DISSERTATION

DEVELOPMENT OF A CATALYTIC ENANTIOSELECTIVE INTRAMOLECULAR STETTER REACTION: CATALYST DEVELOPMENT AND SYNTHETIC APPLICATIONS

Submitted by

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY MARK STEVEN KERR ENTITLED DEVELOPMENT OF A CATALYTIC ENANTIOSELECTIVE INTRAMOLECULAR STETTER REACTION: CATALYST DEVELOPMENT AND SYNTHETIC APPLICATIONS BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS OF THE DEGREE OF DOCTOR OF PHILOSOPHY.

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ABSTRACT OF DISSERTATION

DEVELOPMENT OF A CATALYTIC ENANTIOSELECTIVE INTRAMOLECULAR STETTER REACTION: CATALYST DEVELOPMENT AND SYNTHETIC APPLICATIONS

A triazolinylidene carbene-catalyzed enantioselective intramolecular Stetter reaction has been developed. The process involves direct conversion of an aldehyde into a chiral acyl anion equivalent and its addition into a pendant electron-deficient olefin. The development of chiral bicyclic nucleophilic carbene catalysts has allowed for increased efficiency and selectivity in this reaction, as well as an overall broadening of its synthetic utility.

The highly stereoselective formation of five- and six-membered rings has been realized in this reaction manifold. Extensive catalyst development has identified a number of catalysts which often provide complementary reactivity and selectivity. Aliphatic and aromatic aldehydes both participate in the addition to a variety of Michael acceptors. Synthetically important enantioenriched 1,4-dicarbonyl compounds can be generated in a single operation from achiral materials.

The Stetter reaction has been developed to construct challenging quaternary stereocenters with good efficiency and very high selectivity. The scope of this transformation is quite broad, and holds significant promise for further reaction development.

Synthetic applications have been investigated in the arena of natural product synthesis. Progress has been made utilizing the Stetter reaction for a key bond

construction in an effort to enantioselectively synthesize a complex alkaloid. The key Stetter reaction in this system affords the desired product in good yield and excellent enantioselectivity.

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Finally, I have to thank my parents for all of their support, and teaching me things I could never have made it through here without knowing.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AcOH	acetic acid
Boc_2O	di-*tert*-butyl dicarbonate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-(dimethylamino)pyridine
LiHMDS	lithium hexamethyldisilazide
NaHMDS	sodium hexamethyldisilazide
KHMDS	potassium hexamethyldisilazide
Hünig's Base	di-isopropylethyl amine
TFA	trifluoroacetic acid
TsOH	*para*-toluenesulfonic acid
Py	pyridine
TBAF	tetrabutyl ammonium fluoride
TFAA	trifluoroacetic anhydride
KO*t*-Bu	potassium *tert*-butoxide
TBSCl	*tert*-butyldimethylsilyl chloride
LAH	lithium aluminum hydride

Chapter 1

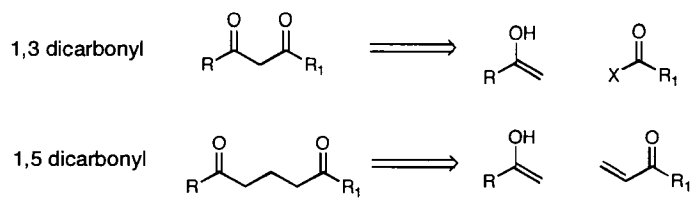
The Development of Chiral Bicyclic Nucleophilic Carbenes for the Catalytic Enantioselective Intramolecular Stetter Reaction

1.1 Introduction

1.1.1 Acyl Anion Equivalents in the Synthesis of 1,4-Dicarbonyl Compounds

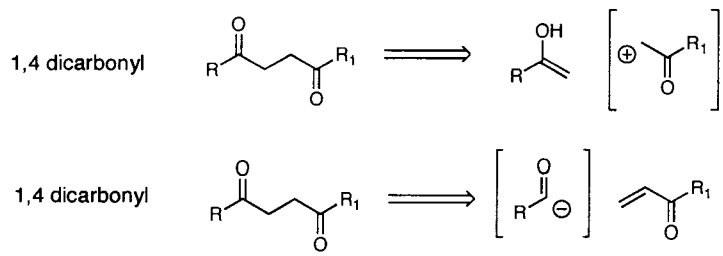
Small organic molecules possessing the 1,4-dicarbonyl relationship represent an important building block for the synthesis of complex molecules. Unfortunately, few reliable methods exist for their direct generation, particularly with control over absolute and relative stereochemistry.[1] Many specific transformations allow for the synthesis of these molecules, yet a general solution to this problem remains lacking. One reason for the paucity of methods to synthesize molecules containing this functionality pattern lies in the conventional reactivity of carbonyl compounds. When considering carbonyl reactivity, one envisions the α-carbon nucleophilic, with the carbonyl center electrophilic. Enolate addition into an activated acid functionality allows for facile generation of 1,3-dicarbonyl compounds, Figure 1. For α,β-unsaturated carbonyl compounds, the β-position is also rendered electrophilic. Taking advantage of this type of reactivity allows for the 1,5-dicarbonyl system to be accessed through enolate/Michael acceptor reactivity. The Mukaiyama Michael reaction has been extensively studied as a method to execute this strategy, and effective enantioselective variants have been developed.[2]

Figure 1.



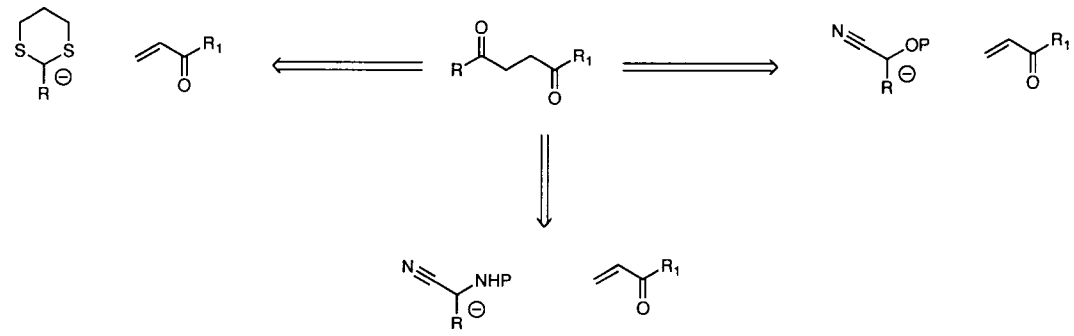
An attractive approach to obtaining 1,4-dicarbonyl compounds is through polarity reversal (Umpolung[3] reactivity), either in the context of an electrophilic atom α to a carbonyl, or a nucleophilic carbonyl (acyl anion equivalent), Figure 2. The former has yet to be demonstrated as a widely viable way to access this relationship.[4] However, the generation of acyl anion equivalents appears to be an attractive solution to this problem.

Figure 2.



A number of stoichiometric methods are available for the conversion of an aldehyde into a nucleophilic functional group, Figure 3. One of the most common involves the conversion of an aldehyde into a dithiane. The dithiane can then be deprotonated with a strong base such as butyl lithium, and then add into an electrophile.[5] While this has been accomplished in asymmetric fashion with chiral dithiane dioxides, results have been mediocre at best, and require 3 extra functional group manipulations.[6] Another way of accessing a chiral acyl anion equivalent involves the generation of a cyanohydrin.[7] In addition to these two most commonly employed strategies, aminonitriles have been utilized to function as chiral acyl anion equivalents.[8]

Figure 3.



Several problems are inherent with these systems. Most importantly, extra steps are required for installation and removal of this functional group. Another drawback is the requirement of strong base, typically alkyl lithium reagents to form the anion. A direct, catalytic method for generation of an acyl anion equivalent would represent a significant advance in this field and provide a powerful way for synthetic chemists to look at molecular disconnections.

The first report of a chemical reaction involving an acyl anion intermediate dates back nearly to the beginning of organic chemistry. As early as 1832, synthetic chemists had known of the Benzoin reaction.[9] Wohler and Liebig were the first to report this transformation, and a mechanism was proposed in 1903.[10] These reports involved the use of cyanide ion to create an acyl anion equivalent from benzaldehyde, which then reacts with another molecule of of benzaldehyde to give benzoin. Cyanide has been extensively utilized in the catalysis of the Benzoin reaction, and a large body of work has been published on this topic.[11] In 1973, this reactivity was extended by Stetter and coworkers to capture this generated acyl anion with a Michael acceptor to form 1,4-dicarbonyl compounds.[12]

1.1.2 N-Heterocyclic Carbenes and the Catalytic Generation of Acyl Anion Equivalents

The chemistry of nucleophilic carbenes has experienced an explosion of growth since the seminal report of a stable, crystalline carbene from Arduengo and coworkers in 1991.[13] The use of these carbenes as modifying ligands for transition metals has attracted an enormous amount of attention and been of extreme importance to recent advances in organometallic chemistry.[14] Another topic of growing interest is the use of these carbenes as catalysts or reaction mediators in organic transformations.[15] Among the organic reactions catalyzed by heteroazolium ylides/carbenes, a majority of efforts have focused on the generation of acyl anion equivalents.

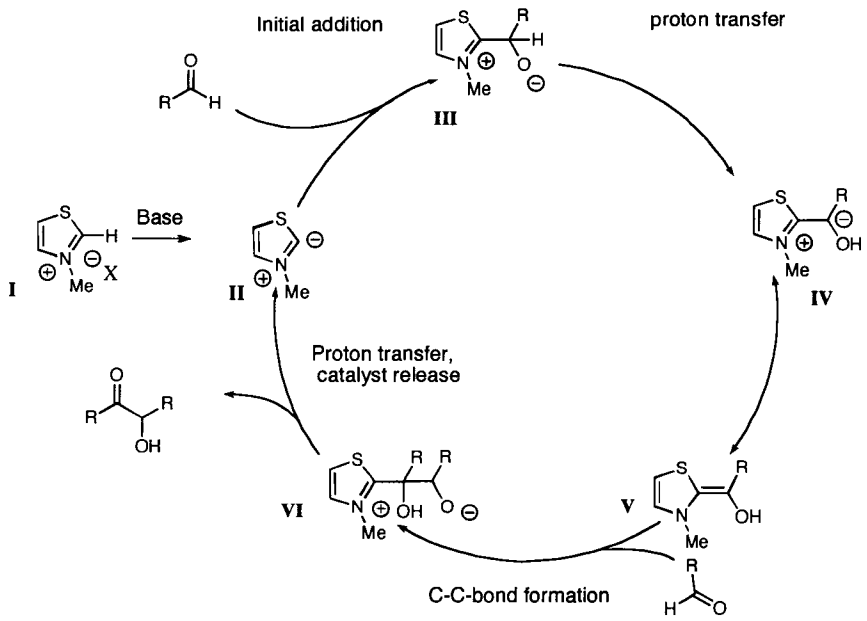
Ukai and coworkers were the first to identify the ability of thiazolinylidene ylides to catalyze the Benzoin reaction.[16] These thiazolium salt catalyst precursors are necessarily related to nature's variant, thiamine pyrophosphate (vitamin B_1). This molecule is the catalytic cofactor for biochemical reactions catalyzed by a variety of enzymes such as pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and transketolase.[17]

The mechanism of the thiazolinylidene ylide-catalyzed Benzoin reaction was proposed by Breslow in the 1950's, Scheme 1.[18] Thiazolium salt **I** is deprotonated to provide active catalyst **II**. The catalytic cycle begins with nucleophilic addition of the ylide into an aldehyde. This generates a zwitterionic tetrahedral intermediate, **III**. The thiazolium ring acts as a strong electron withdrawing group and renders the former aldehydic proton acidic. Proton transfer gives **IV**, the acyl anion equivalent, a resonance form of **V**. This nucleophilic species can then react with another equivalent of aldehyde in order to form the second tetrahedral intermediate **VI**. Proton transfer and collapse of this tetrahedral

intermediate forms the benzoin product, and regenerates the thiazolinylidene ylide for reentry into the catalytic cycle.

Of particular interest in this catalytic cycle are intermediates **IV** and **V**, the acyl anion equivalent. One can imagine if the thiazole moiety is chiral and non-racemic, the C-C bond formation may occur enantioselectively.

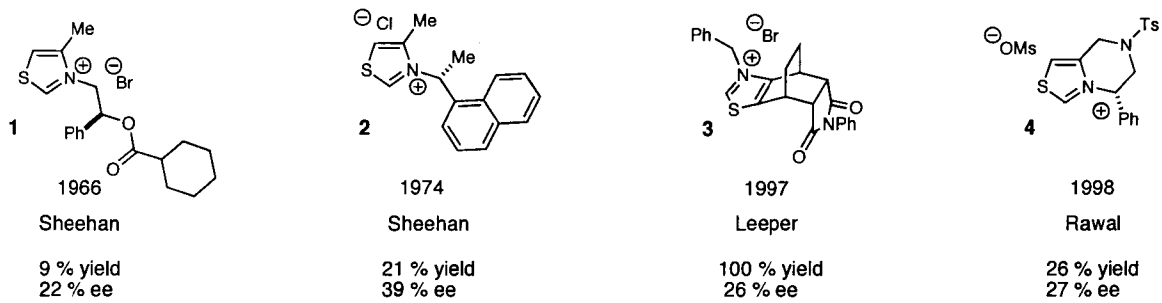
Scheme 1.



An asymmetric variant of this transformation was reported by Sheehan in 1966, one of the first homogeneous catalytic asymmetric reactions.[19] An enantiomeric excess of 22 % was obtained employing chiral thiazolium salt **1** (Figure 4) as a catalyst precursor. Attempts have been made ever since to improve on the selectivity and reaction efficiency. Over the following 30 years, a number of attempts were made to tune the properties of thiazolium salts as catalyst precursors for the enantioselective Benzoin reaction.[20] Some examples of thiazolium salt catalyst precursors are shown in Figure 4. Among the

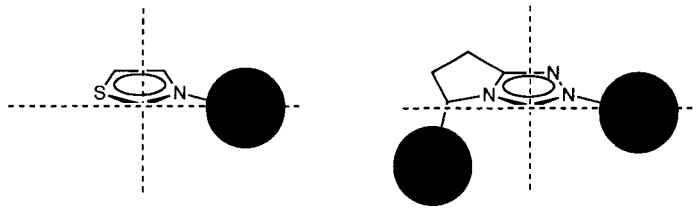
advances in the field are the introduction of chirality closer to the thiazole ring by Sheehan (catalyst precursor **2**), an adjustment that nearly doubled the enantiomeric excess obtained in the reaction.[21] Also relevant is the implementation of a polycyclic catalyst by Leeper and coworkers (**3**), giving a highly increased yield, albeit little increase in selectivity.[22] Further work by Rawal led to the use of a chiral, bicyclic system with the chirality locked into place near the reactive site of the catalyst (**4**).[23] While this served as an important conceptual advance, the yields and enantioselectivities were not significantly improved.

Figure 4.



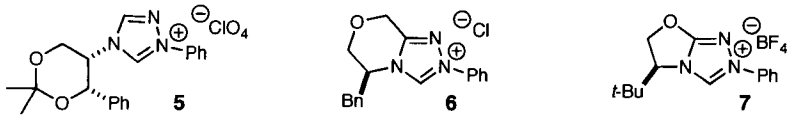
An inherent problem with the use of thiazolium salts as catalyst precursors involves the drawback of being able to possess steric bulk on only one side of the catalyst, as divalent sulfur cannot support another substituent, Figure 5. Examination of a chiral, bicyclic thiazolium salt such as that reported by Rawal[23] (**4**, Figure 4) illustrates that occupation of only two quadrants of the catalytic space about the reactive center is possible. However, exchanging sulfur for trivalent nitrogen allows for substitution on both sides of the catalyst. The use of an imidazolium or triazolium salt with proper substitution could potentially allow for the occupation of three quadrants of the chiral space about the catalytic site.

Figure 5.



This concept has led to several catalysts capable of achieving high enantioselectivity in the Benzoin reaction, Figure 6. The first example by Enders and coworkers demonstrated that triazolium salt **5** is a highly competent catalyst precursor for the Benzoin reaction.[24] New benchmarks were reached with the implementation of this triazolium salt in the presence of potassium carbonate as base. In a further advance in catalyst design for the Benzoin reaction, Leeper and coworkers combined the use of a bicyclic system (**6**) in order to lock the chiral information into place around the triazolium scaffold.[25] This catalyst proved capable of catalyzing the reaction and providing benzoin in 80% enantiomeric excess. The high water mark for efficiency and selectivity in the Benzoin reaction was later reached by Enders with *tert*-leucinol-derived triazolium salt **7**.[26]

Figure 6.

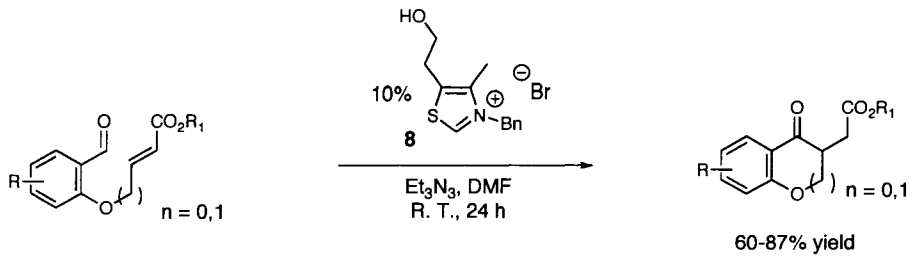


1996	1998	2002
Enders	Leeper	Enders
75 % yield 66 % ee	45 % yield 80 % ee	83 % yield 90 % ee

Along with the development of the Benzoin reaction, attempts have been made to harness the chemistry of a catalytically generated acyl anion equivalent into a variety of different electrophiles. The first successful implementation of the acyl anion equivalent was performed with a Michael acceptor. The pioneering work by Stetter in this field has led to a wealth of examples of this reaction in the intermolecular variant. Early reports demonstrated the feasibility of cyanide as a catalyst for the addition of aromatic aldehydes to α,β-unsaturated ketones and esters.[27] This was expanded upon in the Stetter laboratories with the use of a thiazolium salt precatalyst which allowed for the catalyzed addition of aliphatic aldehydes into a variety of Michael acceptors.[28] The reaction has been extensively studied for the addition of aldehydes to a variety of monosubstituted Michael acceptors such as acrylonitrile, vinyl ketones, and acrylates.[29] The catalyst of choice for these transformations has historically been a thiazolium salt in the presence of weak base. The reaction has been invoked in several total syntheses of natural products, employing the commercially available thiazolium salt catalyst precursor.[30]

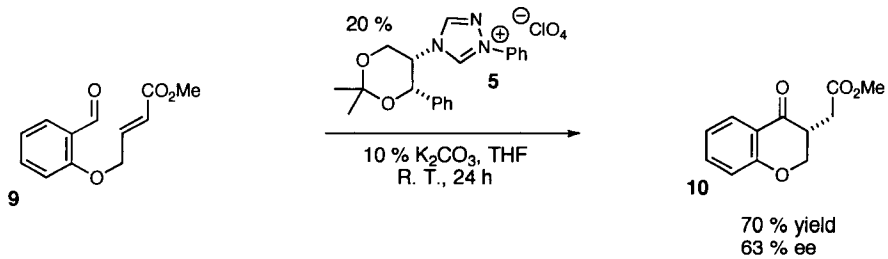
A significant drawback to much of this research is that the catalytic system breaks down when beginning to deal with more substituted Michael acceptors. One of the ways this problem was dealt with involved tethering the Michael acceptor to the aldehyde. This was accomplished in a single step by the alkylation of salicylaldehyde with either 4-bromo-crotonate or an alkyl propiolate. Ciganek demonstrated that both chromanones and benzofuranones could be efficiently synthesized with a catalytic amount of commercially available thiazolium salt **8** in the presence of weak base, Scheme 2.[31]

Scheme 2.



Enders used this template as a model substrate in the Stetter reaction employing chiral triazolium salt **5** and was able to demonstrate modest yields and enantioselectivities in the cyclization of aldehyde **9** to chromamanone **10**, Scheme 3.[32] A variety of aromatic aldehydes possessing substitution about the aromatic ring were competent partners in this reaction, however the highest obtained enantiomeric excesses were around 65%.

Scheme 3.

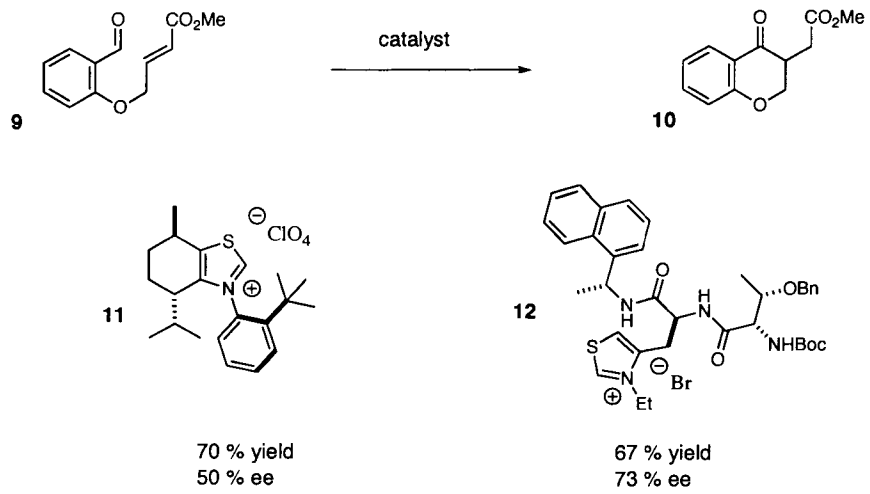


Salicylaldehyde-derived substrate **5** has been the standard testing grounds for new catalytic systems in this reaction. After the publication of our results, several more catalysts capable of effecting this transformation were reported, Scheme 4. Bach and coworkers have demonstrated that thiazolium salt **11**, possessing central and axial chirality, is a competent catalyst in the formation of chromanones.[33] They were able to

obtain moderate yields and an enantiomeric excess of around 50% utilizing a thiazolium salt catalyst precursor derived from menthone.

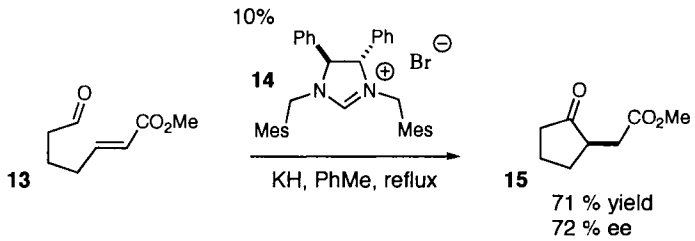
Miller and coworkers have shown that peptide-like molecules possessing a thiazolium salt can also catalyze this reation.[34] Their best results were obtained when employing a dipeptide possessing an unnatural thiazolylalanine residue coupled to α-methylnapthyl amine and benzyl-protected threonine, **12**. They were able to obtain the chromanone product in 73 % ee and moderate yield.

Scheme 4.



Another example of the enantioselective Stetter reaction has appeared in which dihydro-imidazolium salt **14** has been implemented for the formation of cyclopentanones, Scheme 5.[35] Tomioka and coworkers demonstrated that precatalyst **14** is capable of mediating the Stetter reaction of aliphatic aldehyde **13** to cyclopentanone **15**. This work illustrated that chirality in the backbone of a dihydroimidazolinylidene carbene can be translated to enantioenrichment in the product.

Scheme 5.



Concurrent with our explorations in this area, this field of chemistry has become a fertile ground for new reaction development and asymmetric catalysis. The use of heteroazolium carbene-derived acyl anion equivalents has not been limited to aldehydes and their additions to aldehydes and Michael acceptors. Since 2001, many examples have emerged involving the generation of acyl anion equivalents and their addition to electrophiles. Johnson and coworkers have elegantly illustrated the use of acyl silanes as precursors to acyl anion equivalents in the Benzoin reaction.[36] The Johnson group has advanced this concept with the development of chiral metallophosphites allowing for good enantioselectivity in the intermolecular Stetter reaction.[37] Murry and coworkers have demonstrated thiazolium salts as effective precatalysts in the addition of aldehydes to *in-situ* generated acyl-imines.[38] Miller and coworkers have utilized their thiazolylalanine catalysts to render this process asymmetric.[39] Enders[40] and Suzuki have performed an enantioselective cross-Benzoin reaction involving ketones as the electrophile. Scheidt has capitalized upon the use of acyl silanes and achiral thiazolium salts in the non-enantioselective variants of a number of these reactions.[41]

Furthermore, internal redox pathways have been identified utilizing these carbenes and suitably functionalized aldehydes.[42] This pathway has allowed for enantioselective protonations,[43] lactone formations,[44] and hetero Diels-Alder reactions.[45] The use of N-

heterocyclic carbenes as catalysts for asymmetric transformations has indeed grown into a booming field over the last 5 years.

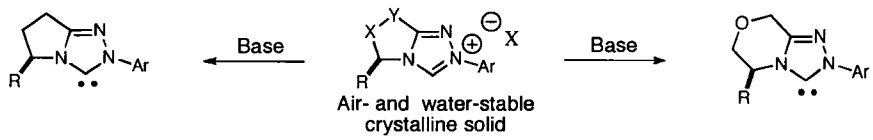
Portions of our work on the development of a catalytic asymmetric intramolecular Stetter reaction have been published.[46]

1.2 Catalytic Asymmetric Intramolecular Stetter Reaction

1.2.1 Initial Catalyst Design and Reaction Development

We were attracted to the triazolium scaffold for these bicyclic *N*-heterocyclic carbenes due to its facile accessibility from the chiral pool and various hydrazines. This scaffold is easily tunable both sterically and electronically in order to optimize catalytic properties. In addition, these triazolium salts are highly air- and water-stable solids. Simply treating the triazolium salt with base allows for the *in-situ* generation of carbene, the active catalytic species, Figure 7.

Figure 7.

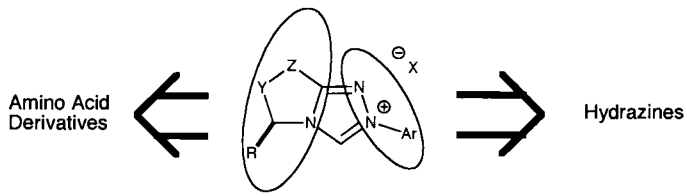


In comparison with thiazolium salts it is expected that the substitution on both sides of the carbene center will impart a higher degree of order into transition states, allowing for a better transfer of chirality (see Figure 5). In comparison to the thiazolium salt carbene precursor which allows for occupation of only two quadrants of the chiral space around the transition state, a triazolium salt is able to occupy up to three quadrants of the space around the reactive entity.

We began research with the synthesis of chiral bicyclic triazolium catalyst precursors. These catalysts are readily available from amino alcohols and allow for a large amount of diversity in the properties of the active catalyst. Since these are derived ultimately from amino acids, either antipode is typically available. The triazolium salt catalyst precursors are almost always crystalline. These salts are also highly air- and water-stable. No decomposition has been observed in samples 5 years old.

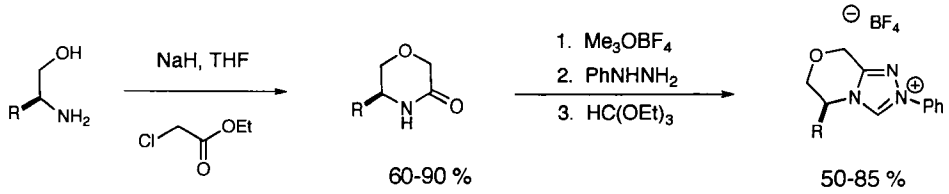
These salts are prepared in a modular fashion, Figure 8. A variety of amino alcohols can be used, giving rise to a wide range of steric properties about the fused ring system. In addition, an assortment of aryl and alkyl hydrazines can be used to further vary the steric and electronic properties around the triazole ring.

Figure 8.



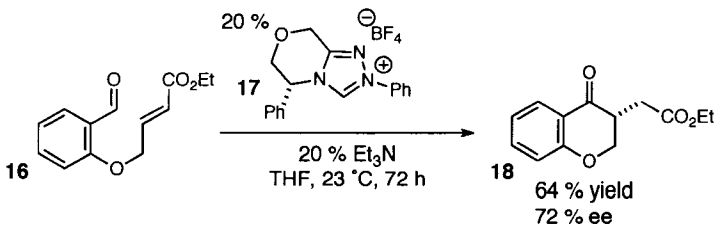
The synthesis of these triazolium salts is described in Scheme 6. From readily available amino alcohols, treatment with sodium hydride, followed by ethyl chloroacetate gives the corresponding morpholinone. Activation of the amide, then addition of phenylhydrazine affords the hydrazinium tetrafluoroborate. Upon heating this with trimethyl orthoformate, the triazolium salt is formed.[25] These syntheses are carried out by first making and purifying the morpholinone.[47] The next three steps are then executed in a one-pot procedure to form the triazolium salt. The triazolium salt can typically be purified by precipitation and recrystallization, although sometimes column chromatography is required.

Scheme 6.



Our initial endeavors into the enantioselective intramolecular Stetter reaction on the salicylaldehyde-derived substrate[31] began with phenylglycinol-derived catalyst **17**, Scheme 7. We found that under unoptimized conditions, chromanone **18** could be formed from aldehyde **16** in good selectivity in moderate isolated yield. The enantiomeric excess was found to be 86% upon chiral stationary phase HPLC analysis.[48] Comparison of the optical rotation to a known compound[32] allowed for the assignment of absolute configuration.[49]

Scheme 7.

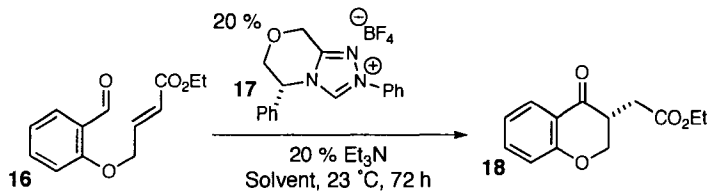


Since thorough studies on reaction conditions had not been previously reported in the Stetter literature, we began to look at the many variables that we thought might lead to enhanced efficiency.

The majority of thiazolium salt-catalyzed reactions involve the use of triethylamine as a base. For this reason, it was decided to screen a number of solvents when using this base.

A variety of solvents ranging from nonpolar (toluene) to polar (acetonitrile) were examined while attempting to optimize the reaction with this catalyst, Table 1.

Table 1.



Entry[a]	Solvent	Yield (%)	ee (%)[b]
1	PhMe	33	70
2	1:1 THF/PhMe	75	78
3	THF	64	72
4	Et_2O	33	69
5	$EtNO_2$	19	64
6	CH_2Cl_2	20	70
7	MeCN	17	65

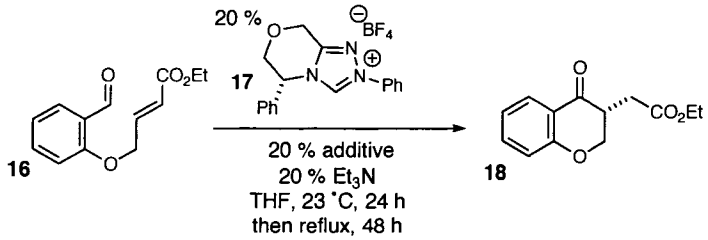
[a]Reactions conducted in the presence of **17** (20 mol %) and triethylamine (20 mol %) for 72 hours at 23 °C. [b]enantiomeric excess determined by HPLC analysis.

Mediocre selectivities were obtained with all of the solvents. A range of 65 to 78% enantiomeric excess was acquired under these conditions. The highest reactivity was obtained with a 1:1 mixture of toluene and THF, giving the product in 75% yield, entry 2. One of the observations that was made during this solvent screen was that in the case of the less polar solvents (toluene, toluene/THF, and ether) the reaction mixture remained heterogeneous throughout the course of the reaction. This suggested that the active catalyst may not be forming in the quantities we had expected. One of the reasons for this may be due to solubility. While the carbene itself should be soluble, the salt may not be sufficiently soluble in order to be deprotonated and form the active catalyst. Another may be due to the acidity of the proton on the thiazolium salt. Indeed, while some

elegant work has been reported with pKa studies of thiazolium salts and imidazolium salts, no reports of the pKa of triazolium salts have been disclosed. The pKa of thiazolium salts has been reported to be around 17 in DMSO.[50] This allows for enough deprotonation by triethylamine to keep a low amount of the active catalyst in solution. The imidazolium salts have been shown to be significantly less acidic, around 23 in water,[51] 23 in DMSO,[50] and 20 in THF.[52] We expect the extra nitrogen in the triazolium salt to render the carbene less basic than the imidazolinylidene carbene, but probably more basic than the thiazolium salt-derived ylide.

We envisioned two ways to get around the problem of the insolubility of the catalyst precursor. One investigation involved the use of tetraalkyl ammonium halides in an attempt to execute an *in-situ* counterion exchange. The rationale behind this effort was to increase the solubility of the catalyst precursor to make more available to make more of it available for deprotonation by the base. We hoped that tetrabutyl ammonium bromide or iodide would allow for displacement of the tetrafluoroborate and pull the triazolium cation into solution, Table 2.

Table 2.



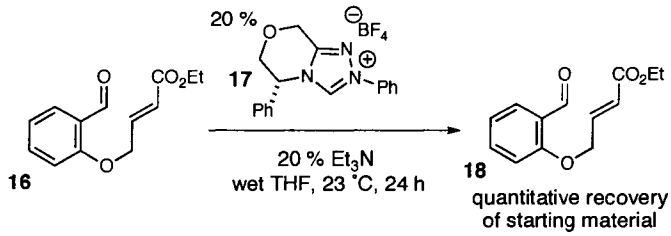
Entry[a]	Additive	Yield (%)	ee (%)[b]
1	Bu_4NI	20	44
2	Bu_4NBr	30	44
3	Me_4NCl	0	-
4	Bu_4NF	0	-

[a]Reactions conducted in the presence of **17** (20 mol %), triethylamine (20 mol %) and additive (20 mol %) for 24 hours at 23 °C and an additional 48 hours at 72 °C. [b]enantiomeric excess determined by HPLC analysis.

Unfortunately, conducting the reaction in the presence of these additives led to poor conversion. After allowing the reaction to proceed at room temperature for 24 hours, little product had formed, prompting heating of the reaction for an additional 48 hours. Upon column chromatography, it was found that both of the reactions which worked (entries 1 and 2) gave poor conversion and diminished enantioselectivity. A possible explanation of the poor reactivity may stem from the tetrabutyl ammonium halides being wet. We suspected that the reaction would not proceed in the presence of water.

To test this hypothesis, a control experiment was run using wet THF. After allowing the reaction to proceed for 24 hours, it was found that no product was obtained, Scheme 8.

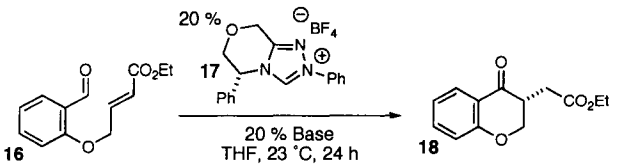
Scheme 8.



Since we were not able to increase the reactivity by the use of these additives, we continued to look at other conditions to provide better conversion. Another way we envisioned increasing the concentration of active catalyst in solution was to form the carbene with a stronger base. It was assumed that the stronger base would irreversibly form the carbene and a higher concentration of active catalyst would be present in the reaction. A number of stronger bases were screened for the reaction with catalyst **17** in THF, Table 3. We found an interesting trend when looking at strong bases with alkali metal counterions. When using butyl lithium and lithium hexamethyl disilazide to form the carbene, very little product was generated. Fortunately, a better yield was obtained

with sodium hexamethyl disilazide, along with a high enantioselectivity. Upon running the reaction with KHMDS, the highest yields were obtained in the series, along with good selectivity.

Table 3.



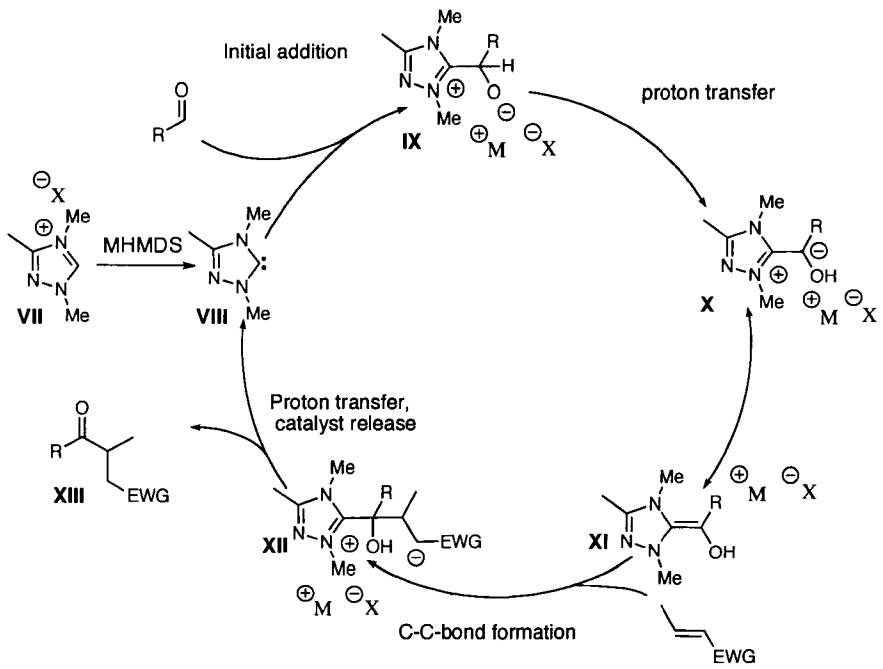
Entry[a]	Base	Yield (%)	ee (%)[b]
1	*n*-BuLi	0	--
2	LiHMDS	< 5	--
3	NaHMDS	27	75
4	KHMDS	48	80

[a]Reactions conducted in the presence of **17** (20 mol %) and triethylamine (20 mol %) for 72 hours at 23 °C. [b]enantiomeric excess determined by HPLC analysis.

A possible explanation can be suggested upon a closer inspection of the mechanism. Scheme 9 shows a catalytic cycle, beginning with an alkali hexamethyldisilazide base deprotonating the triazolium salt (**VII**). Since the catalyst precursor has an anion associated with it, the counterion from the hexamethyl disilazide will become associated with it once the salt is deprotonated to form the carbene (**VIII**). Upon addition of the carbene into the aldehyde, the generated alkoxide, **IX**, may coordinate to the metal ion originally associated with the base. The next step involves a proton transfer. The association between the metal ion and the alkoxide may influence the proton transfer. A potential reason for why potassium hexamethyldisilazide works much better than the lithium base (Table 3) in the Stetter reaction is that the potassium alkoxide is more reactive than the lithium alkoxide. It seems less likely that carbon-carbon bond formation from **XI** will be affected by different counterions. The final proton transfer

again involves proton transfer to the enolate in **XII**. This is another step that could potentially be affected by the identity of the counterion.

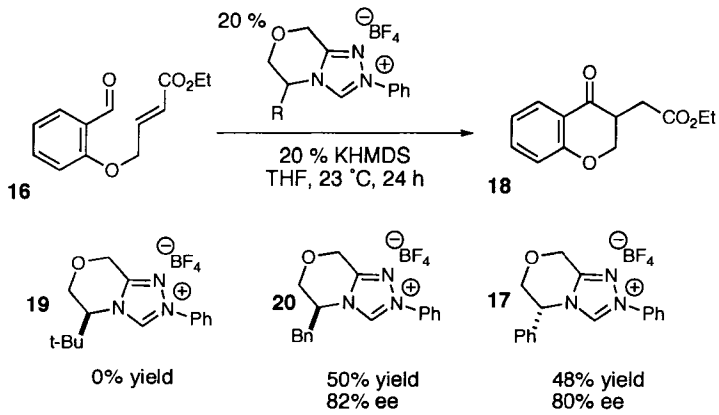
Scheme 9



Since we were able to access a number of different alkyl groups on the catalyst and we had discovered good reaction conditions, it was decided to investigate the effect of different steric properties of the phenylhydrazine-derived catalyst. Three catalysts were prepared and subjected to these reaction conditions, Scheme 10. *tert*-Leucinol-derived catalyst **19** was synthesized, along with phenylalaninol-derived catalyst **20**.[25] Interestingly, the *t*-butyl catalyst gave no conversion to product. This can be attributed to the extreme steric bulk around the reactive site of the carbene carbon. We found that catalyst precursor **20** with a benzyl group gave slightly higher selectivity and conversion than the phenyl catalyst **17**. In fact, under a variety of conditions, this catalyst

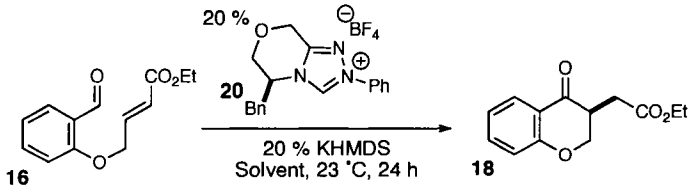
consistently outperforms the phenylglycinol-derived catalyst. For this reason, it was decided to continue utilizing this catalyst for further reaction optimization.

Scheme 10



Several polar solvents were screened in the reaction with catalyst **20** and KHMDS as base, Table 4. The polar solvents did not appear to give ideal results in the reaction. It could be seen that, in general, the less polar solvents gave somewhat better yield. Both acetonitrile and dimethyl formamide gave low conversion. Dichloromethane was slightly better. The best yield was obtained in ether, and the highest enantioselectivity was achieved in THF.

Table 4.

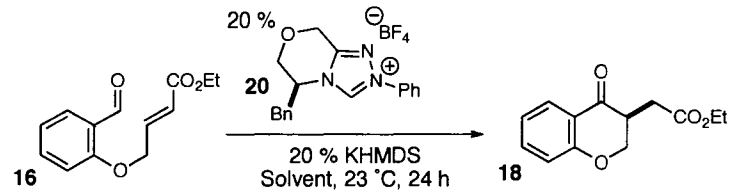


Entry[a]	Solvent	Yield (%)	ee (%)[b]
1	DMF	17	64
2	MeCN	17	59
3	CH_2Cl_2	23	72
4	THF	50	82
5	Et_2O	72	65

[a]Reactions conducted in the presence of **20** (20 mol %) and KHMDS (0.5 M in PhMe), (20 mol %) for 24 hours at 23 °C. [b]enantiomeric excess determined by HPLC analysis.

It was decided to run this catalyst with a variety of non-polar solvents, Table 5. Less polar solvents proved very beneficial for increasing the conversion and selectivity with catalyst **20**. The reaction conducted in pentane gave a modest yield, but with a very good ee of 85 %. Hexanes provide an excellent yield and enantioselectivity, the first reaction conditions to hit the benchmarks of 90% yield and ee. Strangely, the use of heptane gives both poorer conversion and selectivity. Excellent results were obtained when using both toluene and xylenes.

Table 5.



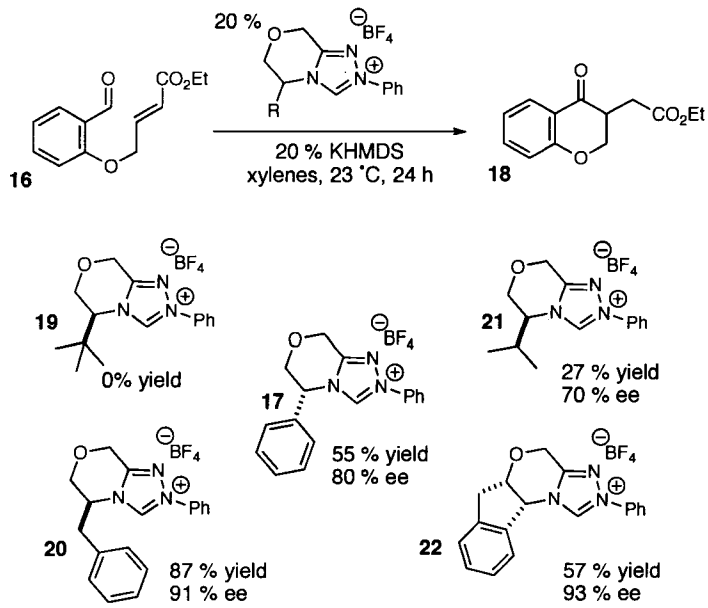
Entry[a]	Solvent	Yield (%)	ee (%)[b]
1	Pentane	55	85
2	Hexanes	90	90
3	Heptane	78	72
4	Toluene	85	89
5	Xylenes	87	91

[a]Reactions conducted in the presence of **20** (20 mol %) and KHMDS (0.5 M in PhMe), (20 mol %) for 24 hours at 23 °C. [b]enantiomeric excess determined by HPLC analysis.

Since xylenes gave the highest selectivity, this solvent was chosen along with KHMDS as base for a further catalyst screening. Upon finding these optimal reaction conditions, a more thorough study was undertaken to find the optimal steric properties of these triazolium salt carbene precursors, Scheme 11. As the two key components involved in the catalyst synthesis are chiral lactam and hydrazine, it was decided to keep the hydrazine constant while varying the chiral portion of the molecule. A variety of triazolium salt catalyst precursors were prepared from amino alcohols. First examined were catalysts prepared from readily available amino alcohols. Good results were obtained with moderately bulky groups. Under these new optimized conditions, moderate selectivity was found with isopropyl-substituted catalyst **21**, but with poor conversion. Phenylglycinol-derived catalyst **17** gave slightly better conversion with a similar selectivity. Of interest is the fact that this catalyst performs nearly identically in xylenes and THF. Better conversion was obtained with aminoindanol-derived catalyst

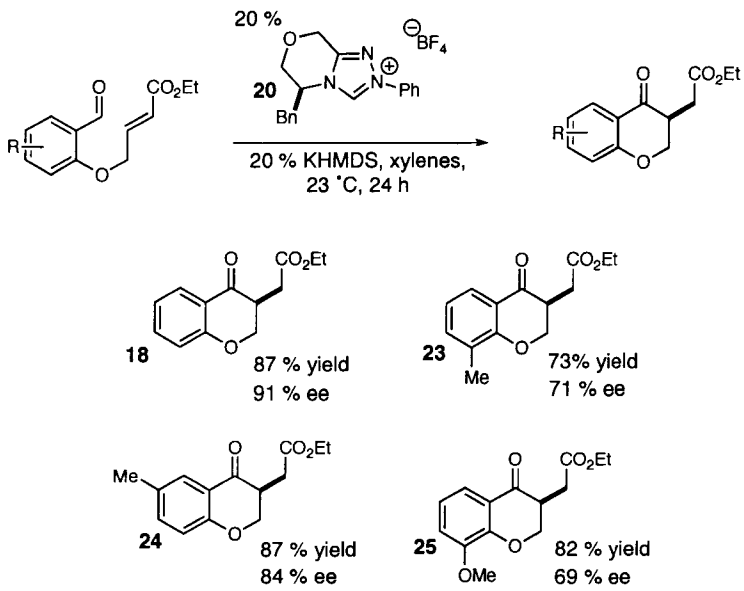
22, along with the highest enantioselectivity in the study. The best conversion was achieved with benzyl–substituted catalyst precursor **20.**[1] A very good 87% yield and 91% ee were obtained. Even under these modified reaction conditions, *tert*-leucinol-derived catalyst **19** failed to give any desired product.

Scheme 11



As catalyst **20** had been found to provide good enantioselectivity and yield, a study was undertaken to test the scope and limitations of the reaction. A variety of substrates were prepared to test the effects of substitution about the aryl ring. Commercially available salicylaldehydes were alkylated with 4-bromocrotonate to provide the aromatic aldehydes with tethered Michael acceptors. When subjected to 20 mol% preformed catalyst in xylenes, the corresponding chromanones were formed in good yield and enantioselectivity, Scheme 12.

Scheme 12.



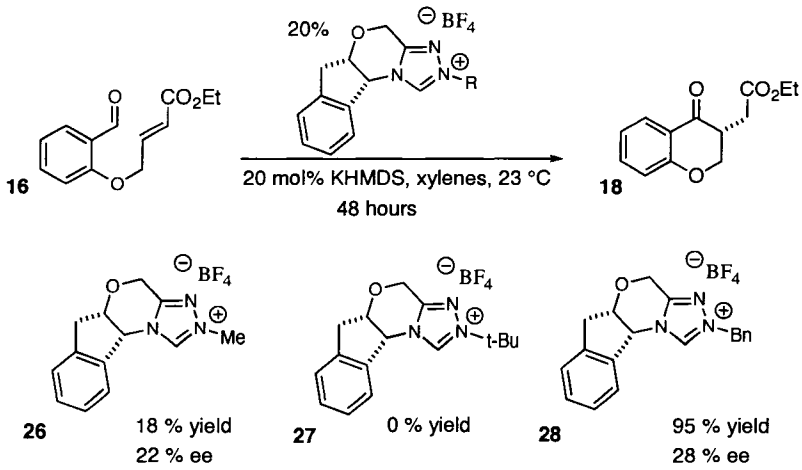
When changing the proton at the 5-position of the aromatic backbone to a methyl group, little effect was seen on the outcome of the reaction. However, when substituents were present next to the phenolic ether linkage, a significant decrease was seen in the enantioselectivity, nearly a 20% drop in enantiomeric excess. The yield also experienced a large decrease in the case of methyl-substituted chromanone **23**.

These results were not ideal, therefore we set out to further tune the reactivity on the catalysts. We postulated that changing the group directly on the triazole might allow for changes in reactivity and efficiency of the catalysts. Since aminoindanol-derived catalyst **22** gave the best selectivity, we decided to implement its scaffold into several catalysts which should have different electronic properties, imparted by the group on the triazole.

The first catalysts prepared set out to answer the question of whether an aromatic ring was necessary for the desired reactivity and selectivity, Scheme 13. When running the reaction with *N*-methyl catalyst **26**, it was found that poor reactivity and selectivity

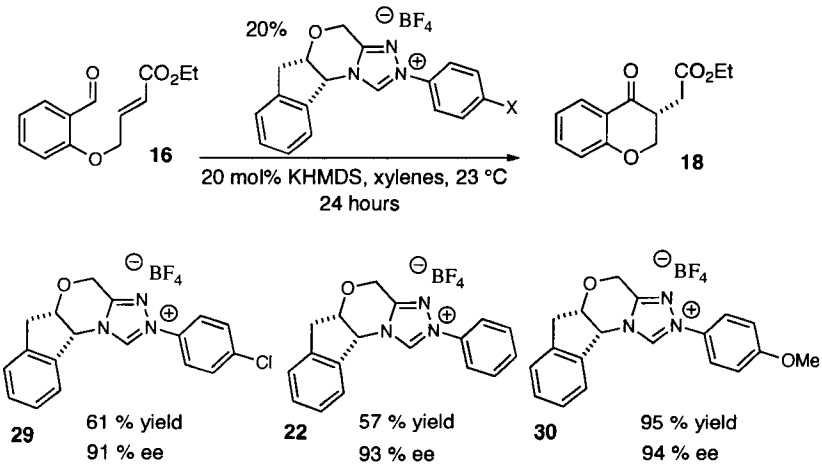
accompanied the reaction. In the case of *tert*-butyl catalyst **27**, no product formation was observed. This can be rationalized by the excessive steric bulk flanking the reactive site of the carbene. An interesting result was obtained with the benzyl-substituted catalyst. The reactivity in this case was good, and a 95% yield was obtained in the reaction. Unfortunately, the selectivity (28% ee) was hardly better than with a methyl group at the position.

Scheme 13.



Since the aliphatic catalysts performed poorly in this reaction, it was decided to focus on a variety of catalysts with aromatic rings on the triazole. We hypothesized that the difference in electron-withdrawing and electron-donating ability of a variety of *para*-substituted phenyl rings may shed light on what is required to obtain satisfactory reactivity. When comparing the parent phenyl catalyst **22** to the *p*-chlorophenyl (**29**), little difference was observed in conversion, Scheme 14. However, *p*-methoxyphenyl catalyst **30** provides excellent yield and enantioselectivity in the reaction.

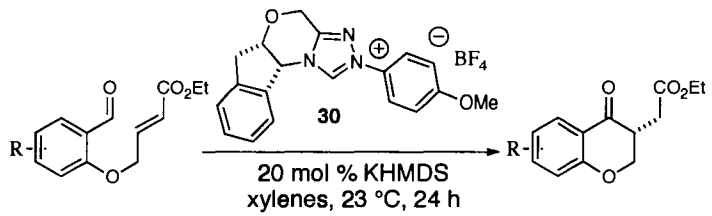
Scheme 14.

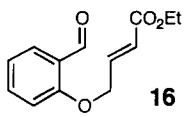
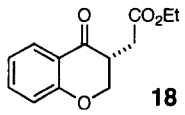
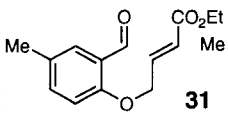
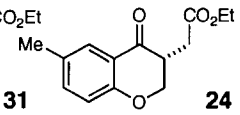
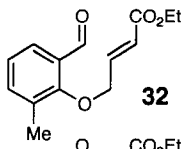
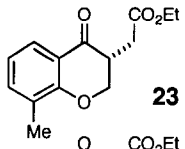
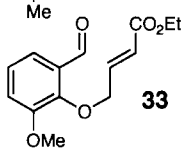
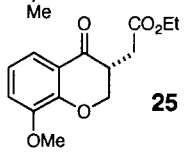


1.2.2 Substrate Scope

With these optimized conditions in hand, it was decided to look again at the scope of the reaction. A variety of aromatic aldehydes participate in the reaction to give product chromanones with high yield and enantioselectivity, Table 6.

Table 6.



Entry[a]	Substrate	Product	Yield (%)	ee (%)[c]
1	 16	 18	94	94
2	 31	 24	80[b]	97
3	 32	 23	90	84
4	 33	 25	95[b]	87

[a]Reactions conducted in the presence of **30** (20 mol %) and KHMDS (0.5 M in PhMe), (20 mol %) for 24 hours at 23 °C. [b]10 mol% catalyst used. [c]enantiomeric excess determined by HPLC analysis.

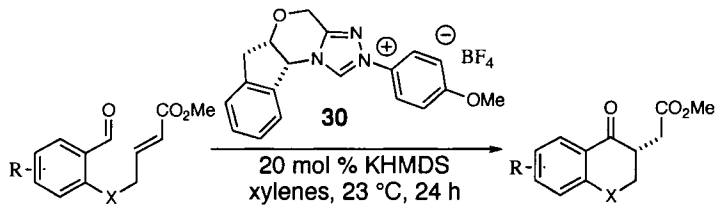
Unlike the phenylalaninol-derived catalyst, a dropoff in reactivity and selectivity was not seen when substitution was placed on the aromatic ring of the substrate. In fact, both 4-methyl (**31**) and 2-methoxy (**33**) substrates were run in the presence of 10 mol% catalyst and underwent satisfactory ring closure to the desired chromanones. For example, substrate **33**, bearing methoxy substitution on the aromatic ring, provided the desired chromanone in 95% yield.

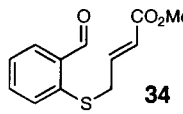
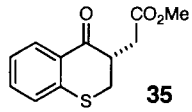
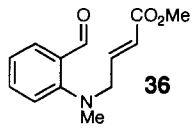
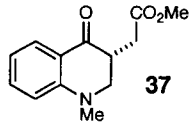
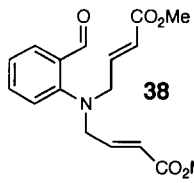
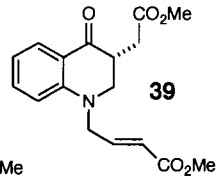
Having established that a variety of chromanones could be formed, we decided to turn our attention to aromatic aldehydes possessing other atoms than oxygen in the tether between the reactive ends. The scope of the aromatic substrates was explored further for

two reasons. One was to demonstrate the synthetic utility of this C-C bond forming reaction. Another was to investigate the effect of aldehyde electronics on the reaction. We had noticed that the electronic properties of the catalyst play a large role on the efficiency of the reaction. We thought that the electronic characteristics of the aldehyde may significantly effect the outcome, potentially leading to insight about the catalytic cycle.

Upon exposure of thioether **34** to the optimized conditions, we obtained the desired product with an excellent selectivity, however with slightly diminished reactivity, Table 7. Due to the importance of nitrogen-containing compounds in biological systems, we were interested in the feasibility of cyclization of 2-formyl aniline derivatives. While the reactivity and enantioselectivity of these cyclizations were slightly decreased, we were able to isolate good yields of the desired dihydroquinolones.

Table 7.

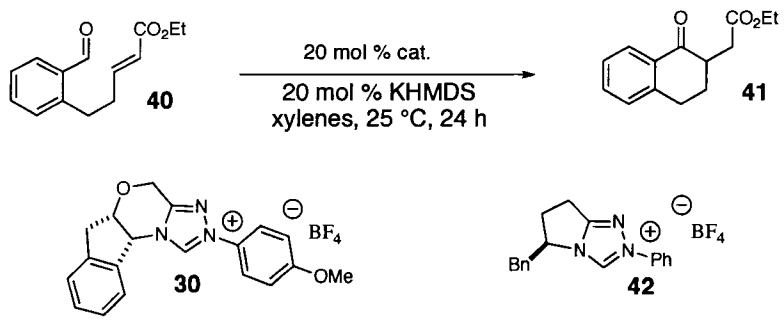


Entry[a]	Substrate	Product	Yield (%)	ee (%)[b]
1	 **34**	 **35**	63	96
2	 **36**	 **37**	64	82
3	 **38**	 **39**	72	84

[a]All reactions conducted in the presence of 20 mol% catalyst and 20 mol% KHMDS (0.5 M in toluene) in xylenes for 24 h at 23 °C. [b]Determined by HPLC analysis.

All of the previously described substrates possess heteroatoms in the linker, and we were intrigued by the effects of the Stetter reaction on a substrate with an all-carbon backbone. When catalyst **30** was used in the reaction on all-carbon linked substrate **40** we obtained a disappointing 35% yield of **41**, but with good enantioselectivity (92%), Scheme 15. During the development of this reaction, my colleague Javier Read de Alaniz had been developing a catalyst with a slightly modified structure derived from chiral pyrrolidinones. When the phenylalanine-derived catalyst **42** was implemented in this reaction, it was found that the yield could be increased to 90% with no noticeable decrease in enantioselectivity.

Scheme 15.



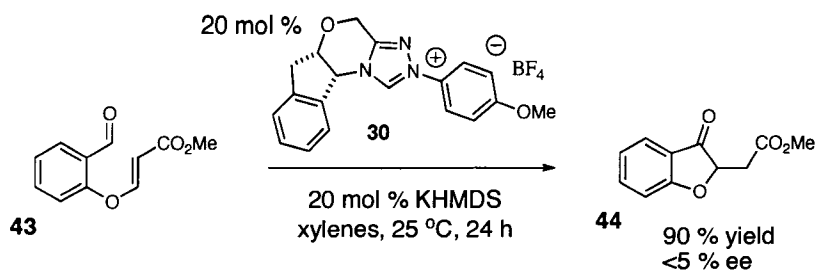
35 % yield
94 % ee

90 % yield
92 % ee

Having established that a variety of 6-membered rings could be formed from aromatic aldehydes possessing tethered electron-deficient alkenes, we turned our focus to the formation of 5-membered rings. The first investigation was carried out with a substrate synthesized in one step from methyl propiolate and salicylaldehyde. Although it had been shown by Ciganek that these types of systems could participate in intramolecular Stetter reaction, we were concerned whether our catalysts would be capable of executing the cyclization onto these electron-rich substrates. We were also concerned whether we would achieve good selectivity, and finally whether the stereocenter would remain intact under the reaction conditions.

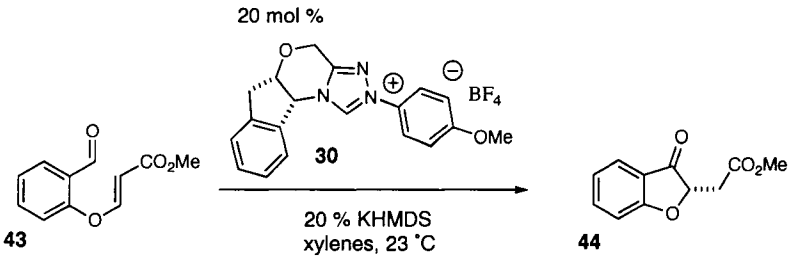
Upon exposure of vinylogous carbamate to the optimized reaction conditions, we found that efficient cyclization occurred and the desired product was formed in 80% yield, Scheme 16. Unfortunately, the enantiomeric excess was found to be very low after HPLC analysis.

Scheme 16.



We envisioned two possible reasons for this lack of enantioenrichment in the product. The worst case scenario would involve the five-membered ring formation being unselective in general. One could imagine a lack of selectivity with the catalysts that give high induction in the formation in six-membered rings. This could arise from less bias being introduced into the diastereomeric transition states preceeding the C-C-bond forming event. While this may be fixed by further catalyst design, we were also curious about whether this may be a racemization process. The benzofuranone proton is quite acidic (pKa around 13)[53] and it could easily be removed by the basic carbene. The basicity of the carbenes has not been reported in the literature, but the pKa's are likely well over 13. Another possible reason for this racemization involves a phenoxide elimination/conjugate addition sequence. This seems less likely, but either mechanism could be in operation. Since racemization appeared to be the problem, an experiment was conducted to monitor the enantiomeric excess as a function of time and conversion in the reaction, Table 8.

Table 8.



Entry[a]	Time	Conversion (%)	ee (%)[b]
1	12 h	90	< 5
2	6 h	55	33
3	0.5 h	10	80

[a]Reactions conducted in the presence of **20** (20 mol %) and KHMDS (0.5 M in PhMe), (20 mol %) for 24 hours at 23 °C. [b]Enantiomeric excess determined by HPLC analysis.

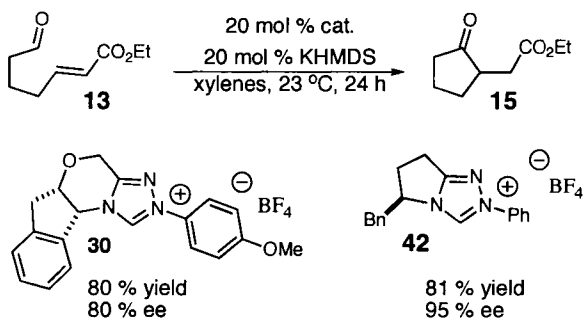
The reaction of **43** to **44** was followed by chiral stationary phase HPLC analysis to determine if the product was formed in good enantiomeric excess, but racemizing under the reaction conditions, Table 8. Three reactions were set up side by side, and quenched and analyzed at different times.[54] The first reaction to be analyzed was stopped after thirty minutes. Column chromatography and HPLC analysis showed a low conversion, but with good enantioselectivity. When stopping the reaction after 6 hours, we found that the yield was 55% and the enantiomeric excess had attenuated to 33%. When the reaction was quenched after 12 hours, the reaction had reached complete conversion and a 90% yield was obtained. However, under these conditions, the product had become nearly racemic.

Since this substrate did not give the desired product with high selectivity, it was decided to investigate a substrate that would be less prone to racemization. We thought that a substrate with an aliphatic backbone may render the substrate less susceptible to

scrambling of the newly formed stereocenter. A Wittig reaction was performed on the known aldehyde acetal prepared from ozonolysis of cyclopentene and workup according to the protocol described by Schrieber.[55]

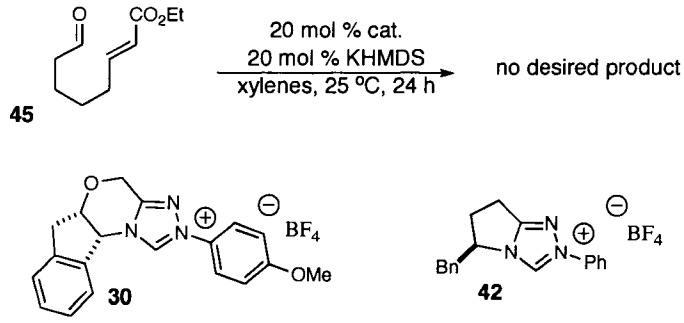
Our initial concerns were that the aliphatic aldehyde may not effectively be converted to a nucleophile with our triazolinylidene carbenes. The reaction was run initially with indanyl-derived catalyst **30**, Scheme 17. We found that aliphatic aldehyde **13** cyclized efficiently under these conditions. Upon HPLC analysis, we discovered that good enantiomeric excess was obtained. Since we had seen higher reactivity in other reactions with phenylalanine-derived catalyst **42**, we were interested in whether better results could be obtained. Indeed, a higher selectivity was obtained in this reaction, with about the same reaction efficiency.

Scheme 17.



Since the five-membered ring was cyclized under these conditions, we were interested in whether the corresponding six-membered aliphatic ring could be generated. The requisite substrate (**45**) was formed in a short sequence from cyclohexene, however all efforts to cyclize it were unsuccessful, Scheme 18.

Scheme 18.



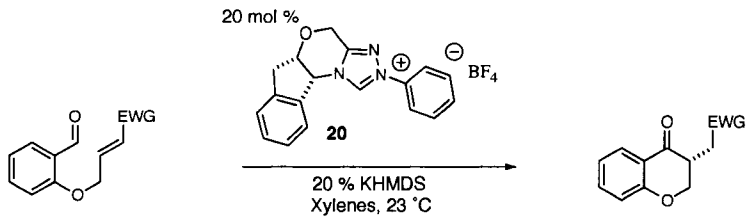
This inability to cyclize the 6-membered ring precursor demonstrated a limit in this methodology. We hypothesized the identity of the Michael acceptor may play a role in the reaction. We thought we might be able to overcome this limitation by employing a more suitable electrophile.

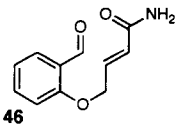
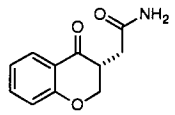
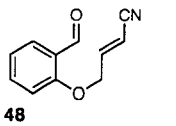
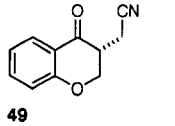
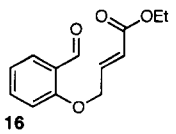
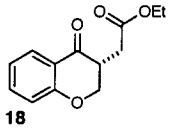
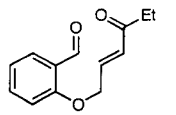
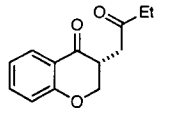
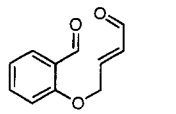
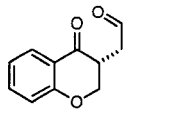
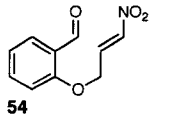
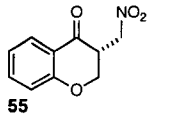
The aforementioned results demonstrate that a wide variety of aldehydes are capable of acting as nucleophiles in this reaction. Despite the electronic properties around the aromatic ring, little difference is seen in the efficiency of the reaction. However, the reaction was still limited to 6-membered aromatic aldehyde cyclizations and 5-membered aliphatic cyclizations. Since it had been shown that the aldehyde component of the reaction was rather general we began to investigate the other component, the Michael acceptor. A more reactive electron-deficient olefin may allow for enhanced reaction efficiency. We also hoped that studying the effects of different Michael acceptors may help us to establish a more solid understanding of the mechanism. When considering the mechanism, if the rate limiting step is carbon-carbon bond formation, it would be expected that the reaction would be significantly faster for more electrophilic Michael acceptors. This might allow for not only a broader range of products from the reaction,

but the possibility to reduce catalyst loading. While many of the reactions described work well with 20 mol% catalyst, fewer of the substrates give the desired conversion when 10 mol% catalyst is employed. We were also interested in expanding the scope of this reaction beyond enoate Michael acceptors in order to expand its synthetic utility. We had noticed that some of the substrates prepared do not undergo effient cyclization under the reaction conditions that we had developed.

It was expected that there would be a range of activating groups that would participate in the reaction. A rough estimate of the electron-withdrawing capacity can be found by comparing the pKa of compounds. Inspection of this property shows that a dialkyl amide would be a poor activating group as its pKa is around 35. Acetonitrile has a pKa slightly lower, at 31. Esters and sulfones are similar as they both appear in the upper 20's. Alkyl ketones are slightly lower, near 26, and aryl ketones lower still at 24. One of the strongest commonly encountered activating groups is the nitro group with a pKa of 17.2.

Table 9.



Entry[a]	Starting Material	Product	Yield (%)	ee(%)[b]
1	 **46**	 **47**	0 No Reaction	
2	 **48**	 **49**	78	75
3	 **16**	 **18**	58	95
4	 **50**	 **51**	95	92
5	 **52**	 **53**	0 Decomposition	
6	 **54**	 **55**	0 Decomposition	

[a]Reactions conducted in the presence of **20** (20 mol %) and KHMDS (0.5 M in PhMe), (20 mol %) for 24 hours at 23 °C. [b]Enantiomeric excess determined by HPLC analysis.

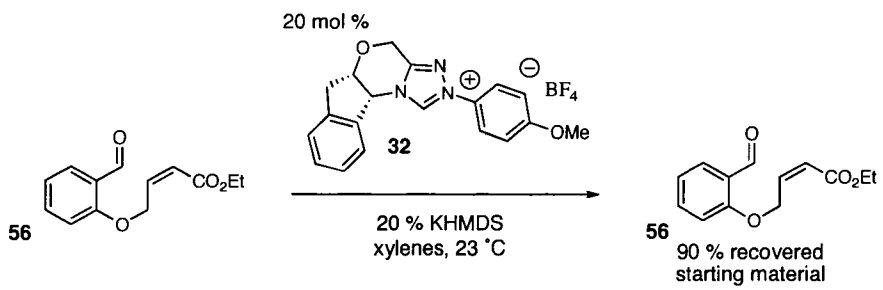
We decided to carry out this study with catalyst **20** due to its lower reaction efficiency, Table 9. We thought that we would see larger differences than if we were employing the most active catalysts which give full conversion in a short time with 20 mol% catalyst. Upon preparation of primary amide **46**, we found that no reaction occurred. Nearly

quantitative recovery of starting material accompanied this experiment. The α,β-unsaturated nitrile **48** provides a lower enantioselectivity, along with lower conversion.

As shown previously, the ethyl ester **16** gives a moderate yield after 24 hours with a very good enantioselectivity. The best result was found using ethyl ketone **50**. Upon exposing the substrate to the pre-formed catalyst, full conversion was obtained in only one hour. The enantioselectivity was found to be excellent, providing chromanone **51** with 92% ee. The aldehyde Michael acceptor was prepared as well. Unfortunately, when subjecting this substrate to Stetter conditions, it decomposed and gave no product. Decomposition also occurred in the reaction of nitroalkene **54**.

We also investigated *Z*-olefin **56**, Scheme 20. Upon exposure to our optimized conditions, we found that no reaction occurred.

Scheme 19.

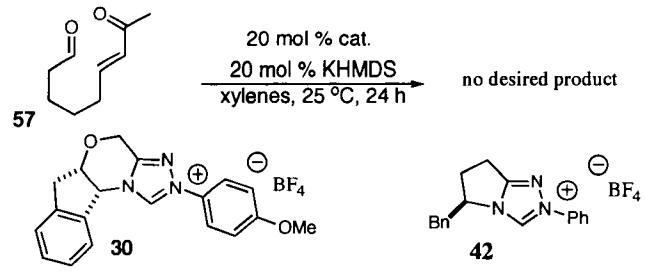


One rationale for this is a lack of activation for the olefin since the ester must lie out of plane to the π-system. Another rationale may be based on the argument that in the transition state, the cis-geometry causes steric repulsions which do not allow the nucleophile and electrophile to come into the vicinity of each other.

With knowledge gained from these experiments, it was decided to implement a ketone Michael acceptor in the cyclization of an aliphatic six-membered ring precursor. Methyl

ketone **57** was synthesized and subjected to reaction with catalysts **30** and **42**, Scheme 20. Unfortunately, attempted cyclization with both catalysts failed to generate significant quantities of the desired product.

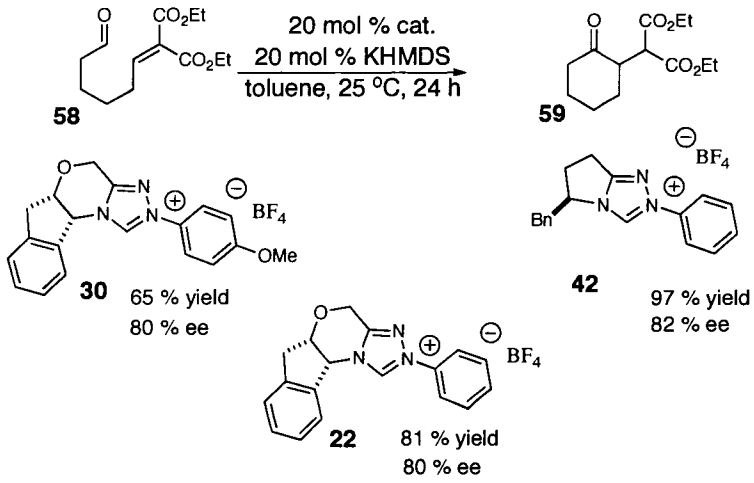
Scheme 20



Scheme 21: Attempted 6-membered ring formation

Since Michael acceptors with stronger electron-withdrawing groups seemed to participate more readily in the Stetter reaction, we decided to implement an alkylidene malonate to activate the olefin. Upon synthesizing alkylidene malonate **58**, it was subjected to standard reaction conditions, Scheme 21. We were able to obtain a good yield and enantioselectivity in the formation of cyclohexanone **59** using phenyl catalyst **22**. Use of *p*-methoxyphenyl catalyst **30** gave slightly higher yield, along with an enantiomeric excess of 80 %. When utilizing phenylalanine-derived catalyst **42**, an excellent yield (97%) was obtained with good enantioselectivity.

Scheme 21.



Implementation of the alkylidene malonate Michael acceptor in the successful formation of a cyclohexanone further solidified our hypothesis that more activated olefins are sometimes necessary when attempting difficult cyclizations.

1.2.3 Further Catalyst Development

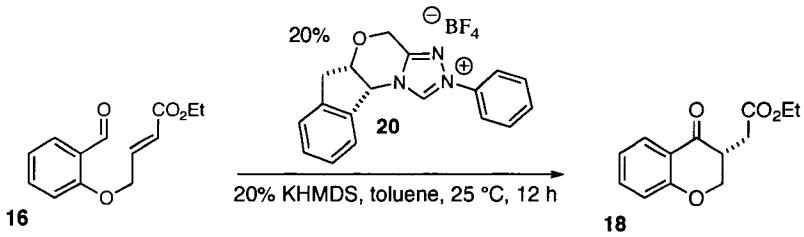
Following our initial success at establishing a broad reaction scope, further attention was directed at catalyst improvement. The previously described catalytic reactions typically involve 20 mol% catalyst, although some could be performed with 10 mol%. We thought designing better catalysts would help to improve reaction efficiency. We also hoped that we could further expand the substrate scope, as well as gain insight into the reaction mechanism.

Throughout these studies, we were interested in elucidating some of the reasons why we could not reduce the catalyst loading any lower than 10 or 20 mol%. We knew the reaction did not proceed in the presence of water.[56] Another reason for small catalyst turnover numbers may be undesired side reactions of the reactive intermediates. The

Breslow intermediate, or the nucleophilic alkene that is formed in the catalytic cycle, has been shown to undergo oxidation reactions.[57] This species can act as an acylating agent when external nucleophiles are present.[58] A considerable amount of attention has come to this intramolecular redox manifold in recent years.[42, 43]

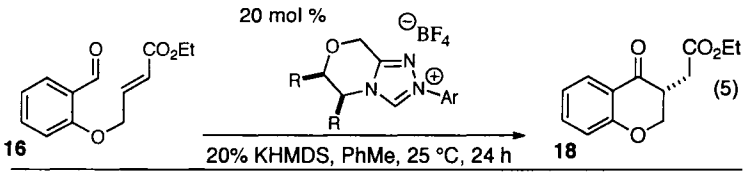
We knew that water was detrimental to the reaction and throughout the course of these studies took extreme care to keep the reactions anhydrous. We began to think that small amounts of oxygen could effect catalyst decomposition. Even under a positive pressure of inert argon, a certain amount of oxygen can enter a reaction vessel. To minimize this, we began to run reactions in toluene dispensed from a solvent system which kept an inert atmosphere of argon over it at all times. Another precaution was taken by sparging the reaction flask with argon after the addition of toluene, after the addition of base, and after the addition of substrate. After the substrate had been added to the active catalyst, and bubbling argon through the solution for several minutes, the reaction was kept under a positive pressure of argon. We were pleased to see that reactivity indeed increased from 57 to 82%, Scheme 22. This allowed for increased catalyst efficiency with the parent phenyl catalyst. While not completely understood, we rationalize this result by assuming that oxygen is able to oxidize the nucleophilic alkene, which then is vulnerable to various decomposition pathways.

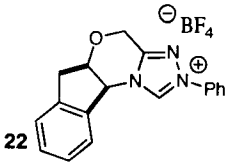
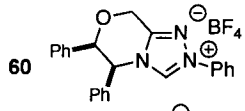
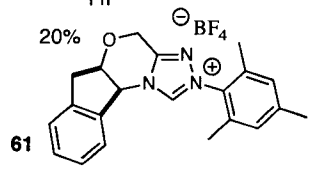
Scheme 22.



Although we had obtained what seemed to be a good chiral scaffold capable of inducing asymmetry in a variety of these cyclizations, we were still interested in improving this selectivity. As the *t*-butyl catalyst appeared too bulky, we thought about the use of a group with steric bulk between that and the indanyl structure. To this end, we prepared cis-diphenyl catalyst **60**. We found that quite satisfactory results were obtained with this catalyst, very similar to that obtained with indanyl catalyst **22**, Table 7. An effort was also made to render the aromatic group more bulky by changing it from phenyl to mesityl. Good results were obtained with this catalyst (**61**) as well. However, since both of these new catalysts did not significantly improve the reactivity or selectivity, it was decided to continue working with the aminoindanol-derived structure.

Table 10.



Entry	Catalyst	Yield (%)	ee (%)[b]
1	 22	80	92
2	 60	80	90
3	 61	85	90

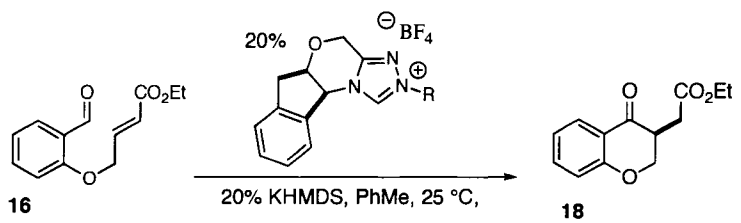
Reactions conducted in the presence of 20 mol % cat, and KHMDS (0.5M) in PhMe. [b] Enantiomeric excess determined by chiral HPLC analysis.

With these experiments further solidifying our belief that we had obtained the optimal chiral scaffold for the Stetter reaction, we wanted to re-investigate the effect of alkyl substituents on the triazole moiety.

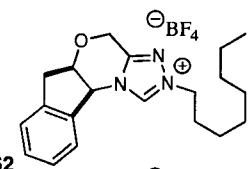
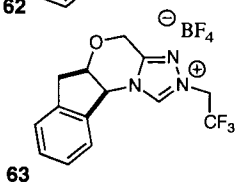
From the previous screen of alkyl substituents, we had noticed that large groups such as *t*-butyl shut down the reaction, and that small groups such as methyl gave both poor selectivity and reactivity. However, benzyl gave good reactivity with poor selectivity. We were not sure why the benzyl catalyst gave good reactivity, but thought that a deeper understanding may provide further insight into the requirements for favorable reativity. One possible explanation is that the benzyl group may provide better solubility, both for the carbene and the triazolium salt, which would allow for a higher concentration of

active catalyst. Another potential reason for this may be the electron-withdrawing capacity of the benzyl group. In order to test this idea, two more aliphatic catalysts were prepared. The octyl-substituted catalyst was expected to be significantly less polar than those previously prepared, and indeed was very soluble in organic solvents. The reactivity of this catalyst was comparable to the methyl catalyst. In thirty-six hours, a low conversion was obtained in the reaction, Table 11. This suggests that the culprit for this lack of reactivity was not the solubility. A 2,2,2-trifluoroethyl catalyst was prepared as well. We thought that this substituent should be more electron-withdrawing than the benzyl. Interestingly, we were able to achieve enhanced reactivity in this reaction, with the desired product formed in high yields in only 2 hours. This suggests that more electron-deficient groups on the triazole facilitate the reaction. Poor selectivity was obtained in this reaction, suggesting that an aromatic group may be necessary to obtain good selectivity.

Table 11.



16 18

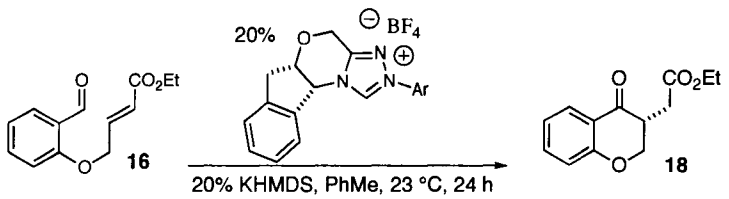
Entry[a]	Catalyst	Time (hours)	Yield (%)	ee (%)[b]
1	 62	36	40	28
2	 63	2	90	32

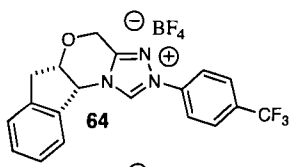
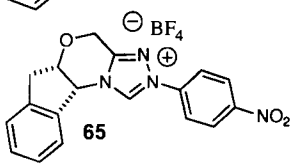
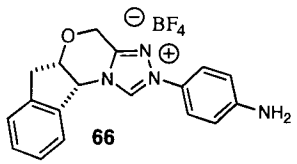
[a]Reactions conducted in the presence of 20 mol % cat and 20 mol % KHMDS (0.5M in PhMe) in PhMe. [b] Enantiomeric excess determined by chiral HPLC analysis.

Further catalyst optimization was conducted, this time with aromatic groups on the triazole ring. From the initial studies which showed that the *p*-methoxyphenyl catalyst gave the highest reactivity, we were led to believe that more electron-rich catalysts gave the highest yields. However, from the aliphatic catalyst studies, we saw that more electron-deficient catalysts give the best conversion in this reaction. In order to test the effects of aromatic groups with different electronic properties, the *p*-trifluoromethylphenyl catalyst was prepared. An interesting result was obtained in this experiment, as the reaction works very similarly to the *p*-methoxyphenyl catalyst, entry 1, Table 12. This result is in disagreement with previous hypotheses that more electron-rich catalysts work better than electron-deficient. One way to explain this phenomena is that different catalysts can promote different steps in the catalytic cycles, and maybe even change the rate limiting step of the reaction. Other catalysts were prepared as well, with hopes of imparting different electronic characteristics into the carbene. We were intrigued by the possibility of utilizing *p*-nitrophenyl catalyst **65**, since it should be even more electron-poor than the trifluoromethylphenyl catalyst. The solubility of this catalyst precursor was significantly poorer than all previously described catalyst precursors, which concerned us that the active catalyst, the carbene, would have serious solubility problems as well. In the event of exposure of this catalyst to the model substrate **18**, we found that full conversion had occurred in only two hours, and a very good enantioselectivity was obtained in the formation of **18**. Since highly electron-deficient catalysts worked well, we decided to look at electron-rich catalysts also. This was accomplished by hydrogenation of the *p*-nitrophenyl catalyst **65** to the corresponding *p*-aminophenyl catalyst **66**. Reaction of this catalyst with model substrate **16** gave a poor

conversion to the chromanone, however with a good enantioselectivity. One reason for this poor reactivity may be the acidity of the aniline protons. Since the triazolium cation itself is a strong electron-withdrawing group, it may render the aniline protons more acidic than the triazolium proton. This may only allow for a small amount of active catalyst in the reaction at any time. An alternative explanation could involve a more rapid catalyst decomposition.

Table 12.



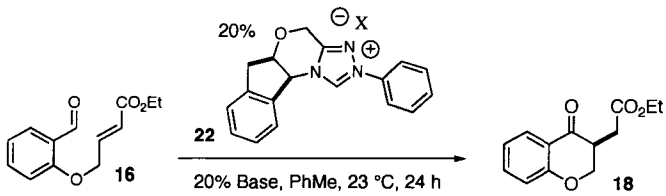
Entry	Catalyst	Time (hours)	Yield (%)	ee (%)[b]
1	 64	24	94	95
2	 65	2	90	95
3	 66	96	25	95

[a]Reactions conducted in the presence of 20 mol % cat and 20 mol % KHMDS (0.5M in PhMe) in PhMe. [b]Enantiomeric excess determined by chiral HPLC analysis.

Since the solubility of these chiral triazolium salts presents a potential problem with certain non-polar solvents, we were interested in the effect of exchanging the tetrafluoroborate counterion with an anion that would render the catalyst precursor significantly more soluble. Simply stirring the triazolium tetrafluoroborate with an

equivalent of sodium tetraphenylborate in a 1:1 biphasic solution of water and dichloromethane allowed for quantitative counterion exchange.[59] Since the active catalyst is a neutral species and should not be associated with the counterion, we expected that the reactivity should not be affected. While the physical properties of this new compound and solubility differ significantly, we indeed found that Stetter reaction of the parent substrate **16** proceeds identically for both compounds using KHMDS as base, Table 13. Also interesting in this case is the implementation of weaker base such as triethylamine gives significantly decreased yield when tetrafluoroborate is used compared with tetraphenylborate, entries 3 and 4. We attribute this decreased reactivity to the fact that the triazolium salt is almost completely insoluble in toluene at room temperature. As it was demonstrated that the tetrafluoroborate salt works similarly to the less polar tetraphenylborate salt, it was decided to continue investigations with the more polar salt for practical reasons.

Table 13.

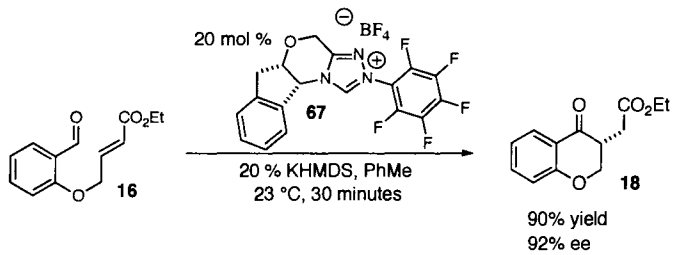


Entry[a]	Counterion	Base	Time (hours)	Yield (%)	ee (%)[b]
1	BF_4	KHMDS	12	80	90
2	BPh_4	KHMDS	12	80	90
3	BF_4	Et_3N	48	10	80
4	BPh_4	Et_3N	48	85	90

[a]Reactions conducted in the presence of 20 mol % cat and 20 mol % base in PhMe. [b]Enantiomeric excess determined by chiral HPLC analysis.

With the *p*-nitrophenyl catalyst appearing to give the highest reactivity, it was decided to attempt to make a catalyst from 2,4-dinitrophenylhydrazine. This hydrazine is readily available and quite inexpensive. We were hoping that if one nitro group on the olefin was good, that two may be better. Unfortunately, the more electron-deficient the hydrazine becomes, the poorer the final step in the catalyst synthesis works. We have not succeeded in forming this catalyst precursor.

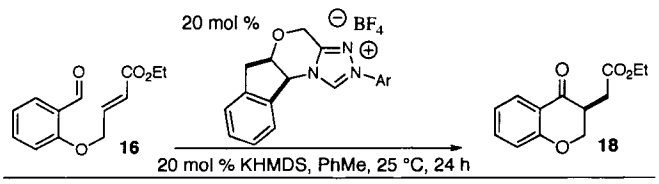
Scheme 23.

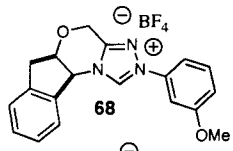
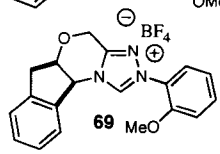
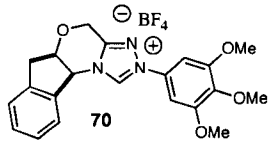


Upon synthesis of the pentafluorophenyl catalyst and reaction with the model substrate, we found that the reaction was complete in one hour and excellent enantioselectivity was obtained in the reaction, Scheme 23.

The pentafluorophenyl catalyst is among the most electron-deficient catalysts we could imagine, and we thought it would be difficult to go to a group that had much more electron withdrawing capacity. This prompted us to begin investigating the more electron-rich catalysts in the hopes that we may find an electron-rich aromatic that may function as well as the pentafluorophenyl.

Table 14.



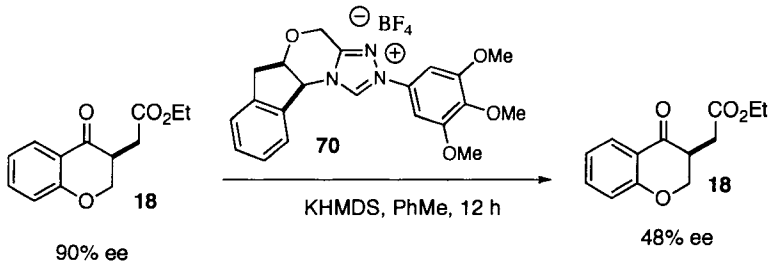
Entry[a]	Catalyst	Time(hours)	Yield (%)	ee (%)[b]
1	 **68**	24	80	90
2	 **69**	2	90	90
3	 **70**	0.5	95	58

[a]Reactions conducted in the presence of 20 mol % cat and 20 mol % KHMDS (0.5M in PhMe) in PhMe. [b]Enantiomeric excess determined by chiral HPLC analysis.

We thought a good place to begin looking at electron-rich catalysts would be with various methoxyphenyl catalysts. Looking at the various anisyl-substituted catalysts, we observed reactivity governed by the electron donating and withdrawing capacity of the aromatic ring, Table 13. Similarly to the 4-anisyl catalyst, the 2-methoxyphenyl catalyst (**69**) gives high reactivity with excellent enantioselectivity, providing the desired product in only two hours. The speed of the reaction was diminished in the case of 3-methoxyphenyl catalyst **68**, a substitution pattern that has been shown to be electron-withdrawing.[60] In the case of this catalyst, high yields were obtained, however with prolonged reaction times. When moving to trimethoxy aromatic catalyst **70**, we found a significant increase in reactivity, as well as a marked decrease in the enantioselectivity.

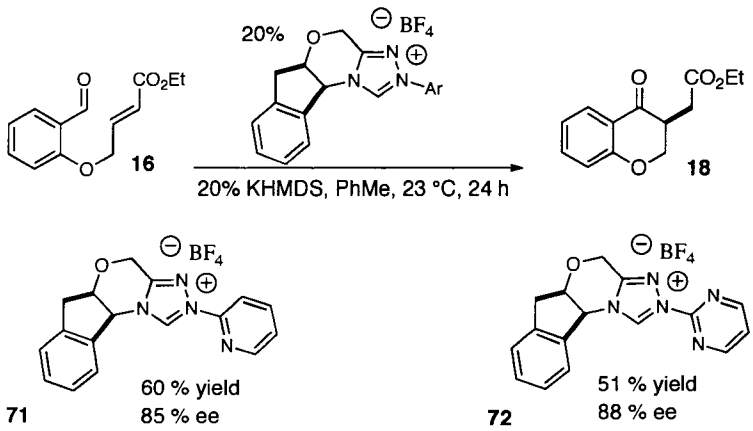
As the ortho,- meta,- and para-substituted catalysts gave similar selectivity we assumed that the decrease in enantioselectivity was due to the increased basicity of the catalyst. Indeed, when subjecting product **18** of 90% ee, to 10% pre-formed catalyst **70** for 12 hours, we see an attenuation of enantiomeric excess to 48%, Scheme 24.

Scheme 24.



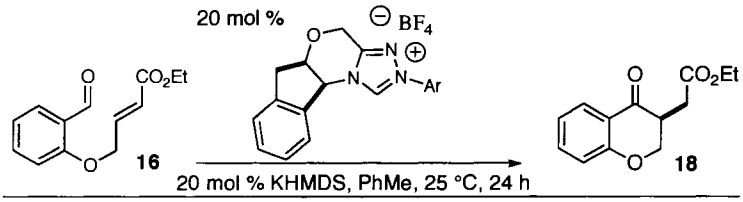
This dichotomy of behavior in electron-rich and electron-poor catalysts prompted us to investigate catalysts with heteroaromatic groups on the triazole. We were interested in heteroaromatic groups such as pyridyl and pyrimidyl rings. We were curious whether there may be some sort of interaction between some of the intermediates in the catalytic cycle with a lone pair on either a pyridine or a pyrimidine ring. If a proton transfer could be facilitated somewhere in the catalytic cycle, it may serve to allow for dramatic rate enhancement in the reaction. Unfortunately, we saw no improvement in the reaction with these catalysts. Both pyridyl catalyst **71** and pyrimidyl catalyst **72** gave poorer conversion than the parent phenyl, Scheme 25.

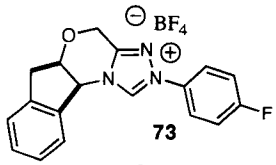
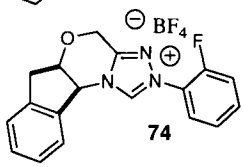
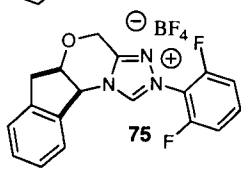
Scheme 25



Since the heteroaromatic catalysts did not provide enhanced reactivity, we became interested in whether the pentafluorophenyl catalyst was so active due to the electron-deficiency associated with it or whether it was certain fluorine atoms on the ring that were necessary. We decided to look at a variety of catalysts with fluorine around the aromatic ring. One of the possibilities we considered was that substituents at the 2-position about the aromatic ring may interact with intermediates in the catalytic cycle. We prepared catalysts possessing 4-fluorophenyl substitution, 2-fluorophenyl substitution, and 2,6-difluorophenyl substitution. It appears that it doesn't matter where the fluorine is around the ring, as all catalysts perform at nearly the same efficiency. This data, along with the results for the 4-nitrophenyl catalyst suggests that a strongly electron-withdrawing group on the triazole is the overriding factor in achieving high reactivity.

Table 15.



Entry[a]	Catalyst	Time (hours)	Yield (%)	ee (%)[b]
1	 73	4	90	90
2	 74	2	95	92
3	 75	2	95	90

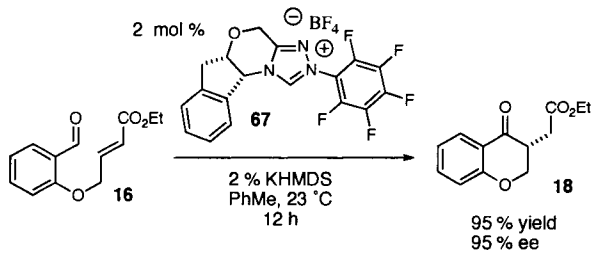
[a]Reactions conducted in the presence of 20 mol % cat and 20 mol % KHMDS (0.5M in PhMe) in PhMe. [b] Enantiomeric excess determined by chiral HPLC analysis.

Our early attempts to understand the reactivity of these catalysts hinged around a closer inspection of the mechanism. In order to generate product, the proposed cycle for the Stetter reaction must involve two proton transfer steps and two carbon-carbon bond forming events. These proton transfer steps should be facilitated by an electron-deficient catalyst as stabilization of the forming anion should be greater. However, the carbon-carbon bond additions of both the carbene into the aldehyde and generated acyl anion equivalent into the Michael acceptor should be promoted by a more electron-rich catalyst. Our current rationale for the dichotomy of behavior involves a change in the rate

determining step when different catalysts are employed, along with different susceptibility to decomposition.

As we had found what seemed to be the best catalyst for the intramolecular Stetter reaction, along with the best conditions, it was decided to investigate the possibility of reducing catalyst loading. When implementing pentafluorophenyl catalyst **67**, with our optimized reaction conditions, it was found that the reaction remained efficient with catalyst loading as low as 2 mol%, Scheme 26.

Scheme 26

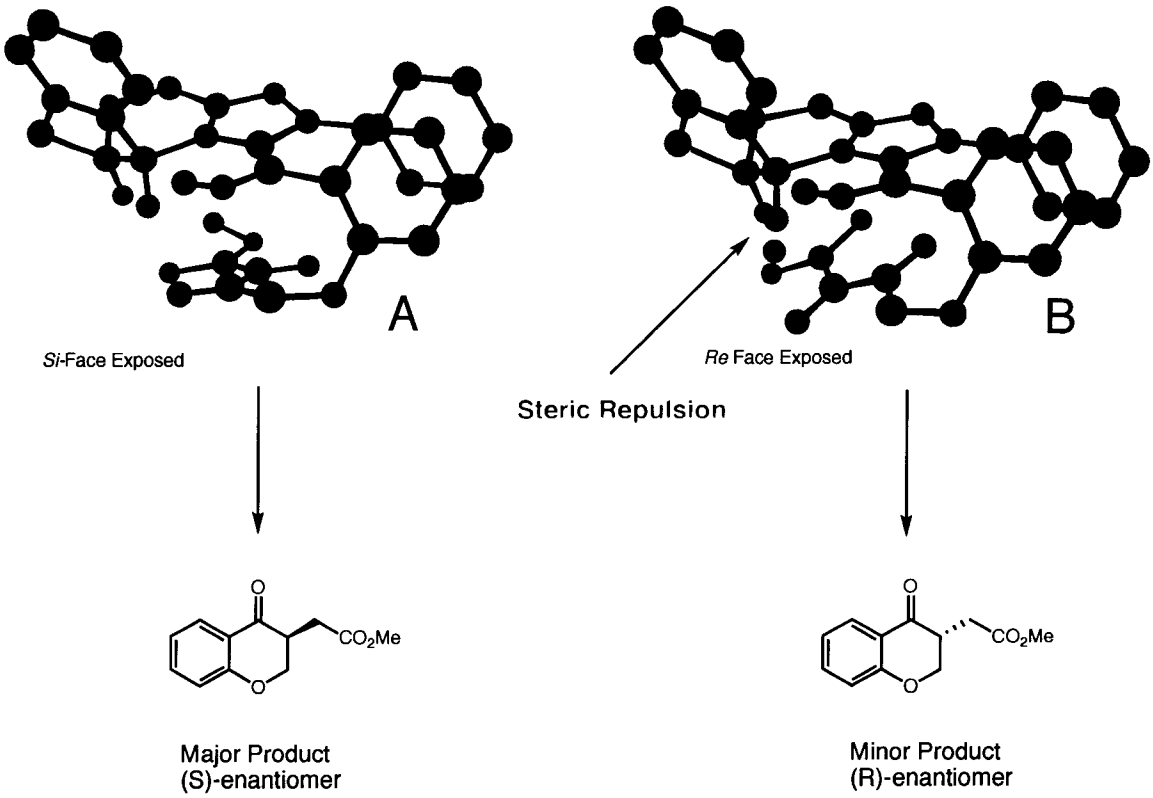


1.3 Stereochemical Model

A stereochemical model can be presented for the selectivity in this reaction, Figure 7. It is necessary to assume that carbon-carbon bond formation is the enantiodetermining step in the catalytic sequence. We further assume that the *E* isomer of the Breslow intermediate is the reacting species. This is supported by computational work from Houk and coworkers.[61] The necessity of an aryl ring on the triazole suggests this plays a major role in the organization of a transition state. We attribute this to the the phenyl ring on the triazole adopting a conformation perpendicular to the triazole moiety. This forces the aromatic ring of the substrate into a perpendicular arrangement to the nucleophilic

alkene. The chiral portion of the molecule shields the top face of the Breslow intermediate, forcing the Michael acceptor to the opposite face (underneath as illustrated in Figure 7). The orientation of the Michael acceptor then dictates the stereoisomer formed in the addition. The major product can be rationalized from transition state A. When the nucleophile and Michael acceptor are positioned in close proximity, this transition state is largely free of steric interactions. The Breslow intermediate attacks the *Si* face of the Michael acceptor to give the S enantiomer. In the minor observed product, interactions with the hydrogens on the morpholine ring and the ester can be envisioned, raising the energy of this transition state and disfavoring this pathway.

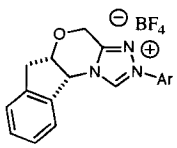
Figure 7.

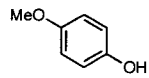
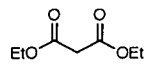
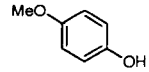
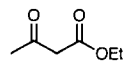
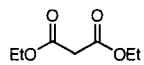
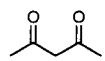
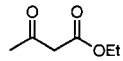
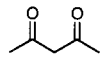


1.4 Mechanistic considerations

The different aromatic groups have been shown to significantly alter the reactivity in the Stetter reaction. One way to investigate the electronic properties imparted onto these systems is to look at the basicity of a variety of the carbenes. We did this by generation of the carbene and quenching with organic acids of known pKa.[62] Our results suggest that the pKa range can be tuned significantly by changing the aryl group on the triazole ring, Figure 8. The most electron-deficient catalysts require carboxylic acids for protonation. They can exist in solution with organic acids such as 1,3-diketones and malonic esters without apparent change. The most electron-rich catalysts possess pKa's near that of electron-rich phenols.

Figure 8.

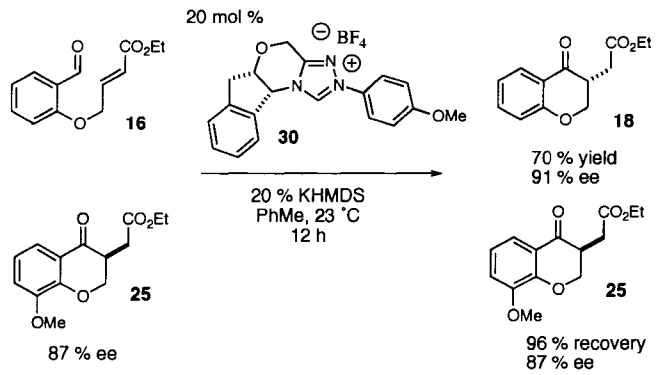


Catalyst	pKa Range Bordwell (DMSO)		Quenching agents	
3,4,5-trimethoxyphenyl	19.1	20.8		
4-methoxyphenyl	16.2	19.1		
phenyl	14.2	16.2		
4-fluorophenyl	13.3	14.2		
pentafluorophenyl and 4-nitrophenyl	12.8	13.3		

To determine if product inhibition of the reaction is in operation, an experiment was carried out with an equimolar mixture of enantioenriched product **25** and substrate **16**, Scheme 27. Catalyst precursor **30** was treated with KHMDS in order to form the active catalyst. To this was added a solution of the product and starting material. Upon stirring for 12 hours, product **25** was obtained nearly quantitatively and the ee was determined to

be 87%, demonstrating that the enantiomeric excess does not diminish over the course of the reaction. Also, substrate **16** was consumed and converted to the corresponding chromanone in 70% yield and 91% ee, demonstrating that the reaction proceeds nearly the same in the presence of product as in its absence. This suggests that no appreciable amount of product inhibition is occurring.

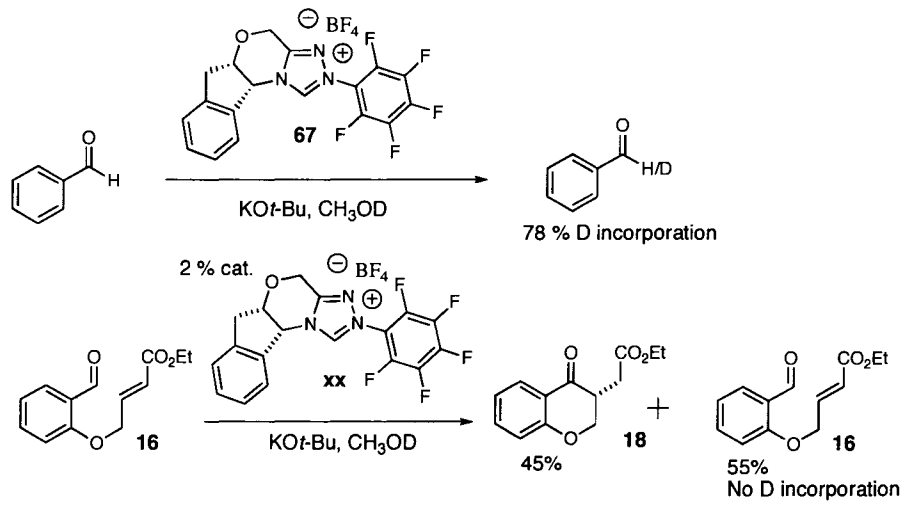
Scheme 27.



In an experiment designed to test the reversibility of the various steps of the catalytic cycle, it was decided to run the reaction in deuterated methanol, Scheme 28. Early investigations pertaining to the benzoin reaction involved the subjection of benzaldehyde to catalyst **67**, in methanol-d1 as solvent. We found that very little benzoin was formed, although at the end of the reaction, significant amounts of deuterium had been incorporated into the aldehyde. This demonstrates that the catalyst is adding to the aldehyde and proton transfer is occurring to form the Breslow intermediate. This is then trapped with a deuteron from the solvent. If we were able to stop an intramolecular Stetter reaction at partial completion and find deuterium incorporation in the aldehyde of the Stetter substrate, this would suggest that in protic solvents, the Breslow intermediate

does not always add into the Michael acceptor, but can also be protonated to give back the aldehyde, suggesting that carbon-carbon bond formation is slow relative to other processes. In the event of running the reaction of parent substrate **16** in methanol-d1 with pentafluorophenyl catalyst **67**, and stopping the reaction at 45% conversion, we found no deuterium incorporation in the recovered aldehyde.

Scheme 28.



This result demonstrates that in this system, carbon-carbon bond formation is faster than deuteration of the Breslow intermediate. My colleague Javier Read de Alaniz has performed mechanistic studies suggesting that proton transfer, and not carbon-carbon bond formation, is rate limiting in the intramolecular Stetter reaction.[63] He has also been part of a collaboration with professor Daniel Singelton that suggests the first irreversible step in the catalytic cycle occurs before carbon-carbon bond formation.[64] Although this reaction was run under different conditions than their work, it stands as another piece of evidence to add to the mechanistic understanding of the reaction.

1.5 Conclusion

In conclusion, we have developed a highly enantioselective catalytic intramolecular Stetter reaction. Fundamental to this reaction improvement was the implementation of chiral bicyclic triazolium salt catalyst precursors. The optimal steric and electronic properties were identified and allow for an expansion of the reaction scope. A pentafluorophenyl-substituted catalyst has been identified to allow for reduction of loading to as low as 2 mol% with a model substrate. The scope of this reaction has been expanded to include the synthesis of 5- and 6-membered rings with good efficiency and selectivity. Aliphatic and aromatic aldehydes participate in this reaction, and a variety of Michael acceptors are effective electrophilic components.

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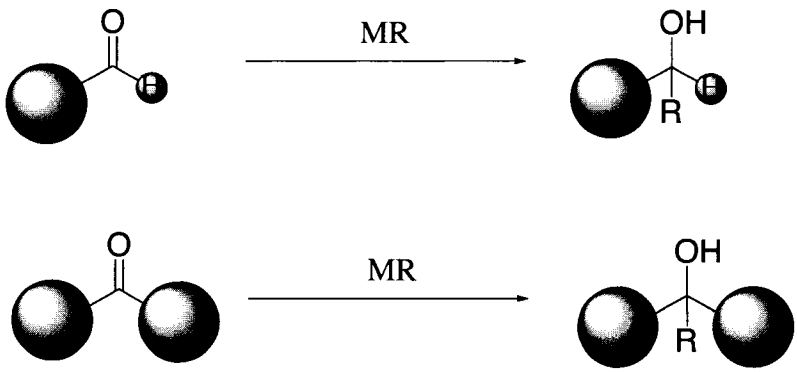
Chapter 2

Generation of Tetrasubstituted Carbon Stereocenters via a Catalytic Asymmetric Stetter Reaction.

2.1 Introduction

The stereocontrolled generation of fully substituted carbon centers remains a formidable challenge to synthetic chemists.[1] An enormous body of research has been directed at the stereoselective creation of tertiary stereocenters, and many general solutions have arisen to allow for their synthesis. Unfortunately, many of these solutions are not amenable to the problem of quaternary stereocenters. An appropriate analogy to this involves the large body of research in carbon-carbon bond forming reactions employing aldehydes as electrophiles that fail with ketones as electrophiles.[2] Literally hundreds of catalysts will promote the addition of zinc alkyl groups to aldehydes.[3] Only a handful have been demonstrated to add these reagents to unactivated ketones.[4] A number of reasons exist for this discrepancy in reactivity. One involves the lower reactivity due to extra substitution. Related to this is the extra steric bulk of an alkyl group versus a hydrogen atom. A second issue is the problem of selectivity; it is much easier for reagents to discriminate between the faces of a π system with a hydrogen atom and an alkyl group versus two alkyl groups, Figure 1.

Figure 1.



As chemists strive to meet the demand to synthesize increasingly complex target molecules, new and reliable methods are needed to effect a variety of transformations. The struggle to meet the need to produce highly complex molecules efficiently and selectively fuels constant innovation in synthetic chemistry.

The catalytic, enantioselective formation of quaternary stereocenters has received a considerable amount of attention recently, yet remains a very challenging endeavor in organic synthesis. The use of Meyers' chiral bicyclic lactam auxiliaries[5] continues to stand as the benchmark for versatility and predictability in this challenging bond construction. Many recent developments in catalytic enantioselective methods have been reported which allow for the creation of this daunting chemical topographical feature.[6] Included in this company are the intramolecular Heck reaction.[7] Elegant work by Overman has shown that the Heck reaction is a reliable tool for the generation of quaternary stereocenters in the context of extensive natural product synthesis.[8] Another effective method that has been introduced recently is the rearrangement of enol carbonates, catalyzed by planar chiral pyridine mimics.[9] Catalytic, asymmetric versions of the Diels-Alder reaction[10] have also been developed to create quaternary stereocenters.

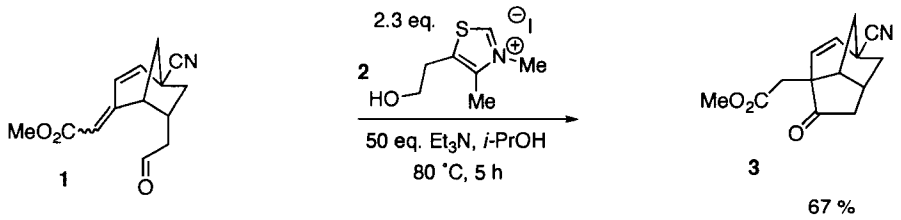
Another well-investigated example in this field involves transition metal mediated π-allyl chemistry.[11] Copper-catalyzed S_N2' displacement of allylic leaving groups has been recently developed.[12] Michael reactions have also been studied in the synthesis of quaternary stereocenters. The quaternary stereocenter may be generated either in the Michael donor or the Michael acceptor. 2-substituted 1,3-dicarbonyl compounds have been used in several systems as the Michael donor. Cristoffers and coworkers have developed palladium-catalyzed versions of this reaction.[13] Examples of small organic molecules catalyzing this type of transformation have also been reported.[14] Hoveyda and coworkers have demonstrated conjugate addition reactions of alkyl zinc reagents to β,β-disubstituted Michael acceptors.[15] Alexakis and coworkers have performed additions of organoaluminum reagents to Michael acceptors as well.[16] In addition, phase-transfer alkylation of 1-indanones,[17] 1,3-dicarbonyl compounds,[18] and arylation of ketone enolates[19] have been demonstrated as viable ways to make fully substituted carbon centers.

Each of these approaches, however, is necessarily limited to specific substrates and many substitution patterns are unattainable by these or even stoichiometric methods.

Upon the realization of chiral bicyclic nucleophilic carbenes as catalysts for the enantioselective Stetter reaction, it was decided to investigate the feasibility of cyclization of the generated acyl anion equivalent addition into a β,β-disubstituted Michael acceptor. In 1979, Trost and coworkers demonstrated the feasibility of this transformation implementing achiral thiazolium salt **2**, Scheme 1.[20] In this synthesis of hirsutic acid, the researchers were able to execute the intramolecular Stetter reaction for the first time while cyclizing an acyl anion equivalent onto a pendant olefin as a mixture

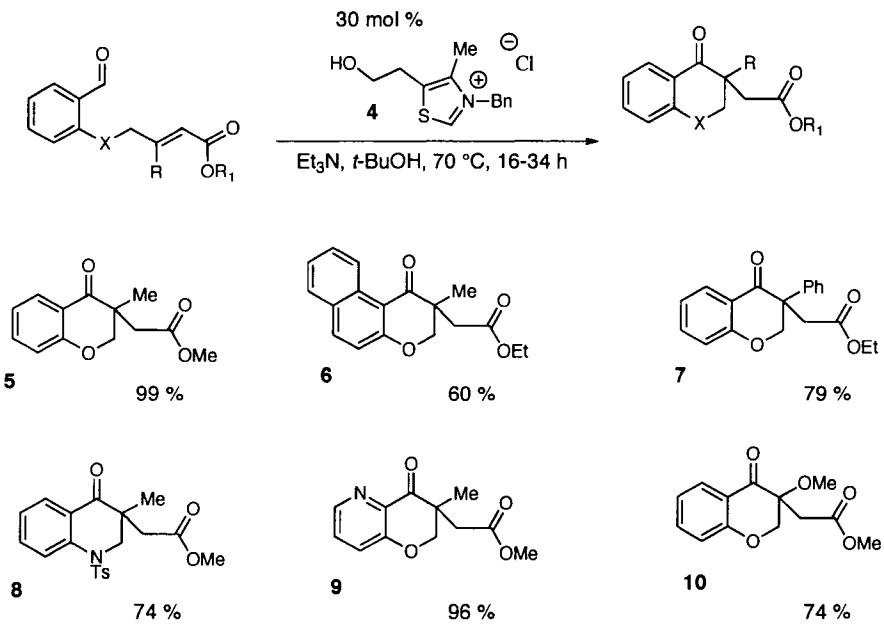
of geometrical isomers. However, non-ideal reaction conditions were required as 2.3 equivalents of catalyst were needed as well as 50 equivalents of triethylamine at elevated temperatures. With the need for a superstoichiometric amount of reaction mediator to provide a reasonable amount of desired product, we were concerned that our triazolium salts may not provide the desired reaction efficiency.

Scheme 1.



After the publication of our results, another report appeared demonstrating the synthesis of a variety of 6-membered rings bearing quaternary stereocenters in a non-enantioselective fashion utilizing thiazolium salt **4**.[21] Hamada and coworkers were able to cyclize a variety of aromatic aldehydes onto pendant α,β-unsaturated esters to form the all-carbon quaternary stereocenters in generally good yields (Scheme 2).[22]

Scheme 2.

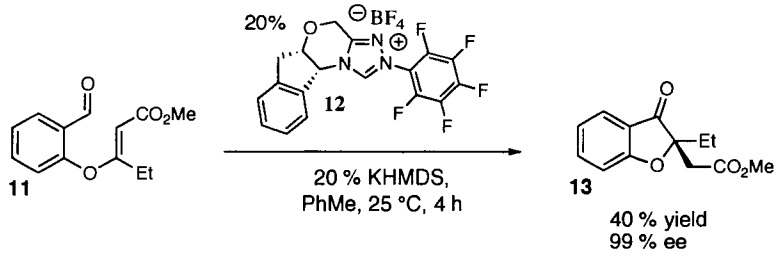


2.2 Results

We set out to determine whether the intramolecular Stetter reaction could be used in the enantioselective formation of quaternary stereocenters. In order to address the potential problems associated with the nucleophilic addition into a β,β-disubstituted Michael acceptor, salicylaldehyde-derived substrate **11** was prepared in a 3-step sequence, providing the desired *E* isomer.

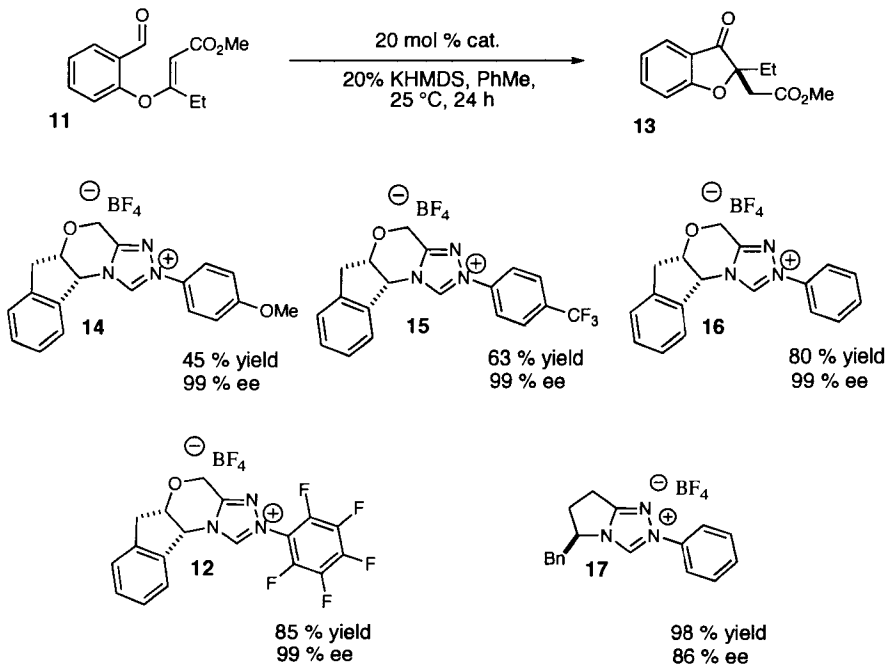
With the requisite substrate in hand, standard conditions for the intramolecular Stetter reaction were tried. Pentafluorophenyl triazolium salt precatalyst **12** was treated with KHMDS, followed by substrate. The reaction after 4 hours gave a moderate 40% yield of benzofuranone **13** with an excellent enantiomeric ratio of 250:1, Scheme 3.

Scheme 3.



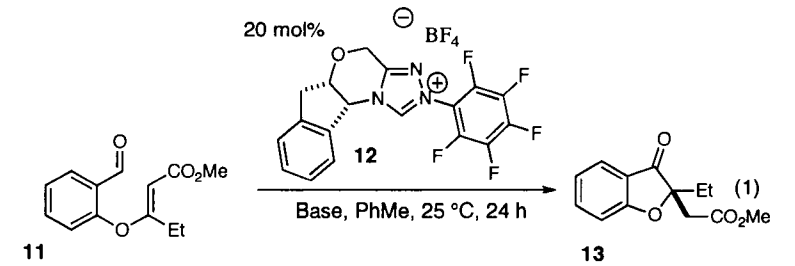
This initial result led us to further investigate reaction optimization. A screen of several catalysts that have proven reliable in the intramolecular Stetter reaction involving disubstituted Michael acceptors demonstrated that pentafluorophenyl triazolium salt **12** was the most effective precatalyst for the execution of this transformation, Scheme 4. Reactions were allowed to run for 24 hours in these experiments, giving higher conversion than in Scheme 3. When *p*-methoxyphenyl catalyst **14** was implemented in the reaction, a lower yield was obtained, although the enantioselectivity remained excellent. The utilization of *p*-trifluoromethylphenyl catalyst **15** gave somewhat increased yields, although not nearly as high as the pentafluorophenyl catalyst. Enantioselectivity was superb with this catalyst as well. The parent phenyl catalyst **16** gave nearly as high of a yield as the pentafluorophenyl, again with 99% ee. We speculated that the reaction efficiency may be increased with phenylalanine-derived catalyst **17**, since we had seen this phenomenon in previous studies. Indeed, an increase in reaction efficiency is obtained with this catalyst, as a nearly quantitative yield is obtained. However, we also see a decrease in enantioselectivity to 86%.

Scheme 4.



Having demonstrated that excellent enantioselectivities can be obtained in this model system, we began to attempt to increase the yield. With this early lead, a variety of bases were screened in toluene in order to see the effect of base on the reaction, Table 1. The reaction was run with the generation of the active catalyst from KHMDS, potassium *tert*-butoxide, as well as triethylamine. While all of the bases provided the product with high enantioselectivity, the yields varied significantly. Ten equivalents of triethylamine to catalyst gave the optimal yield.

Table 1.

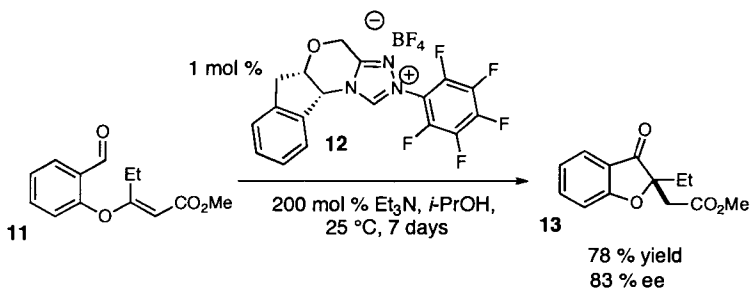


Entry[a]	Base	Yield (%)	ee (%)[b]
1	20 mol% KHMDS	65	99
2	20 mol% KO*t*-Bu	80	99
3	200 mol% Et_3N	96	97

[a]Reactions conducted in the presence of **12** (20 mol %) in PhMe for 24 hours with the indicated base at 25 °C. [b]Enantiomeric excess determined by HPLC.

A variety of different conditions were used in order to attempt to reduce the catalyst loading. After several attempts with different solvents, it was found that utilizing as little as 1 mol% catalyst was feasible, Scheme 5. The use of triethylamine and isopropanol provided the Stetter product in good yield when the reaction was allowed to run for 7 days. A drawback of this strategy to increase the efficiency is that it is accompanied by a decrease of enantiomeric excess to 83%.

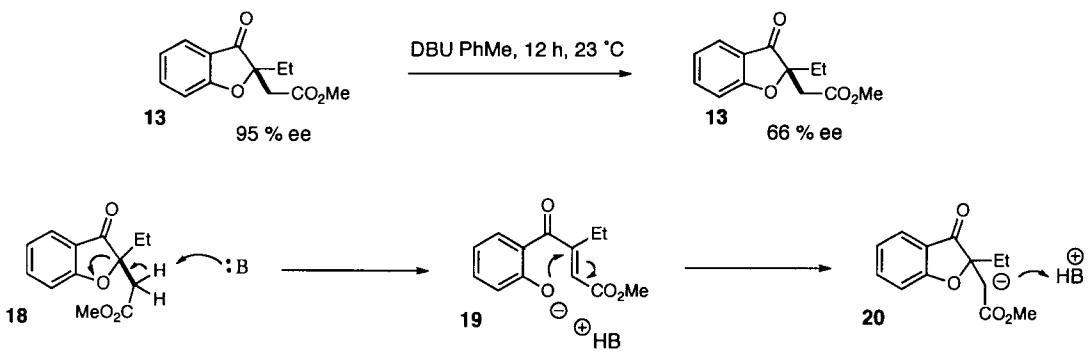
Scheme 5.



This may be an artifact of base-induced racemization. With this enantioenriched product in hand, it was decided to test whether base was capable of racemizing the product. From

previous investigations with this structure lacking the methyl group α-to the carbonyl, we saw a rapid erosion of enantioenrichment during the course of the reaction. Since this product did not have the proton that might be removed in the α-position to the ketone, racemization would require removal of the proton α to the ester and elimination of phenoxide, Scheme 6. This phenoxide elimination should be relatively facile since the ortho position possesses a ketone, which should help to stabilize the developing negative charge. Addition back into the Michael acceptor would be nonselective and cause erosion of the enantiomeric composition. We tested this theory of racemization by stirring a solution of product **13** with DBU in toluene for 12 hours. After column chromatography, we recovered the product quantitatively. Upon HPLC analysis, we found that the ee had diminished to 66%, demonstrating that this molecule is prone to racemization by base.

Scheme 6.

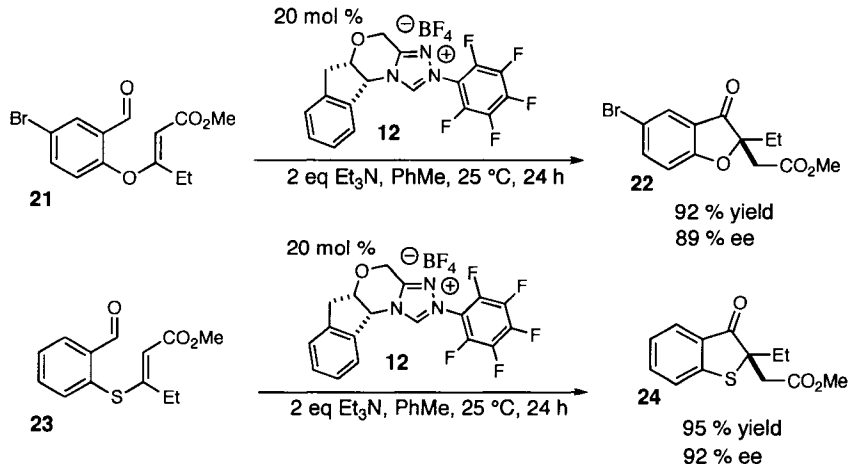


Since it was shown that the Stetter reaction was a feasible method to generate fully substituted stereocenters, it was decided to investigate the scope of the reaction. A number of other substrates were synthesized in the similar fashion to this parent substrate and evaluated under optimized conditions.

As expected from experience with previous studies, substitution about the aromatic ring can be tolerated with little impact on the outcome of the reaction, Scheme 7. 5-Bromo-salicylaldehyde-derived substrate **21** cyclizes in 92% yield and 89% ee, only slightly lower than the parent compound.

Substrates containing other heteroatom linkers are also viable substrates for this transformation, as thioether **23** undergoes Stetter reaction to provide benzothiophenone **24** in 95% yield and 92% enantiomeric excess. Fortunately, this product was isolated as a crystalline solid, and the absolute stereochemistry was determined by single crystal X-ray diffraction.[23]

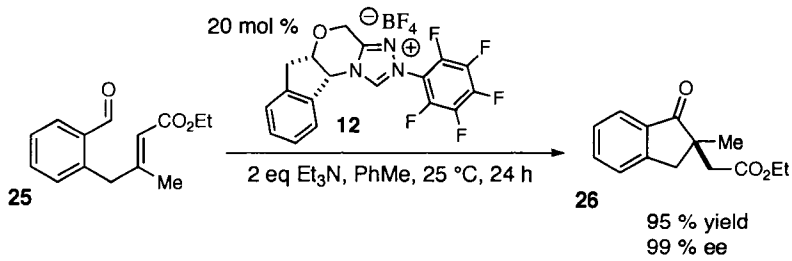
Scheme 7.



Since the enantioselectivities obtained in these reactions were all very good with a product that was prone to racemization, we were curious whether the reaction initially generated product with higher enantioselectivity than the isolated product. In order to test this, we decided to implement a substrate that would give a product incapable of racemization, Scheme 8. We then synthesized α,β-unsaturated ester **25** with an all-carbon tether between the reactive entities. When this was reacted under our catalytic

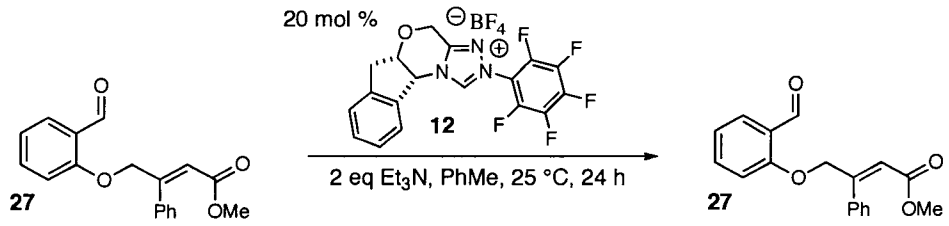
conditions, we found that the selectivity was excellent. This suggested to us that nearly perfect selectivity was obtained in this reaction, and erosion of selectivity in other systems may be an artifact of racemization.

Scheme 8.



We were also interested in forming larger rings in the Stetter reaction. We initiated these studies with the attempted cyclization onto α,β-unsaturated ester **27**. Unfortunately, all attempts to execute the Stetter reaction on this substrate failed. We attribute this to the lack of reactivity of β,β-disubstituted Michael acceptors versus β-monosubstituted Michael acceptors, Scheme 9.

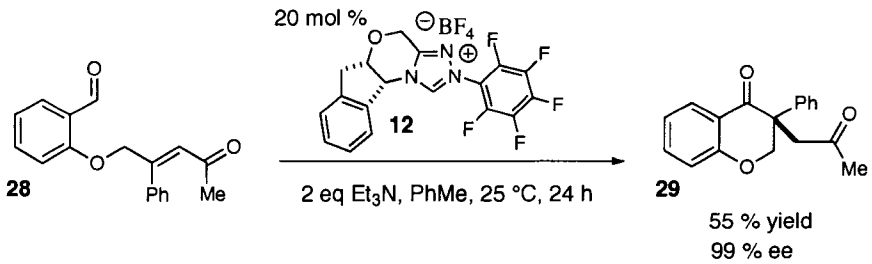
Scheme 9.



Since we had seen variations in reactivity among different Michael acceptors, with ketones giving better results than esters, it was decided to attempt the 6-membered cyclization with the methyl ketone as the activating group on the olefin, Scheme 10. Initial results demonstrated the feasibility of this reaction, as the desired product was

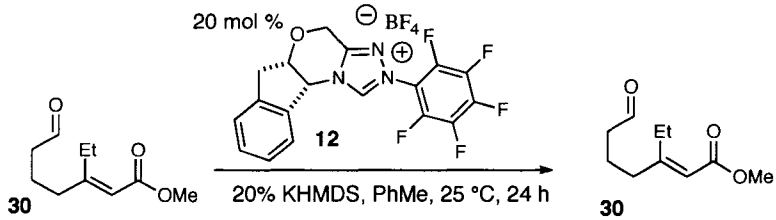
obtained in 30% yield when 20% catalyst was employed. Our attempt to increase the efficiency of this reaction involved adding catalyst in two portions. When adding 10 mol% catalyst **12**, allowing reaction for 12 hours, and addition of another 10 mol% we were able to achieve moderate product formation. The enantioselectivity was again very high, with the product formed in an excellent 99% ee.

Scheme 10.



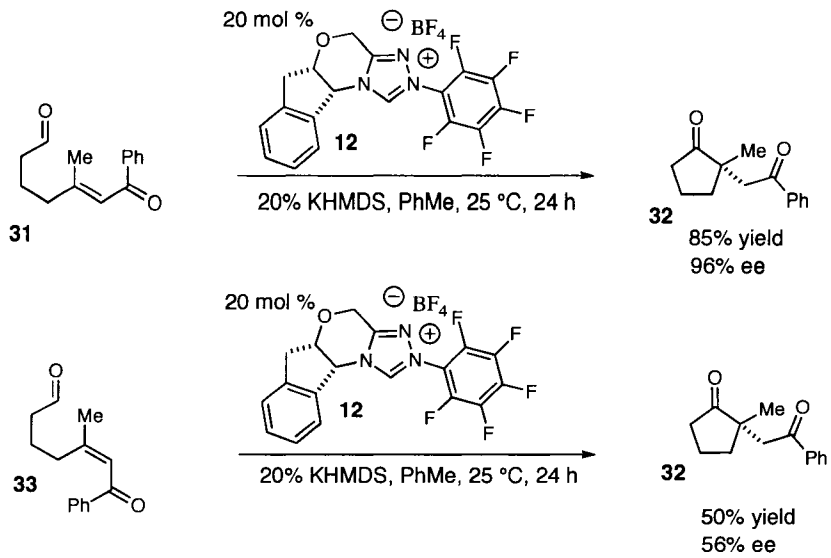
Since we had demonstrated that aromatic aldehydes cyclize with excellent enantioselectivity and in good yield, it was decided to investigate aliphatic aldehydes for cyclopentanone formation and concomitant generation of a quaternary stereocenter. The first substrate examined was ester **30**. Unfortunately, no conversion was seen under the standard reaction conditions, Scheme 11. We suspected this substrate may not be activated enough to undergo Stetter reaction.

Scheme 11.



Since methyl ester **30** did not give any Stetter product, we again thought it may be beneficial to increase the electrophilicity of the Michael acceptor. To test this idea, we prepared α,β-unsaturated phenyl ketone **31**, Scheme 12. Upon exposure to standard reaction conditions, we obtained a good yield and excellent enantioselectivity of the desired cyclopentanone.

Scheme 12.

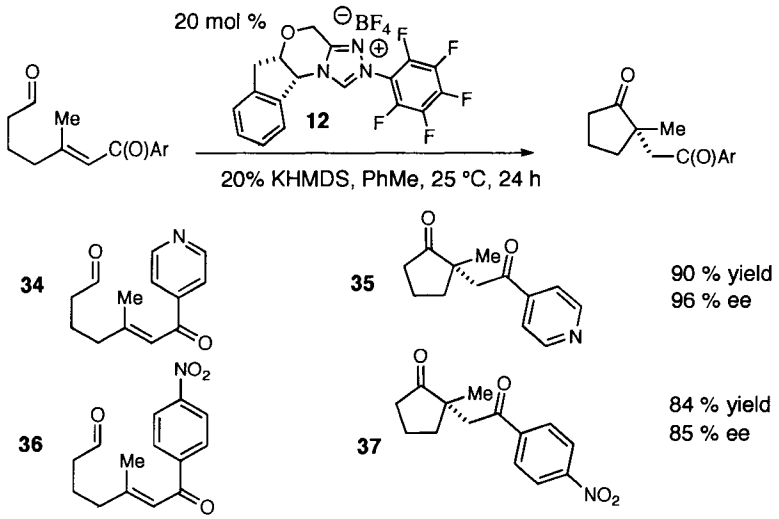


We had seen in earlier studies that the configuration of the double bond plays a crucial role in the reaction of disubstituted olefins. With a previous system, the *Z*-olefin of the model substrate gives no desired product, and starting material is reisolated. We were curious about what role the olefin geometry would play in the cyclization onto trisubstituted olefins. Upon preparation of *E*-olefin **31**, we found that the conversion and enantioselectivity suffered significantly. We ascribe this to steric interactions in the Breslow intermediate which don't allow for the electrophile to fit well into the reactive

site. For this reason, it was decided to investigate substrates possessing the *trans* configuration about the double bond for the rest of the study.

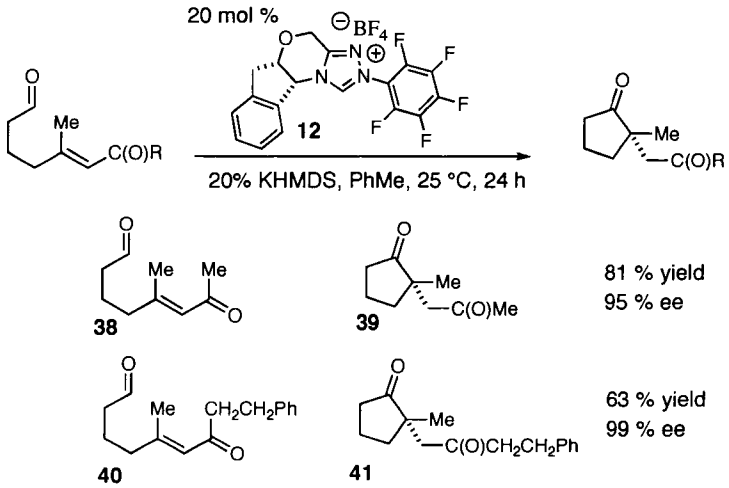
We were interested in looking at the effects of different aromatic ketone Michael acceptors, Scheme 13. We found quite similar reactivity patterns for both 4-pyridyl ketone **34** and 4-nitrophenyl ketone **36**. We ascribe slight differences in reaction efficiency to the electronic characteristics imparted into the Michael acceptor by the different aromatic groups on the ketone.

Scheme 13.



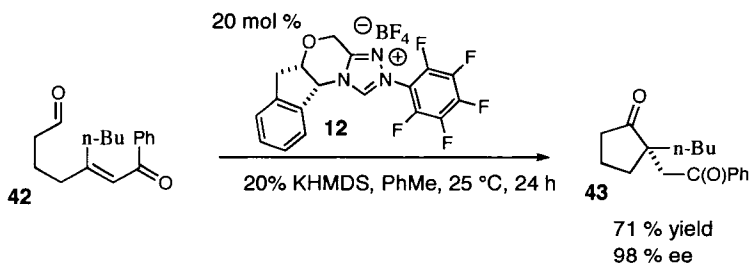
We next turned our attention to the use of aliphatic ketones in this reaction. Once again, we were able to obtain good yields and excellent selectivities in the Stetter reaction, Scheme 14. Both the methyl ketone and dihydrocinnamyl ketone were shown to be competent activators for the Michael acceptor. Comparison of the optical rotation of **39** to the literature value allowed for the assignment of absolute stereochemistry to this product.[24]

Scheme 14.



Since the above examples show the use of a methyl group at the β-position of the Michael acceptor, we were interested in seeing what further substitution could be tolerated. We were able to synthesize Stetter substrate **42** with *n*-alkyl substitution at the β-position of the Michael acceptor. We were pleased to see good reactivity accompany this reaction, along with good selectivity.

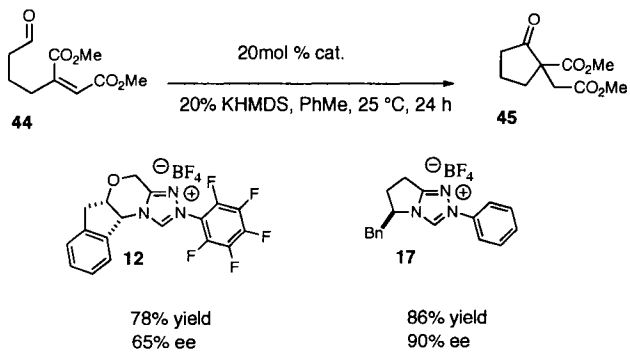
Scheme 15.



Further varying the Michael acceptor allowed for cyclization of bis-ester **44**. As previously shown with **30**, an ester Michael acceptor is not capable of participating with

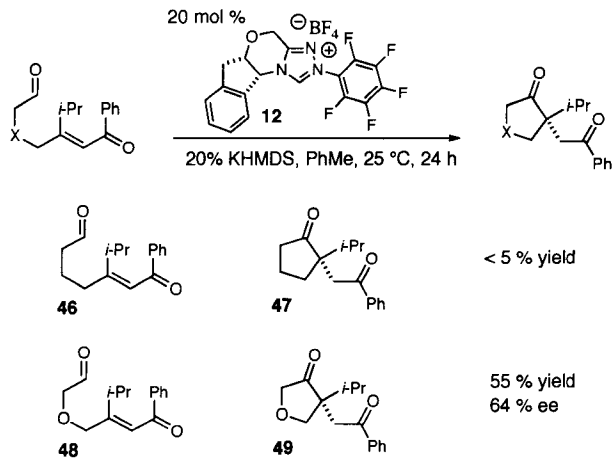
the standard reaction conditions. By increasing the electrophilicity of the double bond with another ester, we are able to achieve the desired reactivity, Scheme 16. When implementing the standard conditions, we obtained disappointing selectivity. However, when implementing phenylalanine-derived catalyst **17**, we found the enantioselectivity increased to 90% ee.

Scheme 16.



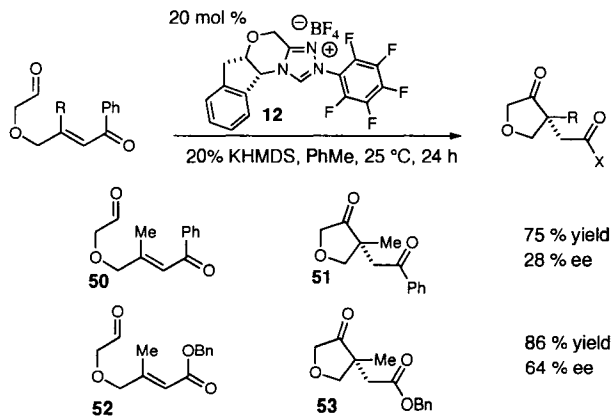
We were interested in whether this reaction could tolerate further steric bulk at the β-position of the Michael acceptor, Scheme 17. When substrate **46** was prepared and subject to reaction conditions, no desired product was formed. This suggests the steric hindrance created by the *iso*-propyl group is too great to allow for reactivity in this system. Upon preparation of **48**, possessing the oxygen linker in the backbone, we see that some product is formed, although with modest enantioselectivity.

Scheme 17.



We see a trend for lower enantioselectivities with substrates possessing oxygen linkers in the tether, Scheme 18. With a methyl group at the β-position, we see significantly diminished selectivity in this series with a phenyl ketone activating group. Substrate **50** cyclizes efficiently to provide the product tetrahydrofuranone (**51**), however the ee is only 28%. When switching to the less activating benzyl ester, **52**, we see a slight increase in selectivity. Tetrahydrofuranone **53** is formed in 64% ee in good yield under these reaction conditions.

Scheme 18.

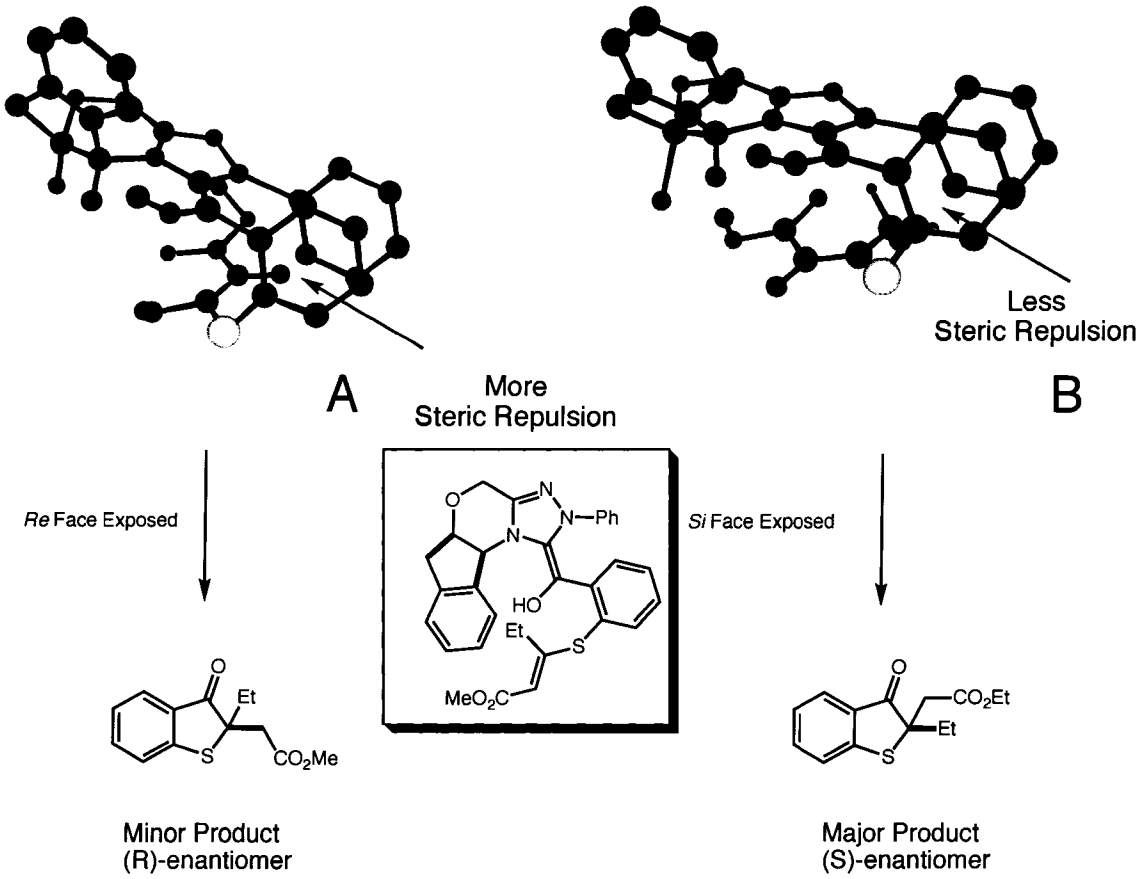


These results demonstrate a limit to this methodology, since larger groups on the Michael acceptor seem to be difficult to accommodate. The backbone also plays a role in the reactivity as well as selectivity in the aliphatic series. However, with the number of catalysts available possessing different properties, potential exists for these problems to be overcome.

2.3 Stereochemical Model

We see a different sense of enantioinduction for different backbones and tether lengths in the intramolecular Stetter reaction. While this is not completely understood, we can rationalize the different antipode of product when different families of substrates are utilized. The absolute stereochemistry of benzothiophenone **24** was established by single crystal X-ray diffraction. In order to rationalize the highly selective formation of the major isomer, it is once again necessary to consider the *E*-isomer of the Breslow intermediate, and the *re* and *si* faces of the Michael acceptor, Figure 2. When looking at transition state A, it is evident that the vinyl proton on the Michael acceptor is directly pointing into the benzene ring on the triazole. In order for the nucleophilic alkene and Michael acceptor to come close to each other, severe steric repulsion is encountered between the vinyl hydrogen and the aromatic ring. When looking at transition state B, the ethyl group appears not to have these same interactions, which would allow for cyclization onto the *Si* face to give the major product.

Figure 2.



2.4 Conclusion

We have demonstrated the ability of the enantioselective intramolecular Stetter reaction to form quaternary stereocenters. Pentafluorophenyl catalyst **12** is capable of cyclizing aromatic and aliphatic aldehydes onto pendant β,β-disubstituted Michael acceptors with good to excellent enantioselectivity. Five- and six-membered rings can be formed in this annulation reaction. The reactivity in these systems is decreased due to an additional β-substitutent on the olefin, but still provides desired reactivity when implementing the proper Michael acceptor. In some cases, ester activating groups are not sufficient to achieve the desired reactivity, although this can frequently be remedied by implementation of a ketone. Olefin geometry has been shown to significantly affect the

outcome of the reaction as well, with the *E*-configuration of the double bond providing the best results.

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[24] The rest of the aliphatic Stetter products were assigned by analogy.

Chapter 3

Implementation of the Catalytic Enantioselective Stetter Reaction in Complex Molecule Synthesis: Progress Toward the Synthesis of Asparagamine A.

3.1 Introduction

The desire to utilize the intramolecular Stetter Reaction in the synthesis of complex molecules exists for several reasons. It serves to push a method to its limits in order to find strengths and weaknesses and point out the flaws associated with it. This pursuit serves to advance basic science and helps to understand the underlying principles associated with the reactivity. Another fundamental reason to do this is to showcase the synthetic utility and its complementarity with other methods. Furthermore, natural product synthesis is an intense area of chemical research since natural products and analogs continue to provide important leads in biological studies. Our attraction to asparagamine A is rooted in the capacity of this method to accomplish all of the aforementioned goals. We have investigated several systems possessing a significant increase in complexity from previously studied systems. The successful implementation of this reaction will demonstrate its power and efficiency in complex molecule synthesis.

3.2 Asparagamine A

3.2.1 Asparagamine A and the *Stemona* Alkaloids

Asparagamine A, or didehydrostemofoline, belongs to a family of hexacyclic *Stemona* alkaloids. The roots and leaves of many Stemonacae species have been implemented in traditional Southeast Asian medicine as anthelmintics and in the treatment of respiratory diseases.[1] This natural product was isolated from the root extract of *Stemona collinsae* in a quantity of 76 mg/kg,[2] and its structure determined by X-ray crystallography.[3] Powerful insecticidal activity has been shown with asparagamine A, with superior activity to the

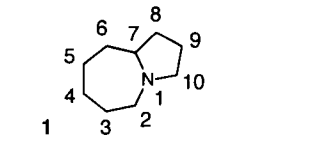
related structures found in stemofoline, isostemofoline, and isodidehydrostemofoline. The LC_{50} of didehydrostemofoline has been reported as 0.84 ppm against neonate larvae of *Spodoptera littoralis*.[4] This compares quite favorably to the LC_{50} of azadirachtin (8.2 ppm), one of the most promising natural insecticides yet investigated.

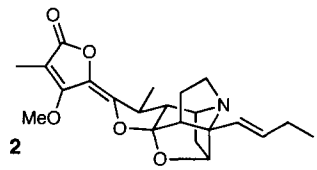
About 60 *Stemona* alkaloids have been isolated from several plants of the Stemonaceae family. Studies on the specific biological activity of the individual members of this alkaloid family have been limited. The most characteristic structural feature of these alkaloids is a 1-azabicyclo[5.3.0.]decane system **1**, Figure 1. Many of these incorporate an α-methyl-γ-butyrolactone substructure in either a fused or spiro manner, or as a substituent.

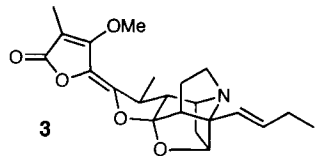
The polycyclic cagelike structure of the core differentiates the stemofolines from the rest of the *Stemona* alkaloids. Four other natural products have been isolated which share this intricate core structure with asparagamine A, **2**. One of these related natural products is isodidehydrostemofoline, **3**, which differs by the olefin geometry connecting the core and the tetronate moiety. Stemofoline, **4**, is identical other than by the degree of saturation of the butenyl sidechain. Another compound that has been isolated from these plants is 2'-hydroxy stemofoline, **5**. This compound possesses a hydroxyl group on the sidechain. Asparagamine A possesses the most potent biological activity of this family.

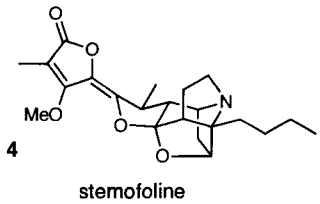
The majority of the *Stemona* alkaloids are characterized by structures such as neostemonine, **6**, lacking the extra cagelike connectivity. Considerably more work has been put forth toward the synthesis of this class of alkaloids.[5]

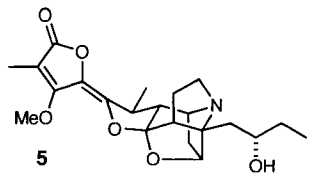
Figure 1.

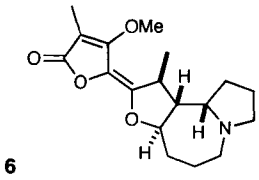












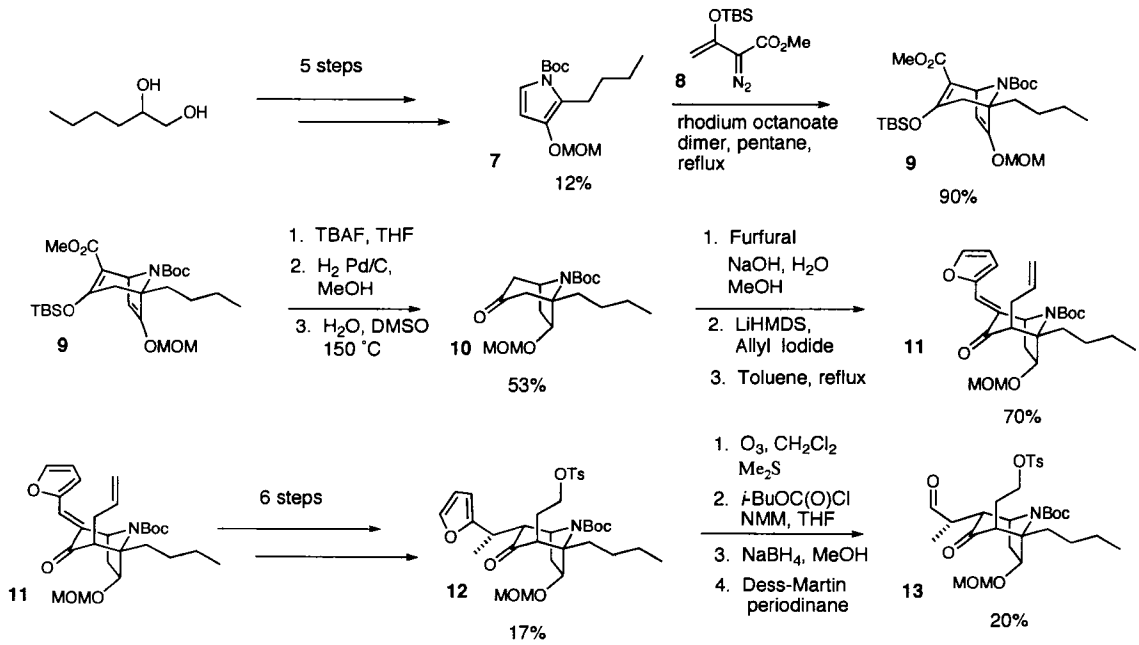
The biosynthesis of these molecules has not been heavily studied. However, one report has been published suggesting they may originate from spermidine and three isoprene units.[6]

The complex architecture of this molecule and stereochemically dense cagelike core makes this molecule an attractive target for synthesis. Potentially one of the most challenging features of this core is the fully substituted stereocenter. The stereocenter contains a nitrogen atom and a butenyl chain, and sits at the vertex of the polycyclic system. An enantioselective approach to this stereocenter would appear to be a good starting point for a stereocontrolled synthesis of this molecule.

3.2.2 Previous synthetic work

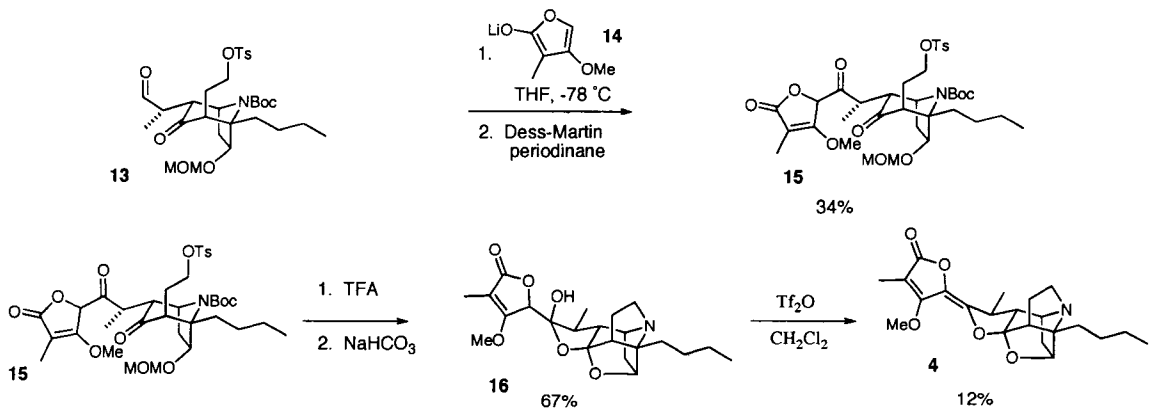
Seminal work was reported in this class of natural products from Kende and coworkers in the racemic synthesis of stemofoline.[7] A key strategy of this synthesis involves a formal 4+3 cycloaddition to form the intricate core structure (Scheme 1). Commencing with 1,2-hexanediol, a 5-step sequence yields pyrrole **7**. The 4+3 cycloaddition is then executed by the decomposition of diazo compound **8** in the presence of the pyrrole to create **9**. This transformation represents a powerful annulation strategy, although enantioselective methodologies to effect this transformation have yet to be reported. Functional group manipulation converts silyl enol ether **9** to the ketone. Hydrogenation of the double bond occurs face selectively, and Krapcho decarboxylation generates **10**. Condensation with furfural installs the olefinic sidechain. The molecule is then alkylated with allyl iodide to afford a mixture of C- and O-allylated materials. Upon heating this mixture in refluxing toluene, a Claisen rearrangement delivers the desired C-allylated product in good yield. Straightforward functional group manipulation allows for the stereoselective Michael addition of methyllithium to α,β-unsaturated ketone **11**. Conversion of the terminal olefin to the tosylate provides **12**. Conversion of the furyl group to the aldehyde by a four step sequence gives aldehyde **13**, ready for a key cyclization sequence.

Scheme 1.



The endgame in this synthesis involves addition of lithium dienolate **14** to the aldehyde, followed by oxidation to the ketone, **15** (Scheme 2). Upon treating compound **15** with trifluoroacetic acid, the *N*-Boc protecting group is removed, along with the MOM group. This sets up a tandem cyclization sequence. The free alkoxide cyclizes onto the pendant ketone, which in turn cyclizes onto another ketone to form a second five-membered ring. Upon neutralization, the free amine displaces the tosyl group to complete the core of the molecule. Treatment of **16** with trifluoromethanesulfonic anhydride gives the target molecule, **4**.

Scheme 2.



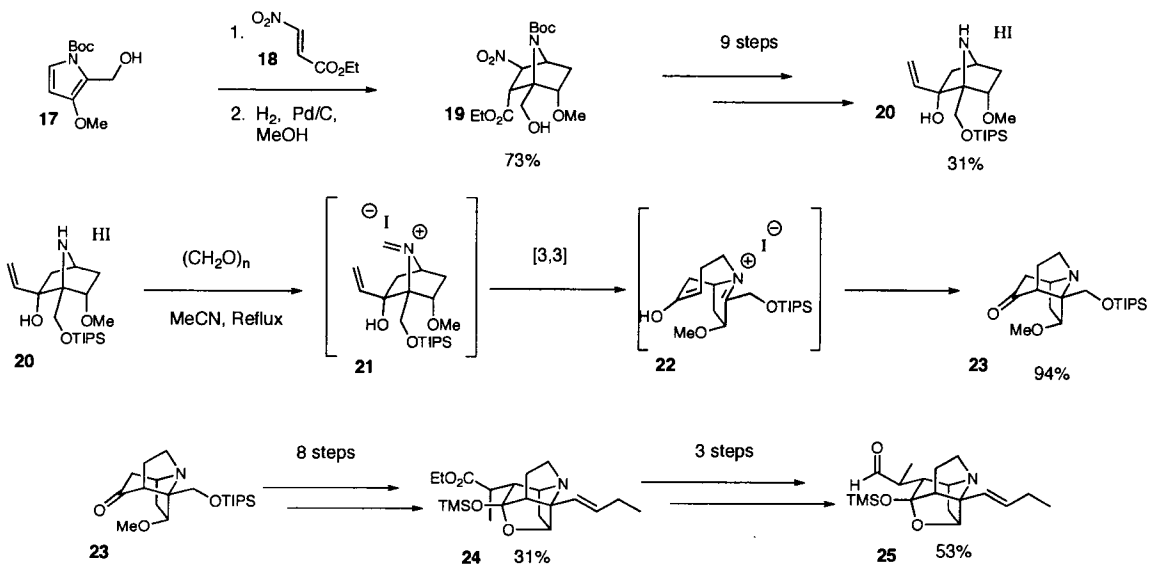
A serious drawback to this synthesis is the lack of efficiency in the last step of the reaction to generate the ylidene tetronate. In this last step, retroaldolization is a significant problem, and a variety of dehydrating conditions give only lactone product. As this step proceeds in only 12% yield, the overall synthetic efficiency is seriously decreased.

Elegant work from the Overman group has culminated in a racemic total synthesis of asparagamine A as well as its geometrical isomer, isodidehydrostemofoline.[8] The key features of this synthesis include a Diels-Alder reaction involving a regioinverted ketene equivalent, an aza-Cope Mannich reaction, and a Corey-Winter reaction to install the tetronate moiety.

The Diels-Alder reaction between *N*-Boc pyrrole **17** and the β-nitroacrylate **18** efficiently assembles the azabicyclo [2.2.1] heptanol system (Scheme 3), which upon hydrogenation of the double bond provides **19**. Standard manipulations are then executed to remove the nitro group and protect the primary alcohol. Conversion of the ester to an aldehyde, followed by silyl enol ether formation and ozonolysis, provides a ketone. Vinyl grignard

addition followed by Boc deprotection gives amine hydroiodide salt **20**. This molecule is now ready to do the feature reaction to generate the skeleton of the target molecule. Treatment of this compound with paraformaldehyde creates the iminium ion, **21**, which executes an aza-Cope reaction to give intermediate **22**. This species spontaneously undergoes a Mannich reaction to provide **23**. This then is subjected to standard functional group manipulations to the ester, including alcohol deprotection, oxidation to the aldehyde, and Julia olefination to install the butenyl sidechain. Alkylation with ethyl iodoacetate follows, and methyl ether removal effects hemiacetal formation. Protection of the hemiacetal as its trimethylsilyl ether and alkylation with methyl iodide gives **24**. The ester is then converted to the aldehyde, and methyl group equilibration is effected by chloroform and silica to give **25** as a single diastereomer.

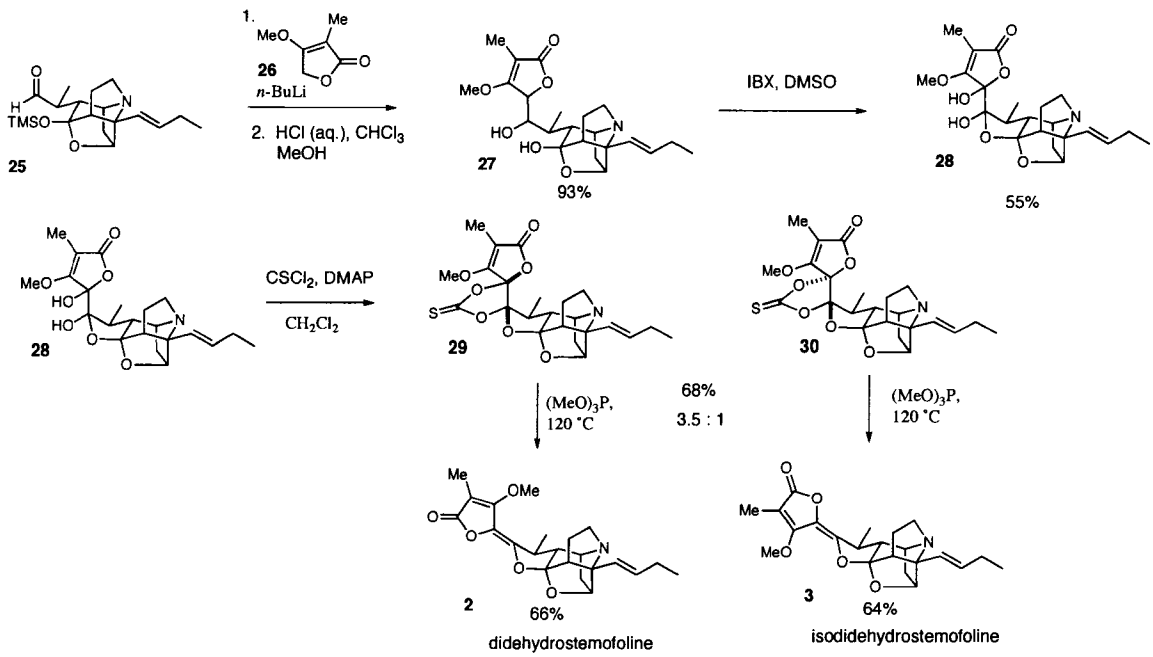
Scheme 3.



The end-game strategy is outlined in Scheme 4. Addition of the lithium anion of furanone **26** to aldehyde **25** gives the rest of the skeleton of the molecule. The silyl protecting group is cleaved with acid to give **27**. Oxidation with IBX generates the

ketone from the secondary alcohol, and also installs a hydroxyl group at the 5-position of the lactone, providing **28**. Treatment with thiophosgene forms the thiocarbonates from the diastereomeric diols, **29** and **30**. Treatment of these compounds with trimethyl phosphite effects a Corey-Winter reaction, generating the natural products. The mixture of diastereomers translates to the formation of both geometrical isomers of the final product.

Scheme 4.

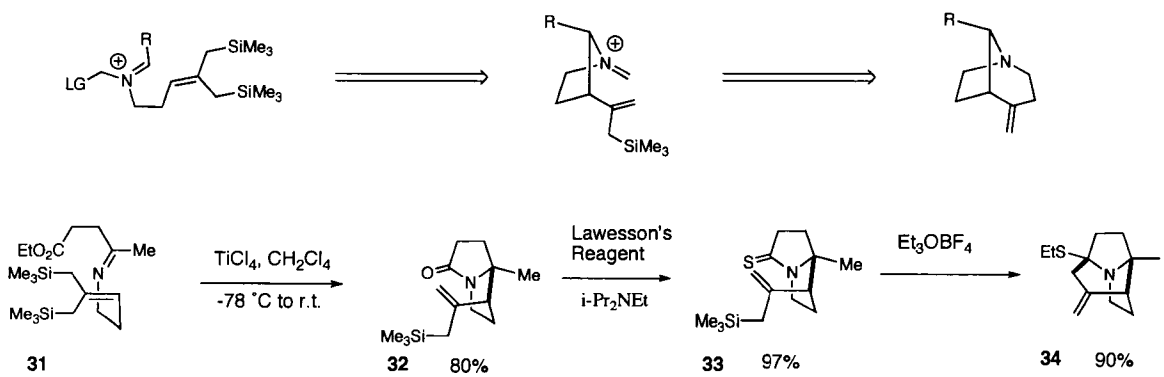


The Corey-Winter reaction to complete the reaction goes in high yield and represents a nice solution to the problems encountered in the final stages of the synthesis of stemofoline by Kende and coworkers.

Several other groups have spent considerable effort toward the synthesis of these compounds and various components of the molecules. Livinghouse and coworkers[9] have published a route directed at the polycyclic core structure (Scheme 5). This strategy involves iminium ion formation followed by nucleophilic attack from a 2-propanylidene

1,3-bis(silane). Upon loss of a leaving group, the second iminium ion is formed. Attack onto this iminium ion from the remaining allylsilane gives the polycyclic structure. This strategy has been reduced to practice, as illustrated by their conversion of **31** to **34**. Treatment of imine **31** with titanium tetrachloride allows for generation of the pyrrolidine. The amine then cyclizes onto the ester to form lactam **32**. Conversion of the lactam into the thiolactam (**33**) with Lawesson's reagent, followed by treatment with triethyloxonium tetrafluoroborate, activates the carbonyl position for nucleophilic attack from the allylsilane, generating polycyclic pyrrolidine **34**.

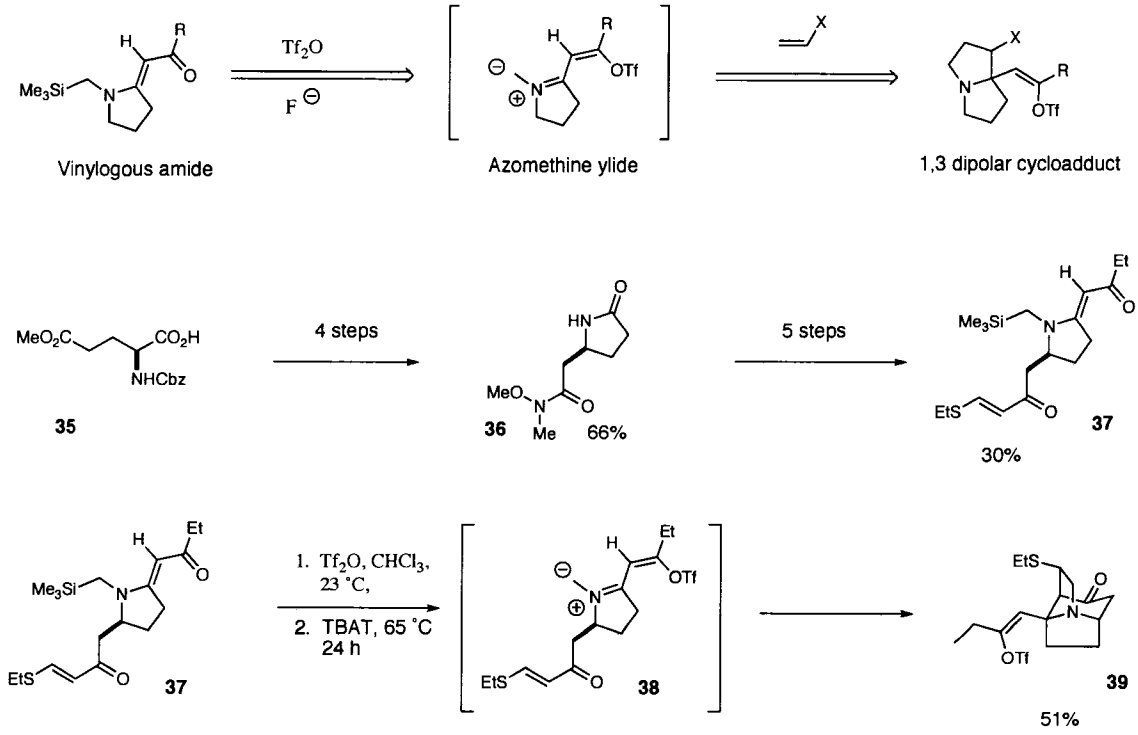
Scheme 5.



Gin and coworkers have also reported considerable progress toward the cagelike core.[10] Their strategy involves an intramolecular azomethine ylide dipolar cycloaddition, Scheme 6. This method involves the generation of the azomethine ylide in a novel fashion from a vinylogous amide with a trimethylsilyl methylene group on the nitrogen. This approach generates the dipolar cycloaddition precursor in 9 steps from the protected glutamic acid monomethyl ester **35.** Treatment of this compound with triflic anhydride followed by fluoride ion generates the azomethine ylide, **38**. Cycloaddition of this intermediate gives **39**. This approach is particularly attractive as it forms two carbon-

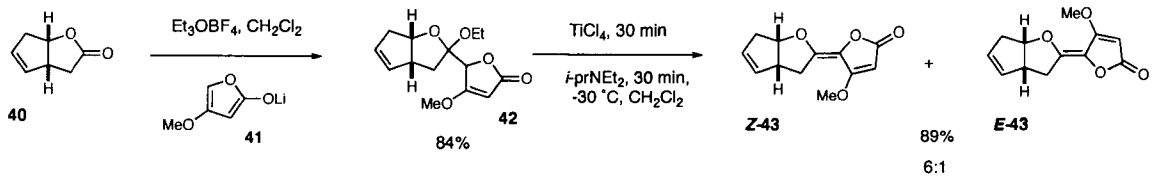
carbon bonds and sets three stereocenters in a single operation. A drawback in this sequence is that 9 steps are required to reach the intermediate necessary for the cycloaddition from commercially available materials.

Scheme 6.



Other work has been published on the synthesis of the tail of the molecule, the ylidenetetronate, Scheme 7.[11] This research focused on the addition of a lithium dienolate of methyl tetronate to an activated lactam. The product of this reaction is the mixed acetal, **42**. Dealkoxylation of this species provides the ylidenetetronate **43** with moderate *Z*/*E* selectivity.

Scheme 7.

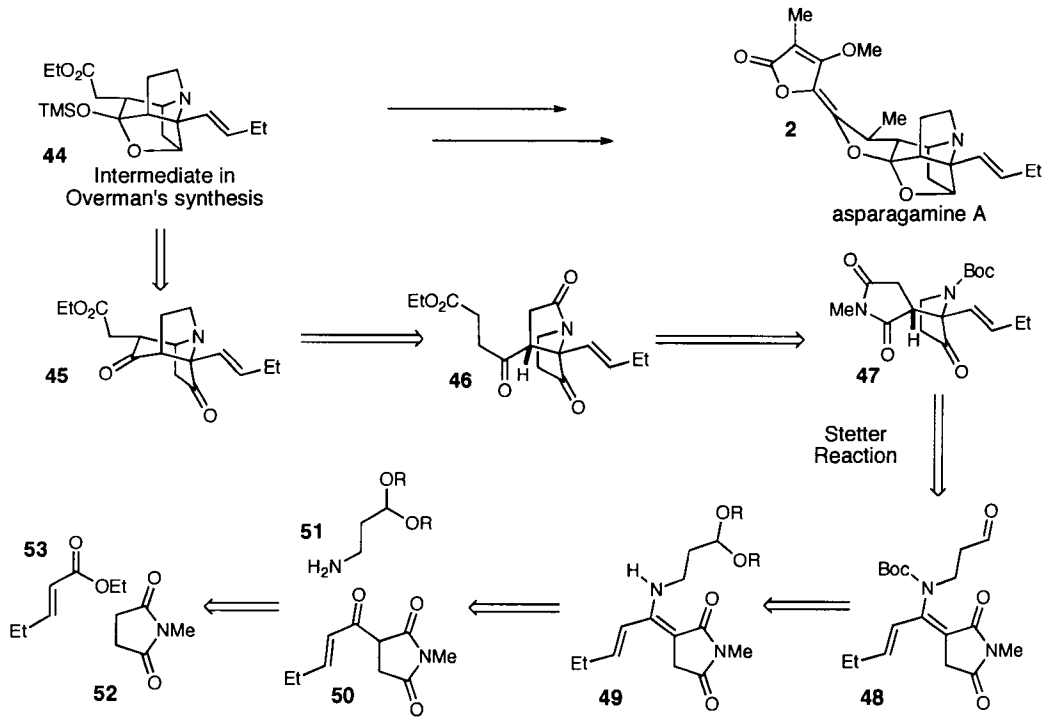


Our interest in asparagamine A stemmed from the idea to utilize the intramolecular Stetter reaction to enantioselectively create the fully substituted stereocenter. As evident by the synthesis of Overman, as well as Kende's synthesis of stemofoline, this stereocenter lies at the heart of the challenging problem of generating the core structure. As we had demonstrated the feasibility of intramolecular Stetter reactions on β,β-disubstituted Michael acceptors as well as α,α-disubstituted Michael acceptors,[12] we became interested in extending the Stetter reaction to the use of tetrasubstituted olefins. Michael additions into tetrasubstituted olefins are exceedingly rare, and enantioselective variants even more uncommon.[13,14] We saw the synthesis of this alkaloid as a platform from which to explore this class of substrates. Successful implementation would serve to expand the reaction scope, as well as demonstrate the reaction's utility in the development of molecular complexity. In addition to extending this to tetrasubstituted Michael acceptors we also planned to demonstrate that olefins possessing protected nitrogen atoms could be forced to participate in the Stetter reaction. Upon realization of this challenging endeavor, we envisioned rapidly intercepting an intermediate in Overman's synthesis.

3.2.3 Synthetic Plan

Our synthetic plan hinges around formation of the five-membered core of asparagamine possessing the fully substituted carbon atom by a Stetter reaction. We hoped to be able to readily prepare a simple starting material which would undergo the key Stetter reaction in enantioselective fashion and generate a skeleton of the molecule. This molecule would be suitably functionalized for further transformation into the target compound. We envisioned the use of a tetrasubstituted olefin Michael acceptor with an imide as the activating group. The imide seemed particularly suited for this for a number of reasons. The imide is a strong electron-withdrawing group, which we expected to be necessary to obtained the desired reactivity. Furthermore, we expected the part of the imide to be implemented into the polycyclic structure later in the synthesis. Our retrosynthetic analysis of asparagamine A is shown in Scheme 8.

Scheme 8.

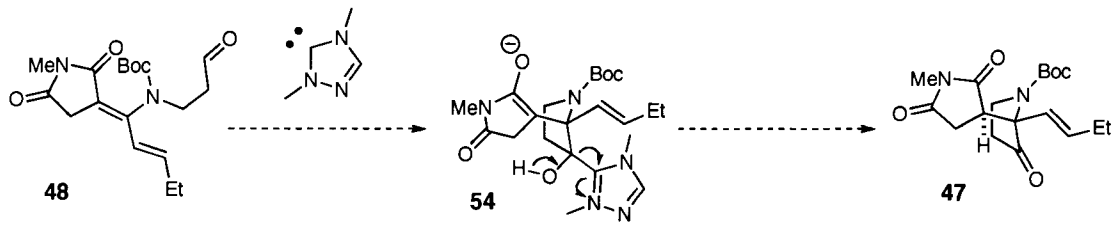


We envision the interception of **44**, an intermediate in Overman's synthesis in order to complete the enantioselective formal synthesis. This may be formed by selective reduction of the ketone in **45**. Upon reduction, the generated alcohol should form a hemiacetal with the other ketone. This will be trapped as its trimethylsilyl ether. Tricyclic intermediate **45** should be available from bicyclic compound **46** by reduction of the amide, and enolate alkylation to the vinylogous amide. This compound in turn should be obtainable from succinimide **47** by removal of the Boc protecting group and subsequent 5-membered ring formation to the succinimide. This compound will be prepared in the key intramolecular Stetter reaction of **48**. If cyclization of achiral succinimide **48** is possible, we may obtain **47** with control over the fully substituted stereocenter, as well as the second stereocenter by an intramolecular proton transfer.[15]

Aldehyde **48** should be available from protecting group manipulation of acetal **49**. This may be synthesized by condensation of amine **51** with β-keto succinimide **50**. The succinimide should be available from alkylation of N-methyl succinimide with an ester of 2-pentenoic acid.

In the key step, we envision addition of the triazolinylidene carbene to aldehyde **48**, generation of the acyl anion equivalent and cyclization onto the Michael acceptor to form intermediate **54** (Scheme 9). Upon Michael addition, we expect the generated enolate to undergo intramolecular proton transfer before rotation about the C-C single bond. This will allow for the selective generation of the second stereocenter.

Scheme 9.

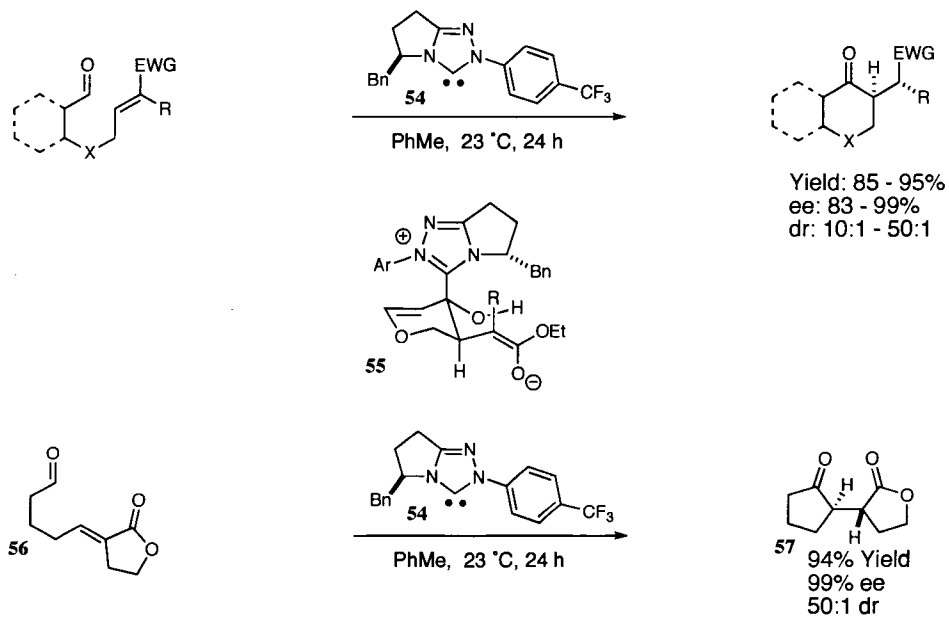


The aggressiveness of this approach deserves comment. Earlier studies have demonstrated that additional substituents on a Michael acceptor retard the reaction of the generated acyl anion and the electrophile. We have seen that increasing substitution on Michael acceptors causes a marked decrease in the efficiency of the reaction. For this reason we were equally concerned about taking the step from the trisubstituted olefin to the tetrasubstituted olefin. Only a handful of examples are known throughout the literature involving the addition of a nucleophile into a tetrasubstituted olefin, and even fewer have been demonstrated in the arena of catalytic, enantioselective reactions.[13,14] Another concern involved the use of a Michael acceptor with a nitrogen attached at one

end. This vinylogous urea functionality poses a challenge concerning the stability of the functional group, as well as the electronic properties associated with it. As we were concerned that an especially activated olefin would be required to effectively take part in the reaction, the amide activator on the olefin would need to be quite electron-deficient. Furthermore, it had not been demonstrated that olefinic sidechains could effectively participate in the intramolecular Stetter reaction. Of the potential problems associated with this are the possibility of 1,6-addition, as well as a significant decrease in reactivity, as the π system may donate electron density into the site which is to act as an electrophile.

The issue of diastereoselectivity in the reaction is also some cause for concern. An elegant body of work has been put together in the Rovis research group by Javier Read de Alaniz addressing this issue of diastereoselective protonation of the generated enolate in the intramolecular Stetter reaction, Scheme 10.[16] A model for the intramolecular proton transfer is depicted by **55**. In a particularly relevant example, the cyclization of aliphatic aldehyde **56** to cyclopentanone **57** has been performed in excellent enantioselectivity and diastereoselectivity with high yield. From this work we have postulated that the Z-geometry of the Michael acceptor should allow for formation of the desired diastereomer of the product. However, it has been shown that the isomer leading to the desired diastereoselectivity may be less reactive.

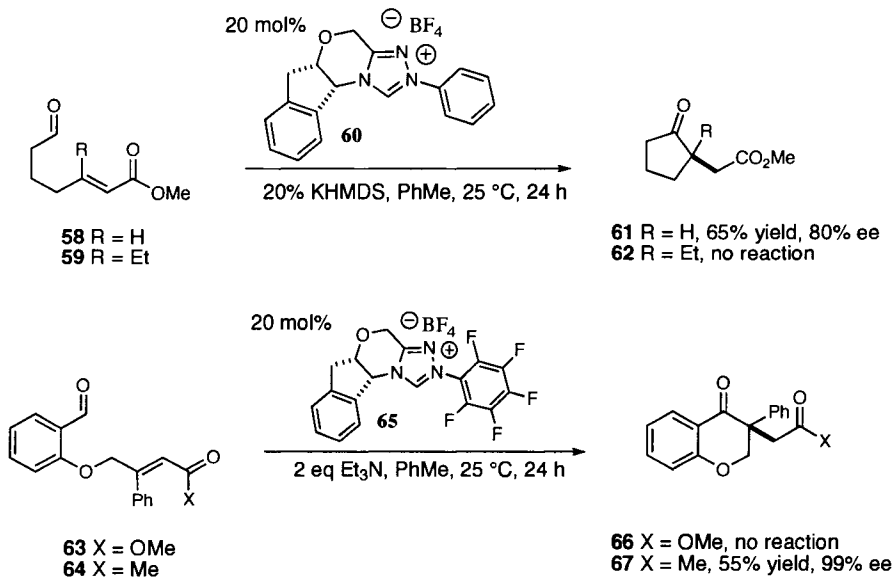
Scheme 10.



Our initial strategy to stereoselectively generate the intermediate on route to intercepting Overman's synthesis involved the use of an imide to activate the olefin for attack of the acyl anion. This was chosen because it should function as a strong activating group. From previous studies directed at the intramolecular Stetter reaction, we have noticed that the substitution and electronic properties of the Michael acceptor play a prominent role in the success of the reaction, Scheme 11. In the cyclization of aliphatic aldehydes to cyclopentanones, we obtain a modest yield of **61** from **58** in which the β-substituent is hydrogen. The reaction completely shuts down in the attempted cyclization of **59** possessing a β-ethyl substituent. This demonstrates that additional substitution retards the reaction. For a six-membered cyclization, we have seen that when an ester is not capable of sufficiently activating the olefin as demonstrated in the attempted cyclization of **63** to **66**. However, when utilizing methyl ketone **64,** cyclization to **67** can be

realized.[17] From these experiments, we reasoned that it would require a very electron-deficient Michael acceptor to allow for cyclization to the desired Stetter product.

Scheme 11.



A balance is also necessary when considering the ultimate goals of this project, creation of a new carbon-carbon bond and two adjacent stereocenters. A strong electron-withdrawing substituent is required to get the desired reactivity. If the newly generated stereocenter possesses too strong of an electron-withdrawing group, then the second stereocenter will almost certainly racemize under the reaction conditions. This would be likely if a Michael acceptor such as a nitro-olefin were employed. The imide functionality seemed to fit the requirements of this balance.

Regardless of these challenges, it was decided to embark on the synthesis of this complex alkaloid.

3.2.4 Progress toward the synthesis of asparagamine A

In order to establish the feasibility of intramolecular Stetter reaction on the key substrate for asparagamine A, a number of model substrates were envisioned. It was decided to evaluate the ability of the reaction to cyclize onto vinylogous amides, Michael acceptors possessing nitrogen substitution on the olefin. Some nice enantioselective work has been published with *N*-protected 2,3-dihydro-4-pyrrolidones and their reaction with organometallic nucleophiles. It has been noticed that these systems are less reactive than cyclohexanone.[18] In fact, good results have been obtained with both reactivity and selectivity in some of these metal-catalyzed reactions. However, the best catalytic and enantioselective results have been obtained with aromatic boronic acids and benzyl carbamate protecting groups. However, much of the literature associated with these systems is limited to carbamate protecting groups. We initially had little idea on how the nitrogen protecting groups would affect the reactivity of the Michael acceptor. We assumed that the electron-withdrawing group on the olefin would dominate.

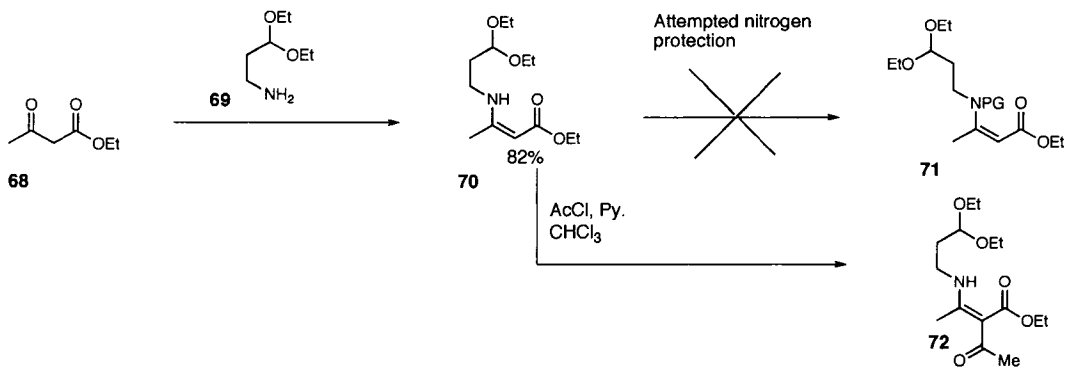
To date, the use of these types of Michael acceptors have been limited to simple systems. As such, no examples have been published that incorporate a β,β-disubstituted Michael acceptor in these reactions. We were confident that the correct electron withdrawing group on the alkene, coupled with the correct nitrogen protecting group, should be able to activate the substrate for intramolecular reaction.

We set out to make a simple model system from readily available materials to familiarize ourselves with the reactivity associated with these compounds. We saw the condensation of a primary amine onto a β-keto carbonyl compound as a facile way to access these substrates. This would allow for the generation of a lot of candidates to make into

substrates to test the ability of these compounds in the Stetter reaction. Condensation of an amine onto a ketone of a β-keto carbonyl compound gives the imine, which tautomerizes to the enamine. This enamine is stabilized by the 6-membered hydrogen bond and should give a single geometrical isomer.

The first system we investigated was the β-keto ester, ethyl acetoacetate, Scheme 12. We were interested in this system since ethyl acetoacetate can be readily alkylated at the acetate with a variety of electrophiles, allowing for a wide amount of diversity.[19] Also, the product 1,4-ketoesters allow for a high degree of further functionalization. Condensation of amino propionaldehyde diethyl acetal (**69**) gives enamine **70** in high yield.[20] Unfortunately, this compound, upon attempted protection of the nitrogen, undergoes alkylation at the α-position to the ester to generate **72**.

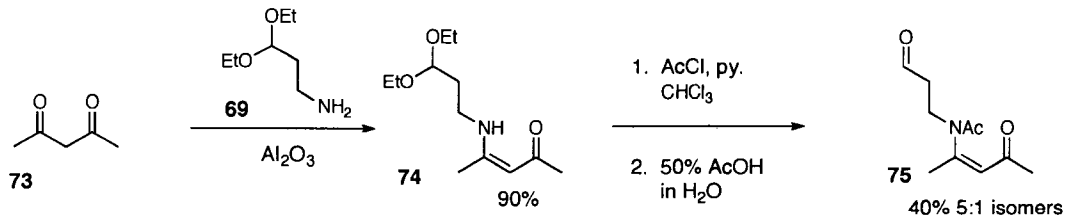
Scheme 12.



In order to validate this strategy of employing β-dicarbonyl compounds as precursors for these substrates, it was decided to attempt the condensation on a β-diketone, Scheme 13. Unfortunately, this has less utility, as it requires a symmetrical diketone to avoid the formation of regioisomers. Heating amine **69** with 2,4-pentanedione neat in alumina allows for smooth conversion into the enaminone **74**. Treatment of this compound with

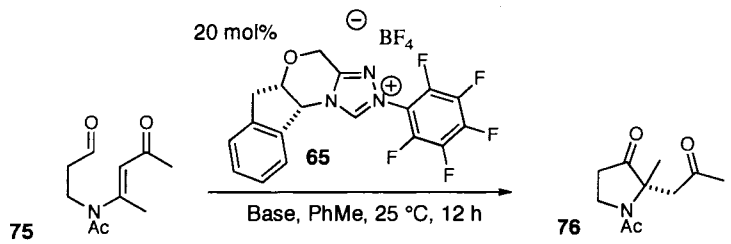
pyridine and acetyl chloride in chloroform allows for N-protection as its acetamide. This reaction is accompanied by scrambling of the olefin geometry. These isomers can be separated, although the acetal deprotection causes scrambling of olefin geometry as well.

Scheme 13.



After separation by column chromatography, it is possible to obtain substrate **75** with the required *E*-olefin geometry. The Stetter reaction was run with a number of reaction conditions, and it was found that high enantioselectivity could be obtained, Table 1. Implementing potassium *tert*-butoxide as base and catalyst **65** gave the highest yield, while use of triethylamine and KHMDS both led to poorer conversion. Gratifyingly, the enantioselection in this cyclization is superb, providing the desired pyrrolidinone (**76**) in 95% ee.[21] The cyclization of this model substrate, while not applicable to the synthesis of asparagamine A, demonstrates the ability of this reaction to cyclize onto these types of Michael acceptors.

Table 1.

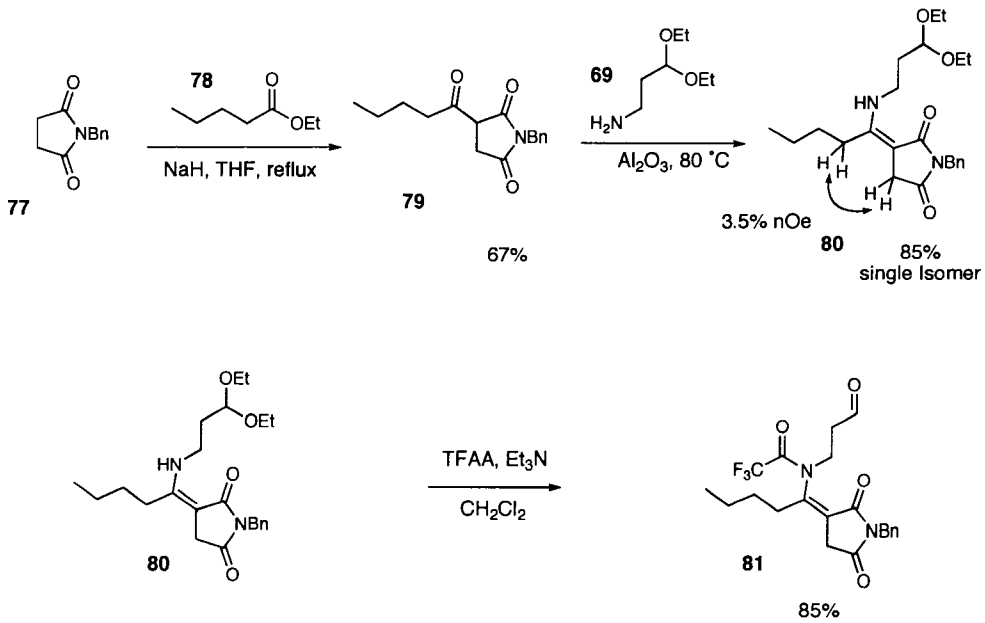


Entry[a]	Base	Yield (%)	ee (%)[b,c]
1	20 mol % KHMDS	45	95
2	20 mol % KO*t*-Bu	65	95
3	200 mol % Et_3N	40	95

[a]Reactions conducted in the presence of **59** (20 mol%) in PhMe for 12 hours with the indicated base at 25 °C. [b]Enantiomeric excess determined by GC. [c]Absolute configuration assigned by analogy to **39**, chapter 2.

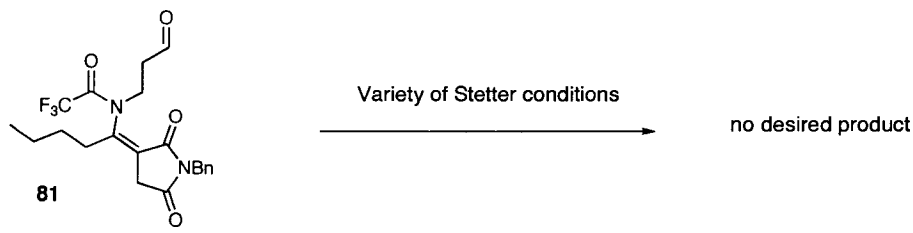
With the confidence gained in this reaction, it was decided to begin working on the model system with the tetrasubstituted olefin. In order to work with the easiest system, but still a relevant system to the target molecule, we decided to use the *n*-butyl sidechain, Scheme 14. We also were interested in a removable protecting group on the succinimide, and chose the benzyl group. Benzyl succinimide (**77**) was made in 10 gram quantities by reaction of succinic anhydride and benzyl amine in glacial acetic acid. Alkylation of this succinimide with valeric acid methyl ester and sodium hydride in THF provided β-dicarbonyl compound **79**. This underwent smooth condensation with amino propionaldehyde diethyl acetal to give **80** as a single geometrical isomer as determined by nOe. Initial attempts were made to install a Boc group. This proved more difficult than anticipated and a trifluoroacetamide protecting group was implemented instead. The conditions employed fortuitously cleaved the acetal to provide **81** to set the stage for the key reaction.

Scheme 14.



As we had developed a large number of catalysts with diverse properties, it was expected that at least some of the catalysts under optimized conditions might be capable of mediating the key cyclization. Unfortunately, all of the reactions attempted with the key substrate failed to give the desired product, Scheme 15.

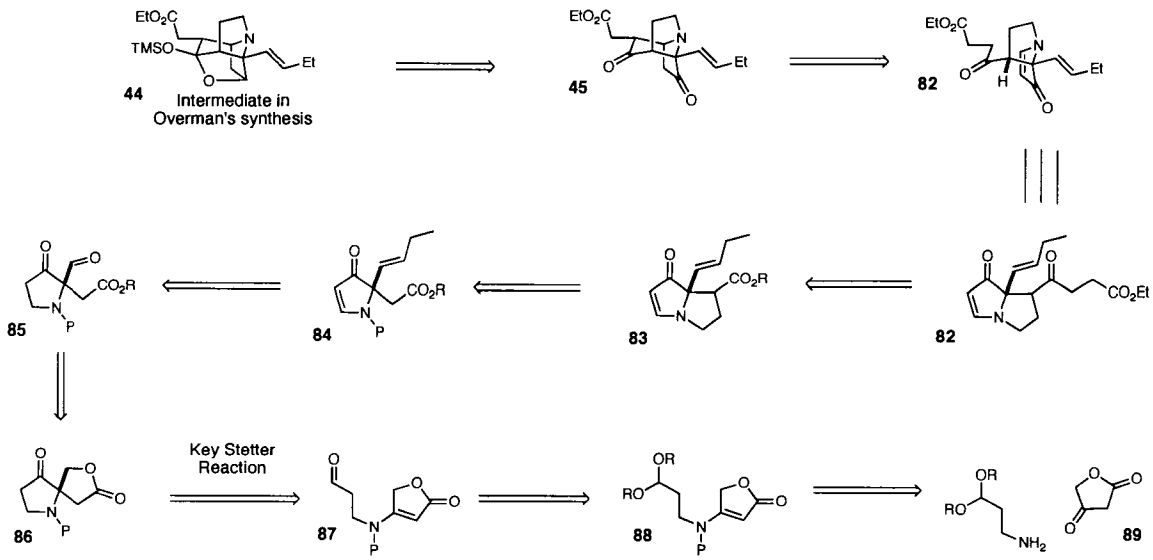
Scheme 15.



Since we had seen in previous studies that the olefin geometry plays a major role in reactivity, we ascribed the failure of this key reaction in part to the cis-relationship about the double bond of the aldehyde and activating group. We also suspected that the tetrasubstituted olefin may simply not be reactive enough to allow for cyclization.

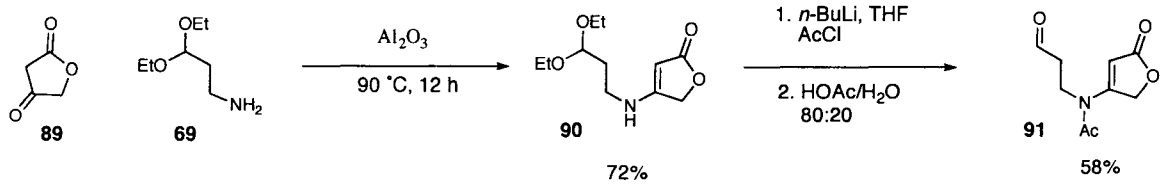
As a way to get around this problem, it was decided to look at a trisubstituted Michael acceptor fused in a ring. This could serve to fix the correct olefin geometry. In order to obtain the correct substitution pattern, it would be necessary to have a functional group near the formed stereocenter, and also a Michael acceptor that would allow for cleavage of the ring initially present in the molecule. We saw a potentially simple solution to this coming from the implementation of tetronic acid as the β-dicarbonyl compound. Our synthetic plan from this route is shown in Scheme 16. Once again, we plan on intercepting intermediate **44** which we will obtain again from diketone **45**. This polycyclic diketone should be accessible from vinylogous amide **82** by an intramolecular enolate addition into the electron-deficient double bond. We intend to obtain this compound from ester **83** by an organometallic coupling reaction between an activated acid derivative and an organometallic nucleophile. We will get this ester from deprotection of the vinylogous amide and installing a two carbon unit between the α-position to the ester and the nitrogen atom. We will synthesize **84** from **85** by first a Wittig reaction, and then installation of unsaturation. The aldehyde will be obtained from opening of the lactone and oxidation of the primary alcohol. Lactone **86** will be created in the key Stetter reaction on aldehyde **87**. In order to generate the substrate for the Stetter reaction, we intend on simple protecting group manipulation of acetal **88**, which will in turn be formed from condensation of the primary amine with tetronic acid (**89**).

Scheme 16.



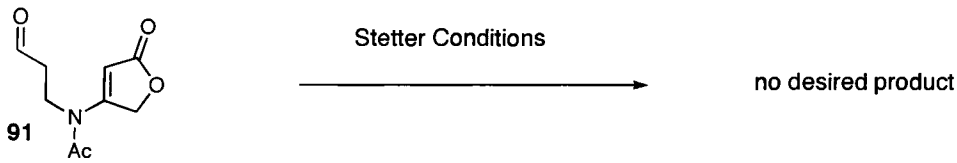
Straightforward condensation of aminopropionaldehyde diethyl acetal and tetronic acid forms **90**, Scheme 17. Acetylation of the nitrogen gives the protected acetal. The acetamide protecting group was chosen in this system due to its lack of reactivity. We were not sure whether the reaction would work in this system, as esters had proven problematic as activating groups when attempting to synthesize quaternary stereocenters. For this reason, we wanted the most stable protecting group to make the key step less problematic and cut down on the potential issues. We were confident the acetamide protecting group could be replaced with a more easily removed group if the Stetter reaction were to work. Deprotection of the acetal with acetic acid and water gives the desired Stetter substrate, **91**.

Scheme 17.

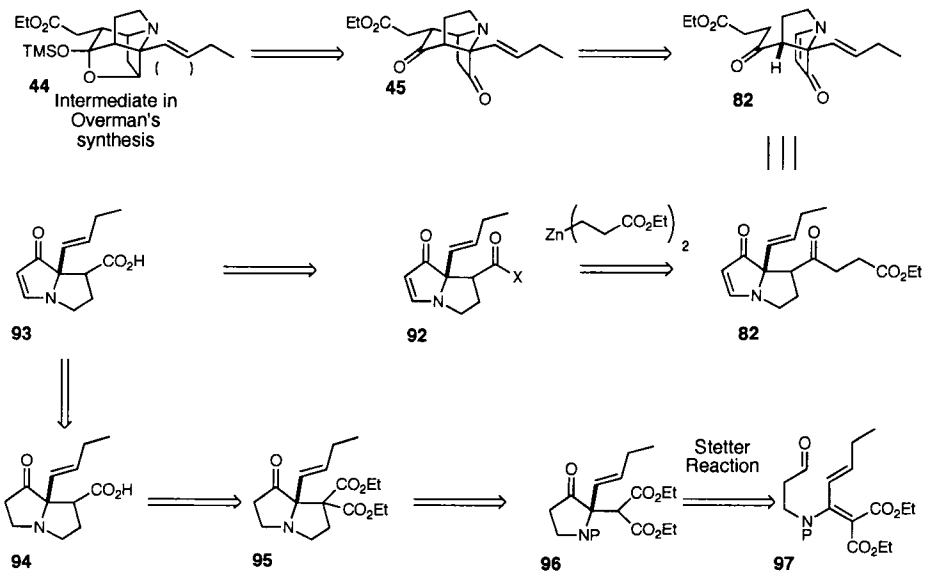


Aldehyde **91** was then subjected to a variety of Stetter reaction conditions. Again, the standard conditions that had been developed for the enantioselective intramolecular Stetter reaction failed to give the desired product, Scheme 18. We attribute this to a lack of electron-withdrawing capacity of the ester. Since the previous examples which involve β,β-disubstituted Michael acceptors required ketones as activating groups, it made sense that the ester may not be a strong enough electron-withdrawing group to activate the double bond for nucleophilic attack.

Scheme 18.



Scheme 19.

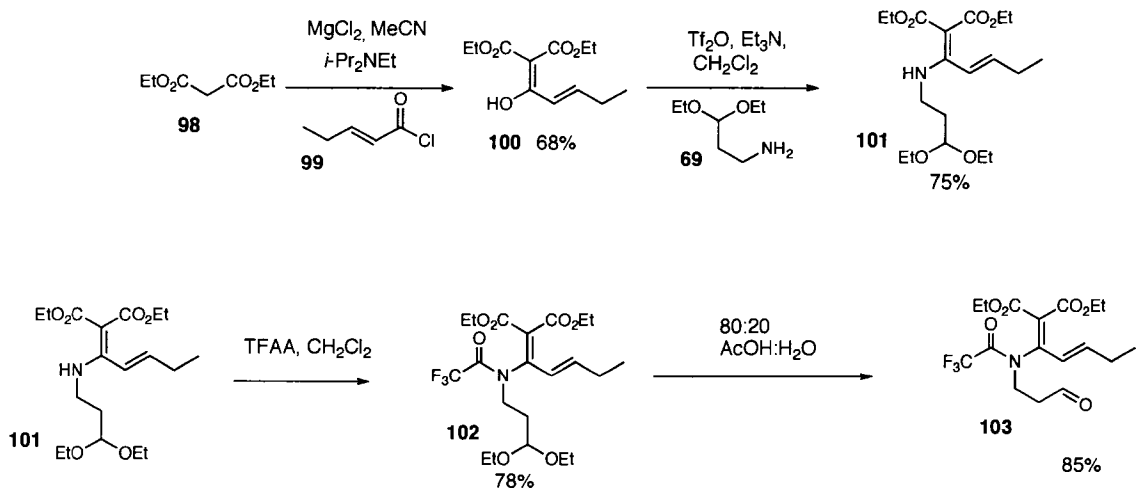


With this in mind, it was decided to attempt cyclization on a more electrophilic Michael acceptor. We decided to implement an alkylidene malonate, as we had obtained good results with this activating group in the past. We envisioned a similar route to that proposed from the previous efforts, Scheme 19. In this route, we propose accessing the intermediate in Overman's synthesis by the same route as previously proposed from activated acid **92**. This should be easily synthesized from acid **93**, which in turn is formed by the installation of the double bond from ketone **94**. This should be available from a decarboxylation of malonate derivative **95.** This will be formed from deprotection of the nitrogen in pyrrolidinone **96** and addition of the two carbon unit. Pyrrolidinone **96** will be formed in the key Stetter reaction of alkylidene malonate **97**.

This system appeared particularly appealing as olefin geometry no longer was of concern. A number of routes could be envisioned to obtain the desired substrate, but we thought the most straightforward would involve acylation of diethyl malonate in order to install the butenyl sidechain. We then thought that activation of the enol form of this tricarbonyl compound, followed by an addition/elimination sequence would provide the desired Michael acceptor.[22] This may be possible by activation as either a triflate or tosylate, with the latter being preferable for reasons of practicality as well as cost. In an ideal situation, the nitrogen nucleophile may be brought in already protected, however, it may be necessary to use the free primary amine and protect later.

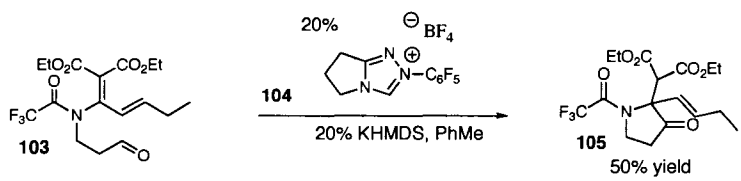
Our synthesis commenced with the acylation of diethyl malonate (**98**) with the acid chloride of trans-2-pentenoic acid (**99**), Scheme 20.[23] The product of this reaction (**100**) exists exclusively as the enol tautomer. Activation of this with trifluoromethanesulfonic anhydride gives the enol triflate,[24] which is unstable and must immediately be reacted with the primary amine. Addition of **69** to the enol triflate provides enamine **101**. Efforts to add anions of carbamates to the enol triflate were attempted, however were met with no success. The nitrogen could then be smoothly converted to its trifluoroacetamide (**102**) by treatment with trifluoroacetic anhydride and triethylamine in dichloromethane. Deprotection proceeds uneventfully to give the desired Stetter substrate (**103**).

Scheme 20.



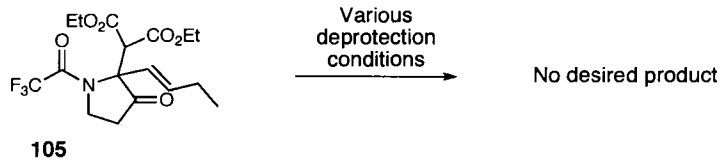
With the appropriate substrate in hand, it was exposed to standard Stetter conditions. Since we had been having trouble generating any product with the previous substrates, it was decided to implement an achiral catalyst, in hopes that less steric bulk around the reactive site should facilitate difficult cyclizations. Gratifyingly, treatment of this substrate with catalyst **104** and KHMDS in toluene gives the desired pyrrolidinone (**105**), Scheme 21. In an unoptimized reaction, we were able to generate the desired product in 50% yield.

Scheme 21.



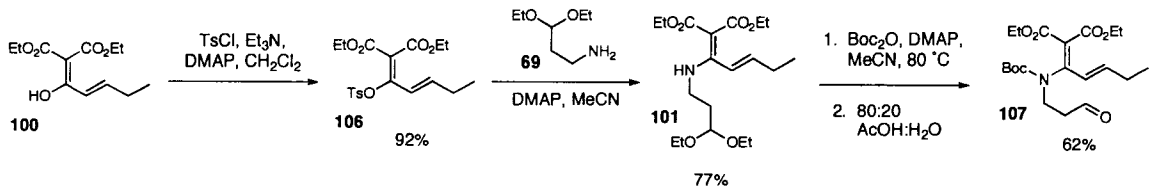
With the key reaction successfully executed, we directed efforts to deprotect the nitrogen and move forward with the synthesis. We initially attempted to do this under mild hydrolysis conditions, however found complex mixtures of products, likely due to ester hydrolysis, Scheme 22. We also attempted hydrolysis under acidic conditions. Due to the strongly acidic aqueous conditions required for trifluoroacetamide hydrolysis, we were not able to move on with this protecting group.

Scheme 22.



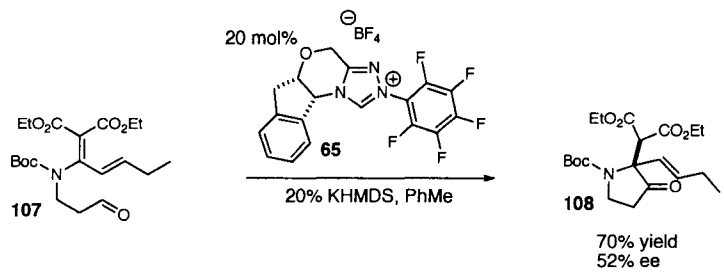
Since the attempted trifluoroacetamide cleavage led to decomposition, it was decided to change to a protecting group that could be removed under milder acidic conditions. We decided to implement the *tert*-butoxycarbonyl protecting group in order to satisfy this requirement. Starting with the acylated malonate derivative, we decided to investigate the activation of the enol with tosyl chloride, Scheme 23. After a short optimization of conditions, we found that the tosyl group could be installed and subsequently displaced by the amine nucleophile. Protection of the nitrogen by treatment with di-*tert*-butyl dicarbonate in acetonitrile in the presence of DMAP at 80 °C proceeds uneventfully. The acetal is then removed to provide the requisite Stetter substrate, **100**.

Scheme 23



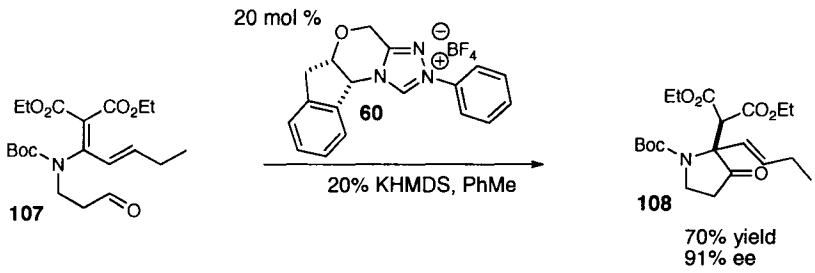
When exposed to standard intramolecular Stetter reaction conditions, a good yield was obtained in the reaction, Scheme 24. However, when we analyzed the enantiomeric composition of this compound by HPLC, we found a modest 3:1 selectivity.[25]

Scheme 24.



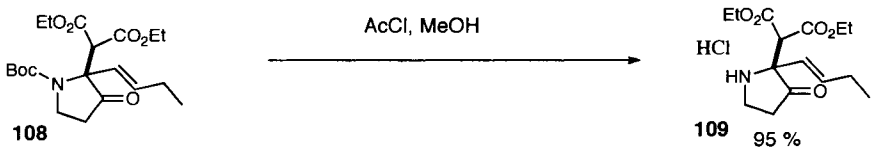
This 52% ee was not acceptable for our purposes, and for that reason we attempted the reaction with another catalyst. We had seen in a variety of other substrates throughout our work on the intramolecular Stetter reaction that the enantioselectivity could be significantly increased by changing catalysts. In fact, implementation of the parent phenyl catalyst allows for the product to be obtained in good yield and 91% ee, Scheme 25.

Scheme 25.



With the key step solved, the next task at hand involved removal of the Boc group from the nitrogen. This was accomplished by stirring the pyrrolidinone in 1M methanolic HCl, Scheme 26. This reaction gives the HCl salt of the secondary amine in excellent yield.

Scheme 26.



Unfortunately, initial attempts to form the next ring on this molecule have met with no success. Efforts aimed at the elaboration of this compound to the intermediate in Overman's synthesis are ongoing.

3.3 Conclusion

In conclusion, we have demonstrated that the intramolecular Stetter reaction can be extended to more complex systems than previously explored. We were able to find limitations in the methodology, and utilize these limitations to find ways around these problems. A solution was found to allow for the rapid enantioselective synthesis of a chiral building block with excellent stereocontrol. This involved an intramolecular

Stetter reaction between a tetrasubstituted olefin possessing a pendant aliphatic aldehyde. The Stetter reaction sets a strategic stereocenter in the product pyrrolidinone. We envision elaboration of this molecule into an intermediate from a previous synthesis of asparagamine A. This establishes that the reaction can be used to generate difficult to access intermediates with a high degree of enantiocontrol. Highly functionalized molecules may now be synthesized in expedient fashion with this newly developed methodology.

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[17] The reaction on this substrate was slow. However, by adding the catalyst in two portions, a moderate yield was obtained. See chapter 2 for details.

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Govek, E.; Patane, E.; Fry, D.; Dayton, B. D.; Brodjian, S.; Falls, D.; Brune, M.; Bush, E.; Shapiro, R.; Knourek-Segel, V.; Fey, T.; McDowell, C.; Reinhart, G. A.; Preusser, L. C.; Marsh, K.; Hernandez, L.; Sham, H. L.; Collins, C. A.; *J. Med. Chem.* **2005**, *48,* 5888-5891.

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[25] The absolute stereochemistry of this compound has not been determined, but has been tentatively assigned (S) by analogy to our work on formation of cyclopentanones possessing quaternary stereocenters.

Chapter 1 Experimental

Intramolecular Stetter Reaction

General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Tetrahydrofuran, diethyl ether, 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. Melting points were measured with a MelTemp II melting point apparatus outfitted with a Fluke 51 thermocouple and are uncorrected. Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. The purity of all compounds was determined to be >95% by ^1H NMR. ^1H NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometer at ambient temperature. Data are 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, 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.

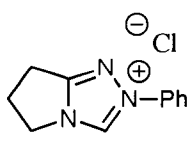
General procedure for the synthesis of triazolium salts:

A flame-dried round bottom flask is charged with CH_2Cl_2 and the appropriate lactam (1 eq., 0.1 M solution). Trimethyloxonium tetrafluoroborate (1 eq.) is added, and the reaction mixture stirred for 12 hours at 23 °C. The appropriate hydrazine is added and the resulting solution allowed to stir for 2 hours at ambient temperature. The solvent is removed *in vacuo* and acetonitrile added (0.1 M solution) along with 10 eq. trimethyl orthoformate and the solution heated to 80 °C for 12 hours. The solvent is removed *in vacuo*, and the product purified by either precipitation, column chromatography, or oiling out from an appropriate solvent.

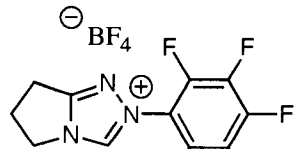
Optimized procedure for the intramolecular Stetter reaction: A flame-dried round bottom flask was charged with triazolium salt (0.2 eq) and 2 ml toluene. To this solution was added KHMDS (0.5M in toluene) (0.2 eq.) via syringe and the solution was stirred at ambient temperature for 15 minutes. Substrate (1 eq.) was added and allowed to stir for 24 h at ambient temperature. The reaction was then poured into a column of silica gel

and eluted with a suitable solution of ethyl acetate in hexanes (typically 1:6). Evaporation of solvent afforded analytically pure product.

Racemic material was prepared by the method of Ciganek,[1] or with achiral catalysts **E1** and **E2** according to the general procedure.

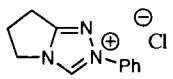


E1



E2

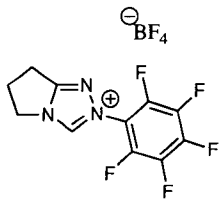
2-Phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium chloride



(E1): A 500 mL round bottom flask equipped with a reflux condenser was charged with 2-pyrrolidinone (10.00 g, 114.9 mmol) and acetonitrile (230 mL). To this was added dimethyl sulfate (12.00 mL, 126.3 mmol) and the reaction mixture heated to 80 °C for 12 hours. This was allowed to cool to room temperature and phenylhydrazine (12.40 mL, 126.3 mM) was added and heated to 80 °C for 4 hours. Upon cooling to room temperature the solution was concentrated and the resulting thick dark red liquid was dissolved in CH_2Cl_2 (250 mL) and added to a 1 L separatory funnel containing 40% KOH (250 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 200 mL), and the combined organics were washed with water (100 mL), dried with brine (100 mL), and then dried over Na_2SO_4. The solution was then filtered and concentrated. 1 M HCl in methanol (125 mL) was added and stirred for 30 minutes, then concentrated. Acetonitrile (100 mL) was added with stirring, followed by toluene (200 mL) and the precipitate was

[1] Ciganek, E. *Synthesis* **1995**, 1311-1314.

collected. This solid was dissolved in *o*-dichlorobenzene (230 mL) in a 500 mL round bottom flask equipped with a reflux condenser. 2 eq. trimethyl orthoformate (26.2 mL, 229.8 mM) was then added, along with 1M HCl in methanol (10 mL) and heated to 120 °C for 12 hours. The solvent was then evaporated and the resulting tan solid was recrystallized from toluene and acetonitrile. This was then heated under vacuum at 110 °C for 12 hours to remove residual water. This yielded the title compound **E1** (15.778 g 62%). Rf (acetone) = 0.09; ^{1}H NMR (300 MHz, D_2O) δ 7.61-7.79 (m, 2H), 7.50-7.59 (m, 3H), 4.38 (dd, 2H, *J* = 7.3, 7.3 Hz), 3.13 (dd, 2H, *J* = 7.3, 7.3 Hz), 2.77 (ddd, 2H, *J* = 15.0, 7.7, 7.7 Hz); ^{13}C NMR (100 MHz, D_2O) δ 163.9, 135.5, 131.0, 130.3, 121.3, 47.5, 26.7, 21.5; IR (NaCl, neat) 1586, 1513, 1426, 1382, 967 cm^{-1}; m.p. 180-184 °C; HRMS (Fab+) calcd for $C_{11}H_{12}N_3$, 186.1031. Found 186.1038.

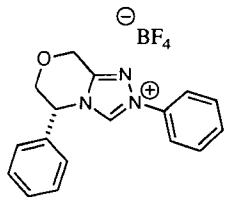


2-Pentafluorophenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoroborate (E2): A flame-dried round bottom flask was charged with 2-pyrrolidinone (0.500 g, 5.88 mM and CH_2Cl_2 (30 mL). Trimethyloxonium tetrafluoroborate (0.871 g, 5.88 mM) was added and the reaction mixture stirred for 12 hours at 23 °C. Pentafluorophenylhydrazine (1.164 g, 5.88 mM) was added and allowed to stir for 2 hours. The solvent was evaporated and chlorobenzene (60 mL) was added, followed by triethyl orthoformate (1.93 mL, 11.76 mmol). The flask was fitted with a reflux condenser and heated to 110 °C and stirred at this temperature for 12 hours. Upon cooling, toluene (60 mL) was added and the white solid product was filtered. This was rinsed with toluene (3 x 5 mL) and heated under vacuum at 120 °C for 6 hours to provide triazolium salt **E2** (1.298 g,

61%): Rf (3:1 CH_2Cl_2 to acetone) = 0.13; ^1H NMR (300 MHz, acetone-D6) δ 10.23 (s, 1H), 4.78 (dd, 2H, J = 7.3, 7.3 Hz), 3.43 (dd, 2H, J = 7.3, 7.3 Hz), 3.01 (ddd, 2H, J = 15.4, 8.1, 8.1 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 165.1, 144.7 (m), 143.9, 142.3 (m), 139.7 (m), 137.1 (m), 48.8, 26.9, 21.9; ^{19}F NMR (470.3 MHz, acetone-D6) δ 45.33, (d, 2F, J = 18.3 Hz), 41.81 (dd, 1F, J = 21.4, 21.4 Hz), 40.34 (s, 1F), 40.29 (s, 3F), 30.18 (dd, 2F, J = 27.5, 9.2, 9.2 Hz); IR (NaCl, neat) 3142, 1602, 1527, 1295, 1076, 989 cm^{-1}; m.p. 248-253 °C; HRMS (FAB+) calcd for $C_{11}H_7N_3F_5$, 276.0560. Found 276.0555.

Substrates **16**, **31**, **32**, and **33** were prepared by the method of Ciganek. **34** was prepared by alkylation of 2-mercapto benzyl alcohol with 4-bromocrotonate methyl ester, followed by Dess-Martin oxidation. **36** and **38** were prepared by alkylation of 2-amino benzyl alcohol with 4-bromocrotonate methyl ester, followed by Dess-Martin oxidation. **41** was prepared by Heck reaction of 2-iodobenzyl alcohol with allyl alcohol. The resulting lactol was subjected a Wittig reaction with ethyl triphenylphosphoranylidene acetate, followed by Dess-Martin oxidation. **13** was prepared by ozonolysis of cyclopentene by the method of Schreiber,[2] followed by Wittig reaction and washing with aqueous HCl.

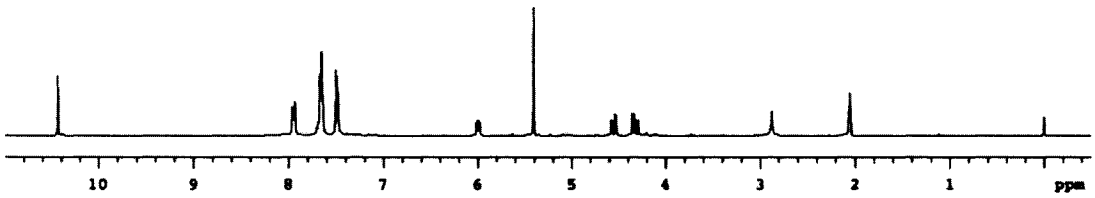
[2] Claus, R. E.; Schreiber, S. L. *Organic Syntheses*, Wiley: New York, 1990; Collect. Vol. VII. Pp. 168-171.

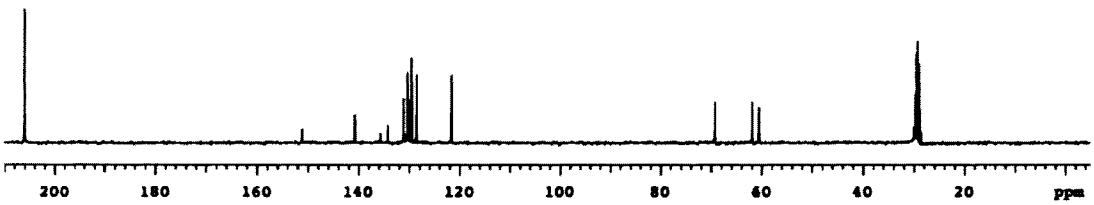


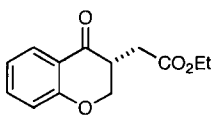
(*R*)-2,5-diphenyl-6,8-dihydro-5*H*-[1,2,4]triazolo[3,4-*c*][1,4]oxazin-2-ium tetrafluoroborate (17): To a 50 mL round bottom flask was added 15 mL CH_2Cl_2 and 0.19 g (1.07 mmol) (R)-5-phenylmorpholin-3-one.[3] Trimethyloxonium tetrafluoroborate (0.160 g, 1.07 mmol) was added and the solution allowed to stir at room temperature for 12 hours. 0.11 mL phenylhydrazine (1.1 mmol) was added and the solution stirred for 30 minutes at room temperature. 1 mL Trimethyl orthoformate (9.1 mmol) was added along with 10 mL acetonitrile. This was heated to 80 °C for 12 hours. The solvent was removed under reduced pressure and EtOAc was added to dissolve the residue. Diethyl ether was added, and the desired product oiled out. The solvent was poured off to give the crude product, which was further purified by recrystallization from diethyl ether to provide 0.242 g **17** (60%) as a red solid; R_f (9:1 EtOAc : *i*-PrOH) = 0.39; $[\alpha]_D^{23}$ = - 119.1° (acetonitrile, c = 45 mg/mL); ^{1}H NMR (300 MHz, acetone-D6) δ 10.44 (s, 1H), 7.98-7.90 (m, 2H), 7.75-7.60 (m, 5H), 7.55-7.43 (m, 3H), 5.99 (dd, 1H, *J* = 7.3, 4.4 Hz), 5.43-5.39 (m, 2H), 4.55 (dd, 1H, *J* = 12.4, 4.4 Hz), 4.32 (dd, 1H, *J* = 12.8, 7.7); ^{13}C NMR (75 MHz, acetone-D6) δ 151.1, 140.7, 135.7, 134.2, 131.1, 130.3, 130.1, 129.5, 128.5, 121.6, 69.2, 61.9, 60.6; IR (NaCl, neat) 3083, 1695, 1585, 1455, 1382 cm^{-1}; m.p. 144-148 °C; HRMS (FAB+) calcd for $C_{17}H_{16}N_3O$ 278.1293. Found 278.1295.

[3] Norman, B. H.; Kroin, J. S. *J. Org. Chem.* **1996**, *61*, 4990-4998.

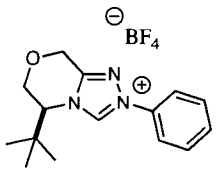
17 ^{1}H and ^{13}C NMR spectra





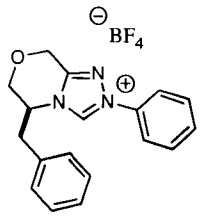


(4-Oxo-chroman-3-yl)-acetic acid ethyl ester (18) According to the general procedure, 5.0 mg (0.012 mmol) of **30** in 2 mL of xylenes was treated with 0.024 mL (0.012 mmol) of KHMDS and allowed to stir at ambient temperature for 15 min. 14 mg (0.06 mmol) of **16** in 1 mL xylenes was added via syringe and the reaction was stirred for 24 h at 23 °C. Upon work-up 13.2 mg (94%) of desired ester was isolated as a colorless oil: Spectral data matched literature description;[1] $[\alpha]_D^{23}$ = -10° (CH_2Cl_2, c = 10 mg/mL); HPLC analysis - Chiracel AD column, 97:3 hexanes to isopropanol 0.5 ml/ min. Major enantiomer 30.2 minutes, minor enantiomer 40.2 minutes.



(*S*)-5-*tert*-butyl-2-phenyl-6,8-dihydro-5*H*-[1,2,4]triazolo[3,4-*c*][1,4]oxazin-2-ium tetrafluoroborate (19): To a 100 mL round bottom flask was added 30 mL CH_2Cl_2 and 0.480 g (3.06 mmol) (R)-5-*t*-butylmorpholin-3-one.[3] Trimethyloxonium tetrafluoroborate (0.450 g, 3.06 mmol) was added and the solution allowed to stir at room temperature for 12 hours. 0.30 mL phenylhydrazine (3.06 mmol) was added and the solution stirred for 30 minutes at room temperature. 2 mL Trimethyl orthoformate (18.2 mmol) was added along with 20 mL acetonitrile. This was heated to 80 °C for 12 hours. The solvent was removed under reduced pressure and diethyl ether was added. Stirring in diethyl ether for 1 hour caused the product to precipitate out as a tan solid. This was further purified by recrystallization from diethyl ether and hexanes to provide 0.300 g **19** (28%) as a white solid; R_f (EtOAc) = 0.19; $[\alpha]_D^{23}$ = + 15.0° (acetonitrile, c = 10 mg/mL); ^{1}H NMR (300 MHz, $CDCl_3$) δ

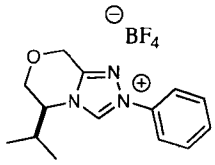
10.10 (s, 1H), 7.98-7.85 (m, 2H), 7.56-7.50 (m, 3H), 5.13 (d, 1H, J = 16.8 Hz), 4.99 (d, 1H, J = 16.8 Hz), 4.48-4.39 (m, 2H), 4.04 (dd, 1H, J = 13.5, 3.3 Hz), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 140.3, 135.0, 131.2, 130.4, 121.2, 64.3, 64.1, 61.5, 35.2, 27.3; IR (NaCl, neat) 3112, 2967, 1578, 1389, 1047 cm^{-1}; m.p. 175-185 °C; HRMS (FAB+) calcd for $C_{15}H_{20}N_3O$ 258.1606. Found 258.1599.



(*S*)-5-benzyl-2-phenyl-6,8-dihydro-5*H*-[1,2,4]triazolo[3,4-*c*][1,4]oxazin-2-ium tetrafluoroborate (20): To a 50 mL round bottom flask was added 15 mL CH_2Cl_2 and 0.187 g (1.07 mmol) (R)-5-benzylmorpholin-3-one.[4] Trimethyloxonium tetrafluoroborate (0.160 g, 1.07 mmol) was added and the solution allowed to stir at room temperature for 12 hours. 0.11 mL phenylhydrazine (1.1 mmol) was added and the solution stirred for 30 minutes at room temperature. 1 mL Trimethyl orthoformate (9.1 mmol) was added along with 10 mL acetonitrile. This was heated to 80 °C for 12 hours. The solvent was removed under reduced pressure and EtOAc was added to dissolve the residue. Diethyl ether was added, and the desired product precipitated out as a white solid to afford 0.260 g **20** (70%). Spectral data matched that of the chloride salt reported by Leeper and Knight.[5]

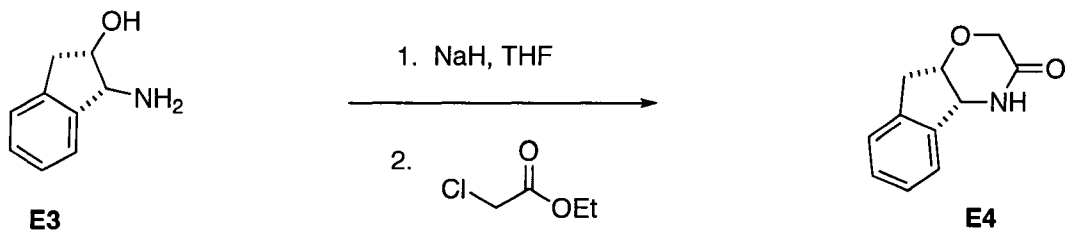
(*S*)-5-*iso*-propyl-2-phenyl-6,8-dihydro-5*H*-[1,2,4]triazolo[3,4-*c*][1,4]oxazin-2-ium tetrafluoroborate (21): To a 100 mL round bottom flask was added 10 mL CH_2Cl_2 and 0.200 g (1.40 mmol) (R)-5-*i*-propylmorpholin-3-one.[3] Trimethyloxonium

[4] Norman, B. H.; Kroin, J. S. *J. Org. Chem.* **1996**, *61*, 4990-4998.
[5] Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 1891-1893.



tetrafluoroborate (0.208 g, 1.40 mmol) was added and the solution allowed to stir at room temperature for 12 hours. 0.137 mL phenylhydrazine (1.40 mmol) was added and the solution stirred for 30 minutes at room temperature. 1 mL Trimethyl orthoformate (9.1 mmol) was added along with 10 mL acetonitrile. This was heated to 80 °C for 12 hours. The solvent was removed under reduced pressure and EtOAc was added. Stirring in EtOAc for 1 hour caused the product to precipitate out as a tan solid. This was further purified by recrystallization from diethyl ether to provide 0.297 g **21** (28%) as tan solid; R_f (EtOAc) = 0.10; $[\alpha]_D^{23}$ = + 33.6° (acetonitrile, c = 14 mg/mL); ^{1}H NMR (400 MHz, acetone-D6) δ 11.25 (s, 1H), 8.15-8.02 (m, 2H), 7.80-7.60 (m, 3H), 5.31 (d, 1H, *J* = 16.5 Hz), 5.16 (d, 1H, *J* = 16.5 Hz), 4.70 (dd, 1H, *J* = 4.4, 0.0 Hz), 4.39 (dd, 1H, *J* = 13.2, 3.3 Hz), 4.25 (dd, 1H, *J* = 12.8, 3.7 Hz), 2.80-2.60 (m, 1H), 1.19 (d, 3H, *J* = 7.0), 1.07 (d, 3H, *J* = 7.0); ^{13}C NMR (100 MHz, acetone-D6) δ 151.0, 141.0, 135.7, 130.9, 130.3, 121.2, 63.8, 61.7, 61.1, 31.0, 18.4, 16.9; IR (NaCl, neat) 2960, 1680, 1578, 1469, 1389 cm^{-1}; m.p. 150-152 °C; HRMS (FAB+) calcd for $C_{14}H_{18}N_3O$ 244.1450. Found 244.1445.

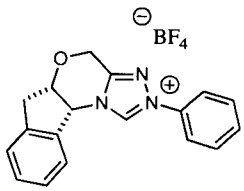
Synthesis of morpholinone **E4**:



E3 **E4**

To a flame dried 250 ml round bottom flask with a magnetic stir bar was added 0.268 g NaH (60% in mineral oil). 50 mL pentane was added and stirred under argon for 5 min.

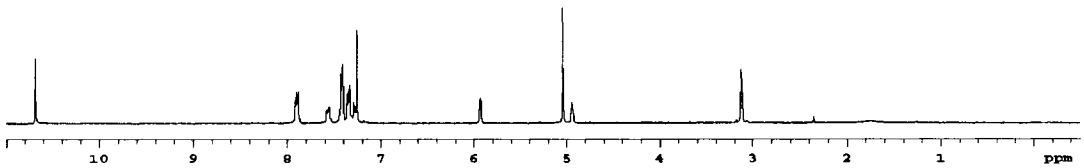
Stirring was stopped and the NaH was allowed to settle for 10 min. Pentanes was removed via syringe. 1.00 g **E3** was added in 65 ml THF (0.1 M soln.) This was heated to reflux and allowed to stir for 30 min under argon. Solution was allowed to cool to r.t. Ethyl chloroacetate (0.662 ml) was then added via syringe. The solution was stirred at reflux for 1 hour under argon. The solution was allowed to cool, and 50 ml 10% HCl, was added. This was extracted with EtOAc (3X50mL) The combined organics were washed with sodium bicarbonate, dried with Brine, and then over $MgSO_4$. Filtration, followed by rotory evaporation affords 1.20 g **E4** as a white solid. . R_f (EtOAc) = 0.18; $[\alpha]_D^{23}$ = - 20.9° (acetonitrile, c = 11 mg/mL)^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (bs, 1H), 7.37 (m, 1H), 7.27 (m, 3H), 4.75 (dd, 1H, *J* = 3.7, 3,7 Hz), 4.51 (dd, 1H, *J* = 4.4, 4.4 Hz), 4.14 (s, 2H), 3.21 (dd, 1H, *J* = 16.9, 4.7 Hz), 3.08 (dd, 1H, *J* = 16.8, 0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 140.9, 139.3, 128.5, 127.6, 125.3, 124.1, 76.3, 66.7, 58.9, 38.0; IR (NaCl, neat) 3223, 2910, 1708, 1635, 1496 cm-1. M.P. 175 °C; HRMS (Fab+) calcd for $C_{11}H_{12}NO_2$, 190.0868. Found 190.0868.

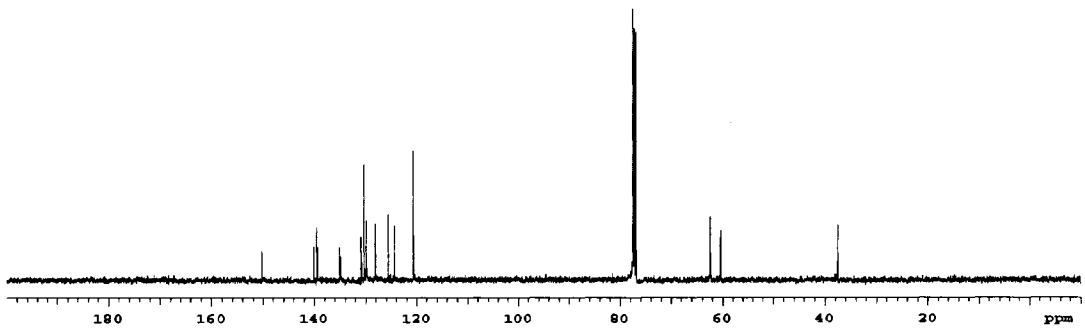


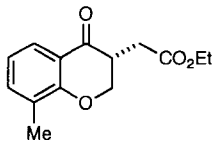
2-Phenyl-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (22): A flame-dried 100 mL round bottom flask was charged with morpholinone **E4** (1.000 g, 5.29 mmol) and CH_2Cl_2 (25 mL). Trimethyloxonium tetrafluoroborate (0.783 g, 5.29 mmol) was added and the reaction mixture was allowed to stir for 12 hours at 23 °C. Phenylhydrazine (0.519 mL, 5.29 mmol) was added and the reaction mixture stirred for 30 min. The solvent was evaporated and chlorobenzene (50 mL) was added, followed by triethyl orthoformate (4.400 mL, 26.45 mmol). The flask was fitted with a reflux

condenser and the reaction was heated to 110 °C and stirred at this temperature for 12 hours. Upon cooling, the reaction was poured onto a column of silica. The flask was rinsed with 9:1 $CHCl_3$:acetone (5 mL) poured onto the silica, and eluted with $CHCl_3$ and then 1:1 hexanes:ethyl acetate. Concentration, followed by stirring in hot toluene (5 mL) for 5 minutes and filtration provided a white solid material. Heating this at 120 °C for 6 hours under vacuum to remove residual water yielded **19** (1.160 g, 46%) as a white solid: Rf (10:1 CH_2Cl_2 to acetone) = 0.20; $[\alpha]_D^{23}$ = -294.4° (acetonitrile , c = 15 mg/mL); ^1H NMR (300 MHz, $CDCl_3$) δ 10.69 (s, 1H), 7.86-7.92 (m, 2H), 7.53-7.59 (m, 1H), 7.38-7.44 (m, 3H), 7.32-7.37 (m, 2H), 7.36-7.30 (m, 1H), 5.93 (d, 1H, *J* = 3.7 Hz), 5.04 (dd, 2H, *J* = 0, 0 Hz), 4.94 (ddd, 1H, *J* = 3.6, 3.6, 1.7 Hz), 3.15 (d, 1H, *J* = 16.5 Hz), 3.09 (d, 1H, *J* = 16.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 140.1, 139.5, 135.1, 135.0, 130.9, 130.3, 129.9, 128.2, 125.7, 124.4, 120.7, 77.5, 62.4, 60.4, 37.5; IR (NaCl, neat) 3133, 3007, 2861, 1590, 1397, 1102, 1079, 768 cm^{-1}; m.p. 203-206 °C; HRMS (Fab+) calcd for $C_{18}H_{16}N_3O$, 290.1293. Found 290.1291.

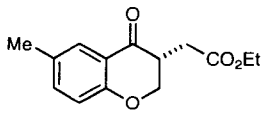
22 ^{1}H and ^{13}C NMR spectra



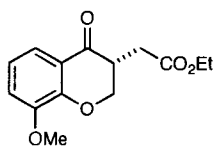




(8-Methyl-4-oxo-chroman-3-yl)-acetic acid ethyl ester (23) According to the general procedure, 5.0 mg (0.012 mmol) of **30** in 2 mL of xylenes was treated with 0.024 mL (0.012 mmol) of KHMDS and allowed to stir at ambient temperature for 15 min. 15 mg (0.06 mmol) of **32** in 1 mL xylenes was added via syringe and the reaction was stirred for 24 h at 23 °C. Upon work-up 13.5 mg (90%) of desired ester was isolated as a colorless oil: Spectral data matched literature description;[1] $[\alpha]_D^{23}$ = - 13° (CH_2Cl_2, c = 11 mg/mL); HPLC analysis - Chiracel AD column, 97:3 hexanes to isopropanol 0.5 ml/ min. Major enantiomer 19.4 minutes, minor enantiomer 25.1 minutes.

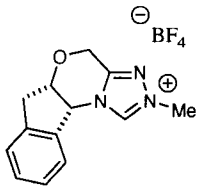


(6-Methyl-4-oxo-chroman-3-yl)-acetic acid ethyl ester (24) According to the general procedure, 2.5 mg (0.006 mmol) of **30** in 2 mL of xylenes was treated with 0.012 mL (0.012 mmol) of KHMDS and allowed to stir at ambient temperature for 15 min. 15 mg (0.06 mmol) of **31** in 1 mL xylenes was added via syringe and the reaction was stirred for 24 h at 23 °C. Upon work-up 12 mg (80%) of desired ester was isolated as a colorless oil: Spectral data matched literature description;[1] $[\alpha]_D^{23}$ = - 11° (CH_2Cl_2, c = 10 mg/mL); HPLC analysis -Chiracel AD column, 97:3 hexanes to isopropanol 0.5 ml/ min. Major enantiomer 25.7 minutes, minor enantiomer 39.2 minutes.

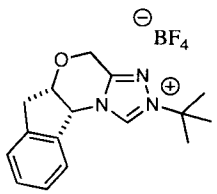


(8-Methoxy-4-oxo-chroman-3-yl)-acetic acid ethyl ester (25) According to the general procedure, 2.5 mg (0.006 mmol) of **30** in 2 mL of xylenes was treated with 0.012 mL (0.006 mmol) of KHMDS and allowed to stir

at ambient temperature for 15 min. 16 mg (0.06 mmol) of **33** in 1 mL xylenes was added via syringe and the reaction was stirred for 24 h at 23°C. Upon work-up 15 mg (95%) of desired ester was isolated as a colorless oil: Spectral data matched literature description;[1] $[\alpha]_D^{23}$ = -15 (CH_2Cl_2, c = 12 mg/mL); HPLC analysis - Chiracel AD column, 97:3 hexanes to isopropanol 1.0 ml/ min. Major enantiomer 27.8 minutes, minor enantiomer 42.2 minutes.

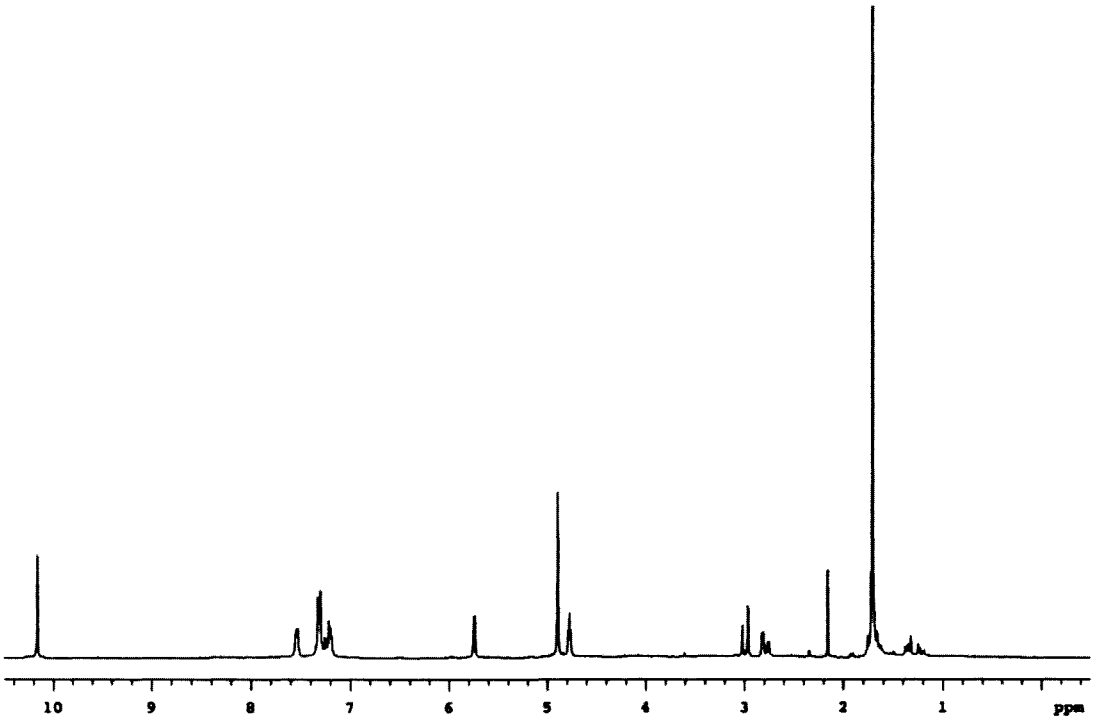


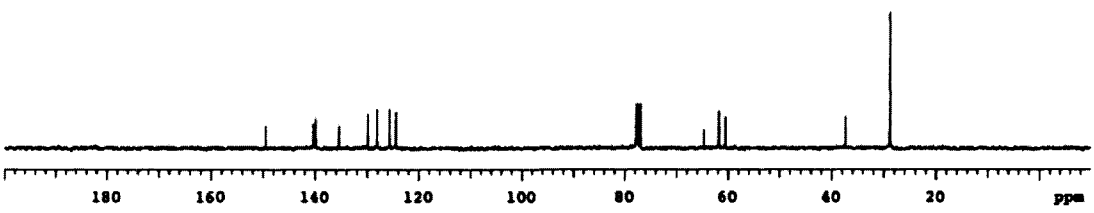
2-methyl,-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (26): To a 50 mL round bottom flask was added 10 mL CH_2Cl_2 and 0.200 g (1.06 mmol) **E4**. Trimethyloxonium tetrafluoroborate (0.157 g, 1.06 mmol) was added and the solution allowed to stir at room temperature for 12 hours. The solution was cooled to 0 °C and 0.046 mL methyl hydrazine (1.06 mmol) was added and the solution was allowed to warm to room temperature. 1 mL Trimethyl orthoformate (9.1 mmol) was added along with 10 mL acetonitrile. This was heated to 80 °C for 12 hours. The solvent was removed under reduced pressure and EtOAc was added. Ether was added to oil out the desired product. This oil was further purified by stirring in $CHCl_3$ for 30 minutes. Concentration of the $CHCl_3$ provided 0.080 g **26** (24%) as a clear oil; R_f (EtOAc) = 0.09; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.1 (s, 1H), 7.46 (d, 1H, *J* = 7.7 Hz), 7.30-7.18 (m, 3H), 5.79 (d, 1H, *J* = 3.8 Hz), 4.91-4.82 (m, 2H), 4.12 (s, 3H), 3.25 (dd, 1H, *J* = 17.3, 4.7 Hz), 3.12 (dd, 1H, *J* = 17.3, 0.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 142.4, 140.1, 135.3, 129.9, 128.9, 128.1, 125.7, 124.1, 77.4, 61.7, 60.3, 39.4, 37.5.

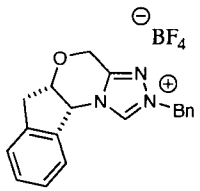


2-*tert*-butyl,-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (27): To a 50 mL round bottom flask was added 15 mL CH_2Cl_2 and 0.25 g (1.32 mmol) **E4**. Trimethyloxonium tetrafluoroborate (0.195 g, 1.32 mmol) was added and the solution allowed to stir at room temperature for 12 hours. *t*-Butyl hydrazine was liberated from its hydrochloride salt by stirring in 1 M NaOH and CH_2Cl_2 and extracting (3 x 15 mL) with CH_2Cl_2. The organics were dried with brine and Na_2SO_4 and filtered, and concentrated. *t*-Butyl hydrazine (0.232 g, 2.64 mmol) was added and stirred for 2 hours. The solvent was removed *in vacuo* and acetonitrile (10 mL) was added. This was heated to 80 °C for 1 hour. with 1 mL trimethyl orthoformate (9.1 mmol). This was heated to 80 °C for 12 hours. The solvent was removed under reduced pressure and CH_2Cl_2 was added. The desired product precipitated from the solution upon addition of diethyl ether to provide 280 mg (59%) of yellow solid; R_f (EtOAc) = 0.29; $[\alpha]_D^{23}$ = - 97° (acetonitrile, c = 30 mg/mL); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.16 (s, 1H), 7.59-7.51 (m, 1H), 7.38-7.18 (m, 3H), 5.74 (d, 1H, J = 4.0 Hz), 4.95-4.85 (m, 2H), 4.77 (dd, 1H, J = 4.4, 4.4 Hz), 3.00 (dd, 1H, J = 17.2, 0 Hz), 2.80 (dd, 1H, J = 16.8, 4.4), 1.70 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 140.3, 139.8, 135.4, 129.8, 128.0, 125.6, 124.4, 76.9, 64.6, 61.7, 60.5, 37.3, 28.7; IR (NaCl, neat) 3142, 2982, 1665, 1578, 1375 cm^{-1}; m.p. 68-70 °C. HRMS (FAB+) calcd for $C_{16}H_{20}N_3O$ 270.1606. Found 270.1608.

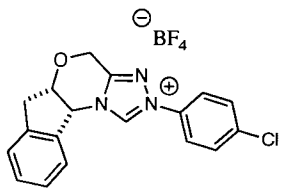
27 ^{1}H and ^{13}C NMR spectra







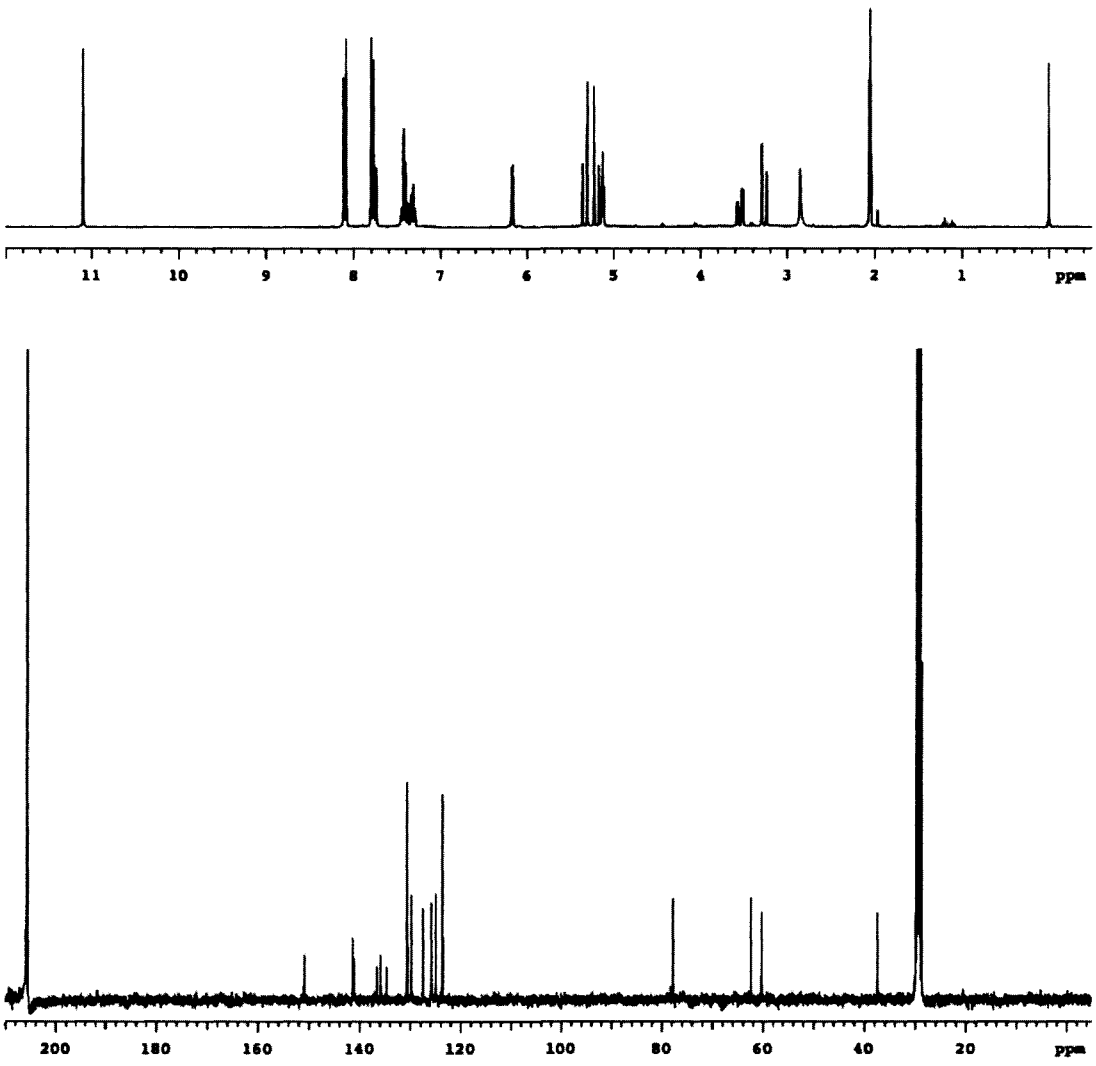
2-benzyl,-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (28): To a 50 mL round bottom flask was added 10 mL CH_2Cl_2 and 0.250 g (1.32 mmol) **E4**. Trimethyloxonium tetrafluoroborate (0.195 g, 1.32 mmol) was added and the solution allowed to stir at room temperature for 12 hours. Benzyl hydrazine was liberated from its hydrochloride salt by stirring in 1 M NaOH and CH_2Cl_2 and extracting (3 x 15 mL) with CH_2Cl_2. The organics were dried with brine and Na_2SO_4 and filtered, and concentrated. 0.161 g benzyl hydrazine (1.32 mmol) was added and the solution stirred for 30 minutes at room temperature. 1 mL Trimethyl orthoformate (9.1 mmol) was added along with 10 mL acetonitrile. This was heated to 80 °C for 12 hours. The solvent was removed under reduced pressure and EtOAc was added to dissolve the oil. Ether and hexanes was added to precitate out the desired product. This was further purified by recrystallization from diethyl ether to provide 0.335 g **21** (65%) as tan solid; R_f (EtOAc) = 0.10; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.4 (s, 1H), 7.58-7.25 (m, 9H), 5.86 (d, 1H, J = 0.0 Hz), 5.62 (d, 1H, J = 14.3 Hz), 5.50 (d, 1H, J = 14.3 Hz), 4.95-4.80 (m, 4H), 3.37-3.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 142.0, 140.0, 135.2, 132.0, 129.9, 129.7, 129.6, 129.4, 128.3, 127.6, 125.7, 124.1, 77.4, 61.8, 60.4, 39.7, 37.6.

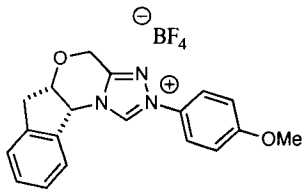


2-(4-Chlorophenyl)-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene (30): To a 50 mL round bottom flask was added 10 mL CH_2Cl_2 and 0.100 g (0.53 mmol) **E4**. Trimethyloxonium tetrafluoroborate (0.78 g, 0.53 mmol) was added and the solution allowed to stir at room temperature for 12 hours. 4-Chlorophenyl hydrazine was

liberated from its hydrochloride salt by stirring in 1 M NaOH and CH_2Cl_2 and extracting (3 x 15 mL) with CH_2Cl_2. The organics were dried with brine and Na_2SO_4 and filtered, and concentrated. 4-Chlorophenyl hydrazine (0.076 g, 0.53 mmol) was added to the activated amide and stirred for 2 hours. Acetonitrile was added and the reaction was heated to 80 °C for 1 hour. Trimethyl orthoformate (1 mL, 9.1 mmol) was added and the solution heated at 80 °C for 12 hours. The solvent was removed under reduced pressure and EtOAc was added. Upon stirring at ambient temperature for 1 hour, the desired product precipitated from the solution to provide 132 mg (60%) as a tan solid; R_f (EtOAc) = 0.19; $[\alpha]_D^{23}$ = - 132.1° (acetonitrile, c = 19 mg/mL); ^{1}H NMR (400 MHz, acetone-D6) δ 11.10 (s, 1H), 8.15-8.05 (m, 2H), 7.81-7.70 (m, 2H), 7.44-7.27 (m, 4H), 6.17 (d, 1H, J = 4.0 Hz), 5.33 (d, 1H, J = 16.1 Hz), 5.20 (d, 1H, J = 16.5 Hz), 5.13 (dd, 1H, J = 4.4, 4.4 Hz), 3.55 (dd, 1H, J = 17.2, 5.1 Hz), 3.27 (dd, 1H, J = 17.2, 0.0 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 150.8, 141.2, 141.0, 136.4, 135.7, 134.5, 130.5, 129.6, 127.3, 125.7, 124.8, 123.4; IR (NaCl, neat) 3098, 1585, 1491, 1214, 1069 cm^{-1}; m.p. 230-234 °C; HRMS (FAB+) calcd for $C_{18}H_{15}N_3OCl$ 324.0904. Found 324.0898.

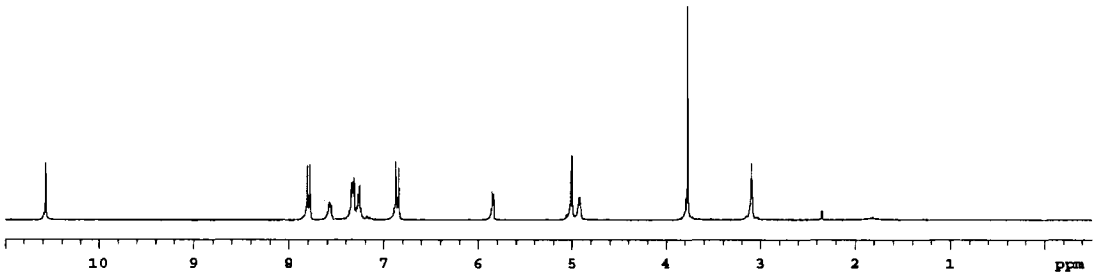
30 ^{1}H and ^{13}C NMR spectra

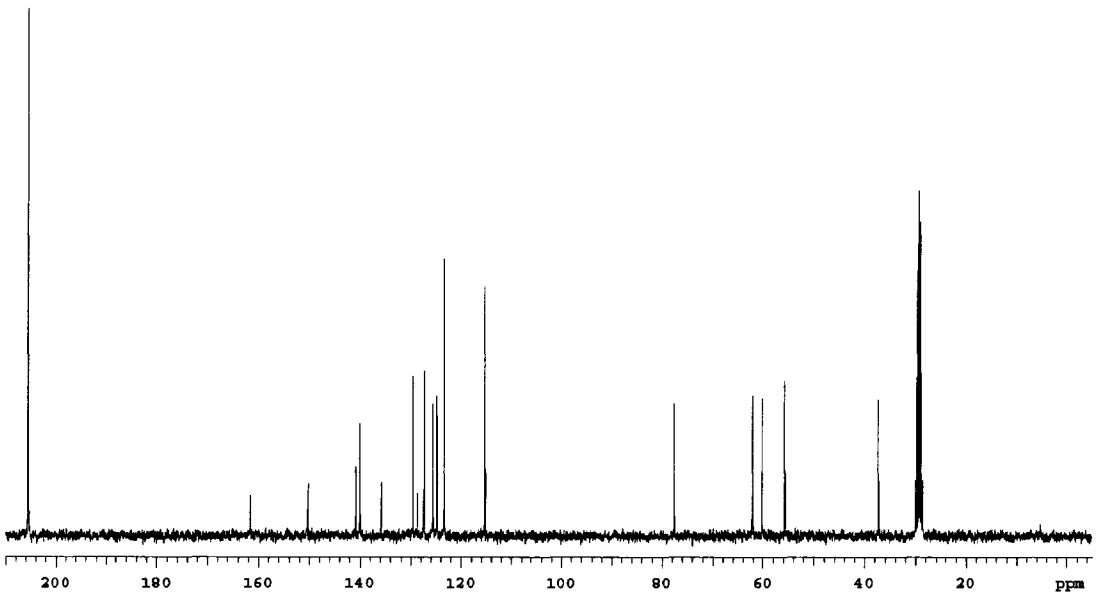


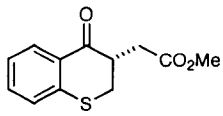


2-(4-Methoxy-phenyl)-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene (30): A flame-dried 100 mL round bottom flask was charged with morpholinone **E4** (1.000 g, 5.29 mmol) and CH_2Cl_2 (25 mL). Trimethyloxonium tetrafluoroborate (0.783 g, 5.29 mmol) was added and the reaction mixture stirred for 12 hours at 23 °C. 4-methoxyphenylhydrazine (0.730 g, 5.29 mmol) was added and allowed to stir for 30 minutes at room temperature. The solvent was evaporated and chlorobenzene (50 mL) was added, followed by triethyl orthoformate (4.40 mL, 26.45 mmol). The flask was fitted with a reflux condenser and heated to 110 °C and stirred at this temperature for 12 hours. Upon cooling, the reaction was poured onto a column of silica. The flask was rinsed 9:1 $CHCl_3$:acetone (5 mL), poured onto the silica, and eluted with $CHCl_3$ and then 1:1 hexanes:ethyl acetate. Concentration, followed by stirring in hot toluene (5 mL) for 5 minutes and filtration provided a light tan solid material. Heating this at 120 °C for 6 hours under vacuum to remove residual water yielded **19** (0.991 g, 58%) as a light tan solid: Rf (10:1 hexanes to ethyl acetate) = 0.13; $[\alpha]_D^{23}$ = -208.2° (acetonitrile c = 15 mg/mL); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.57 (s, 1H), 7.79 (d, 2H, *J* = 9.2 Hz), 7.57 (dd, 1H, *J* = 4.4, 4.4 Hz), 7.34 (d, 1H, *J* = 2.9 Hz), 7.32 (d, 1H, *J* = 3.3), 7.26 (dd, 1H, *J* = 8.4, 4.0 Hz), 6.86 (d, 2H, *J* = 9.2 Hz), 5.85 (d, 1H, *J* = 3.7 Hz), 5.01 (dd, 2H, *J* = 17.9, 16.5 Hz), 4.85-4.98 (m, 1H), 3.77 (s, 3H), 3.10 (dd, 2H, *J* = 16.1, 16.1); ^{13}C NMR (100 MHz, acetone-D6) δ 161.7, 150.3, 140.9, 140.1, 135.8, 129.6, 128.7, 127.4, 125.6, 124.8, 123.4, 115.3, 77.7, 62.1, 60.2, 55.7, 37.4; IR (NaCl, neat) 1707, 1509, 1259, 1102, 1058 cm^{-1}; m.p. 197-200 °C HRMS (Fab+) calcd for $C_{19}H_{18}N_3O_2$, 320.1399. Found 320.1396.

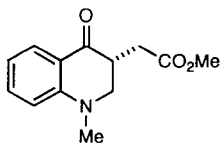
30 ^{1}H and ^{13}C NMR spectra





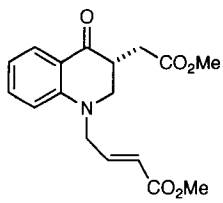


(4-Oxo-thiochroman-3-yl)-acetic acid methyl ester (35) According to the general procedure, 5.0 mg (0.012 mmol) of **30** in 2 mL of xylenes was treated with 0.024 mL (0.012 mmol) of KHMDS (0.5M in toluene) and allowed to stir at ambient temperature for 15 min. 14 mg (6 mmol) of **34** in 1 mL xylenes was added via syringe and the reaction was stirred for 24 h at 23 °C. Upon work-up 9 mg (63%) of desired ester was isolated as a light pink oil: Rf (3:1 hexanes to ethyl acetate) = 0.42; $[\alpha]_D^{23}$ = -107.5 (CH_2Cl_2, c = 9 mg/mL); HPLC analysis - Chiracel AD column, 97:3 hexanes to isopropanol 0.5 ml/ min. Major enantiomer 28.9 minutes, minor enantiomer 33.5 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, 1H, *J* = 8.0, 1.4 Hz), 7.83 (ddd, 1H, *J* = 8.1, 7.1, 1.8 Hz), 7.14 - 7.27 (m, 2H), 3.73 (s, 3H), 3.37 (ddd, 1H, *J* = 9.0, 4.8, 2.0 Hz), 3.34 (dd, 1H, *J* = 12.8, 12.8 Hz), 3.11 (m, 1H), 2.99 (dd, 1H, *J* = 16.8, 5.2 Hz), 2.59 (dd, 1H, *J* = 16.6, 6.8 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 194.3, 1872.0, 141.6, 133.2, 129.6, 26.2127.3, 124.9, 52.0, 44.6, 34.1, 31.0; IR (NaCl, CH_2Cl_2) 2916, 1732, 1674, 1587, 1435, 1167 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{12}O_3S$, 237.0585. Found 237.0585.



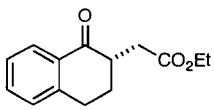
(1-Methyl-4-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid ethyl ester (37); According to the general procedure, 5.0 mg (0.012 mmol) of **30** in 2 mL of xylenes was treated with 0.024 mL (0.012 mmol) of KHMDS and allowed to stir at ambient temperature for 15 min. 14 mg (0.06 mmol) of **36** in 1 mL xylenes was added via syringe and the reaction was stirred for 24 h at 23°C. Upon work-up 9 mg (64%) of desired ester was isolated as a light yellow oil; Rf (3:1 hexanes to ethyl acetate) = 0.25; $[\alpha]_D^{23}$ = -46.6° (CH_2Cl_2, c = 9 mg/mL); HPLC analysis - Chiracel OD-H

column, 90:10 hexanes to isopropanol 0.5 ml/ min. Major enantiomer 29.6 minutes, minor enantiomer 38.7 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, 1H, J = 7.9, 1.6 Hz), 7.41 (ddd, 1H, J = 8.6, 7.1, 1.7 Hz), 6.69-6.79 (m, 2H), 3.73 (s, 3H), 3.50 (dd, 1H, J = 11.4, 5.4 Hz), 3.33 (dd, 1H, J = 12.2, 12.2 Hz), 3.22 (m, 1H), 3.03 (dd, 1H, J = 16.4, 4.86 Hz), 3.00 (s, 3H), 2.36 (dd, 1H, J = 14.4, 8.5 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 194.1, 172.8, 135.5, 129.7, 129.0, 128.6, 117.4, 113.3, 56.0, 52.1, 43.3, 39.5, 31.8; IR (NaCl, CH_2Cl_2) 2953, 1738, 1674, 1605, 1498, 1342, 754 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{15}NO_3$, 234.1130. Found 234.1123.



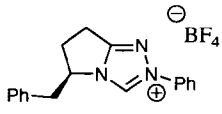
4-(3-Methoxycarbonylmethyl-4-oxo-3,4-dihydro-2*H*-quinolin-1-yl)-but-2-enoic acid methyl ester (39) ; According to the general procedure, 5.0 mg (0.012 mmol) of **30** in 2 mL of xylenes was treated with 0.024 mL (0.012 mmol) of KHMDS and allowed to stir at ambient temperature for 15 min. 19 mg (0.06 mmol) of **38** in 1 mL xylenes was added via syringe and the reaction was stirred for 24 h at 23°C. Upon work-up 13.7 mg (72%) of desired ester was isolated as a light yellow oil; Rf (3:1 hexanes to ethyl acetate) = 0.12; $[\alpha]_D^{23}$ = - 20.8° (CH_2Cl_2, c = 10 mg/mL); HPLC analysis - Chiracel AD column, 90:10 hexanes to isopropanol 0.5 ml/ min. Minor enantiomer 42.3 minutes, major enantiomer 45.7 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, 1H, J = 8.2, 1.6 Hz), 7.37 (ddd, 1H, J = 8.5, 6.8, 1.5 Hz), 6.92 (ddd, 1H, J = 15.8, 15.8, 4.9 Hz), 6.77 (ddd, 1H, J = 8.1, 8.1, 0.7 Hz), 6.60 (d, 1H, J = 8.7 Hz), 5.98 (ddd, 1H, J = 15.7, 15.7, 1.86 Hz), 4.16 (ddd, 1H, J = 18.2, 4.2, 1.7 Hz), 4.14 (ddd, 1H, J = 18.1, 4.1, 1.8 Hz), 3.72 (s, 6H), 3.52 (dd, 1H, J = 11.8, 6.5), 3.48 (dd, 1H, J = 18.2, 11.8 Hz), 3.23 (m 1H), 3.02 (dd, 1H, J = 16.8, 4.8 Hz),

2.36 (dd, 1H, J = 16.9, 8.1 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 193.4, 172.4, 142.3, 135.6, 128.7, 127.9, 122.7, 119.2, 117.7, 113.1, 53.9, 52.4, 51.9, 42.8, 31.5; IR (NaCl, CH_2Cl_2) 2953, 1728, 1674, 1605, 1497, 1173, 754 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{19}NO_5$, 318.1341. Found 318.1340.



(1-Oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetic acid ethyl ester (41) According to the general procedure, 5.0 mg (1.2 mmol) of **30** in 2 mL of xylenes was treated with 0.024 mL (0.012 mmol) of KHMDS and allowed to stir at ambient temperature for 15 min. 14 mg (0.06 mmol) of **40** in 1 mL xylenes was added via syringe and the reaction was stirred for 24 h at 23 °C. Upon work-up 12.5 mg (90%) of desired ester was isolated as a colorless oil; Rf (3:1 hexanes to ethyl acetate) =0.47; $[\alpha]_D^{23}$ = + 15.5° (CH_2Cl_2, c = 9 mg/mL); HPLC analysis - Chiracel AD column, 97:3 hexanes to isopropanol 0.5 ml/ min. Minor enantiomer 21.6 minutes, major enantiomer 23.7 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, 1H, J = 8.1, 1.2 Hz), 7.46 (ddd, 1H, J = 7.5, 7.5, 1.5 Hz), 7.21 - 7.33 (m, 2H), 4.18 (q, 2H, J = 6.5 Hz), 2.93 - 3.19 (m, 4H), 2.42 (dd, 1H, J = 18.3, 8.8 Hz), 2.25 (dddd, 1H, J = 3.0, 4.4, 4.4, 12.6 Hz), 1.97 (m, 1H), 1.28 (t, 3H, J = 7.3 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 198.4, 172.7, 133.6, 129.0, 129.0, 128.9, 127.8, 126.8, 60.9, 45.2, 45.1, 35.5, 29.6, 14.6; IR (NaCl, CH_2Cl_2) 2983, 1730, 1678, 1599, 1161, 762 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{16}O_3$, 233.1178. Found 233.1167.

5-Benzyl-2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-



ium Tetrafluoroborate (42): A flame-dried 100 mL round bottom flask was charged with (*R*)-5-benzylpyrrolidin-2-one[6] (1.000 g, 5.71 mmol) and CH_2Cl_2 (40 mL). Trimethyloxonium tetrafluoroborate (0.930 g, 6.29 mmol) was added and the reaction mixture stirred overnight at room temperature. To the pinkish solution was added phenylhydrazine (0.62 mL, 6.29 mmol) and stirred overnight. The solvent was removed *in vacuo* and the product was used without further purification. To this was added methanol (2 mL) and trimethyl orthoformate (14 mL). The reaction mixture was heated to 80 °C and stirred at this temperature overnight. The solvent was removed *in vacuo* and the product was precipitated from ethyl acetate to give an off white/yellow powder. Recrystallization from hot MeOH affords **7** (0.890 g, 50%) as a white crystalline solid. Rf (3:1 acetone:CH_2Cl_2) = 0.16; ^{1}H NMR (400 MHz, $CDCl_3$), δ 10.02 (1H, s), 7.83-7.80 (2H, m), 7.53-7.51 (3H, m), 7.32-7.27 (3H, m), 7.23-7.20 (2H, m), 5.36-5.28 (1H, m), 3.54 (1H, dd, *J*=13.5, 5.0 Hz), 3.20-3.0 (1H, m), 3.15 (1H, dd, *J*=13. 5, 8.8 Hz), 3.01-2.85 (1H, m), 2.07-2.55 (1H, m); ^{13}C NMR (100 MHz, acetone-D6) δ 163.9, 138.3, 137.0, 136.7, 131.6, 131.1, 130.4, 129.9, 128.3, 122.1, 62.9, 40.3, 33.4, 22.1; IR (NaCl, neat) 1585, 1513, 1222, 1062cm^{-1}; m.p. 195.1-196.5 °C; $[\alpha]_D^{23}$ = + 9.1° (acetonitrile, c = 5 mg/mL); HRMS (FAB+) calcd for $C_{18}H_{18}N_3$ 276.1499, Found 276.1498.

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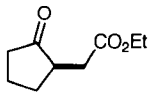
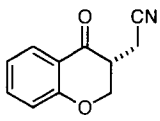
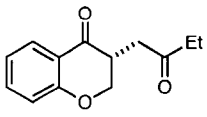
[6] Smrcina, M.; Majer, P.; Majerová, E.; Guerassina, T.; Eissenstat, M. A. *Tetrahedron* **1997**, *53*, 12867-12874.



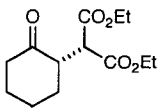
(2-Oxo-cyclopentyl)-acetic acid ethyl ester (15) According to the general procedure, 5 mg (0.013 mmol) of **30** in 2 mL of xylenes was treated with 0.026 mL (0.013 mmol) of KHMDS and allowed to stir at ambient temperature for 15 min. 10 mg (0.065 mmol) of **13** in 1 mL xylenes was added via syringe and the reaction was stirred for 24 h at 23°C. Upon work-up 9 mg (90%) of desired ester was isolated as a colorless oil: $[\alpha]_D^{23}$ = - 65° (CH_2Cl_2, c = 7 mg/mL; Gas chromatography analysis - B-DM column with constant 110 °C oven temperature. Major enantiomer 19.6 minutes, minor enantiomer, 20.5 min.



***(2R)*-(4-Oxo-chroman-3-yl)-acetonitrile (49).** According to the general procedure, 15.0 mg (0.032 mmol) of **20** and 64.0 μL (0.032 mmol) of KHMDS and 30.0 mg (0.160 mmol) of **48** were reacted for 24 hours. Work-up afforded 24.0 mg (88%) of the desired product as a clear oil. R_f (1:1 hexane to ethyl acetate) = 0.7; $[\alpha]_D^{23}$ = - 7.0 ($CHCl_3$, c = 10 mg/mL); HPLC analysis–Chiracel ADH column 90:1 hexanes to isopropanol 1.0 mL/min. Minor enantiomer: 14.8 minutes, Major enantiomer: 15.6 minutes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (1H, m), 7.50 (1H, m), 7.04 (1H, m), 6.98(1H, m), 4.72 (1H, dd, *J*= 5.1, 11.5 Hz), 4.32 (1H, dd, *J*=11.5, 11.7 Hz), 3.17 (1H, dddd, *J*= 4.9, 9.4, 13.8, 13.8 Hz), 2.97 (1H, dd, *J*= 4.7, 17.5 Hz), 2.58 (1H, dd, *J*= 9.2, 17.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 161.6, 136.7, 127.4, 122.0, 119.8, 118.0, 117.0, 69.4, 42.0, 14.1; IR (NaCl, CH_2Cl_2) 2247, 1687, 1607, 1287 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_9NO_2$ 187.0633, Found 188.0719.

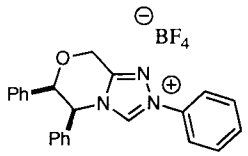


***(2R)*-(3-(2-Oxo-pentyl)-chroman-4-one (51)** According to the general procedure, 9.0 mg (0.019 mmol) of **61** and 37.0 μL (0.019 mmol) of KHMDS and 20.0 mg (0.0916 mmol) of **50** were reacted for 60 minutes. Work-up afforded 19.0 mg (94%) of the desired product as colorless oil. R_f (4:1 hexane to ethyl acetate) = 0.4; $[\alpha]_D^{23}$ = - 6.3 ($CHCl_3$, c = 8 mg/mL); HPLC analysis – Chiracel AD-H column 90:1 hexanes to isopropanol 0.5 mL/min. Minor enantiomer: 18.62 minutes, Major enantiomer: 19.41 minutes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (1H, d, *J* = 7.6 Hz), 7.45 (1H, m), 6.99 (1H, dd, *J* = 7.5, 7.6 Hz), 6.94 (1H, d, *J* = 8.3 Hz), 4.51 (1H, dd, *J* = 5.3, 11.0 Hz), 4.21 (1H, dd, *J* = 11.5, 11.5 Hz), 3.40 (1H, dddd, *J* = 17.0, 17.0, 12.8, 4.9, Hz), 2.99 (1H, dd, *J* = 4.6, 17.9 Hz), 2.61-2.41 (3H, m), 1.08 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 193.4, 161.7, 135.9, 127.2, 121.4, 120.5, 117.8, 70.2, 41.7, 37.6, 36.2, 7.7; IR (NaCl, CH_2Cl_2) 1715, 1687, 1605, 1437 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{14}O_3$ 218.0943, Found 219.1026.

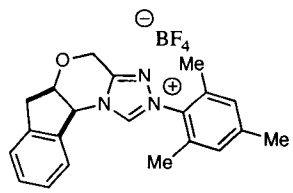


***(2R)*-2-(2-Oxo-cyclohexyl)-malonic acid diethyl ester (59)**: According to the general procedure, 14.1 mg (0.039 mmol) of **42** and 78.0 μL (0.039 mmol) of KHMDS and 50.0 mg (0.195 mmol) of **58** were reacted for 24 hours. Work-up afforded 49.0 mg (97%) of the desired product as colorless oil. R_f (4:1 hexane to ethyl acetate) = 0.4; $[\alpha]_D^{23}$ = - 41.8 ($CHCl_3$, c = 18 mg/mL); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (4H, dq, *J*= 2.3, 7.2 Hz), 3.61 (1H, d, *J*= 9.6 Hz), 3.16 (1H, ddd, *J*=5.5, 9.6, 13.2 Hz), 2.41-2.37 (2H, m), 2.11-1.99 (2H, m), 1.88 (1H, m), 1.74-1.46 (3H, m), 1.23 (6H, dt, *J*=2.5, 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 168.5, 168.3, 61.4, 52.2, 50.2,

41.8, 31.1, 27.7, 25.0, 14.0, 13.9; IR (NaCl, CH_2Cl_2) 1750, 1728, 1452 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{20}O_5$ 256.1311, Found 257.1399.



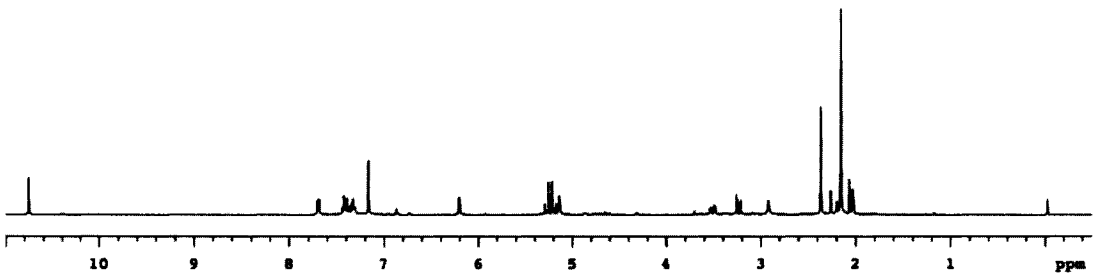
(5*S*,6*R*)-5,6-diphenyl-2-phenyl-6,8-dihydro-5*H*-[1,2,4]triazolo[3,4-*c*][1,4]oxazin-2-ium tetrafluoroborate (60): To a 25 mL round bottom flask was added 10 mL acetonitrile and 0.200 g (0.79 mmol) (5*S*,6*R*)-5,6-diphenylmorpholin-3-one.[3] Trimethyloxonium tetrafluoroborate (0.117 g, 0.79 mmol) was added and the solution allowed to stir at room temperature for 12 hours. 0.080 mL phenylhydrazine (0.79 mmol) was added and the solution stirred for 30 minutes at room temperature. This was heated to 80 °C and stirred for 1 hour. 1 mL Trimethyl orthoformate (9.1 mmol) was added. This was stirred at 80 °C for 12 hours. The solvent was removed under reduced pressure and diethyl ether was added. Hexanes was added until the desired product oiled out. This was further purified by precipitation from diethyl ether and hexanes to provide 0.182 g **60** (52%) as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.93-7.82 (m, 2H), 7.70-7.48 (m, 3H), 7.30-6.98 (m, 10H), 6.31 (d, 1H, J = 0.0 Hz), 5.64 (d, 1H, J = 16.5), 5.61 (dd, 1H, J = 0.0, 0.0 Hz), 5.38 (d, 1H, J = 17.2);

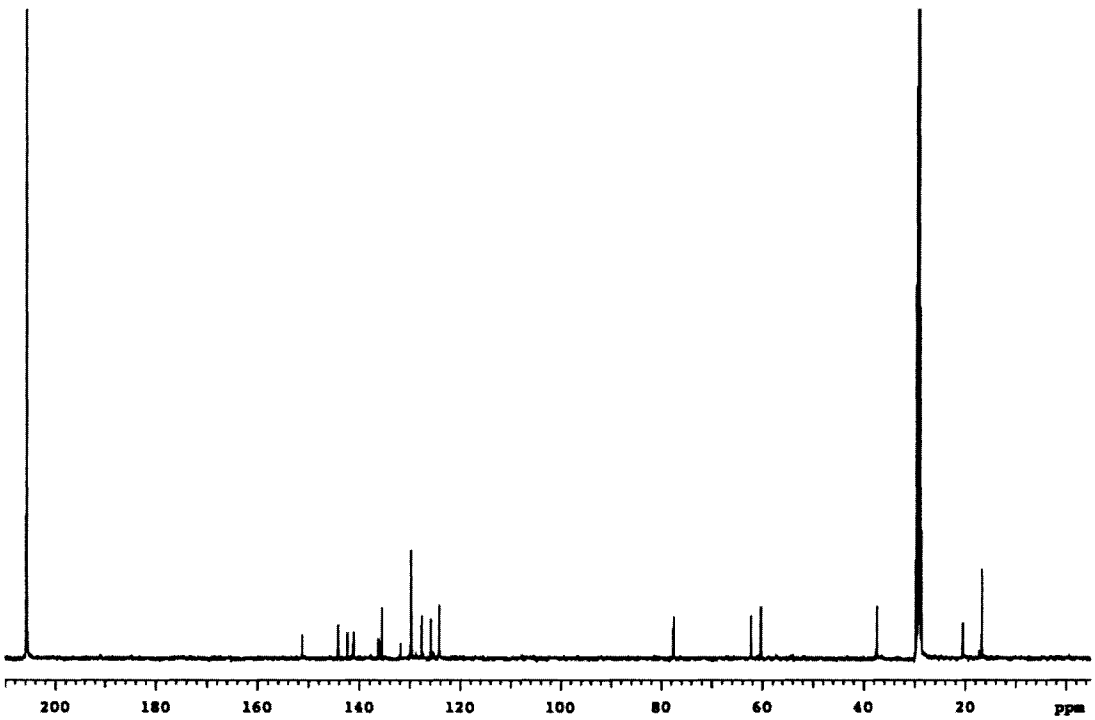


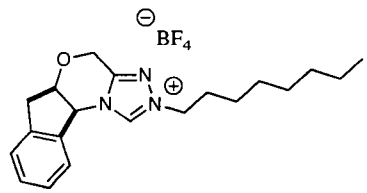
2-(2,4,6-trimethylphenyl)-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (61): To a 50 mL round bottom flask was added 15 mL CH_2Cl_2 and 0.26 g (1.38 mmol) ***ent*-E4**. Trimethyloxonium tetrafluoroborate (0.204 g, 1.38 mmol) was added and the solution allowed to stir at room

temperature for 12 hours. Mesityl hydrazine was liberated from its hydrochloride salt by stirring in 1 M NaOH and CH_2Cl_2 and extracting (3 x 15 mL) with CH_2Cl_2. The organics were dried with brine and Na_2SO_4 and filtered, and concentrated. Mesityl hydrazine (0.207 g, 1.38 mmol) was added along with 1 mL trimethyl orthoformate (9.1 mmol). This was heated to 80 °C for 12 hours. The solvent was removed under reduced pressure and CH_2Cl_2 was added. The desired product precipitated from the solution upon addition of diethyl ether to provide 209 mg (36%) white solid; R_f (EtOAc) = 0.36; $[\alpha]_D^{23}$ = + 65.0° (acetonitrile, c = 20 mg/mL); ^{1}H NMR (400 MHz, acetone-D6) δ 10.76 (s, 1H), 7.70-7.68 (m, 1H), 7.44-7.30 (m, 3H), 7.17 (s, 2H), 6.20 (d, 1H, *J* = 4.0 Hz), 5.27 (d, 1H, *J* = 16.0 Hz), 5.19 (d, 1H, *J* = 16.0 Hz), 5.14 (ddd, 1H, *J* = 4.5, 4.5, 0.0 Hz), 3.51 (dd, 1H, *J* = 17.2, 4.9 Hz), 3.24 (dd, 1H, *J* = 17.3 Hz) 2.36 (s, 3H), 2.15 (s, 6H); ^{13}C NMR (100 MHz, acetone-D6) δ 151.2, 144.1, 142.3, 141.1, 136.2, 135.5, 131.8, 129.8, 129.6, 127.6, 125.8, 124.2, 77.5, 62.2, 60.3, 37.4, 20.4, 16.7; IR (NaCl, neat) 3084, 2924, 1687, 1564, 1461 cm^{-1}; m.p. >250 °C; HRMS (FAB+) calcd for $C_{21}H_{22}N_3O$ 332.1763. Found 332.1758.

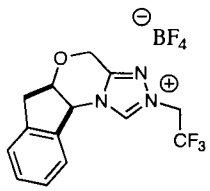
61 ^{1}H and ^{13}C NMR spectra



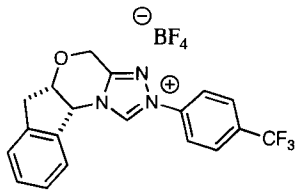




2-octyl-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (62): A flame-dried round bottom flask was charged with morpholinone ***ent*-E4** (0.250 g, 1.32 mmol) and CH_2Cl_2 (15 mL). Trimethyloxonium tetrafluoroborate (0.195 g, 1.32 mmol) was added, and the reaction mixture stirred for 12 hours at 23 °C. Octyl hydrazine was prepared by refluxing hydrazine and octyl bromide with catalytic NaI in acetonitrile and used without further purification. Octyl hydrazine was added to the activated amide and stirred at room temperature for 30 minutes. 10 mL acetonitrile was added along with 1 mL trimethyl orthoformate (9.1 mmol) and the solution was heated to 80 °C for 12 hours. The solvent was removed *in vacuo*, and EtOAc (25 mL) was added. EtOAc was added and the product was oiled out with diethyl ether. The solvent was poured off to provide 185 mg desired product as a clear oil (34%) R_f (EtOAc) = 0.26; $[\alpha]_D^{23}$ = + 95.6° (acetonitrile, c = 9 mg/mL); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H), 7.50-7.46 (m, 1H), 7.37-7.21 (m, 3H), 5.85 (d, 1H, J = 3.2 Hz), 4.98-4.92 (m, 2H), 4.39 (dd, 1H, J = 7.5, 7.5 Hz), 3.28-3.10 (m, 2H), 1.92 (dd, 2H, J = 14.7, 7.5 Hz), 1.39-1.15 (m, 12H), 0.84 (t, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 141.9, 140.0, 135.3, 129.9, 128.2, 125.7, 124.1, 61.7, 60.4, 53.2, 37.6, 31.9, 29.2, 29.1, 26.6; IR (NaCl, neat) 2916, 1651, 1578, 1455, 1069 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{28}N_3O$ 326.2233. Found 326.2234.

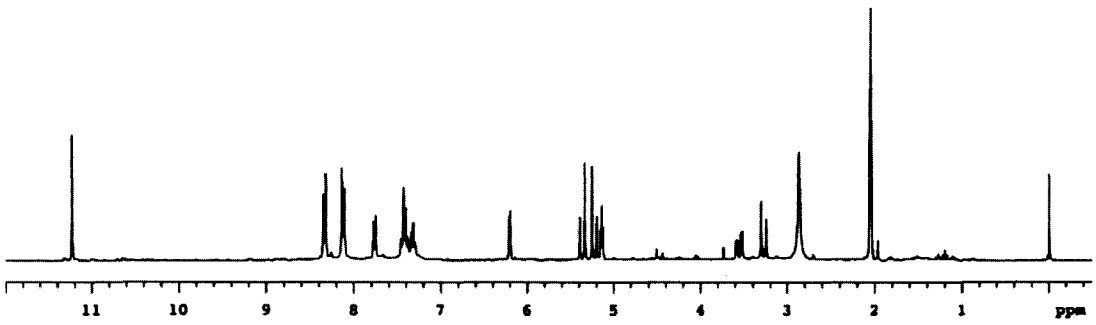


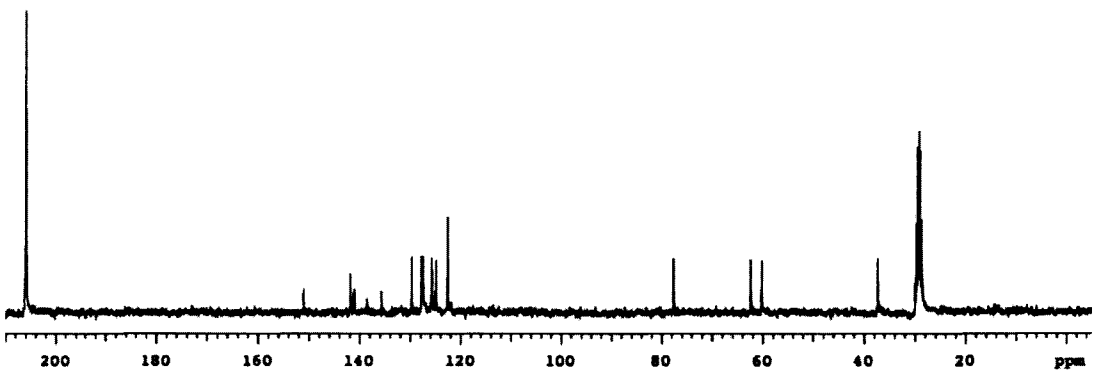
2-(2,2,2-trifluoroethyl)-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (63): To a 50 mL round bottom flask was added 15 mL CH_2Cl_2 and 0.25 g (1.32 mmol) ***ent*-E4**. Trimethyloxonium tetrafluoroborate was added and the solution allowed to stir at room temperature for 12 hours. 0.20 mL 2,2,2-trifluoroethyl hydrazine (1.32 mmol) was added and the solution stirred for 30 minutes at room temperature. 1 mL Trimethyl orthoformate (9.1 mmol) was added along with 10 mL acetonitrile. This was heated to 80 °C for 12 hours. The solvent was removed under reduced pressure and EtOAc was added to dissolve the residue. Diethyl ether was added, and the desired product oiled out. The solvent was poured off to give the crude product, which was further purified by recrystallization from diethyl ether to provide 0.290 g **63** as a tan solid (57%). R_f (EtOAc) = 0.15; $[\alpha]_D^{23}$ = + 248.5° (acetonitrile, c = 6 mg/mL); ^{1}H NMR (400 MHz, CD_3CN) δ 10.10 (s, 1H), 7.50-7.35 (m, 4H), 5.89 (d, 1H, J = 4.1 Hz), 5.40-5.18 (m, 2H), 5.11 (d, 1H, J = 16.4 Hz), 4.92 (d, 1H, J = 16.6 Hz), 4.88 (dd, 1H, J = 4.3, 4.3 Hz), 3.43 (dd, 1H, J = 17.3, 4.9 Hz), 3.19 (dd, 1H, J = 17.3, 0.0 Hz); ^{13}C NMR (100 MHz, CD_3CN) δ 151.0, 144.1, 141.0, 135.2, 129.0, 127.5, 126.0, 124.4, 77.4, 62.0, 60.2, 52.3 (dd, 1C, J = 73.3, 36.7 Hz), 37.1, 30.1; IR (NaCl, neat) 3105, 3025, 1702, 1585, 1265 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{13}N_3OF_3$ 296.1011. Found 296.1016.

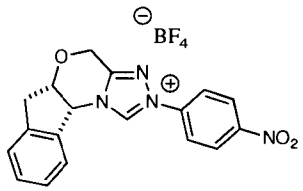


2-(4-trifluoromethylphenyl)-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (64): To a 50 mL round bottom flask was added 15 mL CH_2Cl_2 and 0.25 g (1.32 mmol) ***ent*-E4**. Trimethyloxonium tetrafluoroborate (1.95 g, 1.32 mmol) was added and the solution allowed to stir at room temperature for 12 hours. 4-Trifluoromethylphenyl hydrazine was added to the activated amide and stirred for 2 hours. Acetonitrile was added and the reaction was heated to 80 °C for 1 hour. This was concentrated, followed by addition of 10 mL chlorobenzene and 1 mL trimethyl orthoformate (9.1 mmol). This was heated to 100 °C for 12 hours. The solvent was removed under reduced pressure and EtOAc was added. Upon stirring at ambient temperature for 1 hour, the desired product precipitated from the solution to provide 315 mg (54%) tan solid; R_f (9:1 CH_2Cl_2 : MeOH) = 0.38; $[\alpha]_D^{23}$ = + 24.0° (acetonitrile, c = 10 mg/mL); ^{1}H NMR (400 MHz, acetone-D6) δ 11.24 (s, 1H), 8.34 (d, 2H, *J* = 8.4 Hz), 8.13 (d, 2H, *J* = 8.8 Hz), 7.76 (d, 1H, *J* = 7.3 Hz), 7.50-7.38 (m, 2H), 7.32 (dd, 1H, *J* = 7.7, 7.7 Hz), 6.20 (d, 1H, *J* = 4.0 Hz), 5.36 (d, 1H, *J* = 16.1 Hz), 5.22 (d, 1H, *J* = 16.5 Hz), 5.14 (dd, 1H, *J* = 4.4 Hz) 3.56 (dd, 1H, *J* = 17.2, 4.8 Hz), 3.28 (dd, 1H, *J* = 17.2, 0.0); ^{13}C NMR (100 MHz, acetone-D6) δ 151.0, 148.8, 141.0, 138.5, 135.6, 132.0 129.7, 127.7, 127.4, 125.7, 125.3, 124.8, 122.5, 77.6, 62.4, 60.2, 37.3; IR (NaCl, neat) 3127, 1614, 1578, 1331, 1054 cm^{-1}; m.p. 185-195 °C; HRMS (FAB+) calcd for $C_{19}H_{15}N_3OF_3$ 358.1167. Found 358.1176.

64 ^{1}H and ^{13}C NMR spectra

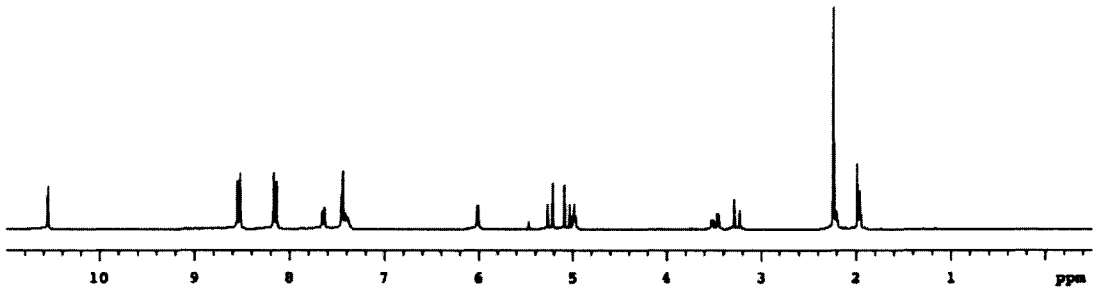


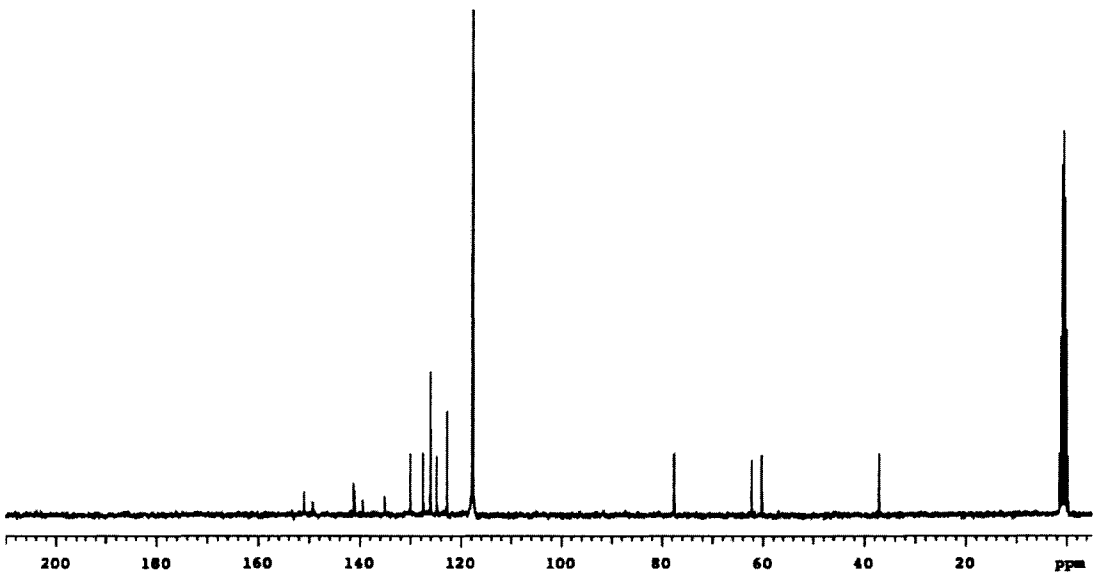


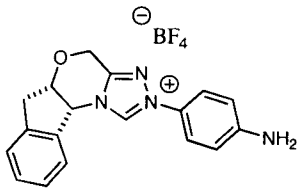


2-(4-nitrophenyl)-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (65): To a 50 mL round bottom flask was added 15 mL CH_2Cl_2 and 0.250 g (1.32 mmol) **E4**. Trimethyloxonium tetrafluoroborate (1.950 g, 1.32 mmol) was added and the solution allowed to stir at room temperature for 12 hours. 4-Nitrophenyl hydrazine was added and stirred for 2 hours. Acetonitrile was added and the reaction was heated to 80 °C for 1 hour. This was concentrated, followed by addition of 10 mL chlorobenzene and 1 mL Trimethyl orthoformate (9.1 mmol). This was heated to 100 °C for 12 hours. The solvent was removed under reduced pressure and EtOAc was added. Upon stirring at ambient temperature for 1 hour, the desired product precipitated from the solution to provide 385 mg (69%) as tan solid; R_f (9:1 CH_2Cl_2 : MeOH) = 0.35; $[\alpha]_D^{23}$ = - 171.0 ° (acetonitrile, c = 20 mg/mL); ^{1}H NMR (300 MHz, CD_3CN) δ 10.56 (s, 1H), 8.53 (d, 2H, *J* = 9.2 Hz), 8.15 (d, 1H, *J* = 9.2 Hz), 7.65 (d, 1H, *J* = 7.3 Hz), 7.49-7.37 (m, 3H), 6.01 (d, 1H, *J* = 4.0 Hz), 5.24 (d, 1H, *J* = 16.5 Hz), 5.06 (d, 1H, *J* = 16.5 Hz), 4.98 (dd, 1H, *J* = 4.4, 4.4 Hz), 3.49 (dd, 1H, *J* = 17.2, 5.1 Hz) 3.26 (dd, 1H, *J* = 17.2, 0 Hz); ^{13}C NMR (75 MHz, CD_3CN) δ 151.0, 149.3, 141.2, 141.0, 139.4, 135.1, 130.0, 127.5, 126.0. 124.8, 122.7, 77.6, 62.3, 60.3; IR (NaCl, neat) 3105, 1592, 1520, 1345, 1055 cm^{-1}; m.p. >250 °C; HRMS (FAB+) calcd for $C_{18}H_{15}N_4O_3$ 335.1144. Found 335.1133.

65 ^{1}H and ^{13}C NMR spectra

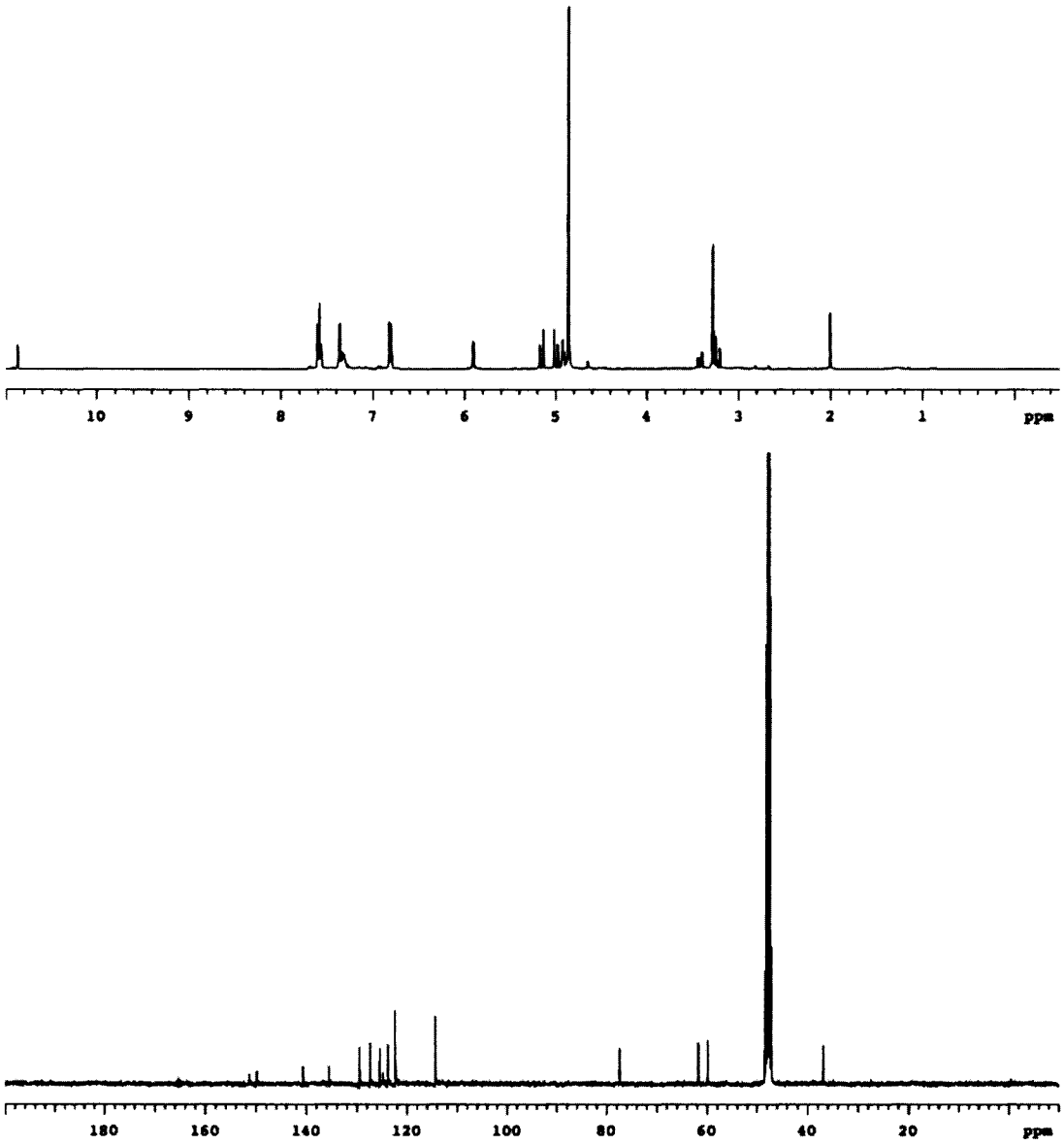


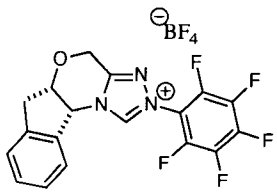




2-(4-aminophenyl)-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (66): Prepared from **65** by hydrogenation. 100 mg **65** was added to 5 mL MeOH and 30 mg 10% Pd/C. The reaction vessel was pressurized to 60 psi with H_2 gas and stirred for 12 hours at room temperature. The solution was filtered through celite and solvent removerd under reduced pressure to provide 90 mg desired product (94%) as a clear oil; R_f (9 : 1 CH_2Cl_2 : MeOH) = 0.25; $[\alpha]_D^{23}$ = - 144.0° (acetonitrile, c = 5 mg/mL); ^{1}H NMR (400 MHz, CD_3OD) δ 10.87 (s, 1H), 7.60-7.56 (m, 3H), 7.40-7.30 (m, 3H), 6.81 (d, 2H, *J* = 8.1), 5.90 (d, 1H, *J* = 4.1 Hz), 5.15 (d, 1H, *J* = 16.2 Hz), 4.99 (d, 1H, *J* = 16.2 Hz), 4.97 (ddd, 1H, *J* = 4.5, 4.5, 0.0 Hz), 3.42 (dd, 1H, *J* = 17.0, 4.9 Hz), 3.22 (dd, 1H, *J* = 17.1, 0.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 151.3, 149.8, 140.7, 135.6, 129.5, 127.4, 125.5, 124.8, 123.8, 122.4, 114.4, 77.4, 61.7, 59.9, 36.9; IR (NaCl, neat) 3484, 3396, 1636, 1607, 1627 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{17}N_4O$ 305.1402. Found 305.1393.

66 ^{1}H and ^{13}C NMR spectra

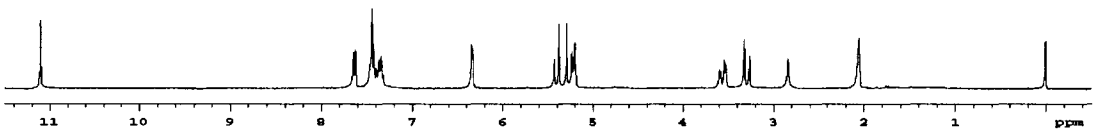




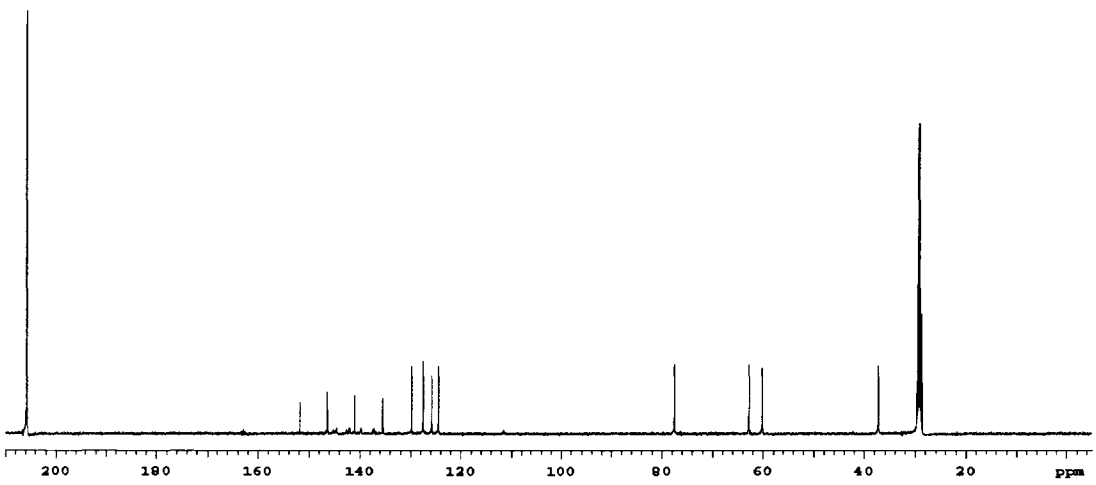
2-Pentafluorophenyl-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (67): A flame-dried round bottom flask was charged with morpholinone **E4** (1.000 g, 5.29 mmol) and CH_2Cl_2 (25 mL). Trimethyloxonium tetrafluoroborate (0.783 g, 5.29 mmol) was added, and the reaction mixture stirred for 12 hours at 23 °C. Pentafluorophenyl hydrazine (0.952 mL, 5.29 mmol) was then added and allowed to stir for 2 hours at ambient temperature. The solvent was evaporated and chlorobenzene (50 mL) was added, followed by triethyl orthoformate (2.20 mL, 13.23 mmol). The flask was equipped with a reflux condenser and heated to 110 °C and stirred at this temperature for 12 hours. At this time, additional triethyl orthoformate (2.20 mL, 13.23 mmol) was added and stirring at 110 °C was continued for 12 more hours. Upon cooling, toluene (50 mL) was added and the light tan solid product was collected by filtration. This was rinsed with toluene 3 x 5 mL and heated to 120 °C for 6 hours under vacuum to remove residual water to provide triazolium salt **21** (1.560 g, 63%): Rf (3:1 CH_2Cl_2 to acetone) = 0.22; $[\alpha]_D^{23}$ = -116.7° (acetonitrile, c = 12 mg/mL); ^{1}H NMR (300 MHz, acetone-D6) δ 11.10 (s, 1H), 7.64 (d, 1H, *J* = 7.7 Hz), 7.24-7.56 (m, 3H), 6.34 (d, 1H, *J* = 4.0 Hz), 5.40 (d, 1H, *J* = 16.5 Hz), 5.26 (d, 1H, *J* = 16.5 Hz), 5.20 (dd, 1H, *J* = 4.4, 4.4 Hz), 3.56 (dd, 1H, *J* = 17.2, 4.8 Hz), 3.29 (dd, 1H, *J* = 17.2, 0 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 151.8, 146.5, 144.7 (m), 142.0 (m), 141.0, 139.8 (m), 137.3 (m), 135.5, 129.8, 127.5, 125.8, 124.5, 77.6, 62.8, 60.2, 37.3; ^{19}F NMR (470.3 MHz, acetone-D6) δ 45.88 (d, 2F, *J* = 18.3 Hz), 42.54 (dd, 1F, *J* = 21.4, 21.4 Hz), 40.91 (s, 1F), 40.85 (s, 3F), 30.57 (ddd, 2F, *J* = 27.5, 18.3, 18.3 Hz); IR (NaCl, neat) 3142, 1709,

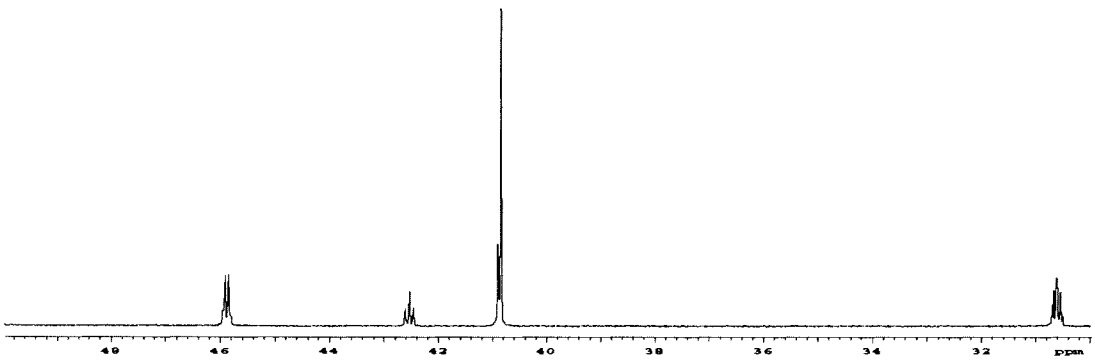
1593, 1527, 1484, 1076, 1004 cm^{-1}; m.p. 222-226 °C; HRMS (FAB+) calcd for $C_{18}H_{11}N_3OF_5$ 380.0822. Found 380.0818.

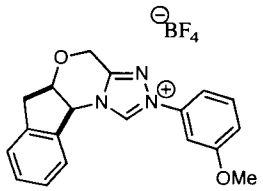
67 ^1H spectra



67 ^{13}C and ^{19}F spectra



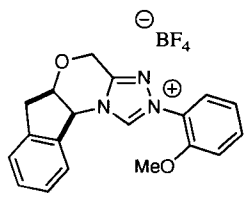




2-(3-methoxyphenyl)-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (68): A flame-dried round bottom flask was charged with morpholinone ***ent*-E4** (0.150 g, 0.79 mmol) and CH_2Cl_2 (10 mL). Trimethyloxonium tetrafluoroborate (0.117 g, 0.79 mmol) was added, and the reaction mixture stirred for 12 hours at 23 °C. 3-Methoxyphenylhydrazine hydrochloride was prepared from 3-methoxy aniline.[7] This was treated with 1 M NaOH and CH_2Cl_2, and stirred for 5 minutes. This solution was extracted with CH_2Cl_2 (3 x 15mL), dried with brine and then over Na_2SO_4, and filtered to provide 3-methoxyphenyl hydrazine. 3-Methoxyphenyl hydrazine (0.109 g, 0.79 mmol) was then added and allowed to stir for 2 hours at ambient temperature. 10 mL acetonitrile was added along with 1 mL trimethyl orthoformate (9.1 mmol) and the solution was heated to 80 °C for 12 hours. The solvent was removed *in vacuo*, and EtOAc (25 mL) was added. The product was oiled out with diethyl ether. The solvent was poured off to provide 215 mg desired product as a tan oil (67%); R_f (EtOAc) = 0.33; $[\alpha]_D^{23}$ = + 201.3° (acetonitrile, c = 8 mg/mL); ^{1}H NMR (300 MHz, acetone-D6) δ 11.10 (m, 4H), 6.13 (d, 1H, *J* = 4.0 Hz), 5.31 (d, 1H, *J* = 16.1 Hz), 5.18 (d, 1H, *J* = 16.5 Hz), 5.11 (dd, 1H, *J* = 4.4, 4.4 Hz), 3.93 (d, 1H, *J* = 16.5 Hz), 5.20 (dd, 1H, *J* = 4.4, 4.4 Hz), 3.56 (dd, 1H, *J* = 17.2, 4.8 Hz), 3.29 (s, 3H), 3.52 (dd, 1H, *J* = 16.8, 4.8 Hz), 3.25 (dd, 1H, *J* = 17.2, 0); ^{13}C NMR (75 MHz, acetone-D6) δ 161.1, 150.6, 141.0, 140.9, 136.7, 135.8, 131.4, 129.6, 127.4, 125.7, 124.9, 117.0, 113.4, 107.0; IR (NaCl, neat) 3105,

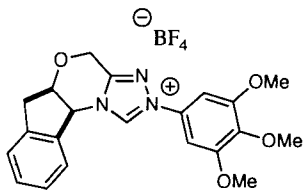
[7] Lagoja, I. M.; Pannecouque, C.; Van Aerschot, A.; Witvrouw, M.; Debyser, Z.; Balzarini, J.; Herdewijin, P.; De Clerq, E. *J. Med. Chem.* **2003**, *46*, 1546-1553.

2931, 1702, 1615, 1498 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{18}N_3O_2$ 320.1399. Found 320.1388.



2-(2-methoxyphenyl)-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (69): A flame-dried round bottom flask was charged with morpholinone ***ent*-E4** (0.200 g, 1.06 mmol) and CH_2Cl_2 (10 mL). Trimethyloxonium tetrafluoroborate (0.157 g, 1.06 mmol) was added, and the reaction mixture stirred for 12 hours at 23 °C. 2-Methoxyphenylhydrazine hydrochloride was prepared from 2-methoxy aniline.[2] This was treated with 1 M NaOH and CH_2Cl_2, and stirred for 5 minutes. This solution was extracted with CH_2Cl_2 (3 x 15mL), dried with brine and then over Na_2SO_4, and filtered to provide 2-methoxyphenyl hydrazine. 2-Methoxyphenyl hydrazine (0.146 g, 1.06 mmol) was then added and allowed to stir for 2 hours at ambient temperature. 10 mL acetonitrile was added along with 1 mL trimethyl orthoformate (9.1 mmol) and the solution was heated to 80 °C for 12 hours. The solvent was removed *in vacuo*, and EtOAc (25 mL) was added and stirred for 1 hour. 305 mg desired product was collected as a tan solid (71%). R_f (EtOAc) = 0.08; $[\alpha]_D^{23}$ = + 225.0° (acetonitrile, c = 6 mg/mL); ^{1}H NMR (400 MHz, acetone-D6) δ 11.08 (s, 1H), 7.89 (d, 1H, *J* = 8.1 Hz), 7.63 (dd, 1H, *J* = 7.7, 7.7 Hz), 7.50-7.36 (m, 2H), 7.31 (dd, 1H, *J* = 7.5, 7.5 Hz), 7.27 (dd, 1H, *J* = 7.9, 7.9 Hz), 6.18 (d, 1H, *J* = 3.6 Hz), 5.29 (d, 1H, *J* = 16.2 Hz), 5.18 (d, 1H, *J* = 16.2 Hz), 5.13 (dd, 1H, *J* = 4.3, 4.3 Hz), 4.09 (s, 3H), 3.51 (dd, 1H, *J* = 17.1, 4.5 Hz), 3.24 (dd, 1H, *J* = 17.1, 0.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 149.7, 143.4, 141.0, 136.1, 132.4, 129.6, 127.3, 125.7, 124.8, 124.6, 124.5, 121.6, 113.4, 77.7, 62.2, 60.2, 56.5, 37.3;

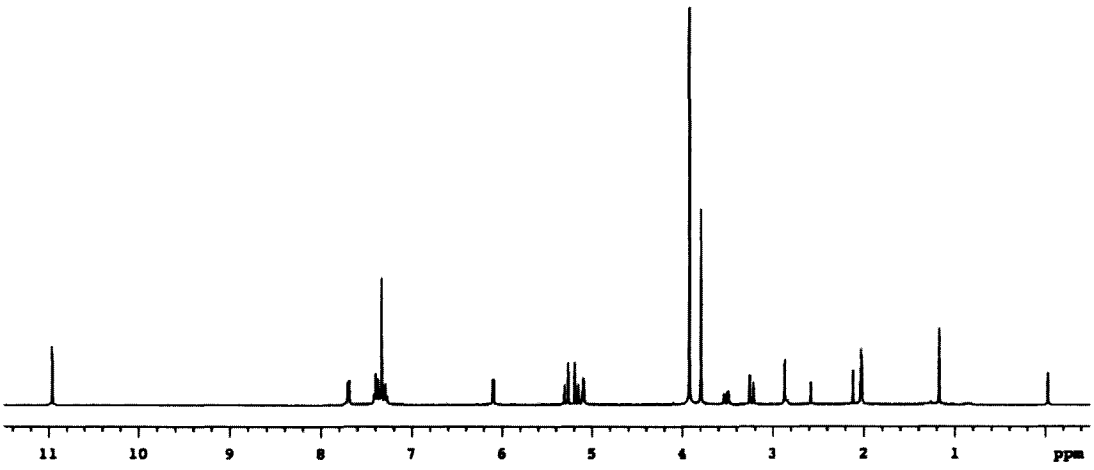
IR (NaCl, neat) 1600, 1585, 1498, 1287, 1258 cm^{-1}; m.p. 210-215 °C HRMS (FAB+) calcd for $C_{19}H_{18}N_3O_2$ 320.1399. Found 320.1414.



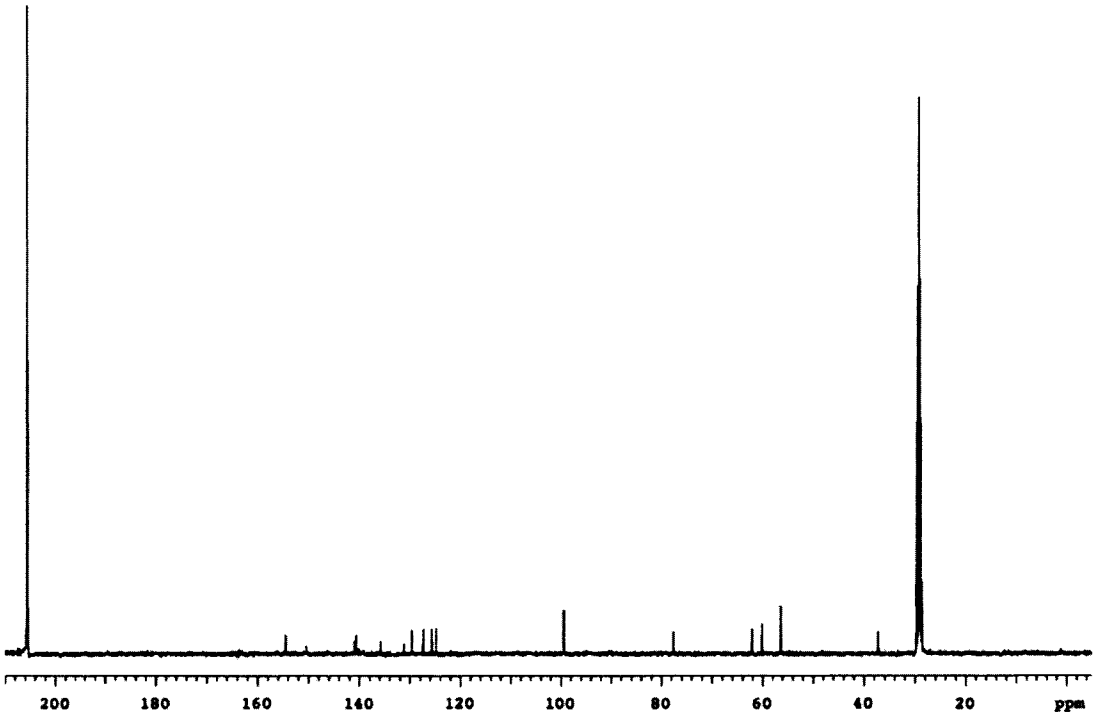
2-(2-methoxyphenyl)-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (70): To a 50 mL round bottom flask was added 15 mL CH_2Cl_2 and 0.200 g (1.06 mmol) ***ent*-E4**. Trimethyloxonium tetrafluoroborate (0.157 g, 1.06 mmol) was added and the solution allowed to stir at room temperature for 12 hours. 3,4,5-Trimethoxyphenyl hydrazine hydrochloride was prepared from 3,4,5-trimethoxyaniline.[2] The free hydrazine was liberated from its hydrochloride salt by stirring in 1 M NaOH and CH_2Cl_2 and extracting (3 x 15 mL) with CH_2Cl_2. The organics were dried with brine and Na_2SO_4 and filtered, and concentrated. 3,4,5-Trimethoxyphenyl hydrazine (0.210 g, 1.06 mmol) was added and stirred for 30 minutes. Acetonitrile (10 mL) was added along with 1 mL trimethyl orthoformate (9.1 mmol). This was heated to 80 °C for 12 hours. The solvent was removed under reduced pressure and EtOAc was added. The desired product oiled out of the solution upon addition of diethyl ether to provide 365 mg (74%) as a clear oil; R_f (EtOAc) = 0.14; $[\alpha]_D^{23}$ = + 155° (acetonitrile, c = 20 mg/mL); ^{1}H NMR (400 MHz, acetone-D6) δ 10.96 (s, 1H), 7.70 (d, 1H, *J* = 7.5 Hz), 7.43-7.24 (m, 5H), 6.10 (d, 1H, *J* = 4.1 Hz), 5.29 (d, 1H *J* = 16.2), 5.17 (d, 1H, *J* = 16.2 Hz), 5.10 (dd, 1H, *J* = 4.5, 4.5 Hz), 3.92 (s, 6H), 3.80 (s, 3H), 3.52 (dd, 1H, *J* = 17.0, 4.7 Hz) 3.24 (dd, 1H, *J* = 17.0, 0 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 154.5, 150.5, 141.0, 140.6, 135.8, 131.2, 129.6, 127.4, 125.7, 124.8, 99.4, 77.6, 62.1, 60.1, 56.3, 37.2; IR (NaCl, neat) 3091, 2945,

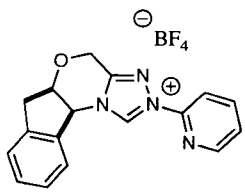
1615, 1469, 1236 cm^{-1}; HRMS (FAB+) calcd for $C_{21}H_{22}N_3O_4$ 380.1610. Found 380.1593.

70 ^1H NMR spectrum



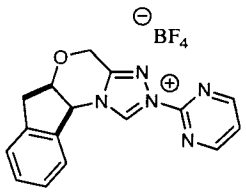
70 ^{13}C NMR spectrum





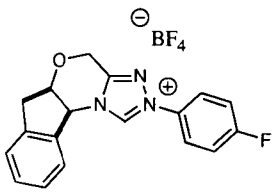
2-(2-Pyridyl)-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (71): To a 50 mL round bottom flask was added 15 mL CH_2Cl_2 and 0.25 g (1.32 mmol) ***ent*-E4**. Trimethyloxonium tetrafluoroborate (1.95 g, 1.32 mmol) was added and the solution allowed to stir at room temperature for 12 hours. 2-Pyridyl hydrazine was liberated from its hydrochloride salt by stirring in 1 M NaOH and CH_2Cl_2 and extracting (3 x 15 mL) with CH_2Cl_2. The organics were dried with brine and Na_2SO_4 and filtered, and concentrated. 2-Pyridyl hydrazine (0.141 g, 1.32 mmol) was added to the activated amide and stirred for 2 hours. Acetonitrile was added and the reaction was heated to 80

°C for 1 hour. This was concentrated, followed by addition of 10 mL chlorobenzene and 1 mL Trimethyl orthoformate (9.1 mmol). This was heated to 100 °C for 12 hours. The solvent was removed under reduced pressure and EtOAc was added. Upon stirring at ambient temperature for 1 hour, the desired product precipitated from the solution as a light brown solid. Recrystallization from EtOAc provided 210 mg (42%). R_f (EtOAc) = 0.12; ^{1}H NMR (300 MHz, CD_3OD) δ 8.68 (d, 1H, *J* = 4.0 Hz), 8.17 (dd, 1H, *J* = 7.7, 7.7 Hz), 8.07 (d, 1H, *J* = 8.1 Hz), 7.67 (dd, 1H, *J* = 7.3, 4.8 Hz), 7.60 (d, 1H, *J* = 7.0 Hz), 7.40-7.31 (m, 3H), 6.01 (d, 1H, *J* = 4.0 Hz), 5.22 (d, 1H, *J* = 16.5 Hz), 5.05 (d, 1H, *J* = 16.5 Hz), 4.97 (dd, 1H, *J* = 4.4, 4.4 Hz), 3.44 (dd, 1H, *J* = 16.8, 4.8 Hz), 3.28 (dd, 1H, *J* = 17.2, 0 Hz;; HRMS (FAB+) calcd for $C_{17}H_{15}N_4O$ 291.1246. Found 291.1260.



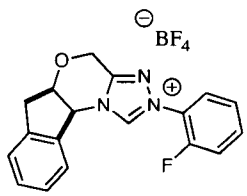
2-(1,3-Pyrimidyl)-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (72): To a 50 mL round bottom flask was added 15 mL CH_2Cl_2 and 0.250 g (1.32 mmol) ***ent*-E4**. Trimethyloxonium tetrafluoroborate (0.195 g, 1.32 mmol) was added and the solution allowed to stir at room temperature for 12 hours. Pyrimidyl hydrazine was prepared by refluxing hydrazine hydrate and 2-chloropyrimidine in EtOH overnight and used without purification. 1,3-pyrimidyl hydrazine (0.141 g, 1.32 mmol) was added to the activated amide and stirred for 2 hours. Acetonitrile was added and the reaction was heated to 80 °C for 1 hour. This was concentrated, followed by addition of 10 mL chlorobenzene and 1 mL Trimethyl orthoformate (9.1 mmol). This was heated to 100 °C for 12 hours. The solvent was removed under reduced pressure and EtOAc was added. Upon stirring at ambient temperature for 1 hour, the desired product precipitated from the

solution as a yellow solid to provide 315 mg (63%); R_f (EtOAc) = 0.08; $[\alpha]_D^{23}$ = + 72.5° (acetonitrile, c = 20 mg/mL); ^{1}H NMR (300 MHz, CD_3CN) δ 10.86 (s, 1H), 9.03 (d, 2H, *J* = 5.1 Hz), 8.37-8.18 (m, 1H, *J* = 7.3 Hz), 7.77 (dd, 1H, *J* = 4.8, 4.8 Hz), 7.57 (d, 1H, *J* = 7.3 Hz), 7.49-7.25 (m, 2H), 6.03 (d, 1H, *J* = 3.7 Hz), 5.26 (d, 1H, *J* = 16.5), 5.06 (d, 1H, *J* = 16.5 Hz), 4.98 (dd, 1H, *J* = 4.4, 4.4 Hz), 3.49 (dd, 1 H, *J* = 17.2, 4.8 Hz), 3.25 (dd, 1H, *J* = 17.2, 0.0); ^{13}C NMR (75 MHz, CD_3CN) δ 151.1, 142.5, 141.0, 135.1, 130.0, 127.4, 126.0, 124.8, 123.8, 77.6, 62.4, 60.4, 37.2; IR (NaCl, neat) 1723, 1758, 1505, 1404, 1200 cm^{-1}; m.p. 115-125 °C; HRMS (FAB+) calcd for $C_{16}H_{14}N_5O$ 292.1198. Found 292.1195.



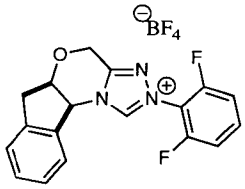
2-(4-Fluorophenyl)-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (73): To a 50 mL round bottom flask was added 15 mL CH_2Cl_2 and 0.25 g (1.32 mmol) ***ent*-E4**. Trimethyloxonium tetrafluoroborate (1.95 g, 1.32 mmol) was added and the solution allowed to stir at room temperature for 12 hours. 4-Fluorophenyl hydrazine was liberated from its hydrochloride salt by stirring in 1 M NaOH and CH_2Cl_2 and extracting (3 x 15 mL) with CH_2Cl_2. The organics were dried with brine and Na_2SO_4 and filtered, and concentrated. 4-Fluorophenyl hydrazine (0.172 g, 1.32 mmol) was added to the activated amide and stirred for 2 hours. Acetonitrile was added and the reaction was heated to 80 °C for 1 hour. This was concentrated, followed by addition of 10 mL chlorobenzene and 1 mL Trimethyl orthoformate (9.1 mmol). This was heated to 100 °C for 12 hours. The solvent was removed under reduced pressure and EtOAc was added. Upon stirring at ambient temperature for 1 hour, the desired product

precipitated from the solution as a red solid to provide 420 mg (76%). R_f (EtOAc) = 0.18; $[\alpha]_D^{23}$ = + 163.1° (acetonitrile, c = 16 mg/mL); ^{1}H NMR (400 MHz, acetone-D6) δ 10.99 (s, 1H), 8.2-8.0 (m, 2H), 7.75 (d, 1H, *J* = 8.1 Hz), 7.60-7.20 (m, 5H), 5.32 (d, 1H, *J* = 16.5 Hz), 5.17 (d, 1H, *J* = 16.5 Hz), 5.10 (dd, 1H, *J* = 0.0, 0.0 Hz), 3.52 (dd, 1H, *J* = 17.2, 4.4 Hz), 3.25 (dd, 1H, *J* = 16.8, 0.0 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 150.7, 141.0, 135.8, 132.2, 129.6, 127.4, 125.7, 124.9, 124.5, 124.4, 117.4, 117.1, 77.6, 62.2, 60.2, 37.3; IR (NaCl, neat) 3113, 2938, 1585, 1505, 1229 cm^{-1}; m.p. 230-232 °C; HRMS (FAB+) calcd for $C_{18}H_{15}N_3OF$ 308.1199. Found 308.1188.



2-(2-Fluorophenyl)-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (74): To a 50 mL round bottom flask was added 15 mL CH_2Cl_2 and 0.25 g (1.32 mmol) ***ent*-E4**. Trimethyloxonium tetrafluoroborate (1.95 g, 1.32 mmol) was added and the solution allowed to stir at room temperature for 12 hours. 2-Fluorophenyl hydrazine was liberated from its hydrochloride salt by stirring in 1 M NaOH and CH_2Cl_2 and extracting (3 x 15 mL) with CH_2Cl_2. The organics were dried with brine and Na_2SO_4 and filtered, and concentrated. 2-Fluorophenyl hydrazine (0.172 g, 1.32 mmol) was added to the activated amide and stirred for 2 hours. Acetonitrile was added and the reaction was heated to 80 °C for 1 hour. This was concentrated, followed by addition of 10 mL chlorobenzene and 1 mL Trimethyl orthoformate (9.1 mmol). This was heated to 100 °C for 12 hours. The solvent was removed under reduced pressure and the thick liquid was purified by column chromatography (elution with CH_2Cl_2 followed by EtOAc)

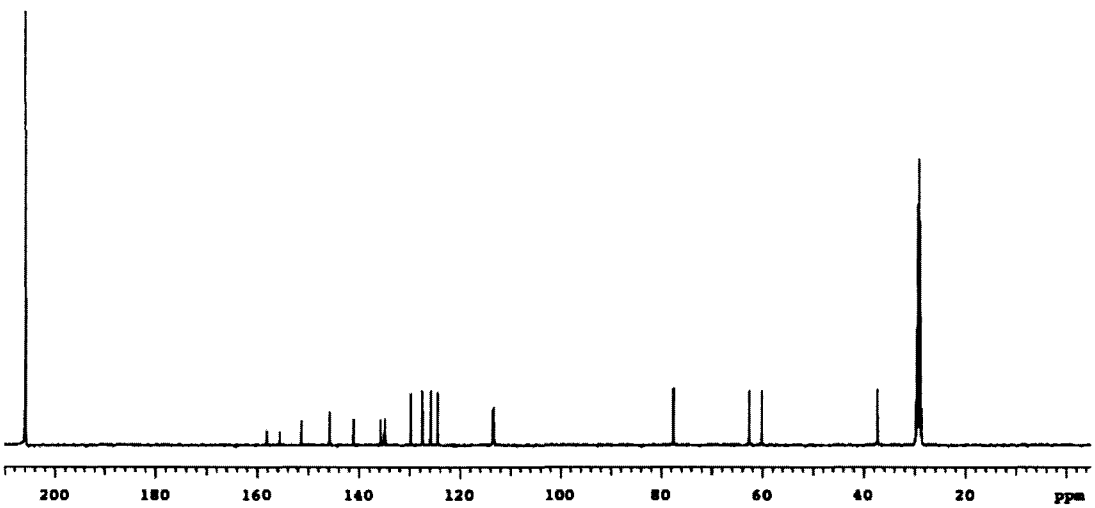
to provide 400 mg (76%) tan solid; R_f (EtOAc) = 0.13; $[\alpha]_D^{23}$ = + 76.7° (acetonitrile, c = 6 mg/mL); ^{1}H NMR (400 MHz, acetone-D6) δ 11.10 (s, 1H), 8.05-8.00 (m, 1H), 7.72-7.52 (m, 3H), 7.46-7.34 (m, 2H), 7.31-7.22 (m, 1H), 6.27 (d, 1H, *J* = 4.0 Hz), 5.35 (d, 1H, *J* = 16.4 Hz), 5.21 (d, 1H, *J* = 16.4 Hz), 5.15 (dd, 1H, *J* = 4.1, 4.1 Hz), 3.58-3.50 (m, 1H), 3.26 (d, 1H, *J* = 17.1 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 150.6, 143.6, 141.0, 135.8, 133.5, 133.4, 129.6, 127.3, 126.2, 125.7, 124.7, 117.6, 117.5, 77.6, 62.4, 60.1, 37.3; IR (NaCl, neat) 2916, 1651, 1585, 1498, 1455 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{15}N_3OF$ 308.1199. Found 308.1202.



2-(2,4-DiFluorophenyl)-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azonia-cyclopenta[*c*]fluorene tetrafluoroborate (75): To a 100 mL round bottom flask was added 30 mL CH_2Cl_2 and 0.50 g (2.64 mmol) ***ent*-E4**. Trimethyloxonium tetrafluoroborate (.390 g, 2.64 mmol) was added and the solution allowed to stir at room temperature for 12 hours. 2,6-Difluorophenyl hydrazine was liberated from its hydrochloride salt by stirring in 1 M NaOH and CH_2Cl_2 and extracting (3 x 15 mL) with CH_2Cl_2. The organics were dried with brine and Na_2SO_4 and filtered, and concentrated. 2,6-Difluorophenyl hydrazine (0.380 g, 2.64 mmol) was added to the activated amide and stirred for 2 hours. Acetonitrile was added and the reaction was heated to 80 °C for 1 hour. This was concentrated, followed by addition of 10 mL chlorobenzene and 1 mL Trimethyl orthoformate (9.1 mmol). This was heated to 100 °C for 12 hours. The solvent was removed under reduced pressure and EtOAc was added. Upon stirring at ambient temperature for 1 hour, the desired product precipitated from the solution as a white solid

to provide 590 mg (54%); R_f (EtOAc) = 0.2; $[\alpha]_D^{23}$ = + 137.3° (acetonitrile, c = 11 mg/mL); ^{1}H NMR (400 MHz, acetone-D6) δ 11.04 (s, 1H), 7.87 (dd, 1H, *J* = 6.4, 6.4 Hz), 7.65 (d, 1H, *J* = 7.3 Hz), 7.58-7.25 (m, 5H), 6.25 (d, 1H, *J* = 2.3 Hz), 5.32 (d, 1H, *J* = 16.2 Hz), 5.21 (d, 1H, *J* = 16.8 Hz), 5.20-5.10 (m, 1H), 3.51 (dd, 1H, *J* = 17.3, 3.8 Hz), 3.25 (dd, 1H, *J* = 17.0, 0.0 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 158.1, 155.6, 151.3, 145.8, 141.1, 135.7, 135.0, 134.8, 129.8, 127.5, 125.8, 124.5, 113.4, 113.3, 77.6, 62.6, 60.1, 37.3; IR (NaCl, neat) 3105, 1702, 1585, 1476, 1251 cm^{-1}; m.p. 225-230 °C; HRMS (FAB+) calcd for $C_{18}H_{14}N_3OF_2$ 326.1105. Found 326.1102.

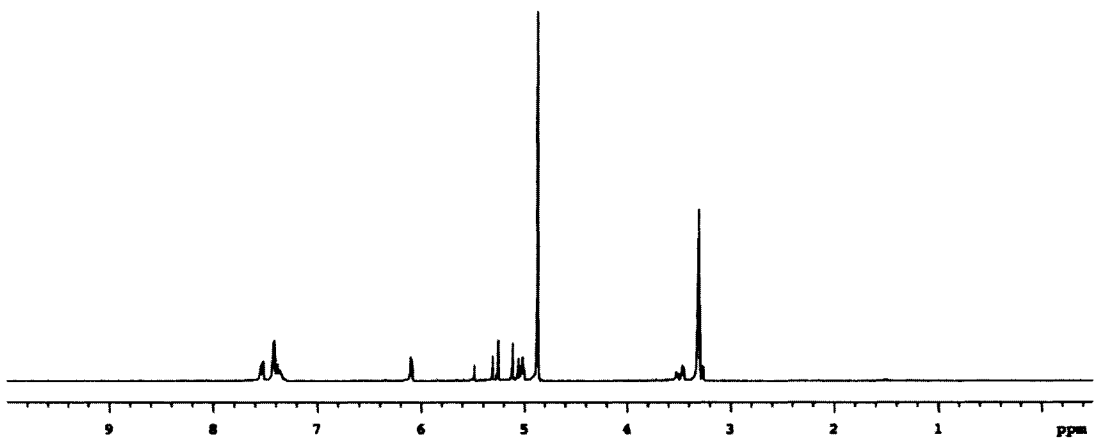
75 ^{1}H and ^{13}C NMR spectra



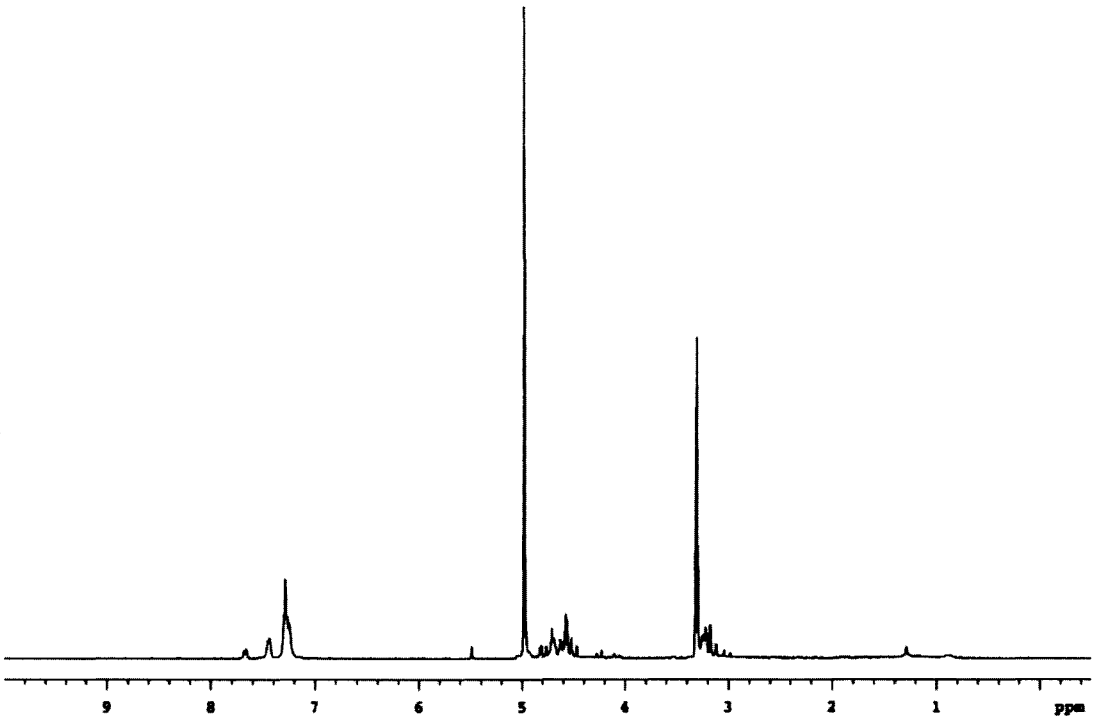
General Procedure for the determination of carbene basicity.

To a 5 mL round bottom flask was added CD_3OD (1 mL) and KH (0.005 g, 0.125 mmol). To this solution was added triazolium salt (0.065 mmol), and a proton NMR spectrum was collected. Organic acid (1.25 mmol) was added and another proton NMR spectrum was collected. This spectrum was compared against the spectrum of the salt in CD_3OD to determine whether the carbene had undergone protonation.

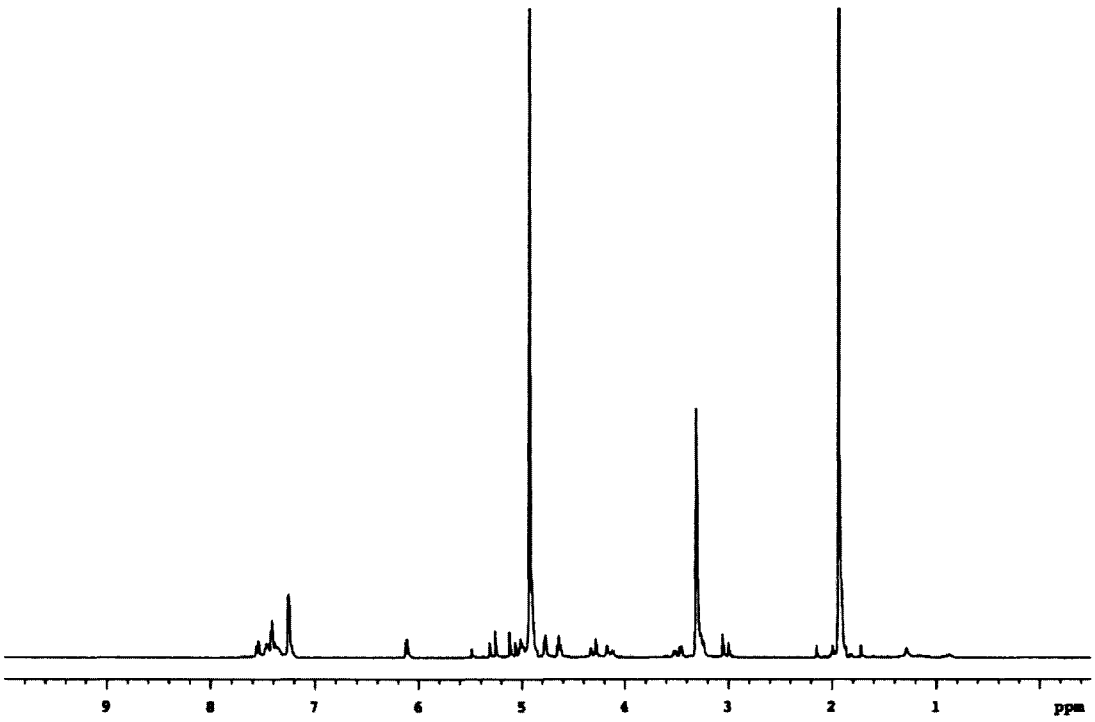
^1H NMR Spectrum of **67** in CD_3OD



67 ^{1}H NMR Spectrum in CD_3OD and KH



^{1}H NMR Spectrum of **67** in CD_3OD and KH after treatment with AcOH



Chapter 2 Experimental

Formation of Quaternary Stereocenters

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. Racemic material was prepared by the method of Ciganek[1] or with achiral catalysts **E1** and **E2** (see chapter 1 experimental) according to the general procedure.

Melting points were measured with a MelTemp II melting point apparatus outfitted with a Fluke 51 thermocouple and are uncorrected. Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. The purity of all compounds was determined to be >95% by ^1H NMR. ^1H NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometer at ambient temperature. Data are 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 =

[1] Ciganek, E. *Synthesis* **1995**, 1311-1314.

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, 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 11 and 21: The dithiane of the corresponding 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 23: 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) then slowly added. After addition complete ice bath removed and reaction allowed to warm to room temperature overnight. Reaction 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. Thiol carried on immediately. Thiol (2.38 mmol, 1 eq) in acetone (24 mL) was added

potassium carbonate (2.38 mmol, 1 eq). After 5 minutes methyl propionate (2.38 mmol, 1 eq) was added and followed by TLC. 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 alcohol were separated by flash chromatography (20% EtOAc in Hexanes) to afford 70% and 30% yields, respectively, and carried on immediately. Alcohol (1.89 mmol, 1 eq) dissolved in methylene chloride (20 mL) followed by addition of Dess-Martin periodinane. After 3h, reaction mixture poured into separatory funnel containing sodium thiosulfate (20 mL), sodium bicarbonate (20 mL), and ether (40 mL). Organic layer washed with water, brine, and dried over magnesium sulfate. Solution concentrated and purified via flash chromatography (20% EtOAc in Hexanes) to provide the desired aldehyde in 30% yield, as a clear oil.

General procedure for 25: Grignard addition into 2-indanone, followed by HCl elimination afforded the indene, which was ozonolyzed to the corresponding keto-aldehyde. Selective protection of the aldehyde was accomplished with 1,3 propanediol. Wittig reaction in refluxing dichlorobenzene, followed by acetal deprotection provided the substrate.

General procedure for 27 and 28: Alkylation of the thioacetal of salicylaldehyde with chloroacetone, followed by Wittig reaction in refluxing dichlorobenzene provided the olefin. The dithiane was subsequently removed with $Hg(O_2CCF_3)_2$ in acetonitrile.

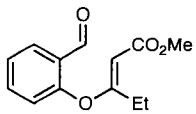
General procedure for 31, 34, 36, 38, and 40: The TBS ether of 5-hexynol was subjected to carboalumination conditions reported by Wipf. [2]The resulting vinylaluminum species was trapped with the corresponding aldehyde. Deprotection of the TBS ether with TBAF/HOAc in THF provided the diol which was oxidized with the Dess-Martin reagent to the keto-aldehyde.

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 minutes, then covered with argon. Substrate (0.1 mmol, 1 eq) was added in toluene (1 ml) via syringe, followed by addition of triethylamine (0.2 mmol, 2 eq to substrate) via syringe and the solution was stirred at ambient temperature under argon for 24 hours. 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 minutes. Substrate (0.01 mmol, 1 eq) was added in toluene (1 ml) via

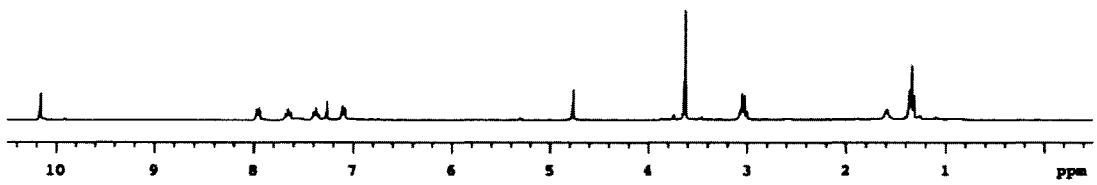
[2] Wipf, P.; Lim, S. *Angew. Chem. Int. Ed.* **1993**, *32*, 1068-1071.

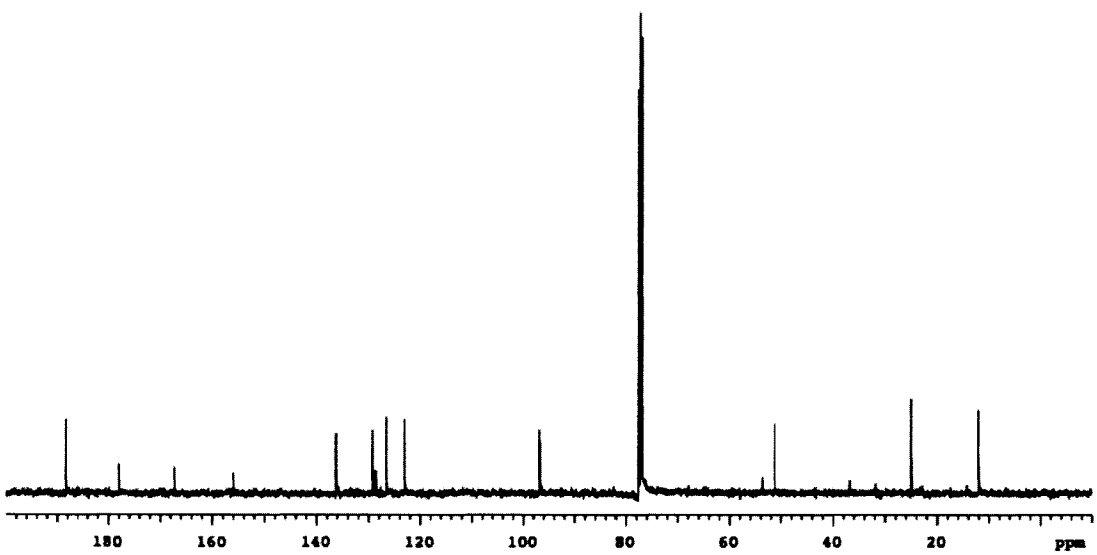
syringe and allowed to stir for 24 h at ambient temperature. The reaction was then poured onto a column of silica gel and eluted with a suitable solution of ethyl acetate in hexanes, to afford analytically pure product.

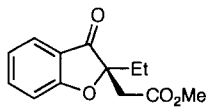


(*E*)-methyl 3-(2-formylphenoxy)pent-2-enoate (11): R_f = 0.46 (4:1 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.12 (s, 1H), 7.96-7.94 (m, 1H), 7.68-7.63 (m, 1H), 7.39-7.34 (m, 1H), 7.11-7.08 (m, 1H), 4.76 (s, 1H), 3.62 (s, 3H), 3.03 (q, 2H, J = 7.3 Hz), 1.33 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 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.

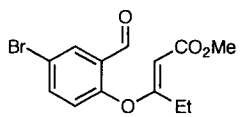
^{1}H and ^{13}C Spectra of **11**



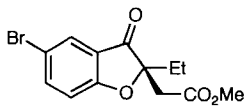




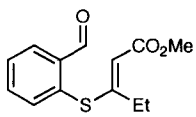
(R)-(2-Ethyl-3-oxo-2,3-dihydro-benzofuran-2-yl)-acetic acid methyl ester (13): According to the general procedure, aldehyde **11** (24.0 mg, 0.10 mmol) in toluene (1 mL) was added to catalyst **12** (9.0 mg, 0.02 mmol) followed by addition of triethylamine (0.029 mL, 0.20 mmol) and allowed to stir at ambient temperature for 24 hours. Flash column chromatography (6:1 hexanes to ethyl acetate) provided 23.0 mg (96%) of **13** as a clear oil: Rf (3:1 hexanes to ethyl acetate) = 0.24; $[\alpha]_D^{25}$ = -74° (CH_2Cl_2, c = 10 mg/mL); HPLC analysis - Chiracel OD-H column, 97:3 hexanes to isopropanol 1.0 ml/ min. Major enantiomer: 20.4 minutes, minor enantiomer: 32.6 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, 1H, *J* = 8.4, 1.5 Hz), 7.59 (ddd, 1H, *J* = 8.1, 7.1, 1.8 Hz), 7.05 - 7.10 (m, 2H), 3.51 (s, 3H), 3.02 (d, 1H, *J* = 16.0 Hz), 2.94 (d, 1H, *J* = 16.0 Hz), 1.89 (q, 2H, *J* = 7.3 Hz), 0.83 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 171.8, 169.2, 137.9, 124.3, 122.0, 113.1, 89.2, 76.7 52.1, 40.6, 30.0, 7.7; IR (NaCl, neat) 2974, 2962, 1721, 1614, 1464 cm^{-1}; HRMS (EI+) calcd for $C_{13}H_{14}O_4$, 234.0892. Found 234.0887.



(*E*)-methyl 3-(4-bromo-2-formylphenoxy)pent-2-enoate (21): R_f = 0.45 (4:1 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.05 (t, 1H, *J* = 1.83 Hz), 7.76-7.72 (m, 1H), 7.02-6.98 (m, 1H), 4.76 (s, 1H), 3.63 (s, 3H), 3.01 (q, 2H, *J* = 7.3 Hz) 1.31 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9, 177.6, 166.9, 154.8, 138.9, 131.9, 129.8, 124.9, 119.9, 97.4, 51.4, 24.8,11.9; IR (NaCl, neat) 2976, 2940, 1714, 1691, 1621, 1471 cm^{-1}; HMRS (FAB+) calcd for $C_{13}H_{13}BrO_4$, 312.0000. Found 312.0070.

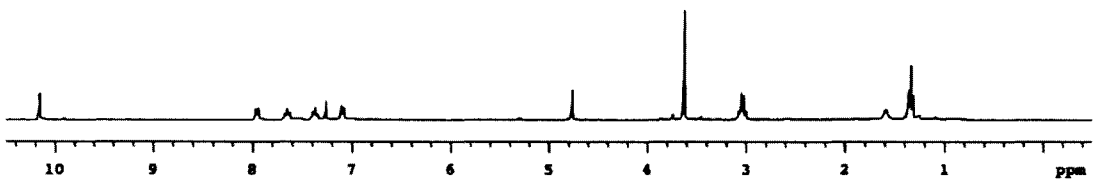


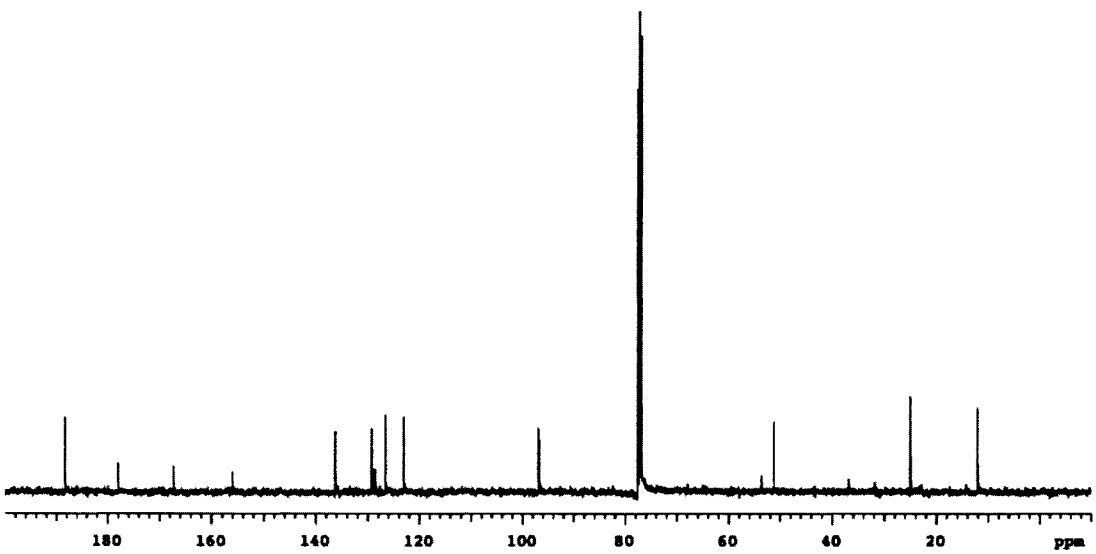
(R)-(5-Bromo-2-ethyl-3-oxo-2,3-dihydro-benzofuran-2-yl)-acetic acid methyl ester (22): According to the general procedure, aldehyde **21** (37.0 mg, 0.123 mmol) in toluene (1 mL) was added to catalyst **12** (12.0 mg, 0.025 mmol) followed by addition of triethylamine 0.036 mL (0.25 mmol) and allowed to stir at ambient temperature for 24 hours. Flash column chromatography (6:1 hexanes to ethyl acetate) provided 34.0 mg (92%) of **22** as a clear oil: Rf (4:1 hexanes to ethyl acetate) = 0.38; $[\alpha]_D^{25}$ = -44° (CH_2Cl_2, c = 15 mg/mL); HPLC analysis - Chiracel OD-H column, 90:10 hexanes to isopropanol 1.0 ml/ min. Major enantiomer: 9.0 minutes, minor enantiomer: 27.6 minutes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, 1H, *J* = 2.1 Hz), 7.63 (dd, 1H, *J* = 8.7, 2.1 Hz), 6.97 (d, 1H, *J* = 8.7 Hz), 3.50 (s, 3H), 3.01 (d, 1H, *J* = 16.6 Hz), 2.94 (d, 1H, *J* = 16.6 Hz), 1.83 (q, 2H, *J* = 7.5 Hz), 0.80 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 170.5, 169.2, 140.4, 126.9, 123.9, 114.9, 114.5, 90.1, 52.1, 40.5, 30.0, 7.5; IR (NaCl, neat) 2973, 1726, 1608, 1464, 1272, 1171 cm^{-1}.

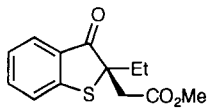


(*E*)-methyl 3-(2-formylphenylthio)pent-2-enoate (23): R_f = 0.40 (4:1 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) d 10.4 (s, 1H), 8.07-8.03 (m, 1H), 7.70-7.58 (m, 3H), 5.04 (s, 1H), 3.60 (s, 3H), 2.91 (q, 2H, *J* = 7.3 Hz), 1.29 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 191.3, 166.2, 164.8, 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.

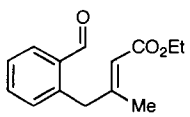
^{1}H and ^{13}C Spectra of **23**







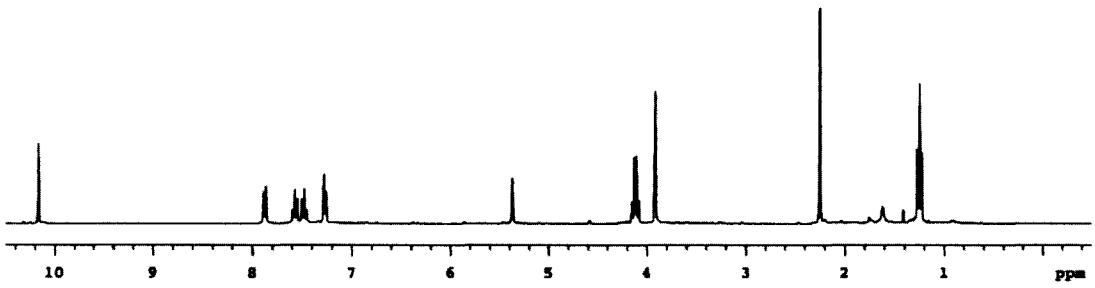
(R)-(2-Ethyl-3-oxo-2,3-dihydro-benzo[*b*]thiophen-2-yl)-acetic acid methyl ester (24): According to the general procedure, aldehyde **23** (20.0 mg, 0.080 mmol) in toluene (1 mL) was added to catalyst **12** (7.5 mg, 0.016 mmol) followed by addition of triethylamine (0.023 mL, 0.16 mmol) and allowed to stir at ambient temperature for 24 hours. Flash column chromatography (6:1 hexanes to ethyl acetate) provided 19.0 mg (95%) of **24** as a white crystalline solid: Rf (3:1 hexanes to ethyl acetate) = 0.26; $[\alpha]_D^{25}$ = +10° ($CHCl_3$, c = 15 mg/mL); HPLC analysis - Chiracel OD-H column, 97:3 hexanes to isopropanol 0.5 ml/ min. Minor enantiomer: 19.1 minutes, major enantiomer: 33.7 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, 1H, *J* = 7.7 Hz), 7.53 (dd, 1H, *J* = 7.3, 0 Hz), 7.38 (d, 1H, *J* = 7.7 Hz), 7.2 (dd, 1H, *J* = 7.3, 0 Hz), 3.57 (s, 3H), 3.07 (d, 1H, *J* = 16.9 Hz), 2.97 (d, 1H, *J* = 16.5 Hz), 1.94 (q, 2H, *J* = 7.3 Hz), 0.88 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 170.5, 152.2, 135.8, 131.5, 126.8, 124.9, 124.2, 63.4, 52.0, 42.6, 34.3, 9.0; IR (NaCl, neat) 2964, 1730, 1701, 1594, 1429 cm^{-1}; HRMS (EI+) calcd for $C_{13}H_{14}O_3S$, 250.0664. Found 250.0653.

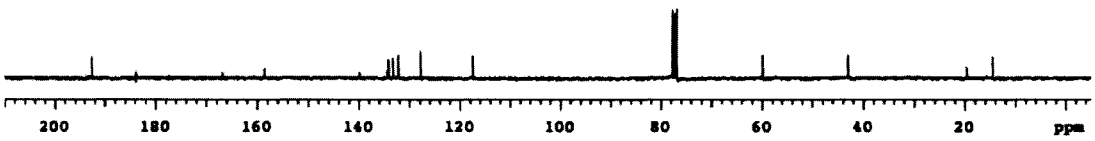


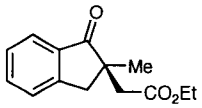
(*E*)-ethyl 4-(2-formylphenyl)-3-methylbut-2-enoate (25): R_f = 0.50 (3:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 7.87 (d, 1H, *J* = 7.5 Hz), 7.60-7.45 (m, 2H), 7.27 (d, 1H, *J* = 6.59 Hz), 5.37 (s, 1H), 4.12 (q, 2H, *J* = 7.14 Hz), 3.92 (s, 2H), 2.25 (s, 3H), 1.25 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 183.9, 158.6, 139.9, 134.4, 134.1, 133.2, 132.2, 127.8, 117.4, 59.9, 43.0,

19.6, 14.5; IR (NaCl, neat) 2975, 2737, 1702, 1636, 1215 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{16}O_3$, 232.1099. Found 232. 1166.

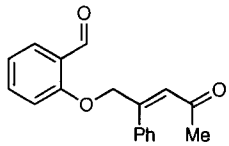
^{1}H and ^{13}C Spectra of **25**



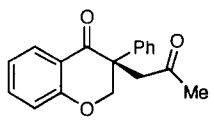




(R)-(2-Methyl-1-oxo-indan-2-yl)-acetic acid ethyl ester (26): According to the general procedure, aldehyde **25** (20.0 mg, 0.085 mmol) in toluene (1 mL) was added to catalyst **12** (8.0 mg, 0.017 mmol) followed by addition of triethylamine (0.025 mL, 0.17 mmol) and allowed to stir at ambient temperature for 24 hours. Flash column chromatography (6:1 hexanes to ethyl acetate) provided 19.0 mg (95%) of **26** as a clear oil: $[\alpha]_D^{25}$ = +22° (EtOH, c = 6 mg/mL); HPLC analysis - Chiracel OD-H column, 97:3 hexanes to isopropanol 1.0 ml/ min. Minor enantiomer: 7.2 minutes, Major enantiomer: 11.1 minutes. Spectral data matched literature description.[3]



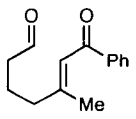
(*E*)-2-(4-oxo-2-phenylpent-2-enyloxy)benzaldehyde (28): R_f = 0.15 (3:1 Hex/EtOAc), ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.43 (s, 1H), 7.85 (dd, 1H, *J* = 7.7, 1.8 Hz), 7.55 (ddd, 1H, *J* = 7.3, 7.3, 1.8 Hz), 7.38-7.50 (m, 3H), 7.22-7.33 (m, 2H), 7.08 (dd, 1H, 7.3, 7.3 Hz), 6.98 (dd, 1H, *J* = 8.4, 0 Hz), 4.89 (s, 2H), 1.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 200.0, 189.5, 160.3, 149.1, 136.5, 136.2, 129.9, 129.2, 129.1, 128.1, 127.8, 125.4, 121.8, 113.0, 71.6, 30.9; IR (NaCl, neat) 2858, 1723, 1680, 1607, 1223 cm^{-1}.



(R)-3-(2-Oxo-propyl)-3-phenyl-chroman-4-one (29): According to the general procedure, aldehyde **28** (20.0 mg, 0.071 mmol) in toluene

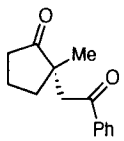
[3] Iwaya, K.; Tamura, T.; Nakamura, M.; Hasegawa, E. *Tetrahedron Lett.* **2003**, *44*, 9317.

(1 mL) was added to catalyst **12** (3.5 mg, 0.007 mmol) followed by addition of triethylamine (0.010 mL, 0.070 mmol) and allowed to stir at ambient temperature for 12 hours. At this time, another aliquot of catalyst (3.5 mg, 0.007 mmol) was added with another 2 eq triethylamine (0.010 mL, 0.070 mmol) and allowed to stir for another 12 hours at 25 °C. Flash column chromatography (6:1 hexanes to ethyl acetate) provided 11.0 mg (55%) of **29** as a colorless oil: Rf (2:1 hexanes to ethyl acetate) = 0.34; $[\alpha]_D^{25}$ = -88° (CH_2Cl_2, c = 8 mg/mL); HPLC analysis - Chiracel OD-H column, 95:5 hexanes to isopropanol 1.0 ml/ min. Minor enantiomer: 14.3 minutes, major enantiomer: 19.5 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, 1H, *J* = 7.7, 1.3 Hz), 7.41 (d, 2H, *J* = 7.9 Hz), 7.36 (ddd, 1H, *J* = 8.7, 1.5, 0 Hz), 7.29 (dd, 2H, *J* = 7.3, 0 Hz), 7.21 (dd, 1H, *J* = 7.2, 0 Hz), 6.94 (dd, 1H, *J* = 7.2, 0 Hz), 6.83 (d, 1H, *J* = 8.3 Hz), 5.10 (d, 1H, *J* = 12.1 Hz), 4.99 (d, 1H, *J* = 12.0 Hz), 3.18 (d, 1H, *J* = 17.5 Hz), 2.99 (d, 1H, J = 17.5 Hz), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 193.2, 161.1, 136.7, 136.1, 129.1, 128.1, 128.0, 126.9, 121.5, 120.3, 117.8, 71.5, 51.7, 49.1, 31.3; IR (NaCl, neat) 2923, 1717, 1684, 1606, 1408, 1458 cm^{-1}; HRMS (FAB+) calcd for M+H, 281.1178. Found 281.1175.

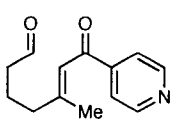


(E)-5-methyl-7-oxo-7-phenylhept-5-enal (31): R_f = 0.26 (3:1 Hex/EtOAc), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.89 (d, 2H, *J* = 9.4 Hz), 7.50 (m, 1H), 7.41 (m, 2H), 6.70 (s, 1H), 2.60 (t, 2H, *J* = 7.2 Hz), 2.27 (t, 2H, *J* = 7.2 Hz), 2.17 (s, 3H), 1.89 (p, 2H, *J* = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 191.8,

158.6, 139.3, 132.6, 128.7, 128.4, 121.4, 43.3, 40.5, 37.3, 20.2, 19.8; IR (NaCl, neat) 2921, 1717, 1657, 1609, 1234 cm^{-1}.



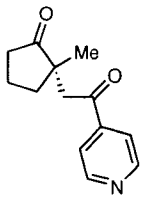
(S)-2-Methyl-2-(2-oxo-2-phenyl-ethyl)-cyclopentanone (32): According to the general procedure, catalyst **12** (5.5 mg, 0.012 mmol) in toluene (1 mL) was treated with KHMDS (0.5M in toluene) (0.024 mL, 0.012 mmol) and allowed to stir at ambient temperature for 5 minutes. Aldehyde **31** (13.0 mg, 0.060 mmol) in toluene (1 mL) was added via syringe and the reaction was stirred for 24 h at 25 °C. Flash column chromatography (6:1 hexanes to ethyl acetate) provided 11.0 mg (85%) of **32** as a white solid: Rf (3:1 hexanes to ethyl acetate) = 0.35; $[\alpha]_D^{25}$ = -4° (CH_2Cl_2, c = 10 mg/mL); HPLC analysis - Chiracel OD-H column, 97:3 hexanes to isopropanol 1.0 ml/ min. Minor enantiomer: 9.8 minutes, Major enantiomer: 11.2 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, 2H, *J* = 7.3 Hz), 7.55 (dd, 1H, *J* = 6.2, 0 Hz), 7.44 (dd, 2H, *J* = 7.7, 0 Hz), 3.36 (d, 1H, *J* = 20.0 Hz), 3.29 (d, 1H, *J* = 20.0 Hz), 2.68 (ddd, 1H, *J* = 18.7, 9.2, 1.5 Hz), 2.39 (dddd, 1H, J = 18.7, 6.6, 2.2, 2.2 Hz), 1.77 – 2.22 (m, 4H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 223.2, 198.0, 136.9, 133.4, 128.8, 128.1, 46.7, 46.1, 37.4, 35.1, 23.4, 19.2; IR (NaCl, neat) 2955, 1727, 1679, 1398, 1356 cm^{-1}; HRMS (EI+) calcd for $C_{14}H_{16}O_2$, 216.1150. Found 216.1147.



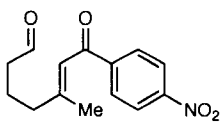
(*E*)-5-methyl-7-oxo-7-(pyridin-4-yl)hept-5-enal (34): R_f = 0.37 (EtOAc), ^1H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.81 (bs, 2H), 7.72 (s, 2H), 6.72 (s, 1H), 2.57 (dd, 2H, *J* = 7.1, 7.1 Hz), 2.34 (dd, 2H, *J* = 7.1, 7.1 Hz), 2.27

(s, 3H), 1.96 (ddd, 2H, J = 15.0, 7.3, 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 201.8, 190.2, 183.9, 162.6, 151.0, 142.8, 120.2, 43.2, 40.9, 20.2, 20.0; IR (NaCl, neat) 2930, 1724, 1665, 1607, 1578 cm^{-1}.

(S)-2-Methyl-2-(2-oxo-2-pyridin-4-yl-ethyl)-cyclopentanone (35):



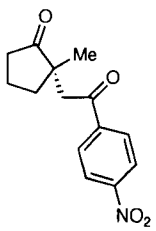
According to the general procedure, catalyst **12** (8.5 mg, 0.018 mmol) in toluene (1 mL) was treated with KHMDS (0.5M in toluene) (0.036 mL, 0.018 mmol) and allowed to stir at ambient temperature for 5 minutes. Aldehyde **34** (20.0 mg, 0.092 mmol) in toluene (1 mL) was added via syringe and the reaction was stirred for 24 h at 25 °C. Flash column chromatography (1:1 hexanes to ethyl acetate) provided 17.0 mg (85%) of **35** as a colorless oil: Rf (ethyl acetate) = 0.28; $[\alpha]_D^{25}$ = -0.8° (CH_2Cl_2, c = 15 mg/mL); HPLC analysis - Chiracel OB-H column, 90:10 hexanes to isopropanol 1.0 ml/ min. Minor enantiomer: 25.0 minutes, major enantiomer: 28.1 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (bs, 2H), 7.69 (bs, 2H), 3.32 (d, 1H, J = 18.7 Hz), 3.27 (d, 1H, J = 19.0 Hz), 2.54 – 2.68 (m, 1H), 2.40 (dddd, 1H, J = 18.3, 7.7, 0.0, 0.0 Hz), 1.77 – 2.20 (m, 4H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 222.6, 197.5, 151.1, 142.7, 121.1, 46.7, 46.1, 37.3, 34.9, 23.2, 19.1; IR (NaCl, neat) 2964, 1736, 1697, 1408, 1356, 1222 cm^{-1}; HRMS (Fab+) calcd for M+H, 218.1181. Found 218.1172.



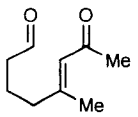
(*E*)-5-methyl-7-(4-nitrophenyl)-7-oxohept-5-enal (36): R_f = 0.14 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.28 (d, 2H, J = 8.7 Hz), 8.02 (d, 2H, J = 8.9 Hz), 6.70 (s, 1H), 2.51 (t, 2H, J = 7.0), 2.31 (t, 2H, J = 7.0 Hz), 2.22 (s, 3H), 1.90 (p, 2H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$)

201.7, 189.5, 162.3, 150.0, 144.1, 129.2, 123.9, 120.5, 43.2, 40.8, 37.3, 20.2; IR (NaCl, neat) 2931, 1731, 1658, 1607, 1527 cm^{-1}.

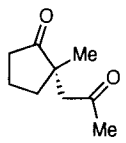
(S)-2-Methyl-2-[2-(4-nitro-phenyl)-2-oxo-ethyl]-cyclopentanone (37):



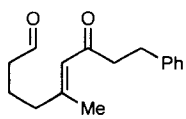
According to the general procedure, catalyst **12** (7.0 mg, 0.015 mmol) in toluene (1 mL) was treated with KHMDS (0.5M in toluene) (0.030 mL, 0.015 mmol) and allowed to stir at ambient temperature for 5 minutes. Aldehyde **36** (20.0 mg, 0.077 mmol) in toluene (1 mL) was added via syringe and the reaction was stirred for 24 h at 25 °C. Flash column chromatography (4:1 hexanes to ethyl acetate) provided 18.0 mg (90%) of **20** as a yellow solid: Rf (2:1 hexanes to ethyl acetate) = 0.40; $[\alpha]_D^{25}$ = -17° ($CHCl_3$, c = 14 mg/mL); HPLC analysis - Chiracel OD-H column, 97:3 hexanes to isopropanol 1.0 ml/ min. Minor enantiomer: 36.3 minutes, major enantiomer: 44.8 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, 2H, J = 9.0 Hz), 8.05 (d, 2H, J = 8.4 Hz), 3.36 (d, 1H, J = 18.3 Hz), 3.30 (d, 1H, J = 18.3 Hz), 2.61 (ddd, 1H, J = 19.0, 10.9, 1.5 Hz), 2.40 (dddd J = 18.8, 8.3, 0, 0 Hz), 2.02 – 2.19 (m, 2H,), 1.85 – 1.98 (m, 1H), 1.77 – 1.84 (m, 1H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 222.6, 196.1, 150.6, 141.3, 129.2, 124.1, 47.0, 46.2, 37.3, 34.9, 23.3, 19.1; IR (NaCl, neat) 3107, 2963, 1736, 1690, 1524, 1345 cm^{-1}; HRMS (Fab+) calcd for M+H, 262.1079. Found 262.1068.



(*E*)-5-methyl-7-oxooct-5-enal (38): R_f = 0.14 (4:1 Hex/EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 6.06 (s, 1H), 2.46 (t, 2H, J = 7.3 Hz), 2.17-2.11 (m, 8H), 1.83 (p, 2H, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 201.9, 199.0, 157.2, 124.3, 43.2, 40.3, 32.0, 10.8, 19.3; IR (Neat, $CDCl_3$) 2931, 1724, 1687, 1607, 1360 cm^{-1}.



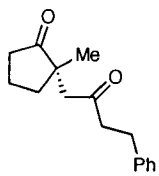
(S)-2-Methyl-2-(2-oxo-propyl)-cyclopentanone (39): According to the general procedure, catalyst **12** (9.5 mg, 0.020 mmol) in toluene (1 mL) was treated with KHMDS (0.5M in toluene) (0.040 mL, 0.020 mmol) and allowed to stir at ambient temperature for 5 minutes. Aldehyde **38** (16.0 mg, 0.10 mmol) in toluene (1 mL) was added via syringe and the reaction was stirred for 24 h at 25 °C. Flash column chromatography (6:1 hexanes to ethyl acetate) provided 13.0 mg (82%) of **39** as a colorless oil: $[\alpha]_D^{25}$ = +11° (EtOH, c = 10 mg/mL); Gas chromatography analysis- Chiraldex B-DM column, gas flow 3ml/min with constant 110 °C oven temperature. Minor enantiomer: 12.9 min, major enantiomer: 14.5 minutes. Spectral data matched literature description.[4]



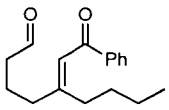
(*E*)-5-methyl-7-oxo-9-phenylnon-5-enal (40): R_f = 0.22 (4:1 Hex/EtOAc), ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, 1H, J = 1.1 Hz), 7.30-7.16 (m, 5H), 6.03 (s, 1H), 2.92 (dd, 2H, J = 8.1, 7.0 Hz), 2.76 (dd, 2H, J = 8.1, 7.0 Hz), 2.44 (ddd, 2H, J = 8.4, 7.3, 1.5 Hz), 2.17-2.12 (m, 5H), 1.81 (p, 2H, J = 7.7 Hz); ^{13}C

[4] Thominiaux, C.; Roussé, S.; Desmaële, D.; d'Angelo, J.; Riche, C. *Tetrahedron: Asymmetry.* **1999**, *10*, 2015.

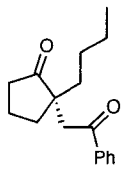
(75 MHz, $CDCl_3$) δ 202.0, 200.2, 157.5, 141.8, 128.7, 128.6, 126.2, 123.9, 46.1, 43.2, 40.4, 30.3, 19.9, 19.5; IR (NaCl, neat) 2938, 1730, 1680, 1614, 1454 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{20}O_2$, 244.1463. Found 244.1542.



(S)-2-Methyl-2-(2-oxo-4-phenyl-butyl)-cyclopentanone (41): According to the general procedure, catalyst **12** (6.0 mg, 0.013 mmol) in toluene (1 mL) was treated with KHMDS (0.5M in toluene) (0.026 mL, 0.013 mmol) and allowed to stir at ambient temperature for 5 minutes. Aldehyde **40** (16.0 mg, 0.066 mmol) in toluene (1 mL) was added via syringe and the reaction was stirred for 24 h at 25 °C. Flash column chromatography (4:1 hexanes to ethyl acetate) provided 10.0 mg (63%) of the **41** as a colorless oil: Rf (3:1 hexanes to ethyl acetate) = 0.38; $[\alpha]_D^{25}$ = +22° (CH_2Cl_2, c = 6 mg/mL); HPLC analysis - Chiraldex B-DM capillary gas chromatography column, 150 °C constant oven temperature, constant gas flow 3.0 ml/ min. Minor enantiomer 119 minutes: major enantiomer: 125 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (dd, 2H, *J* = 6.6, 0 Hz), 7.19 (d, 1H, *J* = 7.4 Hz), 7.19 (d, 2H, *J* = 6.8 Hz), 2.76 – 2.80 (m, 3H), 2.58 – 2.69 (m, 3H), 2.51 (ddd, 1H, *J* = 18.3, 9.5, 1.8 Hz), 2.33 (dddd, 1H, *J* = 18.7, 7.3, 2.2, 2.2 Hz), 1.65 – 2.10 (m, 4H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 223.0, 208.0, 141.0, 128.7, 128.5, 126.3, 50.7, 46.0, 44.6, 37.4, 35.0, 29.8, 23.1, 19.1; IR (NaCl, neat) 2961, 1736, 1713, 1454, 1072 cm^{-1}; HRMS (EI+) calcd for $C_{16}H_{20}O_2$, 244.1463. Found 244.1474.

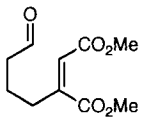


(E)-5-(2-oxo-2-phenylethylidene)octanal (42): R_f = 0.21 (4:1 Hex/EtOAc), ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.92 (d, 2H, J=7.3 Hz) 7.48-7.58 (m, 1H), 7.40-7.38 (dd, 2H, J = 8.1, 8.1 Hz). 6.68 (s, 1H), 2.56 (ddd, 2H, J = 15.7, 7.3, 7.3 Hz), 2.30 (dd, 2H, J = 7.3, 7.3), 1.91 (ddd, 2H, J = 14.6, 7.3, 7.3 Hz), 1.56-1.30 (m, 6H), 0.92 (dd, 3H, J = 6.9, 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 192.0, 163.0, 139.4, 132.6, 128.7, 128.4, 121.1, 43.4, 38.0, 32.7, 31.0, 23.3, 20.3, 14.2; IR (NaCl, neat) 2958, 2923, 1713, 1661, 1598 cm $^{-1}$.



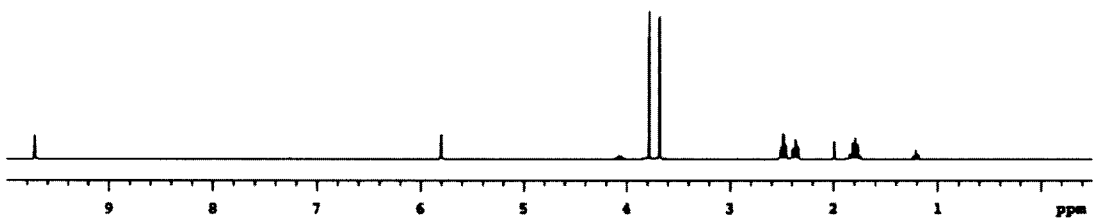
(S)-2-Butyl-2-(2-oxo-2-phenyl-ethyl)-cyclopentanone (43): According to the general procedure, catalyst **12** (5.0 mg, 0.011 mmol) in toluene (1 mL) was treated with KHMDS (0.5M in toluene) (0.022 mL, 0.011 mmol) and allowed to stir at ambient temperature for 5 minutes. Aldehyde **42** (14.0 mg, 0.055 mmol) in toluene (1 mL) was added via syringe and the reaction was stirred for 24 h at 25 °C. Flash column chromatography (6:1 hexanes to ethyl acetate) provided 10.0 mg (71%) of **43** as a colorless oil: Rf (4:1 hexanes to ethyl acetate) = 0.28; $[\alpha]_D^{25}$ = -30° (CH_3CN, c = 7 mg/mL); HPLC analysis - Chiracel OD-H column, 97:3 hexanes to isopropanol 1.0 ml/ min. Major enantiomer: 7.4 minutes, minor enantiomer: 9.2 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, 2H, J = 7.3 Hz), 7.55 dd, (1H, J = 7.3, 0 Hz), 7.44 (dd, 2H, J = 7.7, 0 Hz), 3.37 (d, 1H, J = 18.3 Hz), 3.30 (d, 1H, J = 18.0 Hz), 2.70 (ddd, 1H, J = 19.0, 9.5, 1.5 Hz), 2.35 (dddd, 1H, J = 18.7, 7.3, 2.2, 2.2 Hz), 1.99 – 2.14 (m, 2H), 1.79 – 1.98 (m, 2H), 1.14 – 1.54 (m, 6H) 0.92 (t, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 223.4, 198.2, 137.0, 133.4, 128.7, 128.2, 49.4, 45.3, 37.8, 36.4, 33.7, 26.7, 23.5, 19.1,

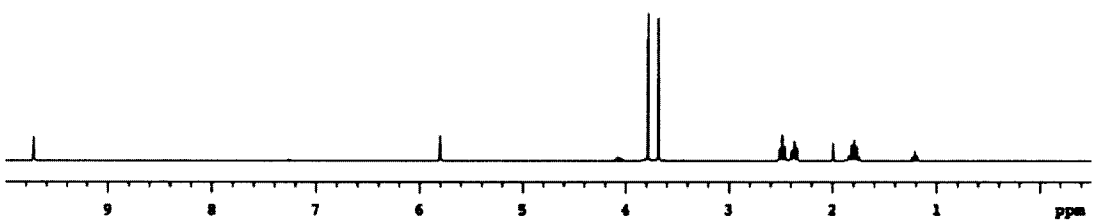
14.2; IR (NaCl, neat) 2957, 2929, 2858, 1734, 1685, 1158 cm^{-1}; HRMS (EI+) calcd for $C_{17}H_{22}O_2$, 258.1620, Found 258.1611.

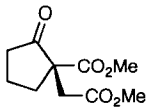


(*Z*)-dimethyl 2-(4-oxobutyl)but-2-enedioate (44): R_f = 0.11 (4:1 Hex/EtOAc), ^1H NMR (300 MHz, $CDCl_3$), δ 7.93 (s, 1H), 5.80 (s, 1H), 3.78 (s, 1H). 3.70 (s, 1H), 2.48 (dd, 2H, *J* = 7.3, 7.3 Hz), 2.30 (dd, 2H, *J* = 7.3, 7.3), 2.36 (dd, 2H, *J* = 9.3, 9.3 Hz), 1.79 (dddd, 2H, *J* = 7.7, 7.7, 7.7, 7.7, Hz), 0.92; ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 169.1, 165.4, 149.4, 120.4, 52.6, 52.1, 42.7, 33.5, 19.6; IR (NaCl, neat) 2954, 2836, 1728, 1649, 1434 cm^{-1}.

^{1}H and ^{13}C Spectra of **44**







(S)-1-Methoxycarbonylmethyl-2-oxo-cyclopentanecarboxylic acid methyl ester (45): According to the general procedure, catalyst **17** (4.0 mg, 0.013 mmol) in toluene (1 mL) was treated with KHMDS (0.5M in toluene) (0.026 mL, 0.013 mmol) and allowed to stir at ambient temperature for 5 minutes. Aldehyde **44** (14.0 mg, 0.065 mmol) in toluene (1 mL) was added via syringe and the reaction was stirred for 12 h at 25°C. Flash column chromatography (4:1 hexanes to ethyl acetate) provided 12.0 mg (86%) of **46** as a colorless oil: $[\alpha]_D^{25} = -20°$ (EtOH, c = 10 mg/mL); Gas chromatography analysis – Chiraldex B-PH column with constant 110 °C oven temperature and constant flow of 1 ml/min. Major enantiomer: 169.3 minutes, minor enantiomer: 170.6 min. Spectral data matched literature description.[5]

[5] Matsui, J.; Bando, M.; Kido, M.; Takeuchi, Y.; Mori, K. *Eur. J. Org. Chem.* **1999**, 2183.

X-ray structure of **24**

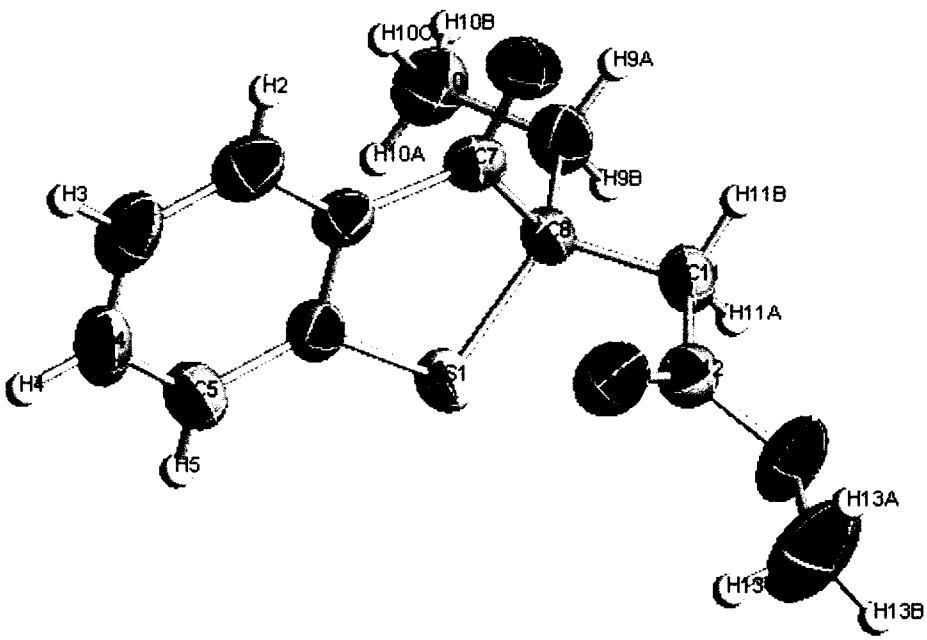


Table 1. Crystal data and structure refinement for **24**

Identification code	rov6m	
Empirical formula	C13 H14 O3 S	
Formula weight	250.30	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.2852(11) Å	α= 90°.
	b = 9.4086(16) Å	β= 90°.
	c = 20.882(4) Å	γ = 90°.
Volume	1234.8(4) $Å^3$	
Z	4	
Density (calculated)	1.346 Mg/m^3	
Absorption coefficient	0.255 mm^{-1}	
F(000)	528	
Crystal size	0.40 x 0.38 x 0.10 mm^3	
Theta range for data collection	1.95 to 28.35∞.	
Index ranges	-8<=h<=8, -12<=k<=12, -27<=l<=27	
Reflections collected	11659	
Independent reflections	3057 [R(int) = 0.0260]	
Completeness to theta = 28.35°	99.6 %	
Max. and min. transmission	0.9749 and 0.9048	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3057 / 0 / 156	
Goodness-of-fit on F^2	1.055	
Final R indices [I>2sigma(I)]	R1 = 0.0348, wR2 = 0.0815	
R indices (all data)	R1 = 0.0456, wR2 = 0.0856	
Absolute structure parameter	0.00(7)	
Largest diff. peak and hole	0.168 and -0.185 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for rov6m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	9781(1)	5632(1)	8549(1)	44(1)
O(1)	4653(2)	3615(1)	8071(1)	54(1)
O(2)	5034(3)	5916(1)	9280(1)	58(1)
O(3)	4879(3)	8204(1)	9023(1)	68(1)
C(1)	7770(3)	3182(2)	8690(1)	39(1)
C(2)	7433(3)	1799(2)	8911(1)	52(1)
C(3)	8917(4)	1194(2)	9305(1)	61(1)
C(4)	10721(4)	1937(2)	9483(1)	60(1)
C(5)	11105(3)	3295(2)	9259(1)	51(1)
C(6)	9606(3)	3909(2)	8865(1)	40(1)
C(7)	6351(3)	3994(2)	8275(1)	40(1)
C(8)	7334(2)	5425(2)	8077(1)	38(1)
C(9)	7841(3)	5364(2)	7356(1)	49(1)
C(10)	9335(4)	4184(2)	7158(1)	62(1)
C(11)	5794(3)	6650(2)	8205(1)	46(1)
C(12)	5211(3)	6835(2)	8896(1)	44(1)
C(13)	4125(6)	8541(3)	9660(1)	103(1)

Table 3. Bond lengths [Å] and angles [°] for rov6m.

S(1)-C(6)	1.7532(16)
S(1)-C(8)	1.8363(16)
O(1)-C(7)	1.203(2)
O(2)-C(12)	1.186(2)
O(3)-C(12)	1.331(2)
O(3)-C(13)	1.447(3)
C(1)-C(6)	1.390(2)
C(1)-C(2)	1.396(2)
C(1)-C(7)	1.460(2)
C(2)-C(3)	1.369(3)
C(3)-C(4)	1.383(3)
C(4)-C(5)	1.381(3)
C(5)-C(6)	1.379(2)
C(7)-C(8)	1.538(2)
C(8)-C(11)	1.528(2)
C(8)-C(9)	1.541(2)
C(9)-C(10)	1.512(2)
C(11)-C(12)	1.498(2)
C(6)-S(1)-C(8)	92.95(8)
C(12)-O(3)-C(13)	116.59(16)
C(6)-C(1)-C(2)	119.90(17)
C(6)-C(1)-C(7)	113.90(14)
C(2)-C(1)-C(7)	126.19(17)
C(3)-C(2)-C(1)	118.9(2)
C(2)-C(3)-C(4)	120.66(18)
C(5)-C(4)-C(3)	121.33(19)
C(6)-C(5)-C(4)	118.05(19)
C(5)-C(6)-C(1)	121.18(16)
C(5)-C(6)-S(1)	124.71(15)
C(1)-C(6)-S(1)	114.11(12)
O(1)-C(7)-C(1)	126.65(15)
O(1)-C(7)-C(8)	121.40(15)
C(1)-C(7)-C(8)	111.84(14)

C(11)-C(8)-C(7)	111.03(13)
C(11)-C(8)-C(9)	109.22(13)
C(7)-C(8)-C(9)	108.23(13)
C(11)-C(8)-S(1)	110.94(11)
C(7)-C(8)-S(1)	106.57(10)
C(9)-C(8)-S(1)	110.80(12)
C(10)-C(9)-C(8)	115.03(14)
C(12)-C(11)-C(8)	114.23(13)
O(2)-C(12)-O(3)	123.74(15)
O(2)-C(12)-C(11)	126.15(15)
O(3)-C(12)-C(11)	110.10(14)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for rov6m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	41(1)	40(1)	51(1)	5(1)	-6(1)	-5(1)
O(1)	47(1)	59(1)	57(1)	-7(1)	-7(1)	-8(1)
O(2)	75(1)	51(1)	49(1)	2(1)	7(1)	-1(1)
O(3)	91(1)	47(1)	67(1)	-6(1)	18(1)	18(1)
C(1)	47(1)	36(1)	35(1)	-1(1)	4(1)	-2(1)
C(2)	67(1)	41(1)	49(1)	-1(1)	8(1)	-6(1)
C(3)	90(2)	41(1)	52(1)	9(1)	11(1)	10(1)
C(4)	75(1)	54(1)	49(1)	9(1)	-3(1)	22(1)
C(5)	51(1)	56(1)	46(1)	1(1)	-6(1)	7(1)
C(6)	46(1)	40(1)	35(1)	2(1)	3(1)	4(1)
C(7)	43(1)	41(1)	35(1)	-5(1)	3(1)	-1(1)
C(8)	39(1)	40(1)	36(1)	1(1)	-5(1)	3(1)
C(9)	57(1)	52(1)	39(1)	5(1)	2(1)	6(1)
C(10)	74(1)	62(1)	49(1)	-2(1)	14(1)	7(1)
C(11)	47(1)	46(1)	45(1)	4(1)	-2(1)	9(1)
C(12)	38(1)	44(1)	51(1)	-4(1)	2(1)	2(1)
C(13)	148(3)	76(2)	84(2)	-20(1)	42(2)	29(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for rov6m.

	x	y	z	U(eq)
H(2)	6221	1298	8791	63
H(3)	8710	273	9455	73
H(4)	11696	1514	9759	71
H(5)	12339	3780	9372	61
H(9A)	6516	5254	7122	59
H(9B)	8461	6265	7229	59
H(10A)	10674	4300	7372	93
H(10B)	9552	4220	6703	93
H(10C)	8727	3283	7272	93
H(11A)	6431	7525	8051	55
H(11B)	4504	6490	7960	55
H(13A)	2658	8270	9699	154
H(13B)	4262	9544	9733	154
H(13C)	4956	8033	9970	154

Chapter 3 Experimental

Application of the Stetter Reaction Toward Complex Molecule Synthesis

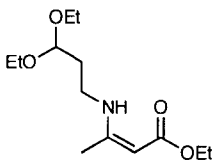
General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Tetrahydrofuran, diethylether, and dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through 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. Racemic material was prepared by the method of Ciganek,[1] or with achiral catalysts **E1** and **E2** (see chapter 1 experimental) according to the general procedure.

Melting points were measured with a MelTemp II melting point apparatus outfitted with a Fluke 51 thermocouple and are uncorrected. Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. The purity of all compounds was determined to be >95% by ^{1}H NMR. ^{1}H NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometer at ambient temperature. Data are 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 =

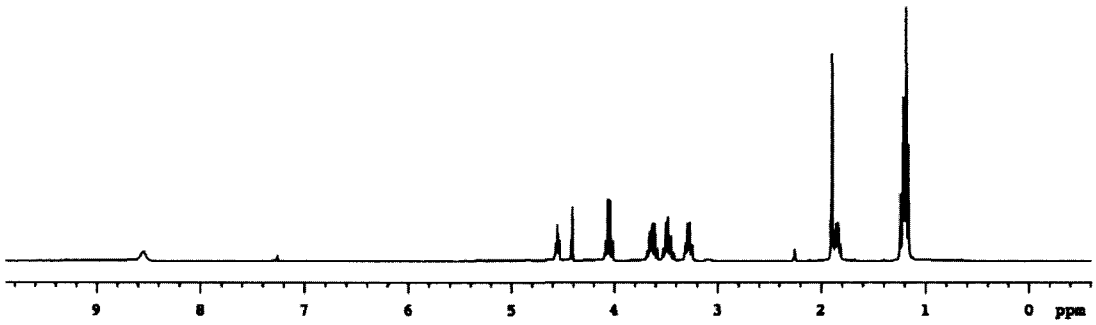
[1] Ciganek, E. *Synthesis* **1995**, 1311-1314.

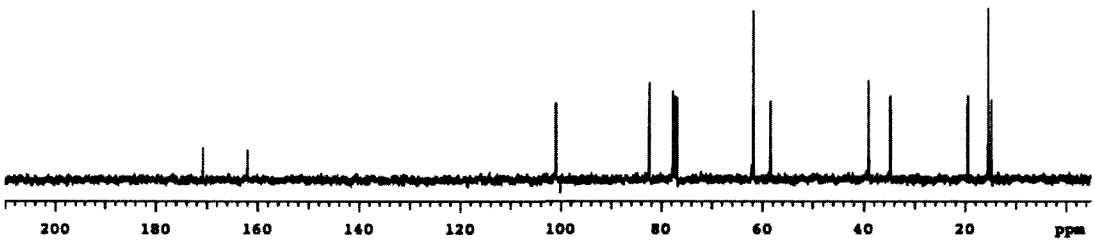
triplet, q = quartet, m = multiplet, and bs = broad singlet), integration, and coupling constant (Hz). ^{13}C NMR were recorded on a Varian 75 or 100 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.0 ppm. Mass spectra were obtained on Fisons VG 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, 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.

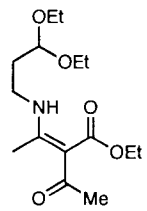


(*Z*)-ethyl 3-(3,3-diethoxypropylamino)but-2-enoate (70): To a 25 mL round bottom flask was added 1.50 g ethyl acetoacetate (11.5 mmol), 1.70 g 1-amino-propionaldehyde diethyl acetal (11.5 mmol), and alumina (2.0 g). This was heated to 80 C for 12 hours with stirring. Column chromatography (1:1 hexanes: EtOAc) provided 2.44 g **70** (82%) as a clear oil R_f = 0.39 (3:1 Hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 8.55 (br s, 1H), 4.55 (dd, 1H, J = 5.5, 5.5 Hz), 4.05 (q, 2H, J = 7.3 Hz), 3.70-3.58 (m, 2H), 3.54-3.42 (m, 2H), 3.28 (dd, 2H, J = 13.2, 6.6 Hz), 1.89 (s, 3 H), 1.84 (dd, 2H, J = 12.8, 7.0 Hz), 1.28-1.12 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 162.0, 100.6, 82.4, 61.8, 58.4, 39.1, 34.8, 19.5, 15.5, 14.9; IR (NaCl, neat) 2982, 2858, 1651, 1607, 1505 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{26}NO_4$, 260.1862. Found 260.1849.

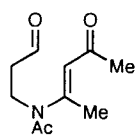
^{1}H and ^{13}C Spectra for **70**







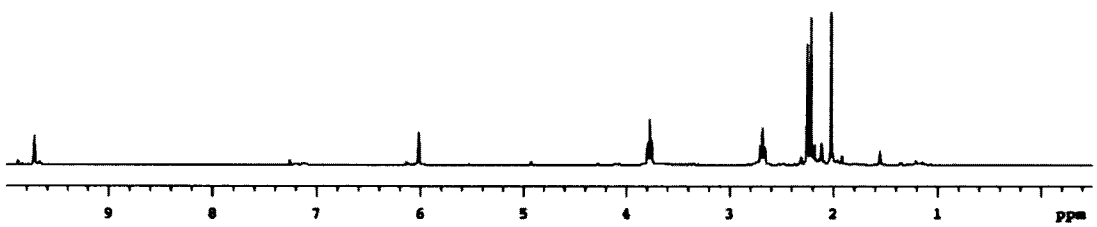
(*Z*)-ethyl 3-(3,3-diethoxypropylamino)-2-ethanoylbut-2-enoate (72): To a solution of **70** (0.5 g, 1.93 mmol) in $CHCl_3$ was added 0.153 mL pyridine (1.93 mmol) and 0.138 mL AcCl (1.93 mmol). This was stirred for 4 hours at room temperature and concentrated. Column chromatography provided **72** as a yellow oil R_f= 0.17 (3:1 Hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.42 (br s, 1H), 4.55 (dd, 1H, *J* = 5.5, 5.5 Hz), 4.19 (q, 2H, *J* = 7.3 Hz), 3.70-3.57 (m, 2H), 3.55-3.42 (m, 2H), 3.38 (dd, 2H, *J* = 13.0, 6.8 Hz), 2.21 (s, 3 H), 2.15 (s, 3H), 1.90 (dd, 2H, *J* = 12.6, 6.8 Hz), 1.38-1.13 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 170.6, 167.5, 100.7, 62.2, 60.4, 39.5, 34.0, 29.7, 21.0, 17.0, 15.5, 14.4; IR (NaCl, neat) 2975, 1702, 1600, 1461, 1200 cm^{-1}.



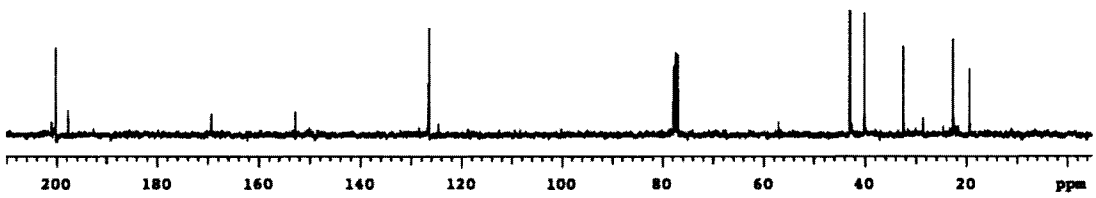
***(E)*-N-(1-Methyl-3-oxo-but-1-enyl)-N-(3-oxo-propyl)-acetamide (75):** Prepared by condensation of 1-amino-3,3-diethoxypropane (10.0 mmol) and 2,4-pentanedione (10.0 mmol) with alumina (1.00 g) at 80 ° C for 12 h. This was acylated with AcCl (20.0 mmol) and pyridine (100.0 mmol) in chloroform (20.0 mL). Deprotection with 80% AcOH in water (2 mL) provided a mixture of geometrical isomers separable by column chromatography (EtOAc). The upper spot by TLC corresponded to the desired isomer and was isolated in 29% yield as a clear oil. R_f= 0.23 (9:1 EtOAc/*i*-PrOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H), 6.02, (s, 1H), 3.77 (dd, 2H, *J* = 6.9, 6.9 Hz), 2.68 (dd, 2H, *J* = 7.0. 7.0 Hz), 2.25, (s, 3H), 2.21 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 197.7, 169.3, 126.4, 42.9, 40.1, 32.4, 22.6,

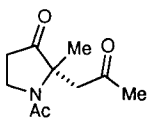
19.4; IR (NaCl, neat) 1714, 1687, 1655, 1612, 1394 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{16}NO_3$, 198.1130. Found 198.1131.

^1H Spectrum for **75**



^{13}C Spectrum for **75**

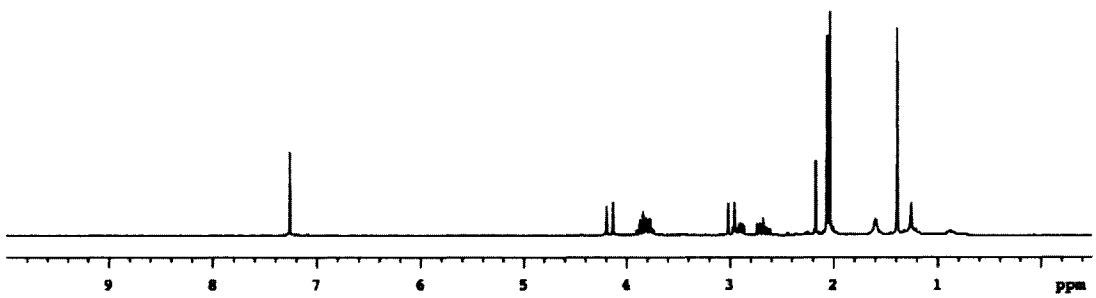




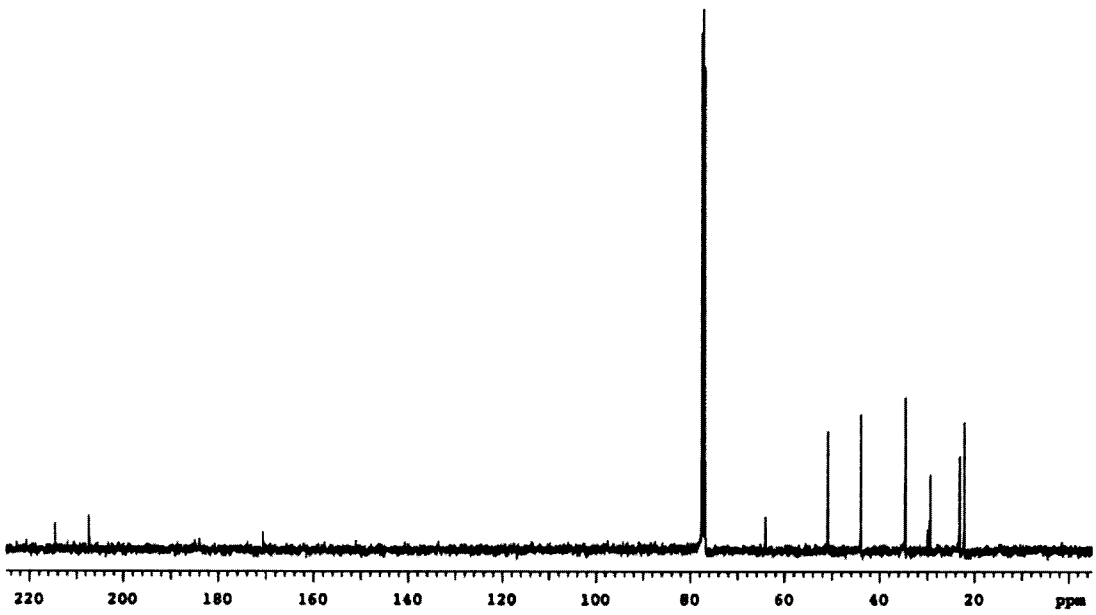
1-Acetyl-2-methyl-2-(2-oxo-propyl)-pyrrolidin-3-one (76): To a 10 mL flame-dried round bottom flask was added catalyst **65** (19 mg, 0.04 mmol) and 4.5 mg potassium *tert*-butoxide (0.04 mmol). To this was added toluene (1 mL) and the solution allowed to stir for 10 min at ambient temperature. Argon was bubbled through the solution for 5 min and 40 mg (0.20 mmol) **75** was added via syringe in 1 mL PhMe. This was allowed to stir at room temperature for 12 hours. The solution was transferred directly to a column of silica gel, and elution with 6:1 hexanes to EtOAc provided 26 mg **76** (65%) as a clear oil. R_f = 0.21 (9:1 EtOAc/*i*-PrOH); $[\alpha]_D^{25}$ = -57.1° ($CHCl_3$, c = 11 mg/mL) GC analysis – chiraldex BPH column, 120 °C 1.5 mL/ min.

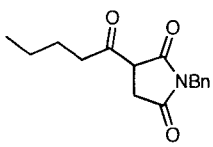
Minor enantiomer: 46.0 min, major enantiomer: 46.2 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (dd, 1H, J = 18.6, 0 Hz), 3.82 (ddd, 1H, J = 18.1, 8.9, 8.9 Hz) 3.75 (ddd, 1H, J = 10.2, 10.2, 3.8 Hz) 2.96 (dd, 1H, J = 18.8, 0 Hz), 2.90 (ddd, 1H, J = 17.9, 9.0, 3.6 Hz), 2.66 (ddd,1H, J = 18.5, 9.4, 9.4 Hz) 2.03 (s, 3H), 2.01 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 207.3, 170.6, 64.1, 50.9, 43.9, 34.6, 29.4, 23.2, 22.2; IR (NaCl, neat) 2915, 1745, 1706, 1634, 1414 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{16}NO_3$, 198.1130. Found 198.1135.

^{1}H Spectrum for **76**



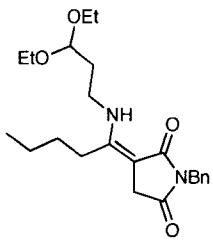
^{13}C Spectrum for **76**



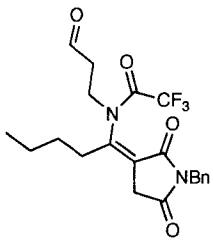


1-benzyl-3-pentanoylpyrrolidine-2,5-dione (79): To a solution of N-benzyl succinimide (1.00 g, 5.7 mmol) in 25 mL THF was added 1.0 g ethyl valerate (8.55 mmol) and 0.275 g sodium hydride (6.8 mmol, 60% dispersion in mineral oil. 10 drops EtOH was added, and the solution was heated to reflux for 24 hours. Saturated aqueous $NaHCO_3$ was added, and the solution was extracted with Et_2O (3 x 25 mL). The combined organics were dried with brine, and $MgSO_4$. Column

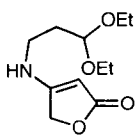
chromatography provided 1.043 g **79** (67%) as a clear oil R_f = 0.24 (3:1 Hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2 (s, 0.12H), 7.42-7.21 (m, 5H), 4.61 (dd, 2H, J = 19.4, 16.1 Hz), 3.92 (dd, 1H, J = 8.4, 4.4 Hz), 3.33-3.18 (m, 1H), 3.02 (ddd, 1H, J = 17.9, 7.3, 7.3 Hz), 2.70-2.55 (m, 2H), 2.18 (dd, 0.24H, J = 7.7, 7.7 Hz), 1.65-1.52 (m, 2H), 1.40-1.25 (m, 2H), 0.90 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 175.5, 172.7, 135.5, 128.9, 128.8, 128.3, 53.2, 43.1, 43.0, 30.2, 25.5, 22.3, 14.0; IR (NaCl, neat) 2960, 2880, 1782, 1701, 1636, 1396 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{20}NO_3$, 274.1443. Found 274.1439.



(*Z*)-1-benzyl-3-(1-(3,3-diethoxypropylamino)pentylidene)pyrrolidine-2,5-dione (80): To a 25 mL round bottom flask was added 0.22 g **71** (0.81 mmol), 0.43 g 1-amino-propionaldehyde diethyl acetal (0.97 mmol), and alumina (0.500 g). This was heated to 80 °C for 12 hours with stirring. Column chromatography (1:1 hexanes: EtOAc) provided 0.277 g **80** (85%) as a clear oil. R_f = 0.26 (3:1 Hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.40-7.20 (m, 5H), 4.65 (s, 1H), 4.57 (dd, 1H, J = 5.1, 5.1 Hz), 3.78-3.59 (m, 2H), 3.58-3.42 (m, 2H), 3.32 (dd, 2H, J = 13.2, 6.6 Hz), 3.17 (s, 1H), 2.20 (dd, 2H, J = 7.0, 7.0 Hz), 1.88 (dd, 2 H, J = 12.2, 6.2), 1.58-1.32 (m, 4H), 1.23-1.18 (m, 6H), 0.93 (t, 3H, J = 7.3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 171.6, 160.3, 137.3, 128.8, 128.7, 100.9, 86.6, 62.0, 41.6, 38.9, 34.9, 33.6, 29.7, 29.6, 23.0, 15.5, 14.0; IR (NaCl, neat) 2989, 2880, 1723, 1651, 1607, 1389, 1222 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{35}N_2O_4$, 403.2597. Found 403.2593.

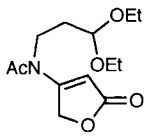


(*Z*)-*N*-(1-(1-benzyl-2,5-dioxopyrrolidin-3-ylidene)pentyl)-2,2,2-trifluoro-*N*-(3-oxopropyl)ethanamide (81): To a solution of 0.250 g **80** (0.62 mmol) in 5 mL CH_2Cl_2 was added 0.171 mL triethyl amine (1.24 mmol) and 0.113 mL trifluoroacetic anhydride (0.80 mmol). This was allowed to stir at room temperature for 30 minutes and was concentrated and purified by column chromatography to provide 0.224 g **81** (85%) as a clear oil $R_f = 0.08$ (3:1 Hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.42-7.21 (m, 5H), 4.71 (d, 1H, J = 13.9), 4.60 (d, 1H, J = 14.3) Hz), 4.23-3.64 (m, 3H), 3.33 (s, 2H), 3.27-3.10 (m, 1H), 2.58-2.40 (m, 1H), 2.35-2.20 (m, 1H), 1.59-1.10 (m, 4H), 0.95 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 200.7, 164.8, 163.9, 153.3, 150,1, 144.2, 123.9, 80.2, 61.2, 61.0, 54.3, 43.4, 42.7, 27.6, 25.9, 13.7, 13.6, 12.5; IR (NaCl, neat) 2945, 1767, 1694, 1658, 1396 cm^{-1}.

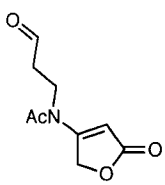


4-(3,3-diethoxypropylamino)furan-2(5*H*)-one (90): To a 25 mL round bottom flask was added 1.0 g tetronic acid (10.0 mmol), 1.47 g 1-amino-propionaldehyde diethyl acetal (10.0 mmol), and alumina (1.50 g). This was heated to 80 C for 12 hours with stirring. Column chromatography (1:1 hexanes: EtOAc) provided 1.650 g **90** (72%) as a clear oil. $R_f = 0.18$ (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (br s, 1H), 4.58 (s, 2H) 4.51-4.48 (m, 2H) 3.62-3.52 (m, 2H), 3.46-3.41 (m, 2H), 3.12 (dd, 2H, J = 12.1, 6.6 Hz) 1.83 (dd, J = 12.1, 6.6 Hz), 1.11 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 169.1, 101.4, 79.7, 68.0, 62.2, 41.0, 32.7, 15.5;

IR (NaCl, neat) 3287, 2967, 1723, 1621, 1061 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{20}NO_4$, 230.1392. Found 230.1389.



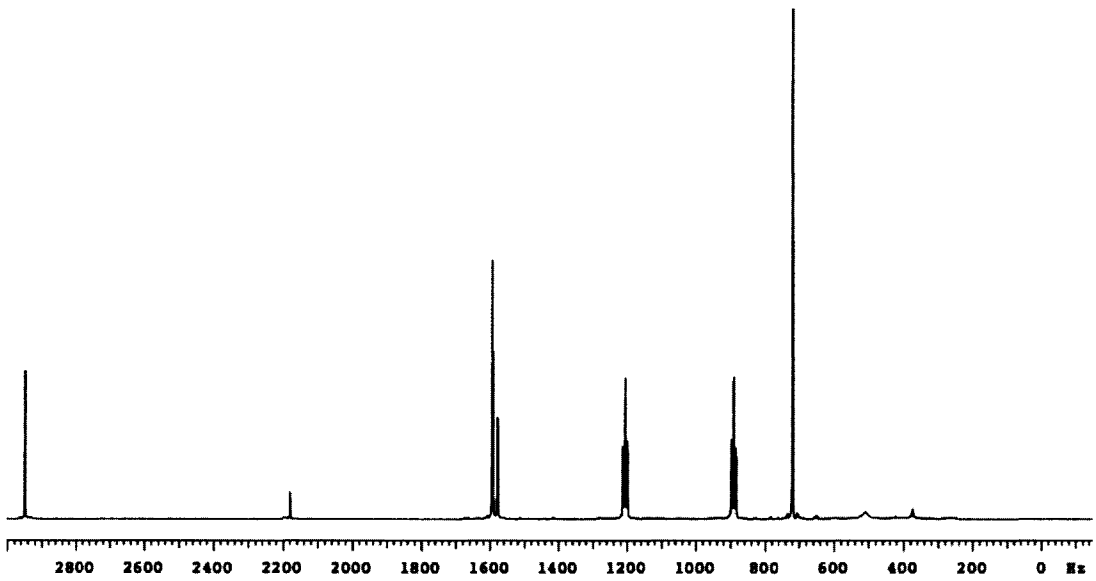
_N_-(3,3-diethoxypropyl)-_N_-(5-oxo-2,5-dihydrofuran-3-yl)ethanamide (90a): To a solution of **90** (0.175 g, 0.78 mmol) in 8 mL THF was added *n*-BuLi (0.75 mmol, 0.469 mL of a 1.6 M solution in hexanes) at 0 °C. After stirring for 10 minutes, acetyl chloride (0.111 mL, 1.56 mmol) was added and stirred at this temperature for an additional 10 minutes. Saturated aqueous $NaHCO_3$ (10 mL) was added and the solution was extracted with EtOAc (3 x 15 mL). The combined organics were dried with brine and $MgSO_4$. Concentration, followed by column chromatography provided 142 mg **90a** (70%) as a clear oil. R_f = 0.26 (EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (s, 1H), 5.29 (s, 2H), 4.54 (dd, 1H, *J* = 4.4, 4.4 Hz), 3.78 (dd, 2H, *J* = 7.3, 7.3 Hz), 3.72-3.60 (m, 2H), 3.52-3.40 (m, 2H), 2.33 (s, 3H), 2.02-1.82 (m, 2H), 1.19 (t, 6H, *J* = 7.0); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 171.3, 163.3, 100.8, 96.2, 71.7, 63.0, 45.0, 31.5, 23.6, 15.5; IR (NaCl, neat) 2960, 1752, 1701, 1593, 1389 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{22}NO_5$, 272.1498. Found 272.1488.



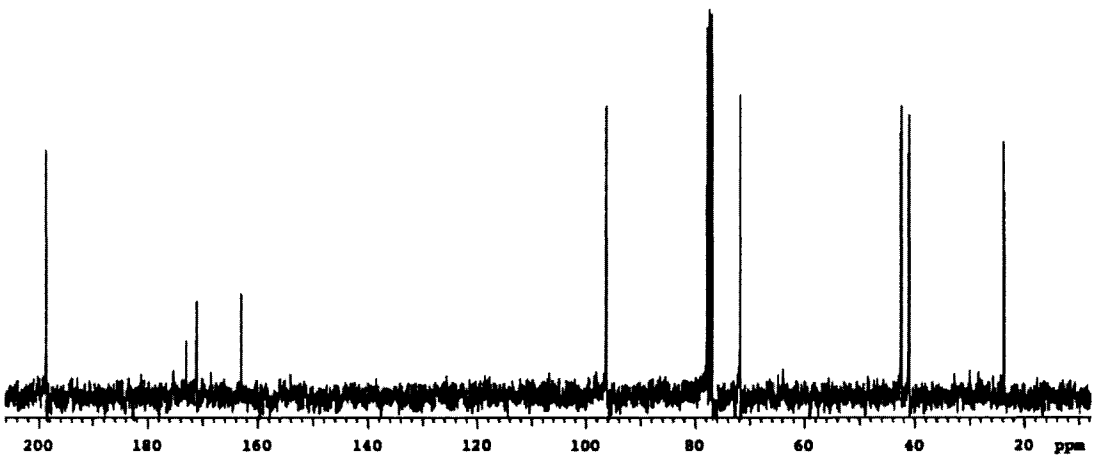
_N_-(5-oxo-2,5-dihydrofuran-3-yl)-_N_-(3-oxopropyl)ethanamide (91): 80:20 AcOH to H_20 was added to **90a** and stirred for 4 hours at room temperature. Upon consumption of starting material, (monitored by TLC) the reaction was poured directly onto a column of silica and eluted with 3:1 hexanes : EtOAc to afford 61 mg **91** (83%) as a clear oil. R_f = 0.11 (EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 5.32 (s, 2H), 5.26 (s, 1H), 4.02 (dd, 2H, *J* = 7.0. 7.0 Hz), 2.97 (dd,

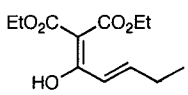
2H, J = 7.0, 7.0 Hz), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 172.9, 171.1, 163.0, 96.2, 71.7, 42.4, 41.0, 23.7; IR (NaCl, neat) 2909, 1745, 1702, 1585, 1396 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{12}NO_4$, 198.0766. Found 198.0775.

^{1}H Spectrum for **91**



^{13}C Spectrum for **91**

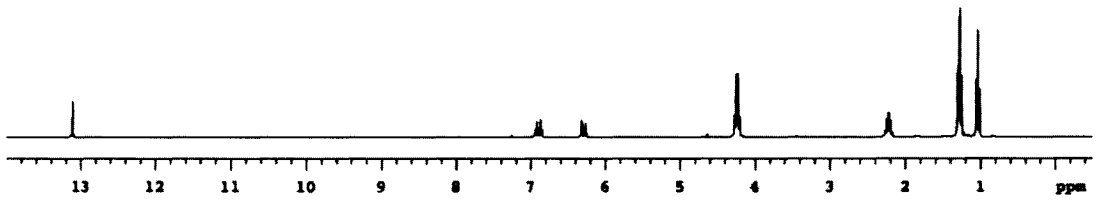


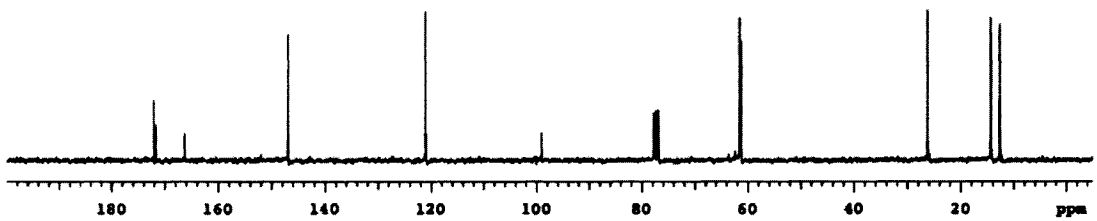


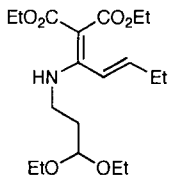
(*E*)-diethyl 2-(1-hydroxypent-2-enylidene)propanedioate (98): *trans*-2-pentenoic acid (1.5 mL, 15.0 mmol) was added to 100 mL CH_2Cl_2 in a 250 mL round bottom flask. Oxalyl chloride (2.61 mL, 30.0 mmol) was added and 5 drops DMF and allowed to stir for 3 hours. The solution was concentrated, followed by addition of 100 mL hexanes. This was filtered and concentrated to afford the corresponding acid chloride, used without further purification. 20 mL Acetonitrile was added to a flame-dried round bottom flask containing 1.360 g anhydrous $MgCl_2$ (14.3 mmol). This was cooled to 0 °C and 2.17 mL ethyl acetoacetate (14.3 mmol) was added and stirred for 10 minutes. 5.0 mL Diisopropylethylamine (28.7 mmol) was added and allowed to stir for 10 minutes. The acid chloride was added (2.30 g, 14.3 mmol) and

allowed to warm to room temperature. This was stirred for an additional hour at room temperature. 6 M HCl was added (20 mL) and poured into a separatory funnel. This was extracted with diethyl ether (3 x 25 mL). The combined organics were dried with brine and Mg_2SO_4. This was filtered and concentrated. Column chromatography (hexanes) provided 2.35 g **98** (68%) as a clear oil. R_f = 0.63 (3:1 Hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.1 (s, 1H), 6.90 (ddd, 1H, *J* = 15.4, 6.6, 6.6 Hz), 6.31 (d, 1H, *J* = 15.4 Hz), 4.32-4.20 (m, 4H), 2.30-2.18 (m, 2H), 1.36-1.20 (m, 6H), 1.04 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 171.7, 166.3, 146.9, 121.0, 99.0, 61.5, 61.3, 26.2, 14.3, 14.2, 12.6; IR (NaCl, neat) 2975, 2865, 1716, 1645, 1571 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{19}O_5$, 243.1232. Found 243.1233.

^{1}H and ^{13}C Spectra for **98**

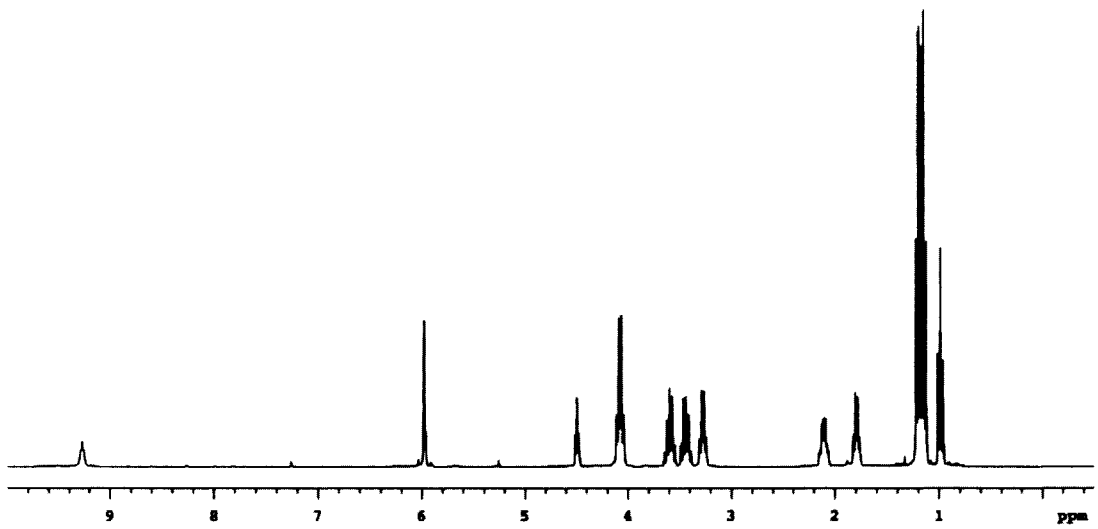


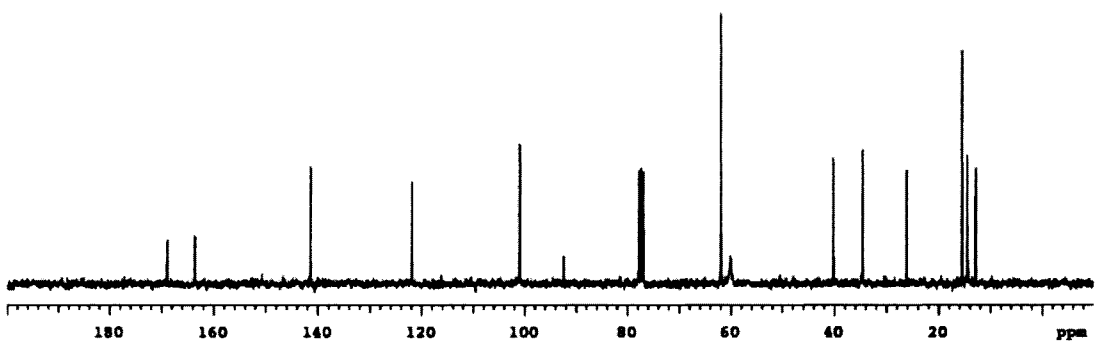


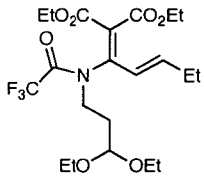


(*E*)-diethyl-2-(1-(3,3-diethoxypropylamino)pent-2-enylidene)propanedioate (101): A flame-dried round bottom flask was charged with 40 mL CH_2Cl_2 and 1.00 g **98** (4.13 mmol) and cooled to 0 °C. 0.837 mL Trifluoromethanesulfonic anhydride (4.96 mmol) was added, followed by 1.2 mL triethylamine (8.67 mmol). This was allowed to stir at 0 °C for 10 minutes. 1.00 mL Propionaldehyde diethyl acetal (6.80 mmol) was added and allowed to warm to room temperature. After stirring for 1 hour at room temperature, the reaction was concentrated and purified by column chromatography to provide 1.15 g **101** (75 %) as a clear oil R_f = 0.41 (3:1 Hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 6.07-5.85 (m, 2H), 4.50 (dd, 1H, *J* = 5.5, 5.5 Hz), 4.18-4.00 (m, 4H), 3.65-3.52 (m, 2H), 3.51-3.38 (m, 2H), 3.28 (dd, 2H, *J* = 13.2, 6.6), 2.20-2.03 (m, 2H), 1.79 (dd, 2H, *J* = 12.4, 7.0 Hz), 1.28-1.10 (m, 6H), 0.99 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 163.5, 141.4, 121.8, 100.9, 92.4, 61.9, 60.1, 40.1, 34.6, 26.1, 15.4, 14.4, 12.8; IR (NaCl, neat) 3258, 2975, 1702, 1651, 1585 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{34}NO_6$, 372.2386. Found 372.2388.

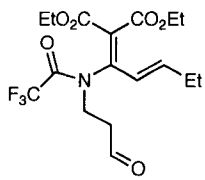
^{1}H and ^{13}C Spectra for **101**





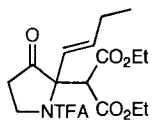


(*E*)-diethyl-2-(1-(*N*-(3,3-diethoxypropyl)-2,2,2-trifluoroethanamido)pent-2-enylidene)propanedioate (102): A flame-dried round bottom flask was charged with 0.450 g **101** (1.00 mmol) and 10 mL CH_2Cl_2 and cooled to 0 °C. 0.277 mL Triethylamine (2.0 mmol) was added, followed by 0.169 mL trifluoroacetic anhydride (1.20 mmol). This was allowed to stir at this temperature for 30 minutes and diluted with saturated aqueous $NaHCO_3$. This was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics dried with brine and $MgSO_4$. Filtration, followed by concentration provided a clear oil which was purified by column chromatography to provide 0.363 g **102** (78%) as a clear oil. R_f= 0.49 (3:1 Hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52–6.37 (m, 2H), 4.55 (dd, 1H, *J* = 5.5, 5.5 Hz), 4.33 (q, 2H, *J* = 8.1 Hz), 4.21 (q, 2H, *J* = 7.0 Hz), 3.78-3.58 (m, 2H), 3.56-3.42 (m, 2H), 2.36-2.24 (m, 2H), 1.91 (dd, 2H, *J* = 13.6, 13.6 Hz), 1.33 (t, 3H, *J* = 7.0 Hz), 1.25 (t, 3H, *J* = 7.3 Hz), 1.17 (t, 3H, *J* = 7.0 Hz), 1.07 (t, 3H, *J* = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 163.0, 157.5, 147.4, 147.3, 124.5, 123.0, 118.2, 114.4, 101.1, 62.1, 61.9, 61.5, 31.2, 25.9, 14.4, 13.2, 11.8; IR (NaCl, neat) 2982, 1731, 1695, 1636, 1585 cm^{-1}; HRMS (FAB+) calcd for $C_{21}H_{32}NO_7F_3$, 467.2131. Found 467.2125.



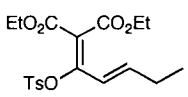
(*E*)-diethyl 2-(1-(2,2,2-trifluoro-*N*-(3-oxopropyl)ethanamido)pent-2-enylidene)propanedioate (103): To a round bottom flask was added **102** and 2 mL 80:20 acetic acid to water. This was stirred for 3 hours at room temperature until all starting material was consumed (by TLC) and directly poured onto a column of silica gel. Elution with 6:1 hexanes to EtOAc provided 0.215 g

102 (85%) as a clear oil. R_f = 0.26 (3:1 Hexanes:EtOAc); ^{1}H NMR (400 MHz, acetone-D6) δ 9.71 (s, 1H), 6.60-6.40 (m, 1H), 6.24 (ddd, 1H, *J* = 14.1, 7.5, 7.5 Hz), 4.28-4.11 (m, 4H), 3.72-3.59 (m, 2H), 2.82-2.70 (m, 2H), 2.24 (ddd, 2H, *J* = 14.3, 7.2, 7.2), 1.48-1.11 (m, 6H), 1.04 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 199.7, 164.1, 162.8, 156.8 (m, 1C), 147.3, 123.0, 61.9, 45.3, 41.1, 26.0, 13.6, 13.5, 12.2; IR (NaCl, neat) 2975, 1738, 1680, 1636, 1592 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{23}NO_6F_3$, 394.1477. Found 394.1487.



(*E*)-diethyl-2-(2-(but-1-enyl)-3-oxo-1-(2,2,2-trifluoroethanoyl)pyrrolidin-2-yl)propanedioate (105): A flame dried round bottom flask was charged with 5 mL PhMe and 0.019 g triazolium salt **104** (0.054 mmol). A needle outlet was inserted and argon was bubbled through the solution for 5 minutes. 0.054 mmol KHMDS (108 μL of a 0.5 M solution in PhMe) was added dropwise over a span of 10 minutes to generate the active catalyst. A separate round bottom flask was charged with 0.100 g **103** (0.27 mmol) and 1 mL toluene and sparged with argon for 5 minutes. This solution was taken up by syringe and added dropwise to the solution of catalyst over 10 minutes. The reaction was allowed to stir at room temperature for 1 hour and poured onto a column of silica gel. Elution with 6:1 hexanes:EtOAc provided 0.050 g **105** (50%) as a clear oil; R_f = 0.30 (3:1 Hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (d, 1H, *J* = 15.7 Hz), 5.52 (ddd, 1H, *J* = 15.7, 6.2, 6.2 Hz), 4.79 (s, 1H), 4.32-4.04 (m, 6H), 2.97-2.70 (m, 2H), 2.09 (ddd, 2H, *J* = 15.0, 7.3. 7.3 Hz), 1.34-1.15 (m, 6H), 0.98 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 206.3, 168.0, 166.6, 135.1, 122.6, 135.1, 122.6, 70.6, 62.3, 57.1,

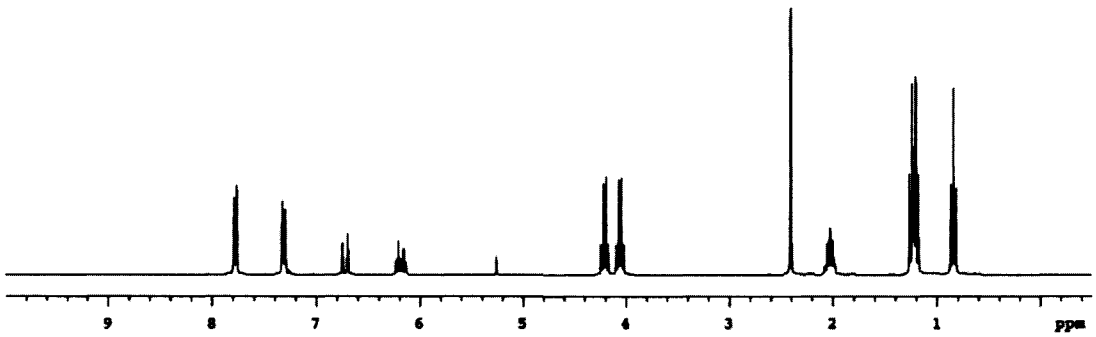
43.1, 34.0, 25.5, 14.1, 13.0; IR (NaCl, neat) 2975, 1775, 1731, 1694,1149 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{23}NO_6F_3$, 394.1477. Found 394.1490.

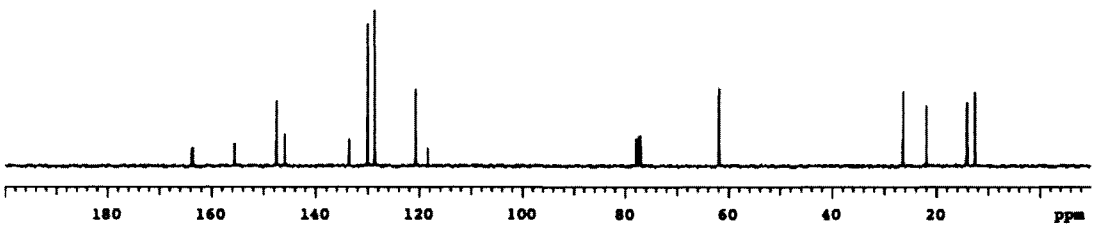


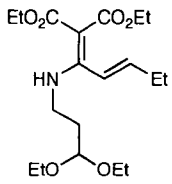
(*E*)-diethyl 2-(1-(tosyloxy)pent-2-enylidene)propanedioate (106): A round bottom flask was charged with 15 mL CH_2Cl_2 and 0.900 g **100** (3.72 mmol). *p*-Toluenesulfonyl chloride (0.709 g, 3.72 mmol) was added at room temperature, followed by 0.045 g DMAP (0.37 mmol), and 0.538 mL triethylamine (3.73 mmol). This was allowed to stir at room temperature for 30 minutes. This was concentrated and purified by column chromatography to afford 1.350 g **106** (92%) as a clear oil R_f= 0.33 (3:1 Hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 2H, *J* = 8.2), 7.31 (d, 2H, *J* = 8.4 Hz), 6.72 (d, 1H, *J* = 15.4 Hz), 6.18 (ddd, 1H, *J* = 15.4, 6.6, 6.6 Hz), 4.21 (dd, 2H, *J* = 14.3, 7.0), 4.06 (dd, 2H, *J* = 14.3, 7.0 Hz), 2.40 (s, 3H), 2.03 (ddd, 2H, *J* = 13.9, 5.9, 5.9 Hz), 1.30-1.18 (m, 6H), 0.87 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 163.5, 155.5, 147.5, 145.9, 133.5, 130.0, 128.6, 120.7,118.3, 61.9, 61.8, 26.4; IR (NaCl, neat) 2967, 1738, 1709, 1638, 1585 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{25}O_7S$ 397.1321. Found 397.1317.

^{1}H and ^{13}C Spectra for **106**

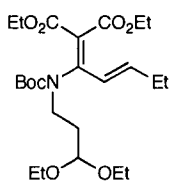
ker-7-43p





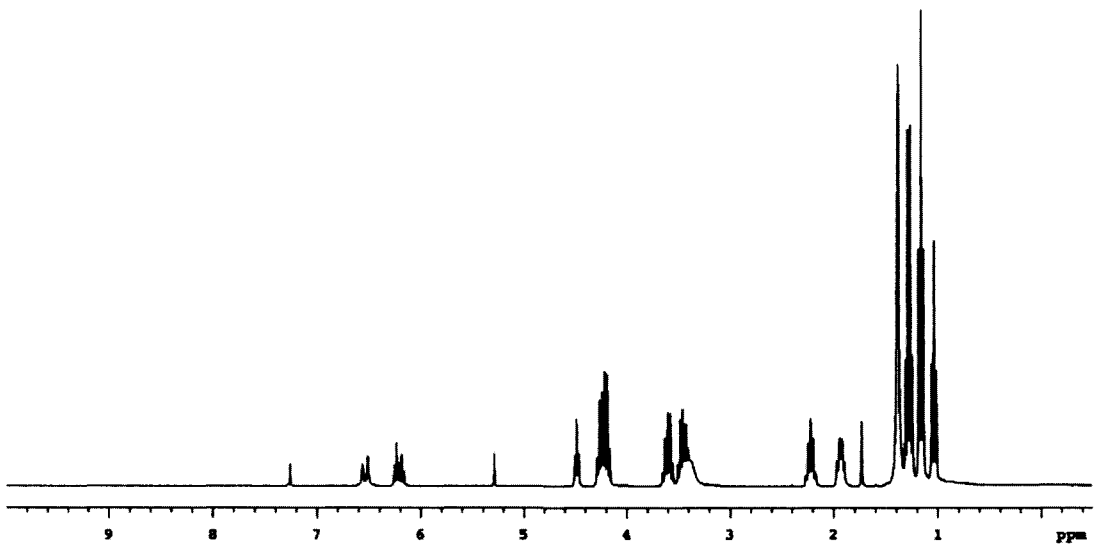


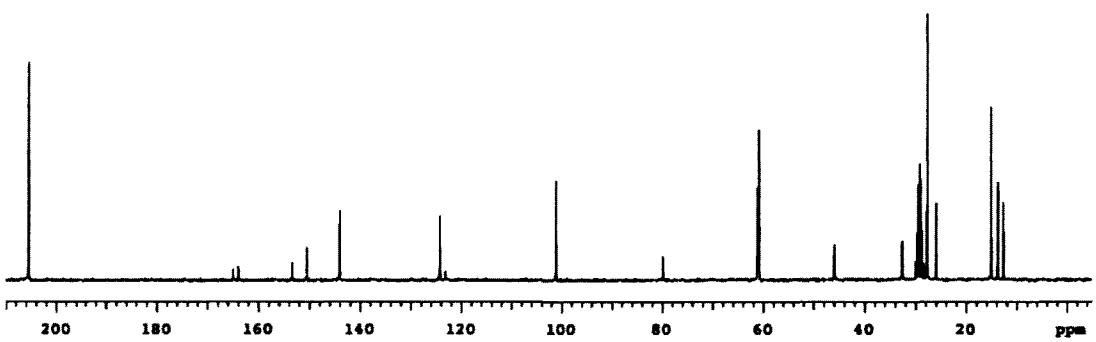
(*E*)-diethyl-2-(1-(3,3-diethoxypropylamino)pent-2-enylidene)propanedioate (101): A flame-dried round bottom flask was charged with 10 ml acetonitrile and 0.80 g **106** (2.00 mmol) and cooled to 0 °C. 0.490 g DMAP (4.00 mmol) was added, followed by 0.367 mL 1-amino-propionaldehyde diethyl acetal (2.50 mmol). The reaction was allowed to stir at this temperature for 10 minutes. After stirring for 1 hour at room temperature, the reaction was concentrated and purified by column chromatography to provide 0.557 g **101** (77%) as a clear oil.

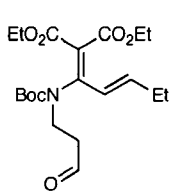


(*E*)-diethyl 2-(1-(*tert*-butoxycarbonyl(3,3-diethoxypropyl)amino)pent-2-enylidene)propanedioate (101a): A round bottom flask was charged with 3 mL acetonitrile and 0.350 g **101** (0.94 mmol). 0.025 g DMAP (0.02 mmol) was added, followed by 0.236 g Boc anhydride (1.00 mmol). This was allowed to stir at room temperature for 1 hour. Concentration, followed by column chromatography afforded 0.350 g **101a** (78%) as a clear oil. R_f = 0.49 (3:1 Hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (d, 1H, *J* = 15.4), 6.21 (ddd, 1H, *J* = 13.2, 6.6, 6.6 Hz), 4.49 (dd, 1H, *J* = 5.9, 5.9 Hz), 4.26 (dd, 2H, *J* = 14.3, 7.0 Hz), 4.20 (dd, 2H, *J* = 14.3, 7.0), 3.68-3.55 (m, 2H), 3.54-3.26 (m, 4H), 2.22 (ddd, 2H, *J* = 15.4, 7.7, 7.7 Hz), 1.93 (dd, 2H, *J* = 14.3, 7.7 Hz), 1.39 (s, 9H), 1.37-1.11 (m, 12H), 1.04 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 164.9, 163.9, 153.3, 150.4, 144.0, 124.2, 123.1, 101.1, 97.8, 61.2, 60.9, 60.8, 45.9, 32.6, 27.7, 25.9, 15.0, 13.7, 12.6; IR (NaCl, neat) 2982, 1702, 1636, 1593, 1222 cm^{-1}; HRMS (FAB+) calcd for $C_{24}H_{42}NO_8$ 472.2910. Found 472.2895.

^{1}H and ^{13}C Spectra for **101a**

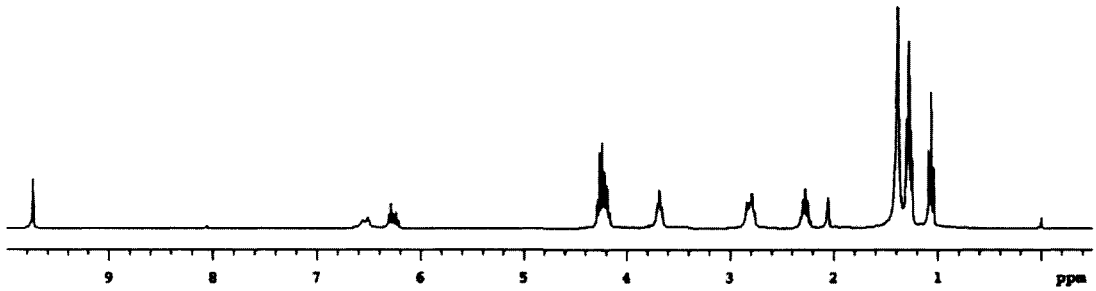


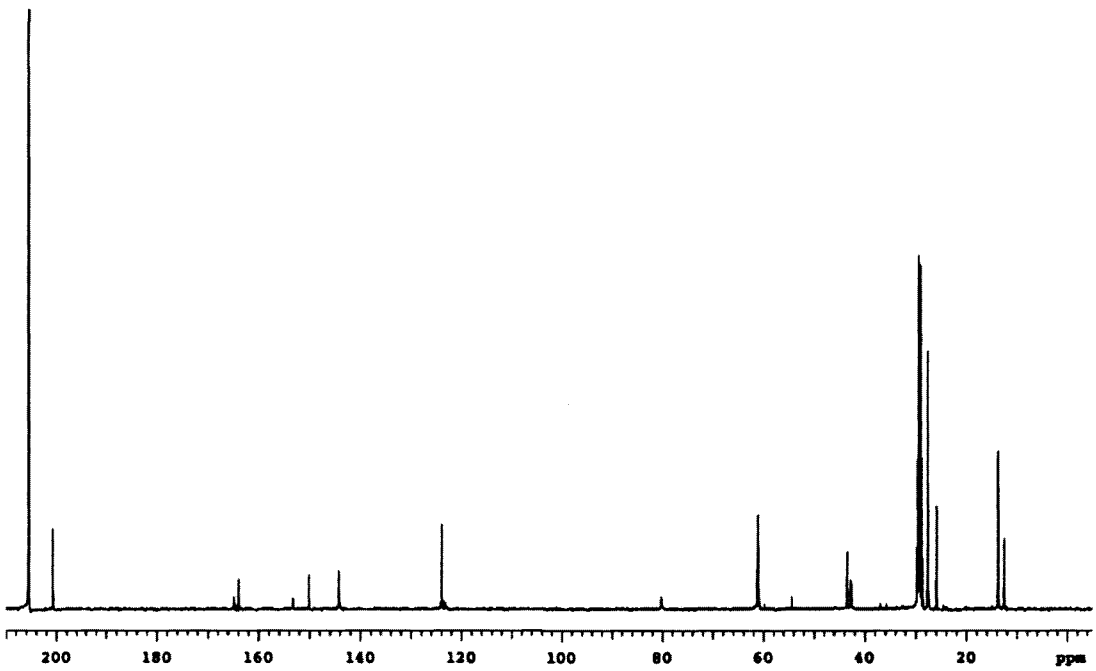


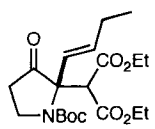


(*E*)-diethyl 2-(1-(*tert*-butoxycarbonyl(3-oxopropyl)amino)pent-2-enylidene)propanedioate (107): To a round bottom flask was added 0.25 g **101a** (0.53 mmol) and 3 mL of a solution of 80:20 acetic acid to water. This was stirred for 3 hours at room temperature until all starting material was consumed (by TLC) and directly poured onto a column of silica gel. Elution with 6:1 hexanes to EtOAc provided (0.166 g) **107** (79%) as a clear oil. R_f = 0.40 (3:1 Hexanes:EtOAc); ^{1}H NMR (400 MHz, acetone-D6) δ 9.74 (s, 1H), 6.63-6.45 (m, 1H), 6.26 (ddd, 1H, *J* = 15.4, 6.6, 6.6 Hz), 4.35-4.15 (m, 4H), 3.68 (dd, 1H, *J* = 6.6, 6.6 Hz), 2.89-2.72 (m, 2H), 2.38-2.20 (m, 2H), 1.38 (s, 9H), 1.36-1.20 (m, 6H), 1.06 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 200.7, 164.8, 163.9, 153.3, 150.1, 144.2, 123.9, 80.2, 61.2, 61.0, 54.3, 43.4, 42.7, 27.6, 25.9, 13.7, 13.6, 12.5; IR (NaCl, neat) 2982, 1731, 1629, 1585, 1360 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{32}NO_7$ 398.2179. Found 398.2176.

^{1}H and ^{13}C Spectra for **107**

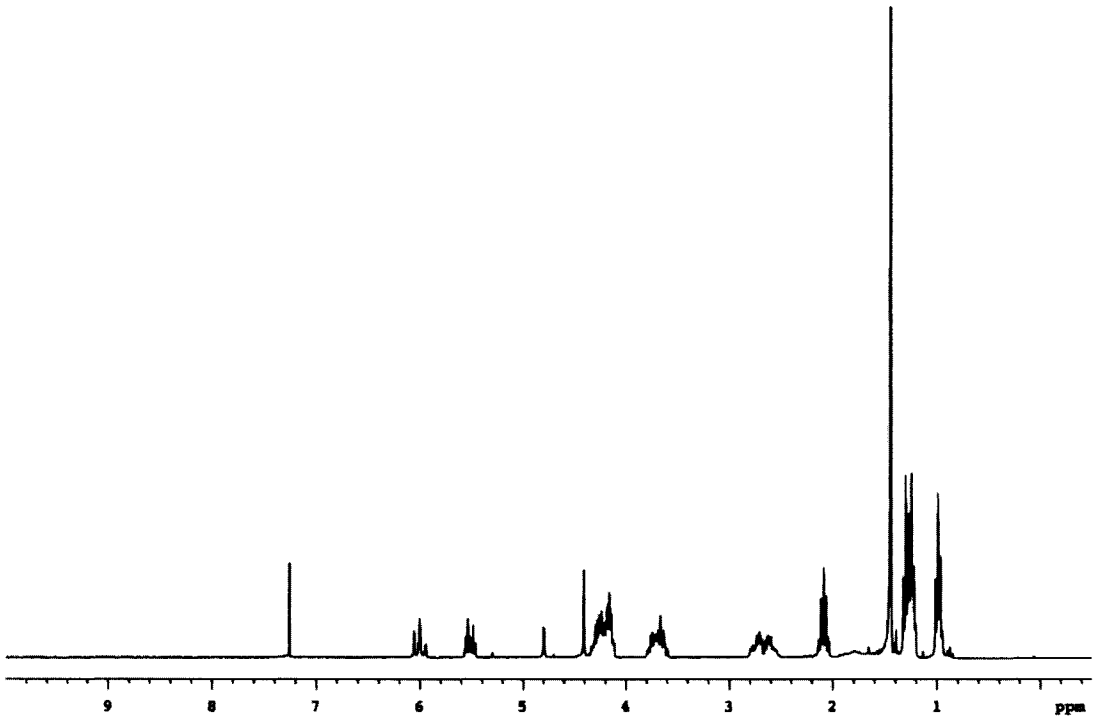


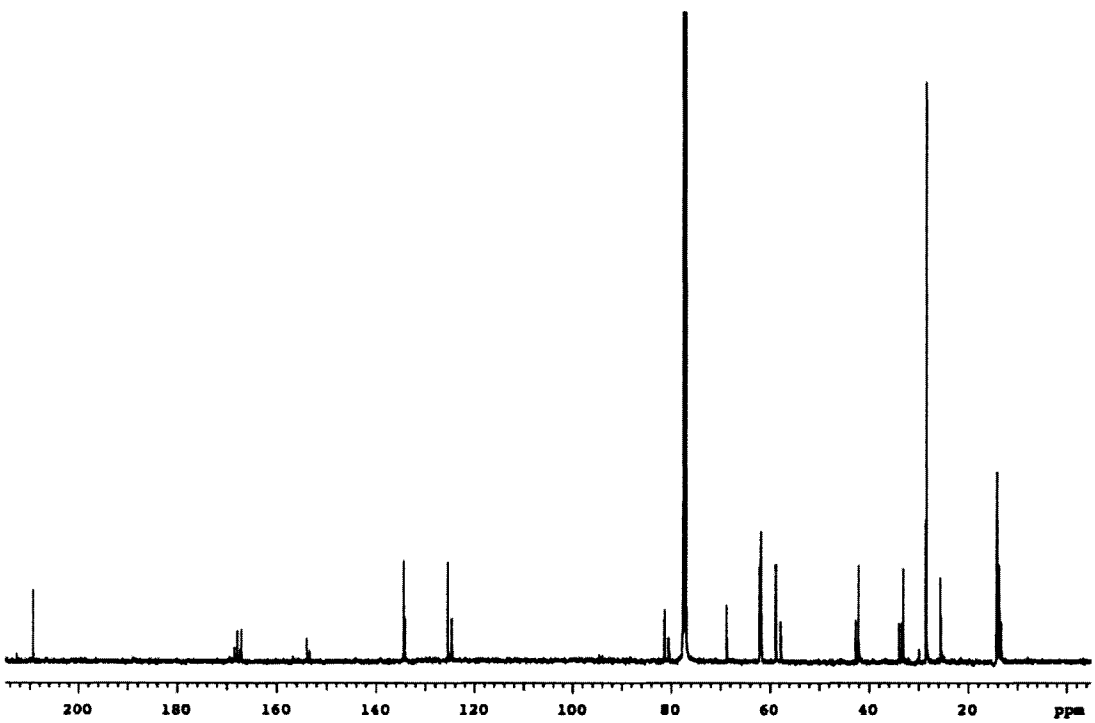


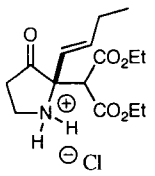


(*E*)-diethyl 2-(2-(but-1-enyl)-1-(*tert*-butoxycarbonyl)-3-oxopyrrolidin-2-yl)propanedioate (108): A flame dried round bottom flask was charged with 5 mL PhMe and 0.019 g triazolium salt **60** (0.05 mmol). A needle outlet was inserted and argon was bubbled through this solution for 5 minutes. KHMDS (100 μL of a 0.5 M solution in PhMe) was added dropwise over a span of 10 minutes to generate the active catalyst. A separate round bottom flask was charged with 0.100 g **107** (0.25 mmol) and toluene and sparged with argon for 5 minutes. This solution was taken up by syringe and added dropwise to the solution of catalyst over 10 minutes. The reaction was allowed to stir at room temperature for 1 hour and poured onto a column of silica gel. Elution with 6:1 hexanes:EtOAc provided 0.70 g **108** (70%) as a clear oil. R_f= 0.45 (3:1 Hexanes:EtOAc); $[\alpha]_D^{23}$ = - 57.5° (CH_2Cl_2, c = 8 mg/mL) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08–5.92 (m, 1H), 5.51 (ddd, 1H, *J* = 12.8, 6.2, 6.2 Hz), 4.80 (s, 0.3H), 4.41 (s, 0.7H), 4.35-4.10 (m, 4H), 3.80-3.59 (m, 2H), 2.81-2.51 (m, 2H), 2.08 (ddd, 2H, *J* = 15.0, 7.0, 7.0 Hz), 1.45 (s, 9H), 1.27 (t, 3H, *J* = 7.0 Hz), 1.24 (t, 3H, *J* = 7.0 Hz), 0.99 (t, 3H, *J* = 7.7 Hz; ^{13}C NMR (100 MHz, acetone-D6) δ 209.2, 167.9, 167.1, 153.9, 134.3, 134.2, 125.4, 124.6, 81.3, 80.4, 68.7, 62.1, 61.8, 58.7, 57.6, 42.6, 42.0, 33.9, 33.1, 28.2, 25.6, 14.2, 13.6 ; IR (NaCl, neat) 2982, 1767, 1738, 1695, 1382 cm^{-1}; HPLC analysis, Chiralcel AD-H column, 97:3 Hexanes : Isopropanol, 1 mL/min. Major enantiomer 7.72 minutes, Minor Enantiomer 10.00 minutes. HRMS (FAB+) calcd for $C_{20}H_{32}NO_7$ 398.2179. Found 398.2185.

^{1}H and ^{13}C Spectra for **108**







(*E*)-2-(but-1-enyl)-2-(1,3-diethoxy-1,3-dioxopropan-2-yl)-3-oxopyrrolidinium chloride (109): To a solution of 0.080 g **108** (0.20 mmol) in 1 mL methanol was added dropwise acetyl chloride (0.142 mL, 2.0 mmol) over 10 minutes. This was allowed to stir at room temperature for 4 hours until all starting material had been consumed. Concentration under vacuum afforded 0.063 g **109** (95%) as a yellow oil. R_f = 0.0 (EtOAc); $[\alpha]_D^{23}$ = - 35.8° (MeOH, c = 12 mg/mL) ^{1}H NMR (300 MHz, CD_3OD) δ 6.07 (ddd, 1H, *J* = 15.7, 6.2, 6.2 Hz), 5.47 (d, 1H, *J* = 16.1 Hz), 4.50 (s, 1H), 4.37-4.13 (m, 4H), 3.95-3.81 (m, 1H), 3.75-3.60 (m, 1H), 2.95-2.80 (m, 2H), 2.20-2.08 (m, 2H), 1.36-1.20 (m, 6H), 1.00 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 205.3, 165.9, 165.0, 140.3, 119.6, 68.7, 63.3, 62.5, 57.6, 40.3, 32.8, 25.7, 13.8, 13.4, 12.3 ; IR (NaCl, neat) 2967, 1767, 1731, 1367, 1250 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{24}NO_5$ 298.1654. Found 298.1655.

^{1}H and ^{13}C Spectra for **109**