Department of Chemistry

Synthesis and Reactions of 3-Unsubstituted 2-Isoxazolines

Antti Pohjakallio

Aalto University

DOCTORAL DISSERTATIONS

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Antti Pohjakallio

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Abstract

2-Isoxazolines are five-membered heterocyclic compounds that serve as versatile synthetic intermediates in organic chemistry. A number of important functional groups, including 1,3-hydroxycarbonyl compounds, β-hydroxynitriles, 1,3-diamines and α,β-unsaturated carbonyl compounds can be accessed via these heterocycles. The powerful 1,3-dipolar cycloaddition reaction between nitrile oxides and alkenes has long served as the most important method to synthesize 2-isoxazolines.

This thesis describes the discovery and development of a new synthetic approach to 3-unsubstituted 2-isoxazolines via subsequent conjugate addition and oxime transfer reactions. Small organic amines combined with various acids were found to catalyze the conjugate additions of oximes and N-hydroxycarbamates to α,β-unsaturated aldehydes. In the case of oximes, the conjugate addition intermediates underwent intramolecular oxime transfer reactions that resulted in the formation of 3-unsubstituted 2-isoxazoline products. Mechanistic studies verified that the isoxazoline formation proceeds via the conjugate addition intermediate and pointed out to acid catalysis in the oxime transfer process. The best catalyst, N-methylanilinium diphenylphosphate, enabled the synthesis of a broad range of racemic 3-unsubstituted 2-isoxazolines from enals with good efficiency. The acid mediated oxime transfer process was combined with a known enantioselective oxime conjugate addition reaction to provide the first enantioselective method for the synthesis of 3-unsubstituted 2-isoxazolines.

The 3-unsubstituted 2-isoxazolines can be converted to β-hydroxynitriles by a base catalyzed isomerization reaction. An improved method for the isomerization process was developed, and combining this with the newly developed enantioselective 2-isoxazoline synthesis was shown to enable an easy two-step synthesis of highly enantioenriched β-hydroxynitriles.

Keywords 2-isoxazoline, enantioselective synthesis, oxime transfer, amine catalysis, acid catalysis

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Tekijä
Antti Pohjakallio

Väitöskirjan nimi
3-Substituoimattomien 2-isoksatsoliinien synteesi ja reaktiot

Julkaisija Kemian tekniikan korkeakoulu

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Tiivistelmä

2-Isoksatsoliinit ovat heterosyklisiä yhdisteitä, joita voidaan käyttää monipuolisesti synteettisinä välivaiheina erilaisten hyödyllisten rakenneyksiköiden valmistamisessa. 2-Isoksatsoliinien hyödyllisyys on pitkään perustunut niiden helppoon synteesiin erityisesti sykloadditioreaktioiden avulla.

Tämän väitöskirjan tutkimusaiheena on ollut 3-substituoimattomien 2-isoksatsoliinien synteesi hyödyntäen oksiimien ja tyydyttymättömien aldehydien välisiä konjugaattiadditioreaktioita. Konjugaattiadditiotuotteita voitiin muodostaa katalysoimalla oksiimien ja tyydyttymättömien aldehydien välistä reaktiota erilaisilla amiinien ja orgaanisten happojen suoloilla. Aniliinisuolojen havaittiin kuitenkin katalysoivan myös 2-isoksatsoliinien muodostusta samoissa olosuhteissa. Mekanismitutkimukset todistivat konjugaattiadditiotuotteiden toimivan välituotteina prosessissa ja syklisoitumisen havaittiin olevan happokatalysoitu reaktio. *N*-Metyylianiliinin difenyylifosfaattisuola havaittiin parhaaksi katalyytiksi erilaisten raseemisten 3-substituoimattomien 2-isoksatsoliinien synteesiin.

Hapon välittämää molekyylin sisäistä oksiiminsiirtoreaktiota käytettiin myöhemmin apuna kehitettäessä uutta enantioselektiivistä menetelmää 3-substituoimattomien 2-isoksatsoliinien synteesiin. Yhdistämällä kirjallisuudessa raportoitu enantioselektiivinen konjugaattiadditioreaktio hapon välittämään oksiiminsiirtoreaktioon, oli mahdollista valmistaa useita erilaisia 2-isoksatsoliiniyhdisteitä optisesti hyvin puhtaassa muodossa ensimmäistä kertaa.

Työssä kehitettiin myös parannettu emäskatalysoitu menetelmä 3-substituoimattomattomien 2-isoksatsoliinien isomerisoimiseksi β-hydroksinitriileiksi. Yhdistämällä uusi menetelmä aiemmin kehitettyyn enantioselektiiviseen 2-isoksatsoliinisynteesiin, voitiin tyydyttymättömistä aldehydeistä valmistaa lähes optisesti puhtaita β-hydroksinitriilejä kahdessa reaktiovaiheessa.

Avainsanat 2-isoksatsoliini, enantioselektiivinen synteesi, oksiiminsiirto, amiinikatalyysi, happokatalyysi

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Hanna, being with you has brought me so much love, joy and happiness. Thank you for all the love and support!

Helsinki, February 2011
Antti Pohjakallio

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List of Publications

The thesis consists of an overview of the authors work and related literature and of the following publications. The publications are referred to in the text by their Roman numerals.

I Pohjakallio A.; Pihko, P. M. *Synlett* **2008**, 827-830.

II Pohjakallio, A.; Pihko, P. M. *Chem. Eur. J.* **2009**, *15*, 3960-3964.

III Pohjakallio, A; Pihko, P. M.; Laitinen, U. M. *Chem. Eur. J.* **2010**, *16*, 11325-11339.

IV Pohjakallio, A.; Pihko, P. M. Liu, J. *J. Org. Chem.* **2010**, *75*, 6712-6715.

Author's Contribution

The author has contributed to the publications as stated below.

I	The author designed the experiments with the co-author and carried out all the experiments and analyses. The article was written together with the co-author.
II	The author designed the experiments with the co-author and carried out all the experiments and analyses. The results were interpreted in collaboration with the co-author. The article was written together with the co-author.
III	The author designed the experiments with the co-author and carried out all the experiments and analyses. The co-author (U. M. L.) was responsible for finding the effect of catalyst impurities on the outcome of the enantioselective reaction. The results were interpreted and the article was written in collaboration with the co-author (P. M. P.).
IV	The author designed the experiments with the co-author and carried out all the reported experiments except the ones leading to entries 3, 4 and 5 in the Table 1. The results were interpreted and the article was written in collaboration with the co-author (P. M. P.).

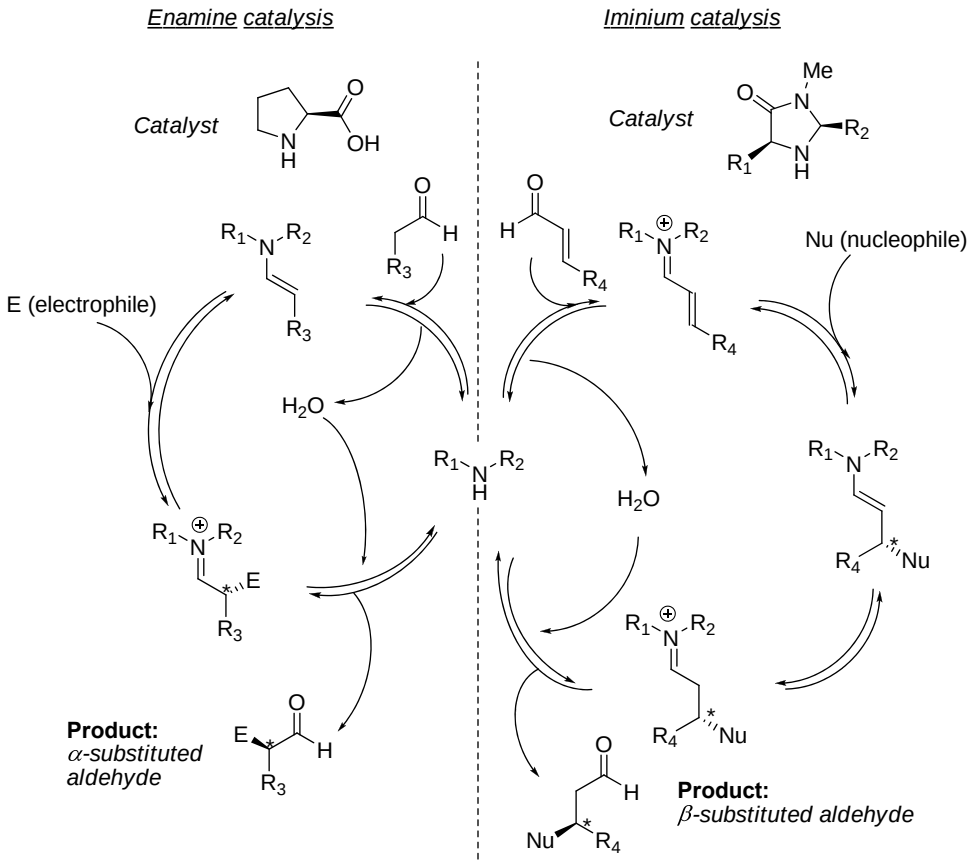
Abbreviations and Symbols

Ac	acetyl
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
cat.	catalytic amount
Cbz	benzyloxycarbonyl
Δ	symbol for heat
d	day
DBU	1,8-diazabicycloundec-7-ene
DCA	9,10-dicyanoanthracene
DIAD	diisopropylazodicarboxylate
DPP	diphenylphosphate
E	electrophile
EDG	electron donating group
EWG	electron withdrawing group
HOMO	highest occupied molecular orbital
KHMDS	potassium hexamethyldisilazide
LUMO	lowest unoccupied molecular orbital
NCS	*N*-chlorosuccinimide
Nu	nucleophile
o	*ortho*
p	*para*
PMB	*para*-methoxybenzyl
p-Ts	*para*-toluenesulfonyl
rt	room temperature
SET	single electron transfer
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Tr	triphenylmethyl

1 Introduction

Catalysis is a fundamental aspect of chemistry that will never lose its value as an important target of both basic and applied research. The virtues of catalytic chemical reactions – economy and control – are becoming increasingly important in the changing world that is facing the dearth of energy and materials.[1] Aside from being vital for a myriad of processes that provide raw materials and products for the modern industry, catalysis continues to excite fundamental researchers in chemistry as a treasure casket of possibilities as it often enables otherwise unfathomable reactivity between compounds.[2,3]

One of the most intensive research areas of the last decade in the organic chemistry has been asymmetric organocatalysis, the application of organic molecules as enantioselective catalysts.[4] The concept of controlling enantioselectivity with this type of catalysts was revitalized at the turn of the century through reports from several research groups that described catalytic enantioselective reactions of prochiral aldehydes with nucleophilic or electrophilic reagents.[5] The first new wave catalysts for these reactions were relatively simple enantiomerically pure secondary amines and their catalytic activity was based on the well-known formation of enamines and iminium ions in the presence of aliphatic and unsaturated aldehydes, respectively (Scheme 1). The enhanced nucleophilic and electrophilic character of these intermediates compared to the parent aldehydes was responsible for the catalytic activity and the equilibrium between the enamine/imine and the aldehyde forms enabled the turnover of the catalyst. The true discovery of these reports, however, was the remarkable chemo- and enantioselectivity shown by the amine catalysts that allowed the synthesis of highly enantioriched functionalized aldehydes with unprecedented ease. Depending on which intermediate is responsible for the enhanced reactivity the catalytic modes are now called enamine catalysis[6] or iminium catalysis[7] (Scheme 1).



Scheme 1. Enamine and iminium catalysis and their catalytic cycles

These discoveries have lead to an unprecedented rush for new synthetic methods in the field of organic chemistry.[8] For example, in attempts to push the envelope of iminium catalysis, nearly every imaginable suitable nucleophilic entity available has been engaged in a conjugate addition reaction with α,β-unsaturated aldehydes in an enantioselective manner within the last ten years.

The work presented within this thesis has also been inspired by these discoveries in catalysis. The original aim of the research was to study whether iminium catalysis could be applied to the enantioselective addition of oxygen nucleophiles to α,β-unsaturated aldehydes. While a catalytic reaction of this kind appeared to be interesting solely from a theoretical point of view, the expected reaction products, β-hydroxyaldehydes, are also potentially valuable building blocks as the products of a formal acetaldehyde aldol reaction.[9] However, as is often the case with research, serendipitous discoveries are made along the way. The efforts aimed at the development of the catalytic enantioselective oxygen conjugate addition reaction led to the discovery of another catalytic process in which the α,β–unsaturated aldehydes and oximes condensed to form chiral but racemic 3-unsubstituted 2-isoxazoline heterocycles. Despite the

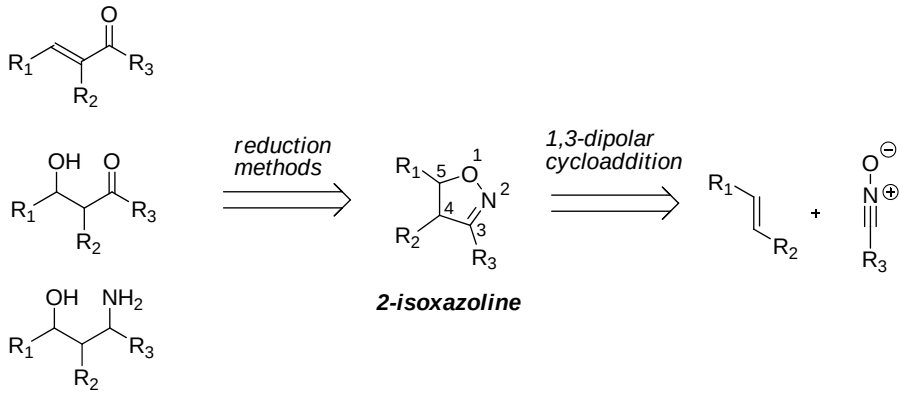
apparent simplicity of the reaction components, the reaction turned out to be totally unexplored. Equally surprisingly, the literature methods for the synthesis of 3-unsubstituted 2-isoxazolines turned out to be rather limited in scope or demanded quite exotic starting materials. Thus, application of right catalyst had offered us an opening to interesting reaction products that were difficult to access by other means. However, the full potential of the novel reaction and its products could only be realized by being able to control the reaction in a selective manner.

This thesis describes the efforts to develop and understand the catalytic condensations of α,β-unsaturated aldehydes and oximes. While the aims to understand the process were only partially achieved, the persistent experimentation and development of the reaction conditions led to a synthetically useful protocol for the preparation of 3-unsubstituted 2-isoxazolines.[I,II,III] More importantly, the information obtained from the process by both experimentation and literature surveys proved to be sufficient for the development of a catalytic enantioselective method.[II,III] As the first step into the chemistry of newly available enantioenriched 3-unsubstituted 2-isoxazolines, an improved base catalyzed method for their conversion into optically active β-hydroxy nitriles was also developed.[IV]

The following chapters provide a short literature review on the synthesis and reactions of 3-unsubstituted 2-isoxazolines. The chemistry developed within this thesis is then shortly reviewed.

2 General Remarks on 2-Isoxazolines

2-Isoxazolines are organic heterocyclic compounds that contain an *O*-alkyl oxime functionality within a 5-membered ring (Scheme 1). As a member of organic heterocyclic compounds, 2-isoxazolines draw interest as structural units of biologically active molecules.[10] In addition to this rather general potential, the 2-isoxazolines have an established position as valuable intermediates in the synthetic organic chemistry. This is attributed to their capacity to mask other functionalities within a stable form that allows both further functionalization of the ring and unveiling of the hidden properties in chemically orthogonal ways.[11] The most important structural units available from 2-isoxazolines include α,β-unsaturated ketones,[12] β-hydroxycarbonyl compounds[13] and 1,3-aminoalcohols.[14] All of these can be accessed from 2-isoxazolines by reductive cleavage of the heterocycle (Scheme 2).

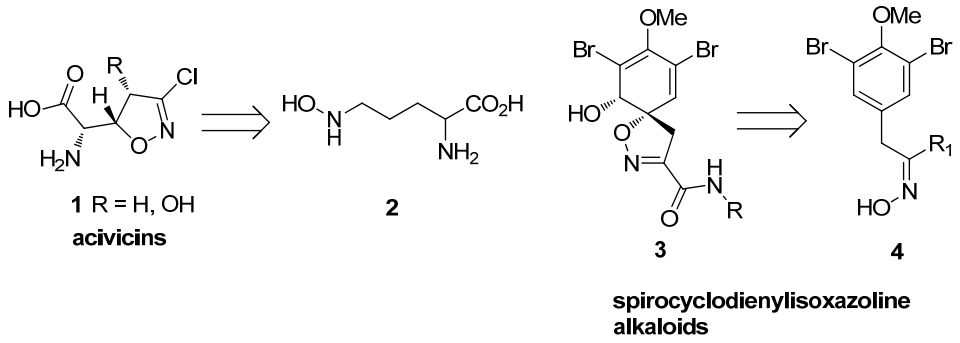


Scheme 2. A retrosynthetic scheme of 2-isoxazolines and their role as intermediates in organic synthesis

However, the status as a valuable synthetic intermediate is naturally tied to the easy synthetic availability of 2-isoxazolines themselves. In this regard, the importance of the 1,3-dipolar cycloaddition reaction of nitrile oxides with alkenes cannot be overstated as this reaction offers an exceptionally versatile and powerful tool for the synthesis of these heterocycles from chemically divergent components (Scheme 2).[15] Without this reaction, which is able to merge different molecular entities with a heterocyclic 2-isoxazoline linker, these compounds would not have enjoyed such a great success as a target of research in organic chemistry.

In fact, it can be argued that 2-isoxazolines themselves have turned out to be rather uninteresting motifs. For example, even though there are numerous studies of 2-isoxazolines as active medicinal compounds,[16] the ring structure was not present in any

of the 200 most sold pharmaceuticals in 2008.[17] Similarly, the 2-isoxazoline ring appears to be a rare functionality in secondary metabolites found in nature. 2-Isoxazolines are encountered only within a relatively small group of compounds called isoxazole alkaloids.[18] Among the most notable 2-isoxazoline members of these alkaloids are acivicins **1**[19] and marine based bromotyrosine derivatives, spirocyclohexadienylisoxazoline and spirooxepinisoxazoline alkaloids **3** (Scheme 3).[20]



Scheme 3. Natural biosynthetic approaches to 2-isoxazoline ring

A closer look at the biosynthetic proposals of these compounds reveals that nature's way to assemble the 2-isoxazoline ring differs considerably from the main laboratory approach.[20, 21,22] Instead of employing a new carbon-carbon bond-forming cycloaddition reaction, nature appears to build the heterocycle by intramolecular cyclization reactions of late-stage biosynthetic intermediates containing an N-O-functionality such as an oxime or a hydroxylamine.

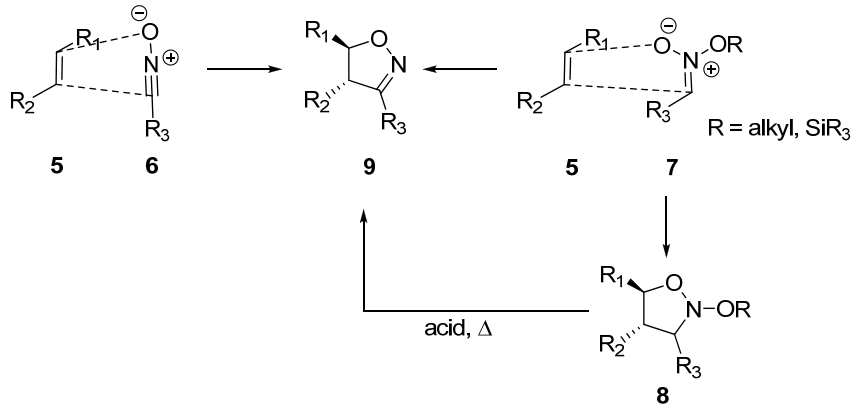
The cyclization reactions employed by the nature also mirror the complementary ways to synthesize 2-isoxazolines in laboratory. Even though cycloaddition reactions have an established position as the most important way to synthesize these compounds, other less widely used approaches exist. These usually involve reactions where one or more bonds between the heteroatoms and the pre-existing carbon chain are formed. As a consequence, the carbon chain has to be synthesized by other means before the formation of the heterocycle and this can usually be considered a major disadvantage for the total efficiency of the process. Thus, whenever the approaches outside 1,3-dipolar cycloaddition are evaluated – or new such strategies are envisioned – special attention should be paid to the possible benefits in the substrate scope and selectivity over the cycloaddition chemistry.

3 Synthesis of 3-Unsubstituted 2-Isoxazolines

3-Unsubstituted 2-isoxazolines are a relatively rare class of 2-isoxazoline compounds that contain only a hydrogen atom at the 3-position of the ring. This rather small modification to the ring has quite a remarkable impact on both the synthesis and the synthetic use of this type of 2-isoxazolines when compared to 3-substituted compounds. Most importantly, the synthesis of 3-unsubstituted 2-isoxazolines via the nitrile oxide cycloaddition is notably more challenging than that of many other 2-isoxazolines due to specific reactivity of the one-carbon dipole, formonitrile oxide. Moreover, the strategic advantage of the cycloaddition approach over other synthetic methods diminishes as the dipole component only adds one carbon to the chain and the ability to link molecular fragments is not used to its full potential. These factors emphasize the role of other synthetic approaches towards these compounds. In this chapter, the existing methods to arrive at 3-unsubstituted 2-isoxazolines are introduced. The emphasis is on methods that seem to enable the synthesis from relatively simple starting materials and potentially have broad applicability. Curiosities tied to specific, more complex substrates are omitted.

3.1 CYCLOADDITION METHODS

As stated above, the most important and versatile method to synthesize 2-isoxazolines is the 1,3-dipolar cycloaddition reaction between a nitrile oxide and an alkene.[15] This pericyclic reaction constructs the heterocycle from highly divergent, yet readily available components in a reaction that concertedly creates new carbon-carbon and oxygen-carbon bonds (Scheme 4). In addition to nitrile oxides, alternative 1,3-dipoles called alkyl or silyl nitronates[15] can be used to arrive at the same 2-isoxazoline products. The reaction between alkyl or silyl nitronate and an alkene yields *N*-alkoxy or *N*-silyloxyisoxazolidines that upon heating or treatment with acid form the 2-isoxazoline.



Scheme 4. Nitrile oxide and silyl nitronate cycloadditions in the synthesis of 2-isoxazolines

The synchronous 1,3-dipolar cycloaddition reaction is generally stereospecific and the stereochemistry of the alkene is transferred to the products. The difficulties associated with these reactions usually arise from the non-perfect regioselectivity of the cycloaddition reaction. These problems are often particularly severe when disubstituted alkenes are used as starting materials, and they can be understood by dissecting the possible interactions between the reactants (Figure 1).

When the reaction components interact to form a pre-transition state assembly, the orientation of the reactants is dictated by the sum of favourable and unfavourable electronic and steric interactions between the reaction components. In 1,3-dipole cycloaddition chemistry, the most important interactions between the dipole and dipolarophile are the ones between the highest occupied molecular orbitals (HOMO) and the lowest occupied molecular orbitals (LUMO) of the components (Figure 1). In nitrile oxide cycloadditions, the strongest interaction between the reactants is usually between the HOMO of the alkene and the LUMO of the nitrile oxide.[23]

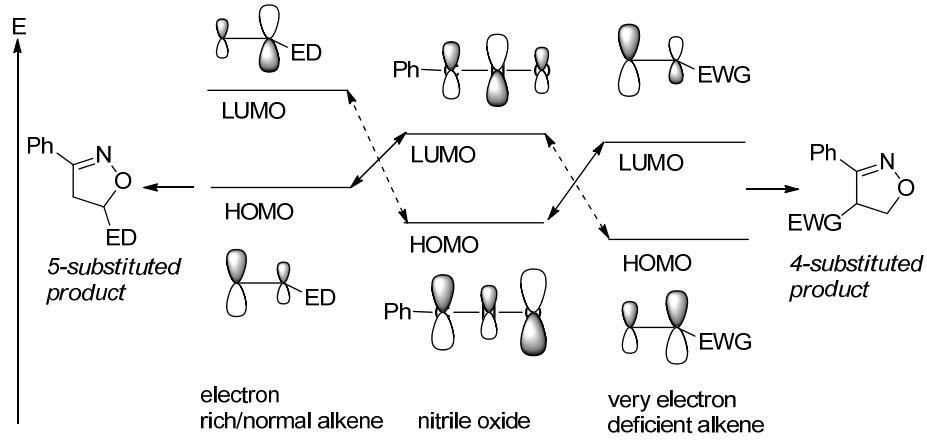


Figure 1. Orbital interactions dictate the outcome of the cycloaddition reactions

The regioselectivity towards the 5-substituted isoxazoline product is the usual result of this interaction, because the largest orbital coefficients of the alkene HOMO and the dipole LUMO are on the unsubstituted end of the alkene and on the dipole carbon, respectively.[23] If the alkene is disubstituted, the orbital coefficients are usually closer to equal, and the regioselectivity drops as a consequence. On the other hand, if a monosubstituted alkene is very electron deficient and has a very low-lying LUMO, the interaction between the LUMO of the alkene and the HOMO of the dipole may become important and consequently the fraction of the 4-subsituted product increases. The reason for this is that the largest coefficient of nitrile oxide HOMO resides on the electronegative oxygen and the LUMO of the electron deficient alkene has its largest coefficient at the unsubstituted end of the alkene. However, the regiochemistry is not solely dictated by the orbital interactions and other factors such as tethering of the reaction components by metal coordination[24] and steric interactions[25] may strongly favour or disfavour one of the transition states.

Structure calculations of the alkyl nitronate dipoles have suggested that the largest orbital coefficient in both the HOMO and the LUMO of the dipole would be on the carbon.[26] As such, the formation of 5-substituted products should be expected in reactions of both electron deficient and electron rich monosubstituted alkenes with alkyl nitronates and related dipoles.

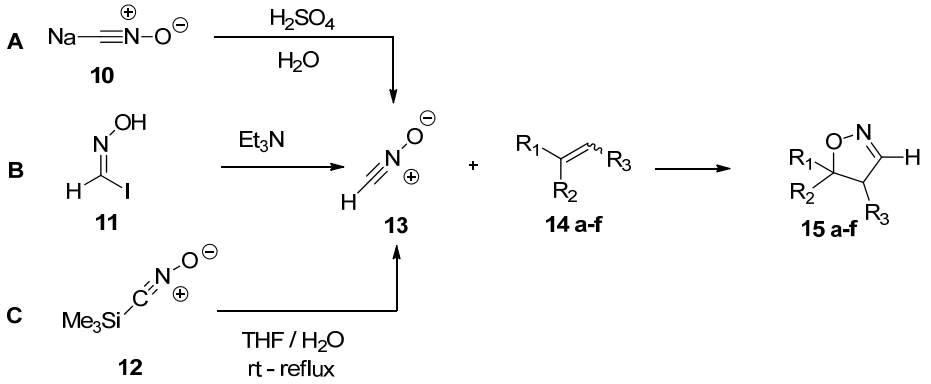
3.1.1 CYCLOADDITION OF ALKENES WITH FORMONITRILE OXIDE

Formonitrile oxide, also known as fulminic acid, can be considered the simplest nitrile oxide and thus the parent compound of nitrile oxides. Even though its structure was revealed over 100 years ago,[27] it is perhaps one of the least synthetically used nitrile oxides today. The first cycloadditions of fulminic acid with acetylene were reported by Quilico in 1939.[28] Similar results with olefins, yielding 3-unsubstituted 2-isoxazolines, were later reported with by Quilico and others.[29] Huisgen and Christl studied the use of fulminic acid in nitrile oxide cycloadditions with a variety of olefinic dipolarophiles and their studies proved its definite yet limited utility in the synthesis of 3-unsubstituted 2-isoxazolines.[30]

On paper, the cycloaddition of fulminic acid with olefins presents a straightforward route to 3-unsubstituted 2-isoxazolines. The problems associated with this reaction arise from the chemical properties of fulminic acid. While all nitrile oxides have tendency to dimerize to furoxanes with variable rates in the absence of other dipolarophiles, fulminic acid oligomerizes to dimers, trimers and tetramers quite rapidly and its half-life in acidic (pH 1) 0.4 M aqueous solution at 0 °C is only 70 minutes.[31] Thus if a reaction with another, preferably more active dipolarophile is desired, fulminic acid has to be generated slowly from a precursor in the presence of the dipolarophile. Fulminic acid is also highly toxic and the metal fulminates needed for the preparation of either fulminic acid or its more convenient precursors, are highly explosive.

The traditional way of generating fulminic acid for synthetic and other purposes is to liberate it from its salts by treatment with acid (Table 1).[28b,31] In this method the reactants had to be water soluble. Quilico and later Huisgen and Christl used the reasonably stable and soluble formohydroxamoyl iodide as the fulminic acid precursor[30b] and their experiments showed that the cycloaddition was only successful with reactive dipolarophiles. An excess of the fulminic acid precursor had to be used to obtain good yields. Later, De Sarlo and co-workers showed that by using the stable trimethylsilanecarbonitrile oxide as the precursor, the yields of the possible cycloadditions can be improved to a good level, even when equimolar amounts of reagents are used.[32] There are also other ways to generate fulminic acid, but these have not been used in the synthesis of 2-isoxazolines.[33]

Table 1. Cycloadditions of fulminic acid with alkenes[30,32]



15	R_1	R_2	R_3	Method	Yield (%)
a)	Ph	H	H	B, C	B: 70, C: 76
b)	CO_2Me	H	H	B	93
c)	CO_2Me	H	Me	B	36[a]
d)	CO_2Me	Me	H	C	80
e)	H			B, C	B: 76 C: 87
f)	H			B	8

[a] 68 : 32 of regioisomers favoring **15c**

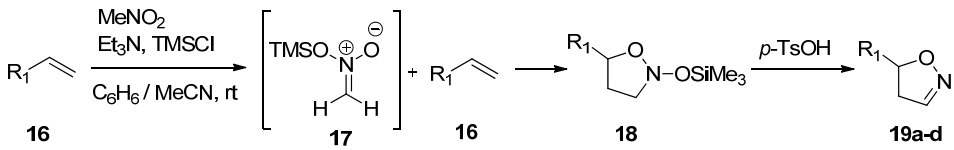
The scope of the alkene dipolarophiles used in the studies mentioned above is quite narrow. Only styrenes, acrylates and bicyclic strained alkenes such as norbornene and norbornadiene have given successful results (Table 1).[30,32] The reactions of terminal alkenes show perfect regioselectivity towards the 5-substituted 2-isoxazoline. However, disubstituted non-symmetrical alkenes such as methyl crotonate and methyl cinnamate reacted more slowly and additionally gave mixtures of regioisomers.[30b]

In conclusion, even though 1,3-dipolar cycloadditions of fulminic acid present a conceptually simple route to 3-unsubstituted 2-isoxazolines, the rather narrow substrate scope limits the use of this reaction in synthetic applications. The applicability is also limited by the explosiveness and toxicity of fulminic acid and its precursors.

3.1.2 CYCLOADDITION OF ALKENES WITH SILYL NITRONATES OF NITROMETHANE

Nitronates constitute another group of dipoles that can be utilized in the synthesis of 2-isoxazolines. Alkyl and silyl nitronates can be generated by *O*-alkylation or silylation of the corresponding nitroalkane. Cycloadditions of these reagents with alkenes were first studied by Tartakovskii in the 1960's and early 1970's[34] but the studies of Torssell[13a,35] 10 years later established the more stable *O*-trimethylsilyl nitronates as the most suitable nitronate reagents for the synthesis of 2-isoxazolines. Specifically, the silyl nitronate of nitromethane is an advantageous one-carbon dipole in the synthesis of 3-unsubstituted 2-isoxazolines due to the difficulties associated with the formation and reactivity of formonitrile oxide. Even though silyl nitronates are generally much more stable than the nitrile oxides, they may decompose at high temperatures and are prone to hydrolysis under protic conditions.[36]

Multiple procedures have been reported for the synthesis of silyl nitronates[13a, 34a, 36, 37] *In situ* generation of the dipole is preferred in the cycloaddition applications. Thus, in the synthesis of 3-unsubstituted 2-isoxazolines, trimethylsilyl chloride is slowly added to the mixture of the dipolarophile, nitromethane and triethylamine at 0 °C (Scheme 5).[13a] Warming up the reaction to room temperature and long reaction times up to several days are typical.



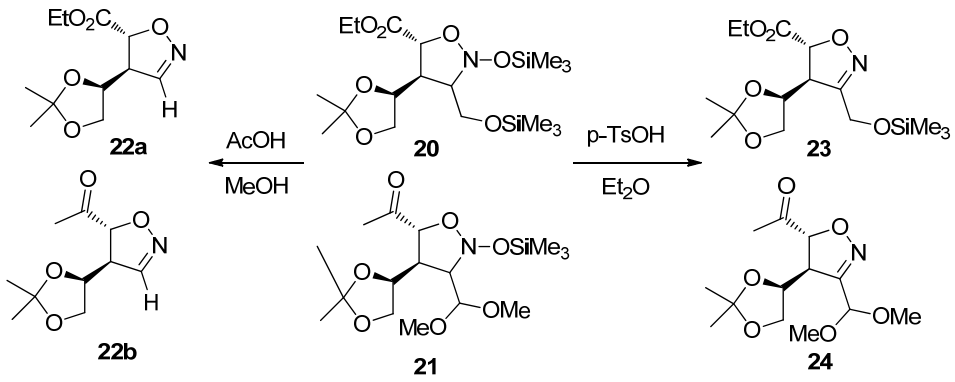
a) R_1 = vinyl, 52% yield
b) R_1 = CN, 62% yield
c) R_1 = Ph, 41% yield
d) R_1= CO_2Me, 34% yield

Scheme 5. Cycloadditions of trimethylsilylnitronate of nitromethane give 3-unsubstituted 2-isoxazolines after elimination of silanol from the isoxazolidine product[13a, 35]

As is the case with cycloadditions of fulminic acid, the reaction is practically limited to electron deficient[13a,35] or strained[38] alkenes. The reactions of non-activated alkenes with silyl nitronates are very slow or the reaction does not occur at all.[13a] However, even simple conjugation is enough to make an alkene reactive towards silyl nitronates and thus for example butadiene is a viable substrate.[35c] The primary product of the cycloaddition reaction, *N*-trimethylsiloxy 2-isoxazolidine, can be converted to the 2-isoxazoline by treatment with acid or by heating. In some applications this conversion has been reported to be spontaneous.[13a,39]

In addition to the trimethylsilyl nitronate of nitromethane, other nitronates have also been employed in the synthesis of 3-unsubstituted 2-isoxazolines. In their study of

diastereoselective silyl nitronate cycloadditions, Pätzel and co-workers observed a fragmentation reaction of the initial *N*-siloxyisoxazolidine products that yielded 3-unsubstituted 2-isoxazolines (Scheme 6).[39] Interestingly, the standard treatment of these intermediates with *p*-toluenesulfonic acid in diethyl ether gave the 3-substituted 2-isoxazolines, whereas fragmentations to give **22a-b** took place when the products were treated with less acidic acetic acid in methanol.



Scheme 6. Conversion of *N*-trimethylsiloxyisoxazolidines to 3-substituted and unsubstituted 2-isoxazolines[39]

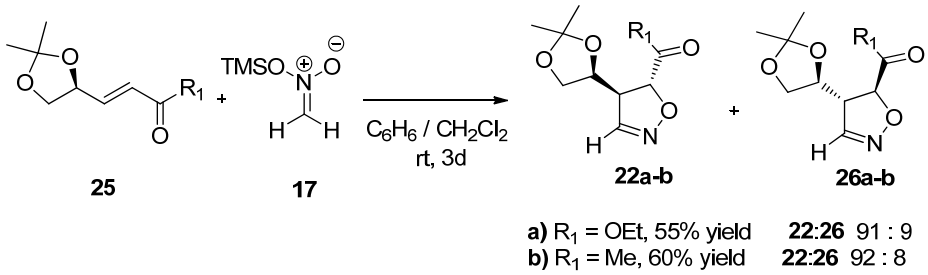
In conclusion, cycloadditions of silyl nitronates of nitromethane offer a viable access to 3-unsubstituted 2-isoxazolines. The relative stability of the silyl nitronate compared to fulminic acid makes it the dipole of choice for synthetic applications, despite the limited substrate scope and long reaction times. In particular, the reactions of butadienes and acrylates enable the synthesis of 3-unsubstituted 2-isoxazolines with a proper synthetic handle at the 5-position, which allows both further processing of the product and the use of chiral auxiliaries in the synthesis of enantiomerically enriched 2-isoxazolines.

3.2 ASYMMETRIC SYNTHESIS OF 3-UNSUBSTITUTED 2-ISOXAZOLINES

With the exception of a single example involving microbial reduction, asymmetric synthesis of 3-unsubstituted 2-isoxazolines has relied solely on the cycloaddition methods prior to this thesis. It may also be argued that apart from conjugate addition methods, none of the alternative synthetic approaches presented in the following chapters can be easily turned into an asymmetric version.

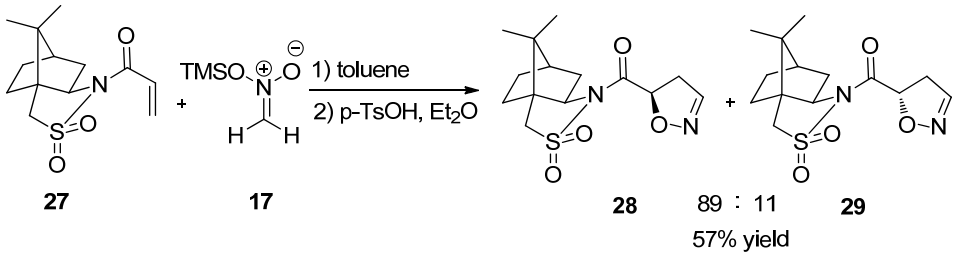
Asymmetric cycloadditions rely either on internal or relayed asymmetric induction for the transfer of chiral information. All the reported asymmetric cycloadditions leading to 3-unsubstituted 2-isoxazolines employ silyl nitronates of nitromethane as the dipole component and the dipolarophile is always the source of asymmetric induction. In a notable study of silyl nitronate cycloadditions between enantiomerically

pure **25** and various silyl nitronates, good diastereoselectivity was attained in the reaction with silyl nitronate **17** (Scheme 7).[39] Importantly, the cycloaddition to the disubstituted enone was facile and highly regioselective and the diastereomers **22** and **26** were the only reported products. Both the reactivity of the enone and the regioselectivity of the reaction were better than could have been anticipated from the reports of Torssell and co-workers.[13a]



Scheme 7. High diastereoselectivity and regioselectivity in silyl nitronate cycloaddition[39]

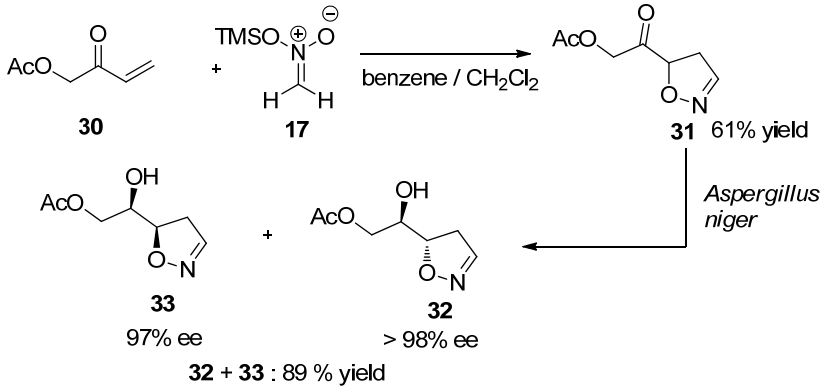
Oppolzer's camphorsultam derivatives are the only chiral auxiliaries that have been studied in the synthesis of 3-unsubstituted 2-isoxazolines.[40] Whereas the reactions have generally given good results in regard to yield and selectivity, the substrate scope of the dipolarophile has been limited to compounds that can be easily attached to the auxiliary. Thus, only acrylic amides have been used as dipolarophiles. Nevertheless, the reaction of *N*-acryloyl camphorsultam **27** with trimethylsilyl nitronate of nitromethane is reportedly facile and fairly diastereoselective (Scheme 8). The cleavage of the auxiliary was not demonstrated with the 3-unsubstituted product.



Scheme 8. Oppolzer's chiral sultam auxiliaries in the synthesis of 3-unsubstituted 2-isoxazolines[40]

External asymmetric induction has also been used in the synthesis of 3-unsubstituted 2-isoxazolines. Gefflaut and co-workers used microbial reduction with the fungus *Aspergillus niger* in the synthesis of enantiomerically enriched 2-isoxazolines.[41] The 3-unsubstituted 2-isoxazoline, synthesized by the silyl nitronate cycloaddition method,

was selectively reduced by the fungus in 89% total yield. The highly enantiopure diastereoisomers were successfully isolated (Scheme 9).



Scheme 9. Enantioselective synthesis of 3-unsubstituted 2-isoxazolines by microbial reduction[41]

In conclusion, while there are multiple examples of successful asymmetric induction in the synthesis of 3-unsubstituted 2-isoxazolines these examples have been limited to rather special cases and no general method has been available.

3.3 2-ISOXAZOLINES VIA FUNCTIONALIZATION AND ISOMERIZATION REACTIONS

In addition to cycloaddition reactions, only a handful of synthetic methods of broader applicability exist for the synthesis of 3-unsubstituted 2-isoxazolines. Whereas in the cycloaddition methods the isoxazoline ring is formed simultaneously with the C-C bond formation, in the other synthetic methods the carbon chain already exists and the intramolecular oxime functionality is generated via functionalization and isomerization reactions. Since in these approaches the strategic advantage of carbon-carbon bond formation is lost, it is very important for the usability and versatility of the synthetic method that the reactant containing the carbon chain is easily accessible. The three most important alternative methods for the synthesis of 3-unsubstituted 2-isoxazolines are the reaction of cyclopropanes with nitrosonium cation, the isomerization of *O*-propargylic hydroxylamines and conjugate addition methods.

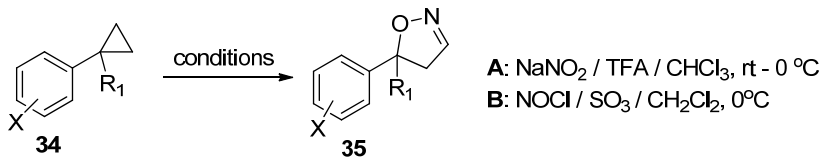
3.3.1 SYNTHESIS OF 2-ISOXAZOLINES FROM CYCLOPROPANES UNDER NITROSATION CONDITIONS

Shabarov, Saginova and Gazzaeva first reported in 1982 that the 2-isoxazoline ring can be formed by treating arylcyclopropanes with sodium nitrite in acidic conditions.[42,43,44] Formation of 2-isoxazoline from phenylcyclopropane in a reaction with nitrosonium tetrafluoroborate ($NOBF_4$) was later reported by Kim and Kochi in their studies of electron donor acceptor complexes with nitrosonium cation.[45] The reaction was studied

in detail by Otsuji and co-workers.[46] They showed that the same result could be achieved photochemically by 9,10-dicyanoanthracene (DCA) mediated sensitization of nitrogen oxide (NO) in the presence of arylcyclopropanes.

Saginova together with Bondarenko and Zyk revisited the topic with new co-workers over twenty years later, now using nitrosyl chloride (NOCl) as the source of nitrosonium ion and sulfur oxides as the reaction co-solvent.[47] A series of studies established the combination of NOCl and sulfur(VI) trioxide as the most efficient reagent for the isoxazoline synthesis. This method and the original $NaNO_2$/TFA method have also been demonstrated to work very well in the synthesis of 3-unsubstituted 5-aryl-2-isoxazolines (Table 2). The substrate scope outside arylcyclopropanes has not been surveyed but a single report shows an excellent result with a benzylcyclopropane when the $NaNO_2$/TFA -method was used.[48]

Table 2. Selected examples of nitrosonium ion addition to phenylcyclopropanes[43,47]



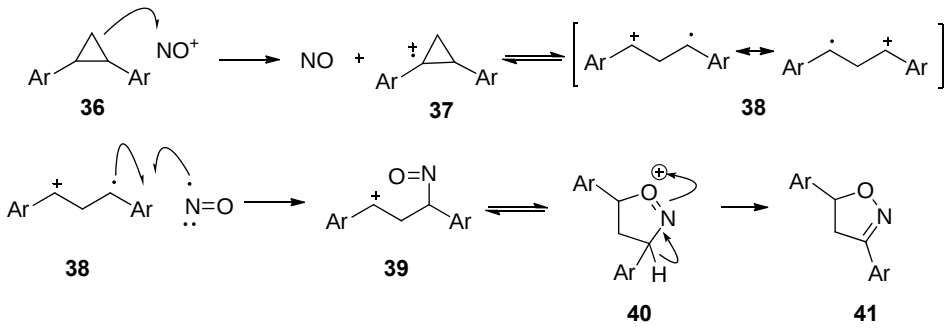
34 35

X	R1	A: yield (%)	B: yield (%)
H	H	85	95
H	Me	90	93
p-NO	H	44	85
o-NO	H	23	
p-MeCO	H	-	62
p-I	H	84	99
o-I	H	75	
p-Cl	H	86	
o-Cl	H	78	
p-Br	H	80	99
o-Br	H	69	
p-Me	H	92	
p-MeO	H	86	
p-cyclopropyl	H	89	

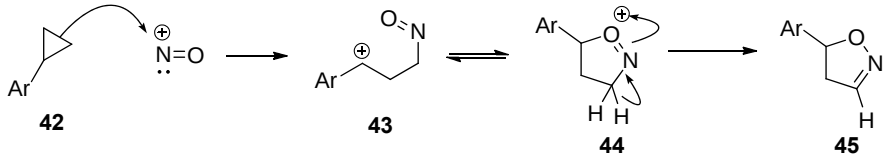
Various sources of nitrosonium ion have been reported in the reaction with arylcyclopropanes. However, mechanistic studies point out to somewhat differing reaction mechanisms depending on the nature of the cyclopropane (Scheme 11). Diarylcyclopropanes with low oxidation potential seem to react predominantly via a single electron transfer (SET) mechanism, where the nitrosonium ion oxidizes the cyclopropane to form nitrogen oxide and a cyclopropylium radical cation **38** (Scheme 10).[46] The radical cation reacts with the nitrogen oxide, giving an aryl-stabilized

cationic intermediate **39** that can be attacked by the proximal NO-group. Loss of proton from the cyclic intermediate leads to 2-isoxazolines.

Proposed reaction mechanism with diaryl cyclopropanes



Proposed reaction mechanism with arylcyclopropanes



Scheme 10. Suggested reaction mechanisms for nitrosonium ion addition to arylcyclopropanes

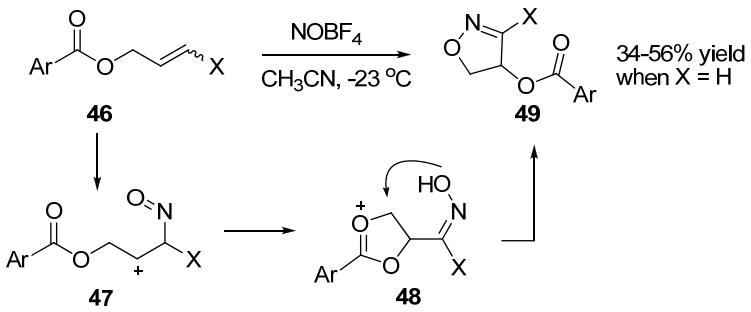
The nitrosonium cation has been speculated not to be able to oxidize cyclopropanes containing only a single aryl group. Thus, the reaction with these substrates could proceed along an ionic pathway where the cyclopropyl ring is directly attacked by the NO^+-cation. The ensuing benzylic cation **43** would then cyclize in the same way as in the SET-pathway (Scheme 10).

There are some regioselectivity issues consequent on the outlined mechanisms. Unsymmetrical aryl substitution at different carbons of the cyclopropyl ring usually leads to a mixture of regioisomers, where the major isomer is formed via the supposedly more stable benzylic cation.[46] The initial reaction between NO^+ and cyclopropane may also occur at different carbons of the cyclopropane ring and this may likewise lead to a mixture of regioisomers. Accordingly, the reaction is most useful with singly substituted arylcyclopropanes, with the selectivity towards the 3-unsubstituted isoxazolines being usually perfect.

In conclusion, the reactions of aryl cyclopropanes with nitrosonium ion offer a versatile method for the synthesis of 3-unsubstituted 5-aryl-2-isoxazolines. While the rather exotic $NOBF_4/SO_3$-reagent combination has been demonstrated to give the best yields in most cases, the easy handling and availability of the $NaNO_2$/TFA-reagent combination makes this method probably the simplest way to access these heterocycles. Even though the efficiency of the aryl cyclopropane synthesis is often modest,[49] the easy access to these compounds from relatively inexpensive starting materials further increases the usability of this protocol.

3.3.2 SYNTHESIS OF 2-ISOXAZOLINES FROM ALLYLBENZOATES UNDER NITROSATION CONDITIONS

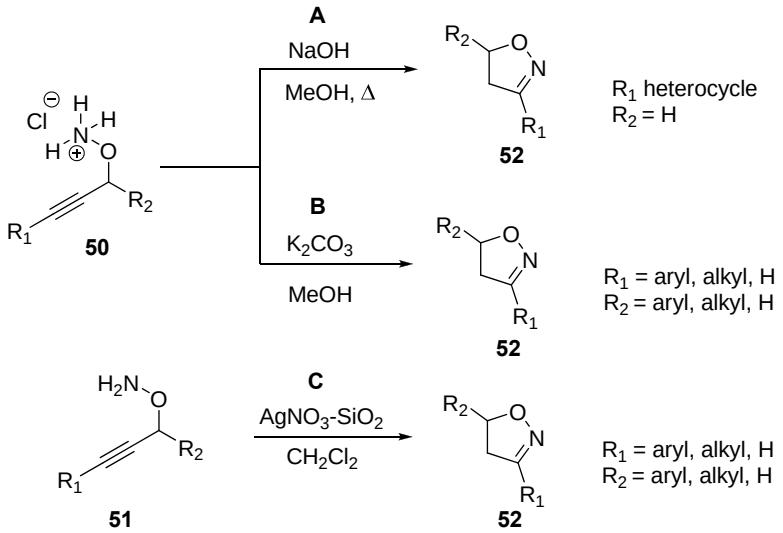
In a communication related to the cyclopropane openings, Chang and Kim reported a reaction of allylic benzoates with $NOBF_4$ that yielded 4-benzoyloxy-2-isoxazolines in moderate yields (Scheme 11).[50] Better yields were generally observed with compounds containing a 3-substituent. The reaction was suggested to proceed via the formation of cationic intermediates **47** and **48**.



Scheme 11. The nitrosation of allylbenzoates with $NOBF_4$[50].

3.3.3 SYNTHESIS OF 2-ISOXAZOLINES VIA ISOMERIZATION OF *O*-PROPARGYLIC HYDROXYLAMINES

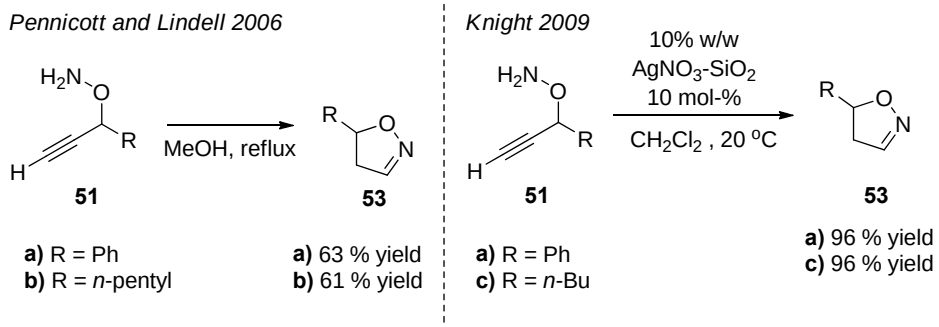
The interest in propargylic hydroxylamines as bioactive compounds[51] has created new openings in their chemistry as well. In their studies towards *O*-pyrazolylpropynyl-hydroxylamines Rodríguez-Franco and co-workers found a new rearrangement reaction that yielded 2-isoxazolines as the product (**A**, Scheme 12).[52] In their hands, the heating of propargylic hydroxylamine hydrochloride **50** in basic solution gave the 2-isoxazoline **52** in modest yield. Pennicott and Lindell studied this rearrangement and noticed that the same reaction took place in less basic conditions (K_2CO_3 in methanol) with improved efficiency (**B**, Scheme 12).[53] They applied the method to the synthesis of various 5-substituted 2-isoxazolines and further showed that the reaction could be used in the synthesis of 3-unsubstituted 2-isoxazolines as well.



Scheme 12. Conditions applied in the conversion of propargylic hydroxylamines to 2-isoxazolines[52,53,54]

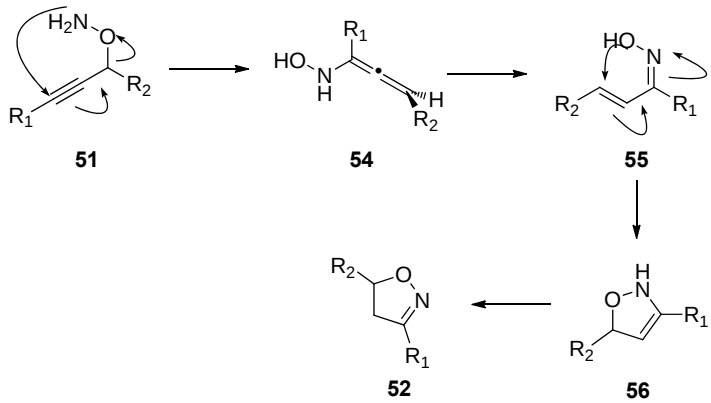
The most recent report by Knight and co-workers describes a similar, albeit an improved version of this reaction. Free propargyl hydroxylamines were used as the substrates in the presence of a catalytic amount of silver nitrate adsorbed on silica gel ($AgNO_3$-SiO_2) (**C**, Scheme 12).[54] This procedure worked well in dichloromethane and enabled the synthesis of both 5-aryl and 5-alkyl-3-unsubstituted 2-isoxazolines in excellent yields.

In the studies of Pennicott and Lindell, free hydroxylamines had to be used as the reactants to obtain the 3-unsubstituted 2-isoxazolines. Applying the standard conditions containing K_2CO_3 as the base to the hydrochloride salts of *O*-propargylic hydroxylamines gave only the corresponding β-hydroxynitriles as products. This transformation was proposed to proceed via a 3-unsubstituted 2-isoxazoline intermediate. Less basic reaction conditions, however, allowed the isolation of **53a** and **53b** in moderate yields (Scheme 13). In the report of Knight and co-workers the use of the $AgNO_2$-SiO_2 -catalyst with similar free hydroxylamine substrates gave significantly better results. Peculiarly, they also reported that in their hands, heating of the free hydroxylamines in methanol did not result in 2-isoxazoline products.



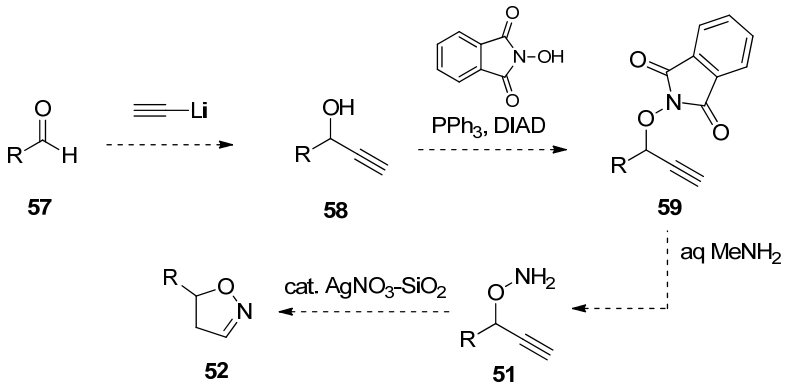
Scheme 13. Synthesis of 3-unsubsituted 2-isoxazolines from *N*-propargylic hydroxylamines[53,54]

The mechanism of the isomerisation reaction has not been studied. Pennicott and Lindell propose that the non-catalytic process involves a [2,3]-sigmatropic shift that produces an unsaturated oxime via an allene intermediate. This unsaturated oxime **55** would then engage in a fairly difficult 5-endo-trig cyclization to yield the 2-isoxazoline product (Scheme 14). Due to the existence of the achiral intermediate **55**, the use of enantiomerically enriched propargylic hydroxylamines should lead to racemic 2-isoxazolines if the proposed mechanism is operational.



Scheme 14. Proposed mechanism for the isomerization reaction

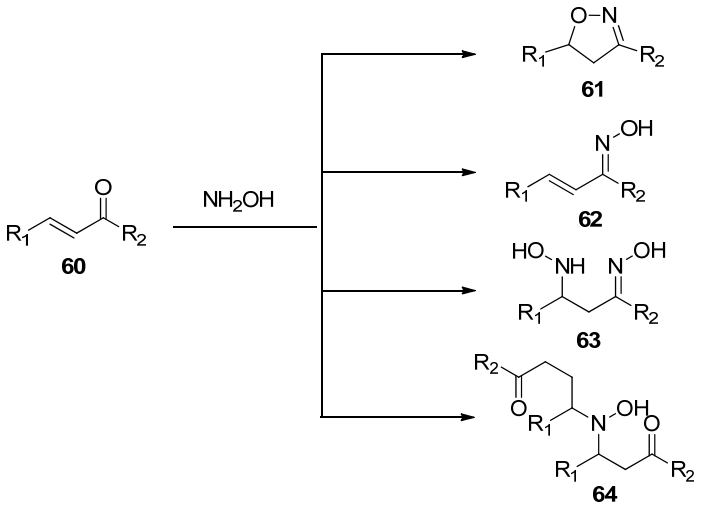
In conclusion propargyl hydroxylamines offer yet another route to the synthesis of 3-unsubstituted 2-isoxazolines. In contrast to the other methods presented thus far, this approach is not limited to isoxazolines bearing an electron deficient substrate at the 5-position. In fact, a versatile four-step synthesis of any 3-unsubstituted 2-isoxazoline could be envisioned by applying the route described by Knight and co-workers (Scheme 15). However, considerably more effort and materials have to be invested in the synthesis of the products via this route than in the silyl nitronate cycloaddition method.



Scheme 15. A proposed four-step method for the conversion of aldehydes to 2-isoxazolines

3.3.4 THE CONJUGATE ADDITION METHODS PRIOR TO THIS WORK

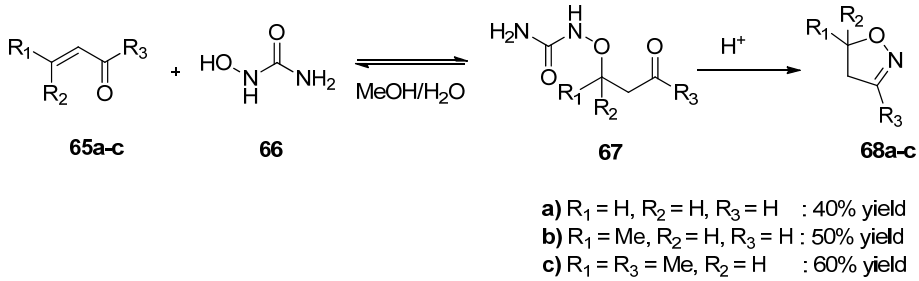
The formation of 2-isoxazolines can be easily envisioned from the reaction of an α,β-unsaturated carbonyl compound and hydroxylamine. However, it is equally easy to predict that this reaction may suffer from selectivity issues related to the nucleophilic character of both heteroatoms of hydroxylamine. This method has indeed been used in the synthesis of 2-isoxazolines, but the reaction has also been documented to be complicated and to yield a variety of products (Scheme 16).[55] A selective synthesis of 3-unsubstituted 2-isoxazolines with this method has not been documented.



Scheme 16. Reaction of hydroxylamine with enones

The problems associated with the use of hydroxylamine in these condensations can be overcome through the use of nucleophiles that function as hydroxylamine equivalents.

Whereas the use of oximes as hydroxylamine equivalents is described for the first time in this thesis, hydroxyurea has been successfully employed as a similar reagent already 35 years ago. In a 1975 report, Jacquier, Olive and Pétrus describe the conjugate addition of hydroxyurea with crotonaldehyde which upon workup with hydrochloric acid gives the corresponding 3-unsubstituted 2-isoxazoline as the product.[56] Later, they used this method in the synthesis of three different 3-unsubstituted 2-isoxazolines, including the parent unsubstituted 2-isoxazoline **68a** (Scheme 17).[57]



Scheme 17. Conjugate addition of *N*-hydroxyurea to α,β-unsaturated enals[57]

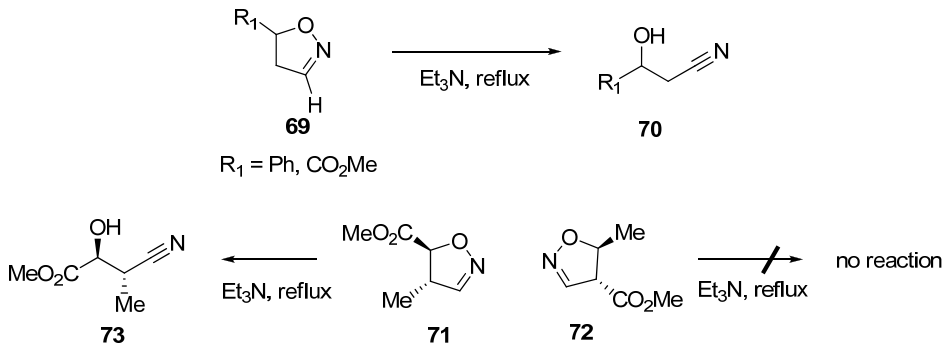
While the reaction has not been demonstrated with many different enals, our experiences from similar reactions with oximes suggest that the protocol might be successful with a range of unsaturated aldehydes.

4 Reactions and Synthetic Applications of 3-Unsubstituted 2-Isoxazolines

The reactivity of 3-unsubstituted 2-isoxazolines is characterized by the proton at the 3-position of the heterocycle. Treatment of 3-unsubstituted 2-isoxazolines with a base results in the isomerization of the heterocycle to the corresponding β-hydroxynitrile. Due to the facility of this process, many established reactions of their 3-substituted analogues are difficult or even impossible for 3-unsubstituted 2-isoxazolines. For example, the α-functionalization of the heterocycle via *endo*-deprotonation[58] and many nucleophilic additions of basic organometallic reagents[59] have not been reported for 3-unsubstituted 2-isoxazolines. On the other hand, reduction of the internal oxime functionality to an amino alcohol is feasible and selective scission of the N-O-bond has also been reported. In addition to this, some of the unique properties of these compounds may not have been studied due to their limited availability until recent years. In the following sections, the established reactivity of 3-unsubstituted 2-isoxazolines is reviewed and highlighted with selected synthetic applications when possible.

4.1 BASE-INDUCED ISOMERIZATION TO β-HYDROXYNITRILES

The base-induced isomerization of 3-unsubstituted 2-isoxazolines to β-hydroxynitriles was reported by Huisgen and Christl in connection with their fulminic acid cycloaddition studies.[30] The cycloadducts of styrene and methyl acrylate were found to isomerize to β-hydroxynitriles upon heating in triethylamine (Scheme 18).

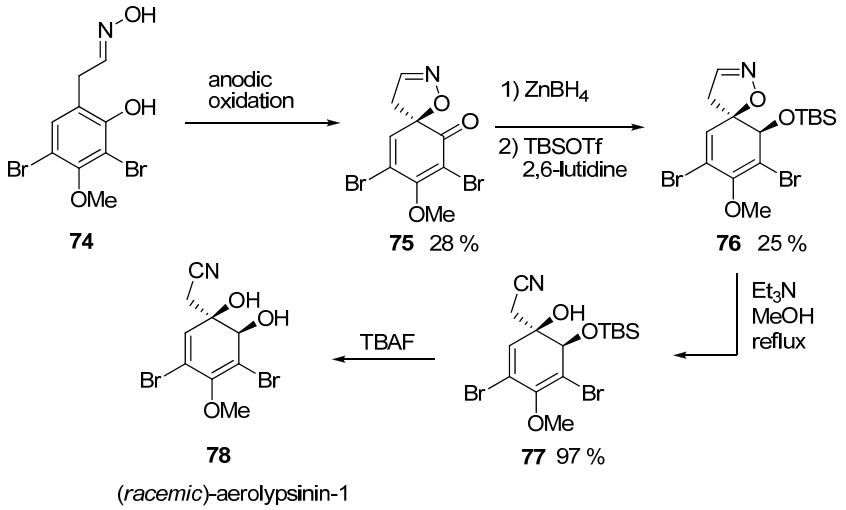


Scheme 18. Isomerization of 2-isoxazolines to β-hydroxynitriles by the method of Huisgen and Christl[30b]

Huisgen proposed that the reaction occurs as a concerted base-induced process without any intermediates and that the stability of the alkoxide anion plays a role in the

feasibility of the reaction under these conditions. This was backed by their experiments, in which only the regioisomer **71** underwent the reaction in the conditions mentioned above.

The same reaction has since been employed by many research groups in their synthetic endeavours.[35b,38,39,60,61] Different conditions ranging from the use of sodium methoxide in methanol to triethylamine in acetonitrile have been applied to this transformation but the 2-isoxazoline substrates employed in these cases have always contained an anion stabilizing functionality at the 5-position of the heterocycle or there has been considerable additional strain in the substrate. A practical use of this reaction in a total synthesis was demonstrated by Nishiyama and Ogamino in their synthesis of aerolypsinin-1 (Scheme 19).[60a]

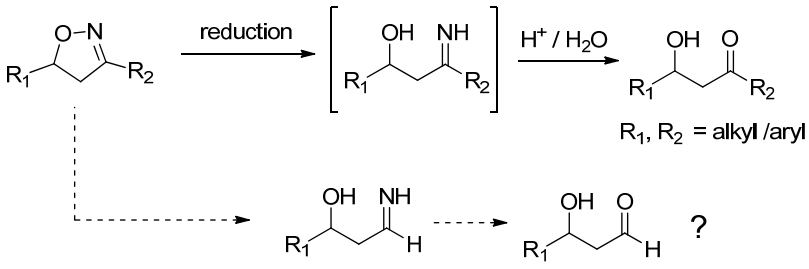


Scheme 19. Total synthesis of aerolypsinin-1[60]

After the construction of 3-unsubstituted spiroisoxazoline **75** by anodic oxidative cyclization of the oxime **74**, the total synthesis of aerolypsinin-1 was completed by the base-induced isomerization of the heterocycle to β-hydroxynitrile and the subsequent cleavage of the protecting groups. Notably, the isomerization reaction was fast when methanol was used as the reaction solvent.

4.2 SELECTIVE REDUCTION OF THE N-O BOND

Probably the synthetically most important reaction of 2-isoxazolines is the selective reductive scission of the N-O-bond which in combination with careful hydrolysis of the resulting β-hydroxyimine intermediate can be used to synthesize β-hydroxyketones (Scheme 20).

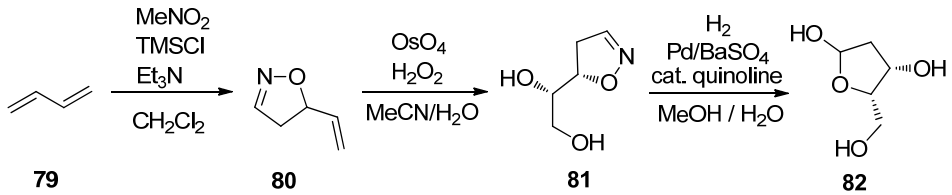


Scheme 20. Reduction of the N-O-bond of the 2-isoxazolines followed by hydrolysis gives β-hydroxyketones

Together with the 1,3-dipolar cycloaddition chemistry, this strategy gives a powerful tool for polyol and polyketide synthesis, as demonstrated masterfully by Carreira[62] and others.[63]

The reductive cleavage of the N-O bond of a 3-unsubstituted 2-isoxazoline would liberate a β-hydroxyaldehyde. Unsubstituted β-hydroxyaldehydes and the corresponding imine intermediates are extremely prone to elimination, and whereas a multitude of different conditions for the N-O-bond scission of 3-substituted 2-isoxazolines have been reported in the literature,[64] the suitability of the methods to β-hydroxyaldehyde synthesis has not been commented. However, the acidic conditions usually employed in the hydrolysis of the intermediate imine definitely set this kind of an aldol product in a great danger.

Nevertheless, in their synthesis of racemic deoxyribose and other sugars, Torssell and co-workers demonstrated that at least under the slightly basic reaction conditions the lactol form of the product is stable enough (Scheme 21).[35c]



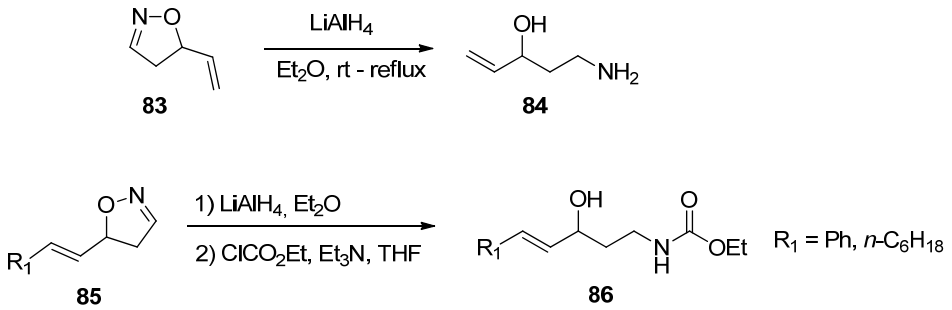
Scheme 21. 3-Step synthesis of racemic deoxyribose from butadiene applying the liberation of β-hydroxyaldehyde from 3-unsubstituted 2-isoxazoline[35c]

However, the product identity was confirmed only by TLC comparison against authentic deoxyribose in this study.

4.3 REDUCTION TO 1,3-AMINOALCOHOLS

The 3-unsubstituted 2-isoxazoline ring undergoes normal reduction to 1,3-aminoalcohol in the presence of $LiAlH_4$.[65] Torssell and co-workers have reported a

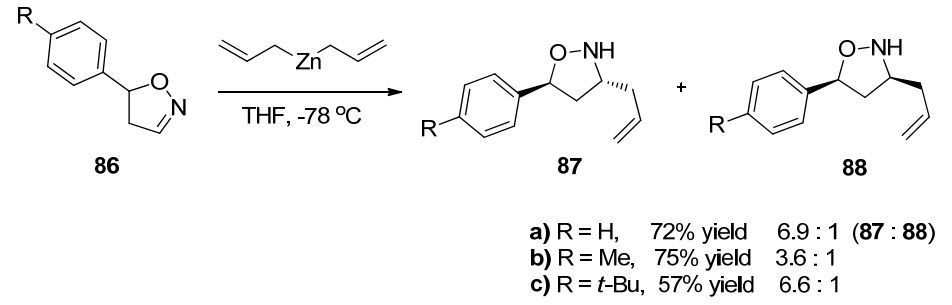
practically quantitative yield from this process with 5-vinyl-2-isoxazoline **83**.[35b] A similar reduction was employed in the study of decarboxylative cyclizations of allylic cyclic carbamates. Reduction of 2-isoxazolines **85** with $LiAlH_4$ and subsequent protection of the amine with ethylchloroformate gave carbamates **86** in a combined 50% yield (Scheme 22).[66]



Scheme 22. Reduction of the 3-unsubsituted 2-isoxazolines to aminoalcohols[35b, 66]

4.4 NUCLEOPHILIC ADDITIONS WITH ORGANOMETALLIC REAGENTS

Considering the sensitivity of 3-unsubstituted 2-isoxazolines to bases, the additions of organometallic reagents to C=N double bond are predictably challenging. In fact, only a single report of successful addition of lithium acetylide[67] had been disclosed before 1999 when Jenkins and co-workers reported that diallylzinc can be successfully added to 3-unsubstituted 2-isoxazolines in moderate yields (57-72%) and with low to moderate diastereoselectivities (3.6:1 - 6.9:1) (Scheme 23).[68] They also reported a complete failure in the addition of organolithium and organomagnesium reagents other than allylmagnesium chloride, which underwent the reaction in low yield (18%) and diastereoselectivity (2.7:1).

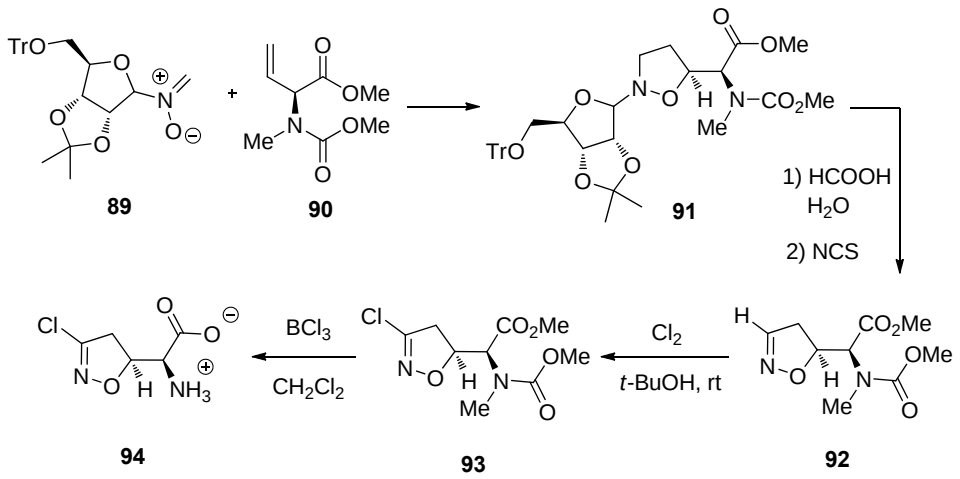


Scheme 23. The addition of diallylzinc to 3-unsubstituted 2-isoxazolines[68]

4.5 CONVERSION TO 3-CHLOROISOXAZOLINES

Although many 3-substituted 2-isoxazolines can be easily synthesized through cycloaddition chemistry, the manipulation of the substitution at the 3-position of the

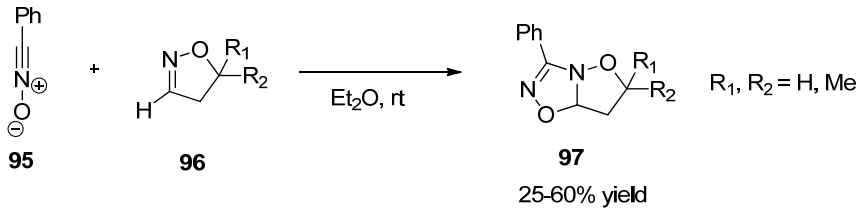
heterocycle is without question one of the most interesting and unique aspects of the reactivity of 3-unsubstituted 2-isoxazolines. However, only chlorination of the 3-position of the heterocycle has been reported so far. Whitney and co-workers employed the cycloaddition of chiral nitrone **89** in their total synthesis of antitumour antibiotic acivicin (Scheme 24).[69] Double asymmetric induction in the cycloaddition step afforded **91** as a single diastereoisomer, which after acidic hydrolysis of the auxiliary was oxidized to the corresponding 3-unsubstituted 2-isoxazoline **92** by treatment with *N*-chlorosuccinimide. This oxidation procedure originally communicated by Vasella, presents yet another method to arrive at 3-unsubstituted 2-isoxazolines.[70] However, no application of this method in addition to these examples has been reported. Extensive screening of chlorinating reagents revealed that the conversion of **92** to the 3-chlorinated compound **93** was only possible by treatment with excess chlorine gas in *t*-BuOH at room temperature. The chlorinated 2-isoxazoline was stable enough for purification and further processing to acivicin.



Scheme 24. The chlorination of 3-unsubstituted 2-isoxazoline in the total synthesis of acivicin[69]

4.6 1,3-DIPOLAR CYCLOADDITIONS WITH BENZONITRILE OXIDE

Pétrus and co-workers employed 2-isoxazolines synthesized by the conjugate addition strategy in cycloaddition reactions with benzonitrile oxide (Scheme 25).[57]



Scheme 25. 1,3-Dipolar cycloaddition of nitrile oxides to 2-isoxazoline[57]

Even though the yields of these reactions with 3-unsubstituted 2-isoxazolines were modest (25-60%) the reactivity of the N=C double bond in cycloadditions was effectively demonstrated. The regiochemistry of the adduct can be explained by assuming that the dipolarophile component reacts via its LUMO in the cycloaddition with nitrile oxide.

5 Synthesis of 3-Unsubstituted 2-Isoxazolines from α,β-Unsaturated Aldehydes and Oximes

5.1 BACKGROUND AND THE DEVELOPMENT OF THE RACEMIC SYNTHESIS PROTOCOL

As mentioned in the introduction, the original aim of the research was to study whether enantioselective iminium catalysis could be exploited in synthesis of enantioenriched β-hydroxyaldehydes. At the time, no asymmetric conjugate additions of heteroatom nucleophiles to α,β-unsaturated aldehydes had been published. The development of the oxy-conjugate addition to enals was expected to be challenging for the reasons depicted in Figure 2.

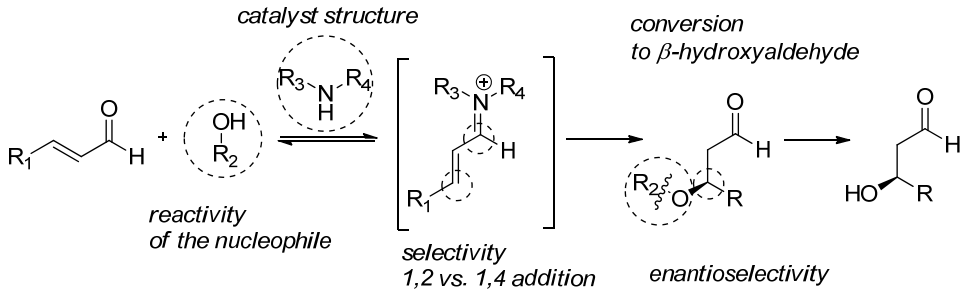


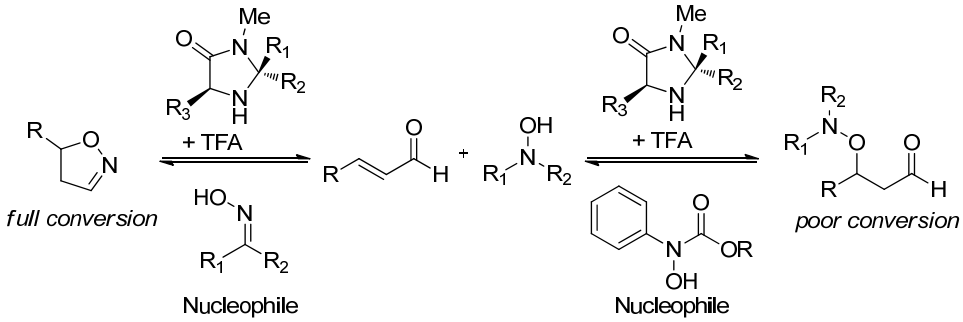
Figure 2. Challenges in the iminium catalyzed β-hydroxyaldehyde synthesis

Firstly, neutral oxygen species such as alcohols were estimated to be rather weak nucleophiles and thus it was questionable whether the iminium ion intermediates formed in the presence of the established catalysts would be reactive enough to facilitate the reaction. Secondly, assuming adequate reactivity, the rather hard oxygen nucleophiles could easily participate in 1,2-additions with the iminium ions – a process that could possibly lead to unreactive intermediates. Thirdly, the linear oxygen nucleophiles in particular were assumed to be sterically different from the ring-shaped nucleophiles that had often been applied in the early examples of enantioselective processes,[71] and these steric effects on the enantioselectivity of the reaction were unknown. In regard to regio- and enantioselectivity of the addition, the structure of the catalyst was thought to play an equally important role. Lastly, to exploit the full potential of the addition, the nucleophile should include an easily cleavable R-group.

Literature precedents[72] and our own studies quickly identified the compounds containing an α-heteroatom in respect to oxygen as the most promising candidates for

oxygen nucleophiles. In particular, oximes and *N*-hydroxycarbamates stood out as reactive and selective nucleophiles in additions catalyzed by imidazolidinone-trifuoroacetic acid catalyst–co-catalyst systems.

While the fear of insufficient kinetic activation by the catalyst turned out to be unfounded, we soon realized that we had overlooked the difficulties related to the thermodynamics of the reaction between oxygen nucleophiles and enals. Consequently, high conversions seemed to be very difficult to obtain in the reactions of *N*-hydroxycarbamates. Serendipitously, however, in the presence of MacMillan's catalysts and TFA co-acid, many *oximes* engaged in surprising and interesting condensation reactions with enals, yielding 3-unsubstituted 2-isoxazolines as the reaction products (Scheme 26).

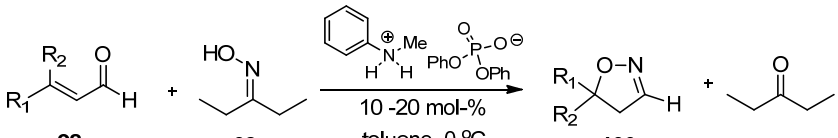


Scheme 26. Reaction of oximes and *N*-hydroxycarbamates with enals in the presence of imidazolidinone catalyst and TFA co-acid

Assuming that the enantiomerically enriched conjugate addition products were intermediates in this reaction, the formation of 2-isoxazolines seemed to provide exactly the kind of thermodynamic trap that was needed to capitalize on the otherwise seemingly useless catalytic conjugate addition process.

However, further exploration into the reaction revealed that the imidazolidinone catalysts were unable to transfer their chiral information efficiently into the products, even after a range of co-catalysts of differing acidity had been tested. Nevertheless, because of the novelty of the transformation and considering the rather limited access to the 3-unsubstituted 2-isoxazoline products, we decided to first optimize the process for a non-chiral catalyst. Diphenylphosphate salt of *N*-methylaniline was found to be the best racemic catalyst for the reaction after extensive screening of amine bases and co-acids.[I,III] Optimization studies also revealed that the simple ketone oximes, particularly the 3-pentanone oxime and cyclohexanone oxime were the most suitable carriers of the N-O-functionality.[I,III] The optimized synthetic protocol with the anilinium salt catalyst was found to be applicable to the synthesis of 3-unsubstituted 2-isoxazolines from a range of unsaturated aldehydes containing an sp^3-carbon at the γ-position (Table 3).

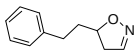
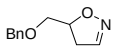
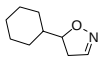
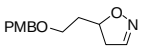
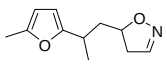
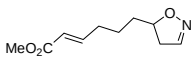
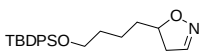
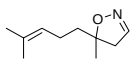
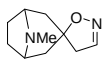
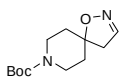
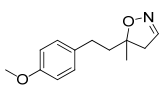
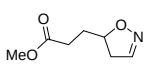
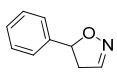
Table 3. Racemic synthesis of 3-unsubstituted 2-isoxazolines[III]



98 **99** **100** **101**

R_1 = alkyl, R_2 = alkyl / H

50-86 % yield

Entry	Product	Time (h)	Yield (%)
1		6.5	55[a]
2		6.5	86
3		15.5	63
4		6.5	73
5		7	73
6		14.5	83
7		15	73
8		7.5	82
9		15	83
10			0
11		4	85
12		14	69
13		15	82
14			0

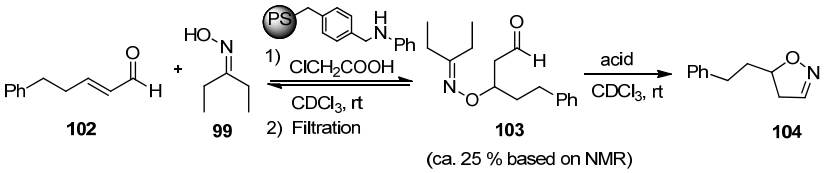
[a] Acetaldehyde oxime was used as the oxime reagent.

The most notable limitation of this synthetic method was its unsuitability towards aldehydes containing additional conjugation to the double bond such as additional alkene, phenyl or ester groups. Thus, the scope of the reaction seemed to be exactly opposite to that of most of the existing synthetic methods for 3-unsubstituted 2-isoxazolines.

5.2 MECHANISTIC STUDIES

Based on the initial experiments where the imidazolidinonium salt catalyzed formation of the 2-isoxazoline was studied in a NMR solvent, the formation of the conjugate addition intermediate and the 2-isoxazoline product appeared to be linked together.[II, III] While the fact that no 2-isoxazoline formation was detected with enal substrates resistant to conjugate addition further indicated connection of this type, we could not consider these observations as direct evidence for the intermediacy of the conjugate addition product in the 2-isoxazoline formation.

The most important finding that supported this order of events was made by studying the assumed conversion of the conjugate addition product to the 2-isoxazoline in isolated experiments. The conjugate addition product could be synthesized without the emergence of the 2-isoxazoline by applying a mixture of polymer bound benzylaniline and chloroacetic acid as the catalyst. Removing the catalyst and most of the oxime starting material from the solution by filtration through a plug of basic alumina resulted in a solution containing mostly enal and the conjugate addition product **103**. Treatment of this solution with various acids resulted in fast generation of the 2-isoxazoline **104** occurring concurrently with the disappearance of the conjugate addition intermediate. While this conversion did not take place in the presence of *N*-methyl aniline, the *N*-methylanilinium salt of diphenyl phosphate was a viable cyclization catalyst. The rate of the cyclization seemed to correlate positively with the acidity of the catalyst (Figure 3).



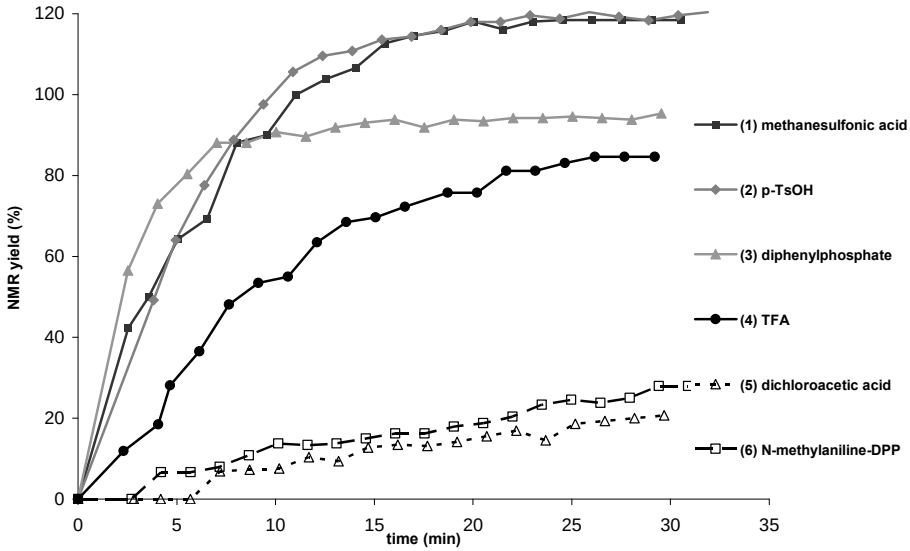
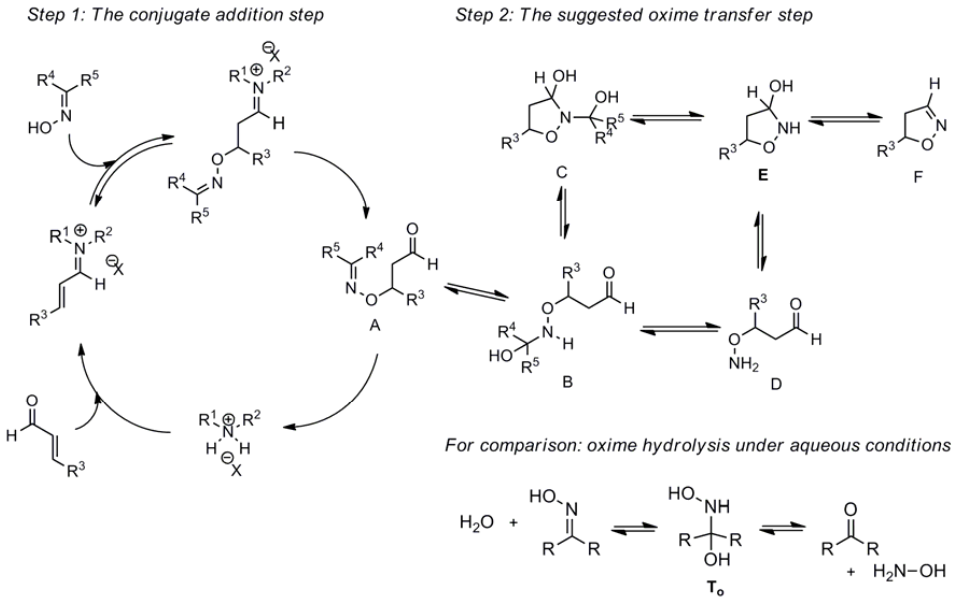


Figure 3: Isolated cyclization of conjugate addition intermediates detected by direct monitoring of the reaction with ^{1}H NMR[III]

The cyclization experiments backed the hypothesis that the 2-isoxazoline formation indeed occurs via the conjugate addition intermediate. While the anilinium salt could be envisioned to catalyze the intramolecular oxime transfer step by multiple ways, the most simple explanation points to a role as a general acid catalyst. The meticulous studies on oxime formation and hydrolysis made by Jencks, Sayer and More O'Ferrall further support this idea.[73,74] The mechanistic proposal for the 2-isoxazoline formation is outlined in Scheme 27.

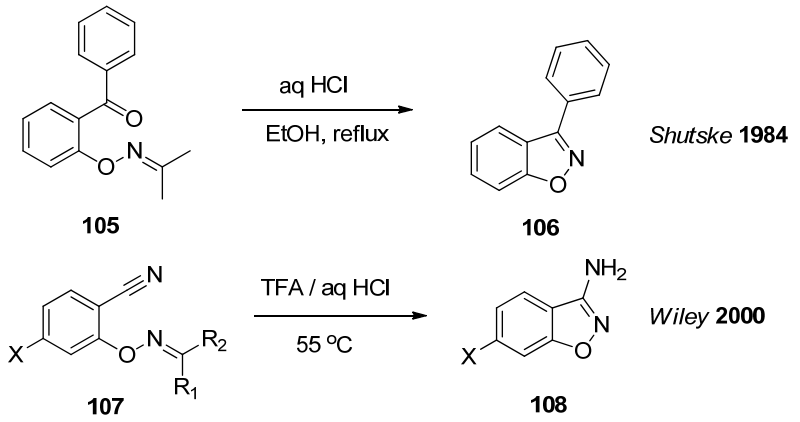


Scheme 27. Mechanistic proposal for the anilinium salt catalyzed formation of 2-isoxazolines[III]

Additional studies on the subtleties of the proposed oxime transfer process were conducted by comparing the reaction rates with different starting materials. Most importantly, it was found that increasing the aldehyde β-substitution seemed to have a notable positive effect on the overall rate of the reaction even though the rate and equilibrium conversion of the conjugate addition step were close to similar in each case. This observation was accounted for by the Thorpe-Ingold-type effect of increasing β-substitution. For this effect to have an impact on the reaction rate, the rate-determining step was assumed to lie in the end of the reaction pathway (intermediates **A-F**, Scheme 27). These results, combined with those from experiments comparing the facility of the process with different oximes[III] pointed out to a rate-determining elimination of water molecule from the intermediate **E.** Even though the rate constant of this step is independent of the oxime structure and presumably only weakly dependent on the β-substitution of the enal, the concentration of the intermediate **E** is dependent on the equilibrium constants of the preceding steps and thus the concentrations of both starting materials manifest themselves in the reaction rate. Due to the obvious complexity of the reaction mechanism, all qualitative conclusions from the experiments should be drawn cautiously as other options exist. However, extracting reliable quantitative kinetic data from the reaction is extremely challenging due to the existence of multiple reaction intermediates and thus solving the exact reaction mechanism with certainty proved to be beyond the scope of this thesis.

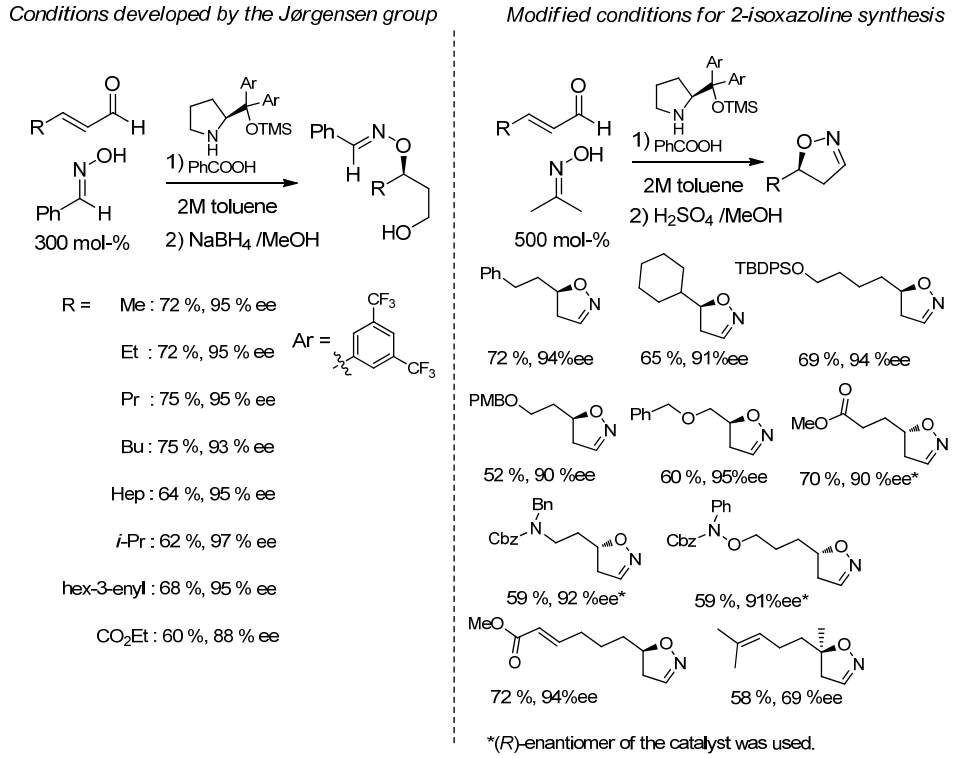
5.3 DEVELOPMENT OF THE CATALYTIC ENANTIOSELECTIVE SYNTHESIS

In light of the complexity of the mechanism proposed in the Scheme 28, it was possible to fathom reasons for the failure in the initial attempts to induce asymmetry with the rather acidic imidazolidinone catalysts. However, it was clear that the minimum condition for the enatioselective process was a highly enantioselective conjugate addition step – an item that we had not yet studied separately. With qualitative understanding of the stepwise nature of isoxazoline formation as well as the role of acid catalysis in the cyclization step it seemed possible to separate the addition and cyclization steps, should it turn out to be necessary for securing the enantiomeric excess. In fact, a similar separate cyclization step had been already used in the isoxazoline synthesis reported by of Jacquier, Olive and Pétrus (Scheme 17). In addition, the oxime transfer under acidic aqueous conditions had been applied to the synthesis of structurally similar benzisoxazolines (Scheme 28).[75]



Scheme 28. Intramolecular oxime transfer reactions in the synthesis of benzisoxazolines.[75]

The timely report from Jørgensen and co-workers describing a successful enantioselective oxy-conjugate addition of benzaldehyde oximes to α,β-unsaturated aldehydes gave us a tool to construct the conjugate addition intermediate enantioselectively.[76] In Jørgensen's study, the silylated diarylprolinol catalyst together with benzoic acid – a presumably much less acidic combination of the catalyst and co-catalyst than our previously employed imidazolidinone based system – had enabled a successful enantioselective conjugate addition reaction. In these reaction conditions, the enantioselectivities were high and no cyclization to 2-isoxazolines was reported. High concentration of the reactants and threefold excess of benzaldehyde oxime were used in the reaction, presumably to force the equilibrium to the side of the product. For isolation, the addition product had to be reduced to the corresponding alcohol by treatment of the reaction mixture with $NaBH_4$ in methanol (Scheme 29).



Scheme 29. Comparison of the synthetic procedures for the protected 1,3-diols and 3-unsubstituted 2-isoxazolines[76, III]

As expected, we observed that treatment of the reaction mixture with strong acids resulted in the rapid formation of 2-isoxazolines. To reach yields and enantioselectivities comparable to the ones obtained for the alcohol products, a mixture of strong mineral acids in an alcoholic solvent had to be used. To maximize the yield and enantiomeric excess of the isoxazoline product, the use of excess acetone oxime nucleophile and longer reaction times proved to be important (Scheme 29). In addition, the purity of the silylated prolinol catalyst was found to be essential for the highly enantioselective process. The commercially available catalyst, supplied by Sigma-Aldrich, was detected to contain variable amounts of impurities that sometimes lowered the enantioselectivity.

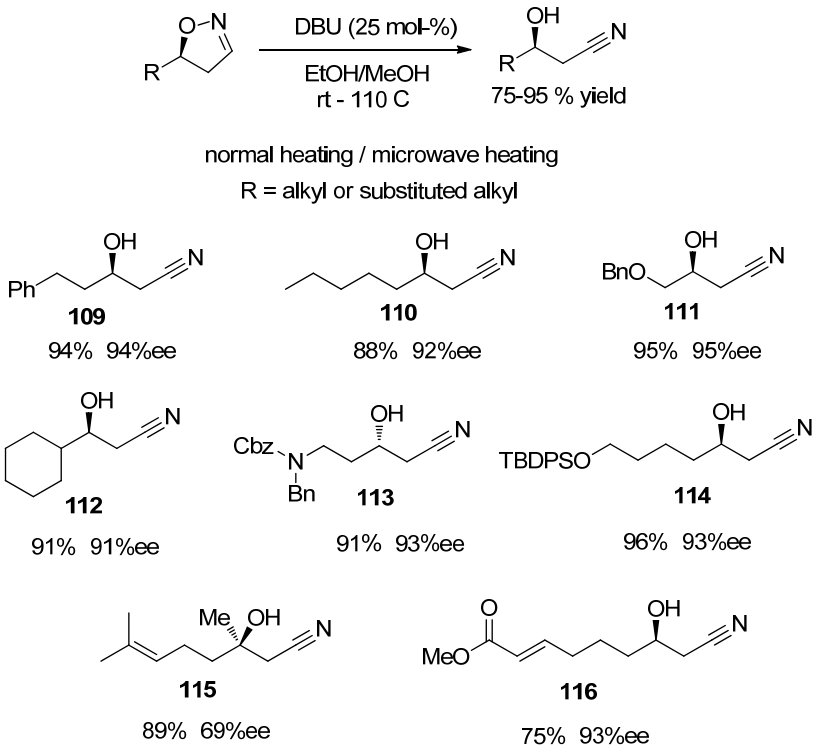
As with the anilinium salt catalyzed reaction, the asymmetric version of the isoxazoline synthesis was restricted to enals with an sp^3-carbon at the γ-position of the aldehyde chain. Despite efforts to improve the reaction efficiency, the yields never exceeded 72% and typically remained between 50-65% for many substrates. However, our own studies[III] as well as the earlier reports by Langenbeck[77] and Jørgensen[76] indicate that the equilibrium constants in the conjugate addition reactions between enals and neutral oxygen nucleophiles are close to unity and as a consequence, improving the yields to a higher level while retaining the reaction parameters required

for the enantioselective process may be extremely difficult. However, the reaction seemed to respond well to scale-up and the best results were generally obtained on a larger scale. The effect of the oxime transfer reaction on the yields and enantioselectivities was found to be very small.

6 Improved Method for the Isomerization of 3-Unsubstituted 2-Isoxazolines to β-Hydroxynitriles

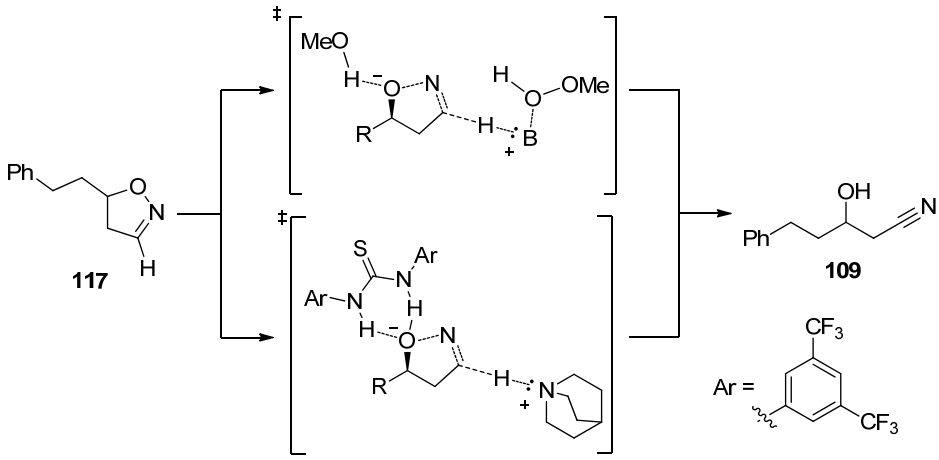
The value of the newly developed enantioselective 2-isoxazoline synthesis was thought to increase if other, more useful optically active compounds could be efficiently derived from 3-unsubstituted 2-isoxazolines. In particular, the reportedly easy isomerization to β-hydroxynitriles was evaluated to be a valuable process as the nitrile functionality can further be converted to a variety of other functional groups. However, we quickly realized that the compounds containing an alkyl substituent at the 5-position were significantly more difficult to isomerize to the β-hydroxynitriles than the ones reported in the literature (Scheme 18). The existing amine based methods were clearly inadequate and while we found the hard anionic bases such as MeONa, KHMDS and KO*t*-Bu very capable for the conversion, the yields were inconsistent and sometimes only moderate. In addition, opening the ring with KO*t*-Bu in THF resulted in deterioration of the enantiomeric excess. Since our isoxazoline synthesis was already hampered by moderate yields, the ensuing reactions to derivatize them should preferably be highly efficient in order to improve the overall synthetic efficiency.

Careful examination of the literature showed that the combination of an organic amine (triethylamine) base with an alcoholic solvent seemed to accelerate the ring opening reaction.[60] As our substrates still reacted very slowly with this combination, efficiency was sought by employing the more basic amidine base, DBU. This rather small change in the reagent proved to be fruitful and we were able to convert a range of 2-isoxazolines to the corresponding β-hydroxynitriles in high yields (Scheme 30).[IV] Importantly, the enantiomeric excess of the substrates was retained in the conversion. To obtain fast reaction rates the mixtures were heated in a microwave reactor, but the traditional bath heating was found to be equally effective. Consistently with the supposed reaction mechanism, only a substoichiometric amount of base was required. It should also be noted, that treating the crude product from enantioselective 2-isoxazoline synthesis directly with DBU in ethanol afforded the β-hydroxynitrile **109** in 73% overall yield and 94% ee.



Scheme 30. Improved conversion of 3-unsubstituted 2-isoxazolines to β-hydroxynitriles[IV]

Our studies are in line with Huisgen's hypothesis of the concerted ring opening mechanism. The alcoholic solvent benefits the reaction by improving charge stabilization in the transition state. Efficient solvation of both the protonated amine base and the negatively charged alkoxide anion is possible in the alcoholic solvent. Additional support for the importance of the charge stabilization was also gained from the experiments conducted in a non-polar solvent. The treatment of the 2-isoxazoline **117** with 20 mol-% of quinuclidine in toluene did not result in a reaction but when 20 mol-% of *N*,*N*'-bis[3,5-bis(trifluoromethyl)phenyl thiourea was added to the reaction mixture, slow conversion to the β-hydroxynitrile **109** was observed (Scheme 31).[78]



Scheme 31. The proposed role of hydrogen bond donors in the stabilization of transition states

7 Conclusions

The work presented in this thesis describes the discovery and development of a new method for the synthesis of 3-unsubstituted 2-isoxazolines from α,β-unsaturated aldehydes and oximes. The process consists of sequential catalytic conjugate addition and oxime transfer reactions. Whereas the conjugate addition of oxime can be catalyzed with varying efficiency by various combinations of amines and organic acids, the efficient formation of 2-isoxazolines from the conjugate addition intermediate is observed only when moderately acidic organic acids such as diphenyl phosphate are combined with weakly basic amines such as anilines and imidazolidinones. According to mechanistic studies, cyclization of the conjugate addition product was most efficiently catalyzed by acids. Thus, it was proposed that the most catalytically active anilinium salts play a dual role in the reaction. They accelerate the conjugate addition via formation of reactive iminium ion intermediates and facilitate the oxime transfer by functioning as general acid catalysts.

The best catalyst found so far, the *N*-methylanilinium diphenyl phosphate, enables a practical and economical synthesis of 3-unsubstituted 2-isoxazolines in racemic form. The yields of the process are only moderate but they compare well with existing methods for the synthesis of these compounds. The easy availability of both starting materials makes this process the best existing method for the synthesis of 3-unsubstituted 2-isoxazolines with alkyl substituents at the 5-position. The biggest drawback of the method, the inactivity of enal substrates containing α-substitution or stabilizing β-substitution is complemented well by other existing methods. These methods include the cycloaddition reaction of fulminic acid or trimethylsilyl nitronate of nitromethane with activated alkenes, the nitrosation of phenylcyclopropanes or allylbenzoates, the isomerization of propargyl hydroxylamines and the condensation of *N*-hydroxyurea with α,β-unsaturated aldehydes.

The combination of the acid catalyzed oxime transfer reaction with the asymmetric conjugate addition reaction developed by Jørgensen and co-workers allowed the catalytic asymmetric synthesis of 3-unsubstituted 2-isoxazolines for the first time. The method also presents probably the most versatile example of asymmetric 2-isoxazoline synthesis from prochiral starting materials. The availability of highly enantioenriched 3-unsubstituted 2-isoxazolines may also open new practical strategies for the synthesis of other useful compounds. This was demonstrated in this work by showing that the DBU-catalyzed ring opening of 3-unsubsituted 2-isoxazolines enables a facile 2-step synthesis of β-hydroxynitriles in highly enantioenriched form. Similar pathways to other optically active compounds accessible from the 3-unsubstituted 2-isoxazolines by known chemistry may well be expected to open. While many simple reactions such as additions and ring cleavages are known for the 3-unsubstituted 2-isoxazolines,

different catalytic processes may enable new useful reactions. Perhaps a new look deeper into the treasure casket of possibilities catches new chemists by surprise.

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