ISOXAZOL-5-ONES: UNUSUAL HETEROCYCLES WITH GREAT SYNTHETIC POTENTIAL

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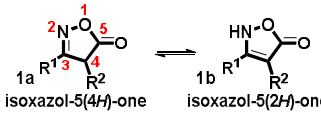
Abstract. *Recent applications of isoxazol-5-ones in organic synthesis are revised in this chapter. The main recent technologies to convert the isoxazolone ring into other functional groups and heterocycles such as alkynes, ketones, 2H-azirines, aziridines, piperidines, pirydines, quinolines, isoquinolines, among others, are presented accompanied by critical discussions on the observed reactivities. Finally, the chapter also describes examples of the use of isoxazolones in the context of the total synthesis of natural products.*

Contents

1. Introduction

1.1. General reactivity

Isoxazol-5-ones **1** (or isoxazolin-5-ones) are heterocyclic compounds of 5 atoms that can be engaged in numerous organic transformations. The reactivity of the isoxazolone ring is generally derived from a few remarkable properties: i) it has three nucleophilic sites: N2, C4 and the exocyclic carbonyl O atom, ii) it has an acidic C4-H bond, of comparable strength to carboxylic acids,[1] and iii) it has a weak N-O bond (BDE=151 kcal.mol^{-1}),[2] which can be cleaved to trigger reaction cascades, while also generally releasing a CO_2 molecule (Scheme 1).



Scheme 1. Presentation of isoxazol-5-ones.

Arguably as a consequence of this rich reactivity platform, isoxazol-5-ones have been identified as promising candidates for the development of new drugs and materials; and have gained increasing popularity as synthetic intermediates.[3]

In the context of the recent burgeoning around the chemistry of isoxazol-5-ones, this chapter is devoted to the presentation and discussion of modern selected examples. For a more detailed presentation of their preparation and early established synthetic methods, the reader is invited to visit previous reviews on this theme.[3]

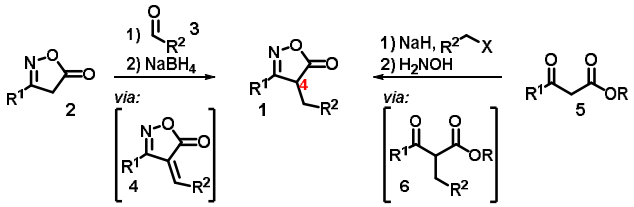
2. Applications in organic synthesis

2.1. Functionalization of the isoxazolone ring

2.1.1. Alkylation

Because the isoxazolone ring has three nucleophilic sites, C4, N2 and the exocyclic carbonyl O atom, the regioselective alkylation of this heterocycle must be carefully planned. Among these nucleophilic positions, N2 and C4 are typically the most reactive; and the result of an alkylation protocol employing a C4-unsubstituted isoxazol-5-one **2** is generally a mixture of regioisomers at these positions.[4] In this context, it is relevant to keep in mind that the Curtin-Hammet principle applies here: the distribution of alkylated compounds will not necessarily reproduce the initial distribution of tautomers, because they are in rapid equilibration.[5]

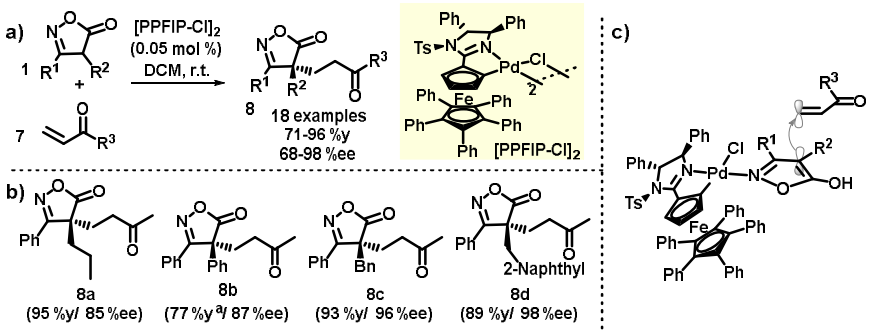
As a consequence of this scenario, early procedures aiming at the preparation of 3,4-disubstituted isoxazol-5-ones **1** were based on a two-step synthetic sequence: i) a Knoevenagel condensation of a 4-unsubstituted isoxazol-5-one **2** with aldehydes **3** (or ketones), leading to a 4-alkylideneisoxazol-5-one intermediate **4**, followed by ii) a hydride addition onto this Michael acceptor;[6] or alternatively, an alkylation strategy based on i) the alkylation of a β-ketoester precursor **5**, thus producing α-alkyl-β-ketoesters **6** followed by ii) cyclization with hydroxylamine to afford the corresponding isoxazol-5-one **1** (Scheme 2).



Scheme 2. Classical approaches for the selective preparation of C4-alkylated isoxazol-5-ones **1**.

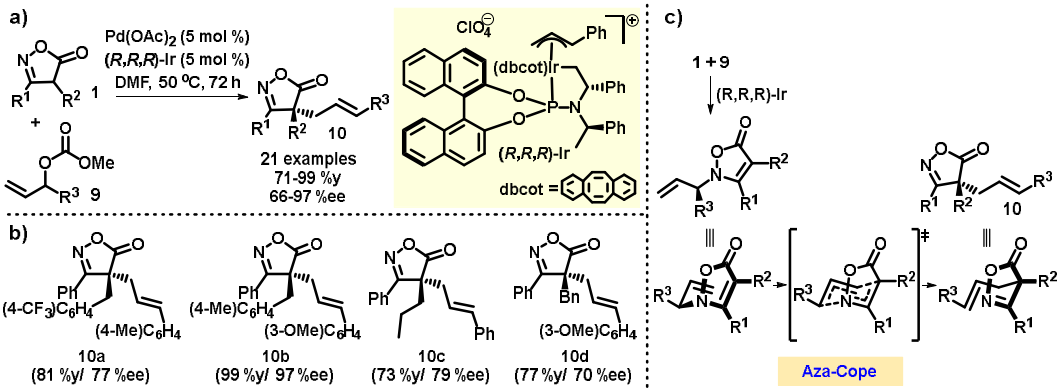
In contrast to these well-established strategies, modern catalytic protocols have been reported by Peters and co-workers, who described two new approaches for the asymmetric alkylation of isoxazol-5-ones **1**. The

first reported route relies on a Pd(II)-catalyzed Michael addition of isoxazol-5-ones **1** onto vinylketones **7**, thus affording the corresponding adducts **8** in high enantioselectivities (Schemes 3a and b).[7] The Pd(II) is suggested to coordinate to N2 of the isoxazolone substrate **1**, thus activating this pronucleophile towards tautomerization and bringing the chiral environment of the catalyst to guide the approach of the nucleophile onto the Michael acceptor **7** (Scheme 3c).



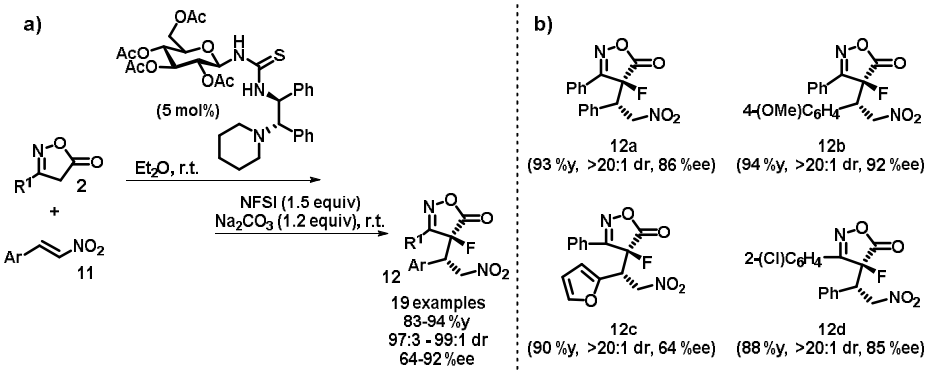
Scheme 3. a) Catalytic asymmetric protocol reported by Peters and co-workers for the Michael addition of isoxazolones **1** onto vinylketones **7**.[a] Using 0.15 mol % of $[PPFIP\text{-}Cl]_2$. **b)** Selected examples.[3c] **c)** Proposed mechanism.

The second synthetic route is based on the combination of Pd- and Ir-catalysts to execute the *N*-allylation of an isoxazolone **1**, followed by an *aza*-Cope rearrangement to afford 4-allylisoxazolones **10**. In this context, $Pd(OAc)_2$ is employed as co-catalyst in order to facilitate tautomerization processes involving isoxazol-5-one **1**, and it has been remarked to increase the enantioselectivity of this process (Scheme 4).[8,9]



Scheme 4. a) Synergistic asymmetric allylation strategy using Pd and Ir catalysts developed by Peters and co-workers. **b)** Selected examples.[3c] **c)** Proposed mechanism.

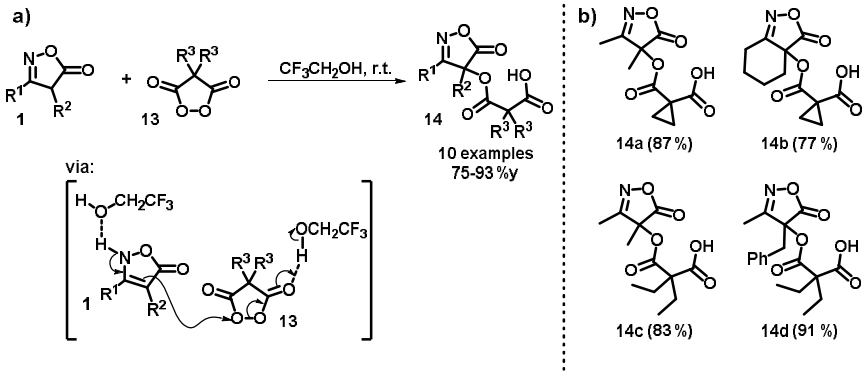
In addition, Ma and co-workers have also reported an asymmetric conjugate addition strategy of 4-unsubstituted isoxazol-5-ones **2** to nitroolefins **11** employing a chiral thiourea catalyst, followed by a fluorination event, leading to isoxazol-5-ones **12** (Scheme 5).[10,11]



Scheme 5. Preparation of isoxazol-5-ones **12** employing an asymmetric thiourea-catalyzed Michael addition/fluorination reaction sequence (NFSI: *N*-fluorobenzenesulfonimide).

2.1.2. Oxidation

Terent´ev and co-workers reported the use of malonyl peroxides **13** to oxidize isoxazol-5-ones **1** and other heterocycles (pyrazolones, barbituric acids and pyrazolidinediones).[12] The C4-oxidized isoxazol-5-ones **14** are most efficiently obtained using trifluoroethanol as the solvent, presumably due to the more efficient activation of the substrates by hydrogen bonds (Scheme 6).



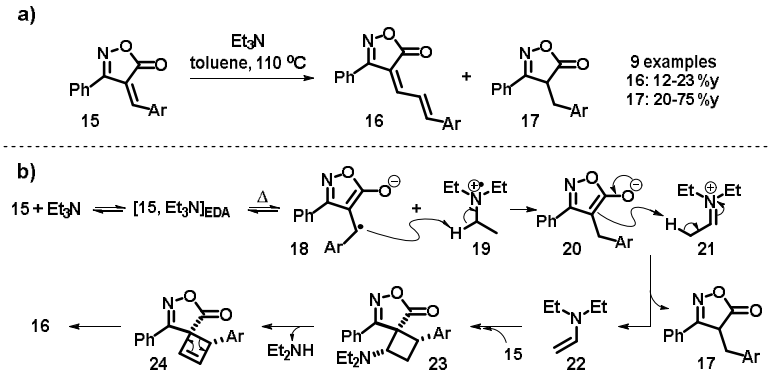
Scheme 6. a) Oxidation of isoxazol-5-ones **1** with malonyl peroxides **13**. **b)** Selected exemples.

2.1.3. EDA complexes

Electron donor-acceptor (EDA) complexes are known to be involved in several redox processes, that can be triggered by photochemical[13] or thermal conditions.[14] In this context, 4-alkylideneisoxazol-5-ones **15** have been reported to produce such transient complexes in the presence of Et_3N, which upon heating promotes an eletron transfer, thus generating an isoxazolone radical anion **18** and an amine radical cation **19**. Sequential hydrogen abstraction affords enolate **20** and iminium ion **21**, which upon proton transfer gives origin to the reduced isoxazolone **17** and an enamine intermediate **22**. Then, a formal [2+2]-cycloaddition takes place with starting 4-alkylideneisoxazol-5-one **15**. Further elimination of Et_2NH from cyclobutane intermediate **23** and 4π-electrocyclic ring-opening of cyclobutene **24** affords the corresponding extended 4-alkylideneisoxazol-5-ones **16** (Scheme 7).[15]

The yields obtained for the extended 4-alkylideneisoxazolones **16** are generally low, 12-23%, presumably due to competing degradation pathways involving enamine intermediate **22** prior to its reaction with 4-alkylideneisoxazol-5-one **15**. On the other hand, reduced isoxazol-5-ones **17** are produced in

moderate to good yields, 20-75% (Scheme 7). Although this is an unusual transformation employing 4-alkylideneisoxazol-5-ones **15**, this reactivity also showcases the high electrophilicity of these Michael-acceptors.



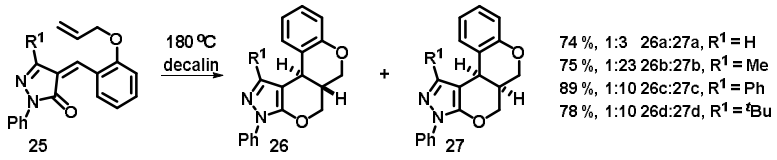
Scheme 7. a) Thermal electron transfer between 4-alkylideneisoxazol-5-ones **15** and triethylamine. **b)** Proposed mechanism.

2.1.4. Annulation

2.1.4.1. Cycloadditions

Tietze and co-workers have been the first to report an intramolecular inverse demand Hetero-Diels-Alder cycloaddition involving 4-alkylidenepyrazol-5-ones **25** and -isoxazol-5-one **28a**.

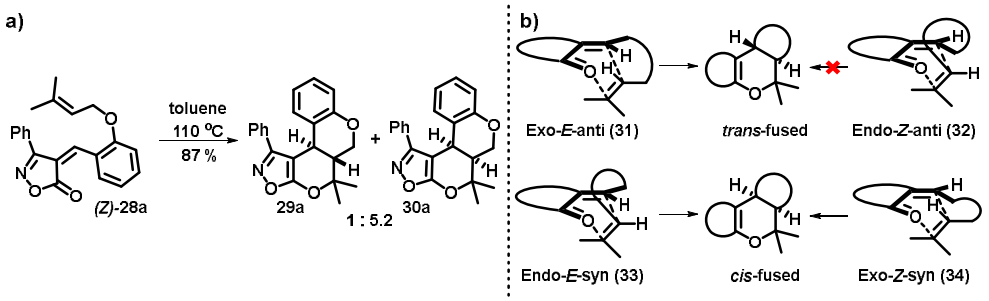
When 4-alkylidenepyrazol-5-ones **25** are used, a mixture of the corresponding *trans*- and *cis*-annulated compounds **26** and **27**, respectively, can be identified (Scheme 8).[16]



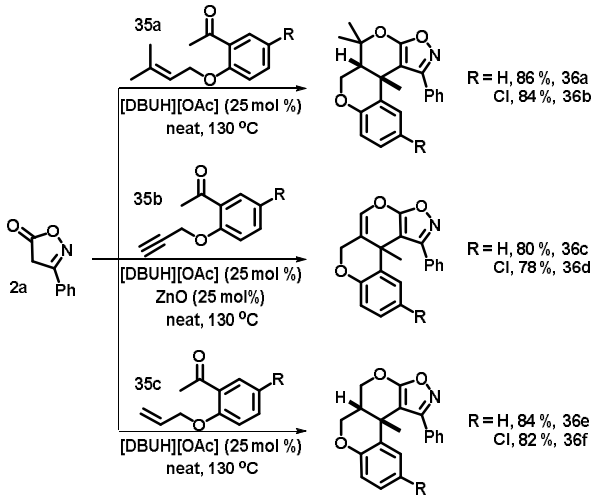
Scheme 8. Intramolecular inverse demand hetero Diels-Alder protocol using 4-alkylidenepyrazol-5-ones **25**.[3c]

A careful analysis of transition states (TS) that could be potentially involved in this transformation reveals that an *exo-E*-anti TS **31** is the only TS that can produce a *trans*-annulated compound, because the alternative *endo-Z*-anti TS **32** would be highly strained, therefore geometrically inaccessible (Scheme 9).[16] Furthermore, taking into consideration that Knoevenagel condensations of 4-unsubstituted pyrazol-5-ones and isoxazol-5-ones with aldehydes generally produce the corresponding *Z*-alkylidene congeners as the exclusive product, an isomerization event must necessarily occur prior to the cyclo-addition step. Indeed, in agreement with this analysis, when the authors investigated the isomerization of 4-alkylidenepyrazol-5-ones **25** under daylight and UV-light irradiation, or in the presence of acids in the dark, they found that an isomerization process does occur under these conditions. This reactivity pattern also matches the reactivity observed for 4-alkylideneisoxazol-5-one **28a** (Scheme 9).[17]

Other Diels-Alder strategies employing 4-alkylideneisoxazol-5-ones have been also reported by Pamar and co-workers. They assembled this reactive intermediate *in situ* employing isoxazol-5-one **2a** and methylketones **35** in the presence of the ionic liquid [DBUH][OAc] as a catalyst, thus producing the corresponding tetracyclic compounds **36** (Scheme 10).[18]



Scheme 9. The cycloaddition reaction employing pure *Z*-**28a** affords a 1:5.2 mixture of *trans*-:*cis*-annulated compounds **29a**:**30a**. This indicates that the alkylidene double bond undergoes isomerization prior to the cycloaddition event.[3c]



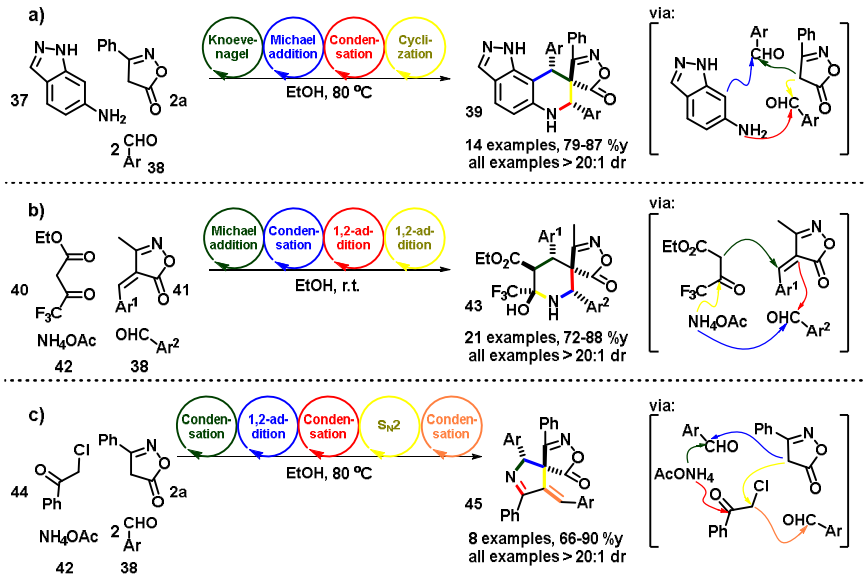
Scheme 10. Tandem reaction sequence employing isoxazol-5-one **2a** and methylketones **35** in the presence of ionic liquid [DBUH][OAc] as catalyst leads to the formation of tetracyclic compounds **36** (DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene).[3c]

2.1.4.2. Spirocyclizations

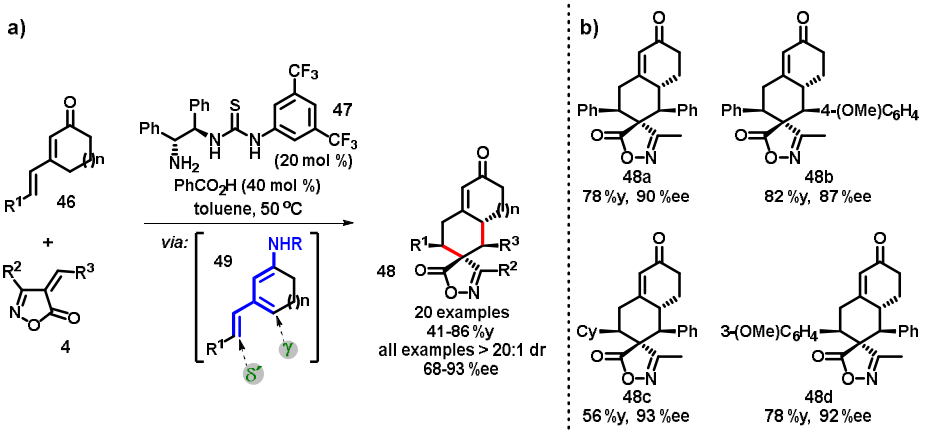
Spiroisoxazol-5-ones, such as **39**,[19] **43**[20] and **45**[21] can be prepared *via* multicomponent protocols in the absence of any catalyst using ethanol as solvent. In all these transformations, the diastereoselectivity observed is perfect (>20:1 dr),[22] which can be assumed as a consequence of thermodynamic control (Scheme 11).

Other examples aiming at the preparation of spiro-isoxazolones also include catalytic approaches. For example, Ouyang, Chen and co-workers reported an aminocatalyzed 1,4-/1,6-conjugate addition sequence employing 2,4-dienone **46** and 4-alkylideneisoxazol-5-one **4** in the presence of a bifunctional organocatalyst **47**. As a consequence, spiro-isoxazol-5-ones **48** can be accessed in good yields and enantioselectivities; and with perfect diastereocontrol (Scheme 12).[23] The reaction mechanism proceeds *via* a cross-trienamine intermediate **49** that is catalytically generated from the condensation of the starting 2,4-dienone **46** and the organocatalyst **47**. The cross-trienamine **49**[24] is an activated nucleophile due to vinylogous HOMO-raising effect. After the first attack of this intermediate onto the 4-alkylideneisoxazol-5-one **4**, a new C-C bond is formed at its γ-position, thus generating an intermediate that contains an extended iminium ion moiety and an isoxazol-5-one enolate moiety. Now, this extended iminium ion motif is an activated electrophile due to

vinylogous LUMO-lowering effect and can undergo an intramolecular 1,6-conjugate addition of the proximal isoxazolone enolate at its δ′-position to form a second C-C bond (Scheme 12).[23]

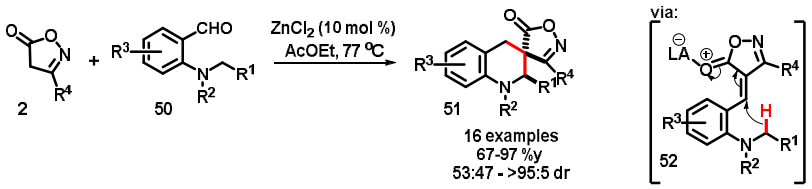


Scheme 11. Examples of multicomponent reactions leading to spiro-isoxazol-5-ones.[3c]



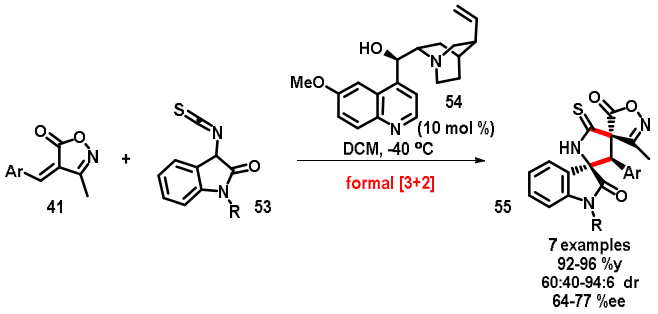
Scheme 12. a) Aminocatalized cascade reaction employing 2,4-dienones **46** and 4-alkylideneisoxazol-5-ones **4** in the presence of the bifunctional organocatalyst **47** leads to spiro-isoxazol-5-ones **48** in high yields and stereoselectivities. **b)** Selected examples.

Another class of spiro-isoxazol-5-one **51** has been reported by Wang and co-workers, who described its preparation *via* an intramolecular $ZnCl_2$-catalyzed condensation/1,5-hydrogen shift/cyclization sequence employing isoxazol-5-ones **2** and aminoaldehydes **50** (Scheme 13).[25] The mechanism of this transformation is proposed to involve a "through space" 1,5-hydride shift.[26]



Scheme 13. A $ZnCl_2$-catalyzed approach for the condensation/1,5-hydride shift/cyclization sequence to access spiro-isoxazol-5-ones **51**.

Finally, Yuan and co-workers have also reported an asymmetric spirocyclization protocol catalyzed by quinine **54** using 3-isothiocyanato oxindoles **53** and 4-alkylideneisoxazol-5-ones **41** to afford the corresponding spiro-isoxazol-5-ones **55** in excellent yields, albeit typically in modest diastereoisomeric ratios and enantiomeric excesses (Scheme 14).[27]



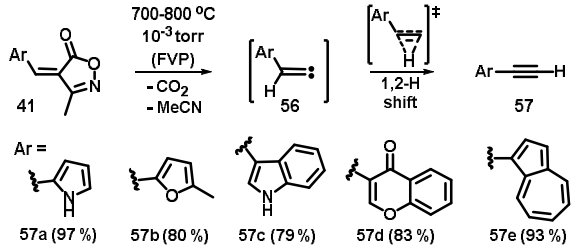
Scheme 14. A quinine-catalyzed spirocyclization protocol involving 4-alkylideneisozaxol-5-ones **41** and 3-isothiocyanato oxindoles **53**.[3c]

2.2. Transforming the isoxazolone ring

2.2.1. Alkynes

2.2.1.1. Flash vacuum pyrolysis (FVP)

In the early 80´s, Wentrup and co-workers described the decomposition of 4-alkylideneisoxazol-5-ones **41** *via* flash vacuum pyrolysis to afford the corresponding terminal alkynes **57** (Scheme 15).[28,29] Computational calculations have indicated that under the reaction conditions, the 4-alkylideneisoxazol-5-one **41** evolves to vinylidene carbene **56**, then being converted to the corresponding terminal alkyne **57** *via* a 1,2-hydrogen shift (*i.e.* a Fritsch-Buttenberg-Wiechell-type rearrangement).[30] Although a 1,2-aryl shift would also lead to the observed alkynes, this process is less favored, due to a higher energy barrier.[30,31]

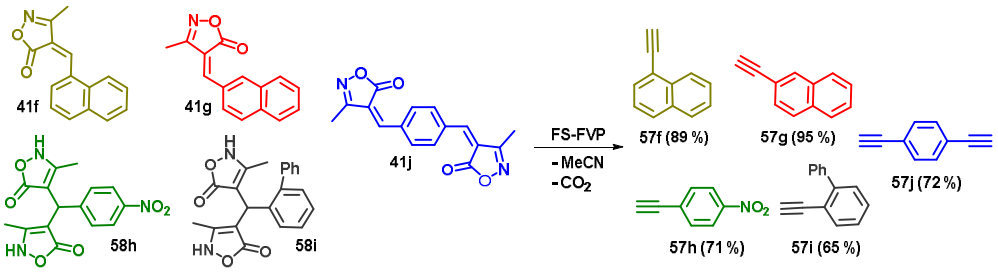


Scheme 15. Examples of terminal alkynes **57** prepared *via* flash vacuum pyrolysis of 4-alkylideneisoxazol-5-ones **41**.[3c]

Additional developments of this previous method by Wentrup and co-workers also include the use of appropriate isoxazol-5-one starting materials to get access to *N*-ethynylamines,[32] ketenimines,[33] isonitriles,[34] organic fulminates,[35] iminopropadienethiones,[36] and isocyanoamines.[37]

In order to produce these molecules, it is important that the starting 4-alkylideneisoxazol-5-ones **41** can be vaporized at relatively "not-so-high" temperatures, which is not always possible when using starting materials containing large substituents. In this context, Wentrup and co-workers went on to develop a strategy based on a falling solid flash vacuum pyrolysis (FS-FVP), which allows the starting solid isoxazolones to be continuously added as a fine-divided powder to a vertical pyrolysis tube, under high vacuum. The advancement of this technology made possible the high-yielding synthesis of an additional number of terminal alkynes **57** (Scheme 16).[38]

During this study, the authors remarked that the general Knoevenagel condensation protocol for the preparation of 4-alkylideneisoxazol-5-ones **41** led sometimes to bis(isoxazolyl)methane compounds **58**, such as **58h** and **58i**. The formation of such products is of no consequence, because during the FS-FVP, these substrates undergo retro-Michael additions, thus forming the corresponding 4-alkylideneisoxazol-5-ones **41h** and **41i**, being then transformed into the corresponding terminal alkynes, **57h** and **57i**, respectively (Scheme 16).[38]



Scheme 16. Examples of terminal alkynes that can be accessed *via* FS-FVP starting from involatile isoxazolones.[3c]

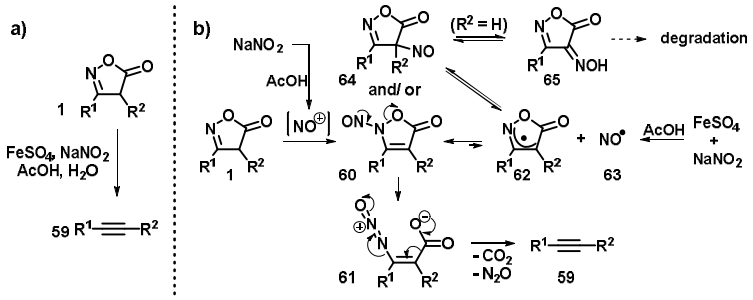
Finally, additional applications of FVP using isoxazolones have been also reported by Prager and co-workers for the preparation of numerous heterocycles, such as imidazoles,[39] oxazoles,[40] and indoles/pyrroles/quinolones.[41]

2.2.1.2. Nitrosative treatment

Because FVP employs very high temperatures, a variety of sensitive functional groups or carbon architectures are not tolerated in the starting isoxazol-5-ones. In contrast to these harsh conditions, Zard and co-workers reported the conversion of 3,4-disubstituted isoxazol-5-ones **1** to the corresponding internal alkynes **59** *via* a nitrosative treatment employing $FeSO_4$, $NaNO_2$, AcOH and H_2O. This synthetic strategy is based on the activation of the isoxazol-5-one ring by a nitrosonium ion (NO^+) generated from the reaction of $NaNO_2$ with AcOH. During this process, N_2O and CO_2 are produced, thus serving as an entropic driving force that generally allows the complete consumption of the starting isoxazol-5-ones in less than 30 minutes (Scheme 17a).[42,43]

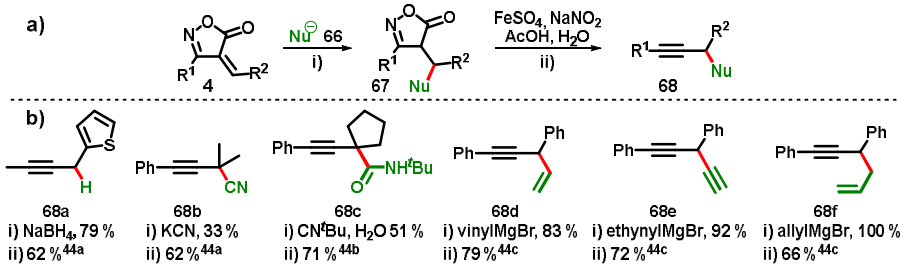
The proposed mechanistic scenario for this reaction starts by the N2-trapping of the isoxazol-5-one **1** with the NO^+ to afford intermediate **60**. Next, this intermediate can undergo N-O bond cleavage to reveal the zwitterionic compound **61**. Then, a decarboxylation event involving this intermediate is also accompanied by the loss of N_2O, thus unmasking the corresponding internal alkyne **59** (Scheme 17b). However, **60** can also undergo a reversible homolytic cleavage of the N-N bond to liberate an isoxazol-5-one radical intermediate **62** and nitric oxide **63**. At this moment, a potential competing pathway is the radical recombination of **62** and **63** to afford the C4-NO trapped isoxazolone intermediate **64**. If the isoxazol-5-one precursor **1** has a substituent at C4 (*i.e.* $R^2 \neq H$), the formation of **64** is typically reversible and has no consequence in the outcome of the reaction. If the starting isoxazol-5-one **1** does not have any substituents at C4 (*i.e.* $R^2 = H$),

then intermediate **64** can tautomerize to the corresponding oxime **65**, followed by further competing pathways leading to degradation. Because isoxazol-5-one intermediates **60** and **64** are in equilibrium *via* homolytic cleavage events, *via* the generation of radicals **62** and **63**, the consumption of intermediate **60** leading to the formation of alkyne **59** displaces the equilibrium toward its formation. In order to favor this process, $FeSO_4$ is also added to the reaction medium, because in the presence of $NaNO_2$, in acidic medium, it produces more nitric oxide **63**, therefore serving as an additional driving force for this transformation (Scheme 17b).



Scheme 17. a) Nitrosative treatment of 3,4-disubstituted isoxazol-5-ones **1** lead to internal alkynes **59**. **b)** Proposed mechanistic scenario for this reaction.[3c]

Early reports of Zard and co-workers in this area described the preparation of internal alkynes **68** employing a two-step approach: i) addition of nucleophiles **66** to 4-alkylideneisoxazol-5-ones **4** to produce the corresponding adducts **67**, followed by ii) nitrosative treatment (Scheme 18).[44] In this context, it is remarkable to observe that Grignard reagents add to 4-alkylideneisoxazol-5-ones **4** exclusively in a 1,4-manner, which is in stark contrast with the expected regioselectivity for α,β-unsaturated carbonyl compounds.

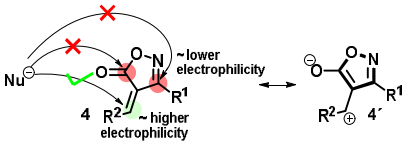


Scheme 18. a) Synthetic strategy employed by Zard and co-workers for the preparation of internal alkynes. **b)** Selected examples.[3c]

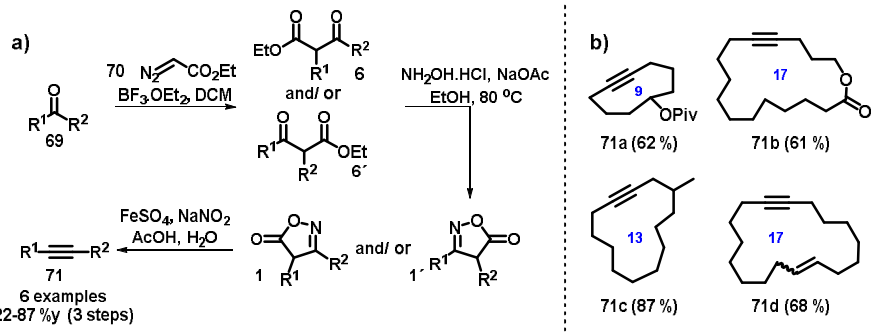
Because this reaction is certainly under kinetic control, this means that the energy barrier for this process is smaller than any competing 1,2-addition.[45] A plausible interpretation for this reactivity is that 1,2-additions are more difficult to occur because they would destroy the aromatic character of **4′**, a resonance form of the 4-alkylideneisoxazol-5-one **4**. Presumably, the resonance form **4′** might have an important contribution to the description of such compounds (Scheme 19).

Furthermore, Zard and co-workers also employed isoxazol-5-ones as strategic building blocks for the preparation of macrocyclic alkynes **71**[46] and 1-chloroalkynes **73**.[47] The synthetic route employed for the preparation of macrocyclic alkynes **71** is based on a three-step sequence starting with the reaction of a ketone **69** with ethyldiazoacetate **70** and a Lewis acid (*e.g.* $BF_3.OEt_2$) to produce a regioisomeric mixture of β-ketoesters **6**+**6′**.[48] Next, treatment with hydroxylamine leads to the formation of the corresponding mixture

of isoxazol-5-ones **1**+**1´**. The mixture of these compounds is of no consequence, because in the next step, the nitrosative treatment of both compounds will lead to an unique internal alkyne **71** (Scheme 20).

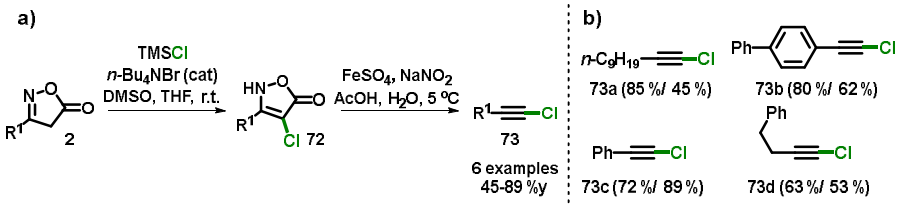


Scheme 19. An important contribution of the resonance form 4´ to the description of 4-alkylideneisoxazol-5-one **4** can be a plausible explanation for the regioselectivity observed for the addition of Grignard reagents to these Michael acceptors.[3c]



Scheme 20. a) Synthetic route developed by Zard and co-workers for the preparation of macrocyclic alkynes **71**. **b)** Selected examples, with combined yields for 3 steps.[3c]

Regarding the preparation of 1-chloroalkynes **73**, a two-step process was employed. First, the C4-chlorination of isoxazol-5-ones **2** is performed using a mixture of TMSCl, TBAB (cat) and DMSO, in THF to afford intermediates **72**.[49] Then, the nitrosative treatment is performed this time at 5 °C to afford the corresponding 1-chloroalkynes **73** (Scheme 21).

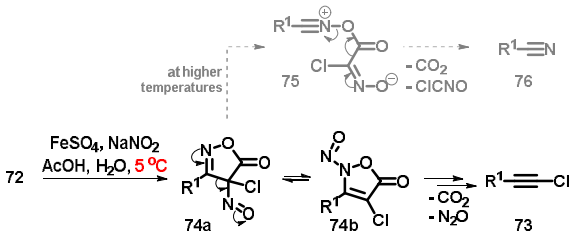


Scheme 21. a) Synthetic route to 1-chloroalkynes **73**. **b)** Selected examples. Yields are reported for individual steps.[3c]

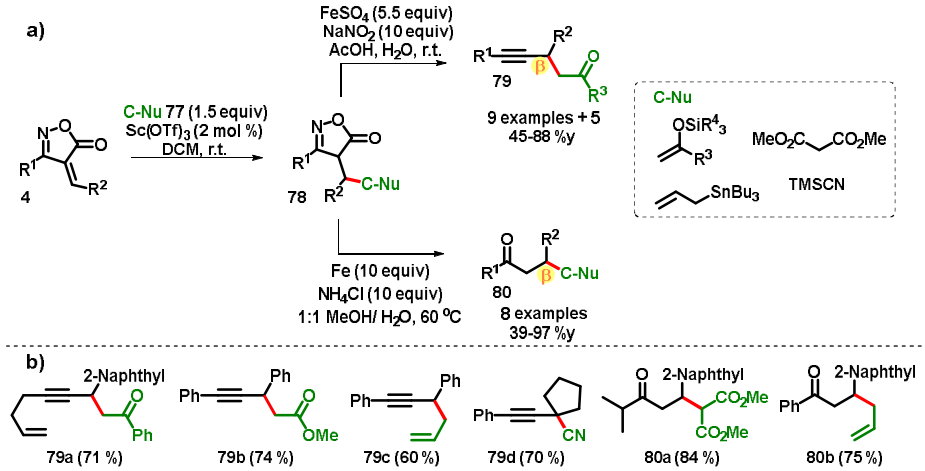
Of note, when the nitrosative cleavage of the 4-chloroisoxazol-5-one intermediates **72** is attempted at room temperature, a competitive pathway leading to the formation of nitriles **76** becomes more important. For instance, when 3-phenyl-4-chloroisoxazol-5-one **72c** is treated under nitrosative conditions at room temperature, the reaction mixture produces benzonitrile **76c** in 48% yield and (chloroethynyl)benzene **73c** in 52% yield. In contrast, when this reaction protocol is performed at 5 °C, the (chloroethynyl)benzene **73c** can be isolated in 89% (Scheme 22).[47]

Also taking advantage of isoxazol-5-ones, Capreti and Jurberg described a divergent approach for the synthesis of β-branched carbonyl compounds **79** and **80**. This strategy takes advantage of a $Sc(OTf)_3$-

catalyzed addition of silylenolethers and other soft carbon nucleophiles, such as allyltributyltin, dimethylmalonate and trimethylsilylcyanide (C-Nu **77**) to 4-alkylideneisoxazol-5-ones **4**. Then, the generated intermediate **78** can be cleaved under nitrosative conditions to reveal the corresponding pent-4-yn-1-ones **79**; or it can be transformed into β-branched ketones **80** *via* a reductive protocol employing Fe and NH_4Cl in MeOH/H_2O (Scheme 23).[50]



Scheme 22. Mechanistic scenario proposed for the formation of 1-chloroalkynes **73** starting from 4-chloroisoxazol-5-ones **72**. At r.t., the formation of nitrile **76** becomes more pronounced.[3c]

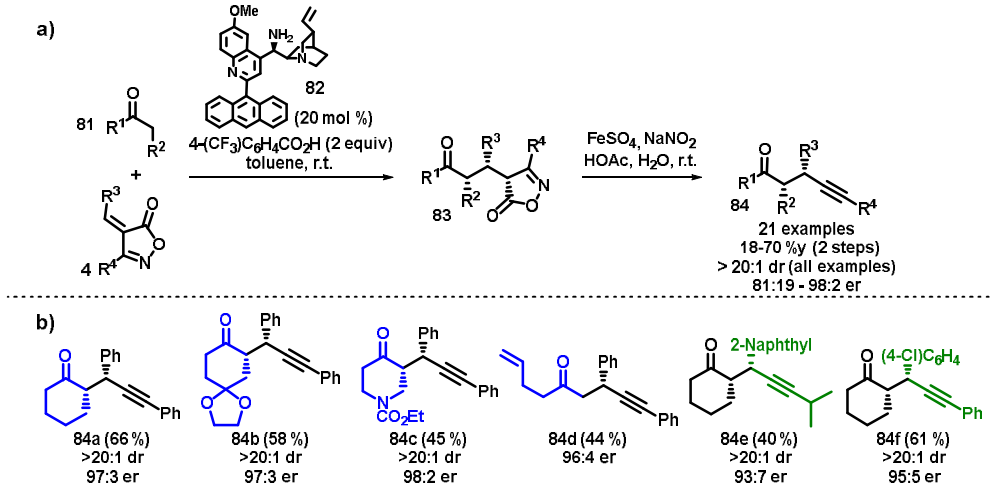


Scheme 23. a) A divergent approach for the synthesis of β-branched ketones. **b)** Selected examples from both synthetic routes. Combined yields for 2 steps.[3c]

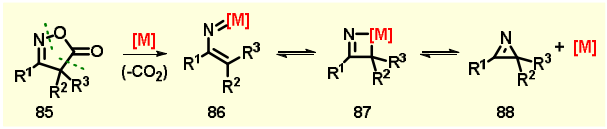
Capitalizing on the previous racemic strategy for the formal α-propargylation of ketones based on the use of silylenolethers, Jurberg moved on to develop an aminocatalyzed stereoselective version of this transformation, thus allowing the direct use of ketones **81** as starting materials. Employing this new two-step strategy, α-propargylated ketones **84** could be generated in good combined yields (up to 70%), with perfect diastereocontrol (all examples, >20:1 dr) and high enantioselectivities (up to 98:2 er), in a highly modular fashion (Scheme 24).[51]

2.2.2. Catalytic methods involving metal-nitrenoid intermediates

The decarboxylation of isoxazol-5-ones **85** *via* metal catalysis is proposed to occur involving vinyl metal nitrenoid species **86** (M=Ir, Pd, Ru), which are presumably in equilibrium with the corresponding metallacycle **87**, and the product of reductive elimination, 2*H*-azirines **88** (Scheme 25).



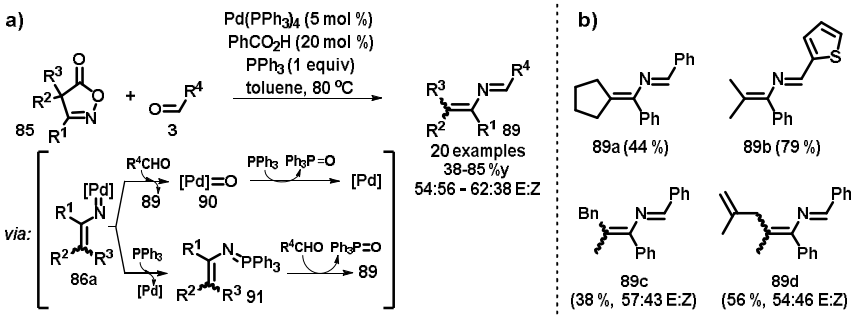
Scheme 24. a) An aminocatalyzed stereoselective approach for the formal α-propargylation of ketones. **b)** Selected examples, with yields reported for 2 steps.[3c]



Scheme 25. Proposed equilibrium of reactive intermediates derived from the metal-catalyzed decarboxylation of isoxazol-5-ones **85**.[3c]

2.2.2.1. Azadienes

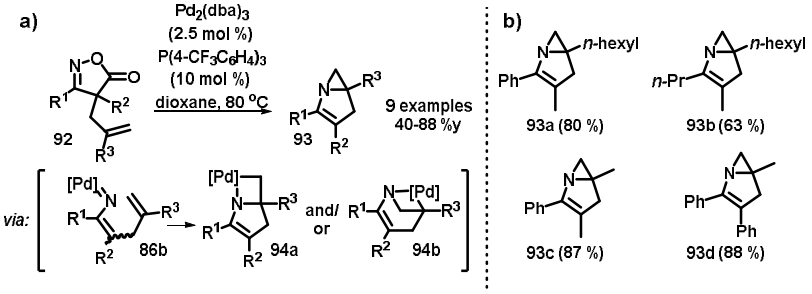
Taking advantage of this general reactivity platform, Okamoto, Ohe and co-workers prepared azadienes **89** *via* a Pd-catalyzed reaction involving isoxazol-5-ones **85** and aldehydes **3**. Two mechanisms are proposed, in order to explain the formation of such azadienes: i) a Tebbe-like pathway that directly affords azadiene **89**, thus also producing an oxopalladium species **90**, that is reduced by PPh_3 and regenerates the Pd catalyst or ii) an aza-Wittig-like pathway that takes place *via* the formation of an iminophosphorane intermediate **91** (Scheme 26).[52]



Scheme 26. a) Synthesis of azadienes **89** *via* a Pd-catalyzed protocol employing isoxazol-5-ones **85** and aldehydes **3**. **b)** Selected examples.[3c]

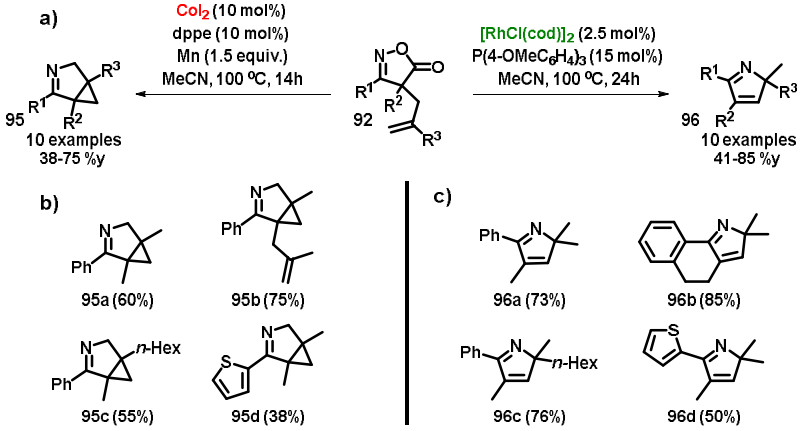
2.2.2.2. 1-Azabicyclo[3.1.0]hex-2-enes and related heterocycles

Okamoto, Ohe and co-worker have also reported the preparation of 1-azabicyclo[3.1.0]hex-2-enes **93** starting from 4-allylisoxazol-5-ones **92**. This reaction is proposed to occur *via* a Pd-catalyzed decarboxylation event that generates a nitrenoid species **86b**, followed by an intramolecular [2+2]-cycloaddition to afford two palladacycles **94a** and/ or **94b**. Finally, reductive elimination generates the bicycle **93** (Scheme 27).[53]



Scheme 27. a) Pd-catalyzed synthesis of 1-azabicyclo[3.1.0]hex-2-enes **93** starting from 4-allylisoxazol-5-ones **92**. **b)** Selected examples (dba: dibenzylideneacetone).[3c]

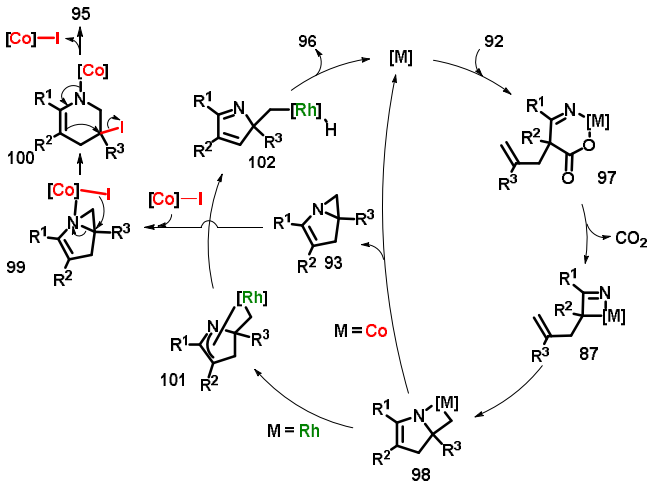
Continuing their work, Okamoto, Ohe, and co-workers explored the use of the same isoxazolones **92** in the presence of CoI_2 and $[RhCl(cod)]_2$ as pre-catalysts. In contrast to the previous results obtained for Pd or Ru, now new products could be obtained. In the case of CoI_2/ dppe catalytic system, isoxazolones **92** are converted to azabicyclic cyclopropanes **95**. However, when $[RhCl(cod)]_2/P(4\text{-}OMeC_6H_4)_3$ is employed, 2*H*-pyrroles **96** are observed[54] (Scheme 28).



Scheme 28. a) Divergent access to aza-heterocycles **95** or **96**, depending on the metal source employed, CoI_2 or $[RhCl(cod)]_2$, respectively. **b)** Selected examples for the use of CoI_2/dppe catalytic system. c) Selected examples for the use of $[RhCl(cod)]_2$/ $P(4\text{-}OMeC_6H_4)_3$ catalytic system (cod: 1,5-cyclooctadiene, dppe: 1,2-bis(diphenylphosphino)ethane).

Both catalytic cycles are proposed to involve azametallacyclobutene **87**. In the case of the Co catalyst, a 1-azabicyclo[3.1.0]hex-2-ene intermediate **93** (identical substitution pattern produced by Pd in Scheme 27) is initially formed, but then undergoes an isomerization process *via* the action of the iodide ligands present in the active catalyst [Co]-I. The iodide anion opens the aziridine ring of intermediate **99** to produce the

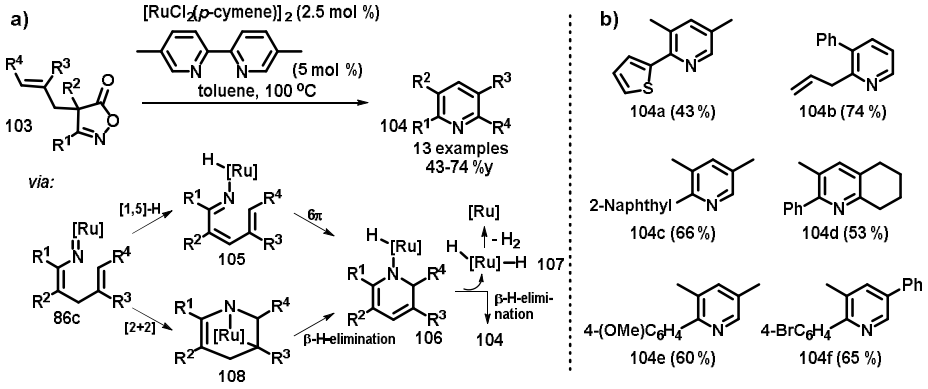
6-membered heterocycle **100**. Intramolecular displacement of the iodide in **100** leads to cyclopropane **95**. In the case of the Rh catalyst, the rhodacycle **98** (M=Rh) can isomerize to an aza-η^3-allylrhodium species **101**, which undergoes β-hydride elimination to produce **102**, which then undergoes reductive elimination to afford 2*H*-pyrrole **96**[54] (Scheme 29).



Scheme 29. Proposed catalytic cycles employing CoI_2 and $[RhCl(cod)]_2$.

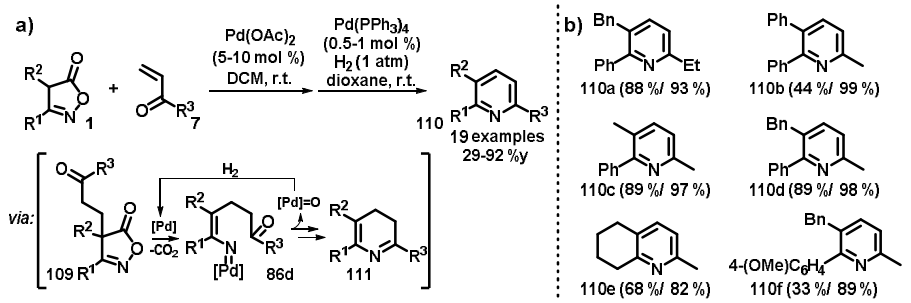
2.2.2.3. Pyridines and piperidines

Okamoto, Ohe and co-workers employed an intramolecular transformation using 4-allylisoxazol-5-ones **103** and a Ru(II) catalyst.[55] The mechanism proposed for this reaction starts with the oxidative addition of the Ru(II) catalyst into the N-O bond of the isoxazol-5-one **103**, then being followed by a decarboxylative event to afford intermediate **86c**. Next, this intermediate can either undergo a [1,5]-hydrogen shift and a sequential 6π-electrocyclization; or alternatively, a [2+2]-cycloaddition and a sequential β-hydride elimination; both pathways being followed by a β-hydride elimination to afford the corresponding pyridines **104** and a ruthenium dihydride complex **107**, which eliminates H_2 to regenerate the starting Ru(II) catalyst (Scheme 30).



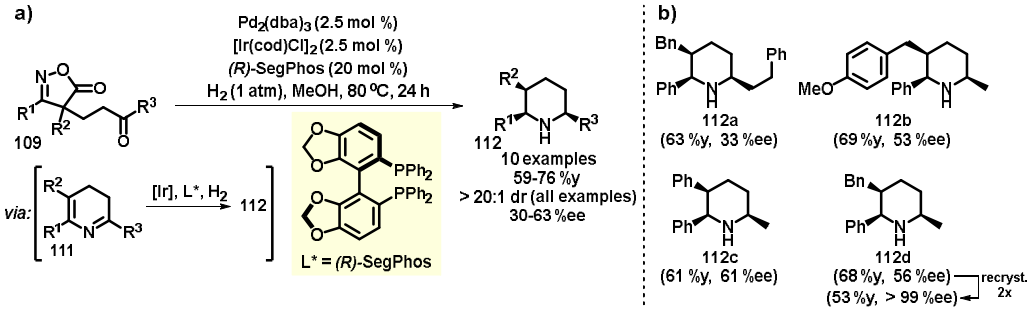
Scheme 30. a) Ru(II)-catalyzed protocol for the conversion of 4-allylisoxazol-5-ones **103** to the correponding pyridines **104**. **b)** Selected examples.[3c]

Peters and co-workers reported the preparation of 2,3,6-trisubstituted pyridines **110** *via* a two-step process starting from isoxazol-5-ones **1** and α,β-unsaturated ketones **7**.[56] The first step is a regioselective conjugate addition promoted by a Pd(II) catalyst that allows the functionalization at the C4 position of the isoxazolone ring to afford the adduct **109**. In the second step, a Pd(0) catalyst is responsible for a reaction sequence leading to the target pyridines **110**. This sequence starts with the oxidative addition of Pd into the N-O bond of the isoxazol-5-one intermediate **109**, followed by a decarboxylation step leading to a Pd-nitrenoid intermediate **86d**. This compound reacts with the proximal carbonyl group *via* an *aza*-Tebbe-type olefination mechanism to produce dihydropyridine **111**. Hydrogen is employed in this protocol to reduce the resulting [Pd]=O species, in order to regenerate the starting Pd-catalyst. The last step of this mechanism involves an oxidation event, presumably promoted by the adventitious air present, thus allowing the access to the corresponding pyridines **110** (Scheme 31).



Scheme 31. a) Reaction sequence employed for the preparation of 2,3,6-trisubstituted pyridines **110** starting from isoxazol-5-ones **1** and α,β-unsaturated ketones **7**. **b)** Selected examples. Yields are reported for each step.[3c]

In addition, Peters and co-workers have been also able to intercept the putative dihydropyridine intermediate **111** using a different hydrogenation strategy. This time, they employed a synergistic combination of Ir- and Pd-catalysts, which allows the synthesis of the corresponding piperidines **112** in good yields and excellent diastereoselectivities, albeit in only moderate enantioselectivities. In some cases, such as for **112d**, the enantioselectivity could be increased by a recrystallization protocol (Scheme 32).[57]

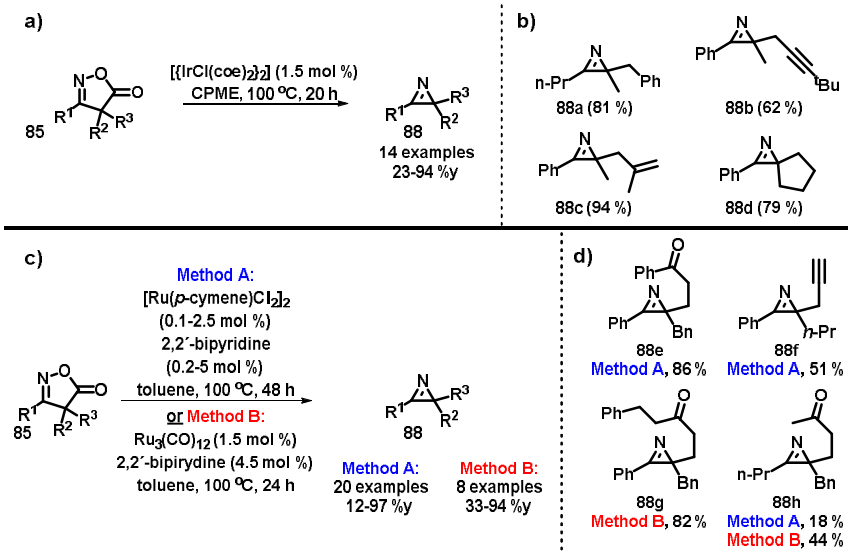


Scheme 32. a) Pd- and Ir-catalyzed stereoselective synthesis of piperidines **112** starting from isoxazol-5-ones **109** (dba: dibenzylideneacetone, cod: 1,5-cyclooctadiene). **b)** Selected examples.[3c]

2.2.2.4. 2*H*-Azirines

In the previous examples, 2*H*-azirines **88** have been proposed as reactive intermediates, that are presumably in equilibrium with metal nitrenoids **86**, derived from a metal-catalyzed decarboxylative process involving isoxazol-5-ones **85**. In fact, when starting from isoxazol-5-ones **85**, 2*H*-azirines **88** have been only

isolated in the presence of an Ir-catalyst, as described by Ohe, Okamoto and co-workers[58] (Scheme 33a and b) and Ru-catalysts, as described by Peters and co-workers (Scheme 33c and d).[59] Furthermore, both research groups were able to demonstrate that 2*H*-azirines **88** can undergo further transformations leading to important heterocycles, such as pyridines[59] and indoles.[58,59]



Scheme 33. a) Use of an Ir catalyst for the preparation of 2*H*-azirines **88**. **b)** Selected examples using Ir.[58] (coe: cyclooctene, CPME: cyclopentyl methyl ether). **c)** Use of Ru catalysts for the preparation of 2*H*-azirines **88**. **d)** Selected examples using Ru.[59,3c]

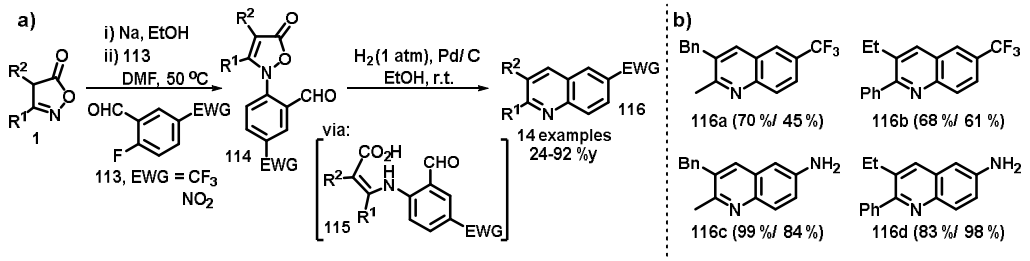
Finally, an asymmetric approach for the preparation of chiral enantioenriched 2*H*-azirines **88** has been also recently reported by Okamoto, Ohe and co-workers. Their synthetic strategy takes advantage of the use of 2-alkoxyisoxazoles as starting materials (which are readily accessible from the corresponding isoxazol-5-ones) in the presence of a Rh-catalyst and a chiral diene ligand (not shown).[60]

2.2.3. Reductive protocols

Other heteroaromatic rings, such as quinolines, isoquinolines and pyridines have been also prepared starting from isoxazol-5-ones **1** *via* different mechanisms, that do not involve 2*H*-azirines as intermediates. In this context, key steps are the N-O bond cleavage, and cyclization events, which generally take advantage of a proximal carbonyl group.

2.2.3.1. Quinolines

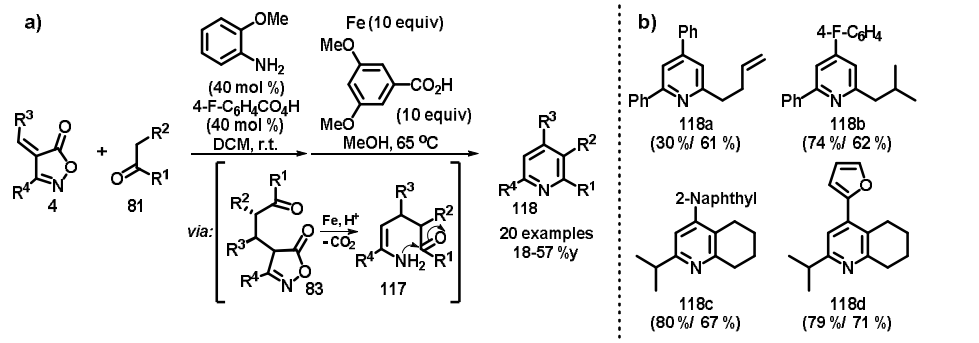
Examples in this arena include the work of Beccalli and co-workers, who reported a two-step sequence for the synthesis of quinolines **116**.[61,62,63] The proposed mechanism describes an initial deprotonation of the starting isoxazol-5-one **1** using Na in EtOH to promote a nucleophilic aromatic substitution onto 2-fluorobenzaldehyde **113**, to produce the *N*-aryl intermediate **114**. N-O bond reduction promoted by H_2 (1 atm) in the presence of a catalytic amount of Pd/C generates the carboxylic acid intermediate **115**, that undergoes decarboxylation to generate an enamine intermediate followed by an intramolecular aldol condensation to afford quinoline **116** (Scheme 34).



Scheme 34. a) Quinolines **116** are prepared *via* a nucleophilic aromatic substitution of isoxazol-5-one **1** onto 2-fluorobenzadehyde derivatives **113**, followed by a hydrogenolysis step. **b)** Selected examples, with yields reported for each step.[3c]

2.2.3.2. Pyridines

Jurberg and co-workers developed a two-step reaction sequence for the preparation of 2,4,6-trisubstituted and 2,3,4,6-tetrasubstituted pyridines **118**.[64] The first step is an aminocatalized Michael-addition of ketone **81** to 4-alkylideneisoxazol-5-one **4**, promoted by *o*-anisidine and 4-fluorobenzoic acid, that leads to racemic intermediate **83**. In the second step, the use of Fe in acidic medium performs the N-O bond reduction of **83**, thus triggering a decarboxylation event that presumably produces an enamine intermediate **117**, that undergoes an intramolecular condensation with the proximal carbonyl group to produce a dihydropyridine intermediate. Finally, the presence of air allows the oxidation of this intermediate to the corresponding densely substituted pyridine **118** (Scheme 35).

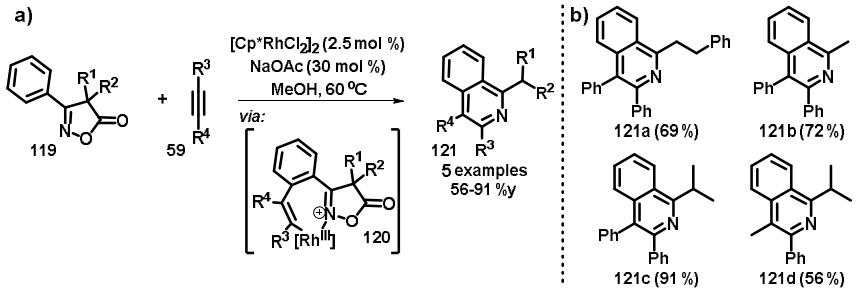


Scheme 35. a) Preparation of densely substituted pyridines **118** *via* an aminocatalyzed Michael addition/iron-mediated decarboxylative cyclization sequence employing 4-alkylideneisoxazol-5-one **4** and ketones **81**. **b)** Selected examples, with yields reported for each step.[3c]

2.2.4. Other metal-catalyzed transformations

2.2.4.1. Isoquinolines

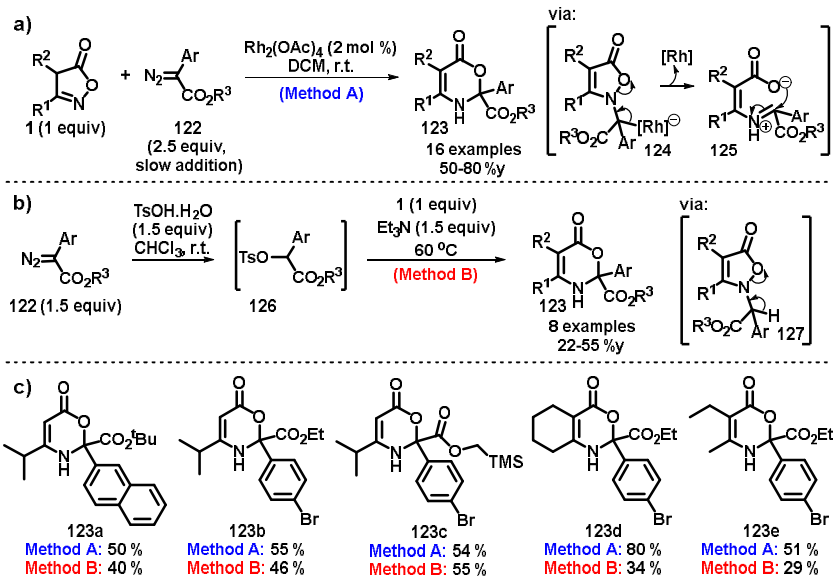
Chiba and co-workers reported a Rh(III)-catalyzed formal [4+2]-cycloaddition process between isoxazol-5-ones **119** and internal alkynes **59** to prepare the corresponding isoquinolines **121** (Scheme 36).[65] The mechanism described for this transformation starts with a C-H activation of the Ph ring promoted by the Rh catalyst, that is directed by the N atom of the isoxazolone ring. Subsequent 1,2-insertion of the alkyne produces a 7-membered rhodacycle intermediate **120**, that can evolve following two possible reaction pathways. It can either undergo a reductive elimination to produce a Rh(I) species and a pyridinium oxide intermediate, which can then be reduced and decarboxylated by the eliminated Rh(I) species to regenerate the Rh(III) catalyst, while also producing isoquinoline **121**; or alternatively, intermediate **120** can directly undergo a redox event, which promotes the decarboxylation step to afford **121**, while also regenerating the Rh(III) catalyst (Scheme 36).



Scheme 36. a) A Rh(III)-catalyzed protocol for the preparation of isoquinolines **121** *via* an annulation strategy involving isoxazol-5-ones **119** and internal alkynes **59**. **b)** Selected examples.[3c]

2.2.4.2. 1,3-Oxazin-6-ones

More recently, Jurberg and Davies reported the ring expansion of 3,4-disubstituted isoxazol-5-ones **1** using aryldiazoacetates **122** to prepare 2,3-dihydro-6*H*-1,3-oxazin-6-ones **123** *via* two alternative strategies: i) a Rh-catalyzed protocol or ii) a two-step, one pot, metal-free process (Scheme 37).[66] The proposed mechanism for the Rh-catalyzed transformation starts with the regioselective N2-addition of the isoxazolone **1** onto the rhodium carbene derived from aryldiazoacetate **122**. Then, the Rh catalyst is eliminated from intermediate **124**, thus presumably promoting the N-O bond cleavage event. This leads to the formation of an iminium ion **125**, that undergoes ring closure to afford 2,3-dihydro-6*H*-1,3-oxazin-6-ones **123**. It is likely that this ring-closure step does not involve the Rh catalyst, because when a number of chiral, enantiopure Rh-catalysts were tested, all failed to produce enantioenriched products (Scheme 37a). The alternative metal-free protocol is proposed to start with the non-catalyzed O-H insertion of *p*-TsOH to the aryldiazoacetate **122** to produce the corresponding tosylate **126**. In the second step, this intermediate is employed as an alkylating agent to the isoxazol-5-one reacting partner **1**, thus generating *N*-alkylated derivatives **127**.

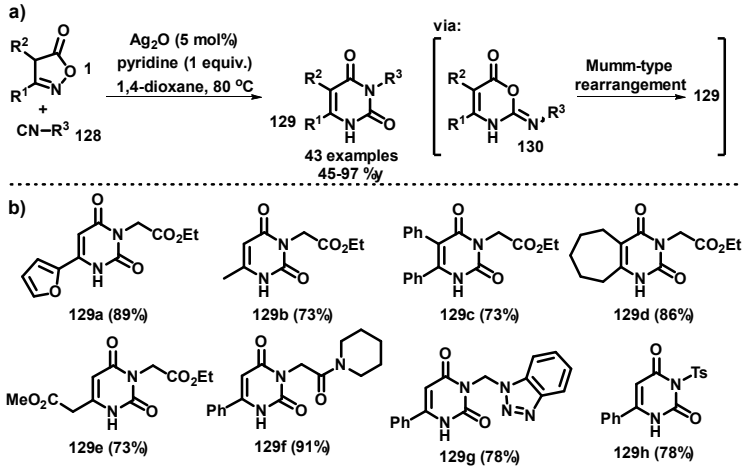


Scheme 37. a) Method A: Rh-catalyzed protocol. **b)** Method B: One-pot, metal-free protocol. **c)** Selected examples prepared by both methods.[3c]

The use of Et_3N in this reaction presumably serves both to deprotonate starting isoxazolone **1** to generate a more reactive nucleophile; and to deprotonate intermediate **127**, in order to promote the N-O bond cleavage event, that generates an iminium ion intermediate **125** needed for an identical ring-closure step leading to 2,3-dihydro-6*H*-1,3-oxazin-6-one **123**, as it has been previously described for the Rh-catalyzed process (Scheme 37b).

2.2.4.3. Pyrimidinediones

Taking advantage of the carbene reactivity of isonitriles, Wei and co-workers have developed a somehow similar strategy to the previous method by inserting isonitriles **128** into the N-O bond of isoxazolones **1**, in the presence of Ag_2O as catalyst, to produce intermediates **130**. At this point, this intermediate is believed to undergo a Mumm-type rearrangement to afford the corresponding Pyrimidinediones **129** in good yields and broad scope (Scheme 38).[67]



Scheme 38. a) Catalytic protocol developed for the preparation of pyrimidinediones **129** starting from isoxazolones **1** and isonitriles **128**. **b)** Selected examples.

2.2.5. Photochemical reactions

2.2.5.1. Photolysis

Photolytic processes involving isoxazol-5-ones have been reported to produce carbene intermediates under UV light irradiation. These reactive intermediates can be further trapped intramolecularly to generate a variety of heterocycles. For instance, *N*-acylisoxazol-5-ones **131** have been irradiated at 254 nm or 300 nm, to generate carbene intermediates **133**, that undergo intramolecular rearrangement to produce modest to good yields of isoxazoles **132** (Scheme 39).[68]

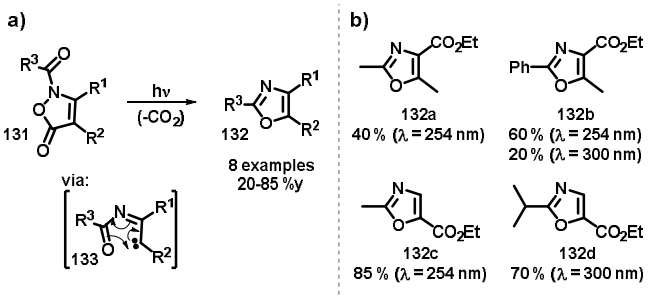
Other isoxazol-5-one derivatives have been also irradiated under UV light to afford other heterocycles, such as indoles and benzofurans,[69] pyrroles,[70] imidazoles and pyrimidones.[71]

2.3. Total syntheses of natural products

2.3.1. Isoxazolones as intermediates

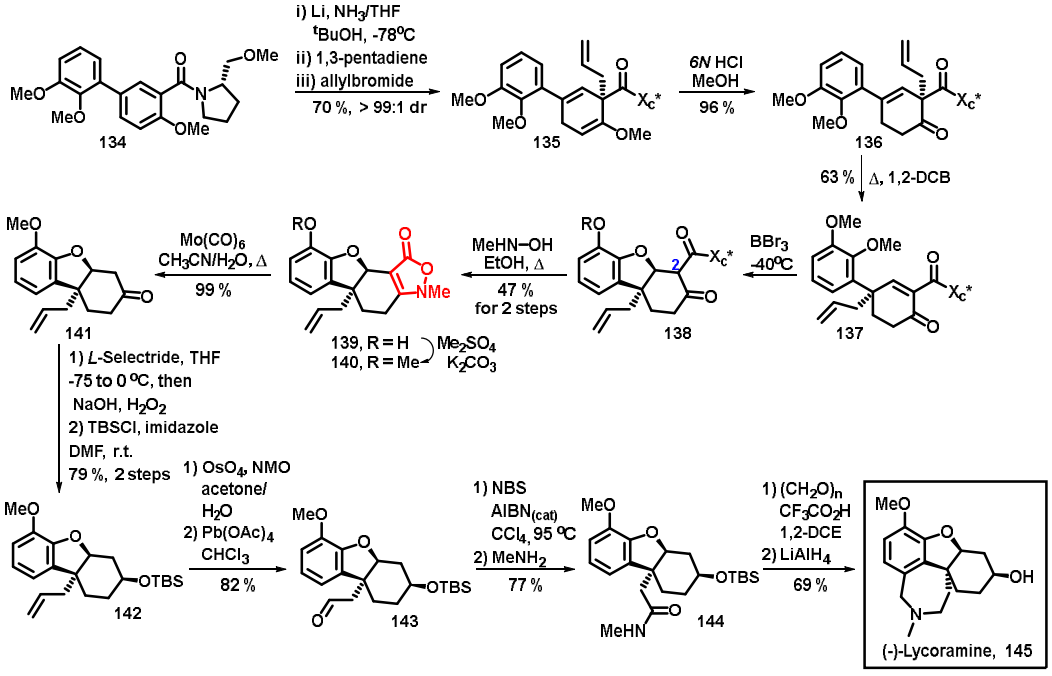
2.3.1.1. Total synthesis of (-)-Lycoramine

Lycoramine is a natural product of the Galantamine family, which has been remarked as active against Alzheimer´s disease. This class of compounds acts both as an acetylcholinesterase inhibitor and as an allosteric potentiating ligand of the nicotine acetylcholine receptor, which is orthogonal to other mechanisms of action associated to most drugs currently available on the market.[72]



Scheme 39. Isoxazoles can be prepared photochemically starting from *N*-acylisoxazol-5-ones.

Malachowsky and co-workers reported the total synthesis of (-)-Lycoramine **145** in 14 steps, 5% overall yield, starting from substrate **134** (Scheme 40). The starting substrate **134** contains a chiral enantiopure pyrrolidine group as a chiral auxiliary that guides the alkylation step of an anion intermediate generated from a Birch reduction protocol, to produce enolether **135**. Next, hydrolysis of this enolether using *6N* HCl produces ketone **136**, that under heating leads to a [3,3]-Cope rearrangement to afford allylated cyclohexenone **137**. This Birch-Cope reaction sequence is responsible for installing the most challenging all-carbon stereogenic center present in the target compound.[73,74] Treatment of intermediate **137** with BBr_3 at a controlled temperature range, between -35 °C and -40 °C, allows selective deprotection of the *o*-OMe group, followed by an intramolecular oxa-Michael addition onto the proximal enone moiety, thus producing dihydrofuran **138** as a mixture of C2-epimers (along with a minor amount of additional deprotection of the *m*-OMe). Further treatment of this mixture with *N*-methylhydroxylamine removes the pyrrolidine chiral auxiliary and affords a mixture of isoxazol-5-ones, enriched in **140**.



Scheme 40. A total synthesis of (-)-Lycoramine **145**, as reported by Malachowsky and co-workers.

Further treatment of this mixture **139**+**140** with Me_2SO_4 translates into a clean conversion to **140**. In the sequence, the isoxazol-5-one ring can have its N-O bond reductively cleaved by $Mo(CO)_6$, thus promoting a decarboxylation event, followed by hydrolysis, to reveal ketone **141**. A diastereoselective reduction of this ketone using *L*-Selectride, followed by protection of the generated alcohol with TBSCl affords alkene **142**. Submission of this substrate to an oxidative cleavage sequence employing OsO_4, followed by $Pb(OAc)_4$, leads to the corresponding aldehyde **143**. Then, an amidation procedure employing NBS and AIBN converts the aldehyde to the corresponding acylbromide *via* a radical oxidative process, which after treatment with methylamine produces amide **144**.[75] The final steps of the synthesis are a Pictet-Spengler cyclization, with the simultaneous removal of the TBS protecting group of the alcohol in the presence of TFA; and the reduction of the amide group using $LiAlH_4$, that allows the isolation of the target compound, (-)-Lycoramine **145** (Scheme 40).

2.3.2. Isoxazolones as synthetic targets

2.3.2.1. Synthesis of Parnafungins A and C models

Parnafungins A (**146**), B (**147**), C (**148**) and D (**149**) are natural products containing an isoxazol-5-one ring isolated from the *Fusarium larvarum* and other Hypocrealean fungi, that act by inhibiting fungal polyadenosine polymerase (PAP).[76] Parnafungins A and B have shown also activity *in vivo* in mice against *Candida albicans*.[76a] Parnafungins C and D exhibit broad, potent spectrum antifungal activity and have also been identified to target fungal mRNA cleavage and polyadenylation (Figure 1).[76b]

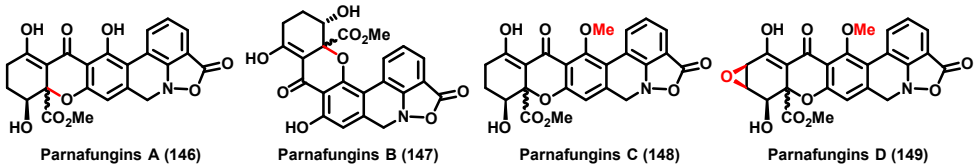
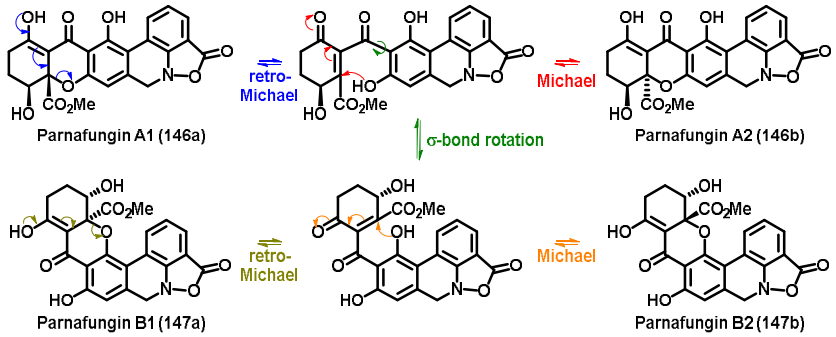


Figure 1. Presentation of Parnafungins A, B, C and D.

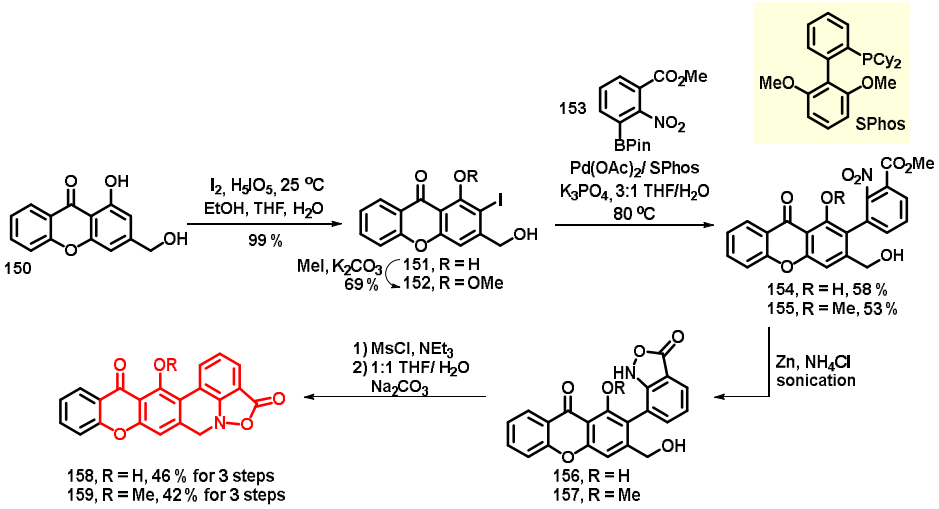
At r.t., Parnafungins A1 (**146a**), A2 (**146b**), B1 (**147a**) and B2 (**147b**) can readily interconvert between each other in *ca.* 1-2 h, *via* retro-Michael and Michael additions involving its pyranone ring (Scheme 41).



Scheme 41. Equilibrium involved between isomeric parnafungins A1 (**146a**), A2 (**146b**), B1 (**147a**) and B2 (**147b**).

Aiming at the preparation of Parnafungins A and C, Zhou and Snyder reported the preparation of molecules **158** and **159** as their model structures, respectively (Scheme 42). These compounds differ from the corresponding target natural products by the substituents and the oxydation level of the furthest cycle from the benzo[c]isoxazol-3-one ring.

The synthetic route starts with the preparation of tricycle **150** in 4 steps from 2-hydroxybenzoic acid and 3,5-dihydroxytoluene (not shown). Sequential iodination of tricycle **150** using a combination of I_2/H_5IO_5 affords iodide **151**, which can be submitted to a selective methylation protocol of the more acidic phenol hydroxy group using MeI and K_2CO_3 to afford the corresponding methylether **152**, *en route* to the preparation of Parnafungin C model **159**. In the case of Parnafungin A model **158**, no methylation is necessary. Next, all the following steps are the same for both Parnafungins, although slight variations in yields are observed. Using iodides **151** or **152** for a Pd-catalyzed Suzuki cross-coupling with boronic acid pinacol ester **153** leads to arylated compounds **154** or **155**, respectively. Sequential reduction of the nitro group employing Zn in acidic medium produces the corresponding hydroxylamine intermediates that cyclize onto the *o*-methyl ester group to afford the corresponding isoxazol-5-ones **156** or **157**. Finally, mesylation of the primary alcohol, followed by an intramolecular S_N2 reaction leads to the structure models of Parnagunfin A **158** (R=H) or Parnafungin C **159** (R=Me) (Scheme 42).[77]



Scheme 42. Synthetic route employed for the preparation of the Parnafungins A and C models, **158** and **159**, respectively.

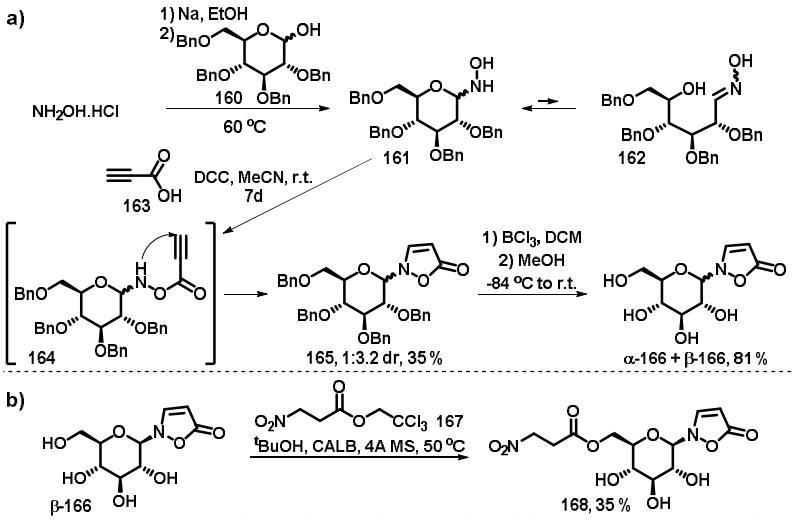
2.3.2.2. Synthesis of isoxazolone glucosides

Boland and co-workers reported the preparation of isoxazol-5-one glucosides **166** and **168** (Scheme 43). The synthetic route starts with the reaction of hydroxylamine with the commercially available 2,3,4,6-tetra-O-benzyl-D-glucopyranose **160** to afford intermediate **161**. This intermediate can be coupled with propynoic acid **163** under Steglich conditions[78] to afford ester **164**, followed by a conjugate addition event to produce the isoxazolone moiety found in **165**. Further deprotection of this intermediate using BCl_3 in DCM affords the corresponding isoxazolone glucoside as a mixture of α- and β-anomers, **α-166** and **β-166**, respectively (Scheme 43a). These anomers can be separated by flash column chromatography. Then, β-anomer of **166** can be selectively acylated at the primary alcohol using the enzyme *Candida antarctica* lipase B (CALB) as catalyst in the presence of trichloroethylester **167** as an activated acyl transfer agent to afford isoxazol-5-one glucoside **168** (Scheme 43b).[79]

3. Conclusions

In summary, this chapter has presented the main recent developments in the chemistry of isoxazol-5-ones. In light of the large variety of structures that can be readily accessed from these heterocycles, such as indoles, pyridines, quinolines, alkynes, 1,3-oxazin-6-ones, azadienes, azirines,

piperidines and 1-azabicyclo[3.1.0]hex-2-enes, among others, a compelling argument can be made in favor of the great versatility of this heterocycle in organic synthesis.



Scheme 43. Preparation of isoxazol-5-one glucosides **a)** α-**166**+β-**166** and **b) 168** (DCC: *N,N′*-dicyclohexylcarbodiimide).

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References

1. Boulton, A. J.; Katritzky, A. R. *Tetrahedron*, **1961**, *12*, 41-50.
2. Benson, S. W. *J. Chem. Educ.* **1965**, *42*, 502-518.
3. For previous reviews on the chemistry of isoxazolones, see: a) Batra, S.; Bhaduri, A. P. *J. Indian Inst. Sci.* **1994**, *74*, 213-226. b) Beccalli, E. M.; Pocar, D.; Zonai, C. *Targets in Heterocyclic Systems - Chemistry and Properties*, Attanasi, O. A.; Spinelli, D.; Eds.; Italian Society of Chemistry, Rome, **2003**, *7*, 31-63. c) da Silva, A. F.; Fernandes, A. A. G.; Thurow, S.; Stivanin, M. L.; Jurberg, I. D. *Synthesis* **2018**, *50*, 2473-2489. For a review on base catalyzed rearrangements involving isoxazol-5(2*H*)-ones, see: d) Prager, R. H.; Williams, C. M. *Heterocycles* **1999**, *51*, 3013-3030. Considering nitroisoxazolones, see: e) Nishiwaki, N. *Curr. Med. Chem.* **2017**, *24*, 3728-3748.
4. Alkylation with alkyl halides: a) Atfani, M.; Lubell, W. D. *J. Org. Chem.* **1995**, *60*, 3184-3188. Alkylation with diazomethane: b) De Sarlo, F. *Tetrahedron* **1967**, *23*, 831-840. c) Van Rompuy, L.; Schamp, N.; De Kimpe, N.; Van Parijs, R. *J. Chem. Soc. Perkin Trans. 1* **1973**, 2503-2506. Pd-catalyzed allylic substitution: d) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *Tetrahedron Lett.* **1994**, *50*, 515-528.
5. a) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83-134. See also: b) Seeman, J. I. *J. Chem. Educ.* **1986**, *63*, 42-48.
6. a) Beccalli, E. M.; Benincori, T.; Marchesini, A. *Synthesis* **1988**, *1988*, 886-888. b) Liu, Z.; Han, B.; Liu, Q.; Zhang, W.; Yang, L.; Liu, Z.-L.; Yu, W. *Synlett* **2005**, *2010*, 1579-1580.
7. Hellmuth, T.; Frey, W.; Peters, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 2788-2791.
8. Rieckhoff, S.; Meisner, J.; Kästner, J.; Frey, W.; Peters, R. *Angew. Chem. Int. Ed.* **2018**, *57*, 1404-1408.

9. For previous investigations of [3,3]-sigmatropic shifts involving isoxazol-5-ones, see: a) Makisumi, Y.; Sasatani, T. *Tetrahedron Lett.* **1969**, *7*, 543-546. b) Gomes, M. J. S.; Pinto, L. F. V.; Glória, P. M. C.; Rzepa, H. S.; Prabhakar, S.; Lobo, A. M. *Chem. Central J.* **2013**, *7*, 94-105. c) Grigg, R.; Sarkar, M. R. A.; Thayaparan, A.; Sridharan, V.; Fishwick, C. W. G. *Tetrahedron* **2007**, *63*, 7213-7228.
10. Meng, W.-T.; Zheng, Y.; Nie, J.; Xiong, H.-Y.; Ma, J.-A. *J. Org. Chem.* **2013**, *78*, 559-567.
11. An asymmetric organocatalytic fluorination protocol of isoxazol-5-ones has been also reported. See: Zhang, H.; Wang, B.; Cui, L.; Bao, X.; Qu, J.; Song, Y. *Eur. J. Org. Chem.* **2015**, 2143-2147.
12. Terent´ev, A. O.; Vil´, V. A.; Gorlov, E. S.; Rusina, O. N.; Korlyukov, A. A.; Nikishin, G. I.; Adam, W. *ChemistrySelect* **2017**, *2*, 3334-3341.
13. For a recent review, see: Lima, C. G. S.; Lima, T. de M.; Duarte, M.; Jurberg, I. D.; Paixão, M. W. *ACS Catalysis*, **2016**, *6*, 1389-1407.
14. For a selection of examples, see: a) Biermann, U.; Butte, W.; Koch, R.; Fokou, P. A.; Türünç, O.; Meier, M. A. R.; Metzger, J. O. *Chem. Eur. J.* **2012**, *18*, 8201-8207. b) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Angew. Chem. Int. Ed.* **2010**, *49*, 3334-3337. c) Cheng, Y.; Yuan, X.; Ma, J.; Yu, S. *Chem. Eur. J.* **2015**, *21*, 8355-8359. d) Sustmann, R.; Lücking, K.; Kopp, G.; Rese, M. *Angew. Chem. Int. Ed.* **1989**, *28*, 1713-1715. e) Fukuzumi, S.; Kitano, T.; Ishikawa, M.; Matsuda, Y. *Chem. Phys.* **1993**, *176*, 337-347.
15. Grassi, G.; Bruno, G.; Risitano, F.; Foti, F.; Caruso, F.; Nicolò, F. *Eur. J. Org. Chem.* **2001**, 4671-4678.
16. Tietze, L. F.; Brumby, T.; Pretor, M.; Remberg, G. *J. Org. Chem.* **1988**, *53*, 810-820.
17. For an additional discussion on the proton catalyzed mechanism of the isomerization of 4-alkylideneisoxazolones, see: Rotondo, E.; Rotondo, A.; Bruschetta, G.; Risitano, F.; Foti, F. *Tetrahedron Lett.* **2002**, *43*, 5989-5991.
18. Sutariya, T. R.; Labana, B. M.; Parmar, B. D.; Parmar, N. J.; Kant, R.; Gupta, V. K. *RSC Adv.* **2015**, *5*, 23519-23529.
19. Feng, B.-B.; Xu, J.; Zhang, M.-M.; Wang, X.-S. *Synthesis* **2016**, *48*, 65-72.
20. Shi, W.; Wang, Y.; Zhu, Y.; Zhang, M.; Song, L.; Deng, H. *Synthesis* **2016**, *48*, 3527-3536.
21. Altieri, E.; Cordaro, M.; Grassi, G.; Risitano, F.; Scala, A. *Synlett* **2010**, *14*, 2106-2108.
22. For additional examples of spiro-isoxazol-5-ones built with perfect diastereocontrol, see also: a) Risitano, F.; Grassi, G.; Foti, F.; Romeo, R. *Synlett* **2002**, *1*, 116-120. b) Vereshchagin, A. N.; Elinson, M. N.; Korshunov, A. D.; Anisina, Y. E.; Novikov, R. A.; Goloveshkin, A. S.; Bushmarinov, I. S.; Zlotin, S. G.; Egorov, M. P. *Synlett* **2016**, *27*, 2489-2493. c) Risitano, F.; Grassi, G.; Foti, F.; Nicolò, F.; Condello, M. *Tetrahedron* **2002**, *58*, 191-195. d) Foti, F.; Grassi, G.; Risitano, F.; Nicolò, F.; Rotondo, A. *Helv. Chim. Acta* **2001**, *84*, 3313-3318.
23. Xiao, W.; Yang, Q.-Q.; Chen, Z.; Ouyang, Q.; Du, W.; Chen, Y.-C. *Org. Lett.* **2018**, *20*, 236-239.
24. For reviews, see: a) Jurberg, I. D.; Chatterjee, I.; Tannert, R.; Melchiorre, P. *Chem. Commun.* **2013**, *49*, 4869-4883. b) Marcos, V.; Alemán, J. *Chem. Soc. Rev.* **2016**, *45*, 6812-6832. c) Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Chem. Sci.* **2013**, *4*, 2287-2300. d) Ramachary D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865-887.
25. Zhao, T.; Zhang, H.; Cui, L.; Wang, C.; Qu, J.; Wang, B. *ChemistrySelect* **2016**, *1*, 3713-3717.
26. For a selection of additional examples see: a) Haibach, M. C.; Seidel, D. *Angew. Chem. Int. Ed.* **2014**, *53*, 5010-5036. b) Peng, B.; Maulide, N. *Chem. Eur. J.* **2013**, *19*, 13274-13287. c) Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2010**, *132*, 3543-3552. d) McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 402-403. e) Jurberg, I. D.; Peng, B.; Wöstefeld, E.; Wasserloos, M.; Maulide, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 1950-1953. f) McQuaid, K. M.; Long, J. Z.; Sames, D. *Org. Lett.* **2009**, *11*, 2972-2975.
27. Cui, B.-D.; Li, S.-W.; Zuo, J.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2014**, *70*, 1895-1902.
28. a) Wentrup, C.; Winter, H.-W. *Angew. Chem. Int. Ed.* **1978**, *17*, 609-610. See also: b) Wentrup, C.; Reichen, W. *Helv. Chim. Acta* **1976**, *59*, 2615-2617.
29. For a description of the FVP apparatus, see: Lân, N. M.; Wentrup, C. *Helv. Chim. Acta* **1976**, *59,* 2068-2073.

30. a) Wentrup, C.; Winter, H.-W.; Kvaskoff, D. *J. Phys. Chem. A* **2015**, *119*, 6370-6376. b) Rzepa, H. S.; Wentrup, C. *J. Org. Chem.* **2013**, *78*, 7565-7574.
31. See also: Mackie, I. D.; Johnson, R. P. *J. Org. Chem.* **2009**, *74*, 499-503.
32. a) Winter, H.-W.; Wentrup, C. *Angew. Chem. Int. Ed.* **1980**, *19*, 720-721.
33. Wentrup, C.; Briehl, H.; Lorenčak, P.; Vogelbacher, U. J.; Winter, H.-W.; Maquestiau, A.; Flammang, R. *J. Am. Chem. Soc.* **1988**, *110*, 1337-1343.
34. Wentrup, C.; Stutz, U.; Wollweber, H.-J. *Angew. Chem. Int. Ed.* **1978**, *17*, 688-689.
35. Wentrup, C.; Gerecht, B.; Laqua, D.; Briehl, H.; Winter, H. W.; Reisenauer, H. P.; Winnewisser, M. *J. Org. Chem.* **1981**, *46*, 1046-1048.
36. Kappe, C. O.; Kvaskoff, D.; Moloney, D. W. J.; Flammang, R.; Wentrup, C. *J. Org. Chem.* **2001**, *66*, 1827-1831.
37. a) Reichen, W.; Wentrup, C. *Helv. Chim. Acta* **1976**, *59*, 2618-2620. b) Wentrup, C.; Winter, H.-W. *J. Org. Chem.* **1981**, *46*, 1045-1046.
38. Wentrup, C.; Becker, J.; Winter, H.-W. *Angew. Chem. Int. Ed.* **2015**, *54*, 5702-5704.
39. Prager, R. H.; Singh, Y. *Tetrahedron* **1993**, *49*, 8147-8158.
40. Clark, A. D.; Janowski, W. K.; Prager, R. H. *Tetrahedron* **1999**, *55*, 3637-3648.
41. Cox, M.; Heidarizadeh, F.; Prager, R. H. *Aust. J. Chem.* **2000**, *53*, 665-671.
42. Review: Zard, S. Z. *Chem Commun.* **2002**, 1555-1563.
43. The development of this reaction can be traced back to the early reports of Abidi. See: a) Abidi, S. L. *J. Chem. Soc., Chem. Comm.* **1985**, 1222-1223. b) Abidi, S. L. *Tetrahedron Lett.* **1986**, *27*, 267-270. See also: c) Abidi, S. L. *J. Org. Chem.* **1986**, *51*, 2687-2694. For mechanistic discussions about the Abidi reaction, see: d) Corey, E. J.; Seibel, W. L.; Kappos, J. C. *Tetrahedron Lett.* **1987**, *28*, 4921-4924. e) Boivin, J.; Elkaim, L.; Ferro, P. G.; Zard, S. Z. *Tetrahedron Lett.* **1991**, *32*, 5321-5324.
44. a) Boivin, J.; Huppé, S.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 8735-8738. b) Dias-Jurberg, I.; Gagosz, F.; Zard, S. Z. *Org. Lett.* **2010**, *12*, 416-419. c) Renard, D.; Rezaei, H.; Zard, S. Z. *Synlett* **2002**, *8*, 1257-1260.
45. This does not mean that 1,2-additions to the carbonyl group of isoxazolones are not possible. See for instance: a) Beccalli, E. M.; Gelmi, M. L.; Marchesini, A. *Tetrahedron* **1998**, *54*, 14401-14406. b) Beccalli, E. M.; Marchesini, A.; Pilati, T. *Synth. Commun.* **1993**, *23*, 685-702. c) Rao, M. H.; Reddy, A. P. R.; Veeranagaiah, V. *Synthesis* **1992**, *1992*, 446-448.
46. Boivin, J.; Huppé, S.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 5737-5740.
47. Huppé, S.; Rezaei, H.; Zard, S. Z. *Chem. Commun.* **2001**, 1894-1895.
48. a) Liu, H. J.; Ogino, T. *Tetrahedron Lett.* **1973**, *14*, 4937-4940. b) Liu, H. J.; Majumdar, S. P. *Synth. Commun.* **1975**, *5,* 125-130. c) Nagao, K.; Chiba, M.; Kim, S.-W. *Synthesis* **1983**, *1983*, 197-199. d) Mock, W. L.; Hartman, M. E. *J. Org. Chem.* **1977**, *42,* 459-465; e) Mock, W. L.; Hartman, M. E. *J. Org. Chem.* **1977**, *42,* 466-472. f) Vinod, D.; Warnhoff, E. W. *J. Org. Chem.* **1983**, *48,* 2590-2598.
49. a) Fraser, R. R.; Kong, F. *Synth. Commun.* **1988**, *18*, 1071-1077. For a somehow similar halogenation procedure, see also: b) Klimczyk, S.; Huang, X.; Farès, C.; Maulide, N. *Org. Biomol. Chem.* **2012**, *10*, 4327-4329.
50. Capreti, N. M. R.; Jurberg, I. D. *Org. Lett.* **2015**, *17*, 2490-2493.
51. Jurberg, I. D. *Chem. Eur. J.* **2017**, *23*, 9716-9720.
52. Okamoto, K.; Shimbayashi, T.; Tamura, E.; Ohe, K. *Chem. Eur. J.* **2014**, *20*, 1490-1494.
53. Okamoto, K.; Oda, T.; Kohigashi, S.; Ohe, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 11470-11473.
54 Shimbayashi, T.; Matsushita, G.; Nanya, A.; Eguchi, A.; Okamoto, K.; Ohe, K. *ACS Catal.* **2018**, *8*, 7773-7780.
55. Okamoto, K.; Sasakura, K.; Shimbayashi, T.; Ohe, K. *Chem. Lett.* **2016**, *45*, 988-990.
56. Rieckhoff, S.; Hellmuth, T.; Peters, R. *J. Org. Chem.* **2015**, *80*, 6822-6830.
57. Rieckhoff, S.; Frey, W.; Peters, R. *Eur. J. Org. Chem.* **2018**, 1797-1805.
58. Okamoto, K.; Shimbayashi, T.; Yoshida, M.; Nanya, A.; Ohe, K. *Angew. Chem. Int. Ed.* **2016**, *55*, 7199-7202.
59. Rieckhoff, S.; Titze, M.; Frey, W.; Peters, R. *Org. Lett.* **2017**, *19*, 4436-4439.

60. Okamoto, K.; Nanya, A.; Egushi, A.; Ohe, K. *Angew. Chem. Int. Ed.* **2018**, *57*, 1039-1043.
61. Abbiati, G.; Beccalli, E. M.; Broggini, G.; Zoni, C. *Tetrahedron* **2003**, *59*, 9887-9893.
62. For early examples of heterocycles prepared *via* N-O bond cleavage, followed by a cyclization event, see: a) Beccalli, E. M.; Marchesini, A. *Synthesis,* **1991**, *1991*, 861-862. b) Beccalli, E. M.; Marchesini, A.; Pilati, T. *Synthesis*, **1991**, *1991*, 127-131. c) Jeffery, D.; Prager, R. H.; Turner, D.; Dreimanis, M. *Tetrahedron*, **2002**, *58*, 9965-9972.
63. For examples of N-O bond cleavage events, followed by decarboxylation or other fragmentation steps, see: Zvilichovsky, G.; Gurvich, V.; Segev, S. *J. Org. Chem.* **1995**, *60*, 5250-5254.
64. Stivanin, M. L.; Duarte, M.; Sartori, C.; Capreti, N. M. R.; Angolini, C. F. F.; Jurberg, I. D. *J. Org. Chem.* **2017**, *82*, 10319-10330.
65. Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688-5691.
66. Jurberg, I. D.; Davies, H. M. L. *Org. Lett.* **2017**, *19*, 5158-5161.
67 Liang, H.-W.; Yang, Z.; Jiang, K.; Ye, Y.; Wei, Y. *Angew. Chem. Int. Ed.* **2018**, *57*, 5720-5724.
68. a) Ang, K. H.; Prager, R. H.; Smith, J. A.; Weber, B.; Williams, C. M. *Tetrahedron Lett.* **1996**, *37*, 675-678. See also: b) Prager, R. H.; Smith, J. A.; Weber, B.; Williams, C. M. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 2665-2672. c) Khalafy, J.; Svensson, C. E.; Prager, R. H.; Williams, C. M. *Tetrahedron Lett.* **1998**, *39*, 5405-5408.
69. Prager, R. H.; Williams, C. M. *Aust. J. Chem.* **1996**, *49*, 1315-1323.
70. Cox, M.; Prager, R. H.; Riessen, D. M. *Arkivoc* **2001**, *vii*, 88-103.
71. Singh, Y.; Prager, R. H. *Aust. J. Chem.* **1992**, *45*, 1811-1823.
72. a) Bullock, R. *Expert Rev. Neurother.* **2004**, *4*, 153-163. b) Corey-Bloom, J. *Int. J. Clin. Pract.* **2003**, *57*, 219-223.
73. a) Paul, T.; Malachowski, W. P.; Lee, J. *J. Org. Chem.* **2007**, *72*, 930-937. b) Paul, T.; Malachowski, W. P.; Lee, J. *Org. Lett.* **2006**, *8*, 4007-4010.
74. In a different context, see also: a) Burke, S. J.; Malachowski, W. P.; Mehta, S. K.; Appenteng, R. *Org. Biomol. Chem.* **2015**, *13*, 2726-2744. b) Schultz, A. G.; Harrington, R. E. *J. Am. Chem. Soc.* **1991**, 113, 4926-4931. c) Schultz, A. G.; Lee, H. *Tetrahedron Lett.* **1992**, *33*, 4397-4400.
75. Marko, I. E.; Mekhalfia, A. *Tetrahedron Lett.* **1990**, *31*, 7237-7240.
76. a) Jiang, B.; Xu, D.; Allocco, J.; Parish, C.; Davison, J.; Veillette, K.; Sillaots, S.; Hu, W.; Rodriguez-Suarez, R.; Trosok, S.; Zhang, L.; Li, Y.; Rahkhoodaee, F.; Ransom, T.; Martel, N.; Wang, H.; Gauvin, D.; Wiltsie, J.; Wisniewski, D.; Salowe, S.; Kahn, J. N.; Hsu, M.-J.; Giacobbe, R.; Abruzzo, G.; Flattery, A.; Gill, C.; Youngman, P.; Wilson, K.; Bills, G.; Platas, G.; Pelaez, F.; Diez, M. T.; Kauffman, S.; Becker, J.; Harris, G.; Liberator, P.; Roemer, T. *Chem. Biol.* **2008**, *15*, 363-374. b) Overy, D.; Calati, K.; Kahn, J. N.; Hsu, M.-J.; Martín, J.; Collado, J.; Roemer, T.; Harris, G.; Parish, C. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1224-1227. c) Bills, G. F.; Platas, G.; Overy, D. P.; Collado, J.; Fillola, A.; Jiménez, M. R.; Martín, J.; del Val, A. G.; Vicente, F.; Tormo, J. R.; Peláez, F.; Calati, K.; Harris, G.; Parish, C.; Xu, D.; Roemer, T. *Mycologia* **2009**, *101*, 449-472. d) Adam, G. C.; Parish, C. A.; Wisniewski, D.; Meng, J.; Liu, M.; Calati, K.; Stein, B. D.; Athanasopoulos, J.; Liberator, P.; Roemer, T.; Harris, G.; Chapman, K. T. *J. Am. Chem. Soc.* **2008**, *130*, 16704-16710.
77. a) Zhou, Q.; Snider, B. B. *J. Org. Chem.* **2010**, *75*, 8224-8233. b) Zhou, Q.; Snider, B. B. *Org. Lett.* **2009**, *11*, 2936-2939.
78. Neises, B.; Steglich, W. *Angew. Chem. Int. Ed.* **1978**, *17*, 522-524.
79. Becker, T.; Görls, H.; Pauls, G.; Wedekind, R.; Kai, M.; von Reuβ, S. H.; Boland, W. *J. Org. Chem.* **2013**, *78*, 12779-12783.