate, and concentrated. (*E*)- and (*Z*)-isomers of sulfide were separated by flash chromatography (20% EtOAc in Hexanes) to afford 40% and 10% yields, respectively, and carried on immediately. To a stirred mixture of magnesium

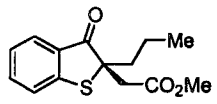
sulfate (3.97 mmol, 9 eq) and *m*-CPBA (1.32 mmol, 3 eq) in dry methylene chloride (4.5 mL) was added a solution of sulfide (0.44 mmol, 1 eq) in methylene chloride (.1M). Reaction mixture stirred overnight, then filtered off precipitate and washed thoroughly with methylene chloride. Combined organics concentrated and purified by flash chromatography (20% EtOAc in hexanes, increasing to 50% EtOAc in hexanes). Sulfone obtained in 93% yield and carried on immediately.

The sulfone (1.12 mmol, 1 eq) was dissolved in 4:1 methylene chloride (11 mL) was added triethylamine (7.28 mL) and solid SO_3·pyridine complex (3.92 mmol, 3.5 eq). Reaction stirred for 90 min and treated with sodium bicarbonate (5 mL) and extracted with 2:1 hexanes/ether. Combined organics washed with brine and dried over magnesium sulfate. Aldehyde purified by flash chromatography (30% EtOAc in hexanes) to afford substrate in 15% yield. R_f = 0.14 (7:3 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 6.78 (s, 1H), 3.80 (s, 1H), 3.33 (t, 2H, J = 7.4 Hz), 3.00 (t, 2H, J = 7.3 Hz), 2.81 – 2.75 (m, 2H), 1.67 (ddq, 2H, J = 7.3, 7.3, 18.1 Hz) 1.01 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 164.4, 156.3, 128.1, 52.6, 45.8, 36.1, 30.2, 23.4, 14.6; IR (NaCl, neat) 2964, 1728, 1435, 1314 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{17}O_5S$, 249.0797. Found 249.0796.



(1,1,3,-Trioxo-2-propyl-tetrahydro-1,6-thiophen-e-yl)-acetic acid methyl ester (41). R_f = 0.15 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ = +24.5° ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.65 (ddd, 1H, J = 12.5, 11.7, 8.5 Hz), 3.50 (ddd, 1H, J = 12.5, 9.2, 2.4 Hz), 3.17 (d, 1H, J = 17.9 Hz), 3.11 (ddd, 1H, J = 17.9, 8.5, 2.2 Hz), 3.10 (d, 1H,

J = 17.9 Hz), 2.88 (ddd, 1H, J = 17.9, 11.6, 9.1 Hz), 1.87 (ddd, 1H, J = 14.1, 9.3, 7.1 Hz), 1.70 (dm, 1H, J = 14.1 Hz), 1.48 (ddq, 2H, J = 9.3, 7.1, 7.1 Hz), 0.93 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 171.4, 65.8, 52.8, 50.7, 39.4, 36.7, 36.3, 17.7, 14.4; IR (NaCl, neat) 2964, 1732, 1439, 1313 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{16}O_5S$, 248.0718. Found 248.0705.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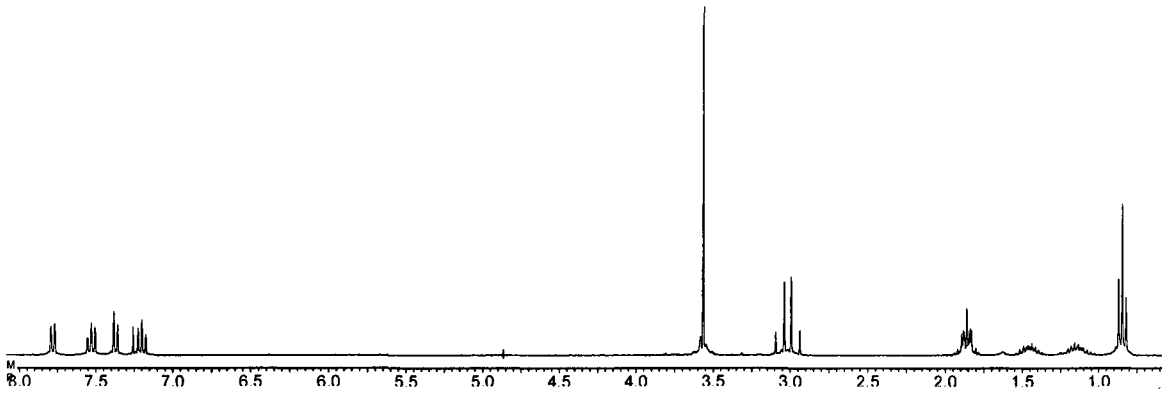
Me
S
CO2Me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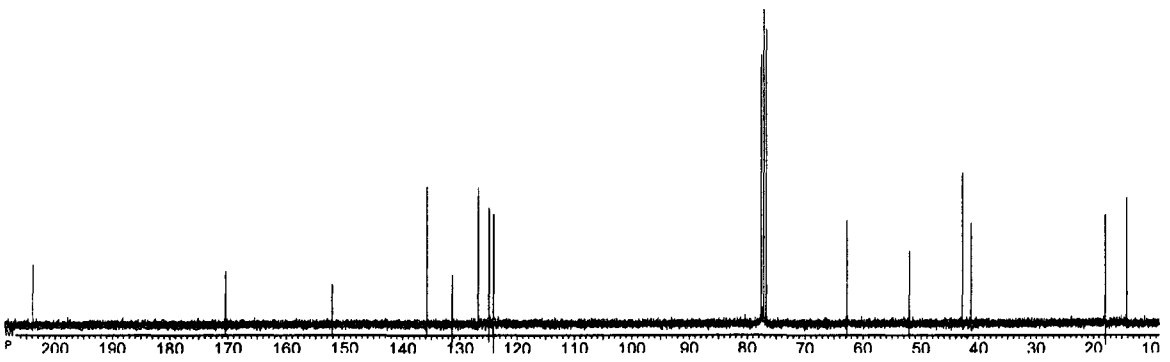
1.0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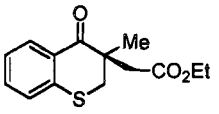
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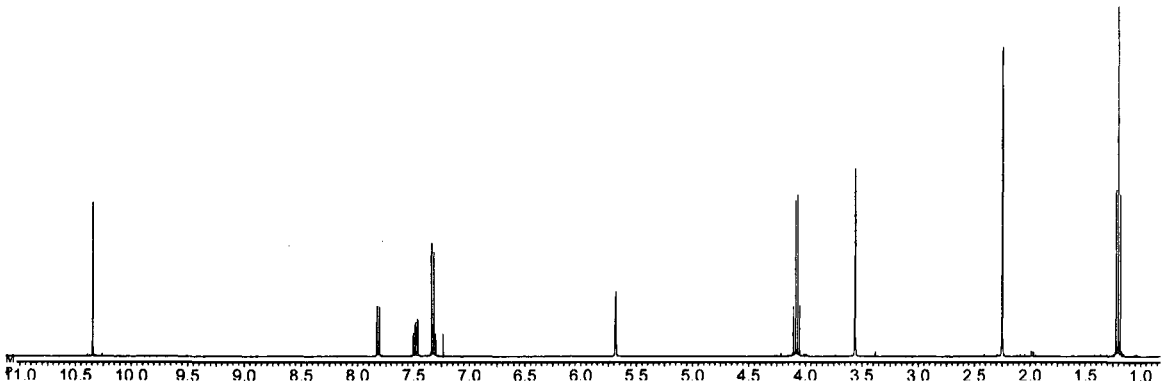
S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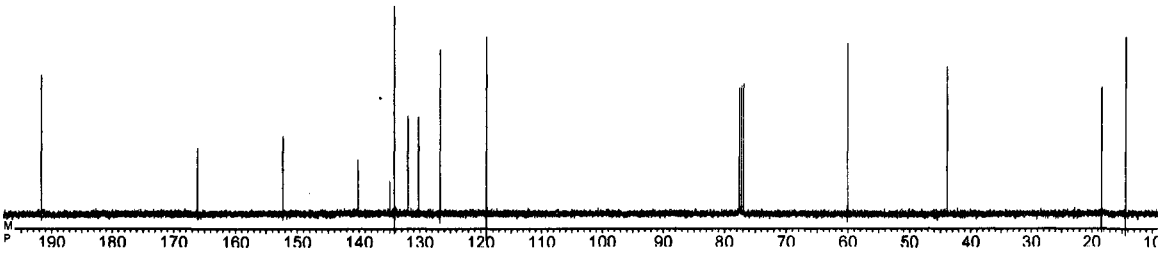
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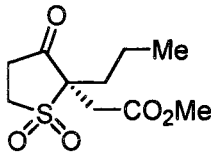
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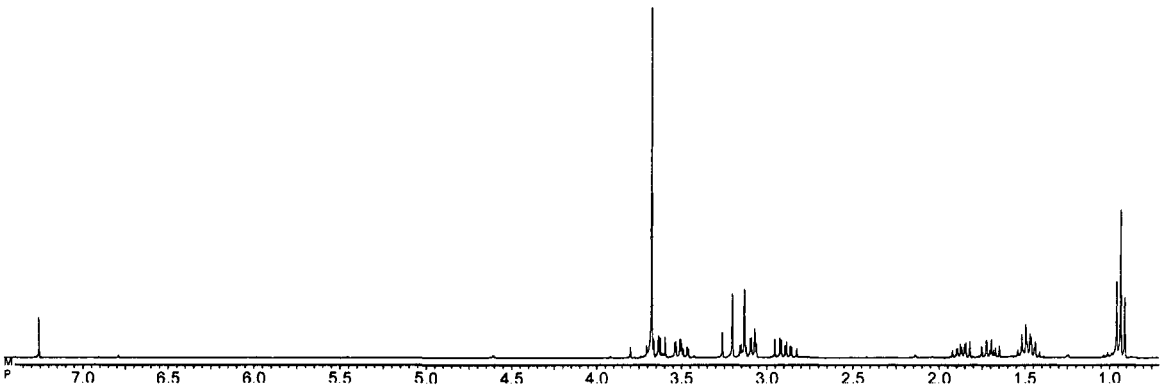
S
O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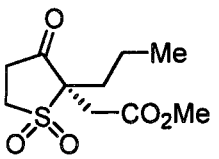
1.0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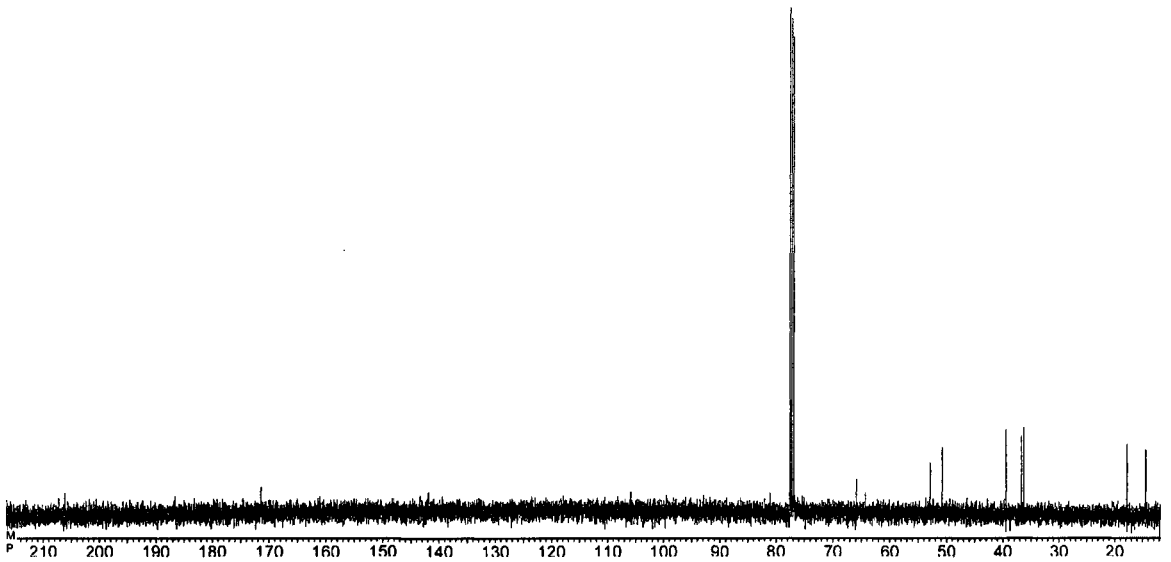
O
S
O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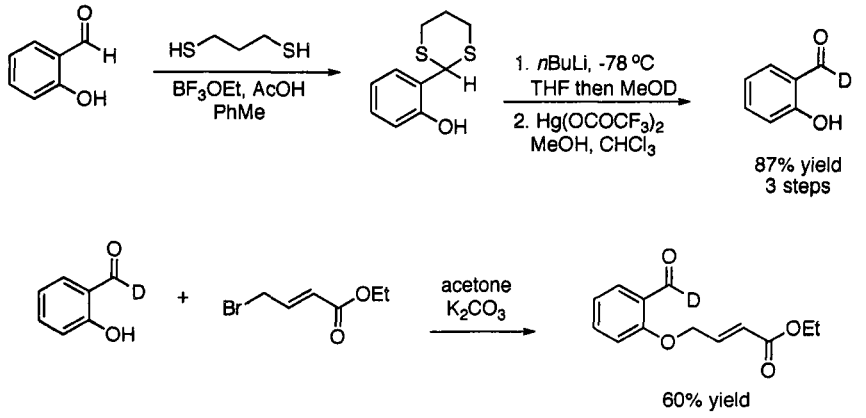
Chapter 3 Experimental

Mechanistic Investigation of the Enantioselective Stetter Reaction

General Methods: All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, or $KMnO_4$ followed by heating. KHMDS was purchased from Aldrich Chemical Co. and used without purification. 0.5 M solutions in toluene were prepared prior to each reaction in an inert atmosphere glove box. The purity of each compound is >95% as determined by ^1H NMR. Analytical high performance liquid chromatography (HPLC) was performed on a Dynamax model SD-200 HPLC equipped with a Dynamax model UV-1 variable wavelength UV detector using a Chiracel OD-H, AD-H, or OB-H (0.46 cm X 25 cm) chiral column. Gas chromatography was performed on a Varian Cp 3800 gas chromatograph equipped with a flame ionization detector using a Chiraldex B-DM or Chiraldex B-PH capillary gas chromatography column.

Substrate 7 and 7-D, Products 8 and 8-D were previously reported.[1]

Preparation of substrate 7-D:

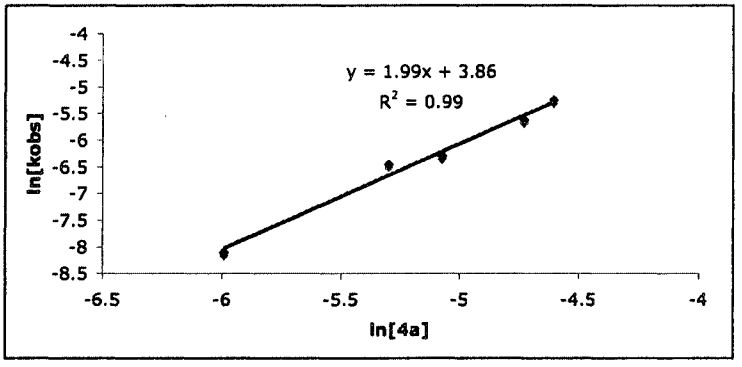


General procedure for the asymmetric intramolecular Stetter reaction monitored by gas chromatography (*in situ*): To a flame dried round bottom flask was added **2a** (10.8 mg, 0.030 mmol) and 1mL toluene. The solution was degassed for 5 min with argon bubbling through the solution. To this solution was added 120 μL KHMDS (0.030 mmol, 0.25 M solution in toluene prepared for each reaction), 4 mL toluene , cooled to 0 °C and stirred for 5 min. To the reaction mixture was added a solution, in 1 mL toluene, of aldehyde **7** (149 mmol, 34.8 mg) and di-*tert*-butyl-biphenyl (internal standard) (0.074 mmol, 20.0 mg). The resulting solution was stirred at 0 °C and 0.1 mL aliquots were taken at set time intervals. The aliquots were immediately worked up by passing through a small pipet column and eluted with 100% ethyl acetate. GC analysis – CP Wax 52CB column 180 °C at 3mL/min. Product **8**: 2.1 min, starting material **7**: 2.9 min, di-*tert*-butyl-biphenyl: 4.9 min.

[1] Read de Alaniz, Javier, Thesis, Colorado State University, Fort Collins, CO, 2006.

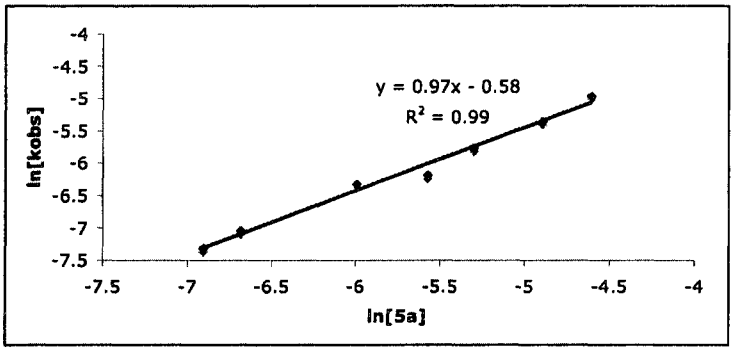
General procedure for the asymmetric intramolecular Stetter reaction monitored by gas chromatography (free carbene): To a flame dried round bottom flask was added **2a** (10.8 mg, 0.030 mmol) and 1mL toluene. The solution was degassed for 5 min with argon bubbling through the solution. To this solution was added 120 μL KHMDS (0.030 mmol, 0.25 M solution in toluene prepared for each reaction), stirred for 5 min and concentrated under vacuum for 30 min. The residue was then dissolved in 5 mL of toluene. To the reaction mixture was added a solution, in 1 mL toluene, of aldehyde **7** (149 mmol, 34.8 mg) and di-*tert*-butyl-biphenyl (internal standard) (0.074 mmol, 20.0 mg). The resulting solution was stirred at 0 °C and 0.1 mL aliquots were taken at set time intervals. The aliquots were immediately worked up by passing through a small pipet column and eluted with 100% ethyl acetate. GC analysis – CP Wax 52CB column 180 °C at 3mL/min. Product **8**: 2.1 min, starting material **7**: 2.9 min, di-*tert*-butyl-biphenyl: 4.9 min.

Figure 1



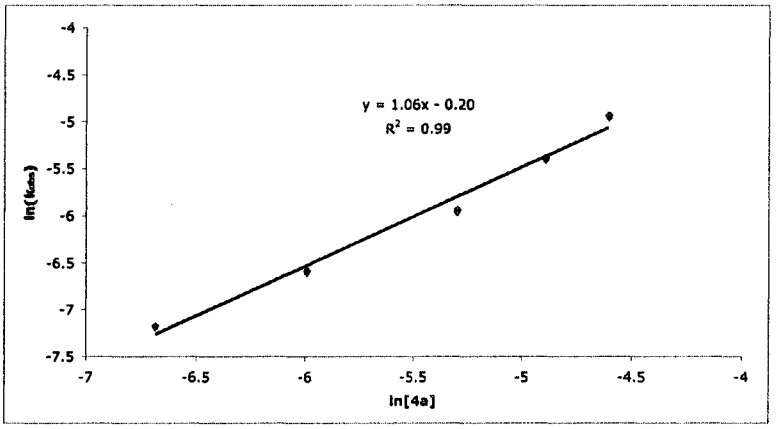
entry	[7] M	[2a]^2 M	k_{obs}(M s-1)	k (M^{-2} s^{-1})
1	0.025	6.25E-06	3.42E-04	2.19E+03
2	0.025	6.25E-06	2.69E-04	1.72E+03
3	0.025	2.50E-05	1.51E-03	2.42E+03
4	0.025	2.50E-05	1.53E-03	2.45E+03
5	0.025	2.50E-05	1.67E-03	2.67E+03
6	0.025	3.91E-05	1.85E-03	1.89E+03
7	0.025	7.78E-05	3.52E-03	1.81E+03
8	0.025	7.78E-05	3.74E-03	1.92E+03
9	0.025	1.00E-04	5.30E-03	2.12E+03
10	0.025	1.00E-04	5.23E-03	2.09E+03
11	0.025	1.00E-04	5.20E-03	2.08E+03

Figure 2



entry	[7] M	[5a] M	k_{obs}(M s-1)	k ($M^{-1} s^{-1}$)
1	0.025	0.001	6.68E-04	2.67E+01
2	0.025	0.00125	8.54E-04	2.73E+01
3	0.025	0.00125	8.83E-04	2.83E+01
4	0.025	0.00125	8.81E-04	2.82E+01
5	0.025	0.0025	2.08E-03	3.33E+01
6	0.025	0.0025	1.46E-03	2.34E+01
7	0.025	0.0025	1.92E-03	3.07E+01
8	0.025	0.0038	2.03E-03	2.14E+01
9	0.025	0.0038	1.80E-03	1.89E+01
10	0.025	0.0038	2.38E-03	2.51E+01
11	0.025	0.005	3.32E-03	2.66E+01
12	0.025	0.005	2.71E-03	2.17E+01
13	0.025	0.005	3.40E-03	2.72E+01
14	0.025	0.0075	4.71E-03	2.51E+01
15	0.025	0.01	7.12E-03	2.85E+01
16	0.025	0.01	7.23E-03	2.89E+01
17	0.025	0.01	6.67E-03	2.67E+01

Figure 3



entry	[**9**] M	[**4a**] M	k_{obs}(M s-1)	k ($M^{-1} s^{-1}$)
1	0.025	0.00125	7.71E-04	2.47E+01
2	0.025	0.00125	7.18E-04	2.30E+01
3	0.025	0.00125	8.15E-04	2.61E+01
4	0.025	0.0025	1.23E-03	1.97E+01
5	0.025	0.0025	1.39E-03	2.22E+01
6	0.025	0.0025	1.54E-03	2.46E+01
7	0.025	0.005	3.10E-03	2.48E+01
8	0.025	0.005	2.64E-03	2.11E+01
9	0.025	0.005	2.59E-03	2.07E+01
10	0.025	0.005	2.43E-03	1.94E+01
11	0.025	0.005	2.47E-03	1.98E+01
12	0.025	0.0075	4.50E-03	2.40E+01
13	0.025	0.0075	4.82E-03	2.57E+01
14	0.025	0.0075	4.90E-03	2.61E+01
15	0.025	0.0075	4.10E-03	2.19E+01
16	0.025	0.01	7.46E-03	2.98E+01
17	0.025	0.01	7.31E-03	2.92E+01
18	0.025	0.01	6.83E-03	2.73E+01