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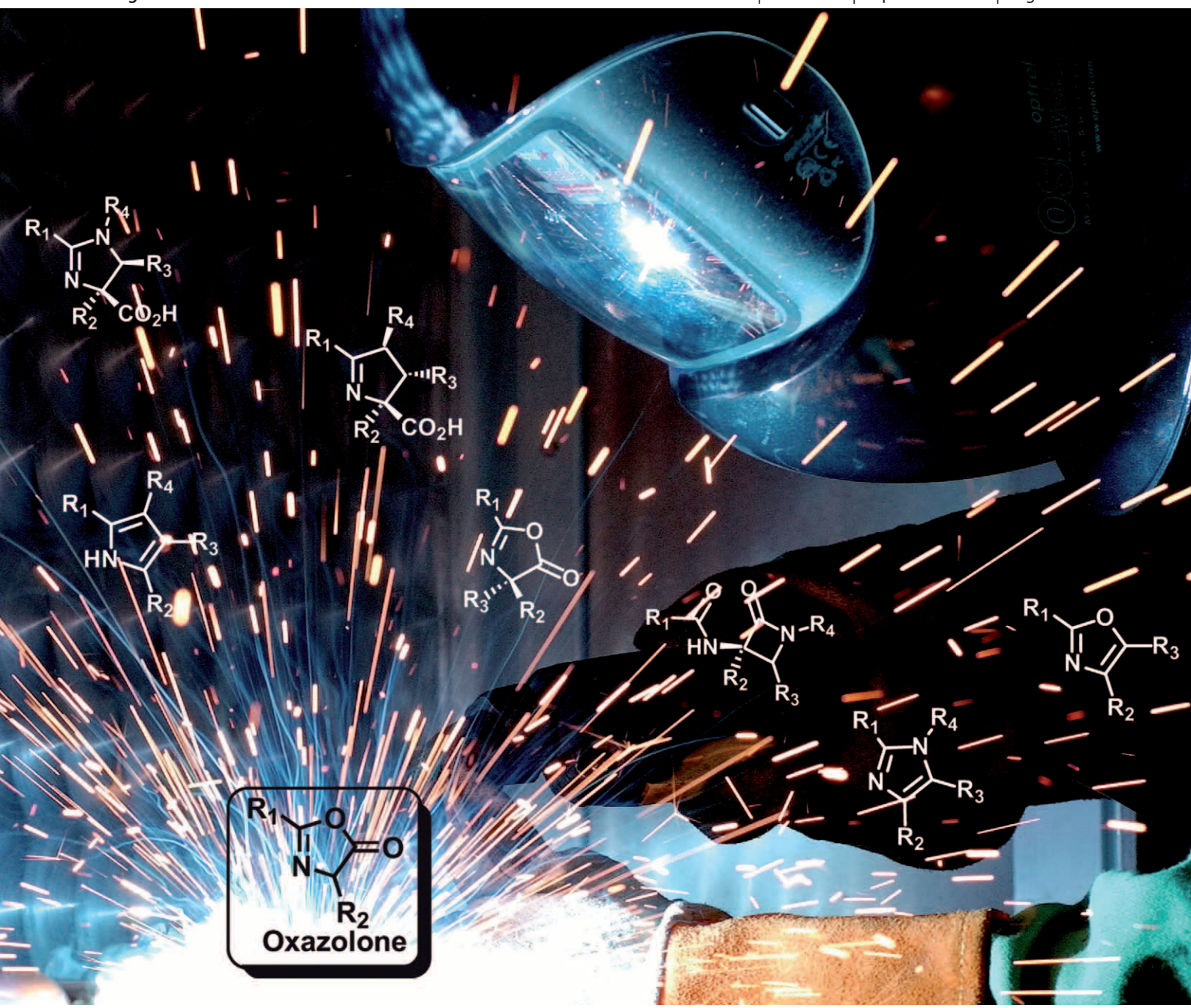

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The diverse chemistry of oxazol-5-(4*H*)-ones

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The assembly of structurally diverse scaffolds *via* substrate controlled diversity oriented synthesis (DOS) has proven to be an effective tool in the discovery of novel biologically important compounds. This tutorial review aims to summarize some of the more recent applications of oxazolones as a general template for the stereoselective syntheses of amino acids and heterocyclic scaffolds. A brief introduction covers a short history, nomenclature and general reactivity of oxazolones. The main body of this *tutorial review* highlights several applications of oxazolones as starting blocks for the diverse and stereoselective synthesis of amino acids, oxazoles, β-lactams, pyrroles, imidazolines, pyrrolines, and imidazoles.

1 Introduction

During recent years, diversity oriented synthesis of small molecule libraries has become increasingly important to the development of new pharmaceuticals.[1] New synthetic methods are allowing for efficient and rapid production of libraries of small yet complex molecules of biological importance. Screening of these libraries leads not only to identification of new drug candidates, but also to new therapeutic protein targets, which could be regulated by small molecules.

Oxazol-5-(4*H*)-ones (referred to as oxazolones throughout the rest of the article) contain numerous reactive sites allowing for a diverse set of possible modifications. This diverse reactivity makes them excellent substrates for their use in diversity oriented synthesis (Scheme 1). Highly substituted heterocyclic scaffolds can be directly accessed from oxazolones relatively easily and in a stereoselective manner. Natural and unnatural amino acids can also be easily isolated in enantiopure form by using oxazolone intermediates. This review will aim to summarize some of the applications of oxazolones in preparation of a wide variety of biologically interesting scaffolds.

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1.1 History

The first oxazolone was synthesized by Plöchl more than a century ago in 1883 *via* a condensation of benzaldehyde with

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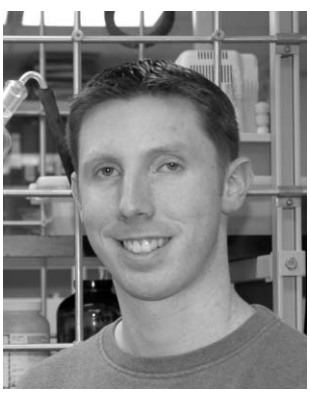
Jetze J. Tepe was born in Gouda, The Netherlands in 1968. He received his BS degree in 1992 from Jacksonville University, Florida and was awarded a PhD from the University of Virginia in 1998 where he worked with Prof. Timothy L. Macdonald. Following his PhD studies, he joined the laboratory of Prof. Robert M. Williams as a post-doctoral researcher. In 2000 he joined the faculty at Michigan State University as an Assistant Professor. In 2003 he received the American Cancer Research Scholar award and he was promoted in 2006 to Associate Professor. Dr Tepe is currently an editorial advisory board member of Current Bioactive Compounds and has served in various capacities including consultant and scientific advisory board member of several corporations including TCH Pharmaceuticals and ChemGenex Therapeutics.



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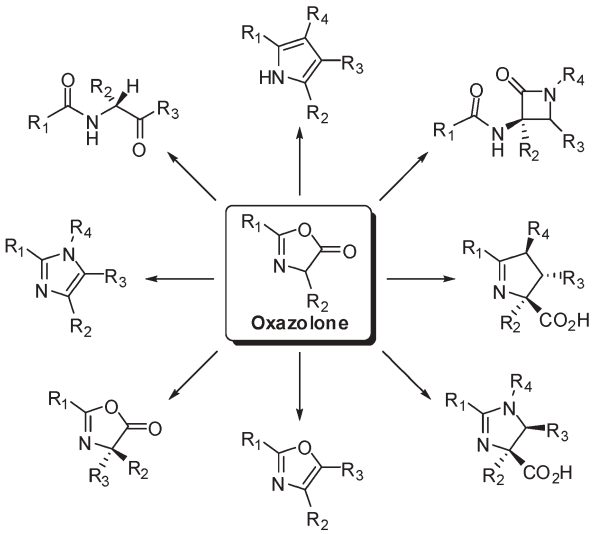


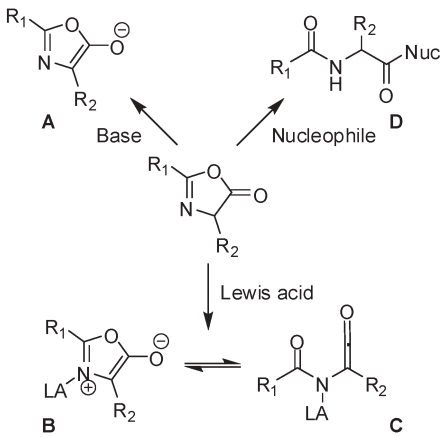
Scheme 1 Oxazolones in diversity oriented synthesis.

hippuric acid in the presence of acetic anhydride.[2] However, it was Erlenmeyer who established the first correct structure of oxazolones naming them ''azlactones'' in 1900.[3] The chemistry of oxazolones remained fairly unexplored until the 1940's, at which time the structure of penicillin was incorrectly thought to be an oxazolone.[4] Due to the high interest of penicillin at the time, many research groups focused on the reactivity of oxazolones. Although it was eventually determined that the structure of penicillin actually contained a β-lactam ring system instead of an oxazolone ring, the information obtained from these studies led way to the future development of new chemistry using the oxazolone scaffold.

1.2 Synthesis and general reactivity of oxazolones

Since the discovery of the Erlenmeyer azlactone synthesis, new methods have appeared in the literature for making oxazolones. Presently, oxazolones are commonly synthesized under much milder conditions by reacting N-acylated amino acid derivatives with dehydrating reagents. These dehydrating reagents usually consist of activated anhydrides or carbodiimides.[5]

The oxazolone ring system contains numerous reactive sites allowing for a wide variety of transformations (Scheme 2). The acidic nature of the proton(s) found at the C-4 position ($pK_a \approx 9$)[6] of the oxazolone scaffold allows for the easy formation of an oxazole enolate **A**, which can react with a range of electrophiles (Scheme 2). Alternatively, the use of Lewis acids with the oxazolones results in the formation of either the 1,3-dipole **B** (also known as a münchnone) or the reactive ketene intermediate **C** (Scheme 2), each yielding the possibility of synthesizing novel heterocyclic compounds *via* cycloaddition reactions.[7] Additionally, the oxazolone ring can be opened readily by a nucleophilic attack at the carbonyl of the ring system to form various types of protected amino acids (**D**). The remainder of this review will focus on the use of this rich reactivity of oxazolones in the synthesis of biologically interesting molecules.



Scheme 2 Reactivity of oxazolones.

1.3 Nomenclature

A variety of methods appear in the literature for naming oxazolones.[3,8] The ring is generally numbered according to the Hantzsch–Widman rules giving priority to the oxygen atom and numbering the ring in the direction of the nitrogen atom as shown in Fig. 1.[8]

One method refers to the oxazolone substrate as an amino acid derivative.[3] For example, the oxazolone derived from *N*-benzoyl alanine would be referred to as benzoyl alanine azlactone. A second method for naming oxazolones describes the substrate as a dihydrooxazole.[8] The oxazolone derived from *N*-benzoyl alanine would then be referred to as 5-oxo-2-phenyl-4-methyl-4,5-dihydrooxazole. This review will primarily use a third system which consists of naming the scaffold as an oxazolone derivative. The compound is given the parent name of oxazolone and the substituents are described in correspondence to their position on the ring. Using this system the oxazolone prepared from *N*-benzoyl alanine would be described as 2-phenyl-4-methyl-5-oxazolone.

2 Amino acids

Natural amino acids and their derivatives have become very important substrates for the synthesis of chiral ligands, pharmaceuticals, organocatalysts, as well as many other useful molecules. As a result, methods for creating novel amino acids are still of current interest in the synthetic community. Oxazolones have been proven to be excellent substrates for creating such compounds. The acidity of the oxazolone α-protons allows for a variety of transformations not traditionally seen when attempting to derivatize amino acids themselves. The following section of this review article will discuss some of the more recent developments in using oxazolones as key intermediates in the synthesis of amino acids.

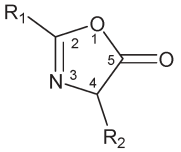
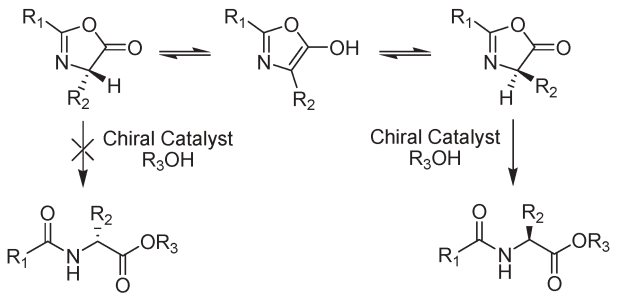


Fig. 1 Oxazolone ring system.



Scheme 3 Dynamic kinetic resolution of oxazolones.

2.1 Dynamic kinetic resolution

One method for the preparation of enantiomerically pure nonquaternary amino acids is the dynamic kinetic resolution of oxazolones (Scheme 3).[9] This process takes advantage of the fact that oxazolones epimerize readily under mild reaction conditions. A chiral catalyst reacts preferentially with one of the two enantiomers of the racemate forming an irreversible amino ester product. At the same time, the unreactive enantiomer undergoes epimerization to the more reactive enantiomer allowing theoretically for complete conversion of the racemate to the desired stereoisomer (Scheme 3).[9]

The dynamic kinetic resolution (DKR) of oxazolones has been reported using both enzymatic[10–12] and small molecule catalyst systems.[13,14] While enzymatic resolutions of oxazolones have been shown to be successful, this review will focus only on some of the more recent small molecule resolutions of oxazolones. One of the first successful examples using a small molecule to catalyze the dynamic kinetic resolution of oxazolones was demonstrated by Fu and coworkers in 1998.[14] The authors described the use of planar-chiral derivatives (*e.g.* Fig. 2) of 4-(dimethylamino)pyridine (DMAP) to catalyze the methanolysis of oxazolone substrates resulting in enantiomerically enriched amino acids.[15] These DMAP derivatives catalyze kinetic resolutions of most oxazolones with excellent yields of greater than 90% and enantiomeric excesses in the range of 44% to 61% (Scheme 4). Examples using both aromatic and aliphatic substitution on the oxazolone ring have been demonstrated (Scheme 4).[14] It appears that the level of enantiomeric excess is solvent dependent with toluene furnishing the highest level of stereoselectivity. Adding steric bulk to the alcohol nucleophile increases the enantioselectivity of the reaction but also lengthens reaction times.

More recent work in this area was published by Berkessel and coworkers in 2005 in which they utilized urea and thiourea bifunctional organocatalysts to promote the dynamic kinetic

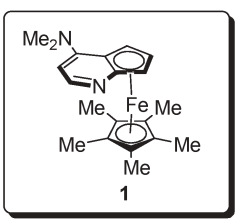
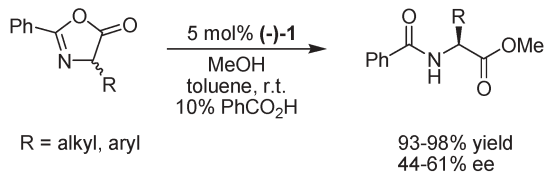
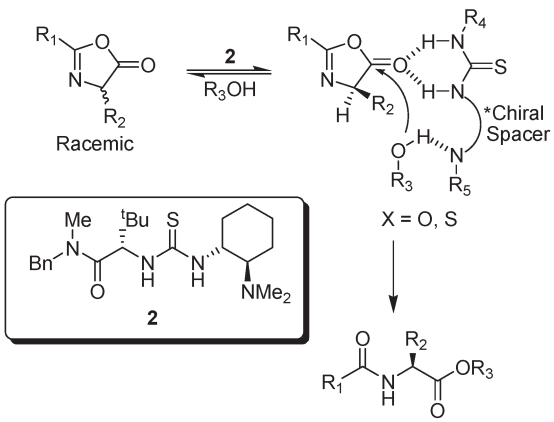


Fig. 2 Chiral DMAP derivative.



Scheme 4 DKR of oxazolones using DMAP derivatives.



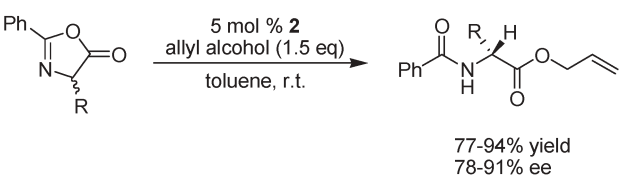
Scheme 5 DKR of oxazolones using thiourea bifunctional catalysts.

resolution of oxazolones.[13] The Lewis acidic thiourea moiety of the catalyst is believed to activate the oxazolone carbonyl *via* hydrogen bonding forming a chiral environment around the oxazolone (Scheme 5). After complexation of the oxazolone to the catalyst, a tethered Lewis basic portion of the catalyst is proposed to direct the approach of the alcohol to the desired face of the oxazolone by means of a second hydrogen bonding interaction (Scheme 5).

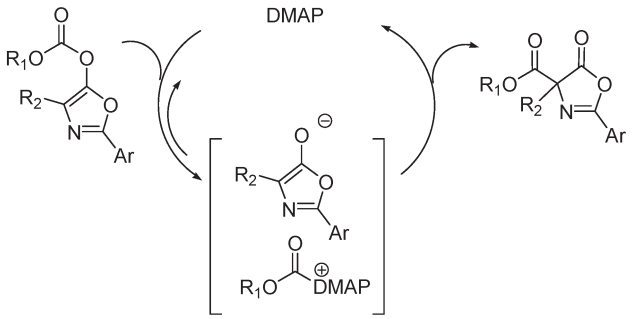
These catalysts work well with a wide range of oxazolones providing enantiomeric excesses up to 91% (Scheme 6). The use of smaller primary alcohols results in higher conversion rates than bulkier alcohols. Allyl alcohol was found to yield the best results. To complement the theory that complexation of the catalyst to the substrate occurs *via* hydrogen bonding, solvents that are hydrogen bond acceptors, such as THF, provide little or no stereoselectivity. Similar to Fu's work in this area, toluene was found to be the optimal solvent for reactions with these catalysts.[14]

2.1 Enantioselective acylation

Quaternary substituted amino acid derivatives can be accessed directly from the nucleophilic ring opening of quaternary substituted oxazolones. One reaction to produce such oxazolones is the Steglich reaction.[16] The Steglich reaction involves a catalyzed rearrangement of O-acylated oxazoles to form C-4



Scheme 6 DKR of oxazolones using thiourea bifunctional catalyst.



Scheme 7 Steglich reaction.

acylated oxazolones (Scheme 7). This reaction was first discovered by Steglich and Hofle in 1970.[16] The authors found that nucleophilic bases such as DMAP readily promote the rearrangement forming oxazolones containing a quaternary center (Scheme 7). The initial reaction of DMAP with the O-acylated oxazole is believed to be reversible, while formation of the product appears to be irreversible due to the stability of the oxazolone product (Scheme 7).[17] Since that time, chiral nucleophiles have been used to make new enantiomerically enriched oxazolone scaffolds in a similar fashion.[18–21]

The first asymmetric acyl migration of oxazolones was reported in 1998 by Fu and Ruble.[15,17] The authors reported a different DMAP derivative named PPY* (**3**), which was found to be more effective than their original catalyst in these types of systems (Fig. 3).

Alkyl substituents at the 2-position of the oxazolone provide lower enantioselectivity than aryl and heteroaryl substituents at that same position. The reaction appears to tolerate a wide range of substituents at the C-4 position of the oxazolone resulting in high enantioselectivity (Scheme 8). Choosing the appropriate migrating acyl group can enhance the stereoselectivity of the reaction. The use of benzyl substituted acyl groups tend to result in higher stereoselectivity than most aliphatic groups.[17]

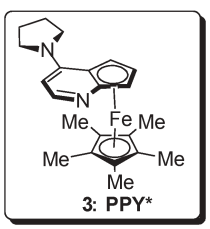
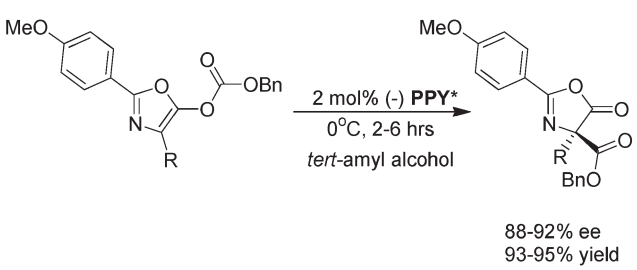
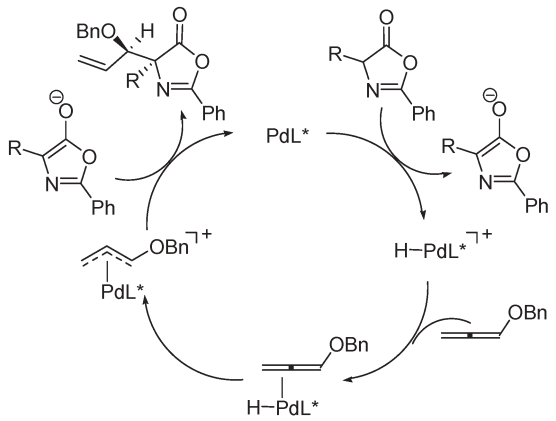


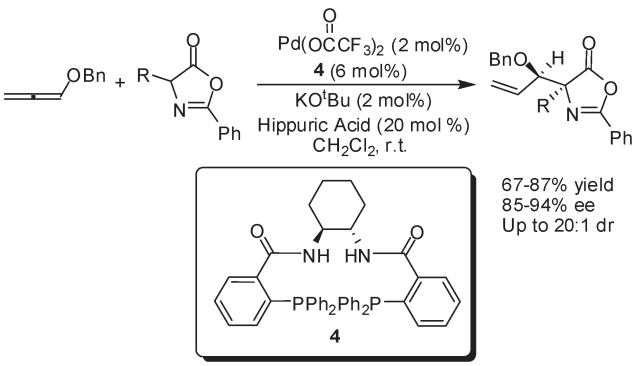
Fig. 3 Fu's PPY* DMAP derivative.



Scheme 8 PPY* catalyzed Steglich reaction.



Scheme 9 Proposed mechanism of alkylation using allenes.



Scheme 10 Alkylation of oxazolones using allenes.

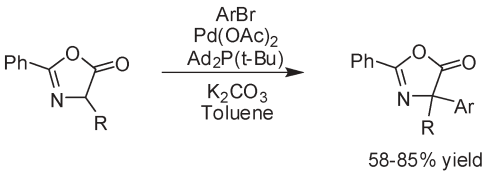
2.3 Enantioselective alkylation

A second asymmetric transformation that results in the formation of quaternary oxazolones is the alkylation of oxazolones in the C-4 position.[22] One of the more novel alkylations of oxazolones was reported by Trost and coworkers involving a palladium-catalyzed addition of oxazolones to electron rich allenes (Scheme 9).[23] The reaction overcomes regioselectivity problems generally associated with allene chemistry by substituting one end of the allene with an electron rich alkoxy group.

The overall reaction works very well for generating a quaternary center at the C-4 position of the oxazolone ring. Oxazolones with aliphatic substituents at the C-4 position work best for this reaction resulting in high yields (67–87%) and excellent enantiomeric excesses (90–94%) (Scheme 10). The diastereoselectivity was also reported to be high in these reactions usually occurring in about a 20 : 1 ratio (Scheme 10). The combination of potassium *tert*-butoxide and hippuric acid is required to sufficiently buffer the reaction, allowing for catalysis to occur.

2.4 Arylation

Arylation of oxazolones in the C-4 position results in novel quaternary amino acids. In 2003, Hartwig and Liu reported the first palladium catalyzed arylation of oxazolones for the synthesis of quaternary amino acids (Scheme 11).[24]



Scheme 11 Arylation of oxazolones.

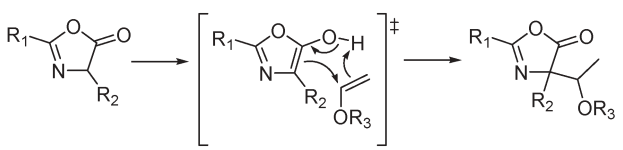
Oxazolones are reactive towards such a transformation due to their high acidity and nonsterically encumbering cyclic structure. The reaction involves the coupling of the sp^2 carbon of arenes with the enolate of oxazolones. The catalyst system consists of using $Pd(OAc)_2$ along with the sterically hindered electron rich ligand $Ad_2P(t\text{-}Bu)$ (Scheme 11, Ad = adamantyl). K_2CO_3 was found to be the optimal base for this particular reaction. Reactions in aromatic solvents result in much higher yields than those conducted in THF, DMF, or CH_3CN.

The reaction provides good yields with a wide range of aryl bromide substrates. The use of electron rich or electron neutral aryl groups produces the best results (75–85%), whereas electron poor aryl groups tend to give slightly lower yields ($\sim$60%). Aryl groups that can undergo Heck reactions, such as 4-bromostyrene, underwent the desired coupling reaction in good yields (75%). The use of the vinyl bromide 1-bromo-2-methylpropene also works well in the reaction resulting in a 60% yield. Aryl substrates with a pyridyl nitrogen tend to deactivate the palladium catalyst and result in the decrease of product formation. A wide range of oxazolone substrates consisting of both aliphatic and aromatic substituents undergo the desired coupling reaction in good yields.

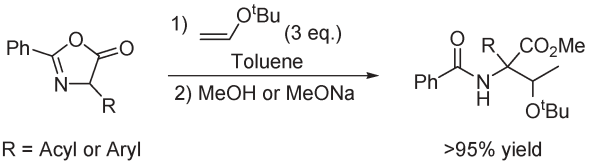
2.5 Ene reactions

Recently our group developed an intermolecular ene reaction using oxazolones in combination with enol ethers (Scheme 12).[25] The reaction takes place under much milder conditions than normal ene reactions, which is presumably due to the strong enol character of the oxazolone ring.

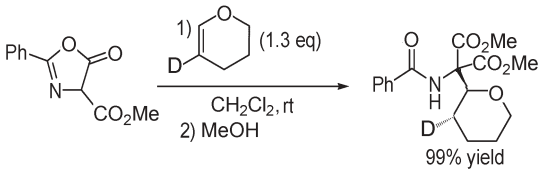
Oxazolones containing substituents that help stabilize the substrate's enol tautomer appear to facilitate the reaction much more readily than those that do not. Oxazolones substituted with acyl groups in the C-4 position provide ene reaction products in minutes at room temperature, whereas oxazolones with aryl substituents usually require higher temperatures to promote product formation (Scheme 13). On the other hand, alkyl substituents in the C-4 position of oxazolones do not react under the present set of conditions. Labeling studies indicate that the reaction proceeds *via* a concerted mechanism and not mere protonation of the enol ether substrate (Scheme 12). Ring opening of the ene adduct with methanol or water results in the formation of quaternary substituted amino esters or acids (Scheme 13).



Scheme 12 Intermolecular ene reaction with enol ethers.



Scheme 13 Ene reaction with various oxazolones.



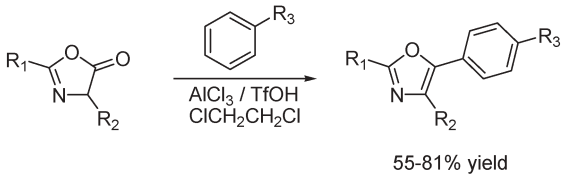
Scheme 14 Ene reaction of oxazolones with substituted enol ethers.

Higher substituted enol ethers also provide the ene products in good yields. 1,2-Substituted enol ethers provide the desired products in good yields, albeit with longer reaction times of up to 10 hours (Scheme 14). Even higher substituted enol ethers provide ene-products in good yields after refluxing in CH_2Cl_2 for 24 hours. The nature of the oxygen protection group of the enol ether substrate appears to be critical to the success of the reaction. Reduction of the electron density of the enol ether decreases the reaction rates and in certain cases results in isolation of only starting materials after several hours. The choice of solvent does not affect the reaction rates or yields significantly as seen by the fact that CH_2Cl_2, THF and toluene all provide similar results at room temperature.

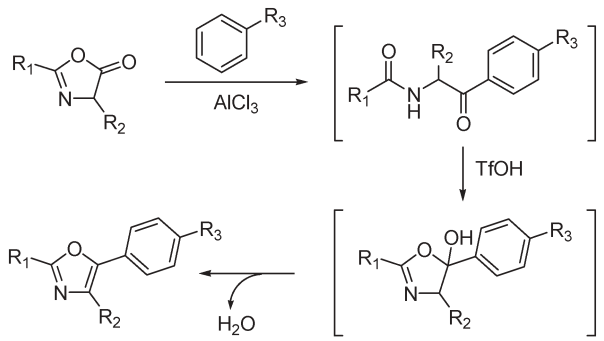
3 Oxazoles

The oxazole scaffold is found in a great variety of biologically important molecules. A large number of methods for producing oxazoles already exist in the literature; however, due to the importance and great variety of oxazoles found in biologically active molecules, new methods for synthesizing oxazoles are still of great interest.

In an effort to develop a new route to highly substituted oxazoles, our group devised a protocol consisting of a one-pot Friedel–Crafts/Robinson–Gabriel synthesis for producing 2,4,5-trisubstituted oxazoles from oxazolones (Scheme 15).[26] The idea originated from the fact that the Robinson–Gabriel cyclodehydration of 2-acylamino ketones is one of the most versatile routes for producing oxazoles, while at the same time it is known that 2-acylamino ketones can be prepared from oxazolones *via* a Friedel–Crafts reaction.[26] The one-pot reaction is carried out utilizing a combination of aluminium chloride and trifluoromethanesulfonic acid, resulting in the



Scheme 15 One pot Friedel–Crafts/Robinson–Gabriel synthesis.



Scheme 16 Proposed mechanism for oxazole formation.

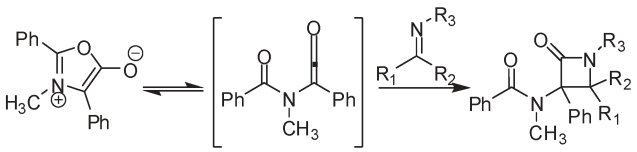
formation of oxazoles directly from oxazolones. The reaction appears to work well for a wide variety of oxazolone substrates including both aromatic and alkyl substituted oxazolones. As expected, the reaction works best with either electron neutral or electron rich arenes. Electron deficient arenes provide little or no product formation.

It is believed that the oxazolone is first activated by the aluminium chloride, followed by nucleophilic addition of the aromatic species to the oxazolone yielding a 2-acylamino ketone (Scheme 16). The ketone carbonyl is then protonated by the trifluoromethanesulfonic acid, activating the substrate towards cyclization and dehydration to the corresponding oxazole (Scheme 16).

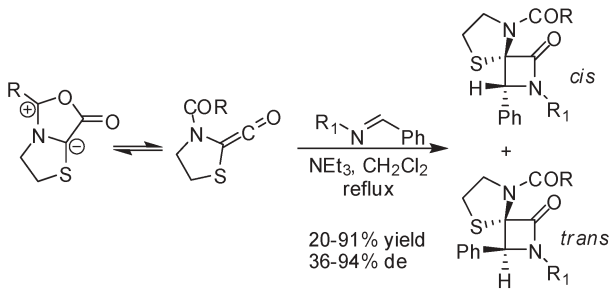
4 β-Lactams

The β-lactam scaffold is accessible *via* the reaction of imines with oxazolones, as demonstrated by Huisgen and Funke.[27] The authors investigated ketene formation from münchnones followed by a [2 + 2] cycloaddition reaction in the presence of imines (Scheme 17). The imines tested for this reaction contained alkyl and phenyl substituted nitrogens (R_3) and contained either one or two aryl substituents at the imine carbon (R_1 and R_2).

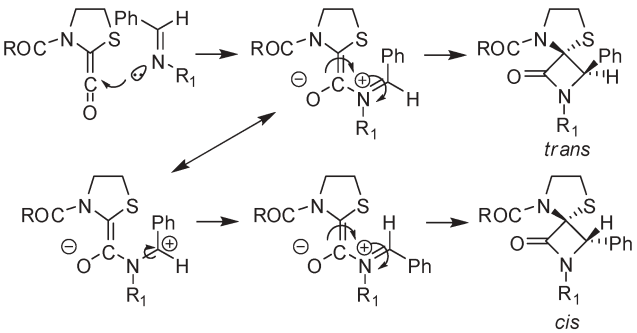
β-Lactams have also been prepared by Cremonesi and coworkers utilizing bicyclic münchnones with imines under basic conditions (Scheme 18).[28] The authors illustrated good control of diastereoselectivity through manipulation of the imine N-substituent. The reaction provided mainly the *cis*-product (with respect to the sulfur and phenyl groups) when performed with imines containing electron withdrawing moieties. Conversely, high yields of *trans*-β-lactams could be selectively formed when imines contained electron donating groups.[28] Both products are proposed to arise from initial attack of the imine to the least-hindered side of the ketene, as shown in Scheme 19. When R_1 is an electron donating group the initial iminium intermediate is stabilized and the reaction



Scheme 17 Proposed mechanism of β-lactam formation.



Scheme 18 β-Lactam formation.



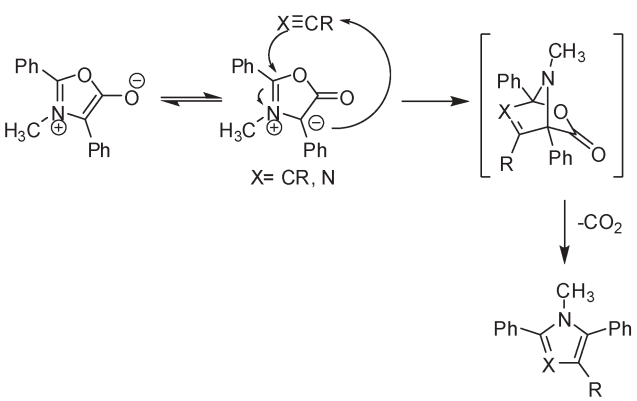
Scheme 19 Reaction diastereoselectivity.

undergoes a [2 + 2] cycloaddition to afford the *trans*-products. However, the iminium intermediate is destabilized when R_1 is an electron withdrawing group, causing double bond isomerization, which gives rise to the thermodynamically favored *cis*-products.[28]

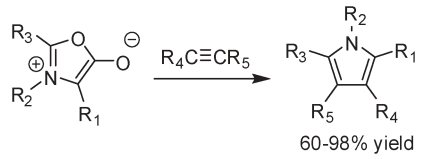
5 Pyrroles

Pyrrole and imidazole scaffolds constitute a large part of the literature regarding products formed from 1,3-dipolar cycloadditions using oxazolones.[7] This cycloaddition is promoted when the oxazolone is in its münchnone form, wherein it acts as a dipole and reacts with dipolarophiles such as alkynes and nitriles, respectively (Scheme 20).

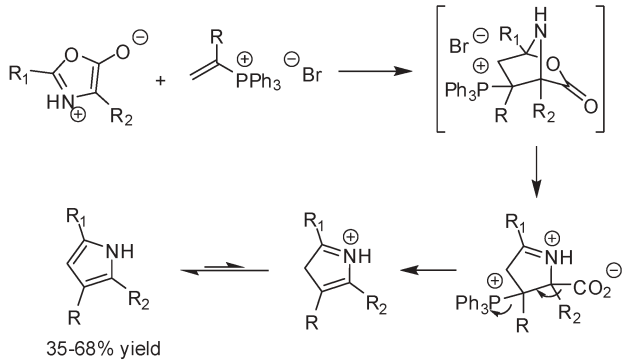
The majority of pyrrole scaffolds obtained from oxazolones arise from reaction with alkynes and alkyne derivatives.[7] Earlier syntheses of pyrroles *via* oxazolones were performed by



Scheme 20 Representative 1,3-dipolar cycloaddition.



Scheme 21 Pyrrole formation.



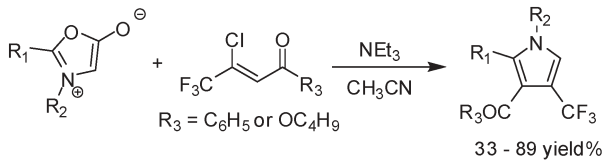
Scheme 22 Pyrrole formation from vinyl phosphonium salts.

reacting münchnones with alkynes through decarboxylative cycloadditions.[29] Pioneering work by Huisgen demonstrated the preparation of a wide range of pyrroles with substituent diversity at every atom of a pyrrole scaffold (Scheme 21).[29] These early studies focused on pyrrole scaffolds wherein $R_1 = R_3$ or $R_4 = R_5$ (Scheme 21). Reaction times and temperatures varied for most reactions and yields were generally high.[29] More recently, this procedure was amended to include *in situ* N-alkylation through the addition of 2,6-di-*tert*-butylpyridine and a highly reactive alkylating reagent.[30] In this way *N*-alkyl pyrroles could be produced from unsubstituted *N*-acyl amino acids.

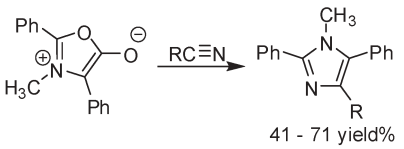
Similarly, pyrroles have been synthesized from münchnones through their reaction with alkyne equivalents. The use of vinyl phosphonium salts as alkyne equivalents in cycloaddition reactions with münchnones has been reported.[31] In these reactions, cycloadditions were performed under refluxing (THF–DMF solvent mixture) or sonication conditions and PPh_3 was eliminated after decarboxylation to afford the anticipated products in moderate yields (Scheme 22). The pyrroles in this reaction were regioselectively produced, driven by the strong interaction between the phosphonium and the carbonyl groups. The preparation of pyrroles has also been reported *via* the reaction of münchnones with vinyl-chlorinated alkenes (Scheme 23).[32] The reaction was performed using alkenes containing either an ester or a ketone and products were formed regioselectively in each case in good yields. During the reaction, a bicyclic intermediate similar to that shown in Scheme 22 is formed and elimination of HCl after decarboxylation affords the desired pyrroles.

6 Imidazoles

Construction of the imidazole scaffold can be performed by reacting oxazolones with appropriate nitriles or with nitrile equivalents. Huisgen and coworkers reported a decarboxylative cycloaddition reaction wherein imidazole formation



Scheme 23 Pyrrole formation from vinyl-chlorinated alkenes.

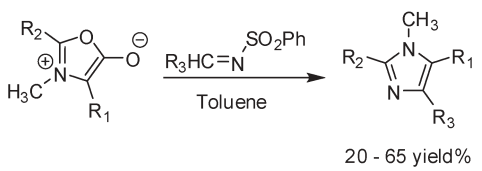


Scheme 24 Imidazole formation with nitriles.

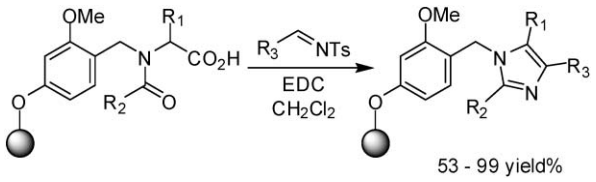
occurred when münchnones were allowed to react with electron-deficient nitriles under various temperature and solvent conditions (Scheme 24).[33] This reaction afforded imidazoles containing electron withdrawing groups in moderate yields.

Studies by Consonni and coworkers also demonstrated a successful imidazole preparation starting from the oxazolone scaffold.[34] Their work involved a 1,3-dipolar cycloaddition reaction of *N*-(phenylmethylene)benzenesulfonamides with oxazolones formed *in situ* (Scheme 25). The resulting bicyclic intermediates consequently decompose, releasing CO_2 and benzenesulfinic acid, to form imidazoles as products. Their approach relies on the presence of a phenylsulfonyl moiety acting as a good leaving group, and its expulsion permits aromatization to the imidazole products. In this way, products are formed where R_1 and R_2 contain H, alkyl, or aryl groups and where R_3 contains aryl groups with both electron donating and withdrawing substituents.[34]

Bilodeau and Cunningham constructed imidazoles *via* similar cycloaddition reactions, but their work is notably different in that solid-support syntheses were used as a means to suppress the self condensation of oxazolones.[35] Their studies involved münchnone formation *in situ* through dehydration of resin-bound amino acids followed by 1,3-dipolar cycloaddition with *N*-tosyl imines to give polymer-linked imidazoles (Scheme 26). Liberation from the resin by heating in acetic acid at 100 °C for two hours then afforded the desired imidazoles. It was reported that moderate to high yields were obtained when all R groups used were aromatic. Furthermore, imidazoles were produced containing electron withdrawing aromatic R_1 substituents, electron withdrawing and donating R_2 substituents, and 3- and 4-pyridyl R_3 substituents.



Scheme 25 Imidazole formation with phenylsulfonyl imines.



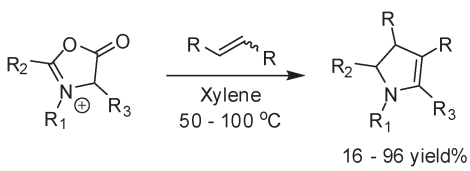
Scheme 26 Solid-support synthesis of imidazoles.

7 Pyrrolines

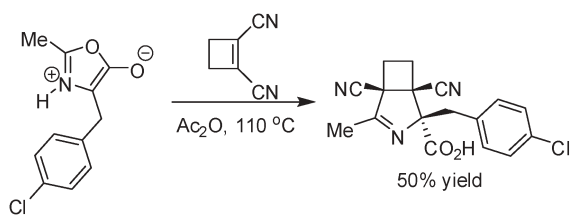
The pyrroline scaffold is readily generated *via* reactions utilizing oxazolones. Early exploration of this chemistry by Gotthardt, Huisgen, and Schaefer involved Δ^2-pyrroline formation through the cycloaddition reaction of oxazolones with alkenes (Scheme 27).[36] It was discovered that alkenes disubstituted with aryl and acyl groups would react with münchnones when heated in xylene to afford pyrrolines in moderate to high yields. Both *cis*- and *trans*-alkenes were used in their studies and racemic mixtures were formed regardless of olefin geometry.

Likewise, the oxazolone scaffold has been utilized by Maryanoff and coworkers in the diastereoselective preparation of a Δ^1-pyrroline.[37] Their work involved *in situ* münchnone generation by acetic anhydride followed by the cycloaddition with an alkene (Scheme 28). It was reported that only the *exo*-bicyclic adduct was isolated in 50% yield after heating 4-chlorophenylalanine with acetic anhydride and 1,2-dicyanocyclobutene.

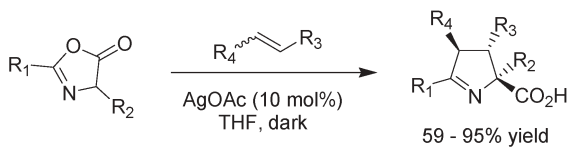
A more recent example reports an *exo*-selective cycloaddition of oxazolones with alkenes affording Δ^1-pyrrolines in good yields (Scheme 29).[38] It was discovered during the exploration of this chemistry that the use of 10 mol% silver acetate with electron deficient alkenes at room temperature



Scheme 27 Pyrroline formation.



Scheme 28 Diastereoselective pyrroline formation.



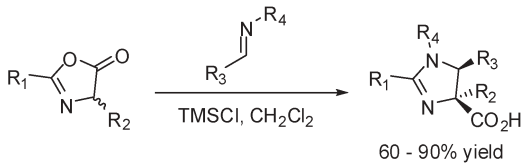
Scheme 29 Silver catalyzed diastereoselective pyrroline formation.

gave good product yields. The *exo*-selectivity provided pyrrolines with R_2 and R_3 *syn* to each other. The relationship between R_3 and R_4 was *trans* in the collected products, regardless of the starting alkene geometry. This *trans* relationship is proposed to arise from isomerization to give the more thermodynamically stable product.

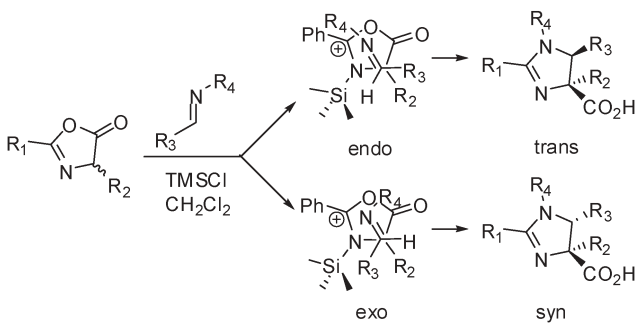
8 Imidazolines

Imidazolines with four point diversity can be diastereoselectively produced *via* a silicon mediated 1,3-dipolar cycloaddition of oxazolones with imines (Scheme 30).[39] The chemistry developed allows for a one-pot reaction of an imine and an *in situ* Lewis acid-generated münchnone. The münchnone and imine are allowed to react at slightly elevated temperatures to give imidazoline products. The range and limitations of the chemistry have been explored and it has been reported that the imidazoline substituents may include alkyl, acyl, aryl, and heterocyclic groups.[39]

The major products in this reaction were predominantly *trans* (with respect to R_2 and R_3) when R_1 was aryl, and it was steric effects which were postulated to direct the stereochemical outcome of the reaction.[39] The reaction proceeded through a cycloaddition where the *endo* approach of the imine was preferred. It was proposed that the *exo* approach was disfavored due to the steric interaction of the bulky silyl group with the imine R_3 substituent (Scheme 31). Through reduction of resonance stabilization with R_1 as alkyl or benzyl, diastereoselectivity was either lowered or lost. Complete reversal of diastereoselectivity was observed when the alkyl R_1, the aryl R_3, and the benzyl R_4 substituents were kept constant, and R_2 substituents changed from alkyl to aryl (Table 1).[40] The *syn* diastereoselectivity appeared to result from π-stacking interactions between the aryl R_2 and R_3 substituents (Scheme 31). The enhancement of *syn* selectivity when R_2 was made a π-donor and R_3 a π-acceptor supports this rationale for reversal of diastereoselectivity.

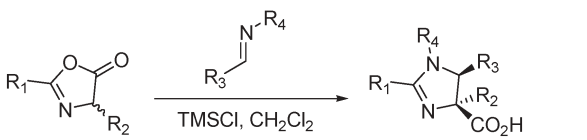


Scheme 30 TMSCl mediated imidazoline formation.



Scheme 31 Diastereoselectivity of imidazoline formation.

Table 1 Regiochemistry of imidazoline formation



R_1	R_2	R_3	R_4	*syn* : *anti*
Me	Bn	Ph	Bn	75 : 25
Ph	Bn	Ph	Bn	>5 : 95
Me	*p*-OMePh	*p*-NO_2Ph	Bn	>95 : 5
Ph	*p*-OMePh	*p*-NO_2Ph	Bn	>5 : 95

Conclusions

Since their initial discovery, oxazolones have emerged as an important class of compounds, useful for synthesizing biologically interesting compounds. As demonstrated in this review, the oxazolone scaffold contains numerous reactive sites allowing for a large diversity of transformations. Through utilization of the high acidity of these compounds, enantiomerically pure natural and unnatural amino acids can be synthesized *via* enolate chemistry. The electrophilic carbonyl of oxazolones accepts a wide range of nucleophiles to produce ring opened products. Mild nucleophiles such as arenes can even react with the oxazolone carbonyl under Friedel–Crafts type conditions. The ability of the oxazolone substrate to react as a 1,3 dipole under Lewis acidic conditions makes them excellent substrates for use in stereoselective cycloadditions. Numerous dipolarophiles can be used in these cycloaddition reactions giving rise to classes of biologically-active, five membered heterocyclic compounds. Further exploitation of the rich chemistry of oxazolones will undoubtedly lead to novel compounds with biological activity and new pharmaceutical applications.

References

1 S. L. Schreiber, *Science*, 2000, **287**, 1964.
2 J. Plochl, *Ber. Dtsch. Chem. Ges.*, 1883, **16**, 2815.
3 E. Erlenmeyer, *Ber. Dtsch. Chem. Ges.*, 1900, **33**, 2036.
4 H. T. Clarke, J. R. Johnson and R. Robinson, The Chemistry of Penicillin, in *Oxazoles and Oxazolones*, Princeton University Press, Princeton, NJ, 1949, pp. 688–848.
5 A. K. Mukerjee, *Heterocycles*, 1987, **26**, 1077.
6 M. Goodman and L. Levine, *J. Am. Chem. Soc.*, 1964, **86**, 2918.
7 A. Padwa and W. H. Pearson, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, 1st edn, 2002, John Wiley and Sons, Hoboken, NJ, pp. 682–747.
8 Reported by IUPAC, *J. Am. Chem. Soc.*, 1960, **82**, 5545.
9 H. Pellissier, *Tetrahedron*, 2003, **59**, 8291.
10 S. A. Brown, M. C. Parker and N. J. Turner, *Tetrahedron: Asymmetry*, 2000, **11**, 1687.
11 J. Z. Crich, R. Brieva, P. Marquart, R. L. Gu, S. Flemming and C. J. Sih, *J. Org. Chem.*, 1993, **58**, 3252.
12 V. Daffe and J. Fastrez, *J. Am. Chem. Soc.*, 1980, **102**, 3601.
13 A. Berkessel, S. Mukherjee, F. Cleemann, T. N. Muller and J. Lex, *Chem. Commun.*, 2005, 1898.
14 J. Liang, J. C. Ruble and G. C. Fu, *J. Org. Chem.*, 1998, **63**, 3154.
15 G. C. Fu, *Acc. Chem. Res.*, 2000, **33**, 412.
16 W. Steglich and G. Hofle, *Tetrahedron Lett.*, 1970, 4727.
17 J. C. Ruble and G. C. Fu, *J. Am. Chem. Soc.*, 1998, **120**, 11532.
18 H. V. Nguyen, D. C. D. Butler and C. J. Richards, *Org. Lett.*, 2006, **8**, 769.
19 J. G. Seitzberg, C. Dissing, I. Sotofte, P. O. Norrby and M. Johannsen, *J. Org. Chem.*, 2005, **70**, 8332.
20 S. A. Shaw, P. Aleman, J. Christy, J. W. Kampf, P. Va and E. Vedejs, *J. Am. Chem. Soc.*, 2006, **128**, 925.
21 S. A. Shaw, P. Aleman and E. Vedejs, *J. Am. Chem. Soc.*, 2003, **125**, 13368.
22 B. M. Trost and X. Ariza, *J. Am. Chem. Soc.*, 1999, **121**, 10727.
23 B. M. Trost, C. Jakel and B. Plietker, *J. Am. Chem. Soc.*, 2003, **125**, 4438.
24 X. X. Liu and J. F. Hartwig, *Org. Lett.*, 2003, **5**, 1915.
25 J. S. Fisk and J. J. Tepe, *J. Am. Chem. Soc.*, 2007, DOI: 10.1021/ja0627904.
26 M. Keni and J. J. Tepe, *J. Org. Chem.*, 2005, **70**, 4211.
27 E. Funke and R. Huisgen, *Chem. Ber.*, 1971, **104**, 3222.
28 G. Cremonesi, P. Dalla Croce and C. La Rosa, *Helv. Chim. Acta*, 2005, **88**, 1580.
29 R. Huisgen, H. Gotthard, H. O. Bayer and F. C. Schaefer, *Chem. Ber.*, 1970, **103**, 2611.
30 F. M. Hershenson and M. R. Pavia, *Synthesis*, 1988, 999.
31 F. Clerici, M. L. Gelmi and P. Trimarco, *Tetrahedron*, 1998, **54**, 5763.
32 T. Okano, T. Uekawa, N. Morishima and S. Eguchi, *J. Org. Chem.*, 1991, **56**, 5259.
33 E. Brunn, E. Funke, H. Gotthard and R. Huisgen, *Chem. Ber.*, 1971, **104**, 1562.
34 R. Consonni, P. D. Croce, R. Ferraccioli and C. Larosa, *J. Chem. Res. (S)*, 1991, 188.
35 M. T. Bilodeau and A. M. Cunningham, *J. Org. Chem.*, 1998, **63**, 2800.
36 H. Gotthardt, R. Huisgen and F. C. Schaefer, *Tetrahedron Lett.*, 1964, 487.
37 C. A. Maryanoff, C. B. Karash, I. J. Turchi, E. R. Corey and B. E. Maryanoff, *J. Org. Chem.*, 1989, **54**, 3790.
38 S. Peddibhotla and J. J. Tepe, *J. Am. Chem. Soc.*, 2004, **126**, 12776.
39 S. Peddibhotla and J. J. Tepe, *Synthesis*, 2003, 1433.
40 V. Sharma and J. I. Tepe, *Org. Lett.*, 2005, **7**, 5091.