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Dioxazolones: Stable Substrates for the Catalytic Transfer of Acyl Nitrenes

Kaj M. van Vliet and Bas de Bruin*

ABSTRACT: Dioxazolones are a convenient class of acyl nitrene transfer reagents. Their application in homogeneous transition-metal catalysis has led to many new amidation reactions. Dioxazolones are typically activated by transition metals at relatively low reaction temperatures. The metal nitrenoids formed by decarboxylative activation of dioxazolones are generally electron deficient and commonly react in a concerted fashion. "Intermolecular" nitrene insertion reactions involving preactivated C–H bonds ("innershell" mechanism) easily compete with the Curtius-type rearrangement, but for intramolecular "direct" nitrene transfer/insertion reactions involving nonpreactivated substrates (i.e., without preceding formation of metal–carbon or metal–hydride bonds) extensive ligand optimization is important to prevent such unwanted side reactions. The ease of dioxazolone synthesis, formation of CO₂ gas as the sole byproduct from reactions with dioxazolones, and the importance of nitrene transfer reactions in general has led to the development of several interesting reactions producing N-aryl amides, oxazoles, and lactams. Since the activation of dioxazolones proceeds under mild reaction conditions, stereo- and enantioselective reactions are also possible, which is useful for the synthesis of bioactive nitrogen-containing compounds. This review provides an overview of these reactions reported in recent years.

KEYWORDS: nitrenes, dioxazolones, amidation reactions, C–H activation, catalysis

METHODS FOR DIRECT C–N BOND FORMATION

Together with carbon, oxygen, and hydrogen, nitrogen is one of the main elements in living cells and natural compounds. The synthesis of nitrogen-containing compounds is important in modern society. For the majority of bioactive molecules nitrogen is an indispensable element. Furthermore, functional nitrogen-containing polymers, such as polyurethane and polyamides, make up a big part of the global polymer production. Nucleophilic substitution, condensation, reductive amination, and hydroamination reactions are a few efficient methods for the incorporation of nitrogen atoms in new molecules (Scheme 1a–c). Ullmann reported, at the start of the last century, a copper-catalyzed nucleophilic aromatic substitution reaction to convert aryl halides into aniline derivatives (Scheme 1d). Other types of catalytic substitution reactions with halide-containing compounds have been reported since. The palladium-catalyzed version by Buchwald and Hartwig is one of the most famous (Scheme 1e), as a wider variety of compounds can be used due to the milder reaction conditions required for Buchwald–Hartwig C–N coupling reactions in comparison to the Ullmann-type transformations.

Substitution of compounds containing a halide or another leaving group still requires prefunctionalization of substrates. From the perspective of sustainability, direct C–N bond forming reactions are highly desired. Transition-metal catalysis enabled scientists to activate various C–H bonds in a regioselective and stereoselective manner. Catalysis including transition-metal nitrenoids have been shown to be efficient in the direct amination of compounds (Scheme 1f). Azides were recognized in an early stage as nitrene precursors. In 1951 the synthesis of carbazoles from o-azidobiphenyls under thermal and photochemical conditions was reported by Smith. The use of nitrenes to form new C–N bonds sparked the interest of researchers to further investigate the use of azides as nitrene precursors. Iminoiodinanes are another class of nitrene transfer reagents widely used in nitrene transfer chemistry, first reported by Okowara in 1975. However, the use of...
iminoiodinanes results in the formation of halogen-containing waste.

Direct amidation of molecules requires the generation of acyl nitrene precursors. Acyl azides are unsuitable for this purpose. While azides have shown to be successful for the transfer of sulfonyl, phosphoryl, alkyl and aryl azides, the use of acyl azides is not straightforward due to their intrinsic instability. In particular, aliphatic acyl azides are hard to isolate and store. The past few years, 1,3,4-dioxazol-2-one derivatives (dioxazolones) have become increasingly popular as more stable and alternative nitrene transfer reagents for direct amidation reactions. Dioxazolones also have other applications, such as in battery development.10 Several reviews have been published that discuss transition-metal-catalyzed nitrene transfer reactions in general.11 In this review, however, the focus is on dioxazolones as acyl nitrene precursors in catalysis, which provides a convenient handle for the further development of direct C–N bond forming reactions.

II EARLY DEVELOPMENT OF THE CHEMISTRY WITH DIOXAZOLONES

Although synthetic applications of dioxazolones have become more popular since 2015, they had been known already for over half a century. Dioxazolones were first synthesized in 1951 by Beck.12 On the basis of the known reaction between acyl hydrazides and phosgene forming an oxadiaxolone,13 he reacted hydroxamic acids with phosgene to form dioxazolones. He also showed that hydroxamic acids could be regenerated by boiling the dioxazolone in water. In 1968, Sauer and Mayer looked at the thermal and photochemical decomposition of dioxazolone compounds.14 They reported the decarboxylation of dioxazolones to form the acyl nitrene intermediates and their rearrangement to form isocyanates (which react further to form urea compounds).14 They reported the decarboxylation of dioxazolones to form the acyl nitrene intermediates and their rearrangement to form isocyanates (which react further to form urea compounds).14

For the Lossen rearrangement, X is a carbonate (such as the intermediate shown in Scheme 2) or sulfonate group. Since the work from Pfizer starts from a hydroxamic acid, their work is considered a Lossen-type rearrangement. For the Hofmann rearrangement, X is a halogen atom. The Curtius rearrangement formally starts from an acyl azide (X = N₂⁻). All three

Scheme 2. Mechanism for Urethane Formation from Dioxazolones, Proposed by Burk (R₂ = Aryl, Alkyl; R₂ ≠ H).16

Inspired by the early work of Sauer and Mayer (vide supra), Pfizer published a paper on a Lossen-type rearrangement from hydroxamic acids via dioxazolones in 2009.15 Instead of generation of the dioxazolone ring by reaction hydroxamic acids with phosgene, the researchers used carbonyldiimidazole (CDI) as the carbonyl source. The resulting dioxazolone is then thermally decomposed to form the isocyanate that can react with various nucleophiles.

A short note on the naming of acyl nitrene type rearrangement reactions should be mentioned here. The Curtius, Hofmann, andLossen rearrangements are very similar and are often mixed in the chemistry literature, and all of these rearrangements result in the formation of an isocyanate from N-X amides, where X is a leaving group (see Scheme 3).20

Scheme 3. Acyl Nitrene Type Rearrangements to Isocyanates from N-X Amides

For the Lossen rearrangement, X is a carbonate (such as the intermediate shown in Scheme 2) or sulfonate group. Since the work from Pfizer starts from a hydroxamic acid, their work is considered a Lossen-type rearrangement. For the Hofmann rearrangement, X is a halogen atom. The Curtius rearrangement formally starts from an acyl azide (X = N₂⁻). All three

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Dioxazolones are considered concerted reactions, which is supported by theoretical and experimental evidence. For clarity, in this paper the term “Curtius-type rearrangement” will be used for the decarboxylative decomposition of dioxazolones leading to isocyanate formation.

**DIRECTED C(sp²)−H AMIDATION**

The field of directed amination of aromatic C−H groups was initially focused on reactions of amines with the use of a sacrificial oxidant. Since 2012, Chang has reported several papers on rhodium-catalyzed directed C−H amination of arenes, where azides were used as a preactivated precursor that allowed for oxidant-free amination reactions at room temperature. Additional mechanistic studies showed that the nitrene insertion mechanism does not proceed via a concerted mechanism but rather involves a rate-determining step in which (formally) a Rh(V)−nitreneoid species is formed. Because of the easy isocyanate formation by the Curtius rearrangement, acyl azides generally invert and bind with the carbon atom (carbamoylation).

Mechanistic studies showed that the binding of acyl azides to pentamethylcyclopentadienylrhodium ([Cp*RhCl₂]) was weaker than the binding of 2-phenylpyridine (1) to the complex, thus leading to substrate inhibition. 3-Phenyl-1,4,2-dioxazol-5-one (2a) possesses a higher binding affinity for the rhodium catalyst (which is similar to imines) in comparison to azides, thus resulting in more efficient nitrene formation in catalysis (see the product distribution of 3 and 6 in Scheme 5). Other dioxazolone-like substrates (2b,c) proved to be less efficient in these types of reactions. Utilization of 3-phenyl-5,5-dimethyl-1,4,2-dioxazole (2b) did allow for crystallization of its Ru-bound form. Instead of pyridyl as a directing group, the reaction also worked with carbamoyl, oxime, and N-oxide groups. In a later article, the authors also showed that the reaction works well in ethyl acetate and could be safely performed on a >40 g scale. In addition, Bolm showed that this type of reaction could be performed under solvent-free conditions using ball milling.

A general mechanism for the directed C−H amidation reaction is shown in Scheme 6. After initiation from a [Cp*XM] source (which commonly includes dehalogenation), where M is a group 9 transition metal, intermediate 7 is formed, to which the dioxazolone can coordinate. Decarboxylative activation of the dioxazolone in adduct 8 results (formally) in the M(V)−nitreneoid species 9 in the case of rhodium and iridium, which subsequently inserts into the M−C bond to from metallacyle 10. The desired product (12) and intermediate 7 are formed upon protodemetalation with the new substrate 11.

In 2016, the Chang group compared [Cp*Rh]⁺ with [Cp*Ir]⁺ for the directed amidation of arenes with dioxazolones. In both cases, a concerted mechanism for the dioxazolone decomposition and M−C nitrogen insertion step from complex 8 to complex 10 is unlikely, because a concerted step would have a significantly higher energy barrier for both metals. There is a lower energy barrier associated with M(V)−imido complex (9) formation for iridium, and the nitrene is more strongly bound to iridium, in comparison to rhodium. When the authors extended the reaction to cobalt catalysis, they found that [Cp*Co]⁺ was superior to the second- and third-row group 9 metals for the directed C−H amidation of pivaloylaniline (13) with dioxazolone 2a (see Scheme 7). Reaction optimization showed an optimal reaction temperature of 40 °C for cobalt. The decrease in yield at higher temperatures was associated with bis-amidation. Whereas for the second- and third-row transition metals rhodium and iridium the (formal) 5+ oxidation state is readily accessible, such high oxidation states are unlikely for cobalt. Therefore, we speculate that for cobalt the nitrene insertion reaction proceeds in a concerted manner, simultaneous with the decarboxylative decomposition of the dioxazolones. Bolm showed that the cobalt-catalyzed directed C−H amidation reaction with dioxazolone could be performed in solvent-free manner using a ball-milling protocol. Since the work of Chang, many groups have reported on group 9 [Cp*XM] catalyzed directed C−H amidation reactions of benzene derivatives with different directing groups (some are shown in Scheme 8). The amide that is formed at the phenyl ring after C−H amidation could also act as a directing group. Therefore, Chang and co-workers looked at the iterative directed C−H amidation of arenes with group 9 metals. [Ru(p-cymene)-(Cl)₂] catalyzed the multiamidation of pivaloylaniline (13).
with 3-\((\text{tert-butyl})\)-1,4,2-dioxazol-5-one (15) (see Scheme 9).\textsuperscript{34} When this catalyst was used, the formation of bis-amidated 17 (17%) and tris-amidated 18 (6%) products (in addition to the monoamidated product 16) was already observed for 1.1 equiv of 15 relative to 13. With 4 equiv of 15, 86% of 13 is converted to the tetrakis-amidated product 19. Amidation of the remaining C–H bond was calculated to require an additional 5 kcal mol\(^{-1}\) of activation energy, preventing formation of the fully amidated product. Additional experiments with pivaloylaniline derivatives containing methyl and halide substituents suggest a steric influence of the number of iterations.

The Lee group reported in 2016 a rhodium-catalyzed directed C–H amidation reaction with azobenzene (20) and dioxazolone 2a to form product 21 (see Scheme 10A).\textsuperscript{35} Symmetrical and asymmetrical azobenzenes could be efficiently amidated with a cyclopentadienylrhodium species as the active catalyst. Asymmetric azobenzenes were used to investigate the regioselectivity of the amidation reaction (a selection is shown in Scheme 10B). The amidation reaction generally occurs at the ortho-substituted phenyl group. Again,
since electron-donating and electron-withdrawing groups do not give different selectivities (see 23–26), there seems to be a steric effect determining the selectivity. With 3 equiv of dioxazolone 2a the azobenzene 20 is efficiently bis-amidated at the same phenyl group to form compound 22 (Scheme 10A).

One year later, Patel reported a cobalt-catalyzed directed C–H amidation reaction with azobenzene derivatives (see Scheme 11).36 The reaction temperature required for this cobalt system, however, is significantly higher than for rhodium. The selectivity for the reaction with asymmetrical azobenzene derivatives was lower for their system.
The amidation of selective C−H has been applied successfully as a directing group for the amidation of benzaldehyde (Scheme 14). The oxygen atom in nitrone substrate 29 via cyclometalation. The amidation of product 30 has been applied successfully as a directing group for selective C−H bond amidation by Wang and Cui (Scheme 13). The amidation of 30 leads to amidated (vide supra) with [(Cp*IrCl2)2] as the catalyst. Li and co-workers showed that the oxidized form of azobenzene, azoxybenzene (28), could be efficiently amidated with dioxazolone 2a and [Cp*Ir] as the catalyst to form product 29 (Scheme 12). Oxidation of one of the nitrogen atoms of the azo bridge blocks metal coordination to one site, leading to the expected selectivity for the amidation reaction via cyclometalation. The oxygen atom in nitroso substrate 30, however, has been applied successfully as a directing group for selective C−H bond amidation by Wang and Cui (Scheme 13). The amidation of 30 leads to amidated (Scheme 16). The selectivity in this reaction for the olefinic C−H bond over the weaker allylic C−H bond is striking. Chang obtained the same selectivity with [(Cp*IrCl2)2] as the catalyst. More examples of directed C(sp3)−H amidation have been reported, including directed C−H amidation on substituted cyclopentadienyl ligands of ferrocene derivatives and C−H amidation reactions directly followed by cyclization steps to form heterocyclic compounds. Considering the mechanistic similarity of the C−H amidation mechanisms, we will not discuss these examples in detail herein.

**DIRECTED C(sp3)−H AMIDATION**

The directed C−H amidation strategy is not limited to C(sp3)−H bonds. Li et al. were the first who directly amidated a methyl group, such as that in methyloquilnine 37, with dioxazolone substrate 2a (Scheme 17). They could efficiently amidate 37 using [(Cp*RhCl2)2] as the catalyst to give product 38 in high yield (91%). Oximes and amides were also successfully used as directing groups. Again, rhodium was quickly replaced by cobalt as a first-row transition-metal alternative. Seayad and Dixon reported a cobalt-catalyzed single amidation of the tert-butyl group in thioamide 39 (see Scheme 18).

Dixon later showed that the dithiane moieity in substrate 41a could be used as a directing group to give 43 upon rhodium-catalyzed amidation with dioxazolone 42 (Scheme 19). The use of a synthetically versatile group, such as dithiane, for directing the C−H activation is useful for further derivatization after the amidination reaction. They showed that a six-membered dithiane ring, formed from an aldehyde, was crucial for the reaction (see 41b,c) and that only C−H bonds from methyl groups containing an α-tertiary carbon atom could be amidated (vide supra).

Recently, Yoshino and Matsunaga reported an enantioselective C(sp3)−H amidation reaction (Scheme 20). By addition of chiral carboxylic acid 45, they could enantioselectively amidate thioamide 44 with 2a and [(Cp*Co(MeCN)3)(SbF6)2] as the catalyst to form the chiral product (S)-46. Deuteration studies indicated that the C−H activation step is irreversible in this reaction, in opposition to what has been shown for the C−H amidation of amines. For C(sp3)−H amidation, this irreversible C−H activation step has also been shown by Zhao for the amidation of silicon bound methyl groups. Yoshino and Matsunaga later showed that also ferrocene-type chiral carboxylic acids, which are easily accessible, could be efficiently amidated (vide supra).

When in 2015 directed C−H amidation started to become a popular method for direct nitrogen incorporation, Jiao showed with [(Cp*Co(MeCN)3)(SbF6)2] as a catalyst that the same strategy for directed arene C−H amidation also works for the directed C−H amidation of olefin 35 to form amide 36 (Scheme 16). The selectivity in this reaction for the olefinic C−H bond over the weaker allylic C−H bond is striking. Chang obtained the same selectivity with [(Cp*IrCl2)2] as the catalyst. More examples of directed C(sp3)−H amidation have been reported, including directed C−H amidation on substituted cyclopentadienyl ligands of ferrocene derivatives and C−H amidation reactions directly followed by cyclization steps to form heterocyclic compounds. Considering the mechanistic similarity of the C−H amidation mechanisms, we will not discuss these examples in detail herein.

**Scheme 14. Rhodium-Catalyzed Directed C−H Amidation of Benzaldehyde via Transient Imine Formation**

![Scheme 14](https://dx.doi.org/10.1021/acscatal.0c00961)

**Scheme 15. Possible Imine Formation Pathway during the Directed C−H Amidation Reaction of Benzaldehyde with Dioxazolones**

![Scheme 15](https://dx.doi.org/10.1021/acscatal.0c00961)

**Scheme 16. Cobalt-Catalyzed Amidation of 2-(Prop-1-en-2-yl)pyridine with Phenylidioxazolone**

![Scheme 16](https://dx.doi.org/10.1021/acscatal.0c00961)
modified, can be used for the enantioselective amidation of thioamides.  

The group of Matsunaga later reported an enantioselective C(sp^3)−H amidation of 8-ethylquinoline 47 (Scheme 21).  

Although the use of chiral acid 42 did also lead to high yields for this reaction, the observed enantioselectivities were low.

Changing to the binaphthyl-type chiral acid 48 and performing the reaction at a lower reaction temperature (4 °C) resulted in the formation of (R)-49 with high enantioselectivity (84% ee). A small amount of Ag_2CO_3 was added as a base for deprotonation of the chiral acid. In addition, H/D-exchange experiments revealed that the C−H activation step is hardly
reversible, as they observed less than 5% incorporation of deuterium. In the absence of substrate 2a, no deuterium incorporation was observed.

### ALLYLIC AMIDATION

The amidation reaction with group 9 metals has also been applied in allylic C–N bond formation. The Rovis group reported an allylic C–H amidation of 1-decene (50) with \([\text{Cp}^*\text{IrCl}_2]_2\) as the catalyst and dioxazolones (such as 51) as nitrene precursors (see Scheme 22).\(^{55}\) C(sp\(^3\))−H (allylic)

### LACTAM FORMATION

The previous reactions are all examples of reactions proceeding via acyl nitrene insertion into preactivated C–H bonds. The M=\(N(\text{acyl})\) double bonds readily insert in the preformed M–C bonds, thus preventing unwanted Curtius-type rearrangements of the acyl nitrene moiety in these “inner-sphere” mechanisms. Reactions between N-acyl nitrene intermediates M=\(N(\text{acyl})\) with non-preactivated substrates in “direct” nitrene insertion mechanisms (i.e., without prior formation of metal–carbon or metal–hydride bonds) are more difficult to control but would give rise to new reactivity. Chang was the first who succeeded in letting acyl nitrenoids from dioxazolones react intramolecularly, but via a “direct” metal nitrene insertion mechanism without formation of M–C or M–H bonds, by carefully studying the reactivity of 62 and 63 with iridium catalyst 61 (Scheme 24).\(^{58}\) The reaction between 61 and 62 leads to nitrene insertion into the Ir–C bond, which was expected on the basis of previous work on directed C–H amidation. Addition of \(\text{PPh}_3\) blocks the coordination side, hampering coordination of a proton source and with that protodemetalation, leading to complex 64. The reaction of 61 with 63, which has a C(sp\(^3\))−H group preorganized close to the dioxazolone moiety by ortho substitution at the phenyl ring, leads to an intramolecular C–H amidation reaction, forming isoidololone 65. By replacement of the previously amidated carbon of the phenylpyridine ligand in complex 61 with a nitrogen atom, the nitrenoid insertion into the Ir–C bond that would result in formation of 64 is avoided, but the Curtius-type rearrangement also needed to be impeded. By an increase in the electron density of the metal center and avoidance of bulky substituents with a quinoline-carbamate ligand, pyrrolidinone 66 could be efficiently obtained with catalyst 67 (Scheme 24B).

The mechanism for the intramolecular C–H amidation toward lactams is shown in Scheme 25. When the Ir(III) complex 68 with a vacant side (or labile ligand) is formed (involving an initiation step that generally requires halide abstraction), dioxazolone 62 can coordinate, giving rise to formation of intermediate 69. Decarboxylation of the substrate at the metal center results in formation of (formally) the Ir(V)−nitrenoid species 70, which is sufficiently electrophilic to interact with the remote C–H δ bond. In a concerted,

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**Scheme 22. Iridium-Catalyzed Allylic Amidation of 1-Decene with Methylidioxazole**

![Scheme 22](image)

**Scheme 23. Comparison of Rhodium and Iridium for the Allylic Amidation of Disubstituted Olefins**

![Scheme 23](image)
“direct” nitrene insertion reaction the nitrogen atom of the nitrene moiety is inserted into the C−H bond without formation of M−C or M−H bonds prior to the C−N bond formation step (see 71), and subsequent ligand exchange then results in coordination of a new substrate and release of lactam 66.

Aromatic intramolecular C−H amidations toward lactams were also shown in the work of Chang, but only with a few examples and not all substrates were transformed efficiently. They envisioned a nucleophilic aromatic substitution pathway, which would lead to the desired intramolecular aromatic C−H amidation. By changing the N,N ligand for an N,O ligand, they could effectively transform 3-phenethyl-1,4,2-dioxazol-5-one derivatives to form six-membered lactams (Scheme 26).

However, an unexpected rearrangement was observed. The CPh−C bond from the backbone of substrate 72 is replaced by the acyl nitrene and shifted to the adjacent CPh−H bond (see product 74). Computational analysis revealed that the
electrophilic (formally) Ir(V)—nitrenoid moiety in complex 75 is preferentially attacked by the tertiary carbon atom instead of the ortho carbon atom, resulting in spirocyclic intermediate 76. Subsequent migrations of the nitrogen or the carbon atom to the adjacent C phenyl atom are both kinetically feasible. However, migration of the nitrogen atom is thermodynamically uphill. Therefore, a carbon migration toward intermediate 77, followed by a tautomerization step, results in formation of lactam 74 in 99% yield. The reaction does not require an electron-donating group at the phenyl, since the use of “unsubstituted” 3-phenethyl-1,4,2-dioxazol-5-one and its p-chloro derivative as substrates also gave the C-migrated lactam products in high yields (95% and 94%, respectively). Substrates containing meta substituents, such as 78, did not react via the spirocyclization pathway but rather via a direct electrophilic aromatic substitution to form isomers 79 and 80 (Scheme 27).

When the phenyl group contained an o- or p-hydroxide group (83), no migration was observed and dearomatized spirocyclic dienones could be isolated in high yields (see product 84 in Scheme 28A). For substrate 85, where the phenyl group is substituted with an indole group, the spirocyclic compound also does not undergo carbon atom migration. Two spirocyclic intermediates react intermolecularly to form complex multicyclic compound 86 (see Scheme 28B).

By using a chiral ligand, the Chang group continued to expand their lactam formation strategy to enantioselective intramolecular C(sp3)−H amidation. From a library of N,O and N,N donors they found that complex 87 was the catalyst giving the highest yields and enantioselectivities for the formation of lactam 68 (see (S)-68 in Scheme 29). The primary amine group of the ligand, which undergoes hydrogen bonding with the carbonyl of the acyl nitrene, appeared to be

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Scheme 27. Iridium-Catalyzed Lactam Formation from Ortho-Substituted Phenylethyl dioxazolones via Direct Electrophilic Aromatic Substitution

![Scheme 27](image)

Scheme 28. Iridium-Catalyzed Spirolactam Formation

A) ![Scheme 28A](image)

B) ![Scheme 28B](image)

Scheme 29. Iridium-Catalyzed Enantioselective Lactam Formation from 3-(3-Phenylpropyl)-1,4,2-dioxazol-5-one

![Scheme 29](image)
crucial to obtain high enantioselectivities. Mono- and dimethylation of the primary amine in 87 resulted in decreased yields and enantioselectivities and increased isocyanate formation via a Curtius-type rearrangement. A large scope of chiral lactams was efficiently cyclized, including aliphatic lactams 88 and 89. Also, the observed diastereoselectivities for the formation of multisubstituted lactams, such as 90, are high for this transformation. Yu used a similar N,N-type ligand
for the same enantioselective reaction catalyzed by Ru(II) \( \pi \)-cymene complex 91, leading to the opposite enantiomer (see Scheme 30).61

In collaboration with the group of Chang, He and Chen reported another enantioselective intramolecular cyclization reaction toward chiral lactams.62 Instead of the hydrogen-bonding strategy that was shown for catalysts containing \( \text{NH}_2,\text{N} \)-type ligands, they used catalyst 92 in a polar solvent mixture of HFIP and water (Scheme 31). The ligand forms a chiral hydrophobic binding pocket in the polar solvent mixture, resulting in enantioselective formation of \( \text{(S)} \)-68. Addition of a halide abstractor is not required in the polar HFIP/H\( \text{H}_2\text{O} \) mixture, which is a strong advantage over the previous methods.

The previous iridium catalysts used by Chang appeared to slightly favor tertiary C–H amidation over benzylic C–H amidation in the intramolecular cyclization reaction of substituted dioxazolone substrate 93 (see Scheme 32). By changing to a ruthenium cyclopentadienyl complex and making use of aromatic \( \pi-\pi \) interactions, they could selectively perform an intramolecular benzylic C–H amidation.63 The polar solvent HFIP increases the strength of \( \pi-\pi \) interaction,64 which resulted in a higher selectivity for the formation of lactam 94 over lactam 95, starting from dioxazolone 93.

Regioselective formation of lactam 97 by benzylic C–H amidation from dioxazolone 96, containing a secondary carbon atom at both the benzyl and the ethyl side, strongly supports the presumption that \( \pi-\pi \) interactions determine the selectivity (and not sterics).

Meggers and Houk developed chiral Ru(III) catalyst 98 containing \( \text{remote-N-heterocyclic carbenes} \) for the enantioselective transformation of 62 to form lactam \( \text{(S)} \)-68 (Scheme 33).65 At low catalyst loadings, 98 could catalyze the formation of the \( \gamma \)-lactam with high enantioselectivity and little isocyanate formation via a Curtius-type rearrangement. However, with its isomer, \( \text{(C}_2 \text{-99)} \), as the catalyst isocyanate 101 was obtained as the main product. The \( \text{(C}_2 \text{-99–nitrenoid intermediate was calculated to be more electrophilic than the 98–nitrenoid, and that led to a preference of the Curtius-type rearrangement over C–H insertion. This effect was even greater when complex 100 was used, which contains less sigma-donating normal NHC ligands. The authors also showed that 98 is extremely efficient for a gram-scale lactam (103) formation reaction of p-bromophenyl dioxazolone 102 (TON = 11200; \text{>99:1 er}).}

## REACTIONS WITH DOUBLE AND TRIPLE BONDS

Dioxazolone moieties are Lewis bases and can therefore, in principle, act as directing groups. Dong showed in 2017 that the ortho C–H bond of phenyldioxazolone 2a can be activated to form a rhodacycle and used for the formation of new C–C and C–N bonds with diphenylacetylene (104) (Scheme 34).66 Their conditions lead to a double addition of 104. After
formation of rhodacycle 107 by directed C–H activation of 2a, diphenylacetylene (104) is inserted into the Rh–C bond followed by decarboxylation nitrone formation and subsequent insertion into the new Rh–C bond to form complex 109. The authors proposed a protodemetalation step to form isoquinolinone 110, which could then be doubly deprotonated to form second rhodacycle 111. A second alkyne substrate insertion step leads to formation of intermediate 112, which upon reductive elimination forms the desired product (105).

In 2019, Zhang and Zhang reported the rhodium-catalyzed formation of isoquinolinone 110 from aryldioxazolones 2a and one molecule of 104 (Scheme 35).67 By a change in the solvent from DCE to the polar protic solvent methanol, the selectivity of the reaction changes to product 110, and the reaction could be performed at room temperature instead of 80 °C. The use of potassium acetate even decreased the reaction time from 12 h to 5 min.

In 2012, He reported the formation of oxazolines 116 or oxazoles 117 from the reaction between styrene (112) or phenylacetylene (113) with dioxazolone 2a catalyzed by a [Ru(TTP)(CO)][CuCl2] bimetallic system (Scheme 36).68 Although it was not clear how, addition of I2 as an oxidant increased the conversion rate of dioxazolone 2a by 4-fold. It was believed that the formation of 116 went via N-benzylaziridine 115, which was observed in the crude reaction mixture by LC-MS. For oxazole products, such as 117, a similar mechanism was proposed, but no experimental evidence was provided to support that.

The Liu group reported in 2016 the formation of oxazoles 119 from the reaction between ynamide 118 and dioxazolone-type acylnitrenoid precursors 5,5-dimethyl-1,4,2-dioxazoles 2b catalyzed by [(IPr)Au]+ (Scheme 37).69 In their proposed mechanism, the ynamide is polarized by coordination...
tion to the metal center, which leads to a nucleophilic attack of 2b. Decomposition of the dioxazole in intermediate 122 results in the formation of gold carbene intermediate 123, which upon cyclization (to form 124) and demetalation yields oxazole product 119. In addition to reporting on the conversion of a wide variety of N-EWG-ynamide substrates (where EWG is an electron-withdrawing group), the authors also showed that 1,3-diphenylprop-2-yn-1-one could be used to form oxazole 125, albeit with a moderate yield (50%).

Li and Wan showed a year later that no transition metal was required for this oxazole formation reaction in the presence of acid, which also lead to an increase in reaction rate.70 By using only 5 mol % of bis(trifluoromethane)sulfonamide (Tf₂NH) as a catalyst, multisubstituted oxazoles were obtained in good yields after only 5 min. In the presence of a strong acid, ynamide 126 is protonated to form keteniminium ion 128, which is sufficiently electrophilic to be attacked by dioxazole substrate 2b, after which a mechanism similar to that with [(IPr)Au(NTf₂)] (vide supra) results in the formation of oxazole 127 (Scheme 38).

Buchwald used copper catalysis to do an enantioselective Markovnikov hydroamidation reaction with styrene and dioxazolone 2a (Scheme 39).71 The copper hydride species 133, which undergoes a hydrocupration reaction with styrene to form 134, was formed by mixing [Cu(OAc)₂], the chiral ligand (S,S)-Ph-BPE, and diphenylsilane. According to their proposed mechanism, Cu−alkyl species 134 oxidatively inserts in the N−O bond of the dioxazolone to form intermediate
135, which is markedly different from the previous work on dioxazolones in which reactive acyl nitrenes are typically proposed as the key intermediates. After decarboxylation and nitrogen insertion into the Cu–C bond (136), copper is replaced for a silyl group with Ph₂SiH₂. During quenching of the reaction with methanol, a protodesilylation step from silyl ether 137 results in formation of the product (S)-132.

Recently, our group reported an efficient copper catalyzed three-component reaction with dioxazolone 138, phenylacetylene (114), and disopropylamine (139) to form N-acyl amidine 140 (Scheme 40). The applied catalyst Xantphos copper acetate [((Xan)Cu(OAc)] forms complex 141 by C–H activation of 114, catalyzed by amine 139. Decarbonylative formation of 142 by coordination of 138 to the metal center leads to a nitrenoid insertion into the Cu–C bond, resulting in the formation of complex 143. Ligand exchange with acetic acid regenerates [((Xan)Cu(OAc)] and generates electrophilic intermediate 144. Addition of 139 to 144 leads to the formation of the desired product 140. The use of nonbulky amines results in catalyst poisoning by amine coordination and does not lead to the desired product. The formation of N-benzoylamidine 145 from dioxazolone 2a was also not efficient with [((Xan)Cu(OAc)]. However, with a slightly longer reaction time and 10% CuI as the catalyst, 145 was obtained in moderate yield (68%).

The Chang group discovered, in their study on the intramolecular cyclization reactions toward lactams (vide supra) with dioxazolones, that alkynyl dioxazolone substrate 146 reacts with the quinolinolate ligand of iridium complex 147 to form product 148 (Scheme 41). This type of ligand participation can also be observed when [(Cp*IrCl₂)] reacts with 146. Acetic acid enables protodemetalation to give...
Scheme 44. Iridium-Catalyzed Syn and Anti Oxoamidation of Olefins with Dioxazolones and Acetic Acid\textsuperscript{74}

- Product 149: By adding sodium chloride and crown ether 15-crown-5, the chlorinated iridium species could be regenerated. Therefore, iridium could be used in catalytic amounts (Scheme 42). Tetrabutylammonium chloride could also be successfully applied as a chloride source. When sodium bromide was used instead of NaCl, the desired product 151 was efficiently formed, but dehydrobromination upon isolation with silica gel resulted in the formation of product 152. The products obtained after the chloroamidation reaction could subsequently be used in palladium-type cross-couplings, such as the Suzuki, Heck, and Sonogashira coupling reactions.

- One year later, Chang showed that the same methodology can also be applied for the chloroamidation of olefins (Scheme 43).\textsuperscript{74} The concerted chloroamidation step, via intermediate 154 for E-153 and via 155 for Z-153, in the intramolecular chloroamidation reaction results in diastereoselective formation of lactams (see 156 and 157). The use of 1 equiv of HCl as either proton or chloride source could replace acetic acid, sodium chloride, and the crown ether. Strong acids such as HCl, however, could induce olefin isomerization, which leads to a loss of diastereoselectivity for the chloroamidation of substrates containing a Z-olefin (such as Z-153). For Z-olefins, the NaCl/crown ether/acetic acid system was therefore used to obtain erythro chlorolactams such as 157 in high yields and with good diastereoselectivity.

- The chlorine-containing products can be used for further derivatization, for example in nucleophlic substitution reactions. Carboxylic acids could also be used directly, resulting in an oxaamidation reaction of olefins (Scheme 44). With a slightly different cyclopentadienyl ligand and acetic acid, sodium acetate, and a chloride abstractor, substrates E-153 and Z-153 are readily transformed into products 158 and 159, respectively, by a syn concerted oxaamidation step. When the phenyl group in the substrates was replaced by a methyl group, anti addition toward products 160 and 161 was observed, which is likely to be caused by an aziridination step followed by a ring-opening nucleophilic substitution step leading to inversion of one of the chiral centers. However, this has not yet been proven.

- **CONCLUSIONS**

Although dioxazolones were discovered nearly 70 years ago, these substrates have only recently gained attention in the field of transition-metal catalysis as an important class of acyl nitrene transfer agents. The examples shown in this review illustrate the convenience of this substrate class in new C–N bond formation reactions. The mild conditions generally applied in these reactions could lead to high stereo- and enantioselectivities, which is useful for the synthesis of bioactive nitrogen-containing compounds. The metal-nitrene species formed by decarboxylative activation of dioxazolones are generally electron deficient and commonly react in a concerted fashion. Intramolecular acyl nitrene C–H insertion reactions involving preactivated C–H bonds easily compete with the Curtius-type rearrangement, while for “direct” intramolecular nitrene transfer/insertion reactions involving non-preactivated substrates (i.e., without preceding formation of metal–carbon or metal–hydride bonds), extensive ligand optimization proved to be important to prevent such unwanted side reactions. Most of the reactions described thus far involve second- and third-row transition-metal catalysts such as Ru, Rh and Ir, but noteworthy examples with the first-row transition metals Co and Cu show a more general applicability of dioxazolones as acyl nitrene precursors in transition-metal catalysis. The ease of dioxazolone synthesis, formation of CO\textsubscript{2} gas as the sole byproduct from reactions with dioxazolones, and the importance of nitrene transfer reactions in general will undoubtedly lead to more interesting reactions in the near future.

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