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## Dioxazolones: Stable Substrates for the Catalytic Transfer of Acyl Nitrenes

van Vliet, K.M.; de Bruin, B.

Review

# Dioxazolones: Stable Substrates for the Catalytic Transfer of Acyl Nitrenes

Kaj M. van Vliet and Bas de Bruin*

Cite This: *ACS Catal.* 2020, 10, 4751−4769

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**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 ("inner-sphere" 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 $CO_2$ 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
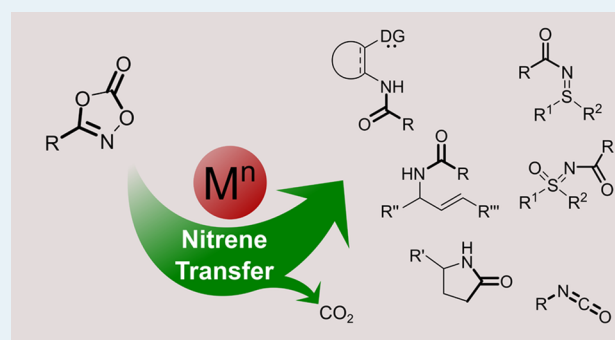
## ■ METHODS FOR DIRECT C−N BOND FORMATION

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.[1] Furthermore, functional nitrogen-containing polymers, such as polyurethane and polyamides, make up a big part of the global polymer production.[2] 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).[3] 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.[4]

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.[5] Catalysis involving transition-metal nitrenoids have been shown to be efficient in the direct amination of compounds (Scheme 1f).[6] 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.[7] 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.[8] Iminoiodinanes are another class of nitrene transfer reagents widely used in nitrene transfer chemistry, first reported by Okowara in 1975.[9] However, the use of
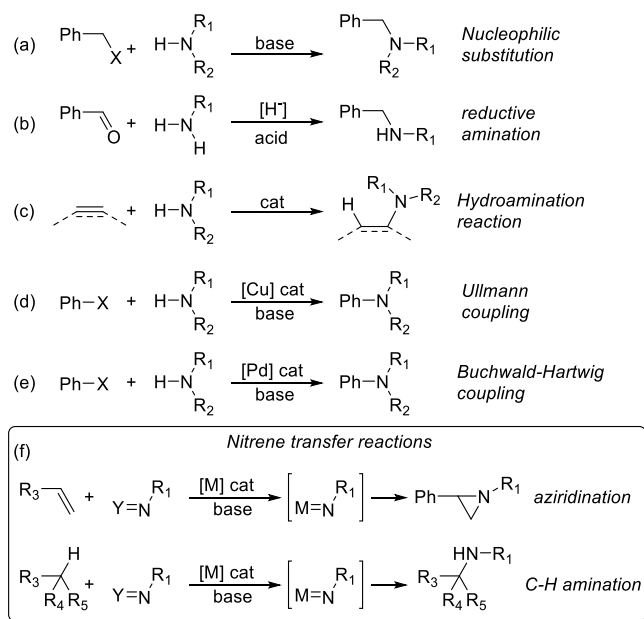
**Scheme 1. Examples of C−N Bond Formation Reactions**



(a) Nucleophilic substitution

(b) reductive amination

(c) Hydroamination reaction

(d) Ullmann coupling

(e) Buchwald-Hartwig coupling

(f) Nitrene transfer reactions — aziridination / C-H amination

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.

## 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). When dioxazolones are heated in DMSO or dimethyl sulfide, the acyl nitrene moiety ends up attached to the solvent to form sulfoximines or sulfimines (respectively). Higher selectivities have been obtained for the reaction between dioxazolones and various sulfoximines or sulfimines by photochemical ruthenium porphyrin catalysis in

2014 by the Bolm group.[15] One year later, they showed that the same Ru catalyst could oxidize sulfimines to sulfoximines.[16] Sauer continued his research in 1987 by studying the intramolecular C−H activation of acyl nitrene precursors, where he compared acyl azides, dioxazolones, and nitrile oxides.[17] Burk used bis-dioxazolone compounds as isocyanate precursors for the formation of polyurethanes.[18] He proposed that the isocyanate was formed via an initial nondecarboxylative ring opening of the dioxazolone moiety induced by ethoxide addition and a subsequent Lossen-type rearrangement (see Scheme 2).
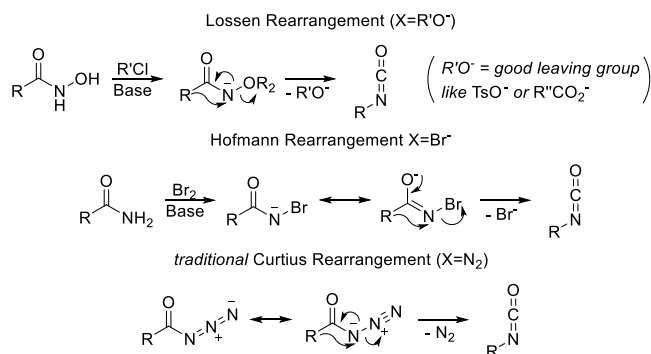
**Scheme 2. Mechanism for Urethane Formation from Dioxazolones, Proposed by Burk ($R_2$ = Aryl, Alkyl; $R_2 \neq$ H).[16]**
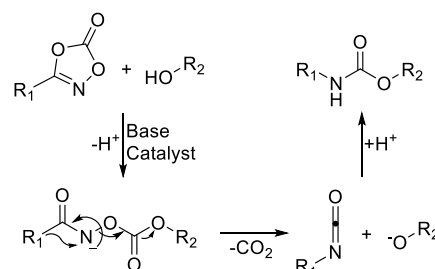


Inspired by the early work of Sauer and Mayer (*vide supra*), Pfizer published a paper on a Lossen-type rearrangement from hydroxamic acids via dioxazolones in 2009.[19] Instead of generation of the dioxazolone ring by reaction hydroxamic acids with phosgene, the researchers used carbonyldiimidazole (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, and Lossen 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 amidates, where X is a leaving group (see Scheme 3).[20]

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



Lossen Rearrangement (X=R'O⁻)

($R'O^-$ = good leaving group like TsO⁻ or R''CO₂⁻)

Hofmann Rearrangement X=Br⁻

*traditional* Curtius Rearrangement (X=N₂)

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** = $N_2^+$). All three

rearrangements 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.[21] 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.[22] 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)−nitrenoid species is formed.[23] Because of the easy isocyanate formation by the Curtius rearrangement, acyl azides generally invert and bind with the carbon atom (carbamoylation).[24] Therefore, Chang could not use the same rhodium catalyst for the directed C−N bond formation with acyl azides (although cyclopentadienyliridium did catalyze the desired C−N bond formation).[25]

In 2015, the Chang group introduced dioxazolones (and their derivatives) as a better alternative for acyl azides for the directed C−H amidation of o-phenylpyridine (1) and its derivatives to form amidated products, such as 3 (Scheme 4).[26]

**Scheme 4. Rh(III)-Catalyzed C−H Amination Using Dioxazolones[26]**
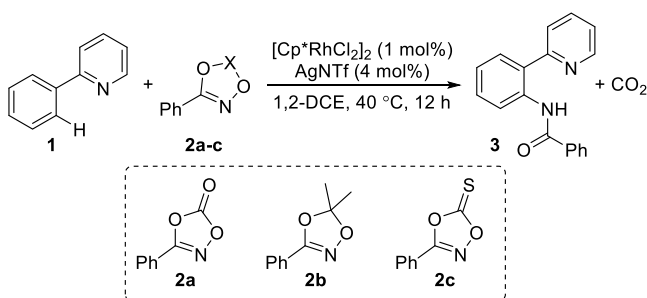


Mechanistic studies showed that the binding of acyl azides to pentamethylcyclopentadienylrhodium ([Cp*Rh^III X₂]) was weaker than the binding of 2-phenylpyridine (1) to the complex, thus leading to substrate inhibition. 3-Phenyl-1,4,2-dioxazol-5-one (2a) possesses a higher binding affinity for the rhodium catalyst (which is similar to imines)[27] 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.[28] In addition, Bolm showed that this type of reaction could be performed under solvent-free conditions using ball milling.[29]

A general mechanism for the directed C−H amidation reaction is shown in Scheme 6. After initiation from a [Cp*M^III] 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)−nitrenoid species 9 in the case of rhodium and iridium, which subsequently inserts into the M−C bond to from metallacycle 10. The desired product (12) and intermediate 7 are formed upon protodemetalation with the new substrate 11.
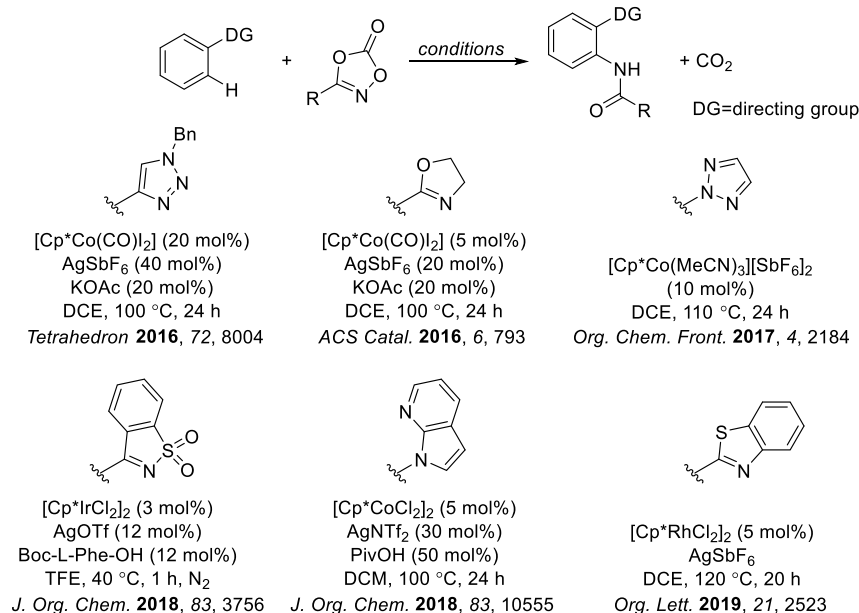
In 2016, the Chang group compared [Cp*Rh]⁺ with [Cp*Ir]⁺ for the directed amidation of arenes with dioxazolones.[30] In both cases, a concerted mechanism for the dioxazolone decomposition and M−C nitrogen insertion step from complex 8 to complex 10 is unlikely, because a concerted step would have a significantly 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).[31] 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.[32] Since the work of Chang, many groups have reported on group 9 [Cp*M]⁺ catalyzed directed C−H amidation reactions of benzene derivatives with different directing groups (some are shown in Scheme 8).[33]

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)-Cl₂}₂] catalyzed the multiamidation of pivaloylaniline (13)

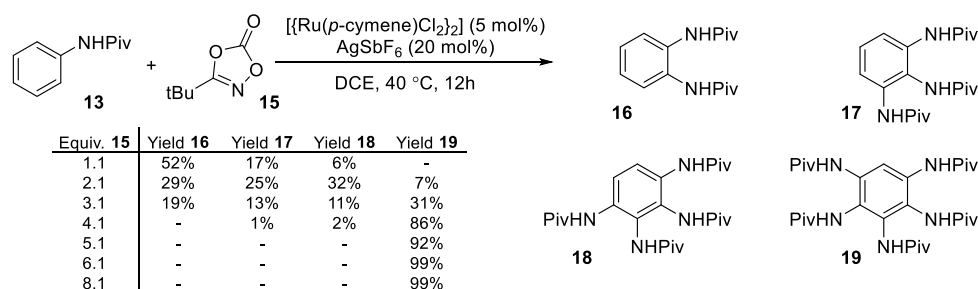**Scheme 5. Competitive Rhodium-Mediated C−N Bond Formation between Dioxazolones and Acyl Azides[26]**
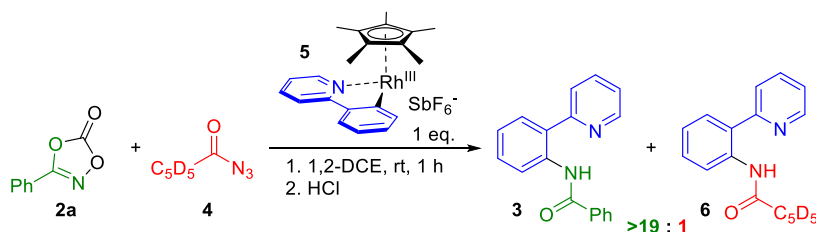
**Scheme 6. General Mechanism for the Group 9 Metal Catalyzed Directed C−H Amidation of Arenes**
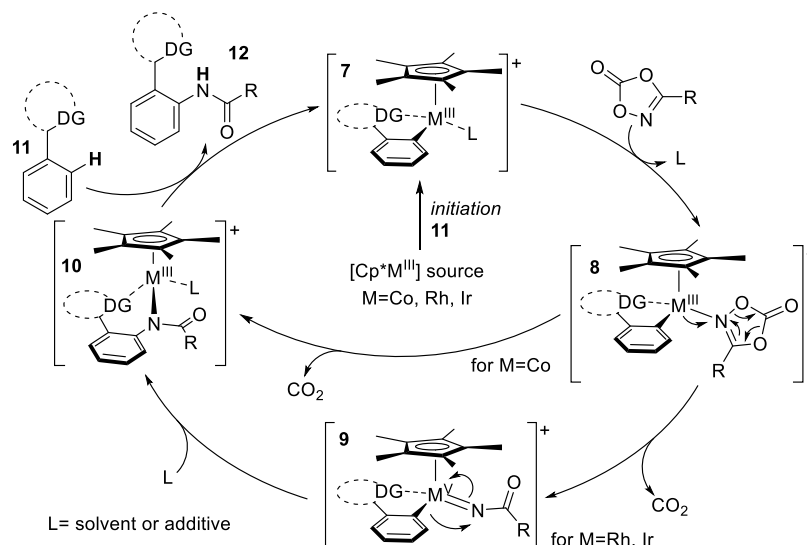


**Scheme 7. Group 9 Metal Catalyzed Directed C−H Amidation of N-Pivaloylaniline[31]**



| M | Yield |
|----|-------|
| Co | 79% |
| Rh | - |
| Ir | 22% |
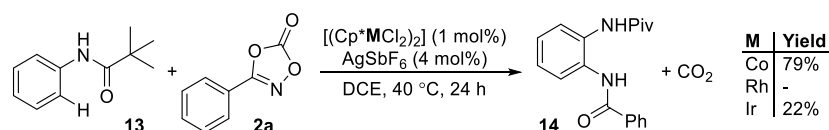
**Scheme 8. Series of Group 9 Metal Catalyzed Phenyl C−H Amidations with Dioxazolones[33]**



[Cp*Co(CO)I₂] (20 mol%)
AgSbF₆ (40 mol%)
KOAc (20 mol%)
DCE, 100 °C, 24 h
*Tetrahedron* **2016**, *72*, 8004

[Cp*Co(CO)I₂] (5 mol%)
AgSbF₆ (20 mol%)
KOAc (20 mol%)
DCE, 100 °C, 24 h
*ACS Catal.* **2016**, *6*, 793

[Cp*Co(MeCN)₃][SbF₆]₂
(10 mol%)
DCE, 110 °C, 24 h
*Org. Chem. Front.* **2017**, *4*, 2184

[Cp*IrCl₂]₂ (3 mol%)
AgOTf (12 mol%)
Boc-L-Phe-OH (12 mol%)
TFE, 40 °C, 1 h, N₂
*J. Org. Chem.* **2018**, *83*, 3756

[Cp*CoCl₂]₂ (5 mol%)
AgNTf₂ (30 mol%)
PivOH (50 mol%)
DCM, 100 °C, 24 h
*J. Org. Chem.* **2018**, *83*, 10555

[Cp*RhCl₂]₂ (5 mol%)
AgSbF₆
DCE, 120 °C, 20 h
*Org. Lett.* **2019**, *21*, 2523

with 3-(*tert*-butyl)-1,4,2-dioxazol-5-one (**15**) (see Scheme 9).[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).[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,

**Scheme 9. Iterative Directed C−H Amidation of Pivaloylaniline[34]**



| Equiv. **15** | Yield **16** | Yield **17** | Yield **18** | Yield **19** |
|---|---|---|---|---|
| 1.1 | 52% | 17% | 6% | - |
| 2.1 | 29% | 25% | 32% | 7% |
| 3.1 | 19% | 13% | 11% | 31% |
| 4.1 | - | 1% | 2% | 86% |
| 5.1 | - | - | - | 92% |
| 6.1 | - | - | - | 99% |
| 8.1 | - | - | - | 99% |

**Scheme 10. Rhodium-Catalyzed Directed C−H Amidation of Azobenzenes with Dioxazolones[35]**
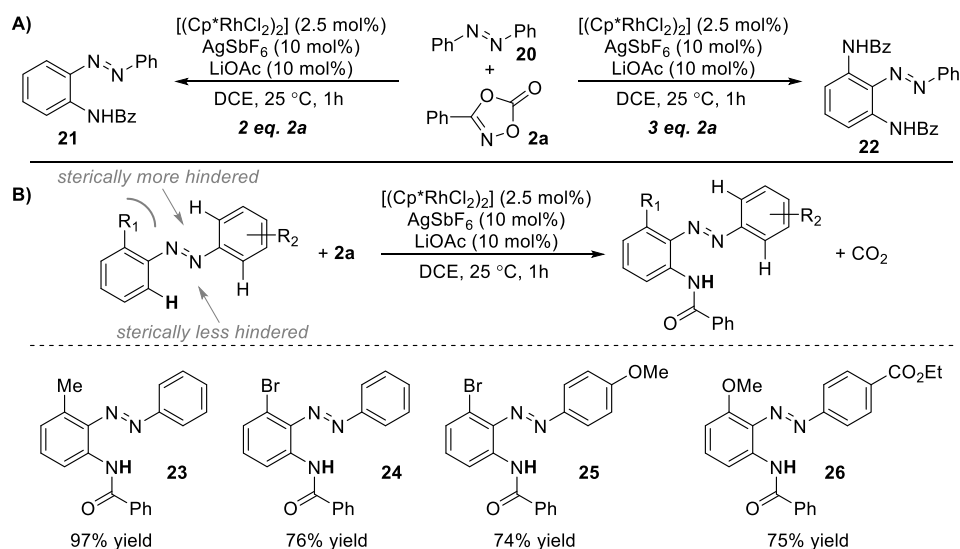


**Scheme 11. Cobalt-Catalyzed Directed C−H Amidation and Bisamidation of Azobenzene with Dioxazolones[36]**
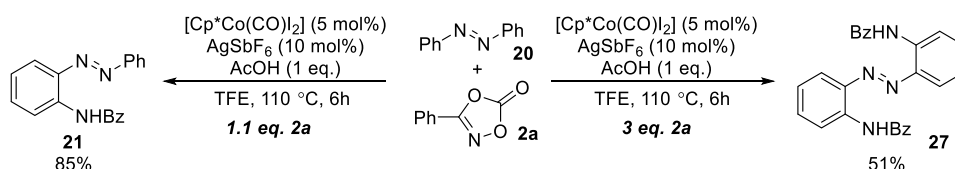


**Scheme 12. Iridium-Catalyzed Directed C−H Amidation of Nitrone 28 with Dioxazolones[37]**
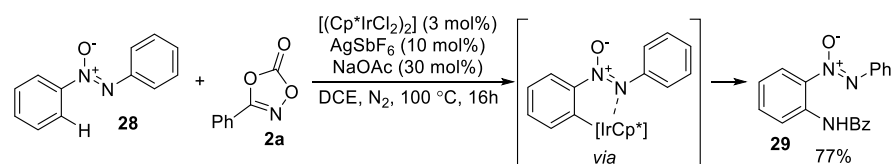


**Scheme 13. Rhodium-Catalyzed Directed C−H Amidation and Aerobic Hydrolysis of N,1-Diphenylmethanimine Oxide[38]**
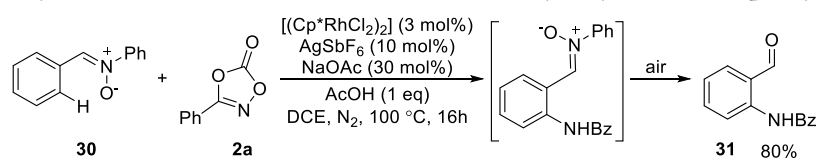


since electron-donating and electron-withdrawing groups do not give different selectivities (see **23**−**26**), there seems to be a steric effect determining the selectivity. With 3 equiv of dioxazolone **2a** the azobenzene **20** is efficiently bis-amidated at the same phenyl group to form compound **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. Interest-

**Scheme 14. Rhodium-Catalyzed Directed C−H Amidation of Benzaldehyde via Transient Imine Formation[39]**
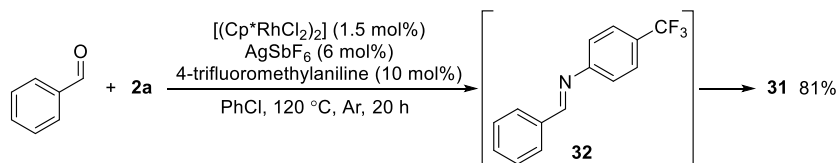


ingly, they observed a product selectivity different from that reported by Lee for the bisamidation of **20** (*vide supra*). With $[Cp*Co(CO)I_2]$, the authors observed the formation of product **27** instead of **22**.

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).[37] 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 nitrone substrate **30**, however, has been applied successfully as a directing group for selective C−H bond amidation by Wang and Cui (Scheme 13).[38] The amidation of **30** leads to aldehyde product **31** via aerobic hydrolysis.

One strategy for the direct conversion of benzaldehyde derivatives for directed C−H amidation with dioxazolones includes the addition of an amine to generate imines as a transient directing group. Jiao used this strategy for the rhodium-catalyzed ortho amidation of benzaldehyde (see imine **32** in Scheme 14).[39] Wu and Li reported a similar strategy for a cobalt-catalyzed ortho amidation of benzaldehyde.[40]

Bao and Zhang reported a direct ortho amidation reaction with aldehydes in the absence of amine as a "directing group or transient directing group free" strategy.[41] However, in their proposed catalytic cycle the aldehyde itself acts as a directing group. On top of that, as was mentioned in a paper by Dong, one should realize that isocyanate formation from the dioxazolone via a Curtius-type rearrangement could still lead to imine formation (Scheme 15).[42]

**Scheme 15. Possible Imine Formation Pathway during the Directed C−H Amidation Reaction of Benzaldehyde with Dioxazolones[42]**
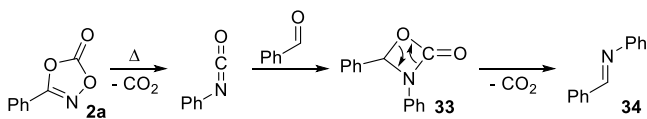


When in 2015 directed C−H amidation started to become a popular method for direct nitrogen incorporation, Jiao showed with $[Cp*Co(MeCN)_3](SbF_6)_2$ as a catalyst that the same strategy for directed arene C−H amidation also works for the directed C−H amidation of olefin **35** to form amide **36**

(Scheme 16).[43] 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 $[(Cp*IrCl_2)_2]$ as the catalyst.[44]

More examples of directed C(sp²)−H amidation have been reported, including directed C−H amidation on substituted cyclopentadienyl ligands of ferrocene derivatives[45] and C−H amidation reactions directly followed by cyclization steps to form heterocyclic compounds.[46] Considering the mechanistic similarity of the C−H amidation mechanisms, we will not discuss these examples in detail herein.
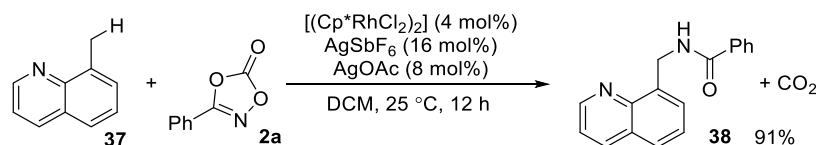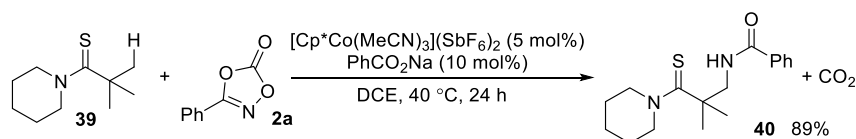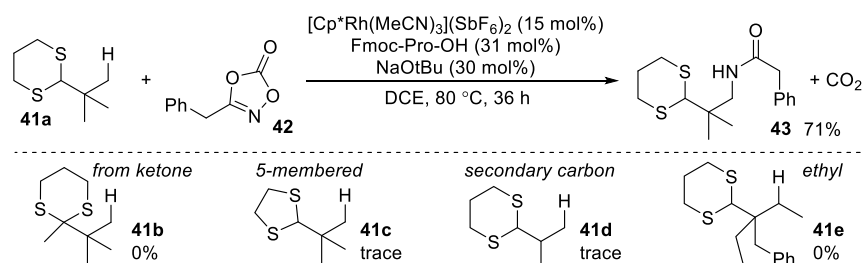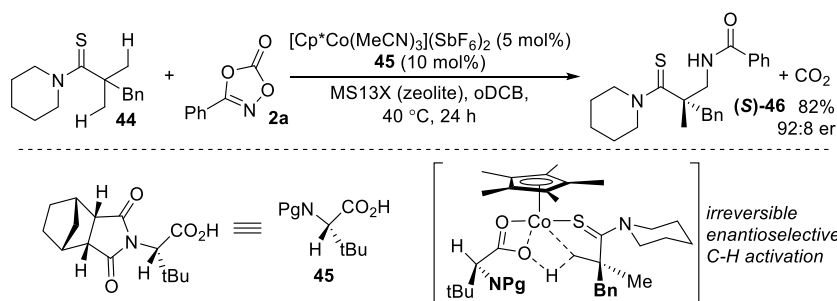
## ■ DIRECTED C(sp³)−H AMIDATION

The directed C−H amidation strategy is not limited to C(sp²)−H bonds. Li et al. were the first who directly amidated a methyl group, such as that in methylquinoline **37**, with dioxazolone substrate **2a** (Scheme 17).[47] They could efficiently amidate **37** using $[(Cp*RhCl_2)_2]$ 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.[48] Seayad and Dixon reported a cobalt-catalyzed single amidation of the *tert*-butyl group in thioamide **39** (see Scheme 18).[49]

Dixon later showed that the dithiane moiety in substrate **41a** could be used as a directing group to give **43** upon rhodium-catalyzed amidation with dioxazolone **42** (Scheme 19).[50] The use of a synthetically versatile group, such as dithiane, for directing the C−H activation is useful for further derivatization after the amidation 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 (see **41d,e**).

Recently, Yoshino and Matsunaga reported an enantioselective C(sp³)−H amidation reaction (Scheme 20).[51] By addition of chiral carboxylic acid **45**, they could enantioselectively amidate thioamide **44** with **2a** and $[Cp*Co(MeCN)_3](SbF_6)_2$ 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 arenes. 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.[52] Yoshino and Matsunaga later showed that also ferrocene-type chiral carboxylic acids, which are easily

**Scheme 16. Cobalt-Catalyzed Amidation of 2-(Prop-1-en-2-yl)pyridine with Phenyldioxazolone[43]**
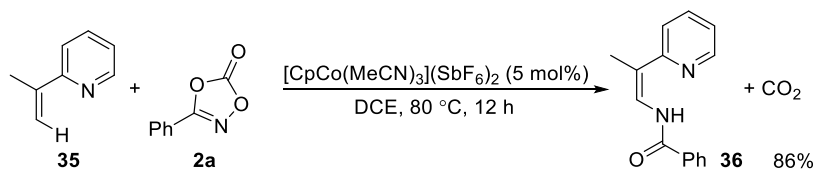
**Scheme 17. Rhodium-Catalyzed Directed C−H Amidation of 8-Methylquinoline with Phenyldioxazolone[47]**



**Scheme 18. Cobalt-Catalyzed Directed C−H Amidation of 39 with Phenyldioxazolone[49]**



**Scheme 19. Rhodium-Catalyzed Directed C−H Amidation of Dithiane Compound 38 with Benzyldioxazolone[50]**



**Scheme 20. Cobalt-Catalyzed Enantioselective C−H Amidation of 44 with Phenyldioxazolone[51]**



**Scheme 21. Rhodium/Chiral Acid Dual-Catalyzed Asymmetric Directed C−H Amidation of 8-Ethylquinoline with Phenyldioxazolone[54]**
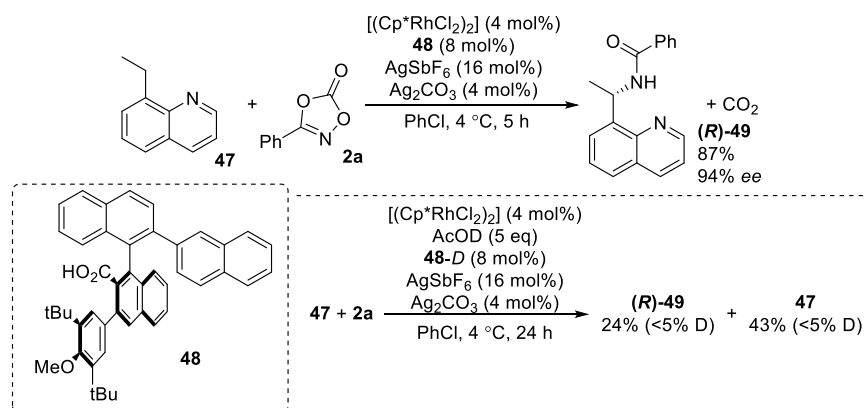


modified, can be used for the enantioselective amidation of thioamides.[53]

The group of Matsunaga later reported an enantioselective C(sp$^3$)−H amidation of 8-ethylquinoline 47 (Scheme 21).[54] 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$_2$CO$_3$ 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 $[(Cp*IrCl_2)_2]$ as the catalyst and dioxazolones (such as **51**) as nitrene precursors (see Scheme 22).[55] $C(sp^3)$−H (allylic)

**Scheme 22. Iridium-Catalyzed Allylic Amidation of 1-Decene with Methyldioxazolone[55]**
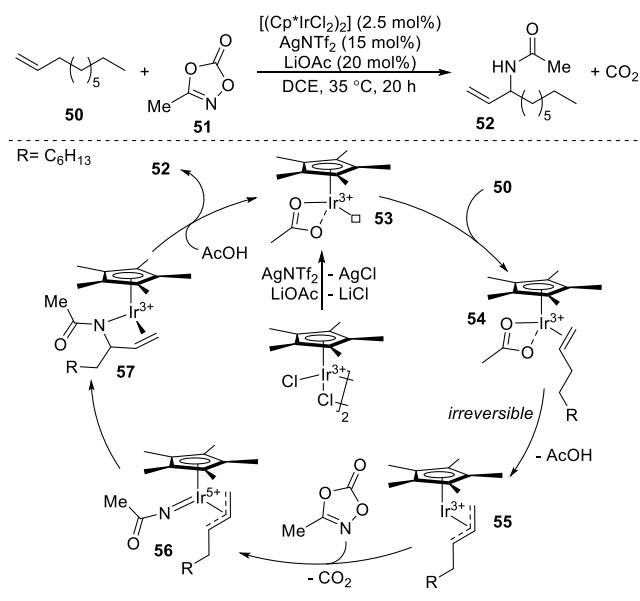


activation of **50** from **54**, after alkene coordination, leads to the formation of the $[Cp*Ir(allyl)]^+$ species **55**. Again, the deprotonation step from complex **54** to **55** was shown to be irreversible. Formation of the (formally) Ir(V)−nitrenoid species **56** from decarboxylative dioxazolone activation leads to an inner-sphere nitrene insertion step to form amide intermediate **57**. No aziridine formation was observed. The acyl nitrene inserts primarily at the internal carbon. The popularity of dioxazolones is reflected by the fact that Glorius simultaneously and independently published the same reaction in a different journal.[56]

Interestingly, Blakey showed that iridium and rhodium could give a different regioselectivity for the allylic C−H amidation of disubstituted aryl olefins (such as **58**) with *tert*-butyl dioxazolone **15** (Scheme 23).[57] The use of $[Cp*Rh(MeCN)_3](SbF_6)_2$ leads to the formation of products with a benzylic C−N bond (see **59**), while $[(Cp*IrCl_2)_2]$ generates a product containing a conjugated double bond such as **60**. The

origin of these opposing selectivities remains unknown. Although it is only a hypothesis, we expect such a large difference in selectivity to come from steric effects. The difference in precursor could lead to a different active species, where for iridium one of the chlorides remains attached to the metal. If so, coordination of the dioxazolone is likely to result in $\eta^1$ coordination of the allyl substrate. In case of the rhodium precursor, which does not contain halides, $\eta^3$ coordination might lead to a different selectivity in comparison to iridium.

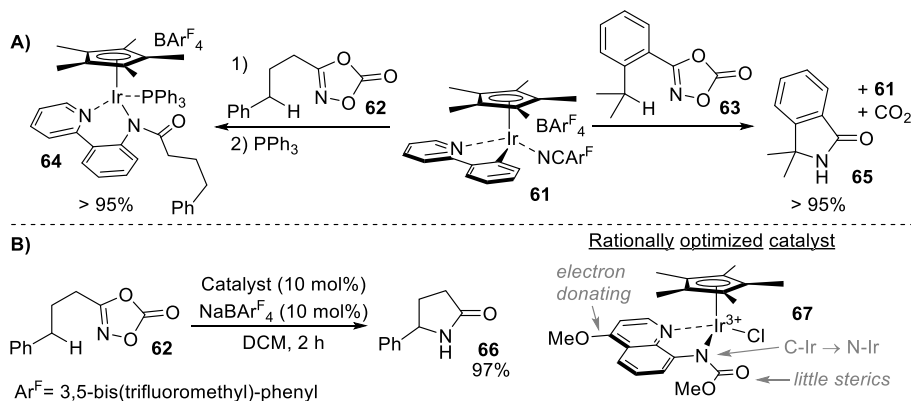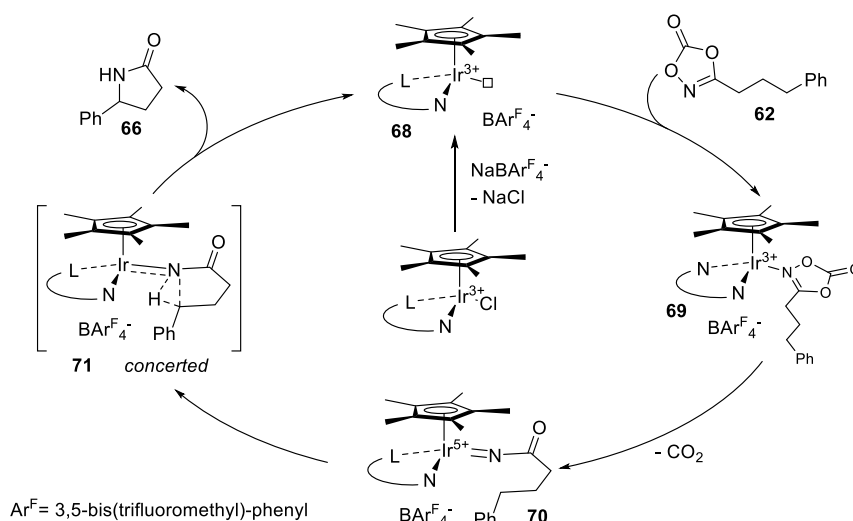## ◼ LACTAM FORMATION

The previous reactions are all examples of reactions proceeding via acyl nitrene insertion into preactivated C−H bonds. The M=N(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(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 $PPh_3$ 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 isoindolinone **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 $\delta$ bond. In a concerted,

**Scheme 23. Comparison of Rhodium and Iridium for the Allylic Amidation of Disubstituted Olefins[57]**



| Cat | Yield (benzylic:conjugated) |
|---|---|
| [Rh] | 78% yield (16:1) |
| [Ir] | 45% yield (1:7) |
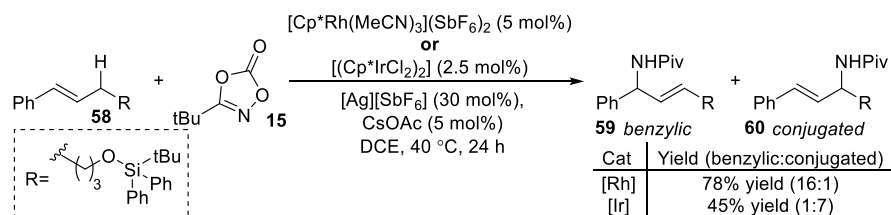
**Scheme 24. Rationally Optimized, Iridium Catalyzed Lactam Formation from 3-(3-Phenylpropyl)-1,4,2-dioxazol-5-one[58]**



**Scheme 25. Proposed Mechanism for the Iridium-Catalyzed Lactam Formation from 3-(3-Phenylpropyl)-1,4,2-dioxazol-5-one[59]**



$Ar^F$ = 3,5-bis(trifluoromethyl)-phenyl

**Scheme 26. Iridium-Catalyzed Lactam Formation from Phenylethyldioxazolones via Spirocyclization[59]**



$Ar^F$ = 3,5-bis(trifluoromethyl)-phenyl
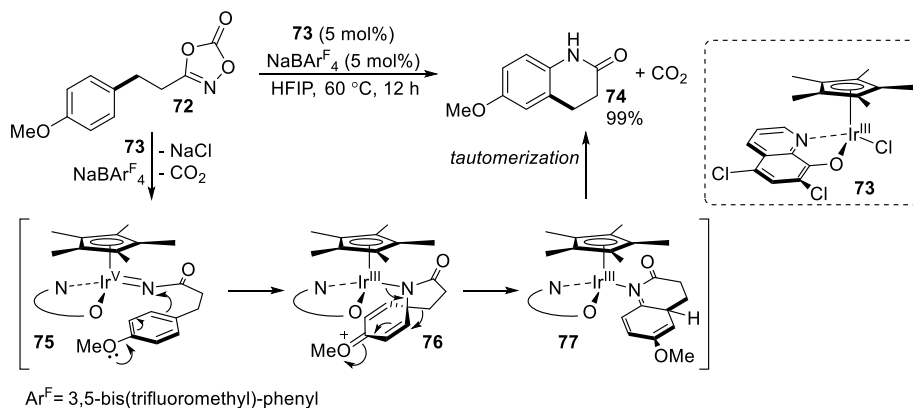
"direct" nitrene insertion reaction the nitrogen atom of the nitrene moiety is inserted into the C−H bond without formation of M−C or M−H bonds prior to the C−N bond formation step (see **71**), and subsequent ligand exchange then results in coordination of a new substrate and release of lactam **66**.

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).[59] However, an unexpected rearrangement was observed. The $C_{Ph}$−C bond from the backbone of substrate **72** is replaced by the acyl nitrene and shifted to the adjacent $C_{Ph}$−H bond (see product **74**). Computational analysis revealed that the

**Scheme 27. Iridium-Catalyzed Lactam Formation from Ortho-Substituted Phenylethyldioxazolones via Direct Electrophilic Aromatic Substitution[60]**
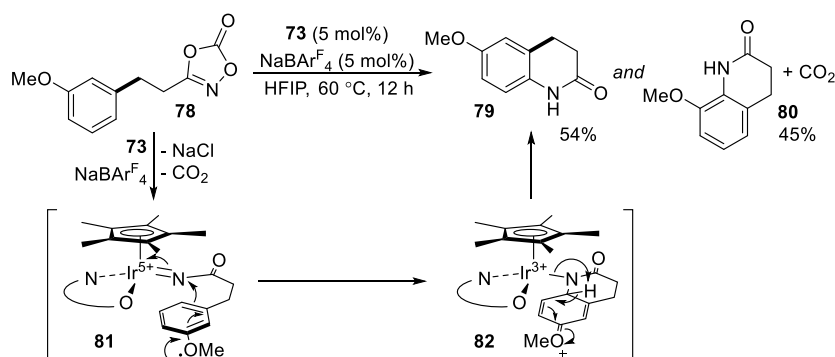


**Scheme 28. Iridium-Catalyzed Spirolactam Formation[60]**
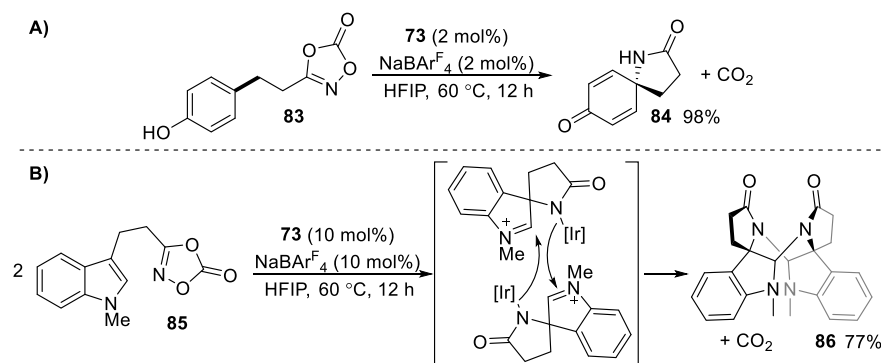


**Scheme 29. Iridium-Catalyzed Enantioselective Lactam Formation from 3-(3-Phenylpropyl)-1,4,2-dioxazol-5-one[60]**
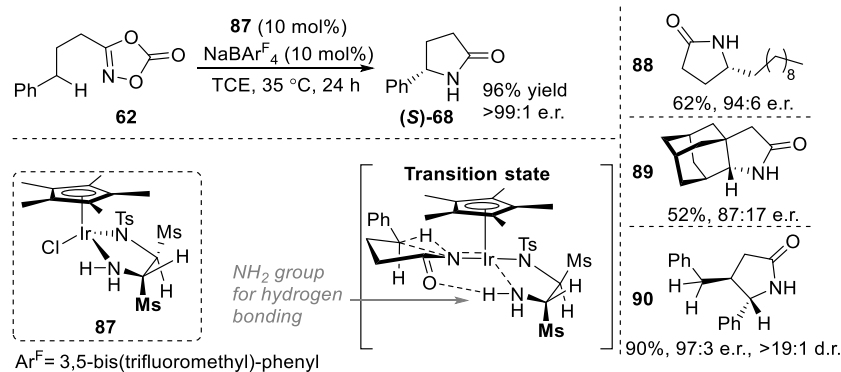


electrophilic (formally) Ir(V)−nitrenoid moiety in complex **75** is preferentially attacked by the tertiary carbon atom instead of the ortho carbon atom, resulting in spirocyclic intermediate **76**. Subsequent migrations of the nitrogen or the carbon atom to the adjacent $C_{Ph}$ atom are both kinetically 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 spyrocyclization 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.[60] 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

**Scheme 30. Ruthenium-Catalyzed Enantioselective Lactam Formation from 3-(3-Phenylpropyl)-1,4,2-dioxazol-5-one via Hydrogen Bonding[61]**



$Ar^F$= 3,5-bis(trifluoromethyl)-phenyl
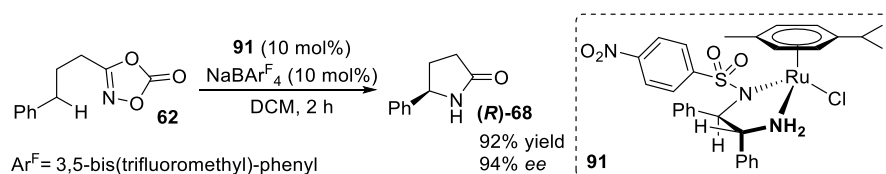
**Scheme 31. Iridium-Catalyzed Enantioselective Lactam Formation from 3-(3-Phenylpropyl)-1,4,2-dioxazol-5-one via Hydrophobic Interactions[62]**
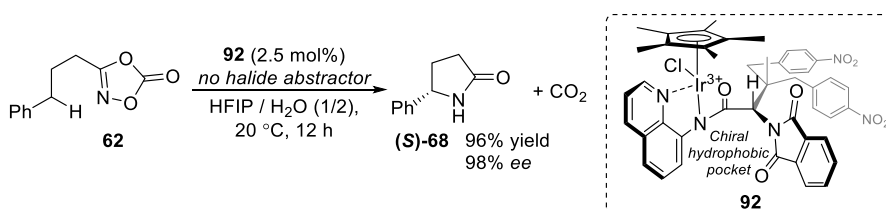


**Scheme 32. Ruthenium-Catalyzed Regioselective Lactam Formation by $\pi-\pi$ Interactions[63]**
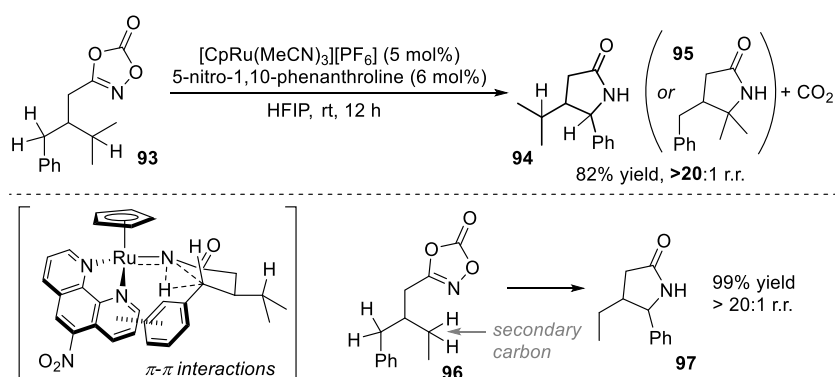


**Scheme 33. Ruthenium-Catalyzed Enantioselective Lactam Formation and Curtius-Type Rearrangement from 3-(3-Phenylpropyl)-1,4,2-dioxazol-5-one with N-Heterocyclic Carbene Ligands[65]**
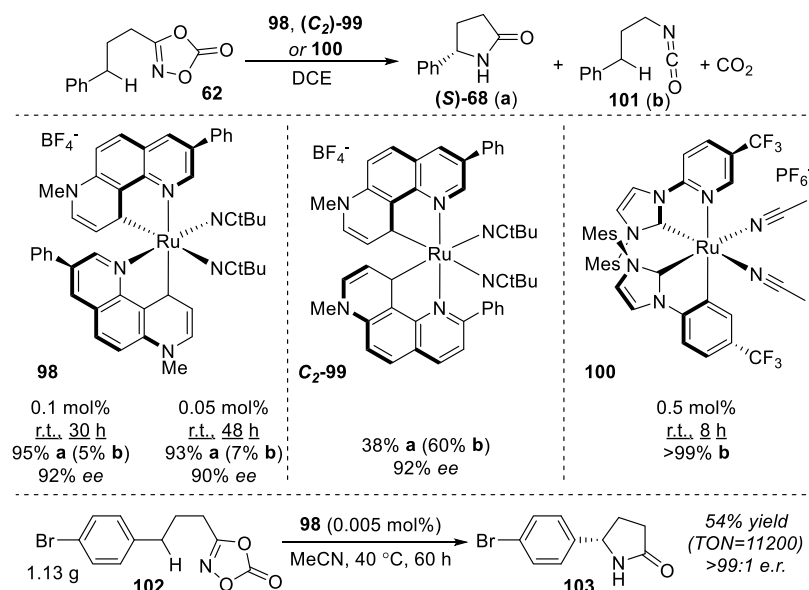


crucial to obtain high enantioselectivities. Mono- and dimethylation of the primary amine in **87** resulted in decreased yields and enantioselectivities and increased isocyanate formation via a Curtius-type rearrangement. A large scope of

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

**Scheme 34. Rhodium-Catalyzed Formation of Polycyclic Amides via Directed C−H Activation and Annulation of Dioxazolones and Alkynes[66]**
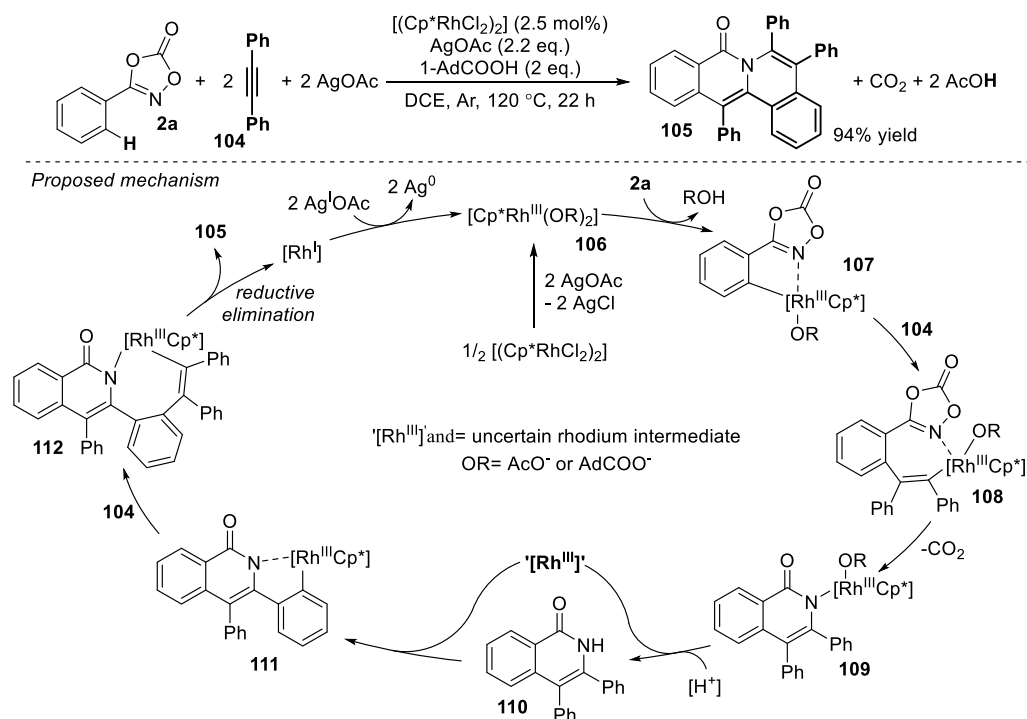


**Scheme 35. Rhodium-Catalyzed Formation of Isoquinolin-1(2H)-ones via Directed C−H Activation and Annulation of Dioxazolones and Alkynes[67]**
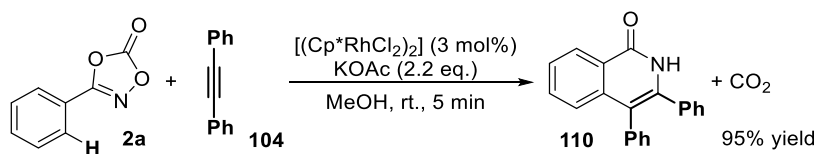


for the same enantioselective reaction catalyzed by Ru(II) *p*-cymene complex **91**, leading to the opposite enantiomer (see (*R*)-**68** Scheme 30).[61]

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 NH$_2$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 (*S*)-**68**. Addition of a halide abstractor is not required in the polar HFIP/H$_2$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 π−π interactions, they could selectively perform an intramolecular benzylic C−H amidation.[63] The polar solvent HFIP increases the strength of π−π 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 π−π interactions determine the selectivity (and not sterics).

Meggers and Houk developed chiral Ru(III) catalyst **98** containing *remote*-N-heterocyclic carbenes for the enantioselective transformation of **62** to form lactam (*S*)-**68** (Scheme 33).[65] At low catalyst loadings, **98** could catalyze the formation of the γ-lactam with high enantioselectivity and little isocyanate formation via a Curtius-type rearrangement. However, with its isomer, (*C₂*)-**99**, as the catalyst isocyanate **101** was obtained as the main product. The (*C₂*)-**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, >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

**Scheme 36. Ruthenium-Catalyzed Formation of Oxazolines or Oxazoles from the Reaction of Styrene or Phenylacetylene Derivatives, Respectively, with Dioxazolones[68]**
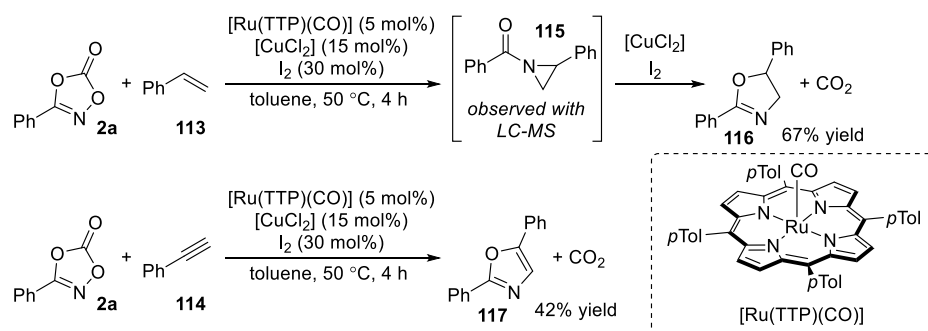


**Scheme 37. Gold-Catalyzed Oxazole Formation from 5,5-Dimethyl-1,4,2-dioxazoles[69]**



**Scheme 38. Tf$_2$NH-Catalyzed Oxazole Formation from 5,5-Dimethyl-1,4,2-dioxazoles[70]**



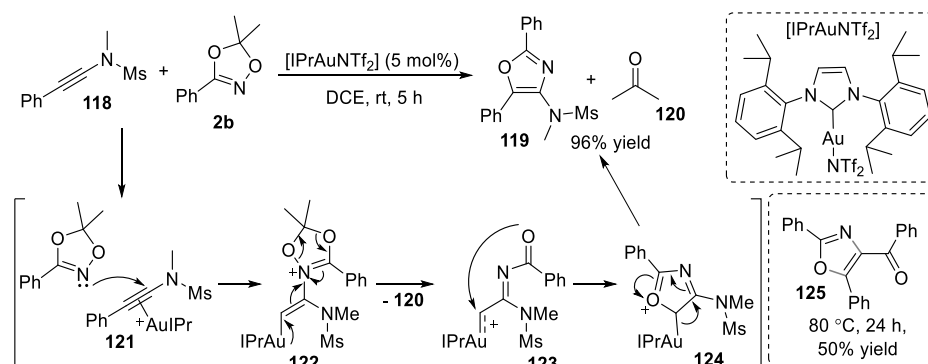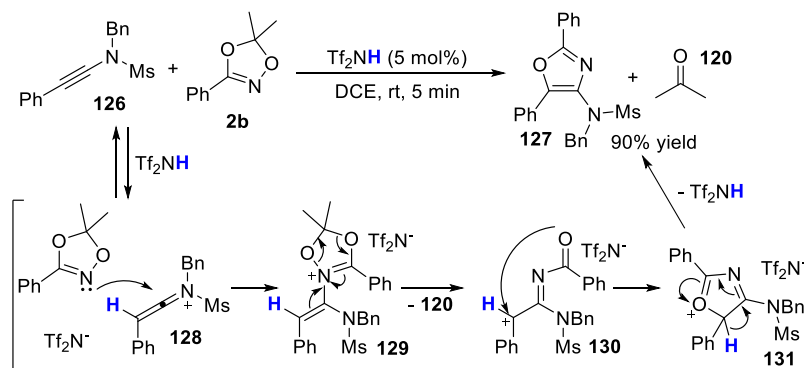formation of rhodacycle **107** by directed C–H activation of **2a**, diphenylacetylene (**104**) is inserted into the Rh–C bond followed by decarboxylative nitrene formation and subsequent insertion into the new Rh–C bond to form complex **109**. The authors proposed a protodemetalation step to form iso-quinolinone **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**). Subsequently, the active Rh(III) species is regenerated by oxidation of Rh(I) by AgOAc.

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 oxazoline **116** or oxazole **117** from the reaction between styrene (**112**) or phenylacetylene (**113**) with dioxazolone **2a** catalyzed by a [Ru(TTP)(CO)]/[CuCl$_2$] bimetallic system (Scheme 36).[68] Although it was not clear how, addition of I$_2$ 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 oxazole **119** from the reaction between ynamide **118** and dioxazole-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 coordina-

**Scheme 39. Copper-Catalyzed Enantioselective Hydroamidation Reaction via Hydrocupration[71]**
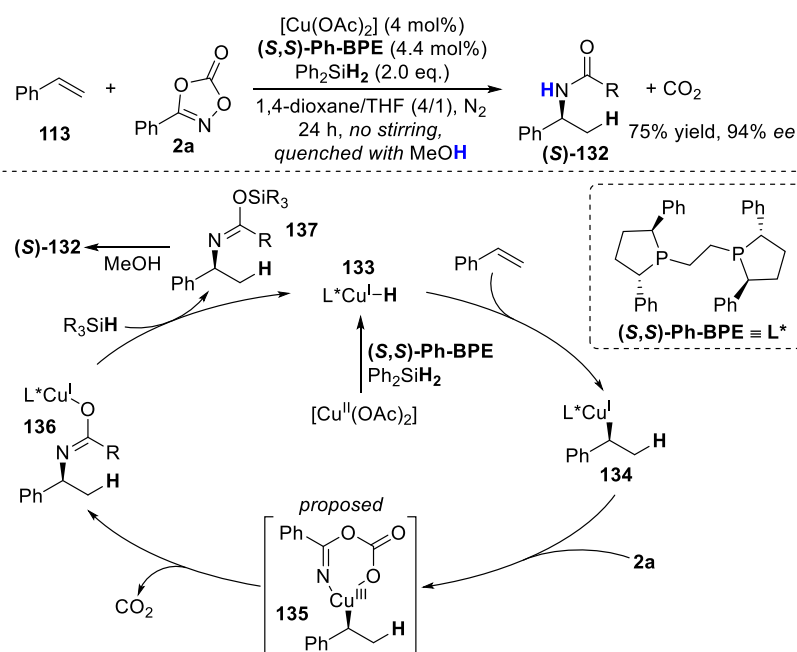


**Scheme 40. Copper-Catalyzed Three-Component Reaction for the Formation of N-Acylamidines[72]**
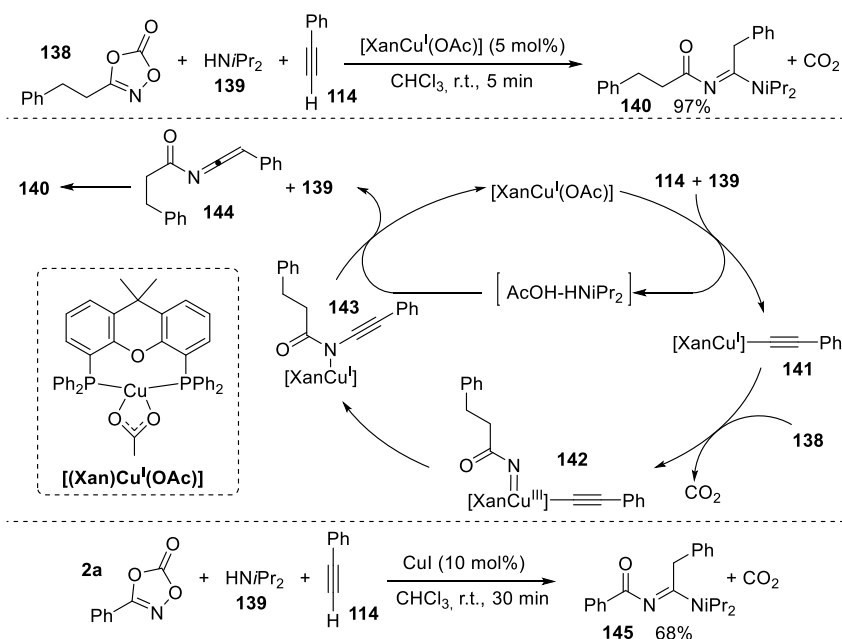


tion to the metal center, which leads to a nucleophilic attack of **2b**. Decomposition of the dioxazole in intermediate **122** results in the formation of gold carbene intermediate **123**, which upon cyclization (to form **124**) and demetalation yields oxazole product **119**. In addition to reporting 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

**Scheme 41. Iridium-Mediated Cyclization of Alkynyldioxazolones with Ligand Participation[73]**
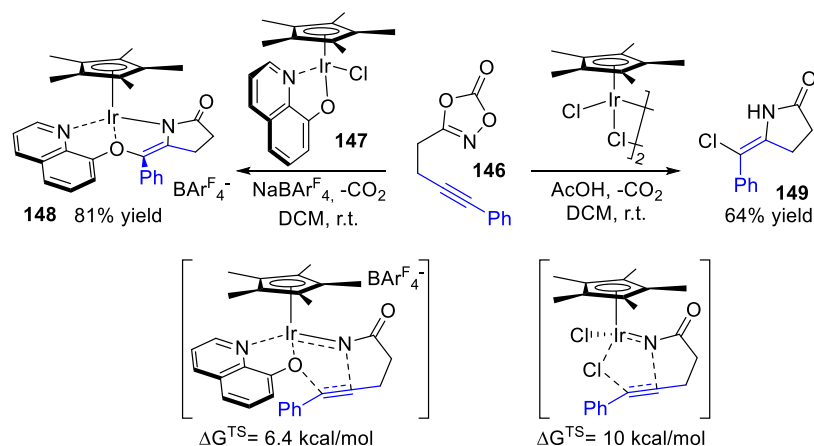


**Scheme 42. Iridium-Catalyzed Haloamidation of Alkynyldioxazolones[73]**
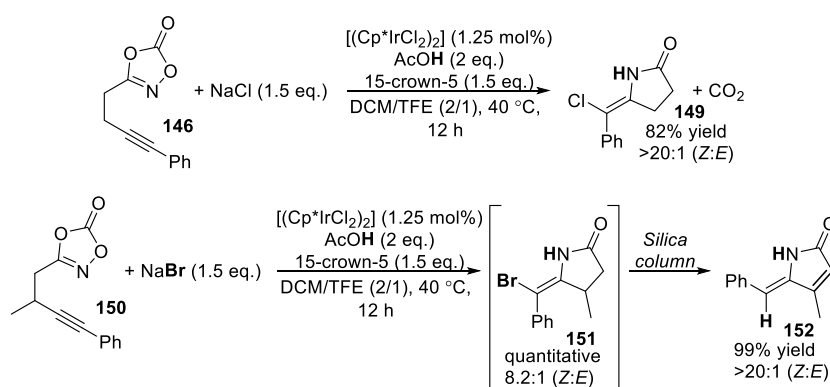


**Scheme 43. Iridium-Catalyzed Chloroamidation of Olefinic Dioxazolones[74]**
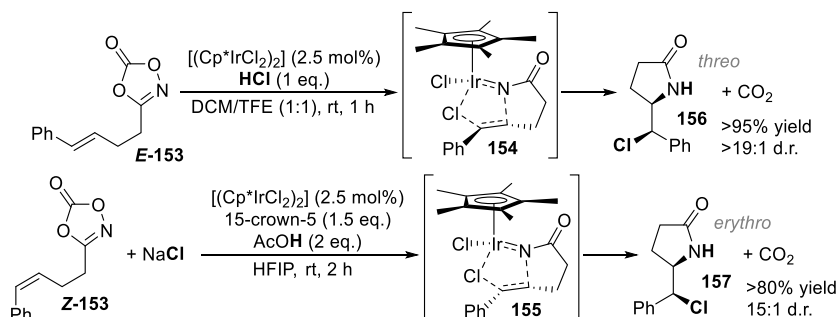


135, which is markedly different from the previous work on dioxazolones in which reactive acyl nitrenes are typically proposed as the key intermediates. After decarboxylation and nitrogen insertion into the Cu−C bond (136), copper is replaced for a silyl group with Ph$_2$SiH$_2$. During quenching of 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, phenyl-acetylene (114), and diisopropylamine (139) to form N-acyl amidine 140 (Scheme 40).[72] The applied catalyst Xantphos copper acetate ([(Xan)Cu$^I$(OAc)]) forms complex 141 by C−H activation of 114, catalyzed by amine 139. Decarboxylative 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$^I$(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$^I$(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).[73] This type of ligand participation can also be observed when [(Cp*IrCl$_2$)$_2$] reacts with 146. Acetic acid enables protodemetalation to give

**Scheme 44. Iridium-Catalyzed Syn and Anti Oxoamidation of Olefins with Dioxazolones and Acetic Acid**[74]
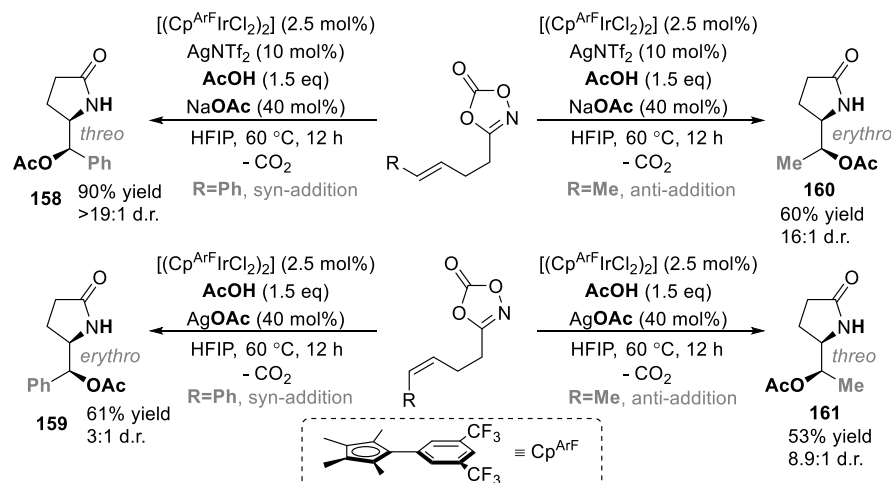


product **149**. By adding sodium chloride and crown ether 15-crown-5, the chlorinated iridium species could be regenerated. Therefore, iridium could be used in catalytic amounts (Scheme 42). Tetrabutylammonium chloride could also be successfully applied as a chloride source. When sodium bromide was 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).[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 nucleophilic substitution reactions. Carboxylic acids could also be used directly, resulting in an oxoamidation 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 oxoamidation 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 $CO_2$ 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.

### AUTHOR INFORMATION

**Corresponding Author**

**Bas de Bruin** − *Van 't Hoff Institute for Molecular Sciences (HIMS), Faculty of Science, University of Amsterdam (UvA), 1098 XH Amsterdam, The Netherlands;* ● orcid.org/0000-0002-3482-7669; Email: b.debruin@uva.nl

**Author**

**Kaj M. van Vliet** − *Van 't Hoff Institute for Molecular Sciences (HIMS), Faculty of Science, University of Amsterdam (UvA), 1098 XH Amsterdam, The Netherlands*

Complete contact information is available at:
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(HRSMC), and the UvA Research Priority Area Sustainable Chemistry.

**Notes**

The authors declare no competing financial interest.

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