REGIOSELECTIVE AND ENANTIOSELECTIVE NITRONE CYCLOADDITIONS TO ALKYNONES

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Kelsey Lynn Dunkle

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

MASTER OF SCIENCE

ABSTRACT

Dunkle, Kelsey Lynn, M.S., Department of Chemistry and Biochemistry, College of Science and Mathematics, North Dakota State University, November 2010. Regioselective and Enantioselective Nitrone Cycloadditions to Alkynones. Major Professor: Dr. Mukund P. Sibi.

There has been a need in agriculture, medicine, and organic chemistry for enantiopure isoxazolines. A direct method for their synthesis is from the cycloaddition of 1,3-dipoles and alkynes. Alkynones are difficult substrates to use in cycloadditions due to their high reactivity and sometimes instability. Due to their high reactivity it is often difficult to control regio- endo/exo, and enantioselectivities in dipolar cycloadditions of alkynones. This thesis details the cycloadditions of nitrones and alkynones using chiral Lewis acids leading to isoxazolines with high regio-and enantiocontrol. A chiral bisoxazoline-zinc(II) complex successfully catalyzed the enantioselective 1,3-dipolar cycloaddition reaction of nitrone and alkynone derivatives. This is the second successful reported method for the catalytic enantioselective 1,3- dipolar cycloaddition of nitrones and alkynone derivatives. Yields for the cycloadducts were good to near quantitative and enantioselectivities were generally good reaching a high of 86 % ee. The 4-isoxazolines were isolated as single regioisomers.

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My friends at NDSU: Thank you all for making classes fun and interesting. Without all of you I wouldn't have enjoyed my time here as much.

DEDICATION

This work is dedicated to

My Family:

Mom, Dad, and Jenessa

I would like to thank my family for all of your love and support through the tough times. Thank you for encouraging and supporting me through this whole process; I am very grateful for having such a great family. I dedicate this thesis to you.

I would also like to thank my amazing boyfriend, **Steve Jacobson**. Thanks for listening when I would tell you about my research and thesis, even though it probably sounded like a foreign language to you. Without your love and support I would not have gotten as far as I am today.

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LIST OF SCHEMES

GLOSSARY

1,3-DC	1,3-Dipolar cycloaddition
Ac	acetyl
Aq	aqueous
Ar	aryl
BINOL	1,1'Bi-2-naphthol
Bn	benzyl
BOC	*tert*-Butyloxycarbonyl
Bu	butyl
t-Bu	*tert*-butyl
cat	catalyst
CLA	chiral Lewis acid
DCM	dichloromethane
Ee	enantiomeric excess
Eq	equivalent
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
GC	gas chromatography
H	hours
HPLC	High Performance Liquid Chromatography

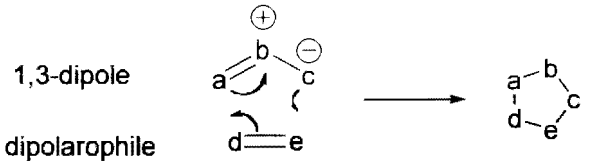
LA	Lewis acid
Lit	literature
Me	methyl
MeO	methoxy
MeOH	methanol
Min	Minutes
NMR	Nuclear Magnetic Resonance
Nu	nucleophile
OTf	triflate
Ph	phenyl
RBF	round bottom flask
Rt	room temperature
Temp	temperature
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

CHAPTER 1. INTRODUCTION OF 1,3-DIPOLAR CYCLOADDITION

Introduction:

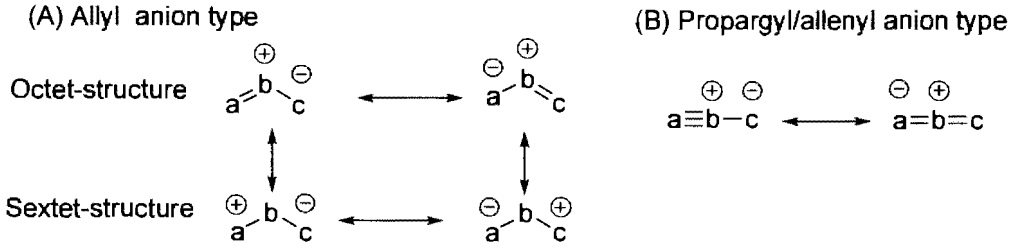
1,3-dipolar cycloadditions are important reactions in synthetic chemistry and are routinely used to prepare five-membered heterocycles.[1] One major reason for their broad utility is because the stereochemistry of the dipole and the dipolarophile is translated to the product. The cycloadditions can be carried out in the presence of chiral auxiliaries or chiral catalysts to access stereochemically rich (a number of chiral centers) products easily. Several methods have been developed for the construction of these optically active heterocycles by dipolar cycloadditions.[2] Lewis acid catalyzed cycloadditions using azomethine imines, diazoacetate, and nitrile oxides to olefins have been thoroughly investigated.[3] The dipolar cycloaddition reaction involves a dipolarophile (*e.g.* alkenes, alkynes, carbonyls, and nitriles) and a 1,3-dipole (Scheme 1).

The dipolarophile is the 2 π component of the 1,3-dipolar cycloaddition. The dipolarophile can be any double or triple bond (C=C, C=N, C=O, etc.).[4] The π-bond may be isolated, conjugated, or part of a cumulene system.[5] The presence of an electron-withdrawing or electron-donating group on the dipolarophile can lead to better reactivity with 1,3-dipoles. The dipolarophile is represented as d and e in the reaction above. The 1,3-dipole is a three-atom four π-electron system, where the π-electrons are delocalized over three atoms, represented as a, b and c in Scheme 1.[6]



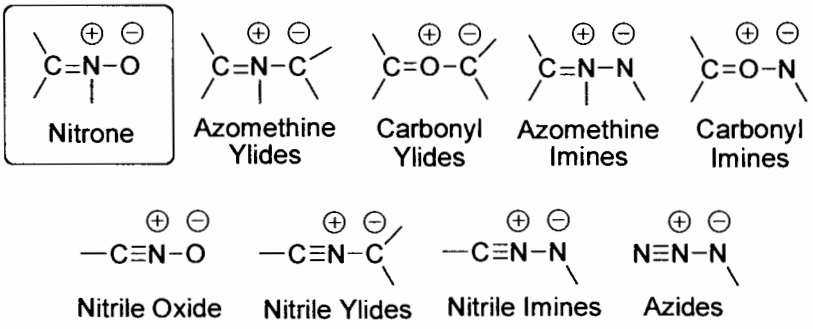
Scheme 1: 1,3-Dipolar Cycloaddition

The 1,3-dipole can be represented by 4 different resonance structures (Scheme 2). The first two resonance structures of the 1,3-dipole are called an octet structure. The second two are sextet structures. In the octet structures, the positive charge is located on the central atom and the negative charge is distributed over the two terminal atoms. In the sextet structures, two of the four π-electrons is localized on the central atom and the positive and negative charges are at opposing ends (Scheme 2).



Scheme 2: Types of 1,3-Dipoles

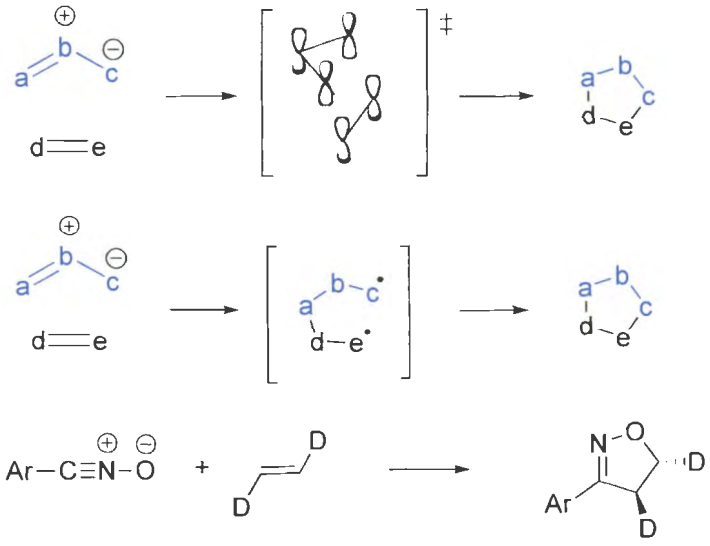
There are two types of 1,3-dipoles: the allyl anion type (Scheme 2A) and the propargyl-allenyl anion type (Scheme 2B).[7] For the allyl anion type, the central atom (b) can be a group V or group VI element and is a bent structure. For the propargyl/allenyl anion type, the center atom (b) is limited to group V because the atom must bear a positive charge in the tetravalent state and is linear in structure (Scheme 3).



Scheme 3: Examples of 1,3 Dipoles

The mechanism of the 1,3-dipolar cycloaddition was greatly debated during the 1960's and continues to be a subject of discussion today.[8] In the 1960's, Huisgen proposed a synchronous concerted mechanism,[9] which is the most widely accepted mechanism, while Firestone proposed a stepwise, diradical pathway (Scheme 4).[10] Huisgen's mechanism has the strongest evidence based on the *cis* nature of the additions. Houk and co-workers took great interest in the debate and tried to help support one mechanism over the other by conducting a series of experiments to observe the products and if the stereochemistry was retained in the product.

In 1985, Firestone and Houk investigated the reaction of benzonitrile oxide with *trans*-dideuterioethylene. The reaction yielded the *trans*-adduct exclusively suggesting that a concerted mechanism is most probable. If a diradical mechanism was operative, one would expect formation of both the *cis* and *trans* adducts due to the ease of rotation around the single bond in the diradical intermediate and rapid cyclization. Since only the *trans* adduct is formed exclusively, a concerted mechanism is most likely.

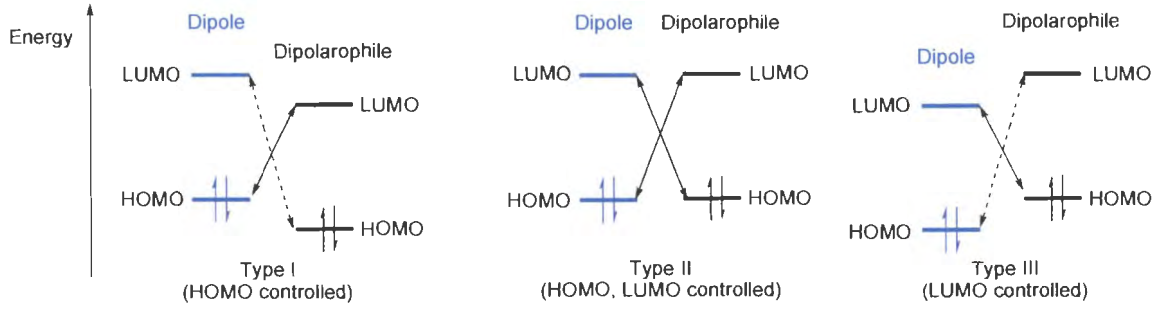


Scheme 4: Mechanisms for 1,3-Dipolar Cycloaddition

There are two types of concerted processes: synchronous and asynchronous. In an asynchronous process, one of the bonds is formed faster than the other. The most widely accepted mechanism for dipolar cycloadditions today is an asynchronous concerted process, since there are two bonds formed during the 1,3-dipolar cycloaddition. Instead of just a single transition state where both bonds are formed simultaneously there would be an intermediate where one bond is formed which is followed by a second bond formation. In a synchronous process it is believed that both bonds form simultaneously in a single transition state, where there are no intermediates. For cycloadditions of nitrones to alkynes it is believed that the process undergoes an asynchronous, concerted mechanism, but electron-withdrawing and electron-donating groups do have an affect on the formation of the bonds, which could cause the mechanism to be asynchronous or synchronous.

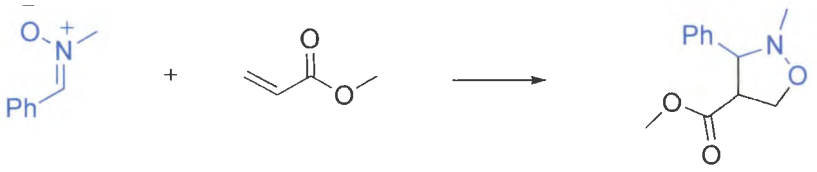
Control of Reactivity and Regiochemistry:

1,3-Dipolar cycloadditions can be classified into three different classes. This classification was proposed by Sustman[11] and is dependent on the dipole and the dipolarophile's HOMO and LUMO levels (Scheme 5).



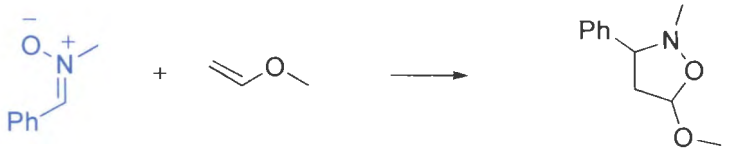
Scheme 5: Frontier Molecular Orbital Diagram for 1,3-Dipolar Cycloaddition

Type I involves the interaction of the LUMO of the dipolarophile and the HOMO of the dipole (electron-deficient dipolarophiles). The opposite interaction, LUMO of the dipole and the HOMO of the dipolarophile is not properly matched because the energy gap between these two levels is too large. This type of interaction is typical for azomethine ylides and azomethine imines. A reaction between methyl methacrylate and benzyl nitrone which undergo a type I 1,3-DC to form an isoxazolidine ring is illustrated in Scheme 6. The reaction proceeds because the dipolarophile is electron-deficient.



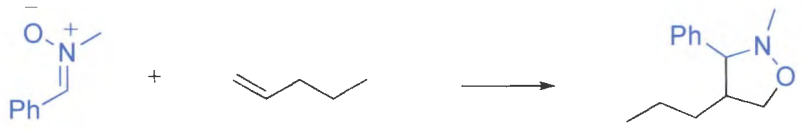
Scheme 6: Example of a Type I Dipolar Cycloaddition

In a Type III interaction, the HOMO of the dipolarophile interacts with the LUMO of the dipole (electron-rich dipolarophiles), as this energy gap is smaller than the reverse. This type of interaction is typical for nitrones and nitrile oxides. An example of type III reaction is shown in Scheme 7, where benzyl nitrone adds to methyl vinyl ether to form the isoxazoline.



Scheme 7: Example of a Type III Dipolar Cycloaddition

For Type II, the frontier orbital (FO) energies of the dipole and dipolarophile are similar and both modes of interaction are possible. If there are no electron-withdrawing or electron-donating groups on the dipole or the dipolarophile, the energy levels are similar to one another but not exactly equal. Since the energy levels are similar it is often difficult to get these types of reactions to proceed without using a catalyst or heat. An example type II reaction is shown in (Scheme 8) where phenyl nitrone adds to 1-pentene to form the isoxazoline ring.



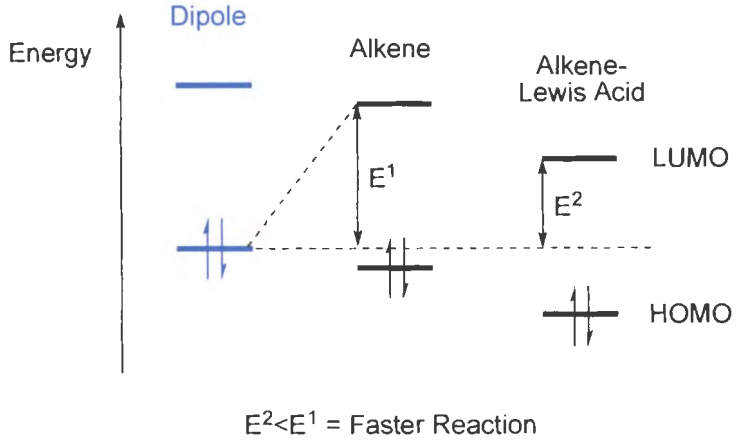
Scheme 8: Example of a Type II Dipolar Cycloaddition

The reactivity of 1,3-dipoles varies from reaction to reaction and a number of factors affect the FO levels. To execute a successful reaction it is best to get the energy difference between the HOMO and LUMO as small as possible. Electron-withdrawing substituents on either the dipole or the dipolarophile lower the level of both the HOMO and LUMO. This lowering of the HOMO and LUMO levels causes the gap between the dipolarophile and dipole to become smaller which in turn causes an increase in reactivity. Electron-donating groups raise the energy of both the HOMO and LUMO levels, while conjugating groups raise the energy of the HOMO but lower the LUMO energy. Another way to control reactivity is to use a Lewis acid as a catalyst.

Role of Lewis Acids in 1,3-Dipolar Cycloaddition Reactions:

The presence of Lewis acids has a great impact on the overall reactivity of 1,3-dipolar cycloadditions. The Lewis acids can affect the energy of levels of either the dipole or the dipolarophile by coordination to a carbonyl or other coordination sites. This Lewis acid coordination to either the dipole or dipolarophile decreases the energy difference between the HOMO and LUMO and hence increases reactivity (Scheme 9).[12] If there is a large energy gap between the HOMO and LUMO levels of the dipole and dipolarophiles, the reaction typically will not proceed but one can add a Lewis Acid to decrease the gap, which causes the reaction to progress. Lewis Acids are usually used as catalysts to make

reactions proceed much faster if a reaction is sluggish. The addition of a Lewis acid causes the energy gap between the dipole and alkene to drop, the smaller the energy gap between the dipole and the alkene, the faster the reaction.



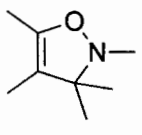
Scheme 9: HOMO and LUMO levels of the Dipole, Alkene and Lewis Acid Coordinated to an Alkene

1,3-dipolar cycloadditions are generally highly stereoselective where the stereochemistry of the original dipolarophile is retained in the cycloadduct. Two chiral centers are usually established during the cycloaddition, one from the dipole and one from the dipolarophile and often diastereomeric products are produced. If the dipole or the dipolarophile bears a chiral auxiliary or if a chiral catalyst is used, then non-racemic cycloadducts can be produced, examples of these cycloadducts will be presented in chapter 4.

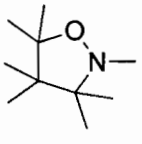
CHAPTER 2. CONTROL OF REGIOCHEMISTRY, STEREOCHEMISTRY, AND DIASTEREOSELECTIVITY IN DIPOLAR CYCLOADDITIONS

Control of Regiochemistry:

Isoxazoline, isoxazolidine, and oxazolines are important heterocycles and serve as building blocks for the synthesis of many natural products and they can be converted to amino ketones and α,β-unsaturated carbonyl compounds (Scheme 10).[13] Given their importance, there is a need not only to produce these heterocycles rapidly[14] but also to control the regio- and stereochemistry of the product of 1,3-dipolar cycloadditions.



Isoxazoline

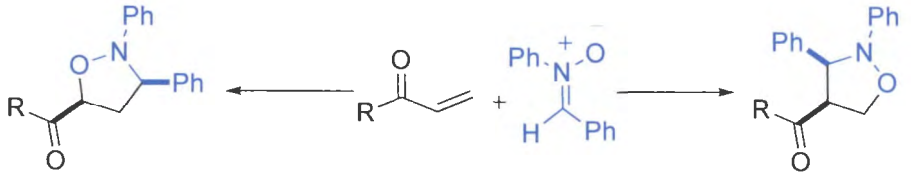


Isoxazolidine

Scheme 10: Isoxazoline and Isoxazolidine

In Chapter I the control of reactivity of cycloadditions was discussed. It is not only important to control reactivity but it is also important to be able to control the regioselectivity of these reactions. In Scheme 11, a cycloaddition of a nitrone and alkene is shown where the nitrone can add in two different orientations that can lead to two isoxazoline products. It is important to control which of the product will be formed because having a mixture of regioisomers often makes separation difficult and is not

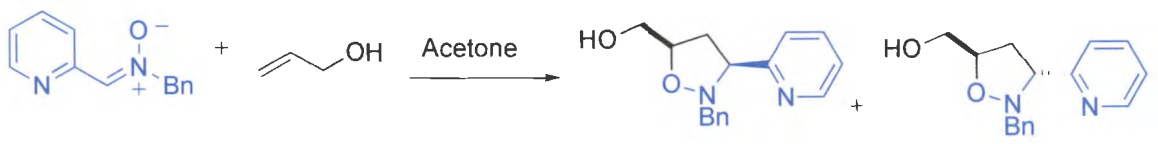
desirable synthetically. Usually 1,3-dipolar cycloadditions are regiospecific based on the interactions of the HOMO and LUMO levels of the dipole and the dipolarophile. Although this is usually the case for most cycloadditions, Type II (according to the Sustmann classification)[15] additions have similar HOMO and LUMO energy levels for the dipole and dipolarophile so the reactions usually produce a mixture of regioisomers, if the reaction even proceeds at all. For these types of reactions it is important to control the regiochemistry to produce only one regioisomer.



Scheme 11: Regioisomeric Products in Cycloaddition of Nitrone and Alkene

One way to control regiochemistry of cycloadditions is to add an electron-donating or electron-withdrawing group to either the dipole or dipolarophile. This can lower the energy gap between the HOMO and LUMO levels, which then leads to regiospecific products. Merino and co-workers in 2003 examined the influence of Lewis acids on the cycloaddition between *N*-benzyl-*C*-(2-pyridyl)nitrone and allylic alcohol (Table 1).[16] In the presence of one equivalent of AgOTf, [$Ag(OClO_3)(PPh_2Me)$], or $Zn(OTf)_2$, the reaction rate was doubled and cis-diastereoselectivity was observed when compared to reaction with no Lewis acid.[16] Another way to control regiochemistry is to add an achiral template and a chiral ligand to the substrate, this allows for both the control of regioselectivity as well as stereochemistry.

Table 1: Cycloaddition of *N*-Benzyl-*C*-(2-pyridyl)-nitrone and Allylic Alcohol



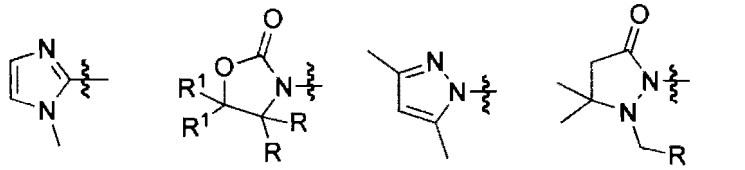
Entry	Lewis Acid	Time (days)	*cis*:*trans*	Yield (%)
1	None	7	70:30	90
2	AgOTf	3.5	>95:5	100
3	$[Ag(OClO_3)(PPh_2Me)]$	5	>95:5	92
4	$Zn(OTf)_2$	3	>95:5	100

Role of Achiral Templates in Dipolar Cycloadditions:

Chiral auxiliaries and achiral templates have played an important role in the development of stereoselective dipolar cycloadditions. They are important for controlling regiochemistry as well as absolute stereochemistry in cycloadditions. Sibi and coworkers, as well as other researchers, have developed several achiral templates that have been utilized for chiral Lewis acid catalyzed enantioselective dipolar cycloadditions. Four commonly used templates are shown in Scheme 12. These achiral templates have allowed many chemists to develop highly regio- and enantioselective products from the cycloaddition of nitrones, nitrile oxides, nitrile imines, and diazoacetates to alkenes.[17] Substrates used with the templates shown in Scheme 12 are in the carboxylic acid oxidation state. This is usually important for coordination of the Lewis acid to the template and the dipolarophile. Even with Lewis acid activation, some substrate-template combinations are still not very reactive, especially true for reactions with less reactive 1,3-dipoles, so identification of alternate templates is important. Each template works differently with the

type of substrate one is trying to activate, so a screen of templates is usually done to ensure the highest reactivity.

It is oftentimes easy to add the template to the substrate and it only requires one additional step to the synthesis. Once the cycloaddition is complete it is generally easy to remove the template to obtain the desired product. There are a number of procedures to remove achiral templates from products after the reaction.[18]



Scheme 12: Templates for Dipolar Cycloadditions

Chiral Lewis acids provide an excellent opportunity to introduce asymmetry into dipolar cycloadditions. It is usually difficult to synthesize chiral starting materials that are enantiopure so it is easier to induce chirality during the reaction than starting with chiral substrates. In 2000 Evans and coworkers published an article on chiral bis(oxazoline)-copper(II) catalyzed enantioselective reactions.[19] In this article they examined the effects of different chiral ligands with copper as a Lewis acid on the enantioselectivities of cycloadditions, Aldol, Michael and carbonyl ene reactions. The achiral template and chiral ligand combination is useful because they can be used for controlling regiochemistry as well as stereochemistry and then they can be removed from the product resulting in a chiral product.

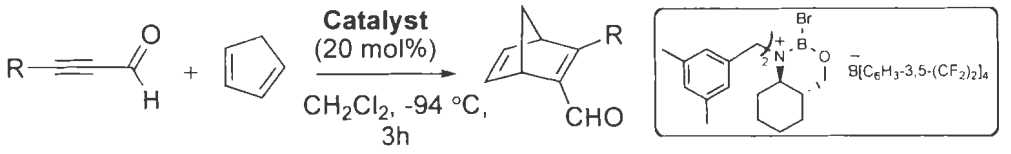
In addition to using templates one can also use chiral starting materials, chiral ligands and Lewis acids to establish stereochemistry. Potentially four chiral centers can be formed in the product, two from the 1,3-dipole and two from the dipolarophile. If there is a chiral dipole and a chiral dipolarophile, there is the potential to have two chiral centers, which then can form diastereomeric products (*cis- and trans*).[20] These products are a result of the *endo* and *exo* transition states, this selectivity is most likely due to a combination of effects which include solvent effects, steric interactions, hydrogen bonds and electrostatic forces. So, it is generally easier to induce chirality in the starting materials to avoid getting a complex mixture of diastereomers.

Controlling Endo/Exo Selectivity:

Lewis acids, achiral templates, and chiral ligands play an important role in controlling the regio- and stereochemistry of many 1,3-dipolar cycloadditions (1,3-DC). But regiochemistry and stereochemistry is not the only thing that you can control in 1,3-DC, one can also control the endo/exo selectivity (diastereoselectivity) of the product. In organic chemistry lectures, the Diels-Alder reaction is a common example given to students for a cycloaddition reaction. This reaction teaches the students about stereochemistry of the resulting products. The products of a Diels-Alder reaction are usually stereoisomers.

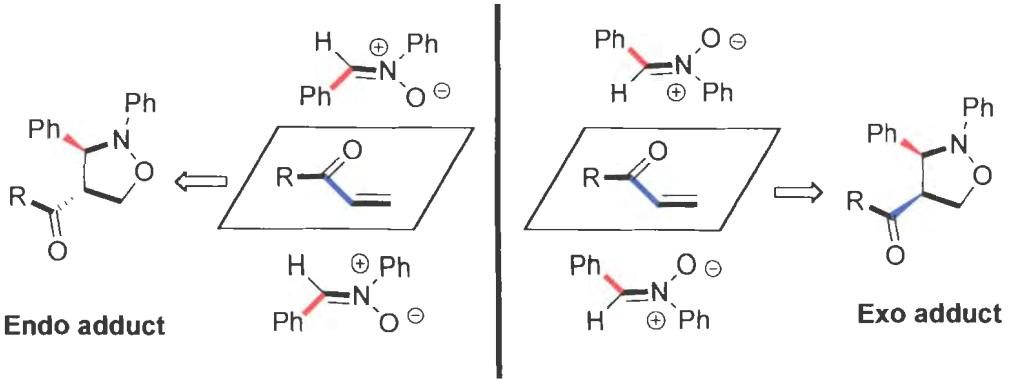
In 1997, E. J. Corey and coworkers published a paper on the enantioselective Diels-Alder reaction between cyclopentadiene and α,β-acetylenic aldehydes catalyzed by a chiral Lewis acid. In this paper they reported an enantioselective version of the Diels-Alder

reaction (Scheme 13).[21] This example is one of the earliest and successful enantioselective Diels-Alder reactions with alkyne dienophiles.



Scheme 13: Diels-Alder Reaction with Alkynones

In a typical example as shown in Scheme 14, the dipole can approach the dipolarophile from either the top or the bottom face leading to a mixture of enantiomers. Additionally, the dipole can approach the dipolarophile either in an endo or an exo mode leading to a mixture of diastereomers. Thus depending on the number of prochiral centers one can obtain a complicated mixture of products in dipolar cycloadditions. The endo/exo selectivity can be controlled by a variety of factors and in general the endo adducts are the preferred products. The face selectivity in the cycloaddition can be controlled by using either chiral reactants or catalysts.



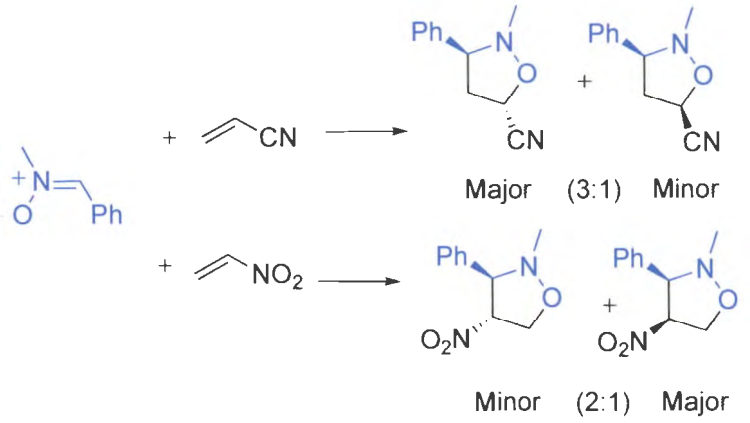
Scheme 14: Face Selectivity for endo/exo Diastereomers

Cycloadditions with Nitrones:

Nitrones are a good example of a 1,3-dipole that gives diverse cyclic products with a variety of dipolarophiles. Nitrones, generally, are stable compounds that do not need to be generated in situ and are easy to handle in air at ambient temperatures. But if the nitrones are kept at room temperature for extended periods of time (a month or longer), light can cause rearrangements to occur, so storing the nitrones in a dark environment is important.

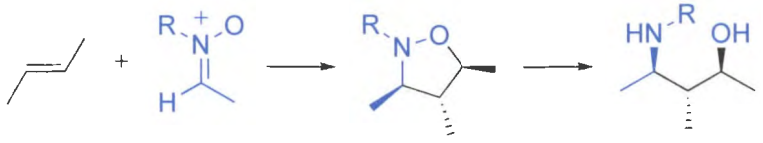
Nitrone cycloadditions are classified as Type II processes by Sustmann. For nitrone cycloadditions to monosubstituted alkenes oftentimes lead to two regioisomeric cycloadducts (Scheme 15). Cycloadditions with electron-rich alkenes are dipole-LUMO controlled. The presence of electron-withdrawing or electron-donating substituents on the dipolarophile or dipole leads to significant rate enhancement in nitrone cycloadditions. For nitrone cycloadditions with moderately electron-withdrawing substituents the dominant interaction is HOMO(dipole)-LUMO(dipolarophile) which controls the reactivity. The LUMO(dipole)-HOMO(dipolarophile) interaction controls the regiochemistry. With very electron-deficient dipolarophiles, the HOMO(dipole)-LUMO(dipolarophile) dominates the interaction and leads to one regioisomer exclusively.

The heterocyclic products from nitrone cycloadditions are usually called isoxazolines, isoxazolidinones or isoxazolidines as introduced above. These heterocycles have attracted a great amount of interest from chemists because of their readiness to undergo cleavage reactions. This reactivity can be attributed to the low thermochemical stability of the N-O bond. There are many ways to reduce or alter these rings so the desire for the synthesis of isoxazolines is quite high.



Scheme 15: Regioselectivity of Nitrone Cycloadditions

The products resulting from the cycloadditions of nitrones to alkenes are important because the cleavage of the isoxazoline system allows access to a variety of attractive compounds such as β-amino alcohols, with the configuration of the chiral centers retained after reduction (Scheme 16).[22]



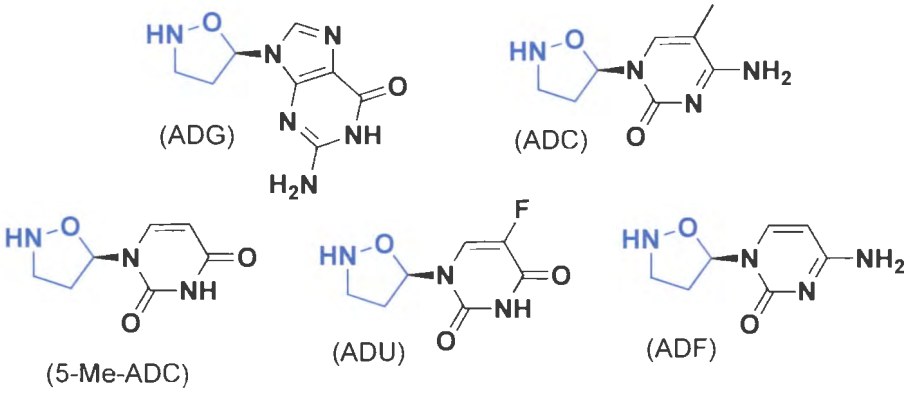
Scheme 16: Reduction of Isoxazolidines

It is common to use Lewis acids as catalysts for dipolar cycloaddition reactions. In the past, Lewis acid catalysis in nitrone cycloadditions was unsuccessful because of the preference for coordination of the Lewis acid to the nitrone instead of the alkene or the alkyne. This was overcome by using an alkene that is capable of a bidentate coordination to the Lewis acid. Many groups have employed alkenes and alkynes attached to templates to prevent competitive coordination of the Lewis acid to the nitrone. By using a chiral

ligand with this combination many researchers were able to achieve stereoselective nitrone cycloadditions using a Lewis acid as a catalyst.

Medicinal Application of Isoxazolidines:

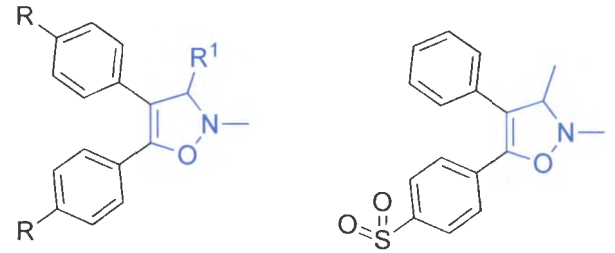
The cycloaddition of nitrones to alkenes have been useful reactions to prepare inhibitors of RNA viral strands.[23] It was found that derivatives of natural nucleic acids play an important role in current chemotherapy as potent and selective antiviral agents in AIDS treatment. The isoxazolidines in Scheme 17 have been evaluated as potential inhibitors of HIV.[24]



Scheme 17: Active Inhibitors of HIV

Another example for the use of isoxazolines in medicinal chemistry is demonstrated in a publication from Knaus in 2001. In this paper they found various isoxazolines to be good cox inhibitors. There was a need for the synthesis of nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of arthritic inflammation and pain. These NSAIDs often caused adverse side effects which included gastrointestinal and renal problems. They believed that a single cyclooxygenase (COX) enzyme was responsible for both the

therapeutic and adverse side effects by these NSAIDs, but it was discovered that there were 2 COX enzymes. COX-2 was found to be responsible for causing adverse side effects so there was a need to find a COX-2 inhibitor so the patient could take the NSAID without the adverse side effects. The COX-2 inhibitors (Scheme 18) have the isoxazoline ring structure that contains various functionalities. There was and is still a need to find efficient syntheses of isoxazolines so that they can be used as therapeutic agents in medicine.[25]



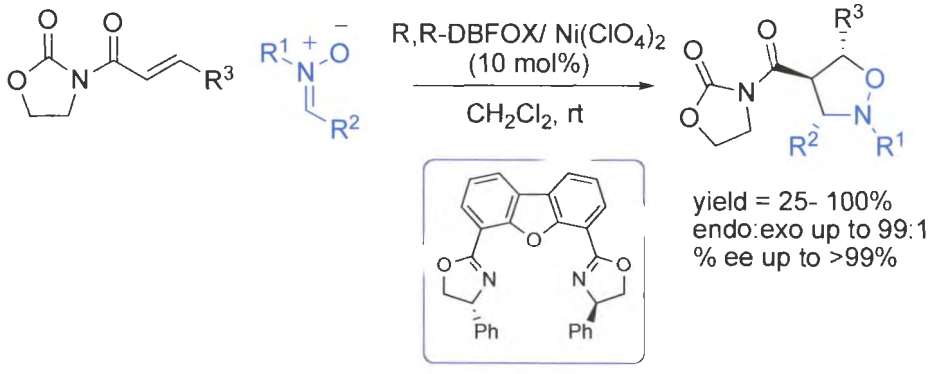
R = H, F, SMe, SO_2Me
R^1= H, Me

Scheme 18: COX Inhibitors

CHAPTER 3. LITERATURE SURVEY OF CYCLOADDITIONS

Exo/Endo Selective Cycloadditions:

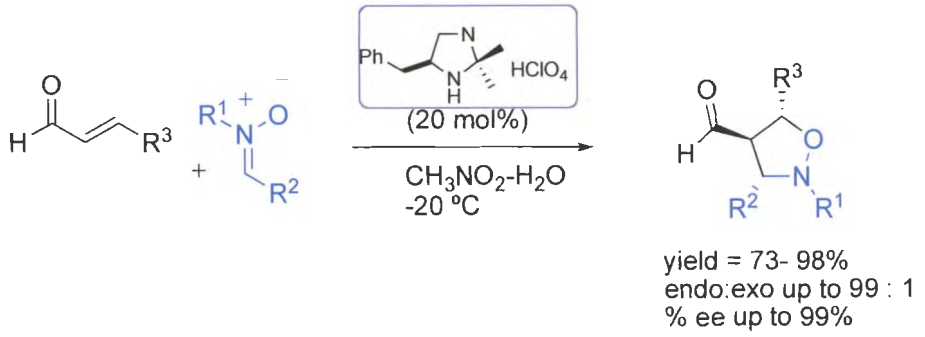
In the last decade several examples of enantioselective nitrone cycloadditions to alkenes have been reported. In 1998, Kanemasa and coworkers reported an endo selective addition of nitrones to alkenes. They employed a combination of nickel perchlorate and R,R-DBFOX as a chiral Lewis acid and oxazolidinone acrylates as dipolarophiles. The product isoxazolidines were obtained in good yields and high endo (>99:1) and enantioselectivities (Scheme 19).[26]



Scheme 19: Endo Selective Nitrone Cycloadditions

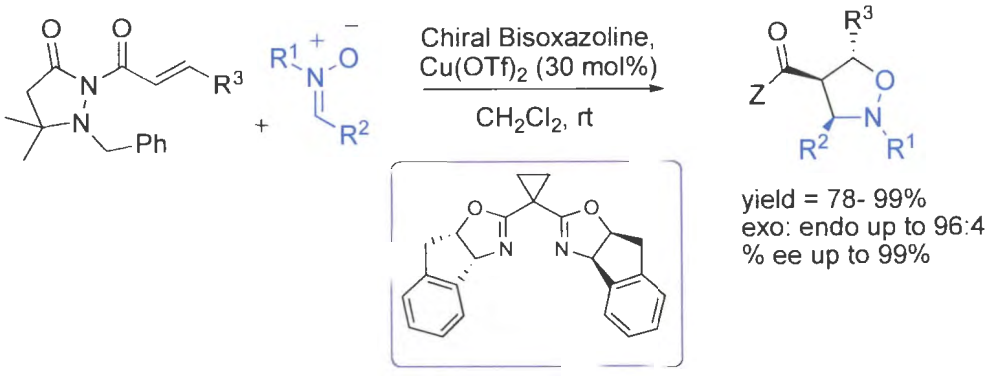
In 2000, MacMillan reported an endo selective nitrone cycloaddition to crotonaldehyde. They were able to control the selectivity by lowering the LUMO of the dipolarophile by using an organocatalyst. The activation of the α,β-unsaturated aldehyde used the reversible formation of iminium ions with chiral imidazolidinones. By using this catalyst they saw endo:exo selectivity of up to 99:1 and enantioselectivity of up to 99%.

These types of aldehydes had previously been difficult substrates to use and this was the first report of organocatalytic 1,3-dipolar cycloadditions to α,β-unsaturated aldehydes (Scheme 20).[27] An achiral template was not required for the reaction which is very common in chiral Lewis acid-mediated reactions.



Scheme 20: Endo Selective Nitrone Cycloaddition to Crotonaldehyde

In 2004 Sibi and coworkers reported an enantioselective nitrone cycloaddition to alkenes.[28] Many cycloadditions had been previously reported where the endo isomer was isolated with high enantioselectivity by using an appropriate ligand/Lewis acid combination. Sibi and coworkers wanted to try and synthesize the exo isomer exclusively because it was oftentimes more desirable and could be used in natural product synthesis (Scheme 21). In order to get the desired exo isomer, they used a combination of a bisoxazoline ligand with copper triflate as the chiral Lewis acid. The coordination of the metal center to the ligand creates a square planar complex. This geometry works well with the pyrazolidinone relay template to force the nitrone to give almost exclusively the exo isomer.



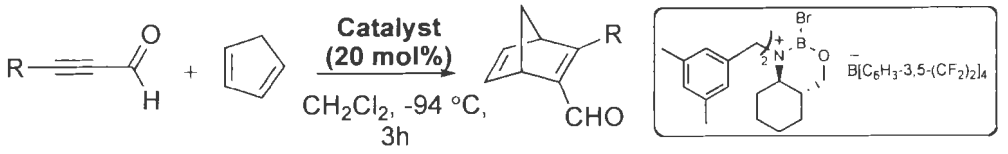
Scheme 21: Exo Selective Nitrone Cycloadditions

In the past, many groups have been successful in achieving high endo selectivity in dipolar cycloadditions using nitrones. By using a proper Lewis acid/ ligand/ template combination, the Sibi group was able to achieve almost exclusively exo selectivity. They were able to get exo:endo selectivity of ~96:4 and enantioselectivities up to 99%.

Cycloadditions to Alkynes and Alkynones:

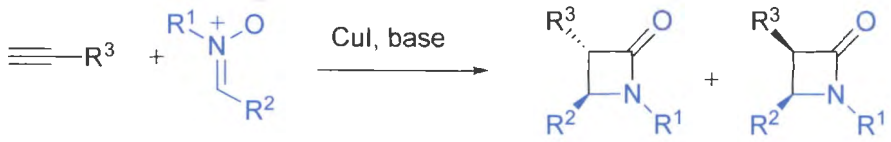
In 1,3-dipolar cycloadditions and Diels-Alder reactions alkynes have been challenging substrates to use when trying to control selectivity. In the past many groups have tried to utilize alkynes in cycloaddition reaction but with little success. It is hard to control the stereochemistry of addition of 1,3 dipoles to alkynes due to the structure of the alkyne, the triple bond allows the dipole to add from many different angles and faces. In 1997 E. J. Corey reported an enantioselective Diels-Alder reaction between cyclopentadiene and acetylenic aldehydes. In the past there were only reports of racemic products obtained from these types of substrates. By using a chiral Lewis acid catalyst they were able to get enantioselective Diels-Alder products (Table 2).[29]

Table 2: Enantioselective Diels-Alder Reaction with Alkynones



Entry	R	Yield (%)	ee (%)
1	TMS	68	87 *(1R,4S)*
2	TES	37	85 *(1R,4S)*
3	Me_2PhSi	50	87 *(1R,4S)*
4	Bu_3Sn	83	80 *(1R,4S)*

Alkynes have been employed as dipolarophiles in nitrone cycloadditions. In reactions between alkynes and nitrones one generally obtains not only the expected five-membered heterocycles, isoxazolines, but also other rearrangement products. The most common example of this alternate type of reactivity is the asymmetric Kinugasa reaction.[30] The Kinugasa reaction involves reacting a terminal alkyne with a nitrone to form a beta lactam. The mechanism shows that the five-membered ring heterocycle is formed but rearranges to the more stable beta-lactam (Scheme 22). This is the most common type of reaction for terminal alkynes and nitrones.

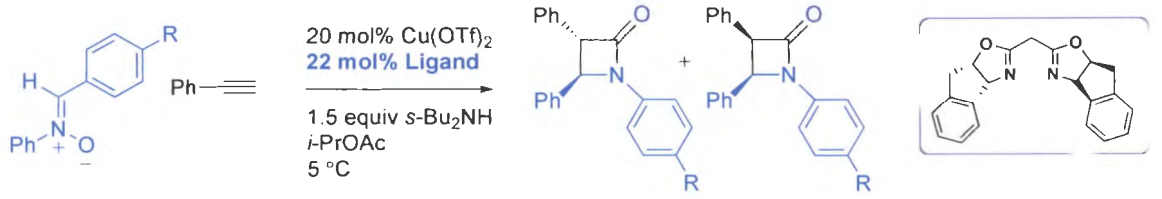


Scheme 22: Kinugasa Reaction

Saito and Otani group published a paper in 2009 describing the enantioselective synthesis of beta lactams via the indabox-Cu(II)-catalyzed Kinugasa reaction.[31] They were able to get good to cis:trans selectivity as well as high enantioselectivity for the cis isomer.

The reactions were efficient even when varying the groups on the nitrone (both electron-withdrawing and donating groups) and the alkyne (Table 3).

Table 3: Variation of the R Group on Nitrone



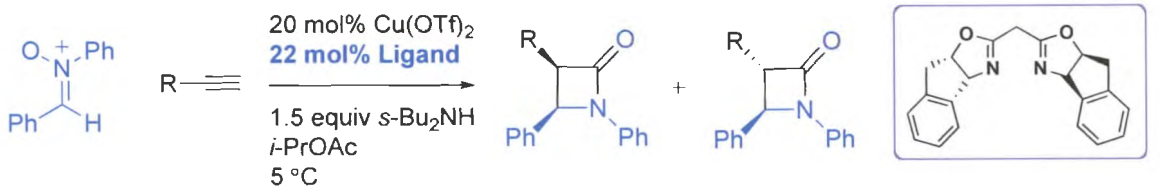
Entry	R	Time (h)	Yield (%)	*cis:trans*	ee (%)
1	Ph	38	47	85:15	90
2	*p*-$MeOC_6H_4$	90	40	83:17	94
3	*p*-BrC_6H_4	336	38	76:24	88
4	*p*-$NO_2C_6H_4$	64	51	18:82	86
5	EtO_2C	0.1	54	*trans* only	32
6	1-cyclohexenyl	36	31	83:17	83

They also varied the R group on the alkyne. They were able to get good enantioselectivity with moderate yields. Reaction time was dependent on the alkyne substituent with the slower ones taking as long as 90-336 hours to reach completion (Table 4).

An example of nitrone cycloaddition to a disubstituted alkyne is shown in Table 5. Boons and Delft reported strain modification by strain-promoted alkyne-nitrone cycloaddition.[32] They were able to use the strain in the alkyne to force an alkyne-nitrone cycloaddition. The yields were quite high for most of the nitrones except when R^1 = Me and R^2 = $CH_2CH_2CO_2Et$, which gave a slow reaction due to the steric hindrance in the dipole. The authors also studied the rates of the cycloaddition reaction and found that the substituents on the nitrone greatly influenced the reaction rates. Changing the N-

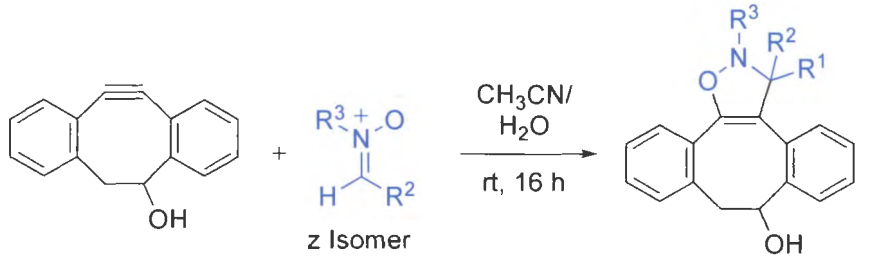
substituent from a methyl to a phenyl led to improved reactivity (compare entry 1 with entry 3).

Table 4: Variation of the R Group on Alkyne



Entry	R	Time(h)	Yield (%)	*cis:trans*	ee (%)
1	H	38	47	85:15	90
2	Me	48	50	80:20	92
3	MeO	40	64	84:16	87
4	Br	48	45	87:13	81
5	CF_3	48	41	84:16	92
6	NO_2	37	47	84:16	94

Table 5: Strain-promoted Alkyne-Nitrone Cycloaddition

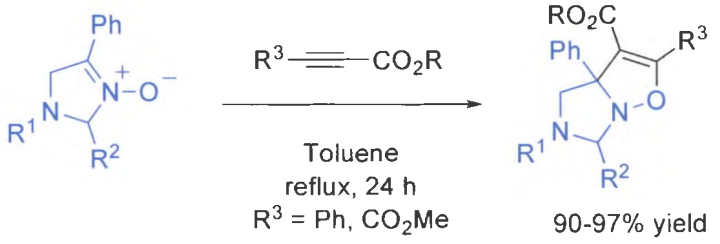


Entry	R^2	R^3	Yield (%)[a]
1	Ph	Me	95
2	CH_2CH_2Ph	Me	80
3	Ph	Ph	89
4	CO_2Et	Me	92
5	C(O)NHBn	Me	93

[a]Yields are for isolated products after column chromatography.

In 2010 Pinho e Melo reported the synthesis of substituted isoxazolines from the cycloaddition of cyclic nitrones with disubstituted alkynes.[33] The reaction requires

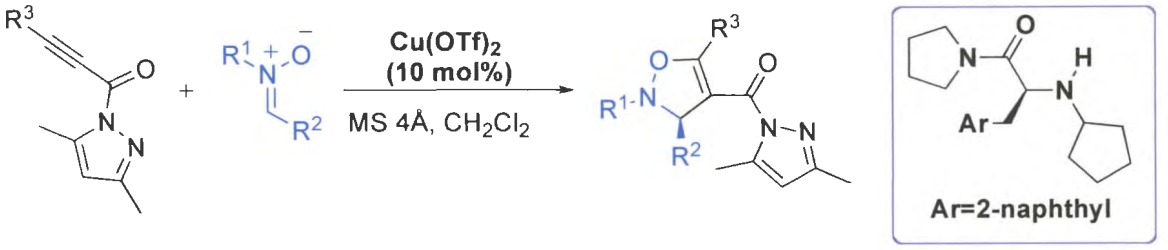
refluxing the nitrone and alkyne for 24 hours in toluene. These conditions are quite harsh especially for cyclic nitrone and disubstituted alkynes, and especially for isoxazolines. Isoxazolines are quite reactive heterocycles and tend to undergo rearrangements or decomposition at high temperatures. Even with these conditions they obtained high yields of up to 97% (Scheme 23).



Scheme 23: Cyclic Nitrone Cycloaddition to Alkynones

There is only one report, to our knowledge, on enantioselective formation of heterocycles from the cycloaddition of nitrones with substituted alkynes.[34] This work was published after all of my thesis work was already completed (Table 6). The enantioselectivities they observed for the heterocycles are excellent with the highest ee of 94%. They varied the R^1 substituent on the nitrone and the R^3 group on the alkynones from methyl to hydrogen. With these variations they were still able to get good yields and excellent selectivities.

Table 6: Enantioselective 1,3-Dipolar Cycloaddition of Nitrones to Propioloylpyrazoles



Entry	R^1	R^2	R^3	T (°C) t (h)	Yield (%)[a]	ee (%)[b]
1	Me	Ph	Me	-20, 1.5	81	74
2	Ph	Ph	Me	-20, 28	39	80
3	DMPM	Ph	Me	-40, 1	82	87
4	1-$NpCH_3$	Ph	Me	-40, 48	91	91
5	Bn	2-Np	Me	-40, 19	97	94
6	Bn	3-Me-furyl	Me	-30, 61	96	84
7	Bn	Ph	H	-40, 21	89	92
8	Bn	2-Np	H	-40, 2	80	94
9	Bn	Ph	$ClCH_2$	-40, 2	79	89
10	Bn	2-Np	$ClCH_2$	-40, 3.5	70	94

DMPM = 3,4-dimethoxybenzyl, 1-$NpCH_2$ = 1-naphthylmethyl,
2-Np = 2-naphthyl, 3-Me-furyl = 3-methylfuran-2-yl
[a]Yields are for isolated products after column chromatography.
[b]Determined by chiral HPLC.

Objective:

The initial objective set out for this project was the formation of nitrogen and oxygen containing heterocycles by a dipolar cycloaddition of nitrones and alkynes, instead of the well-studied nitrone cycloadditions to alkenes. There are many reports of enantioselective nitrone cycloadditions to alkenes but there are very few examples in the literature of cycloadditions of nitrones with substituted alkynes. Alkynes are excellent dipolarophiles in reactions with azides and nitrile oxides. However, no new chiral centers are formed during the cycloaddition with these two dipoles. In contrast, during cycloadditions of alkynes and nitrones a new chiral center is formed and there is potential

for the development of asymmetric methodologies to access chiral dihydroisoxazolines. At the outset of the project we surmised that we would be able to enhance the reactivity of the dipolarophiles by a judicious choice of the template. Furthermore, based on our group's recent work on enantioselective Diels-Alder reactions of alkynones, we were confident that identification of a chiral Lewis acid for the enantioselective dipolar cycloadditions of nitrones to disubstituted alkynones should be possible. Results from our studies on these dipolar cycloadditions are reported in chapter 4.

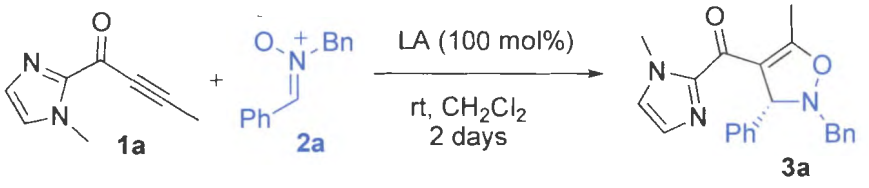
CHAPTER 4. RESULTS AND DISCUSSION

Recently Evans and co-workers have introduced a new achiral template, 2-acyl imidazoles, that provide high selectivity for a variety of chiral Lewis acid catalyzed asymmetric transformations.[35] One key structural feature of 2-acylimidazoles is that the substrate is in the carbonyl oxidation state. This carbonyl oxidation state helps with the binding of Lewis acids to the substrate to increase their reactivity. In the past, using alkynes in cycloaddition reaction has been a challenge, especially for Diels-Alder and other cycloaddition reactions. This challenge could be overcome by using an appropriate template, Lewis acid-chiral ligand combination. We surmised that the imidazole template could provide reactivity enhancements such that reactions with the less reactive disubstituted alkynones should be possible. The availability of a large number of chelating chiral Lewis acids, which could coordinate and activate the substrate, was another factor for use of acyl imidazoles in our work.

Our initial set of experiments was designed to gauge the inherent reactivity of the nitrones and the acyl imidazole dipolarophiles. Results from these studies are shown in Table 7. The required alkynones were prepared following literature procedures.[36] Similarly, a variety of nitrones could be readily accessed using literature procedures and they could be isolated and stored for a reasonable length of time.[37] There was no reaction between alkynone, **3a** and nitrone, **2a** in the absence of any additives. The use of stoichiometric amount of $Sc(OTf)_3$ as a Lewis acid improved reactivity dramatically and gave the cycloadduct in high yield (Table 7). The cycloadduct was formed as a single

regioisomer. Since there is often a need to form enantiopure heterocycles we wanted to see if we could make the reaction enantioselective to demonstrate the versatility of the reaction. A solvent screen was done previously in the Sibi group to determine the best solvent for the reaction. It was found that dichloroethane and dichloromethane were the solvents that gave the best enantioselectivities. Dichloromethane was chosen based on the ease of evaporation and cost. In a significant amount of publications from the Sibi group as well as other research groups it was found that by adding molecular sieves to cycloaddition reactions improved enantioselectivity and yield significantly. 4Å molecular sieves help to remove any excess water from the reaction which can cause formation of undesirable side products. Care was taken to make sure the solvent was freshly distilled and free of most water. Based on this knowledge we decided to include molecular sieves in our chiral reaction screens.

Table 7: Reactivity of Alkynone and Nitrone



Entry	LA	Yield (%)[a]
1	None	-
2	$Sc(OTf)_3$	66%

[a]Yields are for isolated products after column chromatography.

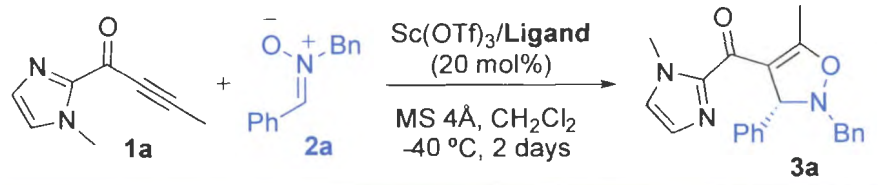
Since there was a significant rate enhancement in the presence of a Lewis acid we decided to gauge the enantioselectivity of the reaction. In past work and publications of from the Sibi group, a significant amount of time was dedicated to finding ideal Lewis acid

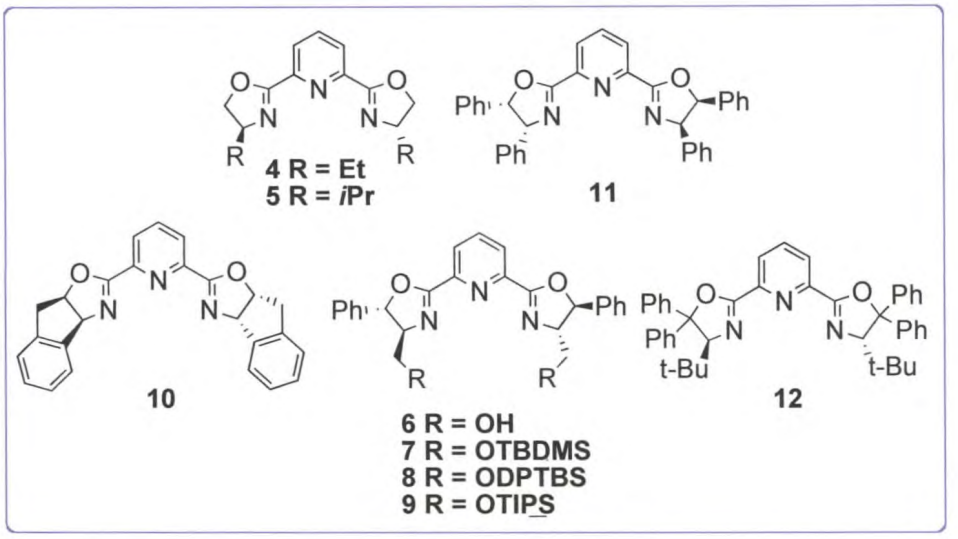
and chiral ligand combinations for a variety of asymmetric transformations. There are a certain number of binding sites for each chiral ligand and this has to be matched with the appropriate oxidation state of the Lewis acid. For example, a tridentate ligand matches well with a metal that has a +3 oxidation state. We decided to test a variety of Lewis acid chiral ligand combinations that worked will in the past. We screened a variety of ligands with the appropriate Lewis acid to see if we observed any significant selectivity. If no enantioselectivity was found for any of these Lewis acid chiral ligand pairings the project would have either been discontinued or the racemic isoxazolidine would have been further investigated. The enantioselectivities for some of the chiral ligands were low, particularly ligands **6**, and **10-12.** But other ligands gave moderate to good enantioselectivities of up to 81%, as well as good to excellent yields (Table 8).

$Sc(OTf)_3$ and ligand **9** gave good yield and enantioselectivity so we decided to test a number of lanthanide triflates to see if selectivity could be improved. We observed that $Sc(OTf)_3$ was substantially the best Lewis acid of the lanthanide series that we screened (Table 9). In the past, Sc(III) has worked well as a Lewis acid in 1,3-dipolar cycloadditions so it was expected that Sc(III) that would work well with our substrates in nitrone cycloadditions.

We wanted to obtain the highest enantioselectivity of the reaction as possible so we performed an extensive Lewis acid and chiral ligand screen. We tested a variety of Lewis acids that were similar in reactivity to that of $Sc(OTf)_3$ as well as ones that have worked well for similar reactions in our previous reports

Table 8: Chiral Ligand Screen

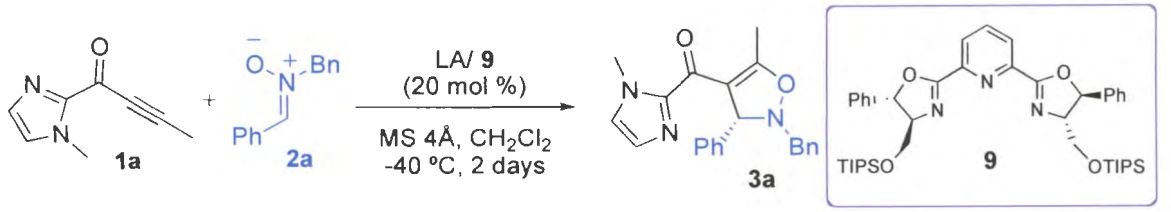




Entry	**Ligand**	Yield (%)[a]	Ee (%)[b]
1	-	66	-
2	**4**	91	63
3	**5**	84	56
4	**6**	>98	35
5	**7**	>98	55
6	**8**	>98	68
7	**9**	>98	81
8	**10**	76	16
9	**11**	82	29
10	**12**	51	00

[a]Yields are for isolated products after column chromatography.
[b]Determined by chiral HPLC.

Table 9: Lanthanide Lewis Acid Screen

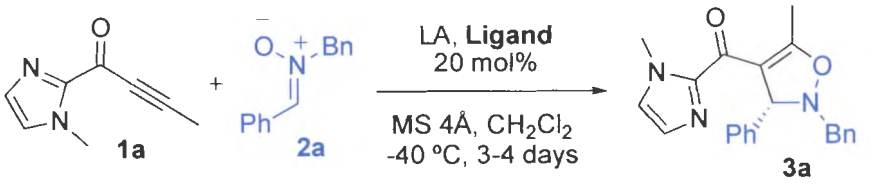


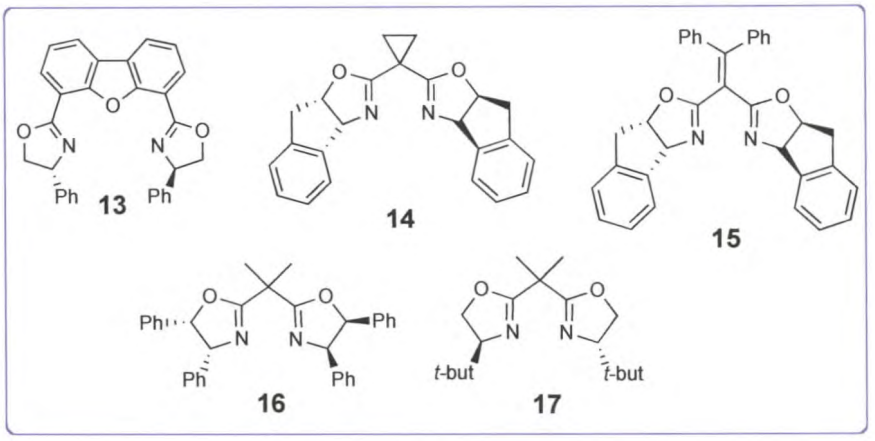
Entry	LA	Yield (%)[a]	Ee (%)[b]
1	$Sc(OTf)_3$	>98	81
2	$Ce(OTf)_4$	62	0
3	$Pr(OTf)_3$	>98	23
4	$Gd(OTf)_3$	>98	34
5	$Dy(OTf)_3$	>98	36
6	$Yb(OTf)_3$	95	12

[a]Yields are for isolated products after column chromatography.
[b]Determined by chiral HPLC.

We found that $Zn(OTf)_2$ along with ligand **14** gave the highest enantioselectivity with a reaction time of 3 days at -40 °C. Reaction time was slower than $Sc(OTf)_3$ but the availability of ligand **12** as well as the ease of synthesis led us to choose zinc triflate/**14** as the ideal chiral Lewis acid combination (Table 10). Copper and nickel Lewis acids usually work well for cycloadditions of alkenes and nitrones, so it was surprising to see that Cu(II) and Ni(II) gave no yield and or no enantioselectivity. A side reaction with $Cu(OTf)_2$ and starting alkynone or nitrone could account for the observation that there was no starting material found after a 2 day reaction time. Proton NMR analysis of the crude from reactions with Cu(II) and Ni(II) as Lewis acids were very messy and complicated so it was hard to determine exactly what happened to lead to this interesting result.

Table 10: Other Chiral Lewis Acids





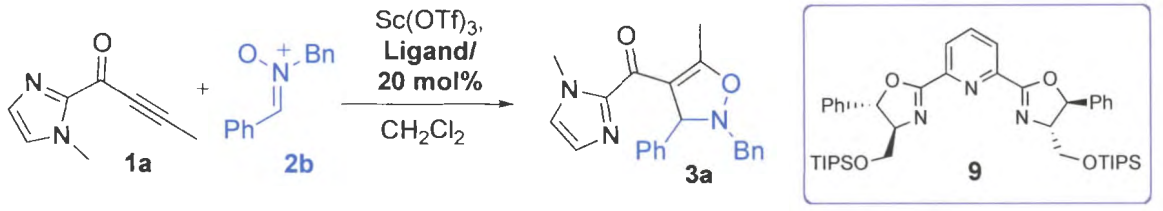
Entry	LA	Ligand	Yield (%)[a]	ee (%)[b]
1	None	-	0	-
2	$Zn(OTf)_2$	-	96	-
3	$Zn(OTf)_2$	**14**	97	86
4	$Zn(OTf)_2$	**15**	85	81
5	$Zn(OTf)_2$	**16**	87	12
6	$Zn(OTf)_2$	**17**	87	15
7	$Zn(NTf_2)_2$	**14**	53	76
8	$Ni(ClO_4)_2$	**13**	95	0
9[c]	$Cu(OTf)_2$	**14**	0	-
10	$Mg(OTf)_2$	**14**	>98	12

[a]Yields are for isolated products after column chromatography.
[b]Determined by chiral HPLC.
[c]No starting material was isolated

A temperature screen was performed to see if lowering the temperature from -20 to -40 °C would improve reaction outcome (Table 11). Interestingly we found that at -20 °C the enantioselectivity increased as well as the yield. We decided to stay with the -40°C reaction conditions because our equipment was more consistent at the -40°C reaction

conditions but one could perform the reaction under -20°C and get slightly improved reaction yields and enantioselectivities.

Table 11: Temperature Screen of Nitrone Cycloaddition



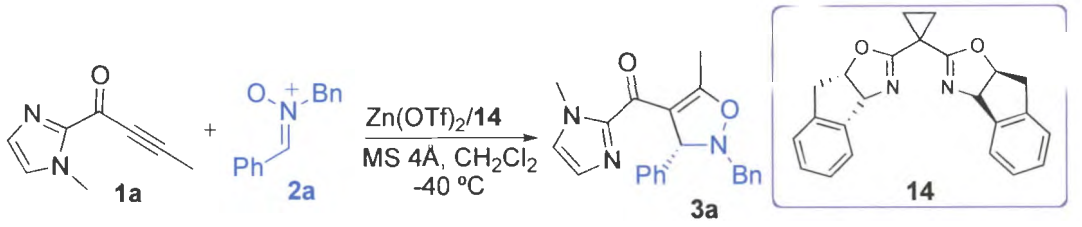
Entry	Time (days)	Temperature (°C)	Yield (%)[a]	ee (%)[b]
1	1	25	66	0
2	3	-40	>98	81
3	7	-75	70	83

[a]Yields are for isolated products after column chromatography.
[b]Determined by chiral HPLC.

The combination of $Zn(OTf)_2$/**14** was chosen as the chiral Lewis acid for further investigation with optimization of catalytic loading. In the past experiments we had chosen to use 20 mol% of the chiral Lewis acid. This worked well for most other reactions but we wanted to see if we couldn't improve selectivity further by increasing the catalytic loading slightly, so that it was still less than a stoichiometric amount but significant to weigh accurately on a 4 place balance. Changing the mol % of chiral Lewis acid from 20 mol % to 30 mol% led to decreased reaction time (faster reaction) but did not increase the selectivity (Table 12). We also wanted to see if we could get similar reactivity when we decreased the ligand loading to 10 and 5 mol%. We observed that the enantioselectivity did not significantly drop when we lowered the catalyst loading to 10 mol% but we did see a small decrease in enantioselectivity, and a 16% drop in yield for a catalytic loading of 5

mol%, with a small drop in enantioselectivity also. We decided to continue using 20 mol% of ligand **14** and zinc triflate for the remainder of our studies.

Table 12: Effect of Catalytic Loading on Yield and Selectivity



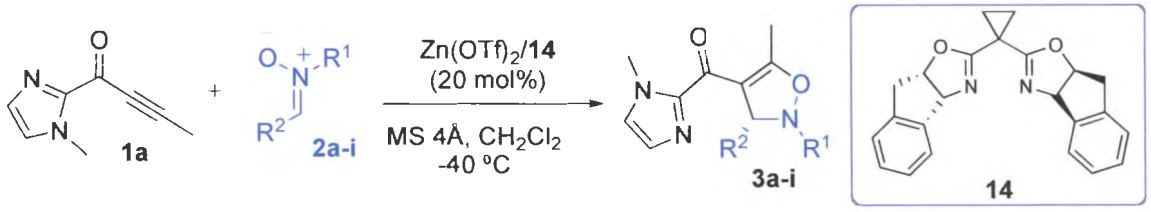
Entry	mol%	Time (days)	Yield (%)[a]	ee (%)[b]
1	30	2	92	82
2	20	4	97	86
3	10	4	90	79
4	5	4	81	74

[a]Yields are for isolated products after column chromatography.
[b]Determined by chiral HPLC.

In order for this chemistry to be useful we needed to demonstrate that we could synthesize a variety of products that were regio- and enantioselective. We were able to vary the substituents on the nitrone which contained either a mild electron-withdrawing or electron-donating group. Halogens are useful substituents because they are often easy to displace with other groups which creates a desired product, which may have been unattainable if the desired substituent was already on the nitrone or the alkyne. The halogen substituents were also useful for determining the absolute configuration of the product by using X-ray crystallography. Now with new X-ray methods halogens are not needed in order to get absolute configuration but those with older X-ray crystallography machines and software would still find these substituents quite useful.

The isoxazoline products can be useful in the synthesis of natural products due to the potential number of stereocenters that can be formed in the heterocycle. We were able to control the selectivity of the newly generated chiral center by changing the substituents on the alkynes and nitrones (Table 13). When the R^2 group on the nitrone is electron-withdrawing it is much harder to get good enantioselectivity, as seen in entries 7-9, but when R^2 is an electron-donating group, such as methoxy, the reaction proceeds quickly and with a high degree of selectivity (entries 1, 2 and 6; Table 13).

Table 13: Substrate Scope: Nitrones

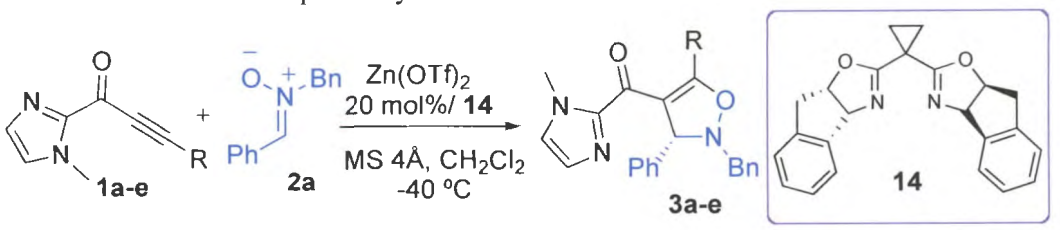


Entry	R^1	R^2	Nitrone	Time (h)	Yield (%)[a]	ee (%)[b]	Product
1	Me	*p*-BrC_6H_4	**2f**	7 days	99	58	**3j**
2	Me	*p*-$MeOC_6H_4$	**2g**	20	73	74	**3k**
3	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	**2h**	20	99	76	**3l**
4	Bn	C_6H_5	**2a**	60	96	86	**3a**
5	Bn	*m*-BrC_6H_4	**2e**	48	87	67	**3i**
6	Bn	*p*-$MeOC_6H_4$	**2b**	20	88	73	**3f**
7	Bn	*p*-ClC_6H_4	**2d**	7 days	92	56	**3h**
8	Bn	*p*-$NO_2C_6H_4$	**2c**	2 days (r.t.)	84	51	**3g**

[a]Yields are for isolated products after column chromatography.
[b]Determined by chiral HPLC.

We also were able to synthesize a variety of alkynones to further demonstrate the usefulness of our chemistry. The R group on the alkynone varied from thiophene to phenyl and good enantioselectivities of up to 77% were observed (Table 14).

Table 14: Substrate Scope: Alkynones

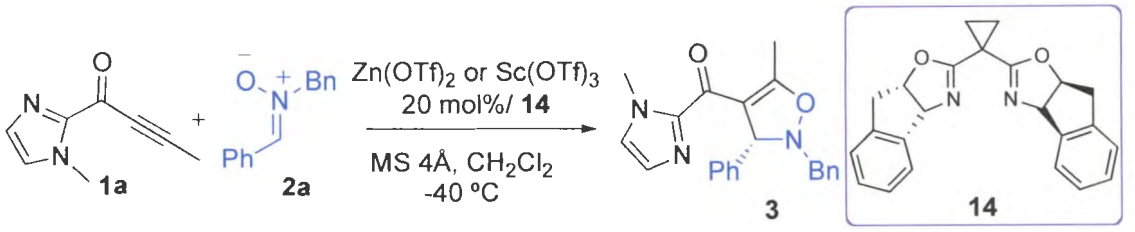


Entry	R	Alkyne	Time (days)	Yield (%)[a]	ee (%)[b]	Product
1	Me	**1a**	4	96	86	**3a**
2	C_5H_9	**1b**	7	82	47	**3b**
3	3-thiophene	**1c**	7	95	72	**3c**
4	Ph	**1d**	7	95	77	**3d**
5	*p*-$MeOC_6H_4$	**1e**	7	91	70	**3e**

[a]Yields are for isolated products after column chromatography.
[b]Determined by chiral HPLC.

After optimizing conditions and finding the ideal nitrone for the cycloaddition we investigated the scope of substrates. Some of the available alkynes were not ideal for addition of the imidazole template to provide alkynones. But we were able to synthesize a variety of substrates that worked well with the imidazole template, some more difficult than others to synthesize. Most of the substrates gave good enantioselectivities (70 %ee) but a couple gave lower numbers or no yield at all. The best substrate was the methyl alkynone. Table 15 shows two substrates that decomposed before the reaction was able to proceed, even at room temperature. Since these two substrates failed to give products we were unable to report yields for either product, these substrates would have been useful but there may be other ways to introduce these groups at a different part of the synthesis.

Table 15: Unsuccessful Substrates



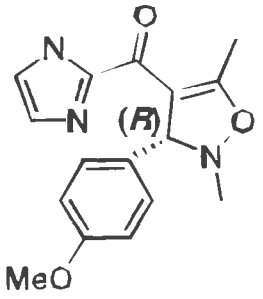
Entry	R	Time (days)	Yield (%)[a]
1	TMS	4	0
2	1-cyclohexene	7	0

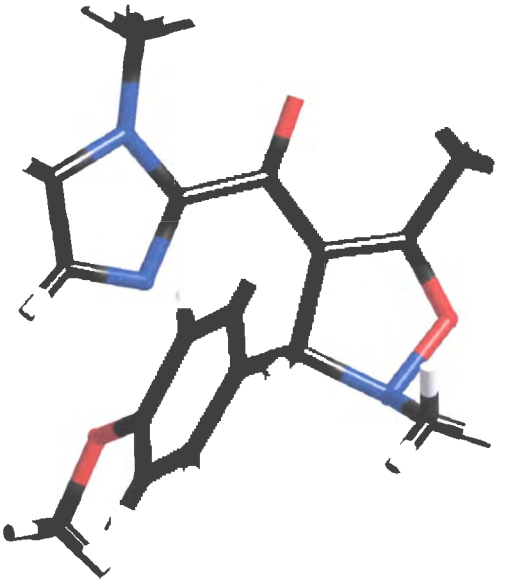
[a]No starting material recovered, messy NMR

Reduction of Isoxazoline System and Cleavage of the N-O Bond:

Several methods were attempted at reducing the isoxazoline system but none of the methods we attempted were able to give a reduced system. Palladium on carbon had traditionally been a good reagent for the reduction of oxazolines but this only gave a complex mixture of products. We still need to work on finding a system that will successfully reduce the system. We also were not successful in removing the imidazole template but there are many reported methods for removing templates so these methods will be tried to further demonstrate the usefulness of our isoxazolines.

We were able to crystallize a couple of the products by dissolving in ethyl acetate followed by addition of hexane and then storing in the fridge for 1 to 2 days. With these crystals we were able to get a good crystal structure of the product (Scheme 24). We then were able to determine the absolute configuration of the product. The stereochemistry of the chiral center was determined to be R. This structure also further validated our work proving that we did in fact synthesize the desired isoxazolines.





Scheme 24: Crystal Structure

Conclusions:

We have successfully prepared chiral isoxazolines from the enantioselective nitrone cycloaddition to alkynones. Although we are not the first to report this type of enantioselective synthesis of isoxazolines, our work demonstrates the advantage of having electron-donating and electron-withdrawing groups on both nitrones and alkynones. All of the work was done prior to the recent publication by Ishihara and co workers, but after viewing their data we are confident that our data is important and can be used by others for the synthesis of natural products or amino alcohols. We are investigating how to successfully reduce the isoxazoline to an isoxazolidine. We are also trying to cleave off the N-methyl imidazole template but so far we have not had any success in cleaving off the template but there are many more ways we can try.

CHAPTER 5. EXPERIMENTAL SECTION

General Experimental Information:

Methylene chloride was distilled from calcium hydride prior to use. Powdered molecular sieves 4 A (MS 4A) was purchased from Aldrich Chemical and dried at 250-300 °C under vacuum before use. Flash chromatography was performed using EM Science silica gel 60 (230-400 mesh) or on an ISCO CombiFlash Companion with Analogix RS-4 columns. Thin layer chromatographic analyses were performed on silica gel Whatmann-60F glass plates and components were visualized by illumination with UV light. All glassware was oven dried, assembled hot and cooled under a stream of dry nitrogen before used. Reactions with air sensitive materials were carried out by standard syringe techniques.

Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H NMR was recorded on a Varian Unity/Inova-500 NB (500 MHz), Varian Unity/Inova-400 NB (400 MHz), or Varian Mercury-300 (300 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using residual $CDCl_3$ (7.27 ppm) as an internal standard. Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, dd = doublets of doublets, dt = doublet of triplets, dq = doublet of quartets, m = multiplet, br = broad, AB sys = AB system), coupling constant(s) and integration. ^{13}C NMR was recorded on a Varian Unity/Inova-500 NB (125 MHz) or a Varian/Inova-400 (100 MHz) spectrometers using broadband proton decoupling. Chemical shifts are reported in parts

per million (ppm) down field from TMS, using the middle resonance of $CDCl_3$ (77.23) as an internal standard. HPLC analyses were carried out on Waters 515 HPLC pump and a 2487 dual λ absorbance detector connected to a PC with Empower Workstation. Optical rotations were measured on a JASCO-DIP-370 polarimeter. High-resolution mass spectra (HRMS) [ESI+] were obtained from the Mass Spectrometry Laboratory, North Dakota State University, Fargo, North Dakota.

Materials and Methods:

$Zn(OTf)_2$ was used as received from Aldrich. The nitrones were synthesized using *N*-methylhydroxylamine hydrochloride, *p*-methoxyphenylhydroxylamine or *N*-benzylhydroxylamine and condensed with the corresponding aldehyde according to literature.[38] The ligands were synthesized according to the method reported by our laboratory.[39]

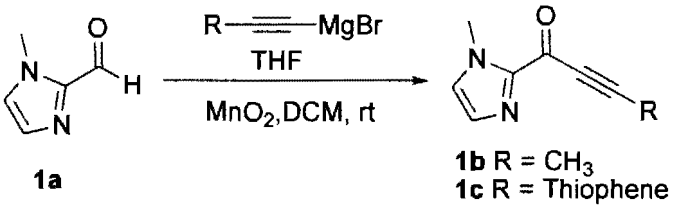
General Procedure for the Synthesis of N-Methyl Imidazole Alkynes (1b-f):

β-Substituted alkynones **1b-f** were prepared starting from 1-methyl imidazole carboxaldehyde **1a** according to modified literature methods.[40]

Procedure A:

1-Methylimidazole-2-carboxaldehyde **1a** (1 equiv.) was stirred in THF (100 mL). The solution was cooled to -78 °C and stirred for 10 minutes. The corresponding Grignard was added dropwise (1.1 equiv., 0.5M soln in THF) and the solution was stirred for 15 minutes (Scheme 25). The solution was then warmed to room temperature and stirred for four hours. The reaction was then quenched with ammonia chloride and solvent was

removed under reduced pressure. The aqueous layer was extracted with ethyl acetate. Organic layer was dried with sodium sulfate. Solvent was removed under reduced pressure and crude product was used directly in oxidation step. The product was dissolved in dichloromethane and manganese dioxide (10 equiv.) was added and stirred for 30 minutes. The solution was filtered through celite to remove MnO_2. The product was purified by column chromatography (0.5:95.5 – 40:60 ethyl acetate/hexane).

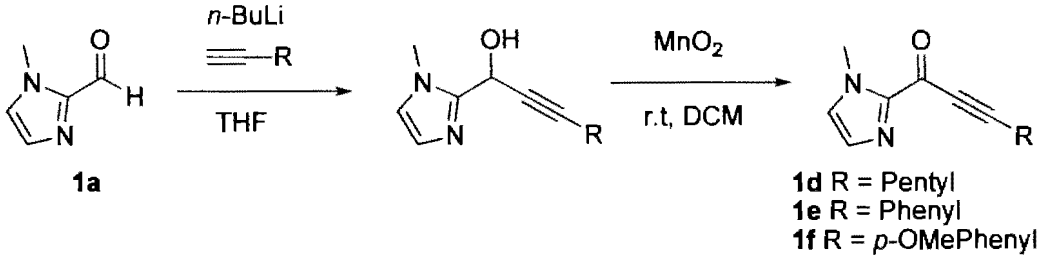


Scheme 25: Preparation of Alkynones Starting from Grignard Reagents

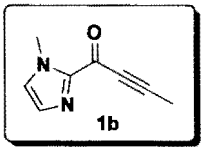
Procedure B:

The corresponding alkyne (1 equiv.) in 50 mL of THF was cooled to -78 °C and stirred for 10 minutes. Butyl lithium (1.1 equiv., 2.5 M) was added dropwise to the solution. The solution was then warmed to room temperature for 15 minutes and was then cooled again to -78°C and stirred for 10 minutes. 1-Methyl-imidazole-2-carboxaldehyde **1a** (1 equiv.) was dissolved in THF (25 mL) and added dropwise to the solution of the alkyne (Scheme 26). The solution was then warmed to room temperature and stirred for four hours. The solution was then quenched with ammonia chloride and solvent was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate. The organic layer was dried with sodium sulfate. The solvent was removed and the crude product was used directly in the oxidation step. The product was dissolved in dichloromethane and manganese dioxide (10 equiv.) was added and stirred for 30 minutes. The solution was

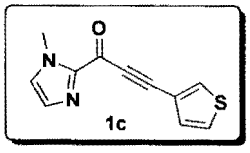
filtered through celite to remove MnO_2. The product was purified by column chromatography (0.5:95.5 – 40:60 ethyl acetate/hexane).



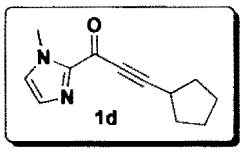
Scheme 26: Preparation of Alkynones Starting from Terminal Alkynes



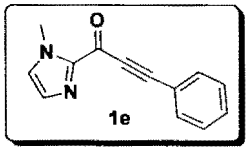
(1-Methyl-*1H*-imidazole-2-yl)-but-2-yn-1one (1b): Yellow solid; yield: 89%; mp = 78-79°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.18 (s, 3H), 4.03 (s, 3H), 7.08 (s, 1H), 7.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.9, 36.2, 78.7, 92.9, 127.6, 131.0, 143.9, 168.3; IR (KBr) 3108, 2961, 2272, 2216, 1633, 1474, 1402, 1255, 1162, 1134, 882 cm^{-1}; HRMS calcd. for $C_8H_8N_2ONa^+$ 171.0534; found 171.0538.



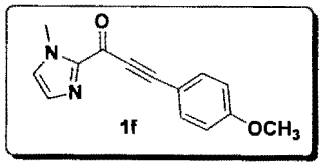
(1-Methyl-1*H*-imidazole-2-yl)-3-thiopheneprop-2-yn-1-one (1c): Yellow solid; yield: 79%; mp = 70-71°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.07 (s, 3H), 7.13 (s, 1H), 7.31 (s, 1H), 7.34 (dd, J = 5.0, 2.9 Hz, 1H), 7.37 (dd, J = 5.0, 1.4 Hz, 1H), 7.90 (dd, J = 2.9, 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.3, 88.2, 88.8, 119.7, 126.1, 127.9, 130.8, 131.1, 134.5, 144.0, 168.3; IR (KBr) 3107, 2196, 1624, 1517, 1462, 1395, 1263, 1156, 1028, 910, 825, 789, 684 cm^{-1}; HRMS calcd. for $C_{11}H_8N_2OSNa^+$ 239.0250; found 239.0256.



(1-Methyl-1*H*-imidazole-2-yl)-3-cyclopentylprop-2-yn-1-one (1d): Bright yellow solid; yield: 80%; mp = 44-45°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.58 (m, 2H), 1.77 (m, 4H), 2.01 (m, 2H), 2.89 (m, 1H) 3.97 (s, 3H), 7.02 (d, J = 1.0 Hz, 1H), 7.20 (d, J = 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.6, 30.6, 33.5, 36.3, 80.1, 105.7, 127.5, 130.9, 144.1, 168.7; IR (KBr) 3106, 2960, 2208, 1628, 1461, 1402, 1250, 1161, 950, 910 cm^{-1}; HRMS calcd. for $C_{12}H_{14}N_2ONa^+$ 225.0998; found 225.0987.



(1-Methyl-1*H*-imidazole-2-yl)-3-phenylprop-2-yn-1-one (1e): Off-white solid; yield: 30%; mp = 108-109°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.06 (s, 3H), 7.11 (s, 1H), 7.30 (m, 1H), 7.41 (m, 3H), 7.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.3, 87.8, 93.2, 120.5, 123.5, 127.9, 128.7, 130.9, 131.2, 133.5, 195.0; IR (KBr) 3107, 2958, 2203, 1103, 1623, 1489, 1399, 1276, 1157, 1030, 996, 916, 759, 689 cm^{-1}; HRMS calcd. for $C_{13}H_{10}N_2ONa^+$ 233.0685; found 233.0679.

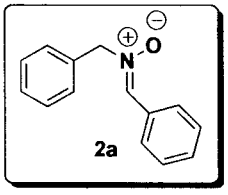


(1-Methyl-1*H*-imidazole-2-yl)-3-*p*-methoxyphenylprop-2-yn-1-one (1f): Yellow solid; yield: 40%; mp = 103-105°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.80 (s, 3H), 4.01 (s, 3H), 6.87 (td, J = 6.9, 1.9 Hz, 2H), 7.08 (d, J = 5.8 Hz, 1 H), 7.24 (dd, J = 12.3, 3.4 Hz, 1H), 7.64 (td, J = 6.9, 1.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.4, 55.7, 87.9, 94.6, 112.3, 114.4, 127.6, 130.9, 135.6, 144.0, 161.9, 168.3; IR (KBr) 2961, 2838, 2191, 1623, 1600, 1511,

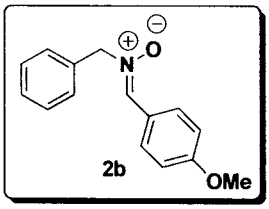
1403, 1254, 1173, 1027, 916, 834 cm^{-1}; HRMS calcd. for $C_{14}H_{12}N_2O_2Na^+$ 263.0791; found 263.0801.

Synthesis of Nitrones (2a-h):

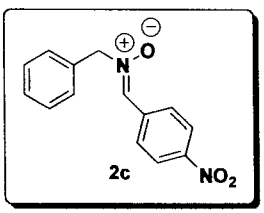
The nitrones were synthesized using *N*-methylhydroxylamine hydrochloride, *p*-methoxyphenylhydroxylamine or *N*-benzylhydroxylamine and condensed with the corresponding aldehyde according to literature procedures.[41]



(*Z*)-*N*-Benzylidene-1-phenylmethanamine oxide (2a): White solid; yield: 96%; mp = 123-124 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.19-8.23 (m, 2H), 7.47-7.51 (m, 2H), 7.38-7.43 (m, 7H), 5.08 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 71.2, 128.5 (2 carbons), 128.8 (2 carbons), 129.1, 129.4, 130.6, 133.5, 134.4.

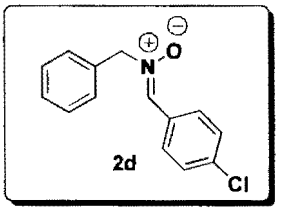


(*Z*)-*N*-(4-Methoxybenzylidene)-1-phenylmethanamine oxide (2b): Off-white sold; yield: 94%; mp = 120-121 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.81(s, 3H), 5.00 (s, 2H), 6.89 (m, 2 H), 7.28 (s, 1H), 7.38 (m, 3H), 7.44 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) 55.5, 70.9, 114.0, 123.6, 129.0, 129.1, 129.4, 130.8, 133.7, 134.0, 161.2.

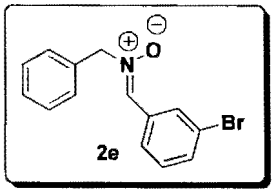


(*Z*)-*N*-(4-Nitrobenzylidene)-1-phenylmethanamine oxide (2c): White solid, yield: 95%; mp = 121-122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.09 (s, 2H), 7.41-7.49 (m, 6H), 8.22 (dt, *J* = 9.0, 2.2Hz,

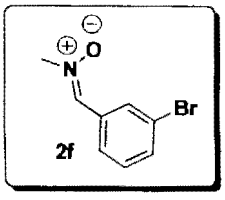
2H), 8.34 (dt, J = 9.0, 2.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 72.3, 124.0, 129.1, 129.4, 129.6, 129.7, 132.4, 132.8, 136.2, 148.1; IR (KBr) 3070, 1565, 1516, 1348, 1151, 862, 714, 688 cm^{-1}; HRMS calcd. for $C_{14}H_{12}N_2O_3Na^+$ 279.0740; found 279.0731.



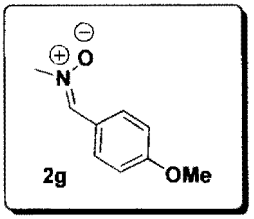
(*Z*)-*N*-(4-Chlorobenzylidene)-1-phenylmethanamine oxide (2d): White solid; yield: 92%; mp = 198-199 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.03 (s, 2H), 7.37 (m, 8H), 8.14 (td, J = 8.5, 2.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 71.5, 128.9, 129.1, 129.2 (2 carbon), 129.3, 129.5, 129.9, 133.3, 136.0.



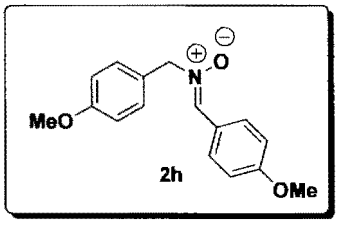
(*Z*)-*N*-(3-Bromobenzylidene)-1-phenylmethanamine oxide (2e): White crystalline solid; yield: 87%; mp = 213-214 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.07 (s, 1H), 7.37 (s, 1H), 7.44 (m, 3H), 7.48 (m, 2H), 7.54 (dt, J = 9.0, 2.4 Hz, 2H), 8.11 (dt, J = 9.0, 2.4Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 71.7, 122.8, 127.2, 129.3, 129.4, 129.5, 130.1, 131.2, 132.5, 132.9, 133.2, 133.4; IR (KBr) 3065, 1577, 1457, 1427, 1271, 1150, 887, 710, 682, 466 cm^{-1}; HRMS calcd. for $C_{14}H_{12}BrNONa^+$ 311.9994; found 311.9985.



(*Z*)-*N*-(3-Bromobenzylidene)methanamine oxide (2f): White solid; yield: 70%; mp = 129-130°C ; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.92 (s, 3H), 7.31 (t, J = 9.0 Hz, 1H), 7.36 (s, 1H), 7.56 (d, J = 9.0 Hz, 1H), 8.10 (d, J = 9.0 Hz, 1H), 8.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 54.8, 127.0, 130.2, 131.0, 132.4, 133.5.



(*Z*)-*N*-(4-Methoxybenzylidene)methanamine oxide (2g): White solid; yield: 80%; mp = 69-70 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.81 (s, 6H), 6.90 (d, J = 9.0 Hz, 2H), 7.26 (s, 1H), 8.17 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 54.1, 55.5, 114.1, 123.7, 130.6, 135.1, 161.3.



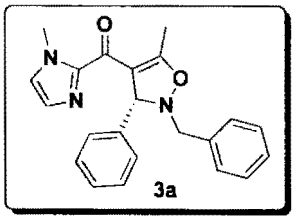
(*Z*)-*N*-(4-Methoxybenzylidene)-1-(4-methoxyphenyl)methanamine oxide (2h): White solid; yield: 95%; mp = 99-100 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.79 (s, 3H), 3.80 (s, 3H), 4.98 (s, 2H), 6.94 (m, 4H), 7.29 (s, 1H), 7.42 (td, J = 9.0, 4.8 Hz, 2H), 8.21 (td, J = 9.0, 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.6, 70.4, 114.0, 114.6, 123.7, 125.6, 130.9, 131.0, 131.1, 133.6, 160.3, 161.2 IR (KBr) 3051, 2974, 2839, 1603, 1507, 1457, 1256, 1172, 1027, 940 cm^{-1}; HRMS calcd. for $C_{16}H_{17}NO_3Na^+$ 294.1101; found 294.1089.

General Procedure for the Preparation of Racemic Samples:

An oven-dried vial was charged with $Zn(OTf)_2$ (0.03 mmol), freshly dried 4Å molecular sieves (150 mg), and substrate (0.15 mmol), and dry CH_2Cl_2 (2 mL) were added. The mixture was then stirred at room temperature for 30 min before nitrone (0.15 mmol) was added. The solution was then stirred at room temperature and monitored by TLC for completion. The reaction mixture was quenched with silica gel. The solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography (silica gel, hexane/ethyl acetate 95:5-70:30), to yield racemic cycloadducts.

General Procedure for Enantioselective Nitrone Cycloadditions with β-Substituted Alkynes (3a-l):

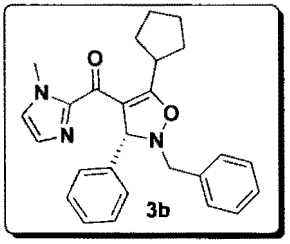
An oven-dried vial was charged with $Zn(OTf)_2$ (0.03 mmol) and the corresponding ligand (0.03 mmol) and 150 mg of freshly dried 4Å molecular sieves were added. Dry CH_2Cl_2 (2 mL) was added and the mixture was stirred for 45 minutes at room temperature. To the solution, alkyne substrate (0.15 mmol) in 0.5 mL dry CH_2Cl_2 was added via syringe. After the mixture was stirred at room temperature for 30 min, nitrone (0.15 mmol) was added. The reaction mixture was cooled and stirred at -40 °C. Reaction progress was monitored by TLC for starting material consumption. The reaction mixture was quenched with silica gel. The solvent was removed under reduced pressure to give the crude product, which was separated by FC (silica gel, hexane/ethyl acetate 95:5-70:30). The enantiomeric excess of the product was determined by chiral HPLC .



(2-Benzyl-5-methyl-3-phenyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1*H*-imidazol-2-yl)methanone (3a):

Oil; $[\alpha]_D^{25}$ = -208.8 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.41 (s, 3H), 3.84 (s, 3H), 4.23 (d, J = 13.0 Hz, 1H), 4.44 (d, J = 13.0 Hz, 1H), 6.27 (s, 1H), 6.88 (s, 1H), 7.07 (s, 1H), 7.20 (m, 5H), 7.35 (m, 3H), 7.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 35.9, 64.0, 73.8, 113.2, 125.9, 127.6, 127.8, 127.9, 128.3, 128.4, 128.6, 129.8, 136.2, 142.5, 144.0, 166.9, 180.3; IR (KBr) 3030, 2922, 2850, 2360, 1644, 1576, 1409, 1286, 1225, 881, 736, 699 cm^{-1}; HRMS calcd. for $C_{22}H_{21}N_3O_2Na^+$ 382.1526; found 382.1519.

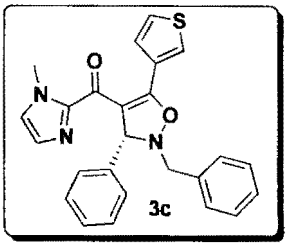
Table 14, Entry 1: The enantiomeric purity for **3a** was determined by HPLC (254 nm, 25 °C) t_R 8.6 min (minor), 9.5 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/*i*-PrOH, 90:10, 1mL/ min] as 86% ee for the cycloadduct.



(2-Benzyl-5-cyclopentyl-3-phenyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1*H*-imidazol-2-yl)methanone (3b):

Oil; $[\alpha]_D^{25}$ = -111.4 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3H), 4.15 (d, *J* = 13.0 Hz, 1H), 4.34 (d, *J* = 13.0 Hz, 1 H), 6.30 (s, 1H), 6.82 (s, 1H), 7.00 (m, 1H), 7.13 (m, 3H), 7.28 (m, 3H), 7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 26.5, 31.0, 31.4, 35.9, 37.4, 63.9, 73.4, 111.9, 125.8, 127.4, 127.6, 127.8, 128.2, 128.4, 128.5, 129.9, 136.2, 142.7, 144.3, 173.5, 180.3; IR (KBr) 2956, 2870, 1634, 1537, 1455, 1409, 1287, 862, 737, 698 cm^{-1}; HRMS calcd. for $C_{26}H_{27}N_3O_2Na^+$ 436.1995; found 436.1982.

Table 14, Entry 2: The enantiomeric purity for **3b** was determined by HPLC (254 nm, 25 °C) t_R 8.0 min (minor), 10.6 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 95:05, 1mL/ min] as 47% ee for the cycloadduct.

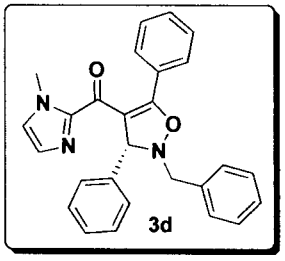


(2-Benzyl-3-phenyl-5-(thiophen-3-yl)-2,3-dihydroisoxazol-4-yl)(1-methyl-1*H*-imidazol-2-yl)methanone (3c):

Oil; $[\alpha]_D^{25}$ = -48.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.02 (s, 1H), 3.77 (s, 3H), 4.28 (d, *J* = 13.0 Hz, 1H), 4.51 (d, *J* = 13.0 Hz, 1 H), 6.55 (s, 1H), 6.85 (s, 1H), 7.02 (s, 1H), 7.14 (m, 5H), 7.31 (m, 5 H), 7.48 (m, 2H), 7.54 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.9, 58.5, 62.4, 63.5, 74.7, 74.8,

105.7, 125.2, 125.9, 127.4, 127.6, 127.7, 127.9, 128.4, 128.5, 128.6, 130.0, 131.6, 133.4, 136.3, 179.6, 190.6; IR (KBr) 2922, 1635, 1558, 1455, 1399, 1284, 847, 737, 697 cm^{-1}; HRMS calcd. for $C_{25}H_{21}N_3O_2SNa^+$ 450.1247; found 450.1220.

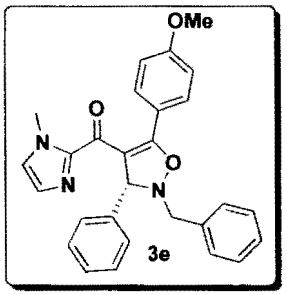
Table 14, Entry 3: The enantiomeric purity for **3c** was determined by HPLC (254 nm, 25 °C) t_R 20.5 min (minor), 29.0 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 90:10, 1mL/ min] as 72% ee for the cycloadduct.



(2-Benzyl-3,5-diphenyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1*H*-imidazol-2-yl)methanone (3d):

Foamy solid; $[\alpha]_D^{25}$ = -169.7 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.77 (s, 3H), 4.36 (d, *J* = 13.0 Hz, 1H), 4.59 (d, *J* = 13.0 Hz, 1H), 6.31 (s, 1H), 6.83 (s, 1H), 6.95 (s, 1H), 7.23 (m, 5H), 7.39 (m, 6H), 7.51 (m, 2H), 7.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.6, 63.4, 71.5, 75.3, 113.1, 125.6, 127.8, 127.9, 128.2, 128.4, 128.5, 128.6, 128.7, 129.6, 129.9, 131.1, 136.1, 141.7, 163.9, 188.0, 190.7; IR (KBr) 3029, 2924, 1637, 1567, 1490, 1402, 860, 755, 697 cm^{-1}; HRMS calcd. for $C_{27}H_{23}N_3O_2Na^+$ 444.1682; found 444.1703.

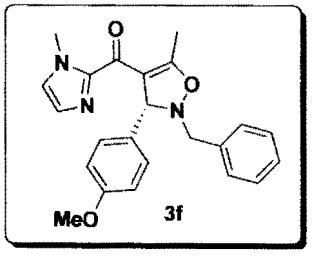
Table 14, Entry 4: The enantiomeric purity for **3d** was determined by HPLC (254 nm, 25 °C) t_R 29.3 min (minor), 47.5 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 95:05, 1mL/ min] as 77% ee for the cycloadduct.



(2-Benzyl-5-(4-methoxyphenyl)-3-phenyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1*H*-imidazol-2-yl)methanone (3e):

Foamy solid; $[\alpha]_D^{25}$ = -94.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.77 (s, 3H), 3.86 (s, 3H), 4.34 (d, *J* = 13.0 Hz, 1H), 4.57 (d, *J* = 13.0 Hz, 1H), 6.36 (s, 1H), 6.84 (s, 1H), 6.98 (s, 1H), 7.23 (m, 4H), 7.44 (m, 5H), 7.52 (m, 3H), 7.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.6, 55.6, 63.3, 71.5, 75.1, 113.7, 114.5, 125.5, 127.7, 127.9, 128.4, 128.5, 128.6, 128.7, 128.9, 129.3, 129.5, 129.9, 130.7, 131.7, 135.7, 190.7; IR (NaCl) 2960, 1602, 1564, 1507, 1456, 1255, 1148, 754, 703, 665 cm^{-1}; HRMS calcd. for $C_{28}H_{25}N_3O_3Na^+$ 474.1788; found 474.1786.

Table 14, Entry 5: The enantiomeric purity for **3e** was determined by HPLC (254 nm, 25 °C) t_R 29.2 min (minor), 33.2 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 90:10, 1mL/ min] as 70% ee for the cycloadduct.

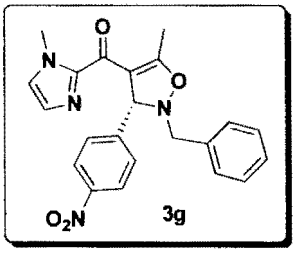


(2-Benzyl-3-(4-methoxyphenyl)-5-methyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1*H*-imidazol-2-yl)methanone (3f):

Foamy solid; $[\alpha]_D^{25}$ = -158.4 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.33 (s, 3H), 3.70 (s, 3H), 3.81 (s, 3H), 4.15 (d, *J* = 13.0 Hz, 1H), 4.36 (d, *J* = 13.0 Hz, 1 H), 6.14 (s, 1H), 6.70 (td, *J* = 8.8, 2.9 Hz, 2H), 6.84 (s, 1H), 7.01 (d, *J* = 1.0 Hz, 1H), 7.04 (td, *J* = 8.8, 2.9 Hz, 2H), 7.30 (m, 3H), 7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 35.9, 55.4, 63.8, 73.3, 113.3, 113.8, 125.8, 127.8, 128.3, 128.5, 129.0, 129.7,

134.6, 136.3, 144.0, 159.0, 166.7, 180.4; IR (KBr) 3061, 2924, 1640, 1590, 1407, 1285, 1226, 879, 737, 700 cm^{-1}; HRMS calcd. for $C_{23}H_{23}N_3O_2Na^+$ 412.1632; found 412.1624.

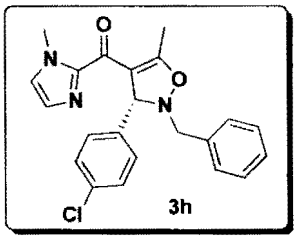
Table 13, Entry 6: The enantiomeric purity for **3f** was determined by HPLC (254 nm, 25 °C) t_R 18.2 min (minor), 20.1 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 95:05, 1mL/ min] as 73% ee for the cycloadduct.



(2-Benzyl-5-methyl-3-(4-nitrophenyl)-2,3-dihydroisoxazol-4-yl)(1-methyl-1*H*-imidazol-2-yl)methanone (3g):

Foamy solid; $[\alpha]_D^{25}$ = -94.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.39 (d, *J* = 1 Hz, 3H), 3.86 (s, 3H), 4.15 (*d*, J = 13.0 Hz, 1H), 4.42 (d, *J* = 13 Hz, 1H), 6.35 (s, 1H), 6.98 (d, *J* = 1.0 Hz, 1H), 6.99 (d, *J* = 1.0 Hz, 1H), 7.31 (m, 7H), 7.99 (dt, *J* = 8.9, 2.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 36.3, 64.0, 72.8, 112.1, 123.6, 124.0, 126.5, 128.3, 128.5, 128.8, 129.8, 135.4, 143.5, 147.3, 150.1, 167.9, 179.4; IR (KBr) 3029, 2926, 1642, 1582, 1521, 1409, 1347, 1265, 1220, 881, 738, 702 cm^{-1}; HRMS calcd. for $C_{22}H_{20}N_4O_4Na^+$ 427.1377; found 427.1383.

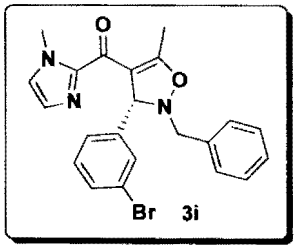
Table 13, Entry 8: The enantiomeric purity for **3g** was determined by HPLC (254 nm, 25 °C) t_R 24.7 min (major), 38.5 min (minor) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 95:05, 1mL/ min] as 51% ee for the cycloadduct.



(2-Benzyl-3-(4-chlorophenyl)-5-methyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1*H*-imidazol-2-yl)methanone (3h):

Foamy solid; $[\alpha]_D^{25}$ = -6.7 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.39 (s, 3H), 3.87 (s, 3H), 4.19 (d, *J* = 13.0 Hz, 1H), 4.43 (d, *J* = 13.0 Hz, 1H), 6.24 (s, 1H), 6.90 (s, 1H), 7.05 (s, 1H), 7.09-7.10 (m, 2H), 7.15-7.17 (d, 2H), 7.35 (m, 3H), 7.41-7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 36.1, 63.9, 73.1, 112.8, 126.2, 128.1, 128.4, 128.5, 128.7, 129.3, 129.8, 133.2, 135.9, 141.1, 143.8, 167.2, 179.2; IR (KBr) 2925, 1642, 1581, 1410, 1372, 1265, 1223, 1089, 1015, 881, 738, 701, 663 cm^{-1}; HRMS calcd. for $C_{22}H_{20}ClN_3O_2Na^+$ 416.1121; found 416.1136.

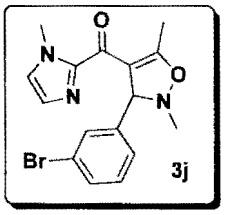
Table 13, Entry 7: The enantiomeric purity for **3h** was determined by HPLC (254 nm, 25 °C) t_R 14.6 min (minor), 15.6 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 95:05, 1mL/ min] as 56% ee for the cycloadduct.



(2-Benzyl-3-(3-bromophenyl)-5-methyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1*H*-imidazol-2-yl)methanone (3i):

Foamy solid; $[\alpha]_D^{25}$ = -78.4 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.38 (s, 3H), 3.86 (s, 3H), 4.16 (d, *J* = 13.0 Hz, 1H), 4.40 (d, *J* = 13.0 Hz, 1H), 6.23 (d, *J* = 1.0 Hz, 1H), 6.89 (d, *J* = 1.0 Hz, 1H), 7.04 (m, 3H), 7.34 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 36.0, 63.9, 73.1, 112.5, 122.5, 126.1, 126.5, 128.0, 128.4, 128.6, 129.7, 129.9, 130.6, 130.9, 135.8, 143.8, 144.9, 167.5, 179.9; IR (KBr) 3013, 1641, 1579, 1473, 1409, 1287, 1217, 1071, 879, 757, 700, 666 cm^{-1}; HRMS calcd. for $C_{22}H_{20}BrN_3O_2Na^+$ 460.0631; found 460.0628.

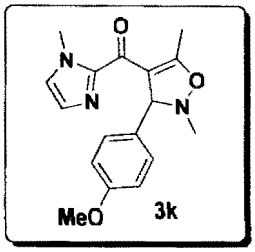
Table 13, Entry 5: The enantiomeric purity for **3i** was determined by HPLC (254 nm, 25 °C) t_R 7.5 min (major), 11.2 min (minor) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 90:10, 1mL/ min] as 67% ee for the cycloadduct.



(3-(4-Bromophenyl)-2,5-dimethyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1*H*-imidazol-2-yl)methanone (3j):

Foamy solid; $[\alpha]_D^{25}$ = -76.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 2.97 (s, 3H), 3.82 (s, 3H), 5.95 (s, 1H), 6.86 (s, 1H), 7.02 (s, 1H), 7.06 (s, 1H), 7.16 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.27 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 36.1, 47.7, 76.1, 112.4, 122.6, 126.2, 126.5, 128.3, 130.1, 130.8, 130.9, 143.8, 144.9, 167.2, 179.8; IR (KBr) 2961, 1641, 1581, 1409, 1372, 1409, 1287, 1226, 1071, 880, 758 cm^{-1}; HRMS calcd. for $C_{16}H_{16}BrN_3O_2Na^+$ 384.0318; found 384.0307.

Table 13, Entry 1: The enantiomeric purity for **3j** was determined by HPLC (254 nm, 25 °C) t_R 6.9 min (minor), 8.7 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 90:10, 1mL/ min] as 58% ee for the cycloadduct.

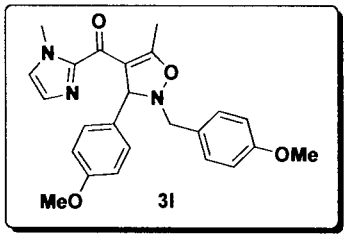


(3-(4-Methoxyphenyl)-2,5-dimethyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1*H*-imidazol-2-yl)methanone (3k):

Foamy solid; $[\alpha]_D^{25}$ = -68.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.35 (s, 3H), 2.96 (s, 3H), 3.71 (s, 3H), 3.79 (s, 3H), 5.87 (s, 1H), 6.73 (dt, *J* = 8.6, 2.9 Hz, 2H), 6.83 (s, 1H), 7.02 (s, 1H), 7.15 (dt, *J* = 8.7, 2.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 35.9, 47.5, 55.4, 76.3, 113.2, 113.9, 125.8, 128.2,

128.9, 134.5, 144.0, 159.2, 166.6, 180.4; IR (KBr) 2917, 2848, 1652, 1558, 1540, 1521, 1506, 1472, 1456, 1247 cm^{-1}; HRMS calcd. for $C_{17}H_{19}N_3O_3Na^+$ 336.1319; found 336.1299.

Table 13, Entry 2: The enantiomeric purity for **3k** was determined by HPLC (254 nm, 25 °C) t_R 10.6 min (minor), 16.3 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/*i*-PrOH, 90:10, 1mL/ min] as 74% ee for the cycloadduct.



3l

(2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-5-methyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1*H*-imidazol-2-yl)methanone (3l):

Foamy solid; $[\alpha]_D^{25}$ = -157.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.38 (s, 3H), 3.73 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 4.13 (d, *J* = 13.0 Hz, 1H), 4.34 (d, *J* = 13.0 Hz, 1H), 6.18 (s, 1H), 6.73 (dt, *J* = 8.8, 2.0Hz, 2H), 6.87 (s, 1H), 6.89 (dt, *J* = 8.7, 2.9 Hz, 2H), 7.07 (dt, *J* = 10.2, 2.9 Hz, 3H), 7.36 (dt, *J* = 10.2, 2.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 35.9, 55.4, 55.5, 63.2, 73.0, 113.2, 113.8, 114.0, 125.9, 128.3, 128.4, 129.0, 131.1, 134.7, 144.0, 159.0, 159.4, 166.8, 180.4; IR (KBr) 3001, 2956, 2836, 1641, 1584, 1512, 1462, 1408, 1247, 1175, 1033, 881, 828, 665 cm^{-1}; HRMS: *m/z* calcd. for $C_{24}H_{25}N_3O_4Na^+$ 442.1737; found 442.1744.

Table 13, Entry 3: The enantiomeric purity for **3l** was determined by HPLC (254 nm, 25 °C) t_R 19.0 min (minor), 24.6 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 90:10, 1mL/ min] as 76% ee for the cycloadduct.

Assignment of Absolute Stereochemistry:

The absolute stereochemistry for cycloadduct **3k** has been assigned as R based on the crystal structure for cycloadduct **3k**.

Crystal Structure for Cycloadduct 3k:

A specimen of $C_{17}H_{19}N_3O_3$, approximate dimensions 0.25 mm x 0.33 mm x 0.36 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

The total exposure time was 10.96 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using an orthorhombic unit cell yielded a total of 14391 reflections to a maximum θ angle of 67.25° (0.84 Å resolution), of which 2612 were independent (average redundancy 5.510, completeness = 95.7%, R_{int} = 2.64%, R_{sig} = 1.85%) and 2608 (99.85%) were greater than $2\sigma(F^2)$. The final cell constants of $\underline{a}$ = 8.8601(2) Å, $\underline{b}$ = 12.1048(3) Å, $\underline{c}$ = 14.5466(3) Å, volume = 1560.12(6) $Å^3$, are based upon the refinement of the XYZ-centroids of 9913 reflections above 20 σ(I) with 9.505° < 2θ < 134.0°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.884. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6655 and 0.7529. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 21 21 21, with Z = 4 for the formula unit, $C_{17}H_{19}N_3O_3$. The final anisotropic full-matrix least-squares refinement on F^2 with 216 variables converged at R1 = 2.48%, for the observed data and wR2 = 6.96% for all data. The goodness-of-fit was 1.094.

The largest peak in the final difference electron density synthesis was 0.203 $e^-/Å^3$ and the largest hole was -0.176 $e^-/Å^3$ with an RMS deviation of 0.056 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.334 g/cm^3 and F(000), 664 e^-.

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APPENDIX A. CRYSTAL STRUCTURE DATA

Table 16: Sample and Crystal Data for 3k

Specification	Data
Identification code	kld2_Cu
Chemical formula	$C_{17}H_{19}N_3O_3$
Formula weight	313.35
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal size	0.25 x 0.33 x 0.36 mm
Crystal system	orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 8.8601(2) Å α = 90°
	b = 12.1048(3) Å β = 90°
	c = 14.5466(3) Å γ = 90°
Volume	1560.12(6) $Å^3$
Z	4
Density (calculated)	1.334 Mg/cm^3
Absorption coeffi ient	0.762 mm^{-1}
F(000)	664
Identification code	kld2_Cu
Chemical formula	$C_{17}H_{19}N_3O_3$
Formula weight	313.35
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal size	0.25 x 0.33 x 0.36 mm
Crystal system	orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 8.8601(2) Å α = 90°
	b = 12.1048(3) Å β = 90°
	c = 14.5466(3) Å γ = 90°
Volume	1560.12(6) $Å^3$
Z	4

Table 16. Continued	
Density (calculated)	1.334 Mg/cm^3
Absorption coefficient	0.762 mm^{-1}
F(000)	664

Table 17: Data Collection and Structure Refinement for 3k

Specification	Data
Theta range for data collection	4.75 to 67.25°
Index ranges	-9<=h<=8, -14<=k<=14, -17<=l<=16
Reflections collected	14391
Independent reflections	2612 [R(int) = 0.0264]
Coverage of independent reflections	95.70%
Absorption correction	multi-scan
Max. and min. transmission	0.7529 and 0.6655
Structure solution technique	direct methods
Structure solution program	SHELXS-97 (Sheldrick, 2008)
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-97 (Sheldrick, 2008)
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	2612 / 0 / 216
Goodness-of-fit on F^2	1.094
Final R indices	2608 data; $I>2\sigma(I)$ R1 = 0.0248, wR2 = 0.0696
	all data R1 = 0.0248, wR2 = 0.0696
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0424P)^2+0.2369P]$ where $P=(F_o^2+2F_c^2)/3$
Largest diff. peak and hole	0.203 and -0.176 $eÅ^{-3}$
R.M.S. deviation from mean	0.056 $eÅ^{-3}$

Table 18: Atomic Coordinates and Equivalent Isotropic Atomic Displacement Parameters ($Å^2$) for 3k

	x/a	y/b	z/c	U(eq)*
O1	0.94840(11)	0.92704(7)	0.17548(6)	0.0248(2)
O2	0.01681(11)	0.44906(7)	0.93977(6)	0.0258(2)
O3	0.81052(11)	0.28118(7)	0.15698(6)	0.0274(2)
N1	0.51396(14)	0.34461(8)	0.20771(7)	0.0260(3)
N2	0.88940(13)	0.52163(8)	0.91127(7)	0.0240(2)
N3	0.52276(13)	0.47806(9)	0.10173(7)	0.0257(2)
C1	0.55517(19)	0.25438(11)	0.27014(10)	0.0336(3)
C2	0.60013(15)	0.39661(10)	0.14211(8)	0.0217(3)
C3	0.75391(16)	0.36219(9)	0.11785(8)	0.0211(3)
C4	0.83309(15)	0.42097(9)	0.04524(8)	0.0201(3)
C5	0.79187(15)	0.52644(10)	0.99528(8)	0.0205(3)
C6	0.82666(15)	0.63133(9)	0.04853(8)	0.0199(3)
C7	0.93191(15)	0.63564(10)	0.11925(8)	0.0223(3)
C8	0.97000(15)	0.73503(10)	0.16078(9)	0.0226(3)
C9	0.90196(15)	0.83279(10)	0.13104(8)	0.0214(3)
C10	0.89149(16)	0.03004(10)	0.14171(9)	0.0275(3)
C11	0.75618(15)	0.72930(10)	0.02249(9)	0.0240(3)
C12	0.79286(15)	0.82989(10)	0.06306(9)	0.0242(3)
C13	0.96821(15)	0.38818(10)	0.01244(8)	0.0225(3)
C14	0.81445(17)	0.45978(11)	0.83726(9)	0.0277(3)
C15	0.07477(17)	0.29981(10)	0.04104(10)	0.0284(3)
C16	0.38539(16)	0.47774(12)	0.14269(9)	0.0308(3)
C17	0.37797(17)	0.39610(12)	0.20799(10)	0.0317(3)

*U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 19: Bond Lengths (Å) for 3k

Bonds	Bond Angles (°)	Bonds	Bond Angles (°)
O1-C9	1.3744(14)	O1-C10	1.4317(15)
O2-C13	1.3586(15)	O2-N2	1.4893(14)
O3-C3	1.2399(15)	N1-C17	1.357(2)
N1-C2	1.3746(17)	N1-C1	1.4666(18)
N2-C14	1.4698(17)	N2-C5	1.4979(16)
N3-C2	1.3369(17)	N3-C16	1.3552(18)
C1-H1A	00001	C1-H1B	00001
C1-H1C	00001	C2-C3	1.4678(19)
C3-C4	1.4540(17)	C4-C13	1.3485(19)
C4-C5	1.5138(16)	C5-C6	1.5190(16)
C5-H5	0.998(15)	C6-C7	1.3894(18)
C6-C11	1.3927(17)	C7-C8	1.3879(17)
C7-H7	00001	C8-C9	1.3966(17)
C8-H8	00001	C9-C12	1.3833(18)
C10-H10A	00001	C10-H10B	00001
C11-H11	00001	C12-H12	00001
C13-C15	1.4862(18)	C14-H14A	00001
C14-H14B	00001	C14-H14C	00001
C15-H15A	00001	C15-H15B	00001
C15-H15C	00001	C16-C17	1.372(2)
C16-H16	00001	C17-H17	00001

Table 20: Bond Angles (°) for 3k

Bonds	Bond Angles (°)	Bonds	Bond Angles (°)
C9-O1-C10	117.14(10)	C13-O2-N2	107.24(10)
C17-N1-C2	106.56(11)	C17-N1-C1	124.15(12)
C2-N1-C1	129.24(12)	C14-N2-O2	104.24(9)
C14-N2-C5	110.90(10)	O2-N2-C5	103.48(8)
C2-N3-C16	105.38(11)	N1-C1-H1A	109.5
N1-C1-H1B	109.5	H1A-C1-H1B	109.5
N1-C1-H1C	109.5	H1A-C1-H1C	109.5
H1B-C1-H1C	109.5	N3-C2-N1	110.97(12)
N3-C2-C3	125.43(11)	N1-C2-C3	123.54(11)

Table 20 Continued

O3-C3-C4	121.69(12)	O3-C3-C2	119.32(11)
C4-C3-C2	118.93(11)	C13-C4-C3	122.78(11)
C13-C4-C5	107.01(11)	C3-C4-C5	130.17(11)
N2-C5-C4	102.69(9)	N2-C5-C6	109.36(10)
C4-C5-C6	114.28(10)	N2-C5-H5	107.2(8)
C4-C5-H5	112.3(8)	C6-C5-H5	110.5(8)
C7-C6-C11	118.06(11)	C7-C6-C5	123.04(11)
C11-C6-C5	118.82(11)	C8-C7-C6	121.20(11)
C8-C7-H7	119.4	C6-C7-H7	119.4
C7-C8-C9	119.65(12)	C7-C8-H8	120.2
C9-C8-H8	120.2	O1-C9-C12	124.51(11)
O1-C9-C8	115.37(11)	C12-C9-C8	120.10(11)
O1-C10-H10A	109.5	O1-C10-H10B	109.5
H10A-C10-H10B	109.5	O1-C10-H10C	109.5
H10A-C10-H10C	109.5	H10B-C10-H10C	109.5
C12-C11-C6	121.67(12)	C12-C11-H11	119.2
C6-C11-H11	119.2	C9-C12-C11	119.25(11)
C9-C12-H12	120.4	C11-C12-H12	120.4
C4-C13-O2	113.40(11)	C4-C13-C15	132.59(12)
O2-C13-C15	114.01(12)	N2-C14-H14A	109.5
N2-C14-H14B	109.5	H14A-C14-H14B	109.5
N2-C14-H14C	109.5	H14A-C14-H14C	109.5
H14B-C14-H14C	109.5	C13-C15-H15A	109.5
C13-C15-H15B	109.5	H15A-C15-H15B	109.5
C13-C15-H15C	109.5	H15A-C15-H15C	109.5
H15B-C15-H15C	109.5	N3-C16-C17	110.45(13)
N3-C16-H16	124.8	C17-C16-H16	124.8
N1-C17-C16	106.63(12)	N1-C17-H17	126.7
C16-C17-H17	126.7		

Table 21: Anisotropic Atomic Displacement Parameters* ($Å^2$) for 3k

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0293(5)	0.0145(4)	0.0305(5)	-0.0019(3)	-0.0034(4)	0.0004(4)
O2	0.0254(5)	0.0215(4)	0.0306(5)	0.0003(4)	0.0049(4)	0.0005(4)
O3	0.0316(5)	0.0199(4)	0.0307(5)	0.0045(4)	-0.0027(4)	0.0016(4)
N1	0.0326(7)	0.0221(5)	0.0234(5)	-0.0017(4)	0.0040(5)	-0.0058(5)
N2	0.0262(6)	0.0200(5)	0.0257(5)	0.0003(4)	0.0013(4)	0.0019(5)
N3	0.0253(6)	0.0267(5)	0.0249(5)	0.0001(4)	-0.0001(4)	0.0015(5)
C1	0.0480(9)	0.0232(6)	0.0298(7)	0.0048(6)	0.0079(6)	-0.0054(6)
C2	0.0261(7)	0.0185(5)	0.0204(6)	-0.0008(5)	0.0009(5)	-0.0027(5)
C3	0.0274(7)	0.0149(5)	0.0211(5)	-0.0023(4)	-0.0032(5)	-0.0017(5)
C4	0.0231(7)	0.0151(5)	0.0220(6)	-0.0020(4)	-0.0013(5)	-0.0009(5)
C5	0.0221(7)	0.0172(6)	0.0223(6)	0.0007(5)	0.0015(5)	0.0001(5)
C6	0.0224(7)	0.0160(5)	0.0213(6)	0.0008(5)	0.0036(5)	-0.0010(5)
C7	0.0233(7)	0.0178(6)	0.0257(6)	0.0030(5)	0.0009(5)	0.0019(5)
C8	0.0244(7)	0.0198(6)	0.0236(6)	0.0015(5)	-0.0016(5)	-0.0007(5)
C9	0.0240(7)	0.0166(6)	0.0236(6)	-0.0012(5)	0.0035(5)	-0.0014(5)
C10	0.0342(8)	0.0154(5)	0.0329(7)	0.0000(5)	-0.0015(6)	0.0020(6)
C11	0.0255(7)	0.0213(6)	0.0251(6)	0.0002(5)	-0.0030(5)	0.0023(5)
C12	0.0287(8)	0.0171(6)	0.0269(6)	0.0017(5)	-0.0013(5)	0.0041(5)
C13	0.0269(7)	0.0159(5)	0.0247(6)	-0.0023(5)	-0.0006(5)	-0.0027(5)
C14	0.0361(8)	0.0233(6)	0.0237(6)	-0.0013(5)	0.0027(6)	-0.0014(6)
C15	0.0279(7)	0.0217(6)	0.0355(7)	-0.0027(5)	0.0008(6)	0.0044(5)
C16	0.0242(7)	0.0369(7)	0.0313(7)	0.0036(6)	0.0024(5)	0.0027(6)
C17	0.0285(8)	0.0347(7)	0.0317(7)	-0.0052(6)	0.0079(6)	-0.0065(6)

*The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[\, h^2 a^{*2} U_{11} + \ldots + 2\, h\, k\, a^* b^* U_{12}\,]$

Table 22: Hydrogen Atomic Coordinates and Isotropic Atomic Displacement Parameters ($Å^2$) for 3k

	x/a	y/b	z/c	U(eq)
H1A	0.4676	0.2342	0.3077	0.05
H1B	0.6377	0.2784	0.3103	0.05
H1C	0.5877	0.1902	0.2342	0.05
H7	0.9786	0.5694	0.1395	0.027
H8	1.042	0.7366	0.2092	0.027
H10A	0.9131	1.0362	0.0758	0.041
H10B	0.9403	1.091	0.1746	0.041
H10C	0.7822	1.0334	0.1516	0.041
H11	0.6812	0.7274	-0.0241	0.029
H12	0.7435	0.8958	0.0443	0.029
H14A	0.8852	0.4491	-0.2138	0.042
H14B	0.7264	0.5013	-0.1844	0.042
H14C	0.7818	0.3877	-0.1394	0.042
H15A	1.0847	0.3001	0.1081	0.043
H15B	1.1737	0.3131	0.013	0.043
H15C	1.0362	0.2279	0.0208	0.043
H16	0.3055	0.5271	0.1282	0.037
H17	0.294	0.379	0.246	0.038
H5	0.6848(18)	0.5265(11)	-0.0259(9)	0.018(3)