UNIVERSITY OF CALGARY

Morita-Baylis-Hillman Reactions and Cyclizations of Aldimines and Activated Diene Systems

by

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Morita-Baylis-Hillman Reactions and Cyclizations of Aldimines and Activated Diene Systems" submitted by Jovina Sorbetti in partial fulfillment of the requirements for the degree of Master of Science.

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Abstract

The Morita-Baylis-Hillman (MBH) reaction, currently at the forefront of chemical research, has become a well-known, atom economical method of carbon-carbon bond formation, allowing for the synthesis of highly functionalized products. This thesis reports a novel extension of the aza-version of the MBH reaction, employing for the first time activated diene systems as substrates.

Reactions of various *N*-(benzylidene)-benzenesulfonamides were carried out with 1-(*p*-toluenesulfonyl)-1,3-butadiene in the presence of 3-hydroxyquinuclidine as a catalyst. Reactions were generally successful, yielding *E*/*Z* mixtures of the desired MBH adducts, in fair to good yields, under mild reaction conditions. The *E*-isomers of the MBH adducts, possessing both an amine functionality and an activated diene moiety, were then made to undergo an intramolecular conjugate addition reaction under basic conditions to afford substituted piperidines. The *Z*-adducts were unable to cyclize due to geometric constraints; however, equilibration of *E*- and *Z*-isomers was effected by irradiation at 300 nm. Thus, cyclizations carried out in the presence of 300nm light provided improved yields of the products.

This newly developed methodology was also applied to MBH reactions employing methyl 2,4-pentadienoate, as opposed to the *p*-toluenesulfonyl activated diene described above. These reactions also provided the desired MBH adducts in reasonable yields, again as mixtures of *E*- and *Z*-isomers. As before, the *E*-adducts could be cyclized to afford the analogous methyl ester-substituted piperidines, while the *Z*-isomers did not react.

Also described in this thesis are investigations into subsequent transformations possible for either the sulfone-substituted MBH adducts or the piperidines obtained from the latter, including a successful Heck reaction to generate a bicyclic system, as well as synthetic steps towards the natural product (±)-anabasine.

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for my dad

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List of Abbreviations

Å	Ångstroms
Ac	acetyl
Anal.	elemental analysis
Ar	aryl
atm	atmosphere
BINAP	(1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine)
BINOL	1,1'-bi-2-naphthol
br	broad
Bu	butyl
°C	degrees Celsius
calcd	calculated
cat.	catalytic or catalyst
cm^{-1}	reciprocal centimeters – wavenumbers
^{13}C NMR	carbon-13 nuclear magnetic resonance
COSY	^{1}H - ^{1}H correlation spectroscopy
d	doublet
δ	chemical shift in ppm downfield from tetramethylsilane
dd	doublet of doublets
ddd	doublet of doublets of doublets
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
de	diastereomeric exess
DEPT	distortionless enahncement by polarization transfer
DMAP	*N,N*-dimethyl-4-aminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
ee	enantiomeric excess
eq.	equivalents

ESI	electrospray ionization
Et	ethyl
EWG	electron withdrawing group
g	grams
h	hours
HMQC	^{1}H - ^{13}C correlation spectroscopy
^{1}H NMR	proton nuclear magnetic resonance
3-HQD	3-quinuclidinol
hν	light
Hz	Hertz
IR	infrared
J	coupling constant
KIE	kinetic isotope effect
LDA	lithium diisopropylamide
M	molar
m	multiplet
m	*meta*
M^{+}	molecular ion
MBH	Morita-Baylis-Hillman
Me	methyl
Mes	mesityl
mg	milligrams
MHz	megahertz
mL	milliliters
μL	microliters
mmol	millimoles
mp	melting point
MPa	mega Pascal
MS	mass spectrometry
M.Sc.	Master of Science
MVK	methyl vinyl ketone

m/z	mass to charge ratio
n or ^{n}	normal
naph	naphthyl
nm	nanometers
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
o-	*ortho*
OTf	trifluoromethanesulfonate
p-	*para*
PCy_3	tricyclohexylphosphine
Ph	phenyl
ppm	parts per million
psi	pounds/square inch
PVK	phenyl vinyl ketone
q	quartet
R	generalized alkyl group or substituent
RDS	rate determining step
rt	room temperature
s	singlet
sc	super critical
t	triplet
t- or ^{t}	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMG	tetramethylguanidine
TMPDA	*N,N,N',N'*-tetramethyl-1,3-propanediamine
TMSCl	chlorotrimethylsilane
Ts	*p*-toluenesulfonyl
w/v	weight/volume

Chapter One: Introduction

1.1. Overview

Carbon-carbon bond formation is one of the most prevalent challenges in synthetic organic chemistry. The Morita-Baylis-Hillman (MBH) reaction has, in the last four decades, become one of the most extensively studied topics in this field, with new research being published nearly every day. The MBH reaction is of particular synthetic interest because it is inherently atom economical and generates highly functionalized molecules that may serve as key intermediates for further transformations. The work presented in this thesis is a new extension of the Back research group's continuing investigation into the utility of unsaturated sulfones and describes a novel direction for the MBH reaction, employing for the first time sulfone-activated diene substrates as the Michael acceptors. We wished to establish this new methodology as well as explore possible extensions of the chemistry, including further transformations of the MBH adducts. This led primarily to the synthesis of substituted piperidine rings. An overview of the development and the current scope and utility of the MBH reaction is presented in the following section. A brief discussion of relevant sulfone chemistry will also be given.

1.2. The Morita-Baylis-Hillman Reaction

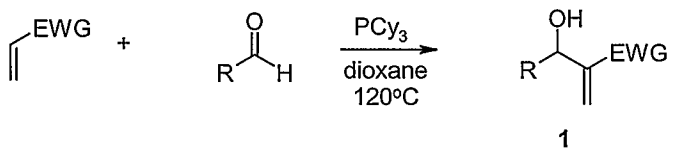
1.2.1. Background

The construction of organic molecular frameworks and target compounds relies primarily on two fundamental processes; carbon-carbon bond formation and functional group interconversions.[1] Over the years, synthetic organic chemistry has been witness to enormous advances in synthetic methodologies. For a reaction to be classified as an efficient synthetic process it must demonstrate good atom economy and selectivity, proceed in reasonable yield and be cost effective, and more and more so of late, take into account environmental considerations. Some of the most important carbon-carbon bond-

forming reactions to date include the aldol reaction and Claisen condensation, the Friedel-Crafts, Grignard, Diels-Alder, and Wittig reactions, all of which today can be found in any introductory organic chemistry textbook. More recently synthetic chemistry has seen the development of Grubb's ring-closing methathesis,[2,3] and a plethora of palladium-catalyzed reactions, including the Heck,[4,5] Stille[6] and Suzuki[7] coupling reactions.

The MBH reaction,[8-10] which also displays good atom economy and generation of highly functionalized products, can be included among the list of important carbon-carbon bond forming reactions in synthetic organic chemistry[11,12]. The reaction was first discovered by Morita's group in 1968 in the form of acrylonitrile or methyl acrylate reacting with various aldehydes in the presence of tricyclohexylphosphine to give allylic alcohol products **1** (Scheme 1).[8] Unfortunately, the reaction as reported by Morita's group suffered from poor conversions (23%), despite reasonable yields based on recovered starting materials (85%).

Scheme 1



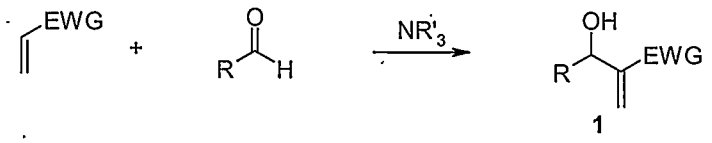
1

R = CH_3, CH_2CH_3, $(CH_2)_2CH_3$, $CH(CH_3)_2$, $(CH_2)_6CH_3$, C_6H_5, *p*-ClC_6H_4, *p*-$CH_3C_6H_4$
EWG = CN, CO_2CH_3

Four years after this work, Baylis and Hillman filed a German patent for the reaction employing several tertiary amine catalysts as a mode of preparation of acrylic compounds.[10] They stated that their nineteen title compounds were synthesized in high yields and that the three catalysts used, DABCO (**2**), pyrrocoline (**3**), and quinuclidine (**4**), remained active for long periods. The reactions were also heat tolerant as they were carried out at temperatures ranging from 10-200°C (Scheme 2). Despite Morita's earlier

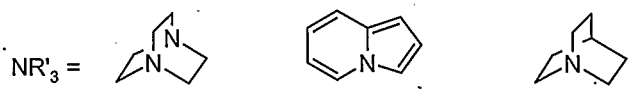
report, the patent of Baylis and Hillman was recognized first and as such this chemistry is often referred to as the Baylis-Hillman reaction.

Scheme 2



1

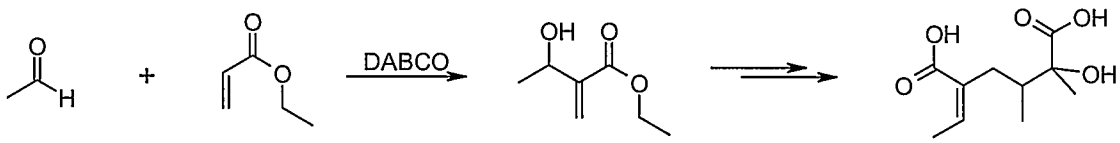
R = CH_3, Ph, $(CH_2)_2CH_3$, C_7H_{15}, *m*-ClC_6H_4, *p*-$CH_3OC_6H_4$, *p*-$NO_2C_6H_4CH_2$, $CH(CH_3)_2$, $CH{=}CHCH_3$
EWG = $CONEt_2$, $COCH_3$, CO_2CH_3, CN, CO_2Et, CO_2Ph, CO_2Cy, $COCH_2Ph$, $CO_2C_6H_4Cl$-*m*, $CO_2C_6H_4OMe$-*p*



2 3 4

Despite its obvious synthetic utility and versatility, the reaction remained unused for nearly a decade. In 1982 it resurfaced in a paper by Drewes who used it in the synthesis of **5**, a precursor to the natural product integerrinecic acid (**6**) (Scheme 3).[13]

Scheme 3

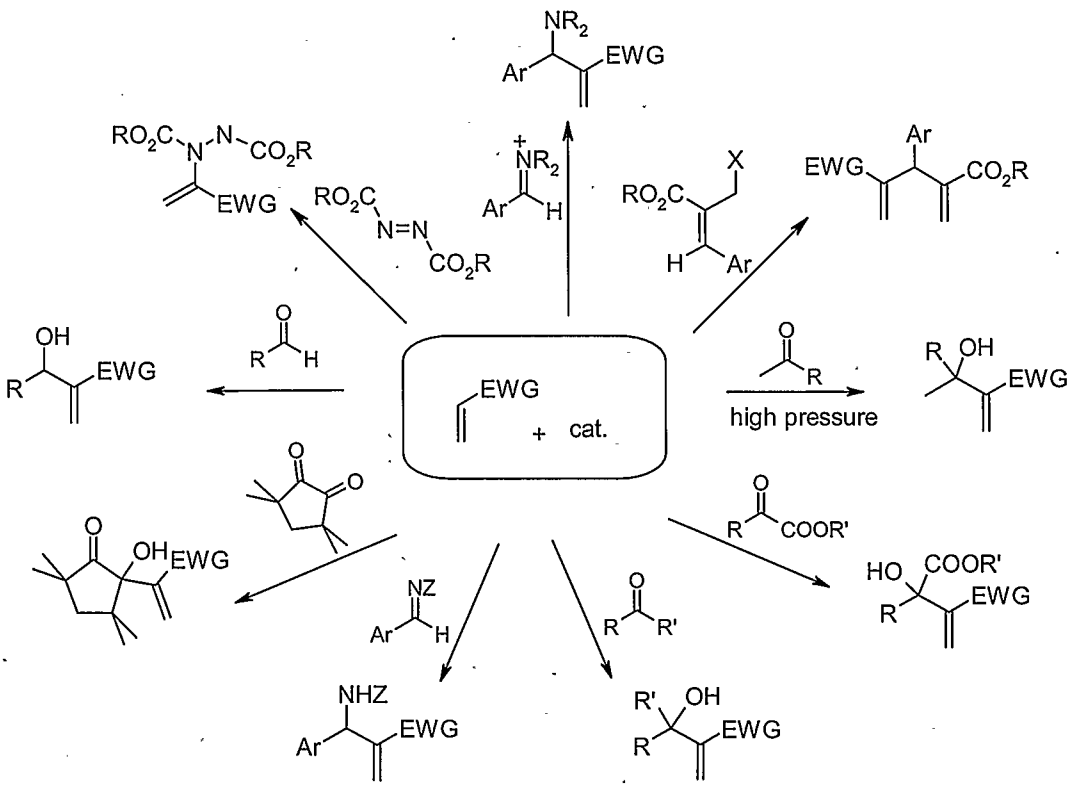


5 6

Since its reappearance, the MBH reaction has become widely investigated and intensely studied. As a result, the scope of the reaction has increased dramatically in a rather short amount of time, leading to a large number of publications and several review papers.[11,12,14,15] To exemplify, a search in SciFinder Scholar® using the terms 'Baylis' and 'Hillman' provide only two hits for the time period 1968 – 1989, over one hundred hits for the 1990's, and nearly one thousand hits from the year 2000 to the present. Initially employing only aldehydes and α,β-unsaturated carboxylic acid derivatives, the reaction

has evolved to include a variety of substrates, as well as making use of a number of different catalysts, as is generalized in Scheme 4.[12,16-18] A review article published by Basavaiah in 1996 offered a broadened definition of the MBH reaction: "a reaction that results in the formation of a carbon-carbon bond between the α-position of activated alkenes and carbon electrophiles containing electron-deficient sp^2 carbon atoms under the influence of a suitable catalyst, particularly a tertiary amine, producing multifunctional molecules."[12] This definition is still generally applicable today.

Scheme 4



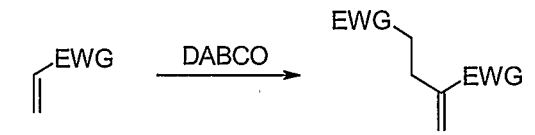
Z = tosyl, PPh_2, SO_2Ph, CO_2Me R, R' = polyfluorinated groups

EWG = CO_2R, CHO, COR, $CONH_2$, CN, SOPh, SO_2Ph, SO_3Ph, $PO(OEt)_2$

A variety of aldehydes have been employed in the reaction, including aliphatic, aromatic, heteroaromatic, and functionalized aldehydes, as well as dialdehydes.[11] In

addition, the MBH reaction can be carried out with numerous other electrophiles, as is exemplified in Scheme 4. Also, a plethora of different electron-withdrawing groups have been used to activate the alkene substrate, for example, sulfones, nitriles, esters, amides, sulfonates, phosphonates, allenic esters and so on.[12] It has been found that in general, alkene molecules having β-substituents, such as crotononitrile, and less reactive alkenes, such as phenyl vinyl sulfoxide, react only under elevated pressure.[19,20] It has also been shown that in the absence of an electrophile, the activated alkenes may act as both the electron donor and acceptor in the reaction, yielding Michael-type dimerization products (7) (Scheme 5). Basavaiah reported this type of dimerization for vinyl ketones and acrylonitrile in the presence of DABCO.[21] Similarly Drewes reported the dimerization of both aryl and alkyl acrylates.[22]

Scheme 5



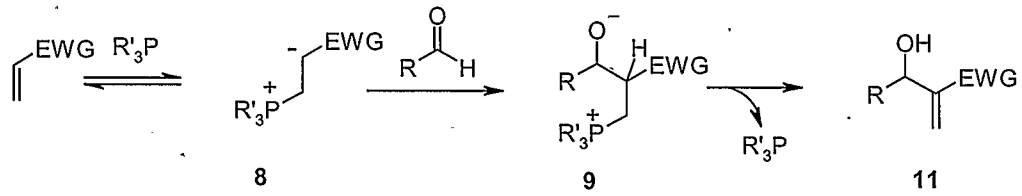
EWG = CN, CO_2R, COR **7**

1.2.2. Mechanism

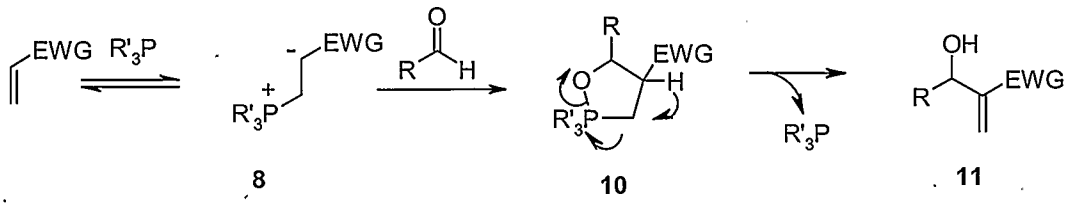
In his original publication, Morita proposed two possible mechanisms for the reaction (Scheme 6).[8] He speculated that the reaction is initiated by a Michael addition of the catalyst to the activated alkene resulting in zwitterionic intermediate **8**. This could then either undergo a nucleophilic attack on the aldehyde to generate another zwitterion (**9**) (Mechanism 1) or it could form the cyclic species **10** (Mechanism 2). The final step in either case is then the elimination of the catalyst and transfer of the α-proton to give the final allylic alcohol product **11**.[8]

Scheme 6

Mechanism 1:

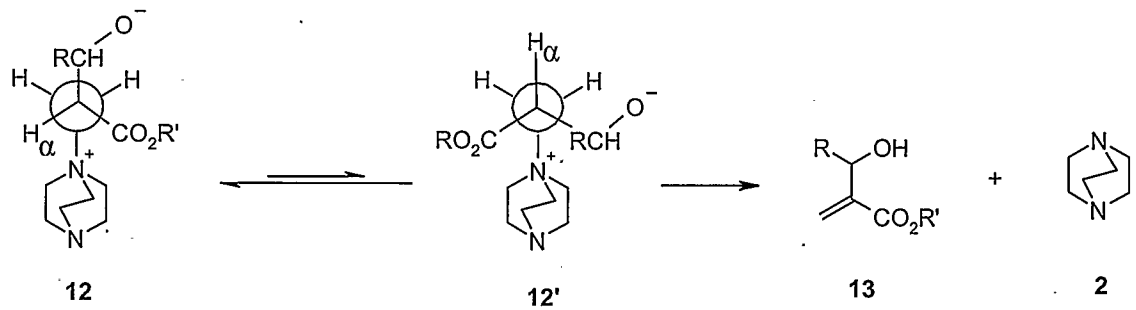


Mechanism 2:



In 1983 Hoffmann and Rabe added further detail to this mechanism, though it was not the primary focus of their publication.[23] These researchers also envisioned that the reaction proceeds by initial formation of a zwitterionic intermediate, shown as the Newman projection **12**, using DABCO as the catalyst. They proposed that this species would exist in equilibrium with its less stable conformer **12'**. It is this disfavored rotamer that provides the molecule with the anitperiplanar conformation required for concomitant elimination of the α-proton and the catalyst, leading to the final product **13** (Scheme 7).

Scheme 7



This mechanism was elaborated and supported by a number of other researchers.[24-26] In 1990 Hill and Isaacs presented their kinetic study on the MBH reaction of

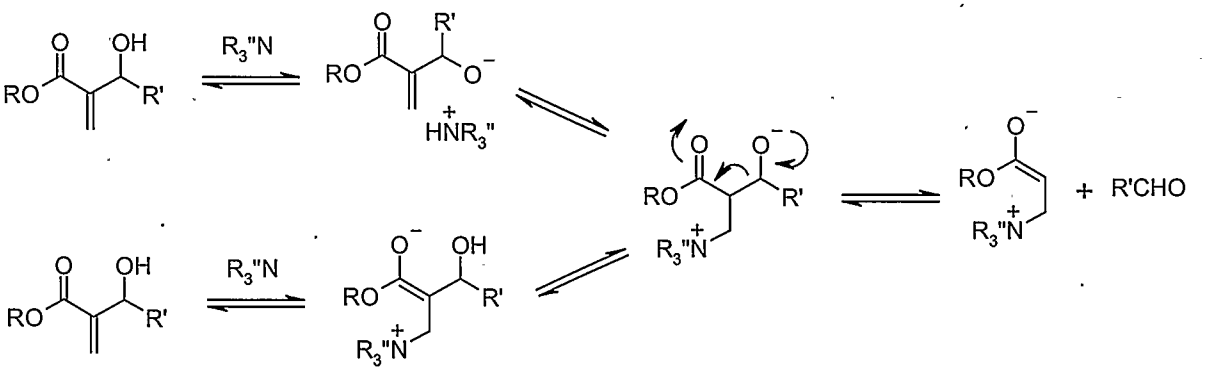
acetaldehyde and acrylonitrile in the presence of DABCO.[24] They found that the reaction was first order in each of the reactants, that is, the alkene, aldehyde, and the catalyst, and fit the rate expression shown in equation 1.

$$\text{rate} = k\,[\text{MeCHO}]\,[\,CH_2CHCN]\,[\,\text{DABCO}] \qquad (1)$$

This rate implies that formation of an intermediate involving each of the reactants must be the slow step of the reaction. The researchers therefore supported the attack of the enolate species on the aldehyde as being the rate-determining step, stating that were the initial enolate formation rate-determining, the reaction would be zero order in aldehyde. They also disregarded the possibility of the final step in the reaction being rate-limiting as they assumed that it would necessitate a second molecule of base to facilitate the elimination of the catalyst. The reaction was also carried out with α-deuterated acrylonitrile and a kinetic isotope effect of 1.03 ± 0.1 was found, implying that the proton transfer does not occur during the rate-limiting step and the authors proposed that proton transfer is actually very fast. In addition, they found a very large, negative value for the volume of activation of the reaction (-79 ± 5 cm^3/mol). The magnitude of the value suggests that this property is not due to bond formation alone, but that solvation most likely also plays a role through electrostriction. They speculated that the value could be accounted for by a mechanism involving the formation of two successive bonds in conjunction with the creation of full charges.[24]

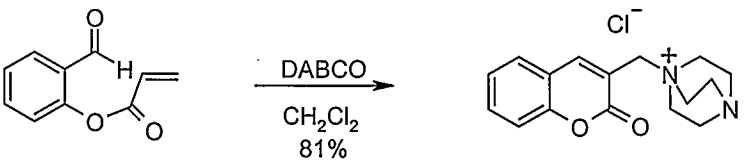
Bode and Kaye[25] also presented evidence for this mechanism in 1991, supporting the third order kinetics (pseudo second order if the concentration of the catalyst is assumed to be constant). In 1992 Caubere's group[26] added the idea that the reaction mechanism is potentially reversible and should be considered as an overall equilibrium. This arose from the observation that if the structure of the final MBH product was susceptible to proton abstraction from the hydroxyl group and concomitant elimination of the aldehyde to give an ester enolate, then they observed retrogradation products, as shown in Scheme 8.[26]

Scheme 8



Drewes, in 1993, presented experimental evidence for the formation of the key intermediates involved in the MBH reaction.[27] When carrying out an intramolecular MBH reaction with the acrylate ester of salicyladehyde (**14**) in the presence of DABCO, the coumarin salt **15** was isolated as a crystalline solid in 81% yield (Scheme 9) and was characterized by X-ray crystallography. The authors presumed that the chloride counter-ion originated from the dichloromethane solvent.

Scheme 9

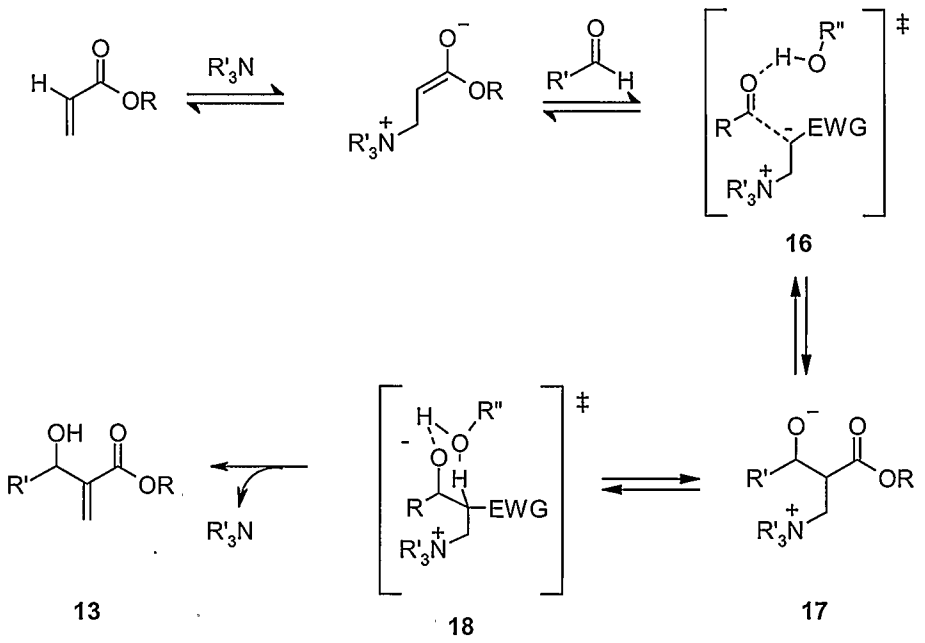


14 **15**

In 2004 significant experimental evidence for the proposed intermediates of the MBH reaction was again obtained when Eberlin's group made use of electrospray ionization mass spectrometry to follow the DABCO catalyzed reactions of methyl acrylate with both *para*-nitrobenzaldehyde and 2-thiazolecarboxaldehyde in methanol.[28] They were able to identify each of the intermediates expected based on the now long-accepted reaction mechanism according to the *m/z* ratios of the ions.

The original mechanism presented by Morita, along with some minor amendments, has thus been, until recently, the commonly accepted one. However Aggarwal suggested an autocatalytic mechanism for the MBH reaction in 2003.[29,30] While carrying out a comparative study of various *N*-catalysts, Aggarwal and coworkers observed that reactions in aprotic media catalyzed by amine compounds devoid of hydroxyl groups showed rate acceleration upon accumulation of the product. This effect was presumed to be due to the OH-group formed in the product. The observation led to the use of protic additives such as water, methanol, formamide, and triethanolamine, which also led to significant rate enhancements.[29] The study was followed up with another article in 2005, elaborating these observations.[30] It was hypothesized that the effect of the hydroxyl group was either to activate the aldehyde, as shown by transition state **16**, or to promote the formal proton transfer in the final step of the reaction via the 6-membered cyclic transition state **18** (Scheme 10).

Scheme 10



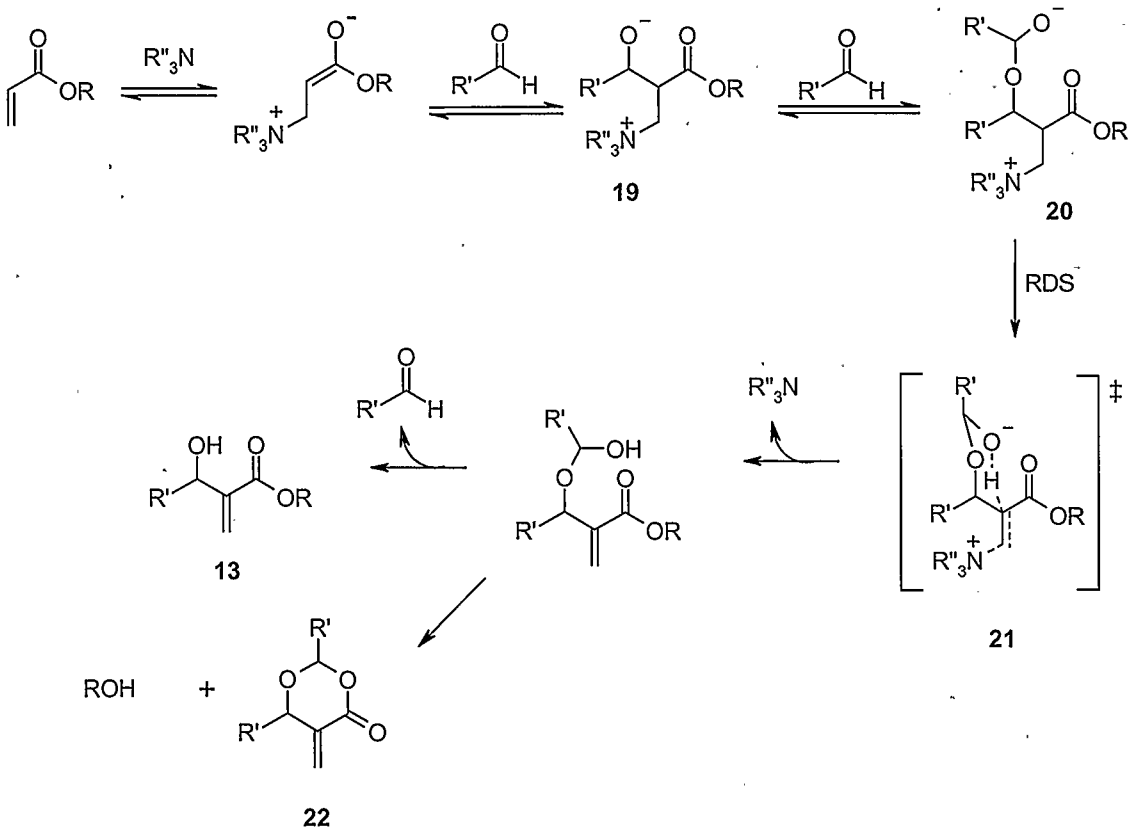
Rate acceleration through a mechanistic pathway involving **16** was thought to be unlikely, as the aldehyde and the enolate would be in competition for hydrogen bonding donors, with the latter being the stronger acceptor. Also, hydrogen bonding to the enolate

would be expected to decrease its reactivity, albeit increase its concentration in solution. Based on kinetic studies carried out with α-deuterated acrylate and the significant primary kinetic isotope effect observed in the early stages of the reaction it was determined that the proton transfer step is the rate-limiting step in the reaction until approximately 20% conversion. As the product accumulates, the final step becomes increasingly efficient and the rate-limiting step then becomes the attack of the zwitterion upon the aldehyde, as had been previously determined. Thus transition state **18** would seem to be more probable. Aggarwal stated that it is likely that this autocatalysis was not previously observed as the KIE would only be observable very early in the reaction and that studies carried out over half-lives for example, would fail to detect it.[30] However, later studies by Leitner's group on the aza-MBH reaction with MVK seem to contradict these results as they failed to detect any signs of autocatalysis.[31] Interestingly though, they found that in the absence of proton donors the reaction fit the rate law shown in equation 2.

$$\text{rate} = k\,[\text{MVK}]\,[\text{catalyst}]\,[\text{imine}]^{0.5} \qquad (2)$$

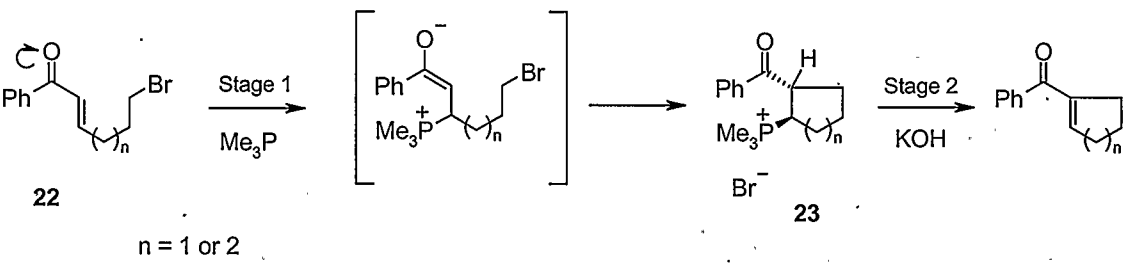
Another new interpretation of the mechanism of the MBH reaction in aprotic solvents was proposed by McQuade's research group in early 2005. They found the reaction to be second order in aldehyde and the rate-limiting step to be the final proton transfer.[32,33] Their proposed mechanism initiates as in the commonly accepted model; however, the second zwitterionic intermediate **19**, rather than undergoing elimination, goes on to react with a second molecule of aldehyde, resulting in the formation of hemiacetal species **20**. This then undergoes the rate-limiting deprotonation via the six-membered transition state **21** and the final product of the reaction is obtained after a series of post-rate-limiting steps (Scheme 11). This mechanism can also be used to explain the dioxane products (**22**) often observed when the alkene substrate is activated by an ester group.[34-37]

Scheme 11



The most recent insights into the MBH reaction were presented in a publication by Kraft and coworkers in 2006.[38,39] An intramolecular MBH reaction of α-β-unsaturated ketones **22** was carried out in a one-pot, two-stage process (Scheme 12).

Scheme 12



The second stage of the reaction required the addition of base to facilitate the final proton-abstraction step and regeneration of the catalyst, as the bromide ion generated in the first stage of the reaction is too weakly basic to carry out this transformation. This allowed for the isolation and characterization of the intermediate **23** (Figure 1). The *trans*-orientation of the substituents on the ring came as somewhat of a surprise, as this implies formation via one of the four transition states shown in Figure 1, none of which would demonstrate a strong electrostatic interaction between the enolate anion and the positively charged phosphorus ion, as would be expected. The intermediate **23** was found to be the kinetic product of the first stage of the MBH reaction indicating that the expected stabilizing phosphorus-oxygen interaction is not the major factor in the stereochemical outcome of the process, nor an explicit requirement of the reaction.[39]

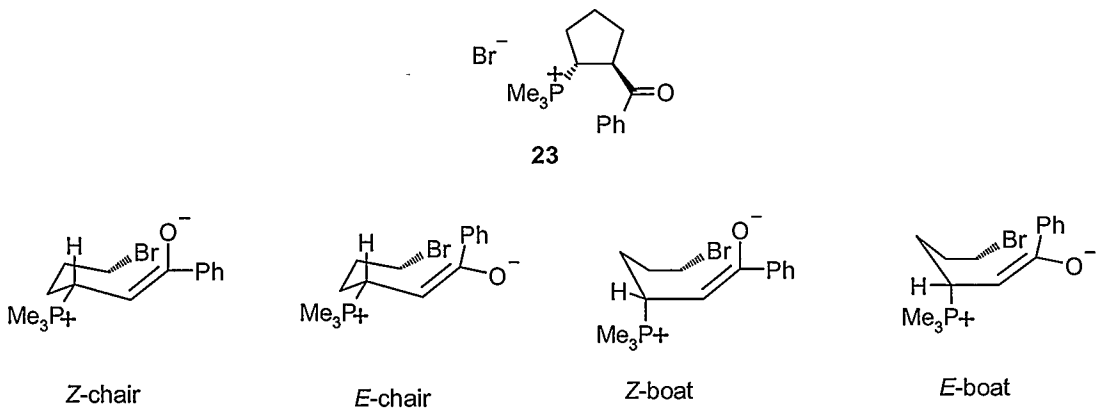


Figure 1. Structure of MBH Intermediate

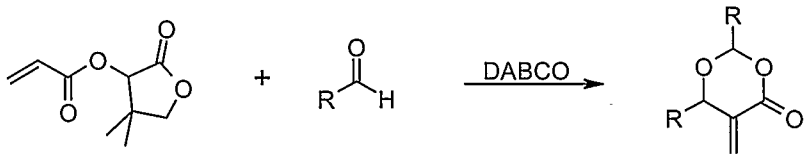
1.2.3. Common Byproducts

Along with the Michael-type dimers mentioned in Section 1.2.1, the MBH reaction has seen several other recurring byproducts. In many cases however, the discovery of these side products has led to the development of new methodologies as the compounds are often synthetically interesting.

1.2.3.1. Dioxanes

One very common side reaction involves the formation of dioxane products, as first reported by Drewes in the case of the reaction of **24** with aliphatic aldehydes (Scheme 13).[34,40] The dioxane product **25** is the result of the reaction of **24** with two molecules of the aldehyde, followed by an intramolecular transesterification (see Section 1.2.2, Scheme 11). In contrast, the reactions employing aromatic aldehydes gave only the MBH products.[34]

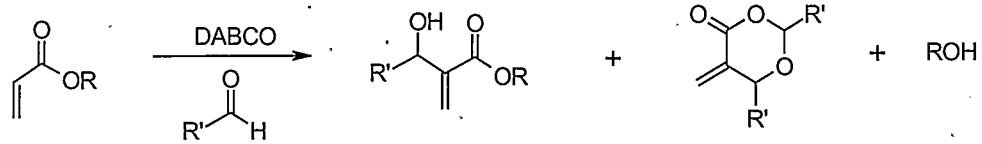
Scheme 13



24 **25**

Similarly, Perlmutter found that aliphatic aldehydes reacted very quickly under MBH conditions to afford the dioxane molecules **26**, whereas those reactions employing aromatic aldehydes preferentially afforded the desired MBH adducts **13**. Interestingly, they also found when either 2,6-dimethylphenyl or mesityl acrylate was employed in the reaction, the MBH products were favored (Scheme 14, Table 1).[35]

Scheme 14



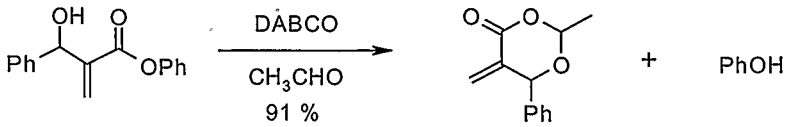
13 **26**

Table 1. Yields of Dioxane versus MBH Products

R	R'	Yield **13** (%)	Yield **26** (%)
Ph	Ph	78	-
Me	Ph	39	-
Ph	Me	-	57
Ph	^{i}Pr	-	95
2,6-$(CH_3)_2C_6H_3$	Me	31	5
Mesityl	Me	38	5

It was also found that the isolated MBH products could subsequently be reacted with acetaldehyde to afford the mixed cyclic acetals **27** (Scheme 15).[35]

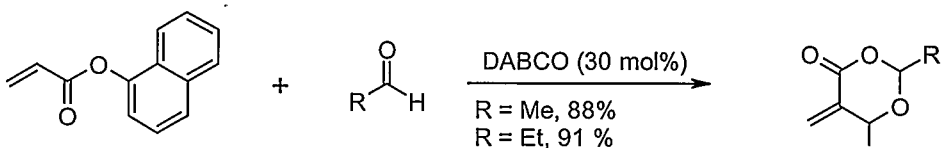
Scheme 15



27

Chen and coworkers observed dioxane byproducts in 3-10 % yields for their reactions employing α-naphthyl acrylate **28** and a variety of different aldehydes.[41] When the reactions were carried out using four equivalents of aldehyde over longer periods, it was found that the cyclic acetals **29** were the predominant products and could be obtained in good yields (Scheme 16).

Scheme 16

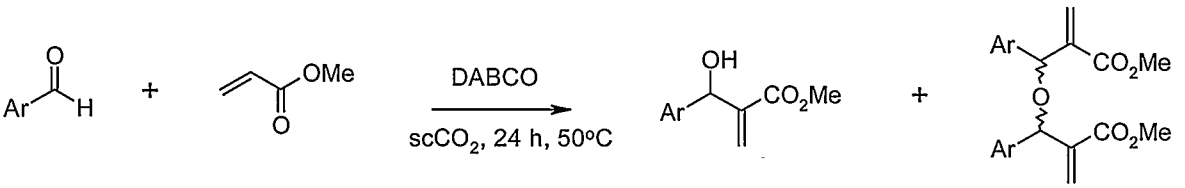


28 **29**

1.2.3.2. Ethers

In a study carried out in supercritical CO_2, Rayner found that while the MBH reaction rates were accelerated, at lower pressures an ether dimerization product of MBH adducts (**30**) was formed preferentially (Scheme 17).[42]

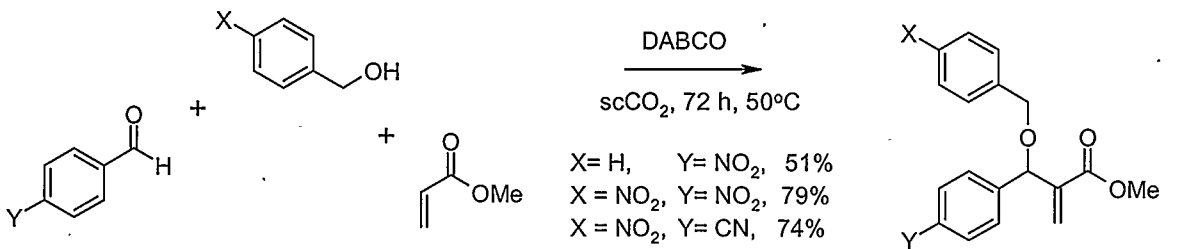
Scheme 17



30

They found that the yields of the dimers could be further increased by carrying out the reaction in two steps, first isolating the MBH-adduct and then re-subjecting it to the reaction conditions, but at higher pressure. This then led to the development of a one-pot, three component reaction involving the initial MBH reactants and an unrelated alcohol, leading to the formation of unsymmetrical ether products (**31**) (Scheme 18).[42]

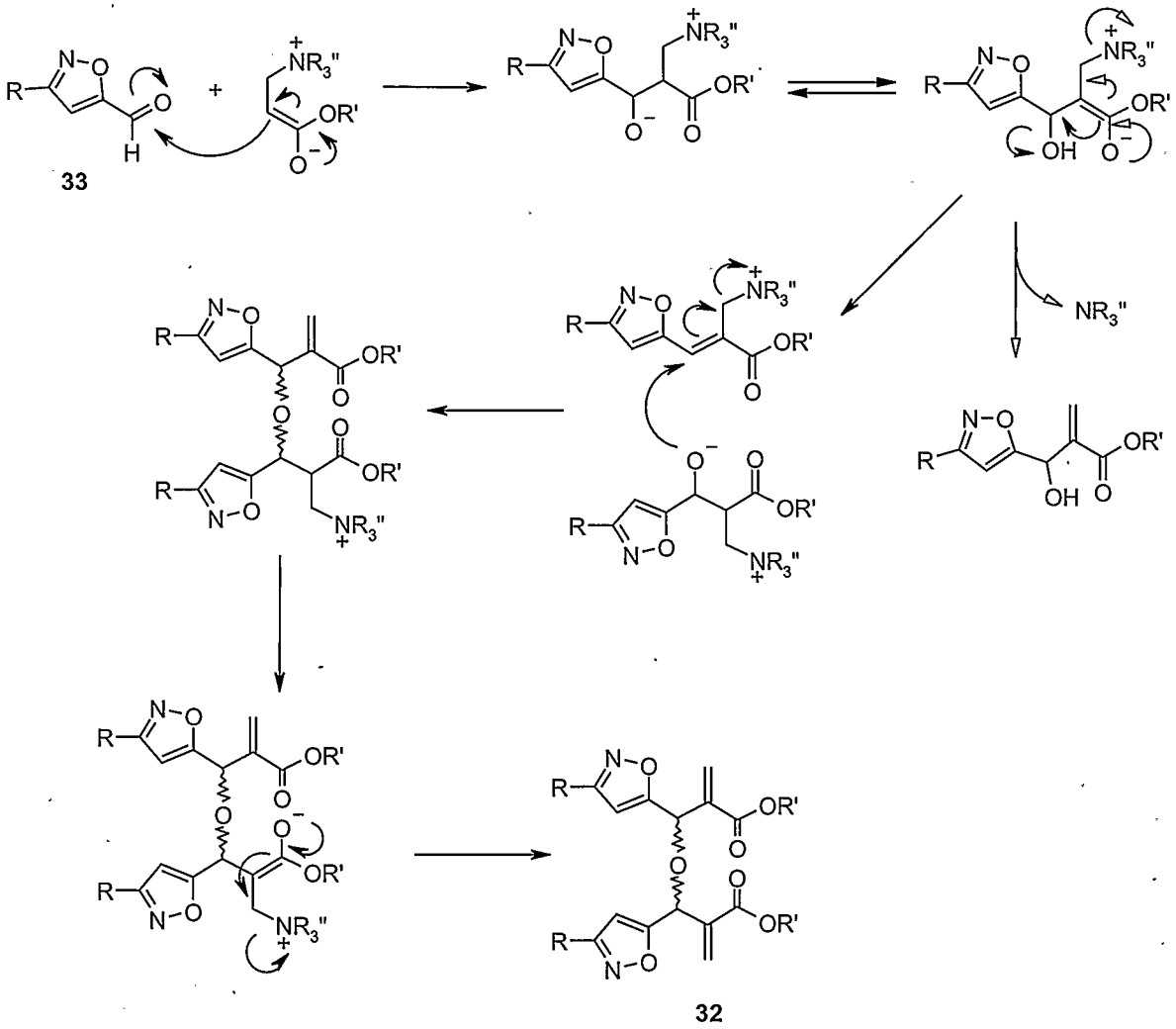
Scheme 18



31

In 2003, Batra and coworkers also observed the formation of ether byproducts **32** when using the fast-reacting 5-isoxazolecarboxaldehyde (**33**) in the MBH reaction with various acrylates and DABCO. In contrast to Rayner's[42] work, they found that they were unable to generate the ether products from the acetates of the isolated MBH adducts themselves, in the presence of DABCO and either 4-nitrobenzyl alcohol or 4-methoxy-benzyl alcohol. Based on these observations they proposed the mechanism depicted in Scheme 19.[43] Substituting the benzyl alcohols for phenol in the reaction with the MBH-acetates did however lead to formation of the desired ether products, presumably due to the greater nuclephilicity of the phenoxide anion as compared to the benzyl alcohols.

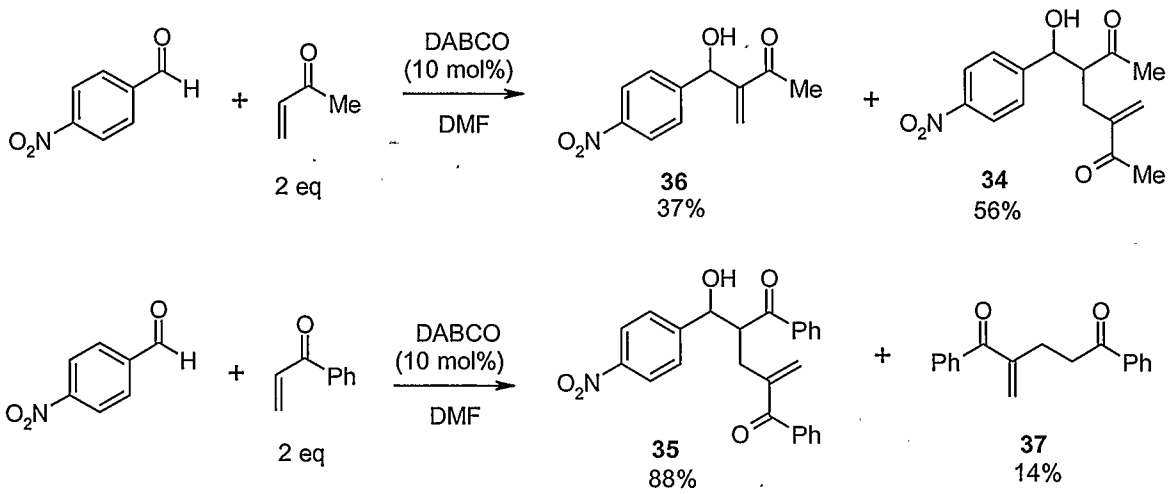
Scheme 19



1.2.3.3. Diadducts

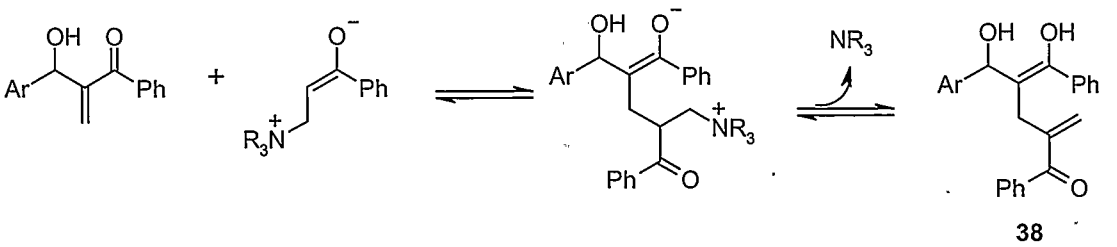
Shi and coworkers reported the formation of what they termed diadducts (**34, 35**) for the MBH reactions of *para*-nitrobenzaldehyde with either MVK or PVK in the presence of DABCO in DMF.[44,45] Reactions employing MVK provided the desired MBH adduct **36** as only a minor product, whereas in the case of PVK, the authors did not observe any of the expected MBH adducts at all, isolating diadduct **35** as the major product, as well as the PVK dimer **37** (Scheme 20).[45]

Scheme 20



Similar yields of diadducts **38** were also obtained using *ortho*- and *meta*-nitrobenzaldehyde, and 2- and 3-pyridylaldehydes. However, in the case of benzaldehyde and *para*-chlorobenzaldehyde, the PVK dimer (**37**) was essentially the only product. Based on the observation that no reaction occurred between *para*-nitrobenzaldehyde and the PVK dimer, the following mechanism was proposed for the formation of **38** (Scheme 21).

Scheme 21



38

1.2.3.4. Abnormal Adducts

The Shi group has also made several reports on their observation of 'abnormal MBH adducts' being formed as side products.[46-48] For the MBH reaction of *N*-benzylidene-4-methylbenzenesulfonamide with MVK they obtained the expected MBH products (**39**) in good yields using either DMAP, DABCO, or, especially PPh_3 as the Lewis base. Neither DBU, NEt_3, nor SMe_2 were successful in catalyzing the reaction. Interestingly, use of PBu_3 as a catalyst led to the production of only abnormal adducts **40** and **41** (Scheme 22, Table 2).

Scheme 22

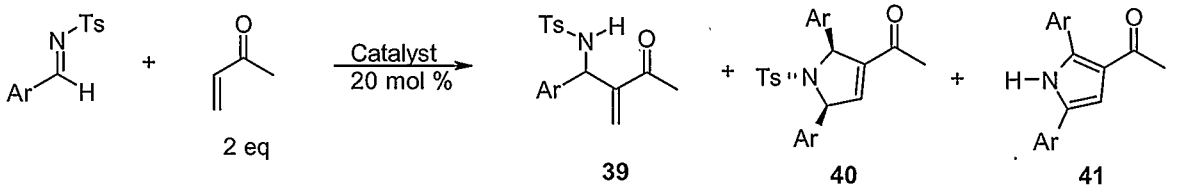
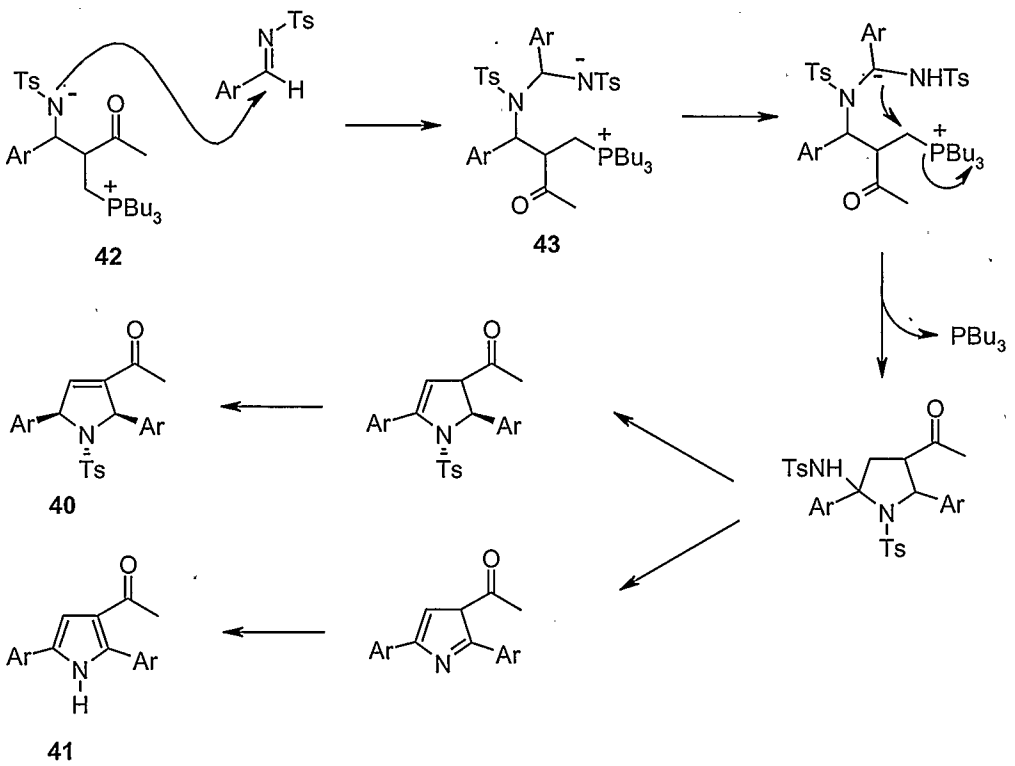


Table 2. Normal and Abnormal MBH Adducts Obtained with MVK in THF

Using PPh_3, 24 h		Using PBu_3, 2 h	
Ar	Yield **39** (%)	Yield **40** (%)	Yield **41** (%)
Ph	75	31	48
p-MeC_6H_4	92	48	28
p-$MeOC_6H_4$	70	65	20
p-ClC_6H_4	80	29	43
2,3-$Cl_2C_6H_3$	45	-	-
m-FC_6H_4	87	18	44
2-furyl	78	42	19

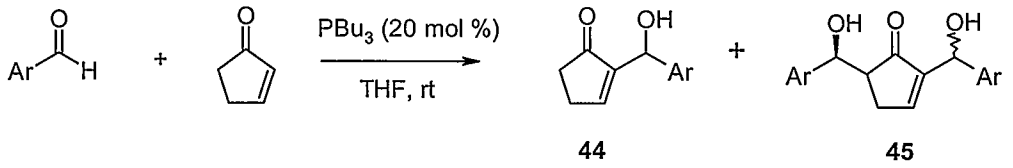
The mechanism proposed for the MBH reaction, initiated by the typical zwitterionic complex (**42**), is shown in Scheme 23. Presumably, the increased nucleophilicity of PBu_3 compared to PPh_3 results in greater concentrations of **42** and the increased reaction rates observed. The greater Lewis basicity would also facilitate the attack of **42** on a second molecule of imine to give intermediate **43**, eventually leading to the cyclic products **40** and **41**.[46]

Scheme 23



The formation of a similar minor product (**45**) was also observed in the reaction of various aryl aldehydes with cyclopentenone, again when using PBu_3 as the catalyst (Scheme 24, Table 3).[47]

Scheme 24



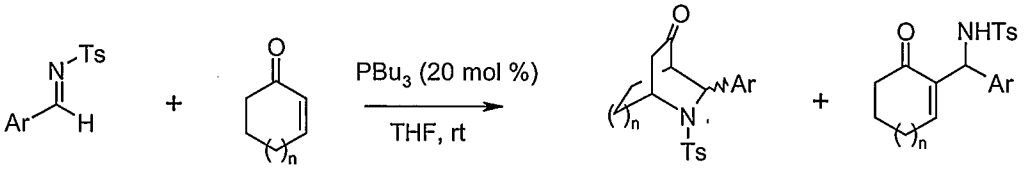
44 45

Table 3. Normal and Abnormal MBH Adducts Obtained with Cyclopentenone in THF

Ar	Time (h)	Yield **44** (%)	Yield **45** (%) (*syn:anti*)
Ph	24	59	24 (65:35)
p-ClC_6H_4	7	79	11 (70:30)
p-EtC_6H_4	24	84	-
p-$MeOC_6H_4$	8	75	-

In the same publication, Shi also reported the formation of some interesting compounds (**46**) formed from the reaction of *N*-arylidene-4-methylbenzenesulfonamides with enolizable ketones, in addition to the MBH adducts **47** (Scheme 25, Table 4).[47,48] These bicyclic molecules are formed via the aldol condensation of the enolate of the ketones with the imines, followed by a subsequent intramolecular Michael addition of the resulting nitrogen anion to the α,β–unsaturated ketone moiety.[47]

Scheme 25



n = 1 or 2

46 47

Table 4. Normal and Abnormal MBH Adducts Obtained in THF at Room Temperature

Ar	Time (h)	Yield **46** (%) (*endo*)	Yield **46** (%) (*exo*)	Yield **47** (%)
Ph	24	16	22	16
p-$NO_2C_6H_4$	24	10	25	15
p-EtC_6H_4	3	10	18	32
p-$MeOC_6H_4$	24	25	23	25

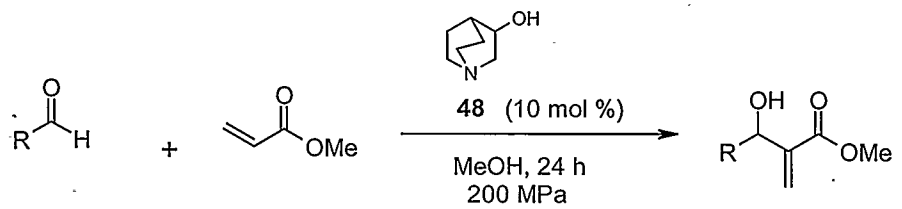
1.2.4. Scope, Limitations, and Improvements

One of the major and most prevalent drawbacks of the MBH reaction is its sluggish rate and its sensitivity to the conditions employed. Many attempts have been made to overcome these deficiencies, which has in turn led to the enhanced scope of the MBH reaction seen today. Variation in the substrates and catalysts has been examined, as well as the effects of temperature, pressure, solvents, and additives. Certain researchers have even made use of techniques such as microwave irradiation[49] and ultrasound[50-52], while others have examined the reaction in ionic liquids[53,54] or supercritical CO_2[42] as solvents in order to increase the reaction rates. Some of the more commonly used techniques are discussed below.

1.2.4.1. Pressure

Several researchers have noticed increased reaction rates for the MBH reaction under increased pressure. As mentioned in Section 1.2.2, Hill and Isaacs found that the MBH reaction has a negative volume of activation, implying that a large rate increase should be possible with an increase in pressure.[24] Hayashi's group[55] has recently used the pressure induced by the freezing of water to increase the rate of the MBH reaction. They found that by placing the reaction mixtures in Teflon tubes inside an autoclave filled with water, which was in turn placed inside a freezer, they could obtain pressures of up to 200 MPa within 12 hours. Thus, under these conditions the reactions of methyl acrylate and a variety of different aldehydes were carried out in methanol in the presence of 3-hydroxyquinuclidine (**48**) (3-HQD) over a 24 hour period and the outcomes were compared to those of the reactions carried out under atmospheric pressure (Scheme 26). In general they noticed large increases in the reaction rates, except in the case of aliphatic aldehydes which gave lower yields under elevated pressure.

Scheme 26



R = C_6H_5, *o*-ClC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-FC_6H_4, p-$MeOC_6H_4$, *p*-$NO_2C_6H_4$, C_4H_3O, C_6H_5CHCH, C_3H_7

Jenner and Salem successfully carried out the MBH reaction of acrylonitrile and a variety of ketones at 300 MPa, obtaining good yields of the desired products. In an attempt to expand this methodology to reactions involving acrylamide; however, they found that they obtained only very low yields of the products. They then examined the effects of increasing the pressure to 900 MP in the case of the acrylamides, which resulted only in the isolation of generally unstable oligomers resembling polyacetals, the exact structures of which are unknown.[56]

1.2.4.2. Temperature

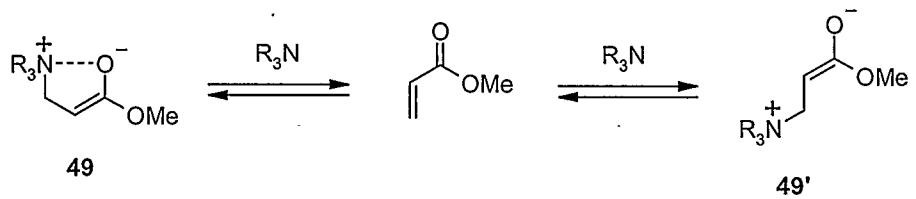
Despite Baylis and Hillman's report that MBH reactions can be carried out at temperatures of up to 200°C,[10] it seems that in such processes an increase in temperature is not necessarily an effective modification of the reaction conditions and may actually lead to unwanted results.

During their study of the use of ultrasound techniques in the MBH reaction, Roos and Rampersadh noted that a gentle increase in temperature led to a notable increase in the rate of the reactions of methyl acrylate and various aldehydes. However, using the slightly harsher conditions of refluxing, either neat or using various solvents, led to the formation of either or both side products and polymeric materials.[50] Similarly, Balan and Adolfsson reported that a slight increase in the yield for the reaction of benzaldehyde and

methyl acrylate could be obtained when the reaction was carried out at 40°C as compared to room temperature, but that any further increase in temperature led to a significant decrease in the yield.[57] In an aza-version of the MBH reaction, Shi's group noticed that at temperatures above 30°C yields were decreased as a result of polymerization of MVK.[58]

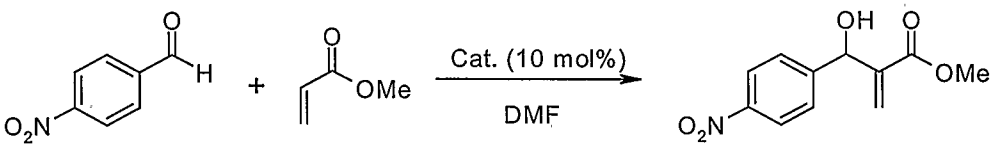
Leahy and Rafel observed that while the rate of the reaction was indeed increased with warming, the methyl acrylate substrate was more likely to polymerize, decreasing the overall yield of the products as well as making them more difficult to purify. Surprisingly, they also observed a rate increase for the reaction of methyl acrylate and acetaldehyde with a decrease in temperature, such that it proceeded more quickly at 0°C than at room temperature.[59] They speculated that this could be due to the equilibrium between two possible conformations of the enolate intermediate (**49** and **49'**), each of which would have a different reactivity with the aldehyde substrate, and that the concentration of the two species would likely be different at high or low temperatures, leading to the different rate increases at both high and low temperature (Scheme 27).[59]

Scheme 27



In 2004, another group reported similar findings with respect to the effects of temperature on the MBH reaction.[60] In the reaction of *para*-nitrobenzaldehyde and methyl acrylate they found that the MBH product **50** was obtained in better yield at -5°C than at 25°C. Perhaps somewhat surprisingly, they also observed an improvement in the rate when the reaction was carried out at 76°C (Scheme 28, Table 5).

Scheme 28



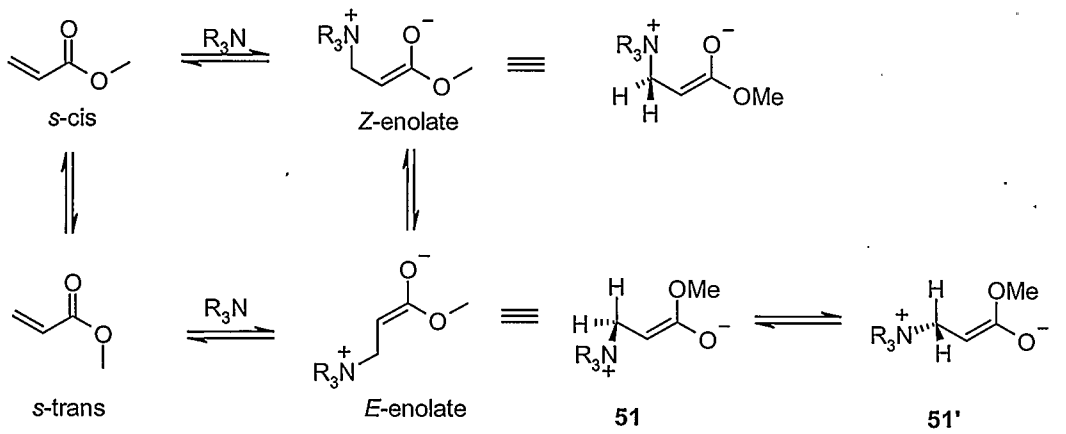
50

Table 5. Effects of Temperature on MBH Reaction with DMAP and DABCO

Using DABCO			Using DMAP		
Temp (°C)	Time (h)	Yield **50** (%)	Temp (°C)	Time (h)	Yield **50** (%)
76	4	98	76	5.5	98
25	5.5	40	25	5.5	10
25	17	98	25	96	98
-5	4	90	-5	5.5	85

They speculated that this was indicative of an entropy driven reaction in which the configurations of the *E*- and *Z*-enolates of the catalyst-acrylate intermediate would have differing temperature-dependent concentrations (Scheme 29). Thus, at lower temperatures, it would be expected that the *Z*-enolate, having a stabilizing electrostatic interaction, would be the preferred conformation. They proposed that this is the more reactive enolate because approach of the aldehyde on either the *re*- or the *si*- face would encounter little in the way of steric hindrance. In contrast, as a result of an interaction between the pi-orbitals of the double bond and the σ* orbitals of the C-N bond, the *E*-enolate is expected to have two predominant conformers **51** and **51'**, both of which would be more sterically crowded with respect to the approach of the aldehyde (Scheme 29).[60]

Scheme 29



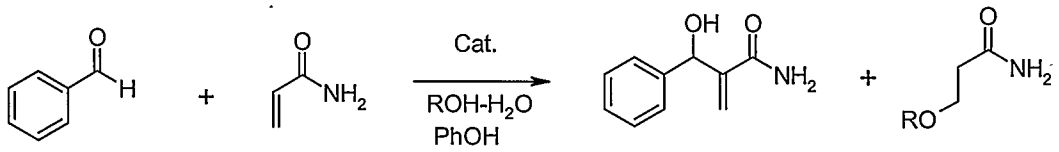
1.2.4.3. Substrates

There have been many attempts to find the 'ideal' substrates for the MBH reaction, contributing greatly to the expansion of scope and increasing our understanding of the effects of differing activating groups, substituents, and carbon electrophiles. Unfortunately however, it seems that there is no generalized formula, and many of the successful reactions seen in the literature are very substrate-specific and not necessarily broadly applicable.

As was alluded to in Section 1.2.1, β-substituted alkenes tend to be less reactive than their unsubstituted counterparts;[20,61] however, there have been examples in which they react under relatively mild conditions.[62] Not surprisingly, the reaction rate appears to depend quite strongly on the electrophilicity of the vinyl component. For example, Amri and Villieras found that in the reaction involving formaldehyde and DABCO, use of MVK, acrylonitrile, and methyl acrylate, required 30 hours, 40 hours, and 7 days respectively.[63] Enonès and enals such as MVK and acrolein generally show greater reactivity than α-β-unstaurated esters.[62] The less electrophilic acrylamides generally don't do well in the MBH reaction, though they have been used successfully under select

reaction conditions.[64-66] Very recently for example, Connon and coworkers found that DABCO in an aqueous alcohol medium with phenol as an additive was effective in promoting the MBH reaction of acrylamide with a variety of aromatic aldehydes, affording the desired products in reasonable to good yields. However, variations of either the solvent or the catalyst often led to formation of the addition byproducts **52** (Scheme 30).[66]

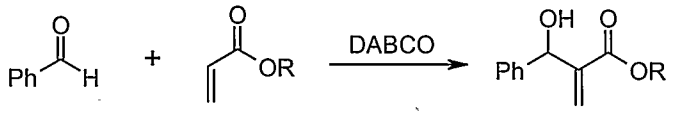
Scheme 30



52

Acrylates appear quite regularly in the MBH literature, and seem often to be reagents of choice for studies relating to the reactivity of the other components involved in the reaction.[11] Aryl acrylates tend to react faster than alkyl acrylates, though the rates of the latter can be increased with electron-withdrawing functionalities on the alkoxy moiety of the ester (Scheme 31).[12,26] Similarly, methyl acrylate has been noted to react faster than the ethyl or isopropyl derivatives, presumably due to the inductive effects associated with the longer alkyl chains.[25] Steric effects also play an important role, with a decrease in rate being observed for bulkier acrylates, which presumably impede catalyst approach.[26] Interestingly, electron-withdrawing substituents on the aromatic rings of the aryl acrylates generally lead to a slight decrease in the reaction rate, likely due to decreased nucleophilicity of the zwitterionic intermediate, impeding its attack upon the aldehyde.[26] Basavaiah found that terminal hydroxyalkyl acrylates showed increased reaction rates, possibly due to an intramolecular stabilization of charged intermediates via hydrogen-bonding.[67]

Scheme 31

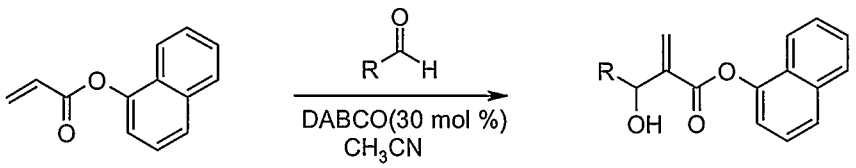


R	Time
CH_2CH_2EWG	2-3 days
CH_2CH_3	3-5 days
Ar	7 days
$C(CH_3)_3$	28 days

EWG = F, Cl, Br

Chen and coworkers found that by using α-naphthyl acrylate as the Michael acceptor in the MBH reaction with benzaldehyde there was a significant increase in the rate as compared to those observed for other esters of acrylic acid (Scheme 32).[41] The same reaction employing β-naphthyl acrylate required five hours to complete, providing a 70 % yield of the product, whereas the α-naphthyl derivative reacted to afford an 88% yield in 20 minutes. They noticed similar rate enhancements for a variety of different aldehydes with reactions generally providing reasonable yields of products after only 10-20 minutes.

Scheme 32

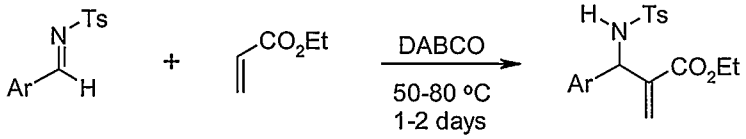


With respect to the carbon electrophiles involved in the reaction, electrophilicity is again a key factor in the reaction rate. Generally speaking, aldehydes tend to react faster than aldimines, keto esters, or simple ketones, which react only under high pressure.[12] Among the aldehydes both aromatic and aliphatic aldehydes have been employed. The reactivity of the aliphatic aldehydes tends to decrease with increasing chain length.[68] Aromatic aldehydes having electron-withdrawing substituents such as nitro groups often show decreased reaction times, though in some cases complex mixtures of products result.[35] Rates of reactions employing aldimines can be significantly increased through

appropriate activation by electron-withdrawing *N*-substituents.[11] Alkyl halides have also been employed as carbon electrophiles in intramolecular MBH reactions,[38,39] similar to allylic halides, which have been used in both intermolecular[17,18] and intramolecular[69] reactions.

Perlmutter and coworkers were the first to employ imines in the place of aldehydes as the electrophilic acceptor in the MBH reaction.[70] They synthesized a variety of tosylimines from aromatic aldehydes and reacted them with ethyl acrylate and 10 mole % DABCO to obtain the corresponding MBH adducts in good yield (Scheme 33).

Scheme 33



Ar	Yield (%)
C_6H_5	80
4-MeC_6H_4	73
4-$MeOC_6H_4$	70
3-$NO_2C_6H_4$	53

Bertenshaw and Kahn carried out the aza-MBH reaction using an in situ generated imine as a route to β-amino acid precursors.[61] They found that the method was successful with both aromatic and aliphatic imines and that those activated by the strongly electron-withdrawing *para*-tolylsulfonyl group resulted in higher yields than the corresponding *N*-Boc or *N*-Cbz derivatives (Scheme 34, Table 6). Use of β-substituted acrylates resulted in no isolable products under the reaction conditions used (Table 6).[61]

Scheme 34

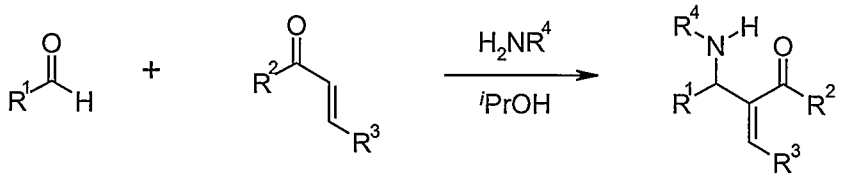
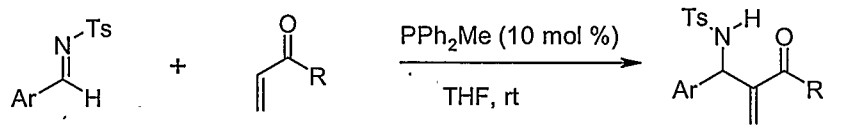


Table 6. In Situ Aza-MBH Reaction

R^1	R^2	R^3	R^4	Yield (%)
Ph	MeO	H	Ts	98
Ph	Me	H	Boc	50
^{n}Pr	MeO	H	Ts	80
Ph	MeO	H	Cbz	53
Ph	MeO	Me	Ts	0

Shi and coworkers have carried out extensive research in the area of the aza-MBH reaction. They found that use of *N*-tosylated imines in the place of aldehydes leads to a rate enhancement in the reactions with α-β-unsaturated aldehydes, ketones, and esters.[58] Reactions were generally complete within an hour and were successful for a wide range of imines, but were particularly sensitive to the conditions employed (Scheme 35). In general, phosphine catalysts were found to be more efficient than amine catalysts, with PPh_2Me providing the best results. Temperatures greater than 30°C led to polymerization of MVK. The substituents on the phenyl ring of the aromatic imines did not affect the reaction rates to any large extent, though as would be expected, slightly faster reactions occurred in the case of electron-withdrawing substituents, particularly for reactions involving acrolein and phenyl or α-naphthyl acrylates. Methyl acrylate was found to react slowly under these reaction conditions and better results were obtained when using DABCO as a catalyst. The authors suggest that in the case of less reactive Michael acceptors such as MVK, phenyl acrylate, or α-naphthyl acrylate that stronger nucleophilic catalysts such as PPh_2Me should provide improved results. Reactions employing aliphatic *N*-tosylated imines with MVK, acrolein, or phenyl acrylate all led to complex mixtures of products.[58]

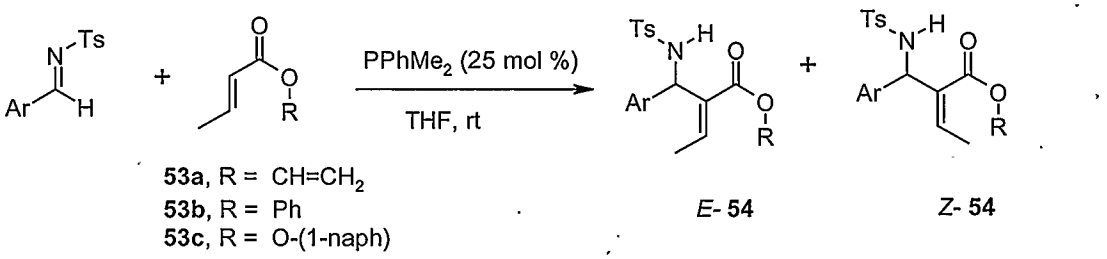
Scheme 35



R = H, Me, MeO, PhO, O-(1-naph)

Expansion of this work came just recently with the successful MBH reactions of vinyl crotonate (**53a**), phenyl crotonate (**53b**), and α-naphtyl crotonate (**53c**) with a variety of *N*-tosylated imines, using $PPhMe_2$ as the catalyst (Scheme 36).[62] Reactions with **53c** resulted in the highest yields of adduct **54**, presumably due to increased stabilization of the charged intermediates through stereoelectronic effects. As had been previously observed,[71] the presence of electron-donating substituents on the aromatic moiety in the imine substrate slowed the reaction in comparison to substrates possessing electron-withdrawing groups.

Scheme 36

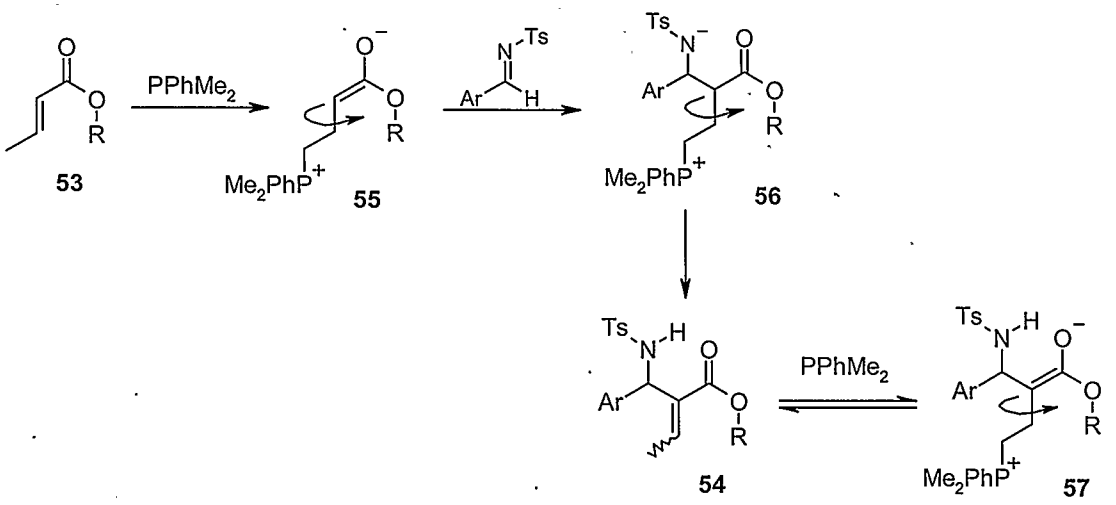


53a, R = $CH{=}CH_2$
53b, R = Ph
53c, R = O-(1-naph)

E- **54** *Z*- **54**

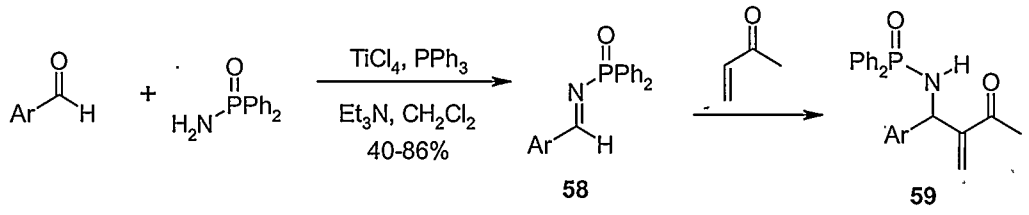
Again, products were obtained as mixtures of geometric isomers, with the *E*-isomer predominating. The isomeric mixtures were determined to arise from the free rotation about the single bond formed upon addition of the catalyst to **53** in the course of the reaction, or, equally as likely, from an addition-elimination reaction of the catalyst to product **54** to generate zwitterions **55-57** (Scheme 37).[71]

Scheme 37



Shi's group has also reported the aza-MBH reaction of *N*-arylidenediphenyl-phosphinamides (**58**) with MVK, methyl acrylate, and acrylonitrile, using a variety of catalysts (PPh_3, PPh_2Me, or DABCO) to form products **59**.[72] This unprecedented reaction was later expanded to include a one-pot version in which the arylidene-diphenylphosphinamide **58** is generated in situ, such that reaction of the aldehyde, MVK, diphenylphosphinamide, and $TiCl_4$ leads directly to the formation of adduct **59** (Scheme 38).[73] The triethylamine was necessary in the reaction to scavenge the HCl produced, but does not act to catalyze the MBH reaction. Replacing MVK with acrylonitrile or acrolein resulted in no reaction taking place.

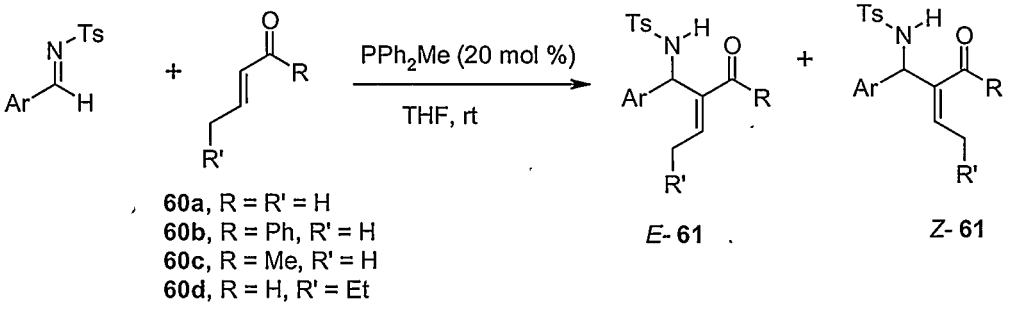
Scheme 38



Ar = *p*-MeC_6H_4, *p*-EtC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-FC_6H_4, *p*-$NO_2C_6H_4$, $C_6H_5CH{=}CH$, 1-naph, *m*-$C_6H_5OC_6H_4$,

In continuation of their studies of the aza-MBH reaction, the Shi group examined reactions employing β-substituted activated olefins with the expectation that the increased electrophilicity of the activated imines would promote attack by the zwitterionic ammonium species even if formed only in low concentration as a result of the steric bulk of the olefins.[71] They again found that PPh_2Me was the optimum catalyst, for reactions employing crotonaldehyde (**60a**) and phenyl-(*E*)-propenyl ketone (**60b**) with a variety of imines carried out at room temperature in THF (Scheme 39). Use of pent-3-en-2-one (**60c**) or (*E*)-hex-2-enal (**60d**) showed no reaction under the above conditions, but produced low to moderate yields when using $PPhMe_2$ in the place of PPh_2Me. All products were obtained as mixtures of the *E*- and *Z*- isomers of **61** with the former predominating. In general, electron-withdrawing substituents on the aromatic imine led to shorter reaction times.[71]

Scheme 39



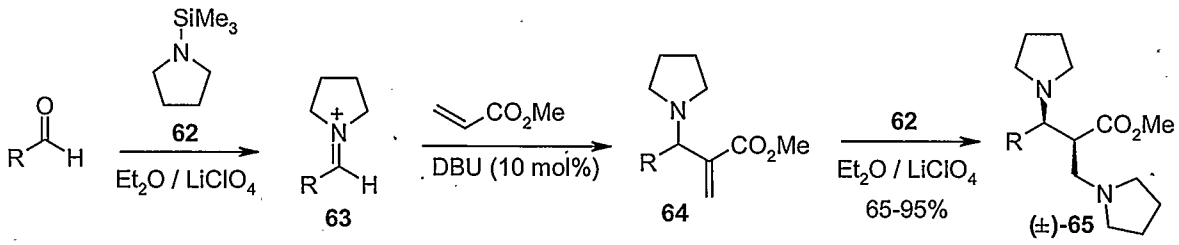
60a, R = R' = H
60b, R = Ph, R' = H
60c, R = Me, R' = H
60d, R = H, R' = Et

E- **61**

Z- **61**

Saidi and coworkers reported their results for the MBH reaction carried out using an in situ prepared iminium salt as the carbon electrophile.[74] In a one-pot process, *N*-(trimethylsilyl)pyrrolidine (**62**) was reacted with a variety of aldehydes in a concentrated ethereal solution of lithium perchlorate to first generate the iminium ion **63**. Subsequent addition of methyl acrylate and DBU afforded the MBH adduct **64**, which reacted spontaneously under the reaction conditions to give the diamine **65** (Scheme 40).[74]

Scheme 40



R = Ph, 2-ClPh, 4-ClPh, 4-BrPh, 4-(MeO)Ph, 3-(NO_2)Ph, 2,4-$(Cl)_2$Ph, ^{i}Pr

1.2.4.4. Solvents and Hydrogen-Bonding

The choice of solvent plays a great role in the rate of the MBH reaction, with polar solvents tending to be optimal. There has been much speculation as to the mode of this acceleration, namely stabilization of the highly polar intermediates, hydrogen bonding effects, and aid in proton transfer. However, the exact nature of the influence of the solvent is still not entirely understood. Common solvents include THF, DMF, CH_3CN, and dioxane among others.[11,12] Ionic solvents have also been found to be effective for the MBH reaction.[53,54] Krishna suggested that sulfolane (**66**), a commercially available polar aprotic solvent, become a standard medium as a result of their successful results and increased reaction rates in comparison to those obtained under aqueous conditions (Figure 2).[65]

66

Figure 2. Structure of Sulfolane

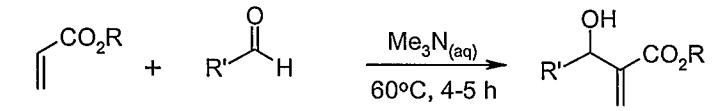
Isaacs and Hill proposed that the more polar solvents could account for the negative volume of activation of the reaction by electrostriction and found that 1,2-diols, for example, led to a reaction rate 400 times faster than ether solvents, presumably due to hydrogen bonding by both hydroxyl groups to the substrate.[24] Augé first studied the effects of aqueous solvents and additives in the MBH reaction.[75] The reaction of

acrylonitrile and benzaldehyde in the presence of 15 mole % DABCO proceeded in 7-8 hours in water, formamide, or ethylene glycol, producing yields of 90-98%. The reaction proceeded more slowly in methanol (34 hours), *N*-methylacetamide (48 hours), and DMF or DMSO (3-5 days) and afforded only very low yields of products even after 7 days of stirring in toluene or THF. The slower rate in *N*-methylacetamide was somewhat surprising based on its large dielectric constant (ε = 183).[75] These results, and the increase in rate despite the decreased solubility of the reagents in water, led to the hypothesis that hydrophobic effects might play a role in promoting the reaction. Based on the volume of activation of the reaction[24] this would be a likely scenario; however, use of a variety of salting-in and salting-out agents did not provide any conclusive results.[75] Aggarwal later also explored the use of salting-in (guanidinium chloride) and salting-out (lithium chloride) agents in his reactions of cyclohexenone and benzaldehyde in water using 3-HQD as a catalyst. A rate increase was observed in both cases, suggesting that the acceleration observed in aqueous media is not due to hydrophobic effects.[76]

Aggarwal also found, however, that water and formamide were excellent solvents for the MBH reaction, having broad scope and applicability, though decreased yields were observed for reactions of acrylates in water due to hydrolysis under the basic aqueous conditions.[76] The addition of $Yb(OTf)_3$ to the formamide solvent provided the best results and avoided problems such as hydrolysis of substrates. This acceleration was proposed to be the result of coordination between the solvent and the Lewis acid, increasing the polarization of formamide N-H bonds and leading to increased effectiveness of hydrogen-bonding. No such acceleration was seen upon the addition of Lewis acids to water. Interestingly, and similar to the results of Augé, *N*-methylformamide led to slower reactions, despite its higher dielectric constant (ε = 182) versus that of formamide (ε = 111), or water (ε = 78.5), indicating that solvation is not the major factor in the observed rate accelerations.[76] Other metal salts such as $La(OTf)_3$ and $LiClO_4$ have also been shown to increase reaction rates, presumably due again to stabilization of the zwitterionic intermediate.[77]

Basavaiah expanded on the results of a European patent,[78] by employing 30% w/v aqueous trimethylamine as a catalyst in the reaction of various aldehydes and arcrylates.[79] Reactions were carried out at 60°C for periods of 4-6 hours resulting in moderate to good yields of 30-74% (Scheme 41).

Scheme 41

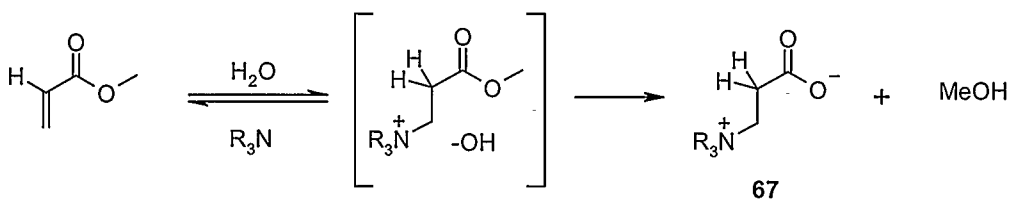


13

R = Me, Et, *n*-Bu, *t*-Bu
R' = H, pyrid-2-yl, 4-$NO_2C_6H_4$, fur-2-yl

Hu's group found that a 1:1 mixture of water and 1,4-dioxane showed dramatic rate accelerations for reactions of methyl acrylate with a variety of aromatic and aliphatic aldehydes compared to either of the two solvents individually, as well as in comparison to other commonly employed solvents.[80] Optimal yields were obtained using a full equivalent of catalyst and 3 equivalents of acrylate. These increased loadings were found necessary in view of a side reaction that formed the isolable betaine product **67,** which resulted in consumption of both the acrylate and the catalyst (Scheme 42).

Scheme 42



67

Tang and coworkers also noted a rate increase when using aqueous trimethylamine, particularly with the addition of organic solvents such as short chain alcohols, THF, CH_3CN, or 1,4-dioxane, used to homogenize the reaction mixture. These conditions were found to be effective for a variety of catalysts, aldehydes, and Michael acceptors.[81] Basavaiah's group made use of methanolic trimethylamine as both the solvent and

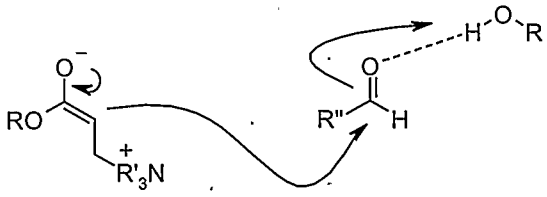
catalyst and found it to be in general better than aqueous trimethylamine at catalyzing the reaction of methyl acrylate, acrylonitrile, and acrolein with a variety of aldehydes.[82]

1.2.4.5. Catalysts and Co-catalysts

DABCO, which was first employed for the MBH reaction by Baylis and Hillman,[10] remained the catalyst of choice for many years.[11,12] Again, with research continually seeking to improve the reaction rates and efficiencies, many other catalysts have been examined. Not surprisingly there does not seem to be any one ideal catalyst and the most effective one is often dependent on the particular reaction. Amine catalysts still seem to predominate in the literature, with examples including quinuclidine, 3-quinuclidone, 3-HQD, indolizidine, and imidazole, among others.[11] Phosphine catalysts are also quite frequently employed, though there is somewhat less attention to the development of new catalysts in this area.

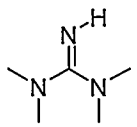
Along with the acceleration observed in polar solvents, it was also found that polar protic additives tend to have a positive influence on the MBH reaction.[24] It is conceivable that Lewis acids or Brønsted acids would stabilize the zwitterionic intermediates generated, shifting the equilibrium forward and accelerating the reactions for which the formation of the zwitterion is rate-determining. Likewise, amine bases that could provide the greatest stabilization of these intermediates should in principle provide better results. Drewes noted a two-fold rate acceleration for DABCO-catalyzed MBH reactions upon addition of methanol and speculated that this was due to activation of either or both the aldehyde and acrylate via hydrogen-bonding (Scheme 43).[83,84]

Scheme 43



Similarly, Ikegami and coworkers reported rate enhancement when using phenols and naphthols as mild Brønsted acids in combination with PBu_3 as a Lewis base catalyst. They obtained good results using phenol, 2-naphthol, and BINOL in the MBH reaction of cylcopentenone with 3-phenyl-1-propanal. Interestingly, when either the mono- or dimethoxy derivatives of BINOL were employed, the rates dropped dramatically in comparison to those obtained with BINOL itself, indicating that both hydroxyl groups are playing a role in the reaction. Methanol, benzoic acid, or *para*-toluenesulfonic acid were all found to be less effective additives. The mechanism of rate enhancement was thought to be analogous to the system shown in Scheme 43, where the aldehyde is activated by the acidic hydroxyl moiety, while stabilization of zwitterionic intermediates via hydrogen bonding is also possible.[85]

Phenol was found to be the optimum additive for a variety of reactions catalyzed by tetramethylguanidine (TMG) (**68**, Figure 3), despite its ability to protonate the active imine functionality in the catalyst.[86] Methanol and ethanol were also very effective and had the advantages of being easily separable from the reaction mixture. Again, when using benzyl alcohol, or *para*-toluenesulfonamide, the effects were much less pronounced. Also, aliphatic aldehydes did not show the same enhancements observed for aromatic aldehydes.[86] In general, other additives such as $LiClO_4$[87] and $La(OTf)_3$ in combination with (+)-BINOL[77,88] have also been effective in promoting the MBH reaction.

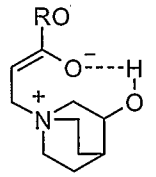


68

Figure 3. Structue of Tetramethylguanidine

Exploration of new catalysts began in the late 1980's. Drewes, in 1988, first employed 3-HQD (**48**) as a catalyst in the hopes that the hydroxyl moiety would be beneficial as a general acid catalyst.[83] They indeed observed a significant rate

enhancement and speculated that this may be due to the hydrogen bonding interaction shown for intermediate **69** (Figure 4).



69

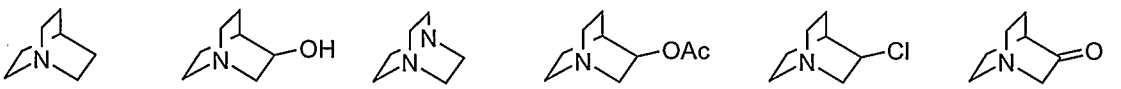
Figure 4. Hydrogen Bonding Stabilization by 3-HQD

Support was lent to this hypothesis via a follow-up study in which the acylated derivative of 3-HQD was tested as a catalyst. Its activity was found to be much lower than when the free hydroxyl group was present.[84] Bode and Kaye carried out a mechanistic and kinetic study using deuterated 3-HQD and observed a small kinetic isotope effect (k_H/k_D = 1.3) implying the involvement of hydrogen bonding.[25] However, the intramolecular hydrogen bonding shown in Figure 4 was later subjected to modeling studies and was found to be highly unlikely due to high levels of strain.[15]

In 1999 Aggarwal and Mereu screened a number of catalysts possessing structures such that a positive charge on the nitrogen atom could be stabilized via conjugation with another heteroatom.[89] The best results, surpassing those of DABCO and 3-HQD, were obtained using DBU as a catalyst, which was found to be effective for a range of activated alkenes and carbonyl compounds, excluding those with enolizable protons. The authors were surprised by these observations as DBU is generally thought of as a hindered and thus non-nucleophilic base. However, they assumed that the increased stabilization of the ammonium ion by conjugation would increase the concentration of the intermediate and thereby promote attack on the aldehyde.

In 2003 Aggarwal's group presented a very detailed study of quinuclidine-based amine catalysts, in which they proposed that quinuclidine was one of the best catalysts for use in the MBH reaction.[29] They found that there was a strong correlation between the basicity of the nucleophile (based on the pK_a's of the conjugate acids) and its activity and

thus proposed the following reactivity order for the catalysts observed: quinuclidine (**4**) > 3-HQD (**48**) > DABCO (**2**) > 3-acetoxyquinulidine (**70**) > 3-chloroquinuclidine (**71**) > quinuclidinone (**72**) (Figure 5). The conjugate acid of DABCO has a higher effective pK_a than 3-acetoxyquinulidine (**70**) when measured in aprotic media, presumably because in hydrogen bonding solvents such as water, association of the solvent and the second nitrogen in the molecule lowers the basicity. The basicity of DBU is similar to that of quinuclidine and so, it should be expected to show similar catalytic activity to the latter.



	4	**48**	**2**	**70**	**71**	**72**
pK_a	11.3	9.9	8.7	9.3	8.9	7.2

(of the conjugate acid, as measured in H_2O)

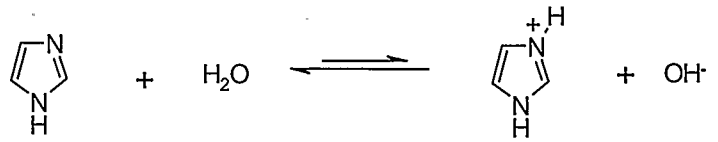
Figure 5. Amine Bases Tested as Catalysts for the MBH Reaction

Vasconcellos compared the reactivity of DMAP, DABCO, and imidazole as catalysts for the reaction of activated alkenes with *para*-nitrobenzaldehyde in neat conditions at 76 °C. They found that in the absence of solvent imidazole did not catalyze the reaction. Under these conditions DABCO and DMAP showed very similar catalytic activity to one another. However, it was noted that when less electrophilic species such as benzaldehyde were employed in the reaction, DABCO provided superior results.[60] The reaction of formaldehyde with a variety of substituted cyclohexenone derivatives was successfully carried out using DMAP as a catalyst, providing the desired products in yields of 68-82%.[90]

Imidazole was successfully used to catalyze the aqueous MBH reactions of cyclopentenone and various aldehydes.[91] This catalyst provided better results than a series of other amines tested, including DABCO, DMAP, Et_3N, pyridine, and *N*-methylimidazole. Phosphine catalysts were found to be ineffective under the reaction conditions. The choice of solvent also proved to be critical in that water was found to be a

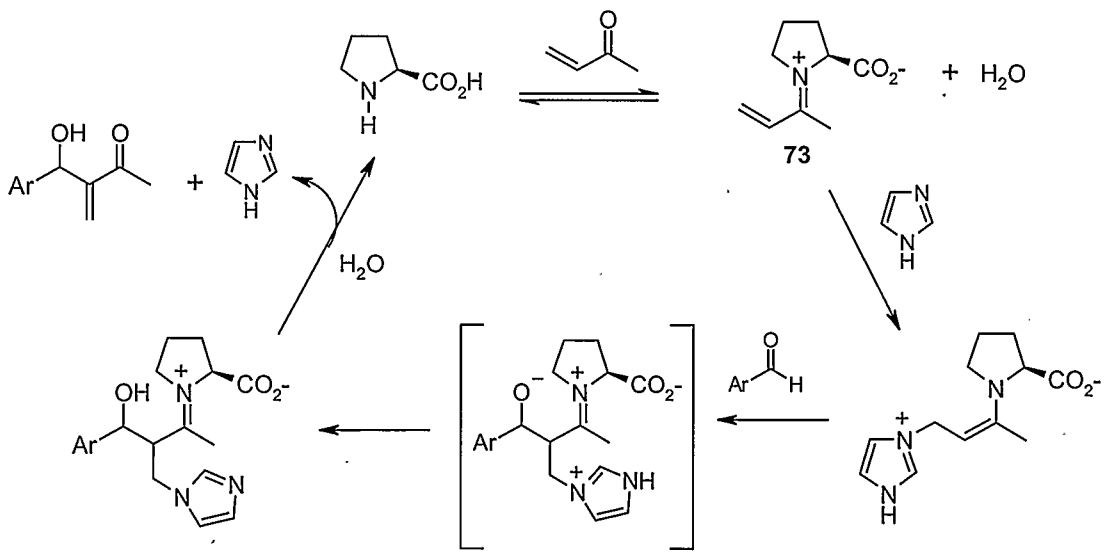
necessary component, while a 1:1 mixture of water and THF gave better results than similar other water-solvent mixtures such as DMF, dioxane, methanol, or acetonitrile.[91] Cheng and coworkers later improved upon their results by carrying out the reaction in aqueous sodium bicarbonate solution.[92] The further increase in rate was thought to be due to the "enhanced basicity" of the imidazole as a result of depressed proton exchange between the solvent and the catalyst (Scheme 44).[92]

Scheme 44



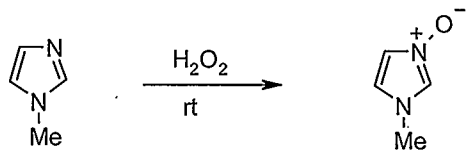
Shi also employed imidazole as a catalyst, but found that it was ineffective on its own in catalyzing reactions with MVK; however, reactions proceeded quite well with the addition of L-proline. A plausible mechanism for the observed acceleration was proposed, involving formation of iminium ion **73** in situ (Scheme 45). While enantiomerically pure L-proline was used, the enantiomeric excess of the products obtained was very low (5-10%).[93]

Scheme 45



Tsai and coworkers prepared 1-methylimidazole-3-*N*-oxide (**74**) by oxidation of *N*-methylimidazole (Scheme 46). They found that **74** acted as a good promoter for the MBH reactions of MVK or methyl acrylate with a series of aldehydes. Reactions generally proceeded smoothly with little in the way of byproducts, especially in the case of aldehydes possessing electron-withdrawing moieties.[94]

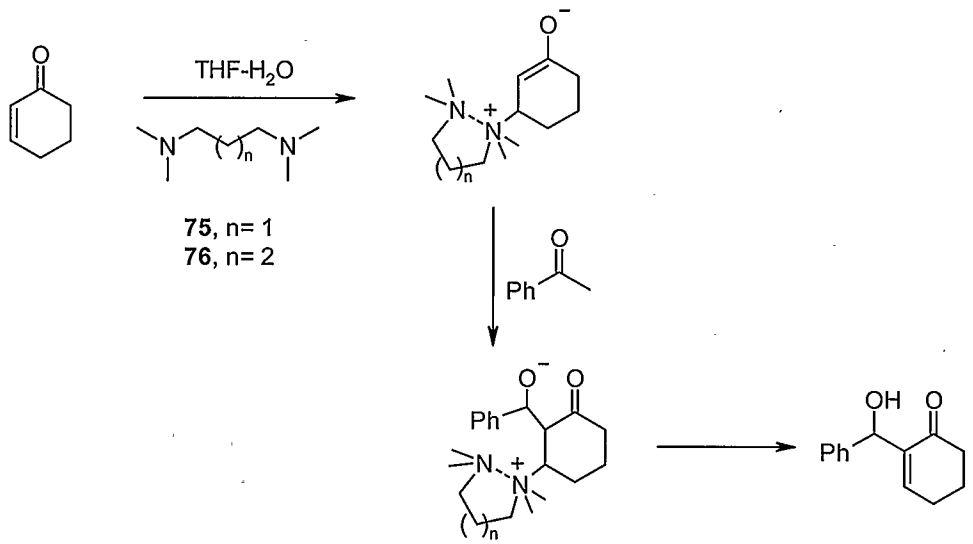
Scheme 46



74

Kim and coworkers found that the commercially available *N*,*N*,*N*',*N*'-tetramethyl-1,3-propanediamine (**75**) (TMPDA) and *N*,*N*,*N*',*N*'-tetramethyl-1,4-butanediamine (**76**) also served as good catalysts in the MBH reactions of cycloalkenones with a variety of aldehydes.[95] The results obtained were better than those with diamines having shorter chain lengths and the researchers propose that it is the ability of **75** and **76** to stabilize the zwitterionic intermediate via five- and six-membered rings that promote the reaction (Scheme 47).

Scheme 47



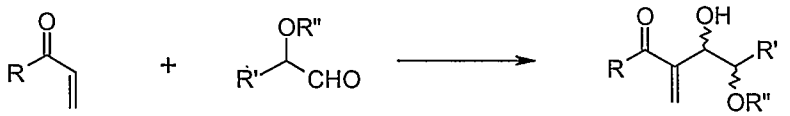
75, n= 1
76, n= 2

In addition to the amine and phosphine-catalyzed reactions discussed in the above sections, there has also been extensive development in the use of chalcogenide and Lewis acid-based catalyst systems. These reactions will not be discussed here as they have been reviewed elsewhere.[96-98]

1.2.5. Stereoselective MBH Reactions

There has also been much research devoted to the asymmetric version of the MBH reaction.[11,99] Studies in this area began in the late 1980's, though initial reports generally suffered from low enantioselectivities. In 1988 Drewes presented his study on the inherent diastereoselectivity for the DABCO-catalyzed reactions employing α-alkoxyaldehydes **77** and activated vinyl systems (Scheme 48).[100] Products **78** were obtained in reasonable yields, but diastereoslectivities were poor with the greatest *syn:anti* ratio of products being only 40:60.

Scheme 48



In a later publication, Drewes made use of chiral, cyclic amino aldehydes **79** and **80**, derived from (L)-serine and (S)-prolinol, respectively, in reactions with methyl acrylate and DABCO (Figure 6).[101] The reactions were complete after 7 days with yields surpassing 75%; however, de's were only 72 and 50%, respectively.

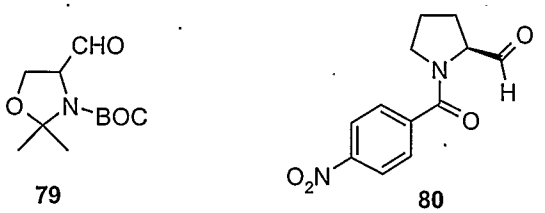
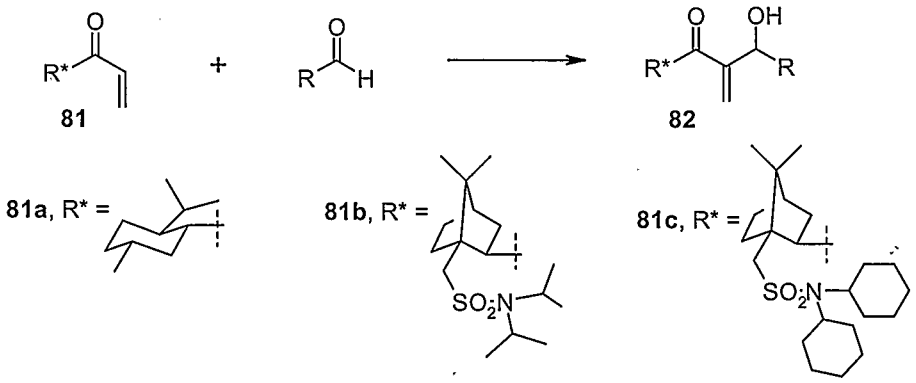


Figure 6. Chiral, Cyclic Amino Aldehydes for MBH reaction

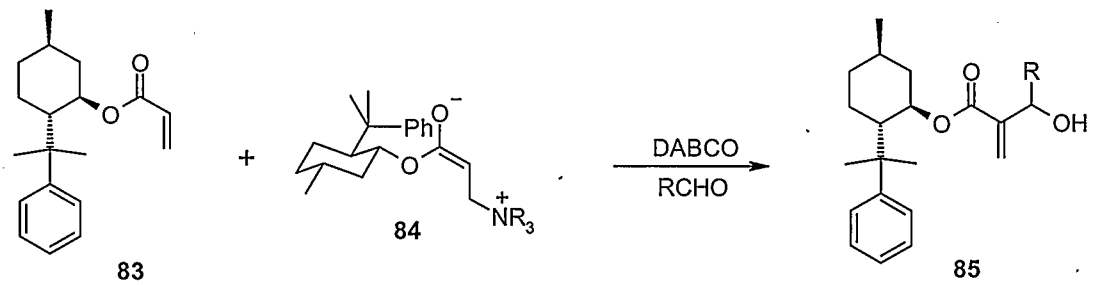
Basavaiah and coworkers reported the use of three chiral acrylates including (–)-menthyl acrylate (**81a**), as well as **81b** and **81c** derived from Oppolzer's chiral auxiliaries, in the reactions with a variety of aliphatic and aromatic aldehydes in the presence of 100 mole % DABCO (Scheme 49).[102] MBH products **82** were obtained in yields of 45-89% with de's ranging from 7-70%.[102]

Scheme 49



Chiral acrylates were also examined as subtrates for the asymmetric MBH reaction by Drewes who made use of 8-phenyl menthol in acrylate (**83**) to induce stereoselectivity (Scheme 50).[103] Based on the structure of **83**, they proposed an intermediate such as **84**, that could transmit stereochemical information via pi-stacking, and eventually lead to products **85**, which were isolated with de's of 2-70%.

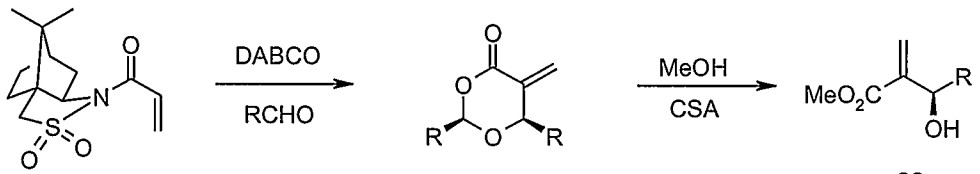
Scheme 50



Hirama's group examined the use of chiral DABCO derivatives for the asymmetric MBH reaction of MVK and *para*-nitrobenzaldehyde.[104] However, reactions were slow, giving only moderate yields of products and the ee's did not surpass 47%. A plethora of other chiral catalysts have been employed including brucine, *N*-methylprolinol, *N*-methylephedrin, nicotine, 3-HQD, and BINAP, but only low to moderate ee's were obtained.[99] The effects of pressure in conjunction with chiral bases were also examined, but again, enantioselectivity was poor.[104,105]

The first highly enantioselective reactions were observed by Leahy's group who made use of Oppolzer's sultam as a chiral auxiliary for the acrylate substrate **86** (Scheme 51).[106] They found that in general reactions proceeded well and the ee's obtained for aldehydes were >99%. However, the products obtained in the reaction were the dioxane molecules **87**. The chiral auxiliary was fortuitously cleaved under the reaction conditions employed, thus providing a renewable source of chirality in the reaction. The dioxane products could subsequently be opened to give α-methylene-β-hydroxy esters (**88**) of high enantiomeric purity.

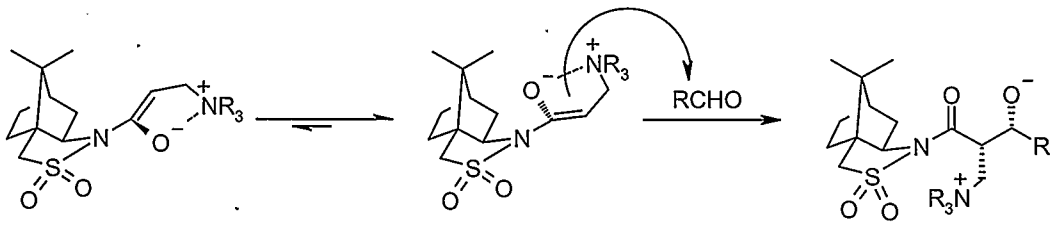
Scheme 51



The authors observed that for aliphatic aldehydes possessing substituents in the α-position, yields were drastically reduced. Low yields also resulted for reactions of aromatic aldehydes. The observed stereochemistry was thought to arise from the preferential addition of the catalyst to form the *Z*-enolate **89**, having an electronic stabilization between the charges, and having the anti orientation (**89'**) of the sulfone and the enolate (Scheme 52). Subsequent addition of the aldehyde should proceed preferentially on the *re*-face of the enolate due to the steric bulk of the pseudo-axial

sulfone oxygen. This stereochemistry is then maintained through the remaining transformations to generate the final products.

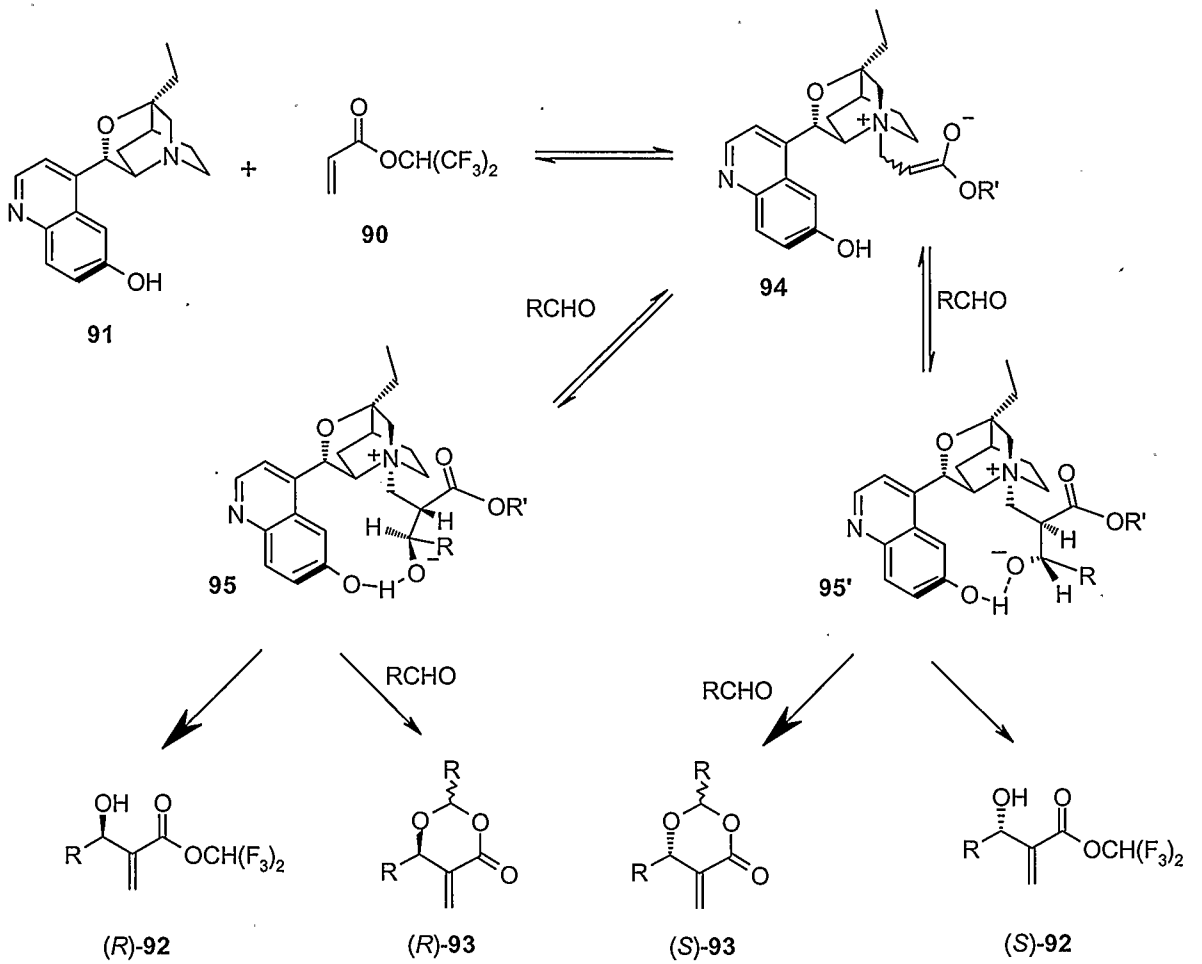
Scheme 52



Some of the best results obtained for the asymmetric MBH reaction were reported by Hatakeyama's group in 1999, who studied Chinchona alkaloid derivatives as chiral catalysts for the reaction of 1,1,1,3,3,3-hexafluoroisopropyl acrylate (**90**) with a variety of aldehydes, both aromatic and aliphatic.[37] The ideal catalyst was found to be **91**, providing enantiomeric excesses in the range of 91-99% for the desired MBH products **92**. Dioxane byproducts **93** were isolated from the reactions, possessing the opposite chirality to that of the desired products **92**. Based on their observations, a mechanism was proposed consisting of differing pathways for the formation of the product and the dioxanone (Scheme 53). The enolate generated from the reaction of **94** and the acrylate would produce several diastereomers upon addition to the aldehyde, the most stable of which should be the betaine intermediates **95** and **95'**, stabilized by hydrogen bonding to the naphthyl hydroxyl group. The authors proposed that the steric interactions in the intermediates are such that **95'** preferentially reacts to form the dioxane product (*S*)-**93**, while **95** undergoes facile elimination to give MBH product (*R*)-**92**.[37] In a subsequent study using the same catalyst for the reaction of *N*-tosylimines and methyl acrylate, they found that the amine MBH products had the opposite configuration to that observed in the case of reactions with aldehydes. The selectivity was again proposed to be a result of the preferential formation of a particular diastereomeric intermediate possessing hydrogen bonding between the anion (in this case a nitrogen anion rather than an oxygen anion) and the hydroxyl group on the naphthalene ring. Thus, elimination of this

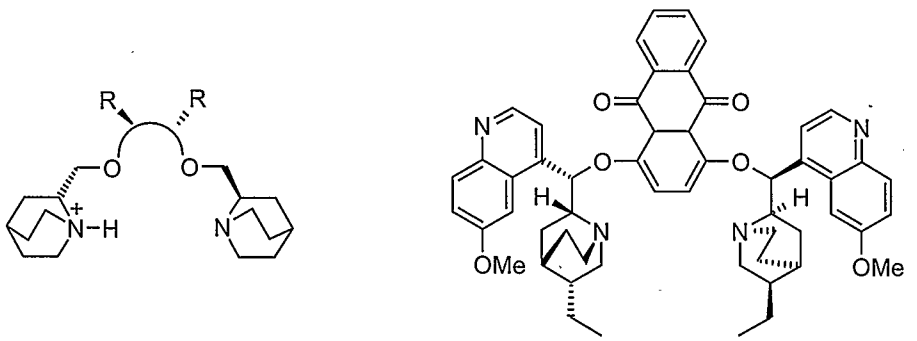
diastereomer proceeds readily to give the (*S*)-MBH product in high enantiomeric excess.[107]

Scheme 53



Bifunctional asymmetric catalysts have also been employed for the MBH reaction. Wariner made use of Sharpless ligands having the general structure **96a** as catalysts (Figure 7). The intention of the catalyst design was that one quinuclidine moiety could act as the required nucleophile, while the second protonated quinuclidine unit could serve to either stabilize the zwitterionic intermediate or to activate the aldehyde towards attack.[108] The best results were obtained with $(DHQD)_2AQN$ (**96b**) in the presence of one equivalent of propanoic acid in THF. Enantiomeric excesses up to 77% were obtained but

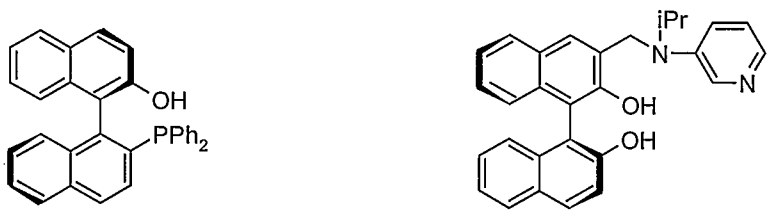
yields were generally less than 10%. In addition the reaction did not display good substrate generality, making it unsuitable as a catalyst itself but potentially offering new insights into catalyst design.



96a 96b

Figure 7. Structure of Bifunctional Sharpless Catalysts

Shi and coworkers used the bifunctional catalyst (*R*)-2'-diphenylphosphanyl-[1,1']binaphthalenyl-2-ol (**97**) for MBH reactions of *N*-sulfonylated imines with MVK and phenyl acrylate (Figure 8).[109] Enantiomeric excesses obtained for the reactions were fair for phenyl acrylate (53-77%) and good to excellent in the case of MVK (60-97%), with all yields falling within a synthetically useful range. It is believed that the phosphine moiety acts as the Lewis base while the hydroxyl group serves simultaneously as a Brønsted acid, stabilizing the anionic functionalities formed in the intermediates. Sasai also obtained good results using the chiral bifunctional catalyst **98** with ee's ranging from 87 to 95% for reactions of various *N*-tosylated imines with methyl and ethyl vinyl ketone and acrolein.[110]



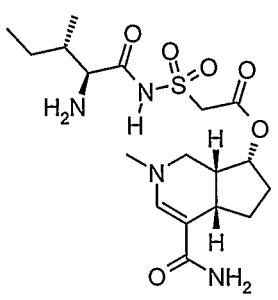
97 98

Figure 8. Structure of Bifunctional Catalysts used by Shi and Sasai

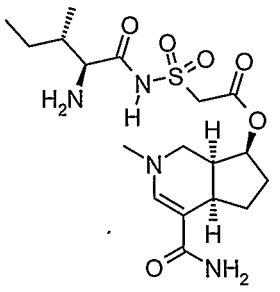
1.2.6. Applications of the MBH Reaction

The asymmetric MBH reaction has successfully been employed in the formation of a large number of natural products, many of which possess biological activity.[11] A few of the more recently devised syntheses will be briefly discussed here, as a showcase of the utility of the MBH reaction.

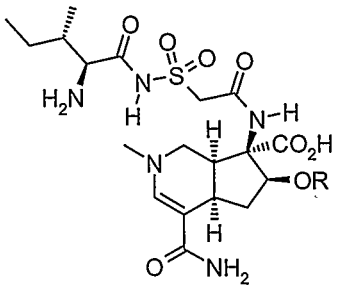
Banwell's group presented the synthesis of **99** and **100,** the biologically active analogues of tRNA synthase inhibitors SB-203207 (**101**) and SB-203208 (**102**) (Figure 9).[111]



99



100



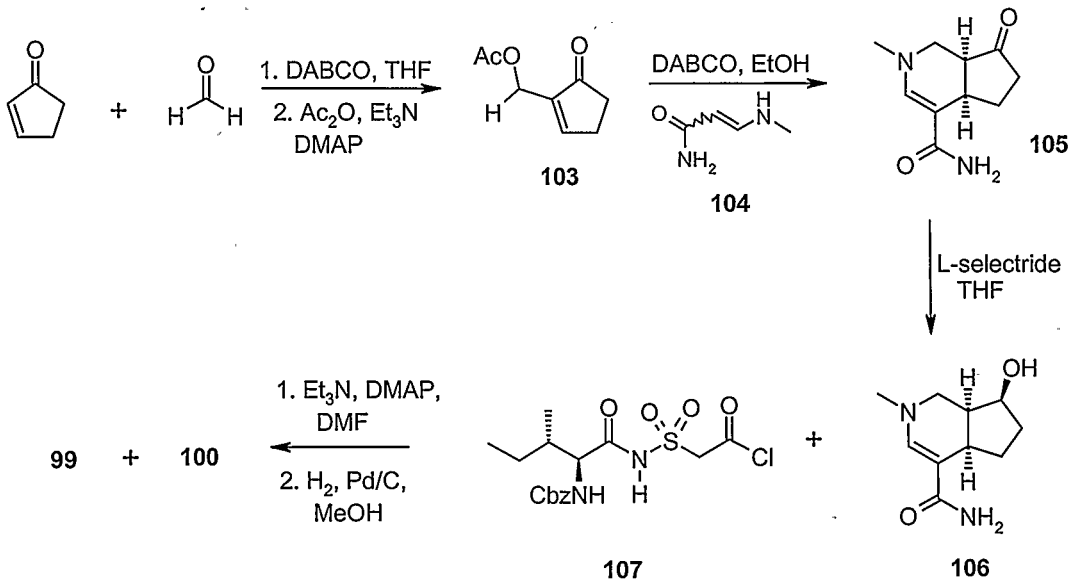
101, R = H
102, R = (*S*,*S*)-COCH(NH_2)CH(CH_3)Ph

Figure 9. Structure of SB-203207 (**101**) and SB-203208 (**102**) and Analogues **99** and **100**

The simple MBH reaction of formaldehyde and cylcopentenone with 25 mole % DABCO provided the expected 2-(hydroxymethyl)cyclopent-2-enone, which was subsequently converted to its acetate derivative **103**. This was then treated with amine **104**, derived from methylamine and propiolamide, to afford the bicyclic key intermediate ketone (±)-**105** (Scheme 54). This was then stereoselectively reduced to the alcohol **106**. Reaction with acid chloride **107** and hydrogenolytic deprotection afforded the desired compounds as a 1:1 mixture. Attempts to generate ketone **105** as a pure enantiomer using some commonly employed chiral catalysts for the MBH reaction gave poor selectivities. Instead, the bicyclic alcohol **106** was resolved (via the acetate derivative) using chiral

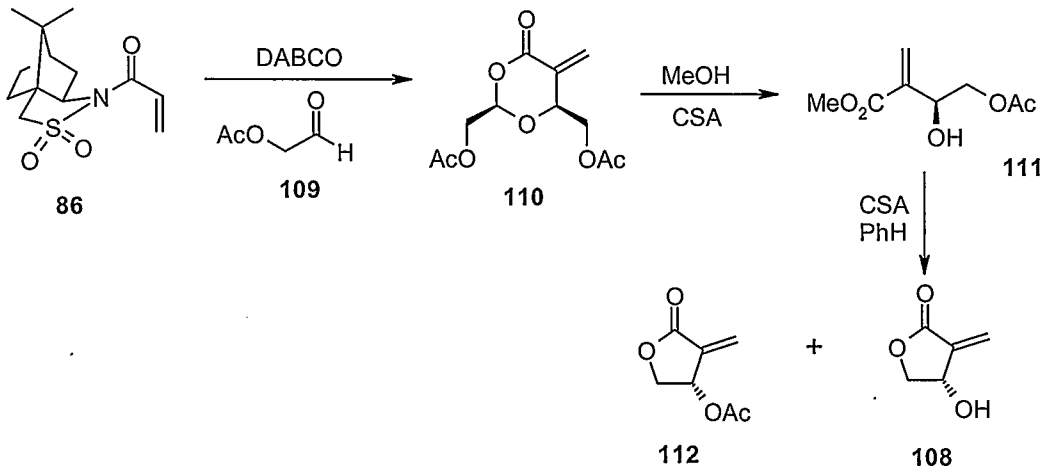
HPLC methods and products **99** and **100** were synthesized separately upon reaction with **107**.[111]

Scheme 54



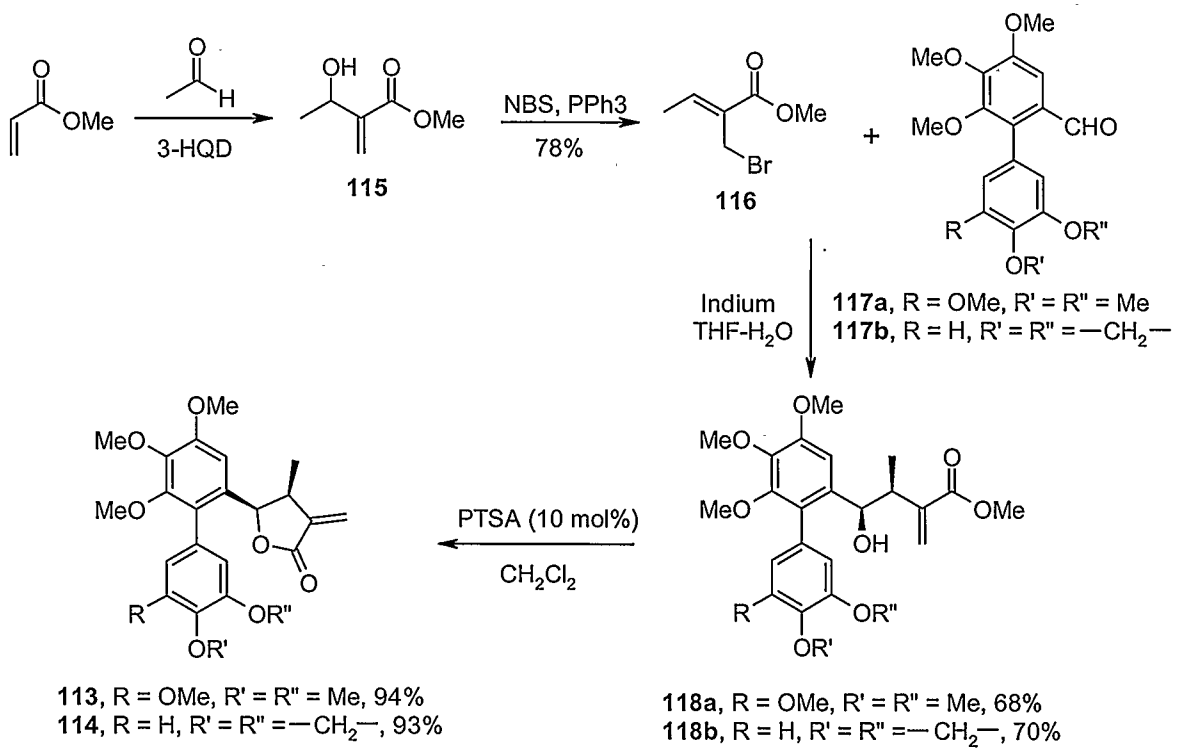
Leahy and coworkers made use of their enantioselective strategy involving Oppolzer's sultam for the synthesis of the natural product tulipalin B (**108**).[106] This was a simple two-step synthesis of the natural product, which is the contact dermatitic agent in tulip bulbs. Reaction of vinyl compound (**86**) and 2 equivalents of aldehyde **109** in the presence of DABCO yielded dioxane product **110** in 68% yield and 99% optical purity (Scheme 55). The dioxane product was then opened to give allylic alcohol **111** and this was subsequently subjected to an intramolecular cyclization to afford a mixture of tulipalin B and its acetate derivative **112**.[106]

Scheme 55



Another example of how a simple MBH reaction can serve in the generation of complex products was presented by Kabalka with the synthesis of eupomatilones 2 (**113**) and 5 (**114**).[112] The initial reaction of methyl acrylate and ethanal gave the MBH adduct **115**, which was subsequently reacted with NBS and PPh_3 to generate the allylic bromide **116**. This was then reacted with **117a** or **117b**, which had been synthesized separately. The resulting adducts (**118**) were obtained as predominantly the *syn* isomers (95:5), which were easily purified from the minor *anti*-isomers and were then made to undergo intramolecular cyclizations to afford the desired products in good yield (Scheme 56).[112]

Scheme 56



These represent only a few of the applications of the MBH reaction, but emphasize how even using simple reagents in this valuable process can lead to highly functionalized products, which may be further manipulated and used towards the syntheses of complex molecules.

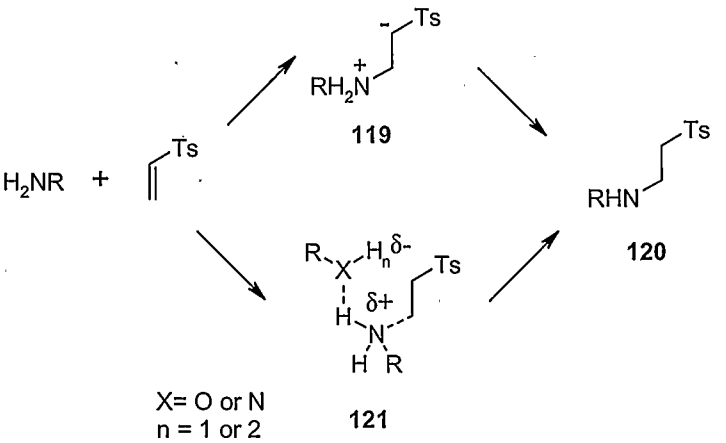
1.3. Vinyl Sulfones

The sulfone moiety has become an extremely useful group in modern organic synthesis. Due to its strongly electron-withdrawing nature it can serve as an efficient activating group, allowing unsaturated sulfone substrates,[113-115] including 1,3-butadienyl sulfones,[113] to act as effective Michael acceptors. In addition, the activation of the neighboring pi-system has led to the use of vinyl and acetylenic sulfones as dienophiles in Diels-Alder reactions.[114,115] The electron-withdrawing properties of the sulfone moiety

also allow for the stabilization of an α-carbanion, such that they may be used to facilitate alkylation reactions.[115] One of the most appealing qualities of the sulfone group however, is that it is removable. Thus, once it has served its purpose in a synthesis it may be removed from the products by a variety of different methods including reductive, oxidative, alkylative, or elimination techniques.[116]

Vinyl sulfones have been shown to be effective in conjugate addition reaction involving amines as nucleophiles.[117] A study by Sterling's group found that an increase in the steric bulk of secondary amines led to a decrease in their rates of addition to *para*-tolyl vinyl sulfone. It was also found that secondary amines reacted much faster than primary amines, presumably due to greater solvation of the latter. This effect could be muted in polar solvents, themselves having large steric requirements, for example *t*-butanol. The authors noted little difference in the reaction rates of amines of comparable bulk but of differing basicity, indicating that the pK_b of the amine does not play a great role in its reactivity. These results are somewhat in contrast to those of Aggarwal (Section 1.2.4.5), who found that catalysis of the MBH reaction was improved according to the basicity of the amine catalyst. Stirling considered two possible mechanisms for the Michael addition of amines to vinyl sulfones (Scheme 57). The addition could occur via a two-step process in which the zwitterionic intermediate **119**, analogous to that seen for the MBH reaction, is first formed, followed by a proton transfer to give the final product **120**. A second possibility is a one-step process in which the transition state **121** is formed, with either a solvent molecule or a second molecule of amine involved in and responsible for the proton transfer step. Such reactions carried out in ethanol showed first order dependence on both the amine and the solvent. In contrast, use of benzene as the solvent led to a significant decrease in the rate of reaction, indicating polar transition states and intermediates, as well as displaying a second order dependence on the amine. Based on these results, Sterling proposed that the mechanism involving transition state **121** was the more likely possibility.[117]

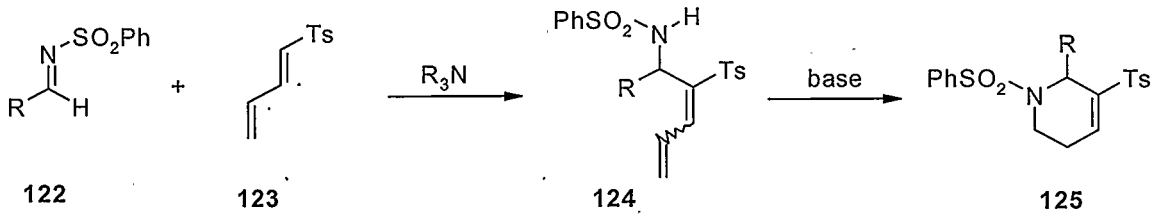
Scheme 57



1.4. Objectives

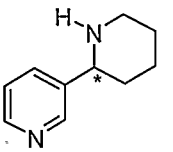
The goals of this work were two fold. We first wished to establish a working methodology for the aza-MBH reaction employing both sulfone-activated imines (**122**) and sulfone-activated diene substrates (**123**). Conjugated dienes, activated by any of the commonly employed electron-withdrawing groups, had not been examined in the context of the MBH reaction prior to this work. Establishing this as a novel methodology was appealing as the resulting MBH adducts (**124**) would retain the butadienylsulfonyl moiety, leaving them open to further transformations. In particular we wish to subject the functionalized adducts to an intramolecular base-catalyzed cyclization reaction via conjugate addition, affording the substituted piperidine rings **125** (Scheme 58). These molecules are of great synthetic interest as they constitute the molecular framework of a number of naturally occurring alkaloids, many of which demonstrate biological activity.

Scheme 58



122 123 124 125

The second objective was to explore any additional chemistry that could be carried out on either the MBH adducts **124** or on piperidines **125**. This led us to explore a variety of possibilities, including Heck reactions, conjugate addition reactions, and cycloaddition reactions. Our studies also led us to explore the utility of other activating groups for the diene unit, including methyl and phenyl ketone groups, a nitrile group, as well as a methyl ester moiety. Only investigations of the latter will be discussed in detail in this thesis as the other activating groups for the diene substrate were primarily examined by K. N. Clary, an honours student in our group at the time. In addition to the above, the feasibility of applying this novel methodology to the synthesis of the naturally-occurring anabasine (**126**) was examined (Figure 10). This minor tobacco alkaloid demonstrates nicotinic receptor agonist activity and has been found to be a potent teratogen.[118-120]



126

Figure 10. Structure of the Natural Product Anabasine

Chapter Two: Discussion

2.1. General Comments

As described in the previous chapter, the utility of the sulfone moiety as an activating group is well documented.[113-115,117] The Back research group has been exploring the use of sulfone chemistry in designing new syntheses, making extensive use of acetylenic sulfones in particular.[121-124] Vinyl sulfones have previously been employed in both the MBH reaction and its aza-version.[57,99,125,126] As mentioned in Section 1.4., one of the main goals of this project involved investigation of the aza-MBH reaction, employing for the first time activated butadienyl substrates. Again, as exemplified in Scheme 58, it was hoped that MBH adducts **124**, possessing both amine and butadiene functionalities, would provide access to the functionalized piperidine systems (**125**) via an intramolecular conjugate addition.

2.2. Starting Materials

The chief starting materials used in this project were synthesized according to literature procedures. A brief summary of the methods used is given below.

2.2.1. Sulfone-Activated Diene Systems

Four different 1-sulfonyl-1,3-diene compounds were initially synthesized for exploration in the MBH reaction (Figure 11).

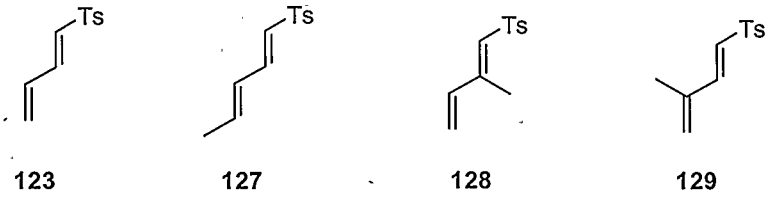
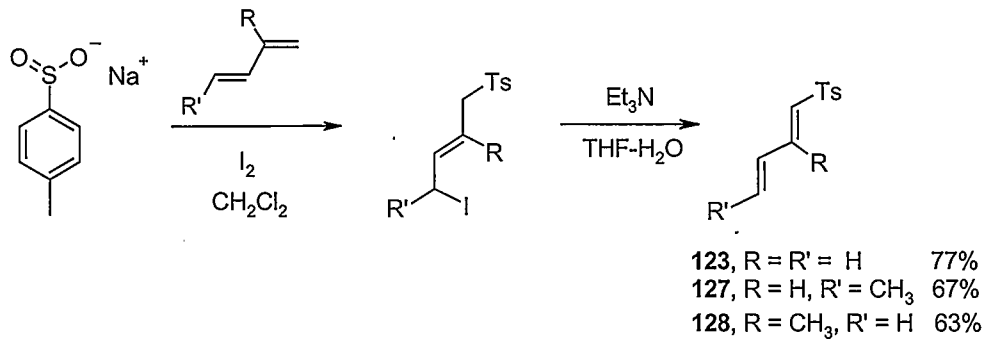


Figure 11. Sulfone Activated Butadienes Examined

Compounds **123**, **127**, and **128** were all synthesized according to the procedure of Barluenga, involving the iodosulfonylation of butadiene, followed by a subsequent base promoted 1,4-iodide elimination (Scheme 59).[127]

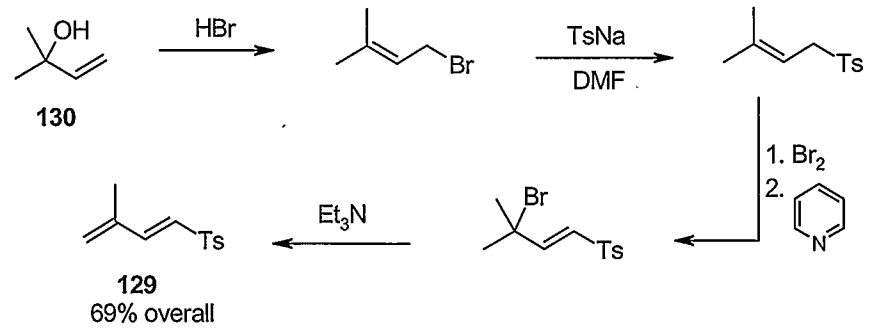
Scheme 59



123, R = R' = H 77%
127, R = H, R' = CH_3 67%
128, R = CH_3, R' = H 63%

Diene **129** was synthesized according to the procedure of Bordwell and Mecca, using the commercially available allylic alcohol **130** and sodium *para*-toluenesulfinate, as outlined in Scheme 60.[128]

Scheme 60



130

129
69% overall

2.2.2. Activated Imines

The sulfone moiety was also chosen to serve as the electron-withdrawing group for the imine substrates **122**. A selection of imines was synthesized, using the general literature procedure reported for the acid-catalyzed condensation of benzaldehyde with benzenesulfonamide (Scheme 61).[129] Table 7 lists the imines used over the course of this project, many of which have been previously synthesized by other methods.

Scheme 61

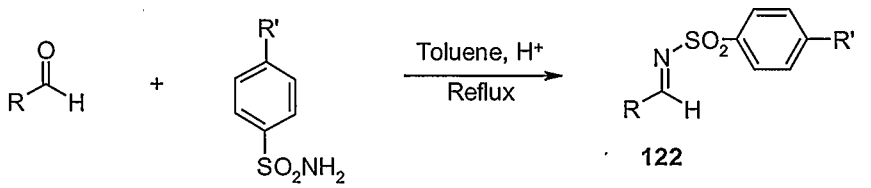


Table 7. Imine Subtrates Synthesized Over the Course of this Work

R	R'	Yield (%)	**122**	Reference
C_6H_5	H	76	**a**	129
p-ClC_6H_4	H	77	**b**	130
m-ClC_6H_4	H	75	**c**	130
o-ClC_6H_4	H	86	**d**	- [a]
p-$CH_3OC_6H_4$	H	70	**e**	130
p-$CH_3O_2CC_6H_4$	H	75	**f**	- [a]
α-Naphthyl	H	65	**g**	- [a]
p-NCC_6H_4	H	56	**h**	- [a]
p-$NO_2C_6H_4$	H	53	**i**	131
Mestityl	H	74	**j**	- [a]
Cyclohexyl	H	93	**k**	132
o-$CH_3O_2CC_6H_4$	H	73	**l**	- [a]
o-IC_6H_4	H	52	**m**	- [a]
o-HOC_6H_4	H	34	**n**	133
3-pyridyl	H	74	**o**	- [a]
C_6H_5	NO_2	50	**p**	134

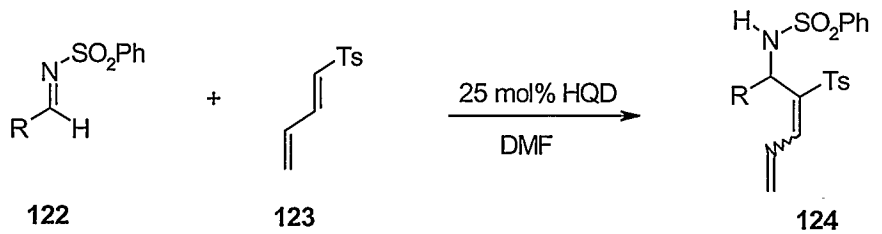
[a] Unreported prior to this work.

2.3. MBH Reactions

With the starting materials in hand, optimization reactions were initiated in order to establish general conditions for the desired MBH reaction, including determination of optimal solvent and catalyst. It must be noted that some of the early work on this project, including the optimization of the formation of **124** (vide infra), was carried out by a former honours student in the group, D. A. Rankic. However, as the results obtained are relevant to the current discussion, they will be included here.

Using *N*-(benzylidene)-benzenesulfonamide (**122a**) and 1-(*p*-toluenesulfonyl)-1,3-butadiene (**123**) as representative reagents for the aza-MBH reaction of interest, a combination of different catalysts and catalyst loadings were screened. Among those investigated, including triethylamine, triphenylphosphine, DABCO, DMAP, and DBU, the most effective was found to be 3-HQD. Catalyst loadings of 0.1, 0.25, 0.5, 1.0, and 3.0 molar equivalents were employed in a variety of different solvents, including acetonitrile, methanol, tetrahydrofuran, dichloromethane, dioxanes, and DMF. Optimal results were obtained with 0.25 mole % loading of 3-HQD in dry DMF. Reactions also proceeded well in THF, though generally at a much slower rate. The other catalysts examined yielded little to no product, or in the case of DBU, resulted only in decomposition products and complex mixtures. The optimized conditions were then applied to a series of MBH reactions and the results obtained are listed below (Scheme 62, Table 8).

Scheme 62



122 **123** **124**

Table 8. Aza-MBH Reactions of Imines **122** and Diene **123**

122	R	Yield **124** (%)	E/Z ratio
a	C_6H_5 [a]	86	70/30
b	*p*-ClC_6H_4 [a]	73	70/30
c	*m*-ClC_6H_4	46	70/30
d	*o*-ClC_6H_4	63	50/50
e	*p*-$CH_3OC_6H_4$ [a]	46	60/40
f	*p*-$CH_3O_2CC_6H_4$	70	70/30
g	α-Naphthyl	61	65/35
h	*p*-NCC_6H_4 [b]	75	75/25
i	*p*-$NO_2C_6H_4$ [a,b,c]	31	70/30
j	Mestityl	--	--
k	Cyclohexyl	--	--

[a] Reaction first carried out by D.A. Rankic. [b] Reaction carried out in THF. [c] Using 1 eq. 3-HQD.

It was found that the majority of reactions proceeded smoothly within four to six hours, at room temperature. This is quite remarkable as the MBH reaction is notoriously slow and the above constitute extremely mild conditions. As is noted in Table 8, reactions involving either the *para*-cyano (**122h**) or *para*-nitro (**122i**) substituted imine derivatives were carried out in THF. It was found that these reactions proceeded too quickly in DMF, leading to complex mixtures of products and decreased yields. In contrast, the reactions in THF proceeded significantly slower, requiring twenty hours, but the reaction also proceeded more cleanly and provided higher yields of products. The *para*-nitro-adduct, **124i**, was however prone to decomposition and consistently low-yielding, requiring one full equivalent of catalyst to isolate the 31% yield reported. Reactions employing the mesityl imine **122j** did not lead to any isolable products, most likely due to the increased steric bulk of the substrate. Likewise, reactions employing **122k** were unsuccessful and resulted only in complex mixtures. All reactions necessitated the use of anhydrous conditions to prevent hydrolysis of the imine substrates, and in some cases a slight excess of imine was employed to compensate for this possibility.

The MBH adducts were obtained as mixtures of both *E*- and *Z*-isomers in all cases. This is presumably due to the free rotation of single bonds in the zwitterionic intermediates formed during the course of the reaction (see Section 1.2.4.3.). The *E*-

isomer was predominant in all cases, apart from **122d**, which gave a 1:1 ratio of geometric isomers. This bias is not unexpected as the thermodynamic stability of the *E*-isomer should be greater. Purification of the crude reaction mixtures by column chromatography on silica gel in 16:1 toluene-ethyl acetate elutant provided pure samples of the *E*-isomer, however the minor *Z*-isomer often eluted as a mixture with the remaining *E*-isomer.

As is shown in Figure 12, the ^{1}H NMR spectra of the *E*- and *Z*-isomers were significantly different from each other, but the spectra of all the *E*-isomers were consistent, each displaying a characteristic doublet of triplets (formally a doublet of doublets of doublets) near δ 6.6 ppm for H_d, as well as the trio of doublets upfield of 6 ppm representing H_b, H_e and H_f. The remaining alkene proton signal H_c is found in the aromatic region. The ^{1}H NMR spectra of the *Z*-isomers were also consistent, with doublets appearing at δ 6.6, 5.8 (H_a), 5.6 ppm, and a multiplet at 5.4 (H_b) ppm.

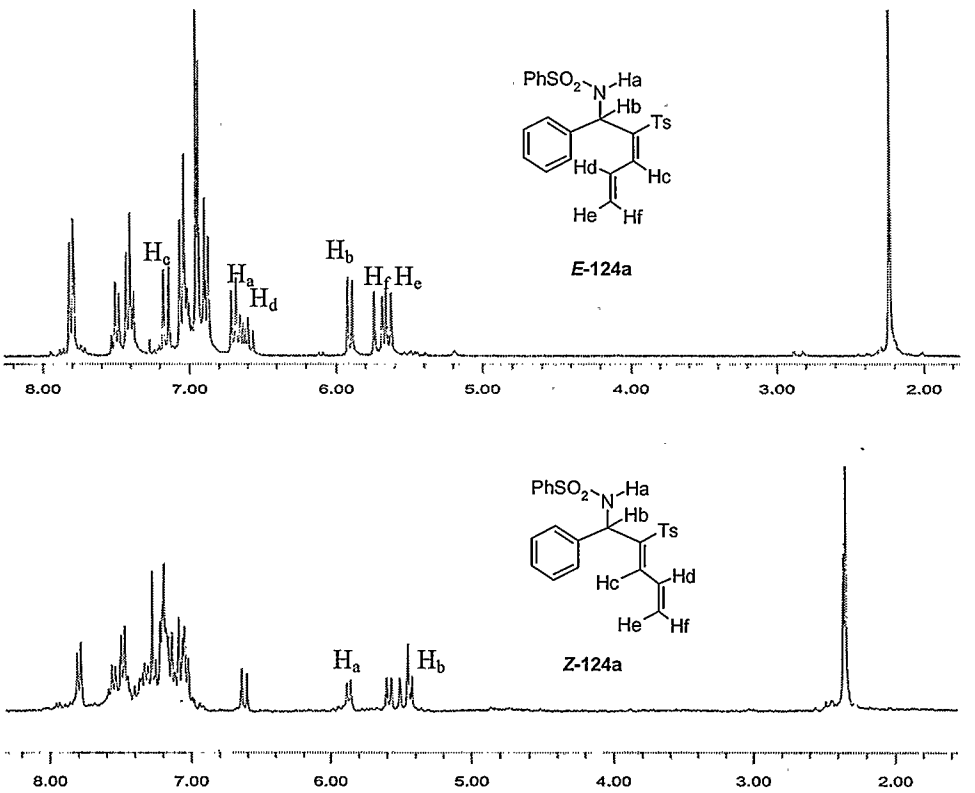


Figure 12. ^{1}H NMR Spectra of *E*- and *Z*-**124a**

The ^{1}H NMR spectra of MBH adducts *E*-**124** are also characterized by a doublet for the amine proton (H_a) near δ 6.7 ppm, which exchanges with D_2O and results in the collapse of the adjacent C-H (H_b) doublet to a singlet (Figure 13).

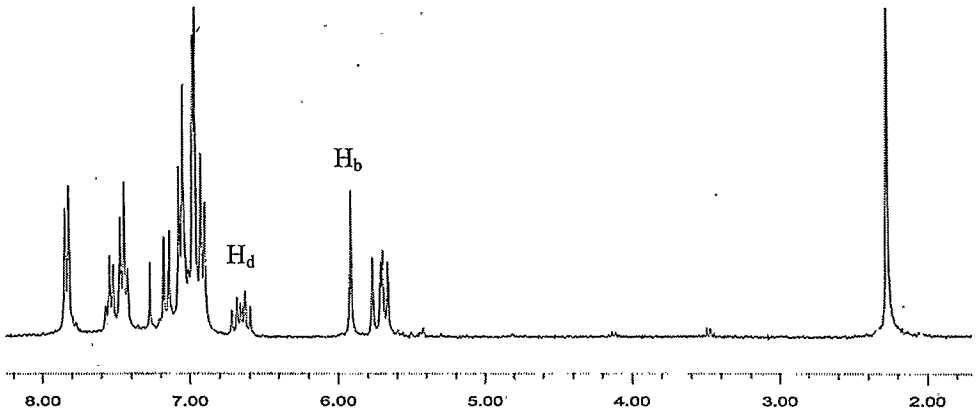


Figure 13. D_2O Exchange for MBH adduct *E*-**124a**

Differentiation of the two geometric isomers was initially made based upon nOe experiments for **124a**. Irradiation of proton H_b (δ 5.9 ppm) led to an enhancement of 16% for H_d (δ 6.6 ppm) while the reverse experiment gave an enhancement of 14%. Subsequently a crystal structure was also obtained for the major isomer of **124a**, clearly demonstrating the *E*-geometry of the compound (Figure 13, Appendix A).

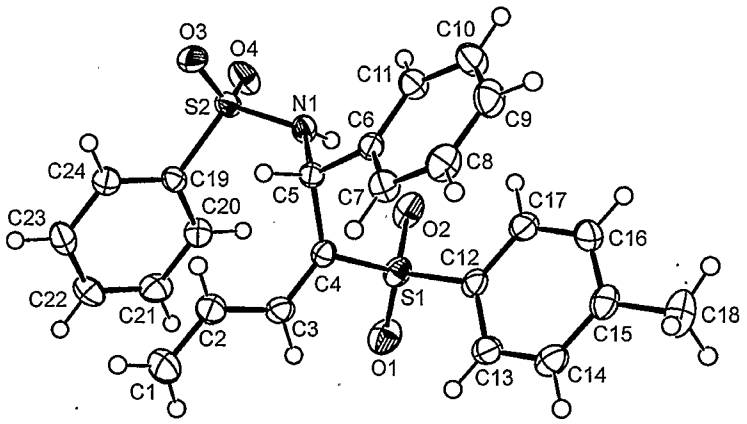
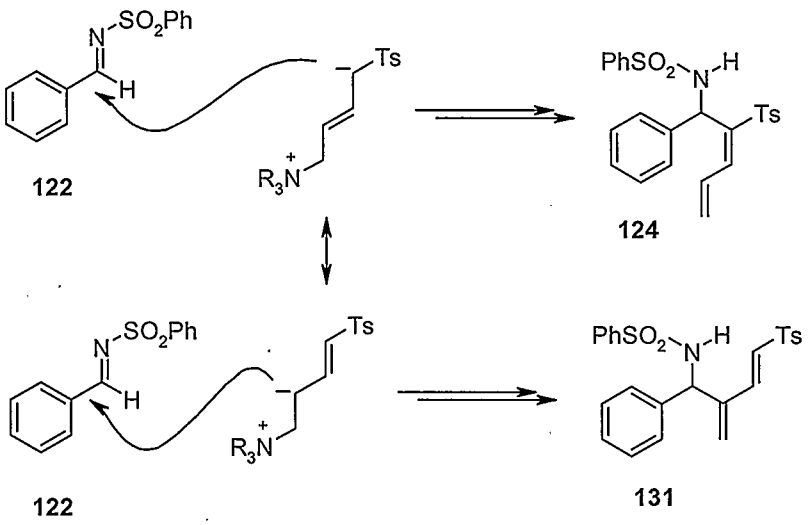


Figure 14. ORTEP Diagram of **124a**

Despite the encouraging results obtained with diene **123**, none of the substituted sulfone-activated diene compounds (**127-129**) reacted in the MBH reaction. This is perhaps not surprising, as MBH reactions tend to be very sensitive to steric interactions. For example, as mentioned in Section 1.2.4.3., β-substituted alkenes generally don't react unless high pressure conditions are employed.[19,20]

Use of the diene substrate also left open the possibility of the formation of the adduct **131**, via resonance of the catalyst-diene complex as shown in Scheme 63. This product was not, however, detected in any of the experiments carried out.

Scheme 63



2.4. Cyclization Reactions

Following the successful syntheses of MBH adducts **124**, cyclization reactions were attempted. Preliminary experiments (carried out by D. A. Rankic) compared a number of different bases including 3-HQD, NaH, and K_2CO_3, with the latter being optimal. Cyclizations of the *E*-isomer in wet DMF containing K_2CO_3 generally proceeded smoothly over a twenty-four hour period, while it was found that the *Z*-isomers did not

cyclize. This is due to the fact that the *Z*-isomer is incapable of adopting a conformation in which the amine is in close enough proximity to the terminal position of the diene unit to react and form the desired six-membered ring (Scheme 64, Table 9).

Scheme 64

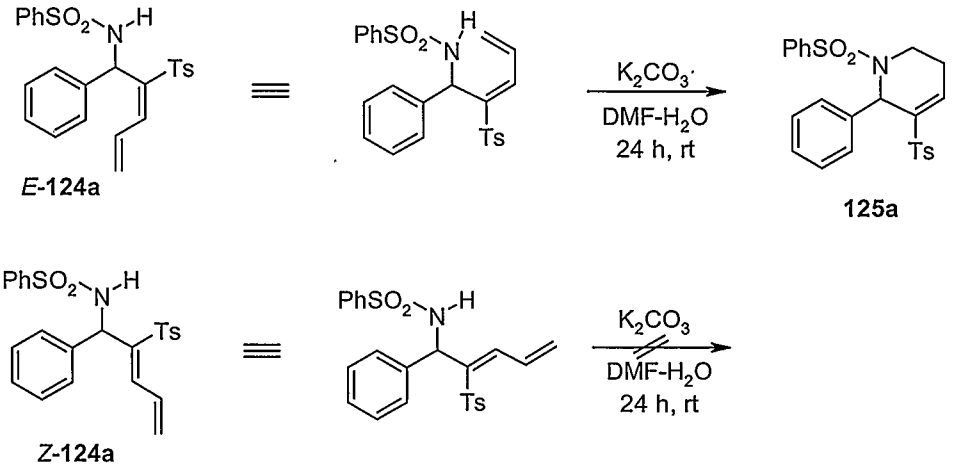


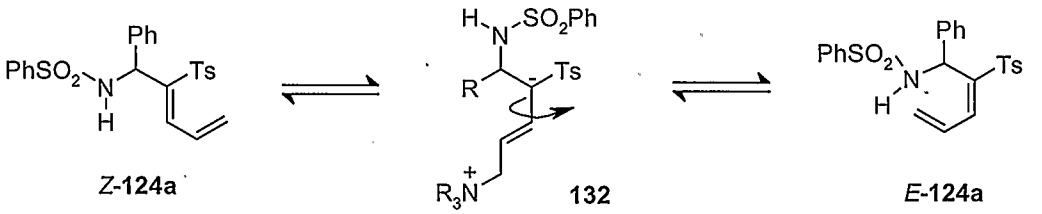
Table 9. Cyclizations of *E*-Adducts **124**

124	R	Yield **125** (%)	**124**	R	Yield **125** (%)
a	C_6H_5 [a]	91	**e**	*p*-$CH_3OC_6H_4$ [a]	79
b	*p*-ClC_6H_4 [a]	95	**f**	*p*-$CH_3O_2CC_6H_4$	65
c	*m*-ClC_6H_4	89	**g**	α-Naphthyl	86
d	*o*-ClC_6H_4	82	**h**	*p*-NCC_6H_4	80

[a] Reaction first carried out by D. A. Rankic.

The cyclizations were generally high yielding, providing easily purifiable compounds; however, the *Z*-isomer was essentially wasted. As a result, an in situ method of isomerizing *E*- and *Z*-adducts, in order to make use of the latter, was sought. Initially examined was use of 3-HQD in DMF, as it was thought the MBH adduct could again undergo an addition-elimination process with the catalyst, generating zwitterionic intermediate **132** and allowing free rotation around the necessary bond for isomerization (Scheme 65).

Scheme 65



Even with gentle heating however, this did not prove to be a successful method for isomerizing between the two species. A similar technique, employing sodium iodide and acetone was then tested, again in hopes that an addition-elimination reaction would be possible, generating the analogous zwitterionic species with the nucleophilic iodide anion. Unfortunately, little isomerization was observed. Also examined was the irradiation of a solution of **124a** in the presence of diphenyl diselenide, which undergoes homolytic cleavage in the presence of ultraviolet light to generate phenylseleno radicals. These can reversibly add to alkene molecules, thus providing access to an enriched mixture of the thermodynamically favored isomer (equations 3 and 4).[135,136]

$$\mathrm{PhSeSePh} \overset{h\nu}{\rightleftharpoons} 2\ \mathrm{PhSe}^{\bullet} \qquad (3)$$

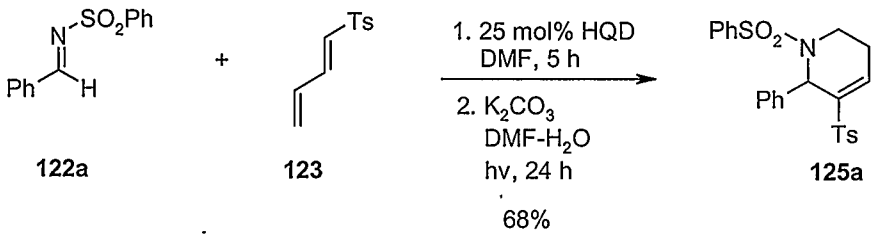
$$\mathrm{PhSe}^{\bullet} + \mathrm{RCH{=}CH_2} \rightleftharpoons \mathrm{RC}^{\bullet}\mathrm{HCH_2SePh} \qquad (4)$$

This however led to a more complex mixture of products than desired and again, resulted in little isomerization of the products. Irradiation without any additives however, effected a very clean isomerization. Comparison of results obtained using ultraviolet light of wavelength of either 250 nm or 300 nm was made and 300 nm was found to be most effective, providing the fastest isomerization with the least decomposition. Thus, irradiation of either a sample of pure *E*-**124a** or pure *Z*-**124a** at 300 nm, over a period of 24 hours, resulted in a mixture consisting of a 70:30 mixture in favor of the *E*-isomer, which therefore represents the equilibrium between the geometric isomers.

To test the applicability of the isomerization protocol, a cyclization reaction was carried out on an unseparated 65:35 mixture of *E*- and *Z*-**124a** in a Rayonet photochemical reactor, with 300 nm lamps for 24 hours. Typical work-up and chromatography of the crude reaction mixture led to isolation of **125a** in 84% yield, clearly demonstrating that some of the *Z*-adduct was indeed cyclizing via the *E*-isomer.

Subsequent investigations involved a one-pot process, in which the MBH reaction and subsequent cyclization could be carried out without the intermediate isolation of the MBH adducts. To this effect, the MBH reaction of imine **122a** and sulfone **123** was carried out as usual; however, instead of working the reaction up when complete it was diluted with wet DMF (DMF:H_2O, 9:1) and irradiated at 300 nm with one equivalent of K_2CO_3 for 24 hours. Work-up and purification of the mixture led to the isolation of **125a** in 68% yield. This was slightly less than the maximum combined yield that was obtained for the two steps when preformed individually (78%), though it eliminated the somewhat difficult purification step of the MBH adduct (Scheme 66).

Scheme 66



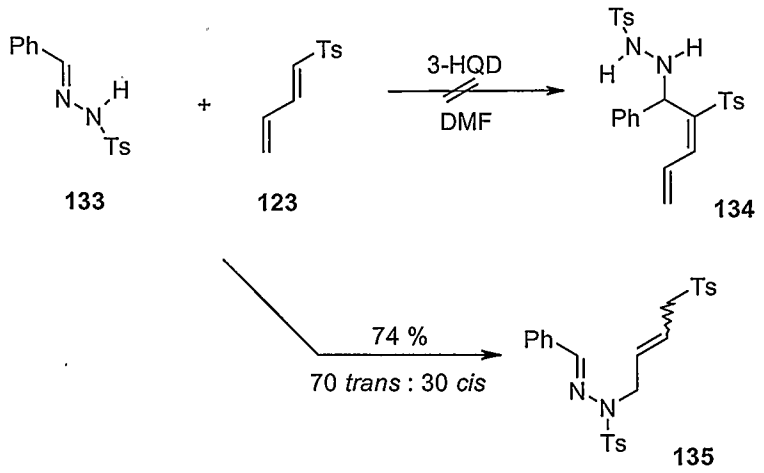
2.5. Substrate Variations

2.5.1. Hydrazones

Similar in structure to the sulfonyl imines are the tosyl hydrazones, which also possess a highly electrophilic carbon atom. Therefore, use of these substrates in the MBH reaction with diene **123** was also examined, with a preliminary experiment carried out by

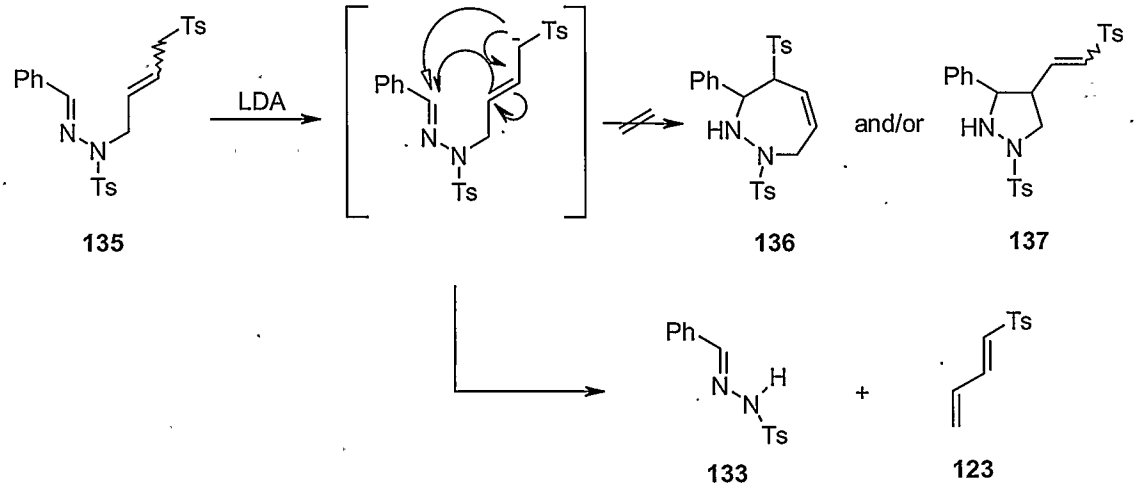
D. A. Rankic. The tosyl hydrazone **133** was synthesized according to the general procedure of Chapman[137] and subjected to the standard MBH reaction conditions. However, rather than the expected MBH adduct **134**, the conjugate addition product **135** was instead obtained as a mixture of *cis*- and *trans*-isomers (Scheme 67).

Scheme 67



While not the desired compound, product **135** was still found to be interesting as it also showed potential for a subsequent cyclization reaction as is shown in Scheme 68. Unfortunately neither product **136** nor **137** was obtained when the reaction was attempted and instead, only retro-addition products were isolated. The electron-withdrawing properties of the sulfonyl group result in the sulfonamide anion being relatively stable, thus making it a good leaving group. Addition of TMEDA to the reaction in an attempt to stabilize the anion alpha to the sulfone moiety and prevent the retrogradation suppressed the reaction completely, leading only to re-isolation of **135**.

Scheme 68



As an alternative approach, the phenyl hydrazone **138** was synthesized from benzaldehyde, according to the literature.[138] It was believed that replacing the sulfone group with the less electron-withdrawing phenyl substituent would perhaps prevent cleavage of the molecule in the presence of base and thus promote the desired cyclization. However, regardless of the conditions employed, neither a conjugate addition reaction nor a MBH reaction occurred between **138** and **123** (Scheme 69, Table 10). An attempt was also made to synthesize hydrazone **139**, however, this proved difficult as the product was prone to spontaneous dimerization to form **140**.

Scheme 69

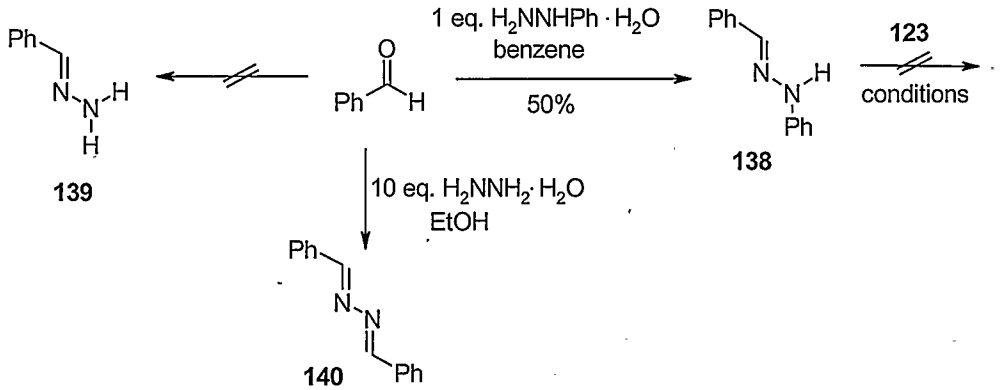


Table 10. Attempted Reaction of Hydrazone **138** with **123**

Conditions	Base	Results [a]
DMF, rt, 7 days	K_2CO_3	SM.
DMF, rt, 6 days	3-HQD	SM
THF, -78°C, 4 h	^{n}BuLi	CM
THF, -78°C, 1 h	^{n}BuLi	CM

[a] SM = Starting material. CM = Complex mixture.

2.5.2. Methyl Ester Activated Dienes

The work in the above section was published as a communication in May of 2005, introducing an activated diene substrate for the first time to the world of MBH chemistry.[139] Shortly thereafter, Shi and Shi published an article, which included a brief discussion of their use of phenyl-2,4-pentadienoate as a diene-substrate in the aza-MBH reaction with a variety of *N*-tosyl imines.[62] They demonstrated that the desired MBH reactions proceeded well in THF using 25 mole % of DABCO as a catalyst over 6 to 120 hours, with the longest reaction times being required for imines possessing electron-donating groups on the benzene ring. Yields were in the range of 32-78% and, similar to our results with diene **123**, the products were consistently obtained as mixtures of *E*- and *Z*-isomers, with the former predominating. Shi and Shi also recognized the possibility of an intramolecular cyclization of the resulting MBH adducts; however, they observed no such process under the MBH conditions employed and did not attempt a separate reaction for the cyclization using the isolated adducts.[62] These results appeared in the midst of our own investigation into whether or not our newly established methodology could be extended to other activating groups for the dienyl substrate, including esters.

The use of methyl ester, methyl ketone, and phenyl ketone moieties as activating groups for the dienyl substrate were all examined. Investigation of the latter two groups will not be discussed here as these were investigated by K. N. Clary, an honours student in the Back laboratory, who also did some work with the methyl ester derivatives discussed below. The methyl 2,4-pentadienoate (**141**) was purchased from Fluka, but could also be prepared in reasonable yield using a literature procedure, if necessary.[140]

The MBH reactions with **141** were again found to proceed fairly well with a range of imine substrates, possessing both electron-donating and –withdrawing groups (Scheme 70, Table 11).

Scheme 70

Table 11. Reaction of Methyl 2,4-Pentadienoate (**141**) with Various Imines.[a]

122	R	Yield **142** (%)	*E*/*Z* Ratio[b]
a	C_6H_5	85	80/20
b	*p*-ClC_6H_5	85	80/20
e	*p*-$MeOC_6H_5$	66	75/25
h	*p*-NCC_6H_5	91	75/25
i	*p*-$NO_2C_6H_5$	61	80/20

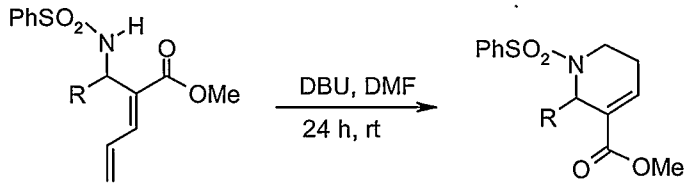
[a] Preliminary reactions carried out by K. N. Clary. [b]As determined by ^{1}H NMR spectroscopy.

Several points can be made in comparing the above data to that of the reactions employing the dienyl sulfones. All reactions were carried out in dry DMF over roughly a 24 hour period, as opposed to the 4-6 hours generally required for dienyl sulfone **123**. Again the *para*-nitro derivative **142i** was obtained in slightly lower yield in comparison to reactions using other imines. Use of dry THF in the place of DMF for the formation of **142i** did not improve the yield as it slowed the reaction dramatically and even after two days yields did not surpass those obtained for reactions carried out in DMF. Similar to the findings of Aggarwal,[29] methanol was found to be an effective additive for these reactions, generally being used in 0.5-1.0 molar equivalent amounts, providing dramatically improved results (**142a** was obtained in 25% yield without methanol). Again, products were obtained as mixtures of both the *E*- and *Z*-isomers, with a consistent bias for the *E*-isomer. As before, the geometric isomers were generally separable by flash chromatography on silica gel, using 16:1 toluene-ethyl acetate as the

eluting solvent. The *E*-isomers eluted first, cleanly, followed by an unseparated mixture of the two isomers.

In contrast to the report of Shi and Shi,[62] cyclizations were also found to proceed for the methyl ester adducts *E*-**142**. However, slightly different experimental conditions were required. The wet DMF solvent was no longer effective as, under the basic conditions necessary to effect the cyclization, significant hydrolysis of the ester was also observed and complex mixtures were often obtained. Dry DMF was ineffective at dissolving the K_2CO_3 and resulted in low yields. DBU was found to be ideal as a base for this reaction, affording good yields of products **143** (Scheme 71, Table 12). As before, the *Z*-isomers were not observed to cyclize and the yields reported are representative of reactions carried out on pure samples of the *E*-adducts.

Scheme 71



E-142 143

Table 12. Cyclization of Methyl Ester MBH Adducts *E*-**142**

E-**142**	R	Time (h)	Yield **143** (%)
a	C_6H_5 [a]	72	77
b	*p*-ClC_6H_5 [a]	24	91
e	*p*-$MeOC_6H_5$ [a]	24	89
h	*p*-NCC_6H_5	24	70
i	*p*-$NO_2C_6H_5$	24	49

[a] Preliminary reactions first carried out by K. N. Clary.

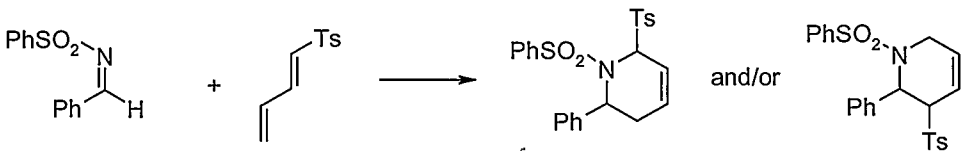
The cyclized products were obtained in fairly good yields, again apart from the *para*-nitro derivative **143i**. Reactions were generally carried out for approximately 24 hours, stirring in dry DMF at room temperature with one equivalent of base. In the case of the unsubstituted phenyl imine **142a**, 3 days were required to obtain the 77% yield shown in the table. Stirring for only one day led to a slightly decreased yield of **143a** in comparison

(67%). Increasing the reaction time for the other substrates **142b**, **e**, **h**, and **i**, did not seem to improve the yields. A one-pot two-step reaction was also attempted for the formation of **143a** from **122a** and **141**; however, this did not seem to be as effective as in the case of the formation of piperidine **125a** from dienyl sulfone **123**, and resulted in a yield of only 47%.

2.6. Another Approach to Substituted Piperidines

In light of the successful one-pot reaction for the formation of **125a**, it was also questioned whether or not it would be possible to carry out a Diels-Alder reaction between the imine **122** and the butadienyl sulfone **123**. If feasible, this reaction would also generate substituted piperidines such as **144** and/or **145** in a single step (Scheme 72).

Scheme 72



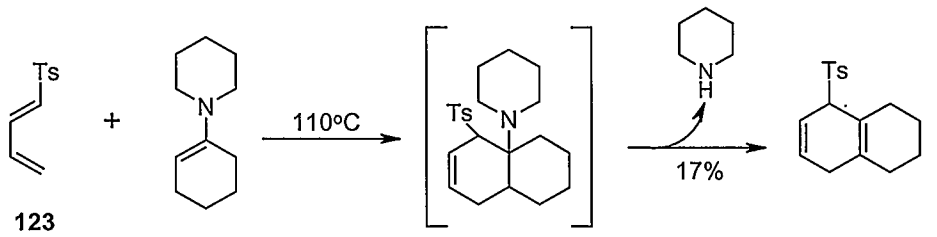
122a **123** **144** **145**

Unfortunately, the reaction did not occur, regardless of the conditions employed. Neither refluxing in benzene or toluene showed any sign of the desired products, and resulted only in the isolation of starting material. Use of $BF_3{\cdot}OEt_2$ as a Lewis acid, either in catalytic or quantitative molar ratios, again resulted only in recovery of the original starting materials. This is perhaps not entirely unexpected, due to the electronic properties of the system. Dienyl sulfones have been shown to undergo Diels-Alder reactions, reacting as either dienes or dienophiles. The electron-withdrawing sulfonyl group makes them viable diene reagents for inverse electron-demand [4+2] cycloadditions, while use

of one double bond of the conjugated system enables them to behave as dienophiles in normal Diels-Alder reactions.[113,114] Examples of dienyl sulfones serving as dienes in normal Diels-Alder reactions are, however, limited to examples in which the dienes also possess strongly electron-donating groups, such as the carbamate substituted sulfone **146**. These have been shown to react successfully with electron-poor dienophiles in normal Diels-Alder reactions.[113] Examples of both normal[141] and inverse[142] electron-demand Diels-Alder reactions are shown in Scheme 73.

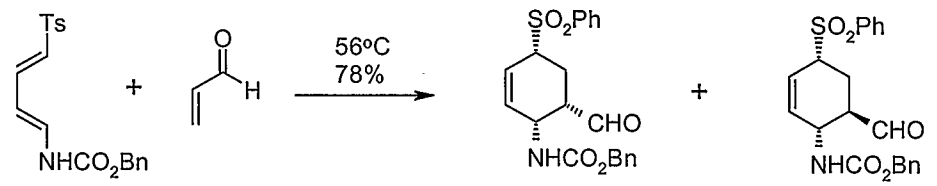
Scheme 73

Inverse Electron-demand:



123

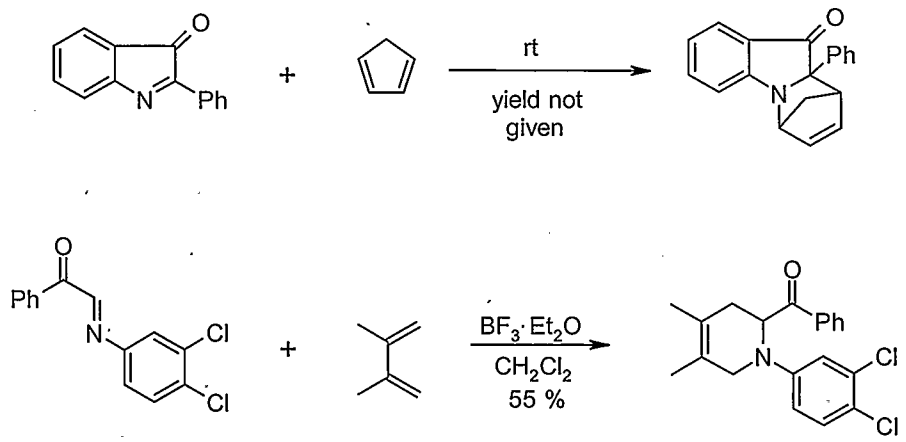
Normal Electron-demand:



146

Similarly, electron-deficient imines, including sulfonyl substituted ones, have been shown to successfully undergo normal Diels-Alder reactions, though it seems that there are relatively few examples involving *N*-aryl imines.[143] Two successful examples of normal Diels-Alder reactions involving *N*-aryl imines are given below (Scheme 74).[144,145] Thus, while the possible reaction conditions were not by any means exhausted in the efforts to effect the desired Diels-Alder reaction, it would seem that the electronic properties of the diene and dienophile are not well matched in the case of substrates **123** and **122a**.

Scheme 74



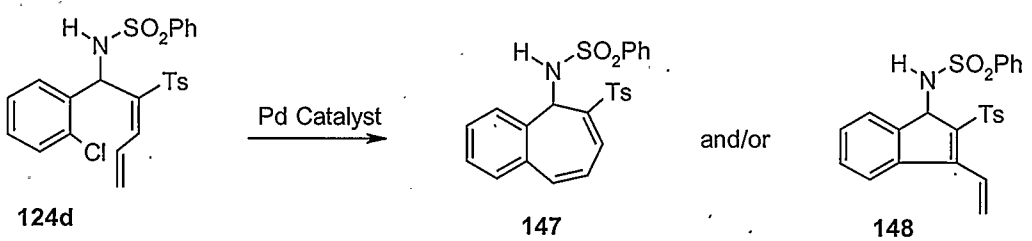
2.7. Further Transformations

One of the original goals of this project was to survey a variety of different chemical reactions, involving the MBH adducts and the functionalized piperidine structures obtained from the latter, in order to establish the versatility of methodology. Thus at this stage, further transformations of adducts **124** and piperidines **125** were investigated.

2.7.1. Heck Reactions

With the *ortho*-chloro MBH adduct **124d** in hand, an intramolecular Heck reaction was attempted, in hopes of creating bicylic ring structures such as **147** and **148** (Scheme 75).

Scheme 75



124d **147** **148**

Adduct *E*-**124d** was therefore subjected to a variety of commonly employed Heck reaction conditions, using palladium acetate and triphenylphosphine, based on procedures reported by Jeffery.[146] Surprisingly, however, neither **147** nor **148** were obtained and the reduced product **149** was instead isolated under all of the conditions employed, except when water was used as the solvent, in which case no reaction occurred (Scheme 76, Table 13). Some reactions using the more complex ferrocene-based palladium catalyst **150** were also carried out, and again yielded only the reduced product **149**.

Scheme 76

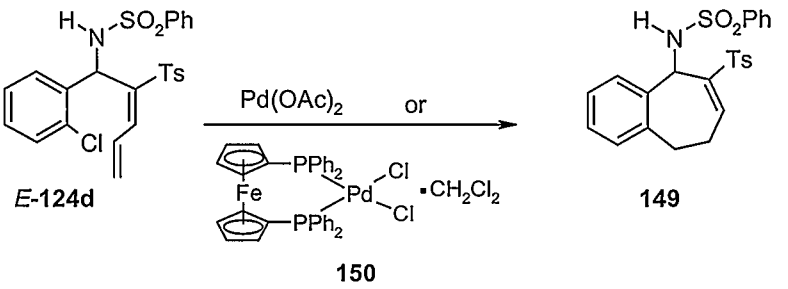


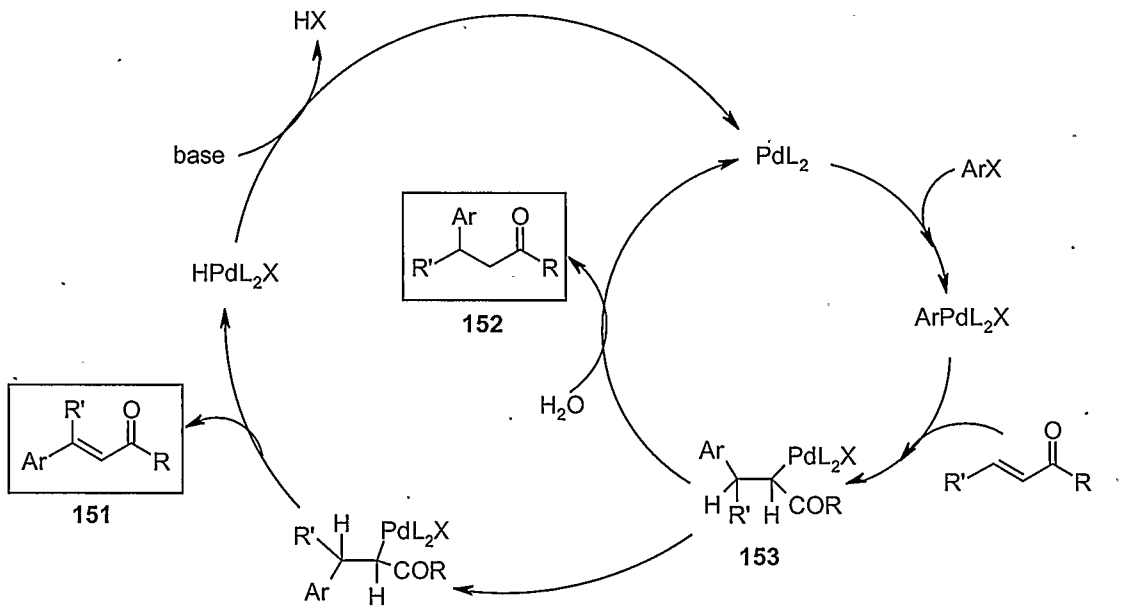
Table 13. Reaction Conditions Employed for the Formation of **149**

Catalyst	Additives	Conditions	Yield **149** (%)
$Pd(OAc)_2$	PPh_3, K_2CO_3, $^nBu_4NBr$	2 h, 50 °C, H_2O	-
$Pd(OAc)_2$	PPh_3, K_2CO_3, $^nBu_4NBr$	2 h, 50 °C, DMF	40
$Pd(OAc)_2$	PPh_3, KOAc, $^nBu_4NBr$	2 h, 50 °C, DMF-H_2O	86
150	Na_2CO_3	4 h, 95°C, DMF- H_2O	70
150	Et_3N	4 h, 95°C, DMF	91

The formation of **149** as the sole product came as a surprise, as none of the reaction conditions included any added reducing agents, such as for example formate salts, which are commonly employed in this type of reductive coupling.[147-149] Analogous products are frequently seen in arylations of β-substituted α,β-unsaturated enones, however. A mechanistic picture of the Heck reaction of an α,β-unsaturated enone and formation of the expected product **151**, along with the formation of possible reduced product **152**, is shown in Scheme 77.[4,150] Both reactions proceed via formation of the organopalladium intermediate **153**, which may undergo an internal rotation followed by a β-hydride

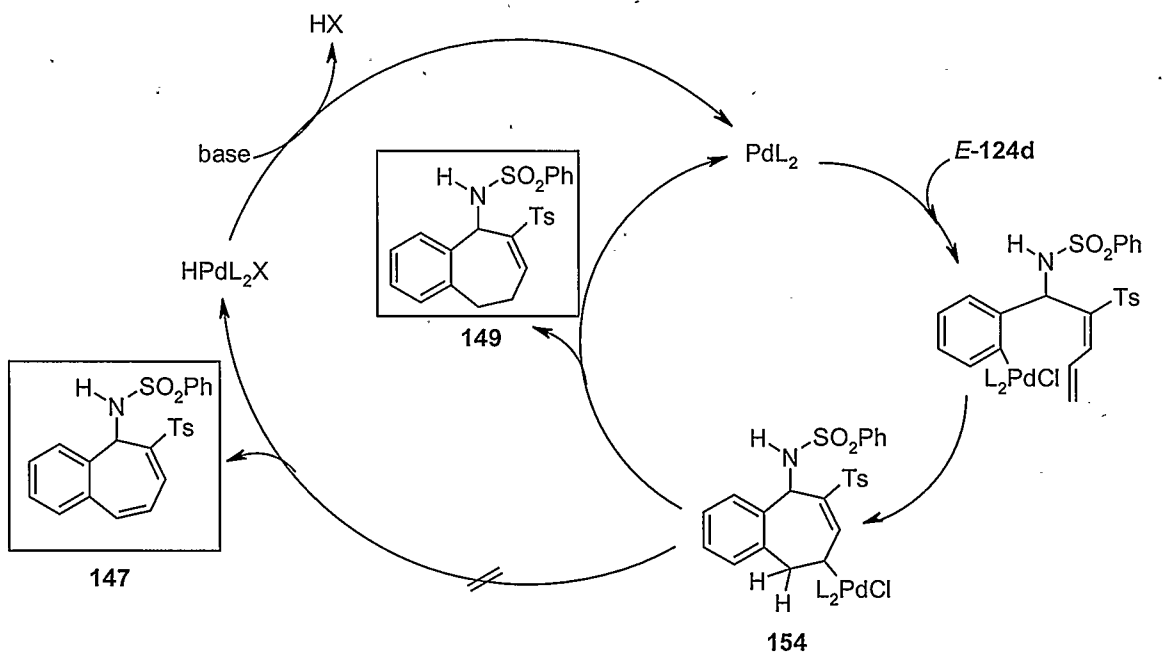
elimination to give **151**. Intermediate **153** has also been observed to undergo protolytic cleavage, yielding the 1,4-addition-type product **152** and a palladium (II) species which must be reduced in order to re-enter the catalytic cycle (Scheme 77).[150]

Scheme 77



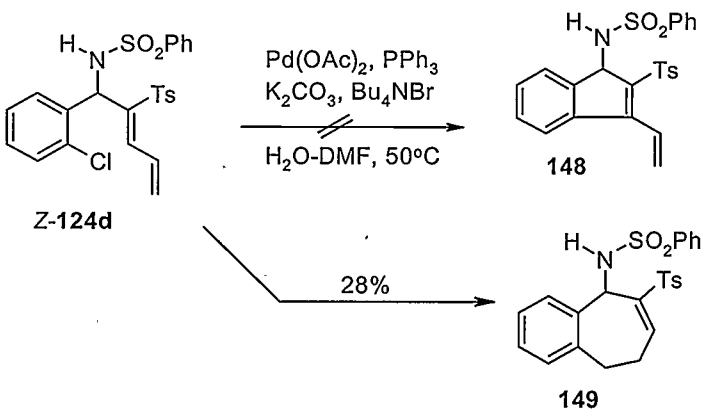
An analogous cycle could thus be envisioned for compound *E*-**124d**, which upon formation of intermediate **154** could undergo a C-Pd heterolytic bond cleavage, rather than undergoing the usual elimination step to generate the cycloheptadiene product **147**. Protonation of the anionic organic fragment would form the observed cycloheptene product **149** (Scheme 78). This mechanism would again lead to the formation of a palladium (II) species which must be reduced before re-entering the catalytic cycle; however, no mechanistic studies have been carried out to determine the exact pathway of the transformation.

Scheme 78



When the cyclization was attempted with *Z*-**124d** instead of the corresponding *E*-isomer, the only product that was isolated was again **149**, although it was obtained in much lower yields than for reactions using *E*-**124d** (Scheme 79).

Scheme 79



2.8. Reactions of the Functionalized Piperidines

2.8.1. Diels-Alder Reactions

The cyclic piperidines **125** possess a vinyl sufone moiety, which prompted examination of the Diels-Alder reaction of **125a** with a variety of dienes. 2,3-Dimethyl-1,3-butadiene (**155**), cyclopentadiene (**156**), and Danishefsky's diene (**157**) were all examined as reaction partners (Scheme 80). Conditions employed ranged from stirring at room temperature to refluxing in a variety of solvents, including benzene, toluene, and xylenes. Despite these harsh conditions, no reactions took place. The addition of Lewis acids to the reaction mixtures again failed to promote the desired cyclizations (Table 14).

Scheme 80

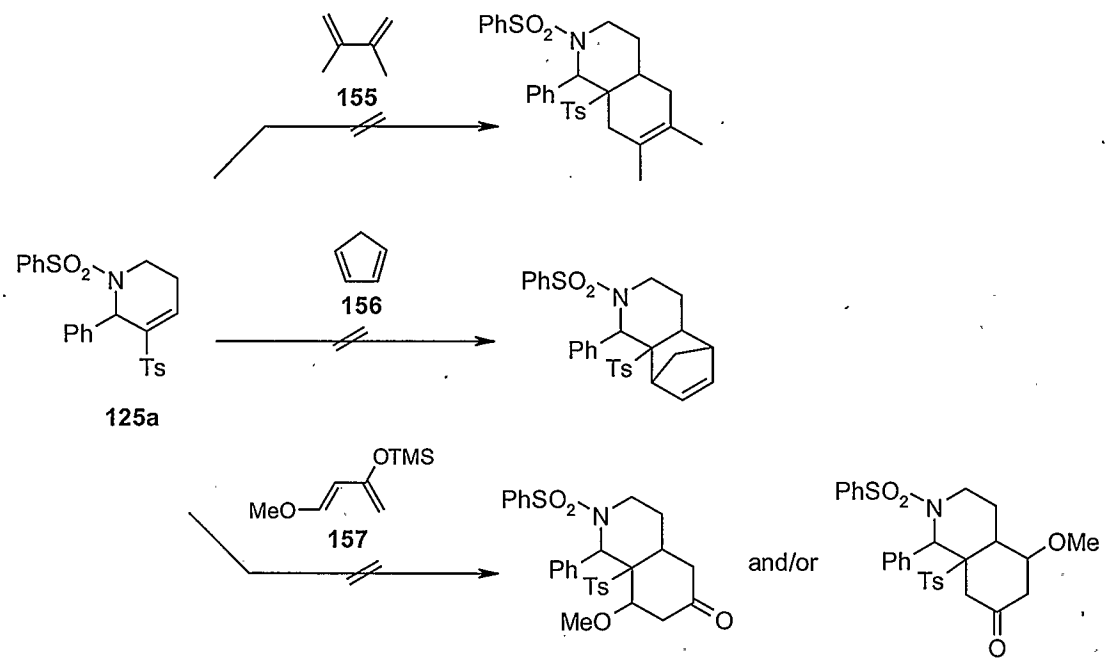


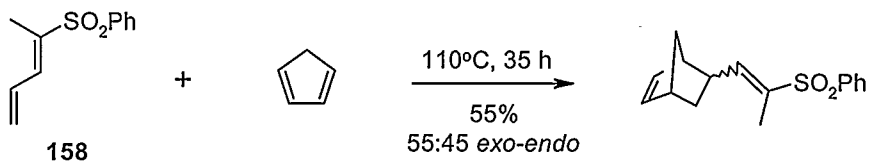
Table 14. Attempted Diels-Alder Reactions of **125a**

Diene	Solvent, Lewis Acid	Temperature (°C)	Time (h)	Results [a]
155	benzene	20	48	SM
155	benzene	70	24	SM
155	xylenes	120	48	SM
155	CH_2Cl_2, $TiCl_4$	20	24	SM
156	toluene	110	48	SM
156	xylenes	120	48	SM
156	CH_2Cl_2	20	24	SM
156	CH_2Cl_2, $ZnBr_2$	20	24	SM
156	CH_2Cl_2, $TiCl_4$	20	8	SM
157	CH_2Cl_2	20	48	SM
157	toluene	100	24	SM

[a] SM = Starting material.

While unsubstituted vinyl sulfones such as phenyl vinyl sulfone have been shown to be useful dienophiles,[114,151] their substituted counterparts tend to be appreciably less reactive.[151] Nonetheless there are many successful examples of Diels-Alder reactions employing substituted vinyl sulfones and activated dienes. In contrast, there are relatively few examples of dialkyl substituted aryl vinyl sulfones reacting with the typical dienes; these rare examples are thought to occur due to specific geometric and electronic contributions of the diene which favor the particular reaction. An example that exemplifies the limited reactivity of the substituted sulfones is given in Scheme 81, where the Diels-Alder reaction takes place at the unactivated position of the dienyl sulfone substrate (**158**).[151]

Scheme 81



2.8.2. Conjugate Additions

Vinyl sulfones are also good reagents in conjugate addition reactions, acting somewhat analogously to α-β-unsaturated carbonyl compounds.[113,114] As such, reactions employing piperidine **125a** as a substrate for conjugate additions were attempted. A variety of commonly employed conditions were used and some rather interesting results obtained (Scheme 82, Table 15).

Scheme 82

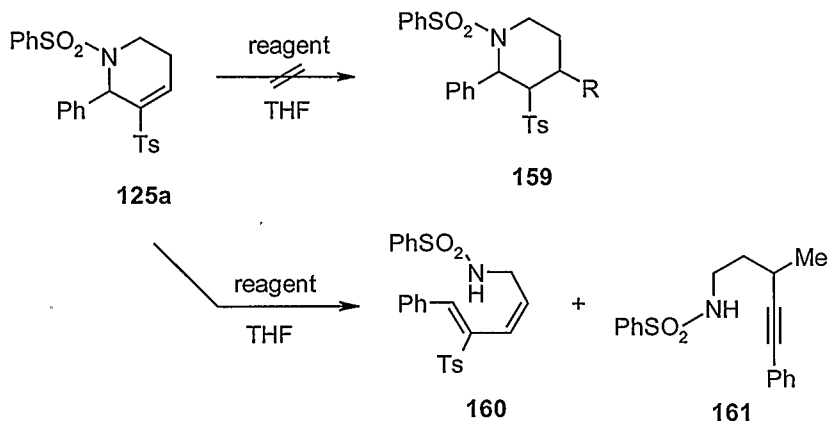


Table 15. Conditions Used for Attempted Conjugate Addition Reactions to **125a** in THF

Entry	Reagent	Conditions	Product (% Yield) [a]
1	Me_2CuLi	-78 – 0°C, 4 h	**160** (50) + **125a** (50)
2	Me_2CuLi	0 – 20°C, 4 h	**161** (76)
3	MeMgBr	0 – 20°C, 24 h	**125a**
4	MeMgBr + CuI [152]	-10 – 20°C, 15 h	**125a**
5	$Me_2CuLi + BF_3OEt_2$ [153]	-78 – 0°C, 3 h	**125a**
6	$Me_2Cu(CN)Li_2$ [154]	-78 – 0°C, 2 h	**125a**
7	PhSHMeCuLi [155]	-78 – 0°C, 4 h	**125a**
8	MeLi	-10°C, 1 h	**161** (24)
9	BuLi	-78 – 0°C, 4 h	CM

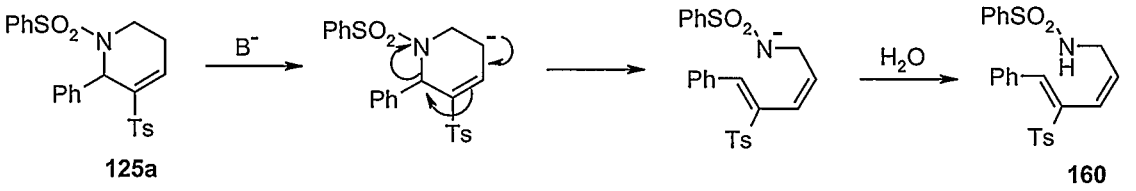
[a] CM = Complex mixture.

When lithium dimethylcuprate was examined, it was found that depending on the conditions employed, the reaction yielded either a mixture of **160** and recovered **125a**, or

compound **161** as the major product (Table 15, entries 1 and 2). Formation of diene **160** most likely occurs via the mechanism shown in Scheme 83, in which the reagent acts as a base rather than a nucleophile, abstracting the proton γ to the sulfone. This results in a ring-opening reaction via expulsion of the sulfonamide, once again demonstrating the ability of the sulfonamide moiety to act as a leaving group. Work-up of the reaction protonates the nitrogen anion, giving the final diene product **160**. The alkyne **161** is presumed to form via addition of a methyl group to the β-position of the sulfone, followed by a ring-opening with expulsion of the sulfonamide unit. A proton transfer step and concomitant elimination of the *para*-toluenesulfinate anion leads to alkyne **161**.

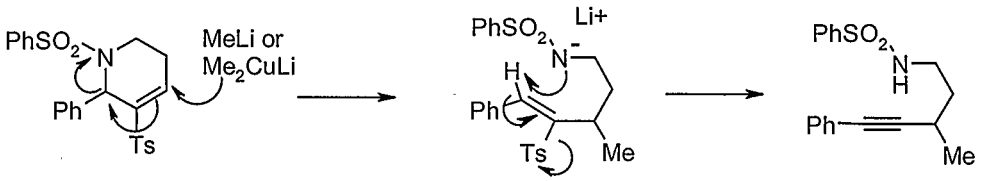
Scheme 83

Formation of **160**:



125a **160**

Formation of **161**:



125a **161**

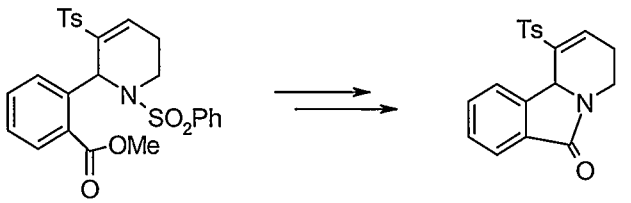
A variety of different reagents, including a Grignard reagent, both on its own and in the presence of catalytic amounts of copper iodide (entries 3 and 4), a cuprate reagent in combination with a Lewis acid (entry 5), as well as some higher order mixed cuprates (entries 6-7) were then examined in order to effect the conjugate addition. None of these proved to be successful, with isolation of only starting material. Use of MeLi generally provided only small amounts of **161**, though the reactions were highly sensitive to the

conditions employed (entry 8). The reaction was also attempted using *n*-BuLi; however, this led only to complex mixtures of products (entry 9).

2.9. Approaches to Extended Ring Systems

In a continued exploration of expansion of the ring structure of the piperidines **125**, a transformation to form compounds such as **162**, as shown in Scheme 84, was attempted. It was hoped that this could be accomplished via synthesis of the *ortho*-methyl ester **125l**, followed by deprotection of the nitrogen, and intramolecular acylation of the resulting nucleophilic amine moiety.

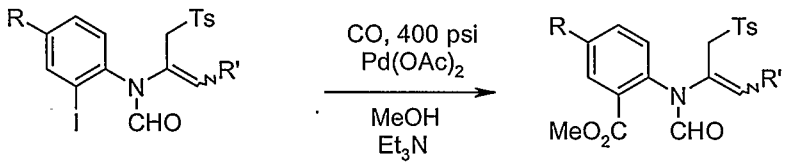
Scheme 84



125l **162**

Unfortunately, problems were encountered early in this approach, with the synthesis of the required MBH adduct **124l** proving to be difficult, perhaps because of steric hindrance. Therefore, an alternative method for formation of the desired **125l** was sought. The Back group has previously made use of a high yielding palladium-catalyzed carbonylation reaction for the transformation of **163** to **164** (Scheme 85).[123] Based on the success of this reaction, synthesis of the *ortho*-iodo piperidine **125m** was carried out. However, again presumably due to steric crowding, the *ortho*-iodo imine **122m** and the dienyl sulfone **123** could not be made to react, even after heating at 100°C for two days (Scheme 86, Table 16). This is in contrast to the *ortho*-chloro derivative **122d**, which reacted normally in the MBH reaction with dienyl sulfone **123**, perhaps because the more strongly electron-withdrawing chloro substituent results in a more electrophilic imine.

Scheme 85

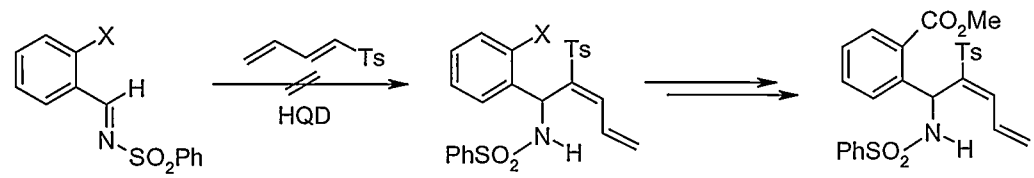


163a, R = H, R' = ^{n}Bu
163b, R = CO_2Me, R' Et

164a, 94%
164b, 94%

The synthesis of the *ortho*-hydroxy derivative **125n** was also attempted, with the desire to convert the hydroxyl moiety into a triflate group for the purpose of the carbonylation reaction (Scheme 86). However, it was again found that despite a variety of conditions employed, the desired MBH products could not be isolated (Table 16). It is likely that the electron-donating hydroxyl group of the imine **122n** diminishes its reactivity in the MBH reaction.

Scheme 86



122m, X = I
122n, X = OH

124m, X = I
124n, X = OH

124l

Table 16. Attempted MBH Reactions with Imines Having *Ortho*-Substituents

X	Conditions	Results [a]
I	DMF, 20°C, 48 h	SM
I	DMF, 80°C, 24 h	SM
I	DMF, 100°C, 48 h	SM
OH	DMF, 20°C, 5 d	SM
OH	DMF, 80°C, 2 d	SM
OH	DMF, MeOH, 70°C, 7 d	SM
OH	DMF, 1.25 eq 3-HQD, 70°C, 7 d	SM

[a] SM = Starting material.

A last attempt was made, reverting to the use of the previously synthesized *ortho*-chloro derivatives **124d** and **125d**, subjecting each to a carbonylation reaction similar to those described above (Scheme 85). Carbonylations of aryl chlorides are, however, notoriously difficult in comparison to those of aryl iodides or aryl bromides.[156] Reactions of **124d** under the conditions listed in Table 17 resulted in formation of an unidentifiable product. Reactions of **125d** under varied conditions resulted only in the isolation of starting materials (Scheme 87, Table 17).

Scheme 87

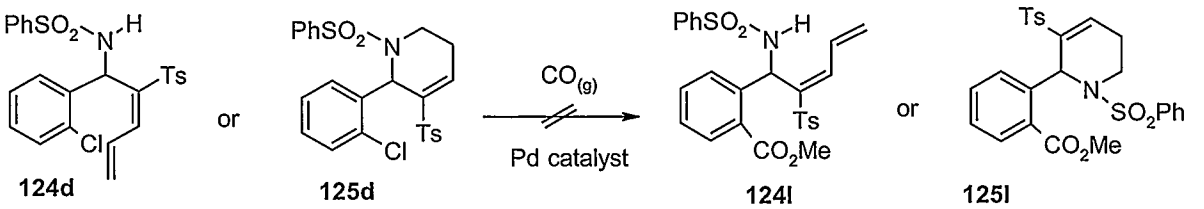


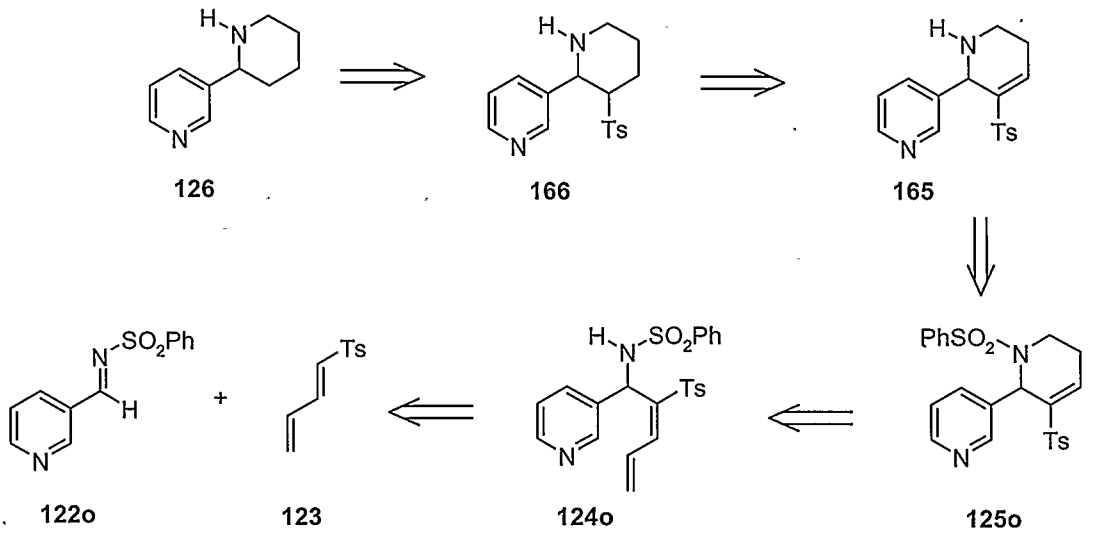
Table 17. Attempted Carbonylation of *Ortho*-Chloro Compounds **124d** and **125d**

Compound	Catalyst	Conditions	Results
124d	$PdCl_2(CH_3CN)$	Na_2CO_3, MeOH, 65°C, 24 h, 1 atm CO	Unknown Compound
124d	**150**	Na_2CO_3, MeOH, 65°C, 24 h, 1 atm CO	Unknown Compound
125d	$Pd(OAc)_2$	Et_3N, 20°C, 48 h, 130 psi CO	**125d**
125d	**150**	Na_2CO_3, 20°C, 48 h, 300 psi CO	**125d**

2.10. Approaches to the Synthesis of Anabasine

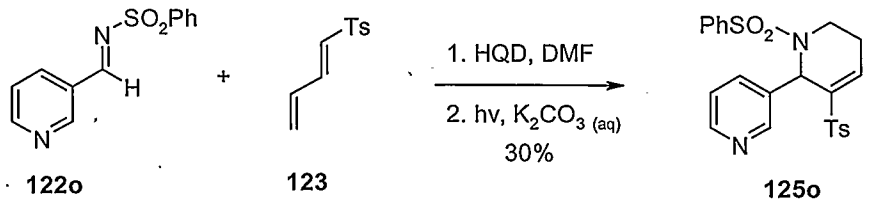
As a showcase for the methodology established with this work, synthesis of the racemic form of the natural product anabasine (**126**) was attempted. A route as outlined in the retrosynthesis in Scheme 88 was envisaged. Piperidine **125o** could be synthesized via the established MBH reaction of imine **122o** and dienyl sulfone **123** and subsequent cyclization of the resulting adduct **124o**. The remaining transformations would include deprotection of the nitrogen atom, reduction of the double bond, and desulfonylation.

Scheme 88



The imine was first synthesized from the commercially available 3-nicotinaldehyde as described in Section 2.2.2. Synthesis of the MBH adduct **124o** according to the standard procedure was then carried out. The reaction proceeded nicely in DMF at room temperature over seven hours according to TLC and ^{1}H NMR analyses. However, isolation of the product proved to be exceedingly difficult as a result of its polarity and insolubility in common chromatographic solvents. Thus, a one-pot cyclization of **122o** and **123** was carried out, in order to form **125o** directly. Initial formation of the MBH adduct and subsequent irradiation of the crude reaction mixture at 300 nm in the presence of one equivalent of potassium carbonate in wet DMF gave the desired product (Scheme 89). This compound, having limited solubility and being very polar, also proved very difficult to purify. Column chromatography on silica gel with 4:1 ethyl acetate:hexanes containing 1% triethylamine afforded the desired product in a consistent but low yield of 30%.

Scheme 89



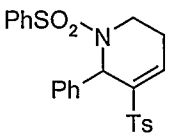
122o **123** **125o**

Next examined was the deprotection of the nitrogen atom, initially using the unsubstituted piperidine derivative **125a** as a model. A number of standard conditions were employed, but the compound proved quite robust and generally only starting materials were isolated (Table 18).

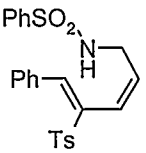
Table 18. Attempted Deprotection of Cyclized Adduct **125a**

Reagent	Conditions	Results [a]
HCl	70°C,1 h	**125a**
H_2SO_4	20°C,6 days	**125a**
$ClSO_2OH$	20°C,6 days	CM
AcOH – $HClO_4$	90°C,7 h	**125a**
NaI – Anthracene	THF, 20°C, 15 min	CM
NaI – TMSCl [157]	CH_3CN, 80°C, 24 h	**125a**
Sodium amalgam	THF, 65°C, 48 h	CM
NaOH (5 M) [158]	MeOH, 65°C, 24 h	**125a**
KO^{t}Bu	DMF, 20°C, 24 h	**125a**
KO^{t}Bu	DMF, 80°C, 24 h	**125a**
Na – $NH_{3(l)}$ [159]	-78°C, 2 h	**160**
Li – $NH_{3(l)}$ [159]	-78°C, 3 h	**160**

[a] CM = Complex mixture



125a

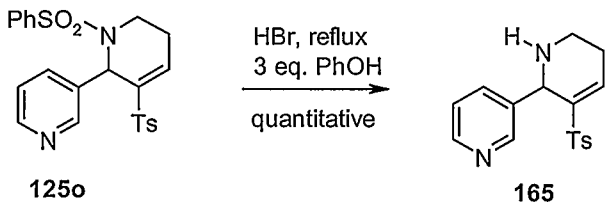


160

As can be seen in the table, Birch reduction conditions were also employed and it was hoped that under these conditions desulfonylation of both the *para*-tolylsulfonyl and the *N*-sulfonyl groups would occur. However, this led to a ring opening reaction, generating the alkene product **160**, as was previously observed for many of the cuprate reactions described in Section 2.8.2. This was, again, presumably facilitated by the strong leaving group ability of the sulfonamide anion. Returning to the use of the pyridine derivative **125o**, the deprotection was finally successfully carried out by refluxing in 48%

hydrobromic acid in the presence of phenol.[160] This led to quantitative isolation of the desired amine **165** (Scheme 90).

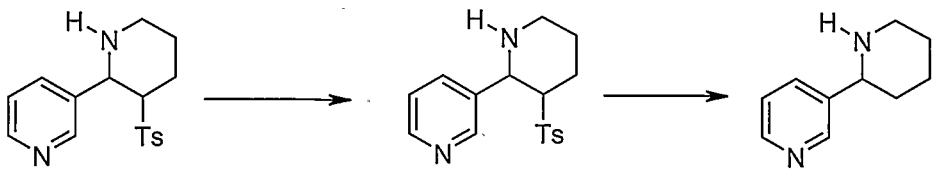
Scheme 90



125o **165**

The remaining steps in the synthesis of the natural product included desulfonylation and reduction of the double bond (Scheme 91). Desulfonylation of **165** was briefly examined using sodium amalgam in THF, but this led to intractable mixtures, from which no clean products could be isolated. As such, reduction of the double bond of **165** was attempted using palladium catalysts (palladium (II) hydroxide or palladium on charcoal) under a hydrogen atmosphere in methanol. This resulted, however, only in the isolation of starting material. The reaction was attempted again, under elevated pressure (400 psi), using a Parr apparatus, but again only starting materials could be detected in the crude reaction mixture. Sodium borohydride was also used in an attempt to reduce the double bond, based on similar procedures employed by Muchowski,[161] but this lead only to decomposition products. While the remaining steps in the formation of anabasine (**126**) from **165** may be viable in future attempts, the synthesis could unfortunately not be completed during the course of this work.

Scheme 91



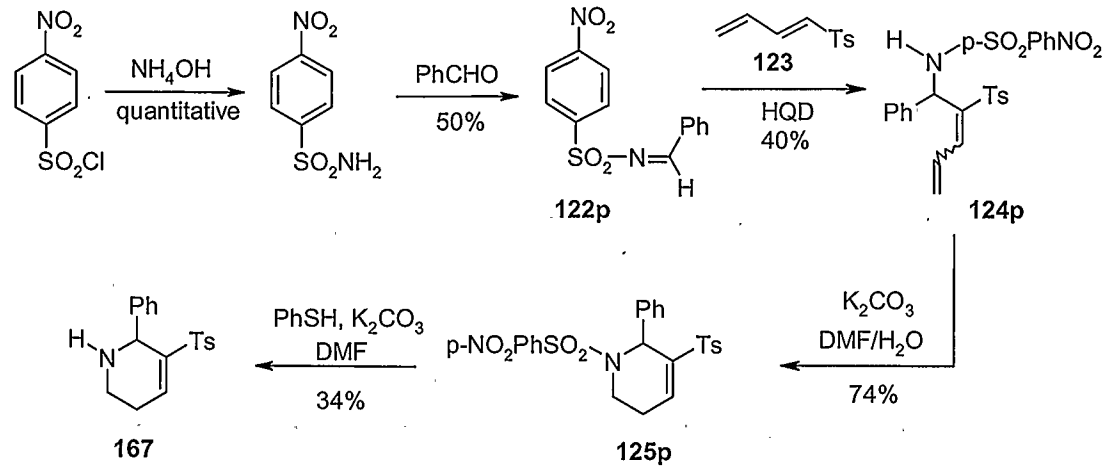
165 **166** **126**

2.11. Variation of *N*-Protecting Group

Due to the difficulties encountered regarding deprotection of the nitrogen atom discussed in the above section, a preliminary study into the use of a modified *N*-protecting group was conducted. The 4-nitrophenylsulfonyl (nosyl) group has been shown to be quite readily cleaved under very mild conditions, via a nucleophilic aromatic substitution process involving thiophenol.[162] Applicability of this protecting group to our system was thus examined.

Synthesis of *para*-nitrobenzenesulfonamide from *para*-nitrobenzenesulfonyl chloride was carried out by a literature procedure.[163] This was then used to synthesize imine **122p**, which was reacted with **123** to give the MBH adduct **124p** in 40% yield. Cyclization of the latter proceeded under typical conditions, yielding 74% of the desired piperidine **125p**. This was then deprotected to give the highly polar amine **167**, which was purified by an acid-base extraction but was only isolated in 34% yield (Scheme 92). Column chromatography of **167** failed as a purification method. Although this unoptimized result is not yet useful for synthetic applications, it demonstrates that *N*-protecting groups, other than those initially examined, may prove useful in the future.

Scheme 92



2.12. Conclusions and Future Work

A novel methodology for the aza-MBH reaction employing activated butadienyl subtrates has been successfully established. Reactions of a variety of *N*-(benzylidene)-benzenesulfonamides (**122**) with either 1-(*p*-toluenesulfonyl)-1,3-butadiene (**123**) or methyl 2,4-pentadienoate (**141**) afforded the desired, highly functionalized MBH adducts **124** and **142**, respectively, in reasonable yields. In both cases, the products were obtained as mixtures of *E*- and *Z*-isomers, which could be separated by column chromatography. The *E*-adducts, when treated with base, could be made to undergo an intramolecular conjugate addition reaction, affording substituted piperidine rings **125** and **143**, respectively. Due to conformational constraints, the *Z*-isomers were incapable of cyclizing. However, in the case of MBH adducts **124**, it was found that the two geometric isomers could be equilibrated in the presence of 300 nm light. As such, cyclization reactions carried out on unseparated isomeric mixtures of MBH adducts in a Rayonet reactor equipped with 300 nm lamps afforded increased yields of the desired piperidine products **125**. A successful two-stage, one-pot reaction was also carried out, providing direct access to piperidines **125** from imines **122** and diene **123**.

In addition, further transformations employing either adducts **124** or piperidines **125** were investigated. Reactions examined using **125** included a variety of Diels-Alder reactions, all of which proved to be unsuccessful, as well as attempted conjugate addition reactions which lead to isolation of unexpected diene and alkyne products **160** and **161**, respectively. An intramolecular Heck reaction of *ortho*-chloro substituted MBH adduct **124d** was carried out successfully, yielding the interesting bicyclic system **149**.

This newly established methodology was also applied towards the synthesis of the naturally occurring alkaloid anabasine. The 3-pyridyl derivative **124o** was successfully synthesized and subsequently deprotected to afford piperidine **165**. Unfortunately, to date, the remaining reduction and desulfonylation of the latter, required for formation of the target compound, have been unsuccessful. These transformations, however, may yet prove feasible and should be examined in future research. In addition, due to difficulties

encountered in the deprotection of piperidine **125a**, further investigation into the use of alternative imine-activating groups, as for example in the case of **122p**, might also be beneficial. Also, as the present work describes only racemic studies of the MBH reaction, future work in this area will inevitably include directions towards enantioselective applications of the methodology, perhaps through application of chiral, enantiopure catalysts.

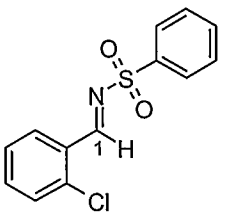
Chapter 3: Experimental

3.1. General Remarks

All ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$, using $CHCl_3$ as the internal standard (^{1}H δ 7.27 ppm; ^{13}C 77.0 ppm), unless otherwise noted. The spectra were recorded on a Bruker DRX 400 (^{1}H, 400 MHz; ^{13}C, 100 MHz), Bruker AC-300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) or Bruker AC-200 instrument (^{1}H, 200 MHz; ^{13}C, 50 MHz). All nOe experiments were performed on the Bruker AC-200 instrument. Assignments of atoms, where indicated, were made with the aid of ^{1}H, ^{13}C, DEPT-90, DEPT-135, COSY, and/or HMQC NMR data. Numbering of compounds in this Chapter is arbitrary, for the purpose of indicating spectral assignments, and does not follow IUPAC nomenclature. IR spectra were recorded on a Nicolet Nexus 470 FTIR ESP instrument. Low and high resolution mass spectra were obtained by EI, unless otherwise indicated, using a Kratos MS80 RFA or Micromass VG7070F mass spectrometer. ESI experiments were run on a Bruker Esquire 3000 instrument. Elemental analyses were determinded using a Perkin Elmer Model 2400 series II CHN instrument. Elemental analyses and mass spectra were obtained by Ms. D. Fox, Ms. Q. Wu, Ms. O. Blagojevic, and/or Ms. Roxanna Smith at the University of Calgary. Melting points were determined on an A.H. Thomas hot-stage apparatus and are uncorrected. Photochemical experiments were carried out in a Rayonet RMR-500 reactor equipped with eight 300 nm lamps. The X-ray crystal structure was solved by Dr. M. Parvez at the University of Calgary, and the data provided by him are listed in Appendix I, without modification. Chromatographic separations were performed by flash chromatography on silica gel (230-400 mesh). DMF was either distilled over CaH_2 and subsequently stored over molecular sieves, or was obtained directly as DriSolv® EMD™ (Aldrich Co.). THF was freshly distilled over lithium aluminum hydride. Toluene was distilled over calcium hydride and subsequently stored over molecular sieves. Methanol was dried using molecular sieves. *n*-Butyllithium was titrated using *N*-benzylbenzamide as both titrant and indicator. Drying of organic extracts was carried out using $MgSO_4$. The preparation of imines **122a-p** was performed according to the general procedure of Davis et al.[129] Imines **122a**,[129] **122b**,[130] **122c**,[130] **122e**,[130] **122g**,[164]

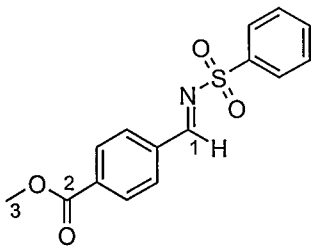
122i,[131] **122k**,[132] **122n**,[133] and **122p**[134] have been reported previously; the properties of new compounds **122d, 122f, 122h, 122j, 122l, 122m, and 122o** are provided below. The data for imines **122d, 122f, 122h, and 122j** was published by this group during the course of this work.[139] Dienyl sulfones **123, 127**, and **128** were obtained by the method of Barluenga et al.[127] Sulfone **129** was synthesized according to Bordwell and Mecca.[128] All other reagents were obtained from commercial sources and were used without further purification. All reactions were monitored by TLC where appropriate.

3.2. Imines



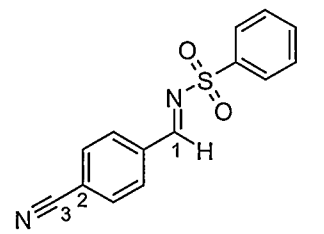
3.2.1. *N*-(2-Chlorobenzylidene)benzenesulfonamide (122d)

Yield: 86%; fine white crystalline solid; mp 135-138 °C (from ethyl acetate-hexanes); IR (film) 1576, 1311, 1156, 1085 cm^{-1}; ^1H NMR (300 MHz) δ 9.54 (s, 1 H, H-1), 8.17 (d, J = 8.2 Hz, 1 H), 8.03 (d, J = 8.2 Hz, 2 H), 7.69-7.46 (m, 5 H), 7.35 (t, J = 7.4 Hz, 1 H); ^{13}C NMR (300 MHz) δ 167.4 (CH, C-1), 139.3 (C), 138.0 (C), 136.0 (CH), 134.0 (CH), 130.7 (C), 130.4 (CH), 130.0 (CH), 129.4 (CH), 128.4 (CH), 127.6 (CH); mass spectrum (*m/z*, %) 244 (26, M^+ - Cl), 141 (49), 77 (100). Anal. calcd for $C_{13}H_{10}ClNO_2S$: C, 55.82; H 3.60; N, 5.01. Found: C, 55.76; H, 3.38; N, 4.93.



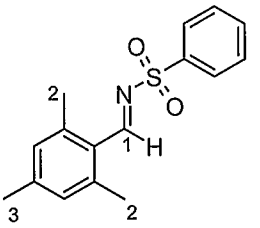
3.2.2. *N*-(4-Methoxycarbonylbenzylidene)benzenesulfonamide (122f)

4-Carboxybenzaldehyde was first converted into methyl 4-formylbenzoate according to the procedure of Lown et al.[165] and then into the imine by the usual method.[129] Yield: 75%; yellow crystalline solid; mp 193-197 °C (from ethyl acetate-hexanes); IR (film) 1725, 1654, 1557, 1311, 1272, 1156, 1079 cm^{-1}; ^1H NMR (300 MHz) δ 9.11 (s, 1 H, H-1), 8.15 (d, J = 8.2 Hz, 2 H), 8.02 (t, J = 7.7 Hz, 4 H), 7.69-7.56 (m, 3 H), 3.96 (s, 3 H, H-3); ^{13}C NMR (75 MHz) δ 169.5 (CH, C-1), 166.0 (C=O, C-2), 137.9 (C), 136.0 (C), 135.6 (C), 134.0 (CH), 131.2 (CH), 130.3 (CH), 129.4 (CH), 128.3 (CH), 52.7 (CH_3, C-3); mass spectrum (*m/z,* %) 303 (1, M^+), 162 (20), 141 (59), 77 (100). Anal. calcd for $C_{15}H_{13}NO_4S$: C, 59.39; H 4.32; N, 4.62. Found: C, 59.38; H, 4.26; N, 4.51.



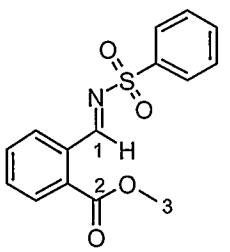
3.2.3. *N*-(4-Cyanobenzylidene)benzenesulfonamide (122h)

Yield: 77%; fine white crystalline solid; mp 169-171 °C (from ethyl acetate-hexanes); IR (film) 2223, 1318, 1156, 1085 cm^{-1}; ^1H NMR (300 MHz) δ 9.10 (s, 1 H, H-1), 8.07-8.02 (m, 4 H), 7.80 (d, J = 8.7 Hz, 2 H), 7.72-7.57 (m, 3 H); ^{13}C NMR (75 MHz) δ 168.4 (CH, C-1), 137.5 (C), 136.0 (C), 134.2 (CH), 132.9 (CH), 131.5 (CH), 129.5 (CH), 128.4 (CH), 117.9 (C, C-2 or C-3), 117.7 (C, C-2 or C-3); mass spectrum (*m/z,* %) 270 (13, M^+), 141 (53), 77 (100). Anal. calcd for $C_{14}H_{10}N_2O_2S$: C, 62.21; H 3.73; N, 10.36. Found: C, 62.00; H, 3.63; N, 10.03.



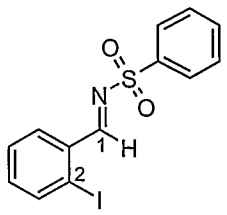
3.2.4. *N*-(2,4,6-Trimethylbenzylidene)benzenesulfonamide (122j)

Yield: 74%; white crystalline solid; mp 110-113 °C (from ethyl acetate-hexanes); IR (film) 1583, 1298, 1143, 1085 cm^{-1}; ^1H NMR (300 MHz) δ 9.48 (s, 1 H, H-1), 8.01 (d, *J* = 7.2 Hz, 2 H), 7.62-7.52 (m, 3 H), 6.93 (s, 2 H), 2.54 (s, 6 H, H-2), 2.32 (s, 3 H, H-3); ^{13}C-NMR (75 MHz) δ 169.6 (CH, C-1), 145.0 (C), 143.2 (C), 139.2 (C), 133.4 (CH), 130.9 (CH), 129.2 (CH), 127.9 (CH), 126.2 (C), 22.0 (CH_3, C-2), 21.7 (CH_3, C-3); mass spectrum (*m/z,* %) 287 (1, M^+), 146 (73), 131 (71), 77 (100). Anal. calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H 5.96; N, 4.87. Found: C, 66.91; H, 6.02; N, 4.80.



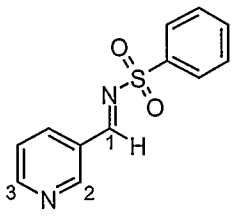
3.2.5. *N*-(2-Methoxycarbonylbenzylidene)benzenesulfonamide (122l)

2-Carbomethoxybenzaldehyde was first synthesized from 2-carboxybenzaldehyde by a known procedure,[166] and then converted into the imine by the usual method. Yield: 73%; white hair-like crystals, mp 122-125°C (from ethyl acetate-hexanes); IR (film) 1716, 1318, 1159, 1087 cm^{-1}; ^1H NMR (300 MHz) δ 9.81 (s, 1 H, H-1), 8.11-7.98 (m, 4 H), 7.65-7.52 (m, 5 H), 3.93 (s, 3 H, H-3); ^{13}C NMR (75 MHz) δ 170.6 (CH, C-1), 166.3 (C=O, C-2), 137.7 (C), 133.8 (CH), 133.6 (CH), 133.1 (C), 132.6 (CH), 132.5 (C), 130.9 (CH), 129.5 (CH), 129.3 (CH), 128.3 (CH), 52.9 (CH_3, C-3); mass spectrum (*m/z,* %) 304 (9, $M^+ + 1$), 272 (26), 163 (56), 162 (100), 141 (59), 130 (100), 77(100); HRMS calcd for $C_{14}H_{10}NO_3S$ (M^+ - OCH_3): 272.03814; Found 272.03666; Anal. calcd for $C_{15}H_{13}NO_4S$: C, 59.39; H 4.32; N, 4.62. Found: C, 59.15; H, 4.33; N, 4.53.



3.2.6. *N*-(2-Iodobenzylidene)benzenesulfonamide (122m)

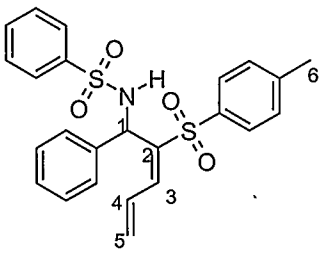
Yield: 52%; white needle-like crystals, mp 132-136°C (from ethyl acetate-hexanes); IR (Nujol) 2923, 1576, 1456, 1158, 798 cm^{-1}; ^1H NMR (300 MHz) δ 9.26 (s, 1 H, H-1), 8.14-7.95 (m, 4 H), 7.70-7.56 (m, 3 H), 7.45-7.40 (m, 1 H),7.30-7.25 (m, 1 H); ^{13}C NMR (75 MHz) δ 173.9 (CH, C-1), 140.5 (CH), 137.5 (C), 135.8 (CH), 133.7 (CH), 133.5, (C), 130.7 (CH), 129.2 (CH), 128.7 (CH), 128.2 (CH), 104.1 (C, C-2); mass spectrum (*m/z,* %) 371 (15, M^+), 244 (20), 230 (42), 141 (13), 103 (32), 77 (100), 51 (38); HRMS calcd for $C_{13}H_{10}O_2NSI$: 370.9477; Found: 370.9478.

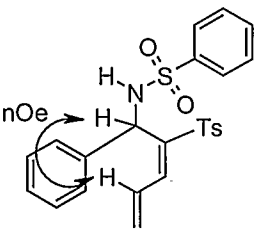


3.2.7. *N*-[(3-Pyridyl)-methylidene]benzenesulfonamide (122o)

Yield: 60%; white crystalline solid; mp 121-124°C (from ethyl acetate-hexanes); IR (film), 1609, 1313, 1158, 1087 cm^{-1}; NMR (300 MHz) δ 9.13 (s, 1 H, H-1), 9.08 (m, 1 H, H-2), 8.84 (d, J = 3.6 Hz, 1 H, H-3), 8.32-8.28 (m, 1 H), 8.05-8.02 (m, 2 H), 7.70-7.56 (m, 3 H), 7.48-7.44 (m, 1 H); ^{13}C NMR (75 MHz) δ 168.1 (CH, C-1), 155.0 (CH), 152.8 (CH), 137.4 (C), 136.9 (CH), 133.8 (CH), 129.1 (CH), 128.0 (CH), 124.0 (CH); mass spectrum (*m/z,* %) 246 (18, M^+), 219 (19), 141 (23), 77 (100), 51 (36); HRMS calcd for $C_{12}H_{10}O_2N_2S$: 246.0463; Found: 246.0473.

3.3. MBH Adducts from 1-(*p*-toluenesulfonyl)-1,3-butadiene



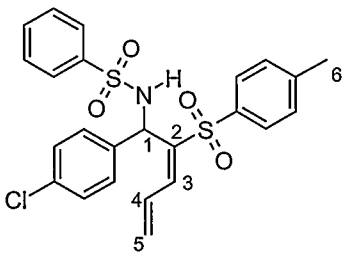


3.3.1. Typical Procedure for Preparation of MBH adducts: *N*-Phenylsulfonyl-1-phenyl-2-(*p*-toluenesulfonyl)-2,4-pentadienylamine (124a)

A solution of 1-(*p*-toluenesulfonyl)-1,3-butadiene **(123)** (160 mg, 0.769 mmol), imine **(122a)** (373 mg, 1.52 mmol) and HQD (24 mg, 0.19 mmol) in 3 mL of anhydrous DMF was stirred for 4.5 h at room temperature. The reaction mixture was poured into 5% HCl solution and extracted with ether. The combined ether layers were washed with brine and water. The organic layer was dried, concentrated and chromatographed (toluene-ethyl acetate, 16:1) to afford 299 mg of **124a** as a white foam (86% based on diene **123**; *E:Z* = 70:30). Further chromatography of the latter product afforded the less polar pure *E*-isomer, followed by a mixture of both geometrical isomers.

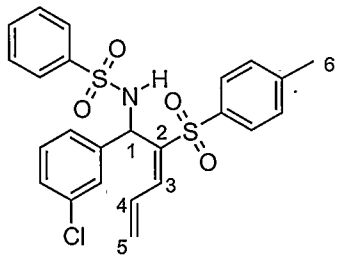
***E*-Isomer**: white crystals; mp 174-176 °C (from ethyl acetate-hexanes); IR (film): 3301, 1343, 1163, 1079 cm^{-1}; ^1H NMR (300 MHz) δ 7.84 (d, *J* = 8.3 Hz, 2 H), 7.57-7.52 (m, 1 H), 7.48-7.43 (m, 2H), 7.16 (d, *J* = 11.1 Hz, 1 H, H-3) 7.08-6.90 (m, 9 H), 6.66 (d, *J* = 9.9 Hz, 1 H, N-H, exchanged with D_2O), 6.64 (ddd, *J* = 15.9 Hz, 10.8 Hz, 9.7 Hz, 1 H, H-4), 5.92 (d, *J* = 9.9 Hz, 1 H, collapsed to s with D_2O exchange, H-1), 5.73 (d, *J* = 15.9 Hz, 1 H, H-5), 5.66 (d, *J* = 9.7 Hz, 1 H, H-5), 2.29 (s, 3 H, H-6); when the ddd at δ 6.64 was irradiated, an enhancement of 14% was observed for the d at δ 5.91, and when the signal at δ 5.91 was irradiated, the one at δ 6.64 was enhanced by 16%; ^{13}C NMR (100 MHz) δ 143.7 (C), 141.8 (CH, C-3), 140.5 (C), 139.0 (C), 137.9 (C), 135.8 (C), 132.8 (CH), 130.6 (CH_2, C-5), 129.3 (CH), 129.1 (CH), 129.1 (CH), 128.2 (CH), 127.4 (CH), 127.2 (CH), 127.1 (CH), 126.2 (CH), 53.8 (CH, C-1), 21.4 (CH_3, C-6); mass spectrum (*m/z*, %) 453 (7, M^+), 376 (16), 312 (49), 296 (55), 156 (93), 91 (93), 77 (100). Anal.

calcd for $C_{24}H_{23}NO_4S_2$: C, 63.55; H, 5.11; N, 3.09; Found: C, 63.54; H, 5.17; N, 3.14. ***Z*-Isomer**: ^{1}H NMR (300 MHz) δ 7.80 (d, J = 8.3 Hz, 2 H), 7.60-7.01 (m, 13 H) 6.61 (d, J = 11.3 Hz, 1 H), 5.87 (d, J = 8.1 Hz, 1 H, exchanged with D_2O), 5.59 (d, J = 9.9 Hz, 1 H), 5.51-5.42 (m, 2 H), 2.37 (s, 3 H).



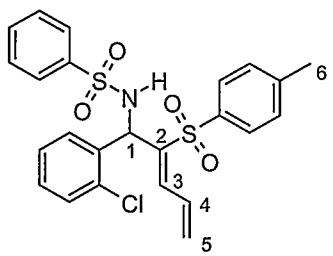
3.3.2. *N*-Phenylsulfonyl-1-(*p*-chlorophenyl)-2-(*p*-toluenesulfonyl)-2,4-pentadienyl-amine (124b).

Yield: 73%. ***E*-Isomer**: pale yellow gum; IR (film): 3298, 1343, 1282, 1163, 1086 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.82 (d, J = 7.2 Hz, 2 H), 7.57-7.42 (m, 4 H), 7.20 (d, J = 11.3 Hz, 1 H, H-3), 7.07-6.87 (m, 7 H), 6.69 (d, J = 9.7, 1 H, N-H, exchanged with D_2O), 6.60 (ddd, J = 16.4 Hz, 11.5 Hz, 10.7 Hz, 1 H, H-4), 5.87 (d, J = 9.7 Hz, 1 H, H-1, collapsed to s with D_2O), 5.76 (d, J = 16.4 Hz, 1 H, H-5), 5.69 (d, J = 10.2 Hz, 1 H, H-5), 2.33 (s, 3 H); ^{13}C NMR (75 MHz) δ 144.3 (C), 141.9 (CH), 140.6 (C), 138.7 (C), 137.9 (C), 134.6 (C), 133.8 (C), 132.9 (CH), 131.0 (CH_2, C-5), 129.5 (CH), 129.2 (CH), 129.0 (CH), 128.3 (CH), 127.7 (CH), 127.3 (CH), 127.2 (CH), 53.3 (CH, C-1), 21.6 (CH_3, C-6); mass spectrum (*m/z*, %) 487 (0.9, M^+), 376 (8), 346 (54), 77 (100). Anal. calcd for $C_{24}H_{22}ClNO_4S_2$: C, 59.07; H, 4.54; N, 2.87; Found: C, 59.01; H, 4.59; N, 2.69. ***Z*-Isomer**: ^{1}H NMR (300 MHz) δ 7.76 (d, J = 8.1 Hz, 2 H), 7.21-6.84 (m, 13 H), 6.07 (d, J = 8.2 Hz, 1 H), 5.59 (d, J = 10.5 Hz, 1 H), 5.47 (d, J = 17.4 Hz, 1 H), 5.38 (d, J = 8.7 Hz, 1 H), 2.36 (s, 3 H).



3.3.3. *N*-Phenylsulfonyl-1-(*m*-chlorophenyl)-2-(*p*-toluenesulfonyl)-2,4-pentadienyl-amine (124c).

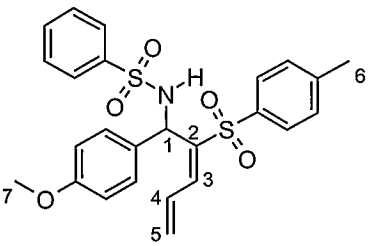
Yield: 46%. ***E*-Isomer**: solid yellow foam; mp 141-144 °C; IR (film): 3295, 1590, 1337, 1285, 1163, 1136 cm^{-1}; ^1H NMR (300 MHz) δ 7.83 (d, J = 7.2 Hz, 2 H), 7.57-7.42 (m, 3 H), 7.22 (d, J = 10.7 Hz, 1 H), 7.11-6.94 (m, 7 H), 6.71 (d, J = 9.8 Hz,1 H, N-H, exchanged with D_2O) 6.66 (s, 1 H), 6.58 (m, 1 H, H-4,), 5.86 (d, J = 9.7 Hz, 1 H, H-1, collapsed to s with D_2O), 5.78 (d, J = 16.4 Hz, 1 H, H-5), 5.73 (d, J = 9.7 Hz, 1 H, H-5), 2.30 (s, 3 H, H-6); ^{13}C-NMR (75 MHz) δ 144.2 (C), 142.0 (CH), 140.3 (C), 137.9 (C), 137.8 (C), 137.5 (C), 134.2 (C), 132.8 (CH), 131.0 (CH_2), 129.5 (CH), 129.3 (CH), 129.1 (CH), 128.7 (CH), 127.5 (CH), 127.1 (CH, two signals), 126.5 (CH), 124.2 (CH), 53.1 (CH, C-1), 21.4 (CH_3, C-6); mass spectrum (*m/z*, %) 487 (0.5, M^+), 346 (20), 91 (68), 77 (100). HRMS calcd for $C_{18}H_{17}ClNO_2S$ (M^+ - SO_2Ph): 346.0669; Found: 346.0660. ***Z*-Isomer**: ^1H NMR (300 MHz) δ 7.57-7.01 (m, 15 H), 6.53 (d, J = 11.3 Hz, 1 H), 5.62 (d, J = 9.7 Hz, 1 H), 5.51 (d, J = 16.4 Hz, 1 H), 5.37 (d, J = 8.7 Hz, 1 H), 2.36 (s, 3 H).



3.3.4. *N*-Phenylsulfonyl-1-(*o*-chlorophenyl)-2-(*p*-toluenesulfonyl)-2,4-pentadienyl-amine (124d)

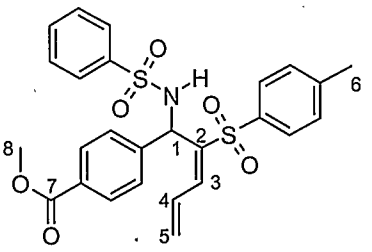
Yield: 63%. ***E*-Isomer:** solid yellow foam; mp 176-178 °C; IR (film): 3296, 1350, 1169, 1085 cm^{-1}; ^1H NMR (300 MHz) δ 7.77 (d, J = 7.7 Hz, 2 H), 7.55-7.27 (m, 4 H), 7.12-6.86 (m, 7 H), 6.79-6.65 (m, 2 H, H-4), 6.53 (d, J = 9.7 Hz, 1 H, N-H, exchanged with D_2O),

5.95 (d, J = 9.7 Hz, 1 H, H-1, collapsed to s with D_2O), 5.74 (d, J = 16.4 Hz, 1 H, H-5), 5.66 (d, J = 9.8 Hz, 1 H, H-5), 2.25 (s, 3 H, H-6); ^{13}C NMR (75 MHz) δ 143.4 (CH), 143.2 (C), 140.9 (C), 136.9 (C), 135.7 (C), 133.1 (C), 132.8 (CH), 132.7 (C), 130.5 (CH_2, C-5), 129.8 (CH), 129.6 (CH), 129.3 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 127.2 (CH), 126.8 (CH), 126.7 (CH), 52.1 (CH, C-1), 21.6 (CH_3, C-6); mass spectrum (*m/z*, %) 487 (M^+, 0.5), 346 (51), 332 (34), 191 (38), 91 (55), 77 (100); HRMS calcd for $C_{24}H_{22}ClNO_4S_2$ (M^+): 487.0679; Found: 487.0665. Anal. calcd for $C_{24}H_{22}ClNO_4S_2$: C, 59.07; H 4.54; N, 2.87. Found: C, 58.91; H, 4.77; N, 2.75. ***Z*-Isomer**: ^{1}HNMR (300 MHz) δ 7.75 (d, J = 8.2 Hz, 2 H), 7.57-7.00 (m, 13 H), 6.57 (d, J = 11.3 Hz, 1 H), 5.94 (d, J = 7.2, 1 H), 5.58 (m, 2 H), 5.46 (d, J = 16.9, 1 H), 2.36 (s, 3 H).



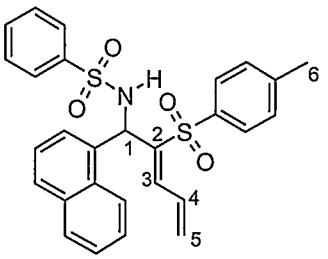
3.3.5. *N*-Phenylsulfonyl-1-(*p*-methoxyphenyl)-2-(*p*-toluenesulfonyl)-2,4-pentadienyl-amine (124e)

Yield: 46%. ***E*-Isomer**: white crystals; mp 128-132 °C (from dichloromethane-hexanes); IR (film): 3295, 1312, 1159 cm^{-1}; ^1H NMR (300 MHz) δ 7.83 (d, J = 8.7 Hz, 2 H), 7.56-7.42 (m, 3 H), 7.14-7.09 (m, 3 H), 6.95 (d, J = 8.2 Hz, 2 H), 6.85 (d, J = 8.7 Hz, 2 H), 6.71-6.59 (m, 2 H, N-H and H-4, 1 H exchanged with D_2O), 6.48 (d, J = 8.7 Hz, 2 H), 5.87 (d, J = 9.2 Hz, 1 H, H-1, collapsed to s with D_2O), 5.73 (d, J = 16.4 Hz, 1 H, H-5), 5.67 (d, J = 10.2 Hz, 1 H, H-5), 3.71 (s, 3 H, H-7), 2.30 (s, 3 H, H-6); ^{13}C NMR (75 MHz) δ 159.3 (C), 143.7 (C), 141.5 (CH), 140.8 (C), 139.5 (C), 138.3 (C), 132.9 (CH), 130.4 (CH_2, C-5), 129.4 (CH), 129.2 (CH), 127.9 (C), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 113.8 (CH), 55.4 (CH_3, C-7), 53.5 (CH, C-1), 21.6 (CH_3, C-6); mass spectrum (*m/z*, %) 483 (0.8, M^+), 342 (17), 275 (25), 134 (62), 77 (100). Anal. calcd for $C_{25}H_{25}NO_5S_2$: C, 62.09; H, 5.21; N, 2.90; Found: C, 62.24; H, 5.43; N, 2.88. ***Z*-Isomer**: ^1H NMR (300 MHz) δ 7.76 (d, J = 8.1 Hz, 2 H), 7.54-6.84 (m, 14 H), 5.56, (d, J = 10.2 Hz, 1 H), 5.48-5.43 (m, 2 H), 3.74 (s, 3 H), 2.38 (s, 3 H).



3.3.6. *N*-Phenylsulfonyl-1-(*p*-carbomethoxyphenyl)-2-(*p*-toluenesulfonyl)-2,4-pentadienylamine (124f)

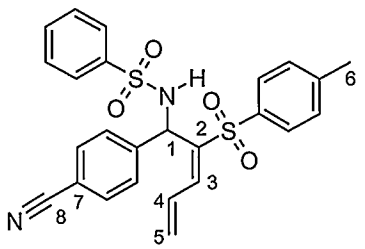
Yield: 70%. ***E*-Isomer**: solid yellow foam; mp 67-70 °C; IR (film) 3289, 1718, 1589, 1285, 1143, 1104, 1085 cm^{-1}; ^1H NMR (300 MHz) δ 7.84 (d, J = 7.2 Hz, 2 H), 7.61-7.40 (m, 5 H), 7.24-7.20 (m, 1 H, H-3), 7.06-7.00 (m, 4 H), 6.88 (d, J = 8.2 Hz, 2 H), 6.72 (d, J = 9.7 Hz, 1 H, N-H exchanged with D_2O), 6.70-6.57 (m, 1 H, H-4), 5.95 (d, J = 9.7 Hz, 1 H, H-1, collapsed to s with D_2O), 5.79 (d, J = 16.9 Hz, 1 H, H-5), 5.72 (d, J = 10.2 Hz, 1 H, H-5), 3.91 (s, 3 H, H-8); 2.26 (s, 3 H, H-6); ^{13}C NMR (75 MHz) δ 166.6 (C=O, C-7), 144.3 (C), 142.2 (CH), 141.1 (C), 140.6 (C), 138.4 (C), 137.8 (C), 133.1 (CH), 131.2 (CH_2), 129.6 (C), 129.5 (CH), 129.5 (CH), 129.3 (CH), 129.0 (CH), 127.4 (CH), 127.3 (CH), 126.4 (CH), 53.8 (CH, C-1), 52.3 (CH_3, C-8), 21.5 (CH_3, C-6); mass spectrum (ESI, *m/z*): 550 ($M + K^+$), 534 ($M + Na^+$). Anal. calcd for $C_{26}H_{25}NO_6S_2$: C, 61.04; H, 4.93; N, 2.74. Found: C, 61.01; H, 4.97; N, 2.55. ***Z*-Isomer**: ^1H NMR (300 MHz) δ 7.93-7.02 (m, 14 H), 6.59 (d, J = 11.3 Hz, 1 H), 6.17 (d, J = 8.7 Hz, 1 H, exchanged with D_2O), 5.61 (d, J = 10.2 Hz, 1 H), 5.48 (m, 2 H), 3.90 (s, 3 H), 2.33 (s, 3 H).



3.3.7. *N*-Phenylsulfonyl-1-(1-naphthyl)-2-(*p*-toluenesulfonyl)-2,4-pentadienylamine (124g)

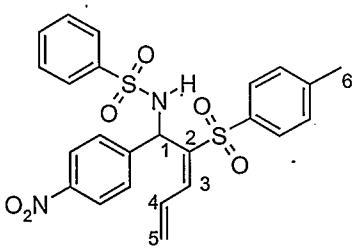
Yield: 61%. ***E*-isomer**: solid yellow foam; mp 119-123 °C; IR (film) 3289, 1324, 1156, 1079 cm^{-1}; ^1H NMR (300 MHz) δ 7.79 (d, J = 7.7 Hz, 2 H), 7.58-7.37 (m, 7 H), 7.27-7.21 (m, 4 H), 7.09-6.96 (m, 1 H, H-4), 6.66 (d, J = 7.7 Hz, 2 H), 6.52-6.38 (m, 4 H, 1 H

exchanged with D_2O), 5.90 (d, J = 16.4 Hz, 1 H, H-5), 5.84 (d, J = 9.8 Hz, 1 H, H-5), 2.02 (s, 3 H, H-6); ^{13}C-NMR (75 MHz) δ 142.6 (C), 141.6 (CH), 141.2 (C), 138.4 (C), 135.6 (C), 133.4 (C), 132.8 (CH), 131.4 (CH_2, C-5), 130.5 (C), 130.1 (CH), 129.2 (CH, two signals), 129.1 (CH), 128.7 (CH), 128.2 (CH), 127.2 (CH), 126.3 (C), 126.2 (CH), 126.1 (CH), 125.4 (CH), 125.1 (CH), 121.7 (CH), 52.0 (CH, C-1), 21.3 (CH_3, C-6); mass spectrum (*m/z,* %) 503 (6, M^+), 362 (35), 206 (60), 91 (45), 77 (100). Anal. calcd for $C_{28}H_{25}NO_4S_2$: C, 66.78; H 5.00; N, 2.78. Found: C, 66.58; H, 4.69; N, 2.57. ***Z*-Isomer**: ^{1}H NMR (300 MHz) δ 7.76-7.20 (m, 15 H), 6.97 (d, J = 7.7 Hz, 2 H), 6.69 (d, J = 11.3 Hz, 1 H), 6.23 (d, J = 6.7 Hz, 1 H), 5.56 (d, J = 9.7 Hz, 1 H), 5.31-5.41 (m, 2 H), 2.29 (s, 3 H).



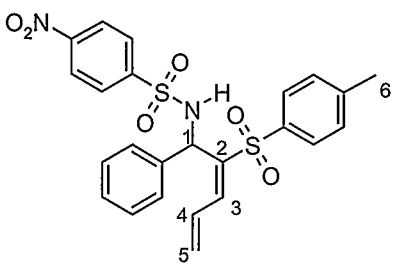
3.3.8. *N*-Phenylsulfonyl-1-(*p*-cyanophenyl)-2-(*p*-toluenesulfonyl)-2,4-pentadienyl-amine (124h)

Yield: 75%. ***E*-Isomer**: solid white foam; mp 99-103 °C; IR (film) 3289, 2223, 1169, 1079 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.82 (d, J = 7.7 Hz, 2 H), 7.58-7.43 (m, 3 H), 7.26-6.95 (m, 9 H), 6.75 (d, J = 9.8 Hz, 1 H, N-H exchanged with D_2O), 6.64-6.52 (m, 1 H, H-4), 5.93 (d, J = 9.2 Hz, 1 H, H-1, collapsed to s with D_2O), 5.80 (d, J = 16.4 Hz, 1 H, H-5), 5.73 (d, J = 10.2 Hz, 1 H, H-5), 2.34 (s, 3 H, H-6); ^{13}C NMR (75 MHz) δ 144.6 (C), 142.4 (CH), 141.4 (C), 140.1 (C), 137.5 (C), 137.4 (C), 132.9 (CH), 131.9 (CH), 131.7 (CH_2, C-5), 129.4 (CH), 129.1 (CH), 128.5 (CH), 127.1 (CH), 127.01 (CH), 126.98 (CH), 118.1 (C, C-7 or C-8), 111.2 (C, C-7 or C-8), 53.3 (CH, C-1), 21.4 (CH_3, C-6); mass spectrum (*m/z,* %) 478 (0.5, M^+), 337 (27), 91 (36), 77 (100); HRMS calcd for $C_{19}H_{17}N_2O_2S$ (M^+ - SO_2Ph): 337.1011; Found: 337.0992. ***Z*-Isomer**: ^{1}H-NMR (300 MHz) δ 7.95-7.06 (m, 14 H), 6.54 (d, J = 11.3 Hz, 1 H), 6.23 (d, J = 8.7 Hz, 1 H), 5.65 (d, J = 10.3 Hz, 1 H), 5.52 (d, J = 16.9 Hz, 1 H), 5.44 (d, J = 8.7 Hz, 1 H), 2.38 (s, 3 H).



3.3.9. *N*-Phenylsulfonyl-1-(*p*-nitrophenyl)-2-(*p*-toluenesulfonyl)-2,4-pentadienyl-amine (124i)

Yield: 31%. ***E*-Isomer**: pale yellow solid; mp 159-161 °C (from dichloromethane-pentane); IR (film): 3295, 1334, 1154, cm^{-1}; ^1H NMR (300 MHz) δ 7.83 (d, J = 7.7 Hz, 2 H), 7.77 (d, J = 8.7 Hz, 2 H), 7.60-7.38 (m, 3 H), 7.25 (d, J = 11.3 Hz, 1 H, H-3), 7.13 (d, J = 8.7 Hz, 2 H), 7.07 (d, J = 8.2 Hz, 2 H), 6.91 (d, J = 8.2 Hz, 2 H), 6.77 (d, J = 9.7 Hz, 1 H, N-H, exchanged with D_2O), 6.60 (m, 1 H, H-4), 5.97 (d, J = 9.7, 1 H, C-1, collapsed to s with D_2O), 5.82 (d, J = 16.4 Hz, 1 H, H-5), 5.75 (d, J = 10.3 Hz, 1 H, H-5), 2.27 (s, 3 H, H-6); ^{13}C NMR (75 MHz) δ 147.3, 144.9, 143.5, 142.6, 140.4, 137.8, 137.6, 133.2, 131.8, 129.5, 129.4, 128.7, 127.4, 127.3, 127.2, 123.2, 53.5 (CH, C-1), 21.5 (CH_3, C-6); mass spectrum (*m/z,* %) 498 (0.7, M^+), 357 (11), 91 (29), 77 (100); HRMS calcd for $C_{18}H_{17}N_2O_4S$ (M^+ - SO_2Ph): 357.0909; Found: 357.0917. ***Z*-Isomer**: ^1H NMR (300 MHz) δ 7.98 (d, J = 8.7 Hz, 2 H), 7.91 (d, J = 8.7 Hz, 2 H), 7.57-7.06 (m, 10 H), 6.28 (d, J = 8.7 Hz, 1 H, exchanged with D_2O), 5.69-5.97 (m, 2 H), 5.54 (d, J = 16.9 Hz, 1 H), 5.47 (d, J = 8.7 Hz, 1 H), 2.35 (s, 3 H).

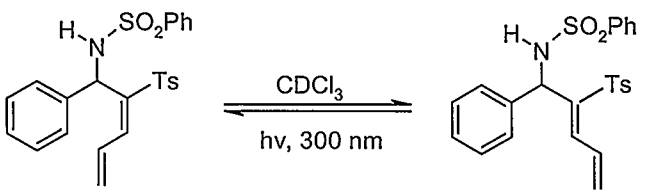


3.3.10. *N*-(*p*-Nitrophenylsulfonyl)-1-(3-pyridine)-2-(*p*-toluenesulfonyl)-2,4-penta-dienylamine (*E*-124p)

Yield: 56%. ***E*-Isomer**: white crystalline solid; mp 126-129 °C (from dichloromethane) ^1H NMR (300 MHz) δ 7.84 (d, J = 7.2 Hz, 2 H), 7.77 (d, J = 8.7 Hz, 2 H), 7.59-7.54 (m, 1 H), 7.49 -7.44 (m, 2 H), 7.27 (d, J = 11.3 Hz, 1 H, H-3), 7.13 (d, J = 8.7 Hz, 2 H), 7.08

(d, J = 8.2 Hz, 2 H), 6.92 (d, J = 8.2 Hz, 2 H), 6.77 (d, J = 9.2 Hz, 1 H, N-H, exchanged with D_2O), 6.66-6.54 (m, 1 H, H-4), 5.96 (d, J = 9.7 Hz, 1 H, H-1, collapsed to s with D_2O), 5.83 (d, J = 16.4 Hz, 1 H, H-5), 5.75 (d, J = 9.8 Hz, 1 H, H-5), 2.27 (s, 3 H, H-6); ^{13}C NMR (75 MHz) δ 147.0 (C), 144.7 (C), 143.3 (C), 142.5 (CH), 140.1 (C), 137.5 (C), 137.4 (C), 133.0 (CH), 131.7 (CH_2, C-5), 129.4 (CH), 129.2 (CH), 128.4 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 123.1 (CH), 53.3 (CH, C-1), 21.3 (CH_3, C-6). mass spectrum (ESI, *m/z*): 521 (M + Na^+). ***Z*-isomer:** ^1H NMR (300 MHz) δ 7.91 (d, J = 8.7 Hz, 2 H), 7.80 (d, J = 7.7 Hz, 2 H), 7.60-7.55 (m, 1 H), 7.51 -7.46 (m, 2 H), 7.41-7.27 (m, 1 H), 7.23-7.17 (m, 4 H), 7.07-7.04 (m, 2 H), 6.57 (d, J = 11.3 Hz, 1 H), 6.27 (d, J = 9.2 Hz, 1 H), 5.67 (d, J = 9.7 Hz, 1 H), 5.54 (d, J = 16.4 Hz, 1 H), 5.46 (d, J = 8.7 Hz, 1 H), 2.35 (s, 3 H).

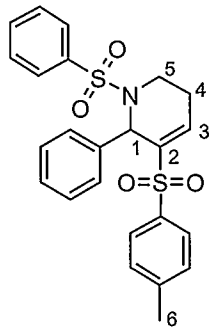
3.4. Isomerization of *E*- and *Z*-124a



E-124a *Z*-124a

A 70:30 mixture of the *E:Z* isomers of **124a** was obtained when either the pure *E*- or *Z*-isomer was dissolved in $CDCl_3$ and irradiated at 300 nm for 24 h in an NMR tube. The ratios were measured at regular intervals by integration of ^1H NMR signals.

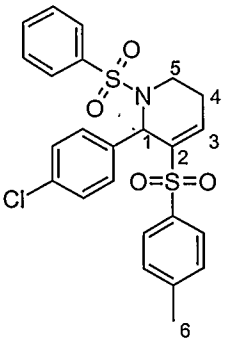
3.5. Cyclization of MBH Adducts 124



3.5.1. Typical Procedure for Preparation of Piperidines 125: *N*-(Benzenesulfonyl)-2-phenyl-3-(*p*-toluenesulfonyl)-3,4-dehydropiperidine (125a)

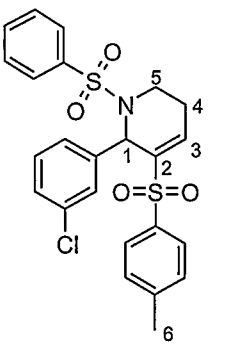
A mixture of *E*-**124a** (50.0 mg, 0.110 mmol) and potassium carbonate (15 mg, 0.11 mmol) was stirred in 2 mL of DMF:H_2O (10:1) at room temperature for 24 h. The reaction mixture was diluted with ether and washed twice with water and once with brine. The organic phase was dried, filtered, and concentrated to afford a crude white solid. This was purified by chromatography (hexanes:ethyl acetate, 2:1) to afford 45.4 mg (91%) of **125a.**

White crystalline solid; mp 155-158 °C (from ethyl acetate-hexanes); IR (film) 1344, 1143, 1085 cm^{-1}; ^1H NMR (300 MHz) δ 7.70 (d, J = 7.7 Hz, 2 H), 7.63-6.98 (m, 13 H), 5.94 (s, 1 H, H-1), 3.73 (dd, J = 6.2, 15.2 Hz, 1 H, H-5), 3.01 (ddd, J = 6.2, 11.3, 15.9 Hz, 1 H, H-4), 2.34 (s, 3 H, H-6), 2.26-2.00 (m, 2 H, H-4 and 5); ^{13}C NMR (75 MHz) δ 144.3 (C), 140.2 (C), 139.8 (C), 138.4 (CH), 136.2 (C), 136.2 (C), 132.8 (CH), 129.4 (CH), 129.1 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 126.9 (CH), 55.1 (CH, C-1), 35.7 (CH_2), 24.1 (CH_2), 21.4 (CH_3, C-6); mass spectrum (*m/z*, %) 453 (3, M^+), 376 (94), 313 (100), 312 (89), 77 (92); HRMS calcd for $C_{24}H_{23}NO_4S_2$: 453.1069; Found: 453.1043. Anal. calcd for $C_{24}H_{23}NO_4S_2$: C, 63.55; H 5.11; N, 3.09. Found: C, 63.39; H, 5.21; N, 3.01.



3.5.2. *N*-(Benzenesulfonyl)-2-(*p*-chlorophenyl)-3-(*p*-toluenesulfonyl)-3,4-dehydropiperidine (125b)

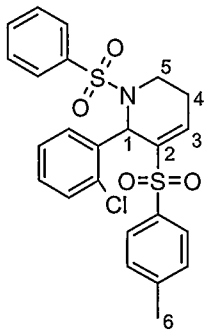
Yield: 88%; white solid; mp 133-137 °C (from ethyl acetate-hexanes); IR (film) 1313, 1165, 1143, 1093 cm^{-1}; ^1H NMR (300 MHz) δ 7.66 (d, J = 7.2 Hz, 2 H), 7.58-6.95 (12 H), 5.94 (s, 1 H), 3.76 (dd, J = 7.2, 15.4 Hz, 1 H), 2.98 (m, 1 H), 2.39 (s, 3 H), 2.24-2.00 (m, 2 H); ^{13}C NMR (75 MHz) δ144.9, 140.3, 139.9, 138.7, 136.3, 135.2, 134.4, 133.1, 130.2, 129.7, 129.3, 128.5, 128.4, 127.1, 54.6 (CH, C-1), 36.0 (CH_2, C-5), 24.3 (CH_2, C-4), 21.7 (CH_3, C-6); mass spectrum (*m/z,* %) 487 (1, M^+), 376 (8), 346 (54), 77 (100); HRMS calcd for $C_{24}H_{22}ClNO_4S_2$: 487.0679; Found: 487.0697.



3.5.3. *N*-(Benzenesulfonyl)-2-(*m*-chlorophenyl)-3-(*p*-toluenesulfonyl)-3,4-dehydro-piperidine (125c)

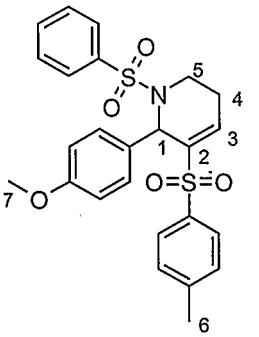
Yield: 89%; white solid, mp 124-127 °C (from ethyl acetate-hexanes); IR (film): 1317, 1149 cm^{-1}; ^1H NMR (300 MHz) δ 7.74 (d, J = 7.2 Hz, 2 H), 7.60-7.55 (m, 1 H), 7.48-7.38, (m, 4 H), 7.12-7.08 (m, 6 H), 6.66 (s, 1 H), 5.99 (s, 1 H), 3.78 (dd, J = 6.7, 15.4 Hz,

1 H), 2.98 (ddd, J = 4.6, 11.3, 16.4 Hz, 1 H), 2.36 (s, 3 H), 2.28-2.05 (m, 2 H); ^{13}C NMR (75 MHz) δ 145.0, 140.3, 139.6, 139.0, 138.5, 136.1, 134.1, 133.2, 129.9, 129.8, 129.5, 128.5, 128.4, 128.3, 127.7, 127.2, 54.8 (CH, C-1), 36.1 (CH_2, C-5), 24.3 (CH_2, C-4), 21.7 (CH_3, C-6); mass spectrum (*m/z,* %) 487 (1, M^+), 376 (26), 346 (85), 190 (33), 91 (39), 77 (100); HRMS calcd for $C_{24}H_{22}NO_4S_2Cl$: 487.0679; Found: 487.0669.



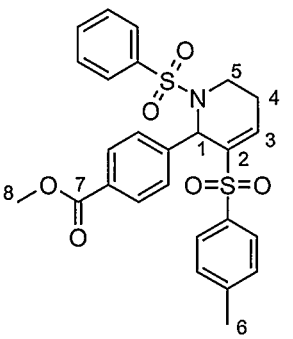
3.5.4. *N*-(Benzenesulfonyl)-2-(*o*-chlorophenyl)-3-(*p*-toluenesulfonyl)-3,4-dehydro-piperidine (125d)

Yield: 82%; white solid; mp 144-147 °C (from ethyl acetate-hexanes); IR (film): 1447, 1319, 1151 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.73-7.70 (m, 2 H), 7.59-7.52 (m, 3 H), 7.44-7.39 (m, 2 H), 7.33 (d, J = 7.7 Hz, 1 H), 7.19-7.12 (m, 4 H), 6.98-6.89 (m, 2 H), 6.35 (s, 1 H), 3.69-3.62 (m, 1 H), 3.12 (m, 1 H), 2.37 (s, 3 H), 2.30-2.29 (m, 2H); ^{13}C NMR (75 MHz) δ 144.7 (C), 139.9 (C), 139.8 (C), 138.7 (CH), 136.1 (C), 134.8 (C), 134.1 (C), 133.2 (CH), 130.8 (CH), 130.6 (CH), 129.9 (CH), 129.8 (CH), 129.2 (CH), 128.5 (CH), 127.9 (CH), 126.2 (CH), 52.0 (CH, C-1), 36.3 (CH_2, C-5), 24.2 (CH_2, C-4), 21.8 (CH_3, C-6); mass spectrum (*m/z,* %) 452 (5, M^+ - ^{35}Cl), 375 (27), 348 (40), 346 (93), 190 (35), 141 (25), 128 (45), 91 (37), 77 (100); HRMS calcd for $C_{24}H_{22}N^{35}ClO_4S_2$: 487.0679; Found: 487.0661. Anal. calcd for $C_{24}H_{22}ClNO_4S_2$: C, 59.07; H 4.54; N, 2.87. Found: C, 59.21; H, 4.55; N, 2.81.



3.5.5. *N*-(Benzenesulfonyl)-2-(*p*-methoxyphenyl)-3-(*p*-toluenesulfonyl)-3,4-dehydro-piperidine (125e)

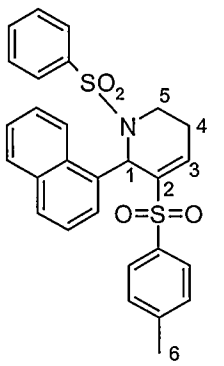
Yield: 79%; white solid; mp 171-174 °C (from ethyl acetate-hexanes); IR (film): 1338, 1147 cm^{-1}; ^1H NMR (300 MHz) δ 7.69-7.66 (m, 2 H), 7.58-7.53 (m, 1 H), 7.45-7.40, (m, 4 H), 7.12 (d, J = 8.2 Hz, 2 H), 7.06 (m, 1 H), 6.94 (d, J = 8.7 Hz, 2 H), 6.61 (d, J = 8.7 Hz, 2 H), 5.92 (s, 1 H), 3.75 (m, 4 H), 3.04 (ddd, J = 5.1, 11.3, 16.4 Hz, 1 H), 2.38, (s, 3 H), 2.24-2.09 (m, 2 H); ^{13}C NMR (75 MHz) δ 159.5 (C), 144.2 (C), 140.3 (C), 140.2 (C), 138.1 (CH), 136.4 (C), 132.8 (CH), 130.0 (CH), 129.4 (CH), 129.1 (CH), 128.5 (C), 128.3 (CH), 127.0 (CH), 113.5 (CH), 55.2 (CH_3, C-7), 54.7 (CH, C-1), 35.7 (CH_2, C-5), 24.3 (CH_2, C-4), 21.5 (CH_3, C-6); mass spectrum (*m/z,* %) 483 (7, M^+), 342 (100), 262 (11), 186 (51), 91 (23), 77 (65); HRMS calcd for $C_{25}H_{25}NO_5S_2$: 483.1172; Found: 483.1188.



3.5.6. *N*-(Benzenesulfonyl)-2-(*p*-carbomethoxyphenyl)-3-(*p*-toluenesulfonyl)-3,4-dehydropiperidine (125f)

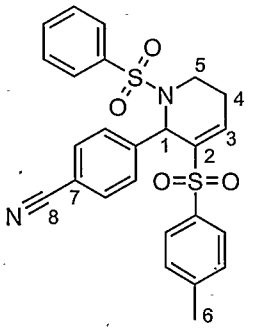
Yield: 65%; white crystals; mp 189-190 °C (from ethyl acetate-hexanes); IR (film): 1721, 1446, 1283, 1151, 1087 cm^{-1}; ^1H NMR δ (300 MHz) 7.76 (d, J = 8.2 Hz, 2 H), 7.68 (d, J = 7.7 Hz, 2 H), 7.59-7.54 (m, 1 H), 7.45-7.39 (m, 3 H), 7.12-7.08 (m, 4 H), 6.00 (s, 1 H),

3.91 (s, 3 H), 3.76 (dd, J = 7.2, 15.4 Hz, 1 H), 2.98 (ddd, J = 4.6, 11.3, 15.9 Hz, 1 H), 2.35 (s, 3 H), 2.28-2.00 (m, 2 H); ^{13}C NMR (75 MHz) δ 166.7, 145.0, 141.4, 140.3, 139.7, 139.0, 136.2, 133.2, 130.0, 129.8, 129.6, 129.5, 128.9, 128.5, 127.2, 54.9 (CH_3, C-8), 52.4 (CH, C-1), 36.1 (CH_2, C-5), 24.3 (CH_2, C-4), 21.7 (CH_3, C-6); MS (*m/z*, %): 511 (2, M^+), 480 (2), 370 (72), 338 (18), 214 (27), 141(21), 91(28), 77 (100); HRMS calcd for $C_{26}H_{25}NO_6S_2$: 511.1123; Found 511.1118.



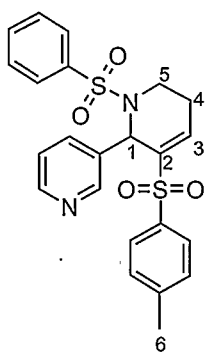
3.5.7. *N*-(Benzenesulfonyl)-1-(1-naphthyl)-2-(*p*-toluenesulfonyl)-3,4-dehydropiperidine (125g)

Yield: 86%; transparent crystals; mp 184-187 °C (from chloroform); IR (film): 1334, 1161 cm^{-1}; ^{1}H NMR (300 MHz) δ 8.75 (d, J = 8.7 Hz, 1 H), 7.83 (d, J = 8.2 Hz, 3 H), 7.69-7.64, (m, 2 H), 7.59-7.52 (m, 2 H), 7.44 (t, J = 7.7 Hz, 2 H), 7.32 (d, J = 8.2 Hz, 2 H), 7.09 (t, J = 3.6 Hz, 1 H), 6.98-6.90 (m, 4 H), 6.78 (d, J = 6.7 Hz, 1 H), 3.64-3.58 (m, 1 H), 3.21-3.10 (m, 1 H), 2.27 (s, 3 H), 2.20-2.15 (m, 2 H); ^{13}C NMR (75 MHz) δ 144.3, 140.4, 139.5, 138.0, 136.1, 134.1, 133.1, 131.3, 131.2, 129.3, 129.2, 129.0, 128.5, 128.1, 127.7, 127.5, 127.2, 126.1, 124.0, 123.8, 51.4 (CH, C-1), 36.0 (CH_2, C-5), 23.6 (CH_2, C-4), 21.4 (CH_3, C-6); mass spectrum (*m/z*, %) 503 (M^+, 36), 376 (17), 362 (72), 361 (23), 207 (25), 206 (100), 179 (34), 178 (49), 165 (16), 141 (29), 91 (24), 77 (79); HRMS calcd for $C_{28}H_{25}NO_4S_2$: 503.1225; Found: 503.1243.



3.5.8. *N*-(Benzenesulfonyl)-2-(*p*-cyanophenyl)-3-(*p*-toluenesulfonyl)-3,4-dehydro-piperidine (125h)

Yield: 80%; white solid; mp 75-78 °C, (from ethyl acetate-hexanes); IR (film): 2227, 1334, 1163, 1150, 1087 cm^{-1}; ^1H NMR (300 MHz): 7.65-7.55 (m, 3 H), 7.46-7.40 (m, 6 H), 7.23-7.12 (m, 5 H), 5.97 (s, 1 H), 3.77 (dd, J = 15.4, 6.7 Hz, 1 H), 2.91 (m, 1 H), 2.42 (s, 3 H), 2.28-2.04 (m, 2 H); ^{13}C NMR (75 MHz): 145.3, 142.0, 140.1, 139.6, 139.2, 136.1, 133.4, 132.2, 130.0, 129.6, 129.5, 128.5, 127.1, 118.4 (C, C-7 or C-8), 112.2 (C, C-7 or C-8), 54.8 (CH, C-1), 36.1 (CH_2, C-5), 24.3 (CH_2, C-4), 21.8 (CH_3, C-6); mass spectrum (*m/z*, %) 478 (1, M^+), 376 (16), 337 (71), 181 (53), 91 (69); 77 (100); HRMS calcd for $C_{25}H_{22}N_2O_4S_2$: 478.1021; Found: 478.1037.

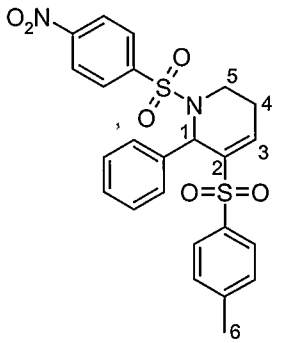


3.5.9. *N*-(Benzenesulfonyl)-2-(3-pyridyl)-3-(*p*-toluenesulfonyl)-3,4-dehydropiperidine (125o)

As isolation of *N*-Phenylsulfonyl-1-(3-pyridyl)-2-(*p*-toluenesulfonyl)-2,4-pentadienyl-amine (**124o**) proved difficult, synthesis of **125o** was carried out in a one-pot fashion as follows. A solution of 1-(*p*-toluenesulfonyl)-1,3-butadiene **(123)** (117 mg, 0.562 mmol), imine **(122o)** (207 mg, 0.841 mmol) and HQD (18 mg, 0.14 mmol) in 5 mL of anhydrous DMF was stirred for 7 h at room temperature under an inert atmosphere. A suspension of

potassium carbonate (77 mg, 0.56 mmol) in 10 mL of DMF:H_2O (10:1) was added to the solution and the mixture was irradiated at 300 nm for 24 hours. The reaction mixture was poured into 5% HCl solution and extracted with ether. The combined ether layers were washed with brine and water. The organic layer was dried, concentrated and chromatographed (ethyl acetate-hexanes, 4:1) to afford 77 mg of **125o** (30% based on diene **123**).

Viscous yellow oil; IR (film) 1595, 1334, 1157 cm^{-1}; ^1H NMR (300 MHz) δ 8.43 (br s, 1 H), 8.21 (br s, 1 H), 7.68 (d, J = 7.2 Hz, 2 H), 7.60-7.55 (m, 1 H), 7.50-7.42 (m, 5 H), 7.18-7.08 (m, 4 H), 5.97 (s, 1 H, H-1), 3.80 (dd, J = 6.7, 15.4 Hz, 1 H, H-5), 2.96 (ddd, J = 5.1, 11.3, 15.9 Hz, 1 H, H-4), 2.39 (s, 3 H, H-6), 2.31-2.05 (m, 2 H, H-4 and 5); ^{13}C NMR (75 MHz) δ 149.5 (CH), 149.1 (CH), 144.9 (C), 139.9 (C), 139.0 (CH), 138.9 (C), 136.2 (CH), 135.8 (C), 133.1 (CH), 129.8 (CH), 129.3 (CH), 128.3 (CH), 127.0 (CH), 123.2 (CH), 123.1 (C), 53.2 (CH, C-1), 35.9 (CH_2, C-5), 24.2 (CH_2, C-4), 21.6 (CH_3, C-6); mass spectrum (*m/z*, %) 454 (5, M^+), 376 (28), 313 (81), 299 (11), 220 (10), 157 (33), 141 (20), 130 (17), 91 (23), 77 (100), 51 (17); HRMS calcd for $C_{23}H_{22}N_2O_4S_2$: 454.1021; Found: 454.0998.

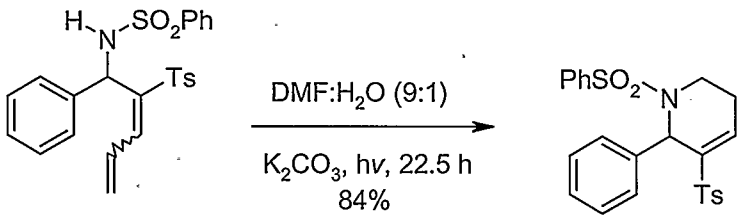


3.5.10. *N*-(*p*-Nitrobenzenesulfonyl)-2-phenyl-3-(*p*-toluenesulfonyl)-3,4-dehydropiperidine (125p)

Yield 74%; white crystalline solid; mp 126-129 °C (from dichloromethane); IR (film) 1596, 1533, 1350, 1150, 1087 cm^{-1}; ^1H NMR (300 MHz) δ 8.22 (pd, J = 6.7 Hz, 2 H), 7.87 pd, J = 7.2 Hz, 2 H), 7.37 (d, J = 8.2 Hz, 2 H), 7.37-7.16 (m, 1 H), 7.11-7.00 (m, 7 H), 6.03 (s, 1 H, H-1), 3.80 (dd, J = 6.9, 15.2 Hz, 1 H, H-5), 2.96 (ddd, J = 5.3, 11.5, 15.2 Hz, 1 H, H-4), 2.35 (s, 3 H, H-6), 2.33-2.18 (m, 2 H, H-4 and 5); ^{13}C NMR (75 MHz) δ 150.1 (C), 146.2 (C), 144.8 (C), 140.3 (C), 138.2 (CH), 136.2 (C), 135.8 (C), 129.7 (CH),

128.9 (CH), 128.5 (CH), 128.40 (CH), 128.38 (CH), 124.5 (CH), 55.6 (CH, C-1), 36.4 (CH_2, C-5), 24.6 (CH_2, C-4), 21.7 (CH_3, C-6); mass spectrum (*m/z*, %) 498 (6, M^+), 421 (26), 313 (41), 312 (100), 156 (82), 139 (14), 128 (57), 122 (33), 91 (62), 77 (32); HRMS calcd for $C_{24}H_{22}N_2O_6S_2$: 498.0919; Found: 498.0956.

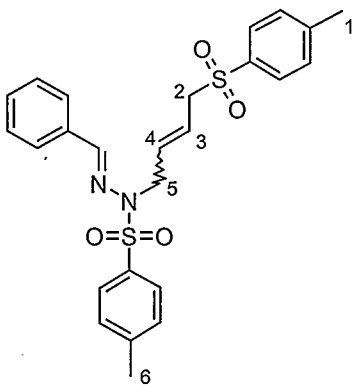
3.6. In situ Isomerization and Cyclization of MBH Adducts 124



124a **125a**

A 65:35 *E:Z* mixture of **124a** was treated under the usual cyclization conditions (K_2CO_3-DMF-H_2O), while the mixture was irradiated for 22.5 h in a Rayonet reactor equipped with 300 nm lamps. The product **125a** was isolated as before, in 84% yield.

3.7. Hydrazone-based Conjugate Addition Product (135)

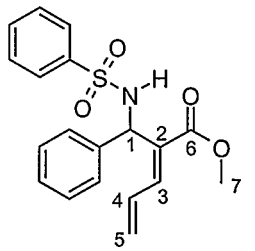


Butadienyl sulfone **123** (91 mg, 0.44 mmol), tosyl phenyl hydrazone (120 mg, 0.437 mmol) and 3-HQD (14 mg, 0.11 mmol, 0.25 eq) were weighed into a dry round bottom flask and placed under an argon atmosphere. Dry DMF (3 mL) was added and the reaction was stirred for 6 h at room temperature. The reaction mixture was diluted with water, extracted into diethyl ether, and washed once with water, and once with brine. The

aqueous layer was then acidified with 5% HCl and back extracted with diethyl ether. The organic phase was dried, filtered, and concentrated. The resulting crude orange oil was purified by column chromatography in 8:1 toluene:ethyl acetate to afford a total of 156.1 mg (0.323 mmol, 74%) of compound **135** as a separated mixture of *cis*- and *trans*-isomers (30:70).

***trans*-Isomer:** white solid, mp 47-50 °C; IR (film): 1610, 1363, 1304, 1175, 1085 cm^{-1}; ^{1}H-NMR (300 MHz) δ 7.78 (d, J = 7.7 Hz, 2 H), 7.70-7.60 (m, 5 H), 7.41-7.40 (m, 3 H), 7.30 (d, J = 7.7 Hz, 2 H), 7.16 (d, J = 7.7 Hz, 2 H), 5.72-5.56 (m, 2 H, H-3 and H-4), 4.28 (d, J = 3.6 Hz, 2 H, H-2 or H-5), 3.76 (d, J = 6.7, 2 H, H-2 or H-5), 2.41 (s, 3 H, H-1 or H-6), 2.37 (s, 3 H, H-1 or H-6); ^{13}C-NMR (300 MHz) δ 146.5 (CH), 144.8 (C), 144.2 (C), 135.2 (C), 134.3 (C), 133.9 (C), 133.5 (CH), 130.3 (CH), 129.8 (CH), 129.6 (CH), 128.7 (CH), 128.2 (CH), 128.1 (CH), 127.5 (CH), 119.8 (CH), 59.4 (CH_2, C-2 or C-5), 49.0 (CH_2, C-2 or C-5), 21.6 (CH_3, C-1 and C-6); mass spectrum (*m/z*, %): (M^+, 1), 327 (3), 143 (100), 91 (88); HRMS calcd for $C_{25}H_{26}O_4N_2S_2$ (M^+) 482.1334, Found 482.1336. Anal. calcd for $C_{25}H_{26}O_4N_2S_2$: C, 62.22; H 5.43; N, 5.80. Found: C, 61.95; H, 5.16; N, 5.80. ***cis*-Isomer:** white solid foam; ^{1}H-NMR (300 MHz) δ 8.75 (s, 1 H), 7.93-7.27 (m, 13 H), 5.74-5.58 (m, 2 H), 4.24 (d, J = 5.6 Hz, 2 H), 4.00 (d, J = 8.2 Hz, 2 H), 2.45 (s, 3 H), 2.41 (s, 3 H).

3.8. MBH Adducts from Methyl 2,4-Pentadienoate

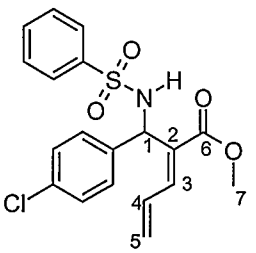


3.8.1. Typical Procedure for Preparation of MBH Adducts 142: *N*-Phenylsulfonyl-1-phenyl-2-(carbomethoxy)-2,4-pentadienylamine (*E*-142a)

A solution of methyl 2,4-pentadienoate (0.20 mL, 1.8 mmol), phenyl imine (425.6 mg, 1.74 mmol), MeOH (60 μL, 1.3 mmol) and HQD (55.3 mg, 0.435 mmol) in 7 mL of

anhydrous DMF was stirred for 24 h at room temperature. The reaction mixture was diluted with water and extracted with ether. The combined ether layers were washed with brine and water. The organic fractions were dried, concentrated, and chromatographed (toluene-ethyl acetate, 16:1) to afford 622.0 mg of product as a thick white oil (85%; *E:Z* = 80:20). Further chromatography of the latter product afforded the less polar pure *E*-isomer, followed by a mixture of both geometrical isomers.

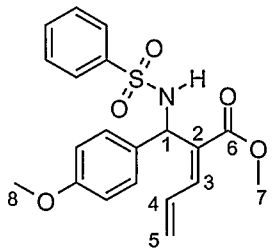
Viscous colourless oil; IR (film) 3292, 1716, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 2 H), 7.53-7.48 (m, 1 H), 7.42-7.37 (m, 2 H), 7.26-7.20 (m, 5 H), 7.14 (d, *J* = 11.8 Hz, 1 H), 6.82-6.69 (dt, *J* = 16.4, 10.8 Hz, 1 H), 6.39 (d, *J* = 10.8 Hz, 1 H, exchanged with D_2O), 5.76 (d, *J* = 10.3 Hz, 1 H), 5.70-5.62 (m, 2 H), 3.57 (s, 3 H); irradiation of the proton at δ 6.82-6.69 showed an nOe of 18% for the signal at δ 5.76 and vice versa; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C=O, C-6), 141.6 (CH), 141.1 (C), 138.8 (C), 132.6 (CH), 130.6 (CH), 128.9 (CH_2, C-5), 128.7 (CH), 128.6 (C), 127.6 (CH), 127.1 (CH), 126.0 (CH), 53.9 (CH), 52.1 (CH_3, C-7); mass spectrum (*m/z*, %) 341 (M^+-O, 11), 216 (10), 200 (26), 185 (17), 141 (18), 104 (13), 77 (100); HRMS calcd for $C_{19}H_{19}NO_3S$ (M^+-O): 341.1086; Found: 341.1102. nOe experiment (200 MHz NMR): Irradiation of δ 6.82-6.69 (m, 1H) showed 18% correlation with δ 5.76 (d, *J* = 10.3 Hz, 1 H) and vice versa.



3.8.2. *N*-Phenylsulfonyl-1-(*p*-chlorophenyl)-2-(carbomethoxy)-2,4-pentadienylamine (*E*-142b)

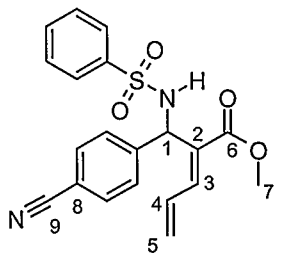
Yield 85%; white solid; mp 129-132 °C (from toluene-ethyl acetate); IR (Nujol) 3270, 1716; 1161cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.2 Hz, 2 H), 7.54-7.50 (m, 1 H), 7.43-7.38 (m, 2 H), 7.25-7.18 (m, 4 H), 7.07 (d, *J* = 11.8 Hz, 1 H), 6.71 (dt, *J* = 16.4, 10.5 Hz, 1 H), 6.35 (d, *J* = 10.3 Hz, 1 H, exchanged with D_2O), 5.72-5.64 (m, 3 H), 3.58

(s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 (C=O, C-6), 141.7 (CH), 140.8 (C), 137.3 (C), 133.4 (C), 132.6 (CH), 130.2 (CH), 129.0 (CH_2), 128.8 (CH), 128.6 (CH), 128.0 (C), 127.3 (CH), 126.9 (CH), 53.3 (CH, C-1), 52.0 (CH_3, C-7); mass spectrum (*m/z*, %) 391 (M^+, 1), 252 (45), 250 (95), 218 (34), 141 (67), 77 (100); HRMS calcd for $C_{19}H_{18}NO_4S^{35}Cl$ (M^+): 391.0645; Found: 391.0627. Anal. calcd for $C_{19}H_{18}ClO_4NS$: C, 58.24; H 4.63; N, 3.57. Found: C, 58.19; H, 4.84; N, 3.33.



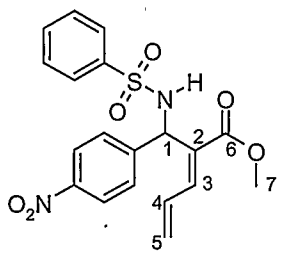
3.8.3. *N*-Phenylsulfonyl-1-(*p*-methoxyphenyl)-2-(carbomethoxy)-2,4-pentadienyl-amine (*E*-142e)

Yield 66%; white solid; mp 140-142 °C (from toluene-ethyl acetate); IR (film) 3292, 1716, 1160cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.7 Hz, 2 H), 7.52-7.47 (m, 1 H), 7.41-7.36 (m, 2 H), 7.18 (d, J = 8.7 Hz, 2 H), 7.04 (d, J = 11.8 Hz, 1 H), 6.80-6.66 (m, 3 H), 6.41 (d, J = 10.3 Hz, 1 H, exchanged with D_2O), 5.72-5.59 (m, 3 H), 3.75 (s, 3 H), 3.56 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C=O, C-6), 158.8 (C), 141.1 (CH), 140.8 (C), 132.3 (CH), 130.6 (CH), 130.3 (C), 128.6 (CH), 128.4 (CH_2), 128.3 (C), 127.0 (CH), 126.9 (CH), 113.7 (CH), 55.1 (CH_3, C-8), 53.2 (CH, C-1), 51.8 (CH_3, C-7); mass spectrum (*m/z*, %) 387 (M^+, 2), 276 (13), 246 (100), 214 (72), 186 (71), 134 (75), 77 (92); HRMS calcd for $C_{20}H_{21}NO_5S$ (M^+): 387.1140; Found: 387.1142. Anal. calcd for $C_{20}H_{21}NO_5S$: C, 62.00; H, 5.46; N, 3.62. Found: C, 61.96; H, 5.36; N, 3.67.



3.8.4. *N*-Phenylsulfonyl-1-(*p*-cyanophenyl)-2-(carbomethoxy)-2,4-pentadienylamine (*E*-142h)

Yield 91%; viscous colourless oil; IR (film) 3296, 2229, 1717, 1608, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8.2 Hz, 2 H), 7.56-7.50 (m, 3 H), 7.43-7.37 (m, 4 H), 7.10 (d, J = 11.3 Hz, 1 H), 6.69 (dt, J = 16.4, 10.6 Hz, 1 H), 6.43 (d, J = 10.3 Hz, 1 H, exchanged with D_2O), 5.76-5.65 (m, 3 H), 3.56 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2 (C=O, C-6), 144.3 (C), 142.1 (CH), 140.5 (C), 132.7 (CH), 132.2 (CH), 129.9 (CH), 129.6 (CH_2), 128.8 (CH), 127.5 (C), 126.8 (CH), 126.6 (CH), 118.4 (C, C-8 or C-9), 111.3 (C, C-8 or C-9), 53.4 (CH, C-1), 52.1 (CH_3, C-7); mass spectrum (*m/z,* %) 366 (M^+-O, 1), 270 (1), 225 (3), 141 (15), 102 (16), 77 (100), 51 (60); HRMS calcd for $C_{19}H_{16}NO_4S$ (M^+ - NCH_2): 354.0800; Found: 354.0796.

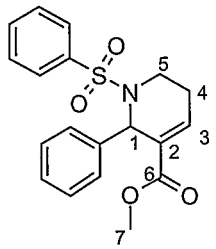


3.8.5. *N*-Phenylsulfonyl-1-(*p*-nitrophenyl)-2-(carbomethoxy)-2,4-pentadienylamine (*E*-142i)

Yield 61%. White solid; mp 124-127 °C (from benzene-hexanes); IR (film): 3295, 1717, 1521, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 8.7 Hz, 2 H), 7.82-7.76 (m, 2 H), 7.57-7.40 (m, 5 H), 7.13 (d, J = 11.3 Hz, 1 H), 6.73 (dt, J = 16.4, 10.5 Hz, 1 H), 6.38 (d, J = 9.7 Hz, 1 H, exchanged with D_2O), 5.81-5.69 (m, 3 H), 3.59 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.3 (C=O, C-6), 146.2, 142.1, 132.7, 129.9, 129.7, 129.0, 128.9, 127.6, 127.0, 126.9, 126.8, 123.6, 53.5 (CH, C-1), 52.1 (CH_3, C-7); mass spectrum

(*m/z*, %) 402 (M^+, 4), 261 (93), 229 (39), 141 (46), 77 (100); HRMS calcd for $C_{19}H_{18}N_2O_6S$ (M^+): 402.0886; Found: 402.0875.

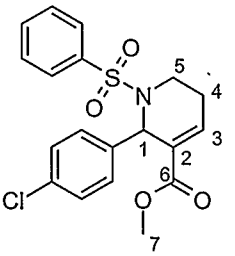
3.9. Cyclization of MBH Adducts *E*-142



3.9.1. Typical Procedure for Preparation of Piperidines 143: *N*-(Benzenesulfonyl)-2-phenyl-3-(carbomethoxy)-3,4-dehydropiperidine (143a)

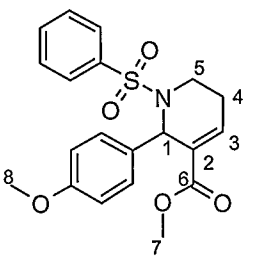
A mixture of the *E*-**142a** (61.1 mg, 0.171 mmol) and DBU (26 μL, 0.174 mmol) was stirred in 4 mL of dry DMF at room temperature for three days. The reaction mixture was diluted with ether and washed once with water and once with brine. The organic phase was dried, filtered and concentrated. The crude product was purified by chromatography (toluene-ethyl acetate, 16:1) to afford 47.0 mg (77%) of product **143a**. A reaction for the same substrate carried out under similar conditions but stirred for only one day afforded a 67% yield of the product. Cyclization reactions for the remaining MBH adducts *E*-**142** were complete after only 24 h.

Off-white solid; mp 114-116 °C (from ethyl acetate-toluene); IR (film) 1714, 1344, 1161, 1102 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 7.2 Hz, 2 H), 7.57-7.51 (m, 1 H), 7.46-7.41 (m, 2 H), 7.30-7.28 (m, 5 H), 7.04 (t, J = 3.6 Hz, 1 H), 6.01 (s, 1 H), 3.82-3.70 (m, 1 H), 3.65 (s, 3 H), 3.05-2.95 (m, 1 H), 2.21-2.14 (m, 2 H); ^{13}C NMR (75 MHz) δ 165.2 (C=O, C-6), 140.8 (C), 139.0 (CH), 138.6 (C), 132.6 (CH), 129.7 (C), 128.9 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 127.0 (CH), 55.0 (CH, C-1), 51.9 (CH_3, C-7), 36.7 (CH_2, C-5), 24.1 (CH_2, C-4); mass spectrum (*m/z*, %) 357 (M^+, 2), 280 (55), 216 (100), 77 (79); HRMS calcd for $C_{19}H_{19}NO_4S$ (M^+): 357.1035; Found: 357.1042. Anal. calcd for $C_{19}H_{19}O_4NS$: C, 63.85; H 5.36; N, 3.92. Found: C, 63.78; H, 5.43; N, 3.84.



3.9.2. *N*-(Benzenesulfonyl)-2-(*p*-chlorophenyl)-3-(carbomethoxy)-3,4-dehydropiperidine (143b)

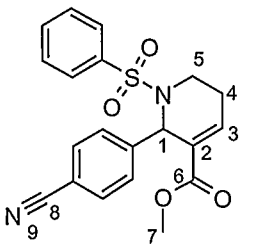
Yield 91%; clear viscous oil; IR (film) 1717, 1343, 1271, 1162, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 7.2 Hz, 2 H), 7.58-7.53 (m, 1 H), 7.47-7.42 (m, 2 H), 7.29-7.21 (m, 4 H), 7.05 (t, J = 3.6 Hz, 1 H), 5.96 (s, 1 H), 3.80 (dd, J = 14.3, 4.6 Hz, 1 H), 3.66 (s, 3 H), 3.00-2.90 (m, 1 H), 2.18-2.13 (m, 2 H); ^{13}C NMR (75 MHz) δ 165.0 (C=O, C-6), 140.7 (C), 139.4 (CH), 137.3 (C), 134.0 (C), 132.7 (CH), 129.5 (CH), 129.3 (C), 129.0 (CH), 128.6 (CH), 127.0 (CH), 54.4 (CH, C-1), 52.0 (CH_3, C-7), 36.7 (CH_2, C-5), 24.1 (CH_2, C-4); mass spectrum (*m/z*, %) 391 (M^+, 1), 280 (36), 252 (32), 250 (100), 77 (83); HRMS calcd for $C_{19}H_{18}{}^{35}ClNO_4S$ (M^+): 391.0645; Found: 391.0634.



3.9.3. *N*-(Benzenesulfonyl)-2-(*p*-methoxyphenyl)-3-(carbomethoxy)-3,4-dehydropiperidine (143e)

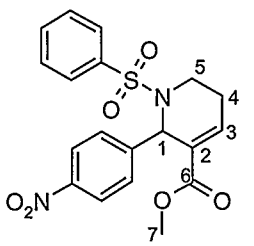
Yield 89%; clear viscous oil; IR (film) 1717, 1339, 1255, 1160, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 7.7 Hz, 2 H), 7.56-7.51 (m, 1 H), 7.46-7.41 (m, 2 H), 7.20 (d, J = 8.7 Hz, 2 H), 7.01 (t, J = 3.1 Hz, 1 H), 6.82 (d, J = 8.7 Hz, 2 H), 5.96 (s, 1 H), 3.78 (s, 3 H), 3.78-3.74 (m, 1 H), 3.65 (s, 3 H), 3.06-2.95 (m, 1 H), 2.19-2.11 (m, 2 H); ^{13}C NMR (75 MHz) δ 165.2 (C=O, C-6), 159.3 (C), 140.9 (C), 138.7 (CH), 132.5 (CH), 130.7 (C), 129.9 (C), 129.3 (CH), 128.9 (CH), 127.0 (CH), 113.7 (CH), 55.2 (CH_3, C-8), 54.5 (CH, C-1), 51.9 (CH_3, C-7), 36.6 (CH_2, C-5), 24.1 (CH_2, C-4); mass spectrum (*m/z*, %) 387

(M^+, 7), 246 (80), 245 (67), 230 (34), 214 (44), 186 (31), 77 (100); HRMS calcd for $C_{20}H_{21}NO_5S$ (M^+): 387.1140; Found: 387.1164.



3.9.4. *N*-(Benzenesulfonyl)-2-(*p*-cyanophenyl)-3-(carbomethoxy)-3,4-dehydropiperidine (143h)

Yield 70%; white solid; mp 140-144 °C (from ethyl acetate-hexanes); IR (film) 2231, 1717, 1340, 1275, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 7.2 Hz, 2 H), 7.62-7.55 (m, 3 H), 7.49-7.41 (m, 4 H), 7.10 (t, J = 3.1 Hz, 1 H), 6.01 (s, 1 H), 3.85-3.79 (m, 1 H), 3.67 (s, 3 H), 2.96-2.86 (m, 1 H), 2.17-2.12 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (C=O, C-6), 144.1, 140.4, 140.1, 132.9, 132.3, 129.1, 128.8, 128.6, 126.9, 118.5 (C, C-8 or C-9), 112.0 (C, C-8 or C 9), 54.5 (CH, C-1), 52.1 (CH_3, C-7), 36.9 (CH_2, C-5), 23.9 (CH_2, C-4); mass spectrum (*m/z,* %) 382 (M^+, 1), 280 (49), 181 (18), 154 (33), 77 (100); HRMS calcd for $C_{20}H_{18}N_2O_4S$ (M^+): 382.0987; Found: 382.0972.

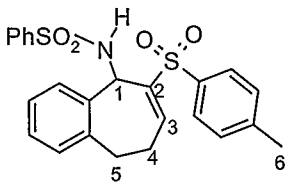


3.9.5. *N*-(Benzenesulfonyl)-2-(*p*-nitrophenyl)-3-(carbomethoxy)-3,4-dehydropiperidine (143i)

Yield 49%; pale-yellow oil; IR (film) 1717, 1348, 1274, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 8.7 Hz, 2 H), 7.80 (d, J = 7.7 Hz, 2 H), 7.60-7.55 (m, 1 H), 7.50-7.45 (m, 4 H). 7.13 (t, J = 3.6 Hz, 1 H), 6.05 (s, 1 H), 3.86-3.79 (m, 1 H), 3.67 (s, 3 H), 2.98-2.90 (m, 1 H), 2.18-2.16 (m, 2 H); ^{13}C NMR (75 MHz) δ 164.8 (C=O, C-6), 147.6,

146.0, 140.4, 140.2, 133.0, 129.2, 129.0, 128.6, 127.0, 123.7, 54.3 (CH, C-1), 52.2 (CH_3, C-7), 36.9 (CH_2, C-5), 24.0 (CH_2, C-4); mass spectrum (*m/z*, %) 402 (M^+, 1), 280 (27), 277 (19), 261 (41), 77 (100); HRMS calcd for $C_{19}H_{18}N_2O_6S$ (M^+): 402.0886; Found: 402.0906.

3.10. Heck Reaction of 124d



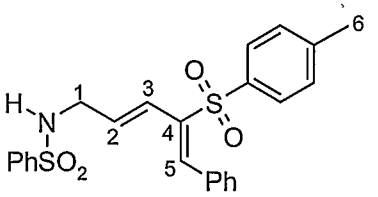
3.10.1. Typical Procedure for the Formation of 149

A suspension of K_2CO_3 (35 mg, 0.25 mmol) and tetra-*n*-butyl ammonium bromide (33 mg, 0.10 mmol) in 0.1 mL of 9:1 DMF-H_2O was stirred for approximately 15 min. To this was added triphenylphosphine (2.7 mg, 0.010 mmol) and **124d** (50 mg, 0.10 mmol). This was stirred for another 15 min before the addition of $Pd(OAc)_2$ (1.1 mg, 0.0049 mmol). The mixture was stirred at 50 °C for 2 h, then diluted with water and extracted into ether and washed with water and brine. The organic fractions were dried, filtered, and evaporated. The crude material was chromatographed on silica gel with 16:1 toluene-ethyl acetate to afford 40 mg (0.088 mmol, 88%) of **149**.

White crystalline solid; mp 161-165 °C (from ethyl acetate); IR (film) 2922, 1641, 1592, 1447, 1324, 1149 cm^{-1}; ^1H NMR (300 MHz) δ 7.73-7.70 (m, 2 H), 7.58-7.57 (m, 3 H), 7.44-7.39 (m, 2 H), 7.34-7.31 (m, 1 H), 7.19-7.12 (m, 5 H, 1 H exchanged with D_2O), 6.97-6.88 (m, 2 H) 6.36 (s, 1 H, H-1), 3.65 (dd, J = 5.4, 15.6 Hz, 1 H, H-4), 3.12 (ddd, J = 6.9, 10.0, 15.6 Hz, 1 H, H-4), 2.37 (s, 3 H, H-6), 2.37-2.27 (m, 2 H, H-5); ^{13}C NMR (75 MHz) δ 144.7 (C), 139.72 (C), 139.68 (C), 138.7 (CH), 136.0 (C), 134.7 (C), 134.0 (C), 133.2 (CH), 130.7 (CH), 130.5 (CH), 129.8 (CH), 129.7 (CH), 129.1 (CH), 128.4 (CH), 127.9 (CH), 126.1 (CH), 51.9 (CH, C-1), 36.3 (CH_2, C-4), 24.1 (CH_2, C-5), 21.7 (CH_3, C-6); mass spectrum (*m/z*, %) 453 (1, M^+), 452 (3), 376 (16), 348 (26), 347 (70), 220 (11),

190 (31), 141 (24), 128 (30), 127 (23), 91 (41), 77 (100); HRMS calcd for $C_{24}H_{23}NO_4S_2$: 453.1069; Found: 453.1065.

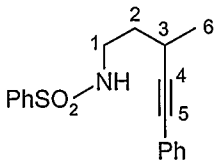
3.11. Attempted Conjugate Additions to 125a



3.11.1. Formation of Diene 160

Copper (I) iodide (213 mg, 1.12 mmol) was weighed into a dry flask, placed under argon, and suspended in 0.5 mL of dry THF. The mixture was cooled to 0°C and MeLi (2.24 mmol, 1.4 M in ether) was added via syringe. The reaction mixture was stirred at 0°C for approximately 30 minutes and was then cooled to -78°C. Piperidine **125a** (101 mg, 0.226 mmol) was weighed into a separate dry flask and dissolved in approximately 2 mL of dry THF under argon. The solution was cooled to -78°C and added to the cuprate solution via cannula. The reaction mixture was stirred at -78°C for 1 h, warmed to -10°C and stirred for a further 3 h. The reaction was quenched with a saturated solution of NH_4Cl, warmed to room temperature and extracted with ether. The organic phase was washed three times with water, once with brine, then dried, filtered and concentrated. The crude material was purified by column chromatography to yield 50.7 mg (50%) of **160**.

White solid; mp 119-123 °C (from dichloromethane); IR (film) 3283, 2253, 1596, 1447, 1312, 1144, 1083 cm^{-1}; ^1H NMR (300 MHz) δ 7.71 – 7.66 (m, 5 H), 7.58-7.31 (m, 10 H), 6.01 (m, 1 H, H-3), 5.92-5.84 (m, 1 H, H-2), 4.23 (t, J = 6.7 Hz, 1 H, N-H, exchanged with D_2O), 3.15 (t, J = 6.9 Hz, 2 H, H-1, collapsed to doublet with D_2O, J = 7.2 Hz), 2.45 (s, 3 H, H-6); ^{13}C NMR (75 MHz) δ 144.9 (C), 139.8 (C), 138.4 (CH), 135.99 (C), 136.97 (C), 135.1 (CH, C-2), 132.74 (CH), 132.71 (CH), 130.6 (C), 130.1 (CH), 129.9 (CH), 129.1 (CH), 128.9 (CH), 128.6 (CH), 127.0 (CH), 122.5 (CH, C-3), 41.3 (CH_2, C-1), 21.7 (CH_3, C-6); mass spectrum (*m/z*, %) 453 (2, M^+), 298 (9), 157 (22), 156 (27), 141 (22), 91 (61), 77 (100); HRMS calcd for $C_{24}H_{23}NO_4S_2$: 453.1069; Found: 453.1072.

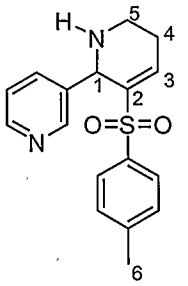


3.11.2. Formation of Alkyne 161

Copper (I) iodide (209 mg, 1.10 mmol) was weighed into a dry flask, placed under argon, and suspended in 2 mL of dry THF. The mixture was cooled to 0°C and MeLi (2.20 mmol, 1.4 M in ether) was added via syringe. The reaction mixture was stirred at 0°C for 10 minutes before adding a solution of **125a** (50 mg, 0.11 mmol) in 2 mL of dry THF via cannula. The solution was stirred at 0°C for 2 hours, then warmed to 20°C and stirred for a subsequent 2 hours. The reaction was quenched with a saturated solution of NH_4Cl and extracted with ether. The organic phase was washed 3 times with water, once with brine, then dried, filtered and concentrated. The crude material was purified by column chromatography to yield 26 mg (76%) of **161**.

Transparent viscous oil. IR (film) 3280, 1492, 1446, 1325, 1160, 1091 cm^{-1}; ^1H NMR (300 MHz) δ 7.90-7.87 (m, 2 H), 7.59-7.46 (m, 3 H), 7.36-7.27 (m, 5 H), 4.84 (t, J = 6.0 Hz, 1 H, N-H, exchanged with D_2O), 3.20 (q, J = 6.7 Hz, 2 H, H-1, collapsed to t with D_2O exchange), 2.74-2.67 (m, 1 H, H-3), 1.81-1.58 (m, 2 H, H-2), 1.22 (d, J = 7.2 Hz, 3 H, H-6); ^{13}C NMR (75 MHz) δ 139.8 (C), 132.6 (CH), 131.5 (CH), 129.1 (CH), 128.2 (CH), 127.8 (CH), 127.0 (CH), 123.2 (C), 92.6 (C, C-5), 82.0 (C, C-4), 41.6 (CH_2, C-1), 36.3 (CH_2, C-2), 24.1 (CH, C-3), 20.9 (CH_3, C-6); mass spectrum (*m/z*, %) 313 (2, M^+), 249 (26), 188 (14), 173 (44), 172 (100), 156 (39), 141 (38), 128 (64), 103 (18), 91 (28), 77 (100) 51 (37); HRMS calcd for $C_{18}H_{19}NO_2S$: 313.1137; Found: 313.1114.

3.12. Approaches to Anabasine

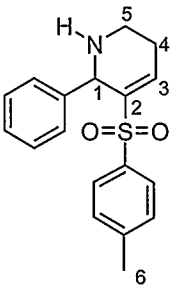


3.12.1. 2-(3-Pyridyl)-3-(*p*-toluenesulfonyl)-3,4-dehydropiperidine (165)

Piperidine **125o** (68 mg, 0.15 mmol) was dissolved in approximately 3 mL of 48% HBr. Three equivalents of phenol were added and the reaction mixture was refluxed for 40 minutes, becoming dark purple. The solution was cooled, and extracted with dichloromethane. The organic fraction was discarded and the remaining aqueous fraction was made alkaline with concentrated sodium hydroxide and re-extracted three times with dichloromethane. The latter organic fractions were combined, dried, filtered, and concentrated to afford **165** in quantitative yield.

Yellow oil; IR (film) 1302, 1150 cm^{-1}; ^1H NMR (300 MHz) δ 8.34 (m, 2 H), 7.45-7.32 (m, 4 H), 7.08-7.05 (m, 3 H), 5.04 (s, 1 H), 3.63 (broad s, 1H), 2.96-2.83 (m, 2 H), 2.56-2.54 (m, 2 H), 2.33 (s, 3 H); ^{13}C NMR (50 MHz) δ 149.9 (CH), 148.4 (CH), 143.8 (C), 141.3 (C), 140.4 (CH), 136.7 (C), 135.8 (CH), 129.3 (CH), 128.7 (C), 127.6 (CH), 122.6 (CH), 54.0 (CH, C-1), 36.9 (CH_2, C-5), 26.3 (CH_2, C-4), 21.4 (CH_3, C-6); mass spectrum (*m/z*, %) 314 (100, M^+), 236 (8), 157 (26); HRMS calcd for $C_{17}H_{18}N_2O_2S$: 314.1089; Found: 314.1072.

3.13. Deprotection of 125p: 2-phenyl-3-(*p*-toluenesulfonyl)-3,4-dehydropiperidine (167)



Piperidine **125p** (34.2 mg, 0.0754 mmol) and two equivalents of K_2CO_3 (20.8 mg, 0.151 mmol) were placed in a dry flask under an argon atmosphere with 1.2 mL of dry DMF. This was cooled to 0°C and 2 equivalents of benzenethiol (15.5 μL, 0.151 mmol) were then added via syringe. The reaction mixture was allowed to gradually warm to room temperature and was stirred for 2.5 h after which the crude mixture was filtered. The filtrate was concentrated under vacuum to remove solvent and excess thiophenol. The crude residue was dissolved in 5% HCl, and washed with dichloromethane. The aqueous layer was then neutralized with a saturated solution of sodium bicarbonate and extracted with three portions of dichloromethane. The organic fractions were combined, dried, filtered, and concentrated to yield 34% of the clean product.

Yellow oil; IR (film) 3317, 1596, 1302, 1148, 1091 cm^{-1} ; ^1H NMR (300 MHz) δ 7.44-7.42 (m, 1 H), 7.32-7.27 (m, 2 H), 7.16-6.97 (m, 7 H), 4.90 (s, 1 H), 2.93-2.79 (m, 2 H), 2.49-2.47 (m, 2 H), 2.33 (s, 3 H), 2.12 (br s, 1 H); ^{13}C NMR (75 MHz) δ 143.5 (C), 141.8 (C), 139.7 (CH), 138.5 (C), 137.0 (C), 129.2 (CH), 128.8 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 56.2 (CH, C-1), 36.8 (CH_2, C-5), 26.2 (CH_2, C-4), 21.4 (CH_3, C-6); mass spectrum (*m/z*, %) 313 (29, M^+), 236 (18), 157 (55), 156 (100), 91 (34); HRMS calcd for $C_{18}H_{19}NO_2S$: 313.1137; Found: 313.1122.

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Appendix I: Crystal Structure Report for MBH adduct *E*-124a

Experimental:

A colorless prismatic crystal of $C_{24}H_{23}NO_4S_2$ was coated with Paratone 8277 oil (Exxon) and mounted on a glass fiber. All measurements were made on a Nonius KappaCCD diffractometer with graphite monochromated Mo-Kα radiation. Cell constants obtained from the refinement[1] of 9572 reflections in the range $3.3 < \theta < 27.5°$ corresponded to a primitive monoclinic cell; details of crystal data and structure refinement have been provided in Table 1. The space group was uniquely determined from the systematic absences. The data were collected[2] at a temperature of 173(2) K using the ω and φ scans to a maximum θ value of 27.5°. The data were corrected for Lorentz and polarization effects and for absorption using multi-scan method[1]. Since the crystal did not show any sign of decay during data collection a decay correction was deemed unnecessary.

The structure was solved by the direct methods[3] and expanded using Fourier techniques[4]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located from a difference map, were included at geometrically idealized positions and were not refined except for the one bonded to N1 that was allowed to refine. The final cycle of full-matrix least-squares refinement using SHELXL97[5] converged with unweighted and weighted agreement factors, R = 0.042 and wR = 0.110 (all data), respectively, and goodness of fit, S = 1.02. The weighting scheme was based on counting statistics and the final difference map was free of any chemically significant features. The figure was plotted with the aid of ORTEPII[6].

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Table 1. Crystal data and structure refinement for $C_{24}H_{23}NO_4S_2$.

Identification code	T. Back – 503 (Jovina-1)	
Empirical formula	$C_{24}H_{23}NO_4S_2$	
Formula weight	453.55	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 10.798(3) Å	α= 90°.
	b = 16.267(5) Å	β= 106.329(15)°.
	c = 13.239(3) Å	γ = 90°.
Volume	2231.6(11) $Å^3$	
Z	4	
Density (calculated)	1.350 Mg/m^3	
Absorption coefficient	0.270 mm^{-1}	
F(000)	952	
Crystal size	0.20 x 0.18 x 0.16 mm^3	
Theta range for data collection	3.3 to 27.5°.	
Index ranges	-13<=h<=13, -20<=k<=21, -17<=l<=17	
Reflections collected	9572	
Independent reflections	5079 [R(int) = 0.033]	
Completeness to theta = 27.5°	99.6 %	
Absorption correction	Multi-scan method	
Max. and min. transmission	0.958 and 0.948	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5079 / 0 / 283	
Goodness-of-fit on F^2	1.02	
Final R indices [I>2sigma(I)]	R1 = 0.042, wR2 = 0.097	
R indices (all data)	R1 = 0.067, wR2 = 0.110	
Largest diff. peak and hole	0.31 and -0.40 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for $C_{24}H_{23}NO_4S_2$. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
S(1)	3273(1)	2035(1)	4105(1)	29(1)
S(2)	3658(1)	1144(1)	7431(1)	26(1)
O(1)	3282(2)	2905(1)	3922(1)	42(1)
O(2)	4473(1)	1649(1)	4687(1)	39(1)
O(3)	2907(2)	560(1)	7811(1)	36(1)
O(4)	5027(1)	1186(1)	7897(1)	39(1)
N(1)	3500(2)	948(1)	6199(1)	24(1)
C(1)	-461(2)	3047(2)	5357(2)	50(1)
C(2)	230(2)	2390(1)	5293(2)	35(1)
C(3)	1249(2)	2412(1)	4775(1)	28(1)
C(4)	2121(2)	1823(1)	4797(1)	23(1)
C(5)	2240(2)	1015(1)	5397(1)	22(1)
C(6)	1966(2)	271(1)	4667(1)	23(1)
C(7)	783(2)	244(1)	3891(2)	29(1)
C(8)	492(2)	-403(1)	3187(2)	35(1)
C(9)	1373(2)	-1034(1)	3242(2)	36(1)
C(10)	2534(2)	-1017(1)	4023(2)	35(1)
C(11)	2832(2)	-367(1)	4730(2)	28(1)
C(12)	2757(2)	1539(1)	2877(1)	26(1)
C(13)	1799(2)	1899(1)	2073(2)	30(1)
C(14)	1387(2)	1503(1)	1111(2)	34(1)
C(15)	1920(2)	753(1)	935(2)	32(1)
C(16)	2876(2)	410(1)	1750(2)	36(1)
C(17)	3303(2)	794(1)	2720(2)	34(1)
C(18)	1495(3)	333(2)	-122(2)	48(1)
C(19)	2984(2)	2117(1)	7530(1)	23(1)
C(20)	3428(2)	2804(1)	7114(2)	29(1)
C(21)	2922(2)	3570(1)	7232(2)	36(1)
C(22)	2003(2)	3643(1)	7771(2)	39(1)

C(23)	1574(2)	2961(1)	8191(2)	39(1)
C(24)	2053(2)	2190(1)	8065(2)	30(1)

Table 3. Bond lengths [Å] and angles [°] for $C_{24}H_{23}NO_4S_2$.

S(1)-O(1)	1.4363(16)
S(1)-O(2)	1.4501(15)
S(1)-C(12)	1.759(2)
S(1)-C(4)	1.7744(19)
S(2)-O(3)	1.4291(15)
S(2)-O(4)	1.4347(15)
S(2)-N(1)	1.6224(16)
S(2)-C(19)	1.7617(19)
N(1)-C(5)	1.476(2)
N(1)-H(1)	0.83(2)
C(1)-C(2)	1.321(3)
C(1)-H(1A)	0.9500
C(1)-H(1B)	0.9500
C(2)-C(3)	1.451(3)
C(2)-H(2)	0.9500
C(3)-C(4)	1.338(3)
C(3)-H(3)	0.9500
C(4)-C(5)	1.522(3)
C(5)-C(6)	1.525(3)
C(5)-H(5)	1.0000
C(6)-C(11)	1.384(3)
C(6)-C(7)	1.397(3)
C(7)-C(8)	1.382(3)
C(7)-H(7)	0.9500
C(8)-C(9)	1.387(3)
C(8)-H(8)	0.9500
C(9)-C(10)	1.383(3)
C(9)-H(9)	0.9500
C(10)-C(11)	1.388(3)

C(10)-H(10)	0.9500
C(11)-H(11)	0.9500
C(12)-C(13)	1.388(3)
C(12)-C(17)	1.389(3)
C(13)-C(14)	1.384(3)
C(13)-H(13)	0.9500
C(14)-C(15)	1.397(3)
C(14)-H(14)	0.9500
C(15)-C(16)	1.384(3)
C(15)-C(18)	1.508(3)
C(16)-C(17)	1.384(3)
C(16)-H(16)	0.9500
C(17)-H(17)	0.9500
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
C(18)-H(18D)	0.9800
C(18)-H(18E)	0.9800
C(18)-H(18F)	0.9800
C(19)-C(24)	1.388(3)
C(19)-C(20)	1.389(3)
C(20)-C(21)	1.386(3)
C(20)-H(20)	0.9500
C(21)-C(22)	1.382(3)
C(21)-H(21)	0.9500
C(22)-C(23)	1.378(3)
C(22)-H(22)	0.9500
C(23)-C(24)	1.384(3)
C(23)-H(23)	0.9500
C(24)-H(24)	0.9500

O(1)-S(1)-O(2)	117.90(10)
O(1)-S(1)-C(12)	108.16(9)
O(2)-S(1)-C(12)	107.28(9)
O(1)-S(1)-C(4)	108.46(9)

O(2)-S(1)-C(4)	107.02(9)
C(12)-S(1)-C(4)	107.61(9)
O(3)-S(2)-O(4)	119.84(10)
O(3)-S(2)-N(1)	108.26(9)
O(4)-S(2)-N(1)	104.26(9)
O(3)-S(2)-C(19)	106.52(9)
O(4)-S(2)-C(19)	108.81(9)
N(1)-S(2)-C(19)	108.80(8)
C(5)-N(1)-S(2)	121.59(13)
C(5)-N(1)-H(1)	113.5(15)
S(2)-N(1)-H(1)	112.2(15)
C(2)-C(1)-H(1A)	120.0
C(2)-C(1)-H(1B)	120.0
H(1A)-C(1)-H(1B)	120.0
C(1)-C(2)-C(3)	121.9(2)
C(1)-C(2)-H(2)	119.1
C(3)-C(2)-H(2)	119.1
C(4)-C(3)-C(2)	126.48(19)
C(4)-C(3)-H(3)	116.8
C(2)-C(3)-H(3)	116.8
C(3)-C(4)-C(5)	125.83(17)
C(3)-C(4)-S(1)	116.21(15)
C(5)-C(4)-S(1)	117.91(13)
N(1)-C(5)-C(4)	111.40(15)
N(1)-C(5)-C(6)	111.91(14)
C(4)-C(5)-C(6)	112.43(14)
N(1)-C(5)-H(5)	106.9
C(4)-C(5)-H(5)	106.9
C(6)-C(5)-H(5)	106.9
C(11)-C(6)-C(7)	118.86(17)
C(11)-C(6)-C(5)	123.36(16)
C(7)-C(6)-C(5)	117.78(16)
C(8)-C(7)-C(6)	120.50(19)
C(8)-C(7)-H(7)	119.7
C(6)-C(7)-H(7)	119.7

C(7)-C(8)-C(9)	120.36(19)
C(7)-C(8)-H(8)	119.8
C(9)-C(8)-H(8)	119.8
C(10)-C(9)-C(8)	119.26(19)
C(10)-C(9)-H(9)	120.4
C(8)-C(9)-H(9)	120.4
C(9)-C(10)-C(11)	120.57(19)
C(9)-C(10)-H(10)	119.7
C(11)-C(10)-H(10)	119.7
C(6)-C(11)-C(10)	120.42(18)
C(6)-C(11)-H(11)	119.8
C(10)-C(11)-H(11)	119.8
C(13)-C(12)-C(17)	120.63(18)
C(13)-C(12)-S(1)	119.31(16)
C(17)-C(12)-S(1)	120.06(15)
C(14)-C(13)-C(12)	119.14(19)
C(14)-C(13)-H(13)	120.4
C(12)-C(13)-H(13)	120.4
C(13)-C(14)-C(15)	121.26(19)
C(13)-C(14)-H(14)	119.4
C(15)-C(14)-H(14)	119.4
C(16)-C(15)-C(14)	118.28(19)
C(16)-C(15)-C(18)	120.5(2)
C(14)-C(15)-C(18)	121.2(2)
C(17)-C(16)-C(15)	121.5(2)
C(17)-C(16)-H(16)	119.2
C(15)-C(16)-H(16)	119.2
C(16)-C(17)-C(12)	119.18(19)
C(16)-C(17)-H(17)	120.4
C(12)-C(17)-H(17)	120.4
C(15)-C(18)-H(18A)	109.5
C(15)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(15)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5

H(18B)-C(18)-H(18C)	109.5
C(15)-C(18)-H(18D)	109.5
H(18A)-C(18)-H(18D)	141.1
H(18B)-C(18)-H(18D)	56.3
H(18C)-C(18)-H(18D)	56.3
C(15)-C(18)-H(18E)	109.5
H(18A)-C(18)-H(18E)	56.3
H(18B)-C(18)-H(18E)	141.1
H(18C)-C(18)-H(18E)	56.3
H(18D)-C(18)-H(18E)	109.5
C(15)-C(18)-H(18F)	109.5
H(18A)-C(18)-H(18F)	56.3
H(18B)-C(18)-H(18F)	56.3
H(18C)-C(18)-H(18F)	141.1
H(18D)-C(18)-H(18F)	109.5
H(18E)-C(18)-H(18F)	109.5
C(24)-C(19)-C(20)	120.88(18)
C(24)-C(19)-S(2)	119.23(15)
C(20)-C(19)-S(2)	119.83(15)
C(21)-C(20)-C(19)	119.23(19)
C(21)-C(20)-H(20)	120.4
C(19)-C(20)-H(20)	120.4
C(22)-C(21)-C(20)	119.9(2)
C(22)-C(21)-H(21)	120.1
C(20)-C(21)-H(21)	120.1
C(23)-C(22)-C(21)	120.7(2)
C(23)-C(22)-H(22)	119.7
C(21)-C(22)-H(22)	119.7
C(22)-C(23)-C(24)	120.1(2)
C(22)-C(23)-H(23)	119.9
C(24)-C(23)-H(23)	119.9
C(23)-C(24)-C(19)	119.19(19)
C(23)-C(24)-H(24)	120.4
C(19)-C(24)-H(24)	120.4

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for $C_{24}H_{23}NO_4S_2$. The anisotropic displacement factor exponent takes the form:

$$-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	25(1)	36(1)	26(1)	2(1)	9(1)	-4(1)
S(2)	31(1)	23(1)	20(1)	-2(1)	3(1)	6(1)
O(1)	54(1)	34(1)	41(1)	2(1)	18(1)	-15(1)
O(2)	20(1)	68(1)	30(1)	5(1)	6(1)	1(1)
O(3)	60(1)	22(1)	30(1)	3(1)	18(1)	3(1)
O(4)	31(1)	45(1)	33(1)	-12(1)	-6(1)	14(1)
N(1)	22(1)	29(1)	20(1)	-3(1)	4(1)	3(1)
C(1)	47(1)	63(2)	43(1)	6(1)	15(1)	27(1)
C(2)	30(1)	44(1)	30(1)	5(1)	9(1)	12(1)
C(3)	30(1)	28(1)	23(1)	2(1)	3(1)	3(1)
C(4)	21(1)	26(1)	20(1)	0(1)	5(1)	-1(1)
C(5)	20(1)	24(1)	20(1)	1(1)	5(1)	3(1)
C(6)	26(1)	23(1)	21(1)	0(1)	8(1)	-1(1)
C(7)	23(1)	33(1)	29(1)	-2(1)	4(1)	0(1)
C(8)	32(1)	40(1)	28(1)	-4(1)	2(1)	-7(1)
C(9)	44(1)	33(1)	32(1)	-10(1)	11(1)	-6(1)
C(10)	39(1)	28(1)	38(1)	-5(1)	11(1)	3(1)
C(11)	27(1)	29(1)	28(1)	-3(1)	5(1)	2(1)
C(12)	25(1)	34(1)	23(1)	5(1)	11(1)	1(1)
C(13)	26(1)	34(1)	30(1)	7(1)	10(1)	4(1)
C(14)	27(1)	45(1)	28(1)	7(1)	6(1)	2(1)
C(15)	36(1)	37(1)	28(1)	1(1)	16(1)	-6(1)
C(16)	44(1)	33(1)	38(1)	3(1)	23(1)	7(1)
C(17)	33(1)	40(1)	30(1)	9(1)	13(1)	10(1)
C(18)	55(2)	60(2)	35(1)	-10(1)	22(1)	-14(1)
C(19)	24(1)	22(1)	21(1)	-4(1)	4(1)	1(1)
C(20)	30(1)	28(1)	30(1)	-2(1)	10(1)	-4(1)
C(21)	46(1)	22(1)	40(1)	0(1)	10(1)	-7(1)
C(22)	51(1)	24(1)	45(1)	-5(1)	16(1)	8(1)

C(23)	45(1)	36(1)	43(1)	-3(1)	23(1)	8(1)
C(24)	35(1)	26(1)	30(1)	1(1)	13(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for $C_{24}H_{23}NO_4S_2$.

Atom	x	y	z	U(eq)
H(1)	4110(20)	1131(13)	6002(17)	29
H(1A)	-298	3553	5059	60
H(1B)	-1123	3014	5701	60
H(2)	55	1888	5594	42
H(3)	1302	2893	4381	33
H(5)	1565	1021	5781	26
H(7)	173	673	3846	35
H(8)	-316	-416	2662	42
H(9)	1181	-1473	2749	44
H(10)	3134	-1454	4076	42
H(11)	3635	-361	5260	34
H(13)	1431	2410	2182	36
H(14)	729	1747	559	40
H(16)	3248	-100	1642	43
H(17)	3961	550	3271	40
H(18A)	815	659	-602	73
H(18B)	1161	-216	-39	73
H(18C)	2232	282	-413	73
H(18D)	1990	-175	-100	73
H(18E)	1645	699	-664	73
H(18F)	574	201	-290	73
H(20)	4070	2749	6754	35
H(21)	3208	4043	6941	43
H(22)	1662	4170	7854	47
H(23)	948	3020	8567	47
H(24)	1749	1717	8342	36

Table 6. Torsion angles [°] for $C_{24}H_{23}NO_4S_2$.

O(3)-S(2)-N(1)-C(5)	63.52(17)
O(4)-S(2)-N(1)-C(5)	-167.84(14)
C(19)-S(2)-N(1)-C(5)	-51.86(17)
C(1)-C(2)-C(3)-C(4)	169.7(2)
C(2)-C(3)-C(4)-C(5)	-1.7(3)
C(2)-C(3)-C(4)-S(1)	-178.88(16)
O(1)-S(1)-C(4)-C(3)	17.63(18)
O(2)-S(1)-C(4)-C(3)	145.81(15)
C(12)-S(1)-C(4)-C(3)	-99.16(16)
O(1)-S(1)-C(4)-C(5)	-159.83(13)
O(2)-S(1)-C(4)-C(5)	-31.65(16)
C(12)-S(1)-C(4)-C(5)	83.38(15)
S(2)-N(1)-C(5)-C(4)	99.65(17)
S(2)-N(1)-C(5)-C(6)	-133.52(14)
C(3)-C(4)-C(5)-N(1)	-118.1(2)
S(1)-C(4)-C(5)-N(1)	59.08(18)
C(3)-C(4)-C(5)-C(6)	115.4(2)
S(1)-C(4)-C(5)-C(6)	-67.46(18)
N(1)-C(5)-C(6)-C(11)	-2.8(2)
C(4)-C(5)-C(6)-C(11)	123.51(19)
N(1)-C(5)-C(6)-C(7)	177.91(16)
C(4)-C(5)-C(6)-C(7)	-55.8(2)
C(11)-C(6)-C(7)-C(8)	-1.1(3)
C(5)-C(6)-C(7)-C(8)	178.25(18)
C(6)-C(7)-C(8)-C(9)	0.0(3)
C(7)-C(8)-C(9)-C(10)	1.4(3)
C(8)-C(9)-C(10)-C(11)	-1.5(3)
C(7)-C(6)-C(11)-C(10)	1.0(3)
C(5)-C(6)-C(11)-C(10)	-178.37(18)
C(9)-C(10)-C(11)-C(6)	0.4(3)
O(1)-S(1)-C(12)-C(13)	-37.36(18)
O(2)-S(1)-C(12)-C(13)	-165.52(15)
C(4)-S(1)-C(12)-C(13)	79.62(17)

O(1)-S(1)-C(12)-C(17)	142.86(16)
O(2)-S(1)-C(12)-C(17)	14.70(18)
C(4)-S(1)-C(12)-C(17)	-100.16(17)
C(17)-C(12)-C(13)-C(14)	0.3(3)
S(1)-C(12)-C(13)-C(14)	-179.43(15)
C(12)-C(13)-C(14)-C(15)	-0.2(3)
C(13)-C(14)-C(15)-C(16)	0.0(3)
C(13)-C(14)-C(15)-C(18)	-178.4(2)
C(14)-C(15)-C(16)-C(17)	0.1(3)
C(18)-C(15)-C(16)-C(17)	178.5(2)
C(15)-C(16)-C(17)-C(12)	0.1(3)
C(13)-C(12)-C(17)-C(16)	-0.3(3)
S(1)-C(12)-C(17)-C(16)	179.50(16)
O(3)-S(2)-C(19)-C(24)	9.55(18)
O(4)-S(2)-C(19)-C(24)	-120.94(16)
N(1)-S(2)-C(19)-C(24)	126.05(16)
O(3)-S(2)-C(19)-C(20)	-173.31(15)
O(4)-S(2)-C(19)-C(20)	56.20(17)
N(1)-S(2)-C(19)-C(20)	-56.80(17)
C(24)-C(19)-C(20)-C(21)	-0.6(3)
S(2)-C(19)-C(20)-C(21)	-177.65(15)
C(19)-C(20)-C(21)-C(22)	1.0(3)
C(20)-C(21)-C(22)-C(23)	-0.4(3)
C(21)-C(22)-C(23)-C(24)	-0.7(4)
C(22)-C(23)-C(24)-C(19)	1.1(3)
C(20)-C(19)-C(24)-C(23)	-0.5(3)
S(2)-C(19)-C(24)-C(23)	176.60(16)

Table 7. Hydrogen bonds for $C_{24}H_{23}NO_4S_2$ [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(2)	0.83(2)	2.07(2)	2.756(2)	140(2)

Appendix II: Presentations of this Work

Oral Presentations

(1) Sorbetti, J. M.; Rankic, D. A.; Wulff, J. E.; Back, T. G. **(2003)** Morita-Baylis-Hillman Reactions and Cyclizations of Aldimines with 1-(*p*-Toluenesulfonyl)-1,3-butadiene. Presented at the 88th Canadian Chemistry Conference and Exhbition of the Canadian Society for Chemistry, Saskatoon, SK on June 14, 2003. This presentation included results from my own work, as well as preliminary research on the project conducted by D. A. Rankic with the aid of J. E. Wulff. All work was carried out under the supervision of Dr. T.G. Back.

(2) Sorbetti, J. M.; Clary, K. N.; Rankic, D. A.; Wulff, J. E.; Back, T. G. **(2005)** Morita-Baylis-Hillman Reactions and Cyclizations of Aldimines with 1-(*p*-Toluenesulfonyl)-1,3-butadiene. Presented at the 2nd Banff Symposium on Organic Chemistry, Banff, AB on November 11, 2005. This presentation included results from my work, as well as results contributed by K. N. Clary, an honours student working under my supervision at the time. Preliminary data was collected by D. A. Rankic with the aid of J. E. Wulff as above. All work was carried out under the supervision of Dr. T.G. Back.

Research Publications

(1) Back, T. G.; Rankic, D. A.; Sorbetti, J. M.; Wulff, J. E. *Org. Lett.* **2005**, *7*, 2377. The work presented in this communication included preliminary studies carried out by D. A. Rankic with the aid of J. E. Wulff. The majority of the results included in the publication included research I conducted towards completion of the project. The body of the manuscript was written by Dr. T. G. Back, while I wrote the experimental section and supporting information.